AN INVESTIGATION

ON

A NEW SYNTHESIS OF PHENAZINES

by

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of Cape Town for the Degree of

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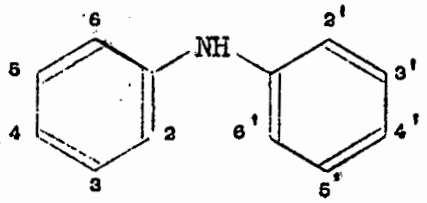
CONTENTS

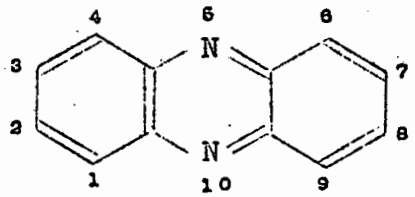
C O N T E N T S

The following numbering system was used

Diphenylamines:



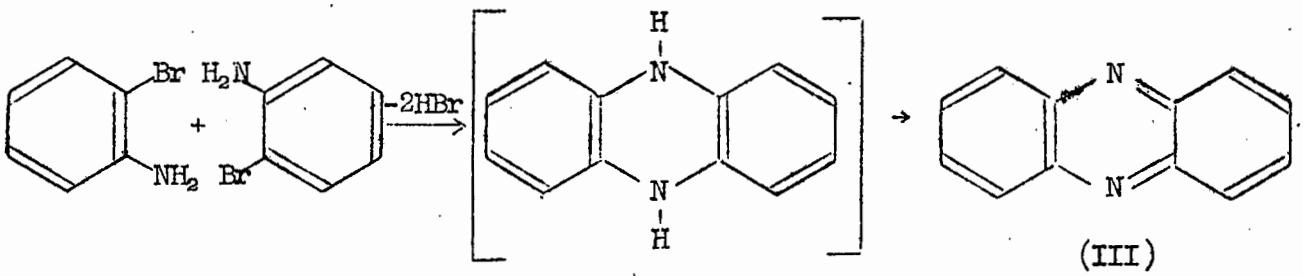
Phenazines:



INTRODUCTION

This method can only be used for the preparation of phenazines bearing the same substituents in the 2 and 7 positions. It has recently[5] been used for the synthesis of 2,7-dicarboxyphenazine.

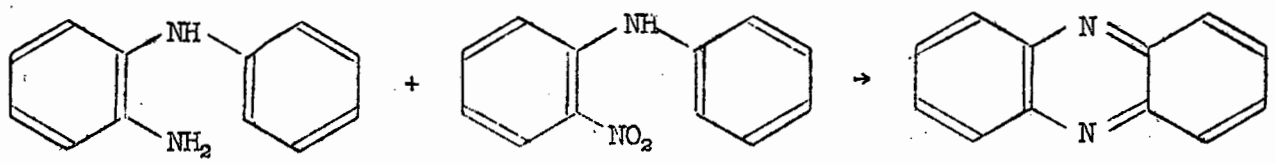
Phenazine (III) was obtained by the self-condensation of o-bromoaniline in boiling nitrobenzene[6]:



(III)

This is the only example to be found of this type of condensation. Gray[7] was unsuccessful in his attempt to obtain 2,7-dinitrophenazine from 2-bromo-5-nitroaniline.

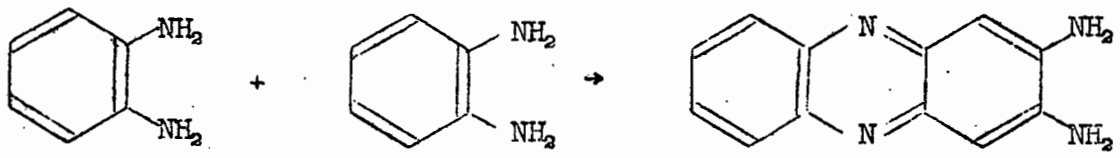
A method has been described[8] by which phenazine can be obtained in 60 - 70% yield by heating 2-aminodiphenylamine (IV), 2-nitrodiphenylamine (V) and sodium acetate at 250 - 300°:



(IV) (V)

However, a number of authors[9,10,11] reported very low yields on repeating this reaction.

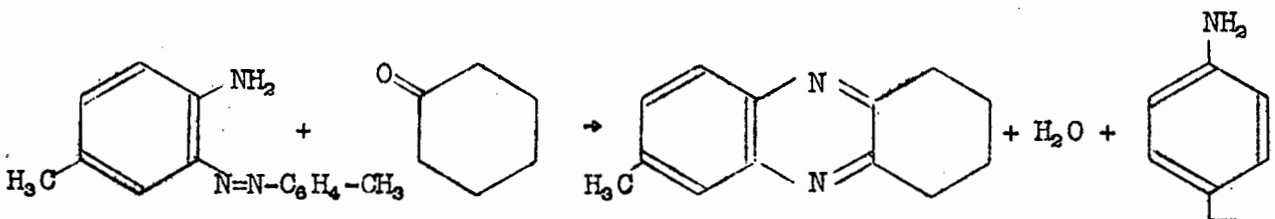
A reaction which has been investigated very thoroughly[12-20] is the oxidation of o-phenylenediamine to give 2,3-diaminophenazine (VI):



(VI)

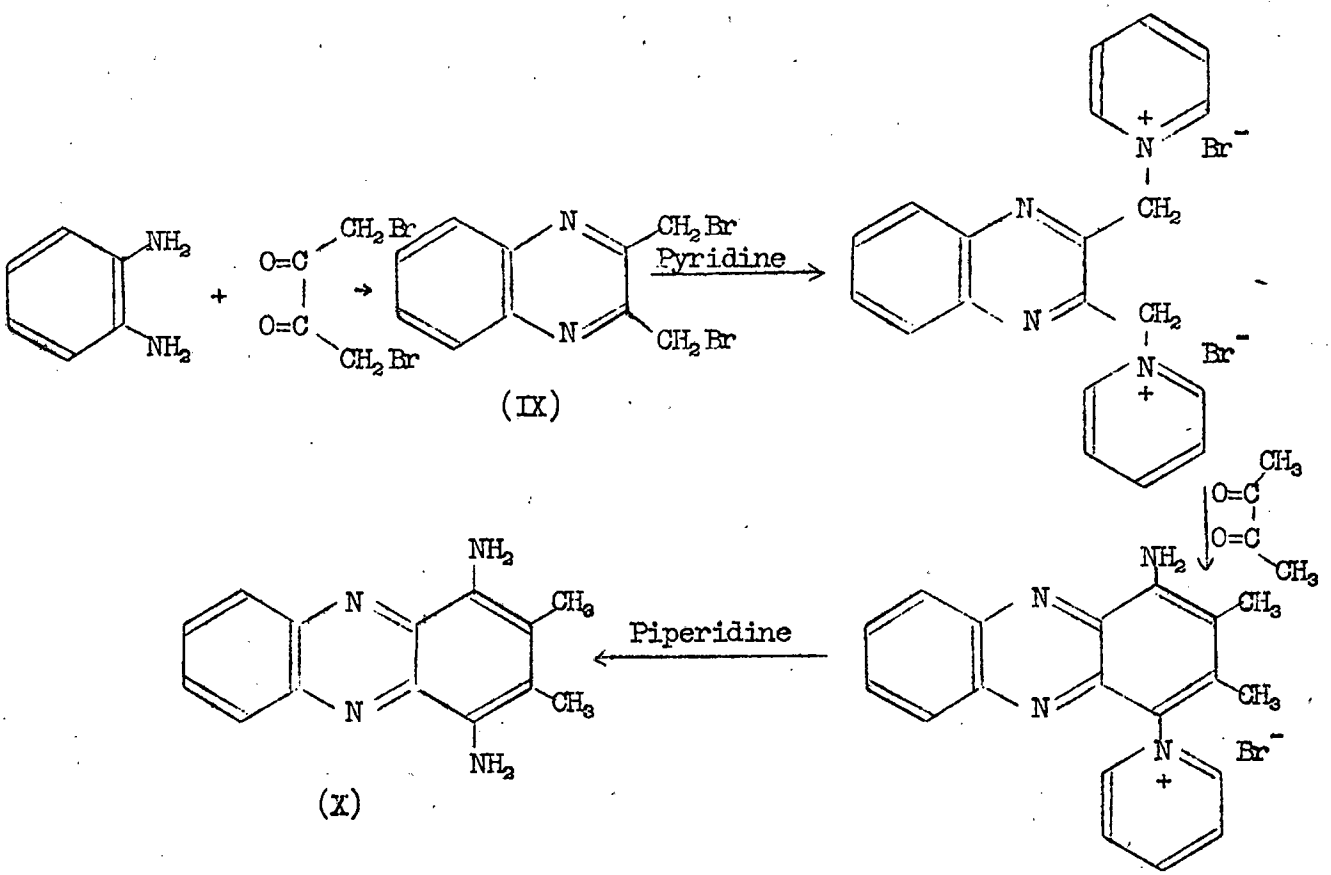
Almost quantitative yields can be obtained using iodine in ethanol as oxidising agent.

Crippa's[21] synthesis of quinoxalines has been extended to the preparation of tetrahydrophenazines. Thus 1,2,3,4-tetrahydro-7-methylphenazine (VIII) was obtained in 45% yield by refluxing a solution of 2-p-tolylazo-p-toluidine (VII) in excess of cyclohexanone[22]:



(VII) (VIII)

Westphal and Jann[23] have recently described the synthesis of 1,4-diamino-2,3-dimethylphenazine (X) from 2,3-bisbromomethylquinoxaline (IX), the sequence of reactions being the following:



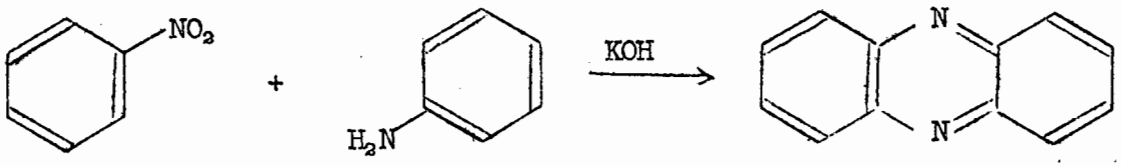
(IX)

(X)

The methods reviewed so far are of little importance for the general synthesis of phenazines, although some are nevertheless useful for the preparation of specific phenazine derivatives.

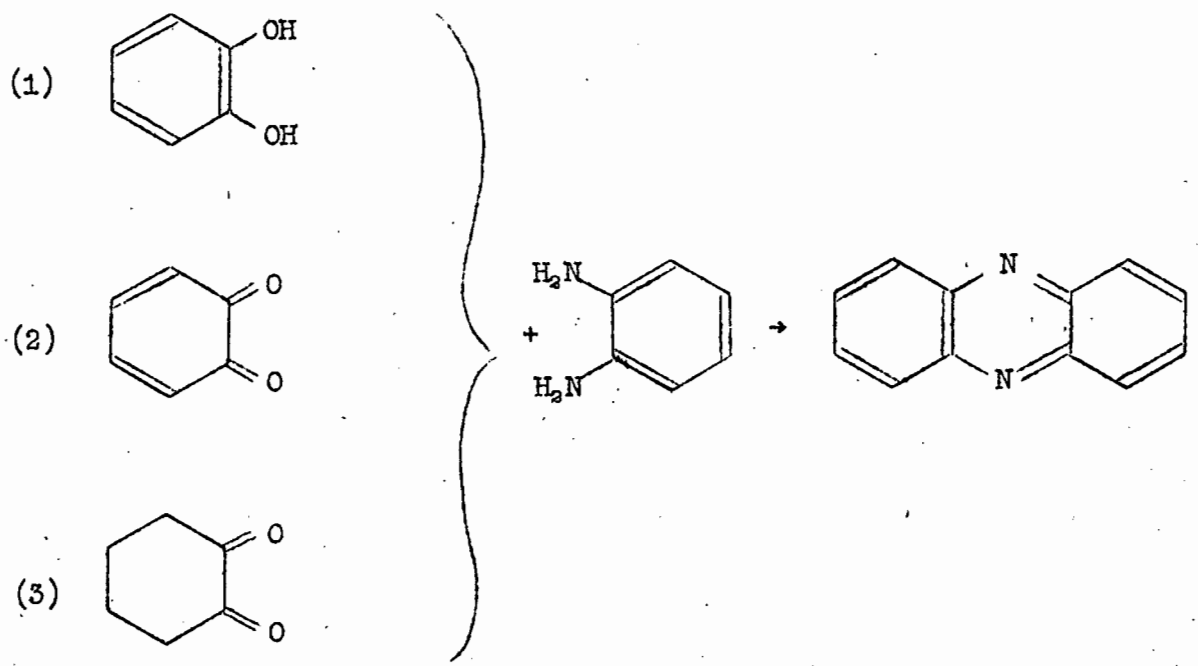
The more widely used methods will now be discussed. These can be divided into three groups: (i) the Wohl-Aue synthesis; (ii) syntheses involving the condensation of o-phenylenediamine with catechol, o-benzoquinone or 1,2-cyclohexanedione; (iii) syntheses involving the cyclisation of 2-amino- or 2-nitrodiphenylamines.

Phenazines can be obtained by the reaction of aromatic nitro compounds with aromatic amines in the presence of NaOH or KOH: this is known as the Wohl-Aue reaction[24].

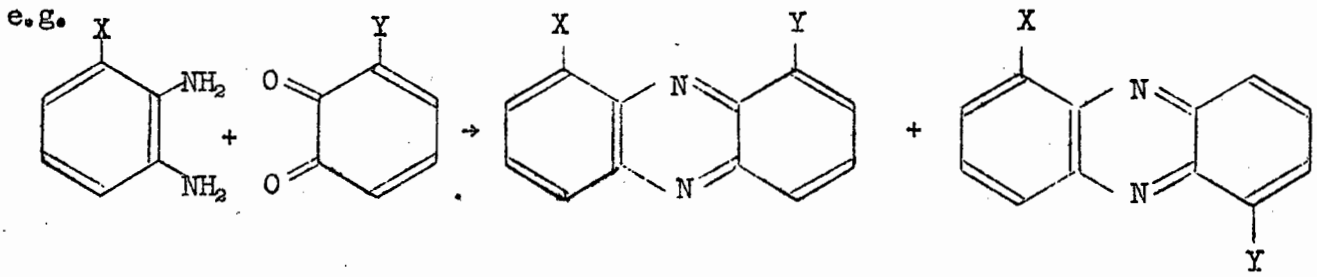


This would be a very convenient method indeed if it were not for the very low yields always obtained. Although a vast amount of work has been carried out on this reaction and a number of modifications to the original method have been proposed, the best yields obtained are never higher than 30%. Yields of the order of 10% or lower are very common; in one case[25], the yield was given as .06% ! Nevertheless, this reaction is still used, since the starting materials are often readily available.

The second important group of reactions involve condensations of the following type:



A common disadvantage to these reactions is the possibility of isomer formation when both rings are substituted:

e.g. 

Reaction (1) was used by Ris[26] for the synthesis of phenazine and by Merz[27] for that of 2-methylphenazine, both in 1886. Campbell et al[11] have found this method very unsatisfactory, but Morley[28] has claimed that this is the best method for the preparation of the unsubstituted phenazine.

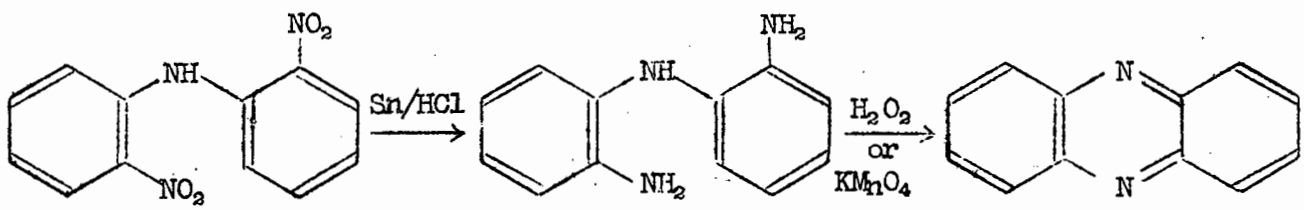
Reaction (2) is known as Hinsberg's method[29]. A number of phenazines have been prepared by this reaction; it is the method of choice for the more complicated derivatives, particularly those with added fused rings as in the benzo- or dibenzoderivatives. The yields are usually not satisfactory for the simple derivatives of phenazine and great difficulties are often encountered in the preparation of the required intermediates, particularly the very unstable o-quinones. Boyer and Morgan[30] have recently synthesised 1-aminophenazine and some of its derivatives by this method, but low yields were recorded for the preparation of most of the required intermediates.

Reaction (3) is the method of Clemo and McIlwain[31]; since cyclohexanediones are used in the condensation, tetrahydrophenazines are obtained. These can be usually quantitatively dehydrogenated to the

phenazines with palladium on charcoal[32,33]. The same disadvantages as for the previous methods are encountered, namely the possibility of isomer formation, usually low yields, and, at times, rather inaccessible starting materials.

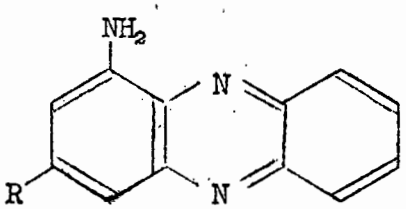
One of the difficulties of the previous methods, the uncertainty in orientation, can be overcome by cyclisation of a diphenylamine bearing a group with a nitrogen atom attached to one of the ortho positions. Such an approach is considered by many phenazine chemists to be a more attractive route to the phenazine nucleus. The various possibilities can be subdivided into three groups: (i) elimination of ammonia from a 2,2'-diaminodiphenylamine, (ii) ring closure of a 2-nitrodiphenylamine; (iii) ring closure of a 2-aminodiphenylamine.

The first example of a phenazine obtained from a 2,2'-diaminodiphenylamine (XI) was reported by Eckert and Steiner[34]:



(XI)

Other workers[35-38] have subsequently obtained quantitative yields using ferric chloride as oxidising agent. This method has generally given satisfactory results but has failed unexpectedly in some simple cases: e.g. although Elderfield et al[36] have prepared 1-amino-3-chloro(and methoxy) phenazine (XII, R = Cl, OMe) by this method, Albert and Duewell[39]



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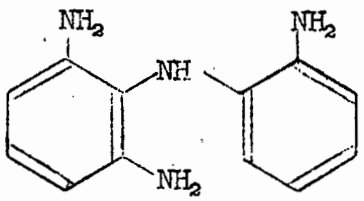

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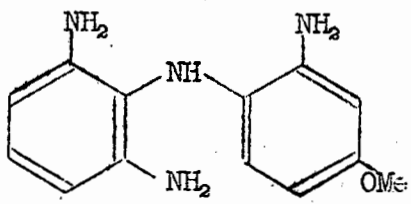
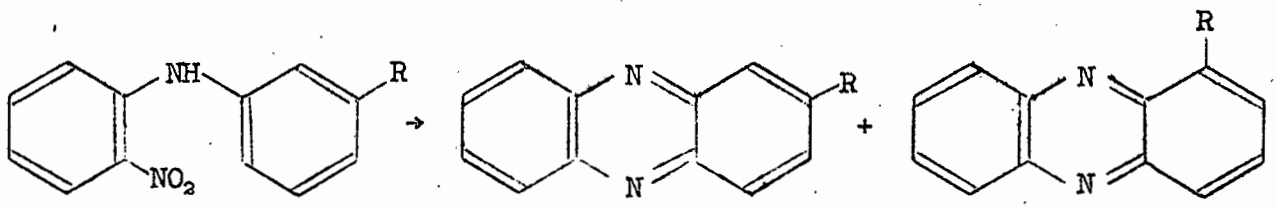


(XIV)

could not prepare 1-aminophenazine itself from 2,2',6-triaminodiphenylamine (XIII). Similarly, Gray (loc. cit. p. 48, 54) failed in his attempt to cyclise 2,4,2'-triamino-4'-methoxydiphenylamine (XIV). Clemo and Daglish[37] have also shown that 1,9-disubstituted phenazines cannot be prepared by this method due to the inaccessibility of 2,2',6,6'-tetrasubstituted diphenylamines.

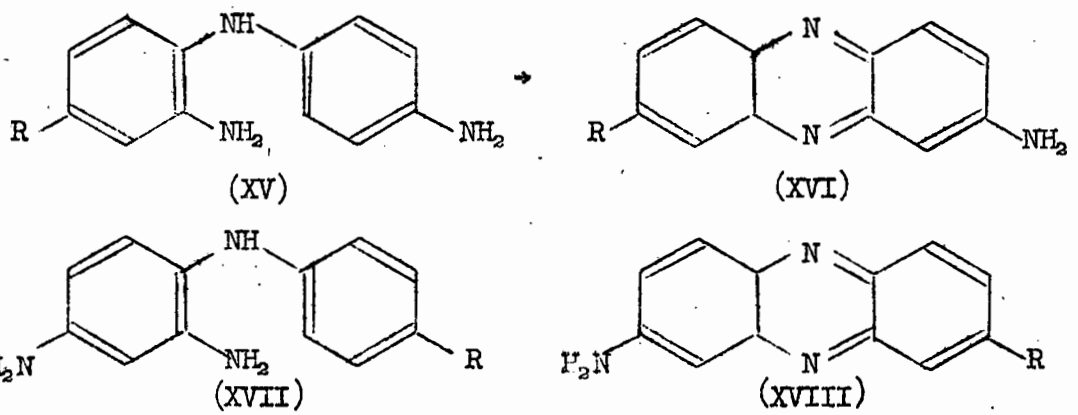
In 1943, Waterman and Vivian[40] patented a method by which phenazine could be obtained directly from 2-nitrodiphenylamine in good yields. The original procedure used Fe as a reducing agent, but later ferrous oxalate and granulated lead in definite proportions were found to give better results. Vivian and his co-workers have published a number of papers[42-50] illustrating the general applicability of this method: phenazines bearing mainly alkoxy[41,42,44], halide[41,43,47,49] or cyano[48] substituents have been prepared in fairly good yields (usually varying between 30 and 60%). Although very useful for the preparation of some simple phenazine derivatives, this method of synthesis has some important limitations: (i) very vigorous conditions are used: the mixture of diphenylamine, ferrous oxalate and lead has to be heated to at least 250°C. Some vigorous explosions may result, especially when additional nitro groups are present[41];

(ii) substituents in the 2' position are either partially (halogens) or completely (alkoxy and amino) eliminated; (iii) the only suitable method of isolation of the phenazine from the reaction mixture is vacuum sublimation, which can be very tedious; (iv) isomers are usually formed when a 2-nitro-3'-substituted diphenylamine is cyclised:

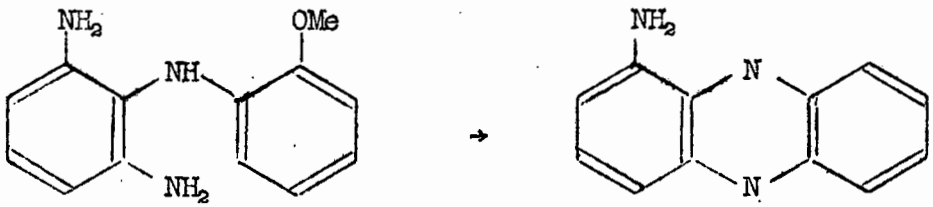


However, in one case[51], only one isomer was obtained.

The last method to be discussed is the ring closure of 2-aminodiphenylamines. Nietzki and Ernst[52] discovered in 1890 that 2,4,4'-triaminodiphenylamine (XV, R = NH_2) could be cyclised to 2,8-diaminophenazine (XVI, R = NH_2) with manganese dioxide under alkaline conditions. Later, Nietzki[53] obtained 2-aminophenazine (XVI, R = H_2) from 2,4'-diaminodiphenylamine (XV, R = H) and 2-amino-8-hydroxyphenazine (XVIII, R = OH) from 2,4-diamino-4'-hydroxydiphenylamine (XVII, R = OH) but failed to effect the ring closure of 2,4-diaminodiphenylamine (XVII, R = H). Fisher[54,55]



obtained better results with lead oxide: he was able to obtain phenazine from 2-aminodiphenylamine and 2-aminophenazine from 2,4-diaminodiphenylamine. He never reported yields, but quotes his colleague's suggestion that his synthesis of 2-aminophenazine should be used as a class experiment ! Later workers[9,41] however have not shared his enthusiasm and have reported very unsatisfactory results with this method. Some modifications have been proposed, e.g. passing the vapours of 2-aminodiphenylamine over red hot lead oxide[11,56]. The reaction can also lead to vigorous decompositions, as was reported by Gray (loc. cit. p. 65) for the reaction of 2,6-diamino-2'-methoxydiphenylamine (XIX) with dry lead oxide; however, heating the reagents in an inert solvent (xylene) improved matters slightly: thus 1-aminophenazine (XX) was obtained in good yield from (XIX), but this

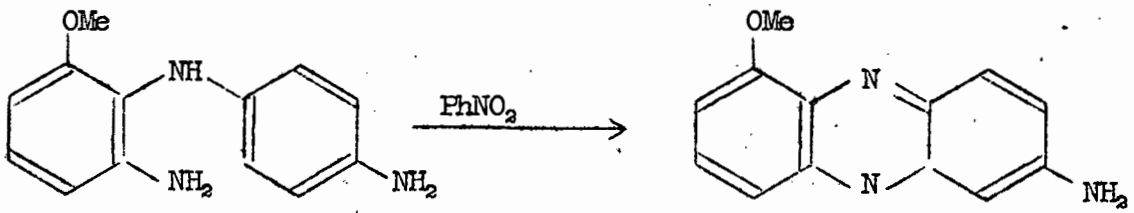


(XIX) (XX)

modification proved unsuccessful with other diphenylamines.

Gray continued the search for a more suitable oxidising agent. Nietzki's manganese dioxide oxidation has to be carried out under alkaline conditions, and the resulting suspension might hinder the reaction: one possibility was to work under acid conditions. Potassium dichromate in dilute sulphuric acid and silver oxide in ether (followed by heating in dilute hydrochloric acid) were tried without success. Another possibility was to find a suitable organic solvent which could also function as an oxidising agent. The choice fell on nitrobenzene, which proved an

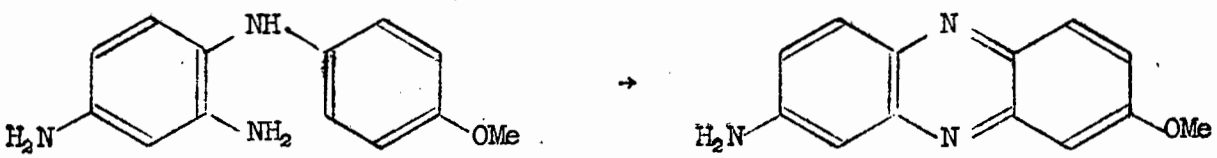
immediate success: 2,4'-diamino-6-methoxydiphenylamine (XXI) was converted to 2-amino-6-methoxyphenazine (XXII) in 43% yield by simply refluxing the diphenylamine in nitrobenzene for 5 hrs.



(XXI) (XXII)

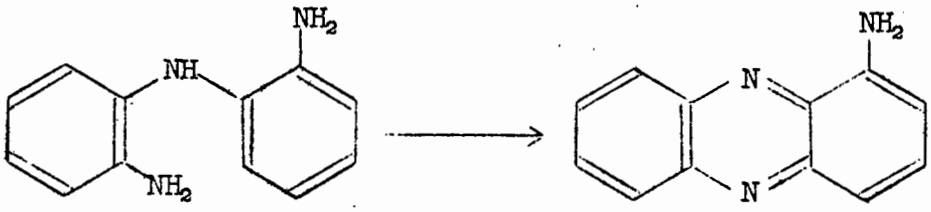
Similarly, 2-amino- (XXIV) and 2-amino-8-methoxyphenazine (XXVI) were obtained in good yields (70 and 64% respectively) from 2,4'-diamino- (XXIII) and 2,4-diamino-4'-methoxydiphenylamine (XXV).

(XXIII) (XXIV)



(XXV) (XXVI)

However, very poor yields were obtained with 2-amino- and 2,4-diaminodiphenylamine. But a very interesting result was obtained with 2,2'-diaminodiphenylamine (XVII), which was converted to 1-aminophenazine in 50% yield.



(XVII)

This was in marked contrast with all other oxidising agents which always eliminate an amino group in the 2'-position. A preliminary account of this work has appeared[67].

Although of apparently limited applicability, this method seemed worthy of further investigation. The aim of this project was to examine the scope of this reaction, particularly with regard to the influence of various substituents and, if possible, to formulate a mechanism from the results obtained. It was also hoped that some catalyst or different reaction conditions might be found so as to obtain good yields of phenazines by the cyclisation of any 2-aminodiphenylamine.

The discussion which follows will be divided in three parts:

(1) the preparation of diphenylamines;

(2) the preparation of phenazines;

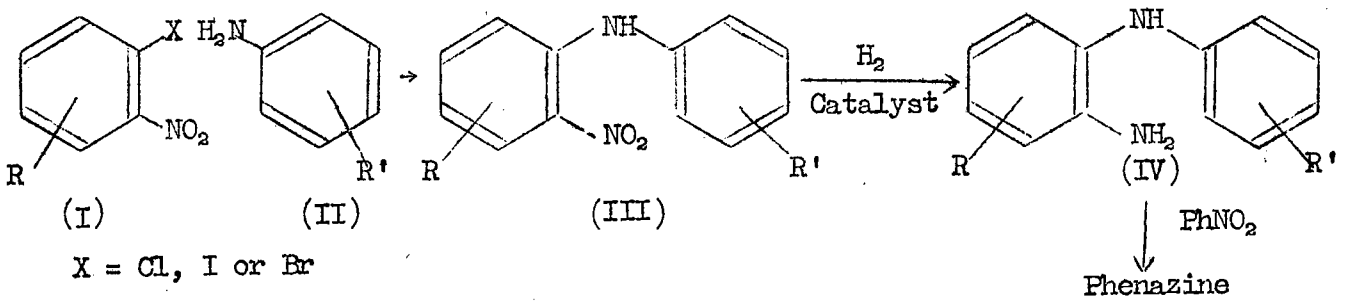
(3) the rates and mechanisms of ring closure of 2-aminodiphenylamines.

DISCUSSION

SECTION I

The Synthesis of Diphenylamines.

The standard approach to the synthesis of phenazines used throughout this thesis was the following:



(I) (II) (III) (IV)

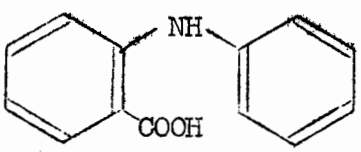
X = Cl, I or Br

The substituted nitrohalobenzenes of type I were either commercially available or easily obtainable from the appropriate nitroanilines via diazotisation and the Gattermann reaction. The conversion III → IV usually went very smoothly by catalytic reduction, and slight difficulties (to be dealt with later) were encountered only in the isolation of the unstable 2-aminodiphenylamines (IV). The discussion will thus be centered mainly on the synthesis of 2-nitrodiphenylamines.

The synthesis of 2-nitrodiphenylamines

The condensation between an aromatic amine and an aromatic halogen compound is referred to as the Ullmann, or Jourdan, or Goldberg reaction, according to the conditions and the nature of the substituents. A large number of diphenylamines have been prepared in view of the fact that these

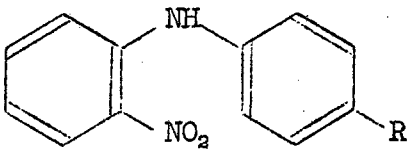
compounds are very useful intermediates for the synthesis of a number of heterocyclic compounds: acridines, phenoxazines, phenothiazines and, of course, phenazines. However, the variety of conditions used in the synthesis of diphenylamines is beyond description. Each individual author favours a method of his own, and "the research worker who has to prepare some new diphenylamine ..., or wishes to improve the yield of an old one, will gain little from the comparison of the yields obtained when various substituted benzene derivatives have been condensed in this way, because so seldom have the conditions been comparable"[68]. Only very recently has there been an attempt at classifying the relevant information. The two reviews[58,59] which have appeared in the last decade have been mainly concerned with diphenylamine-2-carboxylic acids (V) as intermediates in the synthesis of acridones. However, the problems encountered with the diphenylamines described in these reviews are very similar to those faced in the synthesis of 2-nitrodiphenylamines, so that the general principles formulated by Albert[58] or Acheson[59] for the synthesis of compounds of type (V) are in general also applicable to the syntheses of 2-nitrodiphenylamines.



(V)

For the purpose of studying the effect of substituents on the ring closure of 2-aminodiphenylamine, three series of diphenylamines had to be synthesised.

