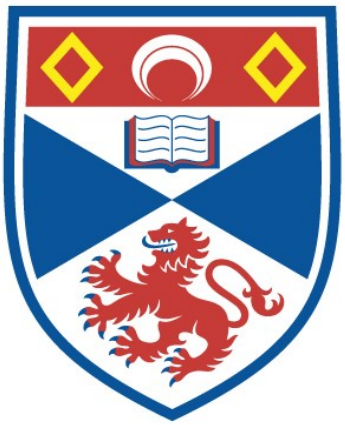
SOME SUBSTITUENT INTERACTIONS OF SUBSTITUTED O-NITROANILINES

John Machin

A Thesis Submitted for the Degree of PhD
at the
University of St Andrews



1977

SOME SUBSTITUENT INTERACTIONS OF SUBSTITUTED o-NITROANILINES

being a thesis

presented by

JOHN MACHIN B.Sc.

to the

UNIVERSITY OF ST. ANDREWS

in application for

THE DEGREE OF DOCTOR OF PHILOSOPHY

St. Andrews September 1977

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9013

DECLARATION

I 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 been presented in application for a higher degree.

The work was carried out in the Department of Chemistry of the University of St. Andrews under the direction of Dr. D.M. Smith.

CERTIFICATE

I hereby certify that Mr. J. Machin B.Sc. has spent eleven terms at research work under my supervision, has fulfilled the conditions of the resolution of the University Court 1967, No. 1, and is qualified to submit the accompanying thesis in application for the degree of Doctor of Philosophy.

29th Sept. 1977

Research Supervisor

ACKNOWLEDGEMENTS

I am most grateful to Dr. D.M. Smith for his advice, interest and encouragement over the past three years.

My thanks are also due to the technical staff of the department, especially Mrs. M. Smith (nmr spectra), Mr. C. Millar (mass spectra) and Mr. J. R. Bews (microanalysis).

I am indebted to Miss Fiona Sutherland for her help in the production of this thesis.

Finally, I am grateful to Professors P.A.H. Wyatt and J.M. Tedder for the award of a research studentship and for the use of the facilities of this department.

To my mother and father

CONTENTS

Abstract

An introduction to the methods of preparation and some general properties of benzimidazole-N-oxides are discussed in Chapter 1.

In Chapter 2, the reaction of N-p-nitrobenzyl-N-p-tolylsulphonyl-o-nitroaniline with sodium methoxide in methanol to give 2-p-nitrophenylbenzimidazole-3-oxide is discussed. With the aid of reaction kinetics a mechanism which involves cyclisation prior to detosylation is established. The corresponding reactions of N-methylsulphonyl, N-acetyl and N-benzoyl-N-p-nitrobenzyl-o-nitroaniline with sodium methoxide similarly involve cyclisation prior to deacylation. For the corresponding cyclisations of N-acetyl and N-benzoyl — N-benzyl-o-nitroaniline to 2-phenylbenzimidazole-3-oxide, a mechanism involving deacylation prior to cyclisation is proposed. The reaction of N-p-nitrobenzyl-N-p-tolylsulphonyl-2,4-dinitroaniline and N-benzyl-N-p-tolylsulphonyl-2,4-dinitroaniline with sodium methoxide does not give expected cyclised product, but gives instead N-p-tolylsulphonyl-2,4-dinitroaniline. Various mechanisms to account for these results are discussed. The reaction of ethyl N-o-nitrophenylcarbamate with base and p-nitrobenzyl bromide gives along with the expected product N-ethoxycarbonyl-N-p-nitrobenzyl-o-nitroaniline, 1-p-nitrobenzyloxy-2-p-nitrophenylbenzimidazole.

In Chapter 3, the reaction of N-phenacyl-N-p-tolylsulphonyl-o-nitroaniline and various substituted analogues with

a selection of bases is discussed. The major product of these reactions in which the base is methoxide, ethoxide, and n-propoxide is the corresponding 2-alkoxybenzimidazole-3-oxide. A mechanism for this reaction is proposed and the steps taken to verify it discussed. The scope and limitations of this type of reaction are considered.

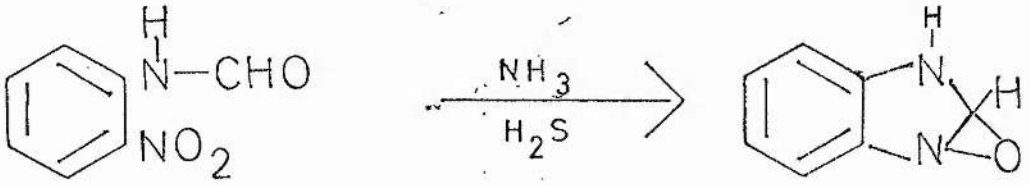
Chapter 4 deals with the attempted synthesis of a reaction intermediate, namely 1-p-tolylsulphonylbenzimidazole-3-oxide, postulated in the reaction scheme used to explain the formation of the 2-alkoxybenzimidazole-3-oxides.

CHAPTER 1

The synthesis, and some general properties, of known Benzimidazole-N-oxides.

In this first chapter, known methods for preparing benzimidazole-N-oxides, and some of the more interesting properties of these compounds, are discussed.

In 1910, von Niementowski[1] reported that the reduction of o-nitroformanilide (1) by an alcoholic solution of ammonium sulphide gave a compound (2) that he regarded as an "oxanhydro base", and which he named oxbenzimidazole. This was in addition to earlier work, also by von Niementowski[2], in which the product (4) of the dehydrobromination of 1,2-dibromo-2,5-dimethyl-1,2-dihydrobenzimidazole (3) by potassium hydroxide was also thought to be an "oxanhydro base".



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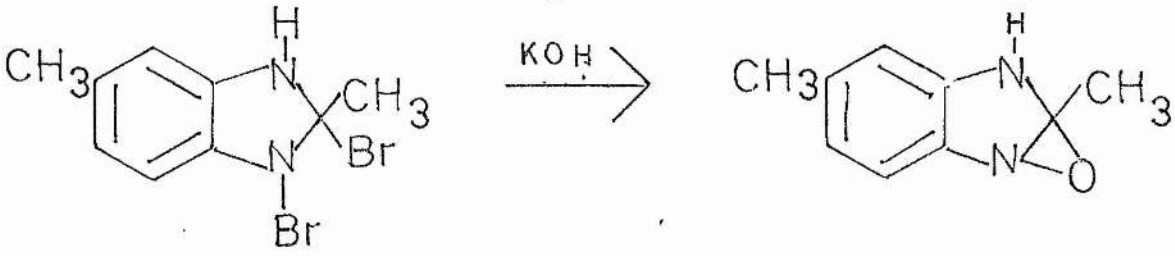
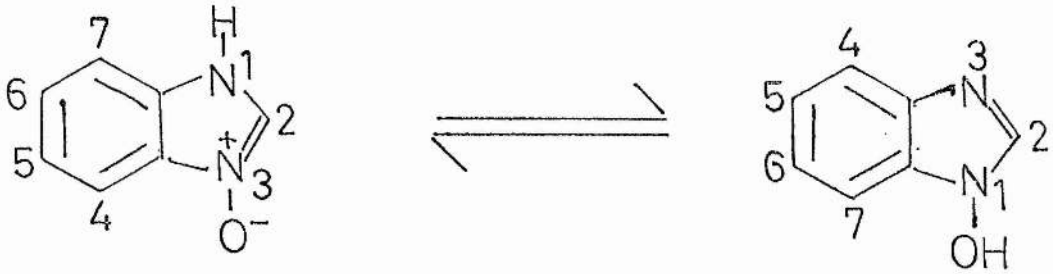


(3) (4)

It was not until 1951 that Wright[3] postulated structures (2a) and (2b) to describe the product of the reaction when (1) was reduced by alcoholic ammonium sulphide.

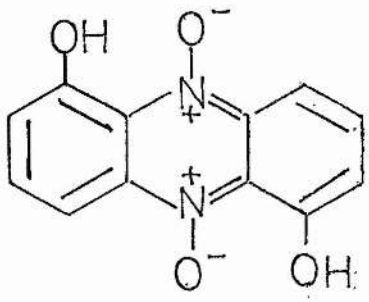


(2a) (2b)

(2a) and (2b) are tautomeric, with (2a) being known as benzimidazole-3-oxide and (2b) as 1-hydroxybenzimidazole. Kew and Nelson[4] in 1962, assigned structure (2a) to the compound that von Niementowski had called oxbenzimidazole on the bases of its physical and chemical properties, such as melting point and solubility, and its chemical reactivities, for example its deoxygenation with phosphorus trichloride to the corresponding benzimidazole. However Takahashi and Kano[5] later showed that the predominating tautomer is dependent upon the conditions under which the tautomerism is studied. For example, in an ethanolic solution, (2b) predominates, whereas in an aqueous solution, the major tautomer is (2a)

From the time of von Niementowski's work until the early nineteen sixties, there was not a significant amount of work published on the synthesis or properties of

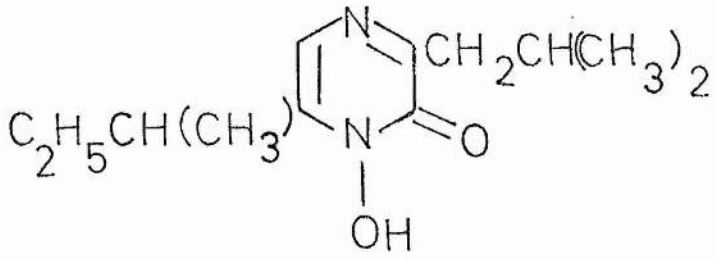
benzimidazole-N-oxides. Since then, however, much more research has been carried out on these compounds, perhaps because of the realisation that they are interesting compounds in their own right, but more than likely due to the strong possibility that benzimidazole-N-oxides could possess interesting pharmacological and physiological properties. For example, it had already been shown that the antibiotics iodinin[6] (5), and aspergillic acid[7] (6), were heterocyclic N-oxides, and the widespread physiological activity of purine N-oxides had been reported[8]. Added interest could have been provided by claims that the conversion of certain alkaloids into their N-oxides led to a reduced toxicity without a parallel decrease in their biological activity[9].



(5)

Iodinin

1,6-dihydroxyphenazine-5,10-dioxide



(6)

Aspergillic Acid (6)

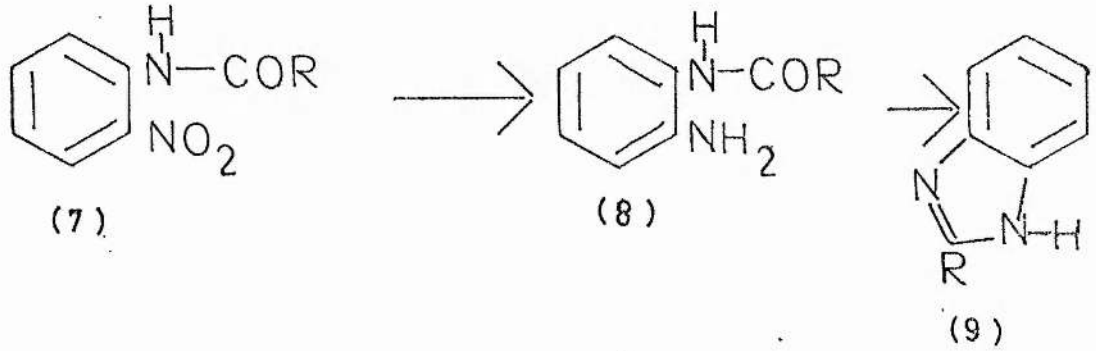
1-hydroxy-3-isobutyl-6-sec-butyl-2-pyrazinone

The knowledge that benzimidazole and its derivatives possessed pharmacological and physiological properties[10] should also have been of use as it provided further support for the idea of benzimidazole-N-oxides being active in these fields.

The seemingly obvious way to synthesise a benzimidazole-N-oxide would be by the direct oxidation of the parent benzimidazole, as benzimidazoles are readily obtainable by a variety of different methods[10]. However, conventional oxidative methods[4,11,12] have been shown to be unsuccessful in converting benzimidazoles into benzimidazole-N-oxides, and alternative routes to these compounds have had to be found. These alternative methods have fallen into four main categories; reductive cyclisations, acid catalysed cyclisations, thermal cyclisations, and base catalysed cyclisations.

Reductive Cyclisations

Acylated o-nitroanilines (7) when reduced with tin and hydrochloric acid or similar reducing agents, ought to yield monoacyl-o-phenylenediamines (8) by reduction of the nitro group in the usual manner. However, under the reaction conditions the diamine derivative is not isolated, but undergoes cyclisation to a benzimidazole derivative (9) by dehydrative ring closure involving the primary amine function and the carbonyl group.

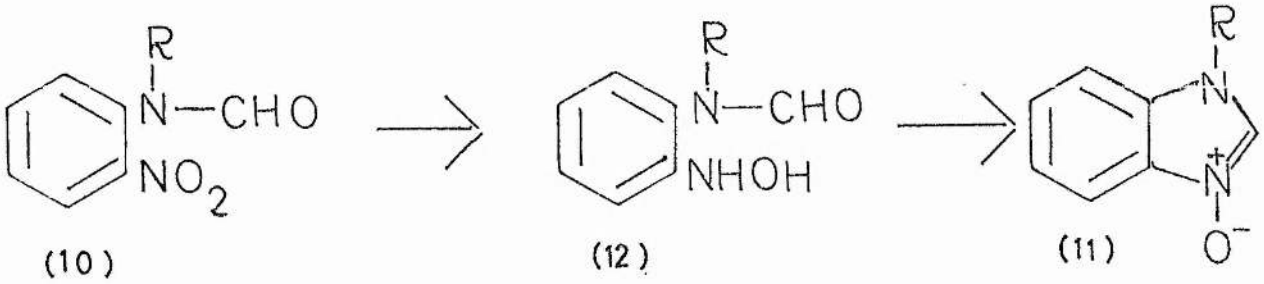


(7) (8) (9)

The acyl derivatives of N-substituted o-nitroanilines lead to 1-substituted benzimidazoles. Numerous examples of this type of cyclisation are known and they have been reviewed elsewhere[3].

As stated previously, von Niementowski[1,2] was the first to show that benzimidazole-N-oxides may also be found among the reduction products of acylated o-nitroanilines. In an extension of this work, Takahashi and Kano[5] reported that the reduction of N-Substituted o-nitroformanilide derivatives (10; R = CH_3, C_2H_5, $C_6H_5CH_2$) with ammonium sulphide gave the correspondingly substituted benzimidazole-N-oxides (11). These reactions are thought to go via the

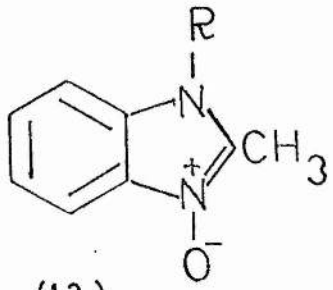
hydroxylamine intermediate (12)



(10) (12) (11)

However, when (10) was heated with zinc in an aqueous ammonium chloride solution, (which is a known reagent for reducing a nitro group to a hydroxylamine group,) only a low yield of (11) was obtained, and neither N-methyl-2'-nitroformanilide (10 R = CH_3) nor 2'-nitroacetanilide (7; R = CH_3) could be converted into the corresponding N-oxide by this reagent.

By using ammonium sulphide, 1-substituted-2-methylbenzimidazole-3-oxides (13) were prepared from (14), and in the case of the N-methyl and N-ethyl derivatives, the corresponding benzimidazoles (15) were also formed.



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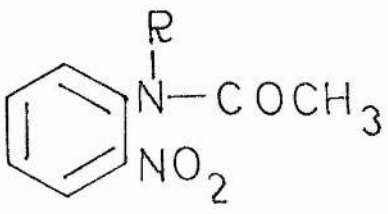

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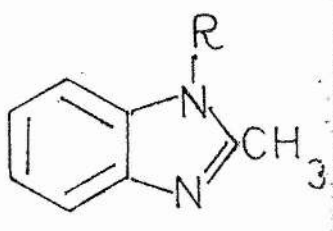
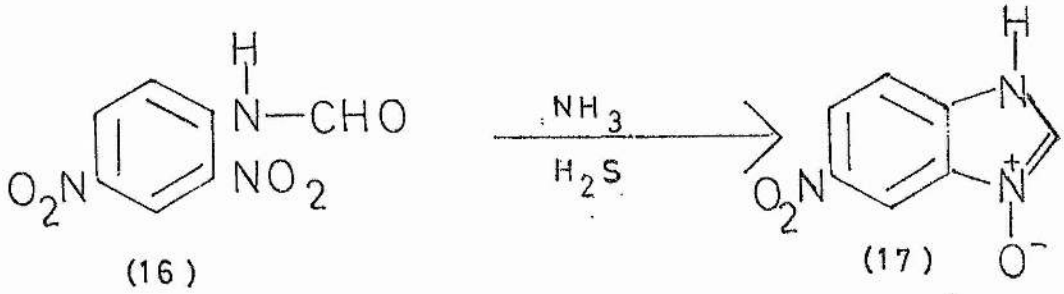


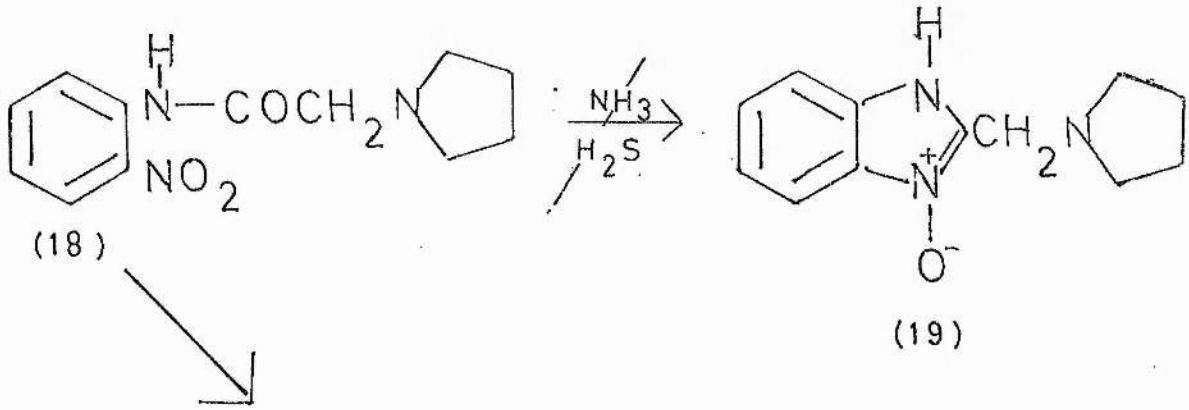
(15)

The selective reduction of the 2'-nitro group by ammonium sulphide in 2,4-dinitroformanilide (16) gave 5-nitrobenzimidazole-3-oxide[13] (17).

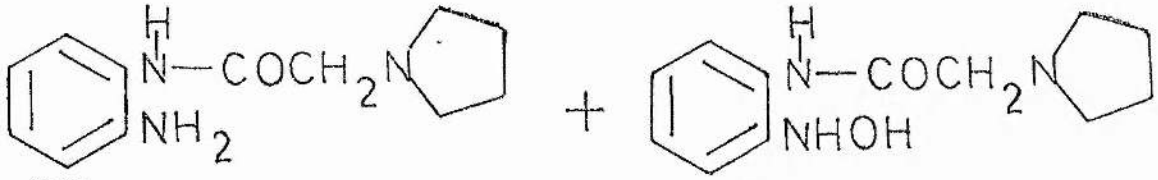


(16) (17)

However, the general synthetic usefulness of this type of reaction was marred by the result of the reduction of 2-(1-pyrrolidinyl)-2'-nitroacetanilide (18) with ammonium sulphide[5]. Instead of the corresponding N-oxide (19), the reaction produced 2-(1-pyrrolidinyl)-2'-hydroxylaminoacetanilide (20) and the amine (21). All attempts to form the N-oxide (19) by heating (20) with 4N hydrochloric acid or phosphoric acid failed.

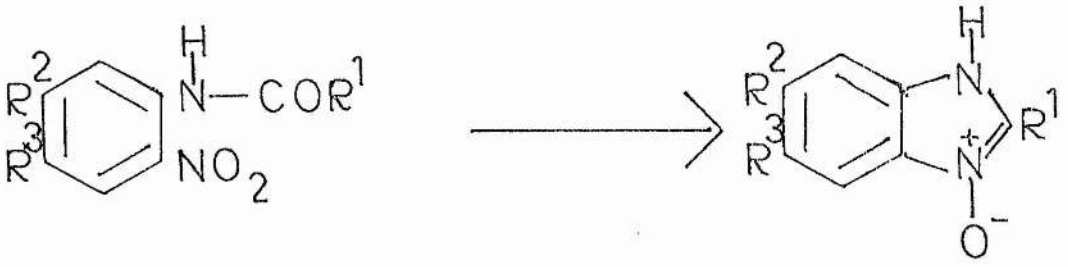


(18) (19)



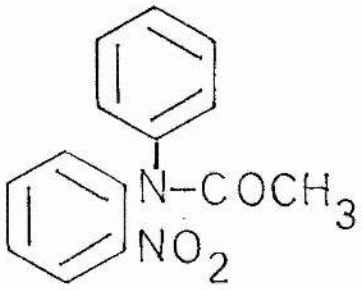
(21) (20)

Other examples of this type of reduction are the formation of 2,5,6-trisubstituted benzimidazole-3-oxides[14] (23) by the reduction of (22) with an alkali metal hydrosulphide in the presence of calcium or barium chloride or bromide, and ammonium chloride or hydrochloric acid or acetic acid, in an organic solvent, and the reduction of o-nitroformanilides by sodium borohydride[15].



(22) (23)

Smith et al[16] reported that while the hydrogenation over a platinum catalyst of o-nitro-N-phenylacetanilide (24) in 50% ethanol gave o-amino-N-phenylacetanilide (25), the same reaction in 95% ethanol gave 2-methyl-1-phenyl-benzimidazole (27). Forbes and Wragg[17] obtained only (25) by hydrogenation of (24) with a Raney Nickel catalyst, understandable as Raney Nickel is not such a powerful catalyst as Platinum. However, further study of this reaction by Schulenberg and Archer[18] gave the results shown in Scheme 1. Hydrogenation of (24) over a platinum catalyst in 50%, 95%, absolute ethanol or ethyl acetate gave in all cases a high yield of the amine (25), a result in direct contradiction to that of Smith et al.



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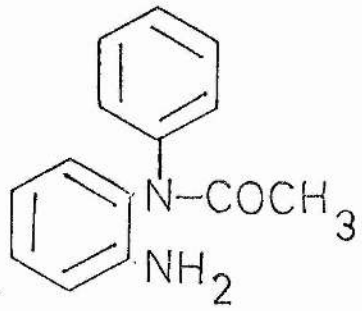

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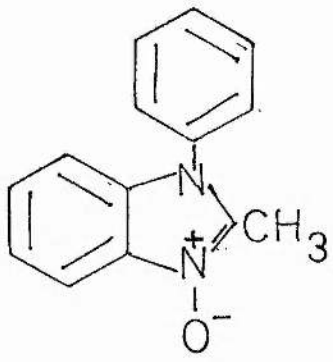
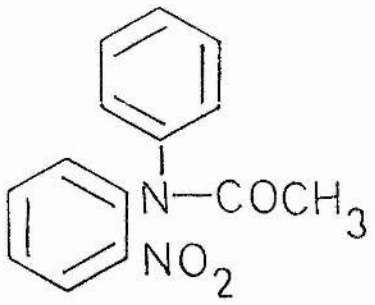


(26)

Indeed, Schulenberg and Archer only obtained the hydrochloride of (26) when the hydrogenation was carried out in the presence of one or more molar equivalents of hydrochloric acid. The reaction in 0.2 molar equivalents of hydrochloric acid followed by treatment of the product with excess hydrochloric acid yielded the hydrochloride of the benzimidazole (27). In the former case, it would appear that the acid catalyses cyclisation of the hydroxylamine intermediate to the point where ring closure is faster than reduction to the primary amine. This idea is supported by the fact that the hydrogenation of 2-chloro-2'-nitro-N-phenylacetanilide (28) in ethanol gave the hydrochloride of (29). In this case it is conceivable that ring closure is catalysed by the hydrogen chloride generated by the reductive dehalogenation of (28). The catalytic hydrogenation of N-methyl-o-nitroacetanilide in ethanol with concentrated hydrochloric acid over a palladium-charcoal catalyst was reported[19] to give a higher yield of 1,2-dimethylbenzimidazole-3-oxide (30) than that obtained by the method of Schulenberg and Archer using a platinum catalyst.



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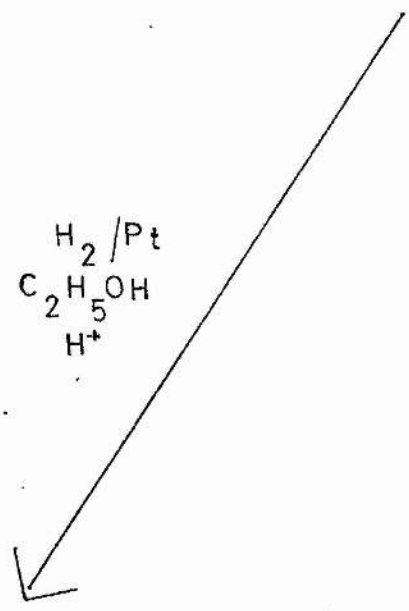

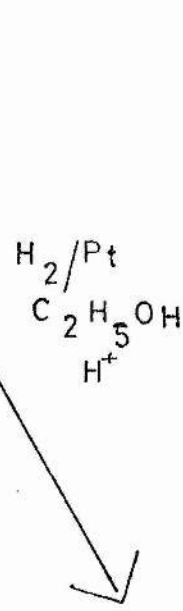

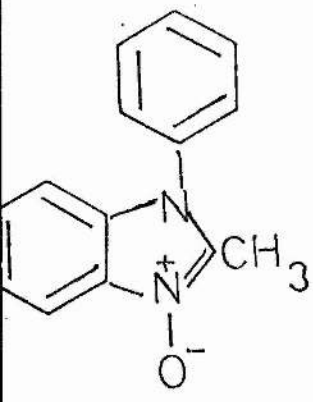

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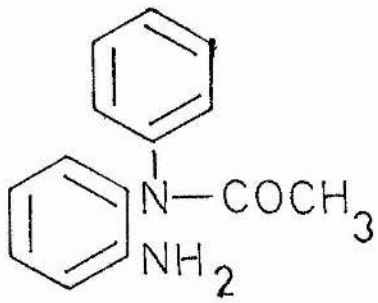

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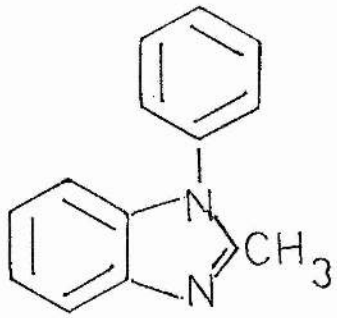

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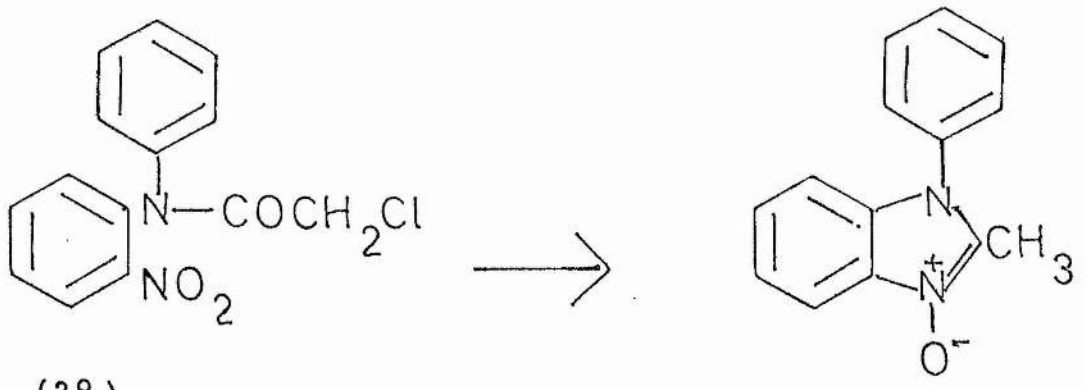
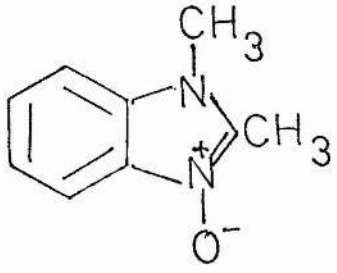
SCHEME 1

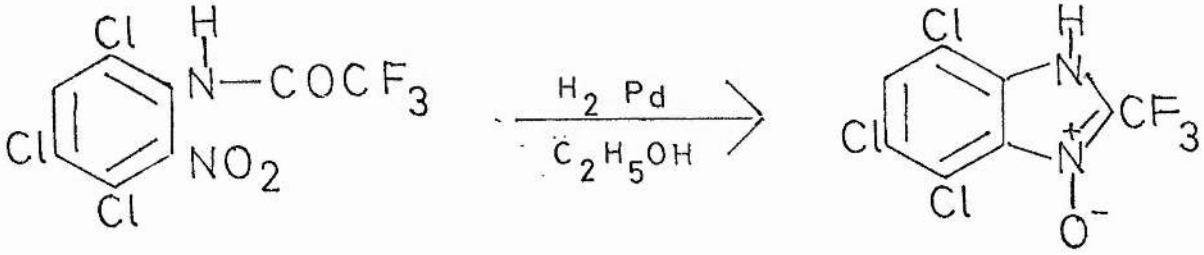


(28) (29)



(30)

A palladium catalyst was also used to obtain good yields of 4,5,7-trichloro-2-trifluoromethylbenzimidazole — 3-oxide (31) by reduction of 2-trifluoro-2'-nitro-3',4',6'-trichloroacetanilide (32) in ethanol[20]. Doherty and Fuhr[21] also obtained various 2-trifluoromethylbenzimidazole-3-oxides using similar conditions (33), (34).



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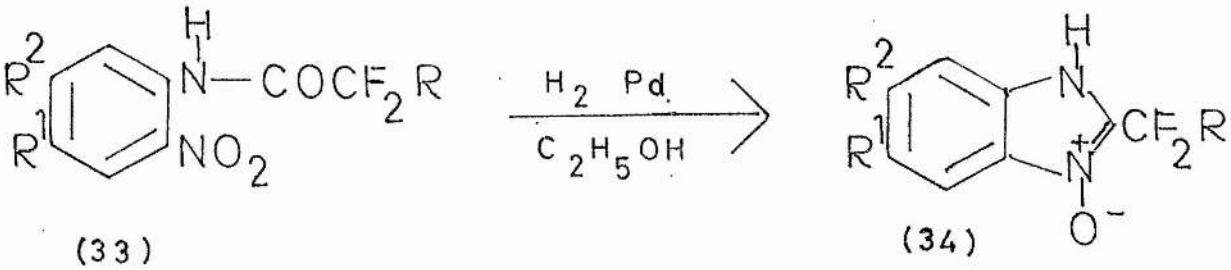
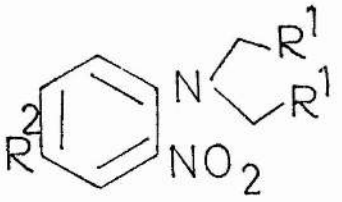


(33) (34)

In some of these reduction reactions, the N-oxide is not the only product formed, and isolation and purification of the required product can be difficult. The controlled potential reduction of o-nitroformanilides[22] to benzimidazole-N-oxides offers a way around these difficulties by avoiding over-reduction by control of the potential. However, using this method under laboratory conditions necessitates working with small amounts of compounds and this is a major drawback.

Acid Catalysed Cyclisations

The action of hot aqueous acid (e.g. hydrochloric acid) on the N,N-dialkyl-o-nitroanilines (35) gave the corresponding benzimidazole-N-oxides as their hydrochlorides (36), and also the minor products (37) and (38).[23]



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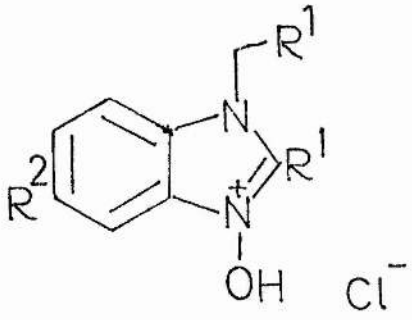
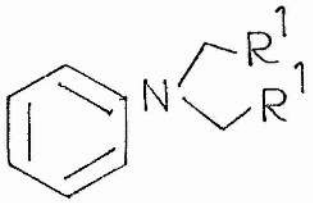


(36)

$R^2 = H$



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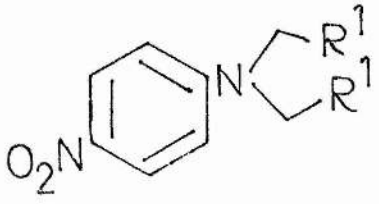
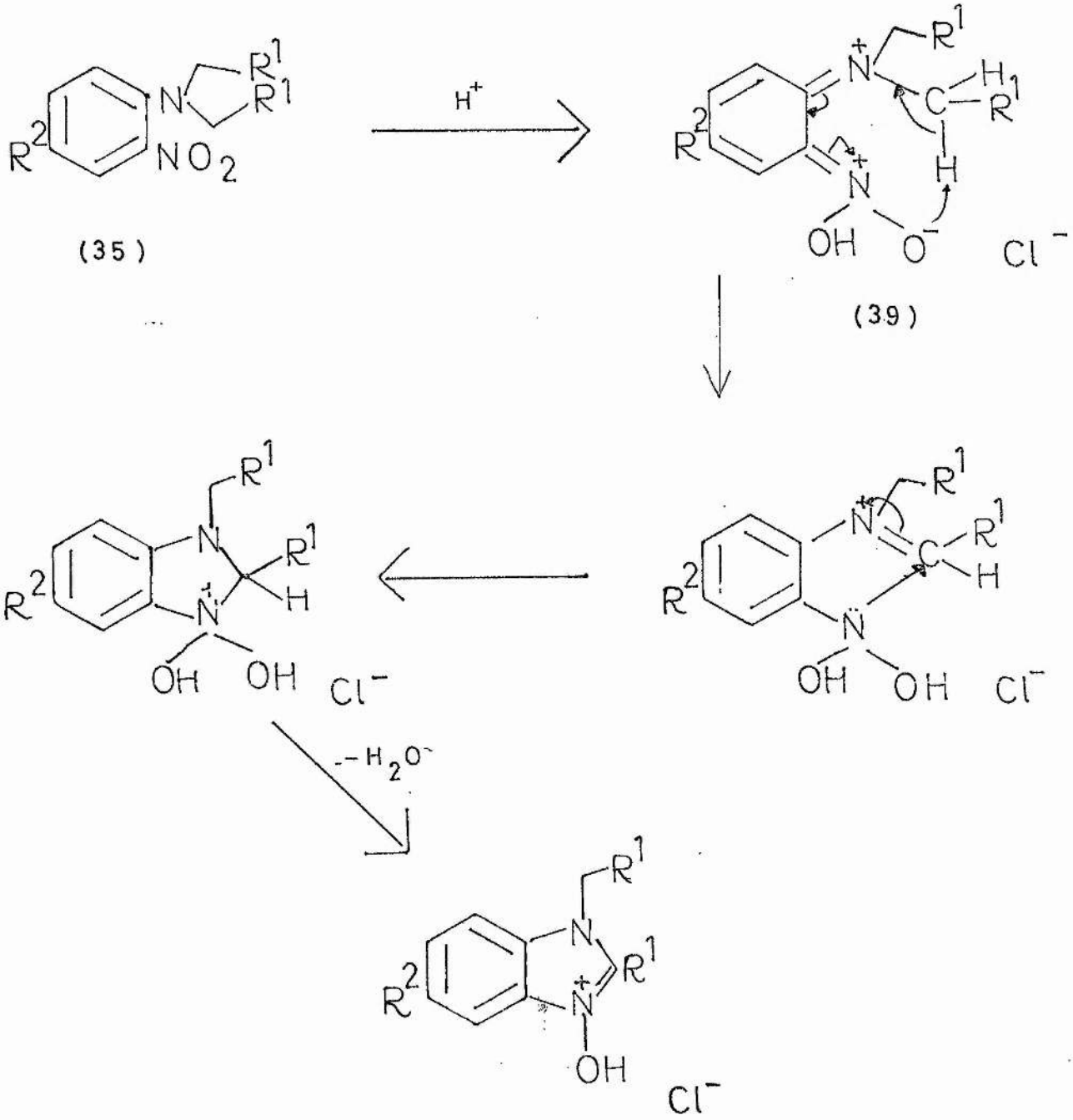


(38)

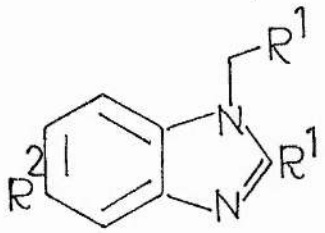
The proposed mechanism for this reaction is shown in Scheme 2.



SCHEME 2

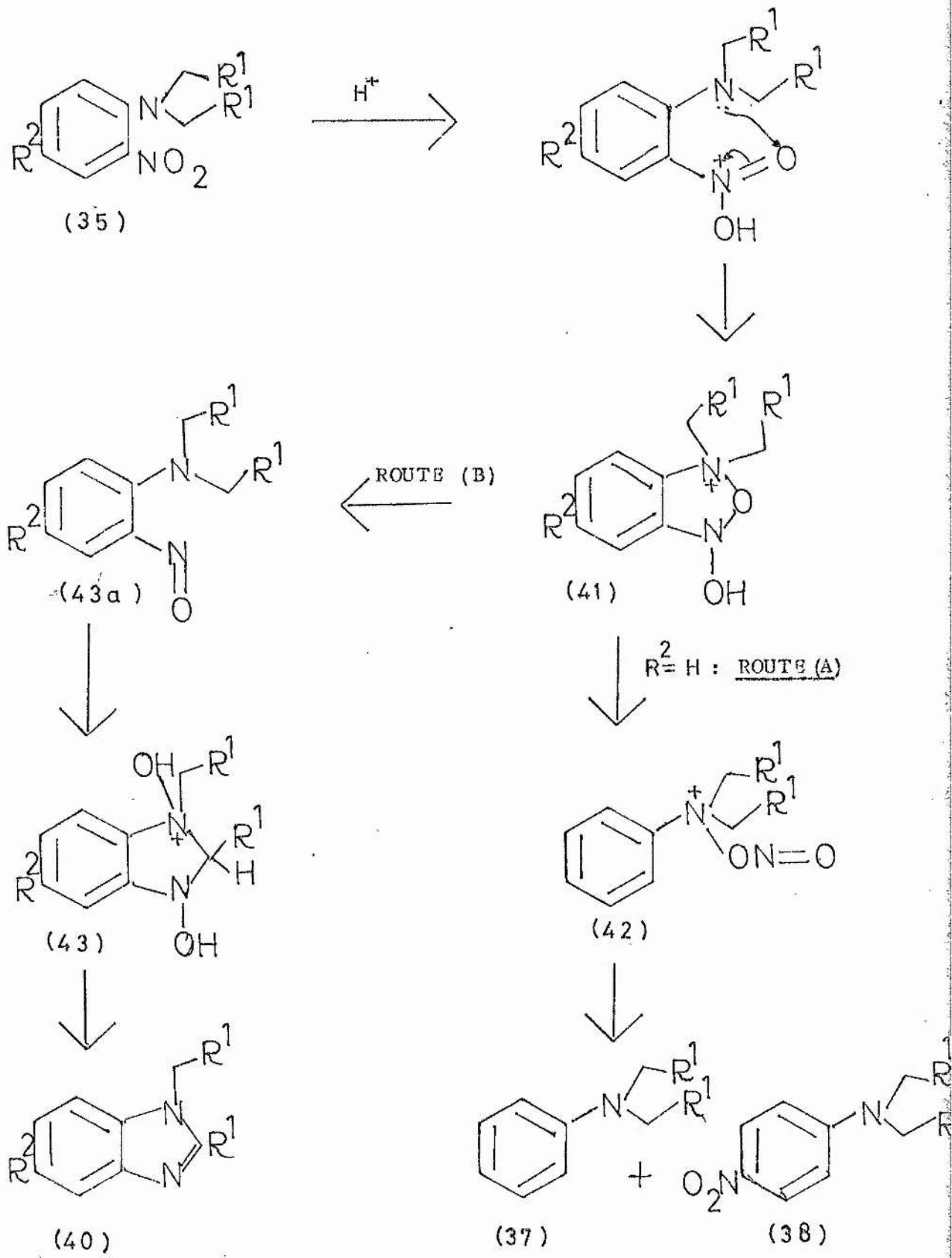
For this reaction an aci-nitro form of intermediate (39) is invoked. This, along with a nitroso type of intermediate, (examples of which will be seen later), are the two most common examples of intermediates postulated for this type of cyclisation.

The photocyclisation in aqueous methanolic hydrochloric acid of the compounds (35) gave the benzimidazole N-oxides (36) in some cases, and the benzimidazoles (40) in others, but not both[24].



(40)

Since the benzimidazole-N-oxides corresponding to the benzimidazoles (40) are photostable under the reaction conditions, they are not the precursors of the benzimidazoles. The proposed mechanism for the formation of the N-oxides under these conditions is the same as that shown in Scheme 2. The proposed mechanism for the benzimidazole and by product formation is shown in Scheme 3.

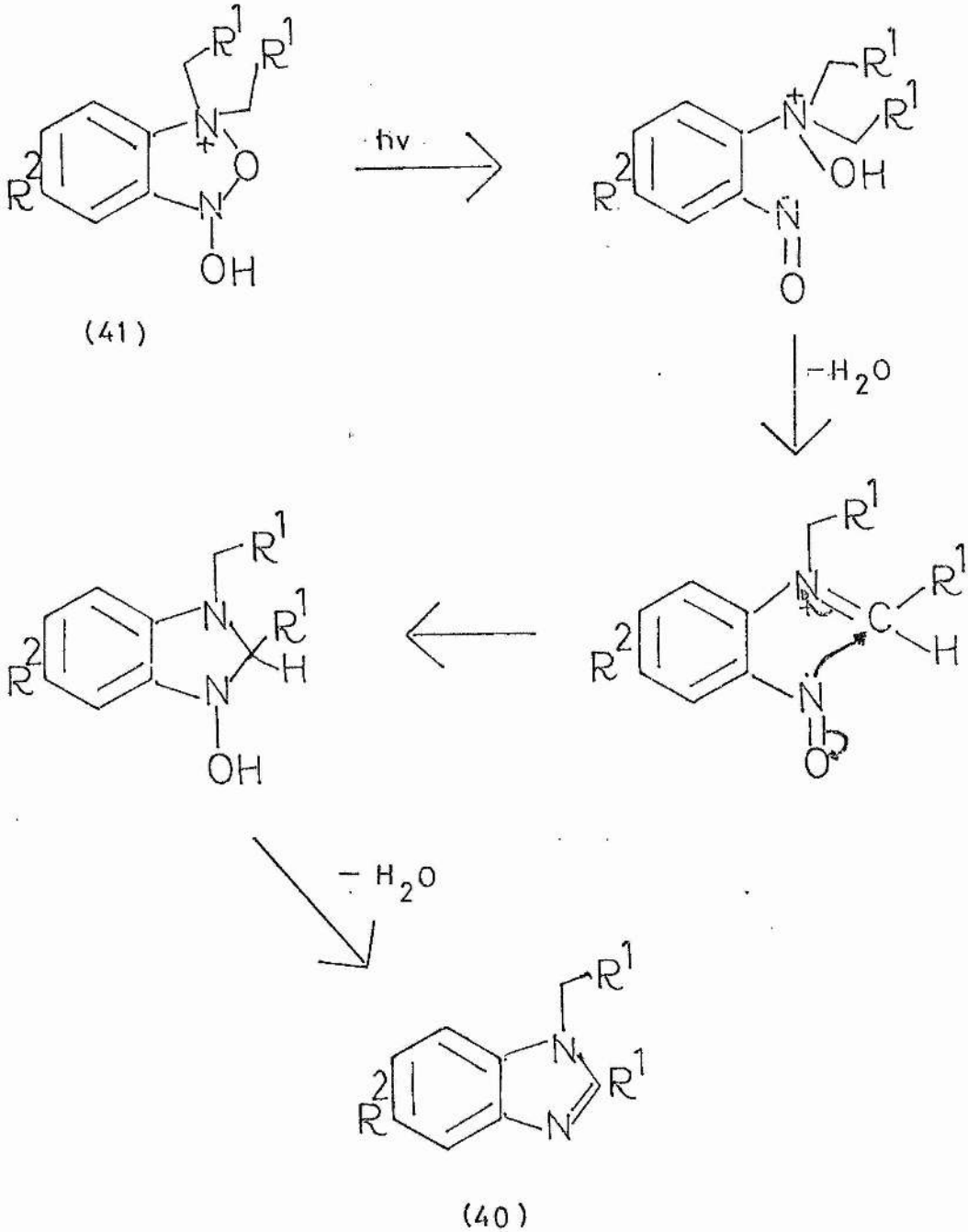


SCHEME 3

The by products (37) and (38) from the thermal reaction can be considered to arise from the reduced furoxan intermediate (41). This rearranges thermally, (route A) to the N-nitrite (42), which, in a manner analogous to the nitramine rearrangements[25], gives the p-nitro compound (38) or loses its nitro group to give the denitrated compound (37). The furoxan intermediate is also invoked to explain the benzimidazole formation (route B), by way of the "o-nitroso-N-oxide" (43a) and the unstable "N-oxide" (43), which by loss of water and oxygen yields (40). A much more plausible pathway to the benzimidazole (40) from the furoxan intermediate (41) is shown in Scheme 4.

In a later communication [26], Suschitzky et al proposed different reaction pathways for the formation of (36) and (40) in the photocyclisation of (35). These mechanisms are shown in Schemes 5 and 6. In Scheme 5, the photo-excitation of the nitro group can lead by way of a diradical to the N-oxide (36). However, larger or more basic heterocycles in the starting material may lead to attack at the tertiary nitrogen atom and hence to the benzimidazoles (Scheme 6)

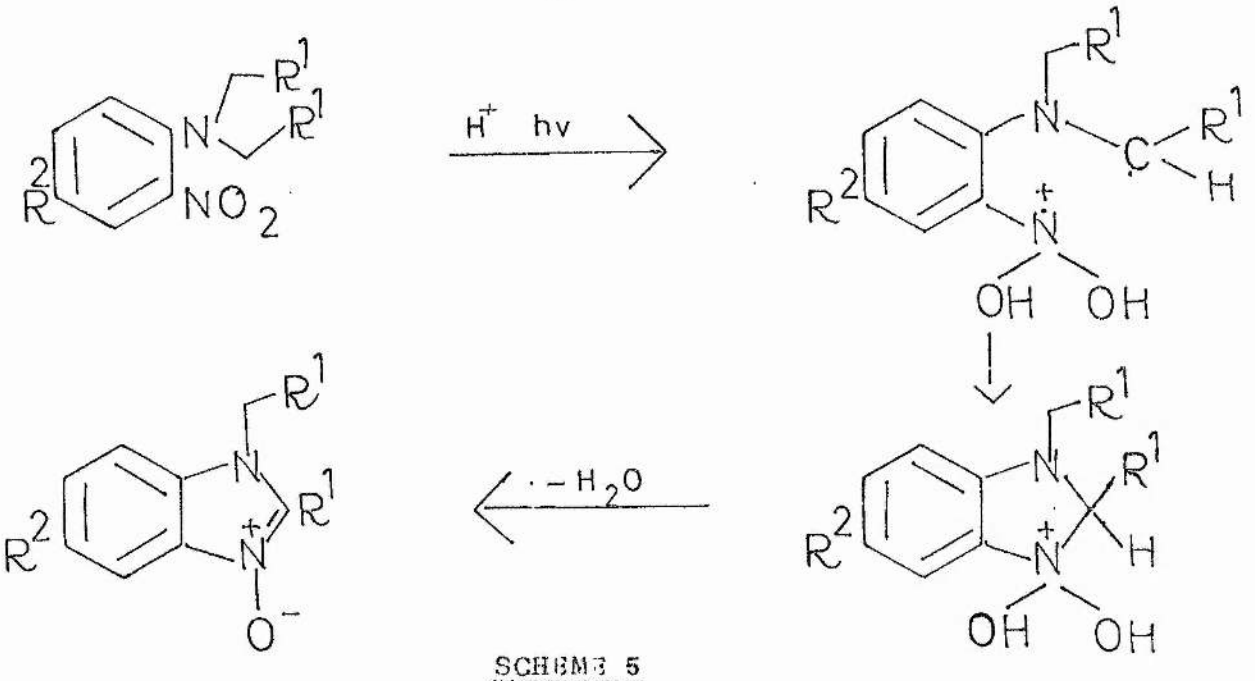
The photolysis of N-2,4-dinitrophenyl derivatives (44) of α-amino-acids in aqueous solution may proceed by two routes depending on the pH of the solution. Russell, Neadle and Pollitt[27] demonstrated that the nature of the products is also dependent on the pH, low pH favouring the formation of a 5-nitrobenzimidazole-3-oxide (45), while reaction at higher pH gave the 2-nitroso-4-nitroaniline (46),



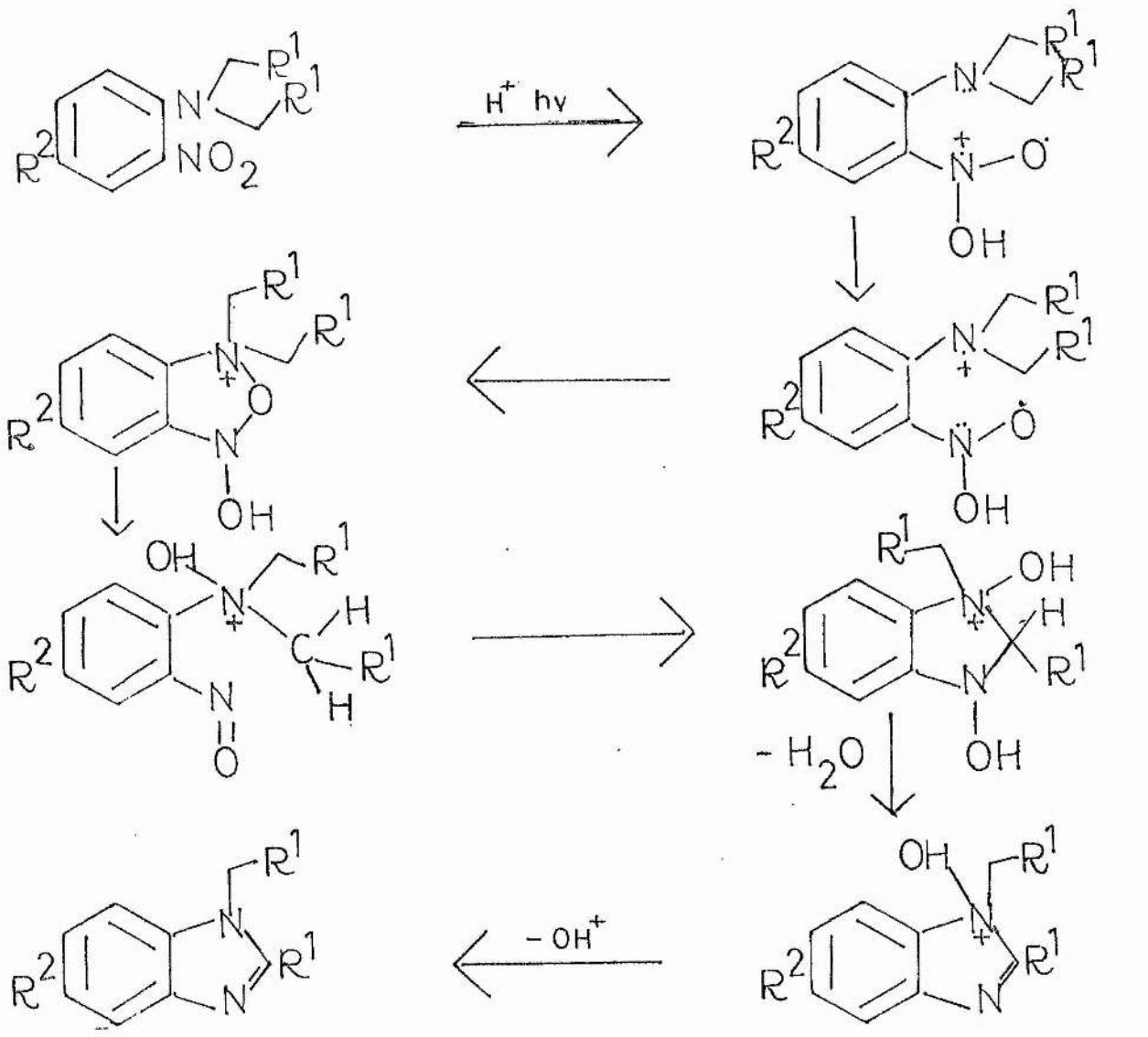
(41)

(40)

SCHEME 4

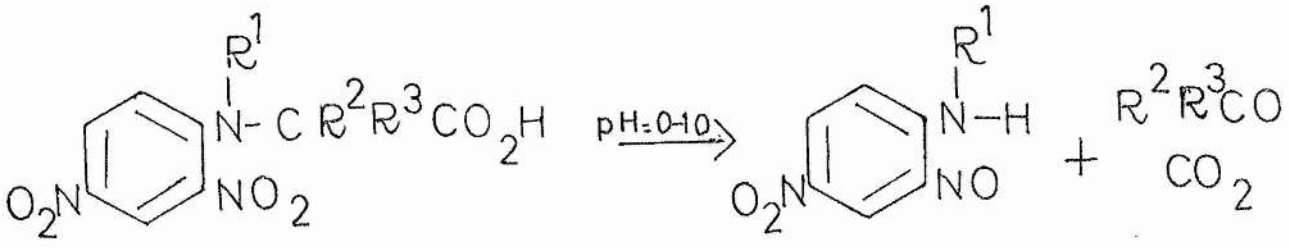


SCHEME 5



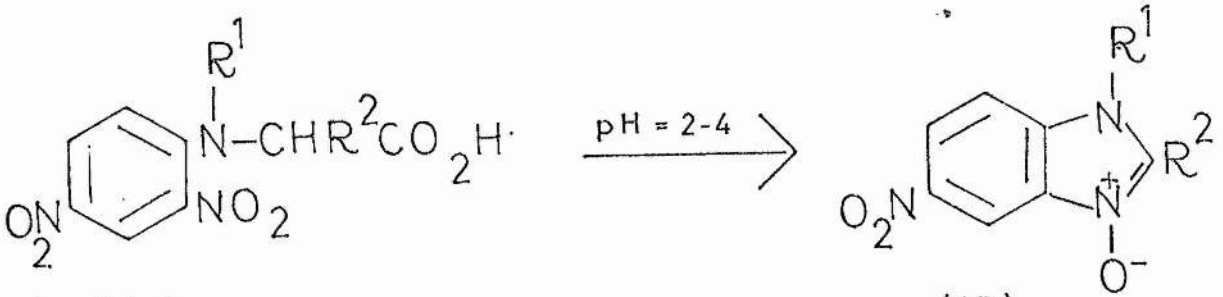
SCHEME 6

and the aldehyde or ketone with one carbon atom less than the parent amino acid.



