

STUDIES OF OPTICALLY LABILE COMPOUNDS.

The author wishes to express his thanks to Professor S. Z. Turner, F.R.S. for his continued help and encouragement, to Drs. D. M. Hall and M. M. Harris for valuable discussions, and to the Department of Scientific and Industrial Research for a Maintenance Allowance.

Thesis presented by WILLIAM GEOFFREY POTTER  
in requirement for the Degree of Doctor of  
Philosophy in The University of London.

---

ProQuest Number: 10097988

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



ProQuest 10097988

Published by ProQuest LLC(2016). Copyright of the Dissertation is held by the Author.

All rights reserved.

This work is protected against unauthorized copying under Title 17, United States Code.  
Microform Edition © ProQuest LLC.

ProQuest LLC  
789 East Eisenhower Parkway  
P.O. Box 1346  
Ann Arbor, MI 48106-1346

The author wishes to express his thanks to Professor E. E. Turner, F.R.S. for his continued help and encouragement, to Drs. D. M. Hall and M. M. Harris for valuable discussion, and to the Department of Scientific and Industrial Research for a Maintenance Allowance.

(b) the effect (steric and inductive) of substituents upon the stereochemical properties.

# CONTENTS.

<u>PART I.</u>	page No.
<u>Preliminary Investigation into Asymmetric Transformation</u>	
Section 1. Introduction, including previous work .....	1
Section 2. Discussion of results.....	13

The object of the work was to investigate some acids of the N-benzoyldiphenylamine series with a view to elucidating:-

PART II  
Effect of Substituents upon Stereochemical Properties  
Section 1. Introduction, including previous work ..... 23  
Section (a) the mechanism of first-order asymmetric transformation, particularly when an excess of ( $\pm$ )-acid was present.

PART III  
Experimental  
(b) the effect (steric and inductive) of substituents upon the stereochemical properties.

Section 1. Discussion of Preparative Methods .....	48
Section 2. Synthetic work and Stereochemical Examinations	54
Section 3. List of New Compounds prepared in this Work ...	135

- | -

C O N T E N T S.

PART I.

PART I.

page  
No.

Preliminary Investigation into Asymmetric Transformation

- Section 1. Introduction, including previous work ..... 1
- Section 2. Discussion of results..... 13

was by Leuchs and Wutke (Ber., 1913, 46, 2420). These workers

found that the addition of brucine to an acetone solution of

(+)-2-b-carboxybenzyl bromide resulted in the formation

PART II

Effect of Substituents upon Stereochemical Properties

- Section 1. Introduction, including previous work ..... 23
- Section 2. Discussion of results ..... 34

base (+)-acid. On reacting the bromide with

salt, an acid was obtained, which readily racemized. Thus

the (+)-Leuchs acid PART III to have been activated by the

Experimental

- Section 1. Discussion of Preparative Methods ..... 48
- Section 2. Synthetic work and Stereochemical Examinations 54
- Section 3. List of New Compounds prepared in this Work ...135

having a negative rotation), but could not isolate an active

acid. In order to correlate this result with those of Read

and McKath (J., 1927, 427, 427a) and those of Pfeiffer

(Ber., 1931, 64, 2657; 1932, 65, 560; 1933, 66, 415). Fahn

suggested the use of the terms "asymmetric transformation of

the first order and asymmetric transformation of the second

order.<sup>2</sup>

It was not however until 1942, when Jaxison and Turner (J., 1942, 437) gave a clear definition of the terms  
PART I.

PRELIMINARY INVESTIGATION INTO ASYMMETRIC TRANSFORMATIONS.

Section 1. INTRODUCTION, INCLUDING PREVIOUS WORK.

The first use of the term asymmetric transformation was by Leuchs and Wutke (Ber., 1913, 46, 2420). These workers found that the addition of brucine to an acetone solution of (+)-2-o-carboxybenzyl- $\alpha$ -hydrindone resulted in the formation of solid base (+)-acid, and in such an amount that nearly all of the base (-)-acid in solution had been transformed to solid base (+)-acid. On removing the brucine from the precipitated salt, an acid was obtained, which readily racemised. Thus the (+)-Leuchs acid was said to have been activated by the brucine.

Kuhn (Ber. 1932, 65, 49) extended ideas upon the topic. He observed that the quinine salt of 4:4'-dinitrodiphenic acid was dextrorotatory in solution and one entity, (quinine having a negative rotation), but could not isolate an active acid. In order to correlate this result with those of Read and McMath (J., 1925, 127, 1572,) and those of Pfeiffer (Ber., 1931, 64, 2667; 1932, 65, 560; 1933, 66, 415), Kuhn suggested the use of the terms "Asymmetric transformation of the first order and asymmetric transformation of the second order."

It was not however until 1942, when Jamison and Turner (J., 1942, 437) gave a clear definition of the terms used, that the position was clarified. They altered the basis of the classification of Kuhn and stated:-

"A configuratively unstable substance in solution (or liquid state) consists of equal quantities of the (+) and (-) form. On addition of a second (but optically stable) (+) or (-) compound which combines with the first substance to form a pair of diastereoisomerides, an equilibrium is set up in which one diastereoisomeride predominates to a greater or lesser extent. The setting up of this equilibrium we have called a first order transformation, and our definition agrees with Kuhn's (Ber., 1932, 65, 49) in so far as it recognises the necessity of the second optically stable substance for the retention of optical activity in the configuratively unstable compound."

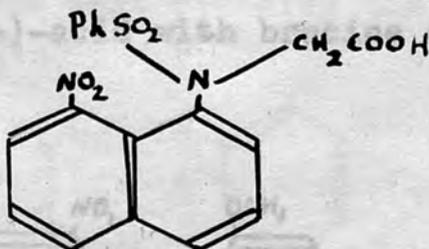
".....Second order transformation in any case in which interconversion of diastereoisomerides is possible (first order transformation) and crystallisation can be induced, may be expected to be almost quantitatively realisable and to give one diastereoisomeride in an optically pure condition. That the optical activity of the configuratively unstable compound, when this is removed from combination with the optically stable substance should be detectable by a physical method. The optical activity of this acid was measured and the (+) acid from acetone in 98% yield. The optical activity of this salt in methyl alcohol gave a 75% yield of the base (+)-acid. Decomposition of the diastereoisomeric salts gave active acids."

measurement, is immaterial for the definition of terms, although it was mainly on this arbitrary point that Kuhn based his distinction between the two types of transformation."

Hence first order asymmetric transformation is concerned with the setting up of an equilibrium in solution, whilst a second order transformation requires the appearance of a second phase.

Since Pope and Peachey's recorded observations (Proc. Chem. Soc. 1900, 16, 42, 116) upon the crystallisation of methylethyl-n-propyltin (+)-camphorsulphonate from water as the (+) (+) salt only, many other examples of second order transformation have been found. Compounds which owe their asymmetry to restricted rotation within the molecule have provided much experimental evidence of this phenomenon.

The first compound of this type to exhibit asymmetric transformations of the first and second orders was N-benzenesulphonyl-8-nitro-1-naphthylglycine (Mills and Elliott, J., 1928, 1291).

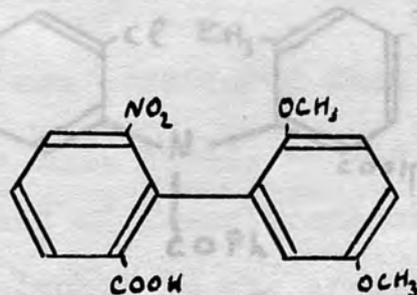


The brucine salt of this acid deposited crystals of the base (-)-acid from acetone in 98% yield, and a solution of this salt in methyl alcohol gave a 75% yield of the base (+)-acid. Decomposition of the diastereoisomeric salts gave active acids.

Similarly Corbellini and Angeletti (Atti R. Accad. Lincei, 1932, 15, 968), prepared 2-( $\alpha$ -hydroxyisopropyl)diphenyl-2-carboxylic acid, and carried out a second order transformation with brucine in ethyl alcohol, the base(-)-acid salt being obtained. Jamison and Turner (J., 1942, 437), re-examined the acid, and gave the first example of the attainment of first and second order asymmetric transformations with one pair of diastereoisomeric salts in the same solvent. These results are in accord with the van't Hoff-Dimroth rule, which predicts that "the stable form is the more soluble" of the salts.

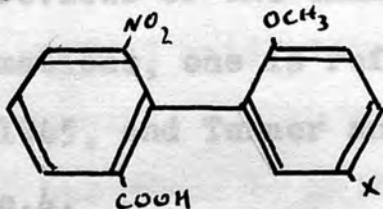
The apparently simple stereochemical features of diphenyl compounds have led to their extensive use in work on relative optical stability. Hence it is not unexpected to find several examples of first and second order transformations in compounds of this type.

2:5-Dimethoxy-2'-nitrodiphenyl-6'-carboxylic acid was found by Yuan and Adams (J. Amer. Chem. Soc., 1932, 54, 2966) to give the base(-)-acid with brucine and cinchonidine in ethyl alcohol.



gave the brucine(-)-acid salt in high yield from ethyl alcohol-ether solution.

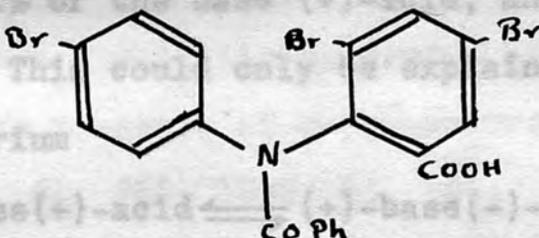
Similarly with



X = CH<sub>3</sub>, Cl, Br, NO<sub>2</sub>.

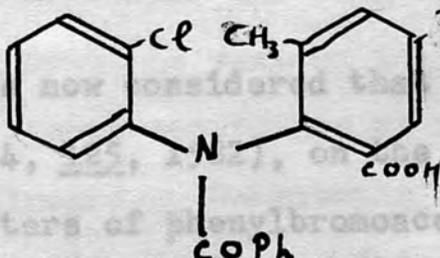
Yuan and Adams (J. Amer. Chem. Soc., 1932, 54, 4434), only one brucine salt was obtained.

A further series of compounds showing optical activity due to restricted rotation in the molecule is that of acids of N-benzoyl diphenylamine. These have been extensively examined by Turner and Harris. Thus N-benzoyl-2:4:4'-tribromodiphenylamine-6-carboxylic acid.



has been made to show first and second order transformations and resolutions, (J., 1938, 1646). A 94% yield of the cinchonidine(+)-acid salt was obtained from acetone solution, decomposition of the salt yielding the active acid.

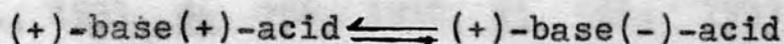
The acid



gave the brucine(-)-acid salt in high yield from ethyl alcohol-ether solution.

For reviews of the examples of first and second order transformations, one is referred to Jamison, Trans. Faraday Soc., 1945, and Turner and Harris, Quart. Reviews, 1947, Vol.I, No.4.

The first recorded example of what was shown later to be a first order asymmetric transformation, was given by Read and McMath in 1925, (J., 1925, 27, 1572). They found that the (+)-hydroxyhydrindamine salts of (+)-chlorobromo methanesulphonic acid in acetone underwent a rotational change, and the resultant equilibrium mixture contained 81% of the base (+)-acid, and 19% of the base (-)-acid. This could only be explained by assuming that the equilibrium



existed in solution, the (+)(+)-salt predominating.

As stated previously, this work, together with that of Pfeiffer (idem, loc. cit.), was correlated by Kuhn with his work on quinine 4:4'-dinitrodiphenate, and led to the terms "asymmetric transformations of the first and second orders".

It is now considered that the work of McKenzie and Smith (J., 1924, 125, 1582), on the mutarotation of (-)-menthyl esters of phenylbromoacetic and phenylchloroacetic acids in ethyl alcohol in the presence of very small amounts of alcoholic potassium hydroxide, fits well with the concept of first order transformations.

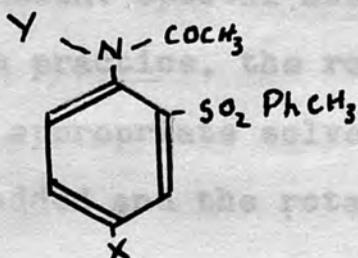
However, the first proof that the mutarotation observed in an optical activation (first order transformation) was due to the formation of an excess of one diastereoisomeride over the other, was given by Mills and Elliott (J., 1928, 1291). On mixing chloroform solutions of equivalent amounts of brucine and N-benzensulphonyl-8-nitro-1-naphthylglycine, a change of rotation of  $0.44^{\circ}$  was observed. To prove that an excess of one form of the salt was present at equilibrium, a similar solution was prepared, and allowed to equilibriate. After removing the brucine, the remaining solution had a positive rotation which changed rapidly to zero at a temperature of  $1.2^{\circ}$ .

When crystallising zinc- $\beta$ -camphorsulphonate from water, in the presence of o-phenanthroline, Pfeiffer and Quehl (Ber., 1931, 64, 266; 1932, 65, 560; 1933, 66, 415) found that the salt  $Zn(phen)_3 \cdot OSO_2C_{10}H_{15}O_7H_2O$  had zero rotation. However, solutions of zinc- $\beta$ -camphorsulphonate changed their rotations by large amounts when 3 mols. of o-phenanthroline were added. The proposed explanation was that the influence of the  $\beta$ -camphorsulphonate ions, caused formation of only one of the possible  $[Zn(phen)_3]^{++}$  enantiomers. Doubt is cast on this, since the ionic nature of the system causes separation of the zinc complex and its activating influence. One example is recorded where both the optically active influence (cinchonine), and the zinc complex being activated,  $[Zn(phen)_3]^{++}$  are both cations. Removal of the cinchonine left an optically inactive zinc salt.

Some recent work by Dwyer and his co-workers (Nature, 1951, 167, 1036; 168, 29), has a definite bearing on this problem. It was shown that a partial resolution of the optically labile compound (+)-  $[\text{Ni}(\text{dipy})_3] \text{I}_2$  could be obtained by the addition of an optically active anion or cation to an aqueous solution of the nickel complex, followed by immediate precipitation with sodium iodide. Such added ions were ammonium-(+)-bromocamphorsulphonate, (-)-quinine hydrogen sulphate and, (+)-  $[\text{Co}(\text{en})_3] \text{Cl}_3$ . A non-ionic species, trisacetylacetonecobalt, has also been used successfully as an activating agent. Dwyer's suggested explanation is that there is preferred interaction of the electric field of the added ion with one form of the ions of the optically labile system, the increased activity coefficient of the ion causing it to be less soluble.

That, in an optical activation, the link between acid and alkaloid need only be of a weak type, was shown by the experimental demonstration of first order asymmetric transformation arising from asymmetric solvent action. Buchanan and Graham (J., 1950, 500), and Glazer, Harris and Turner (J., 1950, 1753) used ethyl (+)-tartrate as solvent and asymmetric influence.

The former works examined chiefly, compounds of the type

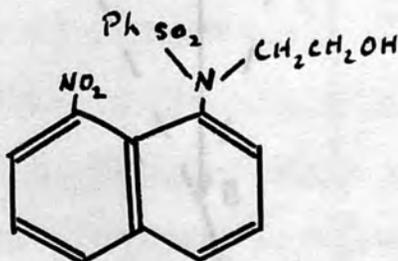


Y = CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>

X = Cl, Br, CH<sub>3</sub>, OCH<sub>3</sub>.

and obtained optical activation in all cases.

Turner and co-workers examined acids and esters of the N-benzoyldiphenylamine series, and showed that they underwent first order transformation with ethyl (+)-tartrate. Further, by this method they gave the first proof of optical activity in the compound

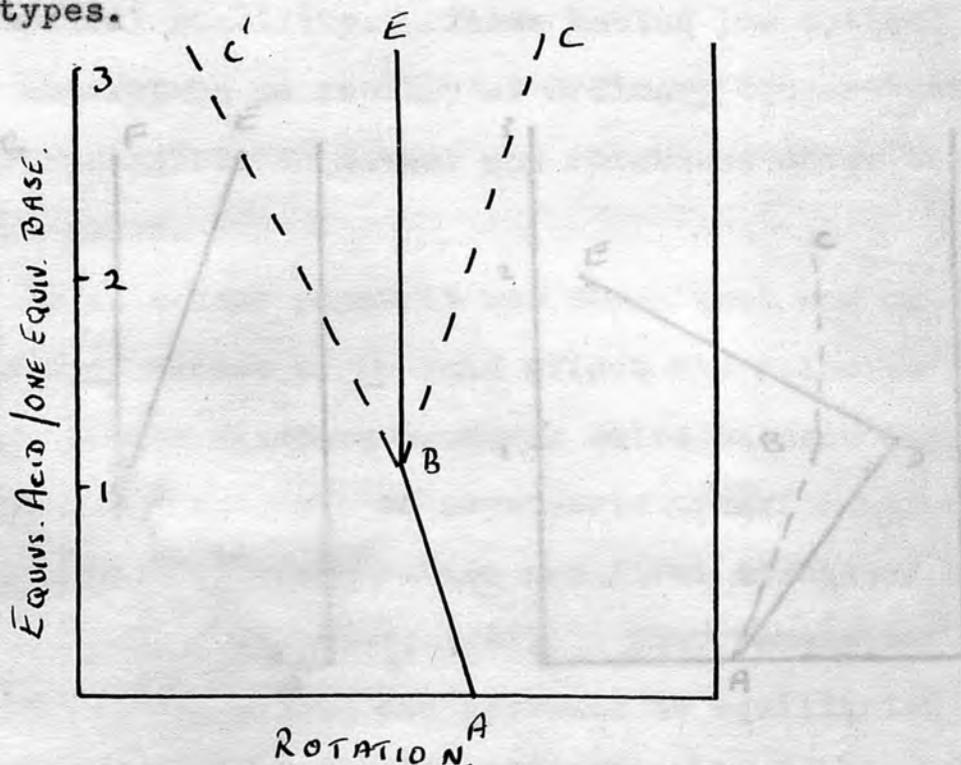


The most intensive attack upon the problems of asymmetric transformations has been made by Turner and Harris in a series of papers (J., 1938, 1646; 1940, 246; 1942, 437). The substances examined were mostly carboxylic acids of appropriately substituted N-benzoyldiphenylamines.

In the first of these papers (1938) it was noted that, working in chloroform, the equilibrium between the two salts of an optically stable optically active base and an optically unstable acid was disturbed by adding an excess of the free (+)-acid. This excess of racemic acid either accentuated or reversed the amount of change occurring when the acid:base ratio was 1:1. From this observation, an "addition curve" technique was evolved for the detection of very transient optical activity.

In practice, the rotation of the optically active base in the appropriate solvent was taken, the equivalents of  $\pm$  acid added and the rotation measured after each addition.

From these results a graph of rotation against equivalents of  $\pm$  acid added, was plotted. The addition curves fell into two types.

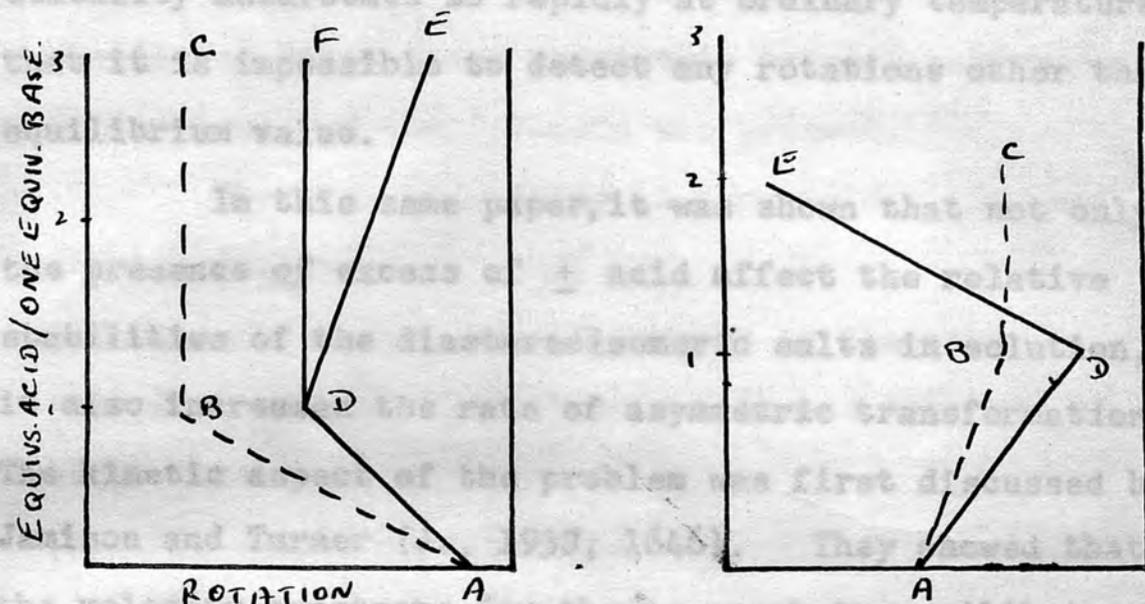


The first type included systems in which the addition of excess  $\pm$  acid above the 1:1 ratio led to no change in rotation. Acids found to fall into this category were structurally symmetrical ones or acids showing very high optical stability. These results were in agreement with the idea that no equilibrium is set up in solution.

The second type of curve was exhibited by acids of low optical stability. Thus addition of  $\pm$  acid in excess of the 1:1 ratio caused a change in rotation along the line BC or BC'. This indicated that the added acid had disturbed the equilibrium between the diastereoisomeric salts.

The "addition curve" technique was further developed (loc. cit. 1942) by studying acids of moderate optical

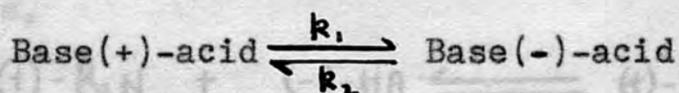
stability which permitted curves to be constructed of the initial as well as the final rotations. obtained with acids of moderate optical stability. These having low optical stability mutarotate so rapidly at ordinary temperatures



Thus above, ABC represents the initial rotation of the system, being obtained by extrapolation of the plot of  $\log (\alpha_t - \alpha_\infty)$  against  $t$ . ADE is the curve of the final readings. In some cases (the activation of N-Benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic acid with cinchonine in chloroform-ethyl alcohol), activation did not occur until an excess of  $\pm$  acid was present. Thus the curve ADF would be the initial rotation curve and ADE the "final" curve. An even more interesting phenomenon is also shown. Here at acid:base ratio 1:1, a mutarotation from a more to a less negative value was obtained. On increasing the amount of acid present, the direction of the mutarotation was changed and the rotation went from a less to a more negative value.

It must be stressed that these curves containing both initial and final rotations were obtained with acids of moderate optical stability. Those having low optical stability mutarotate so rapidly at ordinary temperatures that it is impossible to detect any rotations other than the equilibrium value.

In this same paper, it was shown that not only did the presence of excess of  $\pm$  acid affect the relative stabilities of the diastereoisomeric salts in solution, but it also increased the rate of asymmetric transformation. The kinetic aspect of the problem was first discussed by Jamison and Turner (J., 1938, 1646). They showed that the velocity constants for the approach to equilibrium for the diastereoisomerides considered (optically labile acids and optically stable base), in chloroform solution, were slightly different.



This aspect was further examined in 1940, and it was noted that all mutarotational changes were kinetically of the first order.

Hence in a non hydroxylic solvent there are two possibilities for the interconversion of the salts. Route ① requires that the salts in solution dissociate into acid and base. Route ② does not require this. If ① be correct then what is measured kinetically is the racemisation rate of the acid in the presence of  $R_2N$ . If ② is true, then the rate of mutarotation of the salt is measured.

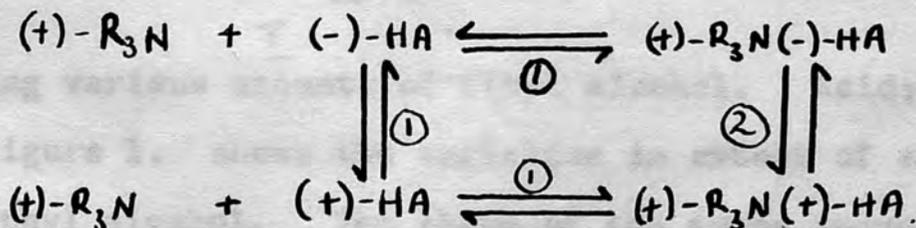
SECTION 2. DISCUSSION OF RESULTS.

The object of the work was to investigate the mechanism of first order asymmetric transformation particularly when an excess of the (+)-acid was present.

The problem arising is threefold. By what mechanism does:-

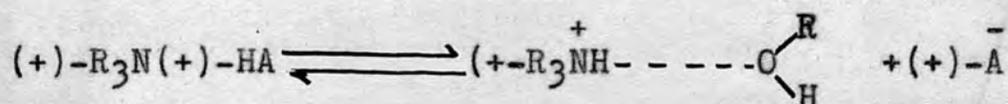
- (a) One diastereoisomeride change to the other
- (b) An excess of the (+)-acid increase the rate of equilibration.
- (c) The excess of acid alter the relative stabilities of the diastereoisomeric salts?

Considering the case where only equimolecular amounts of acid and base are present, the equilibria set up could be as follows,



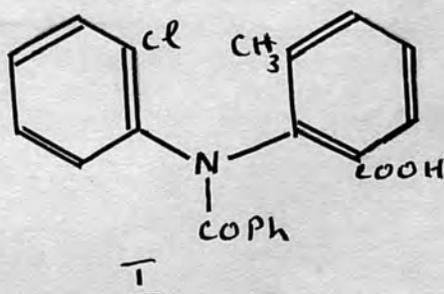
Hence in a non hydroxylic solvent there are two possibilities for the interconversion of the salts. Route ① requires that the salts in solution dissociate into acid and base. Route ② does not require this. If ① be correct then what is measured kinetically is the racemisation rate of the acid in the presence of R<sub>3</sub>N. If ② is true, then the rate of mutarotation of the salt is measured.

In the case where the solvent contains some hydroxylic solvent such as ethyl alcohol, the possibility of the salt dissociating into ions, arises, i.e.



Hence in a solvent such as Solvent 'X' (chloroform containing 2.5% ethyl alcohol by volume) it is conceivable that, if dissociation occurs the acid and the acid ion would both be formed and racemise.

It is advantageous to discuss at this stage the results of measurements of the first order asymmetric transformation of N-benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic acid (I) with quinidine in chloroform



containing various amounts of ethyl alcohol. Acid:base ratio 2:1. Figure 1. shows the variation in extent of activation with % ethyl alcohol. The shape of the curve suggests that two mechanisms are operating, one on the left hand side of the maximum, the other on the right hand side. It also appears that the optimum conditions apply at approx. 6% ethyl alcohol by volume. The dual mechanism idea is supported by the abrupt change in the velocity of the equilibration on passing through the maximum in figure 1. The kinetic data are also plotted in this figure.

THE ACTIVATION OF THE (±)-CHLORO-METHYL ACID BY QUINIDINE  
 IN CHLOROFORM CONTAINING VARIOUS AMOUNTS OF ETHYL  
 ALCOHOL. (ACID:BASE RATIO 2:1).

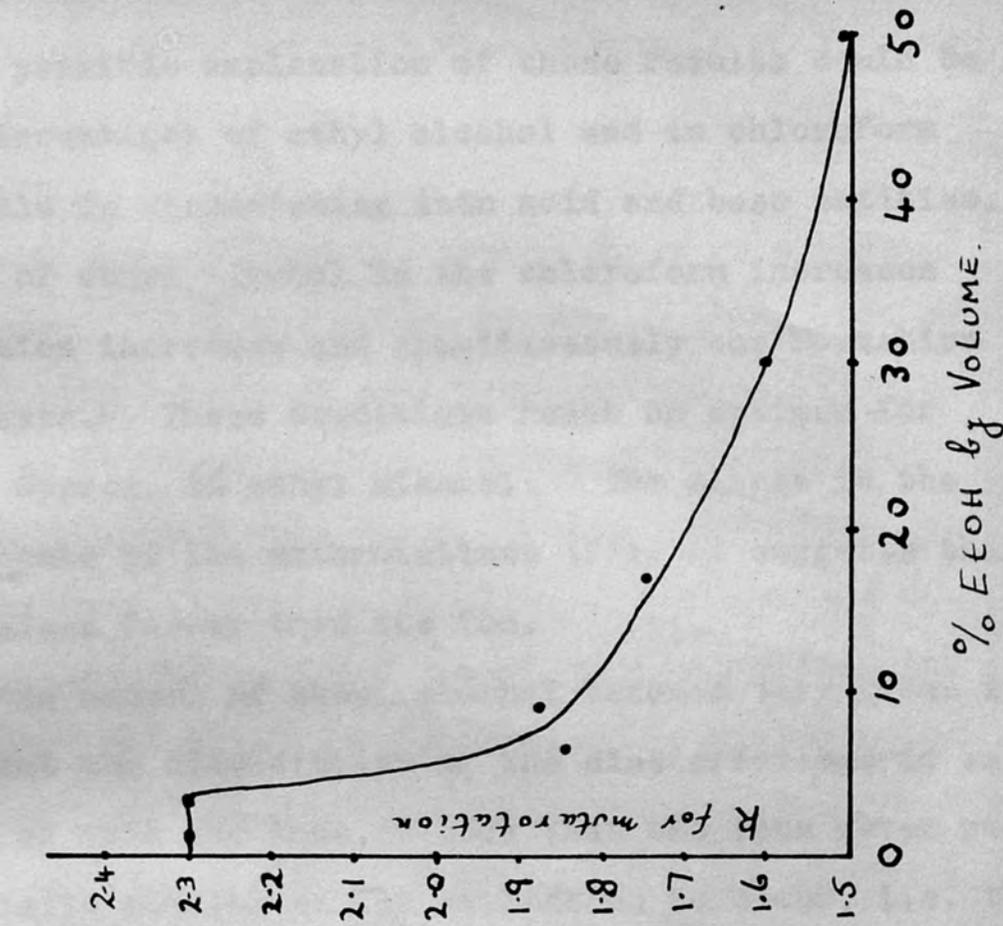
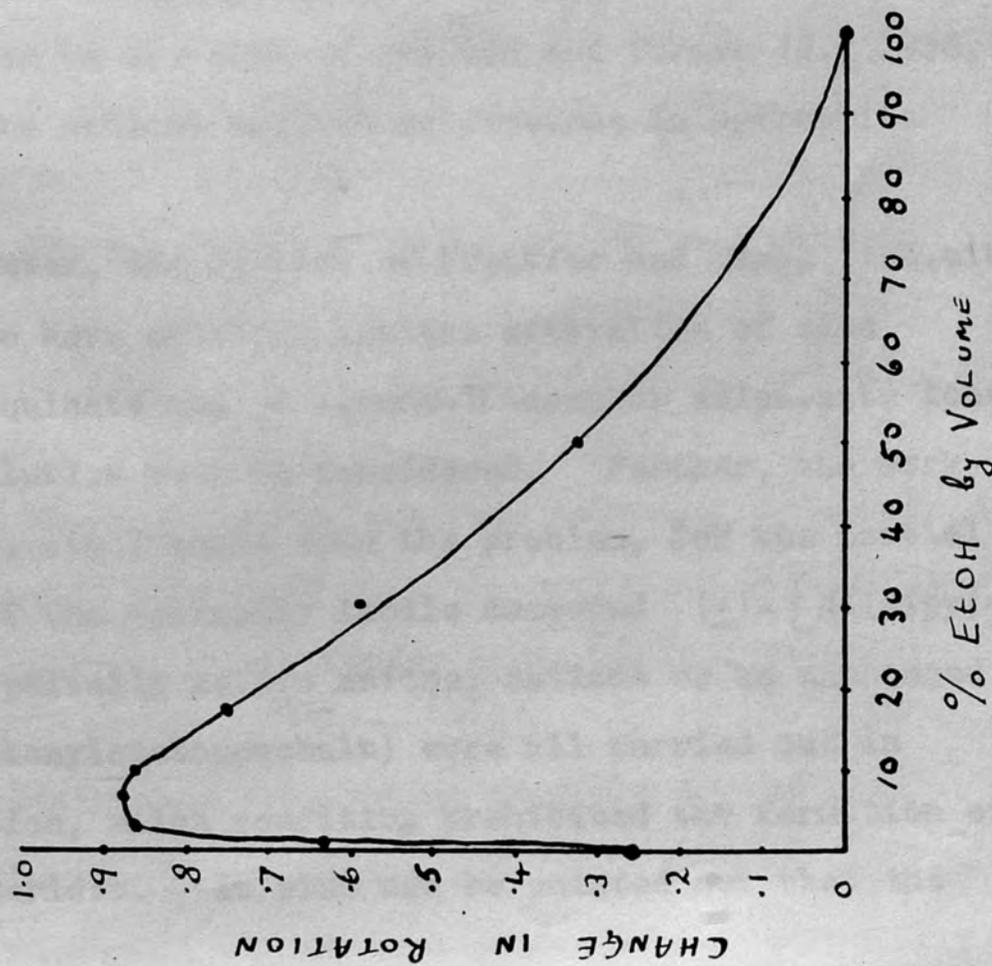


FIG 1

One possible explanation of these results could be that at low percentages of ethyl alcohol and in chloroform itself, the salt is dissociating into acid and base entities. As the amount of ethyl alcohol in the chloroform increases this dissociation increases and simultaneously the formation of ions increases. These conditions reach an optimum for activation at approx. 6% ethyl alcohol. The change in the velocity constants of the mutarotations (fig. 1) suggests that the acid racemises faster than its ion.

