STUDIES IN THE DIPHENYL SERIES

by

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C O N T E N T S

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SUMMARY

Since this thesis is concerned mainly with a study of optical activity of diphenyl derivatives, the various methods of preparation of diphenyl derivatives are given in the General Introduction. The thesis is divided into two parts: Part I is concerned mainly with the reactions of certain benzidine bases with ketones and Part II, the major portion, with diphenyl derivatives of interest from the point of view of optical activity. In this summary, pages to which cross reference has been given contain the main conclusions of this thesis.

Part I is subdivided into three sections: the Introduction, the Theoretical Section and the Experimental Section. The Introduction gives an account of previous relevant work, experimental and theoretical, and furnishes a background to the actual work undertaken. The latter, together with certain theoretical aspects, is discussed in the Theoretical Section. Part I was undertaken in order to provide further information on a subject briefly referred to by Reddelien (page 27) namely, the reactions of aromatic ketones with benzidine bases. At the same time, it was intended to gain

some information on the prospects of optical resolution of appropriately substituted benzidine derivatives by means of the formation of diastereoisomeric anils with optically active ketones.

Benzidine condensed with acetophenone and benzophenone to form the corresponding di-anils, o-tolidine reacted similarly with acetophenone but not with benzophenone, and o-dianisidine did not react with either acetophenone or benzophenone. These observations are discussed (page 39) from a theoretical standpoint with reference to the effects of ortho methyl and methoxyl groups on analagous anil condensations of benzenoid amines. Benzoin reacted with benzidine, o-tolidine and o-dianisidine to form didesyl-derivatives, which in contrast to the di-anils, were extremely resistant to hydrolysis. In addition to the action of nitrosyl chloride on benzidine, the anil condensations of certain other benzidine derivatives were also studied. Ketone anil formation was found to be unsuited for the optical resolution of benzidine derivatives because of the high reaction temperatures and the relative insolubility of the products while the difficulty of hydrolysis of didesyl derivatives precluded the use of optically active benzoin for the same purpose. The following new compounds were prepared during the course of this investigation:-

N:N'-bis(1-phenylethylidene)benzidine.	m.p.242°
N:N'-bis(1-phenylethylidene)-o-tolidine.	m.p.191.5°
N:N'-dibenzohydrylidenebenzidine.	m.p.224°
N:N'-didesylbenzidine.	m.p.220-221°
N:N'-didesyl-o-tolidine.	m.p.192°
N:N'-didesyl-o-dianisidine.	m.p.196-202°
Sodium N:N'-dibenzylidenebenzidine 3-sulphonate.	-
N:N'-disalicylidene-2-nitrobenzidine.	m.p.185°
N-benzylidene-m-anisidine.	b.p.$_{8mm.}$ 192-193°
N-benzylidene-m-anisidine picrate.	m.p.122°
N:N'-dibenzylidene-o-dianisidine.	m.p.155°
N:N'-dibenzylidene-o-dianisidine dipicrate.	m.p.202-203° (dec.)

Part II is concerned with the preparation of diphenyl derivatives of stereochemical interest; three new dibromodimethylbenzidines were the subject of optical resolution experiments. This part is sub-divided into four sections; the Historical Section, the Introduction, the Theoretical Section and the Experimental Section.

The Historical Section, which does not contain any original work performed by the author, consists of a fairly extensive historical review of the stereochemistry of diphenyl

derivatives. The Introduction, which likewise does not contain any of the author's experimental work completes the presentation of the facts and theories leading to the original research. The Introduction also deals with general methods of preparation of compounds analagous to those dealt with in the original work which follows in the Theoretical and Experimental Sections.

The original work and its theoretical significance are discussed in the Theoretical Section. In this Section also, mention is made of certain improvements in existing methods of preparation of previously known compounds. In the interests of clarity, since a large number of isomeric compounds are dealt with in the Experimental Section, the latter has been subdivided into five sub-sections:-

A. Synthesis of 2:2'-dibromo-6:6'-dimethylbenzidine.

B. Synthesis of 2:2'-dibromo-5:5'-dimethylbenzidine.

C. Synthesis of 2:2'-dibromo-3:3'-dimethylbenzidine.

D. Miscellaneous Experiments.

E. Resolution Experiments.

2:2'-Dibromo-6:6'-dimethylbenzidine was prepared and resolved into optical isomers; the active form was extremely resistant to racemisation. 2:2'-Dibromo-5:5'-dimethylbenzidine

was prepared but an optical resolution was not effected although the amine formed well defined crystalline salts with d-tartaric acid and also with d-camphor-10-sulphonic acid. 2:2'-Dibromo-3:3'-dimethylbenzidine was prepared and resolved; in this case only one active form, the l-amine was isolated. The active amine was racemised under moderate conditions. Theoretical considerations are advanced (page 163) to account for the differences in behaviour of these isomers. Proofs of their constitutions are given and, in addition to derivatives of the benzidines, certain new intermediate azo,hydrazo and azoxy compounds are described. Other allied compounds are also described and theoretical consideration (page 151) is given to the behaviour of isomeric bromonitrotoluenes on reduction. The following new compounds, arising out of these investigations, are described:-

3:3'-Dibromo-5:5'-dimethylazobenzene.	m.p.166-166.5°
3:3'-Dibromo-5:5'-dimethylazoxybenzene.	m.p.145°
3:3'-Dibromo-5:5'-dimethylhydrazobenzene.	m.p.131-132°
dl-2:2'-dibromo-6:6'-dimethylbenzidine.	m.p.157.5°
N:N'-diacetyl-2:2'-dibromo-6:6'-dimethylbenzidine.	m.p.146-148°
2:2'-Dibromo-6:6'-dimethyldiphenyl-4:4'-bis [azo-(1)-naphthol-(2)]	m.p.284-286°
N:N'-dibenzylidene-2:2'-dibromo-6:6'-dimethyl-benzidine.	m.p.178°

1-2:2'-Dibromo-6:6'-dimethylbenzidine di-d-tartarate. m.p.201°

$[\alpha]_D^{16}$, + 4.68°; (c, 1.924)

1-2:2'-Dibromo-6:6'-dimethylbenzidine. m.p.177°

$[\alpha]_D^{17}$, - 0.82°; (c, 7.672)

d-2:2'-Dibromo-6:6'-dimethylbenzidine. m.p.166-168°

(32% resolved) $[\alpha]_D^{17}$, + 0.26°; (c, 3.893)

5:5'-Dibromo-2:2'-dimethylazobenzene. m.p.200-201°

5:5'-Dibromo-2:2'-dimethylazoxybenzene. m.p.139-140°

5:5'-Dibromo-2:2'-dimethylhydrazobenzene. m.p.182-182.5°

2:2'-Dibromo-5:5'-dimethylbenzidine. m.p.153°

2:2'-Dibromo-5:5'-dimethylbenzidine dihydrochloride. m.p.344° (dec.)

N:N'-diacetyl-2:2'-dibromo-5:5'-dimethylbenzidine. m.p.306-307°

2:2'-Dibromo-5:5'-dimethyldiphenyl-4:4'-bis [azo-(1)-naphthol-(2)]. m.p.308.5°

N:N'-dibenzylidene-2:2'-dibromo-5:5'-dimethylbenzidine. m.p.193°

2:2'-Dibromo-5:5'-dimethylbenzidine mono-d-tartarate. m.p.196°

$[\alpha]_D^{16}$, + 6.59°; (c, 0.834)

2:2'-Dibromo-5:5'-dimethylbenzidine di-d-camphor-10-sulphonate.

$[\alpha]_D^{16}$, ~ + 2.6°; (c, 1.945)

3:3'-Dibromo-2:2'-dimethylazobenzene. m.p.171°

3:3'-Dibromo-2:2'-dimethylazoxybenzene. m.p.138.5°

3:3'-Dibromo-2:2'-dimethylhydrazobenzene. m.p.132.5°

dl-2:2'-Dibromo-3:3'-dimethylbenzidine. m.p.200°

2:2'-Dibromo-3:3'-dimethylbenzidine dihydrochloride. m.p.324-326°

N:N'-diacetyl-2:2'-dibromo-3:3'-dimethylbenzidine. m.p.308°

2:2'-Dibromo-3:3'-dimethyldiphenyl-4:4'-bis [azo-(1)-naphthol-(2)]. m.p.322° (dec.)

N:N'-dibenzylidene-2:2'-dibromo-3:3'-dimethylbenzidine. m.p.237-238°

l-2:2'-Dibromo-3:3'-dimethylbenzidine mono-d-tartarate. m.p.187.5°

$[\alpha]_D^{17.5}$, -4.98°; (c, 1.988)

l-2:2'-Dibromo-3:3'-dimethylbenzidine. m.p.201-202°

$[\alpha]_D^{16}$, -8.32°; (c, 1.923)

2:2'-Dibromo-5:5'-dimethylazobenzene. m.p.187°

2:2'-Dibromo-5:5'-dimethylazoxybenzene. m.p.168.5°

3-Bromo-5-methylazobenzene. m.p. 57.5°

2:4-Dibromo-6-nitrotoluene. m.p. 69°

3:5:3':5'-Tetrabromo-2:2'-dimethylazobenzene. m.p.224-226°

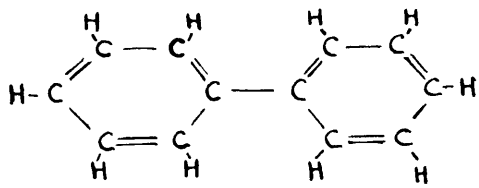
GENERAL INTRODUCTION

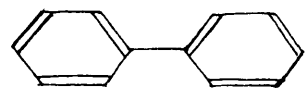
GENERAL INTRODUCTION

NOTES ON NOMENCLATURE

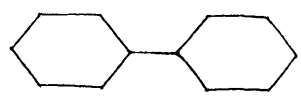
(1) Representation of the Diphenyl Molecule.

The full graphic formula of diphenyl is usually given in one or other of the following ways:-

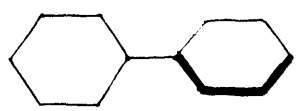




In general, however, throughout this thesis, where the benzene nuclei are known to be coplanar, the diphenyl molecule has been represented by the following contracted form:-

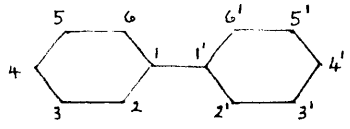


In certain cases, where the benzene nuclei are known to be non-coplanar, the diphenyl molecule has been represented thus:-

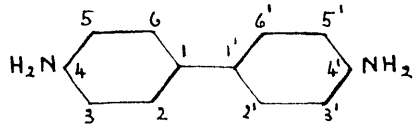


(2) Enumeration of Diphenyl and Derivatives.

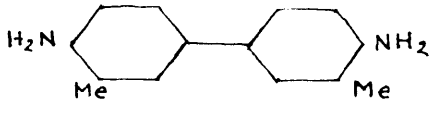
The enumeration of diphenyl and derivatives is that which is now universally adopted:-



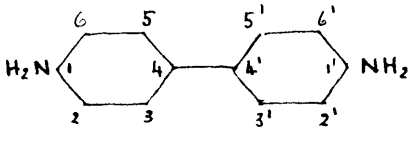
Benzidine is regarded as 4:4'-diaminodiphenyl and is enumerated similarly to diphenyl in accordance with modern practice:-



O-tolidine is thus regarded as 4:4'-diamino-3:3'-dimethyldiphenyl or 3:3'-dimethylbenzidine:-



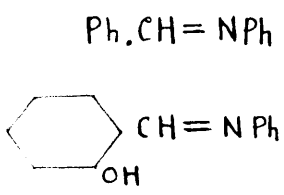
The following system of benzidine enumeration, which was used in America until the end of the year 1936, has been avoided:-



(3) Anils.

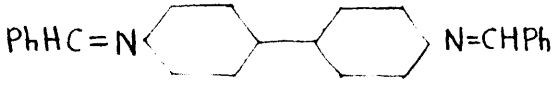
(a) Aldehyde Anils.

These are named as amines according to the system at present used in the Journal of the Chemical Society:-



Ph.CH=NPh — N-benzylideneaniline.

N-salicylideneaniline.

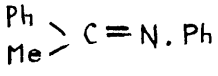


N:N'-dibenzylidenebenzidine.

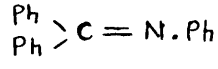
(b) Ketone Anils.

(i) Mono-anils.

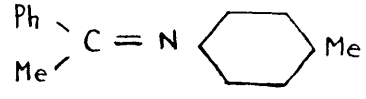
These are named as anils according to the generally accepted procedure which is given precedence in Beilstein's Handbook over alternative systems of nomenclature:-



acetophenone anil.



benzophenone anil.

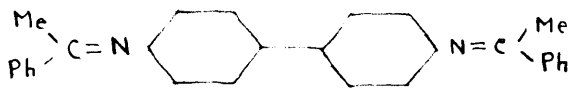


acetophenone p-tolil.

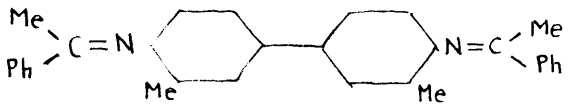
(ii) Di-anils.

The preceding method is cumbersome in the case of di-anils and these are named as amines in accordance with the present system of nomenclature of the Chemical Abstracts (49). The di-anils derived from acetophenone are named as 1-phenylethylidene derivatives:-

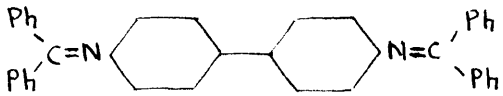
N:N'-bis(1-phenylethylidene)benzidine.



N:N'-bis(1-phenylethylidene)-o-tolidine.

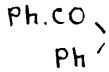


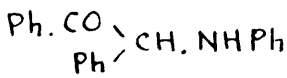
The di-anil derived from benzophenone is named as a benzohydrylidene derivative:-



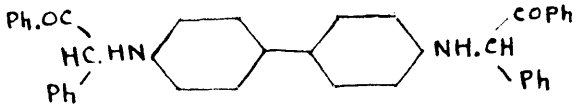
N:N'-dibenzohydrylidenebenzidine.

(4) Desyl Derivatives.

These contain the desyl radical  and are named as amines according to the alternative system of nomenclature given in Heilbron's Dictionary of Organic Compounds (89):-



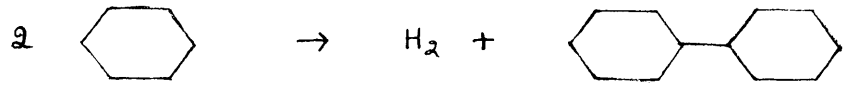
N-desylaniline.



N:N'-didesylbenzidine.

METHODS OF PREPARATION OF DIPHENYL DERIVATIVES.

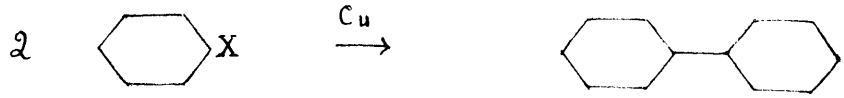
While diphenyl occurs to some extent in the 'Heavy Oil' fraction of coal tar, the main commercial source is benzene. Benzene vapour, on passage through an iron tube packed with pumice or other contact material and at a temperature of 650-800°, is converted to diphenyl by partial dehydrogenation.



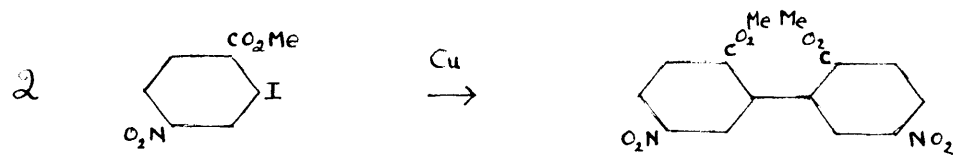
The number of substituted diphenyls which are derived directly from the parent hydrocarbon is rather limited, however, and in most cases it is necessary to have recourse to other methods of synthesis. It is proposed to classify such methods according to whether the resultant diphenyl is (A) symmetrically substituted or (B) unsymmetrically substituted with respect to each benzene nucleus; i.e., class (A) syntheses lead to the formation of diphenyl molecules which can be regarded as being formed by the union of two identically substituted phenyl groups while class (B) syntheses result in diphenyls which can be regarded as formed by the union of two differently substituted phenyl groups.

A. Symmetrical Diphenyl Syntheses.

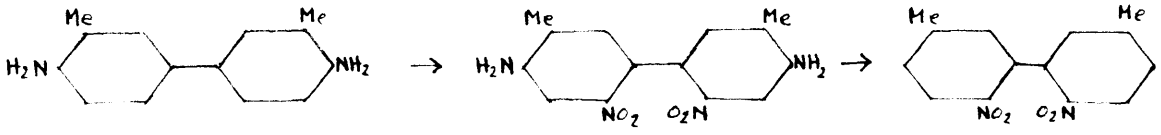
(1) The Ullmann Reaction: A halogenated benzene or benzene derivative is heated with excess copper powder or copper bronze; in some cases, the presence of a solvent (usually nitrobenzene) is advantageous. It is not possible to forecast the optimum temperature as this is determined by the particular reaction in question; the yields are widely variable and also depend mainly on the reaction in question. Where X denotes a halogen, the general reaction may be represented thus:-



A typical example of the Ullmann reaction is the formation of dimethyl 5:5'-dinitrodiphenate in 75% yield (crude product) from methyl 2-iodo-4-nitrobenzoate by stirring with copper bronze for half an hour at 200° (162):-



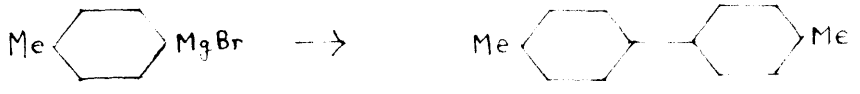
(2). Removal or introduction of substituent groups in a readily available diphenyl is useful in the preparation of relatively few derivatives, e.g. 2:2'-dinitro-5:5'-dimethyldiphenyl (III) is formed by the deamination of 2:2'-dinitro-4:4'-diamino-5:5'-dimethyldiphenyl (II), the latter being obtained from o-tolidine (I) by nitration in the presence of a large excess of concentrated sulphuric acid (47). The overall yield is 33%.



(I) (II) (III)

(3). Where an amino group is present in a benzene derivative, two molecules of the latter may be coupled by diazotisation followed by treatment with cuprous hydroxide. This process does not take place satisfactorily where the amino group possesses two, and sometimes even one, ortho substituent. Diphenic acid, however, is readily prepared from anthranilic acid, in 80% yield, by this procedure (7).

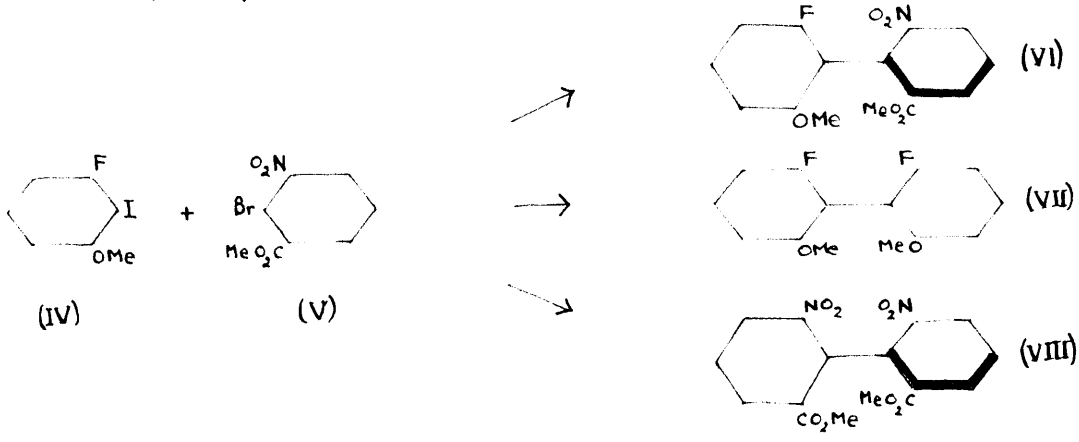
(4). In a limited number of cases in which it is possible to form a Grignard reagent from a halogenated benzene derivative, the method of Sakellarios and Kyrimis using anhydrous cupric chloride may be used to unite two benzene nuclei, e.g. p-tolylmagnesium bromide reacts with anhydrous cupric chloride to form di-p-tolyl in 84% yield (173):-



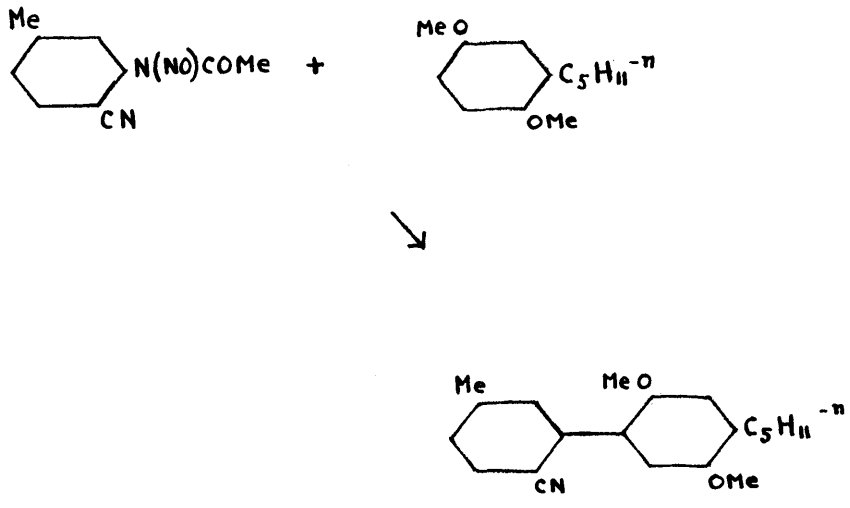
(5). In general, the rearrangement (usually brought about by mineral acids) of hydrazo compounds, in which para substituents are lacking, gives rise to benzidines, i.e. it is thus possible to prepare certain substituted 4:4-diaminodiphenyls from the corresponding hydrazo compounds. The reaction is discussed more fully at a later stage in this thesis (page 132). This rearrangement is illustrated by the formation of o-tolidine by the action of aqueous hydrochloric acid on 2:2'-dimethylhydrazobenzene (181):-

B. Unsymmetrical Diphenyl Syntheses.

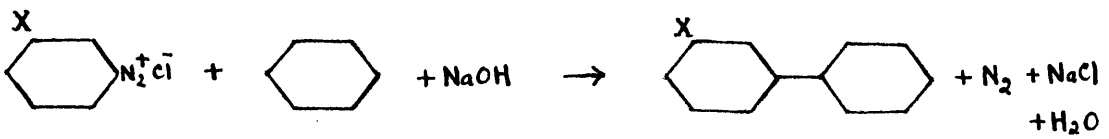
(1) The Ullmann Reaction: By a procedure similar to A (1), it is frequently possible to effect the condensation of two, differently substituted, halogenated benzenes. The formation of the two symmetrical diphenyl derivatives generally takes place at the same time and it is necessary to separate these from the desired product. The yields obtained in this reaction are generally less than in A (1) and the necessary conditions for optimum yield in any particular case can only be found by experiment. Adams and co-workers found that this was the only feasible method for the preparation of certain 2:6:2':6'-tetrasubstituted diphenyls. For example, when copper bronze is added (201), over a period of three hours, to a stirred mixture of 1-fluoro-2-iodo-3-methoxybenzene (IV) and methyl 2-bromo-3-nitrobenzoate (V) at 210-240°, methyl 2'-fluoro-2-nitro-6'-methoxydiphenyl 6-carboxylate (VI) is formed together with the symmetrical products, 2:2'-difluoro-6:6'-dimethoxydiphenyl (VII) and dimethyl 6:6'-dinitrodiphenate (VIII).



(2). The N-nitroso-N-acetylarylamine Reaction: The formation of diphenyl, by the action of N-nitrosoacetanilide on benzene, was described by Bamberger (10). This reaction was developed by France, Heilbron, Hey and collaborators (71, 72, 73, 87) as a method of synthesis of unsymmetrical diphenyl derivatives. It is believed that free radicals contribute to the mechanism of the reaction and in support of this theory it has been found that the usual directive influences of substituent groups do not apply (91, 90). The following example constitutes one stage in a synthesis of an isomer of cannabinol effected by Todd and co-workers (76) and serves to illustrate the reaction:- 2'-cyano-2:5-dimethoxy-5'-methyl-4-n-amyldiphenyl is formed by the addition of 3-N-nitrosoacetamido-4-cyanotoluene over a period of three to four hours to 2:5-dimethoxy-n-amylbenzene at 45-50°:

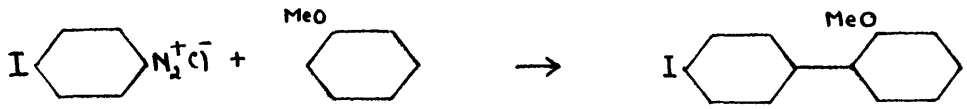


(3). The Diazo Reaction: Closely related to (2), this reaction, which was originally discovered by Bamberger (9,10) and Kuhling (113), has been developed by Gomberg and Bachmann (82) as a method of synthesis of unsymmetrical diphenyl derivatives. In this reaction, a diazotised arylamine ($ArN_2^+ Cl^-$) is converted by the action of alkali to a diazo-hydroxide (Ar-N=N-OH), an extremely reactive intermediate which is capable of reacting with an aromatic liquid to form a diphenyl derivative. The mechanism of the reaction is considered to be identical with that of (2) and to involve free radical formation (91, 90); this view is strongly supported by previous observations (8, 155, 85) on the tautomerism of N-nitrosoacetanilide with benzenediazoacetate, together with the fact that aryldiazoacetates react in a similar manner to aryldiazohydroxides (113). In the case of an arylamine with a m.substituent (X), the overall diazohydroxide reaction may be represented as follows:-



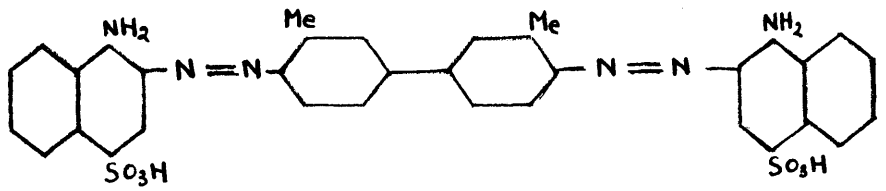
One example, which serves to illustrate the reaction, is the formation of 4-iodo-2'-methoxydiphenyl by the slow addition

of aqueous sodium hydroxide to a stirred, ice-cooled mixture of anisole and an aqueous solution of p-iodobenzenediazonium chloride (86):-



Methods B (2) and (3) are severely restricted in their application because the second coupling component must be liquid at, or only slightly exceeding, room temperature.

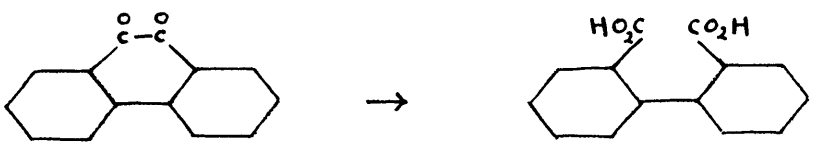
The Ullmann reaction, methods A (1) and B (1), has been extensively utilised on the laboratory scale for the preparation of diphenyl derivatives of stereochemical interest. Since benzidine and its 3:3'-disubstituted homologues (o-tolidine, o-dianisidine and o-diphenetidine) are widely used in the synthesis of direct cotton dyes (e.g. benzopurpurin (IX)), method A (5) finds extensive use on the large scale for the manufacture of these bases. This method is also of general application for the preparation of benzidines



(IX)

substituted in positions other than the 3:3' ; substantive cotton dyes, however, are not produced from 2:2'-disubstituted benzidines and the latter are not therefore produced on a technical scale although a number have been described. The other methods A (2), (3) and (4) and B (2) and (3) have been less widely employed partly because of their limited application and partly because of the limited interest and lack of application of the products.

Further methods of diphenyl formation, which have been still less frequently used, include (a) the formation of diphenyline (2:4'-diaminodiphenyl) and a few of its derivatives from hydrazobenzene and substituted hydrazobenzenes respectively (page 133) and (b) the formation of diphenic acid and a few of its derivatives by the oxidation of phenanthraquinone and substituted phenanthraquinones respectively:

(b) 

PART I.

(A) ANIL CONDENSATIONS OF BENZIDINE AND SOME OF ITS DERIVATIVES.

(B) THE NITROSYL CHLORIDE TETRAZOTISATION OF BENZIDINE.

INTRODUCTION.

I N T R O D U C T I O N.

(A) ANIL CONDENSATIONS OF BENZIDINE AND SOME OF ITS DERIVATIVES.

ANILS.

Anils (azomethines, or Schiff's bases) may be conveniently classified into two types; (a) aldehyde anils, $R'N=C\begin{matrix}H\\R^2\end{matrix}$ and (b) ketone anils, $R'N=C\begin{matrix}R^2\\R^3\end{matrix}$.

(a) Aldehyde anils. Aromatic aldehyde anils constitute the Schiff's bases proper and are, as a general rule, easily formed by the interaction of primary aromatic amines with aromatic aldehydes accompanied by the splitting off of water. According to Schiff (175), the simplest anil of this type, benzylideneaniline, Ph.CH=NPh, is formed from molecular amounts of aniline and benzaldehyde merely on gentle warming. The formation of aromatic aldehyde anils is usually effected by warming a mixture of equimolecular amounts of the aldehyde and amine in ethanolic solution; in a few cases it is necessary to omit the solvent and to heat a mixture of the aldehyde and amine to 100-120°.

(b) Ketone anils. The simplest ketone anil derived from a mixed aliphatic-aromatic ketone and a primary aromatic amine is acetophenone anil, $\begin{matrix}Me\\Ph\end{matrix}\!\!>C=NPh$, while the simplest ketone

anil derived from a purely aromatic ketone and a primary aromatic amine is benzophenone anil $Ph_2C{=}NPh$. The conditions necessary for the formation of these and homologous ketone anils were investigated by Reddelien (165) who found that in order to effect the formation of benzophenone anil, the addition of a catalyst (zinc chloride) to a mixture of benzophenone and aniline heated to 160° was necessary. In contrast, however, when acetophenone was heated with aniline in the presence of zinc chloride (164), the main product of the reaction was 1:3:5-triphenylbenzene while replacement of the zinc chloride catalyst by aniline-zinc chloride resulted in the formation of the required acetophenone anil together with a small amount of dypnone anil, $Ph(Me)C{=}CH.C(Ph){=}NPh$. It had been previously observed that acetophenone reacted with aniline at high temperatures, 250-260°, in the absence of a catalyst to form dypnone anil (88) but, on the other hand, a mixture of acetophenone diethyl acetal and aniline on heating yielded acetophenone anil (55).

These observations tend to show that the formation of ketone anils by condensation of aromatic or mixed aliphatic-aromatic ketones with aniline is not easily effected; reaction temperatures are high compared with those required for aromatic aldehyde anil formation and the presence of a catalyst is often necessary.

Mechanism of Anil Condensation.

In general, aldehydes and ketones condense with primary aromatic amines, hydroxylamine, hydrazine, phenylhydrazine and semicarbazide to form anils, oximes, hydrazones, phenylhydrazones and semicarbazones, respectively. These condensation products all possess the characteristic $>C{=}N-$ linkage and the reactions by which they are formed are considered to possess essentially the same mechanism. In the case of aldehyde anil formation, for instance, the first stage (a), is the combination of one molecule of the aldehyde with one molecule of the amine to form an addition compound (X). In the second stage, (b), the addition compound decomposes to form one molecule of the anil (XI) together with one molecule of water:-

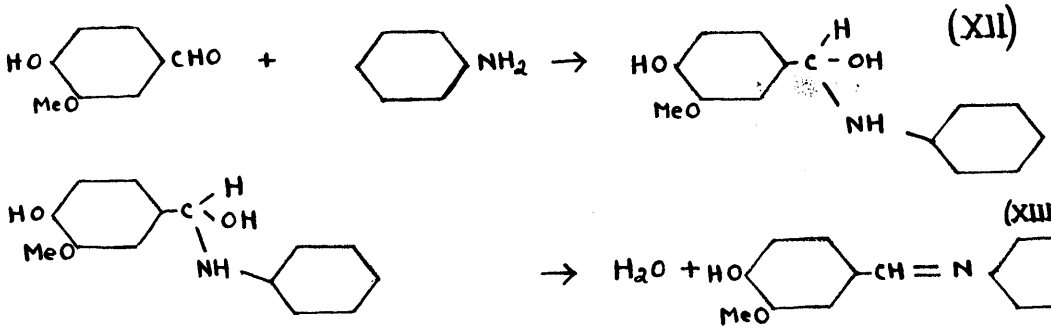
(a) $$R.CHO + H_2N.R' \rightleftharpoons R\text{-}C\begin{matrix}H\\OH\\NHR'\end{matrix} \quad (X)$$

(b) $$R\text{-}C\begin{matrix}H\\OH\\NHR'\end{matrix} \rightleftharpoons H_2O + R.CH{=}NR' \quad (XI)$$

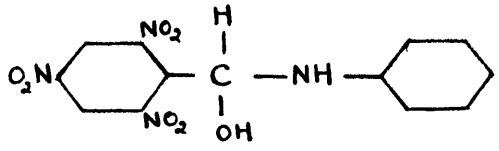
Both stages of the condensation are reversible; the hydrolysis of the anil is represented as proceeding through reverse stage (b) and reverse stage (a) consecutively with the

formation of the original aldehyde and amine.

The isolation in certain cases of such intermediate addition products constitutes chemical evidence for this mechanism of the condensation: for example, vanillinaniline (XII) was prepared and isolated (46); it was shown that when this amine-aldehyde addition product was heated at 115° loss of water occurred with the formation of vanillylideneaniline (XIII):



A similar aldehyde-amine addition product (XIV) was isolated by the action of 2:4:6-trinitrobenzaldehyde on aniline under the appropriate conditions (129):



(XIV)

Dimroth and Zoeppritz (63) described the formation of the hydrochloride of the benzaldehyde-aniline addition product by the action of benzaldehyde on an aqueous solution of aniline hydrochloride. These authors also describe the isolation of the hydrochloride of the benzophenone-aniline addition product; benzophenone-aniline hydrochloride was an unstable substance which was easily decomposed into the component amine and ketone on the one hand, and split off water to form the anil on the other, depending on the conditions. Reddelien (166) found that small amounts of halogen acids (or of the amine hydrohalide) can often be used as catalysts instead of zinc salts (page 22) in effecting the condensation of ketones with amines. This was found to apply in the case of the benzophenone-aniline condensation and, consideration of this fact in conjunction with the previous isolation of benzophenone-aniline hydrochloride (as mentioned above), led Reddelien to suggest the following mechanism of halogen acid catalysed, ketone-amine condensation.

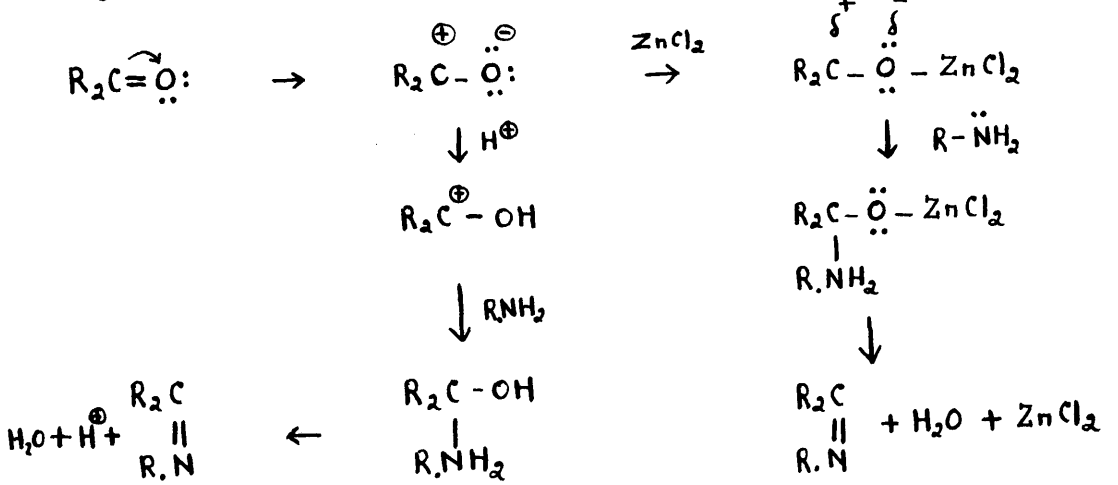
Stage 1. $R'_2.CO + R^2.NH_2 \cdots HCl = R'_2.C(OH)-NHR^2 \cdots HCl$

Stage 2. $R'_2C(OH)-NHR^2 \cdot HCl = H_2O + R'_2C=NR^2 \cdot HCl$

Stage 3. $R'_2C=NR^2 \cdot HCl + R^2NH_2 = R'_2C=NR^2 + R^2NH_2 \cdots HCl$

The ketone combines with the amine hydrochloride (Stage 1) and the addition product hydrochloride formed loses water (Stage 2) to form the ketone anil hydrochloride. The latter is converted to the ketone anil by further reaction (Stage 3) with the more basic free primary amine which is itself converted to its hydrochloride and is available for reaction with further amounts of the ketone (Stage 1).

In modern terms the following electronic interpretation would serve, zinc chloride or halogen acid acting as acid catalyst.



Anils of the Benzidine Series.

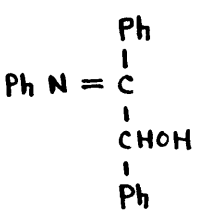
(a) Aldehyde anils. A number of anils which are formed by the condensation of aromatic aldehydes with benzidine, o-tolidine and o-dianisidine respectively have been described in the literature; these are almost invariably dianils of the type, $R.CH{=}NC_6H_4.C_6H_4N{=}CH.R$, in which one molecule of the diamine has reacted with two molecules of the aldehyde. Chemically, these dianils closely resemble the corresponding monoanils derived from aniline and aromatic aldehydes but possess the expected higher melting points and are much less soluble in organic solvents. N:N'-divanillylidenebenzidine, for example, is described as almost insoluble in all the usual organic solvents with the exception of nitrobenzene (185). The formation of these dianils is readily effected, generally by warming together the theoretical proportions of the aldehyde and amine in ethanolic solution. This procedure results for example in the formation of the di-N:N'-5-bromosalicylylidene derivatives of benzidine, o-tolidine and o-dianisidine (33).

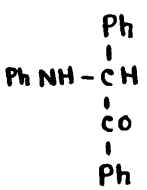
(b) Ketone anils. The condensation of benzidine and its derivatives with mixed aliphatic - aromatic and purely aromatic ketones has received little attention. Reddelien (page 25) does not appear to have further investigated the slow, zinc-

chloride-catalysed reactions of benzidine with benzophenone, benzil or benzoin. The condensation product of benzidine with benzil, however, was the subject of several later investigations which were concerned with the disproof of the Kaufler hypothesis (page 85). These investigations culminated in the identification of the product by Le Fevre and Turner (124) as the dianil, N:N'-bis[α-benzoylbenzylidene]benzidine, $Ph.CO.(Ph)C{=}N.C_6H_4.C_6H_4.N{=}C(Ph).CO.Ph$. It was accordingly decided to investigate the reactions of benzidine with benzophenone and benzoin and, in order to gain further information regarding the general reaction, acetophenone was included as a representative mixed aliphatic - aromatic ketone. Further it was decided to examine the reactions of these ketones with o-tolidine and o-dianisidine in order to ascertain the effect of the introduction of the ortho substituent groups concerned into the diamine molecule.

Reaction of Benzoin with Primary Aromatic Amines.

It was established (44) that desylaniline, the condensation product of one molecule of benzoin with one molecule of aniline, was not an anil (XV) as was formerly supposed but a true desyl compound (XVI):-

(XV) 

(XVI) 

Such desyl derivatives are not easily hydrolysed by dilute mineral acids and are thus differentiated from ketone anils most of which hydrolyse readily. It was also found (45) that ortho substitution inhibited the reactivity of the amino group to such an extent that many ortho substituted amines notably o-toluidine and o-anisidine, did not react with benzoin. It was therefore of interestto ascertain whether or not the benzidine bases would react with benzoin, the nature of any condensation products formed by the reaction and the effect of the ortho substituents on the reactivity of the amino groups.

The Ortho Effect.

The introduction of a second substituent group into a monosubstituted benzene derivative modifies to a greater or lesser extent the properties of the original compound. It has been frequently observed, however, that when a second substituent group is introduced into the ortho position to the original group, the properties of the substituted compound differ more markedly from those of the original compound than when the substituent is introduced into the meta or para positions. In addition, an abnormally large difference in the properties of the ortho substituted compound and those

of the meta and para isomers is frequently observed. This phenomenon, the ortho effect, has been discussed at greater length elsewhere (206, 31, 98a) and the following examples will suffice for illustration:-

The formation of quaternary ammonium salts by the addition of alkyl halide was found to be inhibited in the case of certain di-ortho substituted dialkylanilines (95) and hindered in the case of certain monosubstituted dialkylanilines (196). Also, the formation and hydrolysis of esters of substituted benzoic acids was hindered in certain cases where the acid possessed one ortho substituent (128) and this effect was increased when two such substituent groups were present (81).

