S T E R E O C H E M I S T R Y

O F

T E R V A L E N T N I T R O G E N

Thesis submitted for the Degree of Ph.D. in Science

in the University of London

By

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M.M.J.

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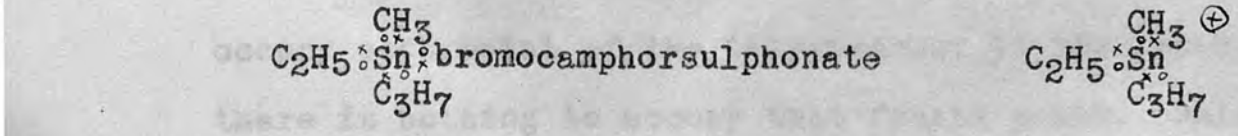
Analyses for halogen content were carried out using the Parr Bomb.

1. THE SPATIAL CONFIGURATION OF THREE GROUPS ATTACHED BY COVALENT BONDS TO A CENTRAL ATOM.

It appears to be impossible for a molecule in which the central atom has six outer electrons to preserve a non planar structure: this is demonstrated by the absence of polarity in the boron halides, BCl_3 and BF_3, indicating that all four atoms in the molecule lie in a plane with the boron atom in the centre. Ammonia, arsine and phosphine, on the other hand, all have measureable dipole moments, and here the central atom holds a lone pair of electrons in excess of those forming the three covalent bonds.

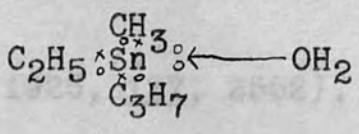
It has been suggested that in the methyl-ethyl-propyl-tin bromocamphorsulphonate resolved by Pope and Peachey, (P., 1900, 42 and 116), asymmetry is preserved by the positively charged methyl-ethyl-propyl tin ion: the compound and the ion have the electronic structures:-



In the ion, apart from the positive charge, the electronic structure is the same as in the boron halides. The resolution was carried out in water, and the rotations taken in aqueous solution: the iodide was optically active and

easily racemised. There seems to be some doubt as to whether the compound is ionised or not: if **not** ionised, then its optical activity can be explained on the tetrahedral model like the carbon compounds: if ionised, then here is a unique kind of asymmetry. According to Bredig, there is a good case for non-ionisation: the hydroxide is a very weak base, the acetate, butyrate etc., are distillable without decomposition, and soluble in ether, as are also the carbonate and nitrate. So it seems quite possible that the compound is covalent; a certain degree of ionisation, if ionisation was accompanied by almost instantaneous racemisation, would account for the rapid disappearance of optical activity of the iodide. The case of this tin compound differs from the others considered by Phillips in his hypothesis that a positive charge stabilises 3-covalent asymmetry, for in the sulphur compounds there is always a full complement of eight outer electrons, and therefore a pair of electrons to occupy each point of the tetrahedron: in the $[Snabc]^+$ ion, there is nothing to occupy that fourth point. Meisenheimer (Ber., 1933, 66, 985), suggests that ionisation does take place - it is very difficult to believe that if it does not, considering the strength of bromocamphorsulphonic acid - but is accompanied by hydration, so that the

4-covalent complex

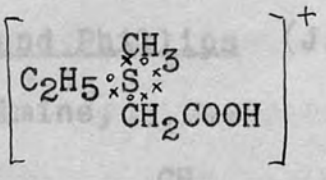


is formed, and there is no question of tercovalent asymmetry.

The following compounds of sulphur and selenium have been resolved in which the central atom carries an integral positive charge:-

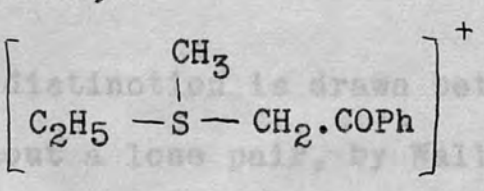
1. Pope and Peachey, (J., 1900, 77, 1072).

Methyl-ethyl-thetine camphorsulphonate and bromo-camphorsulphonate,



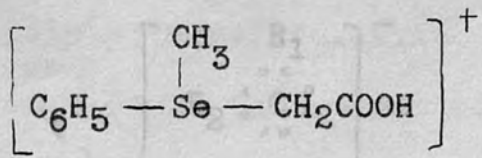
2. Smiles, (J., 1900, 77, 1174).

The thetine,



3. Pope and Neville, (J., 1902, 81, 1557).

The selenetine

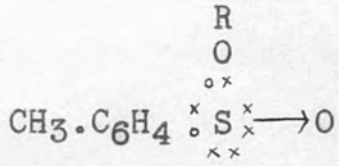


and the following compounds in which the central atom is the donor in a co-ordinate bond, and therefore carries a

positive charge approximating to the electronic charge, having lost a half share in two electrons:-

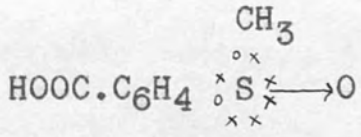
1. Phillips (J., 1925, 127, 2552).

The sulphoxide



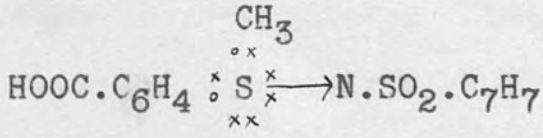
2. Harrison, Kenyon and Phillips (J., 1926, 2079).

The sulphoxide

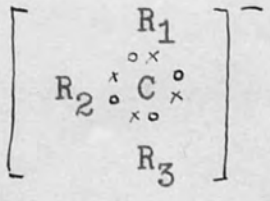


3. Clarke, Kenyon and Phillips (J., 1927, 188).

The sulphimine,

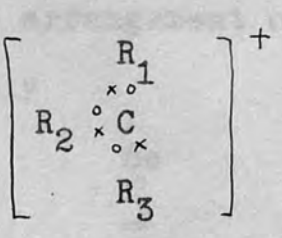


A nice distinction is drawn between the two cases, with and without a lone pair, by Wallis and Adams (J. Amer. Chem. Soc., 1933, 55, 3838). They show that a carbanion of the type



is sufficiently stable to maintain an asymmetric configuration,

while tercovalent carbonium ions

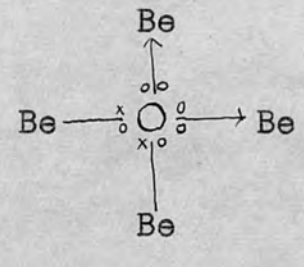


in the absence of a special mechanism which leads to Walden inversion, are optically unstable. It will be noticed that the stable ion here is the negatively charged one: however, carbon, owing to its position in the first period, might be expected to retain tetrahedral asymmetry even if negatively charged; the sulphur and selenium atoms are 'softer'.

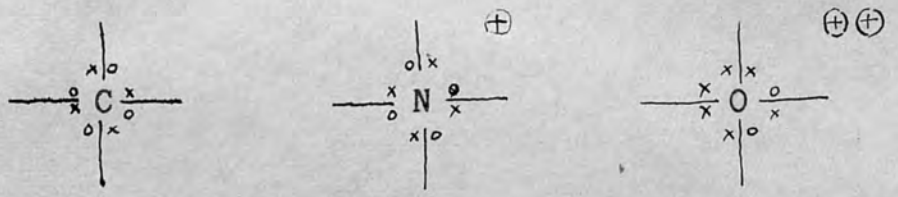
It is interesting to compare the electronic structure of nitrogen compounds with those of carbon and oxygen, its neighbours in the Periodic Table. There are two types of compounds to compare, corresponding to pentavalent and tervalent nitrogen.

The predicted similarity between a compound Cabcd, a quaternary ammonium compound and tetracovalent oxygen has been borne out by experiment. In the last case, Morgan and Bragg, (Proc. Roy. Soc., 1923, 104, 437), showed by X-ray analysis of basic beryllium acetate, $Be_4O.(O.COCH_3)_6$ that the oxygen lies in the centre of a tetrahedron with

the four beryllium atoms at the corners: they do not say anything about the arrangement of the oxygen electrons, but it is presumably

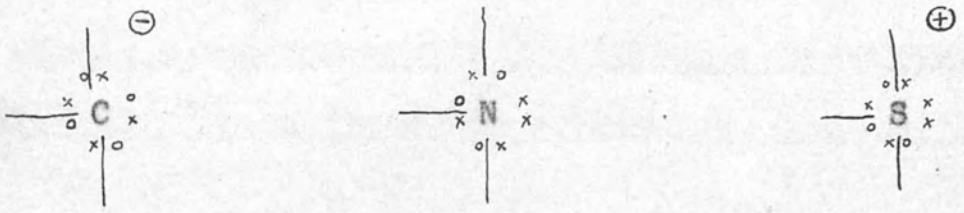


so that we have the series



in which the distribution is tetrahedral in each case.

A similar series can be made with ter-covalent nitrogen in the central position, in which the non-resolution of the nitrogen is the anomaly in the Periodic Law. Unfortunately no oxygen compound has been investigated which can take its place in this series: we can only say that hydrazine and hydrogen peroxide have been shown to be analagous from their Raman spectra, and that the valency angle of oxygen in water and ethers (from dipole measurements) approximates to the tetrahedral angle. However, it seems permissible to consider sulphur in place of oxygen and so we have the series



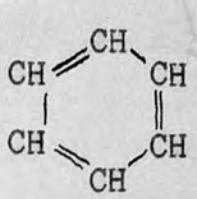
comparing Wallis and Adams' carbon anion, a tertiary amine and Pope and Peachey's thetine ion. Only the nitrogen complex remains unresolved.

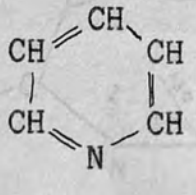
2. EVIDENCE FOR NON-PLANAR DISTRIBUTION OF TERVALENT NITROGEN VALENCIES FROM ITS MODES OF CHEMICAL COMBINATION.

It can be shown that in chemical combination there is distinct resemblance between the nitrogen atom and a carbon atom with an attached hydrogen atom, viz. $\equiv N$ and $\equiv CH$, $-N=$ and $=CH-$, $-NH-$ and $-CH_2-$. This strongly upholds the suggestion that the size of the valency angle of nitrogen is very near to that of carbon, that is, to the tetrahedral angle.

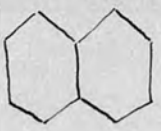
The existence of the nitriles, $R-C\equiv N$ is incompatible with a planar distribution of nitrogen valencies. The structure of cyanogen itself has been proved to be $N\equiv C-C\equiv N$, by its preparation by the dehydration of oxamide; its zero electrical moment shows it to be symmetrical and linear (Braune and Asche, Z. phys. Chem., 1931, B, 14, 18) the latter being confirmed by measurement of electron diffraction of the gas (Brockway, Proc. Nat. Acad. Sci., 1933, 19, 868): in electron diffraction, the molecule resembles diacetylene, $HC\equiv C-C\equiv CH$.

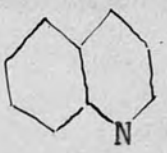
The $-N=$ atom can replace the $-CH=$ group, and the $-NH-$ group the $-CH_2-$ group in ring compounds, without appreciably changing the stability of the rings: pairs of compounds which illustrate this are —



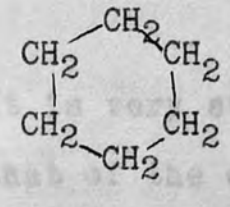


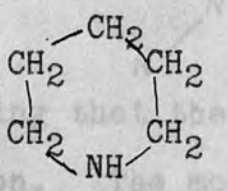
Benzene and Pyridine



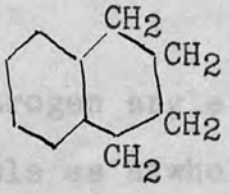


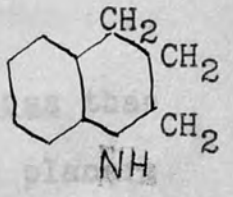
Naphthalene & Quinoline





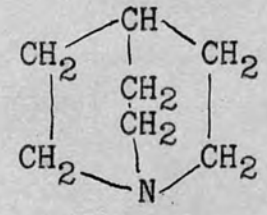
Cyclo Hexane & Piperidine

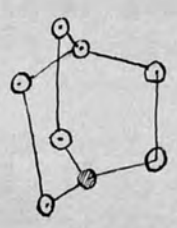




Tetralin & Tetrahydroquioline

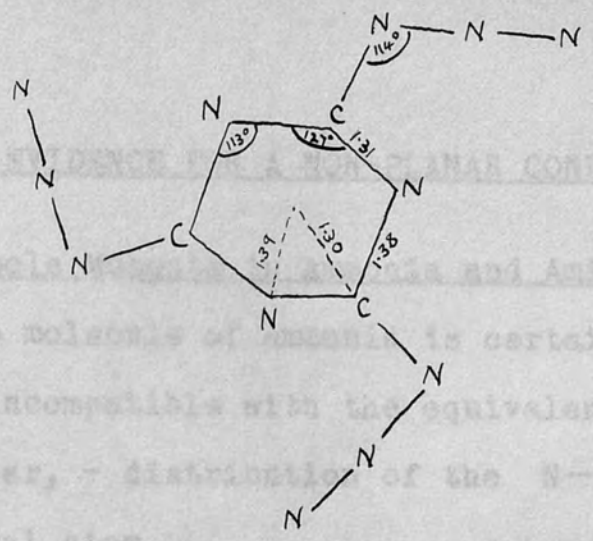
It is necessary to assume a pyramidal arrangement of the nitrogen valencies to account for the ease of the final stage of preparation of various nitrogen containing ring compounds, notably quinuclidine, which to be strain-free must have the structure shown below:-





where the nitrogen atom at one end of the molecule plays a similar part to the $-\overset{|}{C}H-$ group at the other.

In the last three years, very interesting crystallographic measurements have been made on cyanuric triazide, (Knaggs, Proc. Roy. Soc., 1935, (A), 150, 576: Nature 1935, 135, 268). The author finds that it has the structure



It is very striking that the nitrogen angle is <u>less</u> than that of the carbon. The molecule as a whole is planar: the hexagon is distorted, the alternate inter-atomic distances being 1.31 and 1.38 Å: it is assumed that in consequence of the unsymmetrical form of the azide group (resonant forms, $-N=N\rightarrow N$ and $-N\leftarrow N\equiv N$) Kekulé tautomerism is inhibited.

3. PHYSICAL EVIDENCE FOR A NON-PLANAR CONFIGURATION OF AMINES

(i) Dipole Moments in Ammonia and Amines.

The molecule of ammonia is certainly polar, and this fact is incompatible with the equivalent, - that is to say, planar, - distribution of the N—H valencies about the central atom.

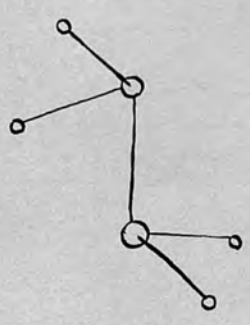
Substance	Dipole Moment in absolute units.	Reference
NH_3	$1.44 - 1.53 \times 10^{-18}$	Jona, Physik Z., 20, 14, 1919. Zahn, Physic. Rev. 27, 455. Watson, Proc. Roy. Soc., 117, 43. Keyes and Kirkwood, Physic. Rev., 36, 1570.
$CH_3.NH_2$	1.23 ± 0.02	Steiger, Helv. Phys. Acta. 3, 161., Physik Z., 32, 425.
$(CH_3)_2NH$	0.96 ± 0.01	" "
$(CH_3)_3N$	0.60 ± 0.02	" "

The electrical moment points to the molecule being pyramidal, with three isosceles lateral faces and the nitrogen atom at the apex. It seems a reasonable assumption,

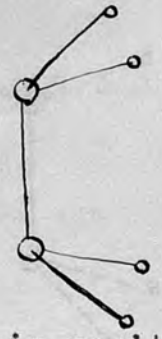
that for three identical non-polar groups attached to a central nitrogen atom forming an amine, the smaller the dipole moment, the more obtuse the pyramid. The successive substitution of methyl groups for hydrogen atoms in ammonia causes the fall in the dipole moment shown in the Table above; trimethylamine is much less polar than ammonia. It is well known that methyl groups are electron donating, and if these groups make the molecule less polar, electron attracting groups should make it more polar: that is, more resistant to racemisation if racemisation consists in the nitrogen atom passing through the plane of the hydrogen atoms.

(ii) Dipole Moments in Hydrazine and its Derivatives.

The dipole moments of hydrazine and some of its derivatives, for example, hydrazo benzene, were measured by Andrieth, Nespital and Ulich, (J. Amer. Chem. Soc., 1933, 55, 673) and found to be considerable. If the nitrogen valencies are given the tetrahedral disposition, then there is one position, - the trans, - in which there is a high degree of symmetry and so no dipole moment.

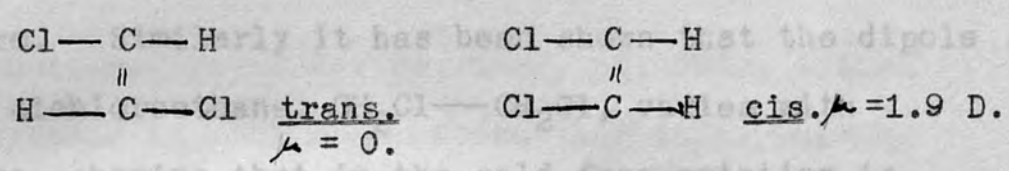


trans position



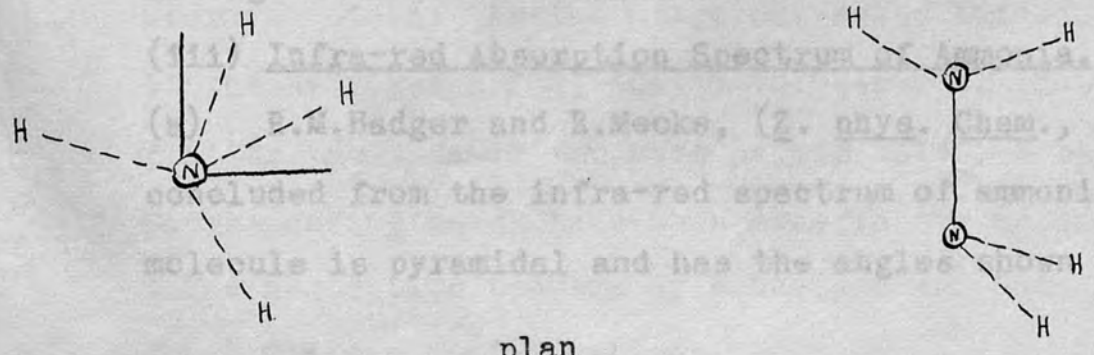
cis position

This is to some extent, (although not entirely, for rotation about the $\rangle N-N\langle$ bond cannot be so efficiently inhibited as it is in the case of a double bond) analagous to substances such as dichloroethylene, which exists in two forms, cis, and trans, and Errera, (Physik. Z., 1926, 27, 754)



states that the dipole moments are 1.9D and 0 respectively. It must therefore be assumed that the hydrazine molecule is generally in the cis form.

Sutherland and Penney, (J. Chem. Physics, 1934, 2, 492) have done further work on this subject: they find from calculations by "the method of electron pairs" that the most stable configuration of the hydrazine molecule is that in which the lines bisecting the H—N—H angles are at right angles to each other.

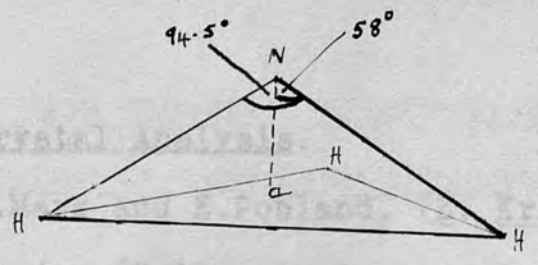


They go so far as to say that free rotation cannot occur at ordinary temperatures. Penney, (Faraday Society Discussion, Sept. 1934), amplified this statement by saying that while dichloroethylene exists in two isomeric forms at ordinary temperatures, about 300° there is an equilibrium mixture of the two forms whose composition varies with temperature. Similarly it has been shown that the dipole moment of dichloroethane, $CH_2Cl—CH_2Cl$, varies with temperature, showing that in the cold free rotation is inhibited about the $\dot{C}—\dot{C}$ bond, doubtless owing to the forces of interaction of the H and Cl atoms of one group with those of the other.

It is also pointed out in the above paper that the structure of hydrazine as concluded from dipole measurements and Raman spectra data is very like that of hydrogen peroxide, H—O—O—H. This is very interesting, for we should expect from the Periodic Law that positively charged oxygen should resemble tricovalent nitrogen, just as positively charged nitrogen has stereochemical properties analagous to tetracovalent carbon.

(iii) Infra-red Absorption Spectrum of Ammonia.

(a) R.M.Badger and R.Mecke, (Z. phys. Chem., B, 1929,5, 333), concluded from the infra-red spectrum of ammonia that the molecule is pyramidal and has the angles shown in the diagram:-



the distance N—H is 0.977×10^{-8} cms.

H—H is 1.43×10^{-8} "

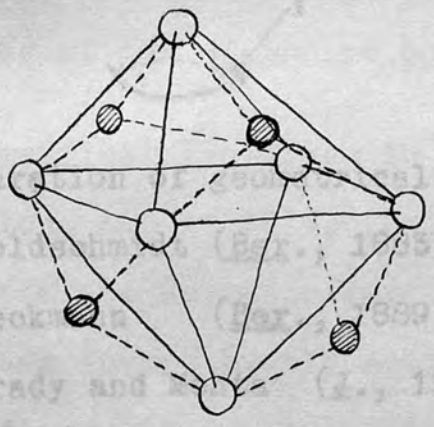
Height is 0.517×10^{-8} "

(b) E.F.Barker, (Phys. Review, 1929, 33, 684), thinks that the pyramid is much more obtuse than this. He resolved the ammonia absorption band from $8\mu - 14\mu$ by means of a grating and found two very small narrow zero branches of nearly equal intensity at 10.3μ and 10.7μ. Both of these bands must be associated with a single fundamental vibration, parallel to the axis of symmetry, and he interprets the double band as formed owing to the close proximity of the two equilibrium positions of the nitrogen atom, one on either side of the plane formed by the hydrogen atoms. From this, and intensities in the 1.9μ band, it is concluded that the ammonia molecule is pyramidal, the maximum height being $\frac{1}{5}$ of the distance between two hydrogen atoms. As the nitrogen passes through the plane of the hydrogen atoms, they move outwards, (note that the flatter the pyramid the more easily this can take place). Corresponding bands have been observed in arsine and phosphine absorption spectra by Robertson and Fox, suggesting still flatter configurations.

(iv) Crystal Analysis.

H.Mark and E.Pohland, (Z. Krist., 1924. 61, 532), I. de Smedt, (Bull.. Acad. roy. Belg., 1925, 11, 655), found that the crystal structure of solid ammonia indicated a pyramidal distribution of the N—H valencies.

Dickinson and Raymond, (J. Amer. Chem. Soc., 1923, 45, 22), had previously shown from X-ray analysis that hexamethylene tetramine had the structure:-

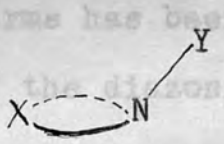


in which the octahedral skeleton is formed by the six carbon atoms, and the four nitrogen atoms sit in the centre of octahedron faces at the apices of triangular pyramids. The valency angle of the nitrogen atom from this work appears to be nearly the tetrahedral angle.

4. EVIDENCE FROM GEOMETRICAL ISOMERISM FOR THE NON-PLANAR CONFIGURATION OF TERVALENT NITROGEN

(a) Oximes, Phenyl hydrazones and Semicarbazones.

The original hypothesis of Hantzsch and Werner that in oximes the disposition of nitrogen valencies is non-planar has been amply confirmed by experiments carried out on the three types of compound above, which all contain the grouping



1. By separation of geometrical isomers,
   cf. Goldschmidt (Ber., 1883, 16, 2176).
   Beckmann (Ber., 1889, 22, 709).
   Brady and Mehta (J., 1924, 2297).
2. By resolution of molecules whose asymmetry depends on non-planar tervalent nitrogen,
   cf. Mills and Bain (J., 1910, 97, 1866)
   Mills and Saunders (J., 1931, 537).
3. By formation of metallic complexes.

   Many aromatic aldoximes form complexes with metals: these can be of three different types, and in all of them it is necessary to assume a tetrahedral configuration of the nitrogen atom of the oxime group to account for the stability of the complex.

cf Sidgwick "Organic Chemistry of Nitrogen" p. 193

Ephraim (Ber., 1930, 63, 1928: 1931, 64, 1215).

Taylor and Roberts (J., 1933, 2, 1439).

Pfeiffer (Ber., 1930, 63, 1811).

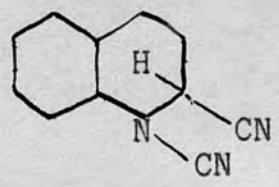
(b) Syn and Anti forms of Diazo compounds.

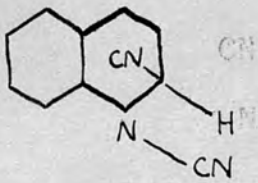
Hantzsch's view that diazo-compounds can exist in syn and anti forms has been substantiated by the discovery of two forms of the diazonium hydrates, cyanides and sulphates.

(c) Geometrical Isomerism in Quinoline Dicyanides.

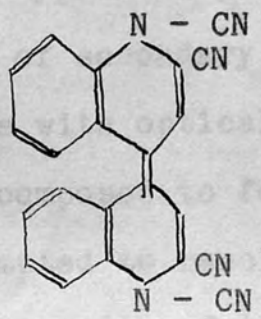
As long ago as 1914, (Ber., 1914, 47, 758), it was found by Mumm and Herrendorfer that a crystalline compound $C_9H_7(CN)_2$ was formed by the action of cyanogen bromide and hydrogen cyanide on quinoline, and on treatment with alcoholic ammonia, this gave a crystalline isomeride.

Mumm and Ludwig, (Annalen., 1934, 514, 34), have extended this work and found that pairs of isomers can be obtained in the cases of 3- and 6-methyl- and 6- methoxy-quinoline. The discoverers think that the two forms are a pair of cis-trans isomerides of a new type.





Both of these compounds give quinoline 2-carboxylic acid with hydrochloric acid at 150°, and both are converted by iodine in alcoholic pyridine solution into the same apocyanine dye,

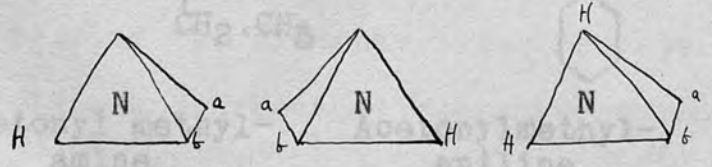


This work seems to be important enough to merit confirmation and further investigation.

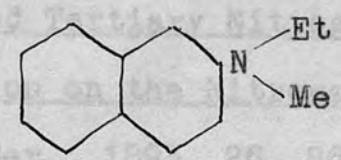
5. ATTEMPTS TO RESOLVE 3-COVALENT NITROGEN COMPOUNDS.

(i) Secondary and Tertiary Amines. Salt forming on the Nitrogen Atom.

The earliest type of experiment which was attempted was the resolution of secondary and tertiary amines by forming their salts with optically active acids. The salts were then to be decomposed to form the amine. Kraft, (Ber., 1890,23,2780) attempted to resolve benzylethylamine by fractional crystallisation of the hydrogen tartrate, and Ladenburg, (Ber., 1893, 26, 864), tried methyl aniline by a similar method. It is now known, of course, that these experiments could not be expected to succeed, for although the secondary amine $\overset{NabH}{\wedge}$ could be expected to exist in two stereo-isomeric forms, the salt $NabH_2X$ could not.



Reychler, (Bull. Soc. Chim., 1902, 27, (iii), 979), describes an attempt to resolve methylethyl-β-naphthylamine,

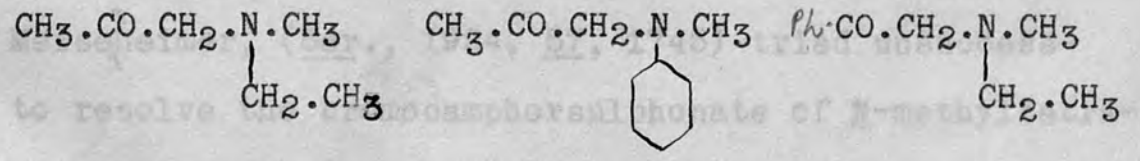


by crystallisation of the d-camphorsulphonate. This should

have been resolvable, but many experiments carried out since this time have not succeeded in demonstrating the optical activity of a nitrogen atom with an attached hydrogen atom: only quaternary ammonium salts were resolved.

A piece of work similar to the above was the attempted but unsuccessful resolution by Behrend and König, (Annalen., 1891, 263, 181)of benzyl hydroxylamine by means of the tartrate and mandelate.

In 1924, it appeared to Meisenheimer, that as the compounds of sulphur and selenium which had been resolved contained acetonyl and phenacyl groups, these groups might be responsible for the activity. So he attempted to resolve the three compounds



Acetonyl methylamine	Acetonylmethylaniline	Phenacylmethylethylaniline

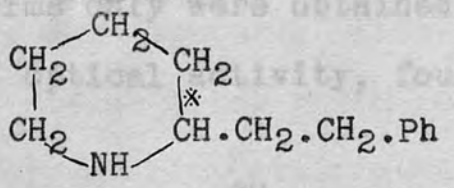
by forming their salts with optically active acids, but achieved no success.

(ii) Secondary and Tertiary Nitrogen in Ring Compounds.

Salt formation on the Nitrogen Atom.

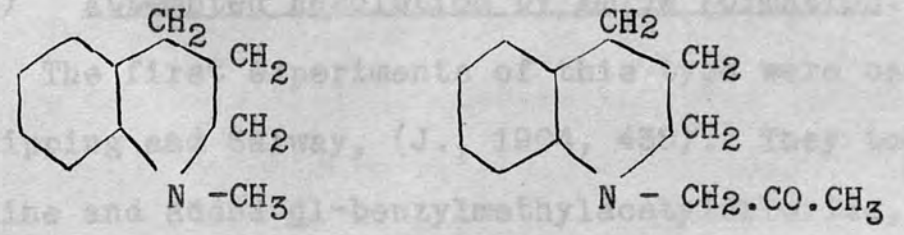
Ladenburg, (Ber., 1893, 26, 864), described the fractional crystallisation of the hydrogen tartrates of

tetrahydroquinoline and tetrahydropyridine: in neither case was a change in rotation observed, a result we could now predict, although at that time these were reasonable experiments to try. Ladenburg resolved stilbazoline



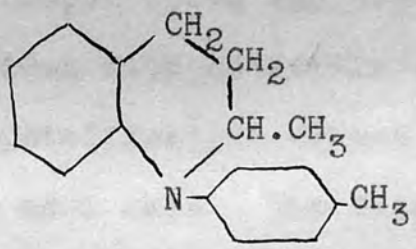
which contains an asymmetric carbon atom, and considered that, as well as the d and l forms expected, there was an iso form, differing in rotation from either, and the existence of which he attributed to the asymmetry of the nitrogen atom. This has since been shown to be an erroneous conclusion, the iso form being a mere impurity.

Meisenheimer, (Ber., 1924, 57, 1745) tried unsuccessfully to resolve the bromocamphorsulphonate of N-methyltetrahydroquinoline and N-acetonyltetrahydroquinoline:-



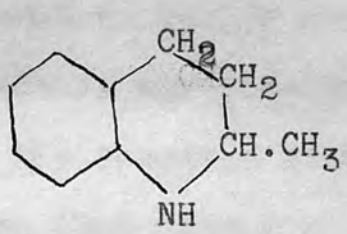
the latter in pursuit of his idea that acetonyl and phenacyl groups might be responsible for the sulphur and selenium resolutions.

Under this heading may be mentioned some experiments by Pope and his co-workers: the object of the experiments was the resolution of asymmetric carbon compounds by forming salts with optically active acids on the nitrogen atoms. In each case two forms only were obtained, whereas had the nitrogen atom shown optical activity, four forms would have been expected.



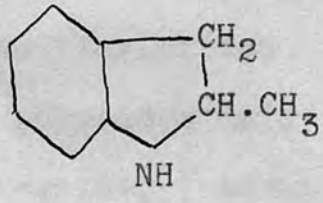
Tetrahydro-p-tolyl-quinaldine.

Pope and Beck, (J., 1907, 458).



Tetrahydro-quinaldine.

Pope and Read, (J., 1910, 2199).



2-Methyldi-hydroindole

Pope and Clarke, (J., 1904, 1330).

It must be pointed out, however, that only two forms were looked for.

(iii) Attempted Resolution by Amide Formation.

The first experiments of this type were carried out by Kipping and Salway, (J., 1904, 438). They took methyl-aniline and added dl-benzylmethylacetylchloride, but got no separation of two compounds. They repeated this experiment with p-toluidine, phenyl hydrazine and benzylaniline, and in no case found the salts dBdA, dBlA, lBlA, lBdA for

which they were looking. In order to eliminate the possibility of the formation of a double racemic salt $\left\{\begin{matrix} \underline{d}B\underline{d}A & \underline{d}B\underline{l}A \\ \underline{l}B\underline{l}A & \underline{l}B\underline{d}A \end{matrix}\right\}$ which would obscure the desired effect, they repeated the work with optically active benzylmethylacetylchloride, but had no more success. Finally, they took a series of optically active bases which contained tertiary nitrogen atoms and asymmetric carbon atoms, and formed their amides with optically active benzylmethylacetylchloride: crystallisation showed the presence of one substance only in each case. The bases used were d-hydrindamine, l-methylhydrindamine, l-menthylamine and l-α-phenylethylamine.

In 1928, Frèrejacque, (Compt. rend. 1928, 187, 894), condensed ethylaniline with camphor-α-sulphonyl chloride to form the amide, but on treating this in various ways was not able to find any change in rotation.

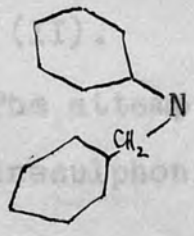
(iv) Compounds in which the Resolving Group is not on the Nitrogen Atom.

The outcome of the work in sections (i) and (ii) above was the decision that no success would be achieved while the nitrogen atom to be resolved was subjected to the electrical disturbance of having the optically active acid group attached to it.

(a) Hydrazines.

The early experiments with hydrazines were done before the evidence above was obtained. Kraft (Ber., 1890,

23, 2782) failed to obtain two forms of the tartrate of p-tolyl-hydrazine, and Behrend and König (Annalen., 1891, 263, 184) were no more successful with benzylphenylhydrazine. H.O.Jones and Millington, (Proc. Camb. Phil. Soc., 1904, 12, (vi) 489), attempted to resolve compounds of the type Nabc in which the active valency of the nitrogen atom was not changed during the resolution. Among other things, they tried N-phenyl-N-benzylhydrazine d-camphorsulphonate,

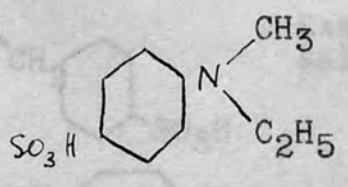


, d-camphorsulphonic acid.

but with no success.

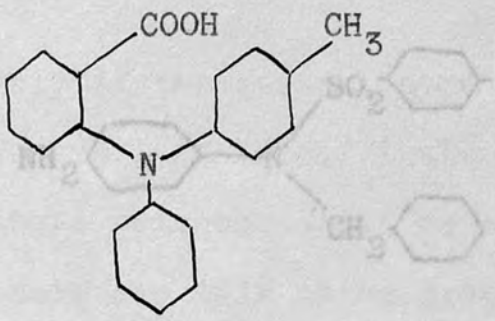
(b) Other Compounds.

In the paper just mentioned above, Jones and Millington describe the fractional crystallisation of the brucine salt of methylethylaniline-p-sulphonic acid:

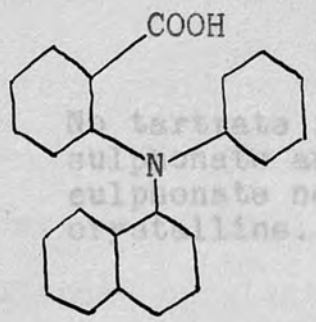


the brucine salt had $(M)_D$, -120°, and this value did not change on repeated crystallisation.

Meisenheimer, (Ber., 1924, 57, 1745), tried to resolve N-p-tolylanthranilic acid (I) by means of the strychnine and quinine salts without success, while the cinchonine,



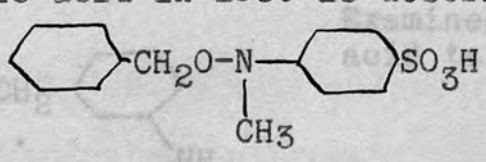
I



II

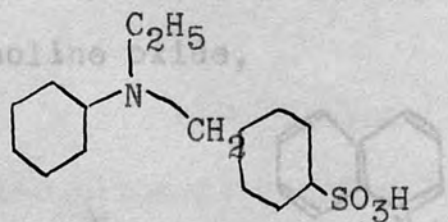
brucine and morphine salts did not crystallise satisfactorily. He also failed to find more than one form of the brucine and morphine salts of N-phenyl-N-α-naphthylanthranilic acid. (II).

The attempted resolution of N-methyl-N-benzyloxy-p-anilinesulphonic acid in 1930 is described as due

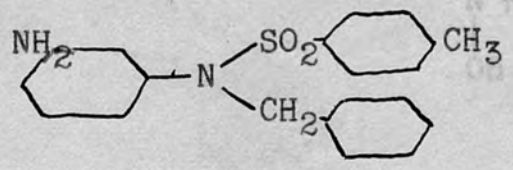


to Denner in Freudenberg's "Stereochemie", p. 1151.

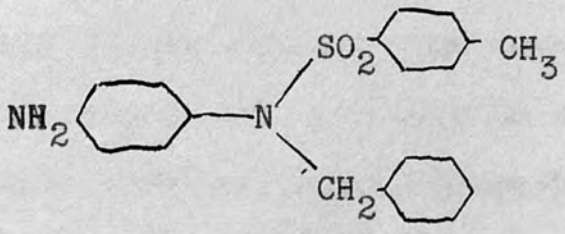
Menon and Peacock, (J. Indian Chem. Soc., 1936, 13, 104) tried to resolve the following compounds without success:-



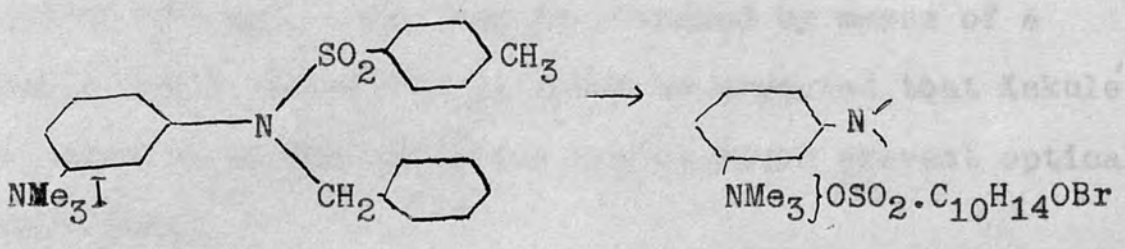
Examined the crystalline brucine salt.



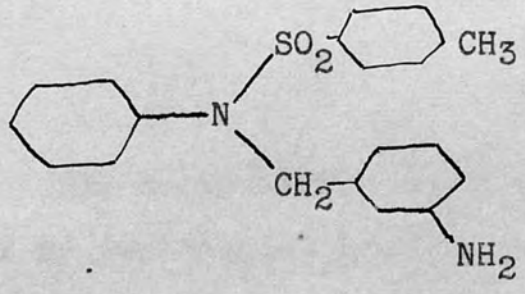
Examined the crystalline acid tartrate.



No tartrate formed. Camphorsulphonate and bromocamphorsulphonate not obtained crystalline.

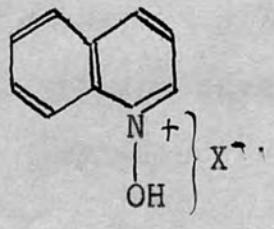


Methobromocamphorsulphonate extracted, but was a gum



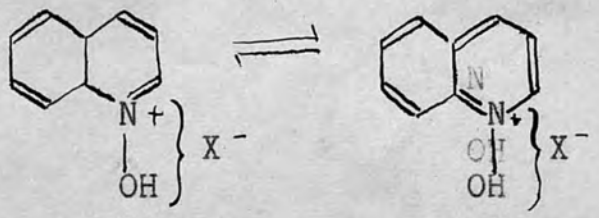
Examined the crystalline acid tartrate.

Meisenheimer, (Ber., 1933, 66, 985), published the result of an unsuccessful attempt to resolve salts of quinoline oxide,



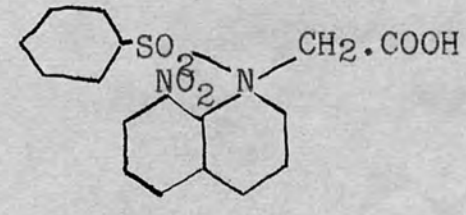
This was done to test the validity of Phillips hypothesis that 3-covalent asymmetry could be established

only if the central atom carried a positive charge. However, it is difficult to see how the nitrogen in the above compound could be considered tervalent, for although there are only three groups attached covalently to the central nitrogen atom, one is attached by means of a double bond: moreover, it would be expected that Kekulé tautomerism in the quinoline system would prevent optical stability.

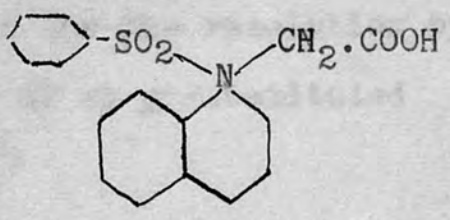


The experiments above were all carried out with a view to resolving tervalent nitrogen: there follows a brief list of resolution experiments which were done with the opposite aim - to show that optical activity in a similar compound was <u>not</u> due to the asymmetry of the nitrogen atom.