As the amount of ethyl alcohol becomes very great it is possible that the dissociation of the diastereoisomeric salt into the ions of acid and base is such that the ions never meet with the requisite conditions for activation to occur, i.e. the diastereoisomerides have no real existence in the solution. One is referred to the work of Jamison and Turner (J., 1938, 1646) for attempts to achieve optical activations in hydroxylic solvents.

However, the results of Pfeiffer and Quehl (loc.cit.), who claimed to have obtained optical activation of zinc complexes by quinate and  $\alpha$ -bromo- $\pi$ -camphor sulphonate ions in aqueous solution must be considered. Further, the work of Dwyer (loc. cit.) bears upon the problem, for the partial resolutions of the optically labile compound  $(+)-[\text{Ni}(\text{dipy})_3]^{12}$  by means of optically active anions, cations or an unchanged body (trisacetonylacetonecobalt) were all carried out in aqueous solution, which condition prohibited the formation of diastereoisomerides. It also can be pointed out that the

cations and the non-ionic material were incapable of forming a salt with the nickel complex.

We must now consider the system where an excess of (+)-acid is present. At the outset it can be shown that by some mechanism, this excess of acid does undergo activation.

To a solution of one mol. amount of quinidine in solvent 'X' was added one mol. amount of the symmetrical acid, N-benzoyldiphenylamine-4-carboxylic acid. The rotation of the solution was observed. To this solution was then added one mol. amount of N-benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic acid and the rotation again taken. The rotation of the solution changed  $0.66^\circ$  in 30 mins. and the measured k was  $0.073$  (temp.  $13^\circ \pm 1^\circ$ ).

This indicates that the added activable acid by some means became activated, and there appear to be two possible mechanisms for this activation.

(1) The alkaloid can link with two or more acid molecules simultaneously. (It must be remembered that the link between acid and alkaloid need only be of a weak type, see Glazer, Harris and Turner, J., 1950, 1753).

(2) The alkaloid is set free as itself or as its ion, by the diastereoisomeric salt with the symmetrical acid dissociating.

The evidence given so far seems to indicate that (2) is correct.

To obtain more information upon the excess acid effect generally, it was desirable to obtain an acid showing a considerable rotational change when activated. Accordingly

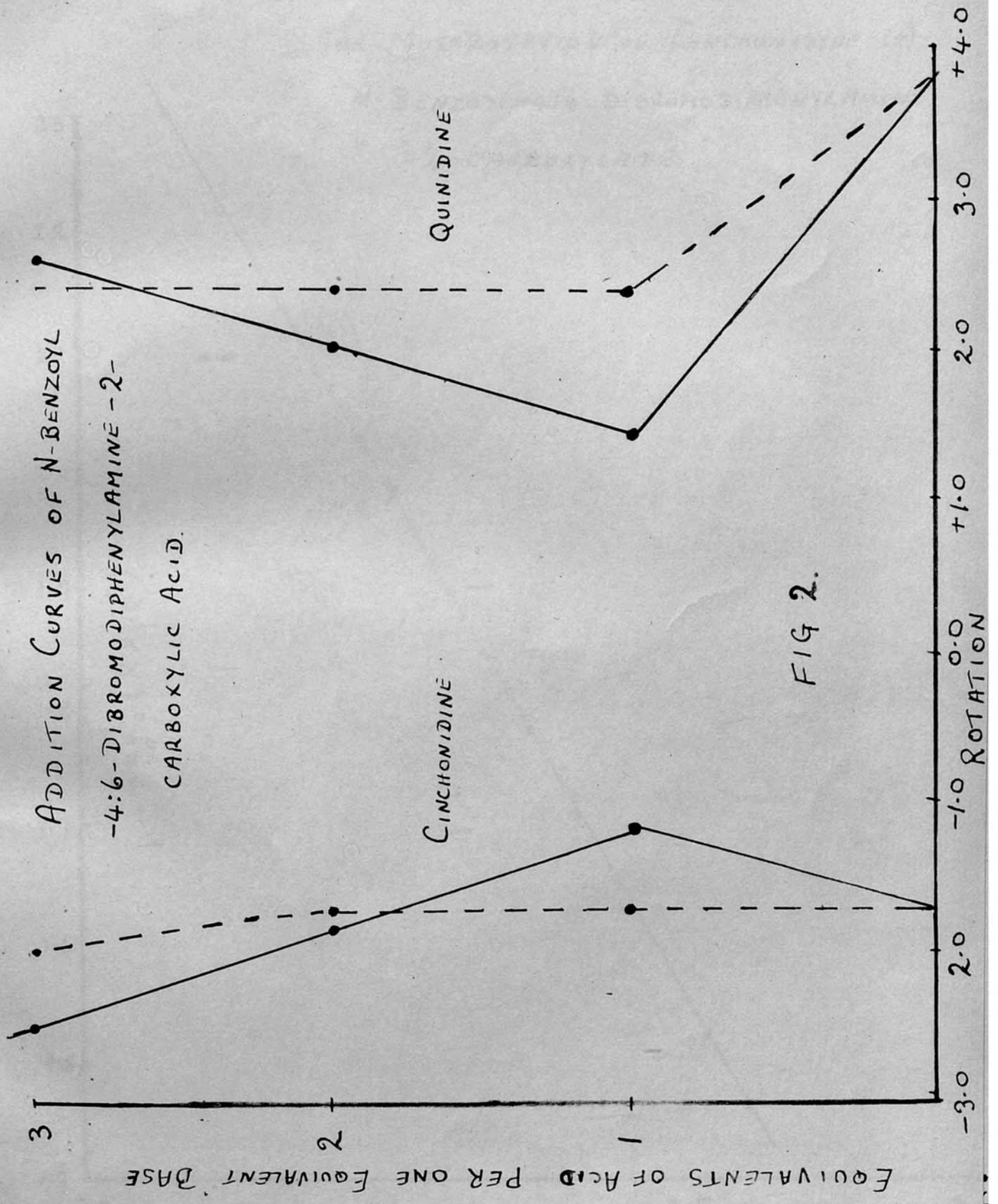


FIG 2.

# ACTIVATION ENERGY STUDIES

THE MUTAROTATION OF CINCHONIDINE (+)-  
N-BENZOYL-4:6-DIBROMODIPHENYLAMINE  
-2-CARBOXYLATE.

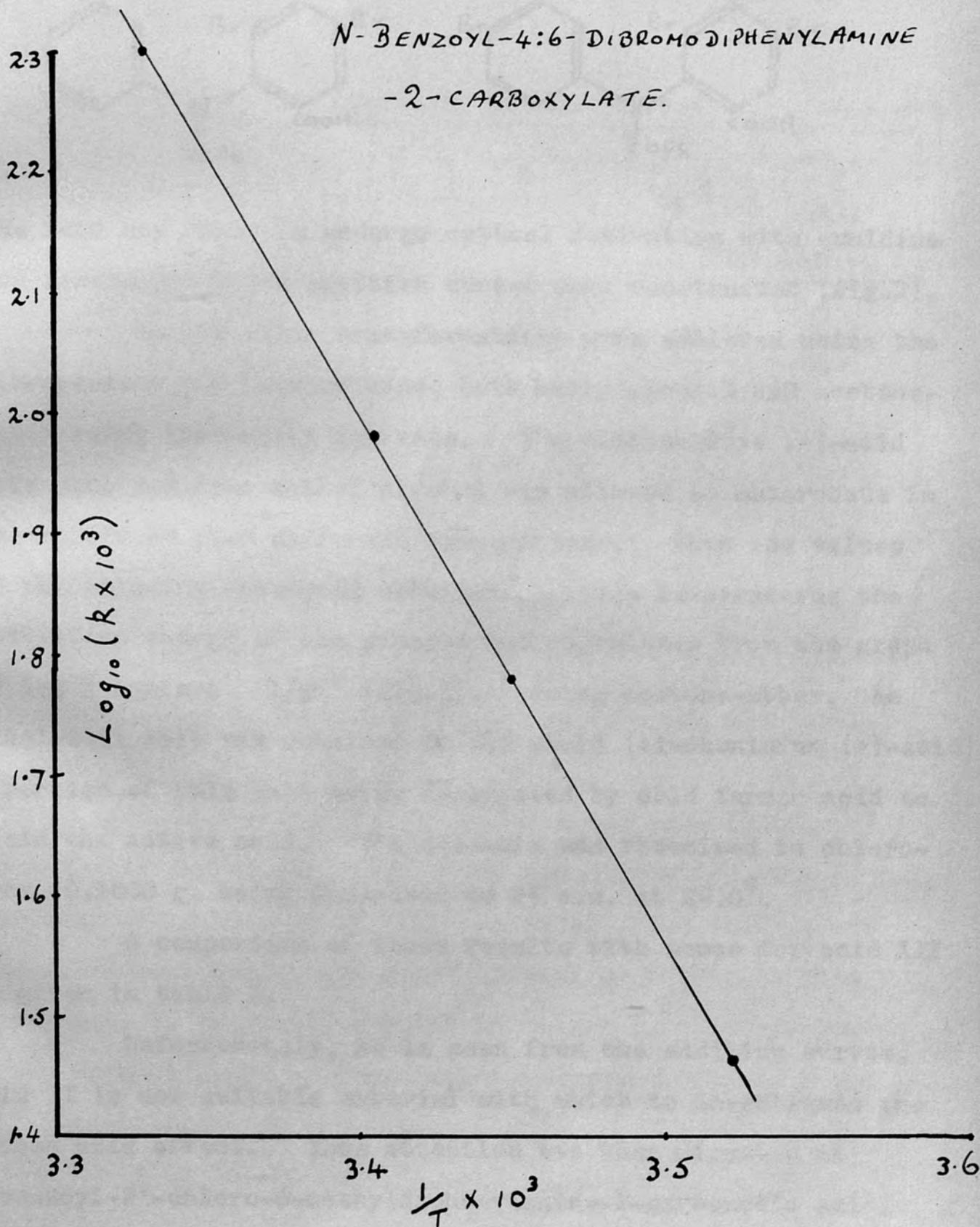
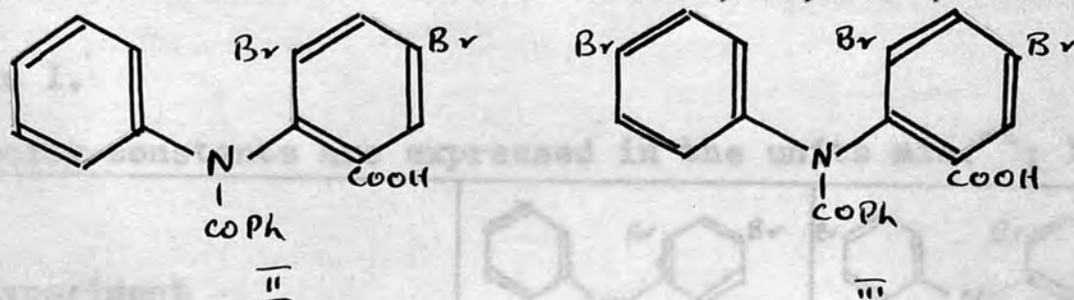


FIG. 3.

the acid II was selected, because of the known optical properties of III (Jamison and Turner, J., 1938, 1646).



The acid was found to undergo optical activation with quinidine and cinchonidine and addition curves were constructed (fig.2). Second order transformations were achieved using the dibromo-acid and cinchonidine, both methylalcohol and acetone-ether being favourable solvents. The cinchonidine (+)-acid salt obtained from methyl alcohol was allowed to mutarotate in chloroform at four different temperatures. From the values of the velocity constants obtained at these temperatures the activation energy of the process was calculated from the graph of  $\log k$  against  $1/T$  (fig.3). Using acetone-ether, the alkaloidal salt was obtained in 84% yield (cinchonidine (+)-acid), a portion of this salt being decomposed by cold formic acid to yield the active acid. The (+)-acid was racemised in chloroform, 0.1000 g. being dissolved to 25 c.c. at  $20.0^{\circ}$ .

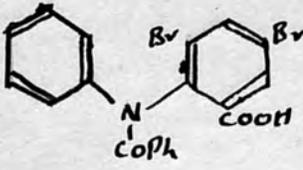
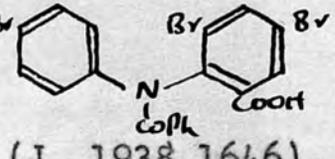
A comparison of these results with those for acid III is given in table I.

Unfortunately, as is seen from the addition curves, acid II is not suitable material with which to investigate the excess acid effect. Thus attention was then directed at N-benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic acid, an acid which had previously been prepared and was known to

give a large change.

Table I.

Velocity constants are expressed in the units  $\text{min.}^{-1}$ ;  $\log_e$

Experiment	 <chem>C1=CC=C(C=C1)N(C2=CC=C(C=C2)C(=O)O)C3=CC=CC=C3</chem>	 <chem>C1=CC=C(C=C1)N(C2=CC=C(C=C2)C(=O)O)C3=CC=CC=C3</chem> (J., 1938, 1646).
Mutarotation of the cinchonidine (+)-acid salt in chloroform	$k = 0.060$	$k = 0.046$
Activation energy of the mutarotation.	19,800 cal./g.mol.	21,200 cal./g.mol.
Racemisation of the (+)-acid.	$k = 0.702$ (20.0°)	$k = 0.345$ (17.5°)

in rotation when activated by quinidine (Jamison and Turner, J., 1940, 246).

An activation energy study of the racemisation of the (-)-acid and of the first order transformation with quinine (acid:base ratio 2:1) was made. The solvent was chloroform containing 6.9% ethyl alcohol by volume. This corresponds to the maximum point in figure 1. The following values were obtained by graphical computation. (figs. 4 and 5).

1. Racemisation of the (-)-acid.

$E = 16,400 \text{ cal./g.mol.}$

ACTIVATION ENERGY STUDIES.

THE RACEMISATION OF (-)-N-BENZOYL-2'-  
CHLORO-6-METHYLDIPHENYLAMINE  
-2-CARBOXYLIC ACID.

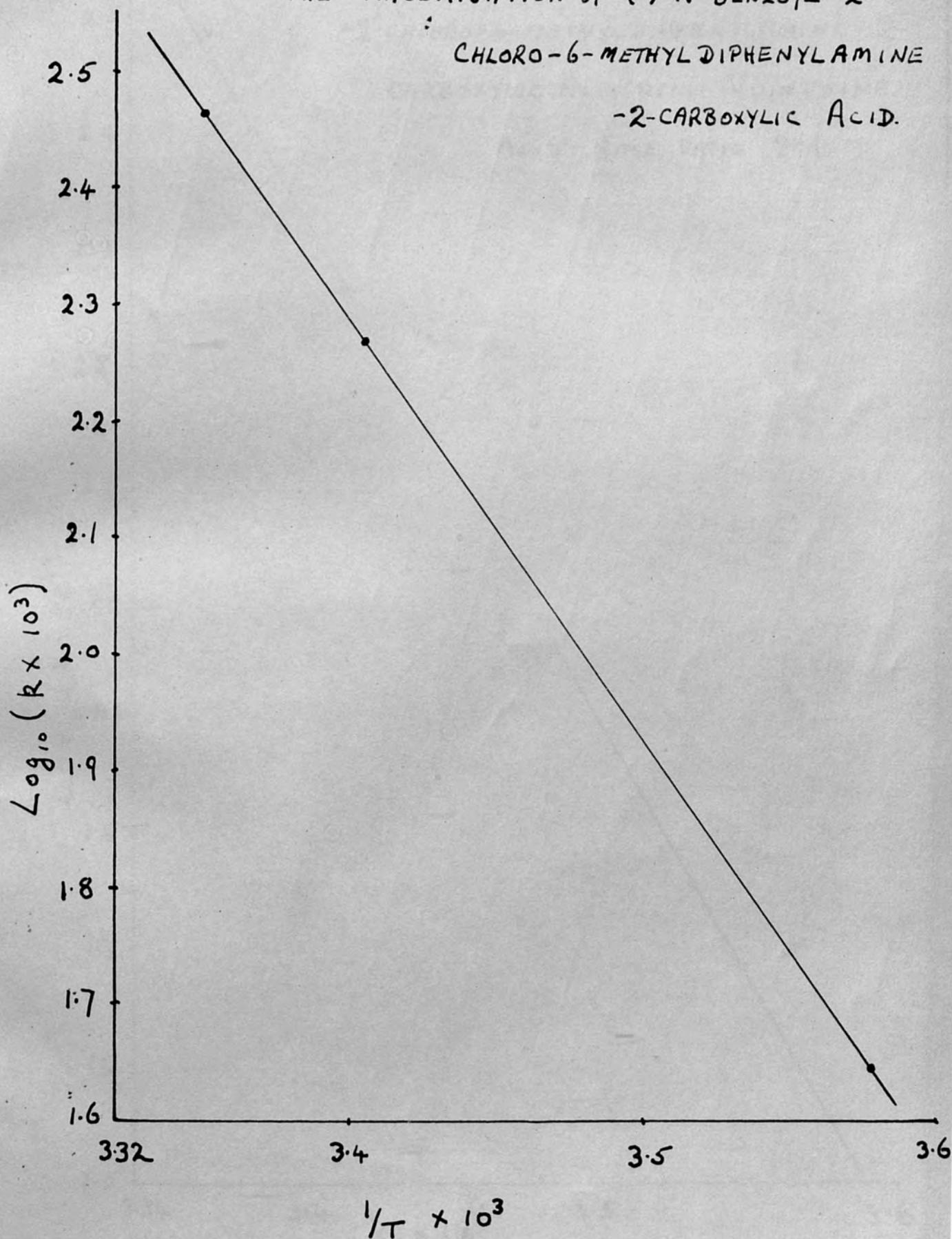


FIG. 4.

# ACTIVATION ENERGY STUDIES.

THE OPTICAL ACTIVATION OF (±)-N-BENZOYL  
-2'-CHLORO-6-METHYLDIPHENYLAMINE-2-  
CARBOXYLIC ACID WITH QUINIDINE.

ACID: BASE RATIO 2:1.

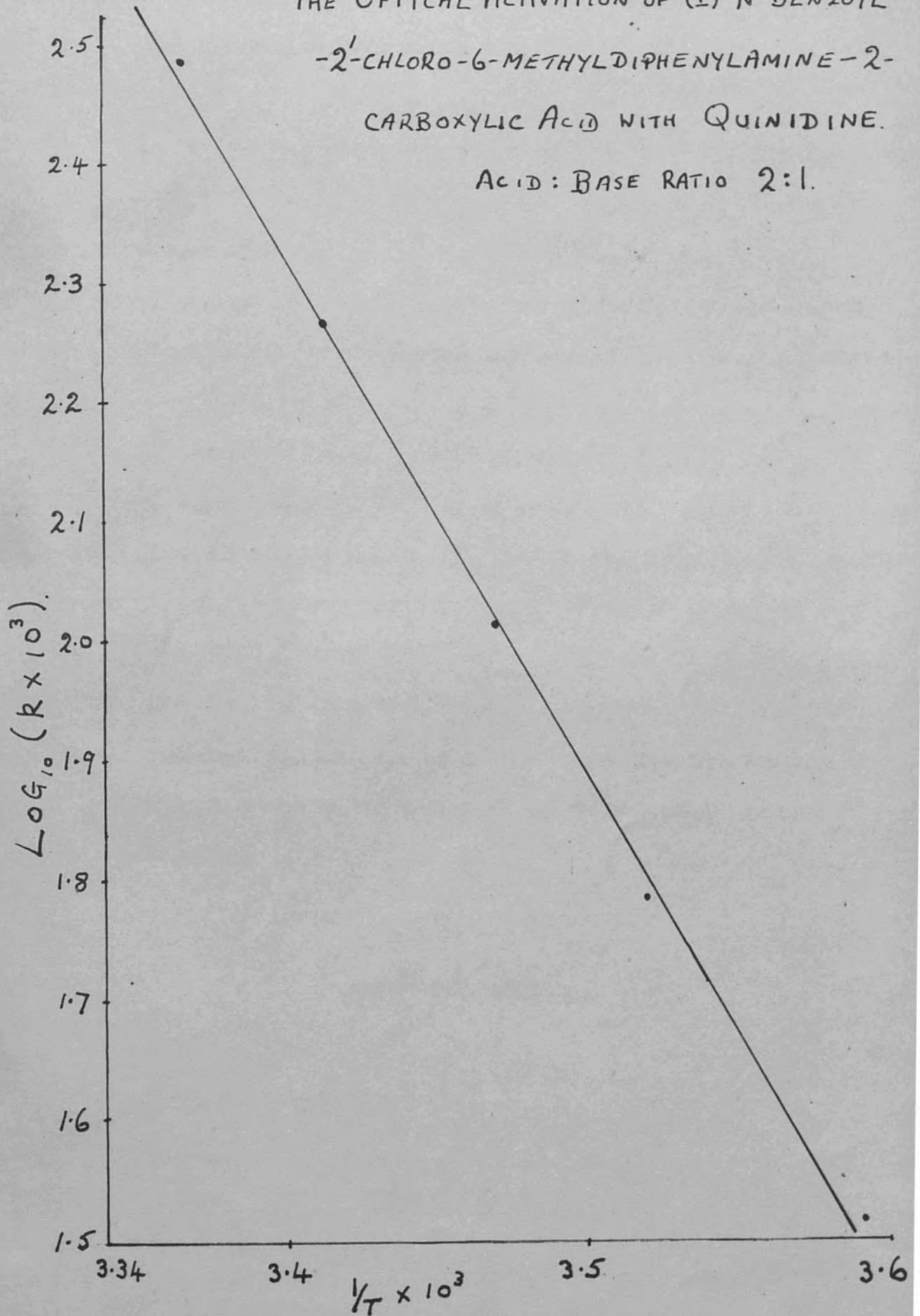


FIG. 5.

TABLE II.

2. First order asymmetric transformation; acid:base 2:1

$E = 19,800 \text{ cal./g.mol.}$

Alkaloid	(+)-Acid	Added Molecule	k(min <sup>-1</sup> ) loge
----------	----------	----------------	----------------------------

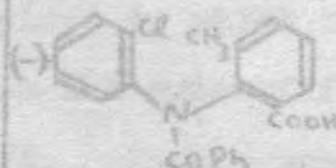
It can be pointed out that the velocity constant for:-

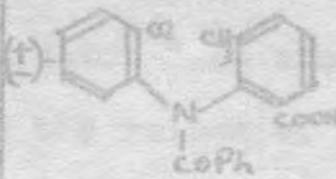
- (1) The racemisation at 20.6° was  $k = 0.185 \text{ min.}^{-1}$  0.274
- (2) The mutarotation at 19.9° was  $k = 0.185 \text{ min.}^{-1}$

indicating that, in this solvent, both systems possessed the same rate of equilibration although having different activation energies.

The activation of (+)-chloro-methyl acid by quinidine was then studied in the presence of various molecules. The results are shown in table II. All the experiments were carried out in chloroform containing 2.5% ethyl alcohol by volume (solvent 'X'), at 20.0°. From the table it is seen that the activation is speeded by adding any acid, but scarcely affected by neutral molecules (the one case considered).

The systems are considered in descending order of velocity constant.

5.			0.147
----	---	--	-------

6.			0.0321
----	---	--	--------

7.			0.0296
----	--	--	--------

TABLE II.

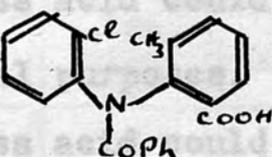
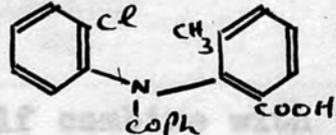
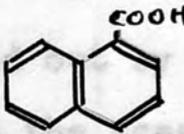
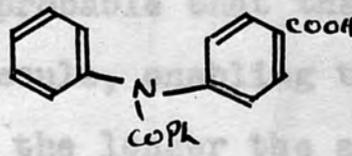
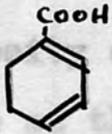
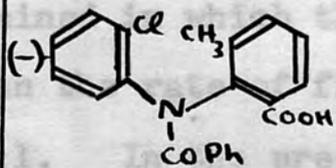
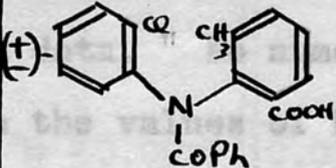
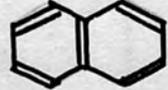
Alkaloid	(+)-Acid	Added Molecule	k(min <sup>-1</sup> loge)
1. Quinidine			0.274
2. "	"		0.197
3. "	"		0.193 (J., 1940, 270).
4. "	"		0.172
5. -		-	0.147
6. "		-	0.0321
7. "	"		0.0296

TABLE III.

The excess acid effect upon k.

An increase in k could be due to two factors which cause liberation of the free acid from the salt

- (1) The excess acid could provide extra molecules for collisional purposes.
- (2) The excess acid could itself combine with the alkaloid present.

Case (1) seems to be ruled out by results (6) and (7).

Case (2) It appears that the necessary condition for increasing k is to have free acid liberated continuously.

Hence on this assumption, it is probable that the excess acid would bond with the alkaloid molecule, enabling the acid to racemise. It then follows that the longer the alkaloid stays linked with the excess acid, the longer the original acid will have to racemise. The observed velocity constant of the mutarotation would therefore increase as the strength of the attachment between alkaloid and excess acid molecule increased.

Up to 1940, the chloro-methyl acid was the only compound examined in which the racemisation of the active acid was slower than the rate of first order transformation; acid: base ratio 2:1. In the present work, this state of affairs has been found to occur in every acid examined. Table III summarises the data. No numerical relationship was found to exist between the values of k obtained.

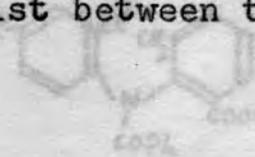
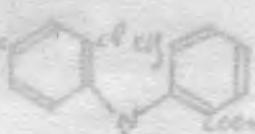
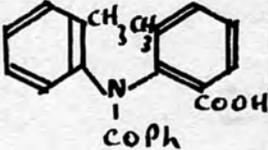
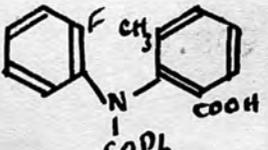
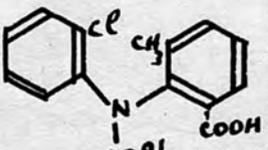
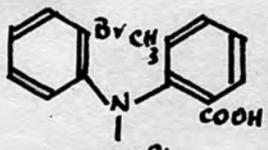
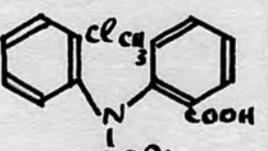
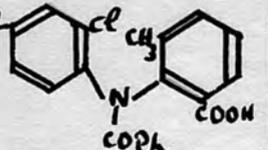
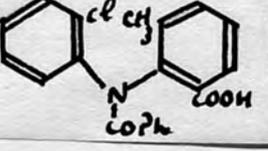
	0.0925	0.0118	0.186	0.235	0.0555	0.185	No Active.
	0.0663	0.0115	0.181	0.291	0.0545	0.142	No Active.

TABLE III.

All measurements were carried out in Solvent 'X' at 20.0°.

All values of k are in the units mins.<sup>-1</sup>, loge.

Acid	Racemisation.	Activation with Quinidine			Activation with Brucine		
		1:1	2:1	3:1	1:1	2:1	3:1
1. 	0.567	0.0602	0.667				
2. 	0.209	0.0339	0.229				
3. 	0.147	0.0321	0.274				
4. 	0.115	0.0160	0.315				
5. 	0.167	$\Delta\alpha$ too small	0.264	0.314	0.0922	0.297	$\Delta\alpha$ too small
6. 	0.0929	0.0118	0.186	0.238	0.0555	0.185	No Activn.
7. 	0.0862	0.0115	0.181	0.251	0.0545	0.142	No Activn.

PART II.

THE EFFECT OF SUBSTITUENTS UPON

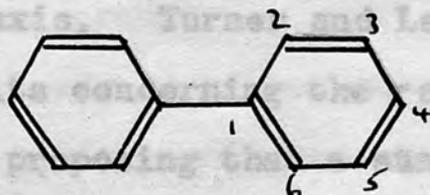
STEREOCHEMICAL PROPERTIES

Section 1. Introduction, including Previous Work.

In compounds which owe their molecular dissymmetry to restricted rotation within the molecule, it is possible to classify the positions of substituents into two broad classes.

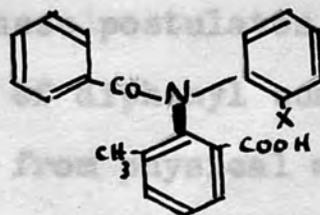
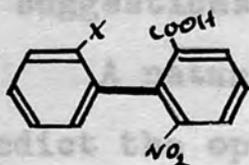
(a) The substituent is in a position where it has a direct hindering action, i.e., the ortho positions of a diphenyl compound.

(b) The substituent is away from the collisional position and has only an indirect effect upon the optical stability of the molecule; i.e., the 3, 4 and 5 positions in a diphenyl compound.



Class (a) Substituents

The chief effect is due to the blocking action of the group, as shown by X in IV and V below



IV

V

In both cases, the hindering groups (including X), restrict

rotation about the thickened bonds shown in the diagram and prevent the molecule from assuming a planar configuration and therefore permitting the molecule to exist in enantiomorphous forms. Variation in X will affect the ease with which the molecule can pass into the planar transition state and undergo inversion.

The basis for these deductions was given in 1926, when Turner and LeFevre (Chem. and Ind., 1926, 45, 831, 883), Bell and Kenyon (ibid., 1926, 45, 864.) and Mills (ibid., 1926, 45, 884, 905) put forward their obstacle theory to account for the resolution of 6:6'dinitro and other substituted diphenic acids by Kenner. All three communications suggested that the benzene rings in the acid were coaxial, and that groups in the 2:2':6:6' positions would, because of their bulk volume or electrical repulsion, prevent free rotation about the co-axis. Turner and LeFevre also accounted for Kenner's results concerning the readiness with which the acids racemised, by proposing that a stabilising effect, causing attraction of the 2:2' carbon atoms, tended to make the molecule coplanar. Although it has since been shown that the acids are quite optically stable, this does not invalidate these suggestions.

A natural outcome of these postulates was an attempt to predict the optical stability of diphenyl compounds using values for atomic radii, derived from physical measurements. Thus using data obtained from X-ray analysis, Meisenheimer and Höring (Ber., 1927, 60, 1425) showed that the amino and

methyl groups in 2:2'-diamino-6:6'-dimethyl diphenyl just touched or even slightly overlapped each other. Further, they resolved the compound, which contained the smallest groups then found to impart resolvability to a diphenyl compound.

