SOME BENZO-FUSED NITROGEN HETEROCYCLES

A thesis presented for the degree of Master of Science

in the Faculty of Science of the University of St. Andrews

by

Ian William Harvey

February 1990

University of St. Andrews

DEDICATION

For my parents,
William Harvey
and
Madeline Stuart Harvey

"She knows you know"

Declaration for the Degree of M.Sc.

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February 1990 Research Supervisor

ACKNOWLEDGEMENTS

My thanks go to Dr. D.M. Smith for his excellent supervision and whole-hearted support and continuing faith in me throughout the period of my work with him.

I would also like to thank the following people for their services:-

Mrs. S. Smith : microanalysis
Mrs. M. Smith : n.m.r. spectroscopy
Mr. C. Miller : mass spectroscopy
Mrs. M. Shand : typing
Mr. M. Charlton : diagrams

Also Drs. I.H. Sadler and Dr. Reed of the University of Edinburgh for some high-field n.m.r. spectra, and Dr. R.K. Mackie for providing the ^{19}F and ^{1}H computer simulated n.m.r. spectra.

ABSTRACT

In Chapter 1 a synthetic route to benzimidazole N-oxides unsubstituted at N-1 and C-2 is described in some detail. The method employed involves the base-induced cyclisation of *N*-cyanomethylated *o*- nitroanilines to give a benzimidazole *N*-oxide having a hydrolysable cyano substituent at C-2. Also included is the preparation of the novel 4- and 7-aminobenzimidazole 3-oxides.

An analysis of the ^{19}F n.m.r. spectra of 5- and 6-fluorobenzimidazole *N*- oxides and precursors is attempted, the analysis being chiefly concerned with an explanation of the splitting patterns arising from fluorine-hydrogen coupling.

Chapter 2 begins with a brief outline of the synthesis of the quinoxalino[2,3-c]cinnoline heterocycle by cyanide-induced cyclisation of Schiff bases. The opportunities for nucleophilic displacement of a halogen in a number of halogenoquinoxalino[2,3-c]cinnolines by the methoxide nucleophile is entered into in depth. An attempt is also made to alter the site of protonation in quinoxalino[2,3-c]cinnolines. The synthesis of 9-fluoroquinoxalino[2,3-c]cinnoline, along with some of its chemical behaviour, is also reported.

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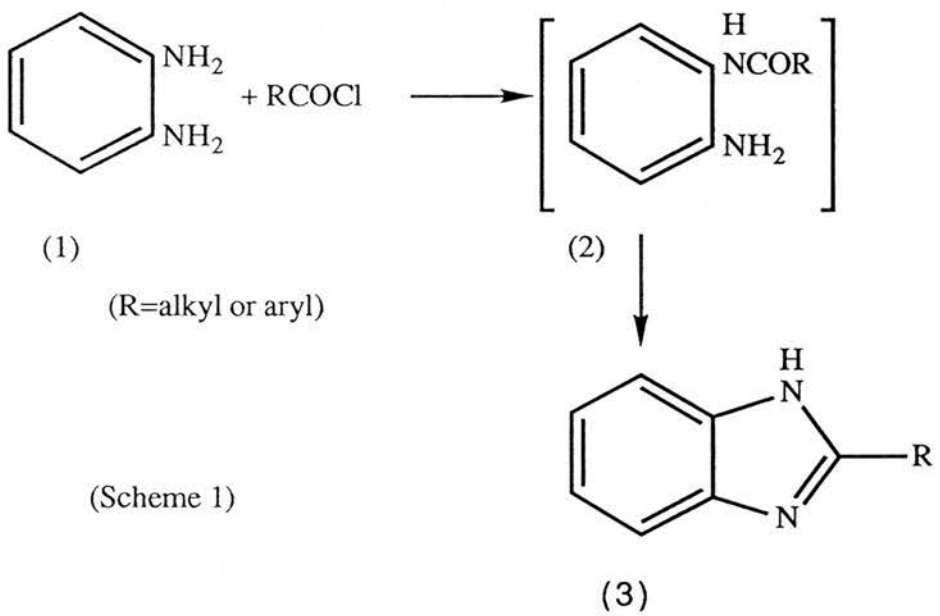
CONTENTS (Contd.)

SOME BENZO-FUSED NITROGEN HETEROCYCLES

PART 1 INTRODUCTION

Benzimidazoles are a class of heterocyclic compounds having a structure composed of an imidazole ring fused at the 4- and 5- positions to a benzene ring. Benzimidazoles were discovered in the last century by Grassi-Cristaldi and Lambardi[1]. Since then a substantial amount of work has been done in the synthesis of benzimidazoles and related compounds.

As a result the methods of synthesis are many and varied.[2] One of the commonest types is shown in Scheme 1.

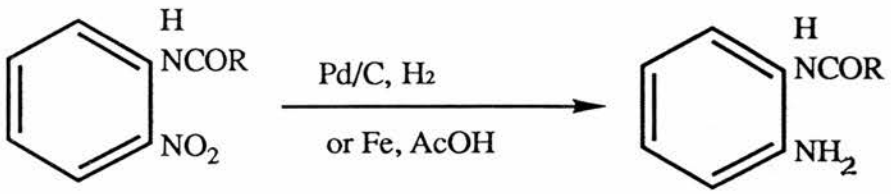


(1) (2) (3)

(R=alkyl or aryl)

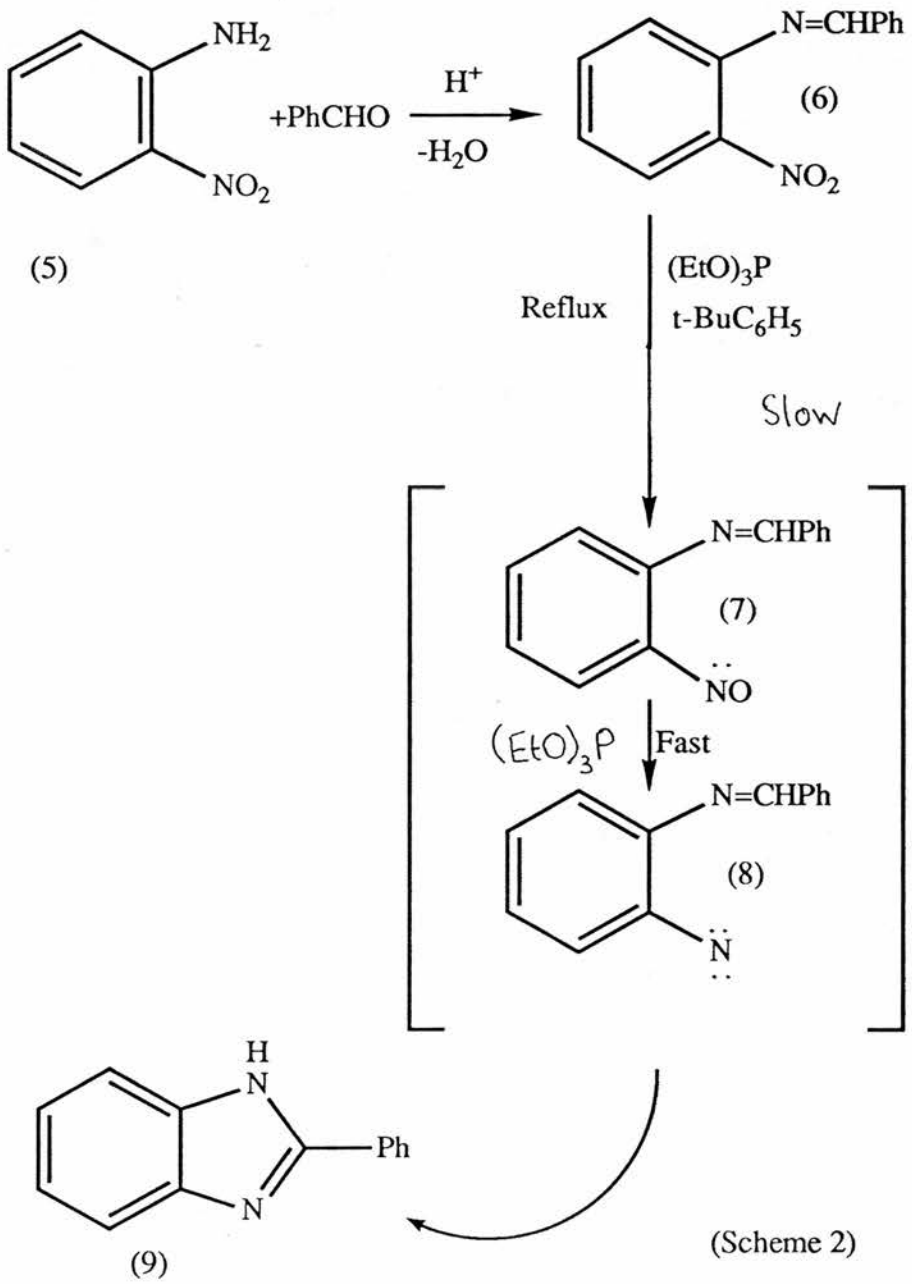
(Scheme 1)

The reaction entails the acylation of an *o*-phenylenediamine, e.g. (1), to form the mono-acylamine intermediate (2) which then spontaneously cyclises forming the benzimidazole (3). The mono-acylamines (2) can also be made by reduction of the corresponding nitro compounds (4) using common reducing agents as shown overleaf.



(4) (2)

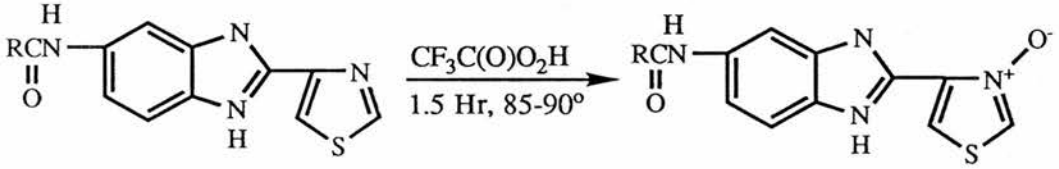
The related nitro compound (5) can undergo a different type of reduction to form a benzimidazole as shown in Scheme 2.



(Scheme 2)

2-Nitroaniline is reacted with benzaldehyde and the resultant condensation gives the Schiff base (6) which then undergoes a two stage reduction forming firstly a nitroso intermediate (7), which is the slower stage, and subsequently the nitrene (8). This then cyclises to give the benzimidazole (9). This type of reaction has a bearing on benzimidazole *N*-oxide synthesis which will now be outlined.

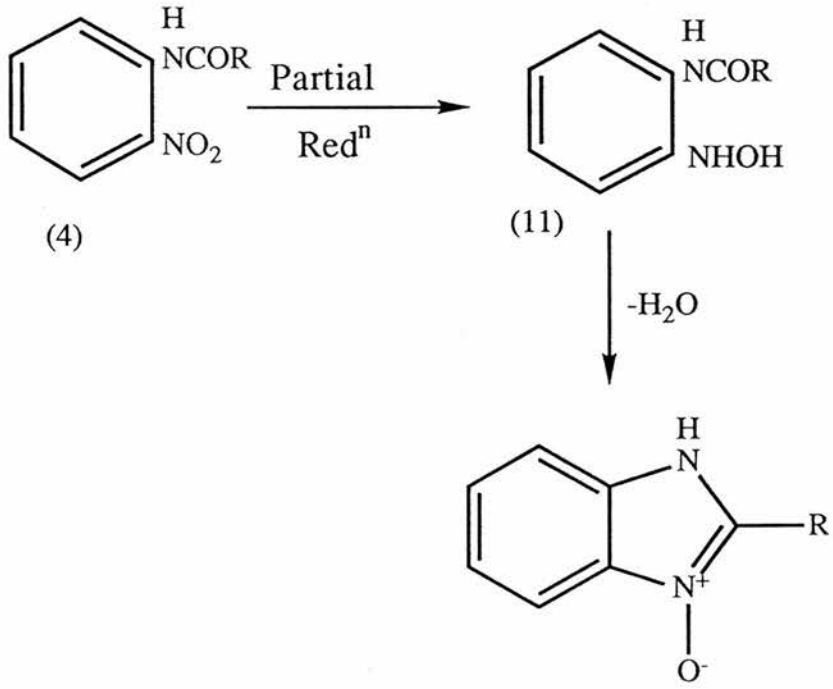
Benzimidazole *N*- oxides cannot be prepared by simple direct oxidation of benzimidazoles, even when employing strong peracids. Bochis[3] found when a 2-(4-thiazolyl)benzimidazole (10) is treated with peroxytrifluoroacetic acid only the thiazole nitrogen is oxidised.



