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THE OPTICAL ACTIVATION OF ACIDS, AND A NEW RESOLUTION PROCESS DEPENDING ON IT

BY

MARGARET M. JAMISON (HARRIS)

AND

E. E. TURNER

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

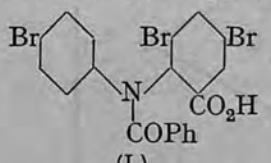
By Margaret M. Jamison and E. E. Turner.

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.

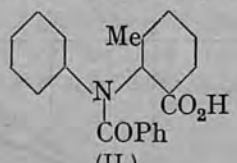
It has been shown that excess of acid, which always increases the *rate* of asymmetric transformation, may either accentuate or reverse a change occurring when base and acid are present in equivalent amounts. In the second case a method becomes available for the isolation, for the first time, of both 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.

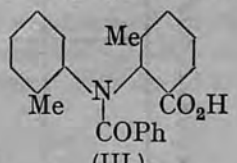
Of the acids studied, only 4 : 6 : 4′-tribromo-*N*-benzoyldiphenylamine-2-carboxylic acid (I) possessed sufficient optical stability for mutarotation due to activation to be observable at the ordinary temperature. With this acid and nor-*d*-ψ-ephedrine in chloro-



(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.

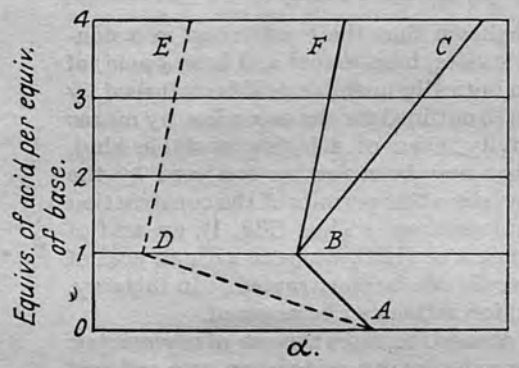
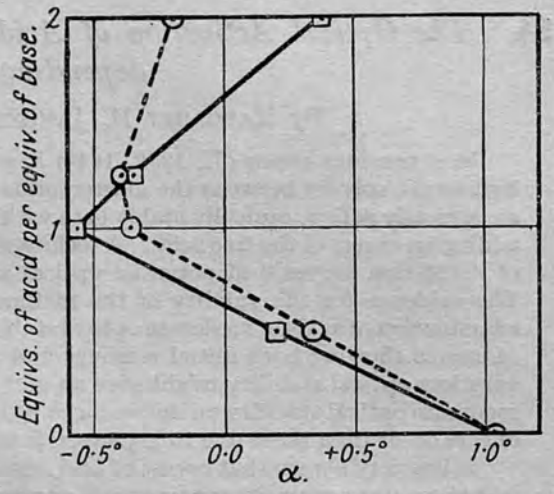


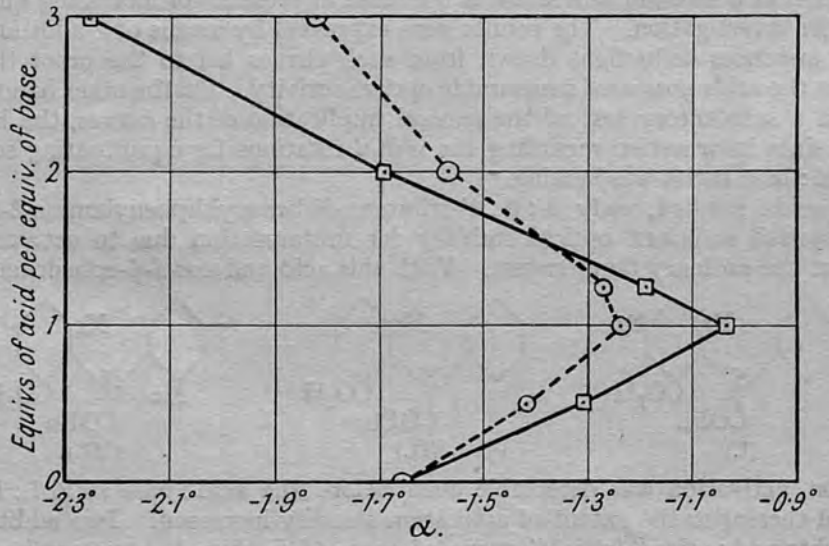
FIG. 2.



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*-ψ-ephedrine in chloroform

FIG. 3.



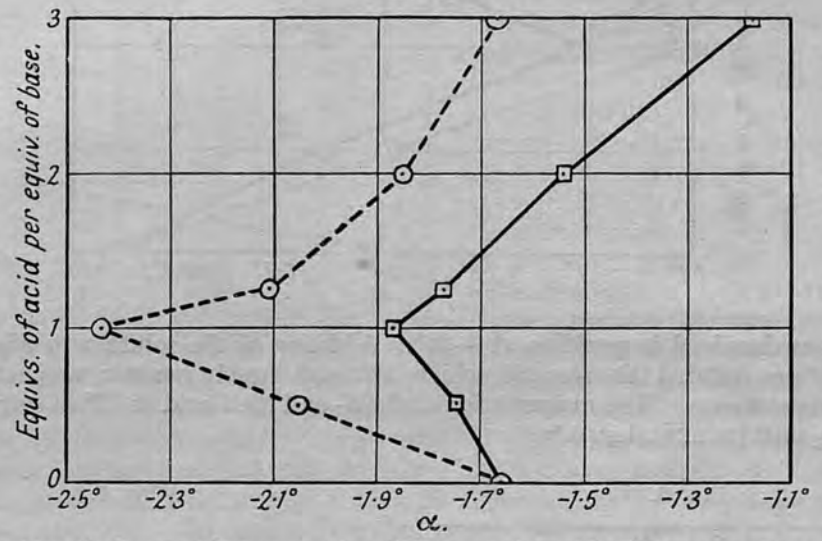
solution, mutarotation occurred when the acid : base ratio was 0·5 : 1, the rotation becoming less positive. At the ratio 1 : 1 the amount of change increased; at 1·25 : 1 it was relatively small, and at 2 : 1 extensive mutarotation occurred in the opposite sense, the positive rotation of the solution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

* Addition curves 2—10 give α 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.

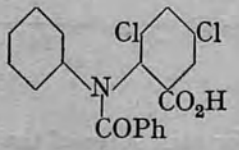
FIG. 4.

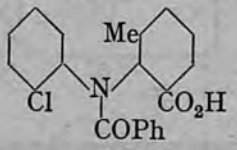


N-*Benzoyl*-2 : 6′-*dimethyldiphenylamine*-2′-*carboxylic acid* (III) was distinctly more stable optically than the 6-methyl acid (II), but was unsuitable in that it solvated with extreme readiness, particularly with water and hydroxylic compounds in general. Moreover, although with cinchonidine in solvent *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*-ψ-ephedrine in chloroform it gave an addition curve

(IV.)





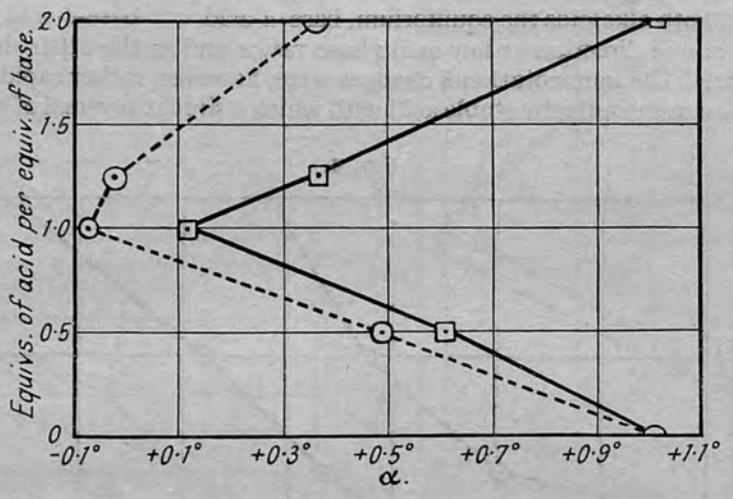
(V.)

(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.

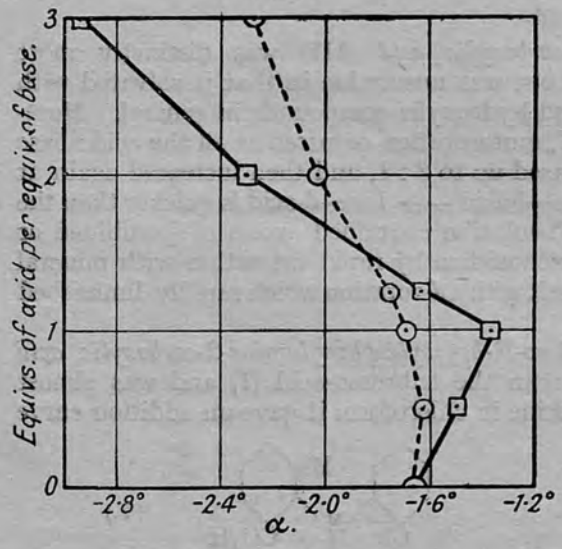
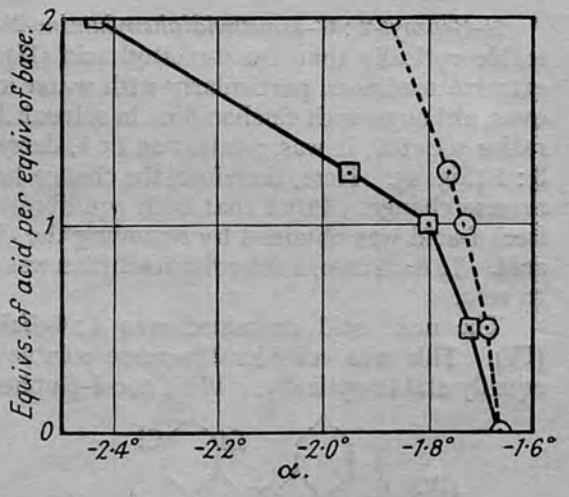


FIG. 7.



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.

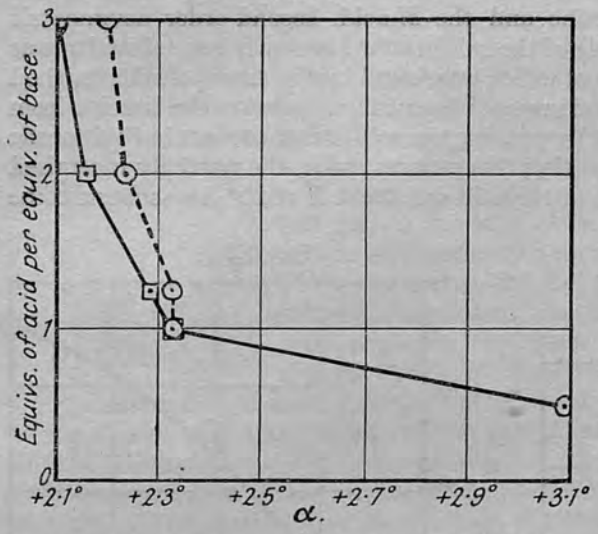
* These units are used throughout, unless otherwise stated, both in this and in the previous paper (*loc. cit.*).

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.

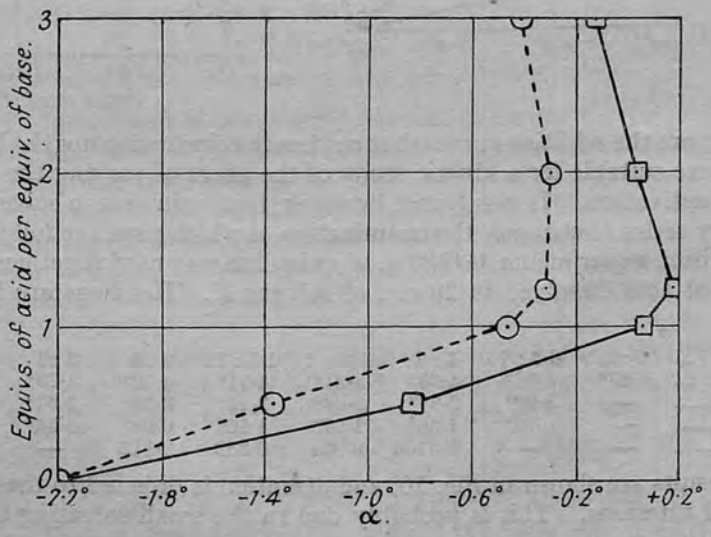
FIG. 8.



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.

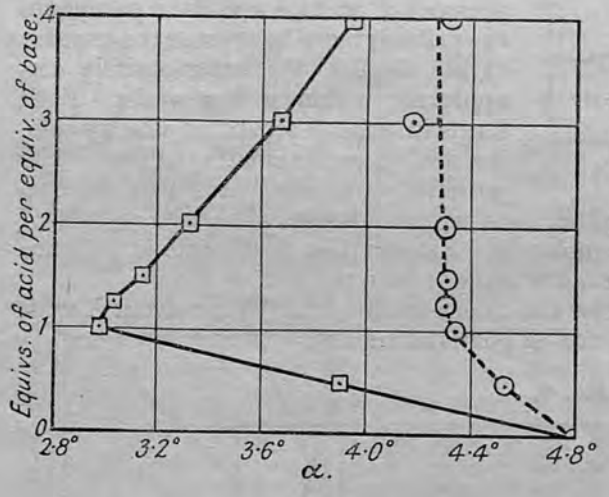
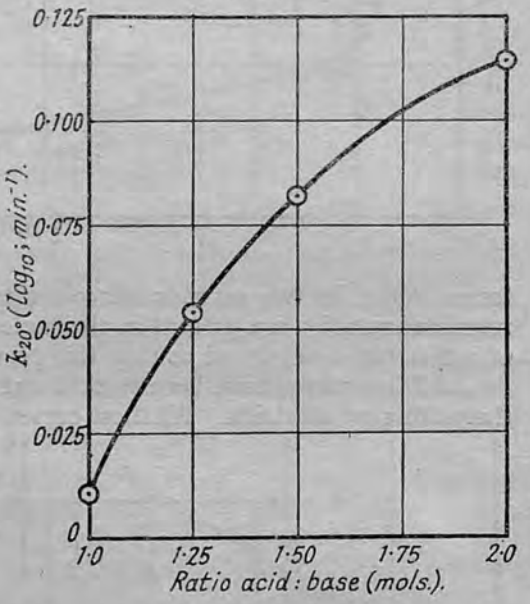


FIG. 11.



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

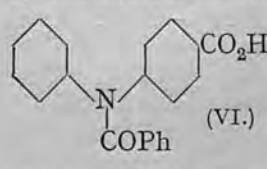
The addition results are shown in Fig. 10, and attention is directed to the almost " ideal " curve for initial rotations. This is probably due to the small solvating tendency of this particular acid.

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	$k = 0{\cdot}0106$
1 mol. Quinidine + 1 mol. chloro-methyl acid + 1 mol. acid. (VI)	$k = 0{\cdot}084$

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.

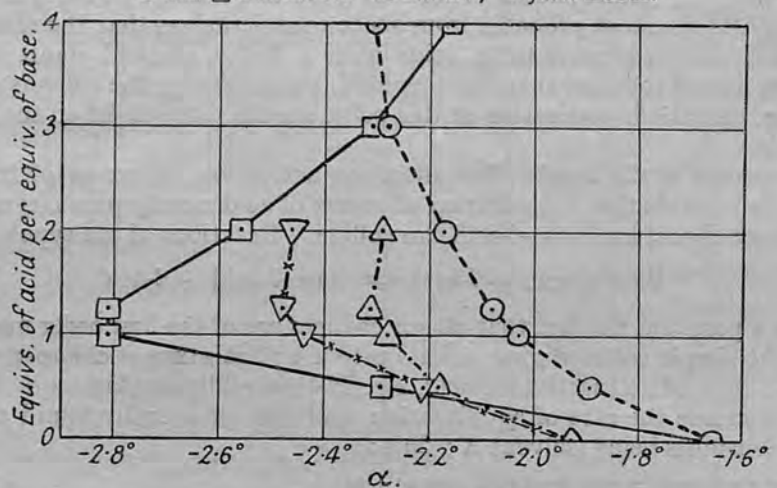
Hitherto, activation has been studied by the addition-curve method only with derivatives of *N*-benzoyldiphenylaminecarboxylic acids. We have now applied the method to the investigation of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (Mills and Elliott, *loc. cit.*). An interesting discovery was made 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 $[\alpha]^{15°}_{5461}$ — 35·5° and — 87·3°, and in (*b*) — 255·5° and — 87·3°. From

FIG. 12.

O *and* □ *Solvent* X. △ *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 benzanilide-iminochloride. 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 $0{\cdot}15 \pm 0{\cdot}02$.

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 $0{\cdot}15 \pm 0{\cdot}02$.

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.	α_t.	$k \times 10^4$.	Time after 3·5 mins.	α_t.	$k \times 10^4$.	Time after 3·5 mins.	α_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 $+3{\cdot}87°$ to $+3{\cdot}32°$; $k = 0{\cdot}116$.

Rate of Racemisation of l-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 $-2{\cdot}78°$ 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 $-2{\cdot}76°$ to zero; $k = 0{\cdot}204$. Repetition of this experiment gave k 0·199.

Rate of Racemisation of the Papaverine Salt of l-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 $-2{\cdot}64°$ 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 $+4{\cdot}19°$ to $+3{\cdot}70°$; $k = 0{\cdot}084$.

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 $\alpha_{5461}^{15°} - 1{\cdot}20°$, whence $[\alpha]_{5461}^{15°} - 35{\cdot}5°$. The final equilibrium rotation was $[\alpha]_{5461}^{15°} - 87{\cdot}3°$ ($l = 2$).

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

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*-ψ-ephedrine, and ψ-ephedrine. Page 1649, line 14: for 0·5 g. read 0·1 g.

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THE MUTAROTATION OF ETHYL-ALCOHOLIC SOLUTIONS OF *l*-MENTHYL BENZOYLFORMATE

BY

MARGARET M. JAMISON (HARRIS)

AND

E. E. TURNER

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94. *The Mutarotation of Ethyl-alcoholic Solutions of* l-*Menthyl Benzoylformate.*

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

The mutarotation at the ordinary temperature of ethyl-alcoholic solutions of *l*-menthyl benzoylformate described by McKenzie and Mitchell (*Biochem. Z.*, 1929, **208**, 456) is shown to require the presence of traces of water. In absolute alcohol the mutarotation is too rapid to be measured at the ordinary temperature, but becomes measurable at 0°. Preference is expressed for the view that mutarotation depends on hemiacetal formation between the ethyl alcohol and the ester.

McKenzie (J., 1904, **85**, 1249) showed that when *l*-menthyl benzoylformate reacted with methylmagnesium iodide, unequal amounts of the diastereoisomeric menthyl atrolactates were formed: saponification of the product gave an optically active atrolactic acid. This was followed by numerous asymmetric syntheses of a similar type. In 1929, McKenzie and Mitchell (*loc. cit.*) made the interesting observation that in certain solvents (Table I) *l*-menthyl benzoylformate exhibited mutarotation and that in others (Tables II*a* and II*b*) it did not:

Table I.

Ethyl alcohol
n-Propyl alcohol
n-Butyl alcohol
*iso*Butyl alcohol
l-Amyl alcohol

Table II.

a.	*b.*
Acetone	Methyl alcohol
Anisole	Allyl alcohol
Benzene	*iso*Propyl alcohol
Chloroform	*tert.*-Amyl alcohol
Ether	*sec.*-Octyl alcohol

Similar observations were made with other keto-esters (McKenzie and Mitchell, *Biochem. Z.*, 1930, **224**, 241; 1931, **228**, 471; McKenzie and Ritchie, *ibid.*, 1931, **231**, 412; **237**, 1; 1932, **250**, 376; McKenzie and Christie, *ibid.*, 1935, **277**, 426: the results were summarised by McKenzie in 1936, *Ergebn. Enzymforsch.*, **5**, 49).

McKenzie connected the results of the earlier and the later series of investigations, and, at a time when the conception of the carbonyl group was attracting considerable attention, saw in his observations evidence for "induced asymmetry" of the carbonyl group. *l*-Menthyl benzoylformate was assumed to be capable of exhibiting diastereoisomerism, expressed by the two forms:

$$Ph—\overset{+}{C}O—CO\cdot O\cdot \overset{-}{C_{10}}H_{19} \qquad\qquad Ph—\overset{-}{C}O—CO\cdot O\cdot \overset{-}{C_{10}}H_{19}$$

In alcohol and Table I solvents generally, mutarotation was observed and was attributed to the slow conversion of the ester into unequal amounts of the above diastereoisomerides. In ether and Table II solvents generally, mutarotation was not observed, and the conversion was therefore assumed to be too fast to be measured. Thus, when an ethereal solution of *l*-menthyl benzoylformate was treated with a Grignard reagent, the latter met unequal amounts of the two diastereoisomerides and so asymmetric synthesis became possible.

We are not aware that any explanation other than this has been offered for the results of the Grignard synthesis, but hemiacetal formation has been considered (McKenzie and Mitchell, *loc. cit.*; Ebert and Kortüm, *Ber.*, 1931, **64**, 342) as an explanation of the mutarotation of ethyl-alcoholic solutions of *l*-menthyl benzoylformate. This, in absence of the Grignard results, would explain why mutarotation cannot be observed in ether, benzene, etc., and the fact that it was not observed with certain alcohols other than ethyl could not be regarded as evidence against the hemiacetal theory. It must be pointed out, in favour of the hemiacetal view, that since such compounds as mesoxalic esters form isolable hemiacetals when treated with ethyl alcohol (cf. Curtiss and Spencer, *J. Amer. Chem. Soc.*, 1909, **31**, 1055), it is at least unlikely that menthyl benzoylformate, with two electron-attracting groups attached to the carbonyl group, would not tend to form a hemiacetal when dissolved in excess of ethyl alcohol.

Theoretically, it should be possible to distinguish by kinetic measurements between "asymmetric induction" at the carbonyl group and hemiacetal formation. The former process would clearly be a unimolecular one in all circumstances, while the addition:

$$\underset{l}{Ph—CO—CO\cdot O\cdot C_{10}H_{19}} \xrightarrow{EtOH} \underset{d \qquad l}{Ph—\overset{OH}{\underset{OEt}{C}}—CO\cdot O\cdot C_{10}H_{19}} + \underset{l \qquad l}{Ph—\overset{OEt}{\underset{OH}{C}}—CO\cdot O\cdot C_{10}H_{19}}$$

should show first-order kinetics when the alcohol is present in excess, but second-order kinetics when alcohol and ester are present in approximately equivalent amounts. We have endeavoured to examine this experimentally. The conditions favourable to the bimolecular reaction could not be realised, because the ester is sparingly soluble in ethyl alcohol, and when the ester and alcohol are mixed in equivalent quantities in inert solvents mutarotation is either too slow or too slight to be detectable. Were the mutarotations observed by McKenzie and his co-workers due to the asymmetric induction effect, it is surprising that it did not occur in so many solvents: absence of mutarotation when alcohol and the ester were mixed in an inert solvent fits in with the hemiacetal explanation, since hemiacetal formation may well require a considerable excess of alcohol to make it appreciable.

McKenzie and Mitchell (*loc. cit.*) found that in ethyl alcohol dried over quicklime and then over calcium the specific rotation of *l*-menthyl benzoylformate changed during 24 hours from $[\alpha]^{25°}_{5461}$ — 54° to — 59° and thereafter remained constant ($c = 2{\cdot}9988$; α changed from — 3·21° to — 3·56°; $l = 2$). They concluded (*Biochem. Z.*, 1930, **224**, 241) that the presence of small quantities of water did not affect the mutarotations they observed with their alcoholic solutions.

In attempting to repeat their experiments, we have found that at 18·8° solutions of the

ester in ethyl alcohol containing amounts of water of the order of 0·05—0·10% exhibit the type of mutarotation they describe, the final specific rotation $[\alpha]_{5461}^{18\cdot8^\circ}$ being $-60\cdot8^\circ$ ($l = 2$; $c = 4\cdot783$). With *absolute* ethyl alcohol we observed no mutarotation at 18·8°, the solution showing from the very outset the specific rotation $-60\cdot8^\circ$. This result suggested that in anhydrous alcohol mutarotation is too rapid to be measurable at the ordinary temperature, but opened up the possibility that it might be observable at lower temperatures. In fact, we were able to demonstrate it at 0°. Moreover, addition of small quantities of water to an absolute-alcoholic solution prepared at 18·8° had no observable effect on the specific rotation either immediately or after 24 hours, thus indicating that mutarotation had already proceeded to completion. The identity of the final rotations in alcohols of different water content suggests that the equilibrium composition is independent of the water concentration if the latter is low : it is unlikely that the figure, $-60\cdot8^\circ$, is the result of change in equilibrium composition being exactly compensated by the change in solvent property.

The decelerating effect of water on the observed mutarotation approaches a constant value which is attained when about 0·15% of water is present. We have demonstrated this by quantitative study of the mutarotation of *l*-menthyl benzoylformate in alcohol containing varying amounts of water. The mutarotations all followed the first-order law, and are summarised below, k being calculated in decadic logarithms here and throughout.

EtOH, %.	Time of first reading after dissolving (mins.).	$[\alpha]_{5461}^{18\cdot8^\circ}$. Initial.	Final.	$k \times 10^3$ (min.$^{-1}$) at 18·8°.
99·98	10	−54·45°	−60·8°	13·0
99·96	11	−51·8	−60·8	0·93
99·86	13	−51·3	−60·5	0·73
99·05	3	−51·6	−60·8	0·78

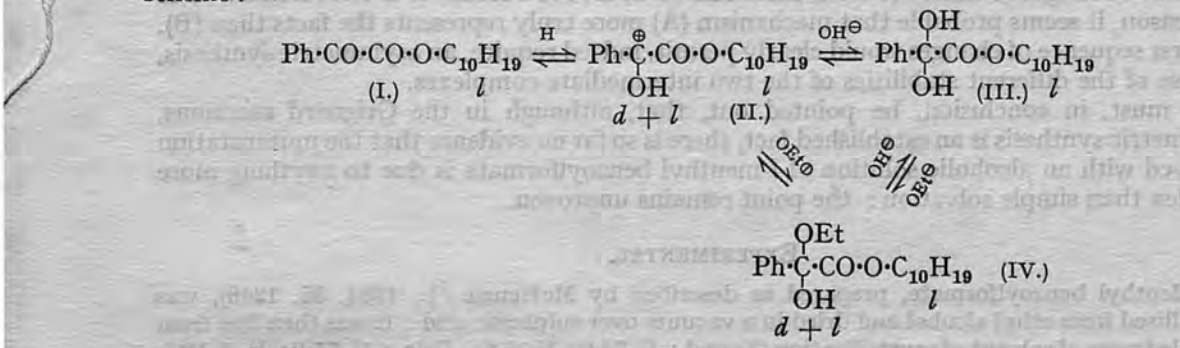
In all experiments, $l = 2$. In the first three experiments, $c = 4\cdot783$, and in the last, $c = 3\cdot5175$.

With different samples of ethyl alcohol, freed as far as possible from all traces of water, three experiments gave the following results :

c.	Time of first reading (mins.).	$[\alpha]_{5461}^{0^\circ}$. Initial.	Final.	$[\alpha]_{5461}^{18\cdot8^\circ}$. Final.	$k \times 10^3$ (min.$^{-1}$) at 0°.
1·775	2·25	−58·0°	−64·0°	—	—
2·371	3·6	−50·5	−64·7	−60·8°	41
2·050	2·6	−52·9	−63·9	—	170

The divergence between the values of k obtained on two different occasions is an indication of the sensitivity of the change to traces of water. It may be noted that the initial specific rotation of *l*-menthyl benzoylformate in " absolute " alcohol could be used to diagnose the freedom of the solvent from water, as consideration of the above figures shows.

Our first explanation of the mutarotational effects observed was based on the following scheme :



In absence of any evidence to the contrary, it may be assumed that the final product in anhydrous alcohol or in alcohol containing small amounts of water is (IV), since the final specific rotation is $-60\cdot8^\circ$ in all cases.

A simple explanation of the changes observed then appeared to be that (I) ⟶ (II)

and (II) ⟶ (III) were fast reactions, but (III) ⟶ (IV) and (III) ⟶ (II) slow reactions. If, then, (II) ⟶ (IV) is much slower than (III) ⟶ (IV), the deceleration due to water is accounted for. On the other hand, we know that in absence of water (I) ⟶ (IV) is a very rapid process. Moreover, it seems extremely unlikely that water, which shows no tendency to combine with (I) in absence of alcohol, should combine with it when alcohol is present in large excess. In this connexion it must be remembered that the relatively very stable chloral hydrate, analogous to (III), can be converted by the action of alcohol in excess into chloral alcoholate, analogous to (IV). Similarly, chloral alcoholate, dissolved in excess of *iso*amyl alcohol, gives chloral "*iso*amyl alcoholate" (Gadamer, *Arch. Pharm.*, 1905, **243**, 30).

In previous communications (Jamison and Turner, J., 1938, 1646; 1940, 264) emphasis has been laid on the large quantitative difference, almost amounting to a qualitative one, between the condition of acid–base combinations in hydroxylic solvents on the one hand and non-hydroxylic solvents on the other. Particular attention may also be directed to the extraordinary effect on the activation of the cinchonidine salt of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine of traces of alcohol in the main solvent used (chloroform).

There is little evidence, apart from the results now communicated, as to the effect upon the velocity of a reaction occurring in ordinary "absolute alcohol" of removing the last traces of water, the reason possibly being that hitherto it was not to be expected that such an inquiry would be fruitful.

Taking the situation as it is, however, it does not seem impossible that, compared with ordinary "absolute alcohol," anhydrous alcohol may behave as possessing only weak proton-donating properties. The point is at any rate worth examining, and leads to the suggestion that, although in slightly wet alcohol reactions of an ionic type begin the process measured as a mutarotation, yet in anhydrous alcohol "hydrogen bond" or resonance complexes such as (V) are concerned. The intramolecular rearrangement of (V) to (IV) should be extremely rapid compared with the bimolecular processes involved in the formation of (II).

$$C_{10}H_{19}\cdot O\cdot CO\!>\!\overset{Ph}{}C{=}O \;\ldots\; HOEt \qquad (V.)$$

We conclude, therefore, that in anhydrous alcohol the mechanism of the rapid mutarotation observed at 0° is that just outlined, and that in alcohol containing small amounts of water an ionic mechanism functions, but that (III) is not necessarily an important intermediate in the conversion of (I) into (IV).

The mechanism of the asymmetric syntheses by the Grignard method may be compared with the above mechanism for the anhydrous alcohol solution:

$$\text{(A)}\quad >C{=}O \longrightarrow >C{=}O{\rightarrow}Mg\}X \longrightarrow >C\overset{R}{}{-}OMg\}X$$
$$\text{(B)}\quad >C{=}O + RMg\}X \longrightarrow >CR{-}OMg\}X$$

Addition of RMgX is different from the addition of EtOH because it is irreversible. For this reason, it seems probable that mechanism (A) more truly represents the facts than (B). The first sequence of changes would clearly permit, indeed require, an asymmetric synthesis, because of the different stabilities of the two intermediate complexes.

It must, in conclusion, be pointed out, that, although in the Grignard reactions, asymmetric synthesis is an established fact, there is so far no evidence that the mutarotation observed with an alcoholic solution of *l*-menthyl benzoylformate is due to anything more complex than simple solvation: the point remains unproven.

Experimental.

l-Menthyl benzoylformate, prepared as described by McKenzie (J., 1904, **85**, 1249), was crystallised from ethyl alcohol and dried in a vacuum over sulphuric acid: it was then free from possible traces of solvent of crystallisation (Found: C, 75·0; H, 8·4. Calc.: C, 75·0; H, 8·4%).

The absolute ethyl alcohol used was obtained by leaving the commercial material over quicklime for several weeks, heating it under reflux with barium oxide, and finally distilling it from fresh barium oxide through a Widmer column. Precautions were taken to exclude moisture, and the alcohol was used within a few minutes of being distilled. Alcohols of definite water

content were made by adding water to the absolute alcohol, the percentages mentioned being those by weight.

Mutarotations at 18·8°.—In these experiments the *l*-menthyl benzoylformate was weighed in a 20-c.c. stoppered flask (if necessary then dried in a vacuum over sulphuric acid), and the alcohol added, with temperature control.

(1) 99·98% Alcohol; $c = 4·783$. The first polarimetric reading ($l = 2$) was made 10 mins. after wetting ester with solvent; $\alpha_{5461}^{18·8°}$ changed from − 5·21° to − 5·82°, whence change in $[\alpha]_{5461}^{18·8°}$ was from − 54·45° to − 60·8°; $k = 0·013$ (min.$^{-1}$) (limits, 0·0155 and 0·0123).

(2) 99·96% Alcohol; $c = 4·783$. First reading in 11 mins. Change in $\alpha_{5461}^{18·8°}$, − 4·96° to − 5·82°. Change in $[\alpha]_{5461}^{18·8°}$, − 51·8° to − 60·8°; $k = 0·00093$ (min.$^{-1}$) (limits, 0·0010 and 0·00087).

(3) 99·86% Alcohol; $c = 4·783$. First reading at 0·22 hr. Change in $[\alpha]_{5461}^{18·8°}$, − 51·3° to − 60·5°. Time (t, in hrs.) is reckoned from 0·22 hr.

t	0·0	2·0	3·0	5·0	6·0	7·0	8·0	9·0	12·0	∞
α_t	−4·91°	−5·08°	−5·15°	−5·26°	−5·315°	−5·355°	−5·385°	−5·42°	−5·51°	−5·79°
k (hr.$^{-1}$) ...	—	0·0465	0·046	0·044	0·0445	0·0435	0·042	0·041	0·041	—

$k = 0·044$ (hr.$^{-1}$) or 0·00073 (min.$^{-1}$).

(4) 99·05% Alcohol; $c = 3·5175$. First reading in 3 mins.; $\alpha_{5461}^{18·8°}$ changed from − 3·63° to − 5·82°, $[\alpha]_{5461}^{18·8°}$ from − 51·6° to − 60·8°; $k = 0·00078$ (min.$^{-1}$) (limits, 0·00070 and 0·00088).

Readings in 100% *alcohol at* 18·8°. (1) $c = 4·783$, $\alpha_{5461}^{18·8°}$ − 5·82°, $[\alpha]_{5461}^{18·8°}$ − 60·8°; first reading in 24 mins.; no change in 24 hours. (2) $c = 4·783$, $\alpha_{5461}^{18·8°}$ − 5·81°, $[\alpha]_{5461}^{18·8°}$ − 60·7°; no change on keeping.

Mutarotations in 100% *alcohol at* 0°. (1) $c = 2·3710$; first reading 3·6 mins. after mixing; t reckoned from this stage.

t	0·0	0·6	1·6	2·1	2·45	3·75	6·5	6·8	7·6
α	−2·52°	−2·56°	−2·61°	−2·63°	−2·66°	−2·73°	−2·86°	−2·86°	−2·89°
k (min.$^{-1}$)	—	0·0420	0·0368	0·0348	0·0389	0·0406	0·0436	0·0416	0·0421

t	9·25	10·8	11·15	11·6	11·9	15·2	16·0	∞
α_t	−2·88°	−2·98°	−2·99°	−2·99°	−3·03°	−3·09°	−3·11°	−3·23°
k (min.$^{-1}$)	0·0332	0·0420	0·0423	0·0406	0·0462	0·0464	0·0483	—

$k = 0·041$ (min.$^{-1}$).

(2) $c = 2·0500$; $k = 0·17$ (min.$^{-1}$) (limits, 0·19 and 0·14).

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UNIVERSITY OF LONDON (BEDFORD COLLEGE), c/o UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

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311. *Some Quantitative Aspects of Asymmetric Transformation.*

By Margaret M. Jamison (HARRIS) and E. E. Turner.

If d-R_3N,d-HA and d-R_3N,l-HA are the two possible diastereoisomeric salts formed by the combination of an optically stable base, d-R_3N, with an optically unstable acid, dl-HA, they can undergo interconversion in suitable solvents. As a rule, they will do so, because their free energies are different, and the optical rotation observed will be that corresponding to the equilibrium d-R_3N,d-HA $\rightleftharpoons$ d-R_3N,l-HA. This process has been called by Kuhn "asymmetric transformation of the first order," a second-order transformation being one in which, not only are the salts interconvertible but, since one of them is the less soluble, this salt crystallises out, and none of the other form appears.

We find that with certain optically unstable acids first-order transformation does not occur to an observable extent with base and acid in equivalent proportions, but does so when excess of the acid is added. This has been proved by carrying out experiments at −30°, and observing the *process* of asymmetric transformation in the case of two substituted *N*-benzoyldiphenylaminecarboxylic acids. The optical activity of these acids is due to restricted rotation within the molecule, and this restriction is so much more marked with a similar, but more highly substituted, third acid that the cinchonidine salt of the latter can be *resolved* at −15°, and caused to undergo second-order asymmetric transformation in warm acetone, in addition to showing first-order asymmetric transformation, with mutarotation, in chloroform at the ordinary temperature. This is the first instance in which one salt has been made to demonstrate all three types of differentiation between diastereoisomerides.

Examination of the kinetics of the first-order asymmetric transformation of salts of the third acid leads to the conclusion that, when the amount of acid is more than that equivalent to the base, not only do the relative proportions of the two diastereoisomerides change, but in addition one form of the free acid is formed in slight excess. The effect of excess of acid in driving back the dissociation of the salts must not be overlooked, but it is probably small, because in non-hydroxylic solvents, in which asymmetric transformation occurs most extensively, the salts are of the non-ionic type, $R_3N \ldots H \ldots A$, and are only very slightly dissociated into base and acid.

Asymmetric transformation or optical activation is a subject of the greatest interest and importance, not only from the purely stereochemical point of view, but also from that of optically selective biosynthesis. Since it also offered a method of approach to the investigation of the stereochemistry of tervalent nitrogen, where, at any rate at first, compounds of low optical stability were likely to come under review, we have made an attempt to define the conditions under which it occurs, and to obtain an insight into its mechanism.

It is necessary in the first place to state the problem. If an optically active, optically stable d-base, R_3N, and an equivalent of an optically unstable acid, HA, are dissolved in a solvent, the two diastereoisomerides, d-R_3N,d-HA and d-R_3N,l-HA, are formed in equal amounts at the moment of mixing. Because of the optical instability of HA, the diastereo-

isomerides can readily pass one into the other, either directly or by a mechanism depending on the optical instability of the free acids themselves. If the relative solubilities of the two salts are such that one salt begins to crystallise, complete conversion into this salt can occur, and the many instances of this kind recorded in the literature have been called by Kuhn (*Ber.*, 1932, **65**, 49) asymmetric transformations of the "second order." To Kuhn, a "first-order" asymmetric transformation is one in which, although the two diastereoisomerides are interconvertible for the reasons just given, neither of them separates, but nevertheless they may be present in different amounts *in solution*, corresponding to the equilibrium d-R_3N,d-HA $\rightleftharpoons$ d-R_3N,l-HA. Preliminary experiments showed that this equilibrium appeared to be altered by adding excess of HA, and we have made use of this fact as a means of investigating the problem of asymmetric transformation.

If the rotation of a solution of one equivalent of an optically active, optically stable base is determined, and successive portions of an acid (*e.g.*, 1, 2, 3, equivs.) are added, and the rotation determined after each addition, a curve can be plotted showing rotation as a function of the acid : base ratio. Such a curve we term for convenience an "addition curve."

The addition curves obtained by using nor-d-ψ-ephedrine in chloroform with a series of acids are shown in Figs. 1 and 2, and those by using cinchonidine as the base in Fig. 3. The addition curves are clearly of two types (Curve F in Fig. 3 is discussed later).

FIG. 1.

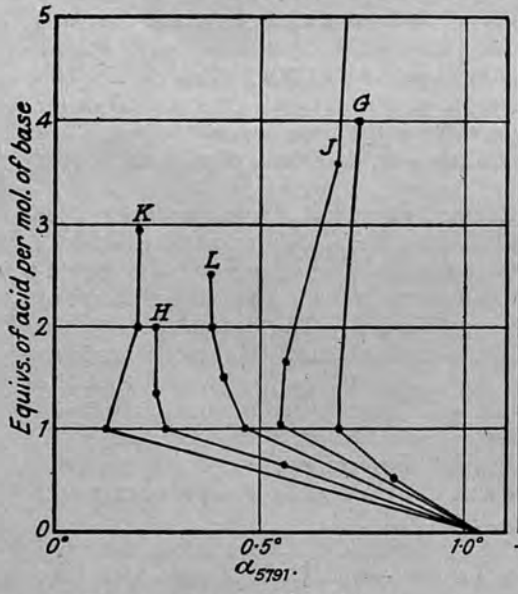


FIG. 2.

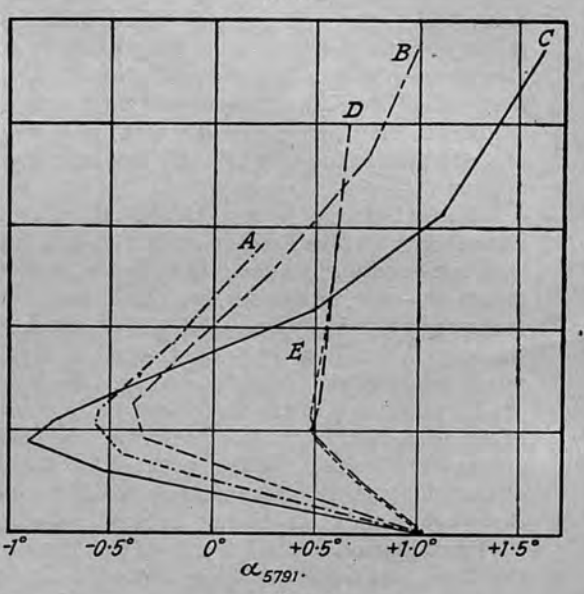


FIG. 3.

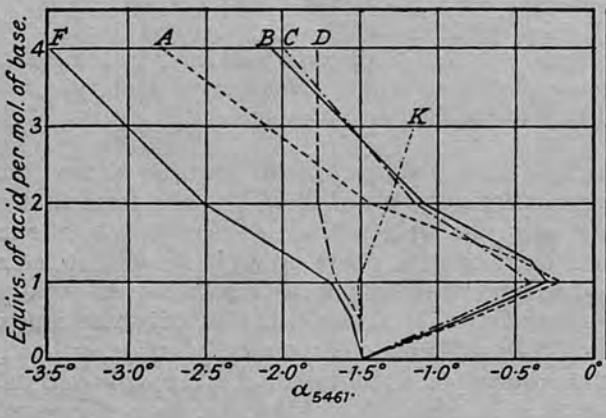
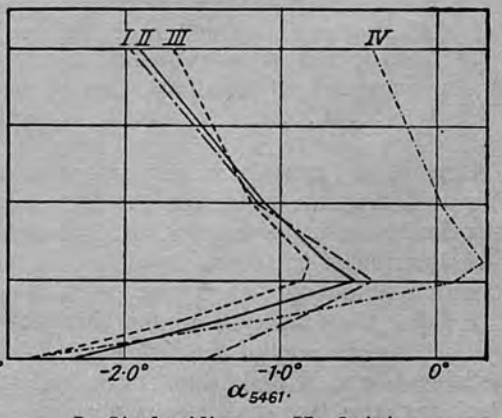


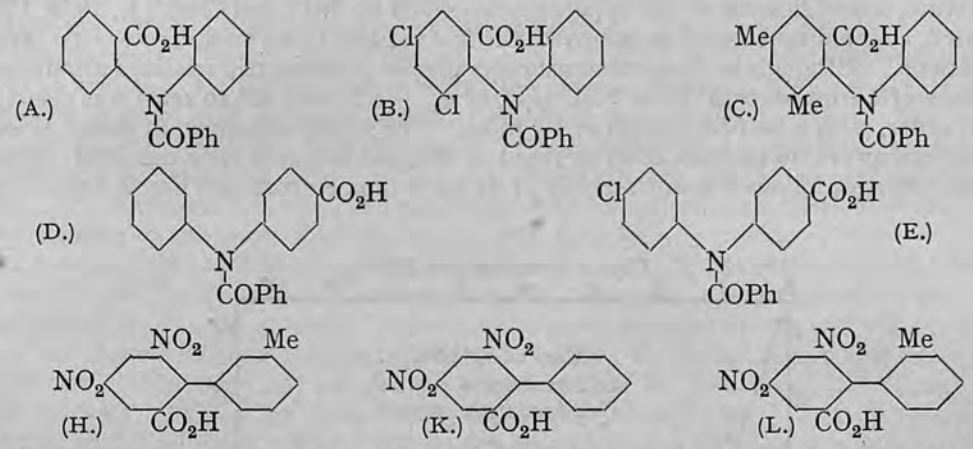
FIG. 4.



I. *Cinchonidine.* II. *Quinine.*
III. *Strychnine.* IV. *Brucine.*

Type I. Here, addition of acid in excess of 1 equiv. has no marked effect on the optical rotation. The acids concerned can be classified stereochemically in four groups : (*a*) The configurationally symmetrical acids, *o*-toluic (G), salicylic (J), and 2 : 4-dinitrodiphenyl-6-carboxylic acid (K). (*b*) The non-resolvable 2 : 4-dinitro-3′-methyldiphenyl-6-carboxylic acid (H) (Lesslie and Turner, J., 1930, 1758). (*c*) The resolvable, optically stable 2 : 4-dinitro-2′-methyldiphenyl-6-carboxylic acid (*idem, ibid.*) (L). (*d*) *N*-Benzoyldiphenylamine-4-carboxylic acid (D) and *N*-benzoyl-4′-chlorodiphenylamine-4-carboxylic acid (E) (Jamison and Turner, J., 1937, 1954).

Type II. In this type, addition of acid in excess of 1 equiv. is accompanied by a comparatively large change in optical rotation. This type includes *N*-benzoyldiphenylamine-2-carboxylic acid (A), *N*-benzoyl-2′ : 4′-dichlorodiphenylamine-2-carboxylic acid (B), and *N*-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid (C) (*idem, ibid.*), which, for reasons given later, should possess molecular dissymmetry of an unstable type, A having by far the least optical stability.



As a working hypothesis, we assumed that where excess of acid produced a marked change in optical rotation, we were observing the consequences of a first-order asymmetric transformation. Acid C was therefore selected as suitable material for examination in chloroform with a number of different alkaloids, and the addition curves obtained are shown in Figs. 4 and 5. All the curves in Fig. 4, and curves III and IV in Fig. 5 indicate

FIG. 5.

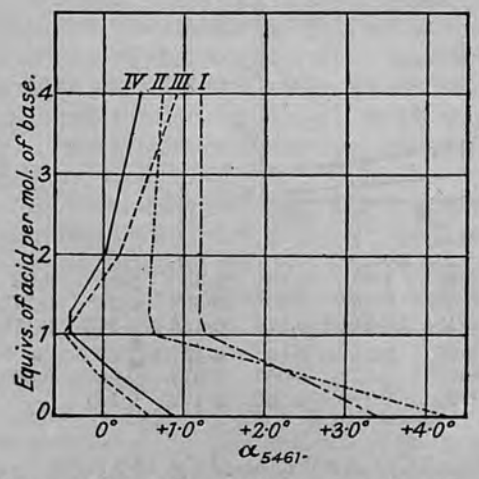
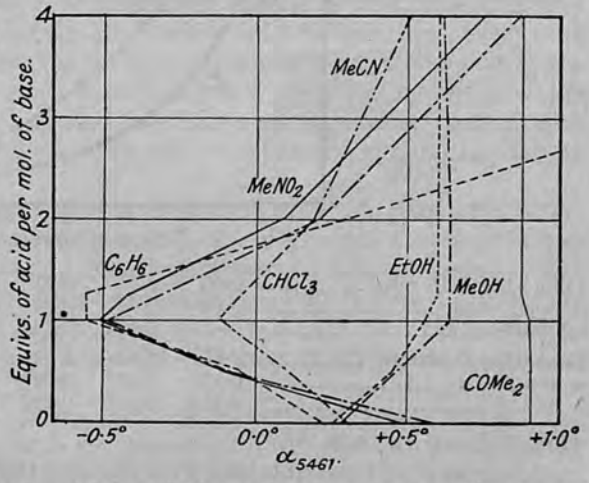


FIG. 6.



change of rotation with excess of acid, and only I and II in Fig. 5 do not. The general conclusion, therefore, was that the assumption of asymmetric transformation was worth pursuing, curves I and II in Fig. 5 being regarded as exceptional.

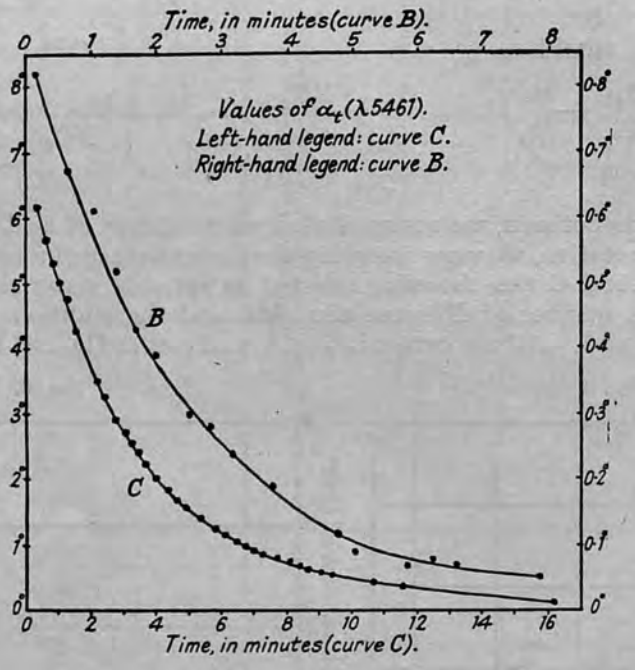
*

The next step was to discover whether the properties of the solvent were a determining factor in producing optical activation: addition curves for acid C and nor-*d*-ψ-ephedrine were obtained in a series of solvents. Fig. 6 shows that excess of acid has a very considerable effect, not only in those non-hydroxylic solvents which, like chloroform, have low dielectric constants, but also in nitromethane and acetonitrile, which have high dielectric constants. On the other hand, in methyl and ethyl alcohols, addition of acid in excess of 1 mol. causes no change in the optical rotation.

Our next objective was to obtain more direct experimental evidence of the inferred asymmetric transformation of acids A, B, and C. By greatly lowering the temperature, the optical stability of these acids must be increased, and we hoped that at — 30° mutarotation of a salt with an optically active base would be observable in the cases of the more stable acids B and C.

A chloroform solution (20 c.c.) containing 1 g. of the dichloro-acid (B), cooled to — 31°, was added to a similar solution (5 c.c.) containing 0·5 g. of nor-*d*-ψ-ephedrine at the same temperature, a modification of the apparatus described by Mills and Clark (J., 1936, 175) * being used. Rapid mutarotation occurred, the first reading being made 9 secs. after mixing the solutions. Although in these circumstances precise polarimetric readings are difficult, the change of α from + 0·19° to + 1·01° (*i.e.*, of $\alpha_\infty - \alpha$ from 0·82° to zero) was clearly of the first order, with a half-life period of 1·7 mins. The results are given in detail, since so far as we are aware no mutarotation as rapid as this has hitherto been recorded, nor any rotational changes followed quantitatively at so low a temperature (see Fig. 7, curve B):

FIG. 7.



Time after 0·15 min.	0·00	0·51	0·91	1·25	1·55	1·85	2·35	2·70	3·03
$a_t = a_\infty - a$	0·82°	0·67°	0·61°	0·52°	0·43°	0·39°	0·30°	0·28°	0·24°
k, min.$^{-1}$	—	0·172	0·141	0·158	0·181	0·174	0·186	0·173	0·176
Time after 0·15 min.	3·65	4·65	4·91	5·27	5·74	6·10	6·45	7·75	∞
$a_t = a_\infty - a$	0·19°	0·12°	0·09°	0·09°	0·07°	0·08°	0·07°	0·05°	0·00°
k, min.$^{-1}$	0·174	0·180	0·216	0·201	0·186	0·166	0·166	0·157	—

whence $k = 0·18$ (min.$^{-1}$).

A similar result was obtained with the dimethyl acid C. A solution of 2 g. (2·9 equivs.) of the acid in 25 c.c. of chloroform was added at — 30° to one of nor-*d*-ψ-ephedrine (1 equiv.)

* Their middle tube (*J*) was dispensed with, and *G* was joined directly to *P*. With two previously filtered solutions, this permits of extremely rapid mixing.

in 5 c.c. of chloroform. The first polarimetric reading was taken 20 secs. after mixing; the results for the change from $-$ 4·03° to + 2·15° are given below and in Fig. 7, curve C:

Time after 0·34 min.	0·00	0·31	0·49	0·69	0·90	1·18	1·83	2·09	2·44
$a_t = a - a_\infty$	6·18°	5·69°	5·32°	5·03°	4·76°	4·29°	3·52°	3·27°	2·91°
k, min.$^{-1}$	—	0·116	0·133	0·130	0·126	0·134	0·128	0·132	0·134
Time after 0·34 min.	2·71	2·92	3·11	3·34	3·66	4·03	4·30	4·60	5·03
$a_t = a - a_\infty$	2·73°	2·56°	2·42°	2·25°	2·01°	1·84°	1·69°	1·58°	1·41°
k, min.$^{-1}$	0·131	0·131	0·131	0·131	0·133	0·131	0·131	0·129	0·128
Time after 0·34 min.	5·51	5·81	6·15	6·41	6·66	6·91	7·39	7·74	
$a_t = a - a_\infty$	1·25°	1·16°	1·06°	0·99°	0·92°	0·85°	0·77°	0·74°	
k, min.$^{-1}$	0·126	0·125	0·125	0·124	0·124	0·125	0·122	0·119	
Time after 0·34 min.	8·06	8·29	8·71	9·06	10·31	11·22	15·86	∞	
$a_t = a - a_\infty$	0·67°	0·64°	0·58°	0·55°	0·44°	0·38°	0·12°	0·00°	
k, min.$^{-1}$	0·120	0·119	0·118	0·116	0·111	0·108	0·108	—	

whence $k = 0·125$ (min.$^{-1}$) and the half-life period is 2·4 mins.

These two sets of observations constitute satisfactory support for our interpretation of the addition curves for the two acids concerned. The possibility that the mutarotations observed were due to the process of combination between base and acid is clearly excluded, because this would have caused a rotational change in the opposite direction. The fact that with the dimethyl acid (C) the rotation on mixing was strongly negative, indicates that combination of base and acid to give the *l*-rotatory salt of the *dl*-acid is extremely rapid. The mutarotation observed must therefore have been a realisation of the change corresponding to the upper limb of curve C, Fig. 2.

Although *N*-benzoyldiphenylamine-2-carboxylic acid (A) appeared from the addition curves (*e.g.*, *A*, Fig. 2) to be capable of undergoing asymmetric transformation, the process of activation could not be detected when a chloroform solution of the acid was mixed with one of nor-*d*-ψ-ephedrine or of cinchonidine at $-$ 30°. We do not regard this as invalidating the main argument, but merely as indicating that the periods of half-change of the mutarotations involved are considerably less than 0·5 min. at $-$ 30°. Although it is admitted that " addition curves " should not be regarded as affording absolute evidence of potential molecular dissymmetry, yet it can hardly be doubted that they would give trustworthy information inside a series of closely related acids such as A, B, and C.

The optical activity of acids A, B, and C could be due to one or both of two causes, " asymmetric tervalent nitrogen " or restricted rotation within the molecule. From the fact that acids D and E gave no indication of being capable of undergoing optical activation, it is concluded that restricted rotation is a sufficient explanation of the activation of B and C. From the very considerable quantitative information available with regard to factors controlling the stability of dissymmetry in the diphenyl series, acid H would not be expected to be capable of activation, and it was for this reason that this acid was selected for comparison with acids D and E. Figs. 8 and 9, which are explained below, show the manner in which restricted rotation can operate, and it may be noted that the case is in some respects similar to, although more complex than, that described, while this investigation was in progress, by Mills and Kelham (J., 1937, 274).

All three diagrams are drawn to scale, the atomic radii used being: C (aliphatic), 0·77; C (aromatic), 0·70; N, 0·70; O, 0·66; Cl, 0·99; Br, 1·14 A. These are based on *X*-ray measurements and give the correct interatomic distances between combined atoms. The effective radius at which any atom or group repels another not combined with it is probably of the order of 0·5 A. more than the diagrams suggest, but since diphenic acid cannot be caused to exhibit optical activity, this 0·5 A. is almost certainly an upper limit external radius correction.

In Figs. 8, 9, and 10, *P* is the aromatic nucleus carrying the carboxyl group, and *Q* is the nucleus carrying either chlorine or methyl (R) in the 2-position to the nitrogen atom (Fig. 9; R and R′ show two possible positions of R). In Fig. 10, nucleus *P* also carries a bromine atom in the 6-position to the nitrogen atom. In all three figures, *S* is the nucleus attached to the carbonyl group and is shown in two positions of rotation (thick circle at top, thin circle at bottom). The three aromatic nuclei are represented by circles exactly enclosing

the six carbon atoms. As drawn with full lines, they are producing their maximum obstructive effect (P, Q, and the two positions for maximum obstruction by S), and as drawn in broken lines, they are in the positions of minimum obstructive effect (Q' and S'). The carboxyl group is shown as T (maximum obstructive effect) and as T' (dotted; minimum obstructive effect). Hydrogen atoms have been omitted : their effect may be taken as included in the 0·5 A. rind of the atoms to which they are attached.

FIG. 8.

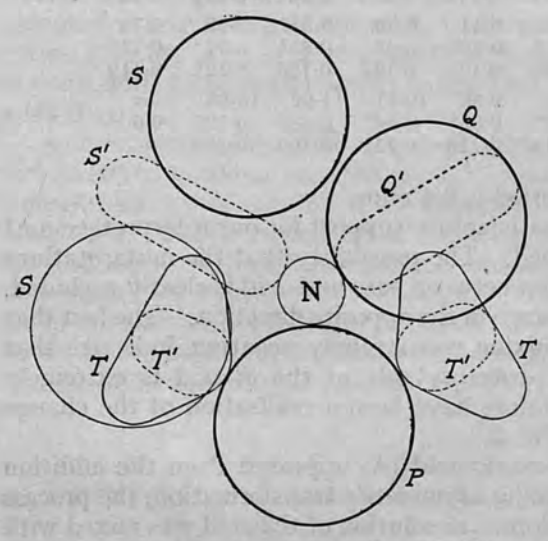


FIG. 9.

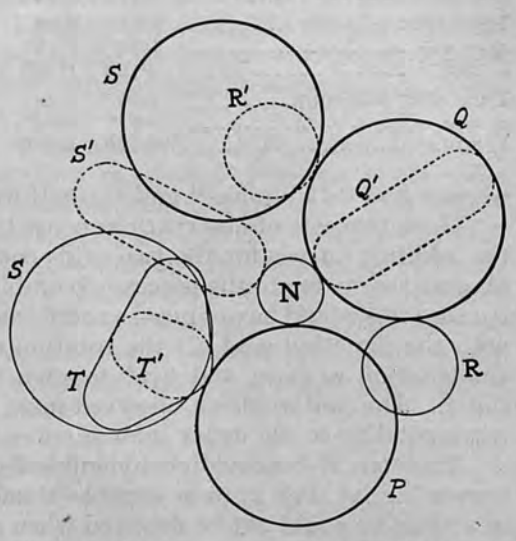


Fig. 8 shows that with P originally in the plane of the paper, Q', S', and T' can be placed in their positions of minimum obstruction without mutual interference, and if P alone is rotated, T' can pass Q' and S'. With Q, S, and T in their positions of maximum obstruction there is clearly considerable interference. Fig. 9 shows the effect of introducing chlorine or methyl (R and R'). At position R there is marked interference with P, and at

FIG. 10.

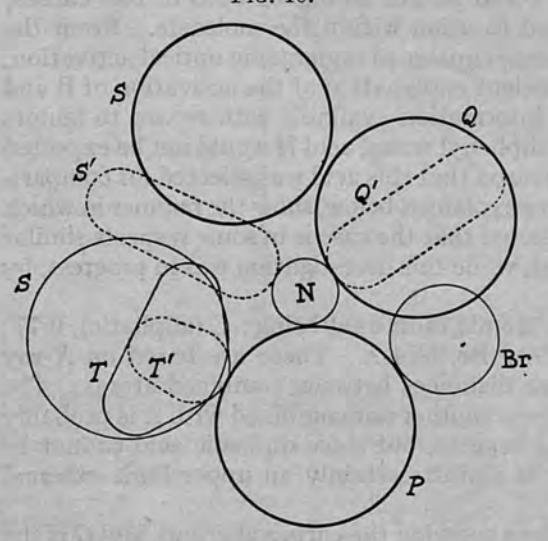
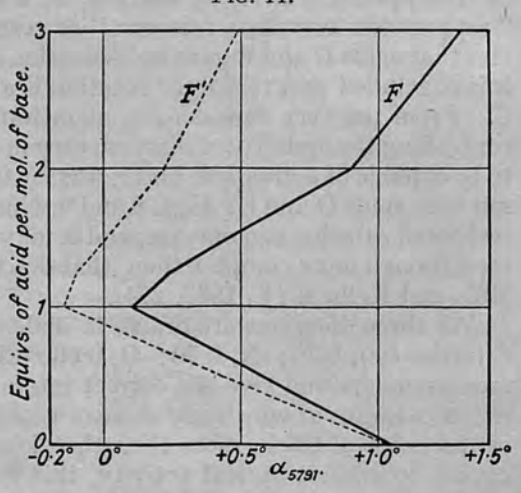
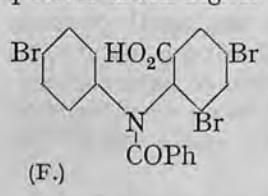


FIG. 11.



R' even greater interference with S. Nuclei Q and S in their positions of maximum obstruction could not approach as near together as the diagram suggests. The bromine atom shown in Fig. 10 could not, in fact, approach as near to Q' as the data used indicate, and this represents a greatly increased interference as compared with the molecules drawn in Figs. 8 and 9. Rotation of one group (Fig. 10) involves rotation of the other two.

N-Benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylic acid (F) should therefore possess much higher optical stability than the dichloro- and the dimethyl acid (B and C) previously considered. It might be expected to have an optical stability of approximately the same order as that of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (Mills and Elliott, J., 1928, 1291). If this were so, the addition curve should be of type II, but only after each new portion of added acid had had time to produce its effect on the equilibrium. Fig. 11 shows the curves obtained for the addition of the tribromo-acid to nor-*d*-ψ-ephedrine in chloroform solution at room temperature. When 1 equiv. of acid is added to 1 equiv. of base, the originally dextrorotatory solution becomes lævorotatory, and after $2\frac{1}{2}$ hours is slightly dextrorotatory. With 2 equivs. of acid, the dextro-mutarotation during the above time interval is much more marked. In this way the two curves *F* and *F*′ were drawn, the points for *F*′ being read 2 mins. after addition, and those for *F* after the rotation had become steady. It may be noted that *F*′ is not strictly of type I, although it is very different from *F*.



(F.)

With cinchonidine in chloroform the tribromo-acid gave the (equilibrium) addition curve *F* in Fig. 3, this being an extreme example of a type II curve owing to the rotation of the cinchonidine salt differing so very slightly from that of the base itself. It shows that, whereas nor-*d*-ψ-ephedrine produces excess of a dextro-activation product, cinchonidine produces excess of a lævo-activation product. Proof of this was also arrived at as follows : a chloroform solution of 5 equivs. of the acid and 1 equiv. of cinchonidine was rapidly evaporated in a vacuum to a glass, *i.e.*, under conditions in which no crystallisation of salt occurred intermediately, so that there was excess of acid over base in the one phase up to the point of " solidification." The glass was dissolved in cooled pyridine, and the solution poured into cooled dilute hydrochloric acid. A solution in pyridine of the acid obtained was strongly lævorotatory, but quickly became inactive (observed change at 18·5° : 0·80° during 40 mins. after first wetting acid with solvent).

These results showed that under suitable conditions it might be possible to realise an asymmetric transformation of Kuhn's " second order," *i.e.*, to isolate as a solid one of a pair of diastereoisomeric salts. After examination of several bases in different solvents, it was found that when the tribromo-acid and 1 equiv. of cinchonidine were warmed with acetone, a clear solution was quickly formed, but that after a few minutes' warming rapid crystallisation set in, and almost the whole of the material which had been dissolved soon separated out as the optically pure *cinchonidine* d-*salt* of the tribromo-acid. It must be borne in mind that, although first-order asymmetric transformation in presence of cinchonidine in chloroform solution produces *l*-salt, yet second-order asymmetric transformation depending on the solubility relations of the *d*- and *l*-cinchonidine salts in acetone produces the *d*-salt. This is in accordance with the van 't Hoff–Dimroth rule (cf. Dimroth, *Annalen*, 1910, **377**, 127; 1913, **399**, 91). The more soluble salt is the more stable.

No quantitative study of optical activation has hitherto been made, and because our tribromo-acid appeared to provide suitable material for such an investigation, we have examined kinetically the attainment of equilibrium between base *l*-acid and base *d*-acid in chloroform solution and the effect upon this process of an excess of the racemic acid.

When the cinchonidine salt of the *d*-acid is dissolved in chloroform, its strong positive rotation falls rapidly at room temperature according to the first-order law to an equilibrium value. We have made a detailed study of the mutarotation of the salt in chloroform solution at four different temperatures (θ), with the following results :

c.	θ.	k (found) (min.$^{-1}$).	k (calc.) (min.$^{-1}$).	Half-life period (mins.).
1·447	1·65°	0·00241	0·00241	125
0·9500	11·9	0·0099	0·00975	30·4
0·6000	17·6	0·0201	0·0204	15·0
0·6360	29·4	0·0855	0·0855	3·5

From the graph of log k against $1/T$, the activation energy of the process was found from the Arrhenius equation to be 21,200 cals./g.-mol. The mean of four values of B was

$1{\cdot}86 \times 10^{14}$, and with the aid of this the calculated values of k were obtained and the experimental accuracy assessed.

By extrapolation of the straight-line plots of log α against time (t), the initial rotations ($t = 0$) were determined. In this way the value of $[\alpha]_{5461}^{18{\cdot}0^\circ}$ for the pure *d*-salt was found to be $+ 194^\circ$ ($c = 0{\cdot}6070$). Considerable increase in concentration was found to have comparatively little effect either on the initial specific rotation of the pure *d*-salt or on the velocity of mutarotation. Thus, for $c = 2{\cdot}125$ in chloroform, $[\alpha]_{5461}^{18{\cdot}0^\circ}$ was $+ 192^\circ$ and k was 0·0206 (min.$^{-1}$).

From the values of E and B, the calculated velocity constant for the mutarotation of the *d*-salt at $- 15^\circ$ is 0·00020 (min.$^{-1}$), whence the period of half-change is about 150 mins. At this temperature, therefore, it should be possible to carry out an ordinary resolution. This was done as follows: equivalent quantities of cinchonidine and the tribromo-acid were dissolved in warm acetone, and, as soon as crystallisation began, the whole was chilled to $- 15^\circ$. An almost theoretical yield of cinchonidine *d*-salt separated during the course of an hour, and by evaporating the strongly-cooled mother-liquor in a vacuum, a solid lævorotatory cinchonidine salt, subsequently shown to consist of 64% of base *l*-salt and 36% of base *d*-salt, was obtained. For the mutarotation in chloroform ($c = 0{\cdot}6000$) of this *l*-salt, the value of k at 17·7° was found to be 0·0200 min.$^{-1}$. The calculated value of k at this temperature for the *d*-salt is 0·0206 min.$^{-1}$, and there is therefore no doubt that the observed constant is the same whether equilibrium is approached from the *d*- or from the *l*-salt. This should be so, as the measured rate constant is $k_1 + k_2$, *i.e.*, the sum of the velocity constants for inversion of the *d*- and the *l*-salt respectively. It is the difference in these two rates that is primarily responsible for activation, and in this case k_1 is a little greater than k_2. The specific rotation of the impure *l*-salt was found by extrapolation to zero time of observations of the rotation of a mutarotating solution to be $[\alpha]_{5461}^{17{\cdot}6^\circ} - 105^\circ$, and knowing the value for the pure *d*-salt and for the partial racemate (see below), we can calculate the composition of the specimen to be as given above.

When the cinchonidine *d*-salt was dissolved in cooled pyridine, and the solution poured quickly into hydrochloric acid and ice, the *d*-form of the tribromo-acid separated. The velocity constants for the racemisation of this acid in absolute ethyl alcohol at three different temperatures were determined, and the energy of activation of the racemisation process found to be 18,200 cals./g.-mol., B being $5{\cdot}35 \times 10^{12}$. The following table shows that there was satisfactory agreement between the found and calculated values of k:

Temp.	0·65°	9·5°	17·7°
k (min.$^{-1}$), found	0·0157	0·0480	0·117
k (min.$^{-1}$), calc.	0·016	0·047	0·116

Decomposition of the impure *l*-salt in a similar way gave a sample of the *l*-acid, which was sufficiently pure for the measurement of its velocity constant of racemisation in absolute ethyl alcohol: k for 0·85° and $c = 1{\cdot}1970$ was 0·0165 (min.$^{-1}$). Racemisations of the *d*-acid in ethyl alcohol at 0·65° and for the *l*-acid under the conditions just mentioned are shown in curves in Fig. 12. Racemisation of the *d*-acid was appreciably faster in chloroform than in alcohol (k, found, at 17·8°: 0·155 min.$^{-1}$ for $c = 0{\cdot}3925$).

By calculation, the specific rotation of the pure cinchonidine *l*-salt is $[\alpha]_{5461}^{18{\cdot}0^\circ} - 274^\circ$ ($c = 0{\cdot}6070$ in chloroform) and $[\alpha]_{5461}^{18{\cdot}0^\circ} - 270^\circ$ ($c = 2{\cdot}125$). The specific rotation of the partial racemate (cinchonidine *dl*-salt) in chloroform was determinable directly, since the actual rotational change during the first 2 or 3 mins. after making up the solution is very small. The value of $[\alpha]_{5461}^{18{\cdot}0^\circ}$ was $- 40{\cdot}4^\circ$ for $c = 0{\cdot}6070$, and $- 39{\cdot}1^\circ$ for $c = 2{\cdot}125$; since each figure is the mean of several determinations, the small difference must be considered as outside the experimental error, and account of it is kept in the subsequent calculations.

A large number of determinations of the equilibrium rotation approached from base + *d*-acid, from base + *l*-acid, and from base + *dl*-acid gave the value $[\alpha]_{5461}^{18{\cdot}0^\circ} - 44{\cdot}5^\circ$ for $c = 0{\cdot}6070$ and $- 43{\cdot}1^\circ$ for $c = 2{\cdot}125$, in chloroform; here again the effect of concentration is seen to be small, but definite. From the difference, $- 4{\cdot}1^\circ$ ($c = 0{\cdot}6070$) in specific rotation due to optical activation, between the value for the partial racemate and that for the equilibrium mixture, the equilibrium constant, K, is 1·035: at equilibrium, the composition is 50·9% *l*-salt and 49·1% *d*-salt. A similar calculation for $c = 2{\cdot}125$ gives the same figures

for equilibrium composition; so that since $k_1 + k_2$ as measured for the *d*-salt is 0·0206, $k_1 = 0·0105$ and $k_2 = 0·0101$ min.$^{-1}$, at either concentration, assuming that we are here dealing with the simple equilibrium *d*-salt $\underset{k_2}{\overset{k_1}{\rightleftharpoons}}$ *l*-salt (see later). Increase in concentration thus has very little if any effect on the amount of activation when base and acid are present in equivalent proportion.

That an excess of *dl*-acid not only increases the extent but also accelerates the process of

FIG. 12.

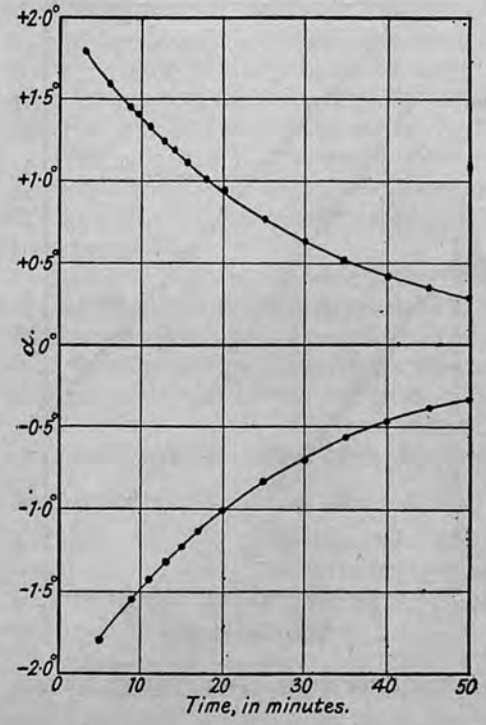
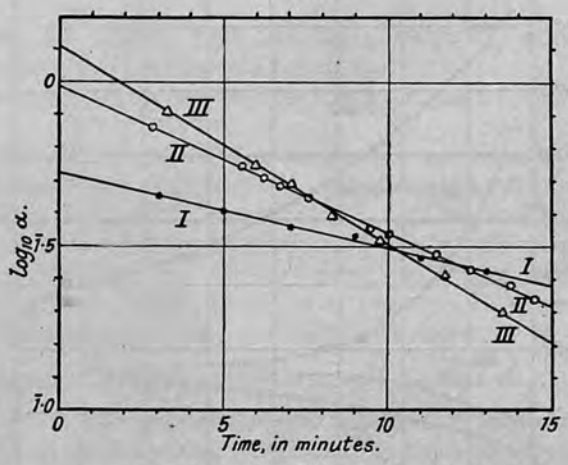


FIG. 13.



I. 1·25 *equivs. of acid per mol. of base.*
II. 2·0 ,, ,, ,, ,,
III. 3·0 ,, ,, ,, ,,

an activation was first shown by three experiments carried out with the tribromo-acid and nor-*d*-ψ-ephedrine in chloroform solution. This particular base was chosen to demonstrate the point as it gives a larger effect than cinchonidine for *small* excesses of acid, as can be seen by comparing curves *F* in Fig. 3 and Fig. 11. The approach to equilibrium obeys the first-order law. The following results were obtained:

Equivs. of acid per mol. of base	1·25	2·0	3·0
Temp.	17·7°	17·7°	17·5°
k (min.$^{-1}$)	0·022	0·044	0·059

The concentration of nor-*d*-ψ-ephedrine was 0·7010 in all three determinations. The logarithmic plots of the results (Fig. 13) clearly demonstrate the accelerating effect of excess of acid on the speed of asymmetric transformation.

We next examined the approach to equilibrium in the case of the tribromo-acid and cinchonidine in chloroform solution, using the ratio base : acid = 1 : 2. For *d*-salt + 1 mol. excess of acid and for *l*-salt + 1 mol. excess of acid, at $c = 0·6070$, the approach to equilibrium (Fig. 14) followed the first-order law, the two rates being identical (see table below and logarithmic plots, I and II, in Fig. 15). At a higher concentration ($c = 2·125$), activation, *i.e.*, approach to equilibrium from cinchonidine + 2 mols. of acid, could also be measured, and the rate constant proved to be identical with that for the *d*-salt + 1 mol. excess of acid at the same concentration. This is seen from the table below and also from the logarithmic plots IV and III in Fig. 15:

$c = 0·6070$.	*d*-Salt + 1 mol. excess of *dl*-acid : k (18·0°)	= 0·0704 min.$^{-1}$
$c = 0·6070$.	*l*-Salt + 1 mol. excess of *dl*-acid : k (18·1°)	= 0·0692 ,,
$c = 2·125$.	*d*-Salt + 1 mol. excess of *dl*-acid : k (18·4°)	= 0·0562 ,,
$c = 2·125$.	1 Mol. cinchonidine + 2 mols. *dl*-acid : k (18·4°)	= 0·056 ,,

The value 0·0704 for the *d*-salt and excess of acid is the most trustworthy as it was obtained from a large number of polarimetric readings. That for the *l*-salt and excess of acid was obtained from a more restricted set of rotations, and that for the activation from data even more restricted, although sufficient for the purpose. In view of the satisfactory agreement of the first two pairs of rate-constants in the above table, it may be assumed that k for 18° and $c = 0{\cdot}6070$ is 0·0704 min.$^{-1}$, and that k for 18·4° and $c = 2{\cdot}125$ is 0·0562 min.$^{-1}$.

FIG. 14.

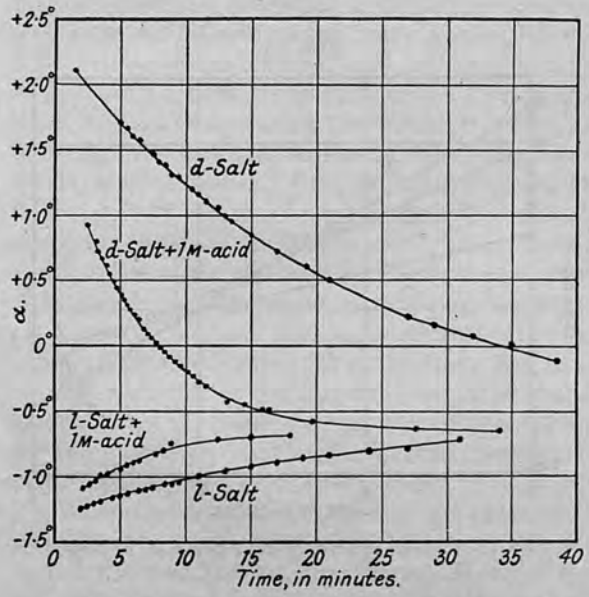
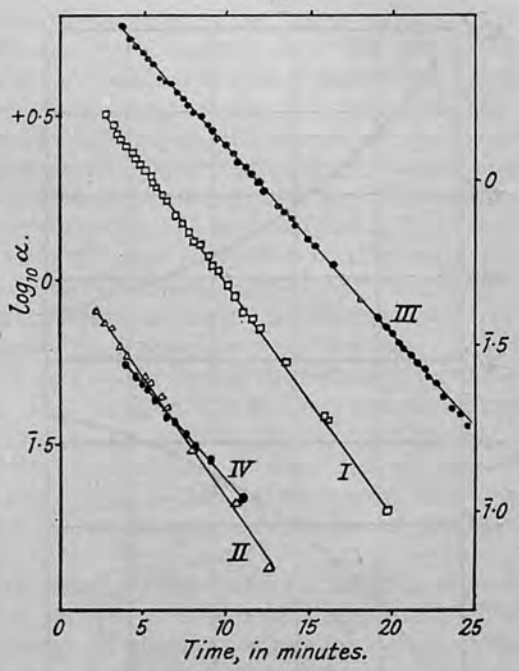


FIG. 15.



Before discussing the results it is convenient to summarise some of the figures for the kinetic measurements :

Cinchonidine salt of tribromo-acid.

	c.	k (~18·0°).
1·0 Equiv. of salt + 0·0 equiv. of acid	0·6000	0·0201
1·0 Equiv. of salt + 1·0 equiv. of acid	0·6070	0·0704
1·0 Equiv. of salt + 1·0 equiv. of acid	2·125	0·0562
0·0 Equiv. of salt + 1·0 equiv. of acid	0·8330	0·155

(In the last case, c is " calculated " as salt.)

Discussion.

Read and McMath (J., 1925, **127**, 1572), who were the first to observe optical activation in solution, found that the equilibrium composition of a solution of *l*-hydroxyhydrindamine *l*-chlorobromomethanesulphonate and the corresponding *l*-base *d*-salt in acetone was: *l*-Base *l*-acid, 81%; *l*-base *d*-acid, 19%. They explained this by saying that " the *l*-base transforms the *dl*-acid largely to *l*-acid," the base providing an " asymmetric influence." They found that the effect produced in acetone was not produced in methyl alcohol, water, or glacial acetic acid; they were unable to employ other non-hydroxylic solvents owing to the insolubility of the salts.

Kuhn and Albrecht (*Annalen*, 1927, **455**, 272) found that 4 : 4′-dinitrodiphenic acid gave a strongly *d*-rotatory quinine salt, and Kuhn (*loc. cit.*) described this result and that of Read and McMath as due to an " asymmetric transformation of the first order." Lesslie and Turner (J., 1934, 347), using diphenic acid, obtained results similar to those of Kuhn and Albrecht : their conclusions and Kuhn's were criticised by Kharasch, Senior, Stanger, and Chenicek (*J. Amer. Chem. Soc.*, 1934, **56**, 1646). It is clear from the present work that the interpretation of addition curves for dibasic acids in presence of bases is complicated. An

explanation of the " mutarotations " observed by Lesslie and Turner will shortly be published. It will be remembered that the optical rotation of the hydrochlorides of the cinchona alkaloids is greatly altered in presence of excess of hydrochloric acid (Emde, *Helv. Chim. Acta*, 1932, **15**, 557), and a similar effect must be involved in the results of Lesslie and Turner and of Kharasch and his co-workers.

Mills and Elliott (*loc. cit.*) referred briefly to the fact that, in the case of the brucine salt of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine in chloroform, optical activation could be followed polarimetrically, and added that a compound *d*-base *d*-acid might be more stable than *d*-base *l*-acid " because, for example, of the closer fitting of the two components of the salt or because of a difference between the coefficients of partial racemisation of the two diastereoisomerides." They observed also that the equilibrium between their brucine salts in solution was slightly disturbed by the addition of a small excess of acid, and attributed this to a dissociation effect.

Pfeiffer and his co-workers (*Ber.*, 1931, **64**, 2667; 1932, **65**, 560; 1933, **66**, 4157) described several examples of optical activation in aqueous solution of metal complexes of the type [Metal (α-phenanthroline)$_3$]$^{++}$, and these Kuhn (*loc. cit.*) regarded as " first-order " transformations.

As regards the present work, the first point which must be discussed is the significance of the addition curves, and it must be emphasised that the complete analysis of all types of addition curves is not even attempted at this stage. The results obtained so far indicate that the kind of asymmetric transformation indicated by an addition curve occurs more extensively in non-hydroxylic than in hydroxylic solvents. This we think can be explained as follows : if equivalent proportions of an optically stable, optically active base, R_3N, and the racemic form of an optically stable active acid, HA, are dissolved together in a hydroxylic solvent, R·OH, the solution in general will contain the three ions, $\overset{+}{R_3}NH....O\langle^{R}_{H}$, *d*-$\bar{A}$ and *l*-$\bar{A}$, and the existence of either of the two diastereoisomeric salts can with certainty only be associated with the appearance of a solid phase. On the other hand, in a non-hydroxylic solvent, the two diastereoisomerides are actually present in solution, being now non-ionic forms of the type, R_3N . . . H . . . A. If the acid HA, although capable of exhibiting optical activity, were optically unstable, the two diastereoisomerides, which would as a rule possess different molar free energies, would pass one into the other until, the energy relations being satisfied, equilibrium was established. In the case of an acid of extreme optical instability, equilibrium would be established almost instantaneously : this would be an example of an asymmetric transformation of the first order.

The equilibrium which must be set up in such a solution, in a non-hydroxylic solvent is

$$\begin{array}{ccc} R_3N + d\text{-HA} & \overset{\overset{+}{K}}{\rightleftharpoons} & R_3N,d\text{-HA} \\ {\scriptstyle K_A}\downarrow\uparrow & & \downarrow\uparrow{\scriptstyle K_S} \\ R_3N + l\text{-HA} & \underset{\underset{-}{K}}{\rightleftharpoons} & R_3N,l\text{-HA} \end{array}$$

where K_A and K_S are the equilibrium constants for the interconversion of the free active acids and the undissociated salts, respectively, and $\overset{+}{K}$ and $\bar{K}$ are the equilibrium constants for the dissociation of the latter. If $\overset{+}{S}$ and $\bar{S}$ are the concentrations of the *d*- and the *l*-salt, $\overset{+}{A}$ and $\bar{A}$ those of the active acids, and B that of the free base, then

$$K_S = \overset{+}{S}/\bar{S} = \overset{+}{K}B\overset{+}{A}/\bar{K}B\bar{A} = K_A\overset{+}{K}/\bar{K}$$

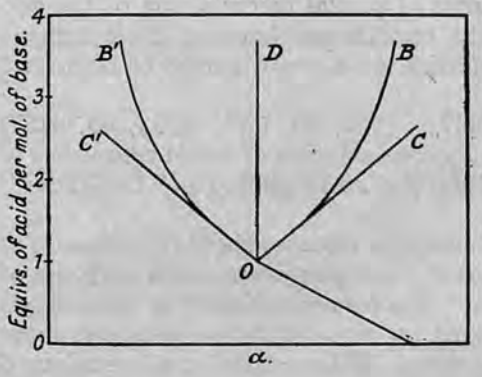
The observed rotation is the sum of the five partial rotations corresponding with $\overset{+}{S}$, $\bar{S}$, $\overset{+}{A}$, $\bar{A}$, and B.

If we apply the above statement of equilibrium to the case in which HA is configurationally symmetrical, K_A and K_S have no significance, and the addition curve must be of

type I (Fig. 16, *OD*), except in so far as the rotation in concentrated solution is modified by the fact that the solvent is changing (*i.e.*, from pure solvent to solvent plus more and more acid—" strong solution effect ").

