THE CHEMISTRY OF SOME o-NITROANILINE DERIVATIVES

being a thesis

presented by

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to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

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Th 5910

DECLARATION

I hereby declare that this thesis is a record of the results of my own experiments, that it is my own composition, and that it has not previously been presented in application for a higher degree.

The research was carried out in the Department of Chemistry, United College of St. Salvator and St. Leonard, University of St. Andrews, under the supervision of Dr. D.M. Smith.

CERTIFICATE

I hereby certify that Robert Marshall has completed twelve terms of research work under my supervision, has fulfilled the conditions of Ordinance 16 (St. Andrews) and that he is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

Research Supervisor

UNIVERSITY CAREER

I entered the United College of St. Salvator and St. Leonard, University of St. Andrews in October, 1963, and subsequently graduated B.Sc. with Upper Second Class Honours in Chemistry in June, 1967.

I was admitted as a research student in the United College, University of St. Andrews in October, 1968, and was awarded an S.R.C. Studentship which I held until October 1971.

PUBLICATIONS

(i) "o-Nitroaniline Derivatives. Part 1. The Preparation and Stability of o-Nitroanils", R. Marshall, D.J. Sears, and D.M. Smith, J.Chem.Soc.(C), 1970, 2144.

(ii) "Reduction of Nitro- and Nitroso-compounds by Tervalent Phosphorus Reagents. Part VIII, Syntheses of Benzimidazoles and Anthranils", J.I.G. Cadogan, R. Marshall, D.M. Smith, and M.J. Todd, J.Chem.Soc.(C), 1970, 2441.

(iii) "o-Nitroaniline Derivatives. Part II. Reactions of Nucleophiles with N-Benzylidene-o-nitroaniline", R. Marshall and D.M. Smith, J.Chem.Soc.(C), 1971, 3510.

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to Dr. D.M. Smith for his help and encouragement throughout this work.

I wish also to express my gratitude to Mrs. P. Cooper who typed this thesis.

I am also indebted to the S.R.C. for financial support.

ABSTRACT

The reactions of o-nitroaniline and its derivatives with benzaldehyde and its derivatives were studied. It was found that the products of reaction varied widely with the reaction conditions. The simple product of condensation, the o-nitroanil, was difficult to obtain, the adduct formed by addition of the o-nitroaniline to the o-nitroanil being commonly found at lower temperatures. At higher temperatures heterocyclic products, the result of interaction between the nitro group and the ortho-side-chain, predominated. However, those reaction conditions most favourable to o-nitroanil production were determined, and a number of o-nitroanils thus prepared.

The reaction of o-nitroaniline with benzaldehyde at high temperatures was investigated and the major products were found to be 1-hydroxy-2-phenylbenzimidazole and/or 2-phenylbenzimidazole. Some evidence was found regarding the possible mechanism of this reaction.

2-Phenylbenzimidazoles were also produced by the reduction of o-nitroanils with triethyl phosphite.

The reactions of N-benzylidene-o-nitroaniline with nucleophiles were also studied. Reactions involving nucleophiles in which the nucleophilic centre is attached to one hydrogen atom involve addition to the C=N group. If the nucleophilic centre carries two hydrogen atoms, the addition may be followed by elimination of o-nitroaniline from the adduct. Cyanide ion, however, was found

to react with N-benzylidene-o-nitroaniline to give 1-hydroxy-2-phenylbenzimidazole and similarly with N-benzylidene-4-methyl-2-nitroaniline to give 1-hydroxy-6-methyl-2-phenylbenzimidazole. A mechanism for this reaction has been proposed, based on the experimental results.

CONTENTS

I Introduction

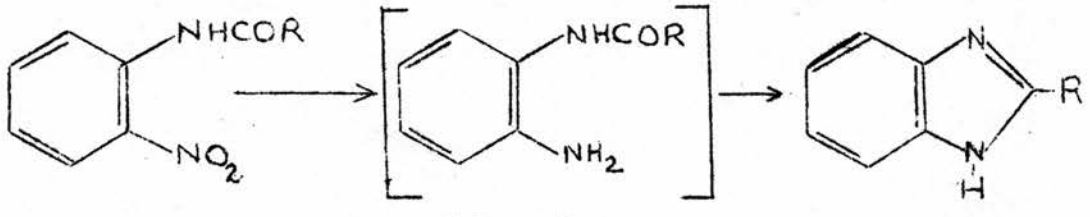
The Formation of Heterocyclic Compounds from o-Nitroaniline Derivatives

The reduction of ortho-substituted nitrobenzene derivatives, giving nitrogen-containing heterocyclic compounds, is a well-known and widely applied method in heterocyclic synthesis. In many reactions, however, cyclisation takes place under apparently non-reducing conditions, giving N-oxygenated heterocycles, while in other reactions N-oxygenated heterocycles are produced even under reducing conditions. This review surveys the cyclisation reactions of those ortho-substituted nitrobenzenes in which the ortho-substituent is attached to the benzenoid system through a nitrogen atom.

A. Reductive cyclisations

(a) N-acyl-o-nitroanilines

Acylated o-nitroanilines, when reduced with tin and hydrochloric acid or similar reducing agents, ought to yield monoacyl-o-phenylenediamines by reduction of the nitro group in the usual manner; however, under the conditions of the reduction the diamine derivative is not isolated, but undergoes cyclisation to a benzimidazole dorivative by dehydrative ring closure involving the primary amine function and the carbonyl group, as shown in Scheme 1.



Scheme 1

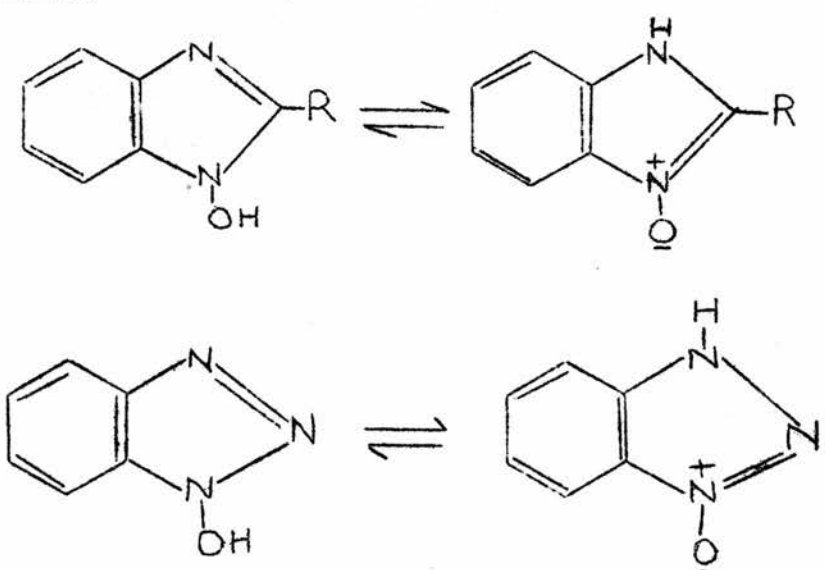
The reducing agents generally employed are tin and hydrochloric or acetic acid, and stannous chloride and hydrochloric acid. Other means that have been used satisfactorily include electrolytic reduction in

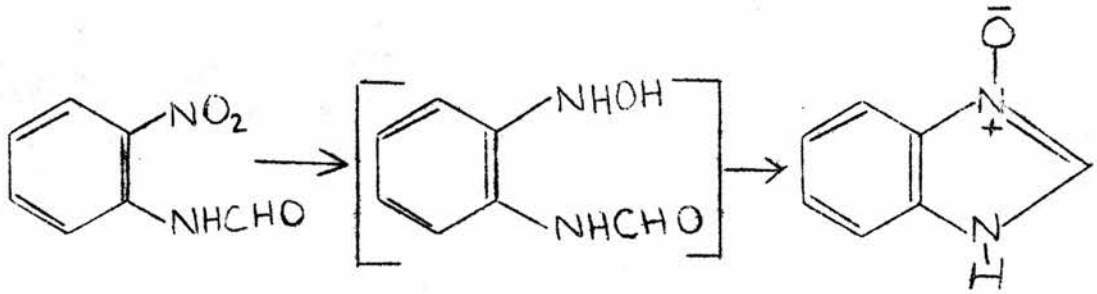
acidic solution, zinc dust and aqueous acetic acid, iron and dilute hydrochloric acid, and catalytic hydrogenation in acetic acid solution with palladium catalyst, or in ether solution, under acid conditions, over platinum oxide. Similarly N-substituted acylated o-nitroanilines lead to 1-substituted benzimidazoles.

Numerous examples of this type of cyclisation are known, and they have been reviewed elsewhere[1].

Von Niementowski was the first to show that benzimidazole oxides+ may be found among the reduction products of acylated o-nitroanilines. Thus, reduction of o-nitroformanilide (1) by an alcoholic solution of ammonium sulphide[2] gave benzimidazole-N-oxide (2). The product is presumably formed by reduction of the nitro group to the hydroxylamino group, followed by dehydrative ring closure between the latter and the carbonyl group.

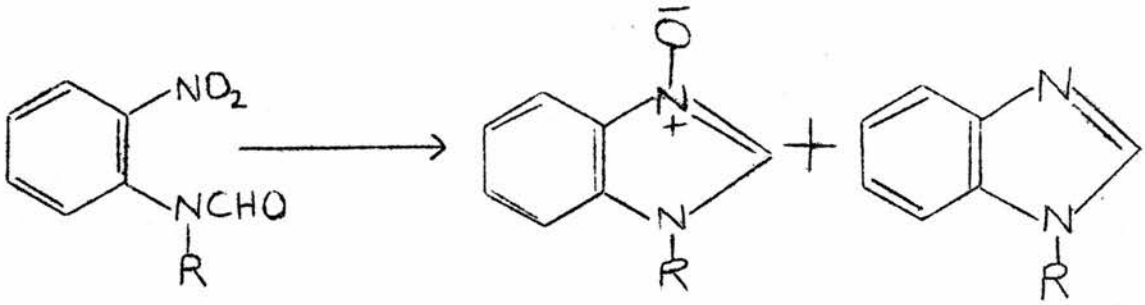
+ Benzimidazole-1-oxides with an unsubstituted 3-position, and benzotriazole-1-oxides with unsubstituted 2 and 3 positions may exhibit tautomerism as shown below. No attempt is made to distinguish between the tautomers in this introduction.





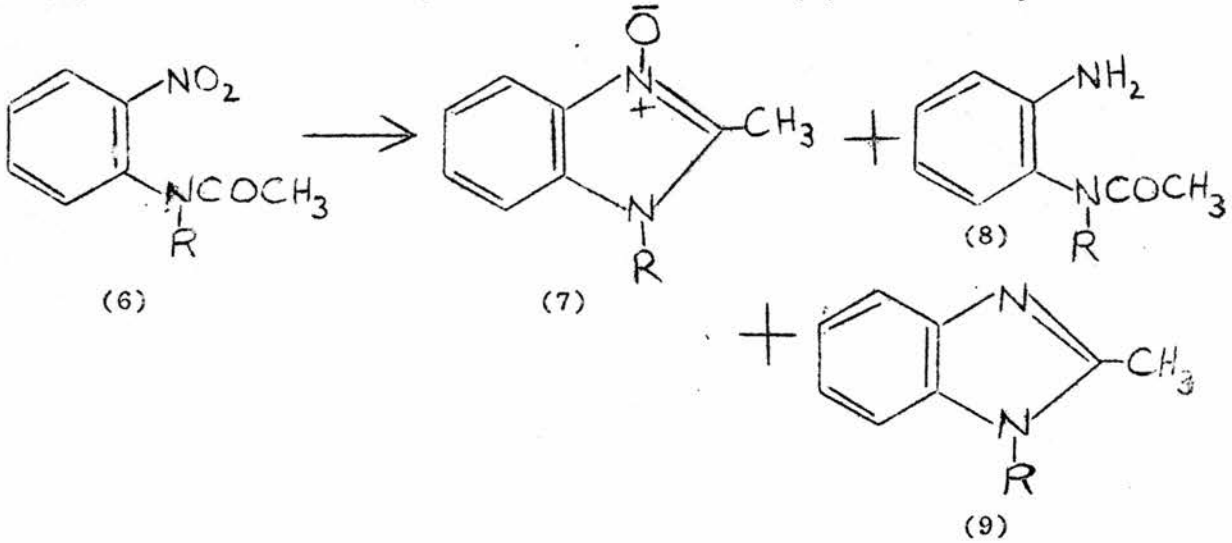
(1) (2)

Takahashi and Kano[3] extended this reaction to the cyclisation of N-substituted o-nitroformanilide derivatives [(3); R = Me, Et, or $PhCH_2$-] to the corresponding benzimidazole-N-oxides (4) and benzimidazoles (5) with alcoholic ammonium sulphide.



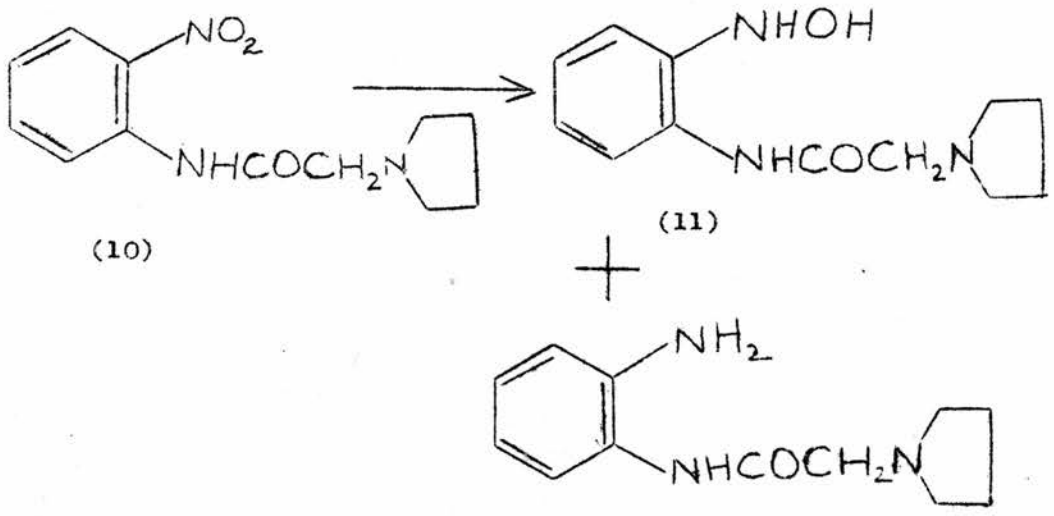
(3) (4) (5)

Similarly, N-substituted-o-nitroacetanilide derivatives [(6); R = Me, Et, $PhCH_2$-] were cyclised to the corresponding benzimidazole-N-oxides (7); the o-aminoacetanilide derivatives (8) and, in the case of the N-methyl and N-ethyl derivatives, the corresponding benzimidazoles (9) were also formed. In all cases the amine (8) was readily



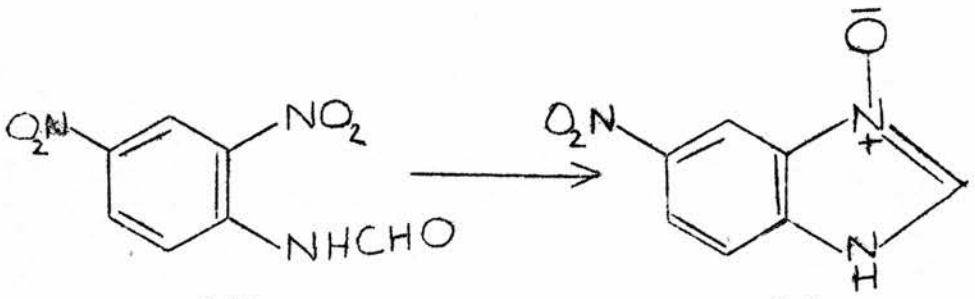
(6) (7) (8) (9)

convertible to the benzimidazole (9) by heating in dilute hydrochloric acid. It was also found[3] that 2-(1-pyrrolidinyl)-2'-nitroacetanilide (10), similarly treated, gave 2-(1-pyrrolidinyl)-2-hydroxylaminoacotanilide (11) and the amine (12), but all attempts to form the N-oxide, for example by heating compound (10) with 4N hydrochloric acid or phosphoric acid, failed.



(10) (11) (12)

Takahashi and Kano[3] also found that, although zinc in aqueous ammonium chloride solution is known to reduce nitrobenzene to N-phenylhydroxylamine, heating with this reagent gave a poor yield of the N-oxide [(4); R = H] from o-nitroformanilide and no N-oxide from N-methyl-o-nitroformanilide and o-nitroacetanilide. Selective reduction of the 2-nitro group in 2,4-dinitroformanilide (13) led to the formation of 5-nitrobenzimidazole-3-oxide (14) with alcoholic ammonium sulphide[4]; and the benzimidazole-N-oxides (16) were prepared from (15) by reduction in an organic solvent by an alkali metal hydrosulphide[5] in the presence of calcium or barium chloride or bromide and ammonium chloride or hydrochloric or acetic acid.



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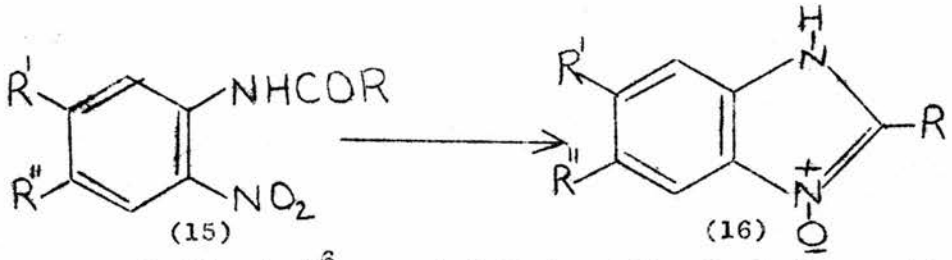
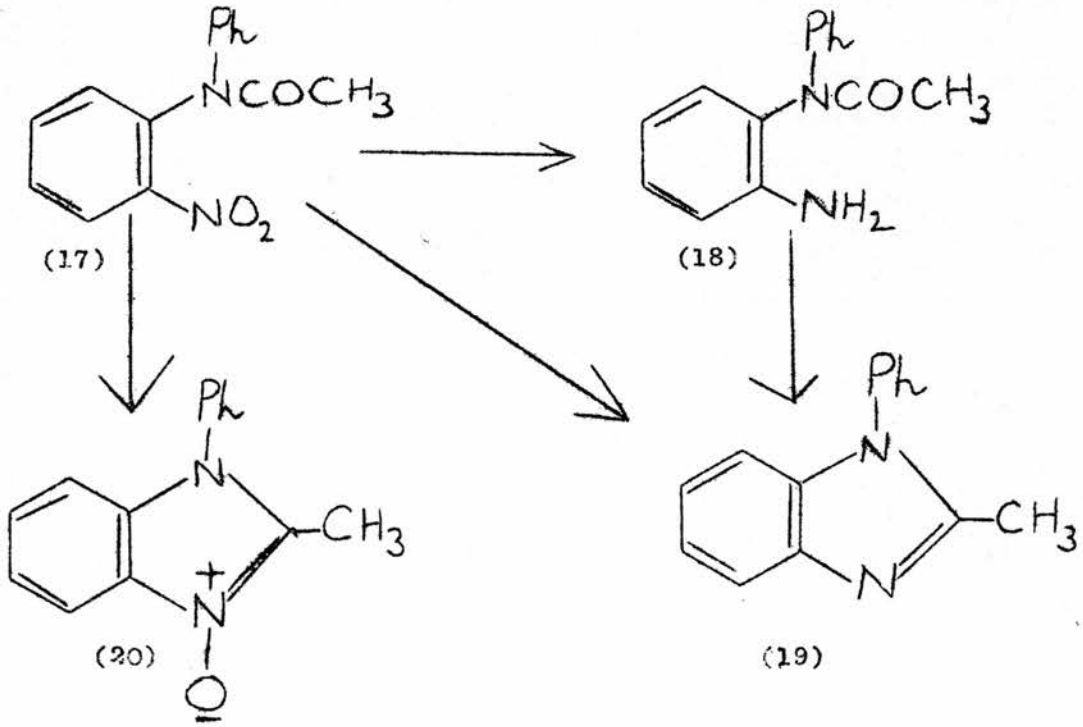


(15) (16)

Smith et al[6] reported that, while the hydrogenation with platinum catalyst of o-nitro-N-phenylacetanilide (17) in 50% ethanol gave o-amino-N-phenylacetanilide (18), the same reaction in 95% ethanol gave 2-methyl-1-phenylbenzimidazole (19). However, Forbes and Wragg[7] obtained

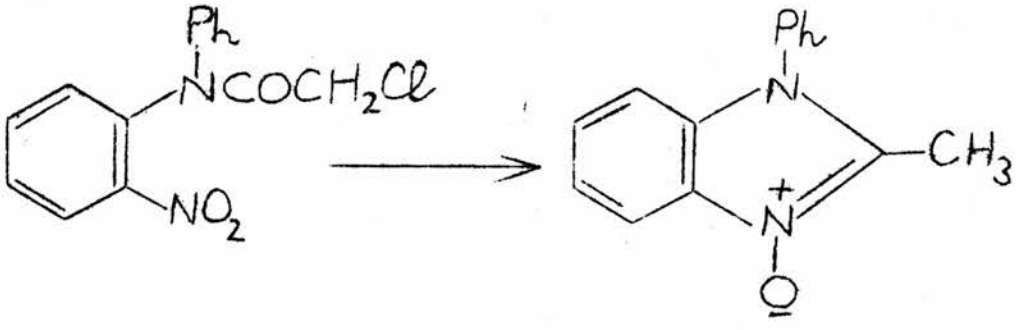


(17) (18) (20) (19)

Scheme 2

only the amine (18) by hydrogenation of (17) in ethanol with Raney Nickel catalyst.

Schulenburg and Archer[8] made a further study of this reaction, the result of which is shown in Scheme 2. Hydrogenation of (17) in 50%, 95%, or absolute ethanol, or in ethyl acetate, gave in all cases a high yield of the amine (18); this was converted to the benzimidazole (19) either by refluxing in xylene, or by treatment with hydrochloric acid at room temperature. Hydrogenation of (17) in ethanol in the presence of 0.2 molar equivalents of hydrochloric acid followed by treatment of the product with excess hydrochloric acid, gave the hydrochloride of the benzimidazole (19). However, if one or more molar equivalents of hydrochloric acid are present, the product was the hydrochloride of the 2-methyl-1-phenylbenzimidazole-3-oxide (20). It would appear that in this case the acid catalyses cyclisation of the hydroxylamine intermediate to the point where ring closure is faster than reduction to the primary amine. Similarly, hydrogenation of 2-chloro-2'-nitro-N-phenylacetanilide (21) in ethanol with platinum catalyst gives the hydrochloride of (20). It is possible that, in

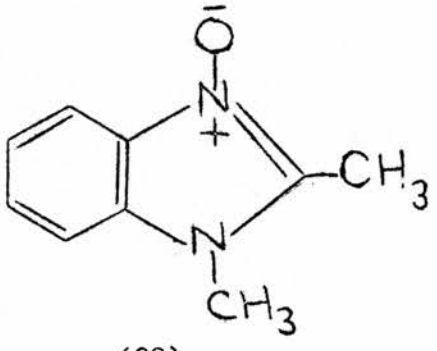


(21) (20)

this case, the ring closure is catalysed by the hydrogen chloride generated by reductive dehalogenation of (21),

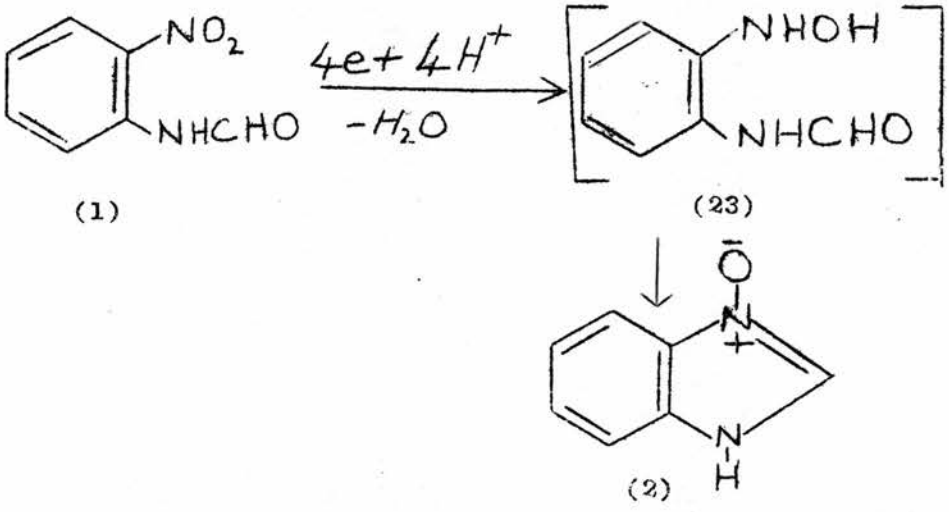
The catalytic hydrogenation of N-methyl-o-nitroacetanilide in ethanol with concentrated hydrochloric acid over palladium/charcoal[9]

was reported to give a higher yield of 1,2-dimethylbenzimidazole-3-oxide (22) than that obtained by the same procedure of Schulenburg and Archer[8] using a platinum catalyst.



(22)

Another reduction employing palladium/charcoal catalyst is that of o-nitroformanilide to benzimidazole-N-oxide, the anilide being added in pyridine solution to a suspension of palladinium/charcoal in an aqueous solution of sodium borohydride[10].



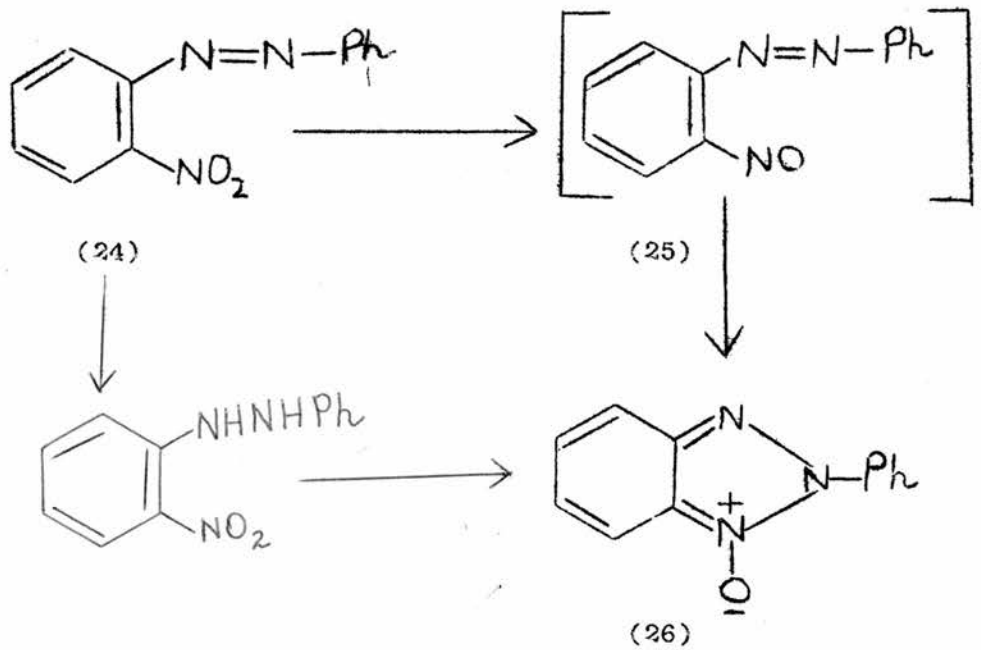
(1) (23) (2)

Controlled potential reduction of o-nitroformanilide (1) gives benzimidazole-N-oxide, presumably through the hydroxylamine intermediate (23).[11] The electrolytic method offers a convenient way to avoid overreduction by control of the potential.

(b) Other o-nitroaniline derivatives

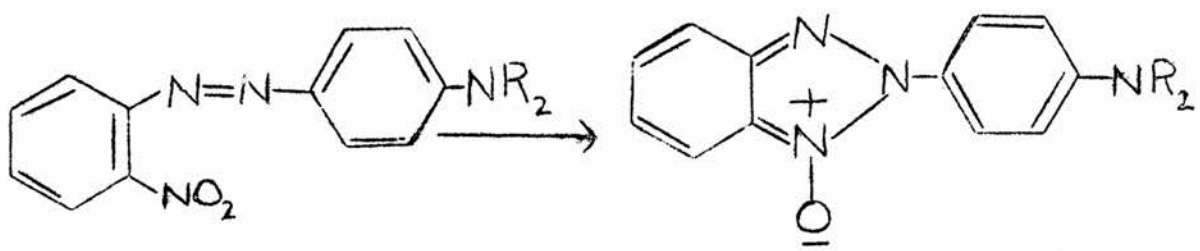
The reduction of o-nitroazobenzene (24) with ethanolic sodium sulphide[12] gave 2-phenylbenzotriazole-1-oxide (26). Rapid ring closure

of an intermediate o-nitrosoazobenzene (25) (cyclisation of o-nitrosoazo compounds to benzotriazole-1-oxides is well documented[13]) possibly accounts for the absence of products arising from further reduction of the o-nitroazobenzene (24).



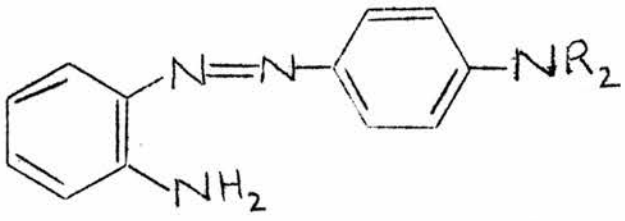
(24) (25) (26)

Similarly, reduction of 4-dialkylamino-2'-nitroazobenzenes (27) with ethanolic ammonium sulphide[14,15] gave 2-(p-dialkylaminophenyl) benzotriazole-1-oxides (28)



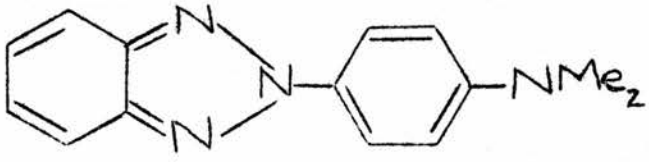
(27) (28)

Reduction of compound (27) (R = Me) with ethanolic sodium sulphide, however, was originally reported to give only the aminoazo derivative [(29); R = Me][14], but Ross and Warwick[15] found that this reduction gave



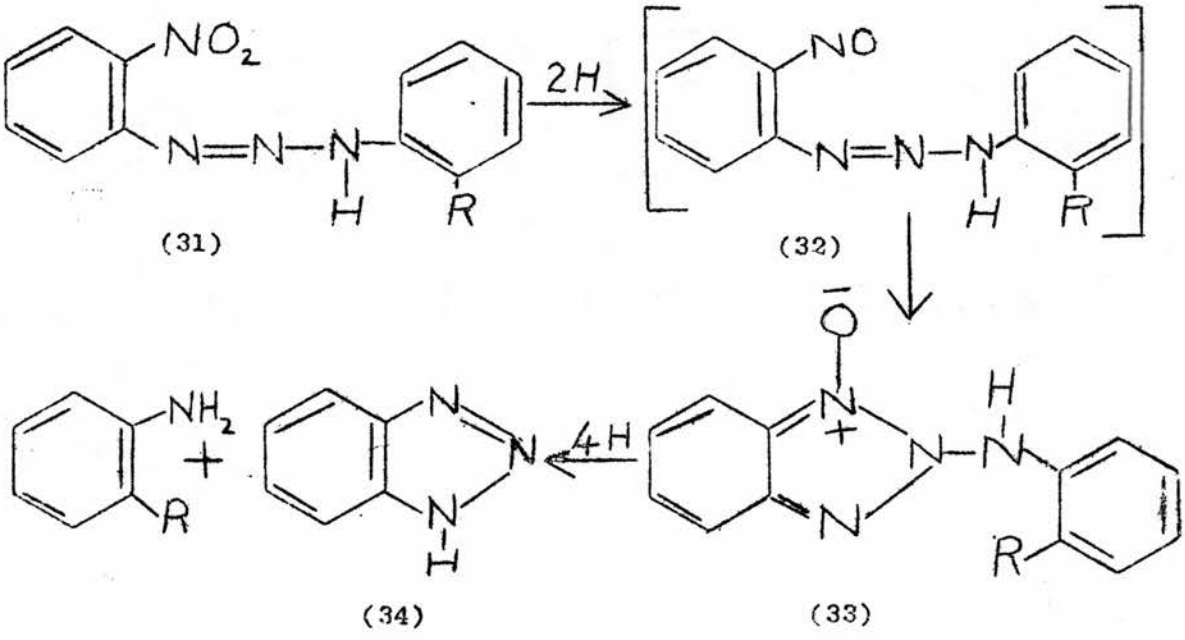
(29)

a mixture of 10% of the aminoazo compound (29) and 90% of the 2-(p-dimethylaminophenyl) benzotriazole (30).



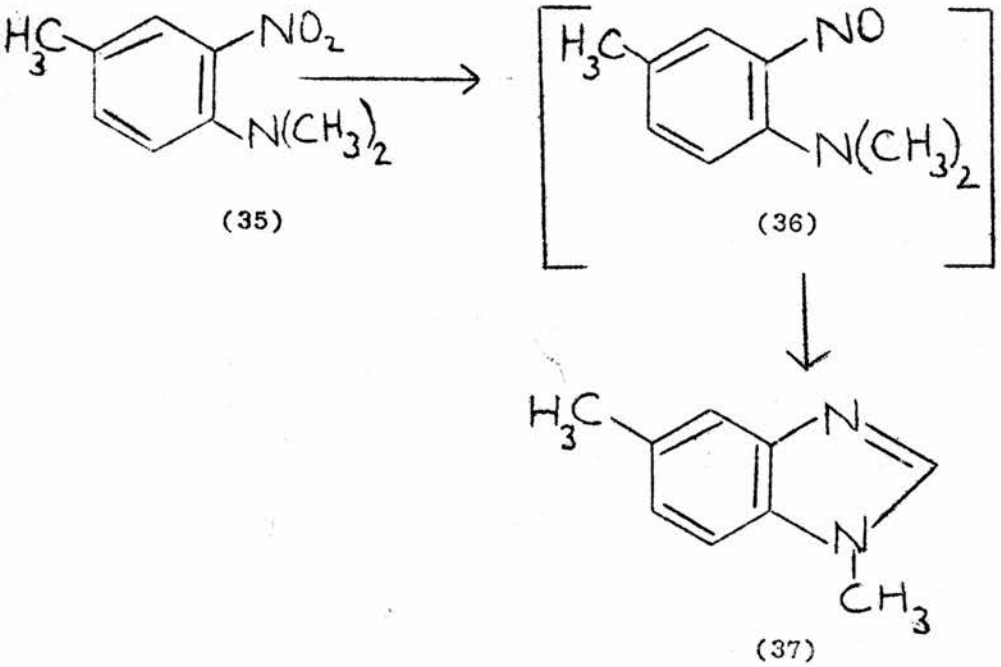
(30) "

1-o-nitrophenyl-3-phenyltriazenes (31) on hydrogenation in ethanol over platinum oxide absorbed three molar equivalents of hydrogen to give benzotriazole (34) and an aniline derivative[16]. The observation that the reaction mixture shows a transient deep green colour suggests that the o-nitrosophenyltriazene intermediate (32) may be formed, and the proposed reaction sequence, involving cyclisation to the benzotriazole-1-oxide (33) and subsequent hydrogenation, is shown in Scheme 3.



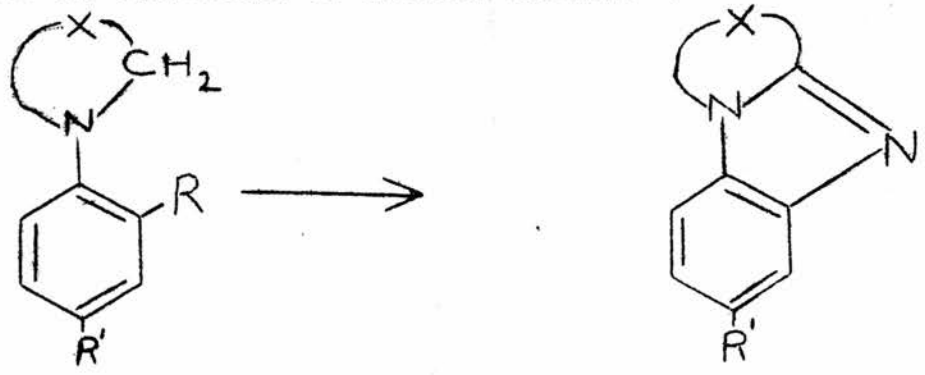
Scheme 3

Reduction of 3-nitro-4-dimethylaminotoluene (35) with tin and hydrochloric acid[17], or with sodium bisulphite[18], gave 1,5-dimethylbenzimidazole (37). The formation of the product was accounted for by assuming dehydrative cyclisation between a methyl group and the nitroso group of the intermediate (36), but an alternative mechanism, not involving reduction is also possible (cf. p.36)



(35) (36) (37)

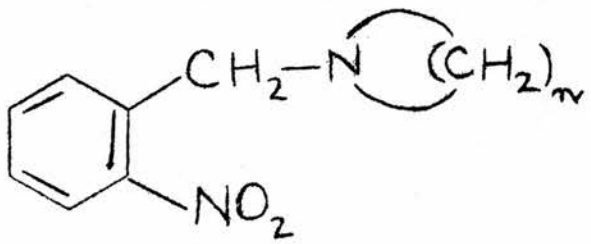
Reduction of the N-2-nitroarylamines (38) with titanous chloride in hydrochloric acid solution gave the hydrochlorides of the corresponding benzimidazoles (39) in quantitative yield on consumption of two equivalents of titanous chloride[19].



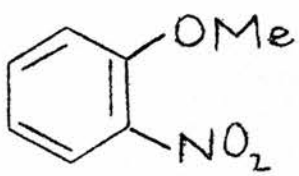
(38) (39)

R = NO_2; R' = H, X = $(CH_2)_3$ or $(CH_2)_5$;
or R' = Me, X = $(CH_2)_4$; or R' = CF_3, X = $(CH_2)_3$.

This reduction might well be expected to proceed by way of ring closure of a nitroso intermediate (cf. ref. 17 above). However, treatment of the compound [(38); R = NH_2, R' = NO_2, and X = $(CH_2)_4$] with Caro's acid (H_2SO_5) which is specific for the oxidation of a primary amine to a nitroso function, failed to effect cyclisation to the benzimidazole.[19] Furthermore, the compounds [(40); n = 4 or 5] and (41) also failed to cyclise,[19] which would probably not be the case if a nitroso intermediate was involved.

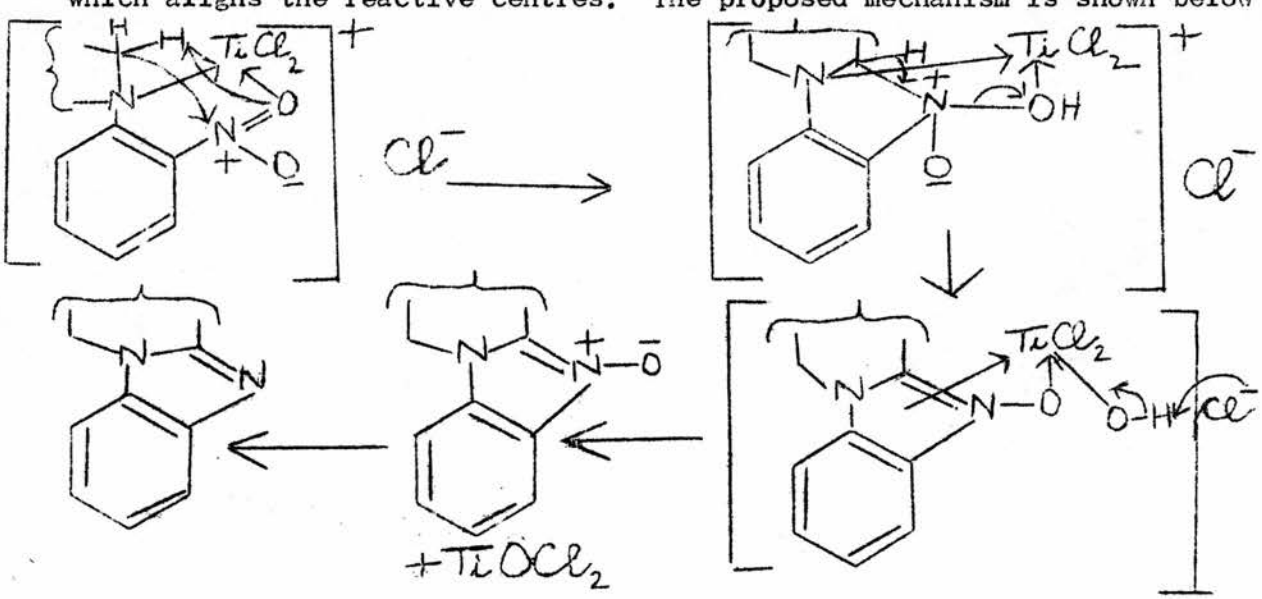


(40)



(41)

These results both emphasize the importance of the role and position of the "tertiary nitrogen" in these reactions and cast doubt on the intermediacy of nitroso compounds in these and similar cyclisations[17,18] under reducing conditions. It would appear that titanous chloride and similar reagents have a dual function in this reaction, namely as a reducing agent, and also as a chelating agent which aligns the reactive centres. The proposed mechanism is shown below[19].

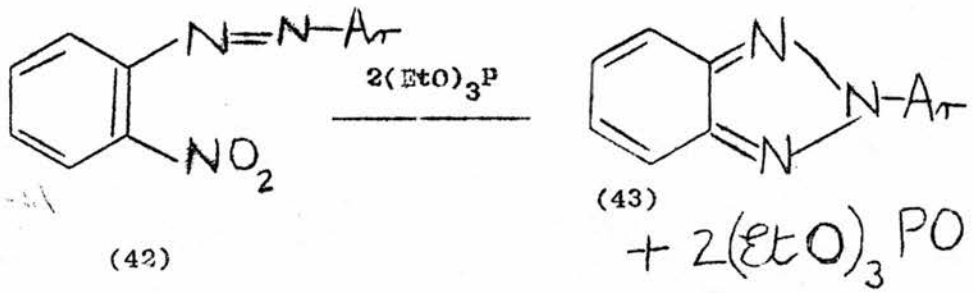


Titanous chloride was shown independently to effect the final deoxygenation step.