The first attempt at a comprehensive prediction of optical stability from the size of substituent groups was made by Adams and Stanley (J. Amer. Chem. Soc., 1930, 52, 1200). From the obstacle theory it appeared that the amount of interference in a diphenyl compound would be determined by the size of the groups present in the ortho positions. Thus making certain assumptions with regard to

- (a) the angle at which a substituent is attached to a benzene ring,
- (b) The calculation of the size of methyl, amino and nitro groups,
- (c) that 94% of the carbon-substituent distances in aliphatic compounds are the distances for aromatic compounds,

Adams and Stanley obtained values for the sizes of various substituents, and used this information to calculate "relative interference values". These were obtained by substituting the appropriate values in the expression,

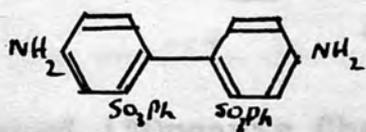
$$V = (d_x + d_y) - 2.90$$

(all values in angstrom units). The terms  $d_x$  and  $d_y$  were the internuclear distances between ortho ring carbon atoms of diphenyl and the centres of substituents attached to them,

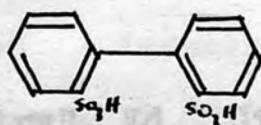
and 2.90 Å the distance between the 2:2' carbon atoms as determined by Dhar (J. Ind. Phys. 1932, I, 43).

The experimental investigations into the variation of optical stability of diphenyl derivatives with ortho groups of different sizes, were made by Lesslie and Turner and by Adams.

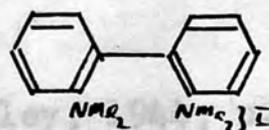
The former workers resolved



J., 1932, 2021

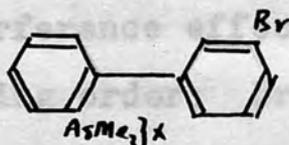


J., 1932, 2394



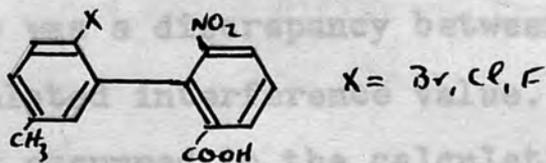
Shaw and Turner  
J., 1933, 135.

and showed

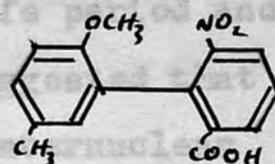


to be capable of optical activity.

Adams and coworkers, proceeding to test how accurately the "relative interference values" could predict optical stability, examined the compounds



Stoughton and Adams  
(J. Amer. Chem. Soc.,  
1932, 54, 4426)

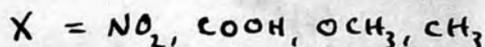
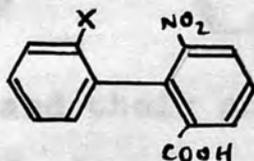


Yuan and Adams  
(ibid., p. 4434).

The rates of racemisation of the active acids obtained by rather empirical methods, were compared and thence the interfering effects of the 2' substituents shown to fall into

the order  $\text{Br} > \text{Cl} > \text{OCH}_3 > \text{F}$ . This was also the order of decreasing interference as determined by Adams and Stanley (loc. cit.).

Adams also examined a series of acids shown below, but did not publish the work.



He stated ("Organic Chemistry", Ed., Gilman, Wiley, 1944, p.362.) that with all the acids considered above

"From the half life periods it appears that the relative interference effects of the seven groups studied are in the following order:  $\text{Br} > \text{CH}_3 > \text{Cl} > \text{NO}_2 > \text{COOH} > \text{OCH}_3 > \text{F}$ "

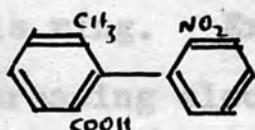
".....It is interesting that the order from first to last parallels the decrease in size of the groups as determined by X-ray data."

However, Adams noted (Chem. Rev., 1933, 12, 299) that with the acid containing methyl as one interfering group, there was a discrepancy between the half life period and the calculated interference value. It was suggested that an error occurred in the calculation of the internuclear distance from the benzene ring carbon atom to the centre of the methyl group and

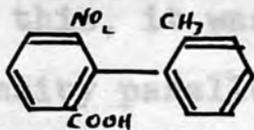
".....There was always a certain experimental error in the determination of the half life periods."

Doubt has been cast upon the ability to predict

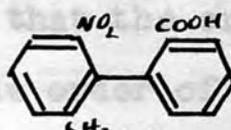
optical stability from considerations of group interference only, by the work of Adams and Hoyle (J. Amer. Chem. Soc., 1939, 2825) and Adams and Finger (ibid., p. 2828). In the first of these papers, the three acids



(1)



(2)



(3)

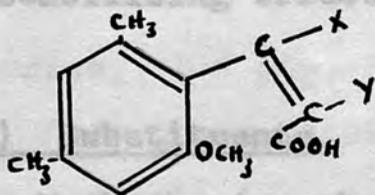
were prepared and their stabilities as indicated by their half life periods determined. Assuming that the sizes of the groups were in the order  $\text{NO}_2 > \text{CH}_3 > \text{COOH}$ , it was deduced that acids (2) and (3) should be of the same order of stability, the smallest groups colliding being  $\text{CH}_3$  and  $\text{COOH}$ , whereas acid (1) should be more stable, owing to  $\text{NO}_2$ ,  $\text{COOH}$  collision. This was not found to be so. The decreasing order of stability was  $(3) > (1) > (2)$ , the racemisation rates being dependent upon the solvent used. The latter fact suggested that the relative blocking effects of the groups depended on their solvation.

Adams and Finger carried out identical experiments with three acids different from the above three in that methoxyl was in the place of methyl. Similar results were obtained.

Commenting on this work, Baddeley (Nature, 1946, 157, 694) suggested that diphenyl compounds of this type would racemise more readily if one of the carbon atoms in the 1 position of the two benzene rings assumed a tetrahedral configuration, and the thus displaced other ring so caused the molecule to be non-coaxial. The occurrence of this must

depend upon the carbon atom acquiring a negative charge, and this would occur in the ring having the greater electron density. It was thus to be expected that the rate of racemisation would be related to the electron density in this ring. Examining this, it was seen that the order of decreasing electron density paralleled the order of increased stability. Further, Baddeley proposed that the effect on the optical stabilities of substituents in the para positions, could be accounted for by similar deductions.

Investigating compounds in which there was restricted rotation about an aromatic-aliphatic link, Adams examined a series of aryldefinic acids (J., Amer. Chem. Soc., 1941, 63, 1589; 1942, 64, 1786; 1943, 65, 2383; 1945, 67, 794, 798). Variation of substituents in these molecules gave acids of different optical stabilities, and this provided a rough measure of the effectiveness of the group in preventing free rotation. Thus in the compounds,

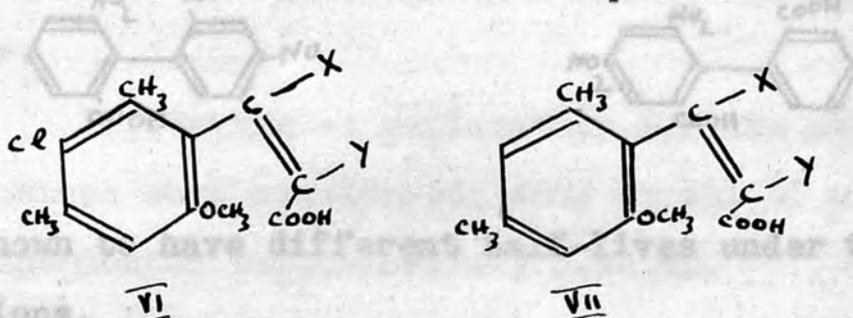


X = Cl or Br

Y = H or CH<sub>3</sub>

all four were resolved and shown to possess moderate optical stability. By consideration of the half-life periods,  $\beta$ -Br was found to be more effective than  $\beta$ -Cl, and  $\alpha$ -CH<sub>3</sub> more than  $\alpha$ -H.

Two further series of compounds



were examined and in VI where  $X = Cl$ ,  $Y = CH_3$  or  $H$ ;

$X = Br$ ,  $Y = H$ , resolution or second order asymmetric transformation was carried out. The blocking of the  $\beta$  groups being  $Br > Cl$ .

When  $X = OCH_3$ ,  $Y = CH_3$  or  $H$ ;  $H = SCH_3$ ,  $Y = H$ , no resolution could be obtained.

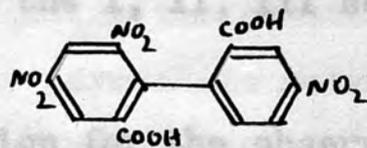
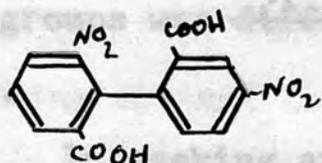
Comparing VI and VII, when  $X = CH_3$ ,  $Y = H$  or  $CH_3$  in VII, the data suggested that the  $\beta$ -Cl had a larger steric effect than the  $\beta$ - $CH_3$ , assuming that the ring Cl in VI played no significant part. Hence the influence of  $\beta$  substituents on the restriction of rotation was in the order  $Br > Cl > CH_3$  whereas for diphenyl it was  $Br > CH_3 > Cl$ .

Evidence was also given to show that an  $\alpha$ - $CH_3$  group had a greater stabilising effect than  $\alpha$ -H.

In all series,  $X = NO_2$ ,  $Br$ ,  $Cl$ ,  $CH_3$  and  $OCH_3$ .

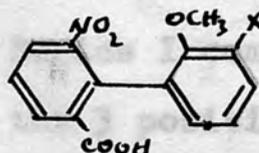
#### Class (b) Substituents.

Work showing that groups away from the hindering positions in a diphenyl derivative affected the optical stability of the compound, was first carried out by Kuhn and Albrecht (Ann., 1927, 458, 221). The optically active forms of the compounds (1938, 60, 1411) found that substituents in the para positions of the ring containing the  $COOH$  and  $NO_2$  groups did affect the optical stability of the parent acid, but only to a very small extent. The order of effectiveness

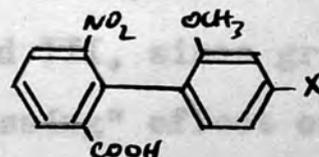


were shown to have different half-lives under the same conditions.

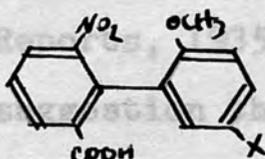
Adams and coworkers followed up this work, and over a period of years examined a large number of substituted diphenyls. Thus the following compounds were examined



Chien and Adams  
(J. Amer. Chem. Soc.,  
1934, 56, 1787)



Hanford and Adams  
(ibid, 1935, 57,  
1592)



Yuan and Adams  
(ibid, 1932, 54, 4434).

In all series, X = NO<sub>2</sub>, Br, Cl, CH<sub>3</sub> and OCH<sub>3</sub>.

From these studies, Adams concluded that in each series the stabilities of the compounds were in the order H < OCH<sub>3</sub> < CH<sub>3</sub> < Cl < Br < NO<sub>2</sub>. Further in the relative stabilities of the series themselves, the order I > III > II appeared to hold with only one exception. Adams and Snyder (J. Amer. Chem. Soc., 1938, 60, 1411) found that substituents in the para positions of the ring containing the COOH and NO<sub>2</sub> groups did affect the optical stability of the parent acid, but only to a very small extent. The order of effectiveness

of the groups was <sup>different</sup> ~~difficult~~ from the I, II, III series however.

In seeking an explanation for the observations, many factors were considered, some or all of which could have contributed to the overall results.

(1) The valency angle between the ortho group and the benzene ring might have been altered. This would change the effective size of the group. This view has a definite bearing upon the increased stability of the acids of Series I compared with series II and III, since groups in the 3 position could have a "buttressing" effect on the adjacent methoxyl substituent. However, the strength of the methoxy-nucleus bond which would be affected by the polar nature of the substituents would play an important part (Turner, Ann. Reports, 1935, 246).

(2) The suggestion that the semi-circular oscillation of the two phenyl rings was varied by substitution in the rings was discarded since, in the acids examined, those containing bromine and chlorine had the same half lives although the halogen substituents had different weights.

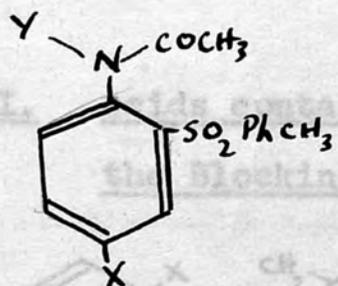
(3) The "non-blocking" groups may have caused the rings to be non-coaxial, or

(4) the 1-1' carbon-carbon distance might have been varied.

(5) The ring - methoxyl distance could have been varied.

one  
No factor gave a satisfactory explanation of the results.

In 1950, whilst investigating the possibility of obtaining optical activation by asymmetric solvent action, as noted previously, Buchanan and Graham (J., 1950, 500) measured the half-life periods of the optically active compounds two series of acids were prepared and investigated.



X = Cl, Br, OCH<sub>3</sub> and CH<sub>3</sub>

Y = CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>.

X = CH<sub>3</sub>, Cl, Br, Y

They found the order of stabilities to be CH<sub>3</sub>O > CH<sub>3</sub> > Cl > Br when Y was either CH<sub>3</sub> or C<sub>2</sub>H<sub>5</sub>. This order was the reverse of that found by Adams in the diphenyl series.

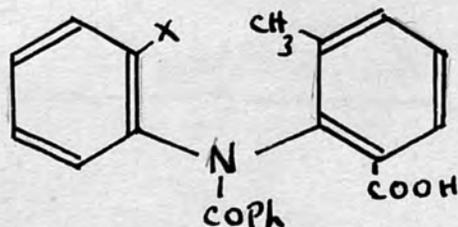
and Turner (J., 1937, 1954), were all found to be optically labile. Thus each acid underwent first order asymmetric transformation with quinidine at different acid:base ratios, and addition curves were constructed (fig.6.). Further, all the acids underwent second order asymmetric transformation with brucine, high yields of the brucine (-)-acid salt being obtained in every case. The details for the four acids are summarised in table IV.

Section 2. Discussion of Results.

Key to Fig. 6.

To investigate the effect of substituents upon the stereochemical properties of substituted N-benzoyldiphenylamines, two series of acids were prepared and investigated.

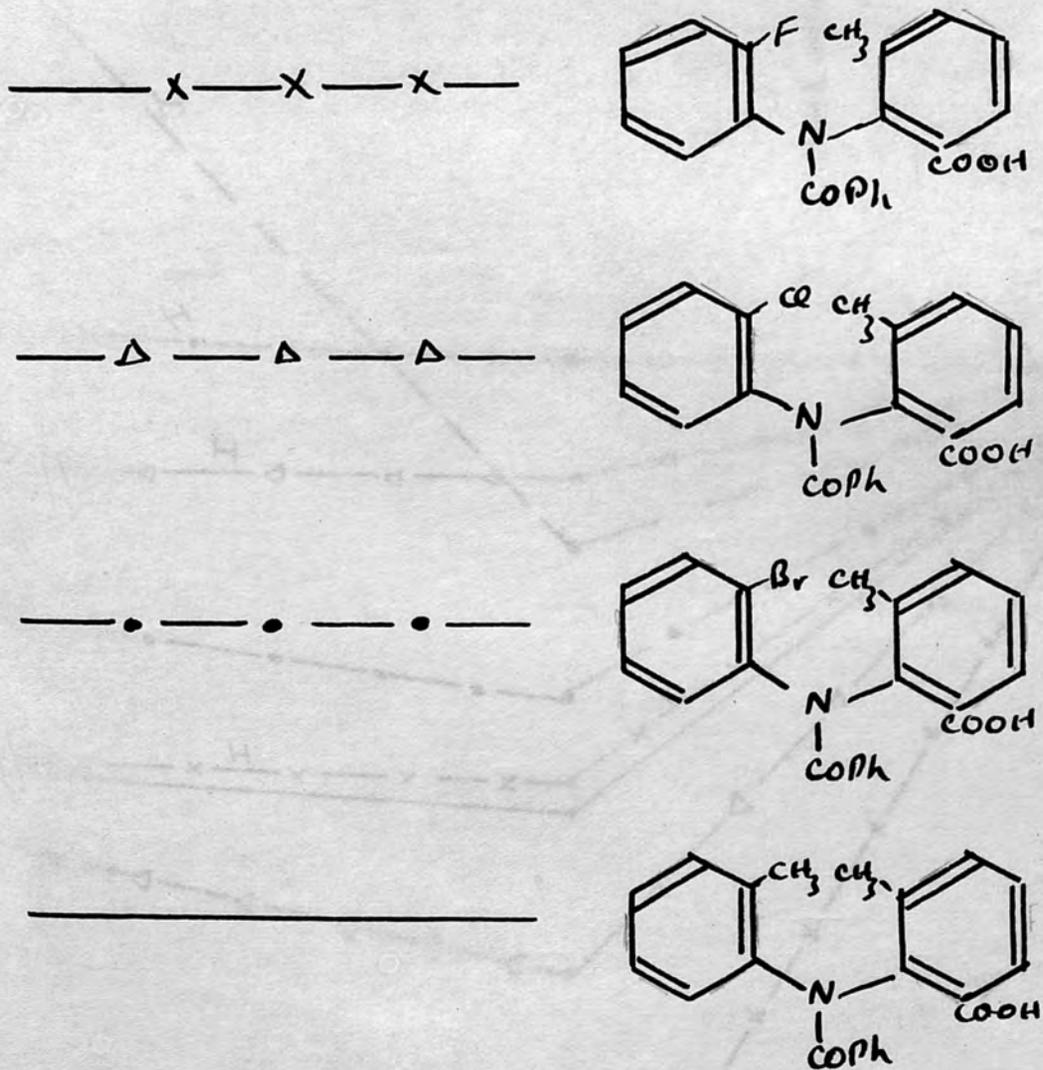
Series I. Acids containing Different Substituents in the Blocking Position.



X = CH<sub>3</sub>, Cl, Br, F

The acids, prepared by the general method of Jamison and Turner (J., 1937, 1954), were all found to be optically labile. Thus each acid underwent first order asymmetric transformation with quinidine at different acid:base ratios, and addition curves were constructed (fig.6.). Further, all the acids underwent second order asymmetric transformation with brucine, high yields of the brucine (-)-acid salt being obtained in every case. The details for the four acids are summarised in table IV.

Key to Fig. 6.



ADDITION CURVES OBTAINED USING  
QUINIDINE AND ACIDS OF SERIES I.

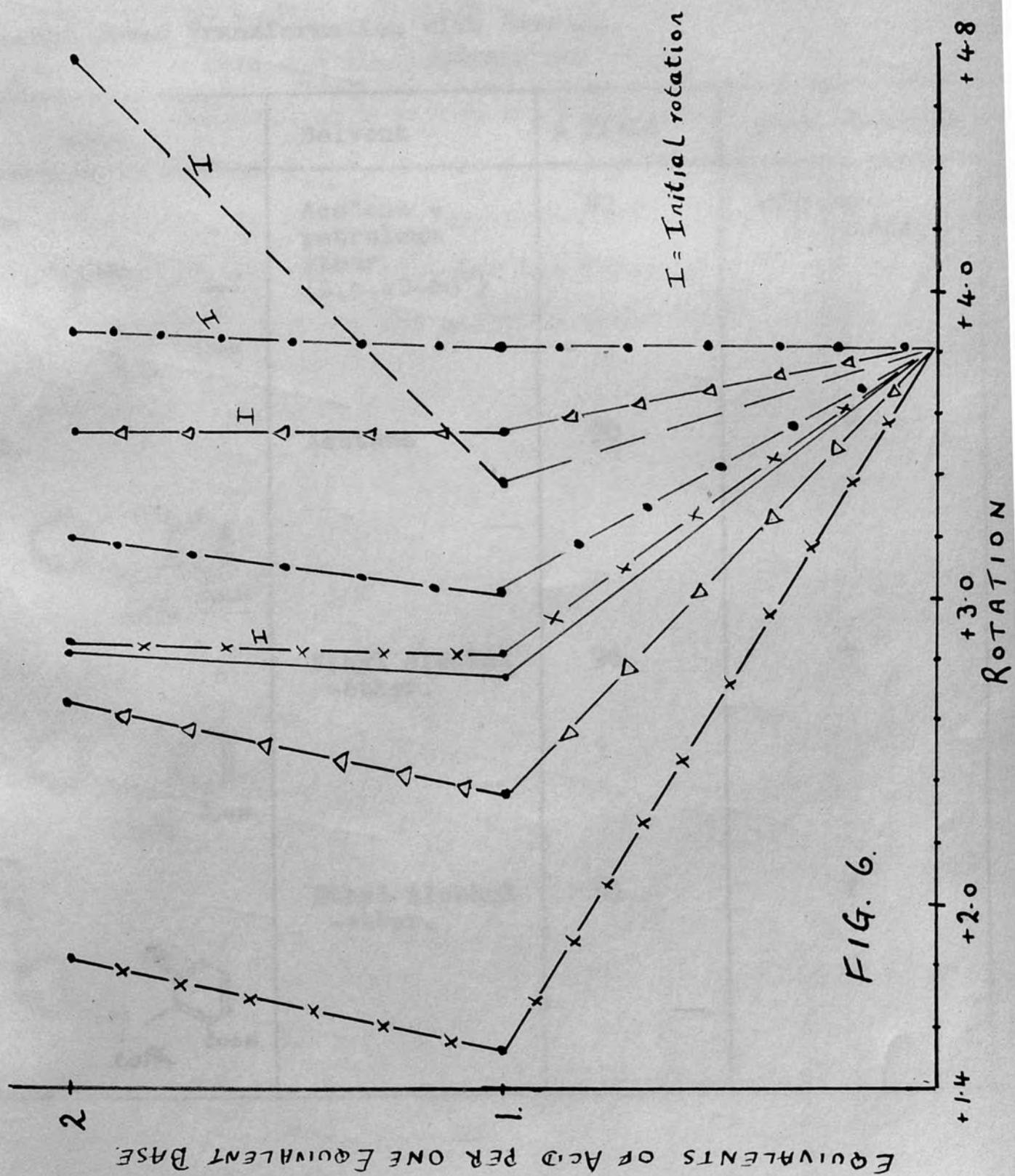
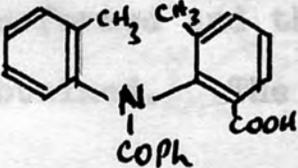
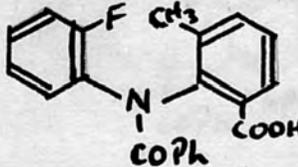
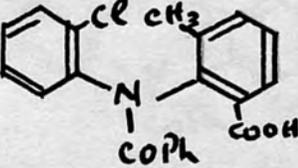
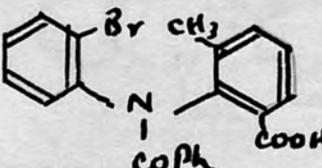


FIG. 6.

The brucine (-)-acid salts obtained were decomposed in the water by dissolving in anhydrous formic acid at 0° and filtering this solution into dilute hydrochloric acid and ice, the process being once repeated.

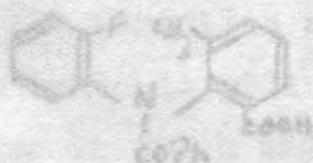
TABLE IV.

Second Order Transformation with Brucine.

Acid	Solvent	% Yield	Salt obtained
1. 	Acetone - petroleum ether (B.p. 40-60°)	87	Brucine (-)-acid.
2. 	Acetone	90	"
3. 	Ethyl alcohol -ether.	96	"
4. 	Ethyl alcohol -ether.	91	"

The brucine (-)-acid salts obtained were decomposed in the normal manner by dissolving in anhydrous formic acid at  $0^{\circ}$  and filtering this solution into dilute hydrochloric acid and ice, the process being once repeated. The active (-)-acid so obtained was then allowed to racemise in solvent 'X' at  $20.0^{\circ}$ , 0.1000 g. being taken in each case and dissolving to 25 c.c. Duplicate experiments were performed and the mean value for the velocity constant obtained. The results are given in table V.

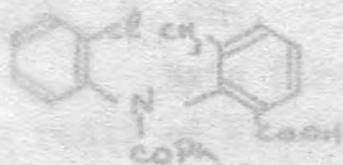
2.



0.202(5)

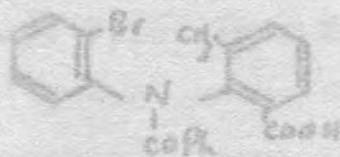
2.3

3.



0.367

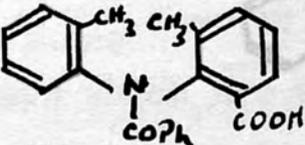
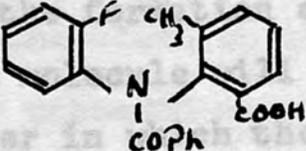
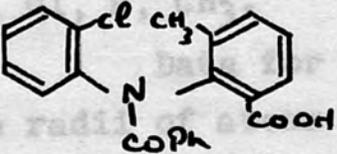
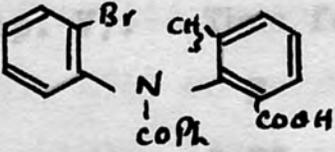
3.7



0.115

6.0

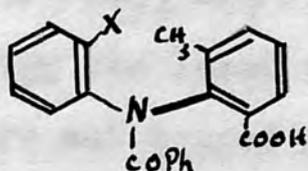
From this data TABLE V. Order of stability of the acids,  
Racemisation of the Active (-)-Acids in Solvent 'X' at 20.0°.

Acid	Mean $k$ ( $\text{min}^{-1}$ ; their loge)	Half-life (mins.)
1. 	0.567	1.0
2. 	0.208(5)	3.3
3. 	0.147	4.7
4. 	0.115	6.0

(the value given here for Fluorine being the rounded one as suggested by Schomaker and Stevens (J. Amer. Chem. Soc., 1941, 63, 37)). The size of the methyl group as determined

From this data the order of stability of the acids, and hence the order of effective blocking action of the substituents is  $\text{Br} > \text{Cl} > \text{F} > \text{CH}_3$ .

Now the compounds examined owe their molecular dissymmetry to restricted rotation about the C - N bond shown thickened in the diagram



The inversion of the active forms of the acids proceeds via a planar intermediate state, and the greater the resistance to the formation of this state, the more optically stable the molecule will be. Hence, on a mechanical view, the order in which the acids decrease in stability should parallel the decrease in size of the substituent X. It is therefore pertinent to consider the sizes of the substituents Br, Cl, F, CH<sub>3</sub>.

Data for the covalent radii of atoms, these being the radii of atoms when linked to another atom by a covalent bond of fixed type, have been summarised by Pauling ("Nature of the Chemical Bond", Cornell University Press 1940, Chap. V). Thus for the halogens the values are:-

F	Cl	Br	
0.72	0.99	1.14	A.

(the value given here for fluorine being the amended one as suggested by Schomaker and Stevens (J. Amer. Chem. Soc., 1941, 63, 37)). The size of the methyl group as determined

by Adams and Stanley (ibid., 1930, 52, 1200) is 1.025A., this being obtained on the assumption that the three hydrogen atoms on the methyl group increase the  $C_{\text{aromatic}}-C_{\text{aliphatic}}$  distance of 1.45 A. by 0.3A., the atomic radius of an aromatic carbon atom having a value of 0.725A.

Thus the order of decreasing size of substituents is

Covalent radii  $Br > CH_3 > Cl > F$ .

However the least distance between two atoms or groups which are not bonded together is much greater than the sum of the covalent radii. An equilibrium position is attained where the attractive Van der Waals forces are opposed by the powerful repulsive forces caused by the interpenetration of the electron shells. The Van der Waals distance between two unbonded atoms when the attractive and repulsive forces balance can be taken to be the sum of the two Van der Waals radii. Pauling (opp. cit.) gives the following Van der Waals radii.

F	Cl	Br	CH <sub>3</sub>	A.
1.35	1.80	1.95	2.0	

The value for the methyl group was derived from the X-ray diffraction measurements of Lonsdale (Proc. Roy. Soc., 1929, A123, 494) on hexamethylbenzene. Robertson and Brockway (J., 1939, 1324) re-examined the compound and obtained substantially the same value for the nearest approach of two methyl groups (4.00 A.) in different molecules. Hexachlorobenzene crystals were examined by Dickinson and Bilicke (J. Amer. Chem. Soc., 1928, 50, 764), and the nearest approach

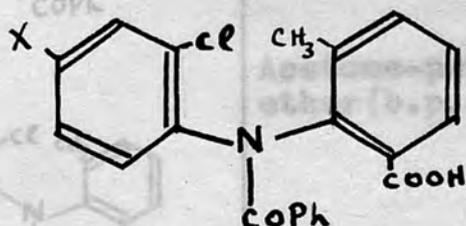
of two chlorine atoms of different molecules found to be 3.60A.

Thus the blocking effect of the groups would be expected to fall in the order  $\text{CH}_3 > \text{Br} > \text{Cl} > \text{F}$ . Summarising the above results, we have

	Order of Stability of Acids.
Covalent radii predict	$\text{Br} > \text{CH}_3 > \text{Cl} > \text{F}$
Vander Waals radii "	$\text{CH}_3 > \text{Br} > \text{Cl} > \text{F}$
Experimental results found in this investigation	$\text{Br} > \text{Cl} > \text{F} > \text{CH}_3$
Results found in diphenyl series (Adams)	$\text{Br} > \text{CH}_3 > \text{Cl} > \text{F}$

It thus appears from these considerations that to explain the anomalous position of the acid containing the methyl group, one or more factors in addition to the mechanical blocking effect must be operative. Before proceeding to discuss this, it is pertinent to consider the second series of acids examined.

Series II. Acids containing Different Substituents Away from the Blocking Position.



$\text{X} = \text{CH}_3, \text{Cl}, \text{Br}.$

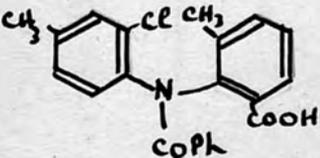
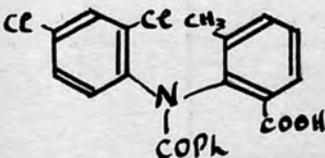
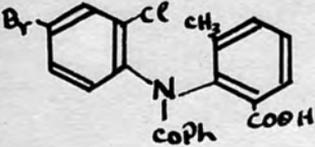
The acids, prepared as series I (Jamison and Turner loc. cit.) were all shown to possess transient optical activity.

Each compound underwent first order asymmetric transformation with brucine and quinidine at different acid:base ratios and addition curves were constructed. (figs. 7 & 8). Second order asymmetric transformations were carried out using brucine, table VI gives the results.

The brucine (-)-acid salts were decomposed with formic acid as before and the rates of racemisation of the active acids determined. 0.1000 G. of (-)-acid was dissolved to 25 c.c. in solvent 'X' at 20.0°. The results are given in table VII.