If HA is the racemic form of an optically stable asymmetric acid, $\overset{+}{K}$ will in general differ slightly from $\overset{-}{K}$, whilst K_A and K_S are indeterminate, since there is no interconversion corresponding to them. Addition of excess of acid could therefore change the observed rotation owing to the decreases in $\overset{+}{A}$ and $\overset{-}{A}$ and the increases in $\overset{+}{S}$ and $\overset{-}{S}$, as required by the mass law. But if at the outset the salts are dissociated to a very small degree only, this could not cause any great departure of the slope of the curve from strict type I. All the curves for non-hydroxylic solvents, by turning sharply at the point corresponding to acid : base = 1, demonstrate the fact that dissociation must be extremely slight.

FIG. 16.



When HA is the racemic form of a configurationally dissymmetric acid of low optical stability, the strong solution effect and the dissociation effect are still applicable, but there is also the possibility of optical activation giving a change of rotation. The truth of this is admirably demonstrated by curves F' and F (Fig. 11), where all extraneous effects must be contained in F' and the sum of these, plus optical activation, in F.

In the case of the optically unstable acids, K_A and K_S first take on a real significance. Let us first assume that as excess of acid is added K_S remains constant, The change in rotation due to *salts* on addition of excess of acid would be expected to be very small, and any great change must be due to a change in the difference between the amounts of *d*-HA and *l*-HA present.

If K_A were equal to unity, a type I curve would result (Fig. 16, *OD*), but if it were unequal to unity and constant, a straight line such as *OC* or *OC'* (Fig. 16) would be obtained. In practice, the curves (*OB* or *OB'*; Fig. 16) begin linearly, but tend to become vertical later; in other words, K_A is at first unequal to unity, but approaches this value with larger excesses of acid.

The explanation of the shape of the curves would therefore appear to be that when small excesses of acid are added to the solution of the salt the asymmetric environment is strong enough to maintain a value of K_A not equal to unity and give the acids, *d*-HA and *l*-HA, different free energies: but that, as more and more acid is added, the asymmetric environment becomes less and less effective, and the difference between the amounts of *d*-HA and *l*-HA present increases more slowly than corresponds to the initial proportionality with the total quantity of free acid present; *i.e.*, the rotation asymptotically approaches a constant value.

If K_A can alter as the concentration of acid relative to base increases, so also can K_S. The partial rotation of the salt will then change, at first proportionately to the excess of acid, and later at a slower rate, just in the same way as the partial rotation of the free acid. The addition curve will record the algebraic sum of these two effects.

It remains to consider the kinetics of approach to equilibrium. In the case of 1 equiv. of salt and 1 equiv. of (optically unstable) acid, it can be shown that the approach must follow the first-order law. To the notation already employed, add the rate constants, k_A^+ for the reaction *d*-HA $\rightarrow$ *l*-HA; k_A^- for the reaction *l*-HA $\rightarrow$ *d*-HA; k_S^+ for the reaction R_3N,*d*-HA $\rightarrow$ R_3N,*l*-HA; and k_S^- for the reaction R_3N,*l*-HA $\rightarrow$ R_3N,*d*-HA. In a straightforward racemisation, $k_A^+ = k_A^-$, but it must be assumed that the effect of an asymmetric environment is to make these values different.

The equilibria represented by $\overset{+}{K}$ and $\overset{-}{K}$ are in all probability very rapidly established,

and therefore their rate constants can be ignored, If it is assumed that there is a negligible accumulation of free active acid, the amount of R_3N,*l*-HA disappearing in a particular unit of time is equal to the amount of R_3N,*l*-HA which is directly converted into R_3N,*d*-HA, plus the amount converted through *l*-HA into *d*-HA, minus the amount of R_3N,*d*-HA which is converted into R_3N,*l*-HA directly, minus the amount converted *via* *d*-HA into *l*-HA, *i.e.*,

$$-\mathrm{d}\bar{S}/\mathrm{d}t = k_{\bar{A}}^{-}\bar{A} - k_{\bar{A}}^{+}\overset{+}{A} + k_{\bar{S}}^{-}\bar{S} - k_{\bar{S}}^{+}\overset{+}{S}$$

and since $\bar{A} = \bar{S}/\bar{K}B$ and $\overset{+}{A} = \overset{+}{S}/\overset{+}{K}B$

$$-\frac{\mathrm{d}\bar{S}}{\mathrm{d}t} = \left\{\frac{k_{\bar{A}}^{-}}{\bar{K}B} + k_{\bar{S}}^{-}\right\}\bar{S} - \left\{\frac{k_{\bar{A}}^{+}}{\overset{+}{K}B} + k_{\bar{S}}^{+}\right\}\overset{+}{S}$$

Let $\bar{S}_0$ be the concentration of R_3N,*l*-HA at zero time, *i.e.*, $\overset{+}{S} = \bar{S}_0 - \bar{S}$. Then the equation is of the form of a reversible unimolecular reaction, the quantities in brackets taking the place of k_1 and k_2. The integrated form is

$$t = \frac{1}{\frac{k_{\bar{A}}^{-}}{\bar{K}B} + \frac{k_{\bar{A}}^{+}}{\overset{+}{K}B} + k_{\bar{S}}^{-} + k_{\bar{S}}^{+}} \log_e \frac{\bar{S}_0 - \bar{S}_\infty}{\bar{S} - \bar{S}_\infty}$$

The conversion is therefore exponential, and the measured rate constant, k, is

$$k = k_{\bar{A}}^{-}/\bar{K}B + k_{\bar{A}}^{+}/\overset{+}{K}B + k_{\bar{S}}^{-} + k_{\bar{S}}^{+}$$

It can be seen from this equation that the addition of small excesses of acid (insufficient to invalidate the simplifying assumption that there is no considerable accumulation of free active acid) would increase k by decreasing B.

The end result of adding a large excess of acid must be to approach asymptotically the rate of racemisation of the acid itself. In the case of the tribromo-acid, we have measured this rate of racemisation : the rate constant is about twice that for the active salts in presence of 1 mol. excess of acid, and this second rate in turn is about 3·5 times that for the pure salts themselves. All three processes were of the first order kinetically : the mathematical analysis shows that this should be true when excess of acid is present in very small amounts or in very large amounts, but the general case of intermediate excesses of acid has not been investigated theoretically.

It has hitherto been thought that in a first-order asymmetric transformation the two diastereoisomerides alone contribute to the total rotation at equilibrium. This must be true if the salts are completely undissociated, but the results now obtained suggest that, if there is any dissociation, the free acid will consist of rather more of one enantiomeride than of the other. When excess of acid is added, this slight disparity will increase. As a result of the interaction of asymmetric environmental factors, the proportions of the two diastereoisomerides must also be altered in presence of excess of acid, and the combined effect of these two changes is shown in an addition curve, in which a very small effect present when base and acid are in equivalent amounts is magnified, and so may first become observable.

Experimental.

(All values of k are given in terms of min.$^{-1}$.)

Addition Curves.—The following notes explain the method used. All readings were made in an all-glass Hilger 2-dm. tube at 17—18°.

Figs. 1 and 2. Initial solution : 0·1051 g. of nor-*d*-ψ-ephedrine in 14·5 c.c. of chloroform.

Fig. 3. Initial solution : 0·1000 g. of cinchonidine in 14·5 c.c. of chloroform.

Figs. 4 and 5. Initial solution : 0·1000 g. of cinchonidine or the equivalent amount of another alkaloid in 14·5 c.c. of chloroform.

Fig. 6. Initial solution : 0·0514 g. of nor-*d*-ψ-ephedrine in 14·5 c.c. of solvent. An acetone solution of the base mutarotates rapidly, presumably owing to combination of base and solvent.

The neutral salt did not mutarotate, and the addition curve is therefore normal above the 1 : 1 point.

Fig. 11. For each point, the requisite amount of the tribromo-acid was placed in a glass tube, 19·3 c.c. of dry chloroform added, and the tube sealed. By placing the tube in boiling water, complete dissolution was effected in a few minutes. The cooled tube was opened, 0·1353 g. of nor-*d*-ψ-ephedrine added, and the rotation determined 2 mins. after mixing. Some of the more concentrated solutions used were actually supersaturated with acid, but the latter did not crystallise out during the period over which observations were made.

Formation of l-N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylic Acid by Optical Activation.*—A solution of 2 g. of the *dl*-acid and 0·2 g. of cinchonidine in 30 c.c. of chloroform was evaporated in a vacuum vessel in a vacuum. The residue was dissolved in 5 c.c. of pyridine at −10°, and the solution poured into dilute hydrochloric acid and ice. The precipitated acid, after being dried in a vacuum, was dissolved in 16 c.c. of pyridine. The following observations were made at 18·5° ($l = 2$) :

Time (mins.)	0·0	0·8	1·2	1·5	2·5	3·1	3·6	4·3
α_{5461}	−1·33°	−1·22°	−1·19°	−1·17°	−1·07°	−1·03°	−0·98°	−0·93°
Time (mins.)	4·7	5·6	6·1	6·8	8·1	9·5	10·9	13·0
α_{5461}	−0·90°	−0·87°	−0·84°	−0·78°	−0·75°	−0·70°	−0·65°	−0·60°
Time (mins.)	15·0	17·0	20·0	23·0	28·0	40·0	∞	
α_{5461}	−0·55°	−0·56°	−0·53°	−0·51°	−0·51°	−0·48°	−0·01°	

Preparation of Cinchonidine d-N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylate.*—16·59 G. of the *dl*-acid were dissolved in 250 c.c. of acetone, and 8·82 g. (1 mol.) of cinchonidine added in fine suspension in a further 250 c.c. of acetone : on warming, all went into solution. The solution was filtered and, on keeping, deposited 23 g. (90·5% of the theoretical quantity) of the *d*-salt in rosettes of colourless needles, which were dried first in air and then in a vacuum. It was found subsequently that the deposition was greatly accelerated if the solution was kept gently boiling, the *salt* then being completely precipitated in a few minutes (yield, 94%) (Found : C, 55·3; H, 3·9; Br, 27·7. $C_{39}H_{34}O_4N_3Br_3$ requires C, 55·2; H, 4·0; Br, 28·3%).

Mutarotation of Cinchonidine d-N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylate.*—This, and all similar measurements described in this paper, were made in a 2-dm. water-jacketed observation tube, the temperature of which was constant to ± 0·05°. All readings in mutarotations are for λ 5461. The solvent, chloroform, was " AnalaR " quality, dried over sodium sulphate.

(*a*) Temp., 17·6°; $c = 0{\cdot}6000$; α_t = the difference between the reading at time t mins. and the final reading at $t = \infty$. Readings were begun 1·5 mins. after the salt had been wetted with solvent.

Time after 1·5 mins.	α_t.	k.	Time after 1·5 mins.	α_t.	k.	Time after 1·5 mins.	α_t.	k.
0·0	2·65°	—	7·5	1·86°	0·0205	13·5	1·407°	0·0204
3·5	2·26	0·0206	8·0	1·84	0·0198	15·5	1·27	0·0206
4·0	2·22	0·0192	9·0	1·75	0·0200	17·5	1·16	0·0205
4·5	2·16	0·0197	9·5	1·72	0·0197	19·5	1·05	0·0206
5·0	2·125	0·0192	10·0	1·66	0·0203	25·5	0·773	0·0210
6·0	2·02	0·0196	11·0	1·60	0·0198	27·5	0·707	0·0208
6·5	1·96	0·0201	11·5	1·55	0·0202	30·5	0·617	0·0208
7·0	1·93	0·0197	12·0	1·51	0·0204	37·0	0·457	0·0206

The values of α_t after $t = 12$ are each the mean of three readings, one taken ½ min. before and one ½ min. after the time stated. The observed rotation changed from + 2·10° to − 0·55°. Mean $k = 0{\cdot}0201$.

(*b*) Temp., 1·65°; $c = 1{\cdot}4470$; mean $k = 0{\cdot}00241$ (limits, 0·00239 and 0·00246). This is the mean of 23 values of k, each corresponding to the mean of three readings taken at $(t - 0{\cdot}5)$ mins., at t mins. and at $(t + 0{\cdot}5)$ mins.

(*c*) Temp., 11·9°; $c = 0{\cdot}9500$; $k = 0{\cdot}0099$, this being the mean of two values obtained from two different experiments ($k = 0{\cdot}00105$ and $k = 0{\cdot}0093$).

(*d*) Temp., 29·4°; $c = 0{\cdot}6360$; $k = 0{\cdot}0855$ (limits, 0·0834 and 0·0871). This is the mean of 19 values, each obtained from one reading : it was impossible to group the readings and take mean values owing to the speed of rotational change.

(*e*) Temp., 18·0°; $c = 2{\cdot}125$; $k = 0{\cdot}0206$ (limits, 0·0198 and 0·0211), the mean of 52 values.

Resolution of Cinchonidine N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylate at* − 15°.—A mixture of 2·94 g. of cinchonidine and 5·56 g. (1 mol.) of the *dl*-acid was warmed with 150 c.c.

of pure acetone until dissolution was complete and the *d*-salt began to separate. The whole was at once chilled to − 15° and kept at this temperature with occasional stirring for an hour. The *d*-salt, 3·85 g., *i.e.*, 90% of that theoretically possible, was filtered off, and the filtrate placed in a vacuum vessel and evaporated as quickly as possible. The finely ground residue was used as crude *l*-salt.

Mutarotation of Cinchonidine l-N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylate*.—Temp. = 17·7°; c = 6·0000; solvent, chloroform. Observations were begun 5 mins. after the salt had been wetted with solvent. The observed reading changed from − 1·2° to − 0·55°. After 4·5 mins., readings given are each the mean of three taken at $(t - 0{\cdot}5)$, t, and $(t + 0{\cdot}5)$ mins.

Time after 5·0 mins.	α_t.	k.	Time after 5·0 mins.	α_t.	k.	Time after 5·0 mins.	α_t.	k.
0·0	0·58°	—	4·5	0·49°	0·0195	14·0	0·303°	0·0212
1·5	0·56	0·0200	6·0	0·45	0·0208	16·0	0·287	0·0200
2·0	0·55	0·0189	8·0	0·41	0·0207	19·0	0·247	0·0203
2·5	0·54	0·0183	10·0	0·377	0·0202	22·0	0·213	0·0204
3·5	0·51	0·0202	12·0	0·347	0·0198	26·0	0·173	0·0207
4·0	0·50	0·0198						

Mean k = 0·0200.

Preparation of d-N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylic Acid*.—The pure cinchonidine *d*-salt was dissolved by grinding with pyridine at − 15°. The solution was filtered at the same temperature into ice and dilute hydrochloric acid. The precipitate was washed with dilute hydrochloric acid and water, and dried in a vacuum (Found : Br, 42·6. Calc.: 43·3%).

The partly racemic *l*-acid was similarly obtained from the crude cinchonidine *l*-salt.

Racemisation of d-N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylic Acid*.—*Solvent*: *absolute ethyl alcohol*.

(*a*) Temp., 0·65°; c = 1·0110. The first reading was made 3 mins. after wetting the acid with solvent: k = 0·0157. The readings are plotted in Fig. 12.

(*b*) *Temp.*, 9·5°; c = 1·0650. Readings were begun 3·46 mins. after wetting acid with solvent. The mean value of k was 0·048 : the values of α_t calculated by using this value of k are given below side by side with the observed readings in order to indicate the order of accuracy attained :

Time after 3·46 mins.	α_t (found).	α_t (calc.).	Time after 3·46 mins.	α_t (found).	α_t (calc.).	Time after 3·46 mins.	α_t (found).	α_t (calc.).
0·00	+1·39°	—	5·86	+0·72°	0·72°	10·43	+0·44°	0·44°
1·28	1·20	1·20°	6·29	0·675	0·69	11·37	0·38	0·39
2·07	1·11	1·105	6·85	0·65	0·65	12·24	0·36	0·36
2·48	1·04	1·055	7·34	0·60	0·60	13·18	0·32	0·32
2·93	0·99	1·00	8·49	0·55	0·54	15·12	0·24	0·26
4·31	0·86	0·86	8·91	0·51	0·515	16·79	0·21	0·215
4·77	0·81	0·82	9·35	0·49	0·49	17·43	0·20	0·20
5·34	0·77	0·77	9·79	0·46	0·47			

(*c*) Temp., 17·7°; c = 1·1060. The first reading was made 2·15 mins. after wetting acid with solvent: k = 0·117 (mean of 13 values; limits, 0·126 and 0·101).

Solvent: chloroform.

(*a*) Temp., 17·5°; c = 0·3925 (equivalent to c = 0·6000 for salt) : k = 0·15 (limits, 0·17 and 0·14).

(*b*) Temp., 17·8°; c = 0·3925 : k = 0·16 (limits, 0·18 and 0·13).

Racemisation of l-N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylic Acid*.—Temp., 0·85°; c = 1·1970. Solvent, absolute ethyl alcohol. Readings were begun 5·0 mins. after wetting acid. After 20 minutes, each reading is the mean of three.

Time after 5·0 mins.	α_t.	k.	Time after 5·0 mins.	α_t.	k.	Time after 5·0 mins.	α_t.	k.
0·0	−1·80°	—	11·0	−1·18°	0·0167	25·0	−0·71°	0·0162
4·0	1·55	0·0163	12·0	1·135	0·0167	30·0	0·57	0·0166
6·0	1·44	0·0162	14·0	1·05	0·0167	35·0	0·48	0·0164
7·0	1·38	0·0165	15·0	1·01	0·0167	40·0	0·385	0·0167
8·0	1·32	0·0168	16·0	0·98	0·0164	45·0	0·34	0·0161
9·0	1·27	0·0168	20·0	0·83	0·0168	140·0	0·01	—
10·0	1·23	0·0165						

whence k = 0·0165.

Optical Activation of N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylic Acid with Nor*-d-*ψ-ephedrine.*—(*a*) Base : acid = 1 : 1·25 mols. The base (0·1353 g.) was dissolved in a solution of 0·6207 g. of acid in 19·3 c.c. of chloroform at 17·7°. Readings were begun 3 mins. after mixing, and changed from − 0·09° to + 0·36°.

Time after 3·0 mins.	0·0	2·0	4·0	6·0	8·0
$\alpha_t = \alpha_\infty - \alpha$	0·45°	0·41°	0·36°	0·34°	0·297°
k	—	0·0202	0·0242	0·0203	0·0226
Time after 3·0 mins.	10·0	13·0	16·0	20·0	25·0
$\alpha_t = \alpha_\infty - \alpha$	0·27°	0·233°	0·197°	0·16°	0·127°
k	0·0222	0·0220	0·0224	0·0225	0·0220

whence $k = 0·0220$.

(*b*) Base : acid = 1 : 2 mols. The base (0·1353 g.) was dissolved in a solution of 0·9930 g. of acid in 19·3 c.c. of chloroform at 17·7°. Readings were begun 2·8 mins. after mixing, and changed from + 0·33° to + 1·05°.

Time after 2·8 mins.	α_t.	k.	Time after 2·8 mins.	α_t.	k.	Time after 2·8 mins.	α_t.	k.
0·00	0·72°	—	7·2	0·35°	0·0435	11·7	0·22°	0·0440
2·75	0·55	0·0425	8·3	0·30	0·0458	13·2	0·19	0·0438
3·4	0·51	0·0440	8·7	0·30	0·0437	13·7	0·18	0·0439
3·85	0·48	0·0457	9·2	0·28	0·0446	14·2	0·17	0·0442
4·3	0·47	0·0431	9·7	0·27	0·0439	16·7	0·127	0·0451
4·8	0·45	0·0425	10·7	0·24	0·0446	19·2	0·097	0·0453
5·65	0·40	0·0451	11·2	0·23	0·0443	23·7	0·063	0·0446
6·65	0·36	0·0453						

whence $k = 0·044$.

This experiment was repeated under similar conditions and gave $k = 0·044$ (limits, 0·042 and 0·048).

(*c*) Base : acid = 1 : 3 mols. To a solution of 1·4896 g. of acid in 19·3 c.c. of chloroform at 17·7° was added 0·1353 g. of nor-*d*-*ψ*-ephedrine. Readings were begun 3·25 mins. after mixing, and changed from + 0·73° to + 1·54°. All readings given after 10 minutes are means of three.

Time after 3·25 mins.	α_t.	k.	Time after 3·25 mins.	α_t.	k.	Time after 3·25 mins.	α_t.	k.
0·00	0·81°	—	4·65	0·43°	0·059	8·35	0·26°	0·059
2·20	0·60	0·059	5·05	0·40	0·061	10·25	0·20	0·059
2·65	0·56	0·060	5·55	0·38	0·059	12·25	0·153	0·059
3·85	0·49	0·0565	6·55	0·33	0·0595	14·75	0·107	0·0595
4·3	0·46	0·057						

whence $k = 0·059$. The plots of log α_t against time for the last three experiments are given in Fig. 13.

(*d*) Base : acid = 1 = 1·83 mols. Temp., 0·80°. 0·1030 G. of nor-*d*-*ψ*-ephedrine was added to a solution of 0·6950 g. of acid in 15 c.c. of chloroform : $k = 0·0073$ (limits, 0·0069 and 0·0076).

Mutarotation of Cinchonidine Salts of N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylic Acid in Presence of One Molecule Excess of the* dl-*Acid.*—(1) At $c = 0·6070$.

(*a*) d-*Salt.* The pure *d*-salt (0·1214 g.) was dissolved at 18·0° in 20 c.c. of a chloroform solution of 0·0794 g. of the *dl*-acid.

(i) Polarimetric readings ($c = 0·6070$) were begun 2·6 mins. after mixing.

Time after 2·6 mins.	α_t.	k.	Time after 2·6 mins.	α_t.	k.	Time after 2·6 mins.	α_t.	k.
0·0	1·60°	—	3·55	0·91°	0·0690	6·15	0·59°	0·0704
1·3	1·30	0·0693	3·8	0·865	0·0703	6·55	0·55	0·0708
1·65	1·22	0·0713	4·3	0·79	0·0713	6·9	0·53	0·0695
1·9	1·17	0·0715	4·55	0·76	0·0710	7·45	0·48	0·0702
2·15	1·13	0·0702	4·8	0·74	0·0698	7·9	0·45	0·0697
2·45	1·07	0·0713	5·15	0·70	0·0703	8·4	0·40	0·0717
2·7	1·03	0·0709	5·4	0·66	0·0712	8·95	0·38	0·0697
2·9	0·99	0·0719	5·7	0·64	0·0698	10·55	0·29	0·0703
3·1	0·96	0·0725						

whence $k = 0·0706$.

(ii) and (iii) The above experiment, repeated under the same conditions, gave $k = 0·0708$ and $k = 0·0697$. Mean of (i). (ii), and (iii) : $k = 0·0704$.

(*b*) l-*Salt.* The determination of k was carried out exactly as for the *d*-salt : $k_{18·1°} = 0·0692$.

(2) At $c = 2·125$.

0·425 G. of *d*-salt was dissolved at 18·4° in a solution of 0·278 g. of *dl*-acid in 20 c.c. of chloroform. Readings were begun 3·7 minutes after mixing.

Time after 3·7 mins.	a_t.	k.	Time after 3·7 mins.	a_t.	k.	Time after 3·7 mins.	a_t.	k.
0·0	5·66°	—	6·65	2·40°	0·0560	16·7	0·64°	0·0566
0·75	5·14	0·0571	7·0	2·29	0·0561	17·0	0·62	0·0553
1·2	4·86	0·0552	7·35	2·18	0·0564	17·45	0·59	0·0562
1·5	4·69	0·0544	7·7	2·09	0·0562	17·8	0·56	0·0564
1·8	4·52	0·0543	8·25	1·96	0·0558	18·15	0·54	0·0562
2·65	4·03	0·0557	8·55	1·86	0·0565	18·45	0·51	0·0566
2·95	3·87	0·0566	9·8	1·59	0·0563	19·0	0·48	0·0564
3·3	3·71	0·0556	10·1	1·53	0·0562	19·5	0·44	0·0568
3·6	3·56	0·0560	10·4	1·47	0·0563	20·0	0·41	0·0570
3·9	3·41	0·0564	11·15	1·33	0·0564	20·5	0·39	0·0566
4·35	3·23	0·0560	11·55	1·26	0·0565	20·95	0·37	0·0566
4·7	3·09	0·0559	12·6	1·11	0·0561	21·35	0·35	0·0567
5·0	2·97	0·0560	14·45	0·87	0·0563	22·8	0·287	0·0566
5·25	2·86	0·0565	15·4	0·77	0·0563	24·8	0·22	0·0568
5·7	2·71	0·0560	15·95	0·73	0·0556	29·8	0·117	0·0565
6·15	2·56	0·0560	16·3	0·68	0·0564			

whence mean $k = 0{\cdot}0562$.

Optical Activation of N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylic Acid* (2 *Mols.*) *by Cinchonidine in Chloroform at* c = 2·125.—0·147 G. of cinchonidine was dissolved in 20 c.c. of a chloroform solution containing 0·556 g. (2 mols.) of the *dl*-acid at 18·1°. Readings were begun 3·85 minutes after mixing.

Time after 3·85 mins.	0·0	1·05	1·85	3·0	3·7	4·35	5·15	7·15	10·65
a_t	0·55°	0·48°	0·43°	0·37°	0·34°	0·31°	0·29°	0·217°	0·127°
k	—	0·0564	0·0578	0·0574	0·0565	0·0572	0·0540	0·0565	0·0598

whence $k = 0{\cdot}0574$.

In a second experiment, readings were started 4·1 mins. after mixing :

Time after 4·1 mins.	a_t.	k.	Time after 4·1 mins.	a_t.	k.	Time after 4·1 mins.	a_t.	k.
0·0	0·54°	—	3·1	0·36°	0·0568	7·9	0·20°	0·0546
0·45	0·51	0·0551	3·85	0·34	0·0522	10·4	0·15	0·0535
1·9	0·42	0·0575	4·35	0·32	0·0523	17·4	0·057	0·0560
2·3	0·41	0·0520	5·9	0·27	0·0510	20·9	0·043	0·0527
2·75	0·38	0·0555						

whence mean $k = 0{\cdot}0541$.

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SOME DERIVATIVES OF DIPHENYLAMINE AND A NEW SYNTHESIS OF *N*-ARYLANTHRANILIC ACIDS AND OF ACRIDONES

BY

MARGARET M. JAMISON (HARRIS)

AND

E. E. TURNER

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411. *Some Derivatives of Diphenylamine and a New Synthesis of* N-*Aryl-anthranilic Acids and of Acridones.*

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

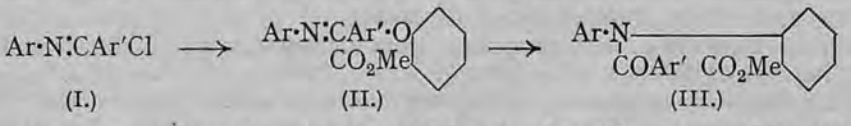
The main subject dealt with is a new synthesis of substituted diphenylamine-2-carboxylic acids, which are important because of their ready cyclisation to acridones or 5-chloroacridines, from which antimalarial drugs are derived.

During an extended stereochemical study of derivatives of tervalent nitrogen, we have had occasion to prepare a number of new substituted diphenylamines. By straightforward application of the convenient method of Chapman (J., 1929, 569 and previous papers) we have obtained 2 : 4′-*dichloro-*, 2 : 4 : 4′-*trichloro-*, 2 : 4 : 6 : 2′ : 4′-*pentachloro-* and 4-*chloro*-4′-*bromo-diphenylamine.* These substances could not be caused to react with *p*-toluenesulphonyl chloride, even in presence of quinoline at high temperatures, and while *p*-chloro- and 2 : 4′-dichloro-diphenylamine were found to give N-*nitroso*-derivatives, under the conditions used by Fischer for nitrosating diphenylamine (*Annalen*, 1878, **190**, 175), pentachlorodiphenylamine could not be induced to react with nitrous acid or its esters in any of the circumstances which seemed likely to favour reaction. Similarly, the pentachloro-compound was indifferent to carbonyl chloride at high temperatures, whereas the trichloro-compound reacted readily with it at 140—150°. This method of preparation of 2 : 4 : 4′-*trichlorodiphenylcarbamyl chloride* has incidentally been applied to the preparation of diphenylcarbamyl chloride itself, which substance is obtainable far more readily by the new process than by those described in the literature (Erdmann and Huth, *J. pr. Chem.*, 1897, **56**, 7; D.R.-P. 285,134).

By reduction of the *N*-nitroso-derivatives of *p*-chloro- and 2 : 4′-dichloro-diphenylamine, we have prepared 4-*chloro-* and 2 : 4′-*dichloro*-NN-*diphenylhydrazine*, but the difficulty of effecting such reductions made a proposed study of the hydrazines impossible.

For another section of the investigation, we required substituted diphenylamine-carboxylic acids. Some of these acids are readily obtainable by condensing anthranilic acids with halogeno-derivatives of aromatic hydrocarbons (Goldberg and Nimerowsky, *Ber.*, 1907, **40**, 2449) or *o*-halogenobenzoic acids with aromatic bases (Ullmann, *Annalen*, 1907, **355**, 312), but of these four types only the last-named permits of much variation. We have found that the Chapman diphenylamine synthesis can be applied to the preparation of *N*-arylanthranilic acids, and the method is available also for obtaining *N*-aroyl-*N*-arylanthranilic acids, which cannot be produced by direct *N*-aroylation.

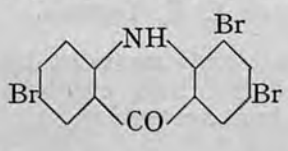
The readily accessible imino-chlorides (I) react almost quantitatively with the sodium derivatives of esters of salicylic acids, and the ethers (II) formed undergo the Chapman

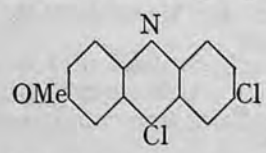


(I.) (II.) (III.)

conversion with unusual ease, to give the aroylarylanthranilic esters (III). The change (II) ⟶ (III) usually occurs at about 270°, and is markedly exothermic, the temperature rising spontaneously as much as 30°, the rise depending partly on the scale of the operation. None of Chapman's recorded changes showed this exothermic effect, which is no doubt due to the acceleration of the process by the carbalkoxy-group, Chapman having already shown (J., 1927, 1743) that the isomerisation of imino-ethers in general is promoted by the presence of an electron-attracting group in the migrating nucleus. Hydrolysis of esters of type (III) proceeds quantitatively, and in this way diphenylamine-2-carboxylic acid and its 4′-chloro-, 2′ : 4′-dichloro-, 4 : 6 : 4′-*tribromo-*, 4-chloro-4′-methoxy- and 2′ : 4′-*dimethyl-* derivatives have been obtained. Former syntheses would have failed in the case of the tribromo-acid, and the present synthesis thus makes possible the preparation of a number of new acridones and the corresponding 5-chloroacridines. From the tribromo-acid, 1 : 3 : 7-*tribromoacridone* (IV) has been obtained by the phosphoryl chloride method of

Drosdov (*J. Gen. Chem. Russ.*, 1934, **4**, 117). Feldman and Kopeliovitsch (*Arch. Pharm.*, 1935, **273**, 488), in studies of substances resembling " atebrin," prepared 3 : 5-dichloro-7-methoxyacridine (V) from 4-chloro-4′-methoxydiphenylamine-2-carboxylic acid, but their

(IV.) 

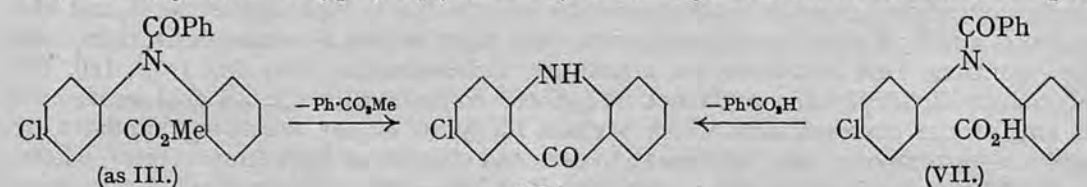


(V.)

synthesis, of the Ullmann type, necessitates the use of the difficultly accessible 2 : 5-dichlorobenzoic acid.

All the *N*-arylanthranilic acids obtained by the new method are free from the impurities which appear to be unavoidable in the products of the older syntheses.

Some methyl esters of type (III) (Ar′ = Ph) lose methyl benzoate when heated and pass



(as III.) (VI.) (VII.)

into the corresponding acridones (VI), although not quantitatively. The one *l*-menthyl ester examined gave *l*-menthene, benzoic acid and the acridone.

Partial hydrolysis of the esters (III) is readily effected. Some of the *N*-aroyl-*N*-arylanthranilic acids (VII) so obtained lose benzoic acid when they are heated for a few minutes and again an acridone is formed. This is actually one of the most expeditious methods of obtaining an acridone, as the yields are good and the product is easily purified. Curiously enough, *N*-benzoyl-*N*-phenylanthranilic acid does not undergo this conversion into acridone at temperatures up to 350°.

Substituted diphenylamine-4-carboxylic acids are readily obtained from *p*-hydroxybenzoic esters.

Experimental.

Preparation of Halogenodiphenylamines.—The experimental procedure described by Chapman (*loc. cit.*) was followed without modification.

N-o-*Chlorophenylbenzimino*-p-*chlorophenyl ether*, large irregular crystals from alcohol, has m. p. 59—60° (Found : Cl, 20·9. $C_{19}H_{13}ONCl_2$ requires Cl, 20·8%). Yield, 90%.

N-*Benzoyl*-2 : 4′-*dichlorodiphenylamine* was formed in 74% yield when the last-named compound was heated at 300° for 2 hours. It crystallised from alcohol in prisms, m. p. 115° (Found : Cl, 20·8. $C_{19}H_{13}ONCl_2$ requires Cl, 20·8%).

2 : 4′-*Dichlorodiphenylamine*, large prisms from alcohol, has m. p. 42° (Found : Cl, 30·3. $C_{12}H_9NCl_2$ requires Cl, 29·8%). Yield, 71%.

N-2 : 4-*Dichlorophenylbenzimino*-p-*chlorophenyl ether* crystallised from alcohol in hexagonal plates, m. p. 81° (Found : Cl, 28·1. $C_{19}H_{12}ONCl_3$ requires Cl, 28·3%). Yield, 96%.

N-*Benzoyl*-2 : 4 : 4′-*trichlorodiphenylamine*, formed in 76% yield by heating the preceding ether for 2 hours at 250—270°, separated from light petroleum (b. p. 80—100°) in rhombs, m. p. 117—118° (Found : Cl, 28·5. $C_{19}H_{12}ONCl_3$ requires Cl, 28·3%).

2 : 4 : 4′-*Trichlorodiphenylamine* crystallised from light petroleum (b. p. 60—80°) in angular plates, m. p. 67—68° (Found : Cl, 39·1. $C_{12}H_8NCl_3$ requires Cl, 39·3%). Yield, 85%.

N-p-Chlorophenyl-*p*-toluimino-2 : 4-dichlorophenyl ether, $C_6H_4Cl{\cdot}N{:}C(C_6H_4Me){\cdot}O{\cdot}C_6H_3Cl_2$, was prepared from 2 : 4-dichlorophenol and *N-p*-chlorophenyl-*p*-toluanilideiminochloride, the latter being obtained by the action of phosphorus pentachloride on *p*-tolu-*p*-chloroanilide. The ether was an uncrystallisable glass.

N-p-*Toluoyl*-2 : 4 : 4′-*trichlorodiphenylamine* was obtained by heating the above glass for 2·5 hours at 280—300°. The black glass which resulted was crystallised from light petroleum (b. p. 80—100°), then twice from alcohol, and finally from glacial acetic acid. The p-*toluoyl* derivative formed irregular prisms, m. p. 157° (Found : Cl, 27·2. $C_{20}H_{14}ONCl_3$ requires Cl, 27·3%).

N-p-*Chlorophenylbenzimino*-2′-(*carbo*-l-*menthoxy*)*phenyl ether* was obtained as an uncrystallisable glass (yield, 88%) from benz-*p*-chloroanilideiminochloride and *l*-menthyl salicylate. When heated at 280—295°, it passed into *N*-benzoyl-4-chloro-2′-(carbo-*l*-menthoxy)diphenylamine, but this at once began to decompose, giving (1) *l*-menthene, b. p. 165°, (2) benzoic acid, and (3) 3-chloroacridone.

N-2 : 4-*Dichlorophenylbenzimino*-2 : 4 : 6-*trichlorophenyl ether* separated from alcohol in prisms, m. p. 86—88° (Found : Cl, 39·9. $C_{19}H_{10}ONCl_5$ requires Cl, 39·8%). Yield, 88%.

N-*Benzoyl*-2 : 4 : 6 : 2′ : 4′-*pentachlorodiphenylamine*, formed in 81% yield by heating the preceding ether for 2 hours at 250—270°, crystallised from alcohol in prisms, m. p. 160° (Found : Cl, 39·6. $C_{19}H_{10}ONCl_5$ requires Cl, 39·8%).

2 : 4 : 6 : 2′ : 4′-*Pentachlorodiphenylamine* crystallised from alcohol in slender needles, m. p. 94° (Found : Cl, 51·6. $C_{12}H_6NCl_5$ requires Cl, 51·9%). Yield, 92%. The *N*-nitroso-derivative could not be obtained by using (*a*) sodium nitrite and hydrochloric acid in alcoholic solution, (*b*) amyl nitrite and hydrochloric acid in glacial acetic acid solution, (*c*) sodium nitrite and concentrated sulphuric acid.

N-p-*Bromophenylbenzimino*-p-*chlorophenyl ether* separated from alcohol in prisms, m. p. 83—84° (0·1698 gave 0·1449 AgCl + AgBr. $C_{19}H_{13}ONClBr$ requires 0·1449 AgCl + AgBr).

N-*Benzoyl*-4-*chloro*-4′-*bromodiphenylamine*, obtained in 75% yield by heating the last-named ether for 2·5 hours at 290—320°, crystallised from alcohol in plates, m. p. 149° (0·1424 gave 0·1194 AgCl + AgBr. $C_{19}H_{13}ONClBr$ requires 0·1249 AgCl + AgBr).

4-*Chloro*-4′-*bromodiphenylamine* formed plates, m. p. 91·5°, from alcohol (0·1272 gave 0·1477 AgCl + AgBr. $C_{12}H_9NClBr$ requires 0·1489 AgCl + AgBr).

N-*Nitroso*-p-*chlorodiphenylamine* crystallised from light petroleum (b. p. 40—60°) in prisms, m. p. 88° (Found : Cl, 15·0. $C_{12}H_9ON_2Cl$ requires Cl, 15·3%). Yield, 83%.

N-*Phenyl*-N-p-*chlorophenylhydrazine*, prepared by reducing the above nitroso-compound with zinc dust and aqueous alcoholic acetic acid by the Fischer method (*loc. cit.*), contained a high proportion of *p*-chlorodiphenylamine, which survived the usual hydrochloride separation. By crystallising the acid oxalate this difficulty was avoided, and the *hydrazine* was obtained as a pale golden oil, b. p. 194°/2 mm. (Found : Cl, 16·1. $C_{12}H_{11}N_2Cl$ requires Cl, 16·2%).

N-*Nitroso*-2 : 4′-*dichlorodiphenylamine* formed yellow needles, m. p. 66—67°, from light petroleum (b. p. 60—80°) (Found : Cl, 26·6. $C_{12}H_8ON_2Cl_2$ requires Cl, 26·6%). Yield, 82%.

2 : 4′-*Dichloro*-NN-*diphenylhydrazine*.—The preceding nitroso-compound was reduced with zinc dust and aqueous alcoholic acetic acid. The resulting paste was extracted with alcohol. The extract was treated with concentrated hydrochloric acid. The crystalline material precipitated was shaken with a mixture of water and light petroleum, whereupon dichlorodiphenylamine passed into the latter and the aqueous layer yielded almost pure *dichlorodiphenylhydrazine*. This was a pale yellow oil, b. p. 241°/8 mm. (Found : Cl, 28·9. $C_{12}H_{10}N_2Cl_2$ requires Cl, 28·1%). Yield, 25%.

N-2-*Chlorophenyl*-N-4-*chlorophenyl*-N′N′-4-*chlorophthalylhydrazine*,

$$N(C_6H_4Cl)(C_6H_4Cl)\cdot N{:}C_2O_2{:}C_6H_3Cl.$$

—Equimolecular quantities of 2 : 4′-dichlorodiphenylhydrazine and 4-chlorophthalic anhydride were heated at 170—190° for an hour. Alcohol was added, the mixture boiled for an hour, the alcohol evaporated, and the residual powder ground with dilute sodium carbonate solution. The *chlorophthalyl* derivative left crystallised from alcohol in yellow clusters of needles, m. p. 142—142·5° (Found : Cl, 25·2. $C_{20}H_{11}O_2N_2Cl_3$ requires Cl, 25·5%).

2 : 4 : 4′-*Trichlorodiphenylcarbamyl Chloride*.—Carbonyl chloride was bubbled through 10 g. of 2 : 4 : 4′-trichlorodiphenylamine at 150—200° until no further increase in weight occurred (about 30 minutes). When the cooled product was crystallised from alcohol, the *chloride* was obtained in needles, m. p. 117—118° (Found : Cl, 42·3. $C_{13}H_7ONCl_4$ requires Cl, 42·4%). Yield, 68%.

Diphenylcarbamyl chloride was obtained similarly (temperature, 140—150°; 15 minutes; yield, 92%).

N-p-*Chlorophenylbenzimino*-o-*carbomethoxyphenyl Ether*.—To a cooled solution of sodium (14·5 g.; 1·25 atoms) in 700 c.c. of absolute alcohol were added in rapid succession (1) 114 g. (1·5 mols.) of methyl salicylate and (2) 130 g. (1 mol.) of benz-*p*-chloroanilideiminochloride, dissolved in dry ether. The mixture became cloudy, and was kept overnight. The ether and most of the alcohol were then removed by evaporation, and water added. The *ether* became solid; it crystallised from alcohol in angular plates, m. p. 130—131° (Found : Cl, 9·9. $C_{21}H_{16}O_3NCl$ requires Cl, 9·7%). Yield, 166 g. (88%).

Methyl N-*Benzoyl*-4-*chlorodiphenylamine*-2′-*carboxylate*.—The above imino-ether (30 g.)

was heated in a wide tube in a bath kept at 270—275°. As soon as the temperature inside the tube attained that of the bath, isomeric change began, and the internal temperature rose to about 300° within a few minutes. When it began to fall, the product was poured into alcohol (2 vols.). On cooling, the *methyl* ester separated in prisms, m. p. 139—140° (Found : Cl, 9·5. $C_{21}H_{16}O_3NCl$ requires Cl, 9·7%). Yield of pure substance, 85—91%.

When the ester was heated at 320°, methyl benzoate (b. p. 199°) distilled, and 3-chloroacridone was formed. The latter crystallised from *cyclo*hexanol in yellow needles, m. p. above 360° (compare Ullmann, *loc. cit.*) (Found : Cl, 15·4. Calc. : Cl, 15·4%).

N-*Benzoyl*-4-*chlorodiphenylamine*-2′-*carboxylic Acid.*—For this, and similar partial hydrolyses of esters of *N*-benzoyl derivatives, it was convenient to have ready a solution (*S*) made by dissolving 2·3 g. of sodium in 100 c.c. of absolute alcohol, and adding 20 c.c. of water. A solution containing the methyl ester (11 g. ; 1 mol.), 60 c.c. of absolute alcohol, 33 c.c. of solution *S* (equivalent to 1 atom of sodium), and 33 c.c. of water was boiled under reflux for an hour. The alcohol was evaporated, and the residue acidified with hydrochloric acid. The precipitate was extracted with sodium hydrogen carbonate solution, and the filtered extract acidified. The precipitate was freed from benzoic acid by extraction with boiling water, dried, and crystallised from acetone–light petroleum (b. p. 40—60°). It formed needles, m. p. 191—192° (Found : Cl, 10·2. $C_{20}H_{14}O_3NCl$ requires Cl, 10·1%). Yield, 8 g. (76%).

Action of Heat on the Preceding Acid.—The acid was heated rapidly to 250° during 5 minutes. The resulting mixture was freed from benzoic acid by extraction with boiling water, and 3-chloroacridone obtained in 90% yield.

4-*Chlorodiphenylamine*-2′-*carboxylic Acid.*—A solution of methyl *N*-benzoyl-4-chlorodiphenylamine-2′-carboxylate (10 g.) in 125 c.c. of alcohol was treated with 40 g. of sodium hydroxide in 40 c.c. of water, and the whole then boiled under reflux for an hour. The alcohol was evaporated, and the aqueous solution acidified with hydrochloric acid. The precipitate was freed from benzoic acid by extraction with boiling water ; the residual carboxylic acid crystallised from alcohol in pale yellow prisms, m. p. 177—178° (Ullmann, *loc. cit.*, gives 177° ; the product obtained by the Ullmann method was less easily purified). Yield, almost theoretical. The acid was readily converted into 3-chloroacridone by Drosdov's method (*loc. cit.*). Yield, 87%.

N-2 : 4-*Dichlorophenylbenzimino*-o-*carbomethoxyphenyl ether*, obtained from benz-2 : 4-dichloroanilideiminochloride and methyl salicylate in 72% yield, crystallised from alcohol in needles, m. p. 85—87° (Found : Cl, 17·6. $C_{21}H_{15}O_3NCl_2$ requires Cl, 17·7%).

Methyl N-*benzoyl*-2 : 4-*dichlorodiphenylamine*-2′-*carboxylate* was obtained in 65% yield by heating the last-named ether at 260—280° for 10 minutes. It formed rods, m. p. 114—116°, from ethyl alcohol (Found : Cl, 17·6. $C_{21}H_{15}O_3NCl_2$ requires Cl, 17·7%).

N-*Benzoyl*-2 : 4-*dichlorodiphenylamine*-2′-*carboxylic acid* was obtained by partial hydrolysis of the benzoyl-methyl ester. After being dissolved in sodium bicarbonate solution and precipitated therefrom with acid, it was hydrated, and therefore was dried in a high vacuum over phosphoric oxide (Found : Cl, 18·5. $C_{20}H_{13}O_3NCl_2$ requires Cl, 18·4%). The acid crystallised from benzene or from light petroleum–acetone in needles, solvated in both cases. The product from the second solvent had m. p. 177°.

2′ : 4′-*Dichlorodiphenylamine*-2-*carboxylic Acid.*—The benzoyl ester was hydrolysed with excess of alcoholic sodium hydroxide. The crude acid obtained (93% yield) had m. p. 243° (Ullmann, *loc. cit.*, gave 249° for the pure acid).

4-m-*Xylylbenzimino*-2′-*carbomethoxyphenyl ether*, formed from benz-4-*m*-xylidideiminochloride in 56% yield, crystallised from alcohol in rectangular prisms, m. p. 87—88° (Found : C, 76·7 ; H, 6·0. $C_{23}H_{21}O_3N$ requires C, 76·85 ; H, 5·9%).

Methyl N-*benzoyl*-2 : 4-*dimethyldiphenylamine*-2′-*carboxylate* was formed in 89% yield by heating the preceding ether at 275° for 10 minutes, and crystallised from methyl alcohol in stout prisms, m. p. 132—133° (Found : C, 76·7 ; H, 5·7. $C_{23}H_{21}O_3N$ requires C, 76·85 ; H, 5·9%). The ester showed no tendency to give the corresponding acridone when heated at 350°.

N-*Benzoyl*-2 : 4-*dimethyldiphenylamine*-2′-*carboxylic acid*, obtained by hydrolysing the methyl ester, crystallised from acetone–light petroleum (b. p. 40—60°) in prisms, softening at 191°, and melting at 192—193° (Found : C, 76·4 ; H, 5·6. $C_{22}H_{19}O_3N$ requires C, 76·5 ; H, 5·7%). Yield, 74%.

Action of Heat on the Preceding Acid.—The acid was heated for a few minutes at 300°. The residue was extracted with boiling alcohol, 1 : 3-dimethylacridone being left as small yellow needles, m. p. 307°. Yield, 71%.

N-*Phenylbenzimino*-o-*carbomethoxyphenyl ether*, obtained from benzanilideiminochloride

and methyl salicylate in 81% yield, formed rhombohedra, m. p. 110—111°, from alcohol (Found : C, 76·2; H, 5·1. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·2%).

Methyl N-*benzoyldiphenylamine*-2-*carboxylate* was formed in 73% yield by heating the last-named ether at 270—275° for 10 minutes. It crystallised from alcohol in diamond-shaped prisms, m. p. 132—133° (Found : C, 75·9; H, 4·9. $C_{21}H_{17}O_3N$ requires C, 76·1; H, 5·2%). Hydrolysis of the ester with excess of alcoholic alkali gave *N*-phenylanthranilic acid in 96% yield.

N-*Benzoyl*-N-*phenylanthranilic* [N-*benzoyldiphenylamine*-2-*carboxylic*] *acid*, obtained from its methyl ester in 76% yield, was crystallised from acetone–light petroleum (b. p. 40—60°) and then from benzene. It formed slender needles, m. p. 186° (Found : C, 75·7; H, 5·0. $C_{20}H_{15}O_3N$ requires C, 75·7; H, 4·8%).

N-p-*Bromophenylbenzimino*-4′ : 6′-*dibromo*-2′-*carbomethoxyphenyl Ether*.—Sodium (3·7 g.; 1·25 atoms) was dissolved in 150 c.c. of absolute alcohol, and a suspension of 50 g. (1·5 mols.) of methyl 3 : 5-dibromosalicylate in 100 c.c. of alcohol added, followed by a solution of 47 g. of benz-*p*-bromoanilideiminochloride in dry ether. The mixture was shaken for a few minutes and left overnight. Most of the solvents were removed by evaporation, and the white oil extracted with warm water until it became a solid. This crystallised from alcohol in long prisms, m. p. 105° (Found : Br, 42·8. $C_{21}H_{14}O_3NBr_3$ requires Br, 42·2%). Yield, 65%.

Methyl N-*benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylate*, obtained in 87% yield by heating the preceding ether at 270°, formed small prisms, m. p. 138—139°, from alcohol (Found : Br, 42·8. $C_{21}H_{14}O_3NBr_3$ requires Br, 42·2%).

N-*Benzoyl*-4 : 6 : 4′-*tribromodiphenylamine*-2-*carboxylic acid*, obtained from its methyl ester, crystallised from acetone–light petroleum (b. p. 40—60°) in slender prisms, m. p. 217—218° (with previous softening) (Found : Br, 42·6. $C_{20}H_{12}ONBr_3$ requires Br, 43·3%).

4 : 6 : 4′-*Tribromodiphenylamine*-2-*carboxylic acid*, obtained from the *N*-benzoyl ester in 90% yield, crystallised from alcohol in sulphur-yellow needles, m. p. 222° (Found : Br, 52·05, 52·05. $C_{13}H_8O_2NBr_3$ requires Br, 53·3%).

1 : 3 : 7-*Tribromoacridone*.—A solution of 4 g. of the last-named acid in 80 c.c. of xylene was treated with 2 g. of phosphoryl chloride, dissolved in 20 c.c. of xylene. The whole was boiled for 2 hours. Solid slowly separated. Water and then dilute alkali were added, and the xylene was removed in a current of steam. The liquid was filtered, and the crude *tribromoacridone* dried (3·5 g.). It crystallised from *m*-cresol in minute yellow needles, m. p. above 300° (Found : Br, 54·7. $C_{13}H_6ONBr_3$ requires Br, 55·5%).

N-p-*Methoxyphenylbenzimino*-p-*chloro*-o-*carbomethoxyphenyl ether*,

$$OMe\cdot C_6H_4\cdot N{:}CPh\cdot O\cdot C_6H_3Cl\cdot CO_2Me,$$

from benz-*p*-anisidideiminochloride and methyl 5-chlorosalicylate, crystallised from alcohol in flat needles, m. p. 105—106° (Found : Cl, 8·7. $C_{22}H_{18}O_4NCl$ requires Cl, 9·0%).

Methyl N-*benzoyl*-4-*chloro*-4′-*methoxydiphenylamine*-2-*carboxylate* was obtained by heating the last-named ether at 200—210° for 10 minutes and then pouring the product into one volume of alcohol. On cooling, 7·5 g. of solid separated, and this on recrystallisation from alcohol gave the methyl ester in prisms and cubes, m. p. 164° (Found : Cl, 9·3. $C_{22}H_{18}O_4NCl$ requires Cl, 9·0%). Complete hydrolysis of the ester gave 4-chloro-4′-methoxydiphenylamine-2-carboxylic acid, m. p. 191—192° (Feldman and Kopeliovitsch, *loc. cit.*, give 185—186°).

N-*Benzoyl*-4-*chloro*-4′-*methoxydiphenylamine*-2-*carboxylic acid*, obtained by the partial hydrolysis of the methyl ester, crystallised from benzene, in which it was only moderately soluble, in slender needles, containing half a molecule of benzene of crystallisation, after being air-dried (Found : Cl, 8·3. $C_{21}H_{16}O_4NCl,1/2C_6H_6$ requires Cl, 8·4%). It softened and lost benzene at 120—125°, but gave no sharp m. p. at higher temperatures. The solvent-free acid was obtained from the solvated specimen by dissolution in very dilute alkali solution (the sodium salt is sparingly soluble), precipitation with dilute acid, and dehydration in a high vacuum over phosphoric oxide (Found : Cl, 9·1. $C_{21}H_{16}O_4NCl$ requires Cl, 9·3%).

Action of Heat on the Preceding Acid.—The acid was heated for 15 minutes at 300°. Benzoic acid sublimed. The mixture was extracted with boiling alcohol and the residual 3-*chloro*-7-*methoxyacridone* (yield, almost theoretical) was crystallised from phenol, to which a little alcohol was added before the solvent solidified. The acridone formed thin yellow hexagonal plates melting above 300° (Found : Cl, 13·1. $C_{14}H_{10}O_2NCl$ requires Cl, 13·7%).

N-p-*Chlorophenylbenzimino*-p′-*carbomethoxyphenyl ether* was obtained from benz-*p*-chloroanilideiminochloride and methyl *p*-hydroxybenzoate in 57% yield (pure). It crystallised from methyl alcohol in prisms, m. p. 78—79° (Found : Cl, 9·4. $C_{21}H_{16}O_3NCl$ requires Cl, 9·7%).

Methyl N-*benzoyl*-4-*chlorodiphenylamine*-4′-*carboxylate* was obtained by heating the above

ether. With the bath at 277° the temperature of the mixture rose to 290°. The ester crystallised from alcohol in prisms, m. p. 140—141° (Found: Cl, 9·4. $C_{21}H_{16}O_3NCl$ requires Cl, 9·7%). Yield, 90%.

N-*Benzoyl-4-chlorodiphenylamine-4'-carboxylic acid*, obtained in 61% yield by the partial hydrolysis of the methyl-benzoyl ester, crystallised from alcohol in slender needles, m. p. 223—224° (Found: Cl, 10·1. $C_{20}H_{14}O_3NCl$ requires Cl, 10·1%).

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FURTHER STUDIES ON UNSTABLE OPTICAL ACTIVITY IN THE *N*-BENZOYLDIPHENYL-AMINECARBOXYLIC ACID SERIES

BY

MARGARET M. HARRIS (née JAMISON),

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Further Studies on Unstable Optical Activity in the N-Benzoyldiphenylaminecarboxylic Acid Series.

By Margaret M. Harris (née Jamison), W. G. Potter, and E. E. Turner.

[Reprint Order No. 5574.]

Suitably substituted *N*-benzoyldiphenylamine-2-carboxylic acids show labile optical activity, although scale models demonstrate that rotation about the three N–C bonds *can* take place when the movement of the three groups attached to nitrogen is synchronised. The relative optical stabilities of fourteen such acids are here assessed by comparison of the rate constants of racemisation and of first-order asymmetric transformations, and the dependence of optical stability upon structure is discussed. Evidence of molecular aggregation (in non-polar solvents containing alkaloids plus excess of acid) beyond that required for simple salt formation is brought forward in explanation of the fact that first-order asymmetric transformation (optical activation) at acid : base ratio 1 : 1 is often different in direction and in degree from that at other acid : base ratios.

This paper reports the synthesis and stereochemical examination of six acids in the *N*-benzoyldiphenylaminecarboxylic acid series to add to the ten other related acids on which some investigations have already been made (Jamison and Turner, *J.*, 1937, 1954; 1938, 1646; 1940, 264). It is now possible to draw wider comparisons which throw more light on the unstable optical activity which is characteristic of the group. Those acids in the series which show optical activity often undergo first- and second-order asymmetric transformation (defined as in *J.*, 1942, 437) of their alkaloidal salts and, in particular, several of them show optical activation to differing extents, perhaps even in reversed directions, when the alkaloid and acid are mixed in solution in varying proportions.

A range of processes, namely, racemisation and optical activation in the presence of different alkaloids, has here been used in order to assess the relative optical stabilities of this set of acids; Table 1 gives the measured values of the unimolecular rate constants. In the graph (Fig. 1) the acids are placed in an order of optical stability which gives the best agreement with all the rate constants.

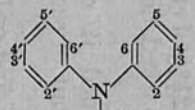
The acids (1) and (2) which have no substituent *ortho* to the nitrogen atom show no signs of optical activity. This is convincing evidence that the optical activity shown by the others is due to restricted rotation within the molecule and not to asymmetric tervalent nitrogen. Acid (3), which shows no activity by the methods listed, has already been inferred to be capable of exhibiting optical activity but to be more labile than acids (4) and (5) (Jamison and Turner, *J.*, 1938, 1646). The remainder all show mutarotations with at least one alkaloid in chloroform or chloroform containing $2\frac{1}{2}\%$ of ethanol (" solvent X "); the concentration of ethanol in the chloroform has a marked effect both on the rate constants and on the extent of the mutarotations.

In every case in which an active acid was obtained it came from an active alkaloidal salt which was the product, not of resolution, but of second-order asymmetric transformation.

It will be noticed that the rate constants of some of the first-order transformations are less than the rate constants of racemisation of the acids involved (*e.g.*, with quinidine, cinchonidine, or brucine at acid : base ratio 1 : 1) and that some are greater (*e.g.*, with quinidine or brucine at acid : base ratio 2 : 1).

Scale models (constructed without consideration of the van der Waals envelopes) show that in even the most hindered molecules, *e.g.*, (14) and (16), rotation about all three

TABLE 1.



Ref. no. of acid	2	4	6	2′	4′	Racemisation: *k*	Temp.	Solvent †	First-order asymmetric transformations: (+)-Nor-ψ-ephedrine in $CHCl_3$: *k*	Temp.	Ratio, acid : base	Quinidine in X at 20·0°: *k* 1 : 1	2 : 1	3 : 1	Brucine in X at 20·0°: *k* 1 : 1	2 : 1	Cinchonidine in X at 15·0°: *k* 1 : 1
1	—	CO_2H	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
2	—	CO_2H	—	—	Cl	—	—	—	—	—	—	—	—	—	—	—	—
3	CO_2H	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
4	CO_2H	—	—	Cl	Cl	—	—	—	0·365 [1]	−31°	4 : 1	—	—	—	—	—	—
5	CO_2H	—	—	Me	Me	—	—	—	0·254 [1]	−30	3 : 1	—	—	—	—	—	—
6	CO_2H	—	Me	—	—	—	—	—	0·322	20	3 : 1	—	—	—	—	—	—
7	CO_2H	—	Me	Me	—	0·567	20°	X	—	—	—	0·0602	0·667	—	—	—	—
8	CO_2H	Cl	Cl	—	—	0·345 [2]	15	X	—	—	—	—	—	—	—	—	0·091 [2]
9	CO_2H	Br	Br	—	—	0·702	20	$CHCl_3$	—	—	—	—	—	—	—	—	0·0495 *
10	CO_2H	Br	Br	—	Br	0·357 [1]	17·8	$CHCl_3$	0·126 [1]	17·5	3 : 1	—	—	—	—	—	—
11	CO_2H	—	Me	F	—	0·180	20	$CHCl_3$	—	—	—	0·0339	0·243	—	—	—	—
						0·209	20	X									
12	CO_2H	—	Me	Cl	Me	0·167	20	X	—	—	—	—	0·242	0·314	0·0922	0·297	—
13	CO_2H	—	Me	Cl	—	0·147	20	X	—	—	—	0·0244 [2]	0·253	—	0·0875	—	—
14	CO_2H	—	Me	Br	—	0·115	20	X	—	—	—	0·0160	0·255	—	0·0880	—	—
15	CO_2H	—	Me	Cl	Cl	0·0929	20	X	—	—	—	0·0118	0·202	0·238	0·0555	0·185	—
16	CO_2H	—	Me	Cl	Br	0·0862	20	X	—	—	—	0·0115	0·174	0·251	0·0545	0·142	—

Values of *k* are in terms of $\log_e$ min.$^{-1}$. * Calc. at 15° from values at three other temps. † X = $CHCl_3$ containing 2½% of EtOH.

[1] Jamison and Turner, *J.*, 1938, 1646. [2] *Idem*, *J.*, 1940, 264.

N–C bonds is still possible, as long as there is *synchronised* movement of the various parts : this is true whether the nitrogen-atom model is taken with valencies at angles of 109° 28′ or of 120°. In the most favourable positions, rotation is unrestricted, but these " favourable rotating positions " must be relatively rarely attained.

FIG. 1.

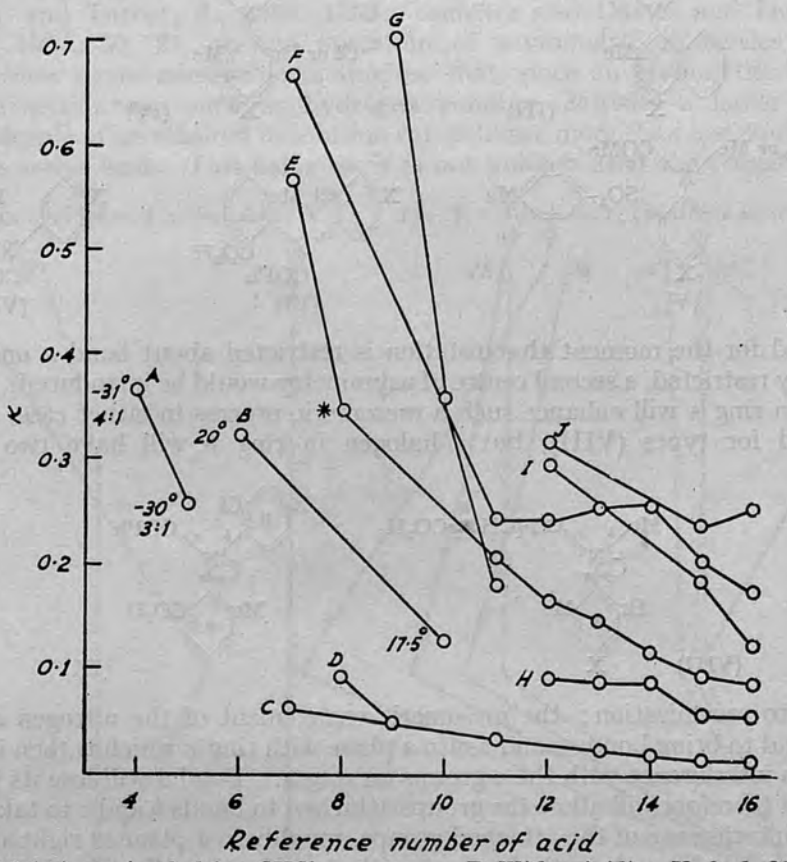
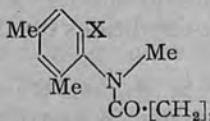
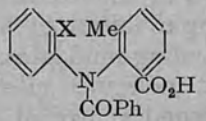


FIG. 1. *A*, *With* (+)-*nor*-ψ-*ephedrine*, $CHCl_3$. *F*, *With quinidine*, X, 2 : 1, 20°.
B, *With* (+)-*nor*-ψ-*ephedrine*, $CHCl_3$, 3 : 1. *G*, *Racemisation of acid*, $CHCl_3$.
C, *With quinidine*, X, 1 : 1, 20°. *H*, *With brucine*, X, 1 : 1, 20°.
D, *With cinchonidine*, X, 1 : 1, 15°. *I*, *With brucine*, X, 20°.
E, *Racemisation of acid*, X, 20°. *J*, *With quinidine*, X, 3 : 1, 20°.
* At 15°.

In the series (I) investigated by Adams and his co-workers (*J. Amer. Chem. Soc.*, 1942, **64**, 1475; 1948, **70**, 2667; 1950, **72**, 2454, 2458) the decreasing order of optical stability is X = I > Br > Cl > OMe > NO_2, which they related to the basic strengths of the corresponding *o*-substituted anilines. In the present series (II) the order is X = Br > Cl > F > Me > H. It is not possible in such series to separate the bulk and the polar influences of the hindering groups. This can, however, be done by comparing the effect of *p*-substituents, which can have no direct steric influence.



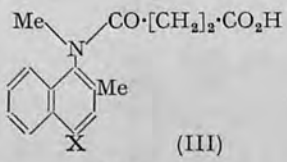
(I)



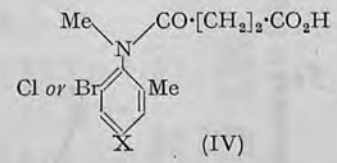
(II)

Adams found in all three pairs of compounds represented by (III) and (IV) a greater optical stability when X = H than when X = Cl; similarly Buchanan and Graham (*J.*, 1950, 500) in series (V) found the order X = OMe > Me > Cl > Br. We find in series (VI) a reversed order of stabilities : X = Br > Cl > H > Me, and in (VII) stability X = Br > H. These results, at first sight contrary to those of Adams, do in fact support

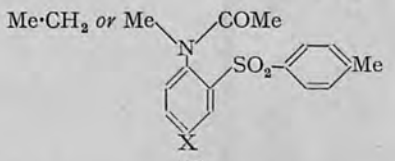
his work. It is true for Adams's compounds (VIII) (*i.e.*, IV) or for those now described (IX) that mesomerism of the type indicated by the curved arrow (along bond *a*) will accelerate racemisation by tending to force bonds *b* and *c* into the plane of ring A: this is the " passing position " or transition state between the two optically active forms



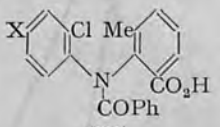
(III)



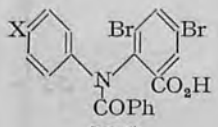
(IV)



(V)

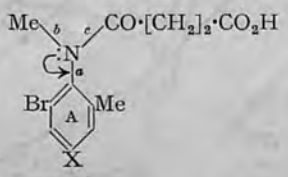


(VI)

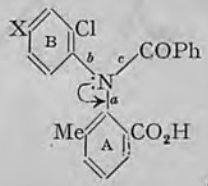


(VII)

(it is assumed for the moment that rotation is restricted about bond *a* only: if bond *b* were similarly restricted, a second centre of asymmetry would be introduced). A *p*-halogen substituent in ring A will enhance such a mesomeric process in either case, as Adams has demonstrated for types (VIII), but *p*-halogen in ring B will have two effects, both



(VIII)



(IX)

decelerating to racemisation; the mesomeric engagement of the nitrogen electrons with ring B will tend to bring bonds *a* and *c* into a plane with ring B which is then in the position for maximum interference with the *o*-groups on ring A. Bond *a* will lose its partial double character and therefore will allow the groups attached to bonds *b* and *c* to take up positions of minimum interference of the attached groups, roughly in a plane at right angles to ring A and containing bond *a*. A methyl group, with its inductive effect in the opposite sense, in position X of (IX) will accelerate racemisation by releasing electrons for conjugation with ring A. It is relevant that the order of basic strengths of *p*-substituted anilines is Me > H > Cl > Br (Dippy, *Chem. Reviews*, 1939, **151**, 209).

It is assumed throughout this discussion that the demand on the nitrogen electrons by the benzoyl group is constant and can therefore be disregarded in drawing comparisons.

The acid (VI; X = OMe) was synthesised in order to correlate the polar effect of the methoxyl group with the rate of racemisation, low optical stability being expected: unfortunately, this compound could not be made to undergo second-order asymmetric transformation, and so was not obtained active. Quinidine activates it, but to so small an extent that accurate kinetic measurements could not be made.

Attempts to synthesise *N*-benzoy-2′ : 4′ : 6 : 6′-tetramethyldiphenylamine-2-carboxylic acid and *N*-benzoyl-2-bromo-6-methoxyl-2′ : 6′-dimethyldiphenylamine-4-carboxylic acid were abandoned owing to failure to find appropriate conditions for the Chapman rearrangement of the corresponding imidoates.

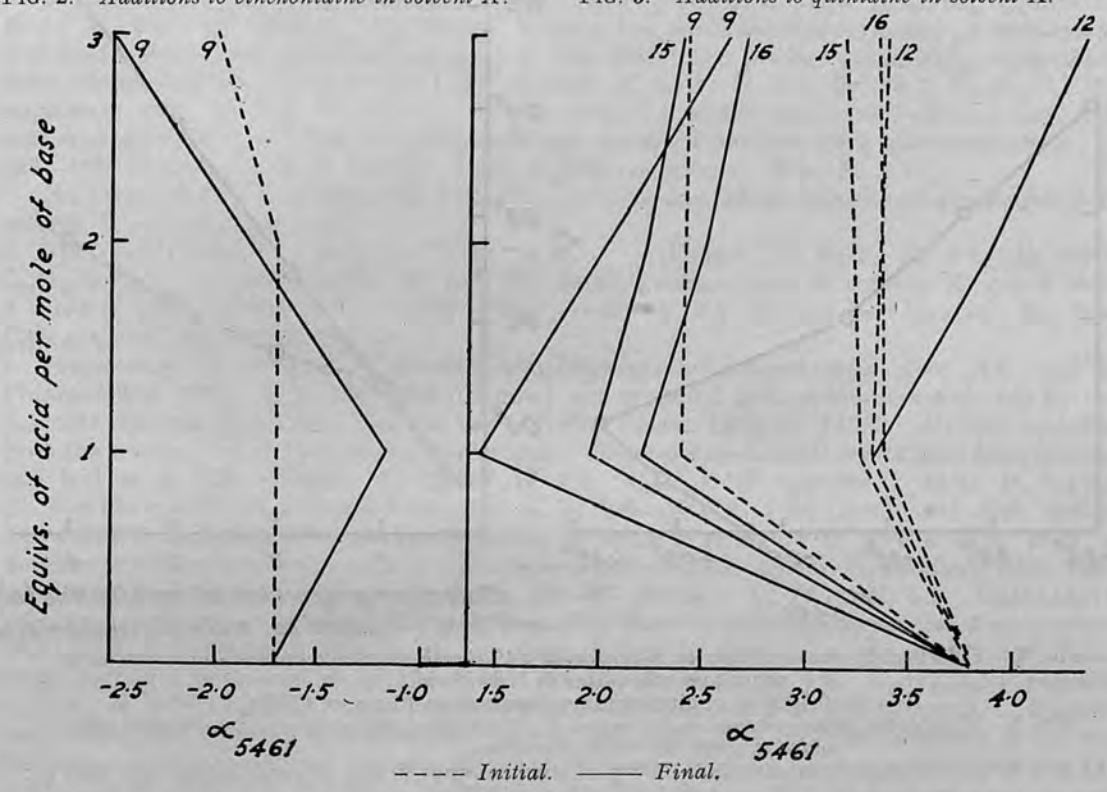
It is possible that molecules substituted in the 2-, 6-, and 2′- or 6′(or both)-positions (*e.g.*, IX) have a second centre of asymmetry, owing to restriction of rotation about bond *b* as well as about bond *a*. As the rate constants for the two racemisation processes are likely to be of a similar order of magnitude, the measured rate constant, $k = k_a + k_b$, can still be calculated according to the unimolecular law.

The second feature of particular interest in this series of compounds is the wide variation in extent and direction of first-order asymmetric transformation in presence of one

equivalent or less of an optically active alkaloid. This is demonstrated in the graphs Figs. 2 and 3.

Since this phenomenon was first discovered in 1938 (Jamison and Turner, *loc. cit.*) the field of application of an " asymmetric influence " has been extended from direct chemical combination to the operation of an asymmetric solvent (Buchanan and Graham, *loc. cit.*; Glazer, Harris, and Turner, *J.*, 1950, 1753; compare also Davies and Dwyer, *Trans. Faraday Soc.*, 1954, **50**, 24, on the operation of asymmetric influences in *aqueous* solutions). It now seems reasonable to suppose that, since an asymmetric solvent can, by some loose attachment, such as hydrogen bonding, activate a labile asymmetric molecule, a molecule of an alkaloid in solution can activate more than one equivalent of an optically labile active acid. This being so, it is not unlikely that the *second* molecule of

FIG. 2. *Additions to cinchonidine in solvent X.* FIG. 3. *Additions to quinidine in solvent* X.



acid " attached " to the alkaloid molecule should be subjected to influences which determine its configuration either in the same sense or in the opposite sense from the first, which is closely bound to it in salt formation.

We have made preliminary experiments with a view to examining the molecular aggregation of an alkaloid with an excess of acid dissolved in non-ionising solution :

(a) *Evidence from solubility.* Solubility determinations were made in dry chloroform (free from ethanol) at 20°; 10 c.c. dissolved 0·0230 g. (0·26 mol.) of *N*-benzoyl-4′-chlorodiphenylamine-2-carboxylic acid. 10 C.c. of chloroform containing 0·0811 g. of quinine (1·00 mol.) dissolved 0·2133 g. of acid (2·42 mol.). 10 C.c. of chloroform containing 0·0986 g. of brucine (1 mol.) dissolved 0·1622 g. of acid (1·84 mol.). It is not surprising that the quinine with its second weakly basic centre should be more effective than the brucine, but both alkaloids have a considerable influence in increasing the solubility of the acid.

(b) *Evidence from freezing-point depressions in bromoform.* Bromoform was chosen as cryoscopic solvent for our investigations because it was thought that the behaviour of the alkaloid and acids in that solvent would parallel closely the behaviour in chloroform, which we have used widely for stereochemical experiments. Accordingly an " addition curve "

was plotted, by adding successive quantities of *N*-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid (5) to a constant amount of cinchonidine dissolved in bromoform and reading the optical rotation of each solution : no mutarotation was detectable at room temperature. The result is plotted in Fig. 4. Next, cryoscopic measurements were made on a similar set of solutions : the results are plotted in Fig. 5, with freezing-point depressions for naphthalene as a standard. Difficulty was experienced with the bromoform, which could seldom be kept, even for a few hours after purification by vacuum-distillation and by freezing, without its beginning to darken. It was not satisfactory to add ethanol, as this would have masked the depression due to the added substances : solutions which darkened

FIG. 4.

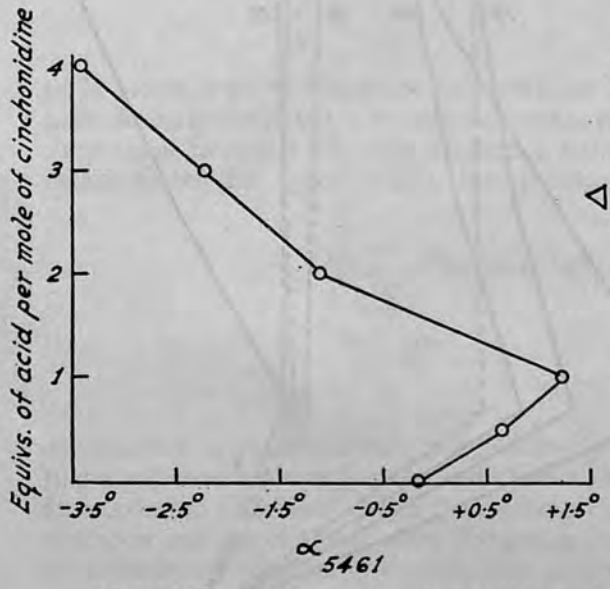


FIG. 5.

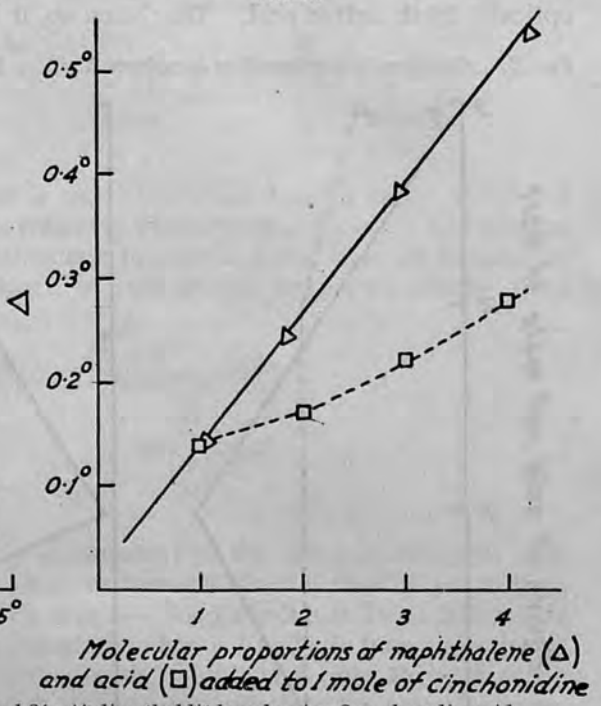


FIG. 4. *Polarimetric measurements in* N-*benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid added to cinchonidine in bromoform.*
($l = 2$; 0·1000 g. of cinchonidine dissolved in 15 c.c. of $CHBr_3$.)

FIG. 5. *Cryoscopic measurements on* N-*benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid added to cinchonidine in bromoform.*
(At 15°, 15 c.c. of bromoform contain 0·1000 g. of cinchonidine; 1 mol. of naphthalene = 0·0435 g.; 1 mol. of acid = 0·1173 g.)

were immediately discarded. However, it was found that solutions did not darken once the cinchonidine was added, and therefore if this stage was reached quickly a satisfactory set of determinations could be made. It will be seen that the depression for two molecules of acid and one of cinchonidine is only slightly larger than that for one molecule of either, and that there is also evidence of very considerable molecular aggregation at four molecules of acid.

The precise nature of the cohesive forces in such large molecules is not certain. Hydrogen bonding is a possibility, or, as Maryott (*J. Res. Nat. Bur. Stand.*, 1948, **41**, 1) has pointed out, organic salts in non-polar solvents are entities with unusually large dipole moments held together by coulombic forces. Such structures would be prone to associate, and such association might well be to some extent stereospecific. It is noteworthy in this connection that the *extent* of mutarotation of mixtures of *N*-benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylic acid and quinidine (molecular ratio 2 : 1) in chloroform containing ethanol varies largely with the composition of the solvent.

Kaufman and Singleterry (*J. Phys. Chem.*, 1952, **56**, 604), by cryoscopic methods, have found a similar association of, among other substances, myristic acid and tri*iso*pentylamine

in benzene solution. They interpret their results as being due to the formation of a molecular complex between the amine and an acid dimer and the existence of equilibria of the types $N + A_2 \rightleftharpoons NA_2$ and $NA_2 + A_2 \rightleftharpoons NA_4$, N being the base and A the acid.

Experimental

The diphenylaminecarboxylic acids were prepared by the same general method (Jamison and Turner, *J.*, 1937, 1954; 1938, 1646; 1940, 264) involving the Chapman rearrangement (*J.*, 1929, 569) of corresponding imidoates.

Preparation of N-*Benzoyl*-2′ : 6-*dimethyldiphenylamine*-2-*carboxylic Acid* (7).—This acid was prepared as described by Jamison and Turner (*J.*, 1940, 264) and had m. p. 183—184°.

Preparation of N-*Benzoyl*-4 : 6-*dibromodiphenylamine*-2-*carboxylic Acid* (9).—(a) 4 : 6-*Dibromo*-2-*methoxycarbonylphenyl* N-*phenylbenzimidoale* crystallised from methanol in prisms, m. p. 102—103° (yield 86%) (Found : C, 51·4; H, 3·1; Br, 32·5. $C_{21}H_{15}O_3NBr_2$ requires C, 51·5; H, 3·3; Br, 32·6%). (b) *Methyl* N-*benzoyl*-4 : 6-*dibromodiphenylamine*-2-*carboxylate*. The imidic ester underwent rearrangement at 190—200°; the *product* (yield 80%) crystallised from methanol in prisms, m. p. 134—135° (Found : C, 51·3; H, 4·0; Br, 32·7. $C_{21}H_{15}O_3NBr_2$ requires C, 51·5; H, 3·3; Br, 32·6%). (c) N-*Benzoyl*-4 : 6-*dibromodiphenyl-amine*-2-*carboxylic acid* crystallised in a solvated form from ethanol, but from benzene gave microcrystals, m. p. 189—190° (Found : C, 50·9; H, 2·9. $C_{20}H_{13}O_3NBr_2$ requires C, 50·5; H, 2·7%).

No mutarotation was observed with the (±)-acid and either brucine or cinchonidine in solvent X at acid : base ratio 1 : 1.

The *cinchonidine* (+)-*acid* salt (Table 2, p.) (Found : C, 61·2; H, 4·6; Br, 19·5. $C_{39}H_{35}Br_2O_4N_3$ requires C, 60·9; H, 4·6; Br, 20·8%) mutarotated in solvent X, $c = 0{\cdot}7600$, k 0·193 at 27·3°, 0·096 at 20·7°, 0·060 at 16·7°, 0·029 at 10·8° [Found for (+)-*acid* : Br, 32·9. $C_{20}H_{13}O_3NBr_2$ requires 33·6%].

Preparation of N-*Benzoyl*-2′-*fluoro*-6-*methyldiphenylamine*-2-*carboxylic Acid* (11).—(*a*) *o*-Fluoroaniline (77%; b. p. 104—106°/56 mm.) was prepared from *o*-fluorobenzoic acid by the Schmidt reaction (Minor and Van der Werf, *J. Org. Chem.*, 1952, **17**, 1425). Air was excluded from the reaction vessel by a stream of nitrogen. *Benzo*-o-*fluoroanilide* crystallised from ethanol and had m. p. 113° (Found : C, 72·25; H, 5·1. $C_{13}H_{10}ONF$ requires C, 72·2; H, 5·1%). (*b*) *N*-*o*-Fluorophenylbenzimidoyl chloride, b. p. 196—200°/27 mm., condensed with methyl 2-hydroxy-3-methylbenzoate in the presence of sodium ethoxide to give a 61% yield of 2-*methoxycarbonyl*-6-*methylphenyl* N-o-*fluorophenylbenzimidoate* which crystallised from light petroleum (b. p. 40—60°) in prisms, m. p. 58—60° (Found : C, 72·7; H, 4·2. $C_{22}H_{18}O_3NF$ requires C, 72·7; H, 5·0%). (*c*) *Methyl* N-*benzoyl*-2′-*fluoro*-6-*methyldiphenylamine*-2-*carboxylate*. The imidoate isomerised at 275° to give an 81% yield of *diphenylamine ester*, which crystallised from methanol in prisms, m. p. 104—106° (Found : C, 72·5; H, 4·8. $C_{22}H_{18}O_3NF$ requires C, 72·7; H, 5·0%). (*d*) N-*Benzoyl*-2′-*fluoro*-6-*methyldiphenylamine*-2-*carboxylic acid*. The ester was hydrolysed with aqueous alcoholic sodium hydroxide, and the acid dissolved in sodium hydrogen carbonate solution, reprecipitated, washed, and dried by azeotropic distillation of the last traces of water with benzene; repeated crystallisation from acetone–benzene gave an *acid* of constant m. p. 187—188° (Found : C, 72·8; H, 4·0. $C_{21}H_{16}O_3NF$ requires C, 72·2; H, 4·6%). Decomposition of the *brucine* (−)-*acid* salt (Found : C, 71·0; H, 6·2. $C_{44}H_{42}O_7N_3F$ requires C, 71·0; H, 5·7%) gave the (−)-acid.

Preparation of N-*Benzoyl*-2′-*chloro*-4′ : 6-*dimethyldiphenylamine*-2-*carboxylic Acid* (12).—(a) 2-*Methoxycarbonyl*-6-*methylphenyl* N-2′-*chloro*-4′-*methylphenylbenzimidoate*. Equimolecular amounts of methyl 2-hydroxy-3-methylbenzoate and *N*-2-chloro-4-methylphenylbenzimidoyl chloride were condensed in the presence of sodium ethoxide. The resulting *imidoate* crystallised from methanol in prisms, m. p. 113—114° (Found : C, 69·1; H, 5·3. $C_{23}H_{20}O_3NCl$ requires C, 70·1; H, 5·1%). (b) *Methyl* N-*benzoyl*-2′-*chloro*-4′ : 6-*dimethyldiphenylamine*-2-*carboxylate* was prepared by rearrangement of the imidoate at 285—290°; it crystallised from methanol in prisms, m. p. 187—188° (79% yield) (Found : C, 70·3; H, 5·0. $C_{23}H_{20}O_3NCl$ requires C, 70·1; H, 5·1%). (c) N-*Benzoyl*-2′-*chloro*-4′ : 6-*dimethyldiphenylamine*-2-*carboxylic acid* was purified through solution in dilute sodium hydrogen carbonate, and recrystallisation from benzene and then from benzene–acetone; it had m. p. 210—211° (Found : C, 69·6; H, 4·7; Cl, 8·9. $C_{22}H_{18}O_3NCl$ requires C, 69·6; H, 4·8; Cl, 9·3%). Decomposition of the *brucine* (−)-*acid* salt (Found : C, 69·7; H, 5·7. $C_{46}H_{46}O_7N_3Cl$ requires C, 69·8; H, 5·3%) gave the (−)-acid.