(c) Reductive cyclisations involving deoxygenating agents

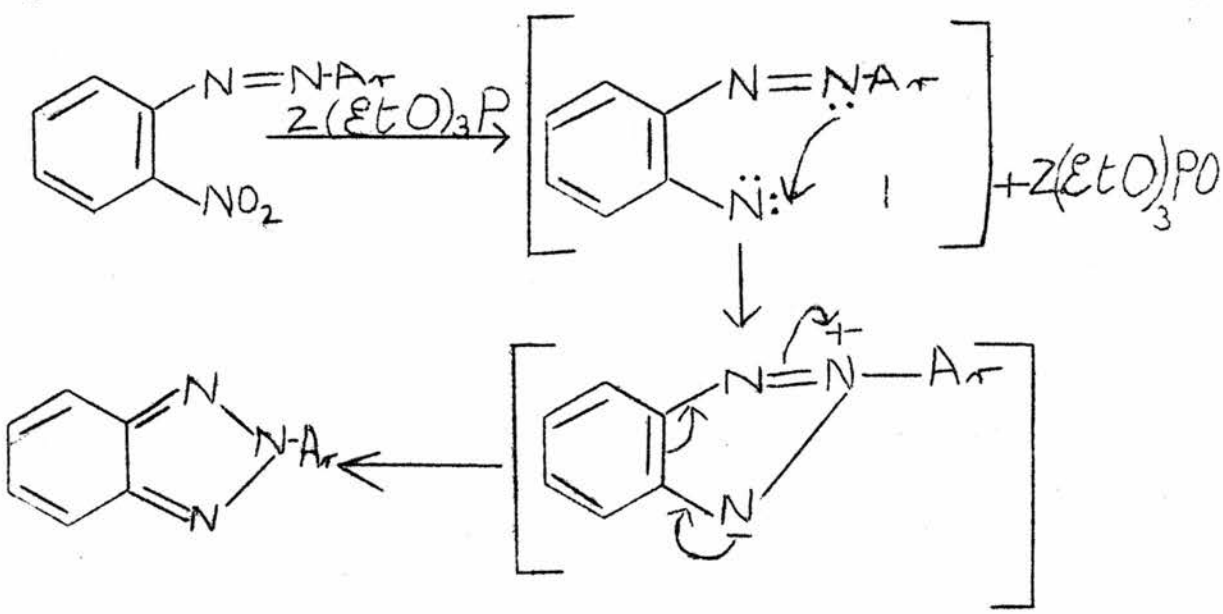
These are well known and those involving the reduction of o-nitroaniline derivatives by tervalent phosphorus reagents are discussed below.

The 2-nitroazobenzenes [(42); Ar = Ph, *p*-BrC_6H_4, *p*-$OMeC_6H_4$, *p*-ClC_6H_4 or *p*-MeC_6H_4] were reduced by boiling with triethylphosphite to the corresponding benzotriazoles (43), triethyl phosphate being produced in the reaction[20].

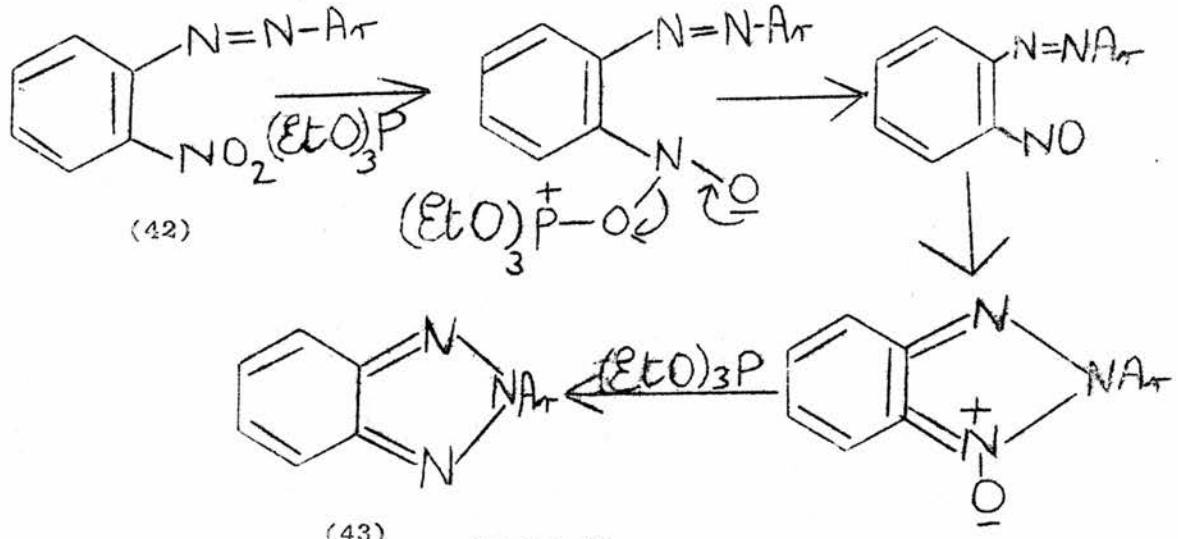


(42) (43) + $2(EtO)_3PO$

The reaction is thought to proceed via generation of a nitrene intermediate from the nitro group by the triethyl phosphite[21], as shown in Scheme 4a, although polar mechanisms have also been suggested, e.g. Scheme 4b.



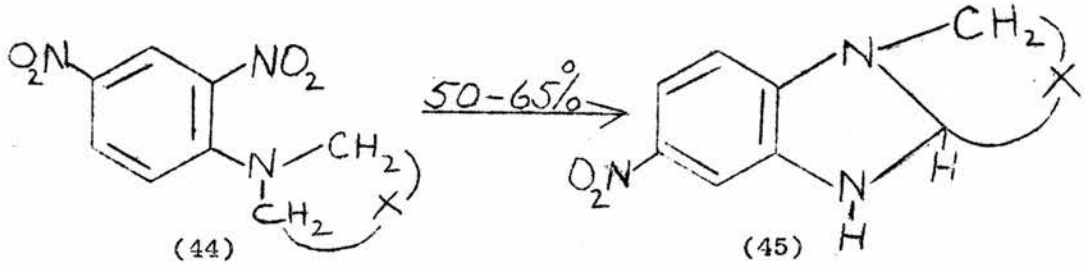
Scheme 4a



(42) (43)

Scheme 4b

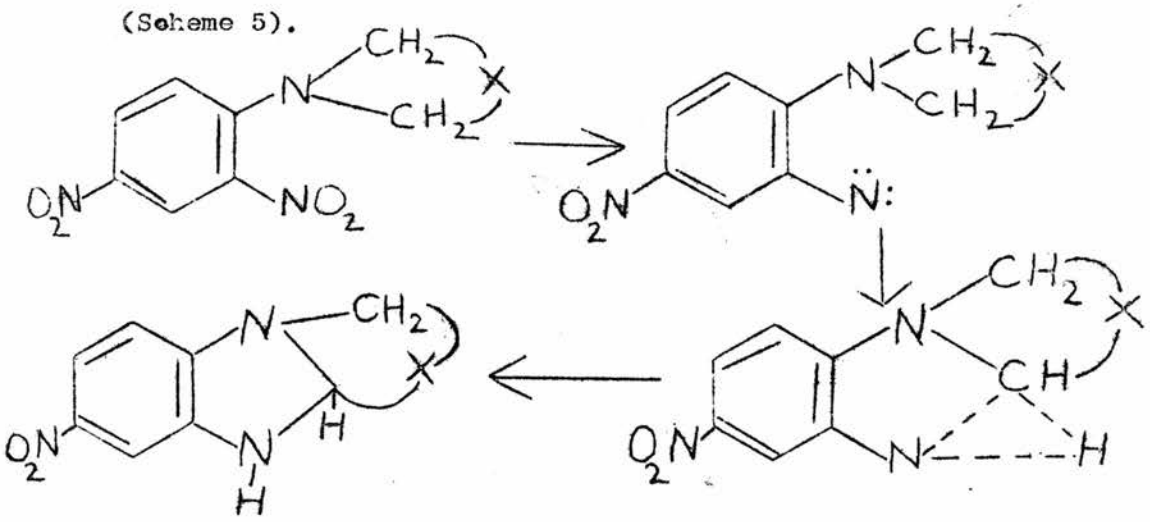
It was found that deoxygenation of the dinitro compounds (44) with boiling trimethyl phosphite gave the dihydrobenzimidazoles (45)[22] as shown below



(44) (45)

X = $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$, $(CH_2.O.CH_2)$ and $(CH_2.NMe.CH_2)$.

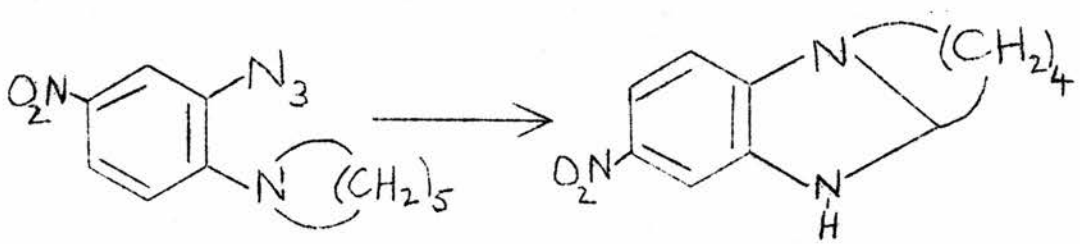
Again a mechanism involving a nitrene intermediate may be involved (Scheme 5).



Scheme 5

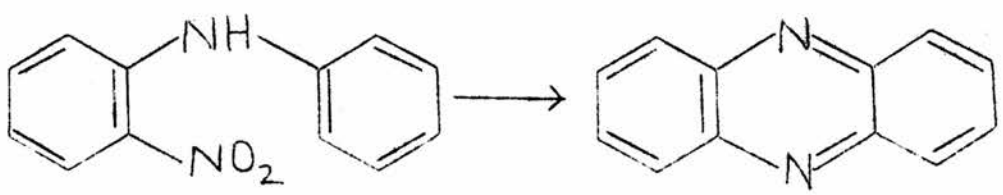
It is interesting that the trialkyl phosphite preferentially attacks the nitro group ortho to the amino-substituent.

Nitrene intermediates are very likely in the above reactions since the same products were obtained from pyrolysis of the corresponding azido compounds, e.g. the N-2-azidophenylpiperidine (46) gave the dihydrobenzimidazole (45)[22].



(46) (45)

Other cyclisations using a deoxygenating agent include the preparation of phenazines by heating 2-nitrodiphenylamines with ferrous oxalate e.g. (47) ⟶ (48)[23].



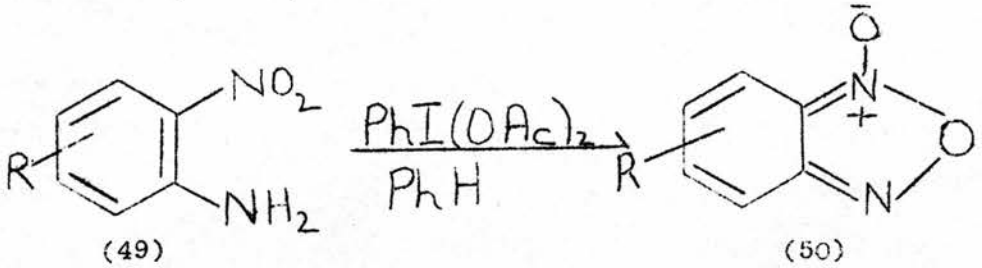
(47) (48)

It has been postulated that reductive cyclisation of aromatic nitro compounds by ferrous oxalate proceeds via the nitrene intermediate produced by deoxygenation of the nitro group[24], again on the basis that pyrolysis of the corresponding azides gave analogous products, though Smith and Suschitzky[25] believe that pyrolysis of (47) to (48) in sand in the presence of ferrous oxalate probably proceeds through the aci-nitro tautomer, and this is duscussed in more detail in the section on thermal cyclisations (p.29)

B. Oxidative cyclisations

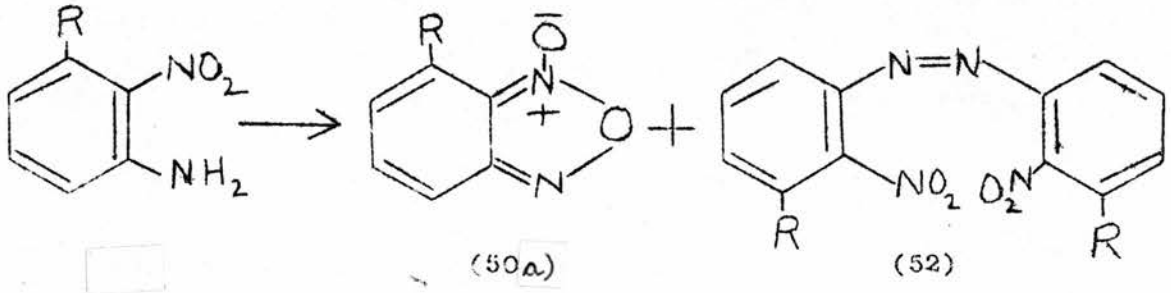
It was found that many 4- and 5-substituted 2-nitroanilines (49)

were converted into the corresponding benzofurazan oxides (50) in excellent yield by oxidation with iodosobenzene diacetate in benzene[26].



(49) (50)

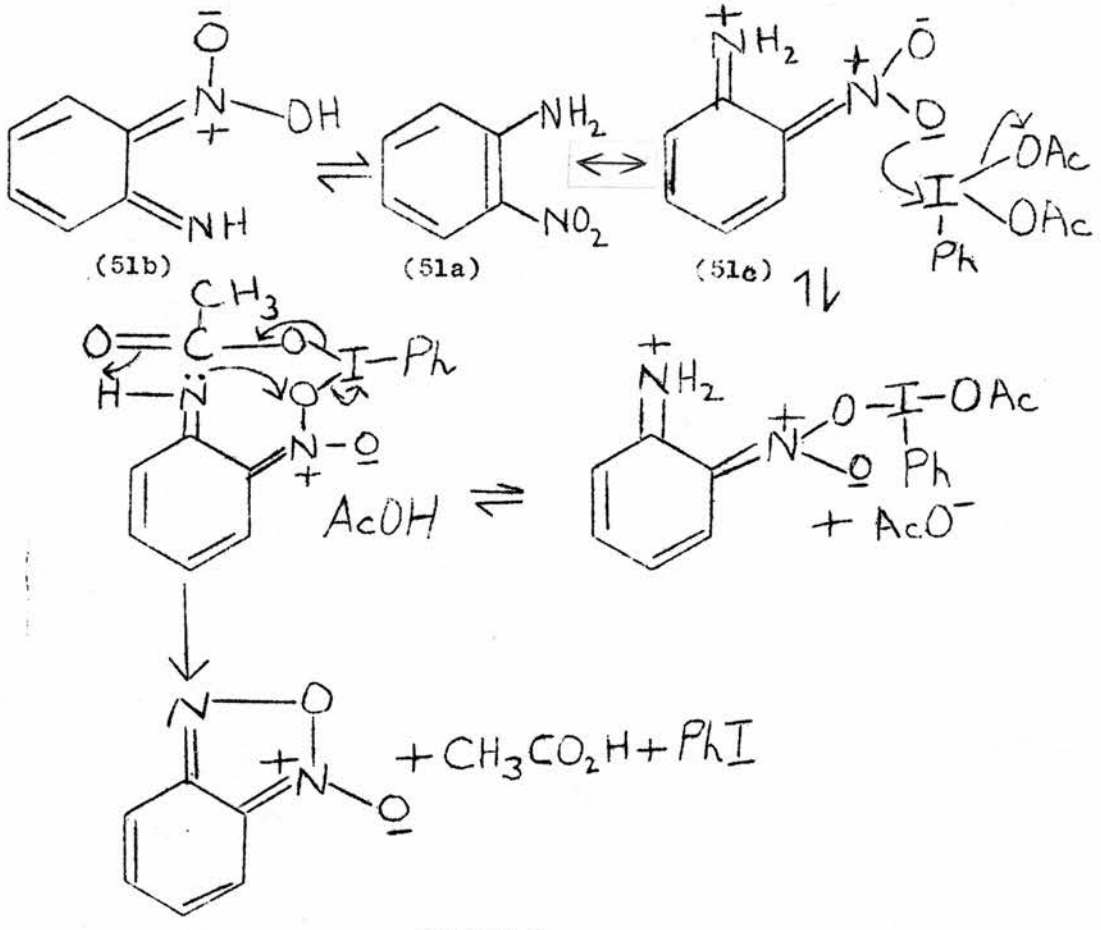
In acetic acid as solvent only moderate yields of the corresponding azo compounds could be isolated[27]. It was proposed that, in benzene solution, oxidation proceeded via attack by the oxidant on the hydroxyl group of the aci-nitro tautomer, (51b) whereas in acetic acid solution the oxidation involved attack on the amine function of o-nitroaniline (51a) to yield the free radical precursors of azo compounds. However, it was found that 3-substituted 2-nitroaniline derivatives gave a mixture of the corresponding benzofurazan oxide (50a) and azo compound (52) on oxidation with iodosobenzene diacetate in benzene solution and in acetone solution the yield of benzofurazan oxide was increased[28].



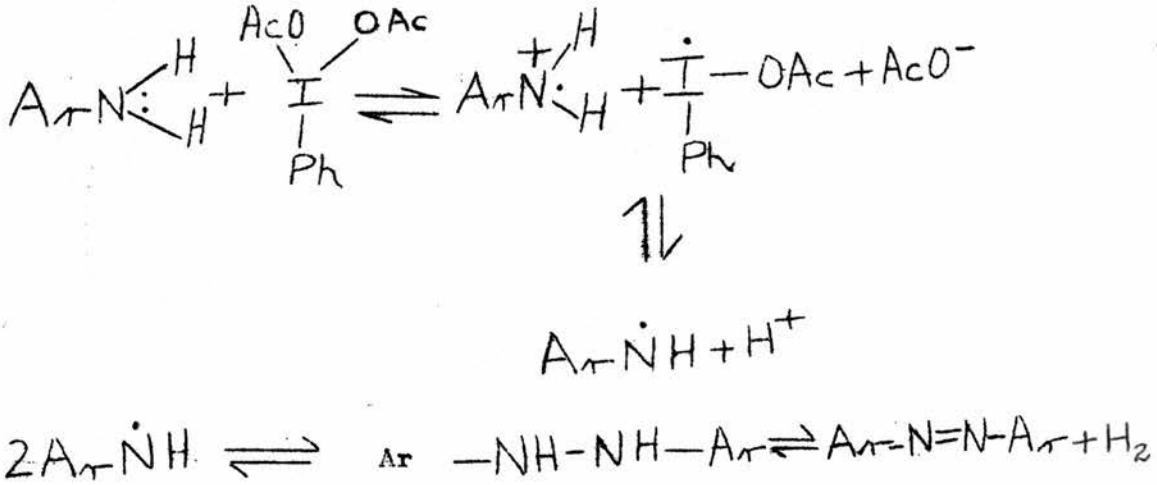
(50a) (52)

It was thought that interference by the solvent with the stabilising intramolecular hydrogen bonding prevented formation of the aci-nitro tautomer in acetic acid solution, thus giving rise to the azo compound, but acetone, which should have the same effect, increased the oxide yield. Thus it would appear that the aci-nitro tautomer is not an intermediate. It seemed likely, therefore, that the reaction involved nucleophilic attack of both the contributing form (51c) and o-nitroaniline

itself on the iodine atom of the oxidant, to give the benzofurazan oxide and the azo compound respectively as shown below in Schemes 6 and 7.



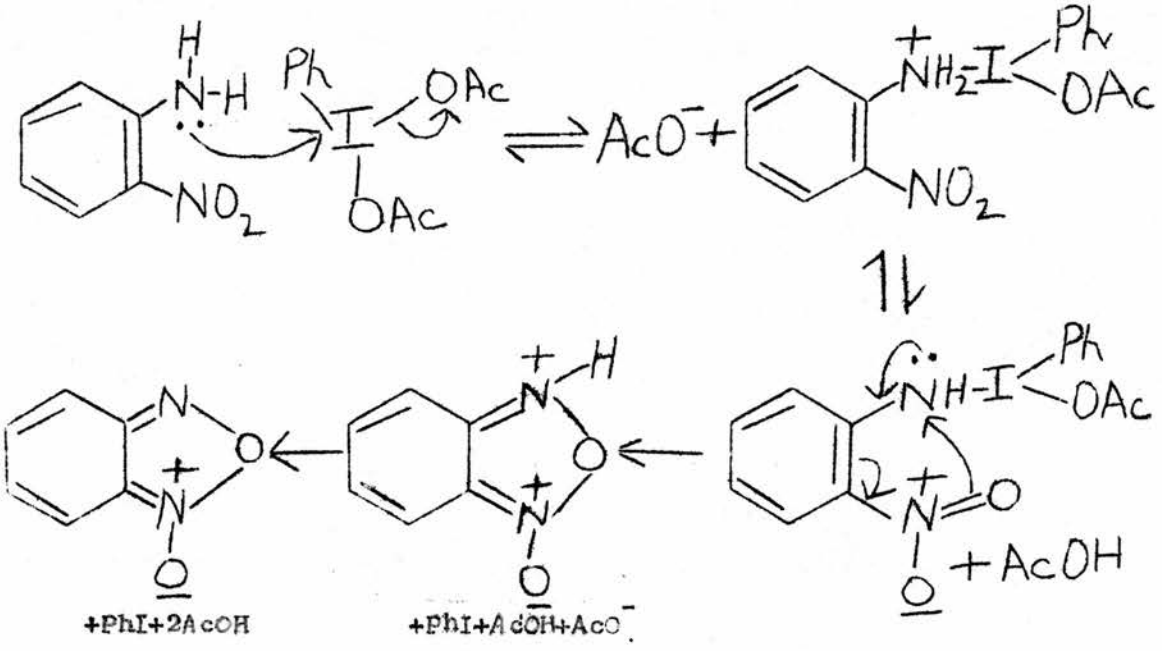
Scheme 6



Scheme 7

The final stage of Scheme 7 is acceptable since hydrazobenzene is oxidized to azobenzene in 92 per cent yield with iodosobenzene diacetate in benzene solution[29].

More recently, however, Dyall and Kemp[30], postulated an alternative mechanism for benzofurazan oxide formation (Scheme 8)

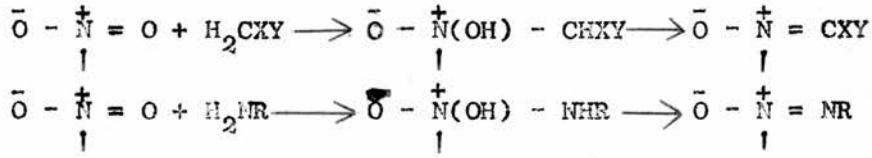


Scheme 8

2-nitroanilines are also oxidized to benzofurazan oxides by alkaline sodium hypochlorite[31], though the mechanism of this reaction has not been elucidated.

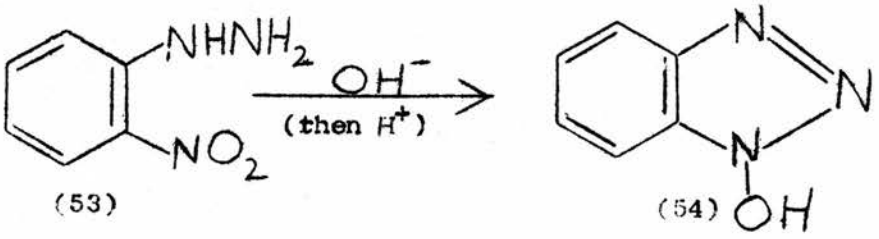
C. Base-catalysed cyclisations

The majority of base-catalysed cyclisations of o-nitroaniline derivatives are most simply expressed by considering the nitro group to provide an electrophilic centre for additive reactions of the aldol condensation type, as shown below.



The reactive nucleophilic centre is in a side-chain ortho to the nitro group, in a position sterically favourable for attack on the nitro group. The situation, however, may be complicated by the possibility of tautomerism and rearrangement within the conjugated system, giving rise to aci-nitro and nitroso intermediates. Moreover, in some cases, reduction by an external reagent may also be a possible step in the reaction.

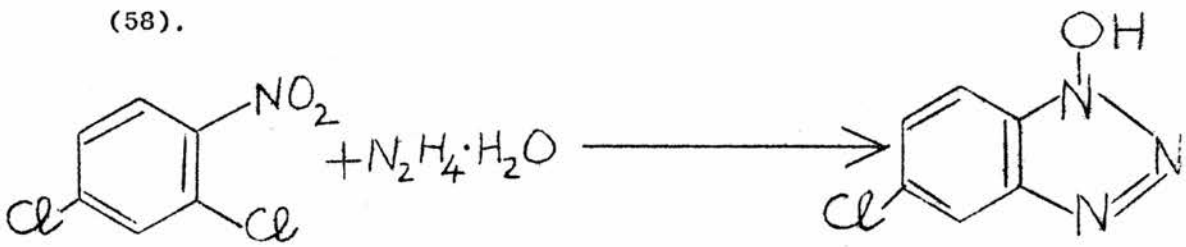
One of the earliest examples of this type of reaction was found by Nietzki and Braunschweig[32], who showed that treatment of o-nitrophenylhydrazine (53) with aqueous alkali gave the anion of 1-hydroxybenzotriazole (54)



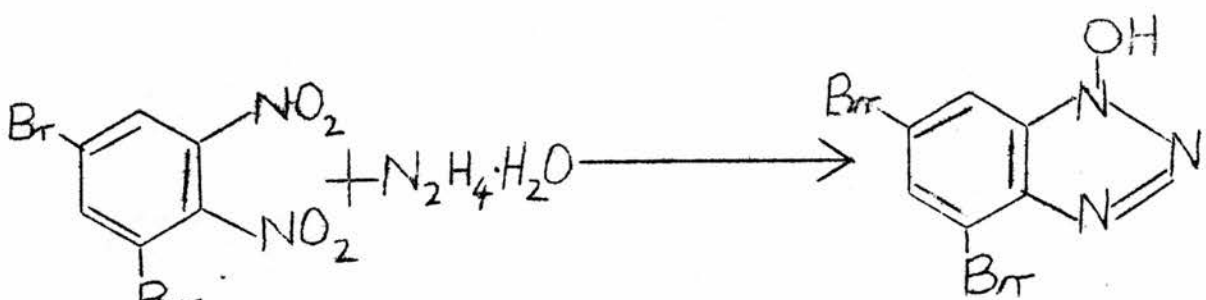
(53) (54)

Similarly, 2,4-dinitrophenylhydrazine was cyclised to 1-hydroxy-6-nitrobenzotriazole by hydrazine hydrate[33]. This reaction was extended to the preparation of hydroxybenzotriazoles by the

reaction of o-halogenonitrobenzenes[34] and o-dinitrobenzenes[35] with hydrazine hydrate: thus the interaction of 2,4-dichloronitrobenzene (55) and hydrazine hydrate led to 5-chloro-1-hydroxybenzotriazole (56) and similarly the reaction of 3,5-dibromo-1,2-dinitrobenzene (57) gave 4,6-dibromo-1-hydroxybenzotriazole (58).

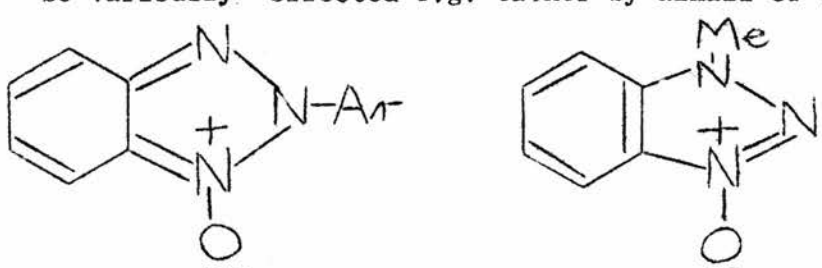


(55) (56)

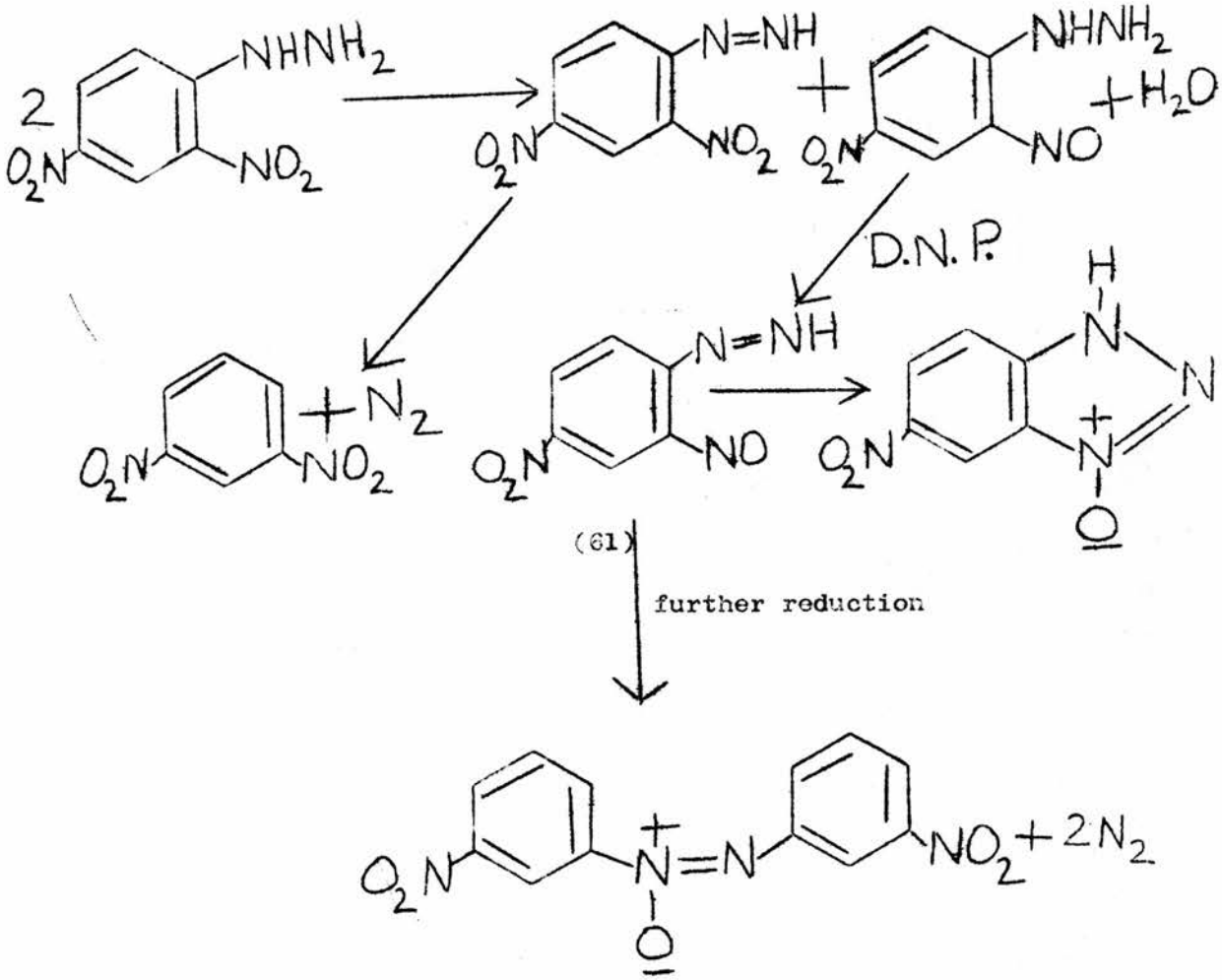


(57) (58)

N oxides of type (59) were prepared similarly, from phenylhydrazine and halogenonitro- or dinitro-benzene, or by cyclisation of preformed 2-nitrohydrazobenzenes[36]. In these reactions reduction to 2-substituted benzotriazoles often occurred and cyclisation could be variously effected e.g. either by alkali or by hot acetic acid.

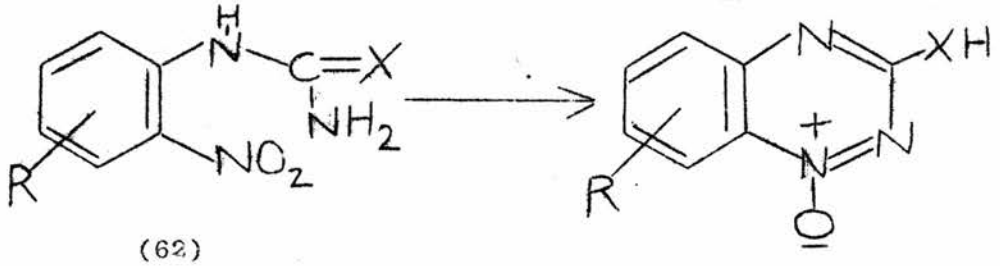


(59) (60)


2
NHNH2
O2N
NO2
N=NH
O2N
NO2
NHNH2
+H2O
O2N
NO
D.N.P.
+N2
O2N
NO2
N=NH
O2N
NO
H
N
N
+
N
O
O2N
(61)
further reduction
O2N
+
N
=N
NO2
+2N2
O

On the other hand, the corresponding reactions with methylhydrazine, which gives 1,1-disubstituted hydrazines with reactive chloronitro- or dinitrobenzenes[37,38] led only to 3-methylbenzotriazole-1-oxide (60)[35] and not to (59: Me for Ar). While the internal aldol mechanism offers a simple interpretation of the formation of these benzotriazole-N-oxides, there is also evidence in these reactions of the powerful reducing properties of hydrazines. For example, Macbeth and Price[39] found that the reaction using 2,4-dinitrophenylhydrazine (D.N.P.) gave 3,3'-dinitroazoxybenzene and m-dinitrobenzene in addition to 6-nitro-1-hydroxybenzotriazole, the proportions varying with the pH of the reaction medium, and the yield of heterocycle being minimal at low base concentrations. A possible scheme for this reaction, involving an intermolecular oxidation-reduction reaction is shown on the facing page. However, a competing intramolecular oxidation-reduction reaction, providing (61) could still provide a route to the benzotriazole-N-oxide.

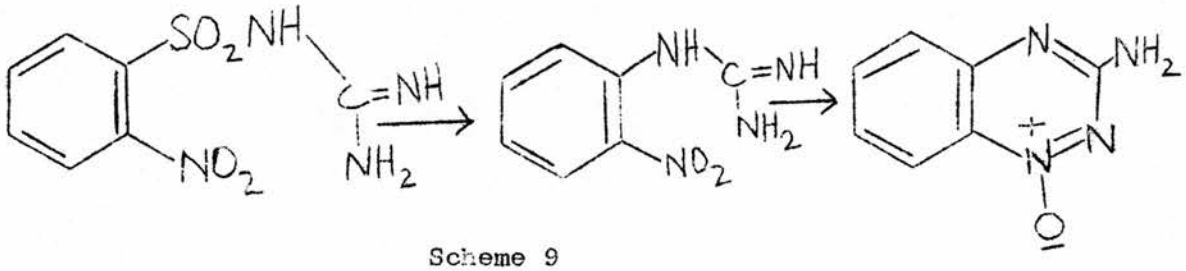
Arndt[40] found that warming o-nitrophenylguanidine [(62); X=NH] with dilute alkali gave 3-aminobenzotriazine-1-oxide [(63); X=NH] rapidly and in high yield. Similar treatment of o-nitrophenylurea, o-nitrophenylthiourea and the N-phenyl derivative of o-nitrophenylguanidine [(62); X=O, S or NC_6H_5] also gave the corresponding benzotriazine-1-oxides [(63), X=O, S or NC_6H_5][40,41], as did various substituted o-nitrophenylguanidines[42] and o-nitrophenylureas[43].



(62)

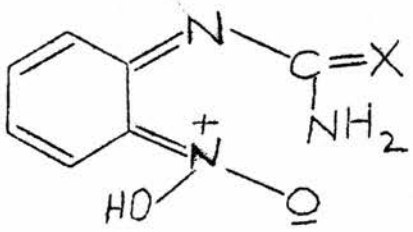
(63)

The o-nitrophenylguanidines and o-nitrophenylureas may be prepared *in situ* by rearrangement of their o-nitrobenzenesulphonyl derivatives by treatment with hot alkali as shown in Scheme 9[44].



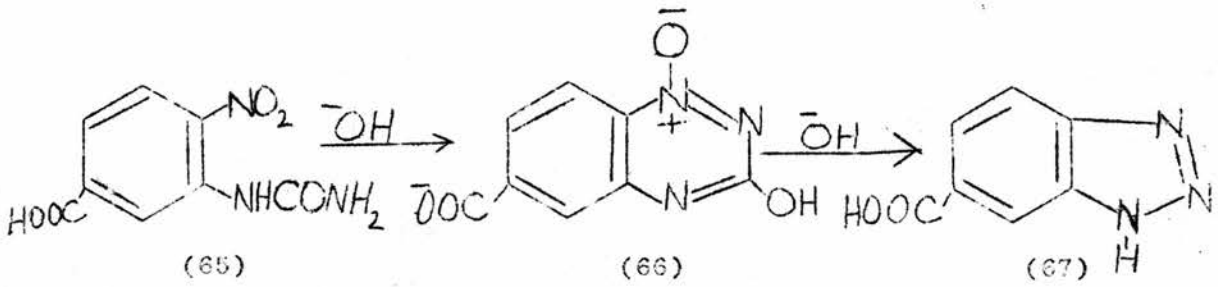
Scheme 9

Although the internal aldol condensation again offers the simplest explanation of this class of reaction, Arndt[40] suggested that, as the reaction often proceeds with first a deepening and then a fading of colour, a salt of the *aci*-nitro-compound (64) might be an intermediate.



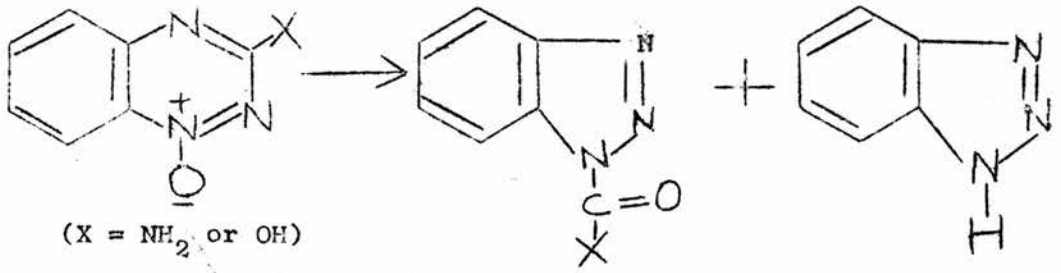
(64)

A closely related transformation was discovered by Griess[45] who obtained benzotriazole-5-carboxylic acid (67) by the treatment of 4-nitro-3-ureidobenzoic acid (65) with hot potassium hydroxide. By analogy with Arndt's work this reaction probably proceeds through the intermediate, 3-hydroxybenzotriazine-1-oxide-6-carboxylic acid (66), since it has been found[46] that both 3-aminobenzotriazine-1-oxide and 3-hydroxybenzotriazine-1-oxide undergo rearrangement in presence of base to benzotriazole-



(65) (66) (67)

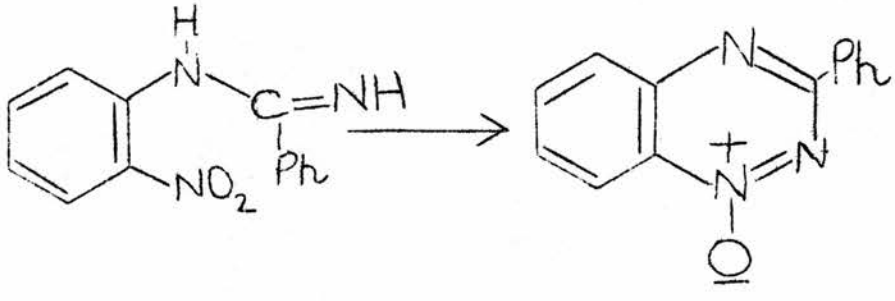
1-carboxamide (68) and its hydrolysis product, benzotriazole (69), in the former case, and (69) alone in the latter.



(X = NH_2 or OH)

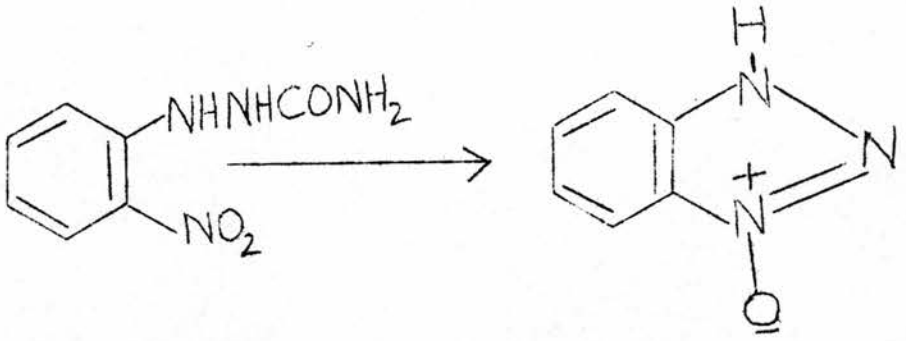
(68) (69)

In another variation on the Arndt cyclisation 3-phenylbenzotriazine-1-oxide (71) was synthesised by cyclisation in alkali of N-o-nitrophenylbenzamidine (70)[47].



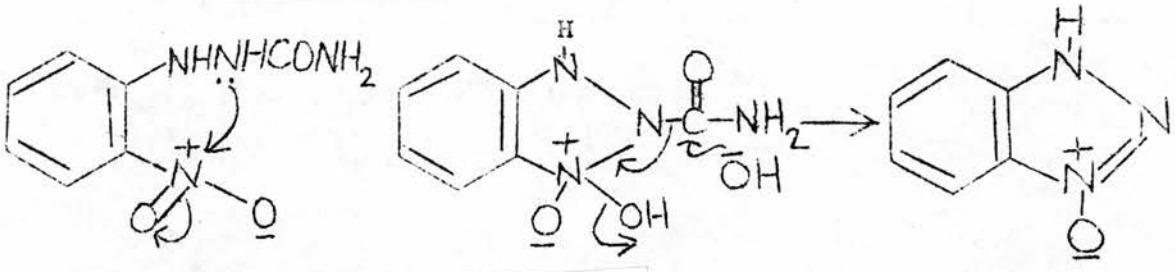
(70) (71)

This reaction has been extended to sodium alkoxide- induced cyclisations of o-nitroaryl benzamidines substituted on the nitroaryl and/or the benzene ring[48]. The treatment of o-nitrophenylsemicarbazide (72) with alkali gives benzotriazole-1-oxide (73).[49]

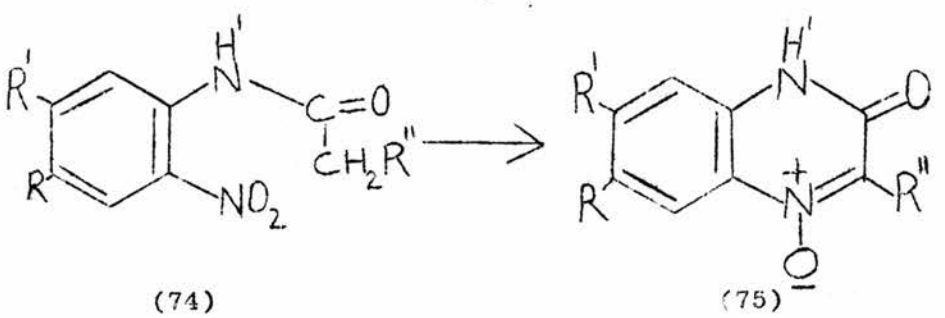


(72) (73)

Unlike the previous cyclisations however, this cyclisation does not occur at the terminal amino group. A likely mechanism is shown below.



o-Nitroacetanilide did not undergo cyclisation to quinoxaline-N-oxide on treatment with base[50], presumably because the methyl group in the side chain is not sufficiently activated to promote carbanion formation necessary for an aldol-type condensation. However, cyclisation of o-nitroacetanilide derivatives has been effected where the methylene group is activated by a suitable substituent. For example, the α-cyano-o-nitroacetanilides (74a) were cyclised to the corresponding 2-cyano-3-hydroxyquinoxaline-1-oxides (75a) on treatment with alkali[51], while similar treatment of the α-acyl- or α-aryl-o-nitroacetanilides (74b, c and d) gave the corresponding 2-acyl[52] or 2-aryl[53]-3-hydroxyquinoxaline-1-oxides (75b, c and d).