First, diphenylamines of type (VI) and (VII) were required, with



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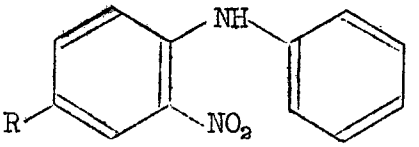
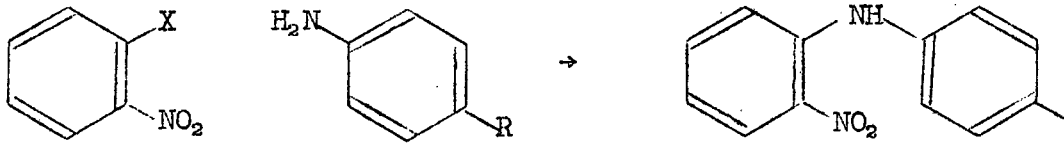


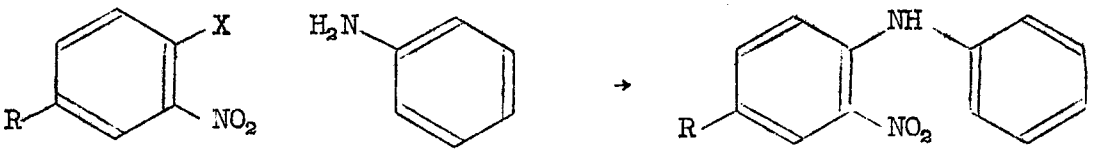
(VII)

R = H, OMe, CH_3, Cl, NO_2, CN, OH. The synthesis of the majority of these diphenylamines has been adequately described in the literature, and no great difficulty was encountered in obtaining reasonable yields. Apart for the synthesis of 4-methoxy-2-nitrodiphenylamine (VII, R = OMe), the usual procedure was to take advantage of the increased reactivity of a halogen atom ortho to a nitro group, thus condensing o-halonitrobenzene (VIII) with a para substituted aniline (reaction 1), or a para-substituted-o-halonitrobenzene (IX) with aniline (reaction 2).



(VIII)

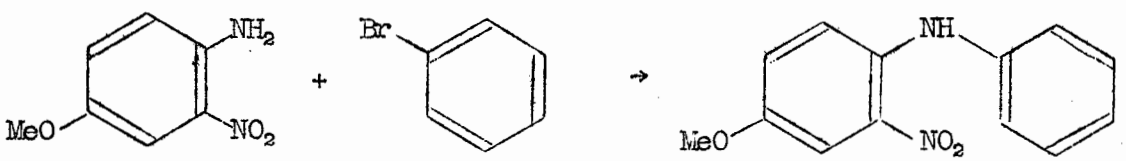
(1)



(IX)

(2)

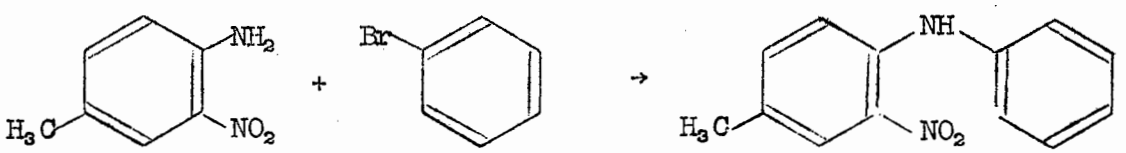
The condensations with aniline were usually successful except in two cases. King, King and Muir[60] failed to obtain 4-methoxy-2-nitrodiphenylamine (XI) by a condensation of type (2) (R = OMe, X = Br), but successfully condensed 4-methoxy-2-nitroaniline (X) with bromobenzene:



(X) (XI)

The failure to obtain (XI) from 4-methoxy-2-nitrobromobenzene (IX, R = OMe, X = Br) and aniline was attributed to the deactivating influence of the methoxyl group on the halogen atom.

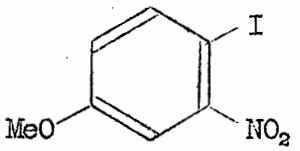
A similar pattern was observed when synthesising the hitherto unreported 4-methyl-2-nitrodiphenylamine (VII, R = CH_3). The condensation between 4-methyl-2-nitroiodobenzene (IX, R = CH_3, X = I) and aniline failed to yield the expected diphenylamine, the latter being obtained from 4-methyl-2-nitroaniline (XII) and bromobenzene.



(XII)

It is doubtful whether a deactivating influence on the reactivity of a halogen atom can also be attributed to a para methyl group. In fact, the author feels that no such deactivation occurs with either a methoxyl

or a methyl group, since 4-methoxy-2-nitroiodobenzene (XIII) and 4-methyl-2-nitroiodobenzene (XIV) were successfully condensed with p-nitroaniline



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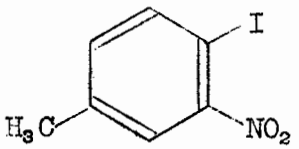
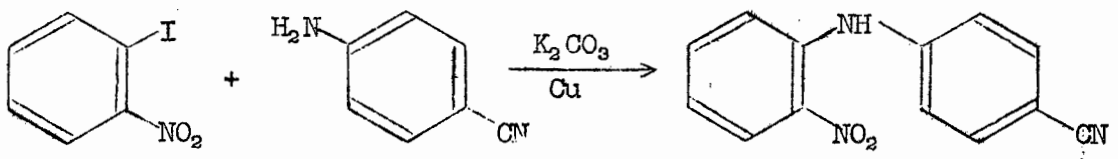


(XIV)

(see p. 20). The failure of (XIII) and (XIV) to react with aniline should rather be attributed to unfavourable reaction conditions.

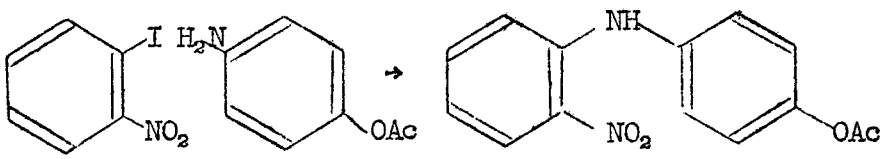
Another new diphenylamine in this series was 4'-cyano-2-nitrodiphenylamine (XVI), which was easily synthesised from o-iodonitrobenzene and p-aminobenzonitrile (XV), with potassium carbonate to remove the acid



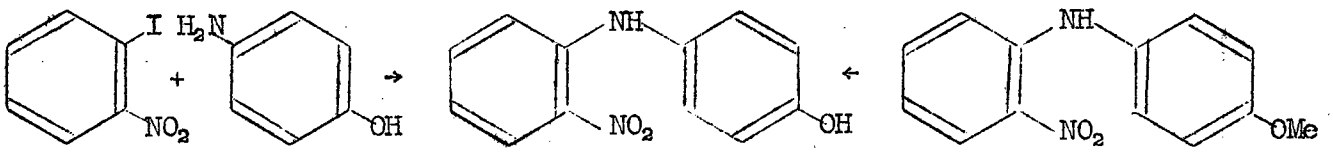
(XV) (XVI)

formed and copper to act as catalyst. No solvent was used, and the reaction appeared to be complete after only 5 minutes heating at 180°, the evolution of carbon dioxide having then ceased.

Three different routes were unsuccessfully attempted for the preparation of 4'-hydroxy-2-nitrodiphenylamine (XVII).



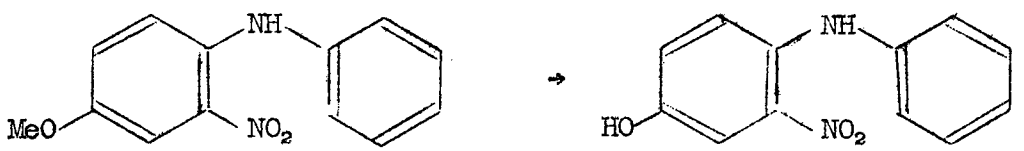
(XIX)



(XVIII) (XVII) (XX)

It was not possible to isolate the required diphenylamine from the condensation of o-iodonitrobenzene with either p-aminophenol (XVIII) or p-aminophenylacetate (XIX). The demethylation of 4'-methoxy-2-nitrodiphenylamine (XX) with 48% hydrobromic acid gave a very poor yield of a product which melted over a wide range and which could not be purified.

Similarly, the demethylation of 4-methoxy-2-nitrodiphenylamine (XXI)

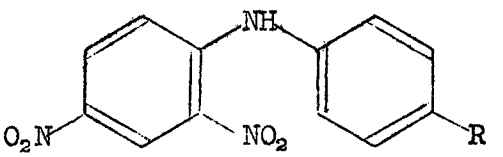


(XXI)

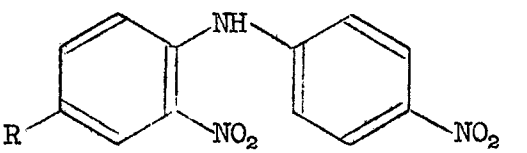
proved unsuccessful. The normal reagent, hydrobromic acid, hydroiodic acid, pyridine hydrochloride, all failed; with an equal volume mixture of glacial acetic acid and 48% hydrobromic acid, a very surprising dibromination

appeared to have taken place: a crystalline compound was obtained, which was unaffected by acid or alkali and which analysed correctly for a dibromo-4-methoxy-2-nitrodiphenylamine. A similar example of this unusual behaviour of hydrobromic acid could not be found in the literature. The percentage yield (for a dibromo compound) was 50, and this may indicate that the nitro group of the diphenylamine molecule has caused oxidation of the hydrobromic acid to produce brominium ions.

The second series of syntheses included diphenylamines of type (XXII) and (XXIII), where R = H, OMe, CH_3, Cl, CN.

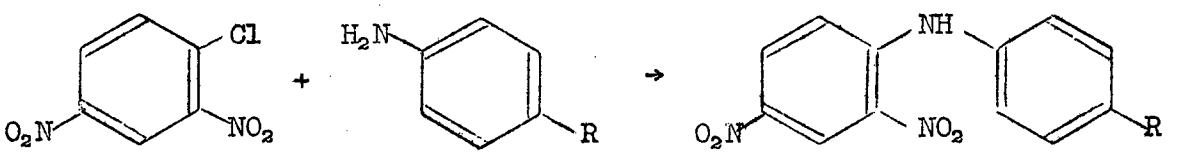


(XXII)



(XXIII)

With one exception (XXII, R = CN) all the diphenylamines of type (XXII) have been described: they are very accessible compounds, since they are obtained from 2,4-dinitrochlorobenzene (XXIV) and a substituted

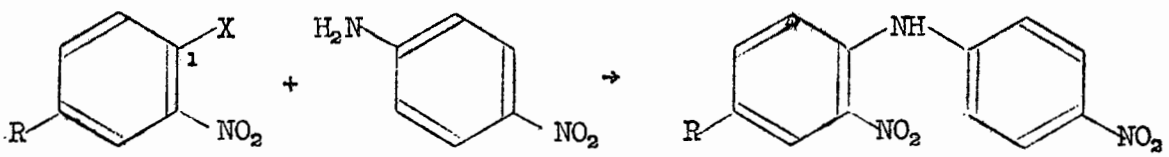


(XXIV) (XXV) (XXII)

aniline (XXV). The chlorine atom in (XXIV) is very reactive on account of the two nitro groups in the ortho and para positions. Good yields can usually be obtained in such condensations; recently, Vorozhtsov and

Yakobson[61] have claimed yields above 90% by heating the reactants with potassium fluoride at 100° without solvent or catalyst. However, if R is strongly electron attracting, it is preferable to use potassium carbonate and copper at a high temperature. Thus 4'-cyano-2,4-dinitrodiphenylamine (XXII, R = CN) was obtained using the latter conditions.

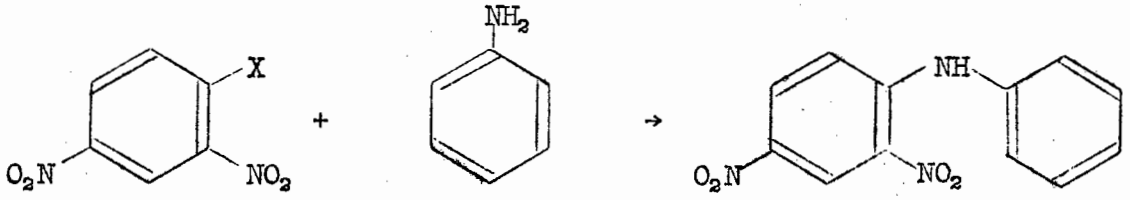
In contrast to those of type (XXII), diphenylamines of type (XXIII) are more difficult to synthesise, and only one (XXIII, R = H) has been described. Two factors now contribute to making the following condensation more difficult:



(XXVI) (XXVII) (XXIII)

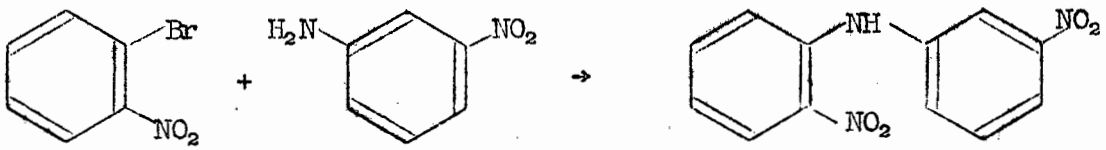
Firstly, the reactivity of the halogen atom in (XXVI) is decreased (unless R = CN), since only one nitro group is present; secondly, the lone pair of electrons of the amino nitrogen in (XXVII), which is presumably involved in a nucleophilic attack on carbon atom 1 of (XXVI), is made less available by the strong electron withdrawing effect of the p-nitro group. Nevertheless, as for the preparation of 4'-cyano-2-nitrodiphenylamine (p. 17), it was found that such diphenylamines could be obtained in good yields in very short reaction times by fusing the reactants with copper and potassium carbonate at 200°C. Yields averaging 50% could be obtained after only fifteen minutes heating. This method however was found to give the best results on small scale preparations (1 - 5 g), somewhat lower

contrast to the behaviour of halogens in the condensation of 2,4-dinitrohalobenzenes with aniline:



This condensation was studied by Franzen and Bockhacker[62], who reported the order Br > Cl > I.

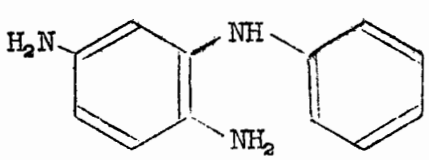
The synthesis of 2,3'-dinitrodiphenylamine (XXX) has been reported by Evans and Smiles[63] who prepared it from o-bromonitrobenzene and m-nitroaniline, but did not quote a yield. A preparation under the same



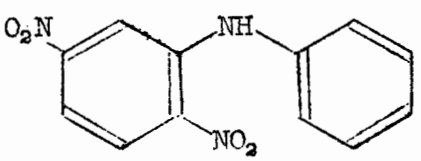
(XXX)

conditions as for 2,2'-dinitrodiphenylamine, using o-iodonitrobenzene and m-nitroaniline gave only a 16% yield which could not be improved upon by increasing the reaction time.

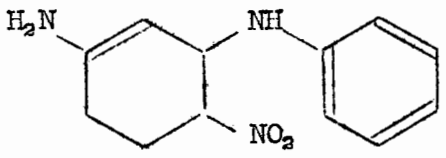
Two possible syntheses of the unknown 2,5-diaminodiphenylamine (XXXI) were considered, the intermediates being either (XXXII) or (XXXIII).



(XXXI)

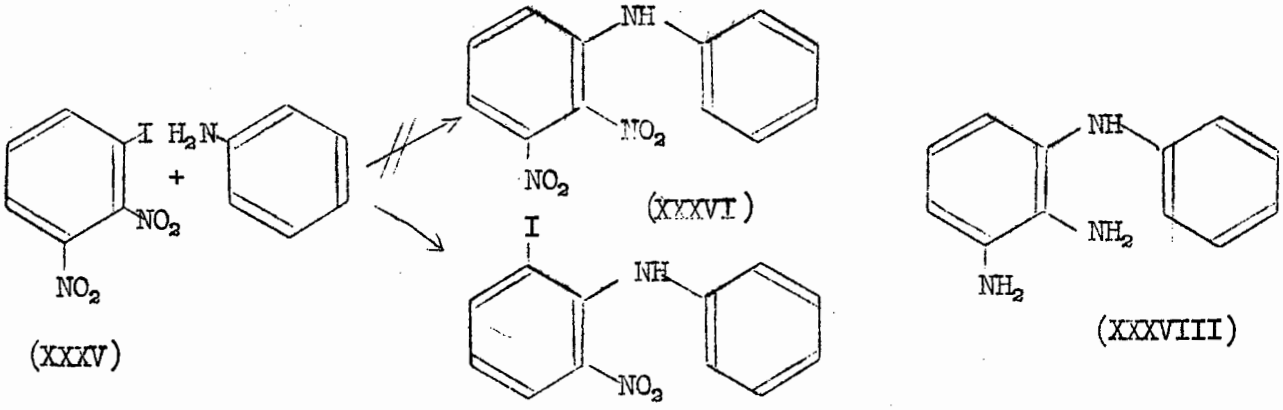


(XXXII)



(XXXIII)

Vivian[49] has shown that if 2,3-dinitroiodobenzene is reacted with aniline, the product is 6-iodo-2-nitrodiphenylamine (XXXVII) and not



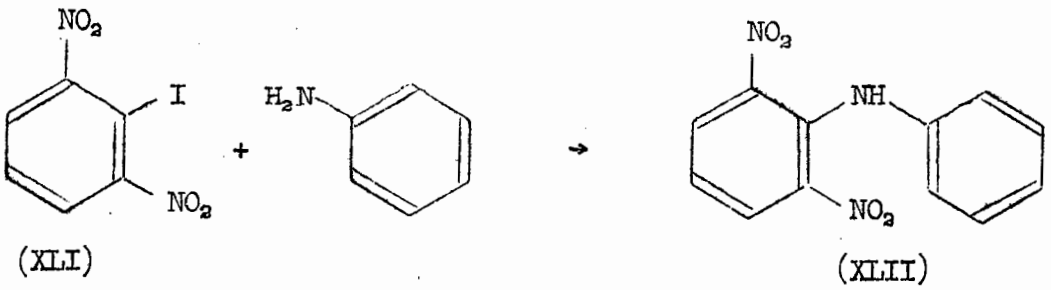
(XXXV) (XXXVI) (XXXVII) (XXXVIII)

2,3-dinitrodiphenylamine (XXXVI). It thus appears that a nitro group is more easily displaced than a halogen atom, eliminating a possible route to the required 2,3-diaminodiphenylamine (XXXVIII). The alternative approach would be through the use of 3-iodo-2-nitroaniline (XL) which apparently can

(XXXIX) (XL)

be prepared by a nitramine rearrangement of (XXXIX)[67]: however, the details of this reaction have not yet been published, and a letter to one of the authors requesting such details has so far remained unanswered.

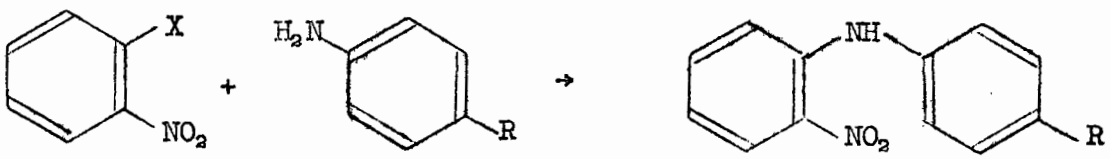
There was no difficulty in obtaining 2,6-dinitrodiphenylamine (XLII) from 2,6-dinitroiodobenzene (XLI) and aniline, since in this case the halogen is far more reactive than either nitro group.



(XLI) (XLII)

In conclusion, it must be stated that a systematic study of diphenylamine synthesis was not intended. However, the author would like to put on record some generalisations, with the reservation that these should not be considered as final.

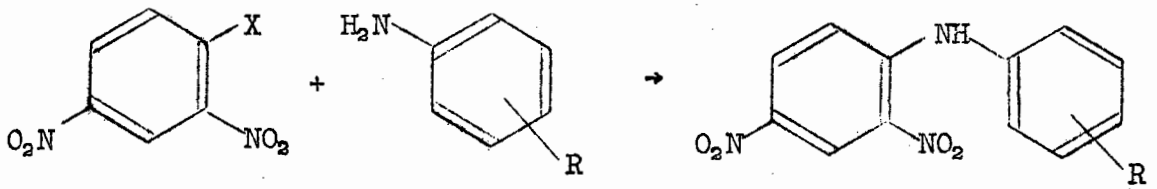
If R is strongly electron attracting in a condensation such as the following:



then X = Iodine is the best halogen for the reaction, and vigorous conditions can be used (potassium carbonate, copper, 200°). The reaction gives the best results with small quantities of starting materials (0.01 moles) and short reaction times (5 minutes to 1 hour). If R is not strongly electron attracting, the preceding conditions often result in charring or reductive dehalogenation: it is then safer to use the chloro compound, sodium acetate, and no catalyst. Heating at about 200° must then usually be carried out for much longer periods. The same applies

to anilines where R is in a position ortho to the amino group.

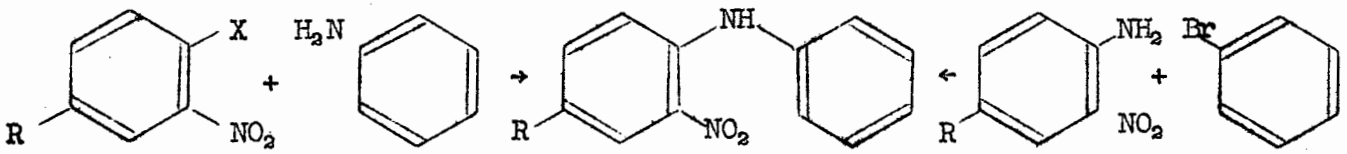
When the halogen is activated by two nitro groups as in (XLIII), then



(XLIII)

the reactivity of a chlorine atom is usually sufficiently high to ensure condensation with any amine. Mild conditions can be used (reflux in ethyl alcohol with sodium acetate or in butyl alcohol), unless R is strongly electron attracting, when more vigorous conditions should be used (potassium carbonate, copper, no solvent, 150°). The use of potassium fluoride in place of potassium carbonate can sometimes give good results.

If a diphenylamine of type (XLIV) is required, both routes should be tried.



Method A (XLIV) Method B

Method A will be the better one if R is electron attracting, method B if R is electron donating.

The reduction of 2-nitrodiphenylamines

The early methods of reduction of nitrodiphenylamines employed mainly stannous chloride, with Fe and Zn occasionally used. However, Elderfield[36] has shown that catalytic reduction is vastly superior to any other method. The present author made extensive use of platinum oxide, which was found to be the most reliable catalyst, and palladium on charcoal. The procedure described by Dewar and Mole[68] (hydrazine hydrate/Pd/C) was found applicable to nitrodiphenylamines and can be used if necessary.

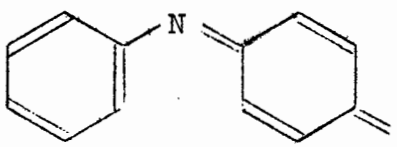
Since aminodiphenylamines, especially if an additional amino group is present, are rather unstable compounds, the following procedure was adopted: after catalytic reduction in alcohol and removal of the solvent and catalyst, the aminodiphenylamine was oxidised in nitrobenzene without further isolation; the diphenylamine was characterised as its acetyl derivative only when a new phenazine was expected from the cyclisation. Elderfield has followed similar lines with the ferric chloride oxidation of aminodiphenylamines.

SECTION II

The Syntheses of Phenazines

Mention was made in the introductory section of this thesis that Gray[7] was able to prepare 2-amino-6-methoxyphenazine by the oxidative cyclisation of 2,4'-diamino-6-methoxydiphenylamine in boiling nitrobenzene*. He then attempted to apply this new method to the synthesis of other phenazines from the appropriate 2-aminodiphenylamines. The results are summarised in table I.

Gray interpreted his results as follows: "These results seem to indicate that the ring closure does proceed mainly via an intermediate indamine. In all those compounds where the following structure (I) could arise by oxidation, good yields were recorded.



(I)

In cases where that intermediate was not possible the yields were poor. A good example of this was the preparation of 2-aminophenazine from

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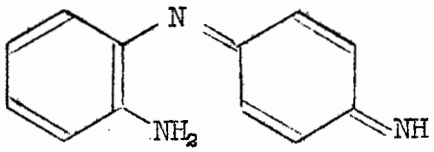
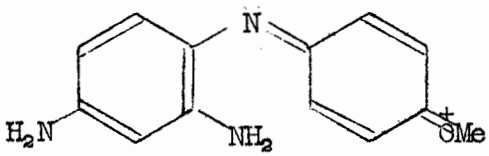
* The specific reaction conditions were: about 1 g of diphenylamine in 25 cc of nitrobenzene, refluxed for 4 - 5 hrs. The phenazine was isolated by removing the nitrobenzene in steam under acid conditions and neutralising the acid solution.

2-4'-diaminodiphenylamine and from 2,4-diaminodiphenylamine. In the first case the 2,4'-diaminodiphenylamine may be oxidised to the following indamine (II):

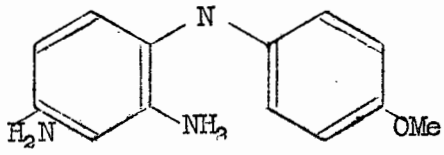


(II)

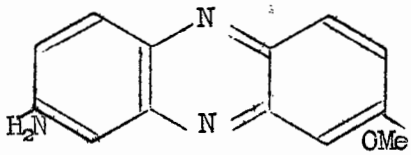
A 70% yield of 2-aminophenazine was obtained. With 2,4-diaminodiphenylamine no such intermediate type of indamine was possible. Only a 5% yield of 2-aminophenazine was obtained ... If this mechanism is applicable, then in the synthesis of 2-amino-8-methoxyphenazine (IIIb) from 2,4-diamino-4'-methoxydiphenylamine (IIIa), the following (III) is possibly the intermediate on the basis of the good yield obtained and the suggested mechanism".



(III)



(IIIa)



(IIIb)

This mechanism and others which were deduced from the present work will be discussed in Section III.

Gray's brief survey of the scope of this reaction was obviously insufficient grounds on which to base any definite conclusions with regard to the mechanism and a number of interesting problems arose from this set of experiments:

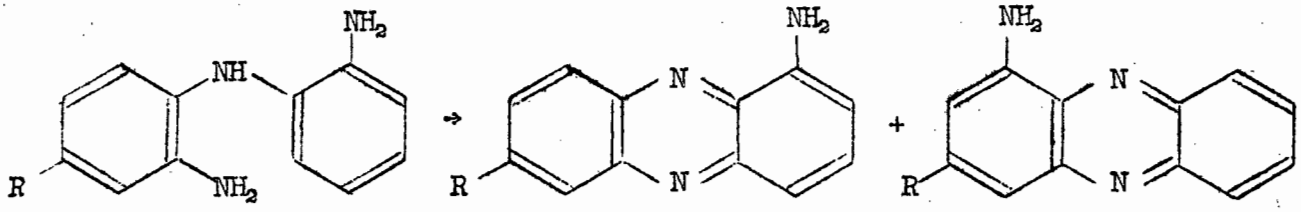
(1) Was the assumption of an intermediate of type II or III correct, and if so, what other groups apart from NH_2 and OCH_3 could give rise to such quinone imine structures ?

(2) Since phenazine was obtained from 2-aminodiphenylamine, although in small yield, methods to increase that yield should be investigated.

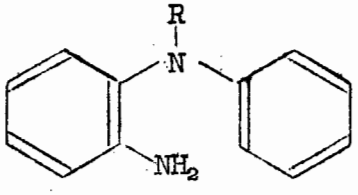
(3) An amino group was retained in the ortho position while a methoxyl group in the same position was eliminated. What would be the fate of groups such as Cl, CH_3, COOH, COOMe, etc. ?

(4) Would a mixture of isomers be obtained from a 2-amino-3'-substituted diphenylamine, and if so, how would the composition of the mixture of isomers be influenced by the group in the 3' position ?

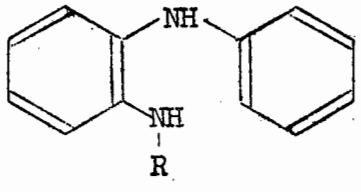
(5) A similar problem arises in the following case:



(6) Could the reaction be extended to diphenylamines of type IV or V, thus providing an unambiguous route to specific phenazinium salts from substituted phenazines ?

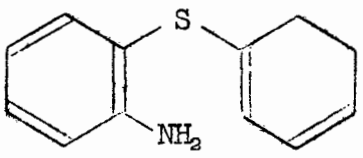


(IV)

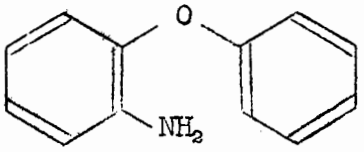


(V)

(7) Could other heterocyclic compounds, such as phenothiazines or phenoxazines, be synthesised by the oxidative ring closure in nitrobenzene of VI or VII ?



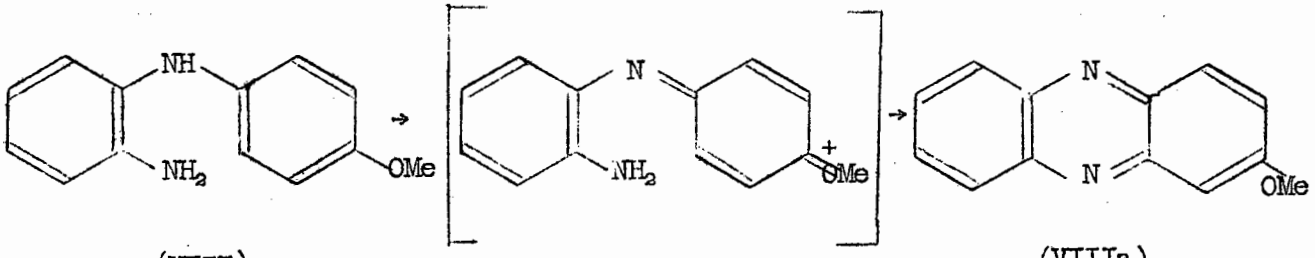
(VI)



(VII)

It was decided that, in the first instance, additional experiments should be undertaken to provide further evidence for or against the proposal that an intermediate of type III is involved in the synthesis of 2-amino-8-methoxyphenazine and, in the light of the results obtained to investigate further the scope of the reaction.

If structure III were indeed the proposed intermediate for the ring closure of 2,4-diamino-4'-methoxydiphenylamine, it followed that 2-amino-4'-methoxydiphenylamine (VIII) should also be converted to 2-methoxyphenazine (VIIIa) in good yield.

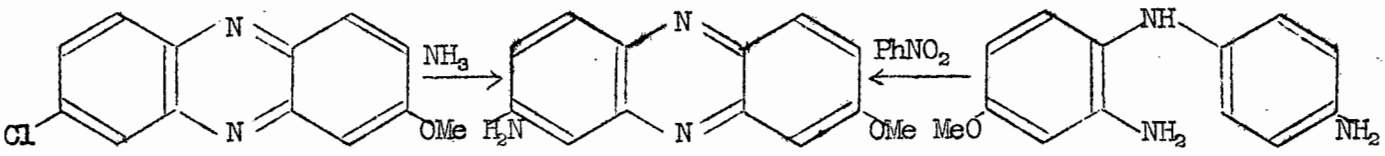


(VIII) (VIIIa)

However, this was found not to be the case: no 2-methoxyphenazine could be isolated by following the same procedure as for the synthesis of 2-amino-8-methoxyphenazine. There seemed little doubt that the compound obtained

by Gray was, in fact, 2-amino-8-methoxyphenazine: it had the correct analysis and the same melting point as that reported by Fischer[55] for the phenazine. But both compounds were obtained by an oxidation of 2,4-diamino-4'-methoxydiphenylamine, Gray's with nitrobenzene and Fischer's with lead dioxide. It was therefore thought advisable that the synthesis should be attempted by an alternative route.

Two possible syntheses were considered:

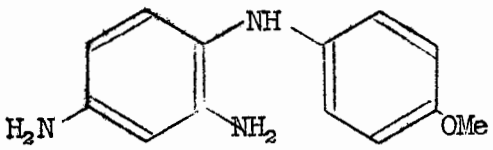


(IX) (X) (XI)

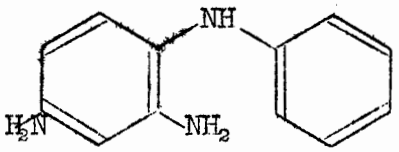
The reactivity of a halogen atom in the 2-position of the phenazine nucleus has been amply demonstrated, its replacement by an amino group by heating with ammonia being shown by Pachter and Kloetzel[69], and Gray[7] showed that cuprous chloride as catalyst markedly increased the yield. 2-Chloro-8-methoxyphenazine (IX) has been prepared by Vivian[44] and an attempt was made to convert this to 2-amino-8-methoxyphenazine (X) by heating with ammonia in a sealed tube in the presence of cuprous chloride. This gave mainly charred material from which a small amount of red product was isolated, melting point 277 - 280°, λ_{max} 270 and 506 mμ. These figures suggested that 2,8-diaminophenazine (m.p. 280°, λ_{max} 272 and 504 mμ) had probably been obtained. This reaction was not further investigated as an alternative route proved successful; this involved the nitrobenzene oxidative cyclisation of 2,4'-diamino-4-methoxydiphenylamine (XI), a

product identical (mixed melting point) to Gray's being obtained.

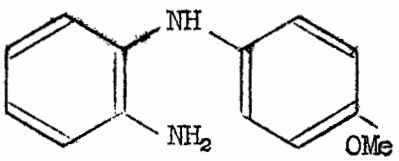
Considerations of these results in conjunction with those obtained by Gray revealed a seemingly paradoxical situation: an amino group in the 4 position favoured the ring closure of 2,4-diamino-4'-methoxydiphenylamine (XII) but not that of 2,4-diaminodiphenylamine (XIII);



(XII)



(XIII)



(VIII)

alternatively, a methoxyl group in the 4' position favoured the ring closure of 2,4-diamino-4'-methoxydiphenylamine (XII) but not that of 2-amino-4'-methoxydiphenylamine (VIII). In an attempt to throw some light on this problem, it was decided to investigate more thoroughly the ring closure of 2,4-diaminodiphenylamine (XIII).