(a) Mills and Elliot, (J., 1928, 1291), resolved <u>N</u>-benzenesulphonyl 8-nitro-1-naphthylglycine (1)



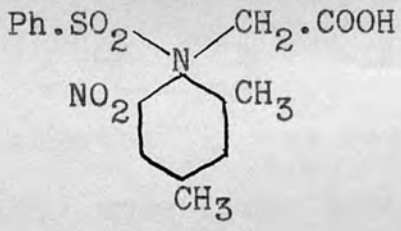
(I)

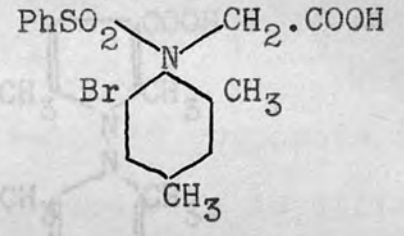


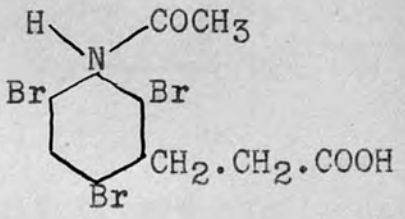
(II)

a compound whose asymmetry is universally attributed to restriction of rotation about the $\rangle C-N-$ bond by the blocking effect of the $-NO_2$ group on the benzenesulphonyl and $-CH_2.COOH$ groups: this was followed by the non-resolution of N-benzenesulphonyl-1-naphthylglycine (II)

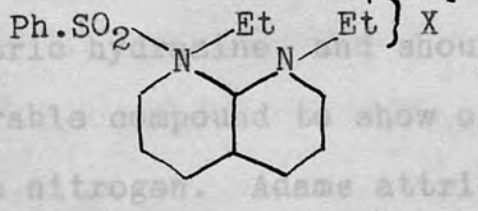
(b) Yuan, Hsu and Hsu, (J. Chinese Chem. Soc., 1936, iv, (3), 131), failed to resolve further compounds of similar type in the benzene series.





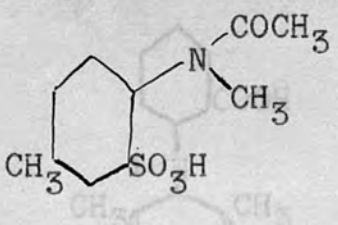


(c) Mills and Breckenridge, (J., 1932, 2209) resolved the quinoline derivative



but failed to resolve the corresponding methiodide or the propyl methiodide, showing that the resolution was not due to asymmetric nitrogen, but to the blocking effect.

(d) This same effect must account for the resolution by Mills and Kelham, (J., 1937, 274), of an o-substituted

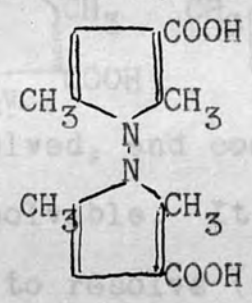


benzene derivative, N-acetyl-N-methyl-p-toluidine-3-sulphonic acid.

(e) Work on dipyrryls and N-substituted pyrroles.

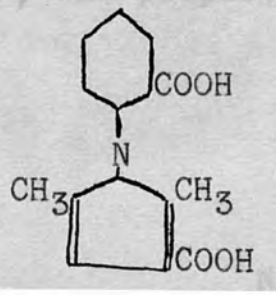
Adams and his co-workers, after a great deal of work on restricted rotation in diphenyl compounds, have looked for analagous effects ih nitrogen compounds.

Chang and Adams, (J. Amer. Chem. Soc., 1931, 2353) resolved 2:5:2′:5′-tetramethyl-3:3′-dicarboxy-dipyrryl,

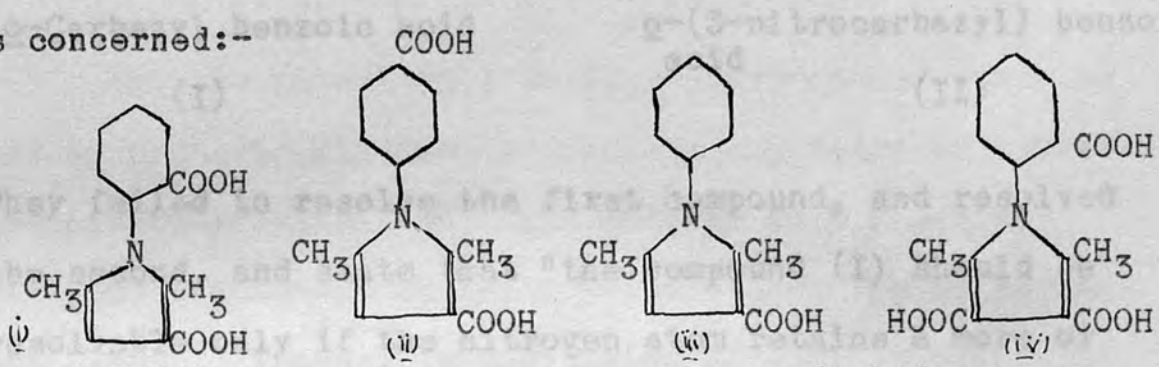


by means of the brucine salt. This compound is analagous to an asymmetric hydrazine, and should therefore be a rather favourable compound to show optical activity due to asymmetric nitrogen. Adams attributes its resolution to the blocking effect of the $-CH_3$ groups on the $\rangle N - N\langle$ bond's rotation.

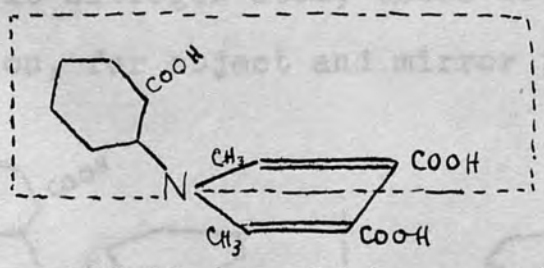
In the N-substituted pyrrole series, a great many compounds have been investigated. Bock and Adams, (J. Amer. Chem. Soc., 1931, 375) resolved



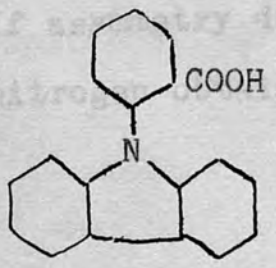
N-2-carboxyphenyl-2:5-dimethyl-3-carboxypyrrole by the brucine salt, and a short while after, (J. Amer. Chem. Soc., 1931, 3519), produced the following evidence to show that conditions in these compounds are similar to those obtaining in diphenyls, as far as restriction of rotation is concerned:-



Compound (i) was resolved, and compounds (ii) (iii) and (iv) were found unresolvable. It is difficult to see why any attempt was made to resolve (iv): if blocking occurs, there is a plane of symmetry, as the authors point out: but if the nitrogen can preserve the tetrahedral configuration there is still a plane of symmetry,



and so no resolution could be expected. The same criticism applies to a piece of work by Paterson and Adams, (J. Amer. Chem. Soc., 1933, 1069), who prepared



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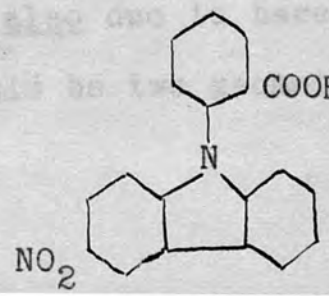

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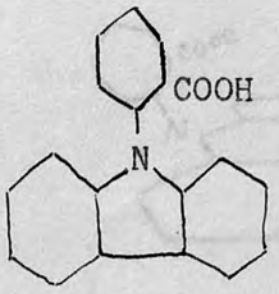
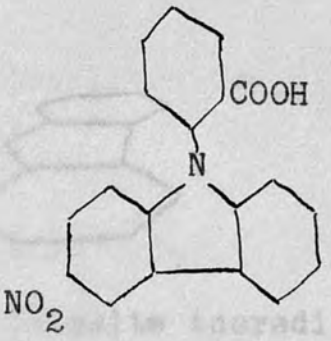


o-Carbazyl benzoic acid

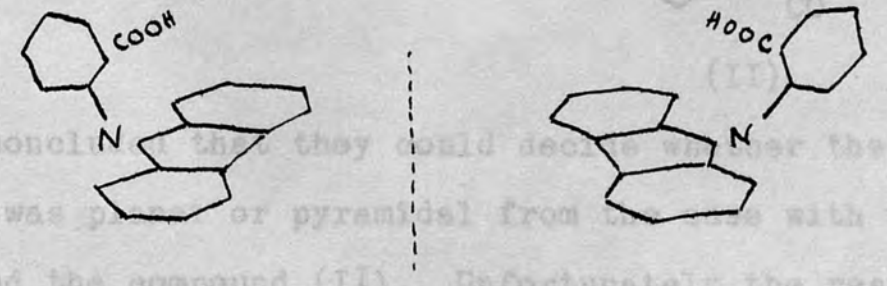
(I)



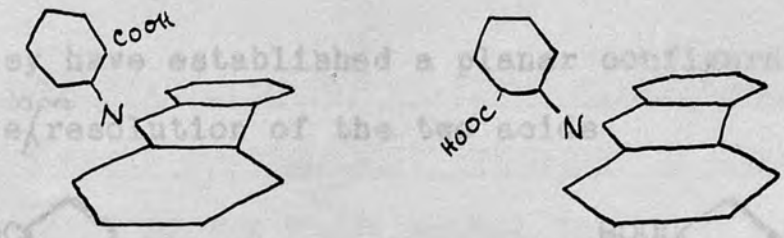
o-(3-nitrocarbazyl) benzoic acid

(II)

They failed to resolve the first compound, and resolved the second, and state that "the compound (I) should be resolvable only if the nitrogen atom retains a more or less fixed tetrahedral structure ..... with a fixed asymmetric structure for nitrogen, both compounds should be resolvable. It appears that the conditions found necessary for resolution of diphenyl compounds hold in this series." However, if (I) contained a stable tervalent asymmetric nitrogen atom, there would not be a chance of resolution, for object and mirror image are superposable,

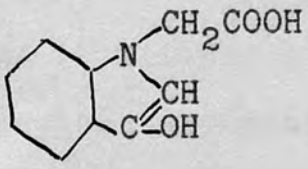


If asymmetry due to blocking and also due to tercovalent nitrogen obtained, then there would be two geometrical isomers;

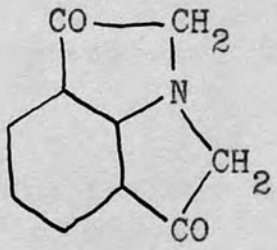


but blocking under these conditions is quite incredible.

All the experiments so far described were carried out in order to find out if tercovalent nitrogen is tetrahedral: they failed, but this affords only negative evidence - which is of small value - that the molecules are planar. Kenner, in two series of experiments tried to find positive evidence that the tertiary nitrogen atom is planar: the first, carried out with Jackson (J., 1928, 575), in which they took the ring compound (I) indoxyl acetic acid,



(I)

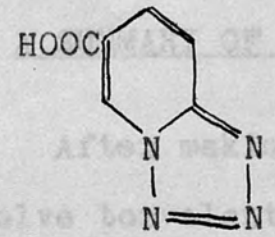


(II)

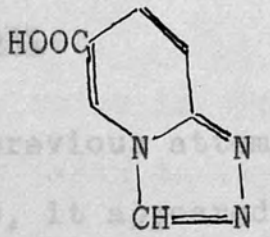
and concluded that they could decide whether the nitrogen atom was planar or pyramidal from the ease with which it formed the compound (II). Unfortunately the result of experiments on shutting the second ring was a mixture from which only small inconclusive quantities were extracted.

Kenner and Statham (Ber., 1936, 69, 187), consider

that they have established a planar configuration of N^3 from the non-resolution of the two acids



and



but this type of compound could hardly be expected to be anything but planar.

6. ATTEMPTS TO STABILISE THE TERTIARY NITROGEN ATOM IN COMPOUNDS WHERE OPTICAL ACTIVITY MIGHT BE EXPECTED: A SUMMARY OF THE EXPERIMENTAL WORK

After making a review of the previous attempts to resolve tervalent nitrogen compounds, it appeared to us that it would be interesting to attempt to modify the availability of the lone pair of electrons on the nitrogen atom, and see if this affected the optical stability. It was postulated that the nitrogen atom in a tertiary amine type of structure could preserve a stable configuration more easily if it carried a positive charge: the reasons for adopting this view being the following:-

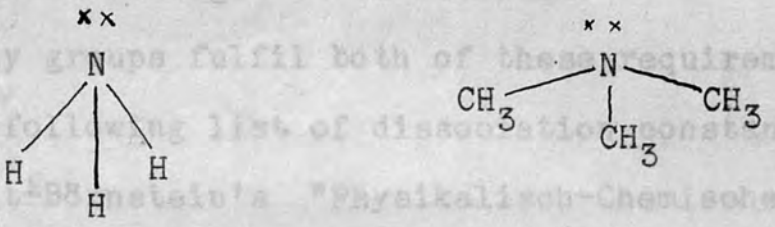
1. By analogy with tercovalent sulphur and selenium compounds which have been resolved, a positive charge (Phillip's hypothesis) stabilises the tercovalent asymmetry.
2. While the lone pair of electrons is free to do so, it will react chemically with anything that presents itself - for example, suppose the resolution is carried out by means of an acid resolving agent: the base can then combine with the hydrogen ion thus,

$$R_3N\overset{\times}{\underset{\times}{}} \quad \rightarrow \quad R_3N\overset{\times}{\underset{\times}{}}\rightarrow H^{+}$$

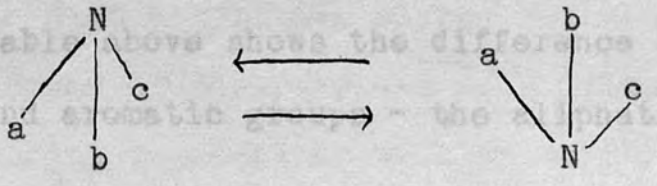
the electrical disturbance to the nitrogen being sufficiently great to cause immediate racemisation. It is well known, however, that tertiary amines of

certain types are non-basic, that is, the lone pair is not available for chemical combination, and this unreactivity should greatly enhance the chance of resolution of the amine.

3. The dipole moment of trimethylamine is smaller than that of ammonia. This can be taken to imply that the trimethylamine pyramid is less steep than that of ammonia,



the methyl group is an electron donator, and would therefore tend to make the nitrogen atom more negative than it is in ammonia. If the the methyl groups have this effect, then electron attracting groups i.e. polar groups with positive end near to the nitrogen, should have the opposite effect, and make the pyramid steeper. If the mechanism of the racemisation of tertiary nitrogen compounds is the passage of the nitrogen atom through the plane of the three groups,



then the steeper the pyramid, the more difficult this will be.

So it was decided to synthesise tertiary nitrogen compounds in which the groups were:-

(a) Substituents decreasing the basicity in amines;

(b) Polar substituents with their positive ends attached to the nitrogen to be resolved.

A great many groups fulfil both of these requirements.

The following list of dissociation constants taken from Landolt-Börnstein's "Physikalisch-Chemische-Tabellen" shows the effect of various groups on the basicity of amines:- (N.B. It is pointed out by Sidgewick ("Organic Chemistry of Nitrogen", p.30), that the true dissociation constant is not obtained by measurement, but given by

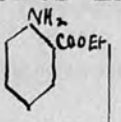
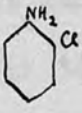
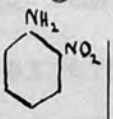
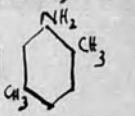
$$K = K_1(b + 1)$$

where K and K_1 are the true and measured dissociation constants and b is $\frac{[R_3N]}{[R_3NHOH]}$. However, the apparent dissociation constants serve for the purposes of comparison.)

Base.	NH_3	CH_3NH_2	$PhNH_2$	$Ph.NH.CH_3$	$Ph.CH_2.NH_2$
Dissociation Constant.	1.4×10^{-5}	5.0×10^{-4}	3.5×10^{-10}	7.4×10^{-9}	2.4×10^{-5}

The table above shows the difference between aliphatic and aromatic groups - the aliphatic groups make

the base slightly stronger, the aromatic groups make it tremendously weaker: interposing a $-CH_2-$ group between the phenyl group and the nitrogen annuls the effect of the phenyl group almost entirely. The next list demonstrates the effect of substituents in the benzene ring of aniline,

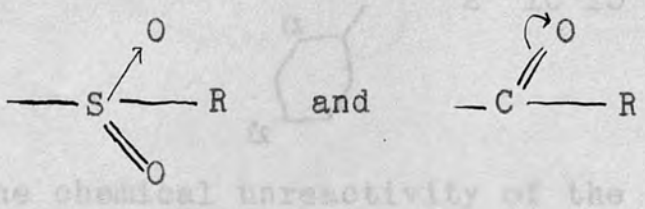
Base							
Dissociation Constant	3.5 x 10^{-10}	1.7 x 10^{-12}	1.2 x 10^{-11}	9.2 x 10^{-13}	1 x 10^{-14}	2 x 10^{-9}	9.6 x 10^{-10}

and shows that o-chlorophenyl, o-nitrophenyl and o-carbethoxy phenyl groups are extremely effective, while methyl groups have a comparatively small effect in the opposite sense.

Sidgwick ("The Covalent Link in Chemistry," p.180), points out that the differences between the dipole moments of groups such as $-NO_2$, -Cl, >CO in aromatic and aliphatic compounds is a measure of the effect produced by the displacement of electrons in the benzene ring, and is of the order of 1/10 of the effect which would be caused by the removal of a single electron. It would seem, therefore, that by attaching three strongly electron attracting groups to the nitrogen atom it would be possible to give the nitrogen atom a positive charge approaching that on the sulphur atom of the resolved sulphoxides.

Useful polar groups as well as substituted benzene

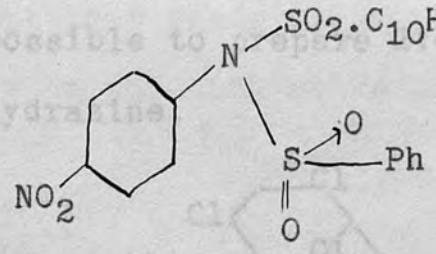
nuclei are



Various types of compound which fulfil the requirements outlined above have been investigated: the experimental work therefore falls into seven sections.

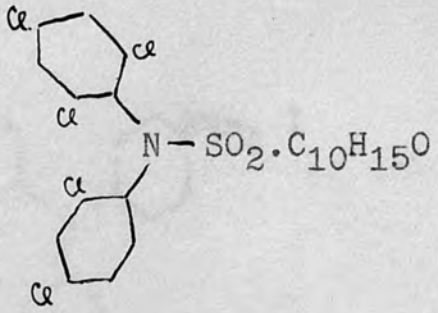
Section I.

The attempted preparation of di-derivatives of p-nitroaniline, such as



Section II.

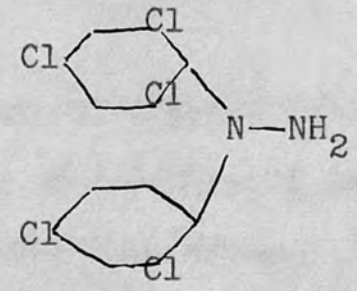
Several asymmetric halogeno-diphenylamines were prepared: these are increasingly non-basic, as is shown from their chemical reactivity:, p-chlorodiphenylamine forms a p-toluenesulphonyl derivative, but more heavily chlorinated ones will not. Pentachlorodiphenylamine is the only one that will not form a nitroso-derivative in any circumstances. This points to the complete chemical inhibition of the lone pair. The type of compound which it was hoped to investigate in this series was



but the chemical unreactivity of the nitrogen made it impossible to synthesise.

Section III.

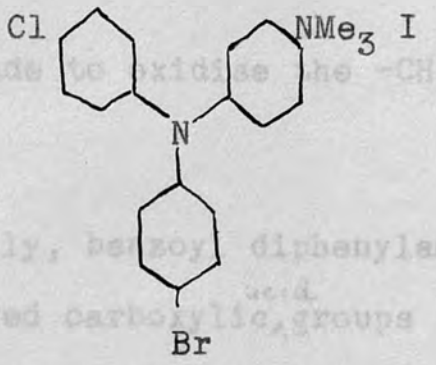
Dipole measurements (loc. cit.) and the low dissociation constant of phenylhydrazine (1.6×10^{-9}) made it seem that investigation of the properties of suitably substituted asymmetric hydrazines would be fruitful. It was unfortunately found impossible to prepare 2:4:6:2':4'-pentachloro-N-N-diphenylhydrazine,



an ideal compound from our point of view, owing to the extreme unreactivity of the pentachlorodiphenylamine. The mono- and dichlorohydrazines could not be obtained in a large enough yield to merit continuing an investigation of their properties.

Section IV.

A triphenylamine derivative, (4-chloro-4'-bromo-diphenylamino) phenyltrimethylammonium iodide,



was synthesised, and the corresponding d-camphor-10-sulphonate submitted to fractional crystallisation. No evidence was found to show that the substance was anything but homogeneous. This compound fulfils the requirements of making the tertiary nitrogen atom non-basic but it was thought that the p-chlorophenyl and p-bromophenyl groups may be too much alike to permit resolution.

Section V.

Having failed to prepare derivatives of halogeno-diphenylamines, it was necessary to find another way of introducing the resolving group. Therefore the carbamyl chlorides of two diphenylamines were prepared (note that the carbamyl chloride of the pentachlorodiphenylamine could not be prepared) and attempts were made to obtain the l-menthyl and d-bornyl esters.

Section VI.

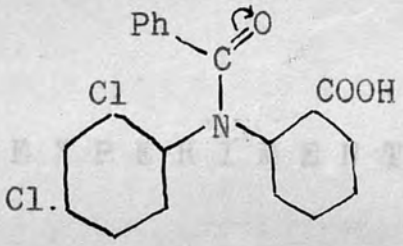
As another way of introducing a salt forming group, p-toluoyl-2:4-4'-trichlorodiphenylamine was prepared by an adaption of the Chapman process, and unsuccessful

attempts made to oxidise the $-CH_3$ group to -COOH.

Section VII.

Finally, benzoyl diphenylamines have been synthesised with attached carboxylic acid groups for resolution. The syntheses were carried out by a modification of Chapman's method, using methyl salicylate as the phenolic group, so that the final compounds,

e.g.



had strongly polar groups on the nitrogen, making it entirely non-basic.

The strychnine and brucine salts of the monochloro-compound were examined by fractional crystallisation, but no conclusive evidence of two optically active forms was found.

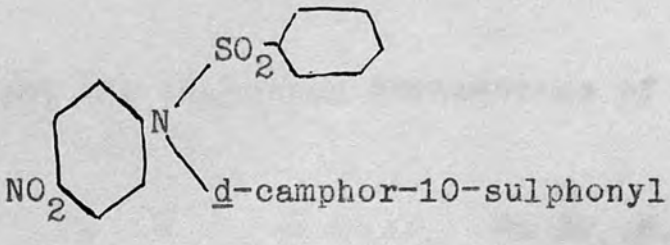
The effect of excess of acid on the alkaloidal salts of these benzoyldiphenylamines was examined, and explained by optical activation and induction stabilised owing to a common ion effect which prevents ionisation of the alkaloidal salt.

7. EXPERIMENTAL WORK

SECTION I

Sulphonyl Derivatives of p-Nitroaniline.

It was hoped eventually to prepare N-benzenesulphonyl-N-d-camphor-10-sulphonyl-p-nitroaniline,



and to investigate its optical properties. Preliminary experiments were made using the p-toluenesulphonyl group in place of the d-camphor-10-sulphonyl group, as the former is more easily accessible.

p-Toluenesulphonyl-p-nitroaniline was easily prepared by the method of Bell (J., 1929, 2788) in good yield, but attempts to introduce the benzenesulphonyl group to this compound met with no success. Di-p-toluenesulphonyl-p-nitroaniline could not be prepared by the usual methods, but was obtained in small yield either by heating the reactants at the fusion point or by long heating ($6\frac{1}{2}$ hours) at 95-100°.

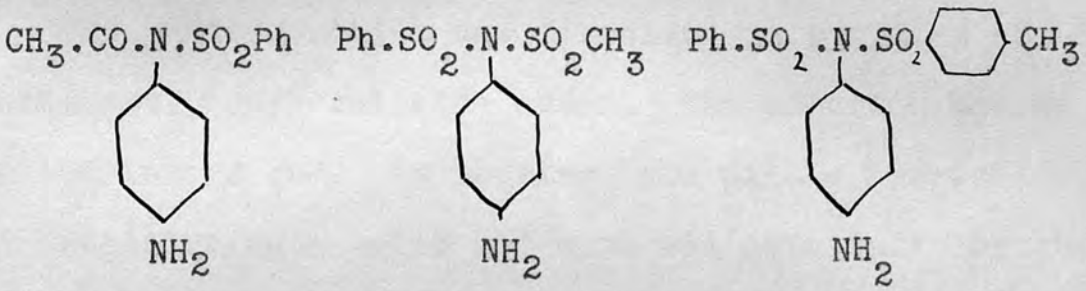
Reversing the order of the first attempted process, benzenesulphonyl-p-nitroaniline was prepared in good yield by Bell's method, but it was not found possible to

introduce the p-toluenesulphonyl group into this compound.

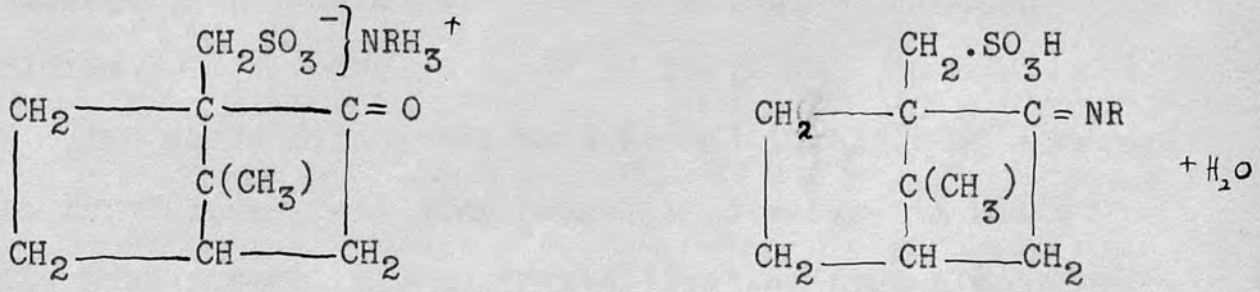
Further investigation into the methods of preparing these compounds was abandoned in view of the fact that similar work was being carried out by

(a) Schreiber and Shriner, (J. Amer. Chem. Soc., 1935, 57, 1306)

They prepared the following derivatives of p-phenylene-diamine -



and found that their salts with Reychler's acid exhibited slow mutarotation. The same phenomenon was observed with the salts of p-phenylenediamine, p-nitroaniline and aniline, and therefore could not be due to the asymmetric nitrogen atom. The effect was eventually traced to the acid, viz.:- the establishment of an equilibrium between the salt and the anil of the d-camphor-10-sulphonic acid,



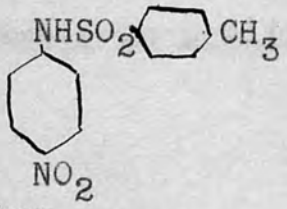
and the work in reality is not a contribution to the stereochemistry of tervalent nitrogen.

(b) Menon and Peacock, (J. Indian Chem. Soc., 1936, 13, 104)

These authors describe unsuccessful experiments on the resolution of p-toluenesulphonyl derivatives of secondary amines. Their work is recounted in the Historical Section of this thesis.

SECTION I EXPERIMENTAL

Attempts to Prepare Unsymmetrical Di-acyl Derivatives of p-Nitroaniline.



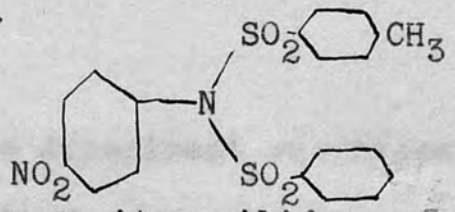
p-Toluenesulphon-p--nitroanilide.

Bell (J., 1929, 2788) gives preparation

p-Nitroaniline	13.8 g.	1 mol.
p-Toluenesulphonyl chloride	19 g.	1 mol.

The p-nitroaniline was dissolved in pyridine and the p-toluenesulphonyl chloride added. The solution became warm and turned red. On pouring into dilute hydrochloric acid and stirring a solid red mass was obtained: crystallising from ethyl alcohol in yellow crystals, M.P. 190° - 192° Yield. 23 g. (79% of theory.)

Attempted preparation of p-Toluenesulphon-benzenesulphon-p-nitroanilide.

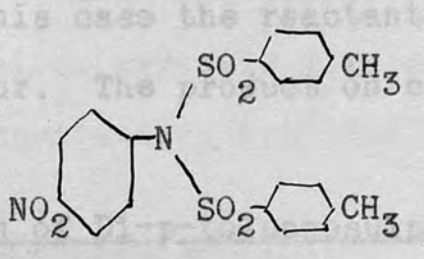


p-Toluenesulphon-p-nitroanilide	5.8 g.	1 mol.
Benzenesulphonyl chloride	3.8 g.	1 mol.
Pyridine	16 g.	10 mol.

The above substances were heated together on a water bath for 6 hours, and then poured into water. A solid white mass formed, and on crystallisation from alcohol gave

white crystals M.P. 192°. Mixed M.P. with p-toluene-sulphonyl-p-nitroanilide, 191°.

Attempted preparation of Di-p-toluenesulphon-p-nitroanilide.



Method I.

p-Toluenesulphon-p-nitroanilide	4.8 g.	1 mol.
p-Toluenesulphonyl chloride	3.2 g.	1 mol.

The p-toluenesulphonyl-p-nitroanilide and p-toluene-sulphonyl chloride were dissolved in pyridine, and the solution poured into water. The resulting mass was crystallised from glacial acetic acid, and formed yellow crystals, m.p. 191° of the original p-toluenesulphonyl-p-nitroanilide.

Method II.

The above experiment was repeated, allowing the reactants to stand overnight in pyridine solution; the same negative result was obtained as before.

Method III.

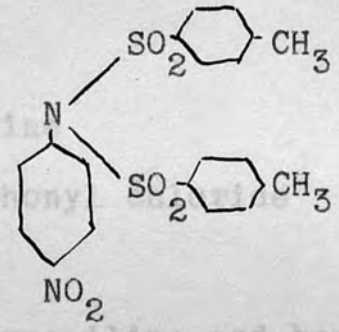
The above experiment was repeated again, heating the reactants in pyridine solution for half an hour on a water-bath. Pouring the solution into water gave a solid product which on crystallisation from benzene

formed crystals, m.p. 180°, indicating that the di-p-toluene-sulphonyl derivative might have been formed in part.

Method IV.

In this case the reactants were heated at 120° for half an hour. The product on crystallisation had m.p. 170-180°.

Preparation of Di-p-toluenesulphon-p-nitroanilide.



p-Toluenesulphon-p-nitroanilide	2.9 g.	1 mol.
p-Toluenesulphonyl chloride	1.9 g.	1 mol.
Sodium carbonate	1.3 g.	1.25 mol.

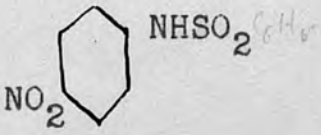
The p-toluenesulphon-p-nitroanilide and p-toluene-sulphonyl chloride were heated to fusion point on a hot plate, and the sodium carbonate added and stirred in. The mass was boiled with water and filtered, and the residue crystallised from benzene. m.p. 216-217°.

Method II.

p-Toluenesulphon-p-nitroanilide	2.9 g.	1 mol.
p-Toluenesulphonyl chloride	1.9 g.	1 mol.
Pyridine	8.0 g.	

The p-toluenesulphonyl chloride and p-toluenesulphonyl-p-nitroanilide were heated in pyridine solution on a water-bath for 6½ hours. On boiling with alcohol (method of extraction Ullmann and Gross, Ber., 1910, 43, 2694.) and cooling, yellow crystals were obtained of the di-p-toluene-sulphonyl derivative, m.p. 216°.

Benzenesulphon-p-nitroaniline.



p-Nitroaniline	42 g.	1 mol.
Benzenesulphonyl chloride	51 g.	1 mol.
Pyridine	20 c.c.	

The p-nitroaniline and benzenesulphonyl chloride were heated with the pyridine on a boiling water-bath for half an hour. The product was poured into hydrochloric acid and water to remove pyridine and the resulting solid mass crystallised from alcohol. m.p. 135°.
Yield 69.5 g. (85 per cent. of theory).

Attempted preparation of p-Toluenesulphon-benzenesulphon-p-nitroanilide.

Benzenesulphon-p-nitroanilide	13.8 g.	1 mol.
p-Toluenesulphonyl chloride	9.5 g.	1 mol.
Pyridine	19.7 g.	5 mols.

The above reactants were heated together on a water-bath for 7 hours, and then poured into water and

hydrochloric acid: the solid mass thus obtained was crystallised from alcohol, m.p. 135-7°. It therefore contained the benzenesulphonyl derivative only.

SECTION II

Preparation of Asymmetrical Halogeno-substituted Diphenylamines and their Derivatives.

We hoped to prepare halogeno-substituted diphenylamines and to make either

(a) N-camphorsulphonyl derivatives direct (this type of experiment was done by Frèrejacque [loc. cit.])

or (b) N-p-toluenesulphonyl derivatives; the $-CH_3$ group would then be oxidised to -COOH and its salts with optically active bases investigated.

(1) Preparation of Halogeno Diphenylamines.

We repeated the work of A. W. Chapman in the synthesis of

(a) p-Chlorodiphenylamine (J., 1927, 1743)

(b) 2:4:6:2'-Tetrachlorodiphenylamine. (private communication to Dr. Turner, Feb. 1929).

and applied this method to the preparation of four new diphenylamines,

(a) 2:4:-Dichlorodiphenylamine.

(b) 2:4:4'-Trichlorodiphenylamine.

(c) 2:4:6:2':4':-Pentachloro-diphenylamine.

(d) 4-Chloro-4'-bromodiphenylamine.

(others are described in the section "Benzoyldiphenylamines")

The Chapman process is described in six papers, (J., 1922, 1676; J., 1923, 1156; J., 1925, 1992; J., 1926, 2296; J., 1927, 1743; J., 1929, 569.) and is briefly as follows:-

Imino-acyl ethers were prepared by the action of a large excess of phenol in absolute alcohol and a small excess of sodium ethoxide on an iminochloride in ethereal solution: (imino chlorides are described by Wallach, Annalen, 1877, 184, 77, and others, and appear never to have been obtained in an entirely pure state.)

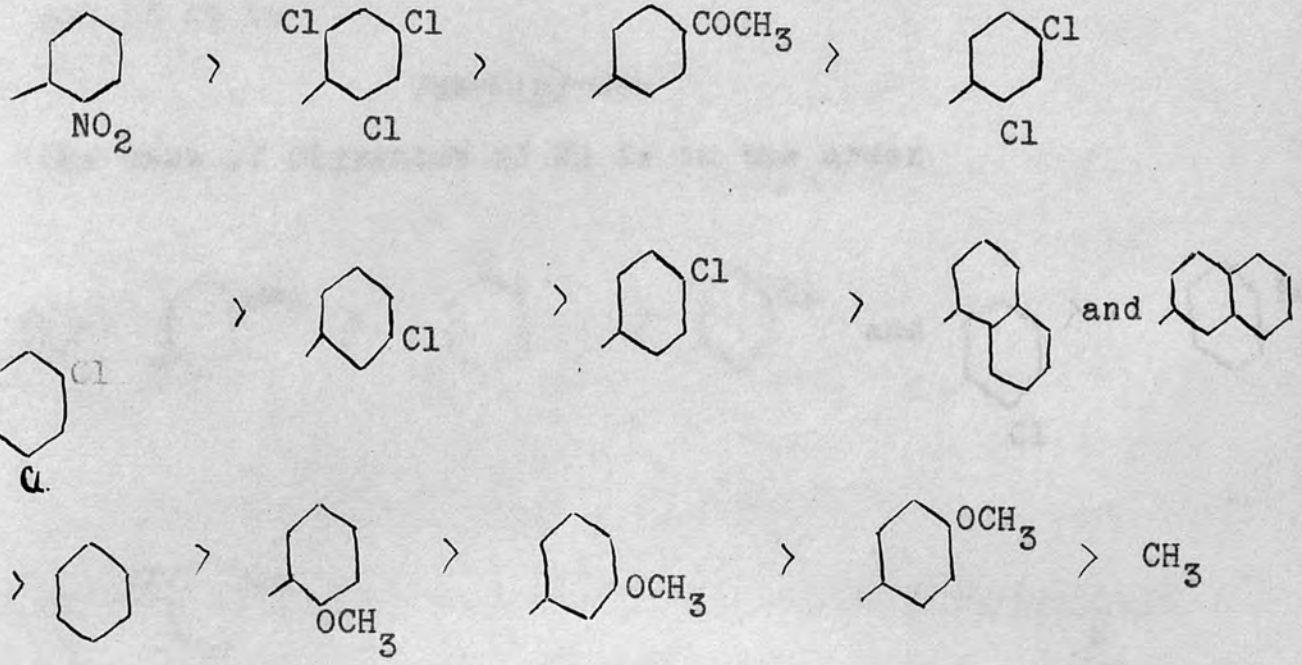
Mumm, Hesse and Volquartz had stated previously (Ber., 1915, 48, 379) that N-phenylbenziminophenyl ether on heating at 240° for one hour gave benzoyldiphenylamine: Chapman repeated this and found it inaccurate, the described change actually taking place on two hours heating at 270 - 300°.

$$Ph\text{-}N = C\begin{matrix}Ph\\OPh\end{matrix} \xrightarrow[2\text{ hours}]{270 - 300^{\circ}} \begin{matrix}Ph\\Ph\end{matrix}N\text{-}COPh$$

This discovery opened up a new field for the synthesis of diphenylamines, and Chapman made a study of the mechanism of the reaction. He found that if the imino ether is

$$PhN = CPh - O(R)$$

(R) is the migrating group, and the ease of migration is in the order

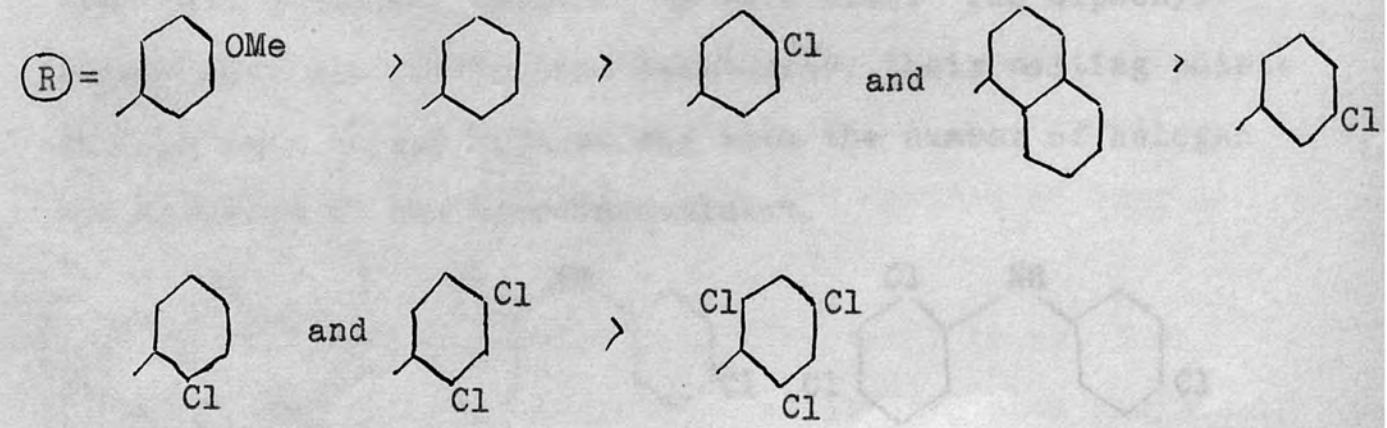


i.e. the order is the same as that of the dissociation constants of the corresponding acids: there can be no steric hindrance, as can be seen from the rates of o-, m- and p-chlorophenyl groups.

If the compound is

Ⓡ N=CPh-OPh

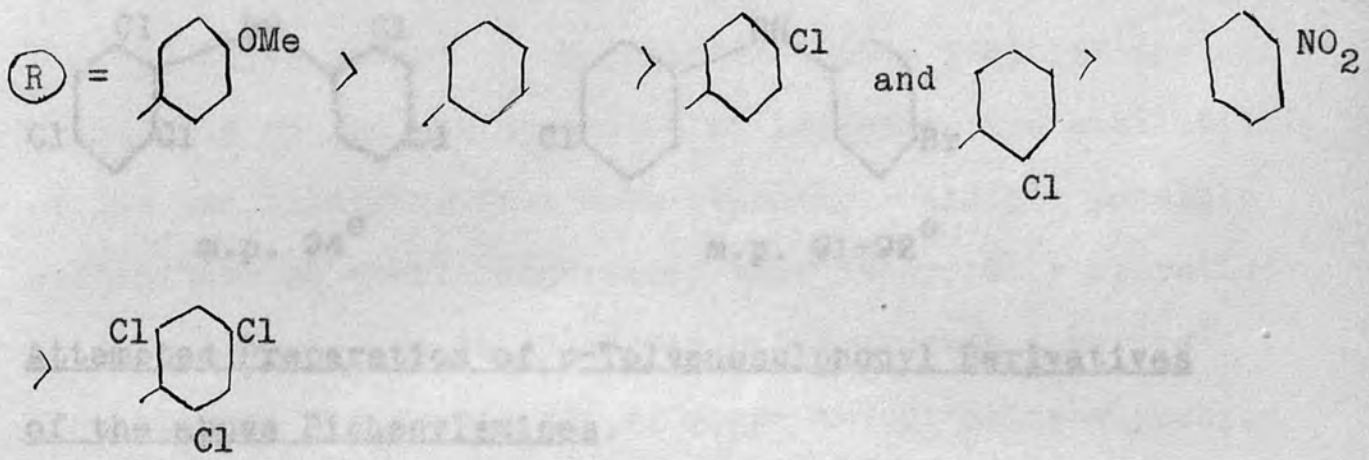
the ease of migration of Ph is in the order



and if it is

$$PhN{=}C(R){-}OPh$$

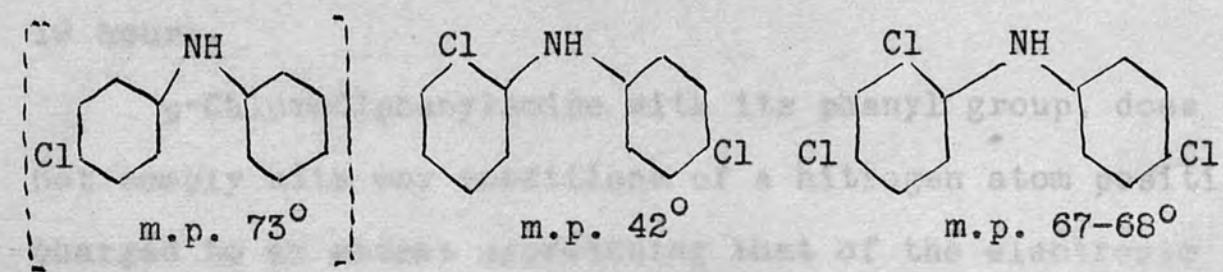
the ease of migration of Ph is in the order

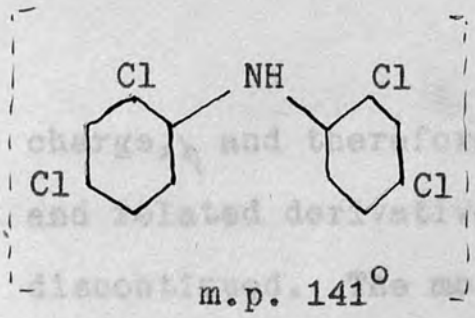


in fact for the last two cases the smaller the attraction of R for electrons, the quicker the change.