Preparation of N-*Benzoyl*-2′-*chloro*-6-*methyldiphenylamine*-2-*carboxylic Acid* (13).—This acid

was prepared as described by Jamison and Turner (*J.*, 1940, 264). It crystallised from acetone in slender needles, m. p. 197°.

Preparation of N-*Benzoyl*-2′-*bromo*-6-*methyldiphenylamine*-2-*carboxylic Acid* (14).—(a) 2-*Methoxycarbonyl*-6-*methylphenyl* N-o-*bromophenylbenzimidoate* crystallised from methanol in prisms, m. p. 100—102° (Found: C, 62·7; H, 4·5. $C_{22}H_{18}O_3NBr$ requires C, 62·4; H, 4·3%). (b) The imidoate isomerised at 280°, giving *methyl* N-*benzoyl*-2′-*bromo*-6-*methyldiphenylamine*-2-*carboxylate*, which crystallised from ethanol in prisms, m. p. 191° (80% yield) (Found: C, 63·1; H, 4·3. $C_{22}H_{18}O_3NBr$ requires C, 62·4; H, 4·3%). (c) N-*Benzoyl*-2′-*bromo*-6-*methyldiphenylamine*-2-*carboxylic acid* was crystallised from ethanol and then from benzene and had m. p. 198—199° which varied with the rate of heating (Found: C, 61·9; H, 4·1. $C_{21}H_{16}O_3NBr$ requires C, 61·4; H, 3·9%). The brucine salt of the (−)-acid mutarotated in solvent X at 20·0° from −4·63° to −0·30° in 31 min. (*c*, 0·8000).

Preparaton of N-*Benzoyl*-2′ : 4′-*dichloro*-6-*methyldiphenylamine*-2-*carboxylic Acid* (15).—(a) 2-*Methoxycarbonyl*-6-*methylphenyl* N-(2 : 4-*dichlorophenyl*)*benzimidoate* crystallised from methanol in prisms, m. p. 74—76°, in 69% yield (Found: C, 63·5; H, 4·2. $C_{22}H_{17}O_3NCl_2$ requires C, 63·8; H, 4·1%). (b) *Methyl* N-*benzoyl*-2′ : 4′-*dichloro*-6-*methyldiphenylamine*-2-*carboxylate*. The imidoate underwent Chapman's rearrangement at 285—290° (70% yield); the *product* crystallised from methanol in prisms, m. p. 131—133° (Found: C, 63·25; H, 4·15. $C_{22}H_{17}O_3NCl_2$ requires C, 63·8; H, 4·1%). (c) N-*Benzoyl*-2′ : 4′-*dichloro*-6-*methyldiphenylamine*-2-*carboxylic acid* was purified through its sodium salt, washed with hot water, and crystallised from benzene–acetone; it had m. p. 201—202° (Found: Cl, 17·2. $C_{21}H_{15}O_3NCl_2$ requires Cl, 17·7%). Decomposition of the brucine (−)-acid salt gave the (−)-acid.

Preparation of N-*Benzoyl*-4′-*bromo*-2′-*chloro*-6-*methyldiphenylamine*-2-*carboxylic Acid* (16).—(a) 2-*Methoxycarbonyl*-6-*methylphenyl* N-(4-*bromo*-2-*chlorophenyl*)*benzimidoate* crystallised from ethanol in prisms, m. p. 87—88° (Found: C, 56·9; H, 3·7. $C_{22}H_{17}O_3NBrCl$ requires C, 57·6; H, 3·7%). (b) *Methyl* N-*benzoyl*-4′-*bromo*-2′-*chloro*-6-*methyldiphenylamine*-2-*carboxylate*. Rearrangement of the benzimidoate at 275° gave the *diphenylamine* ester in 83% yield, as prisms, m. p. 138° (Found: C, 57·7; H, 3·8. $C_{22}H_{17}O_3NBrCl$ requires C, 57·6; H, 3·7%). (c) N-*Benzoyl*-4′-*bromo*-2′-*chloro*-6-*methyldiphenylamine*-2-*carboxylic acid*. The ester was hydrolysed by aqueous alcoholic sodium hydroxide; the *acid*, after purification through the sodium salt and crystallisation from benzene–acetone, had m. p. 186—187°, varying with the rate of heating (Found: mixed halogen, 25·3. $C_{21}H_{15}O_3NBrCl$ requires mixed halogen, 25·9%). Decomposition of the *brucine* (−)-*acid* salt (Found: C, 61·3; H, 5·2. $C_{44}H_{41}O_7N_3BrCl$ requires C, 61·6; H, 4·8%) gave the (−)-acid.

Preparation of N-*Benzoyl*-2′-*chloro*-4′-*methoxy*-6-*methyldiphenylamine*-2-*carboxylic Acid*.—(*a*) *N*-(2-Chloro-4-methoxyphenyl)benzimidoyl chloride (crude) was condensed with methyl 2-hydroxy-3-methylbenzoate to give 2-*methoxycarbonyl*-6-*methylphenyl* N-(2-*chloro*-4-*methoxyphenyl*)*benzimidoate*, prisms (from methanol), m. p. 94—95° (Found: C, 66·8; H, 4·5. $C_{23}H_{20}O_4NCl$ requires C, 67·4; H, 4·9%). (*b*) The imidoate underwent rearrangement at 285° (0·5 hr.) to give 82% yield of *methyl* N-*benzoyl*-2′-*chloro*-4′-*methoxy*-6-*methyldiphenylamine*-2-*carboxylate*, prisms (from methanol), m. p. 124—125° (Found: C, 67·6; H, 4·9. $C_{23}H_{20}O_4NCl$ requires C, 67·4; H, 4·9%). (*c*) Hydrolysis of this *ester* with the calculated quantity of aqueous-alcoholic sodium hydroxide gave N-*benzoyl*-2′-*chloro*-4′-*methoxy*-6-*methyldiphenylamine*-2-*carboxylic acid* which crystallised from benzene–acetone and had m. p. 214—215° (Found: C, 66·8; H, 4·65. $C_{22}H_{18}O_4NCl$ requires C, 66·6; H, 4·6%). This acid did not undergo second-order asymmetric transformation with brucine in a wide range of solvents.

Attempted Preparation of 2′ : 4′ : 6 : 6′-*Tetramethyldiphenylamine*-2-*carboxylic Acid*.—(*a*) *N*-(2 : 4 : 6-Trimethylphenyl)benzimidoyl chloride (b. p. 192—195°/15 mm.) was condensed with methyl 2-hydroxy-3-methylbenzoate to give 2-*methoxycarbonyl*-6-*methylphenyl* N-(2 : 4 : 6-*trimethylphenyl*)*benzimidoate*, as prisms, m. p. 83—85°, from methanol (Found: C, 77·3; H, 6·6. $C_{24}H_{23}O_3N$ requires C, 76·8; H, 5·9). Attempts to cause isomerisation of this to the corresponding diphenylamine derivative resulted either in recovery of the original material or in a tar.

Attempted Preparation of N-*Benzoyl*-2-*bromo*-6-*methoxy*-2′ : 6′-*dimethyldiphenylamine*-4-*carboxylic Acid*.—(*a*) *Methyl* 3-*bromo*-4-*hydroxy*-5-*methoxybenzoate*, m. p. 155—156°, was prepared from the acid by Fischer–Speier esterification (Found: C, 41·95; H, 3·7. $C_9H_9O_4Br$ requires C, 41·4; H, 3·5%). Condensation with *N*-(2 : 4-dimethylphenyl)benzimidoyl chloride gave 2-*bromo*-6-*methoxy*-4-*methoxycarbonylphenyl* N-(2 : 6-*dimethylphenyl*)*benzimidoate* (61%), m. p. 162—164° (Found: C, 61·9; H, 4·8. $C_{24}H_{22}O_4NBr$ requires C, 61·5; H, 4·7%). Attempts to induce the Chapman rearrangement failed; tars were obtained.

Polarimetric Measurements.—These were carried out in a 2-dm. jacketed tube, thermo-

statically controlled; λ_{5461} was used throughout; rate constants are in terms of natural logarithms and min.$^{-1}$.

"*Solvent X*."—"B.P." chloroform was washed, dried, and distilled, and 2·5% by volume of ethanol was added.

Anhydrous Brucine.—See Turner, *J.*, 1951, 842.

Anhydrous Quinidine.—Quinidine crystallised from benzene was dried in a vacuum at 100° over phosphoric oxide: it had $[\alpha]^{20}_{5461}$ +301·1° in solvent X (*c*, 0·8000).

Chloroform for polarimetric experiments was washed free from ethanol and dried.

TABLE 2.

(±)-Acid	Alkaloid	Solvent *	Salt crystallising	Yield (%)	Acid obtained from salt
7	Brucine	$COMe_2$–Pet	B–(−)-Acid	87	(−)
9	Cinchonidine	$COMe_2$–Et_2O	B–(+)-Acid	86	(+)
11	Brucine	$COMe_2$	B–(−)-Acid	90	(−)
12	Brucine	EtOH–Et_2O	B–(−)-Acid	92	(−)
14	Brucine	,,	B–(−)-Acid	91	(−)
15	Brucine	$COMe_2$–Pet	B–(−)-Acid	87	(−)
16	Brucine	,,	B–(−)-Acid	83	(−)

* Pet. = light petroleum (b. p. 40—60°).

TABLE 3. *Racemisation of optically active acids* (*c*, 0·4000; *temp.*, 20°).

Acid	Initial reading: α	Initial reading: Time after dissoln. (min.)	Solvent	*k*	Limits of *k*	
7	−0·23°	3·5	X	0·57	0·53	0·61
9	+0·42	1·85	$CHCl_3$	0·70	0·67	0·73
11	−0·28	1·3	$CHCl_3$	0·18	0·16	0·22
	−2·41	2·52	X	0·21	0·205	0·21
12	−2·74	3·35	X	0·17	0·165	0·17
14	−2·91	2·45	X	0·115	0·11	0·12
15	−2·27	3·95	X	0·092	0·0905	0·094
16	−2·57	3·05	X	0·086	0·084	0·088

TABLE 4. *First-order asymmetric transformations.*

Solvent X; temp., 20·0°; brucine, *c* = 0·7880; cinchonidine, *c* = 0·5880; quinidine, *c* = 0·6480, unless marked * when *c* = 0·8100; (+)-nor-ψ-ephedrine, *c* = 0·5000.

(±)-Acid	Mols. acid per mol. base	Alkaloid ‡	Time (min.) of initial reading after mixing	Initial reading	Final reading
6 †	3	(+)-Nor-ψ-ephedrine	0·8	+0·04°	+0·70°
7	1	Quinidine	1·8	+3·29	+2·73
7	2	,,	3·1	+2·96	+2·82
9	1	,,	4·65	+2·33	+1·41
9	2	,,	3·4	+2·19	+2·02
9	1	Cinchonidine	2·85	−1·68	−1·23
9	2	,,	4·87	−1·78	−1·91
11	1	Quinidine	2·05	+2·83	+1·52
11 *	2	,,	0·8	+2·10	+1·31
12 *	2	,,	1·1	+2·72	+2·94
12	3	,,	2·55	+3·95	+4·35
12	1	Brucine	2·4	−0·40	−0·04
12	2	,,	2·5	−0·35	−0·17
13	1	Quinidine	2·5	+3·34	+2·35
13	2	,,	2·5	+3·10	+2·64
14	1	,,	3·05	+3·80	+3·01
14 *	2	,,	0·07	+2·73	+2·40
15	1	,,	2·85	+3·27	+2·00
15 *	2	,,	1·0	+2·38	+1·67
15	3	,,	3·4	+2·81	+2·44
15	1	Brucine	3·15	−0·43	−0·06
15	2	,,	2·0	−0·24	−0·07
16	1	Quinidine	2·15	+3·39	+2·25
16 *	2	,,	0·8	+2·50	+1·89
16	3	,,	3·2	+3·05	+2·74
16	1	Brucine	3·2	−0·43	−0·05
16	2	,,	3·15	−0·19	−0·07

† Solvent $CHCl_3$ in this case.

TABLE 5. *Variation of extent of first-order asymmetric transformation of* N-*benzoyl*-2′-*chloro*-6-*methyldiphenylamine*-2-*carboxylic acid with quinidine* (2 : 1) *in* $CHCl_3$–EtOH *at* 20°.

(25 C.c. of solution contain 0·1620 g. of quinidine and 0·3657 g. of acid.)

Ethanol (%) in chloroform	Time of first reading after dissoln. (min.)	First reading	Final reading	Extent of mutarotation (α_0 by extrapolation $- \alpha_\infty$)
0·0	4·06	+3·05°	+2·90°	0·26°
1·0	2·65	3·02	2·78	0·43
2·5	2·5	3·10	2·64	1·09
3·2	4·2	2·91	2·58	0·87
6·0	2·6	3·23	2·73	0·87
9·1	3·34	3·26	2·79	0·87
17·0	4·00	3·35	3·00	0·75
30·0	4·1	3·49	3·20	0·59
50·0	3·66	3·62	3·42	0·32
100·0	3·73	1·84	1·84	0·0

Second-order Asymmetric Transformations.—(±)-Acid and alkaloid were used in equimolecular proportions dissolved separately and then mixed; crystallisation took place at room temperature or higher: chilling was avoided as it would slow down the partial inversion of the diastereoisomers in solution.

Results are in Table 2. The number of the acid refers to Table 1.

The active acids were obtained by grinding the salts with cold, anhydrous formic acid, and filtering the solutions from any undissolved particles of salt directly into dilute hydrochloric acid and ice. The precipitated acids were washed with water and dried in a vacuum.

For details of other kinetic results see Tables 3—5.

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THE EFFECT OF TEMPERATURE UPON THE EQUILIBRIUM BETWEEN PARTIALLY LABILE DIASTEREOISOMERS. PART I. QUINIDINE SALTS IN CHLOROFORM SOLUTION

BY

MARGARET M. HARRIS

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The Effect of Temperature upon the Equilibrium between Partially Labile Diastereoisomers. Part I. Quinidine Salts in Chloroform Solution.

By MARGARET M. HARRIS.

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When quinidine and one molecular proportion of an optically labile acid, *N*-benzoyl-6-methyldiphenylamine-2-carboxylic acid (III; R = Me; R′ = R″ = R‴ = H) are dissolved together in chloroform the solution shows a wide variation of optical rotation with temperature. This has been proved to be due to variation in the position of the equilibrium (+)-Acid,Quinidine $\rightleftharpoons$ (−)-Acid,Quinidine with temperature. Several other acids show similar behaviour, in some cases with, and in some without, detectable mutarotation.

THE salts formed between an optically labile acid (±)-R·CO_2H and one form of an optically stable base (+)-B are diastereoisomeric and in suitable circumstances will be in equilibrium, (+)-R·CO_2H,(+)-B $\rightleftharpoons$ (−)-R·CO_2H,(+)-B. The composition of the equilibrium mixture would be expected to be dependent upon temperature, a dependence which would show itself in a change of optical rotation when the equilibrated solution is viewed successively at different temperatures [Ingram (*J.*, 1950, 2318) reports such a case for the optically stable (+)-camphor-10-sulphonic acid with the optically stable base 10-*m*-aminobenzylideneanthrone].

In the series of substituted *N*-benzoyldiphenylaminecarboxylic acids, suitable members of which are known to be optically active and optically labile (Jamison and Turner, *J.*, 1938, 1646; 1940, 264; Harris, Potter, and Turner, *J.*, 1955, 145), it seems reasonable to assume that salt formation between one molecular proportion of quinidine and one of acid is virtually complete because (*a*) addition of further acid causes a *sharp backward* turn of the curve in which equivalents of acid per equivalent of base are plotted against rotation (*e.g.*, Fig. 1) and (*b*) the freezing-point depression for one mol. of acid and one mol. of base (in this case cinchonidine) dissolved together in the comparable solvent bromoform is equal to that for one mol. of naphthalene (Harris, Potter, and Turner, *loc. cit.*).

The optical rotation of certain single substances, alone or in solution, having only one centre of asymmetry is known to vary with temperature (see, for example, Kauzmann, Walter, and Eyring, *Chem. Rev.*, 1940, **26**, 373) and it would be necessary to be aware of any changes of rotation of this nature before attributing an observed change to shifting of equilibrium between members of a diastereoisomeric pair. This can be done in three ways. First, the base and an acid which is incapable of optical activity or is optically stable can be taken as a standard of comparison; it should resemble chemically the acid to be investigated as closely as possible: Ingram (*loc. cit.*) used a similar test in an examination of the large change in rotation with temperature of 10-*m*-[(−)-menthoxyacetamido]benzylideneanthrone in chloroform solution; 9-*m*-[(−)-menthoxyacetamido]benzylidenefluorene and (−)-menthoxyacetanilide showed rotations with a much smaller dependence on temperature. Ingram suggested that the large change in rotation was due to the variation in equilibrium composition of the two diastereoisomeric (−)-menthoxyacetyl derivatives of the 10-*m*-aminobenzylideneanthrone: no other manifestation of optical activity could be found, although the structure of the molecule is such that optical activity should be observable if the degree of restriction of rotation is sufficient. 10-*m*-[(−)-Menthoxyacetamido]benzylideneanthrone is particularly interesting in this connection, because the two optically active centres of the diastereoisomers are in chemical combination and not subject to the uncertainties of salt formation. Secondly, if the optical stability permits, the rotation of

the partially racemic salt, (±)-R·CO_2H,(+)-B, can be found at various temperatures and compared with the rotations of the equilibrium mixtures. Thirdly, removal of the base from the mixtures equilibrated at different temperatures should leave specimens of acid which are in varying degrees optically active. All of these methods are exemplified in the present work.

The *N*-benzoyldiphenylaminecarboxylic acids provide excellent material for this investigation because the series includes examples of a large variation in optical stability, from *N*-benzoyldiphenylamine-2-carboxylic acid itself, which is so unstable optically as to show no mutarotation in chloroform in presence of alkaloids even at −33°, to *N*-benzoyl-4′-bromo-2′-chloro-6-methyldiphenylamine-2-carboxylic acid which is sufficiently stable to be isolated in an active form (Harris, Potter, and Turner, *loc. cit.*).

Throughout the present work quinidine has been used as the optically stable, salt-forming base in chloroform solution and the effect of change of temperature upon the equilibrium rotation of its salts with a variety of acids has been ascertained. The concentration of quinidine was constant in all the determinations and equimolecular proportions of the acids were used; the results, which are directly comparable with each other, are plotted in Fig. 2. It will be seen that the acids fall into two main categories, those in which the rotation alters only slightly with temperature and those in which it changes to a substantial degree. The former are the optically inactive acids, benzoic acid, *N*-benzoyldiphenylamine-4-carboxylic acid (I), and *N*-benzenesulphonyl-*N*-phenylglycine (II); the latter are the *N*-benzoyldiphenylamine-2-carboxylic acids (III) and *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (IV) (Mills and Elliott, *J.*, 1928, 1291), all of known low optical stability. *N*-Benzoyldiphenylamine-2-carboxylic acid has never been demonstrated to be optically active by " classical " methods, but its activity is inferred from the effect of excess of the (±)-acid on its cinchonidine and (+)-nor-ψ-ephedrine salts (Jamison and Turner, *loc. cit.*, 1938).

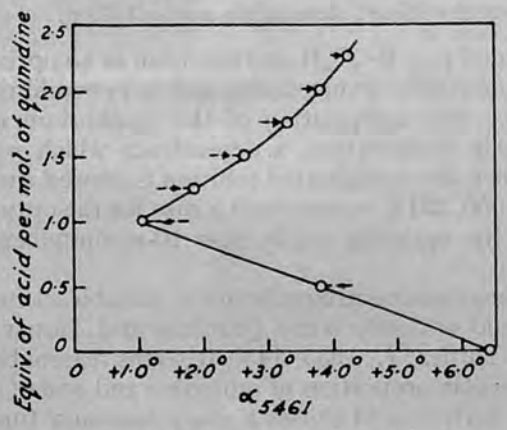
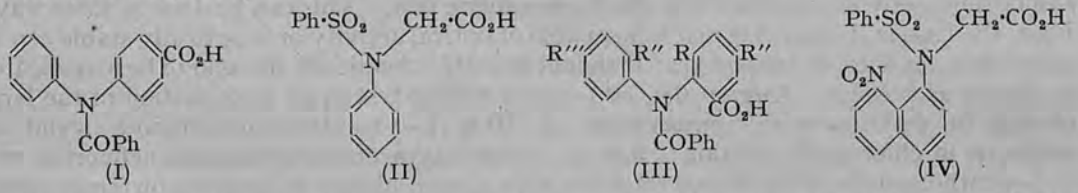


FIG. 1. *Addition of* N-*benzoyl*-6-*methyldiphenylamine*-2-*carboxylic acid to quinidine in chloroform at* 20°.

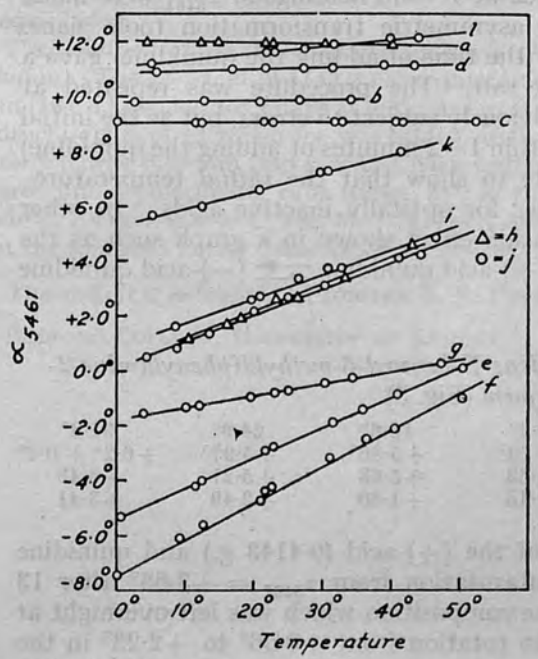
(*The broken lines represent the observed range of mutarotation.*)



The values of the rotations shown in Fig. 2 are in many cases (*h*, *i*, *j*, *k*, *l*) the final values of observed mutarotations (first-order asymmetric transformations); there is little doubt that the same is true of curves *e*, *f*, and *g* but that the mutarotations are too fast for observation at the temperatures employed. *N*-Benzoyl-6-methyldiphenylamine-2-carboxylic acid (III; R = Me, R′ = R″ = R‴ = H) was selected for more detailed study in this connection.

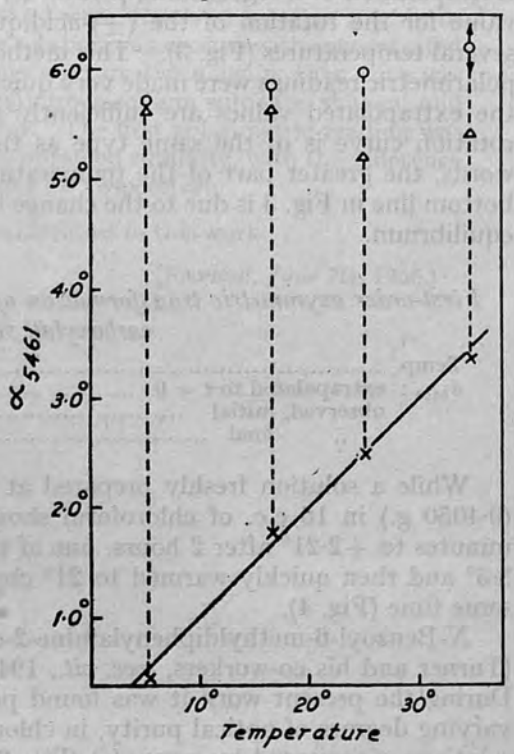
To a solution of 0·4143 g. of this acid dissolved in 16 c.c. of chloroform at temperature *T*° was added 0·4050 g. (1 mol.) of quinidine. The resulting solution was quickly poured

FIG. 2. *Rotation of quinidine salts in chloroform.*



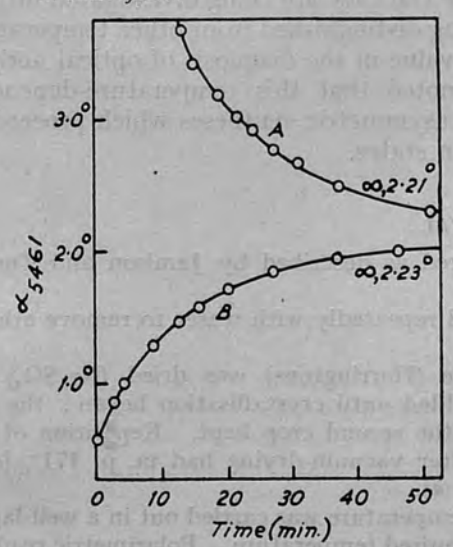
(*a*) *Quinidine alone.*
(*b*) *Benzoic acid.*
(*c*) (I).
(*d*) (II).
(*e*) (III; R = R′ = R″ = R‴ = H).
(*f*) (III; R = R′ = H, R″ = R‴ = Cl).
(*g*) (III; R = R′ = H, R″ = R‴ = Me).
(*h*) (III; R = R′ = Cl, R″ = R‴ = H).
(*i*) (III; R = R′ = Br, R″ = R‴ = H).
(*j*) (III; R = Me, R′ = R″ = R‴ = H).
(*k*) (III; R = Me, R′ = H, R″ = R‴ = Cl).
(*l*) (IV).

FIG. 3. *First-order asymmetric transformation of* N*-benzoyl-*6*-methyldiphenylamine-*2*-carboxylic acid with quinidine in chloroform at various temperatures.*



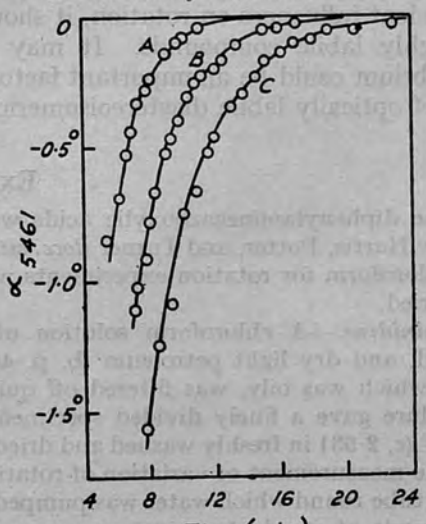
○ *Extrapolated to* $t = 0$.
× *Observed final point.*
△ *Observed first point.*

FIG. 4. N*-Benzoyl-*6*-methyldiphenylamine-*2*-carboxylic acid with quinidine in chloroform.*



A, First-order asymmetric transformation at 20·2°.
B, Equilibration at 21° *of a solution which had been allowed to stand at* 3·5°.

FIG. 5. *Racemisation of* (−)-N*-benzoyl-*6*-methyldiphenylamine-*2*-carboxylic acid in chloroform at* 21°.



From asymmetric transformation at (*A*) 45°, (*B*) 21°, (*C*) 0·8°.

into a polarimeter tube thermostatically controlled at $T°$ and readings of α_{5461} were made at recorded intervals of time while first-order asymmetric transformation took place. Extrapolation of a logarithmic plot to zero time (the time of adding the quinidine) gave a value for the rotation of the (±)-acid,quinidine salt. The procedure was repeated at several temperatures (Fig. 3). This method is obviously subject to errors, but as the initial polarimetric readings were made very quickly (within 1—2 minutes of adding the quinidine) the extrapolated values are sufficiently accurate to show that the *initial* temperature–rotation curve is of the same type as the curves for optically inactive acids. In other words, the greater part of the temperature–rotation effect shown in a graph such as the bottom line in Fig. 3 is due to the change in the (+)-acid,quinidine $\rightleftharpoons$ (−)-acid,quinidine equilibrium.

First-order asymmetric transformation of quinidine N-*benzoyl*-6-*methyldiphenylamine*-2-*carboxylate in chloroform* (Fig. 3).

Temp.		5·2°	16·6°	24·9°	34·6°
α_{5461} :	extrapolated to $t = 0$	+5·70°	+5·86°	+5·97°	+6·2° ± 0·2°
	observed, initial	+5·63	+5·63	+5·21	+5·43
	,, final	+0·45	+1·80	+2·49	+3·41

While a solution freshly prepared at 20·2° of the (±)-acid (0·4143 g.) and quinidine (0·4050 g.) in 16 c.c. of chloroform showed mutarotation from $\alpha_{5461} = +3·68°$ after 13 minutes to +2·21° after 2 hours, one of the same composition which was left overnight at 3·5° and then quickly warmed to 21° changed in rotation from +0·56° to +2·23° in the same time (Fig. 4).

N-Benzoyl-6-methyldiphenylamine-2-carboxylic acid although previously described (Turner and his co-workers, *locc. cit.*, 1940, 1955) had not been obtained optically active. During the present work it was found possible to obtain it in the lævorotatory form, in varying degrees of optical purity, in chloroform solution. When three of the equilibrated solutions represented by curve (*j*) (Fig. 2) were decomposed by ice-cold hydrochloric acid, specimens of active acid were obtained which racemised rapidly in chloroform at 21° (Fig. 5).

Lesslie, Turner, and Winton (*J.*, 1941, 257) observed a large variation with temperature in the rotation of quinine diphenate in ethanol–chloroform solution. It seems probable that they were observing a shifting equilibrium here, analogous to those recorded in Fig. 2.

Although the temperature–rotation work now reported has all been carried out with quinidine as the optically active agent, preliminary experiments show that cinchonidine and cinchonine behave to a certain extent similarly and they are being investigated further. If the phenomenon is general and is capable of being distinguished from other temperature-dependent influences on rotation, it should be of value in the diagnosis of optical activity in highly labile compounds. It may also be noted that this temperature-dependent equilibrium could be an important factor in some asymmetric syntheses which proceed by way of optically labile diastereoisomeric transition states.

Experimental

The diphenylaminecarboxylic acids were prepared as described by Jamison and Turner, and by Harris, Potter, and Turner (*locc. cit.*).

Chloroform for rotation experiments was washed repeatedly with water to remove ethanol and dried.

Quinidine.—A chloroform solution of quinidine (Harringtons) was dried (Na_2SO_4) and filtered, and dry light petroleum (b. p. 40—60°) added until crystallisation began : the first crop, which was oily, was filtered off quickly and the second crop kept. Repetition of this procedure gave a finely divided specimen which after vacuum-drying had m. p. 171°, $[\alpha]_{5461}^{21·5}$ +236° (*c*, 2·531 in freshly washed and dried chloroform).

The measurement of variation of rotation with temperature was carried out in a well-lagged 2-dm. tube round which water was pumped at the required temperature. Polarimetric readings were made at steady temperatures, mounting from point to point up the range shown in the graphs; then the solution was cooled, readings being taken at descending intervals of temperature down to the lowest point recorded, and finally returning to the original temperature ;

this procedure guards against any irreversible change which might be mistaken for a shift of equilibrium.

Preparation of (−)-N-Benzoyl-6-methyldiphenylamine-2-carboxylic Acid in Chloroform Solution.—The (±)-acid (0·4143 g.) and quinidine (0·4050 g.) were dissolved together in chloroform (16 c.c.) and left for 2 days at 0·8°; at $t = 0$ min. the solution was washed with concentrated hydrochloric acid to which ice was added, with the same mixture twice again, then with ice-water; it was then run into a cooled flask containing anhydrous sodium sulphate, shaken, and filtered into a polarimeter tube (temp. 21°) at $t = 5{\cdot}5$ min. The first polarimetric reading was made at 7·8 min. (curve *C*, Fig. 5). Curves *A* and *B* were obtained similarly, with the difference that the solutions before decomposition were left at 45° and 21° respectively.

The author is indebted to Professor E. E. Turner for his interest in this work.

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FIRST-ORDER ASYMMETRIC TRANSFORMATION ARISING FROM SOLVATION

BY

J. GLAZER,

MARGARET M. HARRIS,

AND

E. E. TURNER

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354. *First-order Asymmetric Transformation arising from Solvation.*

By J. Glazer, Margaret M. Harris, and E. E. Turner.

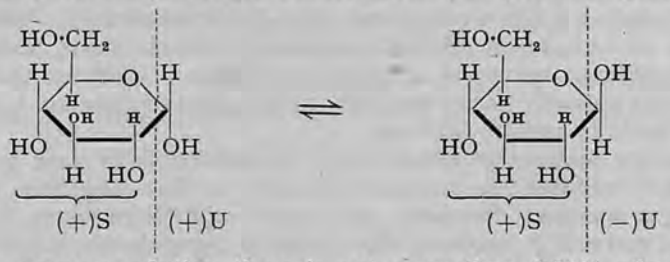
It is shown that first-order asymmetric transformation can occur as a result of solvation between an optically unstable compound and an optically active, optically stable solvent. (Unless solvation extends to solid phases, second-order asymmetric transformation cannot occur.)

The potential optical activity of 8-nitro-*N*-benzenesulphonyl-*N*-(2-hydroxyethyl)-1-naphthylamine has been demonstrated by its optical activation in ethyl (+)-tartrate.

A substance, the molecule of which contains both a centre of stable optical activity [(+)S] and one of unstable optical activity [(+)U or (−)U], when dissolved in a suitable solvent, may be represented as an equilibrium between two diastereoisomerides:

$$(+)S(+)U \rightleftharpoons (+)S(-)U$$

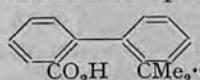
An excellent example of such a substance is the mutarotating sugar glucose, which in aqueous solution undergoes first-order asymmetric transformation to give an equilibrium mixture of



α- and β-glucose [in aqueous solution there is not more than 0·02% of open-chain glucose (Cantor and Peniston, *J. Amer. Chem. Soc.*, 1940, **62**, 2113)]. The substance may be a salt, *e.g.*, of an alkaloid with an optically labile acid; it must then be dissolved in a solvent such as chloroform in which the diastereoisomeric salts exist as such, and not in one such as water in which ionisation or solvolysis predominates. Solvation of one or both of the diastereoisomers would not prevent the establishment of an equilibrium between them, provided that other circumstances were favourable.

During the last ten years we have given much consideration to the possibility of detecting a stereochemical equilibrium which is of the general type outlined but arises from the union such as has often been shown to exist between solute and solvent. There would be no formal covalent or ionic bond between S and U, but a looser association such as might be provided by the hydrogen bridge. The ideal experiment, as we conceived it, was to dissolve an optically labile substance in an optically stable solvent with which it might be expected to associate and to look for the mutarotation which should accompany equilibration (if the optical instability and the extent of disturbance of the equilibrium were in the observable range).

Since carboxylic acids are known normally to form dimeric molecules, it is probable that analogous inter-acid complexes are formed between two acids, so that an obvious type of experiment would be to dissolve an optically unstable acid (U) in an optically stable, resolved acid as solvent (S). So far this has not been found practicable, and we have had recourse to the less satisfactory experimental procedure of dissolving in chloroform two acids, one optically active and optically stable, the other racemic and optically labile. As substance (−)S we selected (−)-*sec.*-octyl hydrogen phthalate and as substance U racemic 2′-(2″-hydroxy-2″-propyl)diphenyl-2-carboxylic acid (I), previous examination (Jamison and Turner, *J.*, 1942, 437) of which had shown it to possess a manageable degree of configurational stability. A mixture of the two acids in chloroform solution did in fact exhibit slow mutarotation well outside experimental error. Moreover, the solubility of the acids appeared to increase with time in contact with the solvent, an indication that some definite change was in progress before rotational examination was possible (cf. Hudson and Janovsky, *J. Amer. Chem. Soc.*, 1917, **39**, 1013).



(I.)

It thus appeared that first-order asymmetric transformation was being witnessed. On attempting to nullify the effect of (−)S by adding (+)-*sec.*-octyl hydrogen phthalate, an inconclusive result was obtained, for although the total rotation changed at once, it then remained constant. Earlier experience had shown that the mutarotation which was observed was almost certainly not caused by lactonisation of the unstable acid, all attempts to obtain an active lactone from an active acid having failed.

N-Benzoyl-2 : 4-dimethyldiphenylamine-2′-carboxylic acid, an acid of very low configurational stability and known (Jamison and Turner, *J.*, 1938, 1646) to give a very characteristic " addition curve " with (+)-nor-ψ-ephedrine in chloroform solution, was selected as suitable material (U) for observing any change in rotation accompanying its addition, in increasing quantities, to a chloroform solution of (−)-*sec.*-octyl hydrogen phthalate. Such a solution had α −5·88° ($l = 2$). Addition of 0·16, 0·32, and 0·48 equivalent of the unstable acid caused an immediate change in rotation of the solution to −6·11°, −6·33°, and −6·48° respectively. Solubility limits prevented further additions, but one interpretation of the results obtained would be that hydrogen-bridged diastereoisomerides are here behaving similarly to salt-diastereoisomerides.

Failing, for the moment, a sufficient supply of an optically stable, active liquid acid with good solvent properties, attention was turned to other types of optically active solvent. The experimental difficulties in attempting to observe first-order asymmetric transformations in such a solvent are considerable. First, very few such solvents are available in any quantity. Secondly, any mutarotation observed in them is likely to be small in comparison with the rotation of the solvent, so that small differences have to be examined very critically; the temperature effect on the pure solvent is often very large and needs close control. Thirdly, observation of mutarotation of a solution of an originally racemic substance in an optically active solvent could not safely be referred to optical activation in absence of evidence that total precipitation of the solute gave an optically active product. Also, if an equilibrium is under investigation, such precipitation must be rapidly achieved.

An optically active hydroxylic solvent which is obtainable in some quantity is ethyl (+) tartrate, particularly suitable for our purpose since, as has long been known, it possesses powerful solvating properties. Moreover, it is readily soluble in water, in which most of the other experimental material is insoluble, thus permitting rapid removal of solvent and " freezing " of the equilibria in the erstwhile racemic solutes, and subsequent polarimetric examination of the solid material obtained.

The first experiments with ethyl (+)-tartrate were conducted using two acids which had previously been shown to possess the desired order of configurational stability (Jamison and Turner, *J.*, 1940, 264). *N*-Benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylic acid could not be dissolved to a sufficient extent in cold ethyl (+)-tartrate, so that direct observation of mutarotation was impossible : but at about 90° a solution was readily obtained and was cooled and kept overnight. The total dissolved solid was recovered by addition of an excess of water : in chloroform solution it was lævorotatory (observed α_{5461} −0·06° 1·4 minutes after being wetted). The next day the solution was inactive. *N*-Benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylic acid was even less soluble than the chloro-methyl-acid in ethyl tartrate, but a similar general procedure led to a feebly lævorotatory acid (observed α_{5461} −0·04°, becoming zero overnight).

The acids of this series being so sparingly soluble in ethyl (+)-tartrate, the corresponding methyl esters were examined. A solution of methyl *N*-benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylate was made by shaking the finely-ground ester (5 g.) with ethyl (+)-tartrate (150 c.c.) at room temperature for 15 minutes. The suspension was filtered. Part (*A*) of the solution was placed in a temperature-controlled polarimeter tube (25°), part (*B*) at once treated with excess of water, and part (*C*) kept at 25° in a thermostat. The observed rotation of *A* changed during 18 hours from +20·51° to +20·47° ($\lambda = 5461$; $l = 2$), indicating a slight optical activation producing (−)-ester–(+)-solvent. The ester similarly obtained from *B* had $[\alpha]^{25}_{5461}$ −2·8° in AnalaR chloroform solution (*c*, 0·900) 2·4 minutes after being wetted with solvent. Racemisation followed first-order kinetics. Solution *C* was treated with water at the time that solution *A* attained constant rotation. The water-precipitated ester had $[\alpha]^{25}_{5461}$ −3·5° in AnalaR chloroform solution (*c*, 3·100) 3 minutes after being wetted with solvent. Racemisation followed first-order kinetics (period of half-racemisation, 6 minutes). From this experiment it was concluded that optical activation of the racemic ester by the solvent was well advanced before polarimetric readings were started. This was confirmed by further experiments.

A solution of 1·00 g. of racemic ester in ethyl (+)-tartrate (40 c.c.) was made at 80° and

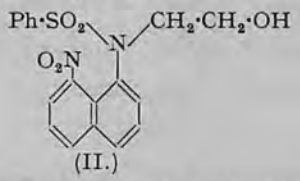
rapidly cooled to 25°, at which temperature it was kept for 30 minutes. Total precipitation by water gave an ester (0·98 g.) with $[\alpha]^{25}_{5461}$ −3·4° in AnalaR chloroform solution 2·5 minutes after being wetted with solvent (period of half-racemisation, 9 minutes).

It would be expected that solvation and therefore optical activation would be less pronounced at 80° than at 25°. A solution of the ester (1·00 g.) in ethyl tartrate (40 c.c.) was made at 80° and kept at this temperature for 5 minutes and then at once treated with water. The recovered ester (0·95 g.) had $[\alpha]^{25}_{5461}$ −1·6° in chloroform solution 2·1 minutes after being wetted. Racemisation followed first-order kinetics.

In other experiments in which the ester was allowed to crystallise from a cooling solution in ethyl tartrate, various crops were obtained and were examined polarimetrically. The majority were optically inactive, but on one occasion a crop having a slight lævorotation was obtained. These crystallisation processes are, of course, not second-order asymmetric transformations, since the two possible solid phases are not diastereoisomeric in type : crystallisation could to some extent, however, be governed by chance inoculation.

A solution of methyl *N*-benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylate in ethyl tartrate was kept for a day at room temperature and the total tribromo-ester recovered by addition of water. A chloroform solution of the ester had no optical activity. Conceivably the considerable steric factors in this ester prevent the union with the solvent which is possible with the less-hindered chloro-methyl-ester.

Hydrogen-bridging between alcohols offered a further field for investigation. In order to obtain an alcohol which might be expected to possess suitable configurational stability and other desirable features, 8-*nitro*-N-*benzenesulphonyl*-N-(2-*hydroxyethyl*)-1-*naphthylamine* (II) was synthesised by condensing 2-chloroethyl alcohol with 8-nitro-*N*-benzenesulphonyl-1-naphthylamide in presence of alcoholic alkali. The alcohol (II) has a number of advantageous properties : it is primary and therefore might be expected to form hydrogen-bridged structures



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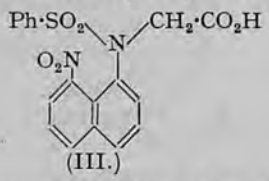

(III.)

with hydroxylic solvents and it should have a configurational stability of an order similar to that of Mills and Elliott's acid (III) (*J.*, 1928, 1291). A solution of the alcohol (II) in ethyl (+)-tartrate was made at 80°, cooled, kept at 25° for 12 hours, and then treated with excess of water. The recovered alcohol had $[\alpha]^{25}_{5780}$ +9·1° in AnalaR chloroform solution 2·5 minutes after being wetted with solvent. Racemisation followed first-order kinetics (half-life, 27 minutes). Repetition of the experiment gave a product with $[\alpha]^{25}_{5780}$ +8·7° (half-life, 25 minutes). This is the only recorded example of a racemic substance, in which the optical activity has been *first* demonstrated by asymmetric solvent action.

A series of experiments was performed with alcohol (II) in other solvents, including *ethylene glycol* (−)-*menthyl ether*, an optically active primary alcohol specially synthesised for the purpose by reducing (−)-menthoxyacetic acid with ethereal lithium aluminium hydride. A solution of the alcohol (II) in the ether was kept for 2 days at room temperature and then treated with excess of light petroleum. The precipitated alcohol was, however, optically inactive.

Numerous experiments were conducted in order to detect possible optical activation of the alcohol (II) in solution in mixtures of chloroform with (+)- and (−)-*sec.*-octyl alcohols, (−)-menthyl glycollate and (+)-citronellol. In each case the solution was kept in a temperature-controlled polarimeter tube. No mutarotational changes exceeding the probable experimental error were observed and total precipitation of the solute was not practicable.

Experimental.

Mutarotation of a Mixture of 2′-(2″-Hydroxy-2″-propyl)diphenyl-2-carboxylic Acid and (−)-sec.-*Octyl Hydrogen Phthalate in Chloroform Solution.*—(*a*) (−)-*sec.*-Octyl hydrogen phthalate (0·927 g.), dissolved in 7 c.c. of chloroform (B.P.), had $a^{26\cdot9}_{5461}$ −6·01° (l = 1; thermostatically controlled jacketted tube; temp. uncorr.). To this solution was added 0·853 g. of (±)-2″-(2′-hydroxy-2″-propyl)diphenyl-2-carboxylic acid, $a^{26\cdot9}_{5461}$ changing to −6·00°. This value changed during 5 days to −5·68°.

(*b*) The experiment was repeated at thermostat temperature [25·0° (corr.)], with use, as solvent, of B.P. chloroform washed with concentrated sulphuric acid to remove alcohol and subsequently washed with water and dried. (−)-*sec.*-Octyl hydrogen phthalate in this solvent had $a^{25\cdot0}_{5461}$ −6·18° (l = 1). The (±)-acid dissolved slowly during 21 hours, at the end of which $a^{25\cdot0}_{5461}$ was −6·05°, changing during the ensuing 3 days to −5·90°.

(*c*) 2·0 G. of (−)-*sec.*-octyl hydrogen phthalate were dissolved in 10 c.c. of chloroform (washed and dried as before) and mixed with a solution of 1·0 g. of the (±)-acid in 10 c.c. of chloroform. Approx. 12 c.c. of this solution were used in the polarimeter tube, the solution having $\alpha_{5461}^{25\cdot0}$ −10·03° ($l = 2$). The rotation changed during 4 days to −9·47° and thereafter remained static. Addition of 0·80 g. of (+)-*sec.*-octyl hydrogen phthalate to this solution resulted in an immediate change in $\alpha_{5461}^{25\cdot0}$ to −2·17°, which was constant for 3 days.

N-*Benzoyl*-2′ : 4′-*dimethyldiphenylamine*-2-*carboxylic Acid with* (−)-sec.-*Octyl Hydrogen Phthalate in Chloroform.*—1·00 G. of (−)-*sec.*-octyl hydrogen phthalate, dissolved in 7·5 c.c. of chloroform, had $\alpha_{5461}^{26\cdot9}$ −5·88° ($l = 1$; thermostatically controlled tube; temp. uncorr.). To this solution was added 0·2 g. of (±)-*N*-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid; the rotation, measured within 2 minutes of mixing, was $\alpha_{5461}^{26\cdot9}$ −6·11° and was unchanged after 24 hours. After this time a further 0·2 g. of (±)-acid was added; $\alpha_{5461}^{26\cdot9}$ changed to −6·33°. A further 0·2 g. caused a change to 6·48°. No mutarotation was observed in any case.

Methyl N-*Benzoyl*-4 : 6-*dichlorodiphenylamine*-2-*carboxylate with* (−)-sec.-*Octyl Alcohol in Chloroform.*—5 C.c. of (−)-*sec.*-octyl alcohol, mixed with 2 c.c. of chloroform, had $\alpha_{5461}^{25\cdot0}$ −5·82° ($l = 1$; thermostatically controlled tube). 5 G. of (±)-methyl *N*-benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylate were added; $\alpha_{5461}^{25\cdot0}$, read within 5 minutes, was −5·69°. This value was unchanged in 24 hours.

Ethyl (+)-*Tartrate.*—It was found unsatisfactory to attempt to obtain the ester by vacuum-distillation of commercial samples. The ester was prepared by the method of Lowry and Cutter (*J.*, 1922, **121**, 532). It had $\alpha_{5461}^{17\cdot3}$ +18·03° in a 2-dm. tube.

Ethylene Glycol (−)-*Menthyl Ether.*—A solution of (−)-menthoxyacetic acid (114 g.) in ether (300 c.c.) was gradually added to lithium aluminium hydride (20 g.) in ether (400 c.c.). Water and then dilute sulphuric acid were added and the ethereal layer was separated, dried, and distilled. The reduction product was distilled at 84—103°/3·5 mm. Redistillation gave 59 g., b. p. 100—101°/3·5 mm. (Found : C, 71·8; H, 12·3. $C_{12}H_{24}O_2$ requires C, 71·9; H, 12·1%). The *ether* had d_{25}^{25} 0·9371 and $\alpha_{5461}^{17\cdot5}$ −18·29° in a 2-dm. tube.

N-8-*Nitrobenzenesulphonyl*-N-(2-*hydroxyethyl*)-1-*naphthylamine.*—8-Nitro-*N*-benzenesulphonyl-1-naphthylamine (14 g.) was dissolved, by warming, in 70% aqueous ethyl alcohol (150 c.c.) containing potassium hydroxide (6 g.). 2-Chloroethyl alcohol (9 g.) was added and the mixture was heated in a pressure-bottle at 100° for 7 hours. The *product*, some of which had crystallised, was precipitated with water and filtered (13·8 g.). It crystallised from ethyl alcohol (charcoal) in pale yellow needles, m. p. 138—139° (74%) (Found : C, 58·5; H, 4·4; N, 7·3; S, 8·7. $C_{18}H_{16}O_5N_2S$ requires C, 58·1; H, 4·3; N, 7·5; S, 8·6%). The molecular weight was determined cryoscopically in ethylene dibromide :

Concn.	Mol. wt. found.	Association, %.
$8\cdot7 \times 10^{-3}$ g.-mol./l.	386	7·2
$12\cdot6 \times 10^{-3}$,, ,, ...	419	22·4

The *acetate* was obtained from the above alcohol in almost quantitative yield by warming it with an excess of acetic anhydride in pyridine for 3 minutes. The mixture was cooled and poured into dilute hydrochloric acid; the gummy product eventually solidified and then crystallised from ethanol in cream-coloured, rhombic needles, m. p. 143—144° (Found : C, 58·3; H, 4·45; N, 6·7. $C_{20}H_{18}O_6N_2S$ requires C, 57·95; H, 4·4; N, 6·8%).

(−)-Menthyl glycollate, prepared by the esterification of glycollic acid with (−)-menthol, was purified by steam-distillation and crystallisation from aqueous alcohol. It had m. p. 88—89° and $[\alpha]_{5461}^{25}$ −97·3°, $[\alpha]_{5780}^{25}$ −86·0° (*c*, 25·06 in chloroform; $l = 2$).

(+)-Citronellol was kindly supplied by Messrs. A. Boake, Roberts and Co., Ltd. It was distilled before use and had b. p. 216°/745 mm., $[\alpha]_{5461}^{25}$ = +5·22°, $[\alpha]_{5780}^{25}$ = +4·57°.

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D. Sc. 1958

UNSTABLE OPTICAL ACTIVITY IN THE *N*-BENZOYL-DIPHENYLAMINE-2-CARBOXYLIC ACID SERIES.

PART V

BY

JEAN W. BROOKS

MARGARET M. HARRIS

AND

K. E. HOWLETT

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456. *Unstable Optical Activity in the* N-*Benzoyldiphenylamine-2-carboxylic Acid Series. Part V.**

By Jean W. Brooks, Margaret M. Harris, and K. E. Howlett.

The optical stabilities of some substituted *N*-benzoyldiphenylamine-2-carboxylic acids are discussed from the viewpoint of newly determined racemisation velocity constants and of E, A, and $\Delta S^{\ddagger}$ values.

Much evidence [1,2,3] supports a certain sequence of optical stabilities in the series of substituted *N*-benzoyldiphenylaminecarboxylic acids (I) † which owe their optical activity to restriction of rotation about one, or perhaps two, carbon–nitrogen bonds. The velocity constants for racemisation of six such acids (the more optically stable) were measured at 20° in chloroform containing 2·5% of ethanol; [3] we now report the measurement of racemisation velocity constants for four more acids (the less optically stable) under identical conditions of solvent and concentration, so that the optical stabilities of ten acids closely related structurally can now be strictly compared at one temperature (Table 1).

Table 1. *Racemisation velocity constants k (min.*$^{-1}$*) for substituted* N-*benzoyldiphenylamine-2-carboxylic acids, A at* 20° *in* $CHCl_3$–2·5% EtOH *and B at* 9·9° *in* $CHCl_3$.

Acid	4	6	2′	4′	k (*A*)	k (*B*)	$t_{\frac{1}{2}}$ (*A*) (min.)	$t_{\frac{1}{2}}$ (*B*) (min.)
(I*a*)	—	Me	—	—	0·72	0·146	0·96	4·7
(I*b*)	—	Me	Me	—	0·61	—	1·1	—
(I*c*)	Br	Br	—	—	0·50	—	1·4	—
(I*d*)	Br	Br	—	Br	0·44	—	1·6	—
(I*e*)	—	Me	F	—	0·214 (0·209 *)	—	3·2	—
(I*f*)	—	Me	Cl	Me	0·166 (0·167 *)	—	4·2	—
(I*g*)	—	Me	Cl	—	0·147 *	—	4·7	—
(I*h*)	—	Me	Br	—	0·119 (0·115 *)	—	5·8	—
(I*i*)	—	Me	Cl	Cl	0·0929 *	—	7·5	—
(I*j*)	—	Me	Cl	Br	0·0862 *	—	8·0	—
(I*k*)	—	Me	—	Me	—	0·158	—	4·4

* See ref. 3.

These four acids, too unstable for resolution, were obtained optically active by crystallisation of alkaloidal salts in which a single diastereoisomer separated in approximately 100% yield (second-order asymmetric transformation). Yet another acid, *N*-benzoyl-6 : 4′-dimethyldiphenylamine-2-carboxylic acid (I*k*), could not be obtained active in this way as none of its alkaloidal salts crystallised. However, a chloroform solution of the (−)-acid was prepared by asymmetric transformation in solution (first-order) in presence of cinchonidine : the alkaloid was then removed by washing with hydrochloric acid, and the remaining chloroform solution washed, dried, and used immediately for determination of the racemisation rate. Thus a velocity constant in chloroform was obtained which could be compared with one, measured also under these enforced conditions, for *N*-benzoyl-6-methyldiphenylamine-2-carboxylic acid (I*a*). The predicted order of optical stabilities [3] has been upheld. Acid (I*a*) was not previously known as an optically active solid, although the active acid had been obtained in solution.

Racemisation velocity constants still form the most widely used criterion for comparing optical stabilities; in this work they provide a series of values which, in a roughly qualitative way, accords with predictions based on the bulk and inductive effects of groups substituted in a common skeleton. Any group added to the skeleton may change the racemisation rate in three ways : by direct electrical effects, by transmitted electrical effects, or, if it is suitably placed, sterically. It was at first somewhat surprising that there was so little difference between the velocity constants of racemisation of the 6-methyl-

* Parts I—IV, *J.*, 1938, 1646; 1940, 264; 1955, 145, 4152.

† *Correction* : In Part IV, formula (III) (p. 4153), the R which appears in position 4 should read R′.

and the 6 : 2′-dimethyl-acid (I*a*) and (I*b*). The experimental results could be explained, to some extent at least, if addition of the second (2′) methyl group in the 6 : 2′-dimethyl-acid (I*b*) had opposing influences on the optical stability : the bulk of the methyl group increasing it and the electron-releasing power decreasing it (see ref. 3). The 6 : 4′-dimethyl-acid (I*k*) was synthesised to test this hypothesis : here the bulk effect of the methyl group is removed from the sphere of hindrance but its electrical effect remains the same as in the 6 : 2′-dimethyl-acid (I*b*). Acid (I*k*) proved to be slightly but definitely *less* stable than the 6-monomethyl-acid (I*a*) at 9·9°; therefore the remote methyl group exercises an accelerating influence on the racemisation. It should be noted in comparison that the 2′-fluoro-6-methyl-acid (I*e*) is much more stable optically than the 6 : 2′-dimethyl-acid (I*b*) in spite of the fact that the van der Waals radii of the fluorine atom and the methyl group are respectively 1·35 and 2·05 Å ; [4] in the 2′-fluoro-6-methyl-acid (I*e*) both the steric and the electrical influences of the fluorine atom appear to be decelerating relative to hydrogen.

The Arrhenius parameters E and A have been measured [1, 5, 6] for the racemisation of a variety of compounds owing their optical activity to restriction of rotation. Comparisons between the values so determined have not been entirely satisfactory [7, 8] owing, partly, to the diversity of structure in the compounds concerned and also to the different solvents and other conditions used in determining the necessary velocity constants of racemisation. As a preliminary experimental approach, racemisation velocities have been measured over a range of temperatures and E, A, and the entropies of activation $\Delta S^{\ddagger}$ (Table 2) have been calculated for the five substituted acids, 6-methyl-, 4 : 6-dibromo-, 2′-fluoro-6-methyl-, 2′-chloro-6 : 4′-dimethyl-, and 2′-bromo-6-methyl- (I*a*, *c*, *e*, *f* and *h*), in chloroform containing 2·5% of ethanol; two other sets of determinations for the 4 : 6 : 4′-tribromo- (I*d*) and the 2′-chloro-6-methyl-acid (I*g*), were made in different solvents.

TABLE 2. *Velocity constants, Arrhenius parameters, and entropy factors for racemisation.*

Acid	10^2k (sec.$^{-1}$)	Temp.	E (kcal. mole^{-1})	A (sec.$^{-1}$)	$\Delta S^{\ddagger}$ (e.u.)
Solvent : Chloroform containing 2·5% of ethanol (by volume).					
(I*a*)	1·20	20·0°	16·2	$10^{10\cdot1}$	−14·1
	0·660	13·8			
	0·327	6·9			
	0·162	0·6			
(I*c*)	0·833	20·0	19·3	$10^{12\cdot0}$	− 4·1
	0·288	10·8			
	0·0858	1·0			
	0·0817	0·6			
(I*e*)	0·663	27·4	14·9	$10^{8\cdot6}$	−20·9
	0·357	20·0			
	0·109	6·9			
(I*f*)	0·654	29·8	15·7	$10^{9\cdot1}$	−18·6
	0·277	20·0			
	0·108	10·2			
	0·0410	0·7			
(I*h*)	0·601	32·0°	16·4	$10^{9\cdot5}$	−16·9
	0·562	31·8			
	0·198	20·0			
	0·0795	10·8			
	0·0274	0·6			
Solvent : Ethanol					
(I*d*)	0·448 [a]	17·7	18·7	$10^{12\cdot2}$	− 6·9
	0·185	9·5			
	0·0603	0·65			
Solvent : Chloroform containing 6·9% of ethanol (by volume).					
(I*g*)	0·483 [b]	25·4	16·6	$10^{9\cdot7}$	−15·4
	0·308	20·6			
	0·0738	6·3			

[a] See ref. 1. [b] Potter, Thesis, London, 1953.

The range of temperature employed in the determination of E is to a large extent dictated by the rapidity of racemisation at the higher temperatures and by the solubility (including the rate of dissolution) at the lower ones. Chloroform containing 2·5% of ethanol by volume has been the most generally useful solvent for the present series of acids.

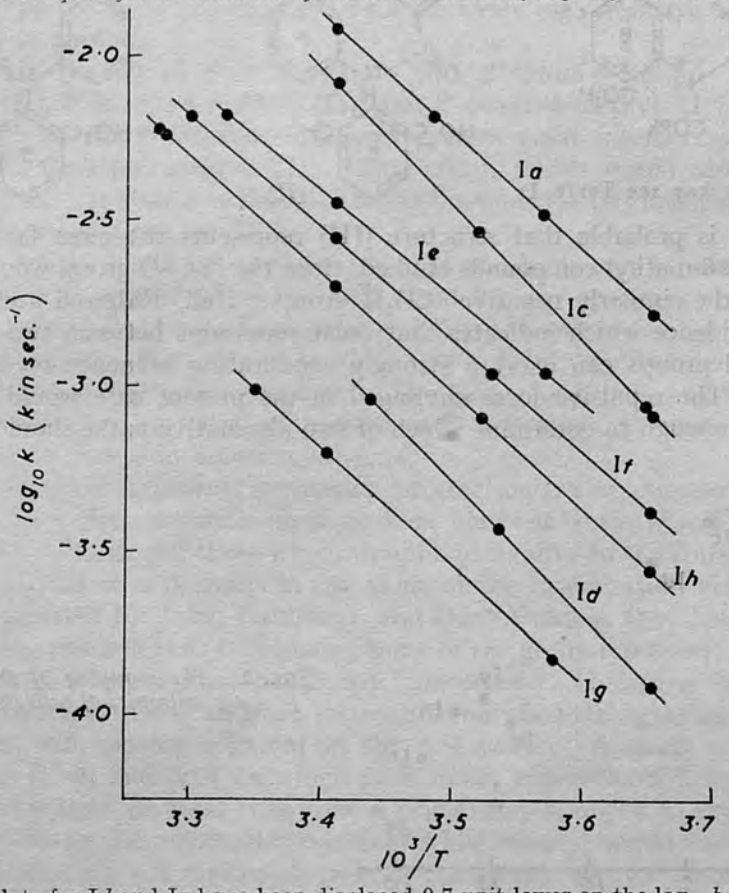
The racemisation velocity constants k are calculated from $k = (1/t) \ln (\alpha_0/\alpha_t)$; as there is no asymmetric influence present, a rate constant, measured for racemisation, is twice the rate constant for inversion of configuration, the physical process occurring on the

molecular scale. In Fig. 1 $\log_{10}k$ is plotted against the reciprocal of the absolute temperature : the relation is closely linear. $\Delta S^{\ddagger}$ is calculated from the formula (see Appendix)

$$k = \kappa e(\boldsymbol{k}T/\boldsymbol{h}) \exp (\Delta S^{\ddagger}/\boldsymbol{R} - E/\boldsymbol{R}T)$$

in which E is the experimentally determined energy of activation; the transmission coefficient κ has been assumed to be unity.

FIG. 1. *Arrhenius plots for racemisation of substituted* N*-benzoyldiphenylamine-2-carboxylic acids.*



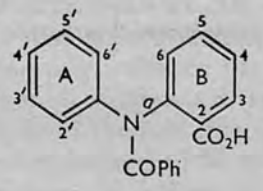
The plots for I*d* and I*g* have been displaced 0·7 unit lower on the $\log_{10} k$ scale.

It is immediately apparent that arguments based on racemisation velocity constants measured at one temperature may lead to different conclusions from those based on E values for racemisation. One can speak of either the 6-methyl- (I*a*) or the 2′-fluoro-6-methyl-acid (I*e*), for example, as the more optically stable of the two according to which criterion is used.

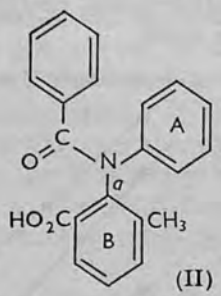
Scrutiny of the E, A, and $\Delta S^{\ddagger}$ values (Table 2) shows that the acids fall into two groups : (1) Those with a 6-methyl substituent have rate equations of racemisation whose energies of activation are 14·9—16·6 kcal. mole^{-1}, A factors $10^{8\cdot6}$—$10^{10\cdot1}$ sec.$^{-1}$, and entropies of activation −14·1 to −20·9 e.u. (2) Those with a 6-bromo-substituent have the values, respectively, 18·7 and 19·3 kcal. mole^{-1}, $10^{12\cdot0}$ and $10^{12\cdot2}$, −4·1 and −6·9 e.u. The grouping of these figures is compatible with the view that among the various acids so far examined it is the resistance to relative rotation about bond (*a*) [see (I)] which is responsible for optical stability.

There are, of course, two paths by which a rotation about bond (*a*) might take place; the benzoyl group might pass the carboxylic acid group in position 2 (II) or, alternatively, it might pass the substituent in position 6 (III). If position 6 carries hydrogen only, the

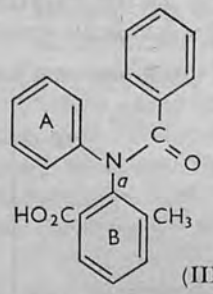
optical stability is very slight indeed and mutarotation is not detectable at room temperatures, even when ring A carries a chlorine atom or a methyl group in an *ortho*-position. [Interference with rotation will be less than appears in formulæ (II) and (III); for example the plane of ring A in the passing position probably lies roughly perpendicular to the plane



(I; for key see Table I)



(II)



(III)

of ring B.] It is probable that structure (III) represents the most favourable passing position for the 6-methyl compounds studied, since the >C=O group would, presumably, avoid passing the similarly negative $-CO_2H$ group: Hall, Ridgwell and Turner [9] have summarised evidence which indicates that polar repulsions between two suitably placed carboxylic acid groups can exert a strongly accelerating influence on a diphenyl-type racemisation. The repulsive force envisaged in the present case would be smaller, but probably large enough to determine which of two alternative paths should be followed.

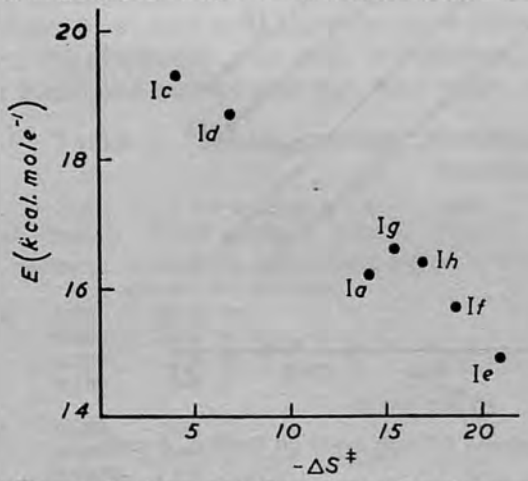


FIG. 2. *The grouping of the energies and entropies of activation.*

The variations of $\Delta S^{\ddagger}$ appear to make a positive contribution to the interpretation of of the optical stabilities. First, the grouping (Fig. 2) suggests a difference between the 4 : 6-di- and the 4 : 6 : 4′-tri-bromo-acids (I*c*) and (I*d*) and the others; reference to models, and the high values of the energies of activation, support the possibility that the alternative passing position [represented by (II), but with bromine in place of methyl] might be used in these two cases. Secondly, as Cagle and Eyring [7] have pointed out in discussing the optical stability of another type of compound showing restriction of rotation, high negative values of $\Delta S^{\ddagger}$ would be expected when the transition state for racemisation is an improbable arrangement of the molecule. Foster, Cope, and Daniels,[10] studying the rearrangement of *α-cyclo*hex-1-enylallylmalononitrile to 2-allyl*cyclo*hexylidenemalononitrile by following the change in refractive index, found a fairly large negative entropy of activation and attributed it to the complicated and improbable shape which the molecule must attain for the rearrangement to take place. Models of the molecules now under discussion show that rings A and B not only must each take up favourable positions but their movements must also be synchronised for rotation about bond (*a*) to occur. Such synchronisation should be easier in the 6-methyl- (I*a*), 4 : 6-dibromo- (I*c*), and 4 : 6 : 4′-tribromo-

acids (I*d*) because ring A is both unsubstituted in the *ortho*-positions and axially symmetrical; the bromo-acids (I*c*) and (I*d*) have the small negative $\Delta S^{\ddagger}$ values already noted, while the methyl-acid (I*a*) has the smallest negative value of all the 6-methyl-acids so far investigated. An *ortho*-substituent in the ring A, *i.e.*, in the 2′-fluoro-, 2′-chloro-, and 2′-bromo-6-methyl-acids (I*e*, I*f*, I*h*, and I*g*), will, both by its bulk and by its polar attractions and repulsions, lower the number of ways of attaining the transition state and will cramp movement in it. Restriction of oscillation and rotation in the activated state would be expected to be accompanied by a relatively high negative value of $\Delta S^{\ddagger}$ and such is found to be the case.

Further, within the set of acids 6-methyl- (I*a*), 2′-fluoro-6-methyl- (I*e*), 2′-chloro-6 : 4′-dimethyl- (I*f*), 2′-bromo-6-methyl- (I*h*), and 2′-chloro-6-methyl- (I*g*), there may be additional rigidity of the transition state arising from polar interactions between the carbonyl and the 6-methyl groups (III). This effect, which would also enhance the negative value of $\Delta S^{\ddagger}$, is absent in the di- and tri-bromo-acids (I*c*) and (I*d*), which have much smaller negative values for $\Delta S^{\ddagger}$.

A possibility which should be considered is that of π-hydrogen bonding between the phenyl group and the methyl group [11] which could become operative if structure (II) represented the passing position. Comparison of the $\Delta S^{\ddagger}$ values for the 6-methyl- and the 2′-fluoro-6-methyl-acid (I*a*) and (I*e*), in which ring A of (I*a*) should be the better electron donor,[12] makes this possibility seem unlikely. The values for the di- and tri-bromo-acids (I*c*) and (I*d*) are too close for valid comparison with each other, particularly as they are derived from measurements in different solvents.

In the development of arguments concerning intramolecular attractions of the hydrogen-bonding type a clear differentiation must be kept between bonds which might stabilise the (+)- and the (−)-form and those which would add rigidity to the transition complex. The former would lead to a decrease in the value of the racemisation velocity constant in the manner indicated by Jaffé, Freedman, and Doak,[13] unless they held the molecule close to the passing position thus overcoming some of the group repulsion; this effect has already been noted where formal bonds are concerned.[6] Hydrogen bonding which operates in the transition state and not (or with diminished strength) in the two interconvertible forms will become apparent in the $\Delta S^{\ddagger}$ values. A study of the effect of solvent in $k_{\text{racem.}}$, E, A, and $\Delta S^{\ddagger}$, on which preliminary experiments have already been made, should throw light on this. Chloroform, for example, might be expected to allow the greater freedom for intramolecular bonding, while ethanol would compete with the substrate and break down internal bonds in both the normal and the transition states.

Experimental

All measurements of rotation, α_{5461}, were made in a 2-dm. jacketed tube thermostatically controlled. "Solvent X" is chloroform containing 2·5% of ethanol by volume.

N-*Benzoyl*-6 : 4′-*dimethyldiphenylamine*-2-*carboxylic Acid*.—This acid was prepared by the general method [14, 1, 2] involving the Chapman rearrangement [15] of the corresponding imidate. (a) 2-*Methoxycarbonyl*-6-*methylphenyl* N-4′-*methylphenylbenzimidate* was crystallised from ethanol, and had m. p. 100—101° (Found: C, 77·0; H, 6·0; N, 3·85. $C_{23}H_{21}O_3N$ requires C, 76·85; H, 5·9; N, 3·9%). (b) The imidate isomerised at 275° giving *methyl* N-*benzoyl*-6 : 4′-*dimethyldiphenylamine*-2-*carboxylate* which crystallised from methanol in prisms, m. p. 122° (70% yield) (Found: C, 76·3; H, 5·7; N, 3·7. $C_{23}H_{21}O_3N$ requires C, 76·85; H, 5·9; N, 3·9%). (c) N-*Benzoyl* 6 : 4′-*dimethyldiphenylamine*-2-*carboxylic acid*, crystallised from aqueous ethanol and dried (P_2O_5) in a vacuum, had m. p. 158—159° (yield 98%) (Found: C, 76·5; H, 5·53; N, 4·1. $C_{22}H_{19}O_3N$ requires C, 76·5; H, 5·56; N, 4·1).

(−)-N-*Benzoyl*-6 : 4′-*dimethyldiphenylamine*-2-*carboxylic Acid in Chloroform Solution by First-order Asymmetric Transformation in Presence of Cinchonidine*.—(±)-Acid (0·345 g., 0·01 mole) and cinchonidine (0·294 g., 0·01 mole) were dissolved in chloroform (25 c.c.) and set aside for 2 hr. At time $t = 0$ (min.) the solution was washed with ice-cold concentrated hydrochloric acid, then with ice–water, dried (Na_2SO_4), and filtered into a polarimeter tube

previously cooled to 9·9°. At time $t = 2{\cdot}80$ (min.) α was $-1{\cdot}61°$ and gradually fell to 0·0°; $k_{\text{racem.}} = 0{\cdot}158$. Repetition gave an identical value for k.

Brucine (−)-N-*Benzoyl*-6-*methyldiphenylamine*-2-*carboxylate*.—The (±)-acid (3·31 g., 0·1 mole) and anhydrous brucine (3·94 g., 0·1 mole) were each dissolved separately in 100 c.c. of hot acetone. The mixed solutions were evaporated to 75 c.c., light petroleum (b. p. 40—60°) was added until crystallisation started, and the whole kept warm while the salt [brucine (−)-acid] crystallised (yield ≈100%). Decomposition of this salt with cold, anhydrous formic acid, followed by precipitation by dilute hydrochloric acid, gave the (−)-acid [(1) α first observed $-1{\cdot}94°$ at 0·6°, solvent X, c 0·400, $[\alpha]^{0{\cdot}6°}$ $-243°$; (2) α first observed $-5{\cdot}11°$ at 20°, chloroform, c 1·324, $[\alpha]^{20°}$ $-193°$, half-life 0·96 min. at 20°].

Appendix

For a unimolecular reaction in the liquid phase $k = \kappa(\gamma^0/\gamma^\ddagger)(\boldsymbol{k}T/\boldsymbol{h})K^\ddagger$, where γ^0 and $\gamma^\ddagger$ are the activity coefficients for normal and activated reactant species respectively; $K^\ddagger = \exp(\Delta S^\ddagger/\boldsymbol{R} - \Delta H^\ddagger/\boldsymbol{R}T)$ is the expression for the modified equilibrium constant between normal and activated species.[16] If we assume that $\kappa = 1$ and that the activity coefficients are equal because the two species are so similar, and since $E = \boldsymbol{R}T^2(\mathrm{d}\log_e k/\mathrm{d}T)$ and $\mathrm{d}\log_e k/\mathrm{d}T = 1/T + \mathrm{d}\log_e K^\ddagger/\mathrm{d}T$,

$$E = \boldsymbol{R}T + \boldsymbol{R}T^2(\mathrm{d}\log_e K^\ddagger/\mathrm{d}T) = \boldsymbol{R}T + \Delta H^\ddagger - p\mathrm{d}v^\ddagger$$

where $\mathrm{d}v^\ddagger$ is the increase in volume accompanying activation. For our reactions $\mathrm{d}v^\ddagger = 0$, hence $\Delta H^\ddagger = E - \boldsymbol{R}T$ and $k = (e\boldsymbol{k}T/\boldsymbol{h})\exp(\Delta S^\ddagger/\boldsymbol{R} - E/\boldsymbol{R}T)$.

Cagle and Eyring [7] use the equation in the form $k = (\kappa\boldsymbol{k}T/\boldsymbol{h})\exp(\Delta S^\ddagger/\boldsymbol{R} - \Delta H^\ddagger/\boldsymbol{R}T)$. It is not uncommon for the experimentally determined value E to be used in place of $\Delta H^\ddagger$ in this form of the equation, an approximation which has sometimes led to confusion (see refs. 10 and 17) and which seems unnecessary in our calculations. If the approximation were used, all the $\Delta S^\ddagger$ values in Table 2 would be about two units less negative.

We thank the Department of Scientific and Industrial Research for a maintenance grant to one of us (J. W. B.).

Bedford College, University of London. [*Received, November 19th*, 1956.]

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D. Sc. 1958.

A REDETERMINATION OF THE RACEMISATION VELOCITIES OF 6-NITRO-, 4 : 6′-DINITRO-, AND 4 : 6 : 4′-TRINITRODIPHENIC ACID IN ALKALINE SOLUTION

BY
JEAN W. BROOKS
MARGARET M. HARRIS
AND
K. E. HOWLETT

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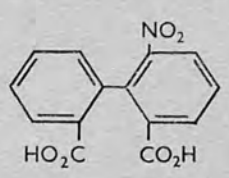
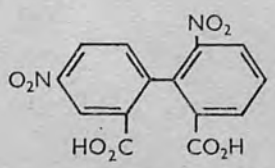
371. *A Redetermination of the Racemisation Velocities of 6-Nitro-, 4 : 6′-Dinitro-, and 4 : 6 : 4′-Trinitrodiphenic Acid in Alkaline Solution.*

By Jean W. Brooks, Margaret M. Harris, and K. E. Howlett.

The mode of operation of the nitro-group in influencing the optical stability of substituted diphenic acids is at present a matter of speculation.[1, 2, 3] Attempts to explain the effect of substituting further nitro-groups in the 4- and 4′-position in 6-nitrodiphenic acid (I) have so far been based upon the experimental work of Kuhn and Albrecht; [4] these authors



(I)



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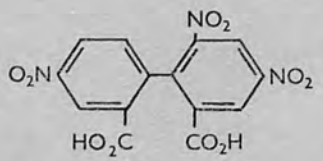

(III)

were the first to show that the decrease in optical activity of diphenyls obeys the first-order kinetic law. Their results are given in Table 1, together with the enthalpies ($\Delta H^{\ddagger}$) and entropies ($\Delta S^{\ddagger}$) of activation calculated by Cagle and Eyring [1] using Kuhn and Albrecht's data.

Table 1.

Acid	$\frac{1}{2{\cdot}303}k$ (min.$^{-1}$) in 2N-Na_2CO_3 [4]	E (kcal. mole^{-1}) [4]	$\Delta H^{\ddagger}$ [1]	$\Delta S^{\ddagger}$ [1]
(II)	0·018 at 98·2°; 0·0014 at 73·5°	26	25·7	−4·2
(III)	0·0060 at 98·6°; 0·00074 at 74·6°	22·4	21·2	−18·5

The racemisation of 6-nitrodiphenic acid (I) in 0·1N-sodium hydroxide was investigated by Adams and Hale [5] at one temperature only, presumably the boiling point of the solution. A half-life of 4·6 minutes was recorded.

We have now repeated the observation of the racemisation of these acids, in greater detail, in 2N-sodium carbonate (not sodium hydroxide [1, 5]) solution. Table 2 shows the first-order racemisation velocity constants and the parameters for the corresponding rate equations.

Table 2.

Acid	Temp.	10^4k (sec.$^{-1}$)	E (kcal. mole^{-1})	A (sec.$^{-1}$)	$\Delta S^{\ddagger}$ (e.u.)
(I)	87·6°	8·05	22·6	$10^{10\cdot6}$	−12·2
	80·6	4·24			
	67·55	1·26			
	57·0	0·435			
(II)	91·0	3·42	22·6	$10^{10\cdot1}$	−14·7
	83·4	1·69			
	74·4	0·769			
	70·4	0·515			
(III)	94·0	1·90	22·6	$10^{9\cdot7}$	−16·3
	84·6	0·85			
	82·0	0·66			
	72·4	0·275			

In calculating $\Delta S^{\ddagger}$ from the formula $k = \kappa e \frac{\boldsymbol{kT}}{\boldsymbol{h}} \exp(\Delta S^{\ddagger}/\boldsymbol{R} - E/\boldsymbol{RT})$ the value of the transmission coefficient κ is taken as unity in each case.

The marked increase in optical stability on addition of a further nitro-group in a *para*-position (where it can exercise neither a blocking nor a buttressing effect) is here shown to reside in the entropy-of-activation factor rather than in the activation energy of the racemisation process.

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THE SEPARATION OF DIASTEREOISOMERIDES BY SELECTIVE ADSORPTION ON OPTICALLY INACTIVE MATERIAL

BY

MARGARET M. JAMISON (HARRIS)

AND

E. E. TURNER

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125. *The Separation of Diastereosiomerides by Selective Adsorption on Optically Inactive Material.*

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

Diastereoisomerides should have different coefficients of adsorption on adsorbents devoid of stereo-orientation. It is shown that *l*-menthyl *d*- and *l*-mandelates are adsorbed selectively on alumina.

There are two ways in which the technique of the adsorption column could be used to separate the active forms of a racemic substance. The first (Karagunis and Coumoulos, *Praktika*, 1938, **13**, 414; *Nature*, 1938, **142**, 162; Henderson and Rule, J., 1939, 1568) consists in running a solution of the racemic mixture down a column of optically active adsorbent (quartz; lactose). In the second, which corresponds more closely to classical methods of resolution, the racemic substance would be converted into diastereoisomerides by combination with a second purely *d*- or *l*-compound, whereupon selective adsorption might be expected to take place on *non*-asymmetrical material, since the diastereoisomerides should have different coefficients of adsorption. Stoll and Hofmann (*Z. physiol. Chem.*, 1938, **251**, 155), apparently without theoretical justification, attempted to separate the two forms of *dl-iso*lyserg-*d*-β′-hydroxy*iso*propylamide, but the facts that they crystallised and inoculated their chromatographically separated fractions (opening up the possibility of resolution) and that their observed rotations were very small make this an unsatisfactory example for the demonstration of the important fundamental principle, apart from the fact that the constitution of lysergic acid is unknown.

In order to investigate the question we have taken the *l*-menthyl esters of *dl*-mandelic acid, which McKenzie (J., 1904, **85**, 378, 1249) was unable to separate by fractional crystallisation during a thorough search using a large variety of solvents. Alumina (Birlec) was used as adsorption material, and all solvents were purified finally by running them down a column of this material.

The following specific rotations of optically pure compounds were determined in ethyl alcohol for reference :

l-Menthyl *l*-mandelate, m. p. 81—82°, $[\alpha]_{5461}^{19\cdot0^\circ}$ −163·5° ($c = 2\cdot3072$; $l = 2$)
l-Menthyl *dl*-mandelate, m. p. 85—86°, $[\alpha]_{5461}^{19\cdot7^\circ}$ −87·3° ($c = 1\cdot2485$; $l = 2$)
l-Mandelic acid, m. p. 133°, $[\alpha]_{5461}^{19\cdot5^\circ}$ −184·6° ($c = 1\cdot6780$; $l = 2$)

The *l*-mandelic acid was obtained from amygdalin; the esters were prepared according to McKenzie (*loc. cit.*), who also gives the m. p. of *l*-menthyl *d*-mandelate as 99—100°.

Experimental.

In the present work three types of experiment have been carried out, all of which demonstrate that preferential adsorption does occur; an example of each follows.

(1) A solution of 5 g. of *l*-menthyl *dl*-mandelate in 500 c.c. of light petroleum (b. p. 80—100°) was run down a column of alumina (4 ft. × ½ in. diam.), followed by 250 c.c. of the pure solvent. The top 6-in. portion of the column was then completely extracted by a mixture of alcohol and benzene, and the solvent evaporated. The resulting solid residue in

ethyl-alcoholic solution had $\alpha_{5461}^{19.7°}$ −1·10° (c = 0·5492; l = 2), whence $[\alpha]_{5461}^{19.7°}$ = − 100·2°, representing 58·5% of *l*-menthyl *l*-mandelate and 41·5% of *l*-menthyl *d*-mandelate. Total saponification of the product by heating for a short time with aqueous-alcoholic potash gave an acid having $\alpha_{5461}^{19.7°}$ = −0·64°, $[\alpha]_{5461}^{19.7°}$ = −18·2° (c = 1·6660; l = 2). This and all other saponification experiments were carried out using an excess of potash, in order to avoid the possibility of partial saponification giving preferential release of one form of the acid: considerable racemisation is inevitable (see McKenzie, *loc. cit.*). Elution of the fourth 6-in. portion of the column gave an ester having $\alpha_{5461}^{19.7°}$ −0·93° in alcohol (c = 1·4820; l = 2), $[\alpha]_{5461}^{19.7°}$ −31·9° (86·5% of *d*-ester). Saponification gave an acid having $\alpha_{5461}^{19.7°}$ +0·57° (c = 0·4450; l = 2), $[\alpha]_{5461}^{19.7°}$ = + 64·0°.

(2) A solution of 5 g. of *l*-menthyl *dl*-mandelate in 1 l. of light petroleum (b. p. 60—80°) was put through a column of alumina (85 g.) (2 ft. × ½ in. diam.). The column was divided into six equal portions, each eluted with alcohol–light petroleum (b. p. 60—80°) (1 : 1), and the solvent removed by evaporation. The properties of the esters obtained and of the acids they yielded on saponification are tabulated below. The rotations are all measured in ethyl-alcoholic solution.

Esters.

	Weight, g.	M. p.	$\alpha_{5461}^{19.7°}$.	$[\alpha]_{5461}^{19.7°}$.	c, %.	Percentage of *l-l*-ester.
1	0·80	82—83°	−0·99°	−99·0°	0·5000	57·5
2	1·00	85—86	−0·95	−95·0	0·5000	55·0
3	0·975	85—86	−0·94	−94·0	0·5000	54·5
4	0·90	85—86	−0·94	−94·0	0·5000	54·5
5	0·70	80—87	−0·54	−54·0	0·5000	28·0
6	0·03	88—92	−0·12	−60·0	0·1000	32·0

Acids.

Sample of ester giving acid.	M. p.	$\alpha_{5461}^{19.7°}$.	$[\alpha]_{5461}^{19.7°}$.	c, %.
1 (above)	115—120°	−0·13°	−13·0°	0·5000
3 + 4	110—117	−0·09	− 9·0	0·5000
5 + 6	105—107	+0·14	+14·0	0·5000

(3) A solution of 5 g. of *l*-menthyl *dl*-mandelate in 250 c.c. of light petroleum (b. p. 60—80°) was run through 68 g. of alumina in a column 2 ft. × 0·45 in. diam. The column was then washed with pure solvent, the filtrate taken off in successive volumes of 250 c.c., each evaporated to dryness, and the residue of ester examined.

Ester from	Weight, g.	M. p.	$\alpha_{5461}^{19.7°}$.	$[\alpha]_{5461}^{19.7°}$.	c.	Percentage of *l-l*-ester.
1st portion } 2nd ,, }	0·52	90—95°	−0·32°	−32·0°	0·5000	14·0
3rd ,, ...	0·33	85—88	−0·57	−57·0	0·5000	30·0
4th ,, ...	0·1	81—82	−0·815	−81·5	0·5000	46·0

Elution of the first 4 in. of the column after this washing gave 0·35 g. of ester having m. p. 81—85°, $\alpha_{5461}^{19.7°}$ − 1·10° (c = 0·5000; l = 2), $[\alpha]_{5641}^{19.7°}$ = − 110·0° (65% of *l-l*-ester).