The yields of 2-aminophenazine obtained by Gray from the oxidative cyclisation of 2,4-diamino- and 2,4'-diaminodiphenylamine were 5% and 70% respectively (cf. Table I). However, the first was based on material recrystallised from dilute alcohol, the second on crude product. Since recrystallisation of 2-aminophenazine from aqueous alcohol is usually accompanied by marked losses, the yields in the two cases cannot be used to draw comparisons with regard to the effectiveness of the two cyclisations. A more acceptable analysis of the yields was therefore sought. It was found that 2-aminophenazine could be separated from the other products of the reaction by paper chromatography; after elution from the

paper, it could be estimated colourimetrically in $\frac{N}{10}$ HCl. By this method it was also possible to follow the rate of ring closure of the diphenylamines by withdrawing samples at suitable intervals from the reaction mixture. The ring closure of 2,4- and 2,4'-diaminodiphenylamine was studied in this manner. As a result of these studies, it appeared that not only could the same high yield be obtained from both diphenylamines, but also that the rates of ring closure were virtually identical. The maximum yield, about 70%, was reached in about 12 hours. An alternative method of assay used subsequently (see page 46) showed that the paper chromatographic method tends to give slightly inaccurate values; however, it served a very useful purpose, pointing the way to a very simple method of synthesis of 2-aminophenazines.

Synthesis of 2-aminophenazine and some simple derivatives

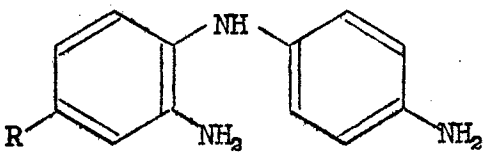
When carrying out the rate experiments, it was found convenient to use more dilute solutions of diaminodiphenylamines in nitrobenzene, roughly 0.003 moles/litre instead of 0.015 moles/litre as used by Gray and by the author in the initial experiments in this work. When such a dilute solution was allowed to stand overnight at room temperature after 12 hours refluxing, red needles of 2-aminophenazine were seen to separate out of solution, although in relatively small amount. By concentrating the solution to almost a fifth of its volume, it was possible to obtain a 50% yield of pure 2-aminophenazine (m. pt. 270 - 274°) without any further recrystallisation. This could be achieved from either 2,4- or 2,4'-diaminodiphenylamine, but from a synthetic point of view, the preparation from 2,4-diaminodiphenylamine is much more attractive because the required

intermediate, 2,4-dinitrodiphenylamine, is very easily accessible. It was interesting to note that if the ring closure of 2,4-diaminodiphenylamine were carried out in the more concentrated solution, an amorphous material, which was very difficult to recover, invariably separated out on cooling. All subsequent cyclisations were therefore carried out at a concentration of ca. 0.003 moles/litre.

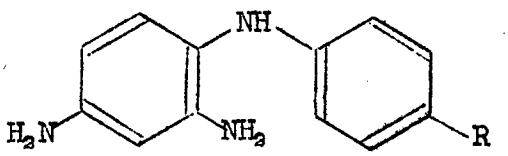
Many methods of synthesis of 2-aminophenazine can be found in the literature: it was originally prepared by Fischer and Hepp[17] by distilling 2,3-diaminophenazine with zinc dust. Nietzki[53] and Hewitt et al[70] obtained it from 2,4'-diaminodiphenylamine by manganese dioxide and potassium dichromate respectively; it was also obtained by Fischer[55] from 2,4-diaminodiphenylamine by lead oxide oxidation. In no case was the yield reported. 2-Aminophenazine was obtained in 20% yield[71] by a Wohl-Aue type of reaction, in 13% yield from 2-chlorophenazine[69]: the latter yield, however, has been greatly improved by Gray (loc. cit. p. 135). Kehrmann and Havas[72] reduced 2-nitrophenazine and Kehrmann and Mermod[73] hydrolysed 2-acetamidophenazine which was obtained in good yield from 4-acetamido-o-quinone and o-phenylenediamine. Finally, from the rather complex 2'-amino-4,6-dinitrodiphenylamine-2-carboxylic acid, Ullmann[74] obtained 2-aminophenazine in unspecified yield. None of these methods can be regarded as really satisfactory because none combines the advantage of a high yield and easily accessible starting materials and intermediates.

The oxidative ring closure in boiling nitrobenzene was then extended to other 2,4- and 2,4'-diaminodiphenylamines to test the general applic-

ability of the method. Positive results having been obtained with an electron releasing group (OMe) in the 4 and 4' position of XIV and XV, (R = OMe) and with the unsubstituted intermediates (R = H), it was decided to attempt the reaction with a relatively neutral group (CH_3) and



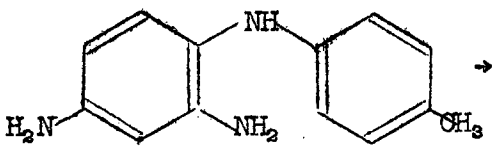
(XIV)



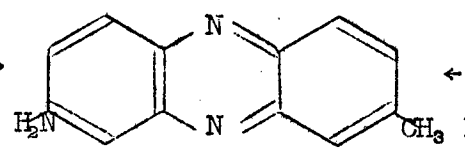
(XV)

electron attracting groups (Cl and CN) in the same positions and, to complete the series, to study the ring closure of 2,4,4'-triaminodiphenylamine (XIV or XV, R = NH_2).

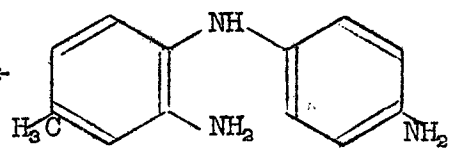
2-Amino-8-methylphenazine (XVII) was synthesised by the same technique as that used for the synthesis of 2-aminophenazine. The yield from both 2,4-diamino-4'-methyldiphenylamine (XVI) and 2,4'-diamino-4-methyldiphenylamine (XVIII) was good.



(XVI)



(XVII)

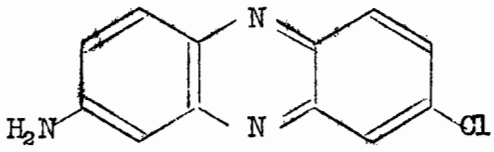


(XVIII)

The acetyl derivative was prepared using acetic anhydride and pyridine, shown by Gray (loc. cit. p. 37) to be successful in the acetylation of 2-aminophenazine.

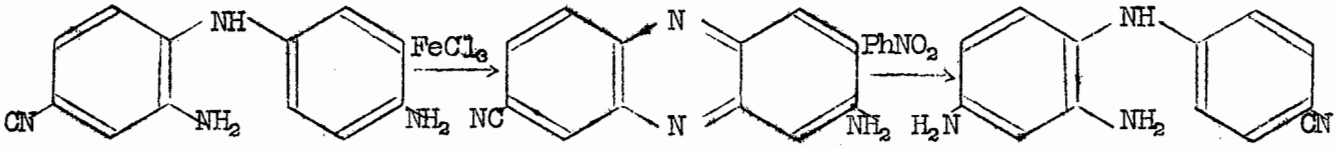
Similarly, there was no difficulty in preparing 2-amino-8-chloro-

phenazine (XVIIa) from 2,4-diamino-4'-chloro- and 2,4'-diamino-4-chloro-diphenylamine. Otomasu[75] has obtained this phenazine by the nitration of 2-chlorophenazine-N-oxide followed by reduction of the 2-chloro-8-nitrophenazine-N-oxide.



(XVIIa)

Professor Holliman[76] has prepared 2-amino-8-cyanophenazine (XX) by the ferric chloride oxidation of 2,4'-diamino-4-cyanodiphenylamine (XIX). Nitrobenzene oxidation of 2,4-diamino-4'-cyanodiphenylamine (XXI)



(XIX) (XX) (XXI)

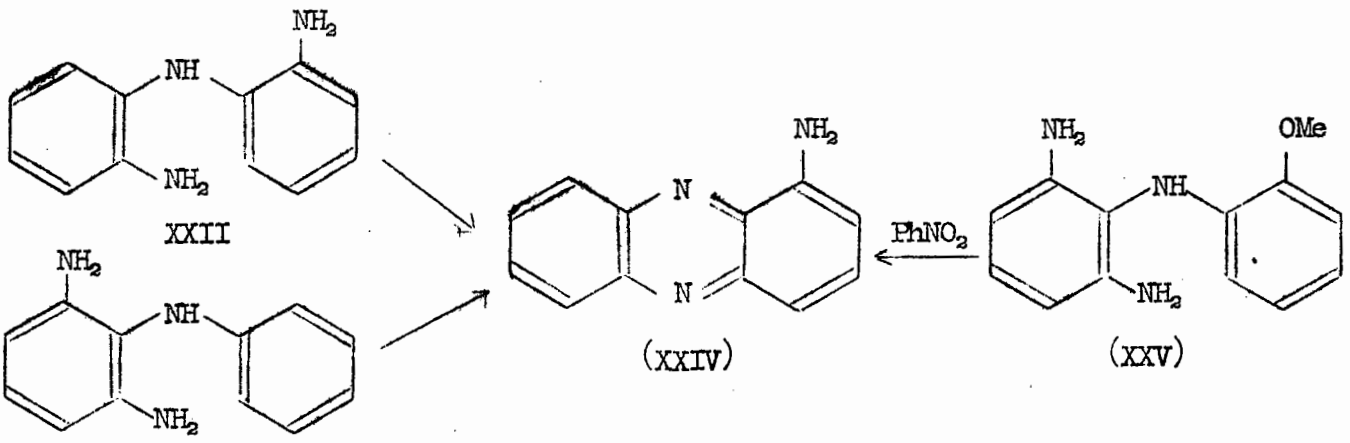
gave the same product.

Finally, 2,8-diaminophenazine was obtained from 2,4,4'-triaminodiphenylamine in very good yield. However, in both this and the previous case, the phenazine was best isolated by column chromatography on alumina.

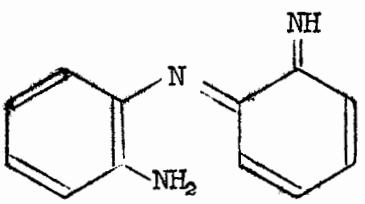
The diphenylamines which have been included in this survey have carried groups which release or remove electrons by the mesomeric and inductive effects and in all cases the oxidative cyclisation to the phenazine has been achieved. It therefore seems likely that the synthesis is of general applicability and a wide variety of 2-amino-8-substituted phenazines could be obtained from the appropriate 2,4-diamino-4'-

substituted or the 2,4'-diamino-4-substituted diphenylamine. Which of these possible starting materials is used would depend on their relative accessibility: in general, 2,4-diaminodiphenylamines would be the more readily synthesised, but in special cases [e.g. 2,4'-diamino-4-cyanodiphenylamine (XIX)], the alternative approach would be more attractive.

Attention was then turned to other possible extensions of the synthesis. Gray[7] has shown that, in the 2'-position, an amino group is retained and a methoxyl group eliminated. Thus 2,2'-diaminodiphenylamine (XXII) gave 1-aminophenazine (XXIV), this phenazine being also obtained from 2,6-diamino-



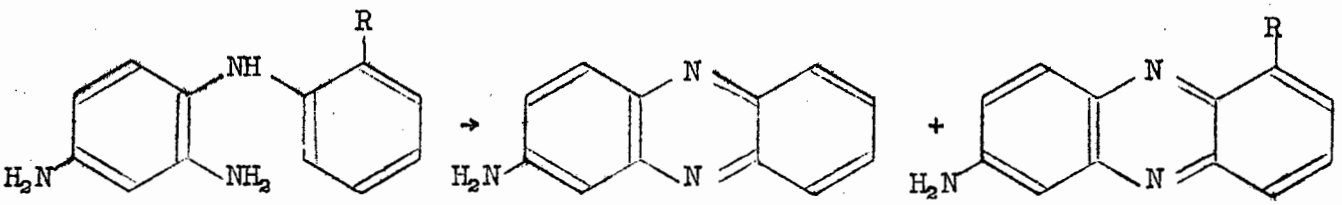
2'-methoxydiphenylamine (XXV). As for 2,4'-diaminodiphenylamine, the intermediate in the conversion of (XXII) to (XXIV) was presumed to be a quinone imine of type (XXVI); and following the same pattern as for the



(XXVI)

2,4-diamino compound, it was shown in this work that 2,6-diaminodiphenylamine (XXIII) could also be converted to 1-aminophenazine (XXIV).

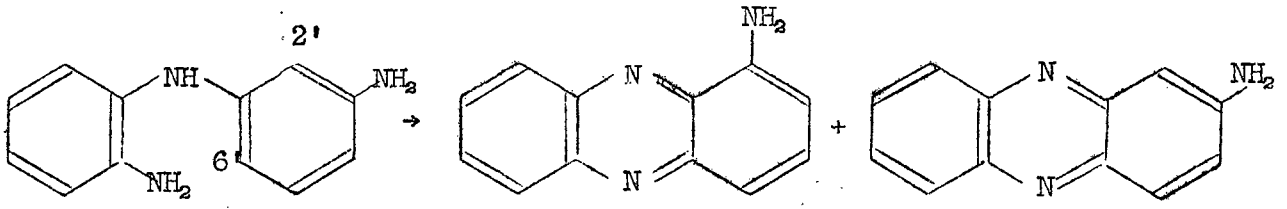
Experiments were then carried out on a number of 2,4-diamino-2'-substituted diphenylamines (XXVII). However, these experiments were only of an exploratory nature, the products obtained being identified by paper chromatography. With a methoxyl, carboxyl, or methoxycarbonyl substituent in the 2' position, two spots were obtained, one corresponding to 2-aminophenazine (XXVIII) the other to the 2-amino-6-substituted phenazine (XXIX). With R = CH_3, no 2-aminophenazine was detected, suggesting that no



(XXVII) (XXVIII) R = OMe, COOH, COOMe (XXIX)

elimination had taken place.

In order to see if phenazine formation was limited to cases where one amino group was situated ortho or para to the diphenylamine nitrogen, it was considered necessary to attempt this reaction with 2-aminodiphenylamines with a second amino group in other positions. Great difficulties were encountered in the preparation of 2,3- and 2,5-diaminodiphenylamine (see p. 23), but 2,3'-diaminodiphenylamine (XXX) was obtained from the corresponding dinitro compound. The cyclisation gave the expected mixture



(XXX)

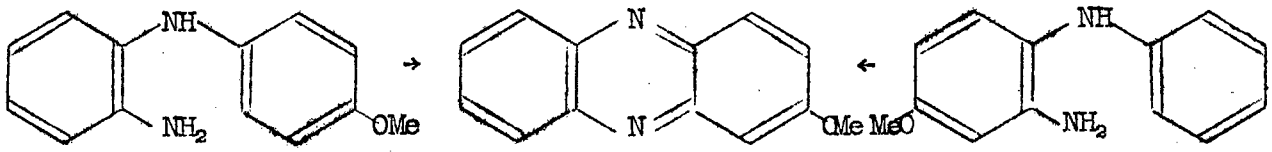
of 1- and 2-aminophenazine. The isomers were separated by column chromatography on alumina: a preliminary experiment on a solution containing a known amount of the phenazines in nitrobenzene confirmed the reliability of the method. The proportion of the two isomers from the ring closure of (XXX) was contrary to expectations. It was anticipated that steric factors would make cyclisation into the 2' position more difficult than cyclisation into the 6' position so that 2-aminophenazine would be produced in a greater proportion than 1-aminophenazine: in fact, the 1-amino compound was present to the extent of twice the amount of the 2-amino compound.

Syntheses of phenazines not bearing amino substituents

The yield of phenazine from the nitrobenzene oxidative cyclisation of 2-aminodiphenylamine was reported by Gray[7] as being "very small". In fact, the presence of phenazine was detected only by paper chromatograms. It was suspected, however, that, as for 2,4-diaminodiphenylamine, different conditions might afford better results. This proved to be the case. When 2-aminodiphenylamine was refluxed in nitrobenzene for 12 hours (solution 0.003 molar), a 12% yield of phenazine was obtained. The product did not crystallise out of solution, but was isolated by steam distillation. This yield was a marked improvement, but still very much lower than that obtained in the ring closure of 2,4-diamino-

diphenylamine. Since no major side products had apparently been formed, it was thought that the reason for this low yield was simply a slower rate of ring closure: refluxing for a longer time should thus improve the yield. This hypothesis proved to be correct,when a 55% yield of phenazine was obtained on refluxing 2-aminodiphenylamine in nitrobenzene for 120 hrs. This time was arbitrarily chosen. A more detailed investigation of the progress of the reaction which was undertaken later showed that the maximum yield could be obtained in 70 hrs.

In the light of this result it was necessary to reinvestigate the possible conversion of 2-amino-4'-methoxydiphenylamine (VIII) to 2-methoxyphenazine (VIIIa) which had earlier been unsuccessful. Using the modi-

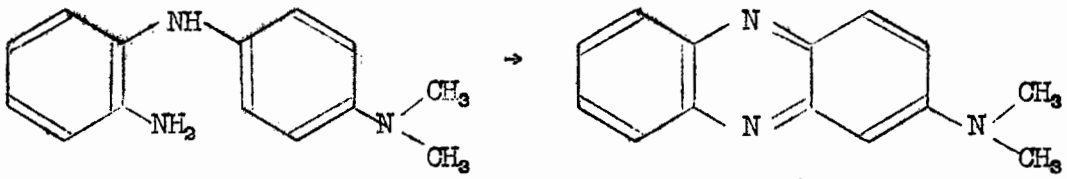


(VIII) (VIIIa) (VIIIb)

fied reaction conditions, 2-methoxyphenazine (VIIIa) was obtained in 14% yield after 12 hours reflux and in 45% yield after 120 hours. Here again the phenazine did not crystallise out of solution, but was isolated by removing the nitrobenzene in steam under acid conditions followed by neutralisation of the acid solution. This method of isolation was not very satisfactory as a rate curve obtained later showed that a 70% yield could be obtained (in 30 hours reflux) provided that 2-methoxyphenazine was isolated by column chromatography on alumina: by reducing the volume of the nitrobenzene solution, it was possible to chromatograph the solution

directly, thus reducing losses to a minimum. 2-Methoxyphenazine was similarly obtained in high yield from 2-amino-4-methoxydiphenylamine (VIIIb).

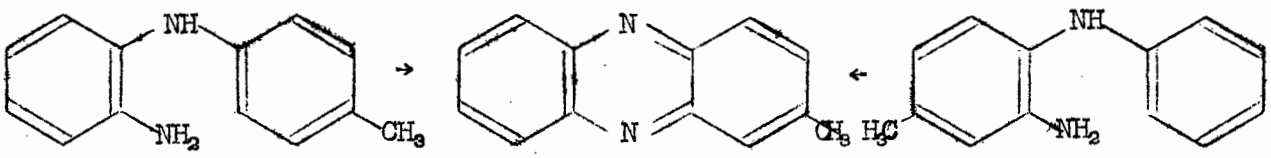
The reaction was then extended to the synthesis of 2-N,N-dimethylaminophenazine (XXXI), which can be regarded as the N-equivalent of 2-methoxyphenazine. It was obtained from 2-amino-4'-dimethylaminodiphenylamine (XXXII) in 45% yield. Although a number of substituted 2-N,N-di-



(XXXII) (XXXI)

methylaminophenazines have been described in the literature[42,48], the parent compound has not been reported.

2-Methylphenazine (XXXIV) was synthesised from (XXXIII) and (XXXV).



(XXXIII) (XXXIV) (XXXV)

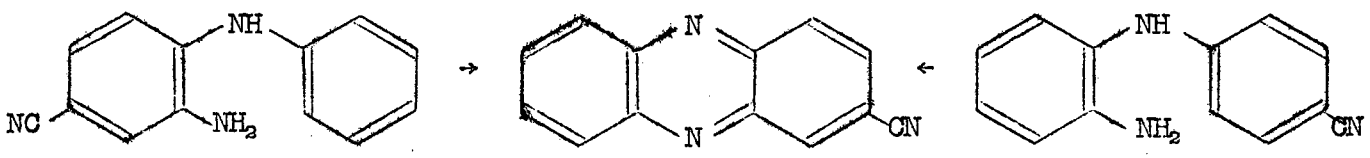
As for 2-methoxyphenazine, better yields were obtained when isolating the phenazine by column chromatography.

The isolation of 2-chlorophenazine presented some difficulty; it could not be separated from nitrobenzene by column chromatography; it was also so steam volatile that it was removed in steam even under acid conditions.

The latter method of isolation was fairly satisfactory since it seemed that 2-chlorophenazine steam distilled only when all the nitrobenzene had been removed. However, low yields were obtained in the cyclisations of 2-amino-4'-chloro- and 2-amino-4-chlorodiphenylamine, and this cannot be defintely attributed either to the influence of the chlorine atom or to the method of isolation.

A minor controversy has appeared in the literature over the physical properties of 2-cyanophenazine (XXXVII). It has allegedly been prepared by Maffei[77] who treated the sodium salt of 2-phenazinesulphonic acid with potassium cyanide: the melting point is given as 180°. Rozum[78] has also reported a compound of same melting point, obtained by dehydrating the oxime of 2-phenazinecarboxyaldehyde. Vivian[46] however has prepared 2-phenazine carbonitrile from 4-cyano-2-nitrodiphenylamine and quotes a melting point of 232 - 234° (corr.). He points out that Maffei's analytical data are incorrect. As for Rozum's compound, it might be 1-phenazine carbonitrile (m. pt. 170 - 172°) because the paper (available only in abstract form) deals mainly with 1-phenazinecarboxylic acid and derivatives.

The oxidative cyclisation in nitrobenzene of both 2-amino-4-cyano- (XXXVI) and 2-amino-4'-cyanodiphenylamine (XXXVIII) gave 2-phenazine-



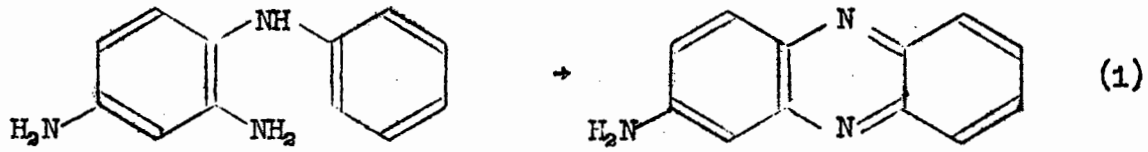
(XXXVI) (XXXVII) (XXXVIII)

SECTION III

SECTION III

(A) Rates of ring closure of 2-aminodiphenylamines in nitrobenzene.

The rate of a simple reaction such as (1) could be followed by measuring either the rate of disappearance of I or the rate of formation



(I) (II) (1)

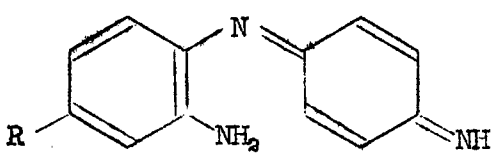
of II. The first possibility presented great difficulties of isolation and estimation and was not investigated. Aminophenazines however have been isolated by paper chromatography, and since they are strongly coloured compounds, they can be estimated in very small amounts by colourimetric assay. By this technique it was possible to follow the rate of formation of 2-aminophenazine from 2,4- and 2,4'-diaminodiphenylamine.

Phenazines not bearing amino substituents had to be handled in a different way because these compounds could not be conveniently isolated by paper chromatography. Furthermore, this technique proved to be rather tedious, and since a large number of such rate studies was envisaged, the development of a more easily applied and quicker method was desirable.

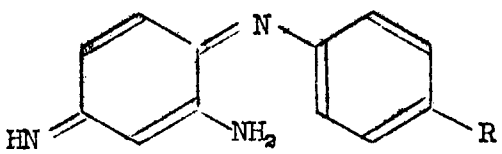
Japanese workers have recently synthesised a number of phenazines by the Wohl-Aue reaction and have worked up their products almost exclusively by chromatography on alumina. . This technique applied to the isolation of phenazines from the nitrobenzene reaction mixture was found to be

These side products were unfortunately rather untractable gummy materials, and the only information obtained was that derived from visible ultra-violet absorption studies which revealed that products very closely related to the parent phenazines had been formed. Elucidation of the nature of these products should prove very interesting but was beyond the scope of this work. Possible structures will be discussed along with mechanisms.

In addition to these bands there always appeared a transitory very strongly adsorbed and highly coloured band, blue with 2,4'-diaminodiphenylamines and deep red with 2,4-diaminodiphenylamines. This band always disappeared once the reaction was complete and was assumed to be an intermediate in the reaction, probably a quinone imine such as III or IV. (See p 63).

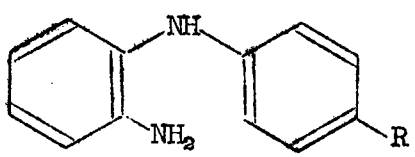


(III)

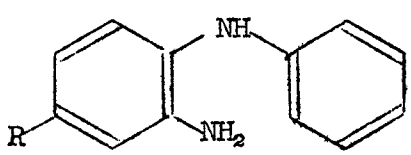


(IV)

When the rates of cyclisation of diphenylamines of type V or VI were followed, a different pattern was observed. The number of unidentified



(V)



(VI)

bands had increased to three or four, moving at a slower rate than the phenazine. Furthermore, the nitrobenzene band, always eluted first and

pale yellow in appearance in the previous cases, now still moved ahead of the phenazine but as an orange-red band, indicating the presence of yet another side product. There was no similarity in colour between the phenazine (pale yellow) and the accompanying side products, which usually included a pink band, and one or two yellow bands. None of these bands disappeared when the reaction was complete. These side products were not investigated.

For a quantitative comparison of effects of various substituents upon the reaction rate, rate constants of the reactions would be required. Unfortunately, in the majority of cases, the formation of a considerable number of side products of unknown constitution prevented the calculation of rate constants; even when no side products could be observed on chromatography of the crude reaction mixture, the yield of phenazine was not quantitative so that it could not be assumed that the amount of diphenylamine remaining at any time was the original amount less that which had been converted to the assayed phenazine. Nevertheless, a qualitative comparison of the various reaction rates could be made by plotting the amount (or the percentage yield) of phenazine against time. The curves thus obtained fell into two distinct groups illustrated by Figs. 1 and 2.

Whenever 2-aminophenazines were expected from the ring closure, a curve of type II was obtained, all other cases showing the normal type I curve. There were two possible explanations for the type II curves:

(1) 2-aminophenazines decomposed on prolonged boiling in nitrobenzene: this was discounted when a sample of 2-aminophenazine was boiled in

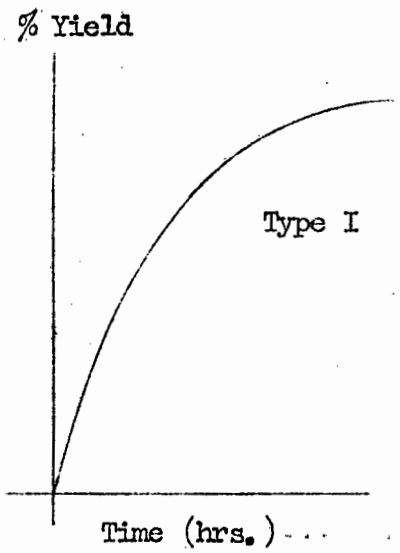


Fig. 1

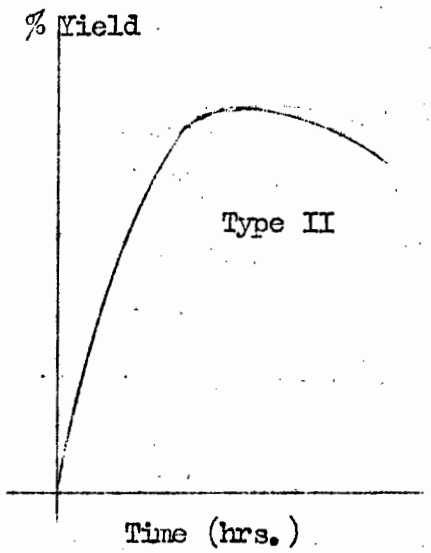


Fig. 2

nitrobenzene over a long period but showed no appreciable change in concentration;

(2) the only other plausible explanation was that 2-aminophenazine reacted through the amino group with a side product formed in the reaction (possibly a reduction product of nitrobenzene), this reaction being slower than the formation of the phenazine. The evidence in favour of such a reaction was that: (i) the side product formed in every ring closure of a 2,4- or 2,4'-diaminodophenylamine appeared to be very closely related to the phenazine formed in the reaction; (ii) with groups other than NH_2 in the 2 position of the phenazine, no such drop in the yield was observed, although side products were formed.

TABLE II

Diphenylamine	Phenazine	Yield, %	Time, hours
2-Amino	Unsubstituted	60	90
2-Amino-4-methyl	2-Methyl	66	50
2-Amino-4'-methyl	"	72	54
2-Amino-4-methoxy	2-Methoxy	75	30
2-Amino-4'-methoxy	"	75	30
2-Amino-4-chloro	2-Chloro	50	100
2-Amino-4'-chloro	"	59	100
2-Amino-4-cyano	2-Cyano	>30	>80
2-Amino-4'-cyano	"	>25	>90
2,4-Diamino	2-Amino	76	12
2,4'-Diamino	"	53	8

TABLE III

Diphenylamine	Phenazine	Yield %	Time, hours
2,4-Diamino	8-Amino	76	12
2,4'-Diamino	"	53	8
2,4'-Diamino-4-methyl	2-Amino-8-methyl	60	9
2,4-Diamino-4'-methyl	"	64	6
2,4'-Diamino-4-methoxy	2-Amino-8-methoxy	40	6
2,4-Diamino-4'-methoxy	"	66	10
2,4'-Diamino-4-chloro	2-Amino-8-chloro	50	5
2,4-Diamino-4'-chloro	"	56	8
2,4'-Diamino-4-cyano	2-Amino-8-cyano	38	50
2,4-Diamino-4'-cyano	"	46	45
2,4,4'-Triamino	2,8-Diamino	92	5

TABLE IV

Diphenylamine	Phenazine	Yield %	Time, hours
2,2'-Diamino	1-Amino	74	10
2,6-Diamino	"	60	30
2,4'-Diamino	2-Amino	53	8
2,4-Diamino	"	76	12
2,3'-Diamino	1- and 2-Amino	75	50

A semi-quantitative comparison of the rates of the reaction can best be made by examining maximum yields and times taken to reach them. The results are grouped in three tables. Table II illustrates the effect of six groups of increasing electron-attracting character in the 4 and 4' position on the ring closure of 2-aminodiphenylamine, table III the effect on the ring closure of 2,4- and 2,4'-diaminodiphenylamine of the same groups in the same positions; and table IV the effect of changing the position of an amino group on the ring closure of 2-aminodiphenylamine.

Two very important facts emerge from the values recorded in Table II. Firstly, all the results indicate that a substituent has the same effect whether in the 4 or 4' position; in fact, the rate curves are almost superimposable. An example is given in Fig. 3.

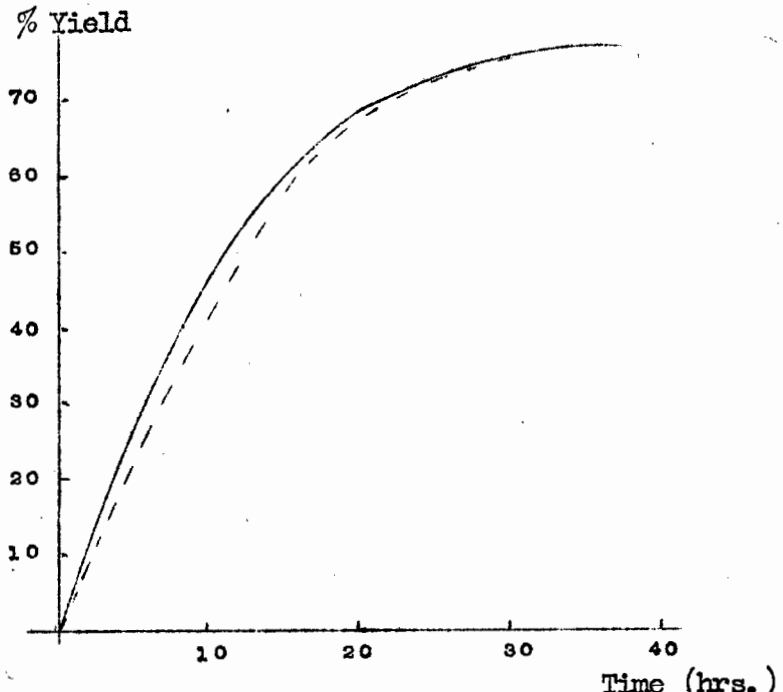


Fig. 3

——— 2-amino-4'-methoxydiphenylamine

- - - 2-amino-4-methoxydiphenylamine

Secondly, there is a marked decrease in the rate with increasing electron-attracting character of the substituents, i.e. the rates follow the order NH_2 > OMe > CH_3 > H > Cl > CN. The reaction with R = CN was so slow that it showed no sign of flattening off after 90 hrs. refluxing.

The results in Table III do not show such a regular decrease in rate with increasing electron-attracting character of the substituents. It rather appears that the middle order substituents, OMe, CH_3, H and Cl, make no appreciable contribution, the effect on the rate becoming noticeable only with the extremes NH_2 and CN, i.e. NH_2 > OMe, CH_3, H, Cl > CN. Although there is a difference of 3 or 4 hours between some of the times recorded for the middle order groups, this is not considered to be very significant because a shorter time is usually accompanied by a lower yield.

It was hoped to study the effect of an NH_2 group in every position on both rings. Unfortunately positions 3 and 5 had to be excluded ar account of difficulties encountered in the preparation of the required intermediates (see Section I). The remaining five possibilities were successfully investigated, including the 3' position which gave the expected mixture of 1- and 2-aminophenazine, the isomers being estimated, separately. As can be seen from Table IV (facing p. 50), the fastest rate was recorded with the second amino group in the 2' position, followed by the 4 and 4' position, then the 6 and finally the 3'.