(10)

Possible reductive routes to benzimidazole *N*- oxides could be envisaged by:

(a) controlled reduction of the *o*-nitro compound (4) and cyclisation thus:

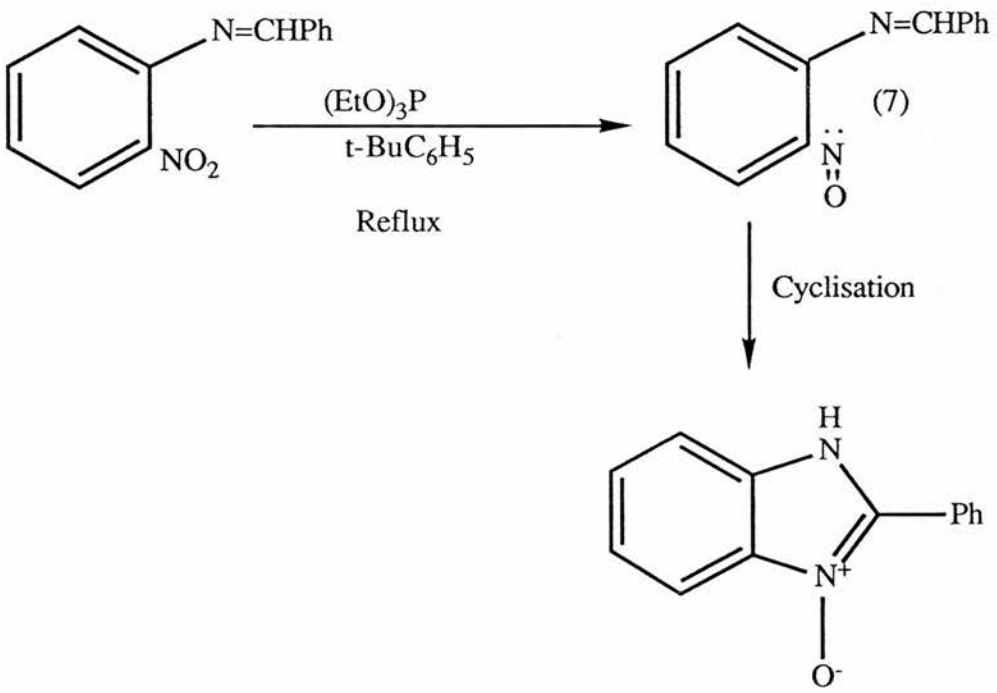


(4)

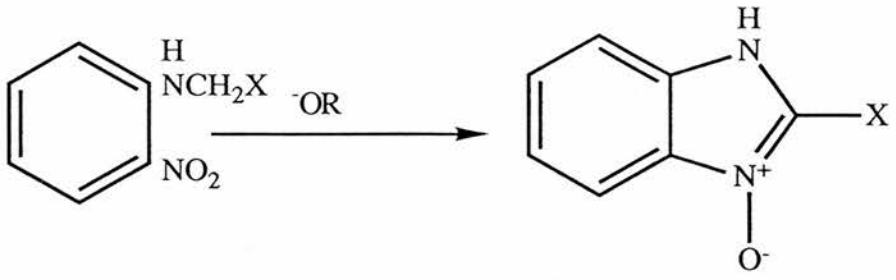
(11)

Unfortunately this partial reduction to a hydroxylamine intermediate (11) is not always easy to achieve. It is very difficult to predict accurately the amount of the reducing agent to use, since further reduction of the hydroxylamine can obviously also occur, and the possibility of additional groups sensitive to reduction in the starting material could also complicate the process.

(b) The cyclisation of the partially reduced nitroso intermediate (7) in Scheme 2 thus:



This method is unsatisfactory because of the slow formation of the nitroso compound in relation to the faster formation of (8) the secondary reduction intermediate. The commonest method of preparing *N*- oxides therefore does not involve a reductive process but an intramolecular condensation in the presence of base, as illustrated on the next page:

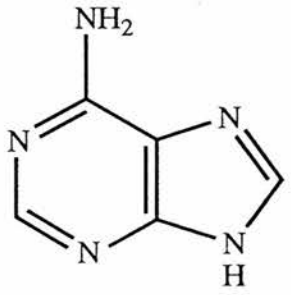


X = electron withdrawing group.

The product of this type of reaction gives in most cases an *N*-oxide which has substituents present at C-2 .

The key to the reaction is the generation of a carbanion from the CH_2 group present in the starting material.

Of particular interest to the St. Andrews research group are benzimidazoles and their *N*-oxides which lack substitution both at N-1 and at C-2. The importance of these unsubstituted benzimidazoles and their *N*- oxides is concerned with their structural similarity to the naturally occurring purines such as adenine (12) and guanine (13)[4],



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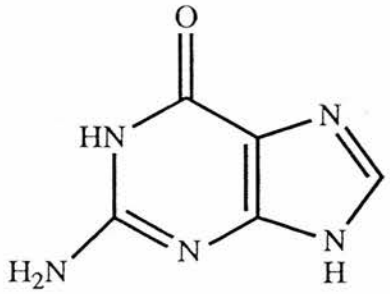
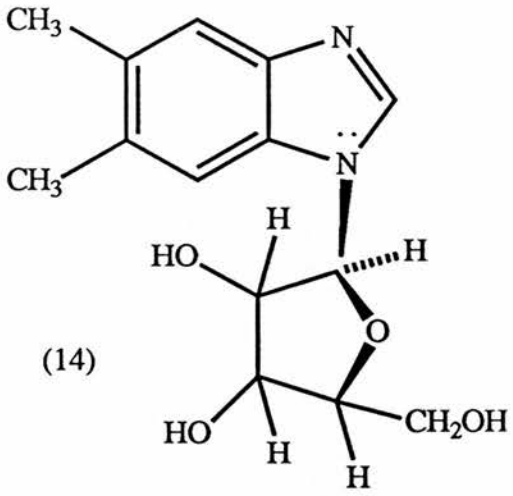


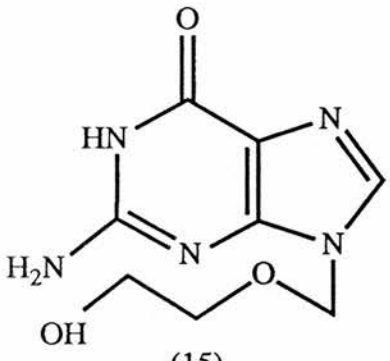
(13)

and also with the discovery that 5,6-dimethyl-1-(α-D-ribofuranosyl) benzimidazole (14) is an integral part of the structure of vitamin B_{12}



(14)

The most recent application of purine analogues is in the field of antiviral agents. A recent review[5] highlights compounds such as acyclovir (A.C.V.) (15) and the isomer 9-(3-hydroxy propoxy)guanine (16) which are both successful antiviral agents, the former against the Herpes simplex virus and the latter showing selective antiherpetic activity.



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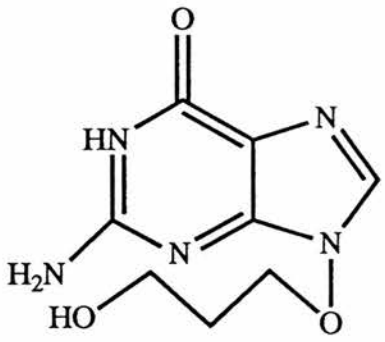


(16)

A compound such as (16) is derived from a purine-9-oxide (in the form of its *N*- hydroxy-tautomer) by alkylation, and it was thus of interest to study the formation and *O*- alkylation of the benzimidazole *N*- oxide analogues of guanine.

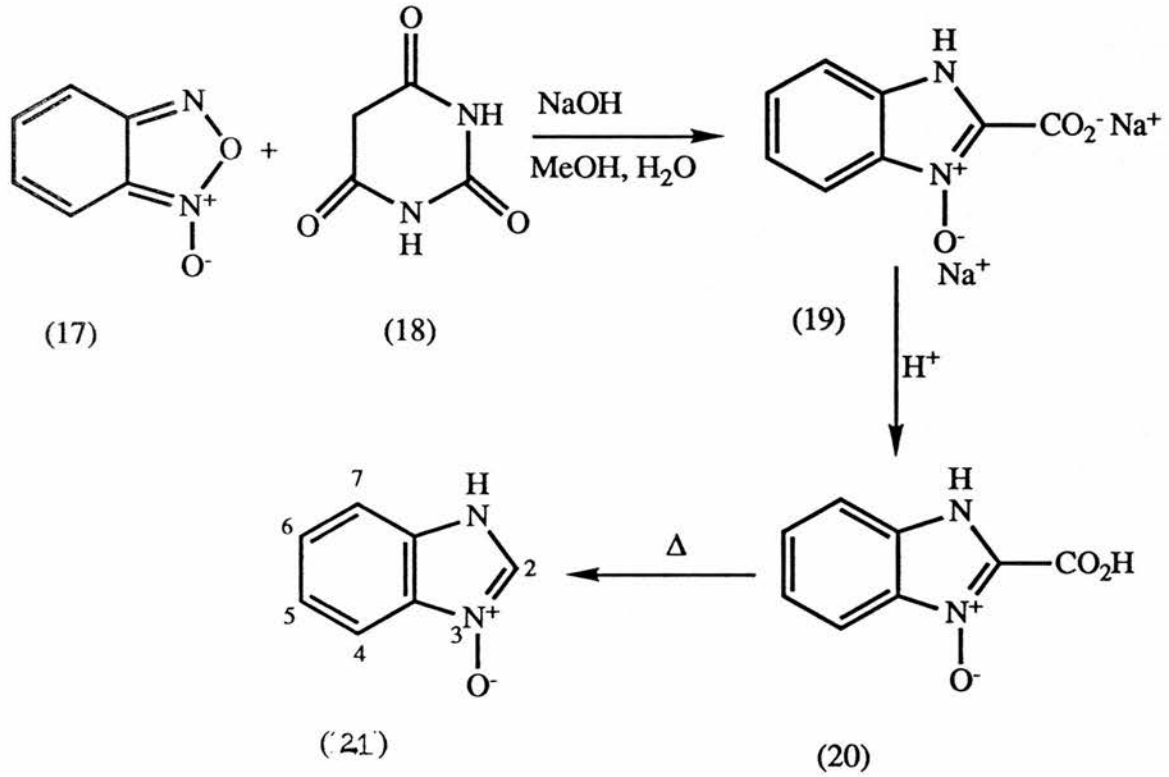
This is one of the reasons why the research group wished to achieve a satisfactory general synthetic route to benzimidazole *N*- oxides unsubstituted at C-2 and N-1.

A review of the previously reported methods of synthesising the benzimidazole *N*- oxides under discussion showed that all the cited routes either contained major drawbacks or, indeed, appeared erroneous.

PART 2 PREVIOUSLY REPORTED SYNTHETIC METHODS

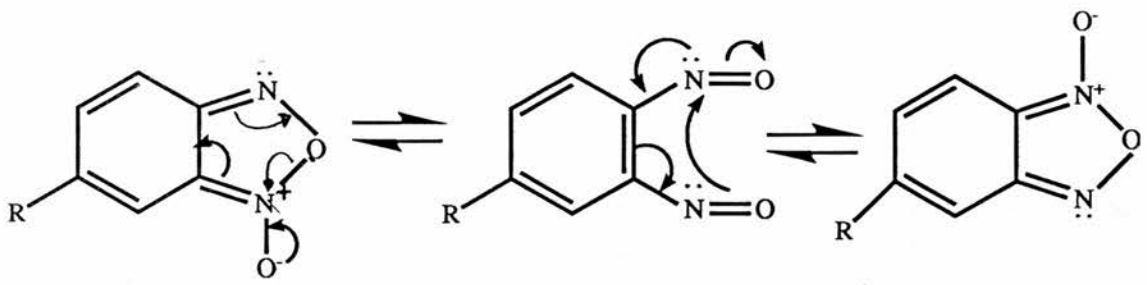
(1) Benzofuroxan with barbituric acid[6]

The first method considered was the reaction of benzofuroxan (17) with barbituric acid (18) in base to produce the salt of benzimidazole-2-carboxylic acid *N*- oxide (19) (Scheme 3). The free acid (20) is then readily decarboxylated on heating to give the unsubstituted *N*- oxide (21).



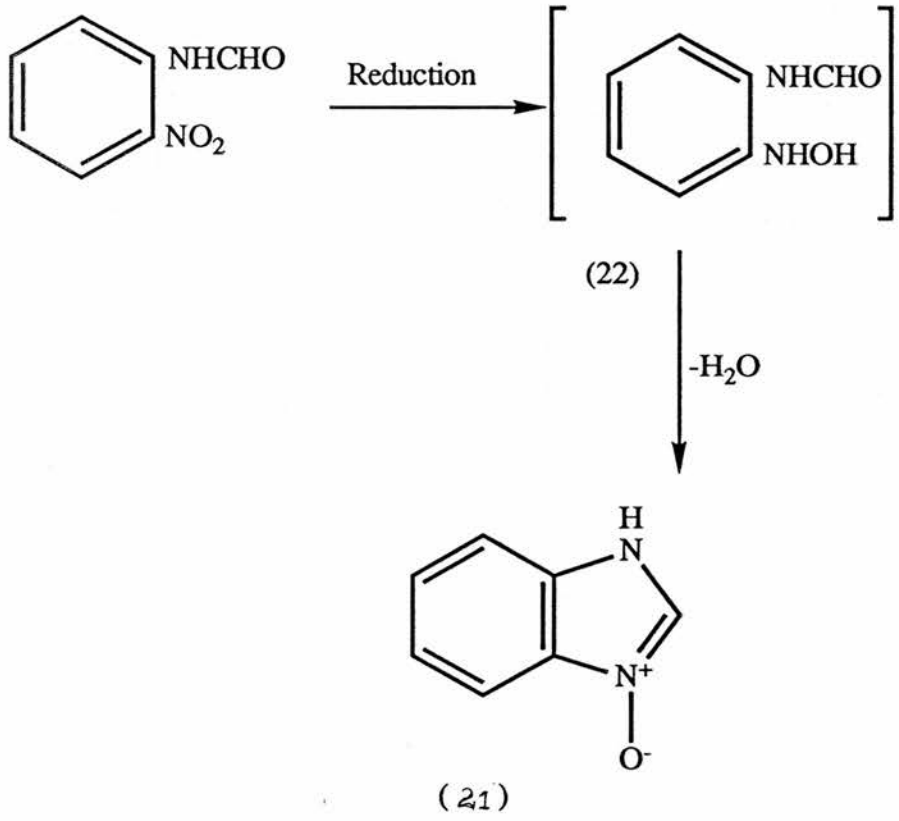
(Scheme 3)

The scope of this method is limited by the fact that if monosubstitution is desired in the product at C-4, 5, 6 or 7 then monosubstituted benzofuroxans would have to be synthesised. Additionally this might lead to two isomeric benzimidazole oxides, because in solution benzofuroxans are known to exist in two tautomeric forms[7], e.g.



(2) Partial reduction of 2-nitroformanilides

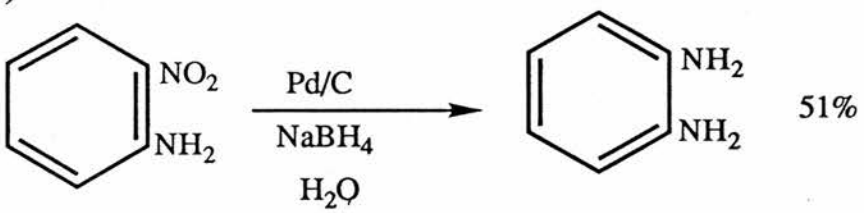
The second method involves the partial reduction of 2-nitroformanilides according to Scheme 4.