The actual observed angles of rotation are much larger than those of any previously recorded work on the use of adsorption in stereochemistry. Examination of the above results leaves no doubt that the coefficient of adsorption on inactive material can be added to the list of physical properties in which diastereoisomerides can be expected to differ. It is probable that, given a suitable adsorbent, diastereoisomeric *salts* could be separated in this way, and experiments in this direction will be undertaken when circumstances permit.

UNIVERSITY OF LONDON, BEDFORD COLLEGE.
c/o THE UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE.

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THE INTER-RELATION OF FIRST- AND SECOND-ORDER ASYMMETRIC TRANSFORMATIONS

MARGARET M. JAMISON (HARRIS)
AND
E. E. TURNER

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84. *The Inter-relation of First- and Second-order Asymmetric Transformations.*

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

The brucine salt of 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid undergoes first-order asymmetric transformation* in chloroform solution, the salt brucine *d*-acid being optically the more stable. Since, therefore,

* It is important to define first- and second-order asymmetric transformations as here used. A configuratively unstable substance in solution (or in the liquid state) consists of equal quantities of the *d*- and the *l*-form. On addition of a second (but optically stable) *d* (or *l*)-compound which combines with the first substance to form a pair of diastereoisomerides, an equilibrium is set up in which one diastereoisomeride predominates to a greater or less extent. The setting up of this equilibrium we have called a first-order asymmetric transformation, and our definition agrees with Kuhn's (*Ber.*, 1932, **65**, 49) in so far as it recognises the necessity of the second, optically stable, substance for the retention of optical activity in the configuratively unstable compound. Only in very rare instances will first-order asymmetric transformation approach complete change into one or other diastereoisomeride, because of the small energy differences controlling these processes in general.

On the other hand, second-order asymmetric transformation, in any case in which interconversion of diastereoisomerides is possible (first-order transformation) and crystallisation can be induced, may be expected to be almost quantitatively realisable, and to give one diastereoisomeride in the optically pure, crystalline condition. That the optical activity of the configuratively unstable compound, when this is removed from combination with the optically stable substance, should be *detectable* by a physical measurement, is immaterial for the purpose of definition of terms, although it was mainly on this arbitrary point that Kuhn based his distinction between the two types of transformation.

It is unfortunate that " first " and " second " are used in the present sense in view of the possible confusion with the terms used in dealing with the kinetic aspect of first-order asymmetric transformations.

this shows that the less stable salt is brucine *l*-acid, the latter should be the first to separate if crystallisation could be induced. This has been verified, and the experiments now recorded constitute the first example of the application of the van't Hoff–Dimroth rule to asymmetric transformation in which both first- and second-order changes can be realised. In no previous work has it been possible to observe both first- and second-order changes without alteration of solvent.

THIS work is an extension into the diphenyl series of the investigation of the equilibrium existing in solution between the two diastereoisomeric salts of an unstably optically active acid and a stably active base (Jamison and Turner, J., 1938, 1646; 1940, 264), and an exploration of the relationship between the direction in which the equilibrium is displaced from the mean position and the sign of the rotation of the salt crystallising if asymmetric transformation of the second order should take place.

An apparently suitable diphenyl derivative, 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid, had already been examined by Corbellini and Angeletti (*Atti R. Accad. Lincei*, 1932, **15**, 968), who were interested in the second-order asymmetric transformation of its brucine salt from alcoholic solution as an easy method of obtaining the optically active acid. These workers observed the " racemisation " of the salt, brucine *l*-acid, in chloroform solution, but failed to see the finer point of its first-order asymmetric transformation in that solvent. Boiling an alcoholic solution of *dl*-2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid with brucine (1 mol.) and allowing it to cool, they obtained the salt, brucine *l*-acid, having m. p. 217°, in 83·3% yield; evaporation of the mother-liquor gave a further lævorotatory crop, rather less pure. It is now found that by modifying the quantity of alcohol used and the duration of crystallisation, a yield of 97·6% of brucine *l*-2′-(α-hydroxy-*iso*propyl)diphenyl-2-carboxylate can be obtained in the first fraction.

Corbellini and Angeletti found that their brucine *l*-acid salt in chloroform solution mutarotated in the dextro-direction, $[\alpha]_D^{24°} = -35{\cdot}35°$ ($c = 1{\cdot}6688$; $l = 1$) changing to $[\alpha]_D^{25°} = -2{\cdot}39°$ during 64 hours. After 3 hours' boiling of a similar solution the specific rotation became $-1{\cdot}87°$ at 24° ($c = 1{\cdot}600$; $l = 1$), a value so like the rotation of the solution of the partial racemate (made by taking equimolecular quantities of the *dl*-acid and brucine in chloroform solution), *viz.*, $[\alpha]_D^{25°} = -1{\cdot}88°$ ($c = 1{\cdot}5980$; $l = 1$), that they assumed unquestioningly that it had the same composition. On considering these results in the light of other work on the effects due to a difference of free energy in mutually interconvertible diastereoisomerides (summarised and discussed by Jamison and Turner, *loc. cit.*), it appeared to us that they were unlikely to be correct unless the free energies differed to only a very small degree. The mutarotation experiments were therefore repeated, with the following results: the brucine *l*-acid salt dissolved in pure dry chloroform mutarotated during 100 hours from $[\alpha]_{5461}^{25·15°} = -47{\cdot}04°$ to $+1{\cdot}46°$ ($c = 6{\cdot}835$; $l = 2$; the first reading was made 25 mins. after wetting with solvent). The first-order velocity constant of mutarotation was found to be $k^{25·15°} = 0{\cdot}0277$ ($\log_{10}$, hours^{-1}), whence the half-life period is 10·9 hours. A chloroform solution containing 1 mol. each of brucine and *dl*-acid in the same concentration was then prepared in order to find the specific rotation of the partially racemic salt. Experience with other optically unstable diastereoisomerides led to the expectation that the observed rotation would change, and that its velocity constant would be equal to that of the mutarotation of the salt. The rotation of the solution was therefore read 6 mins. after its preparation, $[\alpha]_{5461}^{25·15°} = -5{\cdot}08°$, and at intervals during 51 hours; the final value was $+1{\cdot}90°$; the half-life period of the change was 10·75 hours, sufficiently good agreement with that of the salt to confirm the supposition that an optical activation or first-order asymmetric transformation had been observed, and that the equilibrium, brucine *d*-acid $\rightleftharpoons$ brucine *l*-acid, at 25·15° ($c = 6{\cdot}835$ in chloroform) consisted of approximately 58% of the *d*-acid salt and 42% of the *l*-acid salt. The equilibrium position was altered by the addition of a further molecule of *dl*-acid; whereas the observed rotation of the solution containing 1 mol. each of acid and brucine changed from $-0{\cdot}695°$ to $-0{\cdot}26°$ at 25·15°, the one containing 2 mols. of acid and 1 mol. of brucine mutarotated from $+0{\cdot}745°$ to $+1{\cdot}475°$ ($l = 2$), this change, which was more rapid than the other, being according to the first-order law, and the half-life period being 7·5 hours.

The rotation of the equilibrated chloroform solution of the brucine salt had a fairly large temperature coefficient, and therefore efficient temperature control during measurements was essential. Temperature variations would not, however, be sufficient to account for the discrepancies between our results and those of Corbellini and Angeletti, so another cause was sought and found in the ease of formation under certain conditions of the lactone of 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid. This compound should be capable of existing in optically active forms which would be unracemisable except by a mechanism involving the splitting of the lactone ring. Owing to the absence of a salt-forming group, actual or potential, in the molecule, the lactone could be obtained in optically active forms only by asymmetric synthesis, and numerous attempts were made to effect this (*e.g.*, dry hydrogen chloride was passed into a well-cooled solution of the *l*-salt; the *l*-acid was treated with acetic anhydride; the *dl*-acid was heated with *d*-camphor-10-sulphonic acid), but in each case the lactone obtained on working up the product was optically inactive. It seemed safe to assume from these experiments that the optically active lactones could not be prepared without difficulty, although the following experiments demonstrate that the racemic lactone can be obtained extremely easily. A solution of the brucine *l*-2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylate in pure dry chloroform ($c = 6{\cdot}8355$; $l = 2$) had an initial rotation, $[\alpha]_{5461}^{25·15°}$, of $-6{\cdot}52°$; after 3 hours' heating at 78° this rose to $-0{\cdot}86°$, but after a further ½ hour's heating at the same temperature it fell again to $-1{\cdot}02°$; after 7 hours at 100° it became $-5{\cdot}78°$. In another experiment ($c = 5{\cdot}945$; $l = 2$) the initial rotation $[\alpha]_{5461}^{25·15°}$ was $-5{\cdot}67°$; after 34 hours at 100° in a sealed tube water had visibly separated, and the dried solution had $[\alpha]_{5461}^{25·15°} = -6{\cdot}72°$; after 59 hours at 100°

it was −7·36°. If the salt had entirely decomposed to form inactive lactone and free brucine, and if the rotation of brucine in chloroform ($[\alpha]_{5461}^{25\cdot15°} = -145\cdot6°$) is unaffected by the presence of the lactone, then the observed figure would be −10·51°. From these solutions optically inactive lactone, m. p. 124—125°, was obtained. There is therefore little doubt that decomposition of this kind with the release of free brucine was responsible for the negative figure recorded by Corbellini and Angeletti for the final value of the mutarotation after boiling. No doubt slight decompositions of this kind account for the small disagreements in the final specific rotations here recorded (+1·46°, +1·90°), but the degree of lactone formation under the conditions used for the mutarotations at 25·15° must be extremely small, since it does not interfere appreciably with the determination of the first-order rate constant. All the equilibrated solutions on long keeping developed negative rotations.

The behaviour of 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid in chloroform solution in presence of brucine therefore falls into line with our own previous work. The effects are not restricted to brucine salts; mutarotation in the dextro-direction is observed with quinidine and the *dl*-acid in molecular proportion in chloroform solution, and in the lævo-direction with quinine or cinchonidine.

Decomposition of the brucine *l*-acid salt by dissolving it in formic acid and quickly pouring the solution into water gave a specimen of *l*-2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid, having m. p. 134—135°, $[\alpha]_{5461}^{25\cdot15°} = -23\cdot9°$ in chloroform 2 mins. after wetting with solvent ($c = 0\cdot5867$; $l = 2$). The rotation fell to zero during 4 days, the process having a half-life period of 12·4 hours; it therefore racemises more slowly than the brucine salt mutarotates. Similar decomposition of equilibrated solutions of the brucine salt gave products in which activity could not be detected, presumably because of the rather low specific rotation of the acid and the fact that the theoretical maximum optical purity in the specimen would be approximately 16%.

Perhaps the most interesting observation of this whole investigation is one which correlates the position of equilibrium between the *d*- and *l*-acid salts in solution with their solubilities in the same solution. Since, in chloroform, the brucine *d*-acid salt is more stable than the brucine *l*-acid salt, the van't Hoff–Dimroth rule demands that the brucine *l*-acid salt should be less soluble in this solvent, in absence of any interfering factors (Jamison and Turner, *loc. cit.*). Thus it has been possible for the first time to demonstrate the applicability of the van't Hoff–Dimroth principle to the relationship between first- and second-order asymmetric transformations. An equilibrated chloroform solution of the brucine salt, $[\alpha]_{5461}^{25\cdot15°} = +1\cdot46°$, was rapidly evaporated to dryness on a steam-bath, crystallisation being accelerated by continuous stirring. The salt obtained, m. p. 214—215°, had $[\alpha]_{5461}^{20\cdot5°} = -29\cdot7°$ in chloroform ($c = 5\cdot9415$; $l = 2$) read 7 mins. after dissolution. The solution mutarotated at 20·5° during 7 days, the final value of $[\alpha]_{5461}^{20\cdot5°}$ being +1·51°; this shows that the negative rotation observed was due to brucine *l*-acid salt and not to liberated brucine.

Experimental.

(Except in the experiments on the temperature coefficient, all measurements of α were made at 25·15°. All values of α or $[\alpha]$ relate to λ 5461, and all values of k are in terms of Briggsian logarithms and hours^{-1}.)

Preparation of 2′-(α-*Hydroxy*iso*propyl*)*diphenyl*-2-*carboxylic Acid*.—The method of Corbellini and Angeletti (*loc. cit.*) was improved as follows: 19 g. of diphenic anhydride were added in ethereal suspension during 10 mins. to a well-shaken Grignard reagent previously made from 4·3 g. of magnesium, 36 g. of methyl iodide, and 250 c.c. of ether. The mixture was boiled under reflux on the water-bath for 6 hours, cooled, treated with dilute acetic acid, and extracted with ether. The ethereal solution was extracted with concentrated aqueous sodium carbonate, and dilute hydrochloric acid added to the extract until precipitation was complete. The solid mass was at once filtered off, well washed with warm water, and dried in a vacuum over sulphuric acid. It was then crystallised *rapidly* from benzene, 8 g. of acid, m. p. 137—138°, being obtained. Purification through the lactone as recommended by Corbellini and Angeletti is unnecessary.

Brucine 1-2′-(α-*Hydroxy*iso*propyl*)*diphenyl*-2-*carboxylate*.—1·968 G. of *dl*-acid (1 mol.) were dissolved in 5 c.c. of absolute alcohol, 3·030 g. of anhydrous brucine added in 10 c.c. of alcohol and washed in with a further 3 c.c. The solution was heated under reflux on a water-bath for 10 mins. and left to cool overnight. The brucine *l*-acid salt was filtered off and after being dried in a vacuum had m. p. 223°. Yield, 4·8790 g. (97·6%). Evaporation of the mother-liquor gave 0·09 g. of less pure salt.

Mutarotation. (All mutarotations were carried out in pure dry chloroform.) (1) $c = 6\cdot835$; $l = 2$; temperature thermostatically controlled in a water-jacketed polarimeter tube; 25 mins. after first wetting salt with chloroform, $[\alpha] = -47\cdot04°$; after 100 hours, $[\alpha] = +1\cdot46°$; $k = 0\cdot0277$ (limits, 0·0265, 0·0293).

(2) $c = 6\cdot835$; $l = 2$; 20 mins. after first wetting with solvent, $[\alpha] = -47\cdot80°$; after 100 hours $[\alpha] = +1\cdot46°$.

Time, hrs.	α obs.	10^4k.	Time, hrs.	α, obs.	10^4k.	Time, hrs.	α, obs.	10^4k.	Time, hrs.	α, obs.	10^4k.
0·0	−6·54°	—	5·0	−4·74°	270	23·0	−1·42°	269	31·0	−0·77°	272
0·5	−6·34	262	5·5	−4·58	271	24·0	−1·31	271	47·0	−0·15	273
1·0	−6·15	259	6·0	−4·43	272	25·0	−1·21	272	49·0	−0·105	274
1·5	−5·94	270	6·5	−4·30	270	26·0	−1·13	271	51·0	−0·095	266
2·5	−5·59	264	7·0	−4·16	270	27·0	−1·04	272	52·0	−0·06	272
3·0	−5·41	266	7·5	−4·01	273	28·0	−0·98	270	54·0	−0·02	275
4·0	−5·05	271	8·0	−3·985	259	29·0	−0·90	271	56·0	+0·015	279
4·5	−4·98	254	8·5	−3·765	271	30·0	−0·83	272	100·0(∞)	+0·20	—

Mean $k = 0\cdot0269$. Half-life period, 11·2 hours.

Optical Activation of dl-*Acid by Brucine in Chloroform*.—(1) 0·4038 G. of *dl*-acid (1 mol.) and 0·6215 g. of anhydrous brucine (1 mol.) were dissolved to 15 c.c. in chloroform; $l = 2$; 6 mins. after wetting mixture with solvent, $[\alpha] = -5\cdot08°$; after 51 hours $[\alpha] = +1\cdot90°$.

Time, hrs.	α, obs.	10^4k.	Time, hrs.	α, obs.	10^4k.	Time, hrs.	α, obs.	10^4k.	Time, hrs.	α, obs.	10^4k.
0·0	−0·695°	—	4·5	−0·47°	259	7·5	−0·32°	289	26·5	+0·10°	293
1·0	−0·64	258	5·0	−0·44	270	8·0	−0·30	290	28·5	+0·11	282
1·5	−0·61	270	5·5	−0·42	268	8·5	−0·28	291	29·5	+0·12	282
2·0	−0·58	279	6·0	−0·39	279	9·0	−0·26	271	30·5	+0·13	284
2·5	−0·55	286	6·5	−0·37	278	23·5	+0·07	298	31·5	+0·14	286
3·0	−0·53	275	7·0	−0·34	288	25·5	+0·08	284	51·0(∞)	+0·26	—
4·0	−0·495	255									

(Each recorded reading in this and all other mutarotation experiments is the mean of many separate readings.) Mean $k = 0{\cdot}0280$. Half-life period, 10·75 hours.

(2) 0·8076 G. of *dl*-acid (2 mols.) and 0·6215 g. of anhydrous brucine (1 mol.) were dissolved to 15 c.c. in chloroform. Temperature, 25·15°; $l = 2$; α (read first 10 mins. after making up the solution) changed from +0·745° to +1·475°; $k = 0{\cdot}0399$ (limits 0·0369, 0·0426). Half-life period, 7·5 hours.

Temperature Coefficient of Equilibrated Brucine Salt in Chloroform Solution ($c = 6{\cdot}835$; $l = 2$). Readings were made as soon as the solution had attained the required temperature, without allowing time for any possible change in the equilibrium position to assert itself.

Temp.	4·3°	8·85°	14·4°	20·1°	25·0°	29·2°
α	+0·63°	+0·51°	+0·38°	+0·22°	+0·07°	−0·05°

There is therefore an almost linear relationship between rotation and temperature between these limits.

Racemisation of 1-2′-(α-*Hydroxy*iso*propyl*)*diphenyl*-2-*carboxylic Acid*.—2 Mins. after wetting with solvent $[\alpha] = -23{\cdot}9°$ ($c = 0{\cdot}5867$; $l = 2$) in chloroform, falling to zero in 4 days. First-order velocity constant, $k = 0{\cdot}0242$ (limits 0·0235, 0·0254).

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University of London (Bedford College),
c/o The University Chemical Laboratory, Cambridge.

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A REVIEW OF SOME OF THE RECORDED OBSERVATIONS INVOLVING ASYMMETRIC TRANSFORMATIONS

BY

MARGARET M. JAMISON (HARRIS)

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Most of the experimental work to be described here is familiar to all chemists as furnishing answers to the question " Is the compound X optically active or not ? ". The object of the present discussion is to correlate the answers to the question " What happens to X as part of a diastereoisomeric pair when it is present in solution or crystallises out from it ? ", X being optically labile. It must constantly be borne in mind that the authors quoted were usually concerned primarily with the first question, and that the evidence available for answering the second may very well be slight without in any way invalidating the first or affording any ground for criticism.

(1) Second-Order Asymmetric Transformations.

If a pair of diastereoisomers having one optically unstable component is present in saturated solution and one form begins to crystallise, the whole of the product may then appear as the single crystalline diastereoisomer, as long as the rate of interconversion of the two forms is greater than the rate of crystallisation. For example, a salt in which the basic component B is optically stable and the acid A optically unstable, and B*d*-A less soluble than B*l*-A, behaves thus

$$\underset{\text{in solution}}{\text{B}l\text{-A} \rightleftharpoons \text{B}d\text{-A}} \longrightarrow \underset{\text{crystalline, up to 100 \%.}}{\text{B}d\text{-A}}$$

In order to recognise this effect unequivocally it is necessary to remove the stably asymmetric agent B and demonstrate the activity which has been induced in A : factors such as the optical instability of A in absence of B or the chemical character of the entity BA may preclude this incontrovertible proof, and less conclusive though often persuasive stereochemical arguments may have to be called in, *e.g.* the mutarotation of the deposited material in another solvent and consideration of its specific rotation compared with that of salts of B with inactive acids, coupled with effectively complete precipitation of BA as a uniform substance.

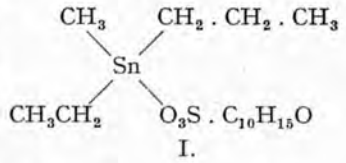
It will be seen from the following examples that this process can take place with diastereoisomers which are ionised in solution and therefore have no reality until the point of crystallisation is reached, as well as with those which because of suppression of dissociation for one reason or another are always entities containing two centres of asymmetry, one labile and the other not.

Examples of Proved Asymmetric Transformation of the Second Order.

Pope and Peachey [1] crystallised methyl-ethyl-*n*-propyltin *d*-camphorsulphonate (I) from water, obtaining only one salt, $[M]_D + 95°$ in water (subtracting the value for the camphorsulphonate ion, $[M]_D$ for the basic radical is about $+ 45°$) ; treatment of this salt with potassium iodide gave *d*-methylethyl-*n*-propyltin iodide. The inversion presumably in-

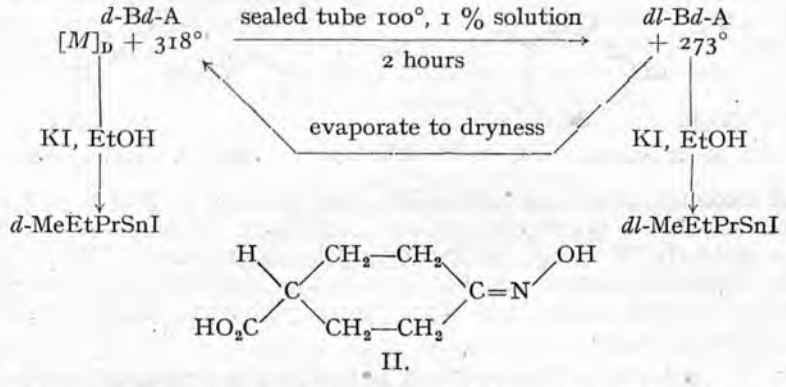
[1] *Proc. Chem. Soc.*, 1900, **16**, 42.

volves a flat tin cation. In their second case of asymmetric transformation, that of methylethyl-*n*-propyltin *d*-α-bromocamphorsulphonate, which crystallised from acetone in fractions of constant specific rotation ($[M]_D$ + 318° in water at ordinary temperature), the same authors carried out an interesting demonstration of the nature of the process.[2] Allowing + 270° for the molecular rotation of the acid radicle they assumed that they had the salt *d*-base *d*-acid, $[M]_D$ + 48° being attributed to the *d*-base part.

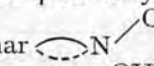
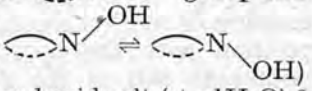


I.

On heating a 1 % aqueous solution of the salt for 2 hours at 100° in a sealed tube the $[M]_D$ fell to + 273° and the solution presumably then contained the *d*-bromocamphorsulphonate of the *dl*-base. On evaporating to dryness, the product had $[M]_D$ + 315° and had obviously undergone reconversion into *d*-base *d*-acid. Decomposition of this salt with potassium iodide gave a dextro-rotatory iodide, while decomposition of the supposed partial racemate gave inactive iodide.



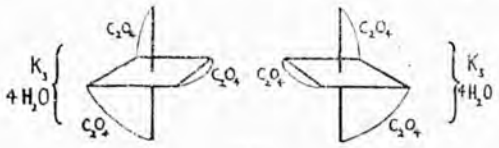
II.

A solution of quinine and oximino*cyclo*hexane-4-carboxylic acid (II) (owing its potential optical activity to the non-planar  group and its optical instability to the ease of the conversion  in 30 parts of water gave an 80 % yield of the quinine *l*-acid salt ($+2\frac{1}{2}H_2O$):[3] the authors, Mills and Bain, observed that the salt crystallised from an inactive mother liquor and appended the classic explanation: "of the two diastereoisomeric quinine salts, that of the *l*-acid must be the less soluble in water, and thus crystallises first from an aqueous solution containing equal quantities of the two salts. The excess of quinine *d*-acid salt thereby left in solution, however, racemises very rapidly, so that in spite of the removal of the quinine *l*-acid salt, an approximate equality is maintained between the quantities of the two salts in the solution." Decomposition of the quinine *l*-salt with sodium hydroxide gave a sodium salt $[M]_D$ − 91°. A similar transformation was effected using morphine in hot ethyl alcohol and gave the salt morphine *d*-acid, which yielded dextro-rotatory ammonium salts on treatment with ammonium hydroxide.

From a hot alcoholic solution of potassium dihydrogen trioxalochromiate and two molecular proportions of strychnine Werner[4] obtained a salt potassium distrychnine trioxalochromiate (+ $4H_2O$) (III) having a specific rotation $[\alpha]_G$ + 430° in water; further crops of crystals from the mother liquor were also dextro-rotatory. The rotation with respect to

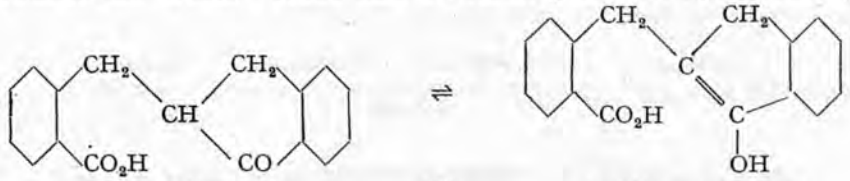
[2] *Proc. Chem. Soc.*, 1900, **16**, 116. [3] *J. Chem. Soc.*, 1910, **97**, 1866.
[4] *Berichte*, 1912, **45**, 3061.

the trioxalochromiate ion mutarotated almost to zero in 1¼ hours, and Werner proved that he was handling the *d*-base *d*-acid by converting it into *d*-tripotassium trioxalochromiate. Furthermore, when potassium distrychnine trioxalochromiate was dissolved in hot water in dilute solution, crystals of tristrychnine *l*-trioxalochromiate (+ $4H_2O$) separated $[\alpha]_G$ − 300° in water, additional fractions being *l*-rotatory also: Werner noted that the mother liquor from which crystallisation was taking place was "practically inactive." This would not be expected if *resolution* was taking place. Decomposition of the *l*-tristrychnine salt with potassium iodide gave the *l*-rotatory tripotassium trioxalochromiate.



III.

Leuchs and Wutke [5] found that 2-*o*-carboxybenzyl-1-hydrindone (IV)

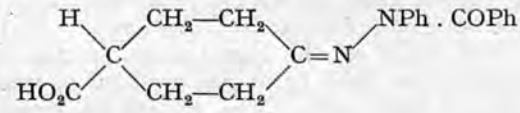


d- or *l*-form. IV. inactive enolic form.

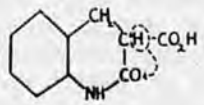
and one molecule of brucine crystallise from acetone to give a 94 % yield of a salt which on decomposition with sulphuric acid leaves a dextrorotatory acid ($[\alpha]_D^{20°}$ + 64°, mutarotating in chloroform). They assume that the optically inactive enolic form is the intermediate between the two active ketonic forms and that the asymmetric transformation is accomplished thus :—

B *l*-acid ⇌ B enolic acid ⇌ B *d*-acid → crystals.

Following up their demonstration of optical activity in the oxime, Mills and Bain [6] found that the quinine salt of the N-benzoylphenylhydrazone of *cyclo*hexanone-4-carboxylic acid (V) crystallises from a mixture of methyl alcohol and water to give the *l*-quinine *d*-salt (decomposition with the appropriate alkali gives the sodium, ammonium or potassium salt of the *d*-acid). Unfortunately, the percentage yield on crystallisation is not recorded, and it is therefore not possible to state



V.



VI.

categorically that the separation is not, on this evidence, a *resolution*; however, the authors record that concentration of the mother liquor yielded nothing but the *d*-acid salt, which makes it appear likely that transformation has taken place. The semicarbazone of *cyclo*hexanone-4-carboxylic acid was "activated" in the same way by crystallisation of its morphine salt from aqueous methyl alcohol, the salt obtained giving a dextro-rotatory ammonium salt on treatment with ammonium hydroxide.

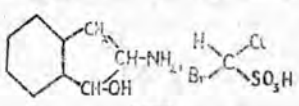
A neat piece of work by Leuchs [7] demonstrates second-order transformation with formal simplicity. 2·4 g. of hydrocarbostyril-3-carboxylic acid (VI) and 4·07 g. of anhydrous quinidine were dissolved in 40 c.c. of methyl alcohol: three crystalline fractions were collected (amounting in all to 6·2 g. of a salt containing two molecules of water of crystallisation). Each fraction was decomposed by hydrochloric acid at − 10°

[5] *Berichte*, 1913, **46**, 2420. [6] *J. Chem. Soc.*, 1914, **105**, 64.
[7] *Berichte*, 1921, **54**, 830.

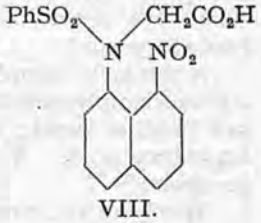
and the acid obtained dissolved in 5·5 % solution in glacial acetic acid and its racemisation watched at 18°. The specific rotations of the samples are given in the accompanying table. Leuchs referred the optical instability to the existence of the inactive enolic form as an intermediate.

Fraction.	Weight.	α_D.	$[\alpha]_D^{18°}$.
1	4 g.	+ 1·08°	+ 56·4°
2	1·5 g.	+ 1·09°	—
3	0·7 g.	+ 1·04°	—

When the *l*-hydroxyhydrindamine salt of *dl*-chlorobromomethane sulphonic acid (VII), $M[\alpha]_D$ in methyl alcohol − 72°, was dissolved in acetone which contained a little methyl alcohol a salt was deposited having $M[\alpha]_D$ in methyl alcohol − 173° initially but exhibiting mutarotation to − 72° on keeping.[8] Read and McMath concluded that the crystallisation had resulted in asymmetric transformation to the *l*-base *l*-acid salt. They also carried out the preparation of the mirror-image salt *d*-base *d*-acid, using *d*-hydroxyhydrindamine under similar conditions. Attempts to remove the optically active base or to replace it with benzidine or β-naphthylamine gave optically inactive products: but by mixing equal quantities of the salts *d*-base *d*-acid and *l*-base *dl*-acid, in which the rotation of the basic parts cancel each other, they obtained a residual $[M]_D$ of + 49° which they attributed to the positive acid. In a later paper [9] these same authors describe interesting behaviour of chlorobromoacetic acid and *l*-hydroxyhydrindamine in their crystallisation as salts from chloroform containing a little methyl alcohol. Slow deposition from a cold solution gave *l*-base *dl*-acid, $[M]_D$ in chloroform containing a little methyl alcohol − 50°, while rapid cooling of a hot solution to supersaturation gave *l*-base *d*-acid in 75 % yield, $[M]_D$ approximately 0°, changing to − 50° on warming and keeping. The mother liquor from this crystallisation deposits *l*-base *dl*-acid. Use of *d*-hydroxyhydrindamine enabled the *d*-base *l*-acid and *d*-base *dl*-acid to be prepared: an attempt to prove the optical activity to be due to the acid and to find its rotation by taking equal weights of *d*-base *l*-acid and *l*-base *dl*-acid in chloroform containing methyl alcohol resulted in a fleeting observation of α_D − 0·1°, 1·5 mins. after wetting with solvent. It is therefore uncertain whether this is a true asymmetric transformation or not.

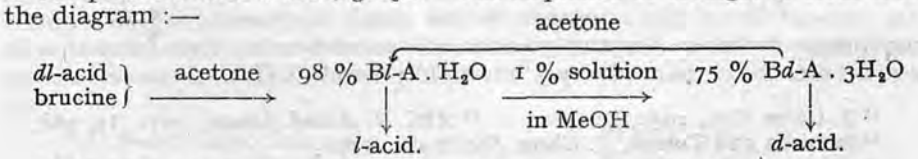


VII.



VIII.

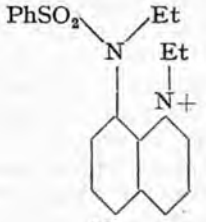
Mills and Elliott [10] extended the scope of the phenomenon when they found one substance, the brucine salt of N-benzenesulphonyl-8-nitro-1-naphthylglycine (VIII), which underwent asymmetric transformation of the labile acid part in opposite directions in two different solvents: each of the diastereoisomeric salts was decomposed to give an active acid, so that the result was in effect as if a resolution had been performed. The first asymmetric transformation, to base *l*-acid, H_2O from acetone, took place almost quantitatively, while that from methyl alcohol gave 75 % of the possible base *d*-acid, $3H_2O$. The sequence of changes is clear from the diagram:—



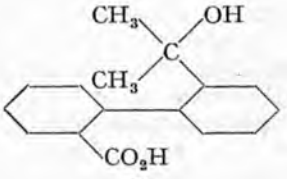
[8] Read and McMath, *J. Chem. Soc.*, 1925, **127**, 1572 [9] *Ibid.*, 1926, 2183.
[10] *Ibid.*, 1928, 1291.

The cause of activity in this molecule is the restriction of the rotation of the substituted amino group by the nitro group, resulting in asymmetry.

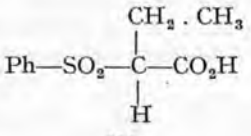
Using another compound owing its potential activity to restriction of rotation, in this case a base, Mills and Breckenridge [11] record similar optical behaviour. 8-Benzenesulphonethylamino-1-ethylquinolinium *d*-α-bromo-camphor-π-sulphonate (IX) crystallised slowly from a mixture of ethyl acetate and acetone giving the salt *d*-base *d*-acid, $2H_2O$ which showed mutarotation in the lævo direction in water, chloroform and ethyl alcohol; on shaking a chloroform solution of the salt *before* mutarotation with aqueous potassium iodide the *d*-quinolinium iodide was obtained. Unfortunately, the percentage weight of salt crystallising is not recorded, so that there is nothing formally to differentiate the crystallisation from a resolution: however, it is unlikely that a substance showing optical instability in three such diverse solvents as chloroform, water and alcohol



IX.



X.



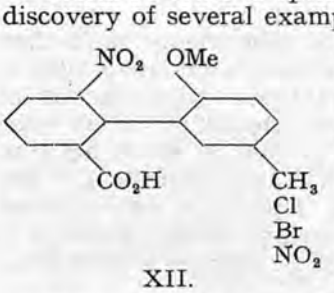
XI.

would be stable enough for resolution in ethyl acetate solution. Using the *d*-α-bromocamphorsulphonate in a mixture of methyl alcohol and ethyl acetate the *l*-base *d*-acid was obtained and gave a lævo rotatory iodide on decomposition.

Corbellini and Angeletti [12] reported that 2′-(α-hydroxy*iso*propyl) diphenyl-2-carboxylic acid (X) and brucine formed a salt which crystallised from ethyl alcohol as brucine *l*-acid in 83 % yield, a figure which was raised to 97·6 % on repetition by Jamison and Turner [13] who also describe an analogous transformation from chloroform solution by evaporating to dryness on a boiling water bath with continuous stirring to accelerate crystallisation. Decomposition with mineral acids gave the *l*-rotatory acid.

A similarly complete conversion has been observed of the brucine salt of α-phenylsulphonebutyric acid (XI), which crystallises from acetone as the salt brucine *l*-acid; this salt is decomposed by hydrochloric acid to give the *l*-rotatory acid. A tautomeric mechanism is postulated for the optical inversion.[14]

Work on relative optical stability within various series has led to the discovery of several examples of second-order asymmetric transformation among substituted diphenyl derivatives. Yuan and Adams [15] have a good case, for example, in the behaviour of brucine *dl*-2: 5-dimethoxy-2′-nitro-6′-carboxydiphenyl which crystallises from water in three fractions amounting in all to 90 % of the theory, and all having the same specific rotation: decomposition with ice-cold hydrochloric acid gave the *l*-acid. The cinchonidine salt behaved similarly. In a later paper [16] the same authors describe equally conclusive evidence for the asymmetric second-order transformation of 2-nitro-6-carboxy-2′-methoxy-5′-methyldiphenyl (XII) and the series with

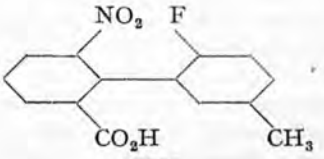


XII.

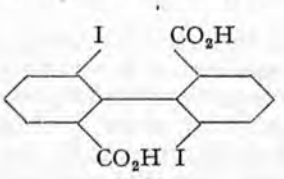
[11] *J. Chem. Soc.*, 1932, 2209. [12] *Atti. R. Accad. Lincei*, 1932, **15**, 968.
[13] Jamison and Turner, *J. Chem. Soc.*, 1942, 437.
[14] *J. Amer. Chem. Soc.*, 1932, **54**, 4410.
[15] *Ibid.*, 1932, **54**, 2966. [16] *Ibid.*, 1932, **54**, 4434.

Cl, Br and NO_2 in the 5′ position by brucine in alcohol containing varying amounts of water. Yuan and Adams among others, use the word "resolution" to describe this process: this would appear to be a misuse of the term, which has hitherto referred to the separation of a racemic mixture into its stereoisomeric constituents, not conversion of it all into one form.

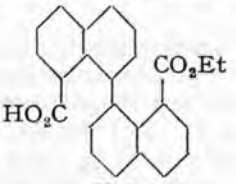
Stoughton and Adams [17] record the dextro asymmetric transformation of 2-nitro-6-carboxy-2′-fluoro-5′-methyldiphenyl (XIII) with brucine from ethyl alcoholic solution: quinine effected the same conversion. Searle and Adams [18] found that the dibrucine salt of 2 : 2′-diiodo-6 : 6′-dicarboxydiphenyl (XIV) crystallised from 95 % ethyl alcohol in three identical



XIII.

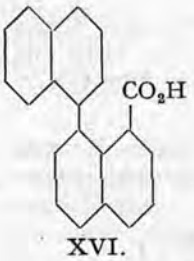


XIV.

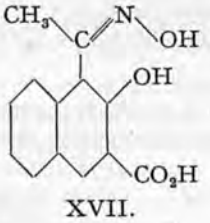


XV.

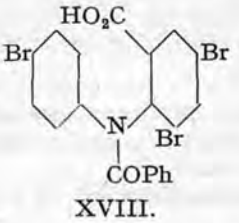
fractions totalling 83 % of the possible quantity, which could be shown by decomposition with 6 N. hydrochloric acid and separation of the *l*-acid to be the single diastereoisomer. It is noteworthy that crystallisation from methyl alcohol did not favour second-order transformation but gave a mixture of crystals of diastereoisomers which could be separated by hand picking. Working in the dinaphthyl series Meisenheimer and Beisswenger [19] found that ethyl hydrogen 1 : 1′-dinaphthyl-8 : 8′-dicarboxylate (XV) underwent theoretical conversion into the brucine *l*-acid, $3H_2O$ salt from ethyl acetate containing a little methyl alcohol: decomposition with dilute mineral acid led to the separation of the *l*-acid. A second acid, 1 : 1′-dinaphthyl-8-carboxylic acid (XVI), and brucine dissolved in ethyl acetate gave a solution which could be made to deposit base *l*-acid . H_2O or base *d*-acid . H_2O according to which of these was used to inoculate it. The same authors, with Theilacker,[20] describe similar activation by alkaloids of β-(2-hydroxy-3-carboxy-1-naphthyl) methyl ketoxime (XVII).



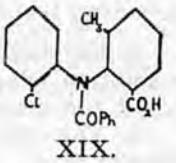
XVI.



XVII.



XVIII.

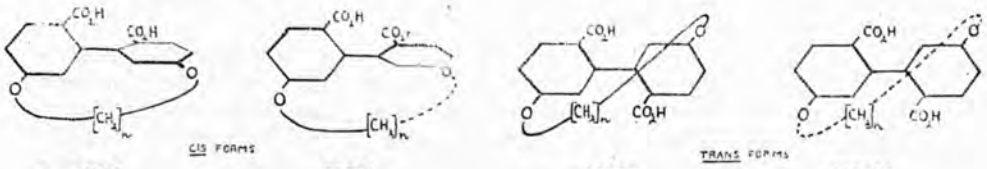


XIX.

N-benzoyl-2 : 4 : 4′-tribromo-6-carboxydiphenylamine (XVIII) when dissolved in acetone containing 1 M. of cinchonidine deposited 1 M. of cinchonidine *d*-salt in 94 % yield: deposition of crystals could be accelerated by boiling the solution without loss of optical purity in the product. Treatment with pyridine followed by dilute HCl gave the *d*-acid.[21] An almost quantitative yield of brucine *l*-N-benzoyl-2′-chloro-2-methyl-6-carboxydiphenylamine (XIX) is deposited from a salt of the racemic acid and brucine by slow crystallisation from a mixture of ethyl alcohol and ether. Decomposition with formic acid and ice-cold hydrochloric acid gave the *l*-acid.[22]

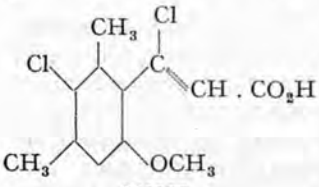
[17] *J. Amer. Chem. Soc.*, 1932, **54**, 4426.
[18] *Ibid.*, 1933, **55**, 1649.
[19] *Berichte*, 1932, **65**, 32.
[20] *Annalen*, 1932, **495**, 249.
[21] Jamison and Turner, *J. Chem. Soc.*, 1938, 1646.
[22] *Idem.*, *J. Chem. Soc.*, 1940, 264.

Adams and Kornblum [23] investigated the effect of chain length in the bridge of the compounds (XX, XXI) on their optical stability, and in the course of the work describe two cases of what now appears to be second-order asymmetric transformation.



XX XX′ XXI. XXI′

When n is large enough, the four forms above, all optically active, should be present together at equilibrium in solution, and a suitable alkaloid and solvent should be capable of bringing out one of the forms as a crystalline salt. The authors found that when $n = 10$, brucine in methyl alcohol gave a 77 % yield of a dibrucine salt in the first fraction, and a further quantity of the same salt from the mother liquor : decomposition with hydrochloric acid gave a dextro rotatory acid. In the case where $n = 8$ cinchonine acts as a transforming agent in ethyl alcohol to give three fractions (representing 91 % of the theoretical quantity) all with the same specific rotation and each giving a *l*-acid on decomposition with hydrochloric acid.



XXII.

Adams and Gross [24] demonstrating optical activity in a substituted benzene derivative found that the quinine salt of β-chloro-β-(2-methoxy-4, 6-dimethyl-5-chlorophenyl) acrylic acid (XXII) was deposited from ethyl acetate in a series of fractions all of which had the same specific rotation and yielded the dextro acid on treatment with hydrochloric acid.

Examples of Inferred Second-Order Asymmetric Transformation in Absence of Direct Observation of Optical Activity in the Separate Activated Substance.

From the study of cases of proved asymmetric transformation listed above it appears that the secondary characteristics (*i.e.* other than the removal of the transforming agent to leave a dectectably asymmetrically activated body) are :—

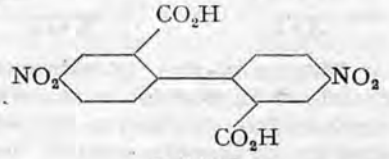
1. Crystallisation produces *one* salt (*i.e.* all fractions identical) from a solution which originally contained the two types, for example, *d*-base *l*-acid and *d*-base *d*-acid.

2. This salt when dissolved in another solvent may

(*a*) mutarotate, or

(*b*) deposit another form, or

(*c*) show a rotation which is strikingly different from that of the resolving agent : this latter kind of evidence can only be accepted with great reserve.



XXIII.

4 : 4′-Dinitrodiphenic acid (XXIII) (1 g., 1 M.) and quinine hydrate (2·3 g., 2 M.) dissolved in 96 % ethyl alcohol deposited the following fractions : (1) 1·75 g. salt, m.p. 207-208°, $[\alpha]_D^{20°}$ + 108·4° in $CHCl_3$; (2) 0·8 g. salt, m.p. 207-208°, $[\alpha]_D^{22°}$ in $CHCl_3$ + 110·3°. Removal of the base from these fractions gave an optically inactive acid ; nevertheless,

[23] *J. Amer. Chem. Soc.*, 1941, **63**, 188. [24] *Ibid.*, 1942, **64**, 1786.

Kuhn and Albrecht [25] assert that this is an asymmetric transformation for the following reasons :—

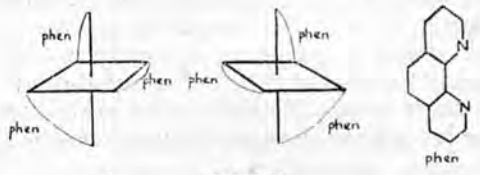
(*a*) the product, all the same substance, represents 80 % of the possible yield,

(*b*) quinine *m*-nitrobenzoate and quinine phthalate have the specific rotations $-163{\cdot}5°$ and $-168{\cdot}2°$ in the same circumstances, pointing to the above being the salt of a dextro acid (but see Kharasch, Senior, Stanger and Chenicek,[25, 26] on the anomalous rotation of quinine salts ; this piece of evidence would appear from their work to be anything but conclusive), and

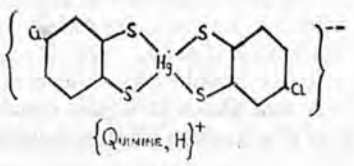
(*c*) the acid falls into a series with two, one and no nitro-groups in the *o*-position in diphenic acid :—

6 : 6′-dinitrodiphenic acid	resolvable with brucine	acid optically stable.
4 : 6′-dinitrodiphenic acid	resolvable with quinine	acid racemises.
4 : 4′-dinitrodiphenic acid	asymmetric transformation with quinine	acid too unstable to see active.

Pfeiffer and Quehl [27] claim to have observed optical activation in the field of octahedral asymmetry. Zinc β-camphorsulphonate with 3·5 M. of phenanthroline (XXIV) crystallised from water to give an 80 % yield



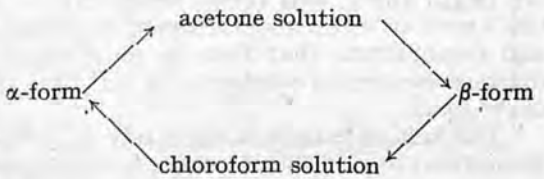
XXIV.



XXV.

of a salt $[Zn(phen)_3]O.SO_2C_{10}H_{15}O.7\,H_2O$. After purification by fractionation from acetone and water a 1/1000 M. in 25 c.c. of water had a rotation α_D of 0·0° while for the zinc camphorsulphonate alone it was + 0·93°. Working in the reverse order, a solution of 1/1000 M. zinc β-camphorsulphonate in 25 c.c. of water, α + 0·92°, was treated with 3 M. of phenanthroline, when α fell immediately to + 0·09°, ammonia, pyridine or ethylenediamine showing no such effect. Pfeiffer and Quehl attribute this change in rotation to the preferential formation of the *l*-$[Zn(phen)_3]^{++}$ complex in presence of the camphorsulphonate ion, although conversion into the corresponding dibromide or dinitrate resulted in optically inactive products.

Mills and Clark [28] prepared the diquinine salt of a complex anion of mercury with 4-chlorobenzene-1 : 2-dithiol (XXV). If the mercury valencies are tetrahedrally disposed the complex can exist in two mirror image forms. Crystallisation produced two distinct forms, styled α and β. The α-form dissolved in acetone began to deposit the β-form within a few minutes : the β-form dissolved in chloroform deposited the α. Both forms come out with solvent of crystallisation. Mutarotation of the freshly dissolved substances was looked for as low as − 35° but was not detected. It would appear that there are three possible explanations of this behaviour :



[25] *Annalen*, 1927, **455**, 272.
[26] *J. Amer. Chem. Soc.*, 1934, **56**, 1646.
[27] *Berichte*, 1931, **64**, 2667.
[28] *J. Chem. Soc.*, 1936, 175.

(*a*) dimorphism of a stable mercury complex salt, involving crystallisation with the solvent, an insufficient explanation since the two forms after loss of solvent retain their difference in solubility ;

(*b*) *cis* and *trans* forms of a flat mercury cation, also inadequate, as dimorphism could then be shown by metallic salts ;

(*c*) second-order asymmetric transformation between diastereoisomers with a tetrahedral mercury cation.

Dismissing (*a*) and (*b*), and proving that internal dissociation does not occur, the authors favour the last explanation.

(2) First-Order Asymmetric Transformations.

Kuhn [28, 29] called the effect which he and Albrecht observed in the case of the quinine salt of 4 : 4′-dinitrodiphenic acid an *asymmetrische Umlagerung erster Art*—referring to an optical activation which ceases to exist when the transforming agent is removed. This definition seemed satisfactory at first but further consideration reveals that it is difficult to apply, for " ceases to exist " is a criterion which may depend on the standard of laboratory technique which is used for the detection of the unstable optical activity. The use of an altered definition was therefore suggested,[21, 22] and clearly set out in 1942.[13]

Suppose, to take a representative example, a configuratively unstable optically active acid exists in solution : it consists of equal quantities of *l*-acid and *d*-acid. On the addition of one form of an optically active, optically stable base there is immediate formation of the diastereoisomers B*l*-A and B*d*-A in equal quantities ; these have different optical stabilities in solution and a change begins to take place until the equilibrium is reached.

$$\left.\begin{matrix} \text{B}l\text{-A} & \rightleftharpoons & \text{B}d\text{-A} \\ 50\ \% & & 50\ \% \end{matrix}\right\} \text{ at time of mixing}$$

$$\left.\begin{matrix} \text{B}l\text{-A} & \rightleftharpoons & \text{B}d\text{-A} \\ x\ \% & & 100-x\ \% \end{matrix}\right\} \text{ at equilibrium.}$$

The setting up of this equilibrium is the first-order transformation.

The primary essential for the operation of the process is the *reality of diastereoisomers in solution,* and therefore it would not be expected to take place in the case of salts in ionising solvents such as water nor, for example, in the diastereoisomeric *d*- and *l*-8-benzenesulphonylethylamino-1-ethylquinolinium-*d*-bromo-camphor-π-sulphonates in $CHCl_3$ prepared by Mills and Breckenridge.[11] This is the salt of a quaternary ammonium base and therefore must be ionised in solution even in chloroform : it did not show first-order transformation, and evidence for its absence is afforded by calculating from the figures given by the authors the extent of mutarotation of the *l*-base *d*-acid and *d*-base *d*-acid in chloroform. These values are $[\alpha]_{5461}$ 108·4° and 106·7° respectively : they represent equality within the limits of experimental error on substances that show mutarotation, and demonstrate that there is no differentiation detectable between the diastereoisomers in solution : in fact they do not exist until crystallisation takes place.

The first milestone in the study of optical activation (first-order transformation) in solution is generally considered to be the work of Read and McMath [8] on *l*-hydroxyhydrindamine chlorobromomethanesulphonate. The salt *l*-base *l*-acid in anhydrous acetone (purified through the bisulphite compound) had $[M]_D$ − 256° three minutes after wetting with solvent, mutarotating to − 187° in less than an hour. The salt *l*-base *d*-acid under the same conditions had an initial $[M]_D$ − 71° changing to − 187° in the same time (see Fig. 1). Assuming proportionality between rotation

[29] *Berichte,* 1932, **65,** 49.

and concentration and no dissociation of the salts, the authors calculated the equilibrium composition to be

$$\underset{81\ \%}{B\textit{l}\text{-A}} \rightleftharpoons \underset{19\ \%}{B\textit{d}\text{-A}}$$

They were not able to carry out the highly desirable experiment of removing the optically active base and demonstrating directly the excess of *d*-acid at equilibrium.

Shortly before this work was done, McKenzie and Smith [30] had made experiments on the rotation of *l*-menthyl esters of phenylbromoacetic and phenylchloroacetic acids in ethyl alcohol in presence of a very small concentration of alcoholic potash. The results, in those cases which are free from complicating factors, demonstrate first-order transformation from all three possible starting points, the *d*-acid *l*-ester, the *l*-acid *l*-ester and the *dl*-acid *l*-ester.[31] For example, changes in rotation make it clear that the following scheme is operable in *l*-menthyl phenylchloroacetate :—

$$\underset{50\ \%}{\text{Ph . CHCl . CO}_2\text{C}_{10}\text{H}_{19}} + \underset{50\ \%}{\text{Ph . CHCl . CO}_2\text{C}_{10}\text{H}_{19}}$$

$$\rightleftharpoons \underset{57\ \%}{\text{Ph . CHCl . CO}_2\text{C}_{10}\text{H}_{19}} + \underset{43\ \%}{\text{Ph . CHCl . CO}_2\text{C}_{10}\text{H}_{19}}$$

$$\left\{\underset{100\ \%}{\text{Ph . CHCl . CO}_2\text{C}_{10}\text{H}_{19}}\right\} \qquad \left\{\underset{100\ \%}{\text{Ph . CHCl . CO}_2\text{C}_{10}\text{H}_{19}}\right\}$$

The most striking effect, mutarotation of a *dl*-mixture of esters in alcohol on adding one drop of alcoholic potash has been shown to take place with the related substances *l*-menthyl *dl*-phenylbromoacetate, *l*-menthyl *dl*-phenylchloroacetate, *l*-menthyl *dl*-mandelate and amygdalin [32] where the transforming agent is the gentiobiose residue. The properties of the diastereoisomeric pairs of esters, their unequal rates of saponification in particular, and the optical instability of the acids means that removal of the activating *l*-menthyl residue to leave the acid in a state which would be reliably indicative of its equilibrated optical composition in solution in the form of the ester is not possible.

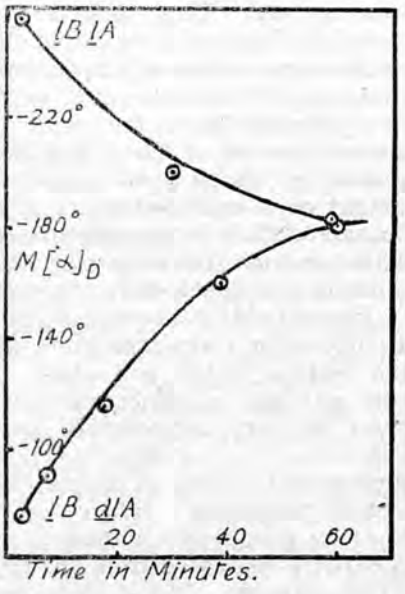


FIG. 1.

McKenzie and Smith say that "the velocity of the catalysis is greater with the *l*-menthyl *d*-phenylchloroacetate than with its diastereoisomeride." They arrived at this conclusion by calculating the percentages of original ester left after certain lengths of time in each case, a calculation which neglects the fact that the system is moving towards an equilibrium composition which is not that of the racemate. However, they publish their actual readings for change of rotation with time in the *d*-*l*- and *l*-*l*-esters, and from these data [30] rate constants for approach to *equilibrium* can be

[30] *J. Chem. Soc.*, 1924, **125**, 1582 ; see also Ritchie, *Asymmetric Synthesis and Asymmetric Induction*, 1933, p. 83.

[31] *Berichte*, 1925, **58**, 894.

[32] Smith, *ibid.*, 1931, **64**, 1115.

calculated which are in as good agreement as might be expected from velocity measurements made without temperature control, and with regard to the possible side reactions; in any event, the evidence is not such as to justify calling the rates different. The authors were prepared to find that there is a difference in the rates of the catalysed reactions of the diastereoisomers, but they failed to see, as did many other workers about this time in the same field, that the relevant "reaction" is *partial inversion* and not partial racemisation. The nature of their material and the fact that the activated group could not be isolated without isomeric change made this work of McKenzie and Smith unsuitable for the inception of a general theory: with the theory established, their experimental work falls into place and lends it convincing support.

Kuhn and Albrecht [25] went so far as to presume an optical activation in solution without seeing any mutarotation in the case of 4 : 4′-dinitrodiphenic acid and quinine in alcoholic solution, entirely on account of a large difference of rotation, carrying it over to the opposite sign, between the quinine and the salt. Lesslie and Turner,[33] observed similar effects in diphenic acid itself with no less than six alkaloids. Since the work of Kharasch, Senior, Stanger and Chenicek,[26] these authors, together with Winton,[34] have reconsidered the results which led them to believe that quinine diphenate mutarotated at ordinary temperatures as a consequence of optical activation, and shown that the optical stability is not of this order but a much lower one and is only just perceptible at − 30°.

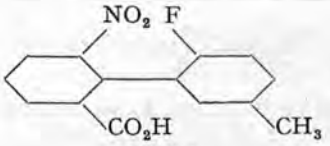
Mills and Elliott were the first to prove by isolation of the activated substance in its optically active form that the mutarotation observed in an optical activation was due to the production of one diastereoisomer in excess over the other.[10] Such proof is very desirable, for mutarotation might in any one case be due to several possible things—slowness of salt formation, solvation with change of rotation, change of temperature on solution, etc. They took 0·183 g. of their N-benzenesulphonyl-8-nitro-1-naphthylglycine in 25 c.c. of chloroform, and 0·221 g. (1·18 M.) of brucine in the same volume of chloroform and mixed the solutions. α_{5461} changed from − 0·78° to − 0·22° ($l = 4$) at a temperature which rose from 0·7° to 1·5° during the experiment. That this change was due to the establishment of excess of the *l*-base *d*-acid over the diastereoisomeric form was proved by taking a solution of 50 c.c. of chloroform containing the same weight of *dl*-acid and 0·211 g. of brucine, leaving it to stand for three hours and then extracting it with ice-cold dilute sulphuric acid adding a little acetone to keep the acid in solution. The chloroform-acetone solution was dextro-rotatory, mutarotating almost to zero at 1·2°.

Several of the observations of Pfeiffer and Quehl [27, 35] have been claimed as first-order transformations, although in no case is there any proof of the reality of the activation. Solutions of zinc β-camphorsulphonate, zinc α-bromo-π-camphorsulphonate and zinc quinate change their rotations by very considerable amounts when (optically inactive) α-phenanthroline or α : α′-dipyridyl is added; the authors attribute this to the preferential formation of one of the two possible mirror-image zinc octahedral complexes. When it is considered that the salt $[Zn(phen)_3]\ X_2$ must be completely ionised in solution, *i.e.*, the complex to be activated is entirely separated from the transforming agent, this seems to be a most striking result. But if their explanation is correct, a more remarkable example is the following: to an aqueous solution of cinchonine hydrochloride and zinc sulphate having a rotation of + 5·29°, 3 M. of α-phenanthroline was added. The rotation immediately became − 1·89° and changed on standing to − 2·46°. A similar observation was made using strychnine sulphate in place of the cinchonine hydrochloride, including the final mutarotation. If this really is a case of asymmetric transforma-

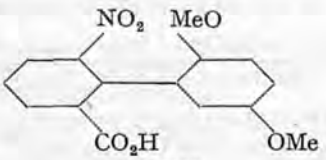
[33] *J. Chem. Soc.*, 1934, 347.
[34] *Ibid.*, 1941, 257.
[35] *Berichte*, 1932, **65**, 560; 1933, **66**, 415.

tion, it is unique that the labile asymmetric *cation* is being influenced by another *cation* which is presumably in no way attached to it. Removal of the cinchonine by precipitation with alkali left an optically inactive zinc salt. An alternative explanation in these cases is that the zinc in solution is originally combined with the alkaloid which is progressively displaced by the phenanthroline, accompanied by mutarotation. There are several other examples of this kind in the papers of Pfeiffer and his co-workers.

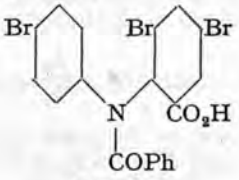
It is possible that a description of a case of first-order transformation lies in an observation in a paper by Stoughton and Adams [17] on the stability of diphenyl compounds. Crystallisation of 2·75 g. of 2-fluoro-5-methyl-2′-nitro-6′-carboxydiphenyl (XXVI) and 3·94 g. of brucine from 150 c.c. of ethyl alcohol resulted in a first crop of salt *l*-B*d*-A . $\frac{1}{4}H_2O$ weighing 5·1 g.: when dissolved in chloroform this substance had $[\alpha]_D^{20} - 3{\cdot}2°$, but the authors record that if the solution was made up at 0° the value of $[\alpha]_D^{20}$ was + 13° and mutarotated to the value − 3·4°. Unless the temperature coefficient of rotation is very large it would appear therefore that + 13° is nearer to that of the base *d*-acid salt and that − 3·4° represents an equilibrium value which might of course be that of the partial racemate, but if it is not, stands for an asymmetric transformation. The authors were concerned with producing series of differently restricted diphenyl compounds and did not pursue this line of investigation.



XXVI.



XXVII.



XXVIII.

Although Yuan and Adams [15] consider that the following evidence does not justify the diagnosis of first-order transformation, it merits a careful survey and inclusion here. Brucine in wet alcohol causes 2 : 5-dimethoxy-2′-nitrodiphenyl-6′-carboxylic acid (XXVII) to undergo second-order asymmetric transformation to the *l*-base *l*-acid salt; the earliest observed $[\alpha]_D$ in chloroform was − 167°; mutarotation occurred to + 3·2° in 100 minutes and the extrapolated value for the initial reading was − 180°. A solution of brucine and the *racemic* acid in equimolecular quantities in chloroform had an initial $[\alpha]_D^{25}$ of − 8·6° changing to + 3·3° in 80 minutes. Yuan and Adams say "this may have been due to slowness of salt formation in the organic solvent. It was not due to the fact that the mixture consisted of unequal quantities of *l*-*l*- and *l*-*d*-salts . . ." because precipitation from the solution with petroleum ether gave a salt which produced an inactive acid on decomposition with hydrochloric acid. Examining these results: if we assume that − 180° and − 8·6° are the specific rotations of the *l*-base *l*-acid and *l*-base *dl*-acid respectively, the specific rotation due to combined *l*-acid is − (180 − 8·6)° = − 171·4°. Mutarotation from *l*-base *dl*-acid to equilibrium takes place over − 8·6 − 3·3° = − 11·9°, this representing 11·9/171·4 × 100, *i.e.* about 7 % disproportionation. In other words the equilibrated solution may be assumed to contain 53·5 % of the *l*-base *d*-acid and 46·5 % of the *l*-base *l*-acid. It is little wonder that precipitation of this solution with petroleum ether, which would hardly be quantitative, produced either the partial racemate or a mixture of salts indistinguishable from it.

Among other acids in a series which provided much good material for the study of the subject in general, N-benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylic acid (XXVIII) was the first to be investigated thoroughly.[21] With many other labile compounds it owes its optical

activity to restricted rotation within the molecule and its optical instability to the fact that given sufficient energy the molecule can pass through an intermediate flat stage to give the mirror image form. This acid underwent first-order asymmetric transformation in chloroform in the dextro direction with *nor-d-ψ*-ephedrine and in the lævo direction with cinchonidine. The latter change was investigated more fully: the cinchonidine *d*-acid salt was prepared by a second-order transformation in acetone, and a mixture of 64 % base *l*-acid and 36 % base *d*-acid salts by a crystallisation amounting to the first stage of resolution in the same solvent at − 15°. Their ranges of mutarotation in chloroform and rates of approach to equilibrium are tabulated :—

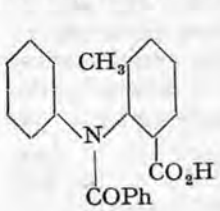
	$[\alpha]^{18\cdot0°}_{5461}$ initial.	$[\alpha]^{18\cdot0°}_{5461}$ final.	$k^{17\cdot7°}$ $\log_{10}$ min.$^{-1}$
base *l*-acid . .	− 105°	− 44·5°	0·0200
base *d*-acid . .	+ 194° (extrap.)	− 44·5°	0·0206
base *dl*-acid . .	− 40·4°	− 44·5°	(range too small for measurement)

The measured velocity constant k of course represents the sum of the velocity constants of inversion, k_d and k_l, of the two diastereoisomers : their difference is responsible for first-order asymmetric transformation. Assuming that dissociation in solution is negligible,

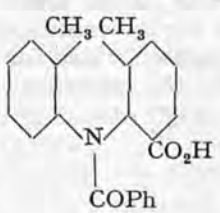
$$\frac{k_d}{k_l} = \frac{\text{concentration } l\text{-base } l\text{-acid at equilibrium}}{\text{concentration } l\text{-base } d\text{-acid at equilibrium}}$$

and in this case, concentration being proportional to rotation, $k_d = 0{\cdot}0105$ and $k_l = 0{\cdot}0101$: the difference is very small, but it is, of course, real.

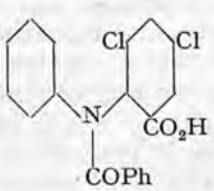
The preparation of a diversity of acids in this series [22] provided material for many more examples of first order transformation. N-benzoyl-2-methyl-diphenylamine-6-carboxylic acid (XXIX) showed mutarotation in presence of *nor-d-ψ*-ephedrine in chloroform containing 1/40 of ethyl alcohol by volume. N-benzoyl-2 : 2′-dimethyldiphenylamine-6-carboxylic acid (XXX) also mutarotated in presence of cinchonidine in the same



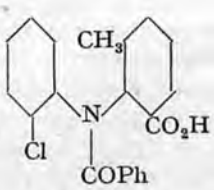
XXIX.



XXX.



XXXI.

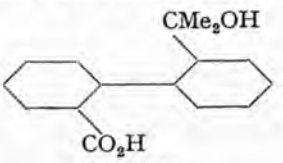


XXXII.

solvent. The originally *l*-rotatory cinchonidine solution became immediately more *l*-rotatory on addition of the *dl*-acid and then mutarotated in the dextro direction. This observation disposes of any possibility of observed mutarotations being due to slowness of salt formation, which would cause mutarotation in the opposite direction. N-benzoyl-2 : 4-dichloro-diphenylamine-6-carboxylic acid (XXXI) showed mutarotation with *nor-d-ψ*-ephedrine in chloroform and with cinchonidine in chloroform containing 1/40 of ethyl alcohol by volume. This solution after equilibration was extracted with mineral acid and gave a specimen of dextrorotatory acid, establishing with certainty the assumed activation. N-benzoyl-2-methyl-2′-chlorodiphenylamine-6-carboxylic acid (XXXII) showed mutarotation with quinidine and with brucine in the same chloroform-alcohol solution. The behaviour of Mills and Elliott's [10] N-benzenesulphonyl-8-nitro-1-naphthylglycine with cinchonidine in chloroform was

examined : the cinchonidine *l*-salt mutarotated from $[\alpha]_{5461}^{15^\circ}$ $-255{\cdot}5^\circ$ to $-87{\cdot}3^\circ$, while the rotation of the cinchonidine *dl*-salt went from $-35{\cdot}5^\circ$ to $-87{\cdot}3^\circ$. This represents an equilibrium composition of 38 % *l*-base *d*-acid and 62 % of *l*-base *l*-acid.

The kinetic experiments on simple optical activation were completed [13] by showing that the rate of approach to equilibrium was the same starting from base *l*-acid and from base *dl*-acid, a result which was, of course, predictable, but which depended for demonstration on finding a large enough range of mutarotation starting with the *dl*-acid. The brucine salt of *l*-2′-(α-hydroxy*iso*propyl)-diphenyl-2-carboxylic acid (XXXIII), obtained by second-order asymmetric transformation from ethyl alcohol, mutarotates from $[\alpha]_{5461}^{25{\cdot}15^\circ}$ $-47{\cdot}04^\circ$ to $+1{\cdot}46^\circ$ with a first-order velocity constant $k^{25{\cdot}15^\circ}$ ($\log_{10}$ hours^{-1}) = 0·0277 in chloroform ($c = 6{\cdot}835$; $l = 2$) the first reading made 20 minutes after wetting. A mixture of the *dl*-acid and brucine in equimolecular proportions in chloroform shows a change of rotation from $[\alpha]_{5461}^{25{\cdot}15^\circ}$ $-5{\cdot}08^\circ$ to $+1{\cdot}90^\circ$, the change following the first-order law with a velocity constant of $k^{25{\cdot}15^\circ} = 0{\cdot}0280$ ($\log_{10}$ hours^{-1}), sufficiently good agreement with that of the salt to show that the same process is under observation. The equilibrium composition in chloroform calculated from these figures is 58 % of the *d*-acid salt and 42 % of the *l*-acid salt, assuming no dissociation.



XXXIII.

First-Order Transformation, Second-Order Transformation and Resolution.

It now becomes interesting to investigate the relation between the two kinds of asymmetric transformation of an optically labile substance and the boundary between the second and optical resolution. An immediate difficulty is presented in the rarity of known substances which will undergo the three or even two of the three processes in or from the same solvent.

The first two effects have been demonstrated with 2′-(α-hydroxy-*iso*propyl)-diphenyl-2-carboxylic acid and brucine in chloroform but not both at the same temperature.[13] The relevant observations were as follows : the equilibrium composition of the brucine salt in chloroform is 58 % of the base *d*-acid and 42 % of the base *l*-acid ; when such a solution is evaporated on a boiling water bath with constant stirring to induce crystallisation as soon as it is possible, base *l*-acid crystallises. If we make the assumption that the equilibrium composition is not sensibly altered between room temperature and 100° (compare the case of α- and β-glucose, ratio of concentrations in solution unaltered between 0° and 40° [36]) it follows that the base *d*-acid is more stable *in* solution while the base *l*-acid has the greater tendency to come out of it, *i.e.* is less soluble.

In the class of second-order transformations involving crystallisation of diastereoisomers which are *ionised* in solution so that the labile centre is not in combination with the activating agent until crystallisation takes place, the diastereoisomers have no joint reality in solution and, as has already been pointed out, there can be no first-order transformation. That is to say, if one diastereoisomeric salt is dissolved in a solvent in which the acid part is labile, mutarotation takes place towards an equilibrium composition which is that of the partial racemate : the rate constant k for the approach to equilibrium from base *d*-acid or base *l*-acid is made up of k_d and k_l, the rates of *partial inversion* of base *d*-acid and base *l*-acid, where these are *equal* and their sum is what has long been referred to as the rate of *partial racemisation*.

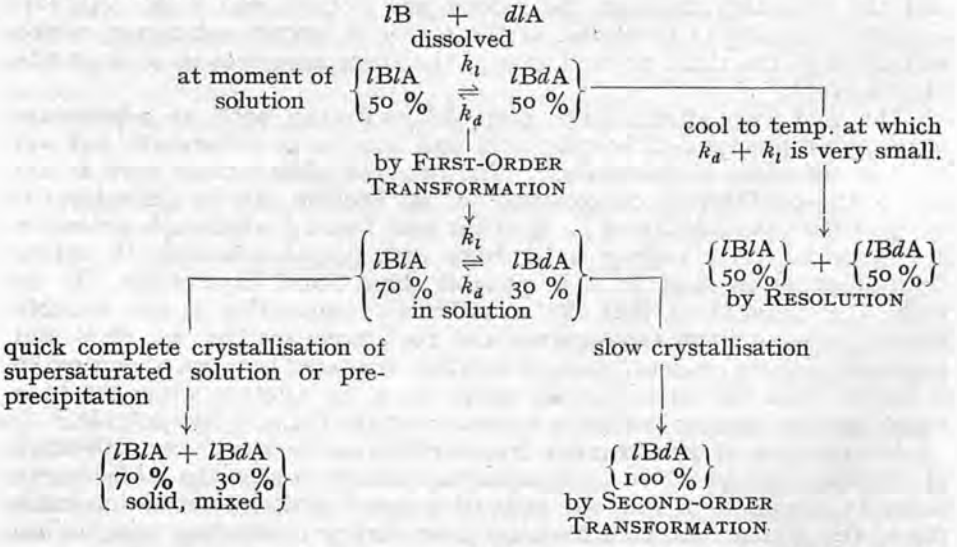
[36] Moelwyn Hughes, *Kinetics of Reactions in Solution*, 1933 edn., p. 45.

Let us consider a hypothetical case in which a *dl*-acid (optically unstable) and a *l*-base (optically stable) are dissolved in a *non*-dissociating solvent: the diastereoisomers have different free energies and mutarotation therefore begins immediately towards an equilibrium, say to

$$\begin{matrix} l\text{B}l\text{A} & \rightleftharpoons & l\text{B}d\text{A}. \\ 70\ \% & & 30\ \% \end{matrix}$$

Neglecting all the complicating possibilities of supersaturation, accidental inoculation, crystallisation of a different entity from those existing in solution (*e.g.* with solvent, if the solvent is not similarly attached in solution) or the separation of a crystalline partial racemate, if, then, the solution becomes saturated by evaporation of the solvent it will begin to deposit crystals: and if the rate of crystallisation is less than the rate of mutarotation, then all of the salt which comes out will be in the one *l*B*d*A form, and the solution from which it is crystallising will show the equilibrium specific rotation. But suppose on the other hand, that the equilibrated solution is taken and cooled quickly to a temperature which brings it well below the saturation point of both salts and at which rate of crystallisation is faster than rate of mutarotation, then the material crystallising might well be mainly base *l*-acid with some base *d*-acid. The third possibility in crystallisation phenomena is that a solution of the base *dl*-acid is cooled immediately after dissolving to a temperature below which mutarotation can occur at an effective speed, when of course, given the usual necessary solubility conditions a straightforward resolution can be carried out and base *d*-acid and base *l*-acid separated by fractional crystallisation.

This is a simplified picture, but it has proved interesting to examine the scant and scattered literature on the subject with it in mind in an attempt to correlate the several valuable but unrelated observations on "optical activation."

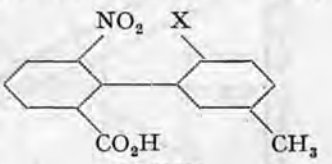


Sometimes the difference in free energy is so slight that one form or the other may crystallise haphazard without apparent difference in experimental procedure: thus Mills and Bain [3] found that in crystallising the quinine salt of their oximino*cyclo*hexane-4-carboxylic acid from ethyl acetate sometimes there was a preponderance of the *d*-acid and sometimes of the *l*-acid in the salt produced. They obtained their purest (optically) specimen of quinine *l*-acid salt by deliberately choosing a solvent, dilute acetic acid, which would secure that the rate of racemisation should be as high as possible compared with that of crystallisation.

Althongh Read and McMath [8, 9] in their two papers describe several experiments which bear an apparent relation to this argument, closer scrutiny shows that interpretation is far from simple because of the large number of solvents, both pure and mixed, which they used. For example, their classic first-order transformation to an equilibrium of *l*B*l*A 81 % ⇌ *l*B*d*A 19 % was carried out in specially purified and dried acetone, while the second-order transformation took place from acetone-methyl alcohol; also, the second crystalline form which can be obtained is not the diastereoisomer but the partial racemate *l*B*dl*A. Another somewhat complicating factor in the use of the results for an argument other than that for which they were employed by the authors, is the fact that *l*-hydroxyhydrindamine as the benezenesulphonate itself shows a certain amount of mutarotation in methyl alcohol—$[M]_D$ in methyl alcohol changes from − 100° to − 76° in eight hours—and that the salt *l*B*l*A is so little soluble in "ordinary" acetone that by the time it can be got into solution by heating its mutarotation is lost. This makes it impossible to bring into line with any certainty the interesting observation that evaporation of an acetone solution deposits crystals having $[M]_D$ − 93° mutarotating in acetone to − 154°: evaporation to crystallisation and redissolving giving a repetition of the optical cycle. In their second paper [9] the crystallisation of *l*-hydroxyhydrindamine chlorobromoacetate was carried out in two ways from chloroform solution containing a little methyl alcohol. Slow deposition in the cold gave the *l*B*dl*A, while rapid cooling of a supersaturated solution gave crystals of *l*B*d*A, but after about an hour, *i.e.* when the solution was cool, *l*B*dl*A began to separate on top of the original crystals.

McKenzie and Smith,[30] during the resolution of *l*-menthyl *dl*-phenylchloroacetate by crystallisation from rectified spirit found, as a result of experience of many crystallisations, that the *l*-menthyl *d*-acid ~~salt~~ was the less soluble of the pair of diastereoisomers: this can now be linked with the fact that the equilibrium state in ethyl alcohol consists of an excess of the *l*-menthyl *l*-acid salt, if it be assumed that the small concentration of potassium hydroxide added has no appreciable effect on the system other than to confer the necessary mobility for the attainment of equilibrium. There is evidence for parallel behaviour in *l*-menthyl *dl*-phenylbromoacetate.

The behaviour of N-benzoyl-2 : 4 : 4′-tribromodiphenylamine-6-carboxylic acid with cinchonidine in acetone provides examples of both second-order transformation and resolution and illustrates the distinction between them.[21] The *dl*-acid dissolved with an equivalent of cinchonidine in acetone at room temperature or at the boiling point deposits *l*B*d*A in almost quantitative yield. Having found values of the velocity constant of mutarotation of this salt at different temperatures and thereby the values of B and E in the Arrhenius equation $k = Be^{-E/RT}$ calculation shows that resolution might be possible at − 15° owing to the smallness of k there. Accordingly 1 M. of *dl*-acid and 1 M. of cinchonidine were dissolved in warm acetone and, as soon as crystallisation began, cooled to − 15°. The *l*B*d*A crystallised out, almost exactly 50 % of the total weight, and evaporation of the filtrate *in vacuo* while still cold gave a mixture of 64 % of *l*B*l*A and 36 % of *l*B*d*A.



XXXIV.

Another general view of the relation of second-order transformation and resolution can be made by considering a series of compounds in which the relative optical stability can be predicted to vary progressively: for example, Kuhn and Albrecht's [25] series of dinitrodiphenic acids, or the set of 2′-substituted (XXXIV) 2-nitro-5′-methyldiphenyl-6-carboxylic acids of Stoughton and Adams,[17] where the 2′ position carries Br, Cl

or F, with brucine in ethyl alcohol. When X is Br or Cl the crystallisation process at room temperature is one of resolution, early crops having negative rotations and later crops positive ; when X is the smaller F atom crystallisation takes place with second-order transformation, all crops having the same rotation : and an apparent first-order transformation has been observed, but not in the same solvent.

The Effect on First-Order Transformation Equilibria of Adding an Excess of the Labile Acid.

The equilibrium rotation of a 1 : 1 acid : base solution (equivalent quantities) in a non-ionising solvent (optically unstable acid, optically stable base) has been found to be extremely sensitive to an excess of the *dl*-acid in several cases, an effect which is not due to suppression of dissociation in the diastereoisometric salts.[21, 22] N-benzoyl-2-methyl-2′-chlorodiphenylamine-6-carboxylic acid and quinidine in chloroform containing 1/40 ethyl alcohol by volume affords a good example.

0·1620 g. of quinidine in 20 c.c. of the solvent, $l = 2$, had a rotation $\alpha^{20°}_{5461}$ of + 4·8°. When 1 M. of the *dl*-acid was added the rotation changed immediately to + 4·35°, and on standing mutarotated to + 2·99°; with

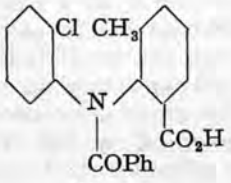
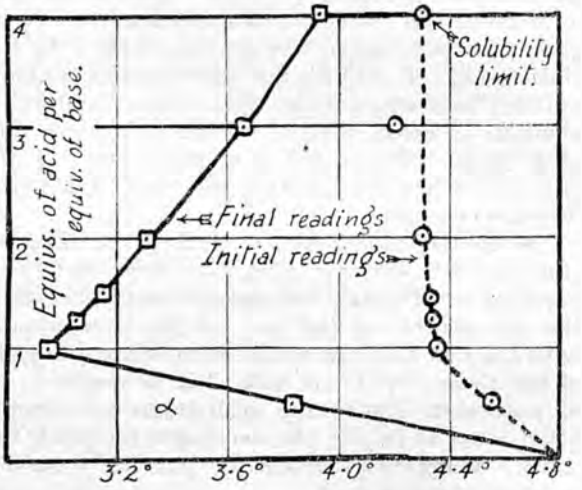


FIG. 2.



2 M. of acid the original $\alpha^{20°}_{5461}$ of + 4·30° changed to + 3·32°; with 3 M. + 4·32° changed to + 3·67°. The total result is clearly seen on the graph (Fig. 2). The rate of approach to equilibrium increased with increase in concentration of acid. Decomposition with mineral acid of equilibrated solutions always gave the *l*-acid.

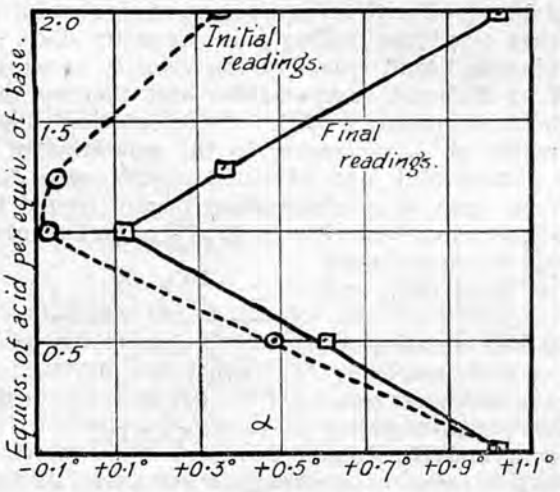
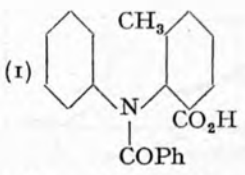


FIG. 3.

Many other examples of this type of behaviour were found : in some cases the curve for mutarotated solutions lay to the other side of the original curve, *e.g.* N-benzoyl-2 : 4-dichlorodiphenylamine-6-carboxylic acid with *nor-d-ψ*-ephedrine in chloroform, the final rotation was nearer to that of the base than the original value (Fig. 3). Also it can be seen that the "initial" curve is not always of the ideal type shown in the first example :

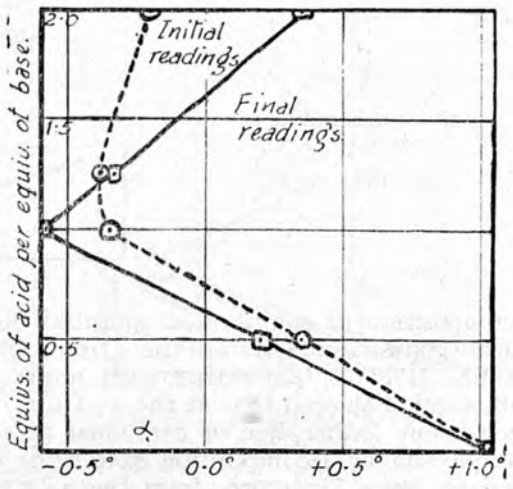
in a case such as this one it is considered to contain all the extraneous effects contributing to change of rotation (such as concentration) while the difference between the initial and final curves can only be due to an optical activation effect.

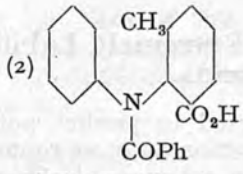
The cases which were most fascinating were those in which the initial and final curves crossed over. This happened with



and *nor-d-ψ*-ephedrine in chloroform

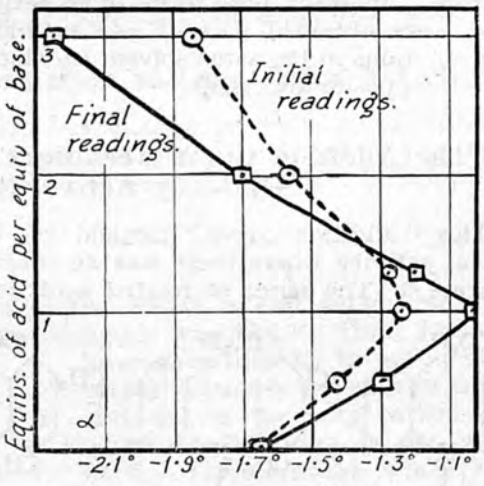
FIG. 4.

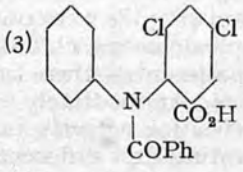




and cinchonidine in chloroform/EtOH

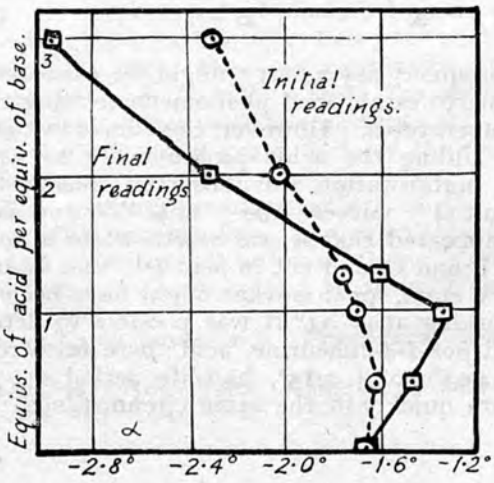
FIG. 5.





and cinchonidine in chloroform/EtOH

FIG. 6.