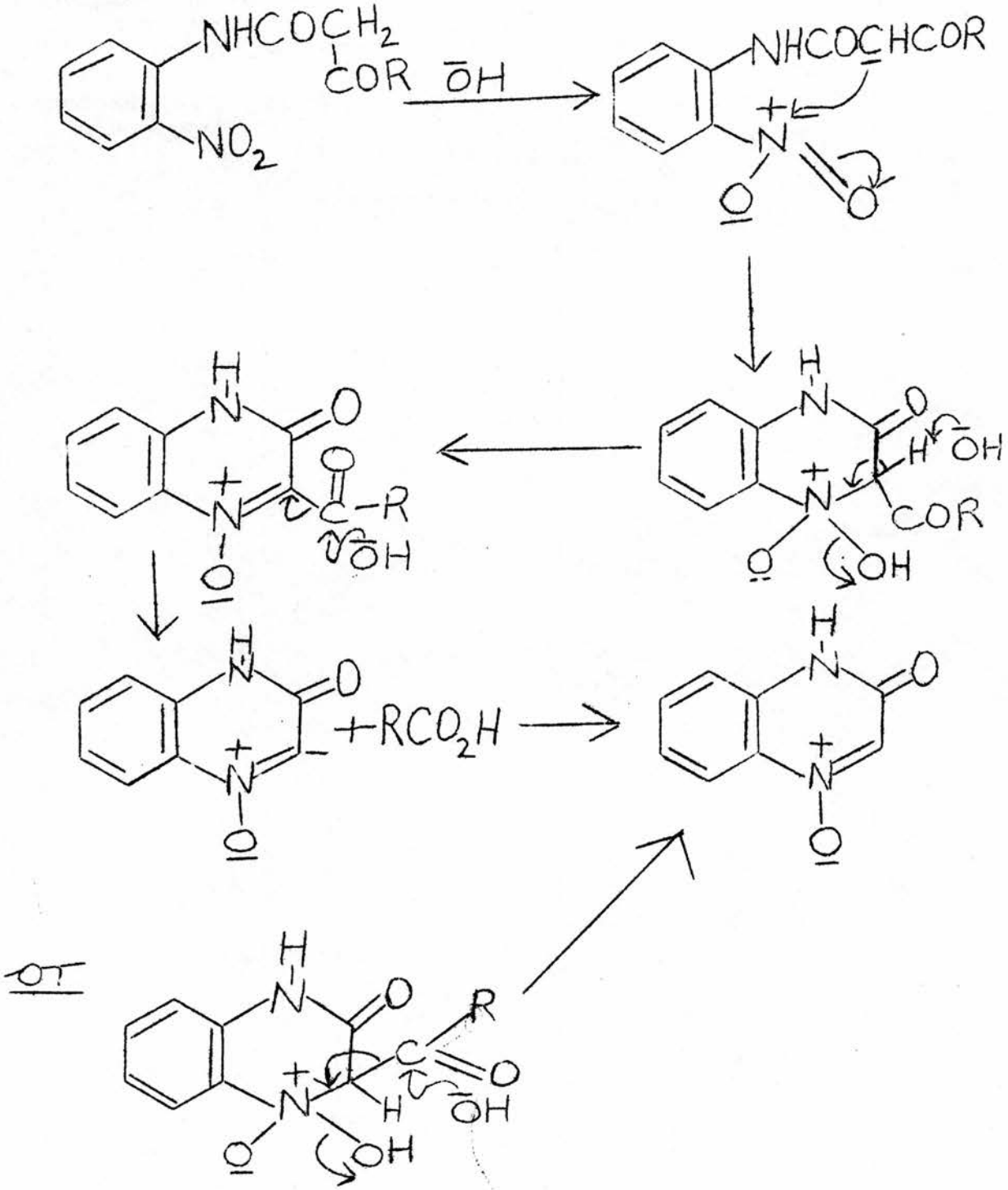


(74) (75)

	R	R'	R"
(a)	H, Cl, EtO, or MeO	H	CN
(b)	H	H	$COCH_3$
(c)	H	H	COPh
(d)	H	H	Ph or $\underline{p}$-$O_2NC_6H_4$-

If in the above reactions the cyclisation step is preceded by the formation of an aci-nitro intermediate, then N-oxide formation would not occur with N-methylated acetanilides. However, the N-methylated acetanilides (74; Me for H', R = R' = H, R" = Ph or CN) gave better yields of the corresponding oxides (75; Me for H', R = R' = H, R" = Ph or CN) on base catalysed cyclisation, than their unmethylated analogues[54], perhaps due to a greater resistance to hydrolysis on the part of these methylated acetanilides.

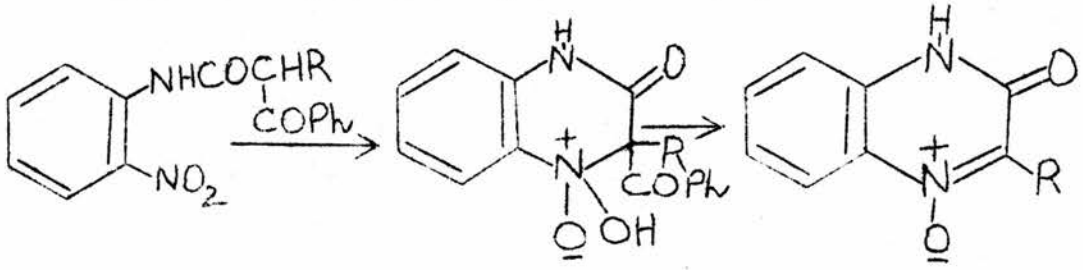
Side reactions may accompany, or follow, the cyclisation process: for example, treatment of the o-nitroacetanilides(74a) with alkali under more severe conditions than above[51] gave the 2,3-dihydroxyquinoxaline-1-oxide (75a; R' = OH), while similar treatment of the α-acyl-o-nitroacetanilides[52] (74b and c) gave 2-hydroxyquinoxaline-4-oxide (75; R = R' = R" = H). In each of these cases treatment of the quinoxaline-N-oxide (75a, b and c) with alkali gave the product obtained as above from the corresponding acetanilide[51,52] i.e. (75a; R'=OH, and 75; R = R'=R"= H).


NHCOCH2
COR
ŌH
NO2
NHCOCHCOR
+
N
O
O
H
OH
COR
OH
R
OH
+RCO2H
OT
H
N
O
R
C
O
H
OH
OH

Scheme 10

The proposed mechanism for the above class of reaction, typefied by the cyclisation of an α-acyl o-nitroacetanilide, is shown in Scheme 10. Two possible routes to the 2-hydroxyquinoxaline-4-oxide are also shown.

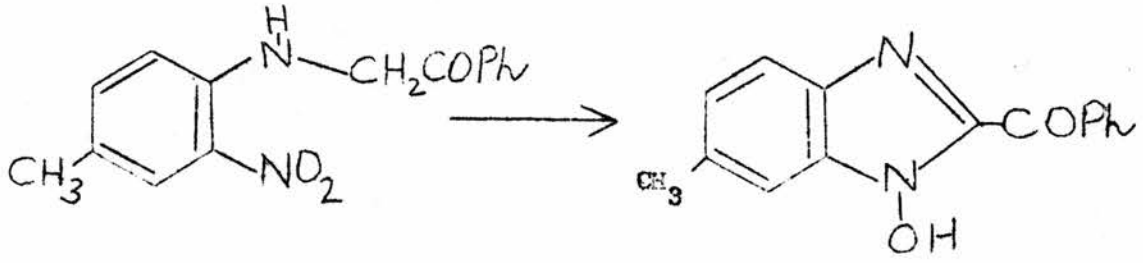
A similar elimination step, involving nucleophilic attack on an acyl group, presumably operates for the cyclisation of the acetanilides (76) to the quinoxalines (77)[54,55]



(76) (77)

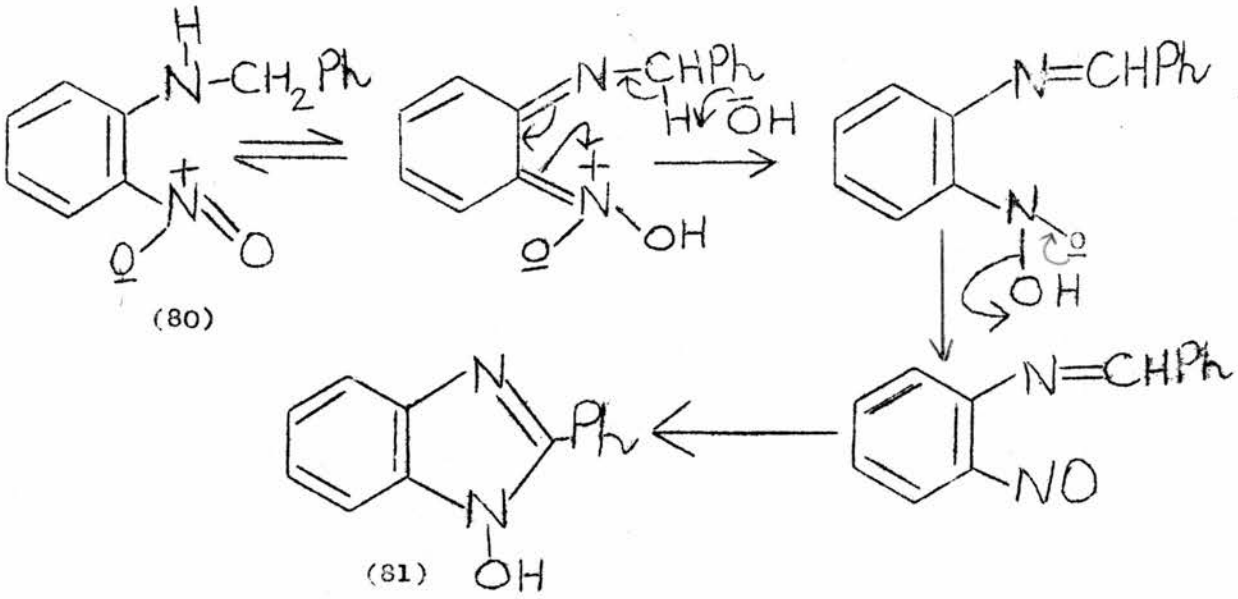
R = CH_3 or C_2-C_7, n-alkyl

A further example of cyclisation of an o-nitroaniline derivative with a reactive methylene group in its side chain is the cyclisation of 2-nitro-N-phenacyl-p-toluidine (78) with alkali to 2-benzoyl-1-hydroxy-6-methylbenzimidazole (79)[56].

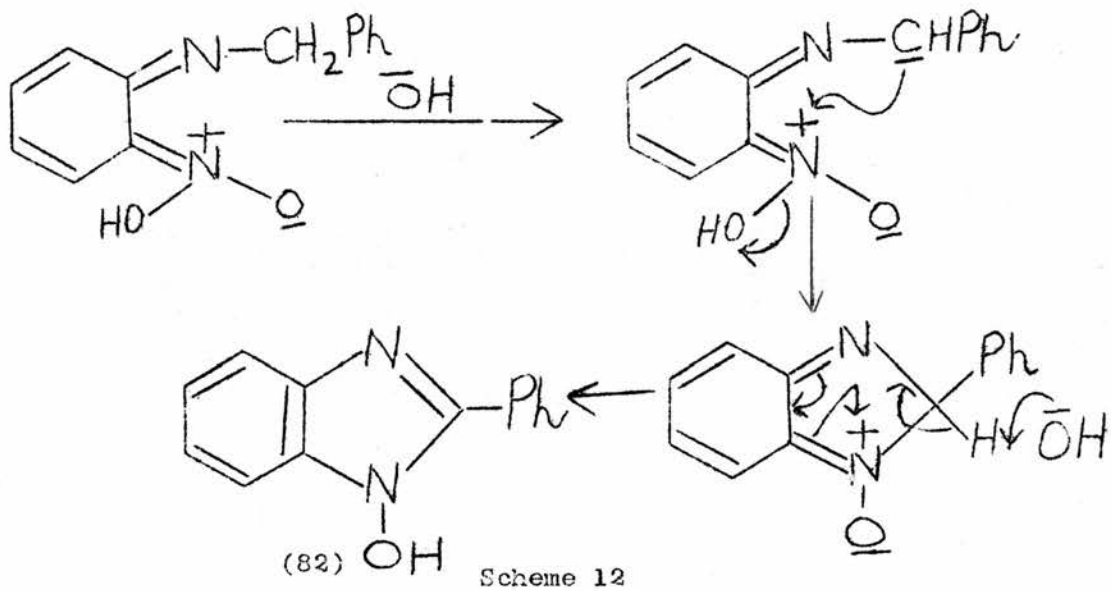


(78) (79)

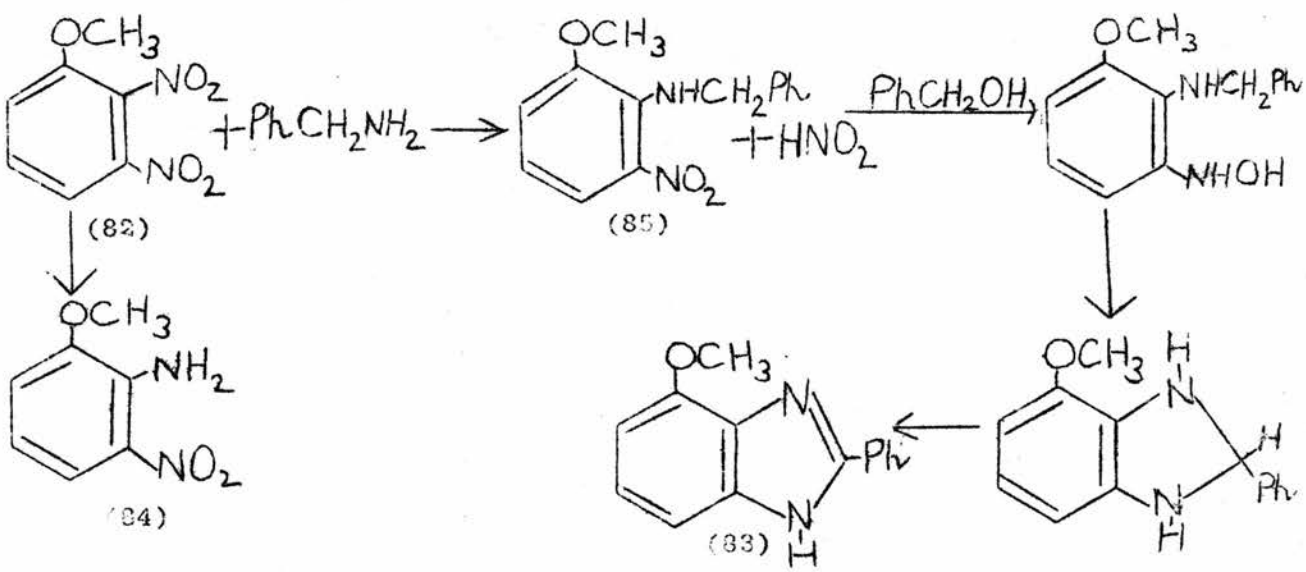
The related cyclisation of N-benzyl-o-nitroaniline (80) to 1-hydroxy-2-phenylbenzimidazole (81) by heating with sodium



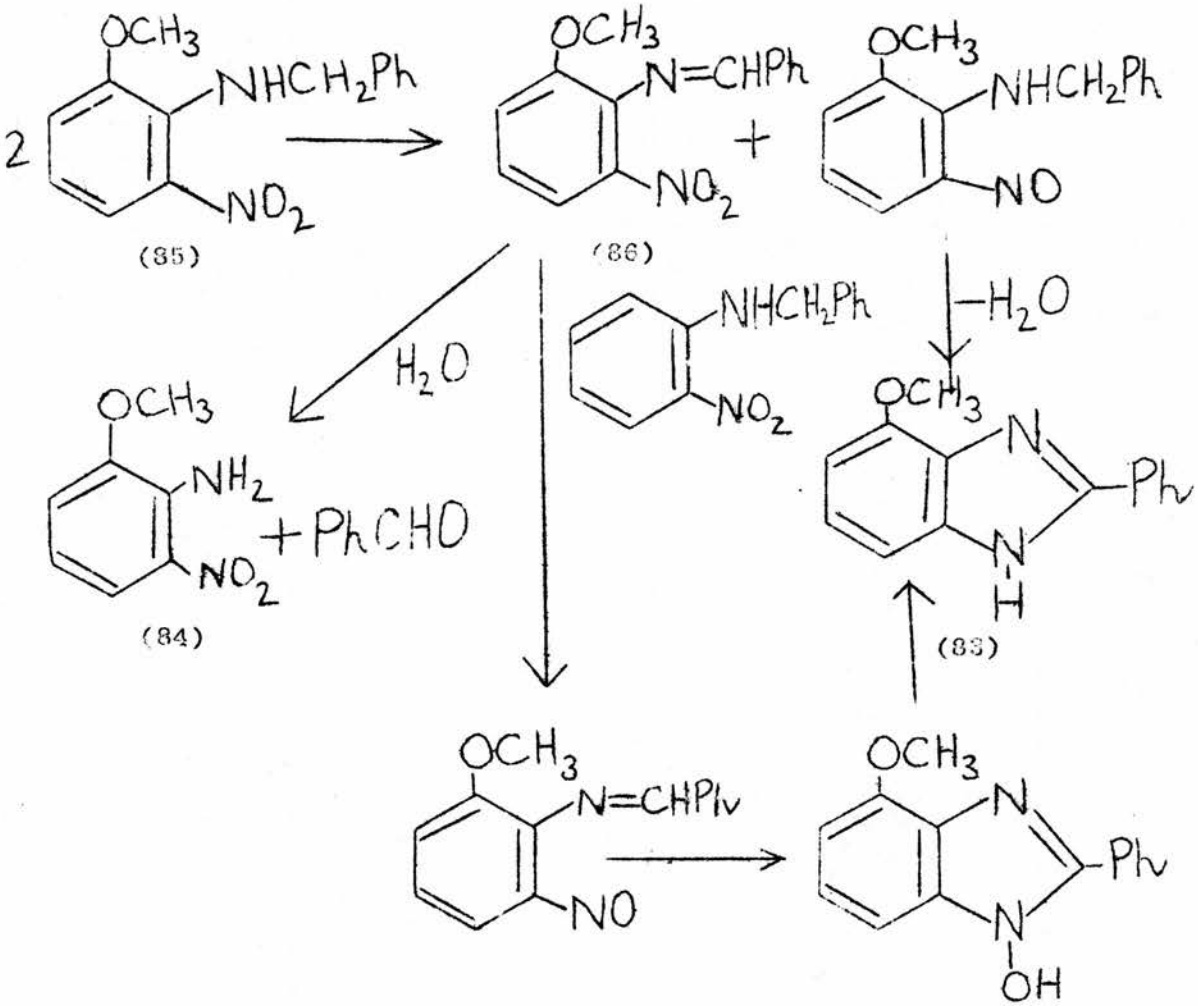
Scheme 11



Scheme 12



Scheme 13


2
OCH3
NHCH2Ph
NO2
(85)
OCH3
N=CHPh
NO2
(86)
+
OCH3
NHCH2Ph
NO
H2O
NHCH2Ph
NO2
OCH3
NH2
NO2
+PhCHO
(84)
-H2O
OCH3
N
Ph
N
H
(83)
OCH3
N=CHPh
NO
OCH3
N
Ph
N
OH

Scheme 14

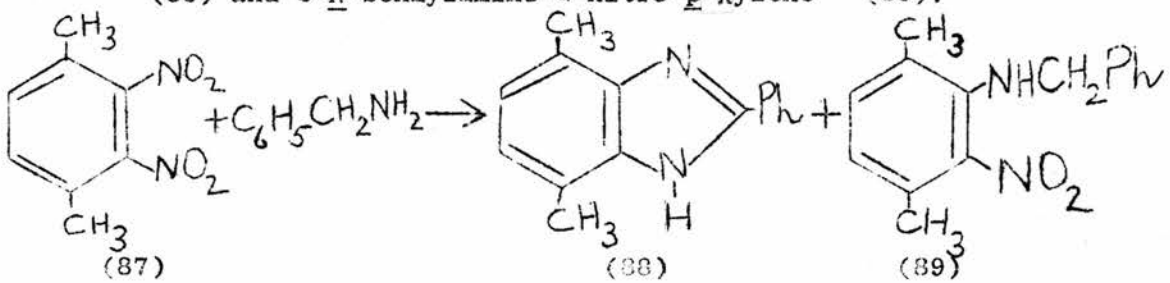
hydroxide,[57] takes place despite feeble activation of the β-methylene centre of the side-chain. In such cases, the presence of an α-hydrogen atom in the side chain of the nitro compound appears to be a facilitating factor in cyclisation , since N-benzyl-N-methyl-o-nitroaniline, which does not posess the α-hydrogen, does not cyclise under the conditions above or under a variety of basic conditions investigated[58]. Two possible routes, involving transfer of this α-hydrogen prior to cyclisation, are shown in Schemes 11 and 12.

The reaction of 2,3-dinitroanisole (82) with two molar equivalents of benzylamine in boiling xylene (30 l.) gave 4(7)-methoxy-2-phenylbenzimidazole (83) and 2-amino-3-nitroanisole (84)[59]. It was proposed that the considerable amount of benzaldehyde formed in the course of the reaction indicated the participation, as reducing agent, of a benzyloxide ion or benzyl alcohol formed by the action of nitrous acid on benzylamine, and the proposed reaction mechanism is that shown in Scheme 13.

It seems more likely, however, that the reaction proceeds via cyclisation of the N-benzyl-o-nitroaniline derivative (85) as described in Schemes 11 and 12, the excess of benzylamine acting as basic condensing agent and the N-oxide thus formed being deoxygenated. As with the cyclisation of 2,4-dinitrophenylhydrazine (cf. p 20) an intermolecular oxidation-reduction reaction, shown in Scheme 14, may also be a route to the benzimidazole (83). Hydrolysis of the o-nitroanil (86) should provide benzaldehyde and 2-amino-3-nitroanisole (84) (cf. Discussion, p. 56).

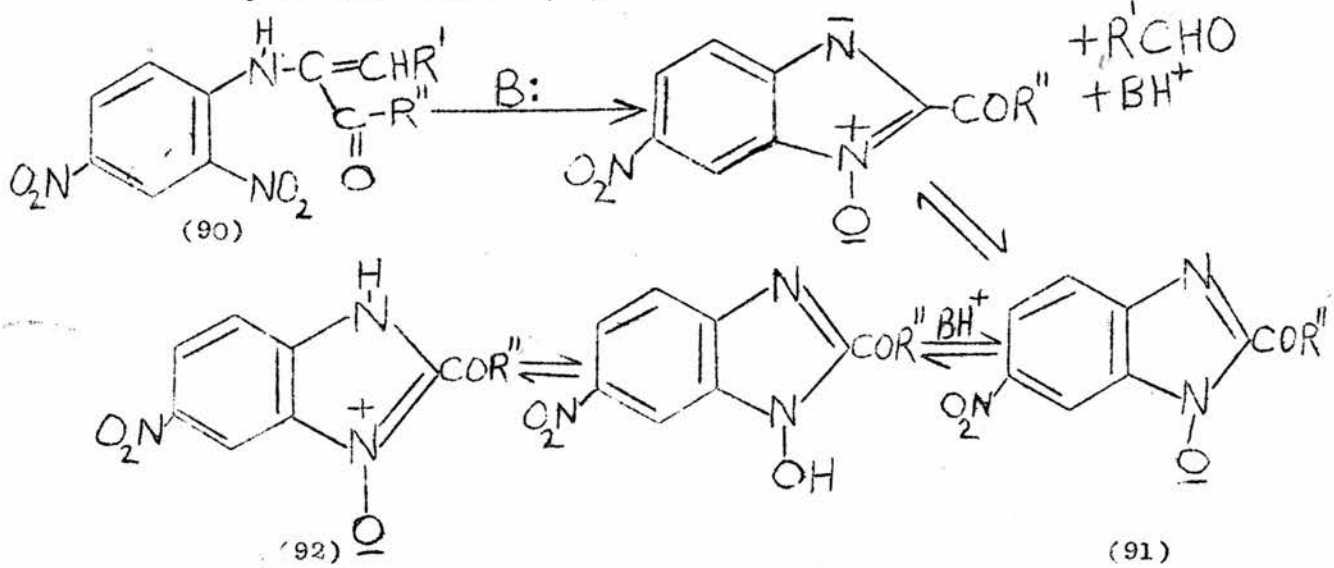
Further support for the reaction mechanisms proposed above

is the fact that boiling a solution of 3-nitro-2-benzylamino-anisole (85) in xylene with two molar equivalents of benzylamine and one of benzyl alcohol (30 h.) gave the benzimidazole (33), but there was no conversion to the benzimidazole on treatment with benzyl alcohol alone. Similar treatment of 2,3-dinitro-p-xylene (87) with benzylamine gave 4,7-dimethyl-2-phenylbenzimidazole (88) and 3-N-benzylamino-2-nitro-p-Xylene[60] (89).



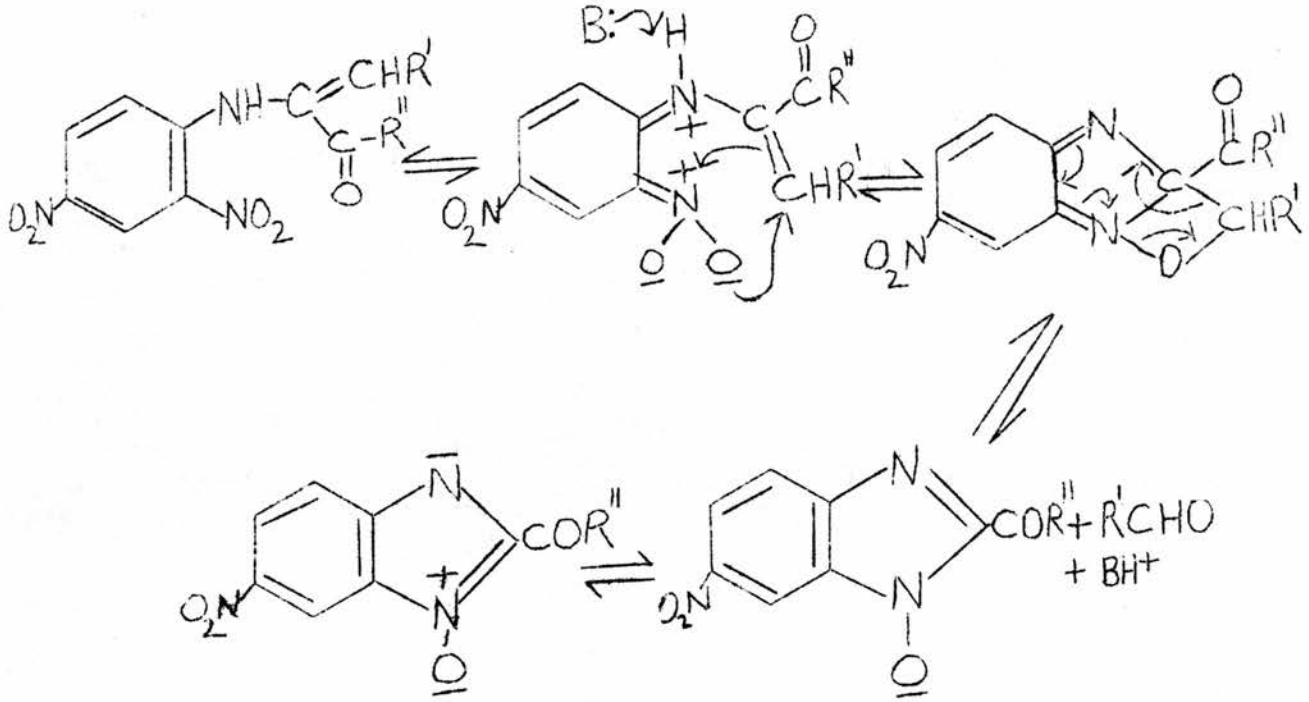
(87) (88) (89)

An interesting reaction is that described by Luetzow and Vercellotti[61], of the cyclisation in basic solutions of the α,-(2,4-dinitrophenyl-amino)-α,β-unsaturated acyl derivatives[(90); R = H, Me, Ph; R" = O-Me or NHPr^n] to the corresponding benzimidazole-1-oxides (92), by way of their anions (91)



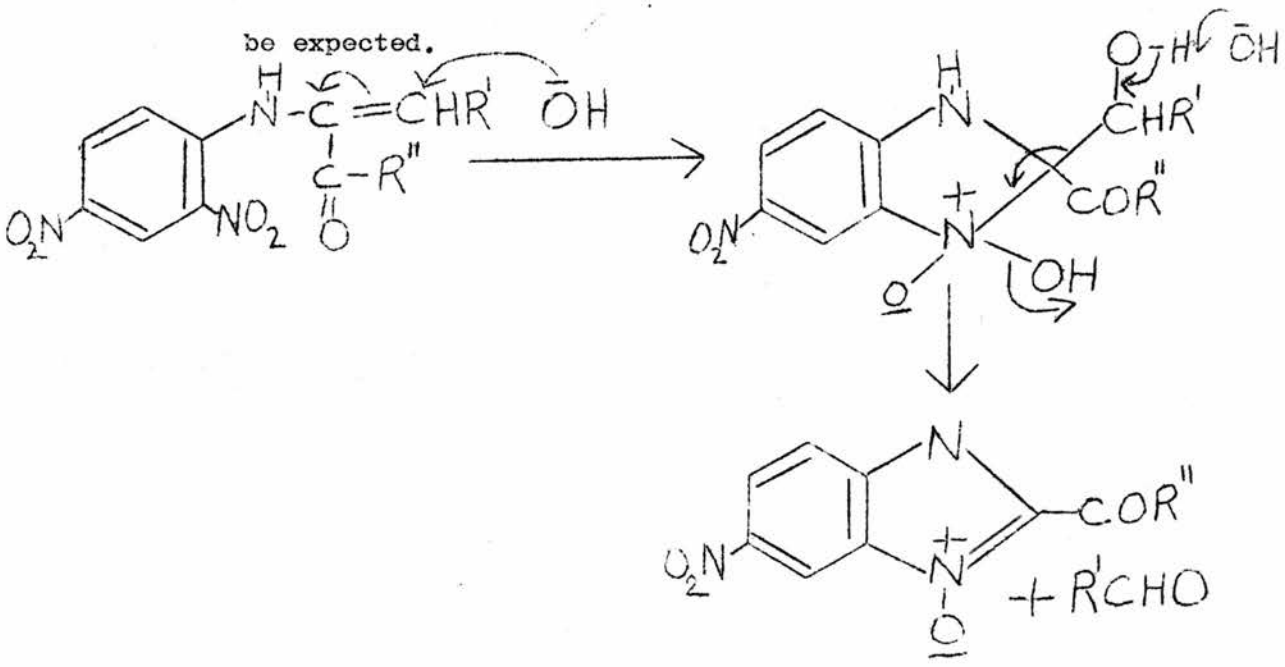
(90) (92) (91)

The concerted mechanism shown in Scheme 15 was suggested as the reaction path.



Scheme 15

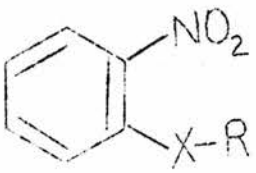
The mechanism suggested below in Scheme 16 however, appears more plausible, since it involves the formation of a stabilised carbanion at a position from which attack on the nitro group is to be expected.



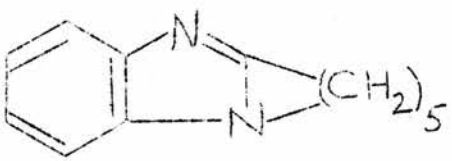
Scheme 16

D. Thermal Cyclisations

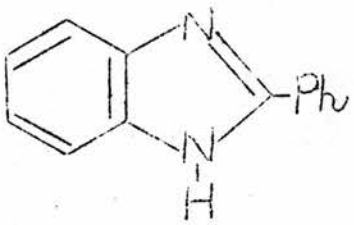
Pyrolysis of the N-substituted o-nitroanilines [(93); R = cyclohexyl, $C_6H_5CH_2$-, or C_6H_5-; X = NH], gave the benzimidazoles (94) and (95) and phenazine (96) respectively, the yields in each case being appreciably higher in the presence of ferrous oxalate.[25]



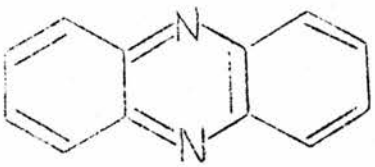
(93)



(94)

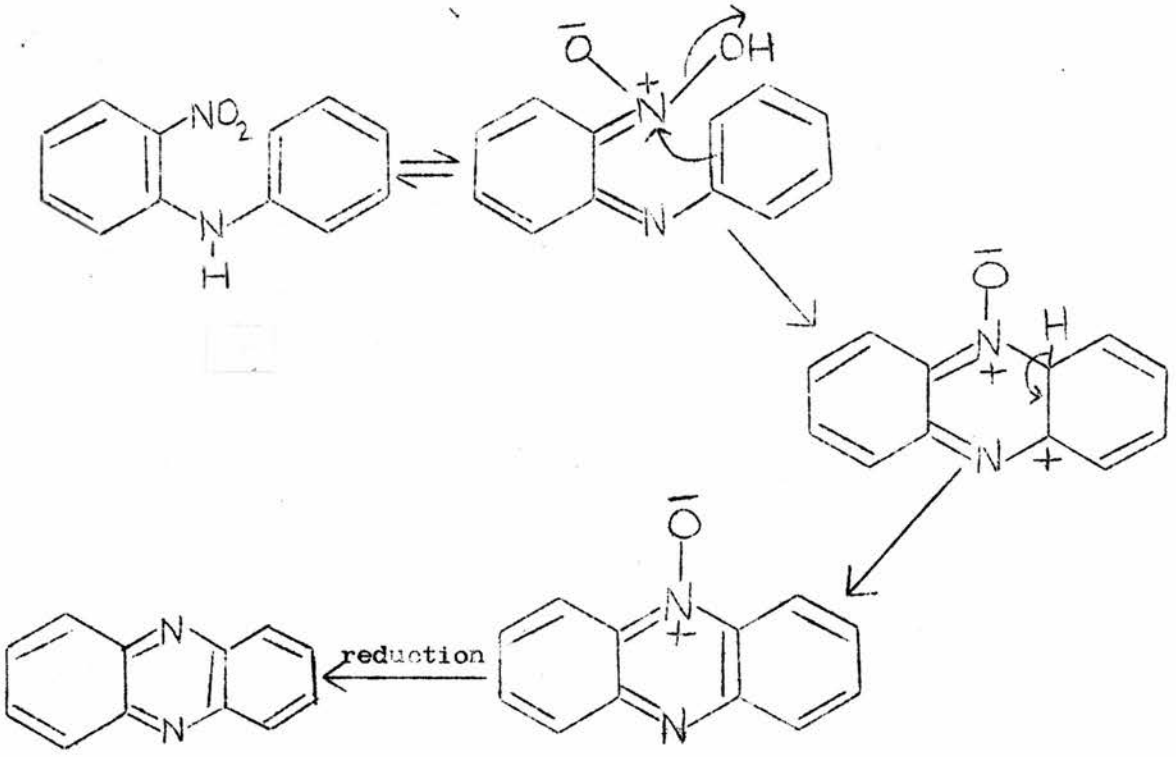


(95)



(96)

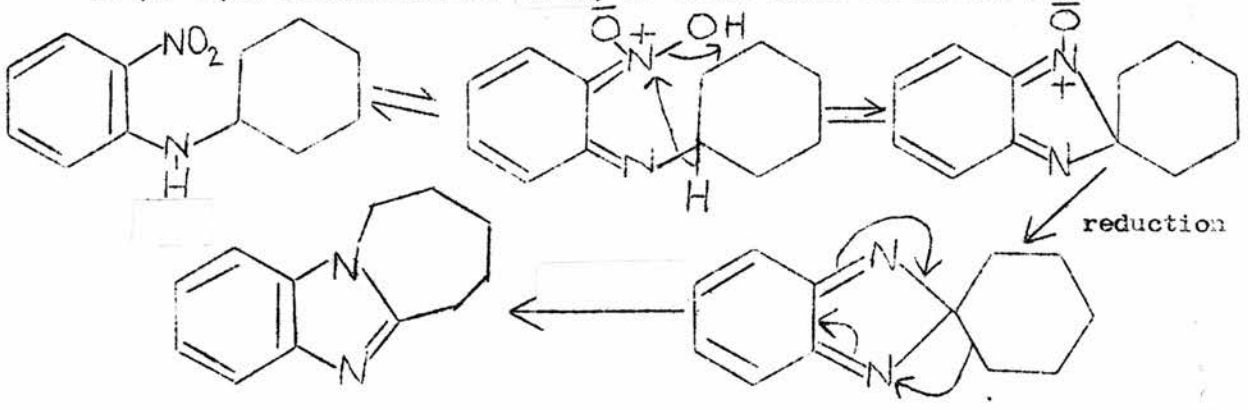
It was suggested that the reaction proceeds via the aci-tautomer of the nitro compound to give an N-oxide by the loss of one molecule of water, the N-oxide then being deoxygenated, e.g. by the ferrous oxalate. (N-oxides are known to deoxygenate, in the absence of a reducing agent, simply on heating[62], but only in low yield; this may account for the improvement in yield with ferrous oxalate present.) Thus, in the cyclisation of 2-nitrodiphenylamine [(93); R = C_6H_5; X = NH], to phenazine] (96) the mechanism shown in Scheme 17 was proposed:



(96) Scheme 17

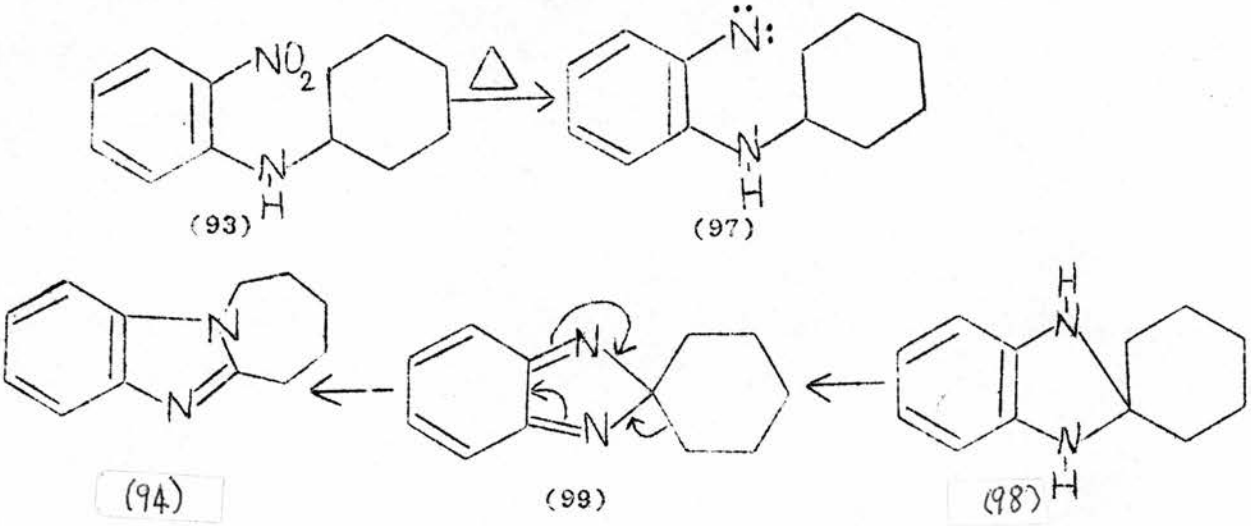
This proposed route via the aci-nitro compound is supported by the observation that the nitro compounds [(93); R = C_6H_5; X = S, SO_2 or O], in which the group X does not contain a hydrogen atom and which are thus incapable of forming the aci-tautomer, fail to undergo cyclisation under the same conditions.

A similar mechanism was proposed for the cyclisation of N-cyclohexyl-o-nitroaniline [(93); R = cyclohexyl; X = NH] to hexahydroazepino-(1',2'-1,2) benzimidazole (94), as shown below in Scheme 18.



(94) Scheme 18

Abramovitch and Davis[63] put forward an alternative mechanism in which the nitro-compound yields a nitrene intermediate on heating: this provides the product (94) by insertion followed by dehydrogenation and rearrangement, as shown below in Scheme 19.



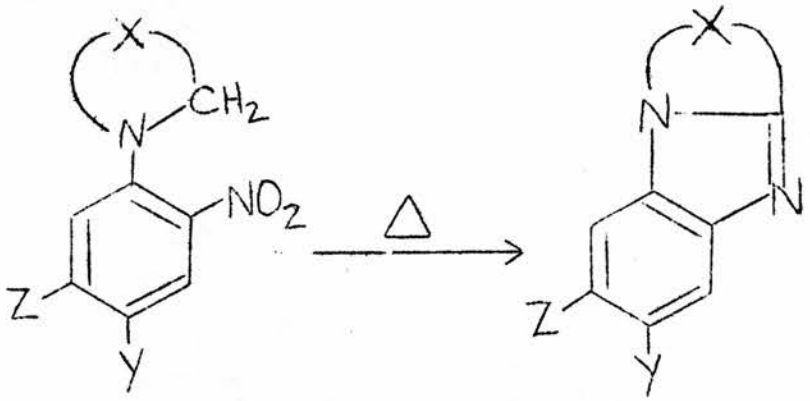
Scheme 19

Subsequently, however, the possibility of an aci-nitro mechanism was conceded[64] for those cases in which such a tautomer could be formed and a deoxygenating agent was absent.

Further evidence supported the aci-nitro route of Scheme 18, rather than the nitrene route, Scheme 19, for thermolysis of (93) in the absence of a deoxygenating agent[65]. The dihydrospirobenzimidazole (98) did not give compound (94) on heating. The azidocyclbhexyl aniline [(93); N_3 for NO_2] which should be a source of the nitrene (97), was synthetically unavailable; however, the reaction of (93) with trialkyl phosphites failed to give any cyclised product. Thermolysis of the N-methyl aniline [(93); Me for H], which cannot form the aci-tautomer, gave only tars.

It was found[65] that heating the isobenzimidazole (99) under the conditions of the above cyclisation gave the benzimidazole (94).

