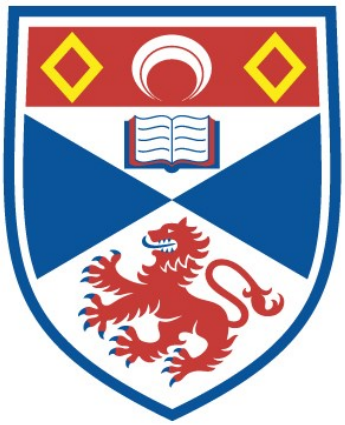
BASE-INDUCED CYCLISATIONS OF ORTHO-SUBSTITUTED NITRO-AROMATICS

Michael David McFarlane

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



1988

BASE-INDUCED CYCLISATIONS OF ORTHO-SUBSTITUTED NITRO-AROMATICS

A THESIS PRESENTED BY MICHAEL DAVID McFARLANE, B.Sc.
TO THE UNIVERSITY OF ST. ANDREWS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY.

MAY, 1988.

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I, Michael David McFarlane, hereby certify that this thesis has been composed by myself, that it is a record of my own work, and that it has not been accepted in partial or complete fulfilment of any other degree or professional qualification.

Signed.....Date..8.5.88.....

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No.12 on 1st October 1984 and as a candidate for the degree of Ph.D. on 1st October, 1985.

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I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate to the Degree of Ph.D.

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I thank the Science and Engineering Research Council for the award of a research studentship.

Finally, I am particularly indebted to my parents for their willing efforts in producing this thesis.

DEDICATION

For my wife Elaine

and my parents

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Publications

M.D.McFarlane and D.M. Smith, Tetrahedron Lett., 1987, 28, 6363.

I.W. Harvey, M.D.McFarlane, D.J. Moody and D.M.Smith, J.Chem. Soc.Perkin Trans. 1, 1988, 681.

M.D.McFarlane, D.J. Moody and D.M.Smith, J.Chem. Soc. Perkin Trans.1, 1988, 691.

I.W. Harvey, M.D.McFarlane, D.J. Moody and D.M. Smith, J.Chem. Soc. Perkin Trans. 1, 1988, paper at proof stage.

ABSTRACT

In Chapter I some of the chemical, biological and physical properties of purine analogues, particularly benzimidazole N-oxides, are briefly discussed.

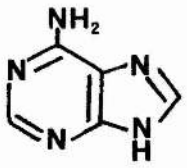
In Chapter II, the preparations of 4-, 5-, 6-, and 7-amino-1H-benzimidazole 3-oxides are described. The methods employed involve base-induced cyclisation of suitably protected aminonitrophenyl glycine derivatives (esters or nitriles) followed by hydrolysis of the ester or nitrile and decarboxylation.

In Chapter III, attempts are made to prepare imidazopyridine N-oxides, an area of N-oxide chemistry little explored. Although few derivatives of this class of compound are synthesised, the preparation of the parent 3H-imidazo[4,5-b]pyridine 1-oxide is accomplished.

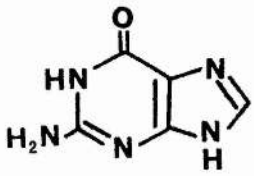
In Chapter IV, the possibility of preparing 1-methylbenzimidazole 3-oxides by the methods used in Chapters II and III is investigated, but unexpected results are obtained e.g. cyclisation of o-nitrophenyl-sarcosine esters gives 1-hydroxy-4-methylquinoxaline-2, 3-diones. These reactions have instigated an investigation into the general mechanism for the base-induced cyclisations discussed in this Thesis.

CHAPTER I: INTRODUCTION

Adenine (1) and guanine (2) are ubiquitous in nature, forming an integral part of eukaryotic, prokaryotic and viral nucleic acids.

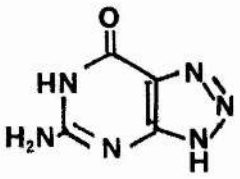


(1)



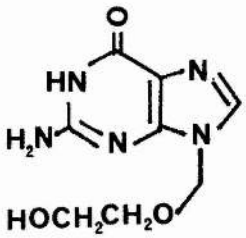
(2)

Although adenine and guanine have been known since 1885 and 1844 respectively [1] it has only been since the 1950's that their precise role and central importance in living systems has been realised (the structure of DNA was elucidated by Watson and Crick in 1953[2]). Since that time the synthesis of base and nucleoside analogues has attracted a vast amount of interest. The preparation of such analogues, which may be incorporated into the growing nucleic acid on the basis of their similarity to the natural species, and which may interfere with normal cellular processes, is of great significance. The ability to interfere selectively with cancerous tissue and the possibility of altering the genetic properties of an organism are two examples of major importance. Shown below are examples of purine analogues (3[3] and 4[4]) which have useful physiological properties.



(3)

8-Azaguanine
anti-neoplastic agent

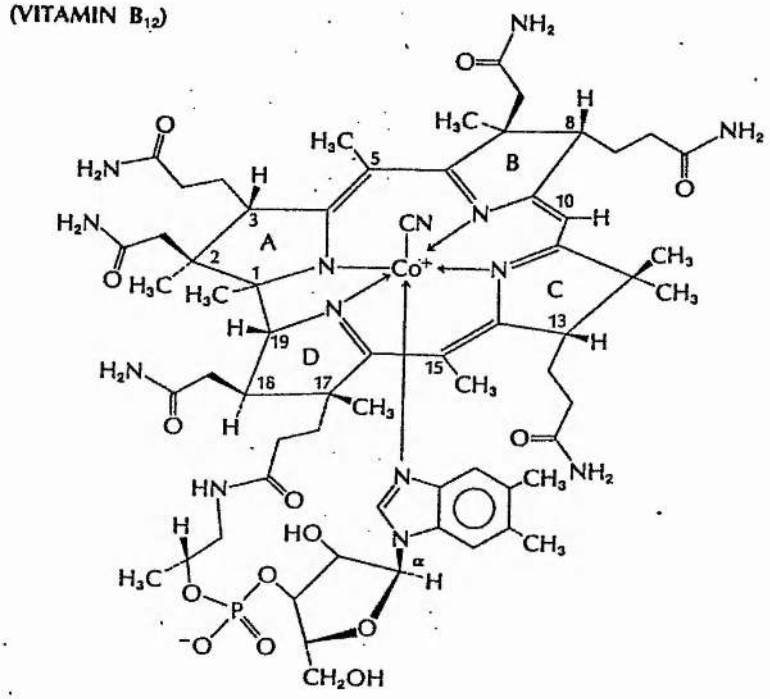


(4)

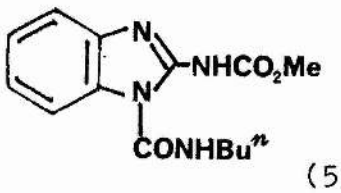
Acyclovir
anti-viral drug

Benzimidazoles, which have structures related to those of the purines, have also attracted much interest in the past twenty-five years, in particular since the finding that 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole is a constituent part of vitamin B_{12}[5] (Fig. 1).

Fig. 1



Some simple benzimidazoles are of biological interest in their own right[6], and out of a number of commercially successful products, the fungicide Benomyl (5) and the anthelmintic Thiabendazole (6) are among the better known[6].



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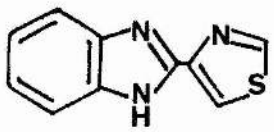
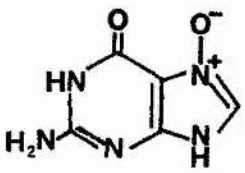


(6)

The N-oxides of these systems have also come under scrutiny, and in some cases biological activity has been reported. For example, the 7-oxide of guanine (7) possesses anti-tumour properties[7] and the 1-oxide of a substituted adenine (8) is reported to be hypocholesterolemic[8].



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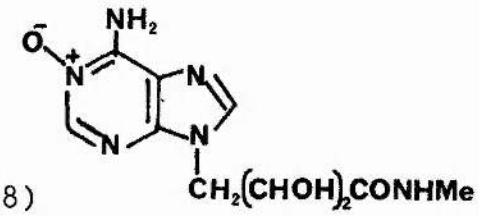
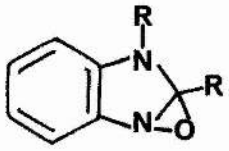


(8)

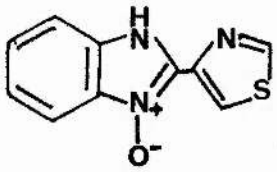
Although benzimidazole N-oxides (9) have been known for one hundred years[9] it was not until 1951 that they were correctly formulated as N-oxides[10], initial researchers assigning them a tricyclic structure (10).

(9)



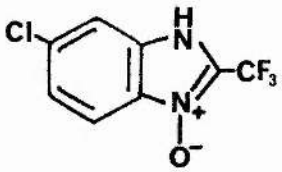
(10)

However, the synthetic approach to these N-oxides has not been systematic, nor has a synthesis of truly general applicability emerged. As a result the variety of existing derivatives is insufficient for there to have been a broad investigation into the potential applications of this system. Such an investigation would be justifiable as the biochemical potency of some derivatives is known e.g. (11)[11] and (12)[12].



(11)

nematocide



(12)

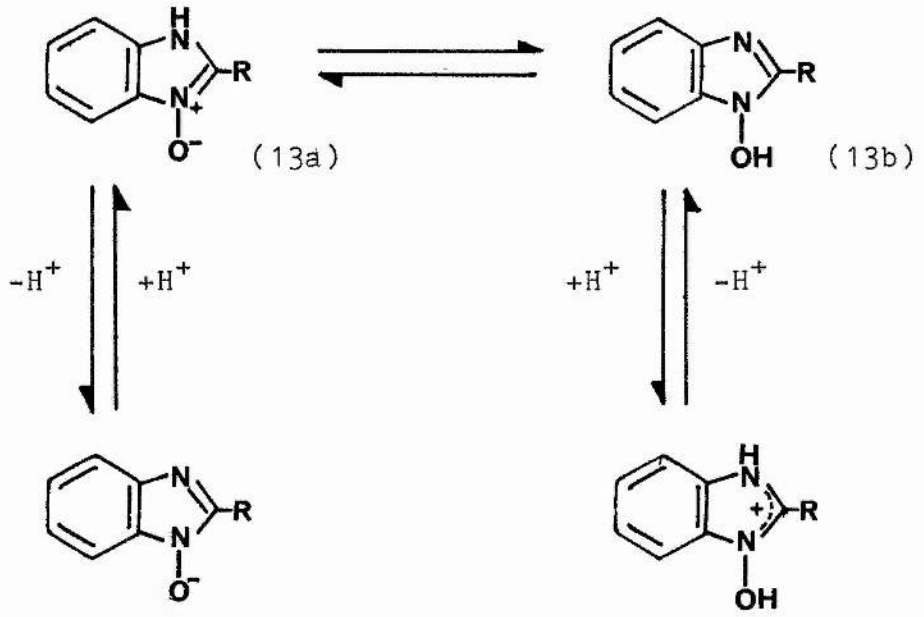
herbicide

The research group in St. Andrews has been interested in benzimidazole N-oxides for the past twenty years and recent activity has been concentrated on devising a

versatile and general procedure for the synthesis of these N-oxides, especially those unsubstituted at the 2-position. The synthetic procedures currently available, together with the new method devised, are discussed in Chapter II.

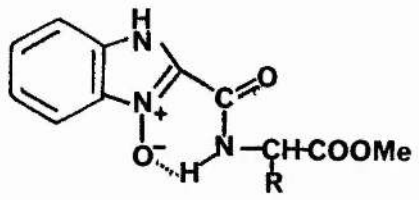
1-Unsubstituted benzimidazole 3-oxides (13a) are tautomeric with N-hydroxybenzimidazoles (13b) (Scheme 1).

Scheme 1



Although there was some initial disagreement [13] regarding the position of the equilibrium for the parent heterocycle, the majority of the evidence[14,15] leads to the conclusion that in aqueous solution the N-oxide form predominates and as the polarity of the solvent decreases

there is a corresponding increase in the proportion of the N-hydroxy tautomer. Similar results have been found for the 5-nitro derivative[16]; however the 2-phenyl compound is reported to exist solely as the N-hydroxy form even in polar media[13]. A recent n.m.r. study has revealed that compounds of type (14) exist (in deuterochloroform solution) predominantly as N-oxides[17].



(14)

The position of the equilibrium in the solid state has not been determined. In the remainder of this thesis, it is to be understood that 1-unsubstituted benzimidazole 3-oxides are capable of tautomerism, even although they are referred to only as "N-oxides".

These N-oxides are also amphoteric (see Scheme 1), a property which has a significant influence on the experimental procedures involved in their synthesis since both the deprotonated and protonated salts are, to a certain extent, water-soluble.

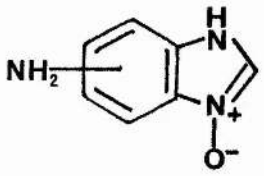
Finally, benzimidazole N-oxide is a colourless, high-melting (210°C), water-soluble solid. However, substituents

in these molecules have a considerable influence on their properties and solubility in aqueous media is sometimes poor. Since the *in vivo* activity of many chemotherapeutic agents depends markedly on their solubility characteristics it was of interest to observe the effect on solubility of introducting polar groups, particularly amino, into benzimidazole *N*-oxides.

CHAPTER II: AMINOBENZIMIDAZOLE N-OXIDES

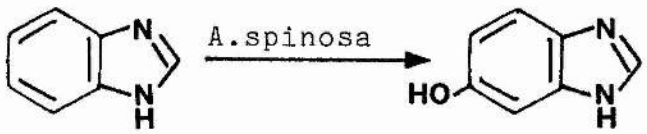
INTRODUCTION

Benzimidazole N-oxides bearing an amino group in the benzene ring (15) can be considered as a simple model system for the natural purines; 5-and 6-amino-1H-benzimidazole 3-oxides possess some of the functionality of guanine, while the 4-and 7-amino isomers are similar to adenine.



(15a) 4-NH_2
(15b) 5-NH_2
(15c) 6-NH_2
(15d) 7-NH_2

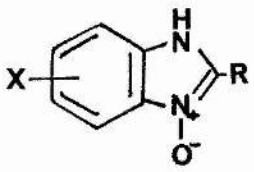
In view of what has been discussed in the preceding Chapter, these compounds are obviously of potential biological interest. Their selective functionalisation is also of interest from a biological viewpoint and the possibility of preparing nucleoside analogues from these N-oxides is explored briefly at the end of this Chapter. Although not investigated in the course of this work experimental procedures also exist whereby hydroxylation in the benzene ring may be possible, thus increasing the functionality in the ring. For example, benzimidazole (16) undergoes enzymatic hydroxylation at position 6 in the presence of Absidia spinosa[18].



(16)

SYNTHETIC OBJECTIVE

A synthetic goal of the St. Andrews group over a number of years has been to devise a simple route to compounds of type (17) where X is variable and R is easily removed. For the purpose of this Chapter the ultimate aim was to obtain 2-unsubstituted N-oxides where $X=NH_2$.



(17)

SYNTHETIC BACKGROUND

There are a few short reviews of benzimidazole N-oxides of which that by Smith[9] (1981) is the most comprehensive and recent. The existing synthetic procedures employed for the preparation of benzimidazole N-oxides are now briefly discussed with a view to highlighting the problems associated

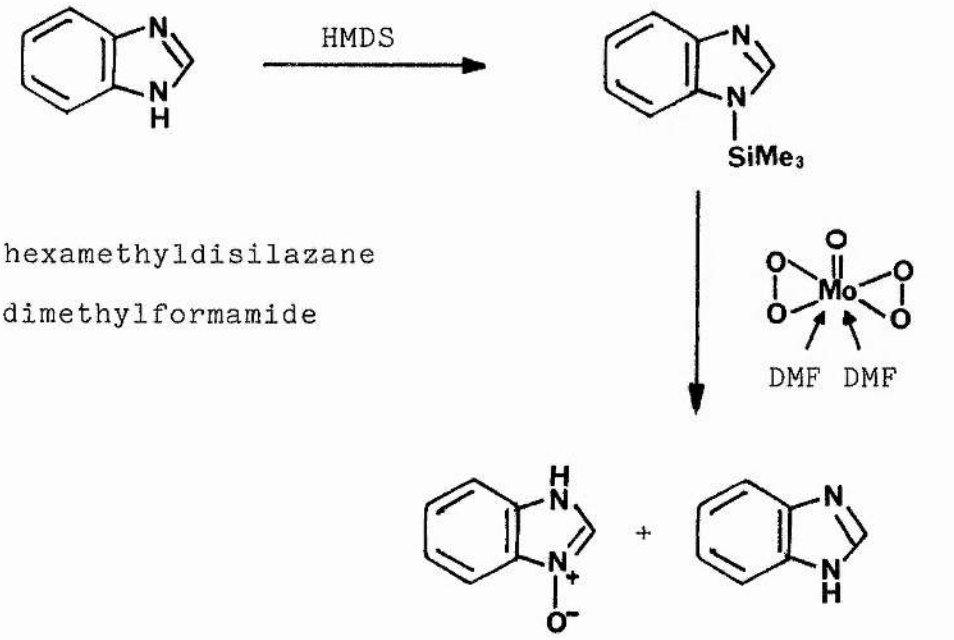
with these methods and particularly their lack of applicability to the case where X = amino. Only the major or more relevant methods are considered and other 'miscellaneous' reactions can be found by reference to the aforementioned review.

1. N-Oxidation of Benzimidazoles

Standard oxidation procedures e.g. using peracids [13,19,20], have proved unsuccessful; either unchanged benzimidazoles or benzimidazolones are obtained under conditions where N-oxidation would be expected. (It is not clear whether or not the N-oxides are the primary products in reactions where benzimidazolones are obtained; the rearrangement of the N-oxides to benzimidazolones is well known[21,22]).

The only recorded example of the successful N-oxidation of a benzimidazole is that by Sammes and co-workers in 1979[23](Scheme 2). Although the yield reported is low, it was thought that this result might point the way to further research; however, no related reports have been found in the literature since that time. This method therefore can currently be discounted as a practicable route to benzimidazole N-oxides.

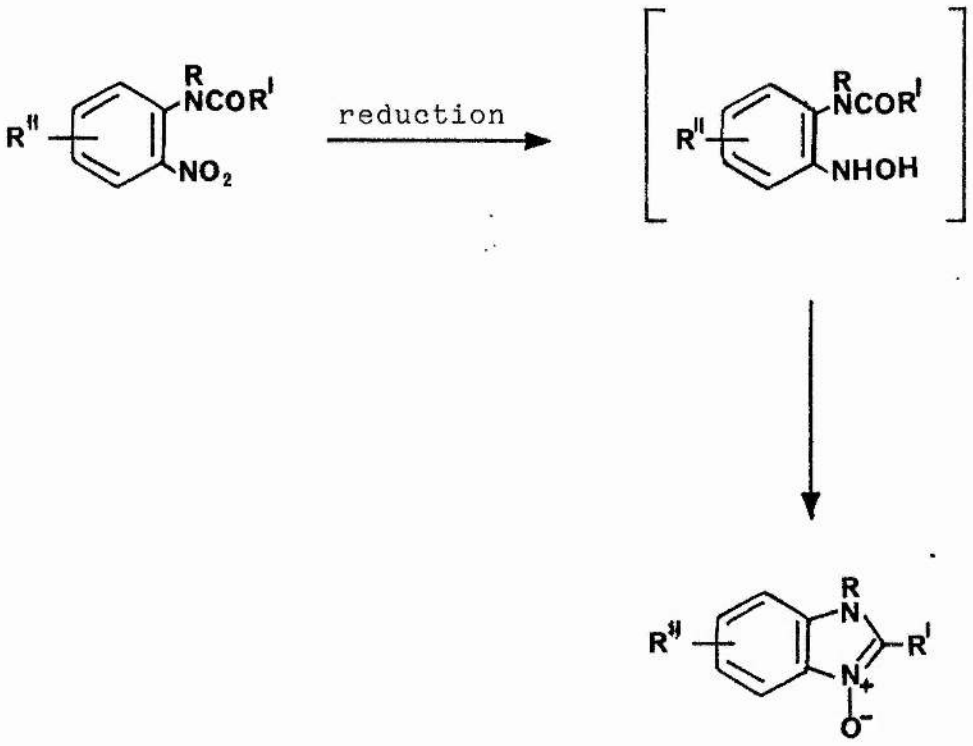
Scheme 2



2. Partial Reduction of o-Nitroanilides (Scheme 3).

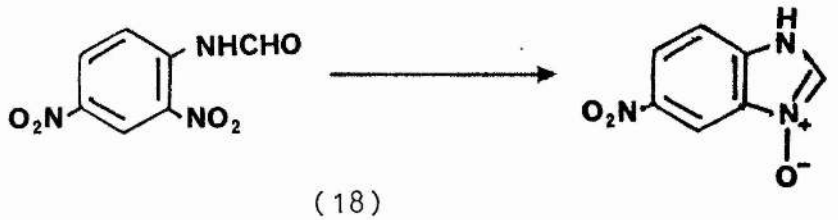
A variety of reducing agents have been used to effect the transformation shown in Scheme 3 including ammonium sulphide [14], and sodium borohydride[24] or hydrogen[13,25] in the presence of a metal catalyst. Although the reductive procedure has met with some success for certain specific groups of compound (e.g.where R = methyl), a number of inherent problems exist.

Scheme 3



(a) Over-reduction: the reaction often gives a mixture of products among which the parent benzimidazoles are commonplace. This difficulty is evidently due to reduction of the nitro group beyond the hydroxylamino stage to give the primary amine which may then condense with the neighbouring carbonyl function. The reduction of the N-oxide itself, once formed, may also be a complicating factor although the extent of this problem is unclear. The reduction of benzimidazole N-oxides to benzimidazoles is known[14]; however, as will be seen later, it is also possible for the N-oxide function to remain intact under reducing conditions.

The nature of the reaction also places limitations on the type of ring substituent. For example, although the reduction of 2,4-dinitroformanilide (18) is known [26], the yield of the nitro N-oxide (19) is low. Presumably this is due, in part, to over-reduction as mentioned above, but also to the reducibility of the second nitro group.

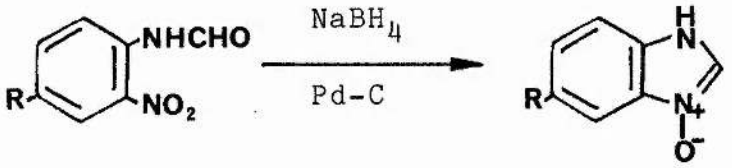


(18) (19)

(b) The presence of an amino group in the ring would also present difficulties as it may interfere with the intramolecular condensation by reacting intermolecularly with the anilide. Protection of an amino group would require careful consideration as many amino-protecting groups can be cleaved reductively[27], e.g. formyl, benzyloxycarbonyl, thiourethane, alkylsulphonyl.

(c) Although the reason is not clear, yields for reductions are generally good where R ≠ H (Scheme 3), but are poor where R = H. As mentioned previously 1-unsubstituted benzimidazole 3-oxides are both acidic and basic in character, and since the work-up procedure often involves aqueous conditions, product loss may occur via a water-soluble salt.

(d) Attempts by D.J. Moody to synthesise some simple N-oxides by the literature methods have been shown to give much poorer yields than those previously claimed. Thus, the reduction of o-nitroformanilide (20a) and 4-methyl-2-nitroformanilide (20b) by sodium borohydride and palladium-charcoal gave poor yields, typically in the 10-20% range[28], whereas the claimed yield in the literature for compound (21a) is 74%[29].



(20a) R=H
(20b) R=CH_3

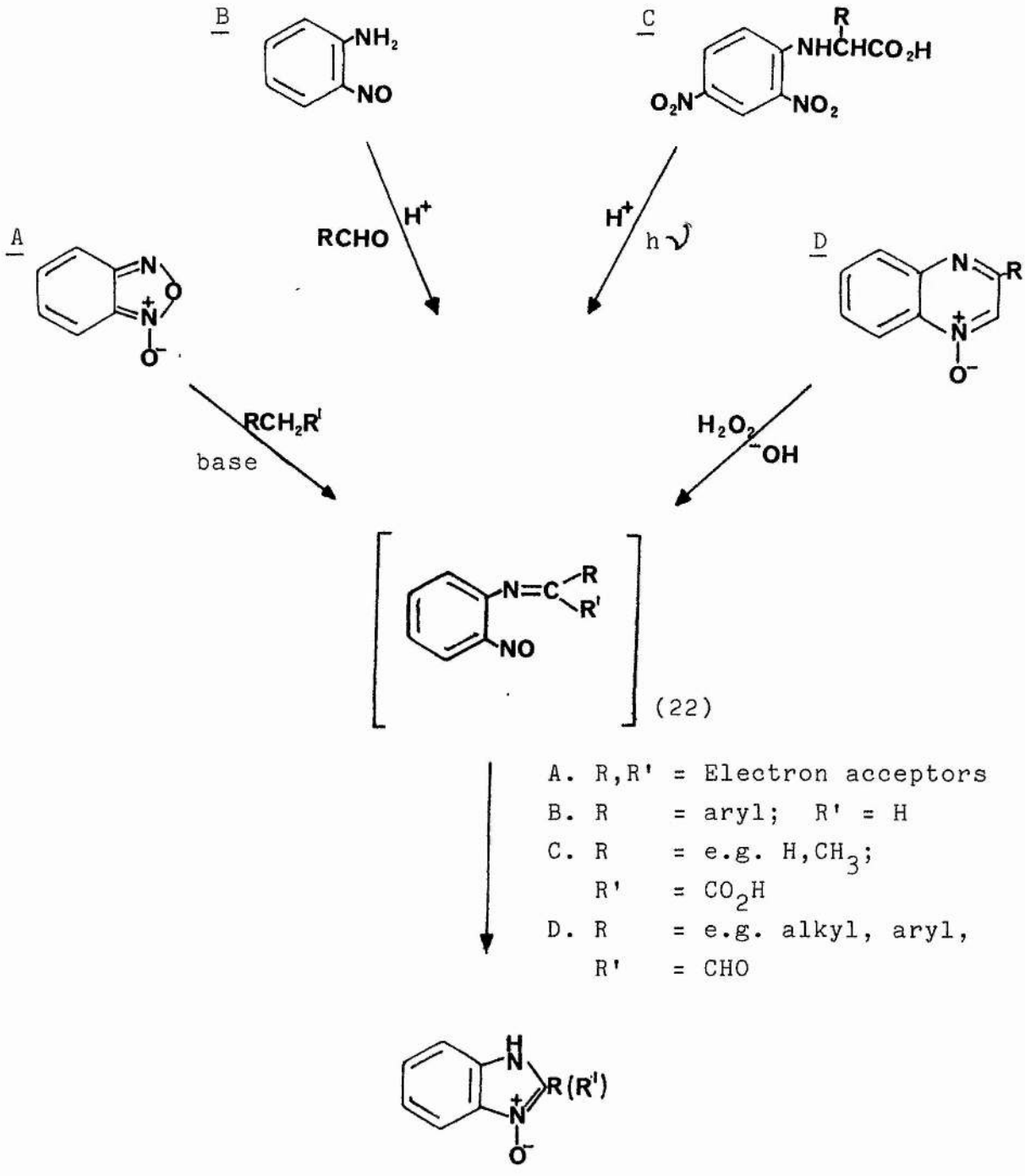
(21a) R=H

In conclusion the reduction of o-nitroanilides as a route to benzimidazole N-oxides presents a number of problems which are augmented when nitro or amino substituents are present in the ring.

3. Formation and Cyclisation of o-Nitrosoanils and Related Species.

Numerous examples exist in which o-nitrosoanils (22) are proposed as intermediates en route to benzimidazole N-oxides[9]. Some of these, in their simplest representation, can be seen

Scheme 4

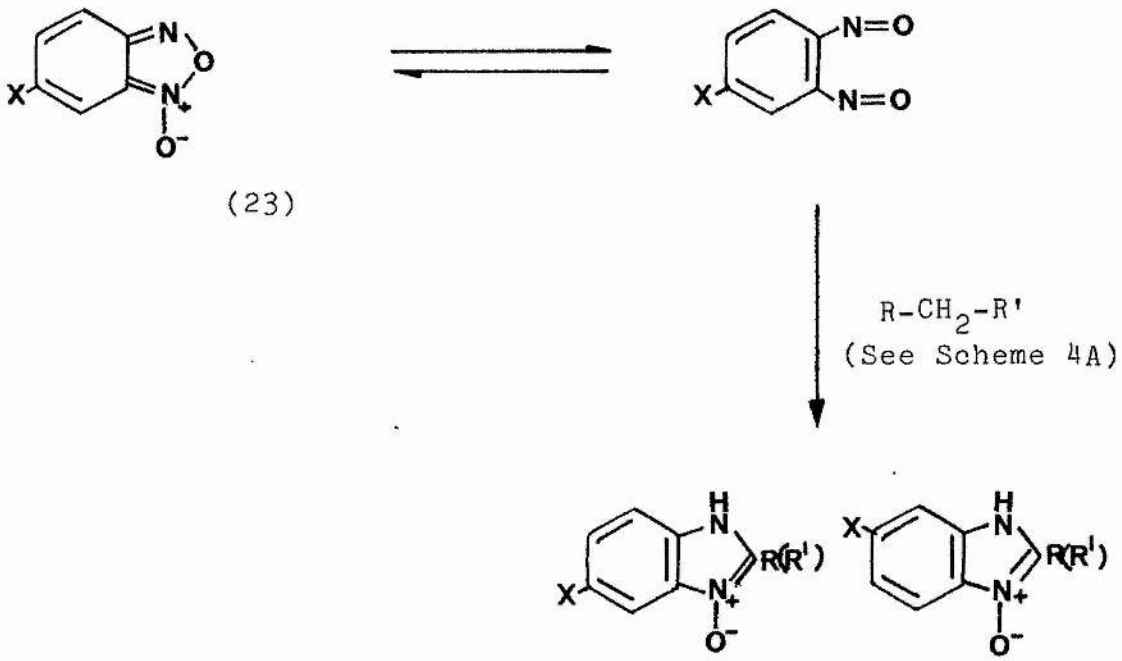

B
C
A
D
RCHO
H+
hν
RCH2R'
base
H2O2
OH
(22)
A. R,R' = Electron acceptors
B. R = aryl; R' = H
C. R = e.g. H,CH3;
R' = CO2H
D. R = e.g. alkyl, aryl,
R' = CHO

in Scheme 4. Each method has a number of associated difficulties.

Method A

Benzofuroxan (23, X=H) may be regarded as the cyclic tautomer of o-dinitrosobenzene and the reaction of substituted benzofuroxans (e.g.23,X ≠ H) with activated methylene compounds could therefore conceivably result in a mixture of isomers (Scheme 5).

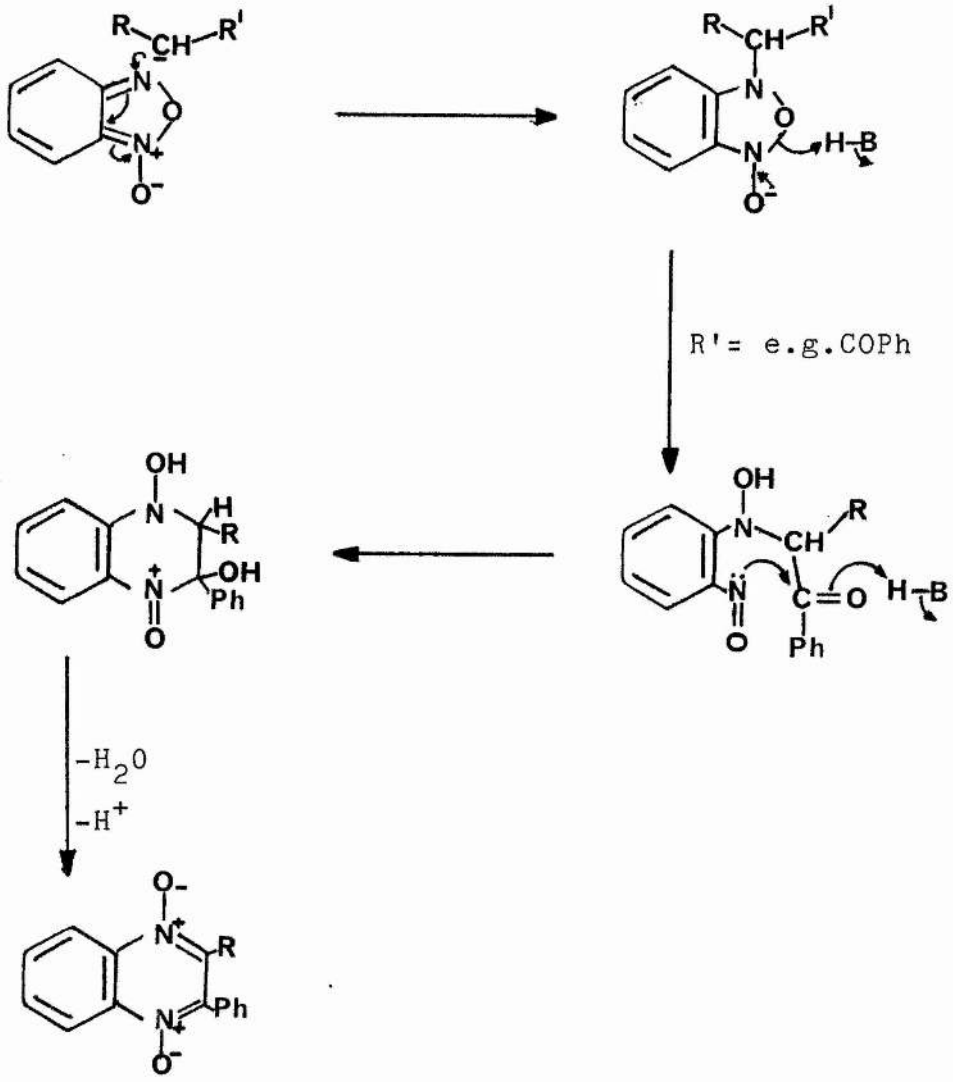
Scheme 5



(23)

In addition, the outcome of the reaction is not always predictable, primarily because nitroso groups can act as electron donors as well as electron acceptors[9]. For example, quinoxaline-1,4-dioxides are sometimes obtained from the reaction of benzofuroxan as shown in Scheme 6[9].

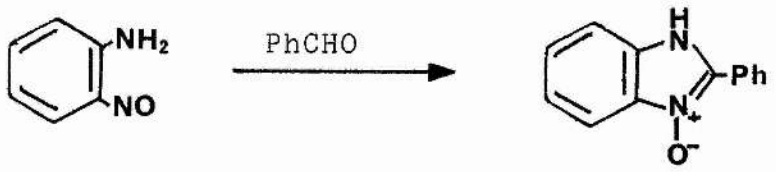
Scheme 6



Finally, substituted benzofuroxans would themselves have to be synthesised and although several methods are known[30], few are straightforward.

Method B

o-Nitrosoaniline (24) reacts with benzaldehyde to give 2-phenyl-1H-benzimidazole 3-oxide (25) in 52% yield[31].



(24) (25)

However, the synthesis of o-nitrosoaniline by the peracetic acid oxidation of o-phenylenediamine occurs in only 17% yield[32]. Little is known about substituted o-nitrosoanilines (see Method C) presumably because of the difficulties encountered in their preparation. This problem therefore limits the scope of Method B.

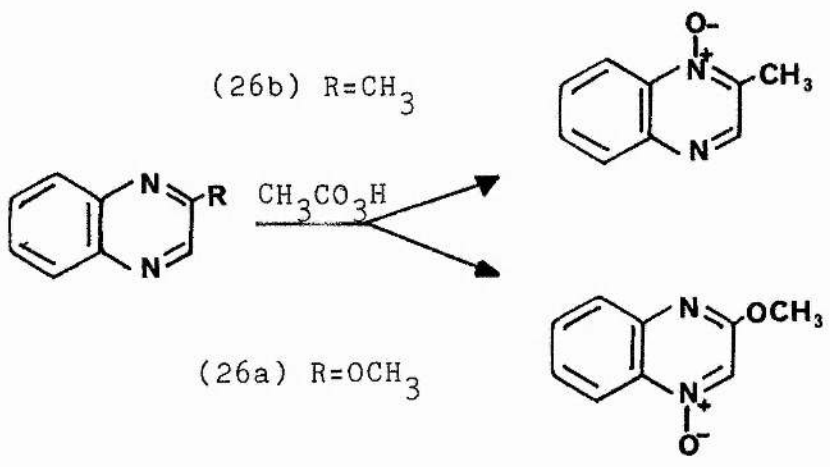
Method C

The photolysis of o-nitrophenylamino acids to give benzimidazole N-oxides has not been widely explored; all reports involve the photolysis of N-(2,4-dinitrophenyl)amino acids[16,33], and the reactions are all carried out on a very small scale. Although the reaction conditions can

be modified (low pH) to give, predominantly, 2-substituted benzimidazole 3-oxides, 4-nitro-2-nitrosoaniline and amino acid-derived aldehydes often occur as co-products. Indeed, the reaction can be designed to give the nitrosoaniline as the major product. This nitrosoaniline has been used in the synthesis of a number of 2-aryl-5-nitro-1H-benzimidazole 3-oxides (by Method B[34]). However, these compounds are unlikely precursors of 5-aminobenzimidazole N-oxides since (a), the reduction of the 2-aryl N-oxides would be impractical due to their poor solubility in the usual solvents for reduction (a problem encountered later in the present Chapter), and (b), the removal of the 2-aryl substituent would present obvious difficulties.

Method D

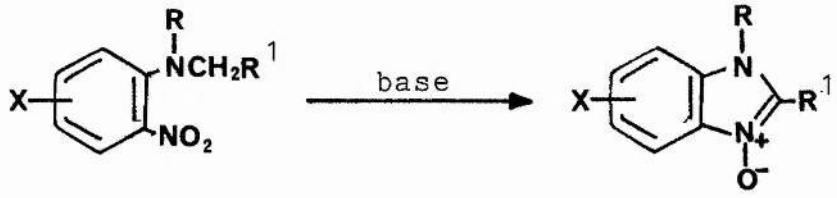
Like benzofuroxans, 2-substituted quinoxaline 4-oxides would have to be prepared. Their preparation by N-oxidation of quinoxalines is unpredictable[35]. For example, although oxidation of 2-methoxyquinoxaline (26a) gives the 4-oxide, 2-methylquinoxaline (26b)undergoes N-oxidation at position 1 under the same conditions.



4. Cyclisation of N-(Activated Alkyl)-o-nitroanilines

The successful route to the aminobenzimidazole N-oxides is based on this method.

Base-induced condensation reactions involving neighbouring group interaction in ortho-substituted nitrobenzene derivatives are well-known and have been used for the preparation of a wide variety of heterocyclic systems including benzimidazole N-oxides[36] (see below).

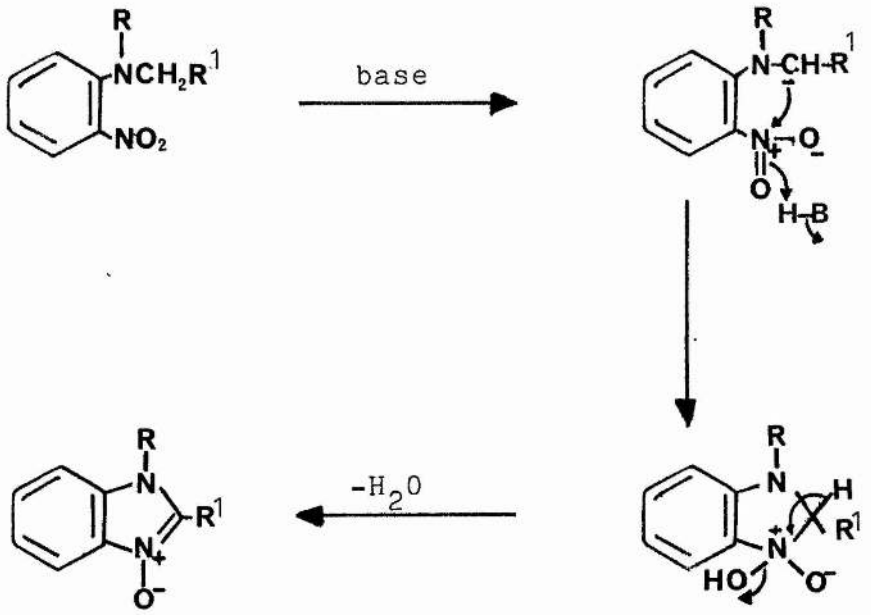


The success of the reaction for the preparation of benzimidazole N-oxides is critically dependent on the nature of R, R^1 and, as is more recently becoming evident, X. Where R = H and R^1 is a carbanion-stabilising group such as nitrile, ester or ketone, the reaction proceeds readily to give benzimidazole N-oxides in good yield[9]. Where R^1 is a weaker electron acceptor such as aryl, cyclisation still occurs, although a stronger base is required[9].

The mechanism of the reaction is usually formulated as an intramolecular aldol-type condensation involving attack on the electrophilic nitro group by the adjacent nucleophilic carbanion followed by dehydration (Scheme 7).

Although this mechanism explains adequately the results in this Chapter alternative mechanisms are considered in Chapter IV.

Scheme 7



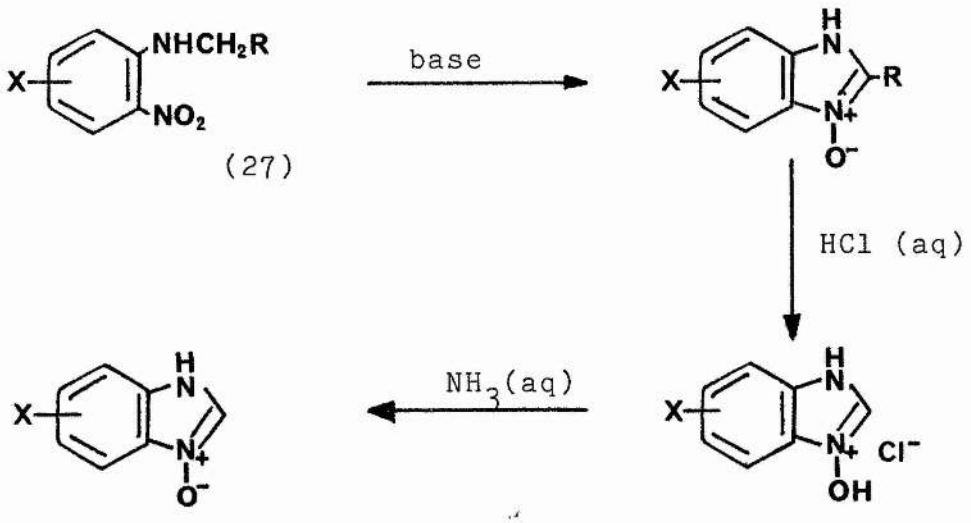
Reactions in which R ≠ H are less predictable. Chapter IV deals with this subject in more detail (particularly for R = CH_3). The effect of X on cyclisation is dealt with later in the present Chapter.

A procedure has recently been developed in this group by D.J.Moody and I.W. Harvey for the synthesis of benzimidazole N-oxides substituted in the benzene ring and unsubstituted at C-2 and N-1[28]. This method has been

applied, in the course of this work, to the synthesis of the aminobenzimidazole N-oxides (15).

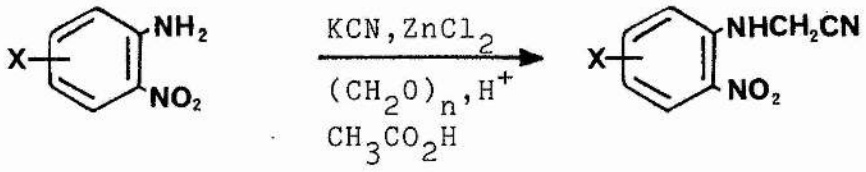
Scheme 8 highlights some of the common features of the general approach used and gives some examples of the N-oxides obtained.

Scheme 8



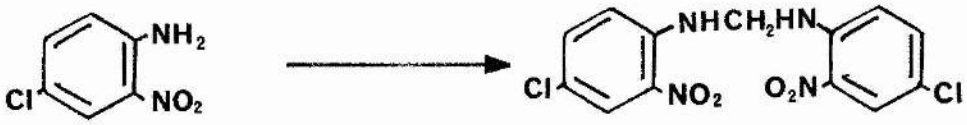
X = eg. 4-NO_2, 5-Cl, 5-OMe, 6-F

The preparation of the trisubstituted benzenes (27) merits comment. They may either be N-cyanomethyl-o-nitroanilines (R=CN) or in some case N-o-nitrophenylglycine esters ($R=CO_2Et$). The nitriles are made by cyanomethylation of the corresponding amine using a method first employed by Dimroth and Aurich[37] (see below).



The success of the process depends markedly on the quantity of Lewis acid used, which is in turn dependent on the basicity of the amine.

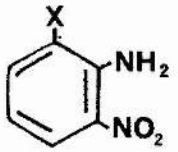
Thus, where X = halogen, a greater amount of zinc chloride is required, and where X = methyl or methoxy less Lewis acid is required, than for o-nitroaniline. In cases where the basicity of the amine is estimated incorrectly, side-reactions can occur. Thus, for example, the use of a smaller quantity of zinc chloride in the attempted cyanomethylation of 4-chloro-2-nitroaniline (28) leads to bis-(4-chloro-2-nitroanilino)methane (29) as the sole product[28].



(28) (29)

The use of a larger quantity of Lewis acid can, in certain cases, lead to bis-cyanomethylation[28], e.g.

Steric factors are also important. It has been demonstrated that 2,6-dinitroaniline (30a) cannot be cyanomethylated by this method[38] (electronic factors are obviously also involved in this case) and the cyanomethylation of 2-methyl-6-nitroaniline (30b), as can be seen in Chapter IV, also presents difficulties.



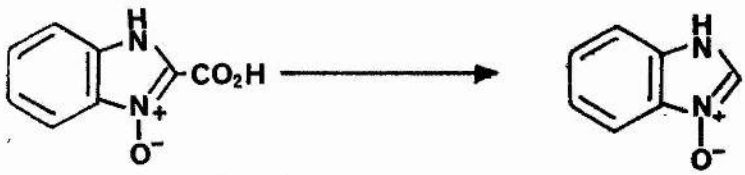
(30a) X = NO_2
(30b) X = CH_3

The use of o-nitrophenylglycine esters in place of the nitriles did not offer any considerable advantage except where their synthesis was more convenient. The esters described were, for the most part, obtained from the nitriles by hydrolysis then esterification.

However, as will be seen, the use of esters in the case

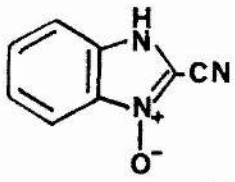
where X = amino did initially appear to offer a significant benefit when the strategy was devised.

Now that the synthesis of the starting materials has been dealt with attention will be refocussed on Scheme 8 (p.22). The first step illustrated, i.e. the base induced cyclisation to give a benzimidazole N-oxide functionalised at position 2, has already been discussed in the introduction of this section. The second important feature in Scheme 8 is the removal of the activating group R, which is accomplished by hydrolysis in concentrated hydrochloric acid followed by alkaline work-up in aqueous ammonia. The hydrolytic step is thought to proceed *via* the carboxylic acid and was devised in the knowledge that benzimidazole-2-carboxylic acid N-oxide (31) undergoes facile decarboxylation when heated in solution (acetonitrile)[39].



(31) (21a)

Thus, benzimidazole N-oxide (21a) itself can be prepared in this manner from 2-cyanobenzimidazole N-oxide (32).



(32)

$$\xrightarrow[2.NH_3(aq)]{1.HCl(aq)} \qquad (21a)$$

The overall procedure has a number of useful characteristics:-

1. The starting materials are readily available and usually inexpensive.

2. The cyclisation step generally occurs in good yield.

3. The existence of a functional group at postion 2 and the subsequent ease of removal allows important product flexibility.

4. The hydrolysis effects complete removal of the activating group and leads to stable, isolable salts.

5. A variety of ring substituents can be used since the method is non-reductive.

6. The isolation of the free N-oxides by evaporation of their ammonium salts appears to prevent rearrangement of the N-oxides to benzimidazolones, a side-reaction previously observed by Takahashi and Kano in some of the reductive cyclisation procedures described above (p.11)[14]. As mentioned previously (p.10), the

rearrangement of the N-oxides to benzimidazolones has also been proposed in connection with the attempted direct N-oxidation of benzimidazoles.

7. The method appeared to offer a route to the previously unknown aminobenzimidazole N-oxides.

Prior to these investigations Moody carried out some preliminary research into the synthesis of aminobenzimidazole N-oxides and indeed prepared a number of useful precursors.

The order in which the following results are presented was chosen for a number of reasons. The 5-aminobenzimidazole N-oxide was studied first since more groundwork had been done previously for this isomer than for any of the others and the variety of potential routes to this compound appeared to provide broad experience which could then be useful in the synthesis of the 4-, 6- and 7- amino N-oxides. Thus, initial results obtained were applied directly to the synthesis of the 6-amino compound. The order 5, 6, then 4, 7 is also logical since the two sets are being considered as models for guanine and adenine respectively.

RESULTS AND DISCUSSION

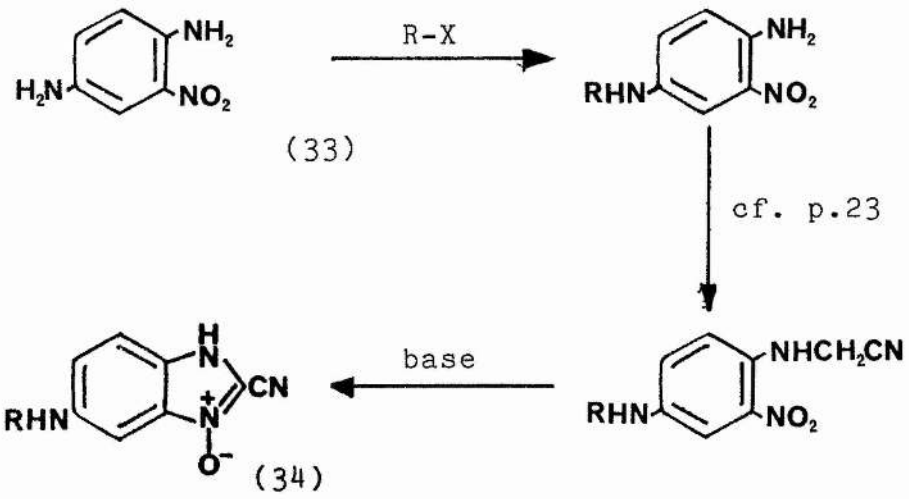
5-Amino-1H-benzimidazole 3-Oxide (15b)

A number of approaches were investigated for the preparation of this compound.

A. from 2-nitro-p-phenylenediamine (33)

The nitriles (34) have recently been synthesised by Moody in the manner shown in Scheme 9[40] and were chosen as suitable candidates for the hydrolytic procedure previously outlined.

Scheme 9



(34a) R = CH_3CO
(34b) R = CO_2Et
(34c) R = CH_3SO_2(Ms)

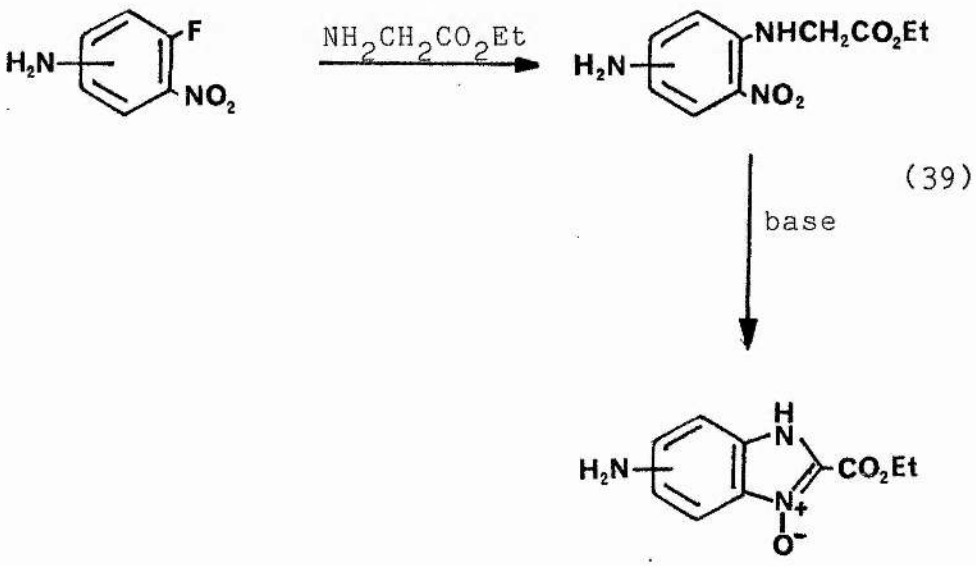
The amino group ortho to the nitro group in (33) is the less reactive since its lone pair of electrons can be delocalised into the nitro group thus decreasing its nucleophilicity. Protection of the meta-amino group was therefore necessary to prevent cyanomethylation in the 'wrong' place.

Hydrolysis of the acetamido compound (34a),(Scheme 10), gave the amino N-oxide as a dihydrochloride (35a) thus effecting removal of both the activating group and the amino-protecting group in one step. At the other extreme the methanesulphonyl group in (34c) resisted hydrolysis completely, (35c) being the sole product isolated from the reaction. Reaction of the carbamate (34b) was intermediate between these, hydrolysis giving a mixture of (35a) and (35b). The reaction of hydrochlorides with aqueous ammonia liberated the free N-oxides (15b, 36, 37).

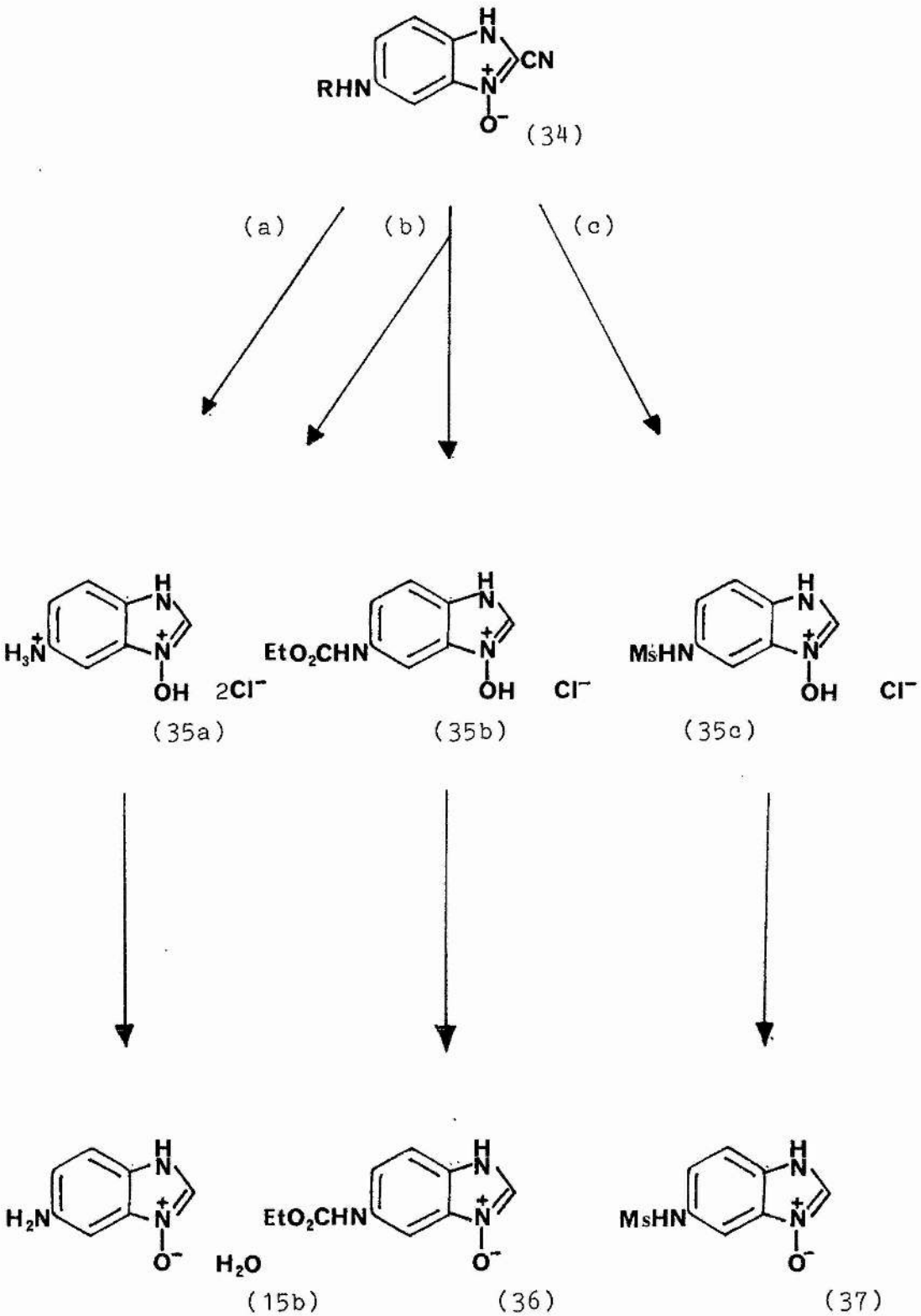
B. from 4-fluoro-3-nitroaniline (38)

As mentioned previously, the use of glycine esters rather than nitriles generally offers no real advantage. However, if amino-substituted o-nitrophenylglycine esters (39) could be made without prior protection of the amino group (Scheme 11), then the possibility existed of synsthesising functionalised aminobenzimidazole N-oxides (40) in two steps:-

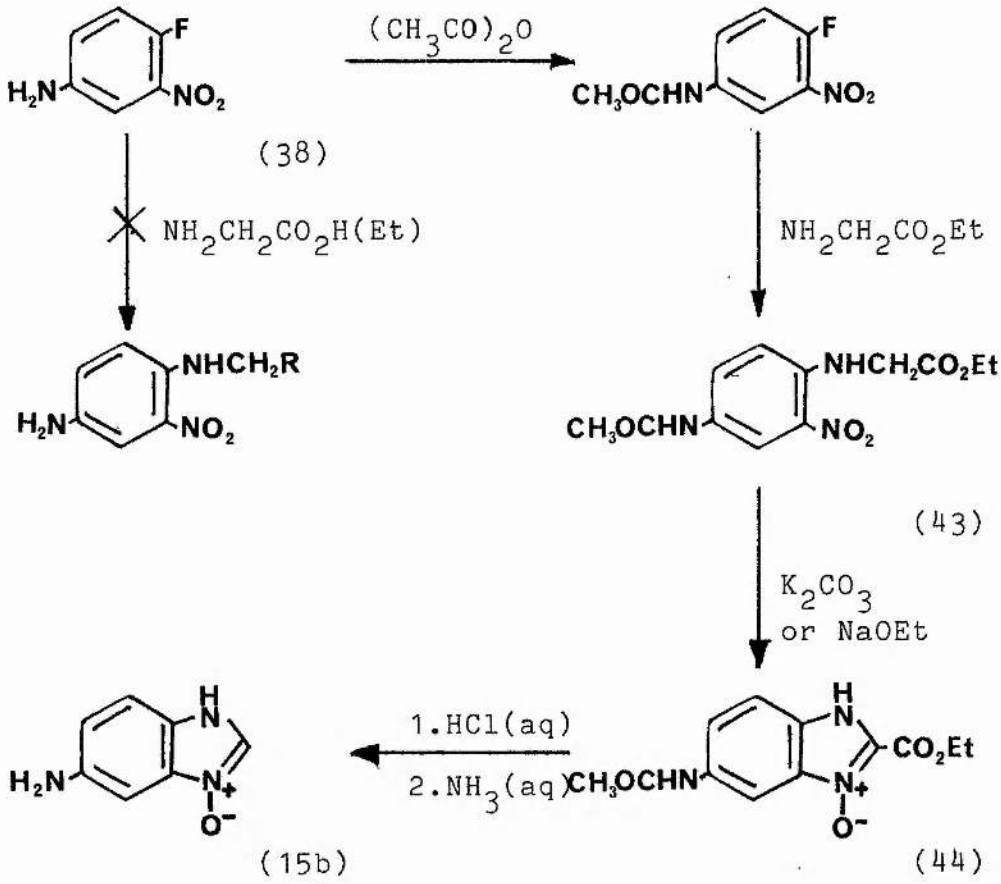
Scheme 11



Scheme 10


RHN
CN
(34)
(a)
(b)
(c)
H3N
OH
2Cl⁻
(35a)
EtO2CHN
OH
Cl⁻
(35b)
MsHN
OH
Cl⁻
(35c)
H2N
O⁻
H2O
(15b)
EtO2CHN
O⁻
(36)
MsHN
O⁻
(37)

Scheme 12



The displacement of halogens from halogenoaromatic compounds by amino acids and derivatives was developed by Sanger who used fluoro-2,4-dinitrobenzene (41) ("Sanger's Reagent") to identify the N-termini of polypeptides[41] (This work led to the structural elucidation of insulin).

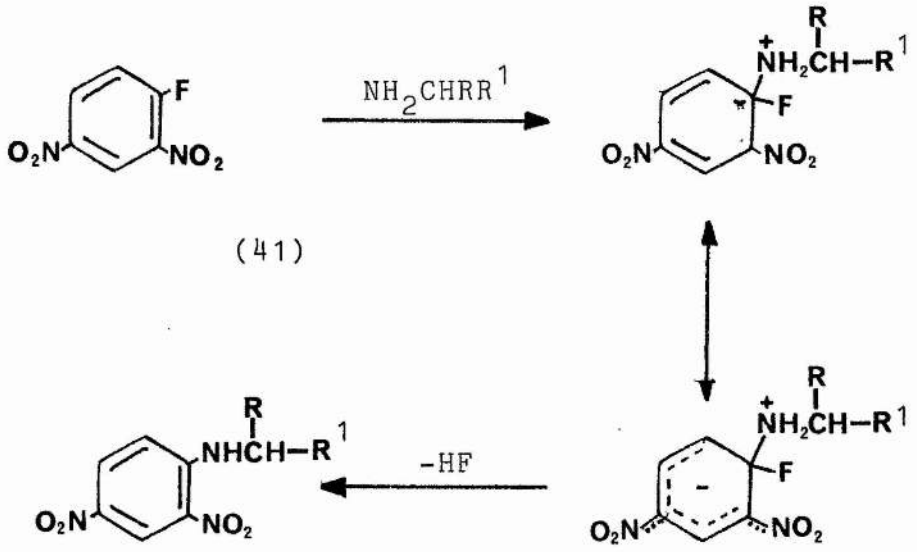
The increased reactivity of fluorine over the other halogens in these reactions is well-known. It has been suggested that the electron-attracting power of the replaceable group usually exerts the major influence on mobility[42].

Unfortunately, attempts to displace the fluorine in

4-fluoro-3-nitroaniline (38) by glycine derivatives, under a variety of conditions, were unsuccessful (Scheme 12).

It is known that strong electron-withdrawing groups such as nitro stabilise the intermediate formed in aromatic nucleophilic substitution reactions[43] (Scheme 13); the success of Sanger's Reagent (41) being a typical example.

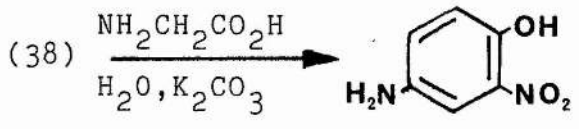
Scheme 13



Electron-donating substituents such as amino destabilise the anionic intermediate, particularly if the substituent is ortho or para to the nucleofuge[43].

Acetylation of the amine (38) (Scheme 12), however, reduces

the mesomeric 'flow' of electrons into the ring and thus facilitates substitution. The initial failure of the glycine to substitute is in agreement with similar previous findings[44] (see below).

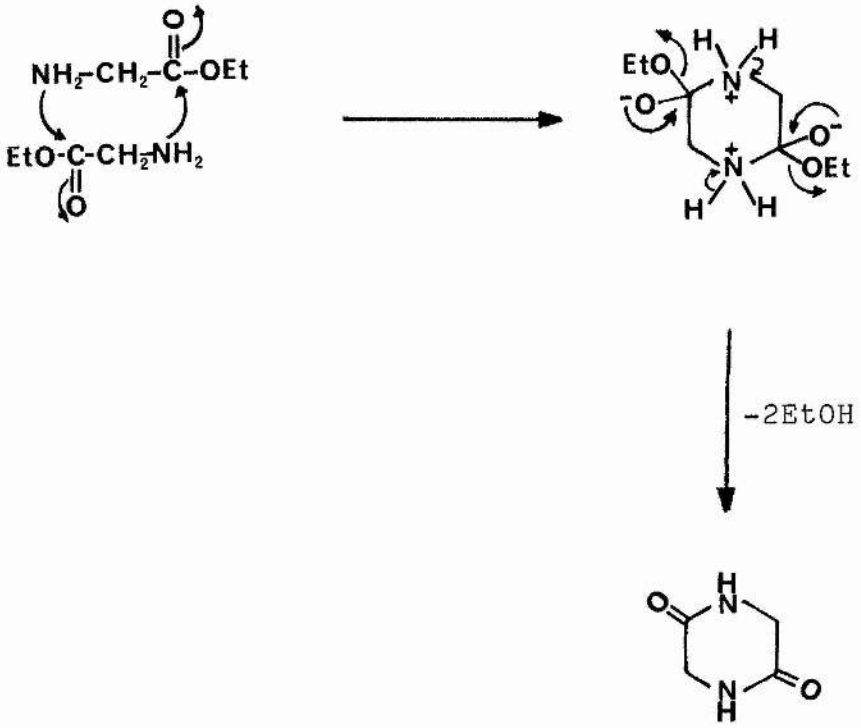


(42)

It is unclear from the literature whether or not the hydroxy compound (42) is the sole product formed in this reaction as no yield is quoted. The formation of the phenol was undetected in any of the displacement attempts made in this investigation with only starting material being recovered.

However, 4-fluoro-3-nitroaniline is known to undergo reaction with nucleophiles such as aniline[45] and ethanolamine[46] presumably due, in the former case, to the high reaction temperatures (140°C) involved and, in the latter case, to the greater nucleophilicity of the amine. The first point draws attention to another problem in the failed reaction. At the higher temperatures attempted (DMSO, 140°C), glycine ethyl ester may undergo self-condensation in the manner shown in Scheme 14[47].

