311. *Some Quantitative Aspects of Asymmetric Transformation.*

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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.

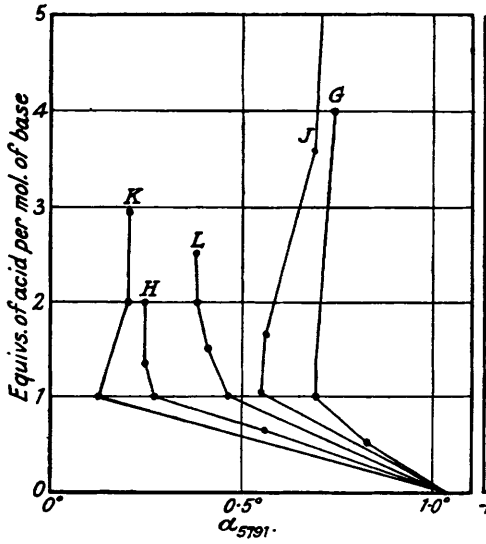


FIG. 2.

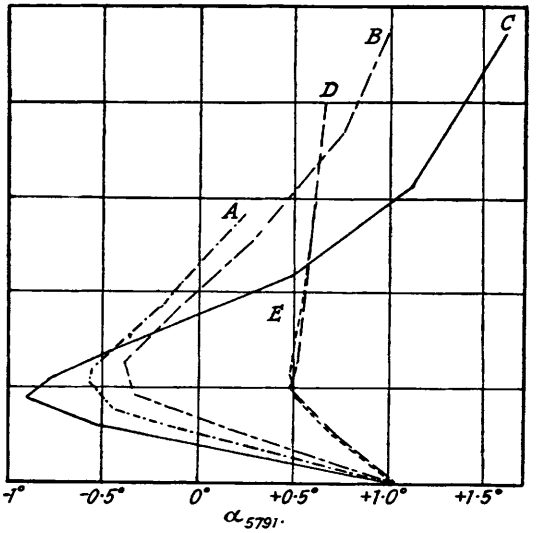


FIG. 3.

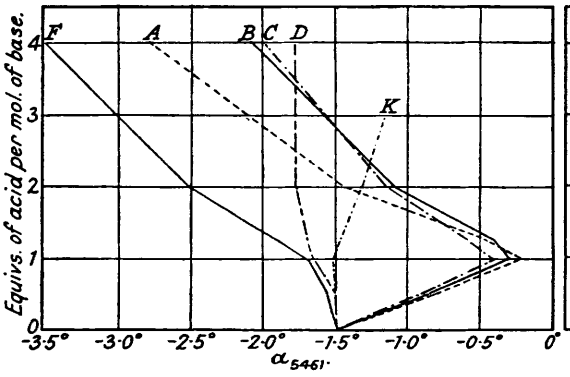
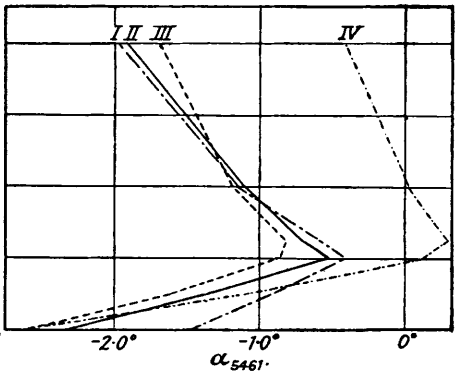


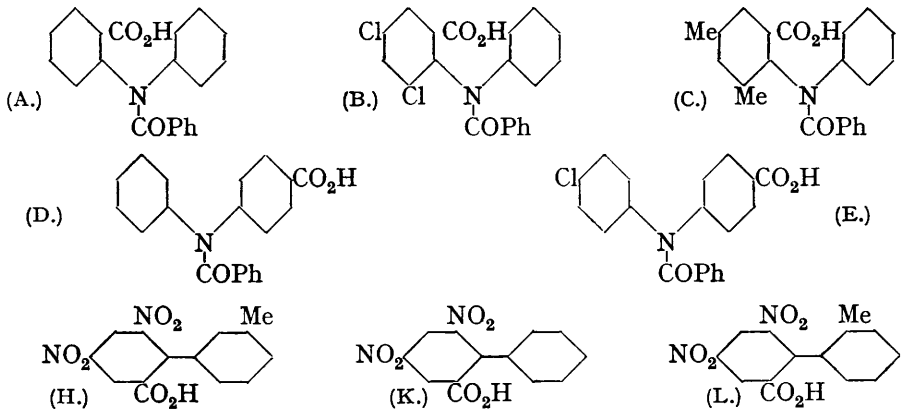
FIG. 4.