(Scheme 4)

The critical step is the formation of the hydroxylamine intermediate (22). This reductive step has been tried using a variety of reducing agents e.g. palladium-charcoal with sodium borohydride[8], and ammonium sulphide[9].

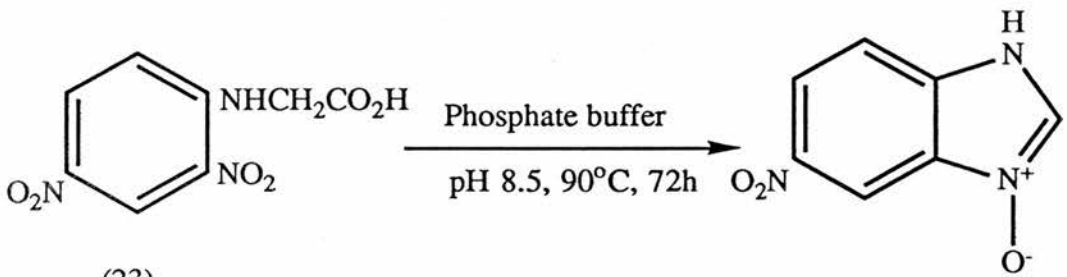
A frequently encountered problem in this type of reaction is over-reduction. For example, the palladium-charcoal/sodium borohydride combination is known[10] to effect the complete reduction of a nitro-group (see below)



Additional complications can arise if the starting material contains more than one reducible group as this makes the calculation of the correct quantity of reducing agent more difficult.

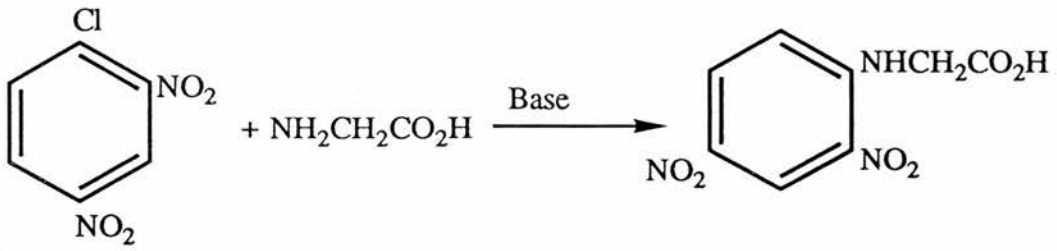
(3) **From 2,4-dinitrophenylglycine (23)**

It has been reported[11] that 5-nitrobenzimidazole *N*- oxide (24) was obtained from (23) by the action of 0.2 M phosphate buffer at pH 8.5 for 72 hrs at 90°C.



(23) (24)

The generality of this method has not been explored further. Because of the presence of a second nitro group at the para position, 2,4-dinitrophenylglycine is easily prepared (Scheme 5),and the experience of other members of the group[12,13] suggests that



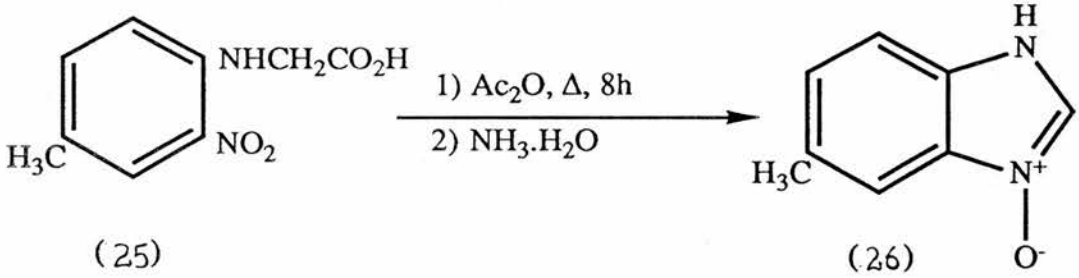
(23)

(Scheme 5)

2,4-dinitrophenylglycine derivatives are much more readily cyclised in basic media than the mono-nitrophenyl analogues.

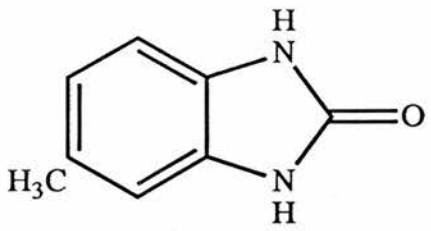
(4) Cyclisation using acetic anhydride

In 1974 Aboulezz and El-Sheikh[14] published a paper containing what at first seemed to be a convenient synthesis of 5-methylbenzimidazole *N*-oxide (26). The presumed cyclisation of 4-methyl-2-nitrophenylglycine (25) occurred in boiling acetic anhydride, then treatment with base gave (26)



(25) (26)

The validity of this method was tested in this Department by Moody[15]. When the reaction was repeated, neither the claimed *N*- oxide nor the stated by-product, the benzimidazolone (27) was isolated; the only product recovered was the *N*- acetylated derivative (28) of the initial starting material.



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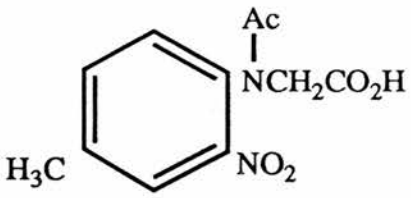


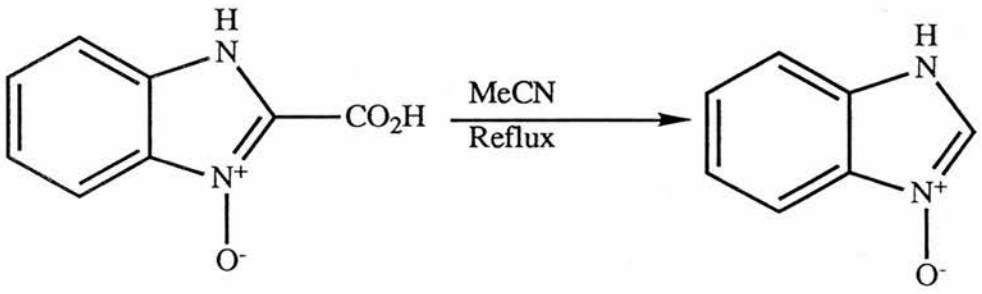
(28)

A second test using the unsubstituted 2-nitrophenylglycine under the same reaction conditions yielded only a complex mixture of products on work-up. The conclusion drawn from this was that this method as published was apparently erroneous. Attempts by Moody to pinpoint the error were unsuccessful.

From this review it is now obvious that a far better method of synthesising benzimidazole *N*- oxides unsubstituted at N-1 and C-2 was needed if our initial aims were to be achieved.

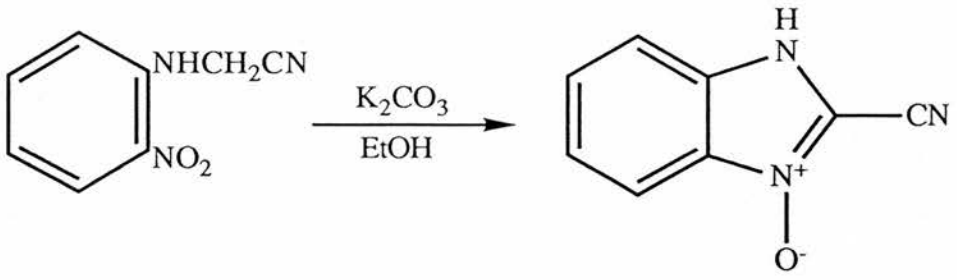
PART 3 THE ORIGINS OF THE SYNTHETIC ROUTE

The new route was found by utilising the fact (already mentioned) that decarboxylation of benzimidazole-2-carboxylic acid *N*- oxide can be carried out by heating in a suitable solvent at a temperature as low as 80°C (see also page 8).



(20) (21)

Generation of the carboxylic acid function *in situ* by hydrolysis of either a cyano or ester group offered an attractive alternative to the previous reaction. Both of the necessary precursors, (29) and (30), were already known[16,17] to be more easily prepared (by base induced cyclisation; see overleaf) than the acid.



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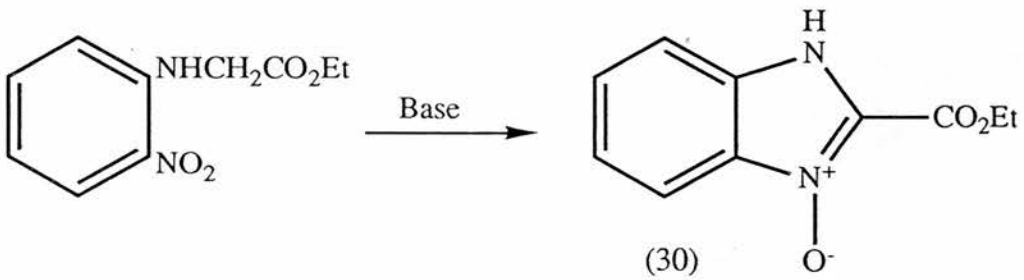
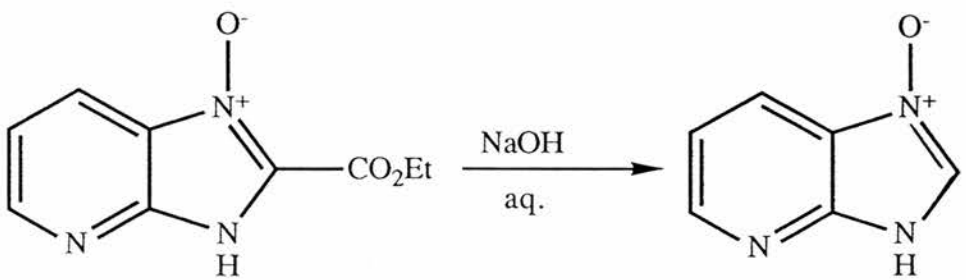


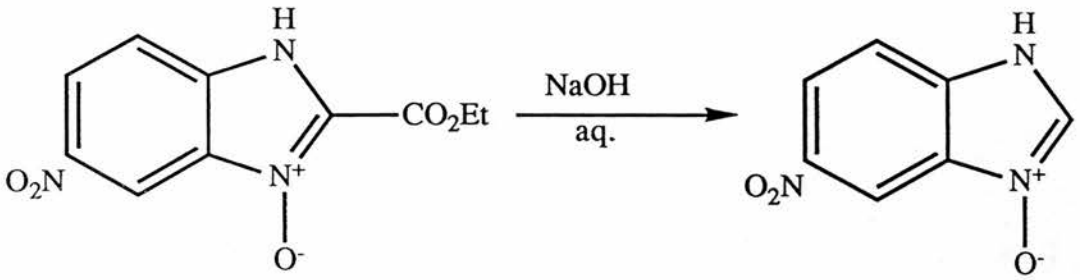
(30)

Both the ester and the nitrile groups can be hydrolysed in either base or acid. Although a variety of different bases were used ranging from sodium ethoxide to ethanolic potassium carbonate under various reaction conditions, only very limited success was obtained. Working with the related imidazo[4,5-b]pyridine *N*- oxide series, McFarlane achieved a satisfactory hydrolysis[12] in base of the ester (31) to give the parent *N*-oxide (32) in 77% yield.

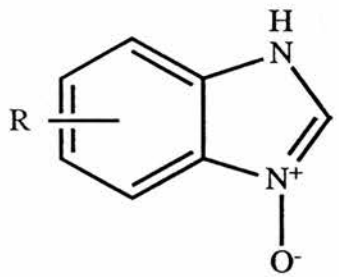


(31) (32)

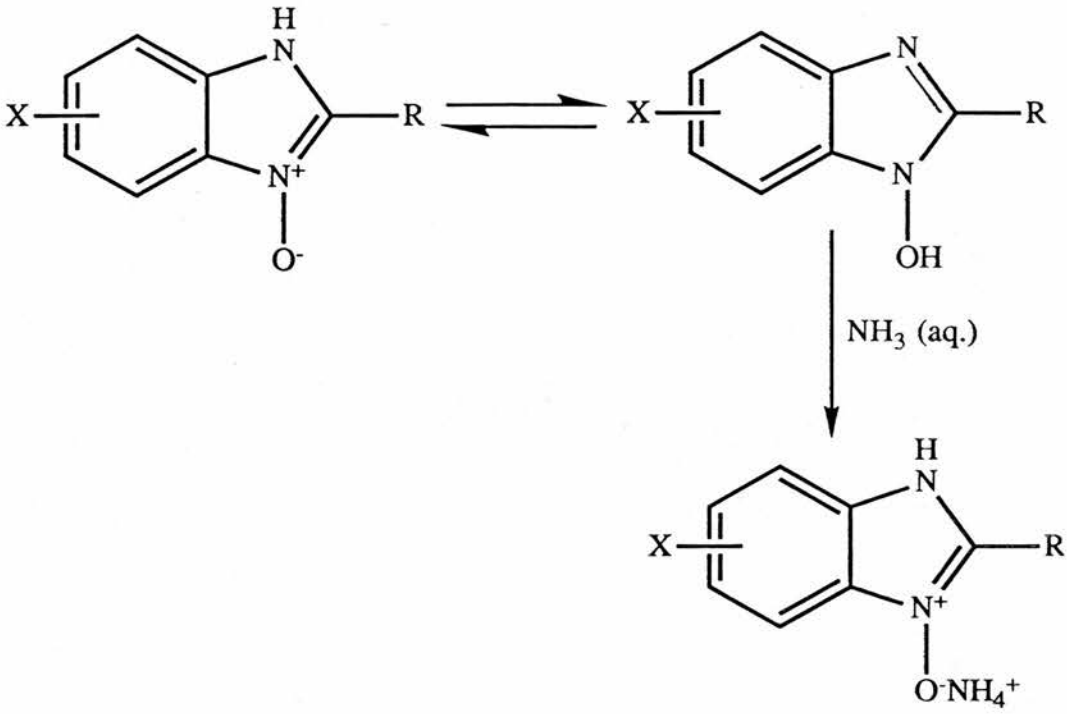
Moody also found that the same base also effected the hydrolysis overleaf in good yield.



However Moody found that other simple benzimidazole *N*- oxides of the type shown below when produced by basic hydrolysis were often difficult to isolate from the aqueous reaction medium due to formation of the soluble salt



by the deprotonation reaction shown overleaf.