Scheme 14



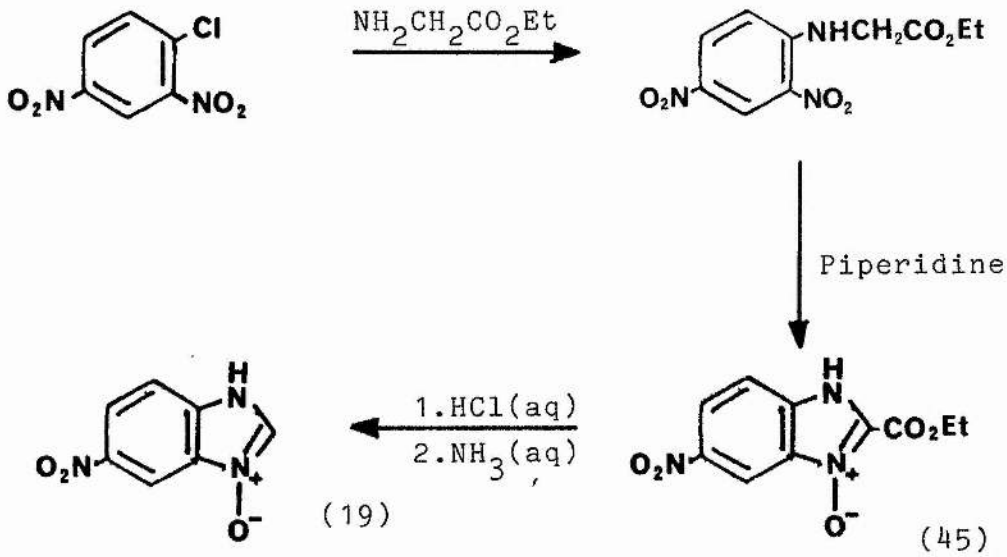
The displacement step is therefore dependent on a number of factors including the nucleophilic strength of the attacking amine, reaction conditions, nature of the nucleofuge, and the electronic influence of ring substituents.

Cyclisation of the ester (43) with potassium carbonate or sodium ethoxide followed by the hydrolytic procedure described previously, afforded 5-amino-1H-benzimidazole 3-oxide dihydrochloride (35a). Thus the ester behaved in an identical manner to the acetamido-nitrile (34a). Subsequent reaction with aqueous ammonia and evaporation of the solution precipitated the desired N-oxide (15b) in hydrated form.

C from chloro-2,4-dinitrobenzene

5-Nitrobenzimidazole N-oxide (19) is one of the few monosubstituted benzimidazole oxides which was known prior to the recent research in this group. It has been synthesised by a number of methods[16,48] (see e.g. partial reduction of o-nitroanilides[26] p.13) and was one of the first compounds to be prepared by the new procedure discussed in this Chapter (see Scheme 15).

Scheme 15

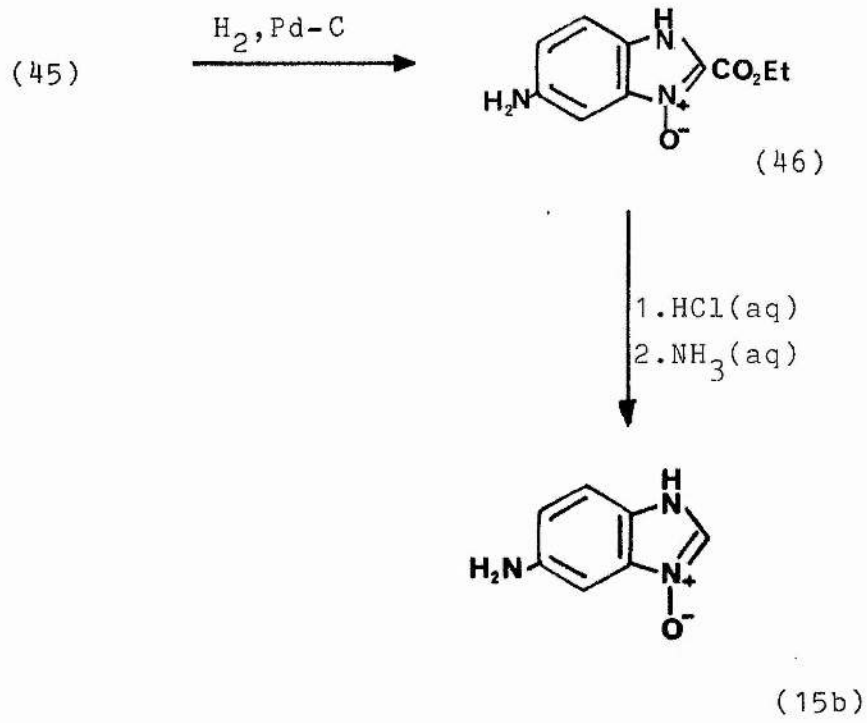


(19) (45)

The displacement and cyclisation steps have previously been reported for the methyl ester[49]. Attempts have been made to reduce (19) but without success[38]. This failure

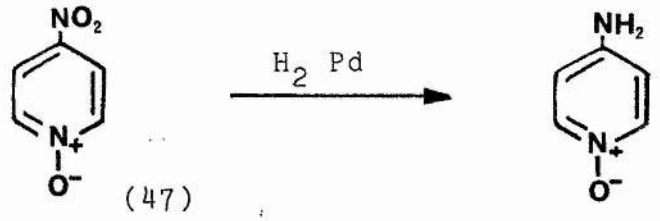
was attributed to the low solubility of the compound in the usual solvents for reduction. The ester (45) is, however, considerably more soluble in ethanol and can be catalytically reduced to the amine (46) (Scheme 16). Although the amino-ester itself was not easily purified (possibly due to self-condensation) it was hydrolysable to the amino N-oxide (15b).

Scheme 16



It is notable that the nitro group in (45) was selectively reduced, the N-oxide oxygen remaining intact. Although many amine oxides, e.g. pyridine N-oxide, can be deoxygenated by catalytic reduction, the selective reduction of substituents has also been observed. Indeed

it has been noted that palladium catalysts generally favour reduction of the substituent, and that the N-oxide group is attacked only on prolonged reaction. For example hydrogenation of 4-nitropyridine-1-oxide (47) by palladium in methanol afforded 4-aminopyridine-1-oxide[50].



(47)

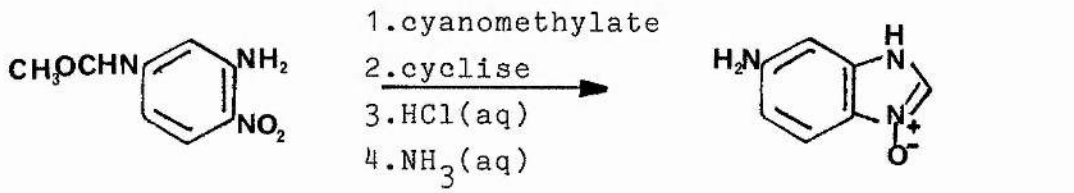
Although, as mentioned previously (p.12), benzimidazole N-oxides can be reduced to benzimidazoles, it has also been noted that these N-oxides can sometimes exhibit stability under reducing conditions [see "Partial Reduction of o-Nitroanilides"(p.11); the success of this method depends, in part, on such stability].

Each route to the 5-amino N-oxide (15b) involved 5 steps; however, there are notable differences in terms of overall yield. In route A, with acetyl as the amino-protecting group, the overall yield to (15b) was 20%. It should be possible, however, by modification of the reaction conditions, to improve the yield in the acetylation step since it is a reaction which normally gives a far higher accountance of acylated product than obtained in this instance. In method B the amino compound (15b) was obtained in 12% yield from the fluoronitroaniline (38)

and was thus the poorest route, in purely quantitative terms. Procedure C gave the greatest accountance of the desired amine (33% from chloro-2,4-dinitrobenzene). It should however be borne in mind that all the routes investigated are valuable in their own right, as all the intermediate N-oxides produced will be screened for biological activity and are thus of potential interest.

6-Amino-1H-benzimidazole 3-Oxide (15c)

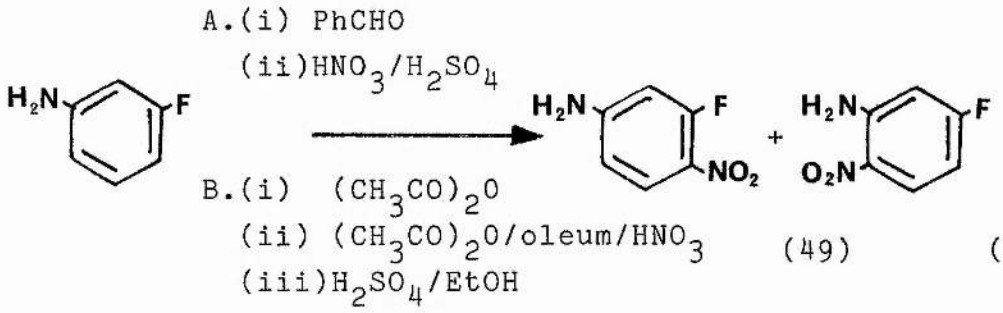
The synthesis of the 6-amino compound (15c) from 3-amino-4-nitroacetanilide (48), as outlined below, was not considered as a viable route since the preparation of the desired acetanilide is not straightforward. In addition to the appropriate diamine having first to be synthesised, its acetylation results in a mixture of mono- and di-acetylated products which are difficult to separate[51].



(48) (15c)

Unlike the isomeric 4-fluoro-3-nitroaniline, 3-fluoro-4-nitroaniline (49) is not commercially available and therefore had to be made. Hodgson and Nicholson have

described two methods[52], the first involving nitration of the Schiff base formed between m-fluoroaniline and benzaldehyde, and the second involving nitration of m-fluoroacetanilide; but the yield of the required isomer (49) is not given in either case.

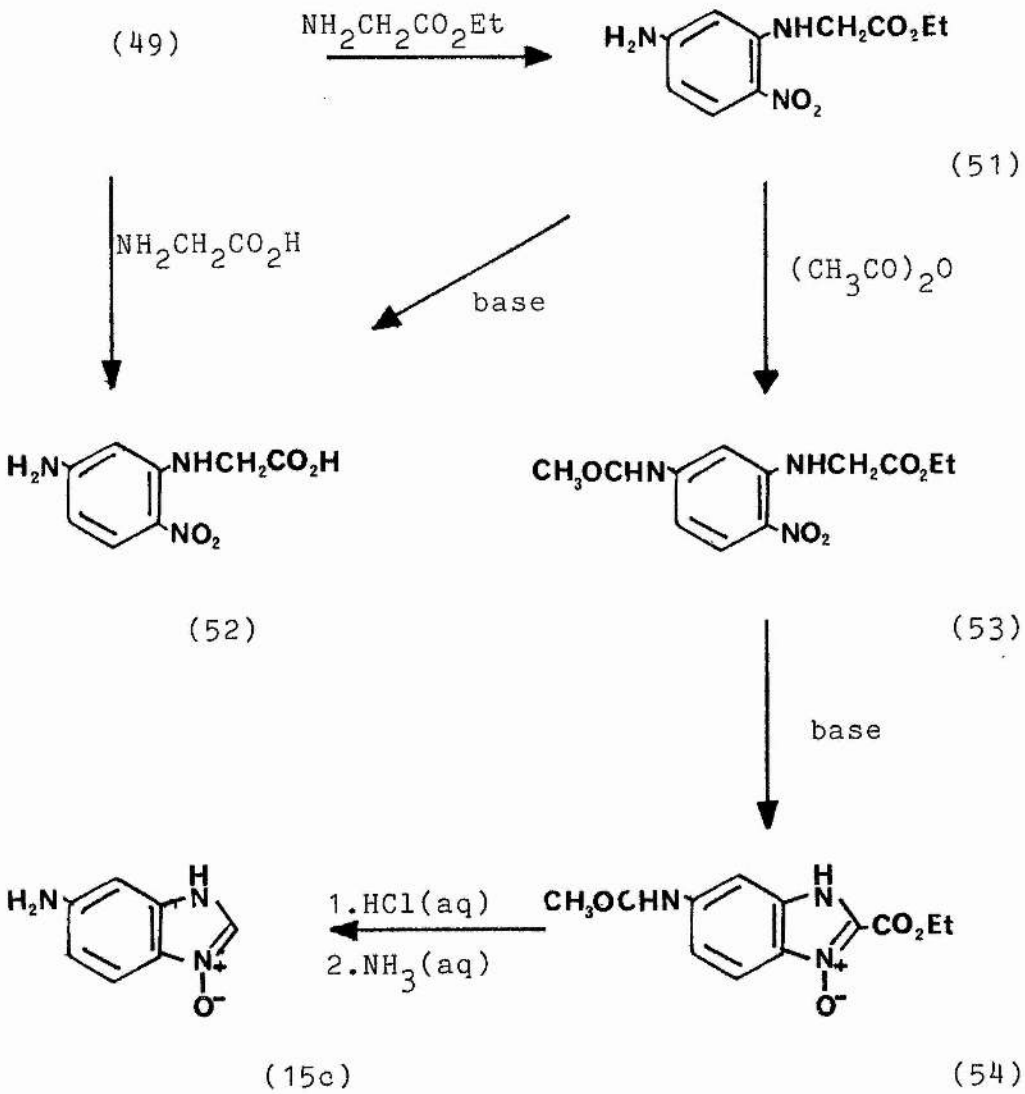


Attempts to synthesise (49) by method A gave at best, 14% of the desired amine and 21% of the 2-nitro compound (50). The poor recovery appeared to be due to two factors; incomplete reaction of m-fluoroaniline with benzaldehyde and the formation of a tarry residue during the steam distillation. A greater overall recovery (30% 4-nitro, 50% 2-nitro) was eventually obtained by isolating m-fluoroacetanilide and then nitrating it by a modified method.

3-Fluoro-4-nitroaniline, unlike the 4-fluoro-3-nitro isomer reacted readily with glycine ethyl ester to give (51) (Scheme 17). The reaction of this ester in the presence of base, however, did not give the expected N-oxide. Surprisingly the sole product formed was the acid (52)

indicating hydrolysis to be the favoured pathway. For comparative purposes compound (52) was also prepared directly from 3-fluoro-4-nitroaniline and glycine.

Scheme 17



The failure of the amino ester (51) to cyclise may be attributed to the mesomeric effect of the primary amino group which deactivates the para nitro function to nucleophilic attack by the adjacent carbanion; a similar phenomenon to that previously described on p.32 . Acetylation of the amine, however, again facilitated reaction by reducing the effect of the amino group. Cyclisation of (53) occurred in the presence of potassium carbonate or sodium ethoxide and hydrolysis of (54) as described for the 5-amino isomer led to 6-amino-1H-benzimidazole 3-oxide dihydrate (15c).

Little is known regarding the effect of ring substituents on the success of such nitro-group condensations. As already mentioned, the nature of the activating group in the alkylamino side-chain has previously been considered to be the crucial factor in determining the ease with which cyclisation proceeds and indeed the experimental results generally fit well with the predicted estimates of reactivity. However, evidence is being accumulated to suggest that ring substituents may also play an important role. For example (see table 1) an additional nitro group in the ring meta to the existing nitro group appears to aid cyclisation.

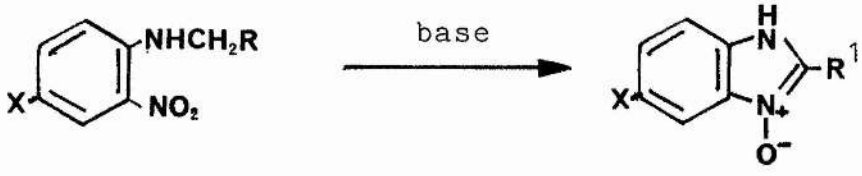
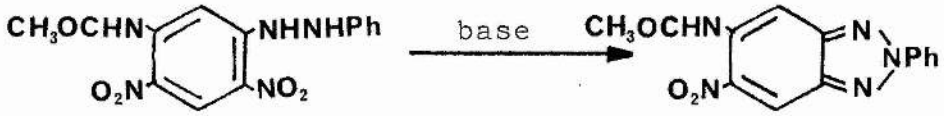


Table 1

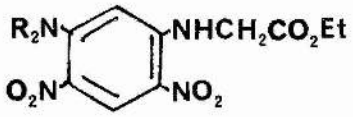
R	X	Base	R^1	Yield	Ref.
Ph	H	H^-	Ph	75%	13
Ph	NO_2	MeO^-	Ph	-	53
CO_2Et	H	EtO^-	CO_2Et	31%	28
CO_2Me	NO_2	CO_3^{2-}	CO_2Me	56%	48
CO_2Et	NO_2	Piperidine	CO_2Et	56%	28
CO_2H	NO_2	phosphate buffer (pH8)	H	73%	47

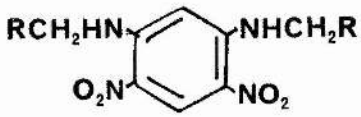
Electron-donating substituents also appear to influence the outcome of the reaction. In 1912 Fries and Roth noted, but offered no explanation for the fact, that the acetamido-dinitrophenylhydrazine (55) was cyclised in the presence of base to the benzotriazole (56) whilst the unacetylated amine was unaffected by base[54].



(55) (56)

More recently it has been shown that compounds such as (57) and (58) are returned unchanged from reactions under conditions where ring-closure was expected[40].





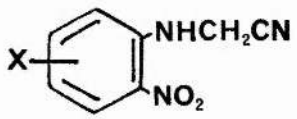
(57) R=H,CH_3 (58) R=CN,CO_2Et

In these examples there is an amino function para, and a nitro group meta, to the nitro in question and cyclisation does not occur. Thus the donating - accepting group influence does not appear to be a simple additive phenomenon and if the ring substituent theory is to be elucidated, further research is required.

4-Amino-1H-benzimidazole 3-Oxide (15a)

Before describing the successful synthesis of the above named compound attention is first turned to an unusual result observed by Moody.

The successful cyclisation of (59) has already been mentioned (p.28). The reaction of the isomeric compound (60) under similar conditions resulted in unchanged starting material being recovered on work-up[55].



(59) X = 4-$NHSO_2CH_3$

(60) X = 3-$NHSO_2CH_3$

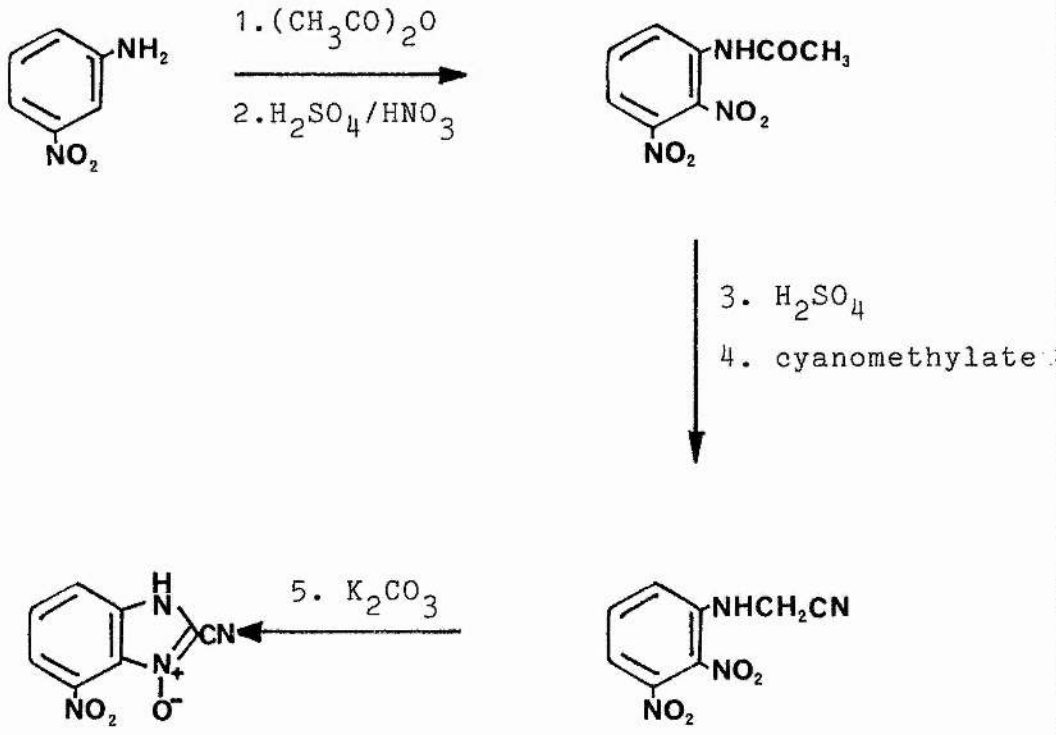
The reason for this was again put down to deactivation of the nitro group to carbanion attack, this time by the deprotonated sulphonamide (see below).

(60)

This problem has been overcome recently by using the acetamide in place of the sulphonamide[55]. Cyclisation and hydrolysis in the manner previously described gave (15a).

2-Cyano-4-nitrobenzimidazole 3-oxide (61) has recently been synthesised in 5 steps from m-nitroaniline[55] (Scheme 18) and provided the starting point in this investigation for the synthesis of 4-amino-1H-benzimidazole 3-oxide (15a).

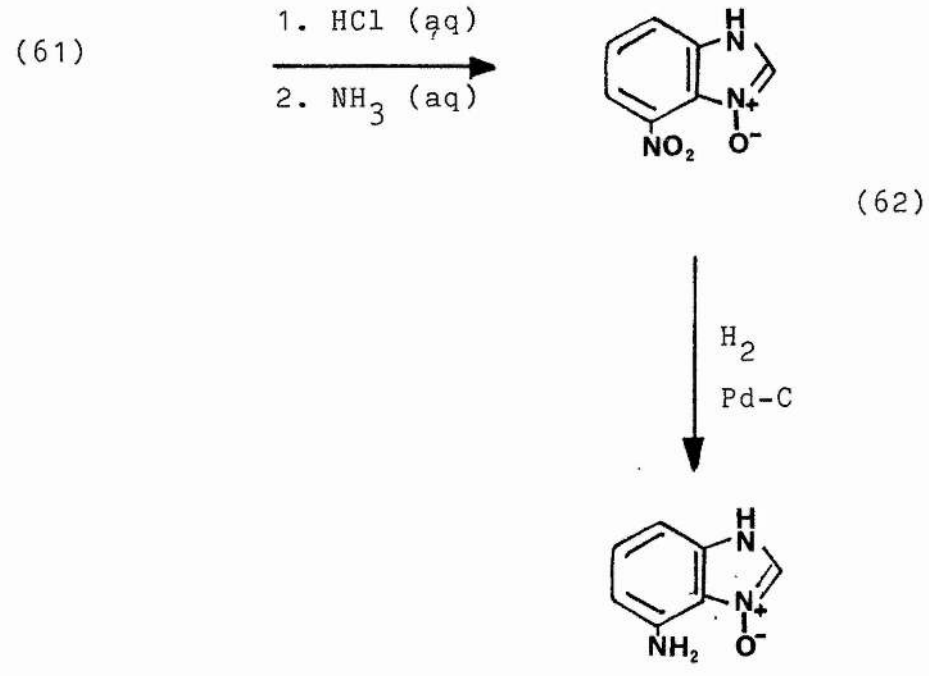
Scheme 18



(61)

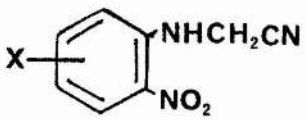
Hydrolysis of (61) followed by reaction with aqueous ammonia gave as expected, 4-nitrobenzimidazole N-oxide (62). This nitro N-oxide (62), unlike its 5-nitro isomer is soluble in solvents such as ethanol and catalytic reduction was therefore straightforward. As observed for compound (45) in the 5-amino series, the reduction resulted in selective transformation of the nitro group, the N-oxide remaining unaffected (Scheme 19).

Scheme 19



7-Amino-1H-benzimidazole 3-Oxide (15d)

Comment has already been made on the successful cyclisation of (59) and the lack of reactivity of the isomer (60) under the same conditions.

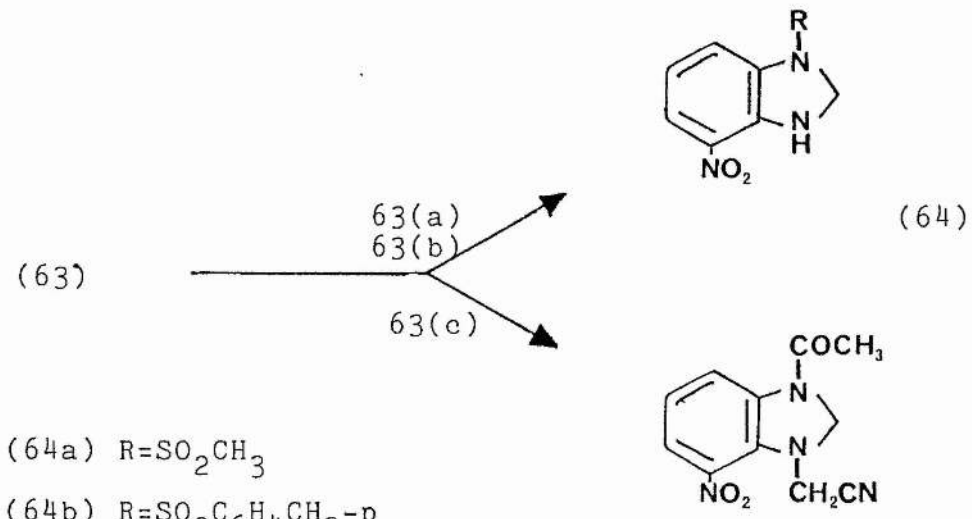


(59) X=4-$NHSO_2CH_3$
(60) X=3-$NHSO_2CH_3$
(63a) X=6-$NHSO_2CH_3$
(63b) X=6-$NHSO_2C_6H_4CH_3$-p
(63c) X=6-$NHCOCH_3$

Recent attempts have been made to synthesise further isomers (63 a-c)[55]. However, attempted cyanomethylation of the appropriate amines gave surprising results. Instead of the expected nitriles, the dihydrobenzimidazoles (64) and (65) were obtained (Scheme 20). It was postulated that cyanomethylation first occurs followed by nucleophilic displacement of cyanide to give the ring-closed product.

The synthesis of 2-fluoro-3-nitroaniline (66) has been reported [56] and by analogy with the previously discussed fluoronitroanilines was considered a suitable precursor to 7-amino-1H-benzimidazole 3-oxide (Scheme 21). However, failure to reproduce the literature synthesis[57] of the desired starting amine prevented an investigation of this route.

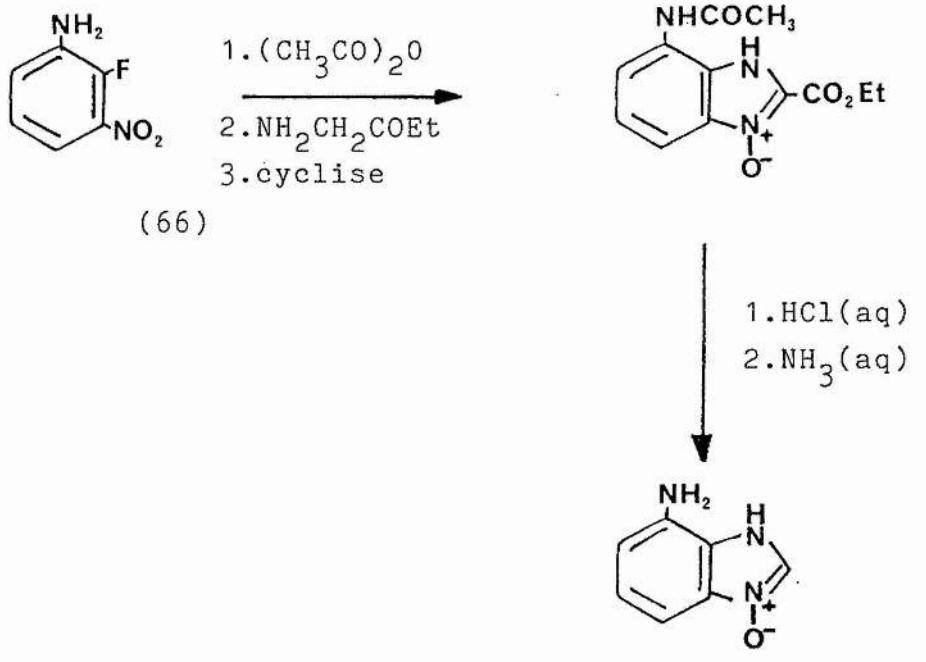
Scheme 20



(64a) $R=SO_2CH_3$

(64b) $R=SO_2C_6H_4CH_3$-p

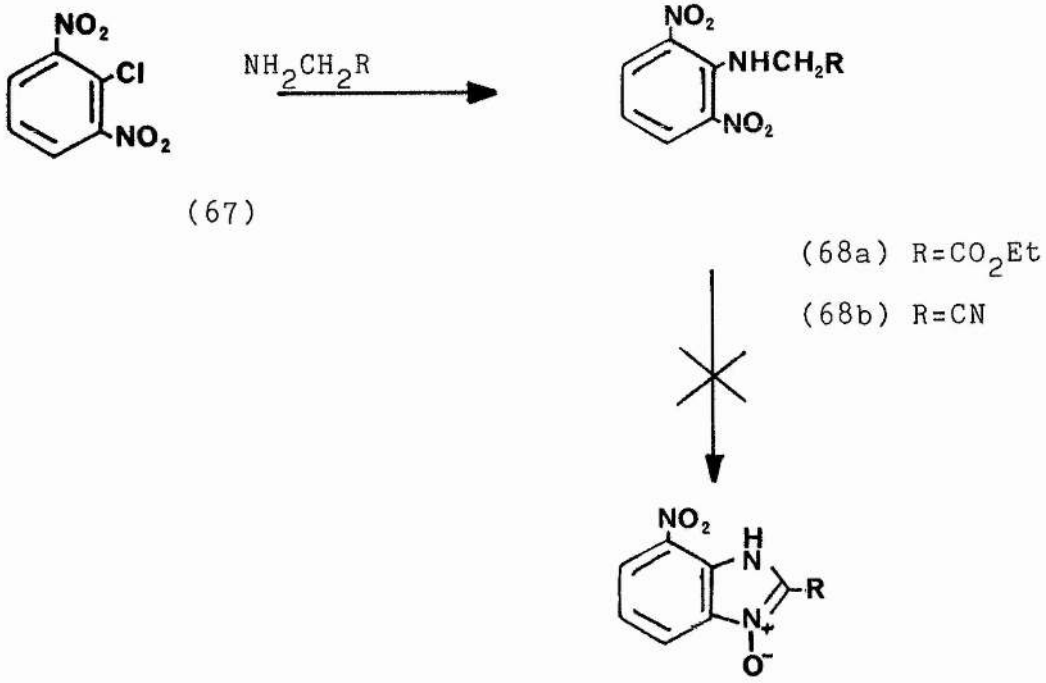
Scheme 21



In view of this failure it was decided to attempt displacement of the chlorine in chloro-2,6-dinitrobenzene and reduce the nitro group after cyclisation.

Chloro-2,6-dinitrobenzene (67) is known to undergo displacement reactions with glycine derivatives[57]. The intended approach was similar to that used for the synthesis of 5-amino-1H-benzimidazole 3-oxide by method C. The success obtained for the 5-amino isomer was not paralleled in this instance (Scheme 22).

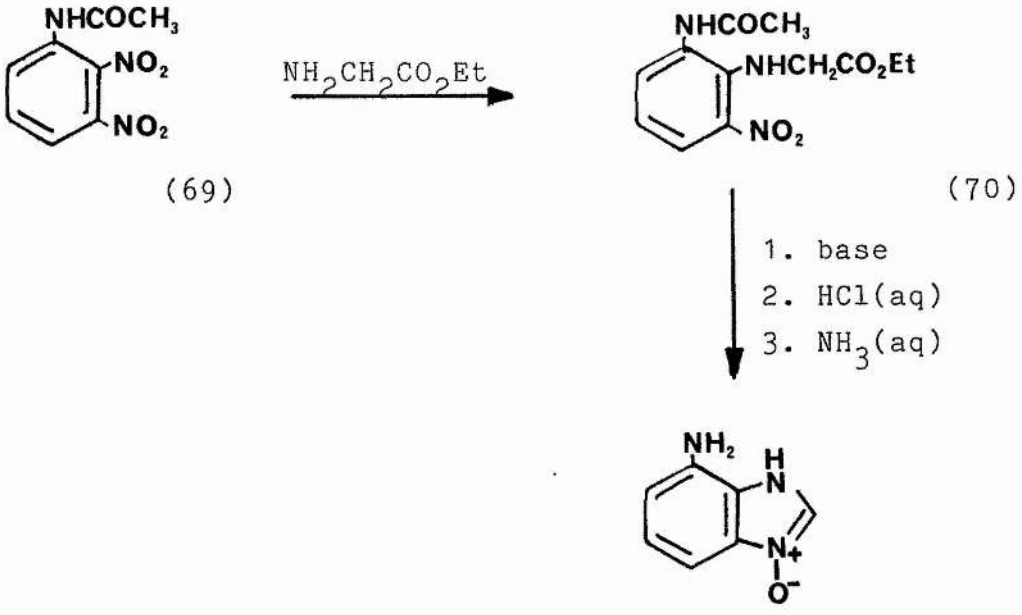
Scheme 22



Both the ester (68a) and the nitrile (68b) reacted with base in a surprising manner, and in neither case was the expected benzimidazole N-oxide obtained. A full discussion of these findings can be found in Chapter IV.

The desired N-oxide (15d) has since been prepared by I.W. Harvey in the manner shown in Scheme 23.

Scheme 23



(69) (70) (15d)

The cyclisation and hydrolytic stages are identical to those previously described. The displacement step, however, merits comment. The determining factor in this reaction is the nature of the nucleophile. It has been found that, in reaction with 2,3-dinitroacetanilide (69),

ammonia and primary aliphatic amines substitute the nitro group at position 2, and secondary amines substitute the nitro group at position 3[58]. Thus glycine ethyl ester substitutes at position 2 and gives an intermediate (70) suitable for cyclisation to the 7-amino derivative. It would be interesting, in the light of the results in Chapter IV, to see if N-methylglycine(Sarcosine)ethyl ester substituted at position 3 of (69).

All four of the isomeric aminobenzimidazole N-oxides have thus been synthesised and their physical and spectroscopic properties are collected in tables 2 and 3.

They crystallise from water in hydrated form and as such do not show typical N-H stretching patterns in the infra-red spectra, presumably due to extensive hydrogen bonding. They are appreciably soluble in water and as such their crystallisation demands the use of a small volume of water; seeding is also often necessary. All are colourless materials in their purest form but they do appear to darken on standing and indeed decompose if left in solution for more than a few days. For this reason, the work-up procedure, whether in a reductive process or by liberation from a hydrochloride, should be performed without delay, and the products are stored preferentially as the stable hydrochlorides.

The ^{1}H n.m.r. spectra of the amino N-oxides and their hydrochlorides are seldom first order and the only diagnostic feature of the spectra is a characteristic low-field singlet for H-2.

Table 2 Some characteristics of Aminobenzimidazole N-Oxides

Benzimidazole N-Oxide	m.p. (°C)	hydration	ν max. (cm^{-1})	m/z
4-NH_2	108-110	1 H_2O	3460,3320,3130	149($M^{+\cdot}$,14%), 148(17%), 133(100%), 132(28%), 121(6%), 120(6%), 106(39%), 105(31%), etc.
5-NH_2	97-98	1 H_2O	3430,3310,3329 3140,3080(br)	149($M^{+\cdot}$,60%), 133(100%) 132(87%), 120(20%), 106(20%), etc.
6-NH_2	185(dec.)	2 H_2O	3360,3160, 3080(br)	149($M^{+\cdot}$,67%), 133(100%), 132(47%), 121(13%) 120(13%), 106(20%), etc.
7-NH_2	118-120	1 H_2O	3500,3400,3310	149($M^{+\cdot}$,100%), 133(74%), 132(72%), 106(21%), 105(74%), etc.

Table 3 ^{1}H n.m.r. Spectra of Aminobenzimidazole N-oxides

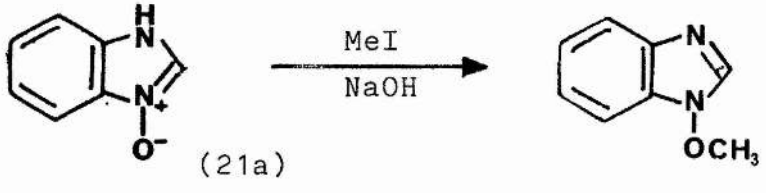
Benzimidazole N-oxide	Chemical Shifts (ppm) in $(CD_3)_2SO$						Coupling Constants (Hz)
	H-2	H-4	H-5	H-6	H-7	Others	
4-NH_2.2HCl[55]	9.85(s)	-	7.0 & 7.18 (8 lines with H-7)	7.46(t)	See H-5	8.60(br s, NH's,OH)	5,6=6,7 =8.0Hz
5-NH_2. 2HCl	9.90(s)	7.79(d)	-	7.51(dd)	7.49(d)	10.63(br s, NH's,OH)	4,6=2.0Hz; 6,7=8.5Hz
6-NH_2. 2HCl	9.96(s)	7.6-7.75(1H,m); 7.9-8.13(2H,m)				9.30(br s, NH's,OH)	not measurable
7-NH_2. 2HCl	9.78(s)	6.75-7.15(2H,m); 7.37(1H,t)				9.50(br s, NH's,OH)	not measurable
4-NH_2. H_2O	8.23(s)	-	6.40 (4 lines)	6.65-7.70 (m, with H7)	See H-6	5.38(br s, NH's,OH H_2O)	not measurable
5-NH_2. H_2O	8.00(s)	6.45-6.63 (m, with H-6)	-	See H-4	7.15-7.33 (1H,m)	5.65(br s, NH's,OH H_2O)	not measurable
6-NH_2. 2H_2O	8.20(s)	7.15-7.35 (1H,m)	6.63-6.85 (m,with H-7)	-	See H-7	4.80(br s, NH's,OH H_2O)	not measurable
7-NH_2. H_2O	8.17(s)	6.42 and 6.70(2 x bd) & H-6)	7.01(1H,t H-5)	See H-4	-	5.70(br s, NH's,OH H_2O)	4,5=5,6 =7.5Hz

SELECTIVE ALKYLATION OF BENZIMIDAZOLE N-OXIDES - PREPARATION OF NUCLEOSIDE ANALOGUES

Nucleoside research has followed a similarly explosive pattern of activity to that observed for the heterocyclic bases from which they are derived. The ultimate goal has also been similar, i.e. to prepare compounds which can act as models for the natural species or which can interact usefully with biological systems. Many combinations of heterocycle (benzimidazoles included[59]) and sugar have been investigated.

Now that satisfactory routes to the four aminobenzimidazole N-oxides had been established attention was focused briefly on the possibility of using these N-oxides to form nucleoside analogues.

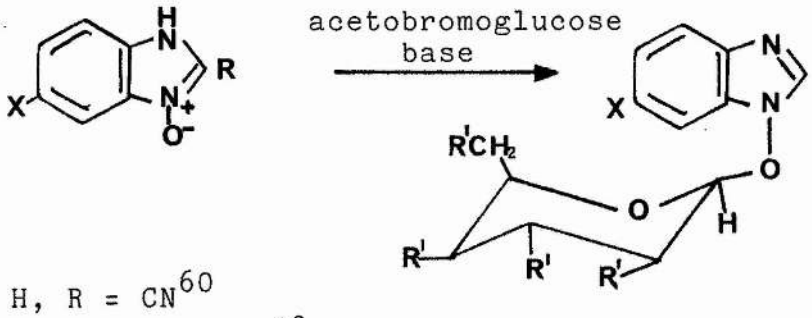
Benzimidazole N-oxides are known to undergo alkylation at oxygen by reaction with an alkyl halide in the presence of base[14]. For example benzimidazole N-oxide (21a) reacts with methyl iodide to give 1-methoxybenzimidazole (71)[14].



(21a)

(71)

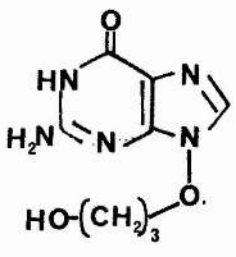
Similarly, the reactions of some 2-substituted benzimidazole oxides with simple sugar derivatives such as α-acetobromoglucose* lead to nucleoside analogues containing an N-O-C linkage[38,60].



e.g. X = H, R = CN[60]
X = NO_2, R = CO_2Et[38]

R' = $OCOCH_3$

Guanosine analogues have attracted much interest recently, particularly those in which the 'sugar' moiety is acyclic[61]. This is mainly as a result of the commercial success of the anti-viral drug acyclovir (4)[4]. Acyclonucleosides in which the atom attached to the heterocyclic base is oxygen have also been the subject of recent research[62]. 9-(3-Hydroxypropoxy)guanine (72) possesses potent and selective anti-herpesvirus activity[62].

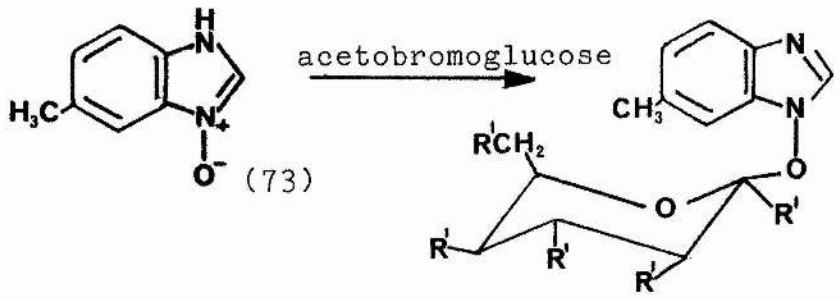


(72)

*Acetobromoglucose - 2,3,4,6-tetra-O-acetyl-glucopyranosylbromide.

The preparation of nucleoside analogues derived from 5-aminobenzimidazole N-oxide was therefore of particular interest since successful reaction with the required substrate would lead to products most closely resembling guanosine-type compounds. However, before attempting any reactions using the amino N-oxide the reactivity of the closely related 5-methylbenzimidazole N-oxide (73) was investigated as a model system since it was available in greater quantity than the amino analogue. Compound (73) was prepared by cyanomethylation of 4-methyl-2-nitroaniline, followed by cyclisation then hydrolysis[28] (the procedure previously described on p.22).

However, the reaction of (73) with acetobromoglucose met with limited success. No reaction was observed when acetonitrile was used as solvent, and only a small amount of product (74) was obtained (as indicated from infra-red and mass spectral data) with quinoline as solvent. The problem in the latter reaction appeared to be in the work-up procedure where a sticky mass was obtained, instead of the expected precipitate.

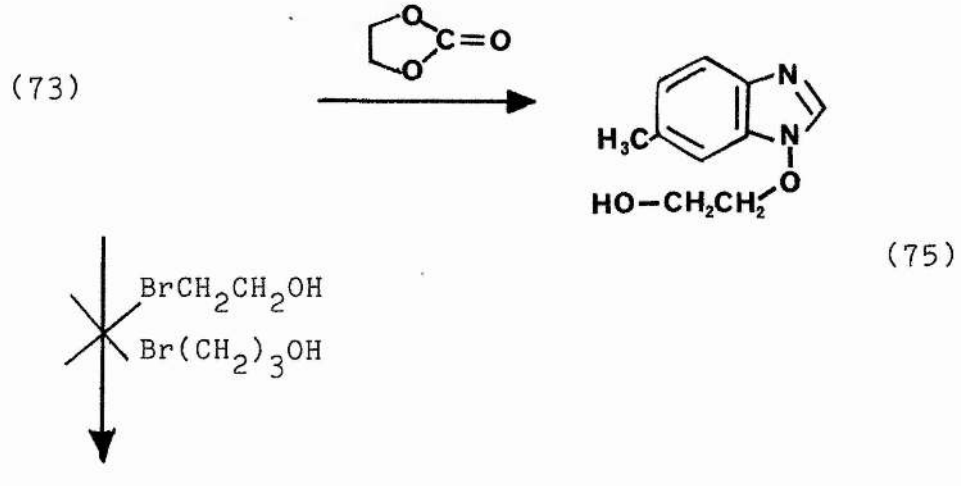


(73)

(74)

In attempts to prepare acyclic nucleoside analogues, 2-bromoethanol and 3-bromopropan-1-ol were initially considered as suitable alkylating agents. However, only unchanged N-oxide or trace quantities of the desired product were obtained on their reactions with (73). A hydroxyalkyl ether (75) was eventually obtained when the N-oxide was reacted with ethylene carbonate (Scheme 24). This type of reaction has been reported previously for the preparation of β-hydroxyethyl ethers derived from phenols[63].

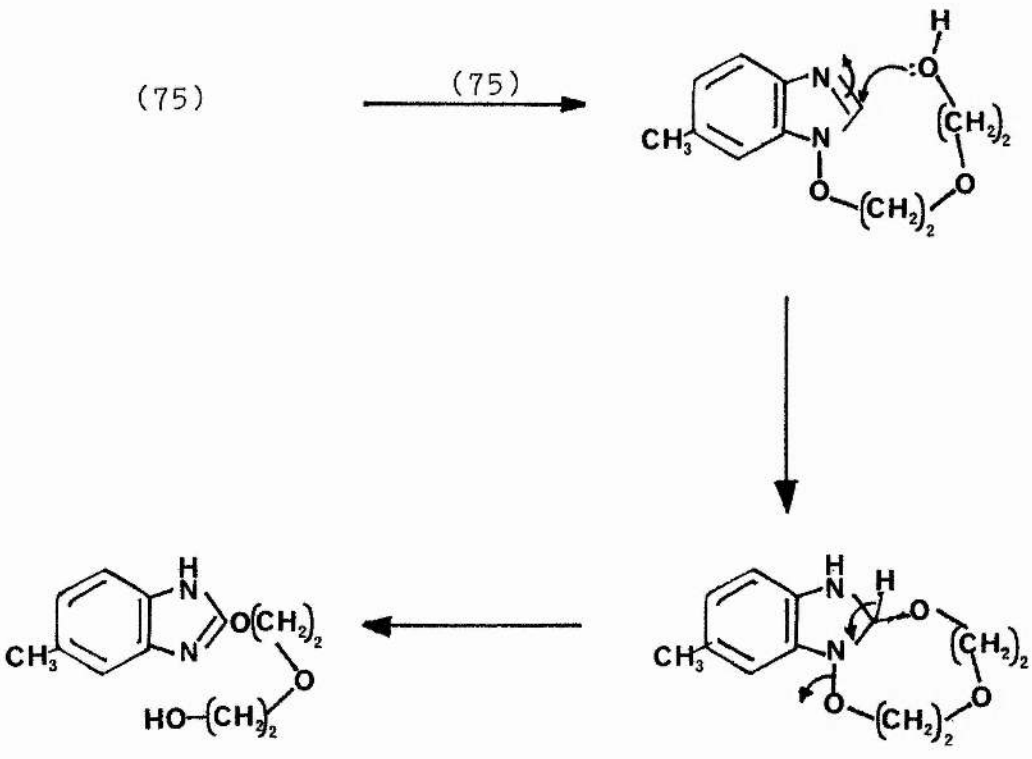
Scheme 24



Although the desired product was undoubtedly formed in this case, attempts to purify the oil by distillation led to a resinous material being formed throughout the

distillation apparatus. N.m.r. indicated that this material was a mixture of at least two products with the absence of the H-2 resonance in the imidazole ring being a notable feature. This, coupled with the molecular ion in the mass spectrum (M^{+} 236) led to (76) being proposed as a possible component of the mixture. Its formation can be rationalised in the manner shown in Scheme 25.

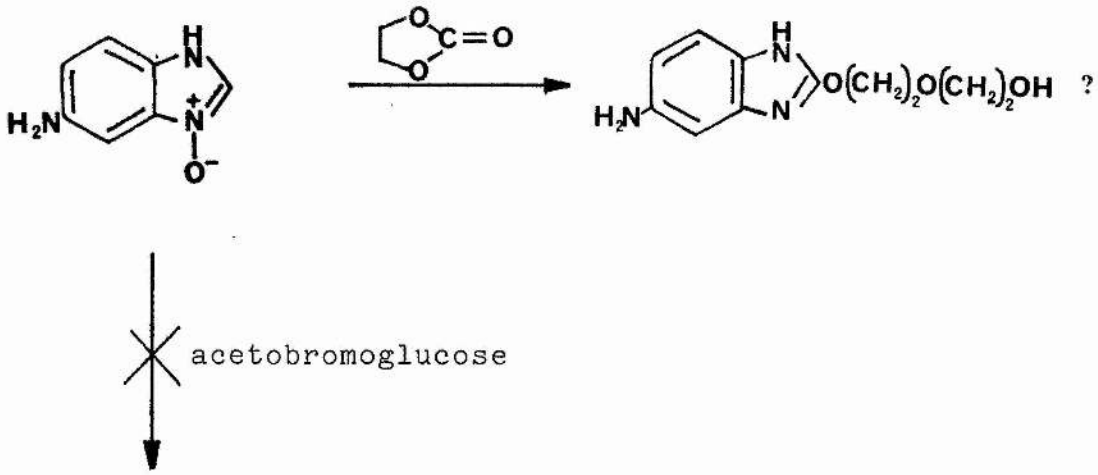
Scheme 25



The reactions of the 5-aminobenzimidazole N-oxide(13b) were approached with an open mind in view of the problems found with the 5-methyl N-oxide and indeed similar difficulties were encountered in the reactions of the amino

N-oxide with acetobromoglucose and ethylene carbonate (Scheme 26). In the former case a precipitate was obtained from the reaction by modifying the experimental conditions slightly. However, this material decomposed on filtration. In the latter reaction work-up yielded a black tar; but this material was sufficiently volatile in the mass spectrometer to give a molecular ion and fragmentation pattern very similar to that obtained for the distillation product in the 5-methyl N-oxide reaction. It is difficult to say in this instance that the product is the direct analogue of (76), since the amino N-oxide may act as a multi-functional nucleophile and as such a number of possible products may result.

Scheme 26



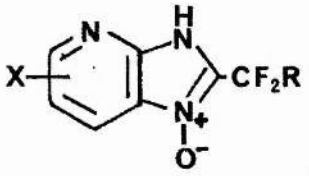
It must be stressed that the reactions in this section were attempted for the most part, only once. This work is thus in its infancy and further research is required to help clarify some of the unusual results obtained here.

CHAPTER III : IMIDAZO[4,5-b]PYRIDINE N-OXIDES

INTRODUCTION

This Chapter is concerned with attempts to cyclise aminonitropyridine derivatives to imidazopyridine N-oxides in a similar fashion to that previously described for the cyclisation of o-nitroanilines. In contrast to benzimidazole N-oxides, imidazopyridines oxidised at an imidazole nitrogen have been relatively little investigated to date, mainly because comparatively few of the necessary starting materials are readily accessible. They cannot be prepared by N-oxidation of the corresponding imidazopyridines, since oxidation procedures using peracids effect N-oxidation in the pyridine ring[64].

Most of the previous research in this area has involved the reductive cyclisation of 2-acylamino-3-nitropyridines to give 3H-imidazo[4,5-b]pyridine 1-oxides of general formula (77)[65](cf partial reduction of o-nitroanilides, p.11). Some of these compounds are biologically active and possess herbicidal and rodenticidal properties[65].

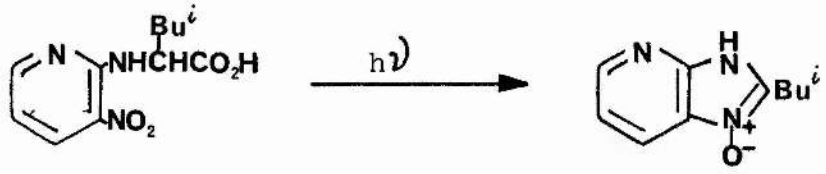


R = e.g.H,Cl,F
X = e.g.Cl,NO_2, alkyl

(77)

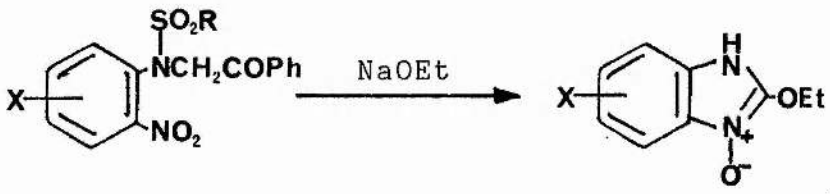
Only two other simple examples of this type of N-oxide are known. One example involves the photochemical formation of 2-isobutylimidazo[4,5-b]pyridine N-oxide (78)

from the leucine derivative (79)[66].



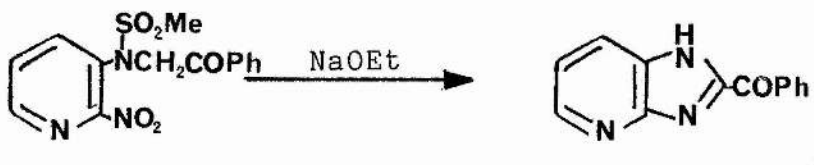
(79) (78)

Base-induced cyclisation of aminonitropyridine derivatives provides the other examples in this area of N-oxide chemistry. As part of a study of heterocyclic N-oxides, research workers in St. Andrews prepared a number of N-(activated alkyl)aminonitropyridines and investigated their reactions in basic media[67]; comparison was made with the corresponding benzene series. The results obtained were often at variance with findings in the analogous system, e.g.



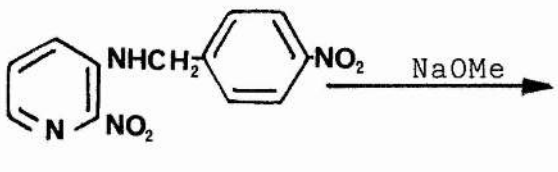
(40-80%)[68]

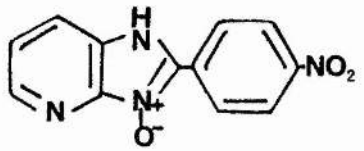
but,



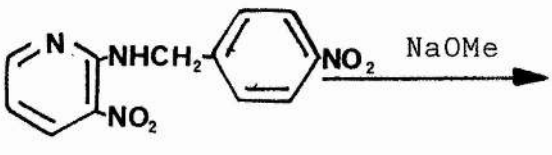
(7%)[67]

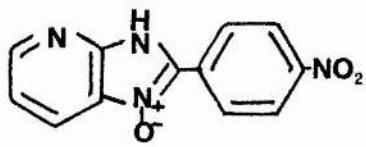
The only successful cyclisation reactions (in terms of yield of N-oxide) were those of 2-nitro-3-(p-nitrobenzylamino)pyridine (80) and its isomer (81). The N-oxides (82) and (83) were both insoluble in common organic solvents and had to be converted into their O-benzoyl derivatives for characterisation purposes.





(80) (82) (93%)



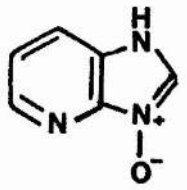


(81) (83) (92%)

From the little that is known regarding the base-induced cyclisation reactions of suitably functionalised aminonitropyridines, it is difficult to assess the effect of the additional nitrogen atom and thus draw valid comparisons with the benzene series. The major aim of this Chapter, therefore, was to attempt to gain a better understanding of this system and in particular to study further the reactions of N-(monosubstituted)aminonitropyridines.

RESULTS AND DISCUSSION

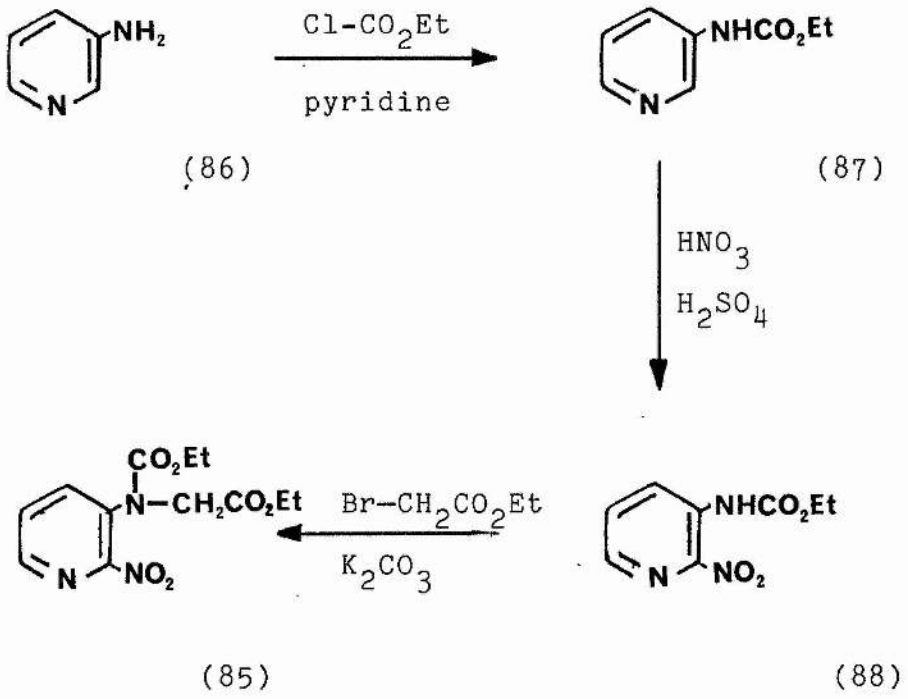
Attempted Preparation of 1H-Imidazo[4,5-b]pyridine 3-Oxide (84) and Derivatives



(84)

Initial research in this area began with the reactions of the diester (85) which was prepared according to Scheme 27. The reaction of 3-aminopyridine (86) with ethyl chloroformate followed by nitration of the carbamate (87), gave (88) in good yield. The nitration step had previously been reported as difficult to control and poor yields were often obtained[67,69]. However, by lowering the reaction temperature, and employing a longer reaction time, nitration occurred readily and no problems were encountered. The nitrocarbamate (88) is known to undergo alkylation at the exocyclic nitrogen in the presence of base[69] and indeed its reaction with ethyl bromoacetate gave the diester (85) in 86% yield.

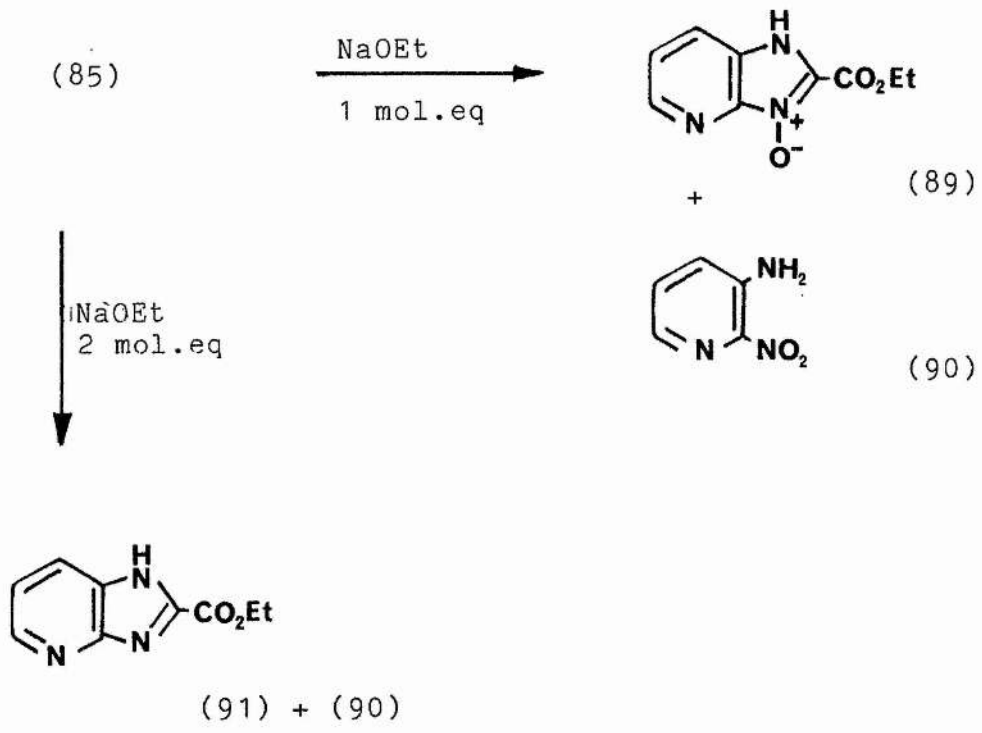
Scheme 27



(86) (87) (85) (88)

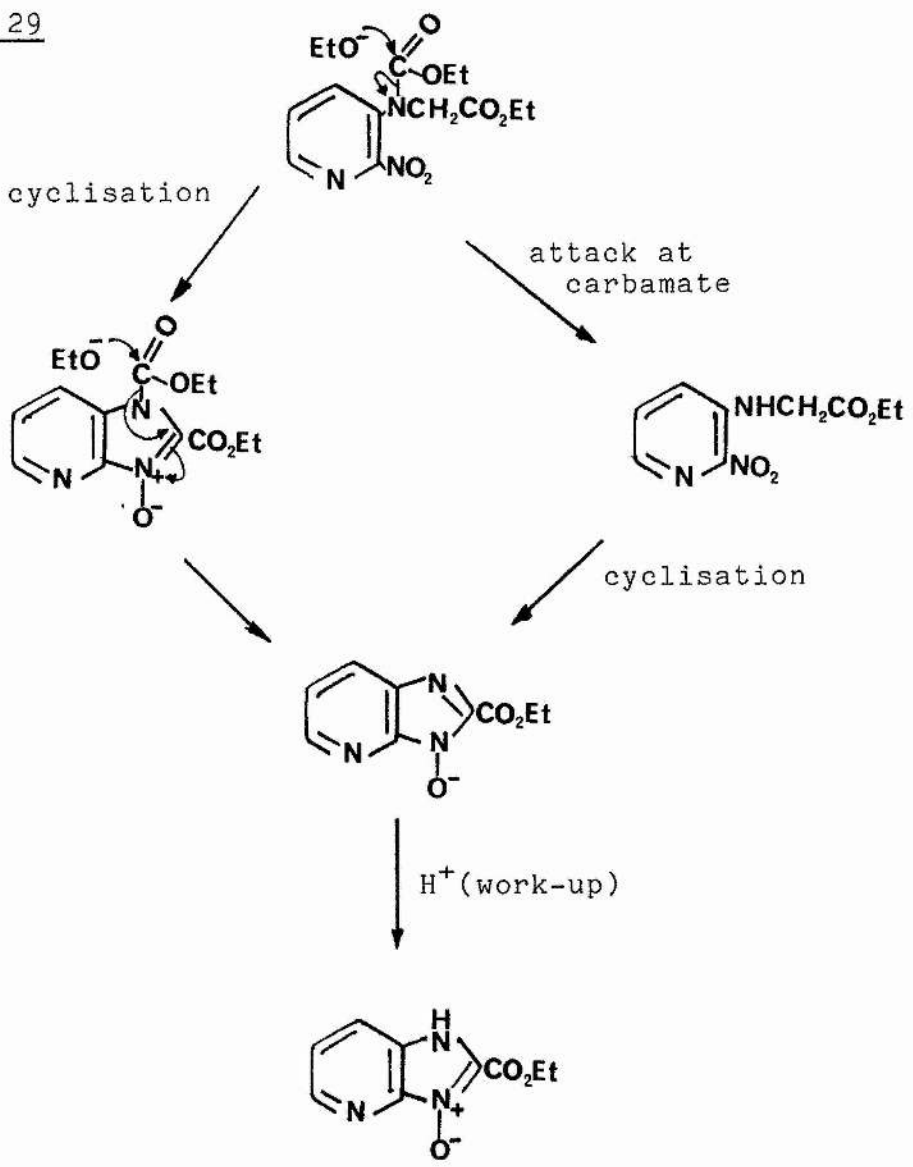
No reaction occurred when (85) was treated with ammonia or diethylamine. Reaction did occur in the presence of sodium ethoxide; however the outcome of the reaction was unpredictable (Scheme 28). When one molar equivalent of base was used the only pure product obtained was the N-oxide (89), although unreacted starting material and 3-amino-2-nitropyridine (90) were also detected (t.l.c.) in the complex mixture. Increasing the quantity of base similarly gave a complex mixture, from which the imidazopyridine (91) and impure cleavage product (90) were isolated. (The latter reaction was not reproducible).

Scheme 28

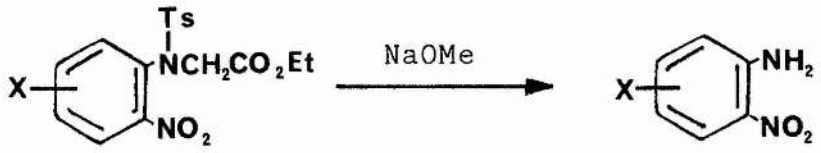


The conventional aldol-type cyclocondensation mechanism (p.21) is again sufficient in explaining the occurrence of the N-oxide (89) with loss of the carbamate ester function possible before or after cyclisation (Scheme 29). Alternative pathways are considered as part of the mechanistic discussion in Chapter IV.

Scheme 29



The occurrence of an aminonitropyridine is common to many reactions described in this Chapter and ample precedent, in both the pyridine[67] and benzene series[68], exists for its formation. Indeed, in certain instances (see below), the primary amine has been found to be the major product isolated from the reaction[68].