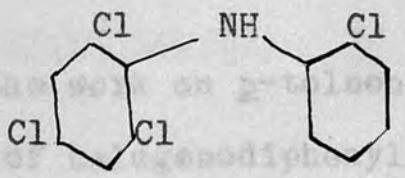
The benzoyl derivatives so formed were hydrolysed with hot aqueous alcoholic caustic soda.

The imino-ethers which we prepared were all hard crystalline colourless substances, easily purified by crystallisation, and the benzoyl derivatives obtained from them were similarly pleasant to work with. The diphenylamines were all crystalline substances: their melting points did not vary in any regular way with the number of halogen substituents in the benzene nuclei:-

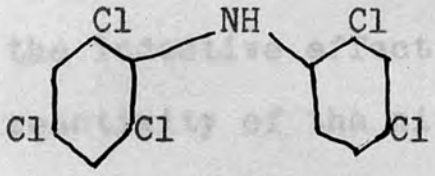




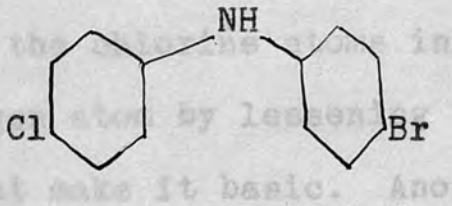
m.p. 141°



m.p. 87-88°



m.p. 94°



m.p. 91-92°

(2) Attempted Preparation of p-Toluenesulphonyl Derivatives of the above Diphenylamines.

(Symmetrical 2:4:2':4'-tetrachlorodiphenylamine made by the direct chlorination of diphenylamine [Gnehm, Ber., 1875, 8, 1040] was synthesised as it is easy to obtain, and used to try out methods of forming p-toluenesulphonyl derivatives.)

Of all the diphenylamines prepared, only p-chlorodiphenylamine could be made to react with p-toluenesulphonylchloride, although a great many methods were tried. The reactants were heated with sodium carbonate, with quinoline, with pyridine, with quinoline and copper bronze, temperatures up to 260° were used, and heating as long as 19 hours.

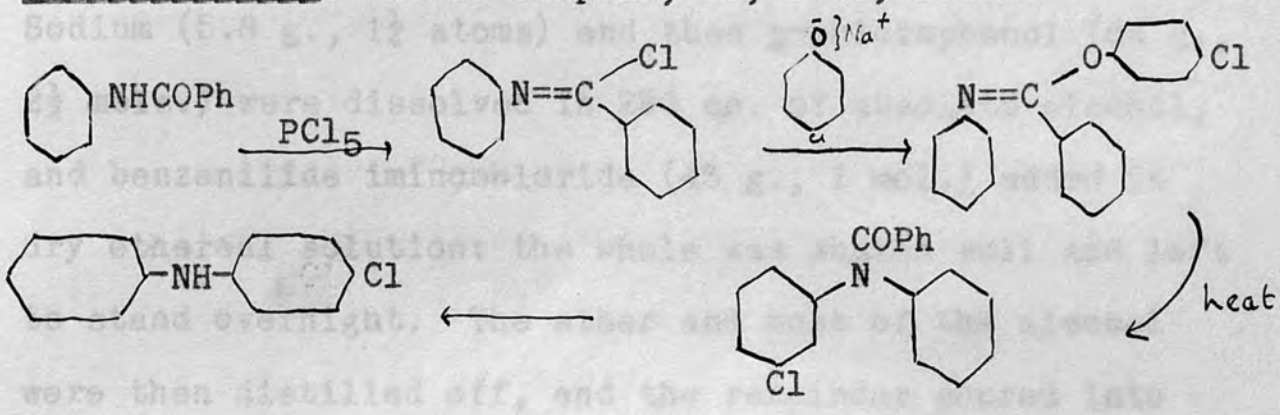
p-Chlorodiphenylamine with its phenyl group, does not comply with our conditions of a nitrogen atom positively charged to an extent approaching that of the electronic

charge, and therefore the work on p-toluenesulphonyl and related derivatives of halogenodiphenylamines was discontinued. The most probable explanation of the unreactivity of the other diphenylamines seems to be that the inductive effect of the chlorine atoms inhibits the reactivity of the nitrogen atom by lessening the availability of the two electrons that make it basic. Another possible explanation is steric hindrance: this is probably operative to some extent, but would surely not draw such a marked line between the reactivity of mono- and di-chlorodiphenylamine as our experiments appear to show.

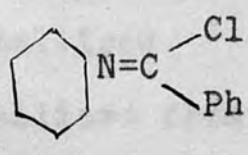
SECTION II. EXPERIMENTAL.

Preparation of p-Chlorodiphenylamine. Cl NH

General Scheme. A. W. Chapman, J., 1927, 1746.



(1) Preparation of Benzanilide-iminochloride.



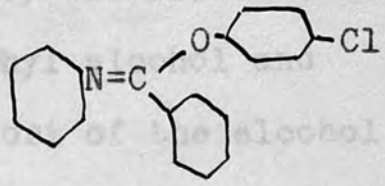
Method given by Wallach, (Annalen, 1877, 184, 77.)

Benzanilide (66 g., 1 mol.) and phosphorus pentachloride (65 g., 1 mol.) were heated together on a boiling water-bath until the evolution of hydrogen chloride ceased and only clear liquid remained. The phosphorus oxychloride formed was distilled off in vacuo, and then the benzanilide-iminochloride distilled, (b.p. 173°/36 m.m.) Benzoyl chloride was present as a slight impurity, and could not be removed by distillation. The iminochloride solidified on cooling, forming pale yellow needles, m.p. 39°.

Yield 50 g. (69% of theory).

(2) Preparation of N-Phenylbenzimino-p-chlorophenyl ether.

A. W. Chapman, (J., 1922, ii, 1992.)



Sodium (5.8 g., 1¼ atoms) and then p-chlorophenol (64 g., 2½ mols.) were dissolved in 290 c.c. of absolute alcohol, and benzanilide iminochloride (43 g., 1 mol.) added in dry ethereal solution: the whole was shaken well and left to stand overnight. The ether and most of the alcohol were then distilled off, and the remainder poured into aqueous sodium hydroxide solution and stirred until the yellow oil became solid. The product was crystallised from light petroleum (b.p. 40-60°) and recrystallised from ethyl alcohol; it formed white crystals, m.p. 88°.

Yield, 24 g. (39% of theory).

(3) Preparation of Benzoyl-p-chlorodiphenylamine.

N-phenylbenzimino-p-chlorophenyl ether (24 g.) was heated for two hours in a metal-bath at 280-290°. The product solidified on cooling to a dark brown glass, and crystallised from ethyl alcohol in colourless prisms, m.p. 108°.

Yield 20 g. (83% of theory).

(4) Preparation of p-Chlorodiphenylamine.

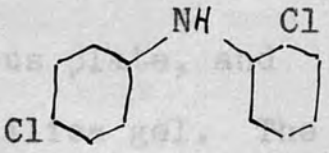
The above benzoyl derivative (20 g.) was heated under reflux for two hours with 250 c.c. of ethyl alcohol and 100 c.c. of 50% aqueous caustic soda. Most of the alcohol was then evaporated off, and the remaining solution poured into a large quantity of water, when the p-chlorodiphenylamine separated as a light brown solid. It was crystallised three times from ethyl alcohol, forming yellow crystals, m.p. 73°.
Yield, 2.5 g. (19% of theory).

Preparation of p-Toluenesulphonyl-p-chlorodiphenylamine.

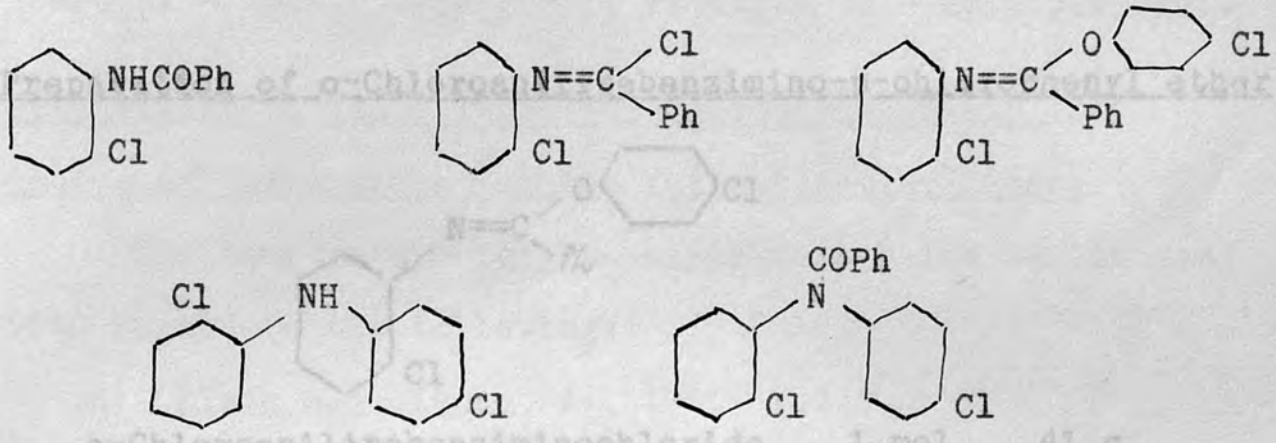
This substance was prepared by the method used by Reverdin and Crèpieux, (Ber., 1902, 35, 1439), for p-toluenesulphonyldiphenylamine.

p-Toluenesulphonyl chloride (1 g., 1 mol.), p-chlorodiphenylamine (1 g., 1 mol.) and 1 c.c. of dry pyridine were heated together on a boiling water-bath for two hours. The resulting mass was crystallised three times from ethyl alcohol, giving the p-toluenesulphonyl derivative as white prisms, m.p. 127°, turning green on exposure to air.

Preparation of 2:4'-Dichlorodiphenylamine.



General Scheme. (Adaption of A. W. Chapman's method.)



(1) Preparation of o-Chlorobenzanilide-iminochloride.

For method see Wallach, Annalen, 1877, 184, 77.

Lander, J., 1902, 591.

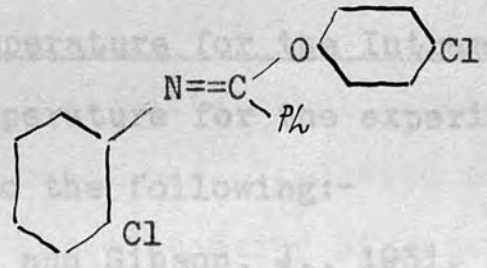
Hantzsch, Ber., 1893, i, 1927.

Benzoyl-o-chloroaniline (104 g., 1 mol.) and phosphorus pentachloride (93 g., 1 mol.) were heated together on a water-bath until no more hydrogen chloride was evolved. Precautions were taken to prevent moisture entering the flask during the heating, as traces of water decrease the yield. The phosphorus oxychloride formed was distilled off in vacuo, and the o-chlorobenzanilide iminochloride distilled (b.p. 187°/12 m.m.). The golden liquid solidified on cooling to yellow needles, and all but the last traces of phosphorus oxychloride

were removed by pressing tightly on a porous plate, and then leaving in a vacuum desiccator over silica gel. The crystals then had melting point 29°.

Yield, 95.5 g., (85% of theory).

(2) Preparation of o-Chloroanilinebenzimino-p-chlorophenyl ether.



o-Chloroanilinebenziminochloride	1 mol.	41 g.
Sodium	1¼ atoms.	5 g.
Absolute Ethyl Alcohol.	250 c.c.	
p-Chlorophenol.	2½ mols.	53 g.

First the sodium - added in small pieces - and then the p-chlorophenol was dissolved in the absolute alcohol: to this was added a solution of the o-chloroanilinebenziminochloride in dry ether. A precipitate of sodium chloride immediately appeared: the mixture was left to stand until the following day. The ether and most of the alcohol was distilled off, and the remainder poured into a solution of sodium hydroxide in water, to remove the excess p-chlorophenol; the o-chloroanilinebenzimino-p-chlorophenyl ether separated as a cream coloured oil,

which after stirring and standing became solid, and was crystallised from ethyl alcohol. It formed large, irregular colourless crystals, m.p. 59-60°.

Yield, 50 g. (90% of theory).

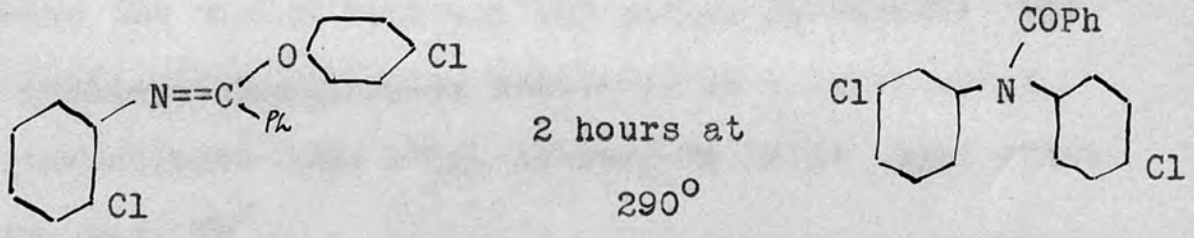
Found Cl = 20.9, $C_{19}H_{13}ONCl_2$ requires Cl = 20.8 per cent.

(3) Preparation of Benzoyl-2:4'-dichlorodiphenylamine.

Choice of Temperature for the Intramolecular Change.

The temperature for the experiment below was chosen with regard to the following:-

(a) Elson and Gibson, J., 1931, 294.



(b) A. W. Chapman.

The ease (i.e. lowness of temperature at which it takes place) of change depends directly on the power of electron attracting of the migrating group.

The o-chloroanilinebenzimino-p-chlorophenyl ether was heated in a metal-bath at 300° for two hours. The resulting dark liquid was poured into a dish, and solidified on cooling to a brown glass: Crystallisation from ethyl alcohol gave the benzoyl derivative in colourless prisms,

m.p. 115°.

Yield, 74 per cent. of theory.

Found Cl = 20.8, $C_{19}H_{13}ONCl_2$ requires Cl = 20.8 per cent.

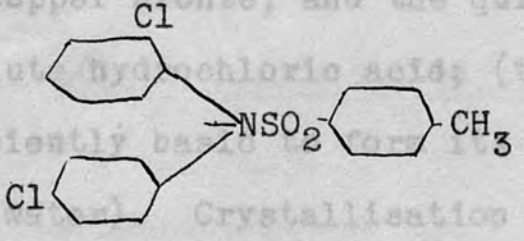
(4) Preparation of 2:4'-Dichlorodiphenylamine.

Benzoyl-2:4'-dichlorodiphenylamine (30 g.) was boiled with 150 c.c. of 50% aqueous caustic soda solution and 375 c.c. of absolute ethyl alcohol for two hours. Most of the alcohol was then evaporated off, and the remainder poured into a large quantity of water, and stirred to dissolve the sodium benzoate and sodium hydroxide: the 2:4'-dichlorodiphenylamine separated as a brown solid, and crystallised from ethyl alcohol in large light brown prisms, m.p. 42°.

Yield 15 g., (71% of theory).

Found, Cl = 30.3, $C_{12}H_9NCl_2$ requires Cl = 29.8 per cent.

Attempted Preparation of p-Toluenesulphonyl-2:4'-dichlorodiphenylamine.



Method 1.

2:4'-Dichlorodiphenylamine.	1.0 g.	1 mol.
p-Toluenesulphonyl chloride.	0.8 g.	1 mol.
Sodium carbonate.	0.8 g.	1¼ mols.

The 2:4'-dichlorodiphenylamine and p-toluenesulphonyl chloride were heated together on a water-bath and the sodium carbonate added. There was no effervescence observed, and crystallisation from alcohol gave the original base.

Method 2.

2:4'-Dichlorodiphenylamine	1.0 g.	1 mol.
p-Toluenesulphonyl chloride	0.8 g.	1 mol.

Each substance was dissolved separately in dry ether, and the solutions mixed. On evaporation and cooling no evidence was obtained for the formation of a p-toluene-sulphonyl derivative.

Method 3.

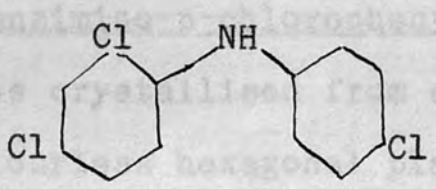
The same quantities of 2:4'-dichlorodiphenylamine and p-toluenesulphonyl chloride were taken as in the last experiment, and heated in quinoline solution to 110°, together with a little copper bronze. The solution was filtered from the copper bronze, and the quinoline removed by washing with dilute hydrochloric acid; (the diphenyl-amine is not sufficiently basic to form its hydrochloride in the presence of water). Crystallisation of the residue from alcohol yielded the original base.

Method 4.

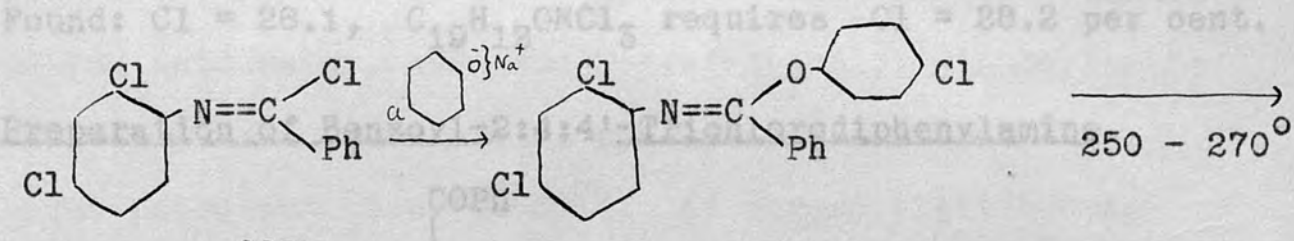
2:4'-Dichlorodiphenylamine	2.4 g.	1 mol.
p-Toluenesulphonyl chloride	1.9 g.	1 mol.
Quinoline	5 c.c.	

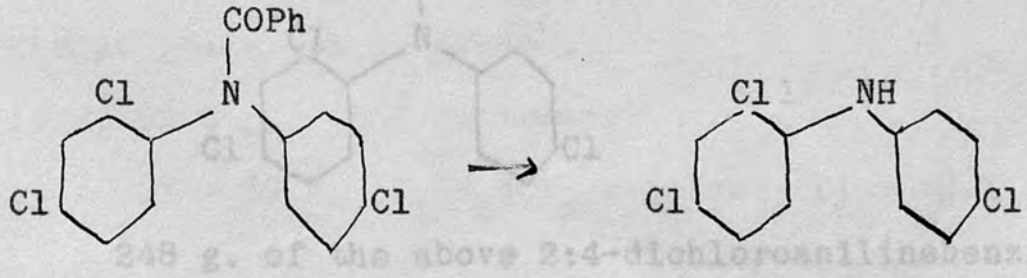
The above substances were heated together for 16 hours at about 120°. The quinoline was removed by washing with dilute hydrochloric acid. It was found impossible to extract any crystalline material from the remaining tar.

Preparation of 2:4:4'-Trichlorodiphenylamine.



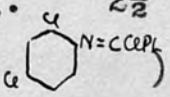
General Scheme.





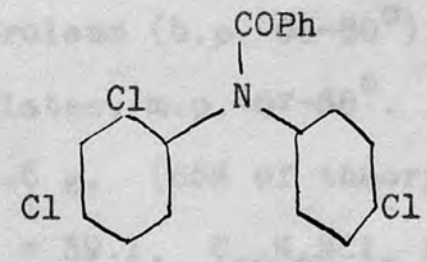
(1) Preparation of N-2:4-Dichlorophenylbenzimino-p-chlorophenyl Ether.

2:4-Dichloroanilinebenziminochloride.	260 g.	1 mol.
Sodium.	23 g.	1¼ mol.
Absolute alcohol.	1250 c.c.	
p-Chlorophenol.	295 g.	2½ mol.

The 2:4-dichloroanilinebenziminochloride () was dissolved in anhydrous ether and added to a

solution of the sodium and p-chlorophenol in the absolute alcohol. Sodium chloride was precipitated, and the whole shaken and left to stand overnight. The ether and most of the alcohol was then distilled off, and the remainder stirred with sodium hydroxide solution, when the excess of p-chlorophenol went into solution, leaving the 2:4-dichloroanilinebenzimino-p-chlorophenyl ether as a white solid. This was crystallised from ethyl alcohol, and appeared as colourless hexagonal plates, m.p. 81°.
Yield, 249 g. (96% of theory).
Found: Cl = 28.1, $C_{19}H_{12}ONCl_3$ requires Cl = 28.2 per cent.

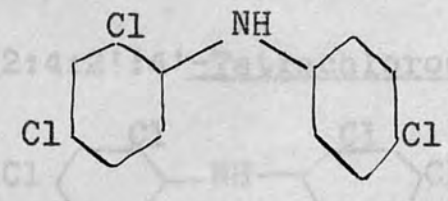
(2) Preparation of Benzoyl-2:4:4'-Trichlorodiphenylamine.



248 g. of the above 2:4-dichloroanilinebenzimino-p-chlorophenyl ether was heated for two hours at 250 - 270°. On cooling, a black tar was obtained which could not be crystallised from any of the usual solvents. After six weeks it had set to a soft brown glass, from which the benzoyl derivative was crystallised from ethyl alcohol and then light petroleum (b.p. 80-100°), in colourless rhombic crystals, m.p. 117-118°.
Yield, 190 g. (76% of theory).

Found: Cl = 28.5, $C_{19}H_{12}ONCl_3$ requires Cl = 28.3 per cent.

(3) Preparation of 2:4:4'-Trichlorodiphenylamine.

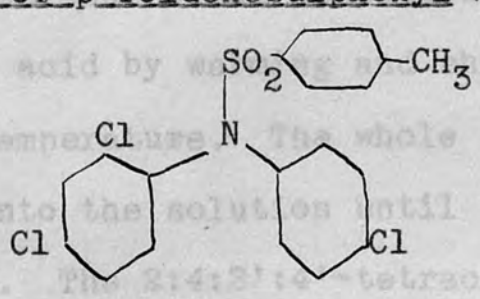


Benzoyl-2:4:4'-trichlorodiphenylamine (100 g.) was heated on a water-bath under reflux for an hour with 50% aqueous caustic soda (500 c.c.) and 1250 c.c. of ethyl alcohol. The alcohol was evaporated off, and the remainder poured into water, when the 2:4:4'-trichlorodiphenylamine separated as a brown solid, and was crystallised from light petroleum (b.p. 60-80°). It formed light brown angular plates, m.p. 67-68°.

Yield, 59.5 g. (85% of theory).

Found Cl = 39.1, $C_{12}H_8NCl_3$ requires Cl = 39.3 per cent.

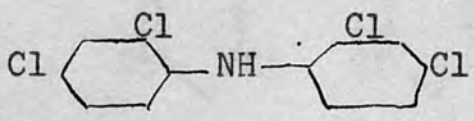
Attempted Preparation of p-Toluenesulphonyl-2:4:4'-trichlorodiphenylamine.



2:4:4'-Trichlorodiphenylamine (1 g., 1 mol.) and p-toluenesulphonyl chloride (1 g., 1 mol.) were heated together (160 - 180°) for six hours in dry conditions. A dark gum was produced

from which no crystalline compound could be extracted, using benzene, ethyl alcohol or the light petroleums (b.p. 40-60°, 60-80°, 100-120°).

Preparation of 2:4:2':4'-Tetrachlorodiphenylamine.



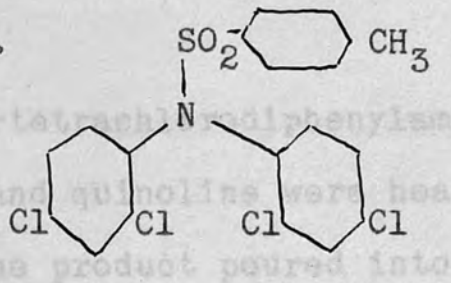
This compound was prepared because it is easily accessible and similar in type to our unsymmetrically substituted diphenylamines, and so could be used to try out methods of forming their p-toluenesulphonyl derivatives. The method of preparation is due to Gnehm, (Ber., 1875, 8, 1040).

Diphenylamine.	42 g.	1 mol.
Sodium acetate.	66 g.	4 mols.
Glacial Acetic acid.	500 c.c.	
Chlorine.	71 g.	8 atoms.

The diphenylamine and sodium acetate were dissolved in the glacial acetic acid by warming and shaking, and then cooled to room temperature. The whole was weighed and chlorine passed into the solution until the weight had increased by 71 g. The 2:4:2':4'-tetrachlorodiphenylamine formed was filtered and crystallised from alcohol, in which it is very slightly soluble cold. A mauve oxidation product was washed out with cold alcohol. m.p. 141°.

Yield 33 g. (After crystallisation). (43% of theory).

Attempted Preparation of p-Toluenesulphonyl-2:4:2':4'-tetrachlorodiphenylamine.



Method I.

(As for p-toluenesulphonyldiphenylamine. Riverdin & Crèpieux, Ber., 1902, (35), 1432.)

2:4:2':4'-tetrachlorodiphenylamine	15 g.	1 mol.
p-Toluenesulphonyl chloride.	9 g.	1 mol.
Pyridine.	10 c.c.	

The 2:4:2':4'-tetrachlorodiphenylamine, p-toluenesulphonyl chloride and pyridine were heated for ¾ hour on a water-bath. The pyridine was removed by stirring with dilute hydrochloric acid and the residue extracted with alcohol. On evaporation and crystallisation the original base was recovered.

Method II.

The above experiment was repeated, with the difference that the heating was carried out on a metal-bath at 160°, instead of the water-bath. The same negative result was obtained.

Method III.

2:4:2':4'-Tetrachlorodiphenylamine.	3 g.	1 mol.
p-Toluenesulphonyl chloride.	2 g.	1 mol.
Quinoline.	10 c.c.	

The 2:4:2':4'-tetrachlorodiphenylamine, p-toluenesulphonyl chloride and quinoline were heated to 260° on a metal-bath, and the product poured into dilute hydrochloric acid. It was found impossible to extract any crystalline material from the resulting tar.

Method IV.

2:4:2':4'-tetrachlorodiphenylamine.	1 g.	1 mol.
p-Toluenesulphonyl chloride.	0.75 g.	1 mol.
Pyridine.	5 c.c.	

The base and pyridine were dissolved in dry ether and the p-toluenesulphonyl chloride added also in dry ethereal solution. The ether was distilled off and the product washed with dilute hydrochloric acid. Crystallisation from alcohol gave the original base.

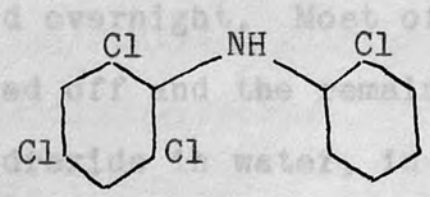
Method V.

2:4:2':4'-Tetrachlorodiphenylamine.	1 g.	1 mol.
p-Toluenesulphonyl chloride.	0.65 g.	1 mol.
Pyridine.	5 c.c.	

The base, p-toluenesulphonyl chloride and pyridine were heated together at 150°on a metal-bath for 19 hours.

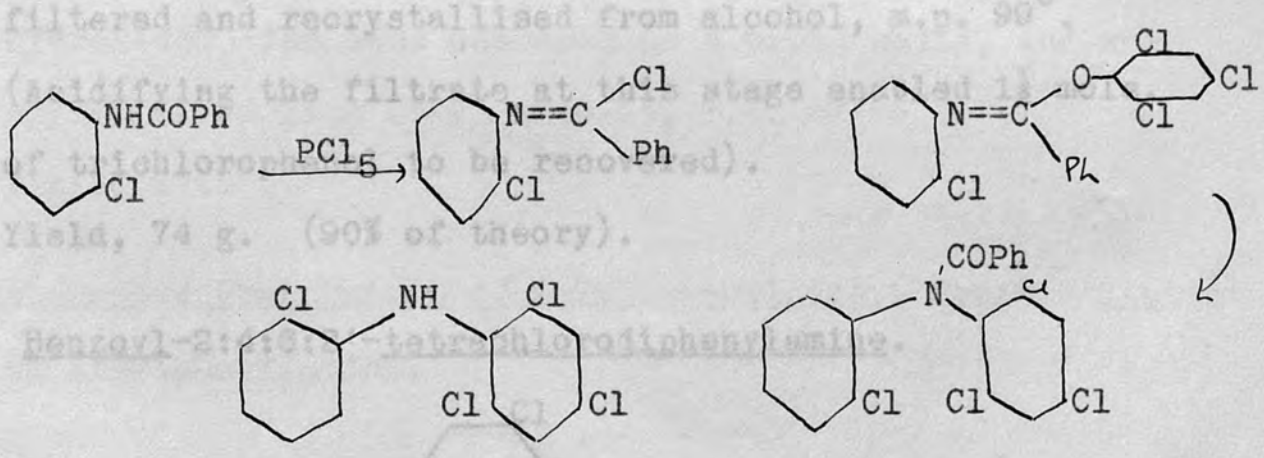
The product was washed with dilute hydrochloric acid and crystallised from alcohol. This gave the original base, m.p. 139°.

Preparation of 2:4:6:2'-Tetrachlorodiphenylamine.

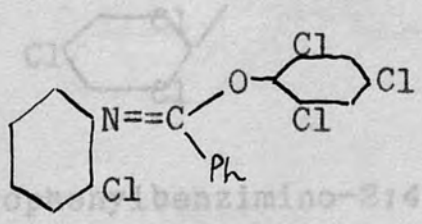


General Scheme.

The preparation is by a method due to A. W. Chapman, (private communication to Dr. E. E. Turner, Feb. 1929).



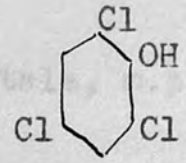
(1) o-Chlorophenylbenzimino-2:4:6-trichlorophenyl ether.



o-Chloroanilinebenziminochloride.  50 g. 1 mol.

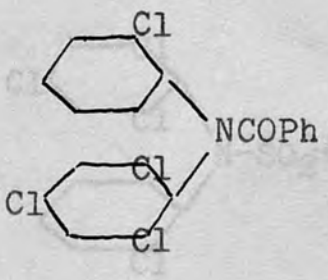
Sodium. 5.75 g. 1¼ mol

Absolute alcohol. 300 c.c.

s-Trichlorophenol.  98.75 g. $2\frac{1}{2}$ mols.

The sodium and trichlorophenol were dissolved in the alcohol, and the o-chloroanilinebenziminochloride added in dry ethereal solution: the whole was shaken and left to stand overnight. Most of the alcohol and ether were distilled off and the remainder poured into a solution of sodium hydroxide in water, in which the trichlorophenol and sodium chloride dissolved, leaving the imino-ether which was at first a cream coloured oil, turning later, on stirring and standing, to a white solid. It was filtered and recrystallised from alcohol, m.p. 99°. (Acidifying the filtrate at this stage enabled $1\frac{1}{2}$ mols. of trichlorophenol to be recovered).
Yield, 74 g. (90% of theory).

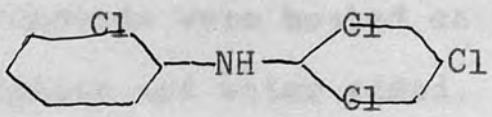
(2) Benzoyl-2:4:6:2'-tetrachlorodiphenylamine.



The o-chlorophenylbenzimino-2:4:6-trichlorophenyl ether was heated for 2 hours in a metal-bath at 265-275°. The product was poured into an evaporating dish and solidified to a brown glass: crystallising twice from

alcohol gave white crystals, m.p. 131-132°.

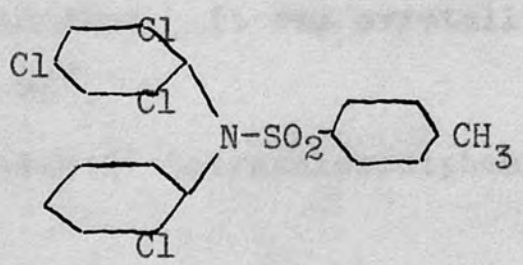
(3) 2:4:6:2'-Tetrachlorodiphenylamine.



Benzoyl-2:4:6:2'-tetrachlorodiphenylamine.	30 g.	1 mol.
50% Aqueous sodium hydroxide.	150 c.c.	
Absolute ethyl alcohol.	375 c.c.	

The mixture was refluxed for two hours, and most of the alcohol then evaporated off. The remainder was poured into a large excess of water to dissolve out the sodium hydroxide. The base appeared as a brown solid, and was crystallised from ethyl alcohol, m.p. 87-88°.
Yield, 17.5 g.

Attempted Preparation of p-Toluenesulphonyl-2:4:6:2'-tetrachlorodiphenylamine.



Method I.

2:4:6:2'-Tetrachlorodiphenylamine.	10 g.	1 mol.
p-Toluenesulphonyl chloride.	6 g.	1 mol.

Sodium carbonate.	5.5 g.	$1\frac{1}{4}$ mol.
Water.	about 5 c.c.	

The 2:4:6:2'-tetrachlorodiphenylamine and p-toluenesulphonyl chloride were heated on a water-bath and the sodium carbonate and water added. Heating was continued for half an hour. Extraction with alcohol and crystallisation gave crystals of pure 2:4:6:2'-tetrachlorodiphenylamine. m.p. 87-88°.

Method II.

2:4:6:2'-Tetrachlorodiphenylamine.	1 g.	1 mol.
p-Toluenesulphonyl chloride	0.75 g.	1 mol.
Pyridine.	5 c.c.	

The 2:4:6:2'-tetrachlorodiphenylamine and p-toluenesulphonyl chloride were fused on a metal-bath at 110° and the pyridine added. Heating was continued for a few minutes, and the product poured into hydrochloric acid, when it solidified. It was crystallised from alcohol. m.p. 87-88°.
Mixed m.p. with 2:4:6:2'-tetrachlorodiphenylamine, 87-88°.

Method III.

2:4:6:2'-Tetrachlorodiphenylamine.	1 g.	1 mol.
p-Toluenesulphonyl chloride.	0.65 g.	1 mol.
Quinoline.	5 c.c.	

The 2:4:6:2'-tetrachlorodiphenylamine, p-toluenesulphonyl chloride and quinoline were heated on a

metal bath at 200° for 9 hours under an air condenser and calcium chloride tube. The product was washed with hydrochloric acid, leaving a black tar from which no crystalline material could be extracted with any of the following solvents:- ethyl alcohol, benzene, carbon tetrachloride, light petroleum, (b. p. 60 - 80°.)

Method IV

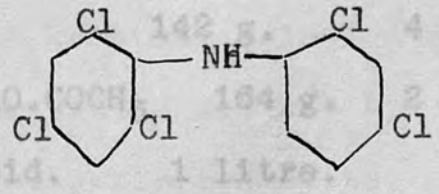
2:4:6:2'-Tetrachlorodiphenylamine.	1 g.	1 mol.
p-Toluenesulphonyl chloride.	1 g.	1 mol.

Quinoline.

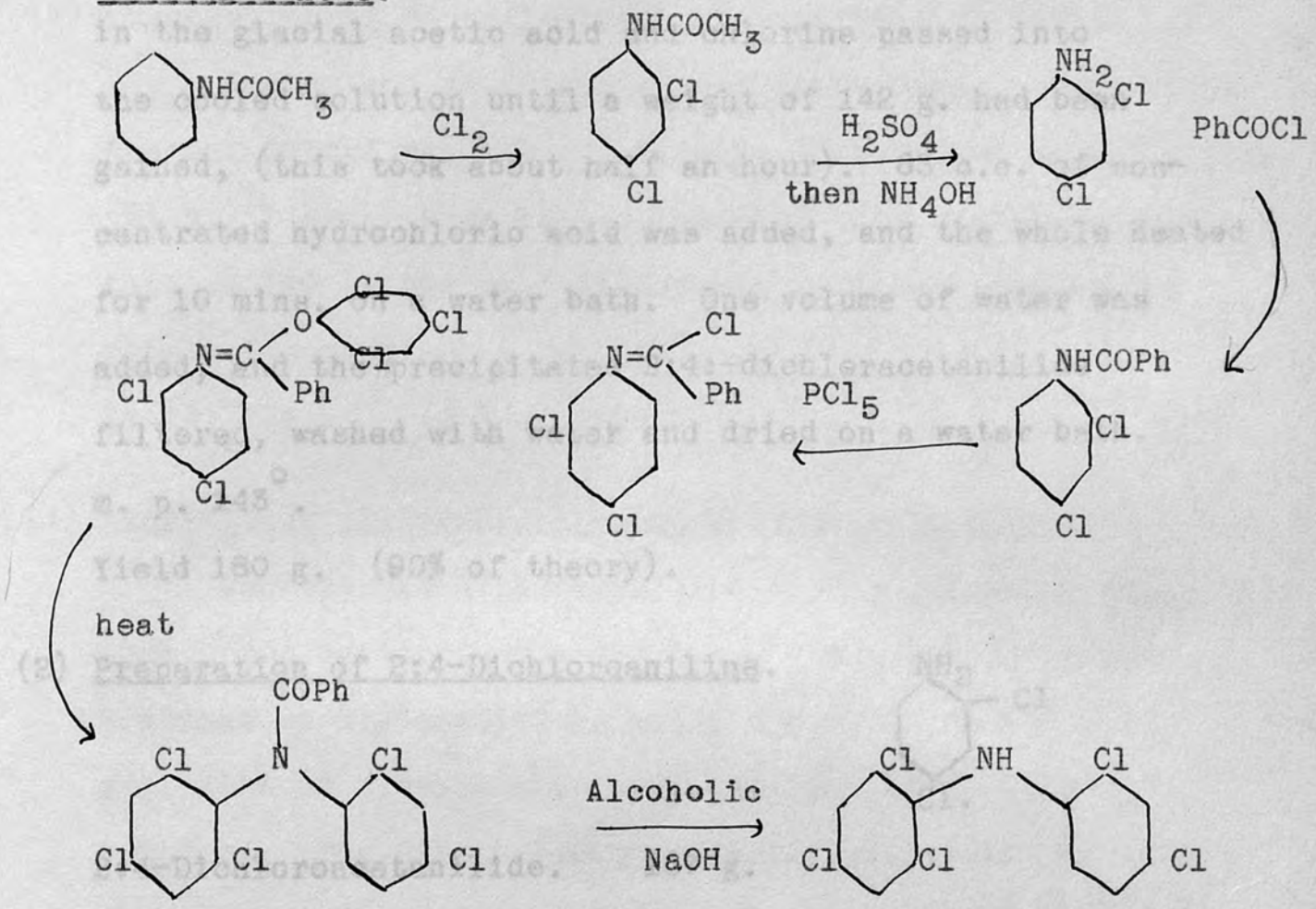
Copper bronze.

The 2:4:6:2'-tetrachlorodiphenylamine and p-toluenesulphonyl chloride were heated to 110° in quinoline solution. On adding a little copper bronze the temperature rose to 140°. The quinoline was removed by extraction with hydrochloric acid: the residue on crystallisation from alcohol yielded the original base.

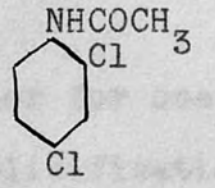
Preparation of 2:4:6:2':4':-Pentachlorodiphenylamine.



General Scheme.



(1) Preparation of 2:4-Dichloroacetanilide.

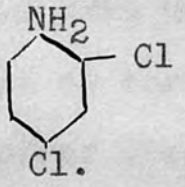


Acetanilide	135 g.	1 mol.
Chlorine	142 g.	4 atoms.
Sodium Acetate $NaO.COCH_3$	164 g.	2 mols.
Glacial Acetic acid.	1 litre.	

The acetanilide and sodium acetate were dissolved

in the glacial acetic acid and chlorine passed into the cooled solution until a weight of 142 g. had been gained, (this took about half an hour). 63 c.c. of concentrated hydrochloric acid was added, and the whole heated for 10 mins. on a water bath. One volume of water was added, and the precipitated 2:4:-dichloracetanilide filtered, washed with water and dried on a water bath.
m. p. 143°.
Yield 180 g. (90% of theory).

(2) Preparation of 2:4-Dichloroaniline.



2:4-Dichloroacetanilide.	157 g.
Sulphuric Acid conc.	314 c.c.
Water.	471 c.c.

The above materials were refluxed together for one hour, then cooled - but not enough to cause solidification - and poured into a mixture of water, ice and ammonia, (sufficient ammonia to keep the solution alkaline). The 2:4-dichloroaniline separated and was crystallised from alcohol, forming colourless needles, m. p. 61°.
Yield. 96 g. (77% of theory).

(3) Preparation of Benzoyl-2:4-dichloroaniline.

The method used is due to Noelting (Ber., 1905, 3506). Benzoyl chloride (87.5 g., 1¼ mols.) and 2:4-dichloroaniline (81 g., 1 mol.) were heated together under reflux on a metal bath at 160°; the product crystallised from alcohol in fine white needles, m. p. 115°.
Yield, 111 g. (83% of theory).

(4) Preparation of 2:4-Dichlorobenzanilide iminochloride.