Acidic hydrolysis, however, removed the problem of deprotonation and was found to be highly successful. This is therefore used here in preference to the basic hydrolysis technique (see page 15).

PART 4 OUTLINE OF THE SYNTHETIC ROUTE

The discussion in this section will be limited to the synthesis of the *N*-oxides other than the amino analogues (X = NH_2 in Scheme 11 and 17) which are discussed later. Two routes are utilised in the synthesis (Schemes 6 and 7), the former being the favoured method. The steps in this first route are now considered in turn.

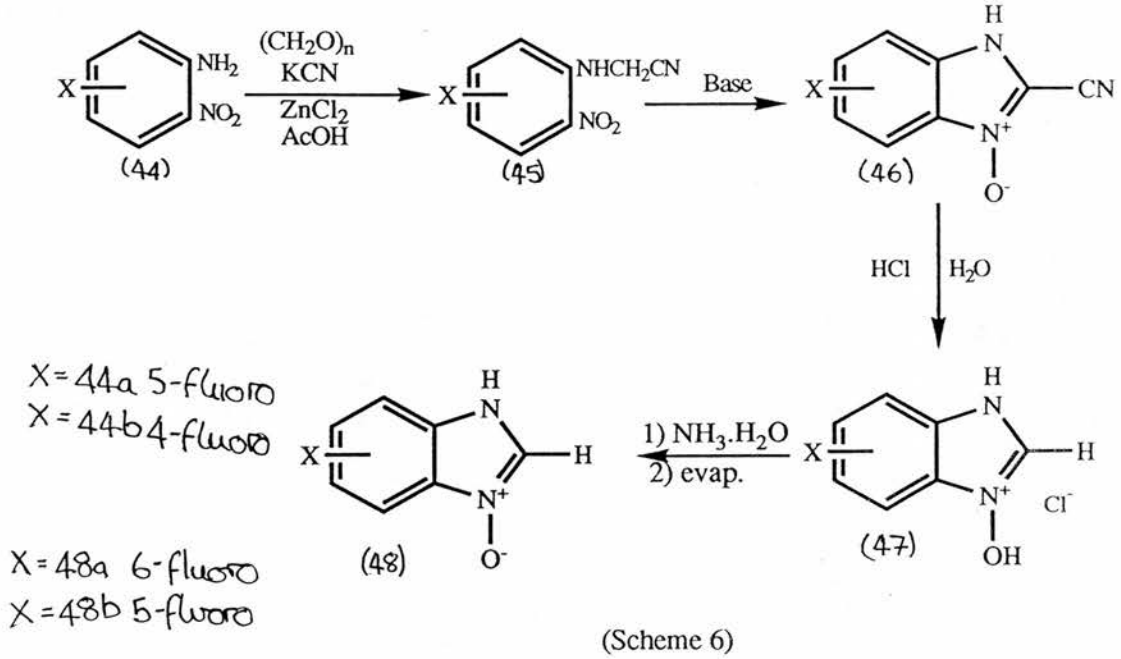
(1) The cyanomethylation procedure

The substrates required for cyclisation are *N*- cyanomethyl-*o*-nitroanilines. These are most conveniently prepared by direct cyanomethylation of the simple *o*- nitroanilines using paraformaldehyde and potassium cyanide in the presence of a Lewis acid (zinc chloride) and acetic acid.

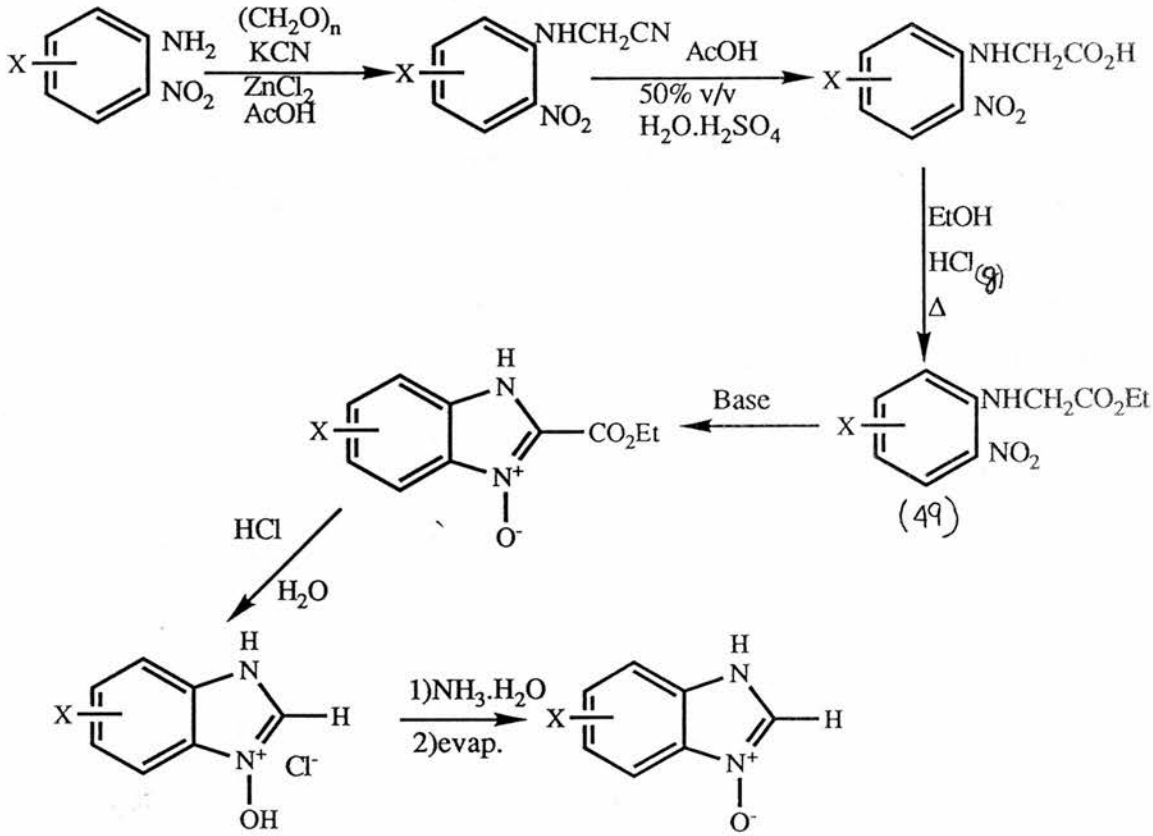
The cyanomethylation procedure, devised by Dimroth and Aurich[18] (Scheme 8), involves the creation of a complex equilibrium system which is pH dependent. The zinc chloride and acetic acid form a complex (shown below) which results in a strongly acidic medium.

$$[(CH_3CO_2 \cdot ZnCl_2)^-]H^+$$

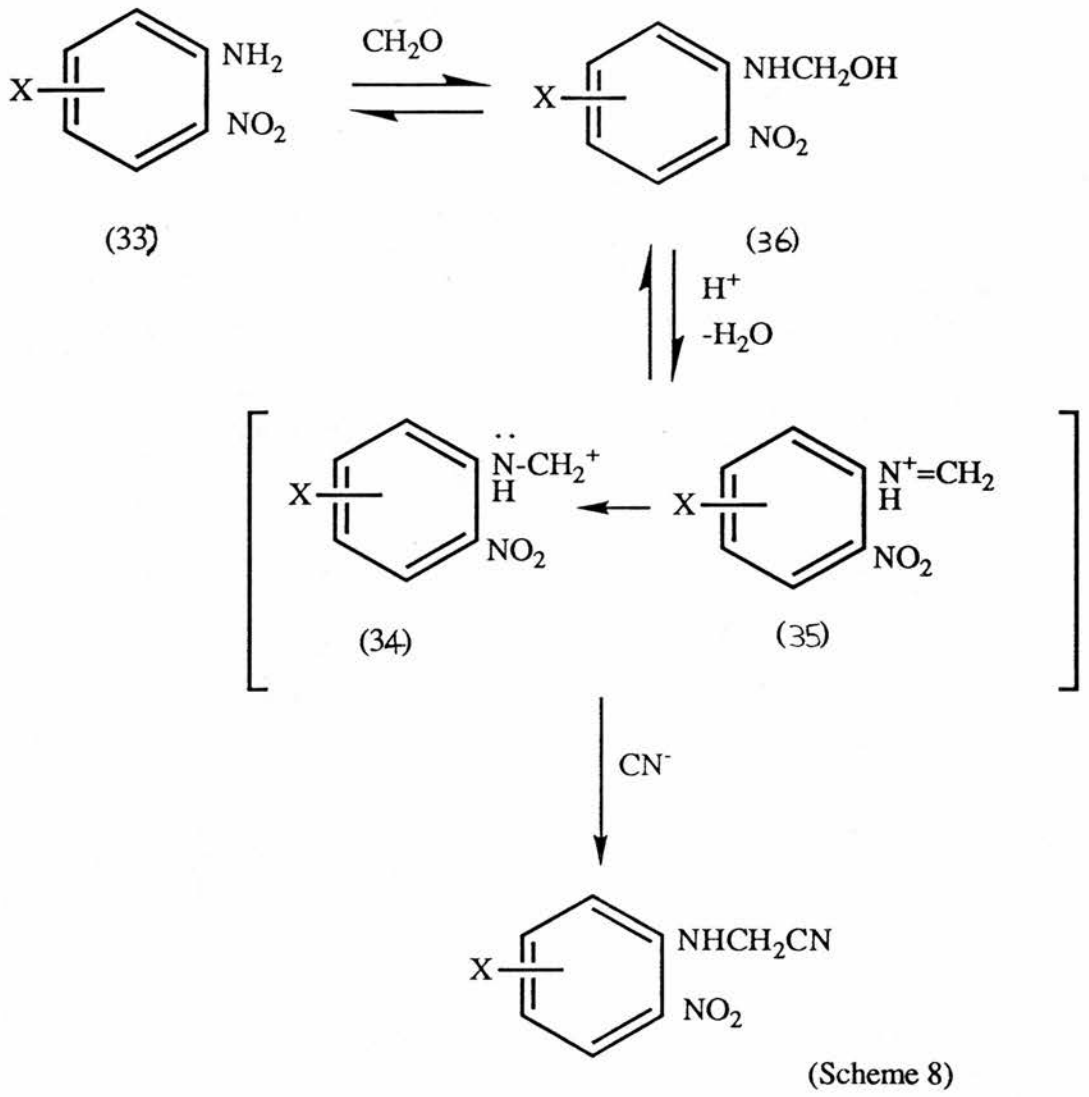
This causes protonation of the formaldehyde which then attacks the amine (33) to give the carbonium (34) or iminium ion (35) via (36). Finally attack on this ion by the cyanide nucleophile gives the desired product.



(Scheme 6)

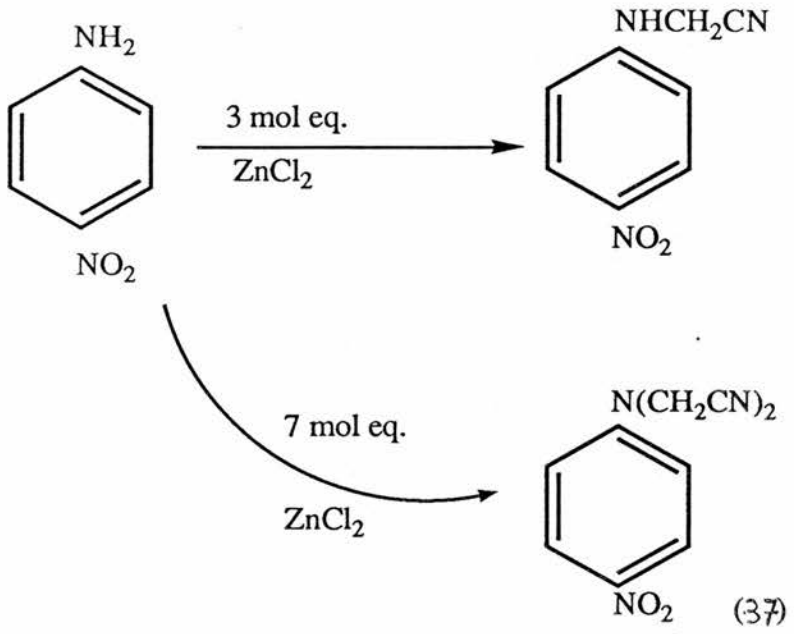


(Scheme 7)



(Scheme 8)

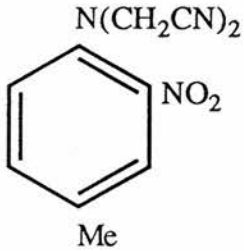
Dimroth and Aurich point out that altering the amount of zinc chloride used in a given reaction influences the products obtained (Scheme 9).



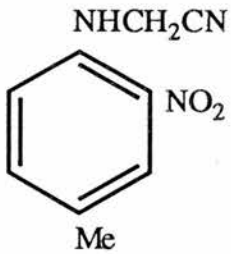
(Scheme 9)

The reactions in Scheme 9 show that more than doubling the amount of zinc chloride causes the formation of the *N,N*- bis-cyanomethyl-4-nitroaniline (37).

In the course of preparation of a series of mono-cyanomethylated amines this problem was experienced at first hand. Dimroth and Aurich's method for the cyanomethylation of *o*- nitroaniline itself involves the use of 4.2 molar eqivalents of zinc chloride. Moody found, however, in the case of 4-methyl-2-nitroaniline, that more than 3 molar equivalents lead to the formation of significant amounts of the bis-cyanomethyl compound (38) along with the desired product (39).