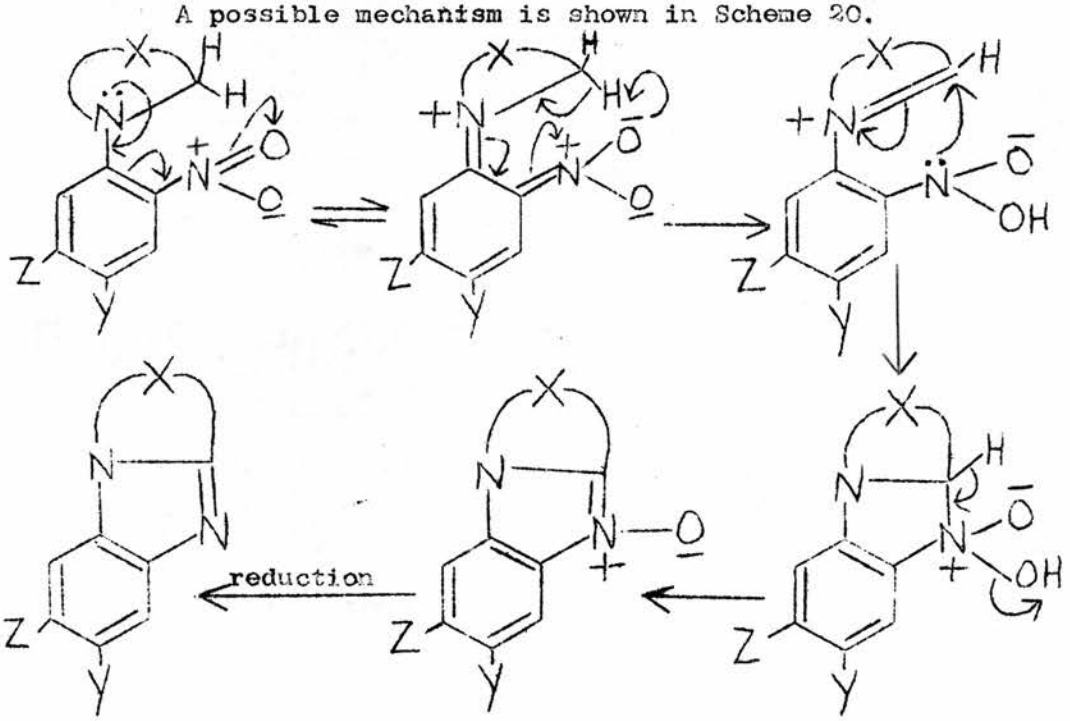
Further examples of this class of cyclisation are provided by the pyrolysis at 220-240°C in sand of the o-nitroaniline derivatives [(100); X = $[CH_2]_n$] which give the corresponding benzimidazoles (101), often in excellent yield[66].



(100) (101)

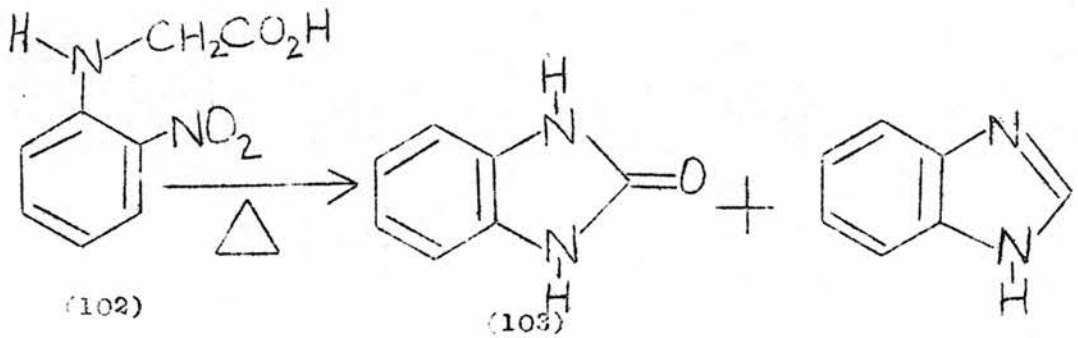
(Z=H; Y=NO_2, CO_2H, CF_3, Cl
Z=NHAc; Y=H, NHAc, Me)

A possible mechanism is shown in Scheme 20.



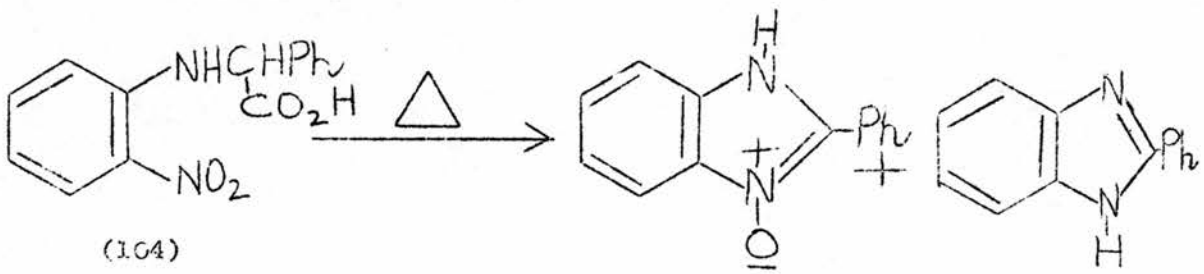
Scheme 20

Goudie and Preston[67] obtained benzimidazolone (103) as well as benzimidazole by the thermal decomposition of o-nitrophenylglycine (102) in sand at 200°C.



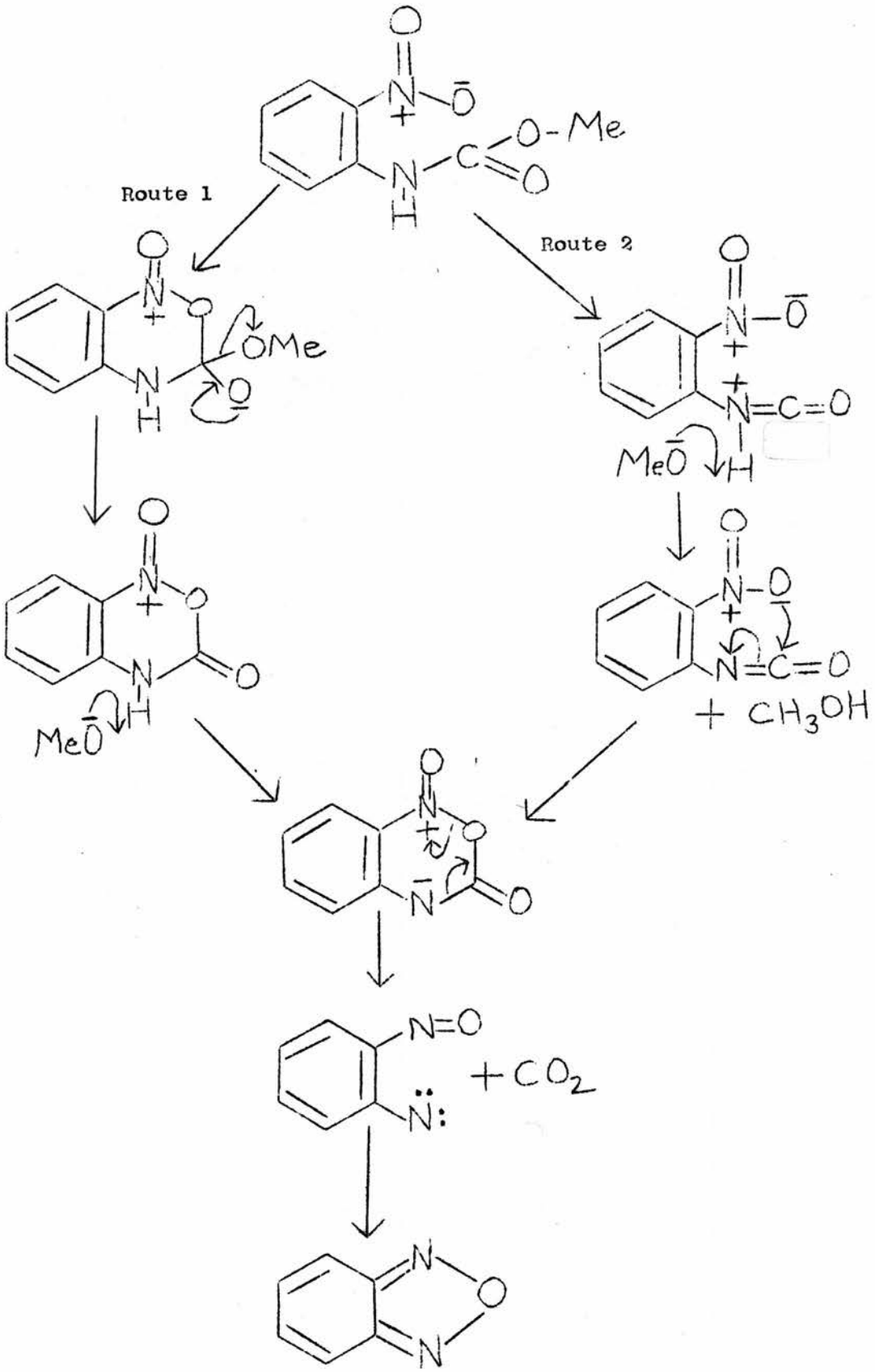
(102) (103)

The corresponding thermal decomposition of o-nitrophenyl-α-aminophenylacetic acid (104) gave 2-phenylbenzimidazole-1-oxide (30%) and 2-phenylbenzimidazole (40%).



(104)

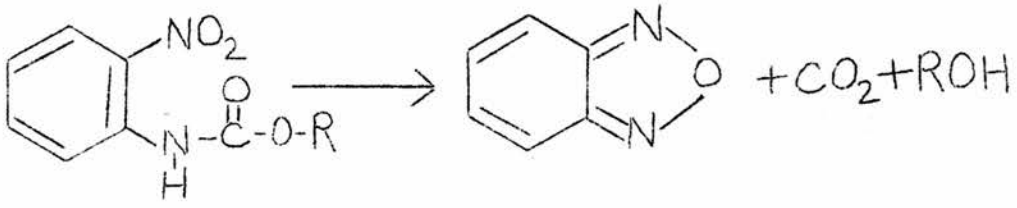
The above reactions are readily rationalised on the basis of the mechanism shown in Scheme 20. The possibility of an initial decarboxylation of (102) is eliminated since N-methyl-o-nitroaniline was recovered quantitatively when subjected to the same reaction conditions. It would, however, be anticipated that decarboxylation could occur easily enough at a later stage of the reaction path. N,N-dimethyl-o-nitroaniline,[67] however, was converted after two hours at 240°C into a mixture of N-methylbenzimidazolone, N-methylbenzimidazole and benzimidazole. With reference to product



Scheme 21

(103), it is worth noting that benzimidazolones are readily obtainable from benzimidazole-N-oxides, either by thermal rearrangement or hydrolytically[68].

Heating alkyl N-(o-nitrophenyl)carbamates (105) at 250-270°C gave benzofurazan (106)[69].



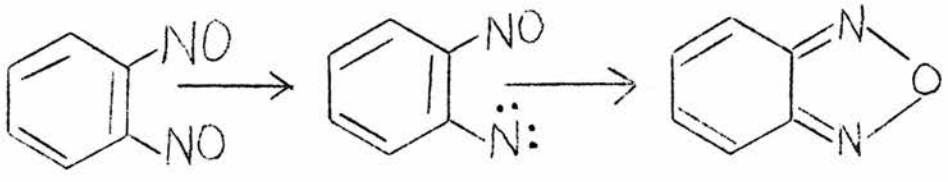
(105) (106)

R = Me, Et, CH_2 = $CH-CH_2^-$, $PhCH_2^-$, p-$MeOC_6H_4CH_2^-$ or p-$O_2NC_6H_4CH_2^-$

Two routes have been tentatively suggested for this reaction as shown, for the methyl carbamate, in Scheme 21.[70]

Pyrolysis of o-nitrophenylisocyanate itself resulted in a lower yield of benzofurazan than pyrolysis of the carbamate and the yield of product thus obtained was unaffected by the addition of base. Also, addition of base in the pyrolysis of methyl N-(o-nitrophenyl) carbamate which should facilitate breakdown of carbamate into isocyanate, drastically reduced the yield of benzofurazan.

Thus route 1 is the more likely mechanism for benzofurazan formation. The nitrene intermediate proposed above recalls the reduction of o-dinitrosobenzene (107) to benzofurazan[71] by triphenylphosphine in which a nitrene intermediate is also proposed (Scheme 22).

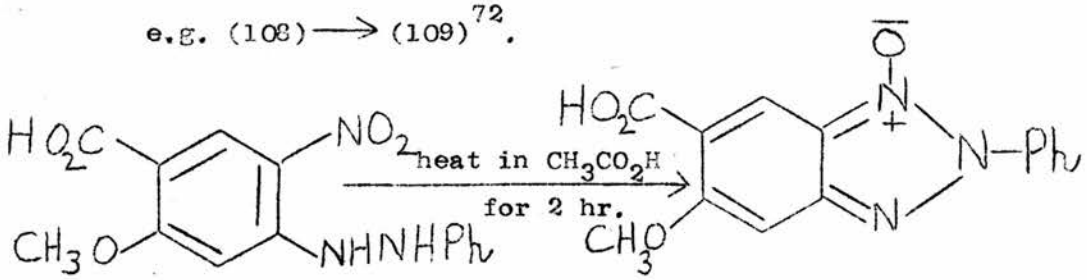


(107) (106)

Scheme 22

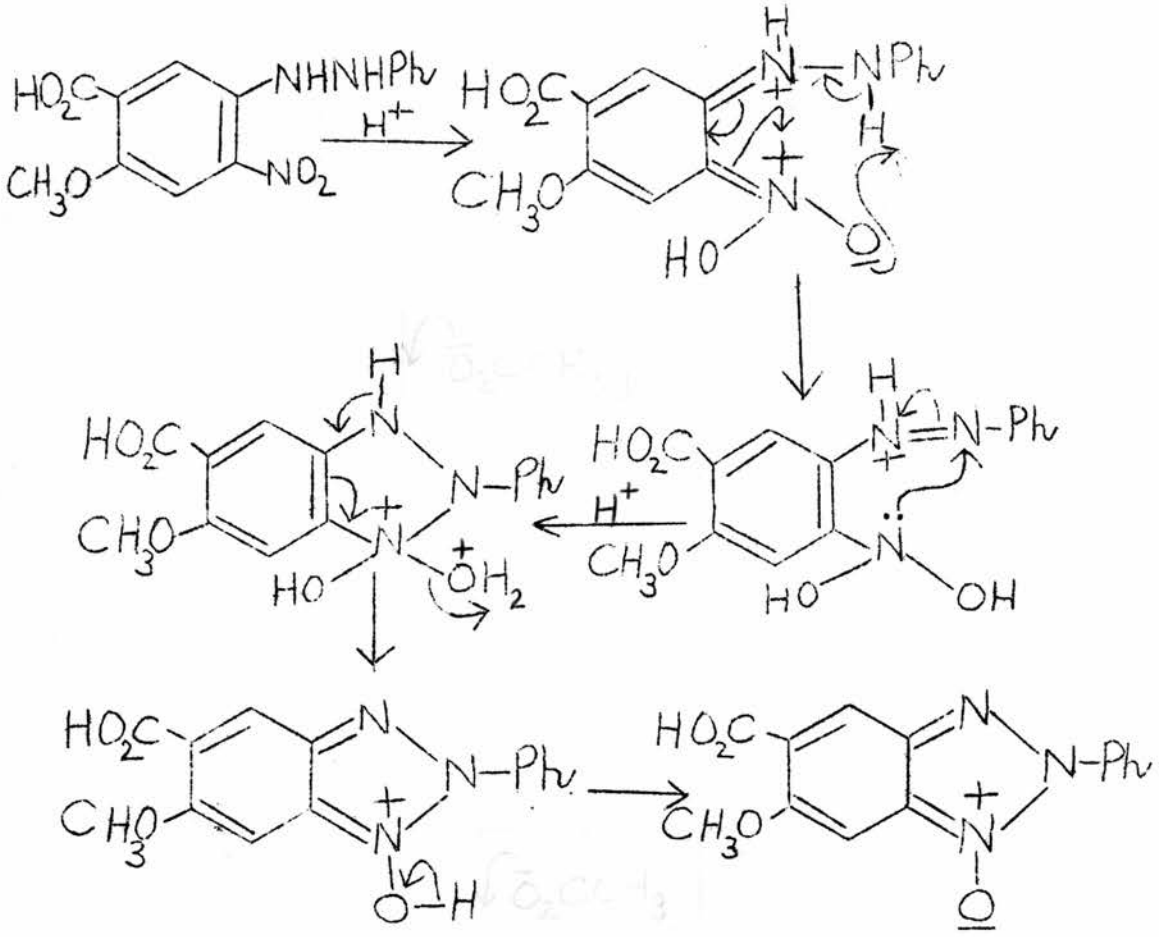
E. Acid catalysed cyclisations.

As mentioned before (p. 19) acid catalysed cyclisation of 2-nitrohydrazobenzenes gives 2-aryl-benzotriazole-1-oxides; e.g. (108) ⟶ (109)[72].



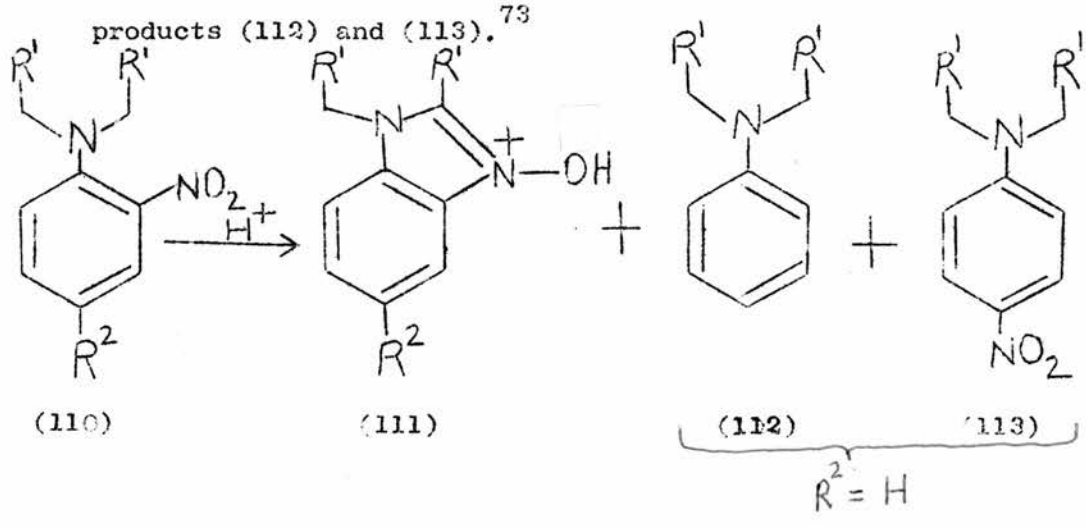
(108) (109)

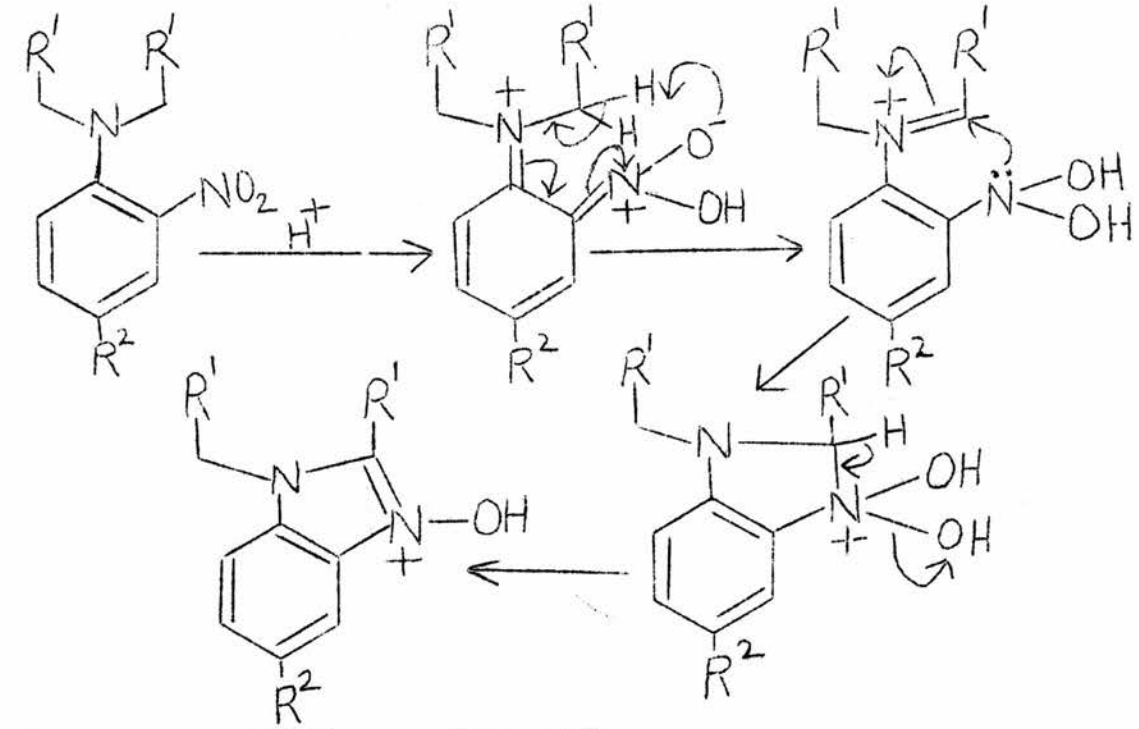
This may be explained by a mechanism similar to that for the cyclisation of o-nitro-NN-dialkylanilines[66] (Scheme 23)



Scheme 23

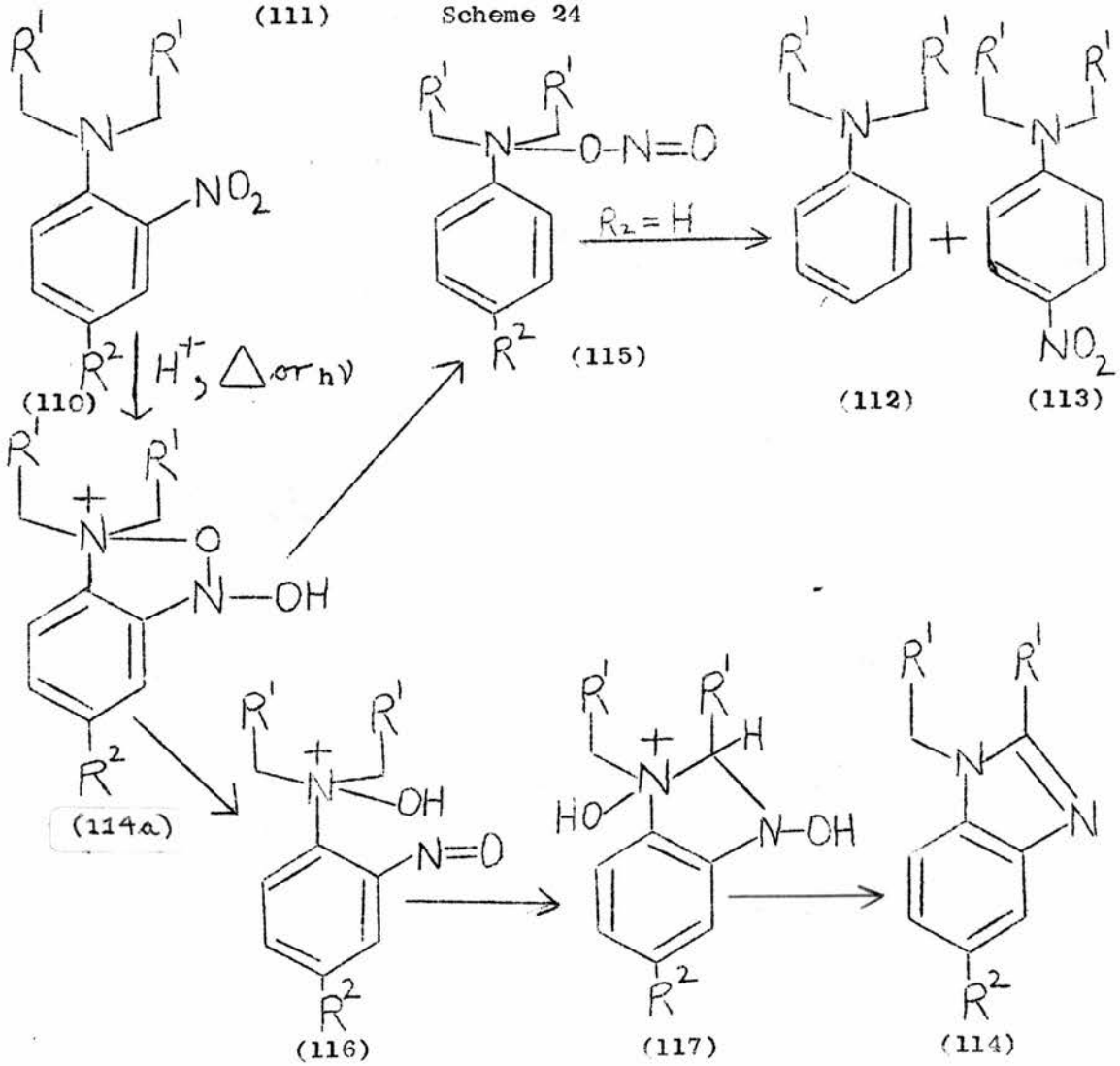
The action of hot aqueous acid, e.g.hydrochloric acid, on the o-nitro-NN-dialkylanilines (110) gave the corresponding benzimidazole-N-oxides as their hydrochlorides (111) and the minor products (112) and (113).[73]





(111)

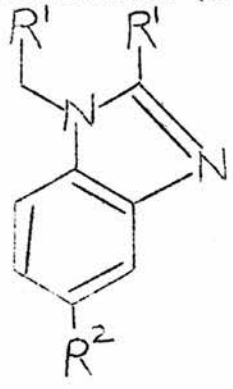
Scheme 24



(110) (114a) (115) (112) (113) (116) (117) (114)

Scheme 25

The photo-cyclisation in aqueous methanolic hydrochloric acid of the compounds (110)[74] gave the benzimidazole-N-oxides (111) in some cases, and the benzimidazoles (114) in others, but not both.



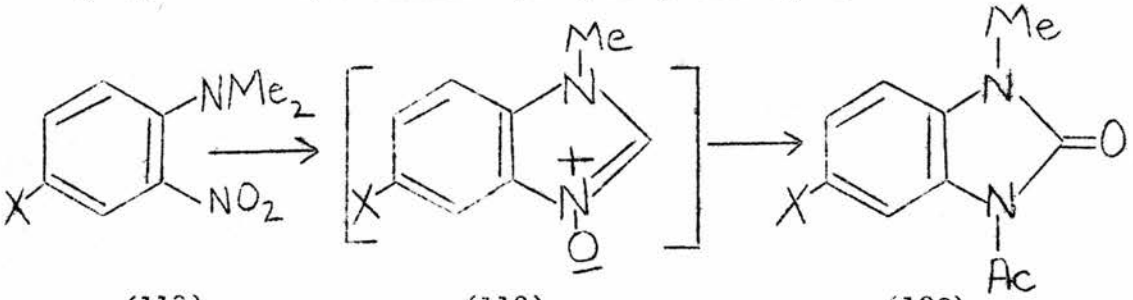
(114)

Since the benzimidazole-N-oxides corresponding to the benzimidazoles (114) are photo-stable under the reaction conditions, they are not the precursors of the benzimidazoles. The proposed mechansim for the thermal or photochemical acid-catalysed reaction to yield the benzimidazole-N-oxide hydrochloride is shown in Scheme 24 and invokes an aci-nitro type of intermediate. The proposed mechanism for benzimidazole formation is shown in Scheme 25.

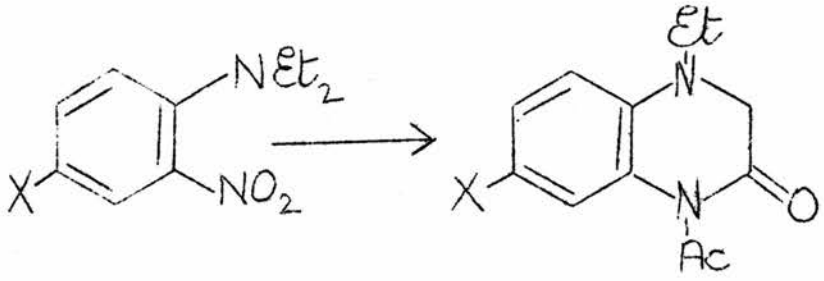
The by-products (112) and (113) from the thermal reaction can then be considered to arise from the reduced furoxan intermediate (114a). This rearranges thermally (route A) to the N-nitrite (115) which, in a manner analogous to the nitramine rearrangement[75], gives the p-nitro compound (113) or loses its nitro group to give the denitrated compound (112). The furoxan intermediate may also be invoked to explain the photochemical formation of the benzimidazole (route B) by way of the o-nitroso-N-oxide (116) and the unstable N-oxide (117).

Van Romburgh reported that certain derivatives of NN-dimethyl-

and -diethyl-o-nitroaniline (118) and (121), on treatment with acetic anhydride in the presence of zinc chloride gave the benzimidazolones (120) and the quinoxalines (122) respectively[76].

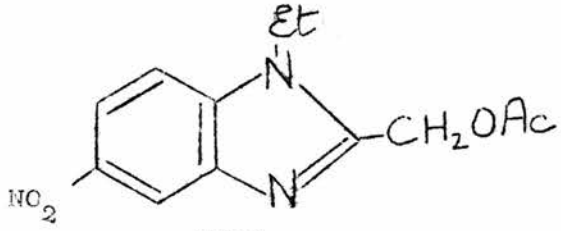


(118) (119) (120)



(121) (122)

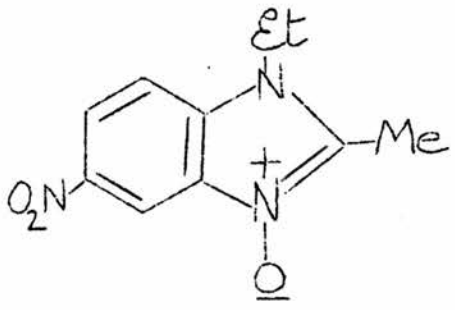
It was subsequently found however[77], that while the product obtained from NN-dimethyl-2,4-dinitroaniline [(119); X = NO_2] was the benzimidazolone, as reported by van Romburgh, the product obtained by reacting NN-diethyl-2,4-dinitroaniline [(121) ; X = NO_2] with acetic anhydride and zinc chloride under reflux was not the quinoxaline but 2-acetoxymethyl-1-ethyl-5-nitrobenzimidazole (123).



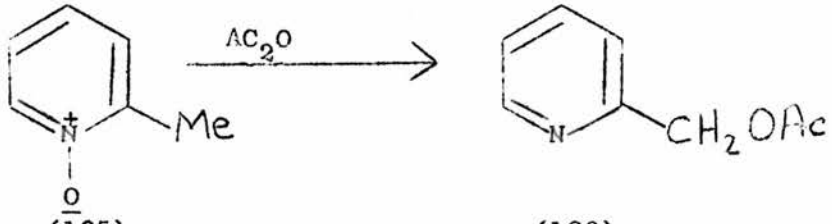
(123)

These reactions probably follow a course similar to that described in Scheme 20 but here the benzimidazole-N-oxides thus formed react with the acetic anhydride to give the above products.

In the case of the intermediate (119) the rearrangement of benzimidazole-N-oxides to benzimidazolones is known (cf. p. 34) while the reaction (121) ⟶ (123) presumably proceeds through the intermediacy of the benzimidazole-N-oxide (124), the conversion of which to the benzimidazole (123) may be regarded as similar to the well known reaction of 2-methylpyridine-N-oxide[78], i.e. (125) ⟶ (126)

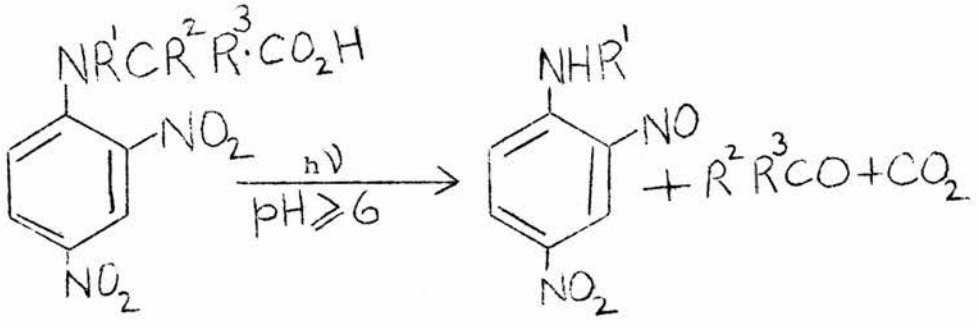


(124)



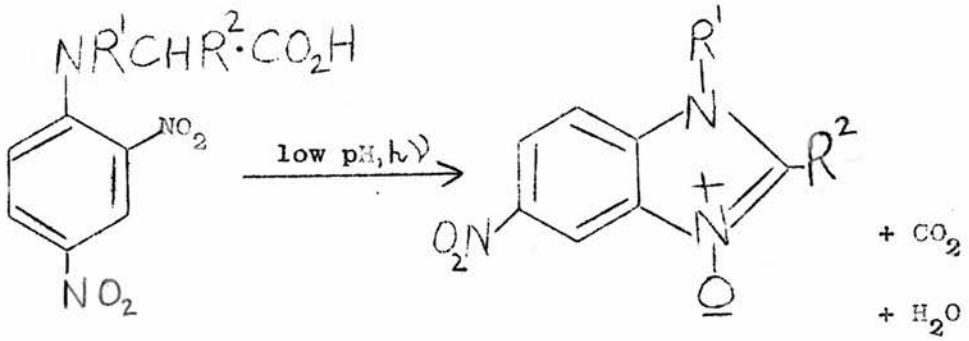
(125) (126)

The photolysis of N-2,4-dinitrophenyl derivatives (127) of α-amino acids in aqueous solution may proceed by two routes depending on the pH of the solution. Russell, and Neadle and Pollitt[80] demonstrated that the nature of products also depend on the pH, low pH favouring the formation of a 6-nitrobenzimidazole-1-oxide (129) while reaction at higher pH gave the 2-nitroso-4-nitroaniline (128) and the aldehyde or ketone with one carbon atom less than the parent amino acid.



(127) (128)

R^1 and R^2 = H or alkyl; R^3 = H, alkyl or aryl

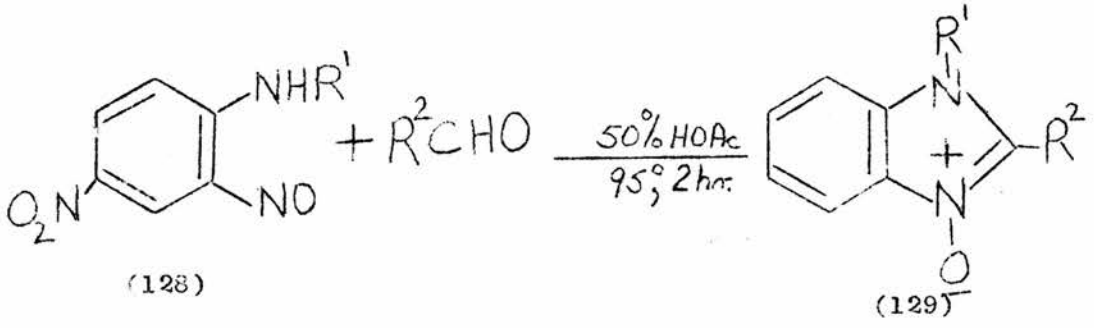


(127) (129)

R^1 = H or alkyl; R^2 = H, alkyl, or aryl

Although formation of the nitroso compound (128) still occurs when neither R^2 nor R^3 is a hydrogen atom, R^3 must be a hydrogen atom for formation of the benzimidazole-N-oxide (129).

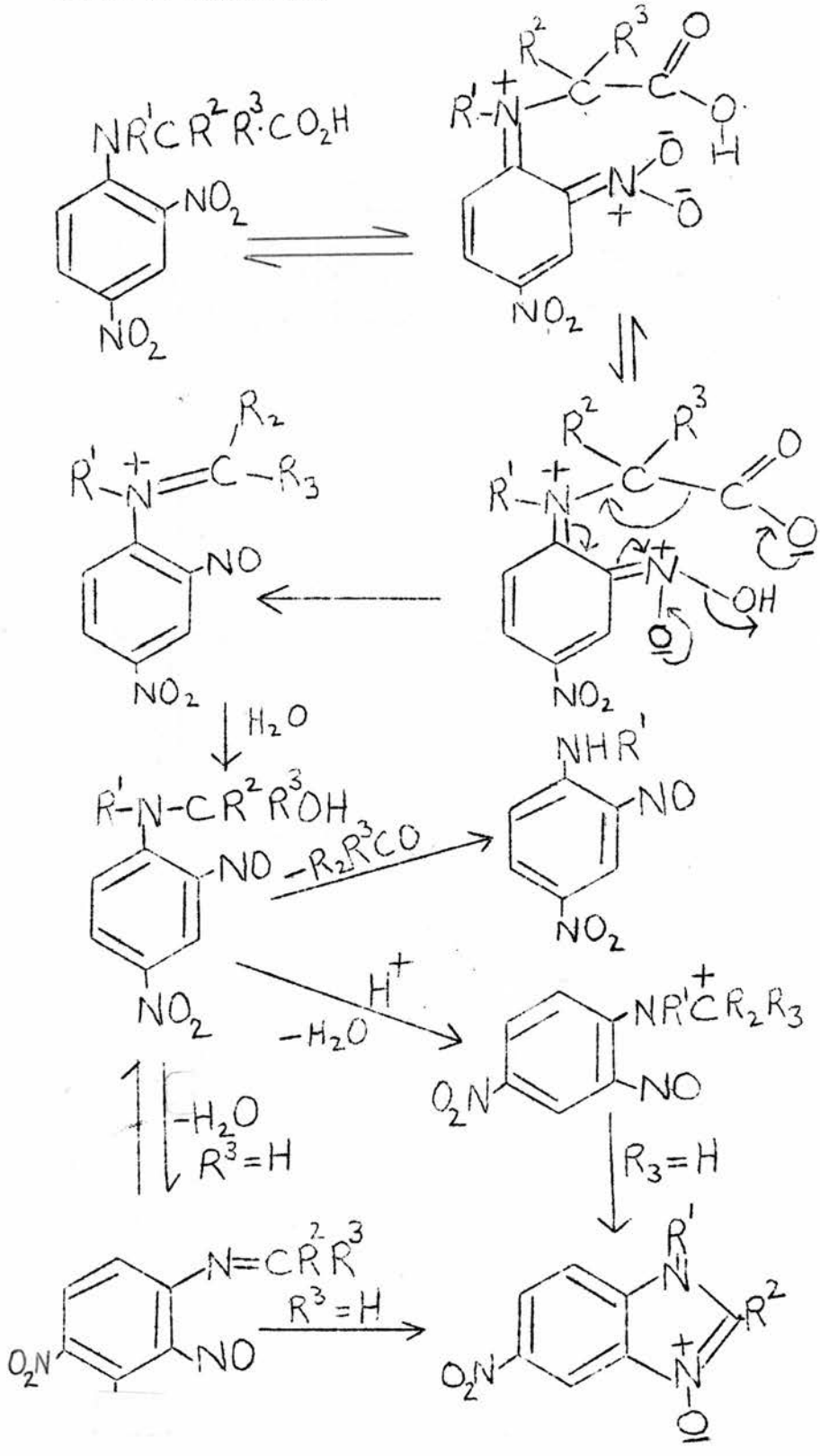
The nitrosoanilines (128) have been shown to react with aldehydes in presence of acid to give benzimidazole-N-oxides (129).[81]



(128) (129)

R^1 = H, R^2 = C_6H_5-, pClC_6H_4-, or pCNC_6H_4-

A reaction mechanism in accordance with the above facts is shown in Scheme 26.

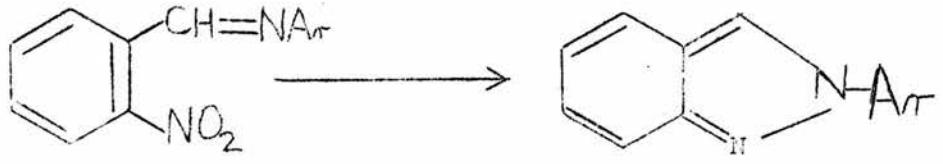


Scheme 26

II Results and Discussion.

A. The Preparation and Stability of o-Nitroanils.

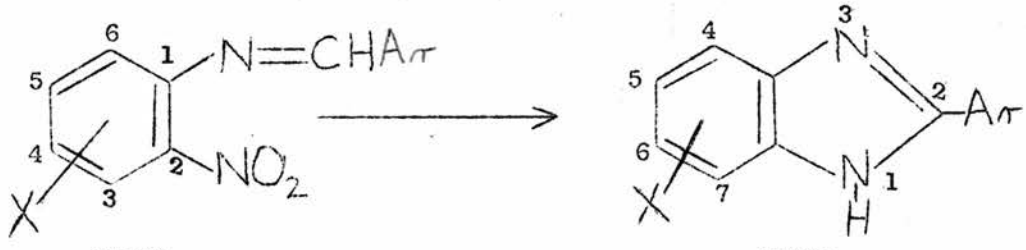
Cadogan et al[20] found that the anils of o-nitrobenzaldehyde (130) were readily converted by triethyl phosphite into the corresponding indazoles (131), by a mechanism similar to that described (cf p. 12) for the corresponding reaction of 2-nitroazobenzenes.



(Ar=Ph, p-MeC_6H_4, p-BrC_6H_4, α-naphthyl, etc.)

(130) (131)

Hence it was obviously of interest to extend the above reaction to the reduction of N-benzylidene-o-nitroaniline and its derivatives (132) to the corresponding 2-arylbenzimidazoles (133).



(132) (133)

However, attempts to prepare N-benzylidene-o-nitroaniline by apparently well-established methods showed the necessity for a detailed examination of the reactions of o-nitroaniline and its derivatives with benzaldehyde and its derivatives.

Aromatic primary amines normally react readily with aromatic aldehydes, in alcoholic solution or in the absence of a solvent, to give Schiff bases[82] as shown in Scheme 27..

$$ArCHO + Ar'NH_2 \rightleftharpoons ArCH = NAr' + H_2O$$

Scheme 27.

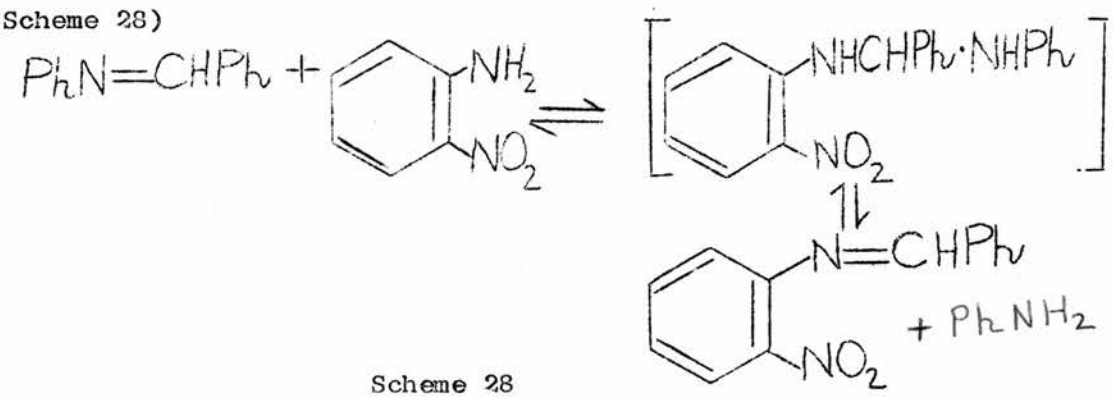
Ingold and Piggott[83] first claimed to have prepared N-benzylidene-o-nitroaniline [(132); Ar = Ph; X = H] by heating benzaldehyde with o-nitroaniline, without a solvent, until water vapour ceased to be evolved, and they described the product as an orange solid m.p. 118°. However, it has been demonstrated that the probable structure of this product is NN-benzylidenebis-o-nitroaniline[57,84] [(134); Ar = Ph; X = H] corresponding to the addition of a molecule of o-nitroaniline to the anil. Before the publication of this revised structure for the product, however, Cadogan and Searle[85] had attempted to repeat Ingold and Piggott's preparation by heating equimolar amounts of o-nitroaniline and benzaldehyde at 100-110° for twenty minutes, but they recovered only o-nitroaniline, as was also the case when the reaction was repeated by heating for eight hours in the presence of one drop of acetic acid.