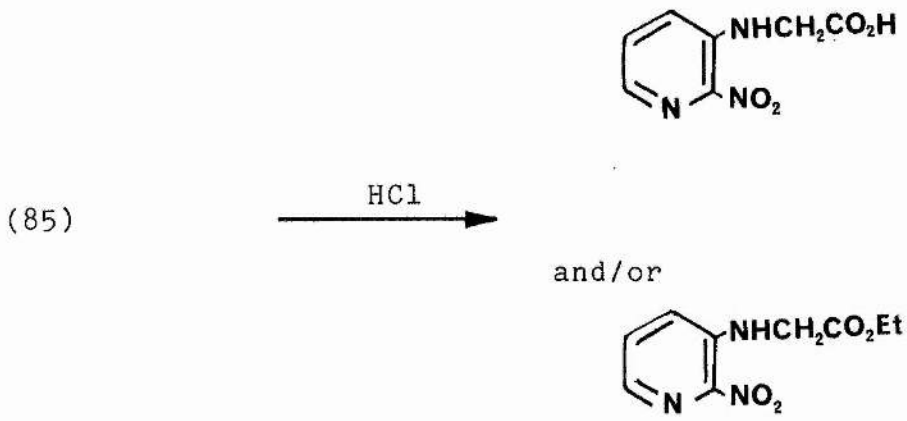


(>50%)

Ts=p-tolylsuphonyl
X =e.g.H,4-Me,4-OMe

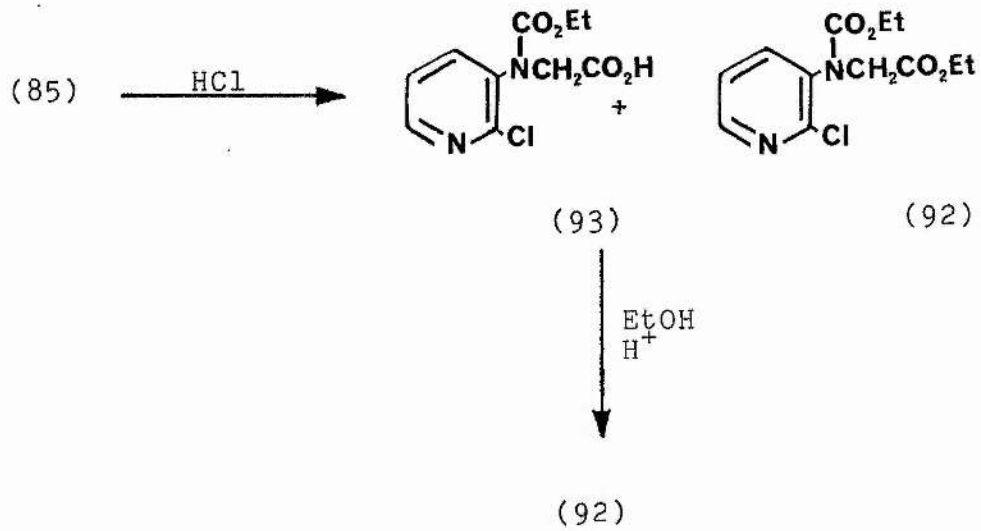
The formation of the reduced imidazopyridine (91) is also not unusual in this type of reaction[67]. It is tempting to suggest that it is produced from the N-oxide (89) since the reaction involving one molar equivalent of base leads to the N-oxide being isolated and no reduced compound detected, and in the case with two molar equivalents of base the converse is true. However, the fact that the overall recovery of material in each reaction was low and that the latter reaction was not reproducible renders any firm mechanistic proposals suspect.

The results described here are typical and highlight many of the problems encountered in the use of N-(disubstituted)-o-aminonitropyridines. Since the successful cyclisations found previously in this series (p.63) involved monosubstituted amines it was decided to focus attention on the simpler starting materials. As part of this objective the hydrolysis of (85) was investigated. Acidic conditions were employed since the diester is sensitive to basic media.



The above diagram illustrates the predicted outcome of the reaction. The actual results obtained were rather more surprising (Scheme 30).

Scheme 30

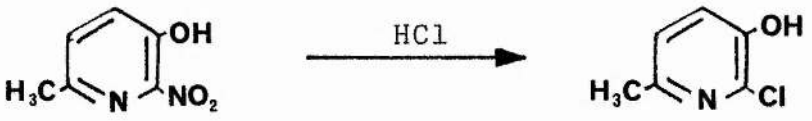


On reaction of (85) with concentrated hydrochloric acid a mixture of chloro-diester (92) and half acid-ester (93) was obtained. The identification of the two components of this mixture initially proved difficult since the aromatic protons of (92) and (93) in the ^{1}H n.m.r. spectrum were

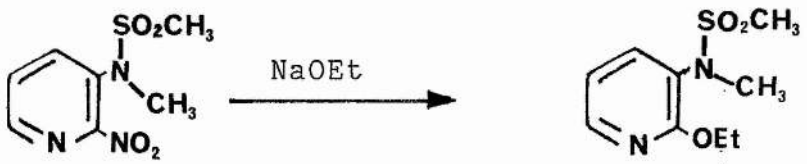
virtually all superimposable, yet the analytical sample corresponded to pure acid (93). Esterification of the mixture gave solely chloro diester (92). The use of sulphuric acid or hydrobromic acid for the hydrolysis instead of hydrochloric acid resulted in the formation of dark residues from which no products were isolated.

The complete resistance of the carbamate function to hydrolysis is slightly surprising although it should be remembered that in Chapter II (p.29) the ethoxycarbonyl group of a protected aminobenzimidazole N-oxide was only partially removed on hydrolysis with concentrated hydrochloric acid.

(The nucleofugicity of the nitro group in aromatic systems is well known[70,71] and two examples relevant to the current discussion are given below (a further example can be found in Chapter II,p.50).



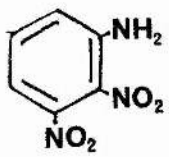
(94) Ref.[72]



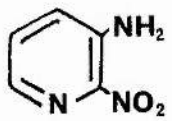
Ref.[67]

Some of the base-induced cyclisations studied in the course of this work (and in particular in this Chapter), involve mixtures in which few of the products are identified. Nucleophilic displacement of the nitro group, as shown in the latter example above, is one possible complicating factor in these reactions.

A further approach considered in the attempted preparation of 1H-imidazo[4,5-b]pyridine 3-oxide involved the cyanomethylation of 3-amino-2-nitropyridine (90) (cf p.23). As mentioned previously, the conditions required for cyanomethylation depend markedly on the basicity of the amine. By simple analogy with cyanomethylation reactions in Chapter II, 2,3-dinitroaniline (95) was considered as having comparable basicity to the aminonitropyridine (90) and therefore the corresponding reaction conditions were employed.



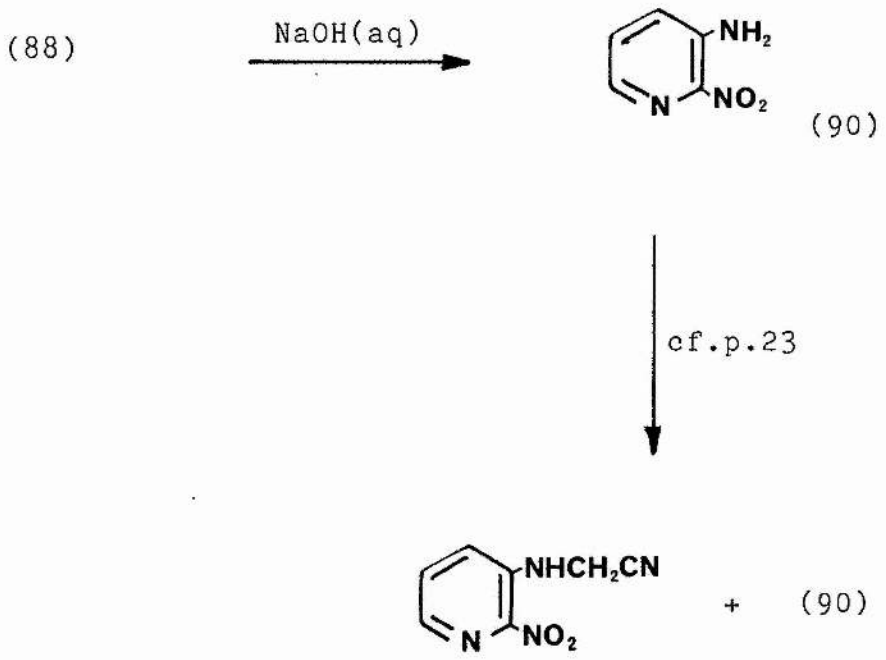
(95)



(90)

However, this reaction never went to completion, even when a longer reaction period was used and attempts to separate the mixture were unsuccessful.

Scheme 31



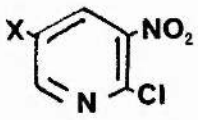
An obvious complication in this reaction is the co-ordinating ability of the pyridine nitrogen which is known to react with Lewis acids. For example Friedel-Crafts reactions fail with pyridine; the heterocycle preferentially co-ordinates with the Lewis acid and does not react further[73]. The formation of such an adduct in this case probably reduces the basicity of the primary amine still further, in addition to removing the zinc chloride from the cyanomethylation system, and this may therefore explain the low reactivity of (90).

When the mixture was treated with base reaction did appear

to occur but only the two components of the initial mixture were identified on work-up.

3H-Imidazo[4,5-b]Pyridine 1-Oxide and Derivatives

2-Chloro-3,5-dinitropyridine (96) and to a lesser extent, 2-chloro-3-nitropyridine (97), have been considered as analogues of Sanger's Reagent (see p.31), and as such their reactions with amines and amino acids have been studied[74].

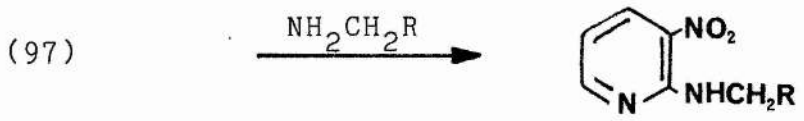


(96) X = NO_2

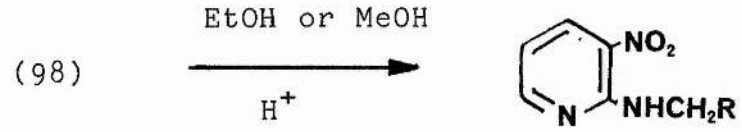
(97) X = H

Indeed in contrast to the 2-nitropyridine series, the glycine ester (99) is known[75] and can be prepared directly or via the acid (98). Scheme 32 shows (i) the reactions of 2-chloro-3-nitropyridine with glycine derivatives and, (ii) the esterification of the acid (98). In practice the ethyl ester (99) was preferentially prepared via the glycine (98) since the purity of the product was higher than that obtained from (97) by direct displacement.

Scheme 32



(98) R = CO_2H
(99) R = CO_2Et
(101) R = CN



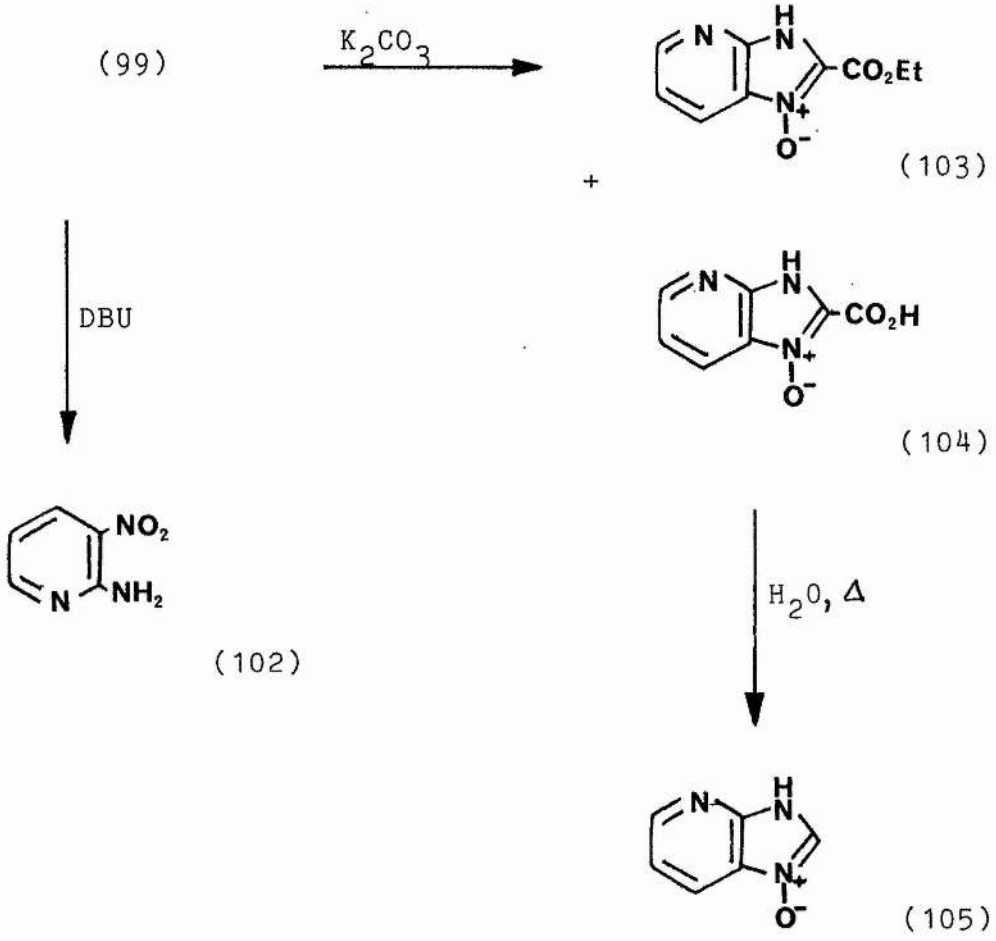
(99) R = CO_2Et
(100) R = CO_2Me

The reactions of the glycine derivatives (99-101) are now considered in turn. No product was isolated from the reaction of the ethyl ester (99) with sodium ethoxide or piperidine; considerable decomposition appeared to occur in both these reactions. Darkening of the reaction solution was also obvious when 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU) was employed as base; however, in this experiment 2-amino-3-nitropyridine (102) was isolated, albeit in impure form.

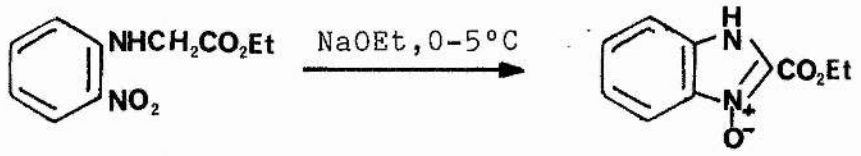
The reaction of (99) in ethanolic potassium carbonate proved more successful. Two different potassium salts were

obtained, one soluble and the other insoluble in the reaction medium. The former on acidification gave the desired ester N-oxide (103). The other, on acidification gave a buff-coloured solid which decomposed with gas evolution on attempted recrystallisation or even during dissolution for n.m.r. investigation. The product of this decomposition was the parent imidazo[4,5-b]pyridine N-oxide (105), and it seems probable that the thermally unstable solid is the carboxylic acid (104). In all of these reactions the presence of 2-amino-3-nitropyridine (102) was indicated by t.l.c.

Scheme 33



In the corresponding benzene series the mononitrophenyl glycine ester (106) was cyclised in ethanolic sodium ethoxide although the yield was low[28]. When the base was added at room temperature, the corresponding carboxylic acid was also obtained[76]. The lability of the proposed acid (104) is not entirely surprising considering the known thermal instability of benzimidazole-2-carboxylic acid N-oxide (31) (p.25).

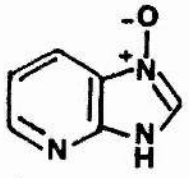


(106) (31%)

To the best of the author's knowledge DBU has not previously been used to effect cyclisation in ortho-substituted nitroaryl compounds. It was initially thought that, as a consequence of the non-nucleophilic nature of the base, certain side reactions (e.g. attack on the ester group) might be suppressed. Since only the aminonitropyridine (102) was isolated from the mixture, the effect of DBU in this type of reaction is unclear other than it would appear to be an unsuitable base, in this example, for cyclisation.

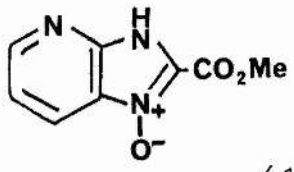
The acid hydrolysis of the ester (103) was investigated in a similar manner to the reactions of the N-(protected amino)benzimidazole N-oxides in Chapter II. However, the results found in this case were markedly different from

those in the corresponding benzene series and are better explained in Chapter IV. The ester (103) did undergo base hydrolysis to give the parent N-oxide (105) in 77% yield.

(103) $\xrightarrow{NaOH(aq)}$  (105)

The reactions of the methyl ester (100) and the nitrile (101) met with less success. Only a small amount (10%) of impure N-oxide (107) was obtained on reaction of the methyl ester (100) in methanolic potassium carbonate; problems arose in the isolation of the N-oxide (107) which decomposed on attempted purification. The reaction was also dissimilar to the cyclisation of the ethyl ester (99) in base in that no carboxylic acid was found in this case.

No product was isolated on treatment of the nitrile (101) with sodium ethoxide or potassium carbonate. A black gelatinous precipitate formed throughout the reaction mixture and separation of this material from the liquid phase proved impossible.

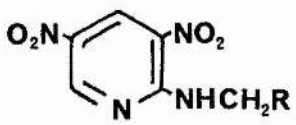
(100) $\xrightarrow{K_2CO_3}$ 

(107)

(101) $\xrightarrow[\text{or NaOEt}]{K_2CO_3}$ no product isolated

The superior reactivity of 2-chloro-3,5-dinitropyridine (96) over the mononitrochloropyridine (97) towards amino acids and peptides has been commented on [77]; its reactions with glycine derivatives (Scheme 34) are effectively instantaneous and the use of triethylamine as base facilitates reaction by allowing a homogeneous medium.

Scheme 34

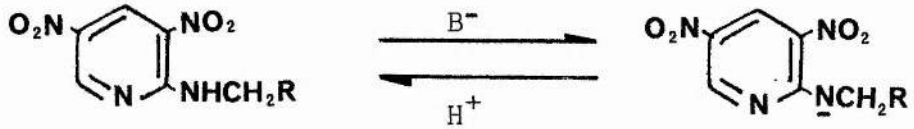
(96) $\xrightarrow[Et_3N]{NH_2CH_2R}$ 

(108) R = CO_2Et
(109) R = CO_2Me
(110) R = CN
(111) R = CF_3

The success achieved in the displacement reactions was not paralleled in the reactions of the dinitropyridyl derivatives (108-111) with bases.

Although in most cases a water-soluble product was obtained from work-up in the usual manner (see experimental), acidification of this solution gave a mixture which generally consisted of starting material and a black polar material. The presence of 2-amino-3,5-dinitropyridine was also indicated from mass spectral evidence (a peak at mass 184 ($M^{\cdot+}$) was more intense than in the mass spectrum of the starting dinitropyridyl compound itself).

It may be that the additional nitro group in the ring renders the amino hydrogen the most acidic, and it is this proton, rather than the methylene proton, that is removed in base. Acidification of the salt (112) would then regenerate the starting material.



(112)

In summary base-induced cyclisation of aminonitropyridine derivatives has, in general, been largely unsuccessful both in this, and in previous research[67]. The main exception here has been the reaction of N-(3-nitro-2-pyridyl)glycine ethyl ester (99) with potassium carbonate.

CHAPTER IV : REACTIONS OF N-METHYL-N-(ACTIVATED ALKYL)-o-NITROANILINES AND RELATED SPECIES IN BASIC MEDIA

INTRODUCTION

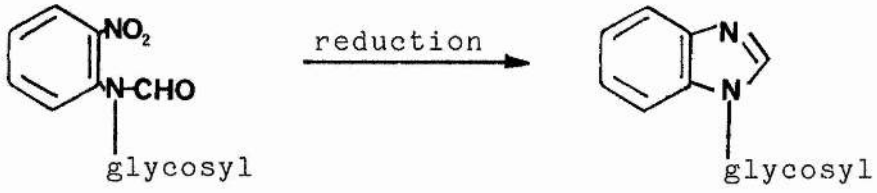
The reactions of N,N-disubstituted-o-nitroanilines (113) are of considerable mechanistic interest and have been the subject, in part and in full, of a number of reviews[9,36,78]. Of particular interest in the context of this work are the reactions of N-methyl-N-(activated alkyl)-o-nitroanilines in basic media.

(113)

The reason for this interest is threefold:-

(i) Although the preparation of N-alkylbenzimidazole N-oxides is possible, mainly by reductive[14,25] or acid-catalysed procedures[79], there is no general method which directly gives N-alkylbenzimidazole N-oxides with functionality at position 2.

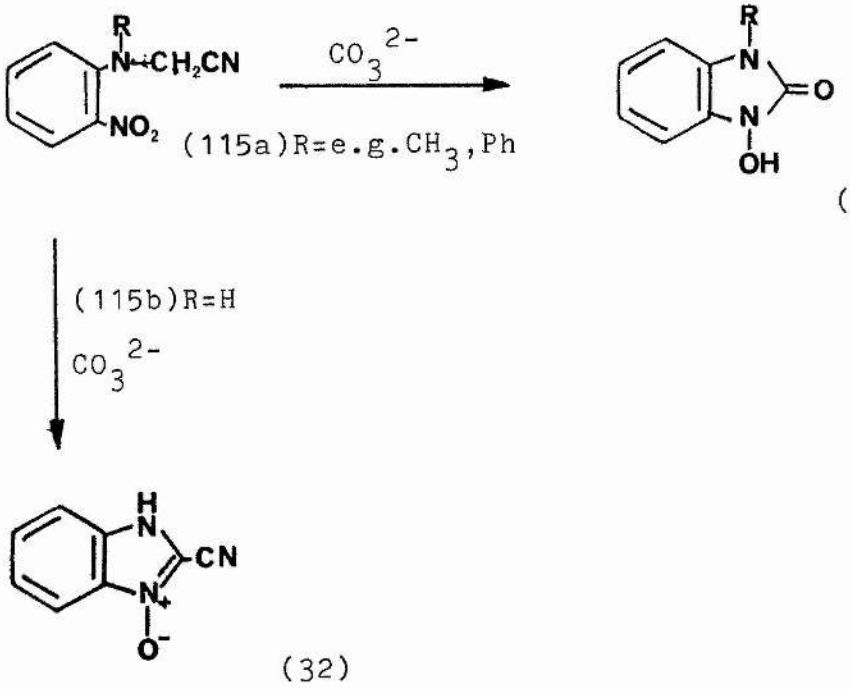
(ii) The preparation of benzimidazole nucleosides by the catalytic hydrogenation of N-acyl-N-glycosyl-o-nitroanilines (114) is known[80].



(114)

It would be interesting therefore, both from a chemical and biological viewpoint, to synthesise 1-N-glycosyl-benzimidazole 3-oxides by a base-induced method, particularly since success has been achieved in preparing the amino-benzimidazole 3-oxides (see Chapter II). N-Alkylbenzimidazole 3-oxides could be considered as simple models for the nucleoside analogues.

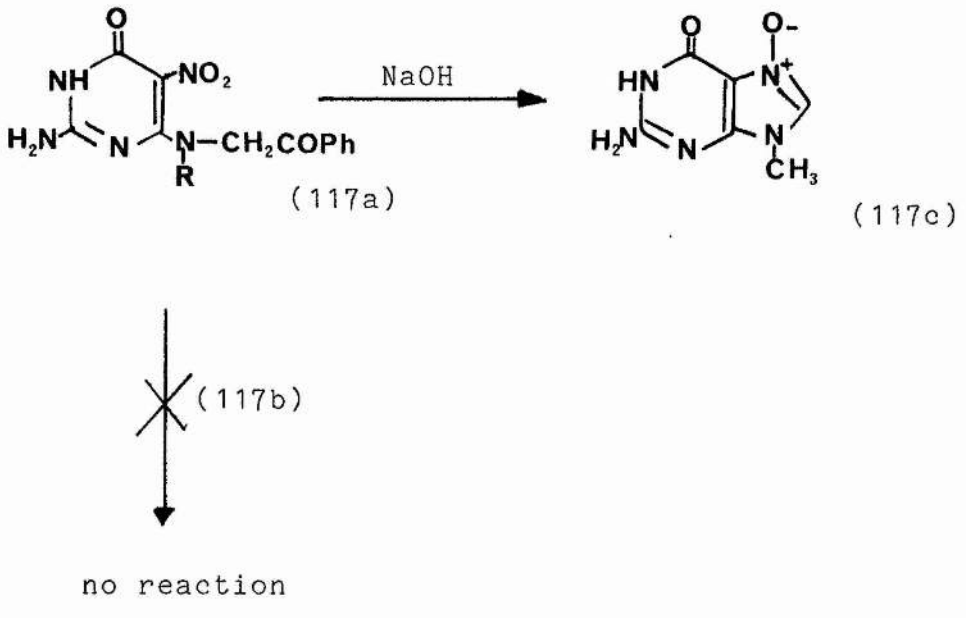
(iii)Research involving the reactions of N,N-disubstituted-o-nitroanilines in basic media has shown that the outcome of these reactions is often at variance with reactions in which the anilino-nitrogen is secondary. (Much of this work has been collected in a review by Smith[9]). For example N-substituted-N-cyanomethyl-o-nitroanilines (115a) react in basic media to give N-hydroxybenzimidazolones (116)[81] whereas N-cyanomethyl-o-nitroaniline (115b) is cyclised by base to 2-cyanobenzimidazole N-oxide (32).



The mechanistic details of this reaction will be dealt with later in this Chapter.

In the related pyrimidine area, the cyclisation of the phenacyl compound (117a) (R = CH_3) has recently been accomplished[7]. However, the unalkylated derivative (117b) (R = H) fails to cyclise under identical conditions.

The preparation of the purine N-oxide (117c) was discovered in the literature after the current research in this Thesis was complete.

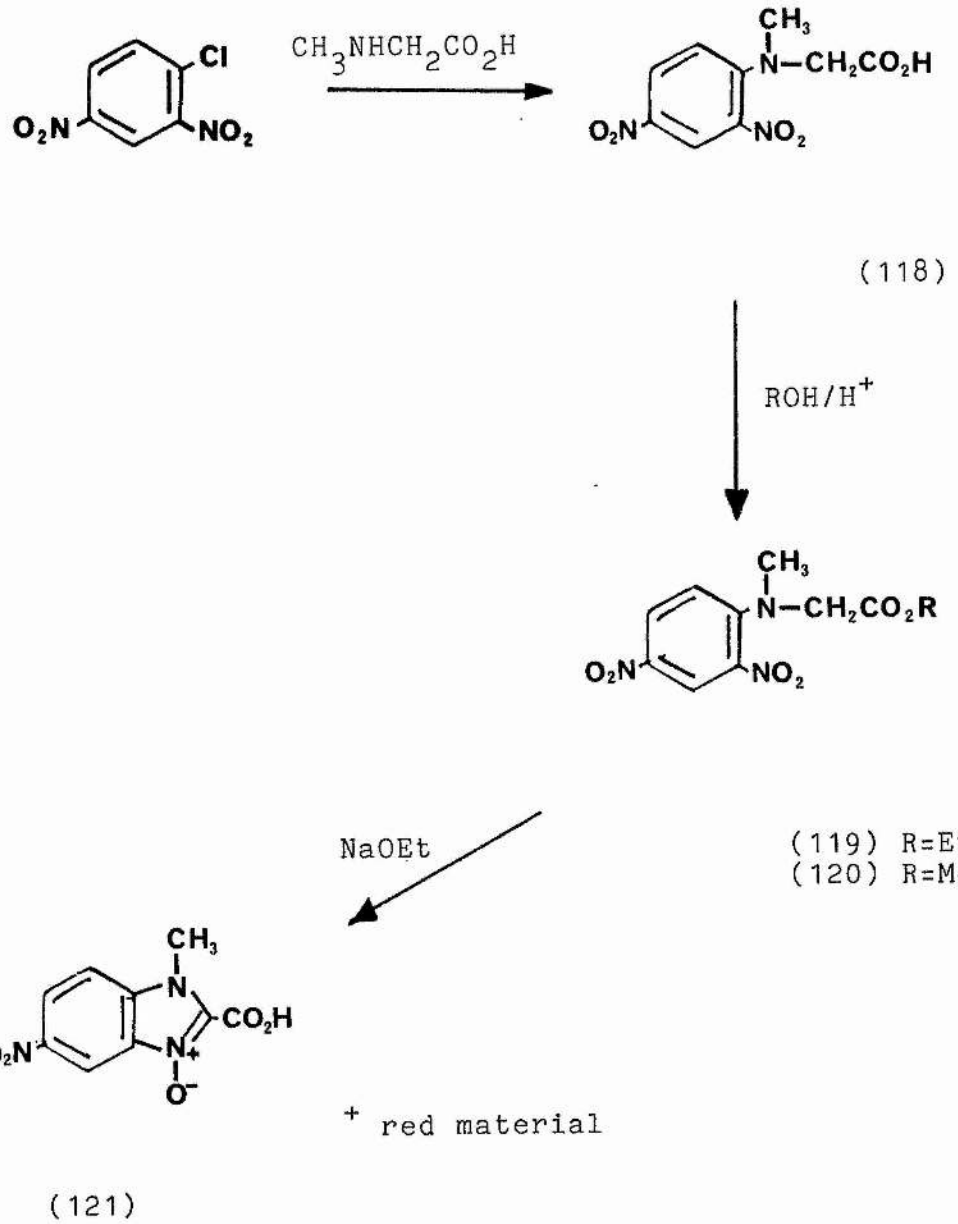


RESULTS

Initial research in this area began with the preparation and reactions of N-(2,4-dinitrophenyl)sarcosine ethyl ester (119), which was obtained via the known acid (118) (Scheme 35).

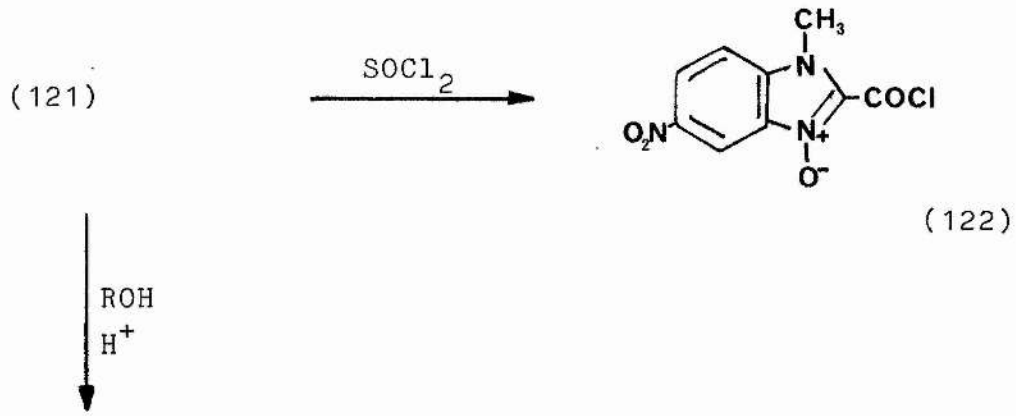
When the ester (119) was treated with sodium ethoxide a brown-red precipitate formed which was filtered and separated into a water-soluble and an acetone-soluble portion. The aqueous fraction gave, on acidification, a buff-coloured material which had spectroscopic and analytical properties corresponding to the carboxylic acid (121).

Scheme 35

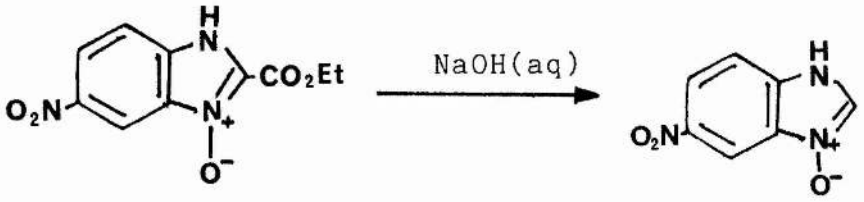


+ red material

Doubt was immediately cast on the proposed structure (121) when the 'acid' failed to undergo esterification under a variety of conditions, and when its reaction with thionyl chloride gave a product with a molecular weight corresponding to the acid chloride (122) yet an ^{1}H n.m.r. spectrum indicating that ring substitution had occurred.

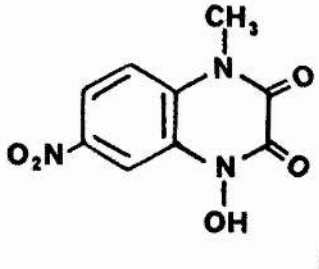


In addition, it has already been mentioned (p.25) that benzimidazole-2-carboxylic acid 3-oxide (31) is prone to decarboxylation at relatively low temperatures yet this 'acid' (121) can be recrystallised unchanged from acetic acid or dimethylformamide. Also, attempts to prepare the unmethylated analogue for comparative purposes by base hydrolysis of the ethyl ester (45) resulted in the (almost instantaneous) formation of 5-nitrobenzimidazole N-oxide (19).

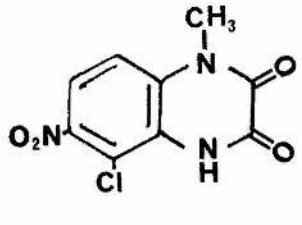


(45) (19)

The structure of the 'acid' was eventually elucidated by X-ray crystallography* and found to be the quinoxalinedione (123). Single crystal analysis of the chlorinated product was also carried out,the structure (124) confirming the suspicion that ring substitution had indeed occurred. The detailed structures of these compounds can be found in the X-ray crystallography appendix.



(123)

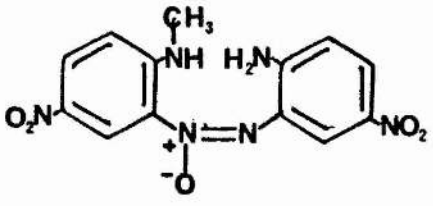


(124)

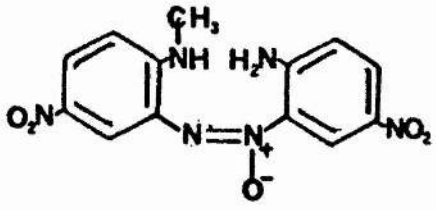
Identification of the other major product from the reaction of N-(2,4-dinitrophenyl)sarcosine ethyl ester with sodium ethoxide also proved difficult initially. The fine, bright-red needles had analytical and spectroscopic properties which, in general, fitted well for an azoxy compound (125a) or (125b) yet the mechanism for its formation was not obvious.

*All the X-ray crystallographic analyses reported were carried out by Professor G. Ferguson and colleagues at the University of Guelph, Ontario, Canada.

Comment has been made in the literature on the difficulty in preparing amino-substituted azoxybenzenes[82,83] and indeed numerous attempts at synthesising these were largely unsuccessful.



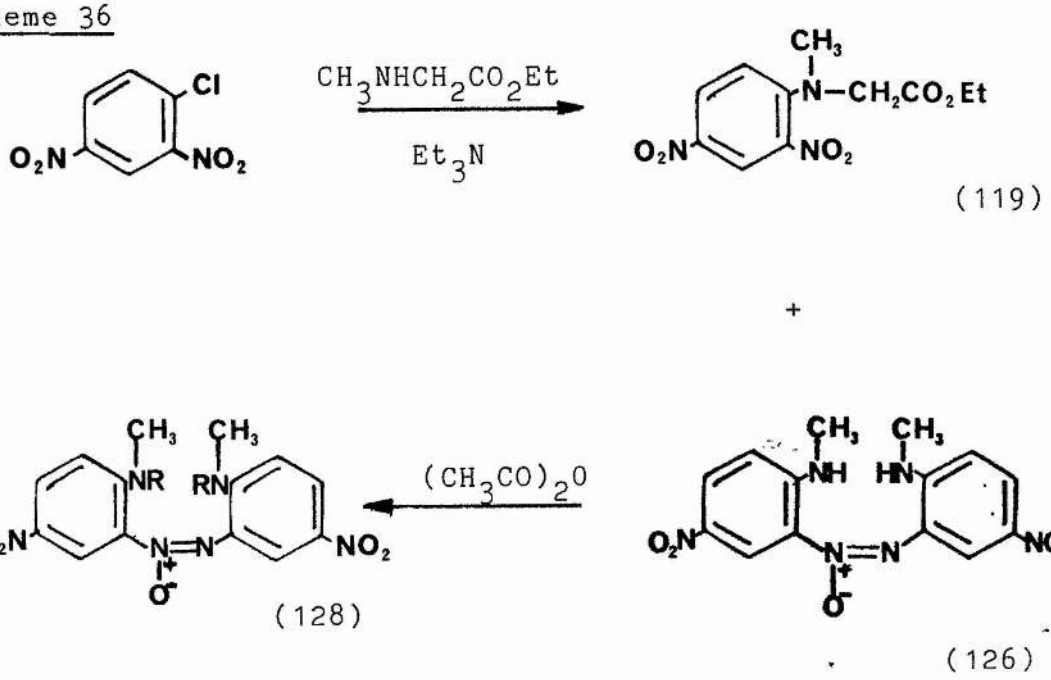
(125a)



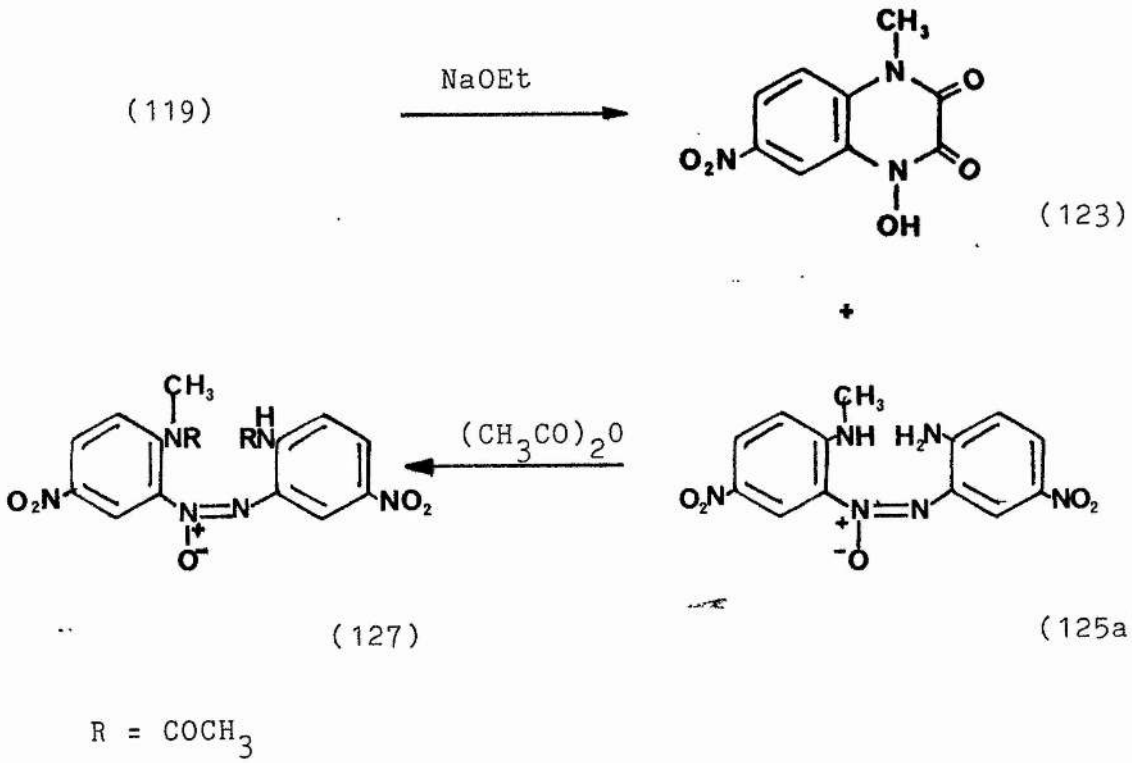
(125b)

An additional complication arose at this time. When the direct synthesis of N-(2,4-dinitrophenyl)sarcosine ethyl ester (119) from chloro-2,4-dinitrobenzene and sarcosine ethyl ester was attempted, in a similar manner to the displacement reactions described in Chapter III using 2-chloro-3,5-dinitropyridine, a red material precipitated from the reaction solution. All the experimental evidence suggested that this material was also an azoxy compound, and in fact appeared to be the N-methyl analogue (126) of (125). These compounds (125) and (126) could not be obtained in suitable form for single crystal X-ray analysis; however the acetylated derivative of (125) crystallised in a form which led to the confirmation of an azoxybenzene structure. The overall reaction sequences for the attempted direct preparation of N-(2,4-dinitrophenyl)sarcosine ethyl ester (119), its reaction with sodium ethoxide, and the acetylation of the azoxy compounds (125) and (126), can be seen in Schemes 36 and 37. The crystal structures and related data can again

Scheme 36



Scheme 37



be found at the end of this Thesis.

In view of the unexpected products obtained in some of these experiments, further reactions of the sarcosine ethyl ester (119), and the methyl ester (120), in the presence of other bases were investigated. The results of this research are collected in Table 4.

As expected, the bis-methylamino azoxy compound (126), obtained from the reaction of chloro-2,4-dinitrobenzene with sarcosine ethyl ester in the presence of triethylamine, was also obtained when the dinitrophenylsarcosine ester (119) when treated with triethylamine. In both cases the quantity of azoxy compound increased when the amount of base used was increased.

The highest yield of quinoxalinedione (123) was found when potassium carbonate was employed as base but in this reaction the yield of the methylamino azoxy compound (125) was considerably less than in the alkoxide reactions. N-(2,4-Dinitrophenyl)sarcosine methyl ester (120) behaved similarly to the ethyl ester (119) in the presence of alkoxide. In reactions involving DBU as base, no azoxy compound was isolated although the presence of the methylamino azoxybenzene derivative (125) was inferred from t.l.c.

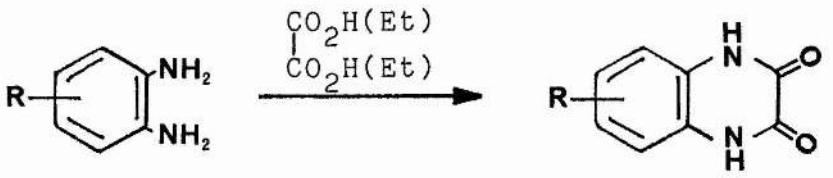
From the results in Table 4 it can be seen that the total recovery in these reactions seldom exceeded 50%. Indeed t.l.c. showed that the reactions were quite complex and many attempts were made, albeit unsuccessfully, to separate the mixtures. Experiments designed to identify other possible products and potential intermediates in these

Table 4 Reactions of N-(2,4-Dinitrophenyl)sarcosine Esters with Bases

Sarcosine Ester (mmol)	Base (mmol)	Solvent	Temperature	Reaction Time (h)	Yield of (125)(%)	Yield of (126)(%)	Yield of (123)(%)
(119) (7.1)	NaOEt (7.1)	ethanol-DMF	room temperature	3	32	-	19
(119) (3.5)	NaOEt (3.5)	ethanol	"	1	20	-	14
(119) (7.1)	K_2CO_3 (7.1)	ethanol-DMF	"	4	4	-	35
(119)(10.6)	Et_3N (10.6)	ethanol	reflux	4	-	7	1
(119) (7.1)	Et_3N (14.2)	ethanol	reflux	4	-	16	-
(119) (7.1)	DBU (7.1)	ethanol-DMF	room temperature	1	indicated by t.l.c.	-	23
(119) (7.1)	DBU (7.1)	DMSO	"	3	indicated by t.l.c.	-	33
(120) (3.7)	NaOMe(3.7)	methanol-DMF	"	3	19	-	21

reactions are discussed later in this Chapter.

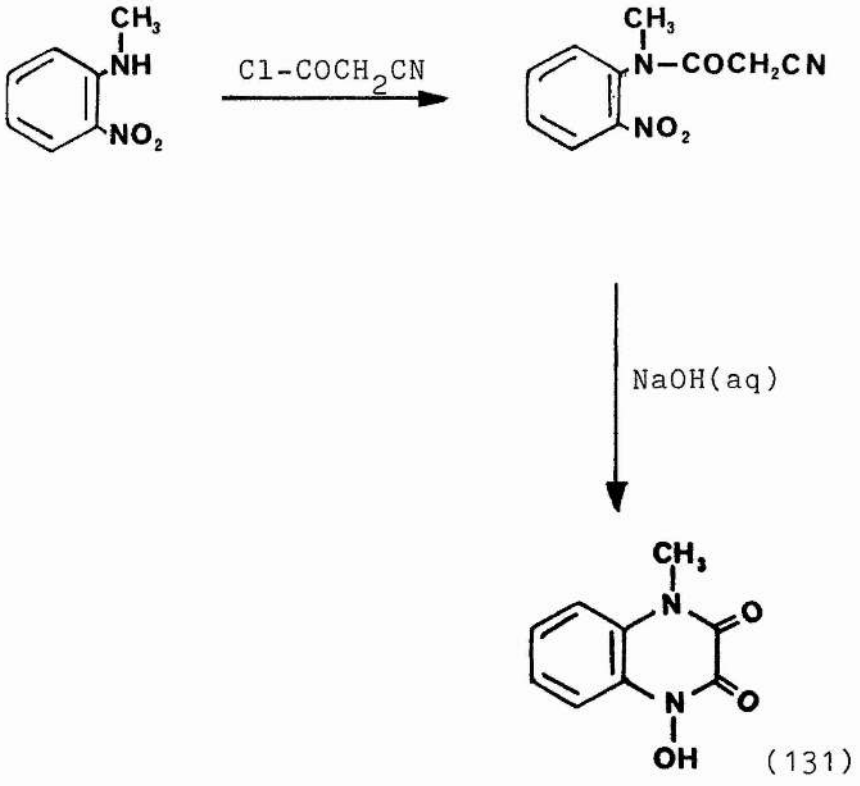
Quinoxaline-2,3-diones (129) are most commonly prepared from the relevant o-phenylenediamine (130) and either oxalic acid dihydrate or diethyl oxalate[84].



(130) (129)

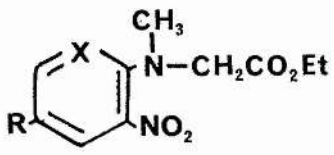
They find uses in a variety of areas including pigments, polymers and veterinary medicines[84]. 6-Nitroquinoxaline-2,3-dione (129) (R = 6-NO_2) possesses insecticidal properties. Although 1-hydroxy-4-methylquinoxaline-2,3-dione (131) is known[85] (prepared according to Scheme 38) no ring substituted derivatives of (131) have been found in the literature. Little is known about quinoxalinediones substituted at both nitrogen atoms and since the quinoxaline-dione (123), prepared from the ester (119), is apparently novel it was decided to investigate the scope of this reaction.

Scheme 38



(131)

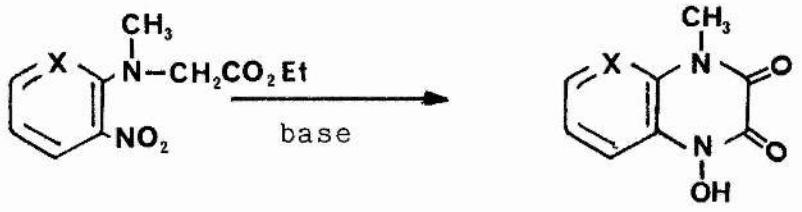
Thus, compounds (132-134) were prepared either directly from the relevant halogenonitroaromatic or via the acid, and their reactions in the presence of base were studied.



(132) R=H, X=CH
(133) R=H, X=N
(134) R=NO_2, X=N

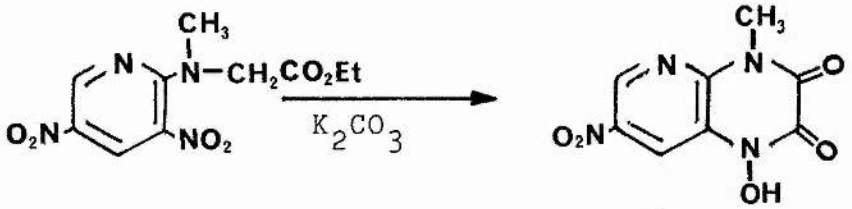
Compounds (132) and (133) behaved similarly giving 1-hydroxy-4-methylquinoxaline-2,3-dione (131) and 1-hydroxy-4-methylpyrido[2,3-b]pyrazine-2,3-dione (135) respectively. In neither case was an azoxy compound isolated. It may be in these examples that the azoxy compounds, if formed, were more soluble in the reaction medium than the azoxy derivatives previously discussed. T.l.c. of the mother-liquor, in both cases, showed a characteristic spotting pattern with a bright orange spot evident just behind (slightly more polar than) unreacted starting material.

The dinitropyridyl compound (134) reacted in the presence of potassium carbonate or sodium ethoxide to give the expected pyridopyrazinedione (136) together with, in the former case, 2,2'-bis(methylamino)-5,5'-dinitro-3,3'-azoxypyridine (137). The isolation here of the bis-methylamino azoxy compound (137) is in direct contrast to the findings in the related benzene series, where the reaction of N-(2,4-dinitrophenyl)sarcosine ethyl ester (119) with potassium carbonate gave the methylamino azoxybenzene (125). However, the yield of azoxypyridine was very low (2%), to the extent that the product was only isolated at all in one experiment.



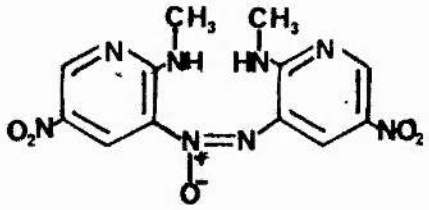
(132) X=CH
(133) X=N

(131) X=CH
(135) X=N



(134)

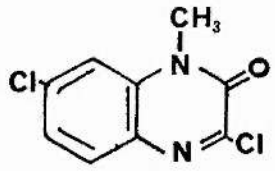
(136)



(137)

When 1-hydroxy-4-methylquinoxaline-2,3-dione (131) was treated with thionyl chloride, in a similar manner to the reaction of the 7-nitro derivative (123) with this reagent, chlorination occurred to give (138) as the major product.

(131)

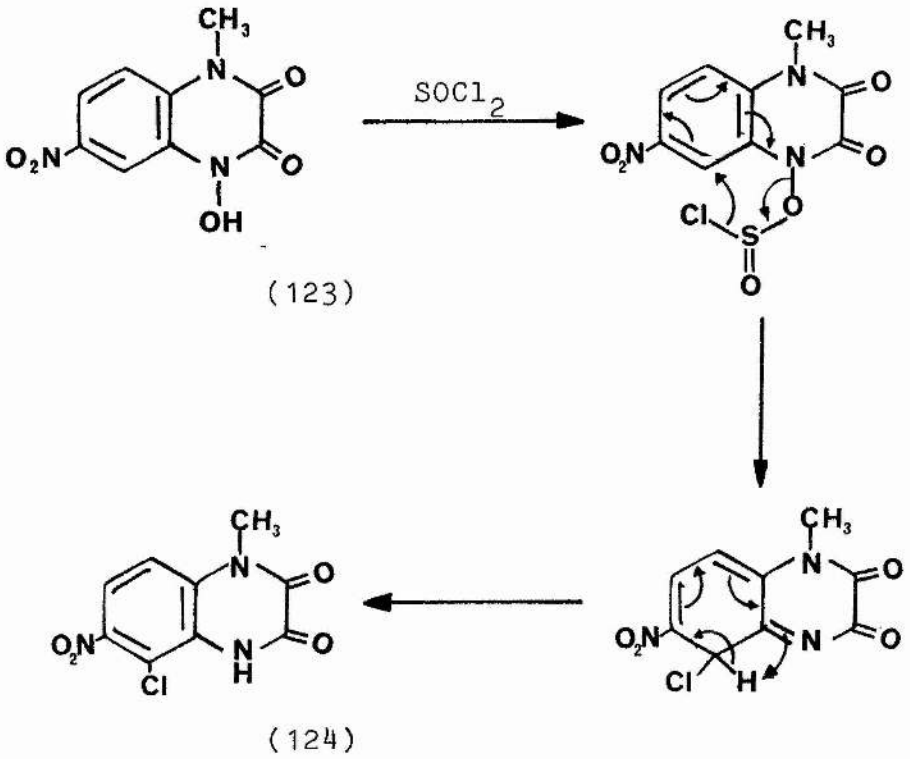


(138)

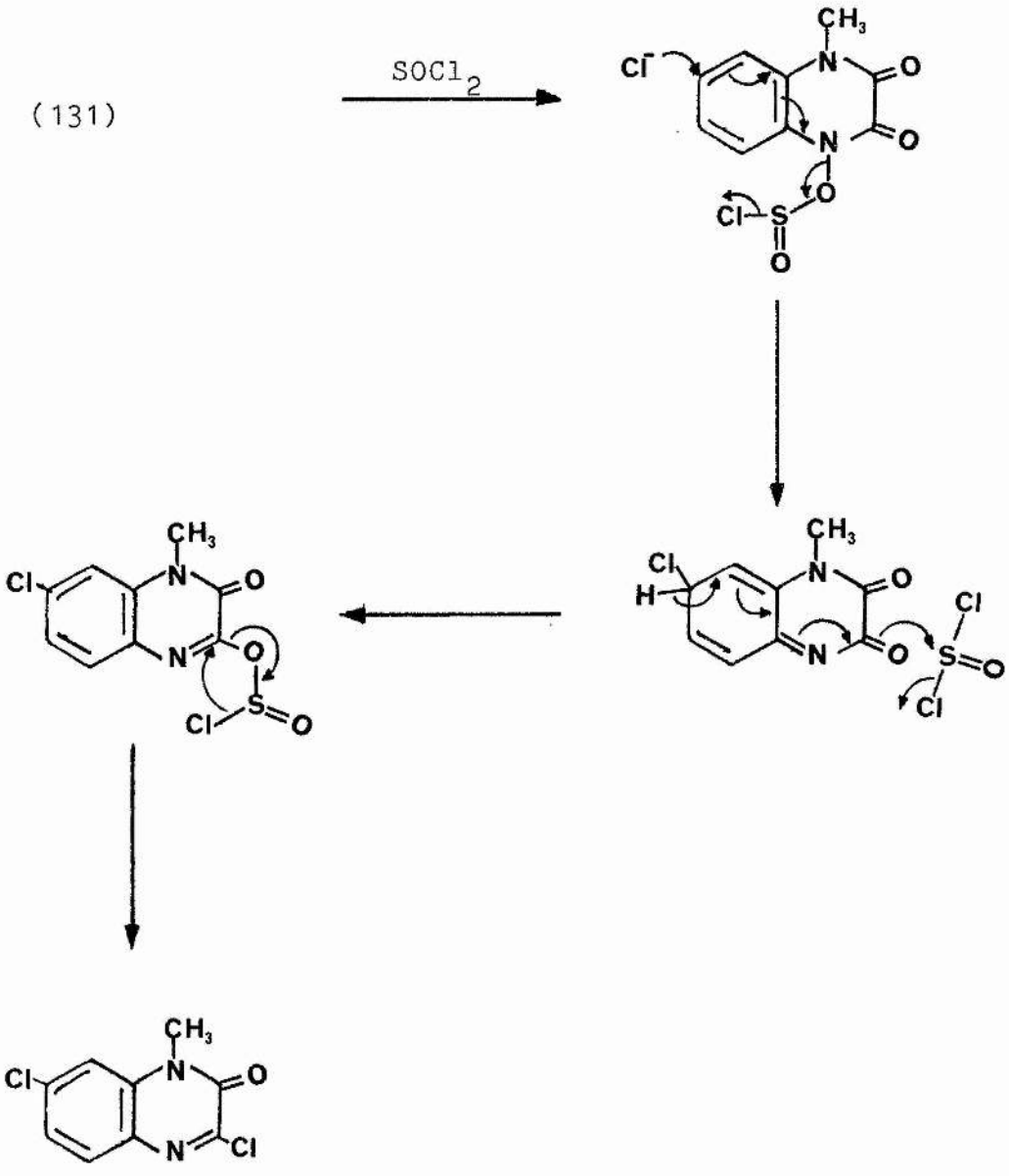
It would appear therefore that two distinct mechanisms for chlorination may operate in this system. In the case of the nitroquinoxalinedione (123) the possibility of an intramolecular mechanism exists (Scheme 39). In the

unnitrated heterocycle (131) chlorination occurs at the 6-position by a process which cannot be intramolecular. A possible mechanism for this reaction is outlined in Scheme 40.

Scheme 39



Scheme 40



In summary, o-nitrophenyl (or pyridyl)sarcosine esters are cyclised in the presence of base to N-hydroxyquinoxalinediones (or hydroxypyridopyrazinediones) instead of the expected fused imidazole N-oxides. The formation of azoxy compounds in some of these reactions is also unusual [no reference has been made in the literature to the isolation or detection of azoxy compounds in the reactions of N-(activated alkyl)-o-nitroanilines with bases]. The only structural difference between the N,N-dialkyl compounds described in this Chapter and the cyclisation substrates in Chapters II and III is that the amino nitrogen is tertiary rather than secondary.

DISCUSSION

Formation of the fused pyrazinediones

It was stated earlier (p.20) that the most commonly accepted mechanism for the formation of benzimidazole N-oxides in basic media involved attack on the nitro-nitrogen by the adjacent carbanion in the amino side-chain, followed by dehydration. In this mechanism the amino proton only becomes significant after cyclisation, when deprotonation in base can occur.

In order to rationalise the formation of the heterocyclic diones described in this Chapter the following possibilities must be considered:-

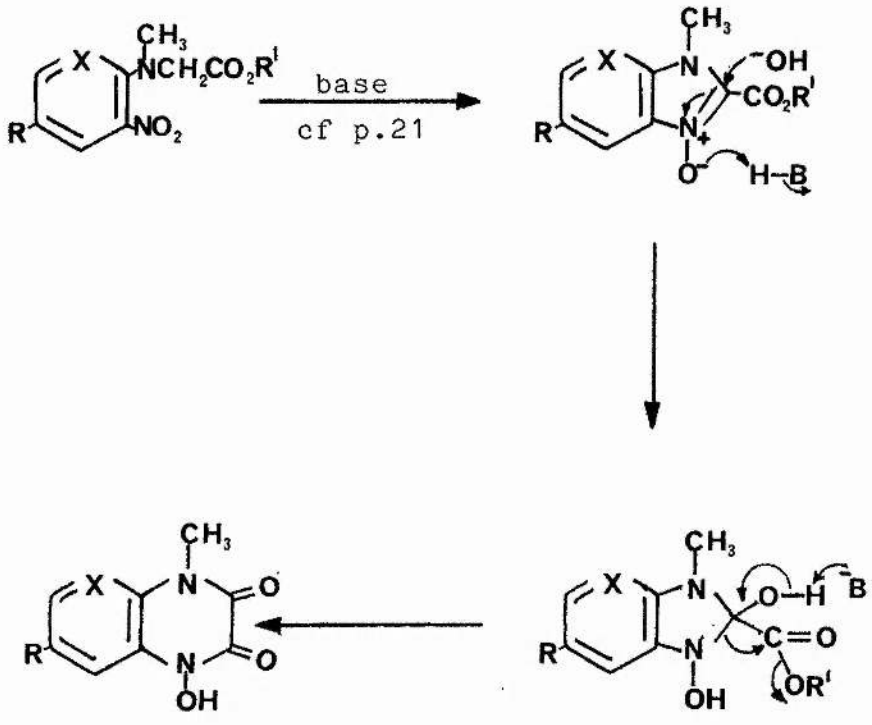
(i) The o-aminonitro compounds firstly cyclise by conventional means to give fused imidazole N-oxides, which then react further by ring-opening and recyclisation;

(ii) an entirely different mechanism operates when the amino nitrogen is tertiary;

(iii) a different mechanism to the aldol-type initially operates whether the amino nitrogen is secondary or tertiary, and then diverges depending upon the degree of substitution.

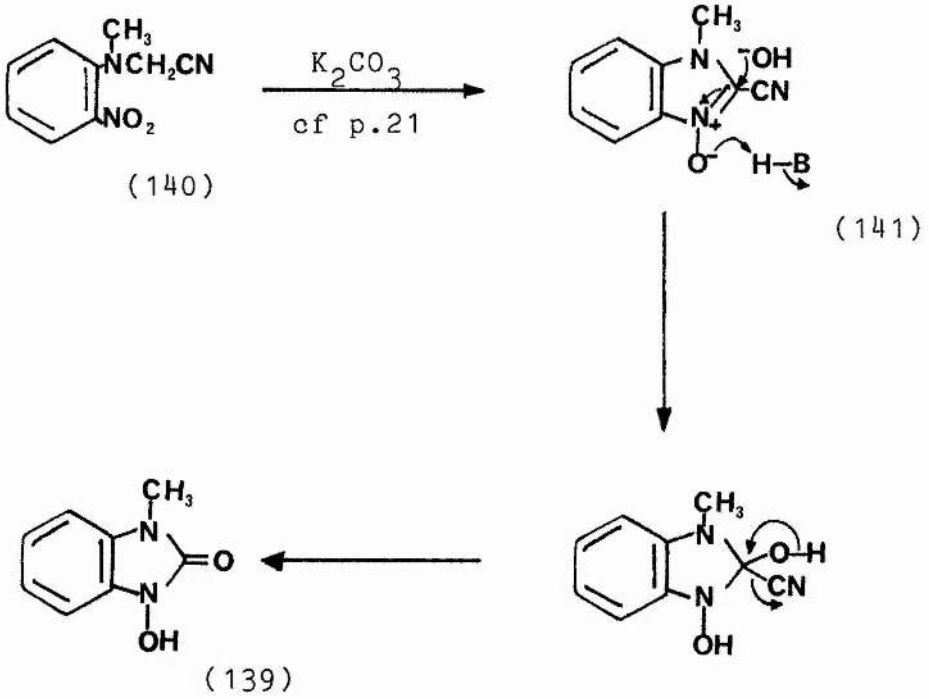
In case (i) a mechanism can be drawn which involves the intermediacy of a fused imidazole N-oxide (Scheme 41).

Scheme 41



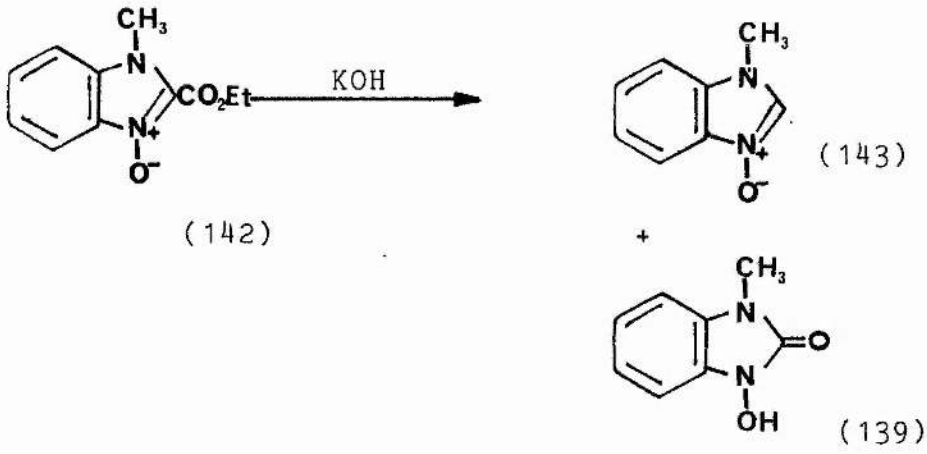
A similar mechanism can be formulated for the synthesis of 1-hydroxy-3-methylbenzimidazolone (139) from the nitrile (140) (see p.81), and indeed this mechanism has been suggested by Livingstone and Tennant[81] (Scheme 42).

Scheme 42



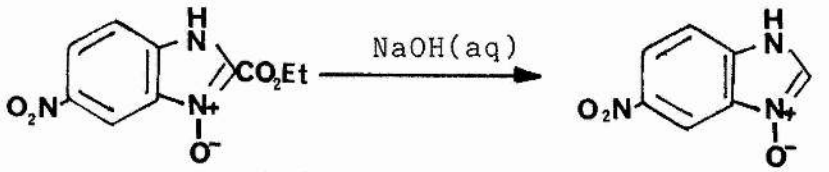
These authors' suggestion that the N-oxide (141) is an intermediate in the conversion of (140) to (139) is supported by the fact that the N-oxide (141) is known to react in the manner indicated [(141)→(139)] when treated with base[24].

Although these mechanisms are attractive and initially convincing, a number of flaws are apparent. Ethyl 1-methyl-benzimidazole-2-carboxylate 3-oxide (142) has been prepared and is known to react with potassium hydroxide to give a mixture of the N-oxide (143) and the benzimidazolone (139)[24].

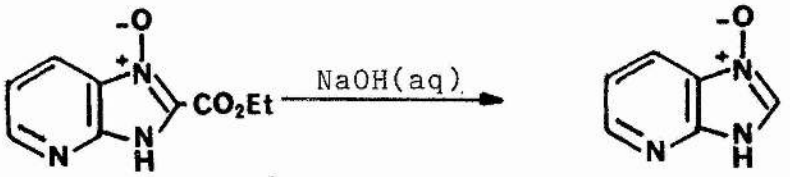


If the formation of the fused pyrazinediones is to be rationalised by the reaction of an intermediate N-oxide with base then it is surprising that no fused pyrazinedione was found in the above reaction.

In addition, the reactions of the esters (45) and (103) in basic media have already been shown to give the 2-unsubstituted fused imidazole N-oxides (19) and (105) (p.86 and 76); no other products were detected in either of these reactions although it is realised here that both starting materials and products are acidic, and that deprotonation and hence stabilisation in base may occur.



(45) (19)



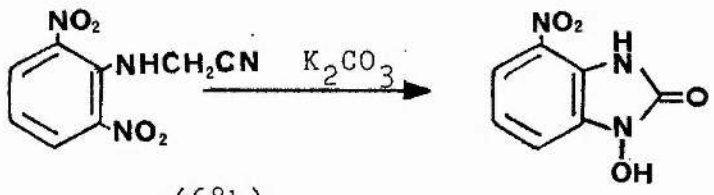
(103) (105)

Although the conversion of 2-cyano-1-methylbenzimidazole N-oxide (141) to the N-hydroxybenzimidazolone (139) is known this does not imply that the N-oxide must be an intermediate in the preparation of (139) from (140). The latter conversion was re-investigated in greater detail to see if any cyano-N-oxide (141) (or for that matter any azoxy compound) could be detected. No reaction occurred at room temperature, and only the reported product (139) was isolated when the reactants were heated under reflux.

Research initially designed with a view to preparing 7-amino-1H-benzimidazole 3-oxide (15d) (p.49) gave the first evidence to support the theory that a different mechanism may operate in some of the reactions discussed here, and that the substitution on the amino nitrogen is extremely

important. In Chapter II it was noted that N-(2,6-dinitrophenyl)glycine ethyl ester (68a) and the related nitrile (68b) were not cyclised in base to give the expected 7-nitro benzimidazole N-oxides. At that time difficulty was encountered in the identification of the reaction products; however, the reactions described in this Chapter have given an insight into the nature of these materials.

