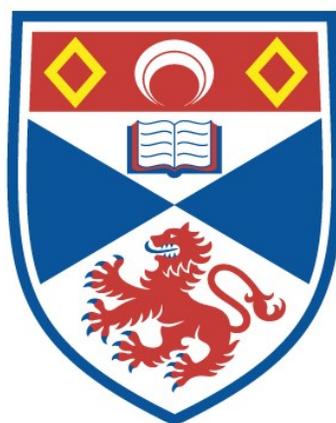


STUDIES OF SOME FUSED IMIDAZOLE DERIVATIVES

David John Moody

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



1986

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STUDIES OF SOME FUSED IMIDAZOLE DERIVATIVES

A THESIS PRESENTED BY
DAVID JOHN MOODY B.Sc.
TO THE UNIVERSITY OF ST. ANDREWS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

MAY 1986



(i)

I, David John Moody, 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.

Signe

Date. 23.5.86..

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on 1st. October 1982 and as a candidate for the degree of Ph.D. on 1st. October 1983.

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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 would like to thank Dr. D.M. Smith for whose enthusiasm and gifted teaching I will always be grateful.

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I must also thank my wife for the many hours that she devoted to the production of this thesis.

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To my mum, dad and Uncle Joe.

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Abstract

The main synthetic routes to benzimidazole N-oxides are outlined and some indication is given as to the current and potential pharmacological usefulness of such materials.

A claim that 4-methyl-2-nitrophenylglycine is cyclised in acetic anhydride to give either 5-methylbenzimidazole 3-oxide or the isomeric 5-methylbenzimidazolone was investigated. This work was found to be impossible to duplicate. It is established that, by employing flash vacuum pyrolysis, the claimed products can be obtained thermolytically from the starting glycine. This is the first recorded example of the formation of an isomerisable benzimidazole N-oxide by thermolytic cyclisation of an o-nitroaniline derivative, and provides a possible explanation for the published findings.

Routes to some aminobenzimidazole N-oxide derivatives (potential analogues of natural purines) are explored. Although several approaches were investigated the most successful was that involving the preparation and cyclisation of (4-protected amino)-N-cyanomethyl-2-nitroanilines. In this way a range of suitably functionalised N-oxides was obtained. The difficulties encountered in using a similar approach in the synthesis of the corresponding 4 and 7-amino derivatives are described and,

in particular, the importance of substituent effects in the base-induced cyclisation of N-(activated alkyl)-2-nitroanilines is established. The preparation of some nucleoside analogues was briefly undertaken.

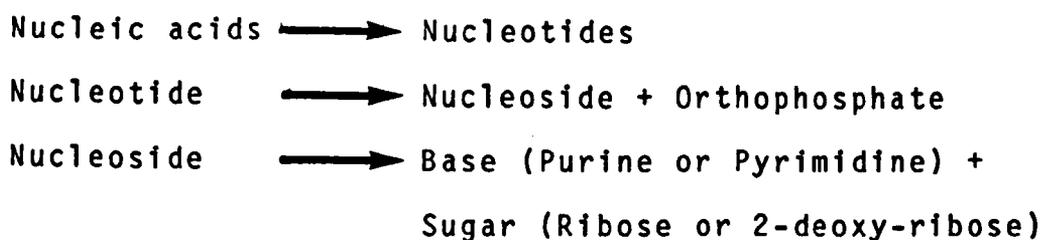
An attempt was made to increase the scope of the base-induced cyclisation of o-nitroaniline derivatives to the preparation of novel tricyclic systems. Although this was for the most part unsuccessful one such system was prepared by cyclisation of a suitably functionalised alkoxybenzimidazole.

A method of preparing a range of symmetrically and unsymmetrically substituted diamino-dinitrobenzenes is described. It was established that for the most part these compounds could not be cyclised in the presence of base. Finally, the reduction of some of these compounds was undertaken and a new route to some pyrazinoquinoxalines thus established.

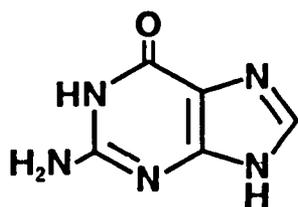
Chapter 1 : Introduction

Since the early 1950's and, in particular, since the elucidation of the structure of DNA by Watson and Crick¹, a vast amount of research has gone into the chemistry and biochemistry of nucleic acids and their constituent parts. The relationship between these parts is illustrated by a hydrolytic sequence [Scheme 1].

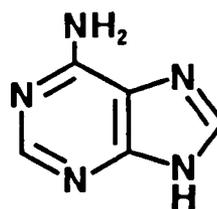
Scheme 1



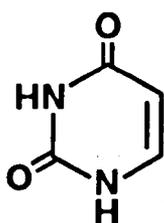
Principal bases from nucleosides



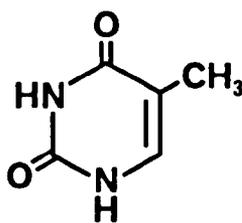
Guanine



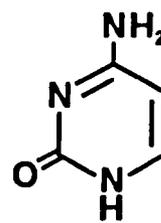
Adenine



Uracil

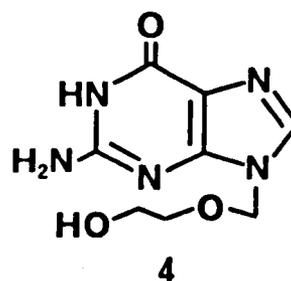
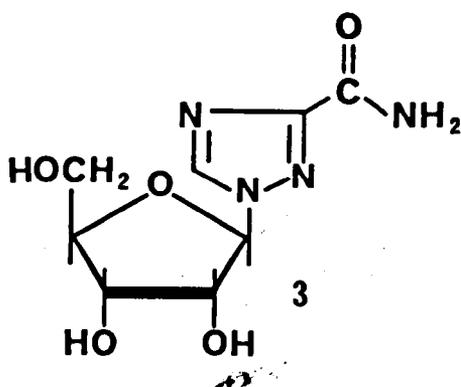


Thymine



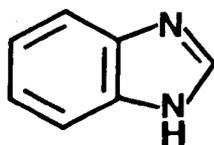
Cytosine

As an understanding of these materials has increased, so has the search for structurally related analogues increased and diversified in the hope of discovering substances that will interact with biochemical systems. A particularly interesting possibility in this regard is the synthesis of base and/or nucleoside analogues that can eventually be incorporated in the growing chain of viral D.N.A., thereby inhibiting virus replication. Although the majority of such substances produced thus far have not yet played a part in the treatment of human diseases, there are important examples of base [e.g. ribavirin (3)] and nucleoside [e.g. acyclovir (4)] analogues successfully used in the treatment of human viral infection².

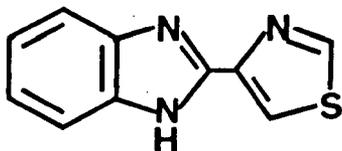


In a related area, the chemistry of benzimidazoles (5) has been greatly exploited as a consequence of their structural similarity to the purines and the discovery that the 5,6-dimethyl-1-(α -D-ribofuranosyl) benzimidazole unit is a component of vitamin B₁₂. This has led to the synthesis of a very large number of benzimidazole derivatives, some of which find use as anthelmintics

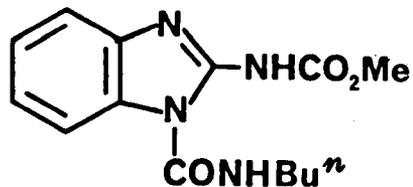
[e.g. thiabendazole (6)] and fungicides [e.g. benomyl (7)].³



5

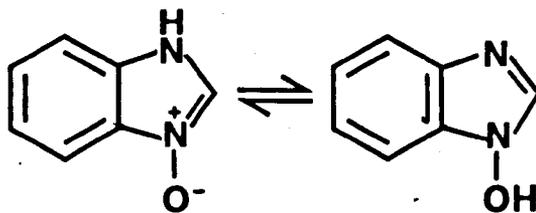


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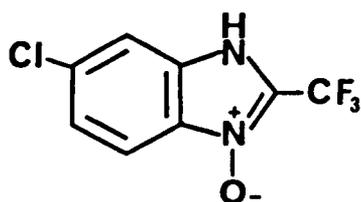
7

Benzimidazole N-oxides (8) [tautomeric with N-hydroxybenzimidazoles (8a)] have also attracted some attention, since the mid-1960's. Some of these are biologically active as herbicides⁴ [e.g. (9)], nematocides⁵ [e.g. (10)] and anthelmintics⁶ [e.g. (11)].

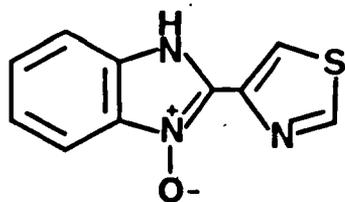


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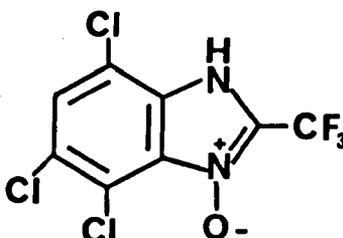
8a



9



10



11

However, although a fairly large number of these N-oxides have been synthesised, a somewhat unselective approach has been pursued, with, perhaps, more regard to the availability of starting materials than to the particular substitution pattern in the final product. This may be the reason that no benzimidazole N-oxides incorporating the functionality of the naturally occurring purines, adenine (2) and guanine (1), have previously been synthesised. Chapter 3 of this thesis explores routes to such materials.

The chemistry of benzimidazole N-oxides has been most recently reviewed by Smith⁷. Since that time (1979),

little progress has been made in developing new synthetic methods, with one interesting exception (see p. 38). For the moment it is appropriate to review methods that have found some general application, with a view to highlighting those that may be useful in the synthesis of novel systems based on benzimidazole N-oxides.

The synthetic methods can be grouped into three main categories [Scheme 2]:

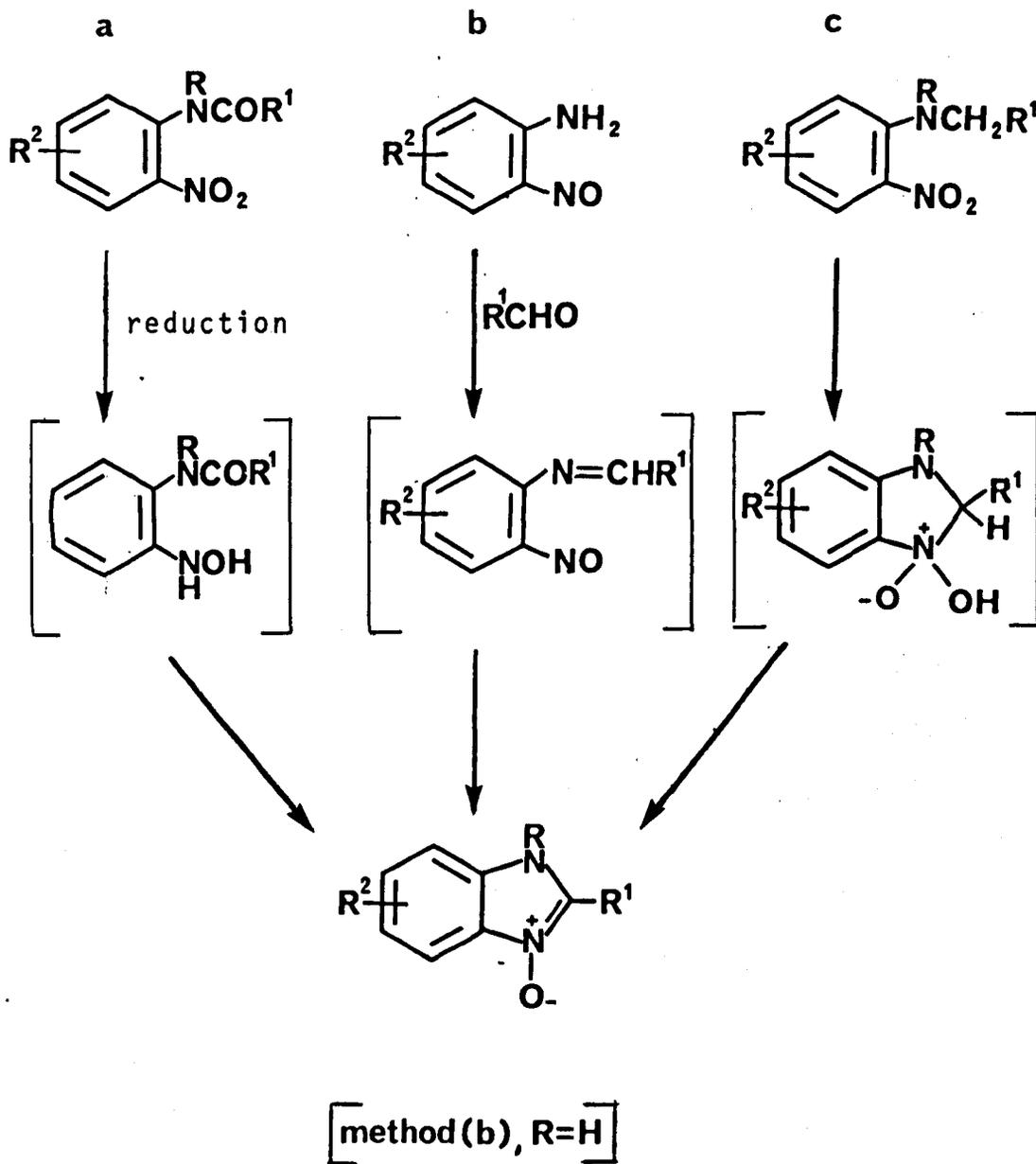
- a) partial reduction of o-nitroanilides,
- b) generation and cyclisation of o-nitrosoanils,
- c) intramolecular condensation of N-(activated alkyl)-o-nitroanilines.

a) Partial Reduction of o-Nitroanilides

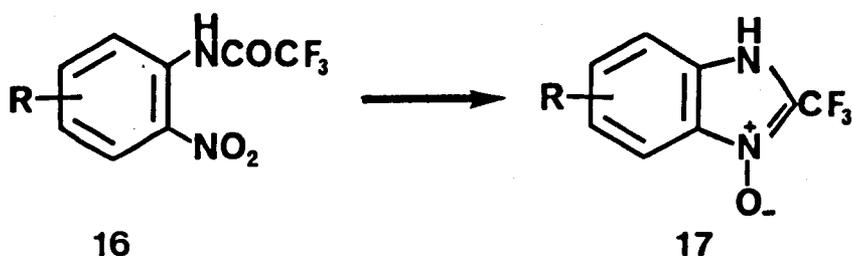
This is by far the most widely used method, being particularly useful in the preparation of 1-substituted derivatives [R≠H in Scheme 2(a)] which are difficult to obtain by other methods. There are two general requirements for success in this route, namely:

- (i) the use of a reagent which will selectively reduce a nitro function to a hydroxylamine, without significant further reduction to the amine.
- (ii) provision of conditions under which cyclisation of the hydroxylamine is favoured.

Scheme 2

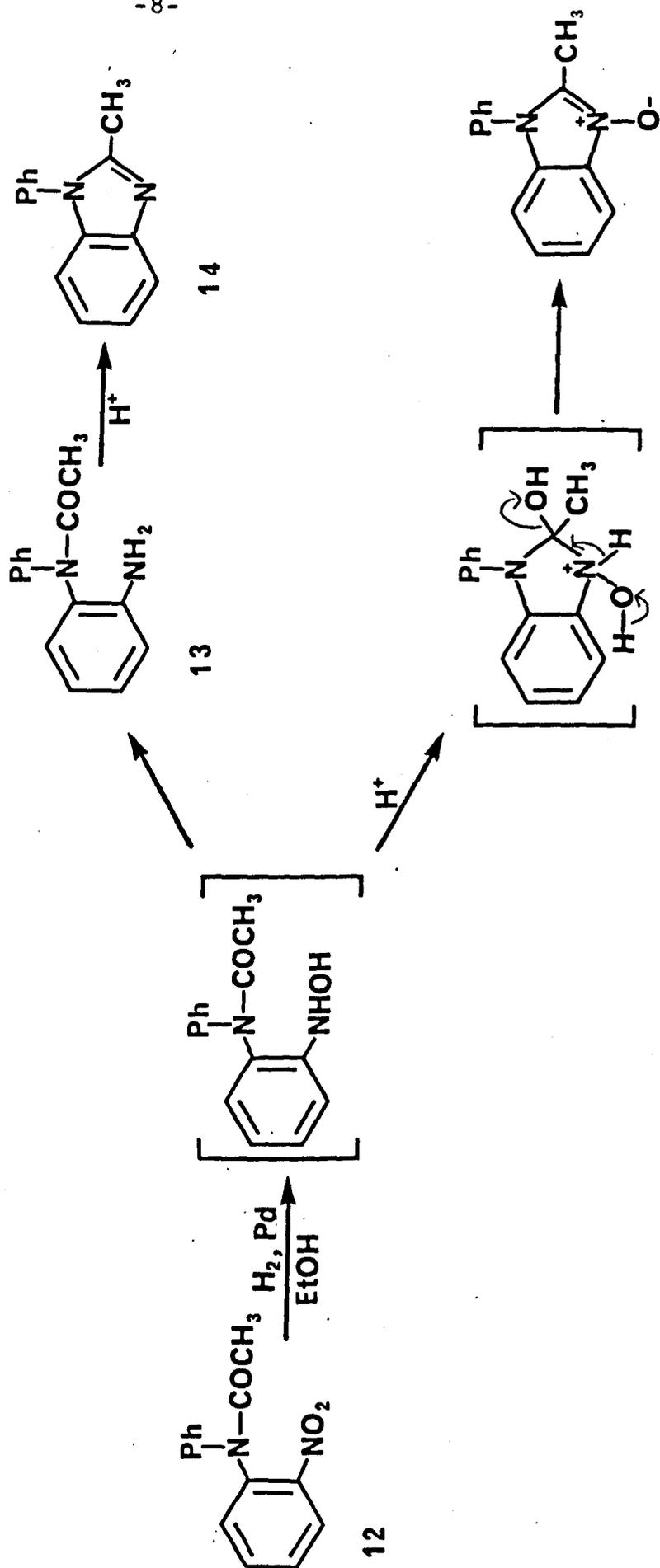


Sometimes, by fulfilling the second requirement (most usually by the addition of one molar equivalent of HCl) it is possible to obtain N-oxides using reagents that would normally be expected to reduce the nitro function beyond the hydroxylamine stage. For example, [Scheme 3] catalytic hydrogenation, over platinum or palladium, of 2-nitro-N-phenylacetanilide (12) gives 2-amino-N-phenylacetanilide (13) which on treatment with hydrochloric acid yields 2-methyl-1-phenylbenzimidazole (14). However, when the reduction is carried out in the presence of at least one molar equivalent of acid, 2-methyl-1-phenylbenzimidazole 3-oxide (15) is obtained in good yield⁸. Evidently, protonation of the carbonyl is involved with the consequent increase in its electrophilic character promoting cyclisation at the hydroxylamine stage. A more recent example involves o-nitroanilides where the carbonyl is attached to an electron-withdrawing group [e.g. CF₃ (16)]. In this case it is claimed that the carbonyl is further activated to nucleophilic attack from the hydroxylamine nitrogen and good yields of (2-substituted) N-oxides (17) are reported⁴.



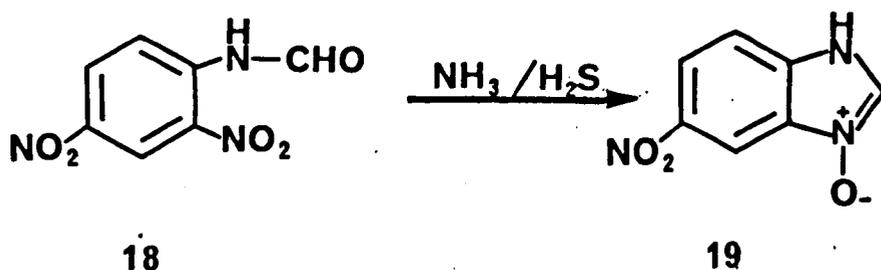
R=e.g. H, Cl.

Scheme 3

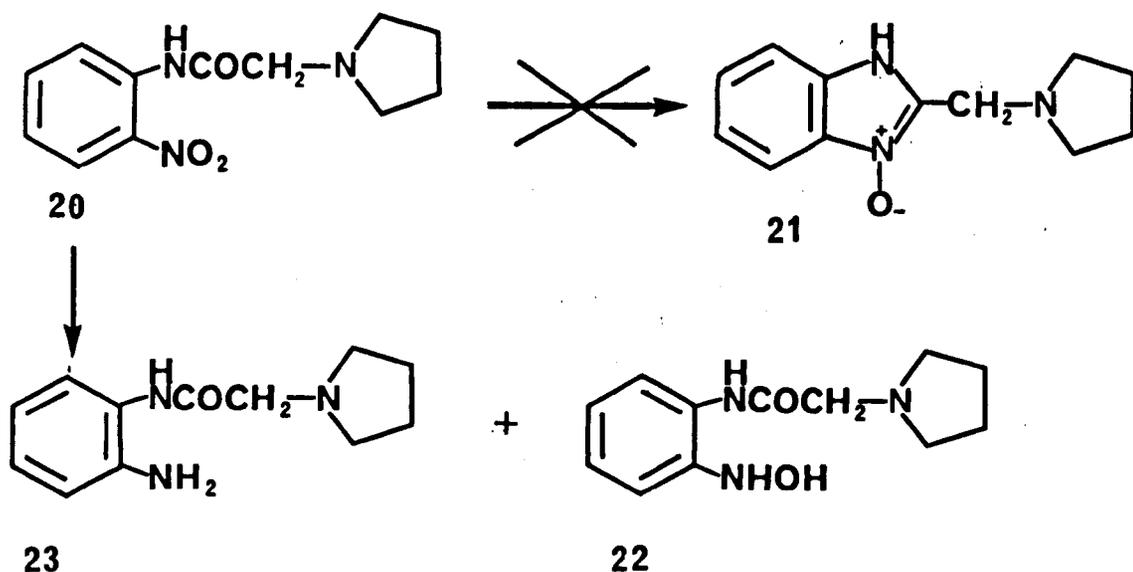


In contrast, the use of a variety of metal hydrides (where, clearly, the use of acid is precluded) in the presence of palladium, platinum or Raney nickel has found some application for benzimidazole N-oxide synthesis^{9,10}. It would appear that such reducing systems are particularly selective in the generation of the desired hydroxylamine intermediate.

Of the non-catalytic methods, ammonium sulphide reductions are the most common. For example, the selective reduction of 2,4-dinitroformanilide (18) gives 5-nitrobenzimidazole 3-oxide (19)¹¹, a potentially useful intermediate in the preparation of 5-amino-benzimidazole 3-oxide (a possible analogue of guanine). [The preparation of (19) is discussed in Chapter 3].



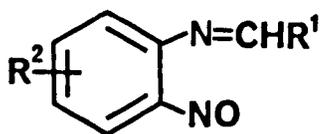
Ammonium sulphide reduction of 2-nitroanilides is by no means a general route to benzimidazole N-oxides, as illustrated by the failure of 2-(1-pyrrolidiny1)-2'-nitroacetanilide (20) to yield the corresponding N-oxide (21). In fact this reaction produced 2-(1-pyrrolidiny1)-2'-hydroxylaminoacetanilide (22) and the amine (23). All attempts to form the N-oxide by heating (22) in acid failed¹².



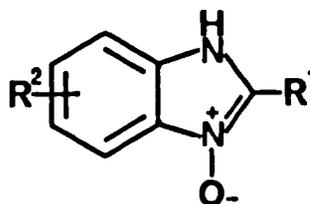
In all of these reductive processes, there is an interesting disparity in yields obtained when $R=H$ and when $R\neq H$ [Scheme 4]; whereas in the latter case the yields are generally high, in the former they show extreme variation. Steric considerations apart, there is an important chemical difference between the two types of product. Where $R=H$ (24,24a), a tautomeric system may exist, allowing deprotonation in base, and since the procedure

b) Generation and Cyclisation of *o*-Nitrosoanils

o-Nitrosoanils (26) have long been established as useful intermediates in the synthesis of benzimidazole N-oxides. Indeed, so reactive are they, none have yet been isolated, with cyclisation to the isomeric N-oxide (26a) being effectively a spontaneous process.



26

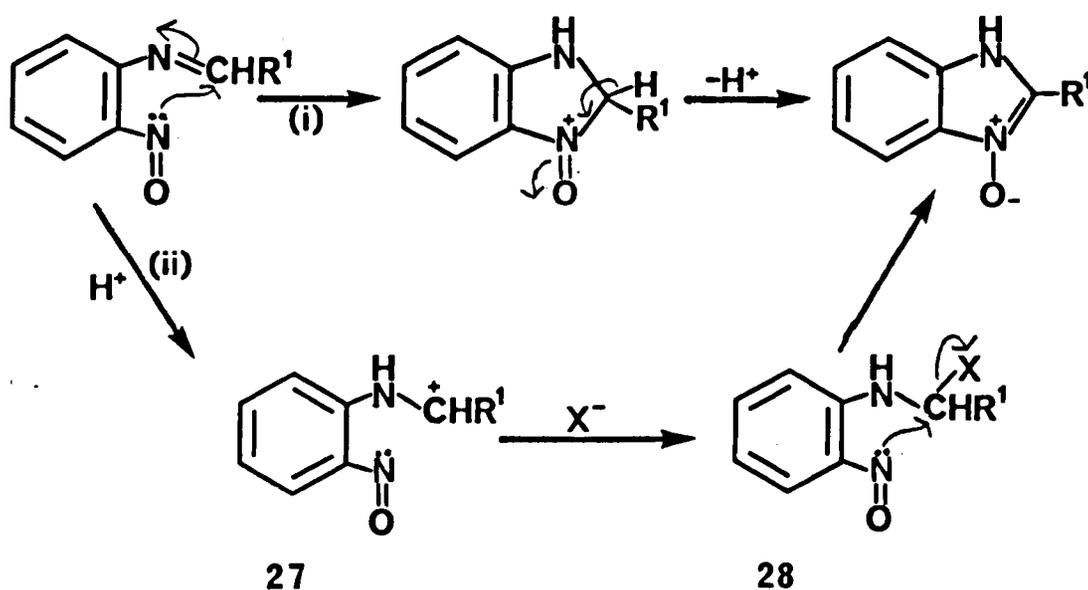


26a

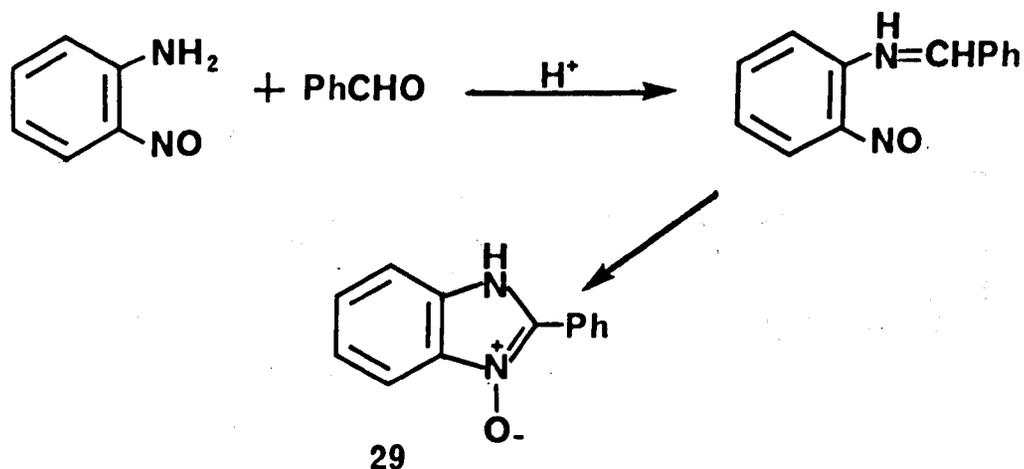
This is illustrated by the simplest type of this reaction: the acid-catalysed condensation between an *o*-nitrosoaniline and an aldehyde¹³ [Scheme 2b]. This particular reaction is of limited applicability due to difficulty in preparing the necessary, somewhat unstable, *o*-nitrosoanilines. As a consequence synthetic approaches have been almost entirely concerned with alternative ways of generating the intermediate Schiff base (26) and a wide range of precursors have been used. Numerous examples are detailed elsewhere⁷ and, therefore, only general mechanisms and a few illustrative examples are included here.

Two cyclisation mechanisms have been described [Scheme 5]⁷. Pathway 5(i) seems unlikely since it requires a, disfavoured, 5-Endo-Trig ring closure¹⁴. However, in the presence of acid (often required for successful reaction) or even in a protic solvent [e.g. ethanol, X=OEt] the cation (27) or the adduct (28) may well be formed. The normal rules governing ring closure may not be applicable to the former and, for the latter, cyclisation is a favoured 5-Exo-Tet process. (Pathway 5(ii))

Scheme 5

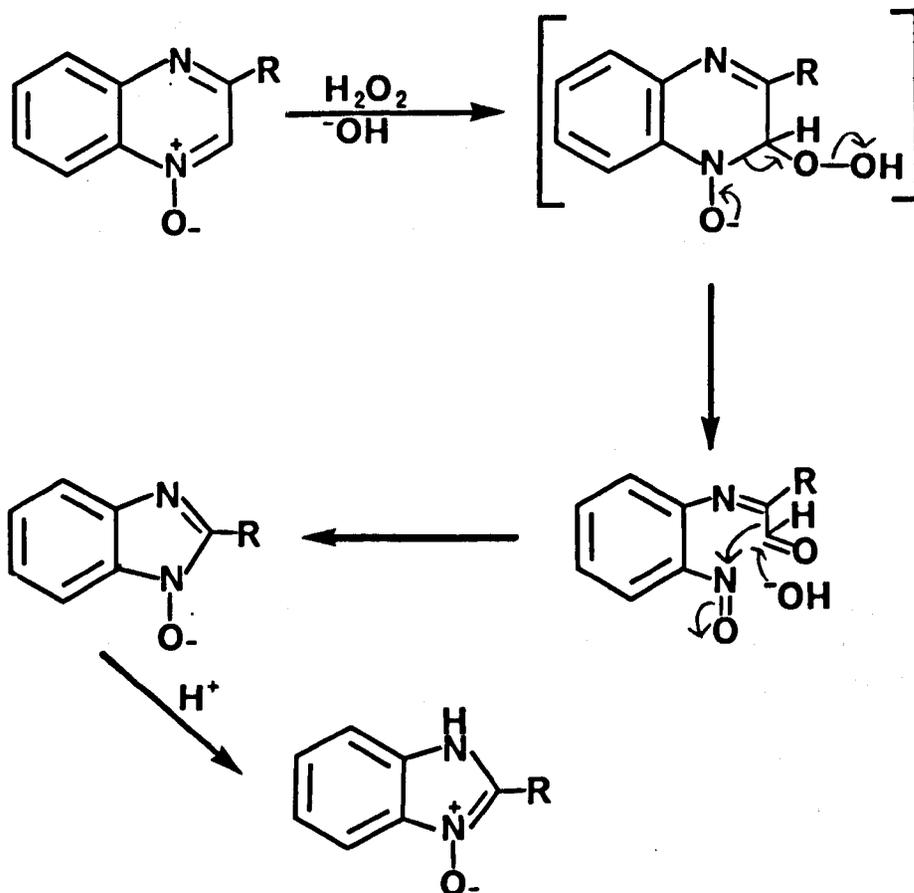


Examples of reactions probably following pathway (ii) include the acid-catalysed condensation between *o*-nitrosoaniline and benzaldehyde to yield 2-phenylbenzimidazole 3-oxide¹³ (29).

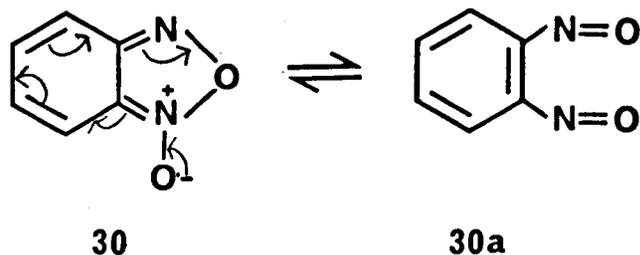


The oxidative hydrolysis of 2-substituted quinoxaline 4-oxides provides a route to benzimidazole N-oxides substituted at position 2, a nitrosoanil being a possible intermediate [Scheme 6]^{15,16}. It is interesting to note that, in contrast to the previous cyclisation mechanism [Scheme 5], the nitroso group acts here as an electron acceptor.

Scheme 6

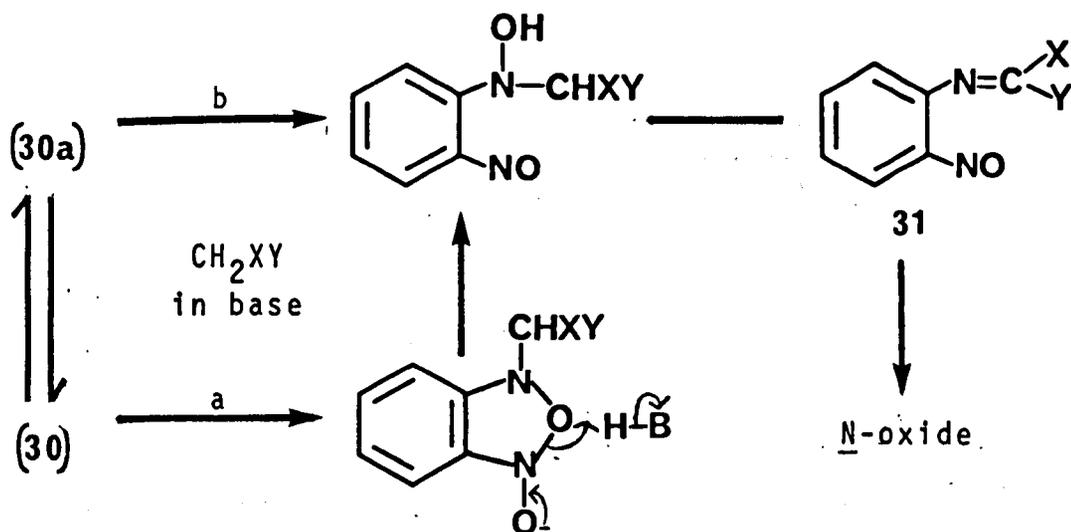


The ability of the nitroso group to act both as an electron acceptor and donor is further illustrated in the use of benzofuroxans as precursors to benzimidazole N-oxides in a reaction of considerable mechanistic interest. Benzofuroxan [benzo[*c*]-1,2,5-oxadiazole-N-oxide (30)] is itself the cyclic tautomer of o-dinitrosobenzene (30a).



Therefore, reaction of this system with an activated methylene compound should, ultimately, yield a benzimidazole N-oxide i.e. Scheme 7.

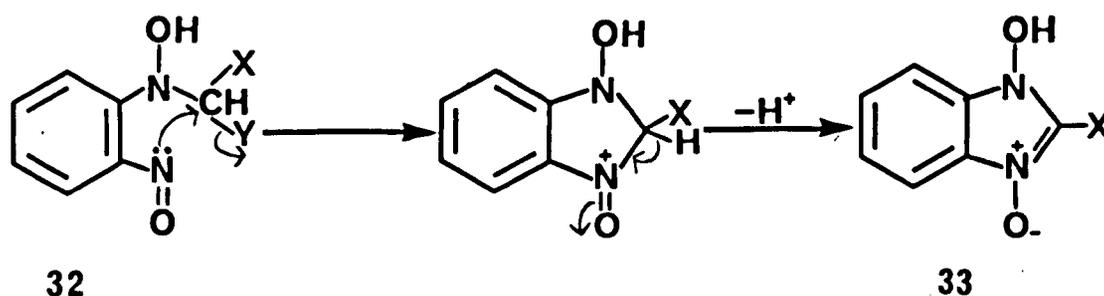
Scheme 7



Note that nucleophilic attack (by $^{-}\text{CHXY}$) can occur on either the cyclic form (30) (pathway a) or the dinitroso form (30a) (pathway b). Although it would be of interest to determine which pathway were followed, this could prove difficult experimentally. In particular, any unsymmetrically substituted derivatives of (30) would quickly equilibrate to give two isomers and thence two isomeric products on reaction with reactive methylene compounds,

whichever pathway were followed. Indeed this problem severely limits the utility of this method in benzimidazole N-oxide synthesis.

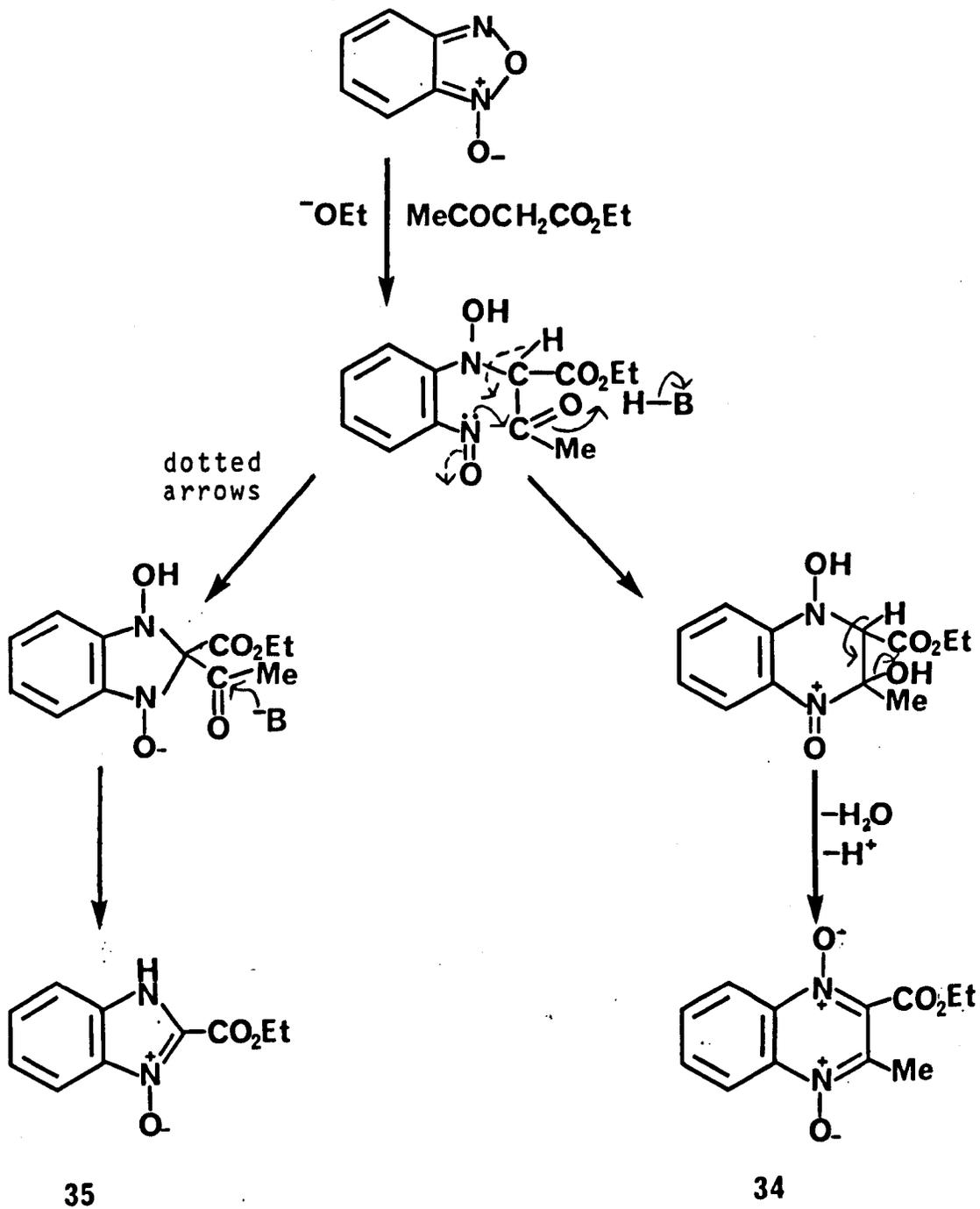
The above considerations apart, the success of this reaction is found to be dependent on the nature of the activating groups (X and Y). For instance, if Y is a leaving group the reaction can take a different pathway after formation of the intermediate (32), with the product being a 1-hydroxy-2-X-benzimidazole 3-oxide (33).



Examples include the reaction of benzofuroxan with cyanoacetamide derivatives ($Y=CN$, $X=CONHR$)^{17,18}, phenylsulphonylacetophenone ($Y=PhSO_2$, $X=COPh$)¹⁹ and nitroalkanes ($Y=NO_2$, $X=alkyl$)²⁰⁻²⁴ to yield the corresponding 2-substituted-1-hydroxybenzimidazole 3-oxide (33).

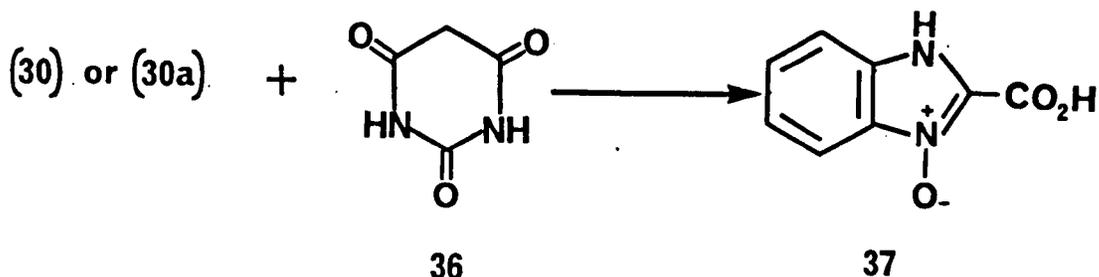
Furthermore if Y is a keto group, interaction with the o-nitroso group can yield a quinoxaline 1,4-dioxide. For example the reaction of benzofuroxan with ethyl acetoacetate gives predominantly ethyl 3-methylquinoxaline-2-carboxylate-1,4-dioxide (34) and only a small quantity of ethyl benzimidazole-2-carboxylate 3-oxide²⁵ (35) [Scheme 8].

Scheme 8



The alternative pathways shown here again show the nitroso group acting either as a donor or acceptor.

Finally, if Y in the intermediate (32) is neither a leaving group nor a ketonic group the o-nitrosoanil (31) may be formed and good yields of benzimidazole N-oxides thus obtained. For example, benzofuroxan (30) reacts with barbituric acid (36) in base to give benzimidazole-2-carboxylic acid 3-oxide (37) in high yield²⁶.



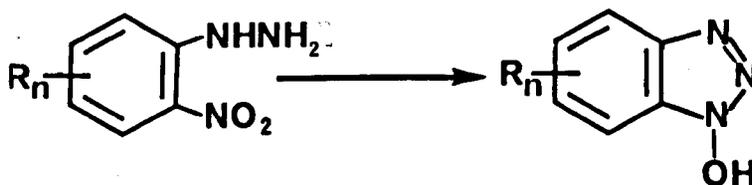
Once again, the synthetic utility of all the above procedures is severely limited by

- a) the difficulty in preparing starting materials [e.g. o-nitrosoanilines],
- b) the possibility of alternative reaction pathways [e.g. benzofuroxan reactions].

c) Cyclisation of N-(activated alkyl)-o-nitroanilines

Intramolecular nucleophilic attack on an o-nitro group constitutes a standard method in the synthesis of heterocyclic-N-oxides from suitably functionalised nitroarenes²⁷.

e.g. 27, 28

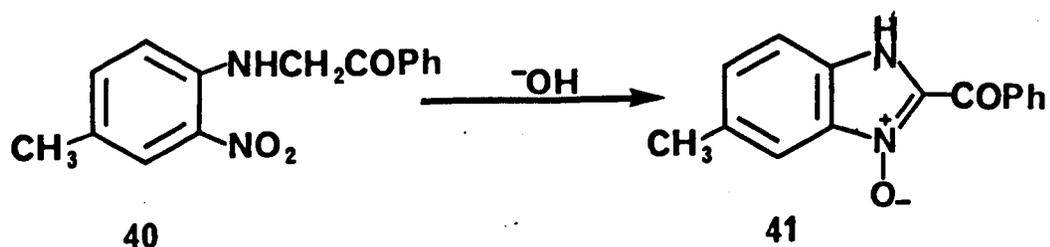


R= e.g. CH_3 , Cl, Br, NO_2 and $n=0,1,2,3$ or 4.

With regard to benzimidazole N-oxides the base induced cyclisation of N-(activated alkyl)-o-nitroanilines has been established as a useful route to derivatives functionalised at position 2⁷. [Scheme 9]. This has been the mainstay of the current research and, therefore, will be given considerable attention here.

(i) The nature of the activating group R¹

In general terms the greater the electron-accepting power of R¹ the more easily the reaction proceeds and the weaker the base required. With poor activation [e.g. R¹=Ph, R=H] reaction is difficult and strong conditions, such as sodium hydride in dimethyl sulphoxide²⁹ at 100°, are required, while with good activation [e.g. R¹=CN, R=H] cyclisation is easily achieved with potassium carbonate in boiling aqueous ethanol³⁰. In addition to the electron withdrawing power, stability of the activating group in the presence of a (usually) nucleophilic base is important. For example, N-phenacyl-4-methyl-2-nitro-aniline (40) yields the corresponding N-oxide (41) in only very low yield, despite the ketonic group being a good electron acceptor³¹.



Clearly, careful choice of both activating group and base is required for success.

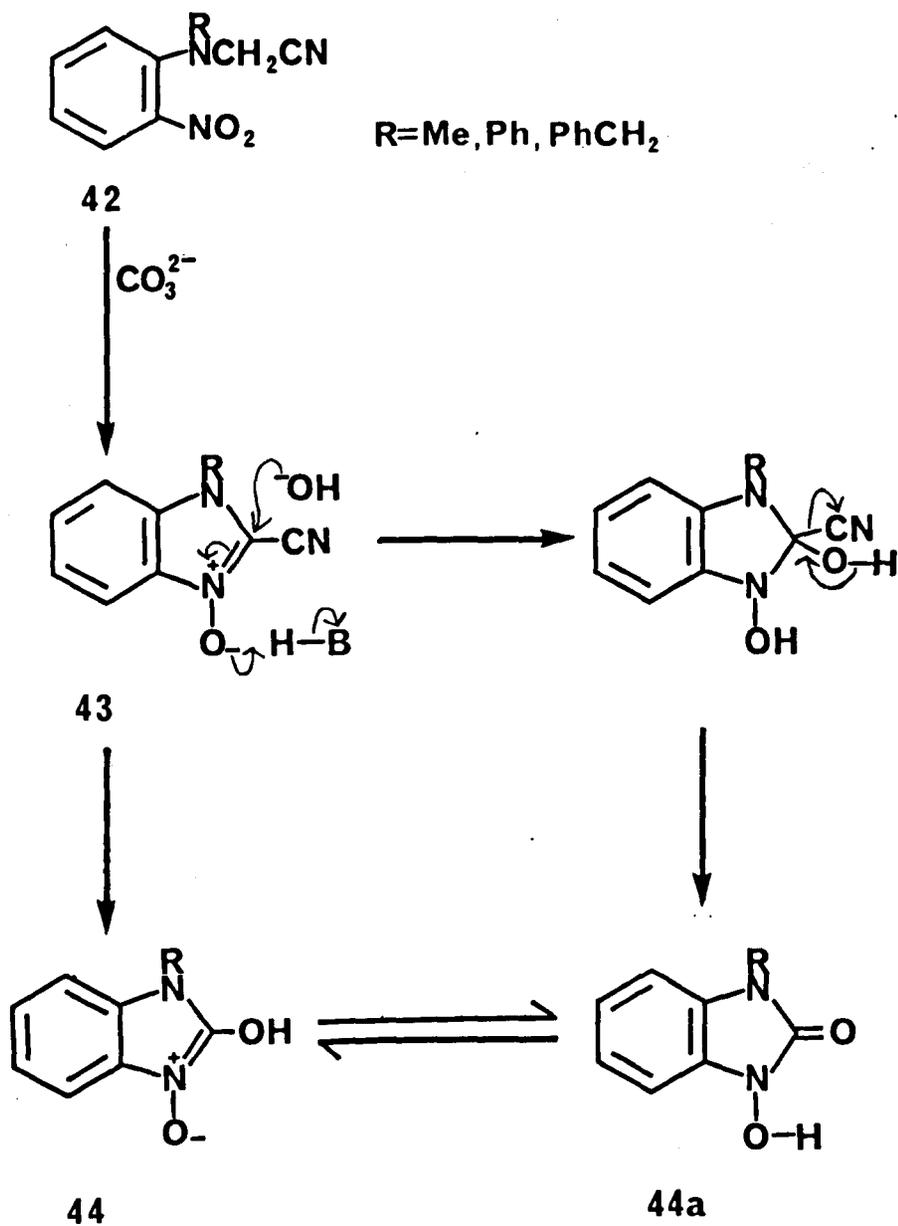
(ii) Substitution on the amino-nitrogen

Although relatively little work has previously been done in this area, the little that is known is mechanistically extremely interesting and potentially very useful for the synthesis of novel benzimidazole N-oxides. The first point to note is that the precise nature of the activating group, R^1 , becomes even more important and the outcome of the reaction may depend on the stability/lability of both R and R^1 in the presence of a nucleophilic base, before and after cyclisation. In consequence, it is useful to divide this section into four categories according to the 'removability' of R and R^1 by nucleophiles.

1) R not removable, R^1 removable

N-substituted-N-cyanomethyl-o-nitroanilines (42) [e.g. where R=Me] cyclise to give not the corresponding 2-cyanobenzimidazole N-oxide (43) but the 2-hydroxy N-oxide (44) [tautomeric with N-hydroxybenzimidazolone (44a)] [Scheme 10]³². The suggested mechanism involves first normal cyclisation to the 1-substituted N-oxide (43). Since this species is incapable of deprotonation, and hence stabilisation, in base, nucleophilic attack at position 2 is favoured. Finally, loss of CN^- yields the observed product (44 or 44a).

Scheme 10



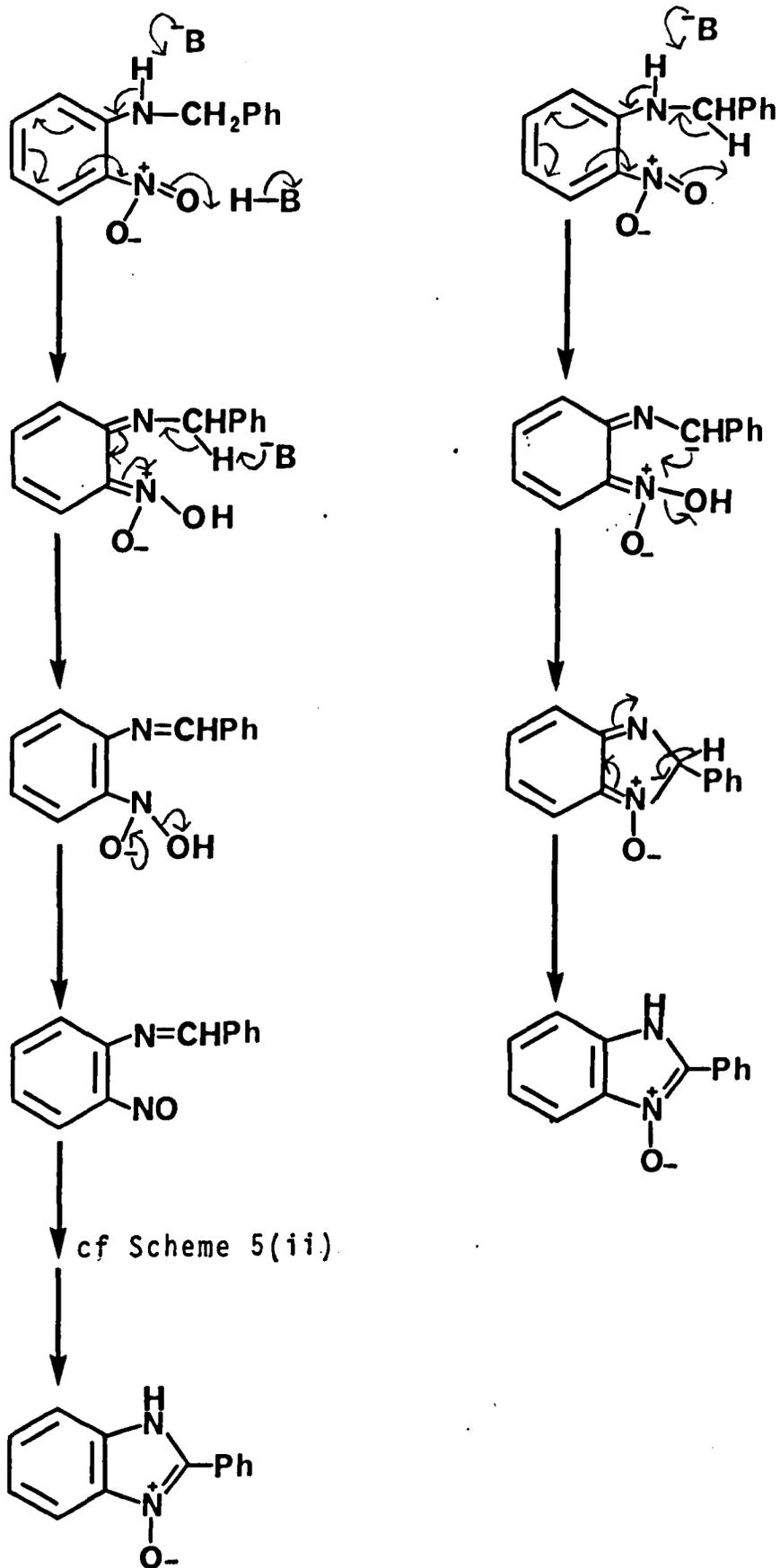
2) Neither R nor R¹ removable

The only known examples of this type are those where R¹=phenyl and such systems have proved to be unreactive towards base²⁹. Indeed it has been suggested that base-induced cyclisations of o-nitro compounds involving a weakly acidic β methylene group in the ortho side chain, proceed only when an α -proton is present³³. Two mechanisms have been proposed to justify this³³ [Scheme 11].