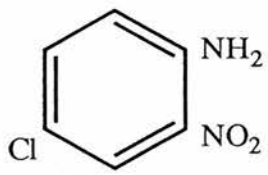
(38)



(39)

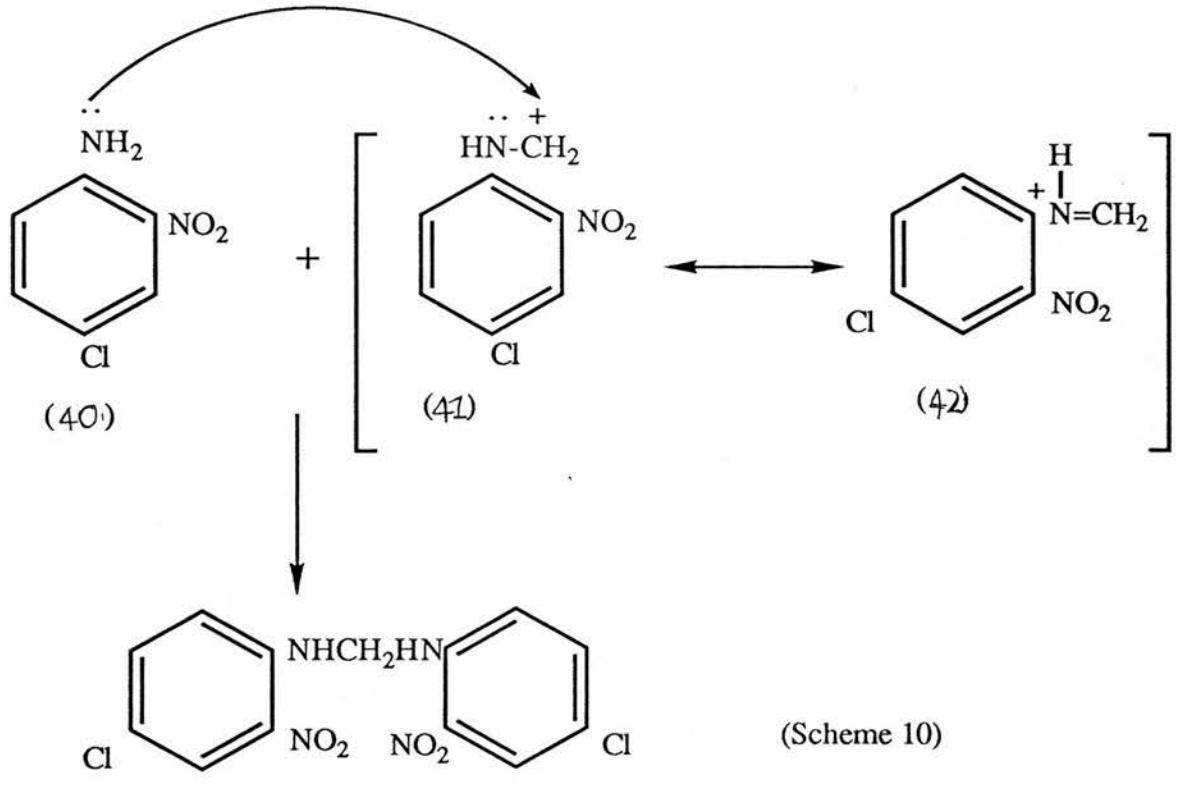
The explanation is that once formed (39) is somewhat more basic and more nucleophilic than the parent compound *N*-cyanomethyl-2-nitroaniline thus allowing the amino group to react with the excess zinc chloride and undergo a second cyanomethylation giving (38).

It is now shown, however, that the situation is altered in the other direction in the case of a more weakly basic amine such as (40).



(40)

The presence of two electron withdrawing groups draws the nitrogen lone pair into the ring, lessening its basicity and nucleophilicity and making it consequently more difficult to protonate or co-ordinate with a Lewis acid. In this case three molar equivalents of zinc chloride serve only to give compound (43) (Scheme 10) as the product.

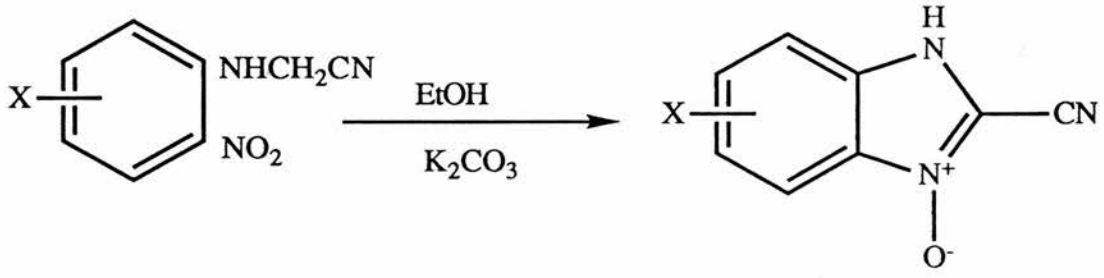


(Scheme 10)

The explanation is that three molar equivalents of zinc chloride is an insufficient quantity to protonate or co-ordinate the amine (40) totally due to its relatively weak basic character. Unchanged amine (40) may then react with (41)/(42) and so give rise to the coupled product (43). It was found that such weakly basic amines as (40), (44a), and (44b), required <u>seven</u> molar equivalents of zinc chloride to ensure successful <u>mono</u>cyanomethylation.

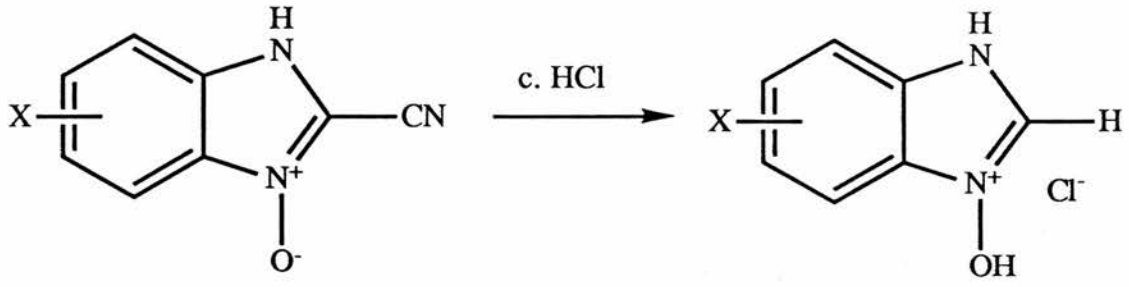
(2) Cyclisation of the *N*- cyanomethyl-*o*-nitroanilines

The method was adapted from the literature precedents of Livingstone and Tennant[17] and Konopski and Serafin[16]. The use of a non-aqueous reaction medium (ethanol) gave the reaction mixture homogeneity and after experimentation with various bases anhydrous potassium carbonate was found to be the most successful one for the reaction below.



(3) The acid hydrolysis of the cyanobenzimidazole *N*- oxides

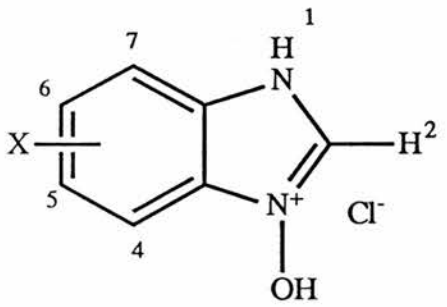
Hydrolysis using concentrated hydrochloric acid removes the difficulties encountered with basic hydrolysis (see page 15). In the general reaction below, separating the desired organic product from the



+ CO_2 + NH_4Cl

ammonium chloride presents a possible problem. Basification of the reaction mixture is of limited use for isolation of the organic product, since the *N*-oxides are all water-soluble to some extent, and are also deprotonated a second time in basic media to yield a water-soluble anion.

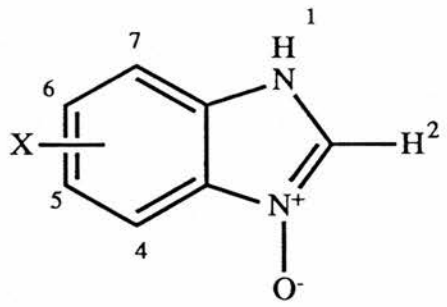
Fortunately, the *N*- oxide hydrochlorides are considerably less soluble than ammonium chloride in concentrated hydrochloric acid, and in every case the hydrochlorides crystallise from the reaction medium in almost pure form. Removal of the inorganic products at this stage ensures a cleaner reaction with the ammonia in the subsequent step. The hydrochlorides also have very characteristic ^1H n.m.r. and infra-red spectra which means that the completeness of the reaction can be judged with relative ease. In the proton n.m.r., the resonance of H-2 (Table 1) always occurs as a sharp singlet which is shifted considerably downfield relative to the other aromatic resonances.



X	H-2 δH (p.p.m.)
H	10.07
5-Me	9.80
5-MeO	9.74
5-F	9.85
6-F	9.78
4-NO_2	9.07
5-Cl	9.81

(Table 1)

The deshielding is not altogether unexpected when the electron-withdrawing nature of the adjacent atoms is taken into consideration. When the oxygen is deprotonated to give the respective *N*- oxide, (Table 2) the H-2 resonance is shifted somewhat upfield of its former value by approximately 1.5 p.p.m. For comparison the resonance of H-2 in benzimidazole itself is 8.29 p.p.m.[2]



X	H-2 δH (p.p.m.)
H	8.35
5-Me	8.23
5-MeO	8.20
5-F	8.38
6-F	8.41
4-NO_2	8.57
5-Cl	8.42

(Table 2)

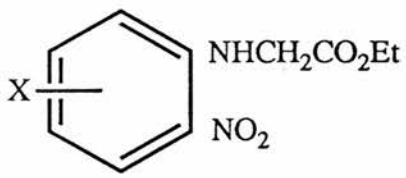
The infra-red spectra of the hydrochlorides are also distinctive, showing a characteristic absorption in the region 3000-2500 cm^{-1} (Figure 1). These absorptions are notably different from those of the nitrile precursor (Figure 2), the loss of the (C ≡ N) stretching absorption at c. 2200 cm^{-1} being significant.

(3) Basification of the hydrochlorides

Obtaining the final *N*- oxide by basification gives almost pure product without recrystallisation. The aqueous reaction medium, rendering the by-product of the reaction (ammonium chloride) totally soluble, allows the organic product to be collected by simple filtration. The overall reaction temperature is low (50°C) which avoids any unwanted thermal decomposition. Lastly any unreacted excess ammonia can be removed cleanly at reduced pressure on a rotary evaporator.

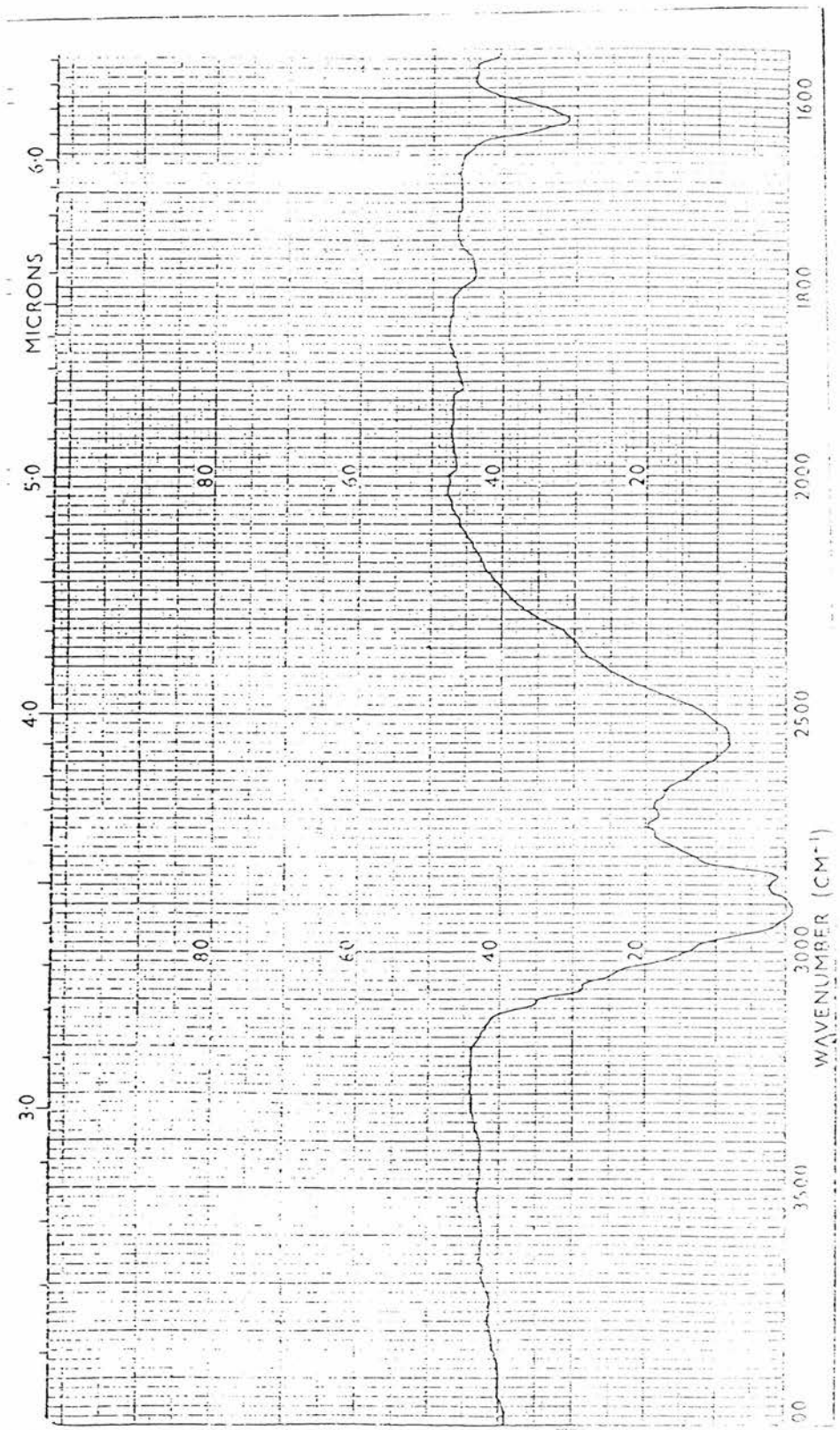
The alternative synthetic route (Scheme 7)

This route involved the synthesis of the esters below, as cyclisation precursors.



These compounds proved difficult to make successfully. Direct synthesis by Moody via the reaction of 4-methyl-2-nitroaniline and ethyl bromoacetate gave low yields of product often contaminated with unreacted starting materials.