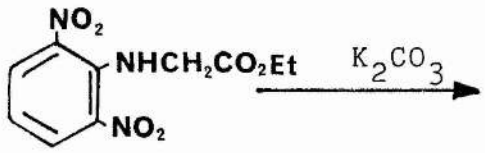
When the nitrile (68b) was treated with potassium carbonate, a thick brown precipitate formed. Dissolution of this solid in water followed by acidification gave a product which showed a peak in the ^{13}C n.m.r.spectrum at 151.5 p.p.m. (well downfield). The ^{13}C n.m.r. spectrum for 1-hydroxy-3-methylbenzimidazolone (139), also shows a peak at 151.6 p.p.m. which is also quite well separated from the rest of the spectrum. Analytical and other spectroscopic data provide strong evidence that the product in this reaction is also a benzimidazolone (144).



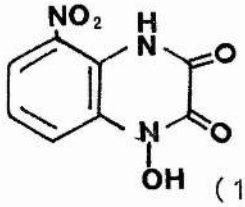
(68b) (144)

The reaction of the dinitro-ester (68a) with base was more complicated. In the presence of potassium carbonate, a complex mixture resulted (at least seven components) and

the only pure product isolated was the quinoxalinedione (145). In the mass spectrum of the crude reaction mixture, a peak at $M^{+\cdot}$ 318 was observed, the accurate mass of which corresponded well to the formula $C_{12}H_{10}N_6O_5$. On the basis of this accurate mass it does not seem improbable that 2,2'-diamino-3,3'-dinitroazoxybenzene (146) is a component of this mixture.

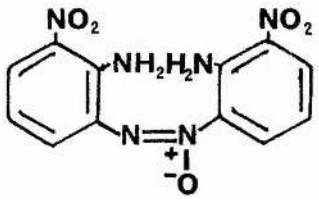


(68a)



(145)

+

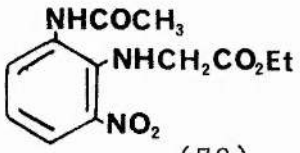


(146)

In both cases then, no benzimidazole N-oxides were isolated or detected. It seems unlikely that their absence is purely an isolation problem since the N-oxides, even in small amounts, would be expected to be insoluble in weakly acidic media (see experimental for work-up).

Thus the examples so far described in which deviation from the 'normal' cyclisation pathway (leading to benzimidazole N-oxide formation) has occurred either involve cases where the amine is tertiary, or is secondary and has an adjacent nitro group.

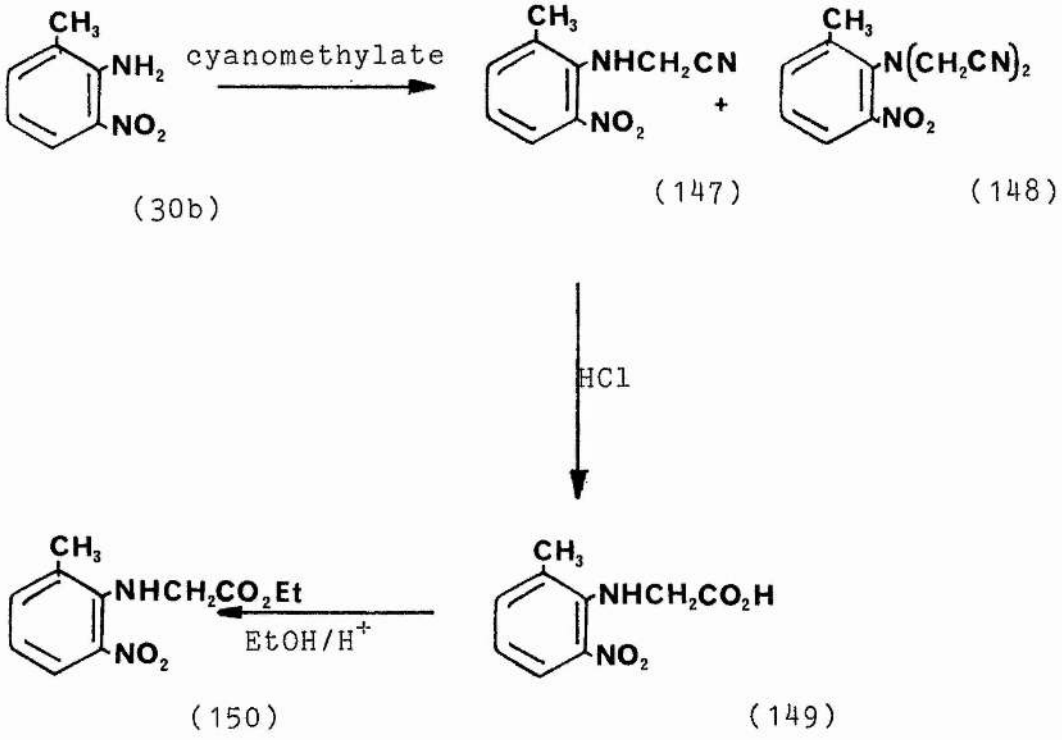
A further complication must be resolved before any viable mechanistic suggestions can be put forward. In Chapter II (p.50) it was revealed that the acetamido-compound (70) cyclised in base to the N-oxide.



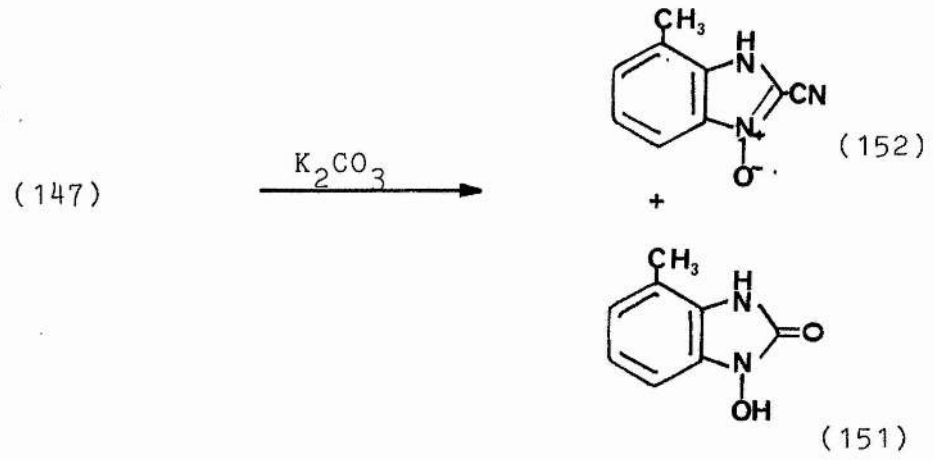
(70)

It is therefore unclear at this stage why this compound (70) should cyclise 'normally' and yet the dinitrophenyl-glycine derivatives do not. If there is an interaction between the amino proton and a neighbouring substituent then the question arises whether this interaction, and consequently the product obtained, is due to steric, electronic or hydrogen bonding effects. In order to help elucidate this problem the preparation of compounds (147) and (150) was undertaken as indicated in Scheme 43.

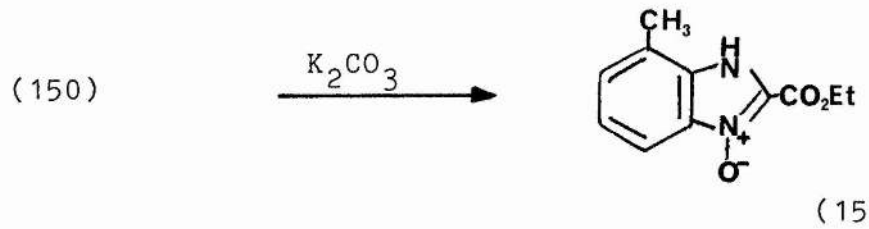
Scheme 43



The reaction of the nitrile (147) with potassium carbonate proved extremely interesting. A mixture of 1-hydroxy-4-methylbenzimidazolone (151) and 2-cyano-7-methyl-1H-benzimidazole 3-oxide (152) was obtained when the reaction time was 2 hours. When the time was increased to 6 hours, or when an additional molar equivalent of base was added, there was no increase in the proportion of benzimidazolone (151). This is an important reaction since it shows that a benzimidazolone can be formed in this type of reaction apparently without the requirement of the 2-cyanobenzimidazole N-oxide (152) as precursor (cf p.99).



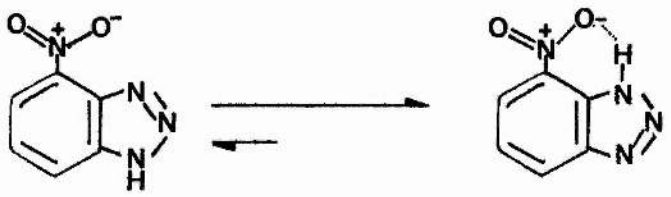
In the reaction of the ester (150) with potassium carbonate no quinoxalinedione was obtained, the N-oxide (153) being the sole product isolated.



It would seem therefore from these results that some form of interaction does indeed take place between the amino hydrogen in the activated side-chain and a neighbouring group, and the extent of the interaction depends upon the nature of the substituent. The very fact that any deviation at all occurs in the pathways taken in these reactions again draws attention to and casts doubt on, the conventional mechanism proposed for the synthesis of benzimidazole N-oxides (in which such interaction would not

be expected to alter the course followed).

In the case of the nitro compounds (68a) and (68b) no benzimidazole N-oxide is isolated and it would therefore appear that the amino hydrogen is either strongly hydrogen-bonded to the nitro oxygen or is inaccessible to some reagent for steric reasons and cannot participate in a pathway which leads to N-oxide formation. This type of interaction has been noted in the related benzotriazole series where chelation restricts tautomerism in favour of (154b) and thus prevents withdrawal or involvement of the hydrogen atom in any further reactions[86].



(154a) (154b)

If this argument is to be maintained then in the acetamido compound (70) the geometry of the carbonyl group must be such that it lies away from the ortho amine. In addition any hydrogen-bonding relationship would involve a 7-membered ring which may not be favourable.

The methyl derivative (150) seems to represent an intermediate situation and although the amount of benzimidazolone (151) formed is small it is significant that it does not appear to result from the reaction of the 2-cyano N-oxide (152).

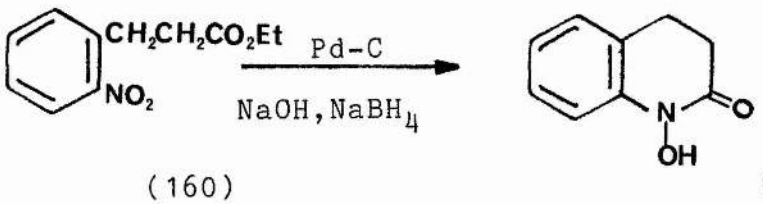
The preceding section demonstrates the importance of an accessible hydrogen atom for successful 'normal' cyclisation (leading to benzimidazole N-oxide formation). Although it is possible that the reactions described here follow completely different mechanistic pathways the possibility that they may initially follow a similar route is an attractive theory.

A number of mechanistic possibilities are considered in Schemes 44 and 45. Pathways (a) and (b) both lead to a common intermediate which, as will be seen, may react in a number of different ways. Pathway (a) involves deprotonation of the activated methylene group in (155) to form a carbanion which attacks the nitro oxygen to give an oxadiazine (156). Nucleophilic attack on nitro oxygen has ample literature precedent. Organolithium compounds and alkyl phosphites have been used to effect the reduction of aromatic nitro compounds to nitroso compounds and in both cases attack at the nitro oxygen has been proposed[87]. Fielden, Meth-Cohn, and Suschitzky have also postulated this type of interaction to explain the acid-catalysed rearrangement of N,N-(dialkyl)-o-nitroanilines (157) (Scheme 46a)[79].

These researchers have also formulated a mechanism similar to steps (bi), (di),(cii) (Scheme 44) to account for the preparation of benzimidazole N-oxides in acidic conditions[79], (Scheme 46b).

The oxadiazine (156) is considered an important intermediate. In cases where the amino group is secondary

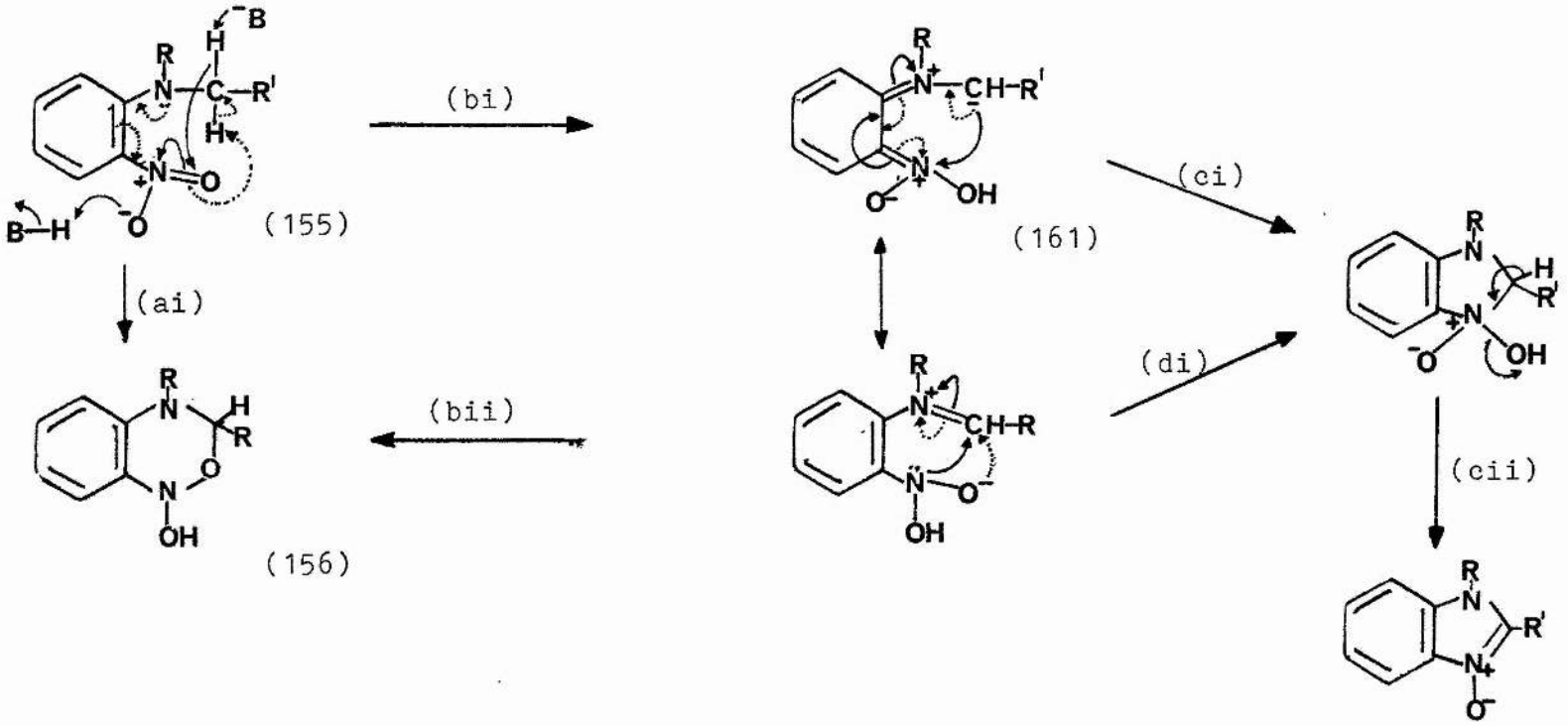
proton abstraction by base could lead to an o-nitrosoanil (ei) which then cyclises to give the N-oxide (eii) (Scheme 45). (cfp.15). Where no amino hydrogen is present [e.g. where R = CH_3 in (156)] or where the proton is inaccessible to base [as in N-(2,6-dinitrophenyl)glycine derivatives] then it is the methylene hydrogen which may be removed to give an amido-ester or amido-nitrile(158)(aii). Thus, an intramolecular redox process may take place in which the alkyl side-chain is oxidised and the nitro group is reduced to the hydroxylamine stage. In the case of the nitriles the hydroxylamino nitrogen may then attack the amidic carbonyl with the resultant expulsion of hydrogen cyanide (aiv). Where R' = CO_2Et attack at the more electrophilic carbonyl group occurs and a molecule of ethanol is lost to form a six-membered ring (aiii). A similar type of reaction has been reported for the preparation of the quinoline (159) by the reductive cyclisation of the nitro-ester (160)[88]; a reaction which presumably involves reduction of the nitro group followed by cyclisation as described above.



(160) (159)

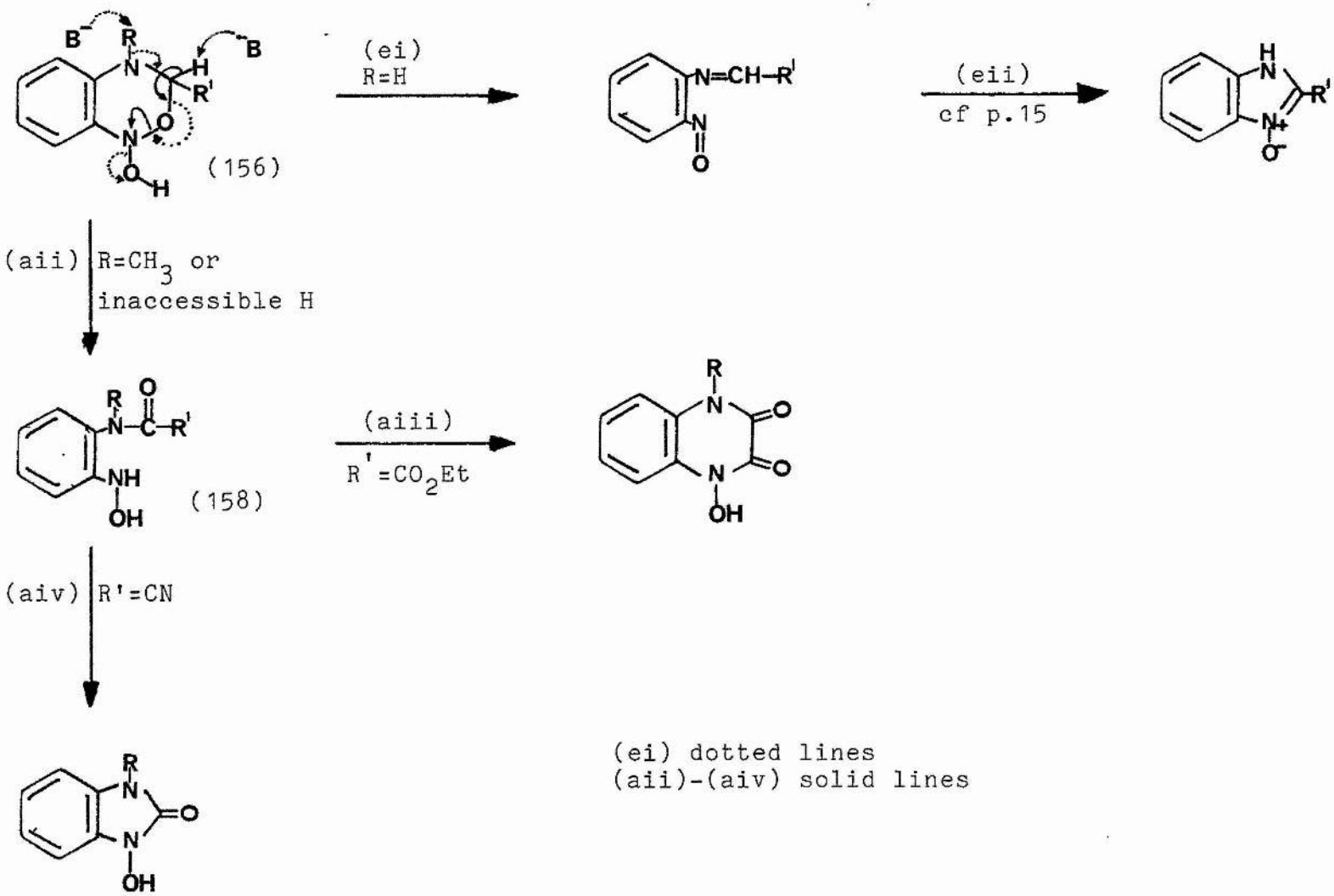
Of the two pathways (a) and (b) (Scheme 44) which lead to oxadiazine formation, (a) is preferred since there are several possible mechanistic diversions along the other

Scheme 44



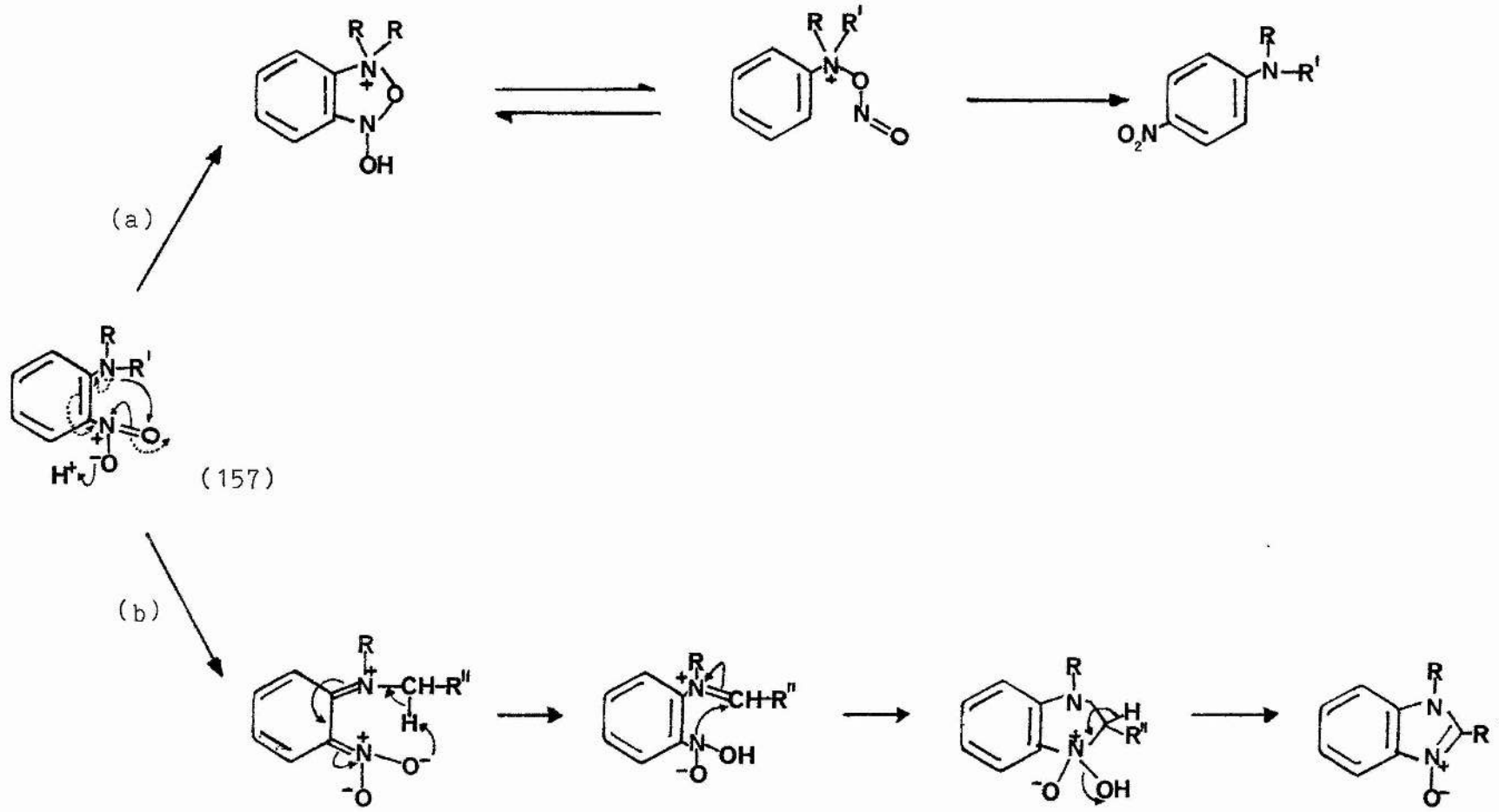
(ai) solid lines
(bi)(bii) dotted lines

Scheme 45



(ei) dotted lines
(aii)-(aiv) solid lines

Scheme 46



route. Thus, the aci-nitro structure (161) has the potential to cyclise (ci) or (di) and dehydrate (cii). In this case it is unclear why such a pathway would not be followed irrespective of whether R = H or R ≠ H.

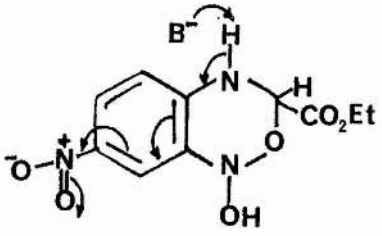
Thus, the oxadiazine (156) is regarded as a versatile intermediate from which all of the observed products may be derived. As will be seen later, it may even be involved in the formation of the azoxy compounds which are found as co-products in some of these reactions.

If this mechanism is to be considered in preference to the conventional aldol-type condensation reaction for the preparation of the 5-membered N-oxides then it must also account for any observed trends encountered. For example, it was noted in Chapter II (p.41) that the cyclisation of N-(activated alkyl)-o-nitroanilines could be facilitated by the introduction of electron-withdrawing groups in the six-membered ring and suppressed in certain cases by the introduction of electron-donating groups ortho or para to the nitro group. The effect of these substituents, as was suggested, is to increase or decrease the electrophilicity of the nitro group and thus alter its susceptibility to attack by the adjacent carbanion. At that time, these explanations were based on the 'normal' cyclisation mechanism.

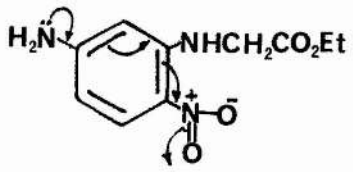
The ring-substituent theory still holds if the alternative mechanisms outlined in Schemes 44 and 45 are applied. Thus, in cases where an additional nitro group

is present meta to the existing nitro group, and cyclisation is facilitated, the acidity of the amino hydrogen in the oxadiazine (162) is increased by the para-nitro group and it is therefore more readily removed by base. Conversely, where an electron-donating substituent is para to the nitro-group, as in (51), then cyclisation fails since the electrophilic character of the nitro-group is considerably decreased.

e.g.

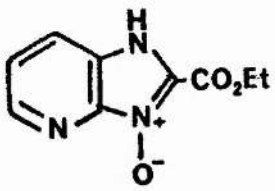


(162)

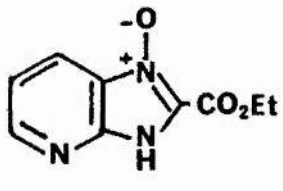


(51)

Two outstanding points, involving the isomeric imidazopyridine esters (89) and (103), can also be re-considered in view of the findings in this Chapter.



(89)

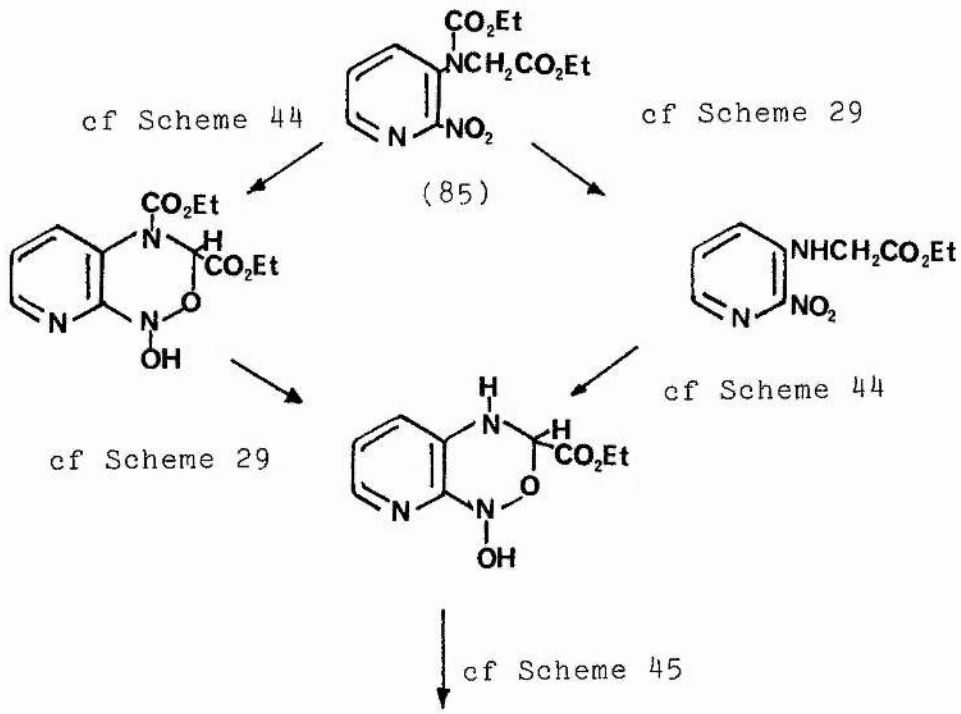


(103)

In Chapter III, the 3-oxide (89) was obtained from the reaction of the diester (85) with sodium ethoxide and its formation was rationalised in the conventional manner (see P.66). The alternative mechanism currently discussed

may also explain its formation, with loss of the carbamate ester function possible before or after oxadiazine formation.

Scheme 47



(89)

In Chapter II a route to 2-unsubstituted benzimidazole N-oxides was described and the method was applied to the synthesis of aminobenzimidazole N-oxides. In an attempt to further expand the scope of the method, the acid hydrolysis of the imidazopyridine ester (103) was investigated. The major product from this reaction initially proved difficult to identify. However, when both the ^{1}H and ^{13}C n.m.r. spectra of this material were compared with the corresponding spectra of 1-hydroxy-4-methylpyrido[2,3-b]pyrazine-2,3-dione (135) a marked similarity was evident (see Table 5 and

experimental). All the available evidence therefore appeared to be consistent with a pyridopyrazinedione structure (163).

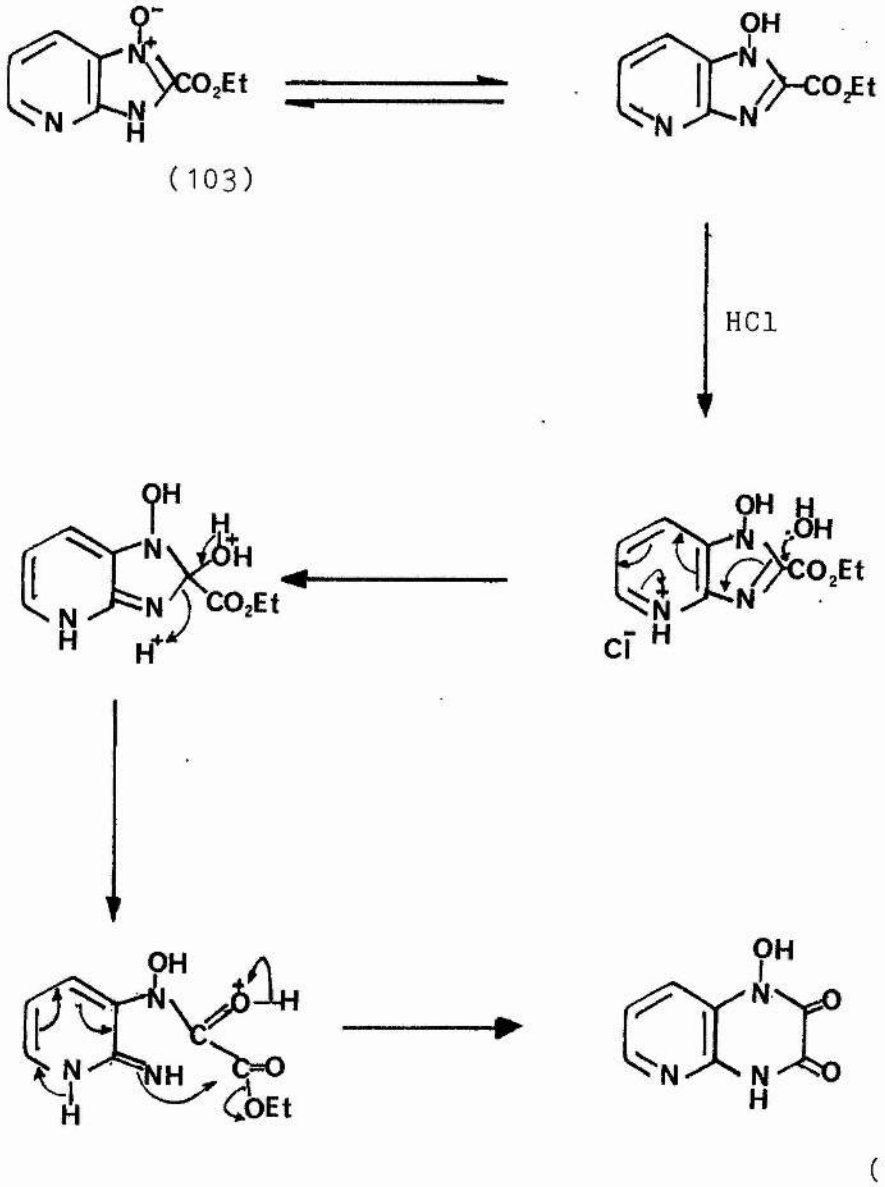
(103) $\xrightarrow{HCl}$ 

(163)

A possible mechanism for the formation of (163) is outlined in Scheme 48. The ability of the pyridine nitrogen to protonate and thus facilitate the transformation of the ester (103) to the pyridopyrazinedione (163) may explain why this sort of reaction is not observed in the corresponding benzene series.

The application of ^{13}C n.m.r. spectroscopy in helping to solve the previous problem illustrates the usefulness of this technique in identifying the fused pyrazinediones described in this Chapter. As can be seen in Table 5 the chemical shift values corresponding to the carbonyl groups are very characteristic.

Scheme 48



(103)

(163)

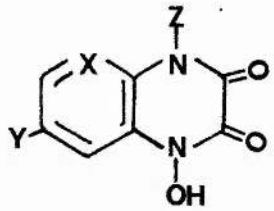


Table 5 ^{13}C n.m.r.spectra of 1-Hydroxyquinoxaline- and -pyrido [2,3-b]pyrazine-2,3-diones

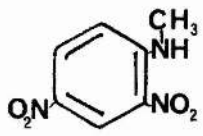
X	Y	Z	Compound	^{13}C chemical shifts (ppm) in $(CD)_3SO$								
				2	3	4a	5	6	7	8	8a	CH_3
CH	7-NO_2	CH_3	(123)	155.2	150.1	130.8	115.8	119.2	142.7	107.8	127.9	30.6
CH	H	CH_3	(131)	154.0	150.2	125.3	114.9	124.2*	123.8*	112.3	127.3	39.9
CH	5-NO_2	H	(145)	154.1	150.5	119.2	134.5	118.9*	122.9	120.3*	129.7	-
N	7-NO_2	CH_3	(136)	155.8	149.8	140.1	N	137.9	141.6	114.4	124.4	29.2
N	H	CH_3	(135)	155.7	149.9	137.2	N	142.3	120.3	119.3	124.0	28.4
N	H	H	(163)	155.4	151.2	136.7	N	142.8	120.3	119.0	123.7	-

* Provisional assignments.

Formation of the Azoxy Compounds

Aromatic nitro compounds can be reduced to azoxy compounds in a variety of ways. Common reducing agents include sodium arsenite[82], zinc and ammonium chloride[89], alkali hydroxides[90] and alkoxides[83].

In the course of this work three different aromatic azoxy compounds have been isolated, two derived from N-(2,4-dinitrophenyl)sarcosine ethyl ester (119) and one from the related dinitropyridylsarcosine ester (134). In the former case the azoxy derivative obtained appears to be dependent on the base used, triethylamine being the only base to give solely 2,2'-bis(methylamino)-5,5'-dinitroazoxybenzene (126). If the formation of these compounds is to be rationalised by a conventional mechanism[90] then the fate of the amino side-chain and of the 'lost' methyl group must be determined. N-Methyl-2,4-dinitroaniline (164) (prepared from chloro-2,4-dinitrobenzene and methylamine) was initially considered to be a possible precursor to the azoxybenzenes (125) and (126), although the loss of the side-chain and the methyl group, either before or after azoxy formation, is not easily explained. This compound (164), however, failed to react with sodium ethoxide and indeed also failed to give an azoxy compound on attempted reduction by the literature methods. There was also no evidence of demethylation in these reactions.



e.g. NaOEt, or KOH, or Na_3AsO_3 → no azoxy compound detected

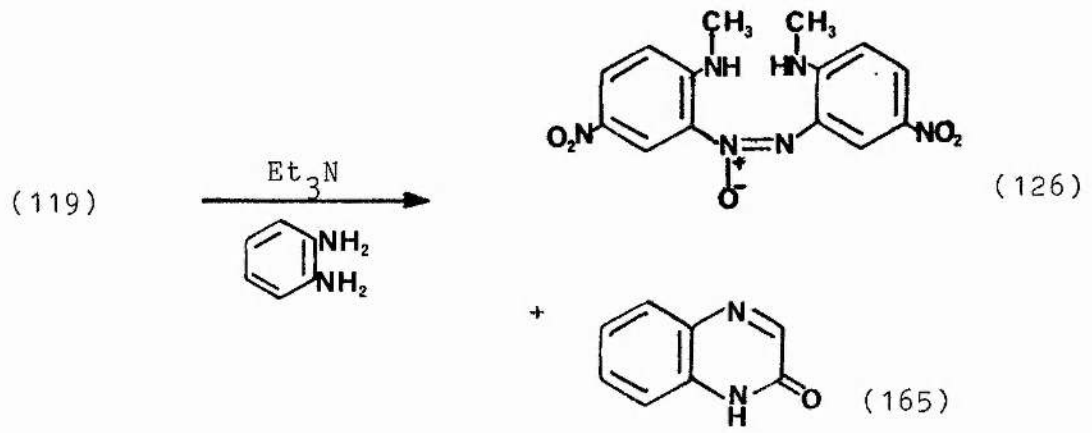
(164)

An alternative possibility for the demethylation may involve direct loss from the bis-methylamino azoxybenzene (126). However, when this compound was treated with sodium ethoxide no reaction was observed.

A further point which seems to cast doubt on a conventional mechanism for azoxy group formation is that if the methylamino compound (125) is to result from the reaction of N-methyl-2,4-dinitroaniline and 2,4-dinitroaniline (or reduced forms of these) then it is surprising that only one product is obtained i.e. (125). A number of possible combinations are feasible.

$$ArNO_2 + Ar'NO_2 \xrightarrow{\text{reduction}} ArN{=}\overset{+}{N}(O^-)\text{-}Ar + Ar'N{=}\overset{+}{N}(O^-)\text{-}Ar' + Ar\overset{\cdot}{N}{=}\overset{+}{N}(O^-)\text{-}Ar + Ar'\overset{+}{N}(O^-){=}N\text{-}Ar$$

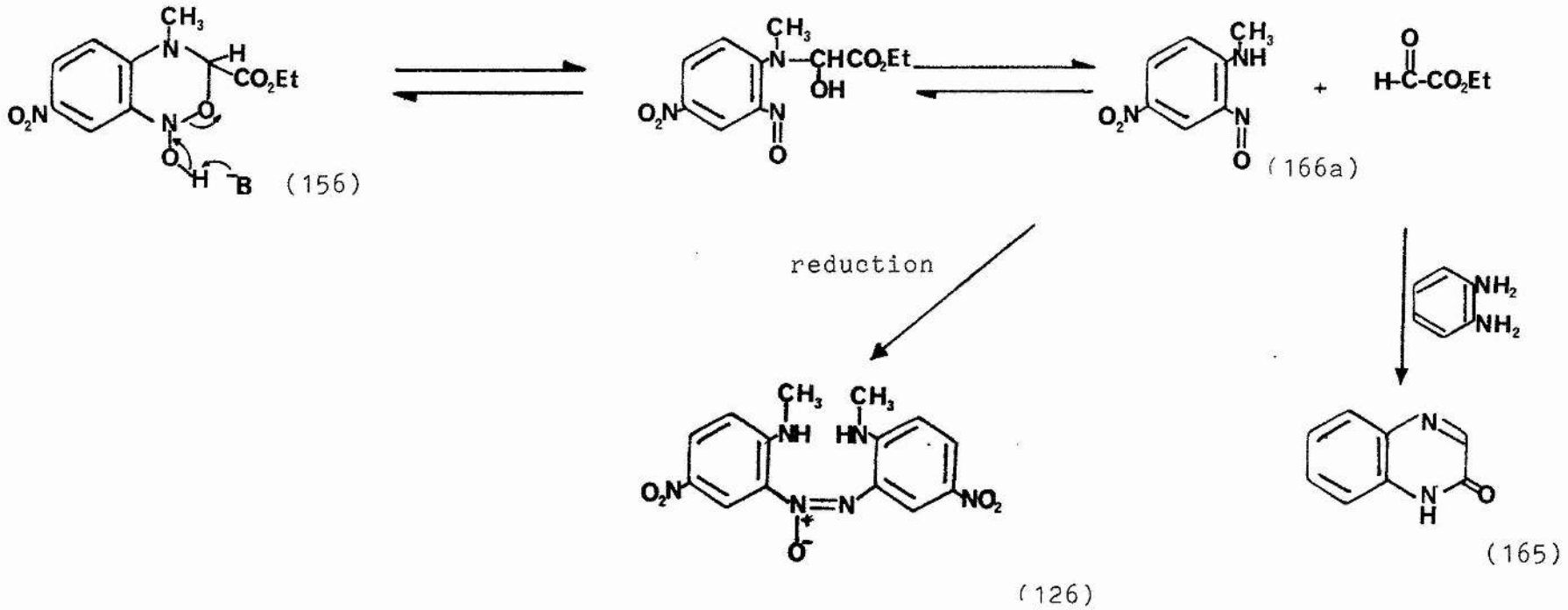
When the reaction of N-(2,4-dinitrophenyl) sarcosine ethyl ester (119) with triethylamine was carried out in the presence of a molar equivalent of o-phenylenediamine the quinoxaline (165) was isolated from the reaction in 16% yield. There was also a marked increase in the yield of the bis-methylamino azoxy compound (126) obtained. It would appear therefore that the side-chain is lost here, at least partly, as ethyl glyoxylate ($HCOCO_2Et$).



When attempts were made to trap ethyl glyoxylate in the reaction of (119) with sodium ethoxide, no quinoxaline(165) was isolated although its presence in the complex mixture was indicated by mass spectrometry.

Scheme 49 outlines a possible mechanistic explanation for the formation of the bis-methylamino azoxy compound (126). The oxadiazine (156)(See Schemes 44 and 45) may again be considered as an important intermediate. Deprotonation of the hydroxy function with ring-opening, followed by rearrangement, gives a possible precursor (166a) to the azoxybenzene (126) and also explains the formation of the quinoxaline (165).

Scheme 49



(156) (166a) (165) (126)

In the reaction involving triethylamine the increased yield of azoxy compound (126) obtained on addition of the trapping agent may be explained by considering the series of reactions in Scheme 49 as reversible. Thus, the addition of o-phenylenediamine may pull the equilibrium in favour of the nitrosoaniline (166a) and ethyl glyoxylate.

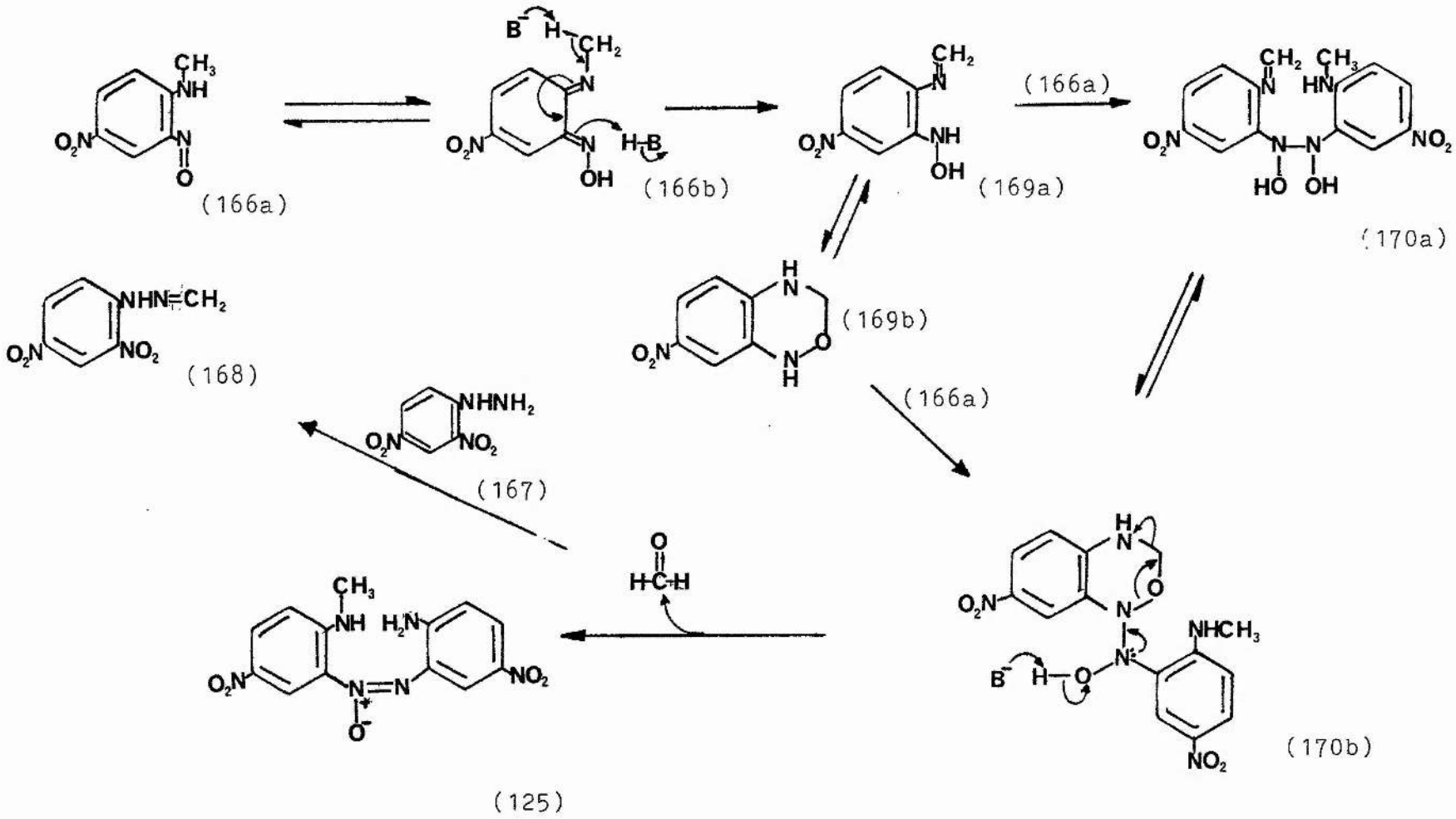
The formation of the methylamino azoxy compound (125) must now be considered. It would not appear to result from the reaction of (126) with base, nor does it seem likely that it is formed from two different anilines.

When a portion of the solvent from the reaction of N-(2,4-dinitrophenyl)sarcosine ethyl ester (119) with sodium ethoxide was distilled into a solution of 2,4-dinitrophenylhydrazine (167) and the mixture concentrated to a small volume, a fine precipitate was obtained which had a molecular ion in the mass spectrum corresponding to the reaction product of (167) with formaldehyde.

Although the yield was minimal, a control experiment using authentic formaldehyde also gave poor quantitative results.

Scheme 50 shows a mechanistic pathway which may explain the formation of (125) and the occurrence of formaldehyde in the reaction. In bases stronger than triethylamine deprotonation of the methyl group of the oxime (166b) may occur leading to formation of the imine (169a). This may then either tautomerise to the oxadiazine (169b) or react directly with a molecule of N-methyl-4-nitro-2-nitrosoaniline (166a) to give (170a) and thence (125). The

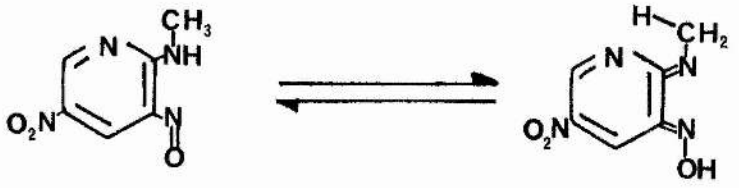
Scheme 50



formation of (125) can also be rationalised by the reaction of the oxadiazine (169b) with the nitrosoaniline (166a).

The mechanisms illustrated in Schemes 49 and 50 provide a possible explanation for the occurrence of the azoxybenzene compounds (125) and (126).

However, the isolation of the bis-methylamino azoxypyridine (137) from the reaction of N-(3,5-dinitropyridyl) sarcosine ethyl ester (134) with potassium carbonate is not easily explained since it implies that either the nitroso pyridine (171a) is more susceptible to reduction or that the methyl hydrogen of (171b) is less acidic than the hydrogen in its benzene counterpart (166b).



(171a) (171b)

As mentioned previously the yield of this material (137) was very low and the reaction from which it was isolated was complex. It is therefore difficult to rule out entirely the presence of the methylamino azoxypyridine in this case.

The results in this Chapter, and the explanations offered for these results, constitute a new section in the chemistry of nitro group condensations. The alternative mechanism (p.111) presented for the formation of the fused imidazole N-oxides adequately accounts for the base-induced cyclisations encountered in Chapters II III and IV. The scope of this mechanism, and of the mechanisms discussed for the formation of other products in this Chapter, remains to be seen.

E X P E R I M E N T A L

Materials and Apparatus

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infra-red spectra were recorded as nujol-mulls Ultra-violet/visible spectra were recorded for dilute solutions in chloroform.

^{1}H n.m.r. spectra were recorded, unless otherwise indicated, at 80MHz on a Bruker WP 80 spectrometer for solutions in dimethylsulphoxide (d-6) with tetramethylsilane as internal reference.

^{13}C n.m.r. spectra were recorded, unless otherwise indicated, at 75.5MHz on a Bruker AM 300 spectrometer for solutions in dimethylsulphoxide (d-6).

Mass spectra were generated on an A.E.I. MS-902 spectrometer, operating at 70eV with a source temperature of 200°C.

Symbols and Abbreviations

n.m.r.	nuclear magnetic resonance
δ	chemical shift
s	singlet
d	doublet
dd	double doublet
t	triplet
q	quartet
m	multiplet
J	spin-spin coupling constant
i.r.	infra-red
ν	wave number
br	broad
sh	shoulder
λ	wavelength
ε	molar extinction co-efficient
M^{+}	molecular ion
m/z	mass to charge ratio
mol eq.	molar equivalent
dec.	decomposition
m.p.	melting point
b.p.	boiling point
t.l.c.	thin layer chromatography
d	density
Ac	acetyl
Ms	methanesulphonyl
DMF	dimethylformamide
DMSO	dimethylsulphoxide

CHAPTER II : EXPERIMENTAL

A number of compounds used in this section were prepared by either I.W. Harvey or D.J. Moody by procedures described in the text (Scheme 8, p.22).

The cyanomethylation and cyclisation steps described below, are given in general terms. Further specific examples, for novel compounds, will be encountered throughout this section.

Cyanomethylation of o-Nitroanilines

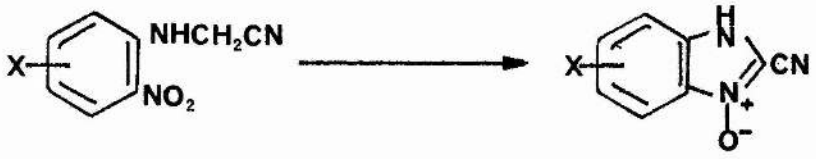
Acetic acid containing a few drops of conc. sulphuric acid was added to a mixture of the amine (1 mol eq), paraformaldehyde (3 mol eq), potassium cyanide (3 mol eq), and zinc chloride (variable), (see table 6). The mixture was stirred vigorously at 50°C for the required time, poured into ice-water, filtered, washed with water, then recrystallised.

Thus the following N-cyanomethyl-o-nitroanilines were prepared:-

Table 6

o-nitro-aniline X =	$ZnCl_2$ (mol eq)	time (h)	m.p. (°C)	recrystall-isation solvent	Yield (%)
H	7.6	8	136-138	ethanol	76
4-CH_3	3.6	8	146-147	ethanol	75
3-NO_2	8.4	20	183-185	acetic acid	74
4-$NHCOCH_3$	3.9	6	228-229	acetic acid	80
4-$NHSO_2CH_3$	3.9	6	169-170	ethanol	82
4-$NHCO_2Et$	3.9	8	194-195	acetic acid	70

Cyclisation of N-cyanomethyl-o-nitroanilines



The appropriate nitrile (1 mol eq) together with potassium carbonate (1 mol eq) was heated in ethanol for the required time. The solvent was then removed in vacuo to leave a water-soluble residue. An aqueous solution of the solid was acidified (HCl) to precipitate the free N-oxide. Thus the following 2-cyanobenzimidazole N-oxides were prepared (Table 7).

Table 7

Nitrile X =	temp.	time (h)	2-Cyanobenzimidazole N-oxide		
			m.p. (°C)	recrystallisation solvent	Yield (%)
H	reflux	4	232-234	ethanol-water	54
4-CH_3	reflux	9	236	DMF-water	53
3-NO_2	50°C	2	203-206	ethanol-water	34
4-$NHCOCH_3$	reflux	0.75	233-234	ethanol-water	71
4-$NHSO_2CH_3$	reflux	1	223-224	ethanol-water	92
4-$NHCO_2Et$	reflux	1.5	215-216	ethanol-water	84

Benzimidazole N-Oxide (21a)

2-Cyano-1H-benzimidazole 3-oxide (32)(0.7g) and conc. hydrochloric acid (15ml) were heated under reflux for 1.5h. On cooling the solution a precipitate formed which was filtered (0.26g). The filtrate was concentrated to ca. 5ml and cooled to afford a further crop (0.26g). The combined solids were recrystallised from propan-2-ol to give benzimidazole N-oxide hydrochloride (0.43g, 57%), m.p. 199-200°C(dec.). (Found: C, 49.4; H, 4.2; N, 16.5. $C_7H_6N_2O.HCl$ requires C, 49.3; H, 4.1; N, 16.4%). $\nu_{max.}$ 2450 cm^{-1} (br,OH). δ 7.7-8.1 (4H, m), 10.07 (1H,s,H-2).

The hydrochloride (0.43g) was dissolved in conc. aqueous ammonia (d.0.88; 10ml) and evaporated to dryness. Recrystallisation of the residue from ethanol gave benzimidazole N-oxide (21a) (0.23g, 68%). It had m.p.

214-216°C [lit.[9], m.p. 210°C(dec.), 215°C(dec.)] δ 7.1-7.8 (4H,m), 8.35 (1H,s,H-2).

Hydrolysis of the N-protected 5-amino-2-cyano-1H-benzimidazole 3-oxides (34a-c)

(a) Hydrolysis of 5-Acetamido-2-cyano-1H-benzimidazole 3-oxide (34a)

The nitrile (34a)(2.0g) and conc. hydrochloric acid (25ml) were heated together under reflux for 1.5h. The colourless dihydrochloride (35a) (1.45g, 71%) crystallised slowly from the cooled solution. 5-Amino-1H-benzimidazole 3-oxide dihydrochloride had m.p. 238°C(dec.)(from conc. HCl). (Found: C, 37.5; H, 4.1; N, 18.9. $C_7H_7N_3O.2HCl$ requires C, 37.9; H, 4.1; N, 18.9%). $\nu_{max.}$ 2600cm^{-1} (very broad, NH,OH). δ 7.51 (1H,dd,H-6), 7.79 (1H,d,H-4), 7.94 (1H,d,H-7), 9.90 (1H,s,H-2), 10.63 (5H,br s, NH_3,NH, OH); $J_{4,6}$ = 2Hz, $J_{6,7}$ = 8.5Hz.

(b) Hydrolysis of 2-Cyano-5-ethoxycarbonylamino-1H-benzimidazole 3-oxide (34b)

Compound (34b) (5.0g), and conc. hydrochloric acid (50ml) were heated together under reflux for 2.5h. 5-Ethoxycarbonylamino-1H-benzimidazole 3-oxide hydrochloride (35b) crystallised from the cooled solution. Recrystallised from ethanol, it had m.p. 210 - 211°C(dec.). Yield, 2.20g(42%). (Found: C, 46.8; H, 4.7; N, 16.2. $C_{10}H_{11}N_3O_3.HCl$ requires C, 46.6; H, 4.7; N, 16.3%). $\nu_{max.}$ 3280, 3200, 3130 (NH), 2600(br,NH,OH), 1720 cm^{-1}(CO). δ 1.29 (3H, t,CH_3), 4.19 (2H,q, CH_2), 7.58 (1H,dd,H-6), 7.78 (1H,d,H-7), 8.11 (1H,d,H-4), 9.83 (1H,s,H-2), 10.13 (1H,s,N<u>H</u>CO_2Et), 12.78 (2H, br s, NH,OH); $J_{4,6}$ = 2Hz, $J_{6,7}$ = 9Hz, $J_{CH_3CH_2}$ = 7Hz.

The reaction mother-liquor was concentrated *in vacuo* to *ca.* 10ml and cooled in ice. 5-Amino-1H-benzimidazole 3-oxide dihydrochloride (35a) (1.57g, 35%) crystallised and was identified by comparison with an authentic sample (see above).

Increasing the reaction time to 7h increased the product ratio (35a) : (35b) but some decomposition also occurred and the products were therefore less easily isolated. A black tarry residue was also obtained.

(c) Hydrolysis of 2-Cyano-5-methanesulphonamido-1H-benzimidazole 3-oxide (34c)

The sulphonamidonitrile (34c) (2.0g), was hydrolysed with conc. hydrochloric acid (25ml) as described above for compound (34a). No crystalline product was obtained on cooling the solution; the acid was distilled off *in vacuo* and the residue washed with warm ethanol (30ml) and filtered. A spectroscopically pure sample of 5-methanesulphonamido-1H-benzimidazole 3-oxide hydrochloride (35c) was collected. Yield, 1.18g(57%). $\nu_{max.}$ 3100 (br, NHMs), 2625 (br, NH,OH), 1320 and 1140 cm^{-1} (SO_2). δ 3.10 (3H,s,CH_3), 7.48 (1H, dd,H-6), 7.69 (1H,d,H-4), 7.86 (1H,d,H-7), 9.82 (1H, s,H-2), 10.32 (1H,s,NHMs). A sample recrystallised from a large volume of ethanol had m.p. 211-212°C (Found: C, 36.5; H, 3.8; N, 15.95. $C_8H_9N_3O_3S.HCl$ requires C, 36.4; H, 3.8; N, 15.9%).

Reaction of the hydrochlorides (35a-c) with concentrated aqueous ammonia

(a) 5-Amino-1H-benzimidazole 3-oxide dihydrochloride (35a)

The dihydrochloride (35a) (1.4g) was dissolved in aqueous ammonia (d.0.88; 10ml) and the solution was immediately evaporated to dryness in vacuo. The residue was washed with a little water, filtered off, and recrystallised from water, giving 5-amino-1H-benzimidazole 3-oxide (15b) (0.6g, 57%), m.p. 97-98°C. (Found: C, 50.0; H, 5.5; N, 25.5. $C_7H_7N_3O.H_2O$ requires C, 50.3; H, 5.4; N, 25.1%). $\nu_{max.}$ 3430(sh), 3310, 3320(sh), 3140, 3080 cm^{-1}(all broad). δ 5.65 (br s, NH_2,H_2O), 6.45 - 6.63 (2H, m), 7.15 - 7.33 (1H,m), 8.00 (1H, s, H-2). m/z 149 ($M^{+\cdot}$, 60%), 133 (100%), 132 (87%), 120 (20%), 106 (20%), 105 (67%), etc.

(b) 5-Ethoxycarbonylamino-1H-benzimidazole 3-oxide hydrochloride (35b)

The hydrochloride (35b) (1.0g) was dissolved in aqueous ammonia (d.0.88; 10ml), the solution was concentrated in vacuo until precipitation commenced, and the mixture was then cooled in ice and the product filtered off and washed with a little water. 5-Ethoxycarbonylamino-1H-benzimidazole 3-oxide (36) (0.44g, 51%), had m.p. 205°C (dec.) (from ethanol). (Found: C, 54.3; H, 5.0; N, 18.8. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%). $\nu_{max.}$ 3310 (NH), 2300 (br, NH,OH), 1700 cm^{-1}(CO); δ 1.28 (3H, t,CH_3), 4.18 (2H,q,CH_2), 7.22 (1H,dd,H-6), 7.54 (1H,d, H-7), 7.86 (1H,d,H-4), 8.28 (1H,s,H-2), 9.71 (1H,s,N<u>H</u>CO_2Et);

$J_{4,6}$ = 2Hz, $J_{6,7}$ = 8.5Hz, $J_{CH_3CH_2}$ = 7Hz.

(c) 5-Methanesulphonamido-1H-benzimidazole 3-oxide hydrochloride (35c)

Reaction of the hydrochloride (35c) with ammonia, as described in the preceding paragraph, gave the sulphonamido-N-oxide (37), m.p. 220-222°C (from ethanol). (Found: C, 42.6; H, 3.9; N, 18.6. $C_8H_9N_3O_3S$ requires C, 42.3; H, 4.0; N, 18.5%). $\nu_{max.}$ 3215 (NHMs), 1320 and 1145 cm^{-1} (SO_2). δ 2.95 (3H,s,CH_3), 7.09 (1H,dd,H-6), 7.39 (1H,d,H-4), 7.59 (1H,d,H-7), 8.31 (1H,s,H-2), 9.70 (1H,s,NHMs), 11.88 (1H, br s, NH,OH); $J_{4,6}$ = 2Hz, $J_{6,7}$ = 9Hz.

Reaction of 4-fluoro-3-nitroaniline (38) with glycine and glycine ethyl ester

(a) 4-Fluoro-3-nitroaniline (1.0g, 6.4mmol), glycine (0.5g, 6.7mmol), sodium bicarbonate (4.5g), ethanol (50ml), and water (20ml) were heated together under reflux for 4h. The solution was then concentrated in vacuo to ca. 20ml and extracted with diethyl ether (2 x 100ml). Acidification (HCl) of the aqueous portion yielded no precipitate. T.l.c. of the organic layer indicated the presence only of unreacted (38).

(b) 4-Fluoro-3-nitroaniline (0.2g, 1.3mmol) and glycine ethyl ester hydrochloride (0.2g, 1.4mmol) were dissolved in DMSO (3ml). Sodium bicarbonate (0.24g, 2.9mmol) was added portionwise to the stirred solution at room temperature. The temperature was increased to, then maintained at, 110°C for 30 min. The cooled solution was poured into ice-water (30ml) and the resulting precipitate filtered off.

The yellow solid (0.1g) had m.p. and the R_f value identical with those of the starting aniline.

Other reaction conditions i.e. longer times, higher temperatures, were also tried; however, no displacement was observed.

N-(4-Acetamido-2-nitrophenyl)glycine Ethyl Ester (43)

4-Fluoro-3-nitroacetanilide, m.p. 140-141°C (from ethanol-water, with charcoal) (lit.[91], 139°C) was prepared in 89% yield by reaction of 4-fluoro-3-nitroaniline (15g) with acetic anhydride (30g) at 25°C, and addition of the mixture to ice-water after 45 min. A suspension of the amide (12.5g, 0.63mmol), glycine ethyl ester hydrochloride (9.7g, 0.70mmol), and sodium bicarbonate (10.6g, 0.126mol) in DMSO (40ml) was stirred for 6h at 60-65°C; the mixture was then poured very slowly, with vigorous stirring, into ice-water (500ml), and the red precipitate filtered off. Recrystallisation from ethanol gave the ester (43) (8.83g, 50%), m.p. 164-165°C. (Found: C, 51.5; H, 5.3; N, 14.9. $C_{12}H_{15}N_3O_5$ requires C, 51.2; H, 5.4; N, 14.9%). $\nu_{max.}$ 3380 (NH), 1725 and 1685 (CO), 1525 and 1320 cm^{-1} (NO_2). δ 1.23 (3H,t,$C\underline{H}_3CH_2$), 2.03 (3H,s,$C\underline{H}_3CO$), 4.16 (2H,q,$C\underline{H}_2CH_3$), 4.20 (2H,d,$C\underline{H}_2NH$), 6.88 (1H,d,H-6), 7.63 (1H,dd,H-5), 8.21 (1H,br t, $N\underline{H}CH_2$), 8.44 (1H,d,H-3), 10.05 (1H,s,$N\underline{H}Ac$); $J_{3,5}$ = 2Hz, $J_{5,6}$ = 9Hz, $J_{CH_3CH_2}$ = 7Hz J_{CH_2NH} = 5Hz.

Ethyl 5-Acetamido-1H-benzimidazole-2-carboxylate 3-oxide (44)

(a) N-(4-Acetamido-2-nitrophenyl)glycine ethyl ester (43) (8.0g, 0.028mol), potassium carbonate (3.93g, 0.028mol), and ethanol (300ml) were heated together under reflux for 2h (a precipitate formed). The solvent was evaporated in vacuo and the residue partitioned between water and dichloromethane; the aqueous layer was acidified (HCl) and the N-oxide(44) filtered off. It had m.p. 133-134°C (from ethanol-water); the yield was 4.84g (61%). (Found: C, 51.2; H, 5.3; N, 15.0. $C_{12}H_{13}N_3O_4.H_2O$ requires C, 51.2; H, 5.4; N, 14.9%). $\nu_{max.}$ 3360 (NHAc), 3300 (br, H_2O), 2650 (br, NH,OH), 1720 and 1655 cm^{-1} (CO). δ 1.35 (3H,t,CH_3CH_2), 2.10 (3H,s,CH_3CO), 4.39 (2H,q,CH_2), 7.26 (1H,dd,H-6), 7.64 (1H,d,H-7), 8.15 (1H,d,H-4), 10.15 (1H,s,NHAc), 12.05 (1H, br s, NH,OH); $J_{4,6}$ = 2Hz, $J_{6,7}$ = 9Hz, $J_{CH_3CH_2}$ = 7Hz.