The ortho effect, first attributed by Victor Meyer to steric hindrance, was later recognised to be of a more complex origin and frequently involved additional factors such as chelation, hydrogen bonding and the electron donating properties of the atoms concerned. It was also recognised that the factors, which operated to produce the ortho effect, varied to some extent with the specific instance concerned.

Reaction of Aromatic Aldehydes with Disodium Benzidine 2:2'-disulphonate and Related Derivatives.

In view of the optical resolutions of diphenyl-2:2'-

disulphonic acid and benzidine 2:2'-disulphonic acid diphenyl ester (page 97), it was considered that the properties of derivatives of benzidine 2:2'-disulphonic acid with respect to anil formation might be studied in order to determine the possibility of achieving an optical resolution of a racemic diphenyl derivative by forming anils with an optically active aldehyde. Although anils are not formed by free sulphonic acids, it has been previously shown (38) that sodium naphthionate condenses readily with benzaldehyde to form sodium 1-benzylideneaminonaphthalene-4-sulphonate and, at the same time, it was stated that benzidine disulphonic acid gives similar products although these were not described. In addition, it has been observed that the sodium salts of 1-aminonaphthalene-5-sulphonic acid and 2-aminonaphthalene-5-sulphonic acid form similar condensation products with benzaldehyde (65, 66). Disodium benzidine disulphonate was accordingly chosen as the first aminosulphonic acid derivative of diphenyl to be studied and the testing aldehyde was benzaldehyde.

(B) THE NITROSYL CHLORIDE TETRAZOTISATION OF BENZIDINE.

At the time when this section of the work was undertaken, January 1939, nitrosyl chloride had recently become commercially available in liquid form for research purposes. It was known that, in general, primary aromatic amines yielded diazonium salts and it was therefore considered that this reagent might lead to the tetrazotisation of benzidine.

The literature revealed that certain amines, e.g. m-nitraniline, gave corresponding diazonium chlorides; other amines, including aniline, diazoamino compounds (198). Aniline hydrochloride, on the other hand, yielded a double salt of the hydrochloride and diazonium chloride (106).

It was decided, in view of these observations, to use benzidine dihydrochloride in order to decrease the risk of diazoamino compound formation.

THEORETICAL SECTION.

THEORETICAL SECTION.

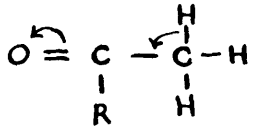
A

(A) ANIL CONDENSATIONS OF SOME BENZIDINE DERIVATIVES.

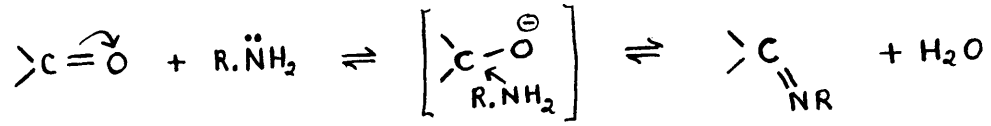
Anil Formation.

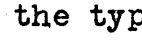
It has been pointed out (page 23) that the condensation of an aldehyde or ketone with a primary amine to form an anil involves the formation of an unstable, intermediate addition compound; the formation of oximes, hydrazones, phenylhydrazones and semicarbazones follows a similar course. The tendency of such carbonyl compounds to react in this manner with nucleophilic reagents (e.g. primary amines, hydroxylamine, hydrazine, phenylhydrazine and semicarbazide) has been ascribed to the electrophilic nature of the carbon atom of the carbonyl group. This electrophilic tendency of the carbon atom is due to resonance between $\rangle C{=}O$ and $\rangle \overset{+}{C}\text{-}\overset{-}{O}$ and in such addition reactions the double bond is polarised towards the oxygen: $\rangle C{=}\overset{\curvearrowright}{O}$, (204).

The lower reactivity of ketones in comparison with aldehydes has been explained (167) by a reduction of the electrophilic nature of the carbonyl carbon atom in ketones due to the weak hyperconjugative influence of the alkyl (or aryl) group as opposed to the lack of such an effect by the hydrogen atom of an aldehyde:



In view of the investigations of Lapworth (119) on the mechanism of formation of cyanohydrins, Watson (205) has suggested a similar mechanism for oxime and hydrazone formation. It is possible to represent analogously the formation of anils:-



The first stage of the condensation consists of the addition of the amine to the carbonyl carbon atom and this is necessarily accompanied by the complete transfer of a pair of electrons from the carbonyl carbon atom to the carbonyl oxygen atom since the covalency of the carbon atom cannot exceed four. The second stage of the condensation is the elimination of the elements of water with the corresponding adjustment of the covalencies to form the anil. In some cases (page 44) an intermediate compound of the type  is formed during the second stage by migration of a hydrogen atom. It is possible that such intermediate addition compounds are formed during all anil condensations but they are seldom sufficiently stable to permit of their isolation. Any factor which operates in such a way as to reduce the availability of the

lone pair of electrons on the nitrogen atom will reduce the tendency of the amine to anil formation.

Effect on Anil Formation of Nuclear Substituents in the Primary Aromatic Amine.

(a) The Nitro Group.

It was observed (121) that m-nitroaniline reacts easily with benzaldehyde to form N-benzylideneamino-3-nitrobenzene; this condensation takes place rapidly at room temperature in the absence of catalyst or solvent and is thus comparable with the aniline-benzaldehyde condensation (page 21). From these reactions it appears therefore that the presence of a nitro group in the meta position to the amino group does not appreciably hinder anil formation. In contrast, however, p-nitroaniline requires to be heated with benzaldehyde for a period of four to five hours at 120 to 130° in order to effect the corresponding condensation to N-benzylideneamino-4-nitrobenzene (141). It appears, therefore, that the effect of a substituent nitro group in the para position to the amino group is to exert a fairly strong hindering effect on anil formation. Furthermore, since o-nitroaniline does not react with benzaldehyde under conditions which permit anil formation in the case of the m- and p-isomers (28), it can be concluded that the presence of the nitro substituent ortho to the amino

group exerts a very strong hindering effect on anil formation.

It is possible to account for these observed facts as follows:- The nitro group is characterised by its powerful resonance effect (-T) which strongly deactivates the ortho and para positions with respect to an electrophilic attacking reagent. In the case of o- and p- nitroanilines, this effect operates to reduce the nucleophilic property of the amino group i.e. the donation of the lone pair of electrons from the nitrogen atom is rendered more difficult and the tendency of these amines to anil formation is consequently reduced. The fact that the ortho is more affected than the para isomer must be ascribed to the additional ortho effect (page 29) of the nitro group in the former which also operates to hinder anil formation. The resonance effect (-T) of the nitro group is not operative in the meta position with the result that anil formation is not retarded; this is fully borne out by the ease of reaction of m-nitroaniline. Theoretically, the inductive effect (-I) of the nitro group must operate to hinder anil formation almost equally whether the nitro group is located ortho, meta or para to the amino group. This effect is likewise due to a reduction in the availability of the lone pair of electrons on the nitrogen atom of the amino group. Theoretically, the inductive

effect of the nitro group is slight compared with its resonance effect and this is borne out by the observation that anil formation is not appreciably hindered in the case of m-nitroaniline in comparison with aniline.

(b) The Methyl Group.

The methyl group is characterised solely by its inductive effect (+I) which operates to increase the electron density in the ortho and para positions. The meta position is probably also activated with respect to electrophilic reagents but to a much smaller extent as is shown by the much smaller proportion of meta compared with ortho and para isomers obtained, for example, on nitration of toluene. The effect of a substituent methyl group in the ortho or para position to the amino group should, therefore, by reason of the increased availability of the lone pair of electrons on the nitrogen atom of the amino group, increase the tendency to condensation. In the meta position, a similar, but much reduced effect should operate to facilitate condensation.

In practice, the tendency of the three (o-, m- and p-) toluidines to condense with benzaldehyde is found to be in agreement with the above considerations. There is no difficulty in effecting condensation of any one of these isomeric

toluidines with benzaldehyde to form the corresponding anil; in each case the reaction takes place, in the absence of a solvent or catalyst, by warming on the water-bath for thirty minutes (120).

(c) The Methoxyl Group.

From theoretical considerations, the methoxyl group which is characterised by its resonance effect (+T) and its much weaker inductive effect (-I), should influence anil formation as follows:- When located in the ortho or para position to the amino group, both effects are operative but, since the former preponderates, condensation should be facilitated because of the increased availability of the lone pair of electrons on the nitrogen atom of the amino group. When located in the meta position to the amino group, only the latter effect (-I), is operative and the availability of the same lone pair of electrons should be slightly reduced. In consequence, condensation should be somewhat retarded.

In practice, o-anisidine reacts with benzaldehyde at room temperature to form the N-benzylidene derivative (36) while the corresponding derivative from p-anisidine is also easily prepared by warming together the appropriate reactants in ethanolic solution (157). N-benzylidene-m-anisidine has

not been previously described but the condensation of m-anisidine with benzaldehyde was found to take place readily with the formation of the required anil. While the most convenient method of separating this liquid anil involves heating the reaction mixture to a temperature exceeding 200° (page 69), the fact that the condensation takes place readily at room temperature, merely on mixing the aldehyde and amine, is shown by the method of formation of N-benzylidene-m-anisidine picrate (page 69).

Discussion of Experimental Results.

A. Reactions of Benzidine, o-Tolidine and o-Dianisidine with Acetophenone and Benzophenone.

(i) Benzidine.

Benzidine was found to condense fairly easily with acetophenone and benzophenone, the di-anils being formed in reasonable yield. The reactions took place rather more easily than was expected in view of Reddelien's observations (page 27) and were not dependent on the presence of a catalyst although the addition of tetralin improved the yield of the benzophenone anil. It is probable that the presence of tetralin assisted in the removal of the water formed in the condensation. In the acetophenone condensations, the same effect was achieved by the use of an excess of acetophenone.

(ii) o-Tolidine.

o-Tolidine reacted easily with acetophenone forming the di-anil but with benzophenone under various conditions of reaction no corresponding product was isolated.

(iii) o-Dianisidine.

o-Dianisidine failed to yield distinctive di-anils with either acetophenone or benzophenone under a variety of conditions.

In those cases above A (ii) and (iii) , where anil formation did not take place, the presence of the catalysts, anhydrous zinc chloride and piperidine, was not effective in promoting the reactions. Where anil formation did take place A (i) and (ii) , the nature of these condensation products followed from their ease of hydrolysis and the identification of the products of hydrolysis. The reactions of acetophenone with benzidine and with o-tolidine resulted in the formation of the corresponding acetophenone anils; in contrast to the acetophenone aniline condensation (page 22), no dypnone anils were isolated. In the experiments where no di-anil was isolated, the unchanged starting materials were recovered in varying amounts except where drastic reaction conditions resulted in extensive decomposition. It is therefore reasonable to conclude that in these cases anil formation was

inhibited and, since benzidine condensed fairly easily with both acetophenone and benzophenone, the inhibition of these reactions was caused by the presence of the ortho methyl and methoxyl groups in o-tolidine and o-dianisidine respectively.

Effect of the Methyl Groups.

Consideration of the condensations of benzaldehyde with o-, m- and p-toluidines (page 37) has demonstrated that the presence of an ortho methyl group, by reason of the inductive effect (+I) of the latter, facilitates condensation to the aldehyde anil. In the case of the acetophenone - o-tolidine condensation, the yield of di-anil was found to be considerably greater than that obtained in the acetophenone - benzidine condensation. This is accounted for by the facilitating effect of the methyl groups. In the case of the attempted benzophenone - o-tolidine reaction, however, the failure to isolate any di-anil appears, at first sight, directly to contradict such considerations. In this case, the results must be ascribed to the operation of a powerful ortho effect (page 29) which hinders the reaction. The operation of an ortho effect which was mainly steric in nature would explain the reaction of o-tolidine with acetophenone as opposed to the failure to react with benzophenone. In the former case, the relatively small methyl group of acetophenone would permit

reaction but in the latter case, the large, corresponding phenyl group of benzophenone would interfere with the condensation.

Effect of the Methoxyl Groups.

The effect of the methoxyl group on aldehyde anil formation has already been discussed (page 38); consideration of the resonance (+T) and inductive (-I) effects has shown that condensation should be facilitated in the presence of an ortho methoxyl substituent. The failure of o-dianisidine to condense with either acetophenone or benzophenone can only therefore be ascribed to the operation of a powerful hindering ortho effect of the methoxyl groups. This effect appears to be more powerful than the ortho effect of the methyl groups which does not inhibit the anil formation of o-tolidine and acetophenone.

It is of interest to note that studies of optically active diphenyls have revealed that the steric effect of the methoxyl group in preventing coplanarity of the benzene nuclei is considerably less than that of the methyl group (page 117) (78). Consideration of this observation would lead to the belief that the hindering ortho effect of the methoxyl groups on anil formation is not mainly due to steric influences.

Another example of an unexpectedly large ortho effect due to a methoxyl group has recently been described; the

steric effect of the ortho methoxyl can scarcely be responsible for the enhanced basicity of dimethyl o-anisidine (197).

B. Reactions of Benzidine, o-Tolidine and o-Dianisidine with Benzoin.

One molecule of each of the three bases: benzidine, o-tolidine and o-dianisidine was found to condense with two molecules of benzoin to form the corresponding didesyl-derivative. The reactions of benzidine and o-dianisidine with benzoin took place at about 140°, the condensation products being formed in good yield. Under similar conditions, o-tolidine did not react with benzoin but, on increasing the temperature to 160° and by prolonging the time of heating, partial condensation resulted. The most suitable method for the o-tolidine - benzoin condensation was to conduct the reaction in boiling tetralin whereby a moderate yield of product was obtained.

From the above observations, it is evident that it is more difficult to condense o-tolidine than either benzidine or o-dianisidine with benzoin while the condensations of benzidine and o-dianisidine with benzoin take place with comparable ease. In this case, the ortho effect of the methyl groups which operates to hinder the reaction must be of greater magnitude than the ortho effect of the methoxyl groups which does not

operate perceptibly. The relative ortho effects of the methyl and methoxyl groups are therefore more in proportion to their steric effects which, as has already been pointed out (page 42), would predict increased difficulty of reaction in the case where ortho methyl groups were present.

C. Reactions of some Salts of Benzidine Sulphonic Acids with Benzaldehyde.

(i) Disodium Benzidine 2:2'-Disulphonate.

Benzaldehyde was found to react, both in aqueous solution and in the absence of a solvent, with this salt; the reaction product was found to be unstable and immediately resinified on removal of the mother liquor. This instability resembles that of the addition product of benzylideneaniline and sodium bisulphite (64).

(ii) Dianiline Benzidine 2:2'-Disulphonate.

Under a variety of reaction conditions, no addition or condensation product was obtained from this salt and benzaldehyde; the starting materials remained unchanged.

The salts of benzidine 2:2'-disulphonic acid thus behave differently from those of certain naphthylamine sulphonic acids (page 31); the former do not yield stable, well defined, condensation products with benzaldehyde. It was

concluded that the unstable products obtained were of a type unsuited to the original purpose (i.e. the attempted resolution of benzidine 2:2'-disulphonic acid and its salts). In view of the unsatisfactory nature of the product obtained in (ii) above, it was considered to be of sufficient interest to investigate one other benzidine sulphonic acid salt of rather a different type in order to ascertain whether this behaviour was general in the diphenyl series.

(iii) Sodium Benzidine 3-Sulphonate.

This salt condensed easily with benzaldehyde to form the benzylideneamino-derivative; the reaction took place in aqueous solution. The method of formation and characteristic properties of the product resembled those of the corresponding products derived from the naphthylamine sulphonic acid salts to which reference has already been made. The formation of unstable reaction products with benzaldehyde is not therefore general with salts of aminosulphonic acids of the diphenyl series.

D. Anil Condensations of 2-Nitrobenzidine.

(i) Acetophenone.

In connection with aldehyde anil formation, it has already been indicated that the introduction of the nitro group into

the meta position does not hinder condensation but that a definite hindering effect is to be expected and is experienced when the nitro group is located in the ortho or para positions. Consideration of these facts, in conjunction with the failure to isolate stable anils from sodium benzidine 2:2'-disulphonate, indicated that a limited investigation of the anil formation of a further benzidine derivative containing the nitro group, also a negative group, in the ortho position to the pivot bond, might reveal some interesting peculiarities. The benzidine derivative chosen was 2-nitrobenzidine, since it appeared likely that mono-anil formation would take place were the influence of the nitro group sufficient to inhibit the reaction of the amino group in the same benzene nucleus.

With acetophenone, however, it was not possible to isolate either a mono or di-anil using the conditions of reaction under which benzidine yields the corresponding di-anil. It is evident that the presence of one nitro group in the 2 position in the benzidine nucleus exerts a powerful hindering effect on the ketone anil formation of both amino groups.

(2) Salicylaldehyde.

With regard to aldehyde anil formation, however, 2-nitrobenzidine appeared to react normally, both amino groups taking

part in the formation of the following di-anils which have been previously described in the literature (202):- N:N'-dibenzylidene-2-nitrobenzidine, N:N'-bis(4-nitrobenzylidene)-2-nitrobenzidine and N:N'-bis(2-hydroxy-3-methoxybenzylidene)-2-nitrobenzidine. These anils are easily formed by condensation of the appropriate aldehyde with 2-nitrobenzidene in ethanolic solution.

Further confirmation of the normal condensations of 2-nitrobenzidine with aromatic aldehydes was forthcoming from a study of the reaction with salicylaldehyde. 2-nitrobenzidine was found to condense normally with two molecules of salicylaldehyde to form N:N'-disalicylidene-2-nitrobenzidine in excellent yield (page 67); this reaction took place in ethanolic solution and also by direct heating of the aldehyde and amine.

E. Condensations of m-Anisidine, o-Tolidine and o-Dianisidine with Benzaldehyde.

The condensation of m-anisidine with benzaldehyde was investigated in order to complete the information required concerning the reactions of the three isomeric anisidines with benzaldehyde (page 39).

The condensation of benzidine with benzaldehyde has been previously described (176). Although the melting point of

N:N'-dibenzylidene-o-tolidine is listed in a recently published handbook of analysis (150), a search of the available literature did not, however, reveal the original reference from which it was desired to ascertain the conditions under which the condensation took place. The condensation of o-dianisidine with benzaldehyde has not been previously described. In order, therefore, to complete the information required for a comparison of the behaviour of benzidine, o-tolidine and o-dianisidine, the condensations of o-tolidine and o-dianisidine with benzaldehyde were investigated.

(1) m-Anisidine. The essential features of this reaction have already been discussed (page 39).

(2) o-Tolidine. The formation of the dibenzylidene derivative took place easily on the addition of benzaldehyde to a hot ethanolic solution of the amine.

(3) o-Dianisidine. The formation of the dibenzylidene derivative of o-dianisidine took place easily on boiling an ethanolic solution of one molecule of the diamine with two molecules of benzaldehyde. The constitution of N:N'-dibenzylidene-o-dianisidine followed from the analysis and the identification of the products of hydrolysis. This anil was much more soluble in organic solvents than the ketone anils derived from benzidine and o-tolidine and, for this reason,

it was possible to prepare a picrate by using solutions of the anil and picric acid in benzene.

It is of interest to note that the anil existed in at least three distinct physical forms; the crude anil was first obtained as a brown liquid resin which solidified to an amorphous solid which, in turn, could be obtained in a crystalline form and which melted on heating to form a clear red liquid. Other examples of polymorphism of aldehyde anils of o-tolidine and o-dianisidine were previously described by Vorländer (203); dianisylidene-o-dianisidine, dicinnamylidene--o-tolidine and dianisylidene-o-tolidine, for example, were obtained in a resinous or glass-like nature at room temperature.

The ease of formation of N:N'-dibenzylidene-o-dianisidine and the corresponding derivatives from benzidine and o-tolidine (176, 150) illustrates the absence of a hindering ortho effect on the aldehyde anil formation as compared with that found in the ketone anil formation of the three bases.

(B) THE NITROSYL CHLORIDE TETRAZOTISATION OF BENZIDINE.

For the reason already stated (page 32), the first experiment was conducted with benzidine dihydrochloride. In order to moderate the reaction and maintain a close

temperature control, benzene was used as a solvent and as a medium for the suspension of the benzidine salt. The reaction was found to be variable and the tetrazotised product invariably contained some unreacted benzidine dihydrochloride, in unfavourable cases amounting to more than 55% of the reaction product. Proof of tetrazotisation was obtained by isolation of the bis[azo-α-naphthol] derivative in low yield, 34%, as compared with the 91% yield obtained by the orthodox procedure (146). The replacement of benzidine dihydrochloride by the free amine resulted in a less satisfactory tetrazotisation.

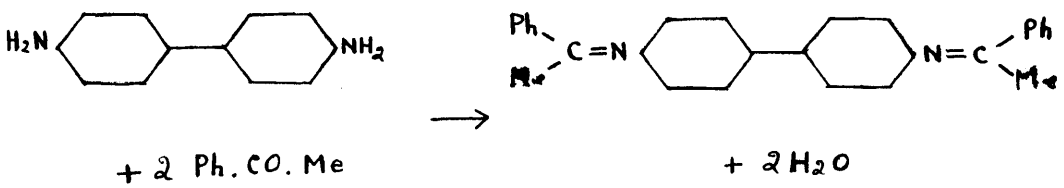
More satisfactory tetrazotisation resulted, however, when the dihydrochloride was replaced by sulphate. Evidence of tetrazotisation of benzidine sulphate was obtained by conversion to 4:4'-dihydroxydiphenyl, in approximately 68% yield which compares not too unfavourably with the 79-83% obtained by the orthodox procedure (94).

EXPERIMENTAL SECTION

EXPERIMENTAL SECTION

(A) ANIL CONDENSATIONS OF SOME BENZIDINE DERIVATIVES.

BENZIDINE-ACETOPHENONE REACTION.



Procedure:

The reaction mixture, benzidine (7.4g., 1 mol.) and acetophenone (23.4ml., 5 mols) was heated and after seven minutes, at a vapour temperature of 100°, a small amount of water distilled. After a further five minutes, when most of the excess acetophenone had distilled (202°) and the total volume of distillate amounted to 10ml., heating was discontinued (Note 1). The reaction mixture, on cooling, solidified to a brownish solid which, on treatment with ethanol, yielded a pale yellow powder, which when filtered, washed with ethanol, pressed on porous tile and dried in vacuo over solid potassium hydroxide, yielded crude N:N'-bis (1-phenylethylidene)benzidine (8.8g., 57%). Recrystallisation

from dioxan gave pale yellow, rhombic plates; m.p.242°. Analysis: Found: N,7.21%. $C_{28}H_{24}N_2$ requires N,7.22%.

N:N'-bis(1-phenylethylidene)benzidine. Properties.

(1) Moderately soluble in hot decalin; slightly soluble in hot benzene, dioxan, carbon tetrachloride or ethylene glycol monomethyl ether and almost insoluble in petroleum ether or ethanol.

(2) Readily hydrolysed by dilute mineral acids.

(3) Soluble in concentrated sulphuric acid to form a yellow solution.

(4) Exposure to the air for a few hours caused superficial decomposition with the formation of characteristic, blue, benzidine oxidation products. It was consequently necessary to store the anil in vacuo.

Note 1. Longer periods of heating caused formation of dark coloured tars of disagreeable odour. Lower yields were also obtained by shorter periods of heating or when the condensation was conducted in boiling ethanol.

Hydrolysis.

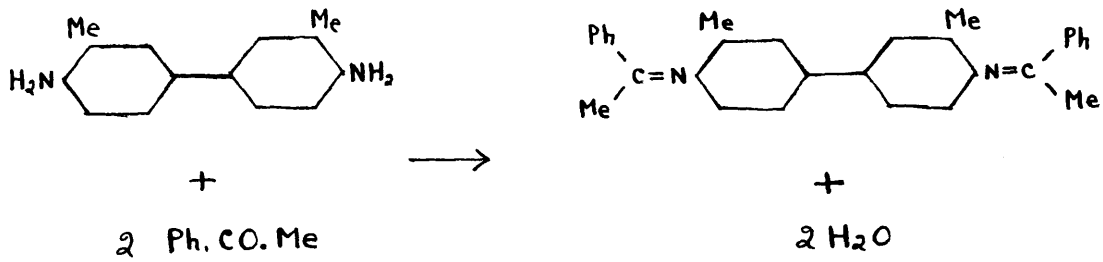
The anil was warmed with excess of 5N. hydrochloric acid when hydrolysis took place almost immediately. While the

solution was still warm, a certain amount of the colourless hydrochloride of the base was precipitated and, on dilution with water and cooling, further precipitation of the hydrochloride of the base occurred. The latter was filtered off and washed with water and with ether. The dry hydrochloride on treatment with warm aqueous ammonia yielded the free base which was filtered off, washed with water and dried; m.p. 127°, undepressed by the addition of authentic benzidine; m.p.127°. The base was dissolved in warm dilute acetic acid and acetic anhydride was dropped into the solution until precipitation of the acetyl derivative was complete. This was filtered off, washed with water and dried; m.p.316-317°, undepressed by the addition of authentic N:N'-diacetylbenzidine; m.p.316-317°.

The combined filtrate and washings from the base hydrochloride was extracted twice with ether and the combined ether extracts on evaporation yielded a ketone which was proved to be acetophenone as follows: The ketone was treated with excess saturated aqueous semicarbazide hydrochloride solution. On addition of a few drops of pyridine and after stirring for a short time, the semicarbazone of the ketone was precipitated in the form of a colourless solid. This was filtered off,

washed with water and dried; m.p.198°, undepressed by the addition of authentic acetophenone semicarbazone, m.p.198°.

O-TOLIDINE - ACETOPHENONE REACTION.



Procedure:

O-Tolidine (8.5g., 1 mol.) and acetophenone (23.5ml., 5 mols.) were heated together in a 100ml. distillation flask. A certain amount of reflux took place and, at a vapour temperature of 100°, a small volume of water distilled. When the excess of ketone had distilled, at a vapour temperature of 202°, heating was discontinued. On cooling, the reaction mixture solidified to a light brown solid which was extracted with ethanol and dried, yielding crude N:N'-bis(1-phenylethylidene)-o-tolidine (12g., 72%). The pure compound (m.p.191.5°) was obtained as pale yellow, well defined, rhombohedra by recrystallisation from dioxan.

Analysis: Found: N,6.82%. $C_{30}H_{28}N_2$ requires N,6.73%.

The general properties of this anil were found to resemble closely those of N:N'-bis(1-phenylethylidene)benzidine (page 52); similar solubilities in organic solvents, superficial decomposition on exposure to the air for a few hours and complete and rapid hydrolysis by dilute mineral acids were observed.

Hydrolysis:

This was effected by the procedure already described for the hydrolysis of N:N'-bis(1-phenylethylidene)benzidine (page 52); free base, m.p.129°, undepressed by the addition of authentic o-tolidine, m.p.129°; acetyl derivative of free base, m.p.314°, undepressed by the addition of N:N'-diacetyl-o-tolidine, m.p.314°; semicarbazone of ketone, m.p.198°, undepressed by the addition of authentic acetophenone semicarbazone, m.p.198°.

O-DIANISIDINE - ACETOPHENONE REACTION.

Procedure:

(a) The procedure described for the preparation of N:N'-bis(1-phenylethylidene)benzidine was repeated using an equivalent quantity of o-dianisidine. The reaction product consisted of the unchanged starting materials together with a small amount of dark tar. Using the same procedure, it was

found that longer periods of heating gave a dark glassy solid which separated from ethanol as a brown, uncrystallisable gum.

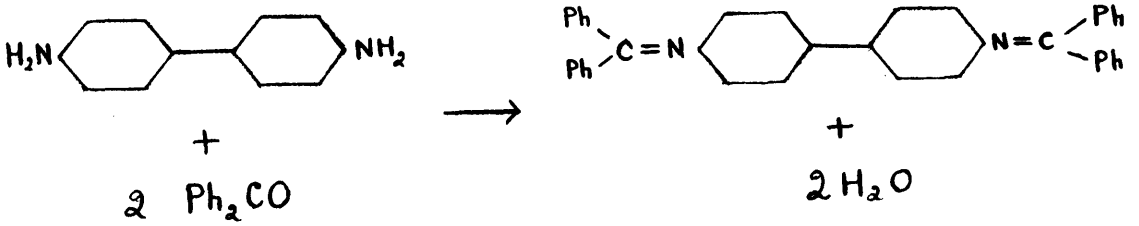
(b) Repetition of the procedures (a) with the addition of a few drops of piperidine to the reaction mixture yielded similar results.

(c) Mixtures of o-dianisidine (1 mol.) and acetophenone (2 mols.) were heated in open vessels at different temperatures and for varying periods of time. These experiments were repeated with the addition of anhydrous zinc chloride to the reaction mixture. In all cases where the starting materials were not recovered from the reaction product, the latter was found to consist of an uncrystallisable gum.

(d) In the presence of tetralin or glacial acetic acid no condensation was effected.

In (a) (b) and (c) above, in those cases where the reaction mixture was heated for considerable periods of time at high temperatures, disagreeable odours similar to those in the benzidine - acetophenone reaction (page 52 , Note 1) were observed.

BENZIDINE - BENZOPHENONE REACTION.



Procedure:

Benzidine (9g., 1 mol.), benzophenone (27g., 3 mols.) and tetralin (10g.) were heated together. At a vapour temperature of 100°, some water distilled and after most of the tetralin had distilled at a vapour temperature of 210°, the reaction mixture, on cooling, formed a viscous resin. This, on treatment with ethanol, was almost completely converted to a yellowish solid which was filtered off, washed with a little ethanol and dried in vacuo. The crude N:N'-dibenzohydrylidenebenzidine (14.5g., 58%) was purified by recrystallisation from dioxan giving yellow needles; m.p.224°.

Analysis: Found: N,5.42%. $C_{38}H_{28}N_2$ requires N,5.47%.

The properties of this anil were also found to resemble closely those of N:N'-bis(1-phenylethylidene)benzidine (page 52) and N:N'-bis(1-phenylethylidene)-o-tolidine (page 54).

Hydrolysis:

This was again effected by the procedure already described for the hydrolysis of N:N'-bis(1-phenylethylidene)benzidine (page 52) giving; free base, m.p.127°, undepressed by the addition of authentic benzidine, m.p.127°; acetyl derivative of free base, m.p.316-317°, undepressed by the addition of

authentic N:N'-diacetylbenzidine, m.p.316-317°; phenylhydrazone of ketone, m.p.137°, undepressed by the addition of authentic benzophenone phenylhydrazone, m.p.137°.

O-TOLIDINE - BENZOPHENONE REACTION.

Procedure:

(a) The procedure described for the preparation of N:N'-dibenzohydrylidenebenzidine was repeated using an equivalent amount of o-tolidine. After the tetralin had distilled at 210°, the vapour temperature rose to 230°, when heating was discontinued. On cooling, the reaction mixture formed an uncrystallisable tar. Similar results were obtained with increased and reduced amounts of tetralin in the original reaction mixture.

(b) A mixture of o-tolidine (1 mol.) and benzophenone (2 mols.), contained in an open vessel, was heated at 220° by means of a metal bath for thirty minutes during which the liquid mixture darkened in colour. On cooling, the mixture solidified to a light-coloured hard material which consisted mainly of unchanged starting materials. Similar results were obtained with the addition of piperidine (12 drops) to the original reaction mixture.

(c) Procedure (b) was repeated; in this case, however, a melt temperature of 270° was maintained for the same period

of time. The starting materials were recovered unchanged and similar results were obtained in the presence of piperidine (12 drops).

(d) Procedure (c) was repeated using anhydrous zinc chloride (4g.) in place of piperidine; similar results were obtained.

O-DIANISIDINE - BENZOPHENONE REACTION.

Procedure:

Utilising the procedures described under the o-tolidine-benzophenone reaction, similar negative results were obtained; in those cases where the starting materials were not recovered from the final reaction mixture, the latter was found to consist of a dark, uncrystallisable tar.

BENZIDINE - BENZOIN REACTION.

Procedure:

A mixture of benzidine (3.7g., 1 mol.) and benzoin (8.5g., 2 mols.) in an open, 100ml., conical flask was slowly heated by means of an oil-bath. The mixture was stirred from time to time by means of a thermometer and after about twelve minutes' heating when the temperature of the mixture was about 140°, frothing took place and steam was evolved.

The oil-bath was maintained at 150-160° for a further eight minutes when the reaction mixture caked to a hard yellow solid. After cooling, the contents of the flask were powdered and extracted with boiling ethanol (40ml.) for ten minutes. The cooled mixture was filtered, the residue washed with ethanol and dried in vacuo; N N'-didesylbenzidine was thus obtained in the form of an amorphous, yellow powder (9.7g., 85%). A portion of the product was purified by recrystallisation from ethylene glycol monomethyl ether from which it separated in the form of four-sided micro needles; m.p.220-221°.

Analysis: Found: N,5.08%. $C_{40}H_{32}O_2N_2$ requires N,4.90%.

N:N'-didesylbenzidine was found to be almost insoluble in ethanol, acetone, ether or petroleum ether; very sparingly soluble in benzene, toluene or decalin; slightly soluble in nitrobenzene, pyridine, tetralin, dioxan or ethylene glycol monomethyl ether. The compound was particularly resistant to hydrolysis; prolonged exposure to the air was without effect while prolonged boiling with concentrated hydrochloric acid produced minute amounts of benzoin leaving the main bulk of the desyl compound unattacked.

O-TOLIDINE - BENZOIN REACTION.

Procedure:

A mixture of o-tolidine (3.5g., 1 mol.), benzoin (7.5g., 2.1 mols.) and tetralin (10g.) was heated for forty-five minutes when a small amount of water and most of the tetralin distilled. A clear, amber-coloured melt was formed and, on cooling and boiling with ethanol, was converted to a brownish-yellow solid which was filtered off and dried in vacuo. The impure N:N'-didesyl-o-tolidine was further purified by a second ethanol extraction which resulted in the formation of a deep yellow solid (5.0g., 50%). The product was recrystallised from dioxan from which it separated as flat, four-sided, microneedles; m.p.192°.

Analysis: Found: N,4.71%. $C_{42}H_{36}O_2N_2$ requires N,4.67%.

N:N'-didesyl-o-tolidine closely resembled N:N'-didesyl-benzidine in its relative insolubility in organic solvents and in its extreme resistance to hydrolysis by mineral acids.

O-DIANISIDINE - BENZOIN REACTION.

Procedure:

A mixture of o-dianisidine (2.4g., 1 mol.) and benzoin (4.2g., 2 mols.) contained in an open, 100ml., conical flask

was slowly heated by means of an oil-bath. The mixture was stirred from time to time with a thermometer and after about seven minutes' heating, when the temperature of the molten mixture was about 140°, frothing took place and steam was evolved. The temperature of the reaction mixture was maintained at 150-160° for a further ten minutes when frothing ceased and the mixture set to a hard, orange-yellow solid. This was powdered and refluxed with ethanol (25ml.) for ten minutes. The cold mixture was filtered and the residue was washed with a little ethanol, pressed on porous tile and dried in vacuo giving N:N'-didesyl-o-dianisidine (5.5g., 88%). A portion was purified by recrystallisation from ethylene glycol monomethyl ether from which it separated in the form of microneedles; m.p.196-202° (with previous softening).

Analysis: Found: N,4.63%. $C_{42}H_{36}O_4N_2$ requires N,4.43%.

This compound also closely resembled N:N'-didesylbenzidine in its low solubility in organic solvents and its resistance to hydrolysis by mineral acids.

OTHER PROCEDURES FOR BENZOIN CONDENSATIONS.

While the three procedures which have just been described resulted in the formation of the desyl derivatives of benzidine, o-tolidine and o-dianisidine respectively, it was found

that these derivatives were not formed by boiling together benzoin (2 mols) with the appropriate diamine (1 mol.) in ethanolic solution. In addition, benzoin (2 mols) failed to condense with o-tolidine (1 mol.) at 140°, while prolonged heating at 160° resulted in partial condensation to the desyl derivative.

DISODIUM BENZIDINE 2:2'-DISULPHONATE - BENZALDEHYDE REACTION

Procedure 1.

Disodium benzidine 2:2'-disulphonate (3g., 1 mol.) was heated in an open vessel with benzaldehyde (5g., 2.5 mols). After boiling for fifteen minutes, the yellowish mixture was set aside to cool when a colourless paste was formed. The latter was extracted with ethanol in which it was almost completely soluble except for a small amount of colourless solid which was filtered off, washed with ethanol and recrystallised from aqueous ethanol. This was found to consist of unchanged sodium salt. On concentration, the ethanolic extract precipitated a gum which was redissolved by the addition of ethanol. The slow dropwise addition of ether to the ethanolic solution produced a yellowish precipitate which resinified to a light brown gum on removal of the mother liquor.

Procedure 2.

A concentrated aqueous solution of disodium benzidine 2:2'-disulphonate (1 mol.) was shaken with benzaldehyde (2 mols) when formation of a deep yellow colour was observed. The solution, on remaining three days at room temperature, produced a small amount of yellowish precipitate which also resinified to a light brown gum on removal of the mother liquor.

DIANILINE BENZIDINE 2:2'-DISULPHONATE - BENZALDEHYDE REACTION.

It was found that dianiline benzidine 2:2'-disulphonate did not condense with benzaldehyde when a mixture of these substances was heated either alone or in the presence of a small amount of piperidine; in both cases the aniline salt was recovered unchanged from the reaction mixture. In addition, when an aqueous suspension of the aniline salt was shaken with benzaldehyde, no reaction occurred.

BENZIDINE 3-SULPHONIC ACID.

This compound was prepared by heating dry powdered benzidine acid sulphate as described by Griess and Duisberg (83, 14).

SODIUM BENZIDINE 3-SULPHONATE.

This compound was prepared by dissolving benzidine 3-sulphonic acid in excess of aqueous sodium hydroxide solution and evaporating to dryness. The residue was extracted with hot ethanol and the undissolved salt was filtered off, washed twice with ethanol and dried at 80°.

SODIUM BENZIDINE 3-SULPHONATE - BENZALDEHYDE REACTION.

Benzidine 3-sulphonic acid (1 mol.) was dissolved in aqueous sodium carbonate solution and a small amount of ethanol and benzaldehyde (2 mols) were added. The mixture was vigorously shaken and allowed to remain at room temperature for several hours when golden-yellow, lustrous, four-sided leaflets were precipitated. These were filtered off, washed with ethanol and dried in vacuo. The filtrate on concentration yielded a further small amount of the same product, sodium N:N'-dibenzylidenebenzidine 3-sulphonate.

Analysis: Found: N,5.97%. $C_{26}H_{19}O_3N_2SNa$ requires N,6.06%.

This anil was not decomposed by cold water but was slowly hydrolysed by boiling water with the liberation of benzaldehyde. Warm dilute hydrochloric acid also hydrolysed the anil with the transient formation of an orange-yellow compound

which almost immediately decomposed with the formation of benzaldehyde and benzidine 3-sulphonic acid. The anil was found to be insoluble in the usual organic solvents.

2-NITROBENZIDINE.

This was obtained from the impure technical product by recrystallisation of the sulphate according to the directions of Cain and May (41). This method was found to be more effective than recrystallisation of the crude base from either water or aqueous ethanol.

2-NITROBENZIDINE - ACETOPHENONE REACTION.

In a distillation apparatus fitted with a fractionating column, 2-nitrobenzidine (5g., 1 mol.) and acetophenone (18g., 7 mols) were heated for one hour when most of the acetophenone distilled. It was noted that the distillate did not contain water. The reaction mixture, on cooling, formed a dark red brown viscous liquid which could not be crystallised. This material was soluble in ethanol from solution in which, however, no crystalline solid was obtained on concentration. The starting materials were recovered from this ethanolic solution of the reaction product as follows: the ethanol was removed by evaporation, the recovered reaction product was boiled with phenylhydrazine and the mixture boiled for a short

time with ethanol. The ethanolic solution, on cooling, precipitated the solid phenylhydrazone which was filtered off, washed twice with ethanol and dried; m.p.105°, undepressed by the addition of authentic acetophenone phenylhydrazone; m.p.105°. The ethanolic filtrate from the phenylhydrazone was warmed and excess acetic anhydride was added when the acetyl derivative of the amine was precipitated. This was filtered off, washed several times with ethanol and dried; m.p.$\nless$310°, undepressed by the addition of authentic N:N'-diacetyl-3-nitrobenzidine; m.p.$\nless$310°.

2-NITROBENZIDINE - SALICYLALDEHYDE REACTION.

Procedure 1.

2-Nitrobenzidine (5g., 1 mol.) and salicylaldehyde (10g., 4 mols) were heated together. At a vapour temperature of 100°, some water distilled and heating was continued for a further fifteen minutes. At this stage, most of the excess salicylaldehyde had distilled and the vapour temperature had risen to 160°. The reaction mixture, on cooling, formed a pale brown solid which was powdered and extracted twice with separate portions of boiling ethanol. The crude anil thus obtained was filtered, washed with ethanol and dried (9.1g., 95%); m.p.178-183°. A portion of the product was purified

by recrystallisation from dioxan from which it separated in the form of pale yellow, glistening, rhombic plates; m.p. 185°.