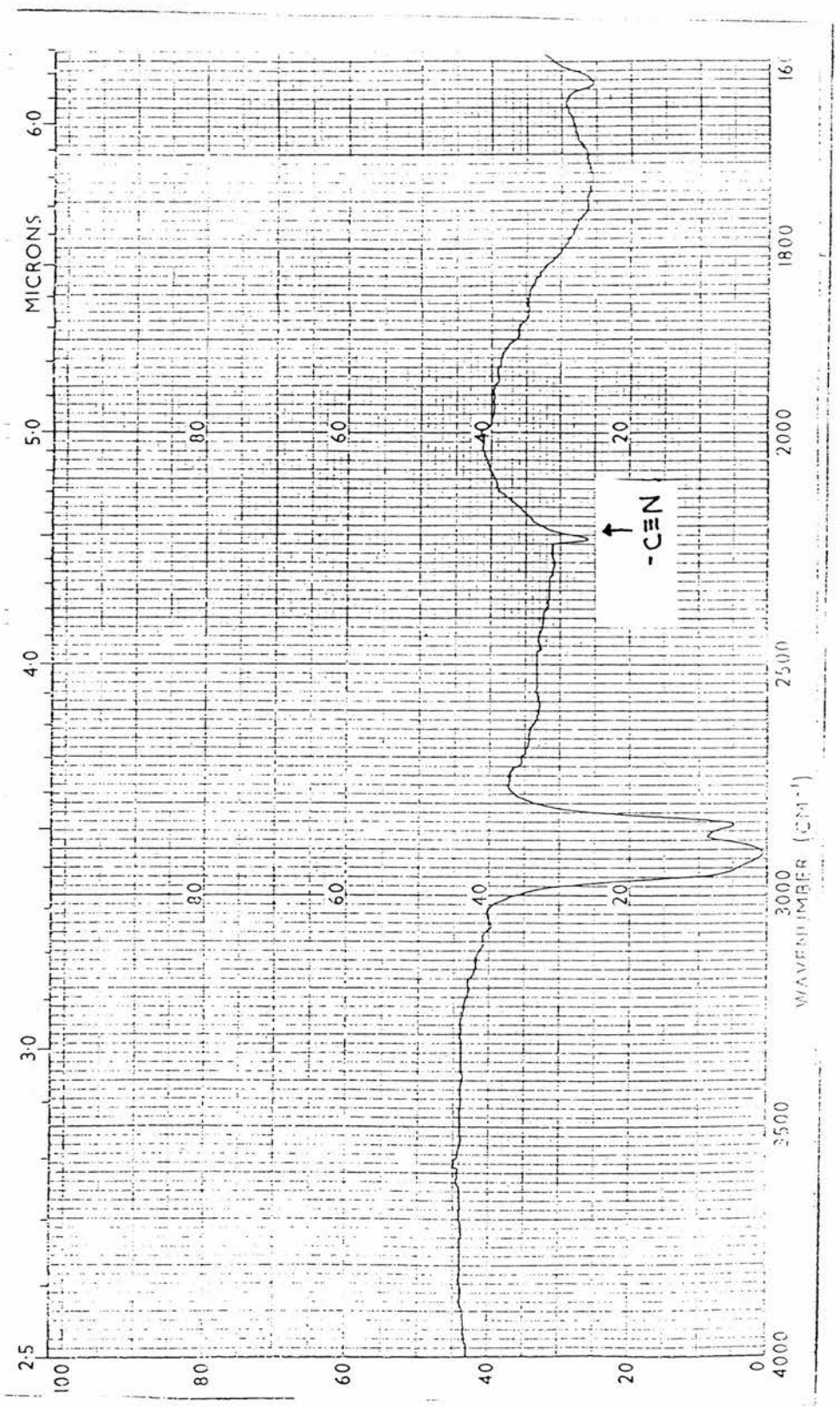
The esters can of course, be prepared from the nitriles via the acids , but this procedure offers no real advantage over direct cyclisation of the nitriles themselves.



(Figure 1)

I.R. spectrum of 5-chloro-1H-benzimidazole 3-oxide hydrochloride.

(Nujol mull)



(Figure 2)

I.R. spectrum of 5-chloro-2-cyano-1H-benzimidazole 3-oxide.
(Nujol mull)

The hydrolysis of the nitriles was a transformation which proved problematic, giving low and unpredictable yields; with *N*-cyanomethyl-4-methoxy-2-nitroaniline the yield was 45% and when using *N*-cyanomethyl-4-methyl-2-nitroaniline the yield at best was 67%. Scheme 7 was also a less direct route taking six steps as opposed to four in Scheme 6. This information led to the adoption of Scheme 6 as the preferred route.

PART 5 THE ^{19}F NMR SPECTRA OF THE 5- AND 6-FLUORO-BENZIMIDAZOLE N-OXIDE SERIES

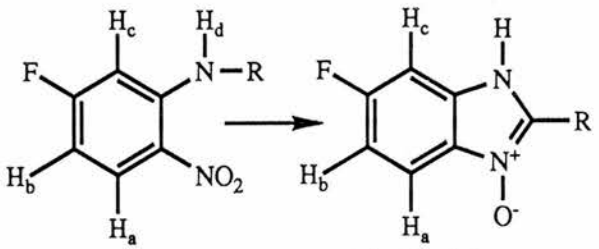
Fluorine resonances occur over a wide range of frequencies (*c.* 200 p.p.m.) which is large compared to the range of hydrogen resonances (*c.* 10 p.p.m.) Shifts can be measured with a variety of references; in this case an internal reference, trichlorofluoromethane was used (δ_F = O). Table 3 overleaf contains all the experimental data and should be referred to throughout this section along with Scheme 6 (page 18).

The chemical shifts of the fluorine atoms relative to the reference merit only a short comment. The values obtained show only the changes in environment experienced by the fluorine in the individual compounds. Briefly, all the shifts occur at the extreme lower end of the range quoted[19] for fluorine attached to a phenyl ring (-110 to -175 p.p.m.); in three cases it lies outside this range.

The major interest is derived from the analysis of the couplings of the fluorine atom with protons H_a, H_b, H_c and H_d. No coupling occurs between fluorine and proton H-2 in compounds 47a, 48a, 47b and 48b as the signal of H-2 in the ^{1}H n.m.r. spectrum always appears as a sharp singlet.

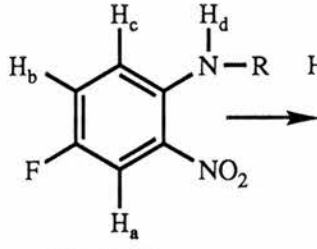
As a whole all the spectra show splitting which is consistent with two *ortho-* couplings and one *meta-* coupling from protons H_a, H_b and H_c. These values are also in agreement with the ranges quoted in literature[19], these being J_{ortho} 7.4-11.8 Hz and J_{meta} 4.3-8.0 Hz. In only two instances are the pair of *ortho-* couplings equal; the majority are unequal, the largest difference being 4 Hz. This is different from proton to proton coupling; normally a pair of *ortho-* couplings in a simple benzene ring give rise to approximately equal coupling constants.

The remaining coupling to proton H_d is the weakest one, and this is reflected in the small coupling constants measured. These values are all

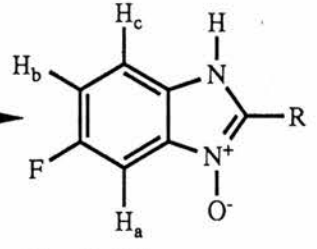


44a R=H
45a R=CH_2CN

46a R=CN
47a R=H (Hydrochloride)
48a R=H



44c R=H
45c R=CH_2CN



46c R=CN
47c R=H H (Hydrochloride)
48c R=H

Comp.	Shift (p.p.m.) from $CCl_3F(\delta = 0)$	Couplings (Hz)				Comp.	Shift (p.p.m.) from $CCl_3F(\delta = 0)$	Couplings (Hz)			
		Ortho		Meta	Other			Ortho		Meta	Other
	$J_{b,F}$	$J_{c,F}$	$J_{a,F}$	$J_{d,F}$				Jb,F	$J_{a,F}$	$J_{c,F}$	$J_{d,F}$
44a	-102.0†	8.0+	10.0+	5.6+	____	44b	-126.6†	9.2	9.2	3.8	____
45a	-99.7*	12.0	8.0	6.0	2.0	45b	-125.5†	7.0	8.7	4.4	____
46a	-117.3*	9.0	9.0	5.0	0.3	46b	-112.8*	9.8	8.4	4.8	____
47a	-114.4*	9.0	9.5	4.9	0.5	47b	-114.0*	9.5	8.3	4.5	____
48a	-121.6*	9.9	9.7	5.1	____	48b	-118.7*	10.0	8.6	4.9	1.5

+Estimations
Solvent † = $CDCl_3$; * DMSO -d_6

(Table 3)

within the quoted[19] range of a *para-* coupled hydrogen-fluorine (0.2-2.7 Hz).

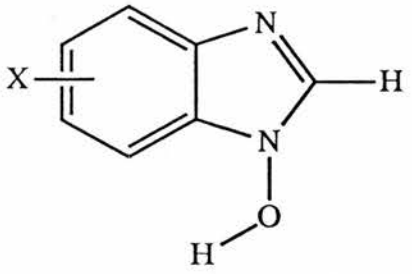
Figures 3 – 7, pages 36 - 40 show the splitting patterns obtained experimentally, and the individual splittings which combine to produce these patterns are shown diagramatically.

To complete the explanation of the results and the presence or absence of a coupling to proton H_d each isomeric pair of compounds will be discussed separately. The anilines are left until last due to the non-first order spectra observed in 5-fluoro-2-nitroaniline.

Before continuing with the discussion of the experimental results obtained, as regards the H_d, F coupling it is crucial that the following statements are kept in mind.

Firstly, proton H_d is bonded to a nitrogen atom and is therefore potentially very labile rendering it susceptible to chemical exchange with the solvent present similar to that experienced by alcohols and thiols in deuterium exchange. Also rapid intermolecular proton exchange can occur in compounds possessing an "acidic" proton, i.e. carboxylic acids, phenols, amines and thiols etc. This type of intermolecular exchange accounts, for example, for the lack of any OH- to CH_2- coupling being observed in a ^1H n.m.r. spectrum of a "normal" commercial sample of ethanol. The residence time of a particular proton on oxygen is not long enough to experience any coupling at all.

Secondly the mobility of proton H_d is very much in evidence when one considers that when benzimidazole N-oxides are in solution this proton is capable of migration, which leads to the formation of the tautomer overleaf

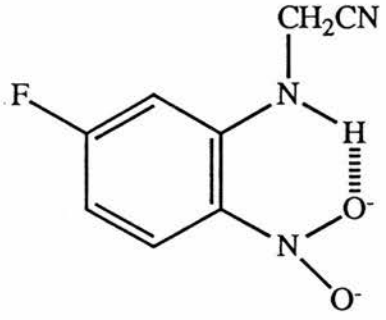


Finally in the compounds where H_d,F coupling has been reported, this does not mean that it was observed every time the spectrum was recorded; in truth its appearance was totally unpredictable. However where the H_d,F coupling is reported as non-existent it is true to say it has never been observed in these compounds on any occasion.

In essence what follows is an explanation of results collected from a number of ^{19}F n.m.r. spectra (not just eight) recorded over a period of time.

(i) The cyanomethylated anilines (45a) and (45b)

Only (45a) shows coupling between the fluorine and proton H_d and this is the largest H_d,F coupling constant seen in the whole series. It is possible that intramolecular hydrogen bonding anchors the N-H proton in a favourable position in space relative to the fluorine atom, i.e. in the plane of the ring (see below).



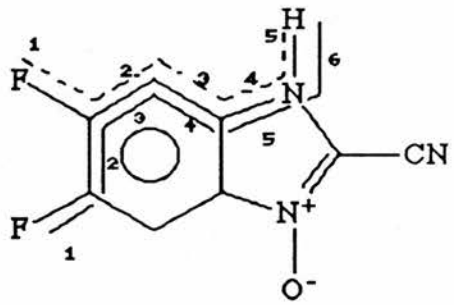
This means that effective five-bond coupling following a "zig-zag" arrangement of bonds is possible. The above idea can also be used to account for a lack of coupling to H_d in (45b). In this case although the hydrogen

bonding is still present, the fluorine and amino-proton are now separated by six bonds, and the "zig-zag" arrangement of bonds is no longer present.

(ii) Compounds (46a) and (46b)

Now that cyclisation has occurred the magnitude of the coupling between F and H_d in (46a) is significantly reduced; the limit beyond which the coupling ceases to operate must be very close.

The smaller J value observed in (46a) is possibly due to the different bond pattern that now exists between F and H_d. If the pattern in (45a) can be likened to a *trans-trans* diene system, then in (46a) it is changed into a *trans-cis* arrangement (see below) and it is well known that *trans-* coupling in alkene groups is larger than *cis-* coupling, in quantitative terms; J_{trans} 11-19 Hz as opposed to J_{cis} 5-14 Hz.



The coupling between F and H_d is not seen in (46b) because with the fluorine now at position 5 the number of bonds between the two nuclei is now six and the pattern of the bonds between them is severely distorted from the "zig-zag". The combination of these factors prevent any F,H_d coupling occurring.

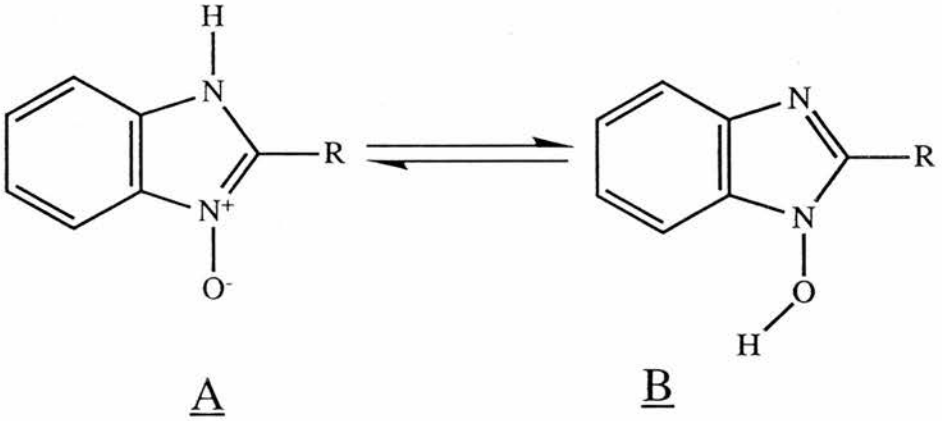
(iii) Compounds (47a) and (47b)

The previous argument functions equally well to explain the appearance and non-appearance of F and H_d coupling observed in the spectra of the title compounds.