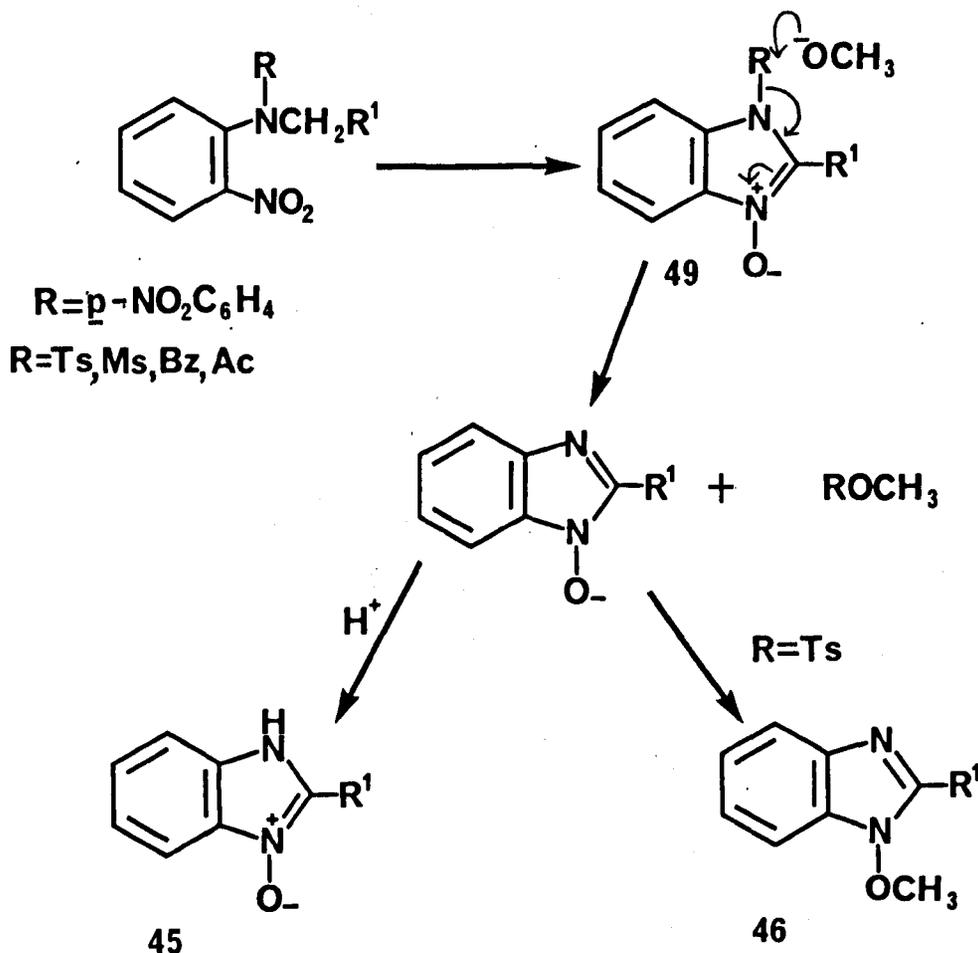
3) R removable, R¹ not removable

Of the four categories this has been the most studied. With regard to the current work, of particular relevance are the reactions of N-p-nitrobenzyl-N-(substituted)-o-nitroanilines with sodium methoxide. [R=p-Toluenesulphonyl (Ts), methanesulphonyl (Ms), acetyl (Ac), benzoyl (Bz)]. In all cases the 2-p-nitrophenylbenzimidazole 3-oxide (45) was formed. [Scheme 12]. Kinetic studies established that cyclisation occurred prior to loss of the R group and the proposed mechanism is outlined³⁴. Of additional interest is that, where R=Ts, some methylation of the initial product occurred, to yield 1-methoxy-2-p-nitrophenylbenzimidazole (46).

Scheme 11



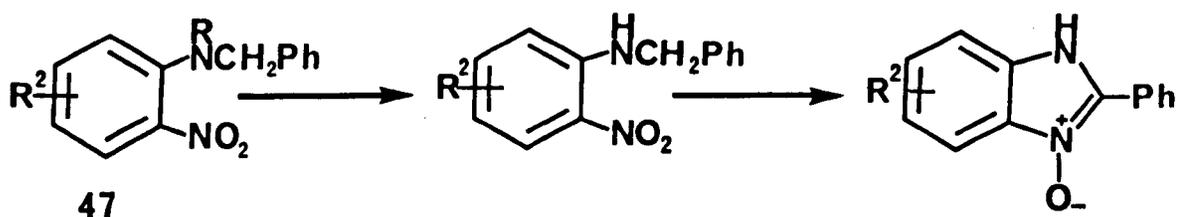
Scheme 12



The use of this type of cyclisation in the formation of a novel tricyclic system incorporating the benzimidazole N-oxide moiety is described in Chapter 4.

Finally, kinetic evidence has established that whereas Scheme 12 adequately represents the mechanism of cyclisation when $\text{R}^1 = \text{p-nitrophenyl}$ and $\text{R} = \text{Ac}$ or Bz , a different mechanism operates in the series where the R^1 (activating) group is phenyl (47). In these cyclisations,

where the activating effect is weaker, removal of the R group evidently precedes cyclisation [cf Section (2), Scheme 11, above]³⁴.



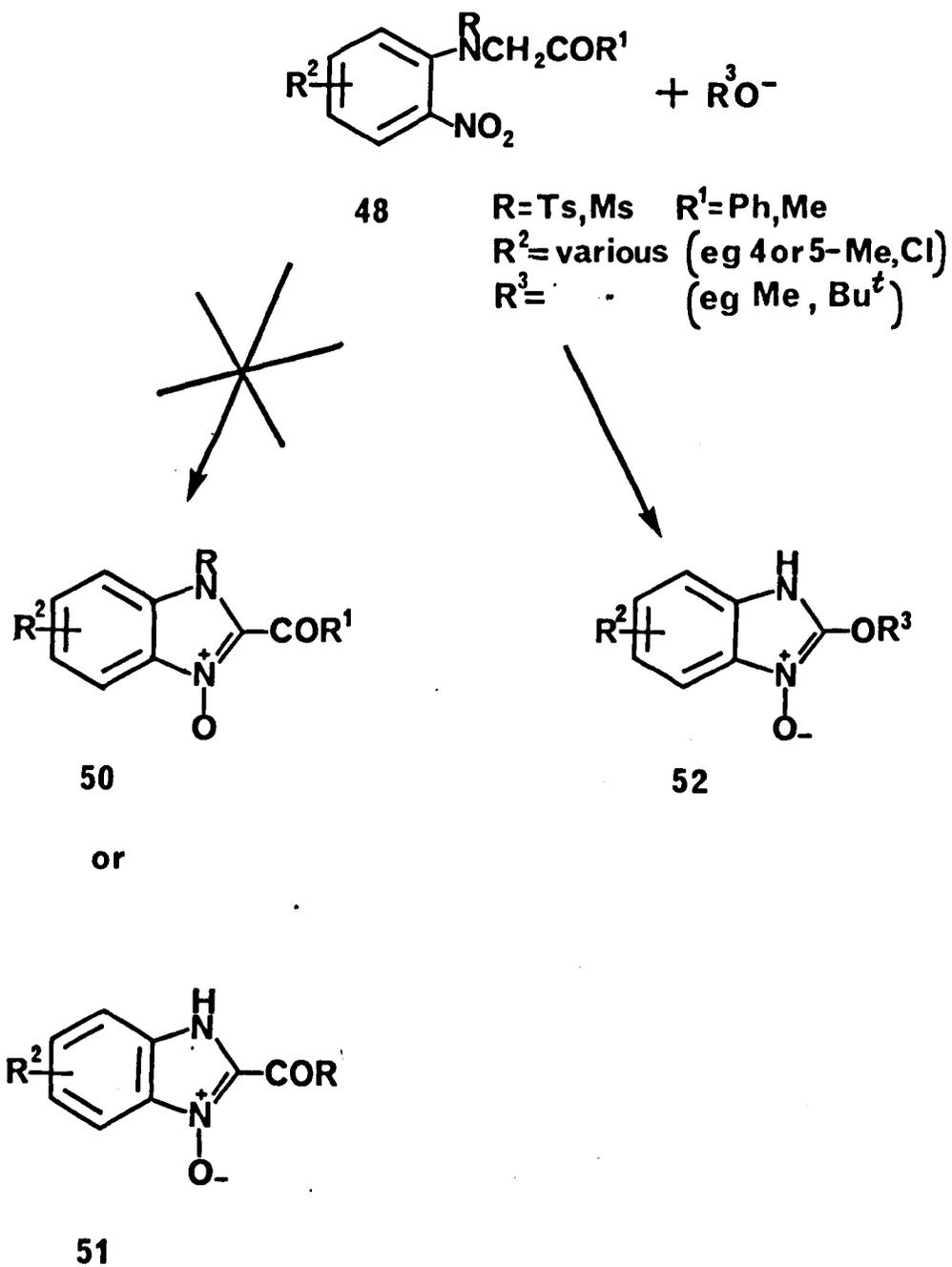
4) R and R¹ both removable

Predictably, this last group is the most complex and the nature of R¹ assumes the utmost importance.

Synthetically the most useful members of this group are N-acylmethylene-N-tosyl (or mesyl)-o-nitroanilines (48). In alkoxide, these compounds do not yield either of the products, (50) or (51), expected from Scheme 12. [i.e. analogues of (49), (45)].

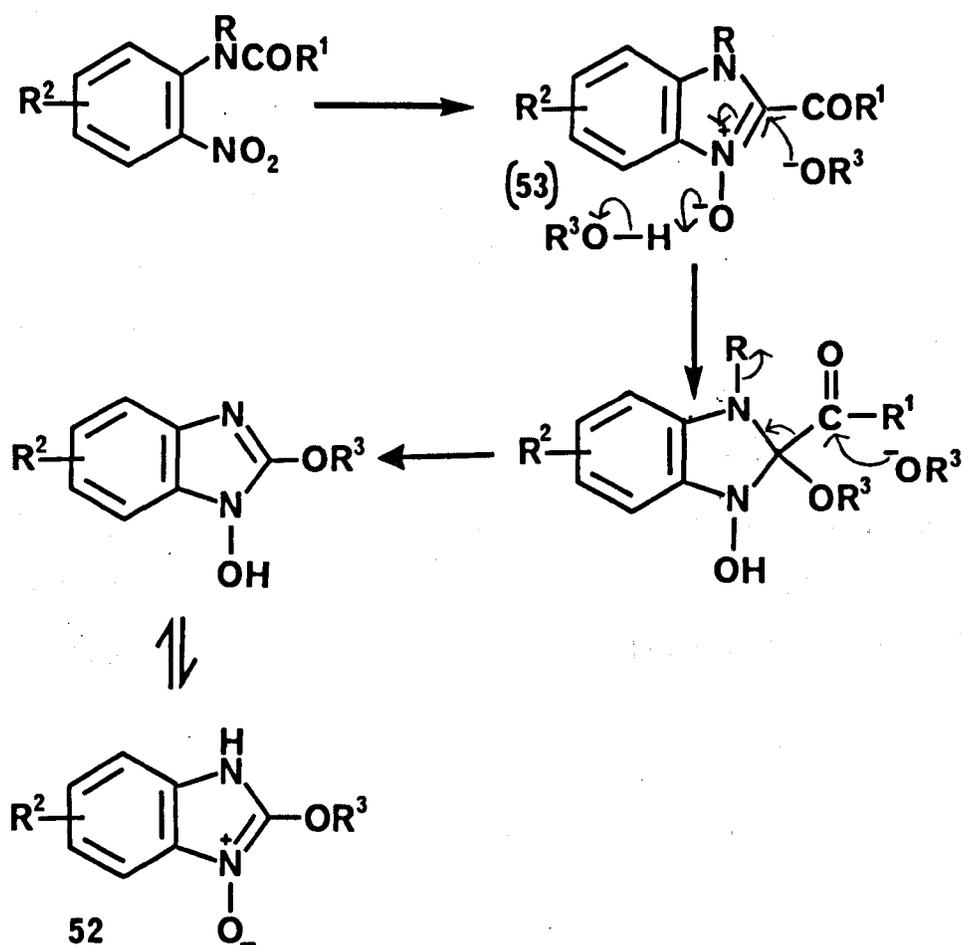
Instead, 2-alkoxybenzimidazole N-oxides (52) are formed in good yield with the alkoxy group (OR³) being supplied by the base [Scheme 13]³⁵.

Scheme 13



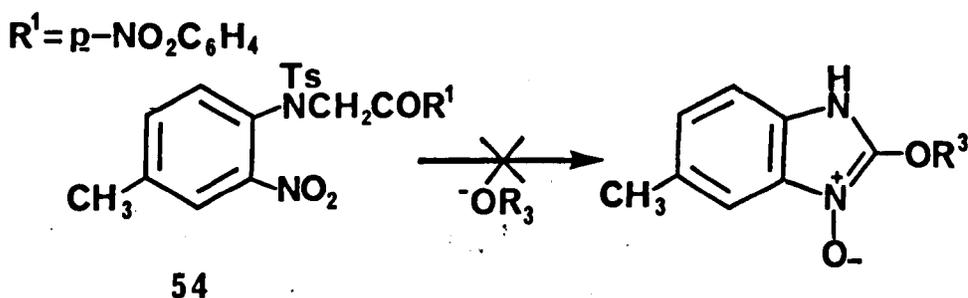
Cyclisation is thought to proceed 'normally' to the intermediate (53). Base-catalysed addition of alcohol across the C₂-N₃ double bond is followed by nucleophilic attack at the carbonyl and consequent elimination of R to give the 2-alkoxybenzimidazole 3-oxide (52). [Scheme 14].

Scheme 14 [R, R¹, R² as in Scheme 13]



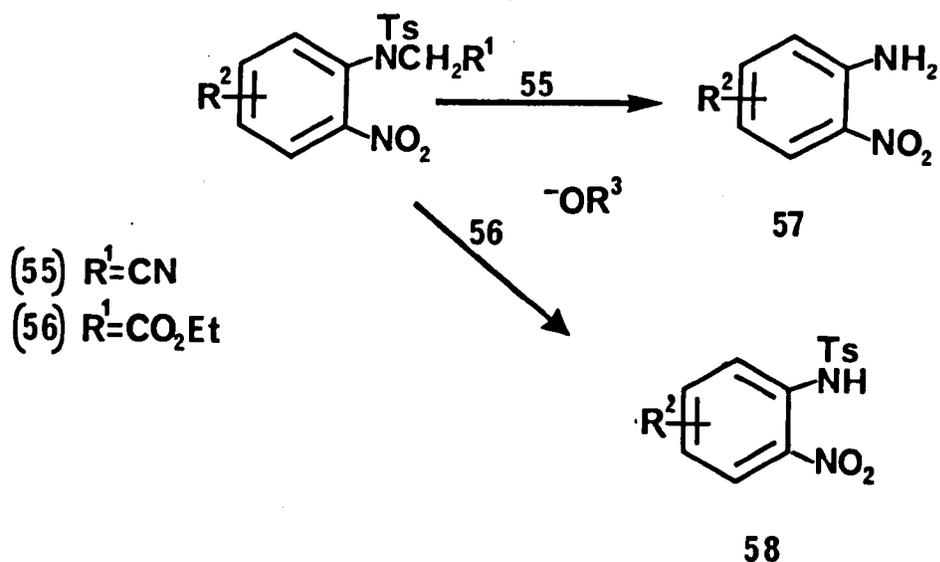
The use of this reaction in developing routes to tricyclic systems is also described in Chapter 4.

The variability of product type encountered in this fourth reaction category is highlighted by the failure of N-p-nitrophenacyl-N-p-tolylsulphonyl-4-methyl-2-nitroaniline (54) to cyclise, 14 different compounds being formed.³⁴



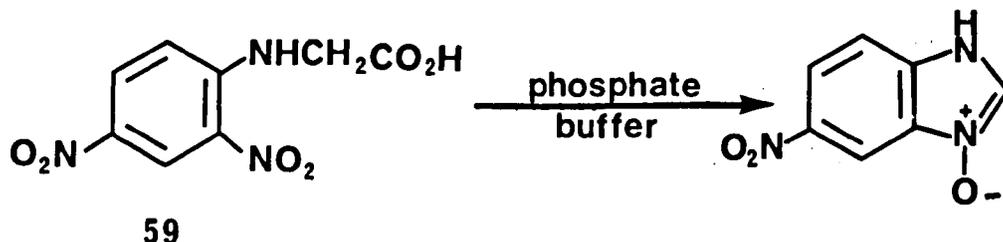
Perhaps this reflects the enhanced reactivity of the carbonyl group towards nucleophiles on going from phenacyl to p-nitrophenacyl.

Finally, the failure of N-cyanomethyl (55) and N-ethoxycarbonylmethyl (56) analogues to yield N-oxides must be noted: here the main products are, respectively, the corresponding primary amine (57) and sulphonamide (58).³⁴



Although one would not expect these materials to react via Scheme 14, to give 2-alkoxy-N-oxides, a pathway similar to Scheme 12 would appear feasible. That this is not the case is further indication that, where R and R¹ are both unstable in base, cyclisation to benzimidazole N-oxides may be extremely difficult.

An additional factor that has emerged in the current research is the nature and position of substituents on the carbocyclic ring. Hitherto, no such substituent effects on the cyclisation have been reported, with the possible exception of the ease with which 2,4-dinitrophenylglycine (59) is cyclised³⁶.



The importance of this factor will be a recurring theme in Chapters 3 and 4

Other Synthetic Methods

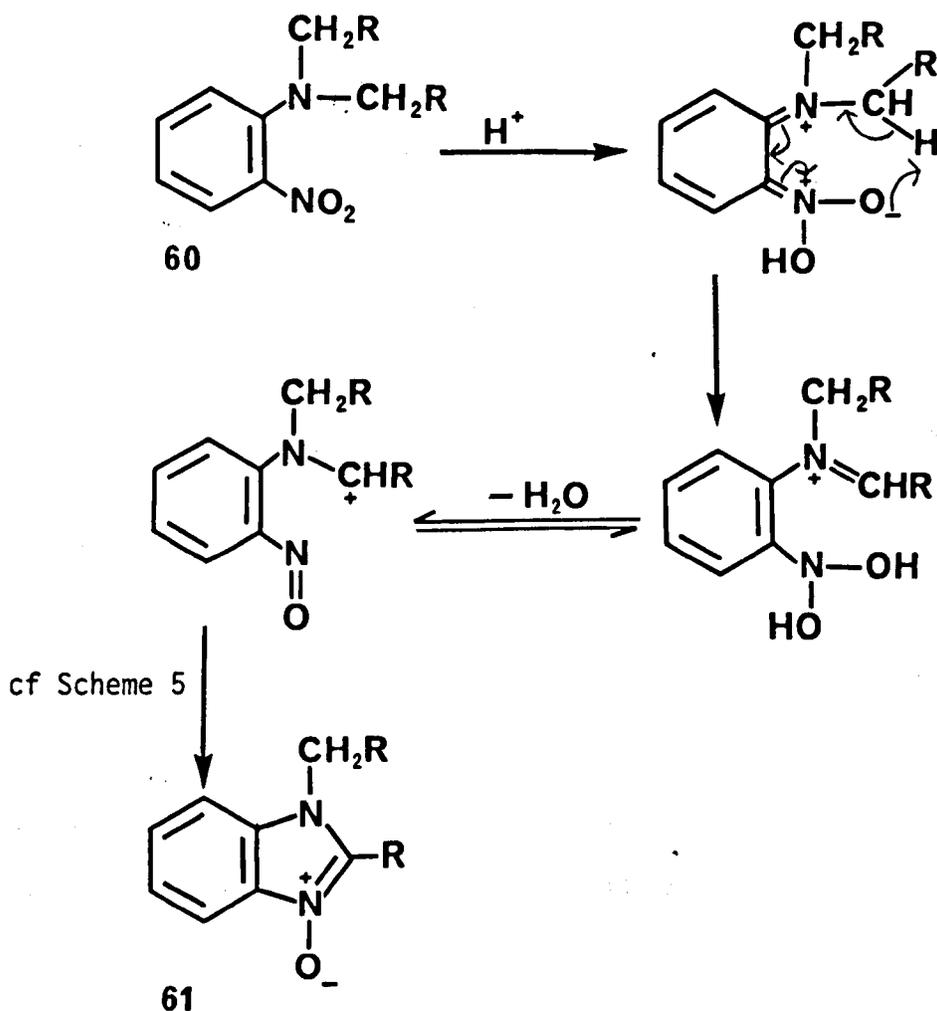
With regard to the work covered in Chapter 2, mention must now be made of two further methods that, in themselves, are of very limited synthetic value: acid-induced and thermal cyclisations.

Acid-Induced Condensations

N,N-Dialkyl-o-nitroanilines (60) can be cyclised to benzimidazole N-oxides (61) by prolonged heating at high temperature in the presence of acid³⁷. One possible mechanism has been proposed⁷ [Scheme 15].

Protonation results in the formation of an aci-nitro intermediate (somewhat similar to that previously encountered in Scheme 11) and cyclisation is then thought to occur via an iminium cation [cf Scheme 5(ii)].

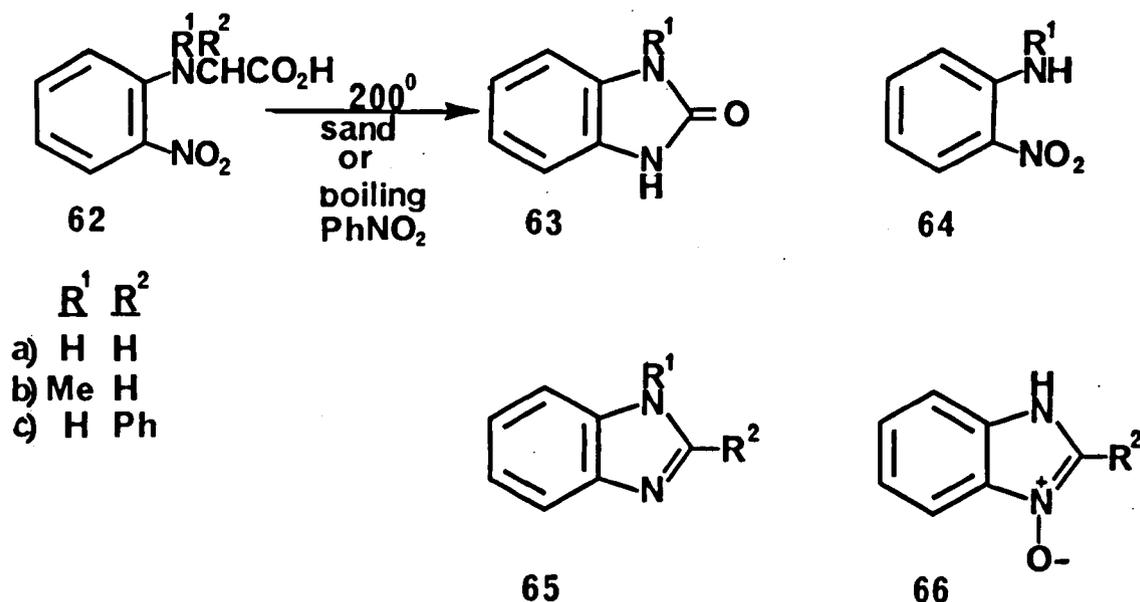
Scheme 15



Thermal Cyclisation

Of particular relevance to the current work is the thermolysis of N-o-nitrophenyl and 2,4-dinitrophenyl- α -amino-acids³⁸. Since these two series gave almost the same results, discussion of the former (62) is sufficient.

Scheme 16



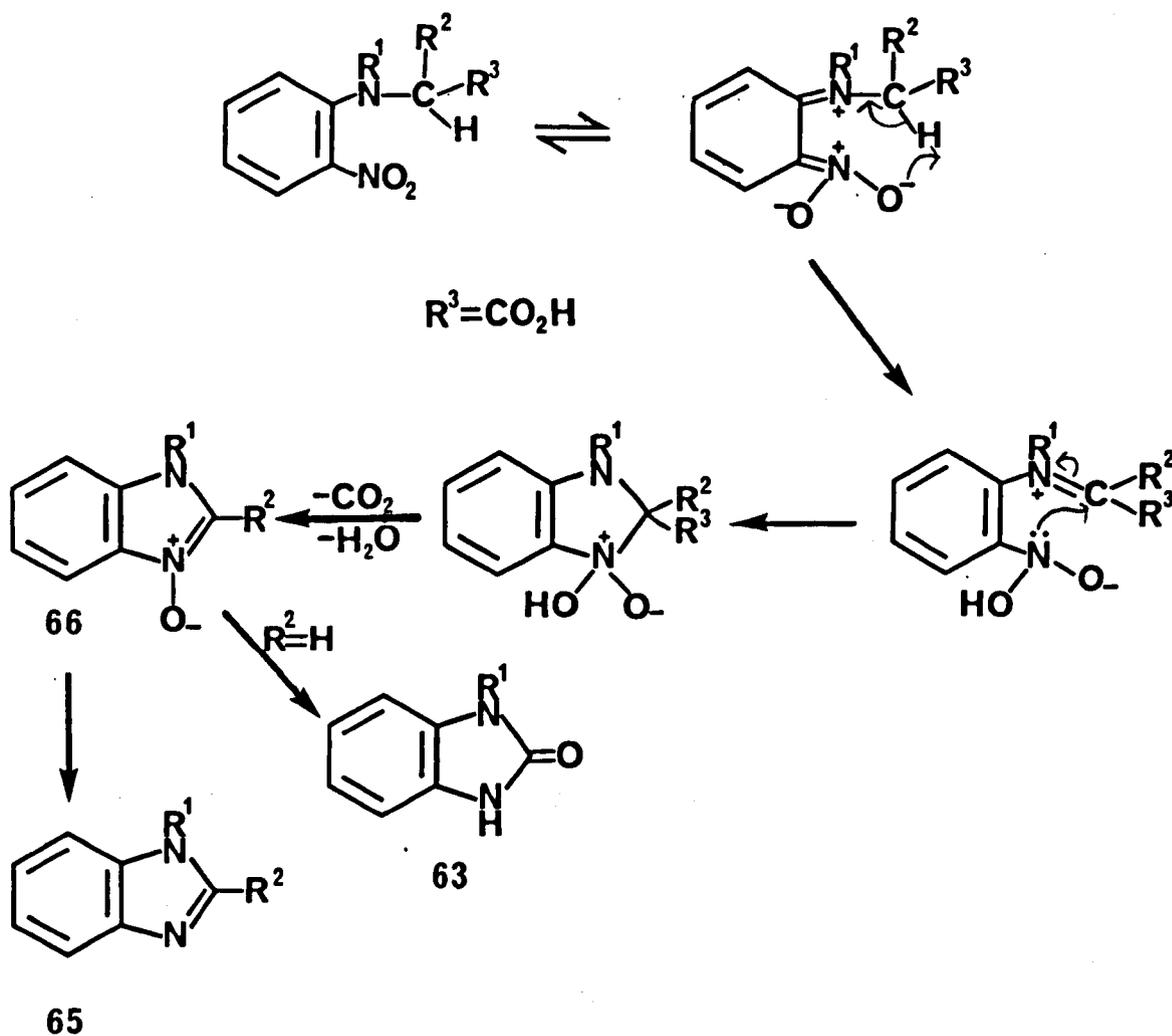
| Compound | Products and Yield % |
|----------|--------------------------------------|
| (62a) | (63a) 60, (64a) 5, (64b) 5, (65a) 10 |
| (62b) | (63b) 42, (64b) 7, (65a) 4, (65b) 8 |
| (62c) | (64a) 10, (65c) 40, (66c) 30. |

The first point of interest is that substitution on the amino group [i.e. $R^1 \neq H$, (62b)] had little effect on the course of reaction. Pyrolysis of o-nitrophenylglycine (62a) and o-nitrophenylsarcosine (62b) gave almost the same product distribution - the corresponding benzimidazolones [(63a), (63b) respectively] being the main products. However, replacement of a methylene hydrogen by phenyl [$R^2 = Ph$, (62c)] completely blocked benzimidazolone formation and 2-phenylbenzimidazole (65c) and 2-phenylbenzimidazole 3-oxide (66c) predominated.

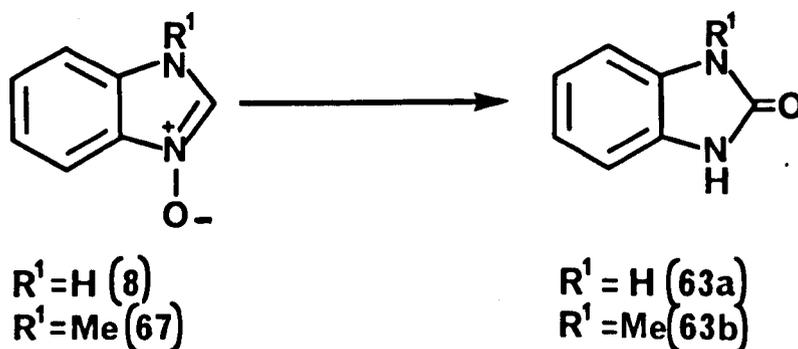
A possible explanation for these findings, proposing an intermediate benzimidazole N-oxide, was given.

[Scheme 17].

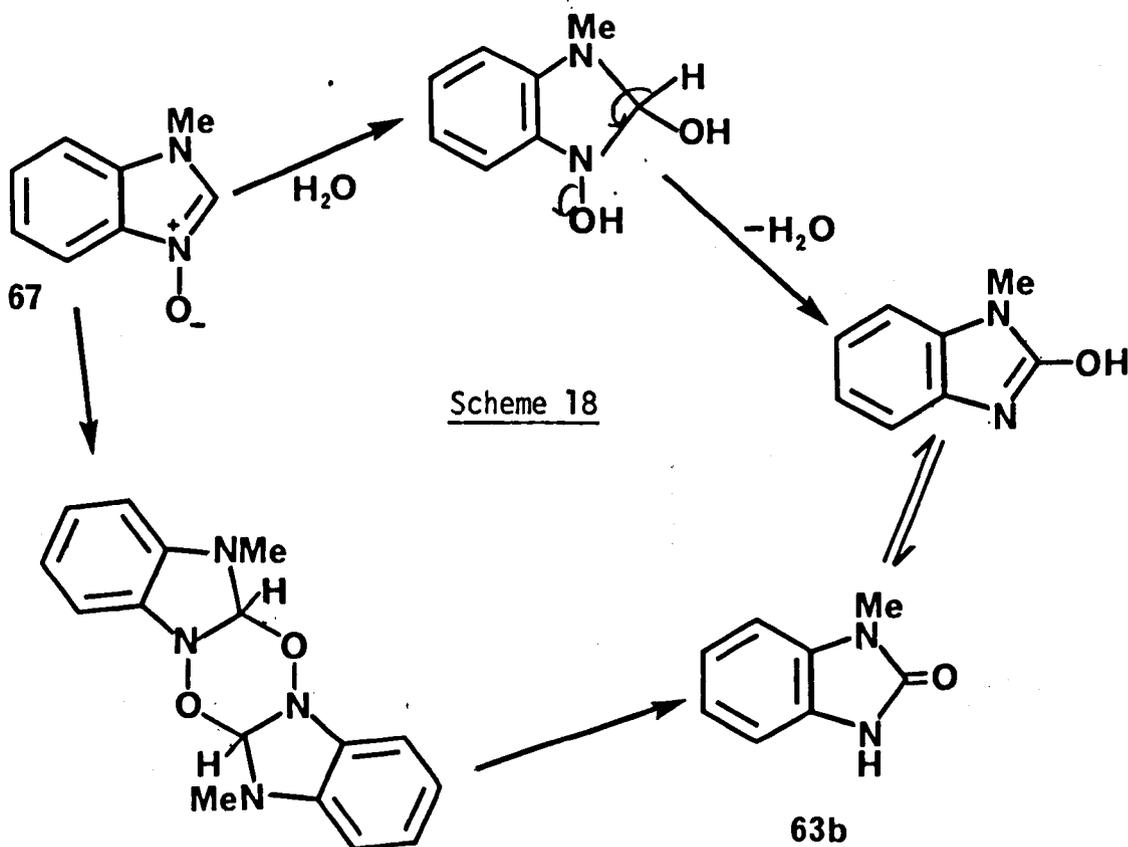
Scheme 17



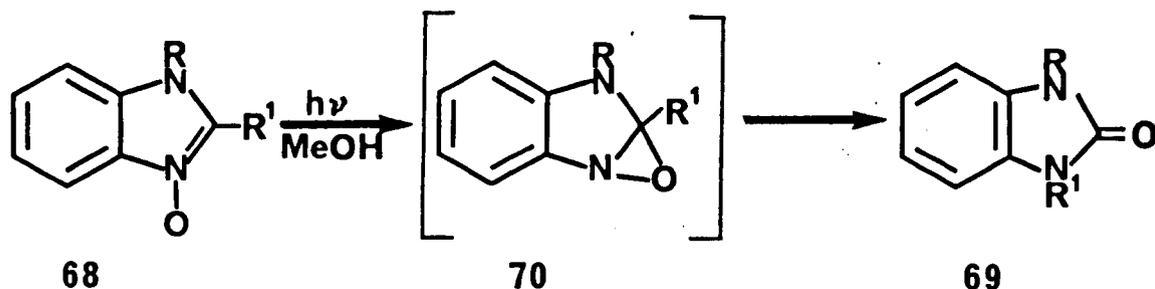
Benzimidazole N-oxides are known to undergo rearrangement to benzimidazolones. Kuhn and Blau³⁹ reported that heating benzimidazole N-oxide (8) with water in a sealed tube at 180° gave benzimidazolone (63a). Somewhat later, Takahashi and Kano⁴⁰ reported the facile rearrangement of 1-methylbenzimidazole 3-oxide (67) to 1-methylbenzimidazolone (63b) by heating in acetone.



The latter reaction has been rationalised as either a water-catalysed or bimolecular process⁷ [Scheme 18].

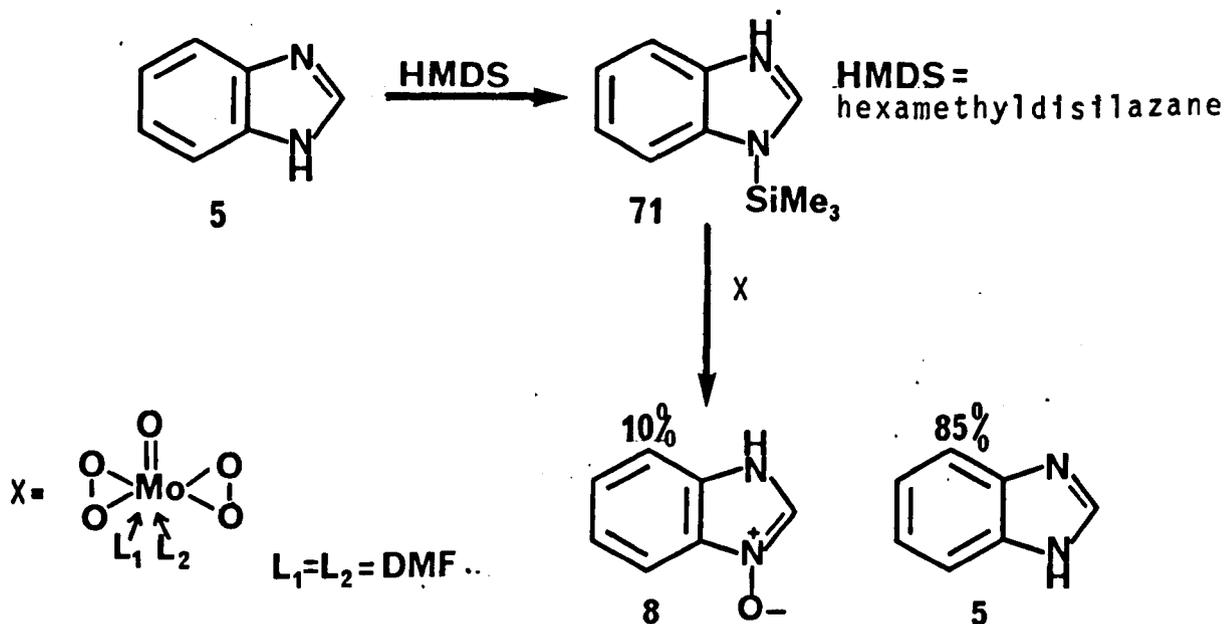


In addition, the photolysis of 1,2-dialkylbenzimidazole 3-oxides (68) is reported to give 1,3-dialkylbenzimidazolones (69)^{41,42} possibly via an oxaziridine intermediate (70).



The pyrolysis of two substituted o-nitrophenylglycines in the gas phase is described in Chapter 2.

Finally, since the last review on benzimidazole N-oxide chemistry⁷ (1979) little development of new synthetic methods has taken place. However, one recent and potentially very useful method involves the chemical oxidation of N-trimethylsilylbenzimidazole⁴³ (71).



Although the conversion is low, this method may point the way for other related procedures, possibly using different metal complexes.

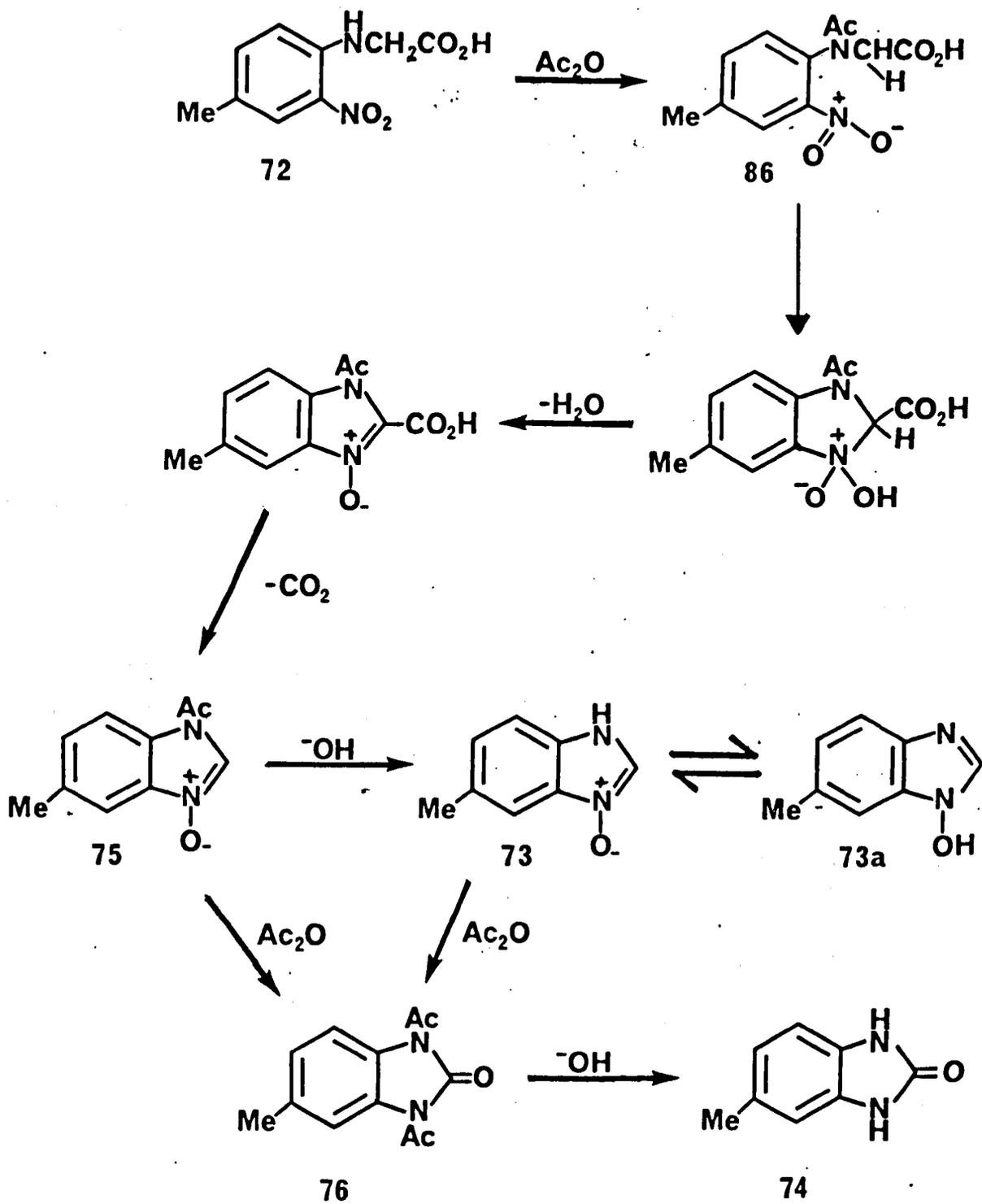
Chapter 2

Cyclisation of some o-nitrophenylglycine derivatives

In 1974 Aboulez and El-Sheikh reported that N-(4-methyl-2-nitrophenyl)glycine (72) underwent cyclisation in boiling acetic anhydride⁴⁴. If the reaction was stopped after 8 hours and the resultant mixture hydrolysed with aqueous ammonia, 5-methylbenzimidazole 3-oxide [(73); tautomeric with 1-hydroxy-6-methylbenzimidazole (73a)] was isolated, albeit in unspecified yield. No spectroscopic data were reported and the product was characterised by micro-analysis alone. If the reaction was allowed to proceed for 12 hours, upon removal of solvent and hydrolysis with aqueous ammonia the product obtained was 5-methylbenzimidazol-2-one (74). The N-oxide (73) was presumed to be an intermediate in the formation of the benzimidazolone (74) and the whole reaction sequence was formulated as in Scheme 19. Only compounds (73) and (74) were isolated.

This work appeared to offer a new and fairly easy route to benzimidazole N-oxides unsubstituted at positions 1 and 2. Mention has already been made (Chapter 1, p.11) of the difficulties encountered in obtaining such materials by the long-established method of partial reduction of o-nitroanilides.

Scheme 19 (after Aboulezz and El-Sheikh.44)



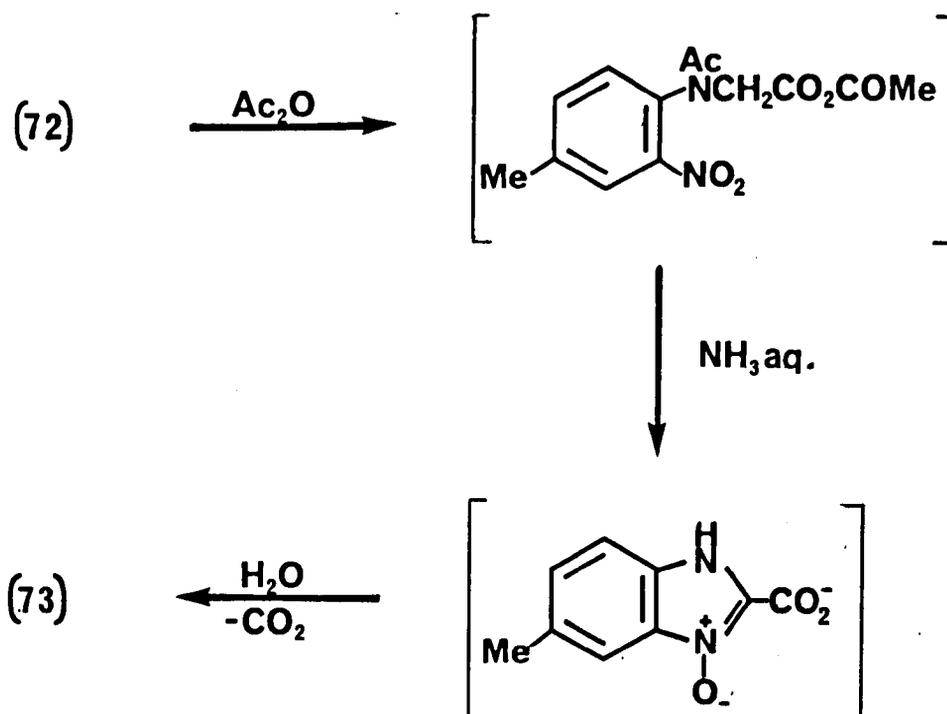
Mechanistically, this reaction also seemed worthy of attention, since that proposed by Aboulezz and El-Sheikh is somewhat unconvincing.

Several problems are apparent.

- 1) The mechanism proposed for initial cyclisation is essentially that for a base-catalysed condensation (cf p 20) unlikely to occur in acetic anhydride alone.
- 2) Even if the reaction proceeds in acetic anhydride as far as the key intermediate, 1-acetyl-5-methylbenzimidazole 3-oxide (75), it seems highly improbable that the latter would be sufficiently stable in boiling acetic anhydride to survive an eight-hour reaction period, but reactive enough to be converted into the diacetylbenzimidazolone (76) after a further 4 hours. Indeed, the thermal instability of a 1-substituted-2-unsubstitutedbenzimidazole-3-oxide has already been discussed (p 37).
- 3) If the isolated N-oxide (73) was formed only after base hydrolysis of (75), it could not be a genuine reaction intermediate if its conversion into the final product (76) required the presence of acetic anhydride.
- 4) Since the second stage of the reaction procedure involved heating in aqueous ammonia it was a possibility that cyclisation took place only at this stage and was

thus base-induced. Indeed, such an alternative mechanism has already been suggested⁷. [Scheme 20].

Scheme 20

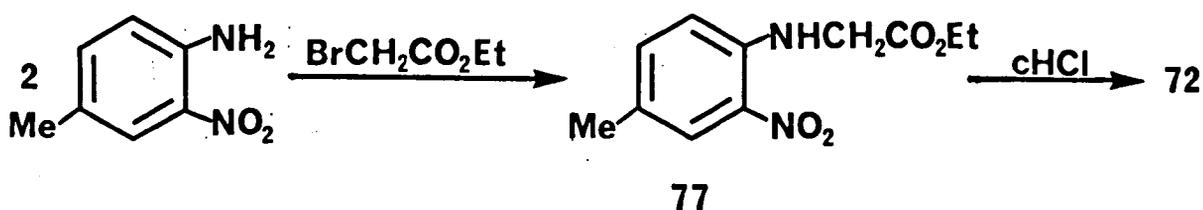


In order to find answers to the above problems it was necessary to attempt to duplicate the work of Aboulezz and El-Sheikh and, in addition, to synthesise independently the alleged intermediates and products.

The synthesis of the glycine (72) gave unexpected problems. Although no reference to its preparation was given in the Egyptian paper, it was already a known compound, having been obtained by melting together 4-methyl-2-nitroaniline and bromoacetic acid⁴⁵, although in unspecified yield. Mention had been made of the

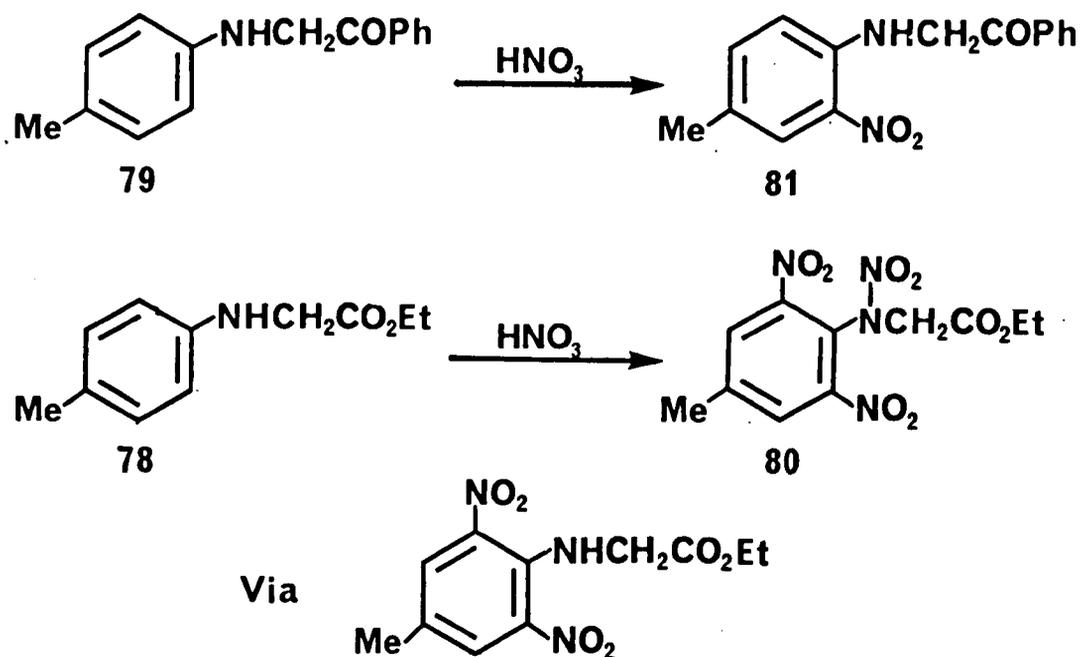
products' thermal instability and this may account for the very low yields of the glycine being obtained here. The use of dimethylformamide as solvent allowed better temperature control, but yields were still unsatisfactorily low (~25%).

The corresponding reaction of 4-methyl-2-nitroaniline with ethyl bromoacetate followed by hydrolysis of the ethyl ester (77) afforded an alternative.



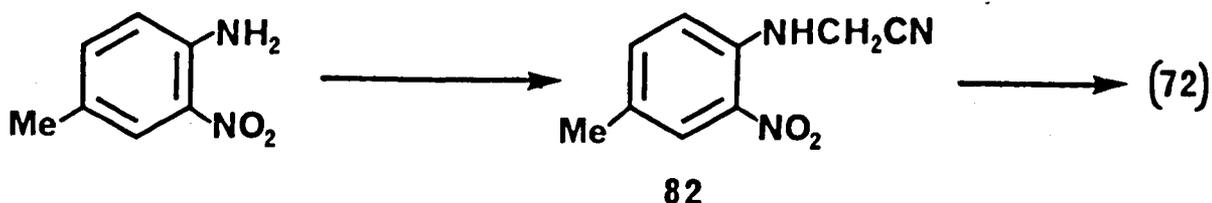
However, the efficiency of this route was marred by low yields in the first step, with heavy contamination of the products by unreacted starting materials.

Mono-nitration of N-(*p*-tolyl)glycine ethyl ester (78) also seemed an attractive possibility in view of the good yields obtained in the corresponding reaction of N-phenacyl-*p*-toluidine⁴⁶ (79).



However, under the nitrating conditions tried, only the trinitro compound (80) was formed, in good yield. The formation of stable N-nitro compounds is well known to sometimes follow polynitration of aromatic amines⁴⁷. The relatively low solubility of the mono-nitro phenacyl-compound (81) in the nitrating medium may explain why it can be isolated.

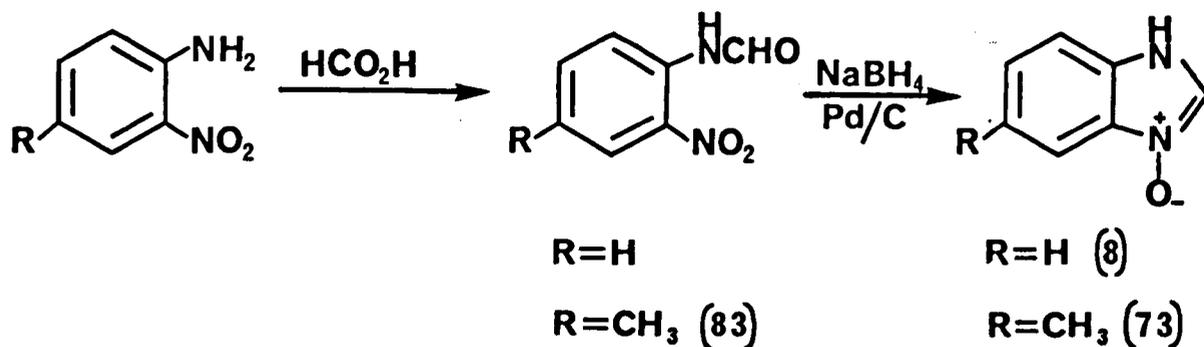
The glycine (72) was finally prepared in high yield and purity via hydrolysis of N-cyanomethyl-4-methyl-2-nitroaniline (82). The latter was obtained from 4-methyl-2-nitroaniline by the method of Dimroth and Aurich⁴⁸ [paraformaldehyde, potassium cyanide, zinc chloride and conc. sulphuric acid in acetic acid] although a reduction in zinc chloride concentration was necessary to prevent di-cyanomethylation, and the nitrile was then hydrolysed in an aqueous sulphuric-acetic acid mixture.



The next objective was the synthesis of the alleged intermediate, 5-methylbenzimidazole 3-oxide (73). Two obvious possibilities existed.

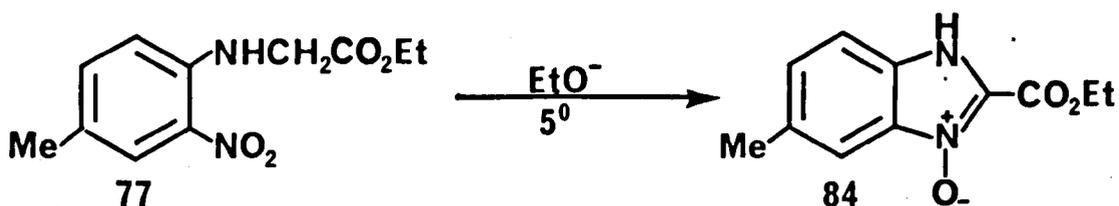
- 1) Partial reduction of 4-methyl-2-nitroformanilide (83) by one of the methods previously described. (p 5).
- 2) Base-induced cyclisation (p 20) of a suitably activated 4-methyl-2-nitroaniline derivative, with subsequent removal of the activating group.

In view of the easy preparation of (83), the first possibility appeared the more simple and direct. The best method for the preparation of 1-unsubstituted N-oxides by this route is claimed to be that using a metal hydride (usually NaBH₄) in the presence of a catalyst, such as palladium or platinum (p. 9). However when the anilide was reduced under the published conditions¹⁰, only a very low yield of the N-oxide (73) was obtained. In addition, the preparation of the parent N-oxide (8) also gave disappointingly low yields, despite the literature claim¹⁰.



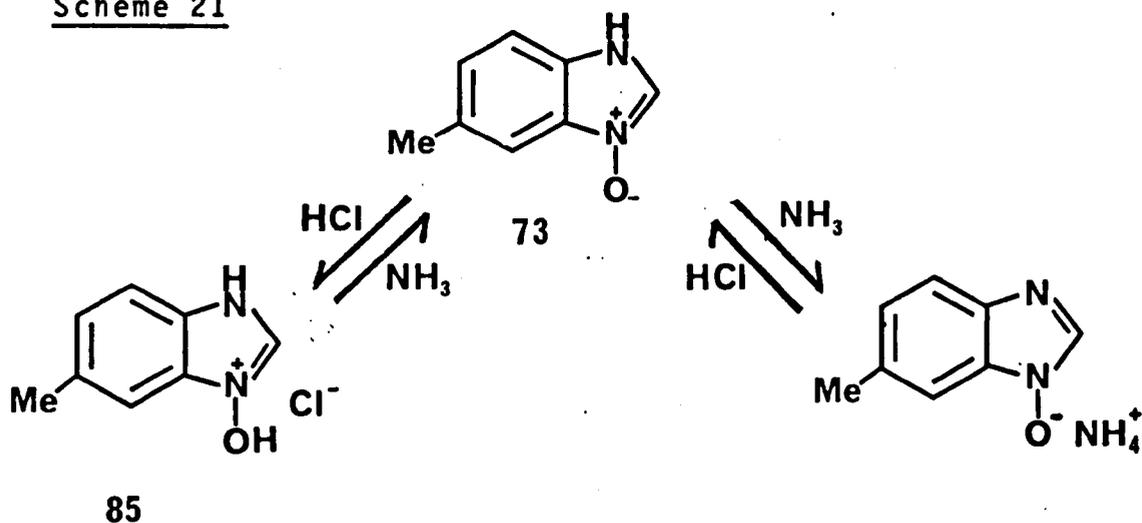
As has previously been suggested (and will subsequently be shown in the case of (73)) the problem is most probably one of isolating the amphoteric N-oxide.

Attention was now turned to the second route: base-induced cyclisation. A suitable substrate had to fulfil three criteria. First, it must be easily prepared. Second, it should be sufficiently activated to promote efficient cyclisation and, thirdly, the activating group must be easily removed. Therefore, N-(4-methyl-2-nitrophenyl)-glycine ethyl ester (77) was used, now made by esterification of the glycine (72). The success of the cyclisation was found to be critically dependent on base strength and reaction temperature. No reaction occurred with sodium carbonate in boiling ethanol, in contrast to the known cyclisation of N-(2,4-dinitrophenyl)glycine methyl ester⁴⁹. (The effect of the second nitro group is discussed in Chapter 3). Cyclisation to ethyl 5-methylbenzimidazole-2-carboxylate 3-oxide (84) was finally accomplished using sodium ethoxide, although low temperature was necessary to prevent further reaction.



The subsequent de-esterification of (84) to yield the desired N-oxide (73) illustrates the amphoteric properties of benzimidazole N-oxides unsubstituted at position 1. Hydrolysis of (84) in conc. hydrochloric acid gave 5-methylbenzimidazole 3-oxide hydrochloride (85) directly. The free N-oxide (73) was not isolated from an aqueous solution of the hydrochloride by addition of aqueous ammonia. Indeed no precipitation occurred in the pH range 3-11 [Scheme 21].