Analysis: Found: N,9.36%. $C_{26}H_{19}O_4N_3$ requires N,9.61%.

N:N'-disalicylidene-2-nitrobenzidine thus prepared was almost insoluble in ether or ethanol and moderately soluble in benzene or dioxan; boiling with dilute hydrochloric acid rapidly hydrolysed the anil with the formation of salicylaldehyde and 2-nitrobenzidine.

Procedure 2.

Ethanolic solutions of 2-nitrobenzidine (2g., 1 mol.) and salicylaldehyde (2.1g., 2 mols) were mixed and, after a few minutes, a dense yellow precipitate was formed. The mixture was then refluxed for a short time and allowed to cool. The solid was filtered off, washed and dried giving the crude anil (3.6g., 94%); m.p.175-180°. A portion was recrystallised from dioxan; m.p.185°, undepressed by the addition of authentic N:N'-disalicylidene-2-nitrobenzidine; m.p.185°, prepared by procedure 1.

M-ANISIDINE.

This compound was prepared according to the directions of Reverdin and de Luc (168) by the following route:-

m-aminophenyl → N-acetyl-m-aminophenyl → N-acetyl-m-anisidine → m-anisidine.[5]

M-ANISIDINE - BENZALDEHYDE CONDENSATION.

m-Anisidine (10.1g.) was added to benzaldehyde (8.7g.) when the liquid mixture warmed spontaneously and became turbid. After remaining at room temperature for four hours, the mixture was distilled under reduced pressure. Water distilled first followed by a pale yellow oil (12.5g., 72%), b.p.$_{9-10mm.}$ 196-200°. A portion of the product was redistilled under reduced pressure giving pure N-benzylidene-m-anididine, b.p. $_{8mm.}$ 192-193°.

Analysis: Found: N,6.55%. $C_{14}H_{13}ON$ requires N,6.63%.

This compound, which did not crystallise on remaining at room temperature for several weeks, was easily hydrolysed by hot dilute hydrochloric acid with the regeneration of m-anisidine and benzaldehyde.

N-BENZYLIDENE-m-ANISIDINE PICRATE.

A slight excess of ethanolic picric acid (1.2mols) was added to a mixture of benzaldehyde (1 mol.) and m-anisidine (1 mol.). The clear yellow solution was shaken and, in the course of a few minutes, spherical clusters of yellow needles commenced to separate. When precipitation was complete, the

product was filtered off and dried. The N-benzylidene-m-anisidine picrate, which was thus obtained in almost theoretical yield, was essentially pure; m.p.122°. A small amount was recrystallised from ethanol.

Analysis: Found: N,12.8%. $C_{20}H_{16}O_8N_4$ requires N,12.8%.

This compound was unstable, decomposing slowly in contact with air.

The same compound was also formed on mixing ethanolic solution of N-benzylidene-m-anisidine and picric acid.

O-TOLIDINE - BENZALDEHYDE REACTION.

This reaction yielded N:N'-dibenzylidene-o-tolidine which has been previously described in the literature (page 48).

To a hot solution of o-tolidine (4g., 1 mol.) in ethanol (30 ml.) was added benzaldehyde (4g., 2 mols). The solution, on cooling, deposited N:N'-dibenzylidene-o-tolidine as a pale yellow, finely-divided solid (5.5g., 76%); m.p.149-150°. A portion of the product was recrystallised from benzene-petroleum ether giving the pure compound as small, yellow needles; m.p.154° (Note 1).

Analysis: Found: N,7.12%. Calculated for $C_{28}H_{24}N_2$: N,7.22%.

Hydrolysis of this compound to benzaldehyde and o-tolidine

was easily effected by means of warm dilute hydrochloric acid.

Note 1. The previously recorded melting point is 152° (page 47).

O-DIANISIDINE - BENZALDEHYDE REACTION.

Procedure:

To a boiling solution of o-dianisidine (4.9g., 1 mol.) in ethanol (40ml.), benzaldehyde (4.2g., 2 mols) was added. After boiling for a few minutes, the solution was allowed to cool to room temperature when a brown, resinous liquid was precipitated on the walls of the containing vessel. This liquid was converted to a pale coloured, amorphous solid by scratching and agitation with a glass rod. After remaining at room temperature for twenty-four hours, the suspension was filtered and the dull yellow solid thus obtained was washed twice on the filter with successive small volumes of chilled ethanol. The crude, powdered anil was further purified by extraction with boiling ethanol (30ml.) after which it was dried in vacuo (7.4g., 88%); m.p.149-151° to a clear red liquid. A specimen of the pure anil, N:N'-dibenzylidene-o-dianisidine, was obtained for analysis by two recrystallisations of the crude product from methanolic benzene and was thus obtained in the form of small, pale yellow plates; m.p.155°, almost insoluble in ether, petroleum ether or methanol,

slightly soluble in hot ethanol and soluble in warm benzene or toluene.

Analysis: Found: N,6.65%. $C_{28}H_{24}O_2N_2$ requires N,6.67%.

Hydrolysis:

Dilute hydrochloric acid was added to a small amount of the pure anil; the latter was immediately coated with an orange coloured solid which quickly decomposed and dissolved on warming the mixture. The latter was heated to boiling, cooled and extracted with ether. The aqueous layer was basified with sodium hydroxide solution and the crude amine thus precipitated was filtered off, dried on filter paper and recrystallised from aqueous methanol. The freshly prepared amine was almost colourless but, on exposure to the air for several hours, discolouration occurred; m.p.137-138°, undepressed by the addition of authentic o-dianisidine, m.p.137-138°. The amine was converted to the diacetyl derivative by the addition of excess acetic anhydride to the solution of the amine in glacial acetic acid, boiling for a few minutes, cooling the solution after dilution with water, and setting aside to crystallise. The diacetyl derivative was filtered off, washed several times with water then with methanol and dried; m.p.242°, undepressed by the addition of authentic

N:N'-diacetyl-o-dianisidine, m.p.242°.

The ethereal layer was filtered, the ether evaporated and a concentrated aqueous solution of sodium acetate and semicarbazide hydrochloride added to the oily residue. The semicarbazone was quickly formed on stirring; this was filtered, washed with water and dried; m.p.222°, undepressed by the addition of authentic benzaldehyde semicarbazone, m.p. 222°.

N:N'-DIBENZYLIDENE-O-DIANISINDE DIPICRATE.

A hot solution of N:N'-dibenzylidene-o-dianisidine (1 mol.) in benzene was added to a hot solution of picric acid (2.5 mols) in benzene. The dipicrate was precipitated immediately in the form of a finely divided, orange solid; m.p. (dec.) 202-203°; (yield, almost theoretical). This compound was almost insoluble in benzene and was decomposed into its constituents by warm ethanol.

Analysis: Found: N, 12.9%. $C_{28}H_{24}O_2N_2+2(C_6H_3O_7N_3)$ requires N, 12.8%.

ANALYSIS.

Estimation of the nitrogen content of the ketone anils was effected by the slightly modified Kjeldahl method described by H.E. Crossley (60). This method afforded satisfactory results with the anils used, the disadvantage being this relatively large quantity of the substance (0.8 - 1.0g.) necessary for duplicate estimations.

(B) THE NITROSYL CHLORIDE TETRAZOTISATION OF BENZIDINE.

CONVERSION OF BENZIDINE TO THE BIS(AZO-α-NAPHTHOL) DERIVATIVE BY MEANS OF NITROSYL CHLORIDE.

To a mechanically stirred suspension of finely powdered benzidine dihydrochloride (5.8g., 1 mol.) (Note 1) in dry benzene (50ml.) at 0°, was gradually added a solution of nitrosyl chloride (3g., 2 mols) in dry benzene (50ml.) cooled to 0°. After the addition of the nitrosyl chloride solution, stirring was continued for fifty minutes, the temperature of the mixture being maintained at -5 to 0°. The suspension was filtered and the residue washed with a small amount of chilled benzene. The light grey solid thus obtained was dried in warm air (Note 2), dissolved in ice-cold water (25ml.) and the solution filtered to free it from a slight amount of suspended matter. This solution (Note 3) was added gradually to a stirred, ice-cold solution of α-naphthol (6.6g.) in ethanol (220ml.). The mixture was allowed to remain at room temperature for twenty-four hours. The solid product was filtered off and warmed with excess of aqueous sodium acetate solution. This solution was filtered and the residue was washed well with water and dried (3.8g., 34%). This solid, on recrystallisation from pyridine, formed a dark green solid; m.p. 212°, undepressed by the addition of authentic diphenyl-4:4'-

bis[(azo-4)-naphthol-(1)], m.p.212°. The characteristic properties of the product were also found to be identical with those of the authentic compound: insoluble in boiling water or dilute hydrochloric acid, sparingly soluble in ether or benzene to give yellow-red solutions and soluble in acetone to give an orange-red solution which was coloured violet on the addition of ethanolic potassium hydroxide.

Note 1. Replacement of the benzidine dihydrochloride by the equivalent quantity of benzidine resulted in the formation of a mixture of benzidine dihydrochloride and benzidine tetrazonium chloride together with a brown, water-insoluble substance - probably a diazoamino compound. The action of nitrosyl chloride on the free base did not result in a satisfactory tetrazotisation.

Note 2. In a separate experiment, the air-dried reaction product was examined as follows. On touching a small piece with a hot metal rod, decomposition occurred with a slight noise and with the copious evolution of fumes. Another portion was dissolved in water and the deeply coloured solution (a) gave a red-blue precipitate on addition to excess alkaline β-naphthol solution and (b) effervesced violently on warming.

Note 3. From this point the procedure is essentially that described by Mohlau and Kegel (146).

DIPHENYL-4:4'-BIS[(AZO-4)-NAPHTHOL-(1)].

This compound was prepared according to the instructions of Mohlau and Kegel (146).

CONVERSION OF BENZIDINE TO 4:4'-DIHYDROXYDIPHENYL BY MEANS OF NITROSYL CHLORIDE.

To a mechanically stirred suspension of finely powdered benzidine sulphate (7.6g., 1 mol.) in dry benzene (80ml.) cooled to 0°, was gradually added a solution of nitrosyl chloride (3.6g., 2 mols) in dry benzene (30ml.) cooled to 0°. After the addition of the nitrosyl chloride solution, the mixture was stirred at 0° for a further fifteen minutes when a bright yellow solid remained in suspension. This was filtered off, washed with a small amount of chilled dry benzene and gently dried in warm air. The dry solid was added to 5% aqueous sulphuric acid(500ml.) and steam was passed through the mixture until the tetrazonium salt was completely decomposed. During the passage of the steam, effervescence took place and a light cream coloured solid was deposited. A small amount of tarry material which adhered to the steam inlet tube was removed and the crude solid product was filtered off and dried (5.3g.). This was recrystallised from boiling water (4 litres) giving the pure product (2.7g.). The aqueous mother liquors on concentration deposited a further 0.7g. of

the product. The product thus amounted to 3.4g. (68%); m.p.271-272°, undepressed on the addition of authentic 4:4'-dihydroxydiphenyl, m.p.271-272°. In addition, the characteristic properties of the product were found to be identical with those of the authentic compound: an almost colourless crystalline solid which was sparingly soluble in water and separated therefrom in small needles, easily soluble in ethanol or ether and which gave a brilliant violet colour with bleaching powder solution.

Note 1. The replacement of benzidine sulphate by the equivalent quantity of benzidine dihydrochloride in this preparation did not give satisfactory results; a lower yield of impure 4:4'-dihydroxydiphenyl was obtained.

Note 2. From this point the procedure is essentially that of Hirsch (94).

4:4'-DIHYDROXYDIPHENYL.

This compound was prepared according to the directions of Hirsch (94).

ESTIMATION OF THE TETRAZOTISATION OF BENZIDINE DIHYDROCHLORIDE BY NITROSYL CHLORIDE.

The first part of the procedure for the preparation of diphenyl-4:4'-bis[(azo-4)-naphthol-(1)], (page 74), was repeated and the dry benzene-washed reaction product (Note 1)

was treated as follows:- The product (2g.) was dissolved in ice-cold water and this solution was slowly added with stirring to a cold, alkaline solution of β -naphthol (2g.); an excess of alkali was used in order to maintain the alkalinity of the mixture after this addition. After remaining overnight, the red-blue precipitate was filtered, washed with a small amount of cold water and dried. The finely powdered solid was extracted with warm dilute acetic acid, filtered and acetic anhydride was added to the filtrate until no further precipitation of solid occurred. The product was filtered, purified by boiling with ethanol and dried (1.2g.); m.p. 316-317°, undepressed by the addition of authentic N:N'-diacetylbenzidine; m.p.316-317°.

If it is assumed that the conversion of benzidine dihydrochloride to N:N'-diacetylbenzidine takes place in theoretical yield, the amount of the former in 2g. of the reaction product was therefore 1.15g., i.e. the reaction product contained 55% of benzidine dihydrochloride. Since benzidine dihydrochloride is almost but not quite wholly converted under these conditions to N:N'-diacetylbenzidine, it is evident that the reaction product consisted of slightly more than 55% of benzidine dihydrochloride.

Note 1. The product was found to be variable in composition; in one experiment reproducible explosion points 99-101° were recorded while in the present experiment, no analagous explosion point was recorded; decomposition took place gradually from 100-200°.

P A R T II.

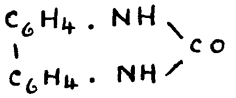
SOME DIBROMODIMETHYLBENZIDINES OF STEREOCHEMICAL INTEREST

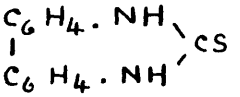
HISTORICAL SECTION

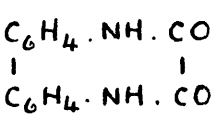
HISTORICAL SECTION

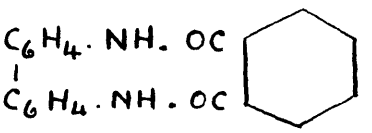
THE STEREOCHEMISTRY OF DIPHENYL DERIVATIVES

Prior to the year 1907, it had been shown (140,27,177,112) that benzidine reacted respectively with phosgene, thiophosgene, oxalyl chloride and phthalyl chloride and in each case, the product was assumed to have been formed by the simultaneous reaction of both benzidine amino groups with the reagent; the products were considered to be carbonylbenzidine (I), thiocarbonylbenzidine (II), oxalylbenzidine (III) and phthalylbenzidine (IV):

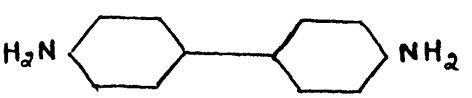
(I) 

(II) 

(III) 

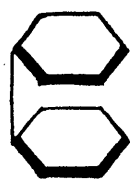
(IV) 

From stereochemical considerations, it was unlikely that the benzene nuclei of benzidine were coaxially united (V) since the relative remoteness of the amino groups would preclude the formation of such condensation products.

(V) 

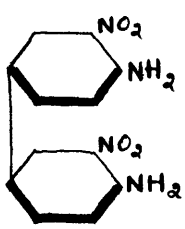
In order to explain the formation of these and other similar (supposedly cyclic) products, Kaufler (107,108), in the year 1907, advanced a hypothesis of the structure of diphenyl derivatives; the two rings in the diphenyl molecule being considered to be spatially situated so that the para positions were adjacent. While Kaufler's diagrams(VI) indicated that the rings were situated in parallel planes, he stated that the planes of the rings were inclined at an angle to each other. If, in structure (VI), the benzene rings are considered to be perpendicular to the plane of the paper, the bold type indicates the sides of the rings nearest to the eye.

(VI)

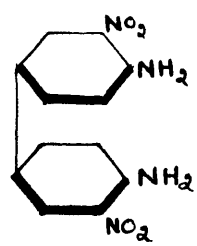


The Kaufler hypothesis was greatly strengthened by the explanation which it offered of the apparent existence of two distinct and, supposedly, geometrically, isomeric, 3:3'-dinitrobenzidines (194,11,35,29,39,40); a rigid folded molecule permitted the existence of these forms:- 3:3'-dinitrobenzidine (VII) and 3:5'-dinitrobenzidine (VIII).

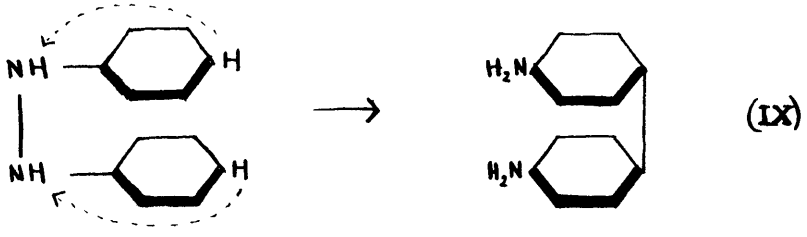
(VII)



(VIII)



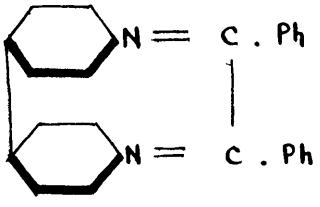
The apparent existence of two, geometrically, isomeric forms of 2:2'-dinitro-6:6'-dicarboxydiphenyl was similarly explained (180,179,109) and Kaufler suggested that the para coupling in the rearrangement of hydrazobenzene to benzidine could be more simply explained on the basis of the folded structure (IX).



(IX)

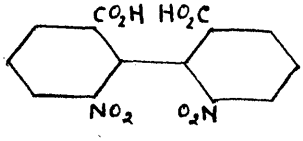
Verification of the Kaufler hypothesis by further experimental work was undertaken by various workers. Additional derivatives were prepared in which it was assumed that both amino groups of the benzidine molecule had reacted with one molecule of the attacking reagent to form cyclic condensation products; the structures of the latter were not established. One such product (X) was prepared by the condensation of benzidine with benzil (42).

(X)

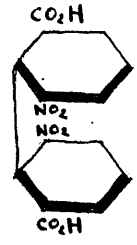


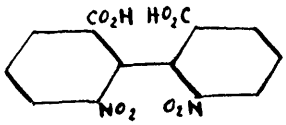
One of the strongest pieces of evidence in favour of the Kaufler hypothesis was the successful resolution (52) in the

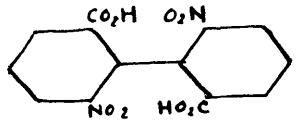
year 1922, by Christie and Kenner, of 6:6'-dinitrodiphenic acid into optically active forms. The acid (XII) was regarded on the Kaufler hypothesis as the trans form (XIV) of the two possible, geometrically, isomeric acids (XIII and XIV), the existence of these two modifications (cis and trans) having already been postulated to account for observed geometrical isomerism (page 82). From stereochemical considerations, the Kaufler, trans modification (XIV) should be optically resolvable and the factual demonstration of this prediction served greatly to strengthen the Kaufler Hypothesis. It was, however, pointed out by Christie and Kenner that, from similar considerations, although neither the cis (XV) nor the trans (XVI) form of an acid in which the benzene nuclei were coaxial and coplanar, should be optically resolvable, the required asymmetry for optical isomerism existed in both geometrically isomeric forms (XVII and XVIII) of the acid in which the benzene nuclei were coaxial and non-coplanar. Due to the apparent existence of geometrical isomers, which was not permitted by a diphenyl molecule in which the benzene nuclei were coaxial and lay in perpendicular planes, the latter possibility was not considered.

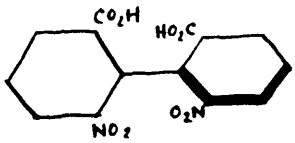
(XII) 

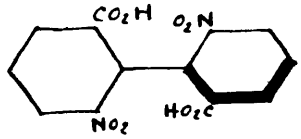
(XIII) 

(XIV) 

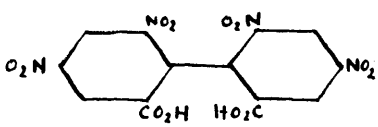
(XV) 

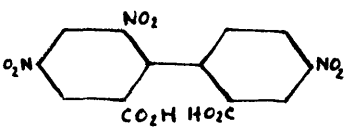
(XVI) 

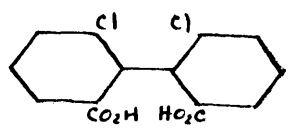
(XVII) 

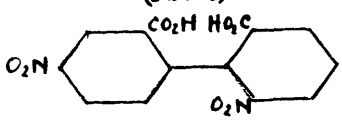
(XVIII) 

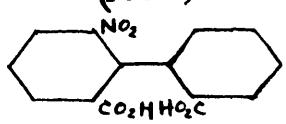
Further investigations (52,53,51,50,20) showed that certain other substituted diphenic acids (XIX,XX,XXI,XXII,XXIII) were capable of resolution into optically active forms:-

(XIX) 

(XX) 

(XXI) 

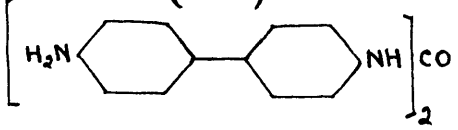
(XXII) 

(XXIII) 

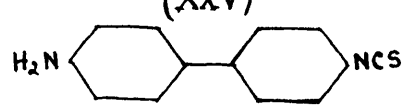
During the period in which research on the optical resolution of these substituted diphenic acids was proceeding, other investigations of the original evidence upon which the Kaufler hypothesis was founded, were carried out. The condensation products of benzidine with phosgene, thiophosgene and phthalyl chloride were found to be correctly represented by (XXIV), (XXV) and (XXVI) respectively, while the condensation product of

benzidine with oxalyl chloride was shown to possess a free amino group (124); the constitutions (I), (II), (IV) and (III) respectively (page 80) formerly assigned to these products were thus shown to be erroneous. Similarly the benzidine - benzil condensation product (X) was shown to be N:N'-Bis (∝-benzoylbenzylidene)-benzidene (Xa) (68, 124).

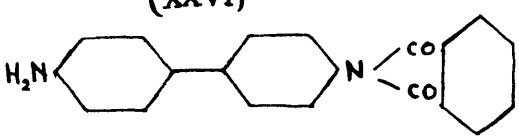
(XXIV)



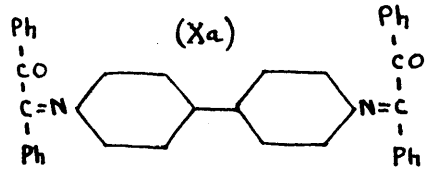
(XXV)



(XXVI)

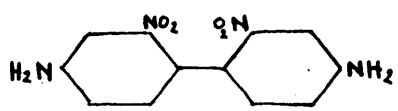


(Xa)

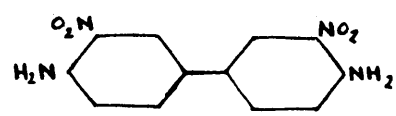


The existence of geometrically isomeric diphenyl derivatives was questioned and reinvestigation revealed that these were positional isomers; thus 3:3'-dinitrobenzidine (VII) and 3:5'-dinitrobenzidine (VIII) were proved (123, 122) to be correctly represented as 2:2'-dinitrobenzidine (XXVII) and 3:3'-dinitrobenzidine (XXVIII) respectively while the cis and trans forms of 6:6'-dinitrodiphenic acid were identified (54, 50) as the positionally isomeric 2:4'-dinitrodiphenic acid (XXIX) and authentic 2:2'-dinitrodiphenic acid (XXX):

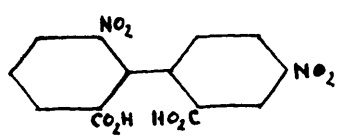
(XXVII)



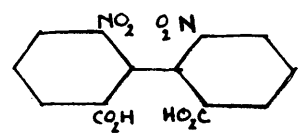
(XXVIII)



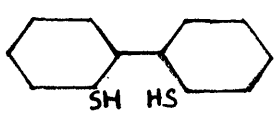
(XXIX)



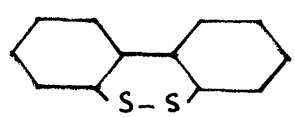
(XXX)



It was pointed out that the benzidine rearrangement was not more satisfactorily explained on the Kaufler hypothesis since molecular rearrangements are not dependent on the proximity of positions and, furthermore, the explanation of the similar and frequently accompanying semidine rearrangement is in no way facilitated on the Kaufler hypothesis. With the exception of the occurrence of optical activity, the various lines of evidence on which the Kaufler hypothesis was founded, were shown to be unsound and further investigations provided fresh evidence against the validity of the hypothesis. It was shown (12) that oxidation of 2:2'-dithioldiphenyl (XXXI) yielded diphenylene disulphide (XXXII) while neither 3:3'-dithioldiphenyl nor 4:4'-dithioldiphenyl yielded a disulphide on oxidation. This was contrary to the Kaufler folded structure which indicated the possibility of disulphide formation from each of the three isomeric dithioldisulphides concerned.



(XXXI)

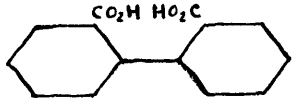


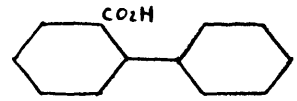
(XXXII)

The dissociation constant of benzidine was determined and comparison (117) with the corresponding values for the three phenylenediamines indicated that the distance between the

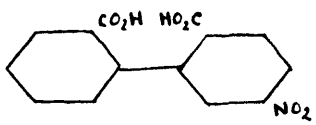
amino groups in the benzidine molecule was greater than the Kaufler structure suggested. Measurement of the dipole moments (209) of diphenyl derivatives also discredited the Kaufler hypothesis: in the case of 4:4'-dichlorodiphenyl and 4:4'-dinitrodiphenyl, the dipole moments were found to be zero proving that the rings were coaxial. The remaining line of evidence for the Kaufler hypothesis, i.e. the occurrence of optical activity in the diphenyl series, was removed when it was found impossible to resolve certain diphenyl derivatives which should, according to the Kaufler structure, exist in optically active forms. The Kaufler hypothesis was thus completely discredited as all the evidence on which it was founded had been shown to be erroneous. The occurrence of optical activity in certain substituted diphenyls required a separate explanation.

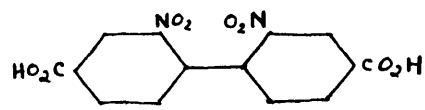
Reference has already been made to the successful resolutions of various substituted diphenic acids (pages 83, 84) and also to the failure to resolve certain other substituted diphenyls. Diphenic acid (XXXIII), the subject of two separate investigations (19), resisted resolution into optical isomers. Similarly, with diphenyl 2-carboxylic acid (XXXIV), 5-nitrodiphenic acid (XXXV), 2:2'-dinitrodiphenyl 4:4'-dicarboxylic acid (XXXVI) and 5:5'-dichlorodiphenyl 3:3'-dicarboxylic acid (XXXVII), no resolutions were effected (18,21,135).

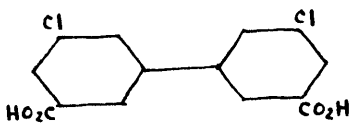
(XXXIII) 

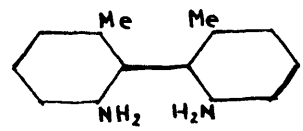
(XXXIV) 

The first diphenyl derivatives which were resolved into optical isomers (page 84) contained substituent nitro and carboxyl groups. The successful resolutions (51,137) of 6:6'-dichlorodiphenic acid (XXI) and 2:2'-diamino-6:6'-ditolyl (XXXVIII) demonstrated, however, that the occurrence of optical isomerism was not dependent upon any specific property of either the nitro or carboxyl group.

(XXXV) 

(XXXVI) 

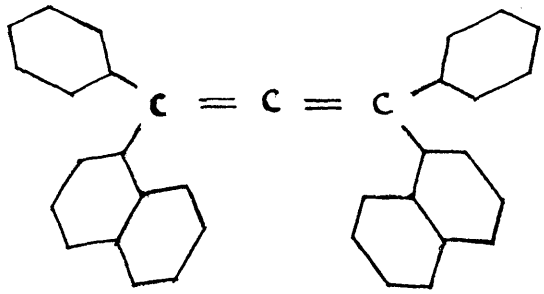
(XXXVII) 

(XXXVIII) 

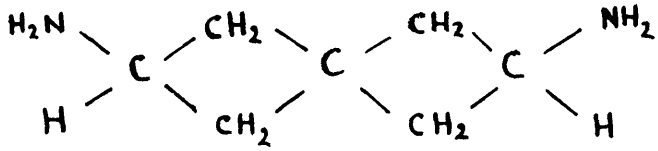
Furthermore, in view of the complete failure of many attempts to resolve simple benzene derivatives into optical isomers, it was apparent that the asymmetry of a single benzene nucleus was not the cause of the optical isomerism. The experimental results were most completely accounted for by the theory advanced by Christie and Kenner (52) (page 89); this theory is universally accepted at the present time; in an optically active diphenyl derivative, the benzene nuclei possess a common axis but do not lie in the same plane. The possibility of the planes of the nuclei being perpendicular was at first excluded by Christie and Kenner since this configuration would not allow of the existence of geometric (cis-trans) isomers. The

existence of such isomers was subsequently disproved (page 85) and the case in which the benzene rings lay in perpendicular planes was no longer excluded. The molecular asymmetry of such substituted diphenyls is thus due, not to the presence of an asymmetric carbon atom, but to the asymmetry of the molecule as a whole. Similar optical isomerism in the absence of an asymmetric carbon atom has been found in other types of organic compounds including the allenes and spiranes; the allene derivative (XXXIX) and the spirocycloheptane derivative (XL) have been obtained (145, 104) in optically active forms.

(XXXIX)



(XL)



In the case of the optically active diphenyls, the benzene nuclei are united by a single bond (pivot bond) and, if the fundamental concept of free rotation about such a bond is allowed, the benzene nuclei become coplanar and the asymmetry of the molecule disappears with consequent loss of optical

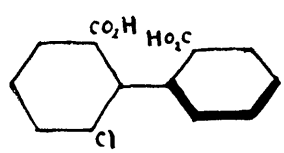
activity. In order, therefore, to complete the explanation, it was necessary to postulate the theory of restricted rotation about the pivot bond. This did not apply to the allene and spirane derivatives where the pivot bond is replaced respectively by double bond and ring systems, neither of which permit of free rotation. Inspection of the positions of the substituent groups in the resolvable (page 84) and the non-resolvable (page 87) diphenyls served to throw some light on the problem. It was evident that the resolvable diphenyls possess three or four substituents in the 2,2',6,6' positions, i.e. ortho to the pivot bond, while the non-resolvable diphenyls were otherwise substituted. These observations led to the theory of restricted rotation (199,17,142) which stated that, in a diphenyl molecule, the free rotation of the benzene nuclei about their common axis is prevented by the presence of certain substituents in the ortho positions to the pivot bond and due to the non-coplanarity of the rings the molecule becomes asymmetric. It was recognised that the asymmetry of the molecule was also dependent on the nature and position of the substituents in the benzene nuclei and if the latter were not both unsymmetrically substituted with respect to their common axis, the resultant diphenyl (although substituted in three or four of the positions ortho to the pivot bond and possessing a coaxial, non-coplanar structure) was not asymmetric and hence was incapable of resolution (page 94)

into optical isomers. It was pointed out (132) that, in a coaxial, non-coplanar, diphenyl molecule, a certain amount of oscillation of the benzene nuclei about their common axis might take place. The theory of restricted rotation accounted for the occurrence of optical activity in diphenyls with ortho substituents to the pivot bond; in such cases the groups are in sufficiently close proximity for mutual interference. The lack of optical activity in those cases where the substituents are located in positions remote from the pivot bond and hence too distant from each other for interference and restriction of rotation is similarly explained. The theory was subsequently developed in the light of later experimental evidence to explain cases of ortho substituted diphenyls which were not resolvable (page 96).

Various ideas were advanced regarding the nature of the influence which prevents free rotation of the benzene nuclei. According to the views of Turner and Le Fevre (199,200), the electrical nature of the substituent ortho groups and the residual affinity of the ortho carbon atoms constituted the controlling factors. In cases where two, mutually repelling, ortho groups were present, provided that the repulsion between these groups exceeded the attractive force due to residual affinity on the ortho carbon atoms, the resultant would cause a coaxial, non-coplanar, diphenyl configuration; where the repulsion was less

than the attractive force, a coaxial,coplanar configuration resulted. According to Bell and Kenyon (17), the electrical nature or the size (or both these characteristics) of the substituents in the 2,6 and 2' positions constituted the controlling factor; the 2- and 6- substituents of the one benzene nucleus blocked the free rotation of the other benzene nucleus by reason of their interference with the 2'-substituent of the latter. The obstacle theory of Mills (142), however, received subsequent general support. Consideration of the size of the ortho substituents, from scale models and diagrams,led to the belief that steric hindrance due to the bulk of these substituents was the primary consideration. In cases where bulky ortho substituents of one ring interfered mechanically with an ortho substituent of the other ring, free rotation of the rings about their common axis was prevented and at no time was a coplanar configuration possible. In the case of 2-chlorodiphenic acid (XLI),for instance, it was observed that the 6' carboxyl group was mechanically prevented from passing either the 2-chloro or the 6-carboxyl group due to overlapping at, or near, the coplanar configuration.

(XLI)

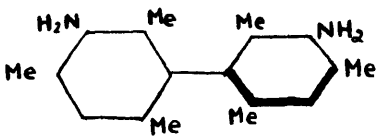


In the case of diphenic acid (XXXIII), on the other hand, the hydrogen atoms in the 6 and 6' positions were not large enough to overlap the 2' and 2 carboxyl groups and prevent free rotation. The coaxial, coplanar configuration was thus permitted in cases where the ortho groups were relatively small and this agreed with the structure of diphenic acid indicated by the experimental failure (19) to resolve this acid into optical isomers. Atomic size values, obtained from X-ray measurements, were used by Meisenheimer (137) to forecast the probability of non-coplanar configuration for 2:2'diamino-6:6'-dimethyldiphenyl (XXXVIII) and this was in agreement with its subsequent resolution (page 88). Use of inter-atomic distances obtained from X-ray data on aliphatic compounds and the radii of atoms and groups was made by Stanley and Adams (189) in calculating "Interference Values" which demonstrated the probability of the resolution of a given diphenyl. "Interference Values" calculated on this basis were in agreement with the failure to resolve 2:2'-dinitrodiphenyl 4:4'dicarboxylic acid (XXXVI) and the successful resolution of 6:6'-dinitrodiphenic acid (XII). The resolution and easy racemisation (page 96) of 2:2'-difluorodiphenic acid was also in agreement with the small positive "Interference Value" calculated by this method.

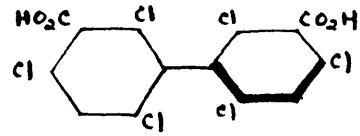
It was mentioned previously that asymmetry in a diphenyl molecule was dependent not only upon a coaxial, non-coplanar

configuration but also upon the unsymmetrical substitution of each benzene ring (with reference to the common axis). The optically active compounds already mentioned, possessed different groups in the 2 and 6 (or 2' and 6') positions and hence fulfilled the latter condition. It was pointed out (133,99), however, that the necessary unsymmetrical substitution would be obtained where a further substituent group was present in both the 3 and 3' (or 5 and 5') positions, i.e. one substituent in each ring meta to the pivot bond. This was demonstrated experimentally by the optical resolutions (134,208) of 3:3'-diaminodimesityl (XLII) and 2:4:6:2':4':6'-hexachlorodiphenyl 3:3'-dicarboxylic acid (XLIII). These resolutions also show that the non-coplanarity of the benzene rings is not due to the electrical nature of the ortho substituents since each of the diphenyls possesses identical ortho substituents.

(XLII)



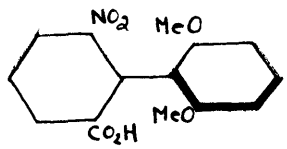
(XLIII)



In the absence of the required unsymmetrical substitution in each ring, a coaxial non-coplanar diphenyl would not possess the required asymmetry for optical isomerism; this was

demonstrated experimentally by the failure (201) to resolve 2-nitro-2':6'-dimethoxydiphenyl 6-carboxylic acid (XLIV) into optical isomers.

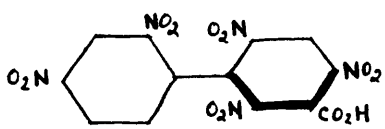
(XLIV)



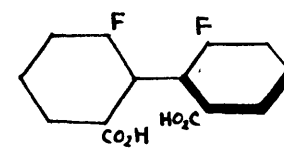
It was observed that racemisation took place on boiling solutions of most optically active diphenyls which possessed three substituents ortho to the pivot bond while optically active diphenyls with four substituents ortho to the pivot bond were stable to racemising influences. These facts were explicable on the obstacle theory by which it was considered that, under racemising conditions (elevation of temperature in solution, action of acid or alkaline media, etc.), a certain amount of slippage occurs between the ortho substituents and the benzene nuclei are free to rotate about the common axis with a consequent conversion of one active form to the other. In the case of the ortho-trisubstituted diphenyls in question, since the fourth ortho position is occupied by hydrogen, the smallest possible substituent, the chances of slippage are much greater than in the case of an ortho-tetrasubstituted diphenyl. It was later demonstrated, however, that the difference in stability of trisubstituted and tetrasubstituted

diphenyls was one of degree and by choosing substituents of appropriate size, it was possible to synthesise a stable, ortho-trisubstituted diphenyl and an easily racemised, ortho-tetrasubstituted diphenyl; 2:4:6:2':4'-pentanitrodiphenyl 3-carboxylic acid (XLV) was found to be unaffected (192) by the usual racemising conditions while 2:2'-difluorodiphenic acid (XLVI) racemised easily (191) in a warm neutral solvent.

(XLV)

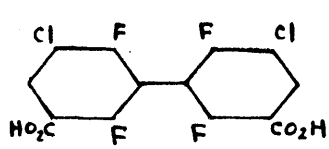


(XLVI)

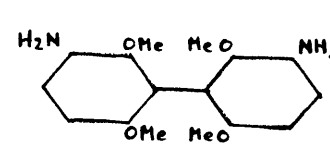


The next logical step in the investigation of the nature of the restricting influence was to explore the possibilities of obtaining ortho-tetrasubstituted diphenyls which were not resolvable due to lack of interference between their small ortho groups. It was found that certain diphenyls including 2:6:2':6'-tetrafluoro-3:3'-dichlorodiphenyl 5:5'-dicarboxylic acid (XLVII) (111) and 3:3'-diamino-2:6:2':6'-tetramethoxydiphenyl (XLVIII) (201) could not be resolved into optical isomers.

(XLVII)



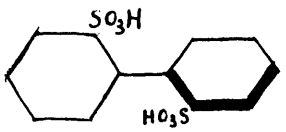
(XLVIII)



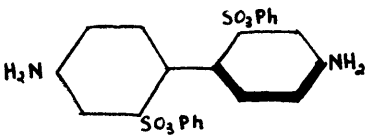
Similarly, from the theory of restricted rotation, it followed

that where the substituents were of sufficient size to interfere with the 6:6' hydrogens, a 2:2'-disubstituted diphenyl would be resolvable. Such substituents were found and the resolution of certain 2:2'-disubstituted dinaphthyls (page 101) was followed by the resolution of certain 2:2'-disubstituted diphenyl derivatives:-(XLIX), (L) and (LI). The optically active forms of diphenyl-2:2'-disulphonic acid (XLIX) (126), benzidine-2:2'-disulphonic acid diphenyl ester (L) (125) and o-(2-dimethylaminophenyl)phenyltrimethylammonium iodide (LI) (186) were found to racemise easily.

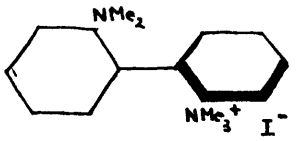
(XLIX)



(L)

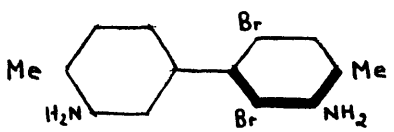


(LI)



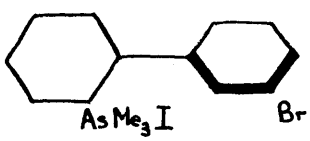
The resolution (154) of 2:6-dibromo-3:3'diamino-4:4'-ditolyl (LII) provided a novel case of restricted rotation as the ortho substituents were in the 2:6 positions i.e. in the same benzene ring.

(LII)



It was reported by Leslie and Turner (127) that 3'-bromodiphenyl-2-trimethylarsonium iodide (LIII), an ortho-monosubstituted diphenyl, forms a d-camphorsulphonate which exhibits mutarotation; this is ascribed to the optical isomerism of the diphenyl in question.

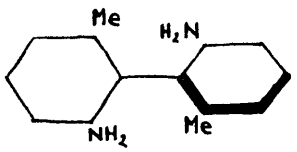
(LIII)



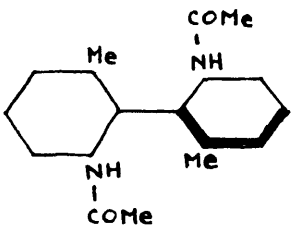
The effect of ring closure between the 2:6' and 2':6 positions of an optically active diphenyl was studied by Meisenheimer and Höring (137). It was found that active d-2:2'-diamino-6:6'-ditolyl (XXXVIII) on acetylation yields an optically active diacetyl derivative (LIV) which, on oxidation, furnishes an optically active dicarboxylic acid (LV). When the latter is treated with cold acid, however, the resultant dilactam (LVI) is optically inactive. Since six membered rings of the type between the 2:6' and 2':6 positions in the lactam are planar, it follows that the entire lactam molecule is planar. Furthermore, since the conditions of ring closure are not capable of causing racemisation of the dicarboxylic acid, it follows that the loss of optical activity is due to the formation of a planar, non-asymmetric structure. This, together with

other similar observations (115,21) on the loss of optical activity on the formation of planar rings between the 2:2' positions, constitutes excellent evidence in favour of the non-coplanar structure of optically active diphenyls.