Prolonged heating (4 days) in the presence of an increased amount of acetic acid, however, gave a compound m.p. 183-187°. Refluxing an equimolar mixture of benzaldehyde and o-nitroaniline without a solvent for three hours gave a product melting at 185-187°,[86] which corresponds to the product m.p. 183-184° reported by Ettling when o-nitroaniline and benzaldehyde (1:2 molar ratio) were heated under reflux in toluene, with water removal for sixty-six hours.[87] The nature of these high melting products will be discussed later (cf p. 72), but in general it would appear that the use of higher reaction temperatures or more prolonged periods of heating leads to the formation of heterocyclic products at the expense of the Schiff base.

Wheeler and Gore[88] reported the preparation of N-benzylidene-o-nitroaniline (m.p. 72°) from a condensation of benzaldehyde and o-nitroaniline in ethanol. However, Searle[85] repeated this reaction

and obtained only o-nitroaniline. The anil (m.p. 76-8°) was also obtained, reportedly in good yield, by the reaction of o-nitroaniline with N-benzylideneaniline[57], the aniline being removed under reduced pressure to displace the equilibrium in favour of the formation of o-nitroanil

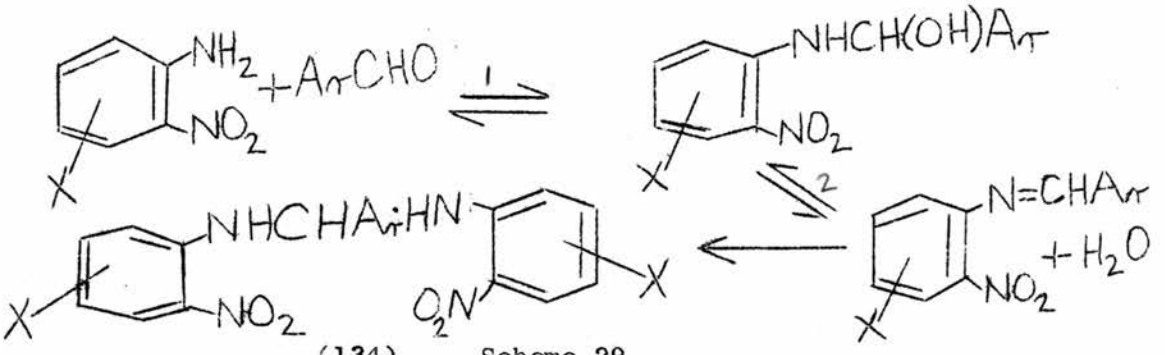
(Scheme 28)



Scheme 28

However, when this reaction was repeated[86], only a small yield of the o-nitroanil was obtained.

A more recent preparation involved heating o-nitroaniline with an excess of benzaldehyde, the latter acting both as solvent and reactant, at 140°. The water produced was allegedly removed in an attached Dean and Stark trap[89], but water removal was found to be extremely difficult by this method. It thus appeared that the most propitious conditions for o-nitroanil formation would involve (i) water removal to displace the equilibrium shown in Scheme 29, step 2, in favour of anil formation; (ii) use of an inert solvent of appropriate b.p., to facilitate water removal, while providing a reaction temperature low enough to avoid heterocycle formation, and (iii) the use of an excess of the aldehyde to reduce the possibility of unchanged o-nitroaniline adding to the anil to give the NN-arylmethylenebis-o-nitroaniline (134).

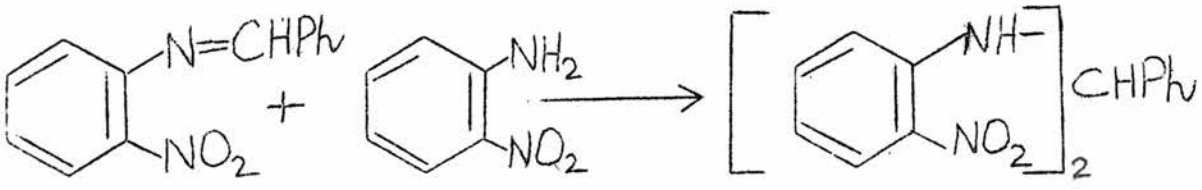


(134) Scheme 29

Although the last preparation described above[89] undoubtedly conforms to the above conditions, we found, on repeating this work, that we were unable to effect efficient water removal at 140°; on the other hand; refluxing the aldehyde solution to facilitate water removal led to the formation of 2-phenylbenzimidazole (cf p. 74). The reaction was therefore performed by refluxing the mixture in an inert solvent to assist water removal. A solution of o-nitroaniline and unpurified benzaldehyde (molar ratio 1:2.5) in toluene (b.p. 110°) was heated under reflux in a reaction vessel connected to a Dean and Stark trap. As soon as the calculated quantity of water had been collected (after some six hours), the mixture was cooled and diluted with light petroleum, giving N-benzylidene-o-nitroaniline in acceptable (45%) yield. However, when the reaction was repeated using purified (cf. p. 85) benzaldehyde, water removal was very much slower, so much so that after fifteen hours' heating only about a half of the theoretical amount of water had been collected. The reaction mixture at this stage was cooled and diluted with light petroleum to give NN-benzylidenebis-o-nitroaniline in 68% yield. This was designated as the compound [(134); Ar = Ph; X=H] by virtue of its i.r. spectrum, which showed N-H stretching absorption at 3345 cm^{-1}, and by mixed m.p. and i.r. spectral comparison with an authentic sample of NN-benzylidenebis-o-nitroaniline.

In this and all other cases where NN-benzylidene bis-o-nitroaniline was obtained as a product from the reaction of o-nitroaniline with benzaldehyde, the m.p. of the crude compound obtained varied widely although the i.r. spectra remained the same. Also recrystallisation from different solvents gave solids varying in melting point within a range of approximately 30°, although once again all showed the same i.r. spectrum. Stacy et al[57] suggested that this indicates heat lability of the compound, but variable temperature n.m.r. analysis of the NN-benzylidenebis-o-nitroaniline shows that it is thermally stable at temperatures considerably above its melting point (cf. p. 79). However, the n.m.r. spectrum of the unrecrystallised product obtained in the preparation of authentic NN-benzylidenebis-o-nitroaniline shows a singlet at 1.62 τ which corresponds to the CH = N proton resonance of N-benzylidene-o-nitroaniline (cf. p. 90). Thus it is possible that in the above reactions an unresolvable mixture of both the anil and NN-benzylidenebis-o-nitroaniline is obtained. Further examination of the interconvertibility of these two compounds is discussed later.

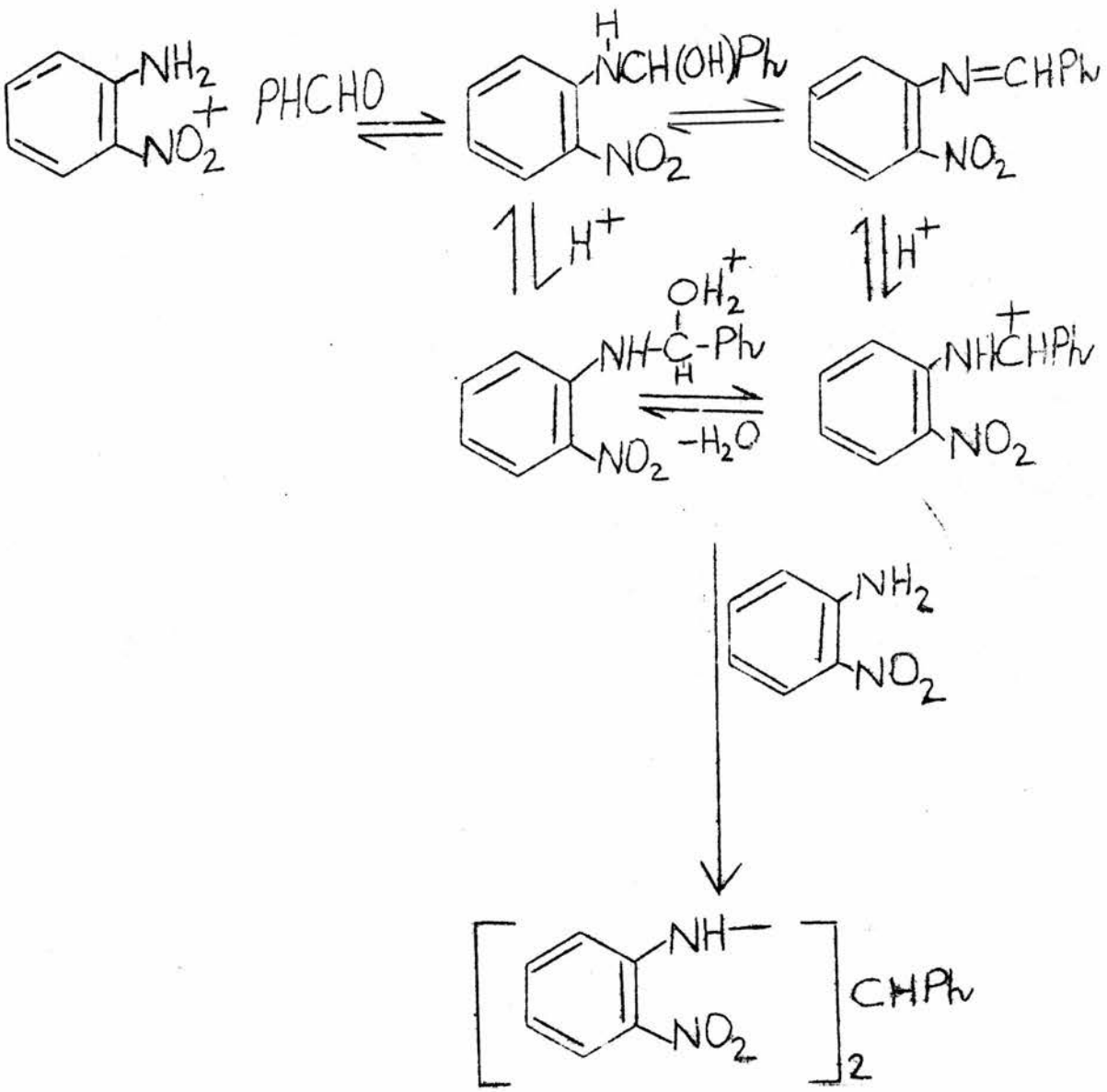
It would appear that NN-benzylidenebis-o-nitroaniline is produced in the reaction of o-nitro aniline with pure benzaldehyde in toluene because, owing to the slow rate of formation of anil, conditions are favourable for the addition of unreacted o-nitroaniline to that anil which has already been formed, as shown in Scheme 30.



Scheme 30

Therefore in an attempt to increase the rate of anil formation, the reaction was repeated with xylene as solvent, but once again reaction was slow, and the only product obtained was NN-benzyliuenebis-o-nicroaniline. The use of higher boiling solvents, e.g. p-cymeme, led to the formation of 2-phenylbenzimidazole (cf, p. 75)

The difference in the reaction products obtained using unpurified and purified benzaldehyde was quite striking and it seemed possible that the formation of anil might very well by catalysed by benzoic acid in the unpurified benzaldehyde. Titration of the benzaldehyde used in the successful preparation of the anil against sodium hydroxide showed the presence of 17% by weight of benzoic acid. As it is known that Schiff base formation is subject to acid catalyses[82], the above reaction was repeated both in toluene and in xylene using purified benzaldehyde to which 17% of benzoic acid had been added. In both cases the rate of water removal was increased, complete water-removal occurring within a few hours, and N-benzylidene-o-nitroaniline in good yield was the reaction product in both cases. However, when a solution of o-nitroaniline and pure benzaldehyde (1:2.5 molar ratio) in xylene containing acetic acid was heated under reflux, although the reaction occurred readily (as shown by the rate of water formation), the only product obtained was NN-benzylidenebis-o-nitroaniline. Benzoic acid is a slightly stronger acid in benzene solution than is acetic acid[90], and this will presumably apply also to xylene, but the difference in strength is too small to account satisfactorily for the difference in catalytic activity between the two. It is possible that the volatility of acetic acid (b.p. 118^{o}) at the reaction temperature (140^{o}) leads to a reduction of its


NH2
NO2
PHCHO
H
NCH(OH)Ph
NO2
N=CHPh
NO2
H+
H+
OH2+
NH-C-Ph
H
NO2
-H2O
NHCHPh
NO2
NH2
NO2
NH
NO2
CHPh
2

Scheme 31

concentration in the reaction mixture, and at low acid concentrations [(134;X=H;Ar=Ph] is the major reaction product (cf. p. 45). The formation of the NN-benzylidenebis-o-nitroaniline may occur as shown in Scheme 31.

Reacting o-nitroaniline with excess benzaldehyde in toluene in the presence of benzoic acid without water removal, gave only NN-benzylidenbis-o-nitroaniline, implying again that when anil formation is slow (in this case because the equilibrium has not been displaced towards anil formation by removal of water), adduct formation is likely, all the more so in this case since an acid catalysed mechanism as shown in Scheme 31 may operate. When the succesful preparation of N-benzylidene-o-nitroaniline with aged benzaldehyde was repeated in benzene, there was no evidence of water production, even after heating overnight, i.e. reaction occurs either very slowly or not at all.

The N-benzylidene-o-nitroaniline prepared as above is readily hydrolysed, even by atmospheric moisture, to NN-benzylidenebis-o-nitroaniline and benzaldehyde (cf.p. 56) and its mass spectrum (p.118) shows, as well as the molecular ion at m/e 226 ions at m/e 243 and 244 [$(M + 17)^+$ and $(M + 18)^+$] indicative of rapid addition of water across the C=N bond of the anil. The compound could, however, be stored for some length of time in a sealed bottle at low temperature without undergoing hydrolysis.

N-Benzylidene-4-methyl-2-nitroaniline [(132 X = 4-Me-;Ar = Ph] was prepared by refluxing 4-methyl-2-nitroaniline and benzaldehyde (1:2.5 molar ratio) in benzene with water removal, while the corresponding reaction of 4-chloro-2-nitroaniline with benzaldehyde to give N-benzylidene-

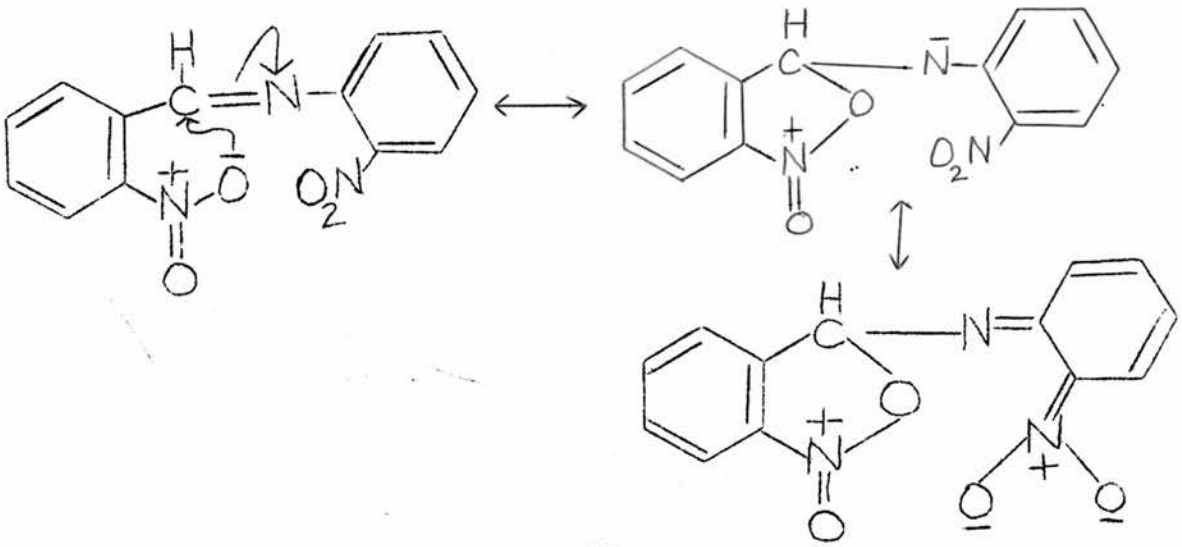
4-chloro-2-nitroaniline [(132); X = 4 - Cl ; Ar = Ph] took place either very slowly or not at all (as evinced by water removal) in toluene and required xylene as solvent. This is presumably because 4-methyl-2-nitroaniline, with the electron-releasing methyl group para to the amine nitrogen, is a stronger nucleophile than o-nitroaniline, whereas 4-chloro-2-nitroaniline, which has an electron-withdrawing chloro atom para to the amino-nitrogen, is less nucleophilic than o-nitroaniline and hence requires more vigorous reaction conditions. The reaction of p-methoxybenzaldehyde with o-nitroaniline with or without acetic acid gave a small amount of p-methoxybenzoic acid as the only identifiable product. However, when the reaction was repeated in the presence of benzoic acid, N-p-methoxybenzylidene-o-nitroaniline [(132); Ar = p-MeO C_6H_4; X = H] was obtained in acceptable yield (64%) p-Nitrobenzaldehyde did not appear to react in the absence of a catalyst even in boiling xylene; in the presence of acetic acid reaction occurred readily, as shown by the rate of water removal, but the only product obtained was NN-p-nitrobenzylidenebis-o-nitroaniline. Repeating the reaction in the presence of benzoic acid, however, gave a compound which, although it did not analyse correctly for N-p-nitrobenzylidene-o-nitroaniline [(132; Ar = p-$NO_2C_6H_4$; X = H] appeared from its i.r., n.m.r., and mass spectra to be essentially this compound.

In the case of the reaction with p-methoxybenzaldehyde, which is the least reactive of the aldehydes used, it might be expected that higher acid concentration might be necessary for condensation to occur, although the formation of water in the absence of added benzoic acid does not support this theory. It may be that, in the absence of benzoic acid, the anil is indeed formed but is subsequently converted into some,

as yet unidentified, product. In the second case, p-nitrobenzaldehyde should form Schiff bases more readily than benzaldehyde, as the electron withdrawing group para to the carbonyl function should further activate it to nucleophilic attack by the aniline. However, the electrophilicity of the benzylic carbon of the anil is also increased, to the extent that the ready reversibility of dehydration step 2 (Scheme 29) may explain the apparent lack of reaction in the absence of acid, while in the presence of acetic acid addition of the type shown in Scheme 31 should occur even more readily than in the case of N-benzylidene-o-nitroaniline. In all the above attempts at o-nitroanil preparation it is obvious that the various reaction routes are very finely balanced and the presence of benzoic acid appears essential to successful o-nitroanil formation.

The reaction of p-chlorobenzaldehyde with o-nitroaniline yielded only p-chlorobenzoic acid and an unresolvable mixture of products. I.r. and n.m.r. spectra of this mixture indicated the presence of both the anil and NN-p-chlorobenzylidenebis-o-nitroaniline. Again, although the presence of the electron-withdrawing chlorine atom para to the carbonyl function should further activate it to nucleophilic attack by the aniline, the electrophilicity of the benzylic carbon of the anil is also increased, facilitating addition of o-nitroaniline to the anil.

In contrast to the p-nitrobenzylidene isomer N-o-nitrobenzylidene-o-nitroaniline[91] was found by Sears[92] to be comparatively stable, and it could be prepared merely by heating equimolar amounts of the aldehyde and aniline in ethanol. It was found that in this case the yield of anil was actually increased by the addition of acetic acid to the reaction mixture[93]. The anil was not hydrolysed by aqueous acid but was hydrolysed under basic conditions. Its stability may be attributable to resonance stabilisation as shown in Scheme 32.



Scheme 32 etc.

As can be seen from the above discussion, the product of condensation of o-nitroaniline and benzaldehyde or of their derivatives is by no means always the corresponding o-nitroanil. It is worth mentioning some other cases in which there are wide variations reported in the product of attempted condensation.

Ingold and Piggott[83] claimed to have prepared N-p-nitrobenzylidene-o-nitroaniline by heating p-nitrobenaldehyde with o-nitroaniline without a solvent until water vapour ceased to be evolved. The product was described as a bright yellow solid m.p. 118°. However, King and Lowy[94] also claimed to have prepared the anil by fusing together equimolar proportions of p-nitrobenzaldehyde and o-nitroaniline in a sealed tube at 115°, the tube containing anhydrous zinc chloride at the cool end. The product was described as a golden-yellow solid m.p. 169°. Ingold and Piggott[83] also claimed to have similarly prepared N-m-nitrobenzylidene-o-nitroaniline. The product was described as a yellow solid m.p. 143-145°. However, Fenech and Tommasini[95] claimed to have prepared this compound by dissolving the amine in ethanol and adding the solution to that of m-nitrobenzaldehyde. The product was described as a yellow solid m.p. 24-25°. These discrepancies remain to be investigated.

B. Reactions of Nucleophiles with N-Benzylidene-o-nitroaniline

From the results of the previous section, it appeared that much of the difficulty encountered in the preparation of o-nitro anils by the condensation of o-nitroaniline or a derivative thereof with an aromatic aldehyde was due to the susceptibility of the anil thus formed to nucleophilic attack. Thus, in some cases, even when an excess of aldehyde was employed and water continuously removed during the reaction, the product of the reaction was the NN-arylmethylenebis-o-nitroaniline(134), representing the addition of a further molecule of the o-nitroaniline to the anil. In those cases where water was not continuously removed during the reaction and the aniline was recovered, the dehydration step 2 in Scheme 29 (cf. p. 45) has presumably not occurred. The ease with which the reverse process, i.e. addition of water to the anil, takes place is, as mentioned previously, illustrated by the appearance of ions $(M + 17)^+$ and $(M + 18)^+$ in the mass spectrum of N-benzylidene-o-nitroaniline. Thus, it was of interest to study the reactions of a range of nucleophiles with N-benzylidene-o-nitroaniline.

A variety of reagents add to the polarized C = N double bond of Schiff bases[96], nucleophilic reagents attacking the carbon atom of the azomethine linkage.

(a) Reagents with the Nucleophilic Centre Attached to One Hydrogen

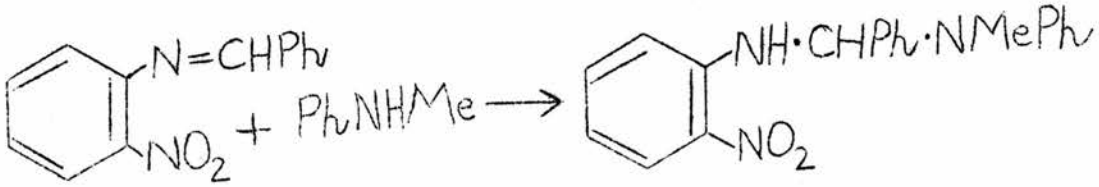
Nucleophilic reagents in which the nucleophilic atom is attached to one hydrogen atom normally react with Schiff bases to form an adduct in the manner shown in Scheme 33.[96]

$$ArCH{=}NAr' + XH \longrightarrow ArCH(X)NHAr'$$

Scheme 33

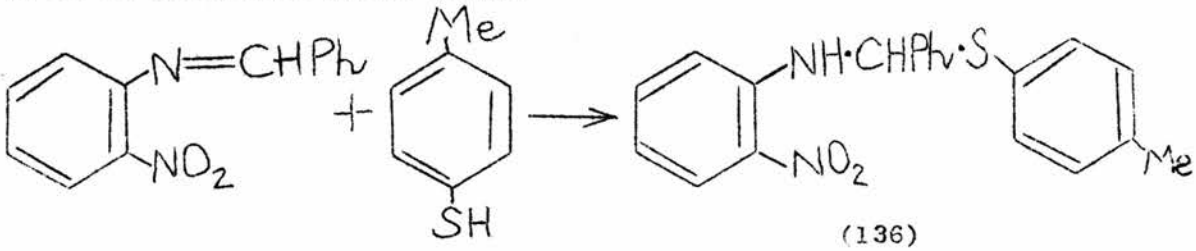
The reactions of some nucleophiles of this type with N-benzylidene-o-nitroaniline were studied.

Heating N-benzylidene-o-nitroaniline with a slight excess of N-methylaniline under reflux in dry benzene for 1 hr. gave the adduct, N-[α-(N-methylanilino)benzyl]-o-nitroaniline (135), in good yield (78%).



(135)

Similarly, stirring a solution of N-benzylidene-o-nitroaniline and toluene-p-thiol (1:1.5 molar ratio) in dry benzene at room temperature overnight gave N-[α-(p-tolylthio)benzyl]-o-nitroaniline (136) in acceptable yield (64%).



(136)

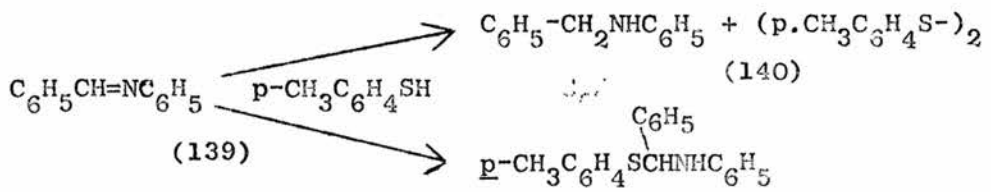
Stacy and Morath[97] found that N-benzylideneanthranilic acid (137) formed crystalline adducts (138) with a variety of thiols.

$$C_6H_5CH{=}NC_6H_4COOH\text{-}o + RSH \longrightarrow C_6H_5\underset{\displaystyle SR}{\underset{|}{C}}HNHC_6H_4COOH\text{-}o$$

(137) (138)

However, the reaction of toluene-p-thiol with N-benzylideneaniline (139) in refluxing xylene with a threefold excess of thiol resulted in N-benzylaniline[98] (140), and only at room temperature or in refluxing benzene with from one to two equivalents of thiol was the

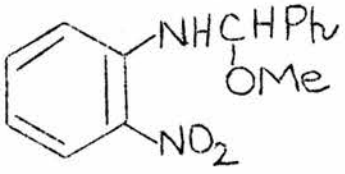
adduct[99] (141) obtained



(141)

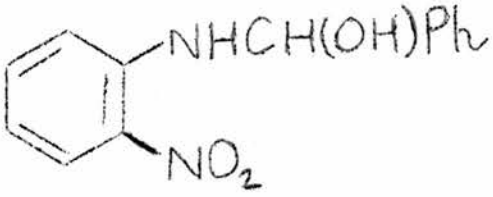
Therefore, when attempting the addition of toluene-p-thiol to N-benzylidene-o-nitroaniline, the conditions employed were those expected to promote adduct formation rather than reduction.

Heating N-benzylidene-o-nitroaniline in dry methanol under reflux gave the adduct (142)



(142)

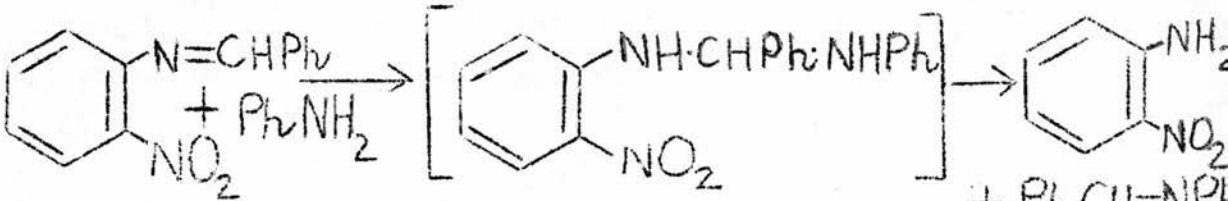
This adduct, identified by its n.m.r. and i.r. spectra, was formed as a viscous oil which gave a low melting solid only after prolonged cooling. Attempts to purify the oil by distillation under reduced pressure or to recrystallise the solid, resulted in the reformation of N-benzylidene-o-nitroaniline, presumably by the elimination of methanol from (142). Heating the adduct in an open flask at 100° for five minutes also led to the reformation of N-benzylidene-o-nitroaniline. This is the only adduct so far found which is unstable under the above conditions. The elimination of methanol from (142) to reform the Schiff base obviously resembles closely the elimination of water from the aldol intermediate (143) (cf. step 2, Scheme 29)



(143)

(b) Reagents with the Nucleophilic Centre Attached to two Hydrogens

With reagents of the above type there is always the possibility that addition to the anil may be followed by elimination. Thus the reaction of N-benzylidene-o-nitroaniline with aniline led to the formation of o-nitroaniline and N-benzylideneaniline (139) by addition of aniline to the C=N bond, followed by the elimination of o-nitroanilin from the adduct (144) as shown in Scheme 34. The adduct (144) was not isolable



(144)

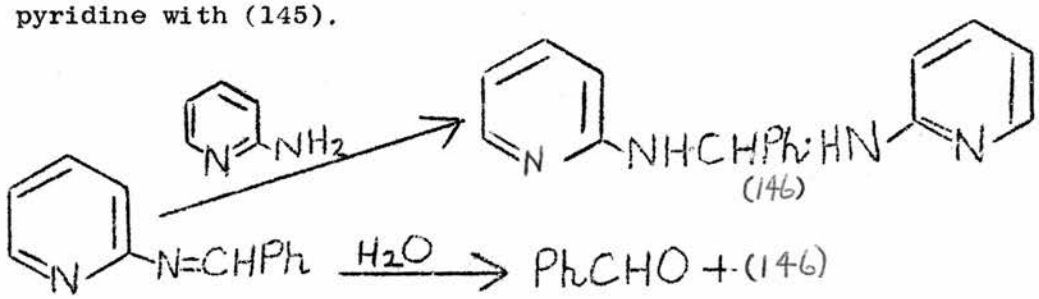
Scheme 34

However, some adducts derived from primary amines and N-benzylidene-o-nitroaniline appear to be stable, e.g. NN-benzylidenebis-o-nitroaniline [(134); Ar = Ph; X = H] and the formation of this adduct as a by-product of the anil synthesis has been described in section 2 (cf. p. 45). Stacy et al[57] claimed that when a solution of equimolar amounts of N-benzylidene-o-nitroaniline and o-nitroaniline in benzene was heated under reflux for 1 hr., NN-benzylidenebis-o-nitroaniline [(134); Ar=Ph; X=H] was formed. When Stacy's experiment was repeated, however, no adduct was formed and the starting materials

were recovered. When the reaction was attempted by melting together equimolar amounts of the two reactants at 100°, again, however, no adduct formation was observed. Heating a solution of equimolar amounts of the two reactants under reflux in benzene in the presence of benzoic acid, however, led to the formation of NN-benzylidenebis-o-nitroaniline. Presumably initial protonation of the Schiff base nitrogen facilitates addition of o-nitroaniline.

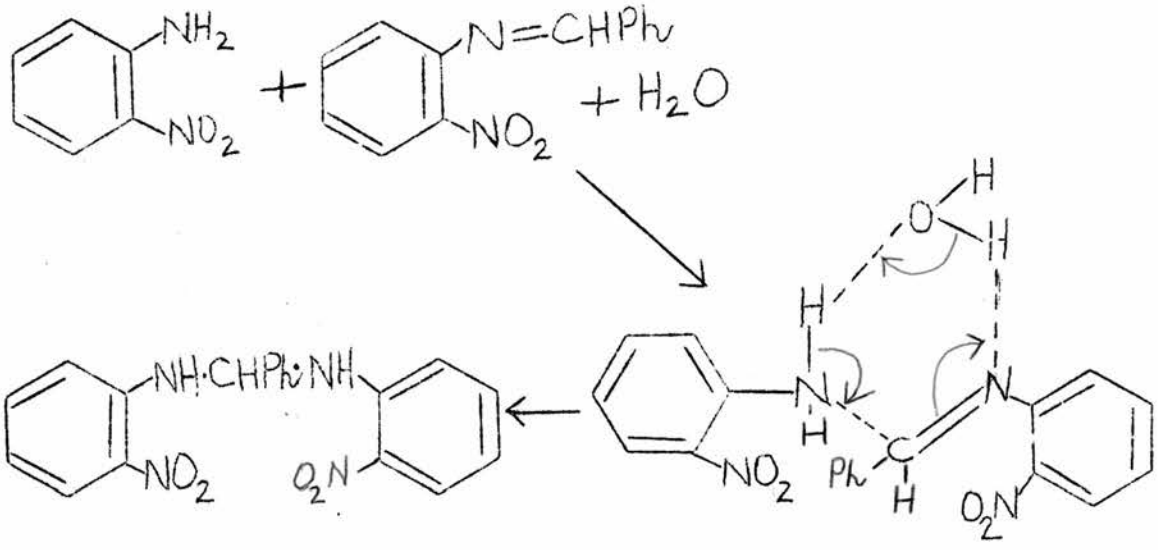
There was also no evidence of adduct formation when a solution of either 2-aminopyridine or p-nitroaniline was heated under reflux for 1 hr with an equimolar amount of N-benzylidene-o-nitroaniline in dry benzene. In both of these cases, repeating the reaction in the presence of benzoic acid failed to give any evidence of adduct formation.

Stacy et al[57] also reported the conversion of the anil to NN-benzylidenebis-o-nitroaniline both by acidic hydrolysis and by exposure to the atmosphere. We found that when N-benzylidene-o-nitroaniline was heated in water at 100°, NN-benzylidenebis-o-nitroaniline was the main product, rather than o-nitroaniline. This recalls the reaction[100] of 2-(N-benzylideneamino)pyridene (145) with water to give the adduct (146) and benzaldehyde, though in this case the adduct (146) was also formed by the reaction of 2-amino-pyridine with (145).



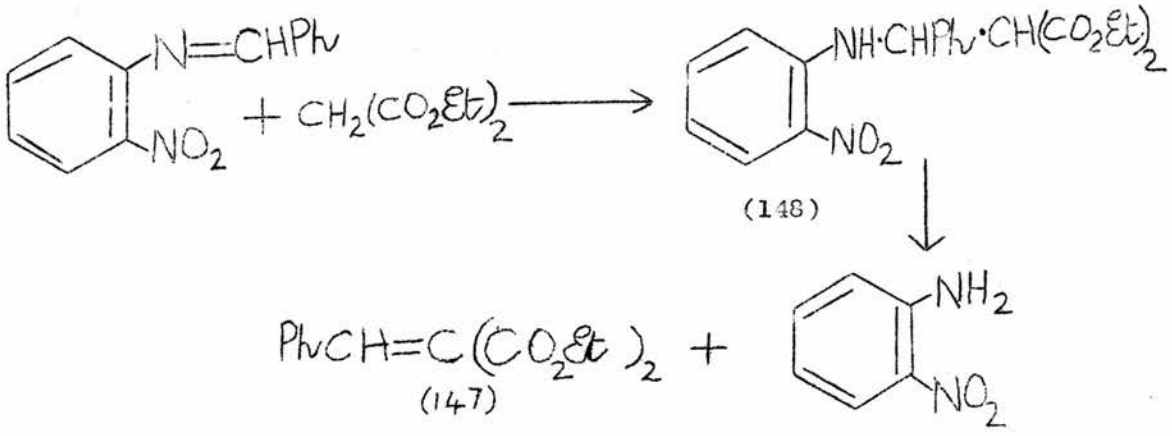
(145)

That the reaction of water with N-benzylidene-o-nitroaniline succeeds in giving the adduct while straight forward addition of o-nitroaniline at the same temperature fails may indicate that addition in the former case proceeds via the aldol intermediate (143) rather than by direct addition to the anil; on the other hand, some mechanism such as that shown below (Scheme 35) may be involved.



Scheme 35

The reaction of N-benzylidene-o-nitroaniline with diethyl malonate, in which there is again the possibility of addition being followed by elimination, was also studied. The reaction in the presence of piperidine gave only diethyl benzylidenemalonate (147) and o-nitroaniline, as shown in Scheme 36. The intermediate diethyl α-(N-o-nitroanilino)benzylmalonate (148) was not isolated.

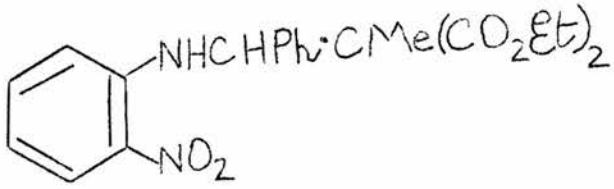


Scheme 36

It was previously reported[101] that N-benzylidene-o-nitroaniline did not react with diethyl malonate. However, the compound which was then described as N-benzylidene-o-nitroaniline[83] has more recently been shown to be NN-benzylidenebis-o-nitroaniline as previously discussed (p.43).

When the anil was treated with the sodium salt of diethyl malonate, a mixture of (147), (148), o-nitroaniline and benzaldehyde was produced; it is possible that in this case the compound (148) was partially converted into its sodium salt which did not undergo elimination.

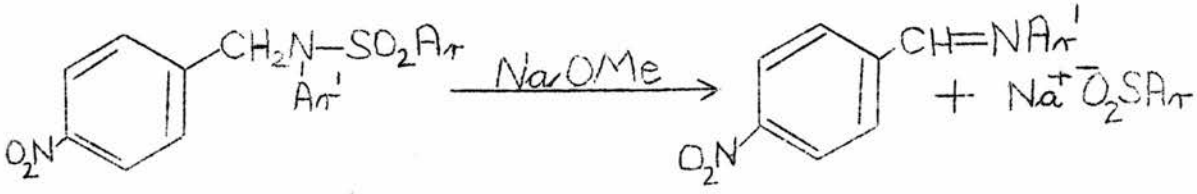
Attempts to extend this reaction to the addition of diethyl methylmalonate to N-benzylidene-o-nitroaniline, using both procedures described above, failed to yield the adduct (149). In view of the results obtained with diethyl malonate it is hard to believe that (149) is not formed at some stage of the reaction. Perhaps, as with the compound (142), this adduct, once formed, readily undergoes elimination to regenerate the starting materials, but unlike (142) this equilibrium at room temperature lies on the side of the starting materials.



(149)

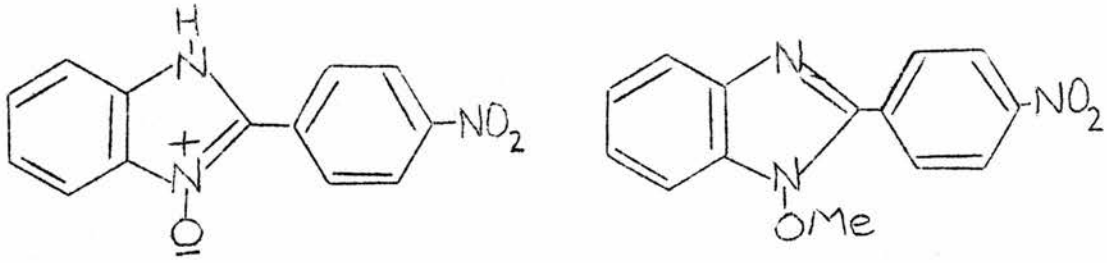
(c) Reagents with No Hydrogens Attached to the Nucleophilic Centre.

It has been shown that Schiff bases may be obtained from the base-induced elimination of toluene-p-sulphonyl groups from sulphonamides,[102] e.g. (150) reacts with sodium methoxide in toluene or methanol to give (151)



(150) (151)

However, attempts to extend this reaction to the preparation of N-p-nitrobenzylidene-o-nitroaniline[103], led easily to the sodium salt of the benzimidazole-N-oxide (152) and its methyl ether (153)



(152) (153)

It was of interest, therefore, to see if the product of normal elimination, i.e. N-p-nitrobenzylidene-o-nitroaniline [(151); Ar' = o-$C_6H_4NO_2$], would give the benzimidazole derivatives

when treated with sodium toluene-*p*-sulphinate in methanol. However since the required anil was not then available, the reaction of *N*-benzylidene-*o*-nitroaniline with sodium toluene-*p*-sulphinate was studied. When these two compounds were heated under reflux together in methanol, under conditions which simulated those of the cyclisation of the above sulphonamide, no apparent reaction occurred.

The reaction of *N*-benzylidene-*o*-nitroaniline with cyanide ion gave an entirely different type of product from any found by the action of those nucleophiles already discussed in this section. This reaction is discussed later (*cf.* p. 63).

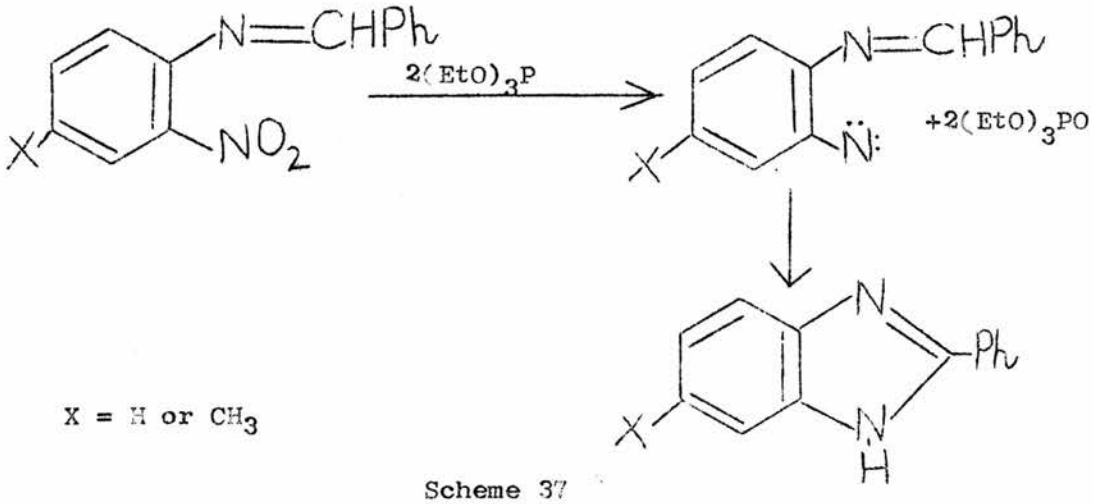
Not surprisingly, *NN*-dimethylaniline which has no hydrogens attached to the nucleophilic atom, showed no apparent reaction with the anil.

C. The Formation of Benzimidazoles and Benzimidazole-N-oxides from o-Nitroaniline and its Derivatives.

(a) Triethyl Phosphite Reduction.

The reductive cyclisation of the anils of o-nitrobenzaldehyde to the corresponding indazoles, by triethyl phosphite, has been described elsewhere (cf. p. 42). The reaction has now been extended to the cyclisation of o-nitroanils.

Heating a solution of N-benzylidene-o-nitroaniline and triethyl phosphite (1:4 molar ratio) in dry t-butylbenzene under reflux for 6.5 hr. gave 2-phenylbenzimidazole in acceptable yield (47%). Similar treatment of N-benzylidene-4-methyl-2-nitroaniline gave 5(6)-methyl-2-phenylbenzimidazole, though in somewhat lower yield. Again the reaction mechanism probably involves the formation of a nitrene intermediate as shown in Scheme 37.