Scheme 21



Evaporation of the solution at pH 7 gave, upon recrystallisation, only a very small quantity of the free N-oxide (73). This difficulty of isolation probably accounts for the very low yield of (73) obtained by the partial reduction route and the general variability in yield of

1-(unsubstituted)benzimidazole-3-oxides obtained by reductive processes [cf p. 10]. Isolation was finally achieved by dissolving the hydrochloride (85) in an excess of ammonia and concentrating the solution under vacuum. Under those conditions the free N-oxide (73) was deposited in almost pure form.

The melting point of 5-methylbenzimidazole 3-oxide (73) thus obtained agreed fairly well with that reported in the Egyptian workers' paper, lending some support to their findings. Unfortunately, however, no spectroscopic data were available for comparison. ¹H n.m.r. of (73) is unremarkable with the only feature of note being the characteristic singlet at low field for H-2. However, comparison with the hydrochloride (85) is interesting, (Table 1) since such data have not previously been reported for benzimidazole N-oxide salts.

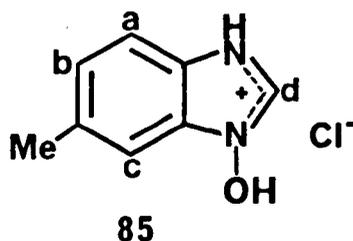
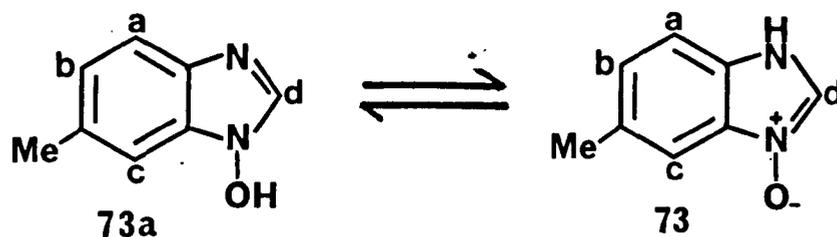


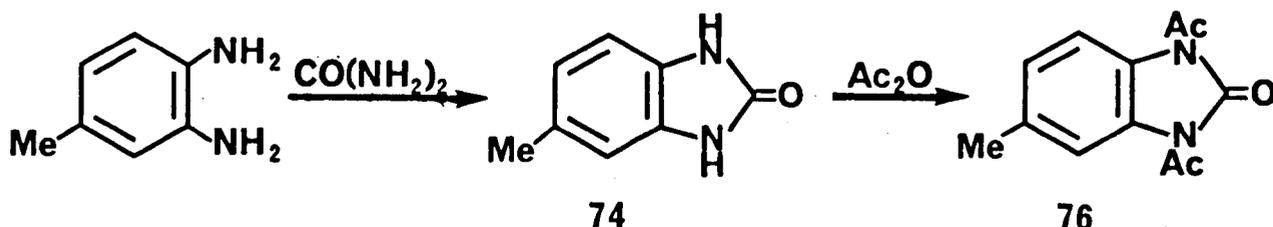
Table 1

^1H n.m.r. spectra of 5-methylbenzimidazole-3-oxide (73) and its hydrochloride (85) in d_6 -DMSO (chemical shifts in p.p.m., J in Hz)

| | CH ₃ | b | c | a | d | J _{ab} | J _{bc} |
|---------------------------|-----------------|------|------|------|------|-----------------|-----------------|
| (73) | 2.40 | 7.00 | 7.25 | 7.45 | 8.23 | 8.0 | 1.2 |
| (85) | 2.53 | 7.45 | 7.70 | 7.75 | 9.85 | 8.0 | 1.2 |
| Chemical shift difference | 0.13 | 0.45 | 0.45 | 0.30 | 1.62 | | |

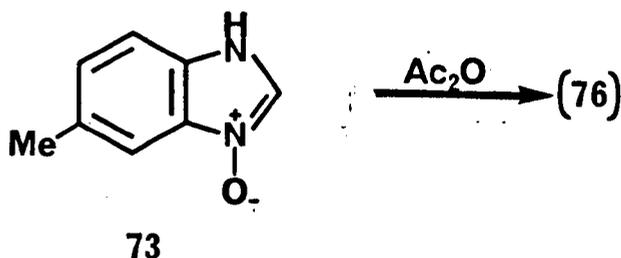
On protonation all the observable ring protons are deshielded, but to different degrees: the difference is very small for the CH₃ protons, moderate for those on the carbocyclic ring and extremely large for H-2.

Synthesis of the other materials allegedly prepared in the Egyptian work was easily done by standard methods. i.e. 5-methylbenzimidazolone (74) was obtained by melting together 4-methyl-1,2-phenylenediamine and urea, and acetylation of (74) by acetic anhydride furnished the diacetylbenzimidazolone (76) [cf Scheme 19].



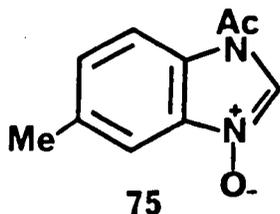
Now that all the products reported in the Egyptian paper had been independently synthesised, a detailed investigation of the literature claims was possible.

Treatment of the N-oxide (73) with boiling acetic anhydride was confirmed to give 1,3-diacetyl-5-methylbenzimidazolone (76), although this merely constitutes another example of a well known reaction⁵⁰.



Far from supporting the claimed pathway, this makes the intermediacy of an isolable N-oxide, generated in acetic anhydride, extremely unlikely: whether it be (73) or the

closely related 1-acetylbenzimidazole 3-oxide (75)
[cf Scheme 19].

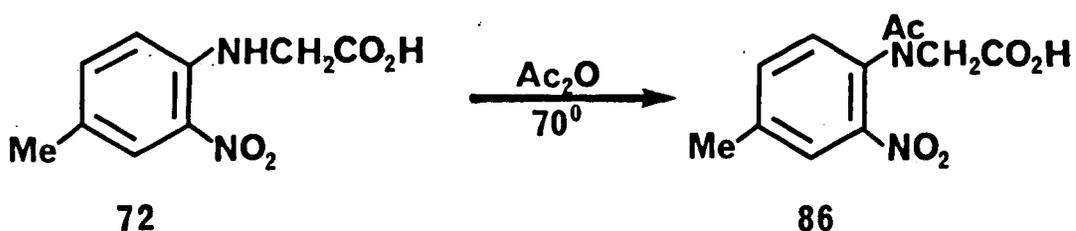


In fact this result indicates that if an N-oxide were formed it must be after removal of acetic anhydride - i.e. during the subsequent treatment with ammonia.

The glycine (72) was now allowed to react with acetic anhydride under both sets of published conditions (8 and 12 hours reaction). All attempts to isolate either the claimed N-oxide (73) or the benzimidazolone (74) from these reactions failed.

The 8-hour reaction gave a black tar from which no identifiable products were isolated. Comparison of the ¹H spectrum of the tar (fig. 1) with those of the fully characterised N-oxide (73) and the benzimidazolone (74) (fig 2a, 2b respectively) showed little correspondence; however, the presence of some N-oxide (73) could not be completely ruled out. It must be noted, however, that the experimental conditions given for the 8-hour reaction were incomplete (giving no indication as to quantity of the glycine (72) and acetic anhydride used). Therefore one was left to assume that the procedure was essentially the same as for the 12-hour reaction. In an attempt to

determine further the composition of the tar arising from the 8-hour reaction, conditions were modified. Most importantly, it was found that if the glycine (72) was heated in acetic anhydride at a reduced temperature (70°) for 1.5 hours, fairly clean N-acetylation took place to give (86) - an intermediate suggested in the Egyptian paper but neither characterised nor isolated.



Analytical and spectroscopic data established the structure (86) with the only feature of note being the non-equivalence of the methylene protons, sometimes encountered in such systems³⁴. Comparison of the ¹H n.m.r. spectrum of (86) (fig 3) with that of the tar (fig 1) showed significant correspondence. However, the complexity of the mixture meant that only tentative assignments could be made.

Attention was now turned to the 12-hour reaction, for which more complete experimental details were given. Once again, the claimed product in this case (5-methylbenzimidazolone (74)) was not isolated. Instead, upon workup a black tar was again produced. Figure 4 shows a ¹H n.m.r. spectrum of this tar (4a) together with spectra for the

Fig 1

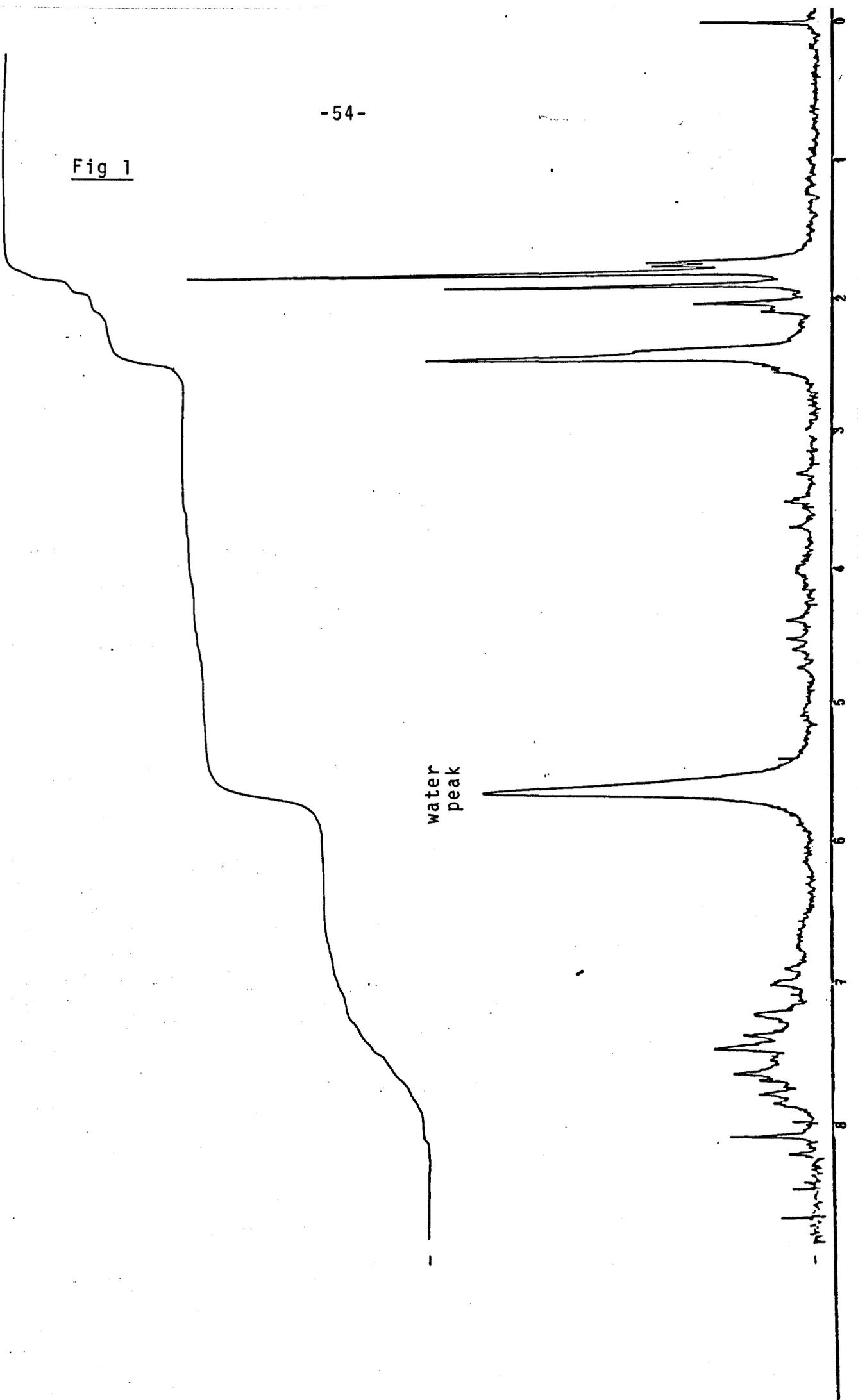


Fig. 2a

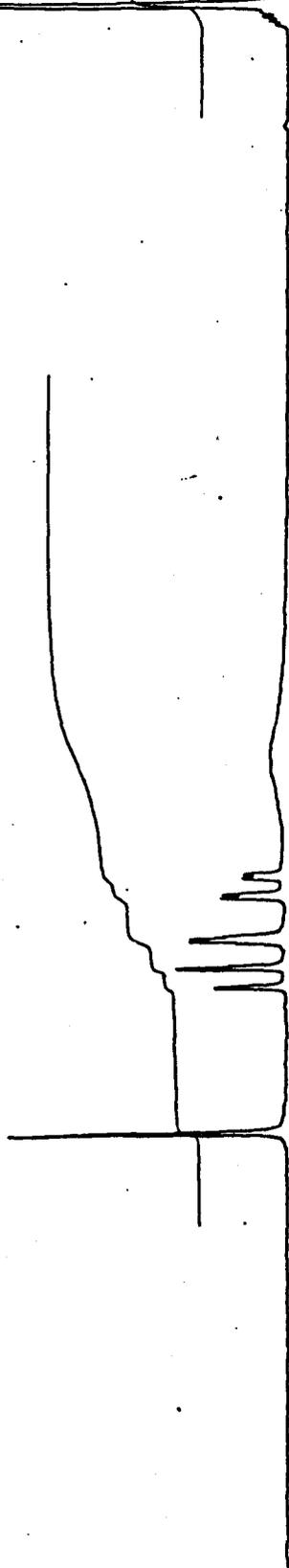


Fig. 2b

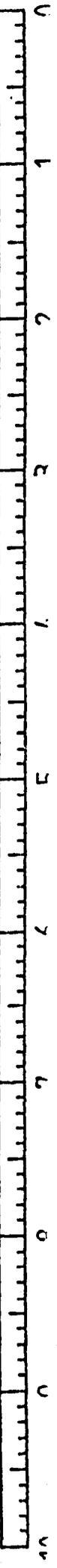
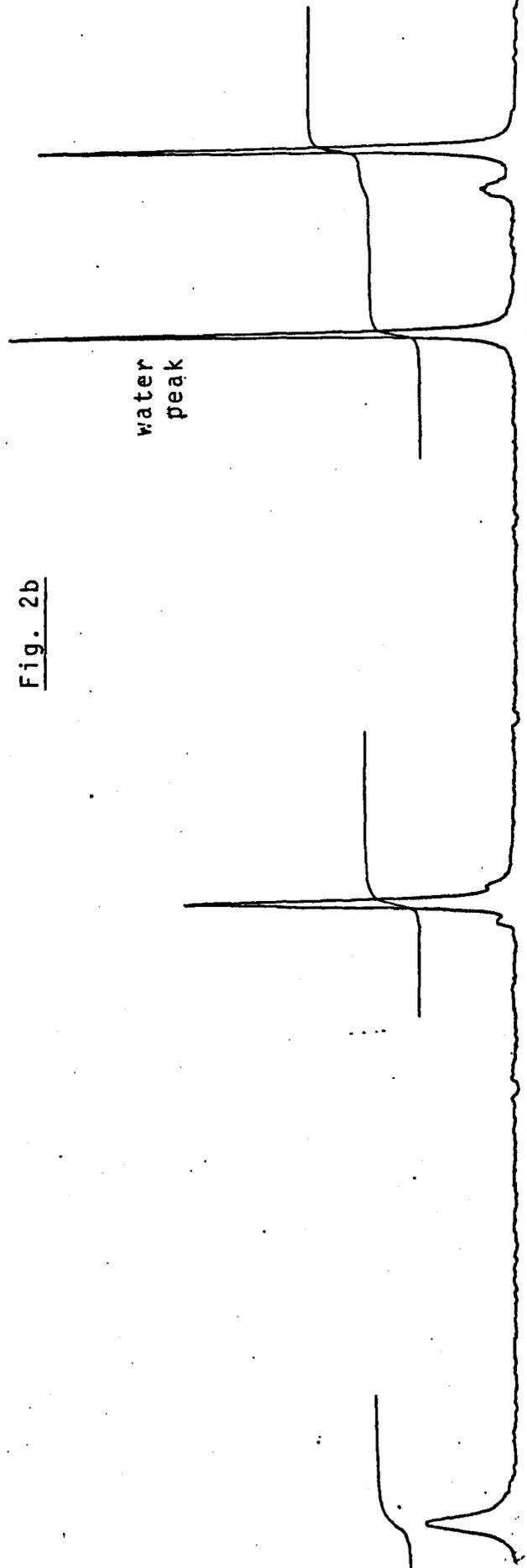


Fig. 3

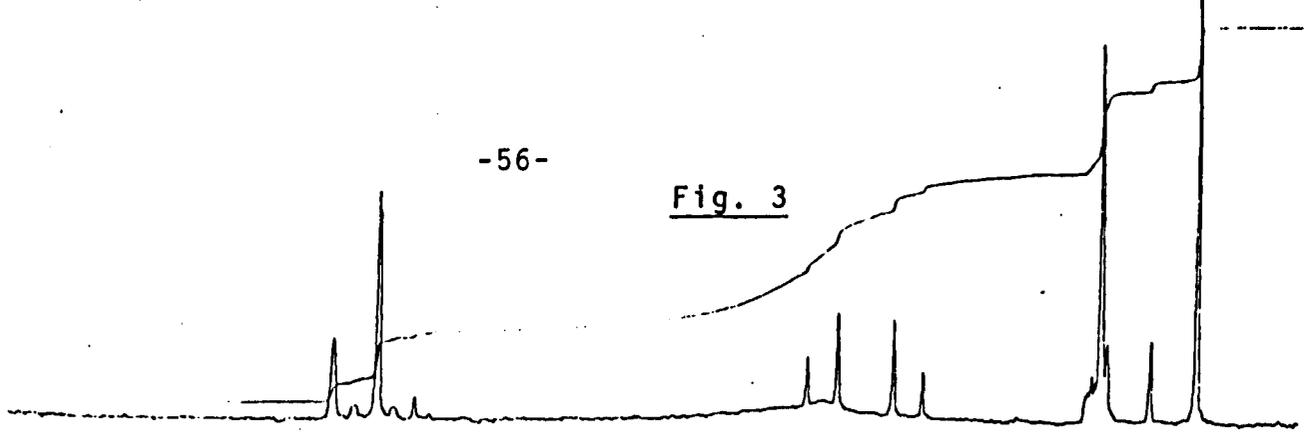


Fig. 4c

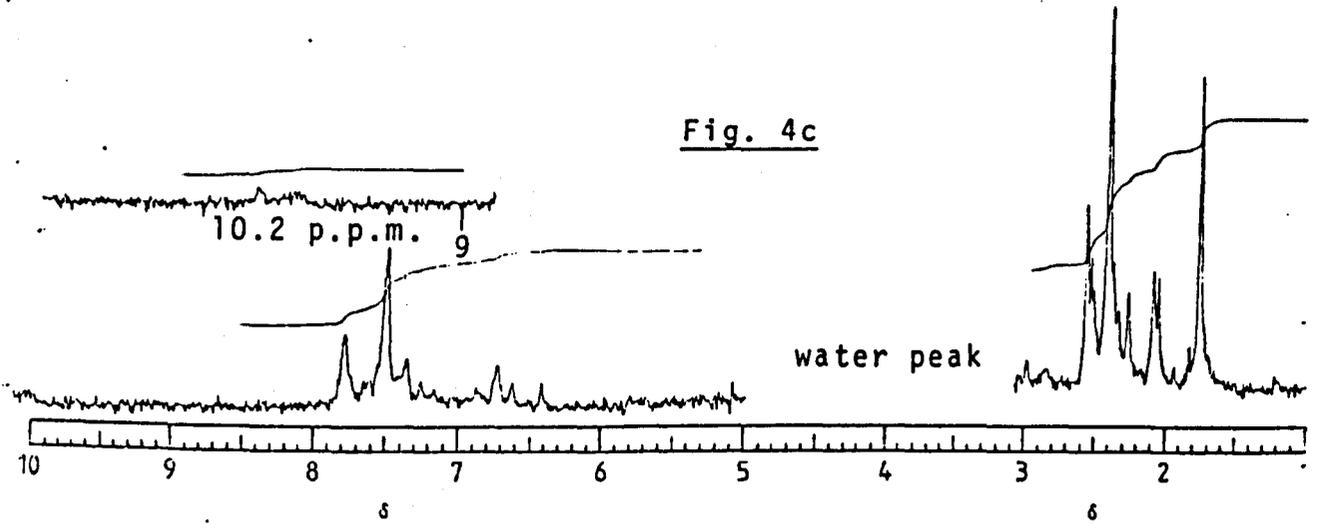


Fig. 4b

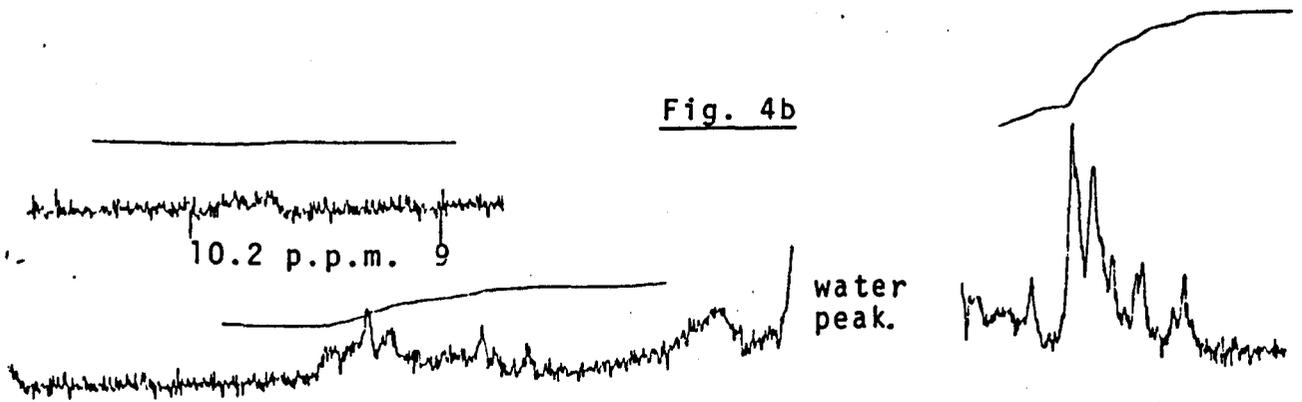
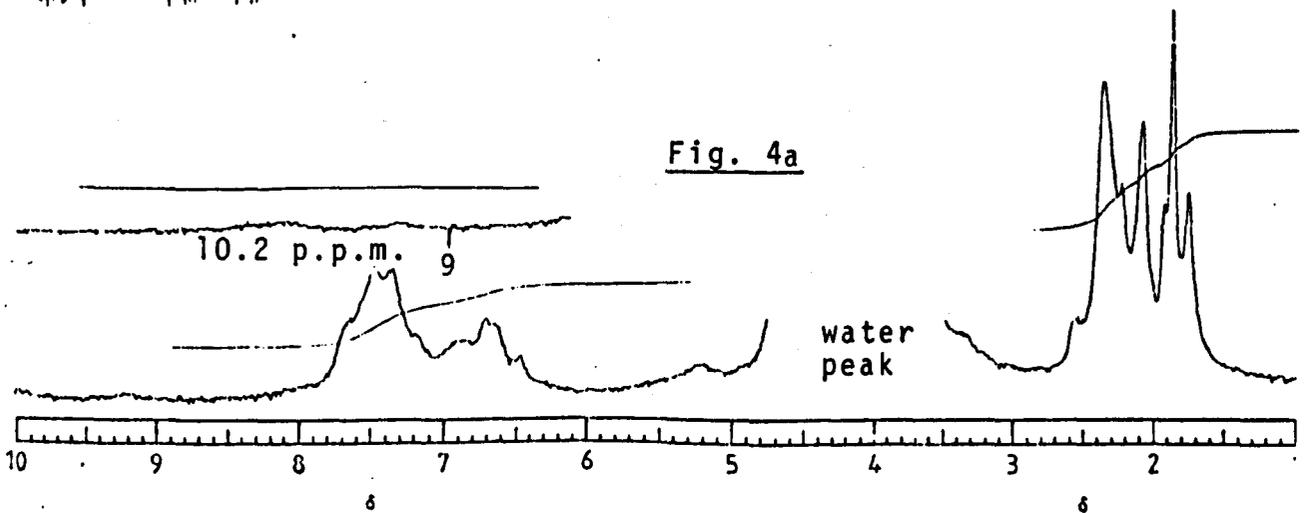


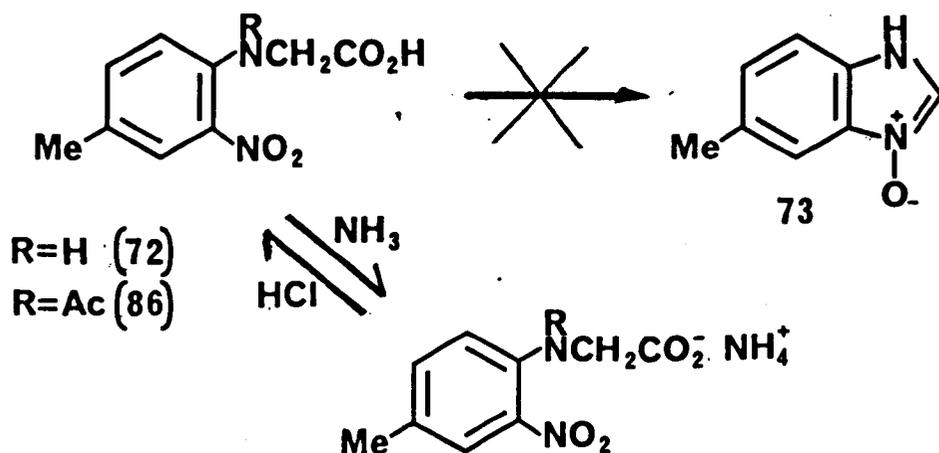
Fig. 4a



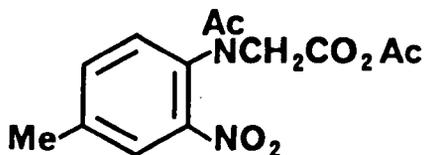
very small quantity of solids (4b and 4c) that were finally isolated from the reaction mixture. One of these products (fig 4c) corresponds well with N-acetyl-(4-methyl-2-nitrophenyl)glycine [(86), fig 3]. The absence of signals corresponding to the benzimidazolone (74) is interesting, since this was claimed to be the major product of this reaction.

Having established that, at best, the literature results were extremely difficult to duplicate, the question still remained as to how the claimed products could have been produced under conditions at least similar to those published.

One possibility was base-induced cyclisation of either the glycine (72) or the N-acetylglycine (86) by aqueous ammonia. However, both (72) and (86) were merely deprotonated by treatment with ammonia under the Egyptian conditions, and were recovered unchanged upon acidification with HCl.



Therefore if base-catalysed cyclisation is involved it would probably have to be via the sort of intermediate already suggested⁷ - the mixed anhydride (87) [cf Scheme 20].



87

However, even if (87) were formed it would by no means be guaranteed to yield a benzimidazole N-oxide on treatment with base. [cf p 28].

Another interesting possibility involves thermal cyclisation of either the glycine (72) or acetylglycine (86) - the latter now known to be present in the reaction mixture. In particular, it was thought that if the Egyptian workers had removed the acetic anhydride at atmospheric pressure some overheating could have taken place in the latter stages of this process.

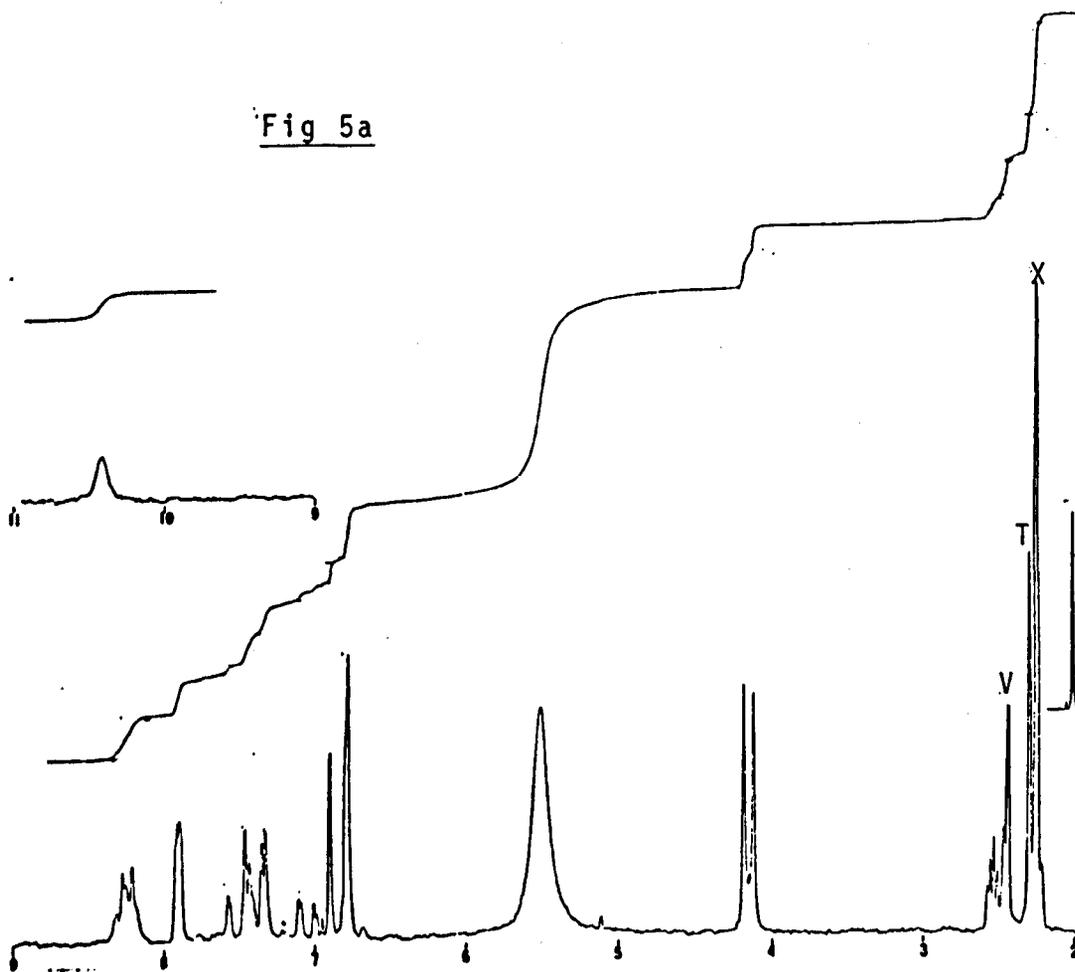
Thermal cyclisations of o-nitrophenylglycine derivatives³⁸ (62) have already been discussed (p 34). Of key importance is that benzimidazolones (63) were the main products, and although benzimidazole N-oxide intermediates were postulated, none were isolated.

Furthermore, it was not shown that the suggested intermediates could be pyrolysed under the same conditions to

yield benzimidazolones, although previous work suggested that this would be likely^{39,40}.

The pyrolytic reactions of N-(4-methyl-2-nitrophenyl)-glycine (72) and its N-acetyl analogue (86) were now examined. Instead of the condensed phase conditions previously employed³⁸, Flash Vacuum Pyrolysis⁵¹ (F.V.P.) appeared to be an appropriate alternative. As the term suggests, F.V.P. involves high temperature, very low pressures and short reaction times. Under these conditions it is often possible to observe primary processes of high activation energy without further reactions taking place. For this reason it was thought that in addition to establishing that (72) and (86) would yield the benzimidazolone (74) on pyrolysis it might be possible to identify 5-methylbenzimidazole 3-oxide (73) as an intermediate.

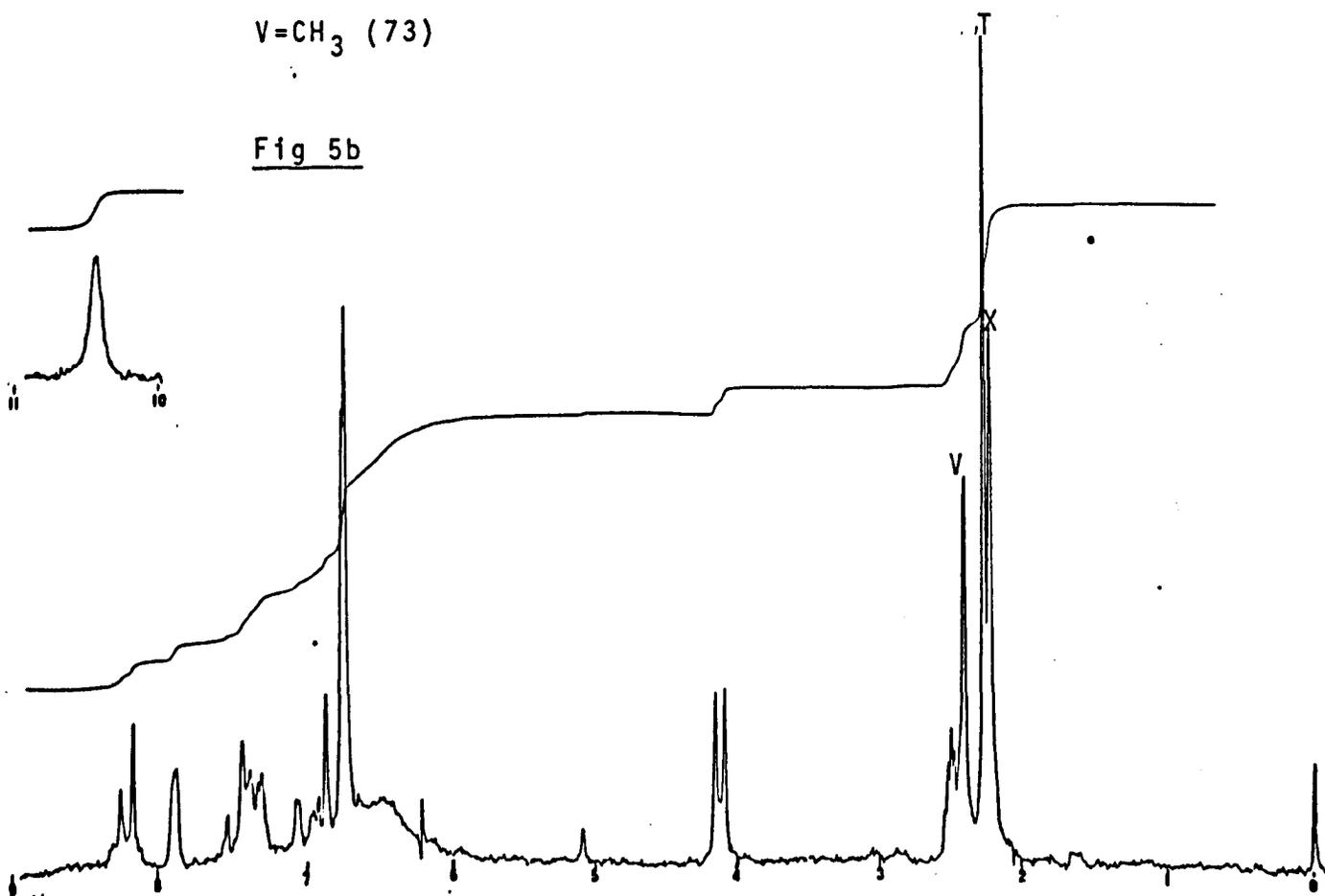
For the pyrolysis of (72) three temperatures were chosen: a) 650°, b) 700°, c) 750°. In all cases a quantity of involatile material was collected near the furnace outlet and its composition examined by ¹H n.m.r. [fig 5a), b), c)]. Comparison of these spectra with those of the starting glycine ((72), fig 5d), 5-methylbenzimidazolone ((74), fig 2b) and 5-methylbenzimidazole N-oxide ((73), fig 2a) yielded the following conclusions.

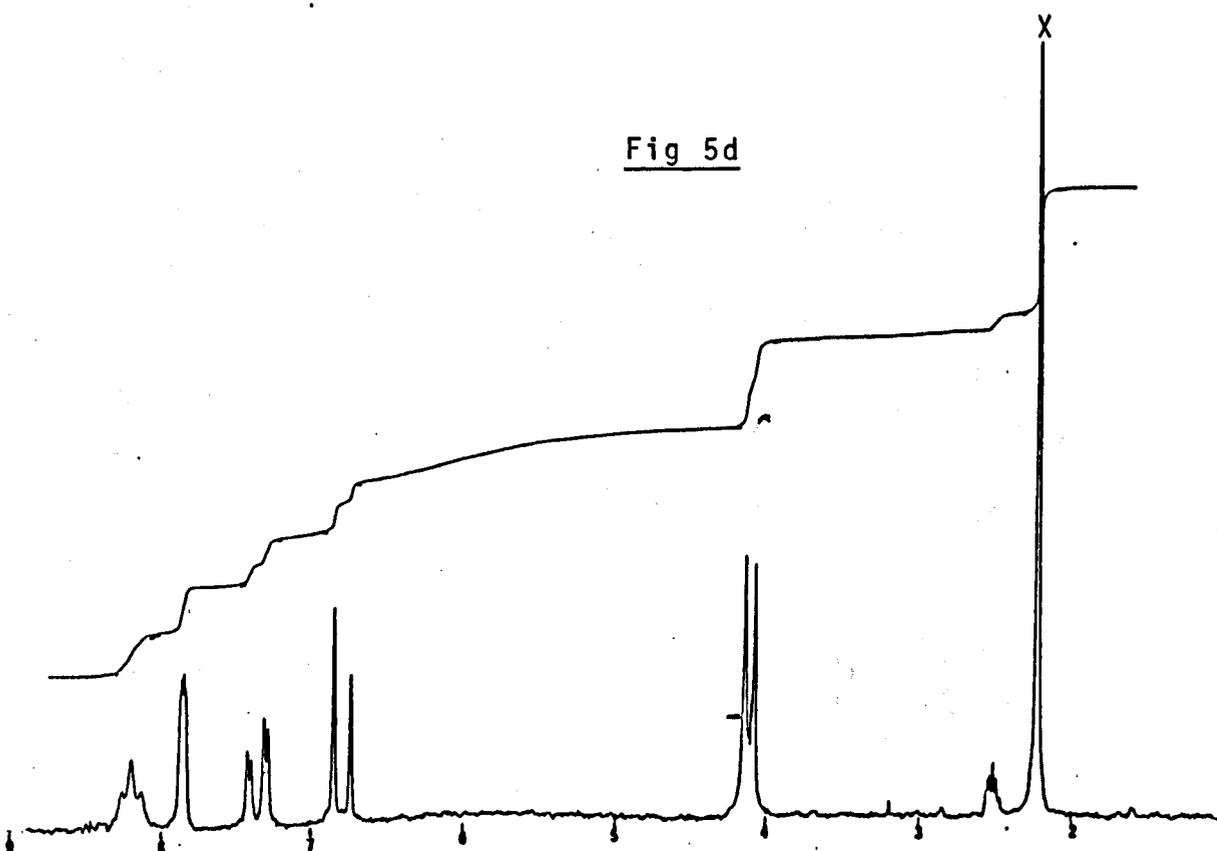
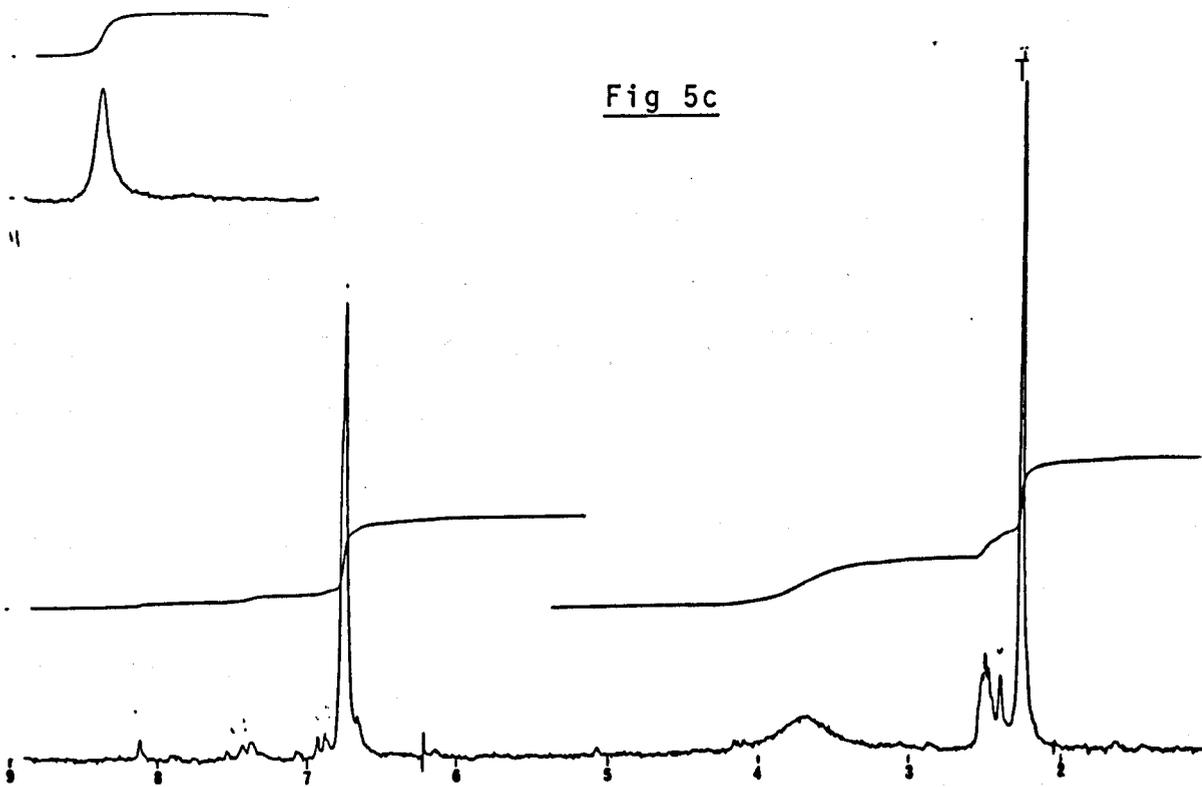
Fig 5a

X=CH₃ (72)

T=CH₃ (74)

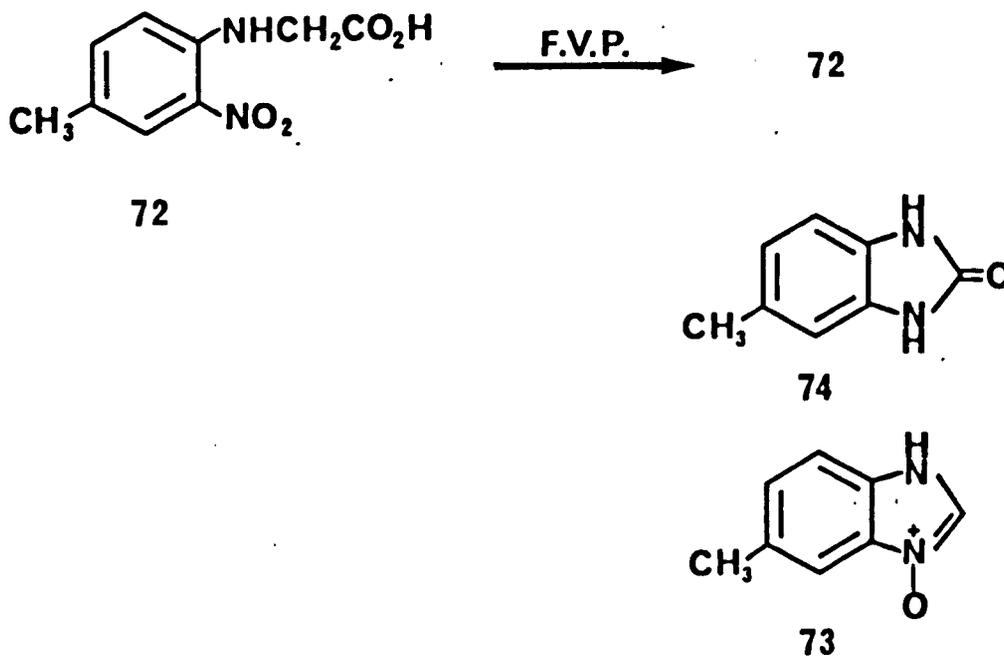
V=CH₃ (73)

Fig 5b

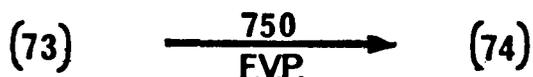


- 1) At 750° the sole component was the benzimidazolone (74) in high purity.
- 2) At 700° a mixture of three products was obtained: the benzimidazolone (74), N-(4-methyl-2-nitrophenyl)glycine (72) and 5-methylbenzimidazole 3-oxide (73) in an approximate ratio of 1:1:0.8 respectively.
- 3) At 650° the mixture is again wholly described as a combination of the same three products but this time in the ratio (74):(72):(73) 1.1:3:1.0.

Of particular interest here is that the complex multiplet appearing in the ^1H n.m.r. spectrum between 8.15 and 8.40 (corresponding to the N-H of the glycine and H-2 of the N-oxide) is simplified to the characteristic H-2 singlet of a (2-unsubstituted)benzimidazole N-oxide on D_2O exchange.

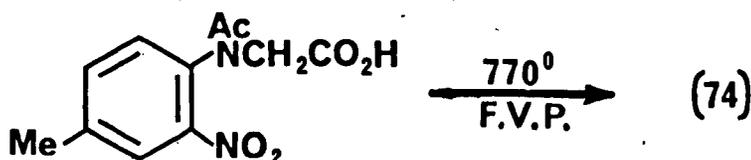


The intermediacy of 5-methylbenzimidazole 3-oxide (73) was further indicated by its conversion into the benzimidazolone (74) in 40% yield at 750°.



Clearly, in the pyrolysis of the glycine (72) a delicate balance exists. In order to convert a significant proportion of (72) into the benzimidazole N-oxide (73), fairly forcing conditions must be employed, with the result that further reaction to the benzimidazolone (74) is almost unavoidable.

Finally, N-acetyl-N-(4-methyl-2-nitrophenyl)glycine (86) was pyrolysed at 770° to yield the benzimidazolone (74). However the relatively low melting point and low volatility of (86) meant that it was not well suited to this technique.



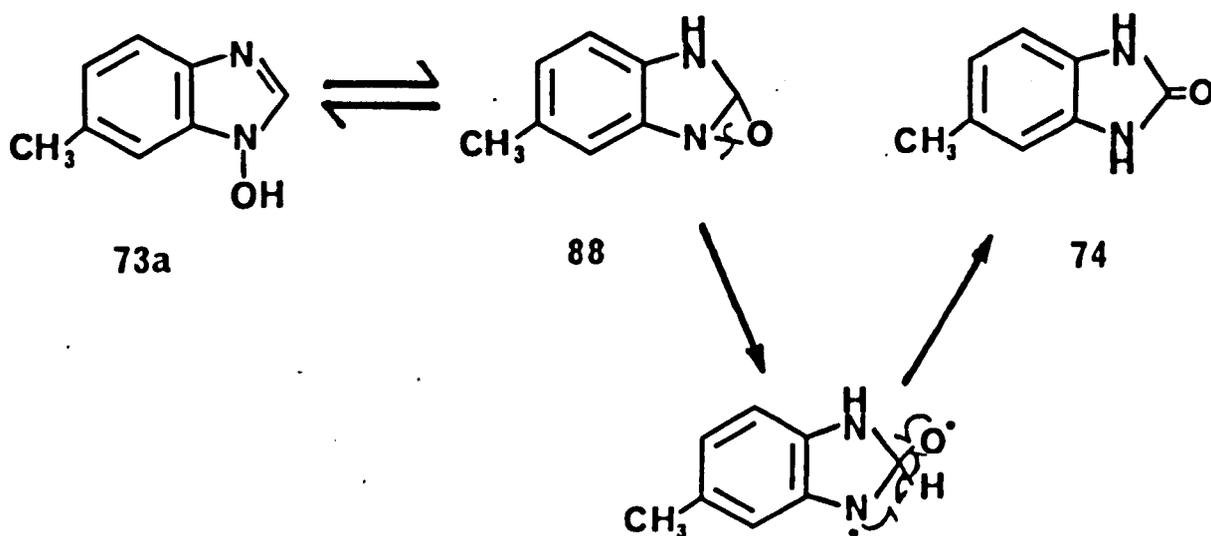
As regards mechanisms of the preceding reactions, the most important point is that, unlike previous workers, we are concerned with processes taking place under high vacuum in

the vapour phase. Such conditions preclude intermolecular reactions and therefore only unimolecular processes are possible. The previously suggested mechanism for cyclisation, proposing an aci-nitro intermediate still seems feasible [cf p 36], although a radical reaction cannot be ruled out.

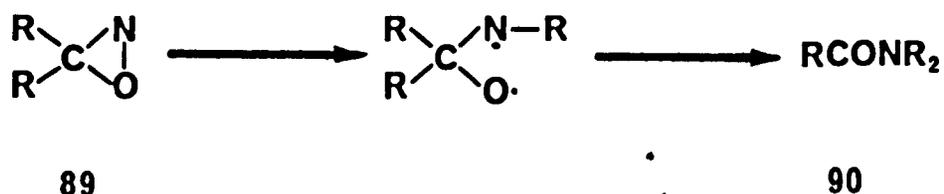
Conversion to the benzimidazolone (74) is however a different matter. Previous suggestions regarding the mechanism of related reactions in the condensed phase have invoked hydrolytic or bimolecular processes (p 37). Clearly, neither is possible under F.V.P. conditions.

One possible alternative involves an oxaziridine intermediate (88) [Scheme 22].

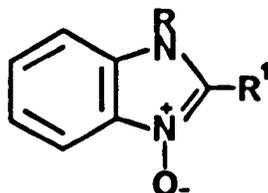
Scheme 22



Some support for this comes from the thermolytic isomerisation of oxaziridines (89) to amides (90) also in the gas phase⁵². Reaction was proposed to involve homolytic O-N fission and alkyl (or H) shift.



As previously described, oxaziridines are thought to be intermediates in the photochemical conversion of 1,2-dialkylbenzimidazole N-oxides into benzimidazolones in alcoholic solution. However, in that case the N-oxide probably reacted as a cyclic nitrene.

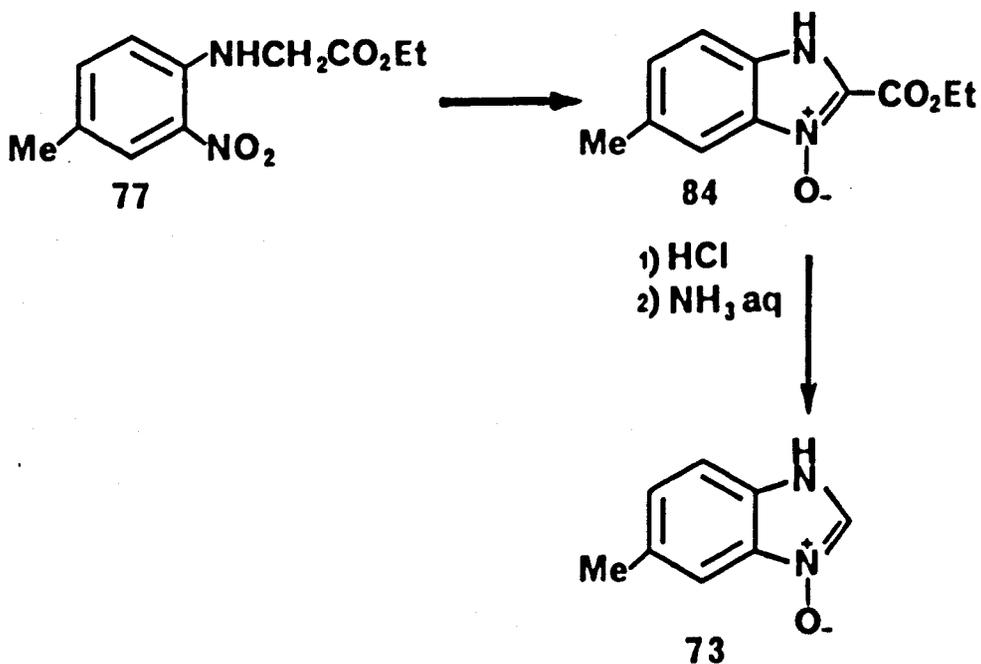


Further evidence for an oxaziridine intermediate in the pyrolysis of 5-methylbenzimidazole N-oxide (73) may come from consideration of the mass spectra of some benzimidazole N-oxides. Correlation between mass spectral and pyrolytic processes has often been used in predicting the course of the latter, although this approach is by no means generally applicable⁵¹. It has been reported⁵³ that the mass spectra of 2-arylbenzimidazole N-oxides show (ArCO)⁺ fragments, the production of which were proposed

to involve rearrangement of the molecular ion to form a bond between the N-oxide oxygen and C-2. The presence of an $(M-HCO)^+$ fragment in the mass spectrum of benzimidazole N-oxide was also mentioned, and, in the current work, 5-methylbenzimidazole N-oxide was found to behave similarly. It is interesting to note that the base peak in the mass spectrum of N-4-methyl-2-nitrophenyl glycine occurs at m/z 148, possibly indicating the formation of the benzimidazolone (74). For the N-acetyl compound (86), however, the main fragmentation processes correspond to loss of ketene and decarboxylation.

With regard to the published claims, the reported result that N-(4-methyl-2-nitrophenyl)glycine is convertible into either 5-methylbenzimidazole 3-oxide (73) or 5-methylbenzimidazolone (74) by the action of acetic anhydride is not reproducible. However, since the melting point quoted for the N-oxide (73) ($176^{\circ} - 178^{\circ}$) agrees well with that obtained here (174°) it may indeed have been produced, although the reaction pathway suggested [Scheme 19] is clearly not feasible. In particular, if the N-oxide was formed, it must have been after removal of most of the acetic anhydride. Indeed, the F.V.P. results indicate that, in principle, both products could have been obtained thermally, and it is conceivable that isolation of a particular one was a result of chance variation in the heating during removal of the acetic anhydride.

In conclusion, the best method of obtaining the N-oxide (73) is by base-induced cyclisation of the ester (77) to yield (84), followed by acid hydrolysis and a basic workup.



Chapter 3

Routes to some aminobenzimidazole N-oxide derivatives - purine and nucleoside analogues

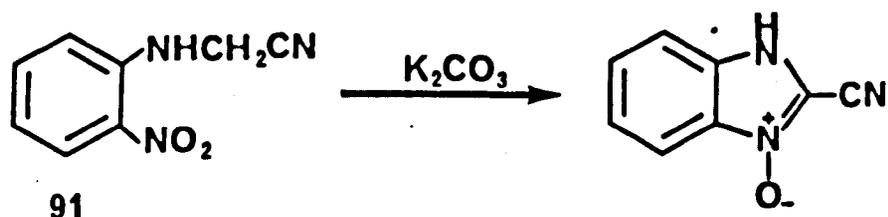
This chapter is mainly concerned with the preparation of benzimidazole N-oxides that exhibit the functionality of the naturally occurring purines, adenine (2) and guanine (1), in the hope that such materials might interact usefully with biochemical systems. At the end of the chapter the possibility of synthesising nucleoside analogues, by forming sugar derivatives of some selected N-oxides, is also briefly explored.

The main synthetic objective was the preparation of N-oxides with an amino function in the carbocyclic ring. Three approaches were adopted, involving:

- 1) the synthesis of N-oxides containing a nitro group that may be converted into an amino function by reduction,
 - 2) the formation of N-oxides incorporating a substituent that may give an amino group by nucleophilic displacement
- and
- 3) the use of preformed amino or protected amino groups in starting materials.