(b) The cyclised ester can also be prepared in a similar manner using sodium ethoxide as base. However, the yield is poorer. Thus, (43) (0.56g, 2.0mmol), was dissolved in ethanol (10ml) and DMF (15ml). A solution of sodium ethoxide [from sodium (0.05g, 2.2mmol) in ethanol (5ml)] was added dropwise to the stirred solution at 0-5°C. The reaction was stirred at room temperature for a further 2h and worked-up as for the previous experiment to yield 0.16g (29%) of the N-oxide(44).

Hydrolysis of Ethyl 5-Acetamido-1H-benzimidazole 2-carboxylate 3-oxide (44)

The above ester (3.0g) and conc. hydrochloric acid (25ml) were heated under reflux for 1.5h. The dihydrochloride (35a) (1.86g, 74%), was obtained in a similar manner to that described previously

Ethyl 5-Nitro-1H-benzimidazole-2-carboxylate 3-oxide (45)

The above compound was prepared as follows according to the method of Moody[28] :-

Piperidine (14g; ca.2.1mol eq) was added to a solution of N-(2,4-dinitrophenyl)glycine ethyl ester (20.8g) in warm ethanol (800ml). The mixture was boiled for 2h, the solvent distilled off in vacuo, the residue dissolved in water and acidified (HCl). The precipitated N-oxide (45) (10.8g, 56%) had m.p. 209-210°C (from ethanol).

Ethyl 5-Amino-1H-benzimidazole-2-carboxylate 3-Oxide (46)

A solution of ethyl 5-nitro-1H-benzimidazole-2-carboxylate 3-oxide (45) (1.0g), in ethanol (250ml) was hydrogenated in the presence of 5% palladium-charcoal (0.3g). When the uptake of hydrogen was complete (15-20 min.) the catalyst was filtered off and the filtrate concentrated in vacuo. The buff-coloured residue was recrystallised from ethyl acetate, giving the amino-ester (46) (0.55g, 63%), m.p. 156-159°C. (Found: C, 54.8; H, 5.1; N, 18.5. $C_1H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%). $\nu_{max.}$ 3485 and 3370 (NH_2), 2600 (br, NH,OH), 1700 cm^{-1} (CO).

δ1.35 (3H,t,CH_3), 4.38 (2H,q,CH_2), 6.60 (1H,d,H-4), 6.72 (1H,dd,H-6), 7.42 (1H,d,H-7); $J_{4,6}$ = 2Hz, $J_{6,7}$ = 9Hz, $J_{CH_3CH_2}$ = 7.5Hz; m/z 221 ($M^{+\cdot}$, 95%), 205 (32%), 175 (55%) 160 (40%), 159 (69%), 133 (45%), 132 (91%), 131 (100%), etc. The amino-ester appeared to darken on storage and so was used immediately without further purification.

Hydrolysis of the amino ester (46)

The crude amino-ester (46) (0.2g) and conc.hydrochloric acid (10ml) were heated together under reflux for 1h. Cooling gave compound (35a) (0.09g), and concentration of the mother-liquor gave a further crop (0.07g; total yield 80%).

3-Fluoro-4-nitroaniline (49)

The above amine was obtained in, at best, 14% yield when the literature method[52] was followed exactly; 5-fluoro-2-nitroaniline (50) (21%), was also recovered. A greater overall yield was obtained by modifying the literature method as follows:-

Acetic anhydride (115ml) was added slowly, with stirring, to m-fluoroaniline (50g) at such a rate that the temperature remained below 40°C. After addition was complete, the mixture was stirred at 50°C for 3h, cooled, and added to ice. The m-fluoroacetanilide (56.1g, 82%) had m.p. 85-87°C (from propan-2-ol-water; lit.[52], m.p.85°C).

A mixture of nitric acid (d.1.5; 17ml) and concentrated sulphuric acid (110ml) was added dropwise,with stirring,

to an ice-cooled solution of m-fluoroacetanilide (37.5g) in concentrated sulphuric acid (110ml) at such a rate that the temperature of the mixture remained below 5°C. The addition required ca. 2h; the mixture was then poured on to ice and the precipitate filtered off, washed with water, and sucked dry at the water-pump.

This mixture of nitration products was hydrolysed in ethanolic sulphuric acid, and the fluoronitroanilines separated by steam distillation, as already described[52]. 5-Fluoro-2-nitroaniline (steam-volatile) was obtained in a yield of 19g (50%) and had m.p. 93-95°C (from ethanol - water; lit.[52], m.p. 98°C). The steam-volatile residue, worked up as in the published method, gave 3-fluoro-4-nitroaniline(49) (11.4g, 30%), m.p. 146-148°C (from ethanol-water; lit.[52], m.p. 153°C).

N-(5-Amino-2-nitrophenyl)glycine Ethyl Ester (51)

3-Fluoro-4-nitroaniline (3.4g, 0.022mol), glycine ethyl ester hydrochloride (4.2g, 0.03mol), and sodium bicarbonate (3.7g, 0.044mol) were stirred in DMSO (15ml) for 4h at 90-100°C. The orange suspension was cooled and added to ice-water (200ml), and the precipitate filtered off and recrystallised from ethanol-water, giving the ester (51) (4.43g, 85%), m.p. 123-127°C. (Found: C, 50.2; H, 5.5; N, 17.8. $C_{10}H_{13}N_3O_4$ requires C, 50.2; H, 5.5; N, 17.6%). $\nu_{max.}$ 3580, 3460, 3330 and 3220 (NH), 1730 (CO), 1560 and 1310 cm^{-1} (NO_2). δ 1.25 (3H,t,CH_3), 4.09 (2H,d,$\underline{CH}_2NH$), 4.20 (2H,q,$\underline{CH}_2CH_3$), 5.69 (1H,d,H-6), 6.04

(1H,dd,H-4), 6.53 (2H,br s, NH_2), 7.81 (1H,d,H-3), 8.60 (1H,t,N<u>H</u>CH_2); $J_{3,4}$ = 9Hz, $J_{4,6}$ = 2Hz, $J_{CH_2CH_3}$ = 7Hz, J_{CH_2NH} = 5Hz.

<u>N-(5-Amino-2-nitrophenyl)glycine</u> (52)

(a) The foregoing ester (51), (0.24g, 1.0mmol), potassium carbonate (0.16g, 1.1mmol), and ethanol (15ml) were heated together under reflux for 1h. The yellow precipitate was filtered off and dissolved in water; acidification (HCl) gave the free acid (52) (0.13g, 62%).

(b) Sodium ethoxide solution [from sodium (0.025g, 1.1mmol) in ethanol (4ml)] was added dropwise to a stirred solution of (52) (0.24g, 1.0mmol) in ethanol (4ml) and DMF (1ml) at 0-5°C. The reaction was allowed to rise to room temperature over 30 min. and stirring was then maintained for 2.5h. Work-up as above gave the crude acid (0.15g, 71%), spectroscopically identical with an authentic sample.

(c) 3-Fluoro-4-nitroaniline (0.75g, 4.8mmol), glycine (0.38g, 5.1mmol), sodium bicarbonate (4.0g), ethanol (30ml), and water (10ml) were heated together under reflux for 3h. The solution was then concentrated <u>in vacuo</u> to <u>ca</u>. 10ml, and acidified (HCl) to precipitate the acid (0.40g, 40%). <u>N-(5-Amino-2-nitrophenyl)glycine</u> had m.p. 210-214°C (from ethanol-water). (Found: C, 45.6; H, 4.35; N, 19.6. $C_8H_9N_3O_4$ requires C, 45.5; H, 4.3; N, 19.9%). $\nu_{max.}$ 3480 and 3380 (NH), 1725 (CO), 1555 and 1300 cm^{-1} (NO_2). δ 4.00 (2H,d,CH_2), 5.70 (1H,d,H-6), 6.03 (1H,dd,H-4), 6.55 (2H, br s, NH_2), 7.84 (1H,d,H-3), 8.59 (1H,br t,N<u>H</u>CH_2); $J_{3,4}$ = 9Hz,

$J_{4,6}$ = 2Hz, J_{CH_2NH} = 5Hz.

N-(5-Acetamido-2-nitrophenyl)glycine ethyl ester (53) m.p. 210-212°C (from ethanol) was prepared by acetylation of the 5-amino analogue (51) (4g), with acetic anhydride (8g) at 100°C for 30 min., and was isolated by adding the mixture to ice-water (150ml). Yield, 3.89g (83%). (Found: C, 51.4; H, 5.3; N, 14.9. $C_{12}H_{15}N_3O_5$ requires C, 51.2; H, 5.4; N, 14.9%). $\nu_{max.}$ 3360, 3340, 3310 (sh)(NH), 1745 and 1695 (CO), 1550 and 1320 cm^{-1} (NO_2). δ 1.25 (3H,t,$C\underline{H}_3CH_2$), 2.11 (3H,s,$C\underline{H}_3CO$), 4.15 (2H,d,$C\underline{H}_2NH$), 4.19 (2H,q,$\underline{CH}_2CH_3$), 6.86 (1H,dd,H-4), 7.29 (1H,d,H-6), 8.06 (1H,d,H-3), 8.49 (1H,br t, $N\underline{H}CH_2$), 10.28 (1H,s,$N\underline{H}Ac$); $J_{3,4}$ = 9Hz, $J_{4,6}$ = 2Hz, J_{CH_2NH} = 6Hz, $J_{CH_2CH_3}$ = 7Hz.

Ethyl 6-Acetamido-1H-benzimidazole-2-carboxylate 3-oxide (54)

(a) The ester (53) (3.5g, 12.5mmol), and potassium carbonate (1.72g, 12.5mmol) were heated under reflux together in ethanol (100ml) for 2h. The cooled solution was then concentrated in vacuo and the residue extracted with water : dichloromethane (1:1). Acidification (HCl) of the aqueous portion gave the cyclised compound (54). It had m.p. 198-200°C (from DMF - water). Yield, 2.34g (67%). (Found: C, 51.2; H, 5.3; N, 15.3. $C_{12}H_{13}N_3O_4.H_2O$ requires C, 51.2; H, 5.4; N, 14.9%). $\nu_{max.}$ 3110 - 3280 (br, NHAc, NH,OH), 1705 and 1660 cm^{-1}(CO); δ 1.36 (3H, t, $C\underline{H}_3CH_2$), 2.08 (3H,s,$C\underline{H}_3CO$), 4.40 (2H,q,CH_2), 7.35 - 7.5

(2H,m) and 7.9 - 8.1 (1H,m), 10.01 (1H,s,NHAc), 12.13 (1H,br s, NH,OH); not 1st order.

(b) The N-oxide (54) was also obtained in 53% yield using sodium ethoxide (1 molar equivalent) as base.

6-Amino-1H-benzimidazole 3-oxide (15c)

The acetamido-ester (54) (4.3g 0.015mol) and conc. hydrochloric acid (70ml) were heated together under reflux for 3h. The solution was evaporated to dryness *in vacuo* to give 6-Amino-1H-benzimidazole 3-oxide dihydrochloride (1.93g, 57%), m.p. 255°C (dec.) (from hydrochloric acid, with charcoal). (Found: C, 37.8; H, 4.4; N, 19.2. $C_7H_7N_3O$. 2HCl requires C, 37.9; H, 4.1; N, 18.9%). $\nu_{max.}$ 2580 cm^{-1} (very broad). δ 7.6 - 7.75 (1H,m), 7.9 - 8.13 (2H,m), 9.3 (br s, NH,OH,NH_3), 9.96 (1H,s,H-2). The dihydrochloride (1.5g) was added in small portions to aqueous ammonia (d.0.88; 15ml) at 0-5°C; the solution was evaporated to dryness *in vacuo*, and the residue washed with ice-cold water (20ml). The buff-coloured N-oxide (15c) (0.86g, 68%), had m.p. 185°C (dec.) (from water). (Found: C, 45.7; H, 5.9; N, 22.8. $C_7H_7N_3O.2H_2O$ requires C, 45.4; H, 6.0; N, 22.7%). $\nu_{max.}$ 3360, 3160 (br), 3080 cm^{-1}. δ 4.8 (br s, NH_2H_2O), 6.63 - 6.85 (2H,m), 7.15 - 7.35 (1H,m), 8.20 (1H,s,H-2). m/z 149 (M^+, 67%), 133 (100%), 132 (47%), 121 (13%), 120 (13%), 106 (20%), 105 (33%), etc.

4-Nitro-1H-benzimidazole 3-oxide (62)

2-Cyano-4-nitro-1H-benzimidazole 3-oxide (61) (1.5g) was dissolved in conc. hydrochloric acid (25ml) and the solution was boiled for 4h. On cooling, dark brown needles were obtained which were filtered off and recrystallised from hydrochloric acid (with charcoal) to give 4-nitro-1H-benzimidazole 3-oxide hydrochloride (1.08g, 69%). It had m.p. 224-225°C (dec.) (Found: C, 38.9; H, 2.8; N, 19.5 $C_7H_5N_3O_3HCl$ requires C, 39.0; H, 2.8; N, 19.5%). $\nu_{max.}$ 2620 (br, NH, OH), 1520 and 1345 cm^{-1} (NO_2). δ 7.53 (1H,t, H-6), 8.0 - 8.2 (2H,m,H-5 and H-7), 9.07 (1H,s,H-2); $J_{5,6}$ = 8Hz, $J_{6,7}$ = 8Hz.

The above hydrochloride (0.63g) was dissolved in aqueous ammonia (d.0.88, 25ml) and evaporated *in vacuo* to a small volume. A precipitate formed which was filtered off and recrystallised from water. The title compound (62) had m.p. 228-230°C (dec.). Yield, 0.33g (63%). (Found: C, 46.7; H, 2.7; N, 23.3; $C_7H_5N_3O_3$ requires C, 46.9; H, 2.8; N, 23.5%). $\nu_{max.}$ 1520 and 1350 cm^{-1} (NO_2). δ 7.38 (1H,t,H-6), 7.9 - 8.1 (2H,m,H-5 and H-7), 8.57 (1H,s,H-2), 12.15 (1H,br s, NH,OH); $J_{5,6}$ = 8Hz, $J_{6,7}$ = 8Hz.

4-Aminobenzimidazole 3-oxide (15a)

A solution of 4-nitro-1H-benzimidazole 3-oxide (62) (0.5g) in ethanol (200ml) was hydrogenated over palladium-charcoal (5%, 0.15g). When the uptake of hydrogen was complete (*ca.* 45 min.), the catalyst was filtered off, the filtrate evaporated to dryness *in vacuo*, and the residue

triturated with ether to induce crystallisation of the product. The aminobenzimidazole N-oxide (15a) (0.27g, 58%) crystallised from water (with charcoal) as a monohydrate, m.p. 108-110°C. (Found: C, 49.9; H, 5.3; N, 24.9. $C_7H_7N_3O.H_2O$ requires C, 50.3; H, 5.4; N, 25.1%). $\nu_{max.}$ 3460, 3320, 3130 cm^{-1}(NH). δ 5.38 (br,NH,H_2O), 6.40 (1H, 4 lines,H-5), 6.65 - 7.10 (2H,m, H-6 and H-7), 8.23 (1H,s,H-2). m/z 149 ($M^{+\cdot}$, 14%), 148 (17%), 133 (100%), 132 (28%), 121 (6%), 120 (6%), 106 (39%), 105 (31%), etc.

Reactions relating to the attempted synthesis of 7-amino-1H-benzimidazole 3-oxide can be found in the experimental section for Chapter IV.

Reactions of 5-Methylbenzimidazole N-oxide (73)

(a) With acetobromoglucose.

(i) To a stirred suspension of (73), (0.25g, 1.7mmol) in acetonitrile (10ml), piperidine (0.14g, 1.7mmol) was added dropwise. Acetobromoglucose (0.69g, 1.7mmol) was added in small portions to the resultant solution and stirring was continued at room temperature for 16h. A colourless precipitate was filtered off and shown by comparison with an authentic sample, to be unchanged starting material (73) (68% recovery).

(ii) Acetobromoglucose (1.45g, 3.5mmol) was added to a stirred solution of (73) (0.5g, 3.4mmol) and piperidine (0.3g, 3.5mmol) in quinoline (3.0g) at room temperature.

After 3h acetic acid (3ml) was added and the solution poured into stirred ice-water (20ml). A sticky mass formed, from which only a small amount (0.05g) of crude solid was obtained. Recrystallisation from propan-2-ol-water gave a white powder (0.02g) which had m.p. 106-108°C. $\nu_{max.}$ 1755, 1740, 1725, 1700 (CO). m/z 478 (M^{+}).

(b) With 2-bromoethanol

The N-oxide (73) (0.25g, 1.7mmol) was dissolved in quinoline (2.4g) containing piperidine (0.14g, 1.7mmol) 2-Bromoethanol (0.21g, 1.7mmol) was added dropwise to the stirred solution at room temperature and after 3h the dark mixture was poured on to ice and left overnight. No precipitate had formed so the solution was extracted with ether, dried (sodium sulphate) and concentrated *in vacuo* to leave a tarry residue which was not purified further.

The reaction was repeated on the same scale as above with acetonitrile (10ml) as solvent. The solution was stirred at room temperature for 24h then concentrated *in vacuo*. Trituration of the residue with ethanol-diethyl ether gave a sticky solid (0.22g), m.p. 124-128°C, which was shown by infra-red and mass-spectral analysis to be mainly unreacted N-oxide (73) with a small amount of product. $\nu_{max.}$ 3320 cm^{-1}(br,OH). m/z 192 (M^{+}, 3%), 148 (M^{+}, 50%).

(c) With 3-bromopropan-1-ol.

The previous reaction was repeated using a molar equivalent of 3-bromopropan-1-ol. After 48h a precipitate

appeared which was filtered off and shown to be unreacted (73) (0.12g, 48%).

(d) With ethylene carbonate

The N-oxide (73) (0.5g, 3.4mmol), together with ethylene carbonate (0.3g, 3.4mmol) and tetraethylammonium iodide (0.2g, 0.8mmol) were dissolved in dimethylformamide (5ml). The stirred solution was heated at 140°C for 4h, evaporated to dryness, then extracted with water:dichloromethane (1:1). Concentration of the organic layer gave a brown oil, attempted distillation of which resulted in the formation of resinous solid in both the distillation flask and collecting vessel.

The reaction was repeated on a larger scale using the N-oxide (1.5g) with all other quantities adjusted accordingly. The stirred solution was heated at 125-130°C until the evolution of carbon dioxide ceased (8h). Work-up as previously described again gave a brown oil. This was chromatographed on silica gel, packed in diethylether: ethylacetate (1:1), and eluted by gradually increasing the solvent polarity from diethyl ether-ethyl acetate to ethyl acetate-methanol. The majority of the fractions were a mixture; however two fractions (ethyl acetate) appeared to contain only one component and these were evaporated *in vacuo* together. 1-(2-hydroxyethoxy)-6-methylbenzimidazole (75) (1.08g) showed $\nu_{max.}$ 3250 cm^{-1} (br,OH). δ 2.48 (3H,s,CH_3), 3.73 (br,CH_2OH,H_2O), 4.40 (2H,m,CH_2), 7.10 (1H,dd,H-5), 7.48 (1H,d,H-7), 7.60 (1H,d,H-4), 8.46 (1H,s,H-2); $J_{4,5}$ = 8.0Hz, $J_{5,7}$ = 1.5Hz. m/z 192($M^{+\cdot}$),

186, 162, 148, 147 etc.

Attempted purification of the oil by short-path, bulb-to-bulb distillation (Kugelrohr) once again resulted in the formation of a resinous material. A portion of this material was removed from the apparatus and scratched with a spatula to obtain an off-white solid, m.p. 180°C (dec.). The ^{1}H n.m.r. spectrum was complex but showed the notable absence of an H-2 resonance. δ 2.03 (s,CH_3), 2.10 (s,CH_3), 3.25 - 4.50 (m), 6.76 - 7.23 (m,aromatics). m/z 236 ($M^{+\cdot}$), 218, 205, 192, 176, 174, 162, 161, 149, 148, 147 etc.

Reactions of 5-Aminobenzimidazole N-oxide (15b)

(a) With acetobromoglucose

Acetobromoglucose (1.36g, 3.3mmol) was added to a stirred solution of the N-oxide (15b) (0.5g, 3.0mmol) and piperidine (0.28g, 3.3mmol) in quinoline (3.0g) at room temperature. After 2h the solution was poured on to ice. No precipitate appeared so the solution was concentrated *in vacuo* to *ca.* 5ml, stirred in ice, and diethyl ether was added. A precipitate appeared which decomposed on filtration.

(b) With ethylene carbonate

The N-oxide (15b) (0.3g, 1.8mmol), ethylene carbonate (0.16g, 1.8mmol) and tetraethylammonium iodide (0.11g), 0.4mmol) were stirred together in DMF (5ml) at 130°C for 3h. The dark solution was evaporated to dryness to give

a black residue. Extraction of the tar with water and diethyl ether was unsuccessful. The residue was however sufficiently volatile for mass spectrometry. m/z 237 ($M^{+\cdot}$), 221, 206, 193, 190, 177, 163, 162, 161, 149, 148, 147, 146, etc.

CHAPTER III - EXPERIMENTAL

Ethyl N-3-pyridylcarbamate (87) was prepared in 61% yield from 3-aminopyridine and ethyl chloroformate in pyridine according to the literature method[69]. It had m.p. 87-89°C (from water)(lit.[69], m.p. 87-89°C).

Ethyl N-(2-nitro-3-pyridyl)carbamate (88) The literature procedure[69] was modified as follows:- Fuming nitric acid (d. 1.5; 30ml) was added slowly with stirring, to a solution of (87) (15.0g) in concentrated sulphuric acid (30ml) so that the temperature remained below 10°C. The temperature was then raised to 70°C over a 1h period, then kept at 70°C for 1.5h. After cooling to room temperature the mixture was poured on to crushed ice and the precipitated product filtered off. Recrystallised from propan-2-ol, compound (88) (14.3g, 75%) had m.p. 81-83°C (lit.[69], m.p. 82-83°C).

N-Ethoxycarbonyl-N-(2-nitro-3-pyridyl)glycine ethyl ester (85)*. Potassium carbonate (13.08g, 0.095mol) and ethyl N-(2-nitro-3-pyridyl)carbamate (88) 10.0g, 0.046mol) were heated together under reflux in redistilled acetone (150ml) for 30 min. Ethyl bromoacetate (7.93g, 0.047mol) was added dropwise to the mixture and heating was maintained for a further 4h. The mixture was then poured on to crushed ice and left to crystallise overnight. Recrystallisation from diethyl ether-petroleum gave the diester (85) (12.11g, 86%), m.p. 55-57°C [Bush[92] reported 68%, m.p. 53-55°C (from ethanol-water)]. (Found: C, 48.7; H, 5.1; N, 14.1.

$C_{12}H_{15}N_3O_6$ requires C, 48.5; H, 5.1; N, 14.1%). $\nu_{max.}$ 1735 and 1700 (CO's), 1545 and 1315 cm^{-1} (NO_2). δ 1.04 (3H,t,CH_3), 1.23 (3H,t,CH_3), 3.96 - 4.44 (6H,m,3xCH_2), 7.88 (1H,dd,H-5), 8.15 (1H,br d,H-4), 8.55 (1H,dd,H-6); $J_{4,5}$ = 8.0Hz, $J_{5,6}$ = 4.5Hz, $J_{4,6}$ = 1.6Hz.

Reactions of (85) with bases:-

Bush[92] reported the failure of the diester (85) to react in the presence of aqueous ammonia or triethylamine, and the use of sodium ethoxide or potassium hydroxide as base led to mixtures, from which no pure product was isolated. The following attempts to identify any product formed in the reaction of (85) with sodium ethoxide were made.

(a) Sodium ethoxide solution [from sodium (0.08g, 3.5mmol) in ethanol (5ml)] was added dropwise to a stirred solution of (85) (1.0g, 3.5mmol) in ethanol (5ml) at 40°C, and the mixture was stirred at 40°C for 4.5h then evaporated to dryness in vacuo. The residue was partitioned between water (10ml) and diethyl ether (10ml). Acidification (HCl) of the ice-cooled aqueous portion gave (with scratching) a buff-coloured precipitate. The filtrate was saturated with sodium chloride and extracted exhaustively with ethyl acetate. Concentration of the dried (sodium sulphate)

* The preparation of this compound was originally investigated by B.D.Bush[92].

organic solution gave a residue which was triturated with a little diethyl ether then filtered. The filtered solid was combined with the precipitate from the acidification stage and recrystallised (with charcoal) from water. Ethyl 1H-imidazo[4,5-b]pyridine-2-carboxylate 3-oxide (89) (0.12g, 18%) had m.p. 163-164°C. (Found: C, 52.6; H, 4.3; N, 20.5. $C_9H_9N_3O_3$ requires C, 52.2; H, 4.4; N, 20.3%). $\nu_{max.}$ 1735 cm^{-1} (CO). δ 1.38 (3H,t,CH_3), 4.45 (2H,q,CH_2), 7.43 (1H,dd,H-6), 7.24 (1H,dd,H-7), 8.59 (1H,dd,H-5), 12.30 (1H,s,NH,OH); $J_{CH_2CH_3}$ = 7Hz, $J_{5,6}$ = 5Hz, $J_{5,7}$ = 1.5Hz, $J_{6,7}$ = 8Hz. The ether layer from the initial extraction was dried (sodium sulphate) and concentrated in vacuo. The residue (0.51g) was shown by t.l.c. to consist of starting material, 3-amino-2-nitropyridine (90) and five other products. Attempts to purify the mixture by recrystallisation or column chromatography were unsuccessful.

(b) The above reaction was repeated on a larger scale using the diester (2g, 6.7mmol) and sodium ethoxide (0.16g Sodium, 7.0mmol). The N-oxide (89) (0.21g, 15%) was again the only product isolated in any reasonable purity.

(c) The diester (2.9g, 10mmol) was dissolved in ethanol (20ml) at 40°C and a solution of sodium ethoxide [from sodium (0.51g, 22mmol), in ethanol (10ml)] was added dropwise to the stirred solution. After 2.5h the solvent was removed in vacuo and the residue extracted with water : diethyl ether$^+$ (1:1). Acidification (HCl) of the aqueous layer gave a brown precipitate which was filtered and recrystallised (with charcoal) from ethanol. This material was found to

be Ethyl 1H-imidazo[4,5-b]pyridine-2-carboxylate (91) (0.19g, 10%), m.p. 206-208°C. (Found: C, 56.6; H, 4.6; N, 21.9. $C_9H_9N_3O_2$ requires C, 56.5; H, 4.7; N, 22.0%). $\nu_{max.}$ 1705 cm^{-1} (CO). $\delta_{(CDCl_3)}$ 1.55 (3H,t,CH_3), 4.72 (2H,q,CH_2), 7.60 (1H,dd,H-6), 8.55 (1H,dd,H-7), 9.03 (1H,dd,H-5); $J_{CH_2CH_3}$ = 7Hz, $J_{5,6}$ = 6Hz, $J_{5,7}$ = 1.5Hz, $J_{6,7}$ = 8.5Hz. The aqueous filtrate was saturated with sodium chloride and extracted with diethyl ether. Concentration of the dried (sodium sulphate) ether layer gave a residue which was shown by i.r. and t.l.c. to be mainly 3-amino-2-nitropyridine (90). T.l.c. of the initial diethyl ether extract+ indicated the presence of unreacted (85), aminonitropyridine (90) and at least four other products.

All attempts to isolate the imidazopyridine (91) in subsequent reactions were unsuccessful; only a very small amount of black precipitate was obtained at the acidification stage.

Attempted hydrolysis of the diester (85)

(a) The diester (3.0g) and concentrated hydrochloric acid (20ml) were heated under reflux together for 3.5h. The red solution was then poured into ice-water to give a white precipitate which was filtered off and recrystallised from water. The recrystallised material (1.6g) had m.p. 160°C and was found to be a mixture of N-ethoxycarbonyl-N-(2-chloro-3-pyridyl)glycine (93) and its ethyl ester (92). The mixture had $\nu_{max.}$ 2480, 2575 and 2690 (OH), 1695,

(br,CO's). δ 1.07 (t,CH_3), 1.21 (t,CH_3), 3.94 - 4.50 (m,CH_2's), 7.48 - 7.51 (4 lines), 7.92 - 7.96 (6 lines), 8.36 - 8.37 (4 lines), 12.92 (s,OH). A further recrystallisation from water resulted in the isolation of an analytically pure sample of the acid (93). It had m.p. 163-164°C. (Found: C, 46.3; H, 4.2; N, 10.7. $C_{10}H_{11}ClN_2O_4$ requires C, 46.4; H, 4.3; N, 10.8%).

A portion (1.0g) of the mixture was dissolved in ethanol (30ml) and dry HCl gas (0.63g) was added. The solution was heated under reflux for 4h then the solvent was evaporated in vacuo to give a brown oil. Distillation (Kugelrohr, 200°C/0.05mm Hg), gave pure (92) (0.64g). (Found: C, 50.2; H, 5.25; N, 9.7. $C_{12}H_{15}ClN_2O_4$ requires C, 50.3; H, 5.3; N, 9.8%). $\nu_{max.}$ 1750 and 1715 cm^{-1} (CO's). δ 1.07 (3H,t,CH_3), 1.20 (3H,t,CH_3), 4.02 - 4.49 (m,3 x CH_2), 7.51 (1H,dd,H-5), 7.94 (1H,dd,H-4), 8.38 (1H,dd,H-6). $J_{4,5}$ = 7.8Hz, $J_{4,6}$ = 1.8Hz, $J_{5,6}$ = 4.7Hz, $J_{CH_2CH_3}$ = 7.1Hz.

(b) The diester (85) (1.0g) was dissolved in a mixture of concentrated sulphuric acid (10ml) and water (10ml), and the solution heated under reflux for 0.5h. No precipitate was obtained when the dark solution was poured into ice-water and extraction of the neutralised solution (sodium hydroxide) with diethyl ether was unsuccessful. Concentration of the solution in vacuo gave an intractable tar.

(c) The above reaction using hydrobromic acid (48%) gave similar results to (b) and no product was isolated.

Attempted Cyanomethylation of 3-Amino-2-nitropyridine (90)

3-Amino-2-nitropyridine (90) (2.27g, 82%), m.p. 193 - 194°C (from ethanol-water) (lit.[69], m.p. 195 - 196°C) was prepared by the alkaline hydrolysis of the carbamate (88) (4.2g) using the literature method[69].

The above amine (90) (1.39g, 0.01mol), paraformaldehyde (0.9g, 0.03mol), potassium cyanide (1.95g, 0.03mol) and zinc chloride (10.88g, 0.08mol) were heated together, with stirring, in glacial acetic acid (26ml), containing 4 drops of conc. sulphuric acid, at 50°C for 2 days. A further portion of potassium cyanide (0.01mol) was added and stirring was maintained at 50°C for 2 more days. The mixture was then poured into ice-water and left overnight. No precipitate had formed so the solution was saturated with sodium chloride and extracted with chloroform. The organic layer was dried (sodium sulphate) and evaporated to dryness to give a yellow solid (0.74g). This material was found (by t.l.c. and ^{1}H n.m.r.) to be a mixture of staring amine (90) and one other product [probably 3-(Cyanomethylamino)-2-nitropyridine] in an approximately 1:1 ratio. Attempts to purify this mixture by chromatography or recrystallisation were unsuccessful, the two compounds having very similar polarities and solubility characteristics.

The mixture (0.65g) was dissolved in methanol (20ml) and potassium carbonate (0.26g) was added portionwise to the stirred solution. The mixture was heated under reflux for 1.5h, cooled, then evaporated to dryness. The residue was extracted with diethyl ether: water and the layers

separated. T.l.c. of the organic portion indicated only the presence of the two initial components of the mixture. Acidification (HCl) of the black aqueous portion yielded no precipitate.

N-(3-Nitro-2-pyridyl)glycine ethyl ester (99)

(a) Via the glycine (98)

Sodium glycinate (11.6g, 0.12mol) in water (50ml) was added to a suspension of 2-chloro-3-nitropyridine (10g, 0.06mol) and potassium carbonate (9g, 0.06mol) in ethanol (250ml). The mixture was heated under reflux for 3.5h, then cooled to 0°C and the yellow product filtered off; a second crop was obtained by addition of ethanol to the filtrate. The combined precipitates were dissolved in water, and the solution acidified (HCl) to give N-(3-nitro-2-pyridyl)glycine (98) (11.0g, 89%), m.p. 170°C (dec.) (from ethanol-water) (lit.[77], m.p. 175 -176°C).

The glycine (98) (8.0g) was heated for 6h under reflux in ethanol (100ml) containing conc. sulphuric acid (2g). The solution was then concentrated *in vacuo* to *ca.* 25ml, added to ice-water and set aside at 5°C for 2h. The crude ester was filtered off and purified by chromatography (in ether solution) through a short column of silica. N-(3-Nitro-2-pyridyl)glycine ethyl ester (99) (8.39g, 92%) had m.p. 40- 41°C. (lit.[75], b.p. 143°C/0.25 mm Hg; not reported as a solid). (Found: C, 48.1; H, 4.9; N, 18.8. Calc. for $C_9H_{11}N_3O_4$: C, 48.0; H, 4.9; N, 18.7%) $\nu_{max.}$ 3360 (NH), 1720 (CO), 1555 and 1335 cm^{-1} (NO_2); $\delta_{(CDCl_3)}$ 1.30

(3H,t,CH_3), 4.33 (2H,q,$C\underline{H}_2CH_3$), 4.46 (2H,d,$C\underline{H}_2NH$), 6.86 (1H,dd,H-5), 8.5 - 8.7 (3H,m,H-4, H-6, and NH); $J_{CH_3CH_2}$ = 7Hz, J_{CH_2NH} = 6Hz, $J_{4,5}$ = 8Hz, $J_{5,6}$ = 5.1Hz.

(b) By direct displacement

Glycine ethyl ester hydrochloride (2.78g, 0.02mol) was added in portions to a stirred solution of 2-chloro-3-nitropyridine (1.58g, 0.01mol) and potassium carbonate (2.76g, 0.02mol) in DMSO (15ml) at 40°C. After 2h the solution was poured into ice-water and the precipitate filtered off(0.6g). The filtrate was extracted with diethyl ether, dried (sodium sulphate), and concentrated <u>in vacuo</u> to give a yellow oil (0.6g). This was combined with the precipitate and purified by column chromatography (silica gel, packed in, and eluted with, diethyl ether) to give the ester(99) (1.68g, 75%) m.p. 36 - 38°C.

<u>N-(3-Nitro-2-pyridyl)glycine methyl ester (100)*</u>

<u>N</u>-(3-Nitro-2-pyridyl)glycine (98) (3.8g) was heated under reflux for 6h in methanol (50ml) containing conc. sulphuric acid (1.2g). The product which crystallised from the cooled solution was collected. A further crop was obtained by evaporating the filtrate to <u>ca</u>. 20ml, then pouring it into water. The combined solids were recrystallised from methanol-water to give the methyl ester(100)

* Although this compound (100) has previously been prepared no analytical or spectroscopic data were reported[93].

(3.26g, 80%) m.p. 96 - 97°C. (Found: C, 45.1; N, 4.4; H, 20.0. Calc. for $C_8H_9N_3O_4$: C, 45.5; N, 4.3; H, 19.9%) $\nu_{max.}$ 3370 (NH), 1740 (CO), 1560 and 1345 cm^{-1} (NO_2). δ($CDCl_3$) 3.70 (3H,s,CH_3), 4.36 (2H,d,CH_2), 6.89 (1H,m,H-5), 8.45 - 8.60 (2H,m,H-6 and H-4), 8.80 (1H,br t,NH); J_{CH_2NH} = 6Hz.

2-(Cyanomethylamino)-3-nitropyridine (101)

(a) Aminoacetonitrile hydrochloride (5.58g, 0.06mol) was added portionwise to a stirred solution of 2-chloro-3-nitropyridine (4.74g, 0.029mol) and sodium bicarbonate (5.04g, 0.06mol) in DMSO (30ml) at 80°C. Starting material was detected by t.l.c. after 1h stirring so a further molar equivalent of both nitrile and base were added. After 1h stirring at 80°C the reaction mixture was poured into ice-water and the precipitate filtered off. The nitrile (101) (2.1g, 39%) (from propan-2-ol; with charcoal) had m.p. 120 - 122°C. (Found: C, 47.0; H, 3.4; N, 31.5. $C_7H_6N_4O_2$ requires C, 47.2; H, 3.4; N, 31.4%). $\nu_{max.}$ 3370 (NH), 1560 and 1340 cm^{-1} (NO_2). δ 4.53 (2H,d,CH_2), 7.00 (1H,dd,H-5), 8.50 - 8.85 (3H,m,H-4, H-6 and NH); $J_{4,5}$ = 8Hz, $J_{5,6}$ = 5Hz, J_{CH_2NH} = 6Hz.

(b) 2-Chloro-3-nitropyridine (1.58g, 9.9mmol) was dissolved in DMF (5ml). Aminoacetonitrile hydrochloride (2.4g, 25mmol) and potassium carbonate (3.46g, 25mmol) were added in turn to the stirred solution at room temperature. The solution was stirred at 60°C for 2h then poured into ice-water. The precipitated solid was filtered off and recrystallised from propan-2-ol to give (101) (0.3g, 17%), m.p. 120 - 122°C. The initial filtrate was found to contain mainly unreacted

starting material along with some product and one other unidentified substance.

A variety of other conditions were tried, without success, in an attempt to increase the yield of (101).

Reaction of N-(3-nitro-2-pyridyl)glycine ethyl ester (99) with bases.

(a) With sodium ethoxide.

Sodium ethoxide [from sodium (0.1g, 4.3mmol) in ethanol (20ml)] was added dropwise to a stirred solution of (99) (1g, 4.4mmol) in ethanol (15ml) at 0-5°C. The solution was stirred at room temperature for 3h then concentrated in vacuo. The black residue was partitioned between water and diethyl ether (1:1). Acidification (HCl) of the aqueous portion gave a black solid which resisted further purification. The organic layer was shown by t.l.c. to be a mixture of starting material and 2-amino-3-nitropyridine.

(b) Similarly, decomposition occurred on reaction of (99) with piperidine (1mol eq). No solid was obtained on acidification of the black aqueous solution and unreacted starting material together with aminonitropyridine (102) were the only products identified in the organic layer.

(c) The reaction of (99) with DBU (1mol eq), in ethanol resulted in the precipitation of a small amount of 2-amino-3-nitropyridine (0.09g) from the solution. Work-up as usual gave similar results to (b).

(d) With potassium carbonate.

The ester (99) (4.05g, 0.018mol), potassium carbonate (2.62g, 0.019mol), and ethanol (90ml) were heated together under reflux for 5h. The cooled mixture was filtered and the precipitate washed with a little ethanol; it was then dissolved in water, and the solution decolourised with charcoal and acidified (HCl). The resulting solid was collected,* redissolved in boiling water (gas was evolved), and the solution evaporated to dryness in vacuo. The sticky residue was washed with a little diethyl ether and recrystallised from ethanol, giving 3H-imidazo[4,5-b]pyridine 1-oxide (105) (0.27g, 11%), m.p. 173 - 175°C. (Found: C, 53.25; H, 3.6; N, 31.05. $C_6H_5N_3O$ requires C, 53.3; H, 3.7; N, 31.1%). $\nu_{max.}$ 2200 - 2500 cm^{-1} (br,NH,OH). δ 7.33 (1H,dd,H-6), 8.00 (1H,dd,H-7), 8.46 (1H,dd,H-5), 8.63 (1H,s,H-2), and 12.0 (1H,br s,NH,OH); $J_{6,7}$ = 8.3Hz, $J_{5,7}$ = 1.5Hz, $J_{5,6}$ = 4.4Hz.

The ethanolic reaction mother-liquor was evaporated to dryness in vacuo and the residue dissolved in water. The solution was acidified (HCl) to pH 3-4, saturated with sodium chloride, and extracted repeatedly with dichloromethane. The extract was dried (sodium sulphate) and evaporated, and the residue washed with a little ether and recrystallised from propan-2-ol. Ethyl 3H-imidazo[4,5-b]pyridine-2-carboxylate 1-oxide (103) (1.49g, 42%) had m.p. 150°C. (Found: C, 52.35; H, 4.5; N, 20.5. $C_9H_9N_3O_3$ requires C, 52.2; H, 4.4; N, 20.3%). $\nu_{max.}$ 2300 - 2700 (br, NH,OH) and 1730 cm^{-1}(CO). δ 1.40 (3H,t,CH_3), 4.46 (2H,q,CH_2),

7.46 (1H,dd,H-6), 8.09 (1H,dd,H-7), 9.11 (1H,dd,H-5), and 12.5 (1H,br s,NH,OH); $J_{CH_3CH_2}$ = 7.0Hz, $J_{6,7}$ = 8Hz, $J_{5,6}$ = 4.6Hz, $J_{5,7}$ = 1.8Hz.

The ratio of (105) to (103) can be altered by increasing the reaction time e.g. (105) (18%) and (103) (30%) after 5h; (105) (43%) and (103) (20%) after 11h.

*In one of the reactions of (99) with potassium carbonate this solid was isolated and studied. It had m.p. 115°C (dec. with effervescence). $\nu_{max.}$ 2700 - 2450 (NH,OH), 1620 cm^{-1} (CO_2^-?). Attempts to crystallise this material resulted in evolution of gas and the formation of the parent N-oxide (105). Similarly the ^1H n.m.r. of the compound was identical with that of (105). Vacuum sublimation of this material gave a white solid with an i.r. spectrum identical to that of (105); the mass spectrum showed m/z 135 ($M^{\cdot+}$) and a similar fragmentation pattern to that of (105). The compound was also soluble in cold basic media and could be reprecipitated using either hydrochloric or sulphuric acid. On the basis of these findings the compound was considered to be the carboxylic acid (104) of (105).

Reaction of (103) with sodium hydroxide

The ester (103)(0.2g) was dissolved in sodium hydroxide solution (2.5M, 5ml) and left standing for 2 days. The solution was evaporated to dryness, the residue dissolved in a little water then acidified (HCl). Filtration of the precipitate and recrystallisation from ethanol gave the

N-oxide (105) (0.1g, 77%) m.p. 169 - 170°C.

Reactions of N-(3-nitro-2-pyridyl)glycine methyl ester (100) with Potassium carbonate.

(a) Potassium carbonate (0.65g, 4.7mmol) was added in portions to a stirred solution of (100) (1.0g, 4.7mmol) in methanol (50ml) at 40°C. T.l.c. indicated after 1h that very little reaction had taken place and the temperature was therefore increased to reflux. After a further 1.5h the solvent was removed in vacuo and the dark residue extracted with water : diethyl ether (1:1). The organic layer was shown by t.l.c. to be a mixture of unreacted (100), 2-amino-3-nitropyridine and at least one other component. Acidification (HCl) of the aqueous layer (after treatment with charcoal) gave a brown precipitate (0.09g, 10%) which had m.p. 130°C (dec.). $\nu_{max.}$ 1700 cm^{-1} (CO). m/z 193($M^{+\cdot}$), 177, 135, 119, 105, 80, etc. The ^{1}H n.m.r. spectrum was very complicated and poorly resolved (decomposition of the sample appeared to have occurred).

(b) (100)(4.0g, 0.019mol) was dissolved in methanol (150ml) and potassium carbonate (2.6g, 0.019mol) was added in small portions to the stirred solution at room temperature. The mixture was stirred for 3 days at room temperature then evaporated to dryness in vacuo. The residue was partitioned between water and dichloromethane. The organic layer was dried (sodium sulphate) and concentrated in vacuo to give a dark residue (0.12g) which was shown (t.l.c.) to consist of starting ester (100), aminonitropyridine (102) and a dark polar material. Acidification (HCl) of the aqueous portion

to pH4 yielded no precipitate so the solution was saturated with sodium chloride and extracted exhaustively with dichloromethane then ethyl acetate. The dichloromethane extract yielded 0.72g of a brown solid on work-up. No solid was obtained from the ethyl acetate extract. Attempts to recrystallise the brown solid from either ether propan-2-ol or ethyl acetate resulted in extensive decomposition.

Reactions of 2-(Cyanomethylamino)-3-nitropyridine (101) with bases

(a) The nitrile (101) (1.0g, 5.6mmol) was dissolved in methanol (60ml) and potassium carbonate (0.78g, 5.7mmol) was added in portions to the stirred solution at room temperature. The solvent was removed *in vacuo* after 2h and the black residue partitioned between water and dichloromethane A black gelatinous precipitate formed in the separating funnel, and the addition of more of either solvent did not facilitate solution. Attempts to separate this material from the extraction medium were unsuccessful.

(b) Piperidine (0.48g, 5.6mmol) was added dropwise to a stirred solution of (101) (1.0g, 5.6mmol) in methanol (50ml) at 35°C. No reaction was apparent after 30 min so the temperature was increased. The mixture was heated under reflux for 3h then concentrated *in vacuo*. Attempts to partition the residue between water and diethyl ether were unsuccessful, a black substance contaminating both layers. An aliquot of the aqueous layer was removed and acidified (HCl), however, no precipitate formed. T.l.c. of the ether

layer indicated the presence of starting material (101), 2-amino-3-nitropyridine, and two other unidentified components.

In view of the difficulties encountered both in the preparation of the nitrile (101) and in its reactions with base, this area was not pursued further.

Preparation of N-(3,5-Dinitro-2-pyridyl)glycine derivatives (108 - 111).

General Procedure

The appropriate amine hydrochloride (1mol eq) was added in one portion to a stirred solution of 2-chloro-3,5-dinitropyridine (96) (1mol eq) and triethylamine (2mol eq) in ethanol* (ca. 40ml per g). With the exception of (111)+ the product crystallised almost immediately and after 5 - 10 min was filtered off and recrystallised.

* For the preparation of (109) methanol was used as solvent.

\+ In this example the solution was stirred for 1h then poured into ice-water and the precipitate filtered off.

Thus, the following were prepared:-

N-(3,5-Dinitro-2-pyridyl)glycine ethyl ester (108) yield 84% (from ethanol) m.p. 95°C, (lit.[94], m.p. 89°C). $\nu_{max.}$ 3355 (NH), 1720 (CO), 1540 and 1335 cm^{-1} (NO_2). δ 1.21 (3H,t,CH_3), 4.6 (2H,q,$C\underline{H}_2CH_3$), 4.41 (2H,d,$C\underline{H}_2NH$), 9.02 and 9.24 (2H,2 x d, H-4 and H-6), 9.49 (1H,br t,NH); $J_{CH_2CH_3}$ = 7Hz, J_{CH_2NH} = 6Hz, $J_{4,6}$ = 2.5Hz.

N-(3,5-Dinitro-2-pyridyl)glycine methyl ester (109), (yield, 76%) had m.p. 117°C (from methanol). (Found: C, 37.6; H, 3.1; N, 22.0. $C_8H_8N_4O_6$ requires C, 37.5; H, 3.2; N, 21.8%). $\nu_{max.}$ 3355 (NH), 1720 (CO), 1540 and 1335 cm^{-1} (NO_2). δ 3.7 (3H,s,CH_3), 4.45 (2H,d,CH_2), 9.06 and 9.26 (2H,2 x d, H-4 and H-6), 9.50 (1H,br t,NH); J_{CH_2NH} = 6Hz, $J_{4,6}$ = 2.5Hz.

2-(Cyanomethylamino)-3,5-dinitropyridine (110) (yield 76%) had m.p. 178°C (from DMF/methanol). (Found: C, 37.75; H, 2.2; N, 31.4; $C_7H_5N_5O_4$ requires C, 37.5; H, 2.3; N, 31.4%). $\nu_{max.}$ 3360 (NH) 1525 and 1325 cm^{-1} (NO_2). δ 4.64 (2H,s,CH_2), 9.05 and 9.38 (2H,d x d,H-4 and H-6), 9.50 (1H,br s, N<u>H</u>CH_2); $J_{4,6}$ = 2.5Hz.

2-(2,2,2-Trifluoroethylamino)-3,5-dinitropyridine (111) (yield, 77%) had m.p. 53°C (from carbon tetrachloride). (Found: C, 31.7; H, 1.8; N, 21.35. $C_7H_5F_3N_4O_4$ requires C, 31.6; H, 1.9; N, 21.05%. $\nu_{max.}$ 3363 (NH), 1535 and 1310 cm^{-1} (NO_2). δ 4.79 (2H,q,CH_2), 9.04 and 9.31 (2H, 2 x d, H-4 and H-6), 9.4 (1H,br s,NH); $J_{4,6}$ = 2Hz, J_{CH_2F} = 9Hz.

Reactions of N-(3,5-Dinitropyridyl)glycine Derivatives (108 - 111) with Bases.

The Ethyl Ester (108)

(a) Potassium carbonate (0.26g, 1.9mmol) was added portionwise to a stirred solution of the ester (108) (0.5g, 1.9mmol) in ethanol (20ml) and DMF (3ml). After 3h more ethanol (20ml) was added

and the mixture filtered. The solid (0.26g) was dissolved in water and acidified (HCl) to precipitate a black solid (0.06g). It had m.p. 145°C (dec.). $\nu_{max.}$ 3565-3120 (v.br), 1735 cm^{-1} (CO). m/z, 270 ($M^{+\cdot}$), 225, 197, 184, 151, 124, 105 etc. The filtrate was evaporated to dryness and the residue partitioned between dichloromethane and water. Acidification of the aqueous layer yielded no precipitate. The organic portion was dried (sodium sulphate) and evaporated to give starting material (108) (0.13g).

(b) The reaction was carried out on a larger scale using the ester (108) (2.5g, 9.2mmol) with all other quantities adjusted accordingly. In this case acidification (HCl) of an aqueous solution of the initial precipitate gave only a trace of black solid. The mother-liquor was evaporated to dryness and the residue partitioned between water and dichloromethane. The black aqueous layer gave, on acidification, a black solid (1.56g) which (by t.l.c.) contained more starting material but was mostly highly polar and tarry.

(c) Piperidine (0.32g, 3.8mmol) was added dropwise to a stirred solution of (108) (0.5g, 1.9mmol) in ethanol (20ml) and DMF (3ml) at room temperature. After 3h, the solvent was removed in vacuo and the black residue partitioned between water and dichloromethane. No precipitate formed on acidification of the aqueous portion and nothing

was extracted when the saturated solution (sodium chloride) was washed with dichloromethane. T.l.c. of the dark organic layer indicated a complex mixture.

(d) Similar results to (a) were found when the ester was treated with DBU (1mol eq) in ethanol and DMF.

When the dinitropyridyl compounds (109 - 111) were similarly treated with base, e.g. sodium bicarbonate, DBU, similar results to the above were found. Typically, the reactions were separated, after a given time, into aqueous and organic-soluble portions. The aqueous portions gave, on acidification, very dark material which contained starting material. The organic soluble fractions generally contained more starting material as part of a complex mixture.

CHAPTER IV : EXPERIMENTAL

N-(2,4-Dinitrophenyl)sarcosine (118) was prepared by the literature procedure:- Thus a solution of sarcosine (14.63g, 0.16mol) and sodium bicarbonate (41g) in water (250ml) was added to a stirred solution of chloro-2,4-dinitrobenzene (30.0g, 0.15mol) in ethanol (500ml) at room temperature. The mixture was then heated under reflux for 6h, evaporated *in vacuo* to *ca.* 200ml and extracted with diethyl ether (200ml). Acidification (HCl) of the aqueous layer gave the title compound (118) (36.2g, 96%), m.p. 170-172°C (lit.[95], m.p. 185-186°C; lit.[44], m.p. 176°C). The crude acid is suitable for esterification; the melting point can be raised to 174-176°C by recrystallisation from ethanol-water.

N-(2,4-Dinitrophenyl)sarcosine ethyl ester (119)

(a) The crude acid (118) (25.0g) was dissolved in ethanol (300ml) containing dry hydrogen chloride (7.5g) and the mixture was heated under reflux for 5h. On cooling the solution a yellow-green precipitate formed which was filtered off and recrystallised twice (with charcoal) from ethanol to give the ester (119) (22.41g, 81%). It had m.p. 103°C. (Found: C, 46.4; H, 4.6; N, 14.8. $C_{11}H_{13}N_3O_6$ requires C, 46.65; H, 4.6; N, 14.8%). $\nu_{max.}$ 1740 (CO), 1520 and 1330 cm^{-1} (NO_2). δ 1.24 (3H,t,$CH_2\underline{CH_3}$), 2.96(3H, s,$NC\underline{H_3}$),4.35(2H,q,$\underline{CH_2}CH_3$),4.38(2H,s,$NC\underline{H_2}$),7.24(1H,d,H-6),8.26(1H,dd,H-5),8.61 (1H,d,H-3); $J_{CH_2CH_3}$ = 7Hz, $J_{3,5}$ = 3Hz, $J_{5,6}$ = 9.5Hz.

(b) Sarcosine ethyl ester hydrochloride (0.3g, 2.0mmol)

was added to a stirred suspension of chloro-2,4-dinitrobenzene (0.49g, 2.0mmol) and triethylamine (0.4g, 4.0mmol) in ethanol (10ml) at room temperature. The mixture was then heated at 50-60°C for 4h then left sitting overnight. The yellow product was collected from the cooled mixture and found to have identical i.r. spectrum to the ester (119) from reaction (a). Yield, 0.34g (61%).

(c) The above reaction was repeated using chloro-2,4-dinitrobenzene (10.0g, 0.049mol), sarcosine ethyl ester hydrochloride (7.6g, 0.05mol) and triethylamine (10.0g, 0.099mol) in ethanol (250ml). The mixture was heated under reflux for 5h, cooled to ca. 40°C, filtered, and the solid product washed with ethanol. A bright red material (0.5g) was collected and found to be 2,2'-bis(methylamino)-5,5'-dinitroazoxybenzene(126). (Yield, 6%). It had m.p. 276-277°C (from DMF). (Found: C, 48.45; H, 4.1; N, 24.3. $C_{14}H_{14}N_6O_5$ requires C, 48.6; H, 4.1; N, 24.3%). $\nu_{max.}$ 3410 and 3325 cm^{-1}(NH). $\lambda_{max.}$ 283,373,456 nm; log ε 4.12,4.25,3.83. δ_H(360MHz)* 2.92 (3H,d,NHC$\underline{H}_3$), 2.97 (3H,d,N'HC$\underline{H}_3$), 6.83 (1H,d,H-3'), 6.99 (1H,d,H-3), 7.32 (1H,q,N$\underline{H}$CH$_3$), 8.04 (1H,q,N$\underline{H}$CH$_3$), 8.16 (1H,dd,H-4'), 8.24 (1H,dd,H-4), 8.72 (1H,d,H-6), 9.39 (1H,d,H-6'); $J_{3,4}$ = 9.43Hz, $J_{3',4'}$ = 9.41Hz, $J_{4,6}$ = 2.7Hz, $J_{4'6'}$ = 2.68Hz, NHCH$_3$ = 4.99Hz, N'HCH$_3$= 4.98Hz, δ_C(90.6MHz) 29.7($\underline{C}H_3$), 29.9 ($\underline{C}H_3$), 109.6 (C_3), 112.3 (C_3'), 118.4 and 122.1 (C_6,C_6'), 126.5 (C_1), 127.3 and 127.5 (C_4,C_4'), 131.3 (C_1'), 134.1 and 134.6 (C_5C_5'), 147.7 (C_2'), 150.8 (C_2).

* Assignments were made on the basis of decoupling experiments.

The filtrate was evaporated to ca. 200ml, cooled to room temperature, and the precipitate filtered off. The solid was dissolved in boiling ethanol and filtered to give a mixture (0.9g) of the azoxy compound (126) and the ester (119). Treatment of the filtrate with charcoal followed by filtration then evaporation of the solution yielded 4.08g (29%) of the ester (119), m.p. 97-100°C. Evaporation of the mother-liquor gave a dark residue which by t.l.c. was shown to consist of starting material, ester (119), azoxy compound (126) and at least one other component. A portion was removed and partitioned between water and dichloromethane. Acidification (HCl) of the aqueous layer yielded no precipitate and t.l.c. of the organic portion indicated the presence of all the components noted in the above mixture.

The reaction was again repeated using chloro-2,4-dinitrobenzene (5.0g, 0.025mol), sarcosine ethyl ester hydrochloride (3.81g, 0.025mol) and triethylamine (7.58g, 0.075mol). The azoxy compound (126) was filtered off from the hot reaction mixture after 5h. Yield (0.61g, 14%). Attempts to isolate any other products from the reaction were unsuccessful.

N-(2,4-Dinitrophenyl)sarcosine methyl ester (120) was prepared from the acid (118) (5.0g) in methanol (60ml) containing dry hydrogen chloride (1.5g). Recrystallised from methanol (with charcoal) the ester (120) (3.71g, 70%) had m.p. 109-110°C. (Found: C, 44.5; H, 4.1; N.15.6; $C_{10}H_{11}N_3O_6$ requires C, 44.6; H, 4.1; N.15.6%. $\nu_{max.}$ 1750

(CO), 1520 and 1330 cm^{-1} (NO_2). δ 2.98 (3H,s,$NC\underline{H}_3$), 3.75 (3H,s,$CO_2C\underline{H}_3$), 4.38 (2H,s,CH_2), 7.24 (1H,d,H-6), 8.23 (1H,dd,H-5), 8.59 (1H,d,H-3). $J_{3,5}$ = 3Hz, $J_{5,6}$ = 9.5Hz.

Reactions of N-(2,4-Dinitrophenyl)sarcosine esters (119) and (120) with bases

A general procedure is firstly described for the reaction of the above esters in basic media. Specific reaction conditions and products obtained can be found in table 4,p.90.Further reactions of the ethyl ester which do not involve the general method are then described.

(a) General Procedure

A solution or suspension of the dinitrophenylsarcosine ester was treated with base for the appropriate time then filtered. The collected solid was dried and extracted exhaustively with boiling acetone (Filtration apparatus must be kept warm otherwise the extracted product crystallises from solution and blocks the filter). The acetone filtrate was then evaporated to dryness to yield a bright red solid. 2-Amino-2'-methylamino-5,5'-dinitro-ONN-azoxybenzene* (125) had m.p. 259°C (from acetic acid). (Found: C, 46.8; H, 3.6; N, 25.3. $C_{13}H_{12}N_6O_5$ requires C, 47.0; H, 3.6; N, 25.3%). $\nu_{max.}$ 3460 and 3330 (NH). $\lambda_{max.}$ 315(sh), 366, 438 nm; log ε 4.23, 4.53, 4.16 δ_H(360MHz) 2.97 (3H,d,N'HC$\underline{H}_3$), 6.88 (1H,d,H-3'), 6.97 (1H,d,H-3), 7.16 (2H,s,NH_2), 8.04 (1H,dd,H-4'), 8.12 (1H,q,N$\underline{H}$CH$_3$), 8.20 (1H,dd,H-4), 8.74 (1H,d,H-6), 9.40 (1H,d,H-6'); $J_{3,4}$ = 9.41Hz, $J_{3',4'}$ = 9.25Hz, $J_{4,6}$ = 2.70Hz,

$J_{4'6'}$ = 2.65Hz. δ_C(90.6MHz) 29.9 (CH_3), 112.4 (C_3'), 114.4 (C_3), 119.2 and 122.0 (C_6, C_6'), 125.8 (C_1), 126.8 and 127.45 (C_4C_4'), 131.1 (C_1'), 134.5 and 134.6 (C_5C_5'), 147.7 (C_2'), 152.0 (C_2).

* In the reactions with triethylamine as base the red product was 2,2'-bis(methylamino)-5,5'-dinitroazoxybenzene (126).

The acetone-insoluble, buff-coloured solid was dissolved in water and acidified (HCl) to give 1-hydroxy-4-methyl-7-nitroquinoxaline-2,3-dione (123) m.p. 243°C (dec.) (from acetic acid). (Found: C, 45.3; H, 2.9; N, 17.6. $C_9H_7N_3O_5$ requires C, 45.6; H, 3.0; N, 17.7%). $\nu_{max.}$ 1660 (br,CO), 1515 and 1325 cm^{-1} (NO_2). δ_H 3.58 (3H,s,CH_3), 7.63 (1H,d,H-5), 8.11 (1H,dd,H-6), 8.19 (1H,d,H-8), 11.50 - 12.50 (1H,br s, OH). $J_{5,6}$ = 9Hz, $J_{6,8}$ = 3Hz. See table 5, p.118 for ^{13}C n.m.r. data.

Although the quantity of crude material recovered seldom exceeded 50% of the theoretical, no other products were isolated from the mother-liquor which was shown (t.l.c.) to contain starting material, azoxy compound [(125) or (126)] and at least 4 other components. In the reactions involving triethylamine no methylamino azoxy compound (125) was found. In the other reactions the presence or absence of the bis-methylamino azoxy derivative (126) was difficult to ascertain conclusively. Although one spot on the t.l.c. plate had a similar R_f value to that of the bis-methylamino compound it was not the same colour. The difficulty in identification was further augmented by the

fact that N-methyl-2,4-dinitroaniline (a possible product in these reactions)has the same $R_f$value as that of (126).

(b) Reaction of (119) with DBU

(i) DBU (1.08g, 7.1mmol) was added dropwise to a stirred solution of (119) (2.0g, 7.1mmol) in ethanol (50ml) and DMF (30ml) at room temperature. After 3h the solvent was evaporated in vacuo and the residue partitioned between water and dichloromethane. Acidification (HCl) of the aqueous layer followed by recrystallisation (acetic acid) of the resultant precipitate gave (123) (0.39g, 23%) m.p.228°C (dec.); i.r. spectrum identical to that of an authentic sample. The organic layer was dried (sodium sulphate) and concentrated to give a black oil which was shown by t.l.c. to be a complex mixture. [The methylamino azoxy compound (125) was the only component identified].

(ii) DBU (1.08g, 7.1mmol) was added dropwise to a stirred solution of (119) (2.09g, 7.1mmol) in DMSO (10ml) at 0-5°C. The reaction was stirred at room temperature for 1h then filtered. The filtrate was poured into water (50ml), acidified (HCl) and the precipitate filtered. Recrystallisation from acetic acid gave the quinoxalinedione (123) (0.55g, 33%), m.p. 240°C (dec.)

Reaction of Ethyl 5-nitrobenzimidazole-2-carboxylate 3-oxide (45) with sodium hydroxide

The N-oxide (45) (1.5g) was dissolved in sodium hydroxide solution (2M, 45ml) and stirred at room temperature for 0.5h (a dark red precipitate appeared almost instantaneously on addition of the ester to the solution). The

precipitate was filtered off, dissolved in water and acidified (HCl) to give 5-nitrobenzimidazole 3-oxide (19) (0.73g, 68%), m.p. 264°C (from ethanol) (lit.[28], m.p. 274-276°C). The i.r. spectrum of this compound was identical to that of an authentic sample.

Reaction of 2-Amino-2'-methylamino-5,5'-dinitro-ONN-azoxybenzene (125) with acetic anhydride

Of various reaction conditions attempted the following was found to be most successful:-

The azoxy compound (125) (0.25g, 0.75mmol) was stirred at room temperature for 20 min in acetic anhydride (10ml) containing 2 drops of conc. sulphuric acid. The yellow solution was then poured into stirred ice-water (60ml) and the precipitate filtered off. Recrystallisation from ethanol gave 2-acetamido-2'-(N-methylacetamido)-5,5' dinitro-ONN-azoxybenzene (127) as pale yellow needles, m.p. 190-194°C. Yield, 0.18g, (58%). (Found: C, 49.2; H, 3.9; N, 20.3. $C_{17}H_{16}N_6O_7$ requires C, 49.0; H, 3.9; N, 20.2%). $\nu_{max.}$ 3300 (NH), 1710 (CO), 1555 and 1335 cm^{-1} (NO_2). δ ($CDCl_3$) (300MHz), 1.61 (3H,s,$COC\underline{H}_3$),2.29 (3H,s,$COC\underline{H}_3$), 3.42 (3H,s,$NC\underline{H}_3$), 7.59 (1H,d,H-3), 8.31 (1H,dd,H-4'), 8.49 (1H,dd,H-4), 8.69 (1H,d,H-6), 8.77 (1H,s,N$\underline{H}$), 8.83 (1H,d,H-3'), 9.30 (1H,d,H-6'); a peak at 2.20 was attributed to traces of acetic anhydride in the sample.

The structure of (127) was confirmed by X-ray crystallography (see appendix).

Reaction of 2,2'-bis(methylamino)-5,5'-dinitroazoxybenzene (126) with acetic anhydride

The azoxy compound (126) (0.2g, 0.58mmol) was stirred at room temperature for 0.5h in acetic anhydride (5ml) containing 2 drops of conc. sulphuric acid. The yellow solution was then poured into stirred ice-water (50ml) and the precipitate filtered off. When the material was recrystallised from ethanol (with charcoal) two crystal forms were obtained - small pale yellow needles and yellow prisms. Both had the same i.r. spectrum and melting point. 2,2'-bis(methylacetamido)-5,5'-dinitroazoxybenzene(128) was obtained in the latter crystalline form by recrystallisation from ethanol containing a little DMF. Yield, 0.17g, (68%). It had m.p. 160°C. (Found: C, 50.25; H, 4.1; N, 19.5. $C_{18}H_{18}N_6O_7$ requires C, 50.2; H, 4.2; N, 19.5%. $\nu_{max.}$ 1720 (br,CO), 1520 and 1340 cm^{-1} (NO_2). δ ($CDCl_3$)(300MHz) 1.63, 1.93 2.0, 2.24 (4 x s,$COCH_3$), 3.18, 3.24, 3.29, 2.45 (4 x s,NCH_3). The aromatic region between δ 7.5 and 9.3 was complex and poorly resolved.