Benzoyl-2:4-dichloroaniline (111 g., 1 mol.) and phosphorus pentachloride (86.8 g., 1 mol.) were heated together in dry conditions until there was no further evolution of hydrochloric acid gas, and clear liquid remained. The phosphorus oxychloride was distilled off in vacuo, and the iminochloride distilled (b. p. 241° at 4.4 cms.). Yield, 113 g. of pale yellow needles, m. p. 79°.

(5) Preparation of 2:4-Dichlorobenzanilide-2:4:6-trichlorophenyl ether.

2:4-Dichlorobenzanilide-iminochloride	214 g.	1 mol.
Sodium.	19 g.	1¼ atoms.
s-Trichlorophenol.	396 g.	2½ mol.
Absolute ethyl alcohol.	1000 c.c.	

The sodium and trichlorophenol were dissolved in the alcohol and the iminochloride added in dry ethereal solution; the mixture was left to stand overnight after shaking. Most of the alcohol and ether were distilled off, and the remainder poured into aqueous sodium hydroxide solution; the sodium chloride and excess trichlorophenol dissolved, and the iminoether appeared as a cream coloured oil which became solid on stirring and standing, and was crystallised twice from ethyl alcohol forming white prisms, m. p. 86 - 88°. Yield, 293 g.

Found: Cl, 39.9, $C_{19}H_{10}ONCl_5$ requires Cl, 39.8%

(6) Preparation of Benzoyl-2:4:6:2':4':-Pentachlorodiphenylamine.

2:4-Dichlorobenzanilide-2:4:6-trichlorophenyl ether (290 g.) was heated on a metal bath at 250 - 270° for two hours. The product cooled to a black glass, and the benzoyl derivative crystallised from ethyl alcohol in colourless prisms, m. p. 160°.

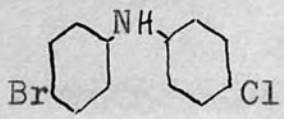
Yield, 235 g. (81% of theory). Found: Cl, 39.6, $C_{19}H_{10}ONCl_5$ requires Cl, 39.8 per cent.

(7) Preparation of 2:4:6:2':4'-Pentachlorodiphenylamine.

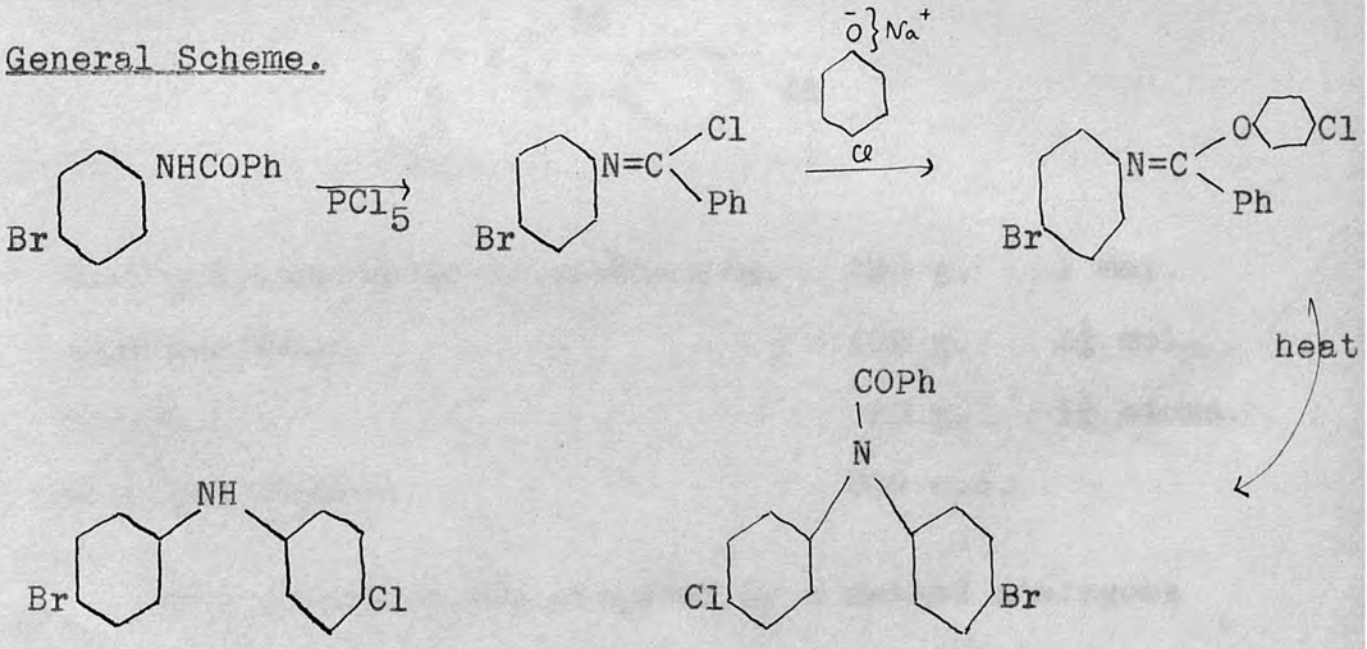
Benzoyl-2:4:6:2':4'-pentachlorodiphenylamine (50 g.) was dissolved in 625 c.c. of ethyl alcohol and heated under reflux on a boiling water bath for 1½ hours with 250 c.c. of 50% aqueous caustic potash solution. The

alcohol was evaporated off, and the remainder poured into water, when the pentachlorodiphenylamine separated as a brown solid, and crystallised from ethyl alcohol in fine white needles, m. p. 94°. Yield, 35 g. after crystallisation.
Found: Cl, 51.6, $C_{12}H_6NCl_5$ requires Cl, 51.9%

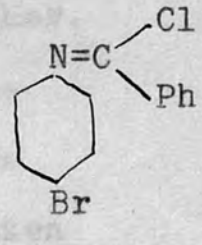
Preparation of 4-Chloro-4'Bromo-diphenylamine.



General Scheme.



(1) Preparation of Benz-p-bromanilide-iminochloride.

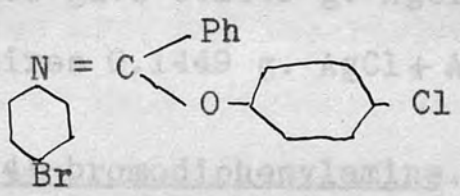


p-Bromobenzanilide.	104 g.	1 mol.
Phosphorus pentachloride.	88 g.	1 1/8 mol.

The phosphorus pentachloride and p-bromobenzanilide were heated on a water-bath under dry conditions until there was no further evolution of hydrochloric acid gas and

all was clear liquid. The phosphorus oxychloride was distilled off in vacuo, and the benz-p-bromoanilide-iminochloride distilled at low pressure, b. p. 220°, / 40 mm.). It solidified in the receiver to a yellow mass (100 g. - theoretical, 110 g.), which could not be separated from an impurity of benzoyl chloride, and was used in this state for the next stage.

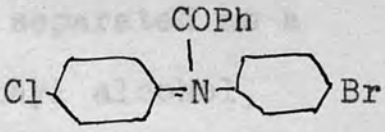
(2) Preparation of N-p-Bromophenylbenzimino-p-chlorophenyl ether.



Benz-p-bromoanilide-iminochloride,	100 g.	1 mol.
p-Chlorophenol	108 g.	2½ mol.
Sodium	10 g.	1¼ atoms.
Absolute alcohol	500 c.c.	

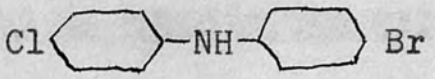
This substance was prepared by a method analagous to that used by A. W. Chapman (J. 1922, 2, 1992), for the preparation of N-phenylbenzimino-p-chlorophenyl ether. The sodium and p-chlorophenol were dissolved in the alcohol, and the benz-p-bromoanilide-imino-chloride added in dry ethereal solution. The whole was shaken and left to stand overnight. The ether and most of the

alcohol were then distilled off, and the remainder poured into sodium hydroxide solution, when both the sodium chloride and the p-chlorophenol went into solution, and the N-p-bromophenolbenzimino-p-chlorophenyl ether appeared as a yellow oil, which on stirring went to a cream coloured solid. It was crystallised from ethyl alcohol, giving colourless prisms, m. p. 83 - 84°.
Yield, 93 g. (72% of theory).
0.1698 g. substance gave 0.1449 g. AgCl + AgBr,
$C_{19}H_{13}ONClBr$ requires 0.1449 g. AgCl + AgBr.

(3) Benzoyl-4-chloro-4'-bromodiphenylamine. 

The above imino-ether (30 g.) was heated for 2½ hours on a metal bath at 290 - 320°, (see Elson and Gibson, J., 1931, 294, preparation of benzoyl-3:4'-dichlordiphenylamine). The product solidified to a brown glass, and was crystallised from ethyl alcohol, giving colourless plates of the benzoyl derivative, m. p. 149°. Yield, 22.5 g.,(75% of theory).
On attempting to repeat this preparation using larger quantities of the imino-ether, it was found impossible to obtain any crystalline material from the tar formed.
0.1424 g. substance gave 0.1194 g. AgCl + AgBr.
$C_{19}H_{13}ONClBr$ requires 0.1249 g. AgCl + AgBr.

(4) Preparation of 4-Chloro-4'-bromodiphenylamine.



Benzoyl 4-chloro-4'-bromodiphenylamine	18 g.
50% sodium hydroxide (aqueous)	90 c.c.
Absolute alcohol,	225 c.c.

The above materials were heated together under reflux on a boiling water bath for an hour. The alcohol was then evaporated off, and the residue poured into water when the 4-chloro-4'-bromo-diphenylamine separated as a brown solid, and was crystallised from ethyl alcohol, giving brown plates, m. p. 91.5°.

Yield, 9.7 g. (75% of theory).

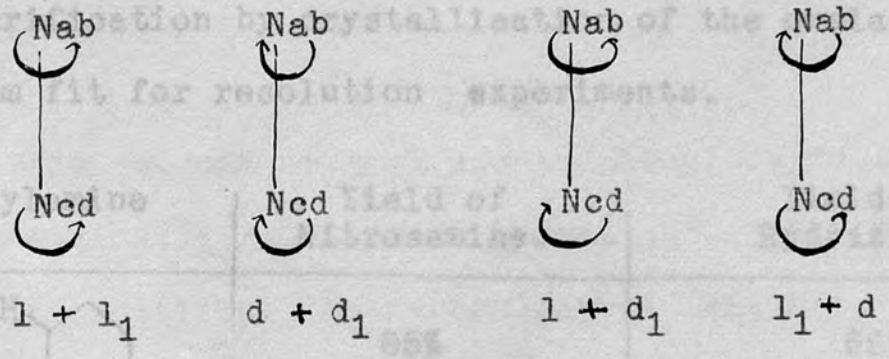
0.1272 g. substance gave 0.1477 g. AgCl + AgBr.

$C_{12}H_9NClBr$ required 0.1489 g. AgCl + AgBr.

SECTION III

EXPERIMENTS ON SUBSTITUTED HYDRAZINES

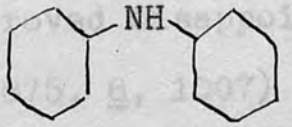
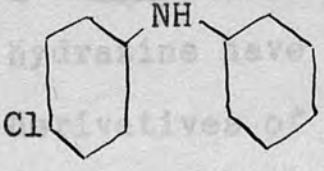
Two series of experiments were made, the first with a view to producing optical isomers, the second, geometrical isomers. The aim in the first case was a compound $R_1R_2N\text{-}N\text{-}R_3R^{*}$ where R_1 and R_2 are different electron attracting groups, such as dichlorophenyl, R_3 the benzene-sulphonyl, p-toluenesulphonyl or benzoyl group, and R^{*} an optically active radical, preferably d-camphor-10-sulphonyl. Theoretically, a compound of this (Nab—Ncd) type should exist in two racemic forms, each resolvable into two antimers. Let l and d be the laevo and dextro rotations of Nab— and l_1 and d_1 those of Ncd—. Then the two racemates would be formed thus:-

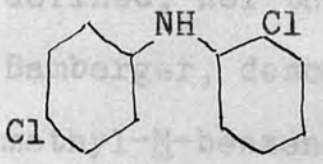
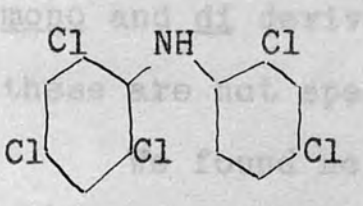


$l + l_1$ $\quad$ $d + d_1$ $\quad$ $l + d_1$ $\quad$ $l_1 + d$

Preparation of N:N-Diphenylhydrazines.

These substances were prepared by Fischer's method (Annalen, 1878, 190, 175) for N:N-diphenylhydrazine, which consists in making the N-nitroso derivative of the corresponding diphenylamine and reducing this with zinc and acetic acid. Unfortunately, introducing electron-attracting groups into the two benzene nuclei of the diphenylamine so decreases the reactivity of the nitrogen atom that it was found impossible to prepare pentachloro-diphenylhydrazine, and impracticable to work on mono- and di-chlorodiphenyl hydrazines, owing to the reduction stage proving unsatisfactory. Actually the yields are worse than those shown on the accompanying diagram, as here the figures for the last stage are given, for purposes of comparison, before the last two compounds underwent a final purification by crystallisation of the oxalates, to make them fit for resolution experiments.

Diphenylamine	Yield of Nitrosamine.	Yield of Hydrazine.
	85%	55%
	83%	About 27% before final purification.

Diphenylamine	Yield of Nitrosamine.	Yield of Hydrazine.
	82%	About 22% before final purification.
	Could not be prepared.	

In the case of N-N-diphenylhydrazine itself, we seem to have found the preparation easier than Fischer describes it, but this was no doubt due to the higher degree of purity of our starting materials and solvents.

An unsuccessful attempt was made to reduce N-nitroso-diphenylamine with hydrogen under pressure, using as catalysts

(a) Raney Nickel and

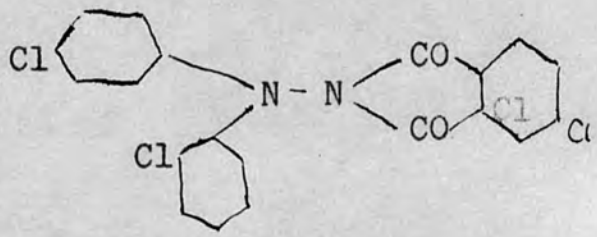
(b) platinum oxide.

On the subject of acyl and sulphonyl derivatives of unsymmetrically substituted hydrazines, the literature proved disappointing. Benzenesulphonyl (Fischer, Ber., 1875, 8, 1007) and p-toluenesulphonyl (Troeger and Uhlmann, J. prakt. Chem., 1895,(ii), 51, 442) derivatives of phenyl-hydrazine have been prepared, and the dibenzenesulphonyl derivatives of N-phenyl-N-methyl- and N-phenyl-N-ethyl-hydrazines (Bamberger, Ber., 1899, 32, 1804) are described:

but it appears that the compounds were not always well defined, nor the methods satisfactory. For example, Bamberger, describing the preparation of N-phenyl-N-methyl-N-benzenesulphonylhydrazine says that the ratio of mono and di derivatives formed depends on "conditions"; these are not specified.

We found no satisfactory method for the preparation of benzenesulphonyl or p-toluenesulphonyl derivatives, the yield in all cases being small, and the product of doubtful constitution. Fischer's preparation of N'-benzoyl-N:N-diphenylhydrazine (Annalen., 1878, 190, 178) was repeated, but heating this compound with p-toluenesulphonyl chloride in pyridine did not give the desired mixed di derivative. An attempt to prepare N':N'-camphoryl-N:N-diphenyl hydrazine was abandoned when it was found that the product was extremely insoluble in all solvents, and therefore useless for resolution experiments.

So the idea of looking for optical activity in hydrazines had to be given up, and attention was turned to the possibility of geometric isomerism, the compound chosen for investigation being 4-chlorophthalyl-2:4'-dichloro-N:N-diphenylhydrazine,

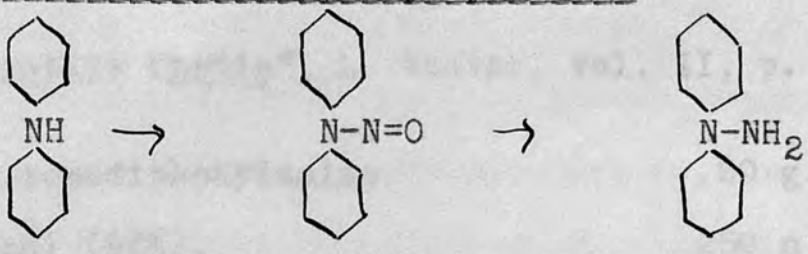


2:4'-Dichlorodiphenylamine was prepared by the Chapman process (loc. cit.) and converted to the nitrosoamine and then to the corresponding hydrazine by Fischer's method. The yield of hydrazine was very small indeed, and in spite of repeated distillation no better analysis was obtained than Cl, 28.9, $C_{12}H_{10}N_2Cl_2$ requires Cl, 28.1%. The 4-chlorophthalyl derivative was prepared, but in too small a quantity to make fractional crystallisation experiments a success, especially as complete purity in this type of experiment is the first necessity.

We felt that from the "electron - displacement" point of view, 2:4:6:2':4'-pentachloro-N:N-diphenylhydrazine would be a most interesting compound to obtain, but apparently the inductive effect of the chlorine atoms in 2:4:6:2':4'-pentachlorodiphenylamine is sufficiently strong to inhibit entirely the chemical reactivity of the nitrogen atom, for it was found impossible to form the corresponding nitrosoamine, even by the most drastic methods.

SECTION III EXPERIMENTAL

Preparation of N:N-Diphenylhydrazine.



(a) Preparation of Nitrosodiphenylamine, $Ph_2N.N=O$

Hans Meyer, ("Lehrbuch der Organisch-Chemischen Methodik." 1. 4 Auflage., p. 795.)

E. Fischer, (Annalen., 190,(1878), 175. (This preparation is well described in "Präparative Chemie," L.Vanino, p. 508.))

100 g. Diphenylamine.

500 c.c. Alcohol.

75 c.c. Conc. hydrochloric acid.

50 g. Sodium nitrite (in 50 c.c. water).

The diphenylamine was dissolved in the alcohol and cooled below 5°. The hydrochloric acid, also cooled below 5°, was added quickly with stirring; then the sodium nitrite added as quickly as possible keeping the temperature below 5°. The whole was poured into water, when the nitrosoamine separated as a yellow solid, and crystallised from light petroleum (b.p. 80-100°) gave yellow needles. m.p. 68°.

Yield 101 g. (85% of theory), after crystallisation.

(b) Preparation of N:N-Diphenylhydrazine by reduction of nitrosodiphenylamine.

"Präparative Chemie", L. Vanino, vol. II, p. 508.

N-Nitrosodiphenylamine	50 g.
Alcohol (96%).	250 c.c.
Zinc dust.	75 g.
Glacial acetic acid.	

The nitrosodiphenylamine was dissolved in the alcohol and cooled to 0°. The zinc dust was added, and then the glacial acetic acid drop by drop, cooling after each addition, until further addition of glacial acetic acid caused no appreciable rise in temperature, and also until a filtered portion of the reaction mixture gave no blue colour with conc. hydrochloric acid. A further 250 c.c. of alcohol was added to the mixture, which was boiled and filtered. It was evaporated down to a quarter of its volume, and poured into concentrated hydrochloric acid, when the diphenylhydrazine hydrochloride appeared in white needles.

The hydrazine hydrochloride was separated from diphenylamine hydrochloride by crystallisation from hot dilute hydrochloric acid; the diphenylamine hydrochloride decomposes in the presence of water to give the free base, whereas the hydrazine hydrochloride is stable in the dilute acid.

The diphenylhydrazine hydrochloride was crystallised from alcohol and appeared in heavy white needles.
Yield 40 g. (75% of theory. [Crude] .)

The hydrazine hydrochloride was decomposed by warming with sodium hydroxide solution, when the N:N-diphenyl hydrazine separated as an oil, solidifying on pouring on to ice. Crystallisation from light petroleum (b. p.80 - 100°) gave hard white crystals, m. p. 36°.

N:N-Diphenyl hydrazine hydrochloride	103 g.
Sodium hydroxide	25 g.
Yield. N:N-Diphenyl hydrazine 62 g.	(73%)

Attempted preparation of N:N-Diphenylhydrazine. $Ph_2N.NH_2$

(a) Catalyst, Raney Ni.

N-Nitrosodiphenylamine	10 g.
Absolute alcohol	100 c.c.
Raney Ni	1 g.

The above substances were put in the cylinder of the hydrogenator (vol. 9440 ± 50 c.c.), and shaken with hydrogen under a pressure of 53¼ lbs/sq.". Apart from a constant fall in pressure due to a leak in the apparatus, there was no pressure change, and therefore no reaction. The presence of hydrazine in the solution was tested for by adding concentrated hydrochloric acid; there was no formation of the crystalline hydrochloride.

(b) Catalyst, Adams PtO_2. (cf. "Organic Syntheses", Vol. 8, p. 92).

N-Nitrosodiphenylamine	20 g.
PtO_2	0.2 g.
Absolute alcohol	

The nitrosodiphenylamine dissolved in alcohol was shaken in an atmosphere of hydrogen with the PtO_2.

Initial pressure 63-64 lbs./sq." } { N.B. including leak.
Final pressure 41-42 lbs./sq." }

The solution smelled strongly of ammonia, and contained nitrosoamine, but no hydrazine.

Attempted preparation of N'-Benzenesulphonyl-N:N-diphenylhydrazine.

(a) Method of Bamberger. B. 1899. (1) p. 1804. (as for $PhMeN.NHSO_2Ph$).

N:N-diphenylhydrazine	1 g.	1 mol.
Benzenesulphonyl chloride	1 g.	1. mol.
Sodium hydroxide 4.8 g.	(60 c.c. bench alkali)	2 mols.

The above reactants were shaken together for ¼ hour, and filtered. The filtrate on acidification with hydrochloric acid gave no precipitate, and therefore it was a assumed that no mono-benzene-sulphonyl derivative was formed.

(b)

Pyridine	30 c.c.
N:N-diphenylhydrazine	0.5 g.
Benzenesulphonyl chloride	0.5 g.

The hydrazine and benzenesulphonyl chloride were shaken in the pyridine, and then poured into hydrochloric acid to remove the pyridine. A small quantity of an orange sticky mass was obtained. This was unidentified.

Preparation of N-p-Toluenesulphonyl-N:N-diphenylhydrazine.

(a)	N:N-Diphenylhydrazine	1 g.	1 mol.
	p-Toluenesulphonyl chloride	1 g.	1 mol.
	Quinoline	2 g.	

The N:N-diphenylhydrazine was dissolved in benzene and mixed with the quinoline. It was heated on a water bath, and the p-toluene sulphonyl chloride added in benzene solution down a condenser, drop by drop. The benzene was evaporated off on a water bath, and the resulting mass shaken with 200 c.c. dilute hydrochloric acid, warming slightly. The solid obtained was crystallised from alcohol, m. p. 138°. This product was warmed with sodium hydroxide solution and filtered, acidifying the filtrate with hydrochloric acid. A white solid was precipitated which on crystallisation from alcohol gave white crystals, shrinking at 145°, m. p. 155°.

(b)	N:N-Diphenylhydrazine	9.2 g.	1 mol.
	p-Toluenesulphonyl chloride	9.7 g.	1 mol.
	Pyridine.		

The N:N-diphenylhydrazine was dissolved in 50 c.c. pyridine, and the p-toluenesulphonyl chloride added drop by drop in pyridine solution (50 c.c.). The solution was divided into two equal portions,

(a) left in ice 2 hours,
(b) " " " overnight.

The two were worked up separately as follows:-
The solution was shaken with 50 c.c. water and 50 c.c. concentrated hydrochloric acid to remove the pyridine. A yellow tar was formed which solidified on further shaking and was ground up under dilute hydrochloric acid. The yellow solid was extracted with boiling sodium hydroxide solution, and on acidifying the filtrate a white solid was obtained,

m. p. (a) 139°. Yield 0.5 g.
" (b) 143°. Yield 0.5 g.

crystallisation from alcohol gave white crystals, m. p. 144°.

Preparation of N'-benzoyl-N:N-diphenylhydrazine.

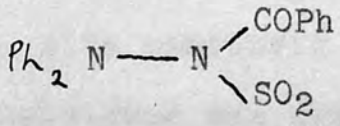
E. Fischer. (Annalen., 190, 178).

N:N-diphenylhydrazine	18 g.	1 mol.
Benzoyl chloride	7 g.	1 mol.
Ether	180 g.	

The N:N-diphenylhydrazine was dissolved in half of

the ether and the benzoyl chloride in the other half. The two solutions were mixed and stirred. A white precipitate was formed, and more obtained on evaporating off the ether solution. Crystallisation from acetone gave white crystals., m. p. 189 - 190°. Yield. 9.7 g. (33% of theory).

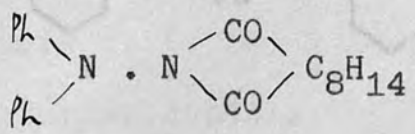
Attempted preparation of N:N-Diphenyl-N':N'-benzoyl-p-toluene sulphonylhydrazine.



N'-Benzoyl-N:N-diphenylhydrazine	3 g.	1 mol.
p-Toluenesulphonyl chloride	2 g.	1 mol.
Pyridine (dry).	45 c.c.	(excess).

The benzoyl-N:N-diphenylhydrazine was dissolved in 30 c.c. pyridine, and the p-toluenesulphonyl chloride in 10 c.c. pyridine, and the latter washed into the former with the remaining 5 c.c. pyridine. The mixture was heated for ½ hour on a water bath, and then shaken with water and hydrochloric acid, adding hydrochloric acid until there was no further smell of pyridine. The white solid formed was crystallised from alcohol, and melted uniformly at 193°. This must be the original benzoyl derivative.

Preparation of N':N'-Camphor-N:N-diphenylhydrazine.



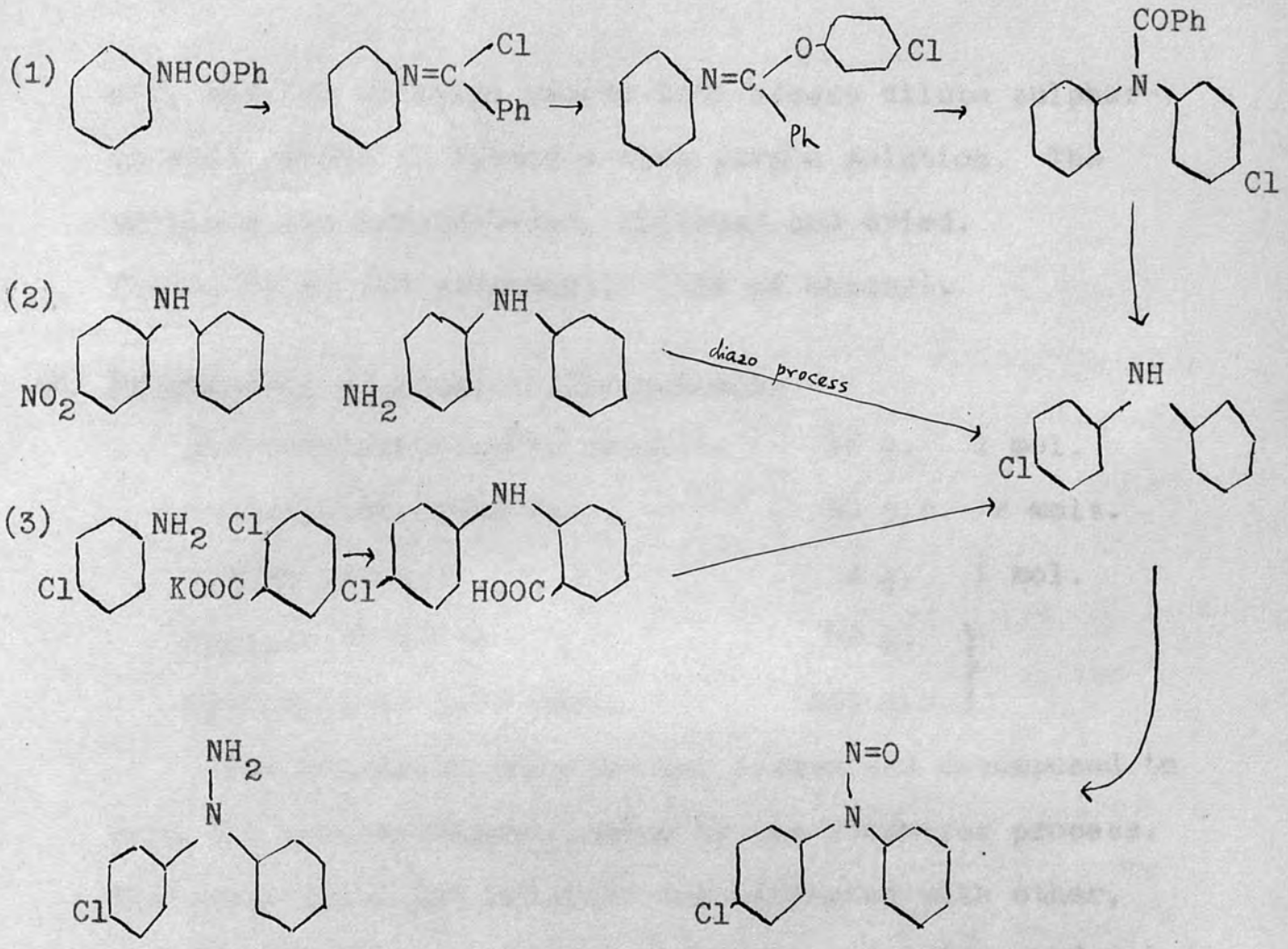
Chaplin, (Ber., 1892, (2), 256).

N:N-Diphenylhydrazine (5 g., 1 mol.) was heated with camphoric anhydride (5 g. 1 mol.) for 2½ hours at 160 - 180°, the temperature raised momentarily to 240°, and then cooled. The resulting solid was boiled with a little alcohol, filtered and crystallised from alcohol, m. p. 240°. Mixed m. p. with camphoric anhydride, 210°.

The substance was almost insoluble in hot ethyl alcohol and acetone, and only very slightly soluble in hot light petroleum (b. p. 60 - 80°), xylene, chloroform and cyclohexanol. Further investigation of the substance was abandoned, as its small solubility made it quite unsuitable for resolution experiments.

Preparation of N-p-Chlorophenyl-N-phenylhydrazine.

This substance was prepared by reduction of the N-nitroso derivative of p-chlorodiphenylamine: the latter substance could be prepared by three different methods; of these, the most successful, due to A.W.Chapman, has already been described (loc. cit.).



Preparation of p-Chlorodiphenylamine. Method 2.

(a) Preparation of p-Aminodiphenylamine.

p-Nitrodiphenylamine	100 g.
Iron filings	100 g.
Glacial Acetic acid	
Water	

The p-nitrodiphenylamine was reduced with iron and acetic acid in the usual way, and the p-aminodiphenylamine extracted with alcohol. Some of the alcohol was evaporated

off, and the solution poured into excess dilute sulphuric acid, where it formed a deep purple solution. The sulphate was precipitated, filtered and dried.

Yield, 36 g. (of sulphate). (33% of theory).

(b) Preparation of p-chlorodiphenylamine.

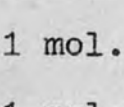
p-Aminodiphenylamine sulphate	36 g.	1 mol.
Hydrochloric acid conc.	50 c.c.	2 mols.
Sodium nitrite	9 g.	1 mol.
Cuprous chloride	50 g.	}
Hydrochloric acid conc.	200 c.c.	}

The diazonium chloride was formed and decomposed to form the p-chlorodiphenylamine by the Sandmeyer process. The green-black gum obtained was extracted with ether, washed with ammonia, sodium hydroxide and water, and dried over potassium carbonate. It was then distilled. b. p. 325°.

Yield, 8 g. before crystallisation. (from methyl alcohol).

Preparation of p-chlorodiphenylamine Method 3.

(a) Preparation of potassium o-chlorobenzoate.



o-Chlorobenzoic acid	168 g.	1 mol.
Potassium carbonate	75 g.	1 mol.

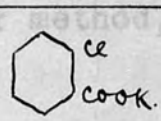
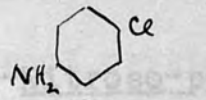
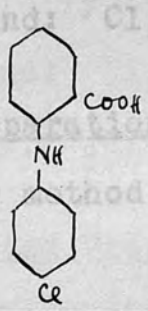
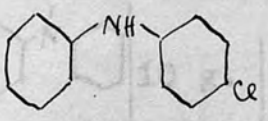
The potassium carbonate was dissolved in a little water in a dish, and heated while the chlorobenzoic acid was stirred in. This was heated with stirring until it became pasty, when it was cooled, ground in a mortar and

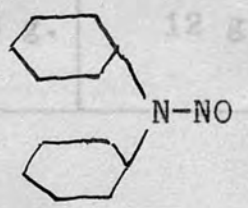
heated in an air oven at 120° until dry. It was then ground again and seived.

(b) Preparation of p-chlorodiphenylamine.

Ullmann. [Annalen, 1907, 355, 312. (preps. p. 339).]

The potassium o-chlorobenzoate, p-chloroaniline, amyl alcohol and copper bronze were heated under reflux together for four hours on a metal bath at 165 - 170°. Then sodium hydroxide and water were added and the amyl alcohol and excess p-chloroaniline distilled off in steam. The residue was filtered, and the solution on acidification with hydrochloric acid gave a heavy precipitate of 4-chloro-2'-carboxy-diphenylamine, which was crystallised from alcohol, appearing in black crystals, (except in one case when the steam distillation was carried out in very dilute solution, when the crystals were yellow). m. p. 167 - 170°. The acid was decarboxylated by heating it on a metal bath at 260 - 270°, distilling the product and crystallising from alcohol. m. p. 66°.

	40 g.	110 g.	110 g.	110 g.	110 g.	110 g.
	60 g.	180 g.	180 g.	180 g.	180 g.	180 g.
Amyl Alcohol	50 cc.	150 cc.	150 cc.	150 cc.	150 cc.	150 cc
Copper Bronze	½ g.	1 g.	1 g.	1 g.	1 g.	1 g.
	ex EtOH (a) 21 g. (b) 7 g.	ex MeOH 75 g.	ex EtOH (a) 62.5g. (b) 37 g.	(a) 86 g. (b) 10 g.	106 g.	125 g.
 On distillation	(a) 7 g. (b) 5 g.	47 g.	56 g.	(a) 48 g. (b) 15 g.	(a) 51 g. (b) 12 g.	56 g.
Ditto after crystallisation		27.5 g.	38 g.	45.8 g.	36.5 g.	38.5 g.

Preparation of N-Nitroso-p-chlorodiphenylamine. 

p-Chlorodiphenylamine	20 g.
Absolute Ethyl alcohol	100 c.c.
Hydrochloric acid conc.	15 c.c.
Sodium nitrite	10 g.

For method, see preparation of

N-nitrosodiphenylamine

N-nitroso-2:4'-dichlorodiphenylamine.

N-Nitroso-p-chlorodiphenylamine crystallised from light petroleum, (b.p. 40-60°) forming fairly large, almost colourless crystals, m.p. 88°.

Yield 19 g. (83% of theory).

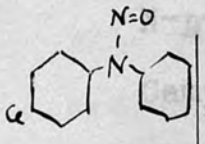
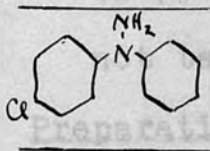
Found: Cl, 15.0, $C_{12}H_9ON_2Cl$ requires Cl, 15.3 per cent.

Preparation of N-p-Chlorophenyl-N-phenylhydrazine.

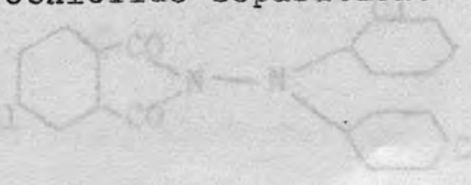
For method see preparations of

N:N-Diphenylhydrazine

2:4'-Dichloro-N:N-diphenylhydrazine.

	10 g.	20 g.	10 g.	10 g.	20 g.	20 g.	20 g.	20 g.
C_2H_5OH (96%)	50 cc	100 cc	40 cc. + 20cc. ether	40 cc + 20cc. ether	100 cc	100 cc	100 cc	100 cc
Zn	15 g.	30 g.	15 g.	15 g.	30 g.	30 g.	30 g.	30 g.
	7 g.	7 g.	3 g.	4.5 g.	13.5g. *	8 g.	12 g.	

*- Without hydrochloride separation.



Distillation of the united products in high vacuum (b. p. 192 - 194°) gave 34 g. This was converted to oxalate, using 84 g. of oxalic acid. The first aqueous extract crystallised, the rest remaining gummy. The crystalline fraction was decomposed with alkali, and the N-p-chlorophenyl-N-phenyl hydrazine obtained distilled in high vacuum, b. p. 194°. It was not found possible to solidify the golden liquid, even at very low temperatures.

Found: Cl, 16.1%

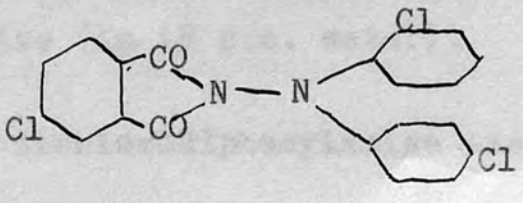
$C_{12}H_{11}N_2Cl$ requires Cl, 16.2%

Attempted Preparation of N-Camphoryl-N-p-chlorophenyl-N-phenylhydrazine.

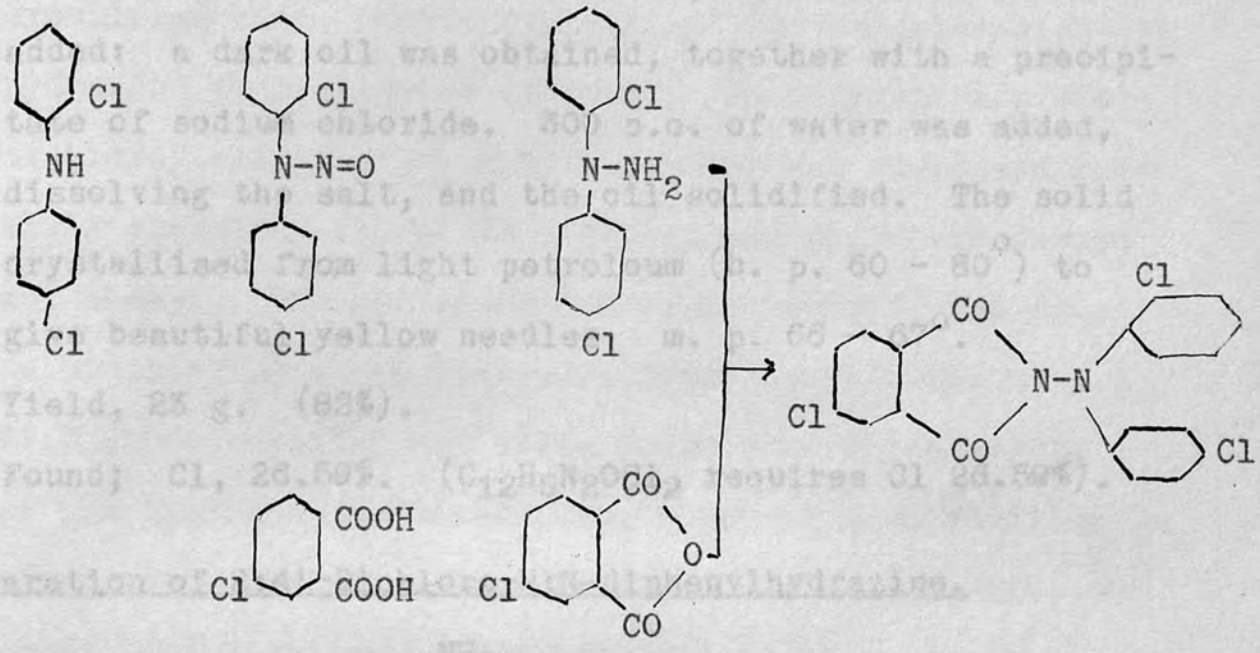
N-p-Chlorophenyl-N-phenylhydrazine,	4.3 g.	1.2 mols.
Camphoric anhydride,	3.1 g.	1 mol.
Tetralin.	23 c.c.	

The above substances were heated in a sealed tube at 180 - 200° for three hours. On cooling, large white crystals were formed, m. p. 216 - 218°. Mixed m. p. with camphoric anhydride, 214 - 218°: the reaction had therefore not taken place.

Preparation of 4-Chlorophthalyl-2:4'-dichloro-N:N-diphenylhydrazine.

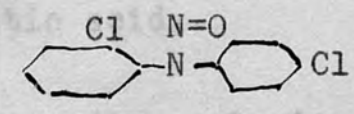


The general scheme was as follows:-



The final stage, condensation of 4-chlorophthalic anhydride with the hydrazine, was tried out first with N:Ndiphenylhydrazine.

Preparation of N-Nitroso-2:4'-dichlorodiphenylamine.



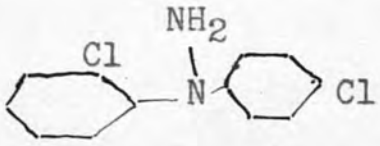
Method as for nitroso-diphenylamine, q.v.

2:4'-Dichlorodiphenylamine	25 g.
Ethyl Alcohol (96%)	125 c.c.
Hydrochloric acid (concentrated)	32 c.c.
Sodium nitrite (in 18 c.c. water).	12.5 g.

The 2:4'-dichlorodiphenylamine was dissolved in the

alcohol and cooled to 5°. The hydrochloric acid, also at 5°, was added quickly and stirred, then the sodium nitrite added: a dark oil was obtained, together with a precipitate of sodium chloride. 300 c.c. of water was added, dissolving the salt, and the oil solidified. The solid crystallised from light petroleum (b. p. 60 - 80°) to give beautiful yellow needles. m. p. 66 - 67°.
Yield, 23 g. (82%).
Found; Cl, 26.59%. ($C_{12}H_8N_2OCl_2$ requires Cl 26.59%).

Preparation of 2:4'-Dichloro-N:N-diphenylhydrazine.



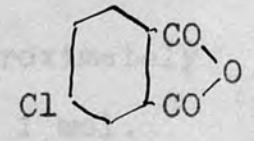
N-Nitroso-2:4'-dichlorodiphenylamine		40 g.
Ethyl Alcohol (96%).		200 c.c.
Zinc dust		60 g.
Glacial acetic acid.	about	40 c.c.