In each of these approaches, base-induced cyclisation of N-(activated alkyl)-o-nitroanilines was chosen as the method of obtaining the benzimidazole N-oxides. This method has two useful characteristics. Firstly it was indicated to be the most reliable way of obtaining 1-unsubstituted N-oxides, being markedly better in this regard than, for example, partial reduction of o-nitroanilides [cf Chapter 2]. Secondly, such cyclisation affords N-oxides functionalised at position 2, thus allowing important product flexibility, including the possibility of removing the functional group to obtain N-oxides more closely related to the natural purine system.

In addition, the cyanomethylation of o-nitroanilines previously described (Chapter 2) provides an efficient and fairly general way of obtaining the necessary precursors for cyclisation. It is for this reason, together with the known efficiency of cyclisation of N-cyanomethyl-o-nitroaniline (91) that this system was chosen.

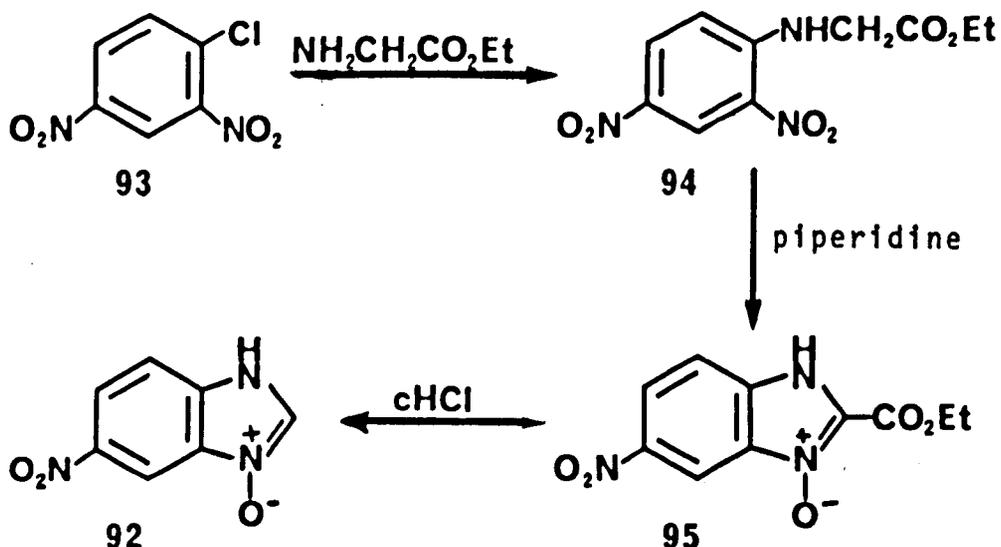


1. Nitrobenzimidazole N-oxides

The synthesis of some nitrobenzimidazole N-oxides has been reported⁷. Almost all of these compounds have the nitro-substituent at position 5 and no corresponding

amino-N-oxides appear to have been synthesised from them.

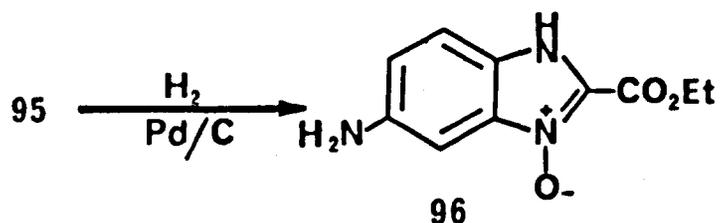
In the current work, 5-nitrobenzimidazole N-oxide (92) was readily obtained in three steps from chloro-2,4-dinitrobenzene (93).



In contrast to previous work⁴⁹, the ester (94) was cyclised by treatment with piperidine, thus permitting a homogeneous reaction. Hydrolysis of the N-oxide ester (95) with concentrated hydrochloric acid furnished (92).

The ester (95) was, however, chosen for reduction for two reasons. First, unlike the N-oxide (92) it was easily dissolved in most solvents commonly used for reduction and second, the ester group offered a good marker for n.m.r. However, although catalytic hydrogenation of (95) went smoothly, isolation of the desired 5-aminobenzimidazole N-oxide (96) proved impossible. The hydrogenation product was not purifiable by recrystallisation from a variety of

solvents. Indeed, although in solid form the product appeared reasonably stable, in solution an instant darkening was noted and evaporation afforded only black tar.

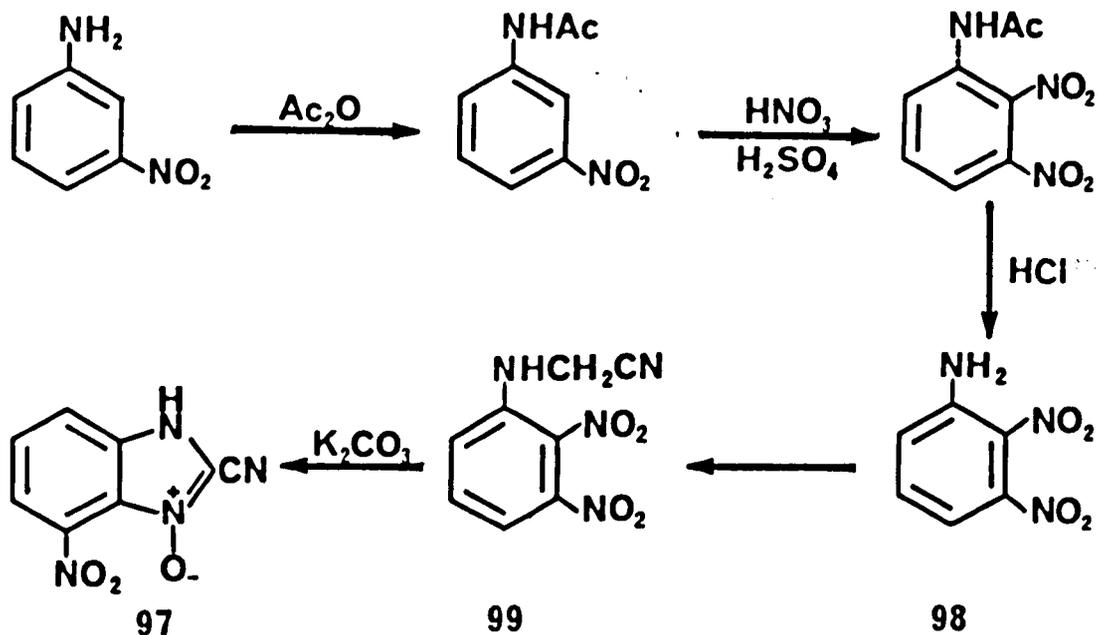


The presence of (96) was indicated spectroscopically but, as expected, micro-analysis of the crude product gave only very poor correspondence with the theoretical composition. Catalytic reduction in the presence of hydrochloric acid yielded only a very hygroscopic material which could not be purified.

In view of the difficulties encountered here, it was decided to form sugar derivatives of the nitro N-oxides before attempting reduction of the nitro function (see p 95).

Attention was now turned to the synthesis of 4-nitrobenzimidazole N-oxides, previously unreported in the literature and potential intermediates en route to adenine analogues. 2-Cyano-4-nitrobenzimidazole N-oxide (97) was prepared in five steps from m-nitroaniline [Scheme 23].

Scheme 23

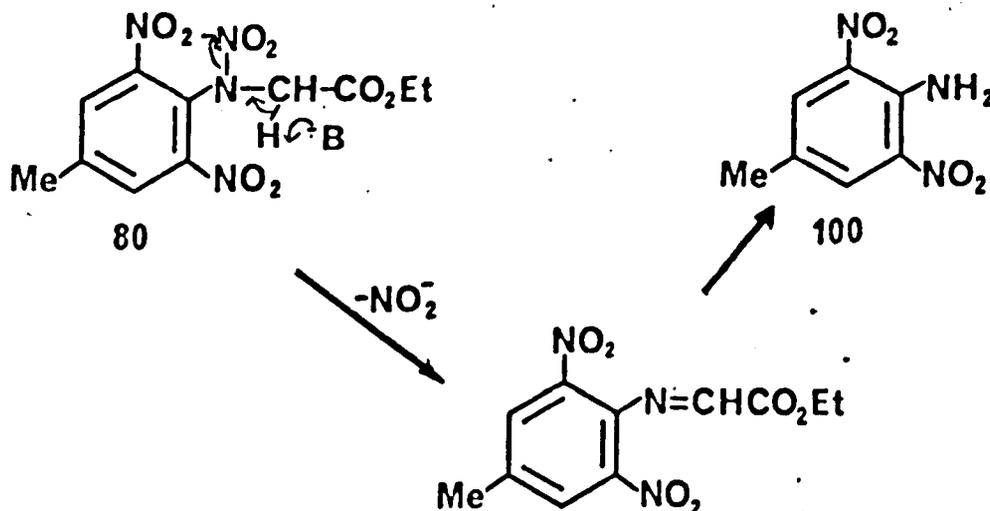


It was found that the cyanomethylation procedure of Dimroth & Aurich⁴⁸ could be extended, with a little modification, to the amine (98). However, cyclisation of the product, N-cyanomethyl-2,3-dinitroaniline (99), gave an unexpectedly low yield (30%) of the N-oxide (97). Indeed, mention has already been made of the ease with which N-cyanomethyl-o-nitroaniline is cyclised, yields of 77³² and 94%³⁰ being reported.

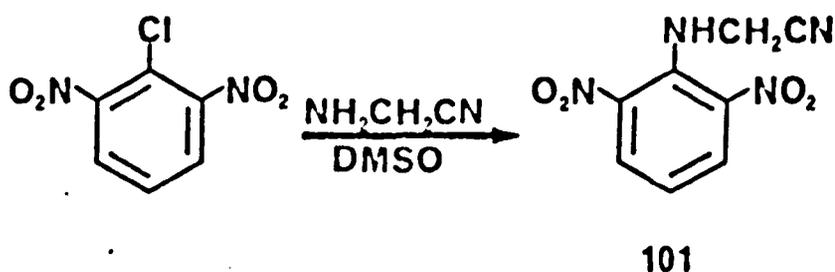
It may be that the extra nitro group twists the 2-nitro function out of the ideal orientation for interaction with the adjacent methylene group. At any rate this result is the first example of substituent effects being important in such base-induced cyclisations. In exploring routes to 7-nitro N-oxides the course of the cyclisation step becomes more unpredictable.

One possible precursor of such compounds had already been

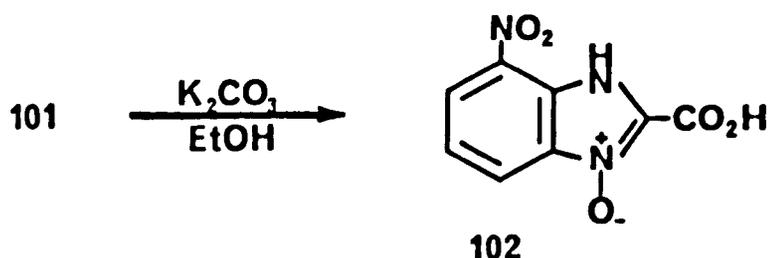
prepared; N-(4-methyl-2,6-dinitrophenyl)-N-nitroglycine ethyl ester (80). However treatment of this compound with base gave 4-methyl-2,6-dinitroaniline (100) in good yield. One possible cause of events is indicated below.



In this series another possible substrate was N-cyano-methyl-2,6-dinitroaniline (101). This could not be prepared by cyanomethylation of 2,6-dinitroaniline, probably due to a combination of steric and electronic factors, but was finally obtained by reaction of chloro-2,6-dinitrobenzene with aminoacetonitrile hydrochloride in the presence of base. It is interesting to note that this reaction failed in ethanol but was successful in dimethyl sulphoxide, although only moderate yields were obtained. The ability of this solvent to promote nucleophilic substitution reactions will be shown to great effect in Chapter 4.



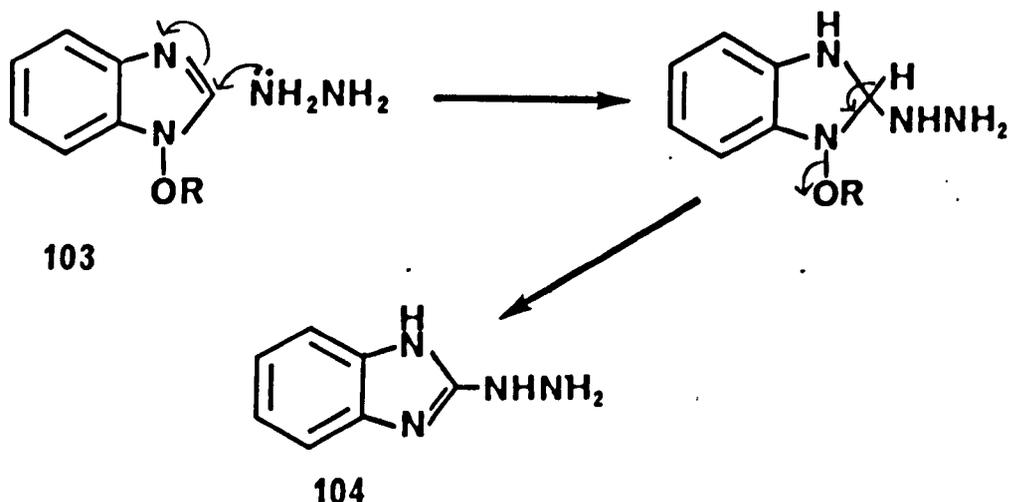
Treatment of compound (101) with base now followed. However, this reaction did not give the expected cyano N-oxide and, instead, (102) was isolated directly from the reaction medium.



Purification of (102) proved extremely difficult and, indeed, it was characterised on spectroscopic evidence alone. In view of this and other problems encountered in the nitro N-oxide series, investigation of this route to amino N-oxides was discontinued.

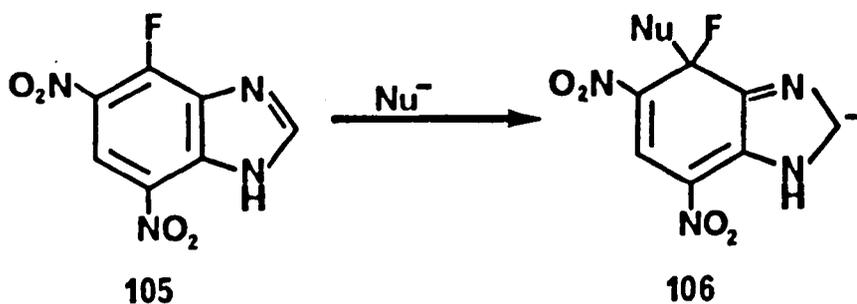
2. Fluorobenzimidazole N-oxides

Simple nucleophilic substitution reactions in the carbocyclic ring of benzimidazole N-oxides are unknown. Most of the addition-elimination reactions undergone involve nucleophilic attack at one position with subsequent elimination from another. An example of this involves the reaction of 1-alkoxybenzimidazoles (103) lacking a 2-substituent with nucleophiles [e.g. hydrazine], to yield the corresponding 2-substituted benzimidazoles (104)¹¹.

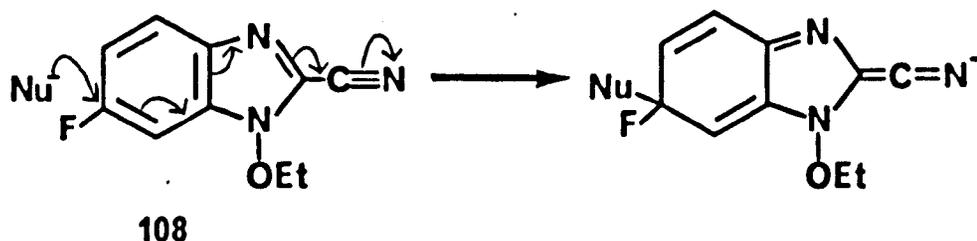
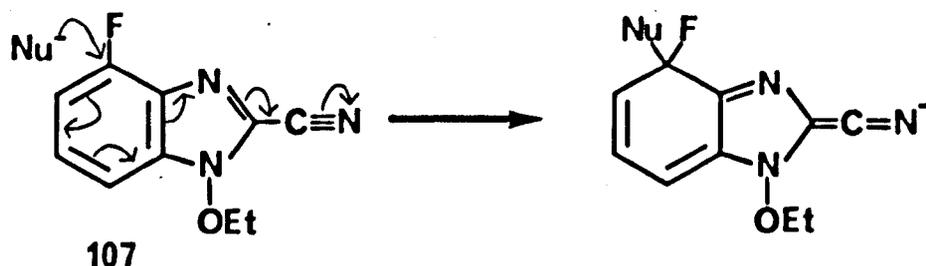


It was thought that if the 2-position were blocked and a sufficiently reactive group present in the carbocyclic ring, 1-alkoxybenzimidazoles might be made to undergo normal nucleophilic substitution reactions.

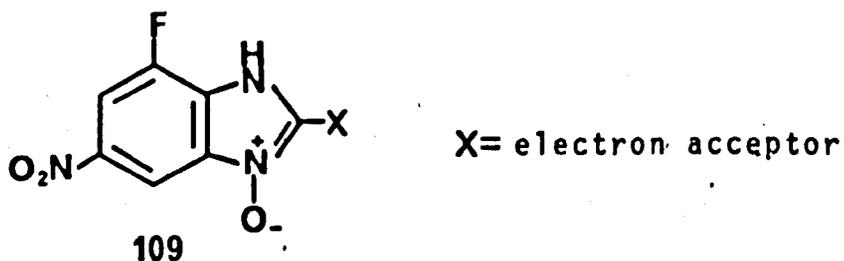
Some support for this idea comes from the nucleophilic substitution reactions of fluorobenzimidazoles. 4-Fluoro-5,7-dinitrobenzimidazole (105) undergoes nucleophilic substitution 84 times faster than fluoro-2,4-dinitrobenzene³. This enhanced rate was thought to be due to activation by the imidazole ring with greater delocalisation of charge being possible in the intermediate anion as indicated by the additional canonical form (106).



Such delocalisation should also be possible in 5 and 7-fluorobenzimidazole N-oxides (107), (108) and may be further enhanced by the presence of an electron acceptor [e.g. CN] in the 2-position.

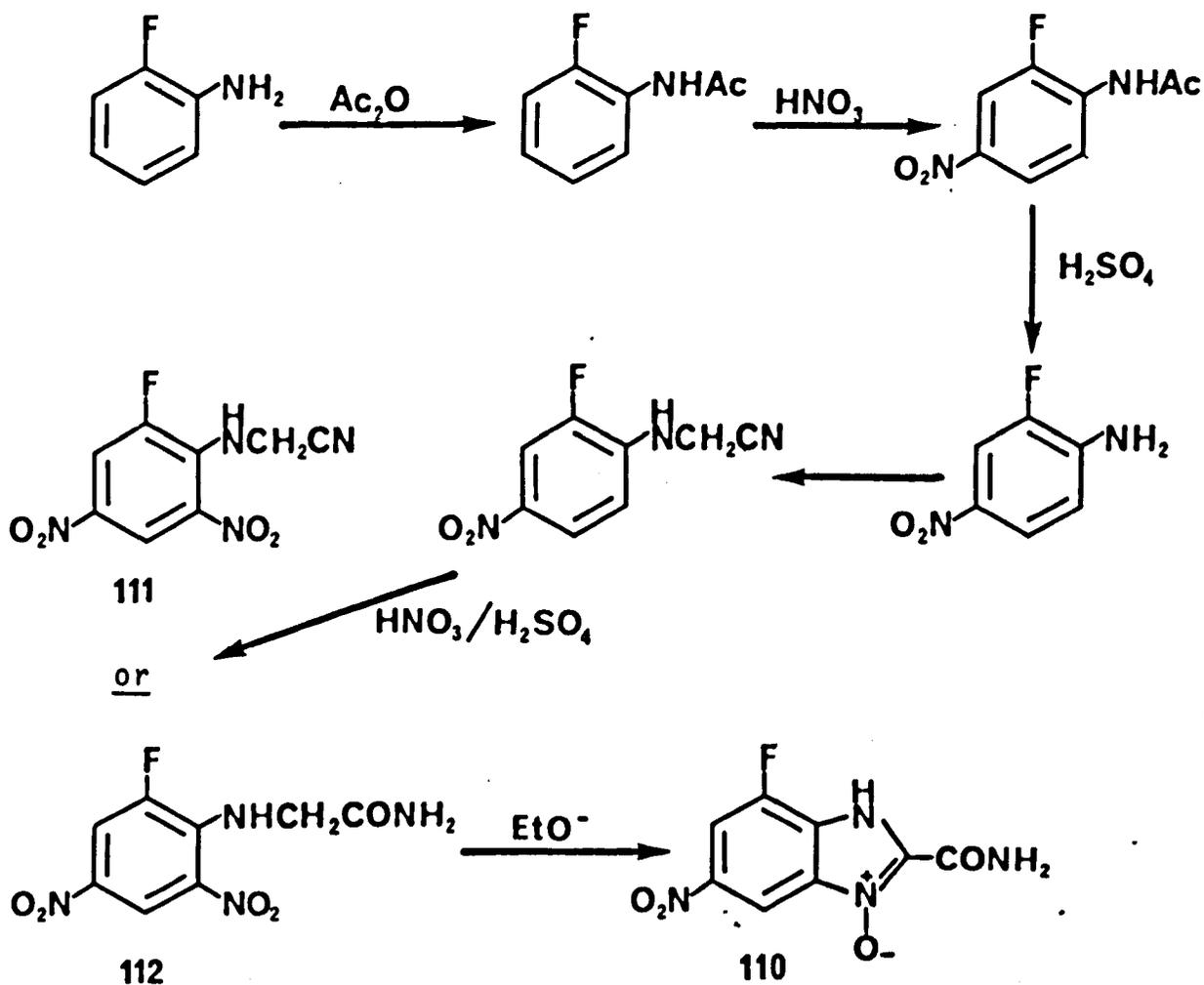


The synthesis of such systems was, therefore, undertaken. A particularly attractive target molecule would be a 5-fluoro-7-nitrobenzimidazole N-oxide (109) since this could provide a route to guanine analogues.



A compound of this type was prepared by a 6-step synthesis from o-fluoroaniline [Scheme 24].

Scheme 24

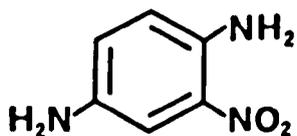


The main problem with this route was an extremely low overall yield ($\sim 2\%$). Several of the steps proceeded in low yield or gave a mixture of products with the final cyclisation giving only a poor accountance of the N-oxide (110). Indeed (110) could not be obtained sufficiently pure for a correct micro-analysis and was characterised by n.m.r. and mass spectrometry alone.

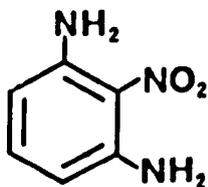
The n.m.r. spectra of some of these compounds will be discussed at the end of this chapter.

3) Routes involving starting materials with preformed amino groups

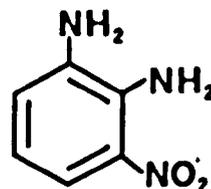
The synthesis of N-oxides with preformed amino or protected amino functions has none of the problems associated with the previous two approaches. However, these are replaced by different problems and the results obtained were found to be highly dependent on the starting material used. For this reason the following discussion will be divided according to the particular nitro-diamine used, viz. (116), (117), (118).



116



117



118

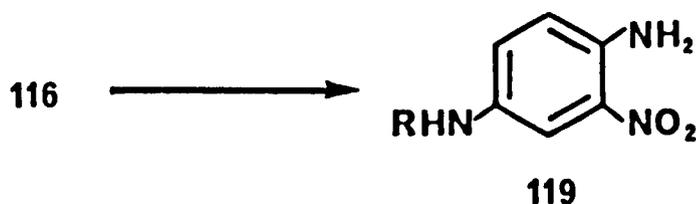
a) 2-nitro-1,4-phenylenediamine (116)

This amine, a potential precursor of a guanine analogue, is readily available, unlike the other two starting materials. However, the formation of an aminobenzimidazole N-oxide still requires the solution of two synthetic problems: first, the building of a reactive methylene group on the amino-group ortho to the nitro function and, second, the efficient cyclisation of the material thus obtained to give stable products.

For reasons already given, cyanomethylation was the preferred method of obtaining the required N-(activated alkyl)-o-nitroanilines. However, protection of the more nucleophilic amino group, meta to the nitro function, is first necessary. This allows cyanomethylation to take place at the appropriate site and, ultimately, should permit the isolation of stable N-oxides. The last point is important since previous work (p 70) indicated that free amino N-oxides might be difficult to handle.

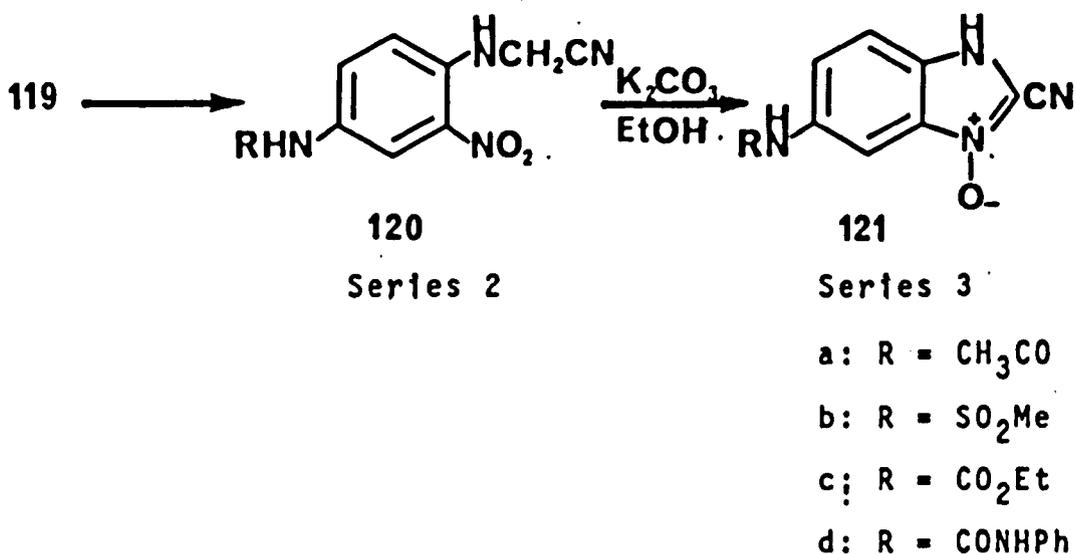
The choice of a protecting group was governed by several considerations. It must be readily formed and stable both to the acidic conditions of the cyanomethylation procedure and the basic conditions of the cyclisation step. In addition it may be important that it be removable at some appropriate stage. Therefore, a range of protecting groups was chosen. [Series 1].

Series 1



- R = CH₃CO (119a)
- = SO₂Me (119b)
- = CO₂Et (119c)
- = CONHPh (119d)

Compounds (119a-c) were all known materials and for the most part were made by the literature procedures⁵⁴, except for the case of the sulphonamide (119b) where a more efficient method was used. The urea (119d) was easily prepared from the amine by treatment with phenyl isocyanate. Cyanomethylation of these protected amino-compounds and subsequent cyclisation now proceeded easily and in high yield to give compounds of series 2 and 3 respectively.

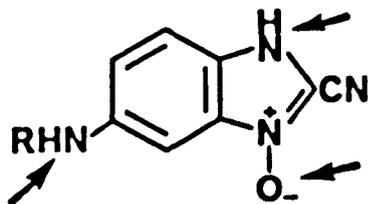


In all cases the protecting group remained intact, although purification problems were encountered for the N-oxide (121d). It would appear that during recrystallisation the protecting group was lost, to produce an unstable free amino N-oxide. This compound was, therefore, not investigated further, although the ready loss of its protecting group may be of use in future work.

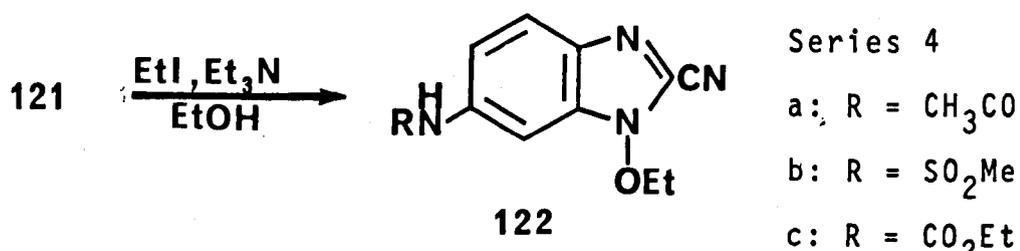
Clearly, this route to guanine analogues is much more

satisfactory than those previously employed, since it involves only three, high-yield steps from a readily available starting material and gives stable products.

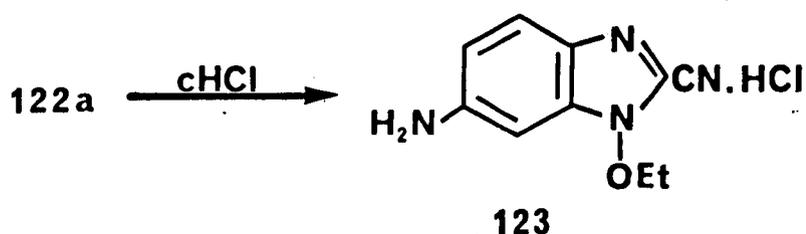
The synthesis of these materials opens up several interesting possibilities, including the preparation of nucleoside analogues and development of a route to tricyclic systems, the latter to be discussed in Chapter 4. However, before any of this work could be undertaken, one point had to be established: the site of alkylation in these systems. In theory, three possibilities existed.



Almost all previous work⁷ indicated that attack at the 1-position was unlikely but the presence of another reactive site might have been a complicating factor. In the event, spectroscopic evidence showed that the N-oxides (121a) to (121c) were each alkylated smoothly on oxygen, to give the corresponding 1-alkoxybenzimidazoles (122) [Series 4].



The acetanilide (122a) was now chosen for deprotection and this was achieved by action of concentrated hydrochloric acid to yield the hydrochloride (123).



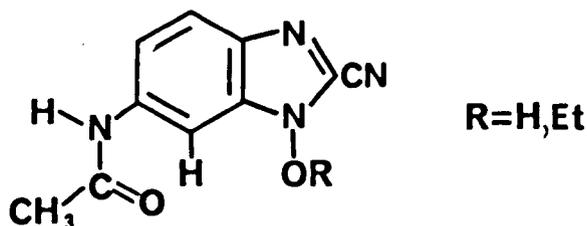
N.m.r. indicated that the reaction had gone cleanly, but, unfortunately, the product could not be obtained in pure enough form for micro-analysis and was characterised on spectroscopic evidence alone. However, this material was considerably easier to handle than the 5-amino N-oxide (96) mentioned previously and this indicated that deprotection of analogous sugar derivatives may yield fairly stable products.

Finally, it is interesting to compare the n.m.r. spectra of the compounds of series 2, 3 and 4, with regard to the chemical shifts of the aromatic protons. [Table 2].

Within each series the chemical shifts of protons (i) and (ii) were almost unaffected by the nature of the protecting group R. In the case of proton (iii) however, variation in R had a marked affect. This was most

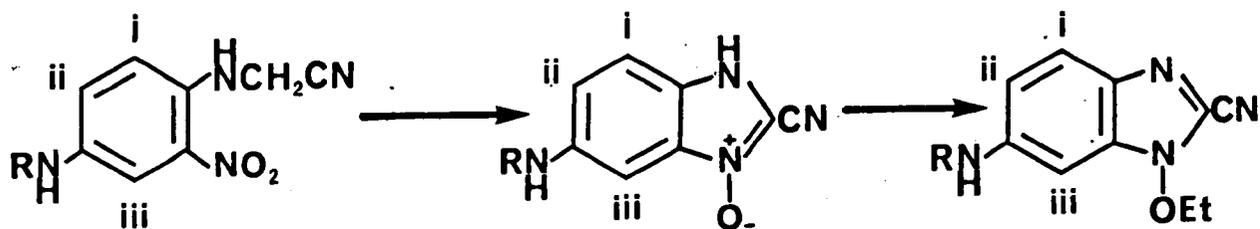
striking with the N-oxides of series 3, where a deshielding of 0.83 ppm was noted on going from the sulphonamide (b) to the acetanilide (a), with a corresponding difference of 0.57 in series 4.

One possible explanation for this is that the planar acetyl group adopts the conformation shown,



Whether or not there is any H-bonding between proton (iii) and the carbonyl, this proton could still fall in the C=O deshielding zone.

In the case of the tetrahedral sulphonyl group no such interaction can take place and, consequently, the chemical shift values of protons (ii) and (iii) are very similar. It was also interesting to note that the carbamates, (121c), (122c) had intermediate chemical shift values for proton (ii), where it would appear that interaction between the ester group and this proton is less favoured. The significance of these findings will be apparent in the nitration study discussed in Chapter 4.



Series 2

(120a)

(120b)

(120c)

a: R = CH₃CO

Series 3

(121a)

(121b)

(121c)

b: R = SO₂Me

Series 4

(122a)

(122b)

(122c)

c: R = CO₂Et

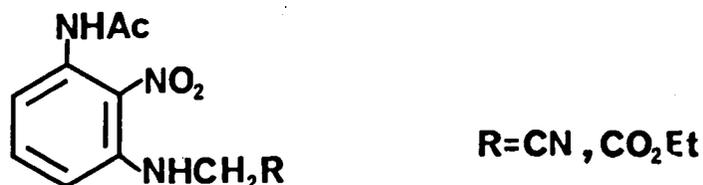
Table 2

¹H n.m.r. spectra of compounds of series 2, 3 and 4 in d₆-DMSO (Chemical shifts in p.p.m., J in Hz)

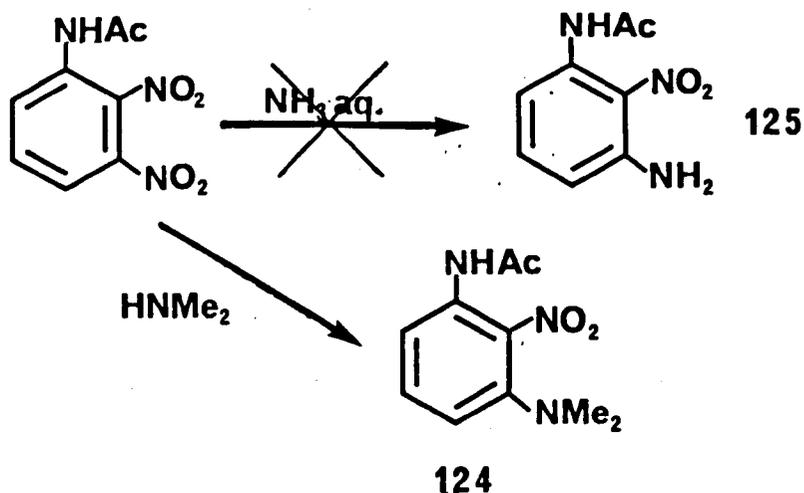
| | (i) | (ii) | (iii) | J _{i,ii} | J _{ii,iii} | J _{i,iii} |
|--------|------|------|-------|-------------------|---------------------|--------------------|
| (120a) | 7.30 | 7.95 | 8.70 | 9.2 | 2.8 | |
| (120b) | 7.35 | 7.75 | 8.20 | 9.2 | 2.8 | |
| (120c) | 7.30 | 7.90 | 8.60 | 9.8 | 2.6 | |
| (121a) | 7.91 | 7.53 | 8.48 | 9.0 | 2.0 | |
| (121b) | 7.95 | 7.45 | 7.65 | 9.2 | 2.0 | |
| (121c) | 7.85 | 7.53 | 8.12 | 9.2 | 2.0 | |
| (122a) | 7.72 | 7.40 | 8.22 | 8.8 | 2.0 | 0.4 |
| (122b) | 7.95 | 7.45 | 7.65 | 8.8 | 2.0 | |
| (122c) | 7.70 | 7.37 | 7.95 | 8.2 | 2.0 | |

b) 2-nitro-1,3-phenylenediamine (117)

Unlike the previous amine (117) was not commercially available and had been reported only once before⁵⁵. However, some previous work⁵⁶ suggested that it might be possible to bypass this amine and obtain compounds of the type shown below.



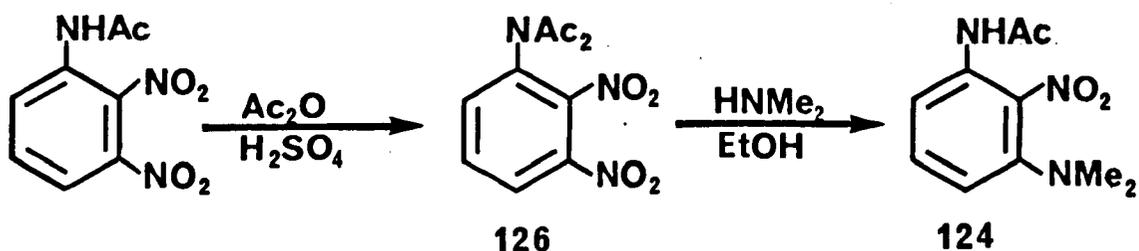
This is due to the finding that 2,3-dinitroacetanilide gave, on treatment with dimethylamine, 3-dimethylamino-2-nitroacetanilide (124). It was also noted that reaction with ammonia solution failed to give the corresponding primary amine (125).



In the current work 2,3-dinitroacetanilide failed to react with reagents such as aminoacetonitrile and glycine ethyl ester, the starting amide being recovered in each

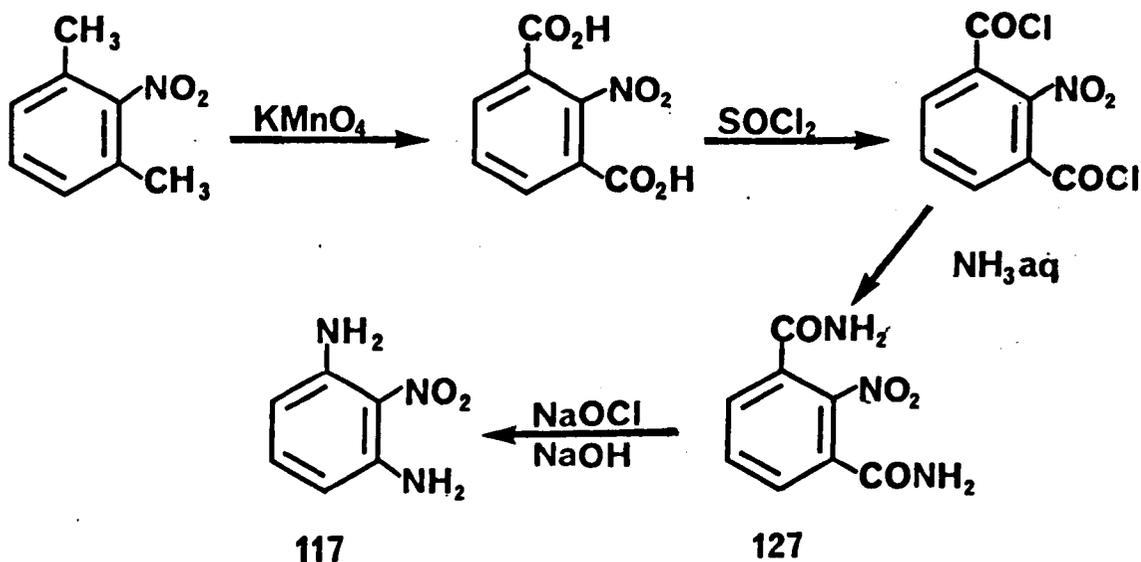
case.

It was thought that N,N-diacetyl-2,3-dinitroaniline (126) might prove a more reactive system to nucleophilic substitution and (126) was found to be readily prepared from 2,3-dinitroacetanilide by treatment with acetic anhydride in the presence of sulphuric acid.

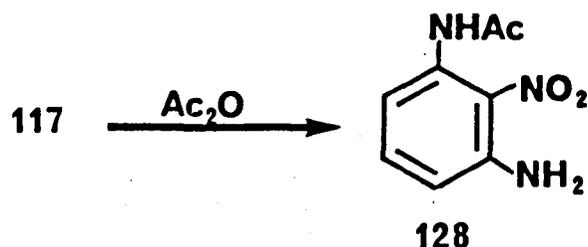


However, reaction of (126) with dimethylamine gave the same product (124) as that obtained from the monoacetyl compound but in reduced yield. This route was, therefore, not explored further.

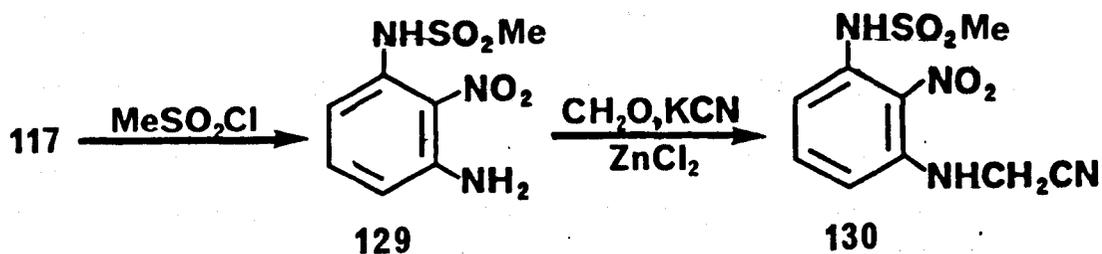
Since no short cuts seemed possible the diamine (117) itself was now prepared, in 4 steps from 2-nitro-m-xylene, essentially by the literature method [Scheme 25].⁵⁵



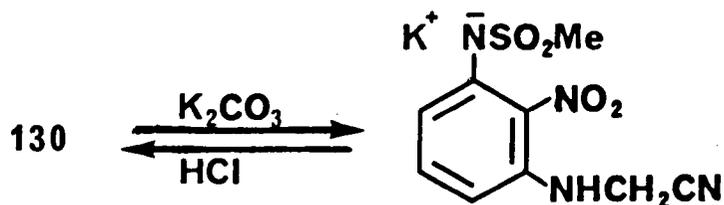
The next step was protection of one of the amino-groups. Unlike 2-nitro-1,4-phenylenediamine (116) however, this amine has two equally reactive amino-groups and mono-protection was therefore less straightforward. Indeed, although 3-amino-2-nitroacetanilide (128) had previously been obtained by mono-acetylation of the diamine (117) only a very small scale reaction was carried out and purification by chromatography was necessary⁵⁵.



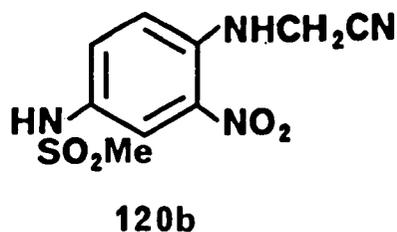
It was thought that mono-mesylation might prove easier and, in fact, the sulphonamide (129) was obtained in fairly good yield even with an excess of methane sulphonyl chloride. Subsequent cyanomethylation was then straightforward to give (130).



However, somewhat surprisingly, attempted cyclisation of (130) failed to yield the desired N-oxide; with starting material being recovered on work-up. The probable course of events merely involves deprotonation of (130) and subsequent reprotonation on treatment with acid.

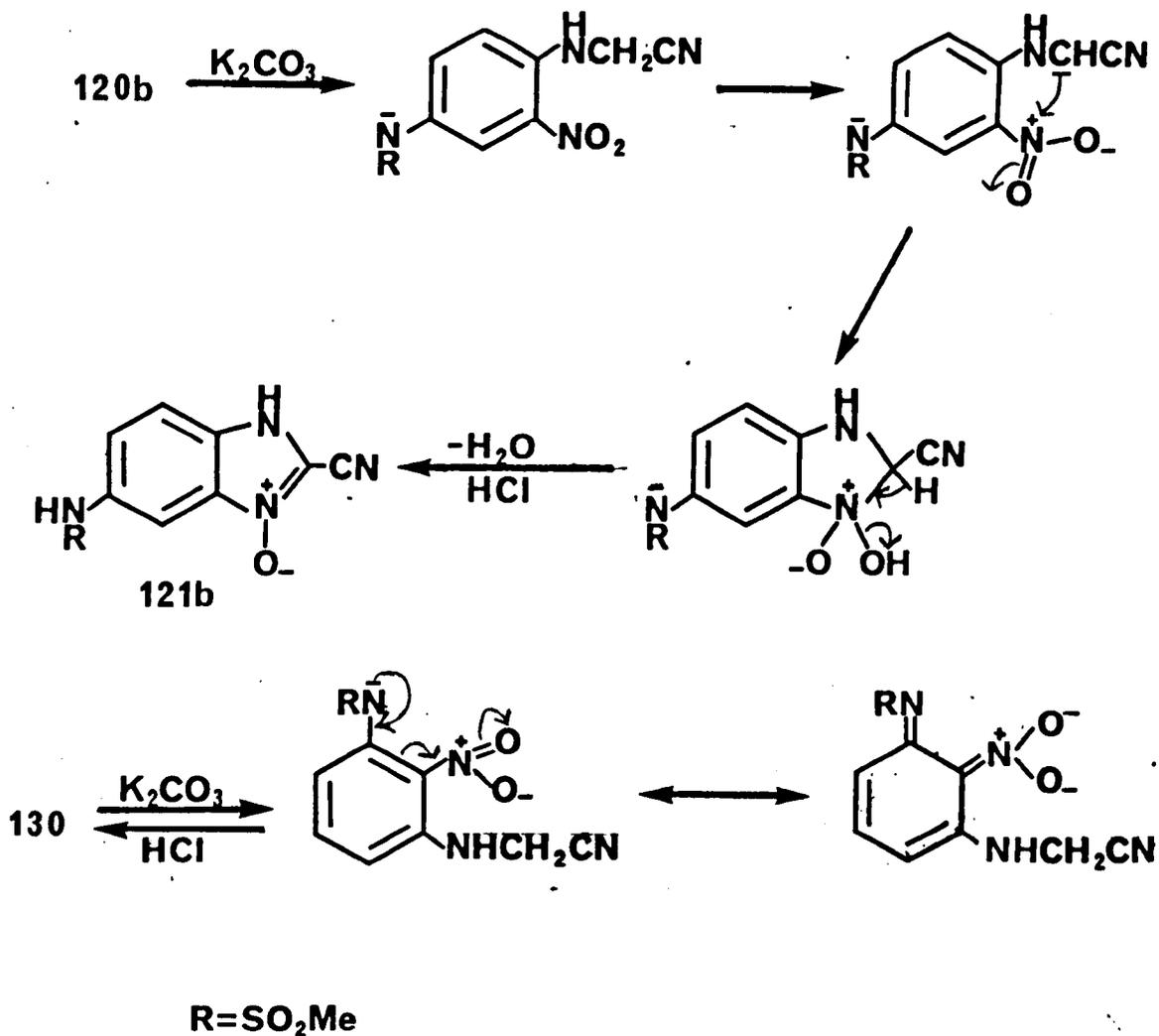


This is a particularly interesting result in view of the ready cyclisation of the isomeric sulphonamide (120b) under the same conditions.



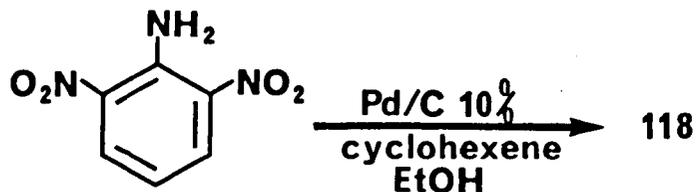
Although the sulphonamide group is clearly more acidic in (130) than in (120b) owing to conjugation of the former with the nitro group, in both cases the mesyl NH is the most acidic proton in the molecule. It would appear, therefore, that the important factor is not this deprotonation per se but subsequent delocalisation of electrons into the nitro-group. Where this can occur, the nitro-group is deactivated to nucleophilic attack from the reactive methylene centre and the cyclisation process is blocked. (Scheme 26).

Scheme 26



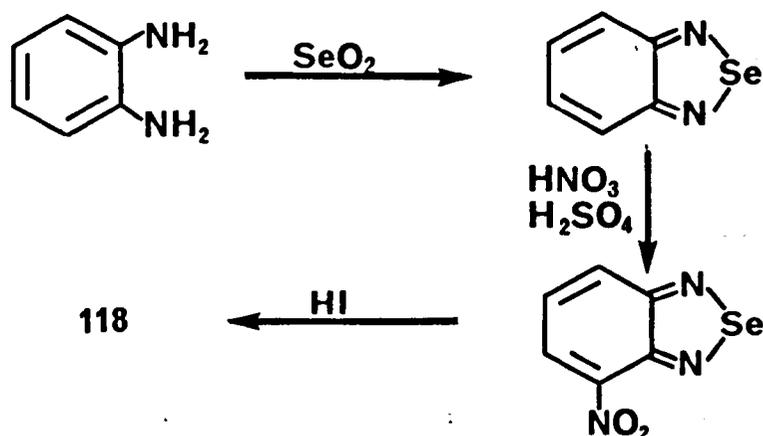
c) 3-nitro-1,2-phenylenediamine (118)

This compound, like the previous amine, is not readily available, although several methods for its preparation appear in the literature. The most recent is by selective reduction of 2,6-dinitroaniline⁵⁷.

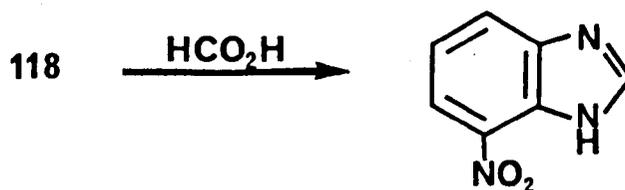


However, although this reaction worked fairly well the starting material was itself not readily accessible. An older method⁵⁸ involved a 3-step synthesis from o-phenylenediamine and this was successful in providing useful quantities of the diamine (118) [Scheme 27].

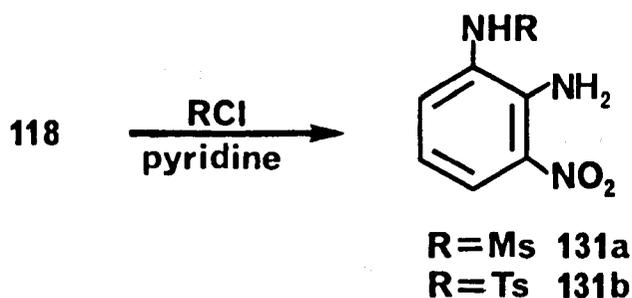
Scheme 27



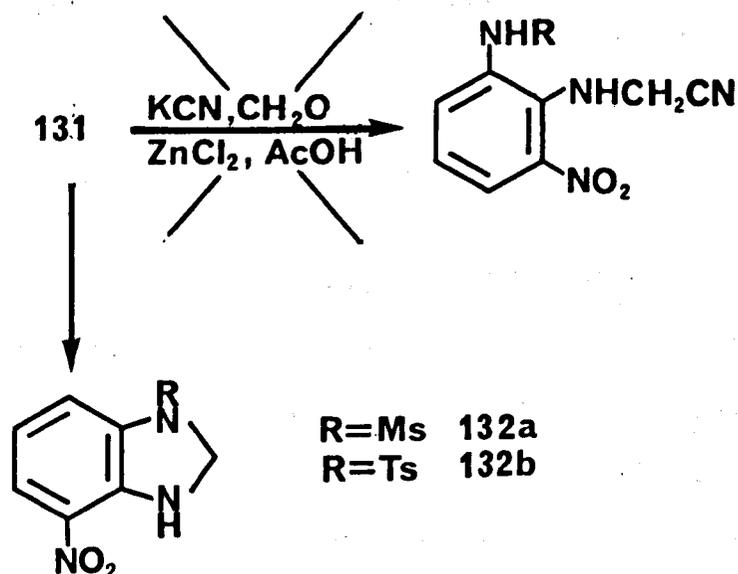
Selective protection of the amino-group meta to the nitro function should be straightforward in view of its greater nucleophilicity. However, the particular choice of protecting group is much more important here than in the previous two cases, due to the proximity of the amino groups. For example, attempts to acetylate the diamine (118) would almost certainly produce the corresponding benzimidazole. Indeed, 4-nitrobenzimidazole has been prepared by treatment of the diamine with formic acid⁵⁹.



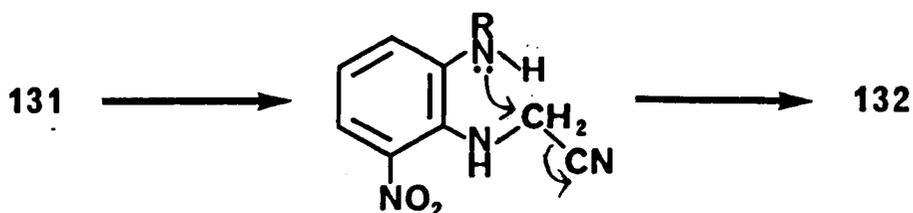
Therefore, mesyl and tosyl were chosen as protecting groups, and preparation of the sulphonamides (131a) and (131b) proved straightforward.



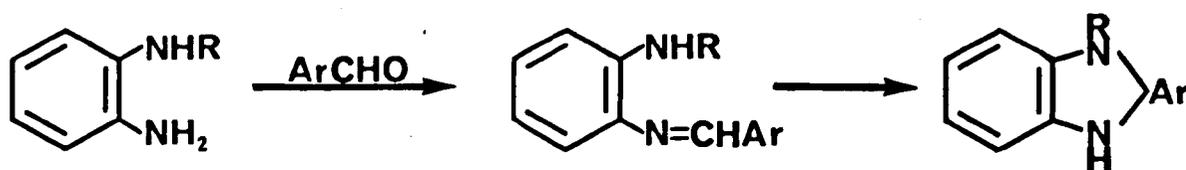
Cyanomethylation of these compounds did not however, proceed normally. Instead the dihydrobenzimidazoles (132a) and (132b) were obtained in good yield.



One possible course of events is that cyanomethylation first occurs and a nucleophilic displacement of cyanide then takes place, involving the adjacent sulphonamido group.

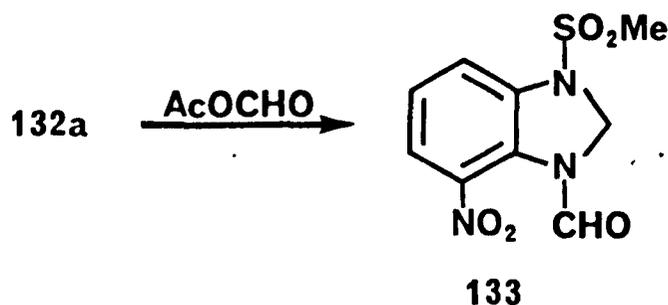


Some dihydrobenzimidazoles with one nitrogen substituted have been reported⁶⁰ but with one exception⁶¹ an aryl group is also present in the 2-position. The reason for this is that their preparation almost always involves reaction of an o-phenylenediamine with an aromatic aldehyde, the product being formed via a Schiff base intermediate.



In the current work, reaction was found to fail in the absence of potassium cyanide, thus showing that the presence of formaldehyde alone, in the cyanomethylation mixture could not give dihydrobenzimidazoles. It would appear, therefore, that this reaction represents a new method of obtaining such compounds. However, it must be

said that the nitro group probably gives added stability to this system and further work is necessary to determine the scope of this reaction. It was noted that the preparation of 1,3-unsymmetrically substituted dihydrobenzimidazoles should be possible from either (132a) or (132b). Indeed (132a) could be formylated to give (133) although acetic formic anhydride was necessary to effect this reaction.