(4) $PhSO_2$ N CH_2CO_2H, NO_2

and cinchonidine in chloroform/EtOH

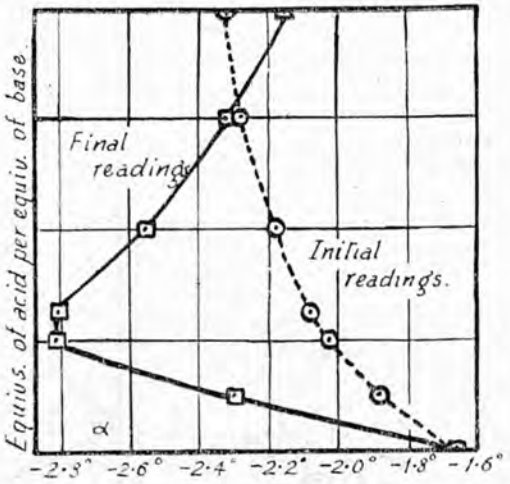
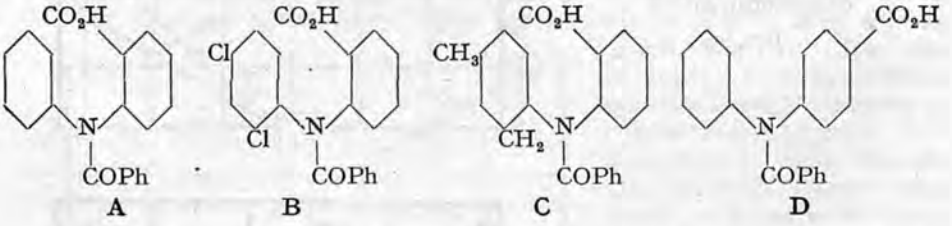


FIG. 7.

Decomposition of equilibrated solutions demonstrated the reality of the transformations underlying these mutarotations: in example (3), for instance (Fig. 6), extraction with mineral acid of the solutions after mutarotation showed that at the 1 : 1 ratio *d*- and at the 3 : 1 ratio *l*-acid was present (either free or combined as salt) in excess. In the fourth example similar decomposition gave acids which, from the 1 : 1 and 2 : 1 mixtures, were *l*-rotatory, from the 3 : 1 inactive and from the 4 : 1 *d*-rotatory. In effect, both forms of an active acid (not, of course, optically pure) were obtained *without ever separating* a salt—extracted directly from solutions in the same solvent in which optical activations had taken place in opposite directions.

The Addition Curve Technique and Extremely Labile Optically Active Compounds.

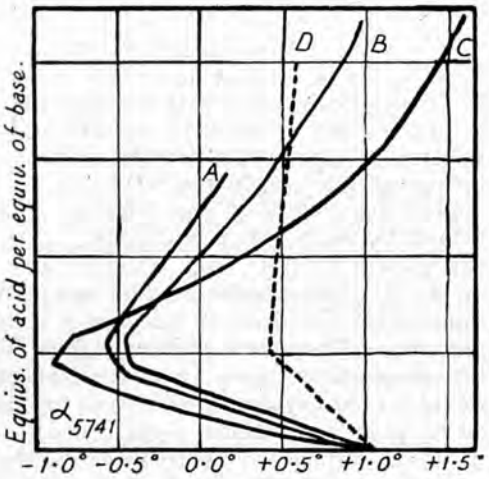
This "addition curve" method has been used to predict potential optical activity where there was no other indication of it at room temperature.[21] The series of related acids in which rotation blocking with



consequent asymmetry might be expected to operate, show none of the hitherto established phenomena relating to optical isomerism at ordinary temperatures. However, the curves in the diagram (Fig. 8) were obtained on adding the acids progressively to *nor-d-ψ*-ephedrine in chloroform: no mutarotation was observed during the experiments—there are no "initial" curves—the "final" curve is obtained immediately. Thus it appeared that it was worth while to look further for activity in acids A, B and C, and not in acid D: that is an interesting first differentiation for a start, for it is what might have been predicted from their structures. Working at $-31°$ it was possible to detect a mutarotation with acid C and *nor-d-ψ*-ephedrine, acid : base ratio roughly 4 : 1, α_{5461} changed from $-4{\cdot}03°$ to $+2{\cdot}15°$, half-life period 2·4 minutes. Acid B mutarotated more quickly in the same circumstances: each process followed the first

order law. Acid A, on the contrary, showed no such mutarotation, but it would hardly be stretching a point to say, as within the series, that its optical activity is demonstrated by the addition curve.

This brief description shows that with discreet handling the "addition curve" technique, far from "obscuring its interpretation and lessening its value as a means of demonstrating optical activity in labile systems" (Mills [37]) extends the field of optical observation covered by the activation process into realms which were hitherto unattainable. The only occasions on which it could "affect the diagnostic value of the activation process" [37] as already outlined previous to this time would be those on which non-equivalent quantities of base and acid were taken and happened by chance to lie on the point where the initial and final curves crossed over: risk of this mistake can easily be eliminated by always looking for mutarotation at more than one acid : base ratio.



(0·1051 g. *nor-d-ψ*-ephedrine in 14·5 c.c. $CHCl_3$; l = 2.)

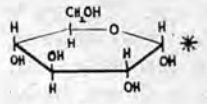
FIG. 8.

Asymmetric Transformation and the Sugar Series.

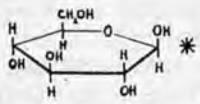
In the light of this collected information on first-and second-order asymmetric transformations it is of the utmost interest to re-examine some well-established data in the sugar series which might be relevant to the subject.

1. *d*-Glucose.

d-Glucose exists in solution in two forms, α- and β-*d*-glucose. Any other forms must be present in negligible quantity.[38] These forms are interconvertible by inversion of the carbon atom marked with an asterisk and this is the only carbon atom whose configuration is not rigidly fixed. Therefore the whole molecule can be considered as if it were one of a pair of diastereoisomers with one labile and one stable component, the α-carbon atom being the unstable and the rest of the molecule the stable part: the diastereoisomers are, of course, "real" as long as the sugar is in the ring form. The optically stable part will exert an asymmetric influence on the unstable part, but it will be impossible to remove the influential group and see the results of first- or second-order transformation in the remainder.



α-*d*-glucose.



β-*d*-glucose.

(*a*) ***d*-Glucose in Water.** The composition of a mixture of the two forms of *d*-glucose in water at equilibrium has long been calculated from the rotations of the two forms and of their equilibrium solution: some of the latest published figures are those of Kendrew and Moelwyn Hughes,

[37] Mills, "The Stereochemistry of Labile Compounds," Presidential Address, *J. Chem. Soc.*, 1943, 194.

[38] Andrews and Worley, *J. Phys. Chem.*, 1927, 1880; Kendrew and Moelwyn Hughes, *Proc. Roy. Soc.*, *A*, 1940, **176**, 353.

who incorporate some values from Hudson and Yanovsky [39]; these are for water solutions :—

α-*d*-glucose	equilibrium	β-*d*-glucose
$[\alpha]_{5893}^{22\cdot2^\circ}$ + 110·0°	+ 52·56°	+ 19·7° at 20°.

The equilibrium composition, assuming dissociation from the ring form to be negligible, is 64 % β- and 36 % α-form. This equilibrium appears to be unaffected by temperature between 0° and 40°.[36] When *d*-glucose is crystallised from cold water α-*d*-glucose . H_2O is *always* obtained,[40] while crystallising from water between 35° and 40° gives the anhydrous form, again of α-glucose.[41] It therefore crystallises out from a solution containing excess of the β-form. Crystals of the β-form cannot be obtained by such gentle methods; Tanret obtained it by long standing of the α-form at 105°, and Whistler and Buchanan [42] obtained it by taking an 85 % glucose solution and evaporating it during two hours (in 50 g. quantities) *in vacuo* at 100° to a solid mass of crystals consisting of β-glucose. (There are various other methods of affecting "second-order transformation" to α- or to β-*d*-glucose : thus Hudson and Dale,[43] recommend a cold crystallisation from aqueous acetic acid resulting in 75 % to 80 % pure anhydrous α-glucose and a hot quick crystallisation giving 93 % of β-glucose : these workers also recognised that the velocity constant for approach to equilibrium k was the sum k_α and k_β and therefore the same from whichever side the measurement started.[44] *d*-Glucose is too soluble in water for the relative solubilities of the α- and β-forms to be measured directly, but general practice would certainly lead one to the view that the α-form is the less soluble.

(*b*) ***d*-Glucose in 80 % Ethyl Alcohol.** Hudson and Yanovsky give the following values :—[39]

$$[\alpha]_D^{20^\circ} \quad \left.\begin{array}{l}\alpha\text{-glucose} + 115\cdot5^\circ \\ \beta\text{-glucose} + 20\cdot3^\circ\end{array}\right\} \text{equilibrium} + 59\cdot3^\circ$$

there is therefore an excess of the β-form in solution at equilibrium. The solubilities found directly were 2·0 g. α-form in 100 c.c., 4·9 g. β-form in 100 c.c. ; the α-form is the one crystallising, but as the hydrate.

(*c*) ***d*-Glucose in Absolute Methyl Alcohol.** Andrews and Worley [38] give the following values :—

$$[\alpha]_{5461}^{25^\circ} \quad \left.\begin{array}{l}\alpha\text{-glucose} + 138\cdot4^\circ \\ \beta\text{-glucose} + 26^\circ\end{array}\right\} \text{equilibrium} + 75\cdot8^\circ$$

there is therefore excess of the β-compound at equilibrium. Lowry [44] obtained crystals of the α-form from methyl alcohol. He also showed that the solubilities in this solvent were small and did not interfere with each other, and in this and a paper by Hudson and Dale it is shown to be justifiable to use the relationship

$$K = \text{equilibrium const.} = \frac{k_\alpha}{k_\beta} = \frac{S\infty - S\alpha}{S\alpha},$$

where $S\alpha$ is the initial solubility of the α-form and $S\infty$ the solubility at equilibrium, to calculate the rotation of the as then unknown β-compounds.

2. *d*-Mannose.

(*a*) ***d*-Mannose in Water.** Hudson and Yanovsky [39] using the solubility-rotation relationship calculated that the specific rotation of the

[39] *J. Amer. Chem. Soc.*, 1917, **39**, 1013.
[40] Tanret, *Compt. rend.*, 1895, **120**, 1061.
[41] Behr, *Berichte*, 1882, **15**, 1104 ; see also Newkirk, *Ind. Eng. Chem.*, 1938, **28**, 760.
[42] *J. Biol. Chem.*, 1938, **125**, 557.
[43] *J. Amer. Chem. Soc.*, 1917, **39**, 320.
[44] See also Lowry, *J. Chem. Soc.*, 1904, **85**, 1551.

then unknown α-mannose was + 30°, knowing that the specific rotation $[\alpha]_D^{20°}$ of β-*d*-mannose was − 17°, and that that of the equilibrated solution in water was + 14·6°. Six years later Levene [45] prepared α-mannose and confirmed their prediction. There is thus excess of the α-form at equilibrium, the *opposite* from the *d*-glucose equilibrium. While *d*-mannose has not been crystallised from water, it is worthy of note that Levene says: "under conditions when glucose and galactose appear in the β-form, mannose crystallises in the α-form and *vice versa*," quoting three cases to support this statement.

(*b*) ***d*-Mannose in 80 % Ethyl Alcohol.** In this solvent also the α-form is present at equilibrium in excess; $[\alpha]_D^{20°}$ β-form − 14·9°, equilibrium + 25·7°, α-form + 35° (predicted by Hudson and Yanovsky and observed by Levene). The β-form is stable under this solvent.

3. Lactose and Galactose.

A similar relationship holds for these sugars in water, in which the β-form is in excess at equilibrium and the α-form crystallises out, but as the hydrate.[39, 46]

This short discussion is sufficient to show that the study of asymmetric transformation is in its infancy; no doubt there are many more examples as yet uncollected and a wealth yet to be discovered as the technique for exploring the phenomena of unstable optical activity becomes finer. Compounds which owe their asymmetry to restricted rotation are highly suitable for the study of optical kinetics, their lability being free from disturbing influences which may complicate other forms of instability; they are not known to occur in nature, but what is predicted from the simple system may be applied with proper discretion to the more complicated. It seems likely that instances of disturbed optical equilibria as well as the second-order transformations may play an important part in the building up of the asymmetric molecules which are characteristic of living matter.

The author wishes to record her indebtedness to Professor E. E. Turner, F.R.S., in whose laboratory the foregoing discussion has largely developed.

Bedford College,
London.

[45] *J. Biol. Chem.*, 1932, 329.
[46] Tanret, *Bull. Soc. Chim.* 1871 (iii), **15**, 195.

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PROGRESS IN STEREOCHEMISTRY

2

Editors:

W. KLYNE, M.A., B.Sc., Ph.D.

P. B. D. de la MARE, Ph.D., D.Sc.

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5

THE STUDY OF OPTICALLY LABILE COMPOUNDS

M. M. Harris

When the stereochemist prepares a new compound which he considers may be optically active he normally tries to resolve it into its two enantiomeric forms. If it is too unstable optically for resolution* under ordinary conditions, there are still several methods of investigating it which depend upon polarimetry: it is the object of this chapter to describe these methods and, as a cognate matter, to point to the stereochemical significance which may be attached to an observed mutarotation.

The types of molecular architecture which lead to optical instability have been described in a number of past reviews (Ritchie, 1933, 1947; King, 1933; Shriner, Adams and Marvel, 1943; Maitland, 1939; Kenyon, 1942; Mills, 1943; Jamison, 1945; Harris and Turner, 1947; Campbell, 1953) so that this account can proceed straight to a description of the attendant properties. There has been appreciable advance in this field during the last few years.

ASYMMETRIC TRANSFORMATIONS

Asymmetric transformation may be undergone by a substance of which the molecule is capable of optical activity and is also wholly or in part optically labile.

The behaviour of the α- and β-forms of D-glucose, in solution and in crystallizing from it, is the prototype of many of the phenomena of labile optical activity in conjunction with stable optical activity. When Dubrunfaut (1846) first observed the 'birotation' (a word discarded by Lowry in 1899 in favour of 'mutarotation') of glucose solutions he was making an important discovery in sugar chemistry and, as he followed it to the end, he was recording the first example of an asymmetric transformation. There were good reasons why this study did not take its place in the main stream of the earlier stereochemistry of optically labile compounds, notably that the structure of D-glucose was not conclusively proved until the late nineteen-twenties (Haworth), nor was the composition of an equilibrated aqueous solution established until 1940 (Kendrew and Moelwyn-Hughes).

* The word *resolution* is used to mean the separation of a racemic compound or mixture into two enantiomers, theoretically 50 per cent of each; it can also be used to describe any part of such a process.

Thus the behaviour of diastereoisomeric salts with one optically labile component, in non-dissociating solvents, was worked out independently of the mutarotation of glucose, and then was found to be obeying similar rules.

In an ideal and complete optical resolution a (±)-mixture of enantiomers would be separated into 50 per cent of each: in an ideal and complete asymmetric transformation the (±)-mixture would be converted into one of the isomerides in 100 per cent yield, or the (+)- or (−)- compound would be converted into the opposite isomeride. Such completion is not in general achieved in an asymmetric transformation in solution, for here an equilibrium is reached in which the free energy difference between the diastereoisomers is not large, but near approach to theoretical yields has often been recorded in asymmetric transformation by crystallization.

These transformations take place in an optically labile compound or group when it comes under the influence of an optically stable, resolved compound or group; the labile part may be bound to this 'asymmetric influence' by chemical, ionic or electrostatic bonds, it may be dissolved in it or with it, or the two may form a crystalline adduct. The very simplest category of asymmetric transformation depends upon crystal forces directing the building of a single isomeride on a seed of the same *laevo* or *dextro* pattern.

Asymmetric Transformation by Crystallization

This process, which is often called 'second-order' asymmetric transformation (*cf* p. 163), is a most useful one for the isolation of optically labile compounds in an optically pure state; it involves the crystallization of a solid, usually (but by no means always) one of a pair of diastereoisomeric salts, formed of optically labile and optically stable, resolved, component parts:

Crystals		*In solution*		*Crystals*
Labile acid				
(+)A.(−)B 100%	$\xleftarrow{a}$	(+)A.(−)B $\rightleftarrows$ (−)A.(−)B	$\xrightarrow{b}$	(−)A.(−)B 100%
Labile base				
(+)B.(−)A 100%	$\xleftarrow{a}$	(+)B.(−)A $\rightleftarrows$ (−)B.(−)A	$\xrightarrow{b}$	(−)B.(−)A 100%

The crystallization must be carried out under conditions of solvent, temperature and concentration in which the diastereoisomers have a faster rate of partial inversion than of crystallization (Mills and Elliott, 1928; Adams and Gross, 1942; Adams and Sundstrom, 1954). A compound of medium optical stability may undergo such asymmetric transformation at room temperature, faster on heating and negligibly slowly at low temperatures, so that there it is resolvable (Jamison and Turner, 1938; Davidson and Turner, 1945).

Usually only one of the crystallizations (*a*) or (*b*) above can be realised experimentally, but sometimes by the use of alternative solvents (Mills and Bain, 1910; Werner, 1912; Mills and Elliott, 1928; Mills and Breckenridge, 1932) or by appropriate seeding (Meisenheimer and Beisswenger, 1932) it may be possible to get both forms by transformation in either direction. Use of different optically stable components also may allow the separation of both optically labile enantiomers (Thomas, 1921; Stoughton and Adams, 1932; Davidson and Turner, 1945).

If the salts represented by (±)A.(−)B or (±)B.(−)A are completely ionized or otherwise dissociated in solution, then the mother liquor from which crystallization takes place may show no optical activity which can be attributed to the labile acid or base; presumably the condition of diastereoisomerism is absent until the crystal is formed, as in Mills and Breckenridge's work (1932). If, on the other hand, the diastereoisomeric salts are not dissociated or if the asymmetric centres are joined by covalent bonds, then asymmetric transformation controls the composition of the solution. Thus α-D-glucose crystallizes from water (below 35° as α-D-glucose.H_2O) while the solution contains 36%α and 64%β. D-Mannose (Isbell and Pigman, 1933; Hudson and Yanovsky, 1917), in which the equilibrium is 68·8%α and 31·2%β, crystallizes from water in the β-form; from a mixture of glacial acetic acid and ethyl alcohol it crystallizes in the α-form. Lactose in water behaves similarly to D-glucose. The 'salt'* brucine 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylate, in which the equilibrium proportions in chloroform are (+)A.B 58% (−)A.B 42%, crystallizes as (−)A.B. It will be noted that in all these cases the diastereoisomer which is in smaller proportion in the solution is the one which crystallizes from it, although there seems to be no valid reason why this should be a general rule.

In combination with suitable partners, the following types of optically labile compounds show asymmetric transformation by crystallization as salts:

(i) Substituted diphenyls: Kuhn and Albrecht (1927); Corbellini and Angeletti (1932); Adams *et al.* (1932, 1933, 1943, 1941).

(ii) Related compounds: Meisenheimer and Beisswenger (1932); Hall, Ridgwell and Turner (1954).

(iii) Compounds in which there is restricted rotation about bonds linked to tervalent nitrogen: Mills *et al.* (1928, 1932); Turner *et al.* (1938, 1940, 1955); Adams *et al.* (1950, 1954—two examples, 1956).

* The compound formed by dissolving equivalent amounts of a carboxylic acid and a base in chloroform solution is referred to as a salt although it is probably a hydrogen bonded complex or an undissociated ion-pair.

(iv) Similar compound in the antimony series: Campbell (1947).

(v) Other compounds showing restricted rotation in the benzene series: Meisenheimer, Theilacker and Beisswenger (1932); Adams and Gross (1942).

(vi) Compounds owing their optical instability to fugitive formation of a carbon cation (presumably flat) or to keto-enol tautomerism: Pope and Peachey (1900); Leuchs and Wutke (1913); Leuchs (1921); Read and McMath (1925, 1926); Ashley and Shriner (1932); Davidson and Turner (1945).

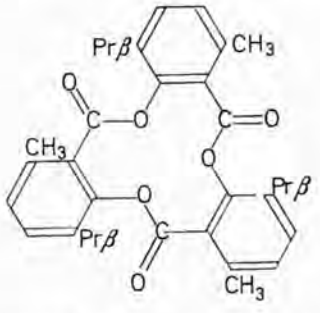
(vii) Oximino type compounds: Mills and Bain (1910, 1914).

(viii) Coordination complexes: Werner (1912); Thomas (1921).

(ix) Overcrowded molecule: Newman (1947).

As Ritchie (1947) has pointed out, asymmetric transformations of this kind must be of importance in optically selective biosynthesis. For example, the storage of amygdalin, the gentiobioside of (+)-mandelonitrile, and not of *iso*amygdalin, the gentiobioside of (−)-mandelonitrile, may be accounted for by the optical instability of mandelonitrile (Smith, 1931) in conjunction with the greater insolubility of amygdalin in comparison with its diastereoisomer (Krieble, 1912). Kuhn (1936) considered that this is a selective deposition which is not dependent upon enzyme action. The subject has also been discussed by Gause (1941).

Tri-*o*-thymotide (I) (Baker, Gilbert and Ollis; Powell; Newman and Powell; 1952) can exist in enantiomeric conformations related as left- and right-handed three-bladed propellers. The forms are optically labile with an activation energy for racemization, E_{racem} = 21·5* kcal.mole^{-1} in chloroform solution, such stability as they have being due to steric hindrance to interconversion by rotation about single bonds. The compound crystallizes from methyl alcohol as the



I

racemate, but from benzene or from *n*-hexane as a compound of the clathrate type. The unit cell in the latter case is found to hold six molecules of tri-*o*-thymotide and three of *n*-hexane. The tri-*o*-thymotide

* This value is a revision of the originally published one of 16, the calculation of which contained an arithmetical error; the *data* in the paper (Newman and Powell) are correct (personal communication to the writer from Dr. H. M. Powell, 1956).

molecules in one cell are either all *dextro* or all *laevo*, and a single crystal is formed all of one isomer. Although it is not possible to identify the enantiomeric crystals by outward appearance, separation can be achieved by removing a large crystal and testing the optical rotation of a solution of a chip of it. Once a crystal of a single enantiomer is obtained, it can be used to inoculate a solution of tri-*o*-thymotide and it will bring the compound out all in one form, as long as the rate of deposition of crystals is kept slower than the rate of racemization. This might be called a self-induced asymmetric transformation by crystallization. The experimental procedure is very similar to that used by Kipping and Pope (1898) to grow *dextro*rotatory sodium chlorate crystals; in one experiment they grew a *dextro* crystal weighing 47 g. This they chopped up and used to inoculate saturated solutions which then deposited the *dextro* form. Many of the tri-*o*-thymotide adducts show similar behaviour in crystallization.

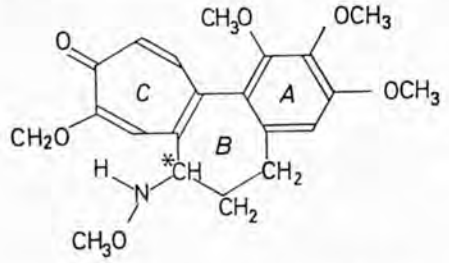
One group of tri-*o*-thymotide clathrates, crystallizing in the trigonal system, has small, closed asymmetric cavities which may be filled stereospecifically if suitable molecules are available. Powell (1952, 1954) has resolved *sec*-butyl bromide by this means. Tri-*o*-thymotide, itself crystallizing from *sec*-butyl bromide either in the *dextro* or in the *laevo* form, selects one enantiomer from the solvent in order to form the crystal lattice. It would be of great interest to find an optically labile compound which would be the guest molecule in such a crystalline clathrate, but it may be that in order to be optically labile it would have to be too large. The *cyclo*dextrin molecule, which can resolve ethyl mandelate and structurally related esters (Cramer, 1952, 1954) might form a better clathrate for such experiments: mandelic acid and its esters are optically labile under alkaline conditions, so there are interesting possibilities of asymmetric transformation here.

Allylethylmethylphenylammonium iodide crystallizes in the (+)- or the (−)-form only, if care is taken to see that it comes out very slowly indeed, from chloroform with a molecule of the solvent; a single crystal may be grown, a crop being formed all of the same enantiomeride (Havinga, 1941). This depends upon presenting the pattern of one form and giving time for racemization processes (such as $MeEtAllylPhN^{+}\}I^{-} \rightleftarrows MeI + EtAllylPhN$) to take place in solution. The asymmetric influence is that of the oriented molecules in the crystal on which the solution builds: in such a way must the crystals of *dextro* and *laevo* quartz be laid down, and the sodium chlorate crystals just described, although the constituent molecules themselves are not enantiomorphic.

Among the many interesting optically labile compounds studied by Adams are numerous examples which undergo asymmetric transformation: when Adams (1943) says that optically active diphenyls are easy to resolve, he classes together processes of true resolution

undergone by salts of the optically stable ones (where the diastereoisomeric salts often differ markedly in solubility) and of asymmetric transformation. The latter process often led him to obtain an optically pure salt in a single crystallization.

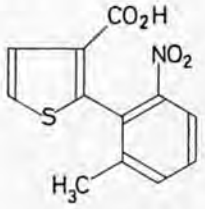
It has lately been discovered that *iso*colchicine (II) exhibits mutarotation in chloroform solution. Evaporation of such a solution to dryness followed by recrystallization from ethyl acetate yields 99·7 per cent of the original *iso*colchicine which again mutarotates in



II

chloroform in the same way. Rapoport and Lavigne (1956) have made a thorough study of this interesting case and suggested that in crystallization only one of a possible pair of diastereoisomers comes out. Since the yield is almost 100 per cent, one of these centres must be labile. The two elements of asymmetry required to explain this behaviour could be provided by the one resolved, optically stable asymmetric carbon atom (C*) and also by restriction of rotation about the bond between rings *A* and *C* leading to labile optical activity of the type recognized in bridged diphenyl structures (see later). The original paper should be consulted for further details and discussion.

Examination of stereochemical literature provides numerous cases, new and old, in which asymmetric transformation appears to have been overlooked and a maximum yield of 50 per cent was expected from a crystallization which in favourable circumstances would have provided 100 per cent of one diastereoisomer. For example, 2-(6-methyl-2-nitrophenyl)-3-thenoic acid (III) was dissolved with brucine in a hot ethanol–water mixture (Owen and Nord, 1951) and placed in a refrigerator at −15°. About 37 per cent of a crystalline salt was



III

deposited, $[\alpha]_D^{20}$ changing from +30·5° to −28·55° during 2·5 hours. The salt on decomposition with hydrochloric acid gave an acid $[\alpha]_D^{20}$ −11·19° changing to 0° in one hour. Two questions spring to mind: (a) if the solution had been allowed to deposit crystals at

room temperature (at which mutarotation takes place) would not the yield of active salt have been larger? ; (b) if the salt had been decomposed much more rapidly would it not have given an acid of larger specific rotation?

Asymmetric Transformation in Solution

Occurrence and Recognition

The distinction between asymmetric transformations in solution and by crystallization may not be a fundamental one in theory, but it is of the utmost importance in practice. It is often not possible to induce a solution of diastereoisomeric substances to deposit crystals, in which case the only means of stereochemical investigation of the labile substance is by observing asymmetric transformation in solution.

This process involves the establishment of an equilibrium between diastereoisomeric pairs, the composition of the equilibrium mixture being different from 50 per cent of each. (It can, of course, occur not only in solution but also in a liquid substance of diastereoisomeric structure, either alone, or under the influence of a suitable catalyst.) Suppose an optically stable, resolved base (−)B (it could be (+)B throughout) is added to one equivalent of a racemic, optically labile acid (±)A under conditions which lead to the immediate formation of diastereoisomeric salts (see footnote, p. 159) which are not dissociated in the solvent used. At the moment of addition the quantities of each diastereoisomer will be equal, but, as they have unequal free energies, and A is optically labile, partial inversion will lead to unequal quantities of the two at equilibrium :—

$$(\pm)\mathrm{A} + (-)\mathrm{B} \longrightarrow \underset{50\%}{(+)\mathrm{A}.(-)\mathrm{B}} + \underset{50\%}{(-)\mathrm{A}.(-)\mathrm{B}} \xrightarrow[\text{transformation}]{\text{Asymmetric}} \underset{x\%}{(+)\mathrm{A}.(-)\mathrm{B}} \rightleftarrows \underset{(100-x)\%}{(-)\mathrm{A}.(-)\mathrm{B}}.$$

This kind of process has been called ' asymmetric catalytic racemization ', ' optical activation ' or ' first-order asymmetric transformation ' ; the words ' first-order ' are a translation, not altogether fortunate, of ' erster Art ' (Kuhn, 1932 ; King, 1933 ; Jamison and Turner, 1942, footnote).

Up to 1947 it seemed that bonding of some formal kind was necessary between the labile and stable centres for the latter to affect the former, but since then it has been shown that an optically active solvent S* can, in certain cases, play a part equivalent to (−)B or (+)B :

$$(\pm)\mathrm{A} + \mathrm{S}^* \longrightarrow \underset{50\%}{(+)\mathrm{A}.\mathrm{S}^*} + \underset{50\%}{(-)\mathrm{A}.\mathrm{S}^*} \longrightarrow \underset{x\%}{(+)\mathrm{A}.\mathrm{S}^*} \rightleftarrows \underset{(100-x)\%}{(-)\mathrm{A}.\mathrm{S}^*}$$

This must be included as a form of asymmetric transformation.

The only entirely satisfactory way of proving that an observed mutarotation is due to asymmetric transformation is to remove the activating agent and to observe the newly created activity in the labile

substance, which may for this purpose be thrown out of solution or extracted by a solvent. The optical activity of the labile substance will then fall to zero according to the first-order kinetic law at a rate dependent upon the solvent in which it is dissolved, the temperature, the concentration, and factors peculiar to itself. Some asymmetric transformations which have yielded active products from an equilibrium mixture will be found in TABLE 1.

When the specific rotation of one of the pure diastereoisomers, (−)A.(−)B say, is known, then it may be possible to calculate, from the extent of mutarotation starting at (±)A.(−)B, the composition of the equilibrium mixture. The accuracy attainable will depend upon various factors, notably that the rate of mutarotation should not be too fast nor the rate of dissolution of the solid material too slow; also, any calculation assumes that there is no significant dissociation of the diastereoisomeric salts. The calculated equilibrium composition of some systems are included in TABLE 1.

TABLE 2. EQUILIBRIA IN ASYMMETRIC TRANSFORMATIONS BETWEEN COVALENT DIASTEREOISOMERS

Substance	Solvent	Equilibrium composition	
(*a*) (−)-Menthyl (±)-phenylchloroacetate	EtOH (With a trace of KOH)	(+)A. ester 57%	(−)A. ester 43%
(*b*) (−)-Menthyl (±)-phenylbromoacetate		47%	53%
(*c*) (−)-Bornyl (±)-phenylchloroacetate		47%	53%
(*d*) (−)-Menthyl (±)-mandelate		54%	46%
(*e*) D-Glucose	H_2O	*α*, 35·8%	*β*, 64·2%
(*f*) D-Glucose	MeOH	44·3%	55·7%
(*g*) D-Glucose	EtOH, 80%	41%	59%
(*h*) D-Mannose	H_2O	68·8%	31·2%
(*i*) D-Lyxose		76%	24%
(*j*) Lactose		36·8%	63·2%

(*a*), (*b*), (*c*) and (*d*) McKenzie and Smith (1924, 1925); (*e*) and (*f*) Andrews and Worley (1927): Isbell and Pigmann (1933): Kendrew and Moelwyn-Hughes (1940); (*g*) Hudson and Yanovsky (1917); (*h*), (*i*) and (*j*) Isbell and Pigmann (1937), see also Kendrew and Moelwyn-Hughes (1940).

Kacser and Ubblelohde (1950), in an investigation of thermodynamic factors in stereospecific processes, noted that the equilibrium constants *K*, where they are known, for first-order asymmetric transformations range between 1 (*i.e.* no stereospecific effect) and 2. This generalization seems to cover most of the equilibria which have been investigated, but not that of (±)-chlorobromomethanesulphonic acid with (−)-hydroxyhydrindamine (see TABLE 1) where *K* is about 4, nor of the cholesteryl dibromides described below, which are of course stereochemically more complex compounds.

A few examples which involve labile and stable centres within one molecule are listed in TABLE 2; examples (*a*), (*b*), (*c*) and (*d*) are optically stable in ethyl alcoholic solution until a drop of alcoholic potassium hydroxide is added. Smith (1931) showed that amygdalin, the gentiobioside of (+)-mandelonitrile, behaves similarly to the menthyl phenylchloroacetates (example (*a*), TABLE 2).

In the sugar series the simple calculation of equilibrium composition from rotation values can be made only for those which exist in two forms, with no significant proportion of a third. The amount of such a third form—for example open chain or furanose ring—in solutions of D-glucose (Andrews and Worley, 1927; Kendrew and Moelwyn-Hughes, 1940; Cantor and Peniston, 1940; Los and Wiesner, 1953), D-xylose, D-mannose or D-lactose is very small indeed. D-Arabinose does not have the simple $\alpha \rightleftarrows \beta$ equilibrium composition, nor do D-ribose, D-galactose and D-talose.

Finally there are cases of shift of equilibrium when an optically labile substance with a single centre of asymmetry is dissolved in an asymmetric solvent (TABLE 3).

TABLE 3. ASYMMETRIC TRANSFORMATIONS IN OPTICALLY ACTIVE SOLVENTS

Racemic substance	Solvent	Active substance recovered
(*a*) Methyl-*N*-benzoyl-2′-chlorodiphenylamine-2-carboxylate	Ethyl (+)-tartrate	(−)-Compound
(*b*) 8-Nitro-*N*-benzenesulphonyl-*N*-(2-hydroxyethyl)-1-naphthylamine	Ethyl (+)-tartrate	(+)-Compound
(*c*) Tris-2-2′-dipyridylnickel chloride	(+)-Tris-ethylenediamine cobalt chloride in H_2O	(−)-Iodide
(*d*) Tris-acetylacetone cobalt	(+)-Tris-ethylenediamine cobalt chloride in EtOH aq.	(−)-Compound
	(−) „	(+)-Compound

(*a*) Buchanan and Graham (1950); (*b*) Glazer, Harris and Turner (1950); (*c*) Dwyer (1951); (*d*) Dwyer (1952).

Structural Factors influencing the Relative Stabilities of Diastereoisomers

It was suggested by W. H. Mills in 1943 that the relative optical stabilities of alkaloidal salts of labile enantiomeric acids could be dependent upon the dipolar attractions between portions of the acid and alkaloid molecules. Since then the study of conformational

TABLE 1. EQUILIBRIA IN ASYMMETRIC TRANSFORMATION OF DIASTEREOISOMERIC SALTS IN NON-DISSOCIATING SOLVENTS

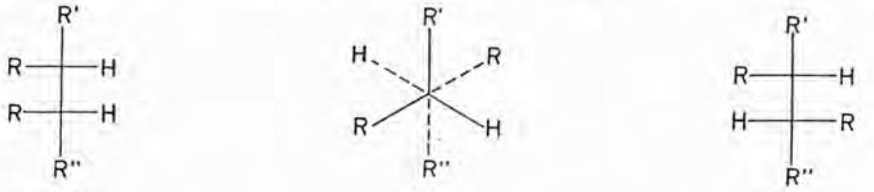
Racemic substance	Activating agent	Solvent	Equilibrium composition	Active substance isolated
a. Bromochloromethanesulphonic acid	(−)-Hydroxyhydrindamine	Acetone	(+)A.B 19% (−)A.B 81%	
b. *N*-Benzenesulphonyl-8-nitro-1-naphthylglycine	(i) Cinchonidine (1·0M)	$CHCl_3$	(+)A.B 38% (−)A.B 62%	(−)A (in solution)
	(ii) Cinchonidine (0·25M)	$CHCl_3$/EtOH	(+)A.B predominating	(+)A (in solution)
	(iii) Brucine	$CHCl_3$	(+)A.B predominating	(+)A (in solution)
c. 2′-(*α*-Hydroxy*iso*propyl)diphenyl-2-carboxylic acid	Brucine	$CHCl_3$	(+)A.B 58% (−)A.B 42%	
d. 2 : 5-Dimethoxy-2′-nitrodiphenyl-6′-carboxylic acid	Brucine	$EtOH/H_2O$	(+)A.B. 53·5% (−)A.B 46·5%	
e. *N*-Benzoyl-4 : 6 : 6′-tribromodiphenylamine-2-carboxylic acid	Cinchonidine	$CHCl_3$	(+)A.B 49% (−)A.B 51%	
f. *N*-Benzoyl-2′-6-dimethyldiphenylamine-2-carboxylic acid	(i) Cinchonidine	$CHCl_3$/EtOH	(+)A.B predominating	(+)A (in solution)
	(ii) Quinidine	$CHCl_3$/EtOH	(−)A.B predominating	(−)A (in solution)
g. *N*-Benzoyl-4 : 6-dichlorodiphenylamine-2-carboxylic acid	(i) Cinchonidine (1·0M)	$CHCl_3$/EtOH	(+)A.B predominating	(+)A solid
	(ii) Cinchonidine (0·5M)	$CHCl_3$/EtOH	(−)A.B predominating	(−)A solid
h. *N*-Benzoyl-4 : 6-dibromodiphenylamine-2-carboxylic acid	Cinchonidine (1·0M)	$CHCl_3$/EtOH	(+)A.B predominating	(+)A

TABLE 1—*continued*

Racemic substance	Activating agent	Solvent	Equilibrium composition	Active substance isolated
i. 1-Phenylnaphthalene-2′-carboxylic acid	Brucine	$CHCl_3$	(+)A.B predominating	(+)A
j. 1-Phenylnaphthalene-2′ : 8-dicarboxylic acid	Brucine	$CHCl_3$/EtOH	(+)A.B predominating	(+)A
k. 10-*m*-Aminobenzylideneanthrone	(+)-Camphor-10-sulphonic acid	$CHCl_3$/EtOH	(−)B.A predominating	(−)-Hydriodide
l. *N*-Benzoyl-6-methyldiphenylamine-2-carboxylic acid	Quinidine	$CHCl_3$	(−)A.B predominating	(−)A (in solution)

a, Read and McMath (1925); *b*, Mills and Elliott (1928): Jamison and Turner (1940); *c*, Corbellini and Angeletti (1932): Jamison and Turner (1938); *f* and *h*, Harris, Potter and Turner (1955); *g*, Jamison and Turner (1940); *i* and *j*, Hall, Ridgwell and Turner (1954); *k*, Ingram (1950); *l*, Harris (1955).

analysis has opened a wide field of knowledge which can be applied to the relative stabilities of diastereoisomers, particularly of non-polar compounds (see, for example, Barton and Cookson, 1956). Of a large number of such compounds which might exist in *erythro* (in simple cases *meso*) or *threo* forms, the *erythro* form is found to be the more stable. Assuming that the groups R′ and R″ are larger than the group R, the *erythro* form (IV) has a stable, staggered conformation



IV IV*A* V

erythro (*meso*, when R′ = R″) *threo*

(IV*A*) which is energetically preferred over even the most stable conformations (V*A*) of the *threo* isomer (V), all of which involve

V*A* V*B* V*C*

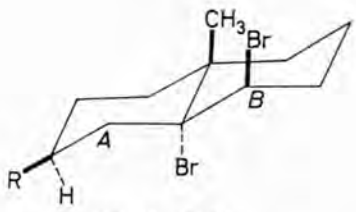
greater compressions of the larger groups.

This assertion has been established both by direct equilibration experiments and also by synthesis under conditions which allow equilibration during the formation of the product: the *erythro* form appears in larger quantity.

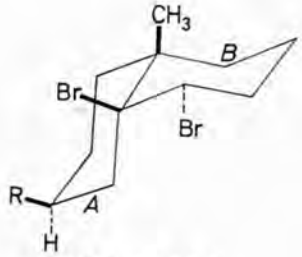
Barton and Robinson (1954) have made the generalization that the reduction of a keto group to form a new asymmetric centre will give the thermodynamically more stable product if it is carried out in alkaline media; it proceeds by way of a carbanion intermediate. The short-lived carbanion would contain an easily inverted tetrahedral carbon, susceptible to the influence of a stable optically active centre. This generalization covers the cases of reduction of ketones and oximes listed by Cram and Abd Elhafez (1952). Turner and Harris considered in 1948 that asymmetric transformation has a definite role in asymmetric synthesis only if the new asymmetric centre is formed reversibly; in Barton's carbanion-intermediate reductions the new asymmetric centre would be present in the optically unstable carbanion and would be fixed by the subsequent addition of a proton. Additions of Grignard reagents are perhaps another matter. Cram (*ibid*) based his rule of steric control of asymmetric synthesis on the stereochemical

result of reactions which he considered to be irreversible and the product composition therefore to be kinetically controlled. Prelog too (1953) assumed a non-reversible Grignard reagent addition to benzoylformic esters to account for asymmetric synthesis in this series.

The cholesteryl dibromides provide an interesting case in which the relative stabilities of diastereoisomers influence the position of equilibrium between them (Barton and Miller, 1950; Grob and Winstein, 1952; Barton, 1955). The first product of addition of bromine to cholestene, cholesterol or cholesteryl benzoate is the $5\alpha : 6\beta$ isomer (partial formula VI). This changes to an equilibrium mixture containing excess of the more stable form, VII; the rate of reaction can be followed polarimetrically in various solvents, and closely follows the first-order kinetic law. The mechanism has been shown by Grob and Winstein probably to be intramolecular (see also de la Mare, 1954).



VI (Labile)



VII (Stable)

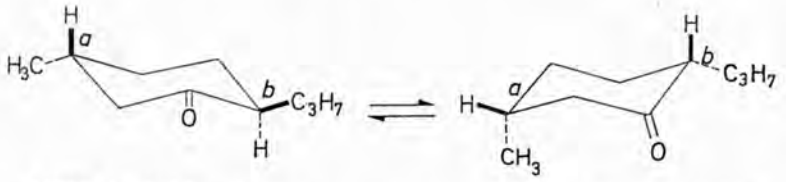
When R is H, in chloroform, the equilibrium is almost entirely displaced to VII; when R is OH or OBz (cholesterol dibromide or cholesteryl benzoate dibromide) the proportions are roughly one part of VI to four parts of VII.

In changing from VI to VII, the 10-methyl group starts as $a_A a_B$ and becomes $e_A a_B$; the 5-bromine atom changes from $a_A a_B$ to $a_A e_B$; the 6-bromine atom from a to e, all these changes contributing towards the stability of VII. The additional stability afforded to structure VI when R is -OH or OBz is attributed to the conformation of R, which is equatorial in VI and axial in VII. For additional information on interconvertible forms in this field, see Klyne (1954).

The relative stability of the β-form of D-glucose in aqueous solution has been related to the equatorial conformation of the hydroxyl group on the labile carbon atom (Reeves, 1951; *cf* Klyne, 1954).

Asymmetric Transformations as Reversible First-order Kinetic Processes

The so-called inversion of (—)-menthone (VIII) has been the subject of further kinetic studies which demonstrate that its behaviour fits into the general pattern of asymmetric transformation (Weissberger, 1943).



VIII (−)-Menthone IX (+)-*iso*Menthone

(The conformations shown, with the larger *iso*-propyl group equatorial, are probably the preferred ones)

The molecule has one centre of stable optical activity (*a*) and one of labile (*b*): the labile centre is in the α-position to the CO group, and rearrangement is accompanied by some prototropic change on the other side of this group which does not affect the optical activity. Weissberger confirmed the findings of Tubandt (1905, 1907, 1910) who showed that catalysed mutarotation of (−)-menthone proceeds according to the first-order kinetic law, $dx/dt = kcx - k'c(1-x)$, where c is the total concentration of (−)-menthone and (+)-*iso*menthone and x and $(1-x)$ are the fractions of the isomers present at time t. The measured velocity constant k_m is the sum of those for the two partial inversions,

$$k_m = k + k' = \frac{1}{t} \log_e \frac{(\alpha_\infty - \alpha_0)}{(\alpha_\infty - \alpha_t)}$$

where α_0, α_t and α_∞ are the values for the optical rotation of the mixture at the start of the observations, after time t and at equilibrium. The composition of the equilibrium mixture of (−)-menthone and (+)-*iso*menthone, has been shown to be identical for all solutions having the same catalyst, concentration, etc. (Read, 1926, 1930), whether the starting material was a menthone of $(\alpha)_D^{20}$ −27·75° or a 'Rechtsmenthon' of $(\alpha)_D^{20}$ + 27·79° or a (+)-*iso*-menthone of $(\alpha)_D^{20}$ +85·6°; the velocity constant for the approach to equilibrium in formic acid was the same in all cases. Tubandt assumed, and Weissberger agrees, that 'Rechtsmenthon', prepared by Beckmann in 1888, is a mixture of (−)-menthone and (+)-*iso*menthone.

The application of the reversed 'unimolecular' law to the equilibration of diastereoisomerides is more remarkable for the wide variety of the examples than for their number. Hudson (1903) showed it for α- or β-lactose in water, Meyer (1908) for α- and β-D-glucose. 'The equation applies alike to the mutarotation of α-D-glucose from +110° to +52°, the mutarotation of the β-form from (+)19° to (+)52°, and to any portion of these changes' (Hudson and Dale, 1917).

Recently Los, Simpson and Wiesner (1956; see also Los and Wiesner, 1953) have determined polarographically at 25° the four velocity coefficients involved when the mutarotation of D-glucose in water is treated according to the equilibrium equation

$$\alpha \underset{k_1'}{\overset{k_1}{\rightleftarrows}} O \underset{k_2}{\overset{k_2'}{\rightleftarrows}} \beta$$

where *O* represents the open chain aldehyde form. The equilibrium concentration of the intermediate free aldehyde was deduced to be $0{\cdot}0026 \pm 0{\cdot}0002$ per cent of the total.

Investigation of cases of optical activation, that is mutarotation observed when a (±) optically labile acid (or base) is mixed in solution with an optically stable base (or acid) (Read and McMath, 1925; Kuhn and Albrecht, 1927; see also Kharasch *et al.*, 1934; Mills and Elliott, 1928; Pfeiffer and Quehl, 1931; Yuan and Adams, 1932; Stoughton and Adams, 1932; Jamison and Turner, 1938, 1940) led to the demonstration that each is part of the process of equilibration of the diastereoisomeric pair, viewed from the starting point of the (±) labile material. Thus the salts brucine (+)- and brucine (−)-2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid undergo mutarotation in chloroform to a larger extent but to the same equilibrium and with the same velocity coefficient as an equimolecular mixture of brucine and the (±)-acid. Similarly the two salts cinchonidine (+)- and cinchonidine (−)-*N*-benzoyl-4 : 6 : 6′-tribromodiphenylamine-2-carboxylate in chloroform solution show mutarotation to the same equilibrium point and with the same velocity coefficient (Jamison and Turner, 1938, 1942). These salts are almost certainly not ionized in solution in chloroform, but are true diastereoisomers of the composition RNH_2,HO_2CR'.

The mutarotations of the diastereoisomeric (−)-menthyl phenylchloroacetates follow the same pattern within the limits of the experimental errors involved (McKenzie, 1924, 1925; Turner and Harris, 1947). Grob and Winstein (1952) showed that the mutarotations of 5α : 6β-dibromocholestane and of cholesteryl dibromide follow closely the form of reversible first-order reactions. The general rule is that in any one case velocity constants for *partial inversion* are different, but velocity constants for *observed mutarotations* are equal, the latter being the sum of the former two.

Extension of these investigations into the field of optically labile metallic complexes has been attempted using (+)- and (−)-tris-1 : 10-phenanthrolinenickel iodides (Davies and Dwyer, 1954) dissolved in aqueous ammonium (+)-bromocamphorsulphonate or in aqueous cinchoninium sulphate. The authors set out to show that the rates of racemization of the (+)- and (−)-nickel complexes were different in the presence of an optically stable ion, and they carried out experiments which purported to do this. However, the reactions, observed as mutarotations, finish at an equilibrium which has *not* the composition of the racemic mixture; the relevant overall process is therefore a reversible inversion of which the forward and reverse components are influenced to different degrees by the asymmetry of the environment. The *measured* velocity coefficients would be expected to be equal, if the equilibrium rotation were taken as end-point in

the calculation of k. The authors find their measured velocity coefficients different, but they use as their end-rotation a value, separately determined, for the *racemic* iodide in the same solvent. That their logarithmic plots (log α against time) show a drift is therefore not surprising; in fact it confirms the existence of the effect they were seeking. Taken all in all, the authors have demonstrated that a stable, asymmetric ion can influence the rate of inversion of a labile one, but it will be interesting to know whether the behaviour of these solutions would conform to the general pattern for the reversed 'unimolecular' reaction and so come into line with substantiated asymmetric transformations in solution*. The mechanism of racemization (and inversion) of octahedral complexes containing three chelate groups has been discussed by Nyholm (1954).

Energies of Activation

From time to time the Arrhenius equation, $k = P\mathcal{Z}e^{-E/RT}$, has been used to calculate a value of E for a process culminating in the establishment of a diastereoisomeric equilibrium. Such calculations often have little value. The two partial inversions, which for simplification may be represented

$$(+)\mathrm{A}(-)\mathrm{B} \rightarrow (-)\mathrm{A}(-)\mathrm{B}$$

and

$$(-)\mathrm{A}(-)\mathrm{B} \rightarrow (+)\mathrm{A}(-)\mathrm{B},$$

will in general have different rates (k_+ and k_-) and different activation energies (E_+ and E_-). The measured velocity coefficient obtained from the polarimetric data using the observed infinity reading can be written in the form:

$$k = k_+ + k_- = P_+\mathcal{Z}_+e^{-E_+/RT} + P_-\mathcal{Z}_-e^{-E_-/RT};$$

use of the simplified expression

$$k = P\mathcal{Z}e^{-E/RT}$$

could be justified if k_+ were equal to k_- (that is, if the two processes did not involve diastereoisomers, but were straightforward inversions in a non-participating environment, leading to racemization; then E_+ would be equal to E_-). If the diastereoisomers differed greatly in stability, then the difference in k_+ and k_- might be so great as to make the larger of them approximately equal to their sum, and a satisfactory value for the activation energy of the faster process would be obtained. In the case in which k_+/k_- did not vary with temperature, the slope of the line log $k/(1/T)$ would lead to a value of E which was correct for both processes $\{k = k_+ + [1 + (k_-/k_+)]$, where k_-/k_+ is constant; the value of $P\mathcal{Z}$ so determined would not be correct$\}$.

* The writer is indebted to Dr. F. P. Dwyer for correspondence on this subject.

It is probable, therefore, that some of the surprisingly low values, recorded for the activation energies of asymmetric transformations, are incorrect because they have been derived, as discussed above, from ' composite ' rate-coefficients. Thus the value of 10·1 kcal.mole^{-1} for the mutarotation of 10-*m*-aminobenzylideneanthrone (+)-camphor-10-sulphonate in chloroform containing 3·25 per cent ethanol (Ingram, 1950) must be incorrect, seeing that the equilibrium composition of the solution varied considerably with temperature. The value of 14·3 kcal.mole^{-1} for the ' inversion ' of menthone (Weissberger, 1943; the value quoted in the paper was calculated using Briggsian logarithms) may also be suspect. Kistiakowsky and Smith (1936) suggested that an activation energy of at least 20 kcal.mole^{-1} would be required for resolution, whilst Mills (1943) considered 16 kcal.mole^{-1} to be a lower limit for the observation of unstable optical activity, both in the neighbourhood of room temperature. These opinions depend on the belief that racemizations and mutarotations of the types under consideration will have normal, or smaller than normal, values of the non-exponential term PZ in the Arrhenius equation. This is the general experience for compounds which owe their activity to restricted rotation, as is shown in some of the data summarized by Cagle and Eyring (1951). Some experimental values for related compounds studied recently, are shown in TABLE 4.

On the whole, the Arrhenius parameters bear out the view (*cf* de la Mare, 1954) that these processes usually have values of PZ of *c.* 10^{11} sec^{-1}; those compounds which have particularly low values of E have, of course, very short half-lives at ordinary temperatures. It is only possible to observe optical activity in the substances with low E values because the PZ values are also low; the low PZ value is probably connected with the necessity for the relative rotation of parts of the molecule to be synchronized before optical inversion can take place.

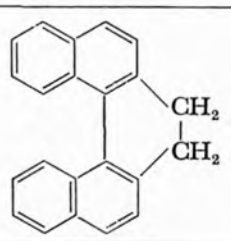
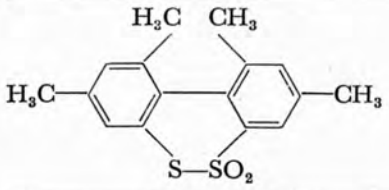
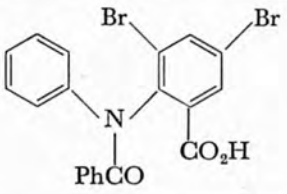
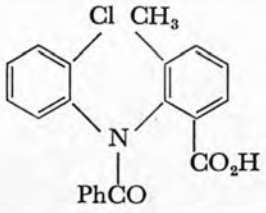
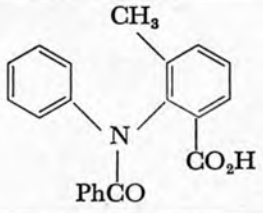
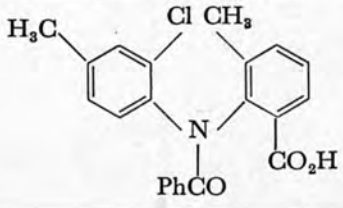
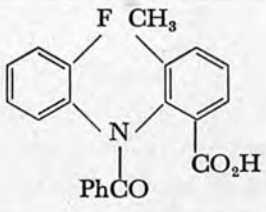
A recent redetermination of the racemization velocities of 6-nitro-, 4 : 6′-dinitro- and 4 : 6 : 4′-trinitrodiphenic acids (Brooks, Harris and Howlett, 1957) in alkaline solution has led to the interesting result that the *differences* in optical stability (half-lives 28, 91 and 208 min., respectively, at 80°) do not depend upon their activation energies, which all equal 22·6 kcal.mole^{-1}. The differences lie in the PZ values, $10^{10\cdot6}$, $10^{10\cdot1}$, $10^{9\cdot7}$, or, alternatively expressed, in the ΔS^{+} values of the absolute reaction rate equation

$$k = \varkappa e \frac{kT}{h} \exp(\Delta S^{\ddagger}/\boldsymbol{R} - E/\boldsymbol{R}T)$$

which are, respectively − 12·2, − 14·7 and − 16·3 e.u.

It should be possible to determine E_{+} and E_{-} for a pair of diastereoisomeric salts; it has been done for $\alpha \longrightarrow \beta$ and $\beta \longrightarrow \alpha$

TABLE 4. ARRHENIUS PARAMETERS FOR RACEMIZATION OF INTERNALLY HINDERED COMPOUNDS

Compound	Conditions	E kcal.mole^{-1}	$\log_{10} PZ$	Ref.
	Dioxan Toluene Ethylbenzene	31	13·5*	Hall (1956)
	Ethylbenzene Toluene	31	13·2†	Armarego and Turner (1956)
Tri-*o*-thymotide	Chloroform	21·4	13·3†	Newman & Powell(1952)
	Chloroform containing 2·5% ethanol	19·3	12·0	Brooks, Harris and Howlett (1957)
	Chloroform containing 6·9% ethanol	16·4	9·7	Potter (1953)
	Chloroform containing 2·5% ethanol	16·2	10·1	Brooks, Harris and Howlett (1957)
		15·7	9·1	
		14·9	8·6	

* Personal communication. † Calculated from the authors' published data.

D-xylose and for $\alpha \longrightarrow \beta$ and $\beta \longrightarrow$ α-D-lactose (for D-glucose the difference between the two values is so slight as to be hardly detectable —Moelwyn-Hughes, 1940). It is necessary for the calculation to measure the optical rotation of (a) one optically pure diastereoisomer (b) the equilibrium mixture and (c) the partial racemate *or* the other diastereoisomer, also optically pure, at each temperature at which k is measured. The measurements (a) and (c) have to be determined by extrapolating back to zero time a logarithmic plot of the mutarotation, and, unless the salts are instantly soluble in the solvent at that temperature, zero time cannot be stated accurately; error from this source increases as the temperature is lowered and dissolution becomes slower. The extent of mutarotation of the partial racemate in going to equilibrium is usually small and is thus subject to increasing error as the temperature is raised.

Partially Labile Diastereoisomeric Equilibria: Excess of One Component

The effect of adding an excess of optically labile acid, (±)A, to the equilibrated salts (+)A(−)B ⇄ (−)A(−)B in solution has presented a problem for several years. The change in rotation, instantaneous or measurably slow, which usually accompanies addition of (±)A, has been shown *not* to be due to suppression of dissociation of the salts. The result of adding excess of acid can be so profound that washing out (−)B from a solution of one acid : base ratio may give (+)A, while from another (−)A is recovered (Jamison and Turner, 1938, 1940).

Some progress has been made towards explaining this phenomenon, using as example *N*-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid and cinchonidine (Harris, Potter and Turner, 1955).

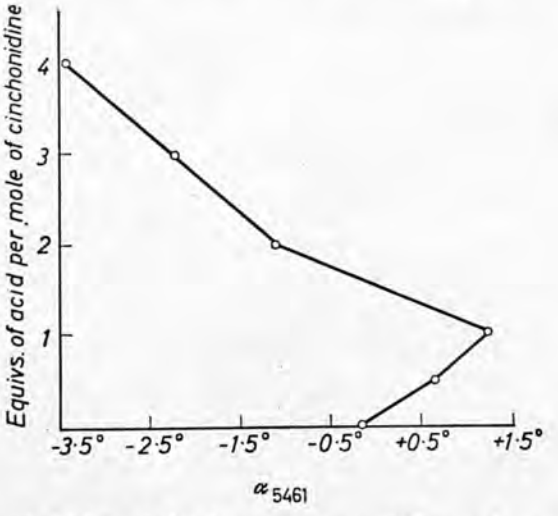


FIGURE 1. Polarimetric measurements

To a solution of cinchonidine (0·1000 g) in bromoform (15 c.c.) were added successive quantities of the (±)-acid, and the optical rotation was measured after each addition; the results are shown in FIGURE 1.

This is similar to the curves found in chloroform, with this and with some other optically unstable acids, and can be interpreted as showing that, as acid in excess of one equivalent is added, a larger and larger excess of (—)A is formed. Side by side with the polarimetric measurements, cryoscopic determinations were made on the same solutions and also on solutions in which naphthalene was added to the cinchonidine salt in bromoform. The results are plotted in FIGURE 2 and show that there is a considerable degree of molecular aggregation in the solutions containing acid and cinchonidine, which does not occur when naphthalene replaces the acid.

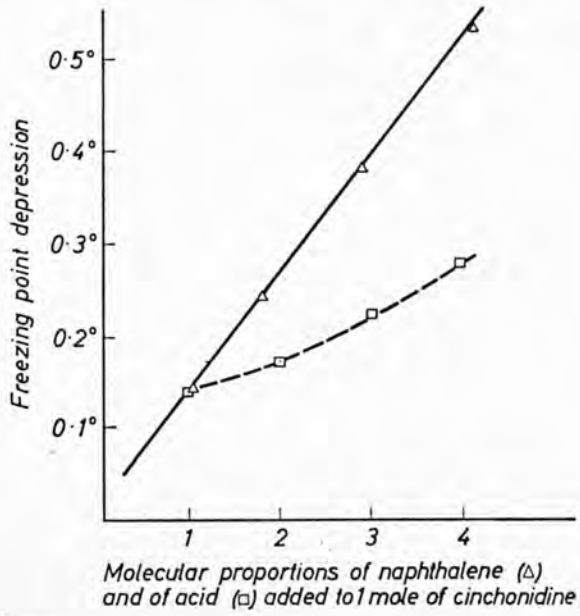


FIGURE 2. Cryoscopic measurements

Without discussing the precise nature of such aggregation and the forces which cause it (see Marryott, 1948) it can be assumed that the molecule of cinchonidine accepts the first equivalent of acid and converts it partially into the *dextro*-isomer. The second molecule of acid which the diastereoisomer then accepts may be influenced in the opposite sense, forming the *laevo*-isomer; this would explain the sharp turn-back of the curve at one equivalent of acid. There are other acids which show not a reversal of direction at this point, but a slope continued in the same sense.

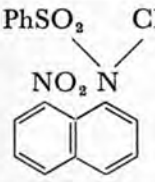
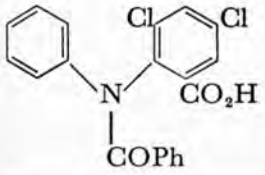
Outside the stereochemical field, association beyond the first acid–base combination has been observed between, for example, myristic acid and tri-*iso*pentylamine in benzene solution by Kaufmann and Singleterry (1952) and between pyridine and trihalogenoacetic acids in chloroform solution by Barrow (1956) together with some other acid–base pairs (see also Bryant and Wardrop, 1957).

Support for the hypothesis that the alkaloid has an influence on more than one equivalent of acid comes from solubility measurements.

10 c.c. of dry chloroform dissolves 0·26 mol. (0·0230 g) of *N*-benzoyl-4′-chlorodiphenylamine-2-carboxylic acid: in the presence of 1·00 mol. of quinine, the same volume of solvent dissolves 2·42 mol. of acid: in the presence of 1·00 mol. of brucine, 1·84 mol. of acid is dissolved.

As a result of reversal of the direction of optical activation by excess of acid, it has been possible to obtain two specimens of acid, (+)- and (−)-rotatory, *without separation of salts*, by decomposition of equilibrated solutions (TABLE 5).

TABLE 5. RESOLUTION OF ACIDS WITHOUT SEPARATION OF SALTS

(±) Acid	Alkaloid	Solvent	Acid obtained free
	Cinchonidine 1·0M	$CHCl_3$	(−)
	Cinchonidine 0·33M	$CHCl_3$	(±)
	Cinchonidine 0·25M	$CHCl_3$/EtOH	(+)
	Cinchonidine 1·0M	$CHCl_3$	(+)
	Cinchonidine 0·5M	$CHCl_3$	(−)

Partially Labile Diastereoisomeric Equilibria: Effect of Temperature

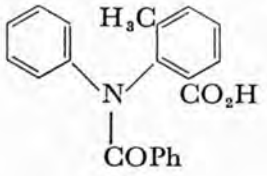
It would be surprising if the equilibrium composition of a pair of partially labile diastereoisomers, (+)A(−)B ⇄ (−)A(−)B, were not sensitive to change of temperature. The case of D-glucose is probably exceptional: the equilibrium constant

$$K = \frac{k_\alpha}{k_\beta} = \frac{[\beta\text{-D-glucose}]}{[\alpha\text{-D-glucose}]}$$

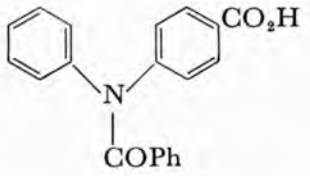
has been shown to be constant over the range of temperature 0·7°–40° (Hudson and Dale, 1917; Moelwyn-Hughes, 1933); this behaviour is not typical of diastereoisomeric substances.

Certain optically stable simple substances, alone or in solution, show a variation of optical rotation with temperature (Kauzmann, Walter and Eyring, 1940; Hargreaves, 1954) so that if the optical rotation of an equilibrated mixture changes with change of temperature it cannot be said without further proof that the equilibrium composition is changing. However, if the rotation of a solution of a diastereoisomeric mixture is found to change, reversibly, with temperature, the possibility of a shifting equilibrium is worth investigating.

The rotation of *N*-benzoyl-6-methyldiphenylamine-2-carboxylic acid (X, optically active and optically labile), and quinidine (1 mol.),



X



XI

dissolved in chloroform, shows linear variation with temperature between 0° and 50° (FIGURE 3, curve *X*; it will be appreciated that the changes in observed rotation are large). This variation is not shown when the acid is replaced by the optically inactive *N*-benzoyl-diphenylamine-4-carboxylic acid (XI) (FIGURE 3, curve *Y*) (Harris,

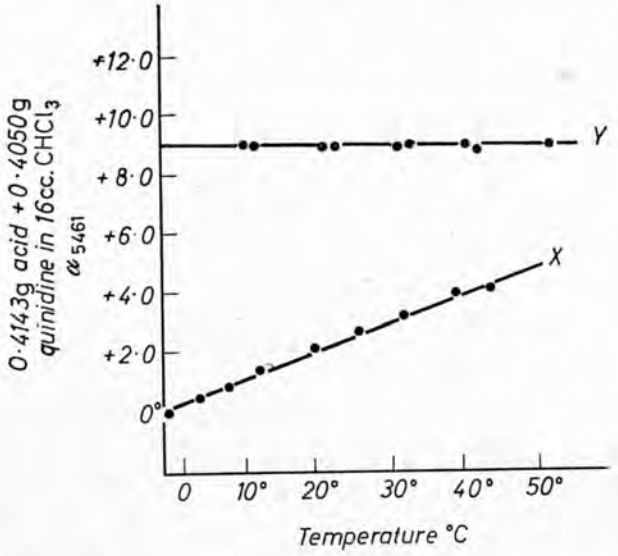
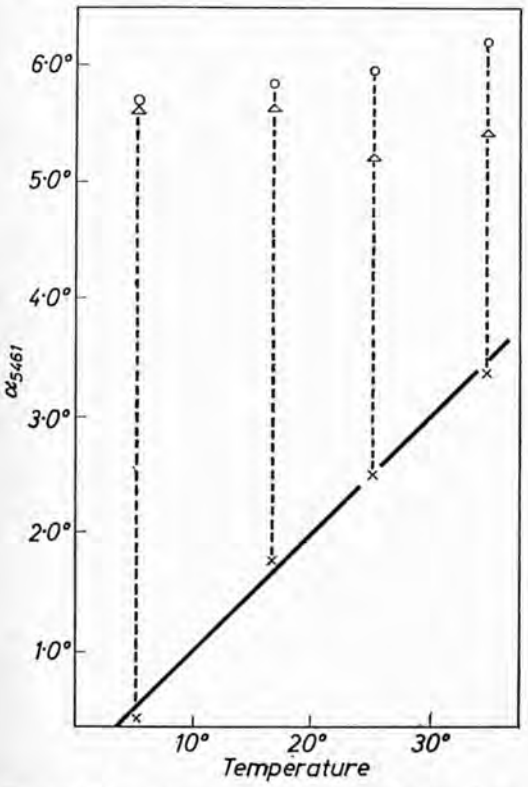


FIGURE 3

1955). When solutions of *N*-benzoyl-6-methyl-diphenylamine-2-carboxylic acid and quinidine (1 mol.) are made up at various temperatures and quickly viewed in the polarimeter, mutarotations are observed. Extrapolation to zero time of the logarithmic plot of α against time gives a reading for each solution at the time of mixing. These values (FIGURE 4) show that the rotations of quinidine (±)-*N*-benzoyl-6-methyldiphenylamine-2-carboxylate at the moment of mixing are approximately equal at the different temperatures, while at equilibrium the rotations are substantially different. This acid had not previously been obtained in the optically active condition, but decomposition of the equilibrated solutions *A*, *B*, *C*, etc. (FIGURE 5) by shaking with mineral acid gave it in chloroform solution in the *laevo*rotatory form in varying degrees of optical purity. The rotation of these samples decayed to 0°. Also, a solution of the quinidine (±)-acid salt, made up and allowed to stand at 3·5°, when warmed to 21° quickly and then observed in the

polarimeter shows mutarotation (FIGURE 6, curve *B*) towards the same equilibrium value as a solution made up at 21° (FIGURE 6, curve *A*). Similar phenomena have been observed with the quinidine salts of some other optically labile acids.



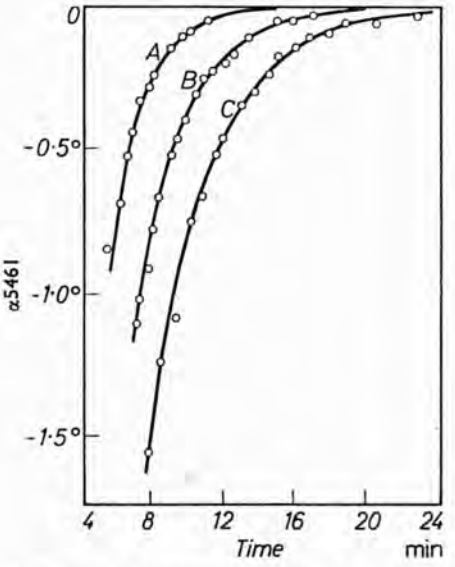


FIGURE 5. Racemization of (−)-*N*-benzoyl-6-methyldiphenylamine-2-carboxylic acid in chloroform at 21°. From asymmetric transformations in solution at (*A*) 45°, (*B*) 21°, (*C*) 0·8°.

FIGURE 4. Asymmetric transformation of *N*-benzoyl-6-methyldiphenylamine-2-carboxylic acid with quinidine in chloroform at various temperatures.

○ Extrapolated to $t = 0$ × Observed final point △ Observed first point

FIGURE 7 illustrates the behaviour of the (+)-camphor-10-sulphonate of 10-*m*-aminobenzylideneanthrone (XII) in chloroform solution containing 3·25 per cent of alcohol (Ingram, 1950). The base is optically active as a result of restricted rotation; the degree of hindrance is slight and the base is therefore optically labile. A salt of the (±)-base with (+)-camphor-10-sulphonic acid in chloroform at 30° had immediate $[M_0]_D$+128° and, undergoing asymmetric transformation, showed mutarotation to $[M_\infty]_D$+50°. When this solution was boiled and rapidly cooled to 30° its mutarotation could be observed following the curve B from $[M_0]_D$−55° back to the same equilibrium point, $[M_\infty]_D$+50° (the half-life periods of these changes are equal). Evidently there is a change in the position of the equilibrium (+)B(+)A ⇄ (−)B(+)A in the *laevo* sense in changing the temperature from 30° to that of boiling chloroform. The range of mutarotation shows that the molecular rotations $[M]_D$ of the 'partial racemate' are nearly independent of temperature, while

the equilibrium rotations change with the temperature (*20°**, +135°→ +72°; *30°*, +133°→+50°; *35°*, +132°→+44°); it was concluded that the salt of $[M_0]_D$ about 133° was the partial racemate because its rotation lies close to that of pyridine (+)-camphor-10-sulphonate.

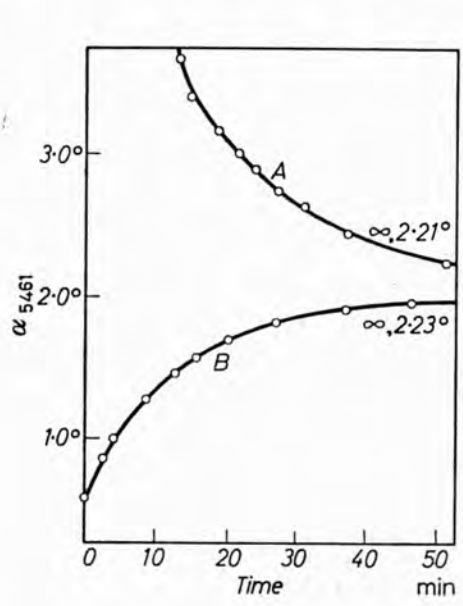


FIGURE 6. *N*-Benzoyl-6-methyldiphenylamine-2-carboxylic acid with quinidine in chloroform.
A, Asymmetric transformation at 20·2°.
B, Equilibration at 21° of a solution which had been allowed to stand at 3·5°.

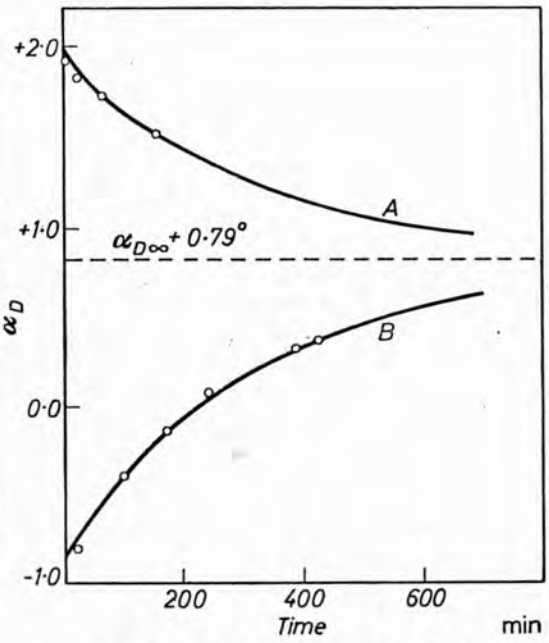
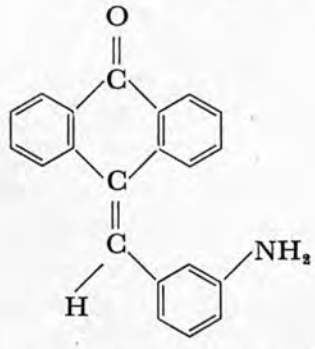


FIGURE 7. (+)-Camphor-10-sulphonate of 10-*m*-aminobenzylideneanthrone in chloroform containing 3·25% of alcohol.
A, Asymmetric transformation at 30°.
B, Equilibration at 30° of a solution which had been heated to boiling and rapidly cooled.



XII

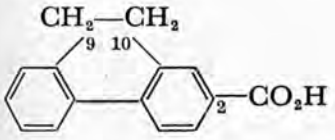
A solution which had been boiled and therefore contained excess of the *laevo* salt was quickly cooled and decomposed by shaking with aqueous potassium iodide; the hydriodide remaining in the chloroform solution had an initial rotation of −187°, and underwent mutarotation towards zero.

* Temperatures in italic figures.

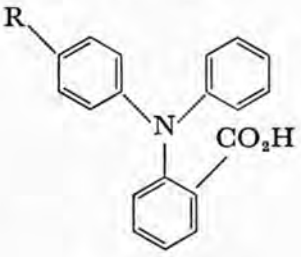
The quinine salt of diphenic acid has an unusually high temperature coefficient of rotation (Lesslie, Turner and Winton, 1941) in chloroform containing ethyl alcohol. Kharasch, Senior, Stanger and Chenicek (1934) have pointed out the dangers of drawing conclusions from the optical rotations of quinine salts, but as diphenic acid mixed with (+)-nor-ψ-ephedrine shows mutarotation at −30°, it seems possible that the changes of rotation with temperature are, at least in part, indicative of a shifting equilibrium.

Grob and Winstein (1952) calculated from mutarotation data that the equilibrium constant for the 5 : 6-dibromocholestanes ($[5\beta : 6\alpha]/[5\alpha : 6\beta] = K$) in carbon tetrachloride solution changed from greater than 100 to 27·6 between temperatures 39·98° and 75·05°.

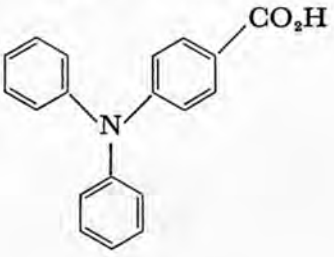
The possibility of using this temperature dependence of equilibrium composition between diastereoisomers to demonstrate new optical activity is very attractive, especially as it would increase the range of optical stability over which polarimetric observations could be made. The phenomenon needs much more thorough investigation before it can be claimed to be diagnostic of optical activity, but it can be reported here that three very interesting acids (recently studied in the laboratories of Bedford College) show a large variation of optical rotation with temperature when observed as their quinidine salts in chloroform solution: 9 : 10-dihydrophenanthrene-2-carboxylic acid



XIII



XIV



XV

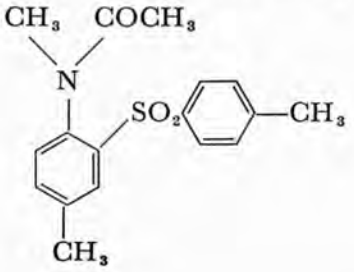
(XIII)* might show optical activity on account of a screw arrangement of the bridged diphenyl structure; Meisenheimer (1924) failed to resolve XIV in which R = CH_3; XV is a less hindered triphenylamine. Neglecting the fact that the nitrogen valencies may be pyramidal, the two opposing forces operating about the pivot bonds in XIV and XV are (a) that due to mesomerism involving the nitrogen lone pair and tending to flatness and (b) steric repulsion of the *o*-atoms or groups. Model requirements show that the molecules cannot be flat, and the possibility arises that they can be arranged as left- or right-handed three-bladed screws (see also Chapters 2 and 6). Simple restricted rotation in absence of the preferred screw conformations could not account for optical activity, however transient, of XV.

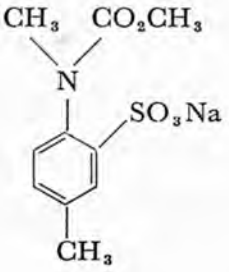
* (XIII) D. M. Hall, M. M. Harris and E. E. Turner; (XIV) M. M. Harris; (XV) M. M. Harris and J. W. Brooks (all unpublished).

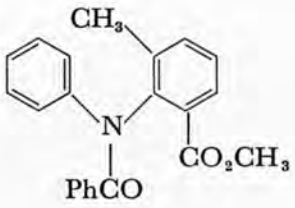
Asymmetric Environment: Optically Labile Compounds in Asymmetric Solvents

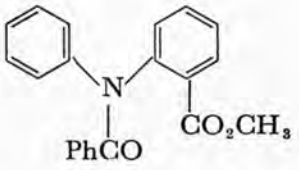
In 1940 Buchanan and Patterson published their finding that the molecular solution volumes of *iso*butyl (+)-tartrate and of *iso*butyl (−)-tartrate are different in (−)-menthyl acetate solution. The difference was only very slight but it was claimed to be outside the experimental error. Ethyl (−)-diacetyltartrate similarly has a larger molecular solution volume than ethyl (+)-diacetyltartrate in the same solvent. This was the first concrete evidence that an asymmetric solvent could behave in any way differently towards two enantiomorphic molecules dissolved in it, apart from the work of McKenzie (1915, 1922, 1923) which will be referred to a little later.

Only recently has ample evidence been gathered of the differences, produced by asymmetric solvents, on the properties, including the solubilities, of optically labile solutes. Buchanan and Graham (1950) found that several optically labile compounds (XVI to XIX for

XVI 

 XVII

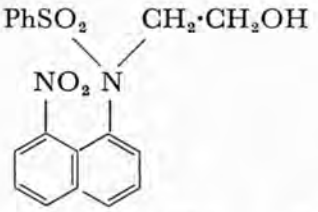
XVIII 

 XIX

example) could be obtained with a small optical activity by dissolving the (±)-form in an optically active solvent and crystallizing or precipitating part of it. Successful solvents were ethyl (+)-tartrate and ethyl (−)-tartrate, (−)-menthyl acetate and (+)*sec.*-butyl alcohol; (+)- and (−)-*sec.*-octyl alcohols gave no separation of enantiomorphs. This work established the fact that an asymmetric solvent can affect the composition of an enantiomorphic mixture which is crystallizing or being precipitated from it. It is often difficult to say whether or not the processes are asymmetric transformations since the proportion of total material recovered in a single operation is too small: the observed activity might be due to resolution or to partial precipitation of one form. However, in one case, methyl *N*-benzoyl-2-chlorodiphenylamine-2′-carboxylate, a 95·5 per cent recovered sample showed a rotation α^{19} of −0·10° in chloroform solution.

Nearly quantitative recovery of activated material was achieved (Glazer, Harris and Turner, 1950) in the case of (±)-methyl *N*-benzoyl-2′-chloro-6-methyldiphenylamine-2-carboxylate which was dissolved in ethyl (+)-tartrate at 80°, cooled to 25° and left for 30 minutes: precipitation by water gave 98 per cent of the ester, $[\alpha]^{25}_{5461}$ −3·4° in chloroform 2·5 minutes after dissolving. The half-life period of racemization was 9 minutes.

In another experiment, *N*-benzenesulphonyl-*N*-(2-hydroxyethyl)-8-nitro-1-naphthylamine (XX) was dissolved in ethyl (+)-tartrate at

XX 

80° and kept at 25° for 2 hours. Addition of excess water led to recovery of 88·5 per cent of the alcohol, $[\alpha]^{25°}_{5780}$ +9·1° in chloroform 2·5 minutes after wetting with solvent, half-life period 27 minutes: the actual observed angle here, α_{5780}, was +0·91°.

These three experiments all indicate that the equilibrium concentrations of (+)enantiomer and (−)enantiomer are displaced from equality in the asymmetric solvents; the effect of the asymmetric solvent seems to be very slight in comparison with that of other modes of connection between a labile centre and an asymmetric influence. Nevertheless, although the observed rotations of the activated materials are small, there is little doubt of their significance, because they decay to zero when left to stand: this test eliminates errors which might be due either to temperature differences or to incomplete removal of the asymmetric solvent. In assessing the value of results which depend upon the crystallization of a specimen which proves to have a small rotation, it is as well to remember the work of Kipping and Pope (1898) who found, on crystallizing sodium chlorate from water, that while the average incidence of *dextro-* and *laevo-* crystals in 46 experiments was 50·08 ±0·11 per cent, the percentage of *dextro-*rotatory crystals in separate experiments varied from 24·14 per cent to 77·36 per cent. Crystallization experiments should therefore be repeatable before they are claimed to be due to more than chance.

Asymmetric Environment: Optically Labile Metal Complexes

The experiments in organic solvents just described could be interpreted on the assumption of an association, possibly by hydrogen bonding, between the solvent and the solute, giving a condition of diastereoisomerism: such a condition was previously thought necessary in order that the optically stable substance might activate the optically

labile one. Dwyer and his collaborators have approached the problem of asymmetric environment from a completely different angle, studying optically labile metal coordination compounds of the type which had already provoked stereochemical interest, on account of their optical lability, in the hands of Werner (1912) and of Pfeiffer (1931, 1932, 1933). The ' solvents ' used were dilute aqueous solutions containing optically stable ions; solvent–solute association of any formal kind seems therefore improbable. The results were discussed by Dwyer according to the concept of ' *configurational activity* ' (Dwyer *et al.*, 1951, 1954).

The solubilities of (+)- and (−)-tris-1 : 10-phenanthroline-ruthenium(II) perchlorate (Dwyer and Gyarfas, 1949) have been determined at 25° in ammonium (+)-bromocamphorsulphonate solutions of varying concentrations up to 2 per cent; the curves were found to diverge, the maximum difference of solubility, about 3–3½ per cent, occurring at a concentration of approximately 1–1½ per cent; after that the curves began to converge, the solubility differences diminishing as the ionic strengths became greater.

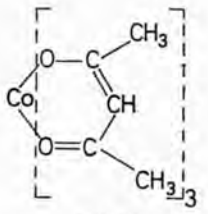
Analogous results were obtained using aqueous potassium (+)-tartrate solutions as the ' solvent ', only here the (−)-isomeride of the solute was the more soluble. One is reminded a little of Lowry (1904) and of Hudson (1917) using the solubilities of the α- and β-forms of certain sugars to predict their equilibrium compositions in the solvents used.

The solubilities of enantiomeric salts (+)A.X and (−)A.X are of course equal in ordinary solvents, and therefore in saturated solutions their thermodynamic activities are equal. The implication of the above experiment is that the addition of a stable optically active anion or cation to such a solution depresses the thermodynamic activities to different extents, making them unequal; this can lead to the phenomenon of asymmetric transformation.

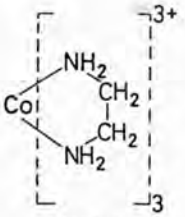
For example, the tris-2 : 2′-dipyridylnickel(II) ion was already known to be optically labile in solution in the form of its iodide (half-life period, 15 minutes at 17°; Morgan and Burstall, 1931) and to behave as if it were undergoing asymmetric transformation in presence of the (+)-camphorsulphonate ion or of the (+)-α-bromocamphor-π-sulphonate ion in aqueous solution (Pfeiffer and Nakatsuka, 1933). When the racemic chloride was dissolved in ammonium (+)-bromocamphorsulphonate solution (1½ per cent) and immediately precipitated in fractions by adding sodium iodide, the first fractions were *dextro*-rotatory and the latter were *laevo*-rotatory. If the solution was left for a day at 20°, during which time its rotation became more negative, and then precipitated similarly, the first fractions were optically inactive and the final were *laevo*-rotatory. This shows that at the moment of mixing the activity of the (−)-ion was less than that of the (+)-ion and therefore, the concentrations being equal, the

(+)-ion was precipitated first: in the sample which had been left for a day the activities became equal, the concentration of the (−)-ion increasing. Precipitation then brought out racemate first (activities of (+)- and (−)-ions being equal) and the excess of (−)-ion at the end. This is convincing evidence in favour of asymmetric transformation. Quinine bisulphate and (+)-trisethylenediaminecobalt(III) also worked as activating agents for this ion. Pfeiffer's results can be described satisfactorily in these terms: the absence of observable optical activity on precipitation in his cases could well be due to very low optical stability.

Following on this work, Dwyer and Gyarfas (1951) have demonstrated asymmetric transformation in a solution of a non-electrolyte, trisacetylacetonecobalt(III) (XXI), using (+) or (−)-trisethylenediaminecobalt(III) (XXII) in aqueous alcohol as activating agent. There could hardly be any direct chemical combination here between the optically active compound and the activating agent.



XXI



XXII

The experiments described above give support to the conclusions, reached in other cases (Pfeiffer and Quehl, 1931; Pfeiffer and Nakatsuka, 1933; Brandt, Dwyer and Gyarfas, 1954) that asymmetric transformations were involved when a substantial increase in optical activity follows the addition of a racemic metal complex to a resolved optically active material in solution.

It is not easy to decide how the asymmetric 'solvents', solutions containing a few per cent of (+)-bromocamphorsulphonate anion or cinchoninium cation, can exert the 'diastereoisomeric' effect upon the solubility or the rate of inversion of dissolved cations. The formally uncharged trisacetylacetonecobalt complex can be influenced by cation or anion equally. Dwyer and his co-workers have expressed the view that the configurational activity effect is due to the large asymmetric electric fields of the large complex ions. Even trisacetylacetonecobalt(III), on account of its structure, may be expected to carry a slight negative charge asymmetrically distributed over its outer surface.