The influence of catalysts

Originally (Gray, loc. cit. p. 69), m-dinitrobenzene was added to the nitrobenzene since similar conditions had been used by Weinmary[79] in the cyclisation of 2-aminobiphenyl to carbazole. However, rate studies carried

out on 2,4'-diaminodiphenylamine showed that this dinitro compound had no effect on the rate of ring closure of this diphenylamine.

Hydrazine reduces nitro compounds in the presence of palladium charcoal as a hydrogen transfer catalyst[68]. It was thought that a similar hydrogen transfer might take place from diphenylamine to nitrobenzene and that this might be accelerated by palladium charcoal. Although in one case the rate of formation of phenazine from 2-aminodiphenylamine was favourably affected by the addition of such a catalyst, this could not be repeated. A rate study on the ring closure of 2,4-diaminodiphenylamine showed that 5% Pd/C did not increase the rate. Negative results were also obtained with palladium on barium sulphate, reduced Adam's catalyst and sulphur. There is obviously scope for more work in this direction.

(B) Mechanisms proposed for the ring closure of 2-aminodiphenylamines in nitrobenzene.

The evidence for the mechanisms will be derived mainly from the results discussed in the preceding section, together with the small amount of information that can be found in the literature on nitrobenzene oxidation, which will now be briefly surveyed.

The use of nitrobenzene for the dehydrogenation of Diels-Alder type adducts has provided the most interesting information regarding its probable mechanism of oxidation. Clon[80] appears to be the first investigator to have recognised the potentialities of nitrobenzene: he pointed out that this reagent was an ideal one, because it could serve the dual function of solvent and oxidising agent. He thus successfully reacted methylene anthrone (VII) with maleic anhydride to give a fully aromatised product (VIII).

Conclusion

From the evidence obtained in this work, it is difficult to formulate a precise reaction mechanism for the oxidative cyclisation. It appears certain that the oxidative cyclisation of 2,4'-, 2,4- and 2,2'-diaminodiphenylamines proceeds through the intermediary of a quinone imine, and that a different mechanism operates in the case of 2-amino and 2,3'-diaminodiphenylamines. Further work involving investigations of different substituents in positions other than the 4, and 4' is desirable and a study of the nature of the side products produced from 2-aminodiphenylamines might throw some light on the mechanism involved. Nevertheless, the mechanisms formulated in this section should serve as a useful guide when the synthesis of substituted phenazines using this method is contemplated, since more than one diphenylamine can generally be cyclised to yield the required phenazine. However, consideration must also be given to the relative accessibility of the various diphenylamines.

EXPERIMENTAL SECTION

EXPERIMENTAL SECTION

PART I

Only preparative experiments are reported in Part I. The rates of formation of phenazines from 2-aminodiphenylamine are reported in Part II.

In view of the fact that most of the diphenylamines which were converted to phenazines were handled in very similar ways, the full details will be given here only. Therefore, the sentence "the aminodiphenylamine, from the corresponding nitrodiphenylamine was refluxed in nitrobenzene" will imply that the given nitrodiphenylamine was catalytically reduced in absolute alcohol with PtO_2 or Pd/C, at a hydrogen pressure of 40 lbs./sq. in.; the alcoholic solution was then filtered free of catalyst and added to the required amount of nitrobenzene; the alcohol was removed by distillation and a few ccs of nitrobenzene were always distilled to ensure the removal of any traces of moisture. Any deviation from this procedure will be indicated when necessary.

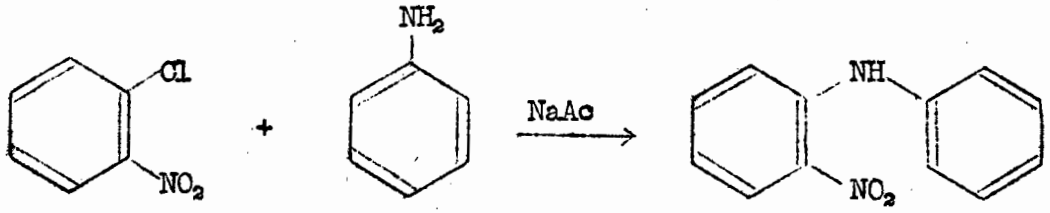
The quantities of catalyst used per gram of diphenylamine were: 50 - 70 mg for PtO_2, 200 - 300 mg for 5% Pd/C. It was sometimes necessary to add fresh portions of catalyst to ensure the completeness of the reduction, when a colourless solution was usually obtained.

The alumina used throughout this work was that supplied by Peter Spence, Grade O.

Melting points are uncorrected.

Synthesis of Phenazine

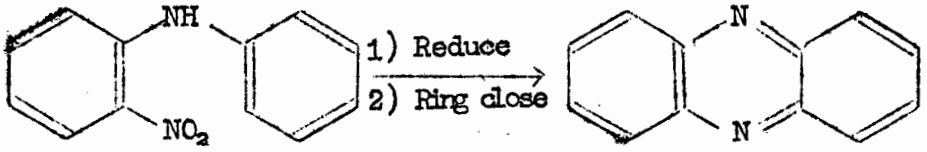
(1) Preparation of 2-nitrodiphenylamine.



cf. Kehrmann and Havas, Ber., 46, 341 (1913).

A 46% yield of 2-nitrodiphenylamine was obtained, m. pt. 71 - 73°.

(2) The ring-closure of 2-aminodiphenylamine.



Several experimental conditions and methods of isolation were used. The ones considered most satisfactory will be given first.

(i) 2-Aminodiphenylamine (from 640 mg of 2-nitrodiphenylamine) was refluxed in nitrobenzene (75 cc) for 70 hrs. The solvent was then evaporated almost completely under reduced pressure and the residue taken up in benzene and chromatographed on an alumina column (25 x 3.5 cm). Traces of nitrobenzene were eluted first, and the pale yellow band which followed was collected, the benzene evaporated and the residue recrystallised from dil. alcohol to give 300 mg (55% yield) of yellow needles, m. pt. 169 - 171°.

Clemo and McIlwain (J.C.S., 1993, 1934) quote a value of 171° for the m. pt. of phenazine.

Analysis

Calc. for $C_{12}H_8N_2$:	Found:
C = 79.9%	C = 79.4%
H = 4.5%	H = 4.8%
N = 15.5%	N = 15.5%.

No yield is given in the method described by Fischer and Heiler[54] (oxidation with PbO), but it is probably very low (cf. McCombie et al[9]). More recently, Mikhailov and Blokhina[56] have obtained phenazine in 40 - 55% yield by passing vapours of 2-aminodiphenylamine over red-hot PbO.

(ii) 2-Aminodiphenylamine (from 2 g of nitrodiphenylamine) was refluxed in nitrobenzene (250 cc) for 120 hrs. The volume of the solution was then reduced to 15 cc and the nitrobenzene steam-distilled under acid conditions (30 cc 5 N HCl). This was followed by steam-distillation under alkaline conditions which gave pure phenazine (m. pt. 169 - 171°) in 33% yield (550 mg).

A reaction time of 12 hrs. gave only 100 mg (6% yield) of phenazine.

(iii) Several unsuccessful attempts were made to improve the yield of the 12 hr. reaction by adding various catalysts to the nitrobenzene solution. Those tried were: 5% Pd/C (300 mg), 30% Pd/C (300 mg), $Pd/BaSO_4$ (300 mg), reduced PtO_2 (100 mg), sulphur (400 mg).

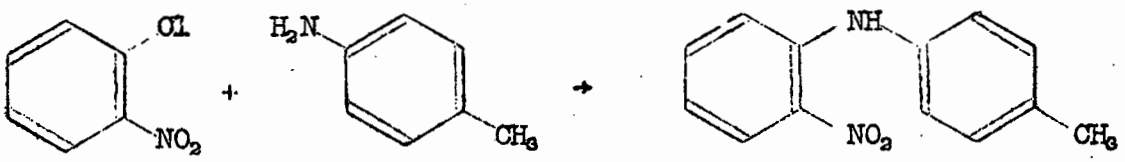
(iv) The ring closure was also attempted in boiling nitromethane, but no phenazine could be detected after refluxing for 12 hrs.

(v) The method of reduction of Dewar and Mole (J.C.S., 2556, 1956) was occasionally used. 2-Nitrodiphenylamine (2 g) was refluxed in abs. alcohol (100 cc) with hydrazine hydrate (2 cc) and Pd/C (200 mg) for 30 min. The filtered colourless solution was added to the nitrobenzene and the alcohol, hydrazine and traces of water boiled off. The experiment was then continued in the normal way. The same yields of phenazine were obtained as in the previous experiments.

Synthesis of 2-methylphanazine

A. From 2-amino-4'-methyldiphenylamine.

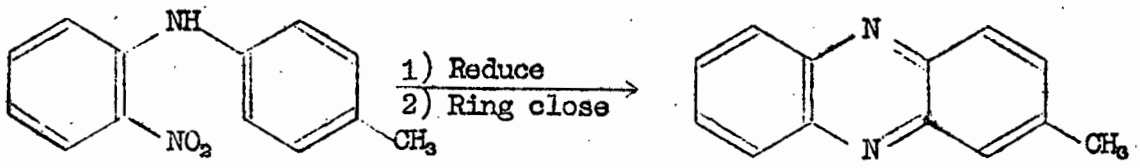
(1) Preparation of 4'-methyl-2-nitrodiphenylamine.



cf. Borsche and Feise, Ber., 40, 383 (1907).

A 22% yield of 4'-methyl-2-nitrodiphenylamine was obtained, m. pt. 67 - 68.5°.

(2) Ring closure of 2-amino-4'-methyldiphenylamine.



4'-Methyl-2-nitrodiphenylamine (800 mg) was reduced with PtO_2 (100 mg) in abs. alcohol. The reduced solution (slightly yellow) was filtered and added to nitrobenzene (100 cc). The alcohol was boiled off and the $PhNO_2$ soln. refluxed for 120 hrs. The solvent was then removed by distillation under reduced pressure and the last traces of nitrobenzene removed by steam-distillation in acid conditions (50 cc 5 N HCl). After filtering, cooling and neutralising with NaOH, 400 mg of crude ppt. was obtained, m. pt. 95 - 105°. This ppt. was purified by chromatography on alumina, with benzene as eluent. 260 Mg (41% yield) of 2-methyl-phenazine were thus obtained, m. pt. 115 - 117°. Recrystallisation from dil. alcohol gave yellow needles, m. pt. 117 - 118°. Clemo and McIlwain (J.C.S., 741, 1935) quote a m. pt. of 117°.

Analysis

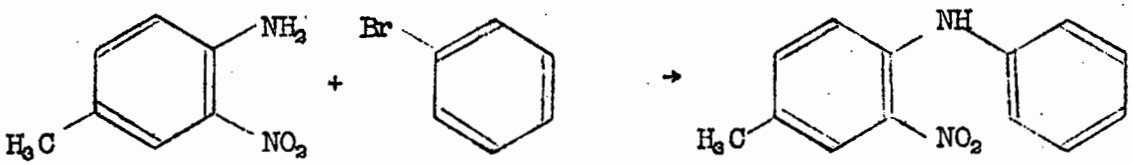
Calc. for $C_{13}H_{10}N_2$:	Found:
C = 80.4%	C = 80.00%
H = 5.20%	H = 6.1%
N = 14.4%	N = 14.2%.

From the rate curve determined subsequently, it became evident that 50 hrs. refluxing would be sufficient to obtain maximum yield. Also, a

better method of isolation of the product would be direct chromatography on alumina of a concentrated nitrobenzene solution.

B. From 2-amino-4-methyldiphenylamine.

(1) Preparation of 4-methyl-2-nitrodiphenylamine.



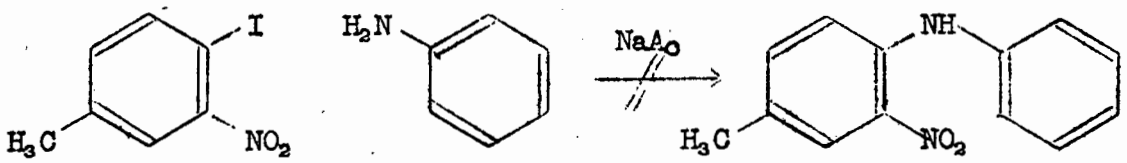
4-Amino-3-nitrotoluene (15 g), bromobenzene (75 g), potassium carbonate (10 g), Cu powder (0.5 g) and potassium iodide (1 g) were refluxed for 24 hrs. Fresh quantities of Cu powder were added from time to time.

The cooled mixture was filtered and the filtrate steam-distilled (2.5 l.). This removed the bromobenzene and part of the unreacted 4-amino-3-nitrotoluene. The oily residue was repeatedly washed with hot 5 N HCl to remove the last traces of starting material, and finally taken up in benzene and dried over $CaSO_4$. A semi-solid red residue (8 g, 35% yield) was obtained on evaporation of the solvent. This product was sufficiently pure to allow catalytic reduction to 2-amino-4-methyldiphenylamine with subsequent ring-closure to 2-methylphenazine as described below. For analytical purposes, however, the product was recrystallised from ether to give red microneedles, m. pt. 35 - 37°.

Analysis

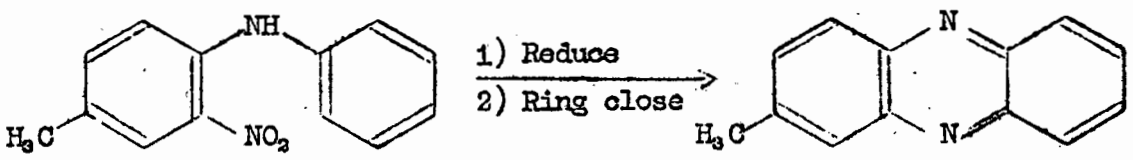
$C_{13}H_{12}N_2O_2$ requires:	Found:
C = 68.4%	C = 68.0%
H = 5.3%	H = 5.3%
N = 12.3%	N = 12.4%

N.B. The normal approach to diphenylamine synthesis, i.e. via 4-iodo-3-nitrotoluene and aniline, failed.



An unidentified red oil was obtained on working up the reaction mixture. Although this material could be catalytically reduced, the reduced product failed to give 2-methylphenazine on prolonged boiling in nitrobenzene.

(2) Ring closure of 2-amino-4-methyldiphenylamine.



4-Methyl-2-nitrodiphenylamine (228 mg) was reduced with PtO_2 (40 mg) in abs. alcohol. The reduced colourless solution was filtered and added

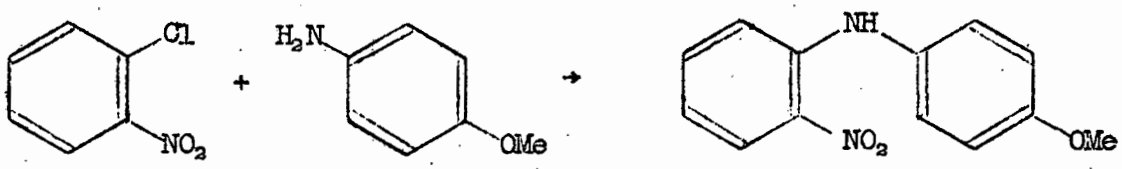
to nitrobenzene (25 cc). The alcohol was boiled off and the $PhNO_2$ solution refluxed for 70 hrs.

The solution was reduced to half its volume by distillation under reduced pressure and then put on an alumina column (15 x 3 cm). Elution with benzene removed first the nitrobenzene (as an orange band) and then 2-methylphenazine as a pale yellow band. Evaporation of the solvent gave 110 mg (56% yield) of yellow product, which was recrystallised from dil. alcohol to give yellow needles, m. pt. 115 - 117°. This melting point was not depressed when a sample from this preparation was admixed with 2-methylphenazine prepared from 2-amino-4'-methyldiphenylamine.

Synthesis of 2-methoxyphenazine

A. From 2-amino-4'-methoxydiphenylamine.

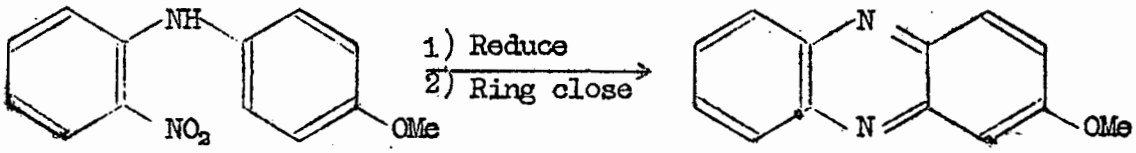
(1) Preparation of 4'-methoxy-2-nitrodiphenylamine.



cf. McCombie et al. J.C.S., 356, (1928).

A 30% yield of 4'-methoxy-2-nitrodiphenylamine was obtained, m. pt. 80 - 84°.

(2) The ring closure of 2-amino-4'-methoxydiphenylamine.



(i) 2-Amino-4'-methoxydiphenylamine (from 400 mg of 4'-methoxy-2-nitrodiphenylamine) was refluxed in nitrobenzene (50 cc) for 120 hrs. The volume of the solution was then reduced to ca. 10 cc, the concentrated solution put on an alumina column (25 x 3.5 cm) and eluted with benzene. Nitrobenzene was eluted first and was then followed by a yellow band of 2-methoxyphenazine. Evaporation of the solvent gave 233 mg (67.5% yield) of 2-methoxyphenazine, m. pt. 122 - 123°. From the rate curve determined subsequently, it became apparent that 30 hrs. refluxing would be sufficient to obtain maximum yield.

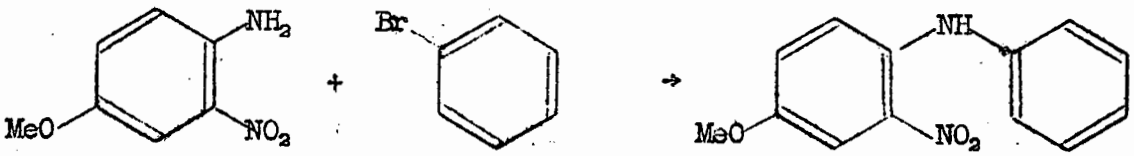
McCombie et al obtained 2-methoxyphenazine (m. pt. 126°) in 5% yield by heating 2-amino-4'-methoxydiphenylamine with litharge.

(ii) Another method of isolating the phenazine was by removal of the nitrobenzene by steam distillation under acid conditions (5 H HCl) followed by neutralisation with NaOH. A very impure precipitate was thus obtained which could best be purified by chromatography. The yield in this case was only 45%.

(iii) Refluxing for 12 hrs and working up as in (ii) gave a 12% yield which was not improved by adding reduced PtO_2 (40 mg) or Pd/C (150 mg) to the nitrobenzene.

B. From 2-amino-4-methoxydiphenylamine.

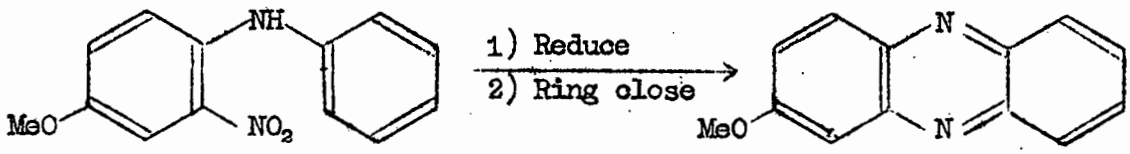
(1) Preparation of 4-methoxy-2-nitrodiphenylamine.



cf. King, King and Muir, J.C.S., 8, (1946).

A 46% yield of 4-methoxy-2-nitrodiphenylamine was obtained, m. pt. 44 - 46°.

(2) Ring closure of 2-amino-4-methoxydiphenylamine.



2-Amino-4-methoxydiphenylamine (from 400 mg of 4-methoxy-2-nitrodiphenylamine) was refluxed in nitrobenzene (50 cc) for 120 hrs. (As shown later by the rate curve, 30 hrs refluxing would be sufficient). Working up as in A.2.(i) gave 221 mg (65% yield) of 2-methoxyphenazine, m. pt. 122 - 123°. No depression of the m. pt. was noted when this product was admixed with the preparation from A.2.(i).

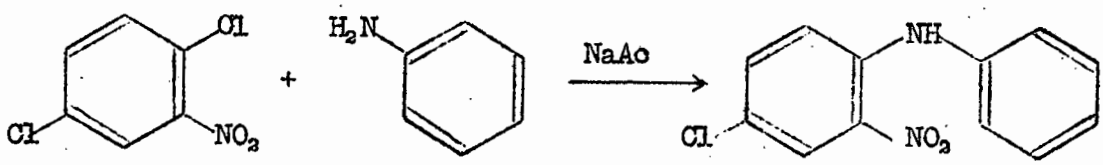
Refluxing for 12 hrs gave a 33% yield.

Synthesis of 2-chlorophenazine

A. From 2-amino-4-chlorodiphenylamine.

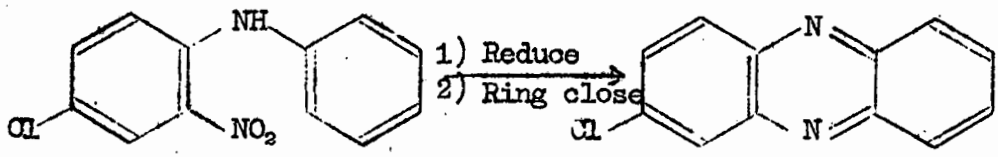
(1) Preparation of 4-chloro-2-nitrodiphenylamine.

cf. Ullmann and Kogan, Ann., 332, 93 (1904).



A 73% yield was obtained, m. pt. 53 - 55°, after recrystallisation from alcohol.

(2) The ring closure of 2-amino-4-chlorodiphenylamine.



(1) 2-Amino-4-chlorodiphenylamine (from 0.5 g of 4-chloro-2-nitrodiphenylamine) was refluxed in nitrobenzene (65 cc) for 12 hrs. After distilling off most of the nitrobenzene under reduced pressure, 5 N HCl (25 cc) was added and the last traces of $PhNO_2$ removed by steam-distillation. Steam-distillation was continued and yellow crystals soon appeared in the distillate. When no more 2-chlorophenazine was produced, the solution was made alkaline, but no product was obtained on further

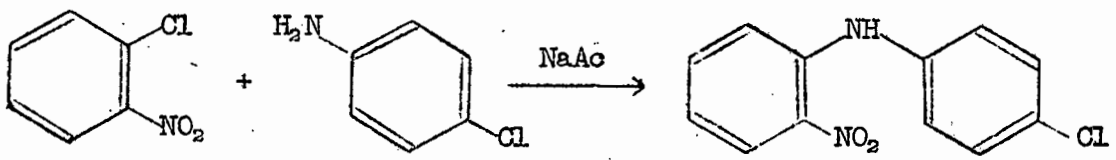
steam-distillation. The yield of 2-chlorophenazine (m. pt. 130 - 133°) was 8 mg (2%). McCombie et al[9] quote a value of 139° for the m. pt. of 2-chlorophenazine.

(ii) The above experiment was repeated but the reduced alcoholic solution was not filtered free of catalyst before adding it to nitrobenzene (see p. 68). On working up the reaction mixture in identical fashion, 30 mg (6.5% yield) of 2-chlorophenazine were obtained, m. pt. 133 - 136° (recrystallised from dil. alcohol).

B. From 2-amino-4'-chlorodiphenylamine.

(1) Preparation of 4'-chloro-2-nitrodiphenylamine.

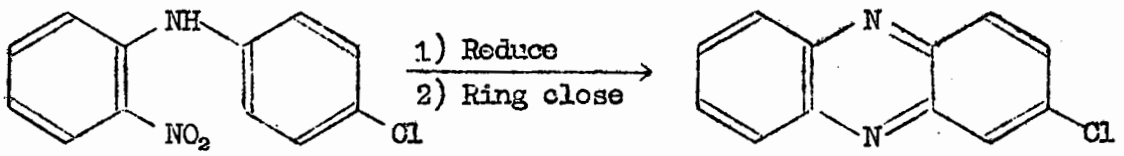
cf. Wilberg, Ber., 35, 957 (1902).



o-Nitrochlorobenzene (15.7 g), p-chloroaniline (12.7 g) and sodium acetate (15 g) were kept at 170° for 10 hrs. After steam-distillation and recrystallisation of the residue from dil. alcohol, 2 g (10% yield) were obtained, red needles m. pt. 139 - 141°.

The yield could not be improved either by using an excess of p-chloroaniline (25 g) or by performing the reaction in nitrobenzene using K_2CO_3 instead of sodium acetate.

(2) The ring closure of 2-amino-4'-chlorodiphenylamine.



(i) 2-Amino-4'-chlorodiphenylamine (from 0.5 g of 4'-chloro-2-nitrodiphenylamine) was refluxed in nitrobenzene (65 cc) for 12 hrs. After distilling most of the $PhNO_2$ under reduced pressure, 2-chlorophenazine was isolated by the procedure described in A. The yield was 40 mg (9%), m. pt. 130 - 133°.

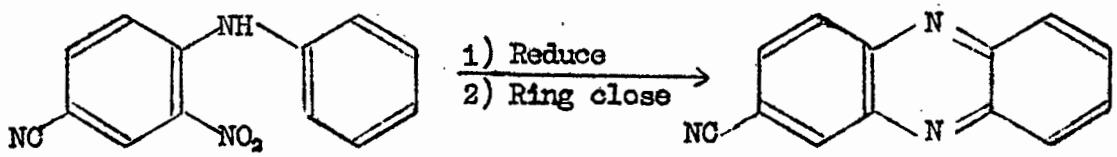
(ii) The experiment was repeated with 0.2 g of 4'-chloro-2-nitrodiphenylamine (reduced with 40 mg of PtO_2), but the alcoholic solution of 2-amino-4'-chlorodiphenylamine was not filtered free of catalyst before adding it to the nitrobenzene (30 cc). The experiment was continued as in (i). The yield was 50 mg (30%), m. pt. 133 - 136° (from dil. alcohol).

A mixed m. pt. of preparations from A and B was not depressed.

McCombie et al[9] obtained 2-chlorophenazine in 5% yield by heating 2-amino-4-chlorodiphenylamine with litharge.

Synthesis of 2-cyanophenazine

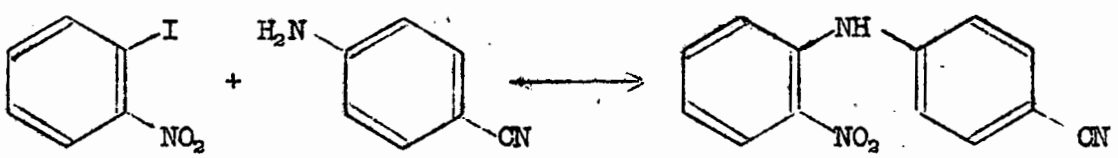
A. From 4-cyano-2-nitrodiphenylamine.



2-Amino-4-cyanodiphenylamine (from 480 mg of 4-cyano-2-nitrodiphenylamine) was refluxed in nitrobenzene (50 cc) for 90 hrs. The volume was then reduced to ca. 15 cc. by distilling $PhNO_2$ under reduced pressure and the conc. soln. was then put on an alumina column (22 x 3.5 cm). Elution was first carried out with benzene which washed the nitrobenzene off the column. 2-Cyanophenazine was rather strongly adsorbed and was best eluted with ether. Evaporation of the solvents gave 210 mg (51%) of 2-cyanophenazine, m. pt. 212 - 218°. This was recrystallised from ethanol (yellow needles) to a constant m. pt. of 225 - 226° (uncorr.). Vivian [J. Org. Chem. 797, 20 (1955)] gives a m. pt. of 232 - 234° (corr.) for 2-cyanophenazine.

B. From 4'-cyano-2-nitrodiphenylamine.

(1) Preparation of 4'-cyano-2-nitrodiphenylamine.

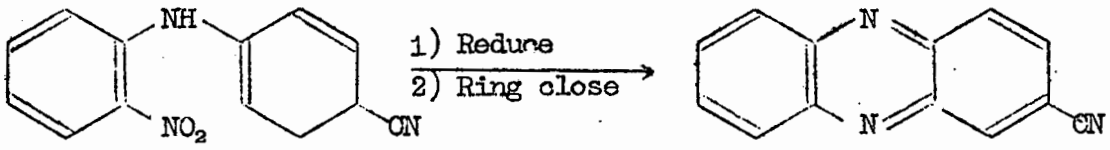


o-Nitroiodobenzene (1.25 g), p-aminobenzonitrile (0.6 g), potassium carbonate (0.7 g) and Cu powder (50 mg) were kept at 170 - 180° for 5 min. The resulting solid was treated with boiling butyl alcohol (20 cc), filtered and cooled. There was obtained 400 mg (34%) of red needles, m. pt. 170 - 174°. Further recryst. from ethanol gave a m. pt. of 174 - 176°.

Analysis

$C_{13}H_9N_3O_2$ requires:	Found:
C = 65.3%	C = 64.6%
H = 3.84%	H = 3.86%
N = 17.6%	N = 18.6%

(2) Ring closure of 2-amino-4'-cyanodiphenylamine.

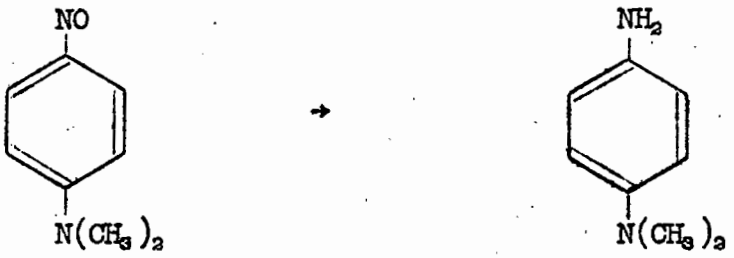


2-Amino-4'-cyanodiphenylamine (from 44 mg of 4'-cyano-2-nitrodiphenylamine) was refluxed in nitrobenzene (5 cc) for 14 hrs. The solution was then put on an alumina column (15 x 3 cm). Elution was first carried out with benzene which washed the nitrobenzene off the column. Elution was then continued with ether and the pale yellow band which followed gave 2-cyanophenazine (6 mg, 15% yield), m. pt. 221 - 223°. Recrystallisation from ethanol gave a m. pt. of 225 - 226°. This m. pt.

was not depressed on admixture with a sample of 2-cyanophenazine prepared from 2-amino-4-cyanodiphenylamine.

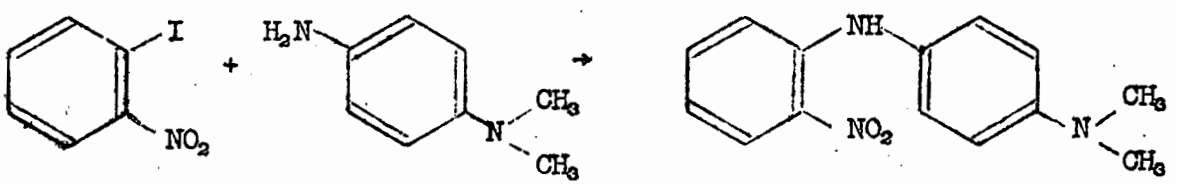
Synthesis of 2-dimethylaminophenazine

(1) Preparation of N,N-dimethyl-p-phenylenediamine.



p-Nitrosodimethylaniline (10 g) was reduced with PtO_2 (60 mg) in abs. alcohol. When the calculated amount of H_2 had been absorbed, the slightly red solution was filtered and the alcohol evaporated under reduced pressure. The residual red liquid was distilled at 1.5 mm pressure, the colourless fraction distilling over the range 106 - 109° being collected. The yield was 6.4 g (71%). Heilbron and Bunbury (Dictionary of Organic Compounds) quote the b. pt. as 95 - 100°/1 mm.

(2) Preparation of 4'-dimethylamino-2-nitrodiphenylamine.



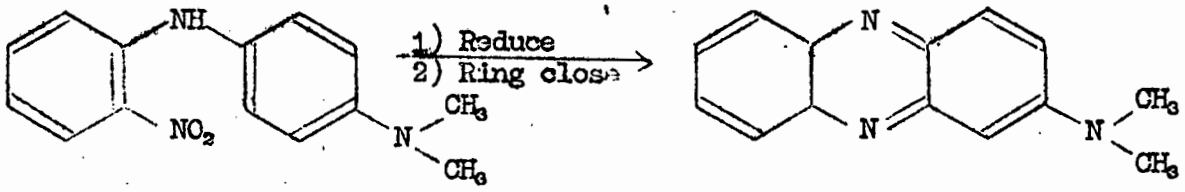
o-Nitroiodobenzene (2.5 g), N,N-dimethyl-p-phenylenediamine (1.5 g) and K_2CO_3 (1.4 g) were kept at 160° for 1 hr. The mixture was then extracted with ether and both solvent and unreacted N,N-dimethyl-p-phenylenediamine were removed by distillation (the latter at 1 mm). The residue was recrystallised from dil. alcohol giving red needles (0.8 g, 30% yield), m. pt. 123 - 124° (shrinking at 118°).

Analysis

$C_{14}H_{15}N_3O_2$ requires:	Found:
C = 65.7%	C = 65.4%
H = 5.9%	H = 6.4%
N = 16.3%	N = 16.1%

N.B. When Cu powder was used in the reaction, a large amount of charring occurred, together with a strong smell of nitrobenzene, after only 2 min. heating at 150°. No diphenylamine was isolated.

(3) Preparation of 2-dimethylaminophenazine.