(iv) Compounds (48a) and (48b)

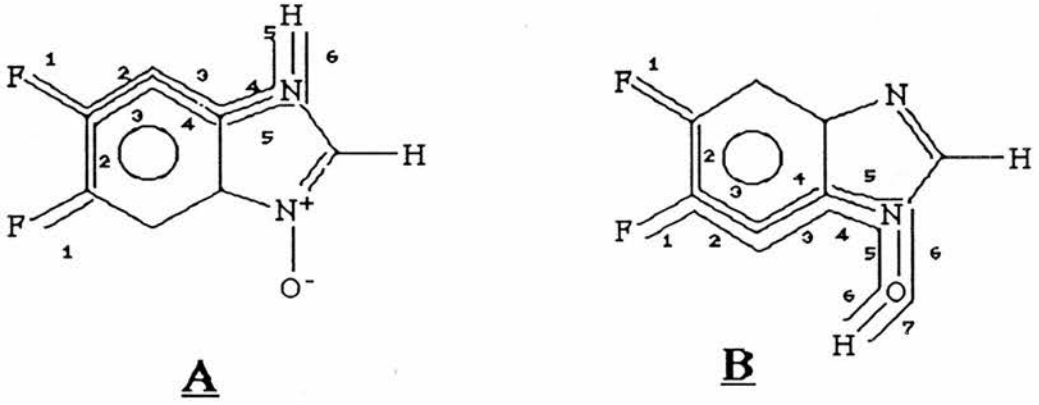
On the basis of the argument put forward to explain the observations in (ii) and (iii) the results from (48a) and (48b) apparently serve only to discredit the proposal. However there is a possible explanation as follows:-

Benzimidazole N-oxides are known[20] to exist as a tautomeric pair in solution as shown below

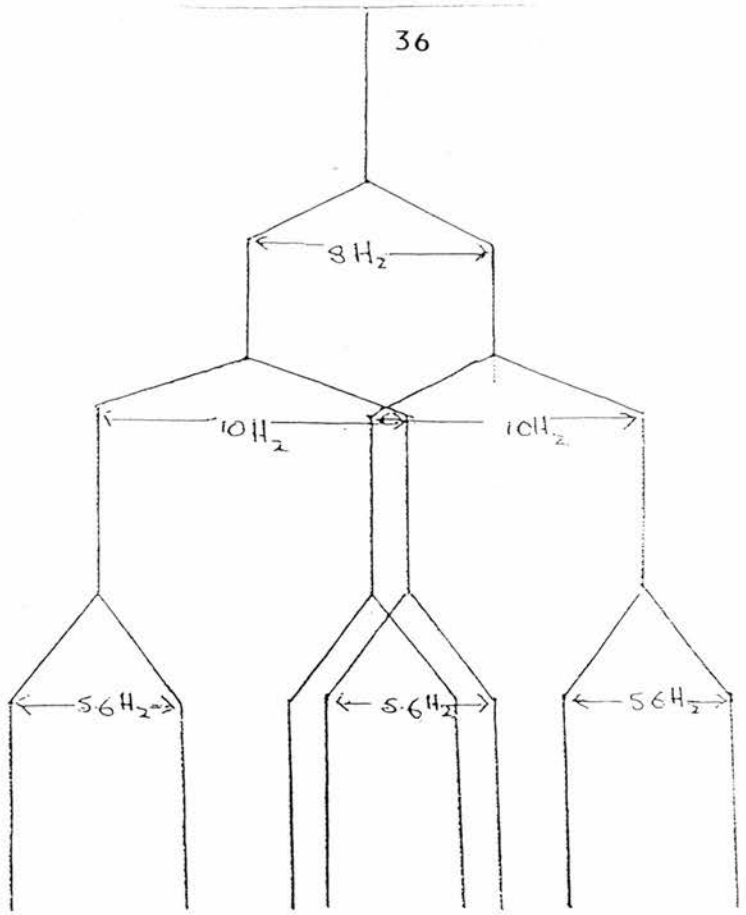


A B

Therefore, if we assume that, under the experimental conditions, for (46a) and (46b), i.e. where R=CN, the tautomer which predominates is A, and in the case of (48a) and (48b) where R=H, the situation becomes reversed, i.e. tautomer B predominates, then this will have a major influence on the H_d,F coupling (see below)

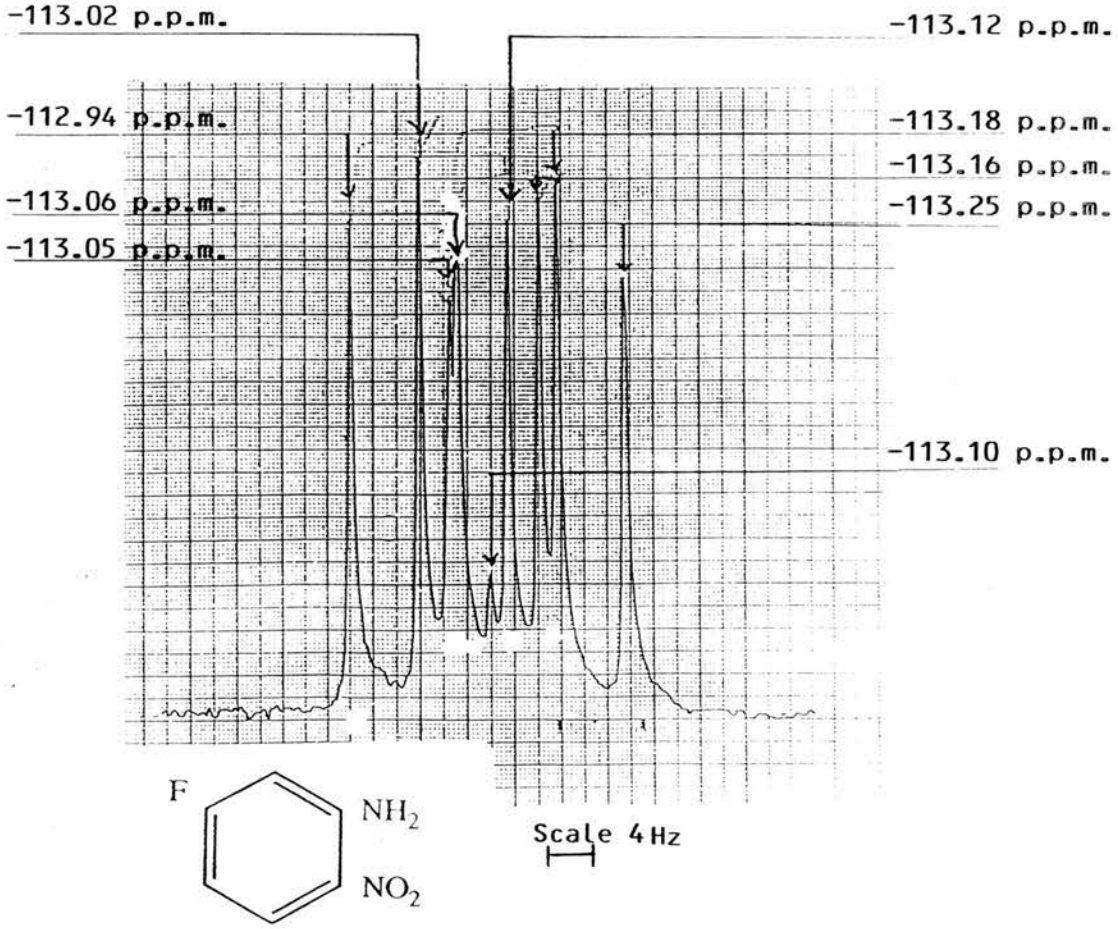


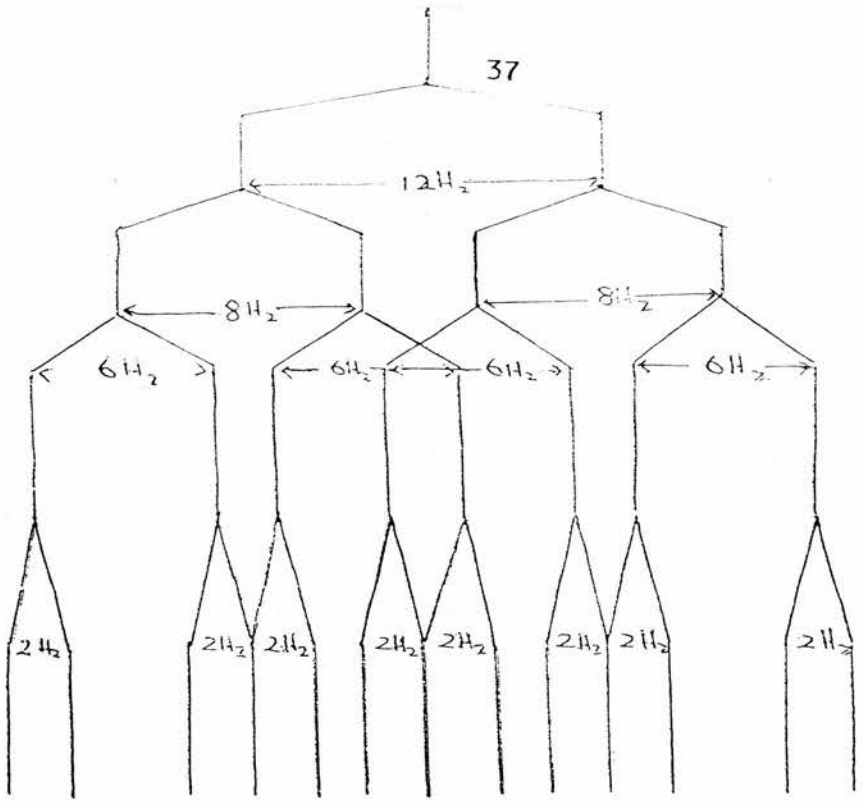
A B



Scale 4 mm/Hz

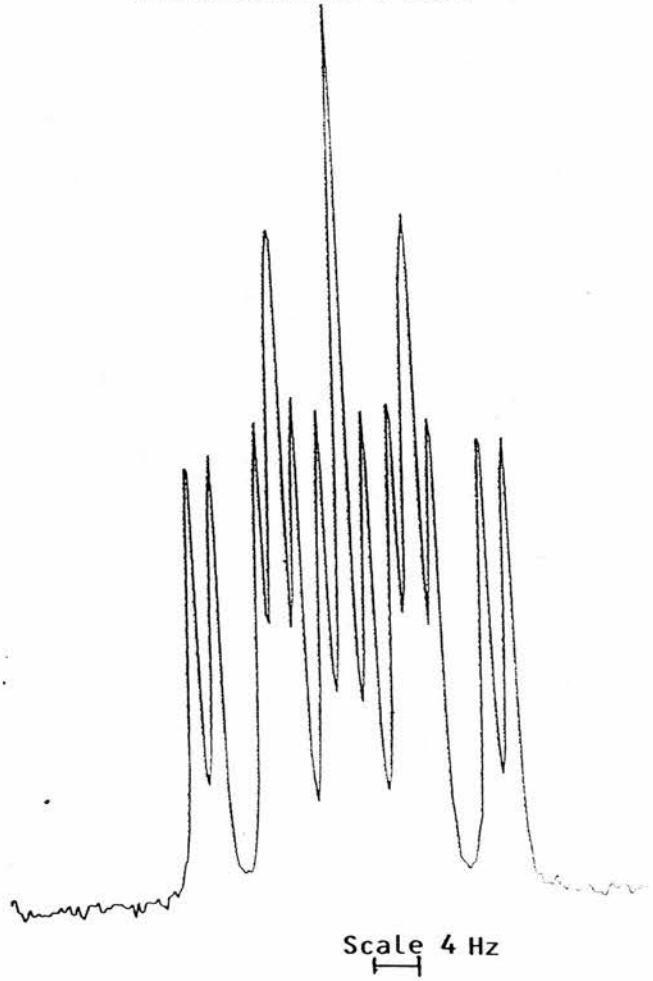
(Figure 3) ^{19}F n.m.r. splitting pattern of 5-fluoro-2-nitroaniline (44)