(44) (46)

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

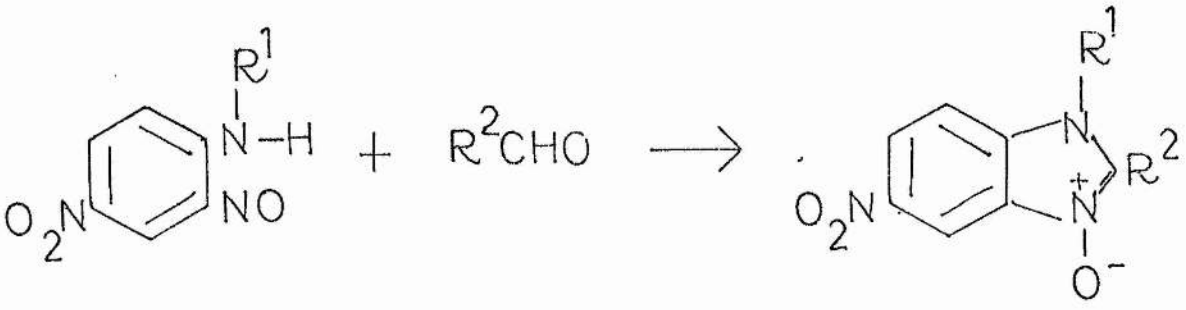


(44) (45)

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

Although formation of the nitroso compound (46) still occurs when neither R^2 nor R^3 is a hydrogen atom, R^3 must be a hydrogen atom for the formation of the benzimidazole-N-oxide (45).

The nitroso anilines (46) have been shown to react with aldehydes in the presence of acid to give benzimidazole-N-oxides[28].



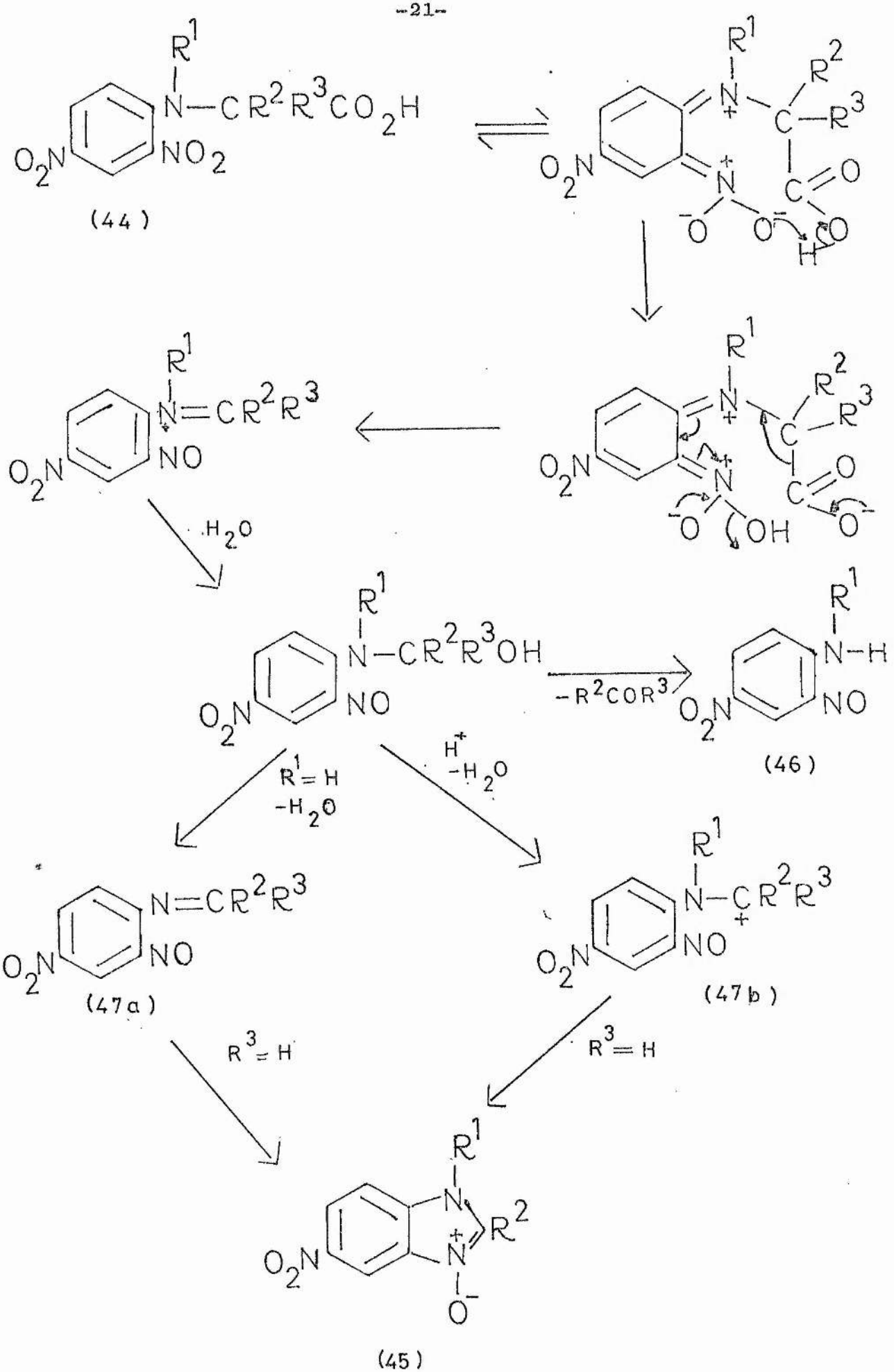
(46) (45)

R^1 = H ; R^2 = C_6H_5, p-ClC_6H_4, p-CNC_6H_4

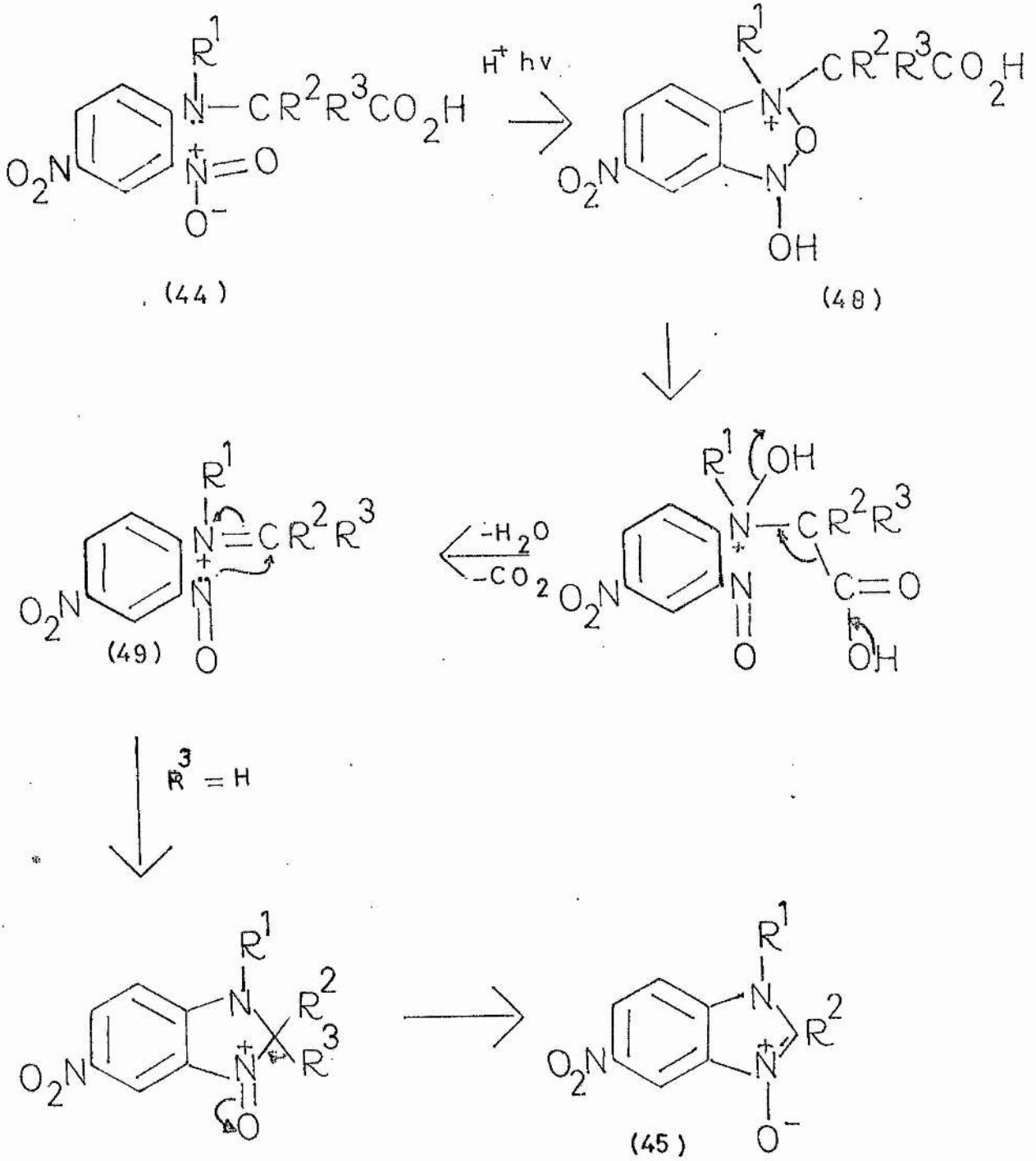
A reaction mechanism is shown in Scheme 7 to explain the above facts.

In Scheme 7, nitroso type intermediates, (47a) and (47b) are again postulated in the formation of benzimidazole-N-oxides. However, in a later publication[29], Meth-Cohn argued that the reaction went via Scheme 8, involving a furoxan intermediate (48) in a similar fashion to reactions already described (see page 16).

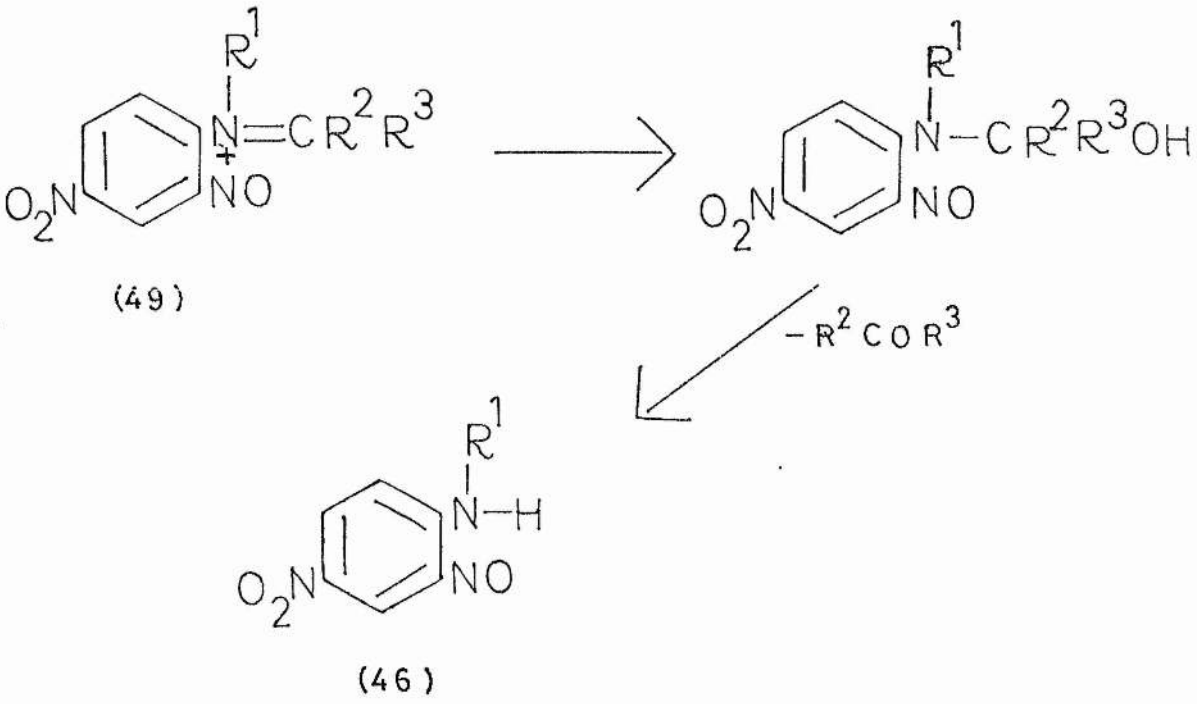
In Scheme 8, the furoxan intermediate (48), rearranges to the immonium ion (49), which is a reasonable precursor for (45) and for (46).



SCHEME 7



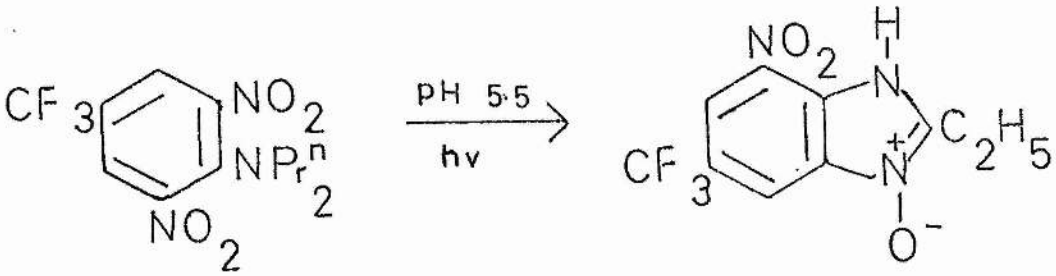
SCHEME 8



(49)

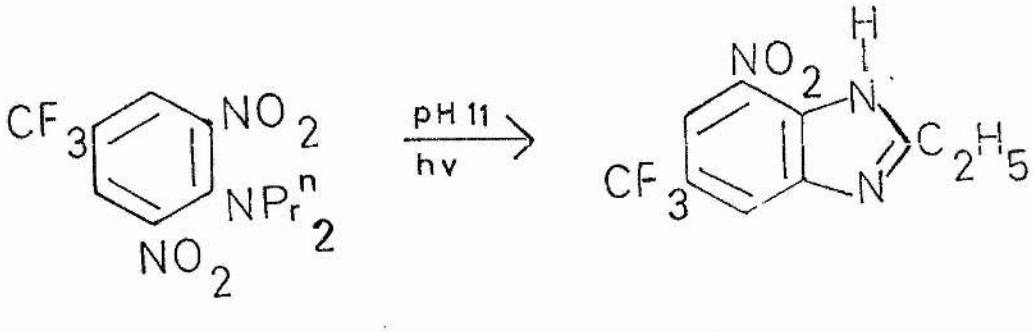
(46)

The photodecomposition of trifluoralin[30] (50) in 10% methanol at a pH of 5.5 gave as one of its products 2-ethyl-7-nitro-5-trifluoromethylbenzimidazole-3-oxide (51). At higher pH, the main product of the decomposition was 2-ethyl-7-nitro-5-trifluoromethylbenzimidazole (52). (51) was also obtained by the decomposition of trifluoroalin in water or aqueous methanol when exposed to sunlight. (51) was degraded to the benzimidazole (52) by heating or by further treatment with radiation[31].



(50) (51)

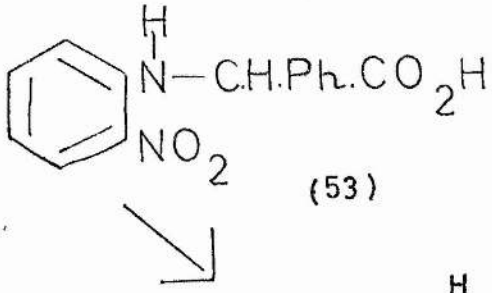
Pr = $CH_2CH_2CH_3$



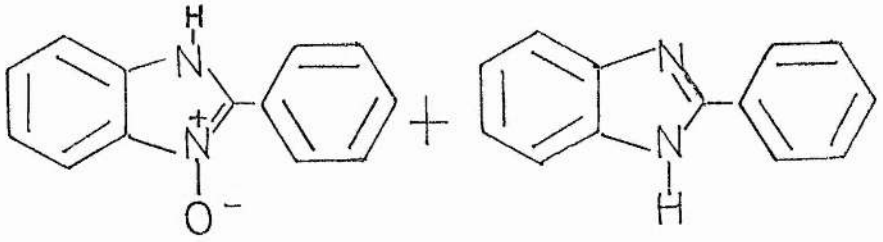
(50) (52)

Thermal Cyclisations

The thermal decomposition of N-(o-nitrophenyl)-α-aminophenylacetic acid (53) gave 2-phenylbenzimidazole-3-oxide (54), (30%) and 2-phenylbenzimidazole (55), (40%)[32].



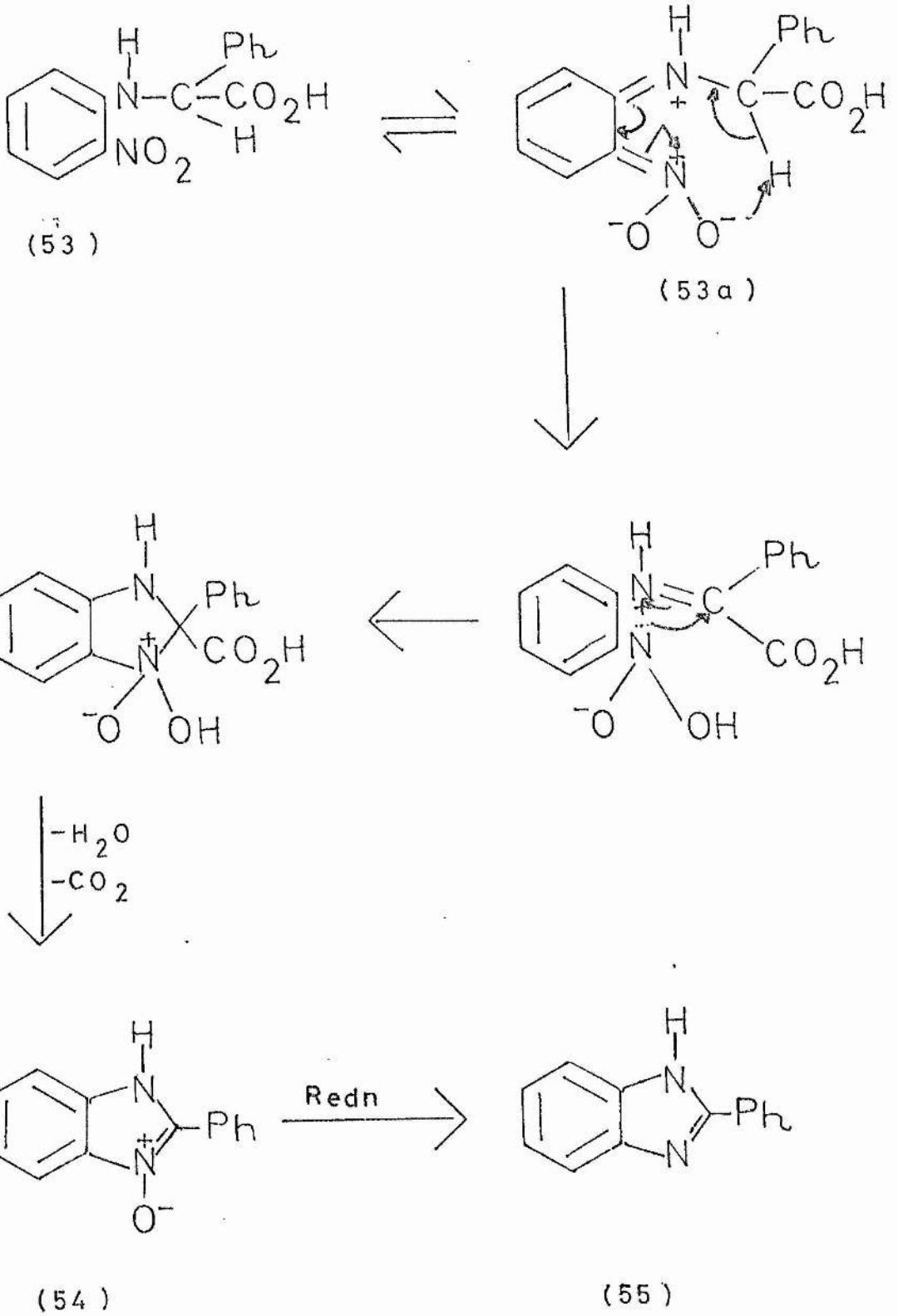
(53)



(54) (55)

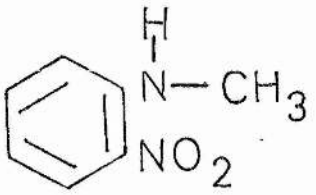
This work was carried out in order to try to clear up the mechanistic disagreement between Meth-Cohn[29] and Neadle and Pollitt[30,31] for the ring closure reactions of N-2,4-dinitrophenyl derivatives of α amino acids (see page 16). In the case of the cyclisations of (53) to (54) and (55), the mechanism proposed (Scheme 9) was similar to that of Neadle and Pollitt. However, it must be stressed that the reaction conditions for the two pieces of work were dissimilar.

The possibility of initial decarboxylation of (53) was eliminated since N-methyl-o-nitroaniline (56) was recovered quantitatively when subjected to the same reaction conditions for the decomposition of o-nitrophenylglycine (57). Evidently, the replacement of H by CO_2H facilities initial nucleophilic attack as depicted by (53a). Decarboxylation can then occur at any subsequent step in the

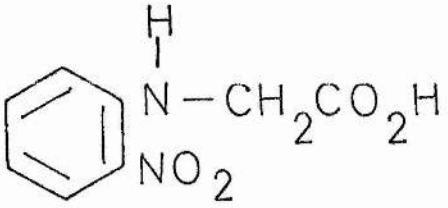


SCH 3MB 9

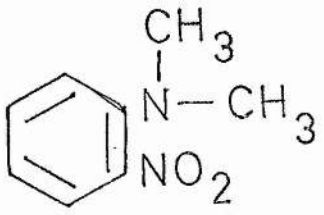
process.



(56)

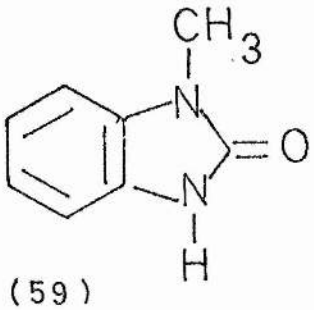


(57)

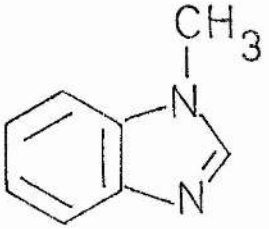


(58)

N,N, dimethyl-o-nitroaniline (58) was however converted after two hours at 240°C into a mixture of N-methylbenzimidazolone (59), N-methylbenzimidazole (60) and benzimidazole, (With reference to product (59), it is worth noting that benzimidazolones are really obtainable from benzimidazole-N-oxides, either by thermal rearrangement or hydrolytically[33]) and it is quite likely that these conditions are too severe for isolation of the N-oxides.



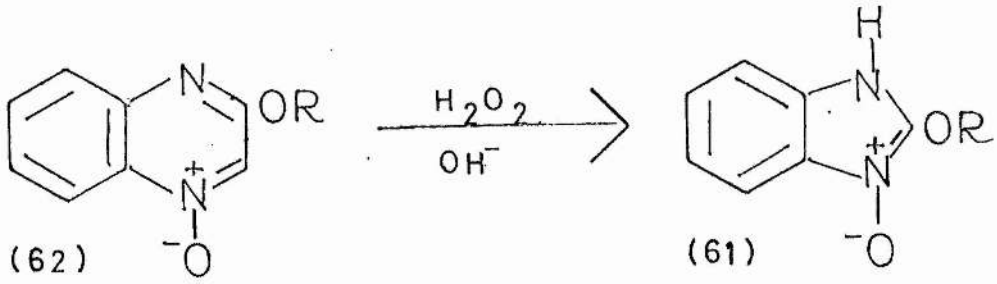
(59)



(60)

Oxidation reactions

Hayashi and Iijima[34a] obtained 2-alkoxybenzimidazole-N-oxides (61) by the oxidation of 3-alkoxyquinoxaline-1-oxides (62) with hydrogen peroxide

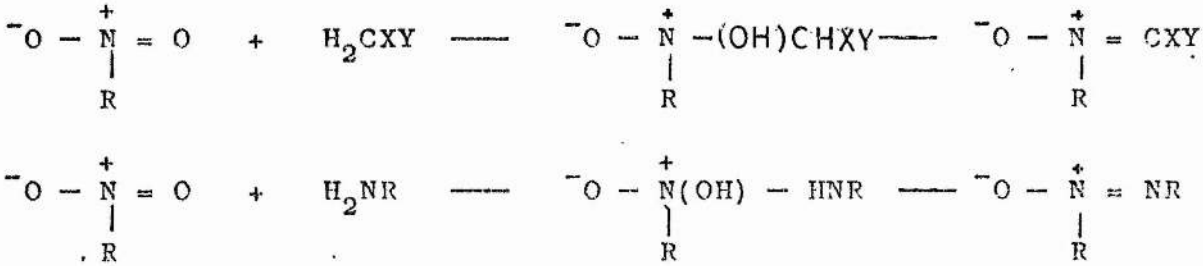


This mechanism is discussed in more detail in Chapter 3.

Base Catalysed Cyclisations

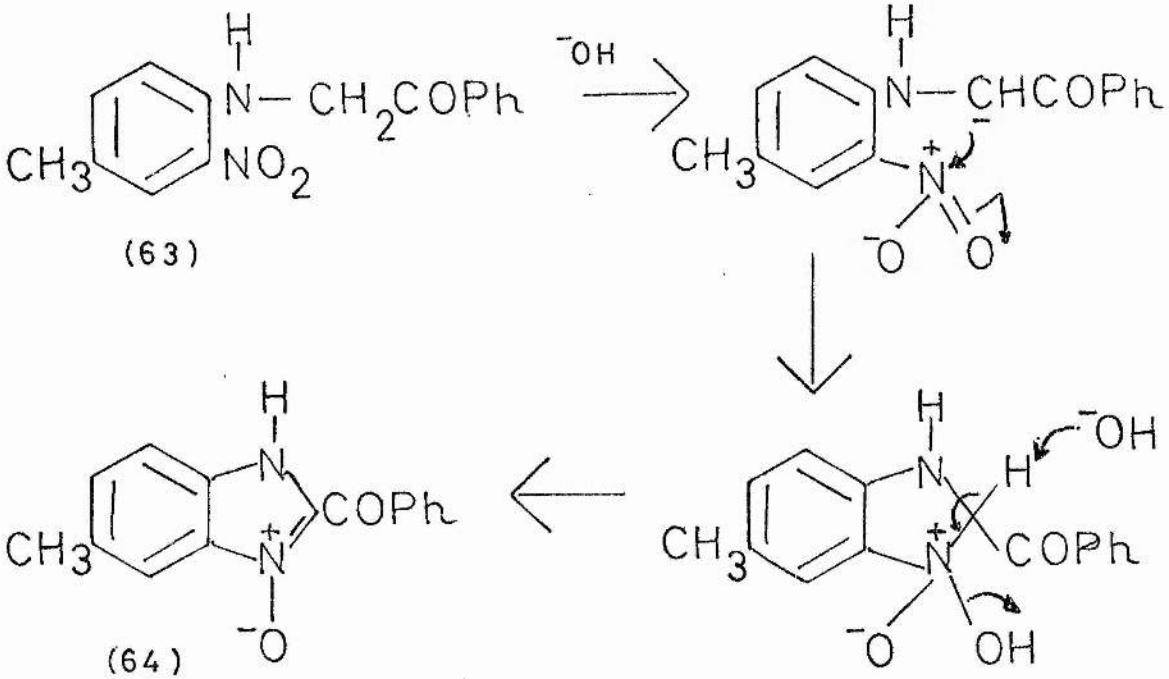
Base catalysed cyclisations have been purposely left until last for discussion as the bulk of chapters 2 and 3 in this thesis are concerned with them.

The majority of base catalysed cyclisations of o-nitroaniline derivatives may be simply described by considering the nitro group as providing an electrophilic centre for additive reactions of the aldol condensation type, as shown below.



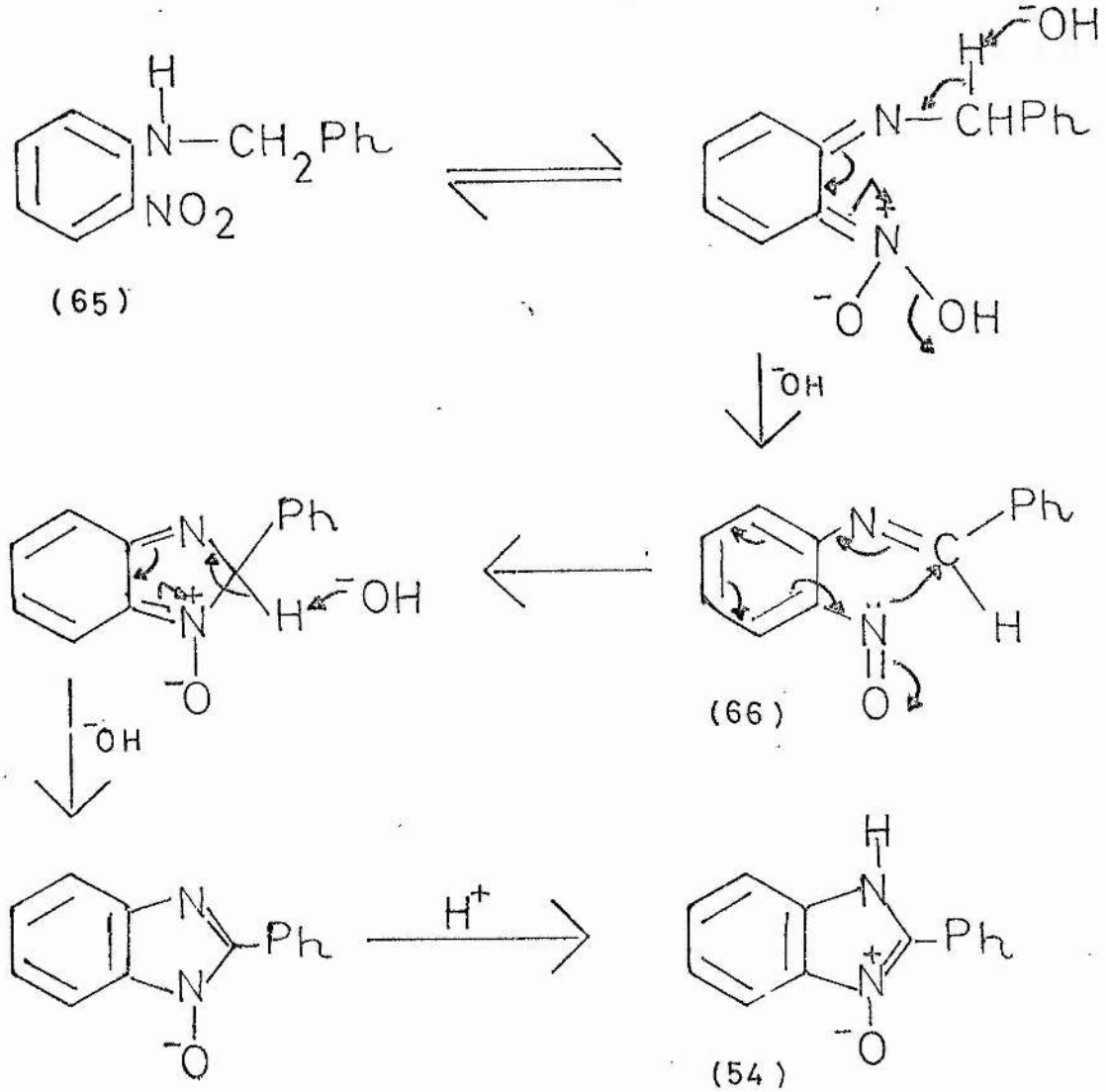
The reactive nucleophilic centre is in a side chain ortho to the nitro group, and in a position sterically favourable for attack on the nitro group. The situation, however, may be complicated by the possibility of tautomerism and rearrangement within the conjugated system, giving rise to aci nitro and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

An example of the 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 (63) with alkali to give 2-benzoyl-5-methylbenzimidazole-3-oxide[35] (64). The reaction is thought to go via Scheme 10.

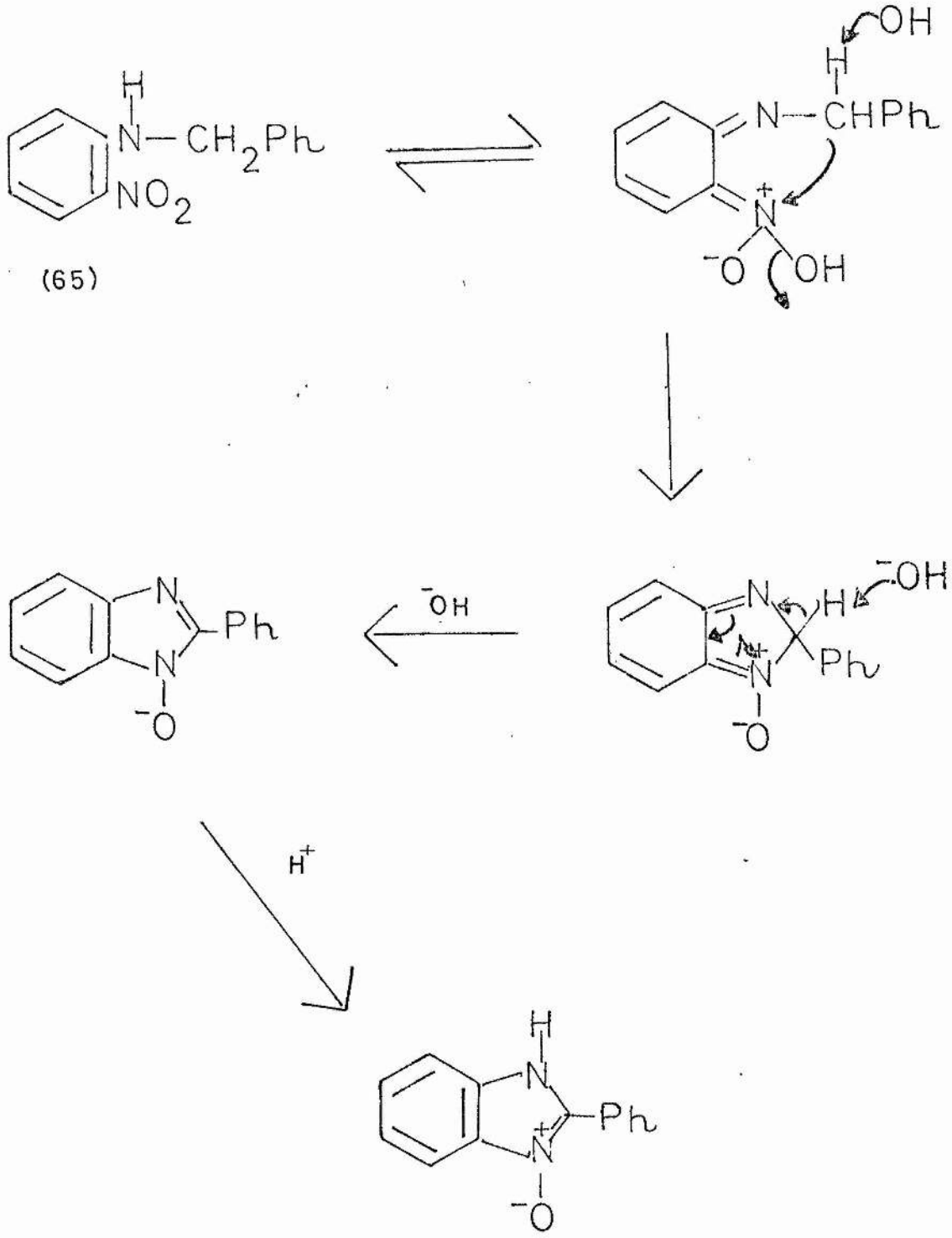


SCHEME 10

The related cyclisation of N-benzyl-o-nitroaniline (65) to 2-phenylbenzimidazole-3-oxide (54) with sodium hydroxide[11] 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 appears to be a facilitating factor in the cyclisation, since N-benzyl-N-methyl-o-nitroaniline, which does not possess an α -hydrogen, does not cyclise under similar conditions, or under a variety of basic conditions investigated[36]. Two possible routes involving transfer of this α hydrogen prior to cyclisation are shown in Schemes 11 and 12.



SCHEME 11



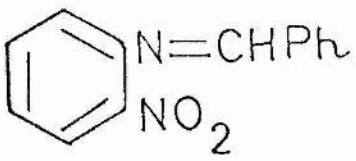
(65)

(54)

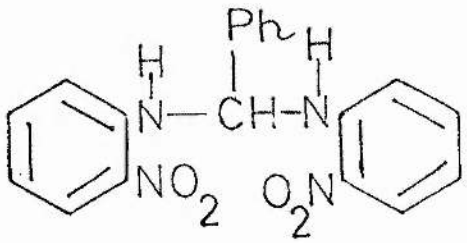
SCHEME 12

In Schemes 11 and 12 there are further examples of an aci nitro type intermediate as well as a nitroso intermediate (66) Scheme 11.)

Schiff bases can also be used as starting materials in the formation of benzimidazole-N-oxides. For example, Stacy et al[11] obtained (54) by heating N-benzylidene-o-nitroaniline (67) or N,N-benzylidenedi(o-nitroaniline) (68) with benzaldehyde in toluene.



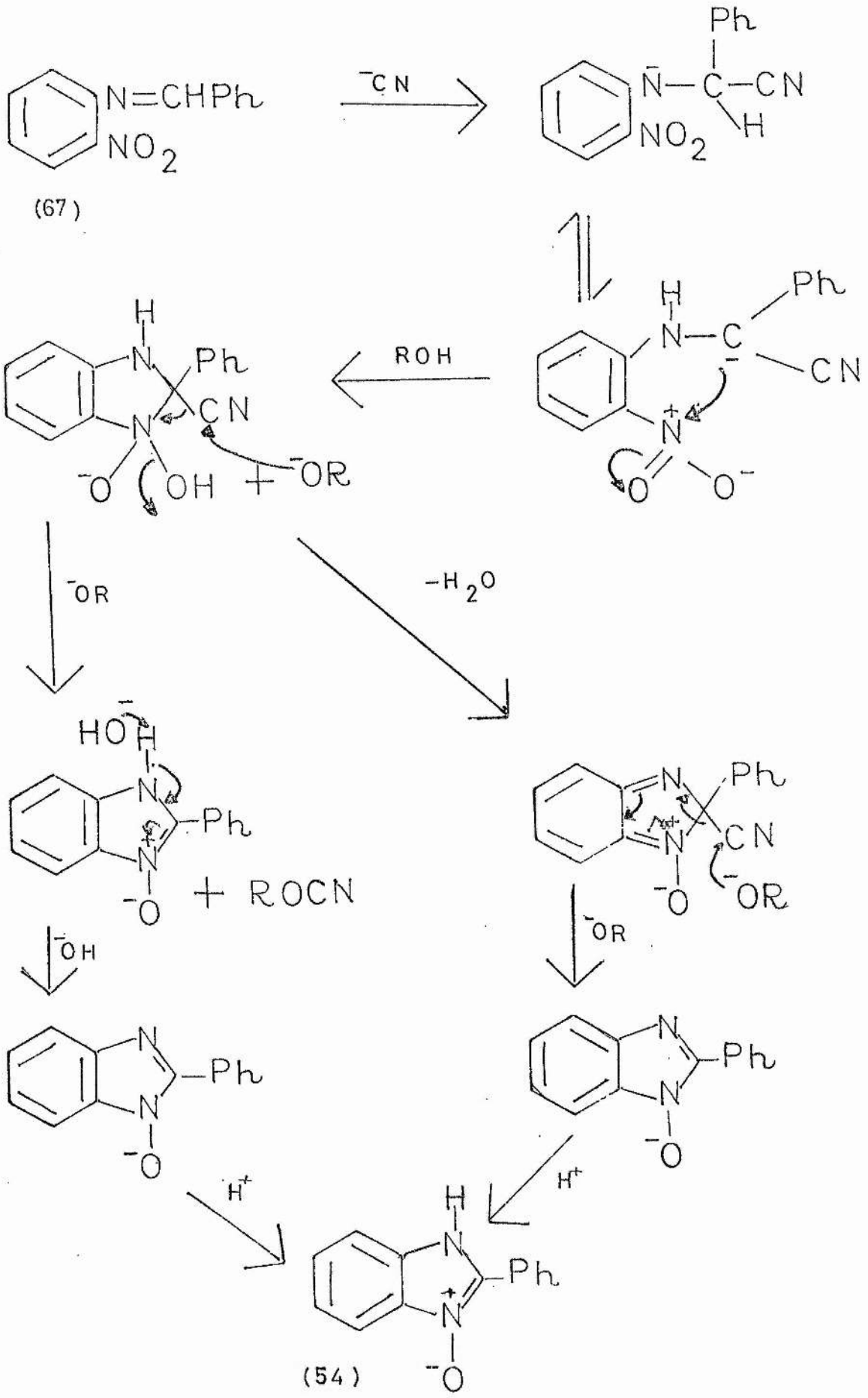
(67)



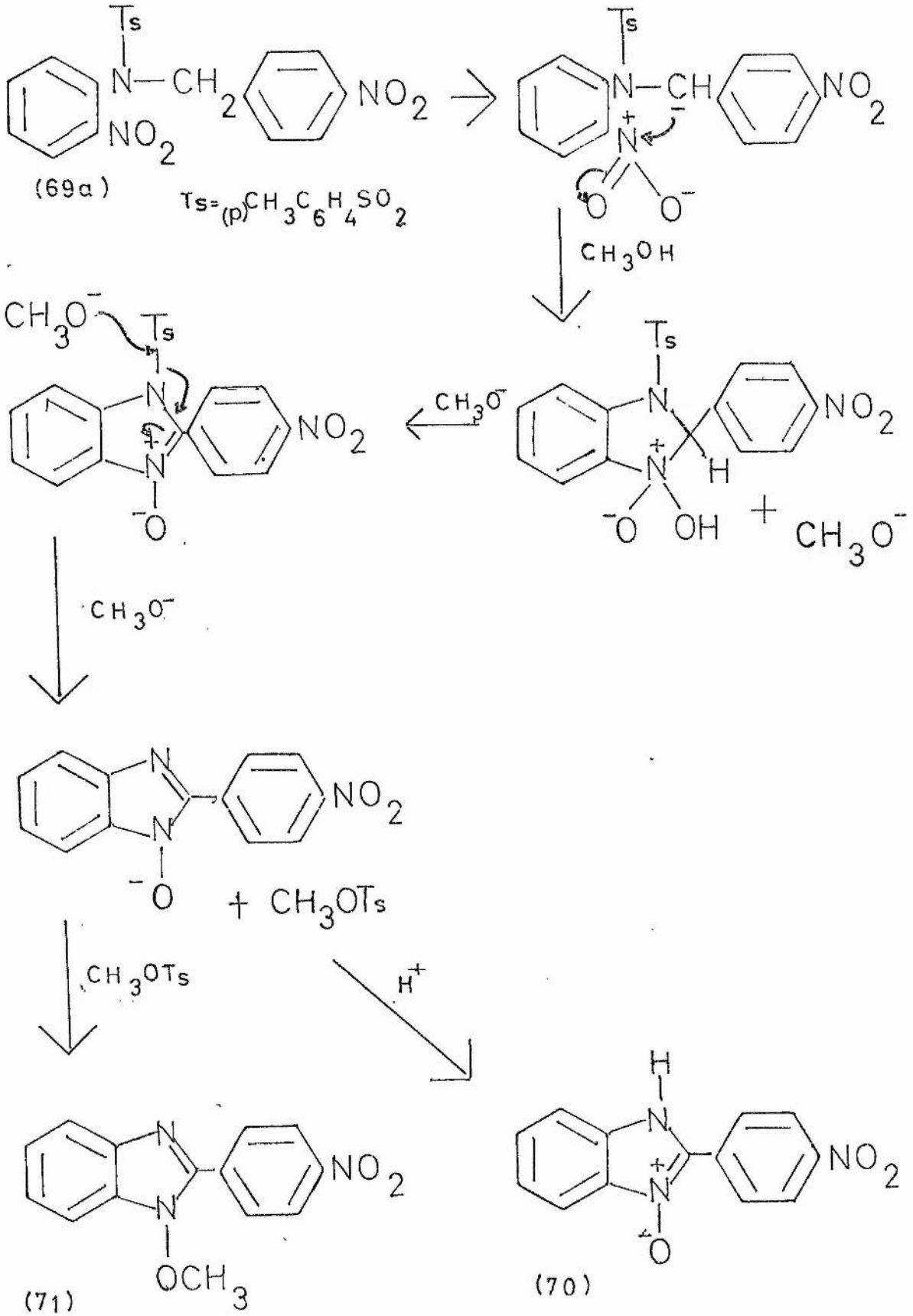
(68)

Marshall and Smith[37] showed that the reaction of (67) with potassium cyanide in methanol also yielded (54). This reaction, which is thought to go via Scheme 13, was extended by Johnston and Smith[38] to obtain various 2-substituted-benzimidazole-3-oxides.

The reaction of N-p-nitrobenzyl-N-p-tolylsulphonyl-o-nitroaniline (69a) with sodium methoxide in methanol was reported by McNab and Smith[39] to give 2-p-nitrophenylbenzimidazole-3-oxide (70) and 1-methoxy-2-p-nitrophenylbenzimidazole (71). The proposed reaction mechanism is shown in Scheme 14.


N=CHPh
NO2
(67)
⁻CN
Ph
N⁻—C—CN
NO2
H
ROH
H
N
Ph
CN
OH
⁻OR
⁻OR
-H2O
HO⁻
H
Ph
+ ROCN
⁻OH
CN
⁻OR
Ph
H+
H+
Ph
(54)

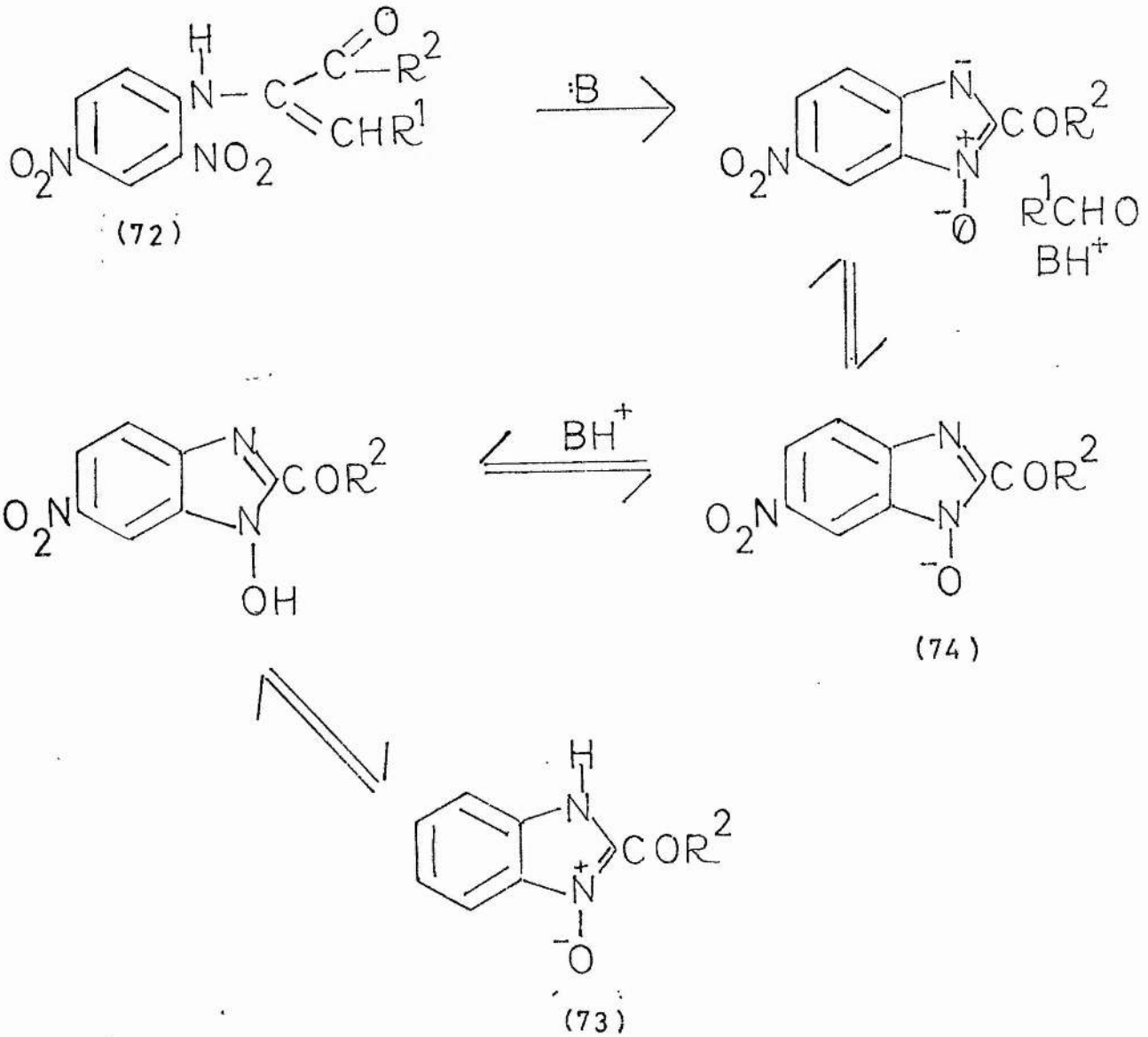
SCHEME 13


Ts
N—CH2
NO2
NO2
(69a)
Ts=(p)CH3C6H4SO2
CH3OH
CH3O⁻
CH3O⁻
CH3O⁻
OH
+ CH3O⁻
+ CH3OTs
CH3OTs
H+
OCH3
(71)
(70)

SCHEME 14

This mechanism is discussed in much greater detail in Chapter 2.