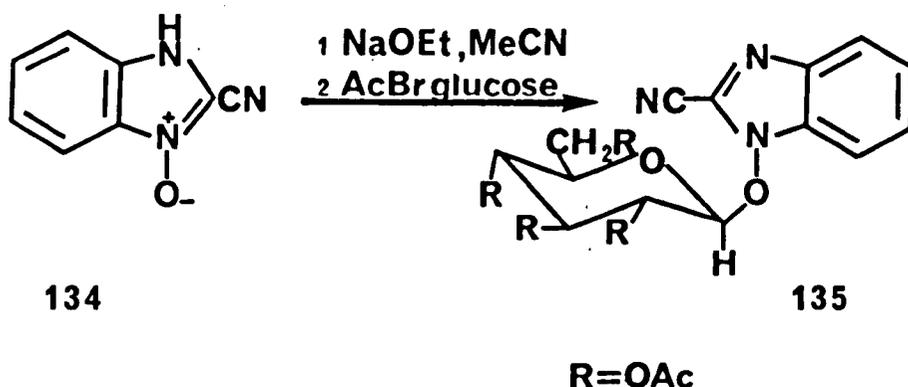


Nucleoside analogues

Now that some benzimidazole N-oxides had been synthesised that possessed, potentially at least, some similarity to the naturally occurring purines, the formation of some sugar derivatives of these N-oxides was briefly undertaken.

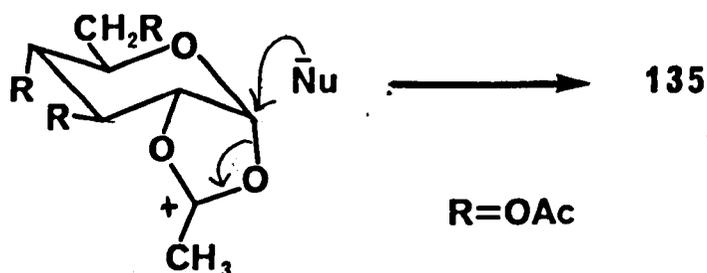
In a study concerned with the formation of nucleoside analogues from a variety of heterocyclic N-hydroxy compounds,⁶² the reaction of 2-cyanobenzimidazole N-oxide (134) with acetobromoglucose* has been reported to give the β -glucoside (135).

*Acetobromoglucose = 2,3,4,6-tetra-O-acetyl- α -D-glucopyranosyl bromide

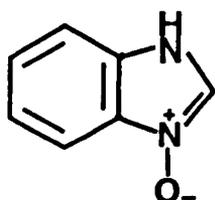


Although detailed spectroscopic data were not given, reaction at the N-oxide oxygen is to be expected from both the present and previous work. Formation of a β linkage is also predictable from the rules governing such reactions - substitution proceeds via an S_N1 mechanism and the carbocation initially generated is stabilised by neighbouring group participation involving the 2-acetoxy group, thus permitting the incoming nucleophile to attack from the opposite side only. The product, therefore, has a 1,2 trans (β) configuration (fig 6).

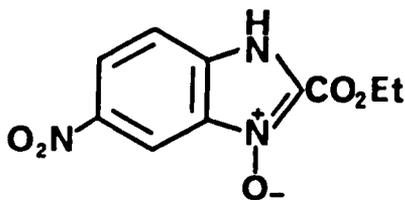
Figure 6



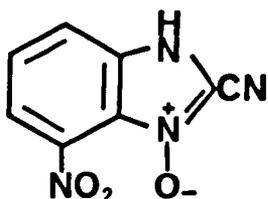
In the current work the following four benzimidazole N-oxides were chosen.



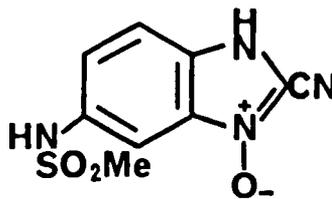
134



92



97



121b

With particular regard to compounds (97) and (121b) it can be seen that the site of reaction with α -acetobromoglucose may not be the N-oxide oxygen. For (97) it could be hoped that both steric and/or electronic interaction between the N-oxide and nitro function might promote attack at position 1, thus affording N-nucleoside analogues. In the case of (121b) it was conceivable that some deprotonation of the sulphonamido group could give another type of N-nucleoside, particularly if a strong base were employed (such as sodium ethoxide, used in the published work). It was for this reason that triethylamine was used in the alkylation of (121b) (p 82).

With these points in mind it was necessary to determine the stereo- and regio-chemistry of any reaction taking

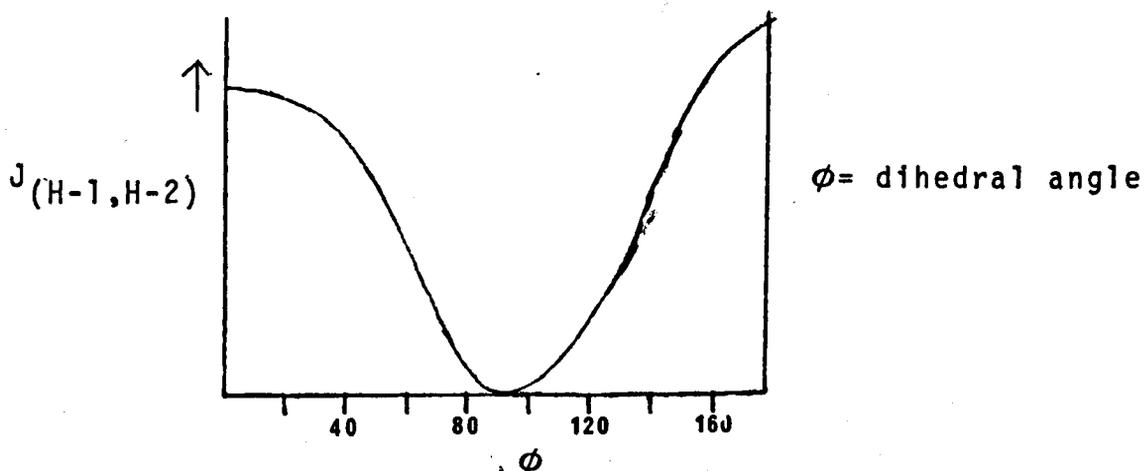
place between the sugar derivative and the N-oxides.

This involved establishing:

- 1) the site of glucosidation - whether an N-O-sugar or an N-sugar bond had been formed and
- 2) the orientation (α or β) at the anomeric centre.

^1H n.m.r. seemed the ideal tool for this task for two reasons. First, the chemical shift of a proton on the carbon of an N-C bond will be different from one on an O-C bond. Second, the coupling constant for the anomeric proton with proton 2 is dependent on the dihedral angle between them. A pictorial representation of the dependence of coupling constants between vicinal protons on their relative orientation is given in fig 7.

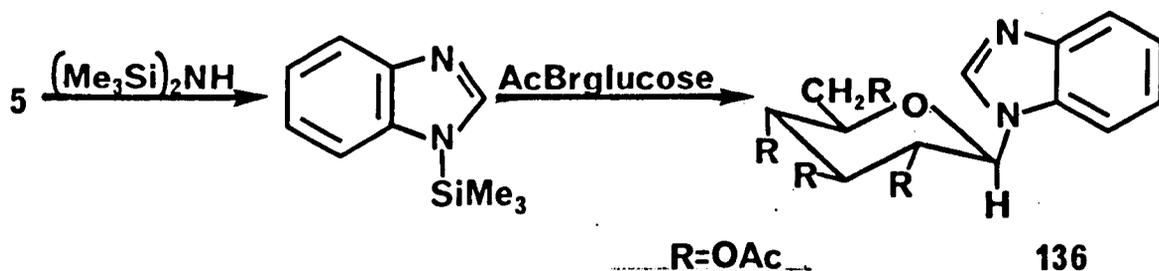
Figure 7



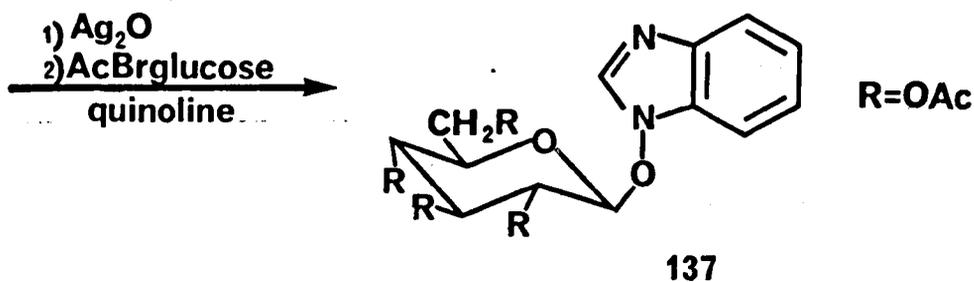
With α -sugars (1e, 2a-cis protons) the dihedral angle (ϕ)

is about 60° and relatively small coupling constants are observed (typically 2-5 Hz). For β sugars (1a, 2a trans-diaxial protons), ϕ is about 180° and relatively large coupling constants are seen (typically 7-10 Hz)⁶³.

For purposes of comparison it was appropriate to synthesise the closely related nucleoside analogue, N-(Tetra-O-acetyl- β -D-glucopyranosyl)benzimidazole (136). Of particular interest is the chemical shift of the anomeric proton in this material since this should give an indication of what to expect in an N-glucoside. (136) was prepared in two steps by the published method⁶⁴; the anomeric proton had a chemical shift 6.4 ppm and a coupling constant of 9 Hz.

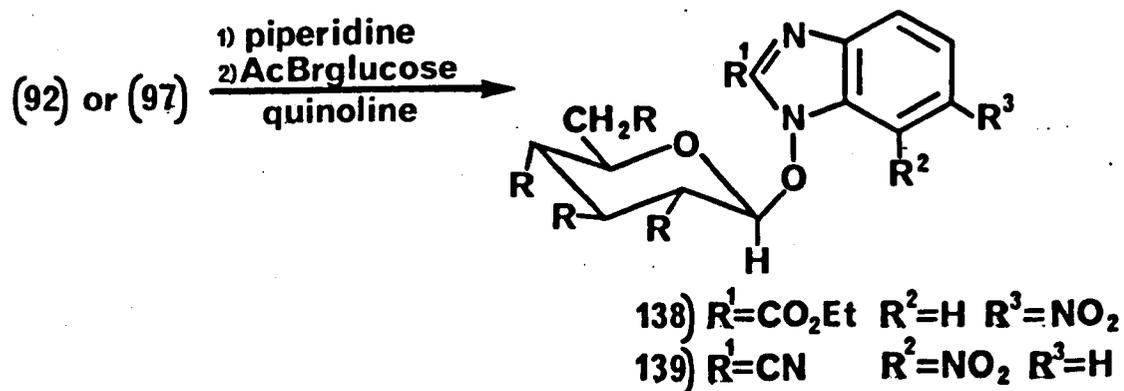


Benzimidazole N-oxide was now allowed to react with aceto-bromoglucose essentially under the conditions used by Robertson and Waters for the preparation of β -phenylglucosides⁶⁵.



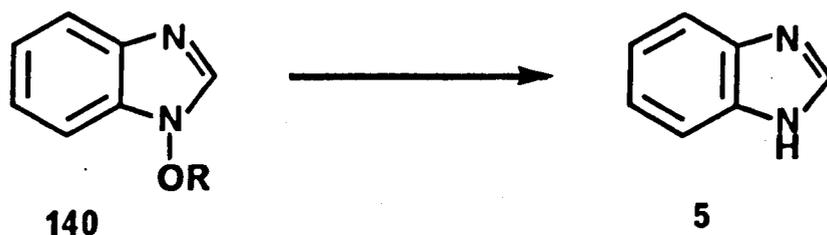
The product (137) was assigned as a β -O-glucoside from the chemical shift and coupling constant of the anomeric proton (5.95 ppm and 9 Hz, respectively). It is interesting to note the upfield shift of the anomeric proton in (137) compared to that in the N-nucleoside analogue (136).

The nitro N-oxides (92) and (97) were now allowed to react with acetobromoglucose. However, instead of employing silver oxide to activate the heterocyclic system (by removing the N-oxide proton), piperidine was used, since it had already been shown to deprotonate the N-oxide (97). This had the dual advantage of using a much cheaper reagent and simplifying work-up procedures. In both cases the corresponding N-O-sugar was formed, with a β configuration.

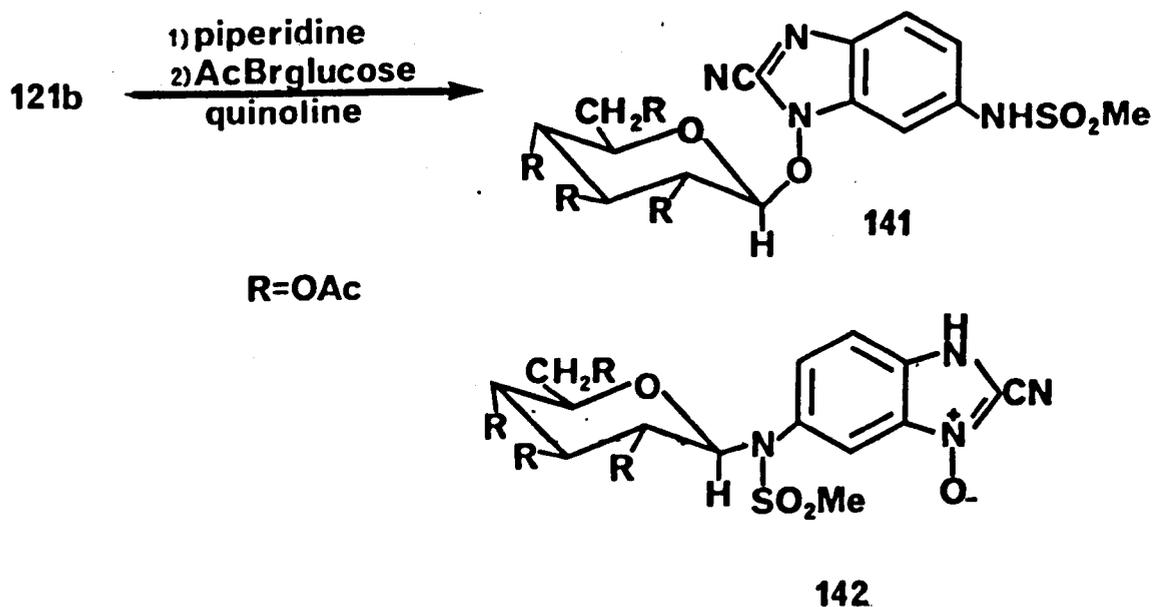


Attempts at selective reduction of the nitro group in either of the glucosides [(138) and (139)] were completely unsuccessful with complex mixtures (by T.L.C.) being obtained. This is perhaps predictable in view of the ready hydrogenolysis of 1-alkoxybenzimidazoles to give the

corresponding benzimidazoles⁶⁶.



Attention was now turned to the reaction of the sulphon-amido N-oxide (121b) with acetobromoglucose. Once again the isolated product was the corresponding O-glucoside (141). However, the presence of M^+ and $(M-16)^+$ peaks in the mass spectrum of some slightly impure product indicated that some N-glucosidation might also have taken place, to give, probably, (142). All traces of this material were lost on recrystallisation.



The structure (141) was confirmed by high-field (360 MHz) n.m.r. with, in particular, selective decoupling experi-

ments allowing the assignment of all the sugar protons (fig 8a and 8b). There are several points of interest here. First, the chemical shift and coupling constant of H-1 is what one would expect for an N-O-sugar with a β -configuration. Second, protons 2¹, 3¹ and 4¹ appear as triplets since all the coupling constants are the same (as to be expected from the trans diaxial relationship of adjacent protons on the pyranose ring). Thirdly, the CH₂ group appears as a complex multiplet rather than a simple doublet since it is adjacent to a chiral centre and the methylene protons are therefore non-equivalent.

The work described in this chapter shows clearly the importance of substituent effects in devising routes to benzimidazole analogues of the naturally occurring purines. The 5-protected amino N-oxides are readily prepared by a standard cyclisation whereas the corresponding 4-substituted N-oxides cannot be obtained in this way (p. 88). In the 7-substituted N-oxide series major problems arise, both in the preparation of suitable substrates for cyclisation and in the cyclisation step itself. Routes to 6-amino N-oxides have not yet been explored but it is likely that these will involve similar problems to those encountered in the 4-amino series.

In addition, N-nucleoside analogues (1-glycosylbenzimidazole 3-oxides) appear not to be accessible by direct glycosylation of N-oxides although the O-glycosides

Fig 8a

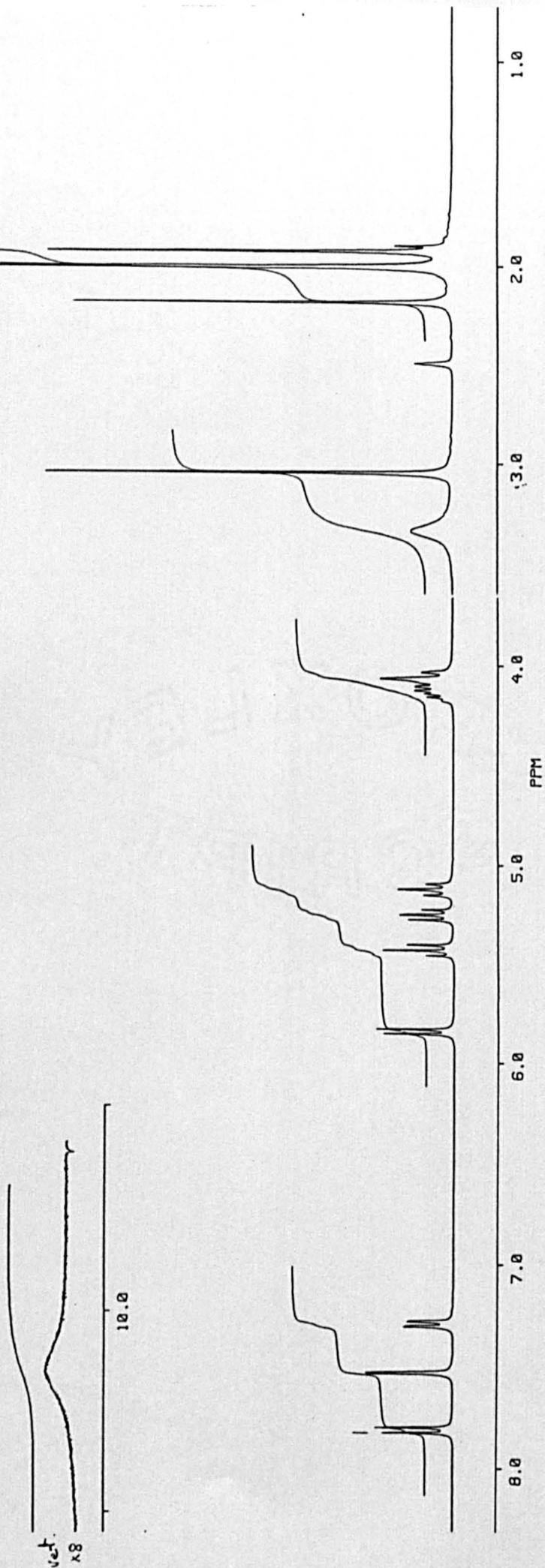
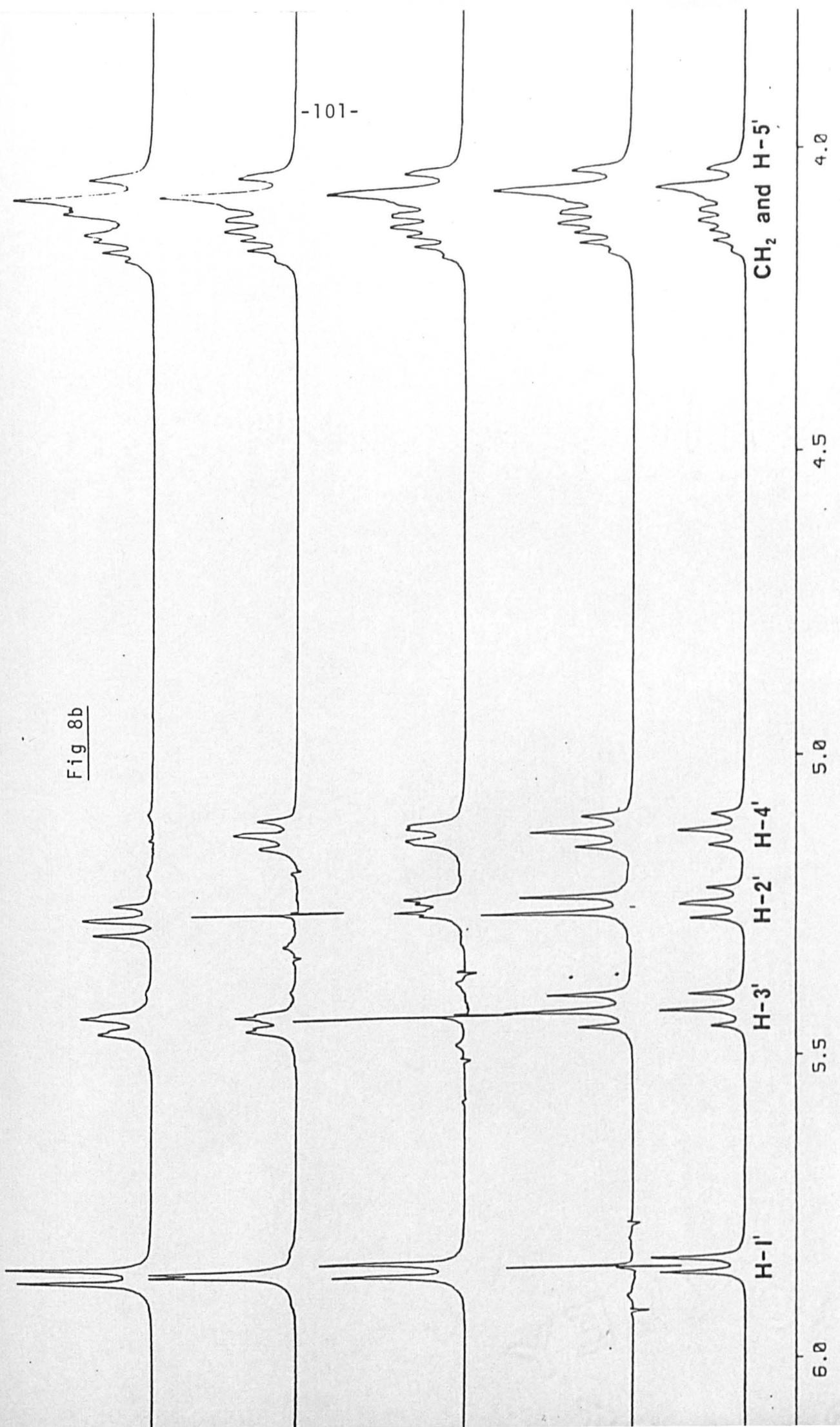


Fig 8b

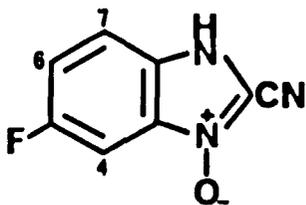


produced may well be of interest in their own right by enhancing the solubility of N-oxides in biological systems. The N-nucleoside analogues could possibly be obtained, however, by cyclisation of an appropriate glycosylated o-nitroaniline and this is under investigation by another member of the research group. Many of the materials prepared in this chapter have been submitted for biological screening and the results obtained should point the way for further research.

N.m.r. Spectra of the 2 and 4-Fluoronitroaniline derivatives

1. 4-Fluoro

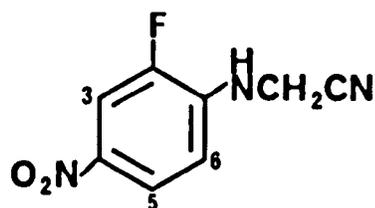
The compounds synthesised in this series gave straightforward spectra and the only point of interest was the variability of ortho H-F couplings within the same molecule. For compound (113), for example, $J_{F,H-4}=8.4$ Hz and $J_{F,H-6}=9.8$ Hz. As a consequence of this such systems generated 8-line fluorine spectra.



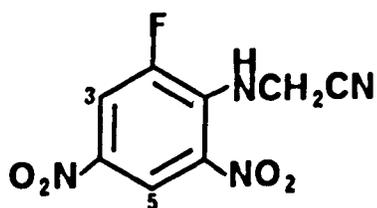
113

2. 2-Fluoro

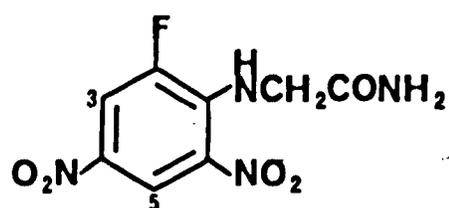
In this series the spectra produced were much more complex and it is appropriate to consider each of the following materials in turn:



143



111



112

a) (143). (Fig 9a, b, c)

Neither the proton (fig 9a) nor fluorine (fig 9b) spectrum is first order, but it is evident that the fluorine is coupled to four protons (H-3, H-5, H-6 and N-H) generating a 16 line ^{19}F spectrum. Computer simulation of these ABCDX spectra using an iterative procedure provided an excellent fit with the observed spectra (fig 9c), and generated the following coupling constants (in Hz):

$$J_{6,5}=8.97; J_{6,3}=0.08; J_{6,F}=8.74; J_{5,3}=2.50;$$

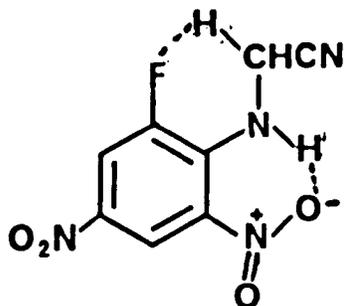
$$J_{5,F}=-1.03; J_{3,F}=11.67; J_{\text{NH},F}=2.00.$$

Of particular interest is the negative value of the coupling constant between fluorine and the para proton. Input of the corresponding positive value for $J_{F,5}$ to the program gave a much poorer fit with the experimentally measured spectra.

b) (111). (Fig 10a, b)

With this compound one would expect straightforward ^{19}F (8 line) and proton spectra, with the latter comprising two double doublets (aromatic protons), a CH_2 doublet and an N-H triplet. In fact an approximately 12 line fluorine spectrum is observed (fig 10a) and comparison with the ^1H spectrum (fig 10b) indicates that the CH_2 doublet in the latter arises as a result of coupling with fluorine and not the adjacent N-H. ($J_{\text{F},\text{H}-5}=14$ Hz, $J_{\text{F},\text{CH}_2}=5.6$ Hz, $J_{\text{F},\text{H}-3}=1.4$ Hz).

One explanation for this is a 'through space' interaction between the fluorine and CH_2 group, possibly via the hydrogen bonded system shown.



Indeed such 'through space' coupling has been noted in polyfluoro aromatic compounds containing a side chain of the type $-\text{XCH}_3$ ($\text{X}=\text{e.g. O, N, S}$)⁶⁷. Of particular interest is that the strongest F,CH_2 couplings were obtained when an ortho nitro group was also present. A similar explanation to that given here for this effect was offered.

Comparison with (143) shows that in the current system an ortho nitro group is essential for this 'through space' coupling to occur. Presumably, the adjacent nitro group holds the N-cyanomethyl function in the correct orientation by a combination of steric and electronic effects.

c) (112). (Fig 11a, b, c)

In this system the same type of interaction is displayed but the spectra are further complicated by the presence of NH-CH₂ and NH-F coupling. The ¹⁹F spectrum (fig 11a) therefore has 24 possible lines (of which 20 are seen) and in the ¹H spectrum the CH₂ protons appear as a double doublet (fig 11b). ($J_{F,3}=14$ Hz; $J_{F,5}=1.5$ Hz; $J_{F,NH}=2.2$ Hz; $J_{F,CH_2}=6.5$ Hz; $J_{CH_2,NH}=5.5$ Hz; $J_{H-3,H-5}=2.5$ Hz).

A computer simulation of the fluorine spectrum using the observed F-H coupling constants is in good agreement with the actual spectrum (fig 11c).

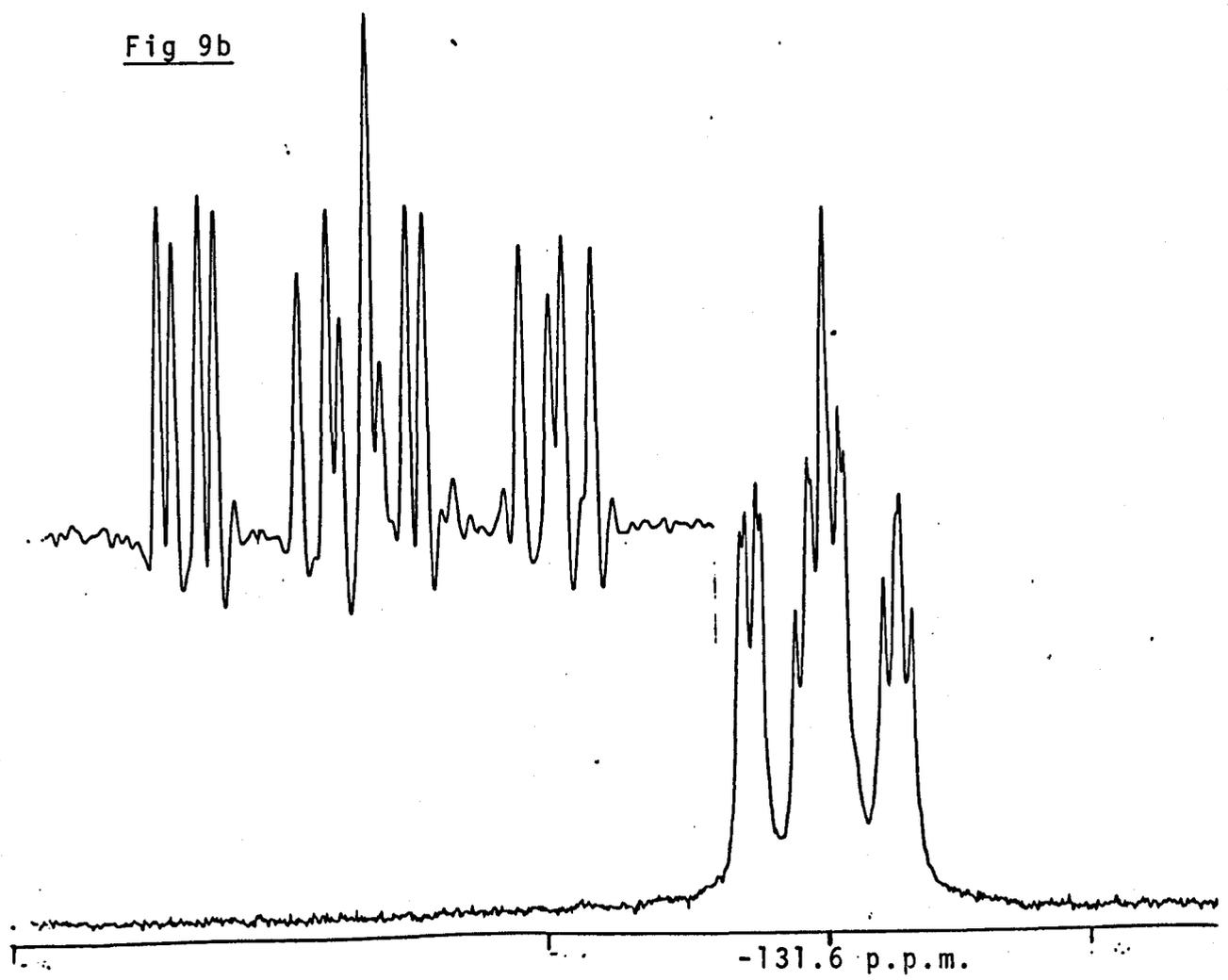
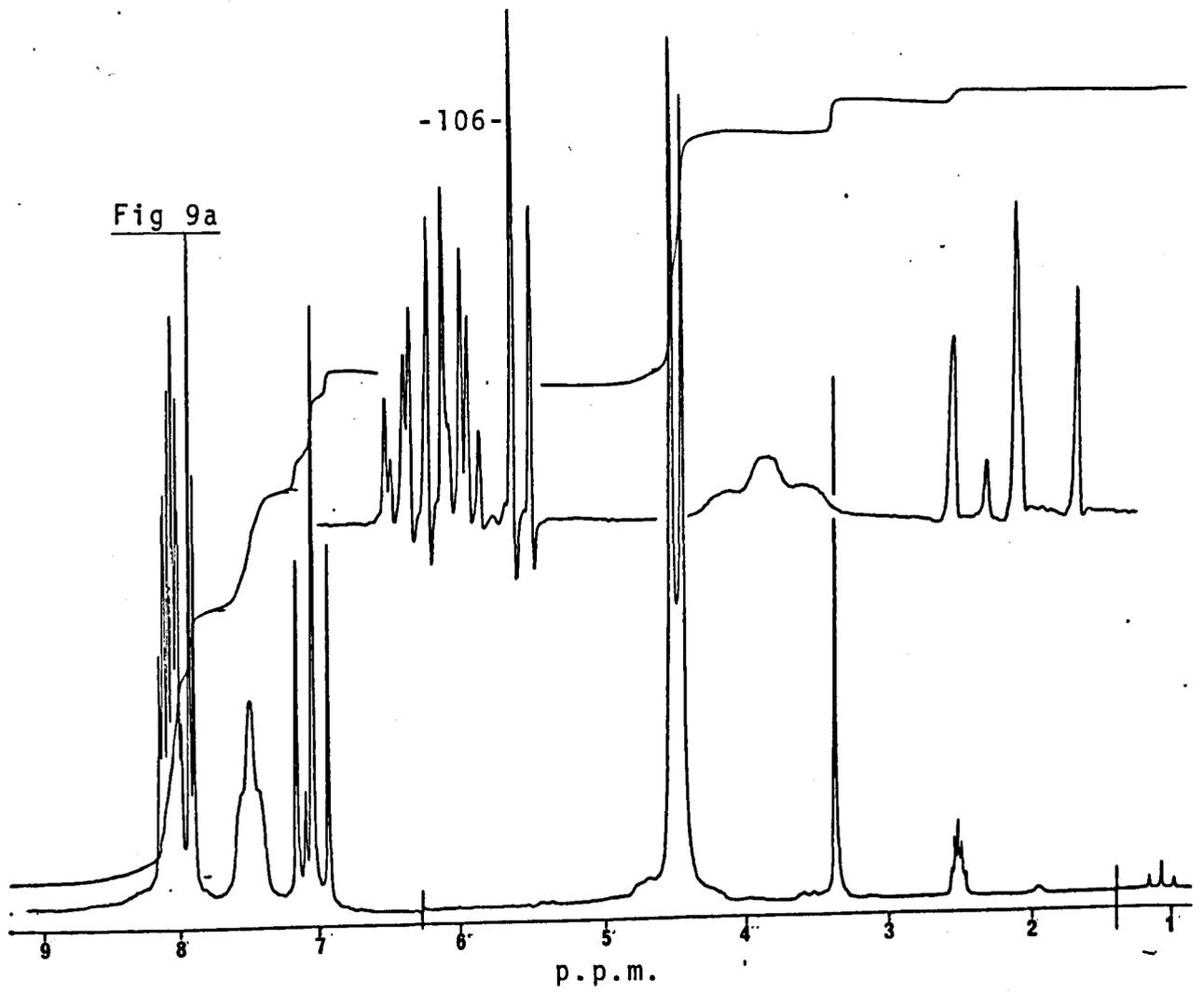
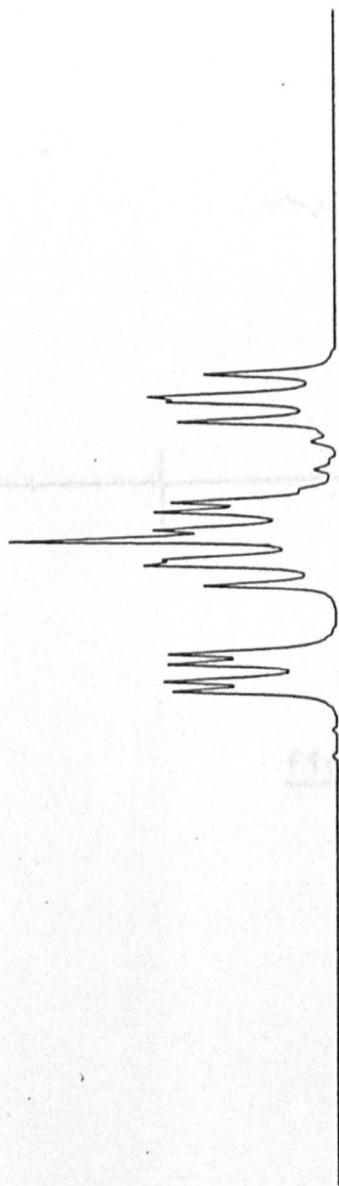


Fig 9c

Simulation of the ^{19}F spectrum



Simulation of the proton spectrum (NH-CH₂ coupling is ignored)



Fig 10a

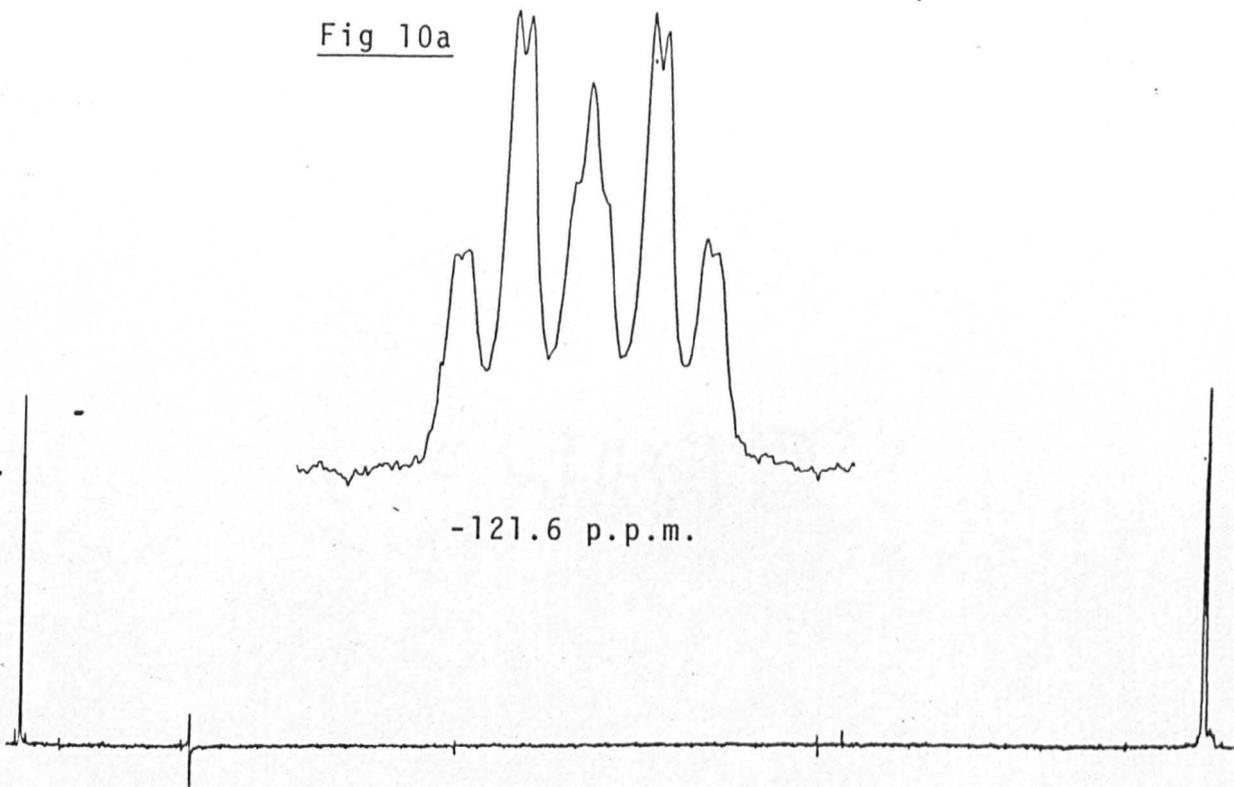


Fig 10b

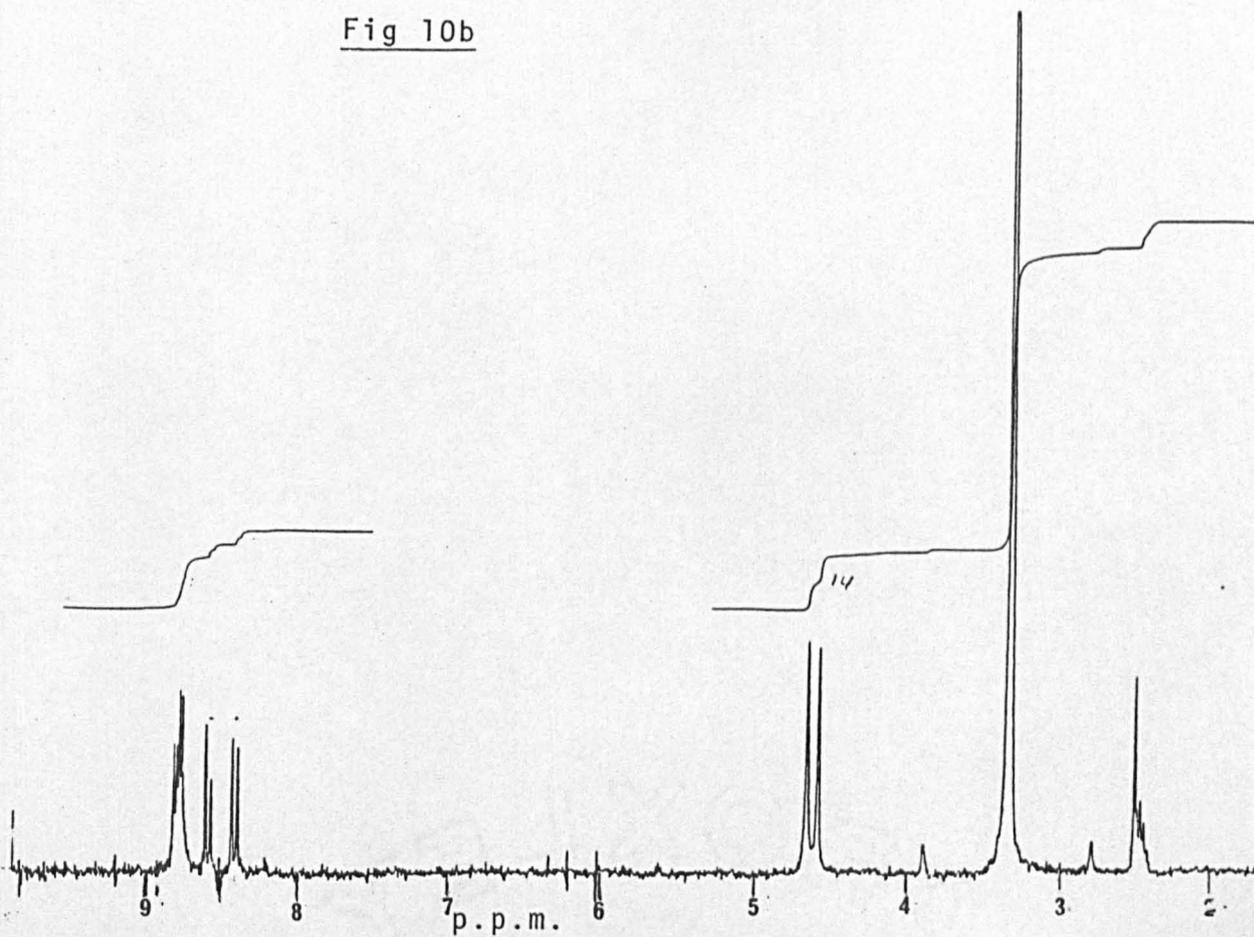
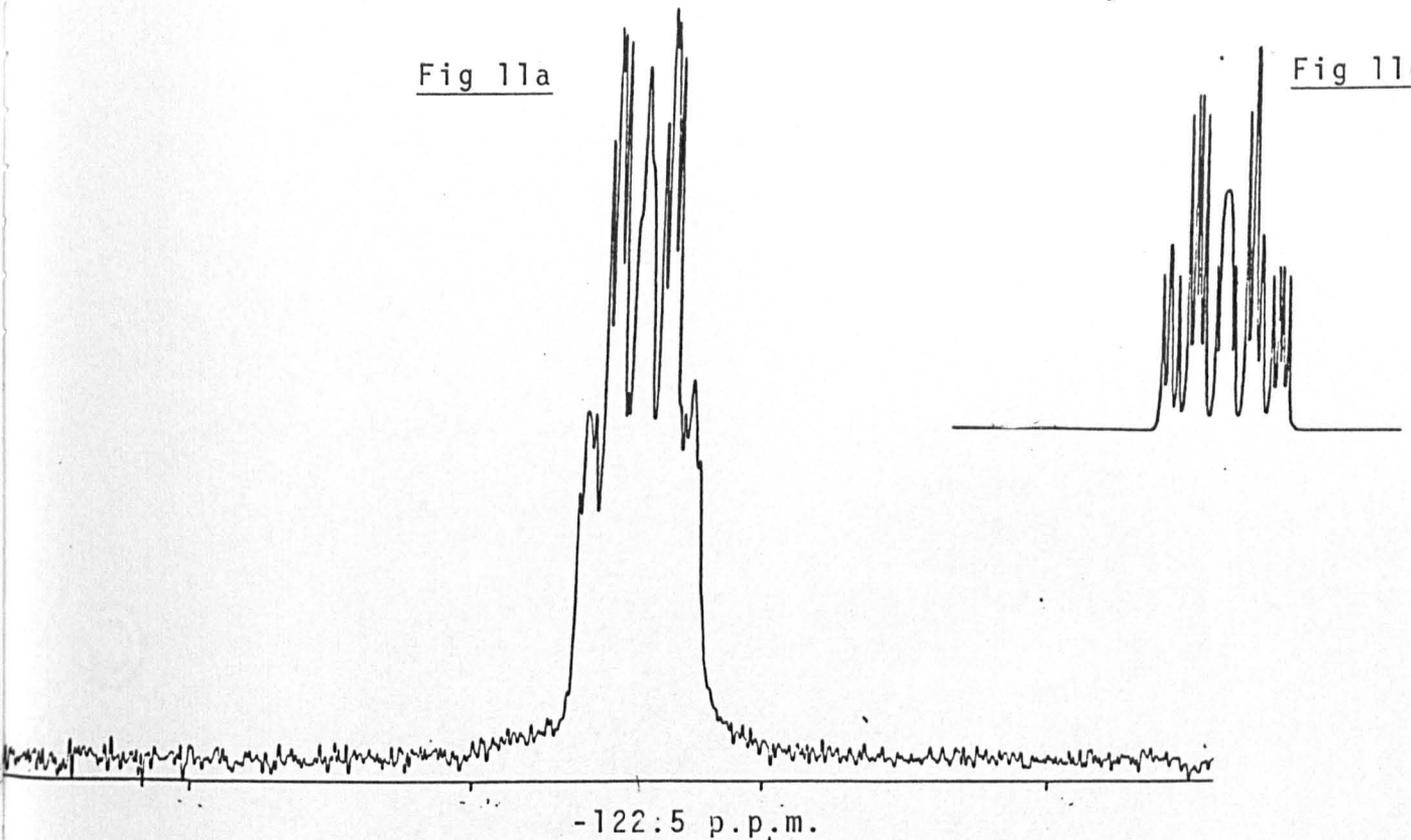


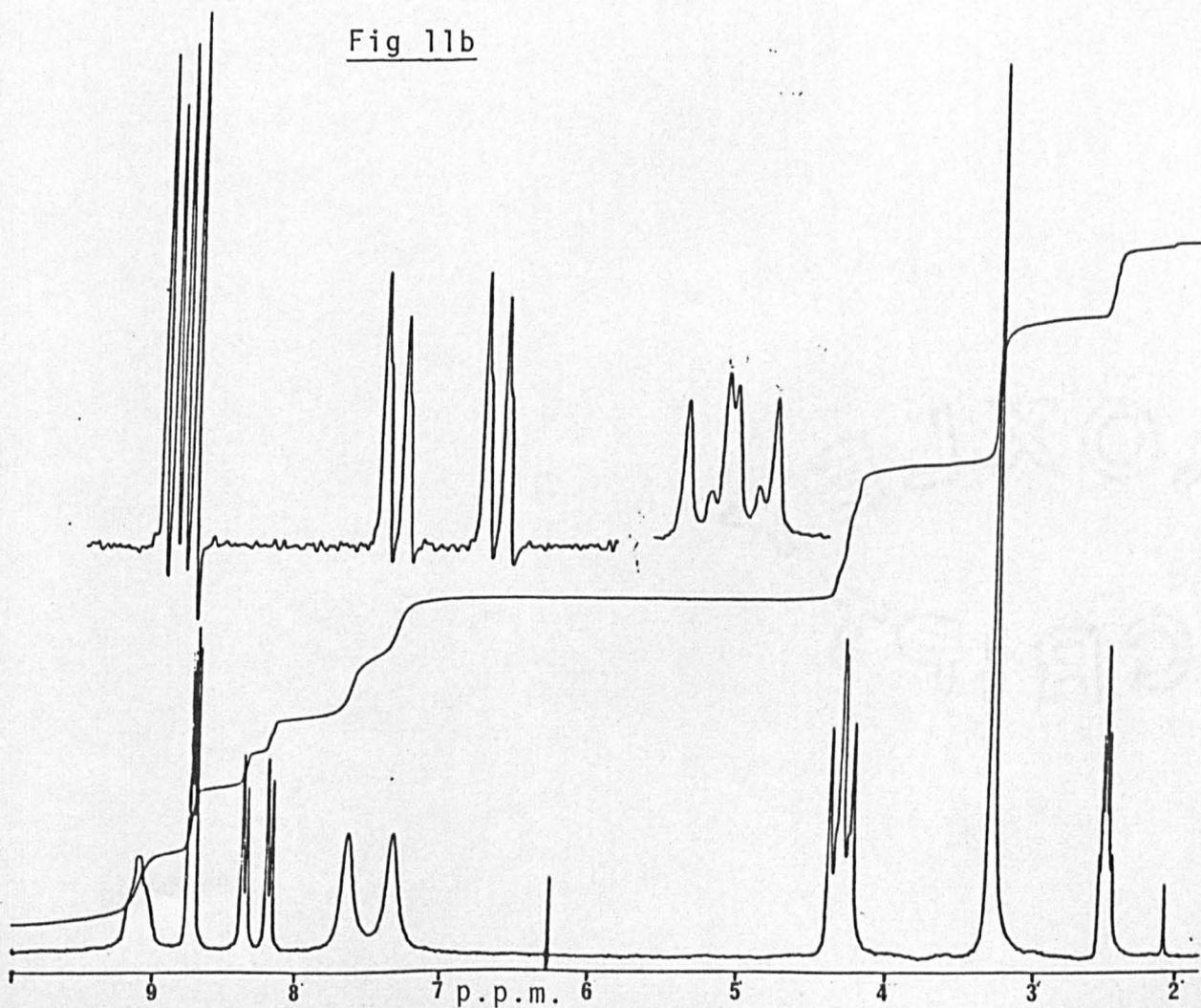
Fig 11a

Fig 11c



-122.5 p.p.m.

Fig 11b



Chapter 4

Routes to some Tricyclic Systems

The synthesis of benzimidazole N-oxide derivatives containing an additional heterocyclic ring fused on to the carbocyclic ring has not been previously reported and in this chapter routes to such systems are discussed.

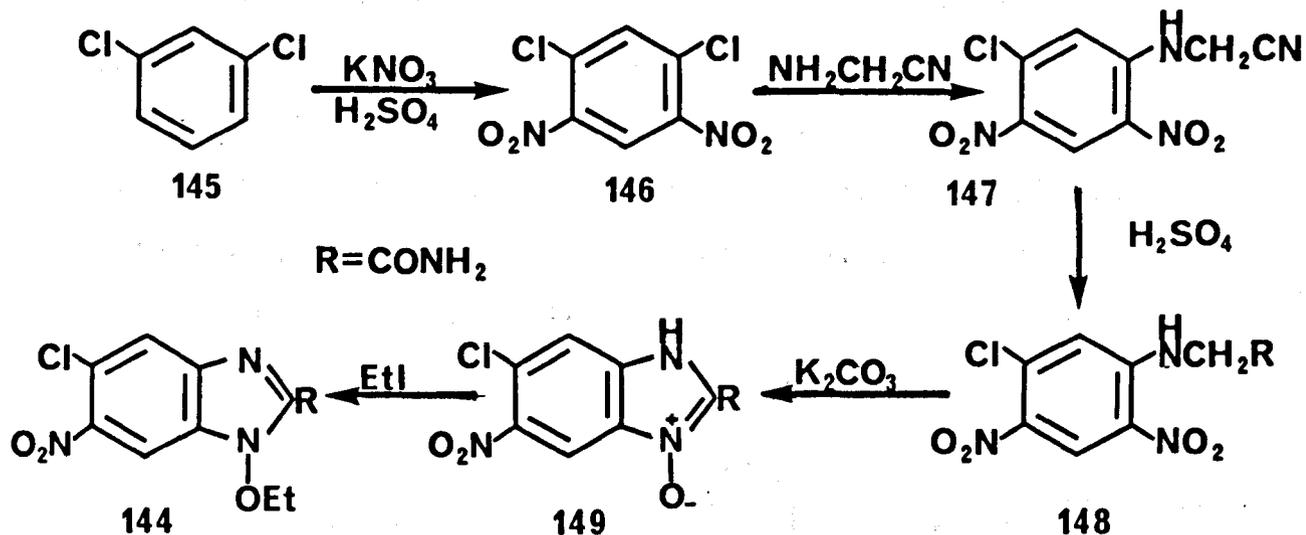
Three approaches were adopted, namely:

- A. The construction of an additional ring on to a suitably functionalised benzimidazole N-oxide derivative.
- B. The synthesis of a heterocyclic system on to which the imidazole moiety could subsequently be built.
- C. The use of benzene derivatives that possess all the necessary functionality for obtaining both heterocyclic rings.

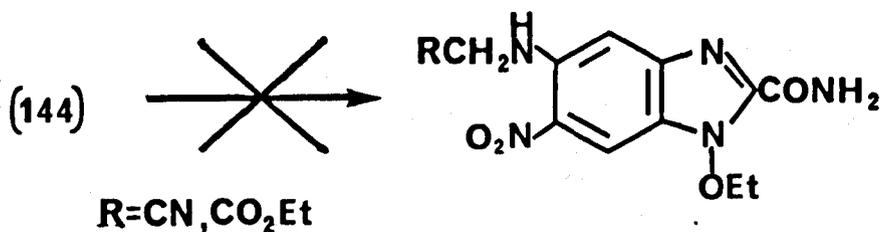
A. Tricyclic systems prepared from benzimidazole N-oxides

In this section attention was directed towards forming a second imidazole ring and this clearly required the preparation of benzimidazole N-oxides containing vicinal nitro and substituted amino groups. The first possibility investigated was nucleophilic substitution of (144), which

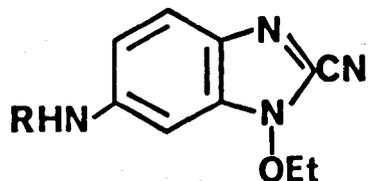
was itself prepared in 5 steps from m-dichlorobenzene (145).



However (144) was unreactive towards nucleophiles such as aminoacetonitrile and glycine ethyl ester and this pathway, therefore, proved unsuccessful.