The nitrosodiphenylamine was dissolved in the alcohol and the zinc dust added. The glacial acetic acid was added drop by drop, allowing the temperature to return to room temperature after each addition; the temperature of the reaction was never allowed to rise above 30°. A further 200 c.c. of 96% alcohol was then added, and the mixture boiled and filtered. The filtrate was evaporated

down to $\frac{1}{4}$ of its volume, and poured into concentrated hydrochloric acid. White crystals of 2:4'-dichlorodiphenylhydrazine hydrochloride appeared. To separate any 2:4'-dichlorodiphenylamine, a little water was added and some light petroleum (b. p. 80 - 100°), and the whole warmed and shaken. The petroleum layer was removed, and found to contain 5.5 g. of 2:4'-dichlorodiphenylamine, m. p. 41.5°. On cooling, the other layer gave white crystals of the hydrazine hydrochloride, which on decomposition with sodium hydroxide gave 10.2 g. of a dark liquid, the crude 2:4'-dichloro-N:N-diphenylhydrazine. On vacuum distillation under a pressure of 8 cms. a pale yellow liquid was obtained, b. p. 241°.

Found: Cl, 28.9% ($C_{12}H_{10}N_2Cl_2$ requires Cl, 28.1%).

Preparation of 4-Chlorophthalic Anhydride.

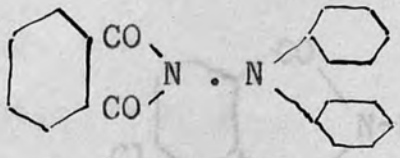


Koenigs and Hoerlin, Ber., 1893, p. 817.

4-Chlorophthalic acid	10 g.	1 mol.
Acetic Anhydride	8 g.	$1\frac{1}{2}$ mol.

The 4-chlorophthalic acid and acetic anhydride were boiled under reflux for $1\frac{1}{2}$ hours. On cooling, a white mass was formed which after washing with light petroleum (b. p. 40 - 60°) had m. p. 92 - 94°. Yield 5.5 g. (60% of theory)

Preparation of N:N-Diphenyl-N':N'-phthalylhydrazine.



Hotte. J. Prakt. Chem. (2). 35. p. 271.

Phthalic anhydride	8 g.	1 mol.
N:N-Diphenylhydrazine	9 g.	1 mol.

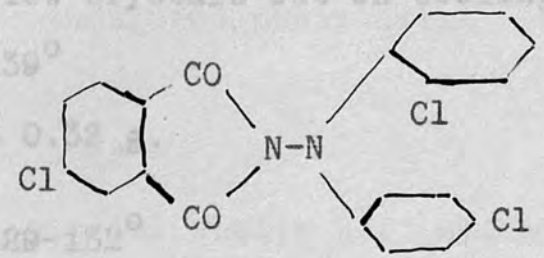
The phthalic anhydride and N:N-diphenylhydrazine were heated for 2 hours on a metal bath at 170 - 190°. The resulting mass was crystallised from alcohol and formed beautiful yellow plates, m. p. 158°. Yield, 8 g. (50% of theory).

To find the effect of the presence of diphenylamine on the preparation of N:N-diphenyl-N':N'-phthalylhydrazine, (as above).

Diphenylamine	4.5 g.	approximately
N:N-diphenylhydrazine	4.5 g.	1 mol.
Phthalic anhydride	8 g.	1 mol.

The diphenylamine, diphenylhydrazine and phthalic anhydride were heated under reflux for 1 hour at 170 - 190°. On pouring into 70 c.c. abs. alcohol, yellow plates separated, m. p. 128°. On boiling the solid with sodium hydroxide solution, yellow plates, m. p. 155° remained. Yield, 7 g. This is almost the theoretical amount calculated on the hydrazine used.

Preparation of 4-Chlorophthalyl-2:4'-dichlorophenylhydrazine.



4-Chlorophthalic anhydride 3.7 g. 1 mol.

2:4'-Dichloro-N:N-diphenylhydrazine. 5.1 g. 1 mol.

The 4-chlorophthalic anhydride and 2:4'-dichloro-N:N-diphenylhydrazine were heated on a metal bath at 170 - 190° for 1¼ hours. 30 c.c. absolute ethyl alcohol was added and the whole boiled under reflux for 1½ hours. The alcohol was then evaporated off and the remaining yellow solid, the 4-chlorophthalyl-2:4'-dichlorodiphenylhydrazine ground with sodium carbonate and water, then filtered and dried. Crude, m. p. 124 - 142°. Yield, 7.95 g. Found: Cl, 25.2%, $C_{20}H_{11}O_2N_2Cl_3$ requires Cl, 25.5%.

Attempt to separate this product into two components.

Crude. m. p. 124 - 142°

Weight 7.95 g.

Dissolved in hot alcohol, filtered, cooled. Yellow crystals appeared in small tussocks. Filtered and dried on water bath.

m. p. 142 - 142.5°

Weight 6.0 g

Evaporated down to ½; nothing out on cooling. Evaporated down to ¼. Yellow crystals out on cooling and scratching.

m.p. 139°

Weight 0.32 g.

m.p. 129-132°

Weight 0.43 g.

Attempted Preparation of N-Nitroso-2:4:6:2':4'-pentachlorodiphenylamine.

Method 1.

The method first tried was that which succeeded in the case of N:N-diphenylhydrazine and its mono- and dichloro-derivatives.

2:4:6:2':4'-Pentachlorodiphenylamine.	22.5 g.
Alcohol.	150 c.c.
Concentrated hydrochloric acid.	7.5 c.c.
Sodium nitrite.	5 g.

The pentachlorodiphenylamine was dissolved in the alcohol and cooled to 0°. The hydrochloric acid was added and stirred, and then the sodium nitrite. There was no apparent action, and on pouring the whole into water, a solid product was obtained which on crystallisation from alcohol proved to be the original pentachlorodiphenylamine.

Method 2.

2:4:6:2':4'-Pentachlorodiphenylamine	9.5 g.	1 mol.
Amyl nitrite	5.75 g.	2 mols.
Glacial acetic acid	20 c.c.	

The base, glacial acetic acid and amyl nitrite were mixed and dry hydrochloric acid gas passed through at 90°. The amyl nitrite was blown off by hydrochloric acid gas at 130°, and the remainder poured into water. Small crystals were formed, m.p. 93°. Mixed m.p. with 2:4:6:2':4'-pentachlorodiphenylamine, 93°. Therefore there was no reaction.

Method 3.

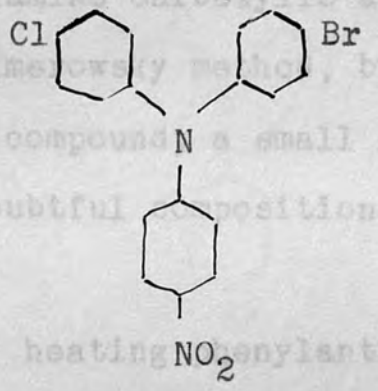
2:4:6:2':4'-Pentachlorodiphenylamine	9.5 g.	1 mol.
Sodium nitrite	2.7 g.	1.5 mols.
Concentrated sulphuric acid.		

The pentachlorodiphenylamine was dissolved in 50 g. concentrated sulphuric acid, and to this added a solution of the sodium nitrite in 30 g. concentrated sulphuric acid (made up below -10°). After leaving to stand for one hour it was poured onto ice, when a crisp pale yellow solid was formed. On standing for half an hour, a brown oil resulted, which on crystallisation from light petroleum, (b.p.40-60°) gave yellow crystals, m.p. 94°. This was the original base recovered.

SECTION IV

Preparation and Attempted Resolution of an Unsymmetrically Substituted Triphenylamine Derivative.

It appeared at the outset that a useful compound to have as a starting point in triphenylamine work would be 4-chloro-4'-bromo-4''-nitrotriphenylamine,



for this has the electron attracting chloro- and bromophenyl groups on the central nitrogen atom, while the nitro-group could be converted into a strongly basic salt forming group by reduction and methylation. Three ways of synthesising this compound, differing in the order of introduction of the -Cl, -Br and $-NO_2$ groups were tried before the successful one: the processes used were adaptions of those of Goldberg and Nimerowsky (Ber., 1907, 40, 2449) and Ullmann (Annalen, 1907, 355, 312).

We tried first to prepare 4-bromotriphenylamine-2'-carboxylic acid, subsequently to be decarboxylated by heating, brominated and nitrated. Heating the p-bromo-

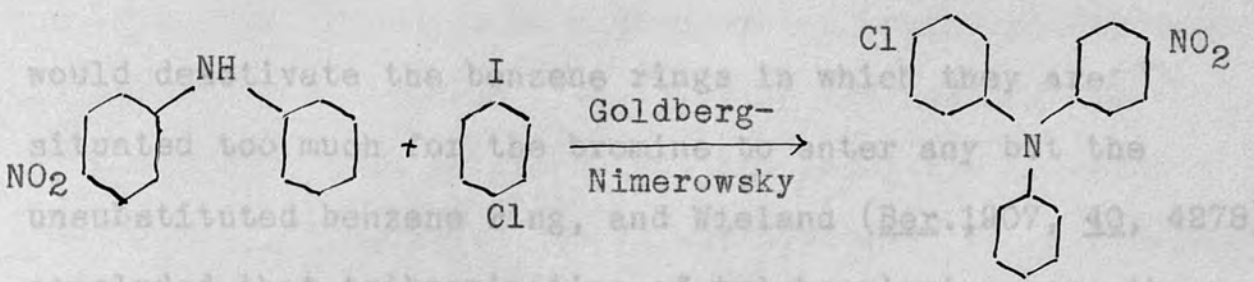
anthranilic acid (or its potassium salt) with p-chloro-iodobenzene (Goldberg and Nimerowsky conditions) gave a yellow solid which could be ground to a powder but went into a tar at 95° with loss of water: it came through a filter in colloidal suspension, could not be crystallised, and analysed to the approximate composition $C_{19}H_{14}O_2NBr,2H_2O$.

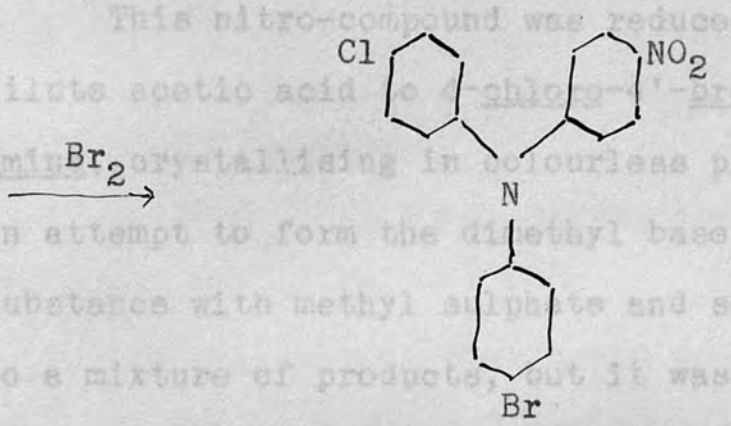
Triphenylamine carboxylic acid was prepared by the Goldberg-Nimerowsky method, but on attempting to brominate this compound, a small quantity of a yellow substance of doubtful composition, probably a mixture, was obtained.

Secondly, heating phenylanthranilic acid, p-chloro-iodobenzene, nitrobenzene, potassium carbonate and a little copper bronze, gave a very small yield of a substance m.p. 164-166°, which was shown by analysis to be 4-chloro-triphenylamine-2'-carboxylic acid. The yield was too small for practical purposes, and with quantities larger than 15 g. of phenylanthranilic acid, the reaction appeared to take an entirely different course.

Thirdly, an attempt to prepare 4-bromo-4'-nitro-triphenylamine from p-nitrodiphenylamine and p-dibromo-benzene by a Goldberg-Nimerowsky type of reaction gave an inseparable mixture.

The synthesis finally adopted for 4-chloro-4'-bromo-4"-nitrotriphenylamine was as follows:-





4-Chloro-4'-nitrotriphenylamine was prepared by the Goldberg-Nimerowsky process from p-nitrodiphenylamine and p-chloroiodobenzene: it is a yellow crystalline substance, m.p. 136-137°. It was brominated in glacial acetic acid and gave a compound analysing as 4-chloro-4'-bromo-4"-nitrotriphenylamine, m.p.217°: it crystallised in two forms, pale yellow regular hexagons and short red rods, the yellow form changing to the red at 179°. Unfortunately we were not able to prove the constitution of this compound, as we had hoped to do, by synthesising it by the other methods already described. However, it seems highly improbable that it has any other orientation than that given to it above. The nitro-group and chlorine atom

would deactivate the benzene rings in which they are situated too much for the bromine to enter any but the unsubstituted benzene ring, and Wieland (Ber.,1907, 40, 4278) concluded that tribromination of triphenylamine gave the 4:4':4"-tribromo-derivative.

This nitro-compound was reduced with iron and very dilute acetic acid to 4-chloro-4'-bromo-4"-aminotriphenylamine, crystallising in colourless plates, m.p. 117°. An attempt to form the dimethyl base by heating this substance with methyl sulphate and sodium hydroxide led to a mixture of products, but it was found that by using an excess of methyl sulphate in this process, the methosulphate of the quaternary salt was formed, and on pouring the aqueous solution into potassium iodide solution, p-(4-chloro-4'-bromodiphenylamino)-phenyl-trimethylammonium iodide separated as colourless plates, and crystallised from ethyl alcohol in colourless needles, m.p. 214-215°. In one case the product crystallised from alcohol in plates: recrystallisation gave needles.

The d-camphor-10-sulphonate of this base was prepared by dissolving the methiodide in dilute ethyl alcohol, adding silver d-camphor-10-sulphonate, boiling and filtering from silver iodide while still hot. The camphor-sulphonate obtained on evaporation to dryness was crystallised from water to free it from traces of silver iodide, and formed white needles, which on air drying

and analysis proved to be a di-hydrate, becoming anhydrous with melting at 145-150°, solidifying and melting again at 245-246°. This substance was too insoluble in water for resolution purposes, so it was dissolved in chloroform and dried over anhydrous sodium sulphate and then crystallised from absolute ethyl alcohol, when it crystallised with one molecule of alcohol, softening at 150°, m.p.245-246°.

Resolution Experiments.

Readings were taken on the yellow 5791 line, and the green 5461 line.

Crystallisation five times from ethyl alcohol gave crops of crystals whose rotation varied only between $[\alpha]^{20°}_{5791}$ +16.8° and +17.4° in chloroform. This corresponds with limits of actual readings of ± 0.01°. In another experiment, the rotations of the first and last crops of twelve successive crystallisations were taken; they had $[\alpha]^{20°}_{5791}$, +16.7° and +16.2°.

Similar results were obtained on crystallising from benzene-chloroform: the limits of $[\alpha]^{20°}_{5791}$ were +15.8° and +16.9°, corresponding with a greatest difference in actual readings of ± 0.035°.

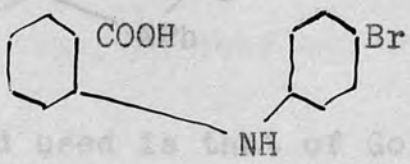
Finally, two crops were obtained using aceto-nitrile as a solvent, and had rotations $[\alpha]^{20°}_{5791}$ +20.10° and +20.6° respectively.

It was concluded that there was no evidence that the substance investigated was anything but homogeneous,

The d-bromocamphorsulphonate of the quaternary base was prepared, but in spite of repeated treatment by processes calculated to induce crystallisation, it has remained a glass, soluble in all solvents, for eight months.

SECTION IV EXPERIMENTAL

Attempted Preparation of 4-Bromotriphenylamine-2'-carboxylic acid.



Method 1

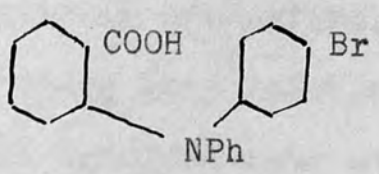
1. Preparation of p-Bromophenylanthranilic acid.

Prepared by Ullmann and Maag, Ber., 1906, 39, 1693.

Potassium o-chlorobenzoate,	40 g.	1 mol.
p-Bromoaniline,	90 g.	2½ mol.
Amyl alcohol,	100 c.c.	
Copper bronze.	0.5 g.	

The above materials were heated together for four hours at 165 - 175°. The resulting mass was made alkaline with sodium hydroxide solution and steam-distilled until the amyl alcohol and most of the excess p-bromoaniline were removed. On acidifying the aqueous solution obtained, the p-bromophenylanthranilic acid was precipitated. It was crystallised first from alcohol, giving 39 g. of slate blue crystals m. p. 170 - 180°. This product crystallised from light petroleum (b. p. 100 - 120°) in colourless plates, m. p. 183°. Yield, 29 g., after recrystallisation. (48% of theory).

2. Preparation of 4-Bromo-2'-carboxy-triphenylamine.



The method used is that of Goldberg and Nimerowsky, Ber., 1907, 40, 2449, as for triphenylamine-2-carboxylic acid, but the quantities employed here are different.

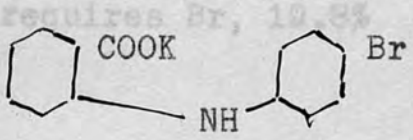
p-Bromophenylanthranilic acid,	15 g.	1 mol.
Iodobenzene,	40 g.	4 mol.
Potassium carbonate,	7 g.	1 mol.
Nitrobenzene,	50 c.c.	
Copper bronze.	0.5 g.	

The above materials were heated for three hours at 215°. The resulting mass was made alkaline with sodium hydroxide solution and steam distilled to remove nitrobenzene, and excess iodobenzene, then filtered and acidified with hydrochloric acid. A yellow powder was precipitated, presumably the 4-bromo-2'-carboxyl-triphenylamine; on drying on a water bath, much water was lost and a black tar remained. The tar was insoluble in hot strong sodium hydroxide solution, but dissolved in sodium carbonate solution; it was reprecipitated with acid, appearing again as a yellow powder, which came through the filter as a colloid on washing with water, and then precipitated again.

Drying on a water bath gave the same tar as before. This material eventually solidified, but could not be obtained crystalline, being very soluble in methyl and ethyl alcohols, glacial acetic acid, benzene and toluene.

Method 2.

1. Preparation of potassium salt of N-p-bromophenylanthranilic acid.



p-Bromophenylanthranilic acid (15 g. 1 mol.) was heated on a boiling water bath with potassium carbonate (4 g., ½ mol.) and a little water, and the aqueous solution evaporated to dryness. The resulting mass was ground up, and dried in an air oven at 150°, giving the potassium salt as a grey powder.

2. Preparation of 4-bromo-triphenylamine-2'-carboxylic acid, using the above anhydrous potassium salt.

The above potassium salt (16.5 g., 1 mol.) was heated for 5 hours at the boiling point with iodobenzene (40 g., 4 mol.) potassium carbonate (7 g., 1 mol.) and nitrobenzene (50 c.c.) with a trace of copper bronze and of potassium iodide as catalysts. The product was steam-distilled in alkaline solution free from nitrobenzene and excess iodobenzene, filtered and cooled, and the solution

acidified. The acid was obtained as a yellow amorphous powder, but on drying on a water bath it went to a tar, which could be ground up but not crystallised from any of the usual solvents.

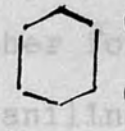
Found: Br, 19.5.

$C_{19}H_{14}O_2NBr$ requires Br, 21.7%

$C_{19}H_{14}O_2NBr, 2H_2O$ requires Br, 19.8%

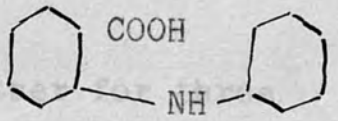
Method 3.

1. Preparation of Potassium o-chlorobenzoate.



Anthranilic acid,	137 g.	1 mol.
Conc. hydrochloric acid,	250 c.c.	$2\frac{1}{2}$ mol.
Sodium nitrite,	70 g.	1 mol.
Copper sulphate,	250 g.	
Sodium chloride	80 g.	
Potassium carbonate,	69 g.	$\frac{1}{2}$ mol.

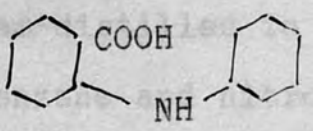
o-Chlorobenzoic acid was prepared from the anthranilic acid by the Sandmeyer diazo process, using the quantities above. The chlorobenzoic acid formed was heated with a little water and the potassium carbonate added gradually until there was no further effervescence. Then the solution was evaporated until it solidified, ground up and dried in an air oven at about 150°. Yield, 185 g.

2a. Preparation of N-phenylanthranilic acid. 

This substance was made by a method due to Ullmann, (Annalen, 1907, 355, 312, [prepn. p. 339]) but the quantities were modified.

Potassium o-chlorobenzoate,	97 g.	1 mol.
Aniline,	140 g.	3 mol.
Amyl alcohol,	250 c.c.	
Copper bronze.	0.5 g.	

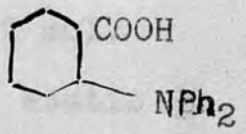
The above materials were heated together for five hours at the boiling point, and the excess aniline and the amyl alcohol distilled off with steam in alkaline solution. The solution was filtered and acidified with hydrochloric acid, when the phenylanthranilic acid was obtained as a white amorphous precipitate. It was crystallised from benzene solution in white needles, (61 g., 57% of theory). m. p. 185°.

2b. Preparation of N-Phenylanthranilic acid. 

The method used here is that of Goldberg, (Ber., 1906, (2), 1691).

Anthranilic acid,	20 g.
Bromobenzene,	32 g.
Potassium carbonate,	20 g.
Copper bronze,	1 g.
Nitrobenzene,	120 c.c.

The above materials were heated together for three hours at the boiling point, and the phenylanthranilic acid worked up from the product by the same method as that described in the last experiment. 28.5 g. (92% of theory) of phenylanthranilic acid was obtained, and crystallised from benzene.

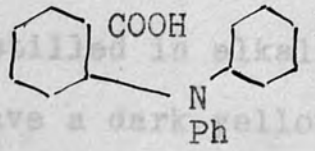
3. Preparation of Triphenylamine-2-carboxylic acid. 

Goldberg and Nimerowsky, Ber., 1907, 40, 2449 (quantities modified).

Phenylanthranilic acid	15 g.	1 mol.
Iodobenzene	40 c.c.	
Potassium carbonate	7.5 g.	
Copper bronze	0.5 g.	
Nitrobenzene	50 c.c.	

The above substances were heated together for $2\frac{1}{2}$ hours at the boiling point, and then steam-distilled in alkaline solution to remove excess iodobenzene and nitrobenzene. The solution was filtered, cooled and acidified with hydrochloric acid, when the triphenylamine-2-carboxylic acid appeared in yellow amorphous aggregates. The product was warmed with a little alcohol to remove unchanged phenylanthranilic acid, and the remaining solid filtered, washed with alcohol and crystallised from benzene, giving yellow crystals, m. p. 208°. Yield, 5 g. (24% of theory).

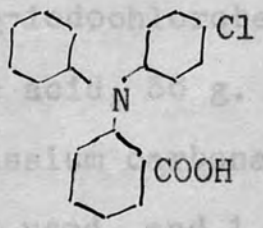
4. Attempted Preparation of 4-Bromo-triphenylamine-2'-carboxylic acid.



Triphenylamine-2-carboxylic acid,	2.89 g.	1 mol.
Bromine,	0.53 c.c.	1 mol.
Glacial acetic acid,	30 c.c.	
Sodium acetate,	1.64 g.	2 mol.

The bromine, dissolved in 5 c.c. of glacial acetic acid, was added drop by drop to the triphenylamine-2-carboxylic acid and sodium acetate in glacial acetic acid solution. The solution was warmed slightly and poured into water; a solid was formed, m. p. 170 - 171°; mixed m. p. with triphenylamine-2-carboxylic acid, 175 - 180°. On crystallisation from benzene, yellow crystals, m. p. 160 - 168° were formed. It was thought probable that the acid had partially dibrominated and a mixture resulted.

Preparation of 4-Chlorotriphenylamine-2'-carboxylic acid.



Phenylanthranilic acid (15 g., 1 mol.) and p-iodo-chlorobenzene (36 g., 2 mols.) were heated under reflux at the boiling point with 60 c.c. of nitrobenzene, potassium

carbonate (5 g., ½ mol.) and a little copper bronze. The product was steam distilled in alkaline solution and the remaining solution gave a dark yellow precipitate on acidification. The acid dried and crystallised twice from light petroleum (b. p. 100 - 120°), giving small yellow prisms, m. p. 164 - 166°, in very small yield, - too small for practical purposes.

Found: Cl, 10.5

$C_{19}H_{14}O_2NCl$ requires Cl, 11.0%.

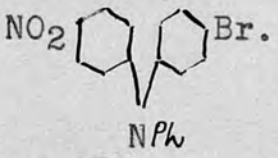
An attempt to repeat the synthesis on double quantities was not successful, the product on acidifying the alkaline extract after steam distillation being separable into three fractions on crystallisation from light petroleum (b.p. 100-120°).

(a) 9.7 g m. p. 185°.

(b) 10.3 g. m. p. 150°.

(c) third crop, gummy mass.

It was also attempted to improve the yield by using a larger excess of p-iodochlorobenzene, taking 7.5 g. (1 mol.) of phenylanthranilic acid, 36 g. (4 mols.) of p-iodochlorobenzene, 2.5 g. potassium carbonate, 30 c.c. nitrobenzene. The above method was used, and 1 g. of yellow crystals (10% of theory) m. p. 157 - 171°, was obtained.



Preparation of 4-Bromo-4'-nitrotriphenylamine.

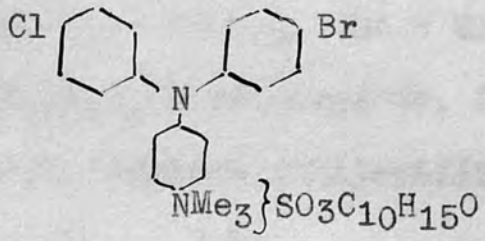
p-Nitrodiphenylamine	21 g.
p-Dibromobenzene	24 g.
Potassium carbonate	7 g.
Nitrobenzene.	80 c.c.

The above substances were heated, together with a trace of copper bronze and potassium iodide, for 30 hours at the boiling point. The p-dibromobenzene (excess having been used) and nitrobenzene were then distilled off in steam, and the remaining tar crystallised from light petroleum, (b. p. 100 - 120°), and then from ethyl alcohol and then from light petroleum (b. p. 100 - 120°) again. Two types of crystal were obtained, the original p-nitrodiphenylamine m. p. 109°, in clusters of light yellow crystals, and also small dark brown prisms, m. p. 165 - 166°. The yellow crystals were removed with a spatula, and the remaining crystals (A) freed from solvent.

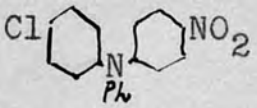
The mother liquor combined with more original material was evaporated, and the residue crystallised from glacial acetic acid and then light petroleum, (b. p. 100 - 120°,) giving crystals m. p. 155 - 160°: this product was then crystallised from absolute ethyl alcohol, and formed dark brown crystals, m. p. 171 - 172° (B). This (B) mixed with

(A) had m. p. 168 - 169°. Therefore (A) and (B) were mixed, and crystallised from absolute ethyl alcohol, giving very small orange prisms. m. p. 171 - 172°.

Preparation and Attempted Resolution of p-(4-Chloro-4'-bromo-diphenylamine-) phenyl trimethyl ammonium d-camphor-10-sulphonate.



1. Preparation of 4-Chloro-4'-nitrotriphenylamine.



The method used here is a modification of the general synthetic process used by Goldberg and Nimerowsky, (Ber., 1907, 40, 2449: see also Piccard and Larsen, J. Amer. Chem. Soc., 1917, 39, 2006).

p-Nitrodiphenylamine,	42 g.	1 mol.
Potassium carbonate,	14 g.	1 atom.
p-Chloroiodobenzene,	48 g.	1 mol.
Nitrobenzene,	160 c.c.	
Copper bronze,	0.5 g.	
Potassium iodide,	0.5 g.	

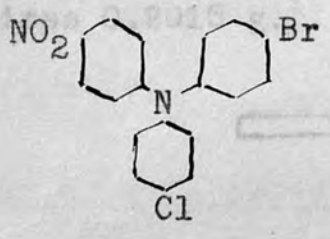
The above materials were heated together under reflux on a metal bath at about 240° for 30 hours. The excess of nitrobenzene and p-chloroiodobenzene was then distilled off in steam, leaving a red-brown tar which solidified on cooling

and standing. This product, 4-chloro-4'-nitrotriphenylamine, when crystallised twice from light petroleum (b. p. 100 - 120°) formed orange micro-crystals, m. p. 135 - 140°. Further crystallisation from ethyl alcohol gave yellow spherical aggregates of plates, m. p. 136 - 137°. Mixed m. p. with p-nitrodiphenylamine, 105°.

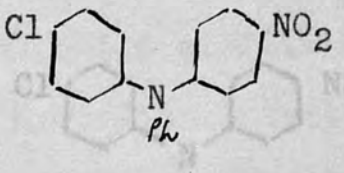
The yield varied from 15 g. - 27.5 g. (33 - 61% of theory).

Found, Cl, 10.7, $C_{18}H_{13}N_2O_2Cl$ requires Cl, 10.9%.

2. Preparation of 4-chloro-4'-bromo-4''-nitrotriphenylamine.

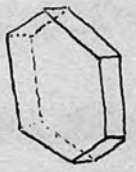


20 g. (1 mol.) of 4-chloro-4'-nitrotriphenylamine



and 7 g. of anhydrous sodium acetate were dissolved in 220 c.c. of glacial acetic acid at about 90°, and 12 g. of bromine (2 atoms) dissolved in 20 c.c. glacial acetic acid was added at this temperature: 4-chloro-4'-bromo-4''-nitrotriphenylamine separated in orange crystals, m. p. 216°, which were filtered off at about 40°.

(Filtering at room temperature allows the separation of an unidentified substance, crystallising from light petroleum (b. p. 100 - 120°) in long yellow needles, m.p. 208°, together with the desired product). Crystallisation from light petroleum (b. p. 100 - 120°) gave two types of crystal, regular pale yellow hexagons (i) and short red rods (ii), both melting at 217°, the yellow form changing to the red at 179°. Yield, 23 g. (92% of theory). Found: 0.2453 g. substance gave 0.1983 g. AgCl + AgBr. $C_{18}H_{12}O_2N_2ClBr$ requires 0.2015 g.



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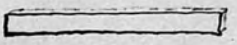
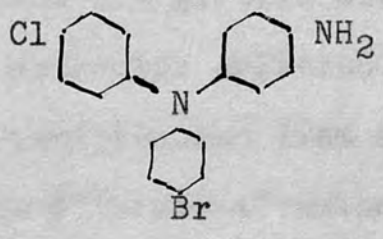


II

3. Preparation of 4-Chloro-4'bromo-4"-aminotriphenylamine.



13 g. of 4-chloro-4'-bromo-4"-nitrotriphenylamine was mixed with 60 g. of iron and a little water, and then heated on a boiling water bath. A few c.c.'s of glacial acetic acid was added, and heating continued until there was no further evidence of reaction; boiling water was

added to the reaction mixture from time to time, as the water present evaporated. When the reaction was finished, the mixture was extracted with about 250 c.c. of alcohol, and the 4-chloro-4'-bromo-4"-aminotriphenylamine precipitated from solution by addition of water. Crystallisation of the solid obtained from methyl alcohol gave colourless plates. m. p. 117°.

Found: 0.3135 g. this substance gave 0.2828 g. AgCl + AgBr.

$C_{18}H_{14}N_2ClBr$ requires 0.2784 g.

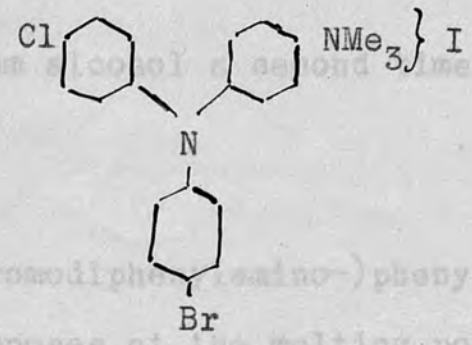
The base formed a hydrochloride, platini-chloride and salicylidene derivative.

3a. Attempted Preparation of 4-Chloro-4'-Bromo-4"-dimethylamino-triphenylamine.

4-Chloro-4'-bromo-4"-aminotriphenylamine (7.5 g., 1 mol.) was shaken with 5.5 g. (2.2 mols.) of methyl sulphate and sodium hydroxide solution. The product was separated by crystallisation from ethyl alcohol into the original 4-chloro-4'-bromo-4"-aminotriphenylamine and a brown gum which could not be identified. This was not gone on with, as it was found (see next preparation) that the methiodide could be obtained without previously isolating the dimethyl base.

4. Preparation of p-(4-chloro-4'-bromodiphenylamino-)phenyl-trimethyl-ammonium iodide.

4. Preparation of p-(4-chloro-4'-bromodiphenylamino-)phenyltrimethylammonium iodide.



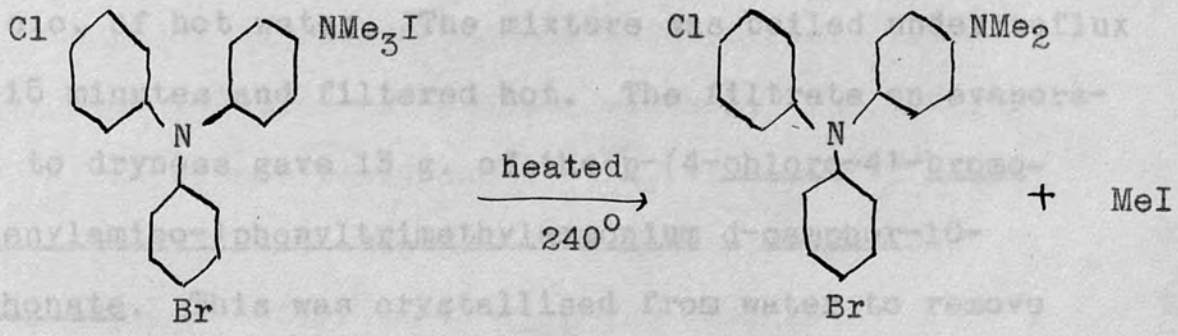
14 g. of 4-chloro-4'-bromo-4"-aminotriphenylamine in about 200 c.c. water was warmed on a water-bath and 56 c.c. of methyl sulphate added gradually in four portions. After each addition of methyl sulphate the reaction mixture was heated on the water-bath for a few minutes and then made alkaline with caustic soda solution. The whole was then heated for about an hour on the water-bath, in presence of caustic soda, and a litre of boiling water added when all went into solution. On cooling, an irridescent precipitate of small white crystals was formed. This redissolved on heating, and the boiling solution was treated with a hot aqueous solution of potassium iodide, when the sparingly soluble methiodide separated in colourless plates, and was cooled and filtered. On crystallisation from methyl alcohol, fine white needles were formed, m.p. 214-215°.

Found: I, 23.4, $C_{21}H_{21}N_2ClBrI$ requires I, 23.4 per cent.

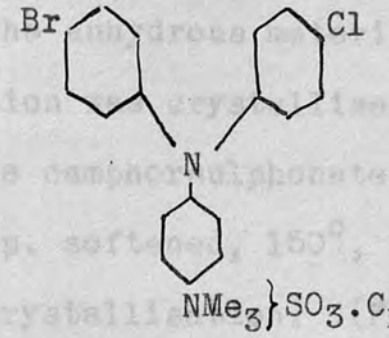
but in one case, the product crystallised from alcohol in the same form as that from the aqueous solution at

its formation, viz., colourless plates, m.p. 215-216°.
Found: I, 23.3 %.
The plates crystallised from alcohol a second time to give needles.
Yield, 12 g.

The p-(4-chloro-4'-bromodiphenylamino-)phenyltrimethylammonium iodide decomposes at the melting point, with loss of methyl iodide. A sample heated in a metal bath at 240° for about half an hour lost methyl iodide and the remainder solidified on cooling, m.p. 84-88°, 4-chloro-4'-bromo-4"-dimethylaminotriphenylamine being formed:-



Preparation of p-(4-Chloro-4'-bromodiphenylamino-)phenyltrimethylammonium d-camphor-10-sulphonate.



The above methiodide (10.88 g.) was dissolved in a mixture of 200 c.c. of absolute ethyl alcohol and 100 c.c. of water. The solution was boiled and treated with a solution of 7.12 g. of silver d-camphorsulphonate in 100 c.c. of hot water. The mixture was boiled under reflux for 15 minutes and filtered hot. The filtrate on evaporation to dryness gave 13 g. of the p-(4-chloro-4'-bromodiphenylamino-)phenyltrimethylammonium d-camphor-10-sulphonate. This was crystallised from water to remove traces of silver salt, and was obtained in glistening white needles, which after being dried in the air proved to be a dihydrate. It melted and became anhydrous at 145-150°, solidified, and then melted again at 245-246°. (0.3286 g. gave 0.1588 g. AgCl + AgBr, $C_{31}H_{36}O_4ClBrN_2S,2H_2O$ requires 0.1592 g. AgCl + AgBr). This hydrate, although a very well defined substance, was much too insoluble in cold water (solubility less than 0.05%) to permit effective

fractional crystallisation for resolution purposes.

The air-dried hydrate was therefore dissolved in chloroform, and the solution dried over anhydrous sodium sulphate. The anhydrous material obtained on evaporation of the solution was crystallised from absolute ethyl alcohol. The camphorsulphonate separated in rhombic crystals (m.p. softened, 150°, melted 245-246°), with alcohol of crystallisation. (Found: C, 57.2; H, 6.2; $C_{31}H_{36}O_4N_2CLBrS,C_2H_6O$ requires C, 57.1; H, 6.1 per cent.)

Resolution Experiments.

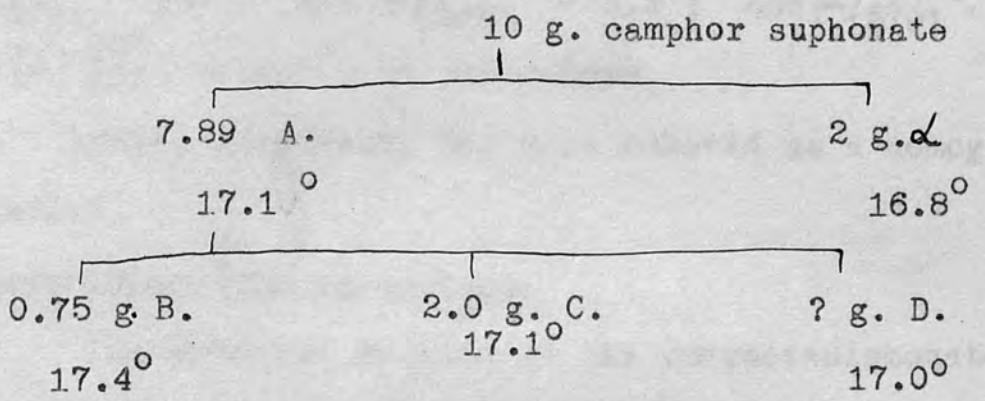
(1) Alcohol as solvent.

10 g. of camphorsulphonate were crystallised slowly from 100 c.c. of absolute alcohol. The 7.8 g. (Crop A) which separated had $[\alpha]^{20°}_{5791} = +17.1°$ and $[\alpha]^{20°}_{5461} = +20.0°$ in chloroform solution. ($\underline{C} = 2.3395$; $\underline{l} = 2$; $[\alpha]^{20°}_{5791} = 0.80°$; $[\alpha]^{20°}_{5461} = +0.95$).

Crop A (7.3 g.) was crystallised from 400 c.c. of absolute alcohol and gave 0.75 g. of Crop B, having $[\alpha]^{20°}_{5791} = +17.4°$ and $[\alpha]^{20°}_{5461} = +20.6°$ in chloroform. The mother liquor from Crop B was evaporated to 200 c.c. and then deposited Crop C (2 g.), with $[\alpha]^{20°}_{5791} = +17.1°$ and $[\alpha]^{20°}_{5461} = 19.9°$. By concentrating further, Crop D was obtained with $[\alpha]^{20°}_{5791} = +17.0$ and $[\alpha]^{20°}_{5461} = +20.1°$.

Evaporation of the mother liquor from Crop A, gave a salt (α) having $[\alpha]^{20°}_{5791} = +16.8°$. and $[\alpha]^{20°}_{5461} = +19.8°$.

These results, given diagrammatically below, with $[\alpha]^{20°}_{5791}$ readings only, show that the salt behaved as a single substance.



Alcohol crystallisation experiments tabulated.

Solvent for rotations, chloroform, $\underline{1} = 2$.

Crop	C	$\alpha^{20°}_{5791}$	$\alpha^{20°}_{5461}$	$\alpha^{20°}_{5791}$	$\alpha^{20°}_{5461}$	$\alpha^{20°}_{5461} / \alpha^{20°}_{5791}$
A	2.3395	+0.80	+0.95	+17.1	+20.0	1.17
B	2.3080	+0.805	+0.95	+17.4	+20.6	1.18
C	2.3135	+0.79	+0.92	+17.1	+19.9	1.17
D	2.3180	+0.79	+0.93	+17.0	+20.1	1.18
α	2.3510	+0.79	+0.93	+16.8	+19.8	1.18

Mean $[\alpha]^{20°}_{5791} = +17.1°$

Limits, $16.8° - 17.4°$ i.e., $\pm 0.3°$. This corresponds with limits of readings less than $\pm 0.01°$.

2. Another experiment with alcohol as solvent.

Another attempt at resolution was made as follows:- 20 g. of the camphor sulphonate were crystallised twelve times from absolute alcohol, and rotations determined of the sixth and the twelfth crops. These had respectively, $[\alpha]^{20^\circ}_{5791}$ +16.7° and $[\alpha]^{20^\circ}_{5461}$ +20.3°; and $[\alpha]^{20^\circ}_{5791}$ +16.2° and $[\alpha]^{20^\circ}_{5461}$ +19.7°, in chloroform.

Again, therefore, the salt behaved as a homogeneous material.