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.

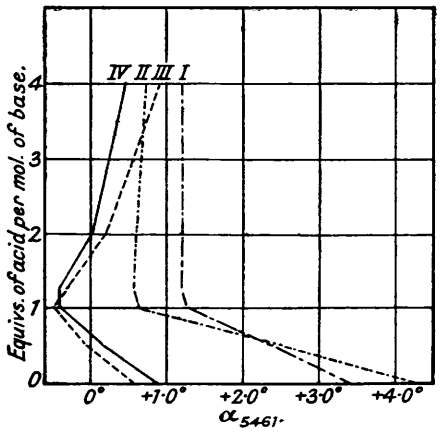
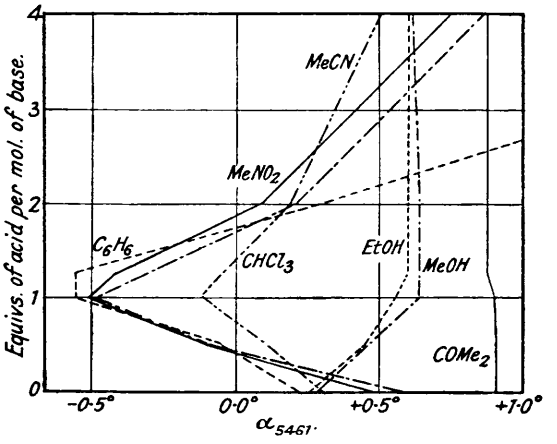


FIG. 6.



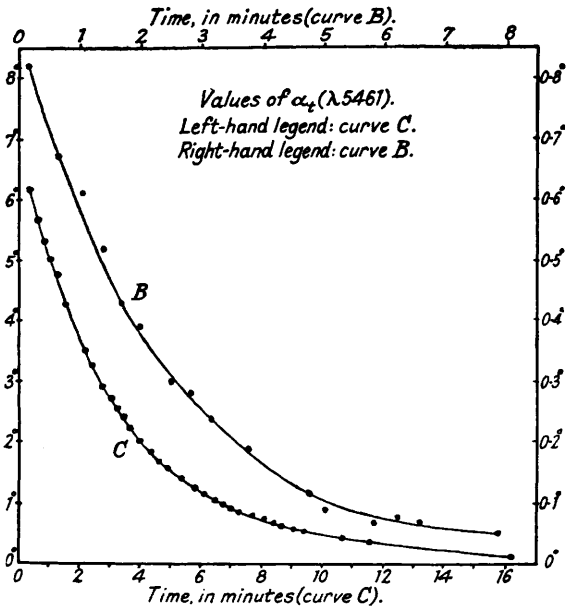
change of rotation with excess of acid, and only I and II in Fig. 5 do not. The general conclusion, therefore, was that the assumption of asymmetric transformation was worth pursuing, curves I and II in Fig. 5 being regarded as exceptional.

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
$\alpha_t = \alpha_\infty - \alpha$	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	∞
$\alpha_t = \alpha_\infty - \alpha$	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 $k = 0{\cdot}18$ (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 $-4{\cdot}03°$ to $+2{\cdot}15°$ 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
$\alpha_t = \alpha - \alpha_\infty$	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
$\alpha_t = \alpha - \alpha_\infty$	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	
$\alpha_t = \alpha - \alpha_\infty$	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	∞	
$\alpha_t = \alpha - \alpha_\infty$	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 $k = 0{\cdot}125$ (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.

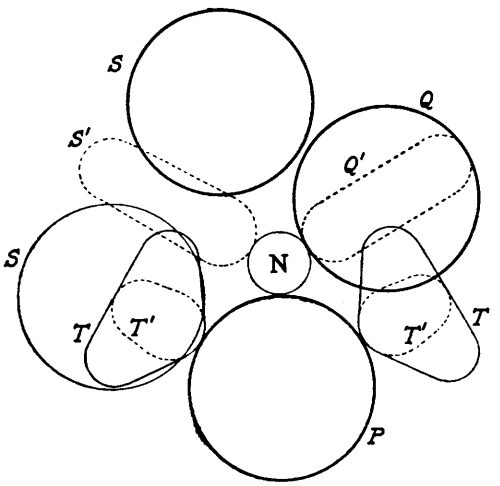


FIG. 9.