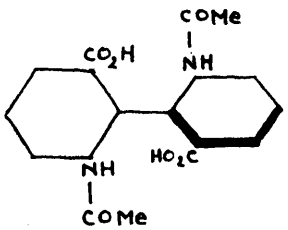
(XXXVIII)



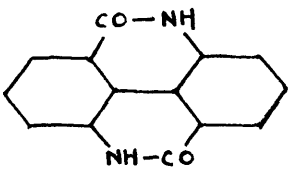
(LIV)



(LV)



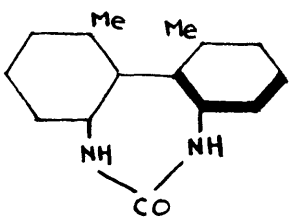
(LVI)



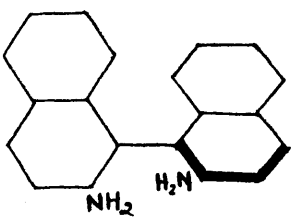
The extension of this research to seven and eight membered rings linking the 2:2' positions of an optically active diphenyl demonstrated that no loss in activity occurred on the formation of such rings. The diphenyl molecule thus formed is not planar and this fact is in agreement with the conception that rings containing more than six members are themselves non-planar.

Active 2:2'-diamino-6:6'-ditolyl (XXXVIII) yielded (174) an active compound (LVII) containing a seven membered ring while the active compound (LIX) derived from active 2:2'-diamino-1:1'-dinaphthyl (LVIII) contained an eight membered ring (116,195).

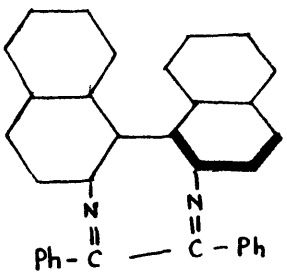
(LVII)



(LVIII)

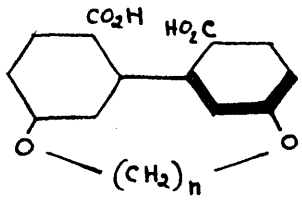


(LIX)



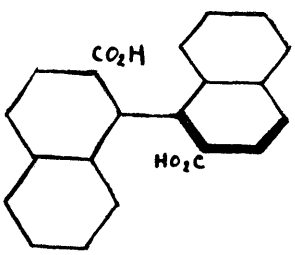
Recently, Adams and Kornblum (1) have described novel cases of restricted rotation in 2:2' substituted diphenyls possessing bridges uniting the 5:5' positions. These authors have prepared and resolved diphenic acids (LX) in which the 5:5' positions were linked by a polymethylene bridge $-(CH_2)_n-$. Since diphenic acid cannot be resolved (19), it is evident that the function of the polymethylene bridge is to restrict rotation of the benzene rings. From the measurement of the racemisation rates of the compounds in which n = 8, and n = 10, it was found that the former was more stable than the latter and it was concluded that the shorter the bridge uniting the 5:5' positions, the less vigorous are the oscillations of the benzene rings about the pivot bond.

(LX)

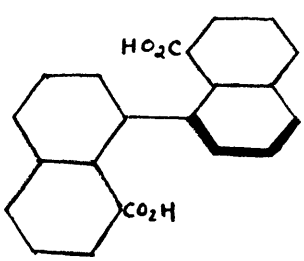


Optical activity induced by restricted rotation of properly substituted groups about a pivot bond is not restricted to the diphenyl series and optical resolutions have been effected in other series of compounds. In the dinaphthyl series, (LVIII) has been resolved. In this series also, 1:1'-dinaphthyl 2:2'-dicarboxylic acid (LXI) (115), 1:1'-dinaphthyl 8:8'-dicarboxylic acid (LXII) (188,59,136) and 1:1'-dinaphthyl 8-carboxylic acid (LXIII) (136) were resolved; (LXI) was stable to racemisation but (LXII) and especially (LXIII) were easily racemised.

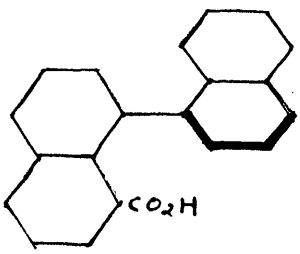
(LXI)



(LXII)



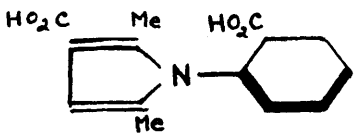
(LXIII)



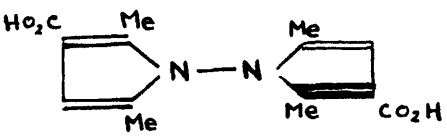
Interesting optical resolutions were obtained by Adams and co-workers on compounds containing ring nitrogen atoms.

N-(2-carboxyphenyl)-2:5-dimethylpyrrole 3-carboxylic acid (LXIV) and 2:5:2':5'-tetramethyl-N:N'-dipyrryl 3:3'-dicarboxylic acid (LXV) yielded optical isomers which were extremely resistant to racemisation (25,48). These workers proved experimentally that the optical isomerism was not due to a tetrahedral nitrogen with restricted non-coaxial rotation of the rings. Experimental evidence (26,153) indicated that restricted rotation about the pivot bond C-N in (LXIV) and N-N in (LXV), was the cause of molecular asymmetry.

(LXIV)



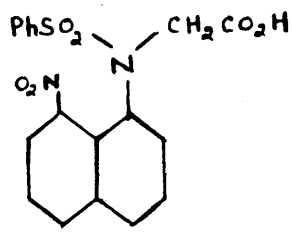
(LXV)



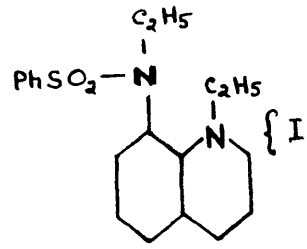
In examples of restricted rotation about a common coaxial pivot bond, already cited, the function of the pivot bond has been to unite two cyclic structures. It was predicted, however, by Mills (144) that sterically hindered rotation might exist in the case of a bond uniting one cyclic structure with a properly substituted group, for example, the C-N bond in peri-substituted naphthalenes. This prediction was justified by the subsequent

resolutions by Mills and co-workers of N-benzenesulphonyl-8-nitro-1-naphthylglycine (LXVI) (144), and 8-benzenesulphonyl-ethylamino-1-ethylquinolinium iodide (LXVII) (143).

(LXVI)



(LXVII)

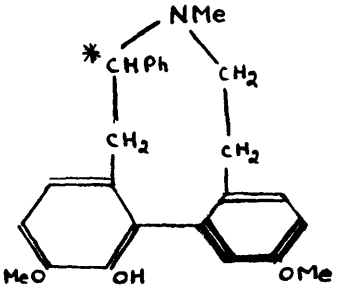


It was previously shown when considering the Kaufler hypothesis, that support was given to the coaxial diphenyl structure by certain physical data (page 86). Certain further information of this type was subsequently available as strong evidence for the non-coplanarity of the benzene nuclei in certain 2:6:2':6' tetra-substituted diphenyls. X-ray investigations (56,158,159) indicated that while the benzene nuclei in diphenyl were coplanar, in certain 2:6:2':6' tetra-substituted diphenyls they were inclined to each other at an angle not greater than 45°, In the case of 2:2'-diamino-6:6'-ditolyl (XXXVIII), dipole moment determinations (22) suggested that the planes of the benzene nuclei were inclined at an angle of 67°. Non-coplanarity of the benzene nuclei of certain substituted diphenyls was also indicated by a study of resonance energies (34). Measurements of absorption spectra revealed a marked difference in the

characteristics of the absorption between diphenyls with free and with restricted rotation. A fuller account of such differences in diphenyl absorption spectra is given later in this thesis (page 120).

All the known compounds which exhibit optical activity due to restricted rotation have until recently been of synthetic origin. In 1947, however, Robinson described the first recorded case of optical activity of this type encountered in a study of a natural product (170). Phenyldihydrothebaine was proved to possess the constitution (LXVIII); in addition to the asymmetric carbon atom (*) the molecule possesses the further element of asymmetry which is characteristic of the optically active diphenyls already described.

(LXVIII)



It was shown by means of models that the nine-membered heterocyclic ring allowed the strainless rotation of the benzene nuclei about their common axis to any angle up to and including 90°. The ultra-violet absorption of (LXVIII) did not indicate the existence of any conjugation between the aromatic rings and thus afforded additional evidence for the non-coplanar structure.

INTRODUCTION

OPTICALLY ACTIVE DIPHENYLS.

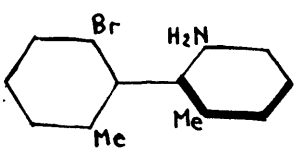
Although the majority of optically active diphenyls contain one or more salt-forming groups in the molecule, a few optically active diphenyls which do not contain such groups have been described. The latter type, however, is invariably derived from the former by replacement of the salt-forming groups by non-salt-forming groups, the optical activity being preserved in the conversion. Optically active forms of 2:2'-diiodo-6:6'-ditolyl and 2:2'-dibromo-6:6'-ditolyl were obtained in this manner from the active form of 2:2'-diamino-6:6'-ditolyl (XXXVIII) by replacement of the amino groups by the appropriate halogens (16, 4). Optically active acids or bases are utilised in the resolution of diphenyls by means of the formation of diastereoisomeric salts with the diphenyl according to whether the latter possesses basic or acidic groups respectively. For example, 2:4'-dinitro-6:6'-diphenic acid (XXIX) and diphenyl-2:2'-disulphonic acid (XLIX) were resolved in this manner by means of brucine and strychnine respectively (50, 126) and, on the other hand, 2:2'-diamino-6:6'-ditolyl (XXXVIII) and o-(2-dimethylaminophenyl)phenyltrimethylammonium iodide (LI) were resolved by means of tartaric acid and camphor 10-sulphonic acid respectively (137, 186).

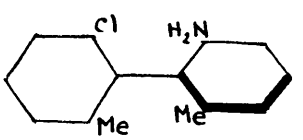
AMINODIPHENYLS.

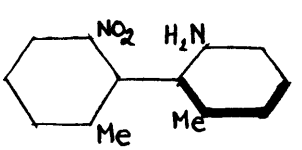
By far the largest proportion of diphenyls which have been resolved into optical isomers possess one or more carboxyl substituents. It was found, however, that up to the present time, some nine optically active diphenyls possessing substituent amino groups have been described in the literature. Since this research is concerned with the preparation and resolution of such derivatives, it is of relevant interest to enumerate these active aminodiphenyls, some of which have already been mentioned in the preceding Historical Section of this thesis. In addition, mention will be made of certain other derivatives of this type which have so far resisted attempts at resolution.

Optically Active Aminodiphenyl Derivatives.

(a) Substituted Monoaminodiphenyls.

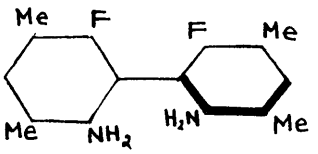
2-bromo-2'-amino-6:6'-ditolyl  (4)

2-chloro-2'-amino-6:6'-ditolyl  (2)

2-nitro-2'-amino-6:6'-ditolyl  (3)

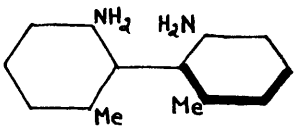
(b) Substituted Diaminodiphenyls.

2:2'-difluoro-6:6'-diamino-3:5:3':5'-tetramethyldiphenyl



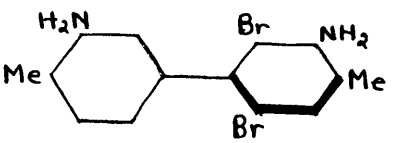
(110)

2:2'-diamino-6:6'-ditolyl (XXXVIII)



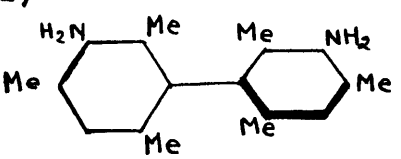
(137)
(page 88)

2:6-dibromo-3:3'-diamino-4:4'-ditolyl (LII)



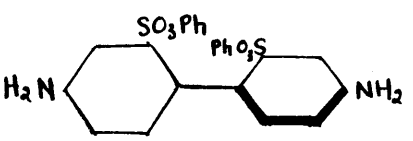
(154)
(page 97)

3:3'-diaminodimesityl (XLII)



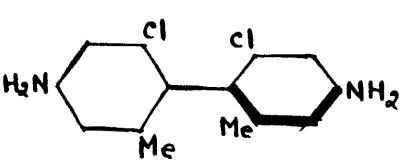
(134)
(page 94)

Diphenyl benzidine -2:2'-disulphonate (L)



(125)
(page 97)

2:2'-dichloro-6:6'-dimethylbenzidine (LXIX)

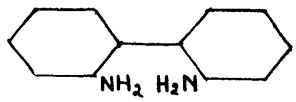


(118)
(page 119)

Optically Inactive Aminodiphenyl Derivatives.

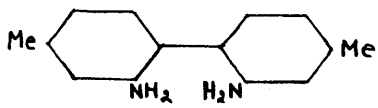
Substituted Diaminodiphenyls.

2:2'-diaminodiphenyl



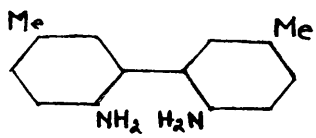
(131)

2:2'-diamino-4:4'-ditolyl



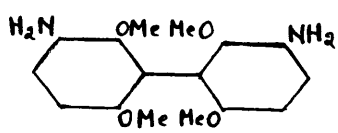
(131)

2:2'-diamino-5:5'-ditolyl



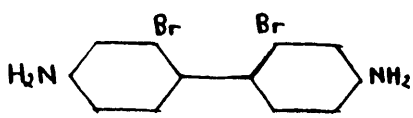
(131)

3:3'-diamino-2:6:2':6'-tetramethoxydiphenyl (XLVIII)



(201)
(page 96)

2:2'-dibromobenzidine (LXXI)



(184)
(page 110)

In every case, the active aminodiphenyls satisfy the conditions necessary for optical activity; requisitely large substituents are present in two or more of the 2:6:2':6' positions (page 90) and the benzene nuclei are unsymmetrically substituted (page 90). In the case of the inactive

aminodiphenyls, 2:2'-diaminodiphenyl, 2:2'-diamino-4:4'-ditolyl and 2:2'-diamino-5:5'-ditolyl, however, the two amino groups in the 2:2'-positions are not sufficiently large to interfere with the rotation of the benzene nuclei. Similar considerations apply in the case of 3:3'-diamino-2:6:2':6'-tetramethoxydiphenyl; rotation is not restricted even when all four 2:6:2':6' positions are occupied by methoxyl groups due to the insufficient size of the latter. The failure to resolve 2:2'-dibromobenzidine, however, cannot be analogously explained and, in view of the nature of this research, the separate discussion which follows is merited.

2:2'-DIBROMOBENZIDINE.

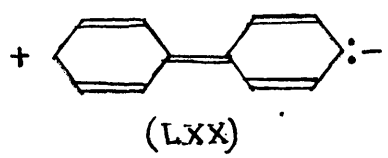
This compound was first described by Gabriel in the year 1876 and, fifty-eight years later, Searle and Adams unsuccessfully attempted its optical resolution. It is proposed to consider the events and the theoretical background which preceded this attempted resolution.

It has already been pointed out in a general way (page 92) that restricted rotation can be attained in a diphenyl by the introduction of sufficiently large substituent atoms or groups to the 2:2' positions. In 1930, by calculation of "Interference Values" (page 93), Adams (190) predicted that

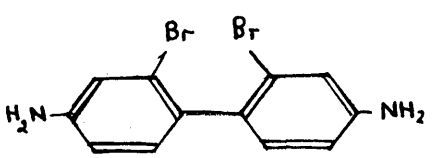
diphenyls possessing bromine atoms or iodine atoms in the 2:2' positions would be resolvable; in the case of 2:2'-dibromodiphenyl, the extent to which each of the 2:2' bromine atoms would interfere with 6':6-hydrogen atoms was estimated as approximately 0.15Å. In 1932, Lesslie and Turner (125) constructed an accurate model of the diphenyl molecule using atomic radii based on X-ray data available at that time and showed that a 2:2'-di(x)substituted diphenyl, where the radius of x exceeded approximately 1.2Å, would exhibit molecular dissymmetry due to a non-planar configuration. In the same paper, these authors provided experimental confirmation of this theory in the successful optical resolution of diphenyl benzidine-2:2'-disulphonate (L) and, later in the same year, described (126) the resolution of diphenyl 2:2'-disulphonic acid(XLIX). In 1933, the resolution of a third 2:2'-disubstituted diphenyl, 2:2'-bis-o-(2-dimethylaminophenyl)-phenyltrimethylammonium iodide (LI) was described by Shaw and Turner (186) and, in the same year, Searle and Adams (183) resolved 2:2'-diiododiphenyl 4:4'-dicarboxylic acid. During the following year, however, the latter authors (184) reported the resolution of 2:2'-dibromodiphenyl 4:4'-dicarboxylic acid (LXXII), but were unable to resolve 2:2'-dibromobenzidine (LXXI).

From the theoretical considerations mentioned above, a 2:2'-dibromodiphenyl should be capable of optical resolution but the experimental evidence showed that 2:2'-dibromodiphenyl was resolvable when the 4:4' positions were occupied by carboxyl groups and was not resolvable when these positions were occupied by amino groups. In the attempted resolution of 2:2'-dibromobenzidine, a technique was employed which would ordinarily preclude the racemisation of any measureably racemisable compound and the non-resolution cannot be ascribed to the experimental conditions. The anomalous behaviour of this compound is accentuated by the successful resolution of the other di-2:2'-substituted benzidine (L).

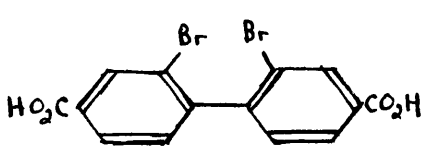
Calvin (43) has suggested the following explanation for the resolvability of 2:2'-dibromodiphenyl 4:4'-dicarboxylic acid compared with the non-resolvability of 2:2'-dibromobenzidine.



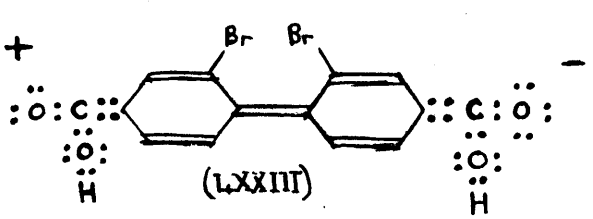
(LXX)



(LXXI)



(LXXII)



(LXXIII)

In order that ionic resonance states of the type (LXX) may contribute to the ground state of a diphenyl it is necessary that the benzene nuclei are capable of assuming a coplanar configuration. When this occurs, the pivot bond will possess some of the character of an olefinic linkage, including a decrease in the $C_1 - C_1'$ distance. This decrease has important consequences on the racemisation rates of certain optically active diphenyls. Since the activation energy for racemisation of a diphenyl is almost totally the energy required to bring the nuclei into a coplanar position and, since this latter energy is in turn a very sharp function of the distance separating the 2:2'-substituents, very small changes in this distance are capable of effecting profound changes in the repulsive force between these substituents. A study of the kinetics of the racemisation of a number of optically active diphenyls in solution and in the gas phase demonstrated that differences of the order of a few hundredths of an Å in the $C_1 - C_1'$ distance would suffice to render certain diphenyls optically resolvable.

In (LXXI) the amino groups are incapable of accepting electrons and are therefore of no assistance in lowering the

energy of the ionic resonance state (LXX). The contribution of (LXX) to the ground state of the molecule is not increased and consequently the $C_1 - C_{1'}$ distance is not decreased.

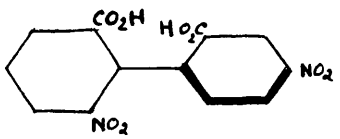
In the case of (LXXII), however, the carboxyl groups are capable both of accepting and providing electrons (LXXIII) and hence assist in the promotion of the contribution of the ionic resonance state to the ground state of the molecule. The small additional contribution of the ionic state would decrease the $C_1 - C_{1'}$ distance by a sufficient margin to render the diphenyl resolvable.

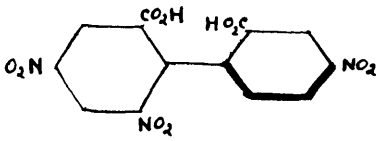
Calvin also suggested that the effects of other meta (3:3') and para (4:4') substituents on the racemisation rates of diphenyls may be accounted for at least in part by such a mechanism.

Substituents in Positions other than the 2:6:2':6'.

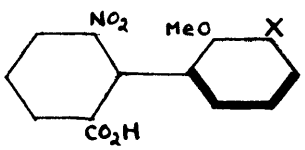
The resolvability of (LXXII) compared with the non-resolvability of (LXXI) demonstrates that the nature of the 2:6:2':6' substituents is not the only factor which governs the occurrence of optical activity in a diphenyl. The existence of other factors is also demonstrated by the fact that 2:4'-dinitrodiphenic acid (XXIX) was found to be more

easily racemised (114) than 2:4:4'-trinitrodiphenic acid (LXXIV).

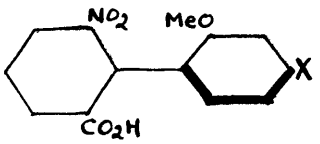
(XXIX) 

(LXXIV) 

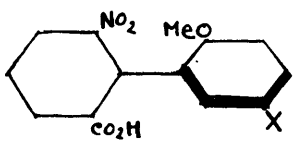
Adams and co-workers (79) studied a series of diphenyls in which x, one of the substituents, was moved from the 3' to the 4' to the 5' position, the remainder of the molecule being unchanged (LXXVa, LXXVb and LXXVc respectively).



(LXXVa)



(LXXVb)



(LXXVc)

The racemisation rates were determined for such compounds where x consisted of hydrogen, methoxyl, chlorine, bromine or nitro respectively and the stability of these derivatives was found to increase progressively from hydrogen to nitro in this order of substituents. This was found to be the case whether these substituents were situated in the 3', 4' or 5' positions. In addition, the 3'-substituted derivatives were

found to be much more stable to racemisation than the corresponding 5'-substituted derivatives which were, in general, rather more stable to racemisation than the 4'-substituted derivatives.

Adams states that while the mechanism and the theoretical basis of these results are still obscure, one or more of the five following factors may operate:-

(1) The variation of the valency angle at which the ortho substituent on the ring is attached, thus changing the effective size of the group.

(2) The modification of the internuclear distance between the carbon atom of the ring and the ortho substituent.

(3) The slowing down of the semicircular oscillation of the two phenyl rings by substituents, thus diminishing the chances of complete rotation.

(4) The modification of the distance between the 1:1'-carbon atoms.

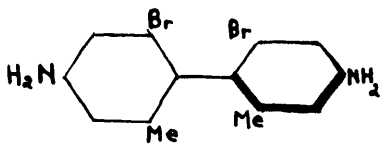
(5) The bending of the linkage between the two rings in such a way that the rings are no longer coaxial.

The suggestion was also made that, in view of the experimental results, cause (3) was not a factor as the

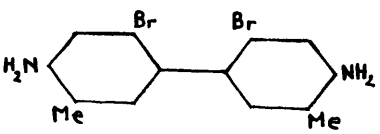
introduction of substituents of different weight such as chlorine and bromine resulted in almost identical effects on the rate of racemisation. It was also noted that the stability of the compound increased with the dipole moment.

2:2'-DIBROMODIMETHYLBENZIDINES.

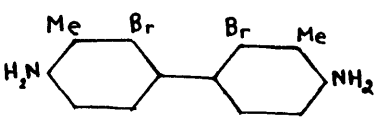
In view of these observations on the effects of groups in the 3 and 5 positions of an optically active diphenyl and of the studies (page 110) on 2:2'-dibromobenzidine (LXXI) and 2:2'-dibromo-4:4'-dicarboxydiphenyl (LXXII), it was considered to be of interest to attempt the preparation and optical resolution of each of the three, following, isomeric 2:2'-dibromodimethylbenzidines (LXXVI, LXXVII and LXXVIII).



(LXXVI)



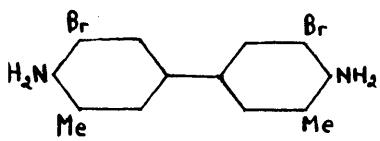
(LXXVII)

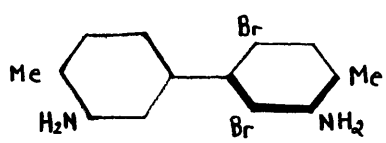


(LXXVIII)

These have not been previously described although the isomeric 3:3'-dibromo-5:5'-dimethylbenzidine (3:3'-dibromo-o-tolidine),(LXXIX) has been described and was prepared by the bromination of o-tolidine (147, 178). This compound is

not of interest from the point of view of optical activity as the lack of substituents in the 2:6:2':6'-positions precludes a non-coplanar, molecular configuration. The occurrence of optical isomerism in a second structural isomer, 2:6-dibromo-3:3'-diaminoditolyl (LII) has already been discussed (page 97).

(LXXIX) 

(LII) 

2:2'-Dibromo-6:6'-dimethylbenzidine (LXXVI).

In the discussion of the origin of optical activity in diphenyls, it was pointed out that, where the necessary prerequisite of unsymmetrical substitution (page 90) was present, the size and number of ortho (2:6:2':6') substituents (page 92) were the principal controlling factors. The relative effects of various ortho (2-) groups was studied (78) by Adams and co-workers who prepared two series of diphenyls, a 2:2':6'-trisubstituted series (193) and a 2:5:2':6'-tetrasubstituted series (212). In each of these series only the 2-substituent group was varied from member to member. The

racemisation of these diphenyls was studied and the relative interference effects as measured by the half-life periods were found to decrease in the following order which was not altered by change of solvent.

$$Br, \quad CH_3, \quad Cl, \quad NO_2, \quad CO_2H, \quad OCH_3, \quad F.$$

It was observed that this order was identical with that of decreasing size of the groups as determined by X-ray data.

In the case of 2:2'-dibromo-6:6'-dimethylbenzidine (LXXVI), the presence of the four relatively large ortho substituents, two bromine atoms and two methyl groups, should result in a high degree of restriction of the rotation of the benzene nuclei and the active compound should be resistant to powerfully racemising conditions.

Additional weight is given to this prediction by the observed stability to racemisation (4) of active 2:2'-dibromo-6:6'-ditolyl. The replacement of the 4:4'-hydrogens of the latter by amino groups results in (LXXVI) and there is no evidence that such a replacement should result in a perceptible change in the stability of the diphenyl where the latter is particularly resistant to racemisation by reason of the pronounced interference of four ortho substituents. Also, the

observed stability to racemisation (118) of active 2:2'-dichloro-6:6'-dimethylbenzidine (LXIX) suggests that the replacement of the 2:2'-chlorine atoms by bromine atoms resulting in (LXXVI) would, if anything, confer an increased stability due to the larger size of the bromine atoms.

The preparation and optical resolution of (LXXVI) was undertaken therefore in order to test the validity of these predictions which are based on the accepted theories of diphenyl optical isomerism.

2:2'-Dibromo-5:5'-dimethylbenzidine (LXXVII).

The researches of Adams (page 114) showed that when the hydrogen atom in the 5 position in an optically active diphenyl is replaced by another atom or group, the stability of the active compound was increased. 2:2'-Dibromo-5:5'-dimethylbenzidine (LXXVII) may be regarded as 2:2'-dibromobenzidine (LXXI) in which the 5:5'-hydrogen atoms are each replaced by a methyl group. It was considered that the combined influence of two substituents, one in each of the 5:5'- positions might be sufficient to turn the scales in favour of an optical resolution since (LXXI) although unresolvable, is probably on the borderline of resolvability (page 111).

2:2'-Dibromo-3:3'-dimethylbenzidine (LXXVIII).

The researches to which reference has just been made also demonstrated that a similar replacement of a hydrogen atom in the 3 position increased the stability of the active diphenyl to an even greater extent. In the case of 2:2'-dibromo-3:3'-dimethylbenzidine (LXXVIII), considerations of a similar nature to those applied to (LXXVII) would lead to an increased expectancy of optical resolution.

Some information regarding the nature of the factors involved (page 115) in the effects of substituents in the 3- and 5-positions on the optical activity of diphenyls would probably be forthcoming from a consideration of the experimental findings with regard to (LXXVII) and (LXXVIII) in conjunction with the failure (page 110) to resolve (LXXI).

ULTRA-VIOLET LIGHT ABSORPTION.

In a recent review (32) of the relation between ultra-violet light absorption and the structure of organic compounds, Braude has summarised the results of several investigations on diphenyls. In general, coplanar diphenyls, on account of the pronounced conjugation between the two phenyl groups, exhibit an intense band near 250mu and o-substituted diphenyls, due

to the non-coplanarity of the phenyl groups, do not possess such conjugation and consequently do not give rise to this intense absorption band. It will suffice for present purposes to consider three of the separate investigations referred to in this review.

The abnormality of the absorption spectra of non-coplanar diphenyls was first pointed out by Pickett, Walter and France (160). From a comparison of the absorption spectra of various chloro and methyl derivatives of diphenyl and of benzene, the conclusion was reached that compounds with restricted rotation exhibit marked differences from those in which free rotation is possible. At the same time, it was pointed out that the effect on the wave-length of the band maxima of substituent chlorine groups in a diphenyl is that which would be predicted from a study of benzene derivatives; the band is displaced towards the visible. The introduction of methyl groups results in a similar displacement of lesser magnitude.

From a study of the absorption spectra of some ortho substituted diphenyl derivatives, O'Shaughnessy and Rhodebush (151) concluded that in those cases where the ortho substituents are of sufficient size to interfere

considerably with the free rotation of the benzene rings, the lack of conjugation between the latter results in a greatly reduced absorption. At the same time it was suggested that the ultra-violet absorption might prove useful in determining the restriction of rotation in those cases where coplanarity was necessary for resonance. It was, however, pointed out that such a spectroscopic test for restricted rotation would not invariably agree with the results of optical resolution; the heat of activation of rotation (ca. 20 large calories) required for optical resolution probably exceeds the degree of interference necessary to maintain an average non-coplanar configuration.

The relation between the nature of the ortho substituents in a diphenyl and the absorption spectra was studied by Williamson and Rhodebush (210). It was pointed out that while departure from the coplanar configuration interferes seriously with the conjugation involving the whole molecule, ortho-para directing groups in the 2:2' positions of diphenyl tend to concentrate electrons in the pivot bond and thus favour the contribution of an ionic resonance state even when the rings are not coplanar. This effect was considered to account for the increased absorption of certain 2:2'

substituted diphenyls compared with the corresponding benzene derivatives; the substituents in question were -Cl, -Me, $-NH_2$ and other ortho-para directing groups.

METHODS OF PREPARATION.

The Ullmann reaction (page 13) has been employed in the majority of cases for the synthesis of diphenyl derivatives of stereochemical interest. The low yields as a rule obtained by this reaction and the relative inaccessibility of the required starting materials, the appropriately substituted bromoiodonitrotoluenes, were the principal factors in deciding against its utilisation for the preparation of the required dibromodimethylbenzidines. This decision was only made possible, however, by the existence of an alternative route, the benzidine rearrangement of the appropriately substituted hydrazobenzenes, which it was proposed to investigate in the first instance. The discussion which follows is concerned with the reactions which have been previously utilised in the general route from nitro aromatic compounds to the corresponding benzidines. These reactions are considered under two headings (a) The formation of hydrazo compounds, and (b) The benzidine rearrangement. Particular mention is made of reactions which have been utilised in the preparation of

products related to those with which this work is concerned.

(a) The formation of Hydrazo Compounds.

Aromatic nitro compounds, on reduction with powerful reducing agents such as stannous chloride and hydrochloric acid, iron and dilute hydrochloric acid, ferrous sulphate and ammonia and hydrogen and platinum catalysts, generally yield the corresponding amino compound. By the use of less powerful reducing agents and by controlled reaction, however, it is possible to obtain various intermediate reduction products. The latter include primary products formed directly by reduction and secondary products formed by interaction of the primary reduction products. In the case of an aromatic nitro compound, $ArNO_2$, the formation of the hydrazo compound (N:N'-diarylhydrazine), ArNH.NHAr, may be represented by the following stages:-

(1) $ArNO_2 \xrightarrow{(H)} ArNO$ (2) $ArNO \xrightarrow{(H)} ArNHOH$

(3) $ArNO + ArNHOH \xrightarrow[\text{alkali}]{\text{catalysed by}} Ar.N{=}NAr \downarrow O + H_2O$

(4) $ArN{=}NAr \downarrow O \xrightarrow{(H)} ArN{=}NAr$ (5) $ArN{=}NAr \xrightarrow{(H)} ArNH.NHAr$

These products are formed mainly by reduction in alkaline media although certain azoxy compounds have been prepared under suitable conditions in the presence of acid (70). Reduction beyond stage (5) results in cleavage of the hydrazo compound to form two molecules of the primary amine ($ArNH_2$). The primary products include nitroso compounds (ArNO) and hydroxylamines (ArNHOH) and the secondary products include azoxy (ArN=NAr, with O above the N), azo (ArN=NAr) and hydrazo (ArNH.NHAr) compounds.

Due to the extreme reactivity of the nitroso compounds, it is not possible to halt the reduction at the end of stage (1). Nitroso compounds are generally prepared by mild oxidation of hydroxylamines or by oxidation of primary amines by means of special oxidising agents such as Caro's acid or peracetic acid. The hydroxylamines, however, are more stable and it is possible to halt the reduction at the end of stage (2). This constitutes the general method for the preparation of such compounds and the controlled reduction is usually effected by means of zinc and aqueous ammonium chloride or by ammonium hydrogen sulphide.

The origin of the secondary reduction products is stage (3) and, by controlled use of the appropriate reducing agents,

it is possible to halt the reaction at the end of stage (3), (4) or (5) in order to isolate the azoxy, azo or hydrazo compound respectively. The secondary products obtained by reduction of an aromatic nitro compound are symmetrically substituted because of the condensation of similarly substituted nitroso and hydroxylamine intermediates (stage 3). Sidgwick (187) has discussed fully the relation between the reaction conditions and the nature of the product; the following general procedures are most commonly employed.

Reduction to the azoxy stage is usually effected by the use of mild reducing agents such as sodium methoxide in methanol or by sodium arsenite. Azoxy compounds are also formed by condensation of the separately prepared nitroso and hydroxylamino compounds, the reaction proceeding readily in the presence of alkali (stage 3). They are also formed from azo compounds by the method of Angeli (5) in which the oxidation is performed by means of peracetic acid. This reaction is effected either at room or boiling water-bath temperature and although, in some cases, several days may be required for completion, extremely high yields are frequently obtained.

Azo compounds are formed by reduction of aromatic nitro compounds by means of alkaline sodium stannite or by means of

zinc dust in aqueous-alcoholic alkali. By using the requisite quantities of the latter reducing reagent, however, it is possible to continue the reduction to the hydrazo stage and this constitutes the most commonly employed procedure for the preparation of symmetrical aromatic azo and hydrazo compounds. Symmetrical and unsymmetrical azo compounds are formed by the condensation of aromatic nitroso compounds with primary aromatic amines; the solvent generally employed is glacial acetic acid or, less often, ethanol.

In addition to the method indicated for the preparation of hydrazo compounds, the latter are also formed by reduction of azoxy and azo compounds using suitable reagents and conditions of reaction.

Since the proposed route to the required benzidine bases necessitates the formation of three of the four possible symmetrical 3:3'-dibromodimethylhydrazobenzenes, it is of interest to mention the method of preparation of (unsubstituted) 3:3'-dibromohydrazobenzene, first described by Gabriel (74). The first stage consisted of the reduction of m-bromonitrobenzene by means of hot ethanolic potassium hydroxide to 3:3'-dibromoazoxybenzene. The latter, after purification, was further reduced in the second stage directly

to the hydrazo compound by means of ethanolic ammonium sulphide.

In addition, 3:3'-dimethylhydrazobenzene is of related interest since by substitution of two bromine atoms in the 5:5' positions, the required hydrazo compound for rearrangement to 2:2'-dibromo-6:6'-dimethylbenzidine (LXXVI) is obtained Also, substitution of two bromine atoms in the 5:5'- or 3:3'-positions of 2:2'-dimethylhydrazobenzene gives rise to the hydrazo intermediates for the preparation of 2:2'-dibromo-5:5'-dimethylbenzidine (LXXVII) and 2:2'-dibromo-3:3'-dimethylbenzidine (LXXVIII) respectively.

3:3'-Dimethylhydrazobenzene was prepared by reduction of the corresponding azo compound using ethanolic ammonium sulphide (80), the azo compound being obtained from m-nitrotoluene by reduction in ethanolic solution using sodium amalgam and water (13, 80) or using zinc dust and ethanolic potassium hydroxide (13).

2:2'-Dimethylhydrazobenzene was prepared from the corresponding azo compound by reduction in boiling ethanolic solution with zinc dust and alkali (163). This reduction was also effected in ethanolic solution by means of sodium amalgam (156). The latter reducing agent was also employed in the

reductions of o-nitrotoluene to the azo and hydrazo compounds (161). Reduction of o-nitrotoluene to the azo compound has also been accomplished by means of a variety of reducing agents which include magnesium amalgam and dilute methanol (67), zinc dust and sodium hydroxide in ethanol (161), and alkaline sodium stannite (211).

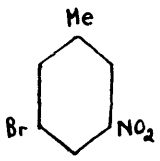
Also of interest is the method of preparation of the related compounds, 3:3'-dichloro-5:5'-dimethylhydrazobenzene, 3:5:3':5'-tetrabromohydrazobenzene and 3:5:3':5'-tetrachlorohydrazobenzene all of which possess four meta substituents of which at least two are halogens. Of these, the first to be described was the 3:5:3':5'-tetrabromo compound and the method used by Meyer, Meyer and Taeger (138) for its preparation consisted of a two stage reduction of the corresponding nitro compound, 3:5-dibromonitrobenzene. The latter was reduced in the first stage to the corresponding azo compound by means of zinc dust, aqueous sodium hydroxide and boiling ethanol. In the second stage, the azo compound was further reduced to the hydrazo compound by zinc dust, glacial acetic acid and boiling ethanol. The 3:3'-dichloro-5:5'-dimethyl and the 3:5:3':5'-tetrachloro compounds were prepared by the same two stage process using the same reducing agents (118, 171).

Ortho Halogen Substituents.

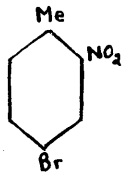
The examples quoted do not include azo or hydrazo compounds with substituent halogen atoms in the 2:2'- (or 6:6'-) positions. In general, it is not possible to prepare such compounds by alkaline reduction of the corresponding o-halogenonitro compounds due to the replacement of the halogen by hydroxyl. This replacement is due to the increased susceptibility of the halogen substituents to attack by nucleophilic reagents when the halogen is situated ortho or para to the nitro group. The characteristic resonance effect (-T) of the nitro group operates in such a manner as to promote an electron deficiency at the ortho and para positions and is thus responsible for this activity. Numerous examples of this exchange have been described and the particular effect on azoxy compound formation from o- and p-chloronitrobenzenes using the sodium alcoholate reduction method is mentioned by Hickinbottom (92) who quotes the original references.

This halogen displacement, however, was not expected to be of immediate concern in the reduction of the bromonitrotoluenes to the hydrazo compounds required for rearrangement to the benzidines. The bromonitrotoluenes in question, 3-bromo-5-nitrotoluene (LXXX), 4-bromo-2-nitrotoluene (LXXXI)

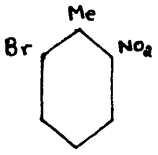
and 2-bromo-6-nitrotoluene (LXXXII), are so substituted that the bromine atoms are situated meta to the nitro groups. In view of the reactivity of ortho and para halogen substituents, however, it was considered to be of interest to investigate the behaviour on alkaline reduction of two bromonitrotoluenes which possess bromine atoms in the ortho position with respect to the nitro group. The two compounds chosen were 4-bromo-3-nitrotoluene (LXXXIII) and 2-bromo-3-nitrotoluene (LXXXIV). These may be regarded as derived from (LXXXI) and (LXXXII) respectively by interchange of the positions of the methyl and bromine substituents.



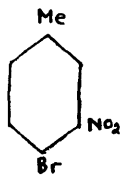
(LXXX)



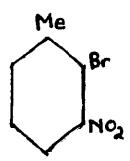
(LXXXI)



(LXXXII)



(LXXXIII)



(LXXXIV)

Alkaline reduction of p-nitrotoluene was observed to yield p:p'-diaminostilbene (69). In view of the fact, however, that none of the bromonitrotoluenes mentioned above possess methyl and nitro groups situated in the para positions

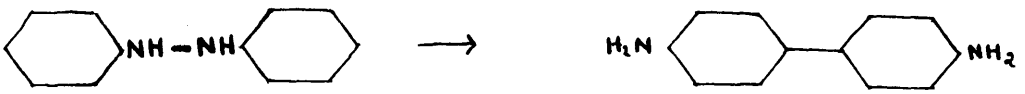
to each other, it was not to be expected that such products would be encountered in the suggested reductions.