3. Benzene-Chloroform as solvent.

The air-dried hydrate of the camphorsulphonate was dissolved in chloroform, and the solution dried over anhydrous sodium sulphate. The material (16.3 g.) obtained by evaporation was dissolved in 200 c.c. of a mixture of benzene (2 volumes) and chloroform (1 volume). On keeping, crop A crystallised in colourless plates (15.1 g.) which were dried in a high vacuum over silica gel., and then weighed 14.85 g. Check experiments were carried out simultaneously with other material in order to make certain that the salt after being so dried attained constant weight and was not hygroscopic, although its behaviour on heating (m. p. first 145 - 150°, and then 245 - 246°), showed that it had solvent of crystallisation.

Crop A had $[\alpha]^{20^\circ}_{5791}$ =+15.8°, and $[\alpha]^{20^\circ}_{5461}$ +18.8°.

It was crystallised from 300 c.c. of a mixture of two volumes of benzene with one volume of chloroform and gave crop B (6.35 g.) having $[\alpha]^{20°}_{5791} = +16.9°$ and $[\alpha]^{20°}_{5461} = 19.8$. Crystallisation of B from 100 c.c. of the same solvent gave crop C with $[\alpha]^{20°}_{5791} +16.7°$ and $[\alpha]^{20°}_{5461} +19.4°$. Evaporation of the mother liquor from B gave crop E, having $[\alpha]^{20°}_{5791} = +16.4°$ and $[\alpha]^{20°}_{5461} = +19.5°$. This set of experiments shows that no resolution had occurred:

16.3 g. (anhydrous salt)
|
14.85 g. A.
+15.8°

B. 6.35 g. +16.9°
C. 1.9 g. +16.7°
Residue 3.85 g.

E. 6.9 g. 16.4°
Residue 0.35 g.

Benzene-chloroform crystallisation experiments tabulated.

Crop	C	$[\alpha]^{20°}_{5791}$	$[\alpha]^{20°}_{5461}$	$[\alpha]^{20°}_{5791}$	$[\alpha]^{20°}_{5461}$	$[\alpha]^{20°}_{5461} / [\alpha]^{20°}_{5791}$
A	2.3840	+0.755°	+0.895	+15.8	+18.8	1.19
B	2.2320	+0.755°	+0.885	+16.9	+19.8	1.17
C	2.3220	+0.775°	+0.90	+16.7	+19.4	1.16
E	2.2560	+0.74°	+0.88	+16.4	+19.5	1.19

Mean. $[\alpha]^{20^\circ}_{5791} = 16.45^\circ$

Limits, $15.8^\circ - 16.9^\circ$, i.e. $- 0.65^\circ + 0.45^\circ$ ie. on either side of the average. These correspond with greatest difference in actual readings of 0.035°.

4. Acetonitrile as solvent.

The anhydrous salt (3 g.) was crystallised from acetonitrile, when 0.95 g. of crop A (plates) were obtained: having $[\alpha]^{20^\circ}_{5791} + 17.0^\circ$, $[\alpha]^{20^\circ}_{5461} + 20.1^\circ$. Concentration of the mother liquor from A gave crop B (needles) with $[\alpha]^{20^\circ}_{5791} = +17.1^\circ$ and $[\alpha]^{20^\circ}_{5461} + 20.6^\circ$.

SECTION V

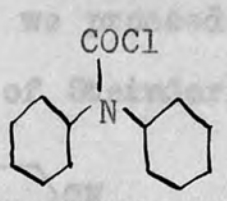
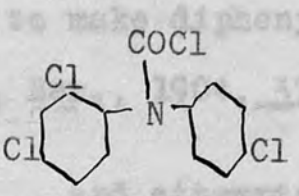
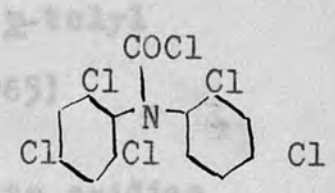
Preparation of Carbamyl Chlorides of Substituted Diphenylamines, and attempts to prepare the Derived Esters.

Our aim in this series of experiments was to make the carbamyl chlorides of the unsymmetrical halogenodiphenylamines prepared by Chapman's process, and then proceed to form l-menthyl and d-bornyl esters.

We first used Erdmann and Huth's process, (J. prakt. Chem., 1897, (ii), 56, 7), to prepare diphenyl carbamyl chloride: phosgene is passed into a solution in carbon-tetrachloride of diphenylamine and pyridine, the reaction taking place at room temperature. When this method was used to prepare 2:4:4'-trichlorodiphenylcarbamyl chloride, it failed: so did many other attempts, and the method finally adopted was that of passing phosgene gas into the melted 2:4:4'-trichlorodiphenylamine at 150 - 200°. The method was so simple and effective, that we tried it on diphenylamine itself, and found it a great improvement on the Erdmann and Huth process. Using a temperature of 140 - 150° we obtained a yield of 92% after crystallisation from ethyl alcohol, while by the old method we obtained only 50% of the theoretical yield.

Neither this method, nor any of the others tried, was of any avail with 2:4:6:2':4'- pentachlorodiphenylamine.

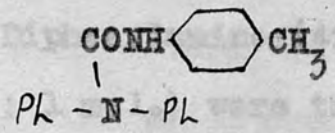
This is an interesting point, as it emphasises the fact already indicated that the chlorine atoms greatly decrease the reactivity of the nitrogen atom.

			
Mode of introduction of phosgene.	1. With pyridine at room temp.	1. Sealed tube at 120-160°	Impossible to prepare under all conditions tried.
	2. 140-150°	2. 150-200°	

Unsuccessful attempts were made to prepare the l-menthyl and d-bornyl esters from diphenylcarbamyl chloride using the method given by Herzog, (Ber., 1907, 40, 1833), for diphenylcarbamyl derivatives of phenols, that is, to heat the phenol with the carbamyl chloride in pyridine. However, it was found that if sodium l-menthoxide was prepared first, diphenyl carbamyl chloride reacted with it to give the desired ester, which crystallised from ethyl alcohol in clusters of angular plates, m. p. 98 - 99°: but using this method to prepare l-menthyl- and d-bornyl-2:4:4'-trichlorodiphenylcarbamate resulted in a glass which could not be crystallised. A similar glass was obtained on attempting to form p-tolyl 2:4:4'-trichloro-diphenylcarbamate, although this carbamyl

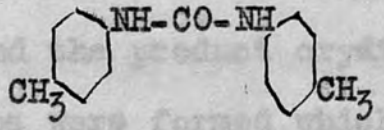
chloride reacted with aniline to form a crystalline anilide N-phenylcarbamyl 2:4:4'- trichlorodiphenylamine.

Having succeeded in the preparation of an anilide of this type, we proceeded to make diphenyl-p-tolyl urea, (method of Steindorff, Ber., 1904, 37, 965)



and attempted to oxidise the $-CH_3$ group to -COOH. The attempt was unsuccessful and so work on these lines was abandoned.

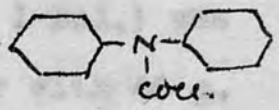
It is an interesting point that when diphenyl p-tolyl urea is boiled with excess of p-toluidine, di-p-tolyl urea,



is formed: we had found previously that N-phenylcarbamyl 2:4:4'-trichlorodiphenylamine was not affected by boiling aniline.

SECTION V. EXPERIMENTAL

Preparation of Diphenylcarbamyl chloride and derived Esters

1. Preparation of Diphenylcarbamyl chloride. 

Method 1. Erdmann and Huth, (J. prakt. Chem. 1897, (ii), 56, 7.)

Diphenylamine (42 g.; 1 mol.) and pyridine (20 g.; 1 mol.) were taken in carbon tetrachloride solution, and phosgene passed in at room temperature until there was no further precipitate of gummy pyridine hydrochloride. Ice and dilute hydrochloric acid were then added, and the carbon tetrachloride layer separated and dried over calcium chloride. The solution was evaporated to dryness and the product crystallised from ethyl alcohol. Pink plates were formed which became darker in the air, m. p. 84°. Yield, 30 g. (50% of theory).

Method 2. The following method based on the one worked out for trichlorodiphenyl carbamyl chloride was found to be simpler and more efficient. Phosgene was passed over 10 g. of diphenylamine at 140 - 150° for 1 hour, then air was bubbled through to remove excess phosgene. the product, 13 g., solidified, and on crystallisation from ethyl alcohol gave white plates, m. p. 87 - 88°. Yield, 92% of theory.

2. Attempted preparation of l-Menthyl diphenylcarbamate. $Ph_2NCOOC_{10}H_{19}$

The method employed was that used by Herzog, (Ber., 1907, 40, 1833) for diphenylcarbamyl derivatives of phenols.

Diphenylcarbamyl chloride (11.5 g., 1 mol.) was heated on a boiling water bath for an hour with 46 g. of pyridine and 8 g., (1 mol.) of l-menthol. The product was stirred with dilute hydrochloric acid, and solidified. Crystallisation from ethyl alcohol gave pink plates m. p. 76 - 80°. Mixed m. p. with diphenylcarbamyl chloride, 84°. Therefore the preparation was not successful.

3. Attempted preparation of d-Bornyl diphenylcarbamate. $Ph_2N.COOC_{10}H_{17}$

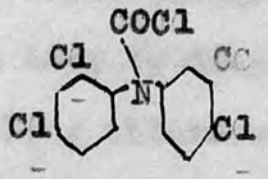
The method used was the same as that described in the last experiment. 11.5 g. (1 mol.) of diphenylcarbamyl chloride was heated with 46 g. of pyridine and 8 g. (1 mol.) of d-borneol. The result, unsuccessful, was the same as in the case of the menthyl ester.

4. Preparation of l- Menthyl diphenylcarbamate. $Ph_2N.COOC_{10}H_{19}$

l-Menthol,	$C_{10}H_{19}OH$,	7.3 g.	> 1 mol.
Sodium,		1 g.	1.2 atoms.
Toluene,		50 c.c.	
Diphenylcarbamyl chloride,		5 g.	< 1 mol.

The powdered sodium , toluene, and 7 g. of menthol were boiled for three hours: some sodium remained undissolved, so a further 3 g. of menthol was added: on boiling for a further two hours and leaving overnight, the sodium dissolved. 5 g. of diphenylcarbamyl chloride was added; heat was developed, and the solution was heated under reflux for half an hour. The solution was made acid with hydrochloric acid, and steam-distilled to remove toluene and menthol. The l-menthyldiphenylcarbamate separated as a gum, solidified, and crystallised from ethyl alcohol in clusters of angular plates, m. p. 98-99°.

Preparation of 2:4:4'-Trichlorodiphenylcarbamyl chloride



Method 1. (Unsuccessful.)

2:4:4'-Trichlorodiphenylamine (5.5 g., 1 mol.) and pyridine (1.6 g., 1 mol.) were taken in 50 c.c. of toluene, and phosgene paased in at 90°. The crystalline product obtained had m. p. 61°, and mixed m. p. with 2:4:4'-trichlorodiphenylamine, 66°.

Method 2. (Unsuccessful)

An attempt was made to prepare the 2:4:4'-trichlorodiphenylamine carbamyl chloride by way of the sodium derivative of 2:4:4'-trichlorodiphenylamine, (Titherley, J. 1897, 71, 460 describes the preparation of sodiudiphenylamine). 2:4:4'-Trichlorodiphenylamine (2.7 g., 1 mol.) was heated with sodamide (0.4 g., 1 mol.) at 120°. The mixture was cooled and then boiled for 5 minutes with excess ethyl chloroformate (Cl.COOEt.) in light petroleum. The excess ethyl chloroformate was evaporated off, and the remainder poured into water, and the resulting solid crystallised from ethyl alcohol Its m. p., 66°, showed it to be the unchanged 2:4:4'-trichlorodiphenylamine.

Method 3. Unsuccessful).

The 2:4:4'-trichlorodiphenylamine in chloroform solution was added drop by drop to a saturated solution of phosgene in boiling chloroform. The product after evaporation of the chloroform was unchanged 2:4:4'-trichlorodiphenylamine, m. p. 66°.

Method 4. (Unsuccessful).

The last experiment was repeated in boiling toluene and met with similar lack of success.

Method 5.

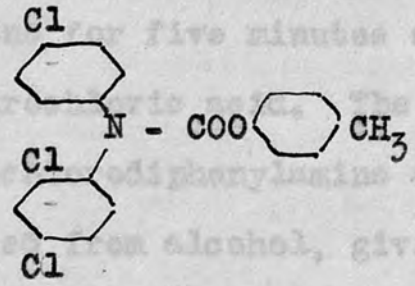
2 g. of 2:4:4'-trichlorodiphenylamine was heated in a sealed tube at 120-160° for one hour with a solution of phosgene in toluene. On evaporation of the toluene, a solid, 2:4:4'-trichlorodiphenylcarbamyl chloride remained, crystallising in needles, m. p. 114-115° from ethyl alcohol.

Method 6.

10 g. of 2:4:4'-trichlorodiphenylamine was heated to 150-200° and phosgene passed through until there was no further evolution of hydrochloric acid gas, (this took about 1 hour). The product 2:4:4'-trichlorodiphenylcarbamyl chloride solidified and crystallised from ethyl alcohol in needles, m. p. 117-118°. Yield, 8.5 g. (68% of theory.)

Found: Cl, 42.3% $C_{13}H_2ONCl_4$ requires Cl, 42.4%

Attempted Preparation of p-Tolyl 2:4:4'-Trichlorodiphenyl carbamate



Herzog, (Ber. 1907, (40), 1883), describes the preparation of diphenylcarbamyl derivatives of phenols.

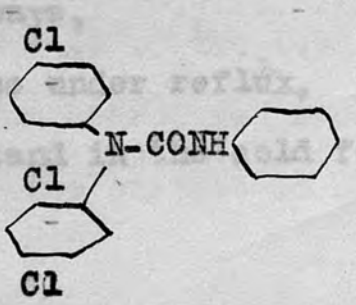
p-Cresol, 1 g.

2:4:4'-Trichlorodiphenyl carbamyl chloride, 1g.

pyridine, 10cc.

The above substances were heated together on a water bath for an hour. The product was dissolved in chloroform, washed successively with dilute hydrochloric acid, water and dilute sodium hydroxide. It was dried over anhydrous sodium sulphate, and the chloroform evaporated off. A clear gum was obtained soluble in every solvent except water: it was not found possible to crystallise it.

Preparation of N-Phenylcarbamyl-2:4:4'-trichlorodiphenylamine

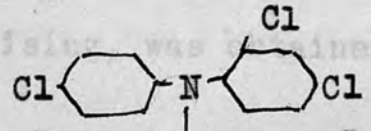


2:4:4'-Trichlorodiphenylcarbamyl chloride was boiled with excess of aniline for five minutes and then poured into dilute hydrochloric acid. The solid N-Phenylcarbamyl-2:4:4'-trichlorodiphenylamine obtained was filtered and crystallised from alcohol, giving colourless needles, m. p. 201 - 202°.

Found: Cl, 26.9

$C_{19}H_{13}ON_2Cl_3$ requires Cl, 27.2%.

Attempted Preparation of l-Menthyl 2:4:4'-trichlorodiphenylcarbamate.



(l-menthyl $C_{10}H_{19}O$)

Sodium 1 g.

Toluene, 100 c.c.

l-Menthol, 10 g. (1½ mols.)

2:4:4'-Trichlorodiphenylcarbamyl chloride, 7.5 g. (1 mol.)

The sodium was powdered and heated under reflux with the menthol in toluene solution until it had all dissolved, (this took about three hours). The trichlorodiphenylamine was added, and the solution treated in either of two ways,

(a) heated for ten minutes under reflux,

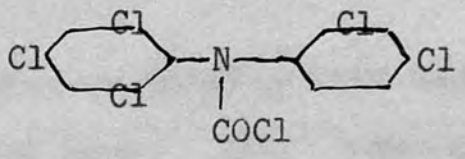
(b) shaken and left to stand in the cold for half an hour.

The excess menthol and toluene were distilled off in steam in weakly acid solution, which was then extracted with chloroform, and the chloroform solution dried over anhydrous sodium sulphate. On evaporation of the chloroform, a clear glass remained which could not be crystallised from any of the many solvents tried.

Attempted preparation of d-Bornyl-2:4:4'-trichlorodiphenylcarbamate

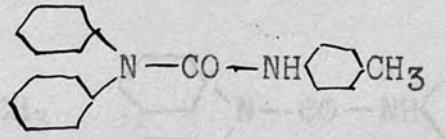
The above experiment was repeated, using d-borneol in place of the l-menthol. A similar glass, not solidifying or crystallising, was obtained

Attempted preparation of 2:4:6:2':4'-Pentachlorodiphenyl carbamyl chloride.



(1) 2:4:6:2':4'-Pentachlorodiphenylamine was heated at 150-200° and phosgene passed through it for one hour. The product on crystallisation of the resulting mass from ethyl alcohol proved to be the original base.

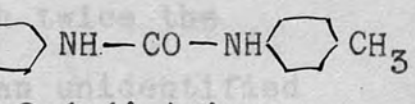
(2) 2:4:6:2':4'-Pentachlorodiphenylamine (5 g.) was placed in a sealed tube with 20 c.c. toluene which had previously been saturated with phosgene at 0°. The tube was heated gradually to 220 - 230° in two hours, and kept at this temperature for four hours. The product on crystallisation was the original base, m. p. 94°

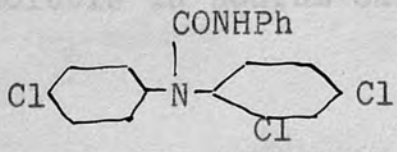
Preparation of Diphenyl-p-tolyl urea. 

Steindorff. (Ber., 1904, 37, 965), gives the following method which we used.

Diphenyl carbamyl chloride (12.5 g., 1 mol.) and p-toluidine (12.5 g., 2 mols.) were heated together on a water bath for an hour. The excess p-toluidine was removed by shaking with dilute hydrochloric acid and the residue crystallised from ethyl alcohol, giving 11.8 g. (77% of theory) of colourless needles, m. p. 131 - 132°. (Steindorff gives 130°).

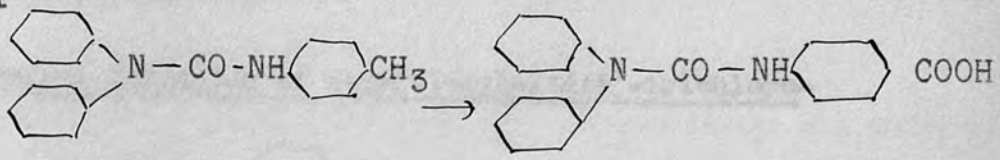
Note.

Diphenyl-p-tolyl-urea on boiling with excess p-toluidine gives s-di-p-tolyl urea, 

We found previously that N-phenylcarbamyl 2:4:4'-trichlorodiphenylamine, 

was not affected by boiling with aniline.

Attempted Oxidation of Diphenyl-p-tolyl urea to Diphenyl-p-carboxyphenyl urea.



First Method.

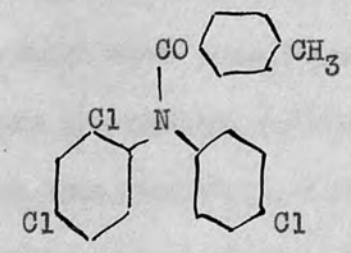
The urea (5 g., 1 mol.) was boiled for an hour with stirring with 5.5 g. (2 mols) of potassium permanganate and 1 g. (2 mols.) of magnesium sulphate ($MgSO_4,7H_2O$) in aqueous solution. The colour of the potassium permanganate went entirely, and after passing carbon-dioxide through the solution the product obtained was quite insoluble in sodium carbonate solution. 4 g. of the original urea was recovered, m. p. 130°.

Second Method.

Repeating the above experiment with twice the quantity of potassium permanganate gave an unidentified product, not readily soluble in sodium carbonate solution, m. p. above 310°.

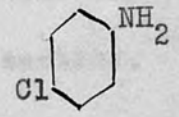
SECTION VI.

Preparation and attempted Oxidation of N-p-Toluoyl-2:4:4'-trichloro-diphenylamine.

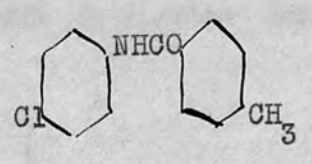


The Chapman process made it possible to synthesis benzoyl derivatives of diphenylamines when these substances could not be prepared by direct benzoylation. We decided to use this method to prepare an unsymmetrical p-toluoyldiphenylamine, oxidise the $-CH_3$ group to -COOH and then examine the alkaloidal salts. A method of carrying out this oxidation has not yet been found.

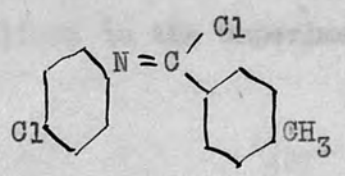
The preparation is done in the following stages:-



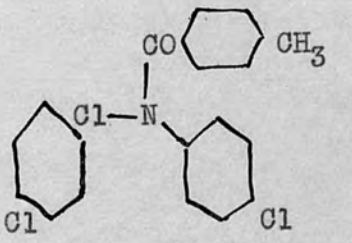
p-Chloroaniline



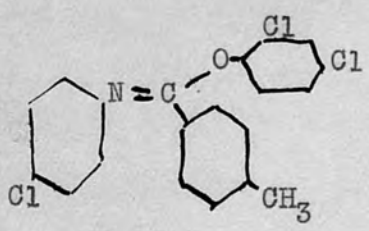
p-Toluoyl-p-chloro-aniline



p-Chloroaniline-p-tolylimino-chloride



N-Toluoyl-2:4:4'-trichloro-diphenylamine.



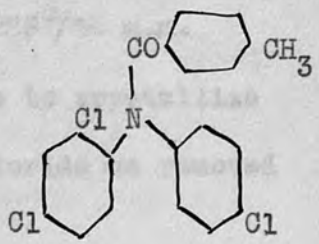
p-Chloroaniline-p-tolylimino-2:4-dichlorophenyl ether.

p-Toluoyl-p-chloroaniline was prepared by the usual method for the corresponding benzoyl derivatives, from p-chloroaniline, p-toluoyl chloride and aqueous caustic soda solution. The imino-chloride was made by heating this substance with phosphorus pentachloride and distilling in vacuo. Adding this in ethereal solution to excess of sodium ethoxide and dichlorophenol in absolute ethyl alcohol gave p-chloroaniline-p-tolylimino-2:4-dichlorophenyl ether. This substance was formed as a clear golden glass, and could not be obtained crystalline. It was used in this state for the next stage, and the fact that the product analysed correctly was taken as a proof that the foregoing imino ether had the constitution assigned to it. Heating the glass at 280-300° for 2½ hours gave N-toluoyl-2:4:4'-trichlorodiphenylamine, crystallising in small irregular prisms, m.p. 157°.

Six methods of oxidation of this substance to the corresponding acid were tried with no success: they are outlined in the experimental section.

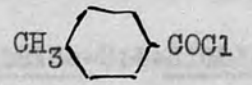
SECTION VI. EXPERIMENTAL.

Preparation of N-p-Toluoyl-2:4:4'-trichlorodiphenylamine.



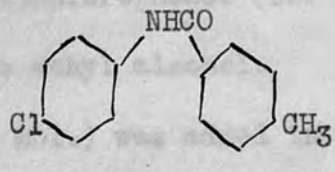
The method used is that employed by A. W. Chapman for benzoyldiphenylamines.

(a) Preparation of p-Toluoyl chloride.



p-Toluic acid((13 g., 1 mol.) and thionyl chloride (272 g., excess of two mols.) were heated under reflux for one hour. On distillation p-toluoyl chloride (145 g., 94 % of theory) was obtained, b.p. 220°-221°, as a colourless, highly refractive liquid, with a sharp smell, and lachrymatory.

(b) Preparation of N-p-Toluoyl-p-chloroaniline.

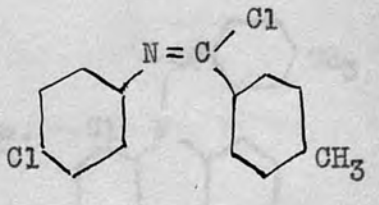


p-Chloroaniline (120 g., 1 mol.) was mixed with 40 g. (1 mol.) of sodium hydroxide and about 500 c.c. of water, and p-toluoyl chloride (145 g., 1 mol.) added gradually with shaking. N-p-Toluoyl-p-chloroaniline was formed as a white solid, crystallised from ethyl alcohol in thin angular plates, m.p. 212°.

Yield, 115 g., (50% of theory).

Found; Cl, 14.45, $C_{14}H_{12}ONCl$ requires Cl, 14.44 per cent.

(c) Preparation of p-Chloroaniline-p-tolylimino-chloride.

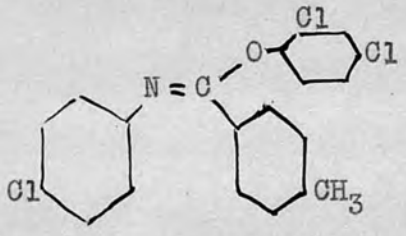


p-Toluoyl-p-chloroaniline (82 g., 1 mol.) and phosphorus pentachloride (70 g. 1 mol.) were heated together in dry conditions on a boiling water-bath until

all was clear liquid. Phosphorus oxychloride was removed by distillation in vacuo, and the imino chloride distilled, b.p. 220-225°/40 m.m. It solidified in yellow needles, but could not be made to crystallise from any solvent; nor could an impurity of benzoyl chloride be removed by distillation.

Yield 81.5 g., (88% of theory).

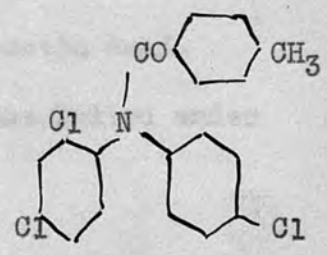
(d) Preparation of p-Chloroaniline-p-tolylimino-2:4-dichlorophenyl ether.



Sodium (10 g., 1¼ mols.) followed by 2:4-dichlorophenol (136 g., 2½ mols.) were dissolved in 500 c.c. of absolute ethyl alcohol. p-Chloroaniline-p-tolylimino chloride (81·5g., 1 mol.) was added in dry ethereal solution, and the whole shaken and left to stand overnight. The ether and most of the alcohol were distilled off, and the remainder poured into water containing 40 g. (3 mols.) of sodium hydroxide. The p-chloroaniline-p-tolylimino-2:4-dichlorophenyl ether was extracted with chloroform; on drying and evaporation of the chloroform, a clear golden glass was obtained which was impossible to crystallise. It was used in this state for the next stage.

Yield, 108 g., (90% of theory).

(e) Preparation of N-Toluoyl-2:4:4'-trichlorodiphenylamine.

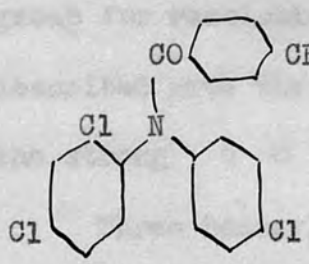


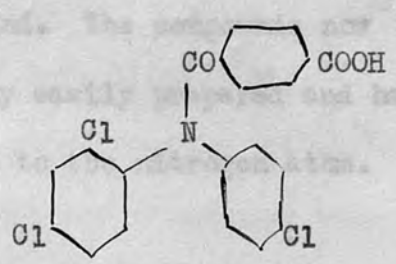
80 g. of the above glassy p-chloroaniline-p-tolylimino-2:4-dichlorophenyl ether were heated

for 2½ hours at 280-300°. The resulting black glass was crystallised successively from light petroleum (b.p. 80-100°) ethyl alcohol (twice) and glacial acetic acid, giving the p-toluoyl-diphenylamine in small irregular prisms, m.p. 157°.

Found: Cl, 27.2 $C_{20}H_{14}ONCl_3$ requires Cl, 27.3 per cent.

Attempted Oxidation of N-p-Toluoyl-2:4:4'-trichlorodiphenylamine to N-p-Carboxylbenzoyl-2:4:4'-trichlorodiphenylamine.





It was found impossible to obtain the desired acid using any of the following methods of oxidation:-

(1) Excess aqueous potassium permanganate, with the compound dissolved in acetone: boiled under reflux.

(2) Aqueous potassium permanganate, with the compound dissolved in nitrobenzene: boiled under reflux.

(3) The compound dissolved in ether was left in the cold with aqueous potassium permanganate.

(4) One mol. of the diphenylamine derivative was boiled with calcium permanganate in acetone solution.

(5) The compound was boiled with chromic oxide in glacial acetic acid.

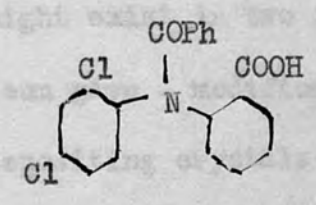
(6) The diphenylamine derivative in nitrobenzene solution was boiled under reflux with 30 per cent. aqueous nitric acid

SECTION VII

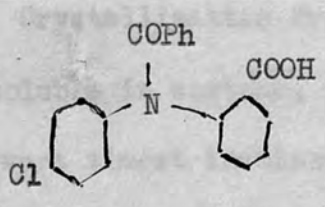
Preparation of Asymmetric Benzoyldiphenylamines containing the Carboxylic acid group.

After failing to oxidise p-toluoyltrichlorodiphenylamine to the corresponding carboxylic acid, another way of introducing an acid group for resolution purposes had to be found. The compounds now described have the advantage of being fairly easily prepared and have the strong C O dipole directly attached to the nitrogen atom.

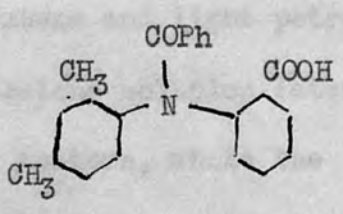
Three benzoyl diphenylamines,



Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid.



Benzoyl-4-chlorodiphenylamine-2'-carboxylic acid.



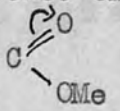
Benzoyl-2:4-dimethyldiphenylamine-2'-carboxylic acid.

have been prepared by a modified Chapman process, using methyl salicylate as the phenolic group.

An interesting point in the preparations is that the reaction:-

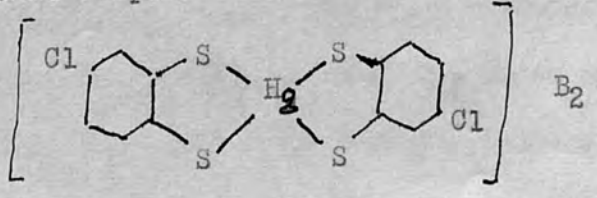
iminoether ⟶ benzoyl derivative

was in each of the three cases exothermic and took place very quickly. This must be due to the carbomethoxy group which is present in each molecule: according to Chapman, the ease of migration is facilitated

by substituents in the migrating group which would increase the strength of the corresponding acid. The carbo methoxy group  should certainly have this effect to a far greater extent than any of the groups examined by Chapman, and is therefore probably responsible for the phenomenon.

The monochloro compound was examined for optical activity by means of its strychnine and brucine salts. No conclusive evidence of optical activity was obtained, although small differences of rotation were observed in crops obtained by fractional crystallisation, and these values changed slightly on heating for some hours in sealed tubes. However, there were undeniable indications that the strychnine salt might exist in two forms. Crystallisation from benzene and light petroleum gave a modification soluble in acetone, the acetone solution later depositing crystals which were almost insoluble in acetone, while the form obtained by crystallisation from methyl alcohol was also almost insoluble in acetone; it is of course possible that this behaviour can be explained by solvation. When the strychnine and brucine salts were crystallised from various solvents, very often almost exactly half of the theoretical quantity of salt was deposited, suggesting the presence of two forms of differing solubility.

This is reminiscent of the work of Mills and Clark (J., 1936, 175) who prepared the metal complex

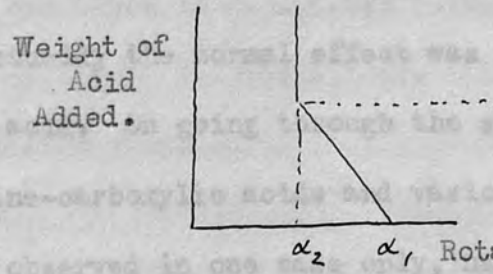


and found two forms, α and β, of the quinine salt having different solubilities. These were concluded to be the diastereoisomers lA1B and dA1B, altough no evidence of mutarotation was obtained.

The Effect of Excess of Acid on these Alkaloidal Salts.

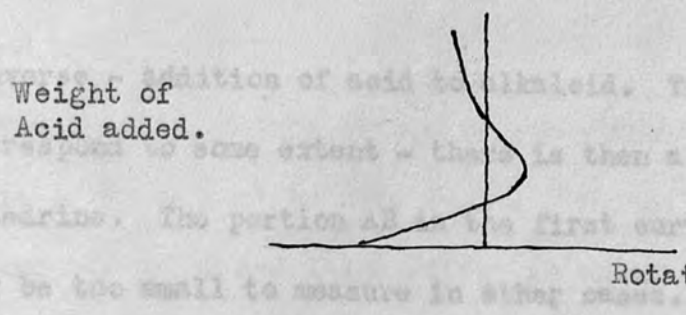
The effect of excess of acid on the rotation of the alkaloidal salts of the above acids has been studied, and proves very interesting. The procedure was to take a solution of the alkaloid in a polarimeter tube and take its rotation; then to add small weighed quantities of the acid to be investigated, taking the rotation after each addition: the weight of acid added was then plotted against the rotations.

The expected result, what might be called the normal effect, was that the rotation should change linearly to a definite value, that of the partial racemate, and then be unaffected by further addition of acid, giving a graph thus:-



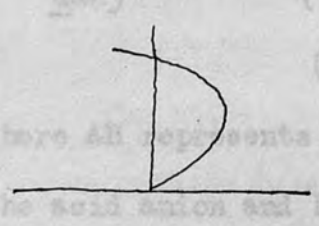
where α_1 is the rotation of the alkaloid and α_2 that of the partial racemate. Curves of this type were obtained by the addition of symmetrical acids such as o-nitrobenzoic acid, salicylic acid and triphenylamine-2-carboxylic acid to nor-d-ψ-ephedrine and brucine.

When we repeated this process with the three new acids, very different curves were obtained. For example, adding the monochloro- and dichloro-acids to brucine gave curves of this type:-

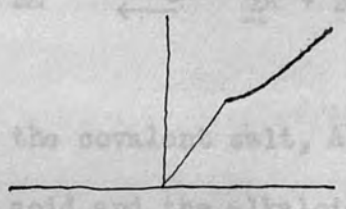


and similar departure from the normal was observed with nor-d-ψ-ephedrine and strychnine: the effect was seen in benzene and chloroform solution, but not in methyl and ethyl alcohol.

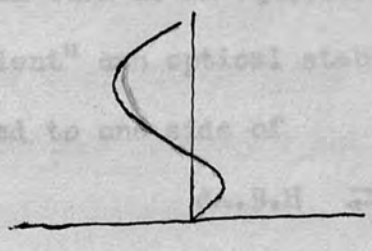
Making the addition in the opposite way, i.e. adding the alkaloid to the acid, would be expected to give a curve like this



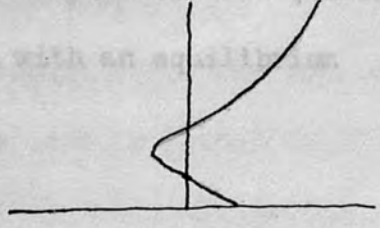
or like this



depending on whether the sign of the rotation of the partial racemate is the same as or different from that of the alkaloid itself. That this was actually the normal effect was shown by adding nor-d-ψ-ephedrine to benzoic acid. On going through the same procedure with the benzoyl-diphenylamine-carboxylic acids and various alkaloids, the anomalous effect was observed in one case only, namely, the addition of nor-d-ψ-ephedrine to the dichloro-acid. The first curve shows the observations from this addition and the second for the



nor-d-ψ-Ephedrine to acid.



Acid to nor-d-ψ-ephedrine.

converse - addition of acid to alkaloid. The regions AB in each graph correspond to some extent - there is then a large excess acid over nor-d-ephedrine. The portion AB in the first curve is very small indeed, and may be too small to measure in other cases. At any rate, the change in rotation due to the addition of the optically active alkaloid may mask the necessarily much smaller effect due presumably to activation.

The mechanism which we suggest to explain this change in rotation, is as follows:-

$$\left.\begin{matrix} \underline{l}AH \\ \underline{d}AH \end{matrix}\right\} + B \rightleftharpoons \left\{\begin{matrix} \underline{d}A.BH & \underset{CHCl_3}{\overset{ROH}{\rightleftharpoons}} & \underline{d}A^- \}BH^+ & \rightleftharpoons & \underline{d}A^- + BH^+ \\ \underline{l}A.BH & \underset{CHCl_3}{\overset{ROH}{\rightleftharpoons}} & \underline{l}A^- \}BH^+ & \rightleftharpoons & \underline{l}A^- + BH^+ \end{matrix}\right.$$

(Covalent)

where AH represents the unionised acid, A.BH the covalent salt, A^- the acid anion and BH^+ the base cation. The acid and the alkaloid combine first to form a covalent compound (there is evidence that such a compound can exist in an aprotic solvent; c.f. Glasstone's "Electrochemistry of Solutions," pp. 173-174.) which is in equilibrium with the electrovalent salt:

$$R.N\begin{matrix} H \\ H \\ \searrow HOOC.R' \end{matrix} \rightleftharpoons R.N\begin{matrix} H \\ H \\ H^+ \end{matrix}\}OOCR'$$

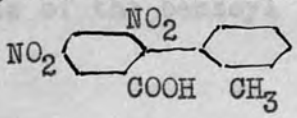
this in turn is in equilibrium with its ions. Only in the state marked "covalent" can optical stability be maintained with an equilibrium shifted to one side of

$$\underline{d}A.B.H \rightleftharpoons \underline{l}A.B.H$$

The mechanism of this change is shown above as a reversible process, one side of which must be more facile than the other, that is to say, the compounds dA.BH and lA.BH differ in energy content so that there is preferential formation of one of them. It must be assumed that the ions of the acid cannot preserve their asymmetry: addition of excess of acid drives back the dissociation to such an extent that the inequality of this equilibrium causes measurable changes in the rotation.

If this explanation is correct, the effect should be annulled by an ionising solvent: this has been shown by the "normal" behaviour of the above acids in methyl and ethyl alcohol.

The effect can therefore be classed as a special case of Kuhn's "Asymmetrische Umlagerung erster Art", and one in which the activation produced by the optically active agent is so small that the induction cannot be observed unless ionisation is repressed. It must be supposed, if this is a true explanation, that the same effect is produced by adding excess of alkaloid, but is obscured by the method of measurement in which it is impossible to find change of rotation due to induction apart from that due to the addition of the alkaloid.

As a final test of this theory, the racemic acid 4:6-dinitro-2'-methyldiphenyl-2-carboxylic acid  was added in the usual way to nor-d-ψ-ephedrine. A "normal" curve was obtained, just as with salicylic and benzoic acids: this acid is potentially optically active, but its great optical stability makes activation impossible.

Previous Work on Optical Activation by Asymmetric Induction.

The possibility that the equilibrium

$$\underline{d}A.\underline{l}B \rightleftharpoons \underline{l}A.\underline{l}B$$

may be shifted to the left or right by the presence of the optically active base lB has been demonstrated on several occasions, although no distinction has been made by previous authors between the possible types of salt (covalent or ionised).

The earliest recorded case is the resolution by Pope and Peachey of methylethylpropyl-tin-camphorsulphonate (P., 1900,16,12, 42, 116) in which the d- form only was obtained on evaporation to dryness. The d- form being less soluble, the equilibrium in solution

$$\underline{l}B.\underline{d}A \rightleftharpoons \underline{d}B.\underline{d}A \downarrow \text{deposited from solution.}$$

must have been constantly shifted to the right by the deposition of one component.

The same mechanism explains the finding of one form only of the quinine and morphine salts of 4-oximinocyclohexane carboxylic acid by Mills and Bain, (J., 1910, 97, 1869) on evaporation: they found the same property in morphine and quinine salts of the benzoyl phenylhydrazone of cyclohexanone-4-carboxylic acid.

Leuchs (Ber., 1921, 54, 830) found that when hydrocarbostyril-3-carboxylic acid was crystallised from methyl alcohol with quinidine, the whole of the original racemic acid was obtained as the d- acid quinidine salt. The mechanism of this change in solution is

l-acid salt $\rightleftharpoons$ salt of enolic acid $\rightleftharpoons$ d-acid salt $\rightarrow$ crystals

Read and McMath (J., 1925, 127, 1572; 1926, 2186) obtained all of chlorobromomethane sulphonic acid as the l-acid-l-base salt by crystallising with l-hydroxyhydrindamine. They consider this a new effect, but it was already described for a different compound by Leuchs and Wutke in 1913, (Ber., 1913,46, 2420). Read and McMath, however, state further that in solution the equilibrium between the two diastereoisomerides is disturbed in the proportions

lB.dA	$\rightleftharpoons$	lB.lA
19%		81%

Other similar cases of activation which have been observed are

(1) Kuhn and Albrecht (Annalen, 1927, 455, 272) showed that 4:4'-dinitrodiphenic acid could be activated in alcoholic solution by quinine and cinchonidine, but no optically active salt could be isolated.

(2) Bell and Robinson (J., 1927, 2234) found that quinine activated 4-nitrodiphenic acid, although they did not recognise their result as one of activation.

(3) Lesslie and Turner found similar properties in the diphenates of several of the cinchona alkaloids (J., 1934, 347).

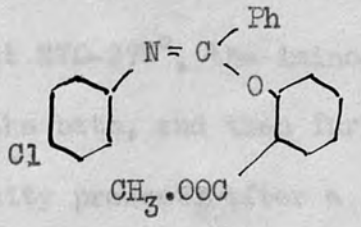
(4) Mills and Elliott (J., 1928, 1291) made the discovery that benzenesulphonyl-8-nitro-α-naphthylglycine with brucine in acetone solution deposited 90% or more of one optically active form. If equal quantities of brucine and acid were mixed and the rotation taken, this initial rotation fell to an equilibrium value owing to partial activation of the acid.

Finally, Pfeiffer and Quehl (Ber., 1931, 64, 2667) extended the work above which was all carried out in organic solvents (except for part of Pope and Peachey's work with tin) by making activation experiments in aqueous solution. They found that if a solution of zinc camphor-sulphonate was taken and α-phenanthroline or 2:2'-dipyridyl added, the rotation changed; (this is considered to be due to the activation of) octahedral cations of the type $Zn[dipy_3]$. The amount of change varied with concentration. Conversely, zinc phenanthroline sulphate could be activated by optically active bases, and in none of these cases could the optically active zinc salts be obtained from the solution.