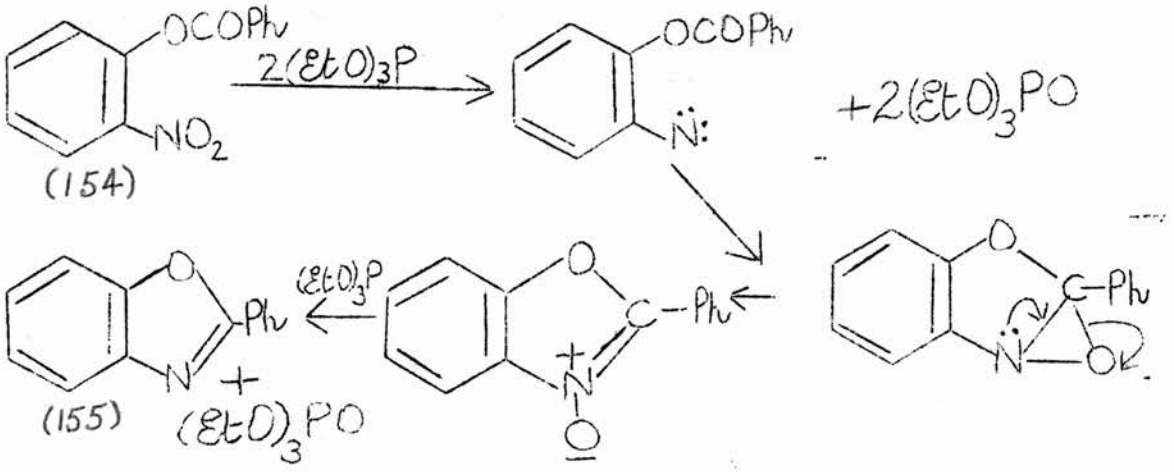


Scheme 37

The product of the similar reaction of N-benzylidene-4-chloro-2-nitroaniline with triethyl phosphite was shown (t.l.c., i.r. spectrum) to contain 5(6)-chloro-2-phenylbenzimidazole, but the crude product could not be further purified, either by recrystallisation, or by

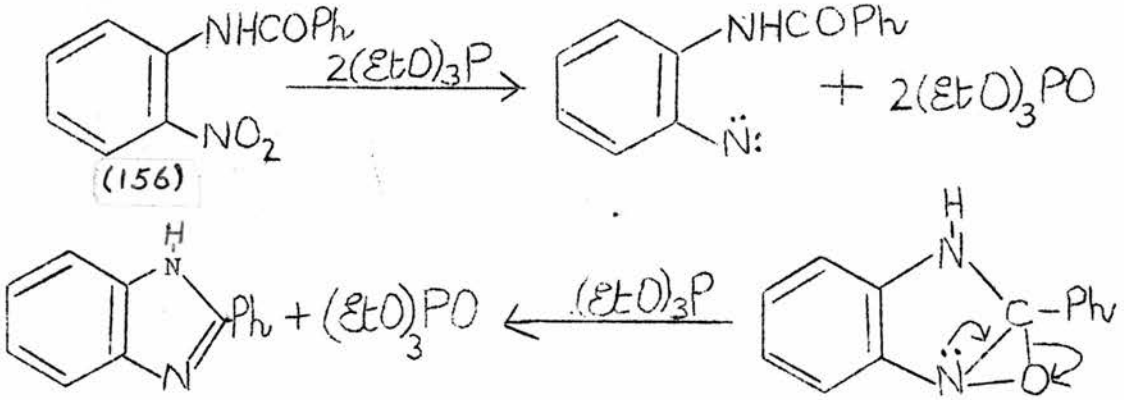
column chromatography.

It was reported that triethyl phosphite reacted with o-nitrophenyl benzoate (154) to give 2-phenylbenzoxazole (155), the mechanism of this reaction probably being that shown in Scheme 38.



Scheme 38

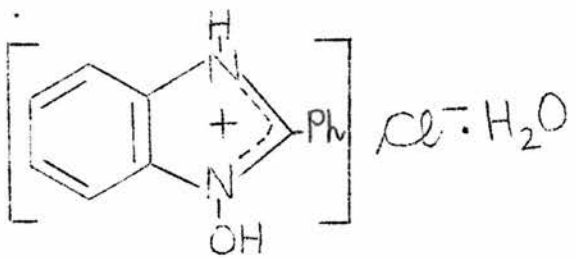
It was hoped that reacting 2'-nitrobenzanilide (156) with triethylphosphite might cause a similar nitrene insertion into the side-chain carbonyl group to yield 2-phenylbenzimidazole.



However, when the reaction was attempted, 2-phenylbenzimidazole was produced in only 3% yield.

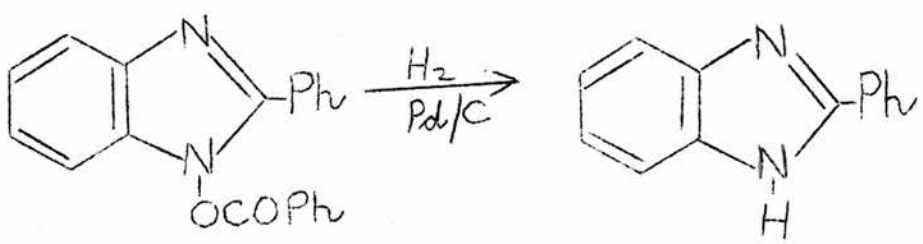
(b) Cyanide-Induced Cyclisation of o-Nitroanils.

Heating a mixture of potassium cyanide (2.5 molar equivalents) and N-benzylidene-o-nitroaniline (1 molar equivalent) in dry methanol, followed by acidification of the reaction mixture with concentrated hydrochloric acid gave a white solid which was identified as the monohydrate of 1-hydroxy-2-phenylbenzimidazole hydrochloride (157).



(157)

This identification was based on (i), a mass spectrum identical to that of 1-hydroxy-2-phenylbenzimidazole (cf. p.120); (ii), analysis; (iii), the conversion of (157) by reaction with benzoyl chloride and sodium hydroxide[57], into 1-benzoyloxy-2-phenylbenzimidazole (158), which was subsequently converted into 2-phenylbenzimidazole by catalytic hydrogenolysis in methanol over palladium-charcoal; and (iv), its conversion to the free 1-hydroxy-2-phenylbenzimidazole (81) and chloride ion by neutralisation with sodium hydroxide.

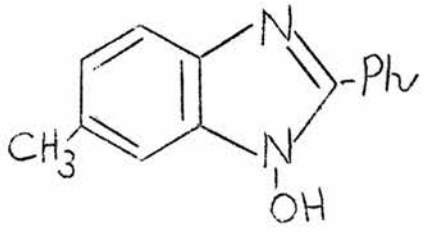


(158)

In an alternative procedure, potassium cyanide was reacted with N-benzylidene-o-nitroaniline as described above, the solvent was removed from the reaction mixture by distillation and the residue was

chromatographed on silica gel to give 1-hydroxy-2-phenylbenzimidazole (79%) and o-nitroaniline (7%) as the only products. It was found that a molar equivalent of potassium cyanide was necessary for the complete conversion of the anil into the benzimidazole-N-oxide, and when equimolar proportions of the anil and potasium cyanide were reacted, cyanide ion could not be detected among the reaction products. When the reaction was repeated using a catalytic amount of potassium cyanide, no heterocyclic product was isolated, showing that although cyanide is not included in the cyclised product, it is still consumed in the course of the reaction.

The similar reaction of N-benzylidene-4-methyl-2-nitroaniline and an excess of potassium cyanide in methanol gave 1-hydroxy-6-methyl-2-phenylbenzimidazole (159)



(159)

Becker[105] found that treatment of the anils shown below with sodium cyanide in dimethylformamide gave the corresponding α, α'-dianilinostilbenes (160).

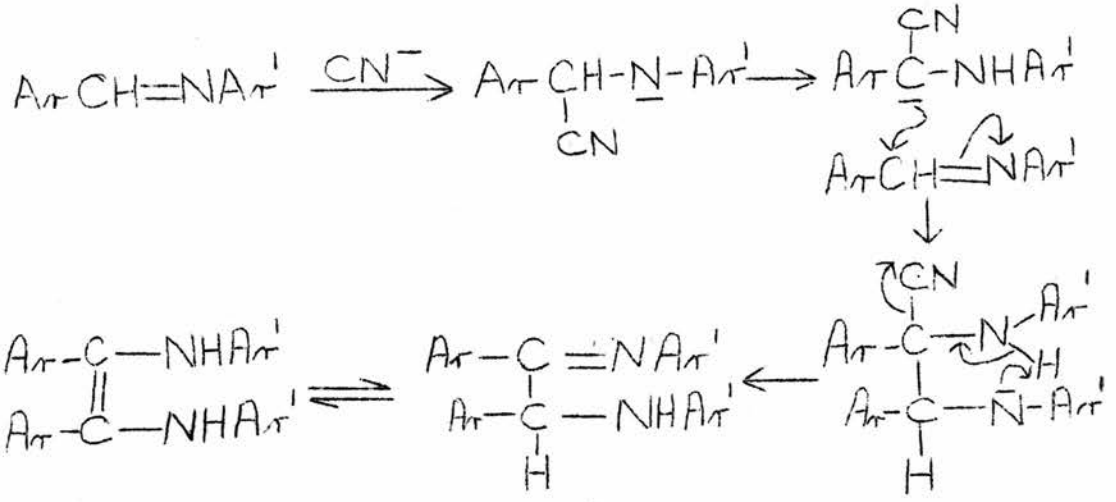
$$ArCH = NAr' \longrightarrow ArC(NHAr'):C(NHAr')Ar$$
(160)

Ar = Ph, p-tolyl, p-$MeOC_6H_4$, and 3,4-$(CH_2O_2)C_6H_3$

Ar' = Ph and p-tolyl.

It seems likely that this reaction proceeds via a mechanism

analogous to that of the benzoin condensation[106] (Scheme 39).

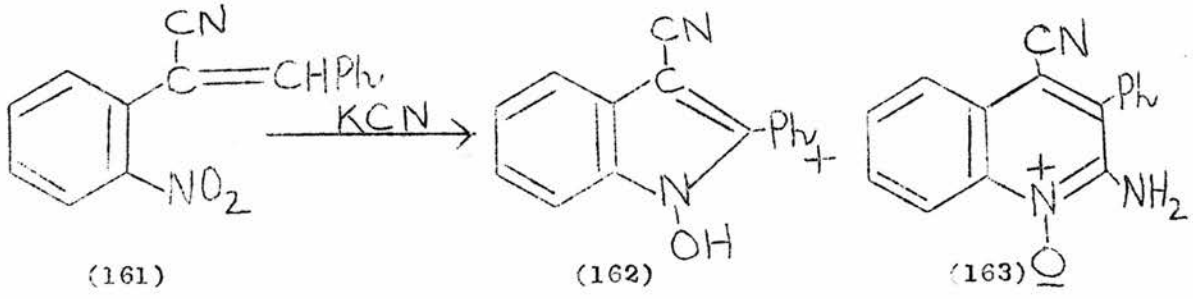


(160)

Scheme 39

Obviously, in the above reaction, unlike that of N-benzylidene-o-nitroaniline with cyanide ion, a catalytic quantity of cyanide ion is sufficient for complete reaction.

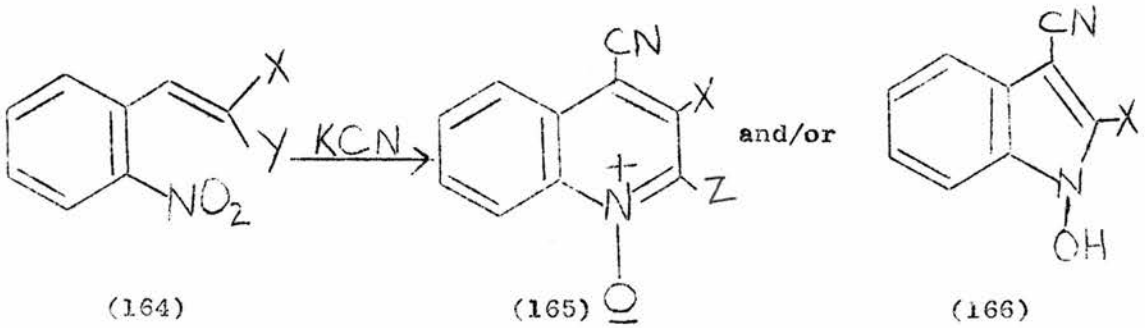
These reactions of o-nitroanils with cyanide ion are formally similar to the cyanide-induced cyclisation[107] of α-o-nitrophenyl-cinnamonitrile (161) to 3-cyano-1-hydroxy-2-phenylindole (162), although the quinoline derivative (163) was also formed in this reaction



(161) (162) (163)

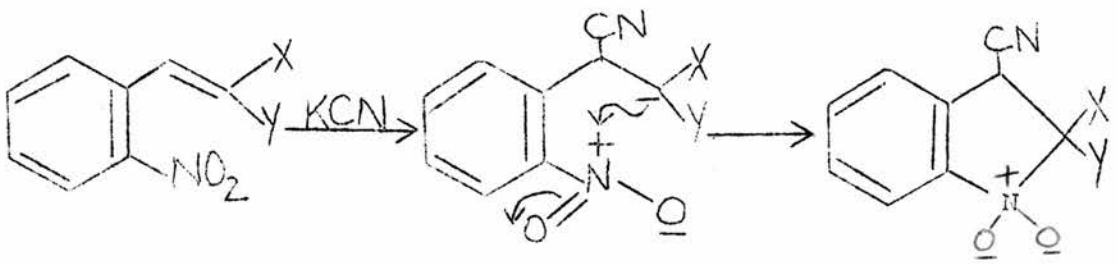
A recent survey has been made of cyanide induced cyclisations of o-nitrobenzylidene compounds[108], showing that compounds of the

type (164), where X and Y are carbon-centred electron-withdrawing groups, were cyclised by potassium cyanide in aqueous ethanol to give, according to circumstances, quinolines (165) and/or indoles (166), e.g. the compound [(164); X = Y = CO_2Et] yielded the quinoline [(165); X = CO_2Et, Z = OH] and the indole [(166); X = CO_2Et].



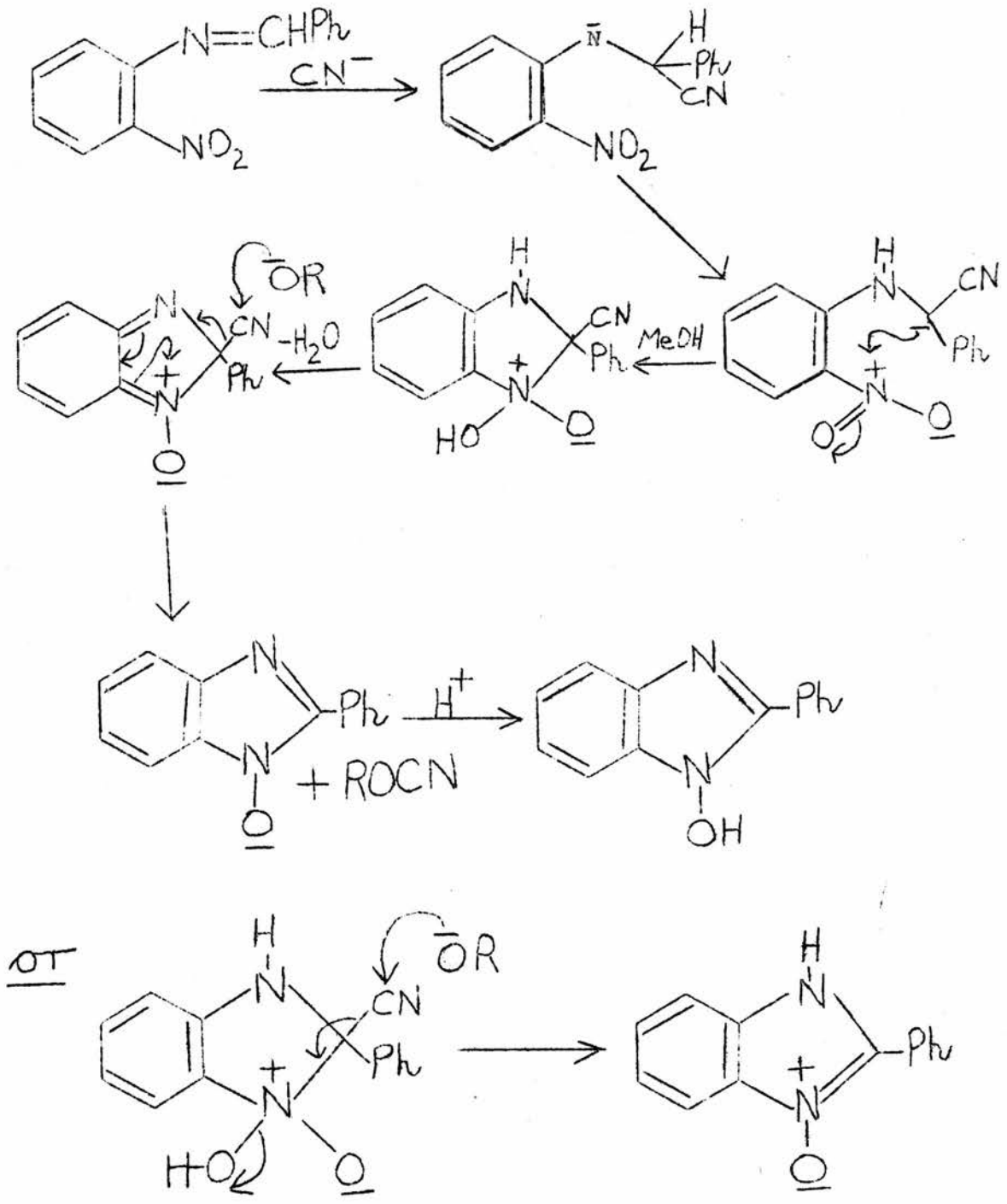
(164) (165) (166)

The nature of the products varied with the pH of the reaction quinoline formation being favoured in strongly basic media), and with the nature of the substituents X and Y. Quinoline formation was favoured when both X and Y were strongly electron-withdrawing groups but indole formation was a competing reaction when this effect was reduced and was exclusive when X was an alkyl group. Indole formation may proceed via the intermediate (167), the result of interaction between a side-chain carbanion and the o-nitro group.



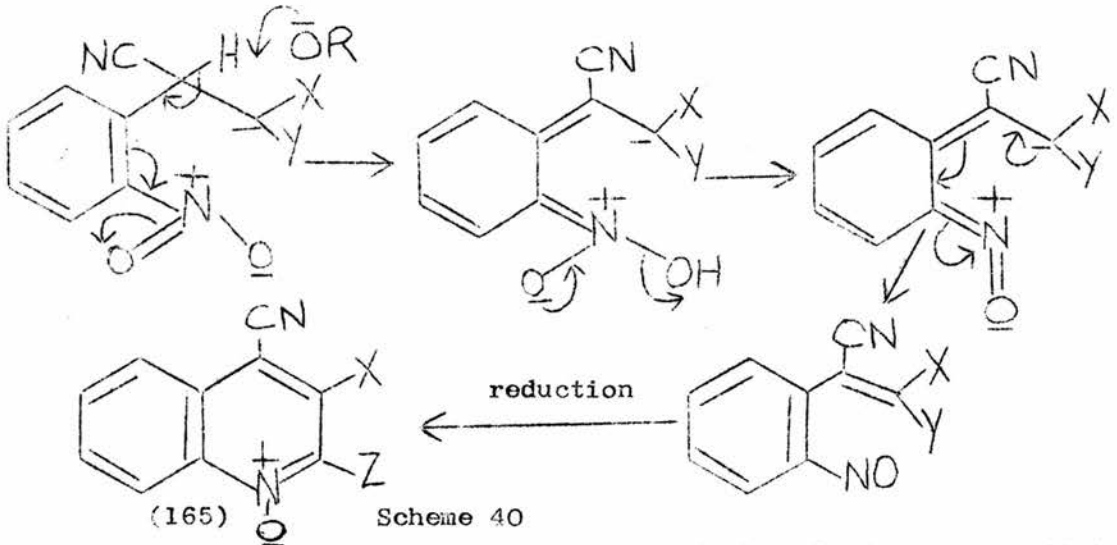
(167)

Formation of quinoline may proceed as shown below in Scheme 40, immediate ring closure to the intermediate (167) being hindered by



Scheme 42

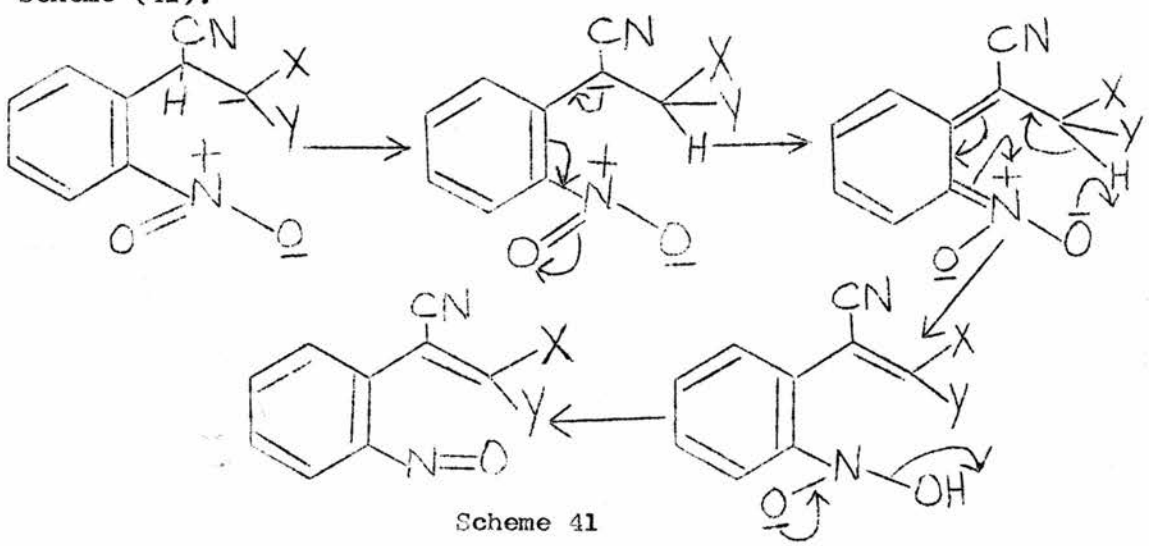
the electron-withdrawing nature of X and Y.



(165) Scheme 40

Reduction of the nitroso intermediate to a hydroxylamine intermediate which can undergo dehydrative ring closure to give (165) is presumably accomplished by the reaction medium.

An alternative route to the nitroso intermediate is shown in Scheme (41).

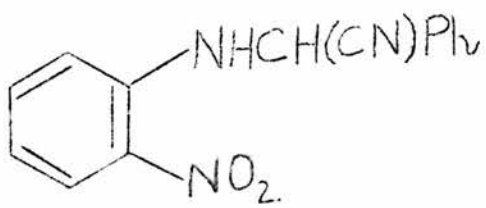


Scheme 41

A mechanism similar to that proposed for the formation of the indole (166) would appear to agree with the known facts about the reaction of cyanide ion with N-benzylidene-c-nitroaniline. The proposed mechanism is shown in Scheme 42. As in Scheme 39 the electron-withdrawing power of the cyanide group promotes the ready

release of the hydrogen attached to the benzylic carbon to yield a carbanion. However, whereas in Scheme 39 the carbanion reacts intermolecularly with another molecule of anil, in the above case the negatively charged benzylic carbon may react intramolecularly with the nitrogen of the adjacent nitro group. The above mechanism is in accordance with the observed facts that an equivalent of cyanide ion is consumed during the reaction although it does not appear in the final product. The mechanism also implies that methyl cyanate and/or cyanate ion should be formed in the course of the reaction (although the former would presumably be unstable under the reaction conditions[109]), but neither cyanate ion nor any product derived from methyl cyanate has been detected in the final reaction mixture. However, it was also found that when potassium cyanate and 1-hydroxy-2-phenylbenzimidazole were heated together under reflux in methanol, cyanate ion could not be detected in the resultant mixture.

If the mechanism of Scheme 42 is correct, then treatment of the compound (168) with sodium methoxide in methanol should also yield the heterocycle.



(168)

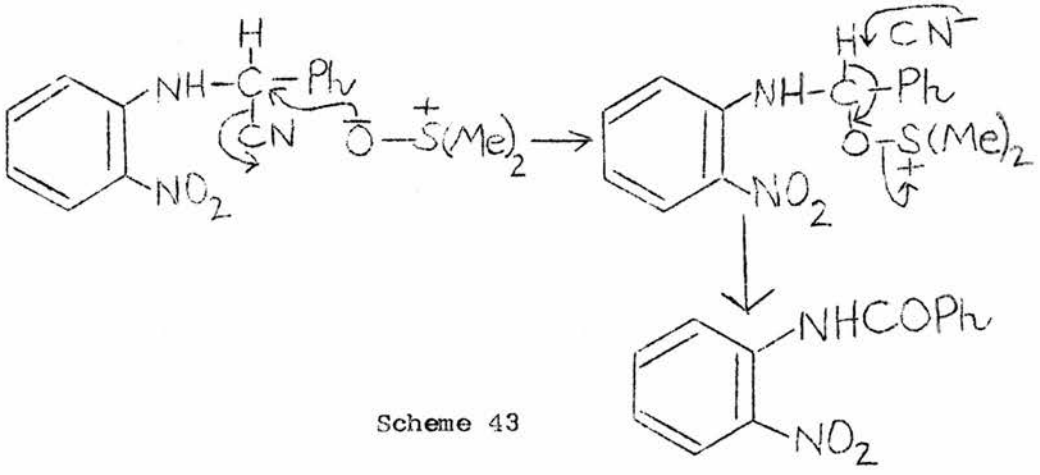
The reaction of hydrogen cyanide with N-benzylidene-p- or N-benzylidene-m-nitroaniline in methanol was reported[110] to give the adduct [(169); Ar' = m- or p- $C_6H_4NO_2$] in quantitative yield

Ar'NHCH(CN)Ph

(169)

However, stirring a solution of hydrogen cyanide and N-benzylidene-o-nitroaniline (ca. 2:1 molar ratio) in dry methanol overnight gave as the only product an intractable oil, the i.r. spectrum of which was the same as that of the methanol adduct (142). Repeating the reaction in the presence of a small amount of base (to encourage formation of cyanide ion) led, not surprisingly, to the formation of 1-hydroxy-2-phenylbenzimidazole.

When N-benzylidene-o-nitroaniline and potassium cyanide (1:1 molar ratio) were reacted in dry dimethyl sulphoxide, no cyclised product was isolated; 2'-nitrobenzanilide and o-nitroaniline, both in low yield, were the only identifiable products. The anil did not react with dimethyl sulphoxide itself. A possible mechanism for the formation of 2'-nitrobenzanilide is shown in Scheme 43.

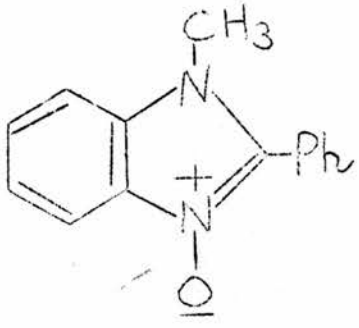


Scheme 43

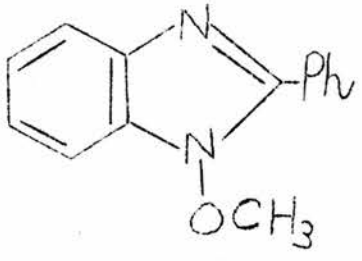
The reaction has not yet been further investigated.

Tautomerism of 1-Hydroxy-2-phenylbenzimidazole.

Stacy et al[58] compared the ultraviolet spectrum of 1-hydroxy-2-phenylbenzimidazole with those of 3-methyl-2-phenylbenzimidazole-1-oxide (170) and 1-methoxy-2-phenylbenzimidazole (171).

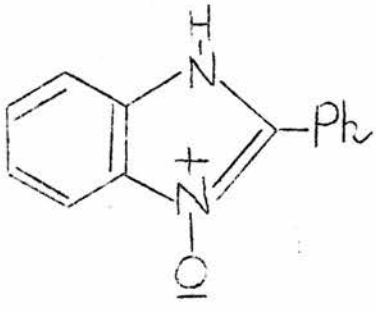


(170)

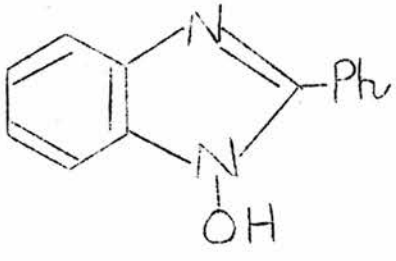


(171)

It was found to be similar to that of (170) in both aqueous and ethanolic solutions indicating that structure (a) rather than (b) predominates in these conditions.



(a)



(b)

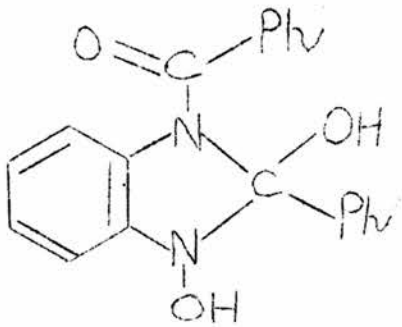
The mass spectrum of 1-hydroxy-2-phenylbenzimidazole (cf. p.120) prepared by the reaction of anil with cyanide ion, showed abundant ions $(M-16)^+$ and $(M-17)^+$ corresponding to the loss of O and OH respectively. The relative abundance of these fragments suggests that the compound exists under mass spectrometric conditions predominantly as the N-oxide tautomer. The mass spectrum[103] of the compound (152) had a fragment ion at $(M-16)^+$ but not at $(M-17)^+$,

suggesting that it existed as the N-oxide tautomer under mass spectrometric conditions.

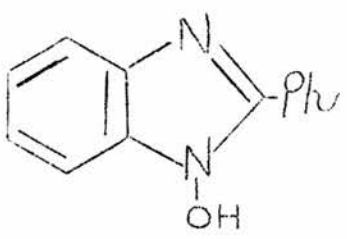
(c) Cyclisation of o-Nitroaniline and its Derivatives with Benzaldehyde.

It has already been mentioned briefly (cf.p. 43) that one of the difficulties encountered when attempting the preparation of N-benzylidene-o-nitroaniline from o-nitroaniline and benzaldehyde is the formation, at high temperatures or after prolonged heating, of high melting apparently heterocyclic products. This type of reaction is examined in greater detail in this section.

Stacy et al[57] reported that when a solution of equimolar amounts of o-nitroaniline and benzaldehyde in xylene was heated under reflux for seven days with water removal, 2-phenylbenzimidazole [(133) X=H; Ar=Ph] was obtained in 20% yield. It was further reported that when a solution of o-nitroaniline and benzaldehyde (1:2 molar ratio) in toluene was similarly heated under reflux for three days the product was 1-hydroxy-2-phenylbenzimidazole (81) Ettling[87] had earlier claimed (cf. p43) that when a solution of o-nitroaniline and benzaldehyde (1:2 molar ratio) in toluene was heated under reflux for sixty-six hours with water removal, the products obtained were 2-phenylbenzimidazole (14%) and 3-benzoyl-1,2-dihydroxy-2-phenylbenzimidazole [(172); 39%; m.p. 183-4°]. This latter compound was the proposed intermediate in the route leading to (81), since by reaction of dilute alkali it gave 1-hydroxy-2-phenylbenzimidazole.



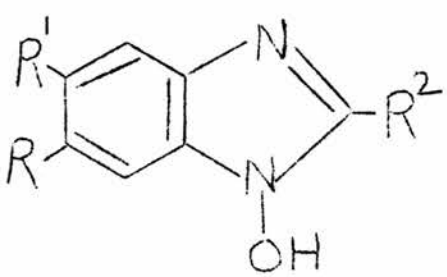
(172)



(81)

However, it seems unlikely that a structure such as (172) would exist as a stable intermediate. A more likely explanation is that the product is either a mixture of (81) and benzoic acid, or the benzoate of (81) which would give the same analysis as (172). This is supported by the fact that treatment of (81) with benzoic acid also gave (172), while the product of heating an equimolar mixture of benzaldehyde and o-nitroaniline without solvent at 180° for three hours was a solid m.p. 185-187° which gave 1-hydroxy-2-phenylbenzimidazole on recrystallisation from ethanol or by simply washing it with a solvent such as acetonitrile[86].

It has also been reported[111] that the related compounds (173) were prepared from 1 mole of a substituted o-nitroaniline and 2 moles of an aldehyde by prolonged heating, with water removal at least in some cases, in an inert solvent. The reaction temperature used varied from 110 to 190°.

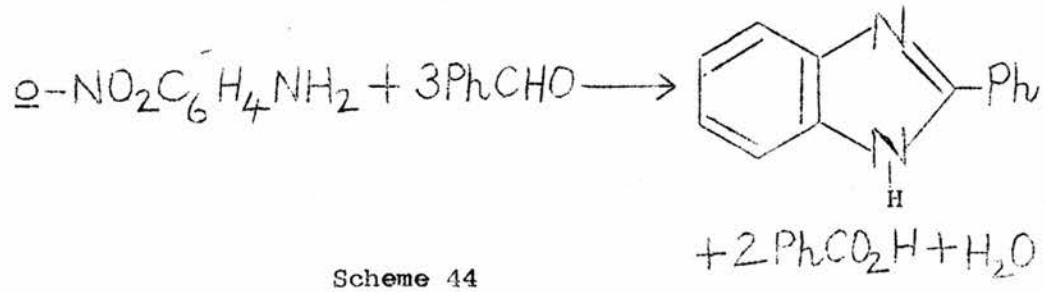


(173)

R=R'=H, R^2=(4-thiazolyl); R=H, R'=F, R^2=(3-thiacoumarinyl)

R=H, R'=PhS-, R^2=(3-pyridyl)

A recent re-examination[112] of the reaction of o-nitroaniline and benzaldehyde in high-boiling solvents showed that almost quantitative yields of 2-phenylbenzimidazole were obtained when the molar ratio of benzaldehyde to o-nitroaniline was greater than 3:1, and that the yield dropped considerably at lower molar ratios. It was also found that benzoic acid was produced during the reaction, but no 1-hydroxy-2-phenylbenzimidazole was detected. Thus the proposed stoichiometry of the reaction was as shown below (Scheme 44).



Scheme 44

The above contrasts with the previous reports in that no 1-hydroxy-2-phenylbenzimidazole was detected under any of the reaction conditions used. It was therefore of interest to examine what factors determined the nature and ratio of the products, if any intermediate products could be isolated, and if information about the mechanism of the reaction might be obtainable.

A mixture of o-nitroaniline and benzaldehyde[‡] (1:10 molar ratio) was heated under reflux (179°) for one hour, 1 molar equivalent of water being collected. The products of reaction isolated were 2-phenylbenzimidazole (70%), which was initially obtained as a mixture with benzoic acid, and further benzoic acid. Heating a solution of

‡ The term "benzaldehyde" is used in this section to denote benzaldehyde which has been purified by the method described on p. 85.

equimolar amounts of o-nitroaniline and benzaldehyde under reflux for 5 hours in p-cymene (b.p. 177°) with continuous water removal resulted in the formation of 2-phenylbenzimidazole (23%) and NN-benzylidenebis-o-nitroaniline (20%) i.e. although the reaction temperature was essentially the same, only one-third of the benzimidazole obtained in the previous reaction was produced. Repeating this reaction in the presence of benzoic acid increased the yield of 2-phenylbenzimidazole to 31%. The similar reaction of benzaldehyde with o-nitroaniline (2.5:1 molar ratio) in p-cymene in the presence of benzoic acid gave 62% 2-phenylbenzimidazole.

So far no 1-hydroxy-2-phenylbenzimidazole had been isolated. However, when a solution of o-nitroaniline and benzaldehyde (1:2.5 molar ratio) in mesitylene (b.p. 165°) was heated under reflux both 1-hydroxy-2-phenylbenzimidazole and 2-phenylbenzimidazole were obtained. The table below shows the products of reaction of o-nitroaniline and benzaldehyde (1:2.5 molar ratio) isolated in the presence of benzoic acid and with water removal, in a variety of solvents.

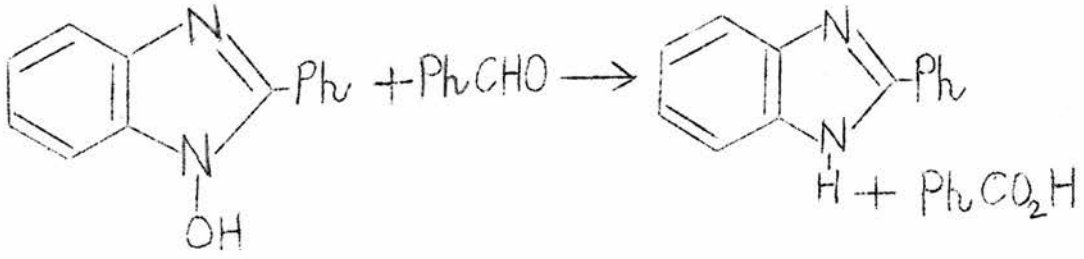
Solvent	Temp°	Time	N-Benzylidene-o-nitroaniline	1-Hydroxy-2-phenyl-benzimidazole	2-Phenyl-benzimidazole
Toluene	110	6 hr.	68%		
Xylene	140	6 hr.	66%		
Mesitylene	165	5 hr.		4%	5%
p-Cymene	177	5 hr.			62%

Heating a solution of equimolar quantities of o-nitroaniline

and benzaldehyde in p-cymene under reflux without water removal gave no heterocycle formation, o-nitroaniline being recovered in high yield. When the reaction was repeated with a 2.5:1 molar ratio of benzaldehyde to o-nitroaniline in the presence of benzoic acid (which appears to increase the yield of heterocycle) only a very small amount of 2-phenylbenzimidazole (7%) was obtained, the majority of the o-nitroaniline being recovered. However, the similar reaction of equimolar amounts of o-nitroaniline and benzaldehyde without solvent gave both 2-phenylbenzimidazole and 1-hydroxy-2-phenylbenzimidazole.

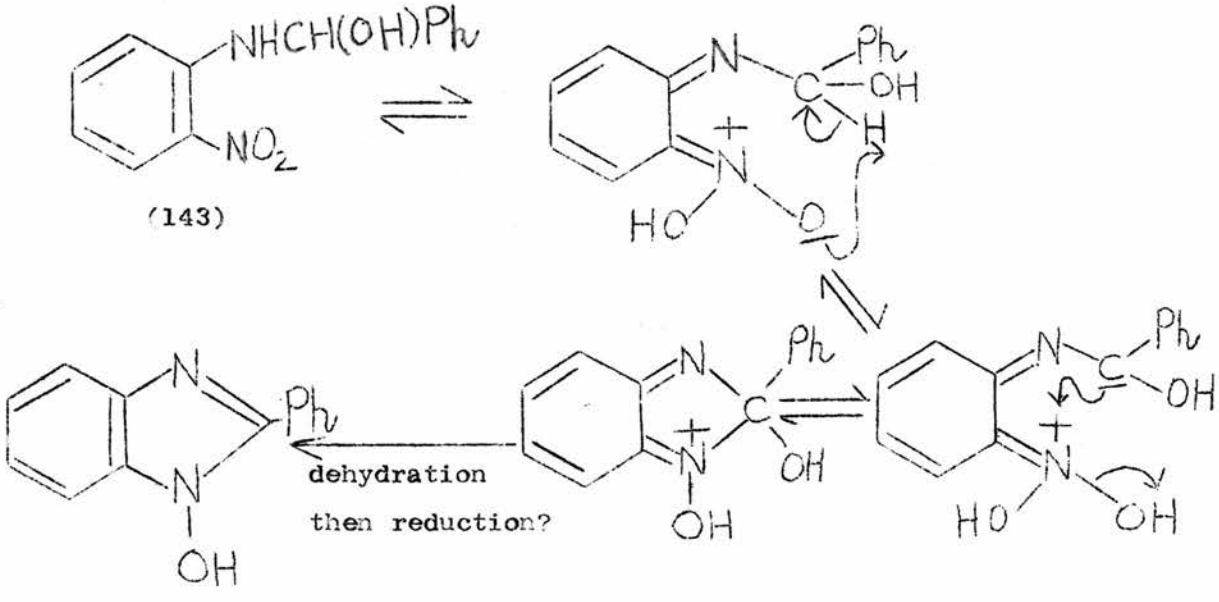
It is noticeable that whereas only a small yield of 2-phenylbenzimidazole was obtained using equimolar proportions of o-nitroaniline and benzaldehyde in p-cymene, there was a dramatic increase in yield when a large excess of benzaldehyde was employed. This would be expected if the reaction had the stoichiometry proposed in Scheme 44.

The fact that, with a lower boiling solvent, i.e. mesitylene, both 2-phenylbenzimidazole and 1-hydroxy-2-phenylbenzimidazole were produced suggests that (81) may be an intermediate in the formation of 2-phenylbenzimidazole, as shown below.



This was supported by reacting 1-hydroxy-2-phenylbenzimidazole with benzaldehyde to produce 2-phenylbenzimidazole and benzoic acid. It is reported that pyridine-1-oxide is similarly deoxygenated by aldehydes.[113]

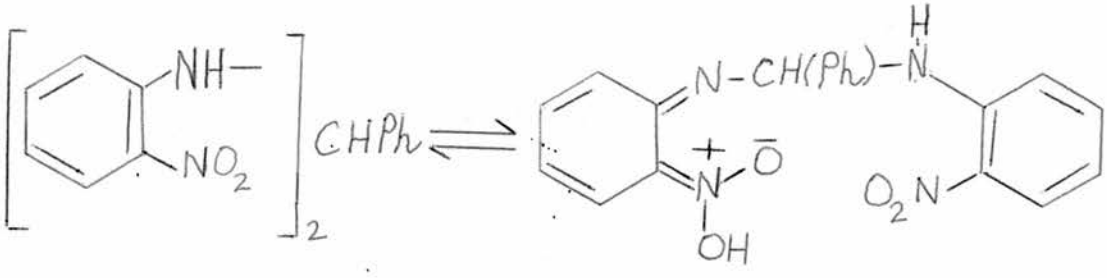
As described above, removal of water appears to be essential to heterocycle formation, as at lower temperatures it was to anil formation. It was also found that there was no apparent reaction when a solution of N-methyl-o-nitroaniline and benzaldehyde (1:10 molar ratio) was heated under reflux. These results suggest that anil formation may be essential to the production of heterocycle. However it is still possible that the cyclisation may involve the aldol precursor (143) reacting in its aci-nitro form as shown in Scheme 45, anil formation being unnecessary.