(b) The Benzidine Rearrangement.

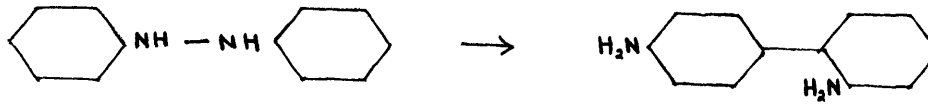
In a recent discussion of the mechanism of the benzidine rearrangement (169) Robinson has pointed out the various types of reaction which are classed under this heading. These have also been outlined by Karrer (105). For the purposes of this work, it remains, therefore, briefly to indicate the reactions involved, to consider previously described rearrangements of certain hydrazo compounds related to those which it is intended to prepare and to quote a recent theory on the mechanism of the reaction.

The Reactions Involved.

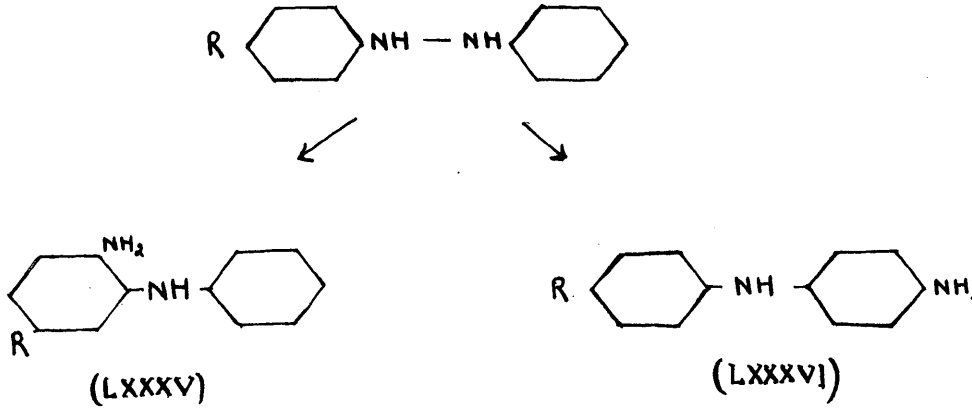
Symmetrical diarylhydrazines (hydrazo compounds) with free para positions, under the influence of mineral acids isomerise to the corresponding benzidines; hydrazobenzene, for example, yields benzidine:-



This principal reaction, known as the benzidine rearrangement or transformation, is sometimes accompanied by a side-reaction which leads to the simultaneous formation of 2:4'-diaminodiphenyls (diphenylines) as by-products, hydrazobenzene for example yields diphenyline in small amounts:-



In those cases where the hydrazo compound possesses a para substituent, the latter may be eliminated during the transformation with the formation of the corresponding benzidine. If the para substituent is not eliminated, however, in addition to the possibility of diphenyline formation, the transformation may result in derivatives of o- and p-semidine, i.e. substituted o- and p-aminodiphenylamines, (LXXXV) and (LXXXVI) respectively:-



(LXXXV) (LXXXVI)

In general, the conditions under which the rearrangement takes place and the nature and location of the substituents are controlling factors in determining the proportions of the various products formed. Detailed studies of these factors were carried out by Jacobson and co-workers who have summarised (102) the information available on this subject up to 1922.

Certain Previously Described Rearrangements.

Since the three required dibromodimethylhydrazobenzenes may be regarded as substitution products of 3:3'-dibromohydrazobenzene, the rearrangement of the latter and of some of its derivatives and allied compounds is of interest. 3:3'-Dibromohydrazobenzene rearranges smoothly to 2:2'-dibromobenzidine on heating with concentrated hydrochloric acid (74); the benzidine is obtained in a pure condition and the formation of isomeric dibromodiphenylines does not appear to occur. The introduction of a further two halogen atoms into the remaining meta positions of the hydrazo compound, however, is accompanied by an increased difficulty of rearrangement. The rearrangement of 3:5:3':5'-tetrabromohydrazobenzene does not take place under the usual conditions; it is necessary to treat this compound either with concentrated hydrochloric acid under pressure

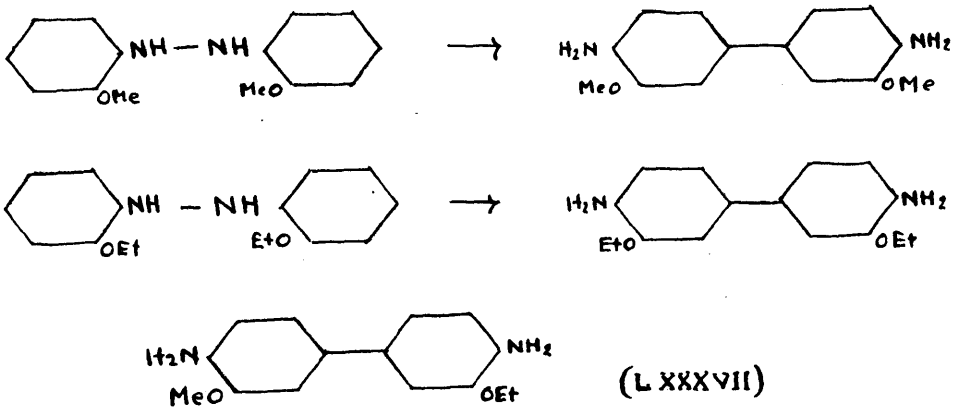
at 100° or, more conveniently, with fairly concentrated sulphuric acid at normal pressure and the same temperature (100°). Under such conditions (139), the principal reaction product is 2:6:2':6'-tetrabromobenzidine but, at the same time, a small amount of 2:6:2':4'-tetrabromodiphenyline is formed. Similar difficulties were encountered in the rearrangement of 3:3'-dichloro-5:5'-dibromohydrazobenzene (118) and in this case the formation of 2:2'-dichloro-6:6'-dibromobenzidine was accompanied by the formation of very considerable amounts of isomeric diphenyline bases. It was also found necessary to employ similar drastic rearrangement conditions with 3:5:3':5'-tetrachlorohydrazobenzene and the purification of the benzidine thus obtained was not easily effected (171).

The presence of two (ortho or meta) methyl substituents in the hydrazobenzene molecule does not adversely affect the benzidine transformation. 2:2'-Dimethylhydrazobenzene rearranges easily yielding relatively less diphenyline derivative than hydrazobenzene (181); the 3:3'-dimethyl- and 3:5-dimethyl hydrazo compounds yield only the corresponding benzidines (101, 97). Since this research is concerned with the preparation and rearrangement of (3:3'-dibromo-2:2'-dimethyl)- and (5:5'-dibromo-2:2'-dimethyl)-hydrazobenzenes,

it is hoped to obtain some information on the effect of the introduction of meta halogen substituents into 2:2'-dimethylhydrazobenzene. Some information regarding the effect of the introduction of such substituents into 3:3'-dimethylhydrazobenzene has already been obtained; 3:3'-dichloro-5:5'-dimethylhydrazobenzene was found to rearrange under relatively mild conditions to 2:2'-dichloro-6:6'-dimethylbenzidine and although the purification of the base presented some difficulty due to a tendency to resinification, no diphenyline derivative was isolated (118). The intended preparation and rearrangement of 3:3'-dibromo-5:5'-dimethylhydrazobenzene should afford a comparison with these observations concerning the corresponding dichloro compound.

Mechanism of the Rearrangement.

In 1933, the benzidine rearrangement was studied by Ingold and Kidd (100) and the process was found to be intramolecular. A mixture of 2:2'-dimethoxy- and 2:2'-diethoxyhydrazobenzene on rearrangement was found to yield only 3:3'-dimethoxy- and 3:3'-diethoxybenzidine; no 3-methoxy-3'-ethoxybenzidine (LXXXVII) was formed.

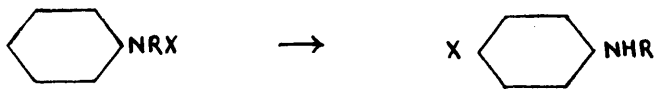


(LXXXVII)

It was known that each of these hydrazo compounds on separate rearrangement yields only the benzidine and that the speeds of rearrangement are comparable. In the rearrangement of the mixture, it followed, therefore, that the 4 and 4' carbon atoms of each hydrazobenzene molecule enter each other's sphere of influence before the rupture of the NH-NH linkage. During the rearrangement, the -NHAr groups are not at any time free otherwise the formation of a certain amount of (LXXXVII) would have resulted.

Electronic theories of the rearrangement were advanced by Robinson (169) and by Hughes and Ingold (98). Dewar has recently pointed out, however, that both these theories involve stereochemical difficulties and he has advanced a new mechanism which is free from such difficulties (61, 62). This is based on the formal analogy between atomic and molecular orbitals and on the idea of bond formation by the sharing of π- electrons between aromatic systems as opposed to

localised electron pairs shared between definite atoms. This mechanism was also applied to related rearrangements of the general type:-



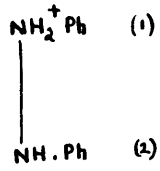
The rearrangements were divided into groups according to the nature of X and the benzidine rearrangement (X = NHAr), was included in the group which consisted of entirely intramolecular rearrangements (page 136). Experimental evidence in favour of this theory was forthcoming from a study of the kinetics of several benzidine rearrangements.

The importance of the benzidine rearrangement in this research was considered sufficient to warrant the inclusion of the following quotation from Dewar's theory of the reaction mechanism.

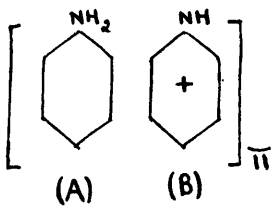
"The present theory is an elaboration of the Robinson mechanism in terms of the quantum theory of aromatic structures."

"It is suggested that in the initial hydrazobenzene salt (I), a non-localised π -electron migrates from ring 2 to ring 1 with consequent fission of the N-N bond to produce the

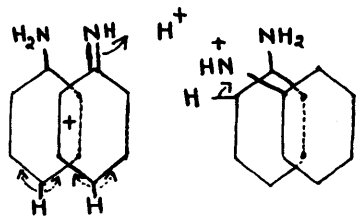
complex molecule (II), composed of the aniline derivative A and the ion radical B. Since the electron levels of the latter are incompletely filled, and since the π -orbitals of the rings will overlap, exchange forces should hold A and B together. The product will be called a π -complex. The π - π bond in it will be of novel type joining aromatic systems and not pairs of atoms but it will be otherwise analogous to the bond in the helium molecule ion He_2^+. Rotation about the bond will be possible, but three positions of stability with intermediate energy-hills will be defined by the alternating polarities round the rings; in them the nitrogens will be opposite each other or 120° apart. The rings in the π -complex will be parallel and co-axial.



(I)



(II)



(X) (Y)

"If the p-substituents in the π -complex can be eliminated as positive ions, process X will be possible (dotted arrows indicate displacements of single electrons), leading to a benzidine. If the reaction is delayed, rotation to a 120°

position will allow the formation of a diphenyline by a type X process. Thirdly, process Y, involving a 60° or 180° orientation of the π -complex, will lead to a semidine; this involves a configuration corresponding to an energy-hill and should be less facile than process X. If we assume that process X is in fact easier than Y only if it involves a p-position of component A, all the data on the benzidine rearrangement can be interpreted in detail."

"The products formed will depend not on the 'migratory aptitudes' of the groups but on the point of attack of the proton catalyst; thus in Y the more basic ring will function as component A and carry the free amino group in the product. A diphenylamine can form only if the more basic ring has a free para position. These conclusions are confirmed in detail by the existing evidence. Moreover, in naphthalene derivatives where rotation of the π -complex should be inhibited since the rings are not symmetrical, diphenylines and p-semidines are in fact never formed."

THEORETICAL SECTION

NITRO COMPOUNDS.

The bromonitrotoluenes were prepared by standard methods. In the case of 3-bromo-5-nitrotoluene, the average yield obtained by previous workers in the deamination of 3-bromo-5-nitro-2-aminotoluene was slightly improved (page 173); this was ascribed to a more gradual and uniform decomposition of the diazonium salt. The first stage in the preparation of 4-bromo-2-nitrotoluene was considerably improved (page 192), the yield in the nitration of p-toluidine being increased by using a lower nitration temperature. The preparation of 2:6-dinitrotoluene, which has never been easily accessible in quantity, was the subject of considerable investigation. The first stage, the reduction of T.N.T. to 2:6-dinitro-4-amino-toluene, was considerably improved; by varying the reaction conditions, a procedure which almost doubled the previously reported yield, was finally evolved (page 209). Since this experimental work was carried out, a recent procedure (152) using slightly alkaline dioxan as solvent is claimed to furnish yet higher yields in this reduction. Deamination of 2:6-dinitro-4-aminotoluene was found to proceed more successfully using hypophosphorous acid in place of ethanol. In such reactions, using ethanol, the replacement of the diazo

group by hydrogen is frequently opposed by ether formation. It has been found (57), however, that this opposition is decreased by the presence of nitro or (para) methyl groups in the aromatic nucleus. In the present case, therefore, the substituents should favour the formation of the required product. In practice, the ethanol procedure did not result in the formation of appreciable amounts of ether but the yield of required product was much lower than that obtained by the use of hypophosphorous acid. The slow, low temperature decomposition of the latter method contrasts with the rapid, high temperature, ethanol decomposition and this may have some bearing on the difference in yields. This constitutes further evidence on the general applicability of hypophosphorous acid as a deaminating agent. The detailed procedure for the reduction of 2:6-dinitrotoluene to 2-nitro-6-aminotoluene (page 214), although based on the general directions of previous workers, was found to result in an improvement in yield.

In view of the time required for the preparation of large amounts of 2-bromo-6-nitrotoluene by the above route, one other possible route was explored. It was considered that 2-bromo-4-aminotoluene might yield, on nitration in presence of excess sulphuric acid, 2-bromo-6-nitro-4-aminotoluene

which by deamination would yield the required product. This expectation, which was based on the meta-directing influence of the ammonium salt group, e.g. the nitration of p-toluidine sulphate to 2-nitro-4-aminotoluene, was not realised. The nitro group was found to enter the ring in the 5-position and the identity of the product, 2-bromo-5-nitro-4-aminotoluene, was substantiated by conversion to 2-bromo-5-nitro-4-acetyl-aminotoluene and 2-bromo-5-nitrotoluene. The nitro group thus enters the 5-position whether the nitration be performed on the amine salt in presence of excess acid or on the acetyl-amino compound under the conditions described by Blanksma (24). This behaviour is quite distinct from that of p-toluidine which yields by these procedures the 6- (or 2-)nitro and the 5- (or 3-)nitro derivatives respectively. The presence of the bromine atom in the 2-position is therefore the controlling factor. The following effects tend to influence the position taken by the entering nitro group:- The bromine atom by reason of its strong inductive effect (-I), tends to deactivate all positions of the ring but the electrophilic attacking group induces an electromeric change in the ortho (3-) and para (5-) positions so that these positions are less deactivated. The 3-position, however, is strongly sterically

hindered due to the presence of the bromo and nitro groups in the 2- and 4-positions and the 5-position alone is favoured. In addition, the substituent bromine atom reduces the basicity of the amine and weakens the salt forming characteristics on which the meta-directing influence of the $[RNH_3]^+$ cation depends. This favours substitution at the 5-position at the expense of the 6-position. The overall effect of the introduction of a 2-bromo substituent in 4-aminotoluene is, therefore, to modify the directive influences; nitration, in presence of excess acid, takes place in the 5- position instead of the 6-position.

2-Bromo-3-nitrotoluene and 4-bromo-3-nitrotoluene (pages 238 and 229) were prepared in moderate and good yield respectively from the amino compounds by the standard Sandmeyer procedure. A convenient method for the acetylation and nitration of o-toluidine facilitated the preparation of 3-nitro-2-aminotoluene. 2:4-Dibromo-6-nitrotoluene was prepared from the diamino compound by the Sandmeyer reaction; the tetrazotisation and replacement were effected in good yield (page 246) by means of a procedure similar to that adopted by Ruggli and Zaeslin (172) for the dichloro isomer.

AZO, HYDRAZO AND AZOXY COMPOUNDS.

(a) Derived from 3-Bromo-5-nitrotoluene.

3:3'-Dibromo-5:5'-dimethylazobenzene was formed smoothly by alkaline reduction (ethanol, aqueous sodium hydroxide, zinc) of 3-bromo-5-nitrotoluene. Although it was found to be more satisfactory to halt the reduction at the azo stage, further reduction to the hydrazo stage proceeded easily under the same conditions. In the latter case, however, the formation of undesirable reduction products occurred. These probably included the amino compound, formed by reductive fission of the molecule and adversely affected the yield of hydrazo compound. For reasons given later, the azo to hydrazo reduction was effected in a more controlled manner, with better yield, using mildly acid conditions (ethanol, acetic acid, zinc). This two stage process has been utilised in preparations of analagous hydrazo compounds (page 129).

Azo compounds, which are highly coloured due to the chromophoric group -N=N-, are characterised by the intense colourations of their solutions in concentrated sulphuric acid. This, according to Hantzsch (84) is due to salt formation, the acid adding on to the nitrogen of the azo

group. 3:3'-Dibromo-5:5'-dimethylazobenzene, which is itself orange coloured, dissolves in concentrated sulphuric acid to form an intensely yellow coloured solution. A convenient method for the conversion of azo compounds to azoxy compounds is that of Angeli (5); peracetic acid or its equivalent, hydrogen peroxide in acetic acid solution, is the oxidising agent (6). Using the latter reagent at 100°, 3:3'-dibromo-5:5'-dimethylazobenzene was slowly oxidised to the azoxy compound. The latter was also prepared directly from the nitro compound, in lower yield, by the Zinin method (213) which utilises the reducing action of boiling ethanolic potash.

(b) Derived from 4-Bromo-2-nitrotoluene.

Under the prescribed conditions, reduction of the nitro compound resulted in a mixture consisting of two-thirds hydrazo and one-third azo compound. This procedure was convenient for two reasons: Firstly, it was difficult to arrest the reduction exactly at the stage where the product consisted wholly of the azo compound and, secondly, a risk of over-reduction was involved by an extension of the reduction under these conditions to the wholly hydrazo stage. With the exception of a small sample for identification purposes,

separation of the azo and hydrazo compounds was unnecessary and the reduction of the azo portion was completed by subjecting the mixed product to the mildly acidic reducing conditions used for the preparation of the previous hydrazo compound (page 198). In this way, the colour change of the reaction mixture indicated the progress of the reduction whereas, in the one stage alkaline reduction, the presence of substantial amounts of excess zinc obscured this indication.

5:5'-Dibromo-2:2'-dimethylazobenzene, which is deeply orange coloured, dissolved in concentrated sulphuric acid to form an intensely red solution. The azo compound, on oxidation by the Angeli method, reacted slowly to form the azoxy derivative but the latter was not formed on attempted reduction (Zinin) of the nitro compound.

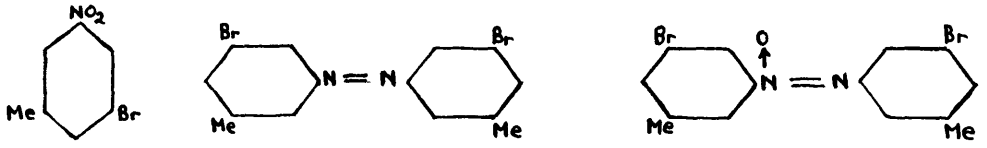
(c) Derived from 2-Bromo-6-nitrotoluene.

On attempting to prepare the azo compound from the nitro compound by the standard method for such reductions (ethanol, aqueous sodium hydroxide, zinc), the azoxy compound was formed in good yield. This compound was, in turn, reduced smoothly to the hydrazo compound when subjected to mildly acid reducing conditions. In this series, the azo compound (3:3'-dibromo-2:2'-dimethylazobenzene), although unobtainable

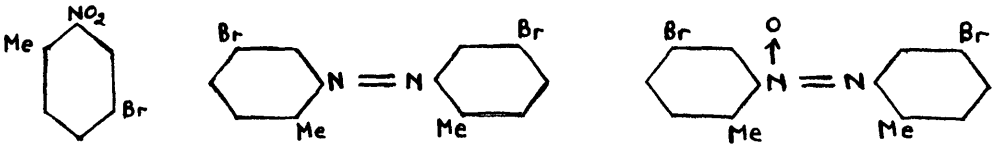
directly from the nitro compound by the usual method of reduction, was, as in series (a) and (b), formed as a by-product during the benzidine transformation of the hydrazo compound (page 220). The azo compound, which formed scarlet needles and dissolved in concentrated sulphuric acid with the formation of an intensely red solution, on oxidation by the Angeli method, very slowly yielded the azoxy compound but the latter was not formed by the Zinin reduction of the nitro compound.

A comparison of the reactions of the isomeric compounds, mentioned in series (a), (b) and (c) above, is of interest since differences must be ascribed to the location of the substituent groups.

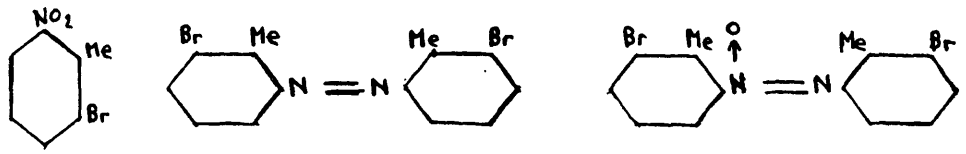
series (a)



series (b)



series (c)



In series (a), the similarity of reaction to the nitrobenzene series is noticeable; the azo and hydrazo compounds are formed by reduction of the nitro compound using conditions under which azo- and hydrazobenzene are formed from nitrobenzene. Similarly, the Zinin reduction converts the nitro to the azoxy compound as is the case with nitrobenzene. In contrast, however, to azobenzene which reacts at room temperature, the Angeli oxidation of the azo to the azoxy compound requires to be conducted at 100°. Although the presence of four meta (3:3':5:5') substituents in the azo compound has the effect of slightly retarding this oxidation, the presence of two meta (3:5) substituents in the nitro compound does not appreciably affect the reduction of the latter. In series (b), reduction of the nitro to the azo and hydrazo compounds takes place under substantially similar conditions to series (a) and to nitrobenzene. The combined presence of an ortho (2-) methyl and a meta (5-) bromine substituent does not affect reduction to the azo and hydrazo compounds but, on the other hand, the Zinin reduction to the azoxy compound is entirely inhibited by these substituents, since the nitro compound does not react under the conditions of the latter reduction. Since, in series (a) and (b), the meta

bromine is similarly situated with respect to the nitro group, this difference must be accounted for by the alteration in position of the methyl group, meta in (a) and ortho in (b). The prevention of the Zinin reduction of 4-bromo-2-nitrotoluene to the azoxy compound must therefore be ascribed to the ortho effect of the methyl group. Since, in series (b), the Angeli oxidation takes place under the same conditions as in series (a), there is no additional hindering ortho effect due to the methyl groups; the 2:2'-dimethyl-5:5'-dibromo substituents affect the reaction similarly to the 3:3'-dibromo-5:5'-dimethyl substituents.

Greater differences, however, are revealed by a comparison of the reactions of compounds of series (c) on the one hand, with those of series (a) and (b) and the unsubstituted compounds on the other hand. In the first place, the normal azo reduction does not take place; the intermediate azoxy compound terminates the reaction. In 2-bromo-6-nitrotoluene, the steric effect of the ortho (1) methyl group is therefore much more pronounced than the steric effect of the same methyl group in 4-bromo-2-nitrotoluene. It is significant that the (2) bromine substituent in the former compound is adjacent (ortho) to the ortho (1) methyl group while in the

latter compound the (4) bromine substituent is more remote from (para to) the ortho (1) methyl group. The effect of an ortho substituent may therefore be considerably increased when this substituent is itself subjected to an ortho effect; that is to say, in a trisubstituted derivative, the ortho effect, of a substituent in the 2-position on a substituent in the 1-position, is greater when a third substituent is present in the 3-position than when this latter substituent is present in the 5-position. Secondly, in series (c), it would therefore be expected that this reinforced ortho effect would operate against the formation of the azoxy compound by the Angeli method. This was shown experimentally; under exactly similar conditions to series (a) and (b), the azoxy compound was formed only extremely slowly. Since the ortho effect in series (b) is sufficient to prevent the Zinin reduction of the nitro compound, it was also to be expected that the reinforced ortho effect in series (c) would act similarly; this was borne out experimentally.

(d) Otherwise Derived.

Although alkaline reduction of 4-bromo-3-nitrotoluene, under the usual conditions for azo compound formation, yielded 2:2'-dibromo-5:5'-dimethylazobenzene in small amount, the main

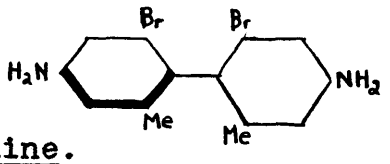
reaction was that of displacement of halogen from the nucleus. The azo compound, which was oxidised (Angeli) to the azoxy derivative, was also formed by the condensation of 4-bromo-3-aminotoluene with 4-bromo-3-nitrosotoluene. Alkaline reduction of 2-bromo-3-nitrotoluene, under the usual conditions for azo compound formation, did not yield the azo compound; evidence of halogen displacement was obtained.

In both the above bromonitrotoluenes, the bromine and nitro substituents are situated in ortho positions with respect to each other. This is in contrast to the bromonitrotoluenes of series (a), (b) and (c) in each of which these substituents are located meta to each other. It is well known that the action of alkali on o- and p-halogenonitrobenzenes results in displacement of halogen from the aromatic nucleus and the factors involved have already been discussed (page 130). The displacement of halogen observed in the alkaline reduction of both 4-bromo- and 2-bromo-3-nitrotoluene is therefore in accordance with theoretical considerations.

In addition, two further new azo compounds were prepared: the first, 3-bromo-5-methylazobenzene, was formed by the condensation of 3-bromo-5-aminotoluene with nitrosobenzene and the second, 3:5:3':5'-tetrabromo-5:5'-dimethylazobenzene, by

the azo reduction of 2:4-dibromo-6-nitrotoluene. The latter azo compound was formed only in small yield indicating that the loading of the aromatic nucleus of nitrotoluene with bromine substituents, even when the latter are not situated either ortho or para to the nitro group, has an adverse effect on the azo reduction.

THE DIBROMODIMETHYLBENZIDINES.



(a) 2:2'-Dibromo-6:6'-dimethylbenzidine.

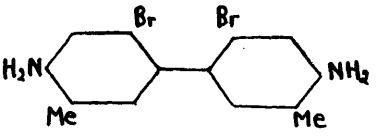
This compound was prepared by the rearrangement of 3:3'-dibromo-5:5'-dimethylhydrazobenzene. Previous research by Kuhn and Rometsch (118), on the rearrangement of 3:3'-dichloro-5:5'-dimethylhydrazobenzene, demonstrated that the reaction proceeded more efficiently under relatively mild conditions. Accordingly, in order to find if similar observations could be made, 3:3'-dibromo-5:5'-dimethylhydrazobenzene was rearranged by two methods, one employing mild reaction conditions and the other severe conditions. Similar observations were made; the mild rearrangement conditions of Kuhn and Rometsch (4N. hydrochloric acid, room temperature) gave a higher yield of purer product than severe conditions (boiling 10N. hydrochloric acid with or without ethanol).

Purification of the crude rearrangement product demanded a certain amount of care since the benzidine was extremely soluble in organic solvents and, if rapidly precipitated, especially at elevated temperatures, showed a tendency to resinification. Also, precipitation of the benzidine by neutralisation of an acid solution of the dihydrochloride, if performed at a low temperature, yielded the base in a finely divided crystalline form but, at higher temperatures, gave rise to an intractable, resinous form. Similar observations have been made with 2:6:2':6'-tetrabromobenzidine, 2:2':6:6'-tetrachlorobenzidine and 2:2'-dichloro-6:6'-dimethylbenzidine (139, 171, 118). Also, as is the case with these analagous benzidines, during the rearrangement a small amount of the hydrazo compound is disproportionated to the azo compound.

The benzidine, which was insoluble in water, dissolved readily in cold dilute mineral acid. The hydrochloride, precipitated by passing dry hydrogen chloride into a solution of the amine in dry ether, was extremely unstable and, in air, rapidly decomposed with resin formation. The benzidine, therefore, exhibits more pronounced basic properties than the isomeric 3:3'-dibromo-5:5'-dimethylbenzidine which is insoluble in dilute hydrochloric acid and of which the hydrochlorid

is hydrolysed by water (147, 178). The benzidine yielded the expected derivatives: The diacetyl derivative was obtained in a crystalline form from methanolic solution; crystallisation from aqueous ethanol yielded an amorphous product. The dibenzylidene derivative was easily prepared in low yield by condensation of the amine with benzaldehyde in hot ethanolic solution. The bis(azo-β-naphthol) derivative, isolated as an insoluble crimson powder, dissolved in concentrated sulphuric acid to form an intensely magenta coloured solution.

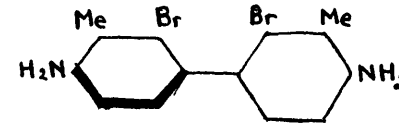
(b) 2:2'-Dibromo-5:5'-dimethylbenzidine.



This compound was prepared by the rearrangement of 5:5'-dibromo-2:2'-dimethylhydrazobenzene. This reaction was conducted in conjunction with an acid purification process, advantage being taken of the insolubility of the hydrochloride and sulphate of the required benzidine in contrast to the solubility of these salts of the other basic by-products of the rearrangement. In order to ensure that no unconverted hydrazo compound, coated with the insoluble benzidine salts, remained, a somewhat prolonged rearrangement treatment was used. The product obtained directly by this process was of

high purity and, in contrast to the isomeric benzidine (section (a)), subsequent recrystallisation was unnecessary. The small amount of azo compound, formed by disproportionation, was previously removed from the product by utilising the solubility of the benzidine in hot aqueous ethanol.

This benzidine, in contrast to the previous isomer (section (a)), yielded by the same method a dihydrochloride which was insoluble and which decomposed more slowly in air. The benzidine yielded the other expected derivatives: The high-melting diacetyl derivative was easily isolated in a crystalline form from boiling glacial acetic acid in which it was slightly soluble. This diacetyl derivative possessed a greater similarity to those of benzidine and o-tolidine which are high-melting, sparingly soluble solids. The dibenzylidene derivative, prepared by the method used for the previous isomer, was obtained in much higher yield. The bis (azo-β-naphthol) derivative formed a dark crimson powder also soluble in concentrated sulphuric acid to form an intensely magenta coloured solution.

(c) 2:2'-Dibromo-3:3'-dimethylbenzidine. 

This compound was prepared by the rearrangement of 3:3'-dibromo-2:2'-dimethylhydrazobenzene. In this reaction, the

formation of the required benzidine was accompanied by disproportionation of a small amount of the hydrazo to the azo compound and also by the formation of other basic products. The latter were removed from the crude rearrangement product by utilising the relative solubility of their hydrochlorides and the insolubility of the benzidine dihydrochloride in 1.6N hydrochloric acid. The azo compound was previously removed by making use of its insolubility in aqueous ethanol as in the previous rearrangement.

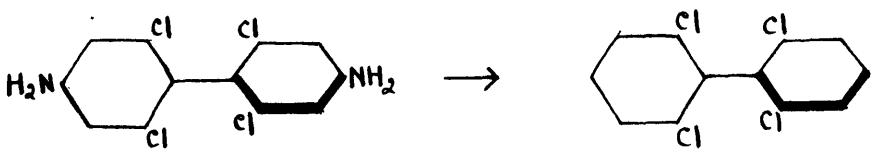
By means of the method previously used, the sparingly soluble dihydrochloride was prepared. In this preparation, due to the low solubility of the benzidine in ether, it was necessary to add ethanol to complete the solution. The dihydrochloride, decomposed rather slowly in air in comparison with that of the previous isomer (b) and much more slowly than that of isomer (a). The benzidine also yielded the expected derivatives: The diacetyl derivative, formed easily in theoretical yield, was high-melting and sparingly soluble and thus resembled the corresponding derivatives of benzidine, o-tolidine and isomer (b). The dibenzylidene derivative was also prepared in good yield while the scarlet bis(azo-β naphthol) derivative dissolved in concentrated sulphuric acid

to form an intensely magenta coloured solution. This colouration, exhibited by the sulphuric acid solutions of the bis(azo-β-naphthol) derivatives of all three benzidines, is therefore characteristic of this substituted diphenyl-4:4'-bis(azo-β-naphthol) structure.

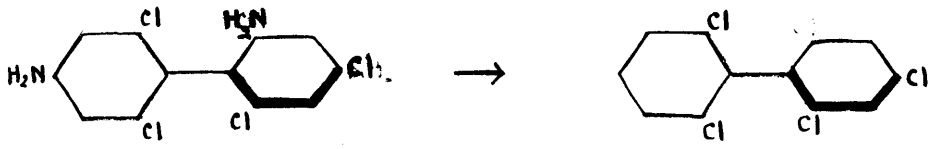
STRUCTURAL EVIDENCE.

Each of the benzidines, which have been described, was formed by the rearrangement of a hydrazobenzene derivative possessing no para substituents. Since, during such reactions there exists the possibility of diphenyline formation even although the latter usually takes place in small yield (pages 133 , 135), it was considered necessary to demonstrate that each of the products described does, in fact, possess the benzidine structure assigned and not that of a diphenyline derivative.

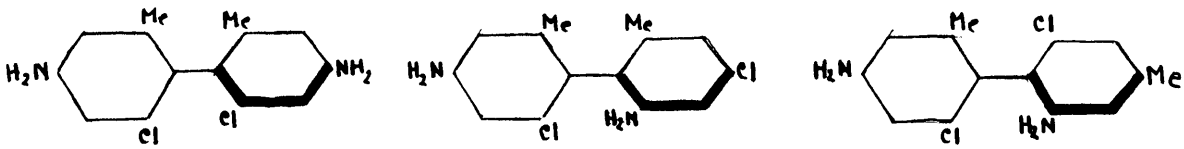
Structural evidence concerning two previously prepared tetra (2:6:2':6') substituted benzidines has been presented as follows: Roosmalen (171) deaminated 2:6:2':6'-tetrachlorobenzidine to 2:6:2':6'-tetrachlorodiphenyl which had been previously described:-



If the original amine had possessed a diphenyline structure, the product of this deamination would have been 2:4:2':6'-tetrachlorodiphenyl:



In the case of 2:2'-dichloro-6:6'-dimethylbenzidine, the structural evidence advanced by Kuhn and Rometsch (118) was based on a dipole moment measurement:



(S^1) (S^2) (S^3)

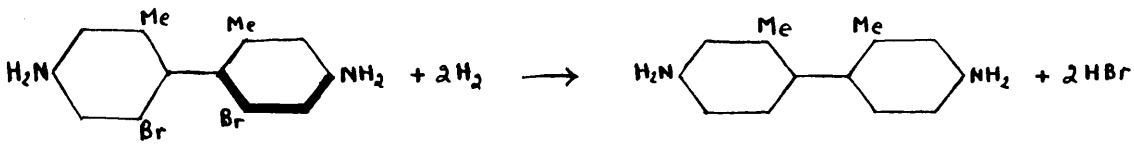
Of the three possible structures(S^1, S^2, S^3), that of the benzidine (S^1) theoretically possesses the smallest dipole moment due to mutual cancellation of the axial components. The measured value of the dipole moment was found to be in good agreement with the calculated value for the benzidine (S^1) and considerably less than the values calculated for the diphenylines (S^2 and S^3).

In the present case, the proof of structure was based on a reaction by means of which aromatic nuclear halogen is replaced by hydrogen. In this way, the dibromodimethyl-

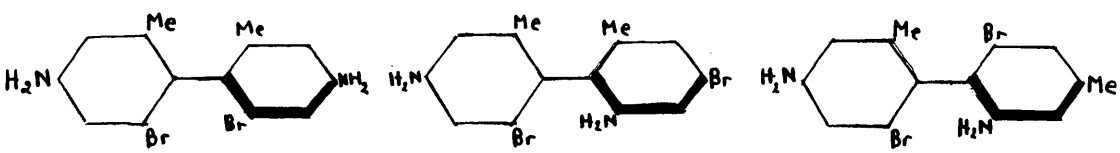
benzidines were converted to previously described tolidines, the identity of the latter being verified by the method of mixed melting points with authentic products. In the case of m-tolidine, a difficulty crystallisable material of doubtful melting point, mixed melting point determinations were conducted on the N:N'-diacetyl derivative which is crystalline and sharp-melting (103).

Although the replacement of aromatic nuclear halogen has frequently been observed during zinc and acid reductions the two general methods which have been described do not make use of this reagent. Busch and Stöve (37) recommended molecular hydrogen in the presence of a catalyst and Schwenk, Papa, Whitman and Ginsberg (182) made use of Raney alloy and alkali. In the present case, the former reagent was preferred since the progress of the reaction could be conveniently assessed by measurement of the hydrogen absorbed. The reductions were carried out at room temperature and atmospheric pressure, the catalyst, palladium-calcium carbonate, being used at a concentration of 0.01g. of palladium metal per 0.00135g.mol. of unreduced compound. The solvent was ethanol to which was added excess potassium hydroxide to absorb the hydrogen chloride released during the reaction. The reaction times

varied with the isomer:- (a), 148 mins.; (b), 37 mins.; (c), 103 mins. and the respective volumes of hydrogen absorbed corresponded to 94, 93 and 95% of the theoretical amounts required for the following reaction, e.g. in the case of isomer (a):



The structures of the isomers are shown by these reactions. Since 3:3'-dibromo-5:5'-dimethylhydrazobenzene rearranged to isomer (a) (page 179), the latter must possess one of the following constitutions:

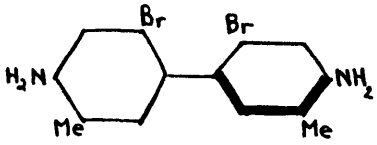


(S^4) (S^5) (S^6)

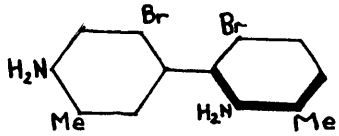
Further, since in isomer (a) replacement of the bromine substituents by hydrogens resulted in m-tolidine and since, of the three structures (S^4, S^5 and S^6), (S^4) alone is theoretically capable of such behaviour, it follows that isomer (a) possesses the benzidine structure (S^4).

Isomer (b) yielded o-tolidine and, for similar reasons, benzidine (S^7) is the only acceptable of the three, following

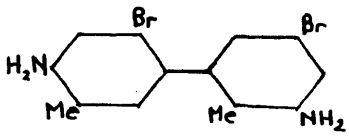
possible structures:



(S⁷)

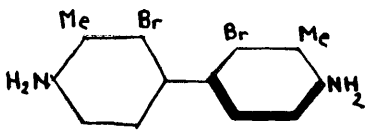


(S⁸)

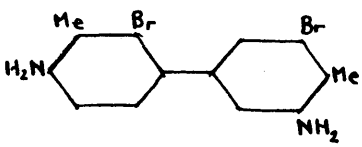


(S⁹)

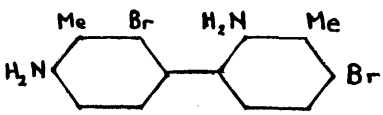
Finally, isomer (c) also yielded o-tolidine and, for similar reasons, benzidine (S[10]) is the only acceptable of the three, following, possible structures:



(S¹⁰)



(S¹¹)



(S¹²)

RESOLUTIONS.

2:2'-Dibromo-6:6'-dimethylbenzidine. The dl-amine formed well-defined, crystalline salts with two molecules of d-tartaric acid, the l-amine d-tartarate being rather more sparingly soluble in ethanol. The l-amine d-tartarate was freed from the d-amine d-tartarate by repeated recrystallisation from ethanol. Rotation measurements on the salt fractions were effected in dilute hydrochloric acid solution. The amine dihydrochloride, formed under these conditions,

did not exhibit any tendency to racemisation. Ethanolic solutions of the salt, on remaining at room temperature for crystallisation of the salt, developed a yellow colour which was easily removed by charcoal treatment. Similar observations were made by Kuhn and Rometsch (118) on the corresponding dichloro compound. Decomposition of the l-amine d-tartarate yielded the l-amine which melted 19.5° higher than the pure dl-amine, m.p.157.5°. From the mother-liquors of the l-amine d-tartarate, the impure d-amine d-tartarate was recovered and decomposition of the latter resulted finally in the isolation of a d-amine, m.p.166-168°, of 32% purity based on the rotation of the l-amine. The l-amine exhibited a singular resistance to racemisation; prolonged refluxing with 3N. hydrochloric acid scarcely affected the optical activity. The low specific rotation; $[\alpha]_D^{17}$,- 0.82°, of 2:2'-dibromo-6:6'-dimethylbenzidine is characteristic of active 2:2'-substituted benzidines; the corresponding value for 2:2'-dichloro-6:6'-dimethylbenzidine was $[\alpha]_D^{16}$, - 1.32° (118) and in the case of diphenyl benzidine 2:2'-disulphonate the rotation was very small, no measurement having been quoted (125).