An interesting reaction is that described by Luetzow and Vercellotti[40], viz the cyclisation in basic solutions of α -(2,4-dinitrophenylamino)-α,β-unsaturated acyl derivatives (72, R^1=H,Me,Ph, R^2=CO_2CH_3, NHP_r^n) to the corresponding benzimidazole-N-oxides (73) by way of their anions (74).

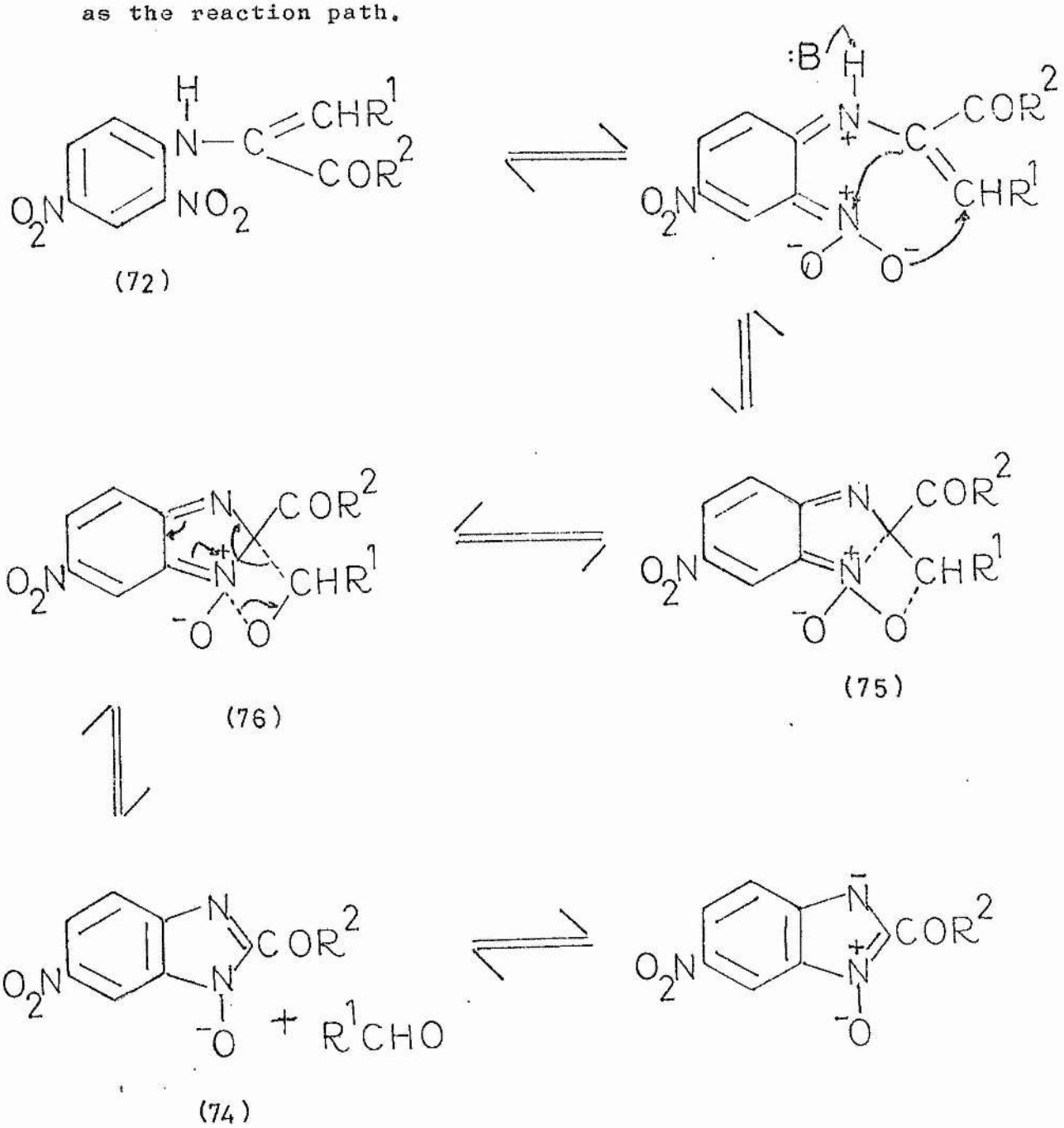


(72)

(74)

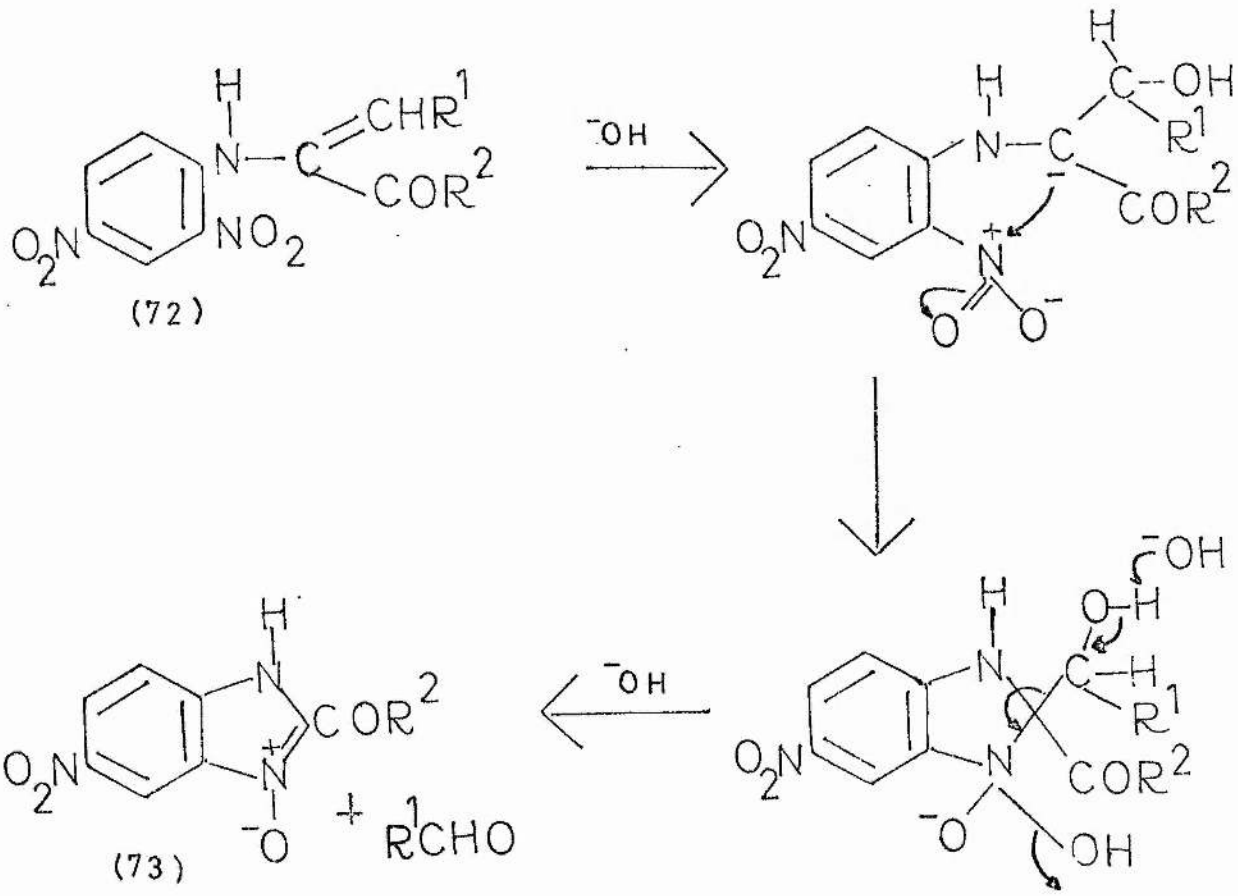
(73)

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



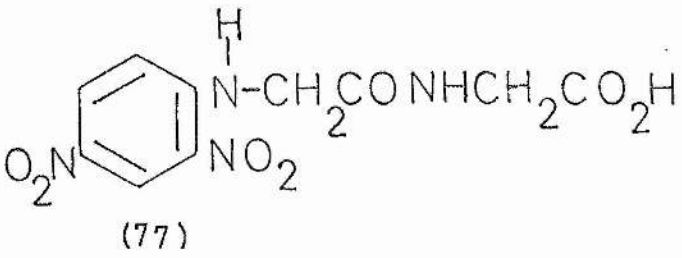
SCHEME 15

The reason for this mechanism was that no intermediates were discernable, hence the proposed four-centred transition state (75) and (76). However, a simple Michael type addition can account for the observed products, and no intermediates would be expected to be isolable from this reaction either. (Scheme 16.) This Michael type addition involves the formation of a stabilised carbanion at a position from which attack on the nitro group is to be expected.

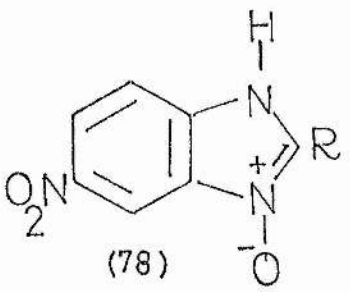


SCHEME 16

More recently the cyclisation of a number of peptides[41] containing a terminal 2,4-dinitrophenylglycine moiety (77) has been effected under mildly basic conditions (i.e. trimethyl ammonium carbonate buffer, pH 8.3) to give the appropriate N-oxide (78).



(77)

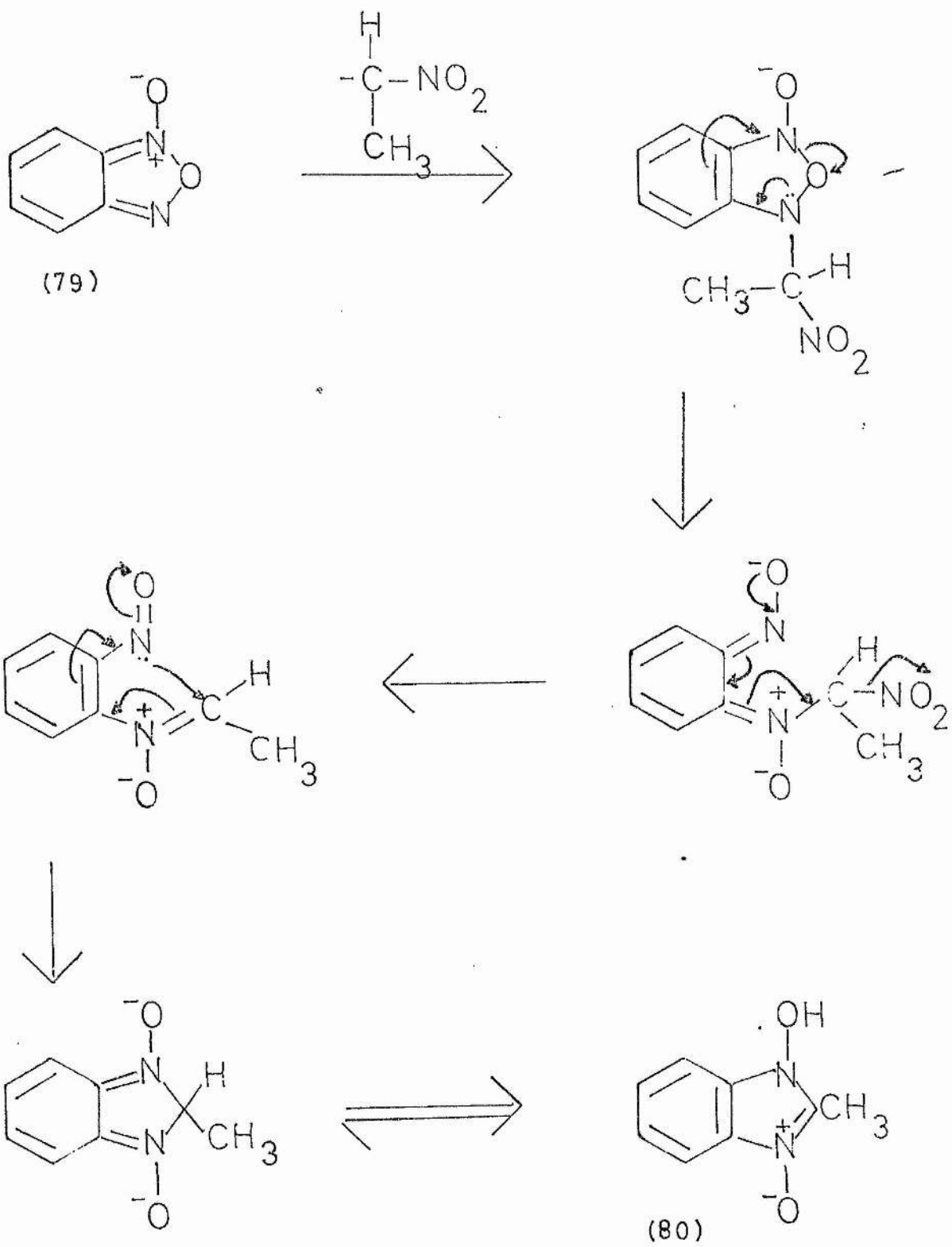


(78)

$R = CONHCH_2CO_2H$

Not all base catalysed cyclisations rely on a nucleophilic centre in a side chain ortho to the nitro group. Issidorides et al[42] reported that the base catalysed reaction of benzofurazan-1-oxide (79) with primary nitroalkanes in tetrahydrofuran gave 2-substituted-1 H-benzimidazole-3-oxides (80). Scheme 17 shows the reaction mechanism. Latham, Suschitzky and Meth-Cohn published similar results a few months later[43].

In more recent base catalysed cyclisations, Bochis[44] reacted 1-chloro-2,4-dinitrobenzene (81) with 4-(aminomethyl)-thiazole (82) in the presence of base and obtained 2-thiazolyl-6-nitrobenzimidazole-3-oxide (83) and Seng and Ley[45] synthesised 2-carboxybenzimidazole-3-oxide (84) by condensing benzofurazan (79) with barbituric acid (85) in the

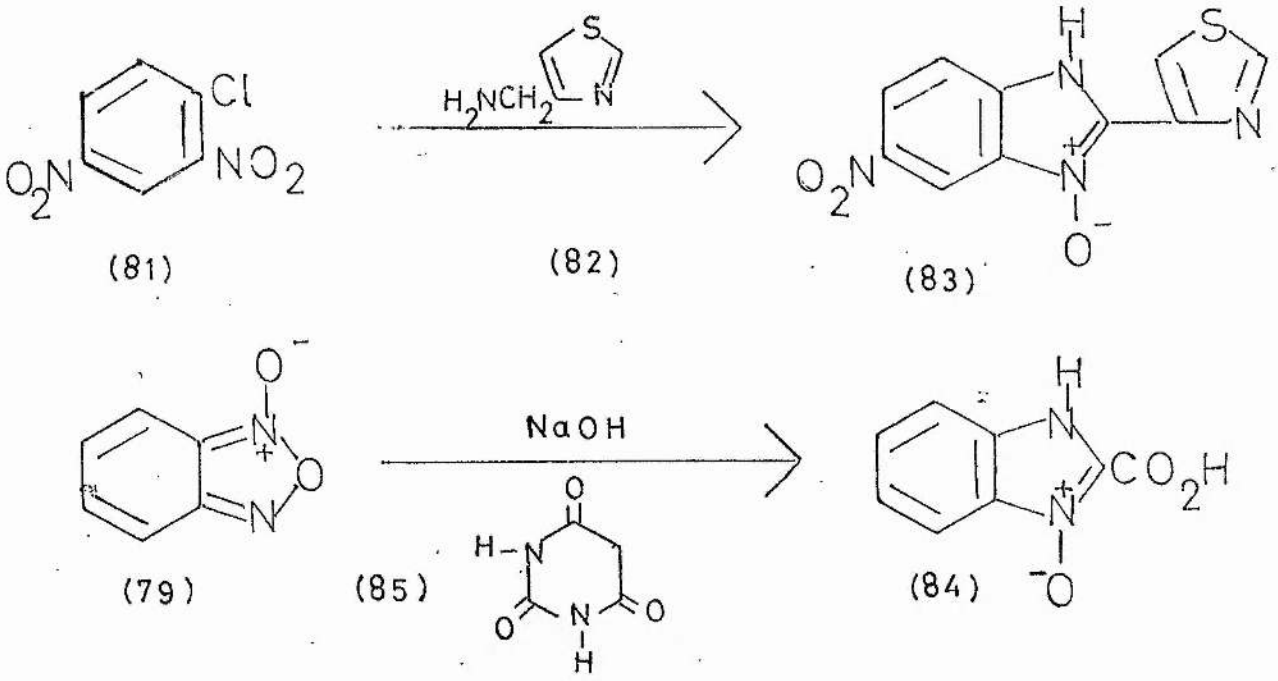


(79)

(80)

SCHEME 17

presence of sodium hydroxide. On heating, (84) was decarboxylated to benzimidazole-3-oxide (2a)



A brief summary of some of the more general properties of benzimidazole-N-oxides follows.

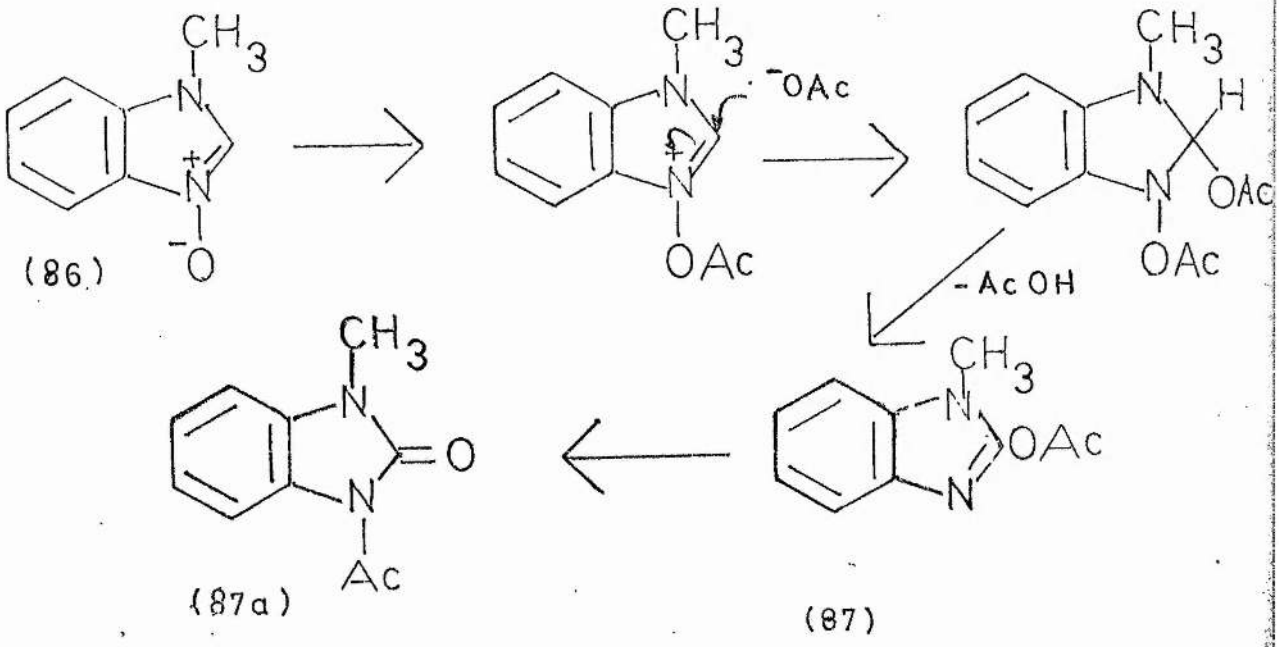
Benzimidazole-N-oxide itself is soluble in water, alcohol and ethyl acetate, but insoluble in non-polar solvents. The solubility of substituted N-oxides is dependent upon the nature of the substituents.

Not a great deal is known about the general spectroscopic properties of benzimidazole-N-oxides. However, in mass spectrometry benzimidazole-3-oxides often show both strong (M−16) and (M−17) peaks. The u.v. spectrum of the N-oxides is dependent upon the solvent and the overall nature of the molecule. For example, although Takahashi and Kano[5] found that the u.v.spectra of benzimidazole-3-oxide were dissimilar

in aqueous and ethanolic solutions, Stacy et al[10] observed no difference in the spectra of 2-phenylbenzimidazole-3-oxide under the same conditions. Katritzky et al[45] concluded that, in non-polar solvents the hydroxy tautomeric form predominates with the N—H form existing in increasing amounts as the polarity of the solvent is increased.

In the solid state it is thought that the N-oxides exist as strongly hydrogen bonded aggregates which makes distinction between the two tautomeric forms difficult.

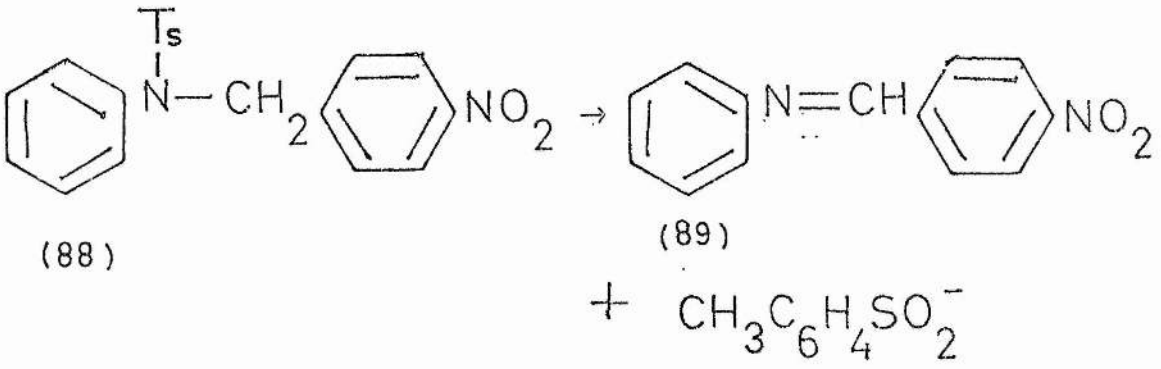
Acylation and alkylation are two of the most important reactions of heteroaromatic N-oxides. It has been found that benzimidazole-N-oxides prefer to alkylate or acylate on oxygen[36,45,59]. However, the reaction of 1-methyl-benzimidazole-3-oxide (86) with acetic anhydride gave a product the analytical value of which corresponded to 1-methyl-2-acetoxybenzimidazole (87). But as in the case of benzimidazole-N-oxide[4], there is the possibility that the product may 1-methyl-3-acetyl-benzimidazolone[33b] (87a).



CHAPTER 2

The cyclisation of N-Acylated derivatives of N-benzyl and N-p-nitrobenzyl-o-nitroaniline

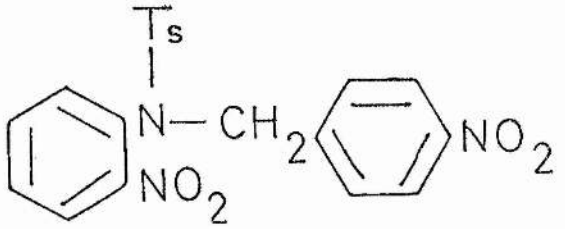
N-Arylsulphonyl derivatives of secondary amines which possess an acidic hydrogen ∝ - to the nitrogen are known to undergo elimination reactions when treated with base[48,49], the products being azomethines and the arenesulphinate ion. For example, N-p-nitrobenzyl-N-p-tolylsulphonyl aniline (88) gave N-p-nitrobenzylideneaniline (89) by reaction with sodium methoxide in toluene. The same products were also obtained by reaction of (88) with sodium methoxide in methanol[39].



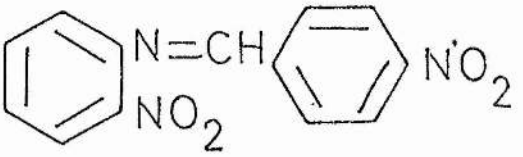
(88) (89)

When the o-nitro derivative of (88) i.e. N-p-nitrobenzyl-N-p-tolylsulphonyl-o-nitroaniline (69a) was reacted with sodium methoxide in methanol (c.f. Chapter 1, p32), the expected elimination product N-p-nitrobenzylidene-o-nitroaniline (90) was not formed, neither were its o-nitroaniline (91: $X=NO_2$) nor methanol adducts (92). (These adducts which are formed from (90) by the addition of one mole of o-nitroaniline or methanol respectively were more likely to be

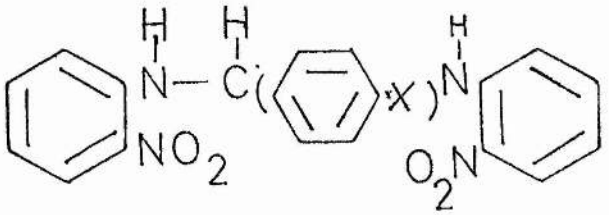
isolated from the reaction than (90) due to the high reactivity of the latter [37]. Instead 2-p-nitrophenylbenzimidazole-3-oxide (70) and 1-methoxy-2-p-nitrophenylbenzimidazole (71) were isolated[39].



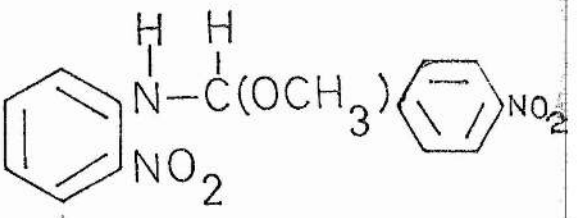
(69a)



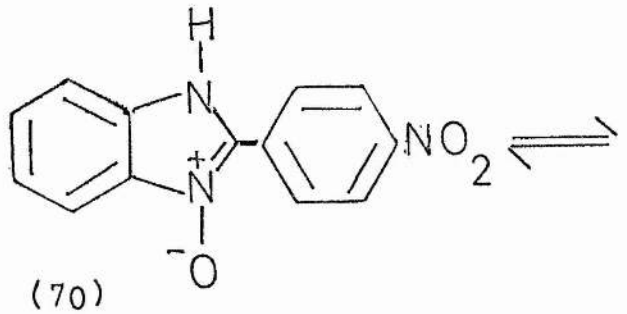
(90)



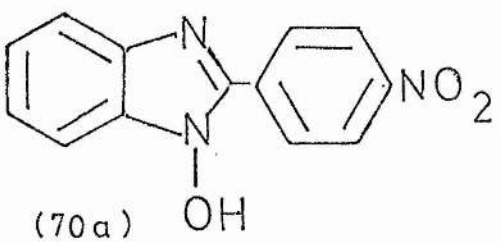
(91) X=NO2



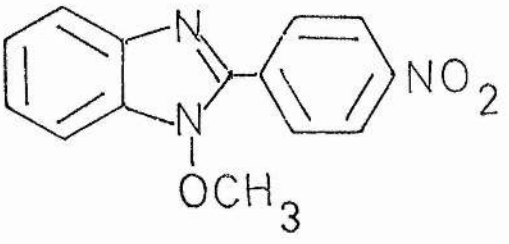
(92)



(70)



(70a)



(71)

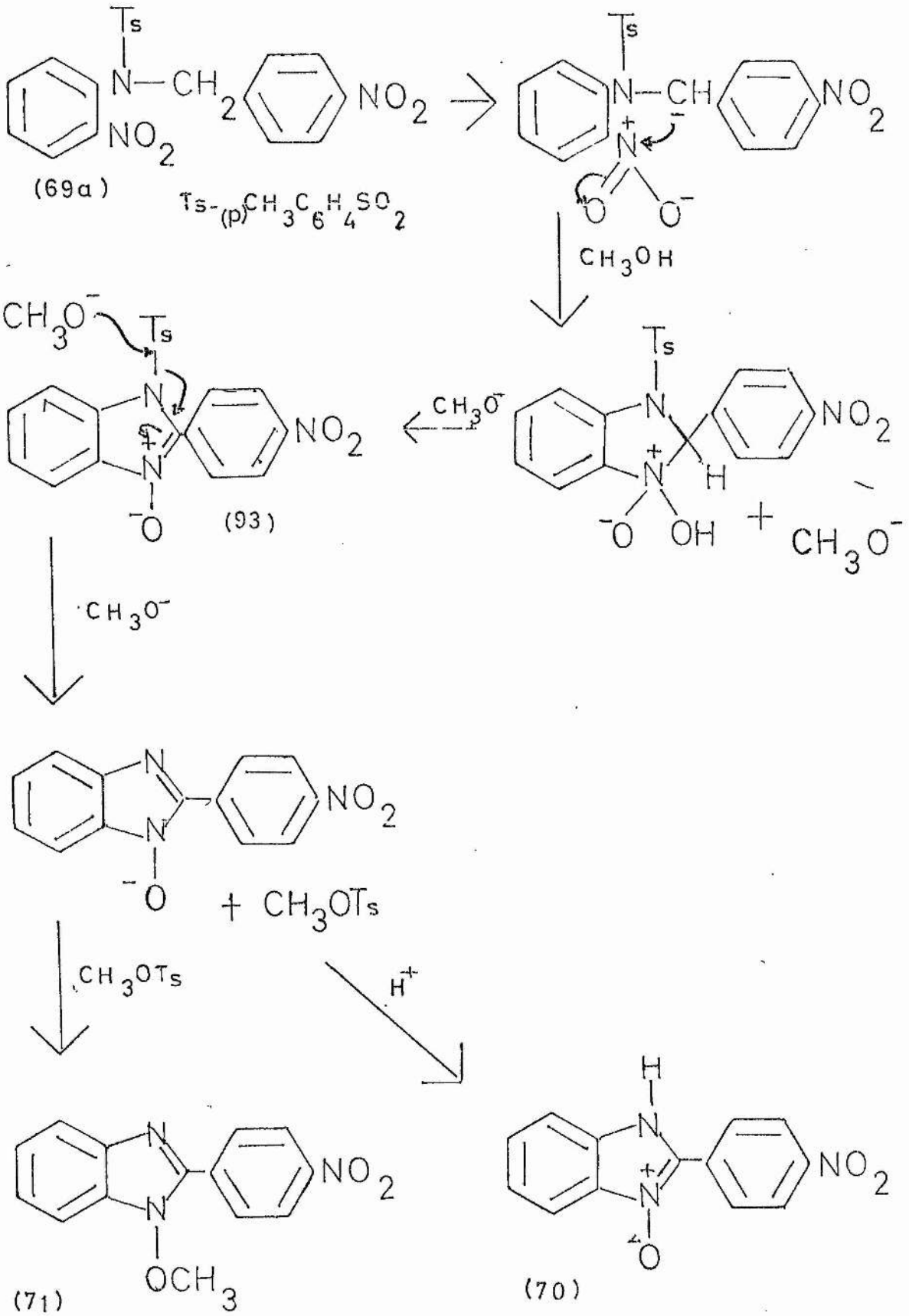
Although structures (70) and (70a) are tautomeric, the position of the equilibrium in this series has never been established[5,36,45].

The proposed mechanism, Scheme 14, for the cyclisation of (69a) to (70) and (71) envisaged a base-catalysed condensation between the methylene group and the nitro group ortho to the amidic nitrogen followed by loss of water to give 2-p-nitrophenyl-1-p-tolylsulphonylbenzimidazole-3-oxide (93). Elimination of the p-tolylsulphonyl group from the intermediate (93) by the methoxide ion gave (70) and methyl toluene-p-sulphonate, and hence (71) by in situ methylation of (70). Evidence in support of this proposed mechanism was provided by the following experimental observations[39].

Toluene-p-sulphonate ions were detected in the reaction mixture by converting them into toluene-p-sulphonamide by reaction with phosphorus pentachloride and ammonia.

When two molar equivalents of methoxide instead of one were used in the reaction, the yield of (70) increased from 29% to 38% and that of (71) fell from 23% to 10%. This decrease in the yield of (71) was due presumably to the excess methoxide ion and the anion of (70) undergoing competitive methylation by the methyl toluene-p-sulphonate formed in the reaction.

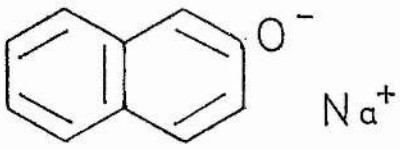
On addition of methyl toluene-p-sulphonate to the reaction mixture prior to work up, the N-methoxy compound


Ts
N—CH2
NO2
NO2
(69a)
Ts-(p)CH3C6H4SO2
CH3OH
CH3O⁻
(93)
CH3O⁻
OH
+ CH3O⁻
+ CH3OTs
CH3OTs
H+
OCH3
(71)
(70)

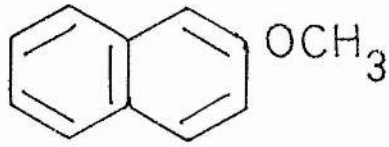
SCHEME 14

(71) was the only product isolated.

When the cyclisation was carried out in the presence of 1 molar equivalent of sodium-2-naphtholate (94), the naphtholate ion underwent methylation in preference to the anion of (70), and 2-methoxynaphthalene (95) was formed instead of the N-methoxybenzimidazole (71).



(94)



(95)

Finally, further evidence that suggested that methyl toluene-p-sulphonate was the methylating agent involved in these cyclisations came when it was shown that the reaction of an authentic sample of the anion of (70) with methyl toluene-p-sulphonate produced (71) in 62% yield.

There was however one other obvious mechanism (shown in Scheme 18) that fitted the above facts. In this reaction pathway detosylation prece s cyclisation. McNab and Smith[39] were aware of this possibility but discounted it on the grounds that since N-benzyl- and N-methyl-p-tolylsulphonyl-o-nitroanilines, which lack the reactive methylene group of (69a) but have a similarly situated p-tolylsulphonyl group, are completely unreactive towards sodium methoxide in methanol, detosylation prior to cyclisation is unlikely. The evidence that was

put forward to rule out Scheme 18 was fairly circumstantial. Therefore it would be of great value if more conclusive evidence for or against either Schemes 14 or 18 could be obtained. The research involved in this, which is described in the first part of Chapter 2, fell into four main categories

i The synthesis of N-p-nitrobenzyl-o-nitroaniline (69b) and the study of its reaction with sodium methoxide in methanol

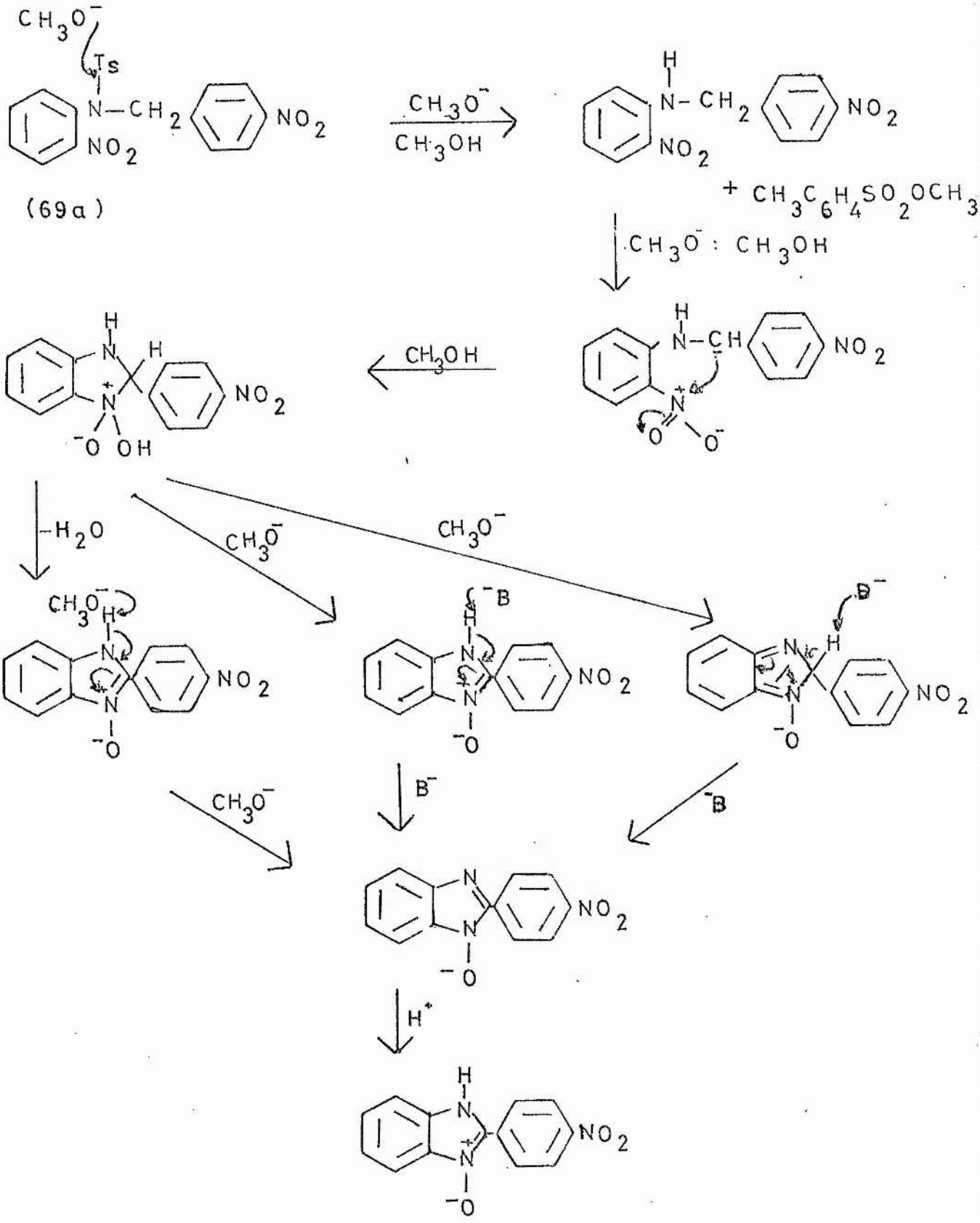
ii The attempted synthesis of the reaction intermediate (93) postulated in Scheme 14.

iii The attempted isolation of (93) from the reaction mixture.

iv The kinetics for the cyclisations of (69a) and (69b) to (70).

i. N-p-nitrobenzyl-o-nitroaniline (69b) was prepared by either detosylating N-p-nitrobenzyl-N-p-tolylsulphonyl-o-nitroaniline (69a) with a mixture of glacial acetic acid and concentrated sulphuric acid, or by heating o-nitroaniline with p-nitrobenzyl bromide in the presence of soda lime[50]. The reaction of (69b) with sodium methoxide in methanol gave (70) in a 37% yield.

ii. If the postulated reaction intermediate (93) could have been synthesised, then its reactions with sodium methoxide in methanol would have given an important indication as to which one of the Schemes 14 or 18 depicted the major reaction pathway for the cyclisation of (69a) → (70).

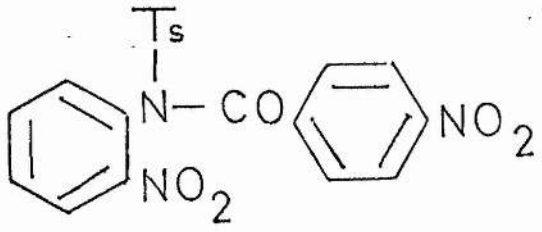


(69a)

(70)

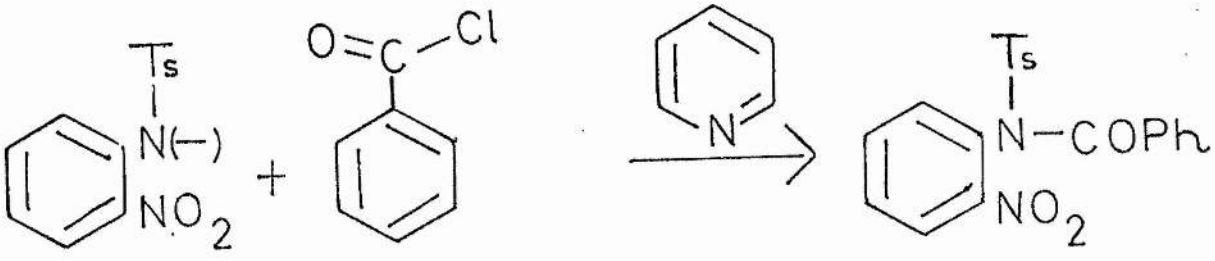
SCHEME 18

The seemingly obvious way to synthesise (93) would be by the selective reduction of N-p-nitrobenzoyl-N-p-tolylsulphonyl-o-nitroaniline (96) using ammonium sulphide.[5]



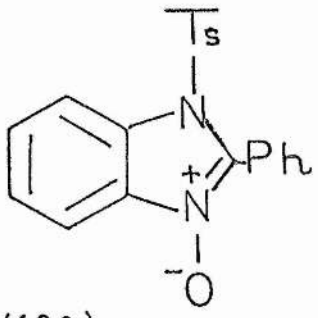
(96)

Unfortunately (96) was unobtainable by conventional means. (i.e. the reaction of the sodium salt of N-p-tolylsulphonyl-o-nitroaniline (98) with p-nitrobenzoyl chloride in pyridine yielded only starting material.) However N-benzoyl-N-p-tolyl-sulphonyl-o-nitroaniline (97) was readily obtainable from (98) and benzoyl chloride (99) in pyridine.



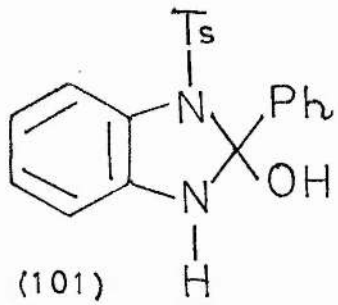
(98) (99) (97)

Reduction of (97) should hopefully have yielded 2-phenyl-1-p-tolylsulphonylbenzimidazole-3-oxide (100), a compound that would be expected to have similar properties to that of (93).



(100)

Unfortunately the reduction of (97) did not give (100) but gave instead what is thought to be 2-hydroxy-2-phenyl-3-p-tolylsulphonyl-1,3-benzimidazole (101).

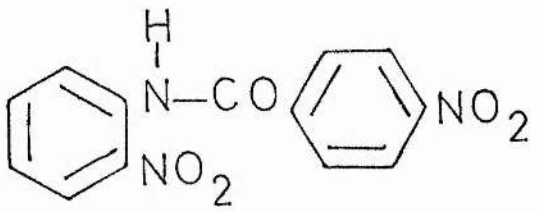


(101)

The structure of (101) was deduced from its spectroscopic properties. For example, the mass spectrum of (101) had a molecular ion peak of m/e 366; and $(M-155)^+$ corresponding to the loss of the p-tolylsulphonyl group was a major fragment. The infra-red spectrum showed the absence of the nitro and carbonyl groups but the presence of an N-H absorption, and the ^1H

nmr spectrum indicated the presence of three aromatic rings, and a methyl group. An N–H resonance was also visible.

iii. With the synthesis of (93) having been unsuccessful the next step was to try and isolate the intermediate (93) from the reaction mixture. To accomplish this, the reaction would have to be stopped after cyclisation and loss of water had occurred. This would require the reaction conditions being altered so as to include a strong base with low nucleophilicity. Sodium hydride in dry dimethyl sulphoxide was chosen, and compound (69a) reacted under these conditions. However as far as the isolation of the intermediate (93) was concerned the reaction was unsuccessful. The only products isolated were o-nitroaniline (58%), p-nitrobenzaldehyde (14%) and N-p-nitrobenzoyl-o-nitroaniline (102), (8%).



(102)

These three products implied the formation of the Schiff base, N-p-nitrobenzylidene-o-nitroaniline (90) during the reaction, with (102) being produced by the oxidation of (90) by the solvent DMSO[37,51], and o-nitroaniline and p-nitrobenzaldehyde by the hydrolysis of (90), either during the reaction or in the work-up.

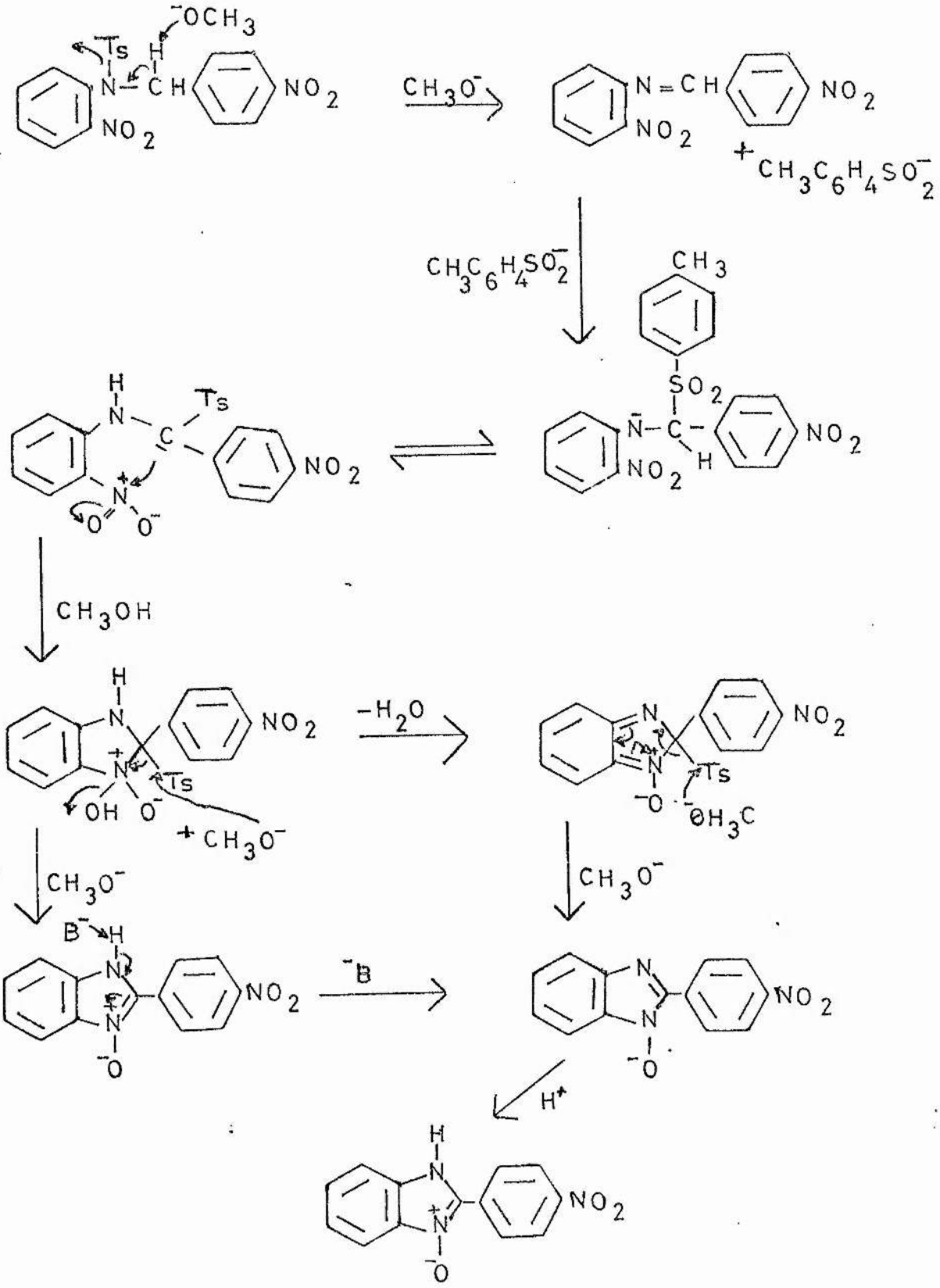
The possibility that the Schiff base (90) was the reaction intermediate, and that the cyclisation had gone via Scheme 19, had now to be considered. The formation of benzimidazole-N-oxides from Schiff bases was known[11,37] (c.f. page (32), Chapter 1); thus (90) was synthesised from o-nitroaniline and p-nitrobenzaldehyde, and a series of experiments performed in order to determine whether (70) was obtainable from (90).

The reaction of (90) with methanol, the methoxide ion and methanol, and the methoxide ion and methanol in the presence of toluene-p-sulphinate ions yielded only o-nitroaniline and p-nitrobenzaldehyde, presumably by the alcoholysis of the Schiff base by methanol or the hydrolysis of it by water contained in the methanol. In an attempt to keep water from the system, the Schiff base (90) was reacted with sodium methoxide in dry dimethyl sulphoxide. This experiment again only yielded o-nitroaniline, p-nitrobenzaldehyde and starting material, presumably by hydrolysis of the Schiff base during the work-up.

The absence of any cyclised products from these experiments show quite conclusively that Scheme 19 is not a major reaction pathway for the cyclisation of (69a) → (70).

iv. In a final attempt to elucidate the mechanism for the cyclisation of (69a) ⟶ (70), the kinetics of the reaction were studied.

Firstly the ultra violet spectra of (69a), (69b) and



(70)

SCHEME 19

the anion of (70) were measured. (Figure 1). It was found that the wavelength for maximum absorption of (69a) was 265 nm, (69b) was 265 and 414 nm and the anion of (70) was 355 nm with both (69a) and (69b) having negligible absorption at 355 nm. Therefore the rate of reactions of (69a) to (70) and (69b) to (70) could be measured by observing the rate of formation of (70) on a u.v. spectrophotometer at a wavelength of 355 nm.