The above evidence makes it clear that the explanation of the newly discovered effect is a legitimate one: it is very difficult to find any other interpretation of the facts, although further experiments to find the limits of optical stability of compounds which demonstrate the phenomenon are necessary before this attractive explanation can be considered definite.

SECTION VII. EXPERIMENTAL.

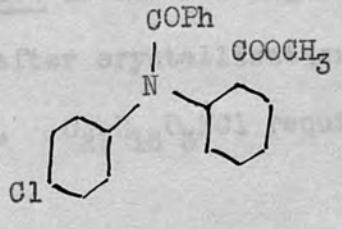
Preparation of 4-Chloroaniline-2'-carbomethoxyphenylbenzimino-ether.



Sodium (14.5 g., 1¼ mols.) was dissolved in 700 c.c. of absolute ethyl alcohol, and the solution cooled to 0°. To this was added 114 g. (1½ mols.) of methyl salicylate, followed quickly by 130 g. (1 mol.) of 4-chloroaniline-benziminochloride in dry ethereal solution, the whole shaken well and left to stand overnight. The ether and most of the alcohol were distilled off, and the remainder poured into water, when a white solid separated. Crystallisation from ethyl alcohol gave the 4-chloroaniline-2'-carbomethoxyphenyl-benzimino-ether in shining white angular plates, m.p. 130-131°. Yield 166 g. (88% of theory.)

Found: Cl, 9.9, $C_{21}H_{16}O_3NCl$ requires Cl, 9.7 per cent.

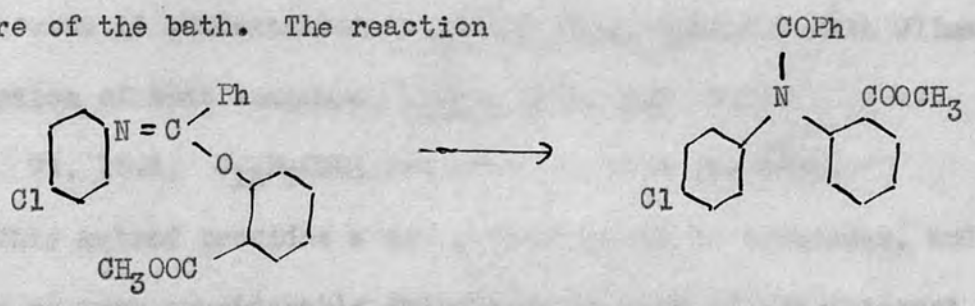
Preparation of Benzoyl-4-chloro-2'-carbomethoxy-diphenylamine.



This substance was originally prepared in fairly good yield by the general method used by Chapman for the conversion of imino-ethers

to corresponding benzoyl derivatives, viz:- heating the imino-ether for about $2\frac{1}{2}$ hours at 270-300°.

It was subsequently observed that on putting the flask containing the 4-chloroaniline-2'-carbomethoxyphenyl-benzimino-ether into the metal bath at 270-275°, the imino-ether melts, its temperature rises to that of the bath, and then further - anything up to 30°, depending on the quantity present: after a few minutes it sinks again to the temperature of the bath. The reaction



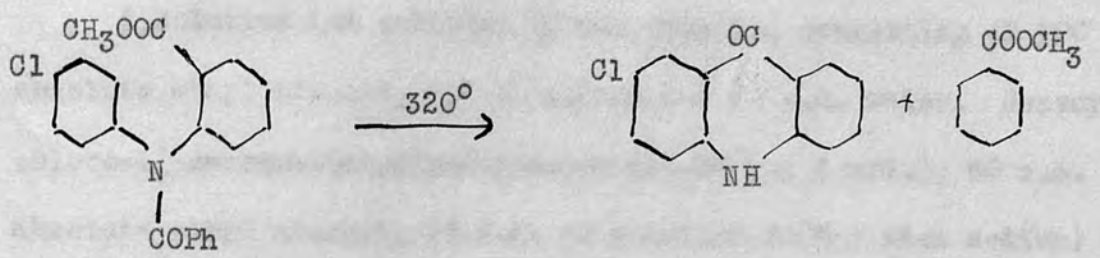
is therefore exothermic, and very rapid at this temperature, so that the method finally adopted for the preparation was as follows:-

The imino-ether was placed in a small round flask in 10 g., 20 g. or 30 g. quantities, and this put into a metal bath at 275-280°. The temperature of the ether rose above that of the bath, and fell again to 275-280°: the reaction was then complete, and took 5-10 minutes. The resulting glass crystallised from ethyl alcohol giving the benzoyl derivative in small irregular white prisms, m.p. 139-140°. Yield, 85-91%, after crystallisation.

Found: Cl, 9.5, $C_{21}H_{16}O_3NCl$ requires Cl, 9.7 per cent.

Note.

On heating this substance at 320°, 4-chloroacridone and methyl benzoate are formed.

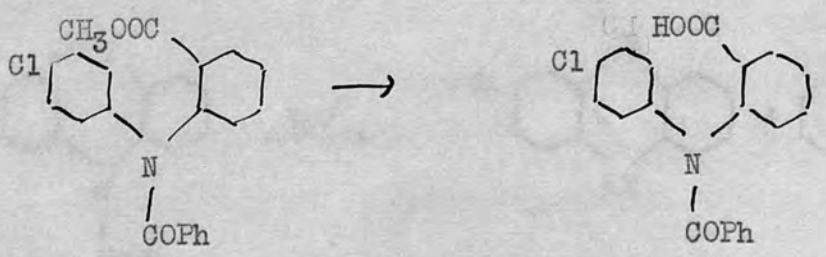


The methyl benzoate was identified by its smell and by the direct determination of its b.p., 199°. The 4-chloroacridone crystallised from cyclohexanol in yellow needles, m.p. $>$ 360°, and showed a green fluorescence in concentrated sulphuric acid, agreeing with Ullmann's description of that compound, (Ann., 1907, 355, 312).

Found: Cl, 15.4, $C_{13}H_8ONCl$ requires Cl, 15.4 per cent.

This method provides a new general route to acridones, and is clearly of very considerable importance in view of the interest which attaches to the pharmacology of acridine derivatives.

Hydrolysis of Benzoyl-4-chloro-2'-carbomethoxy-diphenylamine to Benzoyl-4-chloro-2'-carboxy-diphenylamine.



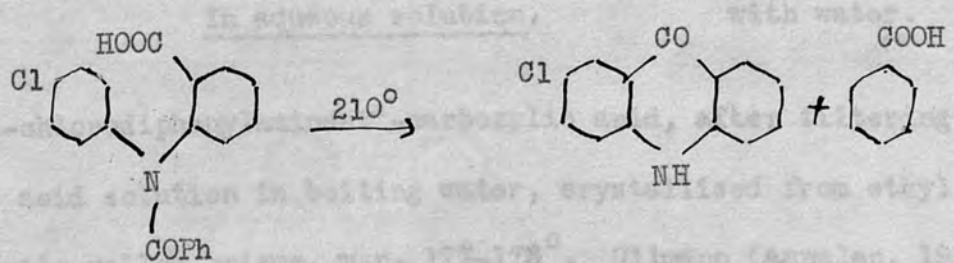
The difficulty encountered here was the prevention of the hydrolysis proceeding to a further stage and forming 4-chloro-2'-carboxydiphenylamine. Various strengths of alcoholic caustic soda, and sulphuric acid were tried as hydrolysing agents, the method finally adopted being as follows:-

A solution (≡ solution B) was made up, consisting of 100 c.c. absolute ethyl alcohol, 2-3 g. sodium and 20 c.c. water. Benzoyl-4-chloro-2'-carbomethoxydiphenylamine (10.98 g.; 1 mol.), 60 c.c. of absolute ethyl alcohol, 33 c.c. of solution B (≡ 1 atom sodium) and 33 c.c. of water were heated under reflux for one hour. The alcohol was evaporated off, and the crude benzoyl-4-chloro-2'-carboxydiphenylamine precipitated with a few drops of dilute hydrochloric acid. The acid was extracted by grinding the solid with aqueous sodium bicarbonate solution, and reprecipitated with hydrochloric acid. It was washed with boiling water to remove traces of benzoic acid, and crystallised from acetone-light petroleum (b.p. 40-60°) in white needles, m.p. 191-192°. Yield 8 g., (76% of theory).

Found: Cl, 10.2, $C_{20}H_{14}O_3NCl$ requires Cl, 10.1 per cent.

Note.

On heating to 210°, the above acid decomposed to give 4-chloroacridone and benzoic acid, m.p. 121-122°.



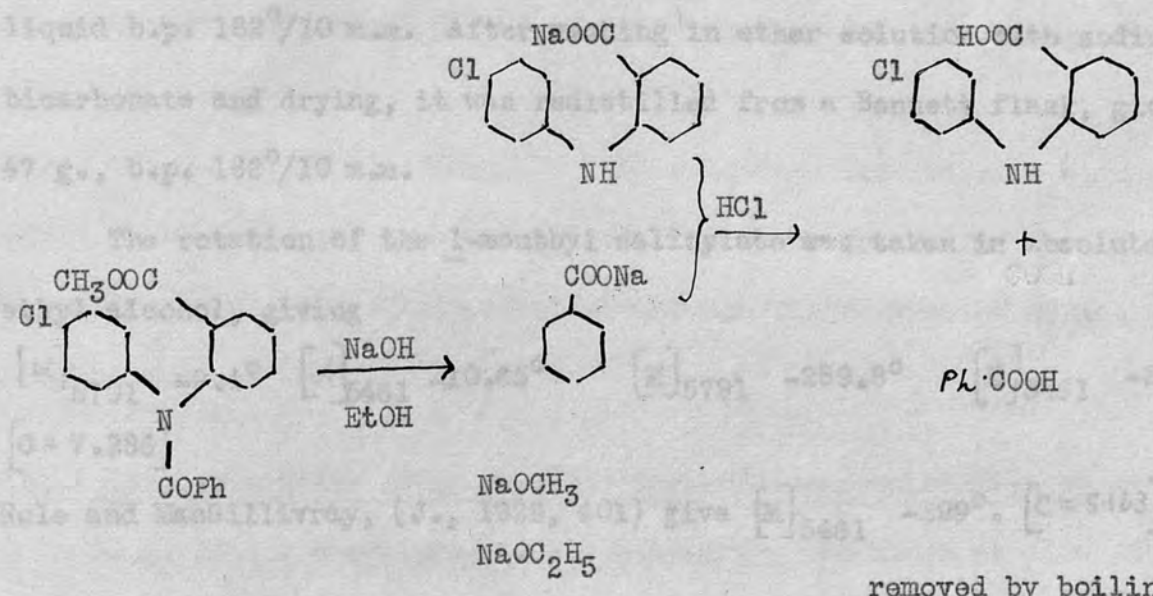
The 4-chloroacridone was identified as before.

Complete Hydrolysis of Benzoyl-4-chloro-2'-carbomethoxydiphenylamine to 4-Chlorodiphenylamine-2'-carboxylic acid.

The method used was that generally employed by A. W. Chapman

(loc. cit.) for the hydrolysis of benzoyldiphenylamines.

Benzoyl-4-chloro-2'-carbomethoxydiphenylamine (10 g.) was dissolved in 125 c.c. of ethyl alcohol, and a solution of 40 g. of sodium hydroxide in 40 c.c. water added: the whole was heated under reflux for 2 hours on a boiling water-bath. The alcohol was then evaporated off and the remainder poured into a large volume of water, when the solid separating was treated as shown in this scheme:-



The 4-chlorodiphenylamine-2'-carboxylic acid, after filtering off the benzoic acid solution in boiling water, crystallised from ethyl alcohol in pale yellow prisms, m.p. 174-178°. Ullmann (Annalen, 1907, 355, 312) gives m.p. 177°.

Preparation of l-Menthyl Salicylate.

Salicylic acid (70 g.) was added gradually to 120 g. of boiling thionyl chloride, boiling being continued until the solution was clear;

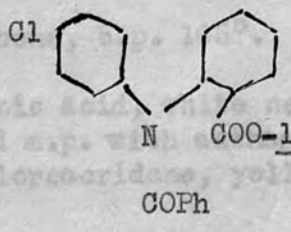
then about half (by volume) of the solution was distilled off. Menthol (140 g.) was added, and there was some evidence of reaction: 100 g. of dry pyridine was added, and the whole heated at 100° for two hours. On shaking with dilute hydrochloric acid, an oil separated out and was dried over anhydrous sodium sulphate. It was distilled from an ordinary flask, b.p. 212° at 43 m.m., then redistilled from a Bennett flask, separating to some high melting solid and the bulk a colourless liquid b.p. 182°/10 m.m. After washing in ether solution with sodium bicarbonate and drying, it was redistilled from a Bennett flask, giving 47 g., b.p. 182°/10 m.m.

The rotation of the l-menthyl salicylate was taken in absolute ethyl alcohol, giving

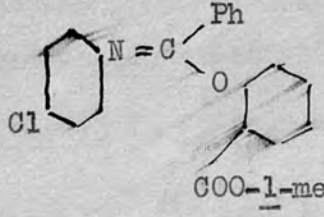
$[\alpha]_{5791}$ -9.4° $[\alpha]_{5461}$ -10.65° $[M]_{5791}$ -259.8° $[M]_{5461}$ -294.0°: [C = 7.286]

Rule and MacGillivray, (J., 1929, 401) give $[M]_{5461}$ -299°. [C = 5.163]

Attempted Preparation of Benzoyl-4-chloro-2'-l-carbomenthoxydiphenylamine.



(a) Preparation of 4-Chloroaniline-benzimino-2'-carboxy-l-menthyl ether.



Sodium ($1\frac{1}{4}$ atoms; 3.2 g.) was dissolved in 150 c.c. absolute ethyl alcohol and cooled to 0°-5°. l-Menthyl salicylate (45.6 g., $1\frac{1}{2}$ mols.) was added, followed by p-chloroaniline-benziminochloride (27.5 g., 1 mol.) in dry ethereal solution. The whole was shaken until a cloudiness due to the formation of sodium chloride appeared, and left to stand overnight. It was then poured into water, extracted with ether, the extract washed with aqueous sodium hydroxide solution to remove excess l-menthyl salicylate, dried and the ether evaporated off.

Yield: 61 g., (88% of theory). The substance was obtained as a clear glass which could not be crystallised, and was used in this form for the next experiment, the result of which was considered a proof of its constitution.

(b) Attempted Preparation of Benzoyl-4-chloro-2'-l-carbomenthoxydiphenylamine.

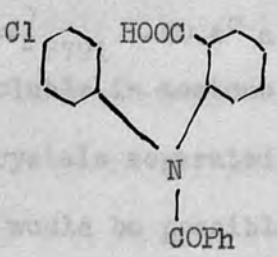
20 g. of the above product was heated for two hours at 280-295°. Instead of the desired intramolecular change, decomposition occurred, and the following products were identified.

(1) Menthene, b.p. 165°.

(2) Benzoic acid, white needles, m.p. 117-120°. mixed m.p. with authentic specimen, 116-120°

(3) 4-Chloroacridone, yellow needles, m.p. > 360°, yellow-purple fluorescence in concentrated sulphuric acid solution, insoluble in alcohol.

Investigation of Alkaloidal Salts of Benzoyl-4-chloro-2'-carboxydiphenylamine.



(1) Strychnine Salt.

(a) Fractional Addition of Strychnine.

The acid (11.7 g.) was dissolved in 100 c.c. of hot absolute ethyl alcohol and 3.7 g. of strychnine (1/3 equivalent) added. The solution gave no crystalline deposit, and none was obtained after adding the remaining two third equivalents of base: the salt was therefore precipitated by the addition of light petroleum (b.p. 60-80°).

(b) Fractional Crystallisation of the Strychnine Salt.

(i) The salt obtained above was dissolved in hot benzene and light petroleum (b.p. 60-80°) added until a slight precipitate was formed. On keeping 10.4 g. (almost half of the quantity of salt present) of salt separated (crop A) having $[\alpha]_{5791}$ -16.3° and $[\alpha]_{5461}$ -19.3° in acetone. Crop A melted at 120°, with loss of solvent: it formed hard spherical aggregates of needles.

The mother liquor from A was evaporated to one-sixth of its volume, and light petroleum added. Glassy material separated, and the whole was evaporated to dryness, finally in a high vacuum. The residue crystallised from absolute methyl alcohol in fine needles (B) which were almost insoluble in acetone and had $[\alpha]_{5971}$ -20.8° and $[\alpha]_{5461}$ -24.5°

in chloroform. Evaporation of the methyl alcoholic mother liquor gave a further crop with $[\alpha]_{5791}$ -20.4° and $[\alpha]_{5461}$ -24.3°, in chloroform. Crop A was readily soluble in acetone, but when the solution was kept for a few minutes, crystals separated which appeared to be identical with B. Although it would be possible to explain this as due to solvation, it is alternatively conceivable that A and B are the two possible diastereoisomerides (not necessarily pure) and that in acetone B is the less soluble, the formation of B from A then being an induction phenomenon.

(ii) The strychnine salt was prepared in hot methyl alcoholic solution from 11.1 g. of base and 11.7 g. of acid. A clear solution was obtained using 1500 c.c. of solvent. On cooling, clusters of needles (P) separated, which, after being dried at 100° and then in a high vacuum over sulphuric acid, weighed 19.2 g., melted at 150-151° with loss of solvent and had $[\alpha]_{5791}$ -22.4°, $[\alpha]_{5461}$ -26.3° in chloroform.

The salt, (18.6 g.) was crystallised from 1 litre of methyl alcohol and gave crop Q (13.3 g.) with $[\alpha]_{5791}$ -21.8°, and $[\alpha]_{5461}$ -22.5° in acetone (3 vols.) - water (1 vol.) solution.

Recrystallisation of Q gave a further crop having $[\alpha]_{5791}$ -22.8°, and $[\alpha]_{5461}$ -26.3°, in chloroform.

The methyl alcohol crops were dissolved in benzene, the solution evaporated to dryness and the residue recrystallised dissolved in benzene. Addition of light petroleum gave ill-defined crystals, which, after being dried at 100°, melted at 193-194°, and were free from solvent. Crystallisation of this salt from acetone gave material which melted at 125-165° with loss of solvent.

(c) Repeated Fractional Addition of Strychnine.

The observations made under (b) suggested that satisfactory results might be obtained by the fractional method in methyl alcohol solution, and therefore 11.7 g. of acid and 3.7 g. of strychnine (1/3 equivalent) were dissolved in 1 litre of hot methyl alcohol. On cooling, a salt separated having $[\alpha]_{5791}$ -21.7°, $[\alpha]_{5461}$ -25.1° in chloroform. Addition of 3.7 g. of base to the hot mother liquor gave a second salt with $[\alpha]_{5791}$ -21.7°, $[\alpha]_{5461}$ -25.7°, and repetition of the process on the last mother liquor gave a salt having $[\alpha]_{5791}$ -22.1° $[\alpha]_{5461}$ -26.1°.

(d) Test for Mutarotation.

A solution in chloroform of equivalent quantities of strychnine and acid underwent no change in rotation during 24 hours at room temperature.

(2) Brucine Salt.

(a) First Series in Ethyl Alcohol.

Equivalent quantities of brucine dihydrate (8.6 g.) and acid (7.0 g.) were dissolved in 500 c.c. of hot absolute ethyl alcohol. No crystallisation taking place, the solution was evaporated to 350 c.c. On keeping, an oil separated which became solid (7.25 g.; m.p. 181-182° with slight darkening). This crop (A) had $[\alpha]_{5791}$ + 5.8° in chloroform.

Salt A (6.8 g.) when crystallised from alcohol gave a crop A_1 (1.05 g.) which formed spherical aggregates, m.p. 170-180° and had $[\alpha]_{5791}$ + 3.7°. The mother liquor was supersaturated, since it shortly afterwards deposited 2.15 g. of white powder having m.p. 160-170°

(with loss of solvent) and $[\alpha]_{5791}$ + 0.8°.

Other crops were obtained with $[\alpha]_{5791}$ +3.2° and + 6.3°.

The rotation of A_1 was not measurably affected by heating in chloroform solution for 2 hours at 95° in a sealed tube. That of A_2 increased slightly, but definitely, in the same conditions (observed angle change 0.07° to 0.10°).

(b) Second Series in Ethyl Alcohol.

A second set of experiments was started using 14.0 g. of acid and 17.2 g. of brucine dihydrate dissolved in 900 c.c. of hot absolute ethyl alcohol. The cold solution deposited crop $\underline{\alpha}$ (15.1 g.) as warty aggregates, melting at 191-195° in a bath previously heated to 175°. Crop $\underline{\alpha}$ had $[\alpha]_{5791}$ + 6.4° in chloroform. The rotation solution was heated in a sealed tube for two hours at 95°, when $[\alpha]_{5791}$ became + 4.5°.

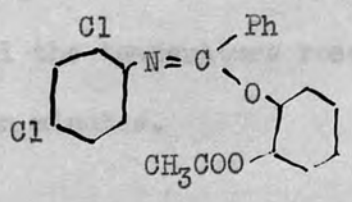
Recrystallisation of crop $\underline{\alpha}$ gave 9.1 g. of crop $\underline{\alpha}_1$ having $[\alpha]_{5791}$ + 6.6° before and $[\alpha]_{5791}$ + 3.9° after heating as described above. Recrystallisation of $\underline{\alpha}_1$ gave 5.9 g. of a salt having $[\alpha]_{5791}$ + 6.2° before and $[\alpha]_{5791}$ + 2.4° after heating as above.

Evaporation of the mother liquor of $\underline{\alpha}$ to half volume, and keeping at 5°, led to the separation of spherical aggregates (β) which were highly solvated and after being dried at 100° and in a high vacuum weighed 2.95 g. and melted at 192-196° in a bath previously heated to 175°. This salt had $[\alpha]_{5791}$ + 4.9° before and $[\alpha]_{5791}$ + 3.3° after being heated in a sealed tube.

Evaporation of the mother liquor of β gave a crop which had $[\alpha]_{5791}$ + 3.5° before and + 0.6° after heating.

A mixture of equivalent quantities of brucine and acid had $[\alpha]_{5791}$ + 5.6° in chloroform. This suggests that crop A (+ 5.8°) was the partial racemate and that A_1 (+ 3.7°) and A_2 (+ 0.8°) either contained excess of alkaloid or were partially resolved. The second alternative is supported by the sealed tube heating experiments, but although the experimental error was known to be small, the low rotations of the salts render a definite conclusion uncertain.

Preparation of 2:4-Dichloroaniline-benzimino-o-carbomethoxyphenyl ether.



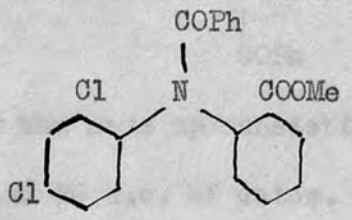
This preparation was carried out in the same way as for the analogous monochloro-compound, (loc. cit.). The quantities involved were as shown in the table.

2:4-Dichloroaniline benzimino-chloride	1 mol.	54.5 g.	69 g.	108 g.
Sodium	1¼ atoms.	5.5 g.	7.1 g.	11.2g.
Methyl Salicylate	1½ mols.	46 g.	58 g.	92 g.
Absolute Ethyl Alcohol		275 cc.	360 cc.	550 cc.
2:4-Dichloroaniline benzimino-o-carbomethoxyphenyl ether		31.5g.	58 g.	109 g.

The imino-ether crystallised in white needles m.p. 85-87°.

Found; Cl, 17.6, $C_{21}H_{15}O_3NCl_2$ requires Cl, 17.7 per cent.

Preparation of Benzoyl-2:4-dichloro-2'-carbomethoxydiphenylamine.



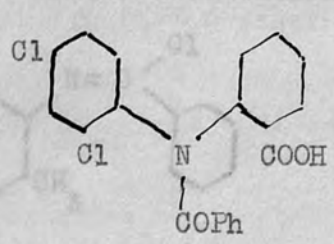
This substance was formed by heating the imino-ether prepared above: the reaction proved to be exothermic (compare mono-chloro-compound). It was found by trial that the best temperature for the reaction was 255-280°, 250° being a little too low for the best results: heating was continued until the temperature rose to a maximum and fell again; this took about ten minutes.

Weight of imino ether.	Maximum Temperature of reaction.	Maximum Temperature of heating bath.	Yield.	Time of Heating.
20 g.	260°	280°	11.7g.	1 hour.
20 g.	250°	280°	15.1 g.	½ "
40 g.	265°	255°	25 g.	10 mins.
40 g.	255°	250°	19 g.	10 "
40 g.	282°	270°	26.1g.	10 "

The yields given are after crystallisation from alcohol: benzoyl-2:4-dichloro-2'-carbomethoxydiphenylamine forms colourless rods, m.p. 114-116°.

Found: Cl, 17.6, $C_{21}H_{15}O_3NCl_2$ requires Cl, 17.7 per cent.

Preparation of Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid.



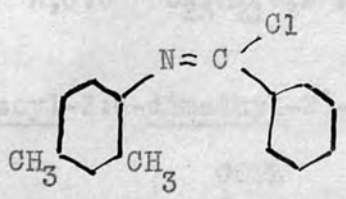
A solution B was made up consisting of 2.3 g. of sodium in 100 c.c. of ethyl alcohol and 20 c.c. of water. The hydrolysis mixture was then as follows:-

Benzoyl-2:4-dichloro-2'-carbomethoxydiphenylamine	5 g.
Ethyl Alcohol	55 c.c.
Solution B.	30 c.c.
Water .	30 c.c.

These were heated under reflux for about 1½ hours, and the alcohol evaporated off. If the remaining solution was allowed to cool at this stage, the sodium salt of the acid crystallised in long opaque colourless needles. The benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid was precipitated with hydrochloric acid, purified by dissolving in sodium bicarbonate solution, filtering and reacidifying. It was then dried and crystallised from acetone and light petroleum in colourless needles, m.p. 178-184°.

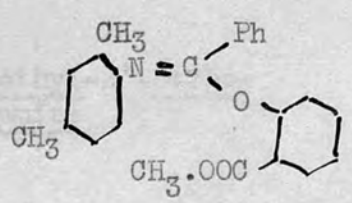
Found: Cl, 18·5 $C_{20}H_{13}O_3NCl_2$ requires Cl, 18·4 %.

Preparation of 2:4-Dimethylaniline benzimino chloride.



Benzoyl-2:4-dimethylaniline (89 g.) was heated on a water-bath with phosphorus pentachloride (90 g., a slight excess of 1 mol.) until all was clear liquid. The phosphorus oxychloride was distilled off in vacuo, and the 2:4-dimethylanilinebenzimino chloride distilled, b.p. 204°/11 m.m. It solidified in yellow needles which contained impurites of phosphorus oxychloride and benzoyl chloride.
Yield. 80 g. (82% of theory).

Preparation of 2:4-Dimethylanilinebenzimino-2'-carbomethoxyphenyl ether.



This substance was prepared by the method used for the analogous dichloro-derivative (loc. cit.)

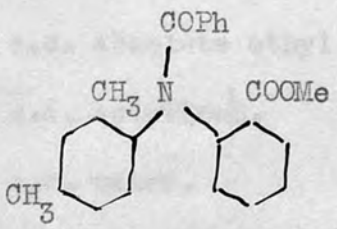
2:4-Dimethylanilinebenzimino chloride	1 mol.	80 g.
Sodium	1¼ atoms.	9.5 g.
Methyl Salicylate	1½ mols.	76 g.
Ethyl Alcohol		500 c.c.

The imino ether melted at 87-88° after crystallisation twice from ethyl alcohol. Yield, 67.5 g. (=56% of theory).

It could be heated to 300° without acridone formation.

Found: C, 76.7, H,6.0 $C_{23}H_{21}O_3N$ requires C, 76.85; H, 5.9 per cent.

Preparation of Benzoyl-2:4-dimethyl-2'-carbomethoxydiphenylamine.



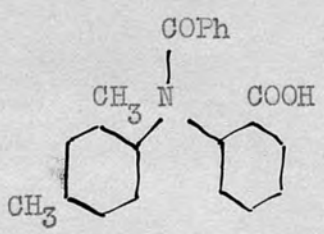
This substance was prepared by heating the above imino ether for 10 minutes in a metal bath at 275°. Again the reaction was exothermic; on one occasion a 20 g. quantity was placed in a bath at 275°; the temperature of the bath fell to 269° while the temperature of the reaction rose to 287°.

Imino ether	10 g.	20 g.	32.8 g.
Benzoyl-2:4-dimethyl-2'-carbomethoxydiphenylamine	7.3 g.	17.4 g.	29 g.

The benzoyl compound crystallised from methyl alcohol in stout prisms, m.p. 132-133°. It could be heated to 350° without acridone formation.

Found: C, 76.7; H, 5.7. $C_{23}H_{21}O_3N$ requires C, 76.85; H, 5.9 %

Preparation of Benzoyl-2:4-dimethyldiphenylamine-2'-carboxylic acid.



A solution B was made up consisting of 2.3 g. of sodium dissolved in 100 c.c. of ethyl alcohol and 20 c.c. of water. The following mixture was heated for 1½ hours under reflux.

9.9 g. of above methyl ester.

60 c.c. absolute ethyl alcohol.

33 c.c. solution B.

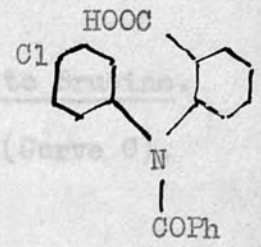
33 c.c. water.

The acid so obtained was purified by dissolving it in sodium bicarbonate solution, filtering and reacidifying: the acidification was done at 100° - if done at room temperature a heavily hydrated acid is obtained - and the benzoyl-2:4-dimethyldiphenylamine-2'-carboxylic acid crystallised from acetone and light petroleum (b.p. 40-60°). It formed prisms, m.p. 192-193°, softening at 191°, and turning deep orange.

Yield, 5.9 g. (74% of theory).

Found: C, 76.4; H, 5.6. $C_{22}H_{19}O_3N$ requires C, 76.5; H, 5.5 %

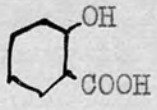
Addition of Benzoyl-4-chlorodiphenylamine-2'-carboxylic acid



to Brucine. (Curve A).

0.2709 g. brucine made up to 20 c.c. in chloroform.

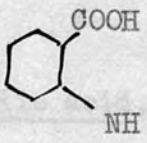
Weight of acid added.		Weight of acid added.	
0	-2.96°	0.2242 g.	+0.27°
0.0202 g.	-2.57°	0.2486 g.	+0.21°
0.0480 g.	-2.02°	0.2848 g.	+0.12°
0.1116 g.	-0.75°	0.3202 g.	+0.03°
0.1814 g.	+0.24°	0.3696 g.	-0.03°
0.1928 g.	+0.27°	0.4116 g.	-0.27°

Addition of Salicylic Acid, 

to Brucine. (Curve B).

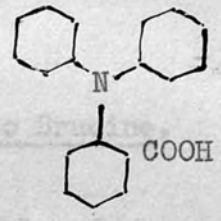
0.2011 g. brucine made up to 20 c.c. in chloroform.

Weight of acid added.		Weight of acid added.	
0	-2.23°	0.0682 g.	+0.40°
0.0046 g.	-1.98°	0.0798 g.	+0.40°
0.0097 g.	-1.75°	0.1214 g.	+0.41°
0.0348 g.	-0.35°	0.1538 g.	+0.40°
0.0548 g.	+0.36°	0.2038 g.	+0.40°

Addition of Diphenylamine-2-carboxylic acid  to Brucine. (Curve C).

0.2178 g. of brucine made up to 20 c.c. in chloroform.

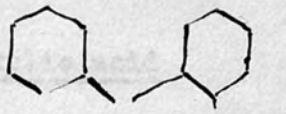
Weight of acid added.		Weight of acid added.	
0	-2.41°	0.1298 g.	+ 0.35°
0.0209 g.	-1.71°	0.1468 g.	+ 0.38°
0.0428 g.	-0.98°	0.1911 g.	+ 0.44°
0.0630 g.	-0.37°	0.2660 g.	+ 0.46°
0.0877 g.	+ 0.14°		

Additon of Triphenylamine-2-carboxylic acid  to Brucine.

(Curve D.)

0.2328 g. of brucine made up to 20 c.c. in chloroform.

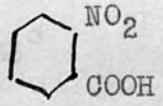
Weight of acid added.		Weight of acid added.	
0	-2.60°	0.1344 g.	-0.79°
0.1043 g.	-2.53°	0.2502 g.	-0.55°
0.0164 g.	-2.33°	0.2618 g.	-0.56°
0.0301 g.	-2.13°	0.2760 g.	- 0.56°
0.0738 g.	-1.44°	0.3049 g.	-0.55°
0.1004 g.	-1.06°	0.3492 g.	-0.53°

Addition of 4-Chlorodiphenylamine-2'-carboxylic acid, 

TO Brucine. (Curve E).

0.2014 g. of brucine made up to 20 c.c. in chloroform.

Weight of acid added.		Weight of acid added.	
0	-2.27°	0.1260 g.	+ 0.20°
0.0205 g.	-1.67°	0.1448 g.	+ 0.21°
0.0519 g.	-0.80°	0.2027 g.	+ 0.27°
0.0917 g.	+ 0.11°	0.2911 g.	+ 0.29°
0.1083 g.	+ 0.16°		

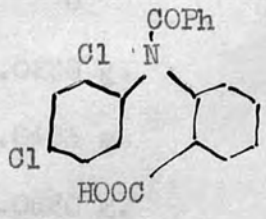
Addition of o-Nitrobenzoic Acid 

to Brucine. (Curve F).

0.1487 g. of brucine made up to 20 c.c. in chloroform.

Weight of acid added.	
0	-1.69°
0.0170 g.	-1.40°
0.0506 g.	-0.90°
0.1174 g.	-0.70°
0.1392 g.	-0.69°

Addition of Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid

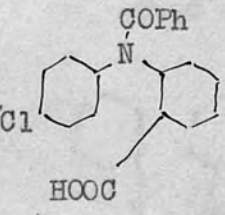


to Brucine. (Curve G).

0.1092 g. of brucine made up to 14.4 c.c. in chloroform.

Weight of acid added.		Weight of acid added.	
0	-1.66°	0.1942 g.	-0.01°
0.0130 g.	-1.42°	0.2242 g.	-0.10°
0.0398 g.	-0.85°	0.3652 g.	-0.35°
0.0720 g.	-0.21°	0.4574 g.	-0.44°
0.0873 g.	+0.33°	0.5602 g.	-0.54°
0.1144 g.	+0.18o	0.6562 g.	-0.56°
0.1358 g.	+0.17°	0.7722 g.	-0.61°
0.1719 g.	+0.06°		

Addition of Benzoyl-4-chlorodiphenylamine-2'-carboxylic acid



to Brucine. (Curve H).

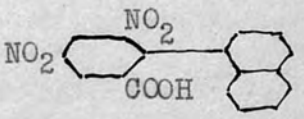
(This experiment is a repitition of a previous one, using the same weight of brucine as above, in order to plot the two on the same graph for purposes of comparison).

0.1092 g. of brucine made up to 14.4 c.c. in chloroform.

~~Weight of acid added.~~		~~Weight of acid added.~~	
~~0~~	~~-1.68°~~	~~0.1468 g.~~	~~0.12°~~

Weight of acid added.		Weight of acid added.	
0	-1.68°	0.1468 g.	+ 0.12°
0.0238 g.	-1.21°	0.1670 g.	+ 0.07°
0.0483 g.	-0.72°	0.1812 g.	+ 0.02°
0.0680 g.	-0.31°	0.1944 g.	-0.12°
0.0778 g.	-0.15°		

Addition of 3:5-Dinitro-2-α-naphthylbenzoic acid

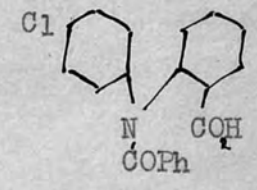


to Brucine. (Curve I).

0.1160 g. of brucine dissolved in 20 c.c. of methyl alcohol.

Weight of acid added.		Weight of acid added.	
0	-0.81°	0.1186 g.	-0.03°
0.0245 g.	-0.50°	0.1458 g.	-0.05°
0.0664 g.	-0.12°	0.1876 g.	-0.05°
0.0944 g.	-0.07°	0.2744 g.	-0.05°

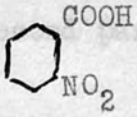
Addition of Benzoyl-4-chlorodiphenylamine-2'-carboxylic acid



to Nor-d-ψ-Ephedrine. (Curve J).

0.1246 g. of nor-d-ψ-ephedrine made up to 20 c.c. in chloroform.

Weight of acid added.		Weight of acid added.	
0	+ 0.90°	0.3128 g.	-0.39°
0.0868 g.	+ 0.28°	0.3339 g.	-0.35°
0.1834 g.	-0.31°	0.3910 g.	-0.19°
0.2790 g.	-0.41°	0.4927 g.	+ 0.05°
0.2914 g.	-0.43°		

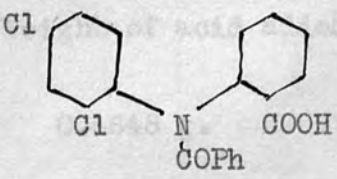
Addition of o-Nitrobenzoic acid,  to Nor-d-ψ-Ephedrine.

(Curve K).

0.1014 g. of ephedrine made up to 20 c.c. in chloroform.

Weight of acid added.	
0	+ 0.75°
0.0400 g.	+ 0.63°
0.0818 g.	+ 0.46°
0.1336 g.	+ 0.45°
0.1888 g.	+ 0.44°
0.3234 g.	+ 0.43°

Addition of Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid



to nor-d-ψ-Ephedrine. (Curve L).

This addition was done in two parts, as it was found impossible to carry the curve far enough with the original concentration of nor-d-ψ-ephedrine before the salt crystallised. Joining the second part of the curve to the first, by multiplying the weights and polarimeter readings by a factor (the ratio of the concentrations of ephedrine) simply amounts to plotting the second part of the curve on a different scale from the first.

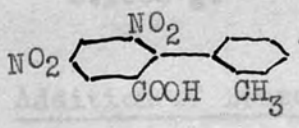
(a) 0.1302 g. of nor-d-ψ-Ephedrine made up to 20 c.c. in chloroform.

Weight of acid added.		Weight of acid added.	
0	+0.91°	0.4587 g.	-0.23°
0.0431 g.	+0.63°	0.5673 g.	+0.05°
0.1421 g.	+0.04°	0.6129 g.	+0.17°
0.2131 g.	-0.35°	0.7567 g.	+0.47°
0.2317 g.	-0.41°	0.8789 g.	+0.69°
0.2499 g.	-0.42°	1.0015 g.	+0.87°
0.2673 g.	-0.48°	1.1083 g.	+0.94°
0.3023 g.	-0.45°		
0.3409 g.	-0.39°		

(b) 0.0698 g. nor-d-ψ-ephedrine made up to 20 c.c. in chloroform.

Weight of acid added.		Wt. of acid x $\frac{0.1302}{0.0698}$	$\frac{0.1302}{0.0698}$
0.4648 g.	+ 0.43°	0.8275 g.	+ 0.77°
0.5736 g.	+ 0.55°	1.02 g.	+ 0.98°
0.6530 g.	+ 0.63°	1.16 g.	+ 1.12°
0.7654 g.	+ 0.68°	1.36 g.	+ 1.21°
0.9116 g.	+ 0.76°	1.62 g.	+ 1.35°
1.0982 g.	+ 0.82°	1.96 g.	+ 1.46°
1.2792 g.	+ 0.82°	2.28 g.	+ 1.46°
1.3862 g.	+ 0.83°	2.47 g.	+ 1.48°
1.5070 g.	+ 0.89°	2.68 g.	+ 1.59°

Addition of 4:6-Dinitro-2'-methyldiphenyl-2-carboxylic acid

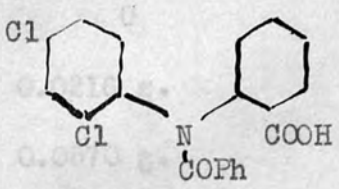


to nor-d- -Ephedrine. (Curve M).

0.0736 g. of nor-d-ψ-ephedrine made up to 14.4 c.c. in chloroform.

Weight of acid added.		Weight of acid added.	
0	+ 0.73°	0.1906 g.	+ 0.31°
0.0582 g.	+ 0.57°	0.3818 g.	+ 0.23°
0.0944 g.	+ 0.38°	1.0552 g.	+ 0.14°
0.1556 g.	+ 0.33°		

Addition of Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid

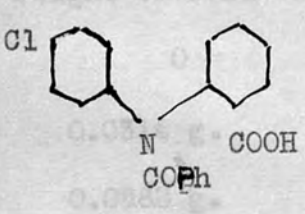


to Strychnine. (Curve N).

0.1653 g. of strychnine made up to 20 c.c. in chloroform.

Weight of acid added.		Weight of acid added.	
0	-3.33°	0.1728 g.	-1.30°
0.0056 g.	-3.27°	0.1975 g.	-1.22°
0.0326 g.	-2.92°	0.2200 g.	-1.22°
0.0584 g.	-2.59°	0.2429 g.	-1.25°
0.0780 g.	-2.34°	0.2730 g.	-1.35°
0.1170 g.	-2.00°	0.3506 g.	-1.60°
0.1368 g.	-1.65°	0.4835 g.	-1.88°
0.1558 g.	-1.47°		

Addition of Benzoyl-4-chlorodiphenylamine-2'-carboxylic acid,



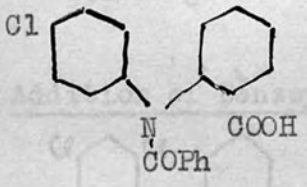
to Strychnine. (Curve O).

0.2328 g. of Strychnine made up to 20c.c. in chloroform.

(Table on next page).

Weight of acid added.		Weight of acid added.	
0	-4.13°	0.2896 g.	-1.29°
0.0216 g.	-3.86°	0.3014 g.	-1.33°
0.0570 g.	-3.36°	0.3188 g.	-1.35°
0.0910 g.	-2.91°	0.3493 g.	-1.41°
0.1274 g.	-2.41°	0.4114 g.	-1.52°
0.1518 g.	-1.88°	0.4772 g.	-1.63°
0.1900 g.	-1.51°	0.5348 g.	-1.69°
0.2454 g.	-1.31°	0.5492 g.	-1.82°

Addition of Benzoyl-4-chlorodiphenylamine-2'-carboxylic acid,

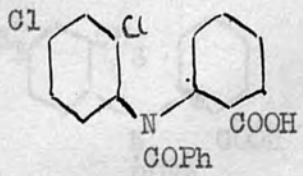


to Morphine. (Curve P).