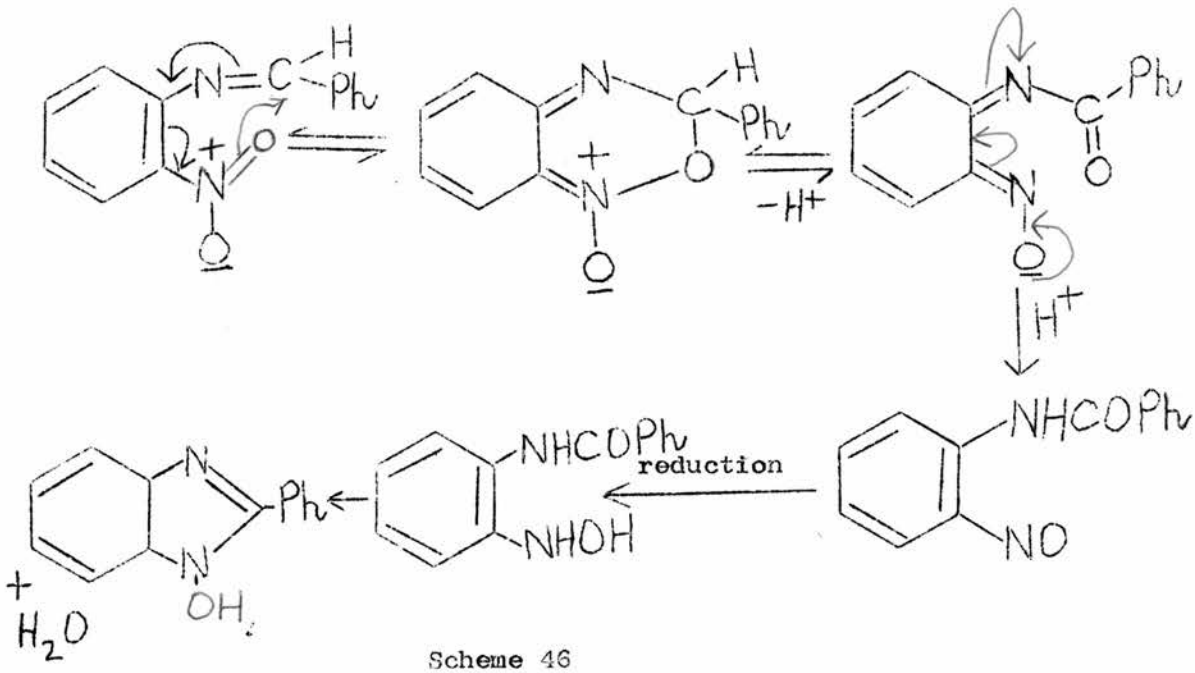
Scheme 45

The formation of (81) and 2-phenylbenzimidazole by heating equimolar quantities of benzaldehyde and o-nitroaniline under reflux without water removal contrasts with the last two results. This may be due to a concentration effect whereby some anil is formed despite the lack of water removal and its removal by heterocycle formation leads to further anil formation.

However, even if the anil is an intermediate, the intermediate which undergoes ring closure might not be the anil itself but NN-benzylidene-bis-o-nitroaniline formed by the addition of o-nitroaniline to the anil. Ring closure might occur through its aci-nitro form shown below.



First it had to be determined if the anil and/or the diamine were thermally stable or not, under the conditions which led to heterocycle formation from o-nitroaniline and benzaldehyde. The anil, for instance, might form 1-hydroxy-2-phenylbenzimidazole by intramolecular oxygen transfer from the nitro group to the side chain to form o-nitrosobenzanilide which somehow undergoes reduction to the hydroxylamine by the reaction medium and subsequent dehydrative ring closure to give the hydroxy-benzimidazole, as shown in Scheme 46.



Scheme 46

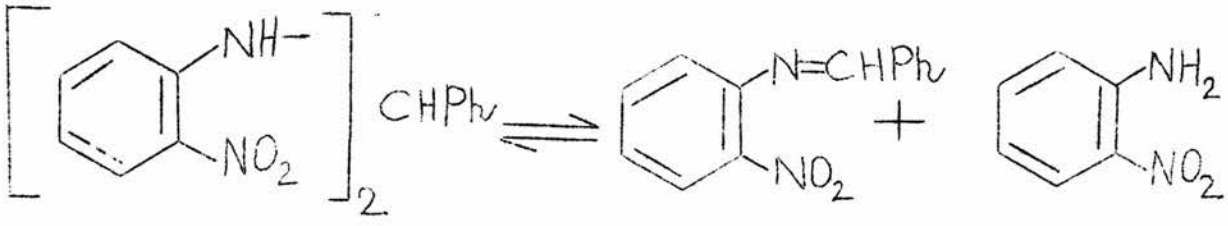
If this were so, however, then one would expect the anil to be thermally reactive. The anil was therefore, heated under reflux in dry p-cymene, but the only product isolated was unchanged anil in good yield. This result must therefore cast doubt on the mechanism of Scheme 46.

Similarly, if heterocycle formation occurred via ring closure of NN-benzylidenebis-o-nitroaniline in its aci-nitro form, it should be thermally unstable under the reaction conditions. However, variable temperature n.mr. studies of the NN-benzylidenebis-o-nitroaniline showed that it remained unchanged even after heating for two hours at 180°.

It remained, therefore, to study the reaction of both of the above compounds with benzaldehyde.

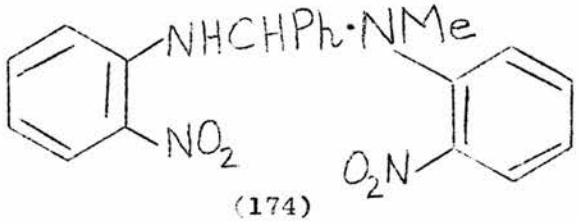
When a mixture of N-benzylidene-o-nitroaniline and benzaldehyde (1:9 molar ratio) was heated under relux for one hour, 2-phenylbenzimidazole (39%) and benzoic acid were obtained in an approximately 1:2 molar ratio. When a mixture of NN-benzylidenebis-o-nitroaniline and

benzaldehyde (1:9 molar ratio) was heated under reflux for 1 hour, 2-phenylbemzimidazole (71%) and benzoic acid were obtained, again in an approximately 1:2 molar ratio. It appears to be significant that not only is the yield of 2-phenylbenzimidazole approximately doubled in the latter case but so also is the yield of benzoic acid. This suggests the possibility that in the above reaction one mole of NN-benzylidenebis-o-nitroaniline and one mole of benzaldehyde give rise to two moles of the anil which then react to give the 2-phenylbenzimidazole. The mass spectrum of NN-benzylidenebis-o-nitroaniline (cf. p.119 , Graph 2) is essentially the same as that of N-benzylidene-o-nitroaniline, showing abundant ions at m/e 226 and 138, and indicates that NN-benzylidenebis-o-nitroaniline is converted into N-benzylidene-o-nitroaniline and o-nitroaniline under mass spectrometric conditions. However, it appears from the n.m.r. studies that, in the above reactions, NN-benzylidenebis-o-nitroaniline does not thermally eliminate o-nitroaniline. It may of course be that the equilibrium shown below exists and that heating in the presence of benzaldehyde causes the removal of o-nitroaniline as anil and hence displaces the equilibrium towards anil formation.



On the other hand, of course, benzaldehyde may somehow react directly with NN-benzylidenebis-o-nitroaniline to give the anil. A variable temperature n.m.r. study of an equimolar mixture of benzaldehyde and NN-benzylidenebis-o-nitroaniline showed no apparent change on heating to 180°. The mixture was left at 180° for several hours, after which time the spectrum showed loss of the benzaldehyde PhCH singlet at 0.00 τ and the appearance of a singlet at 5.08 τ. The nature of the product(s) thus obtained remains to be investigated (cf. p. 83).

In connection with the reaction of benzaldehyde with NN-benzylidenebis-o-nitroaniline, it would have been of interest to study the reaction of the compound (174) with benzaldehyde under similar conditions.

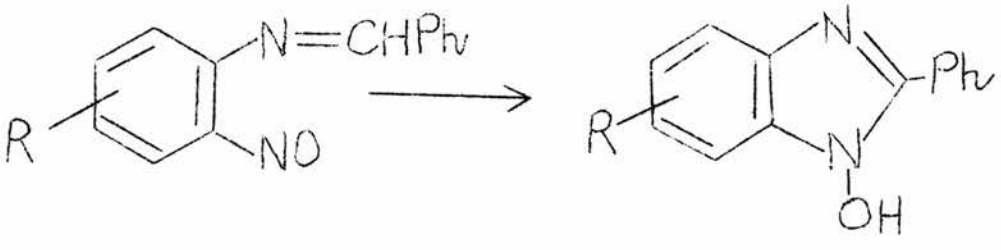


(174)

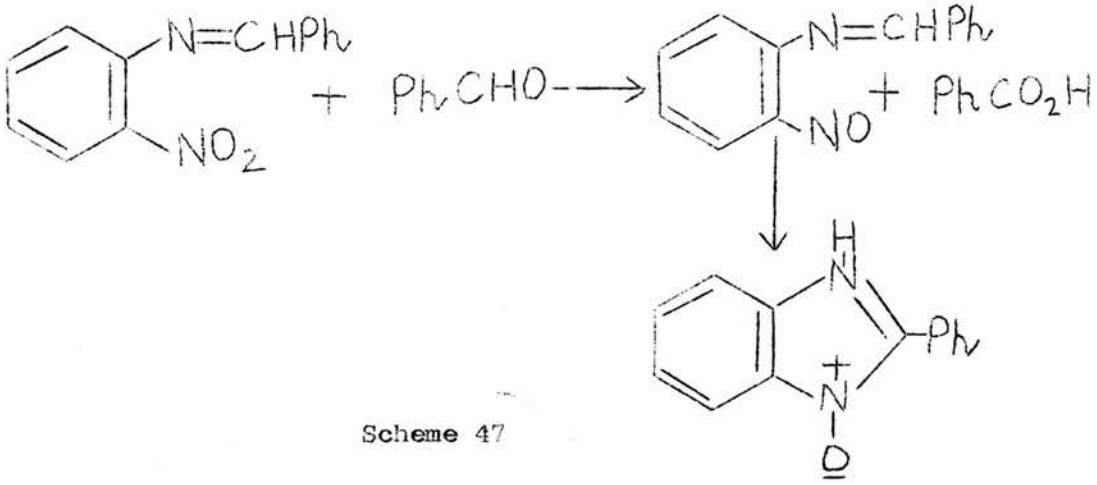
However N-methyl-o-nitroaniline did not appear to add to N-benzylidene-o-nitroaniline, even at high temperatures in the presence of acid.

If the anil is indeed the intermediate which ring closes to give heterocycle then there are several mechanistic possibilities.

We have discussed (cf. p. 40) the formation of hydroxybenzimidazoles from o-nitrosoanils, as shown below.

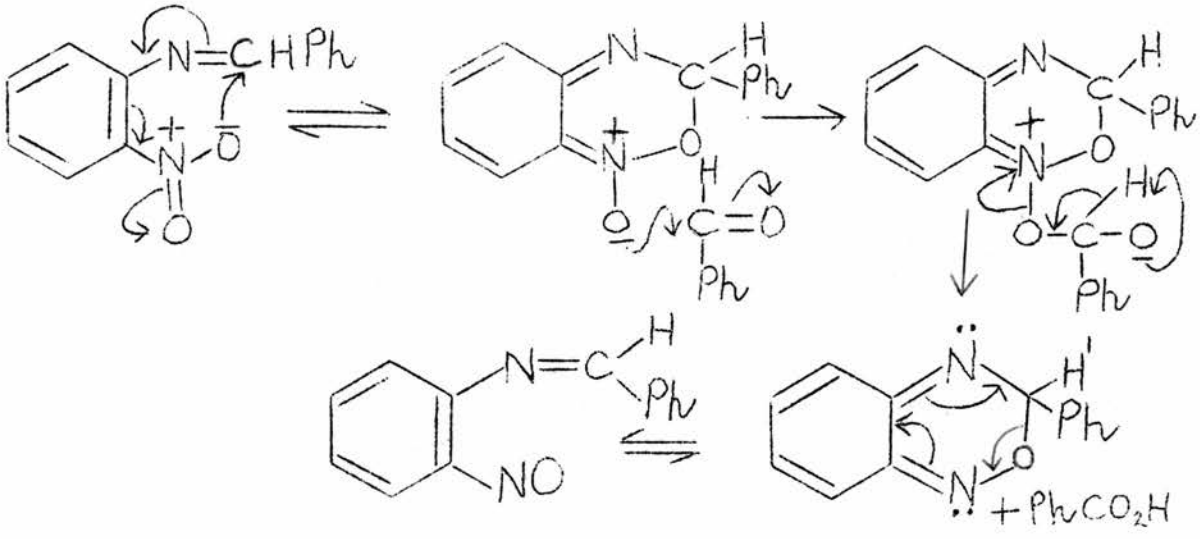


It is an attractive proposition, in keepting with the stoichiometry of Scheme 44 that N-benzylidene-o-nitroaniline reacts with 1 mole of benzaldehyde as shown below to give the nitrosoanil which immediately ring-closes to give the heterocycle as shown below in Scheme 47.



Scheme 47

It was found that the reaction of nitrobenzene with benzaldehyde yielded unchanged nitrobenzene. Thus the nitro-group per se does not react with benzaldehyde. However, in the case of the o-nitroanil a mechanism of the type shown below in Scheme 48 may be possible.



Scheme 48 (a)

It is also known[114] that heating N-benzyl-o-nitroaniline (80) in sand at 220° gives 2-phenylbenzimidazole, so perhaps this should also be considered as a possible reduced intermediate. The n.m.r. spectrum of N-benzyl-o-nitroaniline shows a doublet at 5.52 τ (Ph $\underline{CH_2}$), while that of an equimolar mixture of N-benzyl-o-nitroaniline and benzoic acid shows a singlet at 5.52 τ (Ph$\underline{CH_2}$). As described above, the n.m.r. spectrum of a solution of equimolar amounts of NN-benzylidenebis-o-nitroaniline and benzaldehyde which had been heated for several hours showed a singlet at 5.08 τ, suggesting a deshielded benzylic proton resonance. From the above results this would not appear to indicate the formation of N-benzyl-o-nitroaniline. It is possible that it arises from a proton of the type H' in (a) in Scheme 48. The compound giving rise to this signal has so far not been isolated.

Although the mechanism of heterocycle formation from the reaction of o-nitroaniline with benzaldehyde has not been completely determined, it seems likely from the foregoing that cyclisation proceeds via the intermediacy of a reduced form of N-benzylidene-o-nitroaniline. It is still possible that it is the C=N of the side chain which is reduced to give an intermediate such as N-benzyl-o-nitroaniline. However, it seems more likely that a mechanism of the type shown in Scheme 48, with its analogy to the known deoxygenation of heterocyclic N-oxides by aldehydes operates to produce the o-nitrosoanil which would be expected to form the 1-hydroxybenzimidazole.

III. EXPERIMENTAL

A. General Experimental Procedure.

Melting points were determined on a 'Gallenkamp' melting block.

Infra-red spectra were recorded on a Perkin Elmer 257 instrument using sodium chloride plates, solids as Nujol Mulls and liquids neat as thin films.

Nuclear magnetic resonance spectra were recorded, unless otherwise stated at 60 MHz on a Perkin Elmer R10 spectrometer and measured with respect to internal tetramethylsilane.

Mass spectra were recorded on an AEI M.S.902 instrument.

Ultra-violet spectra were obtained on a Unicam S.P.800 spectrophotometer.

The term "light petroleum" is used to refer to the fraction of b.p. 40-60°.

B. Preparation and Purification of Starting Materials and Authentic Compounds.

Purification of Benzaldehyde.[115]

Benzaldehyde was purified by washing with portions of 10% sodium bicarbonate solution (to remove any benzoic acid present) until the evolution of carbon dioxide ceased. After further washing with water the benzaldehyde was dried over anhydrous sodium sulphate and distilled under reduced pressure.

NN-Benzylidenebis-o-nitroaniline[57] [(134); Ar = Ph; X = H].

A solution of o-nitroaniline (27.6 g, 0.2 mole) and benzaldehyde (10.6 g, 0.1 mole) in toluene (50 ml) was heated under reflux for 6 hr in an apparatus connected to a Dean and Stark trap, in which water (1.5 ml) was collected. The solution was cooled and diluted with light petroleum (50 ml) which precipitated the diamine (above) as an orange solid (28.6 g, 76%) m.p. 90-94°. A portion of the solid recrystallised from benzene-light petroleum, gave an orange solid, m.p. 110-112°.‡ (Found: C, 62.7, H, 3.85; N, 15.45. Calc for $C_{19}H_{16}N_4O_4$: C, 62.6; H, 4.4; N, 15.4%), ν_{max} (N-H) 3345 cm^{-1}, λ_{max} ($CHCl_3$) 254, 266 sh., 400 nm(ε16,600, 13,400, 7,700). The bar graph of the mass spectrum of this compound (Graph 2) is shown on p. 119 and discussed on p. 80

‡ Recrystallisation of the above compound from various solvents gave solids with widely varying melting points. Examination of the above sample obtained by recrystallisation from benzene on a Kofler hot-stage apparatus showed that it melted over the approximate range 90-120°. The n.m.r. spectrum of the unrecrystallized product in CCl_4 showed a singlet at 1.62 τ, which corresponds to the CH=N signal of N-benzylidene-o-nitroaniline.

Diethyl Benzylidenemalonate (147).[116]

A solution of diethyl malonate (10.0 g), benzaldehyde (7.6 g), benzoic acid (0.5 g) and piperidine (0.7 ml) in benzene (40 ml) was heated under reflux for 11 hr, water being collected in an attached Dean and Stark trap. The solution was cooled and washed with water (2 x 20 ml), N hydrochloric acid (2 x 20 ml) and then saturated sodium bicarbonate solution (20 ml). The combined aqueous solutions were extracted with benzene (50 ml), the benzene extract was added to the original organic layer, and the organic solution dried over anhydrous sodium sulphate. After the benzene was evaporated off, the residue was distilled under reduced pressure to give diethyl benzylidenemalonate (12.3 g, 80%) b.p. 176-177°/5 mm.

2 Phenylbenzimidazole [(133); Ar = Ph; X = H].

The method of preparation was essentially that of Weidenhagen.[117] A solution of benzaldehyde (4.5 g) in methanol (50 ml) was added to a solution of o-phenylenediamine (4.5 g) and cupric acetate (16 g) in 50% aqueous methanol (200 ml) and the mixture heated at 100° on a steam bath. After a few minutes, the copper salt of the product began to precipitate from solution. After 30 min. the mixture was cooled; the salt was filtered off and decomposed by treatment with hydrogen sulphide in aqueous ethanol. The cupric sulphide was filtered off, and 2-phenylbenzimidazole (2.2 g, 27%), m.p. 286-288° (lit. 291°), slowly crystallised from the filtrate.

5(6)-Methyl-2-phenylbenzimidazole [(133); Ar = Ph; X = 5(6)-Me].

(a) Reduction of 4-methyl-2-nitroaniline.[118] A solution of 4-methyl-2-nitroaniline (7.6 g, 0.05 mole) and 20% aqueous sodium hydroxide

solution (4 ml) in ethanol (40 ml) was heated on a steam bath, with vigorous stirring, until gentle boiling occurred. Heating was then stopped and zinc dust (35 g) was added in small portions at such a rate that gentle boiling of the solution continued. The solution was then heated under reflux, still with stirring for 2 hr, then filtered while still hot. The residue was extracted with hot ethanol (2 x 50 ml) and the extracts were combined with the filtrate. The resultatnt solution was then concentrated in vacuo and the residue sublimed yielding 4-methyl-o-phenylenediamine (0.7 g) m.p. 85-88° (lit[119] 89-90°).

(b) 4-methyl-o-phenylenediamine (2.4 g) prepared as in (a) was converted, by reaction with benzaldehyde and cupric acetate as described above[117] into 5(6)-methyl-2-phenylbenzimidazole (1.1 g, 27%), m.p. 242-244° (lit.[120] 240°).

5(6)-Chloro-2-phenylbenzimidazole [(133); Ar = Ph; X = 5(6) - Cl].

4-chloro-2-nitroaniline (8.6 g) was reduced as described above[118] to give 4-chloro-o-phenylenediamine (3 g) m.p. 72-74° (lit[121] 76°). Reaction of the diamine with benzaldehyde and cupric acetate as described above gave 5(6)-chloro-2-phenylbenzimidazole, (58%) m.p. 206-208° (lit.[122] 210°)

2'-Nitrobenzanilide[123] (156).

A solution of o-nitroaniline (13.8 g 0.1 mole) and benzoyl chloride (14 g, 0.1 mole) in pyridine (60 ml) was heated under reflux for 5 hr, then poured onto crushed ice. The resultant precipitate was filtered off, washed several times with water, and recrystallised from ethanol to give 2'-nitrobenzanilide (15.2 g, 63%) m.p. 95-97° (lit.[124] 98°).

1-Benzoyloxy-2-phenylbenzimidazole (158)

The method is essentially that of Stacy et al.[57] A suspension of 1-hydroxy-2-phenylbenzimidazole (10.4 g) and benzoyl chloride (1 ml) in 10% sodium hydroxide solution was stirred for 0.5 hr. The precipitate from this reaction mixture was recrystallised from benzene-light petroleum, giving 1-benzoyloxy-2-phenylbenzimidazole (0.37 g, 62%) m.p. 109-112° (lit[57] m.p. 116-118°).

p-Tolylurea.[125]

p-Toluidine (0.2 g) was dissolved in a warm solution of glacial acetic acid (0.2 ml) and water (1.0 ml) which was then diluted with warm water (3 ml). A solution of potassium cyanate (0.15 g) in warm water (1.0 ml) was slowly added to the above solution with stirring, whereupon a white precipitate appeared. The solution was cooled then filtered to give p-tolylurea (0.16 g, 57%) m.p. 175-7° (lit.[126] m.p. 182-3°).

N-Methyl-o-nitroaniline.[127]

A solution of o-nitroaniline (55.5 g) and toluene-p-sulphonyl chloride (76.6 g) in pyridine (50 ml) was heated on the steam bath for 4 hr. The solution was poured into water and an oil separated out which solidified when triturated. The solid was recrystallised from ethanol as N-(toluene-p-sulphonyl)-o-nitroaniline (48.35 g) m.p. 107-110°. This compound (32 g) was suspended in 10% sodium hydroxide solution (160 ml) and dimethyl sulphate (120 ml) was added in 5 ml portions, with stirring, further quantities of sodium

hydroxide solution being added as required to keep the solution alkaline. The precipitate which formed was filtered off and recrystallised from ethanol (21.3 g) m.p. 130-132°. A solution of the methylated product (21.3 g) in glacial acetic acid (11 ml) and concentrated sulphuric acid (24 ml) was heated on the steam bath for 1 hr then diluted with water to give an orange precipitate which was recrystallised from light petroleum as N-methyl-o-nitroaniline (3.6 g) m.p. 33-35° (lit[127] 34-35°). A further crop (2.5 g) of the amine was obtained on pouring the reaction mixture into a mixture of sodium hydroxide solution and crushed ice.

C. The Preparation and Stability of o-Nitroanils.

N-Benzylidene-o-nitroaniline [(132); Ar = Ph; X = H].

(1) A solution of o-nitroaniline (13.8 g, 0.1 mole) and unpurified benzaldehyde (26.5 g, 0.25 mole) in toluene (50 ml) was heated under reflux in an apparatus connected to a Dean and Stark trap. When the calculated volume of water (1.8 ml) had been collected (after 6 hr), the solution was cooled and diluted with light petroleum (50 ml) to precipitate a pale-yellow solid which was recrystallised (at low temperature) from benzene-light petroleum to give N-benzylidene-o-nitroaniline (10.2 g, 45%) m.p. 78-79° (lit.[57], 76-78°) (Found: C, 68.7, H, 4,3; N, 12.5 Calc. for $C_{13}H_{10}N_2O_2$: C, 69.0, H, 4.45; N 12.4%) ν_{max} (C=N) 1630 cm^{-1}, τ ($CDCl_3$) 1.62 (1H, s, CH=N) and 2.0-3.1 (9H, m, aromatic). λ_{max} ($CHCl_3$) 264, 320 nm (ε 16,400, 5.200) [lit. λ_{max} 264, 323 nm (ε 15,700, 8,900)]. The graph of the mass spectrum of the compound (Graph 1) is shown (p. 118) and discussed on p. 48 .

(2) The above reaction was repeated with a solution of o-nitroaniline (6.9 g, 0.05 mole), purified benzaldehyde (cf. p. 85) (13.25 g, 0.125 mole) and benzoic acid (2.26 g, 0.021 mole) in toluene (50 ml). Water (0.9 ml) was collected in six hours, and the reaction mixture was then cooled and diluted with light petroleum (50 ml) to give N-benzylidene-o-nitroaniline (7.64 g, 68%) m.p. 73-76°, i.r. spectrum identical with that of the product obtained in (1).

(3) Repeating reaction (2) in xylene (50 ml) also gave

N-benzylidene-o-nitroaniline (7.5 g, 66%) on diluting with light petroleum, m.p. 73-76°, i.r. spectrum identical with that of the product of (1).

(4) Reaction (1) was repeated in benzene. Even after heating overnight there was no evidence of water production.

Reactions of o-nitroaniline and benzaldehyde giving NN-benzylidenebis-o-nitroaniline [(134); Ar=Ph; X=H].

(1) A solution of o-nitroaniline (0.9 g, 0.05 mole) and purified benzaldehyde (13.25g, 0.5 mole) in toluene (50 ml) was heated under reflux for 15 hr, water being collected in an attached Dean and Stark trap. Water evolution was slow, only ca. 0.4 ml being collected. The solution was cooled and diluted with light petroleum (50 ml), precipitating NN-benzylidenebis-o-nitroaniline as an orange solid m.p. and mixed m.p. 106-109°,[57] I.r. spectrum identical to that of authentic NN-benzylidenebis-o-nitroaniline.

(2) Repeating the above reaction (1) in xylene (50 ml) with o-nitroaniline (10.0 g) and purified benzaldehyde (19.2 g) (1:2.5 molar ratio) gave NN-benzylidenebis-o-nitroaniline (10.2 g, 77%) m.p. and mixed m.p. 94-96°, i.r. spectrum identical with that of authentic NN-benzylidenebis-o-nitroaniline.

(3) A solution of o-nitroaniline (6.9 g) and purified benzaldehyde (13.25 g) in xylene (50 ml) containing acetic acid (0.5 ml) was heated under reflux in an apparatus connected to a Dean and Stark trap. Evolution of water was brisk and after 2 hr 0.9 ml had been collected. The solution was cooled and diluted with

50 ml light petroleum to give NN-benzylidenebis-o-nitroaniline (6.9 g, 76%) m.p. and mixed m.p. 95-98°, i.r. spectrum identical with that of authentic NN-benzylidenebis-o-nitroaniline.

Reaction without water removal

A solution of o-nitroaniline (6.9g) and purified benzaldehyde (13.25 g) containing benzoic acid (2.26 g, 17%) in toluene (50 ml) was refluxed for 5 hr without removing water. The solution was cooled and diluted with light petroleum to give an orange precipitate (4.81 g) m.p. 92-95°, i.r. spectrum identical with that of authentic NN-benzylidenebis-o-nitroaniline (yield 53%). Further cooling of the mother liquor gave an orange-red precipitate which, when recrystallized from benzene-light petroleum, gave o-nitroaniline (0.56 g, 8 %) m.p. and mixed m.p. 70-72°.

N-Benzylidene-4-methyl-2-nitroaniline [(132); Ar = Ph; X=4-Me].

A solution of 4-methyl-2-nitroaniline (11.1 g) and unpurified benzaldehyde (19.4 g) in benzene (50 ml) was heated under reflux for 6 hr., water (1.2 ml) being collected in an attached Dean and Stark trap. The solution was cooled and diluted with light petroleum (50 ml). The precipitated solid was recrystallized from benzene-light petroleum to give N-benzylidene-4-methyl-2-nitroaniline (11.6 g, 66%) m.p. 74-76°. (Found: C, 70.1; H, 5.0; N, 11.7. $C_{14}H_{12}N_2O_2$ requires C, 70.0; H, 5.0; N, 11.7%), ν_{max} (C=N) 1630 cm^{-1}, τ (CCl_4) 1.75 (1H, s, CH=N) 2.1-3.3 (8H, m, aromatic) and 7.64 (3H, s, ArMe).

N-Benzylidene-4-chloro-2-nitroaniline [(132); Ar=Ph; X=4-Cl].

(1) A solution of 4-chloro-2-nitroaniline (17.2 g, 0.1 mole) and unpurified benzaldehyde (26.5 g, 0.25 mole).

in xylene (50 ml) was refluxed for 4 hr., water (1.6 ml) being collected in an attached Dean and Stark trap. The solution was cooled and diluted with light petroleum (50 ml). The precipitated solid was recrystallised from benzene-light petroleum to give N-benzylidene-4-chloro-2-nitroaniline (16.0 g, 61%) m.p. 75-77° (Found: C, 60.1; H, 3.3; N, 10.6. $C_{13}H_9ClN_2O_2$ requires C, 59.9; H, 3.5; N, 10.75%) ν_{max} (C=N) 1630 cm^{-1}, τ (CCl_4) 1.70 (1H, s, CH=N) and 2.05-3.15 (8H, m, aromatic).

Reaction in toluene

Reaction (1) was attempted in toluene (50 ml) with 4-chloro-2-nitroaniline (8.6 g) and benzaldehyde (13.25 g). However, water removal was very slow and the reaction was abandoned.

Reaction of p-Methoxybenzaldehyde with o-Nitroaniline.

(1) Heating a solution of p-methoxybenzaldehyde (17.5 g) and o-nitroaniline (6.9 g) in xylene (50 ml) under reflux in an apparatus connected to a Dean and Stark trap, with or without acetic acid, gave after 3 hr water (0.8 ml). The mixture was diluted with light petroleum to give p-methoxybenzoic acid (ca. 7% yield) identical (mixed m.p. and i.r. spectrum) with the authentic compound. Concentration of the solution by evaporation gave a viscous oily residue from which p-methoxybenzaldehyde was recovered by distillation. No further product was isolated.

(2) A solution of p-methoxybenzaldehyde (17.5 g), o-nitroaniline (6.9 g) and benzoic acid (2.26 g) in xylene (50 ml) was heated under reflux for 2 hr. after which time water (0.9 ml) had been collected. The solution was cooled and diluted with light petroleum. The

precipitated solid was recrystallised from benzene-light petroleum to give N-p-methoxybenzylidene-o-nitroaniline (8.25 g, 64%) m.p. 81-83°. (Found: C, 65.7; H, 4.6; N, 10.85. $C_{14}H_{12}N_2O_3$ requires C, 65.6; H, 4.7; N, 10.9%). ν_{max} (C=N) 1627 cm^{-1}. τ ($CDCl_3$) 1.74 (1H, s, CH=N), 2.05-3.20 (8H, m, aromatic), 6.20 (3H, s, OMe).

Reaction of p-Nitrobenzaldehyde with o-nitroaniline.

(1) A solution of p-nitrobenzaldehyde (18.9 g) and o-nitroaniline (6.9 g) in xylene (50 ml) was heated under reflux for several hours. No evolution of water was observed.

(2) A solution of p-nitrobenzaldehyde (7.5 g) and o-nitroaniline (4.5 g) in xylene (30 ml) containing acetic acid (0.5 ml) was heated under reflux for 6 hr in apparatus connected to a Dean and Stark trap. Water (0.4 ml) was collected. The solvent was evaporated off and the residue was washed with benzene and recrystallised from dimethylformamide-ethanol to give NN-p-nitrobenzylidenebis-o-nitroaniline (2.3 g, 35%) m.p. 118-120° (Found: C, 56.05; H, 3.7; N, 17.4. $C_{19}H_{15}N_5O_6$ requires C, 55.75; H, 3.7 N, 17.1%), ν_{max} (N-H) 3380 cm^{-1}, τ [$(CD_3)_2SO$] 1.4-3.3 (m, aromatic ArCH and NH). The benzene washings gave on evaporation unchanged p-nitrobenzaldehyde.

(3) A solution of p-nitrobenzaldehyde (18.9 g) o-nitroaniline (6.9 g) and benzoic acid (2.26 g) in xylene (50 ml) was heated under reflux for 1 hr after which time water (0.9 ml) had been collected in a Dean and Stark trap. The solution was cooled and diluted with light petroleum to give a yellow solid which was recrystallised from benzene-light petroleum (10.4 g) m.p. 100-105°. A portion of this solid was further recrystallized from benzene-light petroleum

m.p. 112-115° (Found: C, 59.7 [illegible],3.4; N, 14.0; $C_{13}H_9N_3O_4$ requires C, 57.6; H, 3.3; N, 15.5). Subsequent recrystallisation of this sample did not substantially alter this analysis. However the i.r., n.m.r. and mass spectra of the sample indicate that it is N-(p-nitrobenzylidene)-o-nitroaniline: ν_{max} (C=N) 1620 cm^{-1} (no N-H or C=O absorptions); τ ($CDCl_3$) 1.52 (1H, s, CH=N), 1.62-3.03 (8H, m, aromatic); mass spectrum shows parent ion at m/e 271, accurate mass 271.060370 ($C_{13}H_9N_3O_4$ requires 271.059300).

Reaction of p-Chlorobenzaldehyde with o-Nitroaniline

A solution of o-nitroaniline (6.9 g) and p-chlorobenzaldehyde (17.5 g, 1:2.5 molar ratio) in toluene (50 ml) was heated under reflux, in an apparatus connected to a Dean and Stark trap, for 1 hr, water (0.8 ml) being collected. p-Chlorobenzoic acid (0.84 g) m.p. and mixed m.p. 238-240°, crystallised from the cooled solution and was filtered off. The toluene was evaporated off and distillation in vacuo removed most of the excess of benzaldehyde. Crystallisation of the residue from benzene-light petroleum gave a yellow solid, m.p. 65-7° (with partial resolidification and remelting at ca. 140° (Found: C, 59.5; H, 4.1; N, 13.0. $C_{13}H_9ClN_2O_2$ (N-p-chlorobenzylidene-o-nitroaniline) requires C, 59.9; H, 3.5; N, 10.75 %. $C_{19}H_{15}ClN_4O_4$ (NN-p-chlorobenzylidenebis-o-nitroaniline) requires C, 57.2; H, 3.8; N, 14.0%), ν_{max} (N-H) 3370 cm^{-1} τ (CCl_4) 1.69 (s, CH=N) and 1.8-3.4 (m, aromatic, PhCH and NH) (ratio of integrals ca 1:15).

D. Reactions of Nucleophiles with N-Benzylidene-o-nitroaniline.

N-Methylaniline.

A solution of N-benzylidene-o-nitroaniline (0.70 g) and N-methylaniline (0.50 g) in dry benzene (25 ml) was heated under reflux for 1 hr, then cooled and diluted with dry light petroleum (25 ml) to give N-[α-(N-methylanilino)benzyl]-o-nitroaniline (135) (0.80 g 78%) m.p. 90-92° (from benzene-light petroleum). (Found: C, 72.3; H, 5.9; N, 12.7. $C_{20}H_{19}N_3O_2$ requires C, 72.05; H, 5.7; N, 12.6%). ν_{max} 3350 cm^{-1} (N-H), τ (CCl_4) 1.35-1.5 (1H, broad multiplet, NH), 1.73-1.95 (1H, m, o-to NO_2), 2.53-3.80 (14H, m, other aromatic and PhCH), 7.20 (3H, s, Me).

Toluene-p-thiol.

A solution of N-benzylidene-o-nitroaniline (0.20 g) and toluene-p-thiol (0.15 g) in dry benzene (25 ml) was stirred at room temperature overnight; the benzene was evaporated off and the residue triturated with light petroleum. The crude product thus obtained was recrystallised from benzene-light petroleum to give N-[α-(p-tolylthio)benzyl]-o-nitroaniline (136) (0.20 g, 64%), m.p. 85-87° (Found: C, 68.9; H, 4.9; N, 8.05. $C_{20}H_{18}N_2O_2S$ requires C, 68.6; H, 5.2; N, 8.0%). ν_{max} 3360 cm^{-1} (N-H), τ (CCl_4) 1.36 (1H, broad doublet, J = ca. 8Hz, NH), 1.80-2.00 (1H, o-to NO_2) 2.56-3.52 (12H, m, other aromatic), 4.28 (1H, d, J = 8Hz, PhCH-NH), 7.71 (3H, s, Me).

Methanol.

A solution of N-benzylidene-o-nitroaniline (1.0 g) in dry methanol (25 ml) was heated under reflux for 10 min. The solvent was then evaporated off at room temperature under reduced pressure. I.r. and

n.m.r. spectra of the residue (an orange oil) suggested that it contained N-(α-methoxybenzyl)-o-nitroaniline (142). ν_{max} 3,395 cm^{-1} (N-H), τ($CDCl_3$) 1.55 (d, J = 7Hz, NH), 1.86-1.93 (o-to NO_2) 2.18-3.35 (m, aromatic), 4.33 (d, J = 7Hz, PhCH), 6.68 (s, Me).

From the integrals the oil appeared to contain an approximately 1:1 mixture of N-benzylidene-o-nitroaniline and adduct.

Attempts to purify the oil by distillation under reduced pressure led to the reformation of N-benzylidene-o-nitroaniline (identified by mixed m.p. and i.r. spectrum). The reaction was repeated and the residual oil after prolonged cooling and trituration with light petroleum gave a yellow solid (0.75 g) m.p. 34-38°, identical (by i.r.) with N-(α-methoxybenzyl)-o-nitroaniline (68%).

A portion of N-(α-methoxybenzyl)-o-nitroaniline prepared above was heated at 100° in an open flask for five minutes then cooled. The sole product obtained was N-benzylidene-o-nitroaniline (identified by mixed m.p. and i.r. spectrum).

Aniline.

A solution of N-benzylidene-o-nitroaniline (2.26 g) and aniline (0.93 g) in dry benzene or chloroform (30 ml) was stirred at room temperature for 1 hr. The solvent was removed in vacuo, light petroleum (50 ml) was added to the residue, and o-nitroaniline (1.10 g, 80%) m.p. and mixed m.p. 68-70°, was filtered off. Concentration of the filtrate, followed by seeding of the residue with authentic[128] N-benzylideneaniline and recrystallisation from methanol gave N-benzylideneaniline (1.51 g, 83%), m.p. and mixed m.p. 47-49° (lit.[128] 52°).

Lower yields of o-nitroaniline and N-benzylideneaniline (73% and 71% respectively) were obtained from this reaction when the aniline was used in excess (1.4 g) since additional purification steps were necessary to free the products from the excess of aniline.

o-Nitroaniline.

No reaction was observed when a solution of equimolar quantities

of N-benzylidene-o-nitroaniline and o-nitroaniline in dry benzene was heated under reflux for 1 hr. The starting materials were recovered in high yield. The same results were obtained when o-nitroaniline and N-benzylidene-o-nitroaniline were heated together, in the absence of solvent, at 100° for 1 hr. A solution of o-nitroaniline (0.69 g, 1 molar equivalent), benzoic acid (0.2 g) and N-benzylidene-o-nitroaniline, (1.13 g, 1 molar equivalent) in dry benzene (20 ml) was heated under reflux for 1 hr. The solution was allowed to cool and the solvent removed by distillation in vacuo. Trituration of the residue with light petroleum gave a yellow solid which recrystallised from benzene-light petroleum as NN-benzylidenebis-o-nitroaniline (1.45 g, 80%) m.p. and mixed m.p. 95-98°, i.r. spectrum identical with that of an authentic sample.

p-Nitroaniline.

No reaction was observed when a solution of equimolar quantities of N-benzylidene-o-nitroaniline and p-nitroaniline in dry benzene was heated under reflux for 1 hr. The starting materials were recovered in high yield. Repeating this reaction in the presence of benzoic acid failed to yield an adduct of the type obtained above with o-nitroaniline.

2-Aminopyridine

The same results were obtained as in the case of p-nitroaniline when equimolar amounts of the amine and N-benzylidene-o-nitroaniline in dry benzene were heated under reflux with or without the presence of benzoic acid.

Water.

A suspension of N-benzylidene-o-nitroaniline (2.44 g) in water (25 ml) was heated at 100° for 10 min., cooled, and filtered. The residue was recrystallised from benzene-light petroleum, to give NN-benzylidenebis-o-nitroaniline, (1.34 g), m.p. and mixed m.p. 110-112°, thus accounting for 34% of the benzylidene portion of N-benzylidene o-nitroaniline and 68% of the o-nitroaniline portion. The filtrate was extracted with ether, the extract was dried and concentrated and the residual oil triturated with light petroleum to give o-nitroaniline (0.44 g, 30%) m.p. and mixed m.p. 69-71°. The petroleum was evaporated to yield benzaldehyde (0.39g,34%), identified by its i.r. and n.m.r. spectra and as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 237° (from acetic acid).

Diethyl Malonate.

(1) With piperidine.

A solution of N-benzylidene-o-nitroaniline (1.0 g), diethyl malonate (1.0 g) and piperidine (0.1 ml) in dry ethanol (25 ml) was heated under reflux for 4 hr; the solution was concentrated in vacuo, and the residue was chromatographed on silica gel. Elution with benzene gave o-nitroaniline (0.39 g., 64%), m.p. and mixed m.p. 68-70°, and elution with chloroform gave diethyl benzylidenemalonate (147) (0.84 g, 77%) identical (i.r., n.m.r.) with an authentic sample.[116] ν_{max} 1715 cm^{-1} (broad: C=O), τ (CCl_4) 2.42 (1H, s, PhC<u>H</u>=), 2.67 (5H s, aromatic), 5.78 (4H, q, <u>J</u>=7Hz, $\underline{OCH_2}CH_3$), 8.69 and 8.76 (6H, two overlapping triplets, <u>J</u>=7Hz, 2Me).

(2) With the sodium salt of diethyl malonate

Diethylmalonate (0.93 g; slight excess) was added to a solution of sodium ethoxide [from sodium (0.12 g) in dry ethanol (25 ml)] and the mixture was warmed gently on the steam bath for a few minutes. N-benzylidene-o-nitroaniline (1.2 g) was then added, the mixture was heated under reflux for 4 hr, the solvent was distilled off, and the residue was chromatographed on silica gel. Elution with benzene gave a fraction which, on trituration with light petroleum, yielded o-nitroaniline (0.30 g, 41%), m.p. and mixed m.p. 68-70°, traces of benzaldehyde were detected (i.r., n.m.r.) in the petroleum washings. Elution with chloroform gave first diethyl benzylidenemalonate (0.30 g, 23%) identical with the product of (a) (i.r., n.m.r.) and then diethyl α-(N-o-nitroanilino)benzylmalonate (148)

(0.10 g, 5%), m.p. 94-96° (from benzene-light petroleum). (Found: C, 62.4; H, 5.8; N, 7.0. $C_{20}H_{22}N_2O_6$ requires C, 62.2; H, 5.7; N, 7.25%). ν_{max} 3330 cm^{-1} (N-H), 1740 and 1720 cm^{-1} (C=O) τ ($CDCl_3$) 0.70 (1H, broad doublet, J=8Hz,NH), 1.85 (1H, 2d, J=8.5 and 2Hz, o-to NO_2), 2.6-2.8 (5H) and 3.2-3.5 (3H) (aromatic), 4.61 (1H, 2d, J=8 and 6Hz, PhCH-NH-), 5.80 and 5.88 (4H, 2 overlapping quartets, J=6Hz, $-OCH_2CH_3$), 6.07 (1H, d, J=6Hz, $CH(CO_2Et)_2$), 8.7 and 8.83 (6H, 2 overlapping triplets, J=6Hz, CH_3). When the sample was irradiated at 4.61 τ the doublets at 0.70 τ and 6.07 τ collapsed to singlets, thus confirming the above assignments.

Diethyl methylmalonate.

(1) With the sodium salt of diethyl methylmalonate.

Diethyl methylmalonate (0.51 g: slight excess) was added to a solution of sodium ethoxide (from sodium 0.06 g) in dry ethanol (25 ml), and the mixture was warmed gently on the steam bath for a few minutes. N-benzylidene-o-nitroaniline (0.60 g) was then added, the mixture was heated under reflux for 5 hr. and then the solvent was distilled off. The residue was dissolved in ether (25 ml) and the ethereal solution was washed with two 25 ml portions of water, then dried over anhydrous sodium sulphate, and the ether distilled off. The residue was cooled and triturated with light petroleum to give a yellow solid which was recrystallised from benzene-light petroleum as o-nitroaniline (0.26 g, 70%) m.p. and mixed m.p. 68-70°.

