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

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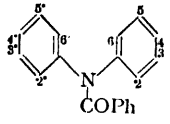
Suitably substituted *N*-benzoyldiphenylamine-2-carboxylic acids show labile optical activity, although scale models demonstrate that rotation about the three N–C bonds *can* take place when the movement of the three groups attached to nitrogen is synchronised. The relative optical stabilities of fourteen 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.

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.

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

FIG. 1.

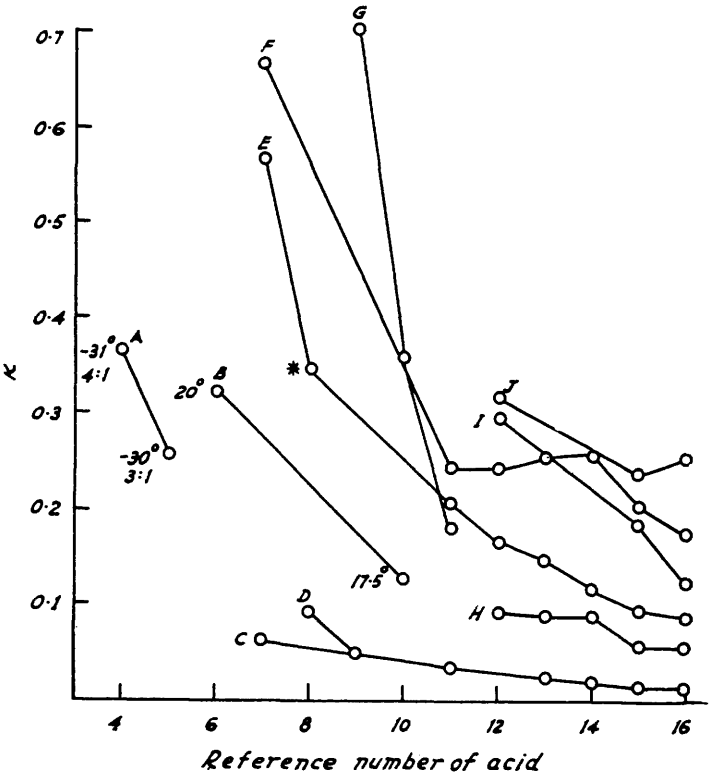


FIG. 1. *A, With* (+)-*nor-ψ-ephedrine*, $CHCl_3$.
B, With (+)-*nor-ψ-ephedrine*, $CHCl_3$, 3 : 1.
C, With quinidine, X, 1 : 1, 20°.
D, With cinchonidine, X, 1 : 1, 15°.
E, Racemisation of acid, X, 20°.
F, With quinidine, X, 2 : 1, 20°.
G, Racemisation of acid, $CHCl_3$.
H, With brucine, X, 1 : 1, 20°.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

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.

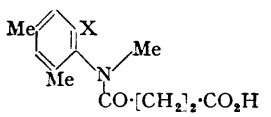
In every case in which an active acid was obtained it came from an active alkaloidal salt which was the product, not of resolution, but of second-order asymmetric transformation.

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).

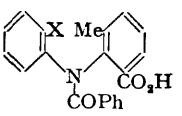
Scale models (constructed without consideration of the van der Waals envelopes

show that in even the most hindered molecules, *e.g.*, (14) and (16), rotation about all three 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.

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.

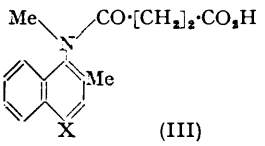


(I)

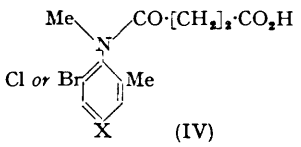


(II)

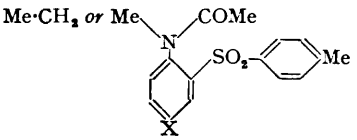
Adams found in all three pairs of compounds represented by (III) and (IV) a greater optical stability when X = H than when X = Cl; similarly Buchanan and Graham (*J.*, 1950, 500) in series (V) found the order X = OMe > Me > Cl > Br. We find in series (VI) a reversed order of stabilities: X = Br > Cl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



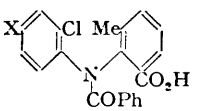
(III)



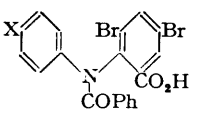
(IV)



(V)

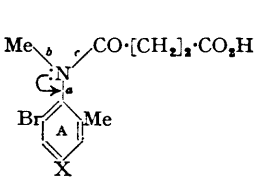


(VI)

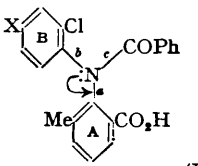


(VII)