From Beer-Lamberts law that

$$OD = \varepsilon.c.l.$$

where

OD = optical density at wavelength λ

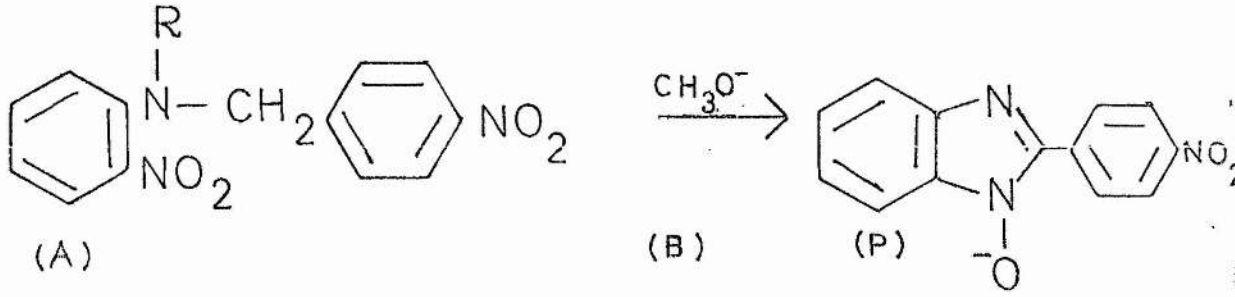
ε = molar extinction coefficient at wavelength λ

c = concentration of solution at wavelength λ

l = path length of cells (cm).

the concentration of (70) could be ascertained at different times (t) during the reaction. (The molar extinction coefficient of the anion of (70) at a wavelength of 355 nm had been previously determined.) The cyclisations of (69a) and (69b) to (70) were carried out in the u.v. cells using a 200:1 excess of methoxide, and the optical density of the solution at 355 nm was measured at constant time intervals t. For a

reaction of the type



(A) (B) (P)

$$-\frac{d[A]}{dt} \qquad -\frac{d[P]}{dt} \qquad K[A][B]$$

however, as B was present in such a large excess the reaction becomes pseudo-first order

$$\text{i.e.} \quad -d[A]/d\,t = d[P]/t = K'[A] \quad \text{where } K' = K[B]$$

$$\log_e[A] = -K't$$

now let $[P_N]$ = concentration of P at conclusion of reaction

$[P_t]$ = concentration of P at any time t

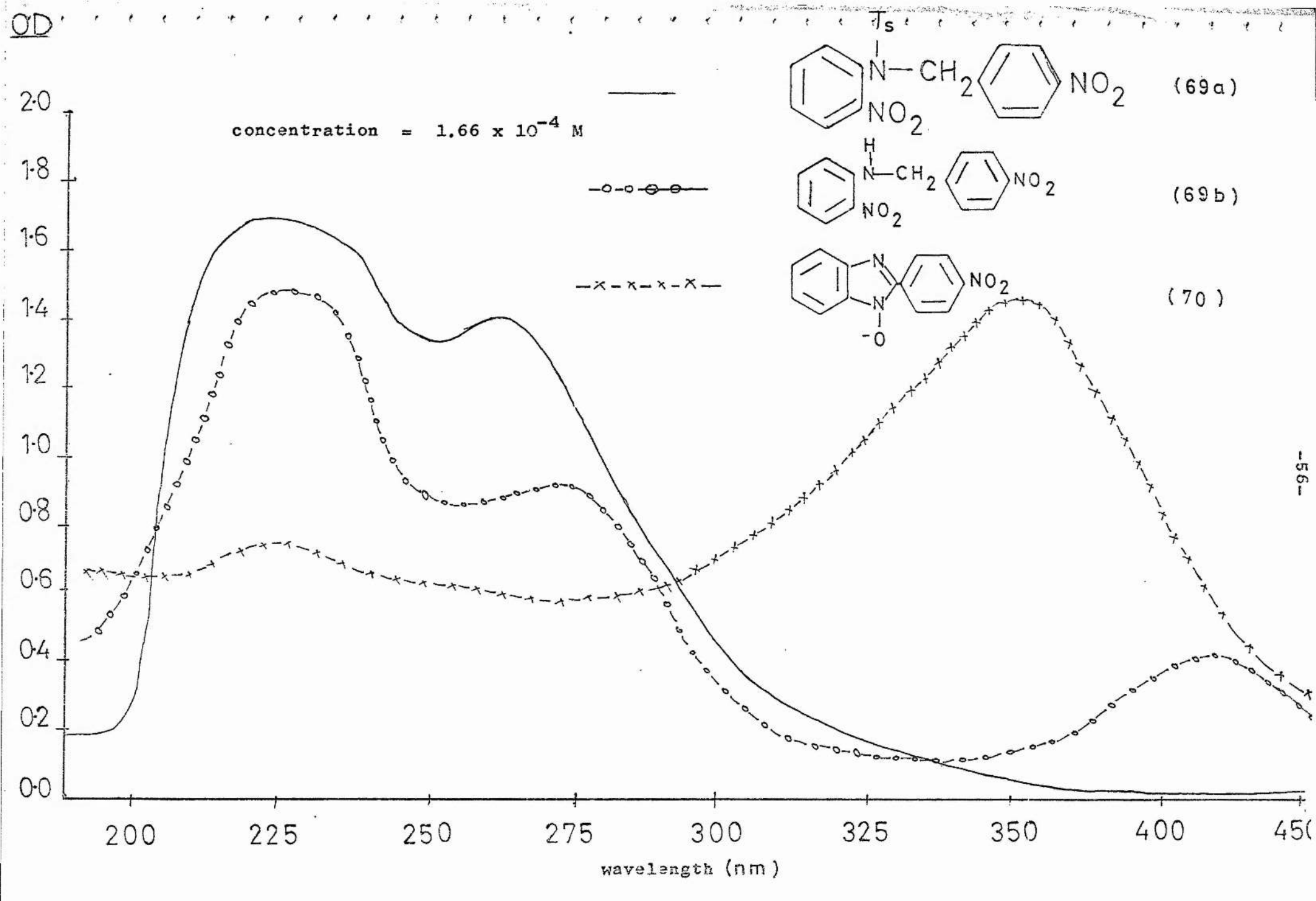
$[A_t] = [P_N] - [P_t]$

$$\log_e([P_N]-[P_t]) = -K't$$

$$\log_{10}[P_N-P_t] = -K't/2.303$$

therefore a plot of $\log_{10}[P_N-P_t]$ against t should give a straight line with slope $-K'/2.303$ and hence the rate constant, K', for the reaction could be found.

The plots of $\log_{10}[P_N-P_t]$ against t for the reactions (69a) → (70) and (69b) → (70) were straight lines, (figure 2), with $K'_{(69a)\rightarrow(70)} = 4.05 \times 10^{-5}\ s^{-1}$ and $K'_{(69)\rightarrow(70)} = 1.54 \times 10^{-5}\ s^{-1}$.


OD
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
concentration = 1.66 x 10⁻⁴ M
Ts
N—CH2
NO2
NO2
(69a)
H
N—CH2
NO2
NO2
(69b)
N
N
NO2
-O
(70)
200
225
250
275
300
325
350
400
450
wavelength (nm)

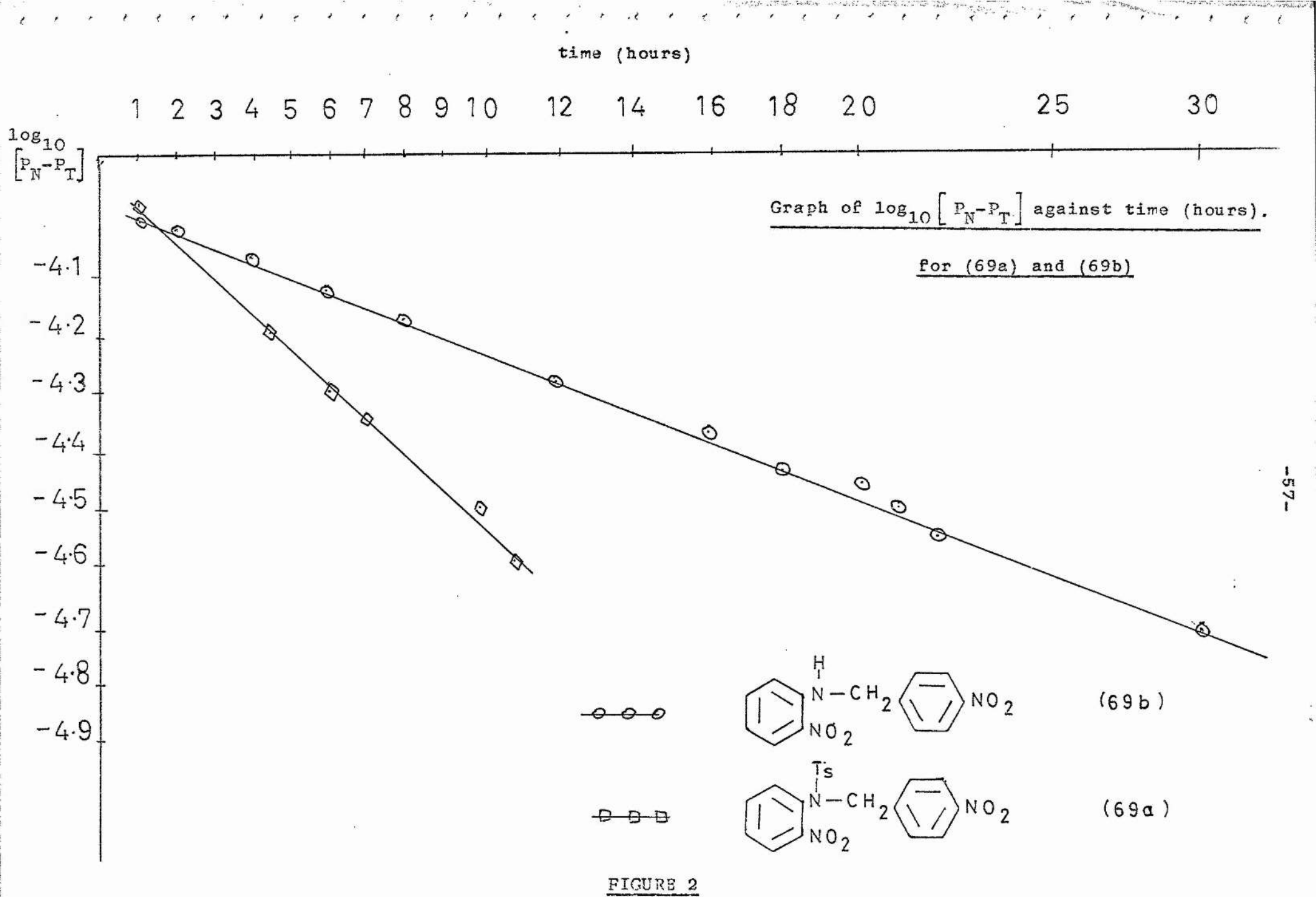
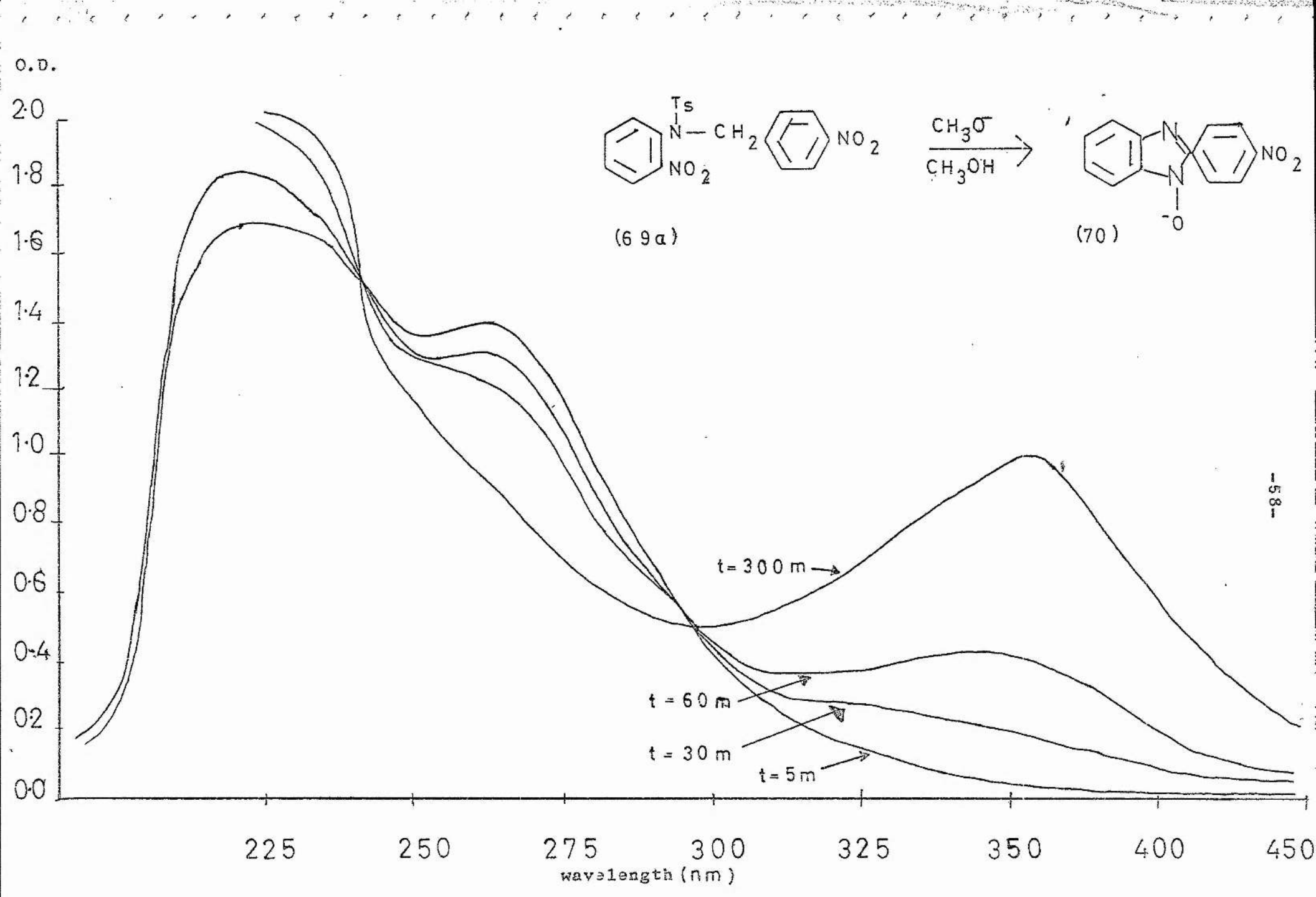
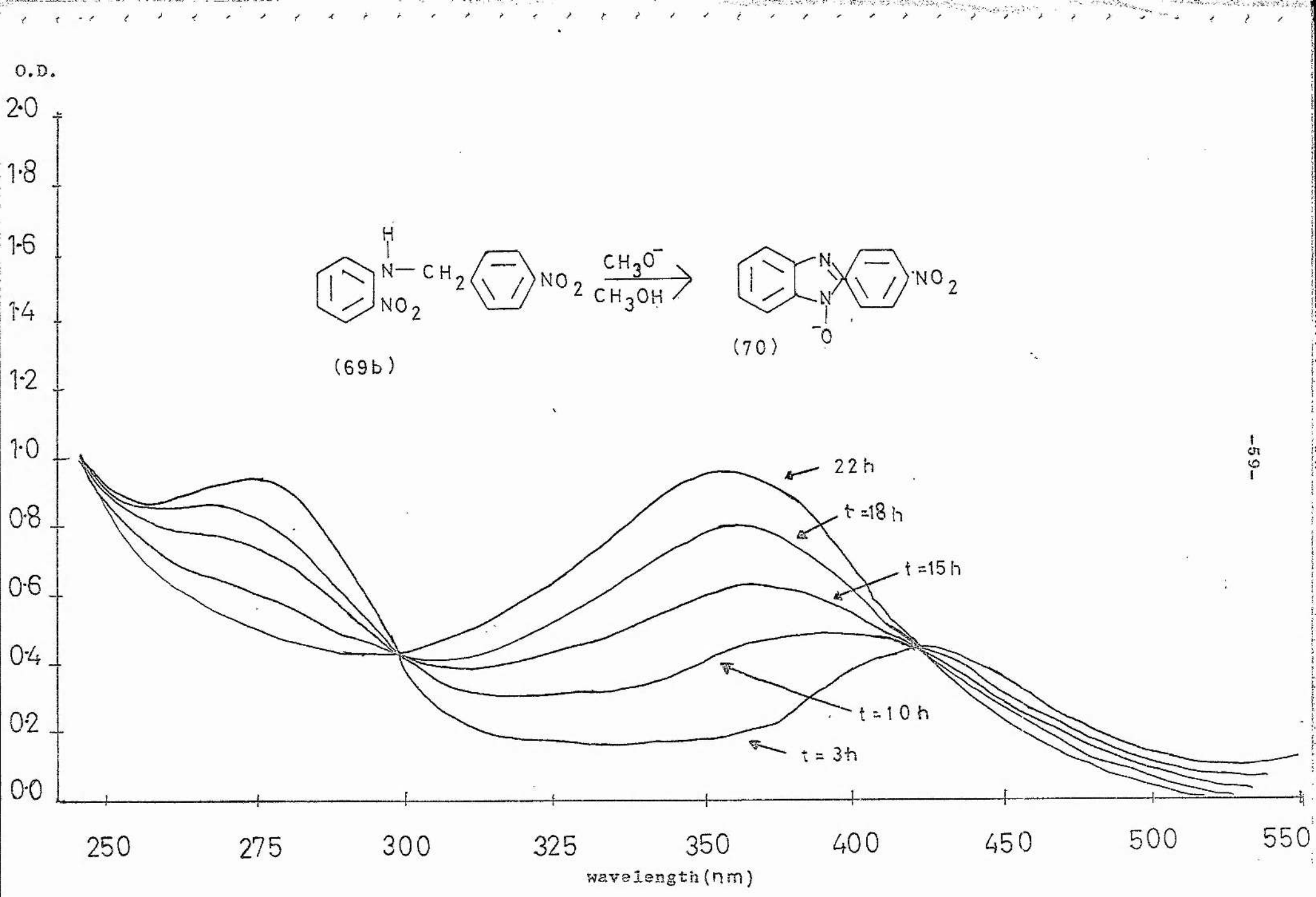

time (hours)
1 2 3 4 5 6 7 8 9 10 12 14 16 18 20 25 30
log10 [PN-PT]
-4·1
-4·2
-4·3
-4·4
-4·5
-4·6
-4·7
-4·8
-4·9
Graph of log10 [PN-PT] against time (hours).
for (69a) and (69b)
H
N—CH2
NO2
NO2
(69b)
Ts
N—CH2
NO2
NO2
(69a)

FIGURE 2

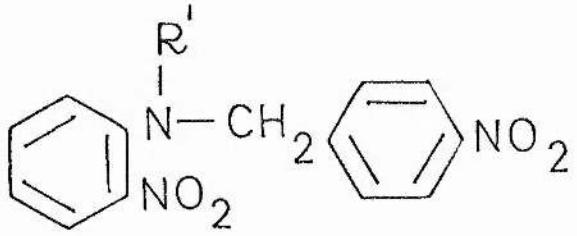

O.D.
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
Ts
N — CH2
NO2
NO2
(69a)
CH3O⁻
CH3OH
N
N
NO2
⁻O
(70)
t = 300 m
t = 60 m
t = 30 m
t = 5 m
225
250
275
300
325
350
400
450
wavelength (nm)


O.D.
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
250
275
300
325
350
400
450
500
550
wavelength (nm)
22 h
t =18 h
t =15 h
t = 10 h
t = 3h
(69b)
(70)

The series of u.v. spectra for the reactions (69a) → (70) (figure 3) show isosbestic points at 245 nm and 297 nm. These showed that the reaction involved only one rate determining step[52,53]. Similar results were obtained for (69b) → (70). (Figure 4). Hence since (69a) → (70) is a faster process than (69b) → (70), the reaction pathway described by Scheme 18 could not have been a major one.

In an extension of this work, analogues of (69a) and (69b) namely, N-methylsulphonyl-N-p-nitrobenzyl-o-nitroanil (69c), N-acetyl-N-p-nitrobenzyl-o-nitroaniline (69d) and N-benzoyl-N-p-nitrobenzyl-o-nitroaniline (69e) were synthesised (Series 1), in order to determine whether (70) was a general product when (69a) → (69e) were reacted with sodium methoxide in methanol. The differences between the carboxamides ((69d) and (69e)) and the sulphonamides ((69a) and (69c)), were also studied.

Series 1



(69a) R' = $CH_3C_6H_4SO_2$

(69b) R' = H

(69c) R' = CH_3SO_2

(69d) R' = CH_3CO

(69e) R' = C_6H_5CO

(69c) was prepared by reacting the anion of N-methylsulphonyl -
-o-nitroaniline with p-nitrobenzyl bromide in dimethylformamide, (69d) was synthesised by acetylating (69b) with a mixture of acetyl bromide and acetic anhydride and (69e) was prepared by benzoylating (69b) with benzoyl chloride in pyridine.

The reaction of (69c) with an equimolar amount of sodium methoxide in methanol gave (70) in an 8% yield and 51% of starting material. No N-methoxy compound (71) was observed. On changing the proportion of base to two molar equivalents, the percentage of (70) formed increased to 50% and 1% of (71) was detected by mass spectrometry. This small amount of (71) was puzzling, as according to Scheme 14, methyl methanesulphona should have been formed, and this should have methylated the anion of (70) to give (71). [It was shown independently that the anion of (70) could be methylated (32% yield) by methyl methanesulphonate ($CH_3SO_2 \cdot OCH_3$), as it could (48% yield) by methyl toluene-p-sulphonate .] These results implied that (71) should have been formed in a larger amount than that observed. However, it is known[54] that alkyl methansulphonates are less reactive than alkyl arenesulphonates towards nucleophilic solvents, and hence are presumably more selective alkylating agents, and so it is conceivable that during the cyclisation of (69c) $\longrightarrow$ (70), when the anion of (70) and the methylating agent, methyl methanesulphonate, were slowly being formed in an excess of methoxide ion, it was the methoxide ion that was methylated at the expense of the anion of (70).

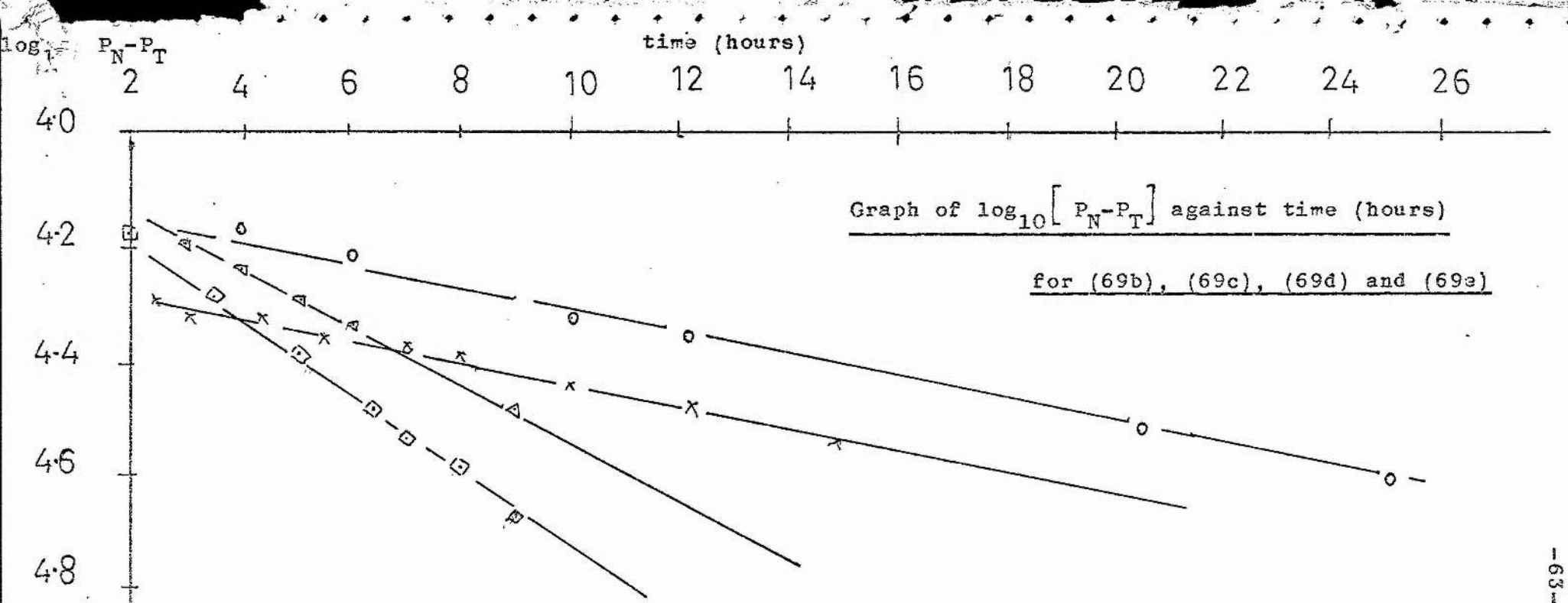
Kinetic measurements similar to those previously described, gave $K_{(69c) \rightarrow (70)} = 4.58 \times 10^{-5}\ s^{-1}$, (figures 5,6), again showing that cyclisation proceeded via Scheme 14 (see Table 2).

In the case of the carboxamides (69d and 69e), cyclisation via Scheme 14 implies the formation of methyl carboxylates. As methyl carboxylates are not methylating agents, the formation of the N-methoxy product (71) was not to be expected. The reaction of (69d) and (69e) with two molar equivalents of sodium methoxide in methanol gave (70) in a reasonable yield and no (71).

Kinetic measurements carried out on the carboxamides showed that they cyclised more slowly than the sulphonamides (figure 5,6) but faster than (69b) Table 2. Therefore, for the series (69a), (69c), (69d) and (69e), cyclisation preceded deacylation, and the reaction pathway was that described by Scheme 14.

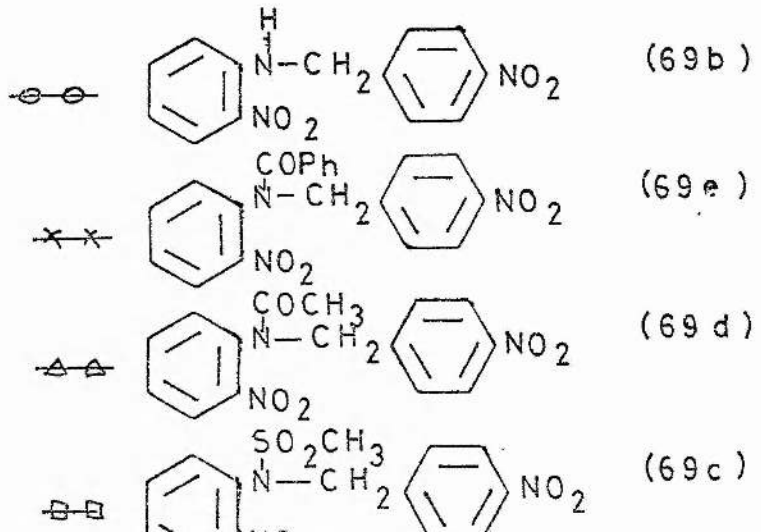
A point of distinction between the carboxamides and sulphonamides of series 1 was apparent in their ^1H nmr spectra. For the sulphonamides, the methylene resonance at room temperature was a singlet, whereas in the carboxamides it was an AB quartet with $J \simeq 14$–15 Hz. (Table 3).

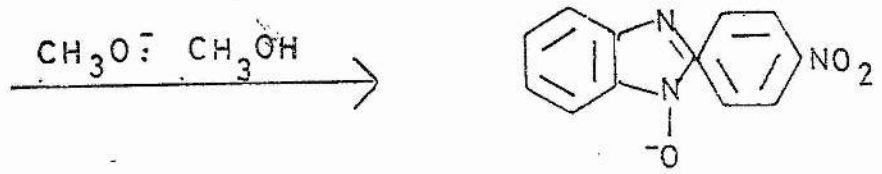
Non-equivalence of methylene protons adjacent to an amidic nitrogen is well known[55,56], and in the case of N-acyl-N-benzylanilines it has been attributed to restricted



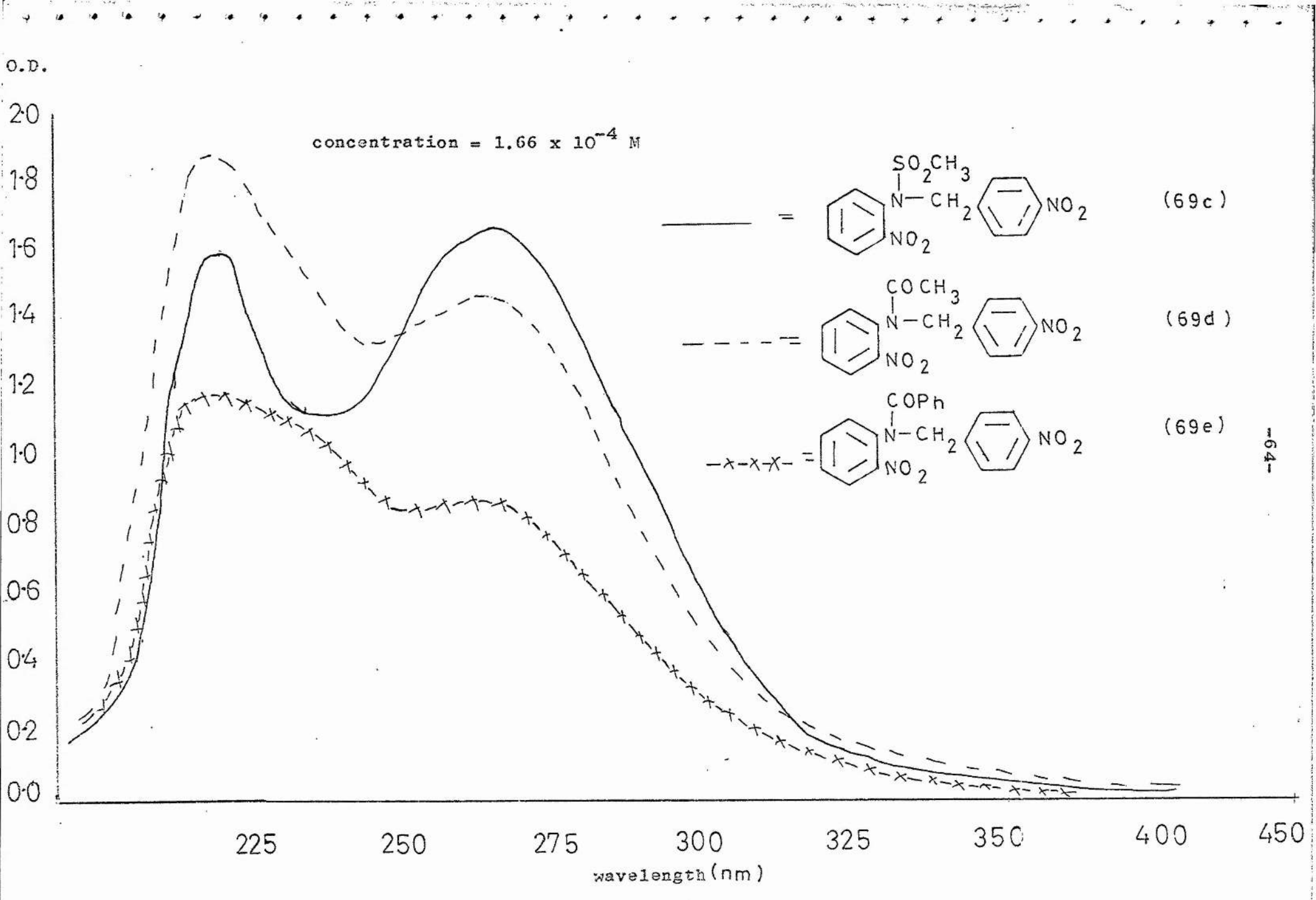
Graph of $\log_{10}[P_N - P_T]$ against time (hours)

for (69b), (69c), (69d) and (69e)





(70)


O.D.
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
concentration = 1.66 x 10⁻⁴ M
——— = (69c)
– – – – = (69d)
–x–x–x– = (69e)
225
250
275
300
325
350
400
450
wavelength (nm)

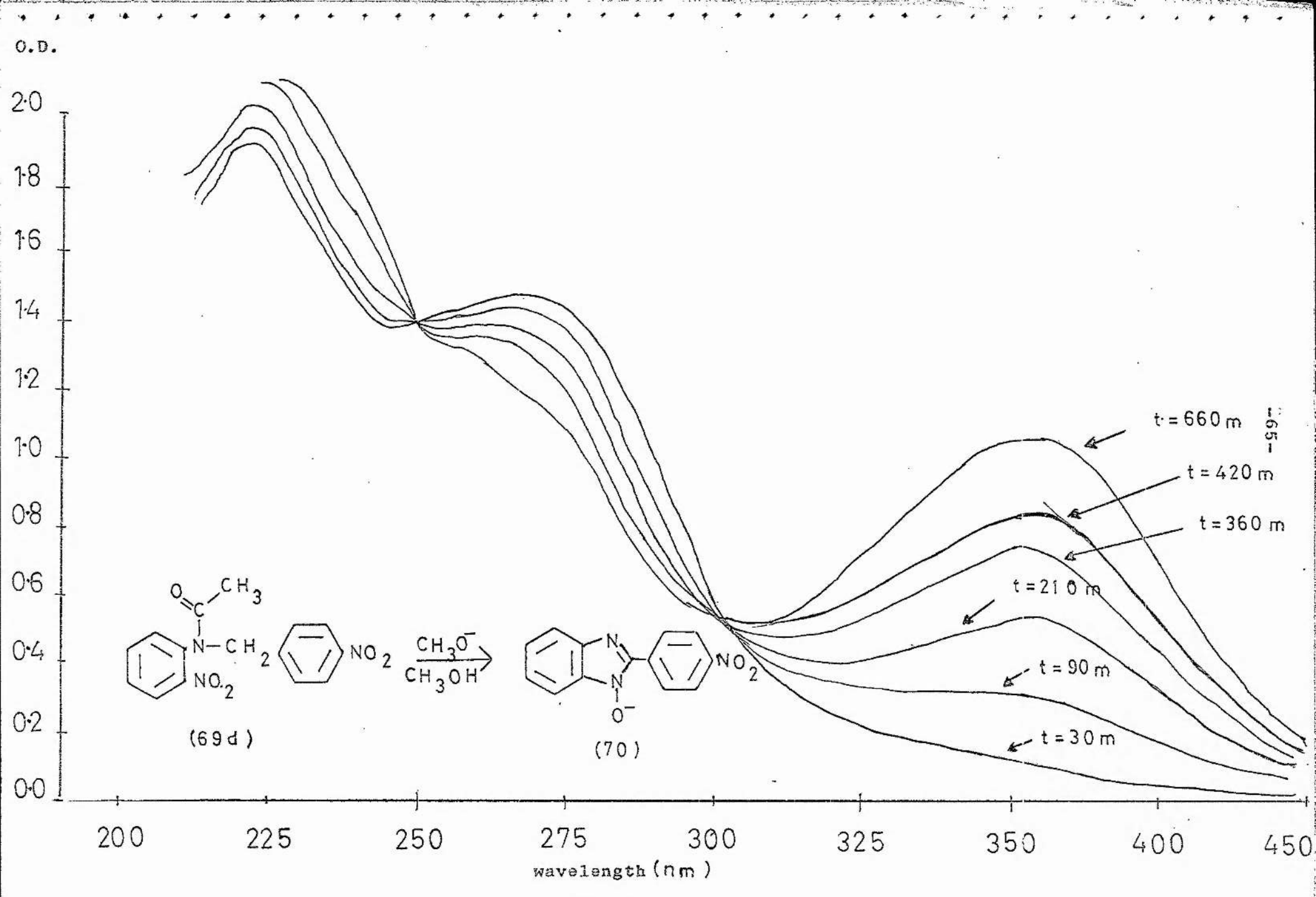

O.D.
2·0
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0·0
200
225
250
275
300
325
350
400
450
wavelength (nm)
t = 660 m
t = 420 m
t = 360 m
t = 210 m
t = 90 m
t = 30 m
(69d)
(70)
CH3O⁻
CH3OH

TABLE 1

Compound	% Yield	
	2-p-nitrophenylbenzimidazole-3-oxide (70)	1-methoxy-2-p-nitrophenylbenzimidazole
(69a)	38	10
(69b)	37	-
(69c)	50	1
(69d)	56	-
(69e)	42	-

TABLE 2

Cyclisation of N-p-nitrobenzyl-o-nitroanilines

Compound	λ_{max} (CH_3OH)/nm; (ϵ)	Rate Constant s^{-1}	Isosbestic points
(69a)	220,265 (71,500;53,300)	4.05×10^{-5}	245,297
(69b)	232,273,415 (27,000; 17800 8,000)	1.54×10^{-5}	245,297,420
(69c)	218 266 (28,500;30,400)	4.58×10^{-5}	256,296
(69d)	208 271 (8,150; 6,200)	3.31×10^{-5}	252,297
(69e)	211 263 (22,300; 27,800)	1.61×10^{-5}	243,288

TABLE 3

^{1}H nmr data for benzylic resonances of series 1.

Compound	Chemical Shift δ at Normal Temperature	Coalescence Temp ‡	Coalescence Temp Compound 104
(69a)	4.88	5° ($(CD_3)_2CO$)	51 (Pyridine)
(69b)	4.63(d,J=6Hz)		
(69c)	4.91	9° ($CDCl_3$) §	21 (Pyridine)
(69d)	4.36,5.33(J=15)	114° ($CDBr_3$)	142 ($PhNO_2$)
(69e)	4.56,5.71(J=14.5)	68° ($CDBr_3$)	98.5 ($PhNO_2$)
(107)	4.78,5.18 br	50° ($CDBr_3$)	

Data for compounds 104 are taken from ref. 53.

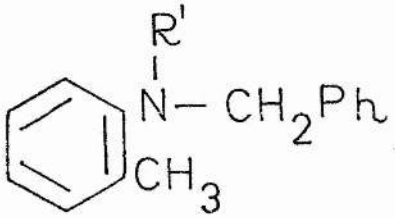
‡ ±1° for series 1 : ±2° for 104

§ in $(CD_3)_2CO$, the protons are accidentally equivalent (singlet down to -85°C)

rotation about the aryl-nitrogen bond[56]. Restricted rotation about the N–CO bond must also play a part, as the effect was less evident in the sulphonamides, where rotation about the $N-SO_2$ bond is freer[57].

Variable temperature nmr studies of the carboxamides and sulphonamides in series (1) showed that in every case the methylene resonance was an AB quartet at low temperatures and a singlet at high temperatures. The coalescence temperatures for the carboxamides lay above room temperature, whereas those of the sulphonamides were below room temperature.

Comparison of these coalescence temperatures with those of the corresponding o-toluidine derivatives[57] (104) (Table 3), showed that the latter were substantially higher in almost every case.



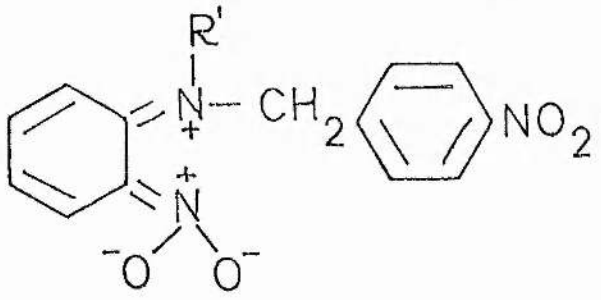
(104a) : R' = $CH_3C_6H_4SO_2$

(104c) : R' = CH_3SO_2

(104d) : R' = CH_3CO

(104e) : R' = C_6H_5CO

This result implied that there was greater restriction to Ar—N bond rotation in each of the compounds (104) than in the corresponding members of series (1). This was an unexpected result, not only on steric grounds, (as the nitro group is expected to be larger than the methyl and should therefore restrict rotation to a greater degree;) but also on electronic grounds, as a little additional restriction to rotation in the o-nitroaniline derivatives because of conjugation (69f) however weak between the amino and nitro group should be expected.



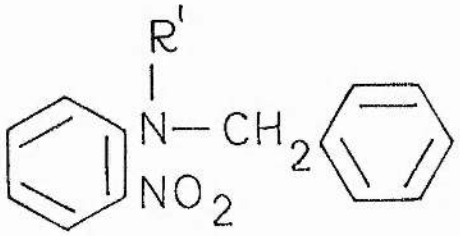
(69f)

A pre-requisite to cyclisation is a reactive methylene group, α to the substituted nitrogen of the amino group. Indeed, ease of cyclisation could be considered as a function of the activity of the methylene group. In the cases previously discussed (series 1), the importance of the p-nitro group in the ortho side chain with regard to cyclisation was great, due to the nitro group being a very powerful electron

withdrawing species, and hence activating the methylene group to such an extent that cyclisation proceeded fairly rapidly.

The next stage of the investigation was to consider the effect of removing the nitro group from the side chain. For this, the action of sodium methoxide in methanol on the compounds of series (2) was studied.

Series 2



(105a) : R' = $CH_3C_6H_4SO_2$

(105b) : R' = H

(105c) : R' = CH_3SO_2

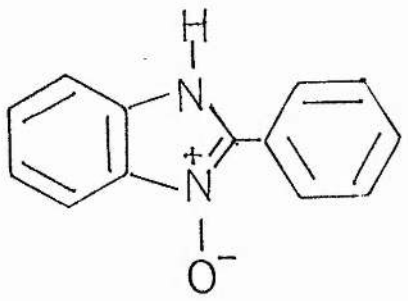
(105d) : R' = CH_3CO

(105e) : R' = C_6H_5CO

The members of series (2) are analogues of those in series (1). Compounds(105a) and (105c) were prepared by methods analogous to those for (69a) and (69c). N-Benzyl-o-nitroaniline was synthesised from o-chloronitrobenzene and benzylamine[54]. Acetylation of (105b) using acetic anhydride and acetyl bromide, gave (105d), and benzoylation (by benzoyl

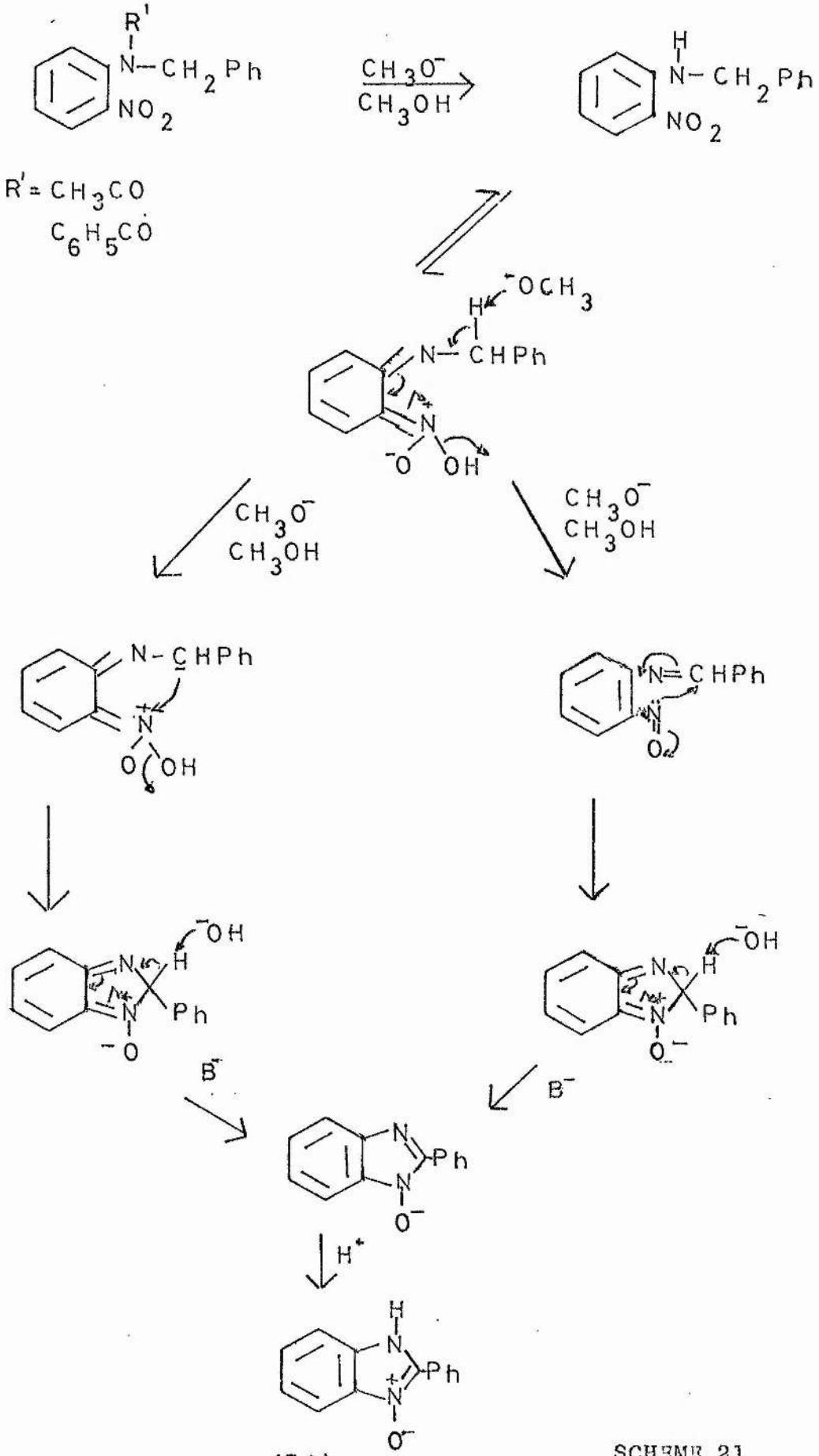
chloride in pyridine) gave (105e).

As had already been shown[39], the attempted reaction of (105a) with sodium methoxide in methanol gave only starting material, and the same was true of (105c): whereas the products of the reactions of (105b), (105d) and (105e) with sodium methoxide in methanol were 2-phenylbenzimidazole-3-oxide (54) and N-benzyl-o-nitroaniline (105b).



(54)

The reaction conditions were varied by changing the amount of solvent and reaction time, table 4; it was found that the optimum yield of (54) occurred when 5 mmols of starting material were refluxed for six hours with two molar equivalents of methoxide in fifty mls of methanol. In dilute solutions with a shorter reaction time, deacylation to (105b) was the only reaction observed. This formation of (105b) suggested that the reaction went via Scheme 21, i.e. deacylation followed by cyclisation, as opposed to cyclisation followed by deacylation, which was observed for the compounds of Series (1).



(54)

SCHEME 21

of Schemes 12 and 13

TABLE 4

Compound	50 mls CH_3OH 2 hrs	50 mls CH_3OH 6 hrs	15 mls CH_3OH 2 hrs
(105b)	(105b) recovered almost quantitatively	70% (105b) 23% (54)	69% (105b) 21% (54)
(105d)	73% (105b) 0% (54)	74% (105b) 17% (54)	81% (105b) 8% (54)
(105e)	70% (105b) 3% (54)	72% (105b) 21% (54)	82% (105b) 12% (54)

The non-formation of (54) from the reaction of (105a) and (105b) with sodium methoxide in methanol can be explained by Scheme 21. The rate of hydrolysis of the sulphonamides is known[59] to be much slower than that of the carboxamides, and so presumably is the rate of alcoholysis, hence (105b) will not be formed during the reaction time and cyclisation does not occur.

The main support for Scheme 21 being the reaction pathway comes from the general rule[60] that base induced cyclisations of o-nitro compounds involving a feebly reactive β methylene centre in the ortho side occur only when the side chain carries a mobile α hydrogen atom. Stacy[36] and his co-workers exemplified this by showing that N-benzyl-N-methyl-o-nitroaniline (105, R' = CH_3) could not be cyclised under

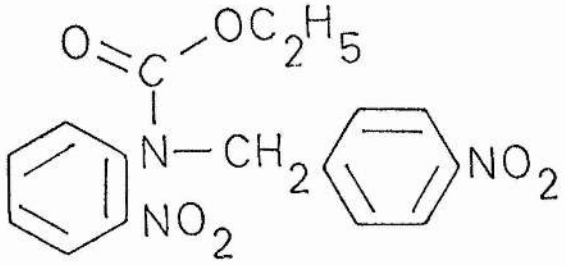
basic conditions, unlike N-benzyl-o-nitroaniline (105b). [Attempts to study the reaction of N-methyl-N-p-nitrobenzyl-o-nitroaniline with sodium methoxide in methanol were unsuccessful as the starting material proved difficult to obtain.]

As in series (1), the H' nmr spectra of the sulphonamides ((105a) and (105c)) differed from those of the carboxamides ((105d) and (105e)) with respect to the resonances of the methylene protons. For the carboxamides they were again a quartet at room temperature, and the sulphonamides a singlet. The coalescence temperatures were also lower than those of compounds (104). (Table 5).

TABLE 5

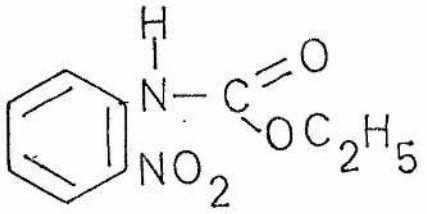
Compounds	Chemical Shift at Normal Temps	Coalescence Temp	Compound 104
(105a)	4.85	0° ($(CD_3)_2CO$)	51°(Pyridine)
(105b)	4.48 (d; J=5)		
(105c)	4.81	18°($CDCl_3$)	21°(Pyridine)
(105d)	4.15,5.31 (J=14.5)	112°($CDBr_3$)	142°($PhNO_2$)
(105e)	4.34,5.76 (J=14)	72°($CDBr_3$)	98.5($PhNO_2$)

The next stage of the investigation involved the replacement of the p-tolylsulphonyl group of (69a) by the ethoxycarbonyl group to form (107).



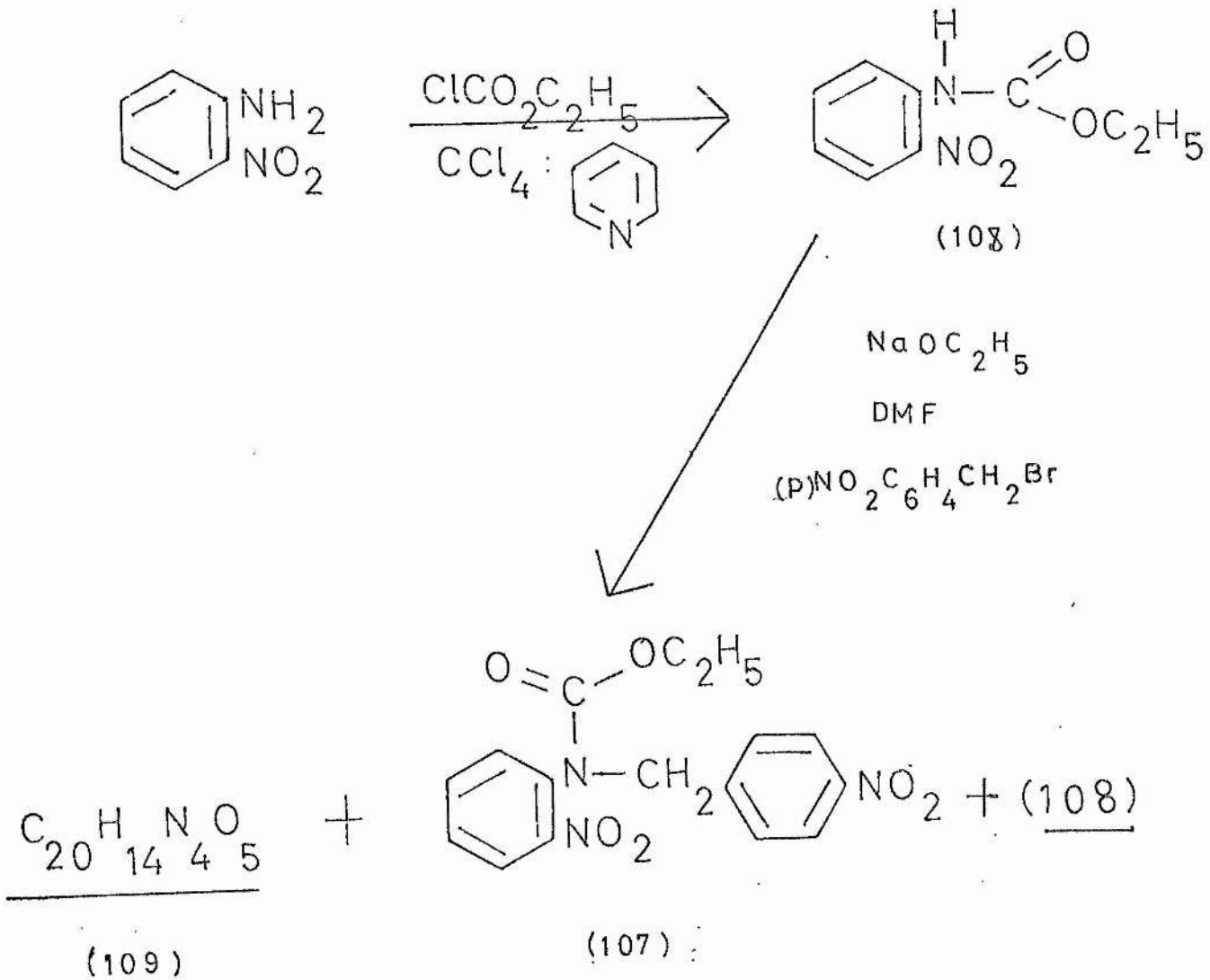
(107)

The first stage in the synthesis of (107) was the preparation of ethyl N-o-nitrophenylcarbamate (108) from o-nitroaniline and ethyl chloroformate[61].