This resolution of 2:2'-dibromo-6:6'-dimethylbenzidine is

in agreement with theoretical considerations (page 118). The presence of four relatively large substituents in the positions ortho to the pivot bond gives rise to a non-coplanar diphenyl molecule. Since both benzene nuclei are unsymmetrically substituted with respect to their common axis, the conditions necessary for optical activity (page 90) are satisfied. Furthermore, since the sizes of these ortho substituents are sufficiently great to lock the molecule in a rigid non-coplanar configuration, great stability of the active forms is to be expected. This is in accordance with the observed resistance to racemisation exhibited by active (1-) 2:2'-dibromo-6:6'-dimethylbenzidine.

2:2'-Dibromo-5:5'-dimethylbenzidine. This amine formed a crystalline salt with one molecule of d-tartaric acid. This salt was recrystallised from ethanol until 46% of the theoretical amount of the salt remained. This fraction gave $[\alpha]_D^{16}$, + 6.59° in pyridine solution and did not exhibit mutarotation. Mild conditions, designed to preclude racemisation, were employed to decompose the salt but the amine obtained was inactive and possessed the same melting point (153°) as the starting material. From the mother-liquors of the first salt fraction was obtained a second fraction which did not

exhibit mutarotation in pyridine, $[\alpha]_D^{17}$, + 6.89°, and which also yielded an inactive amine.

The amine also formed an excellent, crystalline salt with one molecule of d-camphor-10-sulphonic acid. This salt was extracted with ethanol until 45% of the theoretical amount remained. No mutarotation in pyridine was observed $[\alpha]_D^{17}$, ~ + 2.6°, and, on decomposition, an inactive amine was obtained.

The failure to resolve this amine into optical isomers shows that the introduction of methyl groups into the 5:5' positions of 2:2'-dibromobenzidine does not sufficiently decrease the freedom of rotation of the benzene nuclei about their common axis to permit the formation of optical isomers or, alternatively, if such isomers are formed, their stability is extremely slight and racemisation readily occurs. The behaviour of 2:2'-dibromo-5:5'-dimethylbenzidine is similar to that of 2:2'-dibromobenzidine. Although the former amine forms excellent crystalline salts with d-tartaric acid and d-camphor-10-sulphonic acid, and the latter amine (183) with d-camphor-10-sulphonic acid and d-α-bromocamphor-π-sulphonic acid, in neither case was a resolution effected although, under similar experimental conditions, 2:2'-dibromo-

4:4'-diphenic acid was resolved (184). The position of the methyl groups thus exerts a marked influence on the amine. The isolation of extremely stable optical isomers of 2:2'-dibromo-6:6'-dimethylbenzidine, in which the methyl groups are located ortho to the pivot bond, stands in contrast to the failure to resolve 2:2'-dibromo-5:5'-dimethylbenzidine in which the methyl groups are located meta to the pivot bond.

2:2'-Dibromo-3:3'-dimethylbenzidine. This amine formed crystalline salts with d-tartaric acid, the l-amine d-tartarate being the least soluble in ethanol. After purification by several recrystallisations from ethanol, the salt, which did not mutarotate, was decomposed at low temperature by the usual method to yield the active (l-) amine which melted slightly higher (201-202°) than the original (dl-) amine (m.p.200°). The l-amine did not racemise at room temperature either in ethanol $[\alpha]_D^{18}$, - 8.32°, or acetone $[\alpha]_D^{17}$ - 6.68°. Complete racemisation occurred, however, on refluxing the l-amine for thirty minutes with a mixture of 3N. hydrochloric acid and ethanol, the presence of the latter being necessary to effect solution of the insoluble dihydrochloride. The racemic amine possessed the same melting point

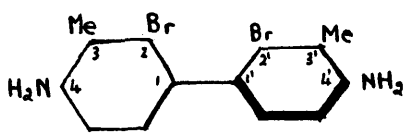
(200°) as the original inactive amine. The mother-liquors from the first salt fraction were worked up to yield a second fraction which was decomposed to impure l-amine, $[\alpha]_D^{17}$, - 1.56° (m.p.200°).

The successful resolution of 2:2'-dibromo-3:3'-dimethylbenzidine contrasts with the previous failures to resolve 2:2'-dibromo-5:5'-dimethylbenzidine (page 164) and 2:2'-dibromobenzidine (184). The observations of Adams on the effect of a substituent in the 3-, 4- or 5-position of an optically active diphenyl have been discussed (page 114). The 3- were found to be more stable to racemisation than the 5-substituted of such isomers. In the present case, however, two substituents may be regarded as having been introduced, one into each of the 3:3'- positions of 2:2'-dibromobenzidine. It might, therefore, be argued that this virtual doubling of the effect would result in a considerable increase of stability.

Against this, however, in the present case, the original amine (2:2'-dibromobenzidine) was optically inactive and the introduction of two (methyl) substituents in the 5:5'-positions did not give rise to optical activity but,

in contrast, the introduction of these substituents to the 3:3'-positions not only conferred optical activity on the amine but the active form of the latter exhibited moderate stability to racemisation. It is suggested therefore that the effect of the introduction of the 3:3'-methyl substituents is greater than would be expected solely on the basis of the observations of Adams.

One important difference between the active diphenyl concerned in the observations of Adams, 2-nitro-6-carboxy-2'-methoxydiphenyl and 2:2'-dibromobenzidine is the absence of 4:4'- substituents in the former. It is suggested that the presence of these substituents is an important factor in the resolvability of 2:2'-dibromo-3:3'-dimethylbenzidine. In the latter compound, the 3:3'-methyl substituents are located in the position between the 4:4'-amino and 2:2'-bromine substituents and, in each benzene nucleus, four consecutive (1:2:3:4-) positions may be considered to be substituted:-



The following mechanism is advanced for the effect which gives rise to optical isomerism. In each of the benzene nuclei, due to the presence of the 4-amino substituent, the 3-methyl substituent is subjected to an ortho effect and, in consequence, an increased ortho effect due to the 3-methyl substituent is relayed to the 2-bromine substituent. These ortho effects are of a cumulative character and the resultant effect on each of the 2-bromine substituents is of considerable magnitude. The effect in this case is probably mainly steric in nature and causes a displacement of each of 2:2'-bromine substituents in a direction which increases their mutual interference during rotation of the benzene nuclei about the pivot bond.

These resolution experiments also throw some additional light on the possible mechanisms advanced by Adams to account for the observed variations in stability of active diphenyls with the location of a substituent (page 115).

Factor (3), the slowing down of the semicircular oscillation of the two phenyl rings by substituents is definitely not operative because of the fact that 2:2'-dibromo-3:3'-dimethylbenzidine is resolvable and 2:2'-dibromo-5:5'-dimethylbenzidine is not resolvable. Any

mechanism of this type should be equally applicable to both isomers which should therefore exhibit similar behaviour on attempted resolution.

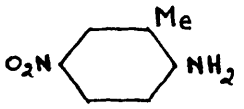
Factor (4), the modification of the distance between the 1-1' carbon atoms is also ruled out because of the difference in behaviour of the isomers on attempted resolution. In both 2:2'-dibromo-3:3'-dimethylbenzidine and 2:2'-dibromo-5:5'-dimethylbenzidine, the methyl groups, although situated on opposite sides of the benzene nuclei, are located in the meta position with respect to the pivot bond and any electronic mechanism which would act in such a manner as to reduce the distance between the 1-1' carbon atoms should therefore be equally applicable to both isomers.

Of the three remaining factors, (1), (2) and (5) it is probable that the observed results are due to the operation of either factor (1) or factor (2) or to a combination of these factors. In the case of 2:2'-dibromo-3:3'-dimethylbenzidine, the ortho effects of the methyl groups (probably of a steric nature in this instance) might reasonably displace the bromine substituents either by alteration of the valency angle of the C-Br bond (factor (1)) or by increasing the internuclear distance C-Br (factor (2)).

EXPERIMENTAL SECTION

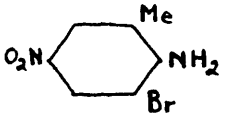
A. <u>2:2'-DIBROMO-6:6'-DIMETHYLBENZIDINE</u>

The synthesis of 2:2'-dibromo-6:6'-dimethylbenzidine was accomplished by means of the following series of reactions:



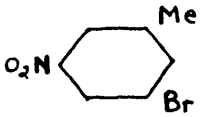
5-nitro-2-aminotoluene.

Stage 1. ↓



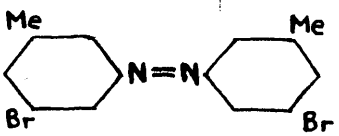
3-bromo-5-nitro-2-aminotoluene.

Stage 2. ↓



3-bromo-5-nitrotoluene.

Stage 3. ↓

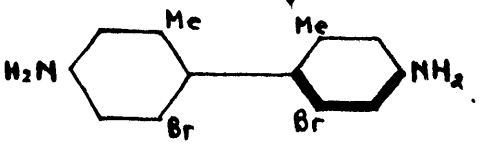


3:3'-dibromo-5:5'-dimethylazobenzene.

Stage 4. ↓

3:3'-dibromo-5:5'-dimethylhydrazobenzene.

Stage 5. ↓



2:2'-dibromo-6:6'-dimethylbenzidine.

Stage 1. 3-BROMO-5-NITRO-2-AMINOTOLUENE

This substance was prepared by the bromination of 5-nitro-2-aminotoluene in glacial acetic acid solution according to the directions of Gibson and Johnson (77). A description of the procedure is given below for the sake of completeness.

Procedure:

5-nitro-2-aminotoluene	70g.
Glacial acetic acid	700ml.
Bromine	23.3ml.

A solution of the nitroamine in the hot glacial acetic acid was quickly cooled to 40° avoiding reprecipitation. Bromine was dropped into the mechanically stirred solution maintained at 40° (external cooling) and a pale yellow solid was precipitated during the course of this addition. The reaction mixture was poured into cold water (1500ml.) and the solid was filtered off, washed twice with cold water and dried in a steam oven. The 3-bromo-5-nitro-2-aminotoluene (100g.,94%) was sufficiently pure (m.p. 174.5°; pure compound, m.p.Lit., 176°) for use directly in the subsequent deamination.

Stage 2. 3-BROMO-5-NITROTOLUENE

This substance was prepared by deamination of 3-bromo-5-nitro-2-aminotoluene according to the general directions of Gibson and Johnson (77); the yield of these workers, 40% (average of four experiments), was slightly improved to 45% (average of three experiments) by means of the following detailed procedure:

Procedure:

3-Bromo-5-nitro-2-aminotoluene	65g.
Ethanol	300ml.
Concentrated sulphuric acid (S.G.,1.84) ..	72ml.
A.R. sodium nitrite	20.8g.

The concentrated sulphuric acid was slowly added to a mechanically stirred mixture of the ethanol and finely divided 3-bromo-5-nitro-2-aminotoluene; during this addition the reaction mixture was cooled externally by means of cold water to prevent rise of temperature. A solution of the sodium nitrite (in water, 45ml.,) was dropped into the vigorously stirred mixture over a period of forty-five minutes during which the temperature was allowed to rise from 14.5° to 23° by regulation of the cooling water. After the addition of the nitrite, the mixture was heated to 80° by immersion in hot

water. Heating was discontinued until the violence of the reaction had subsided and the mixture was heated for a further thirty minutes on the boiling water-bath. The mixture was then allowed to cool and mechanical stirring, which had been continuous from the commencement of the operations, was discontinued. The reaction mixture was steam distilled to 10l. of distillate which was extracted with ether. The ethereal extract was dried (calcium chloride), filtered and concentrated when crystals of pure 3-bromo-5-nitrotoluene were deposited. These were filtered off and dried (24.5g.); m.p.83° (m.p.Lit. 83°). The ethereal mother liquor, on further concentration, yielded a second crop of impure crystals which on recrystallisation from ether gave almost pure 3-bromo-5-nitrotoluene (3.74g.); m.p.82°. The total yield in this experiment thus amounted to 28.24g., 46.5%.

Stage 3. 3:3'-DIBROMO-5:5'-DIMETHYLAZOBENZENE

This substance which has not been previously described was prepared by the alkaline reduction of 3-bromo-5-nitrotoluene.

Procedure:

3-Bromo-5-nitrotoluene	27.1g.
Ethanol	140ml.
A.R. sodium hydroxide	9.1g.
Zinc dust	27.1g.

The apparatus for this reduction consisted of 500ml., three-necked flask of which one side neck carried a dropping funnel fitted by means of a rubber stopper, the centre neck was occupied by a mechanical stirrer fitted by means of a vapour tight gland and the third neck was attached by means of a piece of wide, flexible rubber tubing to a short, vertical, double surface condenser. The apparatus was so placed that, when necessary, a small water-bath could be introduced in order to heat the reaction flask.

The 3-bromo-5-nitrotoluene and ethanol were placed in the reaction flask, stirring was commenced and the mixture was heated when the solid dissolved. Heating was continued until the mixture was boiling briskly and the alcohol vapour was refluxing from the condenser. At this stage, the zinc dust was added as quickly as possible to the solution by momentary removal of the dropping funnel. By means of the latter, a solution of the sodium hydroxide (in water, 56.5ml.) was gradually dropped into the boiling mixture over a period of forty minutes. Care was necessary, especially in the initial stages of this operation, in order to prevent undue frothing; it was necessary to remove the water-bath and to suspend the addition of the alkali from time to time. After the addition of the alkali, stirring was discontinued (Note 1) and most of the ethanol (130ml.) was removed by distillation on the water-

bath. Water (200ml.) was added to the residue which, when cold, was filtered and washed several times with cold water until free from alkali. The residue was dried over concentrated sulphuric acid, finely powdered and extracted with boiling toluene (200ml.) in a drip extractor until all the coloured material was removed. The toluene extract was concentrated to about 30ml. volume and ethanol (30ml.) was added to the hot toluene suspension of the azo compound thus obtained. The mixture, after warming to redissolve the azo compound, was allowed to remain for several hours at room temperature to complete the precipitation of 3:3'-dibromo-5:5'-dimethylazobenzene which formed bright orange needles (8.31g.); m.p.158-160°. The filtrate from the first crop of azo compound yielded after three days, a second crop of similar crystals (2.84g.); m.p. 158-160°. The filtrate from the second crop on concentration and further dilution with ethanol yielded a third, less pure, crop (1.74g.); m.p.145-150°. A total of 12.89g. (55.8%) of crude azo compound was thus obtained. A small amount of the crude azo compound was purified for analysis by two recrystallisations from toluene from which it separated in the form of bright orange, felted needles; m.p.166-166.5°.

Analysis: Found: C,45.8%; H,4.0; Br,43.6.

Required for $C_{14}H_{12}N_2Br_2$: C,45.7%; H,3.3; Br,43.4.

3:3'-Dibromo-5:5'-dimethylazobenzene was found to be soluble in hot petroleum ether, acetone, benzene, chloroform or carbon tetrachloride; moderately soluble in warm ether or hot glacial acetic acid; slightly soluble in hot methanol or ethanol and insoluble in water. Cold concentrated sulphuric acid dissolved the azo compound with the formation of an intensely yellow solution. The azo compound was recovered unchanged after four hours' treatment at the water-bath temperature with excess of a mixture of equal volumes of ethanol and concentrated hydrochloric acid.

Note 1. It was found by experiment that addition of the alkali over a longer period of time or continuation of stirring after the addition of the alkali resulted in the formation of appreciable amounts of the hydrazo compound; in these instances the combined yields of azo and hydrazo compounds were adversely affected.

Stage 4. 3:3'-DIBROMO-5:5'-DIMETHYLHYDRAZOBENZENE

This compound which has not been previously described was prepared from the corresponding azo compound by reduction (zinc and acetic acid).

Procedure:

3:3'-Dibromo-5:5'-dimethylazobenzene	12.9g.
Glacial acetic acid	12.3ml.
Ethanol	215ml.

Zinc dust ..... 6.7g.

The apparatus for this reduction consisted of a 500ml., round bottom flask fitted with a reflux condenser and a short, wide, vertical side arm closed at the upper end by means of a stopper. A mixture of the 3:3'-dibromo-5:5'-dimethylazobenzene, glacial acetic acid and ethanol was heated to boiling and the zinc dust was gradually added in small portions by momentary removal of the stopper. The boiling mixture was shaken from time to time throughout the addition of the zinc which caused the original deep orange colour of the mixture to fade to a pale yellow (Note 1). The mixture was allowed to cool overnight when the precipitated zinc acetate and excess zinc dust was filtered off and washed twice with ethanol to remove hydrazo compound. The filtrate and ethanol washings were combined and heated to boiling when sufficient hot water was added to maintain a faint turbidity at boiling point. The solution, on remaining at room temperature for sixty hours, deposited the required hydrazo compound in the form of almost colourless rhombic plates which were filtered off and dried over potassium hydroxide in vacuo (11.6g., 89.2%); m.p.ca.129° with previous softening. The crude product thus obtained was used directly for Stage 5; a small amount was purified for

analysis by recrystallisation from aqueous ethanol; m.p. 131-132°.

Analysis: Found: C,45.6%; H,3.8; N,7.82; Br,42.6.

Required for $C_{14}H_{14}N_2Br_2$: C,45.4%; H,3.8; N,7.57; Br,43.2.

The hydrazo compound which was insoluble in water, was found to be soluble in most of the common organic solvents and on exposure to air became coated with an orange skin due to oxidation to the azo compound.

Note 1. The amount of zinc was found to be somewhat variable. The amount of shaking during the reduction, the rate of addition of the zinc and the presence (if any) of hydrazo compound in the original azo compound appeared to be controlling factors.

Note 2. Addition of water to the boiling filtrate from the crude hydrazo compound caused only a slight precipitation of solid (0.46g.); this consisted mainly of impure azo compound as on recrystallisation from ethanolic toluene it formed bright orange-yellow needles; m.p.162-163°.

Stage 5. 2:2'-DIBROMO-6:6'-DIMETHYLBENZIDINE.

This compound which has not been previously described was prepared by the rearrangement of 3:3'-dibromo-5:5'-dimethyl-hydrazobenzene.

Procedure 1.

3:3'-dibromo-5:5'-dimethylhydrazobenzene .... 11.6g.

4N hydrochloric acid ..... 232ml.

The 3:3'-dibromo-5:5'-dimethylhydrazobenzene and hydrochloric acid were shaken together in a 500ml., glass-stoppered bottle for sixteen hours. The resultant suspension was filtered through a sintered glass filter and then through filter paper to give a clear, faintly red, filtrate which was made alkaline by the slow addition of sodium hydroxide solution (A.R.sodium hydroxide, 55g., in water, 110ml.). During the neutralisation, the mixture was stirred mechanically and external cooling was applied to maintain the temperature below 20°. The free base which was precipitated in the form of a colourless solid, was filtered off and washed well with water until free of alkali. On drying in vacuo, the base assumed a very faint pink colour (6.61g.); m.p.143-146°. The base was further purified by suspending in water(375ml.), adding 5N hydrochloric acid(15.6ml.) and heating the mixture to boiling when a small amount of reddish-brown material remained undissolved; charcoal (1g.) was added and after boiling for a few minutes, the hot liquid was filtered. The cooled filtrate was made alkaline by the slow addition of sodium hydroxide solution (A.R. sodium hydroxide 3.5g. in water 50ml.). During this

neutralisation the temperature of the mechanically stirred mixture was maintained below 10°. The free base which was precipitated in the form of a colourless solid was filtered off, washed several times with cold water until free of alkali and dried in vacuo (6.1g.); m.p.152-154°. The base was dissolved in ethanol (61ml.) to form an orange - brown solution which was filtered, heated to boiling and hot water (116ml., temperature 95°) was gradually added with stirring until a faint permanent turbidity was produced. The solution on cooling overnight deposited crystals which were filtered off and washed with aqueous ethanol (ethanol 22ml. in water 40ml.). The large, blunt needle shaped, faintly lilac pink, crystals were dried in vacuo giving pure 2:2'-dibromo-6:6'-dimethylbenzidine (5.36g., 46.2%); m.p. 157.5°.

Analysis: Found: C,45.2%; H,3.8; N,7.81; Br,43.3.

Required for $C_{14}H_{14}N_2Br_2$: C,45.4%; H,3.8; N,7.57; Br, 43.2.

A second less pure crop was obtained by boiling the mother liquors to evaporate some of the ethanol and adding water to the boiling solution as previously described (0.37g.); m.p. 150-153.5°.

The pure compound crystallised from aqueous ethanol in almost colourless needles as described above and these on

drying assumed a faint pink colour; on standing exposed to the air for several weeks, there was no discoloration due to the formation of highly coloured oxidation products as is the case with benzidine, o-tolidine and o-dianisidine. The substance was found to be extremely soluble in the usual organic solvents.

The residue from the rearrangement of the hydrazo compound with 4N hydrochloric acid consisted of a cream coloured solid which was washed with water until free of acid and dried in vacuo (4.43g.); m.p., not sharp, ca.,113° to form a bright red liquid. The presence of azo compound in this residue was shown as follows:- The residue was recrystallised from ethanol and dried; m.p., not sharp, ca.115-118° to a bright red liquid. A portion of this material was boiled for five minutes with 10N hydrochloric acid, the mixture was allowed to cool, diluted with water and the suspended material was filtered off and washed with water. The residue was dried; m.p.164-165° and recrystallised from ethanolic toluene; bright orange needles; m.p.,166-166.5°, undepressed on mixing with an authentic specimen of 3:3'-dibromo-5:5'-dimethylazobenzene, m.p.166-166-5°.

Procedure 2.

3:3'-Dibromo-5:5'-dimethylhydrazobenzene ..... 11.6g.

Concentrated hydrochloric acid (S,G.,1.16) ..... 100ml.

The hydrazo compound was gradually added, with stirring, to the hydrochloric acid and the mixture was boiled for ten minutes when a light brown flocculent solid remained undissolved. After the addition of water (200ml.), the solution was boiled for a further five minutes. On cooling, the light brown residue was filtered off, yielding a clear faintly pink filtrate which was made alkaline in the usual manner, the temperature being maintained below 30°. The crude base, which was thus obtained in the form of a faintly lilac coloured solid, was filtered off, washed with water and dried in vacuo (6.94g.); m.p.,not sharp, softened progressively with discoloration from ca.80-126°. The crude base was partially purified as follows:- The crude base (5g.) was dissolved in ethanol (50ml.) and to the boiling solution, hot water (58ml., 80-90°) was gradually added with stirring when a faint permanent turbidity was produced. The solution, on slight cooling, precipitated a dark-brown resinous material containing a few crystals. The clear, supernatant solution was decanted and heated to boiling when a further amount of hot water (60ml.) was added. The hot, faintly turbid solution, on slight cooling, yielded a similar deposit which once again adhered to the bottom of the flask. The supernatant solution was decanted and set aside to crystallise when large, colourless, needles

were formed; these exhibited a tendency to form end-grouped clusters and some of the needles on the bottom of the vessel possessed a faint pink tint. When crystallisation was complete, the solid was filtered off and dried in vacuo (1.47g.); m.p.150-151°.

The light brown residue obtained by treatment of the hydrazo compound with boiling concentrated hydrochloric acid was proved as follows to consist essentially of the azo compound:- The residue was washed with water, dried and recrystallised from ethanolic toluene when it was obtained in the form of bright orange needles; m.p.166-166.5°, not depressed by the addition of authentic 3:3'-dibromo-5:5'-dimethylazobenzene; m.p.166-166.5°.

Procedure 3.

3:3'-Dibromo-5:5'-dimethylhydrazobenzene	11.7g.
Ethanol	50ml.
Concentrated hydrochloric acid (S.G., 1.16).....	50ml.

A mixture of the hydrazo compound and the ethanol was refluxed on the water-bath and the concentrated hydrochloric acid added. Heating at the water-bath temperature was continued for fifteen minutes followed by heating at reflux temperature for one hour. After the addition of water (150ml.), the hot mixture

was filtered; the residual orange solid consisted of the azo compound (2.7g.); m.p.166-166.5°, while the filtrate, on neutralisation with aqueous sodium hydroxide in the manner previously described, precipitated a soft, resinous solid. The latter was dissolved in a small amount of moderately concentrated hydrochloric acid and the solution boiled for a few minutes with the addition of a small amount of charcoal. After removal of the charcoal, the red coloured filtrate was allowed to cool and made alkaline with aqueous sodium hydroxide in the usual manner. The faintly pink solid thus obtained was slightly less gum-like and it was further improved by a repetition of the same procedure. The partly purified material thus obtained was dissolved in ethanol and the solution, after boiling for a few minutes with charcoal, was filtered, heated to boiling and rendered slightly turbid by the addition of the requisite amount of boiling water. After remaining over-night at room temperature, the solution deposited almost colourless needles embedded in a reddish solid. Further purification was effected by repetition of the ethanol-charcoal treatment when the aqueous ethanolic solution was decanted twice while cooling from the reddish oil first precipitated. The partly cooled solution, on remaining over-night at room temperature, deposited faintly pink needles of the required base (2.6g.); m.p.140-143°.

ACTION OF HYDROGEN CHLORIDE ON 2:2'-DIBROMO-6:6'-DIMETHYLBENZIDINE

Dry hydrogen chloride was passed into a solution of the amine (0.2g.) in dry ether (3ml.) and a colourless, finely divided solid was quickly precipitated. The latter was filtered off, washed with a little dry ether and dried in vacuo over potassium hydroxide. The product was extremely soluble in water or ethanol and on exposure to the air decomposed rapidly with the formation of a somewhat resinous solid. Due to the unstable nature of the product, no satisfactory analysis was obtained.

N:N'-DIACETYL-2:2'-DIBROMO-6:6'-DIMETHYLBENZIDINE

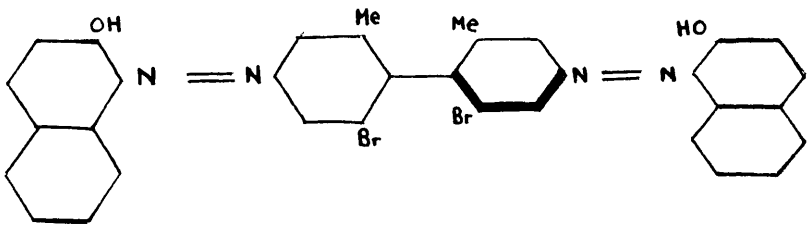
The benzidine (0.5g.) on treatment with acetic anhydride (1ml.) quickly dissolved with the evolution of heat. The solution was further warmed, cooled and diluted with water (15ml.). After twelve hours, a partly resinous, partly crystalline solid had separated. The supernatant liquid was decanted and the solid dissolved in warm ethanol (10ml.), filtered, and water added to the filtrate until a faint permanent turbidity was produced. After remaining several days at room temperature, scales of a faintly pink, transparent lacquer separated. These were filtered, washed with water and dried (0.55g.); m.p. 100°dec. with gas evolution. The product was recrystallised (charcoal) from methanol giving microscopic plates (0.2g.);

m.p. 146-148°.

Analysis: Found: N,6.24%.

$C_{18}H_{18}O_2N_2Br_2$ requires: N,6.17%.

2:2'-DIBROMO-6:6'-DIMETHYLDIPHENYL-4:4'-BIS [AZO-(1)-NAPHTHOL-(2)]



Procedure:

2:2'-Dibromo-6:6'-dimethylbenzidine (0.2g.) was dissolved in a solution of concentrated hydrochloric acid (0.8ml.) and water (5ml.) and diazotised below 10° by the dropwise addition of a 20% aqueous solution of sodium nitrite (end-point by the starch-iodide paper test). The cold, pale lemon-yellow, diazo solution was slowly added with stirring to a cold alkaline solution of β-naphthol (0.3g. dissolved in 4ml. of 10% aqueous sodium hydroxide). The crimson azo derivative was precipitated and after cooling the suspension in a freezing mixture for

half-an-hour, the solid was filtered off, washed several times with cold water and the moist solid thus obtained was recrystallised from glacial acetic acid. The acetic acid moist solid was washed several times with cold methanol and dried in vacuo over potassium hydroxide. The required azo derivative was thus prepared in the form of a crimson powder; m.p. 284-286°, which was almost insoluble in the usual organic solvents but which was soluble in concentrated sulphuric acid with the formation of an intensely magenta coloured solution.

Analysis: Found: N,8.01%.

Required for $C_{34}H_{24}O_2N_4Br_2$: N,8.24%.

N:N'-DIBENZYLIDENE-2:2'-DIBROMO-6:6'-DIMETHYLBENZIDINE

To a hot solution of 2:2'-dibromo-6:6'-dimethylbenzidine (0.2g.) in ethanol (6ml.) was added benzaldehyde (0.1g.). The mixture was allowed to cool to room temperature and after three hours a small amount of solid separated. After several days the precipitated solid was filtered off and dried (0.07g.); m.p.178°. The dibenzylidene derivative thus obtained consisted of a microcrystalline, faintly cream coloured solid.

Analysis: Found: N,4.80%.

Required for $C_{28}H_{22}N_2Br_2$: N,5.13%.

CATALYTIC REDUCTION OF 2:2'-DIBROMO-6:6'-DIMETHYLBENZIDINE

Palladium - Calcium Carbonate Catalyst

The catalyst was prepared according to the general directions of Busch and Stöve (37).

A solution of palladous chloride ($PdCl_2.2H_2O$), (1.0g.) in dilute hydrochloric acid was neutralised with A.R. sodium carbonate solution and added to a stirred suspension of calcium carbonate (50g.) in water. The mixture was warmed gently and stirred from time to time until the supernatant liquid was colourless. The solid was washed once by decantation and several times with distilled water on the filter. The product was dried in vacuo, finely powdered and stored in a well-stoppered bottle.

Reduction.

2:2'-Dibromo-6:6'-dimethylbenzidine (0.5g.) was dissolved in ethanol (25ml.) and after the addition of A.R. potassium hydroxide (0.5g.) and the catalyst (1.0g.), the mixture was shaken with hydrogen at room temperature and atmospheric pressure. After the absorption of 60.0ml. of hydrogen (764mm., 15°) in a period of 148 minutes, no further reduction took place. The mixture was filtered and the residue washed twice with two successive small volumes of ethanol. The combined filtrate

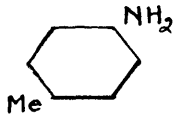
and washings was concentrated to about 10ml. volume and water (ca. 40ml.) was slowly added to the boiling ethanolic extract until a faint permanent turbidity was maintained at the boiling point. The solution, on cooling slowly to room temperature, deposited brownish droplets of oil. The latter was removed by three separate extractions with fresh volumes of ether and the combined ether extracts were evaporated. The oily residue thus obtained was mixed with acetic anhydride (1.5 vols) and warmed to boiling point. Water was added to decompose the excess acetic anhydride and the mixture was allowed to remain at room temperature for one hour. The pale yellow, solid, acetyl derivative which precipitated was filtered and washed several times with water. The crude product (0.35g.); m.p.265° with previous softening, was recrystallised from methanol, the somewhat resinous, less soluble material being rejected. This procedure resulted in a pure product (0.1g., 25%); m.p.281°, not depressed by the addition of authentic N:N'-diacetyl-m-tolidine; m.p.281°.

N:N'-DIACETYL-m-TOLIDINE

The method of Jacobson and Fabian (103) was used for the preparation of m-tolidine and its diacetyl derivative.

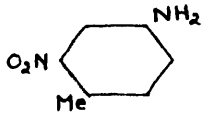
B. 2:2'-DIBROMO-5:5'-DIMETHYLBENZIDINE

The synthesis of 2:2'-dibromo-5:5'-dimethylbenzidine was accomplished by means of the following series of reactions:



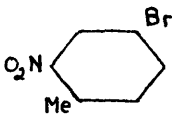
p-toluidine.

Stage 1. ↓



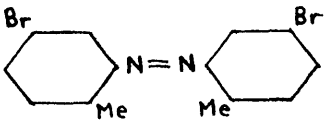
2-nitro-4-aminotoluene.

Stage 2. ↓



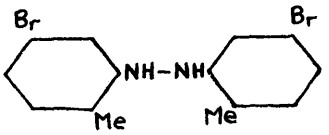
4-bromo-2-nitrotoluene.

Stage 3a. ↓



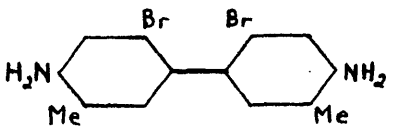
5:5'-dibromo-2:2'-dimethylazobenzene.

Stages 3a,3b. ↓



5:5'-dibromo-2:2'-dimethylhydrazobenzene.

Stage 4. ↓



2:2'-dibromo-5:5'-dimethylbenzidine.

Stage 1. 2-NITRO-4-AMINOTOLUENE

This substance was prepared by the nitration of p-toluidine in presence of excess concentrated sulphuric acid; the general procedure of Nolting and Collin (148) was followed. These workers quote a yield of over 100g. of pure recrystallised product from 100g. of p-toluidine, representing 71% of the theoretical. Certain observations made by these workers were not confirmed over a series of three experiments and this necessitated a slight modification of procedure which, however, resulted in an increase of the yield to 81%; it was found that dilution of the reaction mixture caused copious precipitation of nitro-toluidine sulphate whereas Nolting and Collin describe the precipitation of small quantities of impurities at an equivalent dilution.

Procedure:

Concentrated sulphuric acid (S.G., 1.84)	.....	435ml.
P-toluidine	.....	40g.
Nitrating acid: Fuming nitric acid (S.G., 1.48)	.....	20.25ml.
Nitrating acid: Concentrated sulphuric acid (S.G., 1.84)	..	65.2ml.

The p-toluidine was gradually added to the mechanically stirred sulphuric acid. After the former had completely dissolved, the solution was cooled to -5° by the external

application of an ice/hydrochloric acid freezing mixture. The well stirred mixture was maintained at -5° to -10° over a period of one hour during which the nitrating acid was gradually added by means of a dropping funnel. The mixture was stirred for a further hour, the temperature being kept below 0°, after which it was slowly poured into a well stirred mixture (2 litres) of crushed ice and water at such a rate that the temperature did not exceed 20°. The light yellow nitrotoluidine sulphate which was precipitated was filtered off, suspended in water and decomposed by the addition of excess ammonium hydroxide. The 2-nitro-4-aminotoluene thus obtained was filtered off, washed with water and dried on porous tile (35.8g.); m.p.76.5-77° (pure compound, m.p.Lit.,77°). The acid filtrate from the nitrotoluidine sulphate was diluted to 6 litres with water and neutralised by the addition of powdered sodium carbonate together with a few pieces of ice so that the temperature did not rise above 20°. The orange solid thus obtained, which consisted of crude 2-nitro-4-aminotoluene together with inorganic salts, was filtered off, washed well with warm water, dried on porous tile and recrystallised from aqueous ethanol (with filtration of the hot solution to remove insoluble tarry impurities). The orange-red crystals thus obtained, consisted of slightly less pure 2-nitro-4-aminotoluene (10.4g.); m.p.74-75°. The total yield of product thus amounted to 46.2g., 81.2%.

Stage 2. 4-BROMO-2-NITROTOLUENE

This substance was prepared in the usual manner from 2-nitro-4-aminotoluene (Sandmeyer reaction). The directions which follow utilise the most desirable features of several analogous procedures (58), (23) and (130).

Procedure:

Preparation of Cuprous Bromide Solution

A.R. Copper sulphate ($CuSO_4.5H_2O$) ..... 102g.(0.41 mole)

A.R. Potassium bromide ..... 54.2g.(0.45 mole)

A.R. Sodium hydroxide ..... 14.25g.

Sodium metabisulphite ..... 21.6g.

Concentrated aqueous hydrobromic acid (S.G.1.49)... 289ml.

To a hot, mechanically stirred solution of the copper sulphate and potassium bromide in water (325ml.), a solution of the sodium hydroxide and sodium metabisulphite in water (162ml.) was added over a period of five minutes. The mixture was allowed to cool to room temperature and the cuprous bromide was filtered off, washed with a little water and dissolved in the hydrobromic acid.

Diazotisation and Subsequent Procedure

2-nitro-4-aminotoluene .....49.4g.(0.32 mole)

Concentrated sulphuric acid (S.G.,1.84) ..34.5ml.

Concentrated aqueous hydrobromic acid (S.G.,1.49).....25ml.

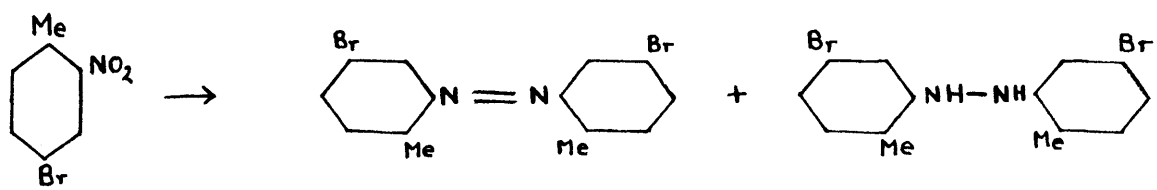
A.R.Sodium nitrite .....22.75g.(0.33 mole).

The amine was dissolved by heating with the concentrated sulphuric and hydrobromic acids and water (325ml.). The solution was cooled in a freezing mixture and rapidly stirred to ensure precipitation of the amine salt in a finely divided condition. This suspension was diazotised with mechanical stirring at a temperature of 15-20° by the dropwise addition (below the surface of the mixture) of a solution of the sodium nitrite in water (41ml.). The end-point of the reaction was determined by means of starch-iodide paper and the excess nitrous acid was destroyed by the addition of a small amount of urea. The diazo solution was filtered to remove a small amount of dark brown material and the bright, ruby red solution was added fairly rapidly to the mechanically stirred cuprous bromide solution which was cooled externally by means of ice-water. After stirring for forty-five minutes, the mixture was allowed to warm to room temperature when it was stirred for a further ninety minutes. After remaining overnight at room temperature, the

mixture was slowly warmed to 60° and then steam distilled. The cooled, aqueous distillate (3 litres) was extracted with ether and the ethereal extract was washed twice with successive, fresh volumes (10ml.) of normal aqueous sodium hydroxide, washed once with water and dried by the addition of calcium chloride. After the removal of the latter by filtration, the ether was distilled off and the 4-bromo-2-nitrotoluene was obtained in the form of a yellow oil which quickly solidified to a very pale yellow solid; (60.2g.,85.7%), m.p.45° (pure compound, m.p.,Lit.,47°). The product was used directly for the subsequent reduction (Stage 3a)

Stage 3a. 5:5'-DIBROMO-2:2'-DIMETHYLAZOBENZENE and 5:5'-DIBROMO-2:2'-DIMETHYLHYDRAZOBENZENE

These compounds which have not been hitherto described were prepared simultaneously by the reduction of 4-bromo-2-nitrotoluene.



Procedure:

4-Bromo-2-nitrotoluene	55g.
Ethanol	286ml.
A.R. Sodium hydroxide	18.5g.
Zinc dust	55g.

The apparatus used in this preparation was identical with that described for the preparation of 3:3'-dibromo-5:5'-dimethylazobenzene (page 175). The zinc dust was added to a well stirred solution of the nitro compound in the ethanol and the mixture was heated to boiling. The sodium hydroxide was dissolved in water (57ml.) and this solution was dropped into the mixture over a period of one hour; care was necessary in the initial stages of this addition to prevent undue frothing. After the addition of the alkali, the mixture was stirred for a further five minutes and ethanol (280ml.) was removed by distillation on the water-bath. The mixture was diluted with water (100ml.) and allowed to cool. The solid material was isolated by filtration and washed several times with water. The dried, finely ground, product was extracted with toluene (125ml.) in a drip extractor until the falling extract was colourless. The dark red toluene solution was evaporated to 85ml. and allowed to remain at room temperature for several hours when crystals were deposited. The product was filtered

off and dried and was found to consist of a mixture of two-thirds by weight of the required hydrazo compound and one-third by weight of the corresponding azo compound. The dried product amounted to 22.3g. (47.5% of the theoretical amount calculated as the stated mixture) and a small amount was separated as follows:- Fractional crystallisation from ethanolic benzene resulted in the isolation of a less soluble fraction ('a'), needles; m.p. ca. 180-190° and a more soluble fraction ('b'), hexagonal plates; m.p. ca. 164-166°. Recrystallisation of ('a') from the same solvent resulted in pure 5:5'-dibromo-2:2'-dimethylazobenzene; deep orange, glistening needles; m.p. 200-201°.

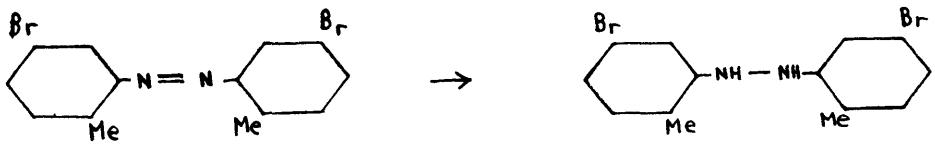
Analysis: Found: C,45.8%; H,3.5.
Required for $C_{14}H_{12}N_2Br_2$: C,45.7%; H,3.3.

This azo compound was found to be soluble in concentrated sulphuric acid with the formation of an intense deep red solution.

Recrystallisation of the more soluble fraction ('b') resulted in impure hydrazo compound; m.p.173-176°.