4'-Dimethylamino-2-nitrodiphenylamine (260 mg) was reduced with PtO_2 (70 mg) as catalyst. The colourless alcoholic solution was filtered and added to nitrobenzene (25 cc). Removal of the alcohol by distillation was followed by refluxing for 14 hrs. The deep red nitrobenzene solution

was evaporated down under reduced pressure until all traces of $PhNO_2$ were removed. A viscous oil was obtained which was taken up in benzene (a black residue remaining undissolved).

The deep red benzene solution was chromatographed on an alumina column (15 x 3 cm). A very strong red band was first eluted with 50% benzene-ether, followed by a narrow orange-red band. The first band on evaporation gave 120 mg (44% yield) of a red product melting at 148 - 152° (softening at 140°). This was rechromatographed and analysed correctly for 2-dimethylaminophenazine.

Analysis

$C_{14}H_{13}N_3$ requires:	Found:
C = 75.3%	C = 74.9%
H = 5.9%	H = 6.2%
N = 18.8%	N = 18.7%

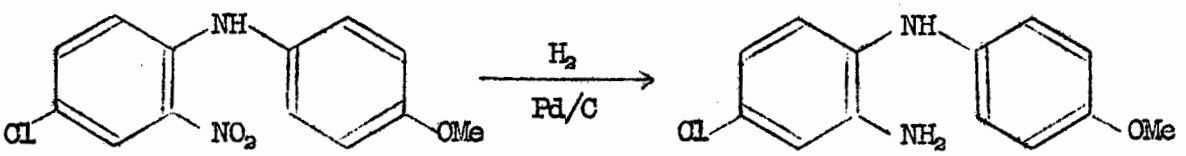
2-Dimethylaminophenazine shows a very strong fluorescence in benzene, but none in alcohol, in which it dissolves giving a red solution. It is partially soluble in water (purple), and its solution in conc. HCl is blue-green turning purple-violet on dilution.

The ultra-violet absorption spectrum showed maxima at 235 mμ (log ε 4.67), 294 mμ (log ε 4.69), 380 mμ (log ε 4.01) and 553 mμ (log ε 4.27). The molar extinction coefficients are given.

The second band yielded a small amount (25 mg) of viscous material which dissolved in conc. HCl giving a blue-green solution turning purple on dilution. Chromatographed (Butanol : HCl, 4 : 1 sat. with H_2O)

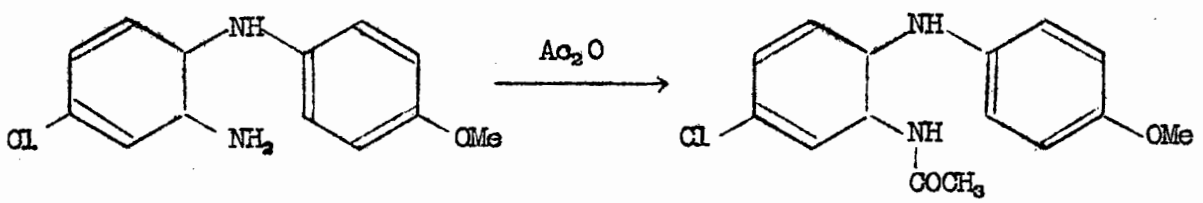
cf. Vivian, Greenberg and Hartwell, J. Org. Chem., 16, 6 (1951). A 50% yield was obtained, m. pt. 150 - 152°.

Preparation of 2-amino-4-chloro-4'-methoxydiphenylamine.



4-Chloro-4'-methoxy-2-nitrodiphenylamine (5 gms) was hydrogenated in abs. alcohol (100 ml) at 40 lbs./sq. in. with Pd/C (0.5 gm) as catalyst. The colourless solution was filtered free of catalyst and then water was added to precipitate all the amine. 4 Gms. (89% yield) of crude white 2-amino-4-chloro-4'-methoxydiphenylamine were obtained, m. pt. 72.5 - 75°. Recrystallisation from pet. ether (b. pt. 60 - 80°) gave white needles, m. pt. 76 - 77.5°, which rapidly turn pink on exposure to air.

Preparation of 2-acetamido-4-chloro-4'-methoxydiphenylamine.



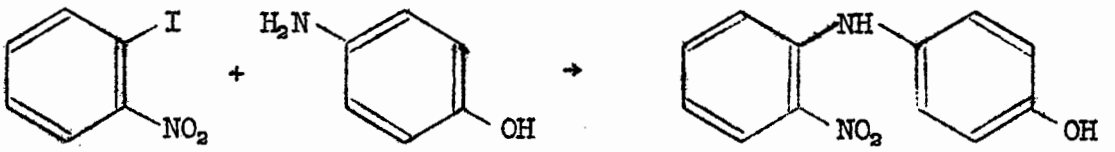
2-Amino-4-chloro-4'-methoxydiphenylamine (0.7 gm) was dissolved in acetic anhydride (10 cc) and left standing at room temperature overnight. The solution was poured into ice and gave 0.7 gm of 2-acetamido-4-chloro-4'-methoxydiphenylamine (85% yield), m. pt. 155.5 - 157° (from dil. alcohol).

Analysis

$C_{15}H_{15}ClN_2O_2$ requires:	Found:
C = 62.1%	C = 62.3%
H = 5.2%	H = 5.2%
N = 9.65%	N = 9.65%.

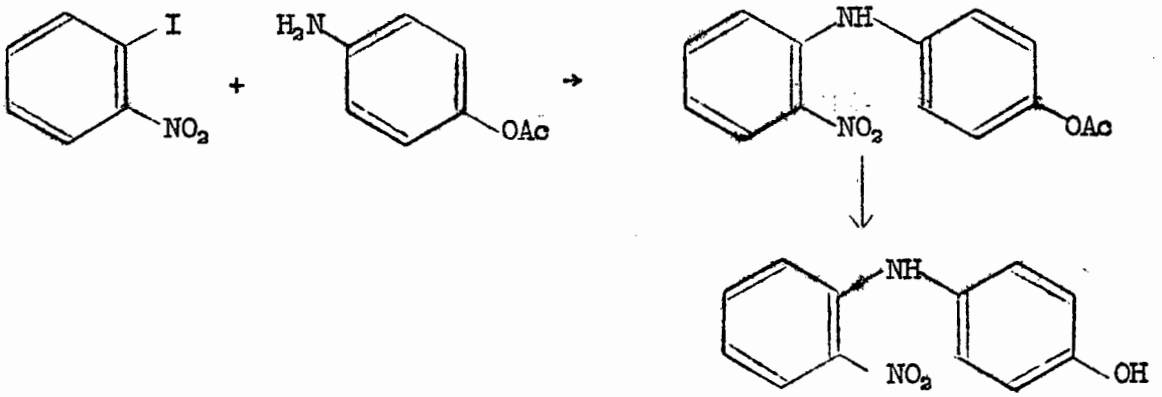
Attempted preparations of 4'-hydroxy-2-nitrodiphenylamine

(1) By condensation of o-iodonitrobenzene with p-aminophenol.



o-Nitroiodobenzene (2.5 g), p-aminophenol (1.1 g), potassium carbonate (1.4 g) and Cu powder (50 mg) were kept in an oil-bath at 130° until the effervescence stopped. A strong smell of nitrobenzene was noted. No product could be isolated from the reaction mixture by the usual methods.

(2) Via 4'-acetoxy-2-nitrodiphenylamine.



p-Aminophenylacetate was obtained in quantitative yield from p-nitrophenylacetate by catalytic reduction, using PtO_2 in alcohol.

(i) o-Iodonitrobenzene (2.5 g), p-aminophenylacetate (1.6 g), K_2CO_3 (1.4 g) and Cu Powder (50 mg) were kept at 120 - 130° for 20 mins., when the

effervescence stopped. Extraction of the reaction mixture with boiling butyl alcohol gave only a small amount of dark brown amorphous material which could not be purified.

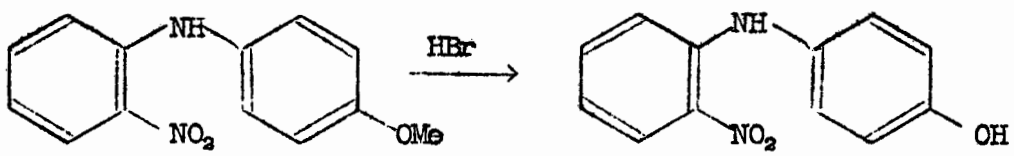
(ii) o-Iodonitrobenzene (2.5 g), p-aminophenylacetate (1.6 g) and sodium acetate (1.5 g) were refluxed in alcohol (50 cc) for 3 days. Only sodium acetate crystallised out on cooling. On adding water, only starting material was obtained.

(iii) Attempts were then made to hydrolyse the 4'-acetoxy-2-nitrodiphenylamine, if formed, without isolating it from the reaction mixture.

As in (i) the reagents were kept at 120 - 130° until the effervescence ceased. N NaOH (30 cc) was added and the mixture warmed on the steam-bath for 30 min. The dark solution was filtered and acidified. A dark brown ppt. was obtained, which could only be recrystallised from water to give a very small amount (20 mg) of an unidentified orange product, m. pt. 139 - 142°.

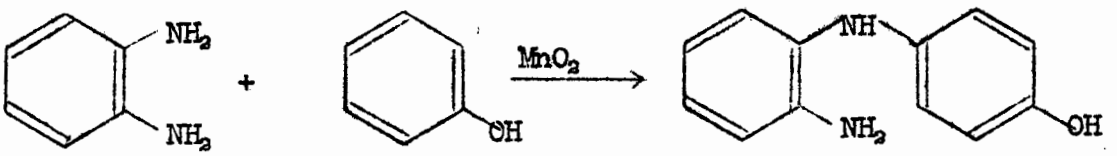
(iv) The reaction conditions in (i) and (iii) being perhaps too vigorous, sodium acetate was tried instead of potassium carbonate and Cu. No product was obtained on working up the reaction mixture as in (iii).

(3) <u>By the demethylation of 4'-methoxy-2-nitrodiphenylamine.</u>



4'-Methoxy-2-nitrodiphenylamine (240 mg) was refluxed for 3 hrs. in glacial acetic acid (15 cc) with 48% HBr (5 cc). The mixture was then made strongly alkaline and filtered; the deep violet solution was acidified with HCl to give 30 mg of a red product, m. pt. 150 - 170°. Recrystallisation from dilute acetic acid did not improve the purity of this compound.

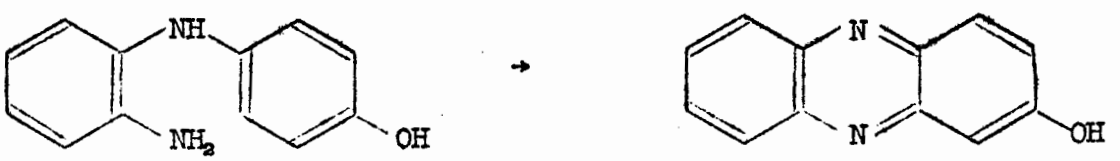
Preparation of 2-amino-4'-hydroxydiphenylamine



cf. Ullmann and Fukin, Ber., 41, 624 (1908).

The yield (60%) recorded by Ullmann and Fukin could not be reproduced. Only a 10% yield of product m. pt. 147 - 150° was obtained. The MnO_2 used was prepared according to the method of Attenburrow et al [J.C.S., 1104, (1952)].

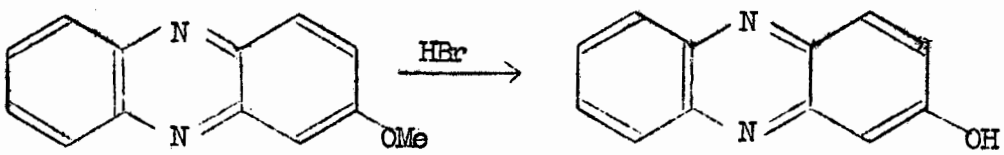
Attempted ring closure of 2-amino-4'-hydroxydiphenylamine



2-Amino-4'-hydroxydiphenylamine (100 mg) was refluxed in nitrobenzene for 6 hrs. No product was obtained on cooling the red solution. The nitrobenzene was steam-distilled under alkaline conditions (200 cc N NaOH) but no precipitate was obtained on careful acidification of the alkaline solution with acetic acid.

Refluxing for 20 hrs. in nitrobenzene gave the same result. Chromatography on alumina (with benzene as eluent) was inconclusive, as only one broad blue band, spreading over the whole column, interfered with any possible separation.

Preparation of 2-hydroxyphenazine



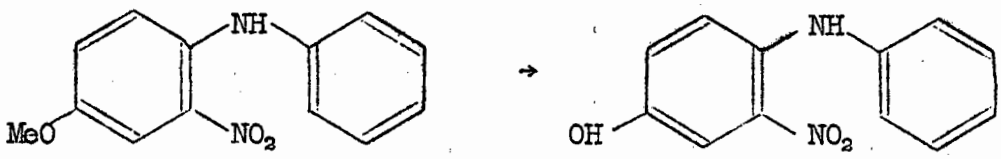
This experiment was modelled on the demethylation of 1-amino-6-methoxyphenazine as described by Gray (loc. cit. p. 181).

2-Methoxyphenazine (0.21 g) was refluxed for 3 hrs. with 48% HBr (5 cc). On cooling, a red precipitate was obtained. The mixture was made alkaline with 5 N NaOH and the deep orange solution filtered. Neutralisation with acetic acid gave a yellow precipitate, which turned red on filtering. However, the yellow colour was restored after drying at 120°. The yield was 170 mg (87%). No melting point was recorded, decomposition taking place at about 250°. Vivian et al [J. Org. Chem., 19,

1136, (1954)] have reported the same properties for 2-hydroxyphenazine.

2-Hydroxyphenazine was found to be fairly soluble in boiling nitrobenzene, but only slightly soluble in the cold.

Attempted demethylation of 4-methoxy-2-nitrodiphenylamine



(i) 4-Methoxy-2-nitrodiphenylamine (200 mg) was refluxed in 48% HBr (5 cc) for 1 hr. An untractable gummy material was obtained on cooling.

(ii) 4-Methoxy-2-nitrodiphenylamine (200 mg) was refluxed for only 10 min. with 48% HBr (5 cc). The solution was then made alkaline, filtered and acidified to give a small amount of unidentified green precipitate.

(iii) 4-Methoxy-2-nitrodiphenylamine (200 mg) was dissolved in glacial aectic acid (25 cc) and 48% HBr (25 cc) and warmed in a boiling water-bath. Red crystals began to separate after 10 min. The mixture was kept at water-bath temperature for one hour. 180 Mg. of a red product were obtained on cooling. This was recrystallised from butyl alcohol as fine red needles, m. pt. 171 - 173°. This compound, however, was insoluble in NaOH, suggesting that no demethylation had taken place. This was confirmed by analysis, which showed that two bromine atoms had rather unexpectedly replaced two hydrogen atoms in the diphenylamine

molecule.

Analysis

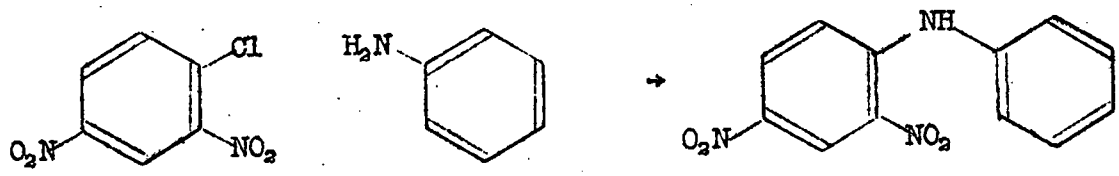
$C_{12}H_{10}N_2O_3$ requires:	$C_{13}H_{10}Br_2N_2O_3$ requires:	Found:
C = 62.6%	C = 38.8%	C = 38.6%
H = 4.3%	H = 2.5%	H = 2.5%
	Br = 39.7%	Br = 39.8%

(iv) 4-Methoxy-2-nitrodiphenylamine (200 mg) and 55% hydroiodic acid (25 cc) were kept at water-bath temperature for one hour. The mixture was then cooled, made alkaline with 5 N NaOH, filtered and acidified. A very small amount of black precipitate was obtained, which was not further investigated.

(v) Easson [J.C.S., 1034, (1961)] has recently demethylated 4,4'-dicyano-2-methoxydiphenylamine using Prey's method [Ber., 74, 1219, (1941)]. This procedure was also attempted.

4-Methoxy-2-nitrodiphenylamine (250 mg, 0.001 m) and pyridine hydrochloride (175 mg, 0.0015 m) were kept at 200° for 4 hrs. The mixture was then cooled, stirred with 50% alcohol and filtered. There was obtained a dark brown product, insoluble in NaOH.

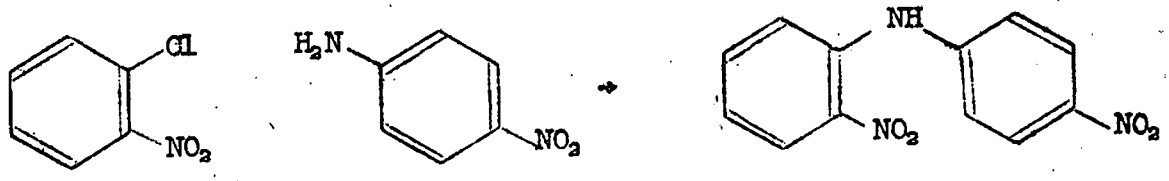
Preparation of 2,4-dinitrodiphenylamine



cf. Hickinbottom, Reactions of Org. Comp. p. 271.

A 50% yield of 2:4-dinitrodiphenylamine was obtained, m. pt. 155 - 157° (from butanol).

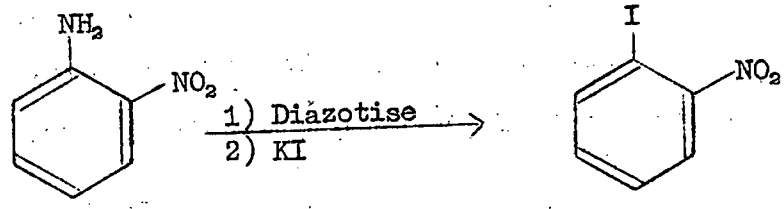
Preparation of 2,4'-dinitrodiphenylamine



cf. Katritzky and Plant, J.C.S., 412 (1953).

A 50% yield of 2,4'-dinitrodiphenylamine was obtained, m. pt. 217 - 220°.

Preparation of o-iodonitrobenzene

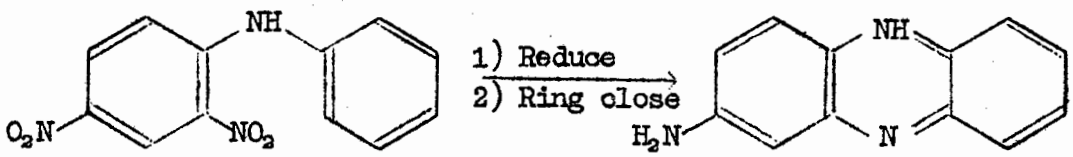


cf. A. Baeyer, Ber., 38, 2760 (1905).

A 94% yield of o-iodonitrobenzene was obtained, m. pt. 51 - 53°.

Synthesis of 2-aminophenazine

A. From 2,4-diaminodiphenylamine.



(i) 2,4-Diaminodiphenylamine (from 2 g of 2,4-dinitrodiphenylamine) was refluxed in nitrobenzene (250 cc) for 15 hrs. The volume of the solution was then reduced to ca. 25 cc by boiling off nitrobenzene under reduced pressure. After filtering and cooling, 2-aminophenazine was obtained (750 mg, 50% yield) as dark red needles, m. pt. 270 - 274°.

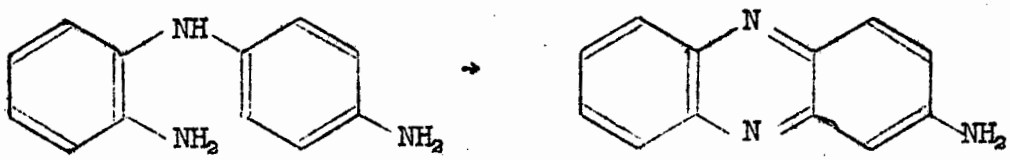
An attempt to recover the 2-aminophenazine left in solution was not very successful: after steam-distilling nitrobenzene under acid conditions, 2-aminophenazine (200 mg) was obtained on basification as a black ppt. which was very difficult to purify.

(ii) The yield of the reaction was not improved by adding Pd/C (300 mg) to the boiling nitrobenzene solution.

(iii) 2,4-Diaminodiphenylamine (from 2 g of 2,4-dinitrodiphenylamine) was refluxed in nitrobenzene (25 cc only) for 14.5 hrs. It was then filtered and cooled. A black amorphous substance separated out, but it was virtually impossible to filter.

Gray (loc. cit. p. 200) obtained only a 5% yield when refluxing 2,4-diaminodiphenylamine (from 1 g 2,4-dinitrodiphenylamine) in nitrobenzene (50 ml) for 4.5 hrs.

B. From 2,4'-diaminodiphenylamine.

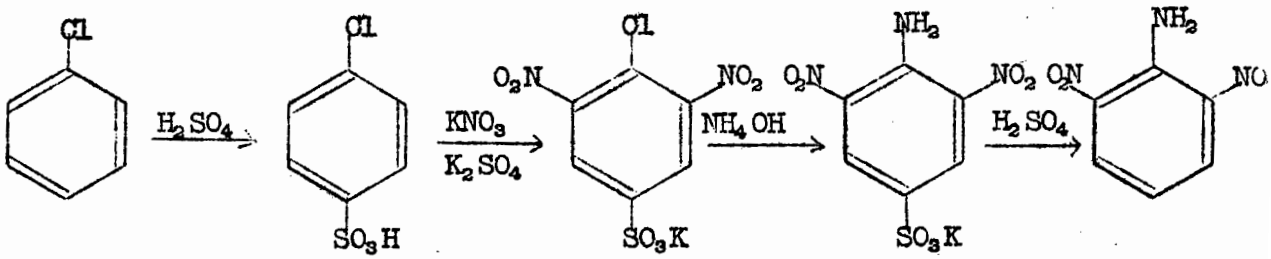


This is a slight modification of Gray's method (loc. cit., p. 199).

2,4'-Diaminodiphenylamine (from 1 g of 2,4'-dinitrodiphenylamine) was refluxed in nitrobenzene (125 cc) for 15 hrs. The solution was then reduced to 20 cc, filtered and cooled. 2-Aminophenazine was obtained in 50% yield as red needles, m. pt. 270 - 274°. No depression in the melting point was observed on admixture with a sample obtained from A.

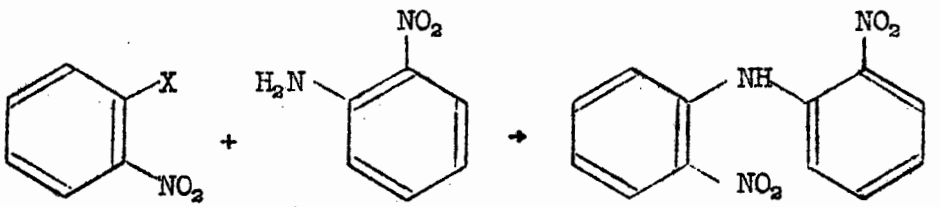
Preparation of 2,6-dinitroaniline

cf. Org. Syn., 31, 45.



A 27% yield of 2,6-dinitroaniline (based on chlorobenzene) was obtained, m. pt. 136 - 140°.

Preparation of 2,2'-dinitrodiphenylamine



X = Br, I and Cl.

cf. Eckert and Steiner, Monatsh. 35, 1153 (1914); through Chem. Zentr. I, 202 (1915).

Using these authors' method of heating o-bromonitrobenzene, o-nitroaniline, Na_2CO_3 and CuCl at 180° for 4 hrs., a 25% yield of 2,2'-dinitrodiphenylamine was obtained, m. pt. 167 - 169°.

However, a better yield and a purer product were obtained in a shorter reaction time by using o-iodonitrobenzene, o-nitroaniline (in slight excess), K_2CO_3 and Cu.

o-Iodonitrobenzene (2.5 g, 0.01 m), o-nitroaniline (2 g, 0.014 m), K_2CO_3 (2 g) and Cu powder (100 mg) were kept in an oil bath at 200° for 1 hr. (The reaction mixture was occasionally removed from the oil bath to allow the vigorous reaction to subside and to prevent sublimation of o-nitroaniline). The excess nitroaniline was then removed by steam-distillation and the remaining product filtered, dried and recrystallised from butyl alcohol to give 1.5 g (60%) of orange needles, m. pt. 170 - 171°.

The tedious steam-distillation can be avoided by using equimolar quantities of o-iodonitrobenzene and o-nitroaniline. A direct recrystallisation of the reaction mixture gave a 50% yield of product

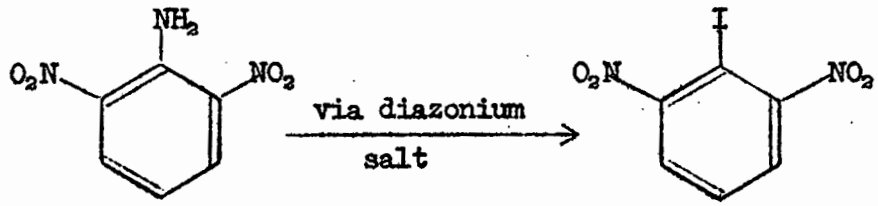
melting at 168 - 169°.

With equimolar quantities of o-chloronitrobenzene and o-nitroaniline and identical reaction conditions, the yield was only 4%. With o-bromonitrobenzene, the yield was 32%.

A recent Russian reference (Zhuravlev and Gritsenko, C.A. 52, 18274, 1958) claims to obtain better yield of diphenylamines with the acetyl derivative of the primary amine. This method fails completely when applied to o-iodonitrobenzene and o-nitroacetanilide, the starting materials being recovered unchanged.

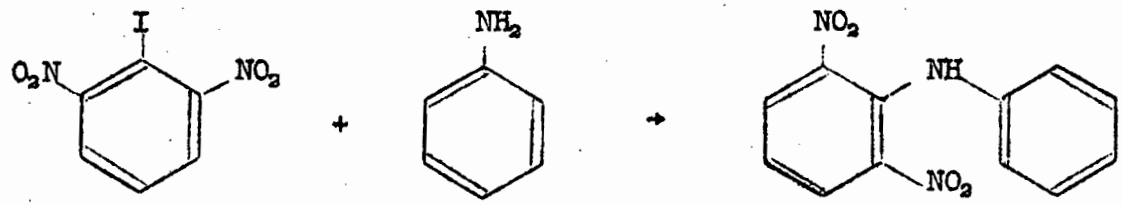
Synthesis of 1-aminophenazine

(1) Preparation of 2,6-dinitroiodobenzene.



The procedure described by Gray (loc. cit., p. 161) was followed. Yield: 83%. M. pt. 110 - 115° (needles from dil. alcohol).

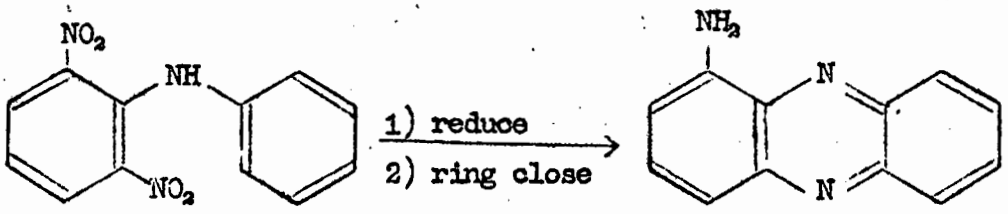
(2) Preparation of 2,6-dinitrodiphenylamine.



cf. W. Borsche and D. Rantscheff, Ann. 379, 167 (1911).

2,6-Dinitroiodobenzene (4.5 gms), aniline (3 gms) and sodium acetate (5 gms) were refluxed in alcohol (60 ccs) for 16 hrs. The red ppt. obtained on cooling was filtered, washed well with water and dried. 3.1 Gms. (79% yield) of 2,6-dinitrodiphenylamine were obtained, m. pt. 103 - 104°. Recrystallisation from dil. acetic acid gave red needles, m. pt. 104 - 106°.

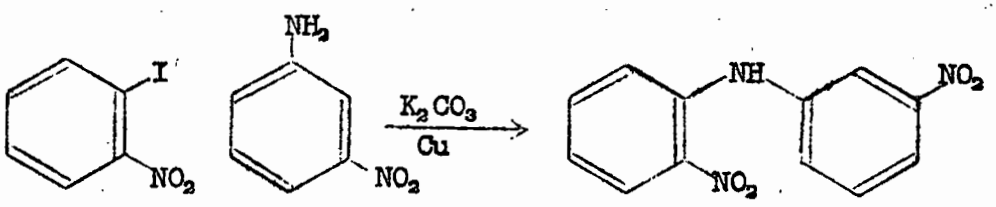
(3) Synthesis of 1-aminophenazine.



2,6-Diaminodiphenylamine (from 1 g of 2,6-dinitrodiphenylamine) was refluxed for 9 hrs. in nitrobenzene (25 cc), containing Pd/C (300 mg). 5 N HCl (40 cc) was added to the cooled solution and the nitrobenzene steam-distilled. The blue-green solution was filtered, cooled and made alkaline. The red ppt. of 1-aminophenazine was collected, washed with water and dried. 360 Mg were obtained, m. pt. 140 - 160°. After one recrystallisation from dil. alcohol, red needles (170 mg) (25% yield) were obtained, m. pt. 174 - 176°.

The m. pt. of 1-aminophenazine is given as 175 - 176° by Albert and Duewell (J. Soc. Chem. Ind., London, 66, 11, 1947), 179 - 181° by Hegedüs (Helv. Chim. Acta, 33, 766, 1950).

Preparation of 2:3'-dinitrodiphenylamine



cf. Evans and Smiles (J.C.S., 187, 1935).

(i) o-Nitroiodobenzene (1.25 g), m-nitroaniline (0.7 g), K_2CO_3 (0.7 g) and Cu powder (100 mg) were thoroughly mixed in a mortar and heated in an oil-bath at 200° for 5 mins. The residue was then refluxed with butyl alcohol (20 cc), filtered, charcoaled, boiled for a few minutes and re-filtered. On cooling, 2,3'-dinitrodiphenylamine, orange needles, was obtained (200 mg, 16% yield), m. pt. 152 - 156°. Recrystallisation from dil. acetic raised the m. pt. to 156 - 157°.

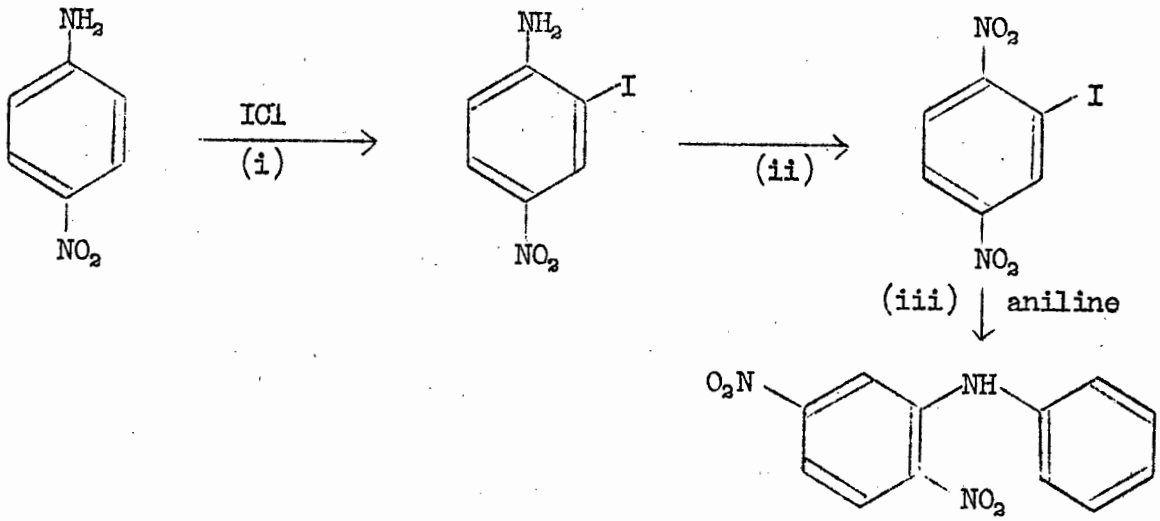
Evans and Smiles used o-bromonitrobenzene, but did not give the yield of the reaction.

(ii) A longer reaction time (4.5 or 7 hrs.) and sodium acetate instead of K_2CO_3 did not improve the yield. Steam-distillation before recrystallisation from butyl alcohol had no effect on the yield.