(108)

Compound (108) was then reacted with p-nitrobenzyl bromide and sodium ethoxide to give (107), together with an ethanol-insoluble by-product (109) of molecular formula $C_{20}H_{14}N_4O_5$, and starting material. (Scheme 22).


NH2
NO2
ClCO2C2H5
CCl4 : N
H
N— C
O
OC2H5
NO2
(108)
NaOC2H5
DMF
(P)NO2C6H4CH2Br
O=C—OC2H5
N—CH2
NO2
NO2
+ (108)
C20H14N4O5
(109)
+
(107)

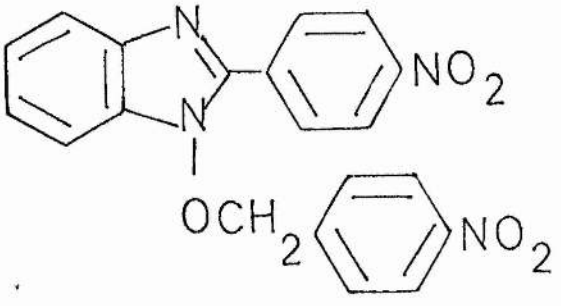
SCHEME 22

In the reaction of (108) to (109) and (107), when one molar equivalent each of ethoxide and p-nitrobenzyl bromide were used (109) was formed in a 7% yield, and the ethanol-soluble mixture gave on chromatography unchanged carbamate (108), 50%, o-nitroaniline (20%) and (107) - (11%).

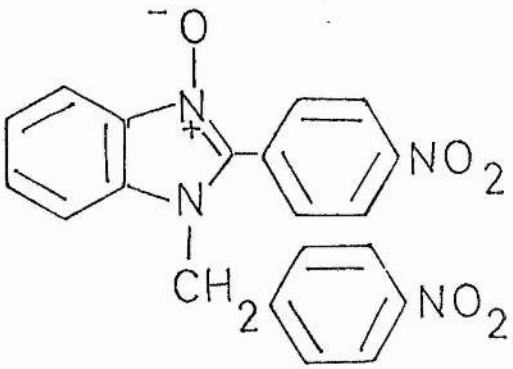
The use of two molar equivalents each of ethoxide and p-nitrobenzyl bromide with (108) gave 23% of (109), 27% of (107), and 22% of unchanged carbamate (108).

The infra-red spectrum of the ethanol-insoluble product (109) showed the presence of a nitro group (or groups,) and the absence of any carbonyl, primary amino or secondary amino functions. From the ^{1}H nmr, it was found that (109) contained three aromatic rings (with an AA'BB' pattern visible) and a methylene group. (The peak for the methylene resonance was a singlet).

All the evidence obtained pointed towards (109) being either 1-p-nitrobenzyloxy-2-p-nitrophenylbenzimidazole (109a) or 1-p-nitrobenzyl-2-nitrophenylbenzimidazole-3-oxide (109b).



(109a)



(109b)

This was further confirmed by reaction of the anion of (70) with p-nitrobenzyl bromide. The product from this reaction was identical in all respects with (109).

1-p-nitrobenzyl-2-p-nitrophenylbenzimidazole was synthesised from o-phenylenediamine and p-nitrobenzaldehyde[62]. The nmr spectrum of this compound was taken and studied with particular reference to the methylene group. The peak for N-$\underline{CH_2}$ occurred at δ = 5.6, which was the same shift as for the $\underline{CH_2}$ resonance in (109). However, despite this result structure (109a) was assigned to the unknown for the following reasons. Firstly, there is a known preference[36,39] for N-oxides like (70) to alkylate or acylate on oxygen (c.f. Chapter 1, page 41).

Secondly, a standard reaction of N-oxides[63] is their deoxygenation by phosphorus trichloride. With (109) only starting material was isolated from this reaction, inferring that structure (109b) was unlikely.

Thirdly the mass spectrum of (109), (figure 8), lacks an $(M-16)^+$ ion, a charateristic property of N-oxides. The most important fragment is the $(M-151)^+$ ion, ($C_{13}H_9N_3O_2$ by accurate mass measurement), which corresponds to the loss of p-nitrobenzaldehyde, a not unexpected thermolytic process for a N-p-nitrobenzoyloxy heterocycle[64].

N-ethoxycarbonyl-N-p-nitrobenzyl-o-nitroaniline, like the sulphonamides and carboxamides of series (1) was cyclised

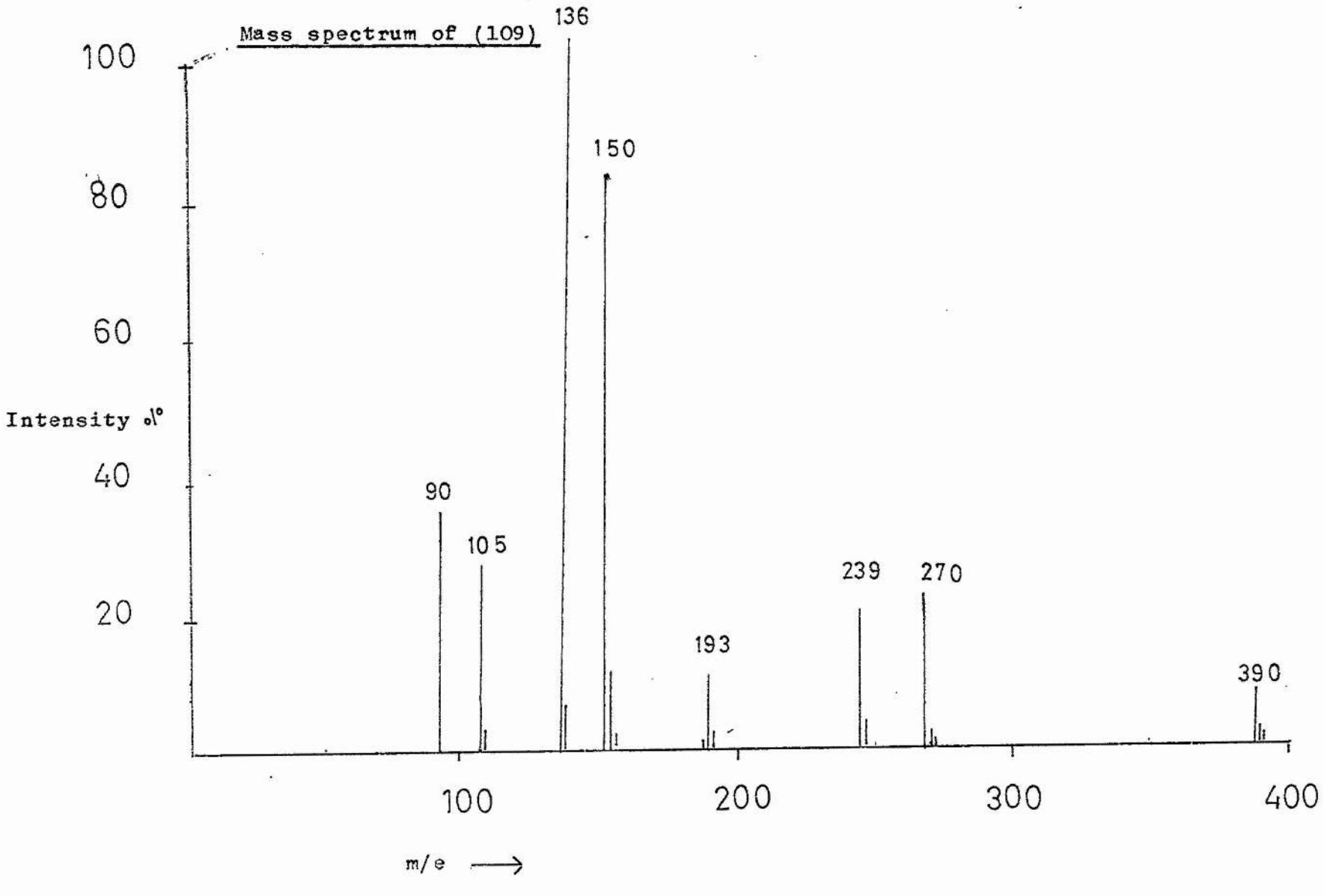
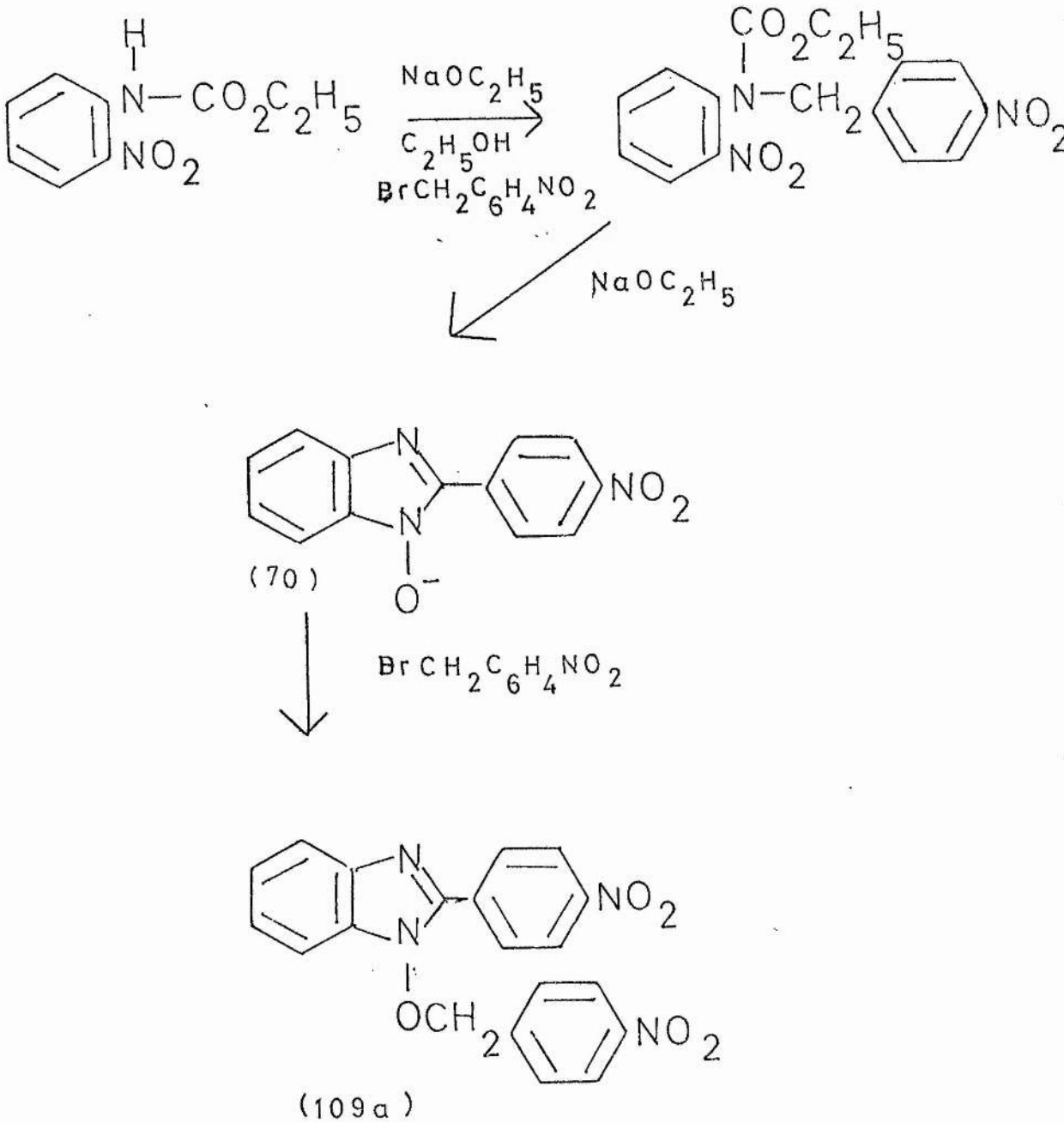

Mass spectrum of (109)
136
150
100
80
60
Intensity %
40
20
90
105
193
239
270
390
100
200
300
400
m/e ⟶

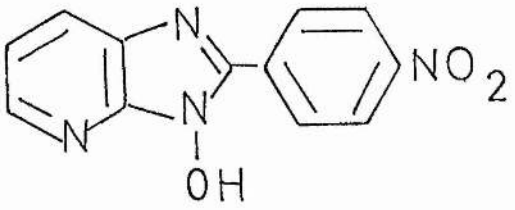
FIGURE 8

by base, in this case sodium ethoxide in ethanol, (ethoxide was used to eliminate any possibility of trans-esterification), to give (70) in 71% yield. The reaction pathway for the formation of (70) and (109a) is shown in Scheme 23. Each step in this pathway has been independently verified.



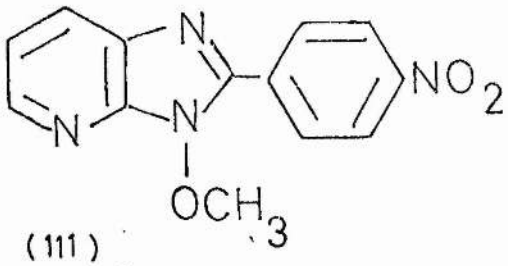
SCHEME 23

It would have been of interest to investigate the extension of the cyclisation reaction described by Scheme 14 to heterocyclic analogues of the o-nitroaniline system in series (1), with a view to the preparation of purine and deazapurine derivatives, such as the compounds (110) and (111).



(110)

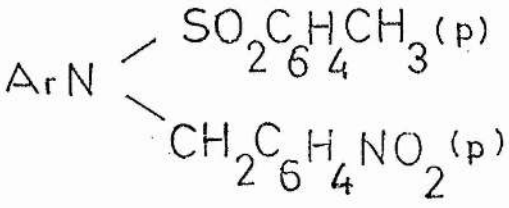
1-hydroxy-2-p-nitrophenyl-imidazo [5,4,-b] pyridine



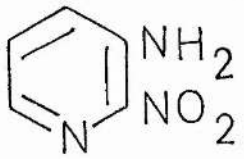
(111)

1-methoxy-2-p-nitrophenyl-imidazo [5,4,-b] pyridine

However, it is more difficult to prepare compounds of the type

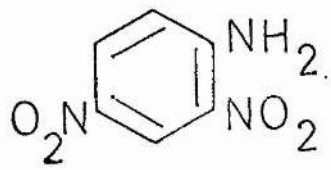


where $ArNH_2$ is a weak base (much weaker than o-nitroaniline) such as the heterocyclic amine 3-amino-2-nitropyridine (112).



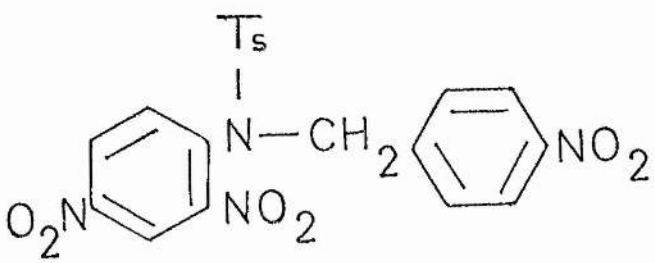
(112)

2,4-Dinitroaniline (113) (pKa -4.53)[65] is a much weaker base than o-nitroaniline (pKa -0.26).[65] Therefore, if N-p-nitrobenzyl-N-p-tolylsulphonyl-2,4-dinitroaniline (114) could be synthesised, and cyclised to 5-nitro-2-p-nitrophenylbenzimidazole-

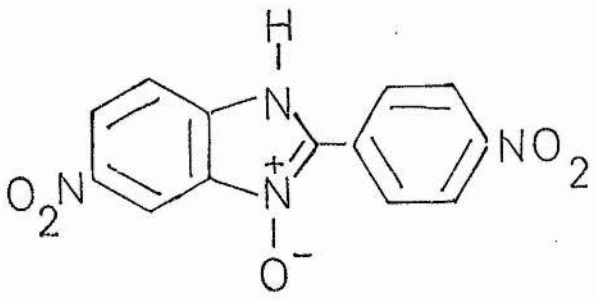


(113)

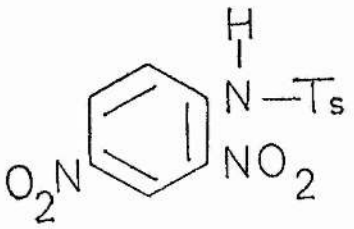
3-oxide (115) this might serve as a useful model for the amino-nitropyridine series.



(114)



(115)



(116)

It was found[66] that N-p-tolylsulphonyl-2,4-dinitroaniline (116) could not be prepared from 2,4-dinitroaniline and toluene-p-sulphonyl chloride. This was because the extra nitro group in the para position of the benzene ring delocalises the lone pair on the amino nitrogen to such an extent that 2,4-dinitroaniline becomes a weaker nucleophile than o-nitroaniline and will not react with toluene-p-sulphonyl chloride under normal conditions.

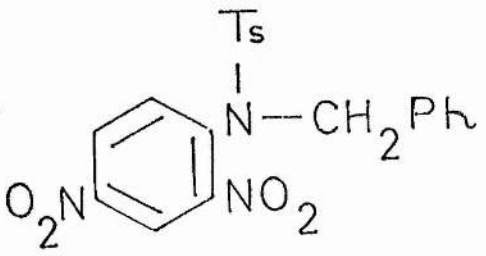
Nitration of (69a) by concentrated nitric acid also proved unsuccessful as nitration did not occur exclusively in the four position as required. Instead nitration occurred in both rings[67].

N-p-tolylsulphonyl-2,4-dinitroaniline (116) was

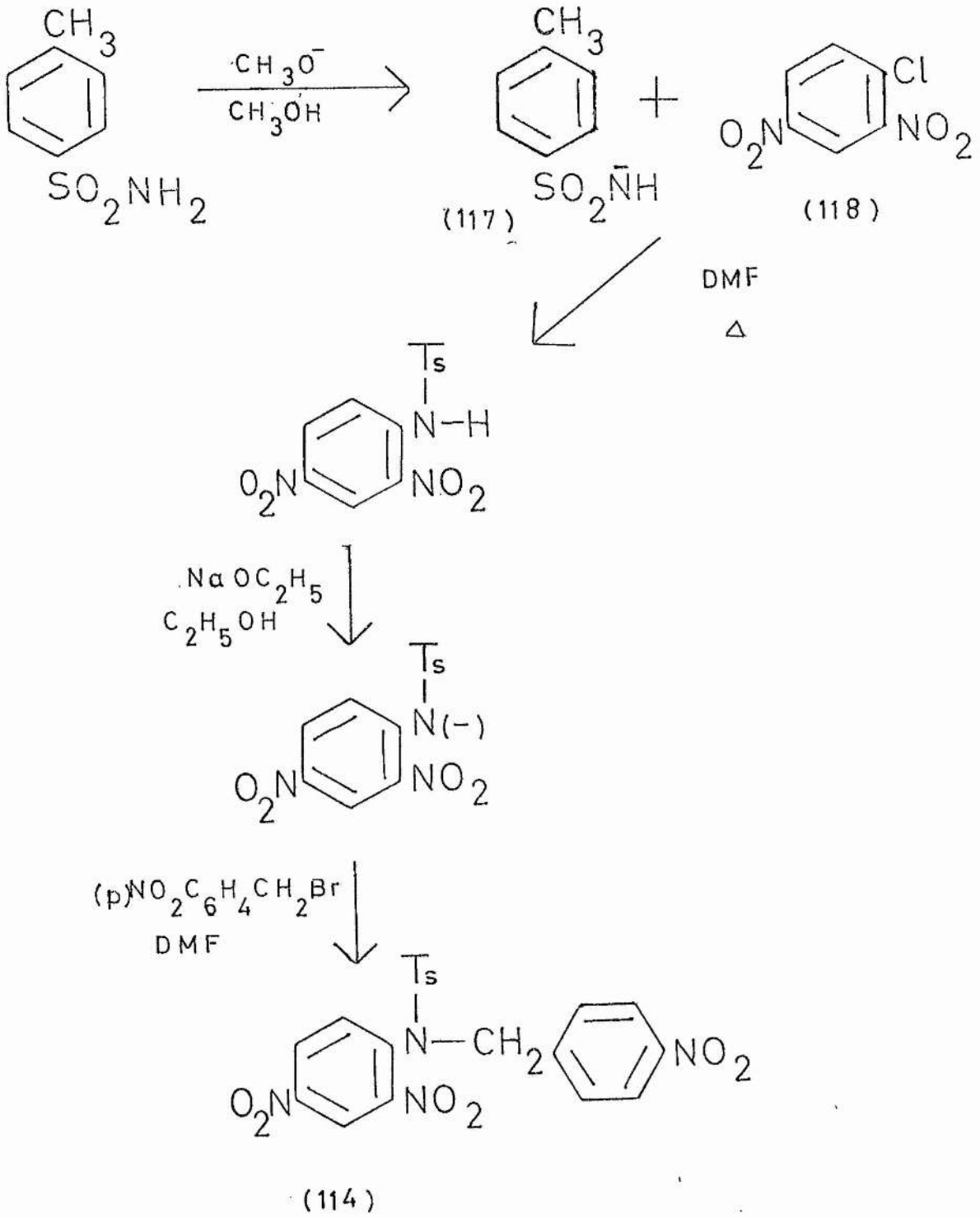
eventually prepared from the sodium salt of toluene-p-sulphonamide (117) and 1-chloro-2,4-dinitrobenzene (118) with dimethylformamide as the solvent. Compound (114) was synthesised from (116) by reaction of its sodium salt with p-nitrobenzyl bromide in dimethylformamide[66]. (Scheme 24).

The reaction of (114) with two molar equivalents of sodium methoxide in methanol did not give (115), but instead gave (116) in 44% yield, the sodium salt of (116) (42%), p-nitrobenzoic acid (3%) and methyl p-nitrobenzoate, (8%). On reducing the concentration of base to 1 molar equivalent with respect to the starting material, 57% of (116) was obtained.

N-Benzyl-N-p-tolylsulphonyl-2,4-dinitroaniline (119) was prepared from (116) and benzyl bromide analogously to (114). Reaction of (119) with two molar equivalents of base gave (116); (35%) and unreacted starting material (119), (44%).



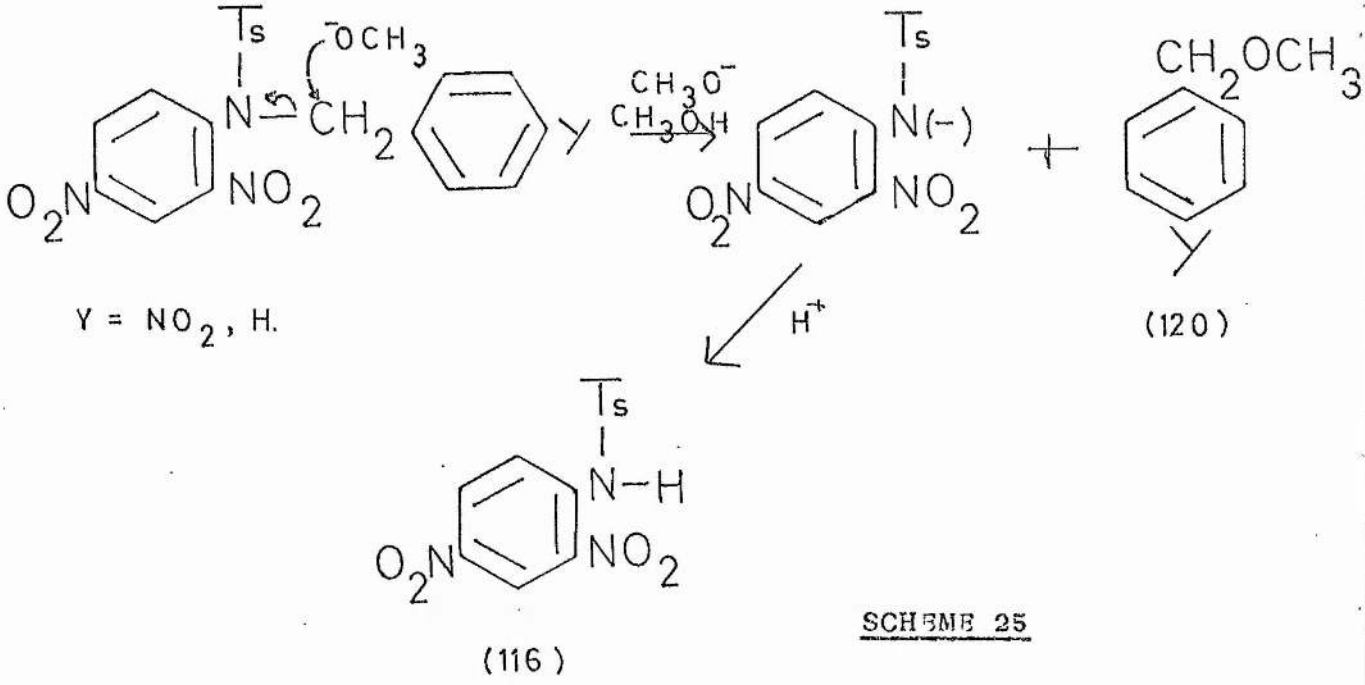
(119)



(114)

SCHÈME 24

A possible major reaction pathway for the reactions of (114) and (119) with base is shown in Scheme 25.



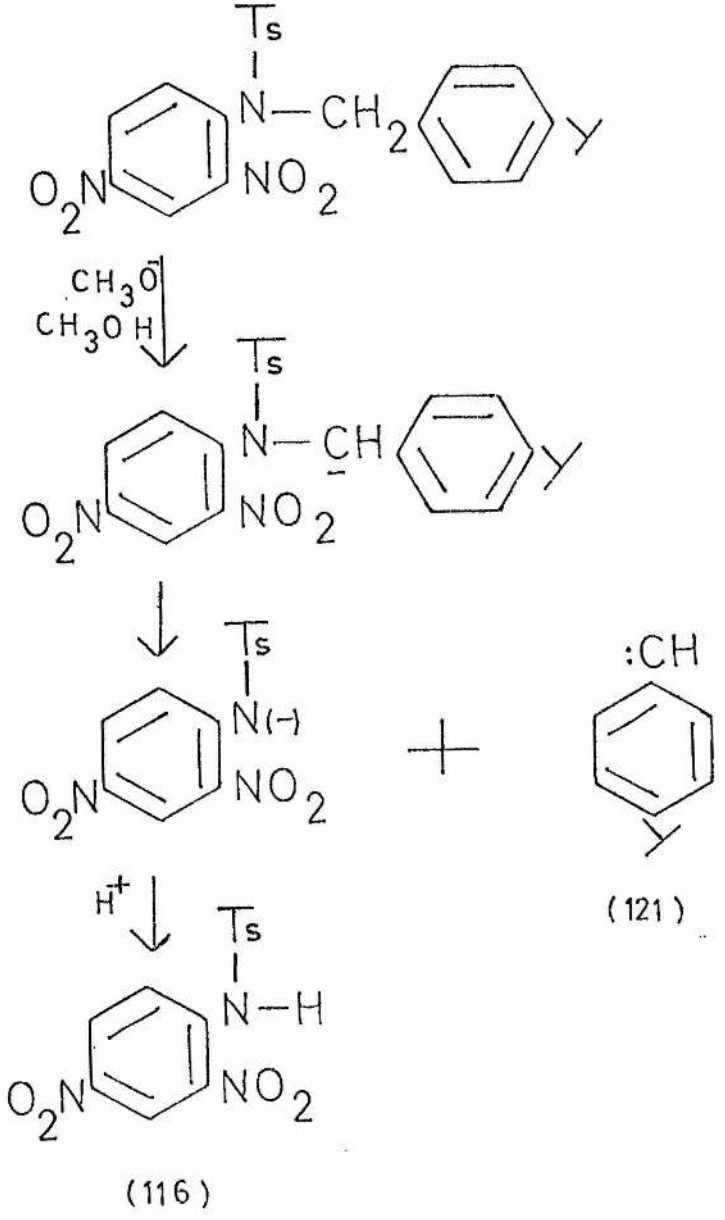
SCHEME 25

This involves a straightforward S_N2 reaction, with methoxide as the nucleophile and N-2,4-dinitrophenyl-tolyene-p sulphonamide as the leaving group.

If this was the case then detection of methyl p-nitrobenzyl ether (120: $y=NO_2$), or benzyl methyl ether (120: y=H) would have provided important evidence in its favour. Authentic samples of the ethers were prepared, (120: $y=NO_2$) by reaction of p-nitrobenzyl chloride with sodium methoxide in methanol[68], and (120: y=H) by reaction of benzyl chloride with methanol in the presence of potassium hydroxide[69]. The comparison, by G.L.C., of the reaction mixtures and authentic samples of (120: $y=NO_2$:H) showed that no ethers were present in the reaction mixtures. By reacting (120: $y=NO_2$:H) with sodium methoxide in methanol it was determined that (120: y=H)

was completely stable to the reaction conditions, and that although (120:y=NO_2) broke down to various products, there was still a sizeable proportion of unreacted starting material. These results implied that Scheme 25 was not a major pathway for the reaction.

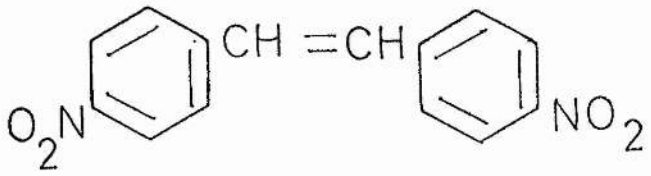
The next reaction pathway considered was that shown in Scheme 26, i.e. the formation of a carbene intermediate (121).



(116) (121)

SCHEME 26

Assuming that Scheme 26 was a major pathway it would have been expected that one of the by-products would have been either cis or trans 4,4'-dinitrostilbene[70,71] (122), which would have been easily isolable due to their low solubility in the reaction medium.

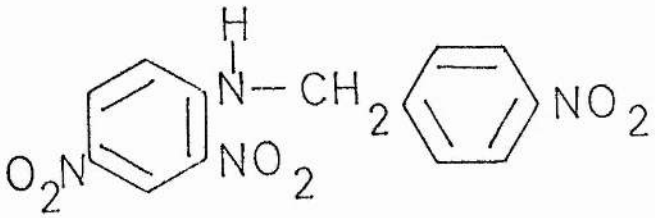


(122)

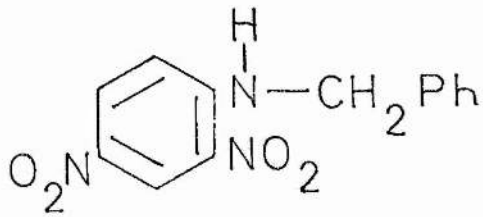
No (122) was detected, therefore no supporting evidence for Scheme 26 was found.

From these experiments, the mechanism for the reaction of (114) and (119) to (116) is not clear.

Detosylation by glacial acetic acid and concentrated sulphuric acid of (114) gave N-p-nitrobenzyl-2,4-dinitroaniline (123). N-Benzyl-2,4-dinitroaniline (124) was synthesised from 1-chloro-2,4-dinitrobenzene and benzylamine.

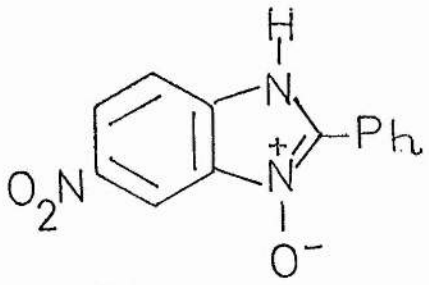


(123)



(124)

Reaction of (123) with sodium methoxide in methanol yielded (115) and that of (124), 5-nitro-2-phenylbenzimidazole-3-oxide (125).



(125)

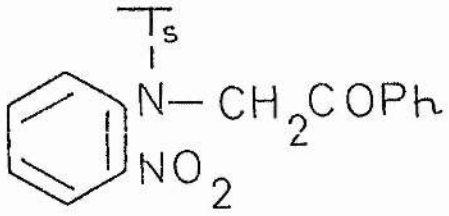
These latter results were the first indication that for the reaction of this type of compound with base, the reaction pathways seem to be very finely balanced. In this chapter we have seen examples of elimination, cyclisation and cleavage. In Chapter 3 these effects are exemplified to an even greater degree as the activating group and base are varied.

CHAPTER 3

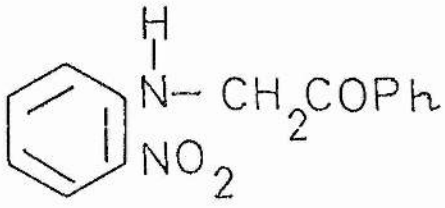
The reaction of N-phenacyl-N-p-tolylsulphonyl-o-nitroaniline derivatives with base to give 2-alkoxybenzimidazole-N-oxides, and other related reactions.

In Chapter 2, compounds of series (1) when reacted with sodium methoxide in methanol underwent cyclisation to give 2-p-nitrophenylbenzimidazole-3-oxide (70). Therefore, by changing the activating group from p-nitrophenyl to benzoyl (COC_6H_5) (benzoyl being a strong activating group similar to p-nitrobenzyl) it might have been expected that the major product of a base catalysed cyclisation of, for example, N-phenacyl-N-p-tolylsulphonyl-o-nitroaniline (126a) or N-phenacyl-o-nitroaniline (127a) would have been 2-benzoylbenzimidazole-3-oxide (128) (by analogy with Chapter 2). At first sight this expectation was borne out by the known[35] reaction of N-phenacyl-4-methyl-2-nitroaniline (127b) with aqueous potassium hydroxide which gave the expected product 2-benzoyl-5-methylbenzimidazole-3-oxide (129).

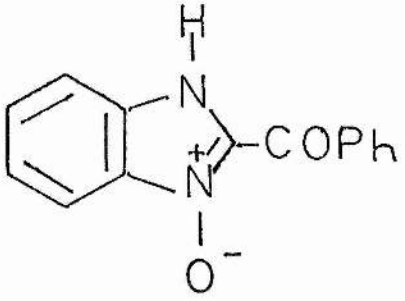
However the reaction of (127b) with methanolic potassium hydroxide only gave the expected product (129) in low yield (7%) along with methyl benzoate (8%) and 4-methyl-2-nitroaniline (130) (12%). This latter product (130) implied a reaction pathway involving some sort of cleavage, a not wholly unexpected result (c.f. Chapter 2), as well as one involving cyclisation. The reaction of (127b) with ethanolic potassium hydroxide produced similar results with (129) being formed in



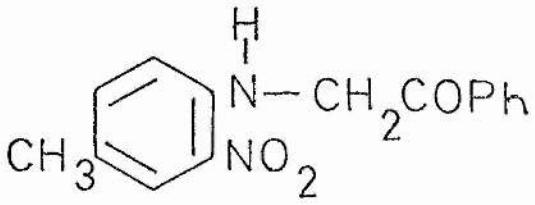
(126 a)



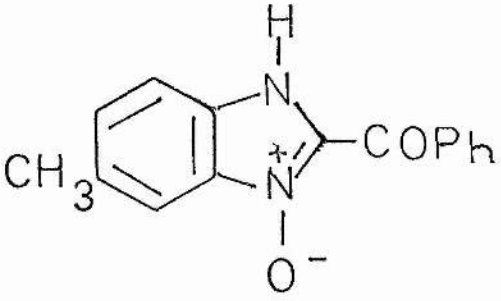
(127 a)



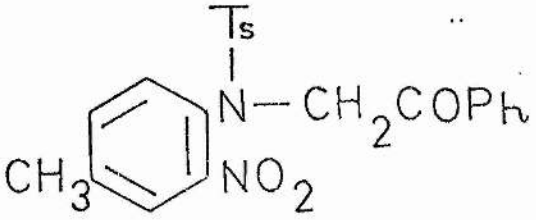
(128)



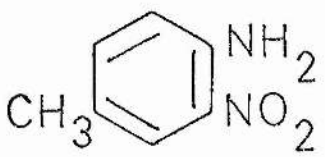
(127 b)



(129)



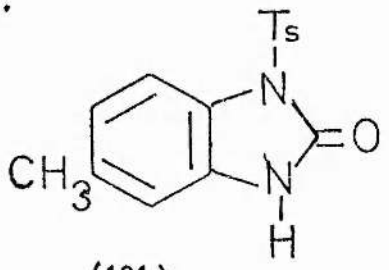
(126 b)



(130)

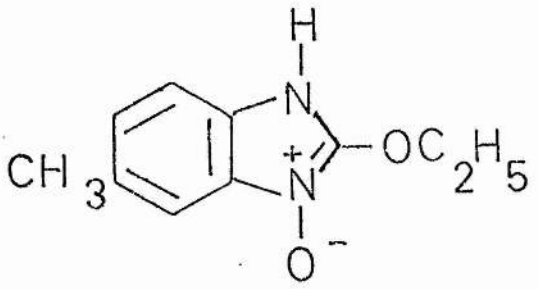
5% yield.

Matters were complicated somewhat by the result of the reaction of N-phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (126b) with methanolic potassium hydroxide. This reaction which would have been expected to give at least some of (129) instead gave 5-methyl-1-p-tolylsulphonyl-2-benzimidazolone (131) in low yield (6%), along with methyl benzoate (3%) and various other unidentifiable products, with no trace of (129).



(131)

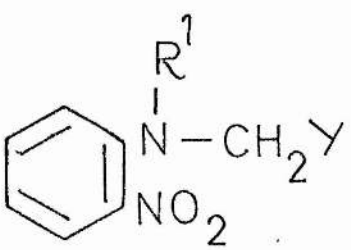
A further complication arose when the reaction of (126b) with ethanolic potassium hydroxide produced neither (129) nor (131). Instead 2-ethoxy-5-methylbenzimidazole-3-oxide (132b) was formed in good yield (53%).



(132b)

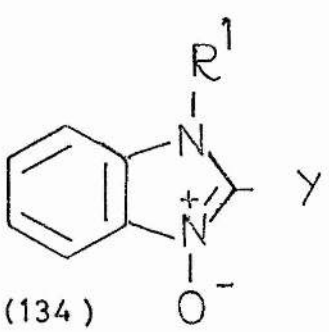
Thus the hypothesis stated at the beginning of the chapter, namely that (126a) and (127a) might undergo base catalysed cyclisations analogous to those of Scheme 14 was becoming doubtful. These fears were realised when the reaction of (127a) with methanolic potassium hydroxide gave methyl benzoate (7%) and o-nitroaniline (10%) as the only identifiable products, and (127a) with ethanolic potassium hydroxide yielded no identifiable products at all. Finally when methyl benzoate was the only isolable product from the reaction of (126a) with methanolic potassium hydroxide it was readily apparent that a seemingly straightforward reaction actually involved many different facets.

The most interesting result obtained from these early reactions was the good yield of (132b). This was because 2-alkoxybenzimidazole-3-oxides had been relatively little studied, presumably because of their comparative inaccessibility. They cannot be prepared from compounds such as (133:y=OR), since cyclisations of the type (133) → (134) require that y be an electron acceptor. They are also not obtainable from the reductive cyclisation of an N-alkoxycarbonyl-o-nitroaniline since under these conditions the corresponding benzimidazolone should be formed.



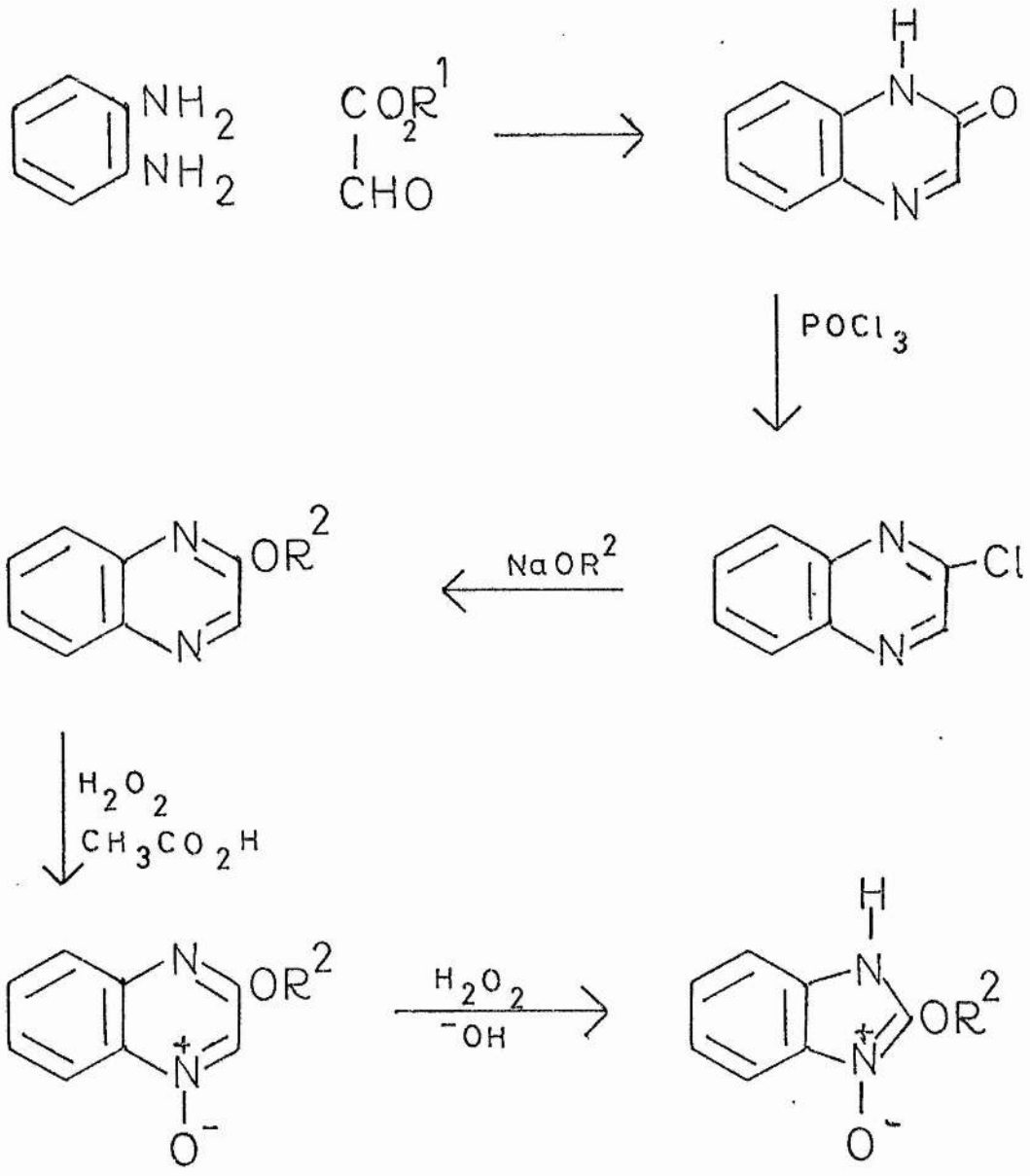
(133)

Y=OR



(134)

They had previously been obtained[34] only by alkaline hydrogen peroxide oxidation of 3-alkoxyquinoxaline-1-oxides (135), which were themselves the end products of a multi-step synthesis[72,73] Scheme 27.



(135)

SCHEME 27

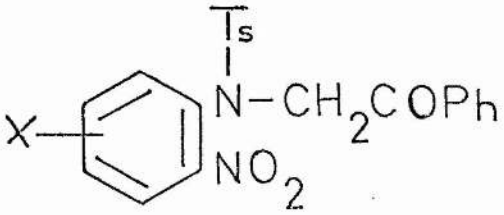
Thus, the two main priorities involved in the research described in the first part of this chapter were

i) to explain satisfactorily the results described above, and

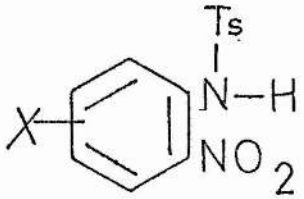
ii) to establish a reaction for which 2-alkoxy-benzimidazole-3-oxides were the major products.

In order to do this a series of compounds, (series 3), were prepared and the reactions of these compounds with various bases were studied.

Series 3



(126)



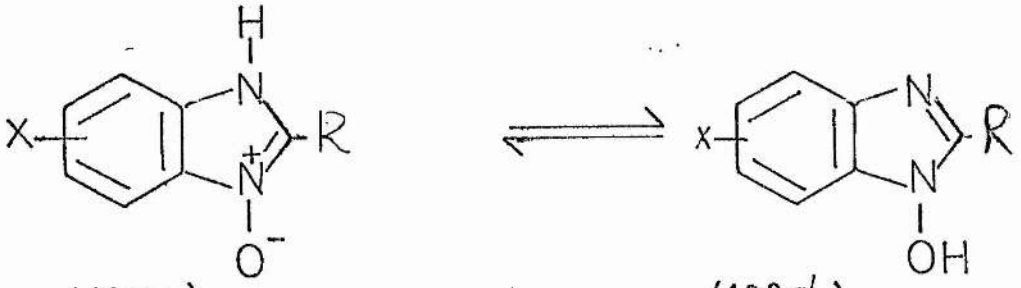
(126')

a) X = H
b) X = 4-CH_3
c) X = 4-Cl
d) X = 4-OCH_3
e) X = 5-CH_3
f) X = 6-CH_3

Compounds (126a → f) were prepared from the sodium salt of the corresponding sulphonamide (126') and phenacyl bromide in dimethylformamide.

The compounds (126a → e) were first reacted with two molar equivalents of sodium ethoxide in ethanol. These conditions were chosen for two reasons. Firstly, the previous formation of (132) had arisen using ethanolic potassium hydroxide as the base, and secondly for the best yields of the cyclised products described in Chapter 2, two molar equivalents of base with respect to the starting material had been used.

N-Phenacyl-N-p-tolylsulphonyl-o-nitroaniline (126a) reacted with the two molar equivalents of sodium ethoxide in ethanol to give 2-ethoxybenzimidazole-3-oxide (132a) (which is tautomeric with 2-ethoxy-1-hydroxybenzimidazole 132a'). The position of equilibrium, like that in the previous Chapter, has not been established.

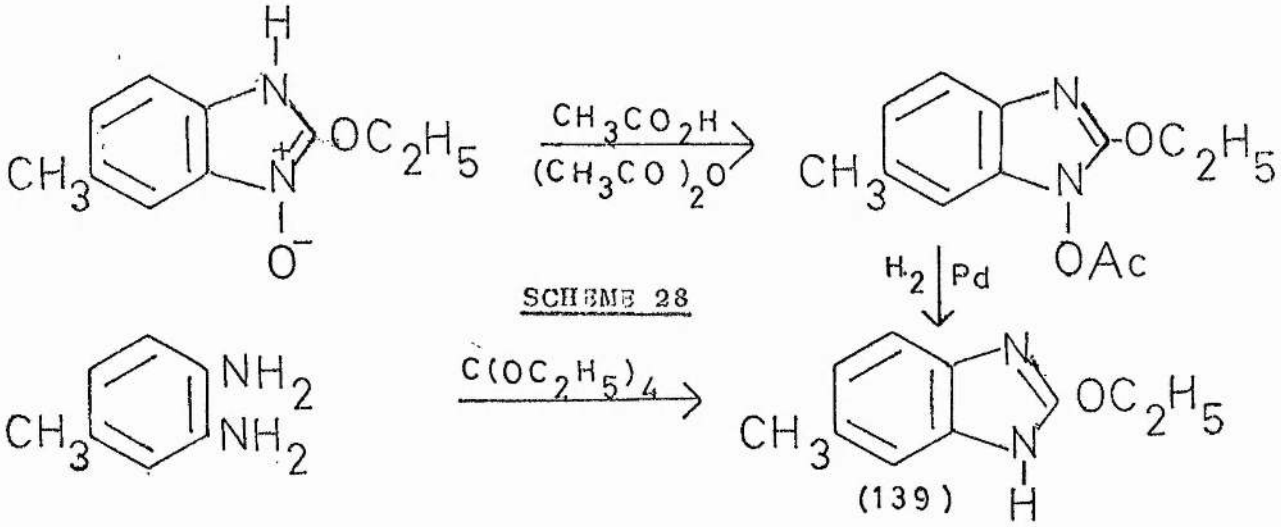


(132a) (132a')

a) X = H
b) X = 5-CH_3
c) X = 5-Cl
d) X = 5-OCH_3
e) X = 6-CH_3

132 R' = OC_2H_5
136 R' = OCH_3
137 R' = $OCH_2CH_2CH_3$
138 R' = $OCH(CH_3)_2$

Similarly, (132b → e) were obtained in good yield by the cyclisation of (126b → e). The structures of these compounds followed from their analyses, nmr and mass spectra, and in the case of the 5-methyl derivative (132b) from deoxygenation to the benzimidazole (139), which was synthesised independently from 3,4-diaminotulene and tetra-ethoxymethane[74]. (Scheme 28).



SCHEME 28

The use of sodium methoxide in methanol in place of ethoxide in ethanol gave the 2-methoxybenzimidazole-3-oxides (136) albeit in lower yield. Sodium n-propoxide in n-propanol and sodium isopropoxide in isopropanol similarly gave the 2-propoxy analogues (137 and 138). The general usefulness of this reaction is illustrated by the results in table 6.

TABLE 6

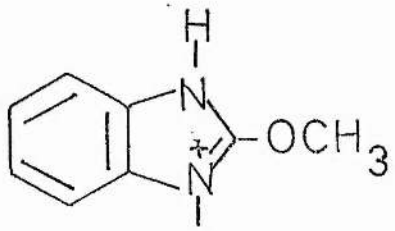
2-alkoxybenzimidazole-3-oxides prepared from N-(acyl methyl)-N-aryl(or alkyl)sulphonyl-o-nitroanilines and sodium alkoxides

(Percentage Yield in parentheses)

Sulphonamide	$NaOCH_3$	$NaOC_2H_5$	$NaOC_3H_7$ n	$NaOC_3H_7$ iso
126a	0	132a (80)		
126b	136b (47)	132b (62)	137b (65)	138b (24
126c	136c (28)	132c (62)	137c (54)	
126d	136d (34)	132d (68)		
126e	136e (45)	132e (41)		

(132b) was also formed from (126b) using NaOH/EtOH and Na_2CO_3/EtOH in 53 and 33% yields respectively. The one instance of zero yield is thought to represent a problem of isolation and not of non-formation. In general the methoxy derivatives are more soluble in aqueous media than their ethoxy or propoxy analogues, and the successful isolation of all these N-oxides from aqueous media depends on careful adjustment of the pH. When anhydrous hydrogen chloride in methanol was used instead of dilute sulphuric acid in the final stage of the isolation procedure of the reaction of (126a) with sodium methoxide, a substance whose mass spectrum had a molecular ion peak corresponding to 164.057611 was detected. Similarly the $(M-31)^+$ ion had an m/e value of 133.040332. Compound (136a) requires a molecular ion peak at m/e 164.058573

and an $(M-OCH_3)^+$ at m/e = 133.040185. From these results it is possible that (136a) or its hydrochloride (140) is present in the reaction mixture . However, all attempts to isolate



(140)

the free base and other derivatives (for example the N-methoxy compound) proved unsuccessful. Also, as this compound (136a or 140) was isolated along with inorganic salts, from which it was very difficult to separate it proved impossible to obtain a correct analysis.