TABLE VI

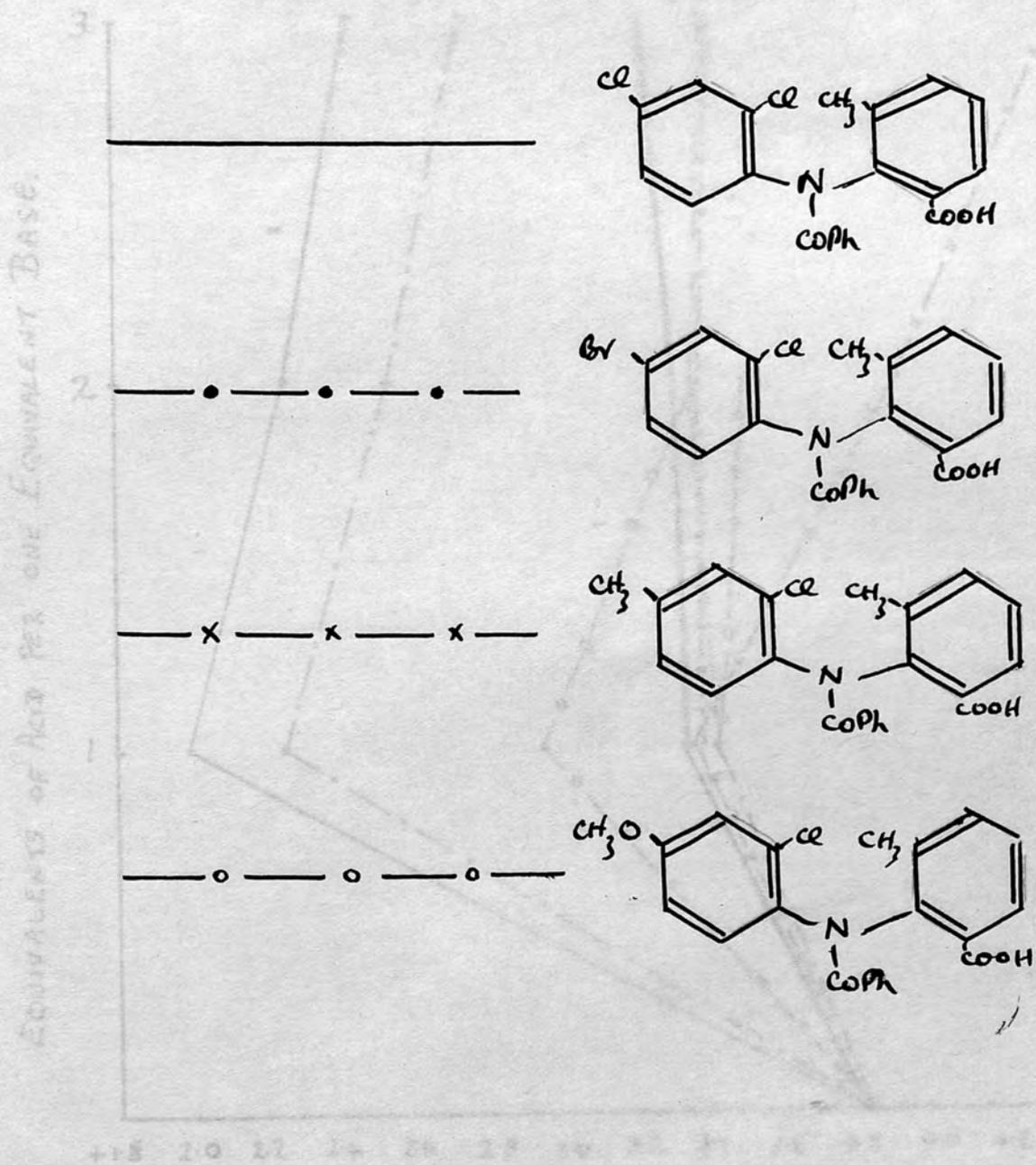
Second Order Transformation with Brucine.

Acid	Solvent	% Yield	Salt obtained
1. 	Ethyl alcohol-ether.	92	Brucine(-)-acid
2. 	Acetone-petroleum ether (b.p. 40-60°)	87	" "
3. 	Acetone-petroleum ether (b.p. 40-60°)	83	" "

Absorption Curves of Various

Dyes. Qualitative Analysis of Figure 7

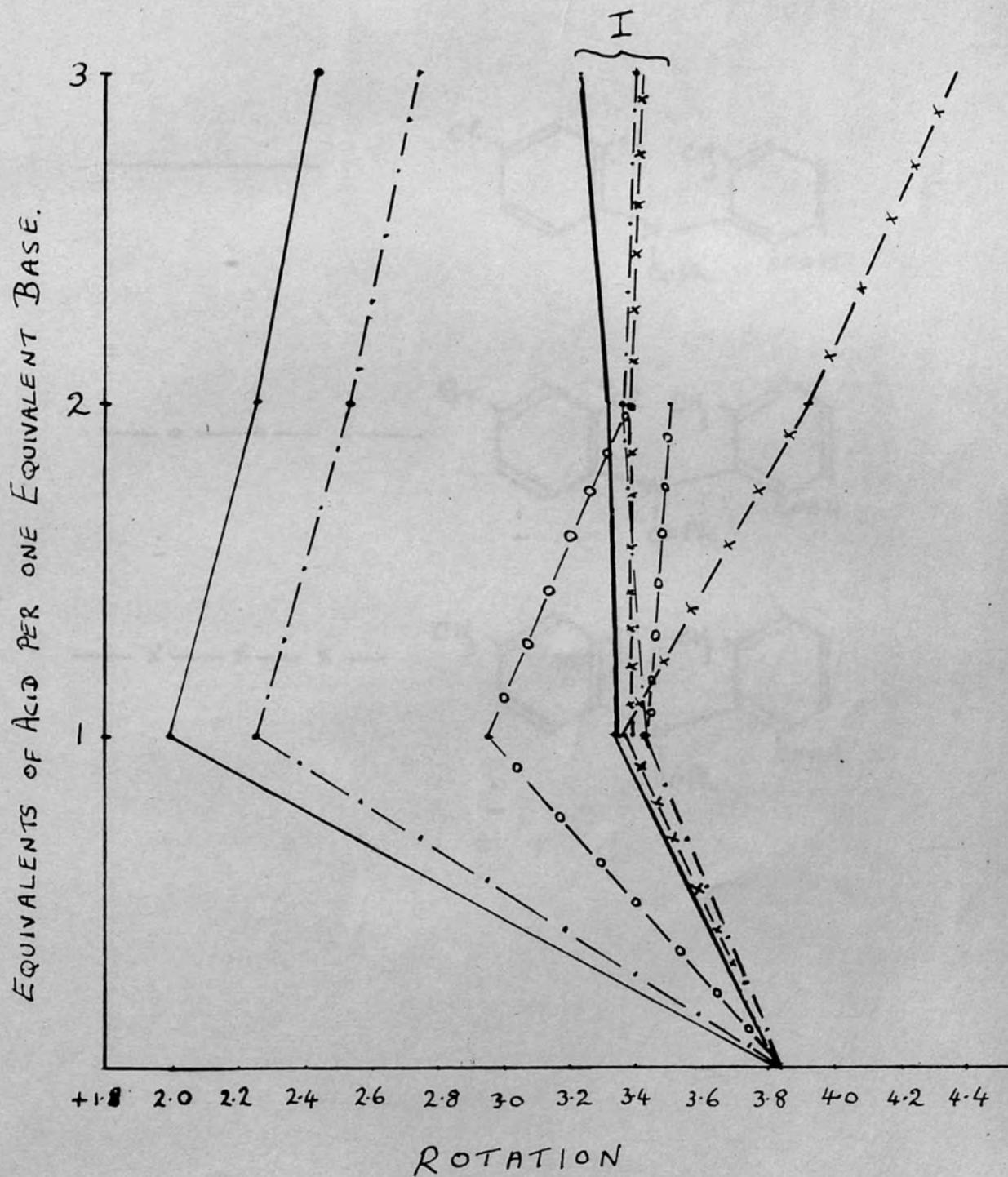
Key to Fig. 7.



L = Total Concentration

# ADDITION CURVES OBTAINED

USING QUINIDINE AND ACIDS OF SERIES II



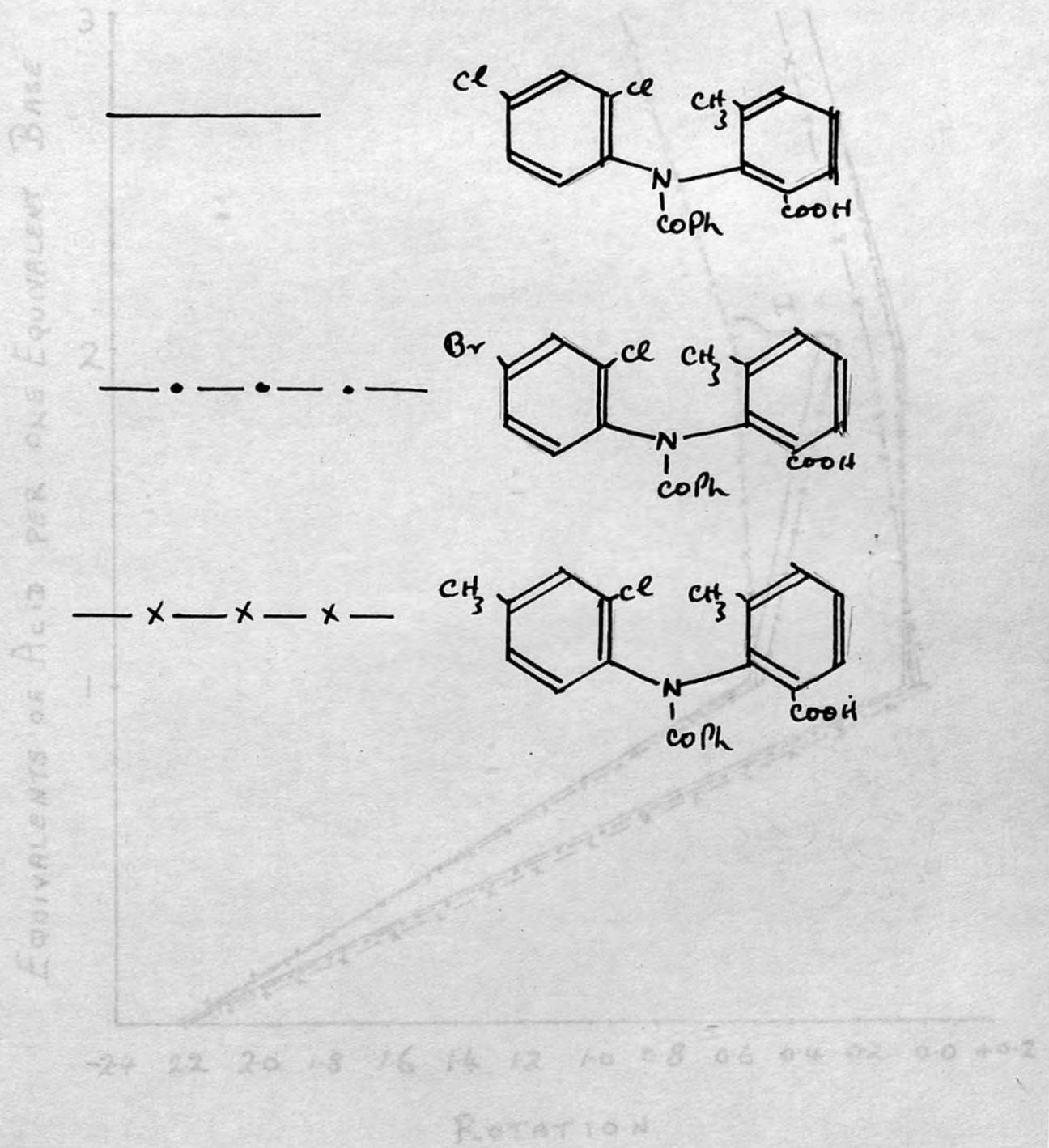
I = Initial Rotations.

FIG. 7.

ADDITION CURVES OBTAINED

USING BROMINE AND ACIDS OF VARIOUS

Key to Fig. 8.



H = Initial Rotation

FIG. 8.

ADDITION CURVES OBTAINED  
USING BRUCINE AND ACIDS OF SERIES II.

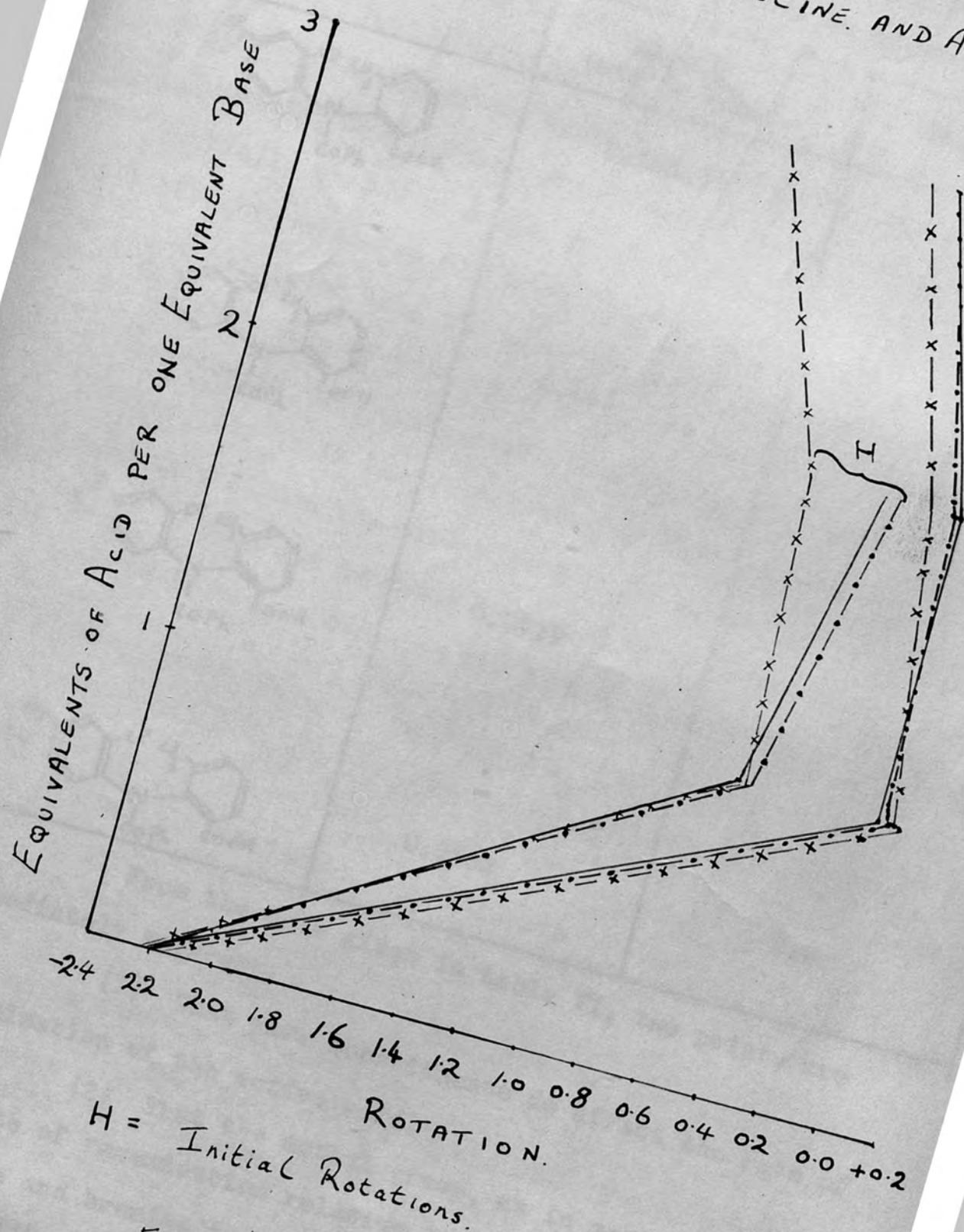
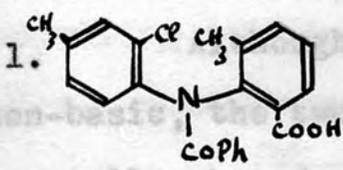
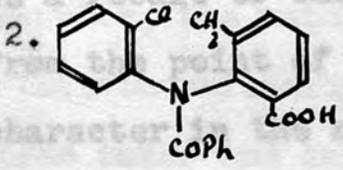
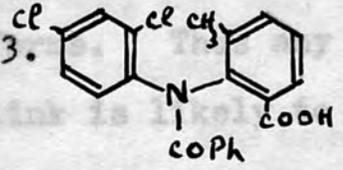
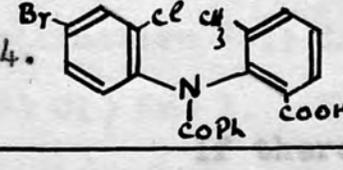


FIG. 8.

**TABLE VII**

Racemisation of the Active (-)-Acids in Solvent 'X' at 20.0°.

Acid	Mean k (min <sup>-1</sup> ; loge)	Half-life (mins.)
<p>1. </p>	0.166(5)	4.2
<p>2. </p>	0.147	4.7
<p>3. </p>	0.0929	7.5
<p>4. </p>	0.0862	8.0

From the data given in table VI, two points are immediately apparent.

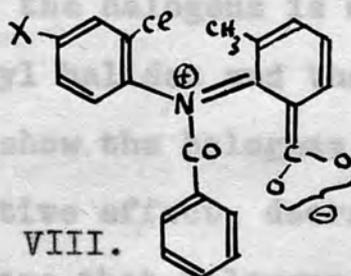
(1) That para substituents do affect the rate of racemisation of the active acid.

(2) That the methyl group, as in series I, increases the rate of racemisation relative to the acids containing chlorine and bromine in the para position, the decreasing order of stability being Br > Cl > H > CH<sub>3</sub>.

Consider Since in series II the groups in the blocking positions are constant, it is possible that other factors are contributing to the optical stability of the molecule.

(a) A polar effect.

Although the nitrogen atom in the molecule is non-basic, the two free electrons of the nitrogen must be partially shared with the aromatic nuclei so that these three nitrogen valencies may become partly double bond in character. As a result of this the molecule would tend to become planar. From the point of view of this investigation, double bond character in the nitrogen-ring containing COOH is the important factor, for it is the restriction of free rotation about this bond that allows the molecule to exist in enantiomorphous forms. Thus any tendency to double bond formation by this link is likely to decrease the optical stability of the molecule.



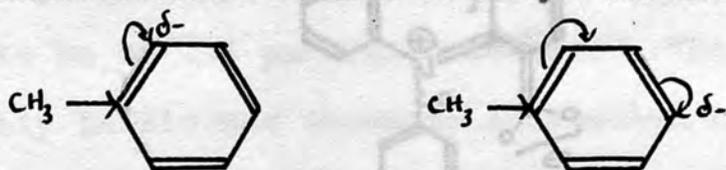
If therefore VIII is a contributory form, the following factors will be operating:-

(1) The double bond character of the N-C link, tending to flatten the molecule.

(2) The polar nature of the COO<sup>-</sup> group, possibly increasing its effective blocking; this being opposed by the decrease in bulk size of the group on assuming a planar resonance state.

Consideration of the inductive and mesomeric effects of  $X$  groups, will give an approximate estimate of the influence of  $X$  substituents upon this state of affairs.

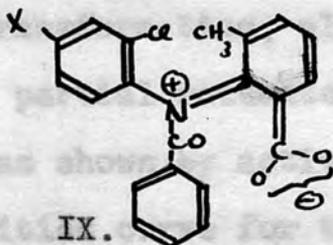
The methyl group is known to possess an electron repelling (+I) inductive effect, this being indicated by dipole moment measurements on alkyl benzenes



Further, the methyl group has been shown to exhibit an electron releasing 'mesomeric effect', termed hyperconjugation (see Baker and Nathan, J., 1935, 1844, 1847). In the resting state of the molecule this effect is overshadowed by the +I effect, and only assumes a significant magnitude at the demand of a reagent.

The case of the halogens is more obscure. The dipole moments of alkyl halides and the strengths of halogenoacetic acids show the halogens to have an electron attractive (-I) inductive effect, decreasing in the order  $F > Cl > Br > I$ . Evidence that halogens attached to an aromatic nucleus have a mesomeric (+M) effect is summarised in (Watson "Modern Theories of Organic Chemistry", Oxford University Press, 1941, pp. 101-105), the decreasing order of the electron repulsive effect being  $F > Cl > Br > I$ . The superposition of the two effects (-I, +M) causes inconstancy in the order of effectiveness of the halogens, this depending on the system considered; but from the point of view of this

investigation it is apparent that, relative to the halogens, the methyl group possesses electron repelling characteristics. Thus from these considerations if the polar effect is operative, the methyl group would favour the formation of structure IX whereas the halogens would not (relative to methyl).

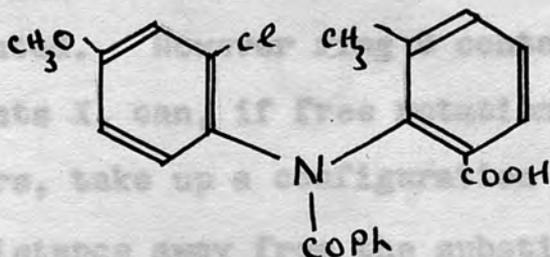


On this basis, the decreasing order of acid stability would be  $(Br, Cl) > H > CH_3$ .

This is seen to parallel the order of the para substituted acids as found experimentally. In acids of series I (ortho substituted), the same effect could operate, and in the same order. Thus reviewing the position again, we have.

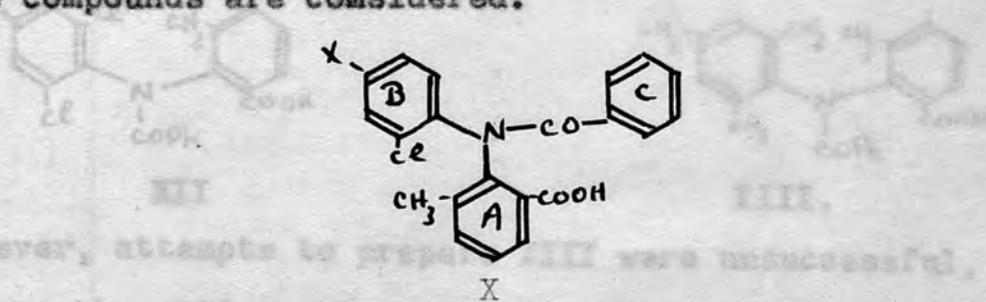
Steric effect (Van der Waals radii) predicts	$CH_3 > Br > Cl > F$
Polar effect	" $Br > Cl > F > CH_3$
Observed order	$Br > Cl > F > CH_3$

To test the possibility of the operation of this polar effect, the acid



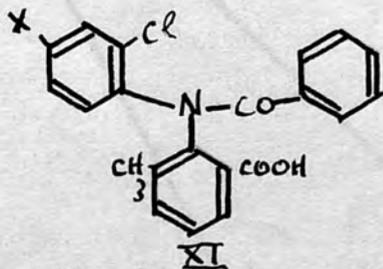
was prepared. The methoxyl group being known to possess powerful (+I,+M) electron donating properties, one would expect, assuming this electrical effect, that the acid would be more optically unstable than any of the acids so far examined. Unfortunately this compound could not be made to undergo second order asymmetric transformation, all crystalline crops were found to be of the partial racemate. That the acid is optically labile was shown by activation experiments with quinidine, the addition curve for the system being included in figure 7. The changes in rotation were very small and thus prohibited any accurate kinetic measurements being made.

(2) A second factor that could influence the optical stability of both series of acids examined, is apparent when models of the compounds are considered.



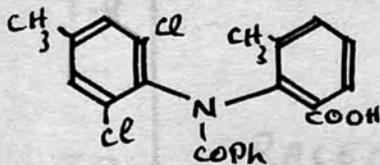
In the absence of hindering groups on the aromatic nuclei, free rotation about all three nitrogen bonds can occur. It is known that rotation is restricted about one link (the N-Aryl ring A in the diagram X), and the aromatic nucleus C is unsubstituted. However ring B containing the different substituents X, can, if free rotation about the N-ring B bond occurs, take up a configuration with chlorine at a maximum distance away from the substituents in ring A, as

shown in XI below.

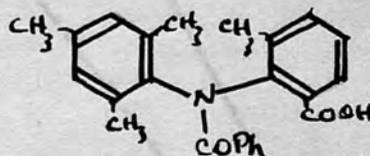


In this position the blocking effect of Cl is decreased. Thus it is possible that para substituents can cause ring B to take up a preferred configuration, and from the experimental results it would appear (if this factor plays a part), that methyl has the greatest effect in causing this orientation. The factors governing this possibility are however, vague.

To eliminate this factor and thus to examine any other effect of para groups it was decided to synthesise the acids, XII and XIII.

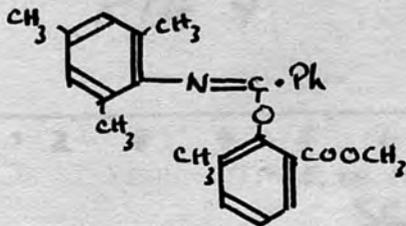


XII

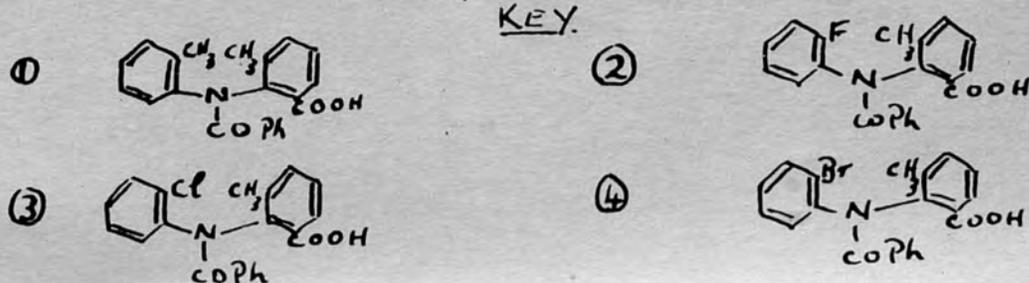
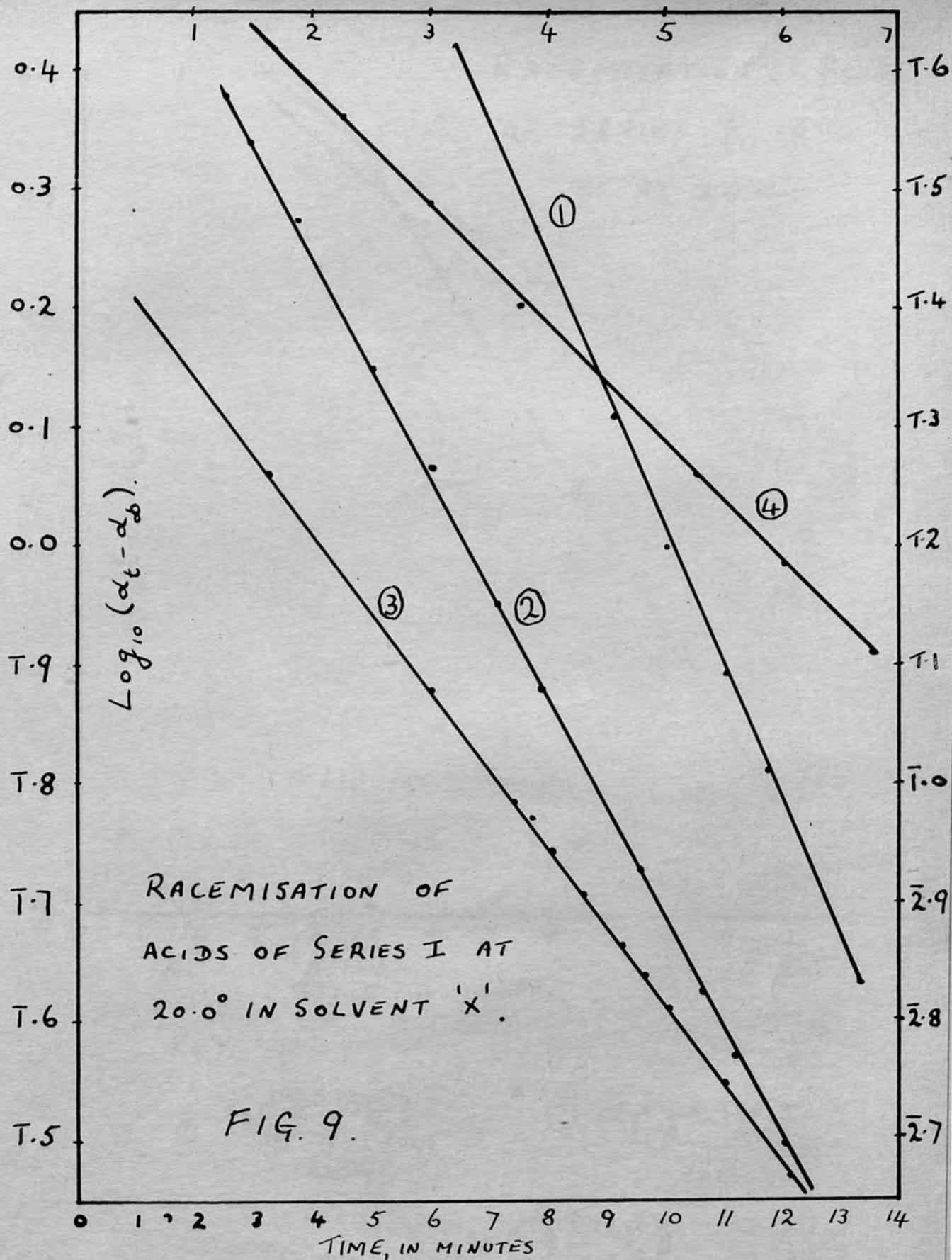


XIII.

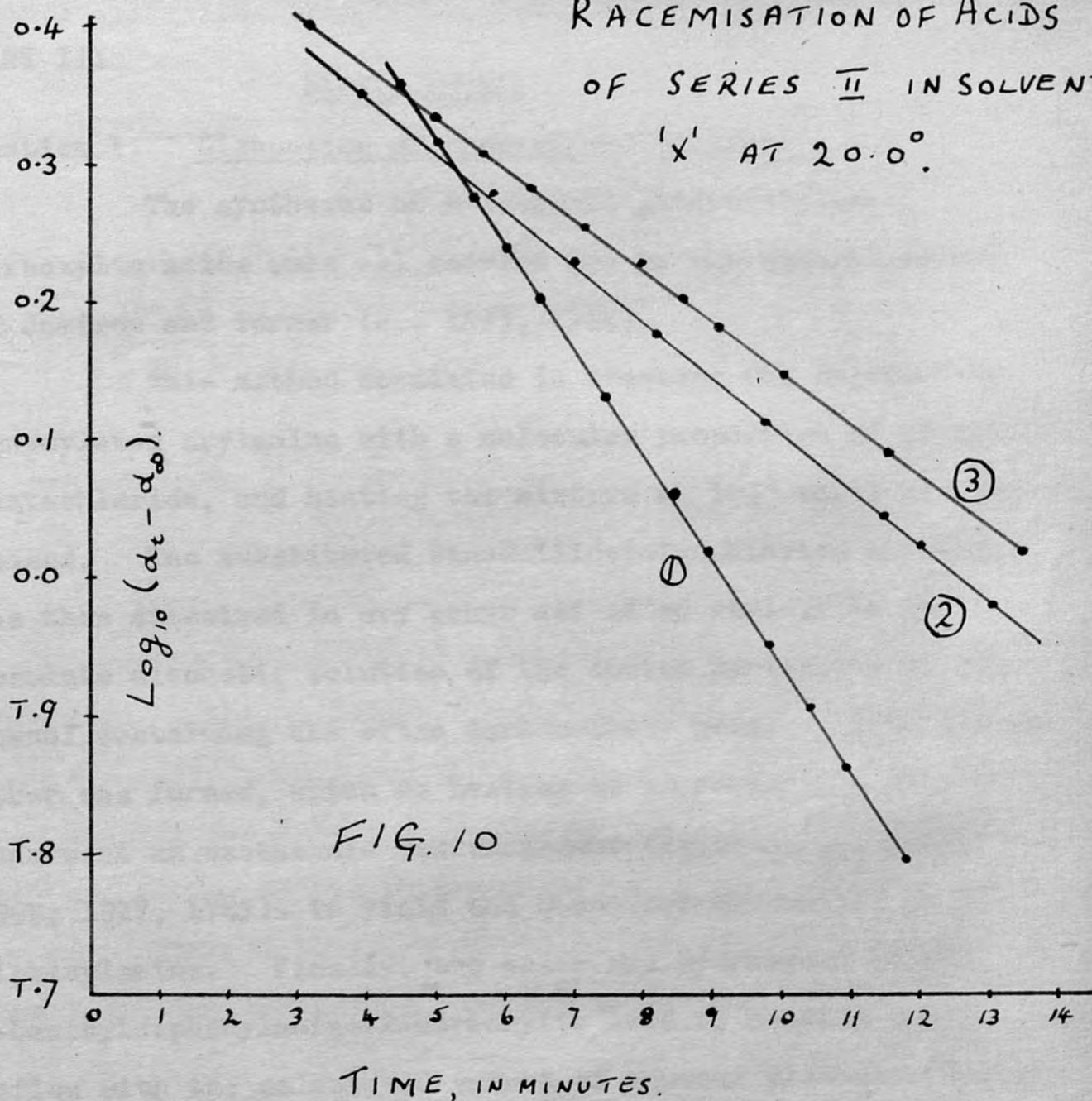
However, attempts to prepare XIII were unsuccessful, the imino-ether XIV would not undergo Chapman's rearrangement.