N-(2-Nitrophenyl)sarcosine ethyl ester (132)

N-(2-Nitrophenyl)sarcosine was prepared by the literature method[22] as follows:-

A solution of sarcosine (2.2g, 0.025mol) and sodium bicarbonate (9.0g) in water (50ml) was added to a stirred solution of 2-nitrofluorobenzene (3.52g, 0.25ml) in ethanol (90ml). The mixture was then heated under

reflux, in the dark, for 8h. The solution was concentrated to ca. 30ml and extracted with diethyl ether (3 x 100ml). The sarcosine was obtained by careful acidification (HCl) of the well-stirred aqueous fraction. Recrystallisation from dichloromethane-carbon tetrachloride (with charcoal) gave the sarcosine as yellow plates. Yield, 3.8g (81%), m.p. 88-92°C (lit.[22], m.p. 75°C).

N.B. The above reaction failed when 2-nitrochlorobenzene was used in place of the fluoro compound; 70% of the starting material was returned unchanged.

N-(2-Nitrophenyl)sarcosine (10.5g) was dissolved in ethanol (150ml) containing dry hydrogen chloride (3.5g). The solution was heated under reflux for 5h then evaporated to dryness. Purification of the residue by distillation (Kugelrohr) gave the ester (132) (10.53g, 88%), b.p. 170°C/0.2mmHg. (Found: C, 55.2; H, 5.9; N, 11.8. $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 5.9; N, 11.8%). $\nu_{max.}$ 1725 (CO), 1560 and 1335 cm^{-1} (NO_2). δ 2.13 (3H,t,$CH_2\underline{CH_3}$), 2.89 (3H,s,$NC\underline{H_3}$), 3.99 (2H,s,$NC\underline{H_2}$), 4.15 (2H,q,$\underline{CH_2}CH_3$), 6.89 - 7.84 (4H,m,aromatics) $J_{CH_2CH_3}$ = 7Hz.

N.B. The direct synthesis of this compound from 2-nitrofluorobenzene and sarcosine ethyl ester (in DMSO) failed to go to completion and purification of the mixture proved difficult.

Reaction of N-(2-Nitrophenyl)sarcosine ethyl ester (132) with sodium ethoxide

Sodium ethoxide [from sodium (0.48g, 0.02mol) in

ethanol (25ml)] was added to a stirred solution of the ester (132) (5.0g, 0.02mol) in ethanol (25ml) at 0-5°C. The reaction was stirred at room temperature for 15h then evaporated to dryness in vacuo. (Although a thick precipitate formed in the reaction vessel, attempts to filter this solid were unsuccessful). The residue was extracted with water : dichloromethane (1:1), the layers separated, and the aqueous portion acidified (HCl) to give a buff-coloured precipitate. Recrystallisation of this material from DMF-ethanol gave 1-hydroxy-4-methyl quinoxaline-2,3-dione (131) (1.79g, 44%), m.p. 255°C (dec.) (lit.[85], m.p. 253°C). $\nu_{max.}$ 1675 cm^{-1} (br,CO). δ_H 3.58 (3H,s,CH_3), 7.23 - 7.64 (4H,m,aromatics), 11.75 (1H,s,OH). See table 5, p.118 for ^{13}C n.m.r. data. T.l.c. of the organic layer indicated the presence of at least 5 components including starting material.

1-Hydroxy-4-methylquinoxaline-2,3-dione (131) was prepared for comparative purposes by the literature procedure[85].

α-Cyano-N-methyl-o-nitroacetanilide (1.1g, 5.0mmol) was heated under reflux for 0.5h in aqueous sodium hydroxide (1M, 10ml). The suspension was cooled to room temperature, acidified (HCl) and extracted with chloroform. 1-Hydroxy-4-methylquinoxaline-2,3-dione (131) was recovered from the dried (sodium sulphate) organic layer. Recrystallisation from ethanol gave (131) (0.51g, 53%), m.p. 246°C (dec.), i.r. spectrum identical with that for (131) from the previous reaction.

N-(3-Nitro-2-pyridyl)sarcosine ethyl ester (133)

A mixture of sarcosine (4.45g, 0.05mol) and sodium bicarbonate (18.5g) in water (100ml) was added to a stirred solution of 2-chloro-3-nitropyridine (7.9g, 0.05mol) in ethanol (250ml). The solution was heated under reflux for 3h then concentrated to ca. 100ml and extracted with diethyl ether. The remaining aqueous layer was acidified (HCl) and the precipitate filtered off. N-(3-Nitro-2-pyridyl)sarcosine (8.56g, 81%) had m.p. 126-128°C (from propan-2-ol-water). (Found: C, 45.5; H, 4.1; N, 19.9. $C_8H_9N_3O_4$ requires C, 45.5; H, 4.3; N, 19.9%). $\nu_{max.}$ 2640, 2560 (br,OH), 1690 (CO), 1545 and 1340 cm^{-1} (NO_2). δ 2.88 (3H,s,CH_3), 4.29 (2H,s,CH_2), 6.86 (1H,dd,H-5), 8.19 (1H,dd,H-4), 8.34 (1H,dd,H-6), $J_{4,5}$ = 8.0Hz, $J_{4,6}$ = 1.6Hz, $J_{5,6}$ = 4.6Hz.

The sarcosine (8.5g) was dissolved in ethanol (150ml) containing dry hydrogen chloride (3.5g) and heated under reflux for 4h. The solution was then evaporated to ca. 50ml, cooled and poured into well-stirred ice-water (300ml). (Complete evaporation of the reaction solution resulted in considerable decomposition of the product). Filtration of the precipitate, followed by recrystallisation from ethanol-water at 60°C (higher solvent temperature also resulted in product loss) gave the ester (133) as yellow-green needles. Yield, 7.38g (77%), m.p. 52°C. (Found: C, 50.2; H, 5.4; N, 17.6. $C_{10}H_{13}N_3O_4$ requires C, 50.2; H, 5.5; N, 17.6%). $\nu_{max.}$ 1740 (CO), 1560 and 1345 cm^{-1} (NO_2). δ 1.19 (3H,t,$CH_2\underline{CH_3}$), 2.89 (3H,s,$NC\underline{H_3}$), 4.12 (2H,q,$C\underline{H_2}CH_3$)

4.35 (2H,s, $\underline{NCH_2}$), 6.87 (1H,dd,H-5), 8.21 (1H,dd,H-4), 8.31 (1H,dd,H-6), $J_{4,5}$ = 8.0Hz, $J_{4,6}$ = 1.7Hz, $J_{5,6}$ = 4.6Hz.

Reactions of N-(3-nitro-2-pyridyl)sarcosine ethyl ester (133) with bases

(a) With potassium carbonate

N-(3-Nitro-2-pyridyl)sarcosine ethyl ester (133) (3.0g, 0.01mol) and potassium carbonate (1.74g, 0.01mol) were stirred together in ethanol (60ml) at room temperature for 15h. The precipitate was filtered off and the filtrate concentrated in vacuo. The precipitate was dissolved in water (60ml) and acidified to give 1-hydroxy-4-methylpyrido[2,3-b]pyrazine-2,3-dione (135) (0.42g, 18%). It had m.p.242-244°C with dec. from 224°C (from DMF-ethanol). (Found: C, 49.85; H, 3.5; N, 21.8. $C_8H_7N_3O_3$ requires C, 49.75; H, 3.65; N, 21.75%). $\nu_{max.}$ 3200 (OH), 1675 (br,CO). δ_H3.56 (3H,s,CH_3), 7.31 (1H,dd,H-7), 7.85 (1H,dd,H-8), 8.24 (1H,dd,H-6). $J_{8,7}$ = 8.0Hz, $J_{8,6}$ = 1.6Hz, $J_{7,6}$ = 5.0Hz. See table 5, p.118 for ^{13}C n.m.r. data.

The residue from the initial filtration was partitioned between water and diethyl ether. The organic layer was dried (sodium sulphate) and evaporated to dryness to give a dark green gel (1.42g) which was shown (t.l.c.) to be mainly unreacted starting material.

(b) With sodium ethoxide

An ethanolic solution of sodium ethoxide [from sodium (0.25g, 0.01mol) in ethanol (15ml) was added dropwise to a

stirred, ice-cooled suspension of (133) (2.5g, 0.01mol) in ethanol (30ml)]. The mixture was stirred at room temperature for 2h then filtered. Dissolution of the precipitate in water followed by acidification (HCl) gave the pyridopyrazine (135) (0.7g, 35%), m.p. 242-246°C (from DMF-ethanol). The mother-liquor was evaporated to dryness and the residue partitioned between water and diethyl-ether. The organic layer was shown (t.l.c.) to contain at least five components and was not purified further.

N-(3,5-Dinitro-2-pyridyl)sarcosine ethyl ester (134)

Sarcosine ethyl ester hydrochloride (3.76g, 24.5mmol) was added to a stirred solution of 2-chloro-3,5-dinitropyridine (5.0g, 24.5mmol) and triethylamine (4.95g 49mmol) in ethanol (120ml) at room temperature. After 0.5h the precipitate was filtered off and the filtrate concentrated to ca. 30ml to yield a further crop. The combined solids were recrystallised from ethanol-water to afford the ester (134) (5.35g, 77%). It had m.p. 77-80°C. (Found: C, 42.3; H, 4.1; N, 19.7. $C_{10}H_{12}N_4O_6$ requires C, 42.3; H, 4.3; N, 19.7%). $\nu_{max.}$ 1715 (CO), 1520 and 1325 cm^{-1} (NO_2). δ 1.21 (3H,t,$CH_2\underline{CH}_3$), 3.0 (3H,s,NCH_3), 4.15 (2H,q,$\underline{CH}_2CH_3$), 4.55 (2H,s,$NC\underline{H}_2$), 8.89 and 9.09 (2H,2xd, H-4 and H-6). $J_{CH_2CH_3}$ = 7.0Hz, $J_{4,6}$ = 2.0Hz.

Reactions of N-(3,5-Dinitro-2-pyridyl)sarcosine ethyl ester (134) with bases

(a) With potassium carbonate

(i) Potassium carbonate (0.49g, 3.6mmol) was added portionwise to a stirred suspension of the ester (1.0g, 3.5mmol) in ethanol (50ml) at room temperature. The mixture was stirred for 6h then filtered. The filtrate was treated with charcoal, filtered and evaporated to dryness. The solids were combined and stirred in water (20ml) for 15 min then filtered. Acidification (HCl) of the filtrate and recrystallisation of the precipitate from DMF-water afforded 1-hydroxy-4-methyl-7-nitropyrido [2,3-b]pyrazine-2,3-dione (136) (0.2g, 24%). It had m.p. 285°C with dec. from 215°C. (Found: C, 40.6; H, 2.6; N, 23.65. $C_8H_6N_4O_5$ requires C, 40.35; H, 2.5; N, 23.5%). $\nu_{max.}$ 3400 (br,OH), 1710 and 1685 (CO). δ_H 3.63 (3H,s,CH_3), 8.34 (1H,d,H-8), 9.08 (1H,d,H-6), 12.25 (1H,br s,OH); $J_{6,8}$=2.0Hz. See table 5,p.118 for ^{13}C n.m.r.data.

The water-soluble material (0.1g) was extracted with ethanol and filtered. The filtrate was treated with charcoal, evaporated to dryness and the red solid (0.04g, m.p. 210-220°C) recrystallised from ethanol to give 2,2'-bis(methylamino)-5,5'-dinitro-3,3'-azoxypyridine (137) (0.01g, 2%), m.p. 272-274°C. $\nu_{max.}$ 3400, 3300 (NH), 1560 and 1325 cm^{-1} (NO_2). δ(360MHz) 3.04 (3H,d,NHC$\underline{H}_3$'), 3.09 (3H,d,NHC$\underline{H}_3$), 8.22 (1H, br d,N$\underline{H}$CH_3'), 8.78 (1H,br d,N$\underline{H}$CH_3), 9.02 (1H,d,H-6), 9.06 (1H,d,H-6'), 9.19 (1H,d,H-4), 9.46 (1H,d,H-4'); $J_{4,6}$=2.5Hz, $J_{4',6'}$=2.6Hz.

(ii) Potassium carbonate (1.5g, 10mmol) was added to a stirred, cooled (0-5°C) suspension of the ester (3.0g, 10mmol) in ethanol (175ml). A further portion (5mmol)

of base was added after 4h at room temperature and stirring was maintained for another 2h. The solvent was evaporated *in vacuo* and the residue extracted with boiling acetone (500ml). The acetone-insoluble material was dissolved in water and filtered. Acidification (HCl) of the filtrate and recrystallisation of the resultant precipitate gave the pyridopyrazine (136) (0.59g, 24%). The acetone extract was shown by t.l.c. to consist of at least seven components, and attempts to separate this mixture by preparative t.l.c. or column chromatography were unsuccessful.

(b) *With sodium ethoxide*

A solution of sodium ethoxide [from sodium (0.13g, 5.7mmol) in ethanol (10ml)] was added dropwise to a stirred ice-cooled suspension of the ester (1.5g, 5.3mmol) in ethanol (85ml). The mixture was stirred for 3h at room temperature then filtered and the solid extracted with boiling acetone. The acetone insoluble material was dissolved in water, treated with charcoal, filtered, and the filtrate acidified (HCl) to give the pyridopyrazine (136) (0.36g, 29%).

Further attempts to isolate the azoxypyridine compound (137) in the above reaction, or in any other reaction of the ester (134) with potassium carbonate, were unsuccessful.

Reaction of 1-Hydroxy-4-methyl-7-nitroquinoxaline-2,3-dione (123) with thionyl chloride

(i) The title compound (123) (0.8g) was heated under reflux in thionyl chloride (25ml) for 3h. The thionyl chloride was then distilled and the residue recrystallised from DMF-ethanol to give 5-chloro-1-methyl-6-nitroquinoxaline-2,3-dione (124) (0.56g, 65%). It had m.p. 278-283°C. (Found: C, 43.0; H, 2.3; N, 16.6. $C_9H_6ClN_3O_4$ requires C, 42.3; H, 2.4; N, 16.4%). $\nu_{max.}$ 1675 (br,CO), 1520 and 1330 cm^{-1} (NO_2). δ 3.58 (3H,s,CH_3), 7.55 (1H,d,H-8), 7.95 (1H,d,H-7). $J_{7,8}$ = 9.0Hz. Although the compound was slightly impure the proposed structure was confirmed by X-ray crystallography (see Appendix).

(ii) In a second experiment the hydroxyquinoxalinedione (123) (0.75g) was heated under reflux in thionyl chloride (30ml) for 8h. Excess reagent was evaporated off, the residue triturated with diethyl ether and filtered. Recrystallisation from acetic acid gave the chloro compound (124) (0.43g, 54%) m.p. 270°C (dec.).

Reaction of 1-Hydroxy-4-methylquinoxaline-2,3-dione (131) with thionyl chloride

1-Hydroxy-4-methylquinoxaline-2,3-dione (131)(0.5g) and thionyl chloride were heated together under reflux for 2.5h. The thionyl chloride was removed in vacuo and the residue triturated with a mixture of ethanol and diethyl ether. The solid was filtered off (0.27g) and shown by t.l.c. to be a mixture of at least four components (^{1}H-n.m.r. spectrum was very complex). Recrystallisation from DMF gave

3,7-dichloro-1-methylquinoxalin-2-one (138) (0.2g, 34%), m.p. 248-249°C. (Found: C, 47.2; H, 2.6; N, 12.2. $C_9H_6Cl_2N_2O$ requires C, 47.2; H, 2.6; N, 12.2%). $\nu_{max.}$ 1655 (CO). δ 3.66 (3H,s,CH_3), 7.46 (1H,dd,H-6), 7.74 (1H,d,H-8), 7.81 (1H,d,H-5). $J_{5,6}$ = 8.5Hz, $J_{6,8}$ = 2.0Hz.

1-Hydroxy-3-methylbenzimidazolone (139)

N-Cyanomethyl-N-methyl-2-nitroaniline (140), a high-boiling viscous liquid, was prepared according to the general procedure described on p.130. It had δ 3.93 (3H,s,CH_3), 4.06 (2H,s,CH_2), 7.1 - 7.83 (4H,m,aromatics).

N-Cyanomethyl-N-methyl-2-nitroaniline (1.0g, 5.2mmol) and potassium carbonate (0.72g, 5.2mmol) were stirred together in ethanol (15ml) at room temperature for 0.5h. No reaction was apparent so the mixture was heated to reflux and maintained at that temperature for 3h. The solvent was evaporated *in vacuo* and the residue partitioned between water and diethyl ether. Acidification of the aqueous portion gave a precipitate which recrystallised as buff-coloured needles. The benzimidazolone (139) had m.p. 198-200°C (from water) (lit.[81], 203°C). Yield, 0.5g (59%). $\nu_{max.}$ 1685 cm^{-1} (CO). δ_C 27.0 (CH_3), 106.4 and 107.9 (C_4C_7), 120.8 and 121.2 (C_5C_6), 126.4 and 128.5 (C_{3a},C_{7a}), 151.6 (C_2).

N-Cyanomethyl-2,6-dinitroaniline (68b)

The method followed was essentially the same as the method of Moody[38]. Thus, sodium bicarbonate (5.0g, 0.06mol) and aminoacetonitrile hydrochloride (3.0g, 0.03mol)

were added to a stirred solution of chloro-2,6-dinitrobenzene (6.0g, 0.03mol) in DMSO (7ml). The mixture was heated at 80-90°C until the effervescence had ceased (ca. 20 min) then kept at 80°C for a further 30 min. The cooled solution was poured into well-stirred ice-water (100ml), the brown precipitate filtered off and recrystallised from ethanol (with charcoal) to give the nitrile (68b)(3.1g,47%) m.p.118-120°C.(lit.[38], m.p. 119-120°C; yield, 36%).

Reaction of N-Cyanomethyl-2,6-dinitroaniline (68b) with potassium carbonate

N-Cyanomethyl-2,6-dinitroaniline (68b) (2.0g, 9.0mmol) and potassium carbonate (1.24g, 9.0mmol) were heated together under reflux in ethanol (100ml) for 0.5h. The suspension was cooled to room temperature and filtered. Although the precipitate was insoluble in cold water it partly dissolved in boiling water. Filtration of the dark suspension and acidification of the filtrate with conc. hydrochloric acid therefore resulted in two solids being obtained. The precipitate (0.88g) from acidification was recrystallised (with charcoal) from DMF-water to give 1-hydroxy-4-nitrobenzimidazolone (144) (0.69g, 39%). It had m.p. 275°C (dec.). (Found: C, 43.0; H, 2.4; N, 21.5. $C_7H_5N_3O_4$ requires C, 43.1; H, 2.6; N, 21.5%). $\nu_{max.}$ 3200 (br,OH), 1735 (CO), 1520 and 1310 cm^{-1} (NO_2). δ_H 7.2 (1H,t,H-6), 7.43 (1H,dd,H-7) 7.80 (1H,dd,H-5), 11.63 (1H,br s,OH); $J_{5,6}$ = 8.5Hz, $J_{5,7}$ = 2Hz, $J_{6,7}$ = 7.5Hz. δ_C 112.0 (C_7), 115.8 (C_5)

120.94 and 120.88 (C_{3a},C_6), 130.6 and 131.9 (C_4,C_{7a}), 151.6 (C_2).

N-(2,6-Dinitrophenyl)glycine ethyl ester (68a)

This compound was prepared by modifying the literature procedure[96] as follows:-

A solution of glycine (4.15g, 0.066mol) and sodium bicarbonate (9.25g) in water (30ml) was added to a solution of chloro-2,6-dinitrobenzene (10g, 0.049mol) in methanol (100ml). After 1.5h at reflux temperature the solution was cooled and evaporated to dryness. Water (500ml) was added to the residue and the insoluble copper-coloured solid filtered off. This solid was treated with a dilute solution of hydrochloric acid until the material turned bright yellow. Filtration and recrystallisation of the product from methanol gave N-(2,6-dinitrophenyl)-glycine (6.78g, 57%). m.p. 173-175°C. (lit.[96], m.p. 173°C).

The glycine (6.0g) was dissolved in ethanol (150ml) containing conc. sulphuric acid, (3.4g) and the mixture was heated under reflux for 4h. The solvent was concentrated to ca. 75ml, cooled in ice, and the bright yellow solid collected by filtration. The ester (m.p. 83-84°C) (lit.[96], m.p. 86°C) was obtained in quantitative yield and was sufficiently pure to use without further purification.

Reactions of N-(2,6-Dinitrophenyl)glycine ethyl ester (68a) with bases

(a) With potassium carbonate

Potassium carbonate (1.02g,7.4mmol) was added portionwise to a stirred solution of the ester (68a) (2.0g, 7.4mmol) in ethanol (80ml) and DMF (10ml). The reaction was stirred at room temperature for 2.5h then filtered, dissolved in water, and filtered again. A black tarry smear was obtained on the second filtration. The aqueous filtrate was acidified and the precipitate (0.04g) filtered off. Extraction of the saturated (sodium chloride) filtrate with dichloromethane gave a further crop of material (0.04g). The combined solids were recrystallised from ethanol to yield 1-hydroxy-5-nitroquinoxaline-2,3-dione (145)(0.05g, 3%). It had m.p. 231-232°C. (Found: C, 42.9; H, 2.2; N, 18.85. $C_8H_5N_3O_5$ requires C, 43.0; H, 2.3; N, 18.8%). $\nu_{max.}$ 3290, 3260, 3180 (NH,OH), 1700 (br,CO), 1530 and 1310 cm^{-1} (NO_2). δ 7.41 (1H,br t,H-7), 7.95 (2H,br t,H-6 and H-8), 11.70(2H,br s,NH,OH). See table 5, p.118 for ^{13}C n.m.r. data.

The mother-liquor was evaporated to dryness and the residue partitioned between water and dichloromethane. Evaporation of the dried (sodium sulphate) organic layer gave a dark oil (0.42g) which was shown by t.l.c. to consist of at least seven components. A considerable quantity of solid (0.37g) was soluble in neither phase and this was filtered off. T.l.c. indicated that this

red-brown solid was also a complex mixture; however mass spectrometry gave the following fragmentation pattern; m/z 318 ($M^{+\cdot}$), 300, 271, 255, 196, 183, 167, etc. (Found: 318.072284 $C_{12}H_{10}N_6O_5$ requires 318.071260). On the basis of this accurate mass a possible component of the mixture may have been 2,2'-diamino-3,3'-dinitroazoxybenzene (146). The aqueous layer was acidified (HCl) to give a further crop (0.09g) of the quinoxalinedione (145). m.p. 210-212°C. (impure).

(b) The reaction was repeated using the ester (1.5g, 5.6mmol) with all other quantities adjusted accordingly. After 2.5h at room temperature ethanol (25ml) was added to the mixture and the precipitate was filtered off and dissolved in water. The solution was then treated with charcoal, filtered, concentrated to ca. 30ml in vacuo and acidified (HCl) (no precipitate was obtained). The aqueous solution was saturated with sodium chloride and extracted exhaustively with ethyl acetate. Evaporation of the organic extracts and recrystallisation of the residue gave the quinoxalinedione (0.06g, 5%) m.p. 231-232°C. Work-up of the remainder of the reaction as before resulted in a complex mixture from which no pure product was isolated.

(c) With piperidine

The reaction of the ester (68a) with piperidine under similar conditions as for (a) and (b) was wholly unsuccessful; the reaction solution immediately turned

black on addition of base and work-up yielded a black tarry residue.

N-Cyanomethyl-2-methyl-6-nitroaniline (147)

(a) 2-Methyl-6-nitroaniline (2.0g, 0.013mol), paraformaldehyde (1.17g, 0.039mol), potassium cyanide (2.54g, 0.039mol) and zinc chloride (6.58, 0.048mol) were heated together with stirring in acetic acid (60ml) (containing 4 drops of conc. sulphuric acid) for 7h. The mixture was poured into ice-water (300ml) and the precipitate filtered off. The pale yellow solid was recrystallised twice from ethanol to give bis-cyanomethyl-2-methyl-6-nitroaniline (148) (0.51g, 17%) m.p. 113-114°C. (Found: C, 57.7; H, 4.4; N, 24.3. $C_{11}H_{10}N_4O_2$ requires C, 57.4; H, 4.4; N, 24.3%). $\nu_{max.}$ 2245 (w,CN), 1525 and 1340 cm^{-1} (NO_2). δ 2.43 (3H,s,CH_3), 4.35 (4H,2 x CH_2), 7.35 - 7.85 (3H, aromatics). The filtrate from the first recrystallisation was concentrated in vacuo to give a yellow solid (0.82g) shown by t.l.c. to consist of starting material, bis-cyanomethyl compound (148) and the desired product (147).

(b) The reaction was repeated using the 2-methyl-6-nitroniline (4.5g, 0.03mol), paraformaldehyde (2.63g, 0.09mol), potassium cyanide (5.71g, 0.09mol) and zinc chloride (9.88g, 0.073mol) in acetic acid (140ml) containing conc. sulphuric acid (4 drops). The mixture was stirred at 50-55°C then poured into ice-water. The precipitate was filtered off and chromatographed on silica

gel (200g) packed in petroleum ether. Unreacted starting material (1.29g) was collected from the first fractions (petroleum ether : diethyl ether, 9:1). Elution with petroleum ether : ether 7:3, gave a fraction containing N-cyanomethyl-2-methyl-6-nitroaniline (147) (1.6g, 29%) m.p. 75°C. (Found: C, 56.7; H. 4.7; N, 22.1. $C_9H_9N_3O_2$ requires C, 56.5; H, 4.7; N, 22.0%). $\nu_{max.}$ 3325 (NH), 2240 (w,CN), 1535 and 1330 cm^{-1} (NO_2). δ 2.39 (3H,s,CH_3), 4.25 (2H,d,CH_2), 6.40 (1H,t,NH), 7.08 (1H,t,H-4), 7.55 (1H,br d,H-3), 7.85 (1H,dd,H-5). J_{CH_2NH} = 7.5Hz, $J_{3,4}$ = 8Hz, $J_{3,5}$ = 1.6Hz, $J_{4,5}$ = 8Hz.

The final fractions consisted of a mixture of mono and bis-cyano compounds (147) and (148).

N-(2-methyl-6-nitrophenyl)glycine (149)

N-Cyanomethyl-2-methyl-6-nitroaniline (147) (2.0g) was heated under reflux in conc. hydrochloric acid (25ml) for 1.5h, then poured into ice-water (150ml). The precipitate was filtered off and recrystallised from ethanol water to give the glycine (149) (1.66g, 76%), m.p. 137-139°C. (Found: C, 51.8; H, 4.7; N, 13.3. $C_9H_{10}N_2O_4$ requires C, 51.4; H, 4.8; N, 13.3%). $\nu_{max.}$ 1720 (CO), 1530 and 1325 cm^{-1} (NO_2). δ 2.36 (3H,s,CH_3), 3.98 (2H,s,CH_2), 6.86 (1H,t,H-4), 7.43 (1H,br d,H-3), 7.80 (1H,dd,H-5). $J_{3,4}$ = 8Hz, $J_{3,5}$ = 1.6Hz, $J_{4,5}$ = 8.5Hz.

N-(2-Methyl-6-nitrophenyl)glycine ethyl ester (150)

The acid (149) (1.0g) was dissolved in ethanol (50ml) containing dry hydrogen chloride (1.1g) and the mixture

heated under reflux for 4h. The solution was cooled and concentrated to dryness *in vacuo*. Purification of the ester was accomplished by dissolving the residue in diethyl ether and passing it down a short column of silica (packed and eluted with ether). The resultant oil was cooled and scratched to give the ester (150) (0.9g, 88%), m.p. 51-52°C. (Found: C, 55.9; H, 6.0; N, 11.85. $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 5.9; N, 11.8%). $\nu_{max.}$ 3355 (NH), 1730 (CO), 1535 and 1340 cm^{-1} (NO_2). δ 1.16 (3H,t,$CH_2\underline{CH}_3$), 2.35 (3H,s,CH_3), 4.02 (2H,d,$NHC\underline{H}_2$), 4.06 (2H,q,$C\underline{H}_2CH_3$), 6.88 (2H,br t,H-4 and NH), 7.42 (1H,br d,H-3), 7.77 (1H,dd,H-5). $J_{CH_2CH_3}$ = 6.3Hz, J_{CH_2NH} = 6.3Hz, $J_{3,4}$ = 7.5Hz, $J_{3,5}$ = 1.3Hz, $J_{4,5}$ = 8.5Hz.

Reaction of N-Cyanomethyl-2-methyl-6-nitroaniline (147) with potassium carbonate

(a) The nitrile (147) (0.3g, 1.6mmol) and potassium carbonate (0.22g, 1.6mmol) were heated together under reflux in ethanol (10ml) for 2h. The cooled mixture was filtered, the precipitate dissolved in water and then reprecipitated with hydrochloric acid. 1-Hydroxy-4-methylbenzimidazolone (151) (0.015g, 6%) had m.p. 240°C (dec.) (lit.[68], m.p. 254-257°C) and i.r. spectrum identical with an authentic sample; δ_C 15.7 ($\underline{C}H_3$), 103.8 (C_7), 118.8 (C_4), 120.8 and 122.0 (C_5C_6), 123.4 (C_{3a}), 129.2 (C_{7a}), 152.1 (C_2). The initial reaction filtrate was evaporated to dryness and the residue partitioned between water and diethyl ether. Acidification of the aqueous portion gave a precipitate which was filtered off and recrystallised from ethanol-water.

2-Cyano-7-methyl-1H-benzimidazole 3-oxide (152) (0.17g, 63%) had m.p. 228-229°C. (Found: C, 62.2; N, 4.0; H, 24.3. $C_9H_7N_3O$ requires C, 62.4; N, 4.1; H, 24.3%). $\nu_{max.}$ 2240 (CN). δ 2.58 (3H,s,CH_3), 7.14 - 7.54 (3H,m,aromatics).

(b) The previous reaction was repeated on the same scale; reflux was maintained for 6h. No precipitate was obtained when the reaction mixture was filtered. The solvent was removed in vacuo, the residue dissolved in water then acidified (HCl), and the product recrystallised from ethanol-water. The N-oxide (152) (0.13g, 48%) had m.p. 228°C. A further crop (0.01g) of material was obtained from the filtrate. The m.p. (190°C) and i.r. spectrum of this solid($\nu_{max.}$ 2240 and 1710 cm^{-1}) indicated that it was a mixture of the N-oxide (152) and the benzimidazolone (151).

(c) The nitrile (0.2g, 1.0mmol) and potassium carbonate (0.29g, 2.1mmol) were heated under reflux in ethanol (6.5ml) for 2h. Work-up as before yielded only the N-oxide (152) (0.08g, 44%), m.p. 230°C.

Reaction of N-(2-methyl-6-nitrophenyl)glycine ethyl ester (150) with potassium carbonate

A suspension of (150) (0.55g, 2.3mmol) and potassium carbonate (0.32g, 2.3mmol) in ethanol (15ml) was stirred at 50°C for 5h, then cooled and evaporated in vacuo. The residue was partitioned between water and diethyl ether and the layers separated. The aqueous layer was

treated with dilute hydrochloric acid until the pH was approximately 7. The precipitate was filtered off, washed with a little water, and recrystallised from ethanol-water to afford Ethyl 7-methyl-1H-benzimidazole-2-carboxylate 3-oxide (153) (0.28g, 55%), m.p. 170-172°C. (Found: C, 59.7; H, 5.5; N, 12.6; $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.5; N, 12.7%). $\nu_{max.}$ 1730 (CO). δ 1.40 (3H,t,$CH_2\underline{CH_3}$), 2.59 (3H,s,CH_3), 4.45 (2H,q,CH_2), 7.06 - 7.45 (3H,m,aromatics), 12.18 (1H,s,NH,OH).

Reaction of Ethyl 3H-imidazo[4,5-b]pyridine-2-carboxylate 1-oxide (103) with hydrochloric acid

The ester (103) was heated under reflux in conc. hydrochloric acid (15ml) for 2h. The solution was then evaporated to dryness, water (30ml) was added, and the non-aqueous soluble material was filtered off and recrystallised from water. The grey feathers (0.25g) had m.p. 310°C (dec.). (Found: C, 44.9; H, 2.95; N, 22.6. $C_7H_5N_3O_3.\frac{1}{2}H_2O$ requires C, 44.7; H, 3.2; N, 22.3%). $\nu_{max.}$ 3400, 3180 (br,NH,OH), 1640 (br,CO). δ_H 7.15 (1H,dd,H-7), 7.83 (1H,dd,H-8), 8.18 (1H,dd,H-6), 12.38 (br s,NH,OH); $J_{6,7}$ = 5.0Hz, $J_{6,8}$ = 1.6Hz, $J_{7,8}$ = 9.0Hz. See table 5, p.118 for ^{13}C n.m.r. data. On the basis of the above analytical and spectroscopic data, and on comparison of these with the N-methyl analogue (135), this material was considered to be 1-hydroxypyrido[2,3-b]pyrazine-2,3-dione (163).

The reaction filtrate was concentrated in vacuo to give a dark residue (0.86g) which, by t.l.c., was a

complex mixture. Attempts to purify this mixture were unsuccessful.

N-Methyl-2,4-dinitroaniline (164) was prepared according to the literature procedure[97]. Thus, ethanolic methylamine (9.4g,33%) was added to a solution of chloro-2,4-dinitrobenzene (10.15g, 0.05mol) in ethanol (150ml) and the mixture was heated under reflux for 0.5h. After cooling to room temperature the yellow precipitate was filtered off and recrystallised from acetic acid to give (164) (8.6g, 88%). It had m.p. 166-168°C (lit.[97], m.p. 178°C). T.l.c. indicated only one spot.

Reaction of N-methyl-2,4-dinitroaniline (164) with sodium ethoxide

A solution of sodium ethoxide [from sodium (0.06g, 2.6mmol) in ethanol (5ml))] was added dropwise to a solution of (164) (0.5g, 2.5mmol) in ethanol (15ml) and DMF (15ml) at 60°C. The reaction was stirred at 60°C for 7h then cooled and filtered. Unreacted starting material (0.34g) was recovered and t.l.c. of the filtrate showed only the presence of more N-methyl-2,4-dinitro-aniline (164).

Reaction of 2,2'-bis(methylamino)-5,5'-dinitroazoxybenzene (126) with sodium ethoxide

The title compound (126) (0.02g, 0.06mmol) was stirred at room temperature in ethanol (0.5ml) and DMF (0.5ml) and a solution of sodium ethoxide (excess) in ethanol was added. T.l.c. indicated that after 0.5h no

reaction had occurred so the temperature was increased to 70-75°C and maintained at that temperature for a further 0.5h. No conversion to the methylamino azoxy compound (125) was observed; the starting material (126) was returned unchanged.

Reaction of N-(2,4-dinitrophenyl)sarcosine ethyl ester (119) with base in the presence of o-phenylenediamine

(a) With triethylamine

A solution of N-(2,4-dinitrophenyl)sarcosine ethyl ester (119) (1.0g, 3.5mmol) and o-phenylenediamine (0.38g, 3.6mmol) in ethanol (25ml) was heated under reflux for 1h. T.l.c. showed that no reaction had occurred. The solution was cooled to ca. 40°C, triethylamine (0.71g, 7mmol) was added and the mixture heated at the boiling point for 4.5h. On cooling the solution a red-brown precipitate formed which was filtered off and found to be a 3-component mixture comprising the bis-methylamino azoxy compound (126), o-phenylenediamine, and one other component*. This solid was washed with ethanol (200ml) and recrystallised from DMF to give 2,2'-bis(methylamino)-5,5'-dinitroazoxybenzene (126) (0.29g, 48%), m.p. 266 - 269°C. The mother-liquor was evaporated to dryness and partitioned between water and dichloromethane. Some material (0.12g) was insoluble in both the organic and the aqueous phase. Recrystallised from ethanol (with charcoal) quinoxalin-2-one (165) (0.08g) had m.p. 258-260°C (lit.[98], m.p. 262-264°C). $\nu_{max.}$ 1695 (CO). δ 7.19-7.86 (4H,m,aromatics), 8.19 (1H,s,H-3), 13.53 (1H,br s,NH,OH).

m/z 146 ($M^{+\cdot}$), 118, 91. The organic layer was dried (sodium sulphate) and evaporated to dryness to give a dark tarry residue (0.69g) which was shown by t.l.c. to consist of at least eight components. No material was extracted into the aqueous phase.

* The R_f value of this component corresponded to that of the methylamino azoxy compound (125).

(b) With sodium ethoxide

Reaction (a) was repeated using the ester (2.0g), o-phenylenediamine (1mol eq) and sodium ethoxide (1mol eq). After 3h at room temperature the precipitate was filtered off and separated into its components according to the general procedure (p.173) 2-Amino-2'-methylamino-5,5'-dinitro-ONN-azoxybenzene (125) and 1-hydroxy-4-methyl-7-nitroquinoxaline-2,3-dione (123) were obtained in yields of 26% and 20% respectively. When the mother-liquor was evaporated and treated as for reaction (a) the insoluble portion was a mixture which resisted further purification. The presence of quinoxalin-2-one (165) was however implicated from mass spectral analysis.

Experiment to trap formaldehyde in the reaction of N-(2,4-dinitrophenyl)sarcosine ethyl ester (119) with sodium ethoxide

(a) Control

Concentrated sulphuric acid (2 drops) was added via a dropping funnel to a 3-necked flask containing a stirred suspension of paraformaldehyde (0.5g) in ethanol (25ml)

and DMF (5ml). The reaction was carried out in an inert atmosphere (N_2). The mixture was heated at 50°C until a precipitate appeared in the adjoining trap containing Brady's solution (2,4-dinitrophenylhydrazine in methanol/ sulphuric acid). The precipitate was filtered off and subjected to mass spectrometry. m/z 210 ($M^{\cdot+}$), 180, 152, 122, etc. (2,4-dinitrophenylhydrazone)(168).

(b) Sodium ethoxide [from sodium (0.34g, 0.015mol) in ethanol (40ml)] was added to a stirred solution of the ester (119) in ethanol (110ml) and DMF (50ml) at room temperature. The reaction temperature was slowly raised to 40-45°C and maintained at that temperature for 2h. No precipitate formed in the adjoining trap containing Brady's solution. The reaction was heated at boiling until ca. 20ml of distillate had collected in the trap. The solution in the collecting vessel was concentrated to ca. 10ml and cooled in ice. A fine precipitate formed which was filtered off and subjected to mass spectrometry as in (a). m/z 210 ($M^{\cdot+}$), 182, 180, 122, etc. (2,4-dinitrophenylhydrazone)(168).

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A P P E N D I X

X-RAY CRYSTALLOGRAPHY

The data and information in this Appendix were provided by Professor G. Ferguson of the University of Guelph, Ontario, Canada.

Crystals of (127), (124) and (123).H_2O suitable for X-ray diffraction experiments were grown from ethanol, dimethylformamide-ethanol, and methanol respectively. For each compound, cell data were determined on a CAD-4 diffractometer from the setting angle of 25 reflections with Θ in the range 10-15° using Mo-Kα radiation.

Crystal data

Compound (127) : $C_{17}H_{16}N_6O_7$, M_r=416.4. Monoclinic, a=19.949(4), b=10.289(4), c=9.101(2)Å, β=97.98(2)°; $\underline{U}$=1850Å^3, $\underline{Z}$=4, $\underline{D}_c$=1.49g cm^{-3}, F(000)=864, μ(Mo-Kα)=1.1 cm^{-1}. Space group $P2_1/n$, uniquely from systematic absences.

Compound (124) : $C_9H_6ClN_3O_4$, M_r=255.6. Monoclinic, a=6.922(1), b=10.857(3), c=13.192(2)Å, β=100.87(1)°; $\underline{U}$=974Å^3, $\underline{Z}$=4, $\underline{D}_c$=1.74g cm^{-3}, F(000)=520, μ(Mo-Kα)=4.0 cm^{-1}. Space group $P2_1/c$, uniquely from systematic absences.

Compound (123).H_2O : $C_9H_7N_3O_5$, M_r=255.2. Monoclinic, a=16.130(3), b=7.173(1), c=18.215(3)Å, β=97.67(2)°; $\underline{U}$=2088Å^3, $\underline{Z}$=8, F(000)=1056, μ(Mo-Kα)=1.3 cm^{-1}. Space group C2/c or Cc from systematic absences: C2/c chosen, and confirmed by the analysis.

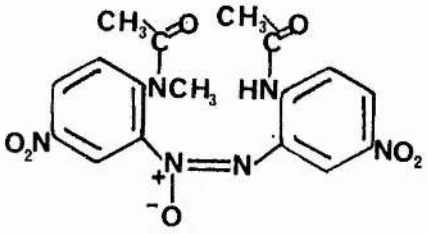
Data collection and processing

Data were collected with a CAD-4 diffractometer, using the $\omega/2\theta$ scan method and graphite-monochromatised Mo radiation. The structures were solved with the aid of MULTAN, and refined by full-matrix least-squares calculations with all non-hydrogen atoms allowed anisotropic motion. All hydrogen atoms were clearly visible in difference maps calculated at intermediate stages in the refinements, and all were included (but not refined) in the final rounds of calculations. For all three structures, the N-H and C-H hydrogens were positioned geometrically 0.95A from the atom to which they were bonded. For (123).H_2O, the co-ordinates of hydrogens bonded to oxygen were taken from the difference maps. For (127), one of the methyl groups (C17) had its hydrogens disordered over two sites.

The weights used in the refinement were based on counting statistics $W = 1/[\sigma^2(F) + p(F_o)^2]$ and scattering factor data were from International Tables for X-ray Crystallography. All calculations were performed on a PDP11/73 system using SDP-Plus.

In the following section the crystal structure of each compound analysed is given, followed by the bond lengths, bond angles and, where appropriate the intra- and inter-molecular contacts. A brief interpretation of the data presented is also given for each structure.

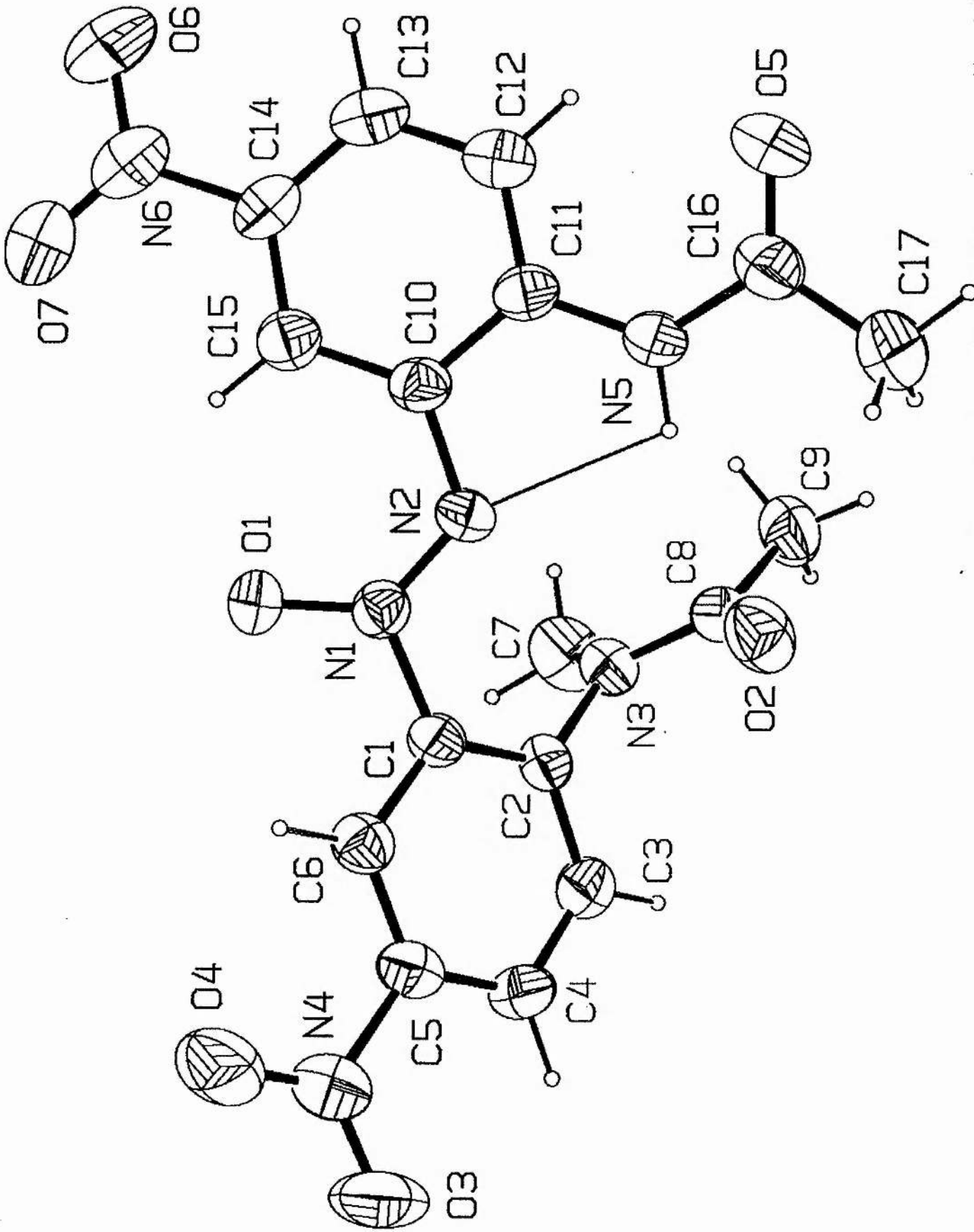
Compound 127



The most remarkable feature of this structure is the intramolecular hydrogen bond between the amino-hydrogen of the acetamido-group and the adjacent azoxy-nitrogen. This interaction serves not only to bring these ortho-located nitrogens closer together (the angles N2-C10-C11 and C10-C11-N5 being 112.3° and 118.8° respectively); it is also conformation-determining for a substantial part of the molecule, since it effectively locks the atoms of the azoxy- and acetamido-groups into the same approximate plane as the 'right-hand' benzene ring. This results, in turn, in the amide carbonyl group being in close proximity to the ortho-hydrogen on the ring, a feature which accounts, presumably, for the large chemical shift difference between this proton (H-3 in experimental section) and its counterpart (H-3') in the other ring [$\Delta\delta$=1.24; cf. $\Delta\delta$=0.09 for the corresponding proton in compound (125)]. There is no analogous conformational restriction in the 'left-hand' benzene ring: there the bulky N-methylacetamido-substituent is accommodated by rotation of this ring by 35° relative to the rest of the molecule, and alignment of the substituent atoms approximately at right angles to the plane of the ring. It is noteworthy that the azoxy-

oxygen does not engage in hydrogen bonding, either intra- or inter-molecularly; it does, however, show a charge-transfer interaction with the nitro-group (N4) of the adjacent molecule.

(e)


O6
C13
C12
O5
C14
N6
C11
C16
O7
C15
C10
C17
N5
N2
C9
O1
C8
C7
N1
N3
O2
C1
C2
C6
C3
O4
N4
C5
C4
O3

Molecular dimensions

Bond distances (A°)

O1	N1	1.256(3)	N6	C14	1.463(4)
O2	C8	1.219(4)	C1	C2	1.382(4)
O3	N4	1.213(3)	C1	C6	1.382(4)
O4	N4	1.215(4)	C2	C3	1.384(4)
O5	C16	1.200(4)	C3	C4	1.366(4)
O6	N6	1.222(4)	C4	C5	1.372(4)
O7	N6	1.216(4)	C5	C6	1.368(4)
N1	N2	1.278(3)	C8	C9	1.493(5)
N1	C1	1.465(3)	C10	C11	1.411(4)
N2	C10	1.407(4)	C10	C15	1.388(4)
N3	C2	1.432(4)	C11	C12	1.393(4)
N3	C7	1.460(4)	C12	C13	1.377(4)
N3	C8	1.354(4)	C13	C14	1.370(5)
N4	C5	1.464(4)	C14	C15	1.373(4)
N5	C11	1.395(3)	C16	C17	1.484(5)
N5	C16	1.376(4)			

Bond angles (°)

O1	N1	N2	127.4(2)	N4	C5	C4	118.4(3)
O1	N1	C1	115.8(2)	N4	C5	C6	119.3(3)
N2	N1	C1	116.7(2)	C4	C5	C6	122.2(3)
N1	N2	C10	120.0(2)	C1	C6	C5	118.0(3)
C2	N3	C7	116.1(2)	O2	C8	N3	121.0(3)
C2	N3	C8	117.9(2)	O2	C8	C9	122.3(3)
C7	N3	C8	124.8(3)	N3	C8	C9	116.7(3)
O3	N4	O4	123.5(3)	N2	C10	C11	112.3(2)
O3	N4	C5	118.4(3)	N2	C10	C15	128.3(3)
O4	N4	C5	118.1(3)	C11	C10	C15	119.4(3)
C11	N5	C16	127.0(2)	N5	C11	C10	118.8(2)
O6	N6	O7	123.1(3)	N5	C11	C12	121.9(3)
O6	N6	C14	117.9(3)	C10	C11	C12	119.3(3)
O7	N6	C14	119.1(3)	C11	C12	C13	120.5(3)
N1	C1	C2	123.1(3)	C12	C13	C14	119.0(3)
N1	C1	C6	115.4(2)	N6	C14	C13	119.5(3)
C2	C1	C6	121.3(3)	N6	C14	C15	117.9(3)
N3	C2	C1	123.8(2)	C13	C14	C15	122.5(3)
N3	C2	C3	117.6(2)	C10	C15	C14	119.0(3)
C1	C2	C3	118.3(3)	O5	C16	N5	124.1(3)
C2	C3	C4	121.2(3)	O5	C16	C17	122.2(3)
C3	C4	C5	118.7(3)	N5	C16	C17	113.7(3)

intra- and inter-molecular contacts (°)

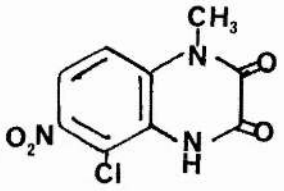
N5(H) ... N2 2.622(3)	HN5 ... N2 2.22	N5-H ... N2 104
O1 ... N4 (I) 2.862(3)	O3 ... O4 (II) 3.083(4)	

The roman numerals refer to equivalent positions

(I) -x, -y, 1-z

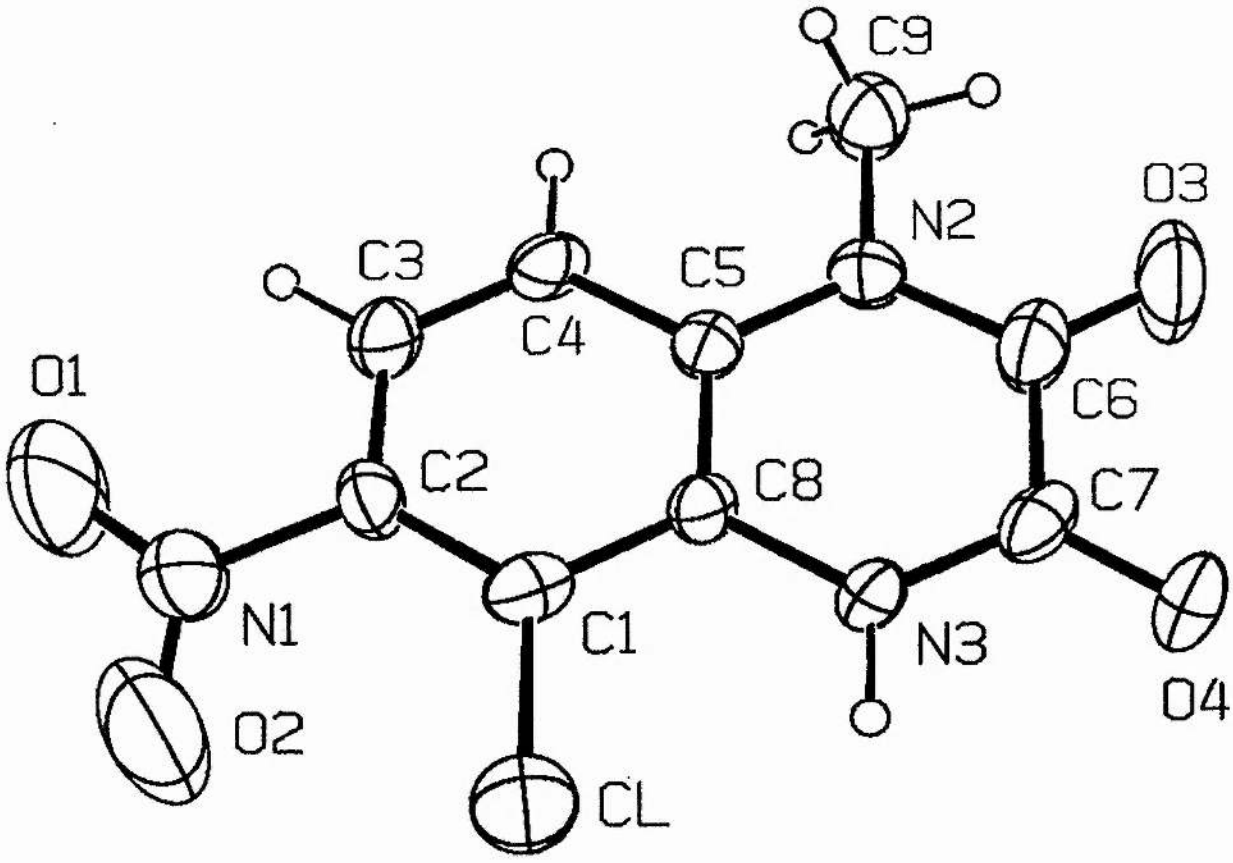
(II) -x, 1-y, 1-z

Compound 124



This exists in the crystal as a centrosymmetric dimer, with the two individual molecules linked by a pair of O...H hydrogen bonds; the carbon-oxygen bond lengths leave no doubt that the molecule is correctly represented as the dione tautomer. The steric interaction between the adjacent chloro- and nitro-substituents is accommodated by the plane of the latter being rotated by 13° from that of the ring system.

(j)



Molecular dimensions

Interatomic distances (A°)

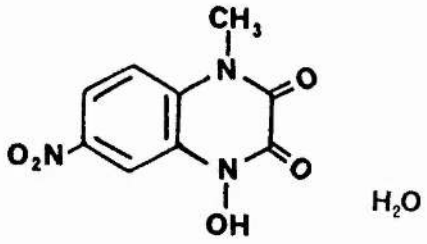
CL	C1	1.706(5)
O1	N1	1.130(6)
O2	N1	1.145(8)
O3	C6	1.202(6)
O4	C7	1.211(5)
N1	C2	1.472(6)
N2	C5	1.394(6)
N2	C6	1.385(6)
N2	C9	1.457(7)
N3	C7	1.341(6)
N3	C8	1.397(5)
C1	C2	1.390(6)
C1	C8	1.404(6)
C2	C3	1.369(7)
C3	C4	1.385(6)
C4	C5	1.395(6)
C5	C8	1.401(6)
C6	C7	1.521(7)
O4	N3*	2.949(5)

The * refers to equivalent position: 2-x,-y, 2-z.

Bond angles (°)

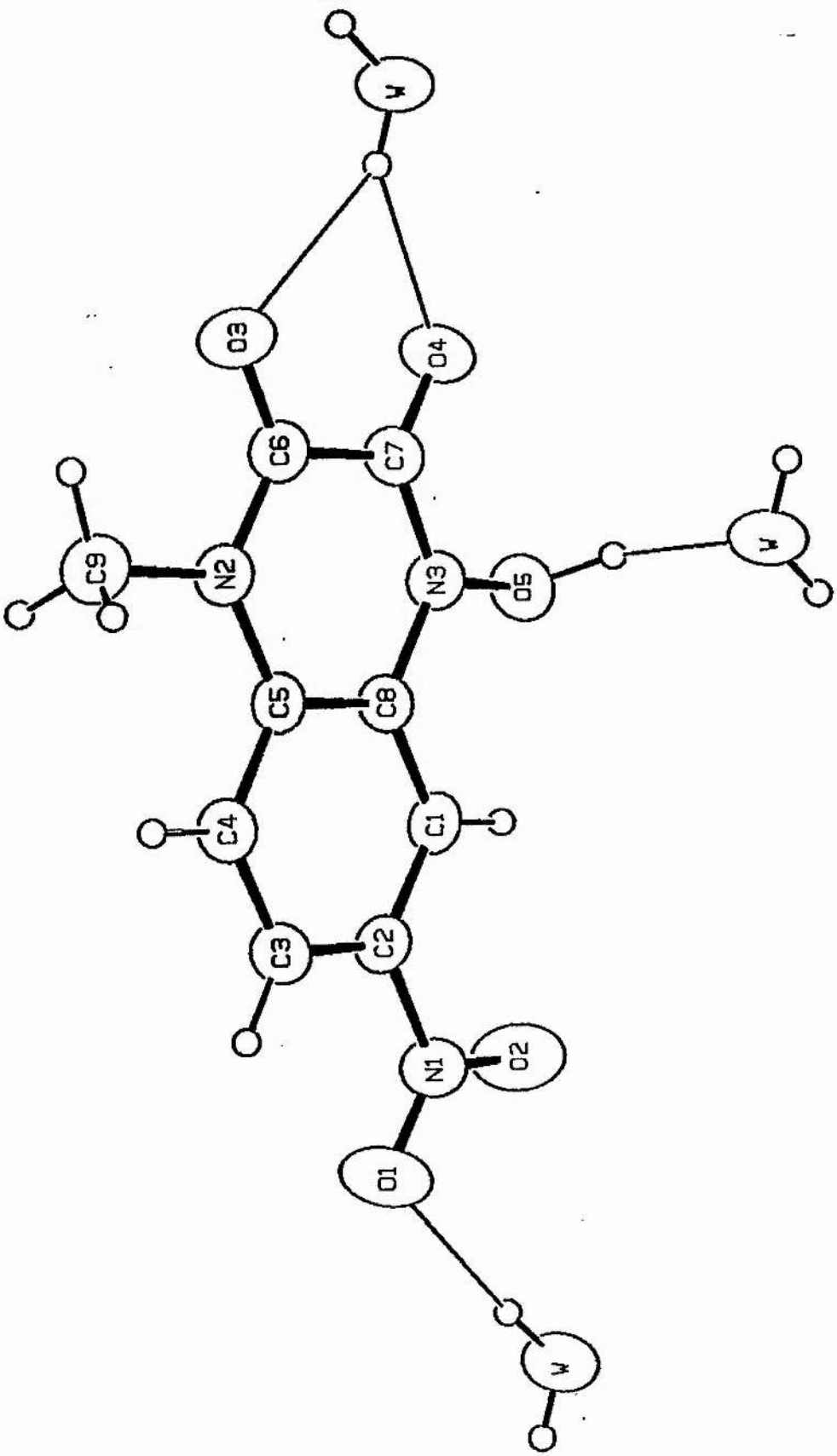
O1	N1	O2	119.0(6)
O1	N1	C2	119.4(5)
O2	N1	C2	121.4(4)
C5	N2	C6	122.7(4)
C5	N2	C9	120.1(4)
C6	N2	C9	117.1(4)
C7	N3	C8	123.9(4)
CL	C1	C2	123.9(4)
CL	C1	C8	117.4(3)
C2	C1	C8	118.7(4)
N1	C2	C1	121.2(4)
N1	C2	C3	116.8(4)
C1	C2	C3	122.0(4)
C2	C3	C4	119.6(4)
C3	C4	C5	120.3(4)
N2	C5	C4	120.7(4)
N2	C5	C8	119.5(4)
C4	C5	C8	119.8(4)
O3	C6	N2	122.8(5)
O3	C6	C7	120.3(4)
N2	C6	C7	116.9(4)
O4	C7	N3	122.7(5)
O4	C7	C6	119.6(4)
N3	C7	C6	117.7(4)
N3	C8	C1	121.1(4)
N3	C8	C5	119.3(4)
C1	C8	C5	119.6(4)

Compound 123.(H_2O)



Although molecules of this type have previously been formulated as 3-hydroxyquinoxalin-2-one 4-oxides, the carbon-oxygen and nitrogen-oxygen bond lengths are indicative of the N-hydroxyquinoxalinedione structure in the crystal. In the absence of the neighbouring chloro-substituent, the nitro-group and the ring system are effectively co-planar, and the single water molecule engages in hydrogen bonding in three directions. One hydrogen interacts with a nitro-oxygen (O1) and the other forms a bifurcated hydrogen bond with the two carbonyl oxygens; whereas the water oxygen interacts with the (acidic) hydroxyl hydrogen.

(n)



Molecular dimensions.

Bond distances (Å)

O1	N1	1.218(3)
O2	N1	1.207(3)
O3	C6	1.220(3)
O4	C7	1.210(3)
O5	N3	1.386(2)
N1	C2	1.463(3)
N2	C5	1.401(3)
N2	C6	1.363(3)
N2	C9	1.469(3)
N3	C7	1.354(3)
N3	C8	1.398(3)
C1	C2	1.378(3)
C1	C8	1.385(3)
C2	C3	1.376(3)
C3	C4	1.384(3)
C4	C5	1.391(3)
C5	C8	1.403(3)
C6	C7	1.514(3)

Bond angles (°)

O1	N1	O2	122.7(2)
O1	N1	C2	118.4(2)
O2	N1	C2	118.9(2)
C5	N2	C6	122.3(2)
C5	N2	C9	120.2(2)
C6	N2	C9	117.4(2)
O5	N3	C7	117.9(2)
O5	N3	C8	116.8(2)
C7	N3	C8	124.9(2)
C2	C1	C8	117.9(2)
N1	C2	C1	117.9(2)
N1	C2	C3	119.0(2)
C1	C2	C3	123.0(2)
C2	C3	C4	118.4(2)
C3	C4	C5	120.8(2)
N2	C5	C4	121.8(2)
N2	C5	C8	119.3(2)
C4	C5	C8	118.8(2)
O3	C6	N2	123.0(2)
O3	C6	C7	118.1(2)
N2	C6	C7	118.9(2)
O4	C7	N3	124.0(2)
O4	C7	C6	120.2(2)
N3	C7	C6	115.7(2)
N3	C8	C1	120.4(2)
N3	C8	C5	118.7(2)
C1	C8	C5	120.9(2)

Hydrogen bond dimensions [(A°) and (°)]

O(W)...O1*	3.013(2)	HW1---O(W)---HW2	123.2
O(W)...O2*	3.129(3)	HW1---O(W)...HO5	108.4
O(W)...O3#	2.968(2)	HW2---O(W)...HO5	111.5
O(W)...O4#	2.838(2)	O(W)---HW1...O1*	174.6
O(W)...O5	2.602(2)	O(W)---HW2...O3#	144.5
O(W)---HW1	0.843	O(W)---HW2...O4#	141.1
O(W)---HW2	0.794	O3#..HW2...O4	74.4
O(5)---HO(5)	0.89	O5---HO5...OW	169.9
O(W)...HO5	1.73		
HW1...O1	2.17		
HW2...O3 #	2.29		
HW2...O4 #	2.18		

The * and# refer to equivalent positions:

* -x, y, 1.5-z; # 0.5-x, 0.5-y, 1-z.

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A NEW ROUTE TO N-HYDROXYQUINOXALINE-2,3-DIONES AND SOME AZA-ANALOGUES

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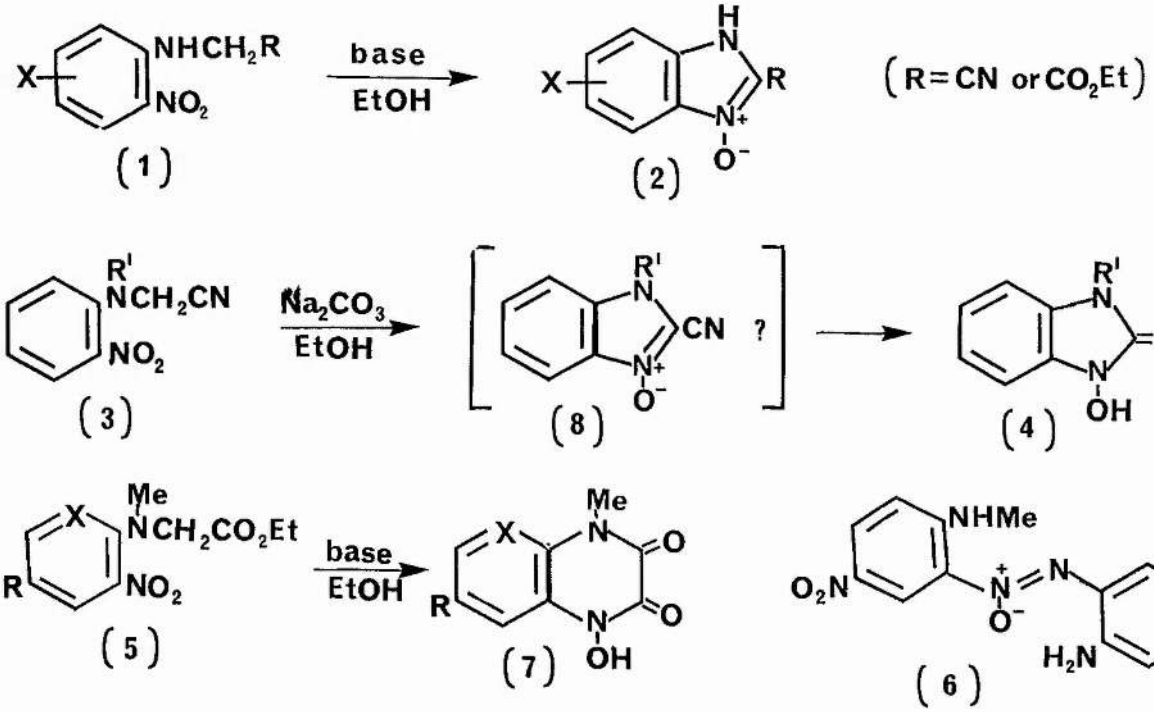
Reactions of N-(o-nitroaryl)sarcosine esters with bases give 1-hydroxy-4-methylquinoxaline-2,3-diones as the principal products; the corresponding reactions of N-(3-nitro-2-pyridyl)sarcosine esters give 1-hydroxy-4-methylpyrido[2,3-b]pyrazine-2,3-diones. The significance of these results, in relation to a general mechanism for nitro-group condensations, is discussed.

It is now well established[1-4] that *o*-nitroaniline derivatives of the type (1), where R is an electron-acceptor, are readily cyclised in basic media to benzimidazole *N*-oxides (⇌*N*-hydroxybenzimidazoles) (2). However, the corresponding reactions of *o*-nitroaniline derivatives in which the amino-nitrogen is tertiary lead to different types of product. Thus Livingstone and Tennant have shown[1] that nitriles of the type (3) (R' ≠ H) are cyclised to *N*-hydroxybenzimidazolones (4); and we now report that the reactions of *N*-(*o*-nitroaryl)sarcosine ethyl esters (5) with bases give 1-hydroxy-4-methylquinoxaline-2,3-diones (7).