As can be seen, the results obtained from using two molar equivalents of methoxide, ethoxide, n-propoxide and isopropoxide with respect to the starting material had solved part two of the initial intention, i.e. a method had been found for synthesising 2-alkoxybenzimidazole-3-oxides in generally good yield. This method had two advantages over the one described by Scheme 27:

i) simplicity

ii) applicability to the preparation of derivatives unsymmetrically substituted in the carbocyclic ring. [if the o-phenylenediamine contains a substituent in the benzene ring, the first stage of the reaction in Scheme 27, i.e. the condensation of the dicarbonyl compound, will give rise

to two isomers, which will probably be very difficult to separate].

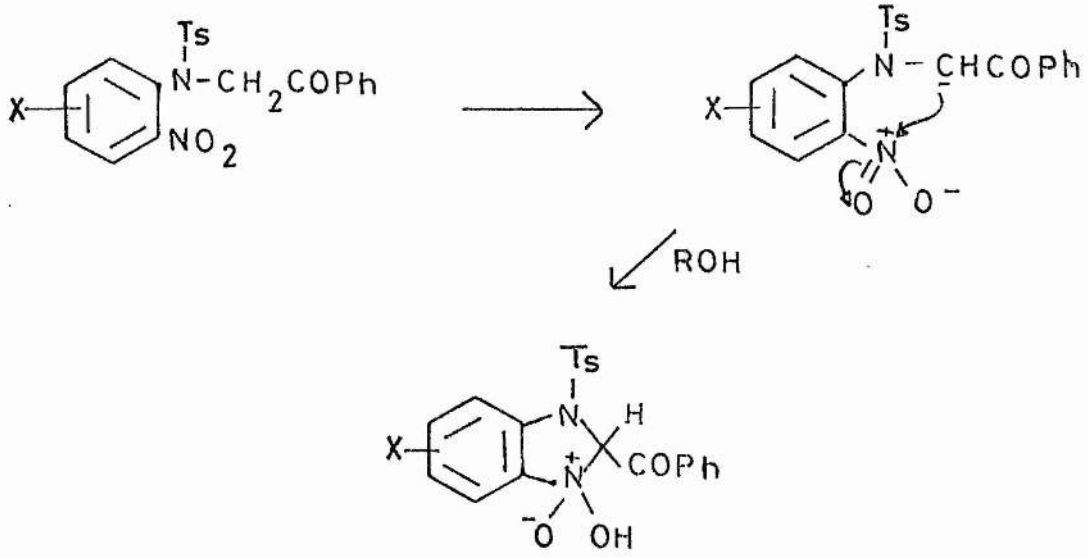
In order to try to elucidate the mechanism of the above cyclisations and to explain the early results in this field, the proportion of base used in the reaction was reduced to an equimolar amount with respect to the starting material. Compound (126b) was reacted under these conditions and three important products were found.

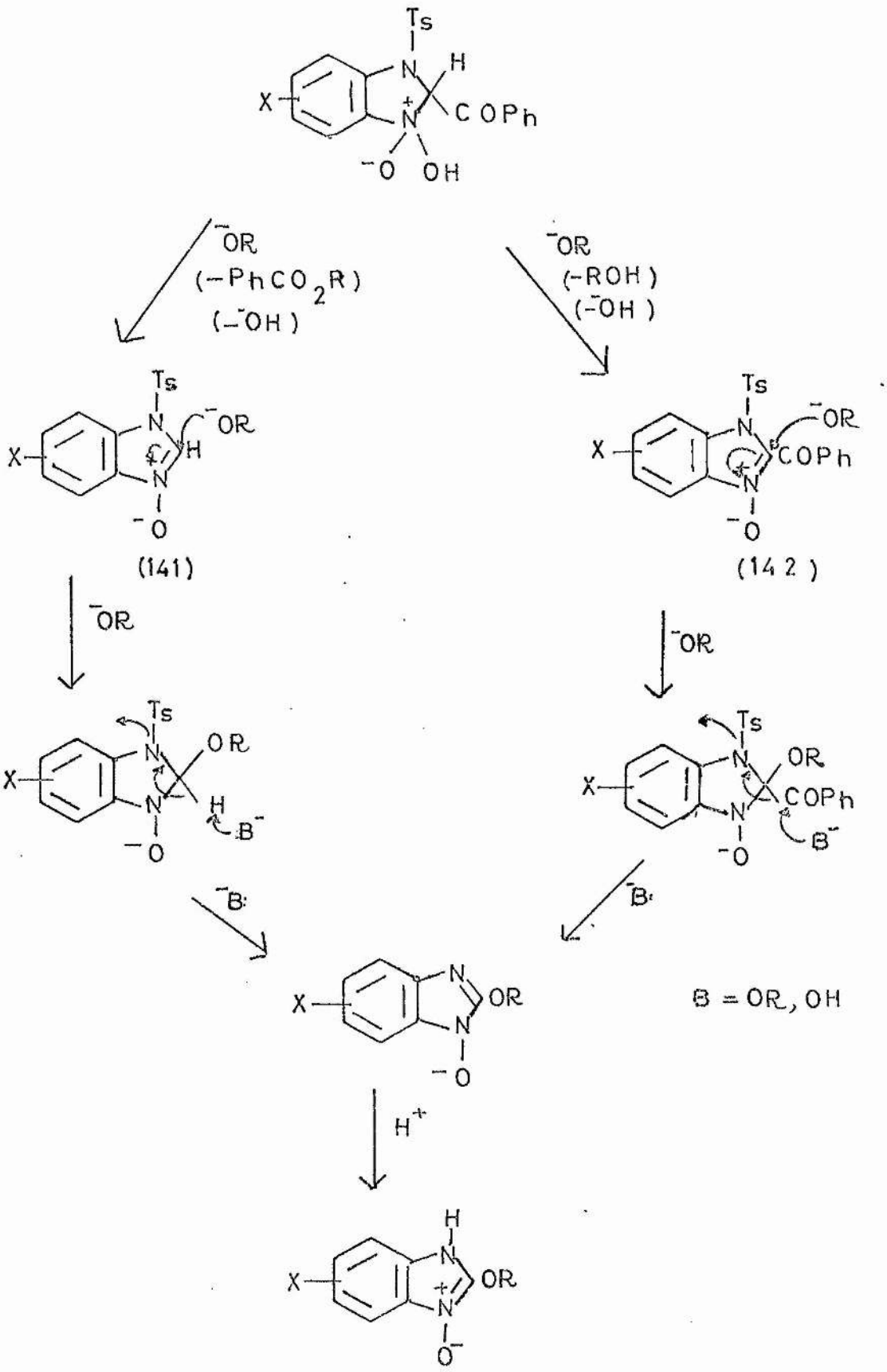
i) 2-benzoyl-5-methylbenzimidazole-3-oxide (129)

ii) 5-methyl-1-p-tolylsulphonyl-2-benzimidazolone (131)

iii) benzoic acid. (the benzoic acid formed was detected by treating the ether insoluble portion of the reaction mixture with methanolic hydrogen chloride and detecting methyl benzoate by high performance liquid chromatography).

Scheme 29 accounts for the results when both one and two molar equivalents of base were used.




Ts
N
H
X
+
N
COPh
⁻O
OH
⁻OR
(-PhCO₂R)
(⁻OH)
⁻OR
(-ROH)
(⁻OH)
Ts
N
⁻OR
X
H
N
⁻O
(141)
Ts
N
⁻OR
X
COPh
N
⁻O
(142)
⁻OR
⁻OR
Ts
N
OR
X
H
N
⁻O
B⁻
Ts
N
OR
X
COPh
N
⁻O
B⁻
⁻B:
⁻B:
X
N
OR
N
⁻O
B = OR, OH
H⁺
H
N
X
+
N
OR
O⁻

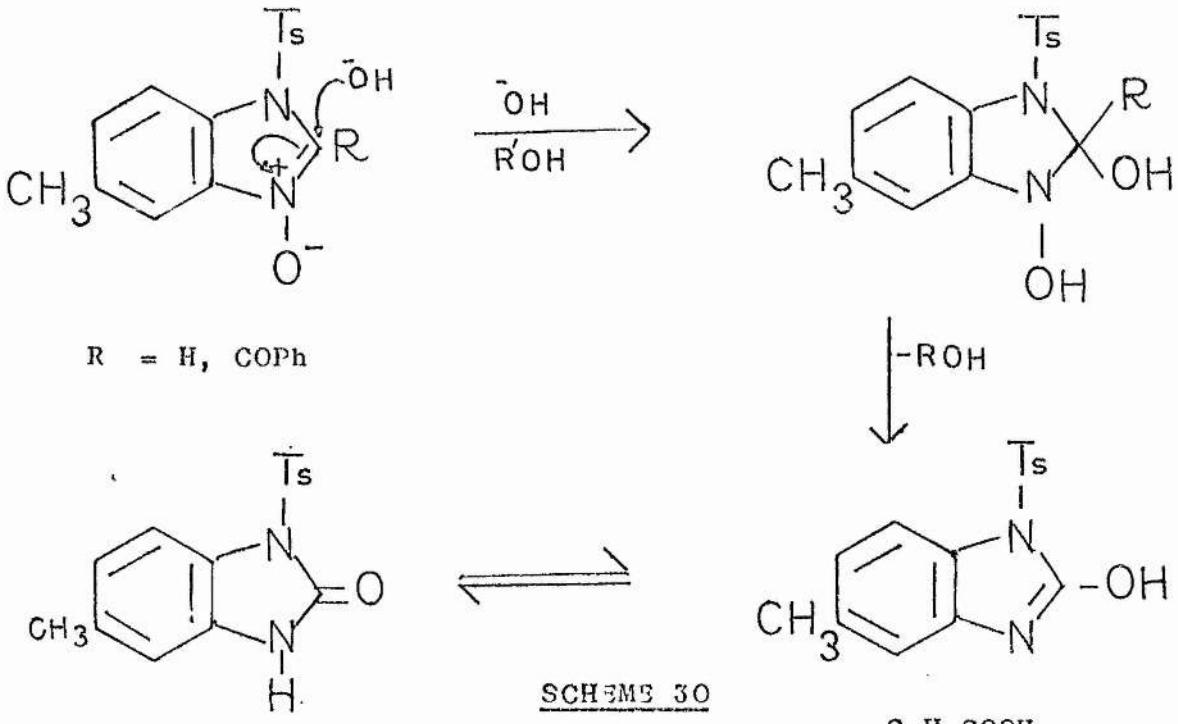
SCHEME 29

Scheme 29 postulates two possible intermediates, namely, 1-*p*-tolylsulphonylbenzimidazole-3-oxide (141) and 2-benzoyl-1-*p*-tolylsulphonylbenzimidazole-3-oxide (142). (There is also the slight possibility of 2-benzoylbenzimidazole-3-oxide being the reaction intermediate. However it is though that under basic conditions, attack by the alkoxide ion at the C(2) position of the anion is unlikely. All attempts to verify this have been unsuccessful since it has not been possible to obtain a sufficient quantity of 2-benzoyl-5-methylbenzimidazole-3-oxide. Work is still proceeding on this aspect of the mechanism).

These intermediates, unlike the corresponding intermediate (93) in Scheme 14, may undergo nucleophilic attack at C(2). (A reaction possible in 1-substituted-*N*-oxides, since the removal of the possiblity of tautomerism makes attack at C(2) likely)[46], and the resulting adduct is then attacked by a further mole of base to give the final benzimidazole-*N*-oxide and the toluene-*p*-sulphinate ion.

Reaction via these intermediates (141) and (142) can also explain the products from the reaction between equimolar proportions of base and starting material.

The formation of the benzimidazolone (131) can be explained by Scheme 30. Once the intermediates (141) and (142) have been formed, and in the absence of any further alkoxide ion, attack by the hydroxide ion at C(2) followed by loss of water or benzoic acid gives (131).



R = H, COPh

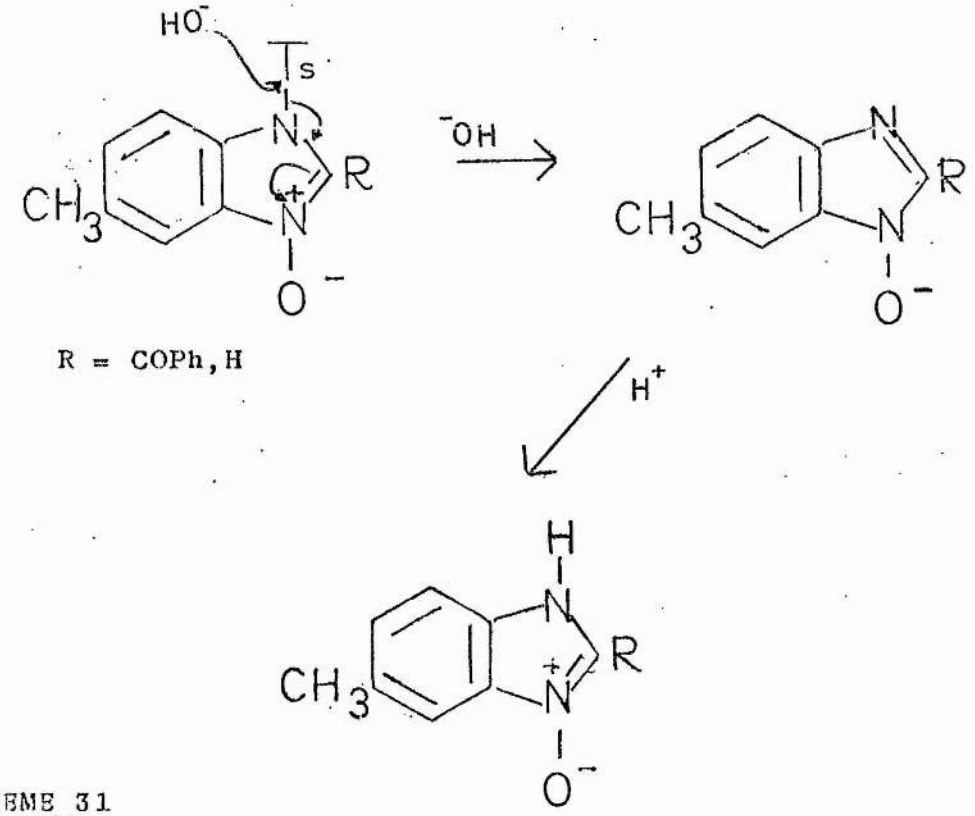
SCHEME 30

+ C_6H_5COOH

(when R = COPh)

The addition of water to the intermediates (141) and (142) followed by loss of water in the case of (141), and benzoic acid in the case of (142) will also give the corresponding benzimidazolone[33].

Attack by the hydroxide ion on the p-tolylsulphonyl group of the intermediates (141) and (142) can also occur. (Scheme 31). In this case the products would be 2-benzoyl-5-methylbenzimidazole-3-oxide (129) and 5-methylbenzimidazole-3-oxide (143). It is however unlikely that (143) would be isolated due to its solubility characteristics in the reaction medium.



SCHEME 31

143 (when R = H)
129 (when R = COPh)

The attempted synthesis of the postulated intermediates (141) and (142) and their reactions with base is the obvious next stage to verify the suggested reaction pathways (Schemes 29, 30, and 31). This research is described in Chapter 4; suffice it to say here that the work was largely unsuccessful.

Scheme 29 and 30 can also help explain the results of the initial experiments of (126a) and (126b) with potassium hydroxide. It seems fair to assume that with weaker bases than the alkoxides (e.g. hydroxide), the reaction proceeds to the

intermediates (141) and (142) and hence in the case of (126b) to (131). It is also possible that other reaction pathways will become competitive with the cyclisation pathway, and this accounts for the variety of products seen and the low yields obtained.

However, it must also be said that the reasons why (126b) in ethanolic potassium hydroxide gave the 2-ethoxy-N-oxide (132b) but did not give the corresponding 2-methoxy-N-oxide (132a) with methanolic potassium hydroxide are still not clear.

The results obtained from the reactions of the detosylated compounds (127a) and (127b) were at first slightly harder to explain. (Compound (127a) with methanolic potassium hydroxide gave only methyl benzoate, o-nitroaniline and starting material as identifiable products whilst with ethanolic potassium hydroxide no identifiable products were isolated. The reactions of (127b) with ethanolic and methanolic potassium hydroxide produced (129) in low yield along with methyl benzoate and 4-methyl-2-nitroaniline).

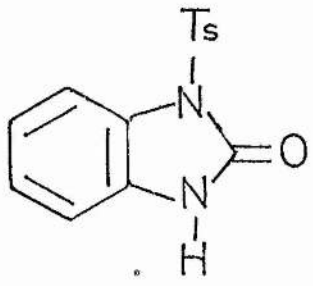
However, when it was shown that (127a) and (127b) did not give the expected 2-alkoxybenzimidazole-N-oxide when treated with two molar equivalents of ethoxide in ethanol or methoxide in methanol, but gave instead a high yield ($\simeq$70%) of the corresponding primary amine, derived presumably from a cleavage pathway of some description, and in the case of (127b) the 2-benzoyl-N-oxide (129) in very low yield (2%), it became apparent that in the case of the detosylated compounds a different mechanism was operable, and an analogue of Scheme

29 cannot be recognised as a major pathway.

Therefore it seems that in the cases already discussed, the strength of the base, the proportion of the base used with respect to the substrate and the p-tolylsulphonyl group all have a major effect in determining the reaction pathway and hence the products formed. Thus, if the reactions were repeated using a weak base like carbonate, results similar to those obtained when hydroxide was the base would be expected. Similarly the use of t-butoxide should also provide some interesting results, since when the base used was iso-propoxide, the 2-alkoxy-N-oxide had been formed along with the corresponding primary amine, pointing to a competitive elimination type reaction as the strength or bulk of the base was increased.

The results of using carbonate as the base were indeed similar to those obtained for the case when hydroxide was the base.

Compound (126a) with methanolic carbonate yielded 1-p-tolylsulphonyl-2-benzimidazolone (144) in low yield (6%).

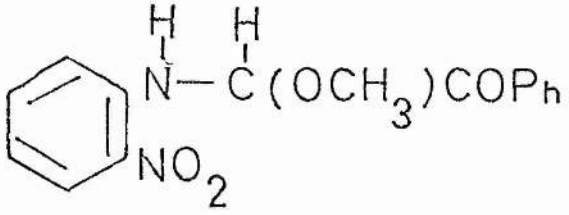


(144)

No products apart from methyl benzoate (5%) were identifiable for the reaction of (126b) under the same conditions. The corresponding 2-ethoxy-N-oxide (131) was again produced when (126b) was reacted with ethanolic carbonate, although in a much lower yield (33%) than that obtained from the hydroxide reaction (53%). The reaction of (126a) with ethanolic carbonate yielded only starting material.

Compounds (127a) and (127b) also yielded similar products with methanolic carbonate to those obtained from methanolic hydroxide. (See Table 7).

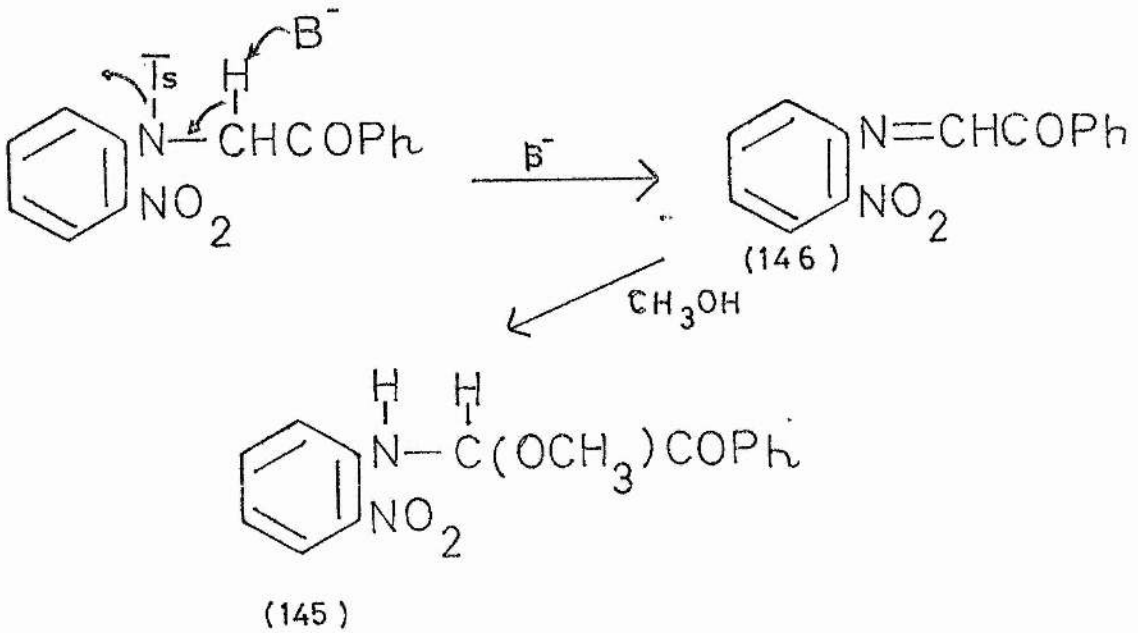
In all the experiments with carbonate and hydroxide described so far the base had been added to a mixture of the starting material in warm alcohol. However, in the case of (126a), when a slurry of carbonate and methanol was made, addition to (126a) yielded N-(o-nitrophenyl)-α-methoxyphenacylamine (145) in excellent yield (84%). In this case it is thought that either the carbonate attacks a proton of the



(145)

methylene group, and (145) is formed by subsequent elimination and addition of methanol or that some sort of equilibrium is set up between the carbonate and methoxide ion, which leads to elimination and the formation of the Schiff base (146) and hence by addition of methanol to (145)

$$CO_3^{2-} + CH_3OH \rightleftharpoons HCO_3^- + CH_3O^-$$



(145)

When (126a) and (126b) were reacted with tertiary butoxide the only isolable product was the primary amine. This result implied that the elimination mechanism (Scheme 32) was now the major reaction pathway. The other expected product of such a reaction phenyl glyoxal (147) was not isolated. This however was not surprising as an authentic sample of (147) was shown to be unstable under the chromatographic conditions.

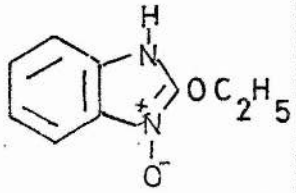
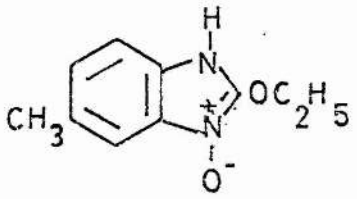
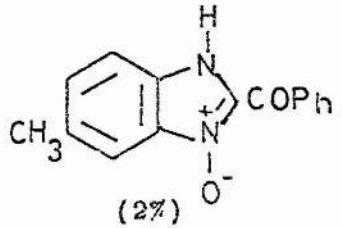
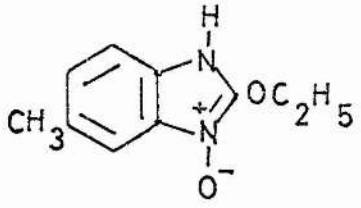
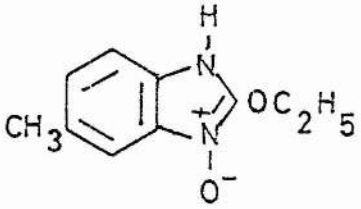
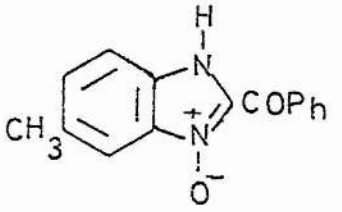
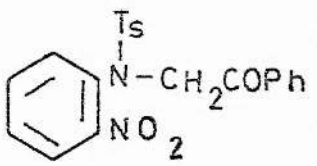
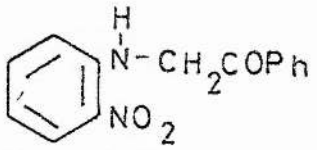
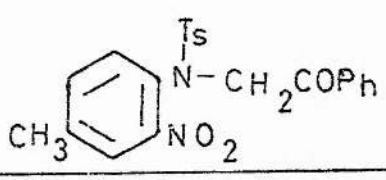
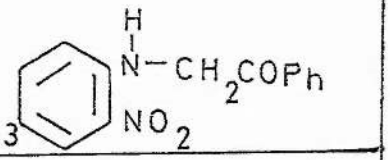
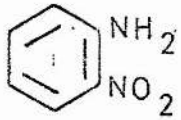
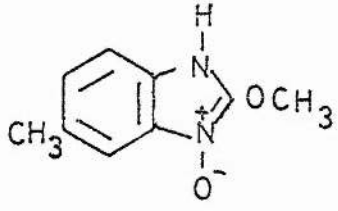
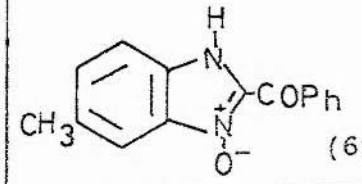
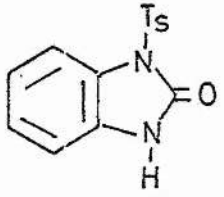
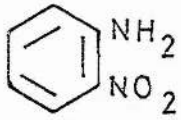
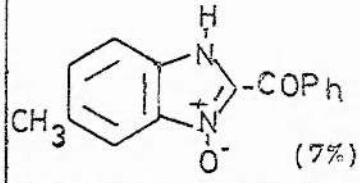
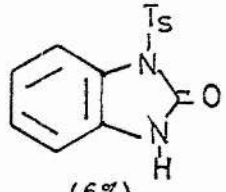
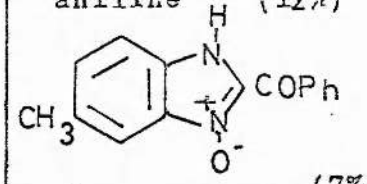
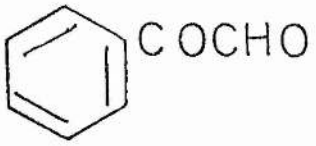
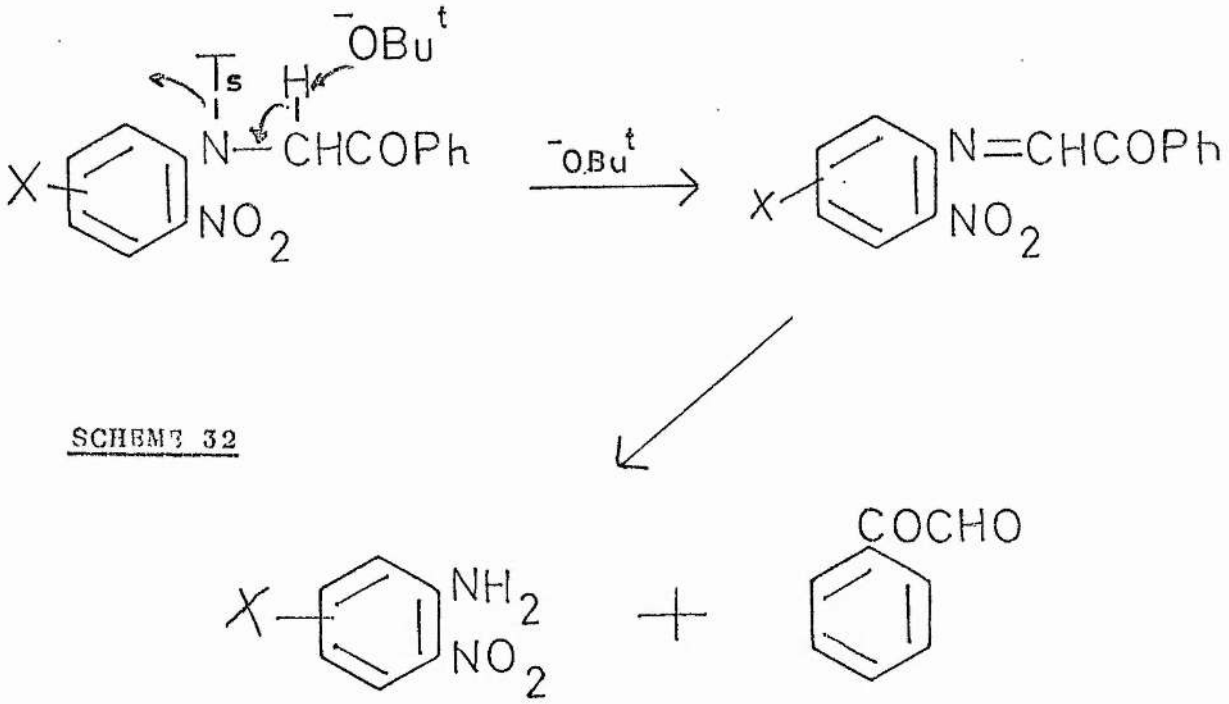
$C_2H_5O^-$ / C_2H_5OH	 (80%)	 (64%)	 (62%)	 (2%) 4-methyl-2-nitroaniline (60%)
CO_3^{2-} / C_2H_5OH	starting material (81%)		 (33%)	
OH^- / C_2H_5OH		Nothing Isolable	 (53%)	 (5%)

TABLE 7

STARTING MATERIAL / BASE				
CH_3O^- / CH_3OH	Nothing Isolable	No Acidic Product methyl benzoate (15%)  (70%)	 (47%)	methyl benzoate (3%) 4-methyl-2-nitroaniline (12%)  (6%)
CO_3^{2-} / CH_3OH	 (6%)	methyl benzoate (14%)  (70%)	acidic product not identifiable methyl benzoate (2%)	methyl benzoate (5%) 4-methyl-2-nitro-aniline (12%) starting material (7%)  (7%)
OH^- / CH_3OH	unidentifiable acidic product methyl benzoate (10%) starting material (4%)	methyl benzoate (7%) starting material (8%)  (10%)	methyl benzoate (3%)  (6%)	methyl benzoate (8%) 4-methyl-2-nitro-aniline (12%)  (7%)



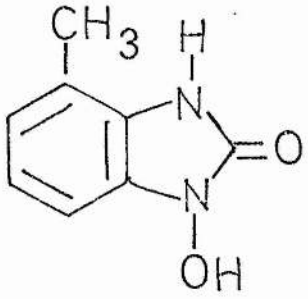
(147)



SCHEME 32

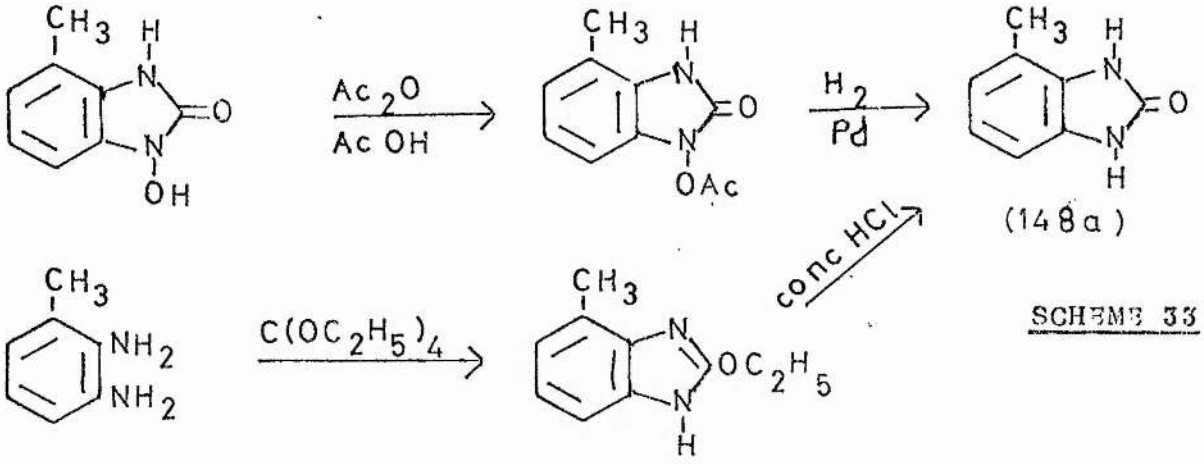
In summary therefore, compounds of series 3 with bases such as hydroxide and carbonate seem to undergo various reaction pathways, including to a minor extent cyclisation. With bases such as methoxide, ethoxide and n-propoxide, cyclisation is the major reaction pathway and good yields of 2-alkoxybenzimidazole-3-oxides are formed. With isopropoxide, elimination as well as cyclisation is evident and with tertiary butoxide elimination is the only reaction involved.

Another apparent anomaly in this series was the reaction of (126f) with two molar equivalents of ethoxide or methoxide. This reaction had as its major product 1-hydroxy-4-methyl-2- benzimidazolone (148).



(148)

The structure of (148) followed from its analytical and spectroscopic properties and from its deoxygenation to the benzimidazolone (148a) which was prepared independently from 2,3-diaminotoluene and tetraeth oxymethane[74] (Scheme 33).



SCHEME 33

The reason for the anomalous behaviour of (126f) with alkoxide is not clear, but it is possible that steric hindrance caused by the 6-methyl substituent may be responsible. Hindered rotation about the Ar—N bond of ortho substituted aniline derivatives is well known[55,56] and can be observed by the non-equivalence of the methylene protons adjacent to the amidic nitrogen (cf Chapter 2). The coalescence temperature of the

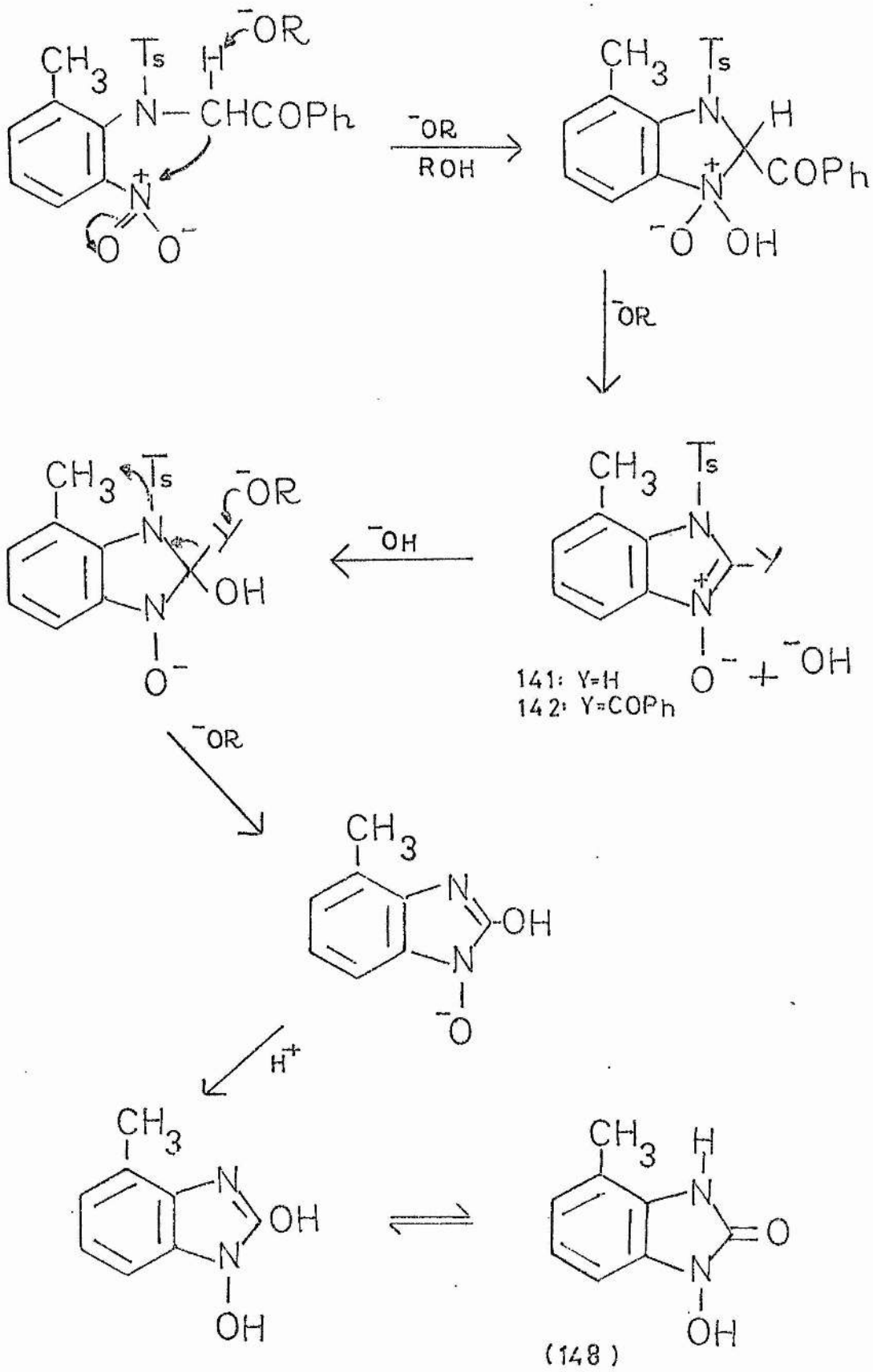
methylene protons of (126f) was greater than 140°, compared to that of (126b) which was 40°).

One of the main factors influencing the restricted rotation observable in (126f) will be the planarity of the amidic nitrogen with respect to the ortho substituents. In the case of (126f), in order to relieve steric strain the C(6)—CH_3 and N—Ts bonds are probably not co-planar, but in the case of the proposed intermediates (141 and 142; x=6-CH_3) of Scheme 29, they must be co-planar as the lone pair of electrons on the amidic nitrogen is required to contribute to the aromaticity of the system. Due to the steric strain now involved, the intermediate (141, 142:x=6-CH_3) will be a very high energy species and will react rapidly with any available nucleophile, which in this case is likely to be the hydroxide ion which has just been expelled in the previous stage of the reaction. The most likely course of reaction giving rise to (148) is shown in Scheme 34.

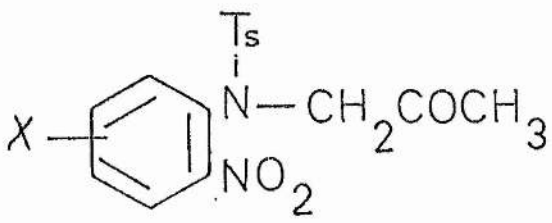
Various other series of compounds (series 4-7) were synthesised to determine whether the products obtained by reacting the compounds of series (3) with two molar equivalents of methoxide, ethoxide and propoxide (iso and normal) were general

Series 4

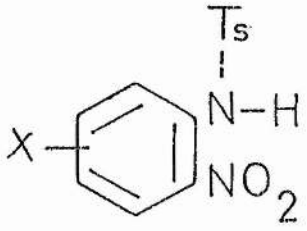
Series 4 involved changing the activating group of series 1 from benzoyl to acetyl ($COCH_3$).


CH3
Ts
H
⁻OR
N—CHCOPh
⁻OR
ROH
COPh
OH
⁻OR
⁻OH
Y
141: Y=H
142: Y=COPh
+ ⁻OH
OH
H+
(148)

SCHEME 34



(149)



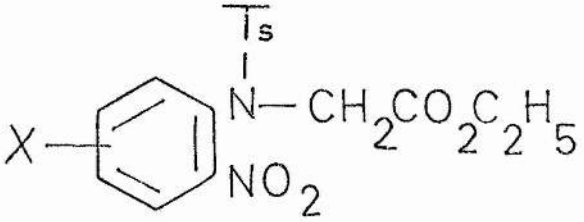
(149')

a X=H
b X=4-CH_3
d X=4-OCH_3
f X=6-CH_3

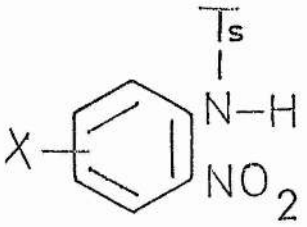
The compounds of series 4 were prepared analogously to those of series 3 i.e. by reaction of the sodium salt of the required sulphonamide (149') with chloroacetone. The results from the reactions of (149a, b, d and f) with two molar equivalents of base were analogous in every case to those of series 3, although the yields were slightly lower. (See Table 8).

In the reactions of (149f) with sodium methoxide and sodium ethoxide the benzimidazolone (148) was again obtained (cf compound 126f). The coalescence temperature of the methylene group in (149f) was again greater than 140°. The coalescence temperature of (149b) was found to be -9°C.

Series 5



(150)



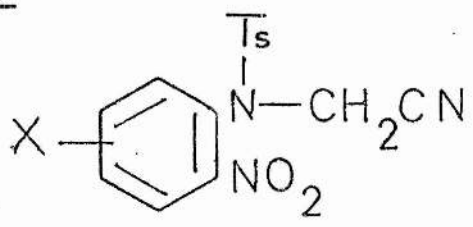
(150′)

a X=H
b X=4-CH_3
c X=4-OCH_3

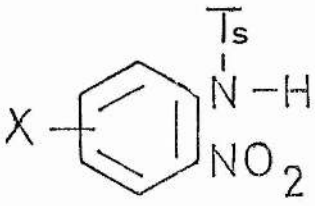
The N-ethoxycarbonylmethyl-N-p-tolylsulphonyl-o-nitroaniline derivatives were prepared from the sodium salt of the corresponding sulphonamide (150') and ethyl bromoacetate.

All the compounds of series 5 reacted with methoxide, ethoxide and t-butoxide to give the corresponding primary amine in good yield implying an elimination then hydrolysis mechanism for the reaction.

Series 6



(151)



(152)

a X=H
c X=4-Cl
f X=6-CH_3

TABLE 8

2-Alkoxybenzimidazole-3-oxides prepared from N-(AcylMethyl)-N-aryl (or alkyl)sulphonyl-o-nitroanilines and sodium alkoxides

(Percentage Yields in parentheses)

Sulphonamide	$NaOCH_3$	$NaOC_2H_5$	$NaOPr^n$	$NaOPr^{iso}$
126a	0	132a (80)		
126b	136b (47)	132b (62)	137b (65)	138b (24)
126c	136c (28)	132c (62)	137c (54)	
126d	136d (34)	132d (68)		
126e	136e (45)	132e (41)		
149a	0	132a (40)		
149b	136b (47)	132b (82)	137b (38)	138b (28)
149c	136c (15)	132b (53)		

Compounds of series 6 were prepared from the corresponding sodium salt of the sulphonamide (152) and chloroacetonitrile. The reaction of series 6 with base produced not the cyclised product nor the primary amine. For this reaction the sulphonamide (152) was isolated in all cases.

The reactions of series 4, 5, and 6, all give different products when reacted under the same conditions. The reasons why one series should give cyclised products, another elimination products and series 6 products derived from cleavage is not clear. But yet again these are further examples of seemingly small changes in molecular structure and (more important) reactivity, giving rise to completely different reaction products, thus exemplifying the fine balance between the elimination, cyclisation and cleavage reactions.

Series 7

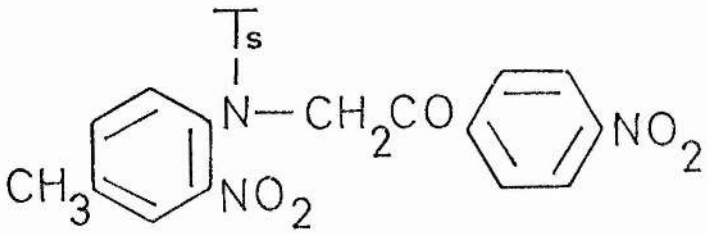
(153)

In series 7, the p-tolylsulphonyl group was replaced by the methylsulphonyl group and the activating group was changed from phenacyl to ethoxycarbonylmethyl.

The reaction of (153:y=COPh) with sodium ethoxide

in ethanol gave the expected product, 2-ethoxy-5-methylbenzimidazole-3-oxide (132b), although in lower yield (31%) compared to the p-tolylsulphonyl derivative of (153:y=COPh) (62%). Similarly the reaction of (153:y=$CO_2C_2H_5$) with ethoxide gave the same product as the p-tolylsulphonyl derivative (150b) namely the primary amine (130) in 35% yield.

The fine balance that exists between the reaction pathways of compounds of type (Series 3-7) with base is most vividly illustrated by considering the reaction of N-p-nitrophenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (126b*) with ethoxide in ethanol or methoxide in methanol.

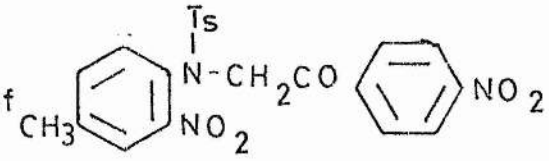


(126b*)

It might have been expected that the reaction of (126b*) with two molar equivalents of ethoxide would have given the 2-ethoxy-N-oxide (132b). However the reaction gave fourteen different products (detected by H.P.L.C.), (figure 9), with no trace of (132b). The corresponding reaction using two molar equivalents of methoxide yielded seventeen different products (again detected by H.P.L.C.) of which methyl benzoate, 4-methyl-2-nitroaniline and N-p-tolylsulphonyl-4-methyl-2-nitroaniline were shown to be present (figure 10).

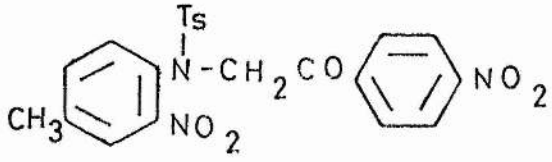
Similarly the reaction of (126b*) with an equimolar proportion of methoxide gave ten products from which methyl benzoate, N-p-tolylsulphonyl-2-nitro-4-methylaniline and starting material were shown to be present (figure 11).

In conclusion therefore, it seems that 2-alkoxy-benzimidazole-N-oxides are most readily obtainable from compounds of series 3 and 4. They are by no means general products for base catalysed cyclisations of the type investigated in this chapter.

H.P.L.C of 

$C_2H_5O^-$
C_2H_5OH

(acidified aqueous layer)

H.P.L.C. of 

$C_2H_5O^-$ / C_2H_5OH

(1) = ethyl benzoate

(organic layer)

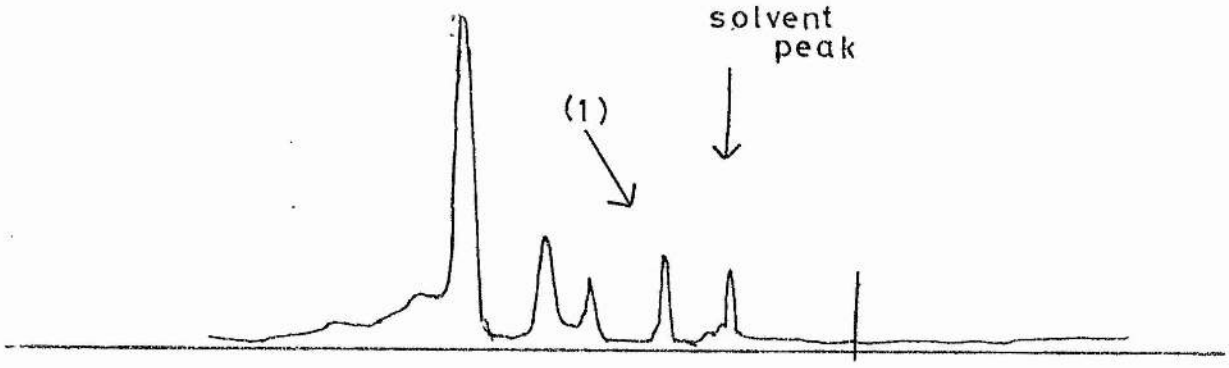
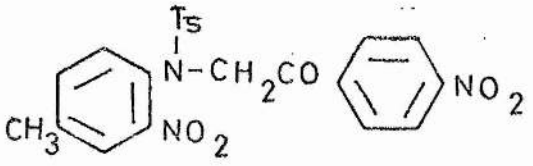
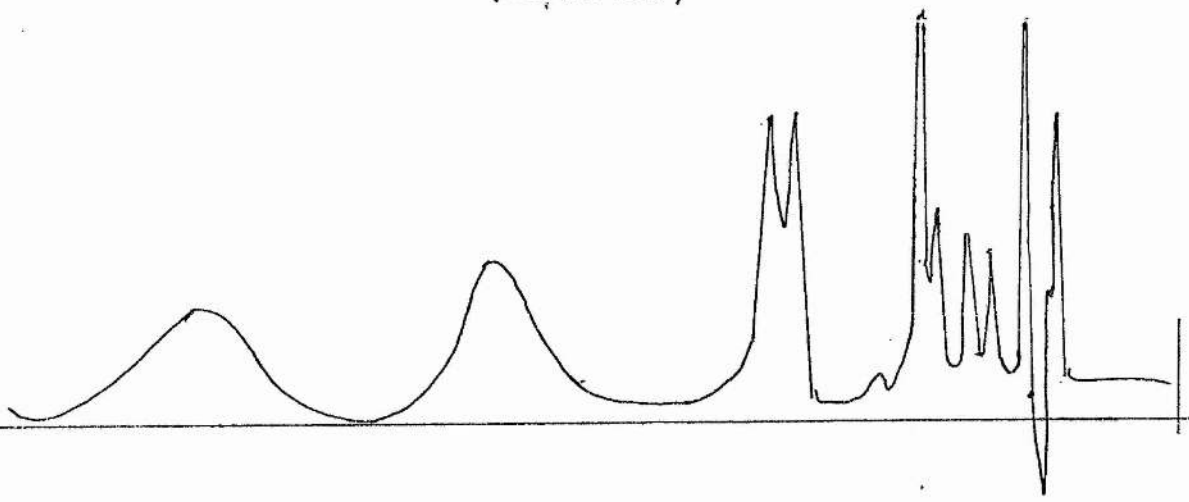


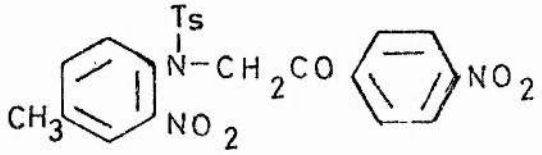
FIGURE 9

H.P.L.C. of 

$\xrightarrow[CH_3OH]{CH_3O^-}$

(aqueous layer)
(acidified)



H.P.L.C of 

$\xrightarrow[CH_3OH]{CH_3O^-}$

(1) = methyl benzoate
(2) = N-p-tolylsulphonyl-4-methyl-2-nitroaniline
(3) = 4-methyl-2-nitroaniline

(organic layer)

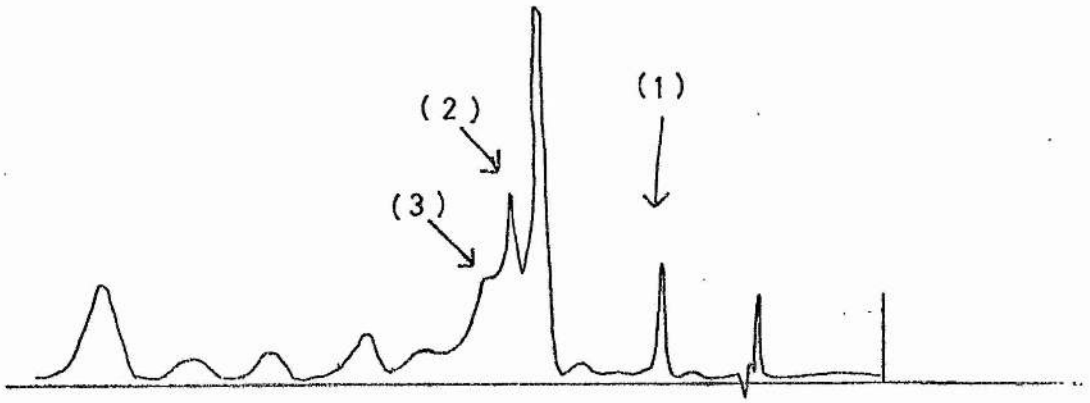
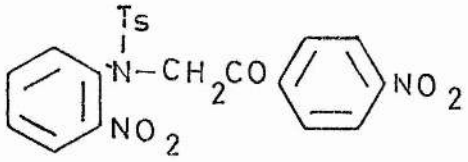


FIGURE 10

H.P.L.C of 

equimolar reaction $\xrightarrow[CH_3OH]{CH_3O^-}$

(1) = methyl benzoate

(2) = N-p-tolylsulphonyl-4-methyl-2-nitroaniline

(3) starting material (organic layer)

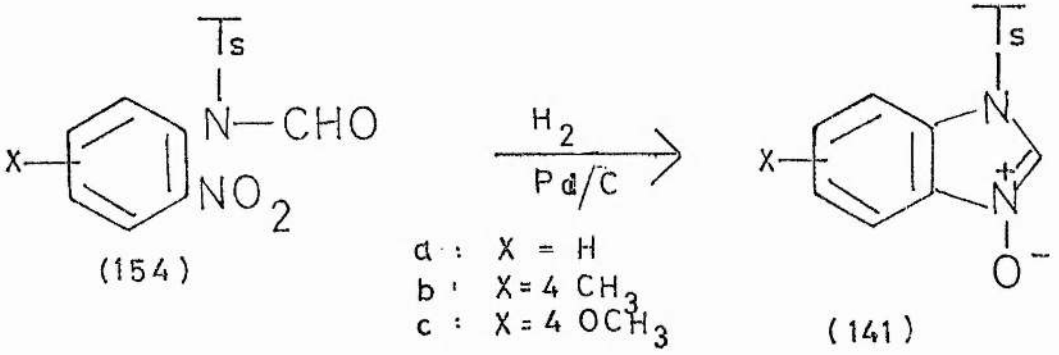
FIGURE 11

CHAPTER 4

The attempted synthesis of 1-p-tolylsulphonylbenzimdazole--3-oxides

In Chapter 3 the mechanism for the formation of various 2-alkoxybenzimidazole-3-oxides was discussed. The reaction scheme (Scheme 29) put forward postulated two alternative intermediates, viz 1-p-tolylsulphonylbenzimidazole-3-oxide (141) and 2-benzoyl-1-p-tolylsulphonylbenzimidazole-3-oxide (142). Chapter 4 describes the work carried out in an attempt to synthesise (141).