(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

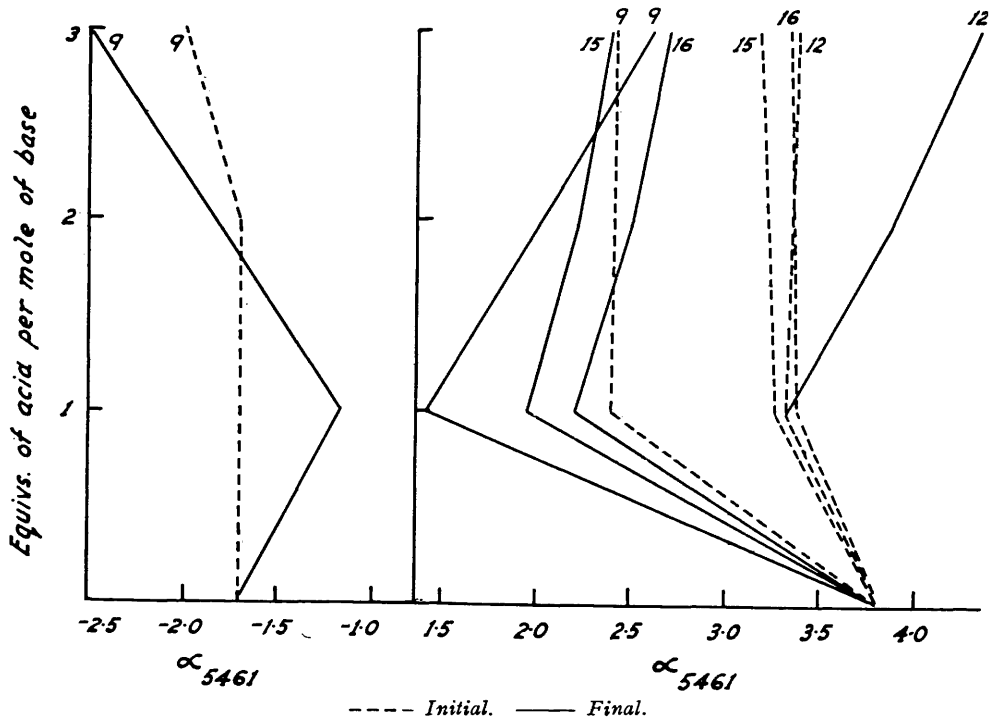
and containing bond *a*. A methyl group, with its inductive effect in the opposite sense, in position X of (IX) will accelerate racemisation by releasing electrons for conjugation with ring A. It is relevant that the order of basic strengths of *p*-substituted anilines is Me > H > Cl > Br (Dippy, *Chem. 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*-benzoyl-2′ : 4′ : 6 : 6′-tetramethyldiphenylamine-2-carboxylic acid and *N*-benzoyl-2-bromo-6-methoxy-2′ : 6′-dimethyldiphenylamine-4-carboxylic acid

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



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 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.

FIG. 4.

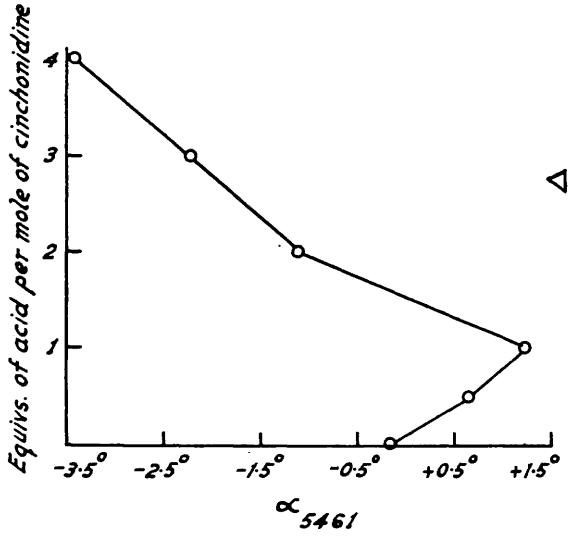


FIG. 5.

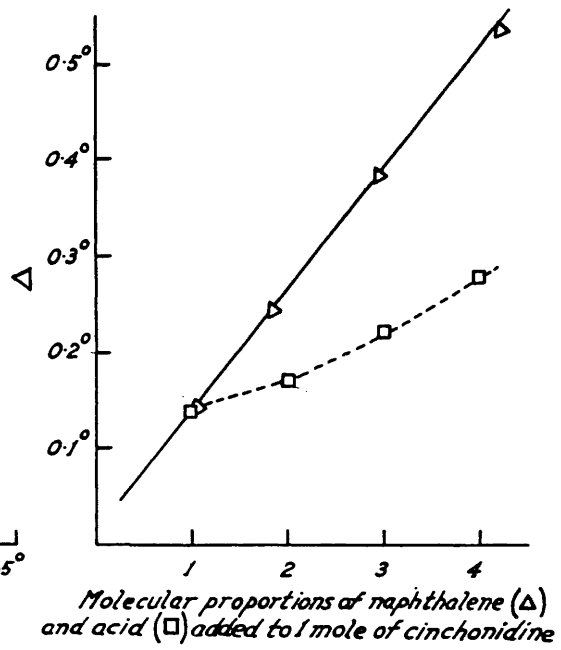


FIG. 4. *Polarimetric measurements in N-benzoyl-2′ : 4′-dimethyldiphenylamine-2-carboxylic acid added to cinchonidine in bromoform.*
(*l* = 2; 0·1000 g. of cinchonidine dissolved in 15 c.c. of $CHBr_3$.)

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.)

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 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-*phenylbenzimidoate* 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-*dibromodiphenylamine*-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. 153) (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, thermostatically 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 $[\alpha]_{5461}^{20}$ +301·1° in solvent X (*c*, 0·8000).

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

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.

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°).

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.

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 − α_∞)
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

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