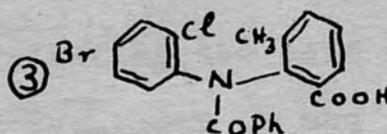
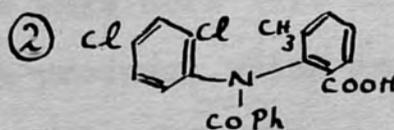
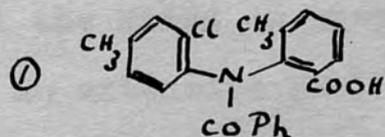
XIV.



RACEMISATION OF ACIDS  
OF SERIES II IN SOLVENT  
'X' AT 20.0°.



KEY.



methyl salicylate, is given below

PART III

EXPERIMENTAL.

Section 1. Discussion of Preparative Methods.

The syntheses of N-benzoyldiphenylamine-2-carboxylic acids were all carried out by the general method of Jamison and Turner (J., 1937, 1954).

This method consisted in treating the appropriate benzoylated arylamine with a molecular proportion of phosphorus pentachloride, and heating the mixture at 100° until all reaction ceased. The substituted benzanilideiminochloride obtained was then dissolved in dry ether and added rapidly to an absolute alcoholic solution of the sodium derivative of the phenol containing the ortho carbomethoxy group. A benzimino-ether was formed, which on heating to approximately 270-280°, underwent an exothermic rearrangement (Chapman. J., 1925, 1992; 1927, 1743). to yield the N-benzoyl derivative of the diphenylamine. Finally, the ester was hydrolysed to the N-benzoyldiphenylamine-2-carboxylic acid by heating under reflux with the calculated amount of aqueous alcoholic sodium hydroxide.

All the acids so prepared in this work were then subjected to an extensive purification process, which included the dissolving of the acids in dilute sodium bicarbonate solution, filtering, and precipitating the acid with dil. hydrochloric acid, followed by treatment of the acid thus obtained, with hot water, and crystallisation to constant m.p. An example of the synthesis, starting with an arylamine and



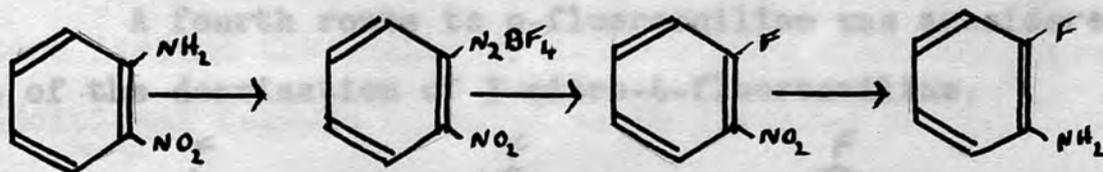
ether in portions of 30 g. or less.

(b) Hydrolysis of the methyl N-benzoyldiphenylamine carboxylates under vigorous conditions (i.e. excess of strong alkali) has been shown to yield the substituted diphenylamine acids (Hall and Turner J., 1945, 694.). Thus the calculated amount of aqueous alcoholic alkali was used in the last stage of the synthesis. (Chem. Zentr., 1919, I, 822) claimed to have

obtained o-fluoroaniline by allowing o-fluorobenzamide to undergo the

Two chief difficulties limited the preparation of substituted N-benzoyldiphenylamines. The first was the ease with which one could obtain the appropriately substituted amines in the requisite yield. In this respect it was hitherto tedious to prepare o-fluoroaniline in large amounts, and a search for a successful preparation of this compd. in high yield was carried out.

The most direct method for preparing o-fluoroaniline was that due to Balz and Schiemann (Ber., 1927, 60, 1186).



Although claiming the formation of o-nitrobenzene-diazonium borofluoride in 74% yield, no yield was recorded for the decomposition of the complex.

This method of preparation was tried many times by the present writer using all the experimental refinements for the decomposition of borofluoride complexes containing the nitro group, as summarised in Organic Reactions, Vol.V, p210.

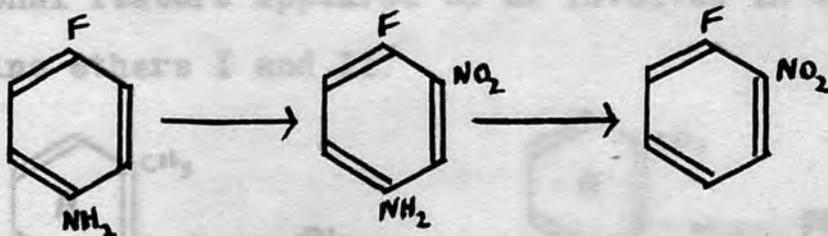
In all cases, only insignificant amounts of o-nitrofluorobenzene were obtained.

Nixon (J., The nitration of fluorobenzene, even with acetyl nitrate, was shown to yield predominantly the para nitrofluorobenzene (Swarts. Rec. Trav. Chem., 1915, 55, 141. Schiemann and Pillarsky, Ber., 1929, 62, 3037).

Rinkes (Chem. Zentr., 1919, I, 822) claimed to have obtained o-fluoroaniline by allowing o-fluorobenzamide to undergo the Hofmann reaction. Schiemann and Pillarsky (Ber., 1937, 70, 1416) considered this the most likely method of useful synthesis and repeated the work, obtaining an 87% yield of o-fluoroacetanilide from 2.15 g. of N-chloro-o-fluorobenzamide, the free amine not being isolated. In the same paper, unsuccessful attempts to carry out the Schmidt and Curtius reactions upon o-fluorobenzoic acid were described.

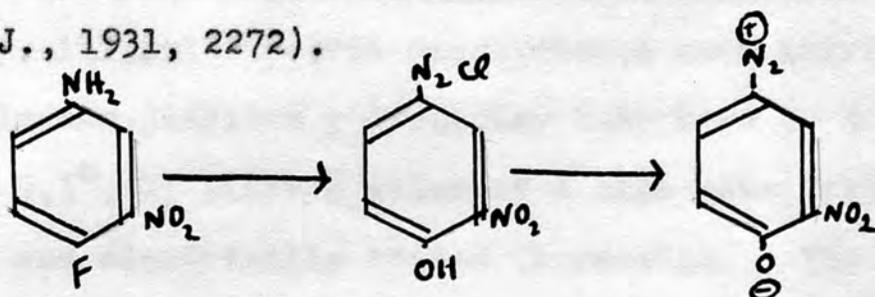
Attempts to repeat the Hofmann reaction on a large scale gave only small amounts of the amine.

A fourth route to o-fluoroaniline was considered, that of the deamination of 3-nitro-4-fluoroaniline.



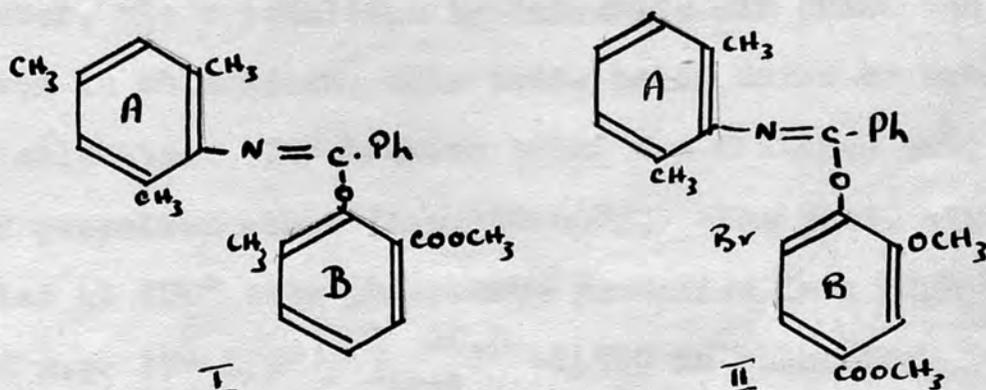
The nitration of p-fluoroaniline was carried out using the directions of Bradlow and Vanderwerf (J. Amer. Chem. Soc., 1948, 70, 654). Two methods were tried in attempting to deaminate this material; thus both ethanol and hypophosphorus acid failed to replace the diazo group

by hydrogen. This inability to react was probably due to the formation of a diazo-oxide, as found by Hodgson and Nixon (J., 1931, 2272).



Attention was now reverted to the Schmidt reaction, for Minor and VanderWerf (J. Org. Chem., 1952, 1429) reported the preparation of o-fluoroaniline in 59% yield by the Schmidt reaction upon o-fluorobenzoic acid. This method was repeated by the present writer and a 79% yield of the amine obtained.

The second limitation to the preparation of substituted N-benzoyldiphenylamines was the inability of certain imino-ethers to undergo the Chapman rearrangement. Chapman shewed (loc. cit.) that the rearrangement was facilitated by electron attractive groups in the migrating nucleus and by electron repulsive groups in the other aryl groups. These factors limited the number of imino-ethers that would rearrange. An additional feature appeared to be involved in the inability of the imino ethers I and II



to undergo rearrangement. Since both molecules had blocking

groups in the four ortho positions of rings A and B, it was possible that this pointed to a steric inhibition of rearrangement.

All polarimetric measurements were carried out using a 2 decimetre jacketed polarimeter tube kept at a constant temp.  $\pm 0.1^\circ$ , by pumping water at a high rate from a mechanically stirred and electrically heated thermostat. The mercury green line  $\lambda_{5461}$  was used throughout, and except where stated, all alkaloids used were anhydrous.

All velocity constants are expressed in natural logarithms and mins.<sup>-1</sup>

#### Solvent 'I'

A standardised solvent was prepared by repeatedly shaking B.P. chloroform with half its volume of distilled water, drying over calcium chloride, and 2.5% ethyl alcohol by volume added. For convenience this was called solvent 'I'.

#### Preparation of Anhydrous Alkaloids.

##### (a) Brucine.

Anhydrous brucine was prepared by the method outlined by E. E. Turner (J., 1951, 842). Commercial B.D.H. brucine,  $[\alpha]_{5461}^{20.0} -135.1^\circ$  in chloroform (C = 0.80), was recrystallised from water, the crystalline tetrahydrate air dried and then dissolved in chloroform, this soln. being dried by anhydrous sodium sulphate. The brucine soln. was filtered into a large bulk of petroleum ether (b.p. 40-60°). The pptd. alkaloid was dried at 100° over phosphorus pentoxide in a high vacuum, and had m.p. 178-179°  $[\alpha]_{5461}^{20.0} -149.0$  in chloroform (C = 0.80).

(b) Quinidine  
Section 2. Synthetic work and Stereochemical Examinations.

All polarimetric measurements were carried out using a 2 decimetre jacketed polarimeter tube kept at a constant temp.  $\pm 0.1^\circ$ , by pumping water at a high rate from a mechanically stirred and electrically heated thermostat. The mercury green line  $\lambda_{5461}$  was used throughout, and except where stated, all alkaloids used were anhydrous.

All velocity constants are expressed in natural logarithms and mins.<sup>-1</sup>

Solvent 'X'

A standardised solvent was prepared by repeatedly shaking B.P. chloroform with half its volume of distilled water, drying over calcium chloride, and 2.5% ethyl alcohol by volume added. For convenience this was called solvent 'X'.

Preparation of Anhydrous Alkaloids.

(a) Brucine.

Anhydrous brucine was prepared by the method outlined by E. E. Turner (J., 1951, 842). Commercial B.D.H. brucine,  $[\alpha]_{5461}^{20.0} -135.1^\circ$  in chloroform (C = 0.80), was recrystallised from water, the crystalline tetrahydrate air dried and then dissolved in chloroform, this soln. being dried by anhydrous sodium sulphate. The brucine soln. was filtered into a large bulk of petroleum ether (b.p. 40-60°). The pptd. alkaloid was dried at 100° over phosphorus pentoxide in a high vacuum, and had m.p. 178-179°  $[\alpha]_{5461}^{20.0} -149.0$  in chloroform (C = 0.80).  
42 g. being obtained (86% of theory).

(b) Quinidine.

The commercial alkaloid,  $[\alpha]_{5461}^{20.0} +280.5^{\circ}$  in solvent 'X' (C = 0.80), was recrystallised twice from benzene, dried, and dissolved in chloroform. After drying over anhyd. sodium sulphate, the soln. was filtered into light petroleum. Pure anhydrous quinidine had, after drying at  $100^{\circ}$  over phosphorus pentoxide in a vacuum,  $[\alpha]_{5461}^{20.0} + 301.1^{\circ}$  in solvent 'X' (C = 0.80).

General Method for Carrying Out Optical Activations.

The alkaloid and acid were weighed into weighing bottles and dissolved in a small amount of preheated solvent. The acid soln. was transferred to a graduated flask, together with washings, and the soln. of the alkaloid rapidly added, the stop clock being started simultaneously. The resultant soln. was made up to 25 cc. and filtered into the jacketed polarimeter tube.

Preparation of N-Benzoyl-4:6-dibromodiphenylamine-2-carboxylic Acid.

(a) Phenylbenzimidino-4:6-dibromo-2-carbomethoxyphenyl ether.

31g. (1 mol.) of 4:6-dibromomethyl salicylate in 600 cc. of dry acetone were added to a soln. of 2.3 g. (1 atom) of sodium in 100 c.c. of absolute alcohol, followed by a solution of 21.5 g. (1 mol.) of benzanilide iminochloride in 65 c.c. of dry ether. After standing over night, the solvents were removed and the residue poured into water. The resultant gum crystallised from methylalcohol in prisms, m.p.  $102-103^{\circ}$ , 42 g. being obtained (86% of theory).

Found. C, 51.4; H, 3.1; Br, 32.5.  $C_{21}H_{15}O_3N Br_2$  requires C, 51.5; H, 3.3; Br, 32.6%.

(b) Methyl N-benzoyl-4:6-dibromodiphenylamine-2-carboxylate.

The ether was found to rearrange at 190-200°, 42 g. being treated in two portions. The product was crystallised from methyl alcohol (prisms) and had m.p. 134-135°, an 80% yield being obtained. Found. C, 51.3; H, 4.0; Br, 32.7.  $C_{21}H_{15}O_3N Br_2$  requires C, 51.5; H, 3.3; Br, 32.6%.

(c) N-Benzoyl-4:6-dibromodiphenylamine-2-carboxylic acid.

25 G. of the ester were hydrolysed with a soln. of 2.3 g. of sodium in 100 c.c. of ethyl alcohol and 20 c.c. of water. Thus the ester was dissolved in ethyl alcohol, the caustic soda soln. added together with a further 66 c.c. of water, and the mixture heated under reflux for an hour. The alcohol was removed and the acid pptd. with dil. hydrochloric acid. After being purified by its soln. in dil. sodium bicarbonate, the acid was recrystallised from benzene to a constant m.p. of 189-190°, an 84% yield of microcrystals being obtained. The acid was found to solvate readily with ethyl alcohol. Found. C, 50.9; H, 2.9.  $C_{20}H_{13}O_3N Br_2$  requires C, 50.5; H, 2.7%.

Activation Experiments with the (+) - Acid and Alkaloids.

Acid + Quinidine.

(i) Acid : Base ratio 1:1. 0.1620 G. of quinidine was dissolved in a soln. of 0.2375 g. of acid in solvent 'X' at 20.0°. This soln. was made up to 25 c.c.

0.2375 g. of acid and the above dissolved to 25 c.c. in solvent 'Y' at 20.0°. The rotation of the solution did not change over 24 hrs.

Time after mixing (mins.)	$\alpha_t - \alpha_\infty$	k
(i) Acid: Base ratio 1:1. 0.1620 G. of quinidine was added to 0.4750 g. of acid dissolved in solvent 'X' at 20.0°. This soln. was made up to 25 c.c. and readings begun 3.4 mins. after mixing.	+0.53	0.103
	0.545	0.106
	0.495	0.107
	0.445	0.104
	0.445	0.105
	0.415	0.107
	0.385	0.104
	0.38	0.106
(ii) Acid: Base ratio 1:1. 0.1620 G. of quinidine was added to 0.4750 g. of acid dissolved in solvent 'X' at 20.0°. This soln. was made up to 25 c.c. and readings begun 3.4 mins. after mixing.	0.355	0.106
	0.345	0.106
	0.310	0.107
	0.295	0.107
	0.265	0.107
	0.235	0.103
	0.215	0.105
	0.195	0.105
	0.185	0.104
	0.17	0.105
(iii) Acid: Base ratio 2:1. 0.1620 G. of quinidine was added to 0.4750 g. of acid dissolved in solvent 'X' at 20.0°. This soln. was made up to 25 c.c. and readings begun 3.4 mins. after mixing.	0.15	0.106
	0.13	0.104
	0.125	0.104

from  $-1.78^\circ$  to  $-1.91^\circ$  was observed, but no kinetic data was obtained. Whence  $k = 0.105$  (limits 0.103 and 0.107).

(ii) Acid: Base ratio 2:1. 0.1620 G. of quinidine was added to 0.4750 g. of acid dissolved in solvent 'X' at 20.0°. This soln. was made up to 25 c.c. and readings begun 3.4 mins. after mixing. No accurate values for the velocity constant were obtained since the observable change in rotation was small

i.e.  $+2.19^\circ$  to  $+2.02^\circ$ .

(iii) Acid: Base ratio 3:1 A mixture of 0.1620 g. of quinidine and 0.7125 g. of acid in 25 c.c. of solvent 'X' at 20.0° had a rotation of  $+2.55^\circ$  which did not change over 24 hrs. Whence  $k = 0.136$  (limits 0.142 and 0.131).

Acid + Brucine.

(i) Acid: Base ratio 1:1. 0.1970 G. of brucine was added to 0.2375 g. of acid and the mixture dissolved to 25 c.c. in solvent 'X' at 20.0°. The rotation of the solution did not change over 24 hrs.

Acid + Cinchonine

(i) Acid : Base ratio 1:1. A mixture of 0.1470 g. of cinchonine and 0.2375 g. of acid was dissolved to 25 c.c. in solvent 'X' at 20.0°. No activation occurred over 24 hrs.

Acid + Cinchonidine.

(i) Acid : Base ratio 1:1. 0.1470 G. of alkaloid and 0.2375 g. of acid was used, being dissolved to 25 c.c. in solvent 'X' at 20.0°. A change in rotation from -1.68° to -1.23° was observed, but reliable Kinetic results could not be obtained because of the small rotational changes.

(ii) Acid:Base ratio 2:1. 0.1470 G. of cinchonidine and 0.4750 g. of acid was used. As in (i) a rotational change from -1.78° to -1.91° was observed, but no Kinetic data was obtained.

(iii) Acid:Base ratio 3:1. 0.470 G. of cinchonidine and 0.7125 g. of acid. Readings were begun 3.69 mins. after mixing.

Time (mins.) after mixing	$\alpha_t - \alpha_\infty$	k	t contd.	$\alpha_t - \alpha_\infty$	k
3.69	-0.31	0.140	11.00	0.12	0.134
4.96	0.27	0.133	15.93	0.07	0.131
5.73	0.23	0.142	18.90	0.04	0.136
6.35	0.23	0.132	23.6	0.02	0.138
7.17	0.195	0.137			

Whence  $k = 0.136$  (limits 0.142 and 0.131).

Preparation of Cinchonidine (+)-N-Benzoyl-4:6-dibromodiphenyl-amine-2-carboxylate.

A suspension of 2.94 g. (1 mol.) of cinchonidine in 50 c.c. of hot acetone was added to a soln. of 4.75 g. (1 mol.) of the (+)-acid in 50 c.c. of acetone. Addition of a further 50 c.c. of acetone and warming caused the solid to dissolve. The soln. was filtered and concentrated to 30 c.c., 50 c.c. of ether added and the soln. kept warm. Crystallisation set in and 6.6 g. (86% of the theory) of the salt were obtained. Found. C, 61.2; H, 4.6; Br, 19.5.  $C_{39}H_{35}O_4N_3Br_2$  requires C, 60.9; H, 4.6; Br, 20.8%.

Mutarotation of the Cinchonidine (+)-acid Salt.

The salt was allowed to mutarotate at four different temps., 0.1900 g. being dissolved to 25 c.c. in solvent 'X' at each temp.

(i) Temp. 16.7°.

Time (mins.) after wetting	$\alpha_t - \alpha_\infty$	k	t contd.	$\alpha_t - \alpha_\infty$	k
4.53	+2.42	0.064	14.00	1.40	0.060
5.12	2.34	0.061	15.61	1.28	0.059
5.85	2.27	0.060	16.63	1.18	0.061
6.66	2.16	0.661	18.10	1.11	0.059
7.39	2.05	0.062	19.37	1.05	0.058
8.18	1.96	0.061	20.05	0.98	0.059
9.05	1.84	0.063	20.75	0.94	0.059
9.70	1.77	0.062	21.53	0.91	0.059
10.91	1.69	0.059	22.65	0.85	0.059
12.00	1.56	0.061	23.33	0.80	0.060
12.68	1.50	0.061	25.15	0.75	0.058
13.42	1.46	0.059	25.90	0.71	0.058

Whence  $k = 0.060$  (limits 0.064 and 0.059).

(ii) Temp. 20.7°.

Time (mins.)	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
4.65	+2.15	0.093	13.37	0.94	0.094
5.70	1.89	0.099	14.73	0.79	0.097
6.80	1.70	0.097	15.65	0.71	0.099
7.45	1.60	0.098	16.50	0.71	0.094
8.15	1.49	0.098	17.15	0.64	0.093
8.85	1.38	0.099	18.00	0.57	0.097
9.73	1.30	0.096	18.90	0.51	0.099
10.68	1.20	0.095	21.21	0.45	0.094
11.47	1.10	0.096	22.23	0.38	0.097
12.40	0.99	0.097	23.55	0.35	0.095

Whence  $k = 0.096$  (limits 0.099 and 0.093).

(iii) Temp. 27.3°.

Time (mins.)	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
4.80	+1.70	0.192	8.62	0.81	0.193
5.40	1.50	0.194	9.14	0.73	0.194
5.95	1.37	0.191	9.87	0.60	0.199
6.57	1.21	0.192	10.39	0.56	0.196
7.25	1.05	0.194	11.20	0.49	0.194
7.65	0.98	0.191	11.90	0.43	0.193
8.15	0.89	0.192			

Whence  $k = 0.193$  (limits 0.199 and 0.191).

(iv) Temp. 10.8°.

Time (mins.)	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
12.00	+1.99	0.027	21.44	1.50	0.029
12.63	1.95	0.028	23.68	1.42	0.029
13.51	1.89	0.029	24.53	1.38	0.029
14.24	1.87	0.028	25.38	1.35	0.029
15.69	1.87	0.029	26.68	1.32	0.028
17.33	1.77	0.029	27.27	1.30	0.028
18.16	1.65	0.029	28.15	1.26	0.028
19.05	1.63	0.028	29.08	1.22	0.029
19.94	1.57	0.029	29.88	1.18	0.029

Whence  $k = 0.029$  (limits 0.029 and 0.027).

Preparation of (+)-N-Benzoyl-4:6-dibromodiphenylamine-2-carboxylic Acid.

The decomposition of the cinchonidine (+)-acid salt by pyridine proved to be inefficient, not all of the alkaloid being removed. However, 2 g. of salt were ground with cold anhydrous formic acid (60 c.c.) and the soln. filtered into dil. hydrochloric acid and ice. The pptd. acid was washed thoroughly with water and dried in a vacuum. m.p. 190°. Found. Br, 32.9  $C_{20}H_{13}O_3N Br_2$  requires Br, 33.6%.

Racemisation of the Active (+)-Acid.

0.1000 G. of acid was dissolved to 25 c.c. in chloroform at 20.0°. Readings were begun 1.85 mins. after wetting.

Acid.

The ester was hydrolysed by boiling it with a soln.

Time after 1.85 mins.	$\alpha_t - \alpha_p$	k
0	+0.42	-
0.38	0.32	0.716
0.75	0.245	0.719
1.10	0.19	0.721
1.45	0.16	0.666
1.90	0.115	0.682
2.20	0.09	0.700
2.55	0.07	0.703
3.00	0.055	0.678
4.15	0.025	0.734

Whence  $k = 0.702$  (limits 0.734 and 0.666).

Preparation of N-Benzoyl-2'-chloro-6-methyldiphenylamine  
-2-carboxylic Acid.

Alcohol. The acid was prepared as outlined by Jamison and Turner. J., 1940, 264.

(a) 2'-Chloro-phenylbenzimidino-2-carbomethoxy-6-methylphenyl  
ether.

The ether, obtained in a 72% yield, crystallised from methyl alcohol in prisms m.p. 85°. Jamison and Turner record m.p. 85-86°.

(b) Methyl N-benzoyl-2'-chloro-6-methyldiphenylamine-2-  
carboxylate.

As reported, the ether underwent rearrangement at 260-270°. 150 G. of ether (in 30 g. portions) gave 130 g. of ester (87% of theory). The product crystallised from methyl alcohol in prisms m.p. 167-168°.

(c) N-Benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic  
Acid.

The ester was hydrolysed by boiling it with a soln.

of aqueous alcoholic sodium hydroxide for 2 hrs. The acid was crystallised twice from acetone - light petroleum (b.p. 40-60°) and once from acetone, slender needles of m.p. 197° being obtained. Found. C, 69.0; H, 4.3; Cl, 10.2. Calculated C, 68.9; H, 4.4; Cl, 9.7%. Jamison & Turner report m.p. 197-198° with previous softening, the m.p. varying with rate of heating.

(iii) Solvent. 6% ethyl alcohol.

The Optical Activation of the Chloro-Methyl Acid with Quinidine in Chloroform containing Varying Amounts of Ethyl Alcohol.

Acid:Base ratio 2:1. Throughout this series of experiments, 0.1620 g. of quinidine was dissolved in the minimum amount of preheated solvent and added to a soln. of 0.3657 g. of the acid in the same solvent at 20.0°. The resulting soln. was made up to 25 c.c.

(i) Solvent. 1% ethyl alcohol.

Time (mins.)	$\alpha_t - \alpha_\infty$	k	t contd.	$\alpha_t - \alpha_\infty$	k
2.65	+0.24	0.220	5.00	0.13	0.241
3.26	0.20	0.228	6.20	0.09	0.246
3.75	0.19	0.212	8.75	0.06	0.228
4.17	0.16	0.231	9.90	0.04	0.232
4.60	0.15	0.230	10.95	0.03	0.234

Whence  $k = 0.230$  (limits 0.212 and 0.246).

(ii) Solvent. 3.2% ethyl alcohol.

Time (mins.)	$\alpha_t - \alpha_\infty$	k	t contd.	$\alpha_t - \alpha_\infty$	k
4.20	+0.335	0.228	6.35	0.195	0.236
4.80	0.285	0.233	7.10	0.16	0.239
5.25	0.255	0.234	8.70	0.115	0.233
5.75	0.235	0.229	9.55	0.095	0.232

Whence  $k = 0.233$  (limits 0.228 and 0.239).

(iii) Solvent. 6% ethyl alcohol.

Time after 2.6 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.49	-
1.40	0.39	0.171
2.55	0.30	0.190
3.05	0.29	0.176
3.60	0.26	0.179
4.40	0.22	0.185
4.96	0.19	0.188
5.55	0.19	0.173
6.15	0.16	0.179
6.70	0.14	0.189
7.15	0.13	0.188
7.78	0.11	0.188
8.40	0.09	0.191
9.00	0.09	0.191
9.60	0.08	0.185
10.65	0.07	0.185

Whence  $k = 0.184$  (limits 0.171 and 0.191).

Whence  $k = 0.175$  (limits 0.185 and 0.191).

(iv) Solvent. 9.1% ethyl alcohol.

Time (mins.)	$\alpha_t - \alpha_\infty$	k
3.34	+0.47	0.188
4.00	0.41	0.191
4.50	0.39	0.181
5.06	0.355	0.179
5.58	0.305	0.190
6.58	0.24	0.197
7.43	0.21	0.193
8.10	0.195	0.186
8.95	0.155	0.194
10.50	0.125	0.186
11.38	0.105	0.187
13.10	0.07	0.193
15.77	0.05	0.182
16.60	0.04	0.186
20.05	0.02	0.189

Whence  $k = 0.188$  (limits 0.179 and 0.197).

(vii) Solvent. 30% ethyl alcohol.

(v) Solvent. 17% ethyl alcohol.

Time after 4.0 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.35	-
1.10	0.30	0.154
1.65	0.26	0.179
3.62	0.18	0.175
4.23	0.16	0.182
5.00	0.14	0.187
6.50	0.10	0.188
9.25	0.06	0.185
10.10	0.06	0.169
13.32	0.04	0.157
13.80	0.03	0.170
14.70	0.02	0.182

Whence  $k = 0.175$  (limits 0.188 and 0.154).

(ix) Solvent. Pure ethyl alcohol.

A very small rotational change was observed but no

Kinetic data could be obtained.

(vi) Solvent. 30% ethyl alcohol.

Time after 4.1 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.29	-
0.93	0.25	0.160
1.40	0.23	0.166
2.37	0.20	0.157
2.93	0.195	0.136
3.65	0.165	0.155
5.45	0.12	0.162
6.83	0.085	0.180
9.66	0.06	0.163
11.17	0.05	0.157
12.15	0.04	0.163
13.13	0.35	0.161

Whence  $k = 0.160$  (limits 0.180 and 0.136).

(vii) Solvent. 50% ethyl alcohol.

Time after 3.66 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.20	-
0.68	0.18	0.155
1.39	0.16	0.171
2.71	0.13	0.159
5.69	0.09	0.140
8.39	0.055	0.154
10.24	0.05	0.135
13.19	0.025	0.158

Whence  $k = 0.151$  (limits 0.171 and 0.135).

(viii) Solvent. 100% ethyl alcohol.

No change in rotation was observed.

(ix) Solvent. Pure chloroform.

A very small rotational change was observed but no Kinetic data could be obtained.

The Optical Activation of N-Benzoyl-2'-chloro-6-methyldiphenyl  
amine-2-carboxylic Acid with Quinidine in the Presence of  
Various Optically Inactive Materials.

Temp. 20.0°. Solvent 'X' previously kept at 20.0° was used in this series of experiments.

Method.

The chloro-methyl acid 0.1829 g. (1 mol.), quinidine, 0.1620 g. (1 mol.), and one molecular amount of the third substance were individually dissolved in the min. amount of solvent. The solns. of quinidine and the third substance were then added in rapid succession to the soln. of the acid, the mixture being made up to 25 c.c.

Whence  $k = 0.274$  (limits 0.255 and 0.293).

(i) Chloro-methyl acid:quinidine ratio 1:1.

Time after 4.5 mins.	$\alpha_t - \alpha_0$	$k$
0	+0.94	
3.00	0.85	0.0324
4.50	+1.035	0.0331
6.00	0.95	0.0322
7.50	0.94	0.0322
9.00	0.92	0.0312
10.50	0.91	0.0318
12.00	0.875	0.0324
13.50	0.85	0.0318
15.00	0.82	0.0318
16.50	0.80	0.0316
18.00	0.775	0.0318
19.50	0.745	0.0312
21.00		0.0320
22.50		0.0316
24.00	0.435	0.0321

Whence  $k = 0.0321$  (limits 0.0312 and 0.0324). Each reading was the mean of three, taken at  $(t-\frac{1}{2})$ ,  $t$ , and  $(t+\frac{1}{2})$  mins.

(ii) Chloro-methyl acid : quinidine ratio 2:1.

Time after 2.5 mins.	$\alpha_t - \alpha_\infty$	k
0.	+0.46	-
0.75	0.375	0.273
1.13	0.34	0.268
1.52	0.30	0.281
2.00	0.27	0.266
3.30	0.19	0.268
3.95	0.15	0.284
4.58	0.12	0.293
5.20	0.11	0.275
6.00	0.09	0.272
7.10	0.055	0.299
7.55	0.065	0.259
8.65	0.045	0.269
9.35	0.04	0.261
10.77	0.025	0.270
13.45	0.015	0.255

Whence  $k = 0.274$  (limits 0.255 and 0.293).