In the reaction of the *N*-(2,4-dinitrophenyl)sarcosine ester (5a) with sodium ethoxide, the quinoxalinedione (7a) is produced in low yield (19%), the main product (32%) being the



(5a,7a): R = NO_2, X = CH (5c,7c): R = NO_2, X = N
(5b,7b): R = H, X = CH (5d,7d): R = H, X = N

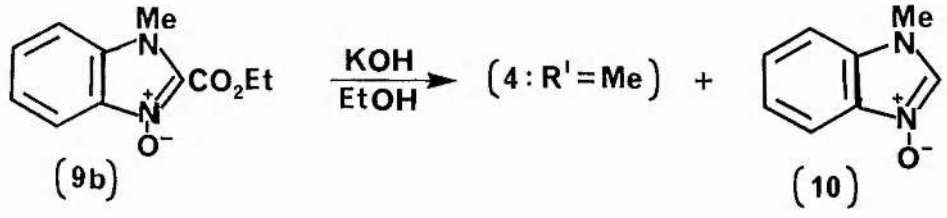
unusual azoxybenzene derivative (6).[¶] Reaction of the ester (5a) with potassium carbonate, however, gives (7a) as the main product, and analogous cyclisations of the esters (5b - d) are observed under appropriate reaction conditions. The products (7a - d) are best characterised by their ^{13}C n.m.r. spectra (see Table).

1-Hydroxyquinoxaline- and -pyrido[2,3-*b*]pyrazine-2,3-diones

Reaction	Product			^{13}C chemical shifts (δ) in $(CD_3)_2SO$								
	No.	Yield,%	M.p.,°C.	2	3	4a	5	6	7	8	8a	Me
(5a) + K_2CO_3	(7a)	35	243(dec.)	155.2	150.1	130.8	115.8	119.2	142.7	107.8	127.9	30.6
(5b) + NaOEt	(7b)	44	255 †‡	154.0	150.2	125.3	114.9	124.2*	123.8*	112.8	127.3	39.9
(5c) + K_2CO_3	(7c)	24	215(dec.)	155.8	149.8	140.1	N	137.9	141.6	114.4	124.4	29.2
(5d) + NaOEt	(7d)	35	242-4‡	155.7	149.9	137.2	N	142.3	120.3	119.3	124.0	28.4
(12a) + K_2CO_3	(16a)	5	231-2	154.1	150.5	119.2	134.5	118.9*	122.9	120.3*	129.7	-

†Lit.,[6] 253 °C (dec.) ‡Some decomposition observed below m.p. *Provisional assignments.

These reactions are of synthetic value to the extent that they offer an easy route to a series of heterocyclic compounds which, except for the parent (7b)[6], are not readily accessible by more conventional cyclisations. They are also of considerable mechanistic interest: although the reaction (3) → (4) may conceivably proceed *via* the *N*-oxide intermediate (8)[1], the corresponding mechanism for the reaction (5) → (7) (Scheme 1a) appears less likely. Hydrolytic ring-opening of the intermediate (9) (a cyclic nitrone) is conceivable, but the ester (9b) is already known[7] to react with ethanolic base in a different way, giving a mixture of (4 : R' = Me) and (10).

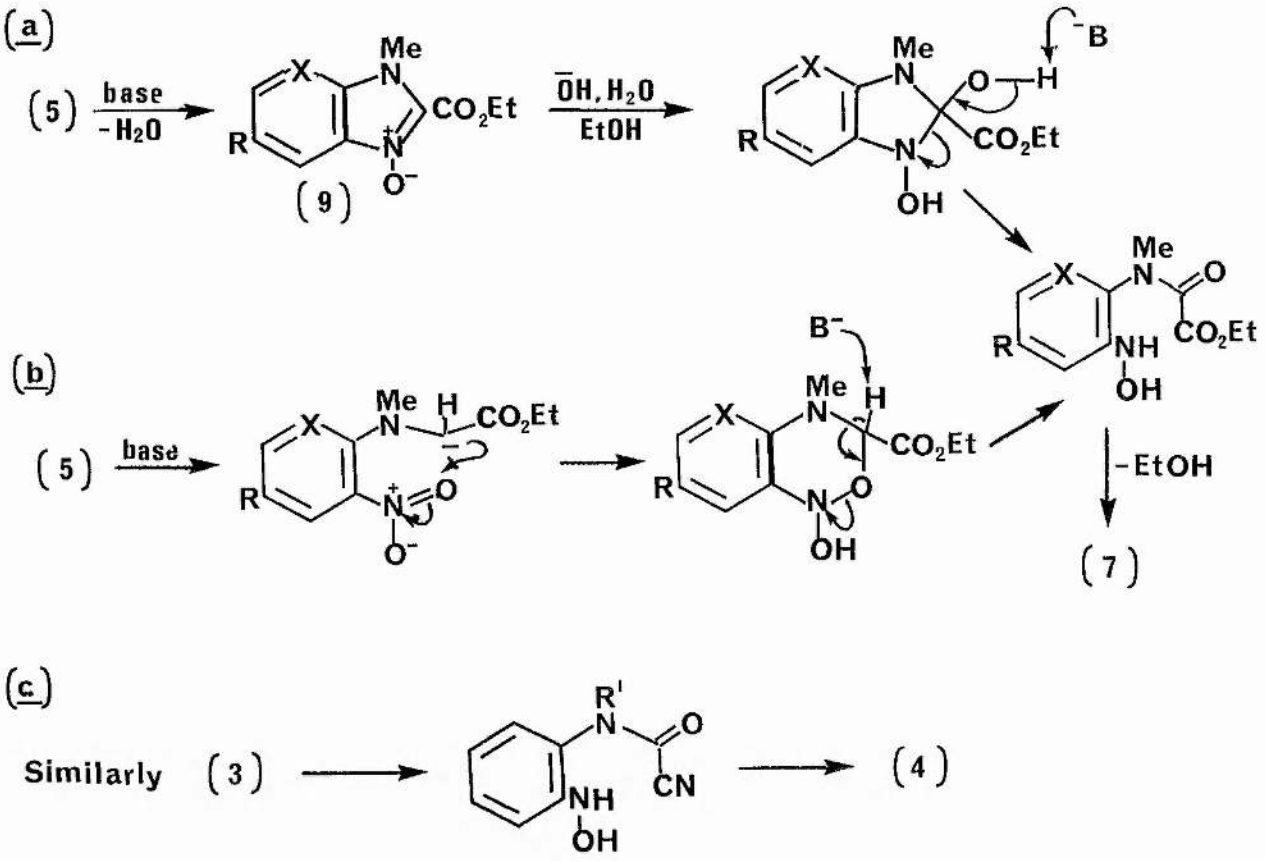


(9b) (10)

It is possible, however, to envisage other mechanisms for the reaction (5) → (7) which do not involve the ester (9). The interaction of *ortho*-situated tertiary amino- and nitro-groups under acidic conditions is believed to involve an intramolecular redox reaction of *aci*-nitro tautomers,[8] and a similar mechanism can be written for a base-induced cyclisation such as (5) → (7). Another possibility (Scheme 1b) involves nucleophilic attack on the oxygen of the nitro-group, followed by ring-opening and recyclisation. A similar mechanism may be written for the reaction (3) → (4) (Scheme 1c).

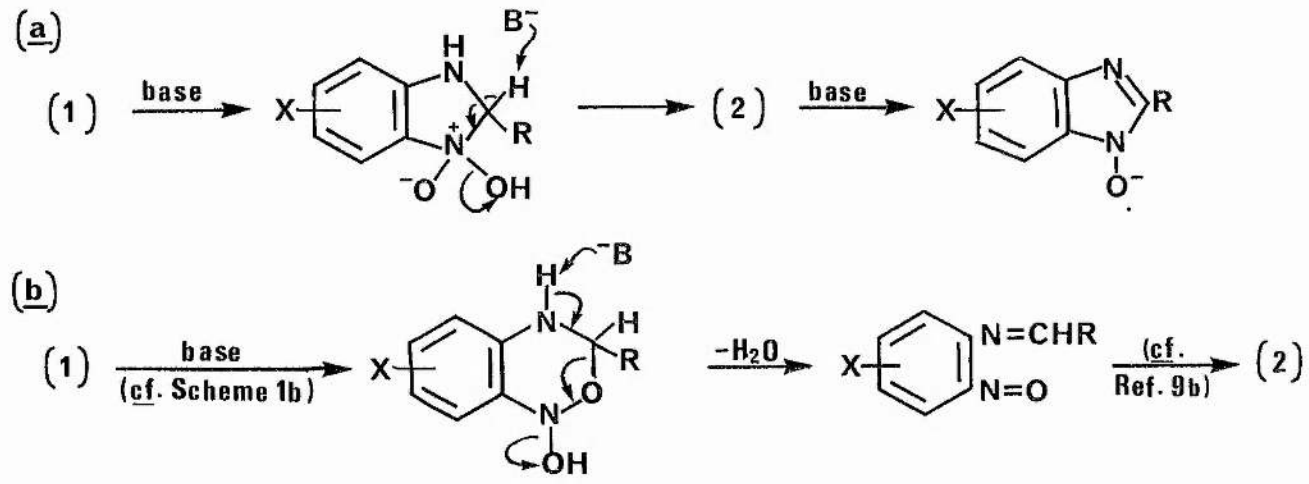
[¶]The structures of (6) and (7a) have been established by X-ray crystallography.[5]

Scheme 1



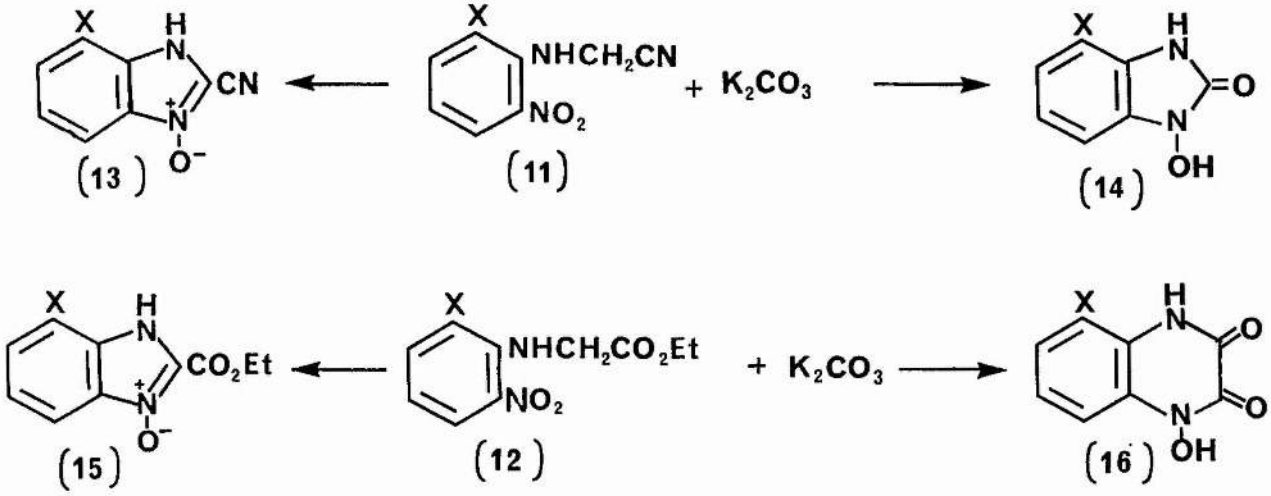
The 'normal' cyclisation of substituted *o*-nitroanilines (1) to benzimidazole *N*-oxides (2) is conventionally represented[9a] as an intramolecular aldol-like condensation (Scheme 2a), in which the amino-hydrogen is removed by the base only after cyclisation is complete. It is thus not immediately obvious why replacement of this hydrogen by a methyl group should have such a profound effect on the outcome of the reaction. However, we have also shown that, if the amino-hydrogen in (1) is not accessible to the attacking base, for steric or other reasons, the

Scheme 2



'normal' cyclisation pathway may be diverted. Thus, for example, *N*-(2,6-dinitrophenyl)glycine derivatives (11a) and (12a) are cyclised, respectively, to (14a) and (16a), instead of (13a) and (15a), and the *N*-(6-methyl-2-nitrophenyl)glycine analogues (11b) and (12b) evidently represent a 'borderline' case, since (11b) gives a mixture of (13b) and (14b), whereas (12b) gives only the 'normal' product (15b).

Scheme 3



(11a - 16a) : X = NO_2; (11b - 16b) : X = Me

It appears, therefore, that the amino-hydrogen in (1) plays a much more important rôle in the 'normal' cyclisation than is implied by the conventional formulation (Scheme 2a). It is, of course, possible that all the steps in Scheme 2a are reversible, and it is only the final deprotonation of the (relatively acidic) product (2) which determines the reaction outcome. However, it is also possible (and to us it seems more likely) that this amino-hydrogen is involved at an earlier stage of the process, and the alternative pathway of Scheme 2b is thus one of the more attractive mechanistic options for this reaction which are now receiving our attention.

We thank the S.E.R.C. for a Research Studentship to M.D.M.

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o-Nitroaniline Derivatives. Part 9.[1] Benzimidazole *N*-Oxides Unsubstituted at N-1 and C-2

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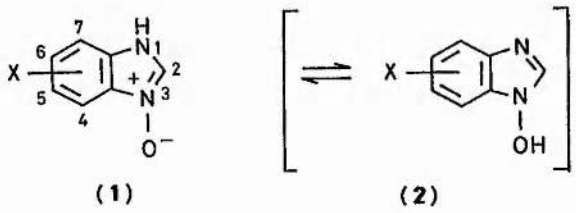
Since previous routes to the title compounds (**1**) have proved unsatisfactory as general methods, a simple new synthesis has been devised. *N*-Cyanomethyl-*o*-nitroanilines (**5**) are cyclised in basic media, giving 2-cyanobenzimidazole *N*-oxides (**12**) in good yield. Hydrolysis of these products with hydrochloric acid gives, directly, the title compounds as their hydrochloride salts (**13**), which may be isolated and purified, and which give the free *N*-oxides (**1**) by treatment with aqueous ammonia followed by evaporation.

o-Nitrophenylglycine esters (**4**) may satisfactorily replace the nitriles (**5**) in certain cases. A modification of this kind in the related nitropyridylglycine series leads to 3*H*-imidazol[4,5-*b*]pyridine 1-oxide (**20**).

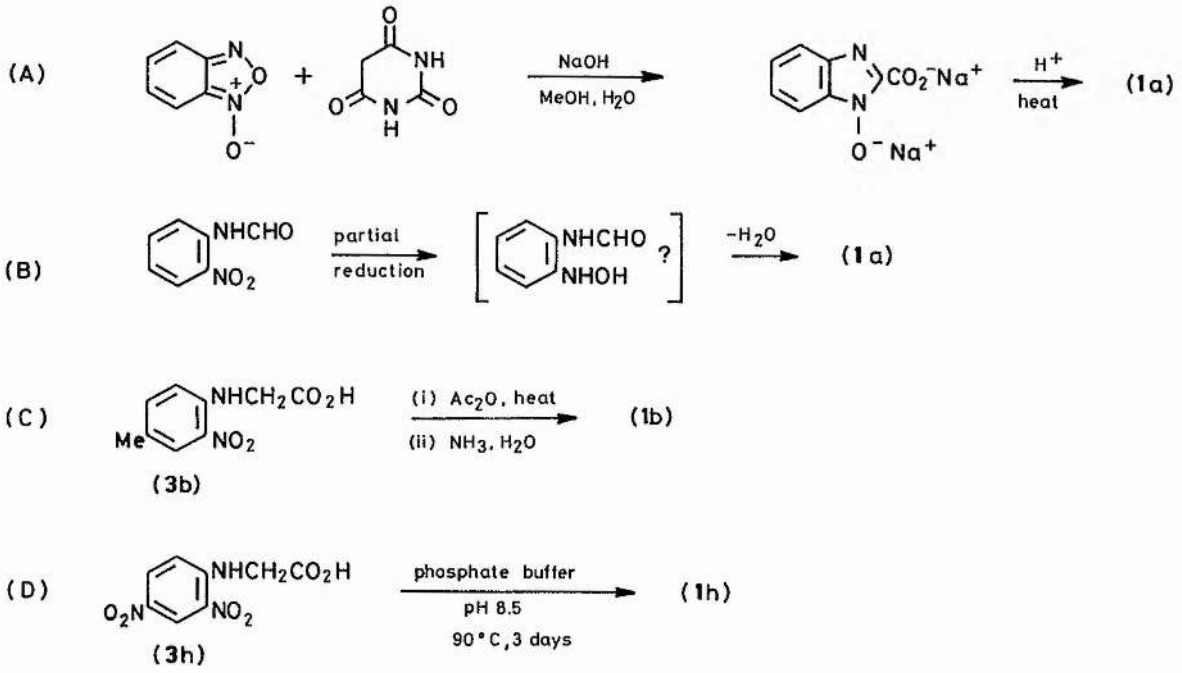
Although benzimidazole *N*-oxide itself [(**1a**); tautomeric with *N*-hydroxybenzimidazole (**2a**)] has been known for many years, and its chemistry extensively investigated,[2] scarcely anything is known about its analogues which bear substituents only in the carbocyclic ring. As part of a study of structural analogues of the natural purines, we have become interested in benzimidazole *N*-oxides with amino and hydroxy substituents, but hitherto no general route to such molecules has been available. In this paper, we describe attempts to develop a useful synthesis of compounds of the general structure (**1**), and in Part 10, which follows, we consider the additional problems associated with the synthesis of 5- and 6-aminobenzimidazole *N*-oxides [X = NH_2 or NHR in (**1**)].



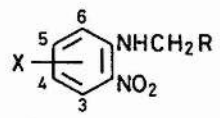
(**1**) (**2**)

	X		X
(**1a**)	H	(**1e**)	6-F
(**1b**)	5-Me	(**1f**)	5-Cl
(**1c**)	5-OMe	(**1g**)	4-NO_2
(**1d**)	5-F	(**1h**)	5-NO_2

Of the previously published routes to the parent compound (**1a**) and its simple analogues (**1b**) and (**1h**) (Scheme 1), reaction A, which is based on benzofuroxan,[3] has not been considered further as a general method. Apart from the fact that substituted benzofuroxans would themselves require to be prepared, monosubstituted benzofuroxans are (in solution, at least) mixtures of tautomers,[4] and might thus be expected to give mixtures of benzimidazole oxides. The generality of reaction D[5] has similarly not been explored; of the *o*-nitrophenylglycine analogues (**3a**—**h**), *N*-(2,4-dinitrophenyl)glycine (**3h**) is not



Scheme 1.



(3) R = CO_2H
(4) R = CO_2Et
(5) R = CN

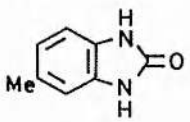
	X
a	H
b	4 - Me
c	4 - OMe
d	4 - Cl
e	4 - F
f	5 - F
g	3 - NO_2
h	4 - NO_2

only the easiest by far to prepare (from a halogeno-2,4-dinitrobenzene), but it is expected to be the easiest to cyclise, by virtue of the second nitro group. (Substituent effects in this type of cyclisation are discussed in Part 10.) The two other methods may now be considered in more detail.

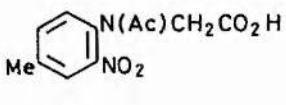
(*B*) *Partial Reduction of* o-*Nitroformanilides.*—Several reducing agents may effect the conversion of *o*-nitroformanilide into (**1a**),[2] but none of these is entirely satisfactory as a general method. Over-reduction, which leads to the parent benzimidazole, is a recurring problem, and other reducible groups in the starting material present obvious difficulties. [2,4-Dinitroformanilide has been successfully reduced to (**1h**) using ammonium sulphide,[6] but the yield is low.] Even the use of sodium borohydride in presence of palladium–charcoal[7]—undoubtedly the cleanest of these reduction methods—is not entirely reliable in this regard, since this combination of reagents is also known[8] to effect complete reduction of nitroarenes (including nitro- and dinitro-anilines) to the corresponding primary amines. There is also likely to be considerable product loss during the work-up (see later).

By following the patented general procedure,[7] we have obtained the parent *N*-oxide (**1a**) and its 5-methyl derivative (**1b**), but only in low yield [10—20%, compared with the patent's claim of 74% for (**1a**)].

(*C*) *Reaction of* o-*Nitrophenylglycine Derivatives with Acetic Anhydride.*—In 1974, Aboulezz and El-Sheikh reported[9] that *N*-(4-methyl-2-nitrophenyl)glycine (**3b**) underwent cyclisation in boiling acetic anhydride. If the reaction was stopped after 8 h and the crude product 'hydrolysed' with aqueous ammonia, the product isolated was the *N*-oxide (**1b**); if the reaction was allowed to proceed for 12 h, the product obtained after 'hydrolysis' was 5-methylbenzimidazolone (**6**). Despite the fact



(**6**)

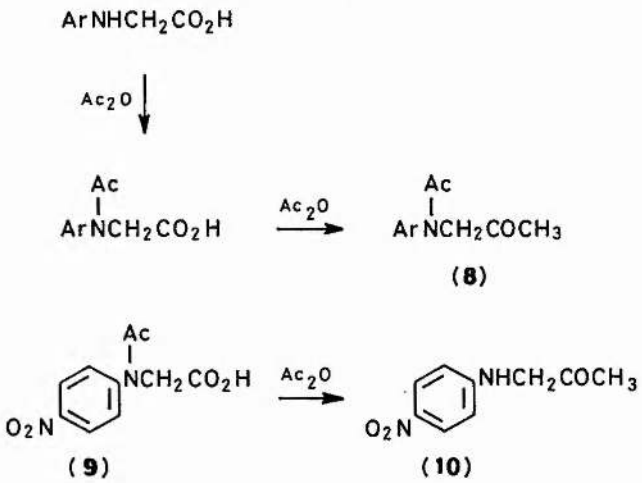


(**7**)

that we found the proposed reaction mechanism unconvincing,* the apparent simplicity of the experimental procedure was obviously attractive.

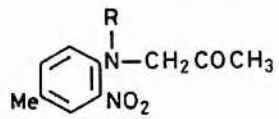
Unfortunately, we have been unable to isolate either the *N*-oxide (**1b**) or the benzimidazolone (**6**) from these reactions. In each case the crude product, both before and after treatment with ammonia, is a complex mixture (by t.l.c.), and the only solid product isolated (from the 12 h reaction) is merely the *N*-acetyl derivative (**7**) of the starting acid. *N*-(*o*-Nitrophenyl)-glycine (**3a**) similarly gives an intractable mixture of products when made to react with acetic anhydride under these conditions. We believe that there must be a serious error or omission in the published experimental procedure, but our attempts to contact the authors of the paper in this connection have so far been unsuccessful.

It is known, however,[10] that other *N*-arylglycines are converted, in boiling acetic anhydride, into α-acetamidoacetone derivatives (**8**) (the Dakin-West reaction), and that this reaction with the *p*-nitrophenyl compound (**9**) leads to the deacetylated amino ketone (**10**) (Scheme 2).† A similar course of events



Scheme 2.

involving compound (**3b**) or (**7**) might be expected to give an *o*-nitroanilinoacetone [(**11**); R = H or Ac], which could conceivably undergo cyclisation and deacetylation in the aqueous ammonia to yield the *N*-oxide (**1b**).



(R = H or Ac)

(**11**)

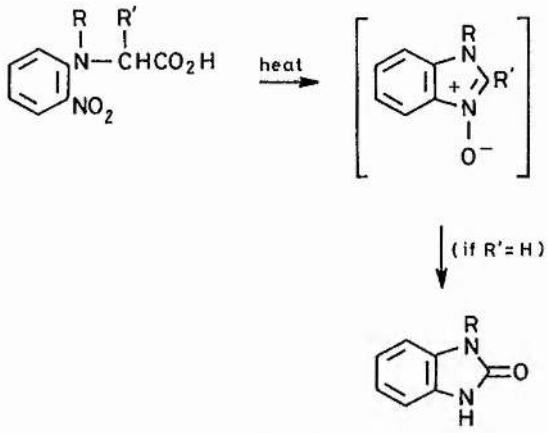
With this last possibility in mind, we have studied the reaction of the glycine (**3b**) with acetic anhydride under milder conditions (1 h at 70 °C; also 1 h at the b.p.), but here again compound (**7**) is the only pure solid isolable from the product mixture. Compound (**7**) is also recovered unchanged after renewed treatment with boiling acetic anhydride for a further 1 h.

A New Route to the N-*Oxides* (**1a—h**).—Since none of these existing procedures provides a satisfactory basis for a general route to the *N*-oxides of type (**1**), we have sought to develop a new and versatile synthesis of such compounds.

In this context, we have reconsidered the thermolysis of *o*-nitrophenylglycine analogues (**3**). Goudie and Preston have shown[11] that the *N*-*o*-nitrophenyl derivatives of glycine and other α-amino acids undergo thermolysis (either in solution or in admixture with sand) to give benzimidazolones, and benzimidazole *N*-oxides have been presumed to be the primary products (Scheme 3). We had hoped that flash vacuum pyrolysis (f.v.p.), in which the very short reaction times and low reactant pressures sometimes permit the isolation of reactive intermediates, might provide a useful route from the acids (**3**) to the *N*-oxides (**1**), and we had in the methyl-substituted glycine

* See ref. 2, pp. 304—305.

† We thank Dr. G. L. Buchanan for bringing these reactions to our attention.

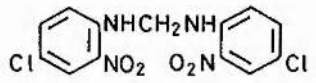


Scheme 3.

(**3b**) an ideal substrate for f.v.p. since the product mixture is easily analysed by ^{1}H n.m.r. F.v.p. of the acid (**3b**) does indeed give the *N*-oxide (**1b**) along with the benzimidazolone (**6**), but the former is never present in sufficient quantity for the method to be synthetically useful.

The successful synthesis of the *N*-oxides (**1a**—**h**), which we now recommend, is based on the previous observation[3] (*cf.* Scheme 1, Reaction A) that benzimidazole-2-carboxylic acid *N*-oxide undergoes particularly facile decarboxylation when heated in a solvent at temperatures as low as 80 °C. The complete reaction sequence is shown in Scheme 4.

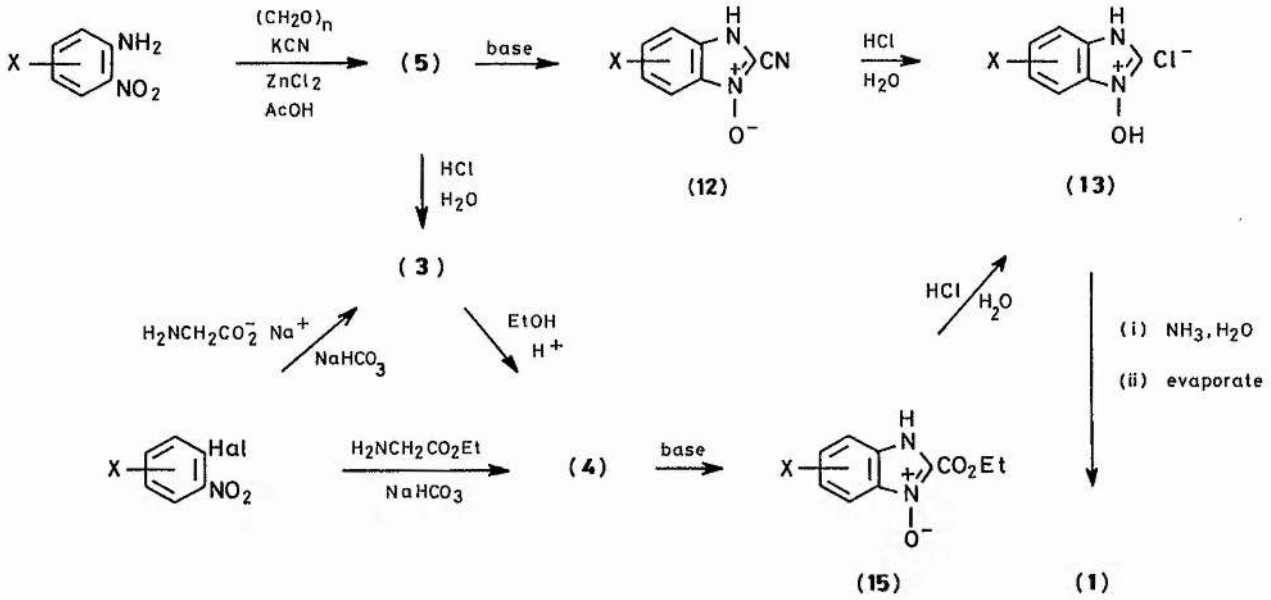
depends critically on the basicity of the amine; thus, for example, reactions involving chloro- and fluoro-nitroanilines require more, and those involving methyl- and methoxy-nitroanilines less, than in the standard procedure for *o*-nitroaniline itself. [In the case of 4-chloro-2-nitroaniline, the use of a smaller quantity of zinc chloride leads to bis(4-chloro-2-nitroanilino)methane (**14**) as the sole product.]



(**14**)

We attribute the success of this synthetic route, in part, to the work-up procedure following the hydrolysis step. Benzimidazole *N*-oxides unsubstituted at the other nitrogen are both weakly basic [the pK_a of protonated (**1a**) being 2.90[14]] and appreciably acidic [the pK_a of (**1a**) being 7.86[14]], and both they and their hydrochlorides are to some extent soluble in water. Our method allows the isolation of the hydrochlorides uncontaminated by inorganic salts; the isolation of the free *N*-oxides by evaporation of their ammonium salts (a method hinted at, although not commented upon, by Aboulezz and El-Sheikh[9]) appears to prevent isomerisation to benzimidazolones, a side-reaction which, under other conditions, may reduce the yield of (**1**).[15]

N-(*o*-Nitrophenyl)glycine esters (**4**) may satisfactorily replace the *N*-cyanomethyl-*o*-nitroanilines (**5**) in the synthesis, although in many cases this modification offers no real advantage, since



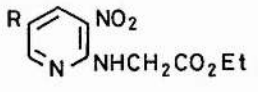
Scheme 4.

Cyanomethylation of *o*-nitroaniline, as described by Dimroth and Aurich,[12] is an efficient synthetic procedure, and the cyclisation of the cyanomethyl compound (**5a**) also proceeds in high yield, giving 2-cyanobenzimidazole *N*-oxide (**12a**).[13] Hydrolysis of (**12a**) in hot concentrated hydrochloric acid leads directly to the hydrochloride (**13a**) of the parent *N*-oxide (**1a**), and the latter is obtained, in high purity, by dissolving the hydrochloride in aqueous ammonia and evaporating the solution to small volume.

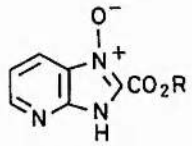
This method may be adapted, with only minor modifications, for the synthesis of the *N*-oxides (**1b**—**g**). In the cyanomethylation step, the quantity of Lewis acid (zinc chloride) required the esters (**4**) are themselves prepared most efficiently from the nitriles (**5**). However, if, in a particular case, an ester is easily obtained (*e.g.* from an *o*-halogenonitrobenzene and glycine ethyl ester), then it may offer a convenient alternative. *N*-(2,4-Dinitrophenyl)glycine ethyl ester (**4h**) is a case in point; its preparation is much simpler than that of the nitrile (**5h**), and its cyclisation to (**15h**) occurs under very mild conditions (piperidine in ethanol). In this particular sequence, the remaining stages are also atypical. The final product (**1h**) is more weakly basic, and much less soluble in water, than the other compounds of the series. It is sufficient in this case to dissolve the hydrochloride (unpurified) in aqueous sodium

hydroxide and make this solution just acid again, whereupon the *N*-oxide is precipitated in good yield.

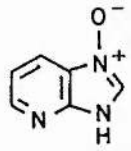
We have attempted to extend this synthetic procedure to obtain some derivatives of 3*H*-imidazo[4,5-*b*]pyridine 1-oxide, since very few representatives of this class have been previously described.[16] *N*-(3-Nitro-2-pyridyl)- and *N*-(3,5-dinitro-2-pyridyl)-glycine ethyl esters (**16**) and (**17**) are easily prepared, but their reactions with base do not parallel those of the corresponding benzene derivatives, (**4a**) and (**4h**). The mono-



(**16**) R = H
(**17**) R = NO_2



(**18**) R = Et
(**19**) R = H



(**20**)

nitro-ester (**16**) is cyclised in ethanolic potassium carbonate to give a mixture of two potassium salts, one soluble and one insoluble in the reaction medium; the former gives, on acidification, the expected imidazopyridine ester (**18**), and the latter, when acidified, gives a thermally labile solid [*possibly* the carboxylic acid (**19**)] which decomposes on warming to give the parent 3*H*-imidazo[4,5-*b*]pyridine 1-oxide (**20**). Interestingly, acid hydrolysis of the ester (**18**) does *not* appear to give a salt of (**20**); this reaction is still receiving our attention.

The dinitropyridylglycine ester (**17**), on the other hand, gives no identifiable product on reaction with potassium carbonate, unchanged starting material (11%) and an intractable black solid (a complex mixture by t.l.c.) being obtained. The reaction of (**17**) with piperidine is similarly unsuccessful; the reason for this failure is unknown.

Experimental

I.r. spectra were recorded for Nujol mulls. ^{1}H N.m.r. spectra were recorded at 80 MHz, and ^{19}F n.m.r. spectra at 75.3 MHz, in [$^2H_6$]dimethyl sulphoxide unless otherwise stated. The ^{19}F chemical shifts are upfield (negative δ) from $CFCl_3$.

Partial Reduction of o-*Nitroformanilides.*—*o*-Nitroformanilide, m.p. 122 °C (from ethanol; lit.,[17] 122 °C) was obtained in 69% yield by heating *o*-nitroaniline (13.8 g) and formic acid (98%; 20 ml) under reflux for 2 h. The product crystallised from the cooled solution. 4-Methyl-2-nitroformanilide, m.p. 124—125 °C (from ethanol; no lit. m.p. quoted[18]), was similarly obtained from 4-methyl-2-nitroaniline; it showed $\nu_{max.}$ 3 260 (NH) and 1 705 and 1 670 cm^{-1} (CO); δ_H($CDCl_3$) 2.42 (3 H, s, Me), 7.60 (1 H, dd, 5-H), 8.10 (1 H, d, 3-H), 8.6—8.9 (2 H, unresolved, 6-H and NH), and 10.0—10.5 (1 H, br, CHO); $J_{3,5}$ 2 Hz and $J_{5,6}$ 8 Hz.

Reduction Procedure.—A solution of sodium borohydride (1.83 g) in water (1.8 ml) was added slowly, with stirring, to a suspension of palladium–charcoal (5%; 1.0 g) in water (15 ml). A solution of the *o*-nitroformanilide (0.02 mol) in pyridine (36 ml) was added to this mixture, at such a rate that the temperature was maintained at 35—40 °C. When the addition was complete (*ca.* 20 min), the mixture was stirred for a further 15 min, the catalyst was filtered off, and the filtrate evaporated under reduced pressure. The residue was dissolved in water (*ca.* 70 ml), acidified (conc. HCl), then concentrated to approximately half volume and neutralised with aqueous ammonia (*d* 0.88) before again being evaporated to dryness under reduced pressure. The residue was extracted with hot ethanol; the extract, when cooled, deposited inorganic material which was filtered off, and the filtrate was further concentrated and cooled to give the *N*-oxide. The yields were variable, but were typically 10—20%. Benzimidazole *N*-oxide itself (**1a**), thus prepared, had m.p. 210—212 °C (from ethanol; lit.,[15] 215 °C), and 5-methylbenzimidazole 3-oxide (**1b**) had m.p. 174—174.5 °C (from ethanol; lit.,[9] 176—178 °C).

N-*Cyanomethyl*-o-*nitroaniline* (**5a**).—The following is adapted from Dimroth and Aurich's procedure.[12]—Acetic acid (125 ml) containing concentrated sulphuric acid (8 drops) was added, with efficient mechanical stirring, to a mixture of *o*-nitroaniline (6.9 g, 0.05 mol), paraformaldehyde (4.5 g, 0.15 mol CH_2O), potassium cyanide (9.75 g, 0.15 mol), and anhydrous zinc chloride (52.5 g, 0.38 mol). The mixture was heated to 50 °C and stirred at this temperature for 8 h. It was then poured into ice–water, and the product filtered off, washed well with water, and recrystallised from ethanol. *N*-Cyanomethyl-*o*-nitroaniline (**5a**) (6.73 g, 76%) had m.p. 136—138 °C (lit.,[12] 139—140.5 °C); $\nu_{max.}$ 3 380 (NH) and 1 510 and 1 340 cm^{-1} (NO_2); δ_H 4.62 (2 H, d, CH_2), 6.92 (1 H, ddd, 4-H), 7.20 (1 H, dd, 6-H), 7.72 (1 H, ddd, 5-H), 8.18 (1 H, dd, 3-H), and 8.32 (1 H, br t, NH); $J_{CH_2,NH}$ 6 Hz, $J_{3,4}$ 8.5 Hz, $J_{4,5}$ 9.5 Hz, $J_{5,6}$ 9 Hz, and $J_{3,5} = J_{4,6}$ 2 Hz.

N-*Cyanomethyl*-4-*methyl*-2-*nitroaniline* (**5b**). This compound, m.p. 146—147 °C (from ethanol), was similarly obtained (7.2 g, 75%) from 4-methyl-2-nitroaniline (7.6 g, 50 mmol), paraformaldehyde (4.5 g), potassium cyanide (9.75 g), and zinc chloride (25 g), in acetic acid (250 ml) and sulphuric acid (4 drops). (The use of a larger proportion of zinc chloride gave increasing proportions of the *N*,*N*-bis-cyanomethyl derivative, as adjudged by n.m.r.) (**5b**) (Found: C, 56.45; H, 4.7; N, 21.95. $C_9H_9N_3O_2$ requires C, 56.5; H, 4.7; N, 22.0%); $\nu_{max.}$ 3 380 (NH), 2 230w (CN), and 1 530 and 1 325 cm^{-1} (NO_2); δ_H 2.30 (3 H, s, Me), 4.65 (2 H, d, CH_2), 7.08 (1 H, d, 6-H), 7.54 (1 H, dd, 5-H), 7.95 (1 H, d, 3-H), and 8.12 (1 H, br t, NH); $J_{CH_2,NH}$ 6 Hz, $J_{3,5}$ 2 Hz, and $J_{5,6}$ 8 Hz.

N-*Cyanomethyl*-4-*methoxy*-2-*nitroaniline* (**5c**). This compound was prepared (yield, 85%) in the same way as (**5b**), and had m.p. 176—178 °C (from ethanol) (Found: C, 52.1; H, 4.35; N, 20.3. $C_9H_9N_3O_3$ requires C, 52.2; H, 4.4; N, 20.3%); $\nu_{max.}$ 3 375 (NH), 2 240w (CN), and 1 505 and 1 340 cm^{-1} (NO_2); δ_H 3.82 (3 H, s, OMe), 4.59 (2 H, d, CH_2), 7.19 (1 H, d, 6-H), 7.44 (1 H, dd, 5-H), 7.63 (1 H, d, 3-H), and 8.10 (1 H, br t, NH); $J_{CH_2,NH}$ 6.5 Hz, $J_{3,5}$ 2.5 Hz, and $J_{4,5}$ 9 Hz.

4-*Chloro*-N-*cyanomethyl*-2-*nitroaniline* (**5d**). Reaction of 4-chloro-2-nitroaniline (6.85 g, 40 mmol) with paraformaldehyde (3.6 g), potassium cyanide (7.8 g), and zinc chloride (42 g) in acetic acid (100 ml) containing sulphuric acid (4 drops) at 50 °C gave, after 10 h, the *cyanomethyl derivative* (**5d**), m.p. 156—158 °C (from ethanol), in 72% yield (Found: C, 45.3; H, 2.8; N, 19.9. $C_8H_6ClN_3O_2$ requires C, 45.4; H, 2.9; N, 19.9%); $\nu_{max.}$ 3 385 (NH) and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 4.60 (2 H, d, CH_2), 7.23 (1 H, d, 6-H), 7.77 (1 H, dd, 5-H), 8.15 (1 H, d, 3-H), and 8.33 (1 H, br t, NH); $J_{CH_2,NH}$ 6 Hz, $J_{3,5}$ 2 Hz, and $J_{5,6}$ 9 Hz.

Attempts to prepare (**5d**) using the same procedure as for (**5b**) (*i.e.* with a smaller proportion of zinc chloride in a larger volume of solvent) gave only bis(4-chloro-2-nitroanilino)methane (**14**), m.p. 266—268 °C (from dimethylformamide; lit.,[19] 266 °C) in 39% yield (Found: C, 43.5; H, 2.7; N, 15.7. Calc. for

Table 1. Benzimidazole *N*-oxide hydrochlorides (**13**)

Compound	Yield (%) from (12)	Yield (%) from (15)	M.p. (°C) (recryst. solvent)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N	Chemical shifts (δ) 2-H	4-H	5-H	6-H	7-H	Other	*J*/Hz
(13a)	57	50	199—200 (Pr^iOH)	$C_7H_7ClN_2O$	49.4	4.2	16.5	49.3	4.1	16.4	10.07 s	(7.7—8.1 m)					
(13b)	64	85	227—230 (EtOH)	$C_8H_9ClN_2O$	51.9	4.8	15.0	52.05	4.9	15.2	9.80 s	7.63 d		7.42 dd	7.73 d	2.52 Me	8.5 (6,7), *ca.* 1.5 (4,6)
(13c)	50	32	215—216 d (EtOH)	$C_8H_9ClN_2O_2$	48.0	4.6	14.0	47.9	4.5	14.0	9.74 s	7.1—7.35 m (with 6-H)		7.1—7.35 m (with 4-H)	7.77 d	3.91 OMe	8 (6,7)
(13d)	51		224—226 d (EtOH)	$C_7H_6Cl_2N_2O$	41.2	2.9	13.6	41.0	2.9	13.7	9.81 s	7.96 d		7.63 dd	7.90 d		9 (6,7), 2 (4,6)
(13e)	88		240—242 d (HCl)	$C_7H_6ClFN_2O$	44.3	3.1	14.7	44.6	3.2	14.85	9.85 s	7.73 dd		7.46 dt	7.88 dd	δ_F −114.0	9.0 (6,7), 2.0 (4,6), 8.4 (4,F), 9.0 (6,7), 4.4 (7,F)
(13f)	79		194—196 (HCl)	$C_7H_6ClFN_2O$	44.8	3.2	15.0	44.6	3.2	14.85	9.78 s	7.90 ddd	7.50 dt		7.73 ddd	δ_F −114.4	9.2 (4,5), 2.4 (5,7), 0.6 (4,7), 9.3 (5,F and 7,F), 4.6 (4,F)
(13g)	69		224—225 d (HCl)	$C_7H_6ClN_3O_3$	38.9	2.8	19.5	39.0	2.8	19.5	9.07 s		8.0—8.2 (with 7-H)	7.53 t	8.0—8.2 (with 5-H)		8 (5,6 and 6,7)
(13h)		97	*ca.* 240 (HCl)	(Crude product only obtained)							9.62 s	8.55 d		8.30 dd	8.00 d		9 (6,7), 2.5 (4,6)

Table 2. Benzimidazole *N*-oxides (**1**)

Compound	Yield (%)	M.p. (°C) (recryst. solvent)	Formula	Found (%) C	Found (%) H	Found (%) N	Required (%) C	Required (%) H	Required (%) N	Chemical shifts (δ) 2-H	4-H	5-H	6-H	7-H	Other	*J*/Hz
(1a)	68	*214—216 (EtOH)								8.35 s	(7.1—7.8 m)					
(1b)	72	†174—174.5 (EtOH–H_2O)	$C_8H_8N_2O$	64.6	5.45	19.0	64.85	5.4	18.9	8.23 s	7.25 d		7.00 dd	7.45 d	2.40 Me	8 (6,7), *ca.* 1.5 (4,6)
(1c)	75	176—177 (H_2O)	$C_8H_8N_2O_2$	58.1	5.0	17.2	58.5	4.9	17.1	8.20 s	6.96 d		6.80 dd	7.50 d	3.82 OMe	8.5 (6,7), 2 (4,6)
(1d)	76	224—226 (H_2O)	$C_7H_5ClN_2O$	49.5	2.9	16.3	49.9	3.0	16.6	8.42 s	7.55 d		7.21 dd	7.65 d		8.5 (6,7), 2 (4,6)
(1e)	57	227—229 (H_2O)	$C_7H_5FN_2O$	55.1	3.2	18.5	55.3	3.3	18.4	8.38 s	7.30 dd		7.03 ddd	7.65 dd	δ_F −118.7	9.0 (6,7), 2.4 (4,6), 10.0 (6, F), 8.6 (4,F), 4.9 (7,F)
(1f)	64	229—231 d (H_2O)	$C_7H_5FN_2O$	55.2	3.0	18.5	55.3	3.3	18.4	8.41 s	7.51 dd	7.14 ddd		7.43 dd	δ_F −121.6	8.8 (4,5), 2.4 (5,7), 9.7 (5,F and 7,F), 5.9 (4,F)
(1g)	63	228—230 d (H_2O)	$C_7H_5N_3O_3$	46.7	2.7	23.3	46.9	2.8	23.5	8.57 s		7.9—8.1 m (with 7-H)	7.38 t	7.9—8.1 m (with 5-H)		8 (5,6 and 6,7)
(1h)	83	‡274—276 d (EtOH)								8.70 s	8.30 d		8.05 dd	7.75 d		9 (6,7), 2 (4,6)

* Lit.,[15] 215 °C. † Lit.,[9] 176—178 °C. ‡ Lit.,[6] 274 °C (d).

$C_{13}H_{10}Cl_2N_4O_4$: C, 43.7; H, 2.8; N, 15.7%); $\nu_{max.}$ 3 360 cm^{-1} (NH); $\delta_H(CF_3CO_2H)$ 4.07 (2 H, s, CH_2), 5.92 (2 H, br s, 2 × NH), 7.58 (2 H, d, 2 × 6-H), 7.82 (2 H, dd, 2 × 5-H), and 8.39 (2 H, d, 2 × 3-H); $J_{3,5}$ 2.5 Hz and $J_{5,6}$ 8.5 Hz.

N-*Cyanomethyl*-4-*fluoro*-2-*nitroaniline* (**5e**). This compound, m.p. 163—164 °C (from ethanol), was obtained in 52% yield by the method described for the chloro analogue (**5d**) (Found: C, 49.55; H, 3.2; N, 21.6. $C_8H_6FN_3O_2$ requires C, 49.2; H, 3.1; N, 21.5%); $\nu_{max.}$ 3 370 (NH), 2 240w (CN), and 1 510 and 1 335 cm^{-1} (NO_2); $\delta_H(CDCl_3)$ 4.57 (2 H, d, CH_2), 7.20 (1 H, dd, 6-H), 7.66 (1 H, ddd, 5-H), 7.92 (1 H, dd, 3-H), and 8.17 (1 H, br s, NH); $\delta_F(CDCl_3)$ −125.5 p.p.m. (8 lines); $J_{CH_2,NH}$ 6 Hz, $J_{3,5}$ 3.0 Hz, $J_{5,6}$ 9.3 Hz, $J_{3,F}$ 8.7 Hz, $J_{5,F}$ 7.0 Hz, and $J_{6,F}$ 4.4 Hz.

5-*Fluoro*-2-*nitroaniline*. Hodgson and Nicholson's method[20] was modified as follows. Acetic anhydride (115 ml) was added slowly, with stirring, to *m*-fluoroaniline (50 g) at such a rate that the temperature remained below 40 °C. After addition was complete, the mixture was stirred at 50 °C for 3 h, cooled, and added to ice. The *m*-fluoroacetanilide (56.1 g, 82%) had m.p. 85—87 °C (from propan-2-ol–water; lit.,[20] 85 °C).

A mixture of nitric acid (*d* 1.5; 17 ml) and concentrated sulphuric acid (110 ml) was added dropwise, with stirring, to an ice-cooled solution of *m*-fluoroacetanilide (37.5 g) in concentrated sulphuric acid (110 ml) at such a rate that the temperature of the mixture remained below 5 °C. The addition required *ca.* 2 h; the mixture was then poured onto ice and the precipitate filtered off, washed with water, and dried under suction.

This mixture of nitration products was hydrolysed in ethanolic sulphuric acid, and the fluoronitroanilines separated by steam distillation, as already described.[20] 5-Fluoro-2-nitroaniline (steam-volatile) was obtained in a yield of 19 g (50%) and had m.p. 93—95 °C (from ethanol–water; lit.,[20] 97 °C). The steam-involatile residue, worked up as in the published method, gave 3-fluoro-4-nitroaniline (11.4 g, 30%), m.p. 146—148 °C (from ethanol–water; lit.,[20] 153 °C).

N-*Cyanomethyl*-5-*fluoro*-2-*nitroaniline* (**5f**), m.p. 129—131 °C (from ethanol–water), was prepared from 5-fluoro-2-nitroaniline by a procedure similar to that used for (**5d**); the yield was 76% (Found: C, 49.4; H, 3.1; N, 21.1. $C_8H_6FN_3O_2$ requires C, 49.2; H, 3.1; N, 21.5%); $\nu_{max.}$ 3 380 (NH), 2 245w (CN), and 1 505 and 1 340 cm^{-1} (NO_2); δ_H 4.60 (2 H, d, CH_2), 6.73 (1 H, ddd, 4-H), 7.04 (1 H, dd, 6-H), 8.26 (1 H, dd, 3-H), and 8.47 (1 H, br t, NH); δ_F −99.7 p.p.m. (16 lines), $J_{CH_2,NH}$ 6.5 Hz, $J_{3,4}$ 9.5 Hz, $J_{4,6}$ 2.5 Hz, $J_{3,F}$ 6.5 Hz, $J_{4,F}$ 8 Hz, $J_{6,F}$ 12 Hz, and $J_{F,NH}$ 2.2 Hz.

N-*Cyanomethyl*-2,3-*dinitroaniline* (**5g**). 2,3-Dinitroaniline, m.p. 123–125 °C (from ethanol; lit.,[21] 127 °C) was prepared from *m*-nitroacetanilide by the published procedure.[21]

2,3-Dinitroaniline (4.0 g), paraformaldehyde (1.97 g), potassium cyanide (4.3 g), and zinc chloride (22.9 g) in acetic acid (55 ml) containing sulphuric acid (4 drops) gave, after 20 h at 50 °C, the *cyanomethyl compound* (**5g**), m.p. 183—185 °C (from acetic acid); yield, 3.6 g (74%) (Found: C, 43.3; H, 2.7; N, 25.35. $C_8H_6N_4O_4$ requires C, 43.25; H, 2.7; N, 25.2%); $\nu_{max.}$ 3 385 (NH) and 1 560 and 1 360 cm^{-1} (NO_2); δ_H 4.50 (2 H, d, CH_2), 7.38—7.90 (4 H, m, ArH + NH); $J_{CH_2,NH}$ 6 Hz.

N-*Cyanomethyl*-2,4-*dinitroaniline* (**5h**). 1-Chloro-2,4-dinitrobenzene (10.2 g), aminoacetonitrile hydrochloride (4.62 g), and sodium hydrogen carbonate (8.4 g) were heated under reflux with ethanol (100 ml) for 2 h. The cooled solution was filtered, and the precipitate was washed with water and recrystallised from acetic acid. The *nitrile* (**5h**) (2.1 g, 19%) had m.p. 162—163 °C (Found: C, 42.9; H, 2.6; N, 25.05. $C_8H_6N_4O_4$ requires C, 43.25; H, 2.7; N, 25.2%); $\nu_{max.}$ 3 330 (NH), 2 240vw (CN), and 1 515 and 1 340 cm^{-1} (NO_2); δ_H 4.72 (2 H, d, CH_2), 7.33 (1 H, d, 6-H), 8.42 (1 H, dd, 5-H), 8.88 (1 H, d, 3-H), 8.98 (1 H, br t, NH); $J_{CH_2,NH}$ 7 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz.

N-(o-*Nitrophenyl*)*glycine* (**3a**).—This compound was obtained (3.11 g, 32%) from *o*-fluoronitrobenzene (7 g), glycine (3.38 g), and sodium hydrogen carbonate (19 g) in ethanol (180 ml) and water (100 ml) according to Goudie and Preston's method.[11] The product had m.p. 188—190 °C (decomp.) [from ethanol; lit.,[22] 192—193 °C (decomp.)].

N-(4-*Methyl*-2-*nitrophenyl*)*glycine* (**3b**). A solution of *N*-cyanomethyl-4-methyl-2-nitroaniline (**5b**) (4 g) in acetic acid (100 ml) and aqueous sulphuric acid (50% v/v; 240 ml) was heated at 100 °C for 2.5 h, then cooled, added to ice, and the precipitate filtered off and washed with water. The acid (**3b**) (2.8 g, 67%) had m.p. 186—188 °C (decomp.) [from propan-2-ol–water; lit.,[22] 189—190 °C (decomp.)]; $\nu_{max.}$ 3 340 (NH) and 1 715 cm^{-1} (CO); δ_H 2.23 (3 H, s, Me), 4.13 (2 H, d, CH_2), 6.83 (1 H, d, 6-H), 7.38 (1 H, dd, 5-H), 7.88 (1 H, d, 3-H), and 8.25 (1 H, br t, NH); $J_{CH_2,NH}$ 5 Hz, $J_{3,5}$ 2 Hz, and $J_{5,6}$ 8 Hz.

N-(4-*Methoxy*-2-*nitrophenyl*)*glycine* (**3c**), m.p. 188—190 °C (from ethanol), was similarly obtained in 45% yield from the nitrile (**5c**) (Found: C, 47.8; H, 4.4; N, 12.3. $C_9H_{10}N_2O_5$ requires C, 47.8; H, 4.5; N, 12.4%); $\nu_{max.}$ 3 345 (NH) and 1 720 cm^{-1} (CO); δ_H 3.75 (3 H, s, OMe), 4.14 (2 H, d, CH_2), 6.89 (1 H, d, 6-H), 7.27 (1 H, dd, 5-H), 7.51 (1 H, d, 3-H), and 8.20 (1 H, br t, NH); $J_{CH_2,NH}$ 5 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz.

N-(o-*Nitroaryl*)*glycine Ethyl Esters* (**4a—c**).—These compounds were prepared by saturating an ethanolic solution of the appropriate acid with gaseous hydrogen chloride, and heating the solution under reflux until reaction was complete. The ester (**4a**), m.p. 82—84 °C (from propan-2-ol; lit.,[23] 80 °C) was obtained in 88% yield; the ester (**4b**), m.p. 64—65 °C (from ethanol; lit.,[24] 65 °C) in 83% yield, and the ester (**4c**), m.p. 76—78 °C (from ethanol), in 87% yield; (**4c**) (Found: C, 52.1; H, 5.55; N, 16.0. $C_{11}H_{14}N_2O_5$ requires C, 52.0; H, 5.55; N, 11.0%) $\nu_{max.}$ 3 345 (NH), 1 730 (CO), and 1 510 and 1 345 cm^{-1} (NO_2); $\delta_H(CDCl_3)$ 1.32 (3 H, t, *Me*CH_2), 3.81 (3 H, s, OMe), 4.09 (2 H, s, *CH*$_2$NH), 4.30 (2 H, q, *CH*$_2$-Me), 6.68 (1 H, d, 6-H), 7.17 (1 H, dd, 5-H), and 7.68 (1 H, d, 3-H); J_{Me,CH_2} 7 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz.

N-(2,4-*Dinitrophenyl*)*glycine Ethyl Ester* (**4h**).—Glycine ethyl ester hydrochloride (14.0 g, 0.1 mol) and sodium hydrogen carbonate (16.8 g, 0.2 mol) were added successively to a solution of 1-chloro-2,4-dinitrobenzene (20.3 g, 0.1 mol) in ethanol (200 ml); the mixture was heated under reflux for 2 h and then added to ice–water. The product was filtered off, washed with ethanol and with water, and recrystallised from acetic acid to give the ester (**4h**) (20.9 g, 78%), m.p. 142—144 °C (lit.,[25] 144 °C).

Reaction of N-(4-*Methyl*-2-*nitrophenyl*)*glycine* (**3b**) *with Acetic Anhydride*.—(a) N-*Acetyl*-N-(4-*methyl*-2-*nitrophenyl*)-*glycine* (**7**). *N*-(4-Methyl-2-nitrophenyl)glycine (**3b**) (1.8 g, 8.6 mmol) was dissolved, with stirring, in warm (70 °C) acetic anhydride (20 ml). When solution was complete the mixture was kept at 70 °C for 1 h, during which time the colour changed from orange to yellow; it was then diluted with water (100 ml), vigorously stirred until homogeneous, set aside overnight, concentrated under reduced pressure (to *ca.* 30 ml), and the product filtered off. N-*Acetyl*-N-(4-*methyl*-2-*nitrophenyl*)*glycine* (**7**) (1.31 g, 61%) had m.p. 148—150 °C (from water) (Found: C, 52.2; H, 4.8; N, 11.1. $C_{11}H_{12}N_2O_3$ requires C, 52.4; H, 4.8; N, 11.1%); $\nu_{max.}$ 1 730 (CO, acid), 1 630 (CO, amide), and 1 530 and 1 360 cm^{-1} (NO_2); δ_H 1.75 (3 H, s, *Me*CO), 2.45 (3 H, s, *Me*-Ar), 3.89 and 4.49 (2 H, AB quartet,* *J* 17 Hz, CH_2), and 7.6—8.0 (3 H, m, Ar-H).

* The non-equivalence of methylene protons in this type of molecule has been discussed in Part 5.[26]

Repetition of this experiment at the b.p. (140 °C) of acetic anhydride, followed by removal of the latter by distillation at reduced pressure, also gave (**7**) as the only isolable product, albeit in lower yield (29%). Compound (**7**) was recovered, almost quantitatively, after further treatment with boiling acetic anhydride for 1 h.

(b) *The procedure of Aboulezz and El-Sheikh.*[9] The glycine (**3b**) (1.3 g) was heated under reflux with acetic anhydride (12 ml) for 12 h. After removal of the acetic anhydride under reduced pressure, the black sticky residue was heated under reflux with aqueous ammonia (25%; 10 ml) for 1 h. No precipitation occurred on evaporation of the ammonia under reduced pressure (in contradiction of the published claims). The tarry product was vigorously stirred with water (20 ml) for 10 min, and the aqueous layer (which contained a little suspended solid) was decanted off, filtered, and acidified (HCl) to give a yellow semisolid (0.15 g), found by n.m.r. to be mainly the *N*-acetylglycine (**7**).

Repetition of the above procedure, with reduction of the initial reaction period to 8 h, gave black tarry material from which no solid product could be isolated.

5-*Methylbenzimidazol*-2-*one* (**6**).—Urea (3.0 g, 50 mmol) was added to a solution of 3,4-diaminotoluene (6.1 g, 50 mmol) in pentan-1-ol (20 ml) and the mixture was heated under reflux until evolution of ammonia ceased (*ca.* 2 h). The colourless product obtained on cooling was filtered off and washed with cold ethanol. The benzimidazolone (**6**) (2.8 g, 38%) had m.p. 297—300 °C (from ethanol) (lit.,[27] 299—300 °C); $\nu_{max.}$ 3 100 (NH) and 1 740 cm^{-1} (CO); δ_H 2.25 (3 H, s, Me), 6.75 (3 H, approx. s, ArH), and 10.42 (2 H, br s, 2 × NH).

Flash Vacuum Pyrolysis (*f.v.p.*) *Experiments.*—The substrates to be pyrolysed were volatilised under low pressures (typically 10^{-1} to 10^{-2} mmHg) and the vapour passed through a horizontal quartz tube (300 mm long × 25 mm i.d.) externally heated to 600—770 °C. The solid products collected near the furnace outlet and their m.p.s, i.r. and ^1H n.m.r. spectra were examined.

F.v.p. of N-(4-*Methyl*-2-*nitrophenyl*)*glycine* (**3b**). (a) *At* 750 °C. The glycine (0.2 g) was volatilised at 130—140 °C/7—9 × 10^{-2} mmHg. Upon pyrolysis, a colourless solid (0.035 g), m.p. 296—300 °C, was obtained; this was identical spectroscopically with 5-methylbenzimidazol-2-one (**6**); yield 18%.

(b) *At* 700 °C. The glycine (0.18 g), volatilised at 120—140 °C/1—2 × 10^{-2} mmHg, gave on pyrolysis a pale orange solid (0.05 g) which was analysed by ^1H n.m.r. This showed that the product was a mixture of the unchanged glycine, the *N*-oxide (**1b**), and the benzimidazolone (**6**), in the appropriate ratio 1:0.8:1.

(c) *At* 650 °C. The glycine (0.30 g), volatilised at 120—130 °C/1—2 × 10^{-2} mmHg, gave on pyrolysis an orange solid (0.15 g; m.p. 135—142 °C) which was shown by ^1H n.m.r. to consist of the same three compounds as in (b), the approximate ratio being (**3b**):(**1b**):(**6**) = 3:1:1.1.

F.v.p. of the N-*oxide* (**1b**).—The *N*-oxide (0.09 g) was volatilised at 120—125 °C/5—7 × 10^{-2} mmHg, and pyrolysed at 750 °C to give 5-methylbenzimidazol-2-one (0.035 g, 39%), m.p. 296—298 °C.

Cyclisation of N-*Cyanomethyl*-o-*nitroanilines* (**5**): 2-*Cyanobenzimidazole* N-*Oxides* (**12**).—*The parent compound* (**12a**) (*cf.* ref. 13). Potassium carbonate (1.22 g) was added to a suspension of *N*-cyanomethyl-*o*-nitroaniline (**5a**) (3.08 g) in hot ethanol (170 ml), and the mixture heated under reflux for 4 h. The solvent was distilled off under reduced pressure, and the residue dissolved, as far as possible, in water. The mixture was filtered, and the filtrate acidified (HCl) to give the pale yellow N-*oxide* (**12a**). It had m.p. 232—234 °C (decomp.) (from ethanol–water; lit.,[13] 232 °C, 240—241 °C); $\nu_{max.}$ 2 240 cm^{-1} (CN); δ_H 7.30—8.0 (unresolved multiplet); yield 1.48 g (54%).

2-*Cyano*-5-*methyl*-1H-*benzimidazole* 3-*oxide* (**12b**). This compound, m.p. 236 °C (from dimethylformamide–water), was similarly obtained (reaction time 9 h) from *N*-cyanomethyl-4-methyl-2-nitroaniline (**5b**) (2.5 g) and potassium carbonate (1.92 g) in ethanol (140 ml); yield 1.20 g (53%) (Found: C, 62.1: H, 4.0; N, 24.1. $C_9H_7N_3O$ requires C, 62.4; H, 4.1; N, 24.3%); $\nu_{max.}$ 2 235 cm^{-1} (CN); δ_H 2.48 (3 H, s, Me), 7.22 (1 H, br d, 6-H), 7.38 (1 H, br s, 4-H), and 7.67 (1 H, d, 7-H); $J_{6,7}$ 8.5 Hz and $J_{4,6}$ not measurable (peaks broadened by Me).

2-*Cyano*-5-*methoxy*-1H-*benzimidazole* 3-*oxide* (**12c**). This compound was similarly obtained (reaction time 4.5 h; yield 51%) from the nitrile (**5c**) (2.5 g) and potassium carbonate (1.77 g) in ethanol (130 ml), and had m.p. 276—277 °C (from dimethylformamide–water) (Found: C, 57.45; H, 3.65; N, 22.3. $C_9H_7N_3O_2$ requires C, 57.1; H, 3.7; N, 22.2%); $\nu_{max.}$ 2 230 cm^{-1} (CN); δ_H 3.90 (3 H, s, OMe), 6.9—7.1 (2 H, m, 4- and 6-H), 7.6—7.75 (1 H, m, 7-H), and 12.9 (1 H, v br, NH/OH).

5-*Chloro*-2-*cyano*-1H-*benzimidazole* 3-*oxide* (**12d**). The nitrile (**5d**) (1 g) and potassium carbonate (0.29 g) in ethanol (60 ml) were stirred for 2 h at 50 °C, the ethanol distilled off, and the residue dissolved, as far as possible, in water. The insoluble portion was identified as 2-(4-*chloro*-2-*nitroanilino*)*acetamide* (0.27 g, 23%), m.p. 211—213 °C (from methanol) (Found: C, 41.8; H, 3.5; N, 18.3. $C_8H_8ClN_3O_3$ requires C, 41.85; H, 3.5; N, 18.3%); $\nu_{max.}$ 3 390 and 3 145 (NH), 1 660 (CO), and 1 505 and 1 340 cm^{-1} (NO_2); δ_H 3.98 (2 H, d, CH_2), 6.81 (1 H, d, 6-H), 7.25 (1 H, br s, amide NH), 7.60 (2 H, overlapping dd and br s, 5-H and amide NH), 8.06 (1 H, d, 3-H), and 8.47 (1 H, br t, *NH*-CH_2); $J_{CH_2,NH}$ 6 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz. The water-soluble portion, when acidified (HCl), gave the N-*oxide* (**12d**) (0.48 g, 58%), m.p. 216—218 °C (from aqueous dimethylformamide) (Found: C, 49.3; H, 2.0; N, 21.5. $C_8H_4ClN_3O$ requires C, 49.6; H, 2.1; N, 21.7%); $\nu_{max.}$ 2 220 cm^{-1} (CN); δ_H 7.43 (1 H, dd, 6-H), and 7.7—7.9 (2 H, m, 4- and 7-H); $J_{4,6}$ 2.5 Hz and $J_{6,7}$ 8 Hz.