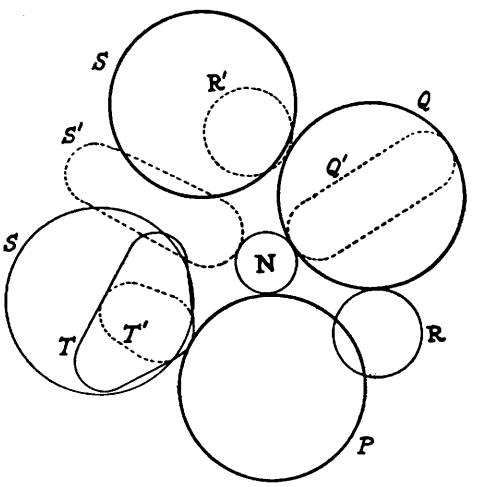


Fig. 8 shows that with P originally in the plane of the paper, Q', S', and T' can be placed in their positions of minimum obstruction without mutual interference, and if P alone is rotated, T' can pass Q' and S'. With Q, S, and T in their positions of maximum obstruction there is clearly considerable 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.

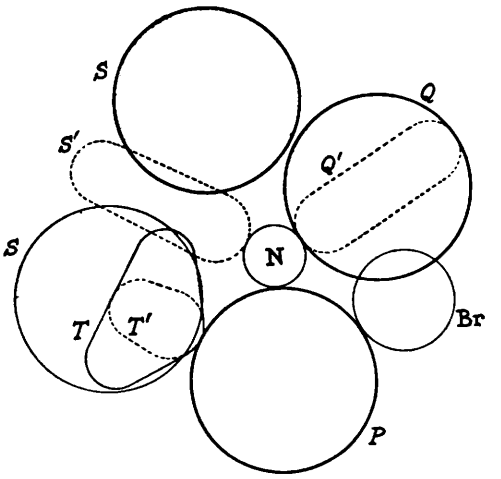
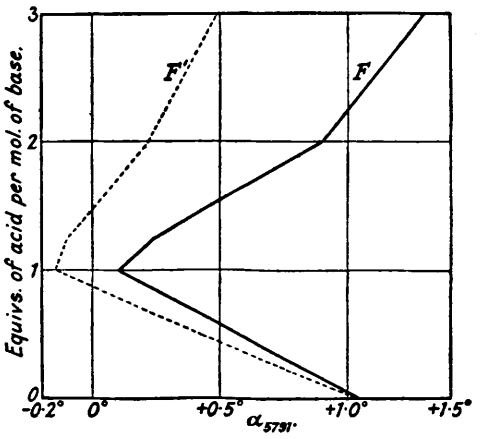
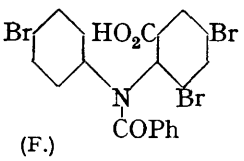


FIG. 11.



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 2½ 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° 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°. 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.

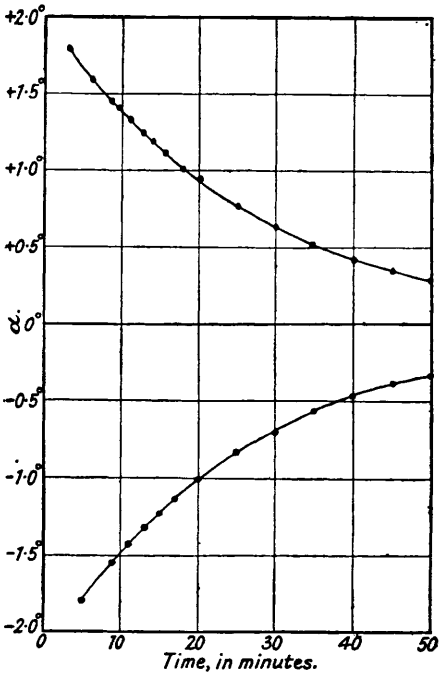
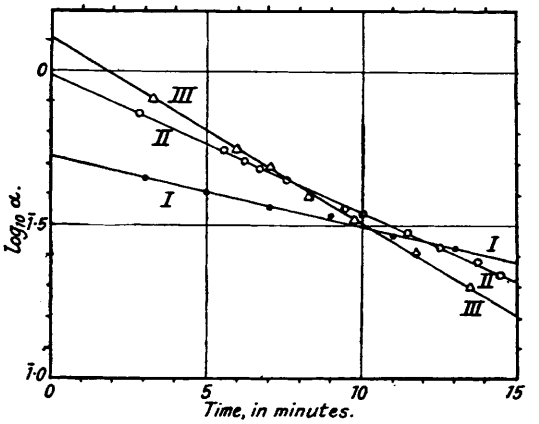


FIG. 13.