(iii) Chloro-methyl acid : quinidine : naphthalene (0.0641 g.)  
ratio 1:1:1.

Time after 2.32 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	+1.005	-	10.31	0.735	0.0300
1.88	0.95	0.0300	11.93	0.715	0.0285
2.43	0.94	0.0275	13.53	0.675	0.0290
3.18	0.91	0.0310	14.98	0.665	0.0280
3.58	0.91	0.0280	18.18	0.58	0.0300
4.53	0.875	0.0310	19.78	0.56	0.0300
5.48	0.86	0.0280	21.38	0.54	0.0290
6.43	0.82	0.0320	22.68	0.52	0.0290
7.68	0.80	0.0300	26.68	0.46	0.0290
8.81	0.775	0.0295	27.68	0.44	0.0300
9.68	0.745	0.0310	28.68	0.43	0.0300

Whence  $k = 0.0296$  (limits 0.0275 and 0.0320).

(iv) Chloro-methyl acid:quinidine: naphthoic acid (0.0871 g.)  
ratio 1:1:1.

Time after 2.78 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	+0.345	-	6.32	0.11	0.181
1.42	0.26	0.199	6.82	0.10	0.182
1.84	0.245	0.186	8.52	0.07	0.187
2.47	0.21	0.201	9.27	0.05	0.208
2.97	0.195	0.192	10.47	0.05	0.185
3.37	0.18	0.193	11.12	0.035	0.206
4.12	0.16	0.195	12.22	0.025	0.215
4.72	0.14	0.191	13.02	0.025	0.202
5.42	0.11	0.211	15.57	0.015	0.201
5.87	0.12	0.180			

Whence  $k = 0.197$  (limits 0.180 and 0.215).

(v) Chloromethyl acid : quinidine : benzoic acid (0.0611 g.)  
ratio 1:1:1.

Time after 2.65 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	+0.37	-	8.45	0.095	0.161
3.75	0.205	0.158	9.50	0.06	0.192
4.35	0.18	0.166	10.00	0.07	0.167
4.95	0.16	0.169	11.45	0.045	0.184
5.50	0.145	0.170	12.75	0.03	0.197
6.05	0.13	0.173	13.80	0.03	0.182
6.70	0.12	0.168	15.15	0.03	0.166
7.25	0.12	0.156	18.35	0.01	0.197
7.85	0.10	0.167			

Whence  $k = 0.172$  (limits 0.156 and 0.197).

(vi) The Racemisation of (-)-N-Benzoyl-2<sup>1</sup>-chloro-6-methyl  
diphenylamine-2-carboxylic Acid.

0.1150 G. of the active acid was taken and dissolved  
to 25 c.c. in solvent 'X' at 20.0°.

Time after 3.25 mins.	$\alpha_t - \alpha_p$	k	Time contd.	$\alpha_t - \alpha_p$	k
0	-1.14	-	6.80	0.42	0.147
1.75	0.88	0.148	7.75	0.36	0.149
2.75	0.76	0.147	8.25	0.345	0.145
3.60	0.675	0.146	8.95	0.31	0.146
4.15	0.625	0.145	9.40	0.28	0.149
4.55	0.59	0.145	10.90	0.23	0.147
4.95	0.565	0.142	11.45	0.21	0.148
5.40	0.52	0.145	12.55	0.18	0.147
6.00	0.47	0.148	13.65	0.15	0.149
6.30	0.45	0.148	14.25	0.135	0.150

Whence  $k = 0.147$  (limits 0.150 and 0.142).

(1) Temp. 23.6°.

Preparation of Brucine (-)-N-benzoyl-2'-chloro-6-methyl  
diphenylamine-2-carboxylate.

4.3 G. of brucine dihydrate and 3.66 g. of the (+)-acid were dissolved in 60 c.c. of ethyl alcohol, the soln. filtered, and 250 c.c. of ether added. When crystallisation began a further 100 c.c. of ether were added followed after an hour by 250 c.c. more. The microcrystalline salt was obtained in 96% yield.

Preparation of (-)-N-Benzoyl-2'-chloro-6-methyldiphenylamine  
-2-carboxylic Acid.

2 G. of the brucine salt were decomposed by dissolving in anhydrous formic acid at 0°. The soln. was filtered into dil. hydrochloric acid and ice and the ptd. acid dried in a vacuum. Found. Cl, 9.1. Calculated Cl, 9.7%.

Whence  $k = 0.147$  (limits 0.150 and 0.142).

Activation Energy Studies.

I. The Optical Activation of N-Benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic Acid with Quinidine.

Acid:Base ratio 2:1. Solvent. Chloroform containing 6.9% ethyl alcohol by volume. A soln. of 0.1620 g. of quinidine was added to a soln. of 0.3657 g. of the chloro-methyl acid and the resulting soln. made up to 25 c.c.

(i) Temp. 23.6°.

Time after 3.8 mins.	$\alpha_t - \alpha_\infty$	k	Time Contd.	$\alpha_t - \alpha_\infty$	k
0	+0.35	-	3.70	0.11	0.307
1.22	0.24	0.314	4.05	0.10	0.304
1.80	0.19	0.330	4.50	0.09	0.309
2.20	0.18	0.307	4.95	0.07	0.320
2.85	0.15	0.303	5.30	0.06	0.313
3.20	0.14	0.292			

Whence  $k = 0.310$  (limits 0.292 and 0.330).

(ii) Temp. 19.9°.

Time after 3.45 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	+0.51	-	4.40	0.23	0.184
0.45	0.47	0.180	4.80	0.21	0.188
0.90	0.43	0.201	5.20	0.20	0.178
1.30	0.40	0.195	5.80	0.18	0.183
1.65	0.37	0.193	6.35	0.15	0.191
2.00	0.35	0.194	7.00	0.15	0.178
2.35	0.33	0.184	7.47	0.14	0.171
2.75	0.31	0.180	8.45	0.11	0.184
3.18	0.28	0.187	9.45	0.10	0.175
3.65	0.27	0.178	10.45	0.08	0.180
4.05	0.24	0.190	11.37	0.06	0.185

Whence  $k = 0.185$  (limits 0.171 and 0.201).

(iii) Temp.  $15.1^{\circ}$ .

Time after 3.02 mins.	$\alpha_t - \alpha_{\infty}$	k	Time contd.	$\alpha_t - \alpha_{\infty}$	k
0	+0.705	-	6.53	0.365	0.101
0.53	0.67	0.096	7.53	0.33	0.101
1.33	0.62	0.097	9.38	0.265	0.104
2.13	0.57	0.100	10.11	0.24	0.107
2.68	0.535	0.103	12.26	0.195	0.105
3.48	0.495	0.102	14.86	0.14	0.109
4.03	0.47	0.101	17.66	0.110	0.105
4.55	0.44	0.104	22.48	0.065	0.106

Whence  $k = 0.103$  (limits 0.096 and 0.109).

(iv) Temp.  $11.0^{\circ}$  = 0.0630 (limits 0.0610 and 0.0650).

Time after 5.02 mins.	$\alpha_t - \alpha_{\infty}$	k	Time contd.	$\alpha_t - \alpha_{\infty}$	k
0	+0.805	-	8.85	0.47	0.0600
0.68	0.77	0.0650	10.33	0.42	0.0630
1.28	0.755	0.0500	12.53	0.365	0.0630
2.42	0.69	0.0640	13.93	0.34	0.0620
2.88	0.67	0.0640	15.68	0.31	0.0610
3.41	0.65	0.0630	16.41	0.30	0.0600
4.46	0.615	0.0600	19.05	0.25	0.0610
5.17	0.585	0.0620	20.53	0.235	0.0600
5.65	0.57	0.0610	20.98	0.225	0.0610
6.45	0.545	0.0610	21.98	0.21	0.0610

Whence  $k = 0.0610$  (limits 0.0650 and 0.0500).

(v) Temp. 5.2°.

Time after 3.25 mins.	$\alpha_t - \alpha_\infty$	k	Time cont d.	$\alpha_t - \alpha_\infty$	k
0	+0.95	-	21.25	0.47	0.0330
0.65	0.925	0.0410	23.25	0.45	0.0320
4.60	0.805	0.0360	25.25	0.41	0.0330
6.20	0.76	0.0360	27.25	0.40	0.0320
7.65	0.75	0.0310	29.25	0.375	0.0320
10.30	0.665	0.0350	31.25	0.33	0.0330
11.85	0.645	0.0330	37.25	0.29	0.0320
13.38	0.595	0.0350	40.25	0.24	0.0350
14.95	0.57	0.0340			
17.25	0.55	0.0320			
19.25	0.50	0.0330			

Whence  $k = 0.0330$  (limits 0.0310 and 0.0410).

Readings after 14.95 mins. were the mean of three, taken at (t-1), t, and (t+1) mins.

(ii) Temp. 20.6°.

II The Racemisation of (-)-N-Benzoyl-2'-chloro-6-methyldiphenylamine-2-carboxylic Acid.

Solvent. Chloroform containing 6.9% ethyl alcohol by volume.

In these experiments, 0.1000 g. of (-)-acid was dissolved to 25 c.c. in preheated solvent.

Time	$\alpha_t - \alpha_\infty$	k	Time	$\alpha_t - \alpha_\infty$	k
0	1.000	-	7.75	0.59	0.187
1.30	0.935	0.185	9.00	0.55	0.183
1.45	0.915	0.185	9.25	0.535	0.182
2.30	0.855	0.185	10.25	0.50	0.185
3.30	0.765	0.186	10.85	0.45	0.186
4.55	0.615	0.183	11.35	0.42	0.187
5.20	0.50	0.183	12.15	0.35	0.184
5.80	0.40	0.185	13.25	0.215	0.180
6.25	0.33	0.186	17.00	0.095	0.186
6.70	0.475	0.185			
7.35	0.59	0.187			

Whence  $k = 0.185$  (limits 0.180 and 0.188).

(i) Temp. 25.4°.

Time after 2.75 mins.	$\alpha_t - \alpha_0$	k	Time contd.	$\alpha_t - \alpha_0$	k
0	-1.58	-	5.07	0.36	0.292
0.40	1.40	0.303	5.40	0.32	0.270
0.89	1.225	0.286	5.85	0.30	0.284
1.30	1.08	0.293	6.15	0.27	0.287
1.65	0.98	0.290	6.57	0.24	0.287
1.97	0.90	0.286	7.05	0.195	0.297
2.75	0.70	0.296	7.57	0.18	0.287
3.10	0.635	0.294	8.45	0.14	0.287
3.53	0.565	0.291	8.92	0.115	0.294
4.00	0.505	0.285	9.68	0.085	0.302
4.25	0.455	0.293	10.80	0.07	0.289
4.70	0.41	0.287			

Whence  $k = 0.290$  (limits 0.303 and 0.270).

(ii) Temp. 20.6°.

Time after 3.3 mins.	$\alpha_t - \alpha_0$	k	Time contd.	$\alpha_t - \alpha_0$	k
0	-2.335	-	7.75	0.55	0.187
1.10	1.90	0.187	8.30	0.51	0.183
1.45	1.785	0.185	9.00	0.455	0.182
2.00	1.61	0.186	9.53	0.40	0.185
2.50	1.465	0.186	10.26	0.35	0.185
3.30	1.265	0.186	10.85	0.31	0.186
4.55	1.015	0.183	11.35	0.28	0.187
5.20	0.90	0.183	12.15	0.25	0.184
5.80	0.80	0.185	13.25	0.215	0.180
6.25	0.73	0.186	17.00	0.095	0.188
6.70	0.675	0.185			
7.35	0.59	0.187			

Whence  $k = 0.185$  (limits 0.180 and 0.188).

(iii) Temp. 6.3°.

Time after 4.25 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-2.43	-	15.75	1.22	0.0438
2.40	2.185	0.0442	19.75	1.025	0.0437
3.30	2.08	0.0471	22.75	0.875	0.0449
4.13	2.035	0.0429	25.75	0.77	0.0445
6.23	1.87	0.0421	28.75	0.68	0.0445
6.65	1.84	0.0418	31.75	0.56	0.0462
8.05	1.71	0.0437	34.75	0.495	0.0458
9.75	1.595	0.432	44.75	0.31	0.0462
12.75	1.39	0.0438			

Whence  $k = 0.0443$  (limits 0.0418 and 0.0471).

Readings after 8.05 mins. were the mean of three, taken at (t-1), t, and (t+1) mins.

The Optical Activation of the (+)-chloro-methyl Acid by Quinidine obtained from its Salt with N-Benzoyldiphenylamine -4-carboxylic Acid.

0.1620 G. of quinidine and 0.1586 g. of the optically inactive acid were dissolved in solvent 'X' and the soln. filtered into a graduated flask. 0.1829 G. of the (+)-chloro-methyl acid was then added, and when dissolved, the soln. was made up to 25 c.c. and examined polarimetrically.

Temp. 13° ± 0.5°.

(d) Benz-o-Bromocinnamide Isomeric.

110 G. of o-bromocinnamide were treated with 92 g. of phosphorus pentachloride. Fractional distillation of the

Time (mins.)	$\alpha_t - \alpha_0$	k	Time contd.	$\alpha_t - \alpha_0$	k
4.35	0.48	0.0740	13.71	0.245	0.0720
6.73	0.395	0.0770	14.95	0.22	0.0740
7.50	0.38	0.0740	16.85	0.19	0.0740
8.00	0.37	0.0730	17.66	0.19	0.0700
8.50	0.36	0.0720	20.37	0.15	0.0730
8.95	0.34	0.0740	22.54	0.125	0.0740
10.28	0.315	0.0720	24.45	0.115	0.0720
11.33	0.30	0.0700	27.25	0.09	0.0730
12.10	0.27	0.0740			

alcohol. Whence  $k = 0.0730$  (limits 0.0700 and 0.0770)

removed and the residue poured into water.

The Preparation of N-Benzoyl-2'-bromo-6-methyldiphenylamine  
-2-carboxylic Acid.

(a) o-Bromonitrobenzene.

(1) This material was obtained in a 79% yield by the diazotisation of o-nitroaniline.

(b) o-Bromoaniline.

The reduction of the nitro body was effected by the method due to West (J., 1925, 127, 494.). An 80% yield of glistening white needles of o-bromoaniline, m.p.  $31^\circ$ , was obtained.

(c) o-Bromobenzanilide.

On heating one molecular amount of the amine with 1.1 molecular amounts of benzoyl chloride, o-bromobenzanilide was obtained in an 85% yield. m.p.  $116^\circ$ .

(d) Benz-o-Bromoanilide iminochloride.

110 G. of o-bromobenzanilide were treated with 92 g. of phosphorus pentachloride. Fractional distillation of the benzene to a constant b.p.  $184-190^\circ$ , which varied with the

reaction mixture yielded 89.5 g. of the imino-chloride

b.p.  $210^{\circ}/26$  m.m. *Found.* C, 61.4; H, 3.93%

(e) 2'-Bromophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether

Preparation. Solutions of 50 g. (1 mol.) of methyl o-cresotate in 300 c.c. of absolute alcohol and 88.5 g. (1 mol.) of the imino chloride in 250 c.c. of dry ether were rapidly added to a soln. of 6.9 g. (1 atom) of sodium in 300 c.c. of absolute alcohol. After a period of 15 hrs., the solvents were removed and the residue poured into water. The resultant gum crystallised from methyl alcohol in prisms. m.p.  $100-102^{\circ}$ ., 79 g. being obtained. *Found.* C, 62.7; H, 4.52. *Calc.* for  $C_{22}H_{18}O_3N$  Br requires C, 62.4; H, 4.29%.

(f) Methyl N-benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylate.

The imino-ether was found to isomerize at  $280^{\circ}$ ; two portions of 30 g. yielded 48 g. of ester (80% of theory). The ester crystallised from methyl alcohol in prisms m. p.  $190-191^{\circ}$ . *Found.* C, 63.1; H, 4.28. *Calc.* for  $C_{22}H_{18}O_3N$  Br requires C, 62.4; H, 4.29%.

(g) N-Benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylic Acid.

A soln. of 48 g. of the ester in 800 c.c. of ethyl alcohol was boiled for an hour with a soln. of 6.9 g. of sodium in 200 c.c. of ethyl alcohol and 120 c.c. of water, a further 120 c.c. of water being added. The crude acid was crystallised from ethyl alcohol and finally from benzene to a constant m.p.  $198-199^{\circ}$ , which varied with the

rate of heating. Found. C, 61.9; H, 4.09.

$C_{21}H_{16}O_3N$  Br requires C, 61.4; H, 3.93%.

Preparation of Brucine (-)-N-benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylate.

4.67 G. (1 mol.) of brucine tetrahydrate and 4.12 g. (1 mol.) of (+)-bromo-methyl acid were dissolved in 110 c.c. of hot ethyl alcohol. The soln. was filtered and kept at  $50^{\circ}$ . When crystallisation began, the flask was cooled and 50 c.c. of ether added followed, after 15 mins., by a further 60 c.c. A 91% yield (8 g.) of the brucine (-)-acid salt was obtained.

On dissolving 0.2000 g. of the salt to 25 c.c. in solvent 'X' at  $20.0^{\circ}$ , the rotation of the soln. fell from  $-4.63^{\circ}$  to  $-0.30^{\circ}$  in 31 mins., the velocity constant of the mutarotation being  $k = 0.0880$ , the mean of 27 readings.

Preparation of (-)-N-Benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylic Acid.

3 G. of the brucine (-)-acid salt were ground with 60 c.c. of anhydrous formic acid at  $0^{\circ}$ , and the soln. filtered through glass wool into dil. hydrochloric acid and ice. The pptd. acid was collected, rapidly dried, and submitted to the process once more, being finally dried in a vacuum over calcium chloride.

Racemisation of the Active Acid.

0.1000 G. of the (-)-acid was dissolved to 25 c.c. in solvent 'X' at 20.0°.

(i)

Time after 2.45 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-2.91	-	9.55	0.95	0.117
0.65	2.71	0.105	11.05	0.80	0.116
1.13	2.58	0.107	12.55	0.67	0.117
2.05	2.32	0.110	14.05	0.56	0.117
3.55	1.95	0.113	15.55	0.47	0.117
5.05	1.58	0.120	17.05	0.39	0.119
6.55	1.36	0.116	19.55	0.29	0.117
8.05	1.14	0.116	22.55	0.20	0.117

Whence  $k = 0.115$  (limits 0.105 and 0.120).

Readings after 3.95 mins. were the mean of three taken at

(ii) Repetition of (i).

Time after 2.45 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-2.91	-	7.55	1.21	0.116
0.55	2.735	0.110	8.55	1.08	0.116
1.55	2.44	0.113	10.55	0.85	0.117
3.55	1.93	0.116	12.55	0.67	0.117
4.55	1.71	0.116	13.55	0.60	0.117
5.55	1.53	0.116			
6.55	1.36	0.116			

Whence  $k = 0.115$  (5) (limits 0.110 and 0.117).

Activations with Quinidine.

Acid:Base ratio 1:1. Solutions of 0.1620 g. of quinidine and 0.2051 g. of the (+)-acid in solvent 'X' at 20.0° were mixed, and the resultant soln. made up to 25 c.c.

Acid:Base ratio 2:1 = 0.4102 g. of acid and 0.1520 g. of minidine were dissolved in 25 c.c. in solvent by ...

(i)

Time after 3.05 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.79	-
1.80	0.77	0.0143
4.85	0.72	0.0178
5.95	0.71	0.0180
7.95	0.69	0.0158
13.95	0.63	0.0174
19.95	0.57	0.0165
25.95	0.52	0.0160
36.95	0.44	0.0155
93.95	0.18	0.0158
132.95	0.09	0.0156
135.95	0.08	0.0160
211.95	0.04	0.0146

Whence  $k = 0.0161$  (limits 0.0146 and 0.0180).

Readings after 5.95 mins. were the mean of three taken at (t-1), t, and (t+1) mins.

(ii) Repetition of (i).

(ii) Repetition of (i)

Time after 3.05 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.79	-
3.55	0.74	0.0166
5.45	0.73	0.0146
7.50	0.70	0.0160
10.95	0.66	0.0165
16.95	0.60	0.0158
22.95	0.54	0.0167
30.95	0.49	0.0153
60.95	0.30	0.0158
110.95	0.13	0.0162

Whence  $k = 0.0160$  (limits 0.0146 and 0.0167).

As in (i), readings after 7.5 mins. were the mean of three.

Acid:Base ratio 2:1 0.4102 G. of acid and 0.1620 g. of quinidine were dissolved to 25 c.c. in solvent 'X' at 20.0°.

(i)

Time after 3.3 mins.	$\alpha_t - \alpha_0$	k
0	+0.25	-
0.60	0.205	0.338
1.07	0.18	0.319
1.66	0.15	0.310
2.40	0.115	0.326
3.65	0.08	0.314
4.20	0.07	0.304
4.80	0.055	0.321

Whence  $k = 0.319$  (limits 0.338 and 0.304).

(ii) Repetition of (i).

Time after 3.5 mins.	$\alpha_t - \alpha_0$	k
0	+0.24	-
0.55	0.20	0.314
1.12	0.17	0.308
1.70	0.14	0.305
2.22	0.12	0.311
3.00	0.09	0.309
3.90	0.07	0.310
5.00	0.05	0.311

Whence  $k = 0.310$  (limits 0.305 and 0.314).

Preparation of N-Benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylic Acid.

Attempts to prepare o-Fluoroaniline.

(i) By the Decomposition of o-Nitrobenzenediazonium fluoroborate

Reference. Organic Syntheses, Vol. II, Wiley, p226.

102 G. of o-nitroaniline were diazotised in borofluoric Acid soln. (42% W/V.), and the borofluoride complex obtained. This was dried in a vacuum and weighed 149 g.

25 G. of the complex were decomposed in 5 g. portions, each portion being added into the same flask, which was fitted with a water condenser and a system of cooled traps.

Throughout the decomposition the flask was kept in an oil bath at 120°. Steam distillation of the alkaline residues gave no o-nitrofluorobenzene.

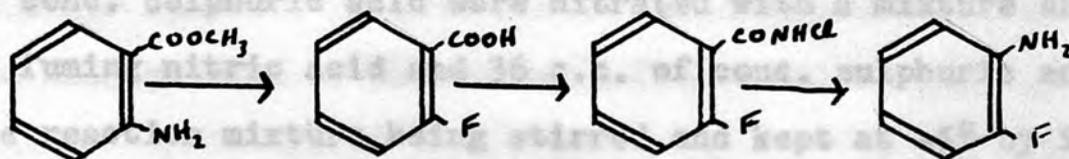
A further 25 g. were decomposed, the material being diluted by intimately mixing it with 125 g. of clean sand. No fluoro cmpd. was obtained. This expt. was repeated using sodium fluoride as the diluent, but with no success.

An attempt was made to obtain the fluoro cmpd. by decomposing the complex, suspended in an inert liquid. Thus 20 g. of complex were vigorously stirred in 250 c.c. of paraffin oil. Steam distillation of the alkaline reaction mixture gave no o-nitrofluorobenzene.

the borofluoride complex so formed, a 40% yield being obtained.

p-Fluoroaniline was obtained by reducing the nitro compd. with hydrogen at 70 lb./sq. inch, using Raney nickel as a catalyst. This amine was nitrated as outlined by Bradlow

(ii) The Hofmann Reaction with N-Chloro-o-fluorobenzamide



*o*-Fluorobenzamide was prepared from methyl anthranillate as outlined by Schiemann and Baumgarten (loc. cit.) The N-chloro amide was obtained by stirring 5.7 g. of the amide with 64 c.c. of a sodium hypochlorite soln. (freshly prepared), and when all solid had dissolved, acidifying the soln. with 100 c.c. of 12% sulphuric acid. The pptd. product was crystallised from benzene m.p. 85-87°.

3.5 G. of the N-chloro amide were added to a soln. of 6.3 g. of barium hydroxide 8H<sub>2</sub>O, and the mixture steam distilled. The distillate was collected in benzene, but all attempts to obtain *o*-fluoroacetanilide by treating the dried benzene soln. with acetyl chloride, failed to yield the desired material. The expt. was repeated three more times, different amounts of N-chloro-amide being used. No fluoroaniline was obtained.

(iii) Attempted Deamination of 3-Nitro-4-fluoroaniline

*p*-Fluoronitrobenzene was prepared by diazotising *p*-nitroaniline in borofluoric acid soln., and decomposing the borofluoride complex so formed, a 40% yield being obtained.

*p*-Fluoroaniline was obtained by reducing the nitro compd. with hydrogen at 70 lb./sq. inch, using Raney nickel as a catalyst. This amine was nitrated as outlined by Bradlow

and Vanderwerf (loc. cit.). Thus 17 g. of amine in 88 c.c. of conc. sulphuric acid were nitrated with a mixture of 4 c.c. of fuming nitric acid and 36 c.c. of conc. sulphuric acid, the reaction mixture being stirred and kept at  $-5^{\circ}$  by internal cooling (solid carbon dioxide). 14 G. of product, m.p.  $98^{\circ}$  (ex. water) were obtained.

In an attempt to deaminate 3-nitro-4-fluoroaniline, the latter (4.7 g.) was diazotised in a cooled mixture of 6.5 g. of conc. sulphuric acid and 40 c.c. of ethanol. A yellow solid separated from the reaction mixture and dissolved again when the mixture was heated for an hour on a water bath. Steam distillation of the soln. gave no o-nitrofluorobenzene.

Secondly, the amine was diazotised in sulphuric acid, the yellow precipitate again being formed. Addition of 10 mols. of hypophosphorus acid (30% W/W soln.) and keeping the mixture at  $3^{\circ}$  for a number of days gave no o-nitrofluorobenzene.

(a) o-Fluoroaniline.

o-Fluorobenzoic acid was prepared as above. To a stirred soln. of 47 g. of o-fluorobenzoic acid in 152 c.c. of conc. sulphuric acid at  $50^{\circ}$  were added 24.5 g. of sodium azide over a period of 3 hrs. The azide was added from a funnel designed for the addition of solids in the absence of air, and air was excluded from the reaction vessel by a stream of nitrogen. After stirring for 12 hrs. at  $50^{\circ}$ , the mixture was cooled, diluted with water and neutralized with a soln. of 144 g. of sodium hydroxide in 310 c.c. of water. The

soln. was extracted with ether, the extracts dried, and the ether removed. Vacuum distillation of the residual oil gave 28.5 g. (77% of theory) of o-fluoroaniline b.p. 104-106°/56 m.m.

(a) o-Fluoroacetanilide, prepared by shaking the amine with sodium acetate and acetic anhydride, had mp. 78-79°. Braun and Rudolph (Ber., 1931, 64, 2469) report m.p. 80°.

(b) Benz-o-fluoroanilide.

28 G. of o-fluoroaniline were heated under reflux with 43 g. of benzoyl chloride. The benzoyl derivative was washed with hot water and crystallised from ethyl alcohol m.p. 113°. Found. C, 72.25; H, 5.06.  $C_{13}H_{10}FON$  requires C, 72.2; H, 5.07%.

(c) Benz-o-fluoroanilide iminochloride.

50 G. (1 mol.) of the anilide and 54 g. (1.1 mols.) of phosphorus pentachloride were heated together. A golden liquid was formed, which after the removal of the phosphorus oxychloride produced in the reaction, gave 46 g. of the required iminochloride, b.p. 196-200°/27 m.m.

(d) 2'-Fluorophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.

To a soln. of 4.5 g. (1 atom) of sodium in 200 c.c. of absolute alcohol was added a soln. of 32.5 (1 mol.) of methyl o-cresotate in 100 c.c. of absolute alcohol, followed by a soln. of 46 g. (1 mol.) of the imino chloride in 100 c.c. of dry ether. The mixture was allowed to stand (24 hrs.), the solvents removed, and the residue poured into water.

The red viscous oil produced was crystallised from petroleum ether (b.p. 40-60°). 44 G. of white prisms, m.p. 58-60° were obtained. Found. C, 72.7; H, 4.20.  $C_{22}H_{18}NO_3F$  and requires C, 72.7; H, 4.99%.

(e) Methyl-N-benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylate.

The imino-ether was found to isomerize at 275°, 41 g. yielding 32 g. (81% of theory) of ester. The product crystallised from methylalcohol in prisms, m.p. 104-106°. Found. C, 72.5; H, 4.80.  $C_{22}H_{18}NO_3F$  requires C, 72.7; H, 4.99%.

(f) N-Benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylic Acid.

A soln. of aqueous alcoholic sodium hydroxide was prepared by dissolving 2.5 g. of sodium in 120 c.c. of absolute alcohol, and adding 25 c.c. of water. This soln. was boiled with 32 g. of the ester in 150 c.c. of absolute alcohol, a further 25 c.c. of water being added. After a preliminary purification as outlined previously the water was removed from the acid by azeotropic distillation with benzene; and the dried product crystallised from benzene-acetone soln. to a constant m.p. 187-188°. Found. C, 72.8; H, 3.97.  $C_{21}H_{16}NO_3F$  requires C, 72.2; H, 4.62%.

Preparation of Brucine(-)-N-benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylate.

3.49 G. (1 mol.) of the (+)-fluoro-methyl acid and 4.66 g. (1 mol.) of brucine 4H<sub>2</sub>O were dissolved in separate 100 c.c. volumes of acetone. The solns. were filtered and united, the soln. concentrated to 50 c.c. and kept warm. Rapid crystallisation set in, 7.3 g. of the salt being obtained, corresponding to 90% of the theoretical yield. Found. C, 71.0; H, 6.2. C<sub>44</sub>H<sub>42</sub>O<sub>7</sub>N<sub>3</sub>F requires C, 71.0; H, 5.69%.

Preparation of (-)-N-Benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylic Acid.

The formic acid method was used. Thus 3 g. of brucine (-)-acid-salt were dissolved in cold anhyd. formic acid and the soln. poured into dil. hydrochloric acid and ice. The process was repeated, the acid collected and dried in a vacuum.

Racemisation of the Active (-)-acid.

0.1000 G. of the active acid was dissolved to 25 c.c. in solvent 'X' at 20.0°.

Activations with Quinidine.

Acid:Base ratio 1:1. 0.1520 G. of quinidine was dissolved in a soln. of 0.1747 g. of acid in solvent 'X' at 20.0°, and the soln. made up to 25 c.c.

(i)

Time after 2.52 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-2.39	-	6.13	0.66	0.210
0.43	2.19	0.204	6.98	0.555	0.209
0.78	2.03	0.209	7.68	0.48	0.209
1.16	1.875	0.209	8.68	0.40	0.206
2.48	1.43	0.207	9.73	0.32	0.207
2.98	1.28	0.210	10.48	0.275	0.206
3.43	1.17	0.208	11.48	0.22	0.208
4.08	1.03	0.206	13.33	0.145	0.210
4.68	0.90	0.209	14.98	0.11	0.206
5.28	0.80	0.207			

Whence  $k = 0.208$  (limits 0.204 and 0.210).

(ii) Repetition of (i).

Time after 3.1 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-2.055	-	5.50	0.65	0.209
0.95	1.68	0.212	6.45	0.53	0.210
1.85	1.40	0.208	7.15	0.475	0.205
2.25	1.29	0.207	8.15	0.37	0.210
2.75	1.15	0.211	9.40	0.29	0.208
3.35	1.02	0.209	10.20	0.25	0.207
4.40	0.82	0.209	13.00	0.13	0.213
4.95	0.72	0.212			

Whence  $k = 0.209$  (limits 0.205 and 0.213).

Activations with Quinidine.

Acid:Base ratio 1:1. 0.1620 G. of quinidine was dissolved in a soln. of 0.1747 g. of acid in solvent 'X' at 20.0°, and the soln. made up to 25 c.c.

(i)

Time after 2.05 mins.	$\alpha_t - \alpha_\infty$	k
0	+1.31	-
4.95	1.11	0.0335
6.45	1.06	0.0329
8.95	0.96	0.0347
11.95	0.865	0.0347
15.95	0.76	0.0341
20.95	0.64	0.0342
30.95	0.45	0.0345
37.95	0.37	0.0333
44.95	0.285	0.0340

Whence  $k = 0.0340$  (limits 0.0347 and 0.0329).