Redistillation of the reaction solvent gave a liquid residue,

the n.m.r. spectrum of which showed the presence of benzaldehyde and diethyl methylmalonate in approximately 1:1 molar ratio (based on the comparison of the integrals of τ (CCl_4) 0.1 (1H, s, PhCHO) and 5.85 (4H, q, OCH_2CH_3). The benzaldehyde was recovered as its 2,4-dinitrophenylhydrazone (0.51 g, representing 68% of the benzylidene portion of N-benzylidene-o-nitroaniline), m.p. and mixed m.p. 237° (from acetic acid)

(2) With piperidine.

A solution of N-benzylidene-o-nitroaniline (0.60 g) diethyl methylmalonate (0.53 g) and piperidine (0.1 ml) in dry ethanol (25 ml) was heated under reflux for 5 hr. and then the solvent was distilled from the mixture. Recrystallisation of the residue from benzene-light-petroleum yielded o-nitroaniline (0.28 g, 76%). The solvent was then evaporated; t.l.c. and the n.m.r. spectrum of the residue showed it to be a mixture of benzaldehyde and diethyl methylmalonate.

Sodium toluene-p-sulphinate.

Equimolar quantities of N-benzylidene-o-nitroaniline and sodium toluene-p-sulphinate in dry methanol were heated under reflux overnight. Both reactants were recovered in high yield.

NN-Dimethylaniline.

No reaction was observed when N-benzylidene-o-nitroaniline was heated with the above amine in dry benzene for 1 hr. N-benzylidene-o-nitroaniline was recovered in high yield.

E. The Formation of Benzimidazoles and Benzimidazole-N-oxides from o-Nitroaniline and its Derivatives.

(a) Triethyl Phosphite Reduction.

N-Benzylidene-o-nitroaniline

A solution of N-benzylidene-o-nitroaniline (1.38 g) and triethyl phosphite (4.3 ml, 1:4 molar ratio‡) in dry t-butylbenzene was heated under reflux, in an atmosphere of dry nitrogen for 6.5 hr. The solution was cooled and the crystalline product was filtered off. The solvent and triethyl phosphite and phosphate were then removed from the filtrate by distillation under reduced pressure. The residue was chromatographed on silica gel, and elution with ether gave a colourless solid, identical (i.r. spectrum) with the previously obtained precipitate, and with authentic 2-phenylbenzimidazole. The solids were combined and recrystallised from ethanol-water to give 2-phenylbenzimidazole, (0.40 g, 47%), m.p. and mixed m.p. 288-290°.

N-Benzylidene-4-methyl-2-nitroaniline.

A solution of N-benzylidene-4-methyl-2-nitroaniline (2.4 g) and triethylphosphite (7 ml, 1:4 molar ratio) in dry t-butylbenzene (20 ml) was heated under reflux in an atmosphere of dry nitrogen, for 6 hr. The solution was cooled but no product crystallised out. The solvent, triethyl phosphite and phosphate were then removed by distillation in vacuo and the residue chromatographed on silica gel. Elution with etner gave 5(6)methyl-2-phenylbenzimidazole (0.7 g, 33%) m.p. 244-246° (from benzene-light petroleum), identical (mixed m.p., i.r. spectrum) with the authentic compound.

‡ The amount of triethyl phosphite used in excess does not appear to be critical.

N-Benzylidene-4-chloro-2-nitroaniline

N-Benzylidene-4-chloro-2-nitroaniline (2.7 g) was similarly reacted with triethyl phosphite (7 ml) with a reaction time of 7 hr. The crude reaction product obtained after removal of solvent, triethylphosphite and phosphate by distillation in vacuo) was shown (t.l.c.. i.r.) to contain 5(6)-chloro-2-phenylbenzimidazole, but the crude product could not be further purified, either by recrystallisation or by column chromatography.

2'-Nitrobenzanilide

A solution of 2'-nitrobenzanilide (2.42 g) and triethylphosphite (7 ml 1:4 molar ratio) in dry t-butylbenzene was heated under reflux in an atmosphere of dry nitrogen, for 7 hr. The solution was cooled and the solvent, triethyl phosphite and phosphate were removed by distillation in vacuo. Chromatography of the residual black viscous liquid (5.8 g) gave on elution with ether, impure 2-phenylbenzimidazole [(0.06 g, 3%), identified by t.l.c. and i.r. spectrum].

(b) Cyanide-Induced Cyclisation of o-Nitroanils.

Reaction of N-Benzylidene-o-Nitroaniline and Potassium Cyanide in Methanol.

Potassium cyanide (1.1g, 2.5 molar equivalents) was added to a solution of N-benzylidene-o-nitroaniline (1.5 g, 1 molar equivalent) in dry methanol (12 ml) and the mixture was heated under reflux for 5 hr.

Alternative procedures. (A) The reaction mixture was cooled, added to water, and acidified with concentrated hydrochloric acid. The precipitated solid (1.3 g) recrystallised from methanol-benzene, had m.p. 228-31° (decomp.). Its mass spectrum was identical with that of 1-hydroxy-2-phenylbenzimidazole (81); although the i.r. and n.m.r. spectra were not completely identical with those of (81), and the mixed m.p. was depressed. The identification of this compound as the hydrochloride (157) was based on: (i) analysis (Found: C, 58.8; H, 4.9; N, 10.5. $C_{13}H_{10}N_2O.HCl.H_2O$ requires C, 59.0 H, 4.9; N, 10.6%): (ii) the compound (0.1 g) was neutralised with 0.1 M sodium hydroxide (3.78 ml, 1 molar equivalent) give 1-hydroxy-2-phenylbenzimidazole (0.06 g, 71 %) m.p. and mixed m.p. 218-20° (dec.). The filtered solution from this reaction, on treatment with silver nitrate solution gave a white ammonia-soluble precipitate indicating the presence of chloride ion: (iii) a suspension of the compound (0.2 g.) and benzoyl chloride (1 ml.) in 10% sodium hydroxide solution (3 ml.) was stirred at room temperature for 0.5 hr. The resultant white precipitate was recrystallised from benzene-light petroleum to give 1-benzoyloxy-2-phenylbenzimidazole (0.17 g., 71%) m.p. and mixed

m.p. 109-112° (lit.[57], 116-118°) (Found: C, 76.4; H, 4.5; N, 8.9. Calc. for $C_{20}H_{14}N_2O_2$: C, 76.05; H, 4.5; N, 8.8%): (iv) Catalytic hydrogenolysis of the 1-benzoyloxy-2-phenylbenzimidazole (0.15 g.) obtained above in (iii), in methanol (5 ml.) over palladium-charcoal gave 2-phenylbenzimidazole (0.07 g., 76%) m.p. and mixed m.p. 288-290°.

(B) The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on a column of silica gel. Elution with benzene gave *o*-nitroaniline (0.06 g., 7%) m.p. and mixed m.p. 68-70°. Elution with methanol gave 1-hydroxy-2-phenylbenzimidazole (1.10 g., 79%), m.p. and mixed m.p. 215- 218° (dec.). The bar graph of the mass spectrum of 1-hydroxy-2-phenylbenzimidazole is included (cf p.120 Graph 3).

The yield of 1-hydroxy-2-phenylbenzimidazole was not diminished appreciably (72% isolated) when *N*-benzylidene-*o*-nitroaniline and potassium cyanide were reacted in equimolar amounts. The reaction mixture was tested for cyanide ion by the "Prussian Blue Test"[129], but the test failed to show the presence of cyanide ion in the reaction mixture.

Reaction of *N*-Benzylidene-*o*-nitroaniline with a Catalytic Amount of Potassium Cyanide.

Potassium cyanide (0.014 g., 0.1 molar equivalents) was added to a solution of *N*-benzylidene-*o*-nitroaniline (0.5 g., 1 molar equivalent) in dry methanol (12 ml.) and the mixture was heated under reflux for 5 hr. The reaction mixture was then cooled, concentrated *in vacuo*, and the residue chromatographed on silica gel. Elution with benzene gave first benzaldehyde [(0.17 g., 75%) identified by i.r. spectrum]

and then o-nitroaniline (0.25 g., 81%) m.p. and mixed m.p. 68-70°. No other products were isolated.

Attempted identification of Cyanate Ion

It was found (cf p. 88) that small quantities (0.075 g., of potassium cyanate were detected) of cyanate ion could be detected by reaction with p-toluidine in acetic acid solution to give p-tolylurea. N-Benzylidene-o-nitroaniline (0.4 g.) was reacted, as above, with an equimolar amount of potassium cyanide. The solvent then was evaporated and the reaction mixture (aqueous solution) was treated with p-toluidine in acetic acid. The only result of this treatment, however, was to precipitate 1-hydroxy-2-phenylbenzimidazole. No p-tolylurea was found either in the precipitated solid, or in the residual solution.

A solution of potassium cyanate (0.16 g) and an equimolar amount of 1-hydroxy-2-phenylbenzimidazole in dry methanol was heated under reflux for 5 hr. Again no cyanate ion could be detected in the reaction mixture.

Reaction of N-Benzylidene-4-methyl-2-nitroaniline with Potassium Cyanide in Methanol.

Potassium cyanide (0.7 g., 2.5 molar equivalents) was added to a solution of N-benzylidene-4-methyl-2-nitroaniline (1.0 g., 1 molar equivalent) in dry methanol (12 ml.) and the mixture was heated under reflux for 5 hr. The reaction mixture was then cooled, concentrated in vacuo, and the residue chromatographed on silica gel. Elution with methanol gave 1-hydroxy-6-methyl-2-phenylbenzimidazole [(159), 0.60 g.,

64%] m.p. 231-233° (dec.) from dimethylformamide-water as the only product (Found: C, 74.6; H, 5.52; N, 12.8. $C_{14}H_{12}N_2O$ requires C, 75.0; H, 5.4; N, 12.5%).

Attempted Preparation of N-(α-cyanobenzyl)-o-nitroaniline (168)

A solution of N-benzylidene-o-nitroaniline (2.26 g.) and hydrogen cyanide (0.5 ml.) in dry methanol (20 ml.) was stirred overnight. The solvent was removed on the water bath under reduced pressure. The residue was an intractable oil, the i.r. spectrum of which was identical with that of the product of reaction of the anil with methanol alone (i.e. N-(α-methoxybenzyl)-o-nitroaniline. There was no evidence of any C≡N absorption. A solution of N-benzylidene-o-nitroaniline (2.26 g.), hydrogen cyanide (0.5 ml.) and potassium carbonate (0.2 g.) in dry methanol (20 ml.) was stirred overnight. The solvent was removed under reduced pressure and the residue chromatographed on silica gel. Elution with benzene gave o-nitroaniline (0.53 g, 38%) m.p. and mixed m.p. 67-70°, and elution with methanol gave 1-hydroxy-2-phenylbenzimidazole (0.59 g, 28 %) m.p. and mixed m.p. 216-219° (dec.). No other products were identified.

Reaction of N-Benzylidene-o-nitroaniline with Potassium Cyanide in Dimethyl Sulphoxide.

A solution of N-benzylidene-o-nitroaniline (1.0 g.) and potassium cyanide (0.29 g., 1:1 molar ratio) in dry dimethyl sulphoxide (20 ml.) containing dry methanol (0.14 g., 1 molar equivalent) was heated at 100° for 1 hr. and then stirred overnight at room temperature. The solvent was distilled off under reduced pressure and the residue absorbed on a column of silica gel. Elution with benzene gave first

2'-nitrobenzanilide (0.11 g., 11%) m.p. and mixed m.p. 92-94° and then o-nitroaniline (0.08 g., 13%) m.p. and mixed m.p. 68-70°. No other identifiable products were isolated.

N-Benzylidene-o-nitroaniline with Dimethyl Sulphoxide alone.

A solution of N-benzylidene-o-nitroaniline (1.0 g.) in dry dimethyl sulphoxide (20 ml.) was heated at 100° for 1 hr. and then stirred overnight at room temperature. The solvent was distilled off under reduced pressure to give a yellow solid which was recrystallised from benzene-light petroleum as N-benzylidene-o-nitroaniline (0.93 g.) m.p. and mixed m.p. 72-75°.

(c) Cyclisation of o-Nitroaniline and its Derivatives with Benzaldehyde.

Reactions of o-Nitroaniline with Benzaldehyde giving 2-Phenylbenzimidazole.

(1) A solution of o-nitroaniline (3.45 g., 0.025 mole) and benzaldehyde‡ (26.6g., 0.25 mole) was heated under reflux for 1 hr., water (0.45 ml., 0.025 mole) being collected in an attached Dean and Stark apparatus. The solution was then cooled and the precipitate was filtered off and washed with ether to give a white solid (4.23 g.) m.p. 148-160°, the i.r. spectrum of which showed the probable presence of benzoic acid [ν_{max} (C=O) 1630-1720 cm^{-1} (broad)]. The precipitate was washed with 10% sodium bicarbonate solution (2 x 50 ml.) to give a residual white solid (2.90 g.) m.p. and mixed m.p. with 2-phenylbenzimidazole 288-290° (dec.). Acidification of the bicarbonate wash with hydrochloric acid gave benzoic acid (0.81 g.) m.p. and mixed m.p. 118-120°. The ethereal wash was extracted with 10% sodium bicarbonate solution (2 x 50 ml.). Acification of this bicarbonate extract with hydrochloric acid gave benzoic acid (1.34 g.) m.p. and mixed m.p. 118-120°. The ethereal layer was dried over anhydrous sodium sulphate, then concentrated in vacuo and washed with light petroleum to remove excess aldehyde. The residue was a brown solid (1.25 g.) m.p. 170-185° which recrystallized from ethanol-water as 2-phenylbenzimidazole (0.50 g.) m.p. and mixed m.p. 288-290°. The mother liquor was concentrated but yielded only an intractable black tar. The total weight of 2-phenylbenzimidazole obtained was 3.41 g. (70%).

‡ The term "benzaldehyde" is used in this experimental section to denote benzaldehyde which has been purified by the method described on p. 85 .

(2) A solution of o-nitroaniline (6.9 g., 0.05 mole) and benzaldehyde (5.3 g., 0.05 mole) in p-cymene (50 ml.) was heated under reflux for 5 hr., water being collected in a Dean and Stark apparatus. The solution was cooled to give a precipitate which was washed with ether and then with 10% sodium bicarbonate solution (2 x 50 ml) to give 2-phenylbenzimidazole (2.21 g., 23%) m.p. and mixed m.p. 288-290°.

The ether wash was concentrated and combined with the filtered p-cymene solution and diluted with light petroleum (50 ml.) to give NN-benzylidenebis-o-nitroaniline [(1.81 g., 20%) m.p. and mixed m.p. 105-108° from benzene-light petroleum] i.r. spectrum identical with that of an authentic sample.

(3) Repeating reaction (2) in the presence of benzoic acid (17% by weight of the benzaldehyde) gave 2-phenylbenzimidazole in 31% yield.

(4) Repeating reaction (3) with a 2.5:1 molar ratio of benzaldehyde gave 2-phenylbenzimidazole in 62% yield.

Reaction in p-Cymene without Water Removal.

(1) A solution of o-nitroaniline (6.9 g.) and benzaldehyde (5.3 g.) in p-cymene (50 ml.) was heated under reflux for 5 hr., without water removal. The solution was cooled to give an orange precipitate which dissolved in ether without leaving a residue. The ethereal solution was concentrated in vacuo and the residue recrystallised from benzene-light petroleum as o-nitroaniline (21.7 g.) m.p. and mixed m.p. 68-70°. The p-cymene solution was diluted with an equal volume of light petroleum to give further o-nitroaniline (3.43 g) which was recrystallised from benzene-light petroleum m.p. and mixed m.p. 68-70° [total recovery of o-nitroaniline 6.13 g (89%)].

(2) The above experiment was repeated, with a 2.5:1 molar ratio of benzaldehyde to o-nitroaniline in the presence of benzoic acid (17% by weight of the benzaldehyde) 2-Phenylbenzimidazole (7%) was obtained. and 83% of the o-nitroaniline was recovered.

Attempted reaction of N-Methyl-o-nitroaniline with Benzaldehyde.

A solution of N-Methyl-o-nitroaniline (3.6 g), benzaldehyde (25.2 g) and benzoic acid (4.3 g) was heated under reflux for 5 hr. in an apparatus attached to a Dean and Stark trap. No water was collected and the N-Methyl-o-nitroaniline was recovered (3.2 g) by chromatographing on silica gel.

Reactions giving both 2-Phenyl and 1-Hydroxy-2-phenylbenzimidazole

(1) A solution of o-nitroaniline (6.9 g) and benzaldehyde (13.25 g) in mesitylene (50 ml) was heated under reflux for 5 hr. water (0.9 ml) being collected in a Dean and Stark trap. The solution was cooled to give a white solid (1.82 g) m.p. 150-160°, the i.r. spectrum of which indicated the presence of benzoic acid [ν_{max} C=O 1630-1720 cm^{-1}]. This solid was filtered off and washed once with 10% sodium bicarbonate solution (50 ml) to give a solid (1.15 g) m.p. 180-190°, the i.r. spectrum of which showed no acidic C=O absorption. Fractional recrystallisation from ethanol gave 1-hydroxy-2-phenylbenzimidazole (0.43 g 4%) m.p. and mixed m.p. 218-220° (dec.), i.r. spectrum identical with that of authentic 1-hydroxy-2-phenylbenzimidazole, and from ethanol-water 2-phenylbenzimidazole (0.51 g, 5%) m.p. and mixed m.p. 288-290°.

(2) A mixture of o-nitroaniline (6.9 g) and benzaldehyde (5.3 g) was refluxed for 3 hr. The reaction mixture was stood overnight, extracted with benzene, filtered and washed with benzene to give a brown solid (2.29 g) m.p. 168-175°. The solid was further washed with 10% sodium bicarbonate solution (50 ml) and the wash acidified with hydrochloric acid to give benzoic acid (0.21 g) m.p. and mixed m.p. 118-120°. Recrystallisation of the remaining solid from ethanol gave 1-hydroxy-2-phenylbenzimidazole m.p. and mixed m.p. 220-222°(dec). The benzene wash was concentrated in vacuo, cooled and triturated with a little benzene to give an off-white solid which was recrystallised from ethanol-water as 2-phenylbenzimidazole (0.41 g, 4%) m.p. and mixed m.p. 288-290°

Reaction of 1-Hydroxy-2-phenylbenzimidazole with Benzaldehyde

A mixture of 1-hydroxy-2-phenylbenzimidazole (1.0 g) and benzaldehyde (5 ml) was heated under reflux for 1 hr. The reaction mixture was cooled to give a precipitate which was filtered off and washed with a little ether to give a white solid (0.64 g) m.p. 150-160°, the i.r. spectrum of which showed the presence of benzoic acid. The solid was then washed with 10% sodium bicarbonate solution (20 ml) to give a residue of 2-phenylbenzimidazole (0.46 g) m.p. and mixed m.p. 288-290° The ether wash and the original filtrate were combined, extracted with 10% sodium bicarbonate solution (20 ml) and cooled to precipitate a white solid which was filtered off and washed with a little ether to give 2-phenylbenzimidazole (0.13 g) m.p. and mixed m.p. 288-290° The total amount of 2-phenylbenzimidazole isolated was 0.59 g (64%). Both sodium bicarbonate solutions were

combined and acidified with hydrochloric acid to give benzoic acid (0.32 g) m.p. and mixed m.p. 118-120°.

Thermal Stability of N-Benzylidene-o-nitroaniline

A solution of N-benzylidene-o-nitroaniline (1.0 g) in dry p-cymene (25 ml) was heated under reflux in a nitrogen atmosphere for 1 hr. The solution was cooled and diluted with light petroleum (25 ml) to give a precipitate which recrystallised from benzene-light petroleum as N-benzylidene-o-nitroaniline (0.8 g, 82%) m.p. and mixed m.p. 75-77°.

Thermal Stability of NN-Benzylidenebis-o-nitroaniline.

A solution of NN-benzylidenebis-o-nitroaniline in deuteriobromoform was subjected to variable temperature n.m.r. spectrum analysis. Spectra were run at intervals of 20° from 40° to 180° but showed no change from that of NN-benzylidenebis-o-nitroaniline. The sample was maintained at 180° for 2 hr but at the end of this time its spectrum still remained unchanged.

Reaction of N-Benzylidene-o-nitroaniline with Benzaldehyde

A solution of N-benzylidene-o-nitroaniline (1.13 g, 1 molar equivalent) and benzaldehyde (4.7 g, 9 molar equivalents) was heated under reflux for 1 hr. The reaction mixture was cooled to give a precipitate which was filtered and washed with ether to give an off-white solid (0.67 g) m.p. 150-160°. This solid was washed with 10% sodium bicarbonate solution (20 ml) to give 2-phenylbenzimidazole (0.38 g, 39%) m.p. and mixed m.p. 288-290°. The organic filtrate was extracted with 10% sodium bicarbonate solution (20 ml portions)

until there was no further evolution of carbon dioxide. The sodium bicarbonate solutions were combined and acidified with hydrochloric acid to give benzoic acid (0.5 g, 42% on the assumption that 2 moles of benzoic acid are formed per mole of 2-phenylbenzimidazole).

Reaction of NN-Benzylidenebis-o-nitroaniline with Benzaldehyde.

(i) A mixture of NN-benzylidenebis-o-nitroaniline (2.13 g, 1 molar equivalent) and benzaldehyde (5.5 g, 9 molar equivalents) was heated under reflux for 1 hr. The reaction mixture was cooled to give a precipitate which was filtered and washed with ether to give an off-white solid (1.09 g) m.p. 130-140°. The solid was then washed with 10% sodium bicarbonate solution (20 ml). A further precipitate (0.28 g) m.p. 135-145° was obtained from the above organic solutions; this was similarly washed with ether and sodium bicarbonate solution. The total organic filtrate was washed with 10% sodium bicarbonate solution (20 ml portions) until the evolution of carbon dioxide ceased, and the bicarbonate extracts combined with the previous bicarbonate washings and acidified with hydrochloric acid to give benzoic acid (1.14 g, 79%, assuming 2 moles of benzoic acid are produced for each mole of 2-phenylbenzimidazole) m.p. and mixed m.p. 118-120°. The organic layer was dried over anhydrous sodium sulphate, concentrated in vacuo, and then triturated with a little ether to give a solid (0.285 g) m.p. 270-280°. This solid was combined with the other two solids obtained from the organic solution (the i.r. spectra of all three were essentially identical with that of 2-phenylbenzimidazole) and recrystallised from ethanol-water to give 2-phenylbenzimidazole (0.81 g, 71%, assuming 1 mole NN-benzylidenebis-o-nitroaniline gives

1 mole 2-phenylbenzimidazole) m.p. and mixed m.p. 288-290°
The ether wash was concentrated *in vacuo* and washed with light petroleum to remove unreacted benzaldehyde. The residue was a black intractable tar.

(2) A solution of equimolar amounts of benzaldehyde and *NN*-benzylidenebis-*o*-nitroaniline in deuteriobromoform was subjected to variable temperature n.m.r. spectrum analysis. The solution was heated to 180° without any apparent change in its spectrum. However, when the spectrum of the sample was taken after several hours' heating at 180° it was observed that the benzaldehyde PhC*H* singlet at 0.01 τ had disappeared while a singlet at 5.08 τ had appeared. The initial spectrum of the sample (Spectrum 1) and that after heating for several hours at 180° (Spectrum 2) are shown (p. 121 and 122) and discussed on p. 82 and 83.

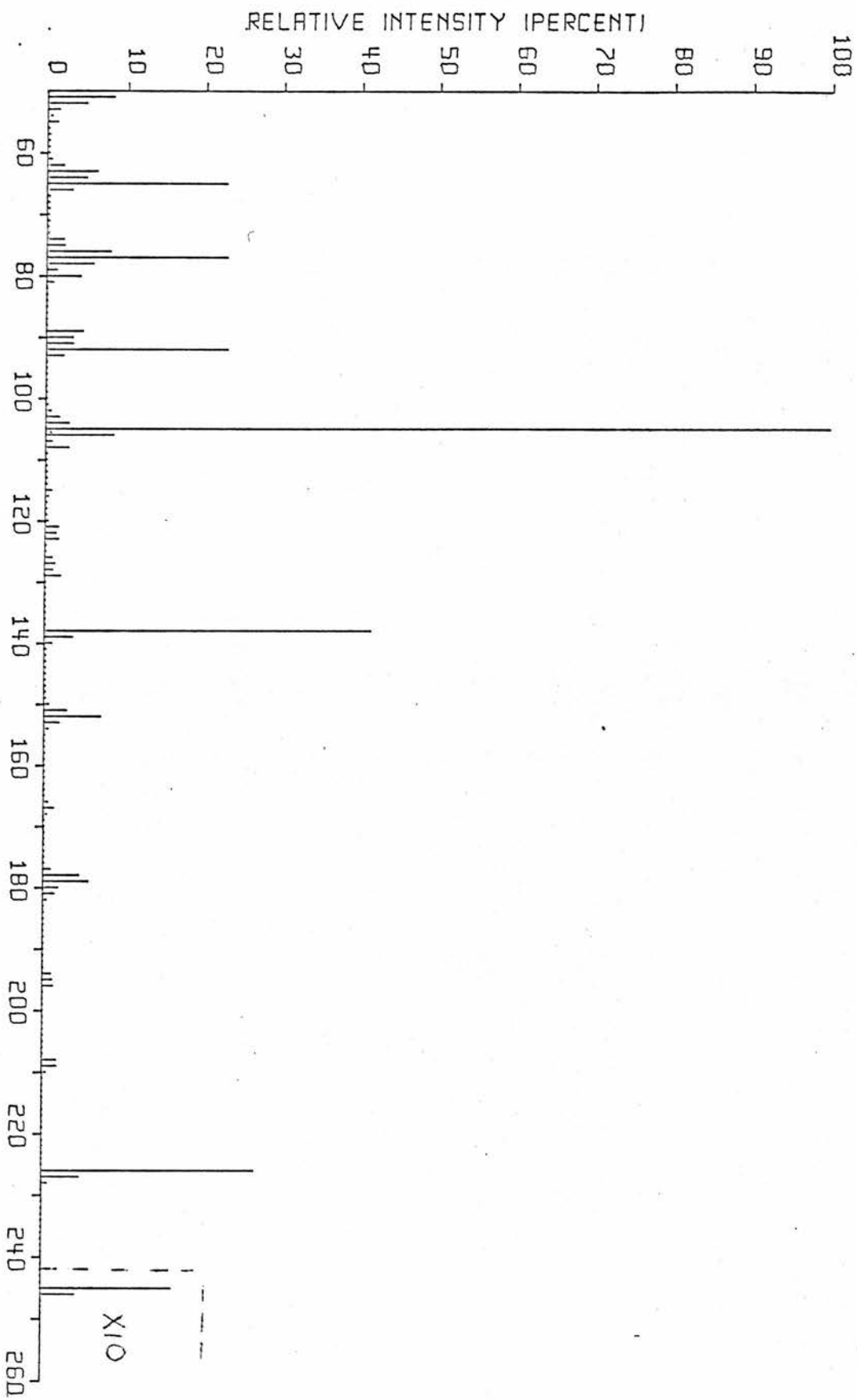
Attempted Addition of *N*-Methyl-*o*-nitroaniline to *N*-Benzylidene-*o*-nitroaniline

A solution of *N*-benzylidene-*o*-nitroaniline (2.26 g, 0.01 mole) and *N*-methyl-*o*-nitroaniline (1.52 g, 0.01 mole) in dry benzene (25 ml) was heated under reflux for 1 hour. The solution was then cooled and diluted with light petroleum (25 ml) to give *N*-benzylidene-*o*-nitroaniline (1.93 g, 85% recovery) m.p. and mixed m.p. 74-76°. Similar results were obtained when the reaction was repeated in xylene and in both xylene and *p*-cymene in the presence of acetic acid. When the reaction was repeated in *p*-cymene in the presence of toluene-*p*-sulphonic acid *N*-benzylidene-*o*-nitroaniline was not precipitated by the addition of light petroleum to the cooled solution.

However, N-methyl-o-nitroaniline (1.35 g, 89% recovery) was isolated by column chromatography on silica gel.

Attempted Reaction of Nitrobenzene with Benzaldehyde

Equimolar quantities of nitrobenzene and benzaldehyde were heated under reflux for 1 hr. No apparent reaction occurred and a high recovery of starting materials was made by column chromatography on silica gel.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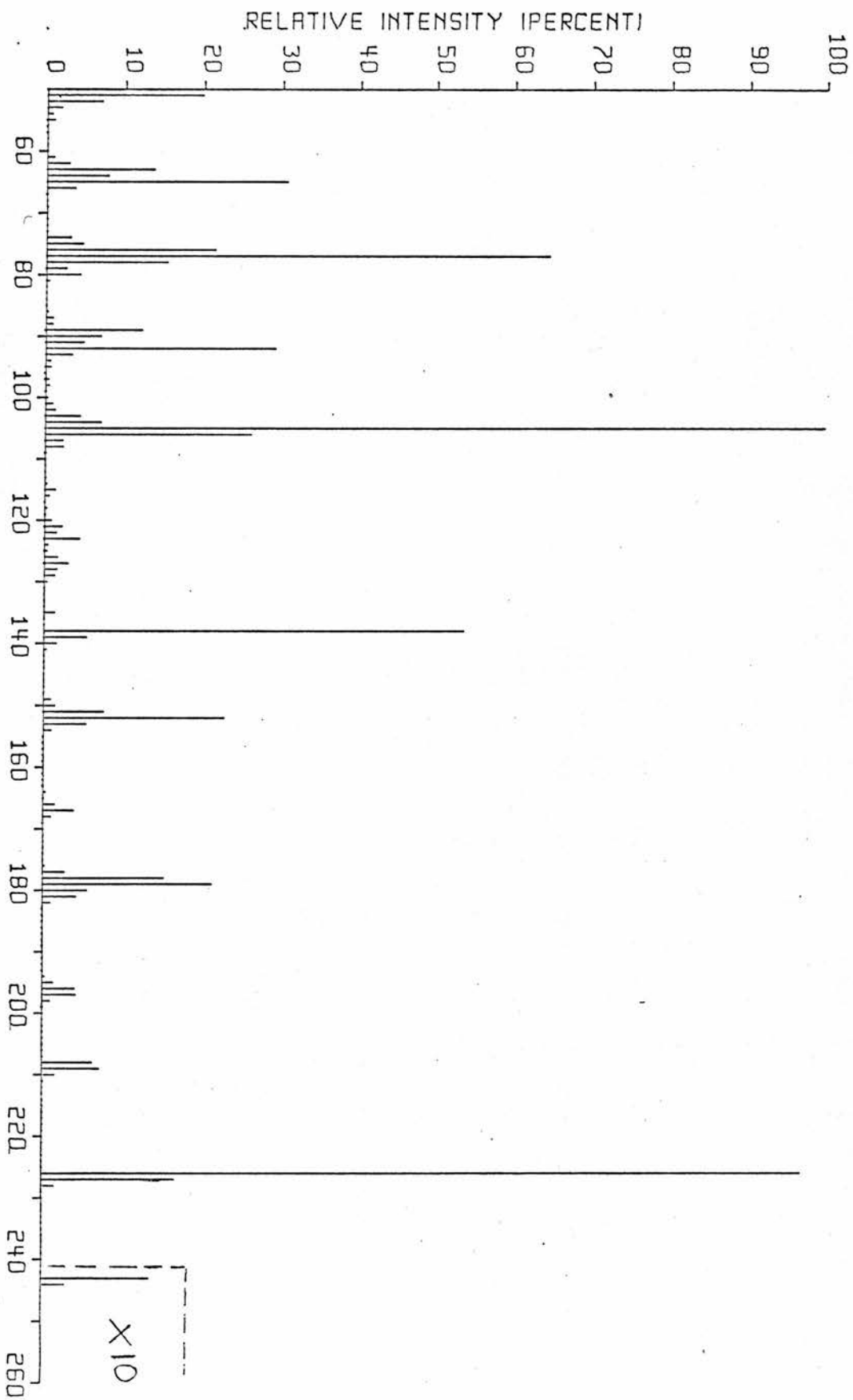
Graph 1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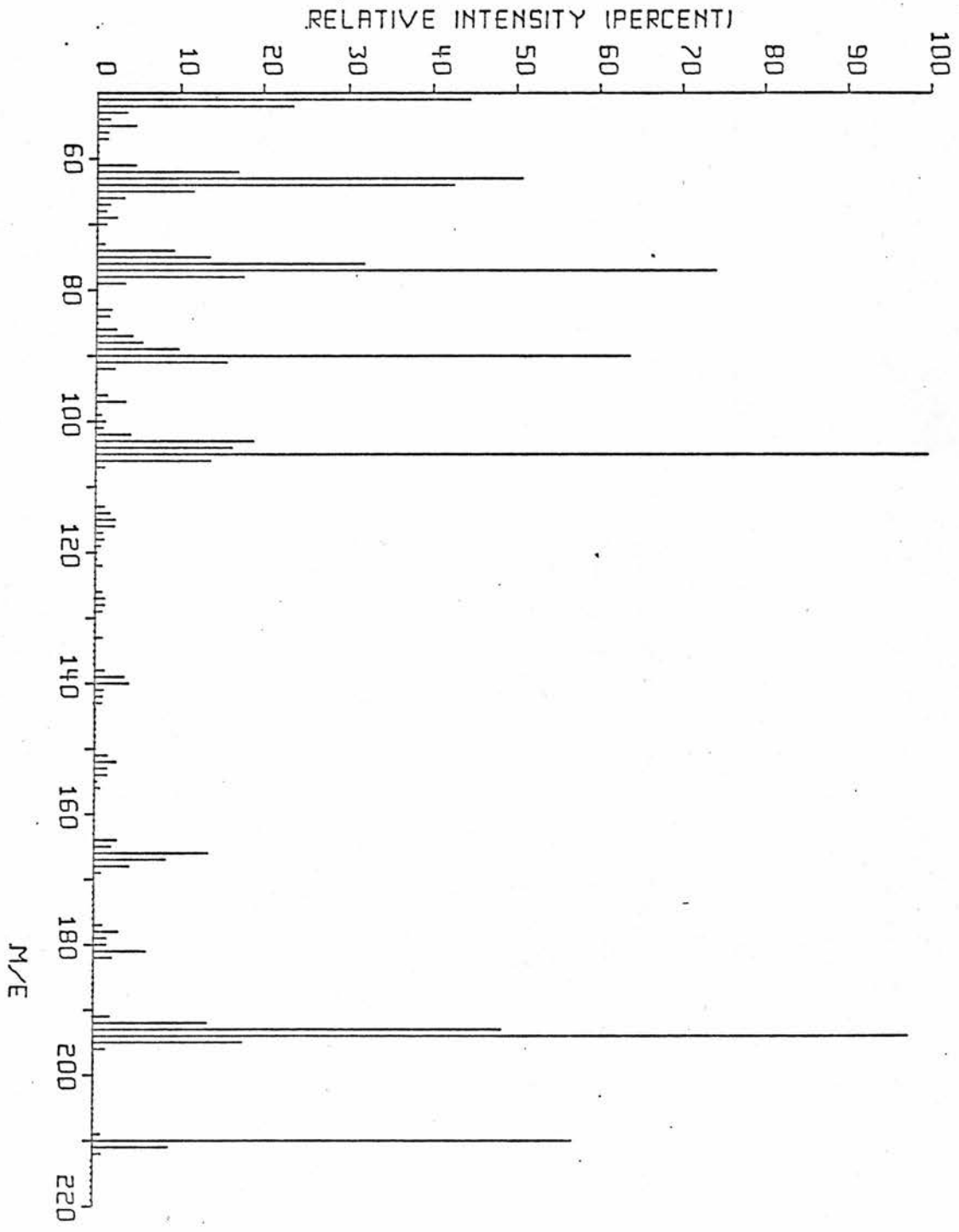
Graph 2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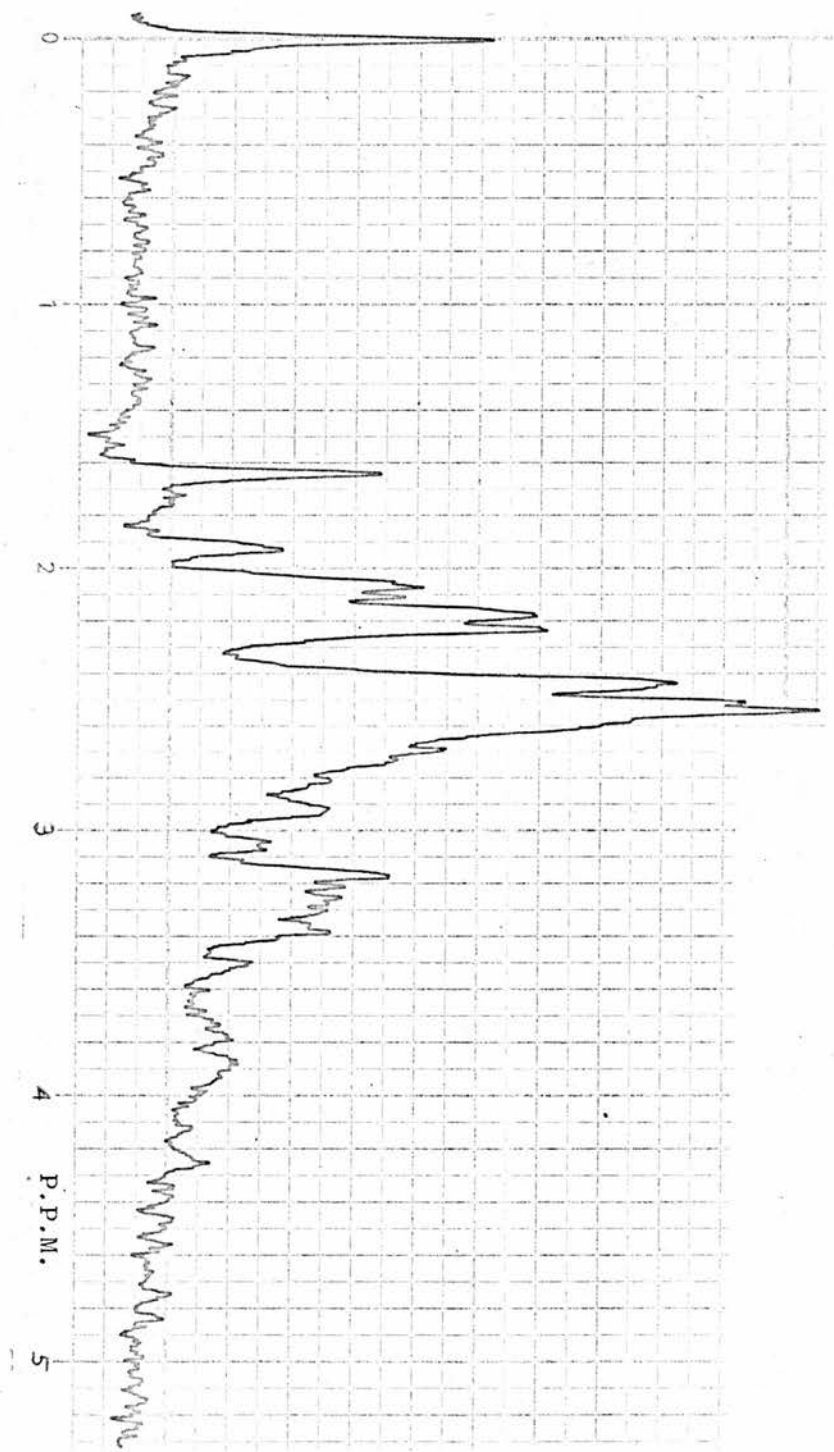
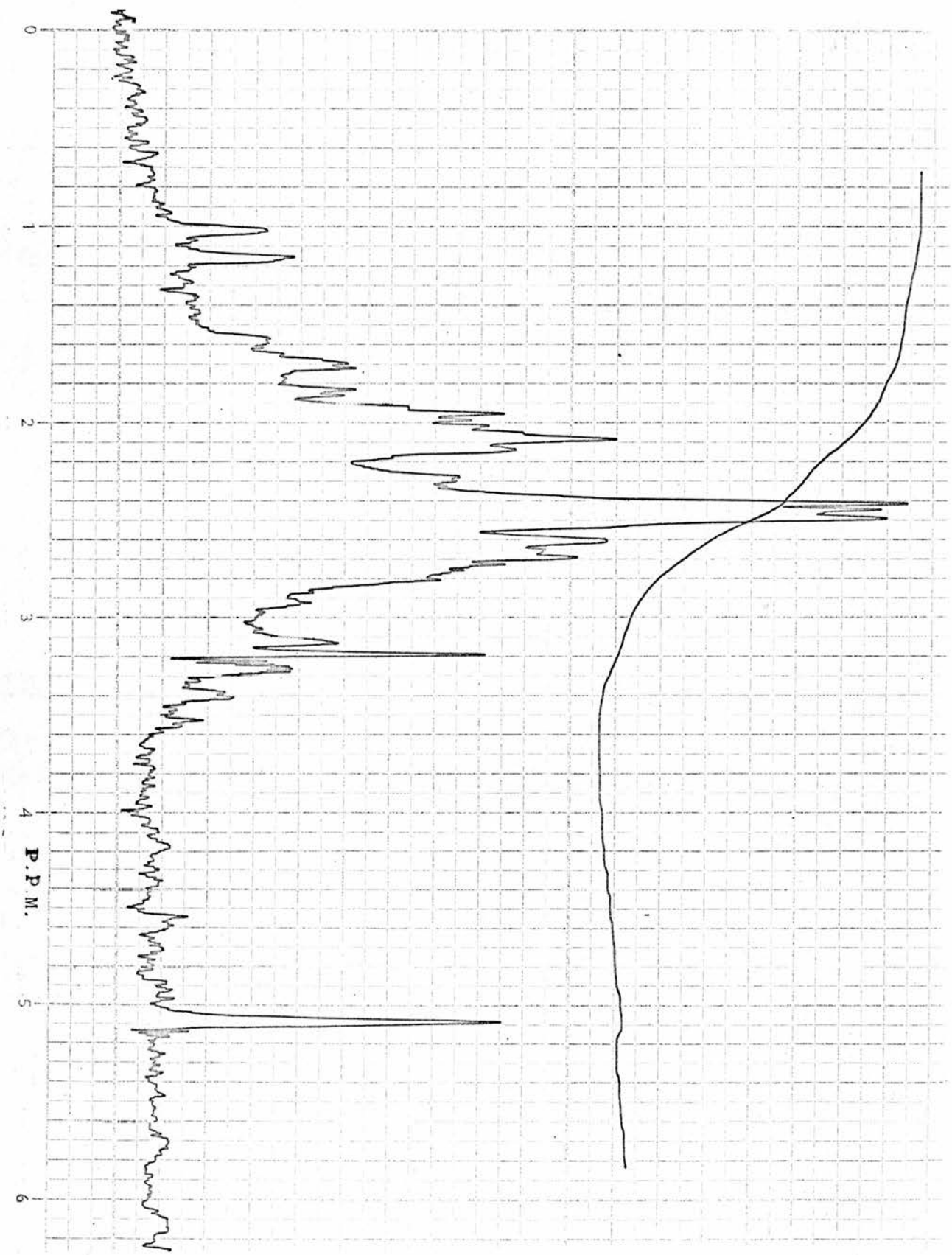
Graph 3



Spectrum 1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