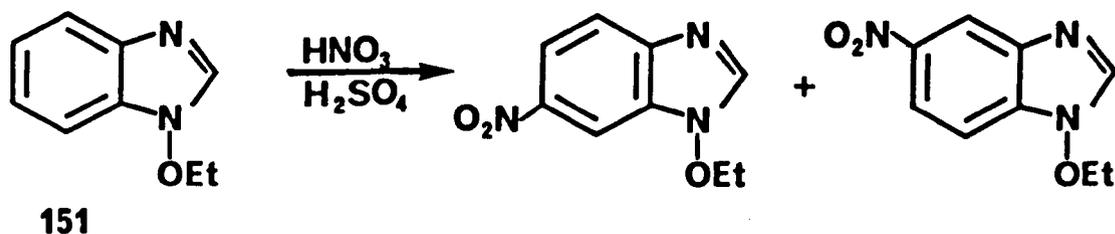
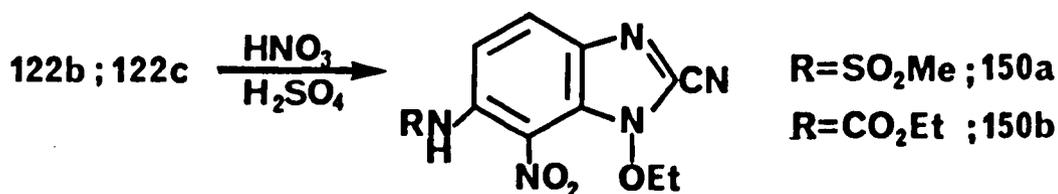
Other possible starting materials were the 6-(protected-amino)-1-alkoxybenzimidazoles described in Chapter 3. (122a, b and c).



$\text{R}=\text{COMe}$; 122a
 $\text{R}=\text{SO}_2\text{Me}$; 122b
 $\text{R}=\text{CO}_2\text{Et}$; 122c

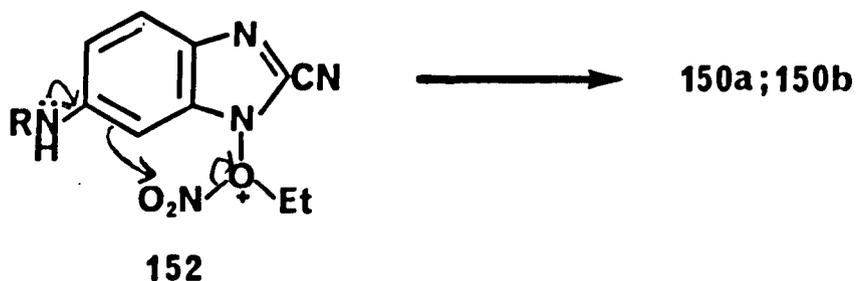
Nitration of these compounds gave some unexpected results. The sulphonamide (122b) and carbamate (122c) both gave the

corresponding 7-nitro derivative [(150a), (150b)], the former in good yield and the latter in low yield. In addition the acetanilide (122a) failed to nitrate under the same conditions, starting material being recovered. These results are particularly interesting in view of the reported result that 1-ethoxybenzimidazole itself (151) is nitrated under similar conditions to give a mixture of 5 and 6-nitro derivatives¹¹.



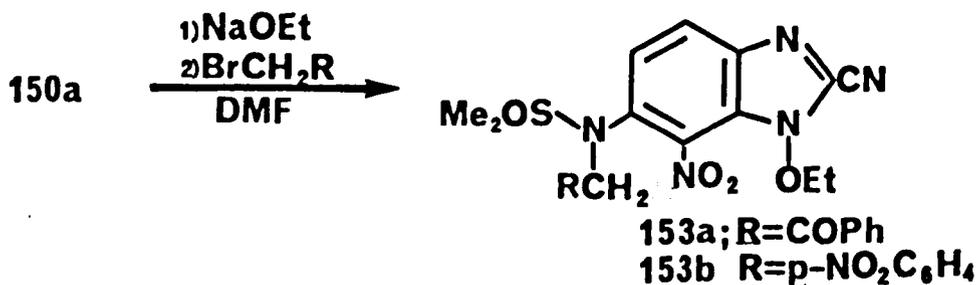
Although in the present system the protected amino group is, obviously, the most powerful director of substitution, how one accounts for nitration at position 7 (not 5) in compounds (122b) and (122c), and the relatively low reactivity of the acetanilide (122a) is far from easy.

One possible explanation is that nitration proceeds via a nitro-oxonium intermediate (152) and that rearrangement then gives, exclusively, the 7-nitro product.



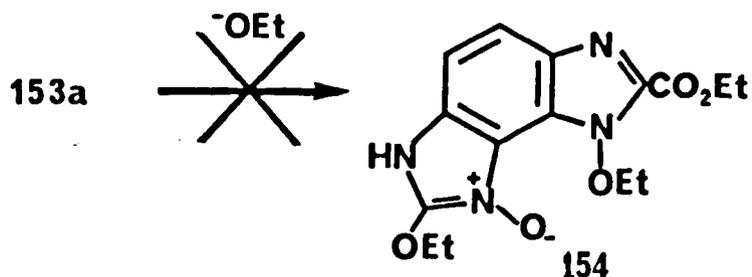
As regards the acetanilide it may be that the protecting group is in an orientation that blocks this rearrangement process. Some evidence that this could be the case comes from the observed deshielding of proton 7 in the acetanilide and the corresponding N-oxide (121a) (see p 84). Indeed it is conceivable that a similar effect could account for the low yield obtained in the nitration of the carbamate (122c). However, without a detailed mechanistic study these suggestions must remain tentative.

The next step involved building a reactive methylene group on to the nitrosulphonamide (150a). From previous work on benzimidazole N-oxide synthesis the phenacyl and *p*-nitrobenzyl groups appeared the best candidates (see p 23). Compounds (153a) and (153b) were, therefore, synthesised, by treatment of the sodium salt of the sulphonamide with the appropriate bromo-reagent.



Attempted cyclisation of (153a) failed to give any

identifiable products and, at any rate, none of the expected tricyclic product (154). It may be that the reaction of (153a) with base can take a number of alternative pathways.



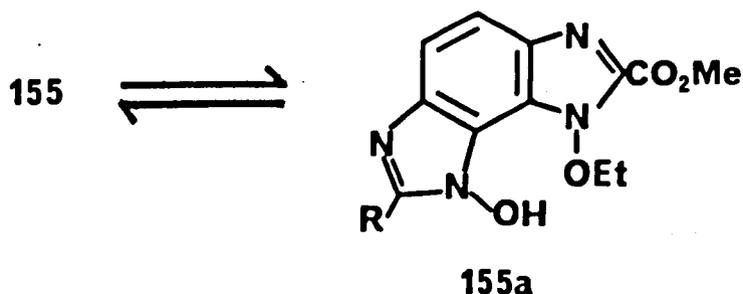
However, no such problems were encountered in the cyclisation of (153b) which proceeded to give the tricyclic product (155). The cyano group had, as expected, been hydrolysed to a methyl ester during the course of the cyclisation.



155; R=p-NO₂C₆H₄

Finally, the spectroscopic behaviour of (155) gave two interesting results. First, its mass spectrum gave only one peak of any intensity (m/z 150) corresponding to p-NO₂C₆H₄CO⁺, mirroring the results previously reported for a variety of 2-aryl N-oxides⁵³. Second, although the position of equilibrium in the potentially tautomeric

system (155) was not established, its n.m.r. spectrum indicated that in DMSO the N-hydroxy form (155a) probably predominates, since the carbocyclic protons have the same chemical shift.



B. Tricyclic imidazole systems from benzo-heterocycles

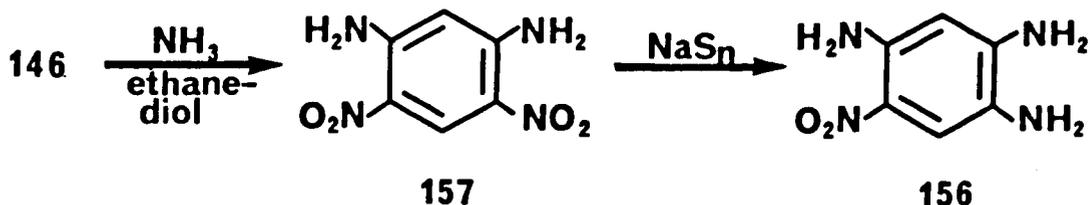
Of the three approaches followed this has been the least studied, principally due to the difficulty in obtaining suitable substrates. For this route to be a realistic way of obtaining these tricyclic systems, two criteria must be satisfied.

(i) The benzo-heterocycle must be easily synthesised.

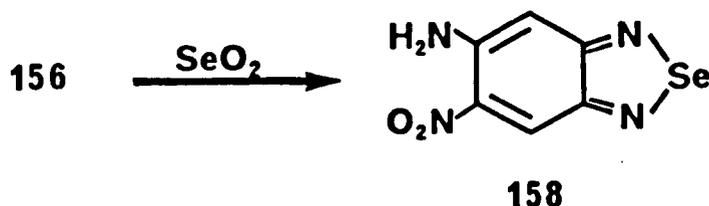
(ii) The building of appropriate functionality on to the above heterocycle must be easily achieved.

With the above points in mind a route was sought which involved the preparation and cyanomethylation of benzo-heterocycles with vicinal nitro and amino groups. An obvious starting point was the nitro-triamine (156), itself prepared in 2 steps from 1,3-dichloro-4,6-dinitro-

benzene (146) by the published procedure⁶⁸.

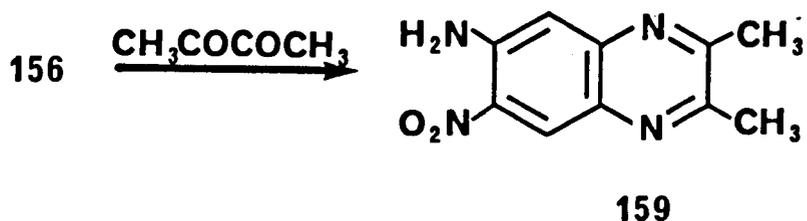


Reaction of (156) with selenium dioxide gave a product which spectroscopic evidence showed to be the selenadiazole (158), although it could not be obtained in sufficiently pure form for a correct microanalysis.



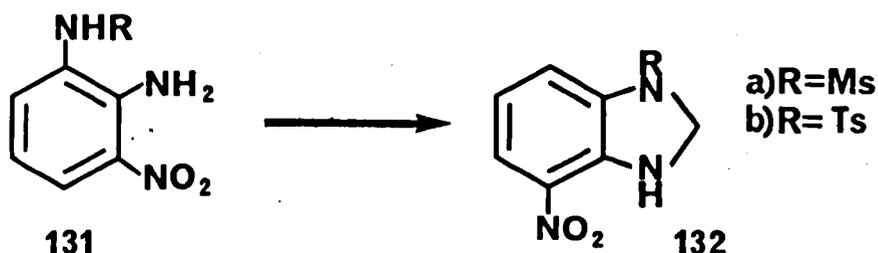
Attempted cyanomethylation of this impure material yielded only a highly insoluble and generally intractable product of high molecular weight (minimum 544) which from the isotope clusters seen in its mass spectrum, contained selenium. It was thought that perhaps the selenadiazole ring system became co-ordinated with the Lewis acid (HZnCl_2^+ , HSO_4^-) present in the cyanomethylation mixture, thus interfering with the normal course of reaction. A much less basic heterocycle was, therefore, sought.

The quinoxaline (159) was now obtained by reaction of the triamine (156) with butanedione according to the published procedure⁶⁸.

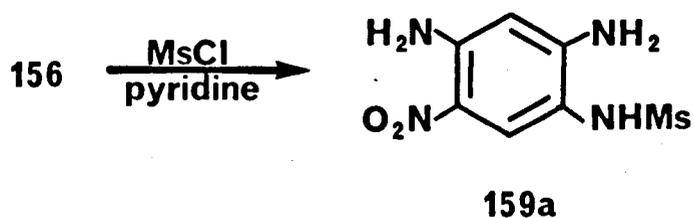


Once again, however, the subsequent cyanomethylation step failed with only an extremely intractable material being obtained.

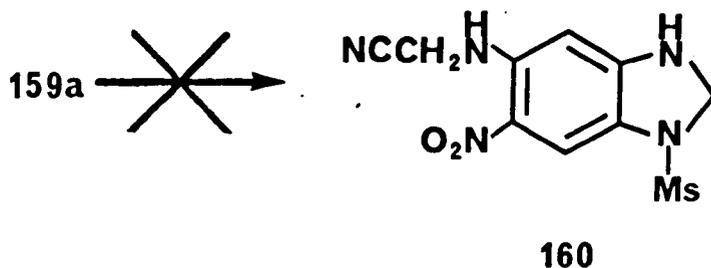
A final attempt within this section involved trying to exploit the one reaction that had been shown to give a heterocyclic system under cyanomethylation conditions. i.e.



Compound (159a) was therefore synthesised by monomesylation of the triamine (156).



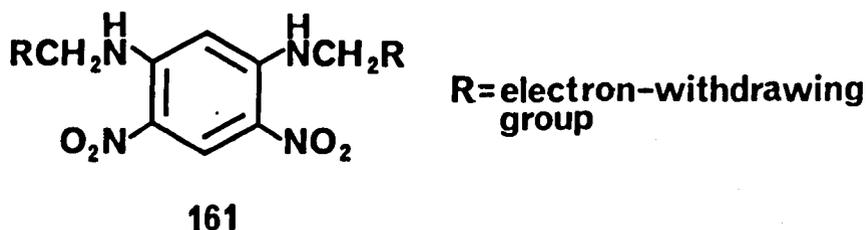
However, reaction of (159a) under similar conditions to those producing the dihydrobenzimidazoles (132) failed completely to give the corresponding product (160) and indeed no workable material was isolated.



It appeared, therefore, that the desired tricyclic compounds could not be prepared by the strategy followed in this section due mainly to problems in building suitable functionality on to the heterocycles. It remains to be seen whether or not the cyanomethylation procedure is applicable at all to a ring system which contains a nucleophilic heteroatom.

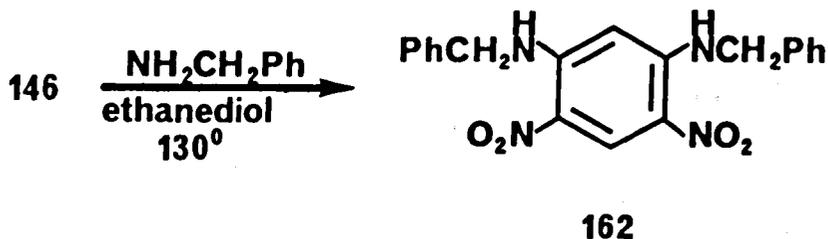
C. Tricyclic systems from tetra-substituted benzenes

In view of the ready preparation of benzimidazole N-oxides from N-(activated alkyl)-o-nitroanilines the synthesis of tetra-substituted benzenes of the type (161) was undertaken.

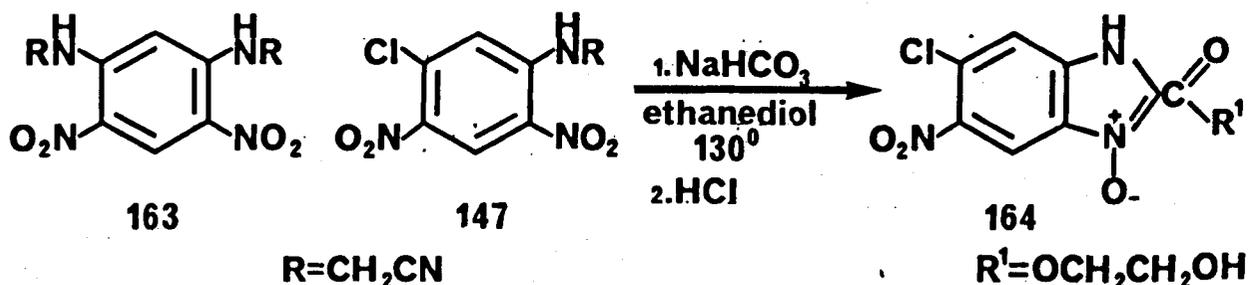


One possible route involved nucleophilic substitution on the dichloro-dinitrobenzene (146). Reaction of (146) with ammonia was known⁶⁸ to give the diamine (157).

An analogous reaction with benzylamine gave the desired product (162).

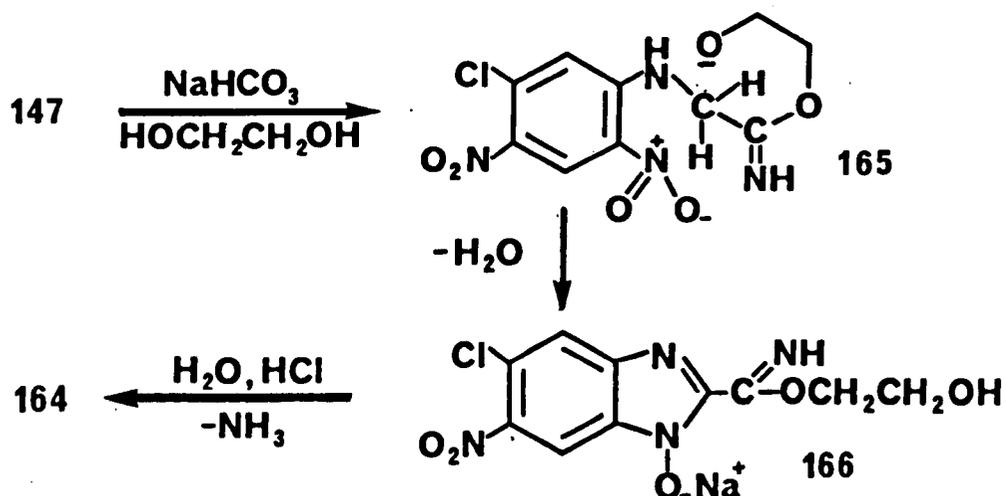


However, as has already been stated (Chapter 1) phenyl is a poor activating group for the base-induced cyclisation step, and preparation of the, potentially much more reactive, cyano compound (163) was, therefore, attempted. Since the mono-substituted material (147) had already been prepared a further substitution reaction with aminoacetonitrile hydrochloride in the presence of base was the obvious route to (163). However, addition of sodium bicarbonate to a hot solution of (147) in ethanediol in itself caused an almost instantaneous reaction and the N-oxide (164) was isolated in fairly good yield.

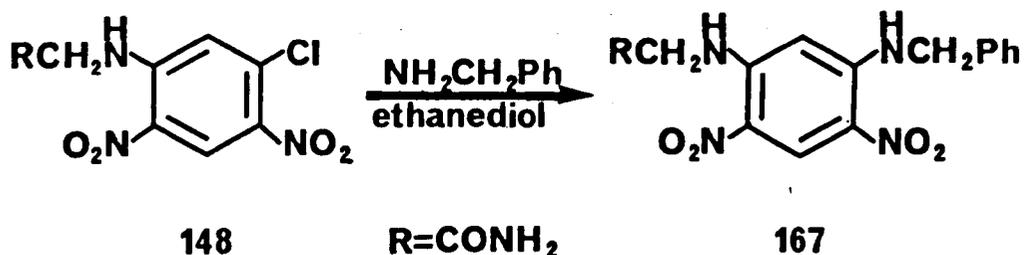


Cyclisation of even a cyano compound at such a rate with a base as weak as sodium bicarbonate is extremely surprising. One intriguing possibility is that the cyano group is not involved in the cyclisation step at all and that the hydroxy imidate ester (165) is formed, which cyclises by

acting as its own base. Hydrolysis of the N-oxide imidate ester (166) on work-up would give the observed product.



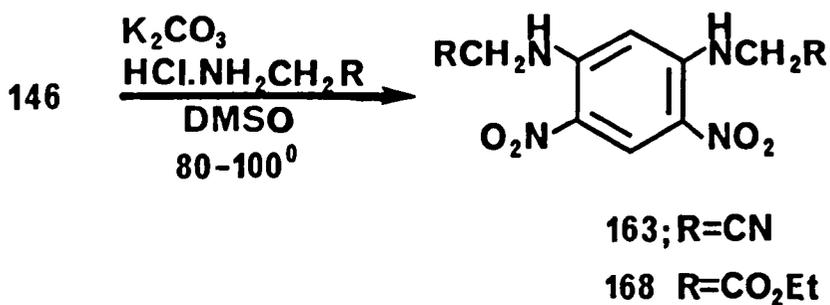
Although the above system is of interest in its own right it would seem to limit the possibility of preparing the desired tetra-substituted benzenes (161) to those reactions not involving sensitive groups such as cyano. The amide (148) promised to be somewhat more stable and, indeed, its reaction with benzylamine did produce some of the desired product (167) although in very low yield (~8%)



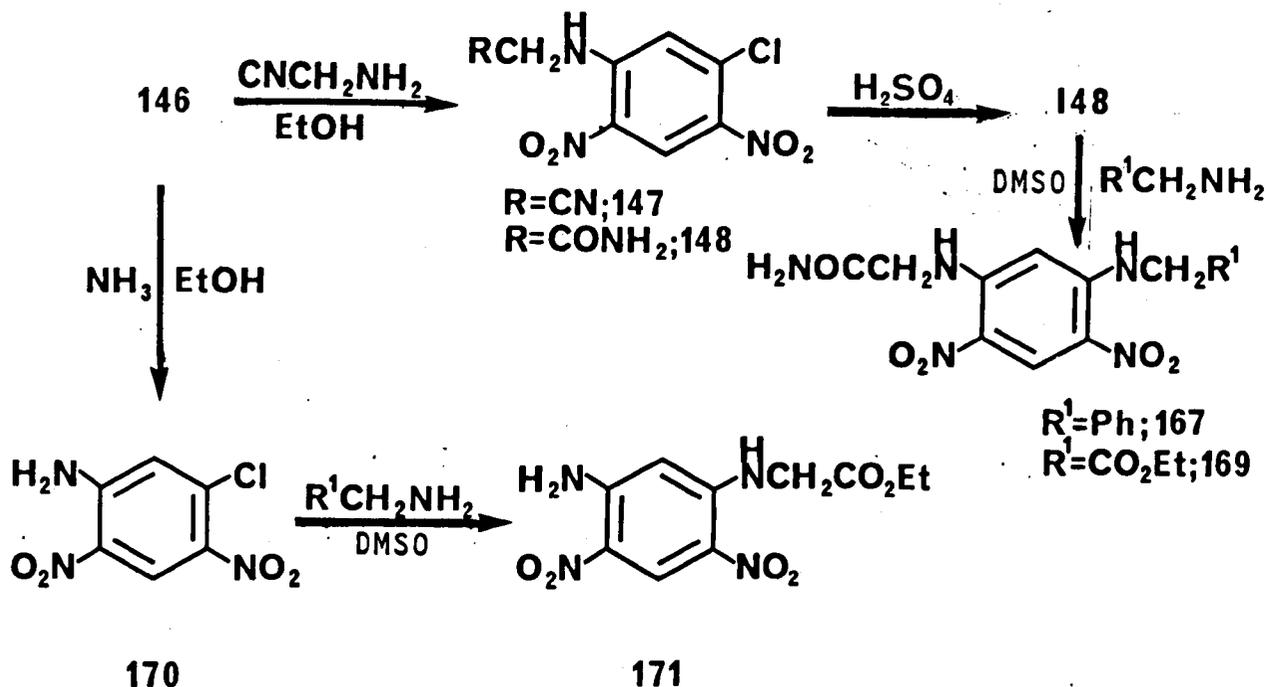
Clearly, an alternative system was needed and the replacement of ethanediol by dimethyl sulphoxide (DMSO) offered important advantages.

- 1) DMSO, unlike ethanediol, is unlikely to react with any of the materials present in the reaction mixture.
- 2) Dipolar aprotic solvents such as DMSO are well known to promote aromatic nucleophilic substitution reactions involving charged species⁶⁹.

Indeed, with DMSO as solvent, the yield obtained in the previous reaction increased by a factor of 8. Two important symmetrically substituted materials (163) and (168), were now obtained in high yield and 'one pot' reactions from the dichlorodinitrobenzene (146).

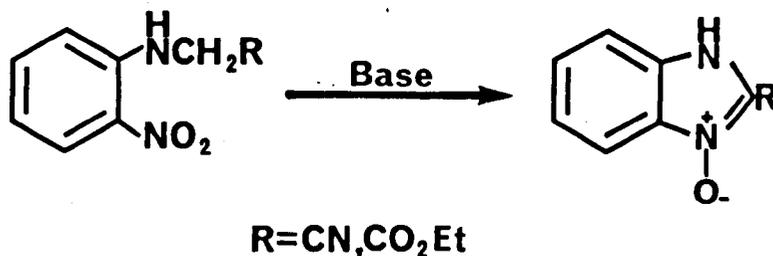


In addition, the synthesis of a variety of unsymmetrically substituted diamines was now possible, the first substitution being performed in ethanol and the second in DMSO.



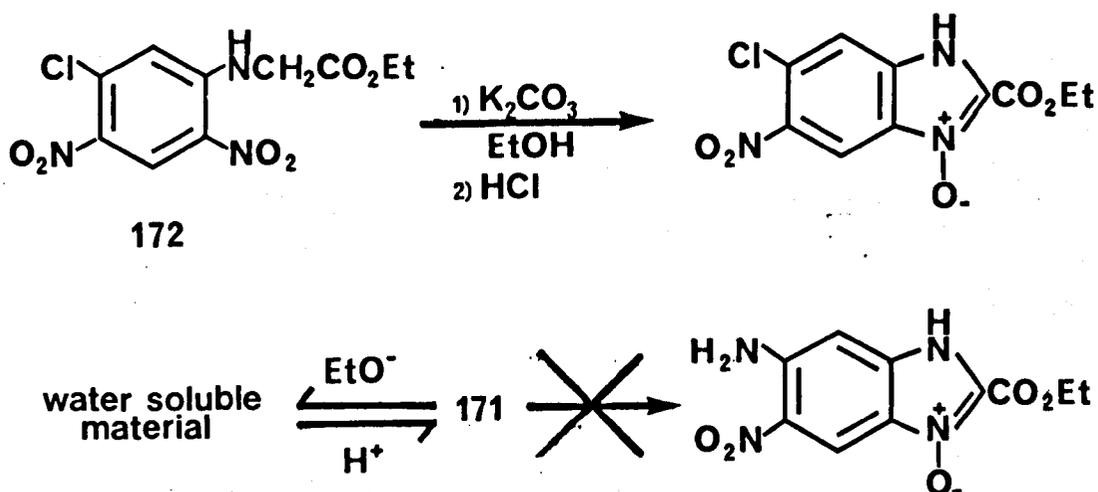
The symmetrical compounds (162), (168) and (163) were now selected for further investigation.

Under a variety of basic conditions both the diester (168) and the dicyano compound (163) failed to yield any cyclised products, even, for the latter material, in the presence of sodium hydride. This result is extremely surprising in view of the known ease with which their disubstituted analogues are cyclised.

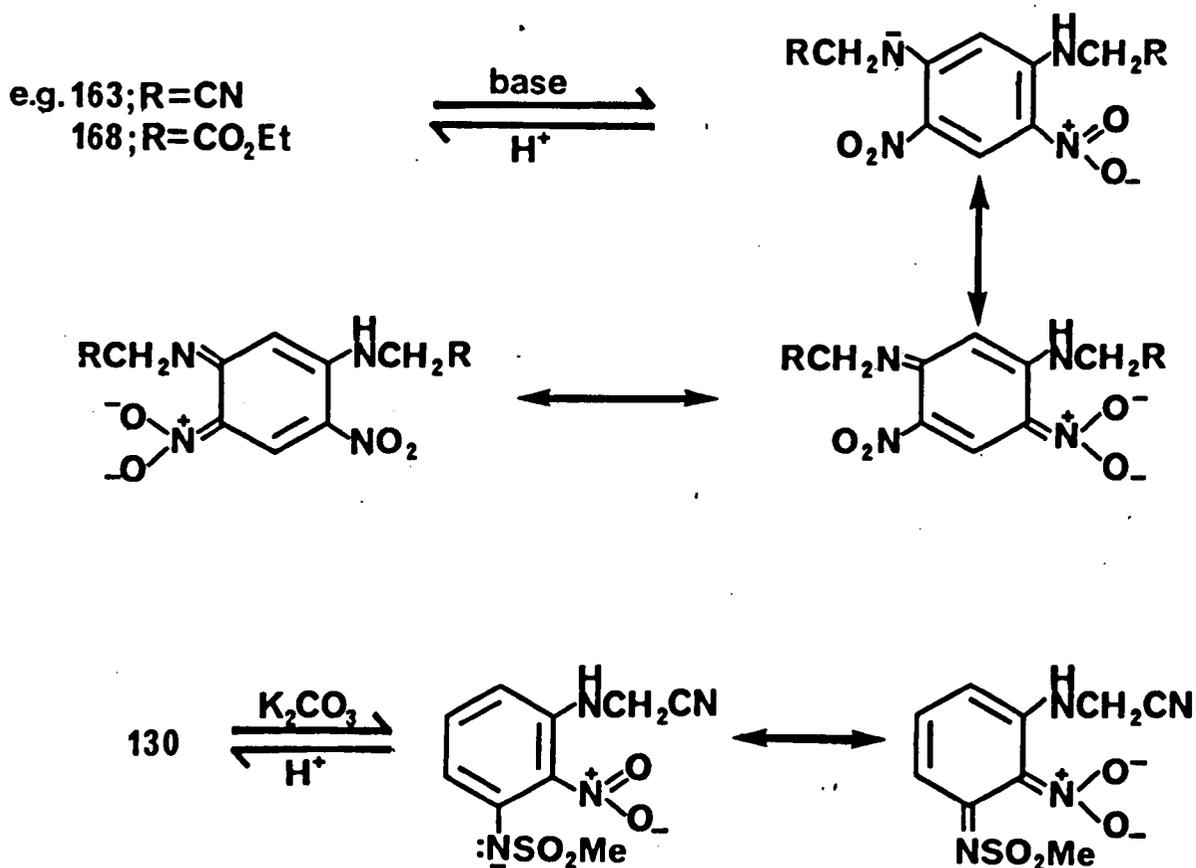


In addition it was shown that while the mono-ester (172) could be cyclised to give the corresponding N-oxide.

albeit in low yield, replacement of the chloro group with an amino function (171) again completely blocked cyclisation. Furthermore, in the reaction of (171) with sodium ethoxide, appropriate choice of solvent system allowed the isolation of a highly water-soluble material, an aqueous solution of which gave, on acidification, the starting amine (171).



From the above results it seems that each of the diamines studied thus far is merely deprotonated in base and that this deprotonation blocks further reaction. In this regard these systems appear to parallel the behaviour of the sulphonamide (130), which was also recovered unchanged on attempted cyclisation (Chapter 3). In these cases it may be, therefore, that the formation of aci-nitro intermediates deactivates the nitro groups and thus prevents cyclisation.

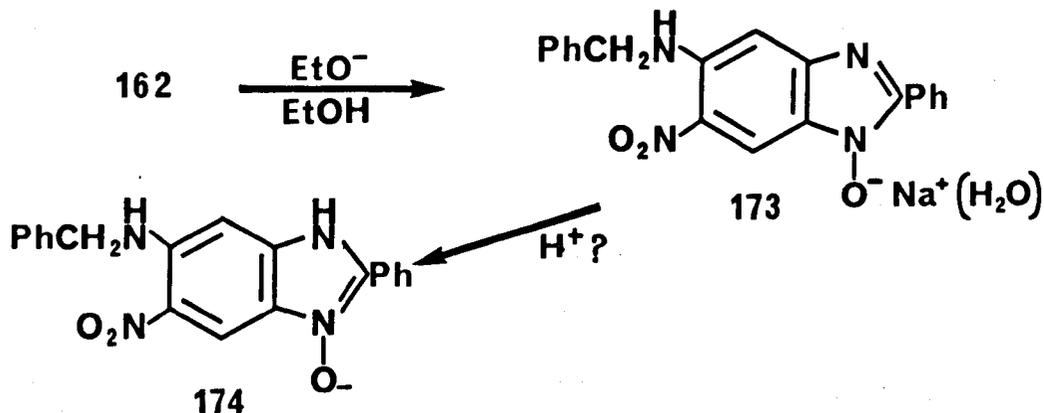


The reaction of the diphenyl compound (162) with base was now investigated, for two reasons.

- 1) It was likely to be much more stable in the presence of base than either (163) or (168) and more forcing reaction conditions could, therefore, be employed.
- 2) N-benzyl-o-nitroaniline itself has been suggested to undergo cyclisation to the corresponding N-oxide via an aci-nitro intermediate (cf Scheme 11 p 11), such as that thought to be produced in the current work.

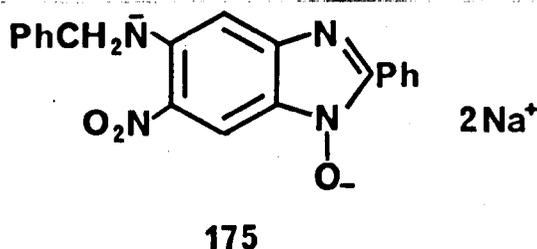
In fact, treatment of (162) with base gave, on acidic work up, a high-melting solid which spectroscopic and

analytical data indicated to be the hydrated N-oxide sodium salt (173).



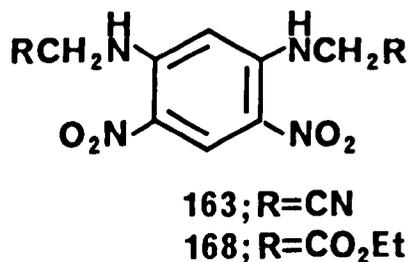
In particular, further treatment of the high melting solid with acid did not yield the starting amine (162) [the sodium salt of which is, of course, isomeric with (173)]. However, no pure material could be obtained in this way and isolation of the free N-oxide (174) remains to be achieved.

Finally, since (173) was isolated only on acidic work-up it would appear that it was further deprotonated in the reaction medium and probably existed as the dianion (175). That (175) did not cyclise further, may be due to some deactivating effect of the deprotonated imidazole ring.



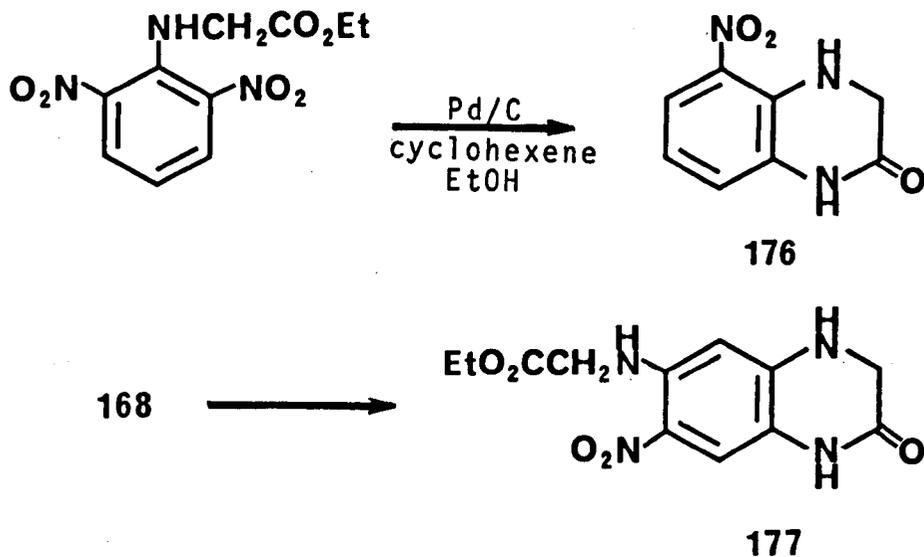
Clearly, the chemistry of the aforementioned systems with regard to their behaviour in base is far from straightforward and merits future research.

For the moment, however, the possibility of obtaining novel tricyclic systems via reduction or partial reduction of the diester (168) and the dicyano compound (169) was investigated. These compounds will be considered in turn.



The reduction of (168)

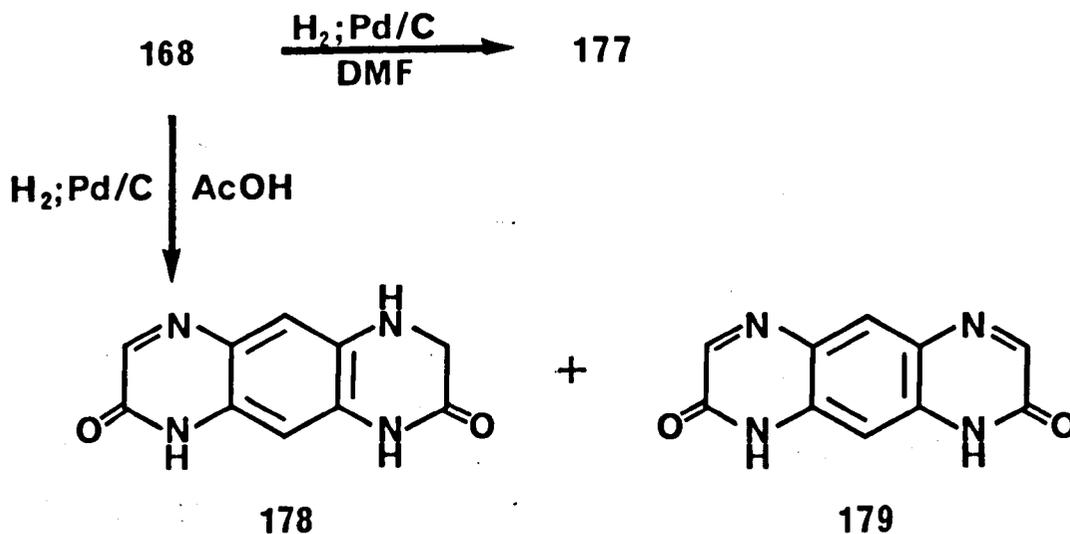
The selective reduction of N-(2,6-dinitrophenyl)glycine ethyl ester has been reported to give the dihydroquinoxaline (176) in good yield⁵⁷ and the reduction of (168) was therefore conducted under similar conditions. In fact this procedure was successful in producing the desired mono-cyclised product (177) in ~13% yield.



The limitation of this procedure was the high catalyst loading required with the consequence that only very small quantities (0.5g) of substrate could easily be reduced at one time. Therefore, the catalytic hydrogenation of (168) was attempted. The results obtained revealed a striking dependence on the solvent used.

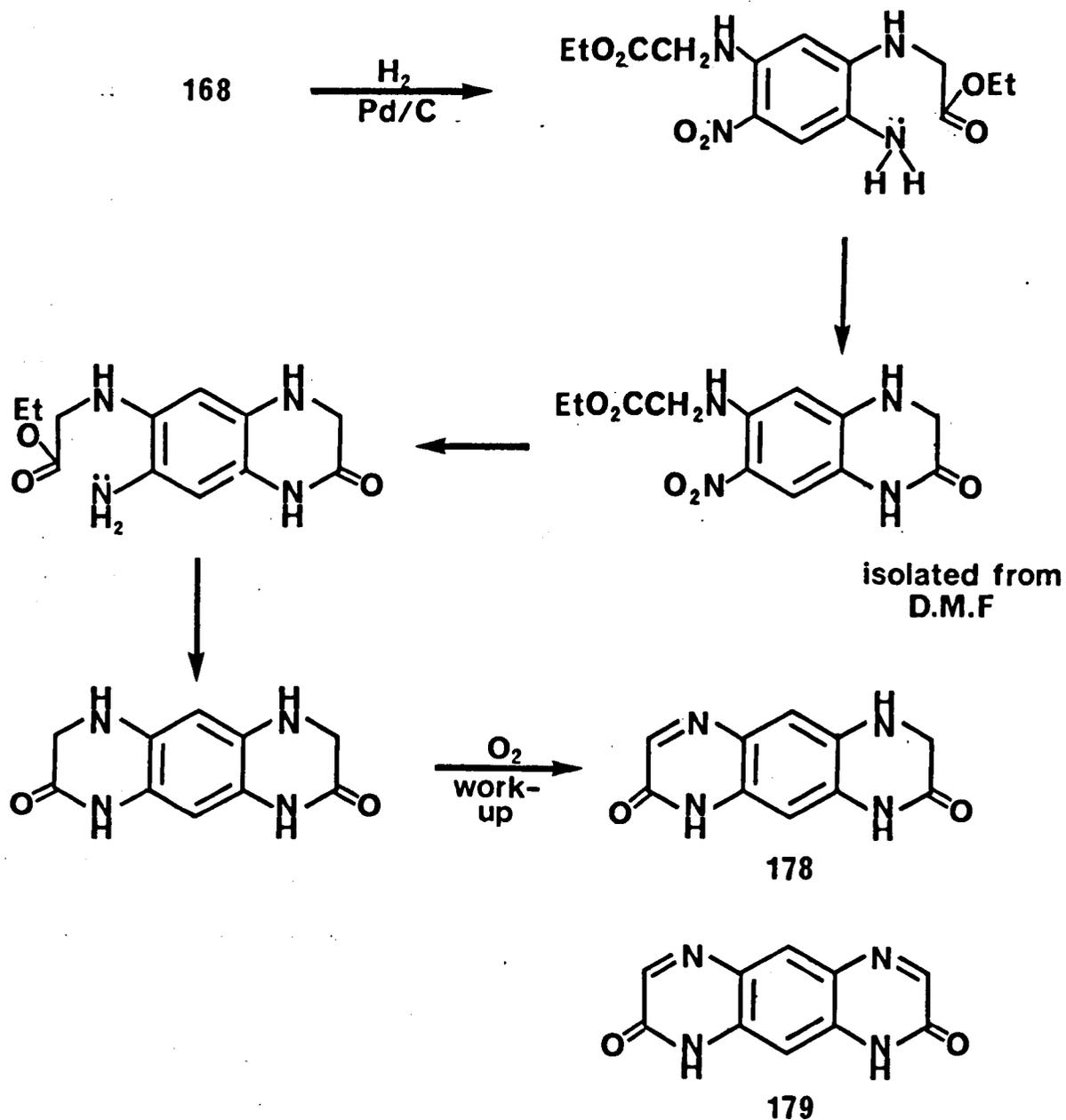
In DMF a small quantity of the dihydroquinoxaline (177) was obtained along with a much larger quantity of starting material. It would appear that in this solvent the catalyst is easily poisoned during the reduction process.

In acetic acid, however, reduction proceeded smoothly to give on work-up a mixture of, predominantly, the dihydro-pyrazinoquinoxaline (178) and some fully oxidised material (179).



For the reduction of (168) the likely course of events is described in Scheme 28.

Scheme 28



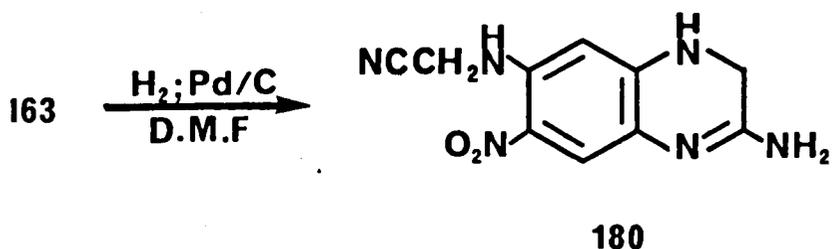
Neither (178) nor (179) has been previously reported in the literature and the above method represents a potentially useful route to such systems, particularly in view of the ease with which the starting ester (168) is obtained and the unambiguous structure of the products.

In addition (178) and (179) may themselves be useful intermediates in the production of a variety of substituted pyrazinoquinoxalines. One possibility for such materials may be in the production of thermally stable polymers since the materials synthesised here have good thermal stability (m.p. > 350°).

The reduction of (163)

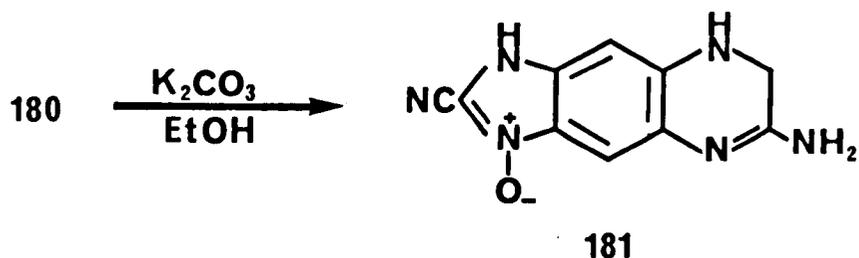
Since the catalytic hydrogenation of the diester (168) in dimethylformamide had produced at least some of the monocyclised material, (177) the corresponding cyano compound (163) was reduced under the same conditions.

This reaction proved extremely unpredictable however, and on only one occasion was the desired product (180) isolated in purifiable form.

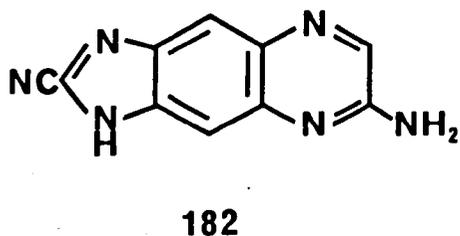


It would appear that with so many alternative reducible centres in both (163) and the initial product (180) the correct choice of reduction conditions is critical and certainly warrants further investigation. To conclude the current work, however, the behaviour of (180) in base was very briefly investigated. Infra-red and mass spectral

evidence indicated that the desired N-oxide (181) had indeed been formed, but unfortunately it could not be obtained in sufficient purity or quantity for full characterisation.



The mass spectrum obtained from the product contained the ion corresponding to M^+ for (181) and $(M^+ - H_2O)$. It is not yet clear whether or not this second ion is generated from the first in the mass spectrometer or whether it arises from a second cyclisation product such as (182).



EXPERIMENTAL

Materials and Apparatus

Melting points were determined in open capillaries and are uncorrected.

Infrared spectra were recorded as Nujol mulls.

N.m.r. spectra: ^1H spectra were recorded, unless otherwise indicated, at 80MHz on a Bruker WP80 for 10% solutions in dimethyl sulphoxide with tetramethylsilane as internal reference.

^{19}F spectra were recorded at 75.3MHz on a Bruker WP80 for 10% solutions in d_6 -dimethyl sulphoxide, unless otherwise indicated, with trichlorofluoromethane as internal reference.

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

Samples were introduced by means of a direct insertion probe.

Flash vacuum pyrolysis experiments: The substrates to be pyrolysed were volatilised under low pressure (typically 10^{-1} to 10^{-2} mm Hg) and the vapour passed through a quartz tube (300mm long x 25mm i.d.) externally heated to 650-770°. The solid products were collected near the furnace outlet, after allowing the system to cool under nitrogen.

Symbols and Abbreviations

| | |
|-------------------|--|
| n.m.r. | nuclear magnetic resonance |
| δ | chemical shift |
| J | spin-spin coupling constant |
| s,d,dd,t,q,m | singlet, doublet, double doublet, triplet, quartet, multiplet |
| i.r. | infrared |
| ν | wave number |
| m.s. | mass spectroscopy |
| m/z | mass to charge ratio |
| M ⁺ | molecular ion |
| F.V.P. | flash vacuum pyrolysis |
| T.L.C. | thin layer chromatography |
| br | broad |
| bs | broad singlet |
| d | (after melting point) with decomposition |
| M | mol dm ⁻³ |
| CDCl ₃ | deuteriochloroform |
| DMSO | dimethyl sulphoxide |
| DMF | dimethylformamide |
| TMS | tetramethylsilane |
| HMDS | hexamethyldisilazane |
| m.p. | melting point |
| b.p. | boiling point |

Chapter 2 : Experimental

N-Cyanomethyl-4-methyl-2-nitroaniline (82)

a) (based on the method of Dimroth and Aurich⁴⁸ for mono-cyanomethylation)

4-Methyl-2-nitroaniline (4.56g, 0.03mol), paraformaldehyde (2.7g, 0.09mol), potassium cyanide (5.85g, 0.09mol) and dry zinc chloride (31.5g) were mixed with acetic acid (75ml) containing concentrated sulphuric acid (3 drops). The mixture was heated, with stirring, to 50° over 0.5h and kept at this temperature for a further 8h. On dilution with water, an orange solid precipitated, which was filtered, washed repeatedly with water and recrystallised from ethanol (5.2g, m.p. 106-107°). N.m.r. indicated this to be an approximately 50:50 mixture of N-cyanomethyl-4-methyl-2-nitroaniline (82) and N,N-bis(cyanomethyl)-4-methyl-2-nitroaniline. The reaction conditions were modified, as shown below.

b) The above procedure was repeated, with a reduced zinc chloride concentration.

4-Methyl-2-nitroaniline (7.6g, 0.05mol), paraformaldehyde (4.5g, 0.15mol), potassium cyanide (9.75g, 0.15mol), zinc chloride (25g), acetic acid (250ml) and concentrated sulphuric acid (4 drops) yielded N-cyanomethyl-4-methyl-2-

nitroaniline (82) (7.2g, 75%), m.p. 146-147° (from ethanol).

(Found: C, 56.45; H, 4.7; N, 21.95; C₉H₉N₃O₂ requires C, 56.5; H, 4.7; N, 22.0%).

$\nu_{\max}(\text{cm}^{-1})$ 3380 (N-H), 2230 (CN), 1530 and 1325 cm⁻¹ (NO₂).

δ 2.30 (3H, s, CH₃), 4.65 (2H, d, J=6Hz, CH₂), 7.23 (1H, d, J=8Hz, H-6), 7.70 (1H, dd, J=8 and 2Hz, H-5), 8.13 (1H, d, J=2Hz, H-3).

N-(4-Methyl-2-nitrophenyl)glycine (72)

a) N-Cyanomethyl-4-methyl-2-nitroaniline (4.0g) was dissolved in glacial acetic acid (50ml). Sulphuric acid (50% v/v, 120ml) was added and the resultant solution heated at 100° for 2.5h. On cooling, the mixture was poured on to crushed ice and the orange solid filtered off, washed with water and recrystallised from aqueous propan-2-ol to yield N-(4-methyl-2-nitrophenyl)glycine (1.4g, 67%), m.p. 186-188° (d) (lit.⁴⁵, 189-190°(d)).

$\nu_{\max}(\text{cm}^{-1})$ 3340 (N-H), 1715 (C=O).

δ 2.23 (3H, s, CH₃), 4.13 (2H, d, J=5Hz, CH₂), 6.83 (1H, d, J=8Hz, H-6), 7.38 (1H, dd, J=8 and 2Hz, H-5), 7.88 (1H, d, J=2Hz, H-3).

m/z 210 (M^+ , 38%), 165 ($M^+ - CO_2H$, 88%), 148 (100%).

b) N-(4-Methyl-2-nitrophenyl)glycine ethyl ester (2.38g, 0.01mol) was heated under reflux in concentrated hydrochloric acid (100ml) for 2h. The acid was then evaporated off in vacuo and the residue recrystallised from aqueous ethanol to give (72) (1.4g, 67%).

c) 4-Methyl-2-nitroaniline (5.7g, 0.038mol) and bromoacetic acid (5.2g, 0.038mol) were heated in DMF (20ml) at 120° for 2h. The solution was poured into ice-water, basified (NaOH) and filtered. The filtrate was acidified (HCl) and the resultant precipitate filtered, washed with water and recrystallised twice from aqueous ethanol (charcoal). Yield (0.94g, 24%), m.p. 184-186°.

d) 4-Methyl-2-nitroaniline (11.4g, 0.075mol) and bromoacetic acid (10.4g, 0.075mol) were melted together at 120° and kept at this temperature for 1h. On cooling, the reaction mixture was extracted with dilute ammonia and the resultant solution acidified (HCl) to give (72) (0.7g, 9%), m.p. 183-187°.

Ethyl p-toluidinoacetate (78)

To a solution of p-toluidine (10.7g, 0.1mol) in ethanol (10ml) was added, dropwise with stirring, ethyl bromo-

acetate (8.4g, 0.05mol). After 1h the mixture was poured into ice-water and the white solid filtered off, washed with water and recrystallised from aqueous ethanol to give (78) (5.1g, 53%), m.p. 46-48° (lit.⁷⁰, 48-49°).

$\nu_{\max}(\text{cm}^{-1})$ 3360 (N-H), 1715 (C=O).

N-(4-Methyl-2,6-dinitrophenyl)N-nitroglycine ethyl ester (80)

a) To ethyl p-toluidinoacetate (4.0g, 0.02mol) was added nitric acid (65%, 120ml) at 0-5° with stirring. After 1h the mixture was poured into ice-water and the white precipitate filtered off and washed with water. Recrystallisation from ethanol gave (80) (2.9g, 44%), m.p. 111-113°.

(Found: C, 40.5; H, 3.7; N, 17.2; $\text{C}_{11}\text{H}_{12}\text{N}_4\text{O}_8$ requires C, 40.25; H, 3.7; N, 17.1%).

$\nu_{\max}(\text{cm}^{-1})$ 1740 (C=O).

δ (CDCl_3) 1.30 (3H, t, $J=6\text{Hz}$, CH_2CH_3), 2.65 (3H, s, CH_3), 4.25 (2H, q, $J=6\text{Hz}$, CH_2CH_3), 4.70 (2H, s, CH_2), 8.25 (2H, s, H-3, H-5).

b) The above procedure using nitric acid (40%) gave (80) as the only isolable product but in greatly reduced yield (5%). With more dilute nitric acid no solid product was

obtained.

N-(4-Methyl-2-nitrophenyl)glycine ethyl ester (77)

a) 4-Methyl-2-nitroaniline (22.8g, 0.15mol) and ethyl bromoacetate (12.6g, 0.075mol) were heated at 120° for 4.5h. The cooled reaction mixture was extracted with dry ether and the extract evaporated to dryness in vacuo to yield an orange-red oil. Recrystallisation (4 times) from ethanol gave (77) (5.1g, 29%), m.p. 61-63° (lit.⁷¹, 65°).

Variation of reaction time and proportions of reagents used failed to improve the yield.

b) A solution of N-(4-methyl-2-nitrophenyl)glycine (1.5g, 7.1×10^{-3} mol) in ethanol (150ml) was saturated with hydrogen chloride gas and then heated under reflux. After 45min esterification was complete, by T.L.C. The solvent was evaporated off and the residue recrystallised from ethanol to give (77) (1.4g, 83%), m.p. 64-65°.

$\nu_{\max}(\text{cm}^{-1})$ 3380 (N-H), 1745 (C=O), 1530 and 1360 (NO₂).
 δ (CDCl₃), 1.33 (3H, t, CH₂CH₃), 2.28 (3H, s, ArCH₃), 4.10 (2H, d, NHCH₂), 4.33 (2H, q, CH₂CH₃), 6.68 (1H, d, H-6), 7.33 (1H, dd, H-5), 8.03 (1H, d, H-3), 8.28 (1H, bs, NH),
 $J_{\text{CH}_2, \text{CH}_3} = 7\text{Hz}$, $J_{\text{CH}_2, \text{NH}} = 5\text{Hz}$, $J(\text{ortho}) = 8\text{Hz}$,
 $J(\text{meta}) = 2\text{Hz}$.

Ethyl 5-methylbenzimidazole-2-carboxylate 3-oxide (84)

a) N-(4-Methyl-2-nitrophenyl)glycine ethyl ester (2.5g) was dissolved in ethanol (90ml) containing DMF (5ml) and the solution cooled to 0-5°. To this mixture was added, dropwise and with stirring, sodium ethoxide solution [from sodium, (0.23g, 0.01mol) in ethanol (20ml)]. An instant colour change from orange to deep red was noted and this solution was allowed to warm to room temperature and stand for a further 2h. The solvent was removed in vacuo and the residue partitioned between ether and water. The aqueous layer was acidified (HCl) and the resultant yellow precipitate filtered off, washed with water, and dried in vacuo (1.9g, m.p. 124-131°). Recrystallisation from ethanol gave (84) (1.0g, 46%), m.p. 144-145°.

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 2600 (broad), 1720 (C=O).