0.1516 g. morphine made up to 20 c.c. in methyl alcohol.

Weight of acid added.		Weight of acid added.	
0	-2.07°	0.1808 g.	-1.89°
0.0314 g.	-2.03°	0.2602 g.	-1.85°
0.0880 g.	-1.97°	0.3354 g.	-1.83°
0.1150 g.	-1.96°	0.4458 g.	-1.83°
0.1504 g.	-1.89°		

Addition of Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid

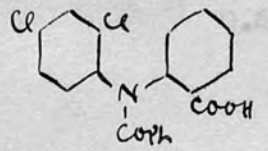


to nor-d-ψ-Ephidrine. (Curve Q).

0.1505 g. of nor-d-ψ-ephidrine made up to 14.5 c.c. with ethyl alcohol.

Weight of acid added.		Weight of acid added.	
0	+ 0.73°	0.3341 g.	+ 1.36°
0.0051 g.	+ 0.73°	0.4081 g.	+ 1.43°
0.0501 g.	+ 0.81°	0.4241 g.	+ 1.46°
0.1455 g.	+ 1.06°	0.5402 g.	+ 1.44°
0.2757 g.	+ 1.26°	0.6861 g.	+ 1.46°

Addition of Benzoyl-2:4-dichloro-diphenylamine-2'-carboxylic acid

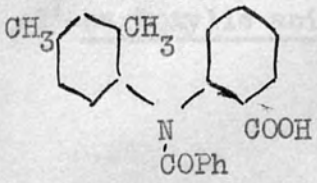


to nor-d-ψ-ephedrine. (Curve R).

0.0405 g. nor-d-ψ-ephedrine made up to 14.5 c.c. in benzene.

Weight of acid added.		Weight of acid added.	
0	+ 0.31°	0.1254 g.	-0.21°
0.0064 g.	+ 0.30°	0.1800 g.	-0.02°
0.0216 g.	+ 0.21°	0.2062 g.	+0.08°
0.0456 g.	+ 0.09°	0.2328 g.	+ 0.18°
0.0818 g.	-0.07°	0.2618 g.	+ 0.33°
0.0926 g.	-0.12°	0.2856 g.	+ 0.38°
0.1148 g.	-0.21°		

Addition of Benzoyl-2:4-dimethyldiphenylamine-2'-carboxylic acid,

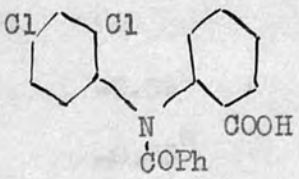


to nor-d-ψ-Ephedrine. (Curve S).

0.0958 g. of nor-d-ψ-ephedrine made up to 14.5 c.c. in chloroform.

Weight of acid added.	
0	+ 0.92°
0.0183 g.	+ 0.72°
0.0775g.	+ 0.32°
0.1864 g.	-0.96°
0.2604 g.	-0.84°
0.4076 g.	+0.34°
0.5656 g.	+1.38°

Addition of Nor-d-ψ-Ephedrine to Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid.

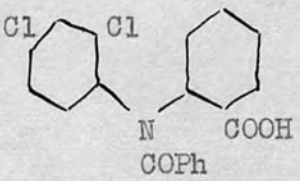


(Curve T).

2.0769 g. of acid made up to 14.5 c.c. in ethyl alcohol.

Wt. of ephedrine added.		Wt. of ephedrine added.	
0	0	0.3670 g.	+ 3.30°
0.0046 g.	+ 0.03°	0.4317 g.	+ 3.74°
0.0100 g.	+ 0.08°	0.4528 g.	+ 3.90°
0.0298 g.	+ 0.30°	0.4761 g.	+ 4.06°
0.0481 g.	+ 0.37°	0.5174 g.	+ 4.36°
0.0728 g.	+ 0.56°	0.5883 g.	+ 4.82°
0.1306 g.	+ 1.31°	0.8470 g.	+ 6.28°
0.1661 g.	+ 1.63°	0.9367 g.	+ 6.68°
0.1865 g.	+ 1.82°	0.9731 g.	+ 6.80°
0.2264 g.	+ 2.17°	1.0788 g.	+ 7.25°
0.2668 g.	+ 2.53°	1.1589 g.	+ 7.58°
0.3126 g.	+ 2.87°		

Addition of Strychnine to Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid.

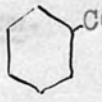


(Curve U).

0.1799 g. of acid made up to 14.3 c.c. in chloroform.

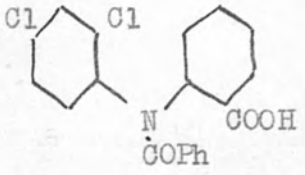
(Table on next page).

Wt. of strychnine added.		Wt. of strychnine added.	
0	0	0.1552 g.	-1.17°
0.0290 g.	-0.32°	0.1734 g.	-1.42°
0.0537 g.	-0.55°	0.1924 g.	-1.74°
0.0908 g.	-0.76°	0.2350 g.	-2.48°

Addition of nor-d-ψ-Ephedrine to Benzoic acid,  (Curve V).

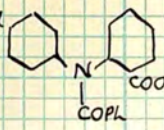
0.7433 g. of benzoic acid made up to 14.4 c.c. in chloroform.

Wt. of ephedrine added.		Wt. of ephedrine added.	
0	0	0.3368 g.	+ 2.24°
0.0100 g.	+ 0.08°	0.5359 g.	+ 2.95°
0.0228 g.	+ 0.20°	0.7156 g.	+ 3.34°
0.0766 g.	+ 0.62°	0.9212 g.	+ 3.68°
0.1168 g.	+ 0.89°	1.1024 g.	+ 4.88°
0.2128 g.	+ 1.54°	1.1548 g.	+ 5.31°
		1.2454 g.	+ 5.96°

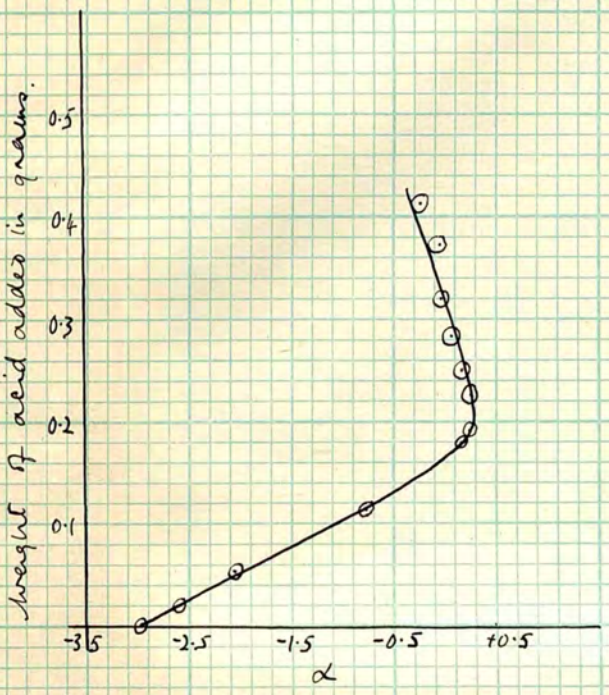
Addition of nor-d-ψ-Ephedrine to Benzoyl-2:4-dichlorodiphenylamine-2'-carboxylic acid,  (Curve W).

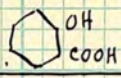
1.9798 g. of acid made up to 14.4 c.c. in chloroform.

Wt. of Ephedrine added.		Wt. of Ephedrine added.	
0	0	0.2029 g.	+ 1.94°
0.0084 g.	+ 0.18°	0.3404 g.	-0.02°
0.0360 g.	+ 0.77°	0.7334 g.	-3.34°
0.0768 g.	+ 1.44°	0.7654 g.	-3.24°
0.1240 g.	+ 1.98°	0.8885 g.	-2.52°
0.1599 g.	+ 2.13°	1.0364 g.	-1.36°

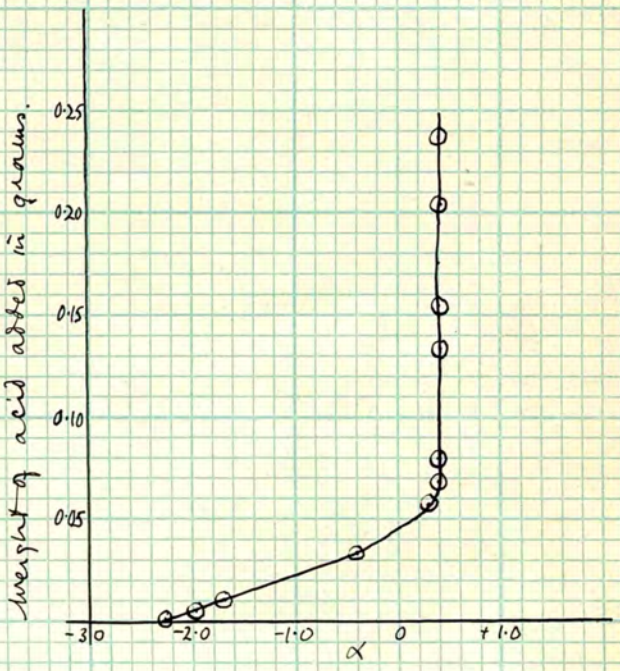
A. Addition of  to Brucine

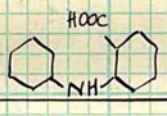
in chloroform.



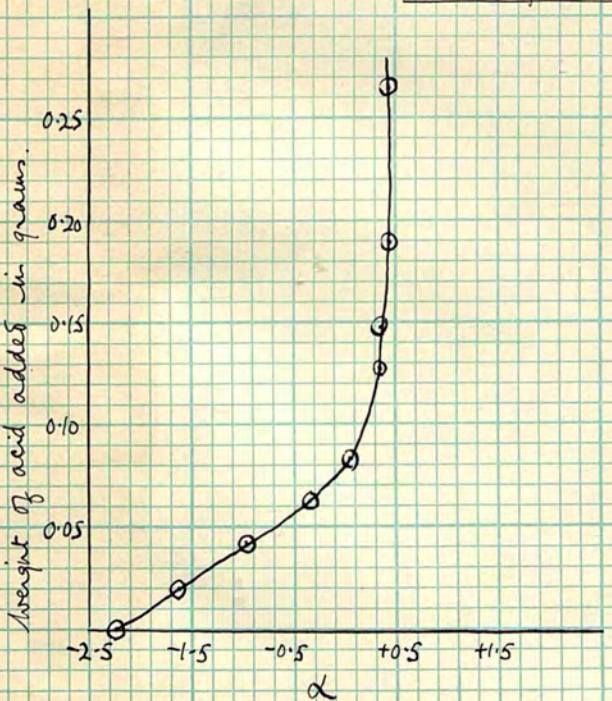
B. Addition of  to Brucine

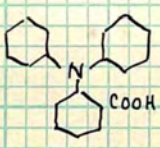
in chloroform.



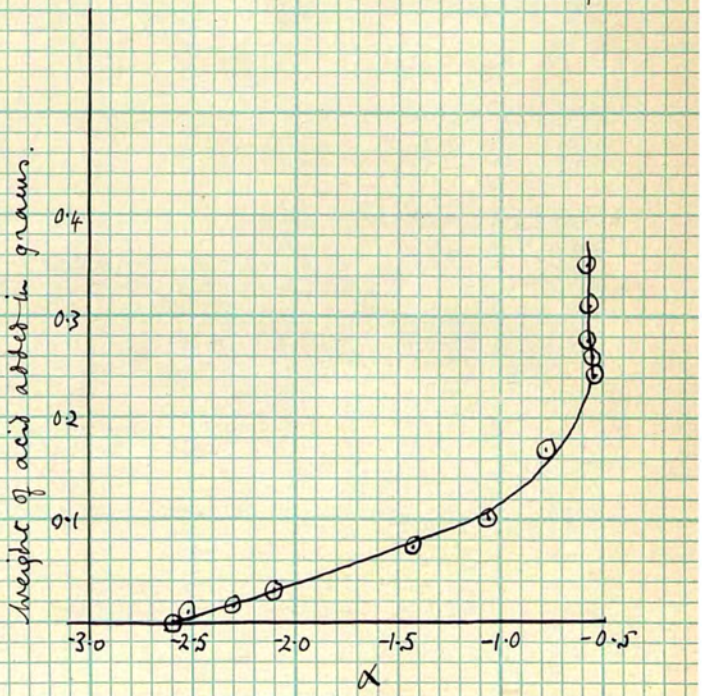
C. Addition of  to Brucine

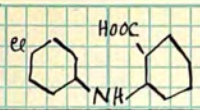
in chloroform.



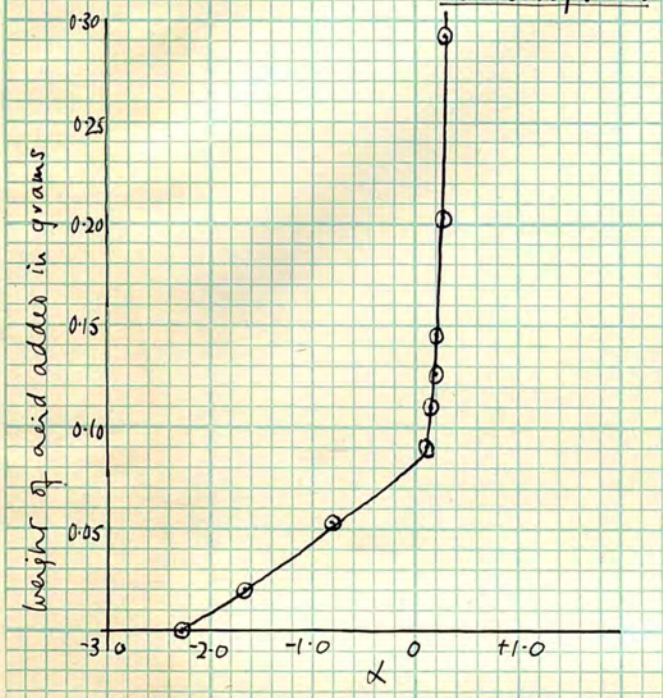
D. Addition of  to Brucine

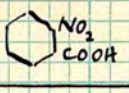
in chloroform.



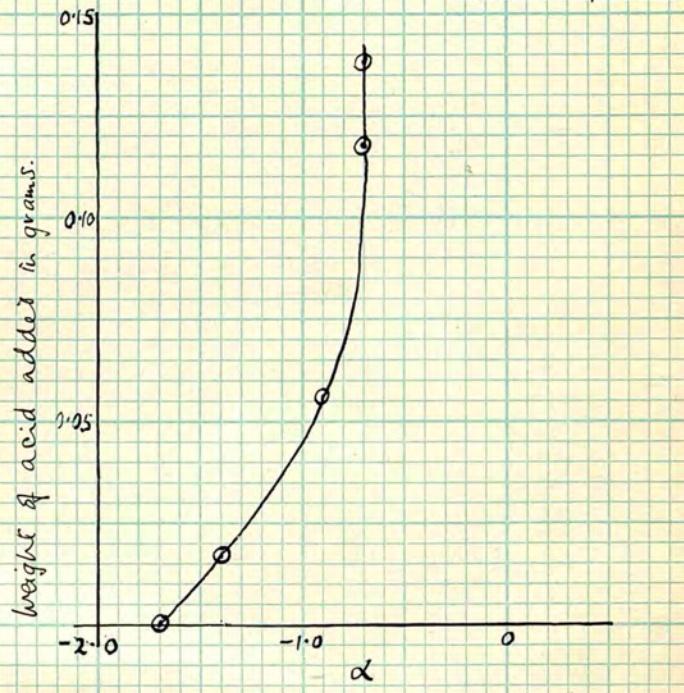
E. Addition of  to Brucine

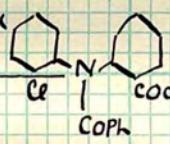
in chloroform.



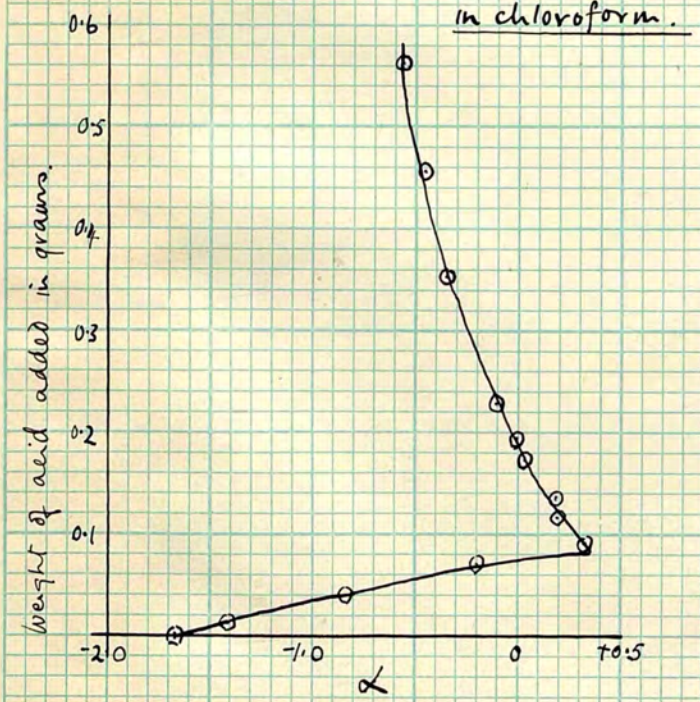
F. Addition of  to Brucine

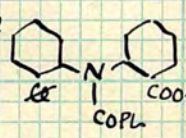
in chloroform.



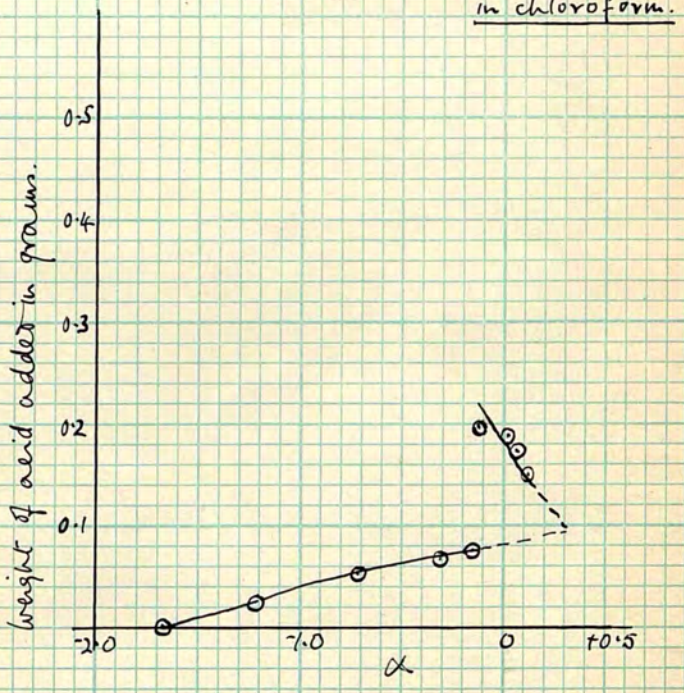
G. Addition of  to Brucine

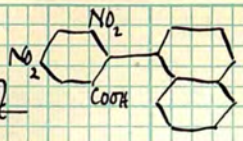
in chloroform.

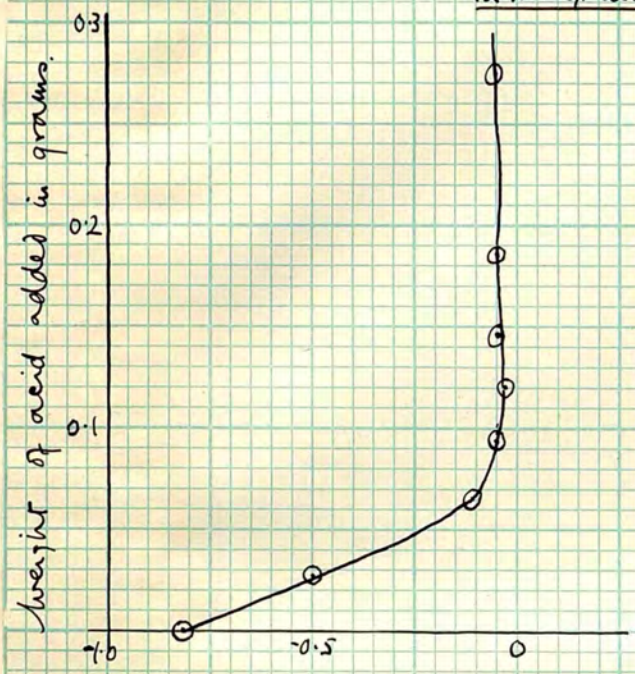


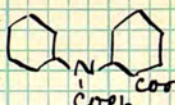
H. Addition of  to Brucine

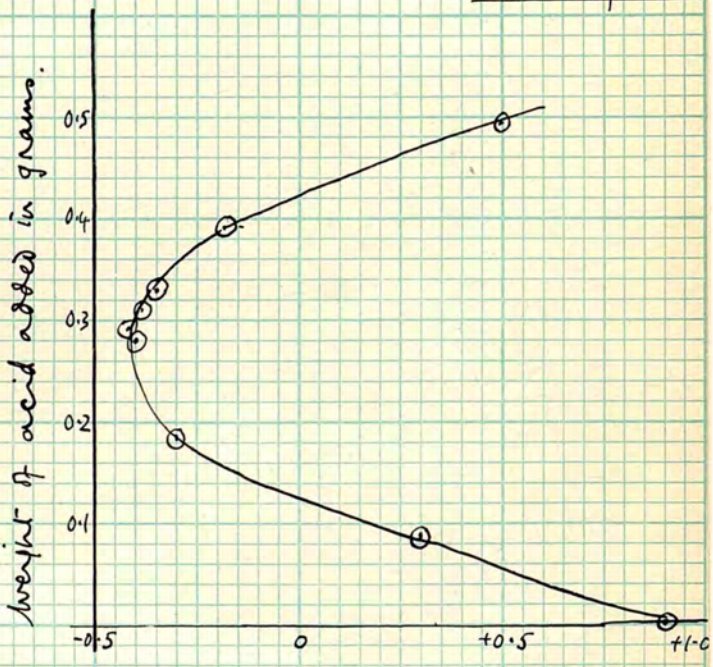
in chloroform.

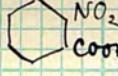


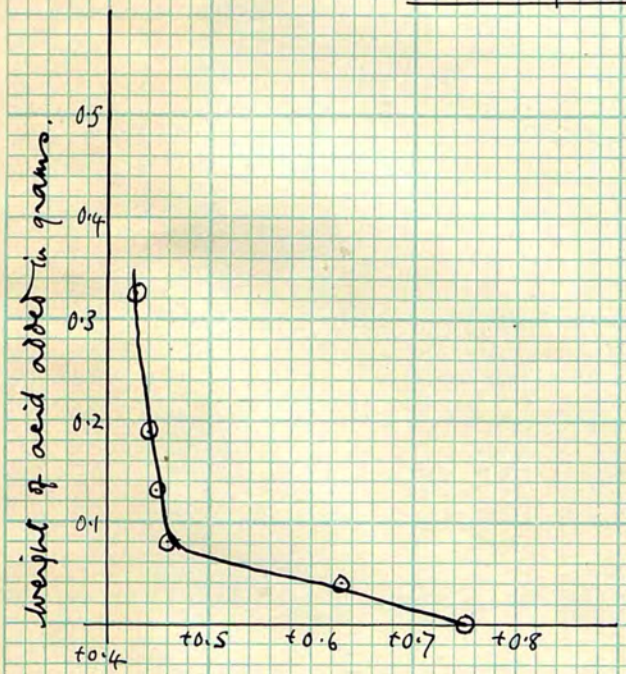
I. Addition of  to Brucine in methyl alcohol.

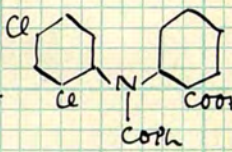


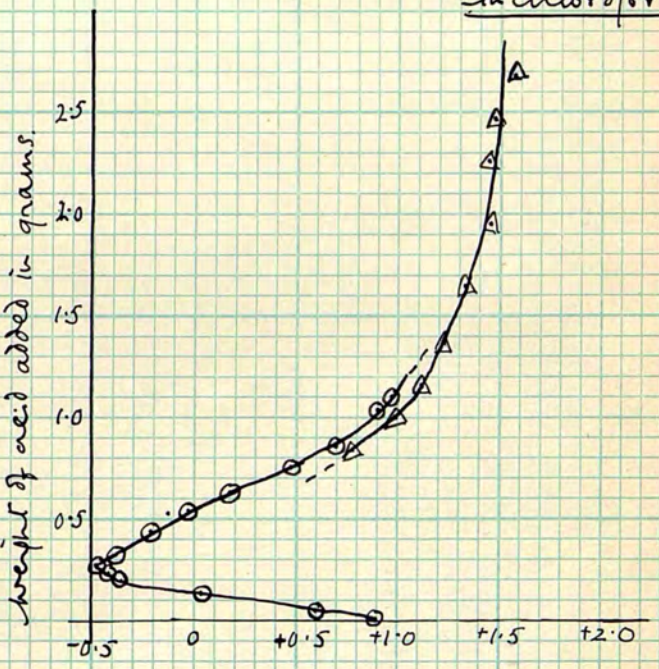
J. Addition of  to nor-d-ψ-ephedrine. in chloroform.

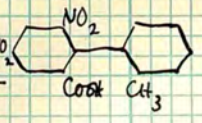


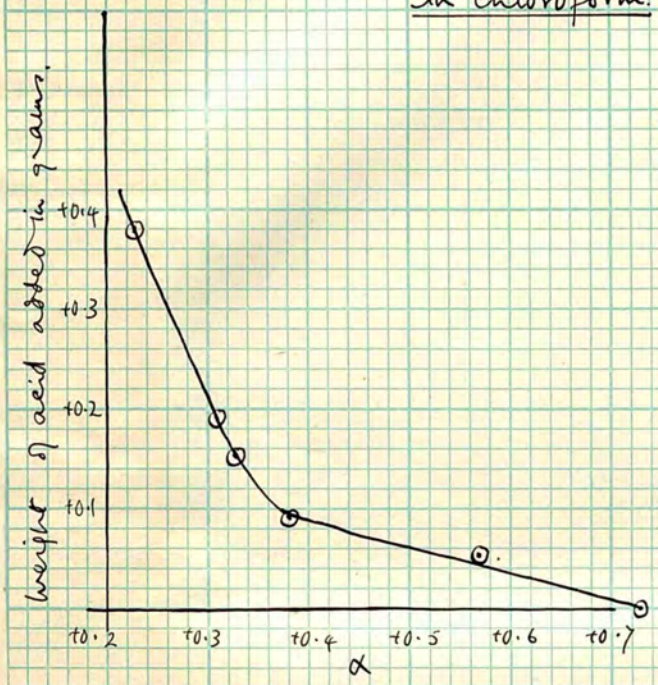
K. Addition of  to nor-d-ψ-ephedrine. in chloroform.

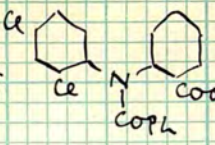


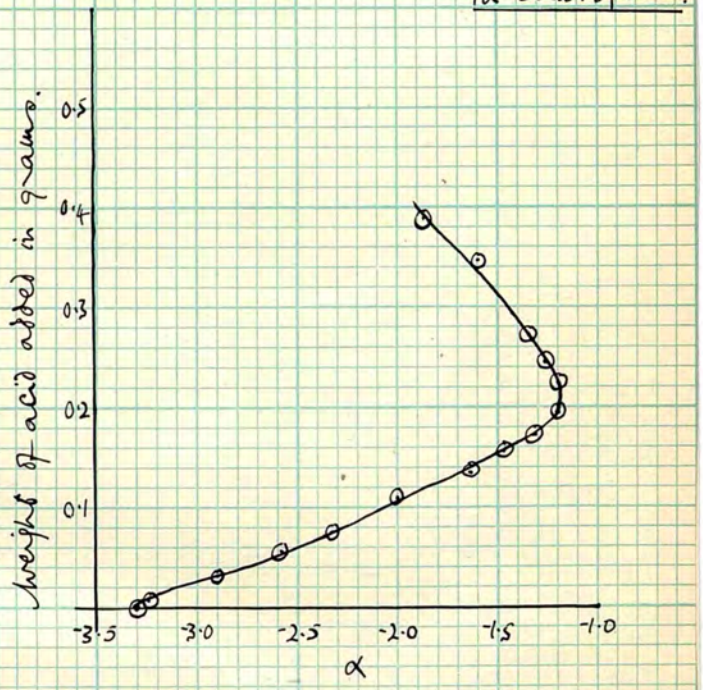
L. Addition of  to nor-d-ψ-ephedrine. in chloroform.

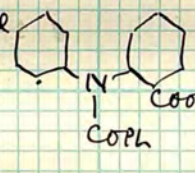


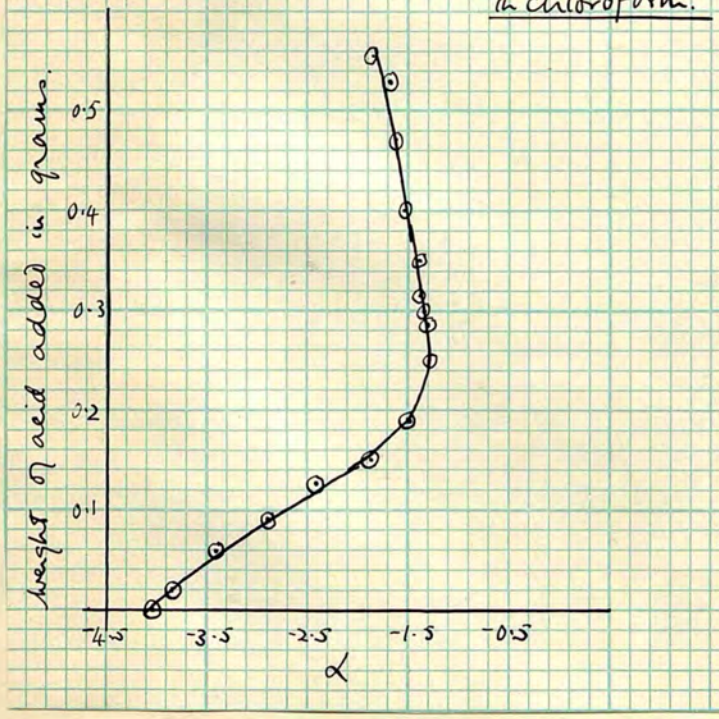
M. Addition of  to nor-d-ψ-Ephedrine in chloroform.

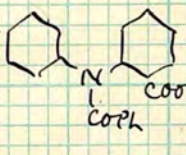


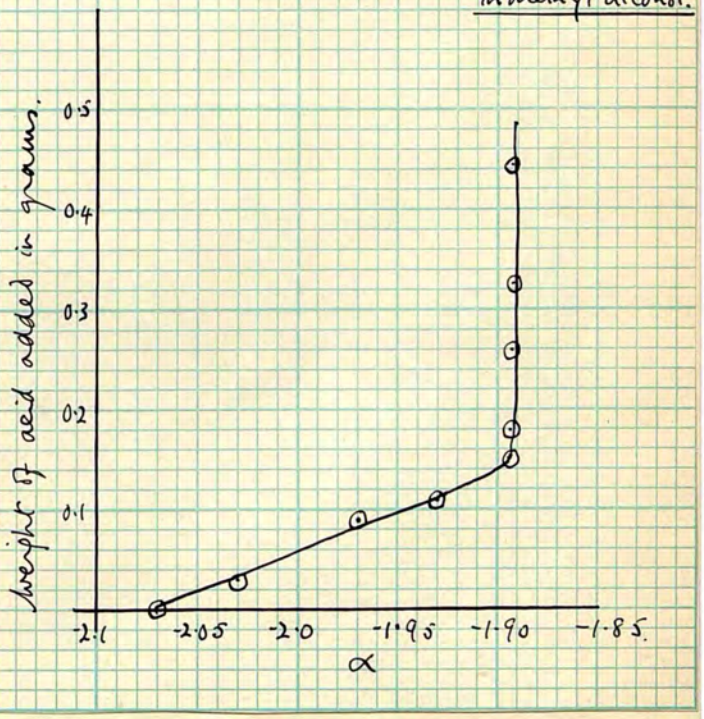
N. Addition of  to Strychnine in chloroform.

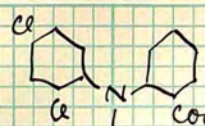


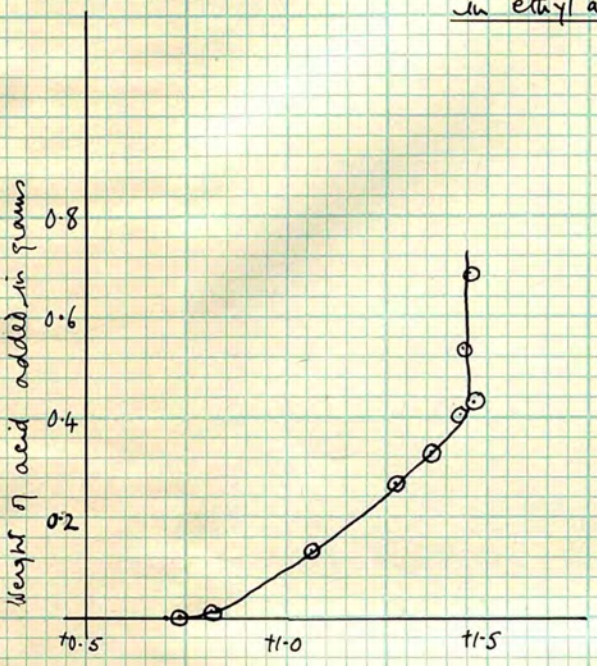
O. Addition of  to Strychnine in chloroform.

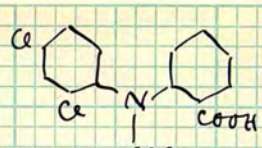


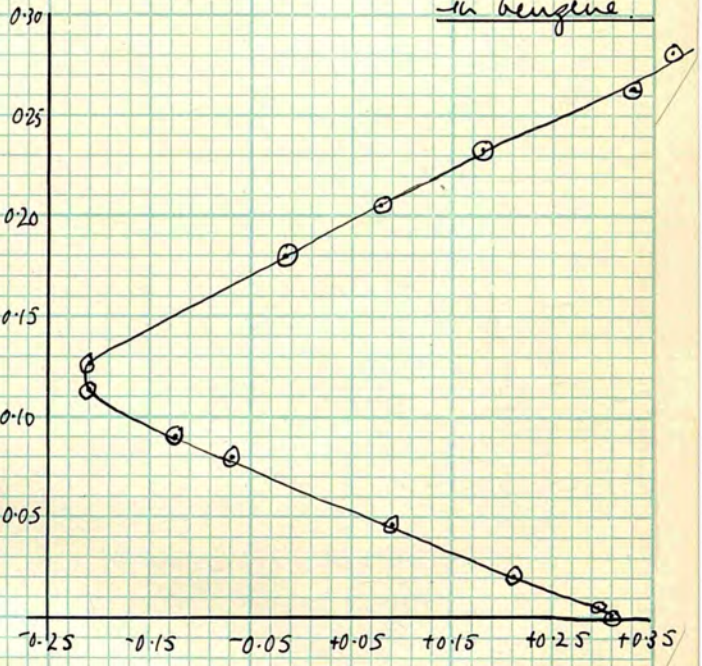
P. Addition of  to Morphine in methyl alcohol.

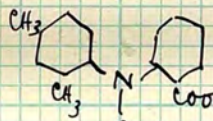


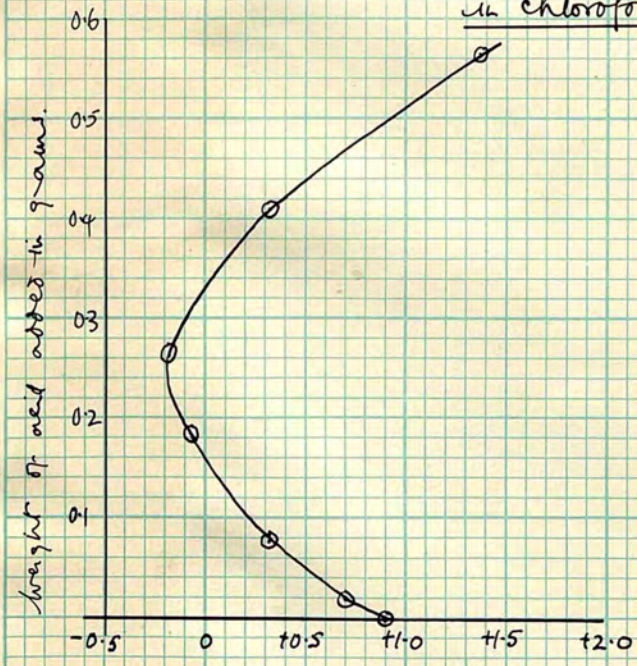
Q. Addition of  nor-d-ψ-Ephedrine in ethyl alcohol.

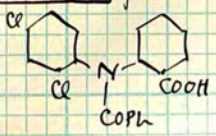


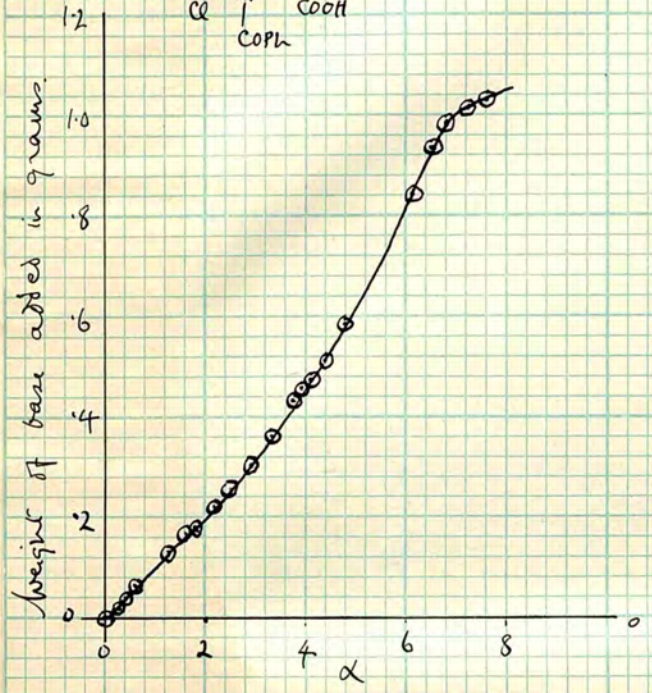
R. Addition of  to nor-d-ψ-Ephedrine in benzene.

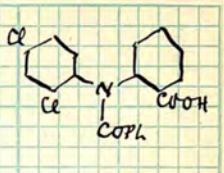


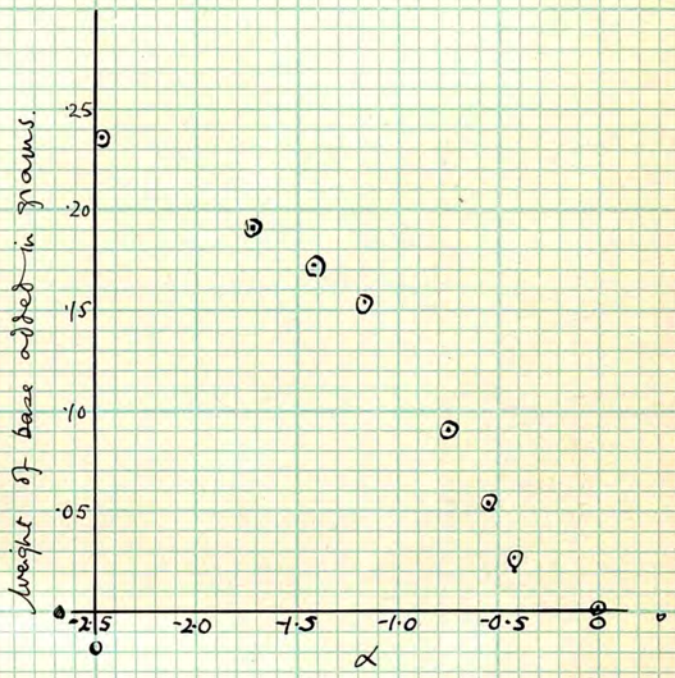
S. Addition of  to nor-d-ψ-Ephedrine in chloroform.



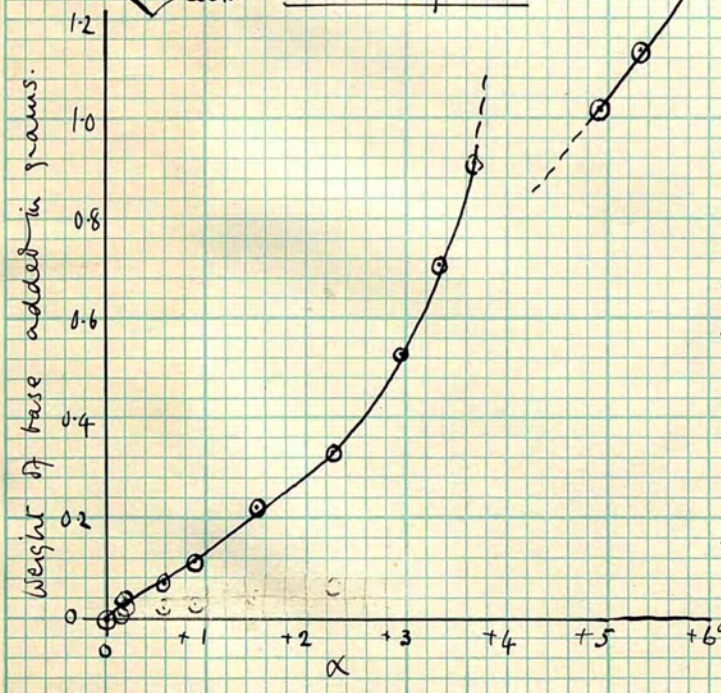
T. Addition of nor-d-ψ-Ephedrine to  in ethyl alcohol.

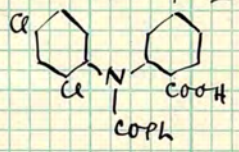


U. Addition of Strychnine to  in chloroform.



V. Addition of nor-d-ψ-Ephedrine to  in chloroform.



W. Addition of nor-d-ψ-Ephedrine to  in chloroform.