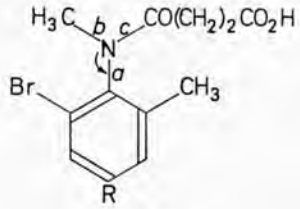
Bailar and Das Sarma (1955) have accomplished the optical activation of *cis*-dichlorotriethylenetetraminecobalt(III) chloride using (+)-antimonyl tartrate ions: the mechanism of this transformation is not yet clear.

Dwyer's precipitation experiments, particularly those which he carried out *before* allowing asymmetric transformation to take place, have something in common with observations by McKenzie and his collaborators (1915, 1922, 1923) on optically stable substances. In these, when (−)-malic acid was added to aqueous potassium racemate solution, a *dextro*-rotatory product of a mixture of potassium hydrogen racemate and potassium hydrogen (+)-tartrate crystallized. Similarly, crystallization of the potassium hydrogen racemate from aqueous (−)-malic acid solution gave potassium hydrogen (+)-tartrate mixed with potassium hydrogen racemate. Fifteen other optically active acids were tried in place of (−)-malic acid and failed to give its asymmetric effect, but (+)-malic acid gave an analogous result in the opposite sense.

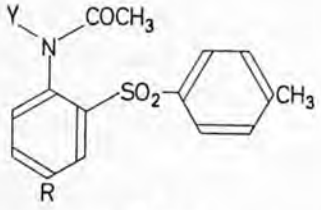
OPTICAL STABILITY AND RESTRICTED ROTATION

The factors which influence the optical stability of compounds which owe their activity to restricted rotation about single bonds are still imperfectly understood, although since 1933, when Adams based his stability series on ' interference values ', other influences have been recognized.

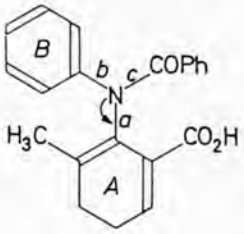
Formulae XXIII, XXIV and XXV each represent a pair of stereoisomers which are interconvertible* by passing through a symmetrical (effectively planar) transition state. Two main opposing factors determine the optical stability: (i) conjugation across the pivot bond *a* tending to bring bonds *a*, *b* and *c* into a plane, leading to optical instability; (ii) repulsive forces due to size or polar character opposing rotation about the pivot bond and hence tending to optical stability.



XXIII



XXIV

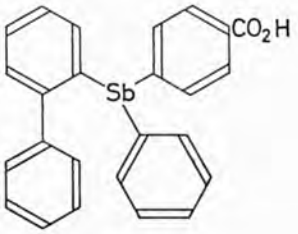


XXV

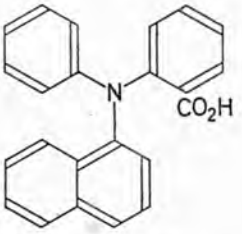
Among many examples Adams (1942, 1948, 1950, 1956, 1957) has shown that the molecule (XXIII) is much less stable when R is Cl than

* It is arguable whether pairs of enantiomorphs of this type should be described as differing in conformation or in configuration. They may be interconvertible without breaking bonds, in which case conformation is obviously the suitable term. If they are so highly hindered that only rupture of the molecule could lead to formation of the mirror image, then configuration seems the better word. However, a change of nomenclature for a property as it differs in degree is hardly satisfactory. Nevertheless, the term configuration has long been in use to describe two substituted diphenyls, related as object and mirror image. This may be a point of nomenclature which is better settled by usage than by definition. Braude and Timmons (1956) have suggested an arbitrary distinction.

when R is H, establishing thus that an electron-attracting group in ring *A* favours the ' passing position ' about bond *a*. Buchanan and Graham (1950) have come to similar conclusions in the series (XXIV). Harris, Potter and Turner (1955) have shown that electron-attracting groups (such as halogen) in ring *B* of molecule (XXV) make the molecule *more* stable optically whereas electron-repelling groups (such as methyl) lower the optical stability. Substituents in ring *B* evidently affect the availability of electrons for conjugation with ring *A*. (The arrangement of the N*abc* structure as a low pyramid is neglected for simplicity in this description.)

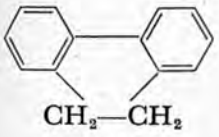


XXVI

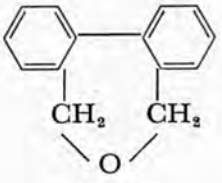


XXVII

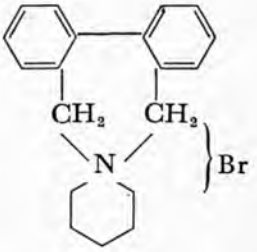
p-Carboxyphenyl-2-diphenylphenylstibine (XXVI) has been resolved (Campbell, 1955) and found to be optically stable, even in boiling xylene : Campbell contrasts this stability with Meisenheimer's inability to obtain evidence of resolution in *N*-α-naphthyl-*N*-phenylanthranilic acid (XXVII). It is suggested that the optical stability of the stibine may be due to the fact that greater energy is required to flatten the pyramidal molecule in this than in the nitrogen case (see also Chapter 6).



XXVIII



XXIX



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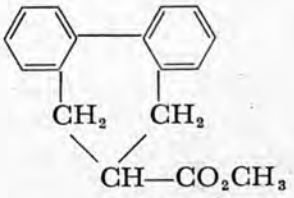
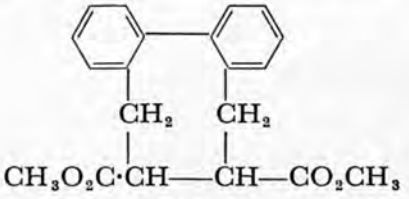


XXXI

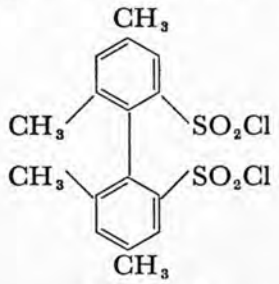


XXXII

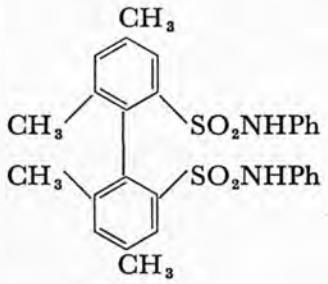
The amount of conjugation (spectroscopically assessed) between the two coaxial rings of *ortho*-bridged diphenyls (XXVIII to XXXII, in some cases with *o*- or *m*-substituents) has been discussed in relation to

the angle between the planes of the rings (estimated from scale models) by Beaven, Hall and Turner and their colleagues (1952, 1954, 1955, 1956). Braude (1955) has applied the empirical relationship $\cos^2\theta = \varepsilon/\varepsilon_0$ (Braude and Sondheimer, 1955) to some of these compounds, where θ is the mean interplanar angle in the ground state, and ε and ε_0 are the molecular extinction coefficients for the absorption resulting from inter-nuclear mesomerism in the compound and in fluorene respectively; this expression is perhaps too simple for its use to be warranted, and, in any case, fluorene differs from the other bridged diphenyls studied in that its rings are not collinear (Brown and Bartner, 1954; Burns and Iball, 1954).

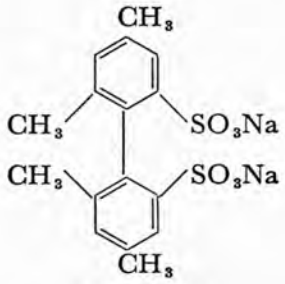
'Bridging' appears to lessen optical stability in some sulphur compounds studied by Armarego and Turner (1956, 1957). Whereas molecules XXXIII*A*, *B* and *C* are not racemized under the most stringent conditions tried, XXXIV in which the sulphur atoms—which must make the greatest contribution to the steric hindrance—are bonded, can be racemized in boiling toluene or ethylbenzene ($E = 31$ kcal.mole^{-1}).



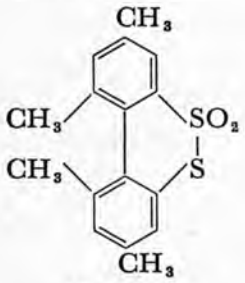
XXXIII*A*



XXXIII*B*



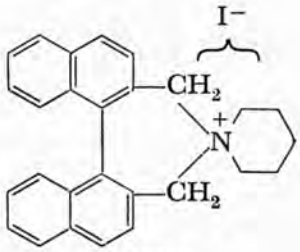
XXXIII*C*



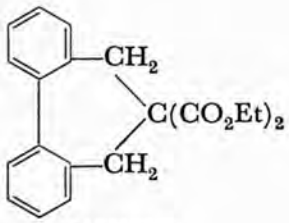
XXXIV

Hall and Turner (1955) have drawn attention to the considerable increase in optical stability that occurs when the bridging ring in a 2 : 2′-diphenyl system is enlarged from six to seven atoms. 2 : 7-Dihydro-4′ : 1″-dimethoxy-3 : 4-5 : 6-dibenzazepinium-1-*spiro*-1‴-piperidinium iodide and 2 : 7-dihydrodinaphtho-(2′ : 1′-3 : 4)(1″ : 2″-5 : 6)azepinium-1-*spiro*-1‴-piperidinium bromide (XXXV) are much more stable optically than 9 : 10-dihydro-3 : 4-5 : 6-dibenzophenanthrene (TABLE 4, first formula); this difference cannot be due to steric

interference, for this is identical in the latter two compounds, but must reflect the greater distortion required to enable the seven-membered ring to pass through the transition state of optical inversion. The preparation of 1 : 1-di(ethoxycarbonyl)-3 : 4-5 : 6-dibenzo*cyclo*hepta-3 : 5-diene (XXXVI) in an optically active form by Iffland and Siegel (1956) lends strong support to this view; this compound has no sterically interfering groups in the two *o*-positions of the diphenyl skeleton which are not involved in the bridge.

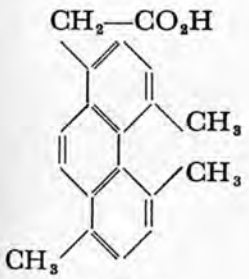


XXXV

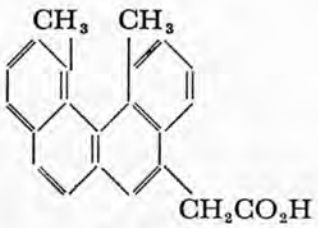


XXXVI

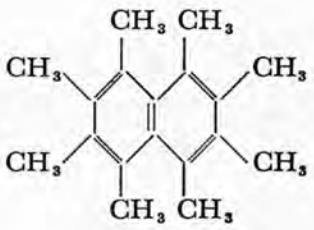
Steric hindrance in the symmetrical transition state can presumably be relieved to some extent by bond bending *in* the plane of the attached ring (a movement in the opposite direction to that forced by buttressing) or by bending *out* of the plane of the attached ring. Presumably the methyl group bonds are bent out in the normal structures of the optically active molecules XXXVII (M. S. Newman and Hussey, 1947) and XXXVIII (M. S. Newman and Wise, 1956).



XXXVII



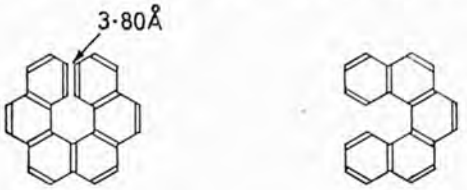
XXXVIII



XXXIX

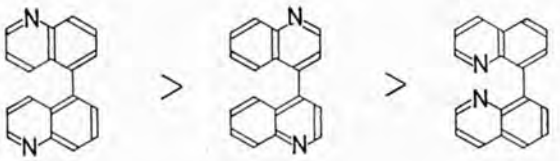
Donaldson and Robertson (1953) have shown that in the octamethyl naphthalene (XXXIX) the α-methyl groups are displaced 0·73 Å and the β-methyl groups $0{\cdot}25 \pm 0{\cdot}4$ Å in the opposite direction out of the main plane: the naphthalene nucleus is also possibly distorted to a smaller extent (*cf* Speakman, Chapter 1). The degree of contortion which an aromatic framework may tolerate can be illustrated by considering the molecule XL; this was resolved by M. S. Newman, Lutz and Lednicer (1955), and is a helical structure in which the non-bonded carbon atoms at the ends of the helix lie over each other (Fitts and Kirkwood, 1955, taking the distance between these carbon atoms as 3·80 Å, calculated $[\alpha]_D$ as $-3640°$, a good agreement with the measured $[\alpha]_D$ $-3010°$). McIntosh, Robertson and Vand (1952)

by x-ray crystallography, found a distance of 3·0 Å between the nearest non-bonded carbon atoms in 3 : 4-5 : 6-dibenzphenanthrene (XLI) which implies a degree of twist brought about by carbon and hydrogen repulsion. Such a force must be operative, although with



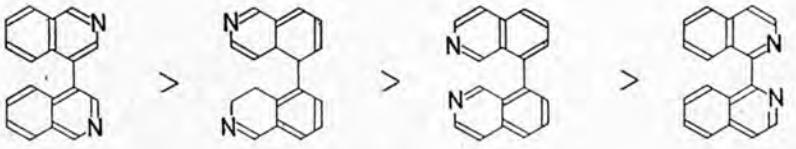
XL XLI

freedom from the aromatic bridge across the 9 : 10 positions (numbering as in the dibenzphenanthrene), in members of the diquinolyl, di-*iso*-quinolyl and dinaphthyl series. Crawford and Smyth (1952, 1954a) quoted the following order of stabilities for diquinolyls and di-*iso*-quinolyls :



XLII XLIII XLIV

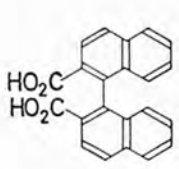
(XLIV was found inactive by Bell and Morgan, 1950)



XLV XLVI XLVII XLVIII

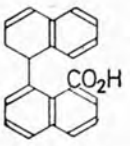
(These drawings show one of the two possible passing positions). One regularity in the results is that replacement of CH by N in a blocking position leads to a lessening of optical stability.

Ten structurally related acids (with one ester included) were placed in order of optical stability by Hall, Ridgwell and Turner (1954) (XLIX, most stable—LVII and LVIII, no optical activity). LVII and LVIII showed no response to any of the tests for optical activity attempted. An interesting point is that acid XLIX is very stable optically in sodium hydroxide solution, whereas acid LIII is extremely unstable in the same circumstances; it would be expected that, in alkali, the carboxylate ion groups would repel each other and the passing positions alternative to the ones shown would be used. Scale models show identical interference in these two, but the degree of flexibility of the bonds may well be different.

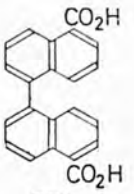


XLIX

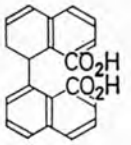
L



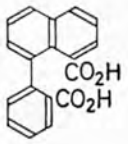
LI



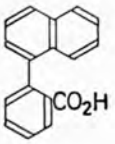
LII



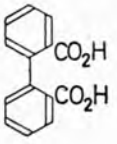
LIII



LIV

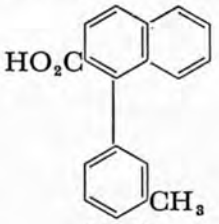


LV

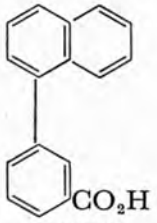


LVI

Baddeley (1946) proposed a special type of structural influence for the inversion of substituted diphenyls. Discussing figures given by Adams and his co-workers (1939) showing that LIX, LX and LXI are in increasing order of stability, and LXII, LXIII and LXIV similarly, he suggested that out-of-plane bending, depending for its

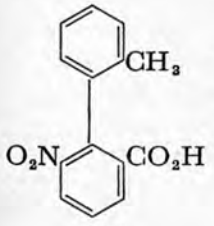


LVII

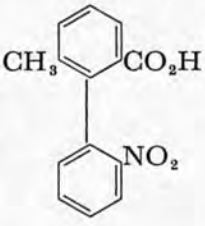


LVIII

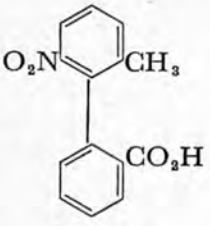
operation on electron availability to make C^- at the junction (LXV), was an adjustment which could lower the energy required for racemization. The electron densities in the upper rings of all these compounds are in the same order as the rates of racemization. Crawford and Smyth (1954) considered that an electrophilic attack



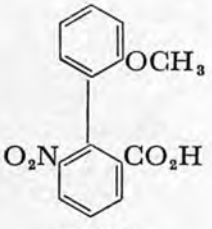
LIX



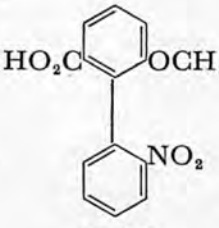
LX



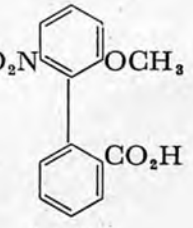
LXI



LXII

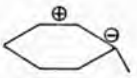


LXIII

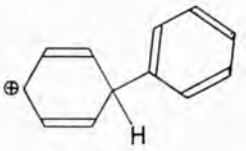


LXIV

by hydrogen might develop an intermediate complex, resembling that proposed for aromatic substitution, and favourable to optical inversion (LXVI). These two proposals have not found general acceptance.



LXV



LXVI

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ASYMMETRIC TRANSFORMATION AND ASYMMETRIC INDUCTION

BY

E. E. TURNER

AND

M. M. HARRIS

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ASYMMETRIC TRANSFORMATION AND ASYMMETRIC INDUCTION

By E. E. Turner, M.A., D.Sc., F.R.I.C., F.R.S.
[Professor of Chemistry (Bedford College), University of London]
and Margaret M. Harris,* B.Sc., Ph.D.
(Lecturer in Chemistry, Bedford College, University of London)

Asymmetric Transformation: Introductory

Asymmetric transformation involves no synthetic factor and is concerned with stereochemical changes only. The term was used by H. Leuchs and J. Wutke [1] in 1913 to describe the observed fact that addition of brucine to *dl*-2-*o*-carboxybenzyl-α-hydrindone (VII) in acetone solution resulted in an "asymmetric transformation" of the initially formed *and dissolved* base.*dl*-acid into *solid* base.*d*-acid, in yield showing that practically all the base.*l*-acid in solution had been transformed into solid diastereoisomeric base.*d*-acid. Removal of the brucine gave a dextrorotatory acid which readily racemised. Other workers discovered analogous cases, and occasionally the words "optical activation" were used: thus the brucine was said to have activated the inactive Leuchs acid. Attention was concentrated on what came out of solution rather than what was happening in solution.

An important experimental observation of a different kind was made by J. Read and A. M. McMath,[2] who found that the *l*-hydroxyhydrindamine salts (I) of *l*- and of *dl*-chlorobromomethanesulphonic acid exhibited in dry acetone solution a rotational change which could only be explained on the assumption of the existence of an equilibrium:

$$l\text{-Base}.l\text{-Acid} \rightleftharpoons l\text{-Base}.d\text{-Acid}$$

which was greatly in favour of the *l.l*-salt. Again the idea of activation of a potentially active molecule (that of the acid) by a stably active molecule (that of brucine) was put forward, although it was found impossible to isolate an optically active specimen of the free acid. In 1928, W. H. Mills and K. A. C. Elliott [3] observed the partial "activation" of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (XII) by means of an approximate equivalent of brucine in chloroform solution; in the same research these authors obtained by processes depending on asymmetric transformation both the *d*- and the *l*-acid, which had low, but appreciable, optical stability.

[1] *Ber.*, 1913, **46**, 2420. [2] *J.*, 1925, **127**, 1572. [3] *J.*, 1928, 1291.
* (*née* Jamison.)

The discovery that the salt of 4 : 4′-dinitrodiphenic acid (XXIII) with the lævorotatory base quinine was strongly dextrorotatory in solution and moreover was apparently a single individual, but that all attempts to liberate an active acid failed, led R. Kuhn [4] in 1932 to introduce the expression " asymmetrische Umlagerung erster Art " to describe this and other cases which seemed to him similar (Read and McMath ; [2] P. Pfeiffer and his co-workers [5]). This expression was translated " asymmetric transformation of the first order," but " sort " or " kind " or " type " would have been a happier rendering of " Art " since " order " raises thoughts of reaction kinetics. R. Kuhn proposed the term " asymmetric transformation of the second order " for cases such as that of Leuchs, where one diastereoisomeride was obtained in preponderating quantity and removal of the activating base led to the isolation of an optically active acid. H. King,[6] in 1933, made a useful survey of the subject up to that date.

M. M. Jamison and E. E. Turner [7] re-defined first-order asymmetric transformation as a phenomenon relating only to the attainment of an equilibrium, while second-order transformation denotes the appearance of a second phase. They showed that one essential condition for first-order transformation was the real existence of diastereoisomerides in solution, the cause of any observed mutarotation being the approach to an equilibrium such as :

$$d\text{-Base}.d\text{-Acid} \rightleftharpoons d\text{-Base}.l\text{-Acid},$$

where the base is optically stable and the acid optically labile : salts will only show the effect in solutions in which ionic dissociation is largely absent. There are, however, numerous examples of diastereoisomerism apart from those concerned with salts ; thus α- and β-sugars are, in the present sense, diastereoisomeric, and their examination can be extended to aqueous solutions, in which salt-diastereoisomerides would as a rule be ionically dissociated. In fact, the " mutarotation " of sugars, which has been long studied, must now be reconsidered in the light of the conception of first-order transformation, as must also the interesting studies of " asymmetric catalytic racemisation " made by A. McKenzie and his co-workers [8] which can be more clearly interpreted now that first-order transformation has been investigated using compounds deliberately synthesised for the purpose.

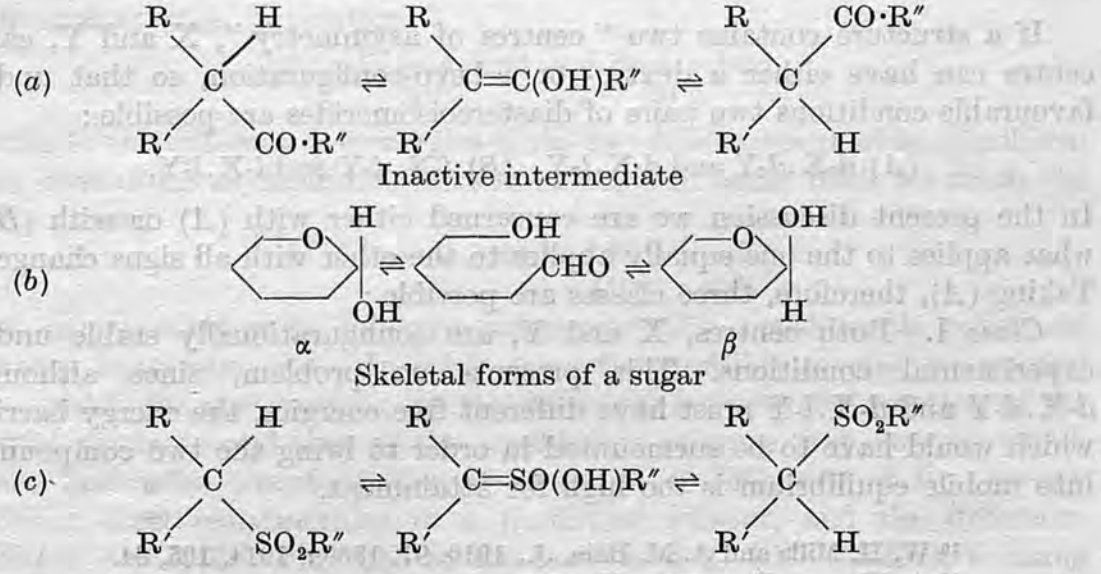
Before discussing individual examples of asymmetric transformation, it is pertinent to consider the kind of molecule which possesses unstable dissymmetry. (Up to the present most experiments have been made in the normal range of temperatures, but, at temperatures considerably higher than the ordinary, many optically stable molecules would become optically labile, and the investigation of derivatives of such compounds as tartaric acid at temperatures at which they racemise readily offers interesting problems.) A large proportion of the experimental evidence in connection with asymmetric transformations has been obtained from a study of molecules

[4] *Ber.*, 1932, **65**, 49. [5] *Ibid.*, 1931, **64**, 2667 ; 1932, **65**, 560 ; 1933, **66**, 415.
[6] *Ann. Reports*, 1933, **30**, 261. [7] *J.*, 1942, 437.
[8] A. McKenzie and I. A. Smith, *J.*, 1924, **125**, 1582 ; *Ber.*, 1925, **58**, 894.

owing their dissymmetry to restriction of rotation about a single bond. A second class of molecule which has contributed is that in which interconversion of antipodal forms is rendered possible by the operation of prototropic changes, this class including some sugars. To these can be added a number of rather miscellaneous compounds, among which are certain complex salts. The total number of compounds the configuration of which can readily be inverted is relatively small ; what might be called the average asymmetric carbon atom offers considerable resistance to inversion. (We are not concerned in the present article with inversion during replacement reactions of the type associated with the name of Walden, although cases can be foreseen where the steric aspects of " aliphatic substitution " and first-order asymmetric transformation may well have common experimental material.)

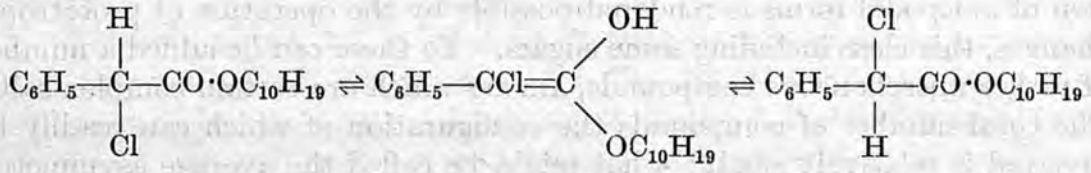
Compounds owing their optical activity to restriction of rotation about a single bond provide the most convenient material for a study of the two types of asymmetric transformations. They are suitable material for examination because their racemisation is of purely physical origin and therefore spontaneous, that is, not generally subject to acceleration by the action of catalysts. Some members of this class give active forms of very high optical stability, *e.g.*, 6 : 6′-dinitrodiphenic acid, while the optically least stable compounds yet known to show measurable mutarotation are certain alkaloidal salts[9] of *N*-benzoyl-2 : 4-dichlorodiphenylamine-2′-carboxylic acid (*B*, p. 325) and *N*-benzoyl-2 : 4-dimethyldiphenylamine-2′-carboxylic acid (*C*, p. 325). These acids belong to one of the most convenient and accessible series of compounds in the restricted rotation class. Substituted diphenyls offer a large field, but particular individuals are difficult to prepare in any quantity. *peri*Disubstituted naphthalenes, of which the Mills–Elliott acid mentioned above is the best example, provide a useful but limited field and are tedious to synthesise.

Enantiomeric pairs which racemise by a tautomeric mechanism are interconvertible in ways such as the following :



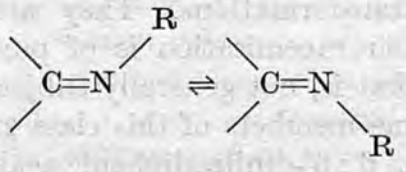
[9] *J.*, 1938, 1646.

These processes are subject to influence by catalysts and in some cases, *e.g.*, the (as it is now classified) first-order transformation :



the equilibrium process is too slow for measurement in absence of suitable catalysts.[8] The sugars provide examples of both types of asymmetric transformation.

Among substances which do not fall under either of these two headings are the oxime (V) (p. 310) and benzoylphenylhydrazone of *cyclo*hexanone-4-carboxylic acid ;[10] here the inversion mechanism is purely a configurational change, depending on the stereochemical instability of the system :



In complex salts, particularly the chromioxalates (II) (p. 308),[11] the mechanism of inversion is unknown, although various obvious possibilities can be conjectured. It may be that optical instability arises from sheer chemical instability, since asymmetric transformation was not observed by Werner in his exhaustive treatment of complex salts of the ammine type, where the chemical stability is considerable. The " asymmetric tin " compounds of W. J. Pope and S. J. Peachey [12] must owe their optical instability largely to ease of inversion in the ion, $MeEtPrSn^+$, or a solvated modification. Optical instability of a molecule owing its dissymmetry to " folding " was described by I. G. M. Campbell [13] in the case of 10-*p*-carboxyphenyl-2-methylphenoxstibine (VI) (p. 310).

If a structure contains two " centres of asymmetry ", X and Y, each centre can have either a dextro- or a lævo-configuration, so that under favourable conditions two pairs of diastereoisomerides are possible :

(*A*) *d*-X.*d*-Y and *d*-X.*l*-Y (*B*) *l*-X.*d*-Y and *l*-X.*l*-Y.

In the present discussion we are concerned either with (*A*) or with (*B*) : what applies to the one equally applies to the other with all signs changed. Taking (*A*), therefore, three classes are possible :

Class I. Both centres, X and Y, are configurationally stable under experimental conditions. This presents no problem, since although *d*-X.*d*-Y and *d*-X.*l*-Y must have different free energies, the energy barrier which would have to be surmounted in order to bring the two compounds into mobile equilibrium is too high for attainment.

[10] W. H. Mills and A. M. Bain, *J.*, 1910, **97**, 1866 ; 1914, **105**, 64.
[11] A. Werner, *Ber.*, 1912, **45**, 3061.
[12] *Proc.*, 1900, **16**, 42, 116. [13] *J.*, 1947, 4.

Class II. One centre, say X, has a high configurational stability, while Y can undergo configurational inversion at a measurable rate under the experimental conditions. An equilibrium can now be established : *d*-X.*d*-Y $\rightleftharpoons$ *d*-X.*l*-Y, and its establishment may be capable of observation as a mutarotation.

Class III. Both centres, X and Y, have low optical stability under experimental conditions. Starting with either *d*-X.*d*-Y or with *d*-X.*l*-Y the final result of equilibration will be a mixture of (*A*) and (*B*), the ratio of *d*-X.*d*-Y to *d*-X.*l*-Y (equal to that of *l*-X.*l*-Y to *l*-X.*d*-Y) being determined by the relative free energies of the diastereoisomerides.

We are here concerned only with Class II. Most of the known examples of asymmetric transformation relate to salts, either the acidic, or much more usually the basic, part containing X, the fixed asymmetric centre. In the sugar series, Y represents the CH·OH group which can adopt either the α- or the β-configuration, X representing the rest of the molecule and usually containing several asymmetric centres of high optical stability which can be thought of as acting together as one unit. The cases dealt with under "asymmetric catalytic racemisation" are esters. For second-order asymmetric transformation to occur with a Class II compound, the two diastereoisomerides need have no real existence in solution : what is necessary is that one salt should crystallise from solution. Thus if *d*-X is a stably active base and *dl*-Y is an optically labile acid, even if in solution there are merely the ions corresponding to base and acid, then, provided, *e.g.*, *d*-X.*d*-Y begins to crystallise, the acid *ion* *l*-Y can *racemise* and in this way provide continually more of the *d*-Y ion and so more *d*-X.*d*-Y. For first-order transformation, however, the two optical centres concerned must be in combination and this means that the solvent must be one in which little ionisation occurs : in particular a non-hydroxylic one. This condition fulfilled, let us suppose the *d*-form of an optically stable base to be in solution. On adding an equivalent of the *dl*-form of an optically unstable acid, there is formed at once, in solution,

$$\begin{array}{cc} \text{(1) } d\text{-Base}.d\text{-Acid} & + \; d\text{-Base}.l\text{-Acid} \\ 50\% & \qquad 50\% \end{array}$$

Owing to the different free energies of the two diastereoisomerides, equilibration (first-order asymmetric transformation) will occur until we reach the composition :

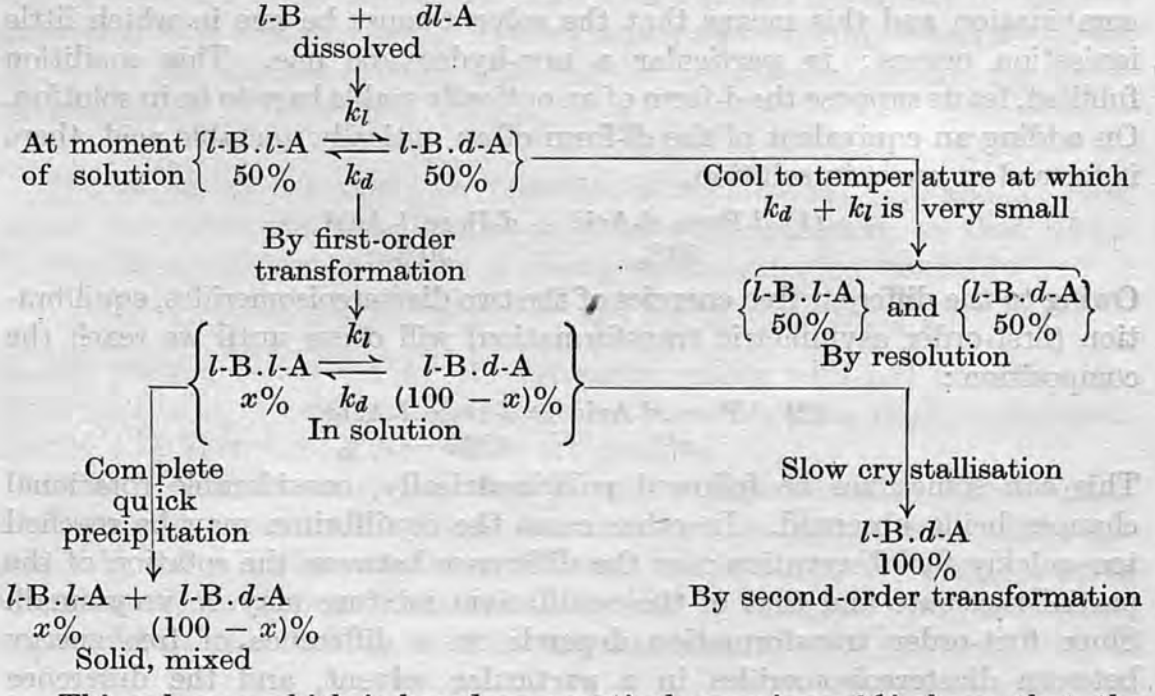
$$\begin{array}{cc} \text{(2) } d\text{-Base}.d\text{-Acid} & \rightleftharpoons \; d\text{-Base}.l\text{-Acid} \\ x\% & \qquad (100 - x)\% \end{array}$$

This can sometimes be followed polarimetrically, considerable rotational changes being observed. In other cases the equilibrium may be reached too quickly for observation ; or the difference between the rotation of the partial racemate and that of the equilibrium mixture may be very small. Since first-order transformation depends on a difference of free energy between diastereoisomerides in a particular solvent, and the difference *d*-X.*l*-Y $-$ *d*-X.*d*-Y may not be the same as *d*-X′.*l*-Y $-$ *d*-X′.*d*-Y, using a second base X′, the stereochemist varies both activating agent and solvent in attempting to bring first-order asymmetric transformation

involving a specific labile group within the measurable range of magnitude and velocity.

In one instance [7] it was possible to prepare the pure *l*-base.*l*-acid and determine the rate constant for the change into the equilibrium mixture, in addition to determining the rate constant for the "activation" process, *viz.*, the change of the 50 : 50 mixture of *l*-base.*d*-acid and *l*-base.*l*-acid into the same equilibrium mixture. The two rate constants were found to be equal, k, the measured value, being the sum of two rate constants k_d and k_l, for the *partial inversion* of base.*d*-acid and base.*l*-acid. (By "partial inversion" we mean the change *l*-base.*d*-acid $\longrightarrow$ *l*-base.*l*-acid or *l*-base.*l*-acid $\longrightarrow$ *l*-base.*d*-acid.) These changes have been described as "partial racemisation", but this term is misleading, since the partial racemate, composed of equivalent weights of *d*-X.*d*-Y and *d*-X.*l*-Y, is not the equilibration product. In *partial racemisation* the values of k_d and k_l are equal : it is their difference that accounts for first-order transformation. In the case raised above in which second-order asymmetric transformations involve crystallisation of diastereoisomerides which become ionised in solution, first-order transformation is excluded and *partial racemisation* accurately describes what happens in solution.

To summarise the practical aspects of resolution, second-order transformation, and first-order transformation, it is convenient to consider a hypothetical case in which a *dl*-acid (optically unstable) and a *l*-base (optically stable) are dissolved in a solvent in which the salts formed are not dissociated, and to predict the results of applying various conditions on the solution and what crystallises or is precipitated from it :



This scheme, which is based on practical experience,[9,14] shows that the appropriate treatment of an optically labile substance, with one activating

[14] M. M. Jamison, *Trans. Faraday Soc.*, 1945, **41**, 696.

agent and one solvent only, can produce an interesting variety of results. There may be greater variety than is here indicated : the difference in free energy between the two diastereoisomerides may be so slight that in second-order transformation one form or the other may crystallise without there being an apparent difference in procedure. Ordinary resolutions, in which the question of optical stability does not normally arise, are sometimes complicated [15a, b] by the separation of the partial racemate in crystalline form, and similarly partial racemates sometimes separate as alternatives to the normal products of second-order asymmetric transformation.

It is understandable that decomposition of an optically pure salt obtained by second-order asymmetric transformation might give an optically inactive, *i.e.* racemised, acid. How, in that case, can the crystallisation be classed as second-order transformation ? Obtaining an active acid is the only entirely satisfactory proof of second-order transformation, but it may be suspected when a solution made up to contain a g. of an optically stable base *d*-X is mixed with one containing the equivalent, b g., of an acid *dl*-Y and crystallisation produces considerably more than $(a + b)/2$ g. of solvent-free, apparently homogeneous salt with a molecular rotation different from that " calculated " for the partial racemate. The suspicion is heightened if crystallisation appears to be progressive rather than sudden and if it is accelerated by gentle heating. It becomes very nearly a certainty (1) if several crops are obtained each with the same rotation and which together weigh nearly $(a + b)$ g., (2) if a solution of the salt in the same or a different solvent exhibits mutarotation, or (3) if when the salt is dissolved in a different solvent a new and uniform salt crystallises, which in turn gives rise to mutarotational changes when dissolved in the same or a different solvent. A striking difference, even of sign, between the rotation of *d*-X and that of the salt which crystallises is not enough to justify the assumption of asymmetric transformation.

Second-order transformations have often been called resolutions : this mistake has led to the judgment that diphenyl compounds are easy to resolve, when in fact it has been found easy to obtain *one* antipodal form only, by second-order transformation.

A problem of great interest is this : if *d*-X.*d*-Y and *d*-X.*l*-Y (X stable, Y unstable, optically) are brought together in equivalent amounts in solution, and first-order asymmetric transformation leads to the equilibrium :

$$d\text{-X}.d\text{-Y} \rightleftharpoons d\text{-X}.l\text{-Y}$$

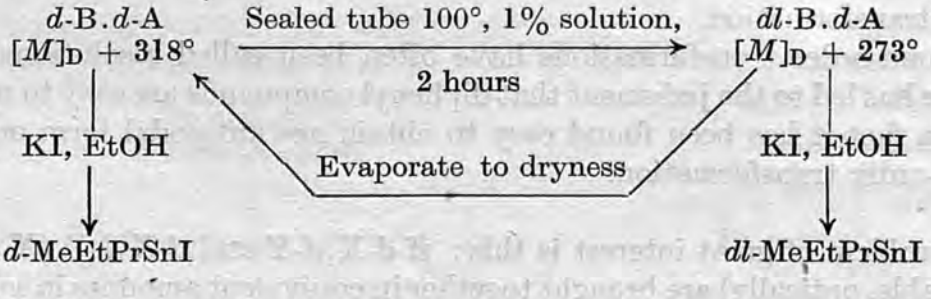
so that more *d*-X.*l*-Y is finally present in solution than *d*-X.*d*-Y, then, if crystallisation begins, which of the two diastereoisomerides will separate ? With a pair of solids such as are met with in a study of allotropy or polymorphism, we should usually have a *stable* form and an *unstable* form (as distinguished from a pair of diastereoisomerides in equilibrium). Generally

[15a] J. Meisenheimer and O. Beisswenger, *Ber.*, 1932, **65**, 32.
[15b] J. Meisenheimer, W. Theilacker, and O. Beisswenger, *Annalen*, 1932, **495**, 249.

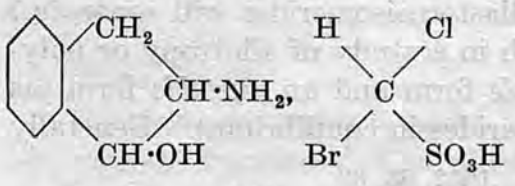
speaking, the stable form would be less soluble than the unstable form, so that, apart from chance inoculation, the stable form would be the one to separate if time were given for stability to assert itself thermodynamically over instability. We should have to hesitate, however, before answering the above question by (apparent) analogy. The answer can be given: "the stable form is the more soluble" in the case of some diastereoisomeric sugars,[26, 31, 32] some esters investigated by McKenzie,[8] and the only example known [7] in which both first- and second-order asymmetric transformations have been observed with one pair of diastereoisomeric salts in one and the same solvent.

Examination of Experimental Material

Two cases of second-order asymmetric transformation appear in Pope and Peachey's demonstration of optical activity in tin compounds.[12] Methylethyl-*n*-propyltin *d*-camphorsulphonate crystallised from water in one form only, $[M]_D + 95°$ in water; $[M]_D + 45°$ is the calculated value for the basic radical from this: the dextrorotation was retained when the camphorsulphonate was converted into the iodide.[12] Secondly, the specific rotations of successive crops of methylethyl-*n*-propyltin *d*-α-bromocamphorsulphonate from acetone solution were constant ($[M]_D + 318°$ in water [12]). Since the acid radical was known to have $[M]_D + 270°$, the authors attributed $+ 48°$ to the basic part and confirmed it by conversion into *d*-methylethyl-*n*-propyltin iodide as before. The aqueous solution, $[M]_D + 318°$, was heated to 100° in a sealed tube for two hours, by which time its rotation had fallen to $+ 273°$: decomposition of this solution with potassium iodide gave the inactive iodide, but evaporation to dryness gave the original *d*-α-bromocamphorsulphonate, $[M]_D + 315°$. They ascribed the fall in rotation on heating to partial racemisation, so that the whole series of changes can be expressed:



Read and McMath [2] were able to carry out a second-order asymmetric transformation using *dl*-chlorobromomethanesulphonic acid in either the *d*- or the *l*-direction by using the *d*- or the *l*-hydroxyhydrindamine. The *l*-hydroxyhydrindamine *dl*-chlorobromomethanesulphonate (I), $M[\alpha]_D - 72°$ in methyl alcohol, crystallised from acetone containing a little methyl alcohol to give a salt which, while it had eventually the rotation $- 72°$, had $M[\alpha]_D - 173°$ when first observed.



(I.)

Proof of the activity of the acid part of the salt could only be obtained by the expedient of mixing equal quantities of the *d*-base.*d*-acid and *l*-base.*dl*-acid salts ; a residual $[M]_D$ of + 49° was then observed : attempts to replace the optically active base by benzidine or α-naphthylamine gave inactive salts.

When the salt *l*-base.*l*-acid was dissolved in specially purified anhydrous acetone it had $[M]_D$ — 256° three minutes after first wetting with solvent, a value which changed to — 187° in less than an hour (Fig. 1). This change might have been considered as consequent on partial racemisation had it not been that the partial racemate itself, *l*-base.*dl*-acid, when dissolved in the same solvent had $[M]_D$ — 71° initially, changing to — 187° on standing. This latter observation has become the classical case of first-order asymmetric transformation. If the salts are not dissociated in solution and their rotations are constant over the concentration ranges employed, the composition, as a simple calculation shows, at equilibrium is

$$\begin{matrix} \text{B}.l\text{-A} & \rightleftharpoons & \text{B}.d\text{-A} \\ 81\% & & 19\% \end{matrix}$$

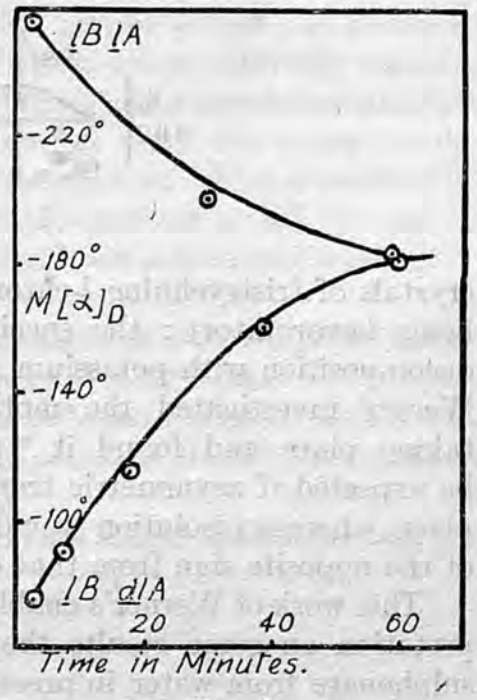


FIG. 1

It was, of course, desirable to remove the *l*-hydroxyhydrindamine from the equilibrated solution to prove that the mutarotation was due to optical activation of the acid (particularly as *l*-hydroxyhydrindamine benzenesulphonate shows (unexplained) mutarotation in methyl alcohol, $[M]_D$ changing from — 100° to — 76° in 8 hours), but the authors were unable to accomplish this. The experiments described are not suitable for correlation of the directions of first- and second-order transformation since the first-order transformation was carried out in specially purified and dried acetone and the second-order from acetone–methyl alcohol : also, the alternative crystalline solid which can be obtained is not the diastereoisomeride but the partial racemate, *l*-B.*dl*-A. An interesting recorded observation which would be worthy of further investigation is that " an acetone solution " of the salt deposits crystals the acetone solution of which has $[M]_D$ — 93° mutarotating to — 154° and yet depositing on evaporation the crystals with $[M]_D$ — 93°.

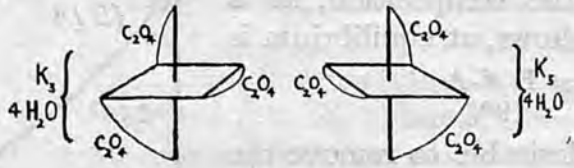
A second series of experiments was made with the same base and chlorobromoacetic acid.[16] A solution of equimolecular quantities of the *l*-base and *dl*-acid was made in chloroform containing a little methyl alcohol ; slow crystallisation gave *l*-base.*dl*-acid, $[M]_D$ — 50° in the same solvent, while quick cooling of a hot solution to supersaturation gave *l*-base.*d*-acid in 75% yield, $[M]_D$ changing from the first observed 0° to — 50° on standing :

[16] *J.*, 1926, 2183. See also H. J. Backer and H. W. Mook, *J.*, 1928, 2125.

*

l-base.*dl*-acid was deposited from the mother liquor. Although the antipodal forms of the above pair of salts, *d*-base.*l*-acid and *d*-base.*dl*-acid, were prepared, attempts by mixing to observe a rotation which was due to acid only failed—an inconclusive observation of $-0{\cdot}1°$ was made 1·5 minutes after wetting with solvent. The naming of the various types of crystal is therefore conjectural.

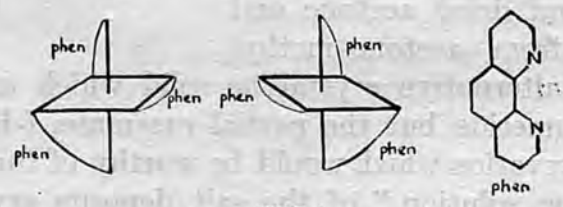
The crystals deposited from a hot solution of potassium distrychnine chromioxalate in ethyl alcohol were shown by Werner [11] to contain asymmetrically activated chromioxalate ion. The rotation of the salt, a tetrahydrate, was $[\alpha]_G + 430°$ in water, the part due to the chromioxalate ion ($+ 0{\cdot}43°$ observed) mutarotating to zero in $1\frac{1}{4}$ hours; the tripotassium salt obtained from a sample of it before mutarotation was dextrorotatory. A dilute solution of potassium distrychnine chromioxalate in water deposited



(II.)

crystals of tristrychnine *l*-chromioxalate ($+ 4H_2O$), all the crops measured being lævorotatory: the specific rotation $[\alpha]_G$ was $-300°$ in water, and decomposition with potassium iodide gave *l*-potassium chromioxalate (II). Werner investigated the mother liquor from which crystallisation was taking place and found it "practically inactive"; this is what might be expected if asymmetric transformation of the second order were taking place, whereas resolution would result in an increase of rotation in solution of the opposite sign from that of the solid coming out.

This work of Werner's enabled P. Pfeiffer and K. Quehl [5] to put an interpretation on some results they obtained in crystallising zinc β-camphorsulphonate from water in presence of *o*-phenanthroline. A solution of zinc



(III.)

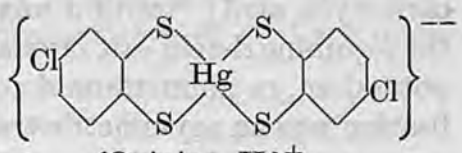
β-camphorsulphonate itself had $\alpha_D + 0{\cdot}92°$ (1/1000-mol. in 25 c.c. of water), while the salt $Zn(phen)_3O{\cdot}SO_2{\cdot}C_{10}H_{15}O,7H_2O$ (as III) obtained in 80% yield by crystallising zinc β-camphorsulphonate from water containing 3·5 mols. of *o*-phenanthroline had α_D 0·0°.

When 3 mols. of *o*-phenanthroline were added to a solution of zinc β-camphorsulphonate, the rotation fell immediately from $+ 0{\cdot}92°$ to $+ 0{\cdot}09°$: neither ammonia, pyridine, nor ethylenediamine produced this diminution. Replacement of the β-camphorsulphonate ions by nitrate or

bromide gave inactive products ; nevertheless Pfeiffer and Quehl accounted for their observations by assuming formation of *l*-$[Zn(phen)_3]^{++}$ under the influence of the β-camphorsulphonate ions. The quinate and α-bromo-π-camphorsulphonate ions [5] appeared to cause similar activation (first order) of zinc complexes, large changes in rotation being observed on adding *o*-phenanthroline or 2 : 2′-dipyridyl to aqueous solutions of these zinc salts. One feels a little hesitant at accepting the interpretation of these experimental observations in solution as first-order changes, since the salts $[Zn(phen)_3]X_2$ must be completely ionised, that is, the transforming agent is separated from the complex it is activating. In comparison with examples of similar phenomena in other fields of molecular dissymmetry, it is more surprising that a cation should be able to activate a cation, as the authors suggest in the following cases : a solution of cinchonine hydrochloride and zinc sulphate in water showed $\alpha_D + 5{\cdot}29°$ before the addition of 3 mols. of *o*-phenanthroline, after which it changed immediately to $- 1{\cdot}89°$ and to $- 2{\cdot}46°$ on standing. Precipitation of the cinchonine by means of alkali left an optically inactive zinc salt. Results of the same type were obtained using strychnine sulphate instead of cinchonine hydrochloride, and indeed there are many similar examples in the work of Pfeiffer and his collaborators. It is possible that these mutarotations are not first-order transformations at all, but result from the replacement of alkaloid by *o*-phenanthroline in a metal complex, with consequent mutarotation.

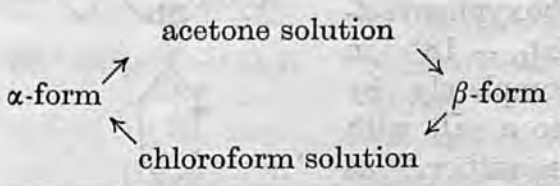
The activation of the ferrioxalate ion by means of *d*- or *l*-α-phenylethylamine recorded by W. Thomas [17] rests on more slender evidence but would be worthy of repetition. J. J. Woldendorp [18] records a crystallisation of strychnine hydrogen chromimalonate $(C_{21}H_{22}O_2N_2{\cdot}H)H[Cr(malonate)_3]$ resulting in deposition of *l*-base . *l*-acid only.

W. H. Mills and R. E. D. Clark's [19] work on the complex anion of mercury with 4-chlorobenzene-1 : 2-dithiol (IV) is particularly interesting on account of the arguments the authors use in favour of a tetrahedral disposition of the mercury valencies. The diquinine salt was formed and on crystallisation from chloroform solution produced an α-form which on crystallisation from acetone deposited a inform, a process which could be repeated β-definitely : each crystalline form has solvent of crystallisation, but the two forms remain different after the solvent is removed. The fact that no two forms of *metallic* salts were discovered may be taken as excluding the possibility that the α- and β-forms are *cis*- and *trans*-forms of a flat mercury cation. In spite of the fact that the authors were unable



{Quinine, H}$_2^+$

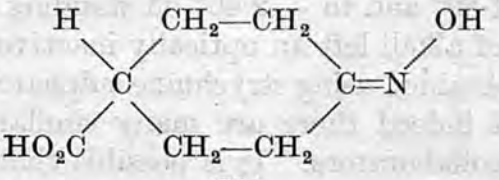
(IV.)



[17] *J.*, 1921, **119**, 1140. [18] *Vers. K. Akad. Wetensch. Amsterdam*, 1919, **27**, 1212.
[19] *J.*, 1936, 175 ; see on a practical point T. S. Patterson, *J.*, 1927, 1717.

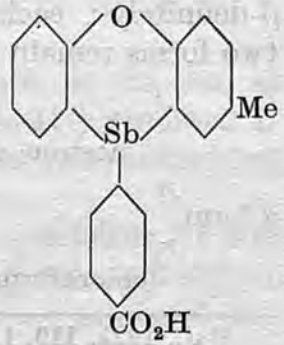
to observe mutarotation of the substances in solution at temperatures as low as − 35° they present the evidence of solubility changes as indicating optical activation of a tetrahedral mercury cation by the quinine, and assume that the mutarotations accompanying the transformations were too quick to measure. Zinc and cadmium salts were prepared which showed similar behaviour.

The oxime of *cyclo*hexanone-4-carboxylic acid (V) was prepared by Mills and Bain [10] in order to investigate the stereochemical configuration of the group $\diagdown C{=}N{-}OH$. When they attempted its resolution with quinine in 30 parts of water, a salt, quinine *l*-acid, $2\frac{1}{2}H_2O$, crystallised in 80% yield of the *total* quantity present; the mother liquor, instead of containing the diastereoisomeride, as would have been expected in resolution, was inactive, and decomposition of the salt with sodium hydroxide yielded a sodium salt, $[M]_D$ − 91° (morphine effected a dextroasymmetric transformation similarly, giving a salt from hot ethyl alcohol which could be decomposed by aqueous ammonia to give dextrorotatory ammonium salts). The authors explained their results as being due to the configurational instability of the oximino-group which is involved in the dissymmetry of the whole molecule: the aqueous solution contains the partial racemate, and as the less soluble quinine *d*-acid salt is removed by crystallisation, equilibrium is rapidly re-established by racemisation of the quinine *l*-acid salt remaining in solution. Similar behaviour was encountered in the crystallisation of the quinine and morphine salts of the *N*-benzoylphenylhydrazone of *cyclo*hexanone-4-carboxylic acid; [10] with a mixture of methyl alcohol and water as a solvent the *l*-quinine *d*-acid salt crystallised first and was converted into the sodium, potassium, or ammonium *d*-acid salt. The authors stated that this crystallisation was an asymmetric transformation and not a resolution although the percentage of the salt crystallising was not recorded in support: they did not obtain any of the *l*-base.*l*-acid salt, which makes resolution appear unlikely. In the same way the semicarbazone of the parent acid was activated by crystallising its morphine salt from aqueous methyl alcohol and converted into a dextrorotatory ammonium salt.



(V.)

A strychnine salt of 10-*p*-carboxyphenyl-2-methylphenoxstibine (VI) having $[\alpha]_D$ − 18° in chloroform was converted almost completely by boiling with alcohol for 30 minutes into a salt with $[\alpha]_D$ + 17°. This was regarded by the author [13] as a case of second-order asymmetric transformation.

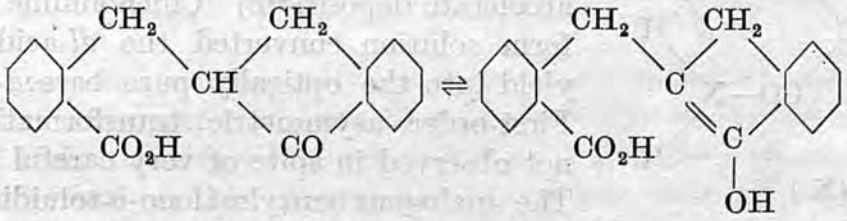


(VI.)

2-*o*-Carboxybenzylindan-1-one (VII) and brucine

crystallise from acetone to give a 94% yield of a single salt : the acid part of the salt, in its ketonic form, shows molecular dissymmetry, and decomposition of this salt with sulphuric acid gave a dextrorotatory acid, $[\alpha]_D^{20°} + 64°$, which mutarotated in chloroform solution. Leuchs and Wutke,[1] who carried out this work, gave the explanation that the optically active forms of the ketonic acid were interconvertible through the inactive enolic form, thus providing a mechanism for asymmetric transformation by the agency of the brucine :

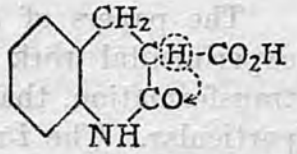
B.*l*-Acid ⇌ B.*enolic* Acid ⇌ B.*d*-Acid ⟶ Crystals



d- or *l*-Form Inactive enolic form

(VII.)

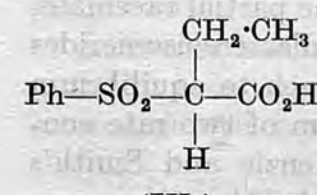
By the use of another compound owing its optical instability to keto–enol tautomerism, hydrocarbostyril-3-carboxylic acid (VIII), Leuchs [20] has provided a very clear example of a second-order asymmetric transformation. The accompanying table shows the weights of three crystalline fractions obtained from 2·4 g. of hydrocarbostyril-3-carboxylic acid and 4·07 g. of anhydrous quinidine in 40 c.c. of methyl alcohol. The dihydrated salt crystallised and was shown to be one form only by removing the quinidine in hydrochloric acid at − 10° and watching the mutarotation of the residual acid in glacial acetic acid solution at 18° ; the rotations of the separate preparations of acid are given



(VIII.)

Fraction.	Weight (g.).	α_D (l = 0·5).
1	4	+ 1·08°
2	1·5	+ 1·09
3	0·7	+ 1·04

in the third column, extrapolated to the time of wetting with solvent. The total weight of salt is seen to be 6·2 g. out of a possible 6·9 g.



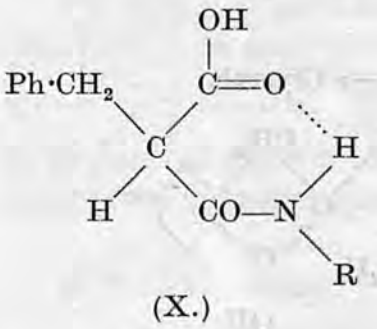
(IX.)

W. C. Ashley and R. L. Shriner [21] found that α-phenylsulphonylbutyric acid (IX) underwent almost theoretical asymmetric transformation of the second order under the influence of brucine in acetone solution to give the brucine *l*-acid salt.

[20] *Ber.*, 1921, **54**, 830. [21] *J. Amer. Chem. Soc.*, 1932, **54**, 4410.

Decomposition gave the *l*-acid, a tautomeric mechanism being envisaged for the optical inversion.

An 83% yield of optically pure brucine *l*-benzylmalonoanilic acid (X) separated from an alcoholic solution of brucine and the *dl*-acid, a second-order asymmetric transformation which the discoverers, E. M. Davidson and E. E. Turner,[22] found to be accelerated by heating. (One of the most impressive things about a crystallisation which is taking place with asymmetric transformation is that the beaker of filtered solution can be left in a warm place rather than in a cold to accelerate deposition.) Cinchonidine in chloroform solution converted the *dl*-acid in 90% yield into the optically pure base.*d*-acid salt. First-order asymmetric transformations were not observed in spite of very careful searching. The analogous benzylmalono-*o*-toluidic acid was activated similarly by cinchonidine from acetone solution to give an 83% yield of the base.*d*-acid salt. This was amply proved to be a second-order transformation by removal of the base to give the *d*-acid, which had very considerable optical stability in formic acid solution and did not racemise at a measurable rate in cold ethyl-alcoholic solution.



(X.)

The papers of A. McKenzie and his school contain much interesting experimental work which is valuable in a study of first-order asymmetric transformation, that classified as " asymmetric catalytic racemisation " in particular. The *l*-menthyl esters of various acids, *dl*-phenylbromoacetic, *dl*-phenylchloroacetic, and *dl*-mandelic, when dissolved in ethyl alcohol and given a very small concentration of alcoholic potash, undergo mutarotation.[8] Evidently the ethoxide ion acts as a catalyst for the inversion of the acid part of the ester and thereby provides a mechanism for the optical activation or first-order asymmetric transformation, under the influence of the *l*-menthyl residue. In these cases the transforming agent and the labile group are in chemical combination. McKenzie and Smith,[8] for example, studied in detail the changes in rotation undergone by *l*-menthyl phenylchloroacetate, starting from the *l*-menthyl *d*-acid, *l*-menthyl *l*-acid, and *l*-menthyl *dl*-acid esters : they came to the conclusion that " the velocity of the catalysis is greater with the *l*-menthyl *d*-phenylchloroacetate than with its diastereoisomeride " by making a calculation based on the measurement of the percentage of the original ester left after a certain time of mutarotation. This calculation assumes that the system is moving towards the partial racemate, whereas in fact the reactions in which the speed of the two diastereoisomerides differ is partial inversion. The rate constant for approach to equilibrium from either diastereoisomeride is the same, being the sum of two rate constants of partial inversion, which are different. McKenzie and Smith's figures for the mutarotations, although they were measured without temperature control, show fairly good agreement when used to calculate the rate of

[22] *J.*, 1945, 843.

approach to equilibrium from either side. The equilibrium composition, calculated on strict proportionality, is 57% of *l*-menthyl *l*-phenylchloroacetate and 43% of *l*-menthyl *d*-phenylchloroacetate.[23]

$$\underbrace{\left\{\begin{matrix}\bar{\text{Ph}}\cdot\text{CHCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19} \\ 50\%\end{matrix}\right. + \left.\begin{matrix}\overset{+}{\text{Ph}}\cdot\text{CHCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19} \\ 50\%\end{matrix}\right\}}$$

$$\left\{\begin{matrix}\bar{\text{Ph}}\cdot\text{CHCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19} \\ 57\%\end{matrix}\right. + \left.\begin{matrix}\overset{+}{\text{Ph}}\cdot\text{CHCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19} \\ 43\%\end{matrix}\right\} \text{equilibrium mixture}$$

$$\left\{\begin{matrix}\bar{\text{Ph}}\cdot\text{CHCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19} \\ 100\%\end{matrix}\right\} \qquad \left\{\begin{matrix}\overset{+}{\text{Ph}}\cdot\text{CHCl}\cdot\text{CO}_2\text{C}_{10}\text{H}_{19} \\ 100\%\end{matrix}\right\}$$

It was not possible to saponify the equilibrium mixture of esters in order to prove that first-order transformation was the cause of the mutarotations, because of their sensitivity to alkali and also because they are saponified at unequal rates and on this account also would lose their equilibrium composition during the reaction.

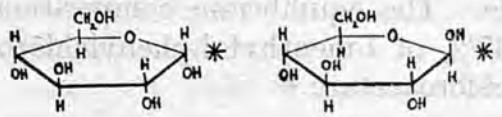
As a result of their experience of many crystallisations carried out in the resolution of *l*-menthyl *dl*-phenylchloroacetate using rectified spirit as the solvent, McKenzie and Smith found that the *l*-menthyl *d*-acid ester was the less soluble diastereoisomeride. This is interesting to note in connection with the direction of mutarotation, towards an excess of the methyl *l*-acid ester, in the same solvent.

I. A. Smith [24] has shown that similar mutarotation phenomena can be observed with amygdalin, where the transforming agent is the gentiobiose residue.

It is interesting to correlate the first- and second-order transformations with mutarotation and crystallisation behaviour in the sugar series. Most of the work to be discussed here is long established as describing the properties of the various sugars, but was not accepted by stereochemists as of general application, probably because it is not possible to remove the "activating agent" from a sugar molecule—it is the whole molecule apart from the labile group—and therefore to *prove* optical activation in any one case. Thus an investigation incorporating many of the features described under restricted rotation compounds was carried out by Hudson and his collaborators [25, 26] for several sugars but owing to the strict formulation of the sugars and their mechanism of partial inversion being in doubt the results could not take a pioneer place in a study of optically labile compounds.

d-Glucose has been the subject of the most extensive experiments, presumably because it crystallises well and is not difficult to obtain. Its composition in aqueous solution at equilibrium has for a long time been

[23] P. D. Ritchie, "Asymmetric Synthesis and Asymmetric Induction", 1933, p. 83.
[24] *Ber.*, 1931, **64**, 1115.
[25] C. S. Hudson and L. K. Yanovsky, *J. Amer. Chem. Soc.*, 1917, **39**, 1013.
[26] C. S. Hudson and J. K. Dale, *ibid.*, p. 320.



α-*d*-Glucose β-*d*-Glucose

(XI.)

calculated from the rotations of the α- and β-forms (XI) and of the equilibrated mixture, a calculation which seems to be justified as any other form must be present in negligible quantity [27, 25] (so long as the sugars are in the ring form the diastereoisomerides are " real " : the carbon atom marked is the unstable centre of asymmetry and the configuration of all the other carbon atoms is fixed).

Some of the latest published figures [27, 25] for the rotations are :

α-*d*-Glucose.	Equilibrium.	β-*d*-Glucose.
$[\alpha]_{5893}^{22\cdot2^\circ}$ + 110·0°	+ 52·56°	+ 19·7° at 20°

the equilibrium composition of 64% β- and 36% α-form being unaltered between 0° and 40°.[28] Crystallisation from cold water invariably produces the α-form as the monohydrate,[29] but if the operation is carried out between 35° and 40° the anhydrous α-*d*-glucose crystallises. The α-form therefore crystallises out from a solution containing excess of the β-form. [In order to obtain the β-form, C. Tanret left the α-form for some hours at 105° : R. L. Whistler and B. F. Buchanan [30] obtained it by evaporating an 85% solution containing 50 g. of glucose in a vacuum at 100° to a solid mass of crystals. " Second-order transformations " to α- or to β-*d*-glucose can be obtained in various other ways ; Hudson and Dale,[26, 31] for example, found that if an aqueous acetic acid solution was allowed to crystallise slowly in the cold 75—80% pure anhydrous α-glucose was produced, while a hot quick crystallisation resulted in 93% of β-glucose.] Hudson and Dale [26, 31] recognised that the measured velocity constant k for approach to equilibrium from α- or from β-glucose was the same and that it was the sum of two constants k_α and k_β. Certainly it would seem that α-glucose is the less soluble of the two forms, although they are both too soluble in water for accurate measurement to be made.

The solubilities could, however, be measured in 80% ethyl alcohol,[25] 100 c.c. of which dissolved 4·9 g. of the β-form and 2·0 g. of the α-form : the α-form is the one crystallising as the hydrate, while the rotation values show that the β-form is in excess at equilibrium :

$$[\alpha]_D^{20^\circ} \left.\begin{array}{l} \alpha\text{-glucose} + 115\cdot5^\circ \\ \beta\text{-glucose} + 20\cdot3^\circ \end{array}\right\} \text{equilibrium} + 59\cdot3^\circ$$

In absolute methyl alcohol Andrews and Worley [27] find that there is excess of the β-compound at equilibrium :

$$[\alpha]_D^{20^\circ} \left.\begin{array}{l} \alpha\text{-glucose} + 138\cdot4^\circ \\ \beta\text{-glucose} + 26^\circ \end{array}\right\} \text{equilibrium} + 75\cdot8^\circ$$

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[27] J. C. Andrews and F. P. Worley, *J. Physical Chem.*, 1927, 1880 ; J. C. Kendrew and E. A. Moelwyn Hughes, *Proc. Roy. Soc.*, 1940, *A*, **176**, 353.

[28] E. A. Moelwyn Hughes, " Kinetics of Reactions in Solution ", 1933 edn., p. 45.

[29] C. Tanret, *Compt. rend.*, 1895, **120**, 1061.

[30] *J. Biol. Chem.*, 1938, **125**, 557.

[31] *J.*, 1904, **85**, 1551.

T. M. Lowry [31] found the α-form crystallising from methyl alcohol, and showed that the solubilities in this solvent were small enough not to interfere with the relationship

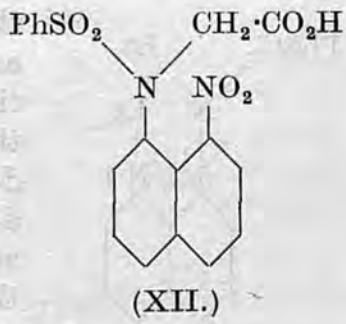
$$K \text{ (the equilibrium constant)} = \frac{k_\alpha}{k_\beta} = \frac{S_\infty - S_\alpha}{S_\alpha}$$

which was also propounded by Hudson and Dale, where S_α is the initial solubility of the α-form and S_∞ the solubility at equilibrium. This relationship was used to calculate the rotations of missing β-compounds.

d-Mannose was sufficiently insoluble in water for Hudson and Yanovsky [25] to use the solubility–rotation relationship to calculate the rotation of the then unknown α-mannose ; they obtained the value + 30°, knowing that for β-*d*-mannose to be − 17° and that for the equilibrated solution to be + 14·6°. P. A. Levene, six years later,[32] confirmed their prediction on isolating α-mannose : he records that mannose crystallises in the α-form under conditions in which glucose appears in the β-form and *vice versa*, a fact which we should link with the equilibrated *d*-mannose solution containing excess of the α-form while glucose contains excess of the β-form.

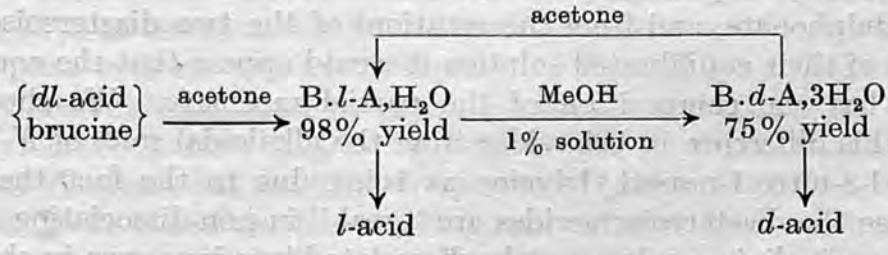
Hudson and Yanovsky also predicted the rotation of α-mannose in 80% ethyl alcohol to be + 35°, which Levene confirmed later. Taken together with a value $[\alpha]_D^{20°}$ − 14·9° for the β-form and + 25·7° for the equilibrium, this means an excess of α-form at equilibrium in a solution under which the β-form is stable.

Similar relationships hold for the α- and β-forms of lactose and galactose, the hydrated α-forms crystallising from aqueous solutions in which the β-forms are present in excess.[33, 25]



(XII.)

N-Benzenesulphonyl-8-nitro-1-naphthylglycine (XII), which owes its optical activity to restriction of rotation of the substituted amino-group by the nitro-group, was shown by Mills and Elliott [3] to undergo second-order asymmetric transformation with brucine in either direction according to the solvent used. It was the first acid found to show the two transformations in this way : decomposition of each of the diastereoisomeric salts gave an active acid :



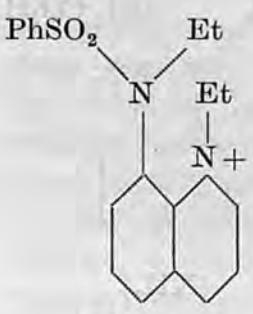
The *effect*, although not the process, was as if a resolution had been performed.

[32] *J. Biol. Chem.*, 1932, 329. [33] C. Tanret, *Bull. Soc. chim.*, 1871, **15**, 195.

From the point of view of the subject of this article, the most important work which these authors carried out on this acid was to *prove* their interpretation of the mutarotation of the brucine *dl*-acid salt as an optical activation (or first-order asymmetric transformation). This they did as follows: 0·183 g. of the *dl*-acid was dissolved in 25 c.c. of chloroform, and 0·221 g. (1·18 mols.) of brucine in a further 25 c.c. of chloroform, and the two solutions were mixed. The initial α_{5461} observed immediately changed from $-0{\cdot}78°$ to $-0{\cdot}22°$ ($l = 4$; $T = 0{\cdot}7$—$1{\cdot}5°$) as the *l*-base.*d*-acid $\rightleftharpoons$ *l*-base.*l*-acid equilibrium established itself with the former in excess. A similar solution, but containing 0·211 g. of brucine only, after being left for 3 hours, was extracted with ice-cold dilute sulphuric acid, the brucine being thus removed. The remaining solution (to which a little acetone had to be added to keep the acid in solution) had an unmistakable dextrorotation which mutarotated almost to zero at 1·2°. This dextrorotation could only be due to the acid which had been activated in solution by the brucine.

At a later date, other workers [34] were attracted to this acid and prepared the cinchonidine *l*-salt which mutarotated in chloroform from $[\alpha]^{15°}_{5461}$ $-255{\cdot}5°$ to $-87{\cdot}3°$, and the cinchonidine *dl*-salt which mutarotated from $-35{\cdot}5°$ to $-87{\cdot}3°$; this means a composition at equilibrium of 62% *l*-base.*l*-acid and 38% *l*-base.*d*-acid, neglecting dissociation or the possibility of a change of specific rotation over the concentrations involved in the calculation.

The 8-benzenesulphonethylamido-1-ethylquinolinium ion (XIII) is structurally very like the substituted glycine which has just been considered, and its range of optical stability is such that it can be made to perform the crystallisations associated with second-order asymmetric transformations. W. H. Mills and J. G. Breckenridge [35] found that 8-benzenesulphonethylamido-1-ethylquinolinium *d*-α-bromocamphor-π-sulphonate crystallised as the *d*-base.*d*-acid,$2H_2O$ salt, from a mixture of ethyl acetate and acetone. This salt could be converted into the *d*-quinolinium iodide by shaking the chloroform solution with aqueous potassium iodide, and it mutarotated in the lævo-direction in water, chloroform, and ethyl alcohol.

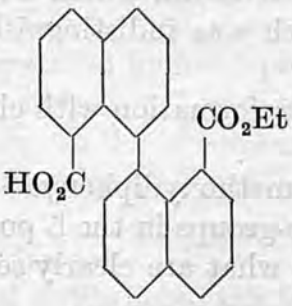


(XIII.)

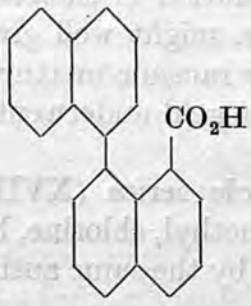
No first-order asymmetric transformation was detectable with the bromocamphorsulphonate, and from the rotations of the two diastereoisomerides and that of their equilibrated solution it would appear that the equilibrium solution has the composition of the partial racemate. We should now explain this difference in behaviour from the alkaloidal salts of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine as being due to the fact that in the latter case the diastereoisomerides are "real" in non-dissociating solvents, while the quinolinium salts must be dissociated into ions even in chloroform solution. Such diastereoisomerides are "real" in this sense only on crystallisation.

[34] M. M. Jamison and E. E. Turner, *J.*, 1940, 264. [35] *J.*, 1932, 2209.

Some members of the dinaphthyl series bear a certain skeletal resemblance to these compounds. Meisenheimer and Beisswenger [15a] found that when ethyl hydrogen 1 : 1′-dinaphthyl-8 : 8′-dicarboxylate (XIV) was crystallised with brucine from ethyl acetate containing a little methyl alcohol, the brucine *l*-acid,$3H_2O$ salt appeared in almost 100% yield : the



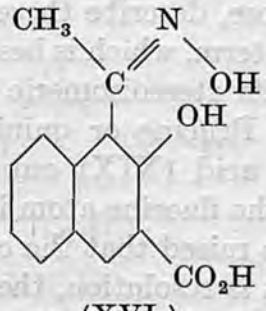
(XIV.)



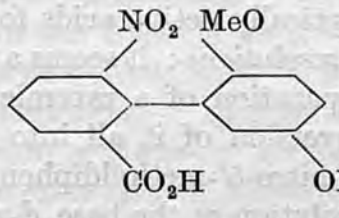
(XV.)

l-acid could be obtained by decomposing the salt with dilute mineral acid. A similar acid (XV), lacking only the carbethoxyl group, formed a monohydrate with brucine, crystallising from ethyl acetate solution as base.*d*-acid or base.*l*-acid on inoculation with the appropriate crystal. Meisenheimer, Theilacker, and Beisswenger [15b] again describe activation by alkaloids of the *β*-oxime of 2-hydroxy-3-carboxy-1-naphthyl methyl ketone (XVI).

The diphenyl nucleus has formed an obvious framework for investigating the effective sizes of groups by observing their influences on the optical stability of potentially active structures. There are therefore several



(XVI.)



(XVII.)

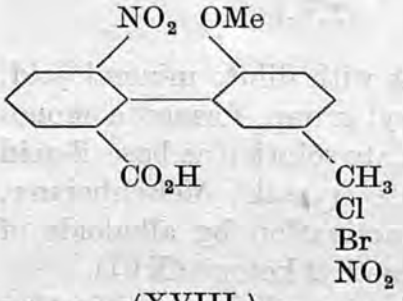
examples of what must be asymmetric transformations to be found in reading accounts of such work. Brucine *dl*-2-nitro-2′ : 5′-dimethoxydiphenyl-6-carboxylate (XVII) dissolved in water crystallised in three fractions, 90% of the total weight, all with the same specific rotation ; on decomposition with ice-cold hydrochloric acid they all yielded the *l*-acid.[36] The base.*l*-acid salt prepared by this second-order transformation mutarotated in chloroform from $[\alpha]_D$ − 167° to + 3·2° in 100 minutes : extrapolation of the recorded readings to zero time (time of wetting salt with chloroform) gave −180° as the proper initial value of $[\alpha]_D$. A solution of brucine and the *dl*-acid in chloroform had an initial $[\alpha]_D$ − 8·6°, changing to + 3·3° in 80 minutes. This latter mutarotation has all the appearance

[36] H. C. Yuan and R. Adams, *J. Amer. Chem. Soc.*, 1932, **54**, 2966.

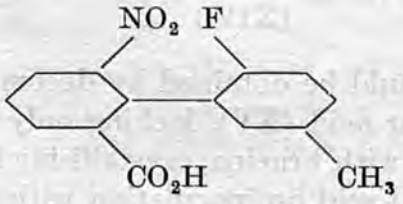
of a first-order transformation, but Yuan and Adams after performing a precipitation experiment on the equilibrated solution conclude that it is not. Examination of their figures [14] shows that if the mutarotation is due to first-order transformation the equilibrium composition by the simple calculation is 53·5% *l*-base.*d*-acid and 46·5% *l*-base.*l*-acid; precipitation of such a solution in chloroform with light petroleum, which would not be quantitative, might well give a product which was indistinguishable from the partially racemic mixture.

The same acid underwent second-order transformation with cinchonidine also.

The whole series (XVIII) of 2-nitro-2′-methoxydiphenyl-6-carboxylic acids with methyl, chlorine, bromine, and nitro-groups in the 5 position have been shown by the same authors[37] to undergo what are clearly second-order



(XVIII.)



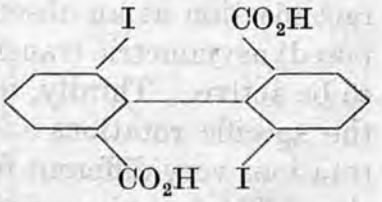
(XIX.)

asymmetric transformation with brucine from alcohol containing varying quantities of water. The authors, who were interested in obtaining specimens of optically active acids for another purpose, describe these crystallisations as *resolutions*: it seems a pity to use this term, which is best reserved for the separation of a racemic mixture into its stereoisomeric forms, to imply conversion of it all into one of them. Brucine or quinine brings 2′-fluoro-2-nitro-5′-methyldiphenyl-6-carboxylic acid (XIX) out of ethyl-alcoholic solution as the base.*d*-acid salt.[38] If the fluorine atom is replaced by chlorine or bromine the optical stability is so raised that the crystallisation process with brucine from the same solvent *is* resolution, the rotations of the crops increasing from negative to positive in the order in which they are deposited.

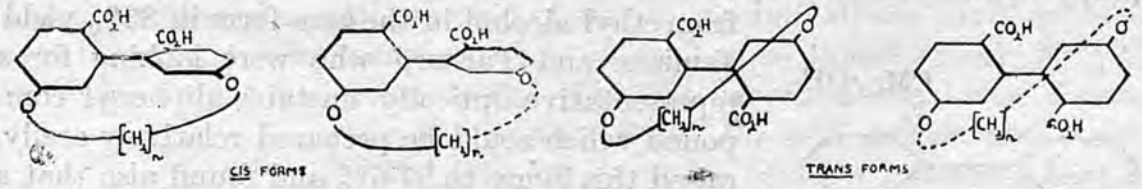
The following evidence may be interpreted as showing that a first-order transformation takes place with the fluoro-acid in chloroform by the agency of brucine. The first crop in the crystallisation of 2·75 g. of the acid and 3·94 g. of brucine weighed 5·1 g. and was identified as the salt *l*-B.*d*-A,$\frac{1}{4}H_2O$. The rotation in chloroform ($[\alpha]_D^{20°}$) was − 3·2°, but, if the solution was made up at 0°, $[\alpha]_D^{20°}$ was + 13° when first observed, and mutarotated to − 3·4°. This may, of course, be due to a large temperature coefficient of rotation, but if it is not, then it would seem that + 13° is nearer to the rotation of the base.*d*-acid salt, while − 3·4° represents an equilibrium composition which is unlikely to be that of the racemic mixture.

[37] H. C. Yuan and R. Adams, *J. Amer. Chem. Soc.*, 1932, **54**, 4434.
[38] R. W. Stoughton and R. Adams, *ibid.*, p. 4426.

The *l*-acid could be obtained [39] from each of three fractions crystallised from 95% ethyl alcohol of dibrucine 2 : 2′-di-iododiphenyl-6 : 6′-dicarboxylic acid (XX) which weighed together 83% of the possible total of salt. When a similar crystallisation was carried out using methyl alcohol as solvent, both diastereoisomeric forms crystallised out, but not as an intimate mixture. They formed discrete crystals which could be separated by hand-picking. R. Adams and N. Kornblum [40] found two cases of what now appears to be second-order asymmetric transformation in diphenyl compounds (XXI) having the 5 : 5′-positions joined by ether linkages to a hydrocarbon chain. When n is 10, brucine in methyl alcohol gives a 77% yield of a dibrucine salt in one fraction and a further quantity from the

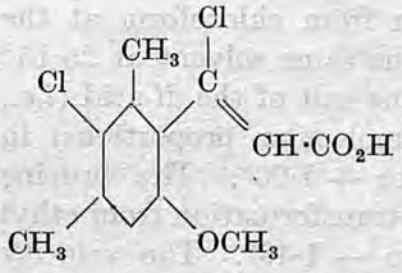


(XX.)



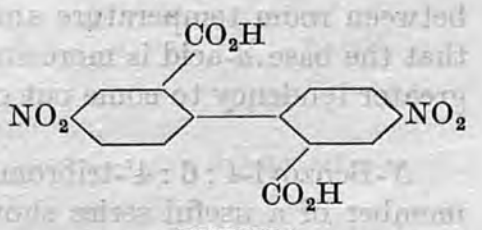
(XXI.)

mother liquor, all of which yielded dextrorotatory acid on decomposition and removal of the brucine. When n is 8, cinchonine in ethyl alcohol produces the *l*-acid salt in 3 fractions totalling 91% of the theoretical quantity, as proved by preparation of the *l*-acid from it. The substituted benzene derivative of R. Adams and J. Gross [41] deposited a quinine salt from ethyl acetate in a series of fractions all of which had the same specific rotation and were decomposed to yield *d*-β-chloro-β-(5-chloro-2-methoxy-4 : 6-dimethylphenyl)acrylic acid (XXII).



(XXII.)

R. Kuhn and O. Albrecht [42] claimed an asymmetric transformation of 4 : 4′-dinitrodiphenic acid (XXIII) by quinine on crystallisation from 96% ethyl alcohol, although removal of the base from the deposited salt gave an acid in which they were unable to detect optical activity. The evidence which they used to support their conclusion was as follows. The deposited crystals, all the same substance, represent 80% of the theoretical yield—1st crop, m.p. 207—208°, $[\alpha]_D^{20°}$ + 108·4° in chloroform ; 2nd crop,

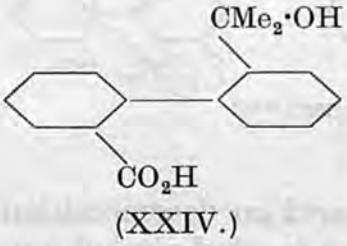


(XXIII.)