(ii) Repetition of (i).

Time after 2.05 mins.	$\alpha_t - \alpha_\infty$	k
0	+1.31	-
2.05	1.225	0.0328
4.95	1.11	0.0335
8.95	0.97	0.0336
11.95	0.875	0.0338
15.95	0.76	0.0341
20.95	0.645	0.0338
30.95	0.455	0.0342
37.95	0.36	0.0337
44.95	0.28	0.0343

Whence  $k = 0.0338$  (limits 0.0328 and 0.0343).

Acid:Base ratio 2:1. 0.9494 G. of acid and 0.1620 g. of quinidine were dissolved to 25 c.c. in solvent 'X' at 20.0°.

(i)

Time after 2.8 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.625	-
0.6	0.545	0.228
1.3	0.47	0.219
2.0	0.39	0.236
2.35	0.36	0.235
2.85	0.32	0.235
3.4	0.29	0.226
4.3	0.235	0.228
5.2	0.19	0.229
5.9	0.16	0.231
6.7	0.14	0.223
8.1	0.10	0.226
9.7	0.075	0.219

Whence  $k = 0.228$  (limits 0.219 and 0.236).

(ii) Repetition of (i).

Time after 2.8 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.625	-
1.65	0.42	0.239
2.50	0.35	0.231
2.95	0.315	0.233
3.65	0.275	0.225
4.83	0.21	0.228
6.03	0.16	0.228
6.35	0.15	0.228
7.62	0.11	0.227
8.25	0.095	0.227

Whence  $k = 0.230$  (limits 0.239 and 0.225).

Preparation of N-Benzoyl-2:6'-dimethyldiphenylamine-2-carboxylic Acid.

The acid was prepared as outlined by Jamison & Turner (J., 1940, 272).

(a) 2-Methylphenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.

This imino-ether was obtained in a 58% yield, being crystallised from methyl alcohol in prisms, m.p. 96-97°.

Jamison and Turner found (loc. cit.) m.p. 96-97°.

(b) Methyl-N-benzoyl-2:6'-dimethyldiphenylamine-2-carboxylate.

The ether underwent intramolecular rearrangement at 280°. Altogether 120 g., in portions of 30 g., were allowed to react. The yield of ester was 105 g. (88% of theory), and it crystallised from methyl alcohol in prisms m.p. 145°, which corresponded to that reported (idem, loc. cit.).

(c) N-Benzoyl-2:6'-dimethyldiphenylamine-2-carboxylic Acid.

The acid was crystallised from benzene and then acetone/light petroleum (b.p. 40-60°) to constant m.p. 183-184°. As found (idem, loc. cit.) the acid solvated tenaciously with acetone and removal of the solvent was attained by drying at 100° in a high vacuum over phosphorus pentoxide.

Preparation of Brucine (-)-N-benzoyl-2:6'-dimethyldiphenylamine-2-carboxylate.

Equimolecular amounts of the (+)-acid (3.45 g.) and brucine 4H<sub>2</sub>O (4.66 g.) were dissolved in separate 100 c.c. volumes of hot acetone, the solns. filtered and then united.

This soln. was concentrated to 75 c.c., and 50 c.c. of 40-60° petroleum ether added. When crystallisation began a further 50 c.c. of petroleum ether were added. The total yield of the brucine (-)-acid salt was 7.2 g., corresponding to 87% of the theoretical.

Preparation of (-)-N-Benzoyl-2:6-dimethyldiphenylamine-2-carboxylic Acid.

An ice-cold formic acid soln. of 3 g. of the brucine (-)-acid salt was filtered through glass wool into dil. hydrochloric acid and ice. This procedure was repeated, the acid collected and dried in a vacuum.

Activations with Quinaldine.

Racemisation of the Active (-)-Acid.

0.1000 G. of the acid was dissolved to 25 c.c. in solvent 'X' at 20.0°.

(i)

Time after 3.5 mins.	$\alpha_t - \alpha_\infty$	k
0.70	-0.23	-
0.40	0.185	0.544
1.05	0.13	0.544
1.50	0.10	0.530
2.00	0.07	0.595
2.40	0.06	0.560
2.85	0.04	0.614
3.40	0.03	0.599

Whence  $k = 0.570$  (limits 0.614 and 0.530).

Whence  $k = 0.0599$  (limits 0.0576 and 0.0611).

(ii) Repetition of (i).

Time after 1.9 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.57	-
0.55	0.41	0.599
1.30	0.265	0.589
1.70	0.215	0.574
2.05	0.18	0.562
2.40	0.15	0.556
2.68	0.125	0.566
3.05	0.105	0.555
3.50	0.085	0.544
3.95	0.07	0.531
5.42	0.03	0.544
6.15	0.015	0.592

Whence  $k = 0.565$  (limits 0.599 and 0.531).

Acid:Base ratio 2:1. Temp. 20.0°. Solvent 'X'. 0.1620 G.

Activations with Quinidine.

Acid:Base ratio 1:1. Temp. 20.0°. Solvent 'X'. 0.1717G.

of acid and 0.1620 g. of alkaloid dissolved to 25 c.c.

(i)

Time after 1.8 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.56	-
1.70	0.51	0.0583
2.35	0.49	0.0586
3.65	0.45	0.0611
5.35	0.41	0.0590
7.90	0.35	0.0600
10.20	0.30	0.0603
11.40	0.28	0.0606
13.20	0.25	0.0611
14.80	0.23	0.0610
16.20	0.22	0.0576
20.20	0.16	0.0609
22.20	0.15	0.0607

Whence  $k = 0.0599$  (limits 0.0576 and 0.0611).

(ii) Repetition of (i)

Time after 2.2 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.55	-
3.80	0.435	0.0600
5.30	0.40	0.0600
6.80	0.36	0.0600
8.80	0.32	0.0606
10.60	0.29	0.0604
11.80	0.27	0.0606
13.20	0.245	0.0607
14.72	0.22	0.0607
16.60	0.20	0.0608
20.40	0.16	0.0607
23.20	0.13	0.0608

Whence  $k = 0.0605$  (limits 0.0600 and 0.0608).

Acid:Base ratio 2:1. Temp.  $20.0^\circ$ . Solvent 'X'. 0.1620 G. of quinidine and 0.3434 g. of acid were dissolved to 25 c.c.

(i)

Time after 3.1 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.135	-
0.60	0.09	0.676
0.96	0.07	0.684
1.45	0.05	0.685
1.83	0.04	0.667
2.10	0.03	0.664
2.87	0.02	0.666
3.90	0.01	0.667

Whence  $k = 0.673$  (limits 0.685 and 0.664).

(ii) Repetition of (i).

Time after 2.83 mins.	$\alpha_c - \alpha_\infty$	k
0	+0.16	-
0.35	0.13	0.658
0.69	0.10	0.668
1.07	0.08	0.661
1.47	0.06	0.658
1.97	0.04	0.660
2.47	0.03	0.662
3.17	0.02	0.659
3.97	0.01	0.658

Whence  $k = 0.660$  (5) (limits 0.658 and 0.668).  
crystallised from ethyl alcohol.

Preparation of N-Benzoyl-2':4'-dichloro-6-methyldiphenylamine  
-2-carboxylic Acid.

(a) 2:4-Dichloroaniline.

Reference. Reed and Orton, J., 1907, 91, 1553.

To a soln. of 100 g. of acetanilide in 800 c.c. of glacial acetic acid were added 131 g. of fused sodium acetate. Chlorine was then passed into the cold soln. until a gain in weight of 142 g. was recorded. At one stage in the passing of chlorine, crystals of p-chloroacetanilide began to separate. The reaction mixture was then heated on a water bath for the remaining period of chlorine absorption. When this was completed, the soln. was cooled and the solid product filtered off, the filtrate diluted with water, and a further crop of crystals obtained.

Yield 183 g. (86% of theory) m.p. 138-140°.

The resulting gum crystallised from ethyl alcohol in prisms, m.p. 74-76°, a 69% yield being obtained.

Found. To obtain the amine from the acetyl derivative, the latter was heated under reflux with 500 c.c. of ethyl alcohol and 70 c.c. of conc. hydrochloric acid for 8 hrs. The alcohol was removed by steam distillation and the free base obtained by steam distillation of the alkaline residual liquor. Yield 116 g. (80% of theory).

(b) 2:4-Dichlorobenzanilide was obtained in a 79% yield by heating together 1 mol. amount of the amine and 1.25 mol. amounts of benzoylchloride. The anilide, m.p.  $114^{\circ}$ , crystallised from ethyl alcohol.

(c) Benz-2:4-dichloroanilide iminochloride.

113.5 G. (1 mol.) of the anilide and 96.3 g. (1 mol.) of phosphorus pentachloride were mixed together and warmed on a water bath. The resulting golden yellow liquid was fractionally distilled at reduced pressure, an 87% yield (104 g.) of the imino chloride being obtained, b.p.  $220^{\circ}/20$  m.m.

(d) 2:4-Dichlorophenylbenzimidino-6-methyl-2-carbomethoxyphenyl ether.

A soln. of 8.3 g. (1 atom) of sodium in 300 c.c. of absolute alcohol was prepared, and to this soln. was added 60 g. (1 mol.) of methyl o-cresotate in 150 c.c. of absolute alcohol. Immediately after, a soln. of 104 g. (1 mol.) of the imino chloride in 200 c.c. of dry ether was added. The reaction mixture was allowed to stand overnight, the solvents evaporated and the residue poured into a large volume (2-3 litres) of water. The resulting gum crystallised from methyl alcohol in prisms, m.p.  $74-76^{\circ}$ , a 69% yield being obtained.

Found. C, 63.5; H, 4.19.  $C_{22}H_{17}O_3NCl_2$  requires (1 mol.)  
C, 63.8; H, 4.14%.

(e) Methyl-N-benzoyl-2':4'-dichloro-6-methyldiphenylamine  
-2-carboxylate.

The imino-ether underwent Chapman's rearrangement  
at 285-290°. 80 G. were allowed to isomerize, yielding  
56 g. of the ester (70% of theory), m.p. 131-133°. The  
product crystallised from methyl alcohol in prisms.

Found. C, 63.25; H, 4.15.  $C_{22}H_{17}O_3NCl_2$  requires C, 63.8;  
H, 4.14%.

(f) N-Benzoyl-2':4'-dichloro-6-methyldiphenylamine  
-2-carboxylic Acid.

The ester, 50 g. in 200 c.c. of ethyl alcohol, was  
boiled for an hour with a soln. of 2.9 g. of sodium in 90 c.c.  
of absolute alcohol and 30 c.c. of water. A further 35 c.c.  
of water were added to the reaction mixture.

After the boiling, the alcohol was removed and the  
acid pptd. with dil. hydrochloric acid. The product was  
purified via its sodium salt, washed with hot water and  
crystallised from benzene-acetone soln. to a constant m.p.  
201-202°. Found. C, 66.0; H, 4.04; Cl, 14.18.

$C_{21}H_{15}O_3NCl_2$  requires C, 63.0; H, 3.78; Cl, 17.7%.

Preparation of Brucine (-)-N-benzoyl-2':4'-dichloro-6-  
methyldiphenylamine-2-carboxylate.

The (+)-acid underwent a second order asymmetric  
transformation with brucine in acetone-light petroleum.

(1) 4.00 G. of the acid (1 mol.) and 4.67 g. (1 mol.) of brucine  $4H_2O$  were dissolved in separate 100 c.c. volumes of hot acetone. These solns. were filtered and united and then concentrated to 100 c.c., 25 c.c. of petroleum ether (b.p.  $40-60^\circ$ ) being added. 7.5 G. of brucine (-)-acid salt crystallised from the warm soln. This corresponds to 87% of the theoretical yield. Found. C, 66.8; H, 5.6.  $C_{44}H_{41}O_7N_3Cl$  requires C, 66.5; H, 5.20%.

Preparation of (-)-N-Benzoyl-2':4'-dichloro-6-methyldiphenyl amine-2-carboxylic Acid.

3 G. of the brucine salt were dissolved in 60 c.c. of anhydrous formic acid at  $0^\circ$ . This soln. was immediately filtered into dil. hydrochloric acid and ice, the pptd. acid collected and dried and rapidly submitted to the same process. The final precipitate was dried in a vacuum and weighed 1 g. Found. C, 60.6; H, 3.85.  $C_{21}H_{15}O_3NCl_2$  requires C, 63.0; H, 3.78%.

Racemisation of the Active (-)-Acid.

0.1000 G. of the acid was dissolved to 25 c.c. in solvent 'X' at  $20.0^\circ$ .

1.33	1.50	0.0946
2.66	1.69	0.0951
3.99	1.62	0.0912
5.32	1.51	0.0926
6.65	1.39	0.0926
7.98	1.30	0.0940
9.31	1.23	0.0929
10.64	1.12	0.0930
11.97	1.04	0.0946
13.30	0.92	0.0941
14.63	0.86	0.0929
15.96	0.74	0.0938
17.29	0.65	0.0920
18.62	0.535	0.0945
19.95	0.50	0.0914
21.28	0.40	0.0938

(i)

Time after 3.95 mins.	$\alpha_t - \alpha_\infty$	k
0	-2.27	-
1.30	2.01	0.0936
1.85	1.92	0.0905
2.25	1.84	0.0933
3.00	1.72	0.0925
4.25	1.53	0.0928
5.65	1.34	0.0933
6.55	1.24	0.0923
7.05	1.17	0.0940
7.55	1.135	0.0918
8.05	1.09	0.0911
8.55	1.025	0.0930
9.05	0.97	0.0939
11.05	0.815	0.0927
12.05	0.75	0.0919
13.05	0.68	0.0924
14.05	0.63	0.0913
15.05	0.56	0.0930
16.05	0.52	0.0919
24.95	0.24	0.0901

(ii) Repetition of (i).

Whence  $k = 0.0924$  (limits 0.0940 and 0.0905).

(ii) Repetition of (i).

Time after 3.4 mins.	$\alpha_t - \alpha_\infty$	k
0	-2.27	-
1.55	1.96	0.0946
3.10	1.69	0.0951
3.70	1.62	0.0912
4.40	1.51	0.0926
5.30	1.39	0.0926
5.93	1.30	0.0940
6.60	1.23	0.0929
7.60	1.12	0.0930
8.25	1.04	0.0946
9.60	0.92	0.0941
10.45	0.86	0.0929
11.95	0.74	0.0938
13.60	0.65	0.0920
15.30	0.535	0.0945
16.55	0.50	0.0914
18.50	0.40	0.0938

Whence  $k = 0.0933$  (limits 0.0951 and 0.0914).

Activations with Quinidine.

Acid:Base ratio 1:1. Temp. 20.0°. Solvent 'X'.  
alkaloid used.

0.2000 G. of (+)-acid and 0.1620 g. of quinidine were dissolved to 25 c.c.

(i)

Time after 2.85 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	+1.275	-	43.15	0.77	0.0118
3.85	1.225	0.0104	47.15	0.74	0.0116
16.65	1.055	0.0114	52.65	0.69	0.0117
19.15	1.03	0.0103	56.65	0.66	0.0116
23.15	1.00	0.0106	61.15	0.64	0.0114
33.15	0.87	0.0116	162.65	0.245	0.0101
38.15	0.82	0.0117			

(ii) Repetition of (i).

Whence  $k = 0.0112$  (limits 0.0101 and 0.0118).

(ii) Repetition of (i).

Time after 2.0 mins.	$\alpha_t - \alpha_\infty$	k	Time Contd.	$\alpha_t - \alpha_\infty$	k
0	+1.31	-	16.00	1.08	0.0120
1.00	1.29	0.0138	19.00	1.04	0.0119
2.00	1.27	0.0132	22.00	1.01	0.0118
3.00	1.26	0.0131	36.00	0.85	0.0119
6.80	1.20	0.0122	42.00	0.79	0.0118
10.00	1.16	0.0121	48.00	0.74	0.0119
13.00	1.12	0.0120			

Whence  $k = 0.0123$  (limits 0.0138 and 0.0118).

Acid:Base ratio 2:1. 0.4000 G. of acid and 0.1620 g. of alkaloid used.

(i)

(Time after 4.1 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k.
0	+0.51	-	4.45	0.225	0.184
1.05	0.41	0.208	4.90	0.21	0.181
1.50	0.38	0.196	6.20	0.17	0.177
1.90	0.345	0.206	6.65	0.15	0.184
2.40	0.315	0.201	7.90	0.11	0.194
3.00	0.275	0.206	9.00	0.095	0.187
3.90	0.23	0.204	10.90	0.07	0.182

Whence  $k = 0.193$  (limits 0.177 and 0.208).

(ii) Repetition of (i).

Time after 3.0 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	+0.59	-	4.00	0.30	0.177
0.50	0.54	0.177	5.00	0.24	0.180
1.20	0.475	0.181	6.80	0.175	0.179
1.85	0.43	0.171	8.40	0.13	0.180
2.50	0.38	0.176	11.00	0.08	0.182
3.40	0.32	0.180			

Whence  $k = 0.178$  (limits 0.182 and 0.171).

Whence  $k = 0.235$  (limits 0.239 and 0.230).

Acid:Base ratio 3:1. Temp. 20.0°. Solvent 'X'.  
 0.6000 G. of acid and 0.1620 g. of base were dissolved in 25 c.c.

of the acid and alkalioid in solvent 'X' at 20.0° were mixed

(i) the resulting soln. was titrated with 0.1 N NaOH

Time after 3.4 mins.	$\alpha_t - \alpha_0$	k	Time contd.	$\alpha_t - \alpha_0$	k
0	+0.37	-	3.15	0.175	0.238
0.98	0.295	0.231	3.75	0.16	0.224
1.45	0.26	0.243	4.70	0.12	0.240
1.80	0.235	0.252	7.73	0.05	0.228
2.30	0.21	0.246	11.00	0.03	0.228
2.65	0.19	0.252			

Whence k = 0.241 (limits 0.252 and 0.224).

(ii) Repetition of (i).

Time after 3.0 mins.	$\alpha_t - \alpha_0$	k	Time contd.	$\alpha_t - \alpha_0$	k
0	+0.40	-	3.00	0.20	0.231
0.50	0.355	0.239	3.60	0.17	0.238
1.00	0.315	0.239	4.30	0.145	0.236
1.40	0.29	0.230	4.80	0.13	0.234
1.90	0.255	0.237	8.60	0.055	0.231
2.50	0.225	0.239			

Time after 2.5 mins. Whence k = 0.235 (limits 0.239 and 0.230).

0	+0.40	-			
1.90	0.36	0.235		0.0555	
5.75	0.235	0.235		0.0553	
8.90	0.245	0.245		0.0551	
11.20	0.235	0.235		0.0555	
12.40	0.195	0.195		0.0559	
15.85	0.16	0.16		0.0559	
21.35	0.115	0.115		0.0564	

Whence k = 0.0557 (limits 0.0564 and 0.0551).

Activations with Brucine.

Acid:Base ratio 1:1. Throughout these activations, solns. of the acid and alkaloid in solvent 'X' at 20.0° were mixed and the resulting soln. made up to 25 c.c.

Used. 0.2000 G. of acid and 0.1972 g. of brucine.

(i)

Time after 3.15 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.375	-
5.60	0.28	0.0522
6.85	0.26	0.0535
7.85	0.245	0.0542
8.85	0.23	0.0553
10.85	0.21	0.0535
11.85	0.19	0.0574
12.85	0.18	0.0572
13.85	0.17	0.0572
15.85	0.155	0.0557
22.25	0.12	0.0574
33.60	0.06	0.0546

Whence k = 0.0553 (limits 0.0522 and 0.0574).

(ii) Repetition of (i).

Time after 2.6 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.40	-
1.90	0.36	0.0555
5.75	0.285	0.0553
8.90	0.245	0.0551
11.20	0.215	0.0555
12.40	0.195	0.0559
15.85	0.16	0.0559
21.35	0.115	0.0564

Whence k = 0.0557 (limits 0.0564 and 0.0551).

Acid:Base ratio 2:1. Used; 0.4000 g. of acid and 0.1972 g. of Brucine.

(i) Readings were begun 3.7 mins. after mixing.

Time after 2.0 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.17	-
1.00	0.14	0.193
1.50	0.13	0.178
2.10	0.115	0.186
3.00	0.095	0.194
3.60	0.09	0.176
6.00	0.055	0.188
8.00	0.04	0.181
8.75	0.03	0.198

Whence  $k = 0.187$  (limits 0.198 and 0.178).

(ii) Repetition of (i).

Time after 2.4 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.16	-
1.10	0.13	0.189
2.04	0.11	0.184
2.90	0.095	0.180
3.85	0.08	0.180
6.40	0.05	0.182
9.23	0.03	0.181

Whence  $k = 0.183$  (limits 0.189 and 0.180).

(1 mol.) of sodium acetate were suspended in 650 c.c. of glacial acetic acid, cooled externally with ice and stirred mechanically. Chlorine was passed in until a gain in weight of 71 g. was recorded. The reaction mixture was then poured into a great excess of water, the ppt. collected and crystallised from alcohol. Yield 153 g., m.p. 151°.

This acetyl derivative was dissolved in boiling Acid:Base ratio 3:1. Used: acid, 0.6000 g. and brucine, 0.1972 g. Readings were begun 3.7 mins. after mixing, but no change in rotation of the soln. was observed over a period of 24 hrs.

Time (mins.) after mixing.	Actual rotation.
3.70	178.98
7.00 (1 mol. of the amide)	178.98 (1.2 mols.)
30.00	178.985
1440.00	178.99

Repetition of this experiment gave the same result.

(c) 2-Chloro-4-bromobenzamide iminechloride.

Equimolecular amounts of the anilide (155 g.) and phosphorus pentachloride (115 g.) were heated together, until Preparation of N-Benzoyl-2'-chloro-4'-bromo-6-methyldiphenyl amine-2-carboxylic acid.

(a) 2-Chloro-4-bromoaniline.

Reference. Chattaway and Clemo. J., 1916, 91.

(d) 214 G. (1 mol.) of p-bromoacetanilide and 82 g. (1 mol.) of sodium acetate were suspended in 650 c.c. of glacial acetic acid, cooled externally with ice and stirred mechanically. Chlorine was passed in until a gain in weight of 71 g. was recorded. The reaction mixture was then poured into a great excess of water, the ppt. collected and crystallised from alcohol. Yield 153 g., m.p. 151°.

ether. To dissolve the imino chloride it was found necessary to pour the molten compound into cold ether.

After standing over night, the solvents were removed from the reaction. This acetyl derivative was dissolved in boiling alcohol, one eighth of its bulk of conc. hydrochloric acid added, and the mixture heated under reflux for 8-9 hrs. The alcohol was removed by steam distillation, the residual liquid cooled, made alkaline to litmus with 30% sodium hydroxide soln., and the solid amine filtered off. The yield of amine, m.p.  $73^{\circ}$ , was 126 g.

(b) 2-Chloro-4-bromobenzanilide.

124 G. (1 mol.) of the amine and 101 g. (1.2 mols.) of benzoyl chloride were heated together at  $130^{\circ}$ . The resultant anilide was washed with 10% sodium hydroxide soln. and water, and finally crystallised from ethyl alcohol, m.p.  $144-145^{\circ}$ . An 83% yield was obtained.

(c) 2-Chloro-4-bromobenzanilide iminochloride.

Equimolecular amounts of the anilide (155 g.) and phosphorus pentachloride (115 g.) were heated together, until a clear yellow soln. was obtained. The separation of the undesired phosphorus oxychloride from the product was achieved by fractional distillation at reduced pressure. 131 G. of the imino-chloride were obtained b.p.  $240^{\circ}/20$  m.m.

(d) 2'-Chloro-4'-bromophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.

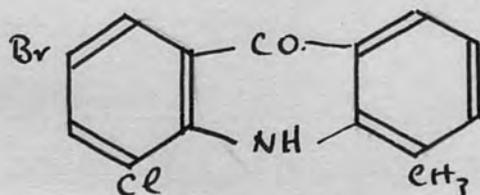
A soln. of 9.2 g. (1 atom.) of sodium in 350 c.c. of absolute alcohol was prepared. To this soln. was added in rapid succession, 66.4 g. (1 mol.) of methyl o-cresotate in 150 c.c. of absolute alcohol and 131.6 g. (1 mol.) of 2-chloro-4-bromobenzanilide iminochloride in 700 c.c. of dry ether. To dissolve the imino chloride it was found necessary to pour the molten compound into cold ether.

After standing over night, the solvents were removed from the reaction mixture and the residue poured into a large volume of water. The resulting gum was crystallised from ethyl alcohol. Prisms, m.p. 87-88° were obtained in a 69% yield. Found: C, 56.9, H, 3.71.  $C_{22}H_{17}O_3N$  BrCl requires; C, 57.6; H, 3.74%.

(e) Methyl-N-benzoyl-2'-chloro-4'-bromo-6-methyldiphenylamine-2-carboxylate.

60 G. of imino-ether, in 30 g. portions, were kept at 275° for 40 mins. The molten material was then poured into cold ethyl alcohol from which solvent it crystallised in prisms, m.p. 138°. An 83% yield of the ester was obtained. Found. C, 57.7; H, 3.80.  $C_{22}H_{17}O_3N$ BrCl requires C, 57.6; H, 3.74%.

On keeping 3 g. of the imino-ether at 300° for 2.5 hrs. a compound of m.p. 212-213° was obtained which differed from the imino-ether and ester in m.p., and depressed the m.p. of both substances. It was concluded that



had been formed.

(f) N-Benzoyl-2'-chloro-4'-bromo-6-methyldiphenylamine-2-carboxylic Acid.

An aqueous alcoholic soln. of sodium hydroxide was prepared by dissolving 10 g. of sodium in 300 c.c. of absolute alcohol and adding 75 c.c. of water.

A soln. of 32 g. of the ester in 200 c.c. of absolute

alcohol was mixed with 67.5 c.c. of the sodium hydroxide soln. and 65 g.c. of water and the mixture heated under reflux for an hour. The alcohol was removed, the residual aqueous soln. of the sodium salt of the acid acidified with dil. hydrochloric acid, and the pptd. acid filtered off. This solid impure acid was dissolved in dil. sodium bicarbonate soln., filtered, and the filtrate acidified. After washing with hot water, the product was crystallised from benzene-acetone soln. to a constant m.p. of 186-187° (the m.p. varied with rate of heating). Found. C, 60.2; H, 3.98; Halogen, 24.6.  $C_{21}H_{15}O_3N$  Br Cl requires C, 56.7; H, 3.40; Halogens, 25.9%.

Preparation of Brucine (-)-N-Benzoyl-2'-chloro-4'-bromo-6-methyldiphenylamine-2-carboxylate.

4.67 G. (1 mol.) of brucine  $4H_2O$  and 4.45 g. (1 mol.) of (+)-acid were dissolved in 120 c.c. of hot acetone, the soln. filtered, and 20 c.c. of 40-60° petroleum ether added. The soln. was kept warm, and when crystallisation began, a further 20 c.c. of petroleum ether were added.

An 83% yield (7.6 g.) of crystalline brucine (-)-acid salt was obtained. Found, C, 61.3; H, 6.20.

$C_{45}H_{44}O_7N_3Br$  Cl requires C, 62.9; H, 6.20%.

Preparation of (-)-N-Benzoyl-2'-chloro-4'-bromo-6-methyldiphenylamine-2-carboxylic Acid.

3 G. of the brucine salt were ground with 60 c.c. of anhydrous formic acid at 0°. The soln. was rapidly filtered through glass wool into dil. hydrochloric acid and ice and the pptd. active acid collected at the pump and dried. After submitting the acid to the process once more, 1 g. of vacuum

dried product was obtained. Found. C, 54.85; H, 3.62.

$C_{22}H_{18}O_3NCl$  Br requires C, 56.7; H, 3.40%

Racemisation of the Active (-)-Acid.

(1) 0.1000 G. of the acid was dissolved to 25 c.c. in solvent 'X' at 20.0°.

(i)

Time after 3.05 mins.	$\alpha_t - \alpha_\infty$	k
0	-2.57	-
1.70	2.23	0.0835
2.60	2.05	0.0869
3.30	1.95	0.0837
4.05	1.82	0.0852
4.85	1.71	0.0840
5.45	1.615	0.0853
6.00	1.52	0.0875
6.95	1.41	0.0864
8.45	1.24	0.0863
10.45	1.04	0.0866
12.95	0.84	0.0863
15.95	0.65	0.0862

Whence  $k = 0.0857$  (limits 0.0875 and 0.0835).

(ii) Repetition of (i).

Time after 3.2 mins.	$\alpha_t - \alpha_\infty$	k
0	-2.545	-
1.20	2.30	0.0845
1.85	2.16	0.0886
2.45	2.06	0.0863
3.00	1.97	0.0854
3.55	1.875	0.0861
4.30	1.75	0.0871
4.80	1.67	0.0878
5.80	1.53	0.0878
7.30	1.35	0.0869
12.80	0.84	0.0866
15.80	0.65	0.0864

Whence  $k = 0.0867$  (limits 0.0866 and 0.0845).

Activations with Quinidine.

Acid:Base ratio 1:1. 0.1620 G. of quinidine dissolved in solvent 'X' at 20.0° was added to a similar soln. of 0.2224 g. of (+)-acid. The resulting soln. was made up to 25 c.c.

(i)

Time after 2.15 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	+1.135	-	22.85	0.87	0.0115
4.20	1.08	0.0118	25.85	0.845	0.0114
4.85	1.07	0.0122	28.85	0.82	0.0113
7.35	1.04	0.0119	31.85	0.79	0.0114
8.95	1.015	0.0125	34.85	0.77	0.0114
10.85	1.00	0.0117	37.85	0.75	0.0109
13.85	0.965	0.0117	61.85	0.58	0.0109
19.85	0.91	0.0111			

Whence  $k = 0.0116$  (limits 0.0109 and 0.0125).

Readings after 8.95 mins. were the mean of three taken at (t-1), t, and (t+1) mins.

(ii) Repetition of (i).

Time after 2.90 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	+1.12	-	15.10	0.95	0.0109
1.10	1.105	0.0123	17.40	0.92	0.0113
2.90	1.08	0.0125	20.90	0.89	0.0110
6.70	1.04	0.0111	23.70	0.86	0.0111
9.70	1.01	0.0107	26.60	0.83	0.0113
11.80	0.98	0.0113			

Whence  $k = 0.0113$  (limits 0.0125 and 0.0107).

Acid:Base ratio 2:1. 0.4448 G. of acid and 0.1620 g. of quinidine were dissolved to 25 c.c. in solvent 'X' at 20.0°.

(i)

Time after 2.6 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.525	-
2.00	0.37	0.0175
2.35	0.335	0.0191
2.90	0.31	0.0182
3.50	0.265	0.0195
4.25	0.245	0.0179
5.70	0.19	0.0178
7.20	0.145	0.0179
9.40	0.09	0.0188
12.40	0.06	0.0178
18.40	0.035	0.0176

Whence  $k = 0.0182$  (limits 0.0175 and 0.0195).

(ii) Repetition of (i).

Time after 2.32 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.55	-
0.58	0.49	0.0181
1.08	0.45	0.0186
2.48	0.35	0.0182
4.18	0.26	0.0175
5.68	0.20	0.0178
7.78	0.14	0.0176
9.08	0.11	0.0177
9.98	0.095	0.0176
13.58	0.05	0.0177

Whence  $k = 0.0179$  (limits 0.0186 and 0.0175).

Acid:Base ratio 3:1. To a soln. of 0.6672 g. of acid in solvent 'X' at 20.0° was added a soln. of 0.1620 g. of quinidine, the whole being made up to 25 c.c.

(i)

Time after 3.2 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.305	-
1.30	0.215	0.269
2.15	0.18	0.245
2.70	0.16	0.239
3.80	0.115	0.257
4.80	0.09	0.254
5.80	0.07	0.254
6.80	0.06	0.239
7.80	0.05	0.232
8.80	0.03	0.263
10.80	0.025	0.247

Whence  $k = 0.249$  (limits 0.269 and 0.237).

(ii) Repetition of (i).

Time after 2.9 mins.	$\alpha_t - \alpha_\infty$	k
0	+0.335	-
0.80	0.275	0.247
1.90	0.205	0.258
2.80	0.16	0.264
4.10	0.115	0.261
5.00	0.095	0.252
6.25	0.07	0.251
7.30	0.055	0.248
9.25	0.035	0.244

Whence  $k = 0.253$  (limits 0.264 and 0.244).