2-*Cyano*-5-*fluoro*-1H-*benzimidazole* 3-*oxide* (**12e**). This compound, m.p. 231—232 °C (decomp.) (from aqueous methanol) was obtained (reaction time 1.5 h; yield 71%) from the nitrile (**5e**) (3.4 g) and potassium carbonate (1.22 g) in ethanol (170 ml) by the standard method (Found: C, 54.6; H, 2.3; N, 24.1. $C_8H_4FN_3O$ requires C, 54.25; H, 2.3; N, 23.7%); $\nu_{max.}$ 2 230 cm^{-1} (CN); δ_H 7.28 (1 H, ddd, 6-H), 7.53 (1 H, ddd, 4-H), 7.86 (1 H, ddd, 7-H), and 13.0 (1 H, br, NH/OH); δ_F −112.8 p.p.m. (8 lines); $J_{4,6}$ 2.6 Hz, $J_{6,7}$ 9.1 Hz, $J_{4,7}$ 0.6 Hz, $J_{4,F}$ 8.4 Hz, $J_{6,F}$ 9.8 Hz, and $J_{7,F}$ 4.8 Hz.

The above procedure with piperidine (1 mol equiv.) instead of potassium carbonate gave (**12e**) in 46% yield.

2-*Cyano*-6-*fluoro*-1H-*benzimidazole* 3-*oxide* (**12f**). This compound was prepared in the same way as (**12e**); the yield was 70%. It had m.p. 233—235 °C (decomp.) (from aqueous dimethylformamide) (Found: C, 54.1; H, 2.3; N, 23.25. $C_8H_4FN_3O$ requires C, 54.2; H, 2.3; N, 23.7%); $\nu_{max.}$ 2 235 cm^{-1} (CN); δ_H 7.3—7.85 (unresolved multiplet); δ_F −117.3 p.p.m. (dt); $J_{4,F}$ 5 Hz and $J_{5,F} = J_{7,F}$ 9.5 Hz.

2-*Cyano*-4-*nitro*-1H-*benzimidazole* 3-*oxide* (**12g**). This compound, m.p. 203—206 °C (decomp.) (from aqueous ethanol with charcoal) was obtained (reaction time 2 h; yield 34%) from the nitrile (**5g**) (2.2 g) and potassium carbonate (1.38 g) in ethanol (120 ml) at 50 °C (Found: C, 47.45; H, 1.9; N, 27.6. $C_8H_4N_4O_3$ requires C, 47.1; H, 2.0; N, 27.4%); $\nu_{max.}$ 2 240 (CN) and 1 520 and 1 335 cm^{-1} (NO_2); δ_H 7.75 (1 H, dd, *J* 8.6 and 7.8 Hz, 6-H) and 8.3—8.55 (2 H, unresolved, 5- and 7-H).

Attempts to prepare the 5-nitro isomer (**12h**) were unsuccessful, only dark red resinous material being obtained.

Cyclisation of N-o-*Nitrophenylglycine Esters* (**4**): *Ethyl Benzimidazole-2-carboxylate* N-*Oxides* (**15**).—*The parent compound* (**15a**). An ice-cold solution of *N-o*-nitrophenylglycine ethyl ester (**4a**) (2.1 g) in ethanol (250 ml) was treated, dropwise with stirring, with a solution of sodium ethoxide (from sodium, 0.21 g; 1 mol equiv.) in ethanol (20 ml) so that the temperature did not exceed 5 °C. The mixture was stirred overnight, after which the solvent was evaporated under reduced pressure and the residue partitioned between ether and water. Acidification (HCl) of the aqueous layer gave the *N*-oxide (**15a**) (0.60 g, 31%), m.p. 168—170 °C (from toluene–ethanol; lit.,[28] 166—167 °C).

*Ethyl 5-methyl-*1H*-benzimidazole-2-carboxylate 3-oxide* (**15b**). This compound was similarly obtained from the ester (**4b**) (2.5 g) in ethanol (90 ml) and dimethylformamide (5 ml), and a solution of sodium ethoxide (from sodium, 0.23 g) in ethanol (20 ml). The reaction mixture was stirred for only 2 h; the yield was 1.0 g (46%). The *ester* (**15b**) had m.p. 144—145 °C (from ethanol) and showed $\nu_{max.}$ 1 720 cm^{-1} (CO); δ_H 1.38 (3 H, t, *Me*CH_2), 2.50 (3 H, s, *Me*Ar), 4.50 (2 H, q, CH_2Me), 7.30 (1 H, dd, 6-H), 7.51 (1 H, d, 4-H), and 7.80 (1 H, d, 7-H); J_{MeCH_2} 6 Hz, $J_{6,7}$ 8 Hz, $J_{4,6}$ not measurable [*cf.* compound (**12b**)] (Found: C, 59.6; H, 5.4; N, 12.8. $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.5; N, 12.7%).

*Ethyl 5-methoxy-*1H*-benzimidazole-2-carboxylate 3-oxide* (**15c**). This compound was obtained in 68% yield by the corresponding reaction of the ester (**4c**). It had m.p. 98—99 °C (from aqueous dimethylformamide) (Found: C, 51.7; H, 5.5; N, 11.0. $C_{11}H_{12}N_2O_4 \cdot H_2O$ requires C, 52.0; H, 5.55; N, 11.0%); $\nu_{max.}$ 1 700 cm^{-1} (CO); δ_H 1.35 (3 H, t, *Me*CH_2), 3.85 (3 H, s, *Me*O), 4.39 (2 H, q, CH_2Me), 6.8—7.0 (2 H, m, 4- and 6-H), and 7.65 (1 H, m, 7-H); J_{MeCH_2} 7 Hz.

*Ethyl 5-nitro-*1H*-benzimidazole-2-carboxylate 3-oxide* (**15h**). Piperidine (14 g; *ca.* 2.1 mol equiv.) was added to a solution of *N*-(2,4-dinitrophenyl)glycine ethyl ester (**4h**) (20.8 g) in warm ethanol (800 ml). The mixture was boiled for 2 h, after which the solvent was distilled off under reduced pressure and the residue dissolved in water and the solution acidified (HCl). The precipitated N-*oxide* (**15h**) (10.8 g, 56%) had m.p. 209—210 °C (from ethanol) (Found: C, 47.8; H, 3.6; N, 16.7. $C_{10}H_9N_3O_5$ requires C, 47.8; H, 3.6; N, 16.7%); $\nu_{max.}$ 1 715 (CO) and 1 540 and 1 340 cm^{-1} (NO_2); δ_H 1.40 (3 H, t, *Me*CH_2), 4.50 (2 H, q, CH_2Me), 8.07 (1 H, d, 7-H), 8.30 (1 H, dd, 6-H), and 8.55 (1 H, d, 4-H); J_{MeCH_2} 6 Hz, $J_{4,6}$ 2 Hz, and $J_{6,7}$ 9 Hz.

Benzimidazole N-*Oxides* (**1**): *General Procedure.*—The nitrile (**12**) or ester (**15**) was heated under reflux with concentrated hydrochloric acid (20—25 ml per g of substrate) for 4 h. The *N*-oxide hydrochloride (**13**) crystallised from the cooled solution, and was purified by recrystallisation as shown in Table 1. The hydrochloride was then dissolved in aqueous ammonia (*d* 0.88; *ca.* 40 ml per g of hydrochloride), and the solution concentrated under reduced pressure at 50 °C until crystallisation commenced. The mixture was then cooled and the *N*-oxide filtered off.

The properties of the hydrochlorides and of the free *N*-oxides are collected in Tables 1 and 2.

In the 5-nitro series [(**15**)→(**13h**)→(**1h**)], the hydrochloride (**13h**), m.p. *ca.* 240 °C, partially decomposed on attempted recrystallisation (from HCl); the crude salt was dissolved directly in 5M sodium hydroxide, and the *N*-oxide precipitated by reacidification.

N-(3-*Nitro-2-pyridyl)glycine Ethyl Ester* (**16**).—The following is more efficient than the previously published method.[29] Sodium glycinate (11.6 g, 0.12 mol) in water (50 ml) was added to a suspension of 2-chloro-3-nitropyridine (10 g, 60 mmol) and potassium carbonate (9g, 60 mmol) in ethanol (250 ml). The mixture was heated under reflux for 3.5 h and then cooled to 0 °C and the yellow product filtered off; a second crop was obtained by addition of ethanol to the filtrate. The combined precipitates were dissolved in water, and the solution acidified (HCl) to give *N*-(3-nitro-2-pyridyl)glycine (11.0 g, 89%), m.p. 170 °C (decomp.) (from ethanol–water; lit.,[30] 175—176 °C).

The glycine (8.0 g) was heated for 6 h under reflux in ethanol (100 ml) containing concentrated sulphuric acid (2 g). The solution was then concentrated under reduced pressure to *ca.* 25 ml, added to ice–water and the mixture set aside at 5 °C for 2 h. The crude ester was filtered off and purified by chromatography (in ether solution) through a short column of silica. *N*-(3-Nitro-2-pyridyl)glycine ethyl ester (**16**) (8.39 g, 92%) had m.p. 40—41 °C (lit.,[29] b.p. 143 °C/0.25 mmHg; not reported as a solid) (Found: C, 48.1; H, 4.9; N, 18.8. Calc. for $C_9H_{11}N_3O_4$: C, 48.0; H, 4.9; N, 18.7%); $\nu_{max.}$ 3 360 (NH), 1 720 (CO), and 1 555 and 1 335 cm^{-1} (NO_2); δ_H($CDCl_3$) 1.30 (3 H, t, Me), 4.33 (2 H, q, CH_2Me), 4.46 (2 H, d, CH_2NH), 6.86 (1 H, dd, 5-H), 8.5—8.7 (3 H, m, 4- and 6-H, and NH); J_{CH_3,CH_2} 7 Hz, $J_{CH_2,NH}$ 6 Hz, $J_{4,5}$ 8 Hz, and $J_{5,6}$ 5.1 Hz.

N-(3,5-*Dinitro-2-pyridyl)glycine Ethyl Ester* (**17**).—The literature method[31] was improved as follows. Glycine ethyl ester hydrochloride (1.40 g, 0.01 mol) was added portionwise to a solution of 2-chloro-3,5-dinitropyridine (2.03 g, 0.01 mol) and triethylamine (2.0 g, 20 mmol) in ethanol (50 ml). Crystallisation of the product began almost immediately; after 5 min, it was filtered off and recrystallised from ethanol. The ester (**17**) (2.29 g, 84%) had m.p. 95 °C (lit.,[31] 89 °C); $\nu_{max.}$ 3 355 (NH), 1 720 (CO), and 1 540 and 1 335 cm^{-1} (NO_2); δ_H 1.21 (3 H, t, Me), 4.16 (2 H, q, CH_2Me), 4.41 (2 H, d, CH_2NH), 9.02 (1 H, d) and 9.24 (1 H, d) (4- and 6-H), and 9.49 (1 H, br t, NH); J_{CH_3,CH_2} 7 Hz, $J_{CH_2,NH}$ 6 Hz, and $J_{4,6}$ 2.5 Hz.

Cyclisation of the Ester (**16**).—The ester (**16**) (8.0 g, 36 mmol), potassium carbonate (5.1 g, 37 mmol), and ethanol (190 ml) were heated together, under reflux, for 5 h. The cooled mixture was filtered and the precipitate washed with a little ethanol; it was then dissolved in water, and the solution decolourised with charcoal and acidified (HCl). The resulting solid was collected, redissolved in boiling water (gas was evolved), and the solution evaporated to dryness under reduced pressure. The sticky residue was washed with a little ether and recrystallised from ethanol to give 3H-*imidazo*[4,5-b]*pyridine* 1-*oxide* (**20**) (0.85 g, 18%), m.p. 173—175 °C (Found: C, 53.25; H, 3.6; N, 31.05. $C_6H_5N_3O$ requires C, 53.3; H, 3.7; N, 31.1%); $\nu_{max.}$ 2 200—2 500br cm^{-1} (NH/OH); δ_H 7.33 (1 H, dd, 6-H), 8.00 (1 H, dd, 7-H), 8.46 (1 H, dd, 5-H), 8.63 (1 H, s, 2-H), and 12.0 (1 H, br s, NH/OH); $J_{6,7}$ 8.3 Hz, $J_{5,7}$ 1.5 Hz, and $J_{5,6}$ 4.4 Hz; *m/z* 135 ($M^{+\cdot}$), 119.

The ethanolic reaction mother-liquor was evaporated to dryness under reduced pressure and the residue dissolved in water. The solution was acidified (HCl) to pH 3—4, saturated with sodium chloride, and extracted repeatedly with dichloromethane. The extract was dried (Na_2SO_4) and evaporated, and the residue washed with a little ether and recrystallised from propan-2-ol. *Ethyl* 3H-*imidazo*[4,5-b]*pyridine-2-carboxylate* 1-*oxide* (**18**) (2.22 g, 30%) had m.p. 150 °C (Found: C, 52.35; H, 4.5; N, 20.5. $C_9H_9N_3O_3$ requires C, 52.2; H, 4.4; N, 20.3%); $\nu_{max.}$ 2 300—2 700 (br, NH/OH) and 1 730 cm^{-1} (CO); δ_H (1.40 (3 H, t, Me), 4.46 (2 H, q, CH_2), 7.46 (1 H, dd, 6-H), 8.09 (1 H, dd, 7-H), 9.11 (1 H, dd, 5-H), and 12.5 (1 H, br s, NH/OH); J_{MeCH_2} 8 Hz, $J_{6,7}$ 8 Hz, $J_{5,6}$ 4.6 Hz, and $J_{5,7}$ 1.8 Hz; *m/z* 207 ($M^{+\cdot}$), 191, 163, and 161 (M − EtOH)$^{+\cdot}$, 135 and 119.

Reaction of the Ester (**17**) *with Bases.*—Potassium carbonate (1.28 g; 1 mol equiv.) was added portionwise to a stirred solution of the dinitro ester (**17**) (2.5 g) in ethanol (100 ml) and dimethylformamide (17 ml). After 3 h more ethanol (100 ml) was

added and the mixture filtered. The precipitate, on dissolution in water followed by acidification (HCl), gave only a trace of black solid. The filtrate was evaporated to dryness and the residue partitioned between dichloromethane and water; the dried (Na_2SO_4) organic layer gave, on evaporation, unchanged starting material (0.28 g, 11%). The (black) aqueous layer on acidification gave a black solid (1.56 g) which (by t.l.c.) contained more unchanged starting material but was mostly highly polar and tarry.

The reaction of (**17**) with piperidine [as described for the dinitrophenyl analogue (**4h**)] similarly gave a black intractable tarry solid.

Acknowledgements

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o-Nitroaniline Derivatives. Part 10.[1] 5- and 6-Amino-1*H*-benzimidazole 3-Oxides

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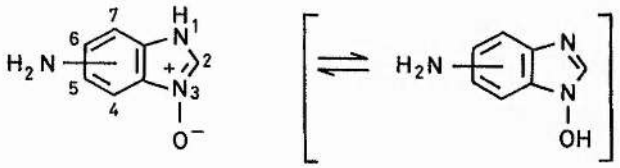
Cyclisation of *N*-(4- or 5-acylamino-2-nitrophenyl)glycine esters in basic media gives alkyl 5- or 6-acylaminobenzimidazole-2-carboxylate *N*-oxides, *e.g.* (**11a**) or (**11b**). Acid hydrolysis of the latter, followed by reaction with ammonia, gives the title compounds (**1b**) and (**1c**), in acceptable yield. The corresponding reaction sequence with 4-acylamino-*N*-cyanomethyl-*o*-nitroanilines also gives (**1b**); where the acyl group is methylsulphonyl, however, the final product is 5-methanesulphonamidobenzimidazole *N*-oxide (**9**). Compound (**1b**) is also obtainable from ethyl 5-nitrobenzimidazole-2-carboxylate *N*-oxide by reduction followed by hydrolysis.

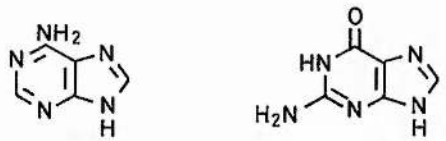
Attempts to cyclise *N*-(*o*-nitrophenyl)glycine derivatives containing a free amino group at the 5-position are unsuccessful. This failure is attributed to mesomeric deactivation of the nitro group by the amino lone pair.

In Part 9[1] we have described a general synthetic route to benzimidazole *N*-oxides which are unsubstituted both at the other nitrogen and at C-2, and we now consider the application of this method to the synthesis of benzimidazole *N*-oxides with an amino substituent in the carbocyclic ring, *viz.* (**1a**—**d**). These hitherto unknown compounds are of potential biological interest in view of their structural resemblance to the natural purines: thus (**1a**) and (**1d**) are obviously related to adenine (**2**), and (**1b**) and (**1c**) possess some of the functionality of guanine



(**1**)

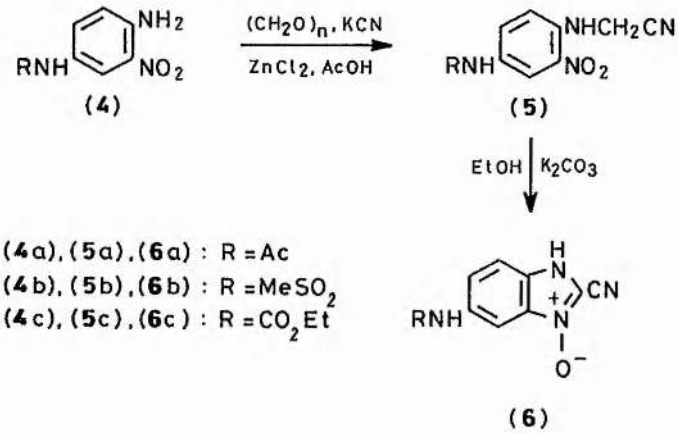
(**1a**) : 4 - NH_2 (**1c**) : 6 - NH_2
(**1b**) : 5 - NH_2 (**1d**) : 7 - NH_2



(**2**) (**3**)

(**3**). The *N*-oxides (**1a**—**d**) are also of chemical interest in their own right, since they may be expected to react as multifunctional nucleophiles. In this paper we describe the syntheses and characteristics of the 5- and 6-amino compounds (**1b**) and (**1c**).

*5-Amino-*1H*-benzimidazole 3-Oxide* (**1b**).—(i) *From* 2-*nitro*-p-*phenylenediamine.* Monoacylation of 2-nitro-*p*-phenylenediamine occurs selectively at the 4-amino group,[2,3] and the acetyl-, methylsulphonyl-, and ethoxycarbonyl protected diamines (**4**) are then cyanomethylated at the other amino group by Dimroth and Aurich's method[4] (*cf.* the preceding paper[1]). Cyclisation of the resulting cyanomethyl compounds (**5**) in ethanolic potassium carbonate[1] gives the 5-acylamino-2-cyanobenzimidazole oxides (**6**) in good yield, and the latter are then hydrolysed in concentrated hydrochloric acid. In



(**4**) (**5**) (**6**)

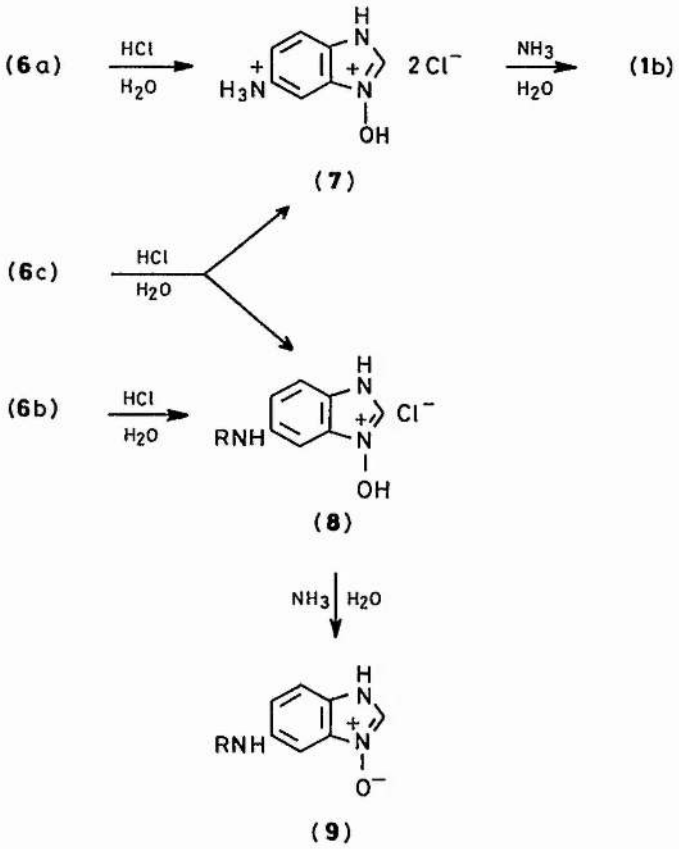
(**4a**), (**5a**), (**6a**) : R = Ac
(**4b**), (**5b**), (**6b**) : R = $MeSO_2$
(**4c**), (**5c**), (**6c**) : R = CO_2Et

the case of the acetamido compound (**6a**), the hydrolysis product is the dihydrochloride (**7**) of the 5-amino *N*-oxide (**1a**), and the free *N*-oxide is obtained by reaction of the dihydrochloride with ammonia (*cf.* Part 9[1]). The amino-protecting groups in (**6b**) and (**6c**), however, are more resistant to hydrolysis; thus the hydrolysis of (**6b**) gives, *via* the monohydrochloride (**8a**), 5-methanesulphonamidobenzimidazole *N*-oxide (**9a**), and the corresponding hydrolysis of the cyanocarbamate (**6c**) gives a mixture of the dihydrochloride (**7**) and the monohydrochloride (**8b**), and thence the *N*-oxides (**1b**) and (**9b**).

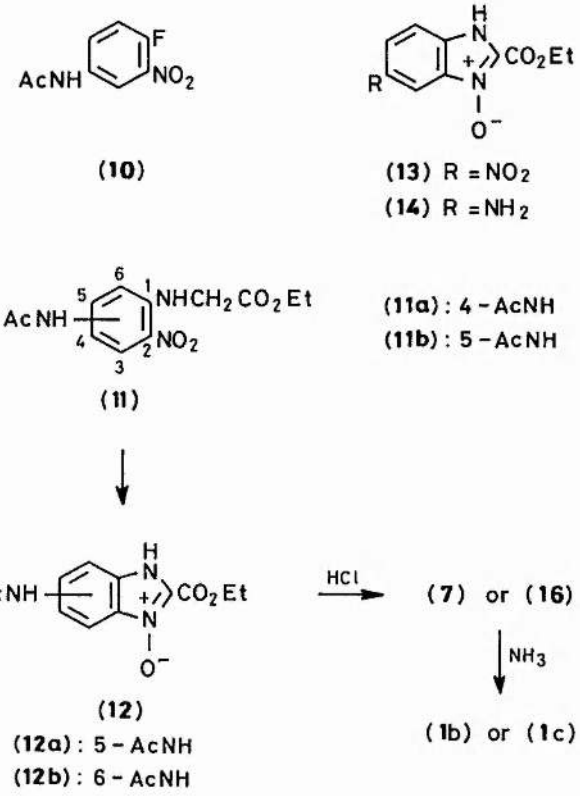
(ii) *From* 4-*fluoro*-3-*nitroaniline.* Although the amino group in this (commercially available) amine deactivates the fluorine towards nucleophilic displacement, the *N*-acetyl derivative (**10**) reacts cleanly with glycine ethyl ester to give the ester (**11a**). This, like the corresponding nitrile (**5a**), is cyclised in base to the benzimidazole oxide (**12a**), and the latter hydrolysed to the dihydrochloride (**7**) and thence to the amino *N*-oxide (**1b**).

(iii) *From 5-nitrobenzimidazole* N-*oxide.* The most obvious route to (**1b**), *viz.* the catalytic hydrogenation of 5-nitrobenzimidazole *N*-oxide,[1] presents practical difficulties because of the low solubility of the nitro compound in the usual solvents. However, catalytic hydrogenation of the nitro ester (**13**) proceeds smoothly, and gives the amino ester (**14**) which, although itself not easily purified, is hydrolysable to the dihydrochloride (**7**) and thence to (**1b**).

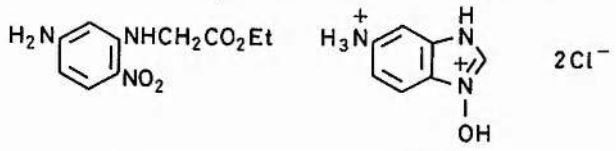
*6-Amino-*1H*-benzimidazole 3-oxide* (**1c**).—3-Fluoro-4-nitroaniline,[5] unlike the 4-fluoro-3-nitro isomer, reacts readily with glycine ethyl ester giving *N*-(5-amino-2-nitrophenyl)glycine



(**8a**),(**9a**) : R = SO_2Me ; (**8b**),(**9b**) : R = CO_2Et



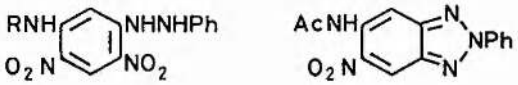
ethyl ester (**15**). Surprisingly, this ester is not cyclised at all in the presence of base, but merely undergoes hydrolysis to the corresponding carboxylic acid. However, the monoacetyl derivative of (**15**), *viz.* (**11b**), is readily cyclised in base to the benzimidazole oxide (**12b**), and hydrolysis of the latter, as described for its isomer (**12a**), leads to the parent *N*-oxide (**1c**).



(**15**) (**16**)

As befits such polar compounds, the *N*-oxides (**1b**) and (**1c**) are appreciably soluble in polar media, and crystallise from water in hydrated form. Presumably as a consequence of the extensive hydrogen bonding, there is no distinct NH stretching absorption in the i.r. spectra; however, the mass spectra show prominent ions for $M^{+\cdot}$, $(M - 16)^+$, and $(M - 29)^+$ (*i.e.* loss of O and CHO),[6] and the ^1H n.m.r. spectra show the characteristic lowfield singlet[1] corresponding to 2-H.

The failure of the glycine ester (**15**) to undergo cyclisation is evidently due to the presence of the primary amino group. The effect of ring substituents on intramolecular condensations involving nitro groups has not been widely or systematically studied: although, for example, we are accumulating evidence that the presence of a second nitro group in the ring may facilitate base-catalysed condensation in certain cases, it is by no means clear, from isolated examples here and there in the literature,[7] to what extent this represents a general trend. The effect of a powerful electron-donor on these condensations is even less well documented. Seventy-five years ago, Fries and Roth[8] reported as 'merkwürdig' (noteworthy, or remarkable) the fact that the aminodinitrodiphenylhydrazine (**17a**) failed to

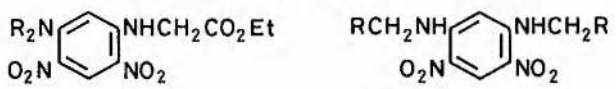


(**17a**) R = H
(**17b**) R = Ac

(**18**)

undergo cyclisation in base, whereas the corresponding acetamido compound (**17b**) was readily cyclised to the benzotriazole (**18**); no explanation was offered for this difference in reactivity, and we are unaware of any other recorded examples in the more recent literature. In the case of the ester (**15**), as in Fries and Roth's experiment, we believe that the mesomeric effect of the *p*-amino group reduces the electrophilicity of the nitro group to such an extent that it is unreactive towards attack by the adjacent nucleophile.

The inhibiting effect of a 5-amino substituent on the cyclisation of an *N*-(*o*-nitrophenyl)glycine derivative is observed even when an additional nitro group is present. Thus, for example, *N*-(5-amino- and 5-dimethylamino-2,4-dinitrophenyl)-glycine ethyl esters (**19a**) and (**19b**) are recovered largely unchanged from treatment with strong base, and attempts to cyclise diaminodinitrobenzene derivatives such as (**20**) and (**21**) in basic media have similarly proved unsuccessful, substantial quantities of starting materials being recovered in each case.



(**19a**) R = H
(**19b**) R = Me

(**20**) R = CO_2Et
(**21**) R = CN

Experimental

I.r. spectra were recorded for Nujol mulls, and ^{1}H n.m.r. spectra were recorded at 80 MHz for solutions in [$^2H_6$]-dimethyl sulphoxide.

4-Amino-3-nitroacetanilide (**4a**).—Acetic anhydride (10.2 g, 0.1 mol) was added, with stirring, to a solution of 2-nitro-*p*-phenylenediamine (15.3 g, 0.1 ml) in acetic acid (150 mol) and the mixture set aside overnight. The crystalline product was filtered off, washed with water, and recrystallised from aqueous ethanol. The amide (**4a**) (11.6 g, 59%) had m.p. 187—189 °C (decomp.) (lit.,[2] 189 °C); $\nu_{max.}$ 3 430 (amide NH), 3 280—3 360 (multiplet; NH_2), 1 660 (CO), and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 2.02 (3 H, s, Me), 7.00 (1 H, d, 5-H), 7.29 (2 H, br s, NH_2), 7.53 (1 H, dd, 6-H), 8.37 (1 H, d, 2-H), and 9.87 (1 H, br s, N*H*Ac); $J_{2,6}$ 2.2 Hz and $J_{5,6}$ 9 Hz.

N-(4-Amino-3-nitrophenyl)methanesulphonamide (**4b**).—Methanesulphonyl chloride (11.5 g, 0.1 mol) was added gradually over 3 min to a solution of 2-nitro-*p*-phenylenediamine (15.3 g) in pyridine (70 ml). The temperature of the mixture rose to *ca.* 70 °C; the solution was set aside for 10 min, and then heated under reflux for a further 15 min. The pyridine was evaporated under reduced pressure, and water added to the residue; the sulphonamide (**4b**) was filtered off, and recrystallised from ethanol (with charcoal); yield 14.6 g (63%), m.p. 166—168 °C (lit.,[3] 168—171 °C); $\nu_{max.}$ 3 480, 3 365, 3 240 (NH and NH_2), 1 515 and 1 345 (NO_2), and 1 310 and 1 140 cm^{-1} (SO_2); δ_H 3.00 (3 H, s, Me), 7.20 (1 H, d, 5-H), 7.50 (1 H, dd, 6-H), 7.55 (2 H, s, NH_2), 8.03 (1 H, d, 2-H), 9.60 (1 H, s, N*H*Ms); $J_{2,6}$ 2 Hz and $J_{5,6}$ 9 Hz.

Ethyl N-(4-Amino-3-nitrophenyl)carbamate (**4c**).—Pyridine (16.0 g, 0.2 mol) was added to a solution of 2-nitro-*p*-phenylenediamine (15.3 g) in acetonitrile (100 ml) and the mixture cooled to *ca.* 5 °C. Ethyl chloroformate (10.8 g, 0.1 mol) was added dropwise, with cooling and stirring, over *ca.* 30 min, and the mixture was allowed to warm to room temperature over a further 1 h. The solvent was evaporated under reduced pressure, the oily residue added to ice–water with vigorous stirring, and the solid product filtered off, washed with water, and recrystallised (twice) from aqueous ethanol (with charcoal), to give the carbamate (**4c**) (16.6 g, 74%), m.p. 129—130 °C (lit.,[3] 129—132 °C); $\nu_{max.}$ 3 320 (br, NH and NH_2), 1 680 (CO), and 1 540 and 1 340 cm^{-1} (NO_2); δ_H 1.28 (3 H, t, Me), 4.25 (2 H, q, CH_2), 7.11 (1 H, d, 5-H), 7.40 (2 H, br s, NH_2), 7.65 (1 H, dd, 6-H), 8.40 (1 H, d, 2-H), and 9.70 (1 H, s, N*H*CO_2Et); $J_{2,6}$ 2.2 Hz, $J_{5,6}$ 9.2 Hz, and $J_{CH_3-CH_2}$ 7 Hz.

4-Acetamido-N-cyanomethyl-2-nitroaniline (**5a**).—To 4-amino-3-nitroacetanilide (**4a**) (15 g, 74 mmol) were added, successively, paraformaldehyde (7.41 g, 0.247 mol CH_2O), potassium cyanide (15.34 g, 0.236 mol), zinc chloride (39.3 g, 0.29 mol), and acetic acid (400 ml) containing concentrated sulphuric acid (15 drops). The vigorously stirred mixture was heated to 50 °C over *ca.* 30 min, and kept at this temperature for 6 h. It was then added to crushed ice; the solid product was filtered off and washed well with water. The *nitrile* (**5a**) (14.4 g, 80%) had m.p. 228—229 °C (from acetic acid) (Found: C, 51.3; H, 4.3; N, 24.0. $C_{10}H_{10}N_4O_3$ requires C, 51.3; H, 4.3; N, 23.9%); $\nu_{max.}$ 3 390 and 3 350 (2 × NH), 2 245w (CN), 1 680 (CO), and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 2.07 (3 H, s, Me), 4.60 (2 H, d, CH_2), 7.30 (1 H, d, 6-H), 7.95 (1 H, dd, 5-H), 8.30 (1 H, br t, N*H*CH_2), and 8.70 (1 H, d, 3-H); $J_{3,5}$ 2.8 Hz, $J_{5,6}$ 9.2 Hz, and $J_{CH_2,NH}$ 6 Hz.

N-Cyanomethyl-4-methanesulphonamido-2-nitroaniline (**5b**). This compound, m.p. 169—170 °C (from ethanol), was similarly obtained (yield 82%) from the sulphonamide (**4b**) (21.2 g) (Found: C, 40.1; H, 3.7; N, 20.6. $C_9H_{10}N_4O_4S$ requires C, 40.0; H, 3.7; N, 20.7%); $\nu_{max.}$ 3 370 and 3 270 (2 × NH), 2 250 w (CN), 1 525 and 1 335 (NO_2), 1 310 and 1 140 cm^{-1} (SO_2); δ_H 3.05 (3 H, s, Me), 4.65 (2 H, d, CH_2), 7.35 (1 H, d, 6-H), 7.75 (1 H, dd, 5-H), 8.20 (1 H, d, 3-H), 8.37 (1 H, br t, N*H*CH_2), and 9.5—10.0 (1 H, br, N*H*Ms); $J_{3,5}$ 2.8 Hz, $J_{5,6}$ 9.2 Hz, and $J_{CH_2,NH}$ 6 Hz.

N-Cyanomethyl-4-ethoxycarbonylamino-2-nitroaniline (**5c**). This compound, m.p. 194—195 °C (from acetic acid), was similarly prepared (8 h reaction time) from the carbamate (**4c**) (8.0 g) in 70% yield (Found: C. 50.1; H, 4.5; N, 21.2. $C_{11}H_{12}N_4O_4$ requires C, 50.0; H, 4.6; N, 21.2%); $\nu_{max.}$ 3 400 and 3 355 (2 × NH), 2 230vw (CN), 1 710 (CO), and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 1.30 (3 H, t, Me), 4.25 (2 H, q, C*H*$_2$Me), 4.65 (2 H, d, C*H*$_2$NH), 7.30 (1 H, d, 6-H), 7.90 (1 H, dd, 5-H), 8.30 (1 H, br t, N*H*CH_2), 8.65 (1 H, d, 3-H), and 9.85 (1 H, s, N*H*CO_2Et); $J_{3,5}$ 2.6 Hz, $J_{5,6}$ 9.8 Hz, $J_{CH_2,NH}$ 6 Hz, and J_{Me,CH_2} 7 Hz.

5-Acetamido-2-cyano-1H-benzimidazole 3-Oxide (**6a**).—4-Acetamido-*N*-cyanomethyl-2-nitroaniline (**5a**) (7.0 g, 0.03 mol) was dissolved, as far as possible, in hot ethanol (320 ml). Potassium carbonate (4.1 g, 30 mmol) was added carefully, and the mixture heated under reflux for 45 min. Evaporation of the solvent under reduced pressure gave a solid which was dissolved as far as possible in water (300 ml). The solution was filtered, and the filtrate acidified (conc. HCl) with cooling and stirring. The colourless product was filtered off, washed with water, and recrystallised from aqueous ethanol. The N-*oxide* (**6a**) (4.6 g, 71%) had m.p. 233—234 °C (Found: C, 55.55; H, 3.7; N, 26.0. $C_{10}H_8N_4O_2$ requires C, 55.6; H, 3.7; N, 25.9%); $\nu_{max.}$ 3 320 (NHAc), 2 600br (NH/OH), 2 230 (CN), and 1 630 cm^{-1} (CO); δ_H 2.17 (3 H, s, Me), 7.53 (1 H, dd, 6-H), 7.91 (1 H, d, 7-H), 8.48 (1 H, d, 4-H), 10.40 (1-H, s, N*H*Ac), and 13.0—13.5 (1 H, br s, NH/OH); $J_{4,6}$ 2.0 Hz and $J_{6,7}$ 9.0 Hz.

2-Cyano-5-methanesulphonamido-1H-benzimidazole 3-oxide (**6b**). This compound, m.p. 223—224 °C (decomp.) (from aqueous ethanol), was similarly obtained (reaction time, 1 h; yield, 92%) from the sulphonamidonitrile (**5b**) (11.4 g) (Found: C, 42.8; H, 3.0; N, 22.3. $C_9H_8N_4O_3S$ requires C, 42.85; H, 3.2; N, 22.2%); $\nu_{max.}$ 3 300br (NH), 2 235 (CN), and 1 320 and 1 145 cm^{-1} (SO_2); δ_H 3.15 (3 H, s, Me), 7.45 (1 H, dd, 6-H), 7.65 (1 H, d, 4-H), 7.95 (1 H, d, 7-H), 10.35 (1 H, s, N*H*Ms); $J_{4,6}$ 2.0 Hz and $J_{6,7}$ 9.2 Hz.

2-Cyano-5-ethoxycarbonylamino-1H-benzimidazole 3-oxide (**6c**). This compound, m.p. 215—216 °C (decomp.) (from aqueous ethanol) was similarly obtained (reaction time, 1.5 h; yield, 84%) by cyclisation of the cyanocarbamate (**5c**) (8.3 g) (Found: C, 53.8; H, 4.0; N, 22.7. $C_{11}H_{10}N_4O_3$ requires C, 53.7; H, 4.1; N, 22.75%.) $\nu_{max.}$ 3 220 (NH-CO_2Et), 3 050br (NH/OH), 2 220 (CN), and 1 680 cm^{-1} (CO); δ 1.30 (3 H, t, Me), 4.30 (2 H, q, CH_2), 7.53 (1 H, dd, 6-H), 7.85 (1 H, d, 7-H), 8.12 (1 H, d, 4-H), 10.07 (1 H, s, N*H*-CO_2Et), 12.7—13.5 (1 H, br s, NH/OH); $J_{4,6}$ 2.0 Hz, $J_{6,7}$ 9.2 Hz, and J_{Me,CH_2} 7.0 Hz.

N-(4-Acetamido-2-nitrophenyl)glycine Ethyl Ester (**11a**).—4-Fluoro-3-nitroacetanilide (**10**), m.p. 140—141 °C (from aqueous ethanol, with charcoal; lit.,[9] 139 °C) was prepared in 89% yield by reaction of 4-fluoro-3-nitroaniline (15 g) with acetic anhydride (30 g) at 25 °C, and addition of the mixture to ice–water after 45 min. A suspension of the amide (**10**) (12.5 g, 63 mmol), glycine ethyl ester hydrochloride (9.7 g, 70 mmol), and sodium hydrogen carbonate (10.6 g, 0.126 mol) in dimethyl sulphoxide (40 ml) was stirred for 6 h at 60—65 °C; the mixture was then poured *very slowly*, with vigorous stirring, into ice–water (500 ml), and the red precipitate filtered off. Recrystallisation from ethanol gave the *ester* (**11a**) (8.83 g, 50%) as orange needles, m.p. 164—165 °C (Found: C, 51.5; H, 5.3; N, 14.9. $C_{12}H_{15}N_3O_5$ requires C, 51.2; H, 5.4; N, 14.9%); $\nu_{max.}$ 3 380 (NH), 1 725 and

1 685 (CO), and 1 525 and 1 320 cm^{-1} (NO_2); δ_H 1.23 (3 H, t, $MeCH_2$), 2.03 (3 H, s, *Me*CO), 4.16 (2 H, q, CH_2Me),* 4.20 (2 H, d, CH_2NH),* 6.88 (1 H, d, 6-H), 7.63 (1 H, dd, 5-H), 8.21 (1 H, br t, $NHCH_2$), 8.44 (1 H, d, 3-H), 10.05 (1 H, s, N*H*Ac); $J_{3,5}$ 2 Hz, $J_{5,6}$ 9 Hz, J_{MeCH_2} 7 Hz, and $J_{CH_2,NH}$ 5 Hz.

N-(5-*Amino*-2-*nitrophenyl*)*glycine Ethyl Ester* (**15**).—3-Fluoro-4-nitroaniline[1,5] (3.4 g, 22 mmol), glycine ethyl ester hydrochloride (4.2 g, 30 mmol), and sodium hydrogen carbonate (3.7 g, 44 mmol) were stirred in dimethyl sulphoxide (15 ml) for 4 h at 90—100 °C. The orange suspension was cooled and added to ice–water (200 ml), and the precipitate filtered off and recrystallised from aqueous ethanol to give the *ester* (**15**) (4.43 g, 85%), m.p. 123—127 °C (Found: C, 50.2; H, 5.5; N, 17.8. $C_{10}H_{13}N_3O_4$ requires C, 50.2; H, 5.5; N, 17.6%); $\nu_{max.}$ 3 580, 3 460, 3 330, and 3 220 (NH), 1 730 (CO), and 1 560 and 1 310 cm^{-1} (NO_2); δ_H 1.25 (3 H, t, Me), 4.09 (2 H, d, CH_2NH), 4.20 (2 H, q, CH_2Me), 5.69 (1 H, d, 6-H), 6.04 (1 H, dd, 4-H), 6.53 (2 H, br s, NH_2), 7.81 (1 H, d, 3-H), and 8.60 (1 H, t, $NHCH_2$); $J_{3,4}$ 9 Hz, $J_{4,6}$ 2 Hz, J_{CH_2Me} 7 Hz, and $J_{CH_2,NH}$ 5 Hz.

N-(5-*Amino*-2-*nitrophenyl*)*glycine*. (*a*) The foregoing ester (**15**) (0.24 g, 1.0 mmol), potassium carbonate (0.16 g, 1.1 mmol), and ethanol (15 ml) were heated together under reflux for 1 h. The yellow precipitate was filtered off and dissolved in water; acidification (HCl) gave the free acid (0.13 g, 62%).

(*b*)[10] 3-Fluoro-4-nitroaniline (0.75 g, 4.8 mmol), glycine (0.38 g. 5.1 mmol), sodium hydrogen carbonate (4.0 g), ethanol (30 ml), and water (10 ml) were heated together under reflux for 3 h. The solution was then concentrated under reduced pressure to *ca.* 10 ml, and acidified (HCl) to precipitate the acid (0.40 g, 40%).

N-(5-*Amino*-2-*nitrophenyl*)*glycine* had m.p. 210—214 °C (from aqueous ethanol) (Found: C, 45.6; H, 4.35; N, 19.6. $C_8H_9N_3O_4$ requires C, 45.5; H, 4.3; N, 19.9%); $\nu_{max.}$ 3 480 and 3 380 (NH), 1 725 (CO), and 1 555 and *ca.* 1 300 cm^{-1} (NO_2); δ_H 4.00 (2 H, d, CH_2), 5.70 (1 H, d, 6-H), 6.03 (1 H, dd, 4-H), 6.55 (2 H, br s, NH_2), 7.84 (1 H, d, 3-H), 8.59 (1 H, br t, $NHCH_2$); $J_{3,4}$ 9 Hz, $J_{4,6}$ 2 Hz, and J_{CH_2NH} 5 Hz.

N-(5-*Acetamido*-2-*nitrophenyl*)*glycine ethyl ester* (**11b**). This compound, m.p. 210—212 °C (from ethanol), was prepared by acetylation of the 5-amino analogue (**15**) (4 g) with acetic anhydride (8 g) at 100 °C for 30 min; it was isolated by adding the reaction mixture to ice–water (150 ml); yield, 3.89 g (83%) (Found: C, 51.4; H, 5.3; N, 14.9. $C_{12}H_{15}N_3O_5$ requires C, 51.2; H, 5.4; N, 14.9%); $\nu_{max.}$ 3 360, 3 340, 3 310sh (NH), 1 745 and 1 695 (CO), and 1 550 and 1 320 cm^{-1} (NO_2); δ_H 1.25 (3 H, t, *Me*CH_2), 2.11 (3 H, s, *Me*CO), 4.15 (2 H, d, CH_2NH),* 4.19 (2 H, q, CH_2Me),* 6.86 (1 H, dd, 4-H), 7.29 (1 H, d, 6-H), 8.06 (1 H, d, 3-H), 8.49 (1 H, br t, $NHCH_2$), and 10.28 (1 H, s, N*H*Ac); $J_{3,4}$ 9 Hz, $J_{4,6}$ 2 Hz, $J_{CH_2,NH}$ 6 Hz, and J_{CH_2Me} 7 Hz.

Ethyl 5-*Acetamido*-1H-*benzimidazole*-2-*carboxylate* 3-*Oxide* (**12a**).—*N*-(4-Acetamido-2-nitrophenyl)glycine ethyl ester (**11a**) (8 g, 28 mmol), potassium carbonate (3.93 g, 28 mmol), and ethanol (300 ml) were heated together under reflux for 2 h (a precipitate was formed). The solvent was evaporated under reduced pressure, and the residue partitioned between water and dichloromethane; the aqueous layer was acidified (HCl) and the N-*oxide* (**12a**) filtered off. It had m.p. 133—134 °C (from aqueous ethanol); the yield was 4.84 g (61%) (Found: C, 51.2; H, 5.3; N, 15.0. $C_{12}H_{13}N_3O_4 \cdot H_2O$ requires C, 51.2; H, 5.4; N, 14.9%); $\nu_{max.}$ 3 360 (N*H*Ac), 3 300br (H_2O?), 2 650br (NH/OH), and 1 720 and 1 655 cm^{-1} (CO); δ_H 1.35 (3 H, t, *Me*CH_2), 2.10 (3 H, s, *Me*CO), 4.39 (2 H, q, CH_2), 7.26 (1 H, dd, 6-H), 7.64 (1 H, d, 7-H), 8.15 (1 H, d, 4-H), 10.15 (1 H, s, N*H*Ac), and 12.05 (1 H, br s, NH/OH); $J_{4,6}$ 2 Hz, $J_{6,7}$ 9 Hz, and $J_{CH_3CH_2}$ 7 Hz.

Ethyl 6-*acetamido*-1H-*benzimidazole*-2-*carboxylate* 3-*oxide* (**12b**). This compound, m.p. 198—200 °C (from dimethylformamide–water), was similarly obtained from the 5-acetamido analogue (**11b**) (3.5 g, 12 mmol) and potassium carbonate (1.72 g, 12 mmol) in ethanol (100 ml); yield 2.34 g (67%) (Found: C, 51.2; H, 5.3; N, 15.3. $C_{12}H_{13}N_3O_4 \cdot H_2O$ requires C, 51.2; H, 5.4; N, 14.9%); $\nu_{max.}$ 3 110—3 280br (N*H*Ac, NH/OH), and 1 705 and 1 660 cm^{-1} (CO); δ_H 1.36 (3 H, t, *Me*CH_2), 2.08 (3 H, s, *Me*CO), 4.40 (2 H, q, CH_2), 7.35—7.5 (2 H, m)† and 7.9—8.1 (1 H, m, ArH),† 10.01 (1 H, s, N*H*Ac), and 12.13 (1 H, br s, NH/OH).

Ethyl 5-*Amino*-1H-*benzimidazole*-2-*carboxylate* 3-*Oxide* (**14**).—A solution of ethyl 5-nitro-1*H*-benzimidazole-2-carboxylate 3-oxide (**13**)[1] (1.0 g) in ethanol (250 ml) was hydrogenated in presence of 5% palladium–charcoal (0.3 g). When the uptake of hydrogen was complete (15—20 min), the catalyst was filtered off and the filtrate concentrated under reduced pressure. The buff residue was recrystallised from ethyl acetate to give the *amino ester* (**14**) (0.55 g, 63%), m.p. 156—159 °C (Found: C, 54.8; H, 5.1; N, 18.5. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%); $\nu_{max.}$ 3 485 and 3 370 (NH_2), 2 600br (NH/OH), and 1 700 cm^{-1} (CO); δ_H 1.35 (3 H, t, Me), 4.38 (2 H, q, CH_2), 6.60 (1 H, d, 4-H), 6.72 (1 H, dd, 6-H), and 7.42 (1 H, d, 7-H); $J_{4,6}$ 2 Hz, $J_{6,7}$ 9 Hz, and J_{MeCH_2} 7.5 Hz; *m/z* 221 ($M^{+\bullet}$, 95%), 205 (32%), 175 (55%), 160 (40%), 159 (69%), 133 (45%), 132 (91%), 131 (100%), *etc.* Although a completely pure sample was not obtained, the amino ester appeared to darken on storage, and so was used immediately without further purification.

5-*Amino*-1H-*benzimidazole* 3-*Oxide Dihydrochloride* (**7**).—(a) *From the acetamido-ester* (**12a**). The ester (**12a**) (3 g, 10 mmol) and concentrated hydrochloric acid (25 ml) were heated together under reflux for 1.5 h. The colourless dihydrochloride (**7**) (1.86 g, 74%) crystallised from the cooled solution.

(b) *From the acetamido nitrile* (**6a**). The nitrile (2 g, 9 mmol) was similarly hydrolysed to give compound (**7**) (1.45 g, 71%).

(c) *From the amino ester* (**14**). The crude amino ester (0.2 g) and concentrated hydrochloric acid (10 ml) were heated together under reflux for 1 h. Cooling gave compound (**7**) (0.090 g), and concentration of the mother-liquor gave a further crop (0.070 g; total yield 80%).

The *dihydrochloride* (**7**) had m.p. 238 °C (decomp.) (from conc. HCl) (Found: C, 37.5; H, 4.1; N, 18.9. $C_7H_7N_3O \cdot 2HCl$ requires C, 37.9; H, 4.1; N, 18.9%); $\nu_{max.}$ 2 600 (v br; NH and OH); δ_H 7.51 (1 H, dd, 6-H), 7.79 (1 H, d, 4-H), 7.94 (1 H, d, 7-H), 9.90 (1 H, s, 2-H), and 10.63 (5 H, br s, $\overset{+}{N}H_3$, $\overset{+}{N}H$, OH); $J_{4,6}$ 2 Hz and $J_{6,7}$ 8.5 Hz.

5-*Amino*-1H-*benzimidazole* 3-*Oxide* (**1b**).—The dihydrochloride (**7**) (1.4 g, 6 mmol) was dissolved in aqueous ammonia (*d* 0.88; 10 ml) and the solution was immediately evaporated to dryness under reduced pressure. The residue was washed with a little water, filtered off, and recrystallised from water to give the colourless N-*oxide* (**1b**) (0.6 g, 57%), m.p. 97—98 °C (Found: C, 50.0; H, 5.5; N, 25.5. $C_7H_7N_3O \cdot H_2O$ requires C, 50.3; H, 5.4; N, 25.1%); $\nu_{max.}$ 3 430sh, 3 310, 3 320sh, 3 140, and 3 080 cm^{-1} (all broad); δ_H 5.65 (br s, $NH_2 + H_2O$), 6.45—6.63 (2 H, m),† 7.15—7.33 (1 H, m),† and 8.00 (1 H, s, 2-H); *m/z* 149 ($M^{+\bullet}$, 60%), 133 (100%), 132 (87%), 120 (20%), 106 (20%), and 105 (67%), *etc.*

5-*Methanesulphonamido*-1H-*benzimidazole* 3-*Oxide* (**9a**).—The sulphonamido nitrile (**6b**) (2 g) was hydrolysed with

* Overlapping signals.

† Not first-order spectrum.

concentrated hydrochloric acid as described above for compound (**12a**). No crystalline product was obtained on cooling the solution; the acid was distilled off under reduced pressure and the residue washed with warm ethanol (30 ml). The *hydrochloride* (**8a**) (1.18 g, 57%) showed $\nu_{max.}$ 3 100br (*NH*Ms), 2 625br (NH/OH), and 1 320 and 1 140 cm^{-1} (SO_2); δ_H 3.10 (3 H, s, Me), 7.48 (1 H, dd, 6-H), 7.69 (1 H, d, 4-H), 7.86 (1 H, d, 7-H), 9.82 (1 H, s, 2-H), and 10.32 (1 H, s, N*H*Ms). A sample recrystallised from a large volume of ethanol had m.p. 211—212 °C (Found: C, 36.5; H, 3.8; N, 15.95. $C_8H_9N_3O_3S$·HCl requires C, 36.4; H, 3.8; N, 15.9%). Reaction of the hydrochloride with ammonia, as described in the preceding paragraph, gave the *sulphonamido* N-*oxide* (**9a**), m.p. 220—222 °C (from ethanol) (Found: C, 42.6; H, 3.9; N, 18.6. $C_8H_9N_3O_3S$ requires C, 42.3; H, 4.0; N, 18.5%); $\nu_{max.}$ 3 215 (*NH*Ms), and 1 320 and 1 145 cm^{-1} (SO_2); δ_H 2.95 (3 H, s, Me), 7.09 (1 H, dd, 6-H), 7.39 (1 H, d, 4-H), 7.59 (1 H, d, 7-H), 8.31 (1 H, s, 2-H), 9.70 (1 H, s, N*H*Ms), 11.88 (1 H, br s, NH/OH); $J_{4,6}$ 2 Hz and $J_{6,7}$ 9 Hz.

Hydrolysis of the Cyano Carbamate (**6c**).—Compound (**6c**) (5.0 g) and concentrated hydrochloric acid (50 ml) were heated together under reflux for 2.5 h. 5-*Ethoxycarbonylamino*-1H-*benzimidazole* 3-*oxide hydrochloride* (**8b**) crystallised from the cooled solution. Recrystallised from ethanol, it had m.p. 210—211 °C (decomp.); yield 2.20 g (42%) (Found: C, 46.8; H. 4.7; N, 16.2. $C_{10}H_{11}N_3O_3$·HCl requires C, 46.6; H, 4.7; N, 16.3%); $\nu_{max.}$ 3 280, 3 200, 3 130 (NH), 2 600br ($\overset{+}{N}H$, OH), and 1 720 cm^{-1} (CO); δ_H 1.29 (3 H, t, Me), 4.19 (2 H, q, CH_2), 7.58 (1 H, dd, 6-H), 7.78 (1 H, d, 7-H), 8.11 (1 H, d, 4-H), 9.83 (1 H, s, 2-H), 10.13 (1 H, s, N*H*CO_2Et), and 12.78 (2 H, br s, NH/OH); $J_{4,6}$ 2 Hz, $J_{6,7}$ 9 Hz, and J_{MeCH_2} 7 Hz.

The reaction mother-liquor was concentrated under reduced pressure to *ca.* 10 ml, and cooled in ice. 5-Amino-1*H*-benzimidazole 3-oxide dihydrochloride (**7**) (1.57 g, 35%) crystallised out and was identified by comparison with an authentic sample.

Increasing the reaction time to 7 h increased the product ratio (**7**): (**8b**) but some decomposition also occurred and the products were therefore less easily isolated. A black tarry residue was also obtained.

5-*Ethoxycarbonylamino*-1H-*benzimidazole* 3-*Oxide* (**9b**).—The hydrochloride (**8b**) (1 g) was dissolved in aqueous ammonia (*d* 0.88; 10 ml), the solution was concentrated under reduced pressure until precipitation commenced, and the mixture was then cooled in ice and the product filtered off and washed with a little water. The N-*oxide* (**9b**) (0.44 g, 51%) had m.p. 205 °C (decomp.) (from ethanol) (Found: C, 54.3; H, 5.0; N, 18.8. $C_{10}H_{11}N_3O_3$ requires C, 54.3; H, 5.0; N, 19.0%) $\nu_{max.}$ 3 310 (NH), 2 300 br (NH/OH), and 1 700 cm^{-1} (CO); δ_H 1.28 (3 H, t, Me), 4.18 (2 H, q, CH_2), 7.22 (1 H, dd, 6-H), 7.54 (1 H, d, 7-H), 7.86 (1-H, d, 4-H), 8.28 (1 H, s, 2-H), and 9.71 (1 H, s, N*H*CO_2Et); $J_{4,6}$ 2 Hz, $J_{6,7}$ 8.5 Hz, and J_{MeCH_2} 7 Hz.

6-*Amino*-1H-*benzimidazole* 3-*Oxide* (**1c**).—The acetamido ester (**12b**) (4.3 g, 15 mmol) and concentrated hydrochloric acid (70 ml) were heated together under reflux for 3 h. The solution was evaporated to dryness under reduced pressure to give the *dihydrochloride* (**16**) (1.93 g, 57%), m.p. 255 °C (decomp.) (from hydrochloric acid, with charcoal) (Found: C, 37.8; H, 4.4; N, 19.2. $C_7H_7N_3O$·2HCl requires C, 37.9; H, 4.1; N, 18.9%); $\nu_{max.}$ 2 580 cm^{-1} (v br); δ_H 7.6—7.75 (1 H, m),* 7.9—8.13 (2 H, m),* 9.3 (br s, $\overset{+}{N}H$, OH, $\overset{+}{N}H_3$), and 9.96 (1 H, s, 2-H). The dihydrochloride (1.5 g) was added in small portions to aqueous ammonia (*d* 0.88; 15 ml) at 0—5 °C; the solution was evaporated to dryness under reduced pressure, and the residue washed with ice-cold water (20 ml). The buff N-*oxide* (**1c**) (0.86 g, 68%) had m.p. 185 °C (decomp.) (from water) (Found: C, 45.7; H, 5.9; N, 22.8. $C_7H_7N_3O$·$2H_2O$ requires C, 45.4; H, 6.0; N, 22.7%); $\nu_{max.}$ 3 360, 3 160br, and 3 080 cm^{-1}; δ_H 4.8 (br s, NH_2, H_2O), 6.63—6.85 (2 H, m),* 7.15—7.35 (1 H, m),* and 8.20 (1 H, s, 2-H); *m/z* 149 ($M^{+\cdot}$, 67%), 133 (100%), 132 (47%), 121 (13%), 120 (13%), 106 (20%), and 105 (33%), *etc.*

1,5-*Dichloro*-2,4-*dinitrobenzene*.—This compound, m.p. 99—101 °C (from ethanol; lit.,[11] 103—104 °C), was prepared in 59% yield by nitration of *m*-dichlorobenzene.[11]

N-(5-*Amino*-2,4-*dinitrophenyl*)*glycine Ethyl Ester* (**19a**).—Aqueous ammonia (*d* 0.88; 200 ml) was added to 1,5-dichloro-2,4-dinitrobenzene (30 g) in ethanol (300 ml), and the mixture heated under reflux for 3 h. The yellow crystalline product was filtered off, washed with water and a little cold ethanol, and recrystallised from ethanol to give 5-chloro-2,4-dinitroaniline (19 g, 69%), m.p. 172—174 °C (lit.,[8] 178 °C). To a warm (60 °C) solution of this amine (10 g, 46 mmol) in dimethyl sulphoxide (40 ml) were added, with stirring, sodium hydrogen carbonate (7.7 g, 92 mmol) and glycine ethyl ester hydrochloride (6.5 g, 46 mmol). Stirring was continued while the mixture was heated to 100—110 °C over 20 min, and kept at this temperature until effervescence ceased (a further 20 min). When cooled, the mixture set solid; water was added, and the product filtered off, washed with water, and recrystallised from acetic acid. The *ester* (**19a**) had m.p. 179—180 °C; yield 8.8 g (67%) (Found: C, 42.6; H, 4.3; N, 19.8. $C_{10}H_{12}N_4O_6$ requires C, 42.3; H, 4.3; N, 19.7%); $\nu_{max.}$ 3 460 and 3 330 (NH), 1 735 (CO), and 1 510 and 1 315 cm^{-1} (NO_2); δ_H 1.25 (3 H, t, Me), 4.20 (2 H, d, CH_2NH),† 4.26 (2 H, q, CH_2Me),† 6.10 (1 H, s, 6-H), 7.90 (2 H, br s, NH_2), 8.60 (1 H, t, N*H*-CH_2), and 9.08 (1 H, s, 3-H); J_{MeCH_2} 7 Hz and J_{CH_2NH} 6 Hz.

N-(5-N,N-*Dimethylamino*-2,4-*dinitrophenyl*)*glycine ethyl ester* (**19b**). This compound was similarly obtained. 5-Chloro-*N*,*N*-dimethyl-2,4-dinitroaniline, m.p. 119—123 °C (from ethanol; lit.,[12] 129 °C) was prepared in 85% yield from 1,5-dichloro-2,4-dinitrobenzene and dimethylamine[12] and was converted into the ester (**19b**) in 42% yield by reaction with sodium hydrogen carbonate and glycine ethyl ester hydrochloride in dimethyl sulphoxide, initially for 30 min at 80 °C followed by 10 min at 95 °C. The *ester* (**19b**) had m.p. 190—191 °C (from acetic acid) (Found: C, 46.1; H, 5.0; N, 17.8. $C_{12}H_{16}N_4O_6$ requires C, 46.15; H, 5.2; N, 17.8%); $\nu_{max.}$ 3 340 (NH), 1 730 (CO), and 1 510 and 1 335 cm^{-1} (NO_2); δ_H 1.24 (3 H, t, *Me*CH_2), 2.93 (6 H, s, Me_2N), 4.22 (2 H, q, CH_2Me),† 4.32 (2 H, d, CH_2NH),† 5.92 (1 H, s, 6-H), and 8.66 (1 H, s, 3-H and 1 H, br t, NH);‡ J_{MeCH_2} 7 Hz and $J_{CH_2,NH}$ 5 Hz.

N,N-(4,6-*Dinitro*-1,3-*phenylene*)*bisglycine Diethyl Ester* (**20**).—To a solution of 1,5-dichloro-2,4-dinitrobenzene (9 g, 39 mmol) in dimethyl sulphoxide (45 ml) were added sodium hydrogen carbonate (13.1 g, 0.156 mol) and glycine ethyl ester hydrochloride (10.9 g, 78 mmol). The mixture was stirred and heated at 60 °C until effervescence had almost ceased (*ca.* 35 min); it was then heated to 90 °C and maintained at this temperature until no more carbon dioxide was evolved (a further 20 min). The mixture was then cooled, diluted with water, and filtered. The solid product was recrystallised from acetic acid to give the *diester* (**20**) (10.7 g, 76%) as bright yellow needles, m.p. 190—191 °C (Found: C, 45.5; H, 4.8; N, 15.1. $C_{14}H_{18}N_4O_8$ requires C, 45.4; H, 4.9; N, 15.1%); $\nu_{max.}$ 3 350

* Not first-order spectrum.

† Overlapping signals.

‡ Coincident chemical shifts.

(NH), 1 715 (CO), and 1 535 and 1 350 cm^{-1} (NO_2); δ 1.28 (6 H, t, 2 × Me), 4.22 (4 H, q, 2 × CH_2Me),* 4.30 (4 H, d, 2 × CH_2NH),* 5.74 (1 H, s, 2-H), 8.67 (2 H, br t, 2 × NH), and 8.98 (1 H, s, 5-H); J_{MeCH_2} 7 Hz and $J_{CH_2,NH}$ 5 Hz.

N,N'-*Biscyanomethyl*-4,6-*dinitrobenzene*-1,3-*diamine* (**21**).—Sodium carbonate (5.7 g, 68 mmol) and powdered aminoacetonitrile hydrochloride (3.15 g, 34 mmol) were added to a solution of 1,5-dichloro-2,4-dinitrobenzene (4.0 g, 17 mmol) in dimethyl sulphoxide (20 ml). The mixture was stirred and heated at 80—90 °C until effervescence ceased (*ca.* 40 min) and was then poured into ice–water (200 ml). The solid product was filtered off, washed with ethanol, and recrystallised from dimethylformamide–acetic acid (1:1) to give the *dinitrile* (**21**) (2.70 g, 58%), m.p. 274—276 °C (Found: C, 43.6; H, 2.9; N, 30.5. $C_{10}H_8N_6O_4$ requires C, 43.5; H, 2.9; N, 30.4%); $\nu_{max.}$ 3 340 (NH), 2 240w (CN), and 1 530 and 1 320 cm^{-1} (NO_2); δ_H 4.80 (4 H, d, 2 × CH_2), 6.30 (1 H, s, 2-H), 9.00 (2 H, t, 2 × NH), and 9.18 (1 H, s, 5-H); $J_{CH_2,NH}$ 7 Hz.

Attempted Cyclisations of Compounds (**19**)—(**21**).—(a) (**19a**) *With sodium ethoxide.* The ester (**19a**) (3 g, 10.5 mmol) in dimethylformamide (10 ml) was added slowly, with stirring, to a solution of sodium ethoxide (from sodium, 0.25 g, 10.8 mmol) in ethanol (200 ml). Precipitation of a yellow solid began almost immediately; when addition of the ester was complete, the mixture was stirred for 30 min, and the solid (2.1 g) filtered off and washed with ethanol. It was dissolved in water, and the solution acidified (HCl) to give only the starting ester (1.7 g), identical with an authentic sample.

(b) (**19b**) *With sodium ethoxide.* The dimethylamino ester (**19b**) (1 g, 2.8 mmol) in dimethylformamide (50 ml) and ethanol (25 ml) was treated dropwise, over 10 min, with sodium ethoxide solution [from sodium (0.074 g, 3.2 mmol) and ethanol (10 ml)]. The mixture was set aside overnight, then diluted with water (400 ml) and filtered; the filtrate was acidified (HCl), giving unchanged starting material (0.80 g).

(c) (**20**) *With sodium ethoxide.* The ethoxide solution [from sodium (0.23 g) and ethanol (10 ml)] was added dropwise over 10 min to a stirred solution of the diester (**20**) (3.52 g, 9.5 mmol) in dimethylformamide (50 ml) at 5—10 °C. The dark red solution was stirred at this temperature for 15 min after which it was evaporated under reduced pressure at 60 °C and the residue dissolved in water. Acidification (HCl) gave the starting diester (**20**) (2.0 g), identical with an authentic sample.

(d) (**21**) *With sodium hydride.* Sodium hydride (50% dispersion in oil; 0.36 g, 7.5 mmol) in dry dimethyl sulphoxide (5 ml) was added dropwise, with stirring and cooling, to the dinitrile (**21**) (1.0 g, 3.6 mmol) in the same solvent (10 ml) so that the temperature was maintained at 20—25 °C. When addition was complete (10 min) the dark red solution was kept at room temperature for a further 45 min and then added to ice–water (100 ml). The sticky black precipitate was filtered off, washed with water and ethanol, and recrystallised from aqueous dimethylformamide, to give the starting dinitrile (**21**) (0.27 g) as the only isolated product.

* Overlapping signals.

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