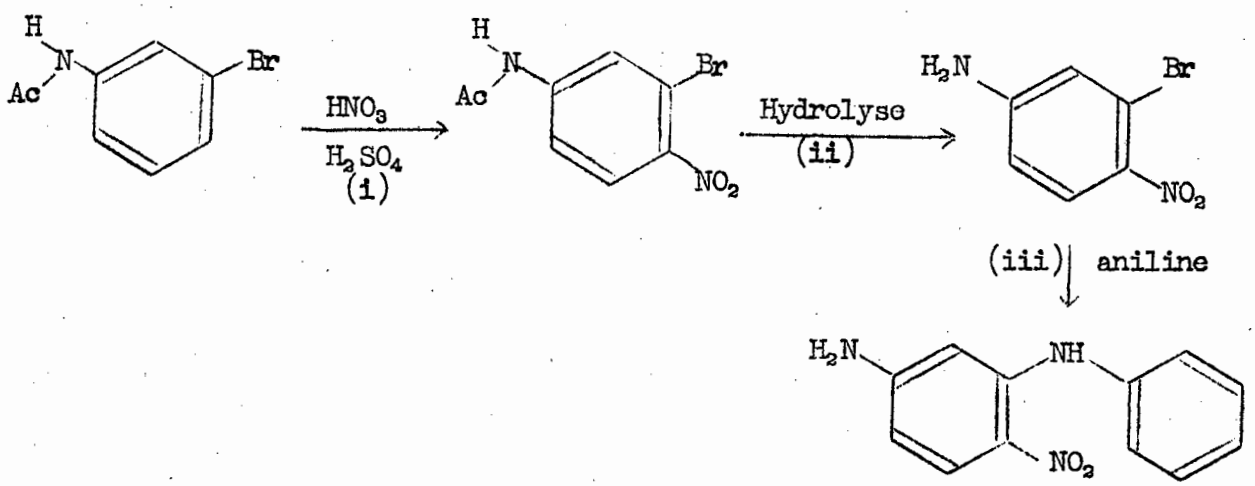
Attempted preparation of 2,5-diaminodiphenylamine

Two routes were tried for the preparation of this compound, which was required to study the effect of an amino group in the 5 position on the rate of ring closure of the 2-amino group.

Method I



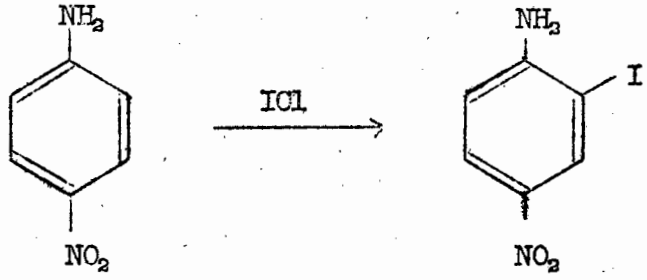
Method II



However, method I got no further than step (ii), when several attempts at replacing the NH_2 group by an NO_2 group (via diazotisation) failed; method II broke down on step (iii), when the condensation of 3-bromo-4-nitroaniline with aniline gave a number of products, none of which on reduction and ring closure (in boiling nitrobenzene) gave the expected 2-aminophenazine.

Method I

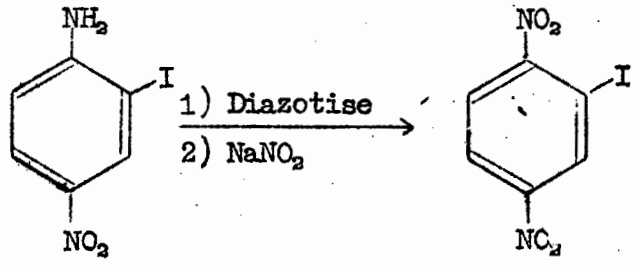
(i) Preparation of 2-iodo-4-nitroaniline



cf. Willegerodt and Arnold, Ber., 34, 3344 (1901).

A 70% yield of 2-iodo-4-nitroaniline was obtained, m. pt. 103 - 105°.

(ii) Attempted preparation of 2,5-dinitroiodobenzene



(a) This attempt was modelled on Körner and Contardi's preparation of 2,5-dinitrochlorobenzene [C.A. 8, 3020 (1914)].

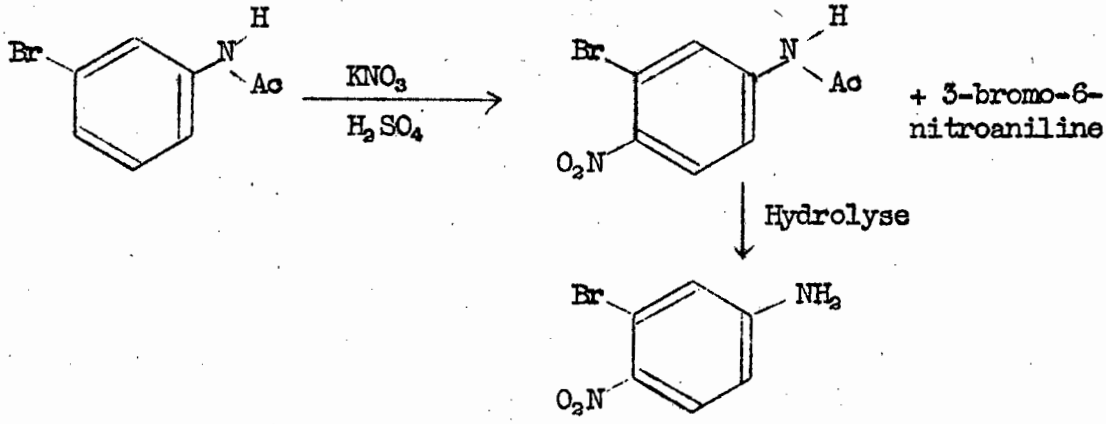
2-Iodo-4-nitroaniline (0.52 g) was dissolved in concentrated H_2SO_4 (5 cc) and H_2O (3 cc) and cooled to 5°C. $NaNO_2$ (0.15 g) in H_2O (5 cc) was then added slowly and the solution stirred until the diazotisation appeared to be complete. The solution was then added dropwise on to $NaNO_2$ (1 g) and $CuSO_4$ (1 g) in H_2O (10 cc). After warming on the water-bath for 30 min., cooling and filtering, a very small amount of unchanged starting material was obtained.

(b) The method described by Hodgson and Walker [J.C.S., 1620, (1933)] for the diazotisation of nitroamines was also tried.

A solution of 2-iodo-4-nitroaniline (0.52 g) in glacial acetic acid (10 cc) was added dropwise on to a cooled, stirred solution of $NaNO_2$ (0.2 g) in concentrated H_2SO_4 (2 cc). The mixture was then added to $NaNO_2$ (1 g) in water (10 cc), and the resulting solution warmed on the water-bath for 2 hrs. A very small amount of gummy material was obtained. This was not investigated any further.

Method II

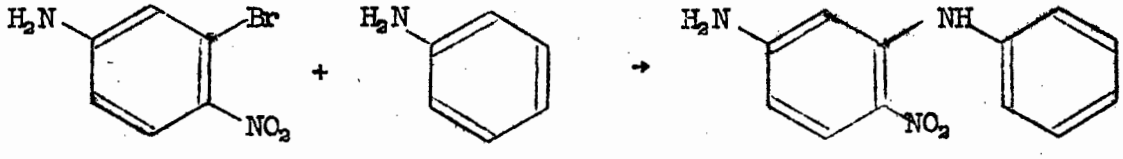
(i) Preparation of 3-bromo-4-nitroaniline



cf. Case and Solviter, J.A.C.S., 59, 2382 (1937).

A 40% yield of 3-bromo-4-nitroaniline was obtained, m. pt. 170 - 173°.

(ii) Attempted preparation of 5-amino-2-nitrodiphenylamine

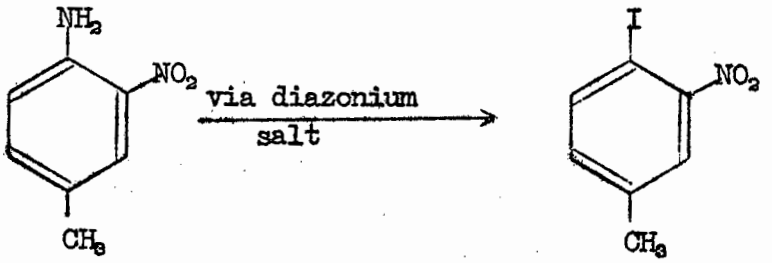


3-Bromo-4-nitroaniline (1.1 g), aniline (2 g) and sodium acetate (1.6 g) were kept at 180 - 185° for 4 hrs. Steam-distillation (to remove excess aniline) left a gummy residue which was taken up in benzene and chromatographed over alumina. There appeared 4 broad bands, none of which being the desired product (cf. p.

The use of K_2CO_3 (instead of NaAc) gave the same result, and the addition of Cu powder resulted in charring.

Preparation of 4-methyl-2,4'-dinitrodiphenylamine

(1) Preparation of 4-iodo-3-nitrotoluene

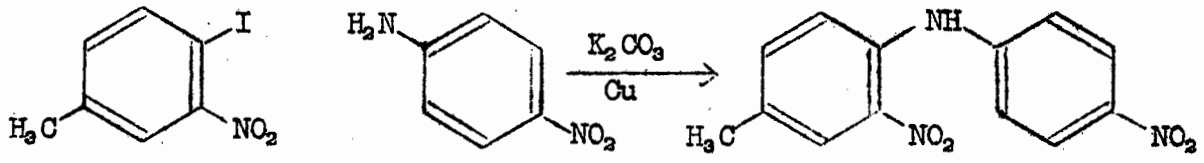


cf. Wheeler, Am. Chem. J., 44, 139 (1910).

4-Amino-3-nitrotoluene (15 g) was dissolved in a mixture of concentrated sulphuric acid (150 cc) and water (100 cc) and diazotised at 5 - 10° by the slow addition of sodium nitrite (10 g) in water (50 cc). The solution was then stirred for 15 mins. to ensure complete formation of the diazonium salt. Excess nitrite was destroyed by the addition of urea. The solution was added dropwise to KI (20 g) in water (200 cc) and then warmed on a water-bath for 30 mins. to ensure completeness of the reaction. The solution was cooled and the precipitated 4-iodo-3-nitrotoluene collected and recrystallised from dil. alcohol. 20.5 G were obtained (76 %

yield) of m. pt. 53 - 55°. Wheeler quotes a m. pt. of 55 - 56°.

(2) Preparation of 4-methyl-2,4'-dinitrodiphenylamine



(a) 4-Iodo-3-nitrotoluene (1.3 g; 0.05m.), p-nitroaniline (0.7 g; 0.05 m.), K_2CO_3 (1 g) and Cu powder (50 mg) were thoroughly mixed in a mortar and then heated to 200 - 210° for 18 hrs. The resulting solid was refluxed with butyl alcohol (35 cc), filtered and cooled. 0.7 G (50% yield) of orange microcrystals were obtained, m. pt. 186 - 190°. Repeated recrystallisations from butanol raised the m. pt. to 189 - 190°.

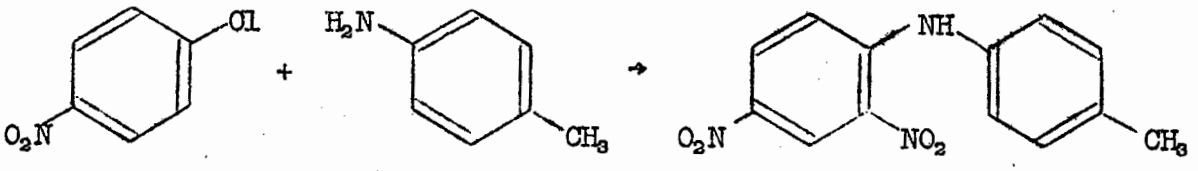
Analysis

$C_{13}H_{11}N_3O_4$ requires:	Found:
C = 57.1%	C = 57.1%
H = 4.06%	H = 4.05%
N = 15.4%	N = 15.8%.

(b) The reaction was repeated with a reaction time of 15 mins. The yield in this case was 0.9 g (64% of the theoretical yield).

(c) A slight excess of p-nitroaniline (1 g; 0.07 m.) did not alter the yield (64%).

Preparation of 4'-methyl-2,4 dinitrodiphenylamine



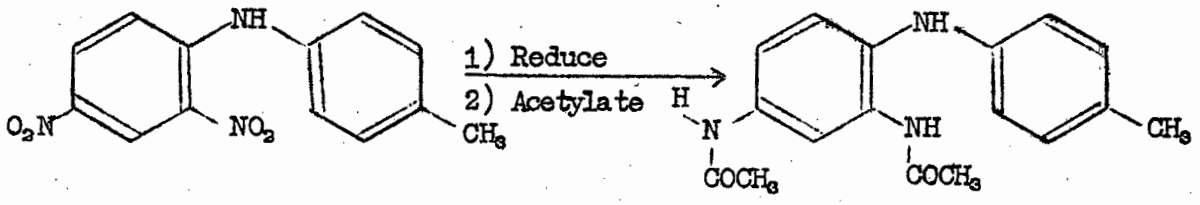
cf. Willgerodt, Ber., 9, 980 (1876).

2,4-Dinitrochlorobenzene (10 g), p-toluidine (6 g) and sodium acetate (5 g) were refluxed in alcohol (100 cc) for 5 hours. After cooling, filtering, washing with water and recrystallising from dil. acetic acid, 11 g were obtained (85% yield), m. pt. 133 - 135°.

Synthesis of 2-amino-8-methylphenazine

(A) From 2,4-diamino-4'-methyldiphenylamine

(1) Preparation of 2,4-diacetamido-4'-methyldiphenylamine



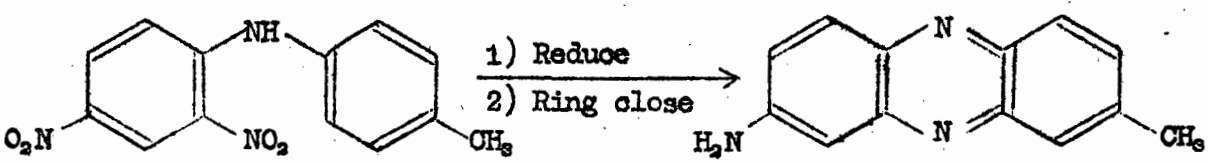
2,4-Dinitro-4'-methyldiphenylamine (1 g) was reduced with PtO_2 (50 mg) in abs. alcohol (50 cc) at a H_2 pressure of 35 lbs/sq. in. The colourless solution was then filtered and the alcohol evaporated under reduced pressure in a nitrogen atmosphere. A mixture of acetic acid (10 cc)

and acetic anhydride (10 cc) was added to the black residue and the solution allowed to stand for 5 hrs. The solution was then poured into water and the ppt. collected. 400 Mg (40% yield) of 2,4-diacetamido-4'-methyldiphenylamine were obtained, m. pt. 186 - 188°. Recrystallisation from dil. alcohol gave white needles, m. pt. 195 - 196°.

Analysis

$C_{17}H_{19}N_3O_2$ requires:	Found:
C = 68.7%	C = 69.1%
H = 6.44%	H = 6.52%
N = 14.1%	N = 13.9%

(2) Preparation of 2-amino-8-methylphenazine



(i) 2,4-Diamino-4'-methyldiphenylamine (from 2 g of 4'-methyl-2,4-dinitrodiphenylamine) was refluxed in nitrobenzene (250 cc) for 12 hrs. After reducing the volume to ca. 25 cc by distilling nitrobenzene under reduced pressure, filtering and cooling, 2-amino-8-methylphenazine (800 mg, 52% yield) was obtained as red needles, m. pt. 227 - 230°. Recrystallisation from dil. alcohol gave red needles, m. pt. 228.5 - 230°.

2-Amino-8-methylphenazine is very soluble in butyl alcohol and hot ethyl alcohol, insoluble in cold water, slightly soluble in chloroform and ether, fairly soluble in benzene and toluene.

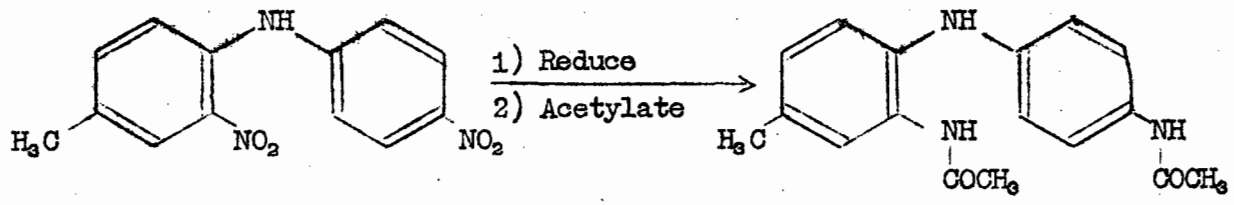
Analysis

$C_{13}H_{11}N_3$ requires:	Found:
C = 74.6%	C = 75.3%
H = 5.30%	H = 5.32%
N = 20.1%	N = 19.6%.

(ii) 4'-Methyl-2,4-dinitrodiphenylamine (1 g) was reduced by refluxing with hydrazine (1 cc of a 95% solution) Pd charcoal (300 mg) in abs. alcohol (50 cc) until the solution became colourless. The solution was then filtered free of catalyst and poured into nitrobenzene (25 cc). The alcohol and the hydrazine were boiled off, a fresh portion of Pd/C added (300 mg) and the solution refluxed for 8 hrs. 5 N HCl (40 cc) was then added and the nitrobenzene removed by steal distillation. The deep purple solution was neutralised with NaOH and on cooling, 2-amino-8-methylphenazine (350 mg, 45% yield) was obtained, m. pt. 223 - 226°. Vac. sublimation raised the m. pt. to 229 - 230°.

(B) From 2,4'-diamino-4-methyldiphenylamine

(1) Preparation of 2,4'-diacetamido-4-methyldiphenylamine



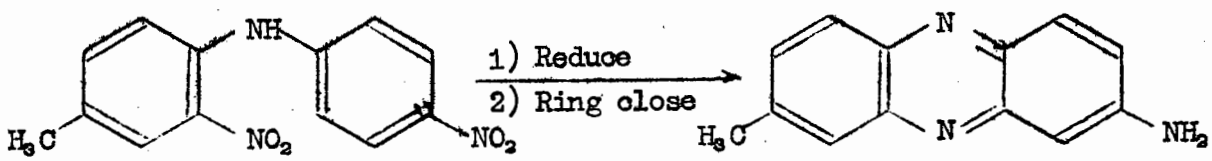
2,4'-Dinitro-4-methyldiphenylamine (1 g) was reduced with PtO_2 (50 mg) in abs. alcohol (50 cc) at a H_2 pressure of 40 lbs./sq. in. The colourless

solution was then filtered and the alcohol evaporated under reduced pressure in nitrogen. A mixture of acetic acid (10 cc) and acetic anhydride (10 cc) was added to the residue and the solution warmed slightly to dissolve the amine. White crystals soon separated out. After letting the solution stand at room temperature for 2 hrs., it was poured into water, allowed to cool for some time and then filtered. This gase 2,4'-diacetamido-4-methyldiphenylamine (0.7 g, 70% yield), m. pt. 224 - 226°. Recrystallisation from dil. alcohol gave fine white needles, m. pt. 232 - 234°.

Analysis

$C_{17}H_{19}N_3O_2$ requires:	Found:
C = 68.7%	C = 68.6%
H = 6.44%	H = 6.44%
N = 14.1%	N = 14.0%

(2) Preparation of 2-amino-8-methylphenazine



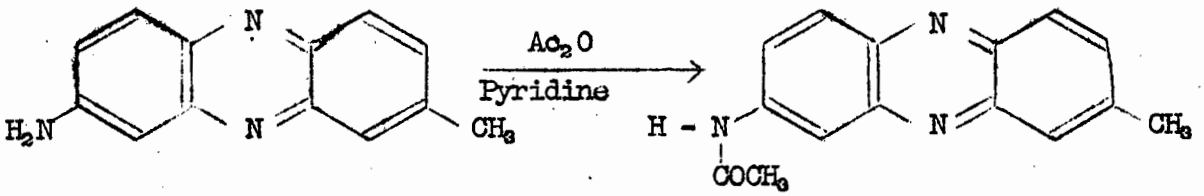
(i) 2,4'-Diamino-4-methyldiphenylamine (from 1 g of 4-methyl-2,4'-dinitrodiphenylamine) was refluxed in nitrobenzene (125 cc) for 12 hrs. The volume was then reduced to 15 cc by distilling off nitrobenzene under reduced pressure. After filtering and cooling, 2-amino-8-methylphenazine was obtained (350 mg, 47% yield) as red needles, m. pt.

227 - 230°. Recrystallisation from dil. alcohol gave red needles, m. pt. 228.5 - 230°.

Mixed m. pt. with a sample prepared from 2,4-diamino-4'-methyldiphenylamine: 228 - 230°.

(ii) 2,4'-Diamino-4-methyldiphenylamine (from 400 mg of 4-methyl 2,4'-dinitrodiphenylamine) was refluxed for 8 hrs. in nitrobenzene (25 cc) containing Pd/C (200 mg). After cooling the solution, 5 N HCl (20 cc) was added and the nitrobenzene steam-distilled. The deep purple solution was filtered and neutralised with NaOH. 2-Amino-8-methylphenazine (130 mg, 47% yield) was obtained, m. pt. 210 - 218°. Recryst. from dil. alcohol gave red needles, m. pt. 227 - 230°.

Preparation of 2-acetamido-8-methylphenazine



2-Amino-8-methylphenazine (750 mg) was dissolved in acetic anhydride (20 cc) and pyridine (1 cc) and the solution kept in a boiling water-bath. Yellow needles began to separate after a few minutes. Warming was continued for 45 min. The solution was then cooled and poured into water. 2-Acetamido-8-methylphenazine was obtained (550 mg, 61% yield), m. pt. 212 - 214°. Recrystallisation from dil. alcohol gave yellow needles, m. pt. 218.5 - 219°.

Analysis

$C_{15}H_{13}N_3O_3,H_2O$ requires:	Found:
C = 66.9%	C = 66.8%
H = 5.6%	H = 6.8%
N = 15.6%	N = 14.9%.

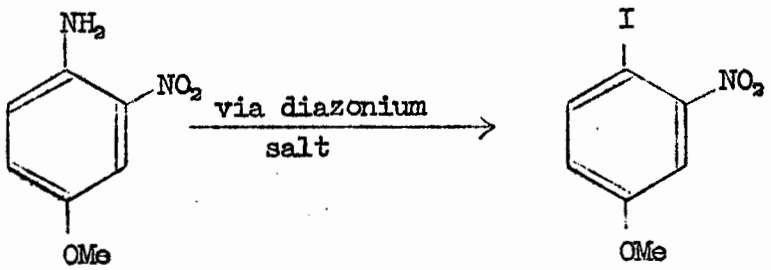
The high value obtained for hydrogen was surprising in view of the good agreement for C and N. However, a sample recrystallisation from toluene gave the correct value for H but a low C and N%.

Analysis

$C_{15}H_{13}N_3O$ requires:	Found:
C = 71.7%	C = 70.0%
H = 5.2%	H = 5.35%
N = 16.7%	N = 15.7%.

Preparation of 4-methoxy-2,4'-dinitrodiphenylamine

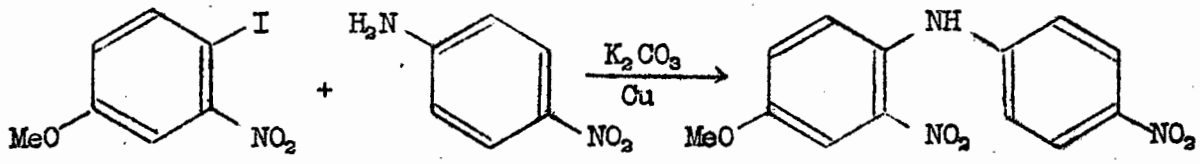
(a) Preparation of 4-methoxy-2-nitroiodobenzene



cf. Reverdin, Ber., 29, 2595 (1896).

A 60% yield of 4-methoxy-2-nitroiodobenzene was obtained, m. pt. 58 - 61° (from cyclohexane).

(b) Preparation of 4-methoxy-2,4'-dinitrodiphenylamine



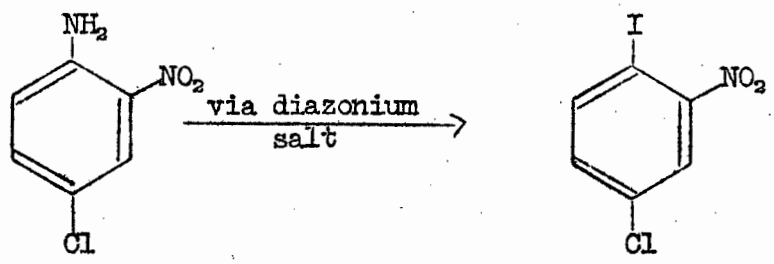
4-Methoxy-2-nitroiodobenzene (2.7 g), p-nitroaniline (1.4 g), K_2CO_3 (2 g) and freshly reduced Cu (0.2 g) were thoroughly mixed in a mortar. The resulting mixture was vigorously shaken up in nitrobenzene (20 ml) and kept at 150 - 170° for 10 hrs. 5 N HCl (20 cc) was added to the cooled mixture and the nitrobenzene steam-distilled. A dark red product (1.5 g) was thus obtained which, on recrystallisation from dil. acetic, gave 4-methoxy-2,4'-dinitrodiphenylamine (100 mg) as red, silky needles, m. pt. 164 - 168°. Further recrystallisations from dil. acetic acid raised the m. pt. to 168 - 170°.

Analysis

$C_{13}H_{10}N_3O_5$ requires:	Found:
C = 54.0%	C = 54.3%
H = 3.81%	H = 3.79%
N = 14.5%	N = 14.1%.

Preparation of 4-chloro-2,4'-dinitrodiphenylamine

(1) Preparation of 4-chloro-2-nitroiodobenzene

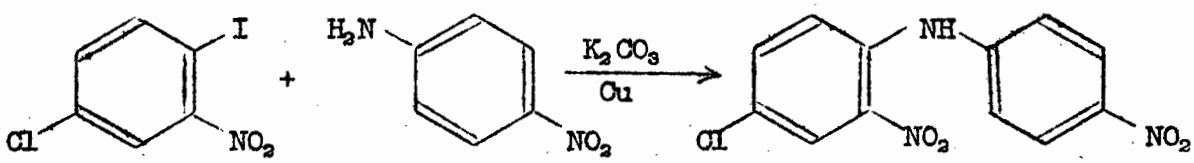


cf. Körner, Gazz. Chim. Ital., 4, 382 (1874).

The procedure described for the preparation of 4-iodo-3-nitrotoluene was followed. A quantative yield of crude 4-chloro-2-nitroiodobenzene was obtained. This product could be conveniently purified by dissolving in alcohol, charcoaling, filtering and then adding a sufficient quantity of water to the cold solution to precipitate most of the product. The 4-chloro-2-nitroiodobenzene thus obtained (m. pt. 60 - 63°) is pure enough for the subsequent reaction.

(2) Preparation of 4-chloro-2,4'-dinitrodiphenylamine

(a)



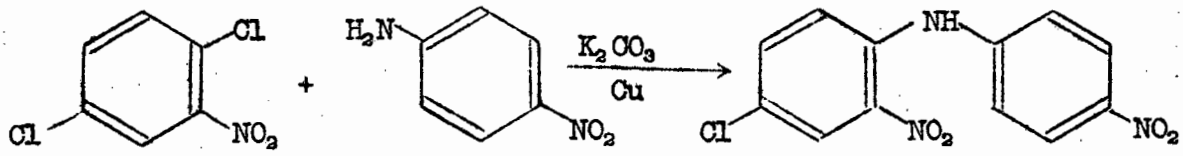
4-Chloro-2-nitroiodobenzene (1.4 g), p-nitroaniline (0.7 g), K_2CO_3 (1 g) and Cu powder (50 mg) were thoroughly mixed in a mortar and heated at 200° for 15 min. The resulting mixture was refluxed with butyl alcohol

(35 cc) and then filtered. 0.7 G (50% yield) were obtained on cooling, m. pt. 189 - 192°. Recrystallisation from butanol gave orange needles, m. pt. 191 - 192°.

Analysis

$C_{12}H_8ClN_3O_4$ requires:	Found:
C = 49.1%	C = 49.1%
H = 2.75%	H = 2.79%
N = 14.3%	N = 14.05%

(b)

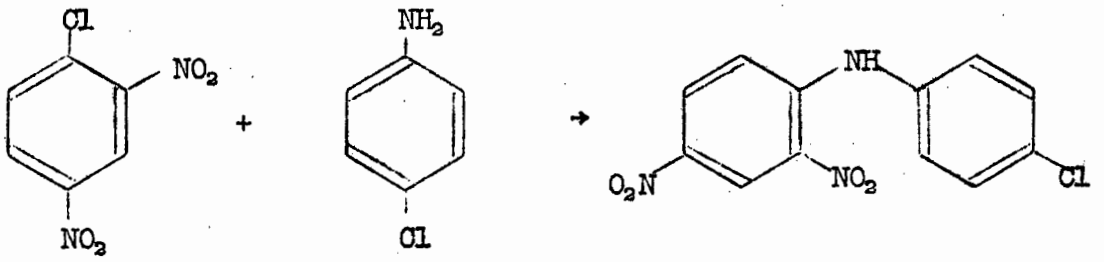


(i) 2,5-Dichloronitrobenzene (19 g), p-nitroaniline (14 g), K_2CO_3 (20 g) and Cu powder (100 mg) were heated together at 190° for 10 hrs. The resulting black mixture was treated with hot HCl-ethanol, filtered and then steam distilled. The resulting product was extracted with boiling benzene and the benzene subsequently evaporated off. 12 G of dark red product were obtained which could not be satisfactorily purified by recrystallisation (m. pt. 180 - 184°).

(ii) 2,5_Dichloronitrobenzene (1.9 g), p-nitroaniline (1.4 g), K_2CO_3 (2 g) and Cu powder (100 mg) were kept at 200° for 1 hr. The solid obtained was treated with boiling butyl alcohol and filtered. 0.6 G

(22% yield) were obtained on cooling, m. pt. 186 - 189°.

Preparation of 4'-chloro-2,4-dinitrodiphenylamine



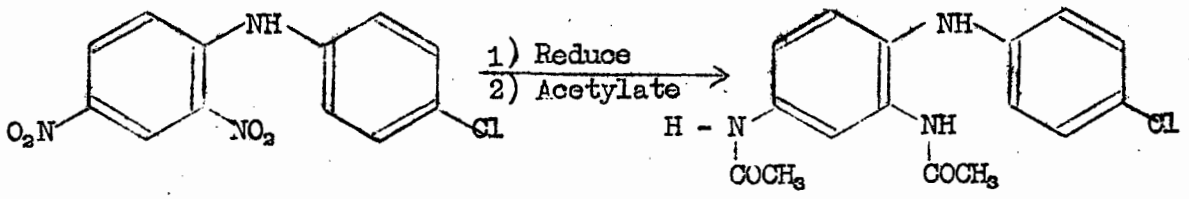
cf. Blom, Helv. Chem. Acta, 4, 1036 (1921).

2,4-Dinitrochlorobenzene (10 g) and p-chloroaniline (6.3 g) were refluxed in butyl alcohol (100 cc) for 2 hrs. On cooling, 4'-chloro-2,4-dinitrodiphenylamine (6.5 g) was obtained (45% yield), m. pt. 163 - 164°.

Synthesis of 2-amino-8-chlorophenazine

A. From 2,4-diamino-4'-chlorodiphenylamine

(1) Preparation of 2,4-diacetamido-4'-chlorodiphenylamine



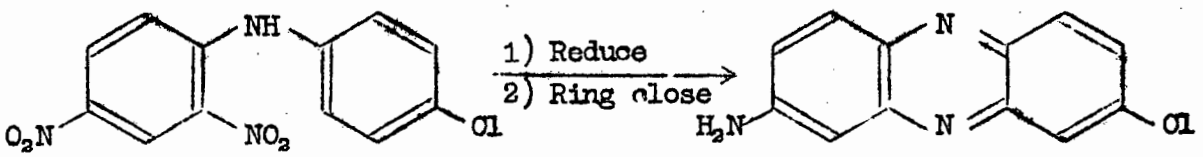
4'-Chloro-2,4-dinitrodiphenylamine (1 g) was reduced with PtO_2 (50 mg) in absolute alcohol (50 cc). When the reduction was complete, the solution was filtered, the alcohol evaporated under reduced pressure (in a N_2

atmosphere) and the residue acetylated with acetic anhydride (10 cc) and glacial acetic acid (10 cc). The solution was kept at room temperature for 4 hrs. It was then poured into water and the white ppt. was collected. 0.8 G were obtained (80%) yield), m. pt. 208 - 212. Recrystallisations from dil alcohol raised the m. pt. to 220 - 222°.

Analysis

$C_{16}H_{16}N_3ClO_2$ requires:	Found:
C = 60.5%	C = 60.2%
H = 5.04%	H = 4.93%
N = 13.2%	N = 13.2%

(2) Preparation of 2-amino-8-chlorophenazine



(i) 2,4-Diamino-4'-chlorodiphenylamine (from 2 g of 4'-chloro-2,4-dinitrodiphenylamine) was refluxed in nitrobenzene for 13.5 hrs. Nitrobenzene was then distilled under reduced pressure until the volume was reduced to 25 cc. This solution was then boiled at atmospheric pressure and filtered. Amorphous 2-amino-8-chlorophenazine (650 mg, 45% yield) was obtained on cooling, m. pt. 238 - 244°. Recrystallisation from dil. alcohol gave red needles, m. pt. 250 - 251°. Otomasu[75] quotes a m. pt. of 251°.

(ii) The above procedure was repeated with the same quantities of material, but Pd/C (300 mg) was added to the $PhNO_2$ after boiling off the alcohol. On working up the reaction mixture in identical fashion, amorphous 2-amino-8-chlorophenazine (810 mg, 55% yield) was obtained, m. pt. 247.5 - 249°. Recrystallisation from dil. alcohol gave red needles, m. pt. 250 - 251°.

Analysis:

The analysis showed that 2-amino-8-chlorophenazine, when recrystallised from dil. alcohol, has half a molecule of water of recrystallisation.

$C_{12}H_8N_3Cl.\frac{1}{2}H_2O$ requires:	Found:
C = 60.4%	C = 60.5%
H = 3.81%	H = 3.88%
N = 17.6%	N = 17.6%

Calculated loss in weight: 3.77%.