δ 1.38 (3H, t, J=6Hz, CH_3CH_2), 2.50 (3H, s, 5- CH_3), 4.50 (2H, q, J=6Hz, CH_2CH_3), 7.30 (1H, dd, J=8 and 1Hz, H-6), 7.51 (1H, d, J=1Hz, H-4), 7.80 (1H, d, J=8Hz, H-7).

b) At 60° in ethanol the above procedure gave an approximately 50:50 mixture (by n.m.r. in CDCl_3) of the ethyl ester (84) and 5-methylbenzimidazole 3-oxide (73).

N-Formyl-o-nitroaniline

A solution of o-nitroaniline (13.8g, 0.1mol) in formic acid (98%, 20ml) was heated under reflux for 2h. On cooling, a crystalline material was deposited which was filtered off and washed with cold ethanol. Recrystallisation from ethanol gave the formyl compound (11.5g, 69%), m.p. 122° (lit.⁷², 122°).

N-Formyl-4-methyl-2-nitroaniline (83) was similarly prepared from 4-methyl-2-nitroaniline (15.2g, 0.1mol) and formic acid (98%, 20ml). Yield (12.9g, 72%), m.p. 124-125° (from ethanol; no lit. m.p. quoted⁷³).

$\nu_{\max}(\text{cm}^{-1})$ 3260 (NH), 1705 and 1670.

δ (CDCl₃) 2.42 (3H, s, CH₃), 7.60 (1H, dd, H-5), 8.10 (1H, d, H-3), 8.60-8.90 (2H, unresolved, NH and H-6), 10.0-10.5 (1H, bs, CHO); $J_{3,5}=2\text{Hz}$, $J_{5,6}=8\text{Hz}$.

Benzimidazole N-oxide (with M. Mitchell; based on a patent method of Shionogi & Co. Ltd.¹⁰)

To a suspension of palladium on carbon (5%, 1.0g) in water (15ml) was added slowly, with stirring, a solution of sodium borohydride (1.83g) in water (1.8ml). To the resultant mixture was added a 10% solution of N-formyl-o-nitroaniline (3.3g, 0.02mol), in pyridine, at such a rate

that the temperature was maintained at 35-40°; when the addition was complete (~20mins) the mixture was stirred for a further 15 min. The catalyst was filtered off and the filtrate evaporated in vacuo. The residue was dissolved in water (~70ml), acidified (conc. HCl), reduced to approximately half volume and neutralised (aq NH₃, d 0.88) before being evaporated to dryness. The residue was extracted with hot ethanol. On cooling the ethanolic solution deposited inorganic material which was filtered off. The filtrate was further concentrated and, on cooling, gave benzimidazole N-oxide (0.5g, 19%), m.p. 210-212° (lit.¹⁰, 210-212°).

5-Methylbenzimidazole 3-oxide (73)

a. Reduction of N-formyl-4-methyl-2-nitroaniline by the method described above for the formation of benzimidazole N-oxide gave (73) in 10-15% yield. It had m.p. 170-173°, (raised to 174-174.5° on recrystallisation from aqueous ethanol). Aboulez and El-Sheikh⁴⁴ reported m.p. 176-178°

(Found: C, 64.6; H, 5.45; N, 19.0. C₈H₈N₂O
requires C, 64.85; H, 5.4; N, 18.9%)

$\nu_{\max}(\text{cm}^{-1})$ 2500, 1650 (br, NH/OH).

N.m.r. see Table 1 p. 50.

m/z 148 (100%), 132 (38%), 131 (45%), 119 (35%).

b. From hydrolysis of ethyl 5-methylbenzimidazole-2-carboxylate 3-oxide (84)

A solution of the ester (84), (1.0g, 4.5×10^{-3} mol) in concentrated hydrochloric acid (25ml) was heated under reflux for 4h. On cooling, a white crystalline solid was deposited, filtered off and dried in vacuo. This highly water-soluble material was 5-methylbenzimidazole 3-oxide hydrochloride (85) in almost pure form (0.7g, 85%). It had m.p. 220-224°, elevated to 227-230° on recrystallisation from ethanol.

(Found: C, 51.9; H, 4.8; N, 15.0; $C_8H_9ClN_2O$ requires C, 52.05; H, 4.9; N, 15.2%).

$\nu_{\max}(\text{cm}^{-1})$ 2500 (broad).

N.m.r. see Table 1 p. 50.

The hydrochloride (0.25g, 1.4×10^{-3} mol) was dissolved in aqueous ammonia (d 0.88; 10ml). The solution was concentrated in vacuo at 50°. 5-Methylbenzimidazole 3-oxide (0.15g, 72%) was precipitated in almost pure form (m.p. 168-170°; n.m.r. identical with an authentic sample).

5-Methylbenzimidazolone (74)

3,4-Diaminotoluene (6.1g, 0.05mol) was dissolved in pentan-1-ol (20ml). Urea (3.0g, 0.05mol) was added and the mixture was heated until ammonia evolution had ceased (2h). On cooling, a white solid was obtained which was filtered off, washed with cold ethanol and recrystallised from ethanol to give 5-methylbenzimidazolone (2.8g, 38%), m.p. 297-300° (lit.⁷⁴, 299-300°).

$\nu_{\max}(\text{cm}^{-1})$ 3100 (broad NH), 1740 (C=O).

δ 2.25 (3H, s, CH₃), 6.75 (3H, m, aromatic), 10.42 (2H, bs, 2 N-H's).

1,3-Diacetyl-5-methylbenzimidazolone (76)

a) 5-Methylbenzimidazolone (0.5g) was heated under reflux for 4h in acetic anhydride (3ml). On cooling in ice a white solid was obtained which was washed with cold ethanol and recrystallised from ethanol to give 1,3-diacetyl-5-methylbenzimidazolone (0.4g, 64%), m.p. 181- 182° (lit.⁴⁴, 176-177°).

$\nu_{\max}(\text{cm}^{-1})$ 1750, 1715 (C=O's).

b) 5-Methylbenzimidazole 3-oxide (0.5g, 3.4×10^{-3} mol) was heated under reflux in acetic anhydride (15ml) for 2h.

The mixture was then cooled, poured into ice-water and the white precipitate filtered off. Recrystallisation from ethanol gave (76) (0.4g, 51%), m.p. and i.r. identical with an authentic sample.

Action of acetic anhydride on (4-methyl-2-nitrophenyl)-glycine⁴⁴ (72)

a) The glycine (72) (1.3g, 6.2×10^{-3} mol) was heated under reflux in acetic anhydride (12ml) for 12h. Upon removal of the acetic anhydride in vacuo the black sticky residue was treated with aqueous ammonia (25%, 10ml) by heating under reflux for 1h. No precipitation occurred on "expulsion of the ammonia"⁴⁴ in vacuo (in contrast to the published claims), even on cooling in ice.

The mixture was now evaporated to dryness to yield a black tar, a small quantity of which (~100mg) was removed, dried in vacuo, and its n.m.r. spectrum recorded (see fig 4a, p. 56). Water (20ml) was added to the remainder of the tar and the heterogeneous mixture stirred vigorously for 10min. A small quantity of precipitate formed, which was decanted off in the aqueous layer. Filtration yielded a very small quantity of brown solid (~20mg) which was dried in vacuo and an n.m.r. spectrum recorded (see fig 4b). Finally, acidification of the filtrate (HCl) gave a yellow semi-solid (~150mg), found to be predominantly N-acetyl-N-

(4-methyl-2-nitrophenyl)glycine (86) by n.m.r. (see fig 4c).

b) The glycine (72) (1.3g) was heated in boiling acetic anhydride (12ml) for 8h. The acetic anhydride was removed in vacuo and the residue treated with aqueous ammonia (25%, 10ml) by heating under reflux for 1h. The mixture was now evaporated to dryness to give a black tar which was dried in desiccator over calcium chloride. N.m.r. spectrum was then recorded (see fig 1). Trituration of the tar with chloroform did not yield any solid, in contrast to the published claims. All attempts to isolate any pure product failed.

N-Acetyl-N-(4-methyl-2-nitrophenyl)glycine (86)

N-(4-Methyl-2-nitrophenyl)glycine (1.8g, 8.6×10^{-3} mol) was dissolved in acetic anhydride (20ml) by heating, with stirring, at 70° over 15 min. The mixture was kept at this temperature for a further 1h, during which time the solution changed colour from orange to yellow. The solution was then diluted with water (100ml) and vigorously stirred until homogeneous. Upon standing overnight a crystalline product was deposited. This was filtered off and recrystallised from water to give N-acetyl-N-(4-methyl-2-nitrophenyl)glycine (86) (0.80g, 37%), m.p. 148-150°.

(Found: C, 52.2; H, 4.8; N, 11.1; $C_{11}H_{12}N_2O_5$
requires C, 52.4; H, 4.8; N, 11.1%).

$\nu_{\max}(\text{cm}^{-1})$ 1730 (C=O, acid), 1630 (C=O, amide), 1530,
1360 (NO_2).

δ 1.75 (3H, s, CH_3 , acetyl), 2.45 (3H, s, CH_3 , (ring)),
4.49, 3.89 (2H, AB quartet, $J=17\text{Hz}$, CH_2), 7.63-8.0 (3H, m,
aromatic).

m/z 210 (50%), 165 (100%).

Action of aqueous ammonia on:

a) N-(4-methyl-2-nitrophenyl)glycine (72)

The glycine (72) (0.4g) was dissolved in aqueous ammonia
(d 0.88, 10ml) and the deep red solution was heated under
reflux for 1h. Acidification (HCl) yielded the starting
glycine (0.32g), m.p. 186-188°.

b) N-acetyl-N-(4-methyl-2-nitrophenyl)glycine (86)

Under the above procedure the acetylglycine (86) (0.2g)
was recovered unchanged (0.16g), m.p. 146-148°.

Flash Vacuum Pyrolysis

N-(4-Methyl-2-nitrophenyl)glycine (72)

1) Furnace temperature 750°

The glycine (72) (200mg, 9.5×10^{-4} mol) was volatilised at 130-140° and a pressure of $7-9 \times 10^{-2}$ mm Hg. Upon pyrolysis, a white solid was collected near the furnace outlet (35mg), m.p. 296-300°. Mixed melting point, i.r. and n.m.r. (see fig 5c) all indicated the product to be almost pure 5-methylbenzimidazolone (74) (18%).

2) Furnace temperature 700°

The glycine (72) (180mg, 8.6×10^{-4} mol) was volatilised at 120-140° and a pressure of $1-2 \times 10^{-2}$ mm Hg. Upon pyrolysis a pale orange solid was collected near the furnace outlet (50mg). N.m.r. indicated this solid to be a mixture of three components in approximate yield (by n.m.r. see fig 5b):

N-(4-methyl-2-nitrophenyl)glycine (72) (12%)

5-methylbenzimidazolone (74) (12%)

5-methylbenzimidazole N-oxide (73) (10%)

3) Furnace temperature 650°

The glycine (72) (300mg, 1.4×10^{-3} mol) was volatilised at ..

120-130° and a pressure of $1-2 \times 10^{-2}$ mm Hg. Upon pyrolysis an orange solid was collected near the furnace outlet. (150mg), m.p. 135-142°. N.m.r. again revealed this to be a mixture of three components in approximate yield (by n.m.r. see fig 5a):

| | |
|---|-------|
| <u>N-(4-methyl-2-nitrophenyl)glycine</u> (72) | (34%) |
| <u>5-methylbenzimidazolone</u> (74) | (12%) |
| <u>5-methylbenzimidazole N-oxide</u> (73) | (11%) |

The yields of (74) and (73), based on the glycine consumed, were 19% and 17% respectively.

N-Acetyl-N-(4-methyl-2-nitrophenyl)glycine (86)

The glycine (86) (70mg, 2.8×10^{-4} mol) was volatilised extremely slowly at 125-130° and a pressure of $4-6 \times 10^{-2}$ mm Hg. Upon pyrolysis at 770° a small quantity of white solid was collected near the furnace outlet (5mg), m.p. 283-286°. I.r. showed this solid to be 5-methylbenzimidazolone (74) (12%).

5-Methylbenzimidazole 3-oxide (73)

The N-oxide (73) (90mg, 6.1×10^{-4} mol) was volatilised at 120-125° and a pressure of $5-7 \times 10^{-2}$ mm Hg. Upon pyrolysis at 750° a white solid was collected near the furnace

outlet (35mg), m.p. 296-298°; I.r. and mixed m.p.
indicated this to be 5-methylbenzimidazolone (74) (39%).

Chapter 3 : Experimental

2,4-Dinitrophenylglycine ethyl ester (94)

To chloro-2,4-dinitrobenzene (20.4g, 0.1mol) dissolved in ethanol (200ml) was added glycine ethyl ester hydrochloride (14.0g, 0.1mol) and sodium bicarbonate (16.8g, 0.2mol). The mixture was heated under reflux for 2h and poured into ice-water. The resultant bright yellow precipitate was filtered off and washed with ethanol and water. Recrystallisation from acetic acid gave (94) (18.5g, 74%), m.p. 142-144° (lit.⁷⁵, 144°).

$\nu_{\max}(\text{cm}^{-1})$ 3320 (N-H), 1725 (C=O), 1575, 1320 (NO₂).

Ethyl 5-nitrobenzimidazole-2-carboxylate 3-oxide (95)

2-4-Dinitrophenylglycine ethyl ester (5.0g, 0.019mol) was dissolved in ethanol (200ml) and piperidine (3.4g, 0.04mol) added. The mixture was heated under reflux for 1h and cooled. The resultant precipitate was filtered off and recrystallised from ethanol to give unreacted ester (94) (1.0g). The filtrate was evaporated in vacuo and the residue dissolved in water. Acidification (HCl) gave a pale yellow precipitate which was filtered off and washed with water. Recrystallisation from ethanol gave (95) (2.0g, 54%), m.p. 209-210°.

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 2500 (b, NH/OH), 1715 (C=O), 1540, 1340
(NO₂).

δ 1.40 (3H, t, J=6Hz, CH_3CH_2), 4.50 (2H, q, J=6Hz,
 CH_2CH_3), 8.07 (1H, d, J=9Hz, H-7), 8.30 (1H, dd, J=9 and
2Hz, H-6), 8.55 (1H, J=2Hz, H-4).

5-Nitrobenzimidazole 3-oxide (92)

Ethyl 5-nitrobenzimidazole-2-carboxylate 3-oxide (1.3g,
 5.63×10^{-3} mol) was heated under reflux in concentrated
hydrochloric acid (33ml) for 4h. The solution was
evaporated to dryness in vacuo and the residue dissolved
in basic solution (NaOH). Acidification (HCl) gave a
white precipitate which was filtered off, washed with
water, ethanol and dried in vacuo to give (92) (0.6g,
67%), m.p. 274-276° (lit.¹¹, 274°).

$\nu_{\max}(\text{cm}^{-1})$ 2300, 1750 (b, NH/OH).

δ (60MHz) 7.75 (1H, d, J=9Hz, H-7), 8.05 (1H, dd, J=2 and
9Hz, H-6), 8.30 (1H, d, J=2Hz, H-4), 8.70 (1H, s, H-2).

Attempted preparation of Ethyl-5-aminobenzimidazole-2-carboxylate 3-oxide (96)

Ethyl 5-nitrobenzimidazole-2-carboxylate 3-oxide (1.0g, 4.3×10^{-3} mol) was dissolved in ethanol (250ml) and hydrogenated at room temperature and atmospheric pressure over Pd/C (5%, 0.3g). Hydrogen (300ml, 0.013mol) was absorbed over 15min; the catalyst was filtered off and the filtrate evaporated in vacuo, to give a buff coloured solid (0.7g), m.p. 101-105° (sublimation/decomposition). Spectroscopic evidence indicated this to be impure (96) but attempts at purification failed.

$\nu_{\max}(\text{cm}^{-1})$ 3420, 3320(NH₂), 1700 (C=O).

δ 1.35 (3H, t, J=7Hz, CH₂CH₃), 4.35 (2H, q, J=7Hz, CH₂CH₃), 6.65 (1H, m, H-4), 6.8 (1H, dd, J=2 and 9Hz, H-6), 7.5 (1H, d, J=9Hz, H-7). The spectrum was very poorly resolved.

m/z 221 (M⁺), 205 (M-16)⁺.

(Found: C, 52.7; H, 5.0; N, 17.8; C₁₀H₁₁N₃O₃
requires C, 54.3; H 5.01; N, 19.0; C₁₀H₁₁N₃O₃ + 0.5H₂O
requires C, 52.2; H, 5.25; N, 18.25%).

m-Nitroacetanilide

m-Nitroaniline (25g, 0.18mol) was dissolved, as far as possible, in acetic acid (40ml) and acetic anhydride (18.4g, 0.18mol) added with stirring. After all the anhydride had been added the resultant hot solution was allowed to stand for 30min. Upon cooling, in ice, a heavy precipitate formed which was filtered off and washed with water. Recrystallisation from ethanol gave m-nitroacetanilide (24.2g, 75%), m.p. 152-154° (lit.⁷⁶, 154-156°).

2,3-Dinitroacetanilide

m-Nitroacetanilide (42g, 0.23mol), dissolved in small portions in nitric acid (d 1.5, 150ml) was added slowly, with stirring to concentrated sulphuric acid (150ml), the temperature being kept at 0-5° by the addition of solid carbon dioxide to the mixture. The solution was then poured on to ice and the crude product filtered, washed with water and dried. Recrystallisation (twice) from ethanol gave 2,3-dinitroacetanilide (12.5g, 24%), m.p. 186-188° (lit.⁷⁶, 188°).

2,3-Dinitroaniline (98)

2,3-Dinitroacetanilide (6.5g, 0.029mol) was heated under reflux in a mixture of ethanol (130ml) and concentrated

hydrochloric acid (26ml) for 3h. The resultant orange solution was cooled and diluted with ice-water to give a yellow precipitate which was filtered off and washed with water. Recrystallisation from aqueous ethanol gave 2,3-dinitroaniline (3.2g, 60%), m.p. 125-126° (lit.⁷⁶, 126°).

N-Cyanomethyl-2,3-dinitroaniline (99)

To 2,3-dinitroaniline (4.0g, 0.022mol) was added para-formaldehyde (1.97g, 0.066mol), potassium cyanide (4.3g, 0.066mol), zinc chloride (22.9g) and acetic acid (55ml) to which had been added concentrated sulphuric acid (4 drops). The mixture was heated with stirring at 50° for 20h. Dilution of the cooled solution with water (100ml) gave a yellow precipitate which was filtered off and washed thoroughly with water. Recrystallisation from acetic acid gave (99) (3.6g, 74%), m.p. 183-185°.

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 3385 (N-H), 1560, 1360 (NO_2).

δ 4.5 (2H, d, $J=6\text{Hz}$, $\text{CH}_2\text{-NH}$), 7.38-7.90 (4H, m, aromatic and N-H). [In D_2O , 4.5 (2H, s, CH_2), 7.38-7.90 (3H, m, aromatic)].

2-Cyano-4-nitrobenzimidazole 3-oxide (97)

N-Cyanomethyl-2,3-dinitroaniline (2.2g, 0.01mol) was dissolved, as much as possible, in boiling ethanol (120ml) and potassium carbonate (1.38g, 0.01mol) was added. The heterogeneous mixture was heated under reflux for 2h to give a dark brown solution. The solvent was evaporated off in vacuo, the residue dissolved in water and filtered. Acidification (HCl) gave a brown precipitate which was filtered off and washed with water. Recrystallisation from aqueous ethanol (twice, with charcoal) gave (97) (0.7g, 34%), m.p. 203-206° (d).

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 2600 (br, NH/OH), 2240 (CN), 1520, 1335 (NO_2).
 δ 7.75 (1H, dd, $J=8.6$ and 7.8Hz , H-6), 8.3-8.55 (m, 2H, H-5, H-7) (not first order).

Reaction of N-(4-methyl-2,6-dinitrophenyl)-N-nitroglycine (80) with sodium carbonate

To a solution of (80) (1.5g , 4.6×10^{-3}) in ethanol (20ml) was added sodium carbonate (0.56g , $5.3 \times 10^{-3}\text{mol}$) and the resultant mixture heated under reflux for 2h. Evaporation of the solvent yielded a brown solid which was washed with

water and filtered off. Recrystallisation from ethanol gave 4-methyl-2,6-dinitroaniline (100) (0.5g, 55%), m.p. 168-170° (lit.⁷⁷, 171-172°).

δ (200MHz) 2.28 (3H, s, CH₃), 8.24 (2H, bs, NH₂), 8.32 (2H, s, H-3, H-5).

N-Cyanomethyl-2,6-dinitroaniline (101)

To a solution of chloro-2,6-dinitrobenzene (6.0g, 0.03mol) in dimethyl sulphoxide (7ml) was added sodium bicarbonate (5.0g, 0.03mol) and aminoacetonitrile hydrochloride (3.0g, 0.03mol). The mixture was heated, with stirring at 80-90° until effervescence ceased (~20min), cooled and poured into ice water. A brown precipitate was filtered off, washed with water and recrystallised from ethanol (twice, charcoal) to give (101) (2.4g, 36%), m.p. 119-120°.

(Found: C, 43.35; H, 2.6; N, 25.3. C₈H₆N₄O₄ requires C, 43.25; H, 2.7; N, 25.2%).

ν_{max}(cm⁻¹) 3320 (N-H), 1520, 1335 (NO₂).

δ 4.25 (2H, d, J=7Hz, CH₂-NH), 7.15 (1H, t, J=8Hz, H-4), 8.10 (1H, t, J=7Hz, NH-CH₂), 8.36 (2H, d, J=8Hz, H-3, H-5).

Reaction of (101) with potassium carbonate

To a solution of (101) (1.0g, 4.5×10^{-3} mol) in boiling ethanol (50ml) was added potassium carbonate (0.62g, 4.5×10^{-3} mol) and the mixture heated under reflux for 30min. A dark brown precipitate was filtered off, washed with water, ethanol and dried in vacuo. Yield 0.5g, m.p. 290° (explosive decomposition). Spectroscopic evidence suggests this material to be 7-nitrobenzimidazole-2-carboxylic acid 3-oxide (102) but attempts at purification failed.

$\nu_{\max}(\text{cm}^{-1})$ 3400 (b, OH), 1715 (C=O), 1520, 1340 (NO_2).

m/z Found 179.0333 (100%); $\text{C}_7\text{H}_5\text{N}_3\text{O}_3$ requires 179.0331 ($\text{M}^+ - \text{CO}_2$).

2-Fluoroacetanilide

2-Fluoroaniline (34g, 0.306mol) was dissolved in acetic acid (20ml) and acetic anhydride (20ml) added slowly with stirring. The resultant hot solution was heated at 90° for 30min and the reaction mixture evaporated in vacuo to give an oily residue. Treatment with water gave a white solid which was filtered off and washed with water. Recrystallisation from aqueous ethanol gave 2-fluoroacetanilide (37.5g, 80%), m.p. $74-75^\circ$ (lit.78, 80°).

$\max(\text{cm}^{-1})$ 3230 (N-H), 1645 (C=O).

2-Fluoro-4-nitroacetanilide

2-Fluoroacetanilide (10g, 0.065mol) was added with stirring to nitric acid (d 1.52, 100ml) at -5 to -10° . When the addition was complete (40min) the mixture was stirred for a further 5min and poured into ice-water (500ml). After 2h the resultant precipitate was filtered off and washed with water. Recrystallisation from ethanol gave 2-fluoro-4-nitroacetanilide (6.6g, 51%), m.p. $198-200^\circ$ (lit.⁷⁹, $204-205^\circ$).

2-Fluoro-4-nitroaniline

2-Fluoro-4-nitroacetanilide (6.6g, 0.033mol) was dissolved in sulphuric acid (70%, 28ml) and the mixture heated under reflux for 1h. The cooled solution was poured on to crushed ice, the resultant yellow precipitate filtered off and washed with water. Recrystallisation from aqueous ethanol gave 2-fluoro-4-nitroaniline (3.4g, 66%), m.p. $128-131^\circ$ (lit.⁷⁹, $133-134^\circ$).

$\max(\text{cm}^{-1})$ 3480, 3380 (NH_2), 1520, 1330 (NO_2).

N-Cyanomethyl-2-fluoro-4-nitroaniline (143)

To 2-fluoro-4-nitroaniline (5.0g, 0.033mol) was added paraformaldehyde (2.9g, 0.097mol), potassium cyanide (6.3g, 0.097mol), zinc chloride (16.3g) and acetic acid (160ml), to which sulphuric acid (4 drops) had been added. The mixture was heated to 50°, with stirring, over 30min and kept at this temperature for a further 5h. On cooling, the mixture was poured into ice-water and left to stand for 1h. The resultant precipitate was filtered off and washed thoroughly with water. Recrystallisation from ethanol gave the cyanomethyl compound (143) (4.0g, 62%), m.p. 151-152°.

(Found: C, 49.4; H, 3.1; N, 21.7; $C_8H_6FN_3O_2$
requires C, 49.2; H, 3.1; N, 21.5%).

$\nu_{\max}(cm^{-1})$ 3330 (N-H), 2260 (CN), 1540, 1340 (NO_2).

N.m.r. see p. 106.

Nitration of N-cyanomethyl-2-fluoro-4-nitroaniline

N-Cyanomethyl-2-fluoro-4-nitroaniline (3.6g, 0.019mol) was dissolved in sulphuric acid (98%, 30ml) at 10-15° and nitric acid (70%, 1.72g) added dropwise, with stirring. The mixture was left to stand for 15min and poured on to

crushed ice. The resultant precipitate was filtered off and recrystallised from ethanol to give the dinitroamide (112) (2.1g, 43%).

(Found: C, 37.4; H, 2.7; N, 21.4; $C_8H_7FN_4O_5$ requires C, 37.2; H, 2.7; N, 21.7%).

$\nu_{\max}(cm^{-1})$ 3380, 3240, 3140 (NH, NH_2), 1675 (CO), 1540, 1320 (NO_2).

N.m.r. see p. 109

b) Repeat of the above experiment gave N-cyanomethyl-2-fluoro-4,6-dinitroaniline (111) (22%) as the only isolable product, m.p. 130-131° (from aqueous ethanol).

(Found: C, 40.0; H, 2.1; N, 23.1; $C_8H_5FN_4O_4$ requires C, 40.0; H, 2.1; N, 23.3%).

$\nu_{\max}(cm^{-1})$ 3300 (N-H), 2240 (CN), 1530, 1330 (NO_2).

N.m.r. see p. 108.

7-Fluoro-5-nitrobenzimidazole-2-carboxamide 3-oxide (110)

The amide (112) (1.7g, 6.6×10^{-3} mol) was dissolved in ethanol (150ml) and sodium ethoxide solution [from sodium

(0.15g, in ethanol (10ml)] added. The mixture was allowed to stand for 1h, the solvent evaporated off in vacuo and the residue dissolved in water. Acidification gave a white precipitate which was filtered off and washed with water. Recrystallisation from acetone gave (110), (0.4g, 35%), m.p. 258-260° in impure form.

(Found: C, 39.2; H, 2.0; N, 22.4; $C_8H_5N_4O_4F$ requires C, 40.0; H, 2.1; N, 23.3%).

δ ¹H 8.10 (1H, dd, $J_{6,F}=11\text{Hz}$, $J_{6,4}=2\text{Hz}$, H-6), 8.35 (1H, d, $J=2\text{Hz}$, H-4), ~8.2, 8.7 (2H, CONH₂).

m/z Found 240.0301(100%); $C_8H_5FN_4O_4$ requires 240.0295.

4-Fluoroacetanilide

To a solution of 4-fluoroaniline (14.0g) in acetic acid (20ml) was added acetic anhydride (20ml) slowly, with stirring. The resultant mixture was heated at 100° for 10min and the solvent evaporated off in vacuo. The residue was washed with water, filtered and recrystallised from aqueous ethanol to give 4-fluoroacetanilide (17.3g, 90%), m.p. 149-151° (lit.⁸⁰, 150-151°).

4-Fluoro-2-nitroacetanilide

4-Fluoroacetanilide (15.3g, 0.1mol) was dissolved in concentrated sulphuric acid (170ml) and the solution cooled to 0-5°. Nitric acid (d 1.42, 6.4ml) was added with cooling and stirring, and the resultant solution poured on to crushed ice. The white precipitate was filtered off, washed with water and recrystallised from aqueous ethanol to give 4-fluoro-2-nitroacetanilide (11.4g, 58%), m.p. 69-70° (lit.⁸¹, 70.5°).

$\nu_{\max}(\text{cm}^{-1})$ 3260 (N-H), 1670 (C=O), 1520, 1340 (NO₂).

4-Fluoro-2-nitroaniline

4-Fluoro-2-nitroacetanilide (11.3g, 0.057mol) was dissolved in sulphuric acid (70%, 47ml) and the mixture heated under reflux for 1h. The cooled solution was poured on to crushed ice and the solid filtered off and washed with water. Recrystallisation from aqueous ethanol gave 4-fluoro-2-nitroaniline (7.9g, 89%), m.p. 90-91° (lit.⁸¹, 92.5°).

N-Cyanomethyl-4-fluoro-2-nitroaniline

To 4-fluoro-2-nitroaniline (6.2g, 0.04mol) was added para-

formaldehyde (3.6g, 0.12mol), potassium cyanide (7.8g, 0.12mol), zinc chloride (42.0g) and acetic acid (100ml), to which had been added concentrated sulphuric acid (4 drops). The mixture was heated, with stirring, to 50° over 30min and kept at this temperature for a further 10h. The cooled mixture was diluted with water (160ml), the resultant orange precipitate filtered off and washed thoroughly with water. Recrystallisation from ethanol gave N-cyanomethyl-4-fluoro-2-nitroaniline (4.0g, 52%), m.p. 163-164°.

(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%).

$\nu_{\max}(cm^{-1})$ 3370 (NH), 2240 (CN), 1510, 1335 (NO_2).

δ ^{19}F ($CDCl_3$) -125.5 (8 lines).

δ 1H ($CDCl_3$) 4.30 (2H, d, $J=6Hz$, CH_2NH), 6.93 (1H, dd, H-6), 7.4 (1H, 8 lines, H-5), 8.00 (1H, dd, H-3), 8.0 (1H, br, NH).

$J_{F,6}=4.4Hz$, $J_{F,3}=8.7Hz$, $J_{F,5}=7.0Hz$, $J_{6,5}=9.3Hz$,

$J_{5,3}=3.0Hz$.

2-Cyano-5-fluorobenzimidazole 3-oxide (113)

a) N-Cyanomethyl-4-fluoro-2-nitroaniline (3.4g) was dissolved in hot ethanol (170ml) and potassium carbonate (1.22g) added. The heterogeneous mixture was heated under

reflux for 1.5h and the solvent evaporated off in vacuo. The residue was dissolved in water and acidified (HCl) and the resultant white precipitate filtered off and washed with water. Recrystallisation from aqueous methanol gave (113) (2.2g, 71%), m.p. 231-232° (d).

(Found: C, 54.6; H, 2.3; N, 24.1; $C_8H_4FN_3O$ requires C, 54.25; H, 2.3; N, 23.7%).

$\nu_{\max}(cm^{-1})$ 2300 (b, OH or NH), 2230 (CN).

δ ^{19}F -112.8 (8 lines).

δ 1H 7.28 (1H, 8 lines, H-6), 7.53 (1H, 8 lines, H-4), 7.86 (8 lines, H-7), 13.0 (1H, br, NH/OH).

$J_{F,7}=4.8Hz$, $J_{F,4}=8.4Hz$, $J_{F,6}=9.8Hz$, $J_{6,4}=2.6Hz$,

$J_{6,7}=9.1Hz$, $J_{4,7}=0.6Hz$.

b) The above procedure with piperidine (1 molar equivalent) instead of potassium carbonate gave (113) (46%), m.p. 227-230°.

Alkylation of 2-cyano-5-fluorobenzimidazole 3-oxide (113)

a) The N-oxide (113), (1.0g, 0.005mol) was added to a solution of sodium hydroxide (0.24g, 0.006mol) in ethanol (12ml) and water (0.5ml). To this mixture was added iodoethane (0.94, 0.006mol) and the resultant mixture heated under reflux for 1h. The solvent was evaporated off in

vacuo and the residue partitioned between ether and water. Acidification of the aqueous layer gave no precipitation, indicating that all of the N-oxide (113) had been consumed. The ether layer was dried over sodium sulphate, filtered and evaporated in vacuo. Recrystallisation of the residue from ether-light petroleum gave the imidate ester (115), m.p. 69-71°.

(Found: C, 57.4; H, 5.7; N, 16.9; $C_{12}H_{14}N_3O_2F$ requires C, 57.4; H, 5.6; N, 16.7%).

$\nu_{\max}(\text{cm}^{-1})$ 3245 (N-H).

δ ^{19}F -115 (8 lines).

δ ^1H 1.40 (6H, 2xt, $J=7\text{Hz}$, 2 CH_3 's), ~4.5 (4H, 2xq, $J=7\text{Hz}$, 2 CH_2 's), 7.35 (8 lines, H-5), 7.75 (8 lines, H-7), 8.95 (8 lines, H-4), 9.35 (1H, s, NH).

$J_{\text{F},4}=4.8\text{Hz}$, $J_{\text{F},7}=8.8\text{Hz}$, $J_{\text{F},5}=10.0\text{Hz}$, $J_{5,7}=2.6\text{Hz}$,

$J_{5,4}=8.9\text{Hz}$, $J_{7,4}=0.4\text{Hz}$.

b) 2-Cyano-5-fluorobenzimidazole 3-oxide (2.0g, 0.01mol) was dissolved in ethanol (50ml) and sodium ethoxide (0.75g, 0.01mol) added. The solvent was evaporated off in vacuo and the solid residue added to acetonitrile (140ml) containing iodoethane (1.9g, 0.012mol). The mixture was heated under reflux for 1h and the solvent evaporated off in vacuo. The residue was purified by sublimation at reduced pressure to give 2-cyano-1-ethoxy-6-fluorobenzimidazole (114) (1.1g, 49%), m.p. 78-79°.

(Found: C, 58.9; H, 3.9; N, 20.5; C₁₀H₈FN₃O
requires C, 58.5; H, 3.9; N, 20.5%).

$\nu_{\max}(\text{cm}^{-1})$ 2235 (CN).

δ ¹⁹F -112 (8 lines).

δ ¹H 1.45 (3H, t, J=7Hz, CH₃CH₂), 4.70 (2H, q, J=7Hz),
7.50 (1H, 8 lines, H-5), 7.93 (1H, 8 lines, H-7), 8.08
(1H, 8 lines, H-4).

J_{F,4}=4.9Hz, J_{F,7}=8.6Hz, J_{F,5}=9.8Hz, J_{5,4}=9.2Hz,

J_{5,7}=2.6Hz, J_{7,4}=0.6Hz.

Reaction of 2-cyano-1-ethoxy-6-fluorobenzimidazole (114)
with sodium ethoxide

Compound (114), (0.15g, 7.3x10⁻⁴mol) was dissolved in ethanol (10ml). A catalytic quantity of sodium ethoxide [0.1mol equivalents in ethanol (10ml)] was added. T.L.C. indicated the reaction to be complete within 10min. The solvent was evaporated off and the residue dissolved, as much as possible, in ether and filtered. The filtrate was evaporated in vacuo and the residue recrystallised from petroleum ether to give (115), (0.10g, 55%), m.p. 69-71° (I.R., n.m.r. identical with authentic sample).

4-Amino-3-nitroacetanilide (119a)

To a solution of 2-nitro-1,4-phenylenediamine (15.3g, 0.1mol) in acetic acid (150ml) was added acetic anhydride (10.2g, 0.1mol), all at once with stirring, and the resultant mixture left to stand overnight. A precipitate was filtered off, washed with water and recrystallised from aqueous ethanol, to give (119a), (9.0g, 46%), m.p. 187-189° (d) (lit.⁸², 189°(d)).

$\nu_{\max}(\text{cm}^{-1})$ 3430 (N-H), 3280 (m) (NH₂), 1640 (C=O), 1535, 1330 (NO₂).

N-(4-Amino-3-nitrophenyl)methanesulphonamide (119b)

To a solution of 2-nitro-1,4-phenylenediamine (15.3g, 0.1mol) in pyridine (70ml) was added methanesulphonyl chloride (11.5g, 0.1 mol) over 3min, with consequent increase in temperature (to ~70°C). The solution was allowed to stand for 10min, and then heated under reflux for a further 15min. The solvent was evaporated off in vacuo and the residue washed with water and filtered. Recrystallisation from ethanol (charcoal) gave (119b), (14.6g, 63%), m.p. 166-168° (lit.⁵⁴, 168-171°).

δ 3.00 (3H, CH₃), 7.20 (1H, d, J=9Hz, H-5), 7.50 (1H, dd, J=9 and 2Hz, H-6), 7.55 (2H, s, NH₂), 8.03 (1H, d, J=2Hz,

H-2), 9.60 (1H, s, N-H).

Ethyl N-(4-amino-3-nitrophenyl)carbamate (119c)

To a solution of 2-nitro-1,4-phenylenediamine (15.3g, 0.1mol) in acetonitrile (100ml) was added pyridine (16.0g, 0.2mol) and the mixture cooled to 5°. Ethyl chloroformate (10.8g, 0.1mol) was added, dropwise, with cooling and stirring, over about 30min and the mixture allowed to warm to room temperature over a further 1h. The solvent was evaporated off in vacuo and the dark oily residue poured into ice-water with vigorous stirring. The resultant solid was filtered, washed with water and recrystallised twice from aqueous ethanol (charcoal) to give (119c), (9.1g, 40%), m.p. 129-130° (lit.⁵⁴, 129-132°).

$\nu_{\max}(\text{cm}^{-1})$ 3320 (b, N-H, NH₂), 1680 (C=O), 1540, 1340 (NO₂).

δ 1.28 (3H, t, J=7Hz, CH₂CH₃), 4.25 (2H, q, J=7Hz, CH₂CH₃), 7.11 (1H, d, J=9.2Hz, H-5), 7.40 (2H, bs, NH₂), 7.65 (1H, dd, J=9.2 and 2.2Hz, H-6), 8.40 (1H, d, 2.2Hz, H-2), 9.70 (1H, s, N-H).

N-Phenyl-N-(4-amino-3-nitrophenyl)urea (119d)

To a solution of 2-nitro-1,4-phenylenediamine (5g,

0.033mol) in acetonitrile (65ml), cooled to 15°, was added phenyl isocyanate (3.93g, 0.033mol) over 15min. A heavy precipitate formed almost immediately and the mixture was stirred for a further 10min after all the isocyanate had been added. The solid was filtered off, washed with acetonitrile and recrystallised from ethanol-dimethylformamide to give (119d), (4.9g, 55%), m.p. 223-5°.

(Found: C, 57.2; H, 4.4; N, 20.45; $C_{13}H_{12}N_4O_3$ requires C, 57.35; H, 4.4; N, 20.6%).

$\nu_{max}(cm^{-1})$ 3460 (N-H), 3280 (b, N-H, NH_2), 1625 (C=O), 1540, 1335 (NO_2).

7.1-7.75 (9H, aromatic and NH_2), 8.43 (1H, d, $J=2.4Hz$, H-2).

4-Acetamido-N-cyanomethyl-2-nitroaniline (120a)

To 4-amino-3-nitroacetanilide (8.7g, 0.045mol), was added paraformaldehyde (4.13g, 0.14mol), potassium cyanide (8.92g, 0.14mol), zinc chloride (22.8g) and acetic acid (230ml) containing concentrated sulphuric acid (9 drops). The mixture was heated to 50° over approximately 30min, with stirring, maintained at this temperature for a further 5h and left to cool overnight. The mixture was then diluted with ice-water and stirred for 30min. The solid was filtered off, washed repeatedly with water and

recrystallised from acetic acid to give (120a), (7.1g, 68%), m.p. 228-229°.

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 3350, 3380 (N-H's), 1670 (C=O).

δ 2.07 (3H, s, CH_3), 4.60 (2H, d, $J=6\text{Hz}$, $\text{CH}_2\text{-NH}$), 8.30 (1H, t, $J=6\text{Hz}$, NHCH_2), aromatic protons as in Table 2 p. 84.

N-Cyanomethyl-4-methanesulphonamido-2-nitroaniline (120b)

To N-(4-amino-3-nitrophenyl)methanesulphonamide (3.1g, 0.022mol) was added paraformaldehyde (1.98g, 0.066mol), potassium cyanide (4.29g, 0.066mol), zinc chloride (11g) and acetic acid (110ml) containing concentrated sulphuric acid (4 drops). The mixture was heated, with stirring to 50°, over about 30min, maintained at this temperature for a further 8h, and left to cool overnight. The mixture was then diluted with ice-water, and the solid filtered off and washed thoroughly with water. Recrystallisation from ethanol gave (120b) (3.1g, 52%), m.p. 169-170°.

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 3360 (N-H), 3260 (N-H), 1560, 1330 (NO₂),
1305, 1135 (SO₂).

δ 3.05 (3H, s, CH₃), 4.65 (2H, d, J=6Hz, CH₂-NH), 8.37
(1H, t, J=6Hz, NH-CH₂), 9.5-10 (1H, bs, NH-SO₂Me),
aromatic protons as in Table 2 p. 84.

N-Cyanomethyl-4-ethoxycarbonylamino-2-nitroaniline (120c)

This was similarly prepared from ethyl N-(4-amino-3-nitro-
phenyl)carbamate (8.0g). Yield (6.4g, 70%), m.p. 194-195°
(from acetic acid).

(Found: C, 50.1; H, 4.5; N, 21.2; C₁₁H₁₂N₄O₄
requires C, 50.0; H, 4.6; N, 21.2%).

δ 1.30 (3H, t, J=7Hz, CH₃-CH₂), 4.25 (2H, q, J=7Hz,
CH₂-CH₃), 4.65 (2H, d, J=6Hz, CH₂-NH), 8.30 (1H, t, 5-6Hz,
NH-CH₂), 9.85 (1H, s, NHCO₂Et), aromatic protons as in
Table 2 p. 84.

N-phenyl-N'-(4-cyanomethylamino-3-nitrophenyl) urea (120d)

This was similarly prepared from N-phenyl-N'-(4-amino-3-
nitrophenyl)urea (4.0g). Yield (3.2g, 70%), m.p. 228-229°
(from ethanol/DMF).

(Found: C, 58.2; H, 4.1; N, 22.5; $C_{15}H_{13}N_5O_3$
requires C, 57.9; H, 4.2; N, 22.5%).

$\nu_{\max}(\text{cm}^{-1})$ 3480, 3300 (br, N-H's), 1630 (C=O).

δ 4.62 (2H, d, $J=7\text{Hz}$, $\text{CH}_2\text{-NH}$), 7.05-7.9 (7H, m, aromatic),
8.60 (1H, d, H-2), 8.82, 8.92 (2H, 2 urea N-H's).

5-Acetamido-2-cyanobenzimidazole 3-oxide (121a)

4-Acetamido-N-cyanomethyl-2-nitroaniline (7.0g, 0.03mol)
was dissolved, as much as possible, in hot ethanol
(320ml). Potassium carbonate (4.1g, 0.03mol) was added
carefully, and the heterogeneous mixture heated under
reflux for 45min. Evaporation of the solvent in vacuo
yielded a pale solid which was dissolved in water (300ml)
and filtered. The filtrate was acidified (HCl), with
cooling and stirring, to give a white precipitate which
was filtered off and washed with water. Recrystallisation
from aqueous ethanol gave (121a) (4.6g, 71%), m.p. 233-
234°.

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 3320 (N-H), 2600 (broad N-H/OH), 2230 (CN),
1630 (C=O).

δ 2.17 (3H, s, CH_3), 10.40 (1H, s, NH), 13.0-13.5 (bs,

OH/NH), aromatic protons as in Table 2 p. 84.

2-Cyano-5-methanesulphonamidobenzimidazole 3-oxide (121b)

This was similarly prepared from N-cyanomethyl-4-methanesulphonyl-2-nitroaniline (5.7g) but with a slightly longer reaction time (1hr) to give (121b), (4.5g, 86%), m.p. 223-224° (d) (from aqueous ethanol).

(Found: C, 42.8; H, 3.0; N, 22.3; C₉H₈N₄O₃S
requires C, 42.85; H, 3.2; N, 22.2%).

$\nu_{\max}(\text{cm}^{-1})$ 3300 (broad N-H), 3200 (broad N-H/OH), 2235 (CN), 1320, 1145 (SO₂).

δ 3.15 (3H, s, CH₃), 10.35 (1H, s, NHSO₂), aromatic protons as in Table 2 p. 84.

2-Cyano-5-ethoxycarbonylamino benzimidazole 3-oxide (121c)

This was similarly prepared from (120c) (6.0g) with a reaction time of 1.5h; yield (3.7g, 65%), m.p. 215-216° (d) (from aqueous ethanol).

(Found: C, 53.8; H, 4.0; N, 22.7; C₁₁H₁₀N₄O₃
requires C, 53.7; H, 4.1; N, 22.75%).

$\nu_{\max}(\text{cm}^{-1})$ 3220 (N-H), 3050 (broad N-H/OH), 2220 (CN), 1680 (C=O).

δ 1.30 (3H, t, $J=7\text{Hz}$, CH_2CH_3), 4.30 (2H, q, $J=7\text{Hz}$, CH_2CH_3), 10.07 (1H, s, NH), 12.7-13.5 (1H, bs, NH/OH), aromatic protons as in Table 2 p. 84.

2-Cyano-5-(phenylureylene)-benzimidazole 3-oxide (121d)

(121d) was similarly prepared from (120d) (1.5g, 53%) m.p. 270° . This material could not be readily purified and was characterised on the basis of its n.m.r. spectrum alone.

δ 7.00-7.90 (7H, m, aromatic), 8.25 (1H, d, $J=2\text{Hz}$, H-4), 8.90, 9.22 (2H, singlets, 2 urea N-H's), 12.5-13.5 (1H, b, N-H/OH).

6-Acetamido-2-cyano-1-ethoxybenzimidazole (122a)

5-Acetamido-2-cyanobenzimidazole 3-oxide (121a) (3.0g, 0.014mol) was dissolved in hot ethanol (80ml) and triethylamine (1.42g, 0.014mol) in ethanol (10ml) added. To this solution was added iodoethane (2.34g, 0.015mol) in ethanol (10ml) and the mixture heated under reflux for 2h. T.L.C. indicated some unreacted N-oxide and the mixture was thus recharged with 0.5molar equivalents each

of triethylamine and iodoethane and heated under reflux for a further 30min. The solvent was evaporated off in vacuo and the oily residue treated with cold water to yield an off-white solid which was filtered and washed with water. Recrystallisation from water/propan-2-ol (5:1) gave (122a) as a partial hydrate (2.8g, 81%), m.p. 128-129° (or 133-135°).

(Found: C, 57.2; H, 4.8; N, 22.3; $C_{12}H_{12}N_4O_2 + \frac{1}{3}(H_2O)$ requires C, 57.6; H, 5.1; N, 22.4%).

$\nu_{\max}(\text{cm}^{-1})$ ca. 3500 ($H_2O?$), 3290 (NH), 2220 (CN), 1670 (C=O).

δ 1.40 (3H, t, $J=7\text{Hz}$, $\text{CH}_3\text{-CH}_2$), 2.12 (3H, s, CH_3CO), 4.55 (2H, q, $J=7\text{Hz}$, $\text{CH}_2\text{-CH}_3$), 10.30 (1H, s, N-H), aromatic, see Table 2 p. 84.

2-Cyano-1-ethoxy-6-methanesulphonamidobenzimidazole (122b)

2-Cyano-5-methanesulphonamidobenzimidazole 3-oxide (7.2g, 0.029mol) was dissolved in hot ethanol (180ml). Triethylamine (3.22g, 0.032mol) and then iodoethane (5.0g, 0.032mol), both in ethanol (10ml), were added. The mixture was heated under reflux for 2h and the solvent evaporated off in vacuo to yield a white solid which was mixed with water and filtered off. Recrystallisation from ethanol gave (122b), (6.0g, 75%), m.p. 199-200°.

(Found: C, 46.9; H, 4.3; N, 19.85; $C_{11}H_{12}N_4O_3S$
requires C, 47.1; H, 4.3; N, 20.0%).

$\nu_{\max}(\text{cm}^{-1})$ 3100 (N-H), 2225 (CN), 1320 and 1130 (SO_2).
 δ 1.43 (3H, t, $J=6\text{Hz}$, $\underline{CH_3-CH_2}$), 3.08 (3H, s, CH_3-SO_2),
4.55 (2H, q, $J=6\text{Hz}$, $\underline{CH_2-CH_3}$), 10.0-10.25 (1H, bs, N-H),
aromatic as in Table 2 p. 84.

2-Cyano-1-ethoxy-6-ethoxycarbonylamino benzimidazole (122c)

2-Cyano-5-ethoxycarbonylamino benzimidazole 3-oxide (121c)
(0.8g, 3.25×10^{-3} mol) was similarly alkylated to give
(122c) (0.60g, 67%), m.p. 162-164° (from H_2O : ethanol,
2:1).

(Found: C, 56.6; H, 5.0; N, 20.6; $C_{13}H_{14}N_4O_3$
requires C, 56.9; H, 5.1; N, 20.4%).

$\nu_{\max}(\text{cm}^{-1})$ 3270 (N-H), 2225 (CN), 1685 (C=O).
 δ 1.28 (3H, t, $J=7\text{Hz}$, $O-CH_2\underline{CH_3}$), 1.33 (3H, t, $J=7\text{Hz}$,
 $\underline{CH_3CH_2}$), 4.15 (2H, q, $J=7\text{Hz}$, $O-\underline{CH_2CH_3}$). 4.55 (2H,
q, $J=7\text{Hz}$, $O-\underline{CH_2CH_3}$), 10.00 (1H, s, NH), aromatic as
in Table 2 p. 84.

6-Amino-2-cyano-1-ethoxybenzimidazole hydrochloride (123)

6-Acetamido-2-cyano-1-ethoxybenzimidazole (1.0g, 4.1×10^{-3} mol) was dissolved in ethanol (30ml) and concentrated hydrochloric acid (6ml) added. The mixture was heated under reflux for 3h and then evaporated to dryness in vacuo and further dried over silica gel to give (123) (0.7g, 71%).

I.R. very poorly resolved but no trace of carbonyl, indicating that deacetylation had occurred.

δ (DMSO + D₂O) 1.45 (3H, t, J=7Hz, CH₃-CH₂), 4.60 (2H, q, J=7Hz, CH₂-CH₃), 7.40 (1H, dd, J=9 and 2Hz, H-5), 7.65 (1H, d, J=2Hz, H-7), 7.90 (1H, d, J=9Hz, H-4). No trace of CH₃CO.

In the absence of D₂O additional protons were present between 7.0-7.5 (NH₂ + HCl).

m/z 202*(40)M⁺; 157(100)M⁺-OEt.

* Found 202.0865; C₁₀H₁₀N₄O requires 202.0854.

N,N-Diacetyl-2,3-dinitroaniline (126)

2,3-Dinitroacetanilide (2.3g, 0.01mol) was heated under reflux in acetic anhydride (20ml), to which had been added

concentrated sulphuric acid (2 drops), for 15min. The reaction mixture was poured into ice-water and the resultant white precipitate filtered off and washed with water. Recrystallisation from ethanol gave (126) (1.5g, 56%), m.p. 131-132°.

(Found: C, 44.9; H, 3.3; N, 15.7; $C_{10}H_9N_3O_6$ requires C, 44.95; H, 3.4; N, 15.7%).

$\nu_{\max}(\text{cm}^{-1})$ 1700 (C=O), 1530, 1340 (NO_2).

δ ^1H 2.35 (6H, s, $2 \times \text{CH}_3$), 8.3 (2H, m, H-5, H-6), 8.70 (1H, dd, $J=7.6$ and 2.0Hz , H-4).

Reaction of N,N-diacetyl-2,3-dinitroaniline (126) with dimethylamine

(126) (1.34g, 5×10^{-3} mol) was dissolved in ethanol (15ml) and dimethylamine (5ml, 40% aq. solution) was added dropwise. The mixture was heated under reflux for 1h and diluted with water (200ml). No precipitate was thus obtained and the aqueous solution was evaporated in vacuo. The resultant red oil was triturated with aqueous ethanol and a yellow solid filtered off. Recrystallisation from aqueous ethanol gave 3-(N,N-dimethylamino)-2-nitroacetanilide (124) (0.22g, 20%), m.p. 121-123° (lit.⁵⁶, 127°).

$\nu_{\max}(\text{cm}^{-1})$ 1640 (C=O), 1520, 1340 (NO_2).

δ (CDCl₃) 2.20 (3H, s, CH₃CO), 2.90 (6H, s, N(CH₃)₂), 7.95 (1H, dd, J=2 and 8Hz, H-6), 7.47 (1H, t, J_{5,4}=J_{5,6}=8Hz, H-5), 6.90 (1H, dd, J=2 and 8Hz, H-4), 9.75 (1H, bs, NH).

2-Nitroisophthalic acid

To a solution of potassium permanganate (42g, 0.29mol) and potassium hydroxide (8.8g, 0.16mol) in water (400ml) was added 2-nitro-m-xylene (10g, 0.066mol). The mixture was heated under reflux, with overhead stirring, for 15h. After cooling, the manganese dioxide formed was filtered off. The filtrate was neutralised (HCl) and any monoacid precipitate filtered off. The filtrate was now acidified (HCl) and the white solid filtered off and washed with water. Recrystallisation from aqueous methanol gave 2-nitroisophthalic acid (6.8g, 49%), m.p. 309-311° (lit.⁸³, 315°).

ν_{\max} (cm⁻¹) 2500 (broad, OH), 1680 (C=O), 1560, 1360 (NO₂).

2-Nitroisophthalic diamide (127)

2-Nitroisophthalic acid (18g, 0.085mol) in thionyl chloride (54ml) containing dimethylformamide (1ml) was

heated under reflux for 4.5h. On cooling the bis-acid chloride precipitated and was filtered, washed with petroleum (40/60) and dried in vacuo. Yield (17.0g, 81%), m.p. 128-130°.

The acid chloride (11.5g, 0.046mol) was added in small portions with stirring to aqueous ammonia solution (d 0.88, 310ml) over 1h. The heterogeneous mixture was stirred for a further 4h and the solid filtered off, washed with water and recrystallised from water to give (127) (7.5g, 75%), m.p. 278-280° (lit.⁵⁵, 278-280°).

$\nu_{\max}(\text{cm}^{-1})$ 3300 (broad, NH_2), 1650 (C=O), 1530, 1370 (NO_2).

δ 7.85 (5H, m), 8.40 (2H, m).

2-Nitro-1,3-phenylenediamine (117)

To a solution of sodium hydroxide (25g, 0.063mol) in water (35ml) was added ice (144g) and a stream of chlorine passed through the mixture until 19.2g had been absorbed. The solution was made up to 200ml to give aqueous sodium hypochlorite (1.35M).

The powdered diamide (127) (5.9g, 0.03mol) was added slowly, with stirring, to this freshly prepared solution of sodium hypochlorite (44ml, 0.06mol), diluted with water to

260ml at 0°. When all the diamide had dissolved (~1h) the solution was diluted with sodium hydroxide (1%, 175ml).

The solution was passed down through the spiral of a condenser (Quickfit C3/12) which was held upright while a rapid current of steam was passed through the body of the condenser. The flow rate was adjusted so that colour formation was complete before the solution was half way through the spiral. 2-Nitro-1,3-phenylenediamine (117) crystallised from the cooled solution. The product was filtered, washed with water and recrystallised from aqueous ethanol. Yield (3.2g, 70%), m.p. 137-139° (lit.⁵⁵, 141°).

δ 6.20 (2H, d, J=8Hz, H-4, H-6), 6.65 (4H, bs, 2xNH₂), 7.12 (1H, t, J=8Hz, H-5).