Activations with Brucine.

Acid:Base ratio 1:1. Temp. 20.0°. Solvent 'X'.

0.2224 G. of acid and 0.1972 g. of brucine were taken.

(i)

Time after 3.2 mins.	$\alpha_t - \alpha_0$	k
0	-0.38	-
2.20	0.335	0.0574
2.70	0.325	0.0579
4.10	0.305	0.0536
5.70	0.275	0.0568
7.50	0.25	0.0559
8.80	0.235	0.0546
9.80	0.22	0.0558
11.80	0.205	0.0523
12.80	0.195	0.0522
13.80	0.19	0.0502
14.40	0.17	0.0559
17.30	0.145	0.0557
28.20	0.08	0.0553

Whence  $k = 0.0549$  (limits 0.0579 and 0.0502).

(ii) Repetition of (i).

Time after 2.2 mins.	$\alpha_t - \alpha_0$	k
0	-0.39	-
2.15	0.345	0.0571
4.00	0.31	0.0574
5.40	0.295	0.0517
7.60	0.27	0.0534
9.10	0.245	0.0511
10.65	0.225	0.0517
13.50	0.19	0.0533
16.80	0.155	0.0550
20.80	0.125	0.0547
25.70	0.11	0.0550

Whence  $k = 0.0540$  (limits 0.0574 and 0.0511).

Time after	Actual
3.45	179.00
7.00	179.00
30.00	179.00
144.00	179.00

Acid:Base ratio 2:1. Temp. 20.0°. Solvent 'X'.

0.4448 G. of acid and 0.1972 g. of brucine were taken.

(i)

Time after 3.15 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.12	-
1.26	0.10	0.145
2.00	0.09	0.144
3.35	0.075	0.140
4.80	0.06	0.145
7.60	0.04	0.145
9.85	0.03	0.141
14.75	0.015	0.142

Whence  $k = 0.143$  (limits 0.140 and 0.145).

(ii) Repetition of (i).

Time after 2.55 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.13	-
1.20	0.11	0.139
2.60	0.09	0.142
4.45	0.07	0.139
6.15	0.055	0.140
10.45	0.03	0.140

Whence  $k = 0.140$  (limits 0.139 and 0.142).

Acid:Base ratio 3:1. Temp. 20.0°. Solvent 'X'. 0.6672 G.

of acid and 0.1972 g. of brucine were dissolved to 25 c.c.

No change in rotation of the soln. was observed over a period of 24 hrs.

(i)

Time after mixing (mins.)	Actual Rotation
3.45	179.00
7.00	179.00
30.00	179.00
1440.00	179.00

(ii) Repetition of (i) gave the same results.

The amide (110 g., 1 mol.,) and phosphorus  
Preparation of N-Benzoyl-2'-chloro-4':6-dimethyldiphenylamine  
-2-carboxylic Acid.

(a) 3-Chloro-4-aminotoluene.

Reference. Fieser and Bowen, J. Amer. Chem. Soc., 20  
1940, 62, 2106.

A soln. of 30 g. of sodium chloride in 40 c.c. of water was added slowly to a soln. of 100 g. of acetyl-p-toluidine in 200 c.c. of glacial acetic acid and 300 c.c. of conc. hydrochloric acid. The reaction mixture was stirred mechanically and kept at 5° by external cooling with ice.

After standing for 30 mins., 200 c.c. of conc. hydrochloric acid were added and the mixture heated under reflux for 2 hrs. The acetic acid was removed by distillation, the residual soln. made alkaline, and the amine obtained by further steam distillation. The distillate was extracted with ether, the extract dried with anhydrous sodium sulphate, and after the ether was removed the product was distilled at 60 m.m. pressure. 101 G. (82% of theory) of the amine were obtained. b.p. 135-140°/60 m.m. 106-112°/20 m.m.

(b) Benz-2-chloro-4-methylanilide.

70.25 G. (1.25 mols.) of benzoyl chloride and 58 g. (1 mol.) of the amine were heated together until all reaction ceased. The crude product was washed with dil. alkali and water, and crystallised from ethyl alcohol. Yield 113 g. m.p. 137-139°.

(c) Benz-2-chloro-4-methylanilide iminochloride.

The anilide (110 g., 1 mol.,) and phosphorus pentachloride (103 g., 1.1 mols.), were heated together for half an hour on a water bath. The resulting liquid was fractionally distilled at reduced pressure, 107 g. (88% of theory) of the imino chloride being obtained, b.p. 210-216°/20 m.m.

(d) 2'-Chloro-4'-methylphenylbenzimidino-6-methyl-2-carbomethoxyphenyl ether.

A soln. of 67.3 g. (1 mol.) of methyl o-cresotate in 100 c.c. of absolute alcohol was added to a soln. of 9.3 g. (1 atom) of sodium in 300 c.c. of absolute alcohol. Immediately afterwards, a soln. of 107 g. (1 mol.) of benz-2-chloro-4-methylanilide iminochloride in 200 c.c. of dry ether was added. Next day the solvents were removed by distillation at reduced pressure and the residue was poured into 2-3 litres of water. A gum was formed, which crystallised from methyl alcohol in prisms, m.p. 113-114°. 108 G. of product were obtained. Found. C, 69.1; H, 5.25.  $C_{23}H_{20}O_3NCl$  requires C, 70.1; H, 5.1%.

(e) Methyl-N-benzoyl-2'-chloro-4':6-dimethyldiphenylamine-2-carboxylate.

100 G. of the imino-ether, in 30 g. portions were heated to 285-290°, at which temp. the ether underwent Chapman's rearrangement. The ester produced was poured into methyl alcohol, from which solvent it crystallised in prisms, m.p. 187-188°. A 79% yield was obtained. Found. C, 70.3; H, 5.02.  $C_{23}H_{20}O_3NCl$  requires C, 70.1; H, 5.11%.

(f) N-Benzoyl-2'-chloro-4':6-dimethyldiphenylamine  
-2-carboxylic Acid.

A soln. of 4.6 g. of sodium in 150 c.c. of absolute alcohol was prepared and 60 c.c. of water added. This soln. was then mixed with a soln. of 78.7 g. of the ester in 300 c.c. of absolute alcohol, 60 c.c. of water added, and the whole heated under reflux for an hour.

Following the usual procedure, the acid was purified by acidifying its soln. in dilute sodium bicarbonate.

Finally the semi-pure acid was recrystallised from benzene and then benzene-acetone soln. to a constant m.p. of 210-211°. Found. C, 69.6; H, 4.7; Cl, 8.9.  $C_{22}H_{18}O_3Cl$  requires C, 66.4; H, 4.8; Cl, 9.3%.

Activations with Quinidine.

Acid:Base ratio 1:1. Solns. of 0.0950 g. of acid and 0.0810 g. of quinidine in solvent 'X' at 20.0° were mixed. There was no observable activation of the racemic acid at this acid:base ratio.

(i)

Time (mins.) after wetting.	Actual rotation
5.60	181.08°
6.20	181.08
22.00	181.07
40.00	181.07
1440.00	181.07

(ii) The expt. was repeated using a different concentration, thus 0.1620 g. of quinidine and 0.1900 g. of acid were taken. No activation was detected, the actual rotation remained at  $182.72^\circ$  over a period of 24 hrs.

Acid:Base ratio 2:1. Temp.  $20.0^\circ$ . Solvent 'X'.

0.3800 G. of acid and 0.1620 g. of quinidine were taken and dissolved to 25 c.c.

Readings were begun 2.3 mins. after mixing.

(i)

Time after 2.3 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.28	-
1.10	0.22	0.225
1.95	0.175	0.241
2.45	0.14	0.283
2.90	0.14	0.239
3.50	0.11	0.287
4.05	0.09	0.297
6.10	0.04	0.254
7.60	0.03	0.294
9.25	0.02	0.285

Whence  $k = 0.266$  (limits 0.225 and 0.294).

Whence  $k = 0.315$  (limits 0.277 and 0.340).

(ii) Repetition of (i).

Time after 2.7 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.28	-
1.10	0.22	0.219
1.80	0.17	0.277
2.25	0.16	0.249
2.70	0.145	0.244
3.30	0.12	0.256
4.05	0.095	0.267
4.50	0.09	0.252
5.10	0.07	0.272
5.55	0.06	0.278
6.30	0.05	0.280
8.10	0.03	0.276

Whence  $k = 0.261$  (limits 0.219 and 0.280).

Acid:Base ratio 3:1. 0.5700 G. of acid and 0.1620 g. of quinidine in 25 c.c. of solvent 'X' at 20.0° were used.

(i)

Time after 2.55 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.405	-
0.50	0.345	0.328
0.85	0.320	0.277
1.40	0.270	0.290
1.80	0.24	0.291
2.13	0.205	0.320
2.55	0.17	0.341
2.93	0.16	0.317
3.70	0.115	0.340
4.10	0.105	0.329
4.65	0.09	0.324
5.50	0.075	0.306
8.85	0.03	0.294
9.85	0.015	0.335

Whence  $k = 0.315$  (limits 0.277 and 0.340).

(ii) Repetition of (i).

Time after 3.1 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.33	-
1.40	0.22	0.290
1.70	0.19	0.325
2.15	0.17	0.309
2.65	0.14	0.324
3.00	0.12	0.337
3.60	0.115	0.293
4.10	0.09	0.317
7.25	0.03	0.331
8.30	0.03	0.289

Acid:Base ratio 1:1 Temp. 20.0°. Solvent 'X'. 0.1900 G. of acid and 0.1972 g. of brucine were dissolved to 25 c.c.

(i)

Activations with Brucine.

Acid:Base ratio 1:1 Temp. 20.0°. Solvent 'X'. 0.1900 G. of acid and 0.1972 g. of brucine were dissolved to 25 c.c.

(i)

Time after 2.4 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-0.435	-	11.20	0.155	0.0922
2.10	0.36	0.0902	12.00	0.14	0.0935
2.60	0.345	0.0892	13.60	0.12	0.0947
5.20	0.265	0.0953	15.25	0.11	0.0902
6.45	0.235	0.0955	16.85	0.10	0.0873
7.60	0.215	0.0927	18.8	0.08	0.0901
8.70	0.195	0.0923	20.85	0.065	0.0912
10.05	0.175	0.0867			

Whence k = 0.0914 (limits 0.0867 and 0.0955).

(ii) Repetition of (i).

Time after 2.35 mins.	$\alpha_t - \alpha_\infty$	$k - \alpha_\infty$	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-0.43	-	6.25	0.245	0.0900
0.50	0.41	0.0953	8.65	0.19	0.0944
0.95	0.395	0.0895	11.65	0.14	0.0963
1.45	0.375	0.0945	14.65	0.11	0.0931
3.35	0.31	0.0977	18.65	0.08	0.0902
5.15	0.26	0.0977	25.65	0.05	0.0839

Whence  $k = 0.0929$  (limits 0.0839 and 0.0977).

Whence  $k = 0.295$  (limits 0.261 and 0.337).

Acid:Base ratio 2:1 Temp. 20.0°. Solvent 'X'. 0.3800 G.  
of acid and 0.1972 g. of brucine were dissolved to 25 c.c.

(i)

Time after 2.5 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.18	-
0.40	0.16	0.295
1.25	0.13	0.261
1.60	0.105	0.337
2.15	0.095	0.297
2.60	0.08	0.313
3.75	0.055	0.316
4.05	0.035	0.299
5.90	0.025	0.278

Whence  $k = 0.299$  (5) (limits 0.261 and 0.337).

The mean value of the velocity constant from (i) and (ii) is  $k = 0.391$  (limits 0.433 and 0.372).

(ii) Repetition of (i).

Time after 2.0 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.20	-
0.93	0.15	0.309
1.35	0.135	0.291
2.10	0.11	0.285
2.75	0.09	0.291
3.15	0.08	0.291
4.03	0.06	0.299
5.38	0.04	0.299

Whence  $k = 0.295$  (limits 0.309 and 0.285).

Acid:Base ratio 3:1. Temp.  $20.0^\circ$ . Solvent 'X', 0.5700 G. of acid and 0.1972 g. of brucine were dissolved to 25 c.c.

(i)

Time after 2.5 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.055	-
0.80	0.04	0.398
1.40	0.03	0.433
2.65	0.02	0.382
3.90	0.02	0.259

(ii) Repetition of (i).

Time after 2.33 mins.	$\alpha_t - \alpha_\infty$	k
0	-0.06	-
0.49	0.05	0.372
1.07	0.04	0.379
2.87	0.02	0.383

The mean value of the velocity constant from (i) and (ii) is  $k = 0.391$  (limits 0.433 and 0.372).

Found. C, 65.6; H, 4.77.  $C_{23}H_{20}O_2$  requires C, 69.56;

H, 4.77%.

Preparation of Brucine(-)-N-Benzoyl-2'-chloro-4':6-dimethyldiphenylamine-2-carboxylate.

3.89 G. (1 mol.) of (+)-acid and 4.66 g. (1 mol.) of brucine  $4H_2O$  were dissolved in separate 200 c.c. volumes of absolute ethyl alcohol. The solns. were filtered and united, the resulting soln. concentrated to about 120 c.c., and 250 c.c. of ether added. On cooling, crystallisation began, and a further 250 c.c. of ether were added. 7.8 G. of white needles were obtained, corresponding to 92% of the theoretical yield. Found. C, 69.7; H, 5.67:  $C_{46}H_{46}O_7N_3Cl$  requires C, 69.8; H, 5.34%.

Preparation of (-)-N-Benzoyl-2'-chloro-4':6-dimethyldiphenylamine-2-carboxylic Acid.

The brucine (-)-acid salt was decomposed by the usual formic acid method. Thus 3 g. of the salt were dissolved in twenty times their weight of cold anhydrous formic acid and the soln. filtered rapidly into dil. hydrochloric acid and ice. The pptd. active acid was quickly dried at the pump, and the process repeated.

Finally the acid was dried at 8 m.m. over calcium chloride. One portion of the acid was dried at  $120^{\circ}$ , and samples of both acids were allowed to racemise under the same conditions. The figures given below suggest that heating the solid active acid caused it to racemise to a large extent. Found. C, 65.6; H, 4.77.  $C_{23}H_{20}O_3NCl$  requires C, 69.56; H, 4.77%.

Racemisation of the Active (-)-Acid.

0.1000 G. of acid was dissolved to 25 c.c. in solvent 'X' at 20.0°.

(a) Acid dried at room temp.

(i)

Time after 3.35 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-2.735	-	6.43	0.94	0.166
1.15	2.26	0.166	7.05	0.85	0.166
1.65	2.08	0.166	7.75	0.76	0.165
2.15	1.91	0.167	8.75	0.63	0.168
2.65	1.76	0.166	9.75	0.53	0.168
3.15	1.61	0.168	10.50	0.48	0.166
4.00	1.41	0.166	11.95	0.37	0.167
5.00	1.195	0.166	12.75	0.33	0.166
5.55	1.07	0.169			

Whence k = 0.166 (limits 0.165 and 0.169).

(ii) Repetition of (i).

Time after 3.45 mins.	$\alpha_t - \alpha_\infty$	k	Time contd.	$\alpha_t - \alpha_\infty$	k
0	-2.425	-	6.25	0.845	0.169
1.15	2.01	0.163	6.95	0.765	0.166
1.50	1.89	0.166	7.50	0.695	0.167
2.75	1.52	0.170	8.20	0.62	0.166
3.30	1.39	0.169	9.05	0.54	0.166
3.70	1.31	0.166	9.60	0.49	0.167
4.10	1.22	0.168	10.28	0.45	0.164
4.65	1.105	0.169	11.97	0.32	0.169
5.10	1.03	0.168	12.70	0.29	0.167
5.70	0.94	0.166			

Whence k = 0.167 (limits 0.170 and 0.163).

(b) Acid dried in an oven.

Time (mins.) after wetting.	$\alpha_c - \alpha_p$
3.70	-0.16
4.70	0.13
6.50	0.10
8.50	0.075
10.45	0.06
13.85	0.04

Preparation of N-Benzoyl-2'-chloro-4'-methoxy-6-methyldiphenylamine-2-carboxylic Acid.

(a) 3-Chloro-p-anisidine.

Reference. Hurst and Thorpe, J., 1915, 938. Found; 200 G. of p-nitroanisole were reduced in 50 g. batches. To a mixture of 50 g. of the nitro body and 100 g. of granulated tin in a large flask equipped with an efficient water condenser, were added 100 c.c. of conc. hydrochloric acid. The reaction was slow initially, but on shaking became very vigorous. When the frothing had subsided, the flask not being cooled, a further 150 c.c. of conc. hydrochloric acid were added and the mixture was heated on a water bath for an hr. After being made alkaline with sodium hydroxide the mixture was steam distilled, the distillate being collected in 250 c.c. of 10% hydrochloric acid. An excess of sodium acetate was added to the distillate and the soln. extracted with ether, the extract dried and the ether removed leaving 13 g. of impure product.

The yields from 4 expts. were united, giving 44 g. of the amine which were purified by forming the benzoyl derivative. 16 G. of this anilide were obtained, m.p. 159-160°.

(b) Benz-2-chloro-4-methoxyanilide iminochloride.

The anilide (16 g. 1 mol.), and phosphorus pentachloride (13.6 g. 1.1 mols.), were heated together. The phosphorus oxychloride formed was removed at reduced pressure and the crude iminochloride not submitted to any further purification, 16 g. of crude material being obtained.

(d) 2'-Chloro-4'-methoxyphenylbenzimidino-6-methyl-2-carbomethoxyphenyl ether.

The crude imino chloride (16 g., 1 mol.) in 50 c.c. of ether was condensed with 9.5 g. (1 mol.) of methyl o-cresotate in 50 c.c. of absolute alcohol in the presence of 1.32 g. (1 atom) of sodium in 30 c.c. of absolute alcohol. The gummy product crystallised from methyl alcohol in prisms, mp. 94-95°. Found; C, 66.8; H, 4.52.  $C_{23}H_{20}O_4NCl$  requires C, 67.37; H, 4.92%.

(e) Methyl-N-benzoyl-2'-chloro-4'-methoxy-6-methyldiphenylamine-2-carboxylate.

11 G. of ester were kept at 285° for half an hour, the molten product being poured into cold methyl alcohol. An 82% yield of brown prisms, m.p. 124-125°, was obtained. Found; C, 67.6; H, 4.90.  $C_{23}H_{20}O_4NCl$  requires C, 67.37; H, 4.92%.

(f) N-Benzoyl-2'-chloro-4'-methoxy-6-methyldiphenylamine-2-carboxylic Acid.

A soln. of 6 g. of the purified ester in 300 c.c. of absolute alcohol was boiled with the calculated amount of an aqueous alcoholic caustic soda soln. The crude acid was

crystallised from benzene-acetone soln. to a constant m.p. 214-215°, 3.5 g. of microcrystalline solid being obtained. Found, C, 66.8; H, 4.65.  $C_{22}H_{18}O_4NCl$  requires C, 66.6; H, 4.58%.

Attempted Second Order Asymmetric Transformation with Brucine.

For the preliminary investigation, 0.198 g. of (+)-acid and 0.233 g. of brucine  $4 H_2O$  were intimately mixed, and small portions of this mixture taken for crystallisation expts.

Solvent	Result
Ethyl alcohol	Very soluble. No crystalline product was obtained.
Benzene	Soluble. A small amount of amorphous material was recovered.
Methyl alcohol	Very soluble. Crystals deposited after 3-4 days.
Acetone	White needles readily obtained.
Ethyl alcohol-ether	White needles.
Petroleum ethers	Insoluble.

In order to investigate the crop obtained from acetone, the expt. was repeated on a large scale and the crystals examined. Thus 0.1000 G. of the crystals was dissolved to 25 c.c. in chloroform at 20.0°.

Time (mins.) after wetting.	$\alpha_t - \alpha_\infty$	$[\alpha]_{5461}^{20.0}$
2.4	-0.10	-18.7°
3.0	0.10	
4.0	0.08	
10.5	0.05	
11.7	0.03	
$\infty$	-	-6.3°

formation from various other solvents were all unsuccessful.

It appeared, from the small change in rotation, that the partial racemate had been obtained from acetone soln., and that the mutarotation of the chloroform soln. of the solid was due to the first order transformation of the 50%:50% mixture to the equilibrium value.

To confirm this view 0.0495 g. of the (+)-acid and 0.0493 g. of brucine were dissolved to 25 c.c. in chloroform at 20.0°, and the soln. examined polarimetrically.

Time (mins.) after mixing.	$\alpha_t - \alpha_\infty$	$[\alpha]_{5461}^{20.0}$
2.0	-0.09	-17.7°
3.0	0.09	
6.4	0.07	
9.0	0.05	
28.0	0.01	
$\infty$	-	-6.3°

examined polarimetrically.

Time after contact  
These readings confirm the supposition that crystals of the partial racemate were obtained from acetone soln.

The crop of crystals obtained from ethanol-ether were next examined, and found also to be the partial racemate, the rotation of a chloroform soln. at  $20.0^{\circ}$ . ( $C = 0.400$ ) changing from  $[\alpha]_{20.0}^{20.0} = 17.5^{\circ}$  to  $-6.3^{\circ}$ .

Again, the crop obtained from methyl alcohol gave the same results. Attempts to obtain a second order transformation from various other solvents were all unsuccessful.

After 24 mins., the soln. was extracted again with acid.  
Attempted Second Order Transformation with Cinchonidine.

As before, many solvents were tried in attempts to obtain the crystallisation of one form of the cinchonidine (+)-acid salt. The only solvent from which crystals were obtained was methyl alcohol, but a chloroform soln. of this solid had a constant rotation  $\alpha = -0.02^{\circ}$ .

Attempted Preparation of 2:6-Diamino-1,4-bis(2-hydroxyethyl)benzylamine  
An attempt to obtain an Indication of the Optical Stability of the Active Acid.

It was intended to decompose a chloroform soln. of the brucine (+)-acid salt with dil. hydrochloric acid, and to examine the chloroform soln. of the acid remaining.

0.1979 G. of (+)-acid and 0.2333 g. of brucine  $4H_2O$  were dissolved in chloroform and allowed to reach equilibrium. This cooled soln. was then extracted twice with cold dil. hydrochloric acid and once with water and the chloroform layer examined polarimetrically.

Time (mins.) after contact with HCl.	$\alpha_t - \alpha_\infty$	$[\alpha]_{5461}^{20.0}$
7.1	-0.56	-4.2°
7.46	0.51	
8.0	0.41	
9.0	0.33	
11.0	0.205	
13.0	0.12	-37.5°
24.0	-	
After 24 mins., the soln. was extracted again with acid.		
5.1		-22.0°
6.25		
7.0		
9.0		-17.6°

Attempted Preparation of 2':4':6:6'-tetramethyldiphenylamine  
-2-carboxylic Acid.

(a) Nitromesitylene

Reference. Organic Syntheses, Pub. Wiley 1943, Vol.14, p.68.

A soln. of 160 g. of mesitylene in 240 g. of acetic anhydride was cooled and stirred mechanically, and was nitrated by the slow addition of 126 g. of fuming nitric acid dissolved in 80 g. of glacial acetic acid and 80 g. of acetic anhydride. The reaction mixture was kept at 15-20° throughout the addition and for an extra 2 hrs. afterwards, and finally was warmed to

50° for 10 mins. After this, it was poured into ice-water, 160 g. of sodium chloride added, the aqueous layer decanted from the oily product and extracted with ether. The extract was washed with dil. alkali and united with the crude product, the ether removed and the residue steam distilled in the presence of 300 c.c. of 20% caustic soda soln. 150 g. of yellow crystalline nitromesitylene were obtained m.p. 42-43°.

(b) Mesidine.

The nitromesitylene was reduced in 2 lots of 70 g. Iron filings, 70 g., and water were mixed to a stiff paste in a large flask fitted with a reflux condenser. To the paste were added 70 c.c. of glacial acetic acid and 70 g. of nitromesitylene, the flask being held in a boiling water bath with constant shaking. The reaction mixture was heated for 1.5 hrs. after all frothing had ceased, made alkaline with ammonia and extracted with a large volume of acetone. The acetone was removed and the residue distilled, the fraction boiling between 228-234° being collected.

Yield from 1st expt. 37 g. 63% of theory

" " 2nd " 48 g. 84% of theory

N-Benzoyl mesidine was prepared by heating a molecular amount of the amine with 1.25 mols. of benzoylchloride. Crystallisation from ethyl alcohol gave 89 g. of product m.p. 193-195°.

(c) Benz-2:4:6-trimethylanilide iminochloride.

89 G. (1 mol.) of the benzoyl derivative and 86 g. (1.1 mols.) of phosphorus pentachloride were allowed to react

Fractional distillation at reduced pressure of the reaction mixture gave an 82% yield of imino-chloride, b.p.192-195°/15 m.m.

(d) 2:4:6-Trimethylphenylbenzimidino-6-methyl-2-carbomethoxyphenyl ether.

A soln. of 51.5 g. (1 mol.) of methyl o-cresotate in 150 c.c. of absolute alcohol, followed by 80 g. (1 mol.) of the imino-chloride dissolved in 300 c.c. of ether, was added to a soln. of 7.15 g. (1 atom) of sodium in 300 c.c. of absolute alcohol. After a 15 hr. period, the solvents were removed, the residue poured into water, and the oily product crystallised from methyl alcohol, 87 g. being obtained; prisms m.p. 83-85°. Found. C, 77.3; H, 6.60.

$C_{24}H_{23}O_3N$  requires C, 76.8; H, 5.89%.

(e) Attempted Rearrangement of the Imino-ether to yield Methyl-N-benzoyl-2':4':6:6'-tetramethyldiphenylamine-2-carboxylate.

1. 15 G. of imino-ether were kept between 275° and 280° for 30 mins., and then poured into methyl alcohol. Crystals of m.p. 70-75° were obtained. The starting material had m.p. 80-85°, and a mixture of the two had m.p. 65-83°.

It was concluded that no rearrangement had occurred.

2. Expt. (1) was repeated at 290° for 6 hrs. Unsuccessful.

3. Expt. (1) was repeated at 275° for 3 hrs., 280° for 0.5 hrs., and 290° for 0.5 hrs. A tar was obtained.

4. 4 G. of material were kept at 200° for 30 hrs.

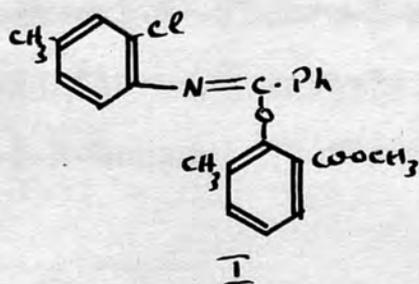
Portions were removed at intervals and the m.p. determined.

crystallising the oily residue from methyl alcohol, crystals

After 1.5 hrs.	crystals from methanol	m.p. 45-65°
" 4.0 hrs.	" " "	m.p. 45°
" 7.75 hrs.	" " "	decomp. 100°
" 30.0 hrs.	" " "	m.p. 40-50°
		decomp. 87-89°
		m.p. 50°
		decomp. 100°.

5. An attempt was made to carry out the Chapman rearrangement in a high boiling point solvent of high dielectric constant. Succinonitrile was selected (b.p. 265-267°), and was prepared in a 30% yield by the addition of an ethanolic soln. of ethylene dibromide to a hot aqueous soln. of potassium cyanide and boiling the mixture for an hour.

Initially an attempt was made to isomerize an imino-ether which was known to react at a certain temp. Thus I was selected. This material had m.p. 112-114°



and underwent isomerization at 285° yielding an ester of m.p. 187-188°.

Three expts. were tried, using 1 g. of I and 3 c.c. of succinonitrile and keeping the mixture at 200-220° for different periods. In all cases, on pouring into water and crystallising the oily residue from methyl alcohol, crystals

having m.p. 98-105° were obtained, indicating only very slight isomerisation.

1. Phenyl Further expts. carried out with this solvent and 2:4:6-trimethylphenylbenzimidino-6-methyl-2-carbomethoxyphenyl ether under different conditions all gave back intractable tars.

4. Cinchonidine (+)-N-benzoyl-4:6-dibromodiphenylamine-2-carboxylate.

5. 2'-Bromophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.

6. Methyl N-benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylate.

7. N-Benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylic acid.

8. Brucine (-)-N-benzoyl-2'-bromo-6-methyldiphenylamine-2-

carboxylate.

9. o-Fluorebenzanilide.

10. Benz-o-fluoreanilide iminochloride.

11. 2'-Fluorophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.

12. Methyl N-benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylate.

13. N-Benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylic acid.

14. Brucine (-)-N-benzoyl-2'-fluoro-6-methyldiphenylamine-2-

carboxylate.

15. 2':4'-Dichlorophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.

16. Methyl N-benzoyl-2':4'-dichloro-6-methyldiphenylamine-2-carboxylate.

Section 3.      New Compounds prepared in this Work.

1. Phenylbenzimidino-4:6-dibromo-2-carbomethoxyphenyl ether.
2. Methyl N-benzoyl-4:6-dibromodiphenylamine-2-carboxylate.
3. N-Benzoyl-4:6-dibromodiphenylamine-2-carboxylic acid.
4. Cinchonidine (+)-N-benzoyl-4:6-dibromodiphenylamine-2-carboxylate.
  
5. 2'-Bromophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.
6. Methyl N-benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylate.
7. N-Benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylic acid.
8. Brucine (-)-N-benzoyl-2'-bromo-6-methyldiphenylamine-2-carboxylate.
  
9. o-Fluorobenzanilide.
10. Benz-o-fluoroanilide iminochloride.
11. 2'-Fluorophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.
12. Methyl N-benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylate
13. N-Benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylic acid.
14. Brucine (-)-N-benzoyl-2'-fluoro-6-methyldiphenylamine-2-carboxylate.
  
15. 2':4'-Dichlorophenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.
16. Methyl N-benzoyl-2':4'-dichloro-6-methyldiphenylamine-2-carboxylate.

17. N-Benzoyl-2':4'-dichloro-6-methyldiphenylamine-2-  
30. 2'-Chloro-4'-methylphenylbenzimidazole-2-carboxylic acid.
18. Brucine (-)-N-benzoyl-2':4'-dichloro-6-methyldiphenylamine-  
31. Methyl N-benzoyl-2'-chloro-4'-bromo-6-methyldiphenylamine-2-carboxylate.
19. 2-Chloro-4-bromobenzanilide iminochloride.
20. 2'-Chloro-4'-bromophenylbenzimidazole-2-carbomethoxy-6-methylphenyl ether.
21. Methyl N-benzoyl-2'-chloro-4'-bromo-6-methyldiphenylamine-  
34. 2':4':6'-trimethyldiphenylamine-2-carboxylate.
22. N-Benzoyl-2'-chloro-4'-bromo-6-methyldiphenylamine-2-carboxylic acid.
23. Brucine (-)-N-benzoyl-2'-chloro-4'-bromo-6-methyldiphenylamine-2-carboxylate.
24. Benz-2-chloro-4-methylanilide iminochloride.
25. 2'-Chloro-4'-methylphenylbenzimidazole-2-carbomethoxy-6-methylphenyl ether.
26. Methyl N-benzoyl-2'-chloro-4':6-dimethyldiphenylamine-2-carboxylate.
27. N-Benzoyl-2'-chloro-4':6-dimethyldiphenylamine-2-carboxylic acid.
28. Brucine (-)-N-benzoyl-4':6-dimethyldiphenylamine-2-carboxylate.

29. Benz-2-chloro-4-methoxyanilide iminochloride.
30. 2'-Chloro-4'-methoxyphenylbenzimidino-6-methyl-2-carbomethoxyphenyl ether.
31. Methyl N-benzoyl-2'-chloro-4'-methoxy-6-methyldiphenylamine-2-carboxylate.
32. N-Benzoyl-2'-chloro-4'-methoxy-6-methyldiphenylamine-2-carboxylic acid.
33. Benz-2:4:6-trimethylanilide iminochloride.
34. 2':4':6'-Trimethylphenylbenzimidino-2-carbomethoxy-6-methylphenyl ether.