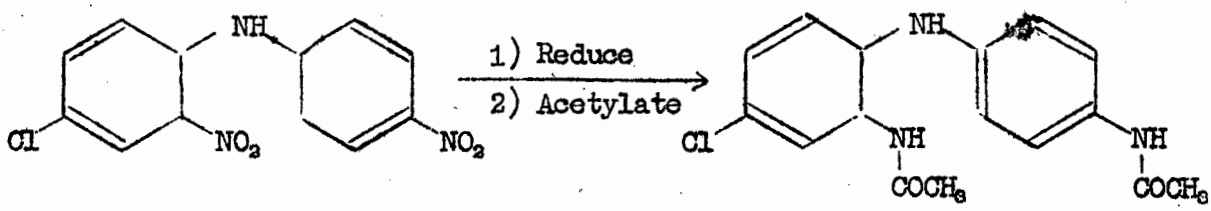
Found after drying in vacuo at 100° for 2 hrs.: 3.78%.

$C_{12}H_8N_3Cl$ requires:	Found:
C = 62.7%	C = 62.4%
H = 3.51%	H = 3.24%
N = 18.3%	N = 18.7%

(iii) 2,4-Diamino-4'-chlorodiphenylamine (from 1 g of 4'-chloro-2,4-dinitrodiphenylamine) was refluxed in $PhNO_2$ (25 cc) and Pd/C (300 mg). After 9 hrs. refluxing, the $PhNO_2$ was steam-distilled under acid conditions (40 cc 5 N HCl added). On neutralisation, 2-amino-8-chlorophenazine (150 mg, 20% yield) was obtained, m. pt. 239 - 243°.

B. From 2,4'-diamino-4-chlorodiphenylamine

(1). Preparation of 2,4'-diacetamido-4-chlorodiphenylamine



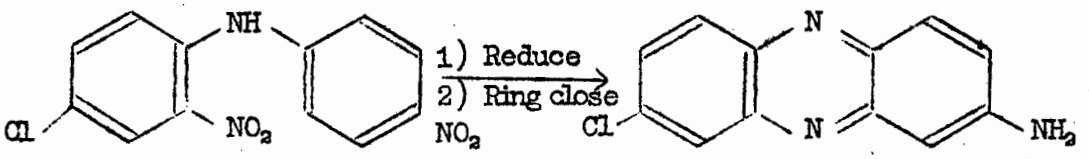
4-Chloro-2,4'-dinitrodiphenylamine (1 g) was reduced with PtO_2 (100 mg) in abs. alcohol (50 cc) at a H_2 pressure of 40 lbs./sq. in. When the reduction was complete the solution was filtered, the alcohol evaporated under reduced pressure (in a N_2 atmosphere) and the residue acetylated with acetic anhydride (10 cc) and glacial acetic acid (10 cc). White crystals began to separate almost immediately. The mixture was kept at room temperature for 4 hrs. It was then poured into water, cooled and filtered. A quantitative yield of 2,4'-diacetamido-4-chlorodiphenylamine was obtained, m. pt. 224 - 229°. Recrystallisation from dil. alcohol gave white needles, m. pt. 239 - 241°.

Analysis

$C_{16}H_{16}N_3ClO_2$ requires:	Found:
C = 60.5%	C = 60.4%
H = 5.04%	H = 5.12%
N = 13.2%	N = 13.0%

N.B. The reduction was found to proceed extremely slowly when only 50 mg of PtO_2 were used, but went fairly quickly with 100 mg.

(2) Preparation of 2-amino-8-chlorophenazine



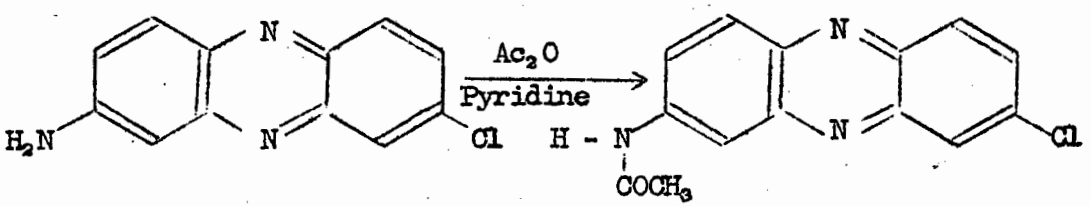
(i) 2,4'-Diamino-4-chlorodiphenylamine (from 1 g of 4-chloro-2,4'-dinitrodiphenylamine) was refluxed in nitrobenzene (125 cc) for 13 hrs.

The volume was then reduced to 10 cc by distilling the nitrobenzene under reduced pressure. After filtering and cooling 2-amino-8-chlorophenazine (220 mg, 30% yield) was obtained, m. pt. 240 - 246°. Recrystallisation from dil. alcohol gave red needles, m. pt. 246 - 249°.

Mixed m. pt. with a sample prepared from 2,4-diamino-4'-chlorodiphenylamine: 247 - 249°.

(ii) 2,4'-Diamino-4-chlorodiphenylamine (from 1 g of 4-chloro-2,4'-dinitrodiphenylamine) refluxed in $PhNO_2$ (25 cc). After 11 hrs. refluxing, the nitrobenzene was steam-distilled under acid conditions (40 cc 5 N HCl were added). On neutralisation with NaOH a red ppt. of 2-amino-8-chlorophenazine was obtained (200 mg, 26% yield), m. pt. 210 - 225°. Recrystallisation from dil. alcohol gave red needles, m. pt. 246 - 249°.

Preparation of 2-acetamido-8-chlorophenazine



2-Amino-8-chlorophenazine (500 mg) was heated with acetic anhydride (15 cc) and pyridine (few drops) in a boiling water-bath for 45 mins. On cooling and pouring on to ice, 2-acetamido-8-chlorophenazine (500 mg, 85% yield) was obtained, m. pt. 250 - 254°. Recrystallisation from dil. alcohol gave yellow needles, m. pt. 253 - 255°. Otomasu[75] quotes a m. pt. of 255°.

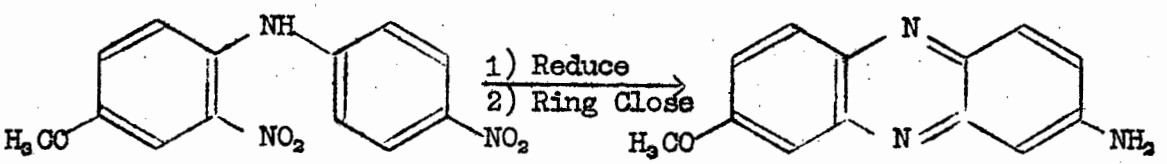
Analysis

The analysis showed that 2-acetamido-8-chlorophenazine, when recrystallised from dil. alcohol, has one molecule of water of recrystallisation.

$C_{14}H_{10}N_3ClO.H_2O$ requires:	Found:
C = 58.1%	C = 58.4%
H = 4.17%	H = 4.35%
N = 14.5%	N = 14.4%.

Preparation of 2-amino-8-methoxyphenazine

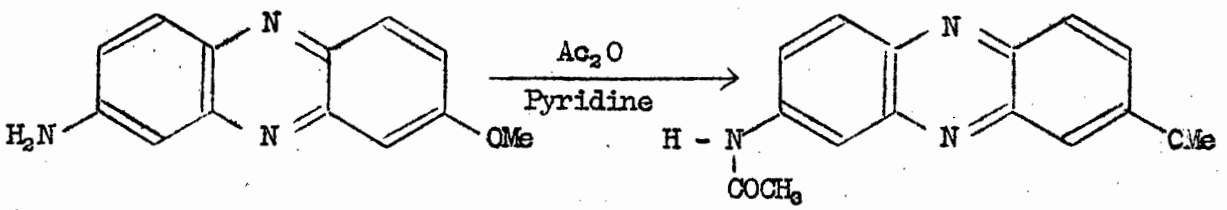
From 4-methoxy-2,4'-dinitrodiphenylamine



2,4'-Diamino-4-methoxydiphenylamine (from 500 mg of 4-methoxy-2,4'-dinitrodiphenylamine) was refluxed in nitrobenzene (30 cc) for 4 hrs., 5 N HCl (20 cc) was then added and the nitrobenzene steam-distilled.

On making alkaline, 2-amino-8-methoxyphenazine was obtained as a dirty yellow ppt. (300 mg), m. pt. 203 - 215°, which on recryst. from dil. alcohol gave orange needles, m. pt. 216 - 218° (200 mg, 54% yield). A mixed m. pt. with a sample prepared from 2,4-diamino-4'-methoxydiphenylamine gave no depression in the m. pt.

Preparation of 2-acetamido-8-methoxyphenazine.

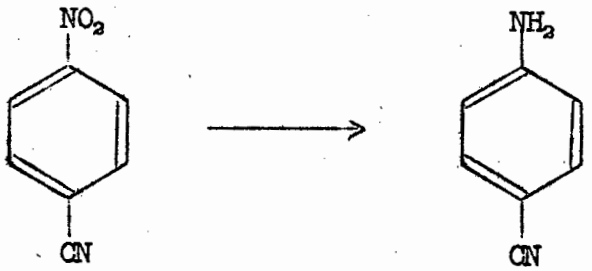


2-Amino-8-methoxyphenazine (200 mg) was dissolved in acetic anhydride (8 cc) and pyridine (4 cc) and heated in a boiling water-bath for 45 mins. After cooling and pouring into cold water, 220 mg (93% yield) of a dirty yellow ppt. were obtained, m. pt. 260 - 264°. Recrystallisation from dil. alcohol gave yellow needles, m. pt. 262.5 - 264°.

Analysis

Calculated for $C_{15}H_{13}N_3O$:	Found:
C = 67.4%	C = 67.5%
H = 4.85%	H = 4.86%

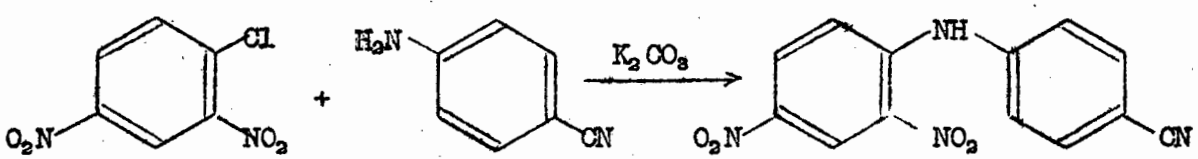
Preparation of p-aminobenzonitrile



p-Nitrobenzonitrile (500 mgm) was reduced in alcohol (30 cc) with PtO_2 (100 mg) at a H_2 pressure of 40 lbs./sq. in. The reduction was complete in 20 min. The colourless solution was filtered, the alcohol evaporated under reduced pressure and the gummy residue recrystallised from water to give 150 mg (38%) of white needles of p-aminobenzonitrile, m. pt. 84 - 85.5°. Heilbron and Bunbury (Dictionary of Org. Comp.) quote the m. pt. as 86°.

On a larger scale (5 g of p-nitrobenzonitrile), the yield was only 15%.

Preparation of 4'-cyano-2,4-dinitrodiphenylamine



2,4-Dinitrochlorobenzene (1 g), p-aminobenzonitrile (0.6 g), potassium carbonate (0.7 g) and Cu powder (50 mg) were kept at 150° for 30 min., the reaction mixture being occasionally removed from the oil-bath

when the reaction became too vigorous. The temperature was then raised to 180° for 2 min. to ensure completeness of reaction.

Treating the product with 5 N HCl was followed by recrystallisation from dil. acetic acid which gave 500 mg (36% yield) of yellow microneedles. These were further recrystallised from butyl alcohol (leaflets) to a m. pt. of 190 - 191°.

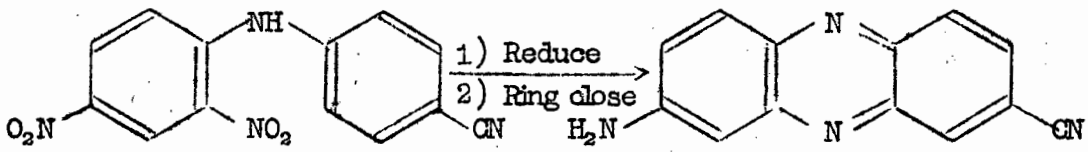
Analysis

$C_{13}H_8N_4O_4$ requires:	Found:
C = 54.9%	C = 54.8%
H = 2.8%	H = 3.1%
N = 19.7%	N = 19.5%.

N.B. When KF (0.6 g) was used instead of K_2CO_3 (Vorozhtsov and Yakabson's[61] method), 350 mg of a product melting at 240 - 245° (red needles from dil. acetic acid) was obtained. The analysis (C = 69.2%, H = 3.5%) showed that this was not the required diphenylamine.

When sodium acetate (0.8 g) was used and the reaction carried out in ethyl alcohol (refluxed for 5 hrs), 440 mg of red needles, m. pt. 190-230°, were obtained. The wide range of the m. pt. suggested that a mixture of the above mentioned products was obtained.

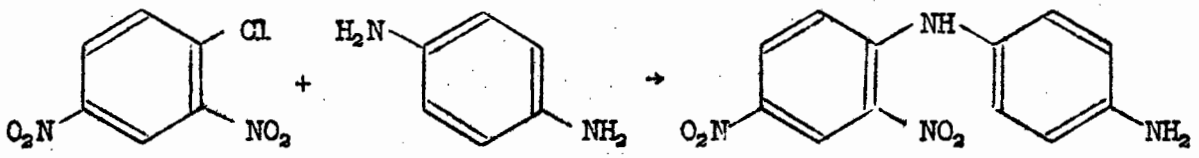
Synthesis of 2-amino-8-cyanophenazine



2,4-Diamino-4'-cyanodiphenylamine (from 109 mg of 4'-cyano-2,4-dinitrodiphenylamine) was refluxed in nitrobenzene (11 cc) for 45 hrs. The solution was then chromatographed on an alumina column (25 x 3 cm). Elution with ether removed first the nitrobenzene, then a very faint pink band. This was followed by a broad pink band of 2-amino-8-cyanophenazine. Evaporation of the solvent gave 40 mg (46% yield) of product melting at 269 - 273°. Professor F.G. Holliman (private communication) has prepared 2-amino-8-cyanophenazine from 2,4'-diamino-4-cyanodiphenylamine, m. pt. 270 - 274°. A mixed melting point of these two samples was not depressed.

Synthesis of 2,8-diaminophenazine

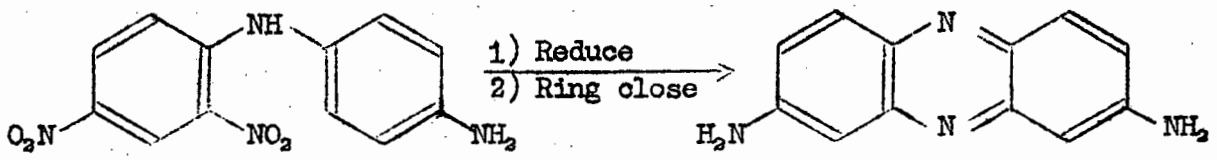
(1) Preparation of 4'-amino-2,4-dinitrodiphenylamine



cf. Nietzki and Ernst, Ber., 23, 1852 (1890).

A 63% yield of 4'-amino-2,4-dinitrodiphenylamine was obtained, m. pt. 183 - 185° (red leaflets from butyl alcohol.)

(2) Preparation of 2,8-diaminophenazine

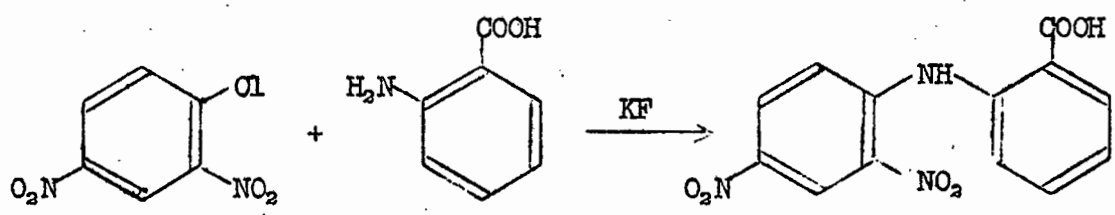


2,4,4'-Triaminodiphenylamine (from 135 mg of 4'-amino-2,4-dinitrodiphenylamine)was refluxed in nitrobenzene (12 cc) for 8 hrs. The solution was then chromatographed on an alumina column (25 x 3 cm). Elution with ether removed the nitrobenzene and a narrow yellow band. The main band of 2,8-diaminophenazine was eluted with absolute alcohol (broad yellow band). On evaporation of the solvent, 72 mg (70% yield) were obtained, m. pt. 274 - 278°. Nietzki and Ernst quote a m. pt. of 280° for 2,8-diaminophenazine.[52]

Analysis

Calc. for $C_{12}H_{10}N_4$:	Found:
C = 68.6%	C = 68.3%
H = 4.8%	H = 4.8%.

Preparation of 2'-carboxy-2,4-dinitrodiphenylamine



of. Vorozhtsov and Yakobson, Zhur. Obshchei Khim. 28, 40 (1958) through C.A. 52, 1784 (1958).

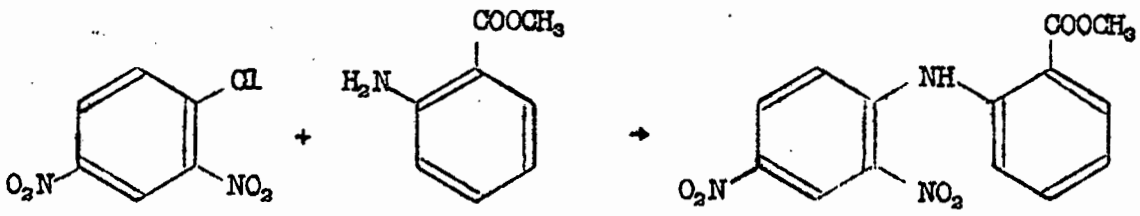
2,4-Dinitrochlorobenzene (2.03 g), anthranilic acid (1.37 g) and KF (1.16 g) were thoroughly mixed in a mortar and kept at 130° for one hour. After removing excess KF with water and heating with 5 N HCl to convert the red potassium salt to the free acid, a quantitative yield of yellow 2'-carboxy-2,4-dinitrodiphenylamine was obtained, m. pt. 240 - 250°. Recrystallisation from butyl alcohol gave yellow needles, m. p. 255 - 258°.

Attempted ring closure of 2,4-diamino-2'-carboxydiphenylamine

2'-Carboxy-2,4 -dinitrodiphenylamine (2 g) was reduced with PtO_2 (50 mg) in abs. alcohol (75 cc) at a H_2 pressure of 40 lbs./sq. in. The right amount of H_2 was absorbed, but the solution assumed a red colour and did not become colourless after adding a fresh portion of catalyst. This solution was filtered and added to nitrobenzene (250 cc). After boiling

off the alcohol, the $PhNO_2$ solution was refluxed for 12 hrs. The volume was then reduced to 25 cc by distilling off nitrobenzene under reduced pressure. No crystals were obtained on cooling. Chromatography (using BuOH:HCl, 4:1 sat. with H_2O) showed traces of 2-aminophenazine and 2-amino-6-carboxyphenazine.

Preparation of 2'-methoxycarbonyl-2,4-dinitrodiphenylamine



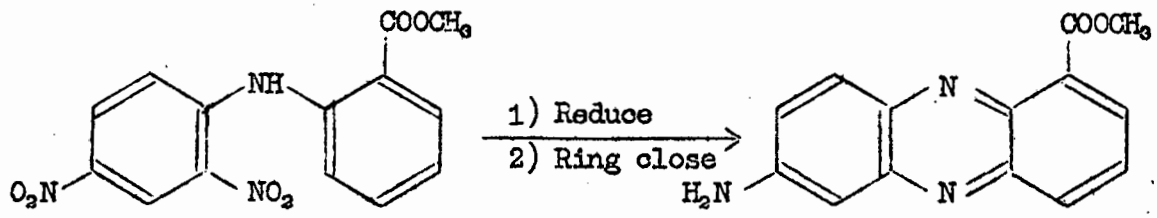
2,4-Dinitrochlorobenzene (5 g) and methylanthranilate (4 g) were refluxed in butyl alcohol (20 cc) for 7 hrs. On cooling, 4.6 g of a yellow product (m. pt. 60 - 100°) were obtained. Upon recrystallisation from alcohol, 2'-methoxycarbonyl-2,4-dinitrodiphenylamine (1 g, 13% yield) was obtained as fine yellow needles, m. pt. 166 - 167°.

Analysis

$C_{14}H_{11}N_3O_6$ requires:	Found:
C = 53.0%	C = 53.1%
H = 3.50%	H = 3.52%
N = 13.2%	N = 13.7%

Heating the reagents with KF at 130° for 2 hrs. (cf. Vorozhtsov and Yakobson[et al.]) was not successful, a very impure product being obtained.

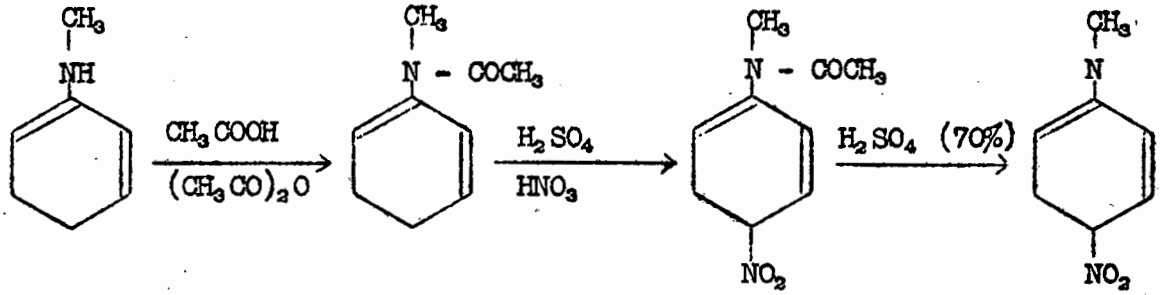
Attempted ring closure of 2,4-diamino-2'-methoxycarbonyldiphenylamine



2'-Methoxycarbonyl-2,4-dinitrodiphenylamine (0.5 g) was reduced in abs. alcohol (50 cc) with PtO_2 (50 mg) at a H_2 pressure of 40 lbs./sq. in. The colourless solution was filtered free of catalyst and added to $PhNO_2$ (65 cc). Removal of the alcohol by distillation was followed by 14 hrs. refluxing. The solution was then evaporated to dryness, but attempts to recrystallise the residue failed. The phenazine is known to recrystallise from toluene (Professor F.G. Holliman, Private communication).

Attempted preparation of N-methyl-2,4'-dinitrodiphenylamine

(1) Preparation of p-nitro-N-methylaniline



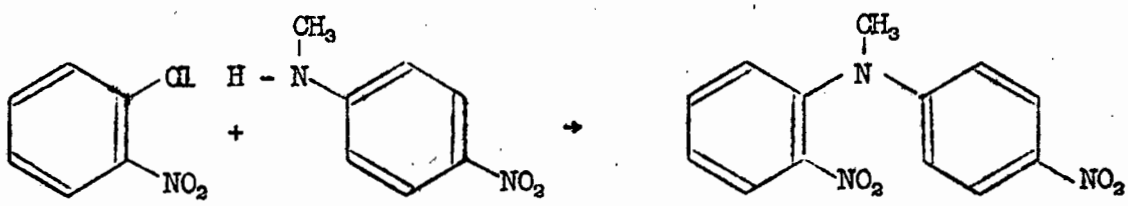
cf. Vogel, "Practical Organic Chemistry", p. 581 (3rd edition).

A 40% yield of p-nitro-N-methylaniline (based on N-methylaniline) was obtained, m. pt. 145 - 148°.

This preparation was based on the method given by Vogel for the preparation of p-nitroaniline. Identical conditions were adopted, except

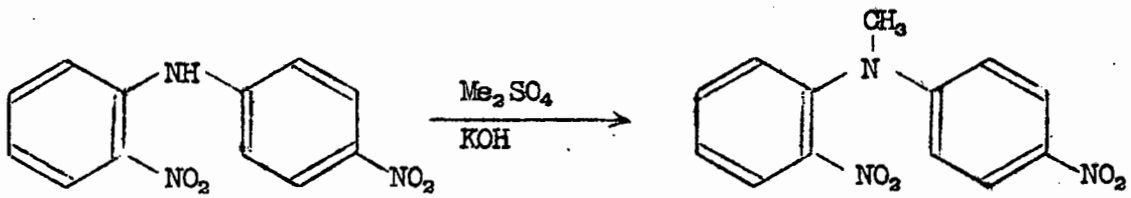
for the nitration reaction. Vogel recommends that the solution be allowed to stand for 1 hour at room temperature after addition of the nitrating mixture. It was found that this time was too short in this case. The best results were obtained when allowing the solution to stand overnight at room temperature.

(2) Attempted preparation of N-methyl-2,4'-dinitrodiphenylamine



p-Nitro-N-methylaniline (6 g), o-chloronitrobenzene (10 g), sodium acetate (6 g) and a little Cu bronze were thoroughly mixed in a mortar and heated at about 220° for 14 hrs. After steam distillation and treatment with hot 5 N HCl, a black tar was obtained which could only be extracted with alcohol. After evaporation of the alcohol, a gummy residue was obtained which could not be recrystallised.

Preparation of N-methyl-2,4'-dinitrodiphenylamine



This preparation is based on the method given by Hey and Mulley (J.C.S., 1952, 2285) for the preparation of N-methyl-2,2'-dinitrodiphenylamine.

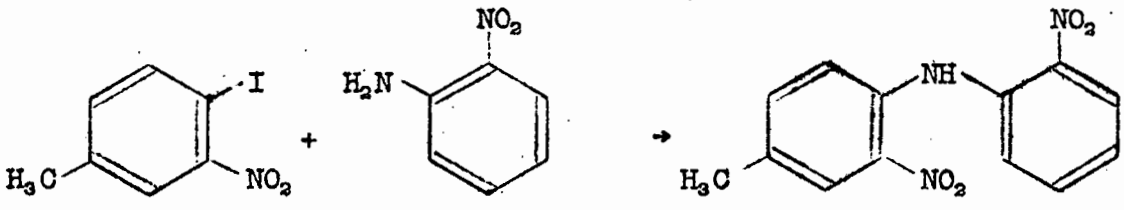
2,4'-Dinitrodiphenylamine (3 g) was dissolved in acetone (300 cc) and KOH (3.1 g) was added. The mixture was heated to boiling and dimethyl sulphate (5 cc) was added dropwise. Refluxing was continued for 1 hour. The mixture was then cooled, poured into water. The precipitate was collected and dried. 2.7 G were obtained (89% yield) of m. pt. 118 - 122°. Recrystallisation from dil. acetic acid did not alter the melting point.

N.B. In the preparation of N-methyl-2,2'-dinitrodiphenylamine, only 5 minutes refluxing is necessary (as described by Hey and Mulley). For the methylation of 2,4'-dinitrodiphenylamine, at least 1 hour refluxing was required.

Analysis

$C_{13}H_{12}N_2O_3$ requires:	Found:
C = 57.1%	C = 57.2%
H = 4.03%	H = 3.90%
N = 15.4%	N = 15.1%

Preparation of 4-methyl-2,2'-dinitrodiphenylamine

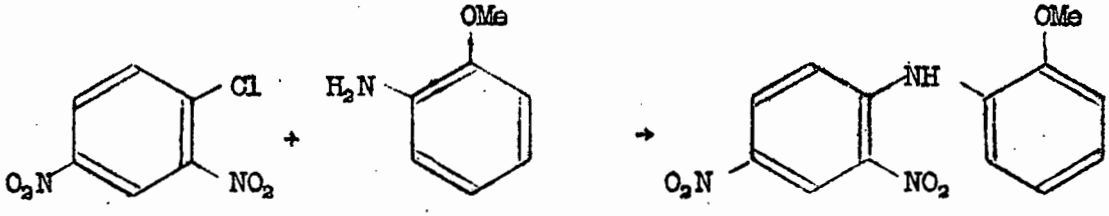


4-Iodo-3-nitrotoluene (1.3 g; 0.05 m), o-nitroaniline (0.7 g; 0.05 m), K_2CO_3 (1 g) and Cu powder (50 mg) were thoroughly mixed in a mortar and then heated to 190° for 1 hr. The resulting solid was refluxed with butyl alcohol (35 cc), filtered and cooled. 0.9 G (64% yield) of orange-red needles were obtained, m. pt. 177 - 179°. Further recrystallisations from butanol gave a m. pt. of 178 - 178.5°.

Analysis

$C_{13}H_{11}N_3O_4$ requires:	Found:
C = 57.1%	C = 57.2%
H = 4.1%	H = 4.0%
N = 15.4%	N = 15.3%

Preparation of 2'-methoxy-2,4-dinitrodiphenylamine



cf. G. Gallas and A. Alonso, Anales soc. españ. fis. quim. 28, 645 (1930) through C.A. 24, 4275 (1930).

o-Anisidine (6.2 g), 2,4-dinitrochlorobenzene (10 g) were refluxed in 75 cc butyl alcohol for 2 hrs. On cooling 8 g (57% yield) of 2'-methoxy-2,4-dinitrodiphenylamine were obtained, m. pt. 158 - 162°. A further recrystallisation from butyl alcohol raised the m. pt. to 162 - 163°.

The reaction carried out in ethyl alcohol gave a product with a wide

m. pt. (145 - 160°) which could not be improved by further recrystallisations.

Attempted ring closure of 2,4-diamino-2'-methoxydiphenylamine

2,4-Diamino-2'-methoxydiphenylamine (from 500 mg of 2'-methoxy-2,4-dinitrodiphenylamine) was refluxed in nitrobenzene (25 cc) for 8 hrs. This was followed by steam distillation under acid conditions (20 cc of 5 N HCl). On neutralisation with NaOH, a dark red ppt. was obtained (150 mg), m. pt. 245 - 270°. Paper chromatography showed this precipitate to be a mixture of 2-aminophenazine and possibly 2-amino-6-methoxy-phenazine.

EXPERIMENTAL SECTION

PART II

RATES OF FORMATION OF PHENAZINES

General procedure

As far as possible, the same method was used to determine all the rates of conversion of o-aminodiphenylamines to phenazines. The general outline of the procedure will be given, and any deviations from it will be indicated later.

The diphenylamine (0.001 m) was reduced in absolute alcohol (25 cc) with PtO_2 (50 mg) at a H_2 pressure of 40 lbs./sq. in. As only small amounts of hydrogen were absorbed, these could not be accurately measured on the gauge; a colourless solution was therefore taken as a criterion of completeness of reduction. This colourless solution was filtered and added to nitrobenzene (25 cc). The alcohol was boiled off, followed by 1 or 2 cc of $PhNO_2$ to ensure the removal of any water present. The nitrobenzene solution was then made up to 25.0 cc and refluxed.

The rate of ring closure was followed by determining the amount of phenazine produced in the reaction. This was done as follows: the reaction vessel was rapidly cooled in ice water and a 0.5 or 1 cc sample pipetted out as soon as possible. When dealing with 2-amino-phenazines, it was essential to carry out this operation as rapidly as possible to avoid the possibility of the phenazine crystallising out of solution. The sample was then put on an alumina column, varying in length but not in diameter (1 cm), and prepared in benzene. Elution was carried

out with benzene, ether, acetone or alcohol, depending on the phenazine. In all the cases studied the nitrobenzene was eluted first, and the phenazine band either followed immediately or was preceded by one or two minor bands. The identity of the phenazine band was established by comparing U.V. absorption maxima and m. pts. with samples of phenazines isolated in other experiments.

A standard curve for the phenazine was determined in either benzene, alcohol or $\frac{N}{10}$ HCl on a Beckmann Model D.U. Quartz Spectrophotometer. When the phenazine was eluted with benzene, the estimation was carried out directly on the eluate; in other cases, the solvent was evaporated and the residue taken up in the required solvent.

For every phenazine, a trial experiment with a solution of known concentration of phenazine in nitrobenzene was performed to test the reliability of the method: the percentage recovery for almost every phenazine was 100 ± 1.

The rate of formation of phenazine

Standard curve

In benzene at 364 mμ, from the following data:

Conc. (mg/l.):	2.5	4.9	6.2	7.4	9.8
Optical density:	.200	.402	.502	.610	.800

Control experiment: 99.2% recovery.

Rate from 2-aminodiphenylamine

Time (in hrs.)	12	24	48	72	120
% Yield of phenazine	26	42	56	57	61

Column: 1 cc samples on 50 cm columns. The nitrobenzene band (orange) was followed by the pale yellow phenazine band (eluted with benzene). Then came a pink band (50% benzene-ether) and a deep yellow band (ether). One or two very faint bands appeared between the pink and the deep yellow band.

Rate of formation of 2-methylphenazine

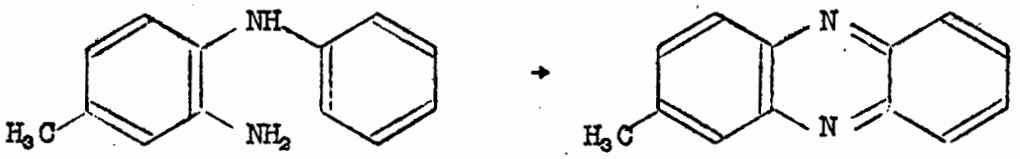
Standard curve:

In benzene at 364 mμ, from the following data:

Conc. (mg/l.):	3.1	4.6	6.1	7.6	9.2	12.2
Optical density:	.213	.312	.409	.525	.630	.838

Control experiment: 99.6% recovery.