3-Methanesulphonamido-2-nitroaniline (129)

2-Nitro-1,3-phenylenediamine (1.2g, 8.0x10⁻³mol) was dissolved in pyridine (9ml) and methanesulphonyl chloride (1.0g, 8.7x10⁻³mol) added. The mixture was heated under reflux for 2h and the solvent evaporated off in vacuo. The residue was dissolved in a little ethanol and the resultant solution poured into ice-water, with stirring. The precipitate was filtered off and recrystallised from aqueous ethanol to give (129) (0.75g, 41%), m.p. 170-173°.

(Found: C, 36.4; H, 3.8; N, 18.1; $C_7H_9N_3O_4S$
requires C, 36.4; H, 3.9; N, 18.2%).

δ 3.05 (3H, s, CH_3), 6.50-6.85 (4H, m, H-4, H-6 and NH_2
(exchanged with D_2O)), 7.1-7.4 (1H, m, H-5).

N-Cyanomethyl-3-methanesulphonamido-2-nitroaniline (130)

To the nitrosulphonamidoamine (129) (2.1g, 9.1×10^{-3} mol) was added paraformaldehyde (0.82g, 0.027 mol), potassium cyanide (1.78g, 0.027 mol), zinc chloride (4.5g) and acetic acid (45ml) containing concentrated sulphuric acid (2 drops). The mixture was heated, with stirring, at 50° for 7h, cooled and poured into ice-water. The orange precipitate was filtered, washed thoroughly with water and recrystallised from aqueous acetic acid to give (130) (1.0g, 41%), m.p. $186-188^\circ$.

(Found: C, 39.8; H, 3.7; N, 20.4; $C_9H_{10}N_4O_4S$
requires C, 40.0; H, 3.7; N, 20.7%).

$\nu_{max}(cm^{-1})$ 3380, 3240 ($NH's$), 1580, 1340 (NO_2), 1360,
1145 (SO_2).

δ 3.05 (3H, s, CH_3), 4.38 (2H, d, $J=6Hz$, $\underline{CH_2NH}$), 7.90 (3H,
m, aromatic and N-H), 7.35 (1H, dd, $J=8$ and $9Hz$, H-5),
9.77 (1H, s, $\underline{NH-SO_2Me}$).

Reaction of (130) with potassium carbonate

Compound (130), (0.75g, 2.8×10^{-3} mol) was dissolved, as much as possible, in boiling ethanol (50ml). Potassium carbonate (0.39g, 2.8×10^{-3} mol) was added and the mixture heated under reflux for 1.5h, solution being attained after 30min. The solvent was evaporated off in vacuo and the residue dissolved in water. Acidification (HCl) gave a red precipitate which was filtered, washed with water and dried over silica gel to yield impure (130) (0.45g, 60% recovery), m.p. 169-171°, I.R. and n.m.r. identical with the authentic sample.

2,1,3-Benzoselenadiazole

To a solution of o-phenylenediamine (36.6g, 0.34mol) in hot ethanol (210ml) was added a filtered solution of selenium dioxide (41.3g, 0.37mol) and the resultant mixture heated under reflux for 10min. The mixture was cooled and a white solid filtered off. Recrystallisation from water gave the selenadiazole, (47.2g, 76%), m.p. 70-73° (lit.⁸⁴, 75°).

4-Nitro-2,1,3-benzoselenadiazole

To a solution of 2,1,3-benzoselenadiazole (50g) in con-

concentrated sulphuric acid (110ml) was added a mixture of nitric acid (d 1.4, 27.2ml) and concentrated sulphuric acid (55ml), with cooling and stirring at 0-10°. On completion of the addition (~1hr), the mixture was allowed to warm to room temperature over 30min and was then poured on to crushed ice. A yellow precipitate was filtered off, washed with water and recrystallised from dimethylformamide to give the nitro-compound (46.6g, 75%), m.p. 216-218° (lit.⁸⁵, 219-221°, from ethanol).

3-Nitro-1,2-phenylenediamine (118)

4-Nitro-2,1,3-benzoselenadiazole (11.4g, 0.05mol) was added to a solution of hydriodic acid (d 1.7, 126ml) and the mixture heated at 50° for 1.5h. The cooled mixture was treated with sodium bisulphite solution (40%w/w, 200ml) to remove iodine and basified with sodium hydroxide (30%, 180ml). The resultant red precipitate was filtered off and washed with water. Recrystallisation from propan-2-ol(charcoal) gave (118) (5.2g, 68%), m.p. 157-158° (lit.⁵⁸, 158-159°).

2-Nitro-6-p-toluenesulphonamidoaniline (131b)

3-Nitro-1,2-phenylenediamine (4.0g, 0.026mol) was dissolved in dry pyridine (40ml) and *p*-toluenesulphonyl

chloride (5.5g, 0.029mol) added. The resultant mixture was heated under reflux for 30min and the solvent evaporated off in vacuo. The oily residue was treated with water and the solid thus obtained filtered off and washed with water. Recrystallisation from ethanol (charcoal) gave (131b) (4.1g, 43%), m.p. 192-193°.

(Found: C, 50.4; H, 4.2; N, 13.6; $C_{13}H_{13}N_3O_4S$
requires C, 50.8; H, 4.3; N, 13.7%).

$\nu_{\max}(\text{cm}^{-1})$ 3480 (N-H), 3370, 3250 (NH_2), 1510, 1340
(NO_2), 1325, 1155 (SO_2).

δ 2.37 (3H, s, CH_3), 6.62 (1H, dd, $J=8$ and 7Hz, H-5), 7.05
(1H, dd, $J=7$ and 2Hz, H-6), 7.0-7.25 (2H, b, NH_2),
7.40-7.90 (4H, AA'BB'= $\text{MeC}_6\text{H}_4\text{SO}_2$), 8.05 (1H, dd, $J=8$ and
2Hz, H-4), 10.80 (1H, s, N-H).

2-Nitro-6-methanesulphonamidoaniline (131a)

(131a) was similarly prepared from 3-nitro-1,2-phenylenediamine (9.0g) and methanesulphonyl chloride (6.9g). Yield (11.6g, 85%), m.p. 221-222° (from ethanol:DMF=4:1).

(Found: C, 36.1; H, 3.85; N, 18.1; $C_7H_9N_3O_4S$
requires C, 36.4; H, 3.9; N, 18.2%).

$\nu_{\max}(\text{cm}^{-1})$ 3470 (N-H), 3360, 3160 (NH_2), 1315, 1125 (SO_2).

δ 3.10 (3H, s, CH₃), 6.80 (1H, dd, J=9 and 8Hz, H-5), 7.25 (2H, s, NH₂), 7.63 (1H, dd, J=8 and 2Hz, H-6), 8.15 (1H, dd, J=9 and 2Hz, H-4), 9.33 (1H, s, N-H).

2,3-Dihydro-1-methanesulphonyl-4-nitrobenzimidazole (132a)

To 2-nitro-6-methanesulphonamidoaniline (131a) (2.0g, 8.7×10^{-3} mol) was added paraformaldehyde (0.78g, 0.026 mol), potassium cyanide (1.69g, 0.026 mol), zinc chloride (4.3g) and acetic acid (43ml) containing concentrated sulphuric acid (2 drops). The mixture was heated, with stirring at 50° for 7h, cooled and poured into ice-water. An orange precipitate was filtered off, washed repeatedly with water and recrystallised from acetic acid to give (132a) (1.2g, 57%), m.p. 171-172°.

(Found: C, 39.3; H, 3.6; N, 17.2; C₈H₉N₃O₄S
requires C, 39.5; H, 3.7; N, 17.3%).

$\nu_{\max}(\text{cm}^{-1})$ 3435 (N-H), 1510, 1350 (NO₂), 1305, 1140 (SO₂).

δ 3.20 (3H, s, CH₃), 5.55 (2H, s, CH₂), 6.78 (1H, dd, J=9 and 7Hz, H-6), 7.38 (1H, dd, J=7 and 2Hz, H-7), 7.70 (1H, dd, J=9 and 2Hz, H-5), 8.57 (1H, s, NH).

2,3-Dihydro-4-nitro-1-p-toluenesulphonyl-
benzimidazole (132a)

To 2-nitro-6-p-toluenesulphonamidoaniline (131b) (1.5g, 5×10^{-3} mol) was added paraformaldehyde (0.45g, 0.015 mol), potassium cyanide (0.96g, 0.015 mol), zinc chloride (5.1g) and acetic acid (12ml) to which had been added concentrated sulphuric acid (2 drops). The mixture was heated at 50° for 5h, poured into ice-water and the resultant orange precipitate filtered and washed thoroughly with water. Recrystallisation from acetic acid gave (132b), (0.95g, 60%), m.p. $145-146^\circ$.

(Found: C, 52.8; H, 4.1; N, 13.2; $C_{14}H_{13}N_3O_4S$
requires C, 52.7; H, 4.1; N, 13.2%).

$\nu_{\max}(\text{cm}^{-1})$ 3380 (N-H), 1510, 1330 (NO_2), 1310, 1160
(SO_2).

δ 2.40 (3H, s, CH_3), 5.57 (2H, s, CH_2), 6.82 (1H, dd, $J=9$
and 7Hz, H-6), 7.50-8.0 (6H, m, aromatic), 8.40 (1H, s,
N-H).

3-Formyl-2,3-dihydro-1-methanesulphonyl-4-nitro-
benzimidazole (133)

2,3-Dihydro-1-methanesulphonyl-4-nitrobenzimidazole (0.5g, 2.1×10^{-3} mol) was added to acetic formic anhydride (10ml)

and stirred overnight. A solid crystallised as orange prisms. Recrystallisation from ethanol (containing a little dimethylformamide) gave (133) (0.43g, 77%), m.p. 193-194°.

(Found: C, 40.1; H, 3.3; N, 15.5; C₉H₉N₃O₅S
requires C, 39.85; H, 3.3; N, 15.5%)

ν_{\max} (cm⁻¹) 1670 (C=O), 1520, 1340 (NO₂), 1295, 1150 (SO₂)
 δ 3.26 (3H, s, CH₃), 5.88 (2H, s, CH₂), 7.40-7.90 (3H, m, aromatic), 8.82 (1H, s, CHO).

N-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)benzimidazole
(136) (with M. Mitchell)

A suspension of benzimidazole (5g) in hexamethyldisilazane (HMDS), to which a few crystals of ammonium sulphate had been added, was heated under reflux, with stirring, until a homogeneous mixture had been obtained (45min). The remaining HMDS was distilled off at atmospheric pressure (b.p. 125°) and the residue distilled at reduced pressure (b.p. 92-94°, 0.1mmHg). The distillate solidified as a white solid (5.3g, 70%), m.p. 55° (lit.⁸⁶, 66-67°) assumed to be (trimethylsilylbenzimidazole) and was used without further purification.

1-Trimethylsilylbenzimidazole (0.95g), acetobromoglucose

(2.055g) and a few crystals of potassium iodide were combined and heated, with stirring at 130-140° for 2h. The residue was dissolved in a mixture of ethanol (20ml) and petroleum (b.p. 60/80°, 13ml) and left to stand for 1 week at 5°. No crystallisation occurred and the solution was decolourised (charcoal) and evaporated to dryness in vacuo. The residue was now recrystallised from aqueous ethanol to give (136) (0.16g, 7%) as white needles, m.p. 140-144°. Further recrystallisation elevated the melting point to 150-152° (lit.⁶⁴, 156-157°).

(Found: C, 55.9; H, 5.4; N, 6.2; calc. for C₂₁H₂₄N₂O₉ requires C, 56.25; H, 5.4; N, 6.25%).

$\nu_{\max}(\text{cm}^{-1})$ 1740 (C=O).

δ 1.73 (3H, s, CH₃CO), 2.00 (3H, s, CH₃CO), 2.05 (3H, s, CH₃CO), 2.10 (3H, s, CH₃CO), 4.30 (3H, m), 5.3-6.5 (3H, m), 6.40 (1H, d, J=9Hz, H-1'), 7.30-8.10 (4H, m, aromatic).

Benzimidazol-1-yl 2,3,4,6-tetra-O-acetyl- β -Dglucopyranoside (137) (with M. Mitchell)

To a mixture of benzimidazole N-oxide (0.96g), and aceto-bromoglucose (3.06g) in pyridine (6ml) was added, with stirring, silver oxide (3.43g). After a short time the pyridine was removed in vacuo and the residue extracted with methanol. The methanolic extract was evaporated to

dryness and the residue recrystallised from aqueous propan-2-ol to give (137) (1.4g, 42%), m.p. 122-124°.

(Found: C, 54.1; H, 5.2; N, 5.95; $C_{21}H_{24}N_2O_{10}$ requires C, 54.3; H, 5.2; N, 6.0%).

$\nu_{\max}(\text{cm}^{-1})$ 1740, 1690 (C=O).

δ 2.00 (9H, 3s, 3xCH₃CO), 2.25 (3H, s, CH₃CO), 4.05-4.30 (3H, b, CH₂, H-5'), 5.05-5.60 (3H, m), 5.75 (1H, d, J=8Hz, H-1'), 7.40-8.00 (4H, m, aromatic), 8.55 (1H, s, H-2).

Reaction of ethyl 5-nitrobenzimidazole-2-carboxylate-3-oxide (92) with acetobromoglucose to give (138)

a) Silver oxide (1.48g, 6.4×10^{-3} mol) was added, with stirring, to a mixture of acetobromoglucose (2.62g, 6.4×10^{-3} mol) and ethyl 5-nitrobenzimidazole-2-carboxylate 3-oxide (0.8g, 3.2×10^{-3} mol) in quinoline (3.3g) and left to stir overnight at room temperature. The resultant mixture was diluted with acetic acid (15ml), with stirring and filtered. The filtrate was poured into ice-water and the resultant white precipitate filtered off and washed with water. Recrystallisation from ethanol gave (138), (0.9g, 48%), m.p. 190-191°.

(Found: C, 49.45; H, 4.5; N, 7.2; $C_{24}H_{27}O_{14}N_3$ requires C, 49.6; H, 4.7; N, 7.2%).

$\nu_{\max}(\text{cm}^{-1})$ 1740 (C=O's). 1560, 1340 (NO₂).

δ 1.40 (3H, t, J=7Hz, CH₃CH₂), 1.77 (3H, s, CH₃CO), 2.02 (3H, s, CH₃CO), 2.05 (3H, s, CH₃CO), 2.20 (3H, s, CH₃CO), 4.15 (3H, m, CH₂, H-5'), 4.55 (2H, q, J=7Hz, CH₂CH₃), 5.50 (3H, m), 5.95 (1H, d, J=8Hz, H-1'), 8.17 (1H, d, J=9Hz, H-4), 8.40 (1H, dd, J=9 and 7Hz, H-5), 8.7 (1H, d, J=2Hz, H-7).

b) To a mixture of ethyl 5-nitrobenzimidazole-2-carboxylate 3-oxide (1.2g, 4.8×10^{-3} mol) and quinoline (4.95g) was added piperidine (0.42g, 4.9×10^{-3} mol) and acetobromoglucose (2.1g, 5.1×10^{-3} mol) combined with the resultant red solution. The mixture was stirred at room temperature for 72h, diluted with acetic acid and poured into ice-water. A white precipitate was filtered off, washed with water and recrystallised (twice) from ethanol to give (138) (1.2g, 43%), m.p. 188-190°, spectroscopically identical with an authentic sample.

Reaction of 2-Cyano-4-nitrobenzimidazole 3-oxide (97) with acetobromoglucose to give (139)

Compound (139) was similarly prepared (method b) from 2-cyano-4-nitrobenzimidazole 3-oxide (0.8g, 4×10^{-3} mol), (0.8g, 38%), m.p. 229-230° (from acetic acid, charcoal).

(Found: C, 49.2; H, 4.2; N, 10.5; $C_{22}H_{22}N_4O_{12}$ requires C, 49.4; H, 4.15; N, 10.3%).

$\nu_{\max}(\text{cm}^{-1})$ 2240 (CN), 1735 (C=O), 1525, 1340 (NO_2).
 δ 1.81 (3H, s, CH_3), 2.0, 2.02 (6H, 2xs, 2CH_3 's), 2.17 (3H, s, CH_3), 3.87 (3H, m, $\text{CH}_2 + \text{H}-5'$), 4.75-5.50 (3H, m, H-2', H-3', H-4'), 5.80 (1H, d, $J=8\text{Hz}$, H-1'), 7.70 (H, t, $J_{5,4} = J_{5,6} = 8\text{Hz}$, H-5), 8.35 (2H, m, H-4, H-6).

Reaction of 2-Cyano-5-methanesulphonamidobenzimidazole 3-oxide (121b) with acetobromoglucose to give (141)

To a mixture of 2-cyano-5-methanesulphonamidobenzimidazole 3-oxide (0.4g, 1.6×10^{-3} mol) and piperidine (0.14g, 1.6×10^{-3} mol) in quinoline (1.65g) was added acetobromoglucose (0.65g, 1.6×10^{-3} mol). The resultant viscous mixture was left to stir at room temperature for 24h, diluted with acetic acid and poured into ice-water. A white precipitate was filtered off, washed with water and recrystallised from aqueous acetic acid to give almost pure (141) (0.4g, 43%), m.p. 201-203°. On further recrystallisation the melting point was elevated to 203-204°. (80% recovery).

(Found: C, 47.3; H, 4.4; N, 9.5; $C_{23}H_{26}N_4O_{12}S$ requires C, 47.4; H, 4.5; N, 9.6%).

$\nu_{\max}(\text{cm}^{-1})$ 3205 (NH), 2210 (CN), 1740, 1715 (C=O's),
1360, 1150 (SO₂).

δ 1.93 (3H, s, CH₃CO), 2.00-2.01 (6H, 2s, 2xCH₃CO), 2.14
(3H, s, CH₃CO), 3.04 (3H, s, CH₃SO₂), 4.1 (3H, m, CH₂ +
H-5'), 5.12 (1H, t, J=9Hz, H-4), 5.24 (1H, t, J=9Hz, H-2'),
5.42 (1H, t, J=9Hz, H-3'), 5.34 (1H, d, J=9Hz, H-1'), 7.29
(1H, dd, J_{5',4'}}=7.5Hz, J_{5',7'}}=2Hz), 7.53 (1H, d,
J=2Hz, H-7'), 7.82 (1H, d, J=7.5Hz, H-4').

δ (quaternary carbons) 122.38, 130.97, 134.14, 138.45
(aromatic).

δ (tertiary carbons) 67.73, 68.97, 71.59, 71.42 (C-2', C-3',
C-4', C-5'), 99.14 (C-1'), 105.42, 118.52, 122.50 (ArH).

δ (secondary carbons) 61.94 (C-6').

δ (primary carbons) 20.22, 20.30 (CH₃CO), 40.0 (CH₃SO₂
under solvent).

δ (CN) 109.82 .

δ (4 CO's) 169.89, 169.56, 169.23 (2 coincident peaks) .

Chapter 4 : Experimental

1,3-Dichloro-4,6-dinitrobenzene (146)

m-Dichlorobenzene (100g, 0.68mol) was added, all at once, with stirring, to a solution of potassium nitrate (140g, 1.39mol) in concentrated sulphuric acid (500ml) at 50°. The temperature rose to 130° over 2min and then dropped to 120° over the next 10min. The solution was kept at this temperature, with stirring, for a further 1.5h, cooled to room temperature and poured on to crushed ice. The resultant precipitate was filtered off, washed with water and recrystallised from ethanol to give (146) (95.0g, 59%) m.p. 99-101° (lit.⁶⁸, 103-104°).

1,3-Diamino-4,6-dinitrobenzene (157)

Ammonia was bubbled into a well stirred solution of 1,3-dichloro-4,6-dinitrobenzene (40g) in ethanediol (270ml) at 130° for 3h. The solution was cooled and the yellow precipitate filtered off, washed with boiling water and then boiling ethanol. Recrystallisation from acetic acid/dimethylformamide (1:1) gave (157) (20g, 60%), m.p. 297-299° (lit.⁶⁸, 300°).

$\nu_{\max}(\text{cm}^{-1})$ 3460, 3345, 1590 (NH₂), 1550, 1310 (NO₂).

δ 6.30 (1H, s, H-2), 7.80 (4H, bs, 2xNH₂), 9.08 (1H, s, H-5).

1,2,4-triamino-5-nitrobenzene (156)

To a well stirred slurry of 1,3-diamino-4,6-dinitrobenzene (15.0g, 0.076mol) in water (100ml) at 100° was added a solution of sodium polysulphide [prepared by heating a mixture of sodium sulphide nonahydrate (20g) and sulphur (4.8g) in water (85ml)], dropwise over about 1.5h. The mixture was kept at this temperature for a further 1.5h then cooled in ice, filtered and the residue extracted with boiling water (600ml). The aqueous extract was filtered and cooled to give a red precipitate which was filtered off and washed with water. Recrystallisation from water (charcoal) gave (156) (5.5g, 43%), m.p. 191-193° (lit.⁶⁸, 206-207°), pure by n.m.r.

$\nu_{\max}(\text{cm}^{-1})$ 3420, 3350, 3250 (NH₂'s), 1520, 1330 (NO₂).
 δ 4.50 (2H, bs, 1-NH₂), 6.03 (1H, s, H-3), 6.21 (2H, bs, 2-NH₂), 7.20 (2H, bs, 4-NH₂), 7.25 (1H, s, H-6).

N-(5-chloro-2,4-dinitrophenyl)glycine ethyl ester (172)

To a solution of 1,3-dichloro-4,6-dinitrobenzene (10g, 0.042mol) in ethanol (250ml) was added glycine ethyl ester hydrochloride (6.0g, 0.042mol) and sodium bicarbonate (7.1g, 0.084mol). The mixture was heated under reflux until all effervescence had ceased (~50min), and then cooled in ice. The resultant yellow precipitate was

filtered off, washed with water, ethanol and recrystallised from ethanol:dimethylformamide (1:1) to give (172) (6.4g, 50%), m.p. 150-151°.

(Found: C, 39.5; H, 3.25; N, 13.6; $C_{10}H_{10}ClN_3O_6$ requires C, 39.55; H, 3.3; N, 13.8%).

max(cm^{-1}) 3310 (N-H), 1725 (C=O).

1.28 (3H, t, $J=7Hz$, CH_3CH_2), 4.33 (2H, q, $J=7Hz$, CH_2CH_3), 4.53 (2H, d, $J=6Hz$, CH_2-NH), 7.48 (1H, s, H-6), 9.05 (1H, s, H-3), 9.1 (1H, br, N-H).

5-Chloro-N-cyanomethyl-2,4-dinitroaniline (147)

To a solution of 1,3-dichloro-4,6-dinitrobenzene (10.0g, 0.042mol) in ethanol (250ml) was added sodium bicarbonate (7.1g, 0.084mol) and the resultant mixture heated to boiling. To the refluxing mixture was added powdered aminoacetonitrile hydrochloride (3.9g, 0.042mol) in portions, over 40min and heating continued for a further 2h. Upon cooling, the yellow precipitate was filtered off, washed with water and recrystallised from acetic acid to give (147) (5.7g, 53%), m.p. 234-235°.

(Found: C, 37.6; H, 1.9; N, 22.1; $C_8H_5ClN_4O_4$ requires C, 37.45; H, 2.0; N, 21.8%).

$\nu_{\max}(\text{cm}^{-1})$ 3320 (N-H), 1530, 1320 (NO_2).

δ 4.80 (2H, bs, CH_2), 7.66 (1H, s, H-6), 9.08 (1H, s, H-3), 9.14 (1H, bs, N-H).

5-Chloro-2,4-dinitroaniline (170)

To a solution of 1,3-dichloro-4,6-dinitrobenzene (15g, 0.063mol) in ethanol (150ml) was added aqueous ammonia (d 0.88, 100ml) and the resultant mixture heated under reflux for 3h. On cooling, a yellow crystalline product was deposited, which was filtered off, washed with water, cold ethanol and dried in vacuo. Recrystallisation from ethanol gave (170) (9.5g, 69%), m.p. 172-174° (lit.⁸⁷, 178°).

N-(5-Chloro-2,4-dinitrophenyl)benzylamine

To a solution of 1,3-dichloro-4,6-dinitrobenzene (10g, 0.042mol) in ethanol (150ml), containing sodium bicarbonate (3.5g, 0.042mol) was added benzylamine (4.9g, 0.046mol) and the mixture then heated under reflux for 45min. After cooling in ice a yellow precipitate was filtered off, washed with water and recrystallised from ethanol to give N-(5-chloro-2,4-dinitrophenyl)benzylamine (7.6g, 59%), m.p. 129-130°.

(Found: C, 50.9; H, 3.2; N, 13.65; $C_{13}H_{10}ClN_3O_4$
requires C, 50.75; H, 3.3; N, 13.7%).

δ 4.85 (2H, d, $J=6\text{Hz}$, $\underline{CH_2-NH}$), 7.30 (1H, s, H-6), 7.52
(5H, m, Ph), 9.08 (1H, s, H-3), 9.50 (1H, $J=7\text{Hz}$, $\underline{NH-CH_2}$).

N-(5-Chloro-2,4-dinitrophenyl)amino acetamide (148)

Powdered 5-chloro-N-cyanomethyl-2,4-dinitro-
aniline (13.8g, 0.054mol) was dissolved in concentrated
sulphuric acid (70ml) and the resultant deep red solution
stirred at room temperature for a further 30min. The
mixture was poured over crushed ice and a yellow
precipitate filtered off, washed with water and
recrystallised from acetic acid to give (148) (11.3g,
76%), m.p. 215° .

(Found: C, 35.2; H, 2.6; N, 20.3; $C_8H_7ClN_4O_5$
requires C, 35.0; H, 2.6; N, 20.4%).

$\nu_{\text{max}}(\text{cm}^{-1})$ 3410, 3280, 3170 (NH, NH_2), 1680 (C=O), 1560,
1310 (NO_2).

δ 4.20 (2H, d, $J=5.5\text{Hz}$, $\underline{CH_2-NH}$), 7.20 (1H, s, H-6), 7.50
(1H, bs, CONH), 7.78 (1H, bs, CONH), 9.05 (1H, s, H-3),
9.18 (1H, b, $\underline{NHCH_2}$).

2-Carbamoyl-6-chloro-5-nitrobenzimidazole 3-oxide (149)

The amide (148) (7.0g, 0.025mol) was dissolved, as far as possible in boiling ethanol (400ml) and potassium carbonate (3.44g, 0.025mol) added. The resultant mixture was heated under reflux for 4h, the solvent evaporated off in vacuo and the residue dissolved in water.

Acidification (HCl) gave (149) as a white precipitate which was filtered off, washed with water and ethanol, and dried in vacuo. Yield (4.3g, 67%), m.p. 268-270°.

Although (149) could be recrystallised, with difficulty, from ethanol/dimethylformamide it could not be obtained pure enough for micro-analysis (probably due to solvent of crystallisation) and was therefore analysed as its alkylated derivative (144) (see below).

δ 8.10 (1H, s, H-7), 8.15 (1H, bs, NH), 8.38 (1H, s, H-4), 8.50 (1H, bs, NH).

2-Carbamoyl-5-chloro-1-ethoxy-6-nitrobenzimidazole (144)

To a solution of the N-oxide (149) (4.2g, 0.016mol) in dimethylformamide (40ml) and ethanol (60ml) was added triethylamine (1.75g, 0.017mol) in ethanol (5ml). The mixture was heated to boiling point and iodoethane (2.7g, 0.017mol) added, dropwise, over 10min. The resultant mixture was heated under reflux for a further 1h and

diluted with water to give a white precipitate which was filtered off and washed with ethanol. Recrystallisation from acetic acid gave (144) (4.2g, 92%), m.p. 270-272°.

(Found: C, 42.3; H, 3.2; N, 19.8; $C_{10}H_9ClN_4O_4$ requires C, 42.2; H, 3.2; N, 19.7%).

$\max(\text{cm}^{-1})$ 3460, 3200 (m), (NH₂), 1700 (br, C=O), 1525, 1330 (NO₂).

1.38 (3H, t, J=7Hz, CH_3CH_2), 4.55 (2H, q, J=7Hz, CH_2CH_3), 8.12 (1H, bs, NH), 8.14 (1H, s, H-4), 8.40 (1H, bs, NH), 8.58 (1H, s, H-7).

Attempted substitution reactions of (144)

No reaction was observed when (144) was treated with the following nucleophiles; starting material was recovered quantitatively in both cases, even after prolonged heating in DMSO at 100°.

(a) Glycine ethyl ester.

(b) Aminoacetonitrile.

2-Cyano-1-ethoxy-6-methanesulphonamido-7-nitro-
benzimidazole (150a)

2-Cyano-1-ethoxy-6-methanesulphonamidobenzimidazole (122b) (2.75g, 9.8×10^{-3} mol) was dissolved in concentrated sulphuric acid (14ml) at 0-5° and a mixture of nitric acid (d 1.5, 0.64g) in concentrated sulphuric acid (5.5ml) added dropwise, with stirring, over 5min. The resultant mixture was stirred at this temperature for a further 15min, allowed to warm to room temperature over another 15min and poured on crushed ice. The pale yellow precipitate was filtered off, washed thoroughly with water and recrystallised from ethanol to give (150a) (2.0g, 63%), m.p. 190-191°.

(Found: C, 40.6; H, 3.35; N, 21.6; $C_{11}H_{11}N_5O_5S$
requires C, 40.6; H, 3.4; N, 21.5%).

$\nu_{\max}(\text{cm}^{-1})$ 3250 (N-H), 2230 (CN), 1560, 1320 (NO₂), 1340, 1140 (SO₂).

δ 1.34 (3H, t, J=7Hz, CH_3CH_2), 3.14 (3H, s, CH_3SO_2), 4.49 (2H, q, J=7Hz, CH_2CH_3), 7.63 (1H, d, J=9Hz, H-5), 8.14 (1H, d, J=9Hz, H-4); N-H not seen.

2-Cyano-1-ethoxy-6-ethoxycarbonylamino-7-nitro-
benzimidazole (150b)

This compound was similarly prepared from 2-cyano-1-ethoxy
6-ethoxycarbonylamino benzimidazole (0.4g, 1.46×10^{-3} mol).
Yield (0.15g, 32%), m.p. 120-121° (from aqueous ethanol).

(Found: C, 48.9; H, 4.1; N, 22.05; $C_{13}H_{13}N_5O_5$
requires C, 48.9; H, 4.1; N, 21.9%).

1.25 (3H, t, J=7Hz, $\underline{CH_3CH_2OCO}$), 1.38 (3H, t, J=7Hz,
 $\underline{CH_3CH_2-O-N}$), 4.15 (2H, q, J=7Hz, CO-O, $\underline{CH_2CH_3}$), 4.50 (2H,
q, J=7Hz, N-O, $\underline{CH_2CH_3}$), 7.30 (1H, d, H-5), 8.10 (1H, d,
H-4) ($J_{4,5}=9$ Hz), 10.10 (1H, s, N-H).

2-Cyano-1-ethoxy-6-(N-methanesulphonyl-N-phenacylamino)-7-
nitrobenzimidazole (153a)

To a solution of (150a) (1.63g, 5.0×10^{-3} mol) in
dimethylformamide (5ml) was added sodium ethoxide
(5.0×10^{-3} mol) in dimethylformamide (5ml). To the
resultant dark red solution, phenacyl bromide (1.05g,
 5.3×10^{-3} mol) was added and the mixture stirred at room
temperature for 48h. A buff coloured precipitate was
filtered off, washed with water and recrystallised from
aqueous acetic acid to give (153a) (0.15g), m.p. 182-
184°. The filtrate was diluted with water (100ml) and the

resultant precipitate filtered off and recrystallised from aqueous acetic acid to give more (153a) (1.1g), m.p. 180-182°. Total yield 1.25g (54%).

(Found: C, 51.7; H, 3.9; N, 15.6; $C_{19}H_{17}N_5O_6S$ requires C, 51.5; H, 3.9; N, 15.8%).

$\nu_{max}(cm^{-1})$ 2230 (CN), 1680 (C=O), 1535, 1320 (NO₂), 1330, 1140 (SO₂).

(d₅-pyridine) 1.34 (3H, t, J=7Hz, CH₃CH₂), 3.58 (3H, s, CH₃SO₂), 4.57 (2H, q, J=7Hz, CH₂CH₃), 5.79 (2H, s, CH₂CO), 7.2-7.7 (3H, m), 8.0-8.35 (4H, m).

2-Cyano-1-ethoxy-6-(N-methanesulphonyl-N-p-nitrobenzyl-amino)-7-nitrobenzimidazole (153b)

To a solution of (150a) (2.4g, 7.4×10^{-3} mol) in dimethyl sulphoxide (10ml) was added sodium ethoxide (7.4×10^{-3} mol) and then p-nitrobenzyl bromide (1.60g, 7.4×10^{-3} mol). The mixture was stirred, overnight, at room temperature, and poured into ice-water. The resultant precipitate was filtered off and recrystallised from ethanol to give (153b) (1.65g, 49%), m.p. 174-175°.

(Found: C, 46.75; H, 3.5; N, 18.1; $C_{18}H_{16}N_6O_7S$ requires C, 47.0; H, 3.5; N, 18.25%).

$\nu_{\max}(\text{cm}^{-1})$ 1520, 1320 (NO_2), 1335, 1140 (SO_2).

δ 1.31 (3H, t, $J=7\text{Hz}$, CH_3CH_2), 3.29 (3H, s, CH_3SO_2), 4.42 (2H, q, $J=7\text{Hz}$, CH_2CH_3), 5.05 (2H, s, CH_2N), 7.50-7.90 (3H, m), 8.05-8.30 (3H, m).

Reactions of (153a) and (153b) with base

(a) To a solution of (153b) (1.1g, 2.4×10^{-3} mol) in methanol (20ml) was added sodium methoxide solution [from sodium (0.11g, 4.8×10^{-3} mol) in methanol (20ml)]. The mixture was then heated under reflux for 2h, the solvent evaporated off in vacuo and the residue dissolved in water. Acidification (HCl) gave a somewhat gelatinous precipitate which was filtered off and washed with water. Recrystallisation from aqueous methanol gave (155) as a monohydrate. Yield (0.3g, 30%), m.p. 169-173°.

(Found: C, 52.3; H, 4.0; N, 16.9; $\text{C}_{18}\text{H}_{17}\text{N}_5\text{O}_7$ requires C, 52.05; H, 4.1; N, 16.9%).

$\nu_{\max}(\text{cm}^{-1})$ 3200 (b, $\text{H}_2\text{O}?$), 2600 (b, NH/OH), 1725 (C=O), 1520, 1335 (NO_2).

δ 1.43 (3H, t, $J=7\text{Hz}$, CH_3CH_2), 3.99 (3H, s, CH_3 , ester), 4.65 (2H, q, $J=7\text{Hz}$, CH_2CH_3), 7.63 (2H, s, H-4, H-5), 8.45 (4H, m, AA'BB'), 12-13 (1H, b, NH/OH).

m/z 150 (100%).

(b) The reaction of (153a) under identical conditions failed to yield any isolable product with, in particular, no water soluble material being obtained at any stage.

N-(2,4-Diamino-5-nitrophenyl)methanesulphonamide (159a)

To a solution of 1,2,4-triamino-5-nitrobenzene (2.75g, 0.016mol) in pyridine (40ml) was added methanesulphonyl chloride (1.9g, 0.016mol), dropwise, with stirring. The mixture was left to stand for a further 1.5h and poured into ice-water. The resultant precipitate was filtered off, washed with ethanol and recrystallised from dimethylformamide:water (1:1) to give (159a) (3.0g, 75%), m.p. 247-248° (d).

(Found: C, 34.2; H, 4.1; N, 22.8; $C_7H_{10}N_4O_4S$
requires C, 34.1; H, 4.1; N, 22.75%).

$\nu_{\max}(\text{cm}^{-1})$ 3470, 3360 (m) (N-H, NH_2 's), 1550, 1310 (NO_2),
1365, 1140 (SO_2).

δ 3.00 (3H, s, CH_3), 6.16 (1H, s, H-3), 6.36 (2H, bs,
2- NH_2), 7.36 (2H, bs, 4- NH_2), 7.93 (1H, s, H-6), 8.82 (1H,
bs, NH).

5-Amino-6-nitrobenzo-2,1,3-selenadiazole (158)

1,2,4-Triamino-5-nitrobenzene (2.5g, 0.015mol) was dissolved, as far as possible, in boiling ethanol (200ml) and a solution of selenium dioxide (1.7g, 0.015mol) in water (15ml) added. An instantaneous red to black colour change was noted with concurrent deposition of a black precipitate. This material was filtered off, washed with water and cold ethanol, and recrystallised from acetic acid (3 times, with charcoal) to give (158) (1.5g, approx. 47%) in impure form.

(Found: C, 30.3; H, 1.7; N, 23.2; $C_6H_4N_4O_2Se$ requires C, 29.7; H, 1.7; N, 23.0%).

The impurity is probably elemental selenium and the material appeared pure by n.m.r.

δ 6.63 (2H, bs, NH_2), 7.21 (1H, s, H-4), 8.75 (1H, s, H-7).

6-Amino-2,3-dimethyl-7-nitroquinoxaline (159)

1,2,4-Triamino-5-nitrobenzene (2.4g, 0.014mol) was dissolved, as far as possible, in boiling ethanol (250ml) and biacetyl (1.23g, 0.014mol) added dropwise. The resultant mixture was heated under reflux for a further 1h, cooled, and a red precipitate filtered off.

Recrystallisation from ethanol gave (159) (2.3g, 74%), m.p. 228-230° (lit.⁶⁸, 238-240°).

δ 2.60 (3H, s, CH₃), 2.63 (3H, s, CH₃), 7.23 (2H, bs, NH₂), 7.41 (1H, s, H-5), 8.60 (1H, s, H-8).

1,3-Bis(benzylamino)-4,6-dinitrobenzene (162)

1. N-(5-Chloro-4,6-dinitrophenyl)benzylamine (2.3g, 7.5×10^{-3} mol) was dissolved in ethanediol (160ml) at 120°. On addition of benzylamine (1.6g, 0.015mol) an almost immediate colour change (yellow to orange) was noted and the mixture was heated at 130-135° for a further 1.5h. The mixture was then cooled, poured into ice-water and the resultant precipitate filtered off. Recrystallisation from acetic acid gave (162) (1.9g, 67%), m.p. 161-162°.

(Found: C, 63.6; H, 4.7; N, 14.7; C₂₀H₁₈N₄O₄ requires C, 63.5; H, 4.8; N, 14.8%).

δ 4.55 (4H, d, J=6Hz, 2xCH₂NH), 5.89 (1H, s, H-2), 7.45 (10H, bs, 2xPh), 9.10 (2H, t, J=6Hz, 2xNHCH₂), 9.20 (1H, s, H-5).

2. To a solution of 1,3-dichloro-4,6-dinitrobenzene (10.0g, 0.042mol) in dimethyl sulphoxide (50ml) was added sodium bicarbonate (7.1g, 0.084mol) and benzylamine (9.0g,

0.084mol). The mixture was heated, with stirring, to 100° over 20min and kept at this temperature until all effervescence had ceased (15min), cooled and poured into ice-water. The resultant precipitate was recrystallised from acetic acid to give (162), as lustrous yellow plates (11.5g, 72%), identical with the product of (1).

Cyclisation of the nitrile (147)

Powdered 5-chloro-N-cyanomethyl-2,4-dinitro-aniline (147) (1.5g, 5.9×10^{-3} mol) was dissolved in ethanediol (150ml) at 120-130° and sodium bicarbonate (1.0g, 0.012mol) added. An almost instantaneous colour change (yellow to black) was noted and the solution was cooled in ice and diluted with water (300ml). Acidification (HCl) gave a buff coloured precipitate which was filtered off and recrystallised from ethanol to give the ester (164) (0.75g, 42%), m.p. 209-210°.

(Found: C, 40.0; H, 2.6; N, 14.05; $C_{10}H_8ClN_3O_6$ requires C, 39.8; H, 2.7; N, 13.9%).

δ 3.85 (2H, t, J=6Hz, $-OCH_2\text{CH}_2OH$), 4.55 (2H, t, J=6Hz, $-O\text{CH}_2\text{CH}_2OH$), 8.35 (1H, s, H-7), 8.60 (1H, s, H-4).

N-(5-Benzylamino-2,4-dinitrophenyl)aminoacetamide (167)

1. The amide (148) (1.5g, 5.5×10^{-3} mol) was dissolved in ethanediol (100ml) at 130-140° and benzylamine (1.18g, 0.011mol) added. The mixture was heated at this temperature for 3h, cooled and poured into ice-water. The resultant, sticky, precipitate was filtered off and recrystallised from aqueous acetic acid (charcoal) to give (167) (0.15g, 8%), m.p. 242-244°.

(Found: C, 52.1; H, 4.6; N, 20.0; $C_{15}H_{15}N_5O_5$ requires C, 52.2; H, 4.4; N, 20.3%).

$\nu_{\max}(\text{cm}^{-1})$ 3430, 3370, 3300, 3180 (2xNH, NH₂), 1660 (C=O), 1510, 1345 (NO₂).

δ 3.85 (2H, d, J=5Hz, NHCH₂Ph), 4.60 (2H, d, J=6Hz, NHCH₂, amide), 5.75 (1H, s, H-6), 7.50 (7H, m, Ph and NH₂), 7.80 (1H, br, NH), 9.05 (1H, s, H-3), 9.1 (1H, br, N-H).

2. The amide (147) (2.0g, 7.3×10^{-3} mol) was dissolved in dimethyl sulphoxide (10ml) at 65° and benzylamine (1.6g, 0.015mol) added over 2min, with stirring. An instant orange to dark red colour change was noted with a concurrent rise in temperature (to 75°). The mixture was heated, with stirring, to 100° over 5min and kept at this temperature for a further 30min before being cooled to room temperature and poured into ice-water. The resultant precipitate was filtered off and recrystallised

from aqueous acetic acid to give (167) (1.6g, 64%), m.p. 244-246°, spectroscopically identical with the previous sample.

N,N-(4,6-Dinitro-1,3-phenylene)bis-glycine diethyl ester (168)

To a solution of 1,3-dichloro-4,6-dinitrobenzene (9.0g, 0.039mol) in dimethyl sulphoxide (45ml) at room temperature was added sodium bicarbonate (13.1g, 0.156mol) and glycine ethyl ester hydrochloride (10.92g, 0.078mol). The mixture was heated, with stirring, at 60° until effervescence had almost ceased (35min). On increasing the temperature to 90°, effervescence recommenced and the reaction mixture was kept at this temperature until no more gas was given off (a further 20min). On cooling, the, now semi-solid, mixture was diluted with water and filtered to give a yellow solid. Recrystallisation from acetic acid gave (168) as bright yellow needles (10.7g, 74%), m.p. 190-191°.

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 3350 (N-H), 1715 (C=O).

δ 1.28 (6H, t, $J=7\text{Hz}$, $2 \times \text{CH}_3\text{CH}_2$), 4.30 (8H, m, $4 \times \text{CH}_2$), 5.60 (1H, s, H-2), 8.85 (2H, br, $2 \times \text{NH}$), 9.18 (1H, s, H-5).

1,3-Bis-cyanomethylamino-4,6-dinitrobenzene (163)

To a solution of 1,3-dichloro-4,6-dinitrobenzene (4.0g, 0.017mol) in dimethyl sulphoxide (20ml) was added sodium bicarbonate (5.7g, 0.068mol) and powdered aminoacetonitrile hydrochloride (3.15g, 0.034mol). The mixture was heated at 80-90° until effervescence ceased (40min), cooled and poured into ice-water (200ml). The resultant brown precipitate was filtered off, washed with ethanol and recrystallised from acetic acid:dimethylformamide (1:1) to give (163) (2.7g, 58%), m.p. 274-276°.

(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%).

$\nu_{\max}(\text{cm}^{-1})$ 3340 (N-H), 1530, 1320 (NO_2).

δ 4.80 (4H, d, $J=7\text{Hz}$, CH_2NH), 6.30 (1H, s, H-2), 9.0 (2H, t, $J=7\text{Hz}$, NHCH_2), 9.18 (1H, s, H-5).

5-(Carbamoylmethylamino)-2,4-dinitrophenylglycine ethyl ester (169)

To a solution of the amide (148) (2.0g, $7.3 \times 10^{-3}\text{mol}$) in DMSO (10ml) at 40° was added sodium bicarbonate (1.23g, 0.015mol) and glycine ethyl ester hydrochloride (1.02g, $7.3 \times 10^{-3}\text{mol}$). The resultant mixture was heated, with stirring, to 100° over 10min and kept at this temperature

until all effervescence had ceased (~20min). On cooling, to 40°, the reaction mixture solidified and was mixed thoroughly with cold water (200ml). The yellow solid was filtered off, washed with ethanol and recrystallised from acetic acid to give (169) (1.6g, 64%), m.p. 204-205°.

(Found: C, 42.5; H, 4.4; N, 20.5; C₁₂H₁₅N₅O₇
requires C, 42.2; H, 4.4; N, 20.5%).

$\nu_{\max}(\text{cm}^{-1})$ 3320, 3100 (NH and NH₂), 1720 (C=O, ester),
1695 (C=O, amide), 1530, 1315 (NO₂).

δ 1.25 (3H, t, J=7Hz, CH₃CH₂), 4.05 (2H, d, J=5Hz, CH₂NH),
4.25 (2H, q, J=7Hz, CH₂CH₃), 4.30 (2H, d, J=7Hz, CH₂NH),
5.68 (1H, s, H-6), 7.45 (1H, bs, CONH), 7.73 (1H, bs,
CONH), 8.88 (2H, m, 2xNHCH₂), 9.13 (1H, s, H-3).

N-(5-Amino-2,4-dinitrophenyl)glycine ethyl ester (171)

To a solution of 5-chloro-2,4-dinitroaniline (10.0g, 0.046mol) in dimethyl sulphoxide (40ml) was added sodium bicarbonate (7.7g, 0.092mol) and glycine ethyl ester hydrochloride (6.5g, 0.046mol) at 60°, with stirring. The resultant mixture was heated to 100-110° over 20min and kept at this temperature until all effervescence had ceased (~20min more). On cooling the, now solidified, reaction mixture was mixed thoroughly with water and filtered to give a bright yellow solid. Recrystallisation

from acetic acid gave (171) (8.8g, 67%), m.p. 179-180°.

(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%).

δ 1.25 (3H, t, J=7Hz, \underline{CH}_3CH_2), 4.20 (2H, d, J=6Hz, \underline{CH}_2-NH), 4.26 (2H, q, J=7Hz, \underline{CH}_2CH_3), 6.10 (1H, s, H-6), 7.90 (2H, bs, NH_2), 8.60 (1H, t, J=6Hz, NH), 9.08 (1H, s, H-3).

Action of base on the diamines (168), (171) and (163)

1. The diester (168) and sodium ethoxide

The diester (168) (3.52g, 0.01mol) was dissolved in dimethylformamide (50ml). The solution was cooled to 5-10° and sodium ethoxide [from sodium (0.01mol) in ethanol (10ml)] added, dropwise, with stirring over 10min. During the addition of base the solution changed colour from yellow to deep red. The solution was stirred at this temperature for a further 15min, the solvent evaporated off in vacuo at 60° and the residue dissolved in water. Acidification (HCl) gave a brown precipitate which was filtered off washed with water and recrystallised from acetic acid to give the starting ester (168) (2.0g), m.p. 186-190°, spectroscopically identical with an authentic sample.

Increasing reaction time and doubling the quantity of base had no effect.

2. N-(5-Amino-2,4-dinitrophenyl)glycine ethyl ester (171)
+ sodium ethoxide

The ester (171) (3.0g, 0.011mol), dissolved in dimethylformamide (10ml) was added slowly, with stirring, to a solution of sodium ethoxide [from sodium (0.011mol) in ethanol (200ml)]. After approximately two-thirds of the ester had been added a yellow precipitate appeared and the remaining ester was added to the now heterogeneous mixture with vigorous stirring. The mixture was left to stir for a further 30min, and the precipitate filtered off, washed with ethanol and dried in vacuo (2.1g). A portion of this material (0.5g) was dissolved in water (30ml) and acidified (HCl) to give a yellow precipitate which was filtered off and dried in vacuo. Recrystallisation from acetic acid gave the starting ester (171) (0.4g), m.p. 171-175°, spectroscopically identical with an authentic sample.

3. The dicyano compound (163) + sodium hydride

To a solution of (163) (1.0g, 3.6×10^{-3} mol) in dry dimethyl sulphoxide (10ml) was added sodium hydride (50% w/w in oil, 0.36g, 7.5×10^{-3} mol) in dimethyl sulphoxide (5ml) with stirring and cooling to keep the temperature at 20-25°.

On completion of addition (10min), the now red/black solution was left at room temperature for a further 45min and then poured into ice-water (100ml). Acidification (HCl) gave a sticky black precipitate which was filtered off and washed with water and ethanol. Recrystallisation from aqueous dimethylformamide gave the starting material (163) (0.27g), m.p. 268-274°, spectroscopically identical with an authentic sample.

Action of base on 1,3-bis(benzylamino)-4,6-dinitrobenzene (162) : formation of the N-oxide (173)

To a solution of (162) (6.0g, 0.022mol) in dimethylformamide (50ml) and ethanol (100ml) was added sodium ethoxide [from sodium (0.044mol) in ethanol (30ml)]. The resultant red/black solution was heated under reflux for 1.5h (90°), cooled, diluted with water (200ml) and acidified (HCl). Recrystallisation from dimethylformamide (400ml) gave (173) (3.6g, 41%), m.p. 265-270° (d).

(Found: C, 60.0; H, 4.4; N, 14.2; $C_{20}H_{15}N_4O_3Na + H_2O$ requires C, 60.0; H, 4.3; N, 14.0%).

$\max(\text{cm}^{-1})$ 3400 (NH), 3280 (br, $H_2O?$), 1515, 1350 (NO_2).
4.65 (s, partially obscured by broad water peak), 6.93 (1H, s), 7.2-7.8 (8H, m), 8.2-8.4 (3H, m).

In D₂O no simplification occurred although movement of the water peak allows the peak at δ 4.65 to be assigned as a broad singlet (2H, CH₂).

m/z Found 105.0336 (100%), 106.0428 (92%). C₆H₅CO requires 105.0342, C₆H₆CO requires 106.0420.

Reduction of the diester (168)

Partial reduction to give (177)

1. To a solution of the diester (168) (0.5g, 1.35×10^{-3} mol) in dimethylformamide (50ml) and ethanol (250ml), at room temperature, was added palladium catalyst (10% on carbon, 0.5g) in ethanol (20ml) and cyclohexene (5.3g) in ethanol (20ml). The resultant mixture was heated under reflux for 30min, cooled and filtered. The filtrate was evaporated in vacuo and the residue recrystallised from acetic acid to give (177) (50mg, 13%), m.p. 252-254°.

(Found: C, 48.9; H, 4.7; N, 18.7; C₁₂H₁₄N₄O₅ requires C, 49.0; H, 4.8; N, 19.0%).

$\nu_{\max}(\text{cm}^{-1})$ 3320 (m, N-H's), 1725 (C=O, ester), 1640 (C=O, amide), 1520, 1335 (NO₂).

δ 1.23 (3H, t, J=7Hz, CH₃CH₂), 4.13 (6H, m, 3xCH₂), 5.78 (1H, s, H-5), 7.5 (2H, bs, H-8 and N-H), 8.68 (1H, t,

$J=5\text{Hz}$, $\underline{\text{NHCH}_2}$), 10.45 (1H, s, N-H).

At 200MHz the peak at $\delta 7.5$ is resolved into two singlets: 7.46 (1H, s, H-8), 7.52 (1H, bs, NH).

In D_2O the peak at 7.5 is simplified to a 1H singlet, confirming the presence of N-H at this position.

2. To a solution of (168) (1.5g, $4.05 \times 10^{-3}\text{mol}$) in dimethylformamide (250ml) was added palladium catalyst (5% on carbon, 0.4g). The resultant mixture was hydrogenated at atmospheric pressure, and room temperature with stirring. On completion of hydrogen uptake ($\sim 270\text{ml}$, 0.012mol) the mixture was filtered and the filtrate evaporated in vacuo. Recrystallisation of the residue from acetic acid gave the starting ester (0.3g), m.p. 185-187°. Concentration of the solution then yielded (177) (40mg), identical with the previous sample.

Complete reduction to give (178) and (179)

To a solution of (168) (1.5g, $4.05 \times 10^{-3}\text{mol}$) in acetic acid (400ml) was added palladium catalyst (5% on carbon, 0.3g). The resultant mixture was hydrogenated at atmospheric pressure and room temperature. On completion of hydrogen uptake (620ml, 0.03mol) the catalyst was filtered off and the filtrate left to stand overnight. The resultant orange precipitate was filtered off, washed with hot

ethanol and dried in vacuo to give a mixture of (178) (predominantly) and (179) (0.65g).

A small portion of this material (200mg) was purified by high vacuum sublimation to yield (178) (140mg) at 275°, 1×10^2 mm Hg as an orange sublimate, (m.p. > 340°).

(Found: C, 55.6; H, 3.6; N, 25.8; $C_{10}H_8N_4O_2$ requires C, 55.6; H, 3.7; N, 25.9%).

$\nu_{\max}(\text{cm}^{-1})$ 3420, 3160 (broad), 1670, 1625 (C=O's).

m/z Found 216.0659; $C_{10}H_8N_4O_2$ requires 216.0647.

The residue (179) 60mg also had a m.p. > 340°.

m/z Found 214.0484; $C_{10}H_6N_4O_2$ requires 214.0491.

Reduction of (163) to give (180)

To a solution of the dicyano compound (163) (1.5g, 5.4×10^{-3} mol) in dimethylformamide (125ml) was added palladium catalyst (5% on carbon, 0.4g). The mixture was hydrogenated at room temperature and atmospheric pressure, with stirring. On completion of hydrogen uptake (~400ml, 0.018mol) the catalyst was filtered off and the filtrate evaporated in vacuo. The resultant red brown semi-solid

was triturated with ethanol and filtered off.

Recrystallisation from aqueous dimethylformamide gave (180), (0.32g, 24%), m.p. 226-227° (d).

(Found: C, 48.6; H, 4.1; N, 34.1; $C_{10}H_{10}N_6O_2$ requires C, 48.8; H, 4.1; N, 34.0%).

$\nu_{\max}(\text{cm}^{-1})$ 3400 (m, NH, NH₂), 2230 (CN), 1525, 1320 (NO₂).
 δ 4.6 (6H, m, 2xCH₂+NH₂), 6.06 (1H, s, H-5), 6.80 (1H, t, J=5.5Hz, NHCH₂), 7.4 (1H, s, H-8), 8.4 (1H, t, J=6.4Hz, NH-CH₂).

In D₂O the multiplet at δ 4.6 is simplified to two singlets (4H, 2xCH₂).

[N.B. All attempts to duplicate this experiment have so far failed].

Cyclisation of (180)

To a suspension of (180) (0.2g, 8.1×10^{-4} mol) in ethanol (60ml) was added potassium carbonate (0.12g, 8.7×10^{-4} mol) and the resultant mixture heated under reflux for 2h. The solvent was evaporated off in vacuo and the residue dissolved in water (12ml) to give a clear brown solution. The pH was lowered to 8 by careful addition of HCl; this gave a pale brown precipitate which was filtered off and

dried in vacuo (80mg). It had m.p. $>340^{\circ}$. An attempted purification by high vacuum sublimation failed.

$\nu_{\max}(\text{cm}^{-1})$ 3300 (br, NH, NH₂, NH/OH), 2205 (strong, CN).

m/z Found 228.0761 (31%), 210.0672 (100%).

C₁₀H₈N₆O requires 228.0760; C₁₀H₆N₆ requires 210.0654.

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