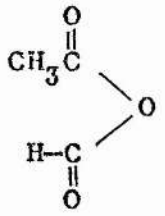
A modification of Schulenberg and Archer's method[18] i.e. the catalytic reduction of derivatives of N-formyl-N-p-tolylsulphonyl-o-nitroaniline seemed the most likely way to obtain (141). This method necessitated the formylation of



(154) (141)

derivatives of N-p-tolylsulphonyl-o-nitroaniline. Many methods are known[75] for formylating sulphonamides, with formylating agents ranging from formamide to formic acid, but these proved unsuccessful in the case of the derivatives

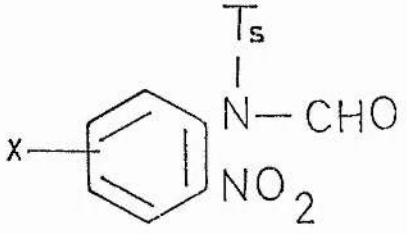
of N-p-tolylsulphonyl-o-nitroaniline. Starting material was recovered in each case. Therefore, to obtain (141), it was necessary to formylate the sodium salt of the sulphonamide. Hence, it was essential that the formylation was carried out in an acid free environment so as to prevent protonation of the salt. Bearing in mind this stipulation, the formylating agent chosen was acetic formic anhydride.



Acetic formic anhydride was prepared by the method of Murumatsu et.al.[76] which involved the reaction of sodium formate with acetyl chloride. Great care had to be taken over the reaction conditions as acetic formic anhydride decomposes at temperatures greater than 60°C, and even at room temperature in the presence of formic acid. (The alternative method[77] for preparing acetic formic anhydride from ketene and formic acid was also tried; however the former method proved more satisfactory).

Formylation of the sodium salts of the sulphonamide derivatives by acetic formic anhydride was successful at room temperature and compounds of series 8 were prepared.

Series 8



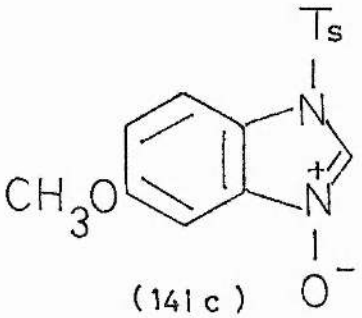
(154)

(a) X = H
(b) X = 4-CH_3
(c) X = 4-OCH_3

Schulenberg and Archer[18] had observed that the best yields of benzimidazole-N-oxides occurred when the catalytic hydrogenation was carried out in the presence of approximately one molar equivalent of acid. When this method was applied to compounds of series 8, it was found that deformylation occurred and the corresponding N-p-tolylsulphonyl-o-nitroaniline was formed. This result was verified by stirring the compounds of series 8 in a molar equivalent of acid at room temperature for eight hours. Complete deformylation was observed.

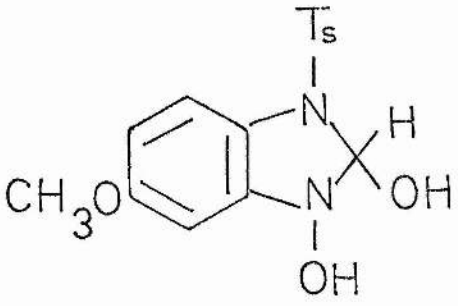
The hydrogenation was then repeated in the absence of acid, and in the case of (154a) and (154b) colourless "gums" were obtained that darkened readily on exposure to the atmosphere and various solvents. It was found that the best solvent for crystallisation of these gums was a benzene-petrol mixture. The mass spectra, infra-red spectra and ^{1}H nmr spectra all pointed towards the required N-oxides being present, but in low purity. For example, the mass spectrum of the product of the hydrogenation of (154b) had the correct molecular ion peak and a strong peak corresponding to the loss of the p-tolylsulphonyl group. The infra-red spectrum showed the absence of the carbonyl and nitro absorptions and the nmr was as to be expected. (i.e. the two methyl groups were visible. The aromatic signal was due to 3 protons, with the C(2)—H resonance hidden amongst the aromatic peaks.) However no correct analyses were obtainable from them. Chromatography was difficult due to the polarity of the compounds. However from a silica gel column with methanol as the eluant, compounds were obtained that had the correct accurate masses for the required N-oxides (141a, 141b), but again no correct analyses were obtainable.

The one exception in series 8 was found in the case of the 4-methoxy compound (154c). Hydrogenation of (154c) gave a crystalline solid, which from spectral evidence seemed to be the required N-oxide (141c).



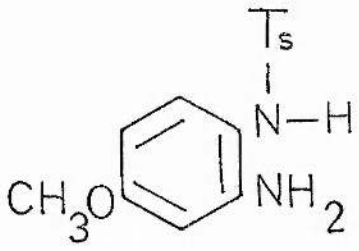
(141c)

However the analysis indicated that one extra mole of water was present, no matter whether the crystallising solvent was a hydrocarbon or an alcohol. There is a possibility that this compound is the hydrated form (155) of the required N-oxide (141c)



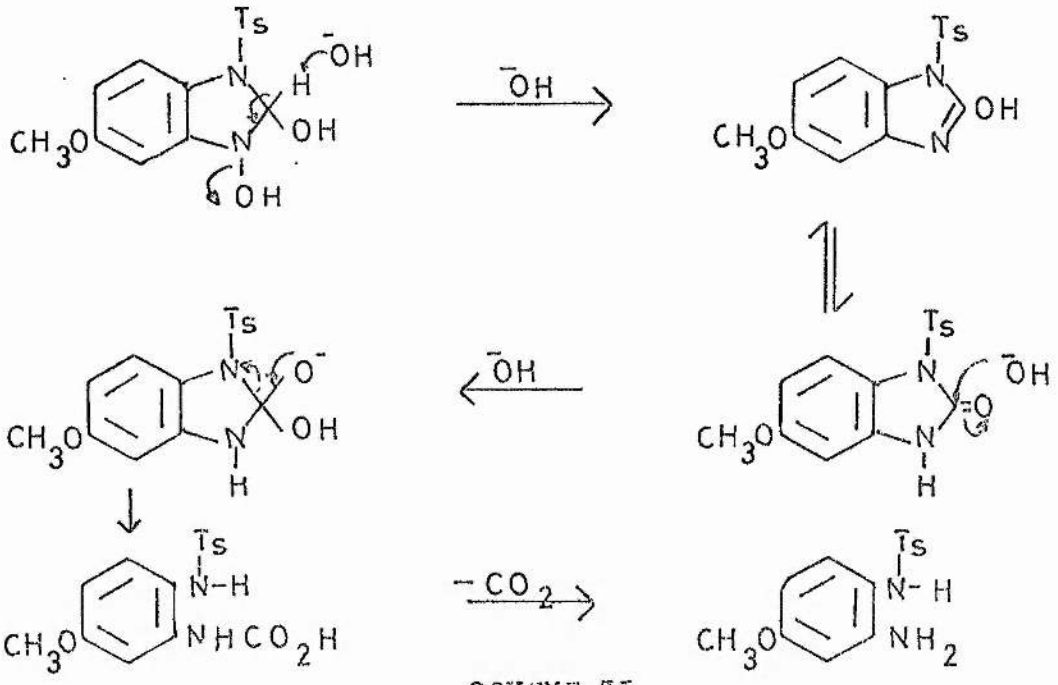
(155)

The reaction of the "hydrated form" (155) of (141c) with one and two molar equivalents of ethoxide in ethanol or methoxide in methanol gave no identifiable products. All that was obtained were black oils of unknown composition. However, the reaction of (155) with 5M sodium hydroxide produced a compound (156) which is thought to be N(1)-p-tolylsulphonyl-4-methoxy-o-phenylenediamine.



(156)

This structure was deduced from its i.r. spectrum, in which the N-H and NH_2 absorptions were clearly visible, and its mass spectrum. A ring opening reaction via Scheme 35 can explain the formation of (156).

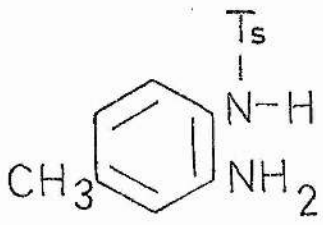


SCHEME 35

When (155) was stirred with concentrated hydrochloric acid for seventy-two hours, what is thought to be N(1)-p-tolylsulphonyl-5-chloro-4-methoxy-o-phenylenediamine (157) was obtained. Scheme 36 describes a possible reaction pathway for the formation of (157).

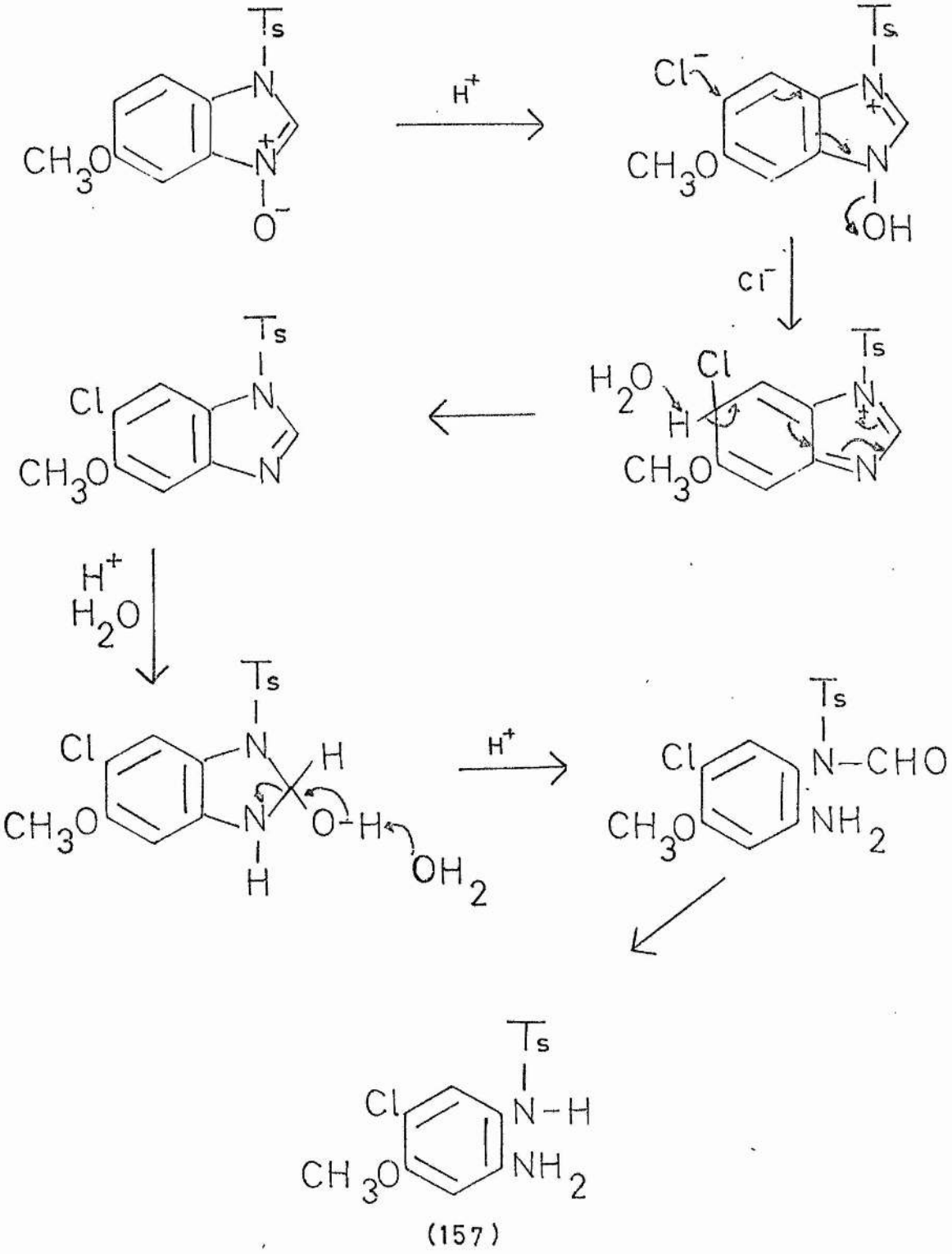
Structure (157) was again deduced from spectral evidence. The chloro substituent was assigned to the 5-position since the nmr of the methoxy-containing ring was a 2-proton singlet. If the chloride had attacked the 3-position, the nmr would have been expected to show ortho coupling of 8 Hz.

In a final attempt to synthesise (141), the reducing conditions were changed from a catalytic hydrogenation to reduction by sodium borohydride[15] in the presence of a palladium-charcoal catalyst (cf. Chapter 1 page 8). For this reduction, (154b) was chosen as substrate. (Although no correct analysis had been obtained for (154b), the mass spectrum of the compound was satisfactory). However, this reaction again yielded a ring opened compound, which from analytical and spectral evidence was deduced to be N(1)-p-tolylsulphonyl-4-methyl-o-phenylenediamine (158). The fact that the ring opened



(158)

compound (158) was formed under conditions known to favour formation of benzimidazole-N-oxides suggests that the benzimidazole-

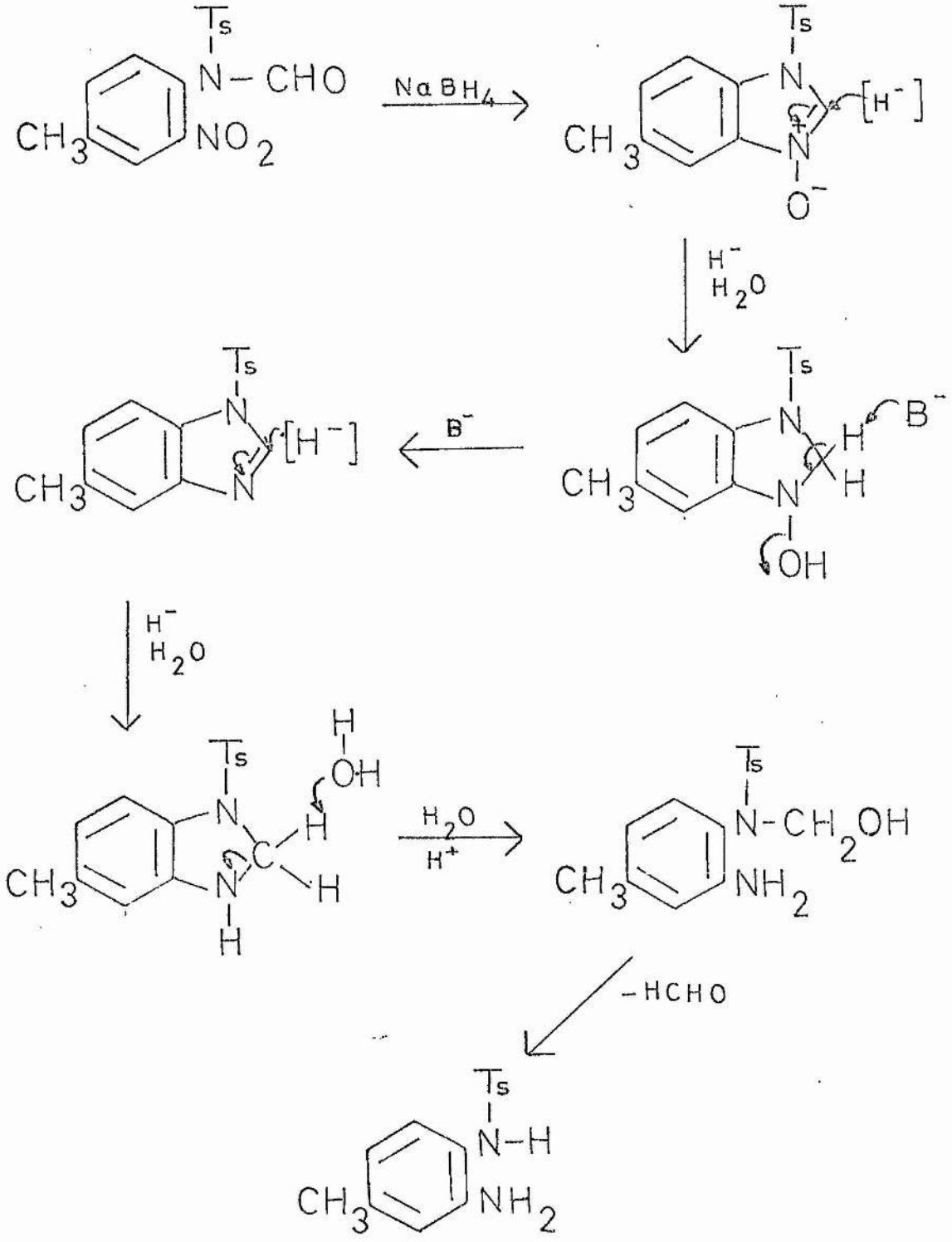


(157)

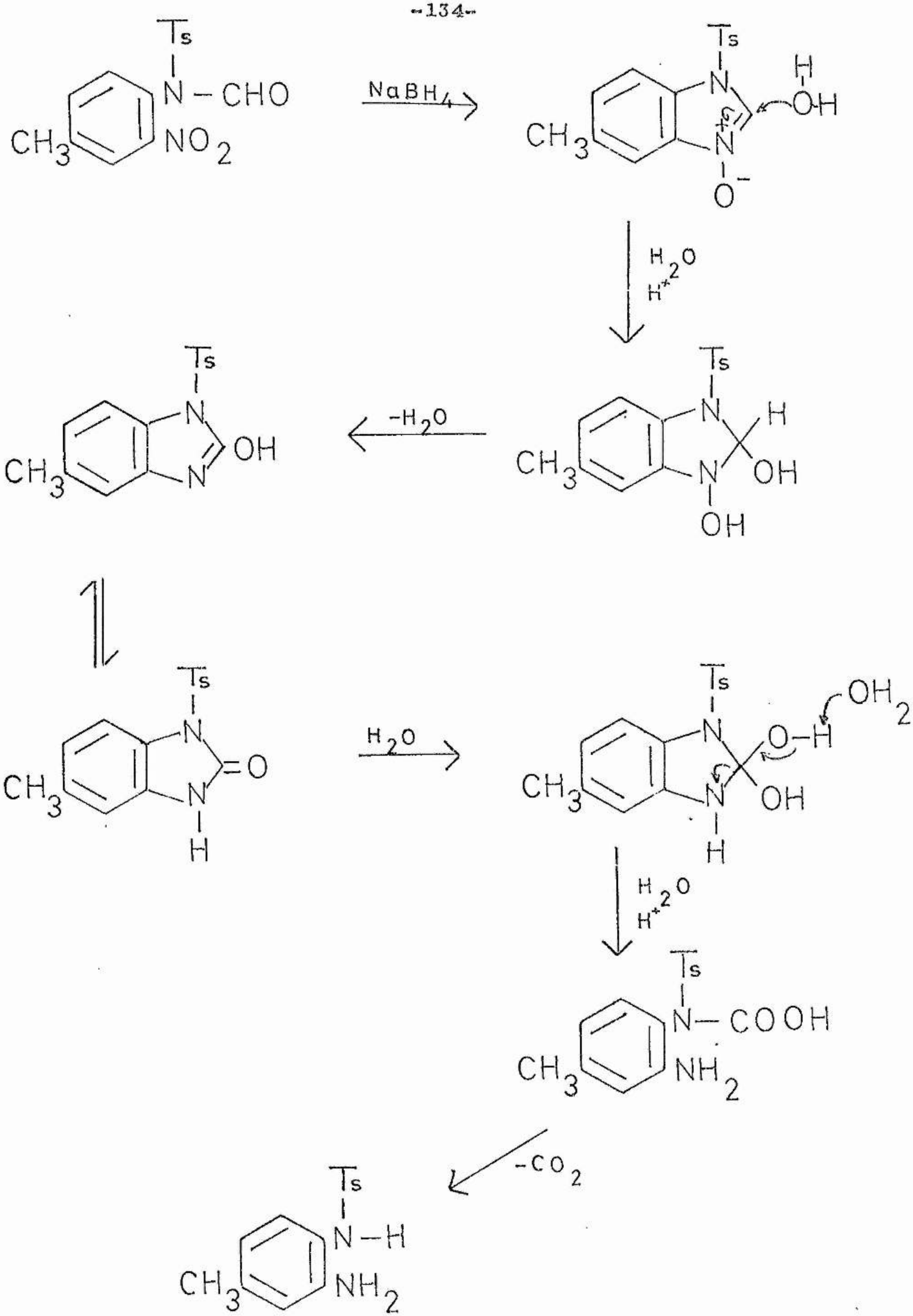
SCHEME 36

N-oxide may have been formed but ring opened at a later stage of the reaction. This result seems to confirm that in the reactions described previously in this Chapter, the required N-oxide was present. Scheme 37 and 38 show two possible pathways for the reaction.

In both these reaction pathways, the 1-p-tolylsulphonyl-N-oxide is formed, with ring opening under basic conditions, described by Scheme 37 or under acidic conditions, Scheme 38. The susceptibility of these "1-p-tolylsulphonyl-N-oxides" to ring opening casts doubt over their authenticity as reaction intermediates in the formation of the 2-alkoxy-N-oxides. However, it must be stressed that until more conclusive evidence as to the structure of these supposed "1-p-tolylsulphonyl-N-oxides" is obtained no definite conclusions can be drawn as to the probability of their being reaction intermediates in the cyclisations described by Scheme 29.



SCHEME 37



SCHEME 38

EXPERIMENTAL

Materials and Apparatus

Light petroleum had boiling range 40-60°, melting points were determined in open capillaries, and are uncorrected.

Ultraviolet spectra are quoted for methanol solutions, analytical samples were used.

Infra-red spectra were recorded for nujol mulls.

N.m.r. spectra were recorded at 60 and 100 MHz for 10% solutions with tetramethylsilane as internal reference.

For high temperature n.m.r.'s, hexamethyldisiloxane was used as internal reference.

The mass spectra were obtained on an AEI MS-902 spectrometer, operating at 70 ev with a source temperature of 200°C. Samples were introduced by means of a direct insertion probe.

Abbreviations

s : singlet
d : doublet
t : triplet
q : quartet
m : multiplet
br : broad
d : (after melting point) with decomposition
DMSO : dimethylsulphoxide
TFA : trifluoroacetic acid
DMF : dimethylformamide
THF : tetrahydrofuran

H.P.L.C.

High Pressure Liquid Chromatographs were performed on a Pye Unicam L.C. 3 Chromatograph.

The column used was a Reeve Angel Partisil^{tm} 10 μm 25 cm x 4.6 mm x 6.4 mm.

The chromatographs were carried out at a wavelength of 254 nm using a solvent system of 10% dioxan in n-hexane.

N-p-Tolylsulphonyl-o-nitroaniline. m.p. 101-102° yield (75%), (from methanol-water), (lit[78] 103°) was obtained from o-nitroaniline and toluene-p-sulphonyl chloride in pyridine.

N-p-Nitrobenzyl-N-p-tolylsulphonyl-o-nitroaniline (69a) m.p. 191-193° (from acetic acid) was prepared by the literature method. (m.p. 192-194°)[39]. Yield 80%.

N-Benzyl-o-nitroaniline (105b). m.p. 72-74°, yield 61% (lit[50] 75°) was synthesised from o-chloronitrobenzene, benzylamine and potassium carbonate by the published method[56].

N-Benzyl-N-p-tolylsulphonyl-o-nitroaniline (105a). m.p. 174-176°, yield 55%, (lit[79] 175-176°) was prepared by the published method

N-Benzoyl-N-p-tolylsulphonyl-o-nitroaniline (97). A solution of sodium ethoxide (from sodium (0.23 g)) in ethanol (70 ml)) was added to N-p-tolylsulphonyl-o-nitroaniline (2.92 g). The ethanol was evaporated in vacuo and a solution of benzoyl chloride (1.62 g) in pyridine (20 ml) added to the sodium salt. After heating at 100° for 2 h the mixture was poured onto crushed ice and the resulting precipitate filtered and recrystallised from acetic acid to give N-benzoyl-N-p-tolyl-sulphonyl-o-nitroaniline (97). (1.61 g; 40%). m.p. 194-196°. (Found: C, 60.7; H, 4.0; N, 7.35 $C_{20}H_{16}N_2O_5S$ requires C, 60.6; H, 4.1; N, 7.1%). ν_{max} (cm^{-1}); 1680 (C=O), 1340 and 1160, (SO_2), 1520 and 1340 (NO_2). δ ($CDCl_3$) 6.75-7.48 (13H, M, aromatic), 2.00 (3H, S, CH_3).

The corresponding reaction with p-nitrobenzoyl chloride gave only starting material.

Reduction of N-benzoyl-N-p-tolylsulphonyl-o-nitroaniline (97) with H_2/Pd. N-Benzoyl-N-p-tolylsulphonyl-o-nitroaniline (1.0 g) in ethanol (25 ml) was hydrogenated over a Pd/C (10%) catalyst (0.2 g). The solvent was removed in vacuo and the product recrystallised from benzene-petrol to give 2-hydroxy-2-phenyl-3-p-tolylsulphonyl-1,H-benzimidazole (101). (0.60 g, 66%). m.p. 181-183° (Found: C, 65.45; H, 5.1; N, 7.6. $C_{20}H_{18}N_2O_3S$ requires C, 65.55; H, 4.95; N, 7.6%). ν_{max}(cm^{-1}) 3330 (N-H), 1320, 1150 (SO_2), δ($CDCl_3$), 2.33 (3H, s, CH_3), 6.6-8.0 (13H, m, aromatic), 8.04 br (1H, s, N-H). m/e 366 (M^+, 9%), 348(2), 211(65), 122(80), 105(92), 77(100), 76(100), 51(100).

When the hydrogenation was carried out in the presence of a molar equivalent of hydrochloric acid, the same product was obtained.

Reaction of N-p-nitrobenzyl-N-p-tolylsulphonyl-o-nitroaniline (69a) with sodium hydride in DMSO. N-p-nitrobenzyl-N-p-tolylsulphonyl-o-nitroaniline (4.27 g) in dry DMSO (70 ml) was refluxed for 2 h with a solution of sodium hydride (0.48 g) in dry DMSO (40 ml). Evaporation of the DMSO in vacuo left a dark red oil, which on addition of benzene separated into a red oil (3.10 g) and a black oil (0.45 g).

Chromatography of the black oil (silica gel, $CHCl_3$) gave o-nitroaniline (.05 g) m.p. 66-68° (lit[80] 71°), N-p-nitrobenzoyl-o-nitroaniline (.07 g) m.p. 214-217° (lit[81] 222-223°) and an unidentified product (0.11 g).

Addition of chloroform to the red oil precipitated out N-p-nitrobenzoyl-o-nitroaniline (0.11 g) m.p. 220-222° (lit[81] 222-223°). Chromatography of the remainder gave o-nitroaniline (0.66 g) m.p. 68-69° (lit[80] 71°), p-nitrobenzaldehyde (0.21 g, 14%) m.p. 103-104° (lit[82] 106°) and N-p-nitrobenzoyl-o-nitroaniline (0.12 g) m.p. 217-220° (lit[81] 222-223°).

The total amount of o-nitroaniline produced was 0.71 g (58%), along with 0.29 g (8%) of N-p-nitrobenzoyl-o-nitroaniline.

N-p-nitrobenzylidene-o-nitroaniline (90). A solution of p-nitrobenzaldehyde (2 g), o-nitroaniline (1.38 g) and p-toluenesulphonic acid (5 mg) in benzene (150 mls) was heated under reflux in an apparatus connected to a Dean and Stark trap until no more water distilled over. The solution was cooled and diluted with dry light petroleum containing a few drops of triethylamine. The precipitate was collected and recrystallised from carbon tetrachloride and petroleum to give N-p-nitrobenzylidene-o-nitroaniline (90) (1.53 g, 57%) m.p. 129-130° (lit[83] 132-134°).

Reactions of N-p-nitrobenzylidene-o-nitroaniline with

a) Methanol

N-p-nitrobenzylidene-o-nitroaniline (1.2 g) was refluxed with methanol (30 mls) for two hours. The methanol was evaporated in vacuo and the residue chromatographed (silica gel, $CHCl_3$) to give o-nitroaniline (0.30 g, 50%) m.p. 66-67° (lit[80], 71°) and p-nitrobenzaldehyde (0.12 g, 10%) m.p. 102-103° (lit[82] 106°).

b) Methoxide and methanol

To N-p-nitrobenzylidene-o-nitroaniline (1.2 g) was added a solution of sodium methoxide in methanol (0.12 g Na, 30 mls MeOH). This mixture was refluxed for 2 h and the solvent removed in vacuo. The residue was extracted into ether:water (1:1, 150 mls). The organic layer was dried over Na_2SO_4 and chromatography (silica gel, $CHCl_3$) yielded o-nitroaniline 0.54 g (54%) m.p. 68-70° (lit[80] 71°) and p-nitrobenzaldehyde 0.10 g (16%) m.p. 102-103° (lit[82] 106°). No product was isolable from the aqueous layer.

c) Methoxide and methanol with p-toluenesulphinate ions present

The reaction was carried out in an analogous fashion to the one above and gave o-nitroaniline (50%) and p-nitrobenzaldehyde (11%).

d) Dry DMSO.

This experiment was carried out in exactly the same way as (a) and gave o-nitroaniline (47%) and p-nitrobenzaldehyde (12%).

e) Dry DMSO and methoxide

For the experimental procedure see (b). o-Nitroaniline (49%) and p-nitrobenzaldehyde (12%) were isolated.

N-p-nitrobenzyl-o-nitroaniline (69b)

(a) N-p-Nitrobenzyl-N-p-tolylsulphonyl-o-nitroaniline (4.27 g) was hydrolysed by a mixture of concentrated sulphuric acid (4 ml) and glacial acetic acid (2 ml) at 100° for 2 h. After cooling, the resulting precipitate was filtered and

recrystallised from an ethanol-acetic acid mixture to give N-p-nitrobenzyl-o-nitroaniline (1.91 g, 70%) m.p. 136-138° (lit[50] 145°. lit[84] 138°).

(b) A mixture of p-nitrobenzylbromide (10.8 g), o-nitroaniline (6.90 g) and soda lime (1 g) was heated at 150°C for 4 h. The cooled mixture, which set solid, was broken up and washed with a mixture (1:1) of methanol and dilute hydrochloric acid, filtered and recrystallised from an ethanol-acetic acid mixture to give the product (69b). 5.10 g (40%), m.p. 136° (lit[50] 145° lit[84] 138°) ν_{max} (cm^{-1}) 3330 (N-H): δ ($CDCl_3$) 4.68 (2H, d, J=6Hz, CH_2), 6.5-6.8 (2H), 7.1-7.6 (3H), 8.0-8.3 (3H) and 8.50 br (1H, N-H).

Cyclisation of N-p-nitrobenzyl-o-nitroaniline. N-p-nitrobenzyl-o-nitroaniline (69b) (0.8 g), dissolved in methanol (30 ml) was treated with sodium methoxide (from sodium 0.14 g) in methanol (5 ml). The mixture was heated under reflux for 6 h, concentrated in vacuo, and the residue extracted into a benzene-water mixture (1:1). Acidification (5M H_2SO_4) of the aqueous layer gave 2-p-nitrophenylbenzimidazole-3-oxide (70) (0.26 g, 37%) m.p. and mixed m.p. 237-240 (d) (lit[39] 243-246°).

Kinetic measurements. These were carried out with a Unicam SP 500 spectrophotometer, operating at 355 nm. Methanolic solutions of sodium methoxide (6.6×10^{-2} M, 0.3 ml) and the nitro compound (3.3×10^{-4} M, 0.3 ml) were added successively to methanol (1.4 ml) in a 10 mm cell. The solution was shaken and placed in the thermostatted (25°C) cavity of the spectro-

photometer. Absorbance measurements were taken (automatically) at 10 or 15 minute intervals over 12 hours, and again after 1-2 days when the reaction was complete.

N-Methylsulphonyl-o-nitroaniline. o-Nitroaniline (20.7 g) was refluxed for two hours with methanesulphonyl chloride (15 mls) in pyridine (37 mls). The mixture was cooled and poured on to crushed ice. The resulting precipitate was filtered and recrystallised from ethanol to give N-methylsulphonyl-o-nitroaniline (24.1 g, 75%) m.p. 99-101° (lit[79] 101-102°).

N-Methylsulphonyl-N-p-nitrobenzyl-o-nitroaniline (69c). (With A.J.G. Sagar). N-methylsulphonyl-o-nitroaniline (6.48 g) was dissolved in sodium ethoxide solution (from sodium (0.70 g) in ethanol (70 ml)) and to the warm solution was added p-nitrobenzyl bromide (7.0 g). More ethanol was added, and the mixture was heated under reflux for 30 min, cooled to 0°C, and filtered. The product was washed with water and recrystallised from acetic acid-ethanol; it formed almost colourless plates. (7.95 g, 76%): m.p. 119-121° (Found: C, 47.9; H, 3.7; N, 12.1. $C_{14}H_{13}N_3O_6S$ requires C, 47.9; H, 3.7; N, 12.0%). ν_{max} (cm^{-1}), 1520 and 1350 (NO_2), 1330 and 1150 (SO_2). δ ($(CD_3)_2CO$) 7.6-8.2 (8H, m, aromatic), 5.1 (2H, s, CH_2), 3.1 (3H, s, CH_3-S).

N-Acetyl-N-p-nitrobenzyl-o-nitroaniline (69d) (With A.J.G. Sagar). To a suspension of N-p-nitrobenzyl-o-nitroaniline (2.7 g) in acetic anhydride (7 ml) were added acetyl bromide (0.75 ml) and concentrated sulphuric acid (a few drops). The

mixture was warmed gently until dissolution, then set aside for 24 h, and poured slowly into cold water. The acetyl compound (69d) was filtered off, recrystallised from methanol and had m.p. 153-154°. (Found: C, 56.9; H, 4.0; N, 13.1. $C_{15}H_{13}N_3O_5$ requires C, 57.1; H, 4.2; N, 13.3%); ν_{max} (cm^{-1}) 1660 (C=O) and 1510 and 1340 (NO_2). δ ($CDCl_3$), 1.94 (3H, s, $\underline{CH_3}$) 4.37 (2H, ABq, $\underline{CH_2}$, J=14 Hz), 6.94-8.19 (8H, m, aromatic) Yield 2.04 g (68%).

N-Benzoyl-N-p-nitrobenzyl-o-nitroaniline (69e). A solution of N-p-nitrobenzyl-o-nitroaniline (7.8 g) and benzoyl chloride (4.1 g) in pyridine (20 ml) was heated under reflux for 4 h, cooled and poured onto crushed ice. The mixture was acidified with hydrochloric acid (5 M). The benzamide (69e), filtered off and recrystallised from acetic acid-ethanol (with charcoal), had m.p. 162-163°. (Found: C, 64.0; H, 4.1; N, 10.95. $C_{20}H_{15}N_3O_5$ requires C, 63.7; H, 4.0; N, 11.0%). ν_{max} (cm^{-1}); 1650 (C=O) and 1510 and 1335 (NO_2) δ ($CDCl_3$), 7.0-8.16 (13H, m, aromatic), 5.00 (2H, q, $\underline{CH_2}$, J=14 Hz) Yield 4.25 g,(40%).

Cyclisation of the N-Acyl-N-p-nitrobenzyl-o-nitroanilines [(69a), (69c), (69d), (69e).] The following procedure was typical. A solution of N-methylsulphonyl-N-p-nitrobenzyl-o-nitroaniline (1.75 g, 5 mmol) and sodium methoxide (from sodium (0.23 g) 10 mmol) in methanol (50 ml) was heated under reflux for 2 h. The methanol was evaporated off in vacuo and the red residue extracted with benzene-water (1:1). Acidification of the aqueous layer (5 M H_2SO_4) gave 2-p-nitrophenylbenzimidazole-3-oxide (70) (0.68 g), 50%), m.p. and mixed m.p. 243-245°

(decomp) (lit[39] 243-246°).

Evaporation of the dried (Na_2SO_4) benzene layer, and chromatography of the residue on silica gel gave a fraction (5 mg) eluted by chloroform, identified as 1-methoxy-2-*p*-nitrophenylbenzimidazole (71) by its mass spectrum[39]. The yields of (70) obtained from these cyclisations are recorded in table 1.(p66)

Methyl methanesulphonate. To a 0.2 M solution of methanol in a methylene chloride solution, containing a 50% molar excess of triethylamine, at 0-10°C was added a 10% excess of methanesulphonyl chloride over a period of 5-10 minutes. Stirring for an additional 10-15 minutes completed the reaction. The reaction mixture was transferred to a separating funnel with the aid of more methylene chloride. The mixture was first extracted with cold water, followed by cold 10% HCl, saturated sodium bicarbonate solution and brine. Drying of the methylene chloride solution (Na_2SO_4) followed by solvent removal gave the product (3.8 g 17%) bp 38-40 at 0.5 mm Hg. (Lit[86] 101-102° at 26 mm Hg), d($CDCl_3$) 3.10 (3H, s, $\underline{CH_3}S$) and 4.00 (3H, s, $\underline{CH_3}O$).

Methylation of the benzimidazole-3-oxide (70). Methyl methanesulphonate (0.15 g) was added to a solution of the -3-oxide (70) (0.44 g) in sodium methoxide (from sodium (0.04 g) in methanol (5 ml)). The mixture was boiled for 2 h, the methanol evaporated off in vacuo, and the residue extracted into benzene-water (1:1). The benzene layer was dried (Na_2SO_4) and evaporated, giving 1-methoxy-2-*p*-nitrophenylbenzimidazole

(71), m.p. and mixed m.p. 155-157° (lit[39] 154-156°). Yield 0.15 g (32%).

N-Benzyl-N-methylsulphonyl-o-nitroaniline (105c) (With A.J.G. Sagar). The sodium salt of N-methylsulphonyl-o-nitroaniline was prepared by dissolving the sulphonamide (2.16 g) in sodium methoxide solution (from sodium (0.23 g) in methanol (60 mls)) and removing the methanol in vacuo. To this salt dissolved in dimethylformamide (20 ml) was added benzyl bromide (2.2 g) and the mixture stirred overnight at room temperature. It was then added to crushed ice, and the precipitate filtered off and recrystallised from methanol, m.p. 138-140° (lit[79] 139-140°) yield 2.2 g (73%).

N-Acetyl-N-benzyl-o-nitroaniline (105d). M.p. 82-83° (from methanol-water) (lit[81,5] 83-85°) was obtained from N-benzyl-o-nitroaniline in a 65% yield in a similar manner to that of (69d) from N-p-nitrobenzyl-o-nitroaniline.

N-Benzoyl-N-benzyl-o-nitroaniline (105e). By a similar method to the preparation of (69e), N-benzyl-o-nitroaniline (6.84 g), benzoyl chloride (6.0 g) and pyridine (20 ml), gave the benzamide (105e) (7.50 g, 75%), m.p. 97-98° (lit[81] 97°) (Found: C, 72.0; H, 4.8; N, 8.1. Calc for $C_{20}H_{16}N_2O_3$: C, 72.3; H, 4.85; N, 8.4%). ν_{max} (cm^{-1}) 1650 (C=O) and 1530 and 1340 (NO_2).

Reactions of N-benzyl-o-nitroaniline (105b) and its derivatives (105d) and (105e) with sodium methoxide. The procedure was

identical with that described for the cyclisation of (69a), (69c), (69d), (69e). Acidification of the aqueous layer (5 M H_2SO_4) gave 2-phenylbenzimidazole-3-oxide (54), identified by comparison with an authentic sample[11,36], or as its benzoyl derivative, m.p. 112-114° (lit.[11] 116-118°). Evaporation of the organic layer gave N-benzyl-o-nitroaniline (105b) which was purified by chromatography on silica gel, with ether:petroleum (1:3) as eluant. The products obtained by reaction of the nitro compounds (5 mmol) and sodium methoxide (10 mmol) under various conditions are tabulated in Table 4 (p.73).

Attempted preparation of N-methyl-N-p-nitrobenzyl-o-nitroaniline

a) Preparation of N-methyl-p-nitrobenzylamine. p-Nitrobenzyl bromide (9 g) in THF (180 ml) was added slowly, over 1½ h, to a warm alcoholic solution of methylamine (33%; 40 ml). A further portion (15 ml) of the methylamine solution was then added, and the solution refluxed for 30 min. The solvent was evaporated *in vacuo*, the residue was dissolved in ethanol, and the solution cooled to 0°, whereupon N,N-bis-p-nitrobenzylmethylamine (2.0 g, 17%), m.p. 101-103° (lit.[87], 104°) slowly crystallised and was filtered off. The filtrate was concentrated *in vacuo*, the residue was extracted with ether, and the extract shaken with 5 M hydrochloric acid. The acid layer was basified (Na_2CO_3) and re-extracted with ether. This ether extract was washed with water, dried (Na_2SO_4), and distilled, giving N-methyl-p-nitrobenzylamine (2.92 g, 42%), b.p. 86-88° / 0.5 mm Hg.

ν_{max} (cm^{-1}), 3320 (N-H), 1520 and 1340 (NO_2). δ ($CDCl_3$), 1.94 (1H, s, N-H), 2.57 (3H, s, CH_3), 3.94 (2H, s, CH_2), 7.48-8.33 (4H, AA'BB', aromatic).

Reaction of N-methyl-p-nitrobenzylamine with o-chloronitrobenzene. N-methyl-p-nitrobenzylamine (0.4 g) was refluxed for 6 h with o-chloronitrobenzene (0.207 g) in benzene (15 ml). Evaporation of the solvent gave a residue which was extracted into ether-water (1:1). Drying of the organic layer (Na_2SO_4) and evaporation of the solvent in vacuo gave an unidentifiable product.

Ethyl N-o-nitrophenylcarbamate[61] (108). This was prepared from o-nitroaniline (13.8 g), ethylchloroformate (20.2 g) and pyridine (8.2 g) in carbon tetrachloride (130 ml). Yield 17.3 g (83%). m.p. 54-55° (from ethanol), (lit[88] 55-56°). ν_{max} (cm^{-1}) 3370 (N-H) and 1745 (C=O), $\delta(CCl_4)$ 1.38 (3H, t, CH_3), 4.20(2H, q, CH_2) 7.03 (1H, dt) 7.57 (1H, dt), 8.13 (1H, dd), 8.57 (1H, dd) and 9.70 br (1H, s, NH). (J_{Et} 7, J_{ortho} 8, J_{meta} 2 Hz).

N-Ethoxycarbonyl-N-p-nitrobenzyl-o-nitroaniline (107) and 1-p-nitrobenzyloxy-2-p-nitrophenylbenzimidazole (109a). Sodium ethoxide (from sodium (0.46 g) methanol (25 ml)) was added to a solution of ethyl N-o-nitrophenylcarbamate (108) (2.10 g) in ethanol (35 ml). p-Nitrobenzylbromide (4.32 g) was added over 10 min to the resulting red solution, and the mixture was stirred at room temperature overnight. It was then filtered, and the yellow residue was recrystallised from DMF-water to give 1-p-nitrobenzyloxy-2-p-nitrophenylbenzimidazole (109a) (0.88 g, 33%), m.p. 223-224°. (Found: C, 61.1; H, 3.5; N, 13.95: $C_{20}H_{14}N_4O_5$ requires C, 61.5; H, 3.6; N, 14.35%). ν_{max} (cm^{-1}) 1505, 1310 (NO_2):

δ (CF_3CO_2H) 5.60 (2H, s, CH_2) and 7.3-8.7 (12H, m, aromatic ; 1AA'BB' pattern visible). m/e 390 (M^+ 8%), 270(22) 239(20)* 150(83) 136(100) 104(26) 78(98) and 51(100).

(* ; Found 239.068560: $C_{13}H_9N_3O_2$ requires 239.069472)

The ethanolic filtrate was evaporated, and the organic portion of the residue extracted into ether. Evaporation of the extract and chromotography of the residue on silica gel with chloroform as the eluant, gave unchanged carbamate (108) (0.45 g 23%) and then N-ethoxycarbonyl-N-p-nitrobenzyl-o-nitroaniline (107). (0.80 g, 27%) m.p. 85-87° (from ethanol-water). (Found: C, 55.6; H, 4.5; N, 12.1: $C_{16}H_{15}N_3O_6$ requires C, 55.65; H, 4.4; N, 12.2%) ν_{max} (cm^{-1}) 1700 (C=O), 1510, 1340 (NO_2): δ ($CDCl_3$) 1.14 br (3H, t, CH_3), 4.15 br (2H, $CH_3 \cdot \underline{CH_2}$), 4.78 and 5.18 (2H, ABq N-$\underline{CH_2}$ cf Table 3) 6.9-8.3 (8H, m, aromatic).

Cyclisation of N-ethoxycarbonyl-N-p-nitrobenzyl-o-nitroaniline (107). A solution of (107) (0.53 g) and sodium ethoxide (from sodium (0.09 g) in ethanol (20 ml))was heated under reflux for 2 h, then worked up as for the other cyclisations described previously. The yield of 2-p-nitrophenylbenzimidazole-3-oxide (70) was 0.27 g (71%).

1-p-nitrobenzyl-2-p-nitrophenylbenzmidazole[62]. m.p. 209-210° (lit[19] 212°) was synthesised from o-phenylenediamine and p-nitrobenzaldehyde by the published method. d($CDCl_3$) 5.57 (2H, s, $\underline{CH_2}$). 7.2-8.5 (12H, m, aromatic).

Reaction of 2-p-nitrophenylbenzimidazole-3-oxide with p-nitrobenzylbromide. To a solution of 2-p-nitrophenylbenzimidazole-3-

oxide (0.255 g) in sodium ethoxide (from 0.23 g sodium) in ethanol (20 ml) was added p-nitrobenzylbromide (0.210 g). The mixture was stirred for 24 h at room temperature, and the resulting precipitate filtered and recrystallised from DMF-water to give 1-p-nitrobenzyloxy-2-p-nitrophenylbenzimidazole (0.14 g 71%) m.p. and mixed m.p. with (109[a]) 223-224°.

Reaction of (109) with phosphorus trichloride. (109) (0.15 g) in chloroform (5 ml) and phosphorus trichloride (0.3 ml) was refluxe for 1 h. The solvent was evaporated under vacuo and the residue extracted into water. Basification (5 M NaOH) gave 0.13 g (87%) of starting material (109) (from DMF/H_2O), m.p. and mixed m.p. with (109) 221-222°.

N-p-tolylsulphonyl-2,4-dinitroaniline (116) (With J. Czyzewski) Sodium methoxide (from sodium, (4.6 g)) in methanol (200 mls) was added to a solution of toluene-p-sulphonamide (34 g) in ethanol (100 ml). The ethanol was evaporated off in vacuo and the sodium salt dissolved is DMF (200 ml). 1-Chloro-2,4-dinitrobenzene (20.8 g) was added to the solution and the resulting mixture heated at 100° for 2½ h, then poured onto crushed ice. Unreacted starting material was removed by filtration, acidification of the filtrate (5 M HCl) gave N-p-tolylsulphonyl-2,4-dinitroaniline 50 g (75%) m.p. 156-157° (from CH_3COOH) (lit[67] 161°). ν_{max} (cm^{-1}) 3200 (N-H), 1500, 1320 (NO_2), 1310, 1160 (SO_2) δ($CDCl_3$) 7.2-9.1 (8H, m, N-H and aromatic), 2.4 (3H, s, CH_3).

N-p-Nitrobenzyl-N-p-tolylsulphonyl-2,4-dinitroaniline (114)

(With J. Czyzewski). To a solution of sodium methoxide (from sodium (0.92 g)) in methanol (200 ml)) was added N-p-tolylsulphonyl-2,4-dinitroaniline (13.48 g) in methanol (100 ml). The solvent was evaporated in vacuo and the sodium salt dissolved in DMF (200 ml). p-Nitrobenzylbromide (8.64 g) was added to this solution and the resulting mixture refluxed for 2½ h and then poured onto crushed ice to give the product (114), 10 g (52%) m.p. 112°. (Found: C,50.58; H, 3.56; N, 11.87. $N_4C_{20}H_{16}O_8S$ requires C, 50.85; H, 3.41; N, 11.86%). ν_{max} (cm^{-1}) 1500, 1300 (NO_2), 1300, 1150 (SO_2), δ ($(CD_3)_2SO$) 7.5-8.7 (11H, m, aromatic), 5.0 (2H, s, CH_2); 2.5 (3H, s, CH_3).

N-Benzyl-N-p-tolylsulphonyl-2,4-dinitroaniline (119). The above procedure, applied to N-p-tolylsulphonyl-2,4-dinitroaniline (6.94 g), sodium methoxide (from sodium (0.4 g)) in methanol (60 ml) and benzyl bromide (2.4 ml) gave (119) (3.70 g) 44%) m.p. 113-115°. (Found: C, 55.87; H, 4.06; N, 9.78. $C_{20}H_{17}N_3O_6S$ requires C, 56.20; H, 4.00; N, 9.83%). ν_{max} (cm^{-1}), 1530 and 1340 (NO_2), 1340 and 1160 (SO_2); δ ($CDCl_3$) 2.45 (3H, s, CH_3), 4.75 (2H, s, CH_2), 7.00-8.66 (8H, m, aromatic).

Reaction of N-p-nitrobenzyl-N-p-tolylsulphonyl-2,4-dinitroaniline with two molar equivalents of $NaOCH_3$. N-p-Nitrobenzyl-N-p-tolylsulphonyl-2,4-dinitroaniline (4.72 g) was refluxed for 2 h with a sodium methoxide solution (from sodium (0.46 g) and methanol (40 ml)). Filtration yielded the sodium salt of N-p-tolylsulphonyl-2,4-dinitroaniline (116) (0.84 g , 42%). m.p. 222-224° (from CH_3COOH).

[This salt (0.6 g) was refluxed with methanolic HCl for 1 h. The solvent was evaporated in vacuo and the residue extracted into $CHCl_3/H_2O$ (1:1). Evaporation of the dried (Na_2SO_4) organic layer gave N-p-tolylsulphonyl-2,4-dinitroaniline (116) (0.48 g) m.p. and mixed m.p. 158-160° (lit[67] 161°)].