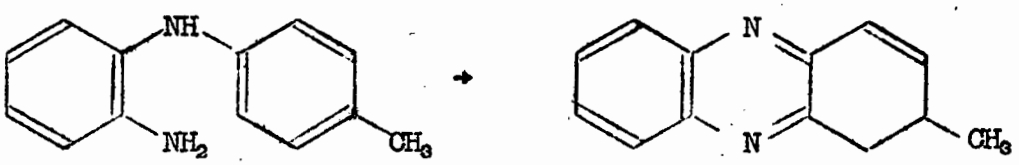
(a) Rate from 2-amino-4-methyldiphenylamine



Time (in hrs.)	10	20.5	35.5	58.5	72
% Yield	18.1	41.2	67.0	72.2	72.2

Column: 0.5 Cc samples on a 40 cm. column. The nitrobenzene band (orange) was followed by the pale yellow 2-methylphenazine band (eluted with benzene). 3 other bands could be eluted with ether: a pink band followed by a pale yellow and a deep yellow band.

(b) Rate from 2-amino-4'-methyldiphenylamine



Time (in hrs.)	11.5	26	50	74	120
% Yield of 2-methylphenazine	32.2	58.	67	64	67

Column: 1 Cc samples on 40 cm columns, which had the same appearance as in (a).

Rate of formation of 2-methoxyphenazine

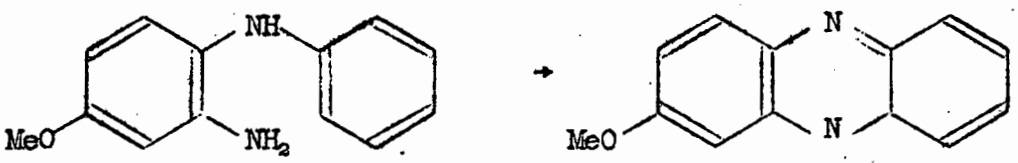
Standard curve

In benzene at 356 mμ, from the following data:

Conc. (mg/l.):	4.2	6.2	8.4	10.5	12.6	14.7	16.8
Optical density:	.185	.285	.376	.472	.570	.670	.758

Control experiment: 99.5% recovery.

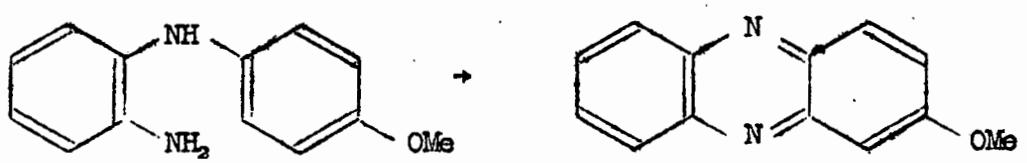
(a) Rate from 2-amino-4-methoxydiphenylamine



Time (in hrs.)	6	11	24	48	72
% Yield	30	43	74	75	75

Column: 1 cc samples on 25 cm columns. The nitrobenzene band (orange-red) was followed by the bright yellow band of 2-methoxyphenazine (eluted with benzene). A narrow brown band at the top seemed to be the only other band present.

(b) Rate from 2-amino-4'-methoxydiphenylamine



Time (in hrs.)	6	12	24	49	73
% Yield	36	59.5	75	74	75

Column: 1 cc samples on 25 cm columns. The nitrobenzene band (yellow-orange) was followed by the bright yellow band of 2-methoxyphenazine. Then came a broad violet band and a narrow brown band at the top.

Rate of formation of 2-chlorophenazine

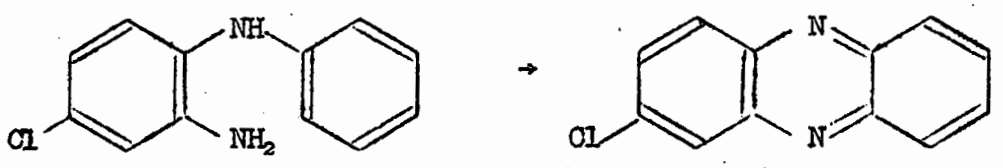
Standard curve

In benzene at 370 mμ, from the following data:

Conc. (mg/l.):	5.0	6.1	7.9	9.8	12.2
Optical density:	.330	.380	.500	.623	.790

Control experiment: It was found that 2-chlorophenazine could not be conveniently separated from nitrobenzene on a 50 cm column. It was therefore necessary to evaporate the nitrobenzene under reduced pressure, dissolve the residue in benzene and chromatograph the solution. Care must be taken to avoid any loss of phenazine by sublimation in the last stages of the distillation. The percentage recovery was 99.

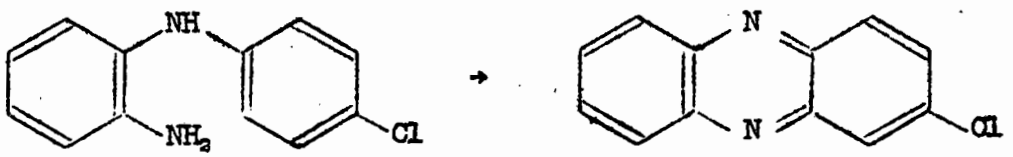
(a) Rate from 2-amino-4-chlorodiphenylamine



Time (in hrs.):	11	24	48	70.5	120
% Yield:	19.5	32.1	35.7	36.2	39.7

Column: 1 cc samples on 50 cm columns. A yellow orange band was eluted first, followed by the pale yellow band of 2-chlorophenazine (eluted with benzene). Then came a very faint pink band, a yellow (broad) band and a very narrow brown band.

(b) Rate from 2-amino-4'-chlorodiphenylamine



Time (in hrs.):	11.5	24	48	71.5	120
% Yield:	24.0	36.0	45.0	49.1	50.0

Column: 1 cc samples on 50 cm columns. The 2-chlorophenazine band was followed by a faint pink band and a broad greyish band.

Rate of formation of 2-cyanophenazine

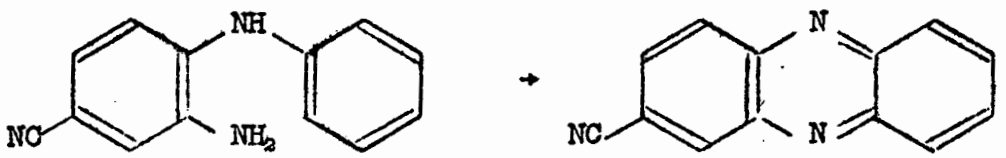
Standard curve

In benzene at 371 mμ, from the following data:

Conc. (mg/l.):	4.6	5.7	6.8	9.1	11.4
Optical density:	.262	.333	.394	.530	.661

Control experiment: 100.5% recovery.

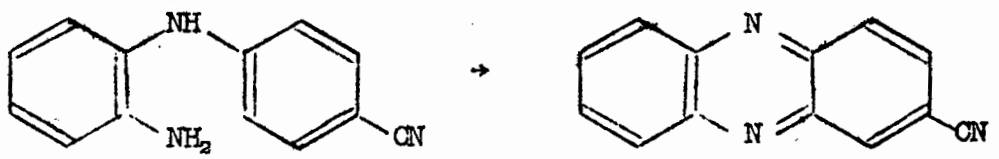
(a) Rate from 2-amino-4-cyanodiphenylamine



Time (in hrs.)	22	34.5	46.5	57.7	69.5	81
% Yield	3	6	11	14	18	20

Column: 0.5 cc samples on 25 cm columns. The nitrobenzene band (pale yellow) was followed by the pale yellow band of 2-cyanophenazine (eluted with 50% benzene-ether). This was followed by a pink band, a purple-grey band and a yellow fluorescent band.

(b) Rate from 2-amino-4'-cyanodiphenylamine



Time (in hrs.):	23.5	35.5	47.5	61	83
% Yield:	9	14	19	24.5	30.2

Column: As above.

Rate of formation of 2-dimethylaminophenazine

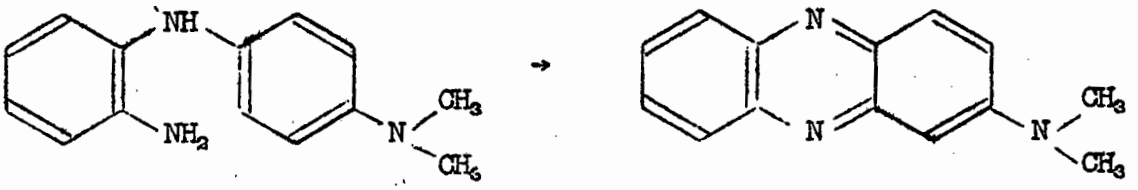
Standard curve

In benzene at 361 mμ, from the following data:

Conc. (mg/l.):	8.4	16.8	25.2	33.6
Optical density:	.213	.421	.620	.820

Control experiment: 99.6% recovery.

Rate from 2-amino-4'-dimethylaminodiphenylamine



Time (in hrs.):	2	5	10.5	24
% Yield	20	35	45.4	45.4

Column: 0.5 cc samples on 25 cm columns. The nitrobenzene band (pale yellow) was followed by the red band of 2-dimethylaminophenazine (eluted with 50% benzene-ether). This was followed by a single, narrow red-orange band.

Rate of formation of 1-aminophenazine

Standard curve

In benzene at 368 mμ, from the following data:

Conc. (mg/l.):	11.7	17.5	23.4	29.3	35.1
Optical density:	.282	.420	.550	.690	.815

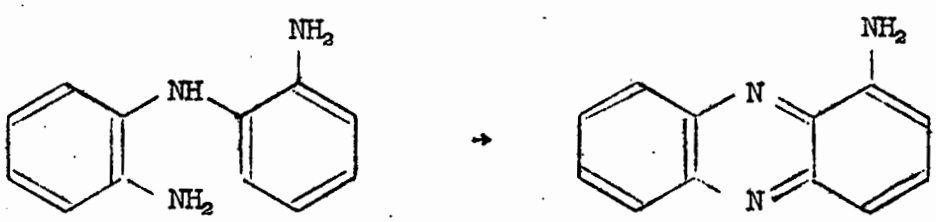
Control experiment: 100.0% recovery.

(a) Rate from 2,6-diaminodiphenylamine

Time (in hrs.)	5	8	11	14	21	24	27	31	48	72
% Yield	16	24	29	34	44	53	60	70	60	45

Column: 0.5 cc samples on 25 cm columns. The nitrobenzene band (pale yellow) was followed by the brown-red band of 1-aminophenazine (eluted with 50% benzene-ether). No other bands appeared.

(b) Rate from 2,2'-diaminodiphenylamine



Time (in hrs.)	1	2	3	4	5	6	9.8
% Yield	21	35	42	52	57	63	72

Column: As above, except for a violet band, following that of 1-aminophenazine, but disappearing after 6 hrs.

Rate of formation of 2-aminophenazine

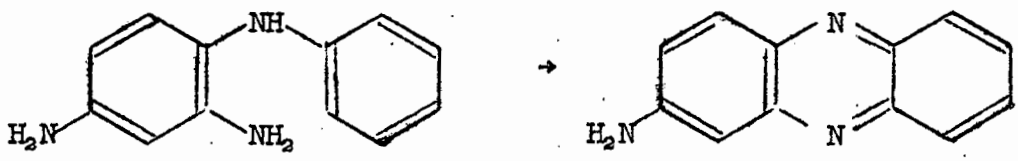
Standard Curve

In $\frac{N}{10}$ HCl at 382 mμ, from the following data:

Conc. (mg/l.):	5.2	10.4	15.6
Optical density:	.240	.480	.720

Control experiment: 99.6% recovery.

(a) Rate from 2,4-diaminodiphenylamine

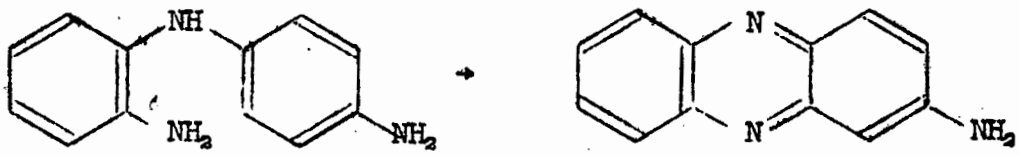


Time (in hrs.):	1	2	4	6	8	10	27
% Yield:	19	31	45	64	68.5	75	73

Column: 0.5 cc samples on 25 cm columns. The nitrobenzene band (pale yellow) was followed by a slight mauvish band. The main 2-aminophenazine band (orange) was eluted with ether. A red band was present at the top of the column but disappeared after 10 hrs. After 4 hrs., the band

following the nitrobenzene appears as a mixture of a mauve and an orange band.

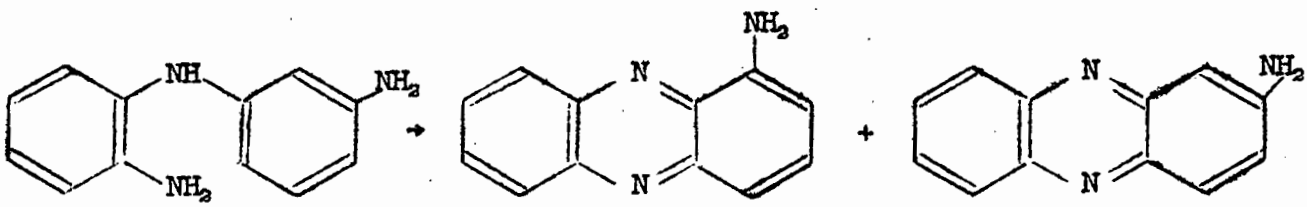
(b) Rate from 2,4'-diaminodiphenylamine



Time (in hrs.):	1	2	4	6	9	22	70
% Yield:	14	28	(33)	50	55	47	33

Column: 0.5 cc samples are 40 cm columns. The nitrobenzene band is followed by a slight orange band. The 2-aminophenazine band is closely followed by a blue band (hence longer column), but this band disappears after 22 hrs.

Rate of formation of 1- and 2-aminophenazine from 2,3'-diaminodiphenylamine



From the preceeding experiments, it can be seen that these 2 isomers can be easily separated on an alumina column, 1-aminophenazine being eluted first with 50% benzene-ether and 2-aminophenazine with pure ether.

Time (in hrs.)	6	11	22	45	71
% Yield of 1-aminophenazine	7	19	36	49	44
% Yield of 2-aminophenazine	4.5	10.5	18	24.5	19.5
Total % yield	11.5	29.5	54	73.5	63.5

Column: 0.5 cc samples on 25 cm columns. At first, the nitrobenzene band (pale yellow) is followed only by 1-amino- and 2-aminophenazine bands. After 11 hrs., a pale violet band appears behind the 2-aminophenazine band.

Rate of formation of 2-amino-8-methylphenazine

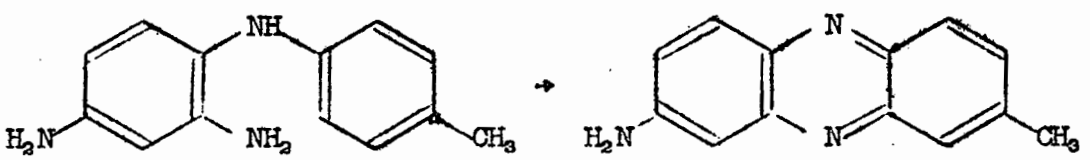
Standard curve

In $\frac{N}{10}$ HCl at 394 mμ, from the following data:

Conc. (mg/l.):	4.8	8.4	12.0	14.4
Optical density:	.255	.442	.640	.758

Control experiment: 99.6% recovery.

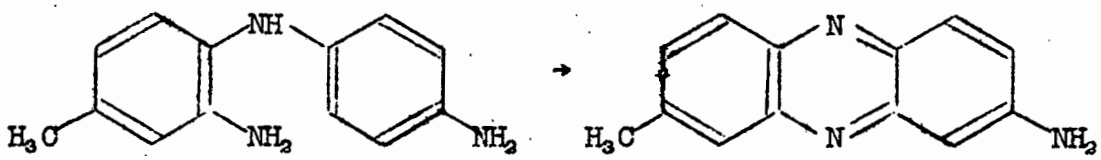
(a) Rate from 2,4-diamino-4'-methyldiphenylamine



Time (in hrs.):	1	2	4	6	9	22	70
% Yield:	19	31	46	56	60	57	41

Column: 0.5 cc samples on 25 cm columns. The nitrobenzene band (pale yellow) was followed by a violet band. The main 2-amino-8-methylphenazine band was eluted with ether. A red band was present at the top of the column, but disappeared after 9 hrs.

(b) Rate from 2,4'-diamino-4-methyldiphenylamine



Time (in hrs.):	1	2	4	7	10	23	70
% Yield:	34	50	63	60	61	55	52

Column: 0.5 cc samples on 40 cm column. Two very close band (mauve and orange) followed the nitrobenzene band (pale yellow). The 2-amino-8-methylphenazine band came next and was fairly closely followed by a pale blue band which disappeared after 6 hrs.

Rate of formation of 2-amino-8-methoxyphenazine

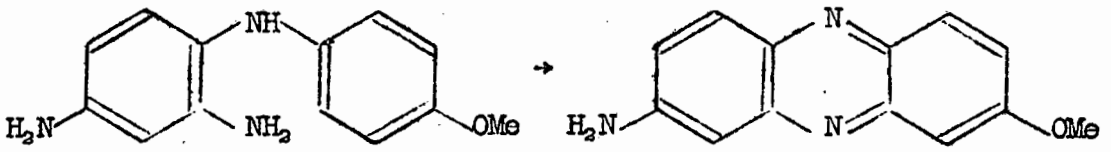
Standard curve

In $\frac{N}{10}$ HCl at 422 mμ from the following data:

Conc. (mg/l.):	3.0	5.9	8.9	11.8	14.8
Optical density:	.154	.316	.470	.615	.780

Control experiment: 98% recovery

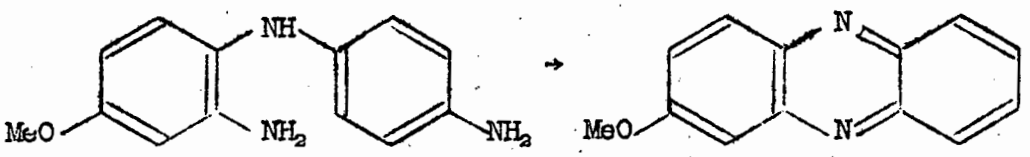
(a) Rate from 2,4-diamino-4'-methoxydiphenylamine



Time (in hrs.):	1	2	3	4	5	8.5	23	95
% Yield:	14.5	33	48	52	58	65	57	42

Column: 0.5 cc samples on 20 cm columns. Two very narrow and close bands (yellow and red) followed the nitrobenzene band (pale yellow). The 2-amino-8-methoxyphenazine band (yellow) came next and was eluted with ether. A red band was present at the top of the column, disappearing after 8.5 hrs. The fast moving red band also disappeared after this time.

(b) Rate from 2,4'-diamino-4-methoxydiphenylamine



Time (in hrs.):	1	2	3	4	5	9	23	70
% Yield:	10	17	27.5	35.5	38	36	31	26

Column: 0.5 cc samples on 40 cm columns. Only one band (yellow) between the nitrobenzene and 2-amino-8-methoxyphenazine band. A pale blue band, disappearing after 9 hrs., followed the phenazine band.

Rate of formation of 2-amino-8-chlorophenazine

Standard curve

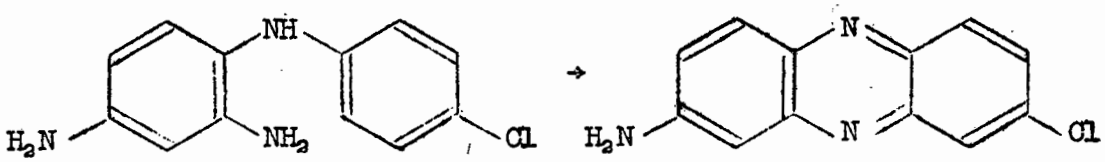
In alcohol at 370 mμ, from the following data:

Conc. (mg/l.):	5.5	11.0	16.8	21.9	27.4
Optical density:	.160	.317	.470	.625	.780

Control experiment: 100.0% recovery.

It was found that 2-amino-8-chlorophenazine is not very easily soluble in $\frac{N}{10}$ HCl, hence the use of alcohol for the standard curve.

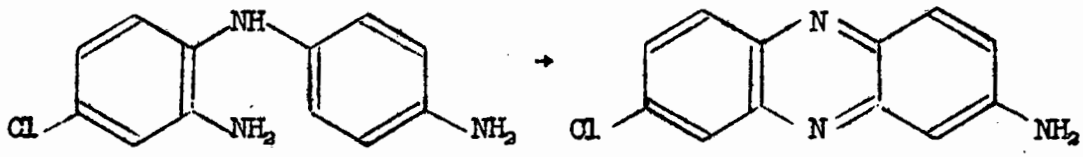
(a) Rate from 2,4-diamino-4'-chlorodiphenylamine



Time (in hrs.):	1	2.5	5	7.5	10	22
% Yield:	10	26	45	56	56	45.5

Column: 0.5 cc samples on 20 cm columns. A slight orange band followed the nitrobenzene band (pale yellow). The 2-amino-8-chlorophenazine band (orange) was eluted with ether. A pale brown band, disappearing after 10 hrs., was present at the top of the column.

(b) Rate from 2,4'-diamino-4-chlorodiphenylamine



Time (in hrs.):	2	4	5	6	8
% Yield:	29	48	50.5	50	50

Column: 0.5 cc samples on 40 cm columns. Two bands, moving very closely to each other (red, then blue) followed the nitrobenzene band. Similarly, the 2-amino-8-chlorophenazine band was followed closely by a blue band; both blue bands disappeared after 6 hrs.

Rate of formation of 2-amino-8-cyanophenazine

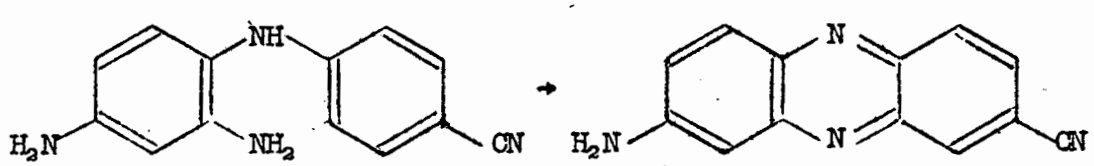
Standard curve

In alcohol at 363 mμ, from the following data:

Conc. (mg/l.):	10.4	20.8	31.2
Optical density:	.238	.462	.692

Control experiment: 98.5% recovery.

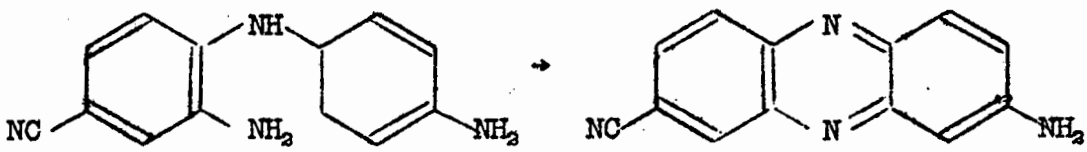
(a) Rate from 2,4-diamino-4'-cyanodiphenylamine



Time (in hrs.):	5	10	21.5	45	73
% Yield:	9	19	42	46	43

Column: 0.5 cc samples on 25 cm columns. A very faint pink band follows the nitrobenzene band (pale yellow). The broad 2-amino-8-cyanophenazine band (pink) was eluted with ether. A red band was present at the top of the column until 45 hrs.

(b) Rate from 2,4'-diamino-4-cyanodiphenylamine



Time (in hrs.):	5	10.5	24	48
% Yield:	10	21	35	38

Column: Same observations as above, except that the band at the top was orange.

Rate of formation of 2,8-diaminophenazine

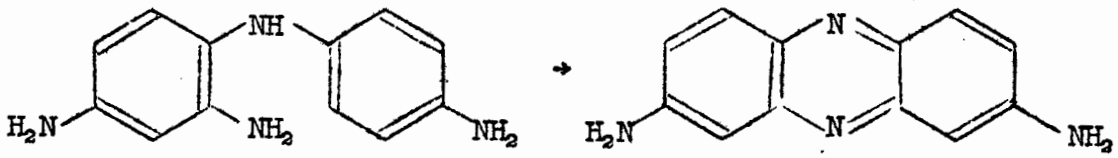
Standard curve

In $\frac{N}{10}$ HCl at 272 mμ from the following data:

Conc. (mg/l.):	1.7	2.6	3.4	4.3
Optical density:	.342	.510	.665	.820

Control experiment: 99% recovery.

Rate from 2,4,4'-triaminodiphenylamine



Time (in hrs.):	2	4	6	8
% Yield:	72	89	89	77

Column: 0.5 cc samples on 25 cm columns. After the nitrobenzene band (pale yellow) two slight yellow bands (first one weaker) were eluted with ether. 2,8-Diaminophenazine was eluted with absolute alcohol as a deep yellow band. A broad blue band followed, present until 4 hrs. This band probably obscured a pale yellow band which was visible after 4 hrs.

Index to the Experimental Section

Underlined entries for phenazines refer to rates of formation of these compounds.

SUMMARY

The new method of phenazine synthesis, discovered by Gray, was investigated: this method involves the oxidative cyclisation of 2-amino-diphenylamines in nitrobenzene. It was originally thought that good yields could only be obtained if p-quinone imine types of intermediates could be obtained from the diphenylamines. Work described in this thesis has shown that, by modifying the reaction conditions, it is possible to obtain good yields of phenazine even when the diphenylamines cannot give quinone imines on oxidation.

The effect, on the ring closure of 2-aminodiphenylamine, of various groups in the 4 and 4' position was investigated, and from a semi-quantitative comparison of the reaction rates, possible mechanisms for the reaction were formulated.

A number of new diphenylamines, which were required for the rate studies, were synthesised, and some comments on diphenylamine synthesis were expressed.

BIBLIOGRAPHY

1. A. Claus, Ann., 168, 1 (1873).
2. G.A. Swan and D.G. Felton, Phenazines, Interscience Publishers (1957).
3. D.E. Pearson, Heterocyclic Compounds, Vol. 6, Chapter 14; edited by R.C. Elderfield.
4. E. Bamberger and W. Ham, Ann., 382, 82 (1911).
5. H. Hopff and C. Ziegler, Chimia (Switz.), 12, 112 (1958); through C.A. 53, 1355 (1959).
6. H. Hillemann, Ber., 71, 42 (1938).
7. A. Gray, The synthesis of phenazines, Ph.D. Thesis, (1957).
8. F. Kehrmann and E. Havas, Ber., 46, 341 (1913).
9. H. McCombie, H.A. Scarborough and W.A. Waters, J.C.S., 353 (1928).
10. F. Kögl and J.J. Postowsky, Ann., 480, 280 (1930).
11. I.G.M. Campbell, C.G. le Fevre, R.J.W. le Fevre and E.E. Turner, J.C.S., 404 (1938).
12. P. Griess, J. prakt. Chem., 3 143 (1871); through J.C.S., 24, 562 (1871).
13. P. Griess, Ber., 5, 192 (1872).
14. H. Salkovski, Ann., 173, 39 (1874).
15. C. Rudolph, Ber., 12, 2211 (1879)
16. F. Wiesinger, Ann., 224, 353 (1884).
17. O. Fischer and E. Hepp, Ber., 22, 355 (1889).
18. F. Ullmann and F. Mauthner, Ber., 35, 4302 (1902); 36, 4026 (1903).
19. M.M. Richter, Ber., 44, 3466 (1911).
20. E. Knoevenagel, J. prakt. Chem., 89, 1 (1914).
21. G.B. Crippa, Gazz. chim. ital., 59, 330 (1929); through Chem. Abstracts 24, 121 (1930).
22. F.E. King, N.G. Clark and P.M.H. Davis, J.C.S., 3012 (1949).
23. O. Westphal and K. Jann, Ann., 605, 8 (1957).
24. A. Wohl and W. Aue, Ber., 34, 2442 (1901).
25. V.P. Chernetskii and A.I. Kiprianov, Zhur. Obshei Khim., 26, 3465 (1956); C.A. 51, 9631 (1957).
26. C. Ris, Ber., 19, 2206 (1886).
27. V. Merz, Ber., 19, 725 (1886).
28. J.S. Morley, J.C.S., 4008 (1952).

29. O. Hinsberg, Ber., 18, 1228 (1885).

30. J.H. Boyer and I.R. Morgan, J. Org. Chem., 26, 1654 (1961).

31. G.R. Clemo and H. McIlwain, J.C.S., 1991 (1934).

32. G.R. Clemo and H. McIlwain, J.C.S., 258 (1936).

33. J.S. Morley, J.C.S., 4008 (1952).

34. A. Eckert and K. Steiner, Monatsh., 35, 1153 (1914); through Chem. Zentr., I, 202 (1915).

35. M.L. Tomlinson, J.C.S., 158 (1939).

36. R.C. Elderfield, W.J. Gensler and O. Birstein, J. Org. Chem., 11, 312 (1946).

37. G.R. Clemo and A.F. Daglish, J.C.S., 1481 (1950).

38. B. Hegedüs, Helv. Chim. Acta, 33, 766 (1950).

39. A. Albert and H. Duewell, J. Soc. Chem. Ind., 66, 11 (1947).

40. H.C. Waterman and D.L. Vivian, U.S. Pat. 2,292,808; Chem. Abst., 37, 892 (1943).

41. H.C. Waterman and D.L. Vivian, J. Org. Chem., 14, 289 (1949).

42. D.L. Vivian, G.Y. Greenberg and J.L. Hartwell, J. Org. Chem., 16, 1 (1951).

43. D.L. Vivian and J.L. Hartwell, J. Org. Chem., 18, 1065 (1953).

44. D.L. Vivian, J.L. Hartwell and H.C. Waterman, J. Org. Chem., 19, 1136 (1954).

45. D.L. Vivian, J.L. Hartwell and H.C. Waterman, J. Org. Chem., 19, 1641 (1954).

46. D.L. Vivian, J.L. Hartwell and H.C. Waterman, J. Org. Chem., 20, 797 (1955).

47. D.L. Vivian, J. Org. Chem., 21, 565 (1956).

48. D.L. Vivian, J. Org. Chem., 21, 824 (1956).

49. D.L. Vivian, J. Org. Chem., 21, 1188 (1956).

50. D.L. Vivian, R.M. Hogart and M. Belkin, J. Org. Chem., 26, 112 (1961).

51. P.Z. Slack and R. Slack, Nature, 160, 437 (1947).

52. R. Nietzki and O. Ernst, Ber., 23, 1852 (1890).

53. R. Nietzki, Ber., 28, 2969 (1895).

54. O. Fisher and O. Heiler, Ber., 26, 378 (1893).

55. O. Fisher, Ber., 29, 1873 (1896).

56. B.M. Mikailov and A.N. Blokhina, Chem. Abstr., 44, 9452 (1950).

57. A. Gray, G. Gaertner and F.G. Holliman, Tetrahedron Letters, No. 7, 24 (1959).

58. A. Albert, The Acridines, p. 42 (E. Arnold and Co., 1951).

59. R.M. Acheson, Acridines, Interscience Publishers, 1956, p. 148.

60. F.E. King, J.T. King and I.H.M. Muir, J.C.S., 5 (1946).

61. N.N. Vorozhtsov and G.G. Yakobson, Zhur. Obshchei Khim. 28, 40 (1958); through C.A. 52, 12784 (1958).

62. H. Franzen and E. Bockhacker, Ber., 53, 1174 (1920).

63. W.J. Evans and S. Smiles, J.C.S., 187 (1935).

64. C.Willgerodt and E. Arnold, Ber., 34, 3344 (1901).

65. W. Körner and A. Contardi, Atti acad. Lincei, 25, I 281; through C.A. 8, 3020 (1914).

66. F.H. Case and H.A. Sloviter, J.A.C.S., 59, 2382 (1937).

67. J.E. Larson and S.H. Harvey, Chem. and Ind., 45 (1954).

68. M.J.S. Dewar and T. Mole, J.C.S., 2556 (1956).

69. I.J. Pachter and M.C. Kloetzel, J.A.C.S., 74, 971 (1952).

70. J.T. Hewitt, S.H. Newmann and T.F. Minmill, J.C.S., 577 (1909).

71. A. Wohl and M. Lange, Ber., 43, 2186 (1910).

72. F. Kehrmann and E. Havas, Ber., 46, 341 (1913).

73. F. Kehrmann and C. Mermod, Helv. Chim. Acta, 10, 62 (1927).

74. F. Ullmann, Ann., 366, 82 (1909).

75. H. Otomasu, Pharm. Bull., 4, 117 (1956); through C.A. 51, 3087 (1957).

76. Professor F.G. Holliman, Private communication.

77. S. Maffei, Gazz, chim. ital., 80, 651 (1950); through C.A., 45, 9063 (1951).

78. Yu. S. Rozum, Ukrain. Khim. Zhur., 21, 361 (1955); through C.A., 49 14772 (1955).

79. V. Weinmayr, C.A. 38, 5228 (1944).

80. E. Clar, Ber., 69, 1686 (1936).

81. F. Bergmann, J.A.C.S., 64, 176 (1942).

82. Ch. Weizmann, E. Bergmann and T. Berlin, J.A.C.S., 60, 1331 (1938).

83. E. Bergmann, L. Haskelberg and F. Bergmann, J. Org. Chem., 7, 303 (1942)

84. G. Swain and A.R. Todd, J.C.S., 626 (1942).

85. L.M. Jackman: Advances in Org. Chem., Methods and Results, Vol. 2, p.347

86. L.R. Morgan and C.C. Aubert, Proc. Chem. Soc., 73, (1962).
87. K. Ziegler and H. Zeiser, Ann., 485, 174 (1931).
88. J.B. Cohen and H.B. Crabtree, J.C.S., 2055 (1921).

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