[39] N. E. Searle and R. Adams, *ibid.*, 1933, **55**, 1649. [40] *Ibid.*, 1941, **63**, 188.
[41] *Ibid.*, 1942, **64**, 1786. [42] *Annalen*, 1927, **435**, 272.

m.p. 207—208°, $[\alpha]_D^{22°}$ + 110·3° in chloroform. Secondly, the acid is one of a series with two, one, and no nitroxyl in the 6 : 6′-positions in the diphenic acid : 6 : 6′-dinitrodiphenic acid is resolvable with brucine and is optically stable ; 4 : 6-dinitrodiphenic acid is resolvable with quinine and shows racemisation at an observable rate ; 4 : 4′-dinitrodiphenic acid shows (supposed) asymmetric transformation with quinine, and the acid is too unstable to be active. Thirdly, quinine *m*-nitrobenzoate and quinine phthalate have the specific rotations — 163·5° and — 168·2° in the same circumstances, rotations very different from the salt under investigation and of the opposite sign. This last piece of evidence, largely owing to the work of M. S. Kharasch, J. K. Senior, D. W. Stanger, and J. A. Chenicek [43] on the anomalous rotation of quinine salts, has been shown not to afford the support it appeared to at first.

A. Corbellini and A. Angeletti reported in 1932 [44] that 2′-(α-hydroxy*iso*propyl)diphenyl-2-carboxylic acid (XXIV) crystallised as the brucine salt from ethyl alcohol in the *lævo*-form in 83% yield. Jamison and Turner,[7] who were looking for a representative optically unstable diphenyl compound which could be prepared relatively easily, raised this figure to 97·6% and found also that a second-order transformation could be effected by evaporating a chloroform solution of the brucine *dl*-acid salt to dryness with stirring on a boiling water-bath. This salt yielded the lævorotatory acid on removal of the brucine by means of dilute acid. Thus second-order transformation takes place in the *lævo*-direction from chloroform at the boiling point, and first-order transformation in the same solvent at 25·15° takes place in the opposite direction. The brucine salt of the *dl*-acid (*i.e.*, a mixture of brucine and the *dl*-acid in equimolecular proportions) in chloroform mutarotates from $[\alpha]_{5461}^{25·15°}$ — 5·08° to + 1·90°. The brucine *l*-acid salt (obtained by second-order asymmetric transformation from ethyl alcohol solution) mutarotates from — 47·04° to + 1·46°. The velocity constants for these mutarotations, $k_{\log_{10}\ \text{hours}^{-1}}^{25·15°}$, were, respectively, 0·0280 and 0·0277, the agreement being taken to show that the same process is being observed in each case. Assuming no dissociation, the equilibrium composition calculated from these figures is 58% of the *d*-acid salt and 42% of the *l*-acid salt. Unless the equilibrium composition varies sensibly between room temperature and the boiling point of chloroform it appears that the base.*d*-acid is more stable in solution while the base.*l*-acid has the greater tendency to come out of solution.



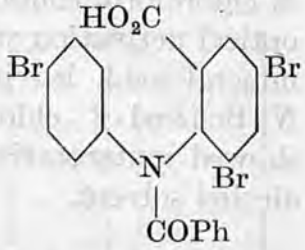
(XXIV.)

N-Benzoyl-4 : 6 : 4′-tribromodiphenylamine-2-carboxylic acid (XXV), a member of a useful series showing optical activity due to restricted rotation, was the first of its kind to be submitted to a thorough stereochemical

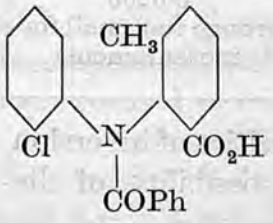
[43] *J. Amer. Chem. Soc.*, 1934, **56**, 1646. See also M. S. Lesslie and E. E. Turner, *J.*, 1934, 347 ; M. S. Lesslie, E. E. Turner, and E. R. Winton, *J.*, 1941, 257.

[44] *Atti R. Accad. Lincei*, 1932, **15**, 968.

investigation. With cinchonidine (1 mol.) in acetone solution it can be made to show first- and second-order transformation and resolution, by appropriate choice of conditions. In the second-order transformation, which can be accelerated by heating, the crystals deposited are 94% of the theoretical quantity and consist of the optically pure cinchonidine *d*-salt. The *d*-acid can be obtained from this by treatment with pyridine followed by dilute hydrochloric acid.[9] The velocity constant of mutarotation of this salt was measured at several temperatures, the value of the Arrhenius constants B and E calculated, which showed that k ($k = Be^{-E/RT}$) might be small enough for resolution to be possible at − 15°. This was put to the test by dissolving *dl*-acid and cinchonidine in warm acetone and chilling to − 15° as soon as crystallisation began. The deposition of crystals, instead of continuing until all was out of solution as in the second-order transformation, stopped when almost exactly 50% of the total weight had come down. The salt deposited was *l*-base.*d*-acid, while the mother liquor on cold evaporation under reduced pressure showed a rotation indicating that it contained two thirds of the *l*-base *l*-acid salt.



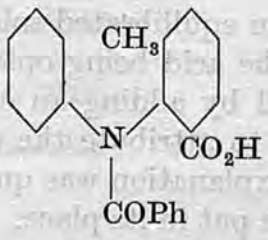
(XXV.)



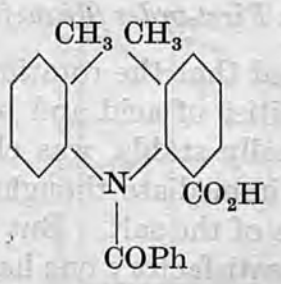
(XXVI.)

dl-*N*-Benzoyl-2′-chloro-2-methyldiphenylamine-6-carboxylic acid (XXVI) is converted by crystallisation as the brucine salt from a mixture of ethyl alcohol and ether into the *l*-form. The *l*-acid was obtained free from brucine on decomposition of the salt by dissolving it in formic acid and stirring with ice-cold dilute hydrochloric acid.

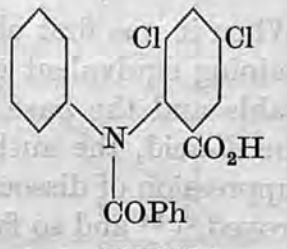
With varying substituents, the *N*-benzoyldiphenylamine-6-carboxylic acids provided material for many more first-order asymmetric transformations.[9] *N*-Benzoyl-2-methyldiphenylamine-6-carboxylic acid (XXVII) in chloroform containing 2·5% of ethyl alcohol by volume underwent mutarotation when 1 mol. of *d*-nor-ψ-ephedrine was present. The related acid



(XXVII.)



(XXVIII.)



(XXIX.)

substituted in the 2 : 2′-positions by methyl groups (XXVIII) mutarotated with cinchonidine in the same solvent, and provided proof that the mutarotations were not due to slowness of salt formation in this way—the originally lævorotatory cinchonidine solution became immediately more lævorotatory

on addition of the acid and then mutarotated in the dextro-direction. *N*-Benzoyl-2 : 4-dichlorodiphenylamine-6-carboxylic acid (XXIX) showed mutarotation with *d*-nor-ψ-ephedrine in chloroform and with cinchonidine in chloroform containing 2·5% of ethyl alcohol by volume. The assumed optical activation was proved by extracting the equilibrated solution with mineral acid, leaving a dextrorotatory acid in the chloroform solution. *N*-Benzoyl-2′-chloro-2-methyldiphenylamine-6-carboxylic acid (XXVI) showed mutarotation with quinidine and brucine in the same chloroform–alcohol solvent.

First-order transformation was observed with cinchonidine in chloroform solution, in the lævo-direction. It was possible to observe the approach to equilibrium from all three starting points, base.*d*-acid, base.*l*-acid (the optically impure mixture from the mother liquor in the — 15° experiment), and base.*dl*-acid :

Starting material.	$[\alpha]_{5461}^{18\cdot0°}$ (initial).	$[\alpha]_{5461}^{18\cdot0°}$ (final).	$k_{\log_{10}\ \text{min.}^{-1}}^{17\cdot7°}$
Base.*l*-acid . . .	— 105°	— 44·5°	0·0200
Base.*d*-acid . . .	+ 194 (extrap.)	— 44·5	0·0206
Base.*dl*-acid . . .	— 40·4	— 44·5	(range too small for measurement)

The measured velocity constant k is the sum of the two velocities of inversion, k_d and k_l, of the diastereoisomerides : neglecting the possibility of dissociation in solution,

$$\frac{k_d}{k_l} = \frac{\text{concentration } l\text{-B}.l\text{-A at equilibrium}}{\text{concentration } l\text{-B}.d\text{-A at equilibrium}}$$

whence $k_d = 0{\cdot}0105$ and $k_l = 0{\cdot}0101$; the difference is very small but there is no doubt that it is real.

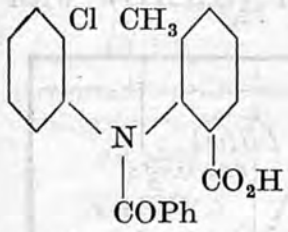
First-order asymmetric transformation of this acid was also observed in the dextro-direction with *d*-nor-ψ-ephedrine in chloroform.

Investigation of the First-order Transformation Equilibria

When it was first observed that the rotation of an equilibrated solution containing equivalent quantities of acid and base, the acid being optically unstable and the base optically stable, was changed by adding an excess of the *dl*-acid, the authors' immediate thought was to attribute the effect to suppression of dissociation of the salt. But this explanation was quickly disproved,[9, 34] and so far no satisfactory one has been put in its place. The added acid may enhance or diminish the existing rotation in different cases, and the effect has been used to explore realms of optical instability which were hitherto unattainable.

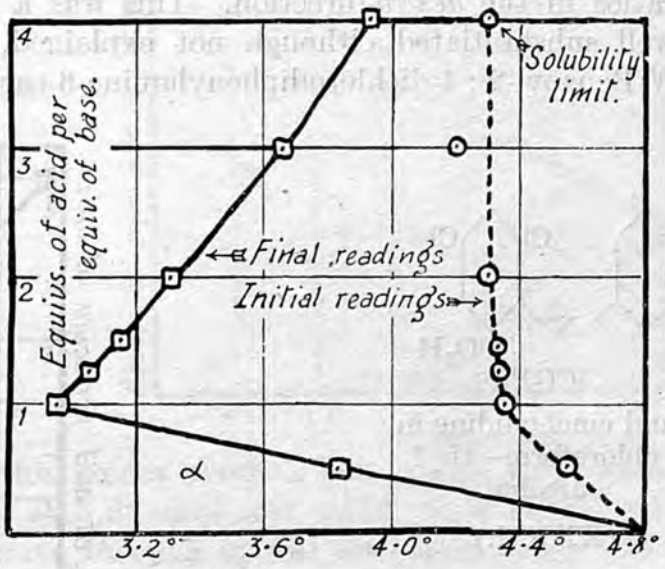
N-Benzoyl-2′-chloro-2-methyldiphenylamine-6-carboxylic acid (XXX) and quinidine in chloroform containing 2·5% of ethyl alcohol by volume behave as follows :

0·1620g. of quinidine in 20 c.c. of solvent showed a rotation $\alpha_{5461}^{20°}$ of + 4·8°, $l = 2$. On the addition of 1 equivalent of the *dl*-acid this rotation changed immediately to + 4·35° and then mutarotated to + 2·99°; 2 equivalents of



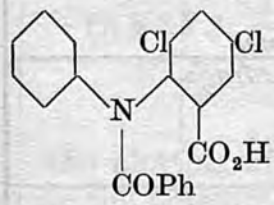
and quinidine in $CHCl_3$–EtOH

(XXX.)



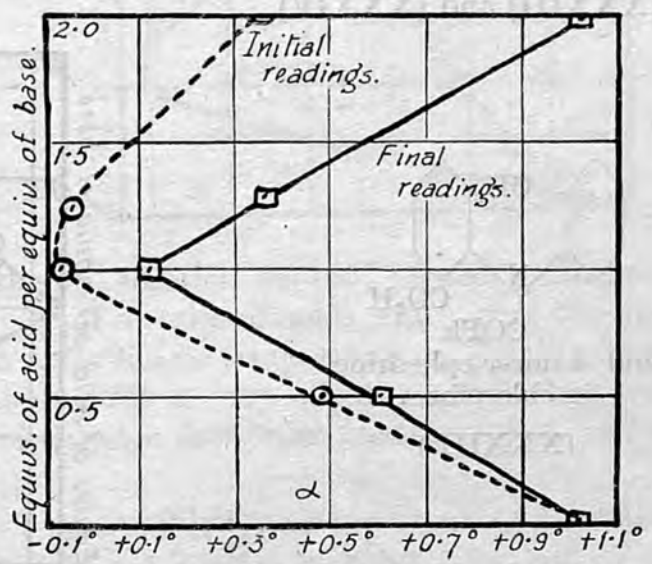
acid caused an immediate change to + 4·30°, mutarotating to + 3·32°; with 3 equivalents, + 4·32° changed to + 3·67°. All these solutions on decomposition with mineral acid afforded the lævorotatory acid: equilibrium was attained more quickly the greater the excess of acid.

Another example selected from many showing this type of behaviour is *N*-benzoyl-2 : 4-dichlorodiphenylamine-6-carboxylic acid (XXXI) which with *d*-nor-ψ-ephedrine in chloroform mutarotates towards the value of the rotation of the base instead of away from it. In a case such as this the



and *d*-nor-ψ-ephedrine in $CHCl_3$

(XXXI.)

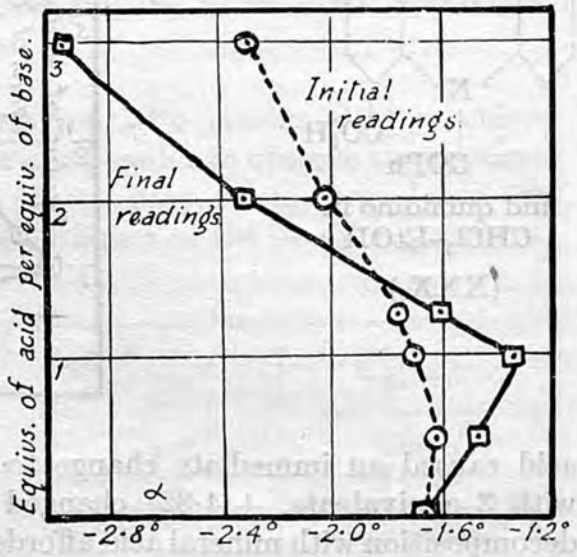


difference between the curves of initial and final readings is considered to be due to optical activation: the departure of the initial curve from the vertical shows that there are other reasons (such as increased concentration) for a static change in rotation present also. (The initial curves described are obtained by extrapolating the observed mutarotations back to zero time.)

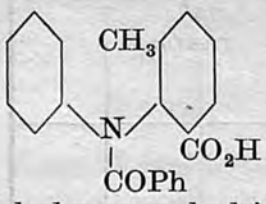
The whole subject would have been much less intriguing had not some of the initial and final curves crossed over : that is to say, at certain acid : base ratios first-order transformation was in the *lævo*-direction, and at other ratios in the *dextro*-direction. This was a new phenomenon, and as it is well substantiated although not explained, worthy of further quotation. *N*-Benzoyl-2 : 4-dichlorodiphenylamine-6-carboxylic acid (XXXII) with

and cinchonidine in chloroform–ethyl alcohol

(XXXII.)

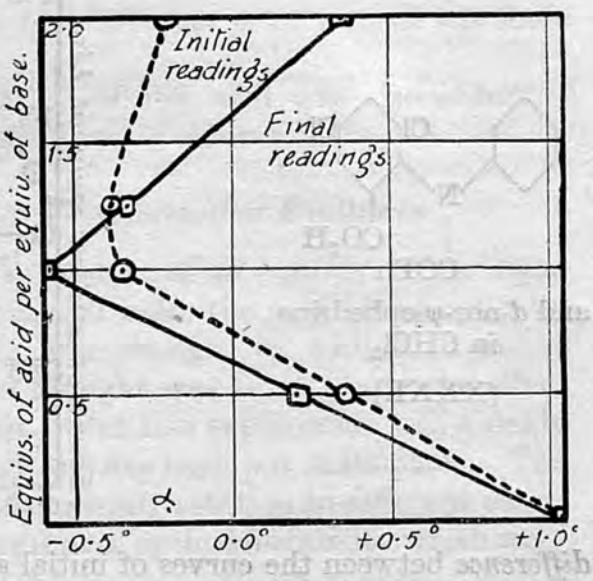


cinchonidine in chloroform–ethyl alcohol mutarotated in the *dextro*-direction at the 1 : 1 ratio and in the *lævo*-direction at the 3 : 1 ratio ; the equilibrated solutions on decomposition yielded *d*- and *l*-acid (not optically pure) respectively. The experiments do not, of course, indicate whether the activated acid is free, or combined as salt. Very similar results were obtained with (XXXIII) and (XXXIV).

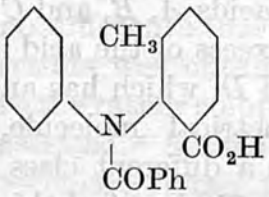


and *d*-nor-ψ-ephedrine in chloroform

(XXXIII.)

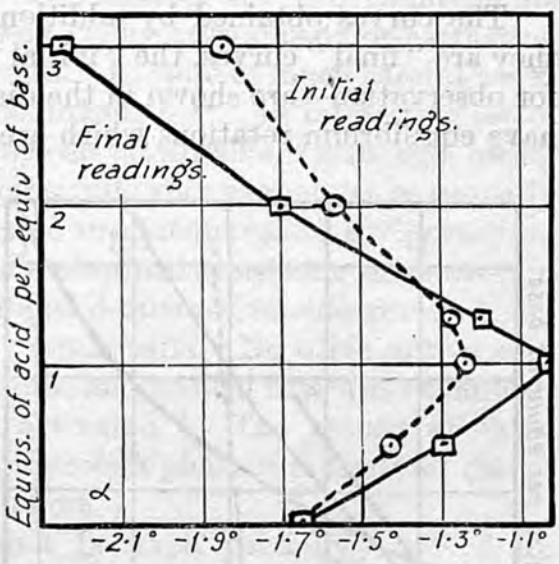


A further point of interest is added in another case in which decomposition of the 1 : 1 and 2 : 1 solutions gave lævorotatory acid, the 3 : 1 solution inactive acid, and the 4 : 1 dextrorotatory acid—the curves for *N*-benzenesulphonyl-8-nitro-1-naphthylglycine (XXXV) and cinchonidine in chloro-

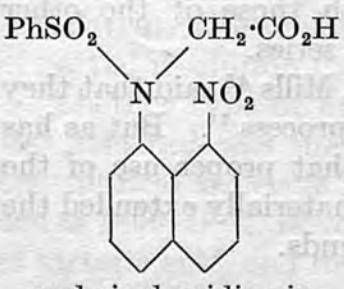


and cinchonidine in chloroform–ethyl alcohol

(XXXIV.)

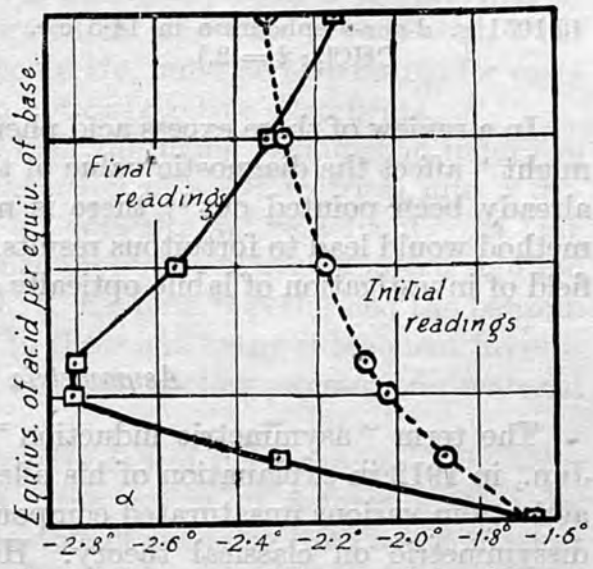


form–ethyl alcohol show how this comes about. This means then, that, without the separation of a salt, both *d*- and *l*-acid could be obtained—not optically pure, but distinctly active, through optical activation in the same solvent and by the same alkaloid.

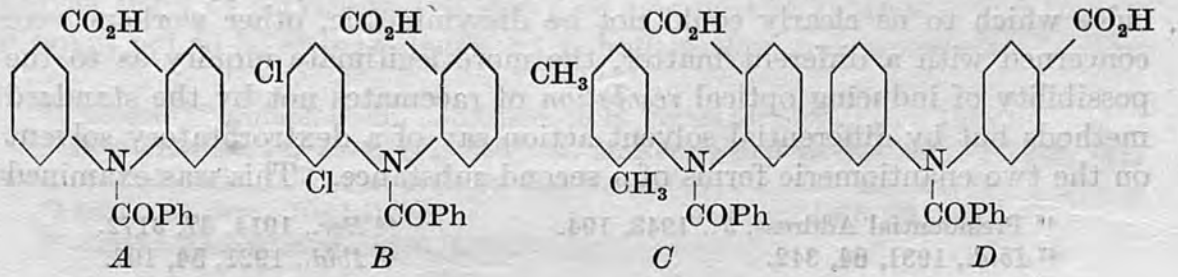


and cinchonidine in chloroform–ethyl alcohol

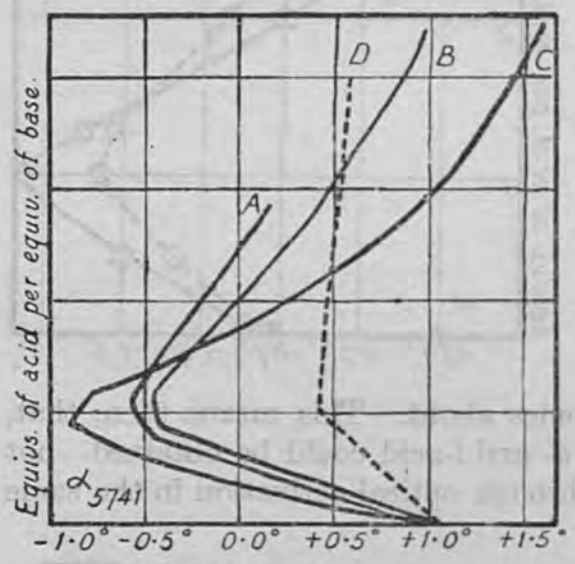
(XXXV.)



The plotting of a series of these "addition curves" served to demonstrate the potential optical activity of a series of acids which were too unstable for the observation of it at ordinary temperatures. The blocking which causes dissymmetry in these acids is very slight, so that they will tolerate neither resolution nor observable first-order transformation under normal conditions.



The curves obtained by addition to *d*-nor-ψ-ephedrine in chloroform—they are "final" curves, the "initial" ones presumably being too ephemeral for observation—are shown in the diagram. The salts of acids *A*, *B*, and *C* have equilibrium rotations which are highly sensitive to excess of the acid: the curve for acid *D*, which has an effectively symmetrical molecule, shows it to be in a different class. Experiments at − 31° justified this distinction: 4 equivalents of acid *C* and one of *d*-nor-ψ-ephedrine in chloroform solution showed a mutarotation α_{5461} changing from − 4·03° to + 2·15°, half-life period 2·4 minutes. Acid *B* mutarotated more quickly in the same circumstances: acid *A* showed no such mutarotation, and its claim to optical activity, until a lower-temperature technique is developed, rests on the curve in the above diagram in conjunction with those of the other acids in the series.



(0·1051 g. *d*-nor-ψ-ephedrine in 14·5 c.c. $CHCl_3$; $l = 2$.)

In a review of these excess acid phenomena W. H. Mills [45] said that they might "affect the diagnostic value of the activation process". But as has already been pointed out [14] there is no indication that proper use of the method would lead to fortuitous results, while it has materially extended the field of investigation of labile optically active compounds.

Asymmetric Induction

The term "asymmetric induction" was introduced by E. Erlenmeyer, Jun., in 1912 in explanation of his alleged successes in "inducing" optical activity in various unsaturated compounds the molecules of which were not dissymmetric on classical theory. He claimed to have induced optical activity in such substances as benzaldehyde and cinnamic acid by heating them with tartaric acid either in presence or in absence of a solvent. E. Wedekind,[46] and L. Ebert and G. Kortüm [47] were unable to confirm Erlenmeyer's results, the references to which are given in the Obituary Notice [48] to Erlenmeyer.

Although Erlenmeyer had attempted the induction of activity in molecules which to us clearly could not be dissymmetric, other workers were concerned with a different matter, the more legitimate inquiry as to the possibility of inducing optical *resolution* of racemates not by the standard methods but by differential solvent action say of a dextrorotatory solvent on the two enantiomeric forms of a second substance. This was examined

[45] Presidential Address, *J.*, 1943, 194.
[46] *Ber.*, 1914, **47**, 3172.
[47] *Ibid.*, 1931, **64**, 342.
[48] *Ibid.*, 1921, **54**, 107.

in two ways: (1) by determining the solubility of the two enantiomeric forms separately in an active solvent, and (2) by crystallising or extracting the racemate by means of an active solvent. In spite of much careful work, no differentiation of the kind sought was found.[23, 49] An interesting set of results was obtained by A. McKenzie and his co-workers,[50] although, owing to the rather complex mixtures used, their significance cannot yet be properly assessed. *l*-Malic acid (1 mol.) was added to an aqueous solution of potassium racemate (1 mol.), and a crop of crystals obtained consisting of potassium hydrogen racemate and potassium hydrogen *d*-tartrate, similar results being obtained with sodium, rubidium, and cæsium salts. No other active acid than malic produced the same kind of result, and no acid that was examined, other than racemic acid, could be "activated". The reality of these observations cannot be doubted, and a thorough phase-rule study of one of the systems would no doubt repay the effort.

Generally speaking, racemates cannot be even partially resolved by crystallisation from an optically active solvent. This is what might be expected, unless one antipode crystallised with solvent of crystallisation. An example remains to be discovered in which association with an optically active solvent, by hydrogen bonding for example, is responsible for solubility differences in a pair of optical isomerides, although it may well be that McKenzie's case can be interpreted in this way. Some such loose association, with preference for one isomeride, must be responsible for cases of partial resolution by adsorption on optically active adsorbents.

Another type of experiment to which the name asymmetric induction was attached was the attempted conversion of a symmetrical into a dissymmetrical molecule in solution in an optically active solvent. As long ago as 1896, D. R. Boyd [51] reduced benzoylformic acid in an aqueous solution of tartaric acid, and four years later F. S. Kipping [52] performed the benzoin synthesis in presence of *d*-camphor. In these and many subsequent investigations, no activity was induced by the non-reacting asymmetric material which had been added.

In 1932, G. Kortüm gave his interpretation of the meaning of the term "asymmetric induction" as follows: the action of a force exerted by asymmetric molecules on molecules capable of changing from a symmetrical into an asymmetrical configuration. He further noted the division of the effect into inter- and intra-molecular types. The examples we have just dealt with are intermolecular, and we now turn to the intramolecular ones.

In 1936, A. McKenzie,[53] commenting on Walden's dismissal of the Erlenmeyer conception of asymmetric induction, said: "Nevertheless, whether the idea of asymmetric induction is right or wrong, it has since proved itself of service in the study of asymmetric synthesis, and to-day it ought not to be at once dismissed as both useless and superfluous." The

[49] Kortüm, "Samml. chem. und chem.-tech. Vortrage", Stuttgart, 1932.

[50] A. McKenzie, *J.*, 1915, **107**, 440; A. McKenzie and N. Walker, *J.*, 1922, **121**, 349; A. McKenzie, H. J. Plenderleith, and N. Walker, *J.*, 1923, **123**, 2875.

[51] Inaug. Dissert., Heidelberg.

[52] *Proc.*, 1900, **16**, 226.

[53] *Ergebn. Enzymforsch.*, 1936, **5**, 49.

view " that in optically active esters of α-ketonic acids the carbonyl group in the α-position might assume a dissymetrical configuration under the influence of an optically active radical " enabled him to correlate the steric course of a long series of reactions between *l*-menthyl benzoylformate or *l*-menthyl pyruvate on the one hand and Grignard reagents on the other, with the direction of mutarotation observed when the two esters mentioned were dissolved in ethyl alcohol. McKenzie suggested that these mutarotations might be due to the establishment of an equilibrium of the type :

$$\underset{(-)}{\mathrm{R{\cdot}CO{\cdot}CO{\cdot}OC_{10}H_{19}}} \rightleftharpoons \underset{(+)}{\mathrm{R{\cdot}CO{\cdot}CO{\cdot}OC_{10}H_{19}}}$$
$$\underset{(-)}{\qquad\qquad}\qquad\qquad\underset{(-)}{\qquad\qquad}$$
$$(A) \qquad\qquad (B)$$

whilst in ethereal solution (in which the Grignard additions were carried out) equilibrium was established too quickly for observation, but that nevertheless the two above forms were present in unequal amounts, this accounting for the success of the asymmetric synthesis and also for the sign of rotation of the resulting α-hydroxy-acids, all the benzoylformate reactions giving lævorotatory acids and all the pyruvate reactions dextrorotatory ones. It seems clear that it would also have been necessary to assume that the rate of addition of the Grignard reagent to the carbonyl group was greater than the rate of equilibration. Nevertheless, the detailed experimental evidence deserves close scrutiny. M. M. Jamison and E. E. Turner,[54] although their evidence did not justify a precise interpretation, preferred to regard the mutarotations in the alcoholic solutions of the esters as due to first-order transformation between the diastereoisomeric hemiacetals formed by the very probable reversible combination of the esters with the solvent :

$$\underset{(l)}{\mathrm{R{-}CO{-}CO{\cdot}OC_{10}H_{19}}} \overset{\mathrm{EtOH}}{\rightleftharpoons} \underset{(d)}{\mathrm{R{-}\overset{\displaystyle OH}{\overset{|}{C}}{-}\overset{\displaystyle OEt}{\overset{|}{C}}O{\cdot}OC_{10}H_{19}}} + \underset{(l)}{\mathrm{R{-}\overset{\displaystyle OEt}{\overset{|}{C}}{-}\overset{\displaystyle OH}{\overset{|}{C}}O{\cdot}OC_{10}H_{19}}}$$

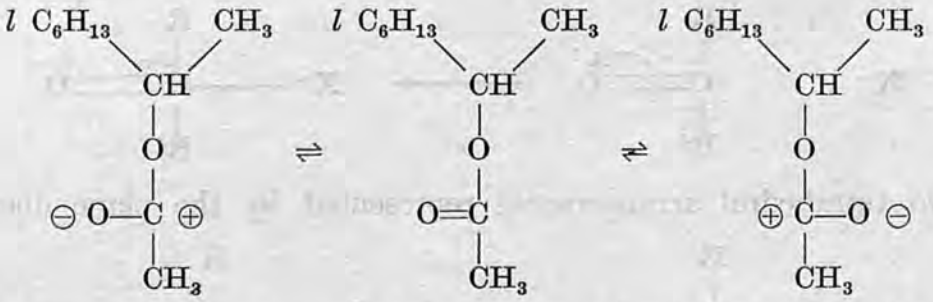
At the same time, the absence of mutarotation in ether was ascribed to the lack of any real distinction between (*A*) and (*B*), the partial stereo-specificity of the many Grignard reagent syntheses then being attributed to first-order asymmetric transformation of optically unstable intermediates. The idea of asymmetric induction, in the sense of a double bond made dissymmetric previous to approach of the reagent, as the cause of an " asymmetric reaction " was not accepted.

Without apparently realising the mass of experimental material which McKenzie and his co-workers, as well as others, had accumulated in their studies of asymmetric synthesis and related matters, T. M. Lowry and E. E. Walker [55] suggested " that an unsaturated group in an asymmetric molecule, *e.g.*, the carbonyl group in camphor, may acquire an induced asymmetry and thus itself become optically active ". This conclusion, which was reconsidered by T. M. Lowry and J. O. Cutter,[56] was based on " the fact that

[54] *J.*, 1941, 538. [55] *Nature*, 1924, **113**, 565. [56] *J.*, 1925, **127**, 604.

the dispersion-equations for camphor and its derivatives are haunted by a low-frequency term *the period of which is definitely characteristic of the ketonic group* ". Lowry and Cutter further said : " We therefore assign this partial rotation to the ketonic group, which is proved to be asymmetric by the unequal yields of two stereoisomeric (diastereoisomeric ?) products which are obtained when the double is converted into two single bonds. This absence of symmetry in a double bond has already been proved in the camphor series by the unsymmetrical reduction of camphor to borneol and *iso*borneol and of its oxime to bornylamine and neobornylamine. . . . Since the two links of a double bond in an asymmetric compound are clearly unequal from the chemical point of view, it would be absurd to pretend that they must be equal from the physical point of view, and no additional justification need therefore be given for using this conception in order to explain the optical properties of camphor or of . . . certain other unsaturated compounds."

H. Phillips [57] saw in the then freshly discovered (but since abandoned) semi-polar sulphoxide bond a means of giving the optical activity of a carbonyl group a physical meaning ; he pictured *l*-β-octyl acetate as the equilibrium :



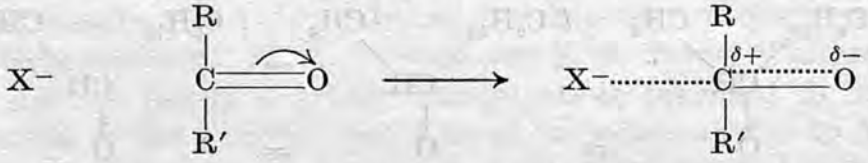
T. M. Lowry and G. Owen,[58] following S. Sugden, J. B. Reed, and H. Wilkins,[59] pointed out that a semi-polar bond with carbonyl would represent the activation limit of a polarisation and not the normal state of the group. They saw in such an activation the origin of the ultra-violet ketonic band shown by camphor. C. E. Wood and S. D. Nicholas,[60] in a study of anomalous rotatory dispersion, concluded that the carbonyl group " need not be regarded as an asymmetric centre but rather as causing a deflecting and disturbing action on the electronic system round the asymmetric centre ". Lowry's view that the two bonds of a double bond in an asymmetric compound are unequal from the chemical point of view is untenable because it over-simplifies the picture of addition reactions.

Part of the present problem is discussed by M. P. Balfe and J. Kenyon.[61] The use of the term " induced anisotropy " instead of " induced asymmetry " is an advantage, since it avoids the implication that the optical and the alleged chemical mechanisms are intimately related. As W. C. Price [62] has pointed out, the π-molecular wave functions are responsible for the production of the optical anisotropy ; they are also concerned with chemical

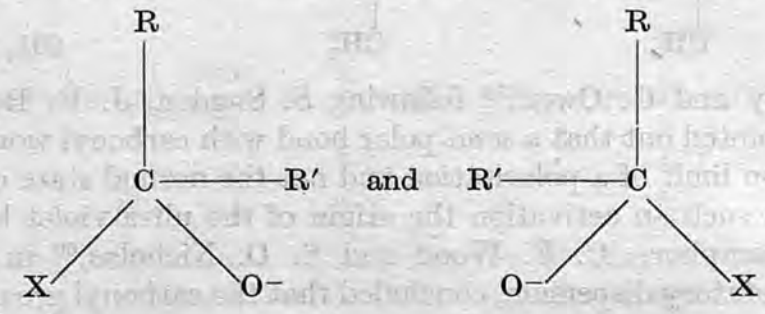
[57] *J.*, 1925, **127**, 2552. [58] *J.*, 1926, 606. [59] *J.*, 1925, **127**, 1525.
[60] *J.*, 1928, 1671. [61] *Ann. Reports*, 1942, **39**, 125. [62] *Ibid.*, 1939, **36**, 52.

addition reactions. In the optical sphere they function as part of the *permanent* state of the molecule ; in the chemical sphere, for all we know to the contrary, they play their normal part in permitting electronic activation of the double bond prior to its two-stage saturation. It seems probable that, at any rate at the moment, only confusion will result from correlating the chemical reactivity (" asymmetric induction ") of a carbonyl group with the rotatory dispersion effects (" induced asymmetry ") associated with it. Until the two effects have been more closely investigated no useful conclusions can be drawn.

In order that a fixed centre of asymmetry shall influence the steric course of an addition reaction at an unsaturated centre in the same molecule in an asymmetric synthesis, there must be some stage at which either stereo-selective addition occurs as an irreversible process or first-order asymmetric transformation takes place. There are at present insufficient experimental data upon which to base an analysis of even the simplest " asymmetric reaction ", but some general lines of argument can be foreseen. Thus, in the addition of XY to a carbonyl group of a molecule already containing a fixed centre of asymmetry (in group R), the first stage may be regarded as the approach of X^- towards the positive end of the polarised carbonyl group:



The two tetrahedral arrangements represented by the plane diagrams:



are possible before the addition of Y^+. If the energy changes concerned in the formation of these two structures are equal, there is no immediate asymmetric addition. If they are unequal (*i.e.*, influenced by existing asymmetry), then we have *asymmetric addition*, which appears to take place even in non-reversible asymmetric reactions of this type (*e.g.*, Grignard reactions). On the other hand, addition which is known to be chemically reversible (*e.g.*, when X^- is CN^-) could be accompanied by first-order asymmetric transformation of the newly forming molecule at this stage, and it would be rash to say, without further experiment, whether the new asymmetry is introduced during or after the first addition or at both stages.

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ORGANIC CHEMISTRY

3. STEREOCHEMISTRY

BY

M. M. JAMISON, (HARRIS)

M. S. LESSLIE,

AND

E. E. TURNER

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3. Stereochemistry.

A total asymmetric synthesis of ethyl *d*-tartrate has been reported by T. L. Davis and J. Ackerman.[1] A mixture of ethyl fumarate and anhydrous hydrogen peroxide in ethereal solution was irradiated with right-handed circularly polarised light of wave-band 2535—7—9 A. Rotations of + 0·073° and + 0·030° (both ± 0·003°) were observed. The rotation increased with time of irradiation up to 120 minutes but thereafter decayed rather rapidly to zero at 190 hours.

It was stated [2] that a specimen of santonin prepared synthetically was subsequently found to be optically active, although it was obtained from inactive materials. Later there was reported [3] the appearance of optical activity during the methylation of 2-formyl*cyclo*hexanone by means of methyl iodide and sodium, the figure $[\alpha]_D$ — 26·22° being given for the rotation of the 2-formyl-2-methyl*cyclo*hexanone formed. C. S. Gibson [4]

[116] "Valency", Cambridge, 1945, p. 226.

[117] J. D. Bernal and (Miss) H. D. Megaw, *Proc. Roy. Soc.*, 1935, *A*, **151**, 384; J. D. Bernal, *Trans. Faraday Soc.*, 1940, **36**, 922.

[118] L. Hunter and J. A. Marriott, *J.*, 1940, 166.

[1] *J. Amer. Chem. Soc.*, 1945, **67**, 486.

[2] K. D. Paranjape, N. L. Phalnikar, B. V. Bhide, and K. S. Nargund, *Current Science*, 1943, **12**, 153.

[3] *Nature*, 1944, **153**, 141.

[4] *Ibid.*, p. 225.

pointed out that this claim should not be allowed to pass without careful examination, and the actual methylation process was examined experimentally in two other laboratories, an inactive product being obtained, as would be expected.[5, 6] The Oxford workers [6] referred to the known element of chance in such syntheses : it is clear that this factor could not permit of activities of the magnitude claimed by the Indian workers, and if they did indeed isolate an active product they must inadvertently have done one or other of the following things : (1) carried out the methylation in presence of singularly efficient circularly polarised light, (2) removed some of their product by selective extraction with an optically active solvent or by selective adsorption on an " asymmetric " adsorbent, (3) introduced an active second substance. It is to be hoped that the origin of the activity will be disclosed in due course.

Since diastereoisomerides differ in all physical properties, they should be separable by distillation, but it is only in comparatively recent years that the efficiency of stills has become high enough to permit of the realisation of this fact. M. E. Bailey and H. B. Hass [7] distilled *d*-2-methylbutyl methylethylacetate in a 60-plate Lecky column.[8] The first 40% and the last 30% of the distillate gave on saponification *l*- and *d*-methylethylacetic acid with $[\alpha]_D^{25°}$ $-$ 0·25° and $+$ 0·29°, respectively. Similar results were obtained with other mixtures of diastereoisomerides. Thus with the *dl-sec.*-butyl ester of *d*-α-propionoxypropionic acid and distilling at 35 mm. resolution was effected to such a high degree that one saponified fraction (the last 15% of the total distillate) gave *d-sec.*-butyl alcohol of 86% optical purity.

Two resolutions are worth noting : that of racemic acid [9] using *d*-amphetamine, in which racemic acid and the *d*-base in aqueous solution gave an 85% yield of *d*-base hydrogen *l*-tartrate as the less soluble salt; and that of *dl*-biotin,[10] where use was made, rather unusually, of arginine; *l*(+)-arginine and *dl*-biotin in aqueous *iso*propyl alcohol gave arginine *d*-biotin in 92% yield, and this after crystallisation and treatment with dilute acid gave pure *d*-biotin.

It now appears to be fairly certain that the sulphur–oxygen link in sulphoxides is a double and not a co-ordinate one.[11] Similarly the phosphorus–oxygen bond in a phosphine oxide and the phosphorus–sulphur bond in a phosphine sulphide is a double bond. These bonds are all much too short to be of the type present in the amine oxides, these being proper dative bonds of length about equal, as would be required, to that of the equivalent covalent bond. The molecule of a sulphoxide is now to be represented as in *A*, which Sutton presumably meant when he used the term

[5] J. M. O'Gorman, *J. Amer. Chem. Soc.*, 1944, **66**, 1041.

[6] J. W. Cornforth, R. H. Cornforth, and M. J. S. Dewar, *Nature*, 1944, **153**, 317.

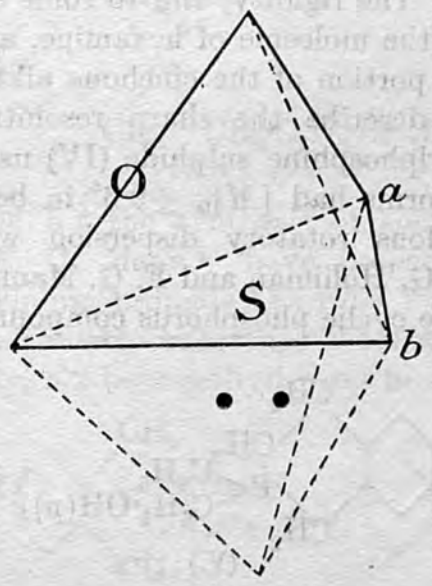
[7] *J. Amer. Chem. Soc.*, 1941, **63**, 1969. [8] *Ind. Eng. Chem. Anal.*, 1940, **12**, 544.

[9] E. Walton, *J. Soc. Chem. Ind.*, 1945, **64**, 219.

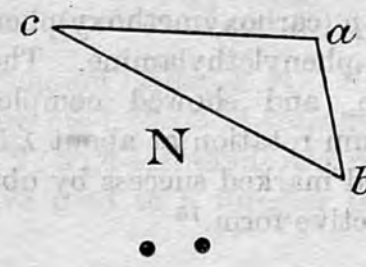
[10] D. E. Wolf, R. Mozingo, S. A. Harris, R. C. Anderson, and K. Folkers, *J. Amer. Chem. Soc.*, 1945, **67**, 2100.

[11] G. M. Phillips, J. S. Hunter, and L. E. Sutton, *J.*, 1945, 146.

" trigonal bipyramid ". In fact, the configuration of a sulphoxide is little different under the new constitution from what it was with the co-ordinate bond structure. In the new configuration, the sulphur atom is situated with respect to groups *a* and *b* and the oxygen atom much as the nitrogen atom is situated with respect to the three groups *a*, *b* and *c* (see *B*) in a tertiary amine. The difference in optical stability between the sulphoxides and the amines may be due (1) to the larger size of the sulphur atom, (2) to the presence of the strong S:O bond, and possibly (3) to stabilising resonance between the electrons of the double bond and the pair of unshared electrons which " occupy " the lower half of the trigonal bipyramid.

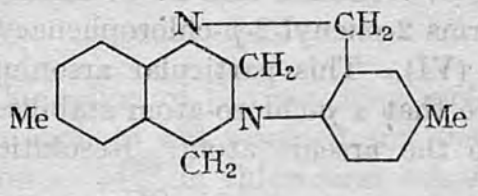


(*A*)

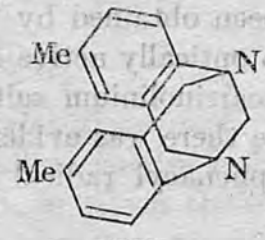


(*B*)

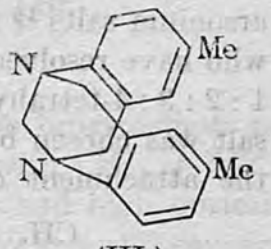
A condensation product of *p*-toluidine and formaldehyde known as Troeger's base was shown by M. A. Spielman [12] to be (I). V. Prelog and



(I.)



(II.)



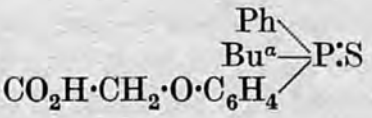
(III.)

P. Wieland [13] noticed that if the nitrogen atoms could assume a stable " tetrahedral " configuration the base should exist in mirror-image forms (II and III). Owing to the weakness of the base, resolution could not be attempted with tartaric acid, and, no doubt owing to the instability of the base to acids, only partial and erratic resolution was effected using camphor- and bromocamphor-sulphonic acids. Complete resolution was achieved by chromatographic adsorption using *d*-lactose hydrate activated by extraction

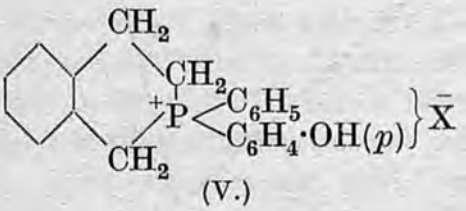
[12] *J. Amer. Chem. Soc.*, 1935, **57**, 583. [13] *Helv. Chim. Acta*, 1944, **27**, 1127.

with chloroform [14] followed by drying and, most essentially, grinding in a steel ball-mill. Using light petroleum as the solvent, the *d*-base was the more strongly adsorbed. The enantiomorphs were obtained with $[\alpha]_D^{16\cdot5°}$ $+ 287° \pm 7°$ and $- 278° \pm 7°$ (in hexane). Although the active forms were rapidly racemised in alcoholic hydrochloric acid, they were little affected by sublimation in a high vacuum. This result is of considerable interest since it provides the first example of a practicable resolution based on chromatography. It hardly bears on the vexed question of the stereochemistry of tervalent nitrogen, since the molecule of Troeger's base has a very rigid structure and the resolution merely provides another rather unusual case of molecular dissymmetry. The rigidity, and to some extent the instability in presence of acid, recall the molecule of hexamine, and, in the first respect that of the quinuclidine portion of the cinchona alkaloids.

W. C. Davies and F. G. Mann [15] describe the sharp resolution of phenyl-*p*-(carboxymethoxy)phenyl-*n*-butylphosphine sulphide (IV) using *d*- and *l*-1-phenylethylamine. The active forms had $[M]_D \pm 9{\cdot}6°$ in benzene solution, and showed complex anomalous rotatory dispersion with a maximum rotation at about λ 5800. F. G. Holliman and F. G. Mann have achieved marked success by obtaining the cyclic phosphorus compound (V) in an active form.[16]

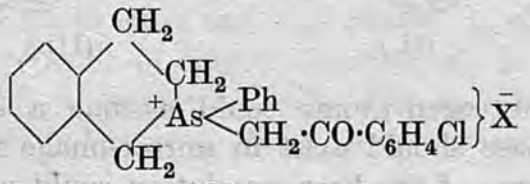


(IV.)

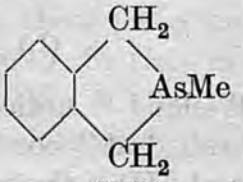


(V.)

Since 1939, when the last report was made [17] on the stereochemistry of arsenic, a number of very interesting and important contributions have been made by F. G. Mann and his collaborators. Chemical evidence for the validity of the dissociation-equilibrium theory of the optical instability of arsonium salts [18] has been obtained by F. G. Holliman and F. G. Mann,[19] who have resolved into optically active forms 2-phenyl-2-*p*-chlorophenacyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinolinium salts (VI). This particular arsonium salt was chosen because there was evidence that a *p*-chloro-atom stabilised the attachment of a phenacyl radical to the arsenic atom. Resolution



(VI.)



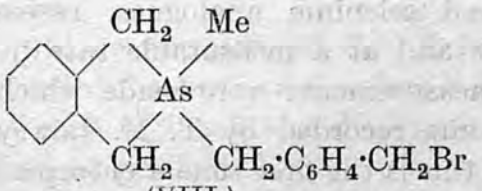
(VII.)

was effected through the bromocamphorsulphonates, from which the *d*- and *l*-picrates were obtained with $[M]_D + 457°$ and $- 450°$, respectively,

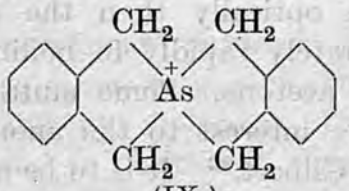
[14] G. M. Henderson and H. G. Rule, *J.*, 1939, 1568.
[15] *J.*, 1944, 276. [16] *Nature*, 1947, **159**, 438. [17] *Ann. Reports*, 1939, **36**, 236.
[18] G. J. Burrows and E. E. Turner, *J.*, 1921, **119**, 426. [19] *J.*, 1943, 550.

in chloroform. The active *l*-iodide, with $[M]_D$ — 354°, did not racemise at all in chloroform solution during five days at the ordinary temperature. This high optical stability taken in conjunction with the chemical stability of the *iso*arsinolinium salts provides strong evidence in favour of the dissociation theory of the optical instability of quaternary arsonium salts.

D. R. Lyon and F. G. Mann [20] have shown that 2-methyl*iso*arsindoline (VII) readily combines with one equivalent of *o*-xylylene dibromide to give 2-*o*-(bromomethyl)benzyl-2-methyl*iso*arsindolinium bromide (VIII) which, when heated, loses methyl bromide with the formation of the highly crystalline *As-spiro*bis*iso*arsindolinium bromide (IX). Using this interesting

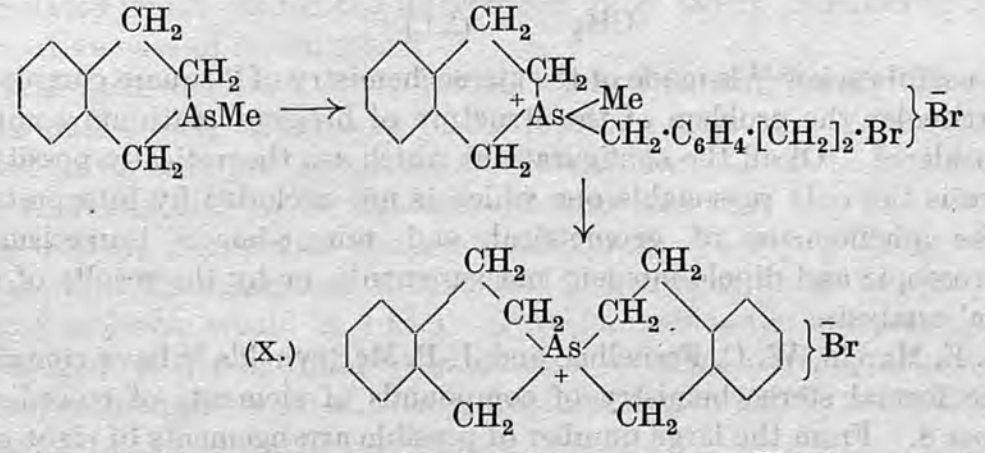


(VIII.)



(IX.)

method for the synthesis of spirocyclic arsonium salts, F. G. Holliman and F. G. Mann [21] have prepared *As-spiro*-bis-1 : 2 : 3 : 4-tetrahydro*iso*-arsinolinium bromide (X) from 2-methyl-1 : 2 : 3 : 4-tetrahydro*iso*arsinoline and a valuable substance these authors have used in a number of ways, namely, *o*-2-bromoethylbenzyl bromide :



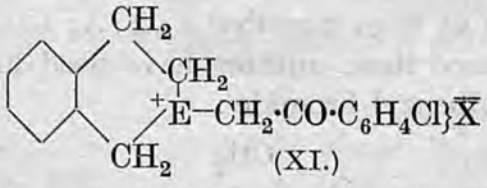
(X.)

The cation of (X) possesses molecular dissymmetry. The bromocamphorsulphonate was resolved and the active iodides isolated with $[M]_D$ + 342° and — 344° in chloroform solution, in which these salts had high optical stability. The authors point out that the resolution of this spirocyclic arsonium salt supports, but does not prove, the tetrahedral configuration of the 4-covalent arsenic atom. If the latter possessed a pyramidal configuration the spirocyclic salt (X) could give rise to geometrical isomerides, and the *trans*-form, having no element of symmetry, could show optical activity. Actually there was no evidence that two such forms existed.

Again making use of *o*-2-bromoethylbenzyl bromide, the same authors [22] have added to the known thio*iso*chroman the corresponding selenium and tellurium compounds and as a result have been able to prepare and resolve

[20] *J.*, 1945, 30. [21] *J.*, 1945, 45. [22] *J.*, 1945, 37.

a eutropic series of compounds (XI) in which E is S, Se, or Te. The actual salts resolved in each case were the bromocamphorsulphonates, which were converted into active picrates. 2-*p*-Chlorophenacylthio*iso*chromanium picrate (E = S) was obtained with $[M]_D$ − 242° and + 250° in acetone. The corresponding seleno-picrate (E = Se) had $[M]_D$ − 533° and + 504° in acetone. Both sets of picrates were optically very stable in solution. The 2-*p*-chlorophenacyltelluro*iso*chromanium ion was not fully resolved, but the optically impure enantiomorphic picrates isolated had $[M]_D$ − 632° and + 575° in acetone, and it was reasoned that the optically pure picrates would have $[M]_D$ greater than 750°. The telluronium salts were much less stable optically than the sulphur and selenium analogues, racemising moderately rapidly in boiling solvents and at a measurable rate in cold moist acetone. Some mutarotation measurements were made which add further interest to the anomalous results recorded by T. M. Lowry and F. L. Gilbert.[23] It is to be noted that this is the first time a eutropic series of optically active compounds has been obtained and that there is a marked increase in molecular rotation in passing from sulphur through selenium to tellurium.



(XI.)

A useful review [24] is made of the stereochemistry of " square complexes ". In particular the problem of the structure of bivalent platinum complexes is considered. Of all the configurations which are theoretically possible the square is the only reasonable one which is not excluded by interpretations of the phenomena of geometrical and mirror-image isomerism and spectroscopic and dipole moment measurements, or by the results of *X*-ray crystal analysis.

L. E. Marchi, W. C. Fernelius, and J. P. McReynolds [25] have contributed to the formal stereochemistry of compounds of elements of co-ordination number 8. From the large number of possible arrangements of eight groups round a central atom, they consider four configurations, the cube, the square Archimedean antiprism (" twisted cube "), a dodecahedron with triangular faces and with symmetry V_d, and a trigonal prism with triangular pyramids joined to the triangular faces. Isomer tables for mono- and bi-dentate groups and these configurations have been developed. Corrections to these tables were published later.[26]

Two of the same authors [27] have made a preliminary study of complex uranium oxalates. By mixing aqueous solutions of tetrapotassium uranium tetraoxalate with aqueous solutions of strychnine sulphate, various precipitates of strychnine salts were obtained, and from these the potassium

[23] *J.*, 1929, 2867. [24] D. P. Mellor, *Chem. Reviews*, 1943, **33**, 137.
[25] *J. Amer. Chem. Soc.*, 1943, **65**, 329. [26] *Ibid.*, 1944, **66**, 1984.
[27] L. E. Marchi and J. P. McReynolds, *ibid.*, 1943, **65**, 332.

salt of the acid $H_4[U(C_2O_4)_4]$ is claimed to have been isolated in four forms, none being optically pure. The four potassium salts obtained, in order of increasing solubility (? of strychnine salt) had α_D in a 2 dcm. tube : + 0·10° (*c*, 0·26), − 0·10° (*c* unknown), + 0·07° (*c*, 0·47), and − 0·05° (*c*, 0·05). The experimental error was given as ± 0·02°. The solutions of the first two salts became inactive at room temperature in under one hour, the solutions of the last two salts retaining their activity for at least twelve hours. The result is taken to indicate that two alternative configurations are possible—the square Archimedean antiprism and the above dodecahedron —but considerable amplification of the experimental evidence is clearly desirable.

It will be remembered that Adams and his school [28] produced figures for so-called " interference values " between two atoms or groups attached one to each of the 2 and 2′ positions in the diphenyl molecule. Thus, if attached to position 2 there was an atom X and to position 2′ there was attached an atom Y, then, from the known (*X*-ray) bond lengths, *a* = Aromatic carbon–X, and *b* = Aromatic carbon–Y, and from the sum, 2·90, of two aromatic bond lengths, the interference value was calculated as (*a* + *b* − 2·90) A. This simple calculation ignores the rather disturbing effect of any great dissimilarity in the magnitudes of *a* and *b*, but the idea served its authors a very useful purpose in that a mass of information was accumulated which related the interference value to experimental figures for comparative ease of racemisation.

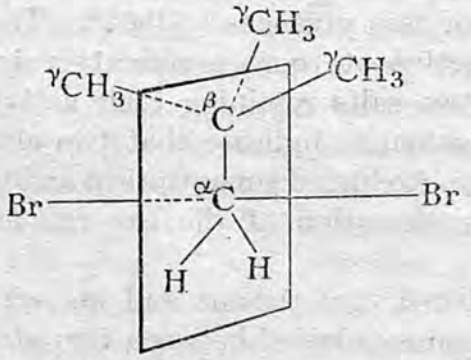
The limited usefulness of the Adams method remains hardly affected by modern data for the dimensions of the diphenyl molecule. Attention may here be drawn to a precise electron-diffraction analysis of the hydrocarbon by I. L. Karle and L. O. Brockway,[29] who find that the 1 : 1′ bond is 1·54 ± 0·03 A., the nuclear bonds all being 1·39 ± 0·04 A. These authors calculate that the separation of the 2 and 2′ hydrogen atoms in a co-planar diphenyl molecule would be 1·84 A. Therefore, since the nearest approach of hydrogen atoms in different molecules, as with durene, hexamethylbenzene, or methane, is 2·0 A., energy would be required to force the diphenyl molecule into the co-planar condition.

Stereochemical workers who have studied the steric factors operating in cases of dissymmetry caused by restriction of rotation will be interested in the calculations made by I. Dostrovsky, E. D. Hughes, and C. K. Ingold [30] of steric hindrance to the substitution reaction $Br^- + RBr \longrightarrow BrR + Br^-$ in terms of activation energies. The reactions studied are bimolecular nucleophilic substitutions in a series of primary bromides, Me, Et, Pr^{α}, Bu^{β} and *neo*pentyl, a series in which rate sequences depend less on polar factors than on the progressive building up of steric hindrance by the addition of methyl groups in the β-position. It is found by experiment that steric hindrance reduces the *neo*pentyl bromide reaction rates by factors of about 10^5 and raises Arrhenius activation energies by about 6 kg.-cals. in

[28] See for example *Chem. Reviews*, 1933, **12**, 261.

[29] *J. Amer. Chem. Soc.*, 1944, **66**, 1974. [30] *J.*, 1946, 173.

comparison with other primary bromides. The picture used for calculating " compression " incorporates the accepted linear transition state Br–C_α–Br, that for *neo*pentyl bromide (XII) being the most complicated case considered :



(XII.)

replacement of the methyl groups successively by hydrogen atoms illustrates all the other members of the series down to methyl bromide. The angles are either tetrahedral or follow from the geometry of the figure : the distances Br–C_α are estimated by adding the covalent radius of carbon to the mean of the covalent and ionic radii of bromine : other bond lengths are taken as the sum of normal covalent radii. A shortening of the maximal van der Waals radii [31] when the bond makes a small or a moderate angle with the direction of a covalency is calculated and used as the distance at which two atoms come into contact as far as energy relations are concerned. From these data, the authors work out a " touching distance " (from the modified van der Waals radii) and a " model distance " (from the transition state model) ; the difference between these two figures is the " compression " for that particular pair of atoms. The compression so evaluated is virtually zero in all the initial states of the molecules, but in the transition state C_β–Br distances are compressed about 0·2 A. and the shortest C_γ–Br distance by something of the order of 1A. : in the *neo*pentyl bromide–Br^- transition state there are two such C_γ–Br distances, accounting for the sharp rise in steric hindrance to reaction as this member of the series is reached (Br–H compressions are also evaluated).

Proceeding then, by transition state methods, the authors calculate the increment in activation energy attributable to these compressions. Assuming rigid bonding forces the results are :

First Upper Limits to Contributions of Steric Hindrance to the Activation Energies of Br Exchange.

	Me.	Et.	Pr^β.	Bu^γ.	Pr^α.	Bu^{iso}.	*neo*Pentyl.
Energy increment, kg.-cals.	0·0	0·9	1·9	2·7	0·9	2·3	12·6

Small differences in these values are obtained (but amounting to nearly 1 kg.-cal. in the last case) by allowing for stretching of the Br–C_α–Br bond : the values are regarded as an upper limit because no allowance is made for

[31] L. Pauling, " The Nature of the Chemical Bond ", Cornell Press, 1940.

bending of the Br–C_α–Br axis, which is expected to bring down the increment substantially.

Comparison with experiment bears witness to the essential correctness of the treatment: data of L. J. le Roux and S. Sugden [32] and of G. A. Elliott and S. Sugden [33] show that the radioactive bromine exchange reaction of three primary alkyl bromides in "90%" acetone is attended by Arrhenius activation energies as follows:

Bromide.	Pr$^{\alpha}$.	Bu$^{\alpha}$.	Bu^{iso}.
E, kg.-cals.	~19	19·3	20·6

that is, there is a difference of about 1·3 kg.-cals. for the added β-methyl group in going from a normal to an iso-structure. The steric effect on activation energy, by calculation, varies very little when one halogen is replaced by another; therefore the size of the substituting ion is not of the first importance and it is relevant to compare ethoxyl–bromine or iodine–bromine replacements with the above calculation:[34]

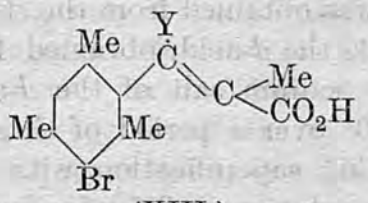
Relative Rates and Arrhenius Activation Energies of Bimolecular Substitution of Primary Alkyl Bromides.

	Me.	Et.	Pr$^{\alpha}$.	Bu^{iso}.	*neo*Pentyl.
Substitution by OEt^- *in* EtOH:					
Relative rates at 55°	17·6	1	0·28	0·030	0·0000042
E, kg.-cals.	20·0	21·0	—	22·8	26·2
Substitution by I^- *in* Me_2CO:					
Relative rates at 64°	—	1	—	—	0·000053
E, kg.-cals.	—	19	—	—	25

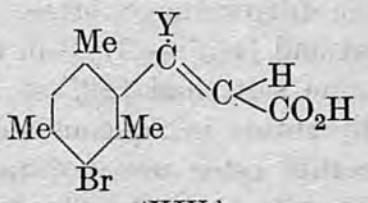
These observed differences in activation energy are roughly of the expected order.

Further developments of this kind of correlation will be awaited with interest.

R. Adams and his collaborators have continued their investigations of restricted rotation in arylolefinic acids, and interesting results have been obtained by varying the substituents in the olefinic grouping. All four optically active molecules of type (XIII) and (XIV), where Y is Br or Cl, show moderate optical stability, and from the rates of racemisation it is



(XIII.)



(XIV.)

obvious that bromine, as would be expected, has a larger steric effect than chlorine, and that the methyl group α to the carboxyl group in (XIII) induces greater stability than a hydrogen atom in the same position.[35,36]

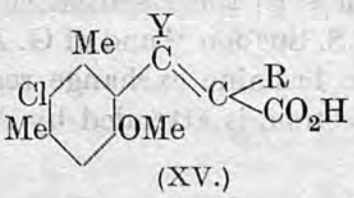
[32] *J.*, 1939, 1279. [33] *J.*, 1939, 1836.

[34] I. Dostrovsky and E. D. Hughes, *J.*, 1946, 157, 161.

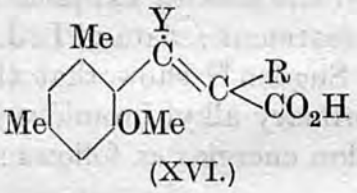
[35] R. Adams, A. W. Anderson, and M. W. Miller, *J. Amer. Chem. Soc.*, 1941, **63**, 1589.

[36] R. Adams and C. W. Theobald, *ibid.*, 1943, **65**, 2383.

In another series of compounds [37] of type (XV) where Y = Cl, R = Me or Y = Cl, R = H or Y = Br, R = H, the optical isomers were relatively



(XV.)

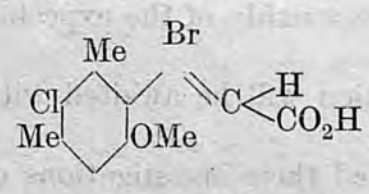


(XVI.)

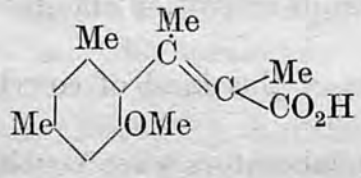
unstable and those compounds in which Y = OMe, R = Me, or Y = OMe, R = H or Y = SMe, R = H, could not be resolved. Compounds in which Y = Me and R = H or Me in a series of type (XVI) were also investigated and it was deduced that the β-methyl group was less effective than the β-chlorine atom in restricting rotation.

The influence of β-substituents on restricted rotation in this arylacrylic acid series would therefore appear to be Br > Cl > Me, in contrast to Br > Me > Cl in the diphenyl series.[38, 39]

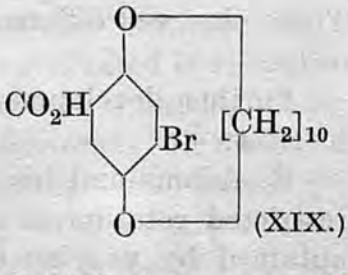
That an α-methyl group in the molecule has a marked stabilising influence was illustrated by comparing the optical stability of (XVII) and (XVIII). In *n*-butyl alcohol at 22° the approximate half-life period of (XVII) was 420 minutes and that of (XVIII) was 700 minutes. Assuming that the effect of chlorine in the ring has negligible influence (demonstrated by earlier results), the greater stability of (XVIII), in spite of the fact that it contains a β-methyl group in place of the larger β-bromine in (XVII), serves to confirm this conclusion.[40, 41]



(XVII.)



(XVIII.)



(XIX.)

In amplification of a previous notice,[42] A. Lüttringhaus and H. Graalheer [43] have obtained 4-bromogentisic acid decamethylene ether (XIX) in mirror-image forms. The *l*-acid was obtained from the strychnine salt and had $[\alpha]_D^{17°}$ — 37·2° in acetone, while the *d*-acid, obtained from the cinchonine salt, had $[\alpha]_D^{17°}$ + 37·5°. The sodium salt of the *d*-acid was optically stable in aqueous solution at 100° over a period of three hours. The methyl ester was not racemised during saponification with methyl-alcoholic potash or when heated in toluene solution at 210° for four hours.

[37] R. Adams and W. J. Gross, *J. Amer. Chem. Soc.*, 1942, **64**, 1786.
[38] R. W. Stoughton and R. Adams, *ibid.*, 1932, **54**, 4426.
[39] H. C. Yuan and R. Adams, *ibid.*, p. 4434.
[40] R. Adams and R. S. Ludington, *ibid.*, 1945, **67**, 794.
[41] R. Adams andJ. W. Meconey, *ibid.*, p. 798.
[42] *Ann. Reports*, 1941, **38**, 217.
[43] *Annalen*, 1941, **550**, 67.

Inhibition of rotation within the molecule arises from the constriction of the benzene nucleus within the outer ether ring, so that rotation about the O–O axis is hampered. For this type of compound the name of *ansa* (handle!) is suggested by the authors. 4-Bromogentisic acid dodecamethylene ether could not be resolved. Whether this is due to optical instability or to other causes was not decided.

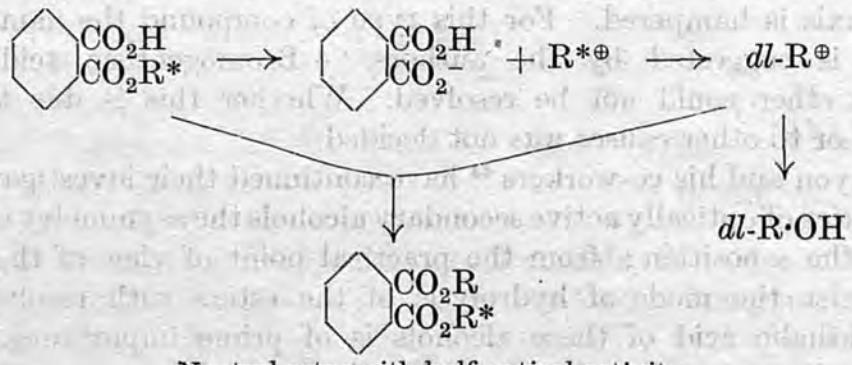
J. Kenyon and his co-workers [44] have continued their investigations into the properties of optically active secondary alcohols the asymmetry of which is seated in the α-position: from the practical point of view of the working stereochemist the mode of hydrolysis of the esters with resolving acids or with phthalic acid of these alcohols is of prime importance. Of the alcohols studied, *p*-methoxybenzhydrol in the form of its esters most readily gives an alkyl cation ($R'\cdot CO_2R \longrightarrow R'\cdot CO_2^- + R^+$), the substituted allyl and then 1-naphthylmethylcarbinyl esters are next in order of stability in this sense, while phenylmethylcarbinyl esters tend still less towards alkyl–oxygen fission.

Optically active 1:3-dimethylallyl hydrogen phthalate in solvolytic reactions with formic and acetic acids, hot methyl alcohol, *n*-butyl alcohol, benzyl alcohol, and phenol gives extensively racemised products (esters or ethers); if the reaction is stopped before it finishes in any of the cases the unreacted ester is shown to be largely racemised also. These results show that alkyl–oxygen fission, both during reaction and by unimolecular solvent-aided ionisation in solution, liberates momentarily a carbonium cation which can racemise. While the optically active hydrogen phthalate is stable in methyl alcohol at 31°, in nitromethane at the same temperature ionisation is facilitated and much racemisation is undergone during two months.

p-Methoxybenzhydrol and its esters and ethers show their tendency to alkyl–oxygen fission by ready conversion into *p*-methoxybenzhydryl chloride on treatment with cold concentrated hydrochloric acid. As might be expected, the hydrolysis of (+)-*p*-methoxybenzhydryl hydrogen phthalate results in almost complete racemisation of the alcohol even when strong aqueous alkali is used: the highest retention of optical activity is obtained when using only 2% of water in the alcohol in an attempt to employ conditions most favourable for suppressing alkyl–oxygen fission; the optically active carbinol becomes racemised even on heating alone in water. The alkyl–oxygen bond is so weak that the separation of an insoluble product (in presence of a reagent) can determine the course of a reaction: for example, when (+)-*p*-methoxybenzhydryl hydrogen phthalate is dissolved in 0·15N-sodium hydroxide (1 mol.), separation of an oil begins immediately, and is complete after eighteen hours, leaving only sodium phthalate in solution. The oil is *p*-methoxybenzhydrol of low dextro-rotation and

[44] M. P. Balfe, H. W. J. Hills, J. Kenyon, H. Phillips, and B. C. Platt, *J.*, 1942, 556; M. P. Balfe, M. A. Doughty, J. Kenyon, and R. Poplett, *J.*, 1942, 605; M. P. Balfe, E. A. W. Downer, A. A. Evans, J. Kenyon, R. Poplett, C. E. Searle, and A. L. Tárnoky, *J.*, 1946, 797.

a di-*p*-methoxybenzhydryl phthalate which contains one (+)-*p*-benzhydryl radical and one which has been racemised during migration :



Neutral ester with half optical activity.

The (+)hydrogen phthalates of 1-naphthylmethylcarbinol and phenylmethylcarbinol react with anhydrous formic acid to give the *dl*-formate. Neither hydrogen phthalate reacts with anhydrous methyl or ethyl alcohol, but on addition of water to the methyl alcohol (increasing the ionising power of the medium) 1-naphthylmethylcarbinyl hydrogen phthalate forms a racemic methyl ether. Hydrolysis of the hydrogen phthalate of optically active 1-naphthylmethylcarbinol with weak alkali (sodium carbonate) results in about 50% racemisation, but similar treatment of phenylmethylcarbinyl esters gives almost as little racemisation as is obtained on using 10N-sodium hydroxide.

Some other cases of alkyl–oxygen fission of alcohols and their derivatives, previously described in detail, are listed by these authors; for example D. I. Duveen and J. Kenyon [45] found that the (−)hydrogen phthalate of 2-furylmethylcarbinol can be hydrolysed by 10N-sodium hydroxide to give the optically pure alcohol, whereas hydrolysis with sodium carbonate yields a racemic alcohol. Attention is drawn to the fact that tendency towards such a mode of reaction parallels the electron-releasing power of the alkyl group.

Under appropriate conditions, similar esters with stable, optically active acids should be interesting material for studies in asymmetric transformations.

Replying to a criticism by H. I. Bernstein and E. S. Wallis [46] that the optical rotations on which J. Kenyon and D. P. Young [47] based their interpretation of the Beckmann change were rather small, A. Campbell and J. Kenyon [48] have provided the fresh experimental evidence in Beckmann, Lossen, and Curtius changes tabulated below :

Starting material.	Product.	Type of rearrangement.	Retention of optical activity (%).	$[\alpha]_D$ of acetyl derivative (pure −168·1°).
(+)Ph·CHMe·C(:NOH)Me (2·5 g.)	(−)Acet-1-phenylethylamide (1·4 g.)	Beckmann	99·6	−167·4°
(+)Ph·CHMe·C(:NOH)·OH (3·8 g.)	(−)1-Phenylethylamine (1·8 g.)	Lossen	99·2	−166·9
(+)Ph·CHMe·CO_2H (5 g.)	(−)1-Phenylethylamine (2·9 g.)	Schmidt (modified Curtius)	99·6	−165·2

[45] *J.*, 1936, 621. [46] *J. Org. Chem.*, 1942, **7**, 262. [47] *J.*, 1941, 263. [48] *J.*, 1946, 25.

Coupled with the studies of C. L. Arcus and J. Kenyon of the Hofmann reaction on (+)hydratropamide, the authors conclude that the evidence points to the retention of molecular asymmetry during the migrations, and also of molecular configuration. A. E. Brodski and G. P. Mikluchin [49] suggest that, since in obtaining benzanilide from benzophenone oxime hydrochloride by a Beckmann change ^{18}O from water used in the final decomposition can be detected in the product, the change must be *inter*-molecular. Campbell and Kenyon point out that this could be so for the hydroxyl group without being true for the migrating group, but that no inference could be drawn from the results of a reaction using phosphorus pentachloride, since the intermediate compound must have the oxygen replaced during the reaction.

M. M. J.
M. S. L.
E. E. T.

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GENERAL INTRODUCTION TO PREPARATION OF HYDROCARBONS

By

M. M. JAMISON, (HARRIS)

M. S. LESSLIE

AND

E. E. TURNER

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GENERAL INTRODUCTION TO PREPARATION OF HYDROCARBONS.

By M. M. Jamison, M. S. Lesslie, and E. E. Turner.

The present communication, the manuscript of which was completed in its present form on July 26, 1944, *describes work done by the authors during their war-time evacuation from Bedford College, London, to the University Chemical Laboratory, Cambridge. The hydrocarbons were prepared for examination by infra-red absorption spectroscopy mainly by Dr G. B. B. M. Sutherland. Although the present account gives little idea of the labour involved in the preparation of pure hydrocarbons, it will provide authenticity for the materials upon which the spectroscopic measurements, when published, were made.*

Part of the expenses for materials was defrayed by the Ministry of Aircraft Production.

The experimental work described in the following pages was carried out by the three authors.

Possible and feasible syntheses were thought out, and the one chosen selected on the basis of :—

(1) availability of starting-out material which could be purified with confidence, *i.e.*, knowing its chemical origin, and making use wherever possible of solid derivatives;

(2) possibility of purifying any intermediates *via* solid derivatives;

(3) use of reactions and reagents which experience has shown are unlikely to cause complications, *e.g.*, reducing action by Grignard reagents, molecular rearrangements, and so on. In this connexion the publications of Whitmore and his collaborators have proved invaluable.

In this way the saturated hydrocarbons finally obtained were expected to contain as impurities only by-products with much lower or much higher boiling points. No reliance was placed on elaborate fractional distillation as a method of purification, as we had neither the quantities of material nor the apparatus necessary for this purpose. Purity of product was based on pedigree. Justification for our procedure was provided by refractive-index data, and by the fact that the infra-red absorption curves were sharp. Frequently fractions boiling as much as 0·5° on either side of the fraction selected as the pure hydrocarbon gave spectra identical with that of the latter.

Iodine and sulphonic acids have usually been preferred by modern workers for the dehydration of alcohols to olefins. In our first syntheses we used iodine, but later gave it up in favour of naphthalene-β-sulphonic acid, because we found that the olefin mixture persistently retained traces of iodine, apparently in a combined condition, and that they poisoned the platinum oxide catalyst. When iodine was used it was found necessary

to shake the olefin, previously washed with alkali to remove visible iodine, with zinc dust and alkali for about an hour.

The products of reduction of olefins with Adam's platinum oxide catalyst in glacial acetic acid frequently contained small amounts of unchanged olefin, and were accordingly shaken vigorously with several successive small amounts of concentrated sulphuric acid for a few minutes, with cooling, until sulphuric acid no longer became coloured. Prolonged action of sulphuric acid was avoided.[1] The washed paraffins were then distilled several times over sodium, usually through an 8-in glass Dufton column, arranged to allow of a small amount of head reflux.

During the first part of our work we had no access to standard thermometers, and " uncorr " boiling points were taken on short unstandardized Anschütz thermometers. " Corr " values were observed with short thermometers recently standardized by the National Physical Laboratory. In all cases, temperatures are meant to indicate range of boiling point of the sample actually examined by the spectroscopists rather than the true boiling point under rigid vapour–liquid equilibrium conditions. Nevertheless, the accuracy of our boiling-point determinations left no doubt that in one or two cases of hitherto unknown hydrocarbons the " calculated " boiling points of Francis [2] were inaccurate, although they constituted a useful guide.

It may be noted that of the eighteen isomeric octanes, one, 3 : 4-dimethylhexane, and of the nonanes, four, viz., 3 : 4-dimethylheptane, 3 : 5-dimethylheptane, 2 : 3 : 4-trimethylhexane, and 2 : 2 : 3 : 4-tetramethylpentane, contain two asymmetric carbon atoms. It would be expected, therefore, that synthesis under different conditions of any of these compounds would give rise to unequal amounts of two racemic forms. It will be interesting to note, when large quantities of any of these hydrocarbons are distilled, if a separation into two forms (in the case of 3 : 5-dimethylheptane into *dl*- and *meso*-forms) is observed (compare the experimental observations on mixtures of diastereoisomeric esters made by Bailey and Hass).[3]

2 : 3-*Dimethylbutane.*

Dimethyl*iso*propylcarbinol was prepared by treating *iso*propyl magnesium bromide with acetone.[4] The yield of carbinol, b.p. 120° to 121°, was 72 per cent.

Dehydration with iodine gave a hexene mixture boiling up to 75°, and hydrogenation of this (acetic acid–platinum oxide) gave 2 : 3-dimethylbutane, b.p. 57·9° to 58·1°/770 mm uncorr, n_D^{20} 1·3755.

Wibaut, Hoog, Langedijk, Overhoff, and Smittenberg [17] prepared the above carbinol from ethyl *iso*butyrate and methyl magnesium iodide : it had b.p. 110° to 119° as they used it for dehydration with oxalic acid. Their 2 : 3-dimethylbutane (made using a nickel catalyst) had b.p. 58·1°/760 mm and n_D^{20} 1·3751.

Brooks, Howard, and Crafton [5] record b.p. 57·999°/760 mm and n_D^{20} 1·37490.

2 : 2-*Dimethylpentane.*

Dimethyl-*n*-propylcarbinol was obtained in 61 per cent yield, b.p 123° to 124°/767 mm, from acetone and *n*-propyl magnesium bromide

Deschamps [6] by the same method obtained a 50 per cent yield, b.p. 122·5° to 123·5°/762 mm.

2-Chloro-2-methylpentane was obtained from the carbinol in 67 per cent yield, b.p. 35°/31 mm. Deschamps found b.p. 50° to 53°/41 mm. The chlorine atom was replaced by a methyl group as follows: 100 g of chloro-compound was placed in an all-glass apparatus with efficient condensing arrangements and filled with moving nitrogen. To it were added during 2 hr 90 g of zinc dimethyl. The mixture was warmed to 60° to 70° for 30 min and then treated with water and dilute acid. The hydrocarbon layer was separated and found to boil at 78° to 81°/767·5 mm (37 g, 45 per cent yield). To remove traces of unsaturated hydrocarbons it was extracted five times with sulphuric acid, washed with water, dried over calcium chloride, and fractionated. The pure 2 : 2-dimethylpentane had b.p. 79·0° to 79·4°/766 mm corr n_D^{20} 1·3828.

Edgar, Calingaert, and Marker [7] by the interaction of *tert*-butyl chloride and *n*-propyl magnesium bromide in presence of mercuric chloride, obtained 2 : 2-dimethylpentane, b.p. 78·2° to 79·5°/760 mm, n_D^{20} 1·38233. Marker and Oakwood,[8] from similar materials but replacing mercuric chloride by cuprous iodide, obtained 2 : 2-dimethylpentane with b.p. 79·0°/760 mm and n_D^{20} 1·3825. Soroos and Willis [9] working similarly but with no catalyst, recorded for their dimethylpentane, b.p. 78·7° to 79°/760 mm and n_D^{20} 1·3822.

3 : 3-*Dimethylpentane.*

Methyldiethylcarbinol was prepared by the action of ethyl magnesium bromide on ethyl acetate.[10] It was converted into the corresponding chloride as described by Schreiner.[11] The chloride was added to ethereal methyl magnesium iodide (3 mol). A vigorous reaction began and was completed by heating under reflux for 2 hr. The mixture was then distilled, first from a water-bath and then from a fusible metal bath, the fraction boiling at 50° to 70° being collected. After being extracted with several successive portions of concentrated sulphuric acid, washing, and drying, it was fractionated. The 3 : 3-dimethylpentane had b.p. 86·0° to 86·5°/771 mm corr, n_D^{20} 1·3913.

Smittenberg, Hoog, Moerbeck, and v.d. Zijden [12] found b.p. 86·10° and n_D^{20} 1·39092.

2 : 4-*Dimethylpentane.*

Pure di-*iso*propylcarbinol (see note on page 603) was converted into 3-bromo-2 : 4-dimethylpentane by the method of *Organic Syntheses, Collected*, Vol. I, p. 25. The bromide, b.p. 42°/12 mm (yield, 89 per cent), was allowed to react with excess of magnesium in ether, the process being completed at the b.p. The mixture was treated with water and dilute acid and then worked up normally. Pure 2 : 4-dimethylpentane was obtained, b.p. 81° to 82°/779 mm uncorr, n_D^{20} 1·3828.

Edgar, Calingaert, and Marker [13] found b.p. 80·8°/760 mm and n_D^{20} 1·3823. Wibaut, Hoog, Langedijk, Overhoff, and Smittenberg [17] gave b.p. 80·8°/760 mm and n_D^{20} 1·3822.

3-*Ethylpentane.*

The method described by Edgar, Calingaert, and Marker [7] was used: ethyl magnesium bromide and ethyl propionate to triethylcarbinol, de-

hydration with iodine, and hydrogenation of the olefin in presence of glacial acetic acid and platinum oxide.

The ethyl propionate, b.p. 98° to 99°/760 mm, was obtained from fractionated propionic acid. The carbinol, obtained in 70 per cent yield, had b.p. 135° to 142°. The olefin mixture boiled at 93° to 98°. Hydrogenation was difficult, probably owing to the presence of combined iodine, and it was necessary to remove unsaturated products from the paraffin before distilling it. The 3-ethylpentane obtained had b.p. 92·5° to 93·5°/766 mm corr, n_D^{20} 1·3920.

Edgar and Calingaert [15] found n_D^{20} 1·39366. Brooks, Howard, and Crafton [5] found b.p. 93·473°/760 mm, n_D^{20} 1·39337.

3-*Methylheptane.*

Methyl *n*-butyl ketone was prepared from α-*n*-butylacetoacetic ester in the usual manner. The ketone was added to 1·5 mol of ethereal ethyl magnesium bromide. The 3-methylheptan-3-ol obtained by usual procedure had b.p. 161° to 162°/752 mm uncorr (yield, 78 per cent). The carbinol was dehydrated by means of iodine, the olefin being freed from traces of iodine, by prolonged shaking with zinc dust and aqueous alkali. Hydrogenation was effected with hydrogen–platinum oxide–glacial acetic acid. Traces of non-hydrogenated material were removed with concentrated sulphuric acid, and after being washed the 3-methylheptane was fractionated over sodium, when it had b.p. 118·2° to 119·2°/771 mm corr, and n_D^{20} 1·3988.