The methanol was evaporated from the filtrate and the residue extracted into benzene-water (1:1). Acidification of the aqueous layer (5 M HCl) gave N-p-tolylsulphonyl-2,4-dinitroaniline (0.76 g, 44%). m.p. and mixed m.p. 159-160° (from C_2H_5OH). The filtrate (C_2H_5OH) was evaporated in vacuo and residue recrystallised from water to give p-nitrobenzoic acid (.05 g, 3%) m.p. and mixed m.p. 236-239° (lit[89] 238).

The organic layer was dried (Na_2SO_4) and the solvent evaporated off in vacuo. Chromatography of the residue on silica gel with chloroform as the eluant gave methyl p-nitrobenzoate (14 g, 8%) m.p. 95-97° (from CH_3OH) (lit[90] 96°) and various other unidentifiable products.

Reaction of N-benzyl-N-p-tolylsulphonyl-2,4-dinitroaniline with sodium methoxide. By the method described above, N-p-tolylsulphonyl-2,4-dinitroaniline (35%) m.p. and mixed m.p. 159-160° (lit[16] 161) and N-benzyl-N-p-tolylsulphonyl-2,4-dinitroaniline (44%) m.p. 113-115° were obtained.

Benzyl methyl ether (120:y=H). Benzyl chloride (24.8 g), methanol (6.4 g) and potassium hydroxide (11.2 g) were refluxed together for 4 h. The potassium chloride formed was filtered and the filtrate dried (Na_2SO_4) and distilled to give (120:y=H) 20 g (82%) (bp 72-74° 22 mm Hg) (lit[69] 170° 760 mm).

Methyl p-nitrobenzyl ether. To a solution of p-nitrobenzyl chloride (5.0 g) in methanol (20 g), sodium methoxide (from sodium (0.61 g)) in methanol (20 ml)) was added. The mixture was refluxed for 2 h. Evaporation of the solvent and crystallisation of the residue from C_6H_6/petrol gave methyl p-nitrobenzyl ether (4.05 g, 80%) m.p. 28-29° (lit[68] 29-30°).

G.L.C. The G.L.C.'s were performed on a 20% DEGS column at 186°C. The reactions mixtures from the reactions of (114) and (119) with sodium methoxide in methanol showed no traces of the corresponding ethers.

Reaction of methyl p-nitrobenzyl ether with sodium methoxide. Methyl-p-nitrobenzyl ether (1.67 g) in methanol (20 ml) was refluxed for 2 h with sodium methoxide. (From sodium (0.46 g)) in methanol (20 ml)). The solvent was evaporated and the residue extracted into benzene-water (1:1). Chromatography of the dried (Na_2SO_4) organic layer (silica gel, $CHCl_3$) gave starting material (0.18 g), m.p. 28-29° (lit[68] 29-30), plus various other unidentifiable products.

Reaction of Benzylmethyl ether with sodium methoxide. By the method described above, only starting material (90%) was isolated.

N-p-nitrobenzyl-2,4-dinitroaniline (123). N-p-Nitrobenzyl-N-p-tolylsulphonyl-2,4-dinitroaniline (2.0 g) was warmed at 100° for 2 h with a mixture of concentrated sulphuric acid (3 ml) and glacial acetic acid (2 ml). The mixture was poured onto crushed ice and the resulting precipitate filtered and recrystallised from acetic acid to give N-p-nitrobenzyl-2,4-dinitroaniline (0.61 g, 40%) m.p. 180-181°. (Found: C, 49.09; H, 3.23; N, 17.46. $C_{13}H_{10}N_4O_6$ requires C, 49.06; H, 3.17; N, 17.60%). ν_{max} (cm^{-1}) 3380 (N-H), 1510 and 1330 (NO_2). δ ($CDCl_3$), 4.72-4.78 (2H, CH_2), 9.10-9.16 (1H, d, aromatic). 8.12-8.33 (1H, dd, aromatic) 7.39-7.57 (1H, d, aromatic), 6.84 (2H, m, aromatic), 6.61 (2H, m, aromatic).

N-Benzyl-2,4-dinitroaniline (124). Benzylamine (1.07 g) and 1-chloro-2,4-dinitrobenzene (2.02 g) were heated together at 100° for 1 h. On cooling the precipitate was filtered to give 2.20 g (81%) of the required product (124). m.p. 115-116° (lit[91] 116°) (from ethanol).

Cyclisation of N-p-nitrobenzyl-2,4-dinitroaniline. N-p-nitrobenzyl-2,4-dinitroaniline (3.60 g) was cyclised in sodium methoxide solution (from (0.46 g Na)) in methanol (30 ml)) by the standard method and yielded 2-p-nitrophenyl-5-nitrobenzimidazole-3-oxide (1.80 g, 54%). (Found: C, 51.9; H, 2.9; N, 18.5. $C_{13}H_8N_4O_5$ requires. C, 52.0; H, 2.7; N, 18.7%). ν_{max} (cm^{-1}), 1510, 1340 (NO_2). ($CDCl_3$), 7.66-8.33 (7H, m, aromati

Cyclisation of N-Benzyl-2,4-dinitroaniline. By the method described above, the cyclisation of N-benzyl-2,4-dinitroaniline (1.36 g) in sodium methoxide solution (from sodium (0.23 g))

in methanol (15 ml) gave N-benzyl-2,4-dinitroaniline (0.10 g 4%) m.p. 114-116° and 2-phenyl-5-nitrobenzimidazol-3-oxide 0.78 g (55%) m.p. 257-260° (lit[92] 258-261°). (Found: C, 60.78; H, 3.66; N, 16.58. Calc. for $C_{13}H_9N_3O_3$ C, 61.18; H, 3.55; N, 16.46). ν_{max} (cm^{-1}), 1520 and 1340 (NO_2). δ (d_6 DMSO), 7.51-8.36 (8H, m, aromatic).

N-p-Tolylsulphonyl-4-methyl-2-nitroaniline. m.p. 102-103° (lit[93] 101°) was prepared in 66% yield from 4-methyl-2-nitroaniline, toluene-p-sulphonyl chloride and dry pyridine.

N-Phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (126b). To N-p-tolylsulphonyl-4-methyl-2-nitroaniline (12.24 g) was added sodium ethoxide solution (0.92 g Na; 60 ml EtOH). The ethanol was removed in vacuo and the residue dissolved in DMF (50 ml). Phenacyl bromide (8.0 g) was added, and the mixture stirred for 48 h at room temperature, poured onto crushed ice and the resulting precipitate filtered and recrystallised from an ethanol-acetic acid mixture (1:2) to give the final product (12.69 g, 75%). m.p. 170-171° (Found: C, 62.3; H, 4.8; N, 6.6. $C_{22}H_{20}N_2O_5S$ requires C, 62.25; H, 4.75; N, 6.6%). ν_{max} (cm^{-1}); 1690 (C=O) 1340, 1150 (SO_2); 1520, 1340 (NO_2). δ ($CDCl_3$); 5.39 (2H, s, CH_2), 7.15-8.09 (12H, m, aromatic), 2.45 (6H, s, $2CH_3$).

N-Phenacyl-N-p-tolylsulphonyl-o-nitroaniline (126a) was prepared analogously to (126b) from N-p-tolylsulphonyl-o-nitroaniline, m.p. 135-136°, yield 83%. (Found: C, 61.45; H, 4.4; N, 6.8; $C_{21}H_{18}N_2O_5S$ requires C, 61.8; H, 4.3; N, 6.7%). ν_{max} (cm^{-1})

1690 (C=O); 1520, 1340 (NO_2); 1340, 1160 (SO_2); δ ($CDCl_3$), 5.36 (2H, s, $\underline{CH_2}$), 7.10-8.00 (13H, m, aromatic), 2.39 (3H, s, $\underline{CH_3}$).

N-Phenacyl-4-methyl-2-nitroaniline (127b). N-Phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (8.0 g) was heated for 1½ h at 100° with a mixture of concentrated sulphuric acid (12 ml) and glacial acetic acid (8 ml). The mixture was poured onto crushed ice and the resulting precipitate recrystallised from ethanol to give the product (127b). (4.10 g, 79%). m.p. 162-164° (lit[94] 163-165°). (Found: C, 66.8; H, 5.4; N, 10.3. Calc. for $C_{15}H_{14}N_2O_3$: C, 66.7; H, 5.2; N, 10.47).

N-Phenacyl-o-nitroaniline (127a). By an analogous method for the preparation of (127b), N-phenacyl-o-nitroaniline was prepared in 85% yield: m.p. 147-149°. (Found: C, 65.5; H, 4.7; N, 11.0. $C_{14}H_{12}N_2O_3$ requires C, 65.6; H, 4.7; N, 11.0%) ν_{max} (cm^{-1}). 3330 (N=H), 1680 (C=O), 1555, 1360 (NO_2). δ($CDCl_3$), 4.69 (2H, d, CH_2, J=2 Hz), 6.66-8.33 (9H, m, aromatic), 8.50 (1H, br, N-H).

Reaction of N-phenacyl-4-methyl-2-nitroaniline (127b) with methanolic potassium hydroxide. N-Phenacyl-4-methyl-2-nitroaniline (1.87 g) in methanol (15 ml) was refluxed for 2 h with potassium hydroxide (0.84 g). The methanol was evaporated off in vacuo and the residue was extracted into ether-water (100ml). Acidification of the aqueous layer (5 M H_2SO_4) yielded 2-benzoyl-5-methylbenzimidazole-3-oxide (0.12 g), 7%) m.p. 127-130° (from ethanol) (lit[38] 132°). Chromatography of the dried (Na_2SO_4) ether layer on a silica-gel column with chloroform as the

eluant gave methyl benzoate (0.08 g, 8%). ν_{max} (cm^{-1}) 1720 (C=O), 4-methyl-2-nitroaniline (0.13 g, 12%), m.p. 111-112° (from benzene-petrol) (lit[95] 113°).

Reaction of N-phenacyl-4-methyl-2-nitroaniline (127b) with ethanolic potassium hydroxide, using exactly the same procedure, yielded 2-benzoyl-5-methylbenzimidazole-3-oxide (0.05 g) m.p. 126-129° (lit[72] 132°) (Yield 5%), methyl benzoate (0.10 g, 10%), and 4-methyl-2-nitroaniline (0.15 g, 13%) m.p. 110-112°.

Reaction of N-phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (126b) with methanolic potassium hydroxide. The reaction and work up were carried out analogously to those already described. 5-Methyl-1-tolylsulphonyl-2-benzimidazolone (131) m.p. 258-261°, (6%), (lit[96] 263-265°) was isolated along with methyl benzoate (3%).

Reaction of N-phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (126b) with ethanolic potassium hydroxide. N-Phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (6.80 g) in ethanol (50 ml) was refluxed for 2 h with potassium hydroxide (2.56 g). The solvent was removed in vacuo and the residue extracted into ether-water (100 ml). Careful acidification of the aqueous layer (5 M H_2SO_4) gave 2-ethoxy-5-methylbenzimidazole-3-oxide (132b) (1.65 g, 53%). m.p. 181-183° (from ethanol). (Found: C, 62.3; H, 6.3; N, 14.5. $C_{10}H_{12}N_2O_2$ requires C, 62.5; H, 6.3; N, 14.6%).

δ(TFA), 4.95 (2H, q, $O\underline{CH_2}$, J=6Hz) 7.44 (3H, s, aromatic), 2.66 (3H, s, CH_3), 1.88 (3H, t, $-OCH_2\underline{CH_3}$, J=7Hz).

Reaction of N-phenacyl-N-p-tolylsulphonyl-o-nitroaniline (126a) with methanolic and ethanolic potassium hydroxide. From a similar method to the reaction of (126b) with methanolic potassium hydroxide, methyl benzoate (10%) and o-nitroaniline (70%), m.p. 69-70° (lit[80] 71°) were isolated from the reaction of (126a) with methanolic potassium hydroxide. No products were isolable from the reaction with ethanolic potassium hydroxide.

Preparation of the remaining compounds of series (3)

N-p-Tolylsulphonyl-4-chloro-2-nitroaniline. m.p. 109-110° (lit[96] 108-109) (79%); N-p-tolylsulphonyl-4-methoxy-2-nitroaniline, m.p. 106-107° (lit[97] 104°) (73%); N-p-tolyl-sulphonyl-5-methyl-2-nitroaniline m.p. 132-134° (lit[98] 135°) (50%) and N-p-tolylsulphonyl-6-methyl-2-nitroaniline m.p. 124-126° (lit[99] 123°) were all prepared by reacting the primary amine with toluene-p-sulphonyl chloride in dry pyridine.

Preparation of the N-phenacyl-N-p-tolylsulphonyl derivatives (126c - 126f). These were synthesised analogously to (126a) and (126b).

N-Phenacyl-N-p-tolylsulphonyl-4-chloro-2-nitroaniline (126c) m.p. 180-182°; yield 73%. (Found: C, 56.6; H, 3.7; N, 6.2. $C_{21}H_{17}N_2O_5SCl$ requires C, 56.6; H, 3.8; N, 6.4%). ν_{max} (cm^{-1}), 1690 (C=O), 1340, 1155 (SO_2), 1530, 1340 (NO_2). $\delta(CDCl_3)$, 2.45 (3H, s, $\underline{CH_3}$) 5.36 (2H, s, $\underline{CH_2}$), 7.15-8.00 (12H, m, aromatic).

N-Phenacyl-N-p-tolylsulphonyl-4-methoxy-2-nitroaniline (126d)

M.p. 160-161°, yield 80%. (Found: C, 59.9; H, 4.7; N, 6.4. $C_{22}H_{20}N_2O_6S$ requires C, 59.9; H, 4.6; N, 6.5%). ν_{max} (cm^{-1}), 1690 (C=O), 1340, 1160 (SO_2), 1530, 1340 (NO_2). δ($CDCl_3$), 5.39 (2H, s, $\underline{CH_2}$), 6.87-8.00 (12H, m, aromatic), 3.85 (3H, s, $\underline{CH_3}$-O), 2.42 (3H, s, $\underline{CH_3}$).

N-Phenacyl-N-p-tolylsulphonyl-5-methyl-2-nitroaniline (126e)

M.p. 157-159°; yield 95%. (Found: C, 62.2; H, 4.8; N, 6.7. $C_{22}H_{20}N_2O_5S$ requires C, 62.3; H, 4.7; N, 6.6%). ν_{max} (cm^{-1}) 1690 (C=O), 1340, 1150 (SO_2), 1510, 1340 (NO_2). δ(TFA), 5.48 (2H, br, -$\underline{CH_2}$), 7.24-8.03 (12H, m, aromatic). 2.48 (3H, s, C(5)-$\underline{CH_3}$), 2.45 (3H, s, $\underline{CH_3}$).

N-Phenacyl-N-p-tolylsulphonyl-6-methyl-2-nitroaniline (126f)

M.p. 167-169°; yield 88%. (Found: C, 62.3; H, 4.75; N, 6.6, $C_{22}H_{20}N_2O_5S$ requires C, 62.3; H, 4.7; N, 6.6%). ν_{max} (cm^{-1}) 1700 (C=O), 1340, 1150 (SO_2), 1550, 1340 (NO_2). δ (TFA), 549 (2H, ABq CH_2, J=16 Hz); 7.33-8.18 (12 H, m, aromatic). 2.51 (3H, s, CH_3); 2.27 (3H, s, CH_3-C(6)).

Formation of 2-alkoxybenzimidazole-3-oxides; using alkoxide as the base. The following procedure was typical. 2-Isopropoxy-5-methylbenzimidazole-3-oxide (138b). N-Phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (4.24 g) in isopropanol (40 ml) was refluxed for 2 h with sodium isopropoxide solution (from sodium (0.46 g)) in isopropanol (20 ml)). The solvent was evaporated off in vacuo and the residue extracted into ether-water (1:1, 200 ml). Acidification of the aqueous layer (5 M H_2SO_4) to pH ~7 gave 2-isopropoxy-5-methylbenzimi-

dazole-3-oxide (138b) (0.49 g, 24%). M.p. 151-152° (Found: C, 63.8; H, 6.75; N, 13.55. $C_{11}H_{14}N_2O_2$ requires C, 64.1; H, 6.8; N, 13.6%). δ (DMSO d_6), 6.78-7.33 (3H, m, aromatic), 5.20 (1H, m, -OCH), 2.39 (3H, s, CH_3), 1.4 (6H, d, 2xC-(CH_3), J=6 Hz).

Chromatography of the dried (Na_2SO_4) ether layer (silica-gel, $CHCl_3$) yielded 4-methyl-2-nitroaniline (0.21 g, 14%) m.p. 111-112° (lit[93] 113°).

The following were prepared similarly:

2-Ethoxy benzimidazole-3-oxide (132a). m.p. 162-164° (lit[34] 166°) 80%. δ (TFA), 4.88 (2H, q, OCH_2, J=6 Hz) 7.57 (4H, s, aromatic), 1.66 (3H, t, $-OCH_2CH_3$, J=7 Hz).

2-Ethoxy-5-methylbenzimidazole-3-oxide (132b) m.p. 183°, 62% (analytical and spectroscopic data see p.155).

5-Chloro-2-ethoxybenzimidazole-3-oxide (132c) m.p. 201-202°, 68%. (Found: C, 50.8; H, 4.3; N, 13.2. $C_9H_9N_2O_2Cl$ requires C, 50.65; H, 4.3; N, 13.2%). δ (TFA). 4.87 (2H, q, OCH_2, J=6 Hz) 7.45-7.60 (3H, m, aromatic). 1.63 (3H, t, OCH_2CH_3, J=7 Hz).

2-Ethoxy-5-methoxybenzimidazole-3-oxide (132d). m.p. 147-148°, 68%. (Found: C, 57.5; H, 5.65; N, 13.5. $C_{10}H_{12}N_2O_3$ requires C, 57.7; H, 5.9; N, 13.45%). δ (TFA) 4.91 (2H, q, $-OCH_2$), 7.10-7.61 (3H, m, aromatic), 4.10 (3H, s, CH_3O-), 1.62 (3H, t, $-OCH_2CH_3$).

2-Ethoxy-6-methylbenzimidazole-3-oxide (132e). m.p. 163-164°, 41% (Found: C, 62.4; H, 5.4; N, 14.5. $C_{10}H_{12}N_2O_2$ requires C, 62.5; H, 6.3; N, 14.6%). δ (TFA); 4.88 (2H, q, $-OCH_2$, J=6Hz)

7.39 (3H, s, aromatic), 2.51 (3H, s, $\underline{CH_3}$), 1.77 (3H, t, $-OCH_2\underline{CH_3}$, J=7 Hz)

2-Methoxy-5-methylbenzimidazole-3-oxide (136b). m.p. 166-168°, 47%. (Found: C, 60.5; H, 5.45; N, 15.7; $C_9H_{10}N_2O_2$ requires c, 60.7; H, 5.7; N, 15.7%). δ (DMSO d_6), 2.40 (3H, s, $\underline{CH_3}$), 4.10 (3H, s, $-O\underline{CH_3}$), 6.82-7.33 (3H, m, aromatic).

5-Chloro-2-methoxybenzimidazole-3-oxide (136c) m.p. 191-192°, 28%. (Found: C, 48.6; H, 3.9; N, 13.7. $C_8H_7N_2O_2Cl$ requires C, 48.4; H, 3.55; N, 14.1%). δ (TFA), 4.69 (3H, s, $-O\underline{CH_3}$), 7.60-7.72 (3H, m, aromatic).

2-Methoxy-5-methoxybenzimidazole-3-oxide (136d). m.p. 144°, 34%. (Found: C, 55.6; H, 5.2; N, 14.3. $C_9H_{10}N_2O_3$ requires C, 55.7; H, 5.2; N, 14.4%). δ (TFA), 4.27 (3H, s, C-$O\underline{CH_3}$), 4.00 (3H, s, CH_3-O); 7.15-7.66 (3H, m, aromatic).

2-Methoxy-6-methylbenzimidazole-3-oxide (136e). m.p. 164-165°, 45%. (Found: C, 60.4; H, 5.8; N, 15.4. $C_9H_{10}N_2O_2$ requires C, 60.7; H, 5.7; N, 15.7%). δ (TFA), 2.24 (3H, s, $\underline{CH_3}$), 4.27 (3H, s, C-$\underline{OCH_3}$), 7.10-7.15 (3H, m, aromatic).

5-Methyl-2-n-propoxybenzimidazole-3-oxide (137b) m.p. 158-160°, 65%. (Found: C, 63.8; H, 6.7; N, 13.6. $C_{11}H_{14}N_2O_2$ requires C, 64.1; H, 6.9; N, 13.6%). δ (TFA), 7.42 (3H, s, aromatic 2.60 (3H, s, CH_3), 4.76 (2H, t, $-OCH_2$, J=6 Hz), 2.14 (2H, sextet, O-$CH_2\underline{CH_2}$). 1.18 (3H, t, $OCH_2CH_2\underline{CH_3}$, J=7 Hz).

5-Chloro-2-n-propoxybenzimidazole-3-oxide (137c) m.p. 183°, 54%. (Found: C, 53.2; H, 5.1; N, 12.7. $C_{10}H_{11}N_2O_2Cl$ requires C, 53.0, H, 4.9; N, 12.4%). δ (TFA), 7.54-7.66

(3H, m, aromatic), 4.86 (2H, t, $-O\underline{CH}_2$, J=6 Hz), 2.15 (2H, sextet, $-OCH_2\underline{CH}_2$), 1.22 (3H, t, $OCH_2CH_2\underline{CH}_3$, J=7 Hz).

2-Ethoxy-5-methylbenzimidazole (139)

a) By reduction of 2-ethoxy-5-methylbenzimidazole-3-oxide (132b) 2-Ethoxy-5-methylbenzimidazole-3-oxide (0.75 g) was stirred for 1 h in a mixture of glacial acetic acid (5 ml) and acetic anhydride (0.2 ml). Dilution of the reaction mixture with ethanol (20 ml) followed by hydrogenation over a Pd/C catalyst (10%, 0.1 g) yielded 2-ethoxy-5-methylbenzimidazole 0.15 g (22%) (from benzene-petrol). M.p. 162-164° (lit[100] 162°). (Found: C, 67.9; H, 6.8; N, 15.75. Calc. for $C_{10}H_{12}N_2O$, C, 68.2; H, 6.9; N, 15.8%).

b) By reaction of 4-methyl-o-phenylenediamine with tetraethoxymethane. Tetraethoxymethane (2.0 g) was added to a solution of 4-methyl-o-phenylenediamine (1.0 g) in glacial acetic acid (5 ml), and the mixture stirred for 24 h at room temperature. Removal of the solvent gave 2-ethoxy-5-methylbenzimidazole 0.95 g (67%) (from benzene-petrol). m.p. 160-161° (lit[100] 162°).

Detection of 2-methoxybenzimidazole-3-oxide (136a)

N-Phenacyl-N-p-tolylsulphonyl-o-nitroaniline (1.025 g) in methanol (10 ml) was refluxed for 2 h with sodium methoxide solution (from sodium (0.12 g) and methanol (10 ml). The methanol was evaporated off in vacuo and ether (100 ml) added to the residue. The ether insoluble product was filtered, dissolved in methanol (50 ml) and anhydrous hydrogen chloride

was passed into the solution until the deep red colour lightened. Evaporation of the methanol in vacuo gave an ethanol insoluble product which was filtered and recrystallised from acetic acid. (0.25 g , m.p. 250°). M/e, 164 (M^+ 11%)*, 133(77)**, 106(100).

* $C_8H_8N_2O_2$ requires 164.058573, found 164.057611

** $C_7H_5N_2O$ requires 133.040185, found 133.040332

Neutralisation by sodium carbonate, sodium hydrogen carbonate and sodium methoxide did not yield the free base.

From the addition of methyl toluene-p-sulphonate to the reaction mixture, the N-methoxy compound, if present, was unable to be isolated due to the large number of products detected.

Reaction of N-phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (126b) with sodium methoxide (1:1). N-Phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (2.12 g) in methanol (10 ml) was refluxed for 2 h with a sodium methoxide solution (from sodium (0.12 g)) in methanol (20 ml). The solvent was evaporated off under vacuo and ether added to the residue. The ether insoluble product was filtered, dissolved in methanol and anhydrous hydrogen chloride passed into the solution until the deep red colour lightened. High performance liquid chromatography of the reaction mixture detected methyl benzoate which implied the formation of sodium benzoate in the original reaction.

Evaporation of the solvent in vacuo gave 5-methyl-1-p-tolylsulphonyl-2-benzimidazolone hydrochloride which was neutralised to the free base (131) by sodium carbonate. (0.62 g, 40%). m.p. 261-264° (lit[96] 263-265°) (from acetic acid) and 2-benzoyl-5-methylbenzimidazole-3-oxide hydrochloride which was neutralised to the free base (129) by sodium carbonate (0.35 g, 28%) m.p. 129-130°. (lit[35] 132°) (from methanol).

Reaction of N-phenacyl-o-nitroaniline (127a) with sodium methoxide in methanol (1:2). N-Phenacyl-o-nitroaniline (2.56 g) in methanol (15 ml) was refluxed for 2 h with a sodium methoxide solution (from sodium (0.46 g) in methanol (40 ml)). The methanol was evaporated off and the residue extracted into ether-water (1:1), 100 ml). Acidification of the aqueous layer (5 M, H_2SO_4) gave no product. Chromatography (silica-gel, $CHCl_3$) of the dried (Na_2SO_4) organic layer yielded methyl benzoate (0.25 g, 14%) and o-nitroaniline (0.70 g, 50%) m.p. 70-72°, (from benzene-petrol) (lit[80] 71°).

The results of the reactions (127a) and (127b) with methoxide and ethoxide are shown in table 9.

Compound	$CH_3O^- \cdot CH_3OH$	$C_2H_5O^- \cdot C_2H_5OH$
(127a)	methyl benzoate (14%) o-nitroaniline	ethyl benzoate (10%) o-nitroaniline (53%)
(127b)	(129) (2%) methylbenzoate (14%) 4-methyl-2-nitroaniline (42%)	(129) (3%) ethylbenzoate (11%) 4-methyl-2-nitroaniline (45%)

TABLE 9

Reaction of N-phenacyl-N-p-tolylsulphonyl-o-nitroaniline (126a) with sodium carbonate.

a) By the cyclisation methods described previously, (126a) (2.05 g), gave 1-p-tolylsulphonyl-2-benzimidazolone (144) (0.07 g, 6%) m.p. 207-210° (from acetic acid). (lit[101] 216-218° 211-215[96]) and methyl benzoate (0.03 g, 5%)

b) N-(o-Nitrophenyl)-α-methoxyphenacylamine (145). To N-phenacyl-N-p-tolylsulphonyl-o-nitroaniline (1.02 g) was added a slurry of sodium carbonate (1.56 g) in methanol (20 ml). The mixture was refluxed for 2 h. The unreacted carbonate was filtered, the solvent removed in vacuo, and the residue washed with water. Crystallisation (CH_3OH) of the remaining product gave N-(o-nitrophenyl)-α-methoxyphenacylamine (0.50 g, 70%). m.p. 110-112°. (Found: C, 63.0; H, 4.9; N, 9.6. $C_{15}H_{14}N_2O_4$ requires C, 63.0; H, 4.9; N, 9.8%). ν_{max} (cm^{-1}) 3330 (N-H), 1520, 1340 (NO_2), 1680 (C=O). δ ($CDCl_3$), 3.16 (3H, s, OCH_3), 6.22 (1H, m, C-H), 7.33-7.66 (5H, m, aromatic), 8.16-8.33 (3H, m, aromatic), 6.82 (1H, d, aromatic,) 9.22 (1H, br, N-H).

Reaction of N-phenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (126b) with tertiary butoxide. By the usual procedure (126b), (1.06 g), potassium t-butoxide (from potassium (0.2 g) t-butanol (15 ml)) gave only 4-methyl-2-nitroaniline (0.31 g, 82%) m.p. (from benzene-petrol) 114-116° (lit[95] 113).

A similar reaction using N-phenacyl-N-p-tolylsulphonyl-o-nitroaniline (126a) with tertiary butoxide gave o-nitroaniline (75%) m.p. (72°) (from benzene-petrol) (lit[80] 71°).

1-Hydroxy-4-methyl-2-benzimidazolone (148). N-phenacyl-N-p-tolylsulphonyl-6-methyl-2-nitroaniline (126f) (2.12 g) in ethanol (15 ml) was refluxed for 2 h with a sodium ethoxide solution (from sodium (0.23 g) and ethanol (25 ml)). The ethanol was evaporated off in vacuo and the residue extracted into ether-water (1:1, 100 ml). Acidification (5 M H_2SO_4) of the aqueous layer to pH 7 gave 1-hydroxy-4-methyl-2-benzimidazolone (148) (0.30 g, 33%). m.p. 254-257° (from ethanol). (Found: C, 58.8; H, 5.0; N, 17.0. $C_8H_8N_2O_2$ requires C, 58.5; H, 4.9; N, 17.1%). ν'_{max} (cm^{-1}), 1700 (C=O) δ (TFA), 7.18 (3H, s, aromatic), 2.42 (3H, s, CH_3). When methoxide in methanol was used instead of ethoxide in ethanol, 22% of (148) was formed.

4-Methyl-2-benzimidazolone (148a). i) (148a) (25%, m.p. 299-302° (d)) (lit[103] 297-300) was obtained from the hydrogenation of 1-hydroxy-4-methyl-2-benzimidazolone by an analogous procedure to the hydrogenation of 2-ethoxy-5-methyl-benzimidazole-3-oxide (132b) (see p. 160).

ii) From 6-methyl-2-nitroaniline. 6-methyl-2-nitroaniline (2.0 g) in ethanol (20 ml) was hydrogenated over a palladium/charcoal catalyst (10%, 0.2 g). The catalyst was removed by filtration and the ethanol evaporated off in vacuo. To the residue glacial acetic acid (5 ml) and tetraethoxymethane (2 g) were added, and the mixture stirred for 24 h at room temperature. Ethanol (70 ml) was added, the solvent evaporated off in vacuo, and to the residue was added concentrated hydrochloric acid (8 ml). This mixture

was warmed on a steam bath for 3 h, poured onto crushed ice, and the addition of ammonia (0.88 M) gave 4-methyl-2-benzimidazolone (0.38 g, 19%). m.p. 296-299° (from acetic acid). (lit[103] 297-300°).

Series 4

The compounds of series 4 were prepared from the sodium salt of the appropriate sulphonamide (149), chloroacetone and DMF, by a method analogous to those of series 3 (pp96)

N-Acetonyl-N-p-tolylsulphonyl-o-nitroaniline (149a). m.p. 100-102°, (50%). (Found: C, 55.1; H, 4.6; N, 8.05. $C_{16}H_{16}N_2O_5S$ requires C, 55.2; H, 4.6; N, 8.0%). ν_{max} (cm^{-1}) 1730 (C=O), 1520, 1340 (NO_2), 1340, 1150 (SO_2). δ ($CDCl_3$), 4.60 (2H, s, $\underline{CH_2}$), 7.0-7.81 (8H, m, aromatic), 2.33 (3H, s, CH_3(tolyl), 2.15 (3H, s, $-C\overset{O}{\leq}_{CH_3}$).

N-Acetonyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (149b). m.p. 132°, (90%). (Found: C, 56.0; H, 5.0; N, 7.7. $C_{17}H_{18}N_2O_5S$ requires C, 56.3; H, 5.0; N, 7.7%). ν_{max} (cm^{-1}), 1730 (C=O), 1520, 1330 (NO_2), 1330, 1160 (SO_2). δ ($CDCl_3$), 4.63 (2H, s, $\underline{CH_2}$), 7.12-7.72 (7H, m, aromatic), 2.21 (3H, s, $C\overset{O}{\leq}_{\underline{CH_3}}$), 2.45 (6H, s, 2xArCH$_3$).

N-Acetonyl-N-p-tolylsulphonyl-4-methoxy-2-nitroaniline (149d). m.p. 91-93°, (77%). (Found: C, 54.0; H, 4.9; N, 7.4. $C_{17}H_{18}N_2O_6S$ requires C, 54.0; H, 4.8; N, 7.4%). ν_{max} (cm^{-1}); 1725 (C=O), 1520, 1340 (NO_2), 1340, 1160 (SO_2). δ ($CDCl_3$),

4.63 (2H, s, $\underline{CH_2}$), 7.15-7.66 (7H, m, aromatic), 3.85 (3H, s, $\underline{CH_3}$-O), 2.45 (3H, s, CH_3(tolyl)), 2.24 (3H, s, $-C(=O)\underline{CH_3}$).

N-Acetonyl-N-p-tolylsulphonyl-6-methyl-2-nitroaniline (149f)

m.p. 94-96° (52%). (Found: C, 56.5; H, 5.1; N, 7.5. $C_{17}H_{18}N_2O_5S$ requires C, 56.3; H, 5.0; N, 7.7%). ν_{max} (cm^{-1}) 1730 (C=O), 1520, 1335 (NO_2), 1335 1150 (SO_2). δ ($CDCl_3$), 3.94-5.30 (2H, q, $\underline{CH_2}$), 7.48-7.81 (7H, m, aromatic), 2.42 (3H, s, CH_3(tolyl)), 2.24 (3H, s, $\underline{CH_3}$-C(6)), 2.06 (3H, s, $-C(=O)CH_3$).

Compounds (149a, b, d) were cyclised analogously to compounds of series 3. (For results see Table 8).

Compound (149f) gave the benzimidazolone (148) (cf compound 126f) in a 25% yield when the base was ethoxide and (148) in a 17% yield when the base was methoxide.

Series 5

Compounds of series 5 were synthesised from the sodium salt of the appropriate sulphonamide (150), ethyl bromoacetate and DMF, analogously to those of series 3.

N-Ethoxycarbonylmethyl-N-p-tolylsulphonyl-o-nitroaniline (150a)

(With D.M. Smith). m.p. 74-75°, yield 73%. (Found: C, 54.0; H, 4.7; N, 7.3. $C_{17}H_{18}N_2O_6S$ requires C, 54.0; H, 4.8; N, 7.4%). ν_{max} (cm^{-1}), 1745 (C=O). δ (CCl_4) 2.20-3.00 (8H, m, aromatic), 5.55 (2H, s, CH_2), 5.85 (2H, ABq, $O\underline{CH_2}$, J= 6 Hz), 8.75 (3H, t, $CH_2\underline{CH_3}$, J=7 Hz).

N-Ethoxycarbonylmethyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (150b). m.p. 59-60° (51%). (Found: C, 55.2; H, 5.0; N, 7.1. $C_{18}H_{20}N_2O_6S$ requires C, 55.1; H, 5.1; N, 7.1%.) ν_{max} (cm^{-1}), 1735 (C=O), 1530, 1330 (NO_2); 1160 (SO_2). δ ($CDCl_3$), 4.57 (2H, s, $\underline{N-CH_2}$), 7.12-7.75 (7H, m, aromatic), 4.17 (2H, q, $C(=O)\underline{OCH_2}$, J=6 Hz), 2.45 (6H, s, $\underline{CH_3}$-C(4); CH_3(tolyl)). 1.39 (3H, t, $O-CH_2\underline{CH_3}$, J=7 Hz).

N-Ethoxycarbonylmethyl-N-p-tolylsulphonyl-4-methoxy-2-nitroaniline (150d). m.p. 82-84°, (57%). (Found: C, 52.7; H, 5.0; N, 6.7. $C_{18}H_{20}N_2O_7S$ requires C, 53.0; H, 4.9; N, 6.9%). ν_{max} (cm^{-1}). 1750 (C=O); 1530, 1330 (NO_2), 1330, 1160 (SO_2). δ ($CDCl_3$), 4.60 (2H, br, $N-\underline{CH_2}$), 6.97-7.69 (7H, m, aromatic), 4.18 (2H, q, $C(=O)\underline{OCH_2}$, J=6 Hz), 3.88 (3H, s, $\underline{CH_3}$-O); 2.42 (3H, s, CH_3(tolyl)), 1.39 (3H, t, $-OCH_2\underline{CH_3}$, J=7 Hz).

The reaction with base of compounds of series 5 yielded the primary amine (obtained by chromatography (silica-gel, $CHCl_3$)) in all cases. For results see Table 10.

TABLE 10

Compound	CH_3O^- : CH_3OH	$C_2H_5O^-$: C_2H_5OH	$^tBuO^-$: ^tBuOH
(150a)	o-nitroaniline (53%)		
(150b)	4-methyl-2-nitro-aniline (61%)	4-methyl-2-nitro aniline (59%)	4-methyl-2-nitr -aniline (67%
(150c)	4-methoxy-2-nitro-aniline (50%)	4-methoxy-2-nitro-aniline (52%)	

Series 6

Compounds of series 6 were synthesised from the sodium salt of the appropriate sulphonamide (152), chloroacetonitrile and DMF, in an analogous way to those of series 3.

N-Cyanomethyl-N-p-tolylsulphonyl-o-nitroaniline (151a).
m.p. 96-98°, yield 50%. (Found: C, 54.4; H, 3.9; N, 12.7. $C_{15}H_{13}N_3O_4S$ requires C, 54.4; H, 3.95; N, 12.7%). ν_{max} (cm^{-1}) 1520, 1350 (NO_2), 1340, 1160 (SO_2). $\delta(CDCl_3)$, 7.16-8.00 (8H, m, aromatic), 4.72 (2H, br, $\underline{CH_2}$), 2.45 (3H, s, $\underline{CH_3}$).

N-Cyanomethyl-N-p-tolylsulphonyl-4-chloro-2-nitroaniline (151c).
m.p. 116-118° (60%). (Found: C, 49.0; H, 3.3; N, 11.4. $C_{15}H_{12}N_3O_4SCl$ requires C, 49.25; H, 3.3; N, 11.5%). ν_{max} (cm^{-1}) 1525, 1335 (NO_2), 1160 (SO_2). $\delta(CDCl_3)$, 4.72 (2H, br, $\underline{CH_2}$) 7.15-8.10 (7H, m, aromatic), 2.45 (3H, s, $\underline{CH_3}$).

N-Cyanomethyl-N-p-tolylsulphonyl-6-methyl-2-nitroaniline (151f)
m.p. 115-116°, (87%). (Found: C, 55.5; H, 4.4; N, 12.1. $C_{16}H_{15}N_3O_4S$ requires C, 55.6; H, 4.4; N, 12.2%). ν_{max} (cm^{-1}), 1520, 1340 (NO_2), 1340, 1150 (SO_2). $\delta(CDCl_3)$, 4.61 (2H, ABq, $\underline{CH_2}$, J=16 Hz), 7.15-7.60 (7H, m, aromatic), 2.40 (3H, s, $\underline{CH_3}$ (tolyl)), 2.24 (3H, s, $\underline{CH_3}$-C(6)).

The reaction with ethoxide in ethanol of compounds of series 6 gave in all cases a low yield of the sulphonamide (152), with no other isolable products (Table 11).

TABLE 11

Compound	$C_2H_5O^-$: C_2H_5OH		
(151a)	(152a)	:	25%
(151c)	(152c)	:	15%
(151f)	(152f)	:	12%

Series 7

The compounds of series 7 were synthesised from the sodium salt of N-methylsulphonyl-4-methyl-o-nitroaniline, and either phenacyl bromide in DMF (153: y=COPh) or ethyl bromoacetate in DMF (153:y=$CO_2C_2H_5$).

N-Methanesulphonyl-4-methyl-2-nitroaniline was synthesised from 4-methyl-2-nitroaniline and methanesulphonyl chloride in an analogous way to the preparation of N-methanesulphonyl-o-nitroaniline. m.p. 105-107°. Yield 35%. (Found: C, 41.6; H, 4.4; M, 12.3. $C_8H_{10}N_2O_4$ requires C, 41.7; H, 4.4; N, 12.2%). ν_{max} (cm^{-1}), 3280 (N-H), 1520, 1360 (NO_2) 1340, 1170 (SO_2). δ ($CDCl_3$), 3.06 (3H, s, $\underline{CH_3}$-S), 2.36 (3H, s, $\underline{CH_3}$-C). 7.24-8.00 (3H, m, aromatic). 9.45 (1H, br, N-H).

N-Methanesulphonyl-N-phenacyl-4-methyl-2-nitroaniline (153: y=COPh). m.p. 89-91°, (72%). (Found: C, 55.2; H, 4.5; N, 8.1. $C_{16}H_{16}N_2O_5S$ requires C, 55.2, H, 4.6; N, 8.0%). ν_{max} (cm^{-1}), 1685 (C=O), 1525, 1330 (NO_2), 1330, 1140 (SO_2). δ($CDCl_3$), 5.27 (2H, s, $\underline{CH_2}$), 2.36 (3H, s, $\underline{CH_3}$C), 3.06 (3H, s, $\underline{CH_3}$-S), 7.30-8.00 (8H, m, aromatic).

N-Ethoxycarbonylmethyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline. (153:y=$CO_2C_2H_5$) m.p. 68-70°, (51%). (Found: C, 45.6; H, 5.1; N, 9.1. $C_{12}H_{16}N_2O_6S$ requires C, 45.6; H, 5.1; N, 8.85%). ν_{max} (cm^{-1}), 1740 (C=O); 1510, 1330 (NO_2), 1330, 1150 (SO_2). δ($CDCl_3$), 7.15-7.72 (3H, m, aromatic). 4.48 (2H, s, N-$\underline{CH_2}$), 4.23 (2H, q, $C^{=O}_{-OCH_2}$ J=6 Hz), 3.10 (3H, s, $\underline{CH_3}$-S), 2.48 (3H, s, $\underline{CH_3}$-C), 1.30 (3H, t, -$OCH_2\underline{CH_3}$, J=7 Hz).

Compound (153:y=COPh) with sodium ethoxide in ethanol gave (126b) in 31% yield. Compound (153:y=$CO_2C_2H_5$) with sodium ethoxide in ethanol gave 4-methyl-2-nitroaniline in 36% yield. These reactions were carried out using the usual conditions described previously.

N-p-Nitrophenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (154). was preprared using p-nitrophenacyl bromide [104] in exactly the same way as compound (126b). m.p. 192-194° (85%). (Found: C, 56.3; H, 4.1; N, 8.9. $C_{22}H_{19}N_3O_7S$ requires C, 56.3; H, 4.1; N, 8.95%). ν_{max} (cm^{-1}), 1700 (C=O) 1510, 1330(NO_2), 1330, 1150 (SO_2). δ($CDCl_3$), 5.33 (2H, s, $\underline{CH_2}$), 7.10-8.36 (11H, m, aromatic). 2.42 (6H, s, 2($\underline{CH_3}$)).

Acetic formic anhydride.

a)[76] Sodium formate (50 g) was added to a solution of acetyl chloride (44.5 ml) in dry ether (30 ml) over a period of 1 h., with the temperature not exceeding 27°. This mixture was protected from moisture and vigorously stirred for 6 h. at room temperature. Sodium chloride and unreacted sodium formate were filtered off and part of the solvent evaporated off in vacuo. No further attempts were made to characterise or purify the product due to its instability, and the crude anhydride was used directly in the next stage.

b)[77] An excess of ketene (derived from the thermal decomposition of diketene at 550°C) was bubbled into formic acid (12 g). No attempts were made to purify the product.

N-Formyl-N-p-tolylsulphonyl-o-nitroaniline (154a). N-p-Tolylsulphonyl-o-nitroaniline (1.6 g) was mixed with a sodium ethoxide solution (from sodium (0.10 g) in ethanol (70 ml)). The solvent was evaporated off in vacuo and a large excess of acetic formic anhydride (derived from method (a)) added and the mixture stirred for 24 h at room temperature. Evaporation of the ether gave the product (154a) which was recrystallised from ethanol. (0.91 g), 54%) m.p. 97-99°. (Found, C, 52.6; H, 3.8; N, 8.85, $C_{14}H_{12}N_2O_5S$ requires C, 52.5; H, 3.8; N, 8.7%). ν_{max} (cm^{-1}), 1700 (C=O), 1520, 1340 (NO_2), 1340, 1160 (SO_2). $\delta(CDCl_3)$, 2.45 (3H, s, $\underline{CH_3}$). 9.30 (1H, s, $C(=O)H$). 7.30-8.24 (8H, m, aromatic).

N-Formyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (154b) was prepared from the sodium salt of N-p-tolylsulphonyl-4-methyl-2-nitroaniline analogously to (154a). m.p. 116-118°, yield 60%. (Found: C, 53.9; H, 4.2; N, 8.4. $C_{15}H_{14}N_2O_5S$ requires C, 53.8; H, 4.2; N, 8.4%). ν_{max} (cm^{-1}) 1710 (C=O), 1530, 1350 (NO_2), 1350, 1160 (SO_2) $\delta(CDCl_3)$, 2.45 (6H, s, 2xAr$\underline{CH_3}$), 9.33 (1H, s, $\underline{CHO}$), 7.00-7.85 (7H, m, aromatic).

N-Formyl-N-p-tolylsulphonyl-4-methoxy-2-nitroaniline (154c) was prepared from the sodium salt of N-p-tolylsulphonyl-4-methoxy-2-nitroaniline analogously to (154a). m.p. 119-120°, yield 87%, (Found: C, 51.5; H, 4.05; N, 8.2, $C_{15}H_{14}N_2O_6S$ requires C, 51.4; H, 4.1; N, 8.0%). ν_{max} (cm^{-1}) 1700 (C=O), 1530, 1350 (NO_2), 1350, 1170 (SO_2). $\delta(CDCl_3)$ 2.42 (3H, s, $\underline{CH_3}$), 3.81 (3H, s, $O\underline{CH_3}$), 9.22 (1H, s, $\underline{CHO}$), 7.0-7.6 (7H, m, aromatic).

Hydrogenation of (154a) in the presence of acid. N-Formyl-N-p-tolylsulphonyl-o-nitroaniline (154a) (1.0 g) in ethanol (20 ml) and concentrated hydrochloric acid was hydrogenated for 4 h over a palladium-charcoal catalyst (10%, 0.1 g). Removal of the solvent in vacuo and recrystallisation of the residue from ethanol gave N-p-tolylsulphonyl-o-nitroaniline (0.71 g, 78%), m.p. 103-104° (lit[78] 103°) identical with an authentic sample.

Reaction of (154a) with hydrochloric acid in ethanol. N-Formyl-N-p-tolylsulphonyl-o-nitroaniline (154a) (1.0 g) was stirred for eight hours at room temperature with a mixture of concentrated hydrochloric acid (0.5 ml) in ethanol (20 ml). Removal of the solvent in vacuo and recrystallisation of the residue gave N-p-tolylsulphonyl-o-nitroaniline (0.83 g, 90%) m.p. 102-104° (lit[18] 103°).

Hydrogenation of (154b). N-Formyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (154b) (1.2 g) in ethanol (20 ml) was hydrogenated over a palladium-charcoal catalyst (10%, 0.1 g). The solvent was removed in vacuo and the residue dissolved in chloroform and chromatographed on a silica-gel column with chloroform as the eluant. After starting material (0.17 g) and various other unidentified products had been removed the eluant was changed to methanol and 5-methyl-1-p-tolylsulphonyl-benzimidazole-3-oxide (141b) was obtained. (0.20 g, 19%) m.p. 121-125°. ν_{max} (cm^{-1}) 1360, 1160 (SO_2), δ ($CDCl_3$) 2.36 (3H, s, CH_3-C(5)), 2.42 (3H, s, CH_3(tolyl)) 7.15-7.48 (8H, m, 7 aromatic, + C(2)-H). m/e 302 (M^+, 20%), 155(10), 147(82), 91(100).

$C_{15}H_{14}N_2O_3S$ requires 302.0725070 found 302.070167

$C_8H_7N_2O$ requires 147.055834 found 147.055986

Hydrogenation of (154c). N-Formyl-N-p-tolylsulphonyl-4-methoxy-2-nitroaniline (154c) (3.10 g) in ethanol (20 ml) was hydrogenated over a palladium-charcoal catalyst (10%, 0.2 g). Removal of the solvent in vacuo and recrystallisation of the residue gave the "hydrated" form (155) of the required product 5-methoxy-1-p-tolylsulphonylbenzimidazol-3-oxide (141c) (2.10 g, 70%) m.p. 133-134° (from benzene-petrol). (Found: C, 53.7; H, 5.0; N, 8.6. $C_{15}H_{14}N_2O_4S + H_2O$ requires C, 53.6; H, 4.8; N, 8.3%). ν_{max} (cm^{-1}) 1330, 1160 (SO_2) δ(DMSO d_6), 2.16 (3H, s, CH_3), 3.48 (3H, s, OCH_3), 6.66-7.42 (8H, m, 7H aromatic, +C(2)-H), m/e 318 (M^+, 16%), 172(100), 163(96), 155(66), 139(90).

Reaction of the "hydrated" form (155) of (141c) with methoxide and ethoxide. These reactions with one and two molar equivalents of methoxide and ethoxide gave no identifiable products.

N(1)-p-tolylsulphonyl-4-methoxy-o-phenylenediamine (156). The hydrated form (155) of 5-methoxy-1-p-tolylsulphonylbenzimidazole-3-oxide (0.35 g) was in sodium hydroxide (5 M, 10 ml) and was warmed on a steam bath for 2 h. Filtration of the precipitate and recrystallation from ethanol gave the product (156). (0.11 g, 40%) m.p. 143-145° ν_{max} (cm^{-1}) 3600, 3520 (NH_2), 3360 (N-H), 1320, 1140 (SO_2). m/e 155 (16%), 137(96), 106(50), 91(100).

$C_7H_9N_2O$ requires 137.071484: Found 137.070956

(N.B. There was not enough pure sample for an analysis and nmr).

N(1)-p-tolylsulphonyl-5-chloro-4-methoxy-o-phenylenediamine (157).
5-Methoxy-1-p-tolylsulphonylbenzimidazole-3-oxide (0.32 g) was stirred for 72 h at room temperature in concentrated hydrochloric acid (10 ml). The precipitate was filtered and recrystallised from ethanol to give the product (157) (0.28 g, 88%). m.p. 176-178°. (Found: C,51.5; H, 4.8; N, 8.55. $C_{14}H_{15}N_2O_3SCl$ requires C, 51.45; H, 4.6; N, 8.6%) ν_{max}(cm^{-1}), 3480,3380 (NH_2), 3200 (N-H), 1360,1150 (SO_2) δ($CDCl_3$), 2.42 (3H, s, $\underline{CH_3}$), 3.72 (3H, s, $\underline{OCH_3}$), 7.24-7.67 (4H, AA'BB'), 6.31 (2H, s, aromatic). m/e 326 (M^+, 8%) 171(100), 155(8%), 144(60), 137(25).

* $C_{14}H_{15}N_2O_3{}^{35}SCl$ requires 326.0491847 found 326.050301

** $C_7H_8N_2O{}^{35}Cl$ requires 171.0313908 found 171.033078

N(1)-p-Tolylsulphonyl-4-methyl-o-phenylenediamine (158).
N-Formyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (2.0 g) in pyridine (20 ml) was added dropwise to a suspension of sodium borohydride (1 g), palladium-charcoal (0.3 g), 10%) and water (40 ml). The mixture was stirred for 30 mins and the product was extracted into ether, washed with base (5 M NaOH) and acid (5 M HCl). The solvent was dried (Na_2SO_4) and evaporated in vacuo to give (158). m.p. -142-144°. (lit[93] 140 (Found: C, 60.5; H, 5.8; N, 10.1. Calc. for $C_{14}H_{16}N_2O_2S$ C, 60.85; H, 5.5; N, 9.87%). ν_{max} (cm^{-1}) 3540, 3440 (NH_2), 3280 (N-H), 1320. 1160 (SO_2). δ($CDCl_3$). 2.42 (3H, s, CH_3(tolyl)) 2.20 (3H, s, CH_3-C), 7.0-7.66 (4H, AA'BB' aromatic), 6.16-6.82 (3H, m, aromatic).

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