Stage 3b. 5:5'-DIBROMO-2:2'-DIMETHYLHYDRAZOBENZENE.

The mixed reduction product from Stage 3a was converted to the hydrazo compound:-



Procedure:

Mixed reduction product	18.5g.
Ethanol	308ml.
Glacial acetic acid	17.7ml.
Zinc dust	4.2g.

The mixed reduction product was dissolved in the ethanol and glacial acetic acid and to the solution boiling under reflux was added (portionwise) zinc dust until the original orange colour of the boiling solution faded to a pale yellow. The mixture which contained a small amount of undissolved zinc dust, was allowed to cool overnight when colourless crystals (hydrazo compound and zinc acetate) were precipitated. These were filtered off, washed with two portions of ethanol (each 20ml.), and the combined washings and filtrate was heated to boiling and diluted with hot water until a faint permanent cloudiness was maintained at the boiling point. This solution on cooling precipitated almost colourless, glistening plates of the

required hydrazo compound. The main bulk of the hydrazo compound was recovered from the original residue in which it was admixed with zinc and zinc acetate as follows:- The residue was extracted with hot water and washed several times with hot water on the filter to remove the zinc acetate and then extracted with four separate portions of boiling ethanol (each 125ml.). The hydrazo compound was recovered from the ethanolic extracts as already described; a further quantity of product was obtained by concentration of the residual aqueous ethanolic filtrates and subsequent similar dilution with water. The hydrazo compound (15.3g.) melted ca.170-180°; the main bulk obtained by ethanolic extraction was found to be rather more pure (m.p.182-182.5°) than the preceding and subsequent crops (m.p.170-174° and m.p.178-180° respectively). Pure 5:5'-dibromo-2:2'-dimethylhydrazobenzene crystallises from aqueous alcohol in colourless, glistening plates which redden on exposure to air; m.p.182-182.5°.

Analysis: Found: C,45.7%; H,3.7; N,7.71.

Required for $C_{14}H_{14}N_2Br_2$: C,45.4%; H,3.8; N,7.57.

Stage 4. 2:2'-DIBROMO-5:5'-DIMETHYLBENZIDINE

This compound which has not been previously described was prepared by rearrangement of the corresponding hydrazo compound (Stage 3b).

Procedure:

4N. Hydrochloric acid .....240ml.

5:5'-Dibromo-2:2'-dimethylhydrazobenzene. 12g.

The hydrazo compound was shaken with the hydrochloric acid for a period of ten hours. The solid was filtered off and washed with water (Note 1). The moist solid was then refluxed with a mixture of 10N. hydrochloric acid (100ml.) and ethanol (10ml.) for a period of four hours and, after the addition of water (100ml.), the solid was filtered off and washed several times with water (Note 1). The pale brown material thus obtained consisted of the crude hydrochloride of the required benzidine together with a certain amount of azo compound formed by disproportionation and further purification was effected as follows.

To a mixture of concentrated sulphuric acid (100ml.) and water (50ml.) heated on the water-bath, the moist solid was added in small portions with frequent stirring. After the addition of the solid, the mixture was maintained at boiling water-bath temperature for thirty minutes and then diluted with water (155ml.) when the suspended material became visibly lighter in colour due to the precipitation of the dissolved portion of the sulphate of the required benzidine. The solid material was filtered off (sintered-glass filter) and the

sulphuric acid extraction treatment was repeated. The moist solid from the second sulphuric acid extraction was refluxed with aqueous-ethanolic potassium hydroxide solution and the hot solution was filtered to remove a small amount of azo compound. The filtrate, on cooling, deposited glistening, colourless, rhombic plates of 2:2'-dibromo-5:5'-dimethylbenzidine. After allowing to remain at room temperature for five hours to complete the precipitation, the solid was filtered off, washed several times with water and dried in vacuo, giving the pure base (Note 2) (5.5g., 46%); m.p.153°. A portion of the product was recrystallised from aqueous ethanol and the melting point was unaltered.

Analysis: Found: C,45.2%; H,4.0; N,7.43; Br,43.6.
Required for $C_{14}H_{14}N_2Br_2$: C,45.4%; H,3.8; N,7.57; Br,43.2.

2:2'-Dibromo-5:5'-dimethylbenzidine was found to be soluble in organic solvents including methanol, ethanol, acetone, benzene and toluene but insoluble in water.

Note 1. The addition of the aqueous washings to the acid filtrate resulted in a faint turbidity due to the precipitation of a slight amount of impure amine dihydrochloride. The dihydrochloride of the required base was very sparingly soluble

in dilute hydrochloric acid and insoluble in water (page 156). Basification of the combined acid filtrate and washings yielded only an extremely minute amount of impure resinous material which was discarded.

Note 2. It was found experimentally that an impure product resulted when the rearrangement was carried out in moderately concentrated sulphuric acid (2 vols. acid: 1 vol. water) without a subsequent hydrochloric acid extraction.

2:2'-DIBROMO-5:5'-DIMETHYLBENZIDINE DIHYDROCHLORIDE

Dry hydrogen chloride was passed into a solution of the amine (0.2g.) in dry ether (3ml.) and a colourless, finely-divided solid was precipitated. The latter was filtered off, washed with a small amount of dry ether and dried in vacuo over potassium hydroxide. The product, which was insoluble in water, hydrolysed slowly in contact with the air; m.p. 344° (dec.) with previous softening.

Analysis: Found : N,6.57%.

Required for $C_{14}H_{16}N_2Cl_2Br_2$: N,6.33%

N:N'-DIACETYL-2:2'-DIBROMO-5:5'-DIMETHYLBENZIDINE

On the addition of acetic anhydride (1ml.) to the amine (0.5g.),the latter quickly dissolved with the evolution of heat and after a few seconds, the mixture solidified due to the copious precipitation of the diacetyl derivative. After the addition of a further quantity of acetic anhydride (1ml.), the mixture was heated to boiling point, water (15ml.) added and allowed to cool overnight to room temperature. The almost colourless solid was filtered off, washed several times with water and dried in vacuo giving the almost pure diacetyl derivative (0.58g., 95%); m.p.306-307°.

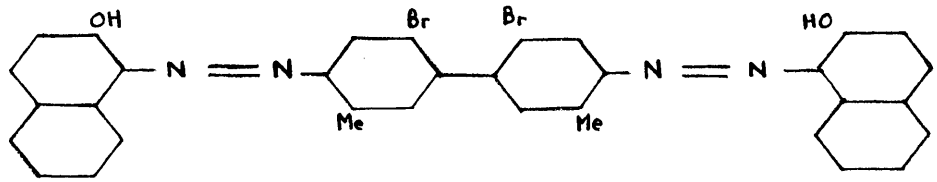
The compound was dissolved in hot glacial acetic acid and precipitated therefrom by the addition of water. The colourless microscopic prisms thus obtained were filtered off, washed several times with water and dried; m.p.309°.

Analysis: Found: N, 6.5%.

Required for $C_{18}H_{18}O_2N_2Br_2$: N,6.19%.

The diacetyl derivative was found to be slightly soluble in hot glacial acetic acid, almost insoluble in boiling methanol and insoluble in water.

2:2'-DIBROMO-5:5'-DIMETHYLDIPHENYL-4:4'-BIS[AZO-(1)-NAPHTHOL-(2)]



Procedure: As for the corresponding azo derivative of 2:2'-dibromo-6:6'-dimethylbenzidine (page 187).

Due to the insolubility of 2:2'-dimethyl-6:6'-dibromo-benzidine dihydrochloride, it was necessary to shake the mixture during the diazotisation process at the completion of which a faintly yellow diazo solution resulted. The azo derivative was recrystallised from boiling glacial acetic acid in which it was very sparingly soluble and from which it separated in the form of a dark crimson powder; m.p.308.5°, soluble in concentrated sulphuric acid to form an intensely magenta coloured solution.

Analysis: Found: Br, 23.3%.

Required for $C_{34}H_{24}O_2N_2Br_2$: Br, 23.5%.

N:N'-DIBENZYLIDENE-2:2'-DIBROMO-5:5'-DIMETHYLBENZIDINE

To a hot solution of 2:2'-dibromo-5:5'-dimethylbenzidine (0.2g.) in ethanol (6ml.) was added benzaldehyde (0.15g.). The mixture was allowed to cool to room temperature and after thirty minutes, precipitation of the dibenzylidene derivative commenced. After several days, the precipitated solid was filtered off, washed with a small amount of ethanol and dried (0.26g.); m.p.193°. The dibenzylidene derivative formed minute, faintly yellow prisms.

Analysis: Found: N,5.29%. Required for $C_{28}H_{22}N_2Br_2$: N,5.13%.

CATALYTIC REDUCTION OF 2:2'-DIBROMO-5:5'-DIMETHYLBENZIDINE

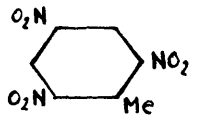
The procedure employed was exactly as for the reduction of 2:2'-dibromo-6:6'-dimethylbenzidine (page 189).

After the absorption of 58.5ml. of hydrogen (774mm., 16°) in a period of 37 minutes, no further reduction took place. The mixture was filtered and the residue washed thrice with three successive small volumes of ethanol. The combined filtrate and washings was concentrated to 3ml. volume and water was added to the boiling ethanolic solution until a faint permanent turbidity was maintained at the boiling point, The solution on cooling deposited large lustrous plates

(0.28g., 98%); m.p. 128.5°, not depressed by the addition of authentic o-tolidine, m.p.128.5°. The product was dissolved in hot dilute acetic acid and acetic anhydride was added to the solution until no further precipitation took place. After the mixture had cooled to room temperature, the colourless solid was filtered off, washed several times with cold water then several times with ethanol and dried; m.p. 314-315°, not depressed by the addition of authentic N:N'-diacetyl-o-tolidine, m.p.314-315°.

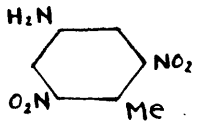
C. 2:2'-DIBROMO-3:3'-DIMETHYLBENZIDINE

The synthesis of 2:2'-dibromo-3:3'-dimethylbenzidine was accomplished by means of the following series of reactions.



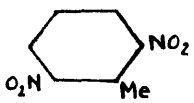
2:4:6-trinitrotoluene.

Stage 1. ↓



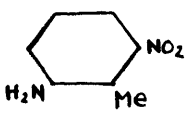
2:6-dinitro-4-aminotoluene.

Stage 2. ↓



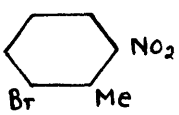
2:6-dinitrotoluene.

Stage 3. ↓



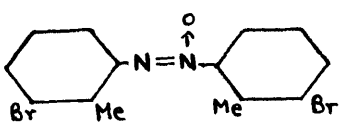
2-nitro-6-aminotoluene.

Stage 4. ↓



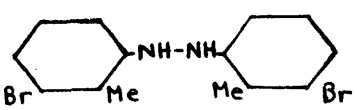
2-bromo-6-nitrotoluene.

Stage 5. ↓



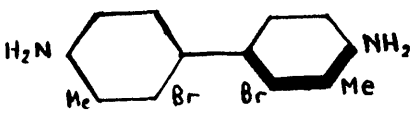
3:3'-dibromo-2:2'-dimethylazoxybenzene.

Stage 6. ↓



3:3'-dibromo-2:2'-dimethylhydrazobenzene.

Stage 7. ↓



2:2'-dibromo-3:3'-dimethylbenzidine.

Stage 1. 2:6-DINITRO-4-AMINOTOLUENE

This substance was prepared from 2:4:6-trinitrotoluene according to the general directions of Holleman and Böesken (96); these workers obtained the required product in 20% yield but do not give exact details of the time and temperature of the reduction nor of the quantities of extraction solvents employed in the subsequent working up process. The procedure which follows remedies these defects and results in a 35-40% yield; the batch quantities are double those employed by Holleman and Böesken.

Procedure.

2:4:6-Trinitrotoluene	100g.
Ethanol	200ml.
Aqueous ammonia (S.G. 0.88)	86ml.
Aqueous hydrochloric acid (S.G. 1.055)	3325ml.
Aqueous acetic acid (40%, W/V)	1800ml.

The required ammonium sulphide solution was prepared by dilution of the aqueous ammonia to 133ml. and saturating the resulting solution with hydrogen sulphide using external (ice-water) cooling. This solution was added over a period of fifty minutes to a mechanically stirred suspension of the finely divided T.N.T. in the ethanol. During this addition,

the reaction vessel was cooled in ice-water and the rate of addition was regulated to maintain the temperature of the reaction mixture between 15 and 25°. Stirring was continued for a further ten minutes and the mixture was allowed to remain overnight at room temperature. The red-brown sludge so formed was evaporated to dryness on the water-bath, finely powdered and extracted with 950ml. of the boiling hydrochloric acid (S.G. 1.055). The filtered residue was then extracted three times with successive volumes: 950ml., 950ml., and 475ml., of the boiling hydrochloric acid. The four extraction filtrates were combined, made alkaline with ammonia and allowed to cool to room temperature. The yellow solid thus obtained was filtered off, washed with water and dried in the steam-oven. The crude product was boiled with 1000ml. of the acetic acid and the hot mixture was filtered. The acetic acid extraction was repeated twice using 600ml. and 200ml. of the acid. The acetic acid extraction filtrates were combined and allowed to cool to room temperature when the required product crystallised. This was filtered off and dried in the steam-oven (34.5g., 39.7%) (Note 1); m.p.170-171° (m.p.Lit.171°).

Note 1. Repetition of this reduction on twice the above scale, i.e. using double quantities of starting materials and extraction solvents, with the addition of the ammonium sulphide

solution over periods ranging from seventy-five to one hundred and sixty minutes, resulted in the formation of the same product in lower yield. The average yield over four such experiments amounted to 26.6%.

Stage 2. 2:6-DINITROTOLUENE.

This compound was prepared from 2:6-dinitro-4-aminotoluene by deamination using hypophosphorous acid. This deamination using ethanol was previously described by Holleman and Böesken (96) who quote an almost theoretical yield of product from 1g. of amine. Repetition of this procedure using 5g. of amine resulted, however, in a low yield, 8%, of the required product. Using hypophosphorous acid, however, deamination on the same scale (5g. amine) resulted in a much higher yield, 42%, of the required product. The hypophosphorous acid deamination procedure was accordingly adopted on an increased scale.

Procedure:

2:6-Dinitro-4-aminotoluene	70g.
Concentrated sulphuric acid	220ml.
A.R,Sodium nitrite	29g.
Hypophosphorous acid (30%)	300ml.

The nitroamine was dissolved in the hot, mechanically-stirred sulphuric acid and the solution then cooled rapidly to 0 - 5° when the finely powdered sodium nitrite was added portionwise over a period of twenty minutes. During the addition of the nitrite, the mixture was stirred and the temperature maintained at 0 - 5° by means of external cooling. Also, during the course of this addition, solid commenced to separate until a thick slurry finally resulted. The latter was then stirred for a further sixty minutes during which the temperature was maintained within the previous limits.

The slurry (Note 1) was added portionwise to a mechanically stirred mixture of the hypophosphorous acid and coarsely crushed ice (300g.). The temperature of the mixture, which was externally cooled (ice and salt), was not allowed to exceed 10° during this addition which occupied twenty minutes. Copious precipitation of a red solid and the evolution of nitrogen accompanied this addition. Stirring was discontinued and the mixture was allowed to remain at 0° for twenty-four hours (Note 2). The mixture was then maintained at room temperature for a further forty-eight hours during which it was occasionally stirred by means of a thick glass rod which easily dispersed the solid containing froth on the surface of the mixture.

The orange-brown solid was filtered off, washed with water, suspended in water and steam-distilled until the distillate contained no more solid. The crude product was filtered off and air-dried at room temperature. This was recrystallised from methanol giving almost pure 2:6-dinitrotoluene (31.5g.); m.p.65-66° (pure compound, m.p.Lit.66°). Concentration of the methanolic filtrate from the first crop yielded a second, less pure crop (4.75g.); m.p.58-59°. Both crops were combined and used directly for the subsequent reduction (Stage 3).

The total yield in this experiment amounted to 36.25g. or 56%; over three such experiments the average yield was 56.5%.

Note 1. In a separate experiment, the slurry was diluted with ice-water containing ice before addition to the hypophosphorous acid; in this case a slightly lower yield (55%) was obtained.

Note 2. It was found by experiment that when the time of chilling was reduced from twenty-four to twelve hours, the yield was slightly reduced (55%).

Stage 3. 2-NITRO-6-AMINOTOLUENE

This compound was prepared from 2:6-dinitrotoluene by partial reduction using ammonium sulphide solution. The two most recent descriptions of this reduction are that of Gibson and Johnson (77) who obtained the product in 49% yield using 20% ammonium sulphide solution and that of Brady and Taylor (30) who obtained a yield of 80% using 15% ammonium sulphide solution. The following, more detailed procedure, which is essentially that of Gibson and Johnson, resulted in the formation of a product of satisfactory purity in an average yield of 88% over the two experiments performed.

Procedure: A saturated aqueous solution of ammonium sulphide was prepared as follows: concentrated ammonium hydroxide solution (S.G. 0.88) (55.5ml.) was diluted to 86ml. and this solution was thoroughly saturated with hydrogen sulphide. During this saturation, the solution was cooled externally by means of ice-water. This solution was used directly for the reduction.

Pure 2:6-dinitrotoluene (43g.) was dissolved in warm ethanol (107ml.) and the solution was cooled rapidly in order to precipitate the 2:6-dinitrotoluene in a finely divided condition. To this suspension, the ammonium sulphide solution

was gradually added in small portions, with thorough shaking of the mixture between each addition. During the addition, the deep red solution warmed to boiling point but no external cooling was applied. Towards the end of the addition, a yellow crystalline precipitate was observed and the mixture was allowed to remain at room temperature for one hour after the addition of the ammonium sulphide. The resultant suspension was evaporated to dryness on the water-bath when a pale yellow residue was obtained. This residue was extracted successively with three volumes (400, 200 and 100ml.) of boiling hydrochloric acid (S.G. 1,075). The combined extracts were basified with aqueous sodium hydroxide and after cooling, the precipitate was filtered off, washed twice with small amounts of water and dried. The solid was recrystallised from benzene - petroleum ether (b.p.60-80°). The product thus obtained amounted to 28.5g. (79.4%); m.p.89-90° (m.p., pure compound, Lit. 92°). A second crop of product was obtained by concentration of the mother liquors; this amounted to 2.5g. (a further 7.0%); m.p.87-89°. Both crops were combined and used without further purification for the preparation of 2-bromo-6-nitrotoluene (Stage 4).

Stage 4. 2-BROMO-6-NITROTOLUENE

The preparation of this compound was carried out according to the general directions of Gibson and Johnson (77); the

slight modifications from the procedure described by these workers are essentially those used in the preparation of certain other isomeric bromonitrotoluenes (pages 194, 229, 238)

Procedure: Using the following quantities of reagents, the procedure was exactly as described for the preparation of 4-bromo-2-nitrotoluene (page 194). The increased quantity of hydrobromic acid was necessary to complete the solution of the amine at boiling point.

Preparation of cuprous bromide solution

A.R. Copper sulphate ($CuSO_4.5H_2O$)	89g.
A.R. Potassium bromide	47.2g.
Sodium hydroxide	12.4g.
Sodium metabisulphite	18.8g.
Concentrated aqueous hydrobromic acid (S.G. 1.49) ..	252ml.

Diazotisation and subsequent procedure

2-Nitro-6-aminotoluene	43g.
Concentrated sulphuric acid (S.G. 1.84)	30ml.
Concentrated aqueous hydrobromic acid (S.G. 1.49) ..	60ml.
A.R. Sodium nitrite	19.8g.

The distillate obtained by the steam distillation of the reaction mixture was filtered and the solid 2-bromo-6-nitrotoluene thus obtained was air dried on filter paper at room

temperature. The product (57.2g., 93.6%) was sufficiently pure; m.p.40-41° (m.p. pure compound, Lit., 42°), for use directly in the following preparation (Stage 5).

Stage 5. 3:3'-DIBROMO-2:2'-DIMETHYLAZOXYBENZENE

This compound which has not been previously described was prepared by the alkaline reduction of 2-bromo-6-nitrotoluene.

Procedure:

2-Bromo-6-nitrotoluene	20g.
Zinc dust	20g.
Ethanol	105ml.
Sodium hydroxide	6.75g.

This reduction was performed in the apparatus already described for the preparation of 3:3'-dibromo-5:5'-dimethylazobenzene (page 175). The nitro compound and ethanol were warmed together in the reaction flask, stirring was commenced and the zinc dust added. Heating was continued until the ethanol was refluxing from the condenser when a solution of the sodium hydroxide in water (21ml.) was dropped into the mixture over a period of twenty to twenty-five minutes. During the reduction, the rate of addition of the alkali and the temperature

of the water-bath were controlled to prevent excessive frothing. Towards the end of the addition of the alkali, the separation of a pale, yellowish solid was observed. After the addition of the alkali, the reaction mixture was diluted immediately with water(200ml.), the mixture cooled by immersion in ice-water for fifteen minutes and the solid filtered off. The latter was washed three times with water and dried in vacuo. The dry, powdered solid was extracted with boiling benzene (100ml.) in a drip extractor until the falling extract was colourless. The benzene extract, on cooling, precipitated the required azoxy compound in the form of glistening, pale golden-yellow needles (8.4g.); m.p.138°. The benzene mother-liquors were concentrated to approximately 20ml. and an equal volume of methanol was added when a second crop was precipitated (6.4g.); m.p.134-135°. The product thus amounted to 14.8g. (87%). The average yield over four reductions performed as above amounted to 86%. A portion of the 3:3'-dibromo-2:2'-dimethylazoxybenzene was purified for analysis by successive recrystallisations from ethanolic benzene and ethanol when it was obtained in the form of felted, glistening, faintly yellow needles; m.p.138.5°.

Analysis: Found: C,43.5%; H,3.0.

Required for $C_{14}H_{12}ON_2Br_2$: C,43.7%; H,3.2.

This compound was almost insoluble in methanol, moderately soluble in ether or hot ethanol and soluble in petroleum ether, acetone, benzene, chloroform, carbon tetrachloride or hot glacial acetic acid.

Stage 6. 3:3'-DIBROMO-2:2'-DIMETHYLHYDRAZOBENZENE

This compound which has not been previously described was prepared by the reduction of 3:3'-dibromo-2:2'-dimethylazoxybenzene.

Procedure:

3:3'-Dibromo-2:2'-dimethylazoxybenzene ..	12.9g.
Ethanol	215ml.
Glacial acetic acid	12.3ml.
Zinc dust	6.7g.

This reduction was carried out in the manner already described for the conversion of 3:3'-dibromo-5:5'-dimethylazobenzene to the corresponding hydrazo compound (page 177). It was necessary to add the zinc dust in small quantities and to suspend heating during each addition in order to avoid excessive frothing. A small amount of the undissolved azoxy compound, present at the commencement, dissolved during the course of the reduction. The reduction was complete when the original

colour of the mixture had faded to a pale yellow. The boiling mixture was filtered and the zinc dust residue was extracted with three successive volumes (each 20ml.) of boiling ethanol. The ethanol extracts were added to the original filtrate and the whole was heated to boiling under reflux. Hot water (ca.135ml.) was added to the boiling solution until a slight precipitation of colourless needles remained permanent at the boiling point. On allowing the solution to cool and remain at room temperature, copious precipitation of similar crystals occurred. These consisted of pure 3:3'-dibromo-2:2'-dimethylhydrazobenzene and were filtered off, washed with dilute ethanol and dried (11.4g., 88%); m.p.132.5°.

Analysis: Found: C,45.6%; H,3.6; N,7.71; Br,43.1.

Req.for $C_{14}H_{14}N_2Br_2$: C,45.4%; H,3.8; N,7.57; Br,43.2.

The hydrazo compound was found to be easily soluble in the usual organic solvents and on exposure to the air became coated with an orange-red skin of the azo compound.

Stage 7. 2:2'-DIBROMO-3:3'-DIMETHYLBENZIDINE and 3:3'-DIBROMO-2:2'-DIMETHYLAZOBENZENE.

These compounds which have not been previously described were prepared by the simultaneous rearrangement and disproportionation of the corresponding hydrazo compound.

Procedure:

3:3'-Dibromo-2:2'-dimethylhydrazobenzene ...	8.36g.
Ethanol	50ml.
5N. Hydrochloric acid	40ml.

To a warm solution of the hydrazo compound in the ethanol, the hydrochloric acid was added in small portions with shaking between each addition. This process was accompanied by the separation of a dull cream solid material. The mixture was boiled for ten minutes, hot water (250ml.) was added and boiling was continued for a further fifteen minutes when the major portion of the suspended solid dissolved. The residual, undissolved solid, which consisted of orange-red needles, was filtered off, washed several times with water and dried (0.56g.) m.p. ca.160° with previous softening. This consisted of impure 3:3'-dibromo-2:2'-dimethylazobenzene and was purified for analysis by two recrystallisations from ethanolic benzene. The pure azo compound formed glistening, scarlet, prismatic needles; m.p.171°.

Analysis: Found: Br, 43.7%.

Required for $C_{14}H_{12}N_2Br_2$: Br, 43.4%.

The azo compound, which was sparingly soluble in ethanol and soluble in benzene, dissolved in concentrated sulphuric acid with the formation of an intensely red solution.

The filtrate from the crude azo compound contained the hydrochlorides of several basic products including that of the required benzidine and the separation of the latter was accomplished as follows. The filtrate was basified with an excess of sodium hydroxide solution, the temperature being maintained at $< 10^{\circ}$ by means of external cooling. This process gave rise to the precipitation of a colourless solid which was filtered off, washed several times with water and dried. The mixture (7.25g.) of basic products thus obtained possessed a faint amine-like odour. The finely powdered product was warmed with 1.6N. hydrochloric acid (190ml.) and the blue-grey undissolved portion was filtered off and boiled with dilute ammonium hydroxide. Ethanol was added to the boiling suspension until all the suspended solid had dissolved to form a yellow solution. The latter was boiled for a few minutes with charcoal which was filtered off and hot water was added to the boiling filtrate until a faint permanent precipitation was maintained at the boiling point. The solution, on cooling, deposited a faintly pink solid in the form of glistening plates and end-grouped clusters of flat needles. The solid was filtered off, washed with a small amount of dilute ethanol and dried giving 2:2'-dibromo-3:3'-dimethylbenzidine (3.79g.,45%); m.p.200°.

Analysis: Found: C,45.7%; H,3.8; Br,43.1.

Required for $C_{14}H_{14}N_2Br_2$: C,45.4%; H,3.8; Br,43.2.

The amine was odourless and was not discoloured on remaining in contact with the air.

2:2'-DIBROMO-3:3'-DIMETHYLBENZIDINE DIHYDROCHLORIDE.

Dry hydrogen chloride was passed into a solution of the base (0.2g.) in a mixture of dry ether (8ml.) and dry ethanol (8ml.). A colourless, finely-divided solid was quickly precipitated and was filtered off, washed with a small amount of dry ether and dried in vacuo over potassium hydroxide. The product which was sparingly soluble in water, hydrolysed slowly in contact with the air; m.p.324-326°, sealed tube, with previous softening.

Analysis: Found: N,6.6%. Required for $C_{14}H_{16}N_2Cl_2Br_2$: N,6.3%.

N:N'-DIACETYL-2:2'-DIBROMO-3:3'-DIMETHYLBENZIDINE.

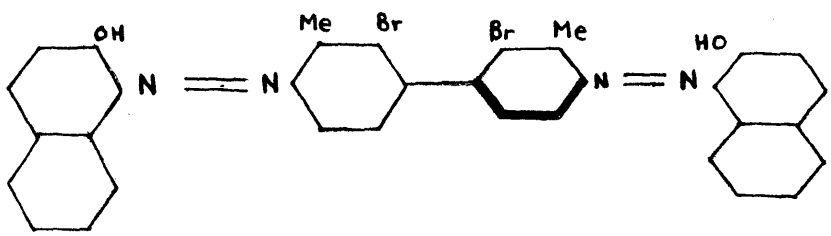
Acetic anhydride (1ml.) was added to the amine (0.5g.) and as the latter quickly dissolved with the evolution of heat, the solid acetyl derivative commenced to separate. A further quantity (1ml.) of acetic anhydride was added and the mixture was heated to boiling and allowed to remain overnight after

the addition of water (15ml.) to decompose the excess acetic anhydride. A faintly lilac coloured powder was precipitated and this was filtered off, washed several times with water and dried in vacuo (0.61g., theoretical yield); m.p.308°. The solid was dissolved in boiling glacial acetic acid in which it was moderately soluble, the solution was filtered and the diacetyl derivative precipitated by the addition of water. The compound formed microscopic needles, mainly arranged in spherical clusters. These were filtered off, washed several times with water and dried in vacuo; m.p.308°.

Analysis: Found: N,6.54%.

Required for $C_{18}H_{18}O_2N_2Br_2$: N,6.17%.

2:2'-DIBROMO-3:3'-DIMETHYLDIPHENYL-4:4'-BIS [AZO-(1)-NAPHTHOL-(2)]



Procedure: As for the corresponding azo derivative of 2:2'-dibromo-5:5'-dimethylbenzidine (page 187).

The diazo and β-naphthol solutions were filtered before coupling and the azo derivative, after washing with water on the filter, was extracted with boiling glacial acetic acid, filtered off, washed several times with water, washed twice with methanol and dried in vacuo. The azo derivative was thus prepared in the form of a scarlet powder, m.p.322° dec., and was almost insoluble in organic solvents including boiling glacial acetic acid and boiling pyridine. The compound was soluble in concentrated sulphuric acid with the formation of an intensely magenta coloured solution.

Analysis: Found: N,8.12%.

Required for $C_{34}H_{24}O_2N_2Br_2$: N,8.24%.

N:N'-DIBENZYLIDENE-2:2'-DIBROMO-3:3'-DIMETHYLBENZIDINE.

To a hot solution of 2:2'-dibromo-3:3'-dimethylbenzidine (0.2g.) in ethanol (5ml.) was added benzaldehyde (0.15g.). Precipitation of the dibenzylidene derivative commenced almost immediately and, after remaining at room temperature for one day to complete the precipitation, the solid was filtered off, washed with a small amount of ethanol and dried in vacuo giving colourless, minute needles (0.2g.); m.p.237-238°.

Analysis: Found: N,5.1%.

Required for $C_{28}H_{22}N_2Br_2$: N,5.1%.

CATALYTIC REDUCTION OF 2:2'-DIBROMO-3:3'-DIMETHYLBENZIDINE

The procedure employed was exactly as for the reduction of 2:2'-dibromo-6:6'-dimethylbenzidine (page 189).

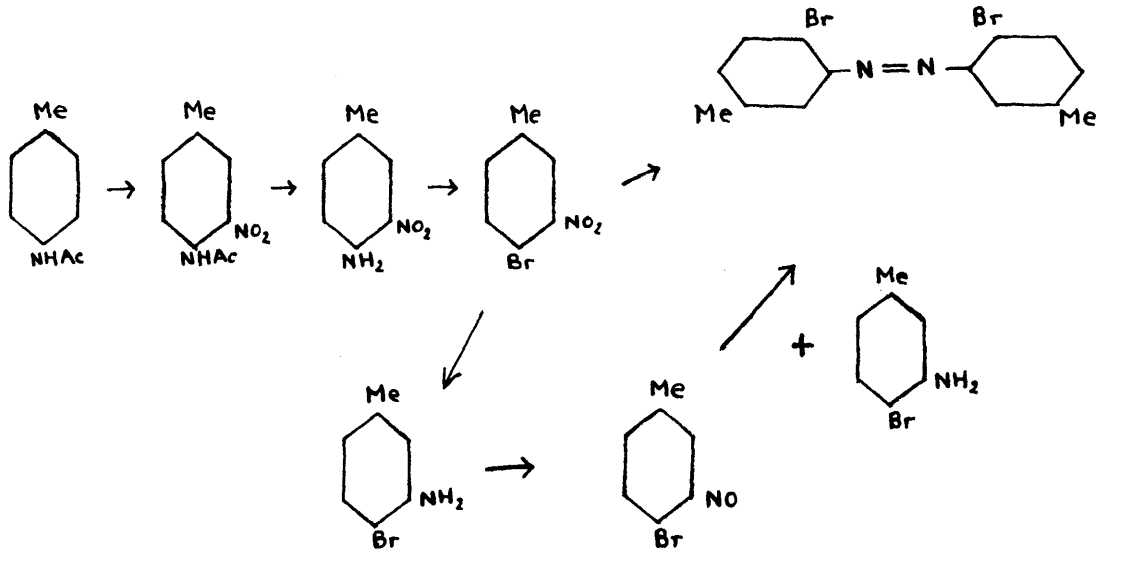
After the absorption of 60.0ml. of hydrogen (768mm., 15°) in a period of 103 minutes, no further reduction took place. The mixture was filtered and the residue washed twice with two successive small volumes of ethanol. The combined filtrate and washings was concentrated to ca. 5ml. volume and hot water was added to the boiling solution until a faint permanent cloudiness was observed. The solution, on cooling slightly, precipitated a small amount of dark amorphous material which was removed by filtration. The solution, on cooling to room temperature, deposited faintly pink, lustrous plates. After precipitation was complete, the solid was filtered off and dried (0.26g.); m.p.128.5°, not depressed by the addition of authentic o-tolidine; m.p.128.5°. The yield of o-tolidine amounted to 91%.

The product was dissolved in hot dilute acetic acid and acetic anhydride was added until no further precipitation took place. After cooling, the colourless solid was filtered off, washed several times with cold water and several times with ethanol and dried; m.p.314-315° not depressed by the addition of authentic N:N'-diacetyl-o-tolidine; m.p.314-315°.

D. MISCELLANEOUS EXPERIMENTS

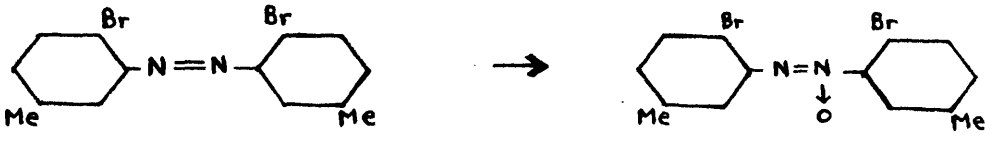
(a) 2:2'-DIBROMO-5:5'-DIMETHYLAZOBENZENE

This compound was prepared by means of the following reactions:



2:2'-DIBROMO-5:5'-DIMETHYLAZOXYBENZENE

This compound was prepared by oxidation of 2:2'-dibromo-5:5'-dimethylazobenzene:



3-NITRO-4-AMINOTOLUENE

This compound was prepared by the method of Noyes (15, 149); aceto-p-toluidide was nitrated to 3-nitro-4-acetylaminotoluene and hydrolysis of the latter resulted in the required compound.

Procedure:

Aceto-p-toluidide	64g.
Concentrated nitric acid (S.G.,1.42)	236ml.
Concentrated sulphuric acid (S.G.,1.84)..	94ml.
Ethanol	150ml.
A.R. potassium hydroxide	32g.

The concentrated nitric and sulphuric acids were mixed in a round bottomed flask fitted with a mechanical stirrer and a thermometer. With rapid stirring, the powdered aceto-p-toluidide was added fairly rapidly, in portions, to the acid. During this addition, the temperature of the mixture was maintained between 30° and 40° by means of external, cold water, cooling. After the addition of the aceto-p-toluidide, the mixture was allowed to remain at 20-30° for fifteen minutes and then poured into cold water (1400ml.). The precipitated yellow solid was filtered off, washed several times with cold water and dried at room temperature on porous tile. The

3-nitro-4-acetylaminotoluene thus obtained was dissolved in boiling ethanol under reflux and the potassium hydroxide (dissolved in water 40ml.) was carefully added. The mixture was refluxed for twenty minutes and cooled rapidly by immersing the containing vessel in cold water. The 3-nitro-4-aminotoluene, which quickly precipitated in the form of a red solid, was filtered off, washed with a little aqueous ethanol and dried. The product (49.7g., 76%) was sufficiently pure; m.p.113-114° (pure 3-nitro-4-aminotoluene; m.p.114° and 116-117° literature) for use directly in the preparation of 4-bromo-3-nitrotoluene.

4-BROMO-3-NITROTOLUENE

This compound was prepared from 3-nitro-4-aminotoluene by means of the Sandmeyer reaction according to the general directions of Gibson and Johnson (77) who do not report the yield. The procedure was similar to that employed in the preparation of 4-bromo-2-nitrotoluene (page 194).

Preparation of cuprous bromide solution

A.R.Copper sulphate ($CuSO_4.5H_2O$	156g.
A.R. Potassium bromide	83g.
Sodium hydroxide	22g.
Sodium metabisulphite	33g.
Concentrated aqueous hydrobromic acid (S.G.1.49)	430ml.

Diazotisation and subsequent procedure

3-Nitro-4-aminotoluene ..... 76g.
Concentrated sulphuric acid (S.G.,1.84) ..... 53ml.
Concentrated aqueous hydrobromic acid (S.G.1.49). 80ml.
A.R. Sodium nitrite ..... 35g.

The reaction mixture was steam distilled to 10l . of distillate and the product was extracted with ether. The ethereal extract was washed with successive volumes (each 15ml.) of cold normal sodium hydroxide, washed with water, dried (calcium chloride) and the ether evaporated. The residual yellow oil on cooling formed a mass of lemon-yellow crystals of the required product (89g., 82%); m.p.29-31°. This material was used directly without further purification for the subsequent reduction; pure compound, m.p,Lit.34°.

2:2'-DIBROMO-5:5'-DIMETHYLAZOBENZENE

(1) By reduction of 4-bromo-3-nitrotoluene.

Procedure:

4-Bromo-3-nitrotoluene ..... 33g.
Ethanol ..... 172ml.
Zinc (dust) ..... 33g.
A.R. Sodium hydroxide ..... 17g.

The apparatus used in this preparation was identical with that described for the preparation of 3:3'-dibromo-5:5'-dimethylazobenzene (page 175). To a well stirred solution of the nitro compound in the ethanol the zinc dust was added and the mixture heated to boiling. A solution of the sodium hydroxide in water (52ml.) was gradually added over a period of fifty minutes, the usual precautions to prevent excessive frothing being observed. The addition of the alkali caused progressive darkening of the mixture to a deep red colour. After the addition of the alkali, stirring was discontinued and ethanol (150ml.) was distilled off on the water-bath. To the dark red residual liquid, water (200ml.) was added and the mixture was allowed to remain at room temperature overnight. The mixture was filtered and a residue of light coloured, finely divided solid together with a very dark red, tarry material remained on the filter.

The dark, red-brown filtrate was tested as follows:
A portion of the filtrate was acidified with dilute nitric acid, silver nitrate solution was added and a colourless solid was precipitated which quickly coloured deep violet showing the presence of halide ion. A second portion of the filtrate was acidified with dilute hydrochloric acid and, on the addition of aqueous ferric chloride solution, an intense red colour was produced indicating the presence of a phenol.

The residue, after draining on the filter, was transferred to a drip extractor and extracted with ethanol (200ml.) until the falling extract was colourless. Towards the end of the extraction process, it was observed that a certain amount of dark red solid had precipitated from the ethanol. The ethanol extract was evaporated to 140ml. and allowed to remain overnight at room temperature when a further amount of reddish dark crystals separated. These were filtered off, dried; m.p.not sharp, ca.160°, weight 4.1g. and recrystallised from toluene (washing twice with successive small volumes of cold ethanol on the filter) giving large, deep red, glistening needles of the azo compound (2.2g., 8%); m.p.180-182°. One recrystallisation from toluene resulted in pure 2:2'-dibromo-5:5'-dimethylazobenzene; flat, glistening, bright red, prismatic needles; m.p. 187°.

Analysis: Found: C,46.0%; H,3.6; N,7.80.

Required for $C_{14}H_{12}N_2Br_2$: C,45.7%; H,3.3; N,7.61.

The azo compound was found to be almost insoluble in ethanol or petroleum ether, slightly soluble in ether, glacial acetic acid, warm ethanol or warm acetone and soluble in benzene, toluene, carbon tetrachloride or chloroform. The azo compound dissolved in concentrated sulphuric acid to form an intensely orange-red solution.

(2) By the condensation of 4-bromo-3-aminotoluene with 4-bromo-3-nitrosotoluene:

4-Bromo-3-aminotoluene was prepared by the reduction of 4-bromo-3-nitrotoluene by the method of Cook and Cook (58). 4-Bromo-3-aminotoluene was oxidised to 4-bromo-3-nitrosotoluene which was condensed with 4-bromo-3-aminotoluene to form 2:2'-dibromo-5:5'-dimethylazobenzene (also prepared by method (1)).

Procedure:

Finely powdered potassium persulphate (35g.) was gradually added to stirred concentrated sulphuric acid (21ml.). The cooled, stirred,acid mixture was diluted to 200ml. with crushed ice and ice-water. The Caro's acid thus prepared was quickly added to 4-bromo-3-aminotoluene (6.1g.) and the mixture was shaken for eighteen hours at room temperature. At the end of this period, a dark oily solid had formed and this was filtered off, washed with water, suspended in water and steam-distilled. This process separated a yellow solid (in the distillate) from a dark tar which remained in the distilling flask. The yellow solid, which melted on warming to a bright green liquid, was filtered off, washed with a small amount of water and dried in vacuo over concentrated sulphuric

acid. The nitroso compound thus prepared was found to be unstable and gradually decomposed to a dark solid. The dried product was slightly decomposed (1.8g., 27%); m.p.ca.77-79°. A portion of this material was used for the condensation which follows.