Smittenberg, Hoog, and Henkes [16] gave b.p. 119·1°/760 mm and n_D^{20} 1·3988, whilst Wibaut, Hoog, Langedijk, Overhoff, and Smittenberg,[17] who also worked through 3-methylheptan-3-ol, but prepared it from methyl ethyl ketone, gave for 3-methylheptane the constants : b.p. 118·9°/760 mm and n_D^{20} 1·3986.

4-*Methylheptane.*

4-Methylheptan-4-ol was prepared by treating *n*-propyl magnesium bromide with methyl acetate.[18] The carbinol was dehydrated by means of iodine, and the resulting olefin, b.p. 116° to 124°/752 mm, hydrogenated (platinum oxide–acetic acid). The 4-methylheptane obtained had b.p. 118·2° to 118·7°/764 mm corr and n_D^{20} 1·3983.

Edgar and Calingaert [15] gave : b.p. 118·0° and n_D^{20} 1·398.

2 : 2-*Dimethylhexane.*

2-Methylhexan-2-ol was prepared by adding acetone to *n*-butyl magnesium bromide, using normal methods. The carbinol, b.p. 135° to 145°, was shaken with concentrated hydrochloric acid until converted into 2-chloro-2-methylhexane, and the latter, after distillation under reduced pressure, allowed to react with methyl magnesium iodide (2 mol), the reaction being completed by heating under reflux overnight. Addition of ice and then dilute acid, followed by normal procedure, gave 2 : 2-dimethylhexane, b.p. 107·0° ±0·5°/760 mm corr, n_D^{20} 1·3940.

Noller [19] who obtained the hydrocarbon from zinc di-*n*-butyl and *tert*-butyl chloride, found b.p. 106° to 107° and n_D^{20} 1·3931.

3-*Ethylhexane.*

Diethyl-*n*-propylcarbinol, obtained in 88 per cent yield, b.p. 74°/18 mm by the action of ethyl magnesium bromide on methyl *n*-butyrate [20] (*n*-butyric acid, a commercial pure material, was fractionated and esterified with methyl alcohol) was dehydrated by means of iodine. The olefin, b.p. 116° to 123°, mainly at 121°/760 mm was hydrogenated in glacial acetic acid. The 3-ethylhexane obtained after washing with concentrated sulphuric acid had b.p. 118·4° to 119·4°/758 mm corr and n_D^{20} 1·4020.

Edgar and Calingaert [21] found b.p. 118·8° and n_D^{20} 1·4016.

2-*Methyl*-3-*ethylpentane.*

Diethyl*iso*propylcarbinol, b.p. 56° to 57°/11 mm, was prepared by adding methyl *iso*butyrate to excess of ethyl magnesium bromide. Pure commercial *iso*butyric acid was fractionated, the fraction b.p. 154° to 154·5°/772 mm being collected. It was converted into the acid chloride by the method of Smith and Lewcock [22]: the chloride had b.p. 93·3° to 93·5°/774 mm. It was allowed to react with excess of methyl alcohol, and the methyl ester obtained fractionated. The fraction, b.p. 92·5° to 92·8°/772 mm was used. The carbinol, obtained in 86 per cent yield, was converted into the corresponding bromide by means of phosphorus tribromide, and the bromide (b.p. 66° to 67°/11 mm, yield 93 per cent) was allowed to react with excess of magnesium in presence of ether. The interaction was completed by prolonged heating under reflux, and the reaction mixture was treated with ice and then dilute acid. Normal subsequent procedure gave 2-methyl-3-ethylpentane, b.p. 113° to 114°/761·5 mm corr, n_D^{20} 1·4050.

Edgar and Calingaert [21] found b.p. 114·0°/760 mm and n_D^{20} 1·4016.

3-*Methyl*-3-*ethylpentane.*

Methyldiethylcarbinol b.p. 42°/11 mm, was obtained in 77 per cent yield by the interaction of ethyl acetate with ethyl magnesium bromide.[23] It was converted into the corresponding chloride by the method of Schreiner,[24] and the chloride was added to zinc diethyl.[17] The 3-methyl-3-ethylpentane finally obtained had b.p. 117·0° to 118·6°/758·5 mm corr and n_D^{20} 1·4086.

Smittenberg, Hoog, and Henkes [16] recorded b.p. 118·4°/760 mm and n_D^{20} 1·4081.

2-*Methyloctane.*

(*a*) *sec*-Octyl alcohol. The redistilled commercial material was converted into the hydrogen phthalate by the method of Levene and Mikeska.[25] After crystallization from light petroleum (b.p. 60° to 80°) it had m.p. 59° to 60° (*Organic Syntheses, Collected*, Vol. I, p. 418, gives m.p. 55°) Saponification of the ester gave pure *sec*-octyl alcohol, b.p. 179·5° to 180°/764 mm uncorr.

(*b*) Methyl *n*-hexyl ketone. Oxidation of the alcohol by means of potassium dichromate and diluted sulphuric acid, followed by purification of the ketone through the sodium bisulphite compound, gave methyl *n*-hexyl ketone, b.p. 172° to 172·5°/762 mm uncorr. Henderson, Henderson,

and Heilbron [26] gave b.p. 172° to 173°/767 mm for the ketone purified through the semicarbazone.

(*c*) Dimethyl-*n*-hexylcarbinol. Interaction of the ketone with ethereal methyl magnesium bromide gave the carbinol in 88 per cent yield, b.p. 81° to 83°/16 mm. Whitmore and Southgate,[27] employing methyl magnesium chloride, gave b.p. 82° to 85°/20 mm (yield, 85 per cent).

(*d*) 2-Methyloctenes. The carbinol was distilled with a little naphthalene-β-sulphonic acid. The distillate was twice again similarly treated. Whitmore and Southgate [27] used iodine as dehydrating catalyst.

(*e*) 2-Methyloctane. The dried nonene mixture was hydrogenated in glacial acetic acid in presence of platinum oxide, and gave 2-methyloctane, b.p. 143·8° to 144·4°/763 mm uncorr, n_D^{20} 1·4030.

Whitmore and Southgate [27] found b.p. 142·80°/760 mm and n_D^{20} 1·40285 for 2-methyloctane obtained by hydrogenation of the nonene mixture in presence of nickel, and b.p. 142·8°/760 mm, n_D^{20} 1·4030 for 2-methyloctane derived from dimethyl-*n*-hexylcarbinol *via* the iodide, the latter being reduced with zinc and alcohol.

3-*Methyloctane*.

Methylethyl-*n*-amylcarbinol was prepared by two different methods :

Method 1. *sec*-Butyl alcohol, b.p. 101°/765 mm, obtained by the fractionation of the pure commercial material, was oxidized to methyl ethyl ketone as follows : A solution of 294 g (1-mol) of potassium dichromate and 400 g (4 mol) of concentrated sulphuric acid in 2 litres of water was gradually added to 222 g (3 mol) of *sec*-butyl alcohol, kept well shaken and cooled below about 25°. This operation completed (30 to 40 min), the methyl ethyl ketone and some water (182 g in all) were removed by distillation and the wet ketone dried over several successive quantities of anhydrous sodium sulphate and finally over potassium carbonate; 82 g of pure ketone, b.p. 78° to 82°, mainly 79° to 80°/757 mm were obtained.

n-Amyl alcohol, purified through the hydrogen phthalate, was converted into *n*-amyl bromide by the general method described in *Organic Syntheses*, Vol. I.

Methyl ethyl ketone (1 mol) was gradually added to ethereal *n*-amyl magnesium bromide (1·2 mol) and the product worked up in the usual way. 74 g (51 per cent yield) of methylethyl-*n*-amylcarbinol, b.p. 83° to 85°/18 mm were obtained.

Method 2. *n*-Butyl alcohol, b.p. 117·2°, obtained by fractionation of the pure commercial material, was converted into *n*-butyl bromide by the method described in *Organic Syntheses*. The bromide had b.p. 101° to 102°.

Methyl *n*-amyl ketone was prepared by the method described in *Organic Syntheses, Collected*, Vol. 1, pp. 248 and 351, and was obtained in 45 per cent yield, b.p. 148·5° to 149·5°/764 mm. The ketone was allowed to react with ethyl magnesium bromide.[28] The yield of methylethyl-*n*-amylcarbinol was 86 per cent, b.p. 83°/18 mm.

Methylethyl-*n*-amylcarbinol was dehydrated with naphthalene-β-sulphonic acid and gave a product boiling up to 150°. 3-Methyloctane was obtained by hydrogenating the nonene mixture in glacial acetic acid in presence of platinum oxide. Two separate preparations gave (*a*) : b.p.

144·0° to 145·0°/756 mm uncorr, n_D^{20} 1·4069, and (*b*) 143·9° to 144·9°/756 mm uncorr, n_D^{20} 1·4062.

Levene and Marker [29] from the Grignard reagent derived from a (+) 1-bromo-3-methyloctane, obtained a lævorotatory 3-methyloctane with b.p. 143°, and the same authors [121] obtained by a similar method, from a (+)-5-bromo-3-methyloctane, a dextrorotatory 3-methyloctane, b.p. 143° to 144°/760 mm.

4-*Methyloctane.*

Methyl *n*-propyl ketone, purified through the semicarbazone melting at 111° to 112°, boiled at 101° to 103°. Interaction of the ketone with *n*-butyl magnesium bromide, prepared from *n*-butyl bromide, b.p. 101° to 102° (ex fractionated *n*-butyl alcohol, b.p. 117·2°) gave methyl-*n*-propyl-*n*-butylcarbinol, b.p. 82° to 83°/18 mm in 66 per cent yield. Whitmore and Woodburn,[30] using the same method, recorded b.p. 78·5° to 79·5°/15 mm and a 68 per cent yield.

Dehydration of the carbinol (28 g) with naphthalene-β-sulphonic acid gave 16·5 g of nonene mixture, b.p. 135° to 145°/761 mm, mainly 143° to 144°. Midgley and Henne [31] obtained 4-methyloct-4-ene from isoprene, sodium, and ethyl bromide, and recorded a b.p. of 136° to 144°, mainly 139°. Hydrogenation of our nonene mixture in glacial acetic acid in presence of platinum oxide gave a product, which, after fractionation, led to 10·5 g of 4-methyloctane, b.p. 142·9° to 143·0°/763 mm uncorr, n_D^{20} 1·4063.

Clarke,[32] who reduced a nonene mixture with hydrogen and nickel, found b.p. 141·7° to 141·9°/771 mm. For the 4-methyloctane present in Oklahoma petroleum, White and Glasgow [33] found b.p. 142·433°.

It may also be noted that Levene and Marker,[29] who found a lævorotatory specimen of 4-methyloctane to boil at 141°/760 mm, later described a " 5-methyloctane " boiling at 53°/25 mm.[29] !

2 : 2-*Dimethylheptane.*

Methyl *n*-amyl ketone was obtained by the method of *Organic Syntheses, Collected,* Vol. I, pp. 248 and 351. The yield of ketone, b.p. 148·5° to 149·5°/764 mm was 62 per cent on the *n*-butylacetoacetic ester (b.p. 112° to 113°/16 mm) and 45 per cent on the acetoacetic ester used.

Dimethyl-*n*-amylcarbinol was prepared by the action of methyl magnesium bromide on methyl *n*-amyl ketone, and was obtained in 84 per cent yield, b.p. 66°/11 mm. Masson,[34] who made the carbinol from methyl magnesium iodide and ethyl *n*-hexoate, recorded b.p. 162°.

2-Chloro-2-methylheptane was made by shaking the carbinol with concentrated hydrochloric acid and calcium chloride. It had b.p. 52°/11 mm and was obtained in 84 per cent yield. Muset [35] prepared the chloride by treating the carbinol with acetyl chloride.

Interaction of the chloride with zinc dimethyl resulted in a violent detonation, and the following method was therefore substituted : To a Grignard reagent prepared from 36 g of magnesium (1·7 atoms) and 213 g (1·7 mol) of methyl iodide and cooled to 0° was added 107 g (1 mol) of 2-chloro-2-methylheptane. When addition was complete, the mixture was allowed to warm up and was then heated under reflux for a day.

Usual working-up gave a crude hydrocarbon, b.p. 126° to 131°/776 mm. This was extracted with small quantities of sulphuric acid until free from unsaturation, washed, dried, and fractionated. The 2 : 2-*dimethylheptane* obtained had b.p. 132·6° to 133·4°/774 mm corr, n_D^{20} 1·4015.

Morton and Fallwell [36] reported that sodium amyl reacted with *tert*-butyl bromide to give a 5·5 per cent yield of 2 : 2-dimethylheptane, but no other details were mentioned.

2 : 3-*Dimethylheptane.*

Methyl *iso*propyl ketone was prepared by the method of *Organic Syntheses*, Vol. XIII, p. 68, from *tert*-amyl alcohol which had previously been fractionated and then had b.p. 101°/752 mm. The yield of ketone, b.p. 94° to 96°, varied within a few grams around the figure given in *Organic Syntheses*.

The ketone (1 mol) was added to 1·2 mol of ethereal magnesium *n*-butyl bromide, the product being worked up in a normal manner. The yield of methyl*iso*propyl-*n*-butylcarbinol, b.p. 75° to 77°/16 mm was 54 per cent. Whitmore and Southgate,[27] using a similar method, found b.p. 75° to 78°/16 mm and yield 65 per cent.

The carbinol (50 g) was dehydrated with naphthalene-β-sulphonic acid, 39 g of nonene mixture, b.p. 139° to 143°, being obtained. Whitmore and Southgate recorded b.p. 135° to 140°/735 mm. The nonene mixture was hydrogenated in glacial acetic acid in presence of platinum oxide. The 2 : 3-dimethylheptane obtained, after repeated fractionation, had b.p. 140·0° ± 0·05°/757 mm corr, n_D^{20} 1·4090. Yield of pure material, 23 g.

Whitmore and Southgate recorded b.p. 140·65°/760 mm and n_D^{20} 1·40850 for 2 : 3-dimethylheptane prepared by hydrogenation of their nonene mixture (obtained by iodine dehydration of the carbinol) in presence of nickel–alumina.

2 : 4-*Dimethylheptane.*

Methyl *iso*butyl ketone was prepared from acetoacetic ester in the usual manner. Interaction with *n*-propyl magnesium bromide [37] gave methyl-*n*-propyl*iso*butylcarbinol, b.p. 174° to 176°/764 mm in 71 per cent yield.

The carbinol was dehydrated with naphthalene-β-sulphonic acid, and the unsaturated hydrocarbon was reduced in glacial acetic acid with hydrogen and platinum oxide. The 2 : 4-dimethylheptane obtained had b.p. 133·3° to 133·5°/758 mm corr, n_D^{20} 1·4030.

Tuot [38] gives b.p. 130°/749 mm and n_D^{20} 1·4023.

2 : 5-*Dimethylheptane.*

Interaction of 82 g (1·1 mol) of methyl ethyl ketone (obtained from *sec*-butyl alcohol as described elsewhere) and 1·33 mol of *iso*amyl magnesium bromide in ethereal solution gave a 75 per cent yield of methylethyl*iso*amylcarbinol, b.p. 73° to 74°/13 mm.

Meyer and Tuot,[39] using the same general method, found b.p. 85°/25 mm for the carbinol, but recorded no yield.

The carbinol (119 g) was dehydrated (two successive operations) with naphthalene-β-sulphonic acid. The washed and dried nonene mixture boiled at 120° to 140°. Fractionation gave 31 g, b.p. 137·0° to 137·4°/762

mm uncorr, and 45 g b.p. 134° to 141°/762 mm (redistillation of combined fractions). These two fractions were hydrogenated (glacial acetic acid–platinum oxide) separately. Fractionation of the two saturated hydrocarbons produced showed them to be identical, and the corresponding best fractions were mixed and the whole refractionated. The pure 2 : 5-dimethylheptane obtained had b.p. 135·6° to 135·8°/753 mm corr, n_D^{20} 1·4044.

Meyer and Tuot [39] dehydrated their carbinol with copper sulphate. Their 2 : 5-dimethylhept-4-ene had b.p. 137°/747 mm and by catalytic hydrogenation they obtained 2 : 5-dimethylheptane, b.p. 133°/741 mm, n_D^{20} 1·4033.

Edgar and Calingaert [15] recorded b.p. 135·9°.

2 : 6-*Dimethylheptane.*

*iso*Butyraldehyde was prepared from previously fractionated *iso*butyl alcohol and purified through the sodium bisulphite compound.

75 g (1 mol) of *iso*butyraldehyde were gradually added to a Grignard reagent made from 240 g (1·5 mol) of *iso*amyl bromide (previously fractionated) and magnesium, of which 73 g (3 atoms) were used, excess being removed by decantation before use. Normal working up gave 142 g (94 per cent yield) of *iso*propyl*iso*amylcarbinol, b.p. 65° to 75°/13 mm (mainly, 73° to 74°/13 mm). Redistillation gave 120 g (80 per cent yield) of pure carbinol, b.p. 178° to 182°/779 mm.

Tuot,[40] using the same starting materials, found b.p. 88°/25 mm.

*iso*Propyl*iso*amylcarbinol proved to be very difficult to dehydrate. It remained almost unaffected after prolonged boiling in presence of naphthalene-β-sulphonic acid, and was recovered by distillation. A little iodine was added and the mixture again boiled. Very little dehydration occurred and the iodine colour disappeared. The carbinol was distilled and again heated with naphthalene-β-sulphonic acid. After several hours 20 cc of nonene mixture were obtained from 115 g of carbinol, the remainder of the product polymerizing. The nonene mixture was boiled under reflux with zinc dust and dilute sodium hydroxide to remove traces of iodine, and finally hydrogenated in glacial acetic acid in presence of platinum oxide. Fractionation of the nonene obtained gave 1 cc, b.p. 134·5° to 135·5°/766 mm, n_D^{20} 1·4096.

The carbinol (1 mol) was therefore converted into 3-bromo-2 : 6-dimethylheptane by means of phosphorus tribromide (2 to 3 mol), starting in the cold and finishing at 100. The yield of bromo-compound, b.p. 76° to 77°/15 mm, was 68 per cent.

The bromo-compound was heated under reflux for 1 hr with excess of magnesium which had previously been activated with ethyl bromide. The mixture was treated with water and dilute acid and the hydrocarbon isolated in the usual manner. It had b.p. 125° to 150°, and since it contained unsaturated material it was hydrogenated in glacial acetic acid in presence of platinum oxide. Fractionation gave pure 2 : 6-dimethylheptane, b.p. 135·2° to 135·6°/766 mm corr, n_D^{20} 1·4010.

White, Rose, Calingaert, and Soroos [41] for 2 : 6-dimethylheptane derived from 2 : 6-dimethylheptan-4-ol recorded b.p. 135·21° ± 0·02°/760 mm and n_D^{20} 1·40073.

*

3 : 3-*Dimethylheptane.*

n-Propylacetoacetic ester was obtained, b.p. 205° to 212°, in 55 per cent yield from acetoacetic ester and *n*-propyl bromide, following usual methods. Hydrolysis with dilute alkali gave a 72 per cent yield of methyl *n*-butyl ketone, b.p. 126° to 128°. *Organic Syntheses, Collected,* Vol. I, p. 351, records yield 50 per cent and b.p. 126° to 128°. Methylethyl-*n*-butylcarbinol was obtained from the ketone in 63·5 per cent yield, b.p. 68°/16 mm. Clarke [42] prepared the carbinol from methyl butyl ketone and ethyl magnesium bromide, and Whitmore and Woodburn [30] from methyl ethyl ketone and butyl magnesium bromide. The latter authors recorded b.p. 65·2° to 65·8°/15 mm.

3-Chloro-3-methylheptane was prepared by shaking the carbinol with concentrated hydrochloric acid and saturating with calcium chloride. It was obtained in 72 per cent yield, b.p. 50° to 54°/16 mm. Whitmore and Woodburn [30] saturated the carbinol with hydrogen chloride and recorded b.p. 55·0°/15 mm.

Conversion of the chloro-compound into 3 : 3-dimethylheptane was effected as follows :—

66 g of the chloro-compound were added to a Grignard reagent prepared from 18 g of magnesium (1·5 atoms) and 74 g of methyl bromide. The reaction was vigorous, and after 2 hr standing the mixture was heated under reflux for 20 hr, cooled, and treated with ice and then dilute acid. Normal working-up gave a crude hydrocarbon boiling at 125° to 132°/765 mm. This was repeatedly extracted with small quantities of concentrated sulphuric acid until free from unsaturation, then washed, dried, and fractionated. A 15 per cent yield of almost pure 3 : 3-dimethylheptane was obtained, and of this the best fraction (6 cc) had b.p. 136·0° to 136·6°/765 mm corr, n_D^{20} 1·4080. Noller,[19] from *tert*-amyl chloride and zinc di-*n*-butyl in tetralin, obtained 3 : 3-dimethylheptane with b.p. 137° to 138°, n_D^{20} 1·4095. Marker and Oakwood [43] from *tert*-amyl chloride and *n*-butyl magnesium bromide in presence of cuprous iodide isolated 3 : 3-dimethylheptane with b.p. 137·2°/760 mm and n_D^{20} 1·4087.

Campbell and Eby [44] (*a*) from 3 : 3-dimethylhept-4-yne obtained by reduction the heptane boiling at 135°/735 mm, n_D^{20} 1·4078 and (*b*) from *tert*-amyl bromide and *n*-butyl magnesium bromide obtained 3 : 3-dimethylheptane in poor yield, b.p. 136°/745 mm, n_D^{20} 1·4084.

3 : 4-*Dimethylheptane.*

Methylethylacetic acid was prepared by the method of *Organic Syntheses, Collected,* Vol. I, p. 361. The *sec*-butyl bromide used, b.p. 91°, was prepared from fractionated *sec*-butyl alcohol. The yield of acid in the last stage was 60 per cent.

Methylethylacetamide was prepared from the acid *via* the acid chloride. This, when shaken in the cold with concentrated aqueous ammonia, gave the amide, which, after being crystallized first from alcohol and then from benzene, melted at 112° to 113°. Schleuble and Löbl [45] found m.p. 112°. In attempting to circumvent the old process of treating the acid chloride with aqueous ammonia, with its tedious working-up, we made the somewhat interesting observation that the chloride does not react with dry ammonia gas in dry ethereal solution. The amide was

converted into *n*-propyl *sec*-butyl ketone as follows: A Grignard reagent (3 mol) was prepared from 48 g of magnesium and 246 g of *n*-propyl bromide. It was stirred, and 68 g (1 mol) of methylethyl acetamide were gradually added, stirring being then continued for a further 21 hr. Normal working-up afforded 41 g of ketone, b.p. 152·5° to 155·5°, *i.e.*, 49 per cent of the possible yield. The b.p. 154°/73 mm recorded by Whitmore and Block [46] must be a misprint. A Grignard reagent was prepared from 16 g (2 atoms) of magnesium and 64 g of methyl bromide. To this, 40 g (1 mol) of the ketone was added. Decomposition by the usual method gave 40 g of methyl-*n*-propyl-*sec*-butylcarbinol (yield, 90 per cent), b.p. 172° to 178°/768 mm. The carbinol was distilled slowly from naphthalene-β-sulphonic acid, the water separated, and the process repeated three times. The nonene mixture boiled up to 145°.

The nonene mixture was hydrogenated in glacial acetic acid in presence of platinum oxide. The hydrocarbon obtained was freed from unsaturation by two extractions with concentrated sulphuric acid, and finally fractionated. The 3 : 4-dimethylheptane obtained had b.p. 139·8° to 140·6°/761 mm corr, n_D^{20} 1·4114.

4 : 4-*Dimethylheptane.*

Method 1. Di-*n*-propylcarbinol was obtained in 78 per cent yield, b.p. 57°/12 mm, by the interaction of *n*-butyraldehyde and 1·2 mol of *n*-propyl magnesium bromide. The carbinol (182 g; 3 mol) was gradually treated with a solution of 242 g (1·5 mol) of potassium dichromate and 220 g (about 4 mol) of concentrated sulphuric acid in 1650 cc of water. When the oxidation was complete, the mixture was distilled in steam, the ketone separated, washed with dilute sodium carbonate, dried, and distilled. The yield of pure ketone, b.p. 146° to 148°/765 mm was 73 per cent.

Interaction of di-*n*-propyl ketone with 1·5 mol of methyl magnesium iodide gave methyl di-*n*-propylcarbinol, b.p. 159° to 162°, in 72 per cent yield. Small amounts of di-*n*-propylcarbinol were also formed. Interaction of the chloride, prepared as above, with 2 mol of methyl magnesium iodide, gave only a poor yield of impure 4 : 4′-dimethylheptane, b.p. 132° to 133°/773 mm.

Method 2. Methyldi-*n*-propylcarbinol, b.p. 159° to 162°, was obtained in 78 per cent yield by the interaction of ethyl acetate with *n*-propyl magnesium bromide (3 mol) and was converted into the corresponding chloride by the action of concentrated hydrochloric acid, compare Halse.[18] To the freshly distilled chloride (b.p. 54° to 55°/16 mm) (71 g) zinc dimethyl (70 cc) was gradually added, with cooling. The mixture was eventually heated in boiling water and kept overnight. Water and dilute hydrochloric acid were added, the hydrocarbon layer separated, dried over calcium chloride, and distilled. It was then extracted with several successive small quantities of concentrated sulphuric acid until free from unsaturation, washed, dried, and distilled. 7 cc of 4 : 4-dimethylheptane were obtained, b.p. 135·0° to 135·7°/773 mm corr n_D^{20}, 1·4078.

3-*Ethylheptane.*

Diethyl ketone, the commercial pure material, was fractionated and added to *n*-butyl magnesium bromide,[47] when diethyl-*n*-butylcarbinol, b.p. 180° to 182° was obtained in 76 per cent yield.

Dehydration of the carbinol with naphthalene-β-sulphonic acid gave an olefin mixture which was hydrogenated in glacial acetic acid in presence of platinum oxide. The 3-ethylheptane formed had b.p. 142·6° to 143·0/766 mm corr, n_D^{20} 1·4091. Whitmore and Southgate [27] gave b.p. 143·1°/760 mm and n_D^{20} 1·4090.

2 : 2 : 5-*Trimethylhexane.*

A pure commercial sample of *iso*amyl alcohol was fractionated, the portion boiling at 121·8° to 122·4°/774 mm being converted into the bromide by the method of *Organic Syntheses*, Vol. I, p. 4. *tert*-Butyl alcohol was purified by freezing and filtering and converted into the chloride. The latter was added (145 g) to *iso*amyl magnesium bromide, the mixture being then heated under reflux for 6 hr. The semi-solid mixture was then distilled from a bath until the temperature of the latter rose to 230°. The distillate was fractionated. The 2 : 2 : 5-trimethylhexane obtained had b.p. 124° to 125°/774 mm and n_D^{20} 1·4002.

Campbell [48] found b.p. 122·9° to 123·0°/736 mm and n_D^{20} 1·3997.

2-*Methyl*-3-*ethylhexane.*

*iso*Butyramide was prepared by converting *iso*butyric acid (b.p. 154°/767 mm) into the chloride by means of thionyl chloride, followed by concentrated ammonia solution. The amide, b.p. 215°, was added to 3 mol of ethereal ethyl magnesium bromide, kept stirred. The interaction was vigorous and was brought to completion by stirring for a further 23 hr. Normal working-up gave ethyl *iso*propyl ketone, b.p. 114° to 116° in 69 per cent yield.

The ketone was allowed to react with *n*-propyl magnesium bromide. The ethyl-*n*-propyl*iso*propylcarbinol obtained showed a tendency to undergo spontaneous dehydration when distilled at the ordinary pressure, but was finally isolated with b.p. 160° to 175°/777 mm. Stas,[49] who used similar procedure, found b.p. 176·5° to 177·5°/755 mm and recorded a theoretical yield.

Dehydration of the carbinol with naphthalene-β-sulphonic acid (two operations) gave a nonene mixture, b.p. 128° to 138°, and hydrogenation of this in glacial acetic acid in presence of platinum oxide gave 2-methyl-3-ethylhexane, the best fraction of which had b.p. 138·6° to 138·8°/773 mm corr, n_D^{20} 1·4134.

3-*Methyl*-3-*ethylhexane.*

Diethyl-*n*-propylcarbinol was prepared by the interaction of *n*-propyl magnesium bromide and diethyl ketone (redistilled pure commercial material; b.p. 104° to 106°) and was distilled first under reduced pressure (b.p. 68° to 72°/12 mm) and then, to remove diethylcarbinol, at the ordinary pressure. The pure carbinol, b.p. 160° to 162°/770 mm uncorr, was isolated in 70 per cent yield. Clarke and Riegel [50] gave b.p. 155° to 159°/756 mm.

The carbinol was converted into 3-chloro-3-ethylhexane by means of concentrated hydrochloric acid. The chloride had b.p. 50° to 53°/15 mm and was obtained in 70 per cent yield.

Butlerow [51] prepared the chloride by treating the carbinol with phosphorus pentachloride. The chloro-compound (120 g) was added gradually to 3 mol of ethereal methyl magnesium bromide. The mixture was then boiled under reflux for 16 hr, treated with ice and dilute acid and the hydrocarbon worked-up normally. The crude material had b.p. 120° to 140° and contained unsaturated compounds which were extracted by means of concentrated sulphuric acid. The pure hydrocarbon had b.p. 140·0° to 140·5°/765 mm corr, n_D^{20} 1·4140.

2-*Methyl*-4-*ethylhexane.*

Two syntheses were carried out :—

Method 1. Pure commercial *iso*valeric acid was dried over phosphorus pentoxide, fractionated (b.p. 176° to 178°), and converted into methyl *iso*valerate, b.p. 118° to 119°.

Interaction of the ester (1 mol) with 3 mol of ethereal ethyl magnesium bromide gave diethyl*iso*butylcarbinol in 80 per cent yield, b.p. 68° to 69°/18 mm, compare Masson.[34] The carbinol, 32 g, dehydrated in two operations with naphthalene-β-sulphonic acid, gave 27 g of nonene mixture, b.p. 128° to 139°. Hydrogenation in glacial acetic acid (platinum oxide) gave, after fractionation, 2-methyl-4-ethylhexane, b.p. 133·8° to 134·1°/767 mm corr, n_D^{20} 1·4070.

Method 2. *iso*Valeric acid (550 g) was left with 1 mol of thionyl chloride for 12 hr. The mixture was then heated at 100° for 1 hr, cooled, and added gradually to excess of concentrated ammonia and ice. The *iso*valeramide was filtered and crystallized from water, when it had m.p. 133° to 134°, subsequent crystallization from acetone not affecting this m.p. The yield of pure amide was 182 g.

The amide (1 mol) was gradually added to 3 mol of ethereal ethyl magnesium bromide, with continuous stirring, which was maintained during a further 24 hr. The mixture was worked up in a normal manner, and gave a 61 per cent yield of ethyl *iso*butyl ketone, b.p. 136° to 137°.

Beis,[52] who obtained the ketone by a similar method, found b.p. 134·5° to 135°/735 mm.

Interaction of ethyl *iso*butyl ketone (68 g) with 2 mol of ethereal ethyl magnesium bromide gave 75 g of crude diethyl*iso*butylcarbinol, b.p. 62° to 64°/12 mm. This, redistilled at ordinary pressure, was found to contain some ethyl*iso*butylcarbinol, formed by the reducing action of the Grignard reagent; 50 g of pure diethyl*iso*butyl carbinol being obtained. The carbinol was dehydrated as before, the nonene mixture boiling at 135° to 140°. On reduction it gave 2-methyl-4-ethylhexane, b.p. 134·1° to 134·4°/767 mm corr, n_D^{20} 1·4072.

4-*Ethylheptane.*

Pure commercial propionic acid was fractionated and converted into ethyl propionate, which was further fractionated. The ester was allowed to react with excess of magnesium *n*-propyl bromide. Halse [53] gives b.p. 179·5° corr. The ethyldi-*n*-propylcarbinol obtained boiled at 182° to 183°/770 mm.

Dehydration of the carbinol with naphthalene-β-sulphonic acid gave a nonene mixture, b.p. 142° to 144°/770 mm, and the latter, after hydro-

genation (glacial acetic acid–platinum oxide) gave 4-ethylheptane, b.p. 140·6° to 140·8°/766 mm corr, n_D^{20} 1·4084.

2 : 4-*Dimethyl*-3-*ethylpentane.*

Di-*iso*propyl ketone was fractionated and then converted into the semicarbazone. This, after being crystallized three times from methyl alcohol, had m.p. 153° to 154°. The semicarbazone (247 g) hydrolysed by boiling with 20 per cent hydrochloric acid, gave 138 g (84 per cent yield) of pure ketone, b.p. 127°.

Interaction of the ketone (138 g; 1 mol) with 2 mol of ethereal ethyl magnesium bromide gave 165 g of crude ethyldi-*iso*propylcarbinol boiling mainly at 65°/15 mm. Distillation of this material at the ordinary pressure gave 149 g, b.p. 160° to 177°, some low boiling material being rejected, compare Whitmore and George.[54] The carbinol was dehydrated with naphthalene-β-sulphonic acid (two operations) and gave 125 g of nonene mixture, b.p. 125° to 140°.

Hydrogenation of the nonene mixture in glacial acetic acid in presence of platinum oxide was slow, but finally led to a product which contained only small amounts of unsaturated material, these then being removed by extraction with concentrated sulphuric acid. Fractionation gave 24 cc of 2 : 4-dimethyl-3-ethylpentane, b.p. 136·6° to 137·0°/775 mm corr, n_D^{20} 1·4138.

An attempt to prepare ethyldi-*iso*propylcarbinol by the interaction of ethyl propionate and 3 mol of *iso*propyl magnesium bromide led, as was anticipated, to a poor yield (8 to 10 per cent).

Note.—For some of this work, di-*iso*propyl ketone was purified as follows, in order to make certain that it contained no unidentifiable impurities :—

Preparation of di-*iso*propyl carbinol : 256 g of sodium were added in small pieces, to a mixture of 228 g of di-*iso*propyl ketone (b.p. 121° to 124°/756 mm, 90 cm Vigreux column) and 2500 cc of absolute alcohol. The addition completed (about 1 hr) water was added and the mixture was extracted three times with ether. The combined ethereal extracts were washed with brine, dried over potassium carbonate, and distilled, when 186 g (80 per cent yield) of carbinol were obtained, b.p. 130° to 138°, mainly 135° to 136°.

A mixture of the carbinol (186 g, 1 mol) with 1 mol each of phthalic anhydride and pyridine, was heated over a free flame to 105°, when spontaneous warming set in. The mixture was heated for 2 hr in boiling water, treated with 200 cc of glacial acetic acid and then poured into 2 litres of dilute hydrochloric acid. The oil separating at once solidified. The solid was filtered and crystallized once from glacial acetic acid without being previously dried. This gave an 82 per cent yield of hydrogen phthalate, m.p. 163° to 164°. Two crystallizations of the crude hydrogen phthalate from alcohol were necessary to effect an equivalent purification, and the yield of pure ester was then only 60 per cent. (Found : C, 68·1; H, 7·6. $C_{15}H_{20}O_4$ requires C, 68·1; H, 7·6 per cent.)

A mixture of the hydrogen phthalate (353 g) with a solution of 225 g of sodium hydroxide in 1150 cc of water was boiled under reflux for 30 min, and the mixture then distilled until no more carbinol came over. The distillate was saturated with sodium chloride, separated, and the

carbinol dried over potassium carbonate and then distilled. 145 g (93 per cent yield) boiled at 137° to 139°, the great majority at 138·3° to 138·5°/753 mm uncorr.

The pure carbinol was oxidized to di-*iso*propyl ketone as follows: A solution of 141 g (1·33 mol) of potassium dichromate and 191 g (5·33 mol) of concentrated sulphuric acid in 950 cc of water was added, in 50-cc lots, to 125 g (3 mol) of carbinol in a 2-litre flask, with initial warming to 60° to start the reaction which then kept the temperature at 60° to 80°. Addition took about 1 hr. The mixture was then distilled until no more oil came over. The distillate was saturated with sodium chloride and the oily layer separated, extracted three times with brine, once with dilute sodium hydroxide and once with water. The moist ketone (108 g) was used for conversion into the semicarbazone, from which pure ketone, b.p. 125·6° to 125·8°/766 mm (uncorr) was obtained, as described above.

cis- and *trans*- 3 : 5-Dimethyl*cyclo*hexanol.

The material was obtained from two sources :—

(1) Messrs Howards. The product (2 lb) was semi-solid and was filtered at the ordinary temperature. The mother liquor was kept at 5° overnight and a second crop of solid filtered. Both solids melted at about 29° to 31° and were therefore mixed, giving in all 292 g. The mother liquor was distilled and boiled at 186° to 188·5°/751 mm.

(2) Imperial Chemical Industries Ltd.

(*a*) A series of fractions were supplied. Those having b.p. between 183·0° and 186·8° were practically solid, those having b.p. between 186·8° and 188·5° being liquid. The solid fractions all had f.p. between 32·5° and 34·5°, and mixtures had the same approximate f.p. A mixture of all the solid fractions had f.p. 33·5°.

(*b*) A series of fractions were supplied. Those having b.p. between 178·6° and 186·0° were solid. The fractions, b.p. 186·4° to 187·7°, were liquid.

(*c*) The total product of hydrogenating 5-*m*-xylenol was supplied. It was distilled through an 8-in Dufton column and boiled from 184° to 194°.

For the purpose of the present work, any sample of dimethyl*cyclo*hexanol which had a freezing point of about 30° was taken as a mixture of *cis* (Me, Me) forms, free from *trans* (Me, Me), since von Braun and Haensel [55] had established the *cis*-configuration of the solid material. The liquid portions were a mixture of both *cis* and *trans* forms. Pure *trans*-carbinol was obtained by converting the mixture into the hydrogen phthalate (by heating for 2 hr at 100° with 1 mol each of phthalic anhydride and pyridine) and saponifying the product after repeated crystallization from 90 per cent acetic acid.

cis-3 : 5-Dimethyl*cyclo*hexanone: Solid dimethyl*cyclo*hexanol (326 g), mainly one *cis* form, and containing no *trans* form, was converted into 3 : 5-dimethyl*cyclo*hexanone by adding to it gradually with shaking a solution of 248 g of potassium dichromate and 340 g of concentrated sulphuric acid in 1600 cc of water. The ketone was steam-distilled from the oxidation mixture, the distillate saturated with calcium chloride, the ketone separated, dried over potassium carbonate, and converted into

the semicarbazone. The latter, after crystallization from ethyl alcohol, had m.p. 201° to 202° (345 g). Hydrolysis with hydrochloric acid, followed by usual procedure, gave 151 g of *cis*-3 : 5-dimethyl*cyclo*hexanone, b.p. 182·9°/765 mm uncorr, and 49 g b.p. 182·9° to 184·1°.

von Braun and Haensel [55] gave m.p. 202° to 203° for the semicarbazone, and 182° to 183° for the b.p. of the pure *cis*-ketone.

trans-3 : 5-Dimethyl*cyclo*hexanone : This was obtained from *trans*-3 : 5-dimethyl*cyclo*hexanol, purified through the hydrogen phthalate. The pure ketone had b.p. 183·0°/758 mm uncorr.

1 : 3-Dimethyl*cyclo*hexane.

(1) *trans*-3 : 5-dimethyl*cyclo*hexanol (30 g), purified through the hydrogen phthalate, was dehydrated with naphthalene-β-sulphonic acid. This process was slow, but gave 21 g of crude dimethyl*cyclo*hexene, of which 18 g had b.p. 122·8° to 123·8°/749 mm uncorr. Hydrogenation in glacial acetic acid in presence of platinum oxide gave 1 : 3-dimethyl*cyclo*hexane, of which 5 cc had b.p. 118·5° to 120·5°/758 mm corr, 7 cc 120·5° to 121·0°, and 9 cc 121·0° to 121·5° corr, n_D^{20} respectively being 1·4250, 1·4251, and 1·4254.

(2) Almost pure *cis*-3 : 5-dimethyl*cyclo*hexanol, similarly treated, gave 1 : 3-dimethyl*cyclo*hexene, b.p. 121° to 123°/764 mm and thence 1 : 3-dimethyl*cyclo*hexane, b.p. 119·5° to 120·7°/769 mm corr.

Spectroscopic examination showed that the two products (1) and (2) were identical, that is, that each was *trans*-1 : 3-dimethyl*cyclo*hexane.

Evans,[56] by catalytic hydrogenation of *m*-xylene, obtained a 1 : 3-dimethyl*cyclo*hexane boiling at 121·6° ±1°/760 mm corr and having n_D^{20} 1·4255. This was evidently the *trans* variety.

1 : 3 : 5-*Trimethyl*cyclo*hexane.*

(1) *cis*. *cis*-3 : 5-Dimethyl*cyclo*hexanone (26 g), purified through the semicarbazone (m.p. 201° to 202°), was added to ethereal methyl magnesium iodide (1·5 mol). The carbinol obtained by usual procedure was dehydrated with naphthalene-β-sulphonic acid and the trimethyl*cyclo*hexene (b.p. 142·2° to 144·2°/769 mm) was reduced with hydrogen in glacial acetic acid in presence of platinum oxide. The 1 : 3 : 5-trimethyl*cyclo*hexane obtained had b.p. 139·7° to 140·2°/763·5 mm uncorr and n_D^{20} 1·4280.

(2) *trans*. *trans*-3 : 5-Dimethyl*cyclo*hexanone (38 g), obtained by the oxidation if *trans*-3 : 5-dimethyl*cyclo*hexanol which had been purified through the hydrogen phthalate, was added to ethereal methyl magnesium iodide (1·5 mol). Usual working-up gave trimethyl*cyclo*hexanol, which, on dehydration with naphthalene-β-sulphonic acid, gave 21 g of 1 : 3 : 5-trimethyl*cyclo*hexene, b.p. 142·8° to 143·8°/766 mm. Catalytic reduction (PtO_2–hydrogen–glacial acetic acid) of the latter gave 1 : 3 : 5-trimethyl-*cyclo*hexane, b.p. 140·3° to 140·8°/749 mm uncorr, n_D^{20} 1·4352.

Previous authors have obtained trimethyl*cyclo*hexane by the hydrogenation of mesitylene. Eisenlohr and Gorr [57] gave the following constants :—

cis	b.p. 140·0° to 140·5°/752 mm
trans	138·0° to 139°/760 mm

αβ′-Dimethyladipic acid and 2 : 4-*dimethyl*cyclo*pentanone.*

The oxidation of the dimethyl*cyclo*hexanols to dimethyladipic acids was carried out by means of nitric acid, but with this particular material it was found possible to effect certain useful improvements, which are incorporated in the following account :—

200 g of dimethyl*cyclo*hexanol were added gradually to 450 cc of 50 per cent (weight) nitric acid at 55° with *vigorous* stirring, keeping the temperature between 55° and 60° by *intermittent* external cooling. With practice this operation was completed in 60 to 70 min. The mixture was then stirred, and if necessary cooled, until spontaneous cooling started. The yellow liquid was then evaporated in a 1-litre distilling flask at about 50 mm pressure, with occasional addition of concentrated formic acid, until nitrous fumes were no longer in evidence. 20 g of crystallized barium hydroxide were added and the mixture heated gradually in a fusible metal bath. Some water and dimethyl-succinic acid passed over first, and when the bath temperature reached about 320° crude dimethyl*cyclo*pentanone distilled. The total distillate was saturated with anhydrous potassium carbonate, the aqueous layer separated and the ketone dried over anhydrous potassium carbonate. Distillation gave 52 g, b.p. 150° to 160°, that is, a 30 per cent yield calculated on the original 200 g of dimethyl*cyclo*hexanol. The whole operation from dimethyl*cyclo*hexanol to dimethyl*cyclo*pentanone was completed in 8 hr, as against the several days required by existing practice involving use of a larger proportion (640 cc) of nitric acid, and prolonged evaporation of the (continually diluted) aqueous oxidation product.

The use of ammonium vanadate, frequently recommended as a catalyst in such oxidations, was found to complicate the working-up, and in no way to aid the oxidation. In this and similar processes, oxidation of *cyclo*hexanols appears to be largely catalysed by nitrous acid, and the initial addition of nitrous acid (*e.g.*, as produced by the interaction of a little alcohol and nitric acid in a test-tube) is to be preferred to that of vanadate in cases where the hexanol itself is not rapidly attacked by the nitric acid.

Numerous operations as above were carried out using both *cis*- and *trans*-dimethyl*cyclo*hexanol. The dimethyl*cyclo*pentanone formed was converted into the semicarbazone, and the latter submitted to systematic fractional crystallization.

Starting with *cis*-dimethyl*cyclo*hexanol, 329 g of crude semicarbazone were obtained. Fractional crystallization gave 222 g of m.p. 174° to 175°, 15 g of m.p. 164° to 165°, and an inseparable mixture of lower m.p.

Starting with mainly *trans*-dimethyl*cyclo*hexanol, 306 g of crude semicarbazone were obtained. Fractional crystallization gave 242 g m.p. 174° to 175°, 22 g m.p. 157° to 158°, and an inseparable mixture of lower m.p.

The semicarbazones of m.p. 174° to 175° from the two different sources were identical, showing that the main product was an individual dimethyl-*cyclo*pentanone whatever the configuration of the dimethyl*cyclo*hexanol started with.

2 : 4-*Dimethyl*cyclo*pentanone.*

The semicarbazone (225 g) of m.p. 174° to 175° was distilled with a mixture of 300 cc of concentrated hydrochloric acid and 300 cc of water. The mixture of water and ketone obtained was saturated with anhydrous potassium carbonate and the separated ketone dried over anhydrous potassium carbonate. The whole of the ketone boiled within the range 152·8° to 153·2°/768 mm corr, the bulk at 152·9°/768 mm corr. Yield, 266 g or 96 per cent of the possible.

From mixtures of semicarbazones obtained from various sources as mentioned above, mixtures of 2 : 4-dimethyl*cyclo*pentanones were similarly prepared.

2 : 4-Dimethyl*cyclo*pentanone was obtained by Zelinsky [58] and by Haller and Cornubert [59] by the action of dilute acid on 1 : 3-dimethyl-*cyclo*pentan-5-one-1-carboxylic acid. Later it was obtained by Wallach [60] by oxidizing 2 : 4-dimethyl*cyclo*pentan-1-ol-1-carboxylic acid with lead dioxide and dilute acid. Wallach found b.p. 152° to 154° for the ketone, the semicarbazone melting at 165° to 166°.

1 : 3-*Dimethyl*cyclo*pentane.*

Method 1. The general plan of Chavanne [61] was adopted :—

(*a*) 4-Methyl*cyclo*hexanol was oxidized with nitric acid to β-methyladipic acid, (*b*) the acid was heated with barium hydroxide at 300° to 320°, giving 3-methyl*cyclo*pentanone, (*c*) the ketone was converted by means of methyl magnesium iodide into 1 : 3-methyl*cyclo*pentanol, (*d*) the carbinol was dehydrated with naphthalene-β-sulphonic acid, (*e*) the dimethyl*cyclo*pentene was hydrogenated (hydrogen–platinum oxide–glacial acetic acid). The dimethyl*cyclo*pentene was a mixture, b.p. 94·0° to 95·0°, the 2 : 4-dimethyl*cyclo*pentane, b.p. 90·6°/752 mm corr, n_D^{20} 1·4095. Spectroscopic examination showed it to be the *trans* form. Chavanne [61] gave b.p. 90·6° to 90·8°/760 mm and n_D^{20} 1·4076. Evans,[56] who started with α-methyladipic acid, obtained for 1 : 3-dimethyl*cyclo*pentane the constants : b.p. 90·5°/760 mm corr, and n_D^{20} 1·4096.

Method 2. *From* 2 : 4-*Dimethyl*cyclo*pentanone.* (*a*) Using ketone obtained by cyclizing a mixture of αβ′-dimethyladipic acids : 85 g of ketone were reduced in 350 cc of ether over about 200 cc of water by the gradual addition of 135 g of sodium. 72 g of carbinol were obtained, b.p. 158° to 162°. Of this, 65 g were dehydrated with naphthalene-β-sulphonic acid, and the resulting unsaturated hydrocarbon, b.p. 98° to 101° (38 g) reduced with hydrogen–platinum oxide–glacial acetic acid. Small amounts of unsaturated material were removed with sulphuric acid. Final distillation gave : 1·5 cc boiling below 91·2°/773 mm corr, 9·5 cc b.p. 91·2° to 91·4°, n_D^{20} 1·4097, 20 cc b.p. 91·4° to 91·8°, n_D^{20} 1·4098, 5 cc b.p. 91·8° to 92·4°, n_D^{20} 1·4099, and a product boiling up to 95° with n_D^{20} 1·4109.

(*b*) Using stereochemically individual ketone, b.p. 152·9°/768 mm corr, obtained from the semicarbazone of m.p. 174° to 175°. The ketone (75 g) was reduced as under (*a*), the crude carbinol dehydrated with naphthalene-β-sulphonic acid, and the unsaturated hydrocarbon reduced as before. The product, after being freed from unsaturated compounds (sulphuric acid), was distilled. 0·5 cc boiled below 90·8°/771 mm corr, 1·0 cc had

b.p. 90·8° to 91·0°, n_D^{20} 1·4091, 23 cc had b.p. 91·0° to 91·4°, n_D^{20} 1·4092, and the remainder (5 cc) had b.p. 91·4° to 92·3°, n_D^{20} 1·4093 to 1·4094.

Method 3. Pure dimethyl*cyclo*pentanone, from the semicarbazone, was reduced by Clemmensen's method. The 1 : 3-dimethyl*cyclo*pentane obtained had b.p. 91·2° to 92·2°/759 mm uncorr and n_D^{20} 1·4095.

1 : 2 : 4-*Trimethyl*cyclo*pentane.*

Zelinsky [62] obtained the hydrocarbon by reducing 1 : 2 : 4-trimethyl-*cyclo*pentanol, obtained from 2 : 4-dimethyl*cyclo*pentanone and methyl magnesium iodide. For the hydrocarbon he gave the constants: b.p. 112·5° to 113° corr and n_D^{20} 1·4156.

The methods adopted in the present work were: (*a*) 2 : 4-dimethyl-*cyclo*pentanone to 1 : 2 : 4-trimethyl*cyclo*pentanol to 1-chloro-1 : 2 : 4-trimethyl*cyclo*pentane to the Grignard reagent to the hydrogen and (*b*) 1 : 2 : 4-trimethyl*cyclo*pentanol to 1 : 2 : 4-trimethyl*cyclo*pentenes to the saturated hydrocarbon.

Method (a) (1) 128 g of 2 : 4-dimethyl*cyclo*pentanone from mixed dimethyl*cyclo*hexanols were added to 1·5 mol of ethereal methyl magnesium iodide. The carbinol, isolated in the usual way, was not distilled but was dehydrated with naphthalene-β-sulphonic acid. 95 g of unsaturated hydrocarbon were obtained, b.p. 115·0° to 120·5°/764 mm, and this on reduction with hydrogen–platinum oxide–glacial acetic acid gave a partly unsaturated product which was freed from unsaturation by being shaken with several successive small quantities of concentrated sulphuric acid. Washing, drying, etc., gave 1 : 2 : 4-trimethyl*cyclo*pentane, b.p. 113·0° to 117·2°/753 mm.

(2) 42 g of 2 : 4-dimethyl*cyclo*pentanone from mixed dimethyl*cyclo*hexanols were similarly converted into 1 : 2 : 4-trimethyl*cyclo*pentanol, which, without purification, was dehydrated by heating with iodine. The trimethyl*cyclo*pentene formed had b.p. 116° to 118° (mainly 117·2° to 117·8°) at 762 mm, and when reduced (hydrogen–platinum oxide–acetic acid) gave 1 : 2 : 4-trimethyl*cyclo*pentane, b.p. 113·5° to 114·3°/752 mm.

(3) 61 g of 2 : 4-dimethyl*cyclo*pentanone, from the semicarbazone, m.p. 174° to 175°, were similarly converted into 1 : 2 : 4-trimethyl*cyclo*pentanol, which (62 g) was dehydrated with naphthalene-β-sulphonic acid, the product then being reduced as above. After removal of unsaturated material with sulphuric acid, 1 : 2 : 4-trimethyl*cyclo*pentane was obtained, b.p. 113·5° to 117·5°/774·5 mm. The value of n_D^{20} increased from 1·4156 for the fraction 113·5° to 114·0° to 1·4179 for the highest 0·5 fraction.

Method (b) (1) 42 g of 2 : 4-dimethyl*cyclo*pentanone, from *cis*-dimethyl-*cyclo*hexanol, was similarly converted into 1 : 2 : 4-trimethyl*cyclo*pentanol (43 g). The latter, without being distilled, was shaken repeatedly with concentrated hydrochloric acid, and the chloride obtained dried over sodium sulphate. 32 g were obtained, b.p. 35° to 39°/20 mm.

The chloride was converted into the Grignard reagent by heating in ethereal solution with an excess of magnesium previously activated with ethyl bromide. Treatment of the Grignard reagent with ice and dilute acid gave a partly unsaturated product, which was submitted to catalytic hydrogenation (hydrogen–platinum oxide–acetic acid). Fractionation of the saturated hydrocarbon gave 1 : 2 : 4-trimethyl*cyclo*pentane, b.p. 115·0° to 116·5°/771 mm.

(2) 112 g of 2 : 4-dimethyl*cyclo*pentanone, from the semicarbazone, m.p. 174° to 175°, was converted by methyl magnesium iodide into the trimethylcarbinol, b.p. 61° to 62°/14 mm (107 g). Concentrated hydrochloric acid converted the latter into 1 : 2 : 4-trimethyl*cyclo*pentyl chloride, b.p. 35° to 39°/20 mm (74 g), and this was heated in ethereal solution with excess of magnesium which had previously been activated with ethyl bromide. Decomposition with ice and dilute acid, followed by separation, drying, and extraction of traces of unsaturated product (sulphuric acid) gave 1 : 2 : 4-trimethyl*cyclo*pentane (76 g), b.p. 113·5° to 116·5°/769 mm corr. The value of n_D^{20} rose from 1·4151 to 1·4172 from the lowest to the highest 0·5 fraction.

Precision fractionation. The products from all five syntheses of 1 : 2 : 4-trimethyl*cyclo*pentane were mixed and sent to Imperial Chemical Industries Ltd., who carried out a precision fractionation. This clearly indicated the presence of two main components :—

(*a*) b.p. 109·1° to 109·4° n_D^{20} 1·4109
(*b*) b.p. 116·2° n_D^{20} 1·4185

It seems probable that the lower boiling isomeride is that in which the 1 and 2 methyls are *trans*, the higher boiling one being that with the 1 and 2 methyls *cis*, and the 4 methyl *trans*. The missing wholly *cis* isomeride probably has a considerably higher b.p.

*Ethyl*cyclo*pentane.*

Purified *cyclo*hexanol was oxidized in the usual manner to adipic acid, and the latter was converted into *cyclo*pentanone by heating it with a little barium hydroxide. The ketone, after being fractionated, was allowed to react with ethyl magnesium bromide.[63] The *cyclo*pentanol underwent dehydration when distilled at the ordinary pressure, giving ethyl*cyclo*pentene, b.p. 109°. Hydrogenation of the ethyl*cyclo*pentene (glacial acetic acid–platinum oxide) gave ethyl*cyclo*pentane, b.p. 102° to 103°/750 mm corr, n_D^{20} 1·4203.

Chavanne and Becker gave b.p. 103·0° to 103·2°/760 mm, $n_D^{19\cdot1}$ 1·4201. Evans [56] gave b.p. 103° ±0·5° and n_D^{20} 1·4201, whilst Pines and Ipatieff [64] found b.p. 103·6°/760 mm, n_D^{20} 1·4196.

1 : 1 : 2-*Trimethyl*cyclo*pentane.*

*iso*Lauronolic acid was prepared by the method of Lees and Perkin [65] and was decarboxylated according to the directions of Crossley and Renouf.[66] The *iso*laurolene obtained was hydrogenated in glacial acetic acid in presence of platinum oxide, and gave 1 : 1 : 2-trimethyl*cyclo*pentane, b.p. 113·6° to 113·8°/753 mm corr, n_D^{20} 1·4232.

1 : 1 : 3-*Trimethyl*cyclo*pentane.*

Pure 4-methyl*cyclo*hexanol was oxidized in the usual manner to β-methyladipic acid and the latter heated with a little barium hydroxide. The 3-methyl*cyclo*pentanone formed was fractionated and allowed to react with methyl magnesium bromide (compare Chavanne [61]). The 1 : 3-dimethyl*cyclo*pentanol obtained had b.p. 54°/10 mm 89 per cent yield. It was converted into 1-chloro-1 : 3-dimethyl*cyclo*pentane by treatment with

concentrated hydrochloric acid and calcium chloride. The chloro-compound was formed in 83 per cent yield, b.p. 40° to 42°/15 mm.

Zinc dimethyl was added gradually to the chloro-compound. When the vigorous reaction was over and addition was complete, the semi-solid mixture was heated for a few minutes and then treated with water and then with dilute hydrochloric acid. The hydrocarbon layer was separated and dried over calcium chloride. The 1 : 1 : 3-trimethyl*cyclo*pentane obtained after fractionation had b.p. 104·0° to 105·0°/749 mm corr, n_D^{20} 1·4115.

Alternatively, the chloro-compound was added gradually to 2 mol of ethereal methyl magnesium iodide, and the reaction completed by heating under reflux. Usual working-up gave a product which was extracted with sulphuric acid until free from unsaturation. The 1 : 1 : 3-trimethyl-*cyclo*pentane obtained had b.p. 104·0° to 105·0°/749 mm corr, n_D^{20} 1·4115. Zelinsky [67] gave b.p. 115° to 116°/760 mm and n_D^{20} 1·4223.

1 : 2 : 3-*Trimethyl*cyclo*pentane.*

Laurolene (1 : 2 : 3-trimethyl-Δ^1-*cyclo*pentene) was prepared from *d*-camphoric acid by the method of Aschan.[68,69] Compare Crossley and Renouf.[70] The hydrocarbon was hydrogenated in glacial acetic acid in presence of platinum oxide and gave dihydrolaurolene (1 : 2 : 3-trimethyl-*cyclo*pentane), b.p. 117·0° to 119·5°/763 mm corr. Fractionation gave various fractions, that with b.p. 117·0° to 117·5° and n_D^{20} 1·4202 being used for spectrographic examination.

1-*Methyl*-2-*ethyl*cyclo*pentane.*

Purified adipic acid was converted into the ethyl ester, b.p. 130°/14 mm. The latter was cyclized to ethyl *cyclo*pentanone-2-carboxylate (b.p. 130°/30 mm; yield, 68 per cent) by the method of Dobson, Ferns, and Perkin,[71] who recorded b.p. 132°/30 mm. Ethylation of the ester was effected by the method of Chiurdoglu,[72] who gave for ethyl 2-ethyl*cyclo*-pentanone-2-carboxylate b.p. 109·4° to 109·6°/11 mm, our product, obtained in 75 per cent yield, having b.p. 127°/21 mm. Conversion of this ester into 2-ethyl*cyclo*pentanone (yield, 80 per cent; b.p. 158° to 159°/754 mm corr) was carried out as described by Vavon and Horeau,[73] who recorded b.p. 158° to 160° and 83 per cent yield. Chiurdoglu, using sulphuric instead of hydrochloric acid for the hydrolysis, found b.p. 159° to 160°/751 mm (yield, 77·6 per cent).

The ketone was converted into the semicarbazone, which, after being crystallized from alcohol and then methyl alcohol, had m.p. 189° to 190° (Chiurdoglu gave m.p. 188° to 188·5°). Hydrolysis of the semicarbazone gave the pure 2-ethyl*cyclo*pentanone, b.p. 158·5° to 159·0°/763·5 mm corr.

The ketone was treated with methyl magnesium iodide, when 1-methyl-2-ethyl*cyclo*pentanol was obtained in 80 per cent yield, b.p. 80° to 90°/25 mm (it is, of course, a mixture of *cis* and *trans* forms). Chiurdoglu, who used methyl magnesium bromide, recorded b.p. 60° to 70°/13 mm.

1-Methyl-2-ethyl*cyclo*pentanol was dehydrated with naphthalene-β-sulphonic acid. The unsaturated hydrocarbon, probably 1-methyl-2-ethyl-Δ^1-*cyclo*pentene, had b.p. 127·2° to 127·7°/765 mm corr. Chiurdoglu, using oxalic acid for the dehydration, found b.p. 127·4° to 127·8°/760 mm.

Hydrogenation of the *cyclo*pentene in glacial acetic acid in presence of platinum oxide gave 1-methyl-2-ethyl*cyclo*pentane, which boiled at 122·0° to 125·2°/765 mm corr. Fractionation with an 8-in Dufton column gave little indication of the separation of two isomerides, and the re-combined fractions were therefore sent to Imperial Chemical Industries, who established the presence of an individual of b.p. 121·30°, n_D^{20} 1·4222, and of another of b.p. 127·70°/760 mm, n_D^{20} 1·4291. The higher boiling isomeride is no doubt the *cis* form.

Chiurdoglu, who performed a careful fractionation of much larger quantities than we were able to prepare, established the presence of two forms of 1-methyl-2-ethyl*cyclo*pentane boiling respectively at 121·40° to 121·75°/760 mm (n_D 1·4220) and 127·70° to 128·02°/760 mm (n_D 1·4291).

1-*Methyl*-3-*ethyl*cyclo*pentane.*

Pure 4-methyl*cyclo*hexanol was oxidized with nitric acid by the method given in *Organic Syntheses*, *Collected*, Vol. I, p. 18. Contrary to the observation of Vogel,[74] the β-methyladipic acid crystallized from the oxidation mixture, and was formed in 50 per cent yield. The acid was converted into 3-methyl*cyclo*pentanone by heating it with barium hydroxide (*Organic Syntheses*, *Collected*, Vol. I, p. 192). The yield of ketone was 75 per cent.

Interaction of the ketone with ethyl magnesium bromide (Zelinsky,[75] used the iodide) gave 1-methyl-3-ethyl*cyclo*pentan-3-ol, and dehydration of the latter by means of naphthalene-β-sulphonic acid gave an unsaturated hydrocarbon. The latter, when hydrogenated (glacial acetic acid–platinum oxide) gave 1-methyl-3-ethyl*cyclo*pentane, b.p. 120·5° to 121·0°/765 mm corr, n_D^{20} 1·4190.

Zelinsky [76] gave b.p. 120·5° to 121° for the (+)-form of the hydrocarbon.

*Phenyl*cyclo*pentane.*

Pure *cyclo*pentanone was treated with phenyl magnesium bromide, and the resulting 1-phenyl*cyclo*pentanol dehydrated with formic acid.[77] The phenyl*cyclo*pentene was hydrogenated using platinum oxide in glacial acetic acid. The resulting 1-phenyl*cyclo*pentane had b.p. 216·5° to 217·5°/778 mm uncorr, n_D^{20} 1·5252.

Nametkin and Pokrovskaya [78] gave b.p. 215° to 216°/750 mm and n_D^{20} 1·531. Ipatieff and Schmerling [79] found b.p. 219°/760 mm, n_D^{20} 1·5290.

1 : 1-*Dimethyl*cyclo*hexane.*

2 : 2-Dimethyl*cyclo*hexanone was prepared from 2-methyl*cyclo*hexanone as described by Haller and Cornubert.[80] It gave a semicarbazone, m.p. 196° to 197°, from which the regenerated ketone was obtained. Reduction of the latter by Clemmensen's method gave 1 : 1-dimethyl*cyclo*hexane, b.p. 119·2° to 119·7°/757 mm corr, n_D^{20} 1·4290.

Chavanne, Miller, and Cornet [81] found b.p. 119·5° to 120°/751 mm for 1 : 1-dimethyl*cyclo*hexane prepared from 1 : 1-dimethyl*cyclo*hexan-3-ol by dehydration followed by hydrogenation.

1-*Methyl*-3-*ethyl*cyclo*hexane.*

Pure 1-methyl-3-ethylbenzene was hydrogenated in glacial acetic acid in presence of platinum oxide. The product had b.p. 148·9° to 150·9°/759

mm corr, n_D^{20} 1·4340. Signaigo and Cramer,[82] who derived the hydrocarbon from 3-methyl-1-ethyl*cyclo*hexanol (dehydration, hydrogenation), found b.p. 148·4° to 150·0° and n_D^{20} 1·4344.

n-*Butyl*cyclo*hexane.*

*cyclo*Hexanone, previously fractionated, was allowed to react with *n*-butyl magnesium bromide.[82] The butyl*cyclo*hexanol obtained was dehydrated with naphthalene-β-sulphonic acid and the unsaturated hydrocarbon hydrogenated in glacial acetic acid in presence of platinum oxide. The *n*-butyl*cyclo*hexane had b.p. 178·8° to 179·2°/761 mm uncorr, n_D^{20} 1·4416.

Signaigo and Cramer found b.p. 180·1° to 181·2°/760 mm corr and n_D^{20} 1·4408. Evans [56] gave b.p. 180·5° ±0·5° corr and n_D^{20} 1·4410.

cyclo*Heptane.*

*cyclo*Heptanone was prepared by the method of Mosettig and Burger,[38] that is, by the action of diazomethane on *cyclo*hexanone. The yield of *cyclo*heptanone, b.p. 77° to 80°/27 mm was 38 per cent, purified through the semicarbazone, m.p. 163° to 164·5°. Reduction as Willstätter [86] gave *cyclo*heptanol, which was dehydrated with naphthalene-β-sulphonic acid. The *cyclo*heptene was hydrogenated in glacial acetic acid in presence of platinum oxide (compare Vogel [87]). Fractionation gave *cyclo*heptane, b.p. 118·0° to 118·6°/750 mm corr, n_D^{20} 1·4447.

Vogel found b.p. 117·5° to 118°/758 mm and n_D^{20} 1·44355; Ruzicka and Seidel [84] found b.p. 116° to 118°/730 mm. Willstätter and Kametaka [85] recorded b.p. 116·4° to 116·8°/726 mm, 118° corr.

*Phenyl*cyclo*hexane.*

The method of *Organic Syntheses* (1939, **19**, 36) was used. The fractionated product had b.p. 240·2° to 240·3°/763 mm uncorr, n_D^{20} 1·5264.

Tsukervanik and Siderova [88] found b.p. 232° to 235°/715 mm and n_D^{20} 1·5237.

Tetrahydronaphthalene.

Naphthalene was reduced with sodium and alcohol.[89] The 1 : 4-dihydronaphthalene obtained, after fractionation, was hydrogenated in glacial acetic acid in presence of platinum oxide. The tetrahydronaphthalene obtained had b.p. 207·4° to 208·2°/772 mm uncorr, n_D^{20} 1·5445.

Evans [90] found b.p. 206·8°, n_D^{20} 1·5438.

Hydrindene.

Pure commercial indene was fractionated. The fraction which had b.p. 183·3°/766 mm uncorr and f.p. −1·9° corr was reduced with sodium and alcohol.[91] The crude hydrocarbon was distilled under reduced pressure, then shaken repeatedly with small quantities of concentrated sulphuric acid until no further change occurred, and then distilled in steam, etc. The hydrindene obtained had b.p. 178·9° to 179·1°/773 mm uncorr, n_D^{20} 1·5389.

Evans [90] found b.p. 177·5° to 178·5° and n_D^{20} 1·5383.

1-*Methylhydrindene.*

β-Phenylpropionyl chloride, b.p. 130°/20 mm, was obtained in 96 per cent yield from the acid, by the method of Ingold and Thorpe,[92] who give b.p. 121° to 122°/22·5 mm.

The chloride was converted into α-hydrindone (yield, 65·5 per cent; m.p. 42° to 43°) by the method of Ingold and Thorpe.[92] When α-hydrindone was caused to react with methyl magnesium iodide,[93] a product was obtained which tended to undergo dehydration when distilled. Dehydration was speeded up by the addition of naphthalene-β-sulphonic acid, but was accompanied by marked polymerization (compare Plattner and Wyss,[93] who recorded a 90 per cent dehydration; see also Ruzicka and Peyer).[94]

The 1-methylindene, b.p. 204° to 205°/759 mm uncorr, was hydrogenated in glacial acetic acid in presence of platinum oxide. After nine distillations from sodium, two best fractions were selected with b.p. 186·2° to 186·6°/759 mm uncorr, n_D^{20} 1·5266, and 186·6° to 187·1°/759 mm uncorr, n_D^{20} 1·5261.

Nenitzescu and Ciorianescu [95] for 1-methylhydrindene prepared by a different method, found b.p. 186° to 187° and n_D^{20} 1·52742. Plattner and Wyss,[93] using different methods for the last stage from 1-methylindene, found n_D^{20} 1·5260 and 1·5204. Ruzicka and Peyer,[94] using nickel as hydrogenating catalyst, found n_D^{20} 1·5222.

2-*Methylhydrindene.*

Indene, previously fractionated (see under hydrindene), was converted into 2-bromo-1-hydroxyhydrindene essentially by the method of Pope and Read.[96] It was found that the addition of a dispersing agent materially accelerated the addition of hypobromous acid. The bromo compound was converted into β-hydrindone by the method of Walters.[97] By means of methyl magnesium iodide the hydrindone was converted into 2-hydroxy-2-methylhydrindene,[98] and the latter compound was dehydrated with naphthalene-β-sulphonic acid (compare Ruzicka and Peyer [94]). Hydrogenation of the 2-methylindene in ether in presence of platinum oxide gave 2-methylhydrindene, b.p. 186·1° to 186·3°/758 mm uncorr, n_D^{20} 1·5220.

Kishner [99] found b.p. 183° to 185°/747 mm and n_D^{20} 1·5070.

5-*Methylhydrindene.*

(*a*) Hydrindene. Pure commercial indene was fractionated and then hydrogenated in ethereal solution in presence of platinum oxide. 50 g of indene gave 45 g of hydrindene, b.p. 176° to 178°.

(*b*) 5-Chloromethylhydrindene. Prepared using hydrochloric acid and formalin solution, Arnold [100] gave a product, b.p. 125°/14 mm. Arnold found b.p. 110° to 112°/4 mm, and Plattner and Roniger,[101] b.p. 125°/11 mm. The orientation of the product was not established by Arnold and was therefore checked as follows :—

(1) The chloromethylhydrindene (2 g) was mixed with 30 cc of water, 2 g of potassium carbonate added, and the whole boiled under reflux for 2 hr. The solid separating on cooling was crystallized from light petroleum (b.p. 60° to 80°) and then had m.p. 73° to 74°.

(2) Hydrindene-5-aldehyde was prepared by the method of Gattermann [91] as modified for *p*-tolualdehyde in *Organic Syntheses*, Vol.

XII, p. 80. The product, b.p. 250° to 260°, was reduced with hydrogen in alcoholic solution in presence of platinum oxide and a few drops of aqueous ferric chloride solution (compare Carothers and Adams [102]). The resulting carbinol was distilled (b.p. 264° to 266°) and then crystallized from light petroleum (b.p. 60° to 80°), when it had m.p. 73° to 74° (Found: C, 81·04; H, 8·14. $C_{10}H_{12}O$ requires C, 81·02; H, 8·16 per cent). A mixture of the two carbinols from the different sources melted at 73° to 74°.

(*c*) 5-Methylhydrindene. 65 g of 5-chloromethylhydrindene were converted into the Grignard reagent in presence of 12 g of magnesium, completing the interaction by heating for 1 hr under reflux. Decomposition with ice and dilute acid, followed by extraction and drying over calcium chloride and distillation from sodium gave 21 g of 5-methylhydrindene. This, on fractionation, gave best fractions having (*a*) b.p. 201·6° to 202·2°/773·5 mm uncorr, n_D^{20} 1·5321 and (*b*) b.p. 202·2° to 203·2°/773·5 mm uncorr, n_D^{20} 1·5324.

Plattner and Roniger gave n_D^{20} 1·5332.

2-*Ethylhydrindene.*

β-Hydrindone, prepared as described under 2-methylhydrindene was treated with ethyl magnesium bromide (2 mol). The 2-hydroxy-2-ethylhydrindene was obtained in 62 per cent yield and was dehydrated with naphthalene-β-sulphonic acid. Considerable polymerization occurred. The 2-ethylindene had b.p. up to 220° and on hydrogenation (glacial acetic acid–platinum oxide) gave 2-ethylhydrindene, b.p. 213° to 214°/767 mm corr, n_D^{20} 1·5176. Ruzicka and Peyer [94] recorded no corresponding constants for their hydrocarbon, which they prepared by the above method.

2 : 5-*Dimethylhydrindene.*

A mixture of 50 g of 2-methylhydrindene (prepared as above), 75 g of 40 per cent formaldehyde solution, and 250 cc of concentrated hydrochloric acid was stirred at 60° to 70° for 14 hr, hydrogen chloride being passed through continuously. The cooled mixture was separated, and the aqueous layer extracted with benzene. The dried (calcium chloride) benzene extract, which had been mixed with the first oil layer, was fractionated, when 38 g of 2-methyl-5-chloromethylhydrindene were obtained, b.p. 138° to 140°/12 mm.

The chloromethyl compound (38 g) was gradually added to 7 g of magnesium in dry ether. A little magnesium previously activated with ether and ethyl bromide was added to start interaction, and when this had subsided the mixture was heated under reflux for 2 hr. Ice and dilute acid were added to the cooled mixture, the ether layer was separated, and the dried ether solution distilled under reduced pressure. The fraction, b.p. 80° to 95°/12 mm, was fractionated and gave 2 : 5-dimethylhydrindene, b.p. 207° to 209°/767 mm corr, n_D^{20} 1·5200.

Toluene.

Pure commercial toluene-*p*-sulphonamide was crystallized twice from methyl alcohol. The m.p. was 138° to 139°. It was mixed with phosphoric

acid and distilled in superheated steam. The toluene formed was distilled repeatedly over sodium, and finally had b.p. 110·6° to 110·8°/762·5 mm corr, and n_D^{20} 1·4971.

Timmermans and Martin [103] recorded b.p. 110·80° and n_D^{20} 1·49685.

p-*Xylene.*

Three methods of preparation were examined :—

(1) *p*-Dibromobenzene and methyl iodide were treated with sodium.[106]

(2) *p*-Tolyl magnesium bromide was treated with methyl sulphate.[107]

(3) *p*-Iodotoluene and methyl iodide were treated with sodium.

No one of these methods was promising, and the combined products were boiled under reflux with sodium until no further change occurred. The distilled hydrocarbon (b.p. 132° to 141°) was shaken with 5 per cent oleum until in solution and water then added until a stiff paste resulted. The crystalline solid sulphonic acid was filtered, dissolved in the minimum water, and the solution boiled until free from oil or smell. The sulphonic acid was filtered from the cooled mixture and distilled in superheated steam in presence of phosphoric acid. The xylene formed was dried and fractionated from sodium. It had b.p. 139·2° to 139·4°/763 mm uncorr and f.p. 13·2° corr, n_D^{20} 1·4966. Richards, Stull, Mathews, and Speyers [104] gave b.p. 136·2° to 136·4°/764 mm corr and f.p. 13·1° to 13·2°. Timmermans and Martin [105] found b.p. 138·4°/760 mm and f.p. 13·35°.

Hemimellitene (1 : 2 : 3-*Trimethylbenzene*).

Commercial pure 4-*m*-xylidine was converted into the formyl derivative, which was crystallized to constant m.p. 166° to 167°. Hydrolysis, followed by a diazo-reaction, gave 4-iodo-*m*-xylene. The Grignard reagent from the latter reacted vigorously with methyl sulphate. The product was worked-up on normal lines and gave hemimellitene, b.p. 174° to 176°/758 mm uncorr, n_D^{20} 1·5128.

Auwers,[108] who prepared the hydrocarbon by a Fittig reaction, found b.p. 175·5°/744 mm, $n_D^{19·55}$ 1·513. Mair [109] gives b.p. 176·1°.

Mesitylene (1 : 3 : 5-*Trimethylbenzene*).

Pure 2-bromomesitylene, f.p. +0·8° corr, was converted into the Grignard reagent, which was treated with ice and dilute acid. Fractionation of the hydrocarbon–ether layer gave mesitylene, b.p. 165·8° to 166·0°/761 mm corr, n_D^{20} 1·4991.

Mair [109] records b.p. 164·6° and n_D^{20} 1·4991.

pseudo*Cumene* (1 : 2 : 4-*Trimethylbenzene*).

The method of von Braun and Nelles [110] was used, and gave a product b.p. 168·7° to 171·6°/764 mm corr, n_D^{20} 1·5051. Smith and Cass [111] found n_D^{20} 1·5048, while Mair [109] records b.p. 169·18°.

1-*Methyl*-2-*ethylbenzene.*

The Fittig reaction between *o*-iodotoluene, methyl iodide, and sodium gave a hydrocarbon, b.p. 163·5° to 164·5°/760 mm corr, n_D^{20} 1·5040.

Auwers,[108] using the same method, found b.p. 164° to 165° and n_D^{20} 1·504.

1-*Methyl*-3-*ethylbenzene.*

Pure *m*-toluidine was converted into *m*-tolunitrile by the diazo-method. Interaction of the nitrile with 2 mol of methyl magnesium iodide gave a 65 per cent yield of *m*-methylacetophenone, b.p. 110°/16 mm. Clemmensen reduction of this ketone [108] gave 1-methyl-3-ethylbenzene, b.p. 160·5° to 162·5°/759 mm corr. Auwers found b.p. 161·5° to 162·5°.

1-*Methyl*-4-*ethylbenzene.*

This compound was prepared by the Clemmensen reduction of pure *p*-methylacetophenone. It had b.p. 160·5°/747 mm corr and n_D^{20} 1·4959.

Auwers,[108] who used the same method, gave b.p. 161° to 162° and n_D^{20} 1·496.

n-*Propylbenzene.*

The most obvious method for the synthesis of this hydrocarbon was to reduce propiophenone by Clemmensen's method, but this proved unsatisfactory, the product containing unsaturated material, a fact suggesting that isomerization might also be suspected.

γ-Phenylpropyl alcohol, obtained in a very pure state by the Bouveault reduction of ethyl β-phenylpropionate, was converted into the bromide by means of phosphorus tribromide. The bromide, b.p. 106° to 107°/10 mm, was allowed to react with excess of magnesium in ether, the reaction being completed by boiling under reflux. Normal working up after treatment with water and dilute acid gave a mixture of *n*-propylbenzene, allylbenzene, and diphenylhexane. This was hydrogenated in glacial acetic acid (platinum oxide) and then fractionated. The *n*-propylbenzene had b.p. 160·5° to 161·3°/760 mm corr, n_D^{20} 1·4921.

Auwers [108] gave b.p. 158° to 159° and n_D^{20} 1·492.

m-*Cymene* (1-*Methyl*-3-iso*propylbenzene*).

Commercial pure *m*-toluic acid was converted into the acid chloride, b.p. 92° to 93°/9 mm, and thence into the amide, which after crystallization from benzene and from carbon tetrachloride melted at 95° to 96°. The acid obtained by hydrolysis of the amide was converted into the methyl ester, and the latter treated with methyl magnesium iodide.[108] The resulting carbinol was dehydrated with boiling acetic anhydride, and the unsaturated hydrocarbon reduced with sodium and alcohol (Auwers). The *m*-cymene obtained had b.p. 172°/752 mm, n_D^{20} 1·4935.

Richter and Wolff [112] found b.p. 175·6° to 175·8° and n_D^{20} 1·4920.

n-*Butylbenzene.*

To small slices of sodium, covered with 150 cc of pure ether, was added a mixture of 176 g of pure bromobenzene and 176 g of *n*-butyl bromide, addition being adjusted so as to keep the steady reaction going. Normal working-up of the finished reaction gave *n*-butylbenzene, b.p. 184·8° to 185·2°/782 mm uncorr, n_D^{20} 1·4901.

Evans [90] found b.p. 182·1° to 183·1°, n_D^{20} 1·4880.

iso*Butylbenzene.*

Owing to the uncertainty in the literature as to the physical properties of this hydrocarbon, it was prepared by six different methods :—

Method 1. Addition of benzaldehyde (1 mol) to 1·1 mol of ethereal *iso*propyl magnesium bromide gave a 20 per cent yield of phenyl*iso*propylcarbinol. When 3 mol of the Grignard reagent were used, the yield of carbinol became 92 per cent, b.p. 108° to 114°/16 mm. The carbinol was similarly prepared by Grignard,[112a] who found b.p. 112° to 113°/15 mm. The carbinol was converted into the corresponding bromide by the action of phosphorus tribromide (2/3 mol), starting at 0° and finishing at 100°. The bromide, b.p. 117° to 118°/15 mm, was obtained in 55 per cent yield. The bromide was allowed to react with excess of magnesium in ether, the process being completed by boiling under reflux for 30 min. The mixture was cooled, treated with ice and dilute acid, and the whole filtered to remove the solid which had separated. The dried ether solution was distilled and gave 10 cc b.p. 160° to 175°. The distillation residue became solid on cooling. It was mixed with the first solid and crystallized from alcohol, in which it was sparingly soluble, even in the warm. Analysis showed it to be αβ-diphenyl-αβ-di-*iso*propylethane (Found : C, 90·6; H, 9·7. $C_{20}H_{26}$ requires C, 90·2; H, 9·8 per cent).

The distillate (10 cc) was slightly unsaturated and was hydrogenated (glacial acetic acid–platinum oxide). The fractionated hydrocarbon resulting had b.p. 171° to 172°/760 mm uncorr.

Method 2. Pure commercial *iso*butyric acid was fractionated and converted into the chloride by the method of Smith and Lewcock.[113] The chloride (1 mol) was condensed with excess of benzene in presence of 1 mol of aluminium chloride, and gave a 51 per cent yield of *iso*butyrophenone, b.p. 218°/765 mm.[114]

Clemmensen reduction of the ketone gave a hydrocarbon which, after several distillations over sodium, had b.p. 176° to 184°. It contained unsaturated material and was therefore hydrogenated (acetic acid–platinum oxide). It then had b.p. 172° to 180°, mainly 173° to 175°, and further refractionation gave *iso*butylbenzene, b.p. 173° to 174°/782 mm uncorr, n_D^{20} 1·4924.

Method 3. A mixture of 176 g of bromobenzene (1 mol) and 176 g of *iso*butyl bromide (1 mol) was gradually added to 69 g (3 atoms) of sodium in fine slices covered with ether. A steady reaction set in, and was maintained by addition of the bromides. After leaving overnight, the mixture was filtered, and the solid extracted with light petroleum (b.p. 60° to 80°). The combined organic solutions were distilled until the vapour reached 120°, and then steam distilled. Much diphenyl was in evidence. Repeated fractionation over sodium gave about 3 cc of liquid having the approximate b.p. (167° to 169°) of *iso*butylbenzene. It had n_D^{20} 1·4865.

Riess [115] claimed the above as a method for obtaining *iso*butylbenzene. In fact, in our hands, the two bromides appeared to react independently, the main products being diphenyl and di-*iso*butyl, together with unsaturated compounds.

Method 4. Benzyldimethylcarbinol was obtained in 86 to 91 per cent yield, b.p. 96°/10 mm or 110°/17 mm, by the interaction of acetone and 1 mol of benzyl magnesium chloride in ether.[116] The carbinol was

dehydrated by heating it with iodine, several repetitions being necessary. The unsaturated hydrocarbon after being shaken with alkali to remove iodine had b.p. 180° to 182°/750 mm (Grignard [117] dehydrated with acetic anhydride and obtained the unsaturated hydrocarbon with b.p. 183° to 185°/748 mm). It was hydrogenated (acetic acid–platinum oxide) and gave *iso*butylbenzene which, after several distillations from sodium, had b.p. 169° to 170°/760 mm uncorr, n_D^{20} 1·4825.

Repetition of this method led to *iso*butylbenzene with b.p.

(*a*) 171·8° to 172·2°/749 mm uncorr and n_D^{20} 1·4860.
(*b*) 172·2° to 172·4°/749 mm uncorr and n_D^{20} 1·4860.
(*c*) 172·4° to 172·5°/749 mm uncorr and n_D^{20} 1·4863.

Method 5. Benzyldimethylcarbinol was converted into the chloride, b.p. 65°/10 mm, by means of hydrogen chloride, and then heated with pyridine.[118] The unsaturated hydrocarbon had b.p. 180° to 183°/760 mm and after hydrogenation (acetic acid–platinum oxide) gave *iso*butylbenzene, b.p. 172·2° to 172·6°/760 mm uncorr, n_D^{20} 1·4871.

Method 6. Benzyl chloride (1 mol) was added to 1·5 mol of ethereal *iso*propyl magnesium bromide, the mixture subsequently being boiled under reflux for a day. Treatment with ice and dilute acid, and normal working-up gave *iso*butylbenzene with b.p. 169·8° to 170·0°/747 mm uncorr, n_D^{20} 1·4872.

Pure iso*butylbenzene.*

The best material from all the above preparations was combined and sulphonated. The barium sulphonate was crystallized from water and then distilled in superheated steam in presence of phosphoric acid. The pure *iso*butylbenzene had b.p. 172·3°/758 mm corr, n_D^{20} 1·4870.

tert-*Butylbenzene.*

The hydrocarbon was prepared by the method of Verley [119] and fractionated over sodium. It then had b.p. 169°/760 mm uncorr, n_D^{20} 1·4932.

McKenna and Sowa [120] gave b.p. 167·0°.

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