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.

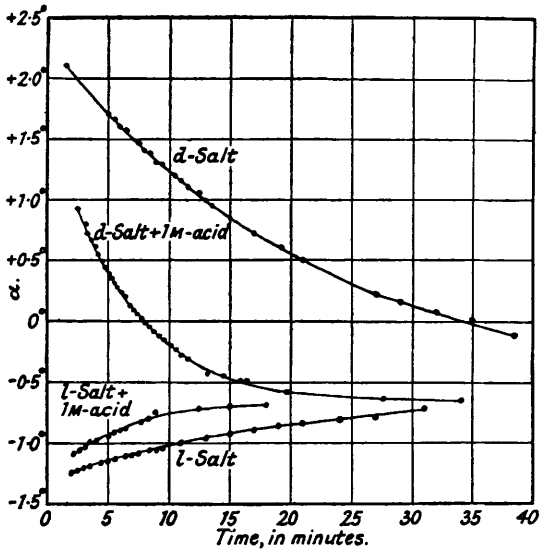
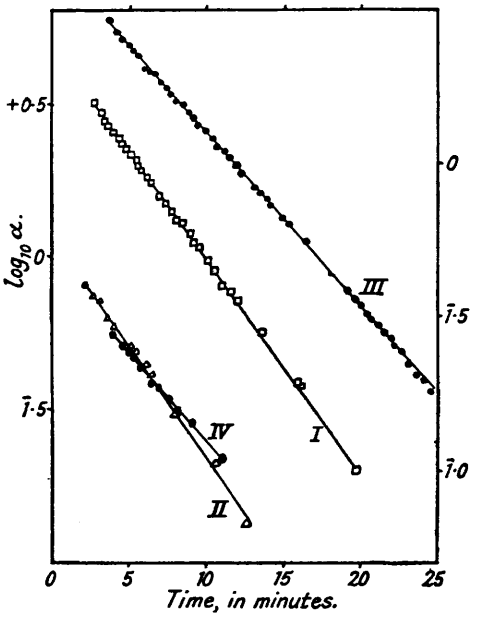


FIG. 15.



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, $R_3N \ldots H \ldots A$. 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

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

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

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

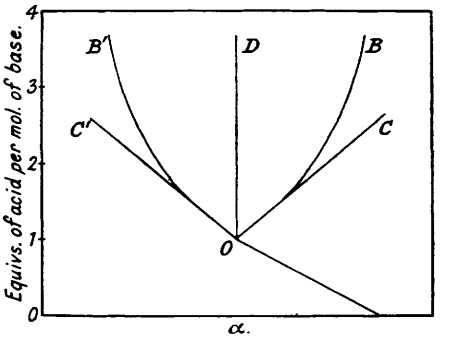
The observed rotation is the sum of the five partial rotations corresponding with $\overset{+}{S}$, $\bar{S}$, $\overset{+}{A}$, $\bar{A}$, and B.

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 possiblity 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 → *l*-HA; k_A^- for the reaction *l*-HA → *d*-HA; k_S^+ for the reaction R_3N,*d*-HA → R_3N,*l*-HA; and k_S^- for the reaction R_3N,*l*-HA → 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.*,

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

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

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

Let $\bar{S}_0$ be the concentration of R_3N,*l*-HA at zero time, *i.e.*, $\dot{S} = \bar{S}_0 - \bar{S}$. 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

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

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

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

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 $(t - 0·5)$, t, and $(t + 0·5)$ 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.	α_t.	k.	Time after 3·7 mins.	α_t.	k.	Time after 3·7 mins.	α_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 $k = 0·0562$.

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
α_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 $k = 0·0574$.

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

Time after 4·1 mins.	α_t.	k.	Time after 4·1 mins.	α_t.	k.	Time after 4·1 mins.	α_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 $k = 0·0541$.

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