4-Bromo-3-nitrosotoluene (0.75g.) dissolved in hot glacial acetic acid (10ml.) was added to a solution of 4-bromo-3-aminotoluene (0.7g.) in glacial acetic acid (3ml.) and the mixture was heated under reflux for twenty minutes. The dark red solution was allowed to cool to room temperature when dark, glistening crystals were precipitated. These were filtered off, washed with methanol and dried (0.28g.); m.p. not sharp, ca. 173°. This product, on recrystallisation from benzene, formed red prismatic needles; m.p.187°, not depressed on addition of 2:2'-dibromo-5:5'-dimethylazobenzene (m.p.187°) prepared by method (1) (page 230).

2:2'-DIBROMO-5:5'-DIMETHYLAZOXYBENZENE

This compound which has not been previously described was prepared by oxidation of 2:2'-dibromo-5:5'-dimethylazobenzene.

A mixture of glacial acetic acid (40ml.), 2:2'-dibromo-5:5'-dimethylazobenzene (0.5g.) and 30% hydrogen peroxide

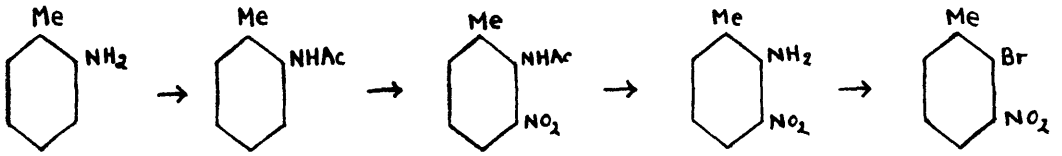
(2ml.) was heated for five days at the temperature of the boiling water-bath. During this period, further additions of hydrogen peroxide (each 2ml.) were made every twenty-four hours. The reaction mixture was then heated to boiling and water was added until a faint permanent cloudiness was observed. The solid, which precipitated on cooling, was recrystallised from methanolic benzene and separated therefrom in glistening orange needles (0.25g.); m.p.163-166°. One further recrystallisation from the same solvent resulted in pure 2:2'-dibromo-5:5'-dimethylazoxybenzene, ochre-yellow, glistening needles; m.p.168.5°. This compound was extremely soluble in benzene but sparingly soluble in methanol.

Analysis: Found: N,7.18%; Br,41.6.

Required for $C_{14}H_{12}ON_2Br_2$: N,7.30%; Br,41.6.

(b) THE ALKALINE REDUCTION OF 2-BROMO-3-NITROTOLUENE

2-Bromo-3-nitrotoluene was prepared by means of the following reactions:



3-NITRO-2-AMINOTOLUENE

This compound was prepared by a modification of the standard procedure of Gabriel and Thieme (75) which consists essentially of the nitration of aceto-o-toluidide in glacial acetic acid/acetic anhydride solution by means of fuming nitric acid dissolved in glacial acetic acid It was found that the preparation of large amounts of aceto-o-toluidide was a lengthy procedure due to the slow drying nature of the product while the presence of moisture in the latter had a deleterious effect on the yield of the desired nitration product. By means of the following modified procedure, the anhydrous acetylation of o-toluidine and the nitration of the product was successively accomplished in one reaction vessel.

Procedure:

O-toluidine	114.5ml.
Glacial acetic acid (.....	78.5ml.
Glacial acetic acid (.....	70ml.
Acetic anhydride	212ml.
Fuming nitric acid (S.G.1.50)	48ml.

The reaction vessel consisted of a one litre, three-necked flask fitted with a thermometer, dropping funnel, and mechanical stirrer. When necessary, the flask was cooled

externally by means of ice-water. The o-toluidine was placed in the flask and stirring was commenced. One portion of the glacial acetic acid (78.5ml.), and the entire amount of the acetic anhydride were added successively, the temperature of the mixture being maintained below 50°. The solution was cooled to 10-15° when a thick slurry was formed and a mixture of the fuming nitric acid and the second portion of the glacial acetic acid (70ml.) was slowly added dropwise; the nitration temperature being maintained at 15-20°. After the addition of the nitrating acid, the mixture was stirred for one hour, the temperature being reduced to 10-15° during this period. The mixture was maintained at a temperature of 0° overnight. The solidified mixture was slightly warmed and the thick slurry thus obtained was poured into a mixture of crushed ice (600g.) and water (600ml.). The precipitated solid was filtered off, washed several times with cold water and dried on porous tile. The mixture of isomeric nitroacetylaminotoluenes thus obtained was hydrolysed by refluxing for two hours with concentrated hydrochloric acid (S.G.1.16) (263ml.), diluted with water to a total volume of 480ml. The hot, acid mixture was poured into water (1200ml.) and allowed to remain overnight. The crude product was filtered

off, washed once with a small amount of cold water and dried on porous tile. Recrystallisation of the crude product from methanol gave slightly impure 3-nitro-2-aminotoluene (73.3g., 45%); m.p.91-93° (m.p.,Lit., pure compound, 97°). The product was used directly for the preparation of 2-bromo-3-nitrotoluene.

2-BROMO-3-NITROTOLUENE

This compound was prepared in the usual manner from 3-nitro-2-aminotoluene by the Sandmeyer reaction according to the detailed procedure already given for the preparation of 4-bromo-2-nitrotoluene (page 194).

Procedure:

Preparation of Cuprous Bromide Solution.

A.R. Copper sulphate ($CuSO_4.5H_2O$)	156g.
A.R. Potassium bromide	83g.
Sodium metabisulphite	33g.
A.R. Sodium hydroxide	22g.
Concentrated aqueous hydrobromic acid (S.G.1.49).	200ml.

The cuprous bromide solution was prepared according to the procedure given on page 194; in this instance, the copper sulphate and potassium bromide were dissolved in water (500ml) while the sodium metabisulphite and hydroxide were dissolved in water (250ml.)

Diazotisation and Subsequent Procedure

3-Nitro-2-aminotoluene	76g.
Concentrated sulphuric acid (S.G., 1.84)	54ml.
Concentrated aqueous hydrobromic acid (S.G., 1.49)	313ml.
A.R. Sodium nitrite	35g.

The diazotisation was carried out according to the directions given on page 195 ; the sodium nitrite was dissolved in water (62ml.) and the addition of this solution occupied a period of one hour. The addition of the diazo solution to the cuprous bromide solution was accompanied by copious frothing. Steam distillation was continued to a distillate volume of 7.5 litres. 2-Bromo-3-nitrotoluene was obtained as an oil which quickly solidified to large, yellow needles (65g. 60%); m.p.37-39° (pure compound; m.p.Lit. 41-42°).

ALKALINE REDUCTION OF 2-BROMO-3-NITROTOLUENE.

Procedure:

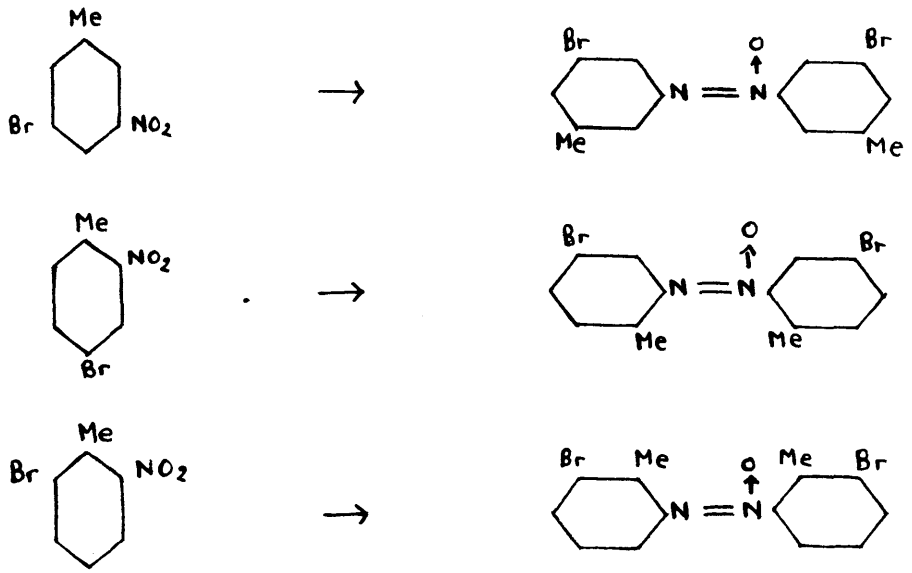
2-Bromo-3-nitrotoluene	55g.
Zinc dust	55g.
Ethanol	180ml.
A.R. Sodium hydroxide	17.5g.

This reduction was carried out by the method already described for the reduction of 4-bromo-3-nitrotoluene to the azo compound (page 230).

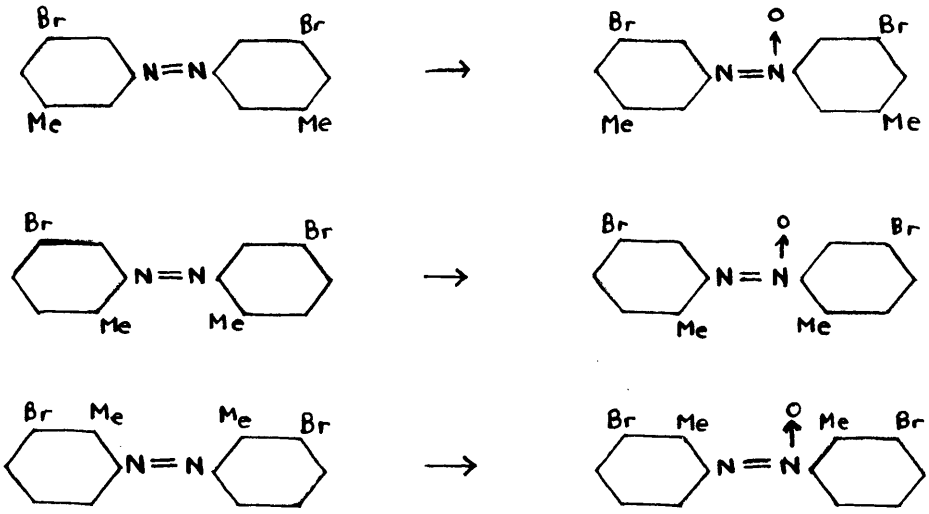
The sodium hydroxide solution (54ml. water) was added over a period of thirty minutes and the mixture was stirred for a further five minutes before part of the ethanol (60ml.) was distilled off. The reaction mixture was diluted with water to 1000ml. when a dark brown tar was precipitated. The latter was extracted with ethanol in a drip extractor and the extract concentrated. The dark tar which separated resisted attempts to crystallise. A portion of the original, aqueous filtrate gave a positive test for the presence of the halide ion.

(c) AZOXY DERIVATIVES.

(1) The method of Zinin was applied to each of the three isomeric bromonitrotoluenes of Sections (A), (B) and (C) respectively; the expected reactions being:



(2) The method of Angeli was applied to each of the three isomeric dibromodimethylazobenzenes of Sections (A), (B) and (C) respectively; the expected reactions being:



(1) REDUCTION OF NITRO COMPOUNDS (ZININ)

3:3'-DIBROMO-5:5'-DIMETHYLAZOXYBENZENE

This compound which has not been previously described was prepared by reduction of 3-bromo-5-nitrotoluene by means of aqueous ethanolic sodium hydroxide.

The nitro compound (3.8g.) was dissolved in ethanol (20ml.) and the solution heated to boiling under reflux. A solution of the sodium hydroxide (4g.) in water (10ml.) was dropped into the mixture over a period of six minutes when the reaction mixture deepened in colour. After boiling for a

further thirty minutes, red-brown crystals were deposited on the sides of the flask. Water (50ml.) was added and the mixture, after re-heating to boiling, was allowed to cool overnight when further deposition of similar crystals occurred. These were filtered off, washed with water and dried in vacuo. The product was recrystallised from ethanolic toluene to give almost pure 3:3'-dibromo-5:5'-dimethylazoxybenzene in the form of a pale red-brown solid (1.68g., 49%); m.p. 140-142°. A portion of the product was purified for analysis by recrystallisation from methanolic toluene from which it separated as pale golden yellow needles; m.p.145°.

Analysis: Found: C,44.1%; H,3.1; N,7.30.

Required for $C_{14}H_{12}ON_2Br_2$: C,43.7%; H,3.2; N,7.30.

Attempts to prepare azoxy compounds from 4-bromo-2-nitrotoluene and 2-bromo-6-nitrotoluene, by this procedure, were unsuccessful; in both cases, the starting material was recovered from the reaction mixture.

(2) OXIDATION OF AZO COMPOUNDS (ANGELI).

3:3'-DIBROMO-5:5'-DIMETHYLAZOBENZENE.

A mixture of the azo compound (0.5g.), glacial acetic acid (35ml.) and 30% hydrogen peroxide (5ml.) was heated for forty hours at 100°. During this treatment, four further

portions of hydrogen peroxide (each 1ml.) were added at intervals. The resultant yellow solution was diluted with water (40ml.) and cooled, when fine, pale yellow needles were precipitated. These were washed several times with water and dried. The product (0.40g.), m.p. 142-143° consisted of 3:3'-dibromo-5:5'-dimethylazoxybenzene since, after recrystallisation from methanolic benzene, no depression of the melt-point resulted on mixing with the authentic azoxy compound, m.p.145°, prepared by the method of Zinin (page 241).

5:5'-DIBROMO-2:2'-DIMETHYLAZOBENZENE

Oxidation of the azo compound (0.5g.) was carried out under similar conditions for seventy hours at 100°. The resultant solution was decanted from a trace of unreacted azo compound, diluted with water (40ml.), and the precipitated fine, orange needles were filtered off, washed with water and dried. The product (0.40g.), m.p.136-137°, on recrystallisation from ethanolic benzene, gave orange needles of 5:5'-dibromo-2:2'-dimethylazoxybenzene; m.p.139-140°.

Analysis: Found: Br, 41.7; N, 7.38%.

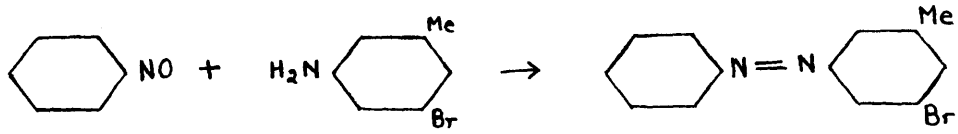
$C_{14}H_{12}ON_2Br_2$ requires: Br,41.6; N,7.30%.

3:3'-DIBROMO-2:2'-DIMETHYLAZOBENZENE

The azo compound (0.5g.), under similar reaction conditions, yielded a product consisting of 60% azoxy compound together with 40% of unchanged azo compound. These were separated as follows: The resultant hot suspension was filtered to remove the unchanged azo compound. The latter, after washing several times with water and once with methanol, formed scarlet needles (0.18g.); m.p. 171°. The filtrate from the azo compound was diluted with water (40ml.) and cooled. The precipitated solid, which was washed with water and dried, formed faintly orange needles (0.275g.); m.p. 132-134°. After several recrystallisations from ethanolic benzene, no depression of the melting point (138°) was obtained on mixing with the azoxy compound prepared directly by reduction of 2-bromo-6-nitrotoluene.

(d) 3-BROMO-5-METHYLAZOBENZENE

This compound which has not been previously described was prepared by the condensation of nitrosobenzene with 3-bromo-5-aminotoluene, the latter being prepared from 3-bromo-5-nitrotoluene according to the method of Gibson and Johnson (77).



Procedure: A solution of nitrosobenzene (7.4g.) in glacial acetic acid (22ml.) at a temperature of 30° was added to a solution of 3-bromo-5-aminotoluene (12.8g.) in glacial acetic acid at the same temperature. The colour of the solution changed from green to red-brown and the temperature gradually rose to 42°. After the temperature had fallen to 20°, the solution was chilled for twelve hours when the product crystallised. The latter was filtered off, washed twice with small amounts of methanol and dried (10.7g.); m.p.56-57°. The filtrate, on concentration, yielded a second crop of impure azo compound which was recrystallised successively from glacial acetic acid (charcoal) and from methanolic benzene (0.5g.); m.p.56.5°. The total yield of 3-bromo-5-methylazobenzene thus amounted to 11.2g. (59%). A portion of the product was recrystallised twice from methanolic benzene and the pure azo compound thus obtained, formed glistening vermillion needles; m.p.57.5°.

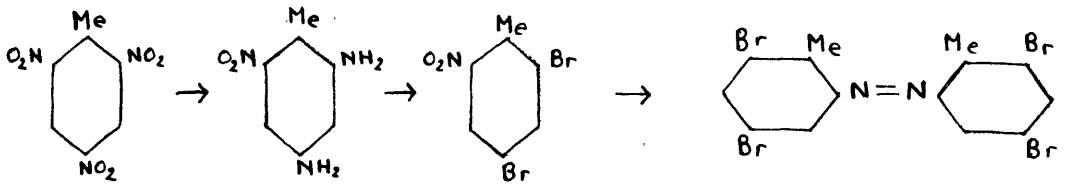
Analysis: Found: C,56.8%; H,4.1; N,10.2.

Required for $C_{13}H_{11}N_2Br$: C.56.7%; H,4.0; N,10.2.

The azo compound dissolved in concentrated sulphuric acid to form an intensely yellow solution.

(e) 3:5:3':5'-TETRABROMO-2:2'-DIMETHYLAZOBENZENE.

This compound was prepared by following route:



2-NITRO-4:6-DIAMINOTOLUENE

This compound was prepared by the reduction of 2:4:6-trinitrotoluene by means of ethanolic ammonium sulphide according to the directions of Ruggli and Zaeslin (172).

2:4-DIBROMO-6-NITROTOLUENE

This compound, which has not been previously described, was prepared from 2-nitro-4:6-diaminotoluene by means of the Sandmeyer reaction.

Procedure: Preparation of Cuprous Bromide Solution

A.R. Copper sulphate ($CuSO_4.5H_2O$)	38.5g.
Sodium bromide	18.5g.
Sodium metabisulphite.....	8.4g.
Sodium hydroxide	5.5g.
Concentrated hydrobromic acid (S.G. 1.49)....	40ml.

To a hot, mechanically-stirred solution of the copper sulphate and sodium bromide in water (120ml.), a solution of sodium metabisulphite and sodium hydroxide in water (60ml.) was gradually added. The mixture was allowed to cool to room temperature and the cuprous bromide was filtered off, washed with water and dissolved in the hydrobromic acid.

Diazotisation

A solution of sodium nitrite (22g.) in water (200ml.) was added dropwise to a warm mixture of the cuprous bromide solution and 2-nitro-4:6-diaminotoluene (20g.) dissolved in concentrated hydrobromic acid (S.G. 1.49; 232ml.). The nitrite solution was introduced below the surface of the mixture by means of a visible dropping funnel. The temperature of the mixture fell from 53° to 35° during the course of this addition which occupied one hundred minutes. The mixture was left overnight and the cream coloured solid was filtered off, washed several times with water and dried in vacuo. The crude product was purified by recrystallisation from ethanol (charcoal), a small amount of insoluble solid being filtered off. 2:4-Dibromo-6-nitrotoluene was thus obtained in the form of glistening, straw-coloured needles (28.5g., 81%); m.p. 67.5°. A portion of the product was further

purified by recrystallisation from ethanol followed by sublimation; m.p.69°.

Analysis: Found: C,28.3%; H,1.9; N,4.87.

Required for $C_7H_5O_2NBr_2$: C,28.5%; H,1.7; N,4.75.

3:5:3':5'-TETRABROMO-2:2'-DIMETHYLAZOBENZENE

This compound which has not been previously described was prepared by the alkaline reduction of 2:4-dibromo-6-nitrotoluene.

Procedure:

2:4-Dibromo-6-nitrotoluene	10.5g.
Ethanol	40ml.
Zinc (dust)	8g.
A.R. Sodium hydroxide	7.5g.

The reduction was carried out by the method already described for the preparation of 3:3'-dibromo-5:5'-dimethylazobenzene (page 174); in this case the sodium hydroxide was dissolved in water (20ml.).

The toluene extract was concentrated to 5ml. and ethanol (10ml.) was added when 3:5:3':5'-tetrabromo-2:2'-dimethylazobenzene was precipitated as flat orange needles (0.7g., 7.5%); m.p.224-226°. The compound was purified by recrystallisation from benzene; m.p.227°.

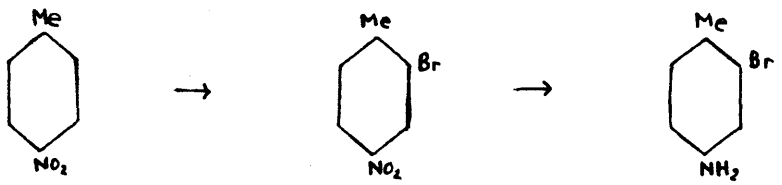
Analysis: Found: N,5.46%.

Required for $C_{14}H_{10}N_2Br_4$: N,5.33%.

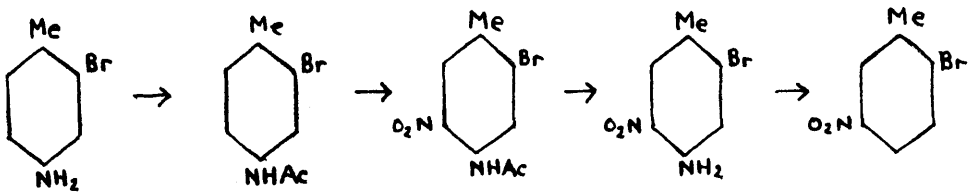
The azo compound was almost insoluble in cold methanol or ethanol, soluble in benzene or toluene and soluble in warm concentrated sulphuric acid to form an intensely orange-red solution.

(f) NITRATION OF 2-BROMO-4-AMINOTOLUENE

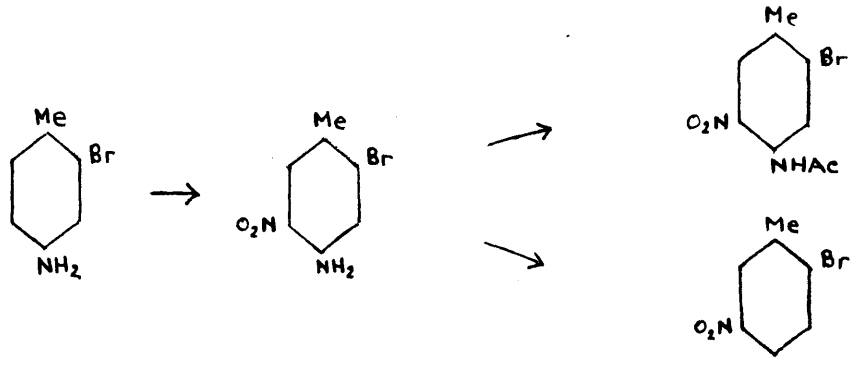
2-Bromo-4-aminotoluene was prepared by means of the following reactions which have been described in the literature:



2-Bromo-4-aminotoluene was nitrated to 2-bromo-5-nitro-4-aminotoluene and the latter was deaminated to 2-bromo-5-nitrotoluene by means of the following reactions which have also been described in the literature:



2-Bromo-4-aminotoluene, on nitration in presence of excess concentrated sulphuric acid, yielded 2-bromo-5-nitro-4-aminotoluene; the latter was converted to 2-bromo-5-nitro-4-acetylaminotoluene and 2-bromo-5-nitrotoluene:



2-BROMO-4-NITROTOLUENE

This compound was prepared according to the directions of Higginbottom, Hill and Short (93).

2-BROMO-4-AMINOTOLUENE

This compound was prepared by reduction of 2-bromo-4-nitrotoluene using West's technique (207) as described by Higginbottom, Hill and Short (93).

The following compounds were prepared from 2-bromo-4-aminotoluene by the series of reactions described by Blanksma (24):

2-bromo-4-acetylaminotoluene, 2-bromo-5-nitro-4-acetylaminotoluene, 2-bromo-5-nitro-4-aminotoluene, 2-bromo-5-nitrotoluene.

NITRATION OF 2-BROMO-4-AMINOTOLUENE

Procedure:

2-Bromo-4-aminotoluene sulphate	19.5g.
Potassium nitrate	8.5g.
Concentrated sulphuric acid (S.G.,1.84)..	150ml.

The amine sulphate was stirred with the concentrated sulphuric acid at 30° until the solid had dissolved. The solution was cooled to 3° and the finely ground potassium nitrate was added in small portions over a period of thirty minutes. The mixture was mechanically stirred during this addition and the temperature was maintained between 3° and 5° by means of external cooling (ice and salt). The mixture was then stirred for a further thirteen minutes with no external cooling when the temperature rose to 19°. The temperature was reduced to 9° by the reapplication of external cooling and the resultant mixture was slowly poured into stirred ice-water (21.) when copious precipitation of a yellow solid took place. The latter was filtered off, washed several times with water and dried; m.p.ca.150-155° with previous softening. Neutralisation of the acid filtrate and washings with sodium carbonate yielded further small amounts of similar material. The product was purified by one

recrystallisation from ethanol from which it separated in the form of orange needles (11.1g., 70%); m.p.164-165°.

A portion of the product was recrystallised from ethanol after treatment of the hot ethanolic solution with charcoal. The large orange needles, thus obtained, on further recrystallisation from ethanol, did not show any further increase in melting point (165°) which was undepressed by the addition of authentic 2-bromo-5-nitro-4-aminotoluene; m.p.165°.

A second portion of the product was acetylated as follows; A mixture of the nitroamine (0.3g.), glacial acetic acid (5ml.) and acetic anhydride (1.5ml.) was warmed on the water-bath until the solid had dissolved. After the addition of a trace of concentrated sulphuric acid and further warming for a few minutes, the mixture was diluted with cold water when a pale yellow solid precipitated. After one hour, this solid was filtered off, washed several times with water and dried, giving the monoacetyl derivative (0.33g., 93%). The melting point of the acetyl derivative (120°) was undepressed by the addition of authentic 2-bromo-5-nitro-4-acetaminotoluene; m.p.120°.

A third portion of the nitration product was deaminated according to the procedure for the preparation of 3-bromo-5-nitrotoluene (page 173). The product thus obtained after recrystallisation from methanol melted at 76-77° and this was

undepressed by the addition of 2-bromo-5-nitrotoluene; m.p.76-77° (m.p.Lit. 78° and 75-76°).

E. RESOLUTION EXPERIMENTS

Resolution Experiments

2:2'-Dibromo-6:6'-dimethylbenzidine.

Anhydrous ethanol (magnesium ethylate dried) was used throughout this resolution.

To a boiling solution of 2:2'-dibromo-6:6'-dimethylbenzidine (3.70g.; 1 mol.) in ethanol (15ml.) was added a boiling solution of A.R. d-tartaric acid (3.00g.; 2 mols.) in ethanol (22ml.). The mixed solution, on cooling slowly to room temperature, deposited hard crusts of the ditartarate. After three days, the colourless salt was filtered off (sintered-glass filter), washed with two successive volumes of ethanol (each 2ml.) and dried in vacuo (5.98g.); m.p.192-195°.

The salt was dissolved in boiling ethanol (50ml.) and the solution filtered and set aside to cool slowly. After about fifteen minutes, feathery clusters of colourless matted needles commenced to separate. After twenty-four hours, these were filtered off and dried in vacuo (4.99g.); m.p. 198-201.5°. The composition of this salt was shown to be 1 mol. amine: 2 mols. acid:-

Analysis: Found: C,39.0%; H,4.0; N,3.9.

$C_{14}H_{14}N_2Br_2 + 2(C_4H_6O_6)$ requires: C,39.4%; H,3.9; N,4.2.

Rotation: The salt (0.1014g.) was dissolved in water to which was added 0.5N. hydrochloric acid (1 ml.) and the solution was diluted with water to 5.202ml.

$[\alpha]_D^{13}$, +7.18° (1,1; c,1.949; α_D +0.140°).

The salt was dissolved in boiling ethanol (40 ml.) and the solution was set aside to cool. Spherical clusters of similar needles quickly separated and after twenty-four hours these were filtered off and dried (4.42g.); m.p.201-202°.

Rotation: The salt (0.1000g.) was dissolved in dilute hydrochloric acid as previously described:

$[\alpha]_D^{14}$, +6.76° (1,1; c,1.923; α_D, +0.130°)

The salt was dissolved in boiling ethanol (35ml.) and the solution on cooling quickly precipitated colourless, spherical clusters of matted needles. After twenty-four hours, these were filtered off and dried (3.94g.); m.p.202°.

Rotation: The salt (0.1023g.) was dissolved in dilute hydrochloric acid as previously described:

$[\alpha]_D^{16}$ +5.44° (1,1; c,1.966; α_D +0.107°).

The salt was dissolved in boiling ethanol (35ml.) and the solution was set aside to cool. In a few minutes,

mushroom-shaped clusters of colourless, matted needles separated. After twenty-four hours, these were filtered off and dried (3.42g.); m.p.201.5-202°.

Rotation: The salt (0.1000g.) was dissolved in dilute hydrochloric acid as previously described.

$[\alpha]_D^{16}$, +4.94° (1,1; c,1.923; α_D,+0.095°).

The salt was dissolved in boiling ethanol (50ml.) and the solution was boiled with a small amount of charcoal for a few minutes. The charcoal was removed by filtration and the filtrate was reheated to boiling in order to redissolve a small amount of separated solid. The solution was set aside to cool and, after one hour, separation of colourless needles commenced. After twenty-four hours, these were filtered off and dried (2.49g.); m.p.201°. (On heating above the melting point, the fused salt quickly decomposed with copious evolution of gas; this behaviour was observed with all the salt fractions so far described in this resolution).

Rotation: The salt (0.1001g.) was dissolved in dilute hydrochloric acid as previously described.

$[\alpha]_D^{16}$, + 4.68° (1,1; c,1.924; α_D,+ 0.090°).

The salt (2.06g.) was dissolved in 0.5N hydrochloric acid (30ml.) and the solution was decolourised by treatment with charcoal at room temperature. To the ice-cold, filtered solution, dilute ammonia was added slowly with stirring until no further precipitation of solid occurred. The latter was filtered off, washed several times with water and dried in vacuo. The l-base formed colourless, microscopic needles, m.p.177° (0.95g.).

Rotation (in ethanol):

$$[\alpha]_D^{17}, -\ 0.82^\circ \quad (1,1;\ c,7.672;\ \alpha_D\ ,\ -\ 0.063^\circ)$$

The combined mother liquors from the first five recrystallisations of the l-base d-tartarate were filtered to remove a small amount salt which had separated. The brown solution was boiled with charcoal, filtered, evaporated to 20ml. and further decolorised by a repetition of the charcoal treatment. The pale yellow filtrate, on cooling, deposited a thick sludge of fine, colourless needles, m.p.185-186° (1.12g.). It was not possible to measure the rotation of this salt due to the colour and opacity of its solution in dilute acid. The salt (0.967g.) was decomposed by dissolving in 0.5N hydrochloric acid (15ml.) and the solution was decolorised by boiling with charcoal. The colourless filtrate was cooled and basified

with dilute ammonia when the d-base was precipitated in the form of a colourless powder, m.p.158-160° (0.386g.). Due to the colour and opacity of an ethanolic solution of the d-base, it was not possible to estimate the rotation at this stage. The crude d-base was purified by dissolving in ethanol and boiling the solution with charcoal. To the hot ethanolic filtrate, water was added until a faint cloudiness persisted and, on cooling overnight, the d-base was precipitated in the form of colourless, felted needles, m.p.166-168° (0.300g.).

Rotation (in ethanol):

$$[\alpha]_D^{17}, +0.26^\circ \quad (1,1;\ c,3.893;\ \alpha_D, +0.01^\circ).$$

RACEMISATION: A small amount of the l-base, m.p.177°, $[\alpha]_D^{17}$, -0.82° was refluxed for one hour with excess 3N hydrochloric acid, the solution was decolorised with charcoal and ammonia was added to the cold, diluted solution to precipitate the colourless base, m.p.176°.

Rotation (in ethanol):

$$[\alpha]_D^{17}, -0.75^\circ \quad (1,1;\ c,2.004;\ \alpha_D, -0.015^\circ).$$

2:2'-Dibromo-5:5'-dimethylbenzidine.

Anhydrous ethanol (magnesium ethylate dried) was used throughout these attempted resolutions.

(a) d-Tartaric Acid. To a boiling solution of the amine (2.00g., 1 mol.) in ethanol (15ml.) was added a boiling solution of A.R. d-tartaric acid (1.62g., 2 mols.) in ethanol (10ml.). The mixed solutions on cooling deposited crusts of minute, straw-coloured plates. After forty-eight hours, these were filtered off and dried; m.p.189-190° (2.93g.). The salt was recrystallised from ethanol (50ml.) to give similar, less coloured plates; m.p.193-195° (2.21g.). Recrystallisation from ethanol (45ml.) (charcoal) gave, after twenty-four hours at room temperature, microscopic prisms; m.p.196° (1.28g.) of the mono-d-tartarate.

Analysis: Found: C,41.7; H,3.8; N,5.35%.

$C_{14}H_{14}N_2Br_2 + C_4H_6O_6$ requires: C,41.6; H,3.9; N,5.39%.

This salt, which was sparingly soluble in ethyl acetate, chloroform, or acetone, dissolved in methyl cellosolve giving a faintly coloured solution which did not yield a rotation measurement due to lack of transmission of light at match point. By the use of pyridine as solvent, however, a colourless solution was obtained and it was possible to measure the rotation of the salt; no mutarotation was observed.

Rotation (in pyridine):

$[\alpha]_D^{16}$, +6.59° (1,1; c,0.834; α_D, +0.055°).

The amine was obtained by decomposition of the salt; the finely-ground salt (0.84g.) was introduced into a hard glass test-tube cooled by immersion in solid carbon dioxide. Concentrated ammonia (S.G.O. 88, 12ml.), similarly cooled, was added and the mixture triturated by means of a glass rod for forty minutes while the temperature was maintained at that of solid carbon dioxide. The mixture was poured into ice-water and the small amount of residual solid was recovered from the test-tube by rinsing with small amounts of ice-water. The colourless solid was filtered (sintered-glass), washed with eight successive portions (10ml.) of ice-water and dried in vacuo. The amine, m.p.154° with previous softening, (0.62g.), was incompletely soluble in cold ethanol and thus contained some undecomposed salt. The latter was removed as follows: The amine was stirred with chilled ethanol (30ml.) for five minutes and the small amount of undissolved solid removed by filtration. To the filtrate was added chilled 1.5N-ammonia (10ml.) followed by ice-water (80ml.) when colourless microscopic plates of the pure amine were precipitated. These were filtered, washed several times with ice-water and dried in vacuo. The amine (0.54g.), m.p.153°, was optically inactive (ethanol).

The mother liquors from the second and third recrystallisations of the mono-d-tartarate were combined and the faintly yellow solution was concentrated by vacuum distillation (water-bath, 40°) to a volume of 5ml. On cooling, crusts of flat, cream-coloured needles (0.99g.), m.p.194-196°, separated.

Rotation (in pyridine):

$$[\alpha]_D^{17}, +6.89^\circ \qquad (l,1;\ c,1.958;\ \alpha_D, +0.135^\circ).$$

No mutarotation was observed. This salt fraction (0.84g.) was decomposed at low temperature and the amine purified as already described for the preceeding salt fraction. The amine (0.48g.) m.p.146-147° was optically inactive (ethanol).

(b) d-Camphor-10-Sulphonic Acid (Reychler's Acid).

To a boiling solution of 2:2'-dibromo-5:5'-dimethylbenzidine (3.70g.; 1 mol.) in ethanol (15ml.) was added a boiling solution of d-camphor-10-sulphonic acid (2.32g.; 1 mol.) in ethanol (10ml.). Almost immediately, separation of faintly pink, boat-shaped microplates commenced and, after remaining at room temperature for twenty-four hours, this solid was filtered, washed with a small amount of ethanol and dried in

vacuo. The salt (2.96g.) did not show a sharp melting point but decomposed and sintered in the region 260-270°. The salt, which was very sparingly soluble in boiling ethanol, was purified by extraction with ethanol (45ml.). The salt (2.71g.) consisted of one molecule of the amine and two molecules of the acid together with two molecules of ethanol of crystallisation, the analysis sample being dried in vacuo at 56°.

Analysis: Found: Br, 17.4; S, 6.61%.

$C_{14}H_{14}N_2Br_2 + 2C_{10}H_{16}O_4S + 2C_2H_6O$ requires: Br, 17.2; S, 6.92%

Rotation: (pyridine) $[\alpha]_D^{16}$, ~+2.6° (1, 1; c, 1.945; α_{D} ~+0.51°)

No mutarotation was observed.

The amine was obtained by decomposition of the salt: The salt (1.89g.) was triturated with concentrated ammonia at low temperature for thirty minutes in the manner already described for the mono-d-tartarate. The crude amine, a finely-divided, pale cream-coloured solid, was reprecipitated from solution in chilled ethanol by the addition of ice-water and the amine was obtained in star-shaped clusters of minute, flat needles (0.75g.) m.p.146-147°. The amine was optically inactive (ethanol).

2:2'-Dibromo-3:3'-dimethylbenzidine.

Anhydrous ethanol was used throughout this resolution. To a boiling solution of the amine (2.00g., 1 mol.) in ethanol (25ml.) was added a boiling solution of A.R. d-tartaric acid (1.62g., 2 mols.) in ethanol (10ml.). The faintly pink solution was set aside to cool slowly; after a few minutes, crystals of the salt began to separate. After forty hours, these were filtered off and dried (2.72g.); m.p. 187.5°.

Rotation (in acetone):

$$[\alpha]_D^{13}, -1.55^\circ. \quad (1,1;\ c,1.938;\ \alpha_D, -0.03^\circ).$$

The salt was redissolved in boiling ethanol (20ml.) and the solution allowed to cool slowly. In about fifteen minutes, spherical clusters of crystals began to separate and after twenty-four hours these were filtered off and dried in vacuo at 56°. The salt (2.06g.), m.p. 187.5°, formed colourless, rectangular tablets and analysed for the mono-acid salt containing one molecule of ethanol of crystallisation.

Analysis: Found: C,42.4; H,4.5; N,4.77%.

$C_{14}H_{14}N_2Br_2 + C_4H_6O_6 + C_2H_6O$ requires: C,42.4; H,4.6; N,4.95%.

This salt assumed a faint,pink colour on keeping for a short time and the rotation could not be measured due to the colour of the acetone solution. The salt was again recrystallised from ethanol (15ml.) and, for the same reason, no rotation estimation was possible. A further recrystallisation from ethanol (20ml.) (charcoal) yielded a colourless salt fraction (0.76g.); m.p.187.5°.

Rotation (in acetone):

$[\alpha]_D^{17.5}$, -4.98° (1,1; c,1.988; α_D, - 0.099°).

No mutorotation was observed. The salt was decomposed to yield the amine: The salt (0.63g.) was decomposed at low temperature by trituration with concentrated ammonia in the manner previously described in the attempted resolution of 2:2'-dibromo-5:5'-dimethylbenzidine (page 260), the purification by reprecipitation from ethanol being omitted. The l-amine (0.39g.) m.p.201-202°, was obtained as an almost colourless powder.

Rotation (in ethanol):

$[\alpha]_D^{18}$, - 8.22° (1,1; c,1.923; α_D, -0.158°).

The l-amine was dissolved in ice-cold ethanol (15ml.) and the solution stirred with a small amount of charcoal. The

latter was removed by filtration and ice-water containing a trace of ammonia was added to precipitate the l-amine which formed flat, short, colourless needles arranged in feather-like clusters. These were filtered off and dried in vacuo; m.p.201-202°.

Rotation (in ethanol):

$[\alpha]_D^{18}$, -8.32°. (1,1; c,1.923; α_D, -0.160°)

No racemisation was observed in ethanol at 18°.

Rotation (in acetone:

$[\alpha]_D^{17}$, -6.68° (1,1; c,1.941; α_D, -0.130°)

Over a period of sixteen hours, no racemisation was observed in acetone at 17°.

RACEMISATION. A small amount of the l-amine was refluxed for twenty minutes with a mixture of 3N-hydrochloric acid (1 vol.) and ethanol (3 vols.). The solution was cooled, basified with ammonia (0.88 S.G.) and water was added to precipitate the amine which formed colourless microscopic needles; m.p.200°. The amine was optically inactive (ethanol).

The mother-liquors from the first, second and third recrystallisations of the tartarate were combined and the bulk of the ethanol was removed by distillation (water-bath) at 40° under reduced pressure. The pink solution (5ml.), on cooling, deposited minute prisms (1.09g.); m.p.180-183° decomp. Due to the colouration of an acetone solution of this salt, it was not possible to estimate the rotation. The salt was decomposed at low temperature and the amine purified by recrystallisation from ethanol as previously described (page 264). The amine (0.37g.), m.p.200°, formed colourless needles and was slightly laevo-rotatory.

Rotation (in ethanol):

$[\alpha]_D^{17}$, - 1.56° (1,1; c,1.923; α_D, - 0.030°).

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