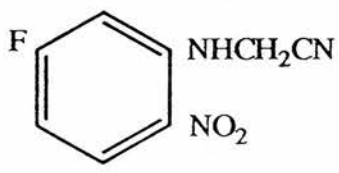


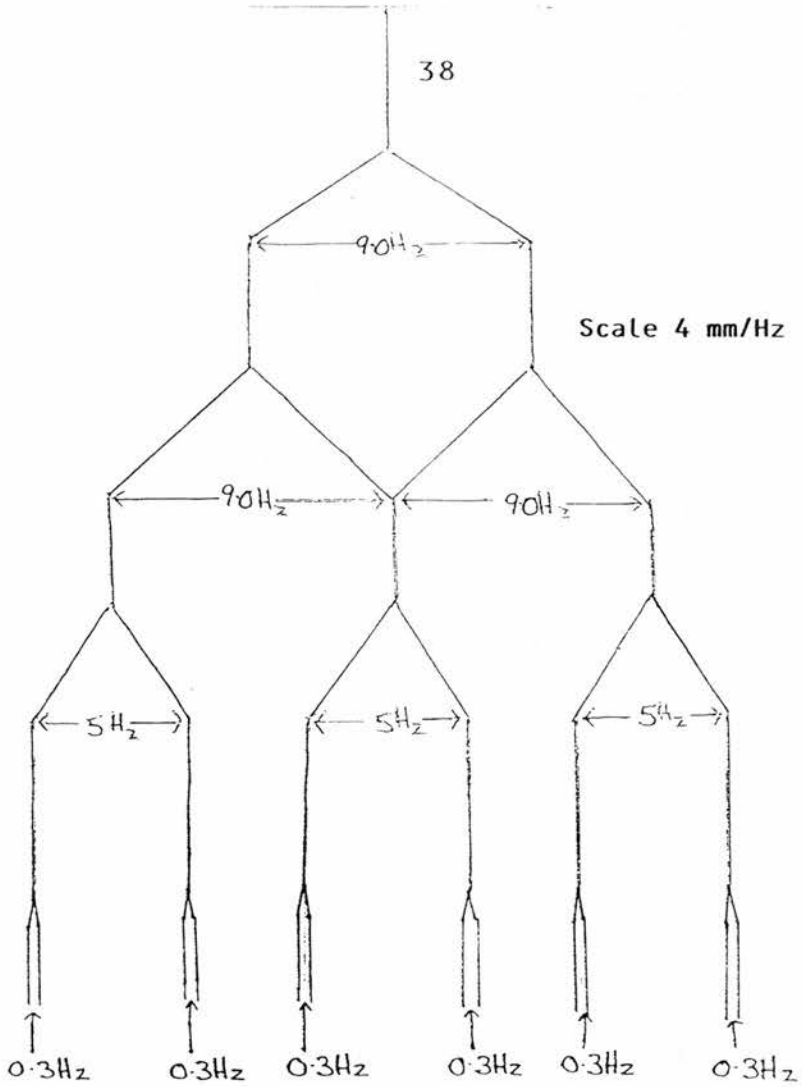
Scale 4 mm/Hz

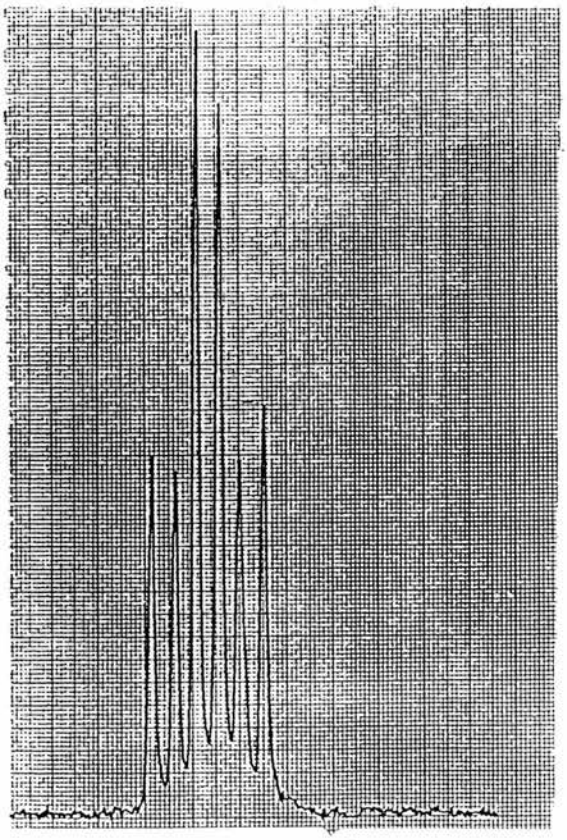
(Figure 4) ^{19}F n.m.r. splitting pattern of N-cyanomethyl-5-fluoro-2-nitroaniline (45a).

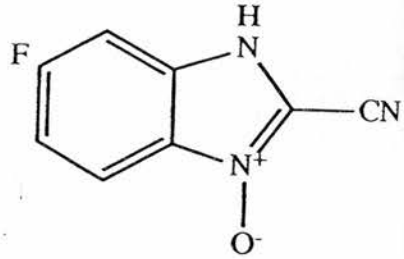


Scale 4 Hz

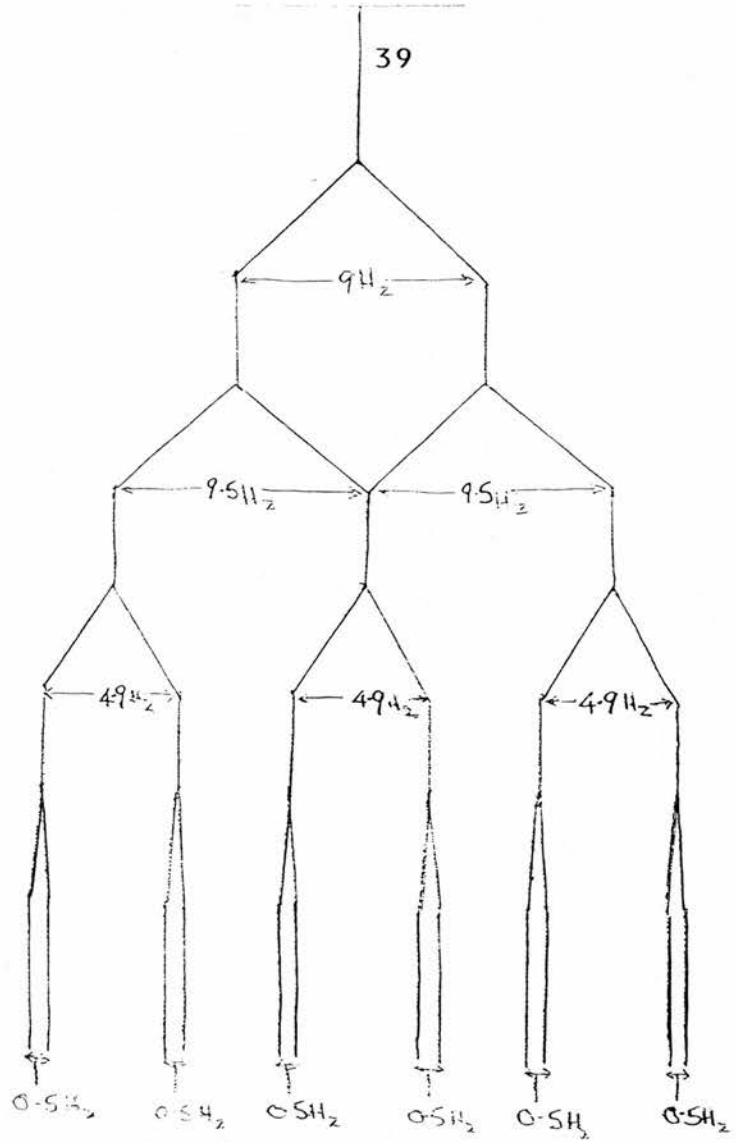




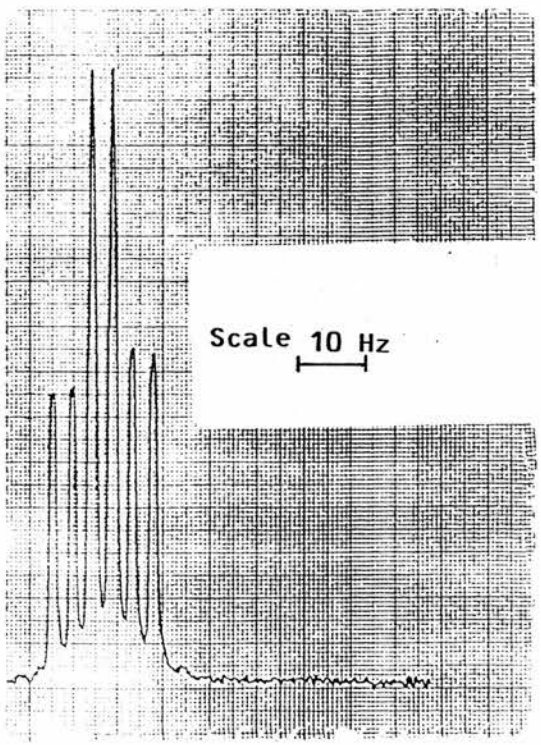


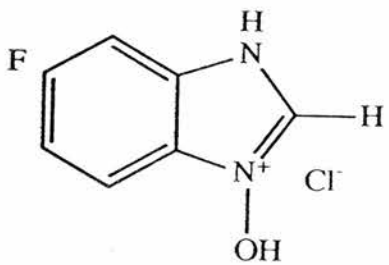


(Figure 5) ^{19}F n.m.r. splitting pattern of 2-cyano-6-fluoro-1H-benzimidazole 3-oxide (46a).

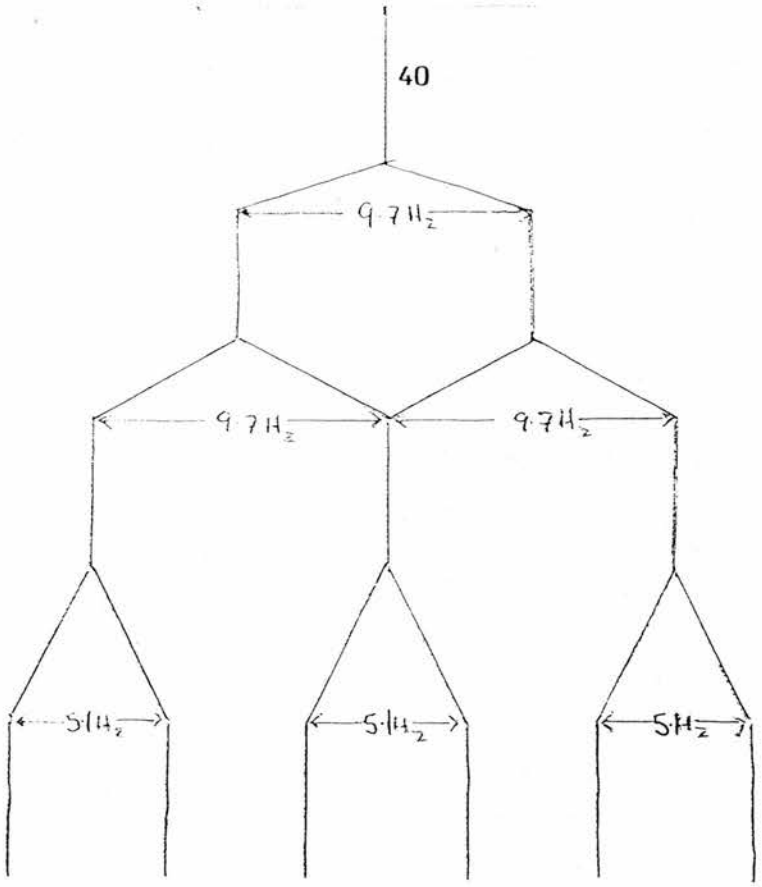


Scale 4 mm/Hz

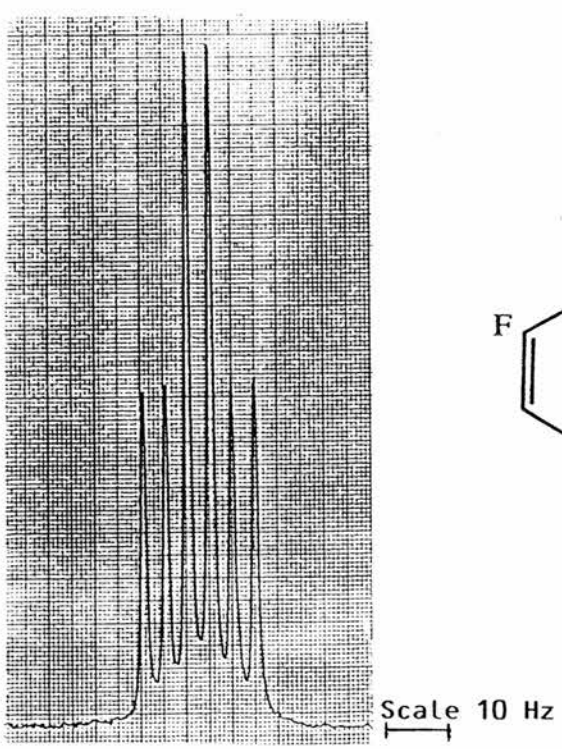


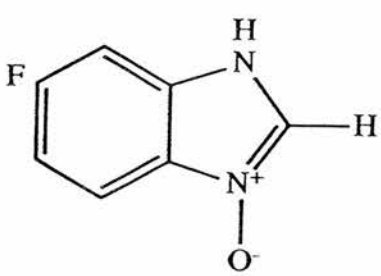


(Figure 6) ^{19}F n.m.r. splitting pattern of 6-fluorobenzimidazole N-oxide hydrochloride (47a).



Scale 4 mm/Hz





(Figure 7) ^{19}F n.m.r. splitting pattern of 6-fluorobenzimidazole N-oxide (48a).

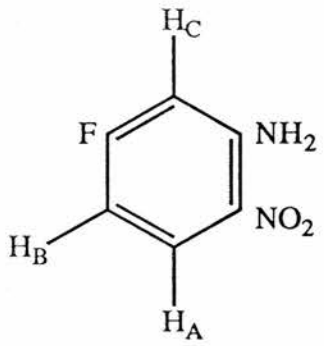
The diagram clearly illustrates that now the 6-fluorobenzimidazole N-oxide (48a) the H_d,F coupling will have to operate through seven bonds while in the 5-fluoro isomer (48b) the coupling can work through six bonds. This is thought to account for the results obtained for (48a) and (48b).

(v) Compounds (44a) and (44b)

It is clear that the fluorine spectrum obtained from (44a) is non-first order. This was not totally unexpected as the corresponding proton spectrum was also non-first order.

First-order behaviour is exhibited by 4-fluoro-2-nitroaniline (44b) and results in the expected eight lines in the fluorine spectrum (Figure 10 , page 45). The proton spectrum (Figure 10 page 45) is also first-order as the chemical shifts of the protons are sufficiently apart to satisfy first-order criteria, unlike the shifts for the 5-fluoro analogue (44a) which have the two protons which are *ortho* to the fluorine almost superimposed on each other in the spectrum (Figures 8 and 9).

A computer simulation was run in an attempt to reproduce the experimentally derived ^{1}H and ^{19}F n.m.r. spectra, since coupling constants cannot be measured directly from non-first-order spectra. The coupling constants chosen for use in the simulation were purely arbitrary, the coupling constants measured from the spectra of the 4-fluoro analogue acting as a guide; and the chosen values were varied until a good fit was obtained with the experimentally derived spectrum. The data used in the simulation are in Table 4 and the simulated spectra generated are illustrated in Figures 11 –13 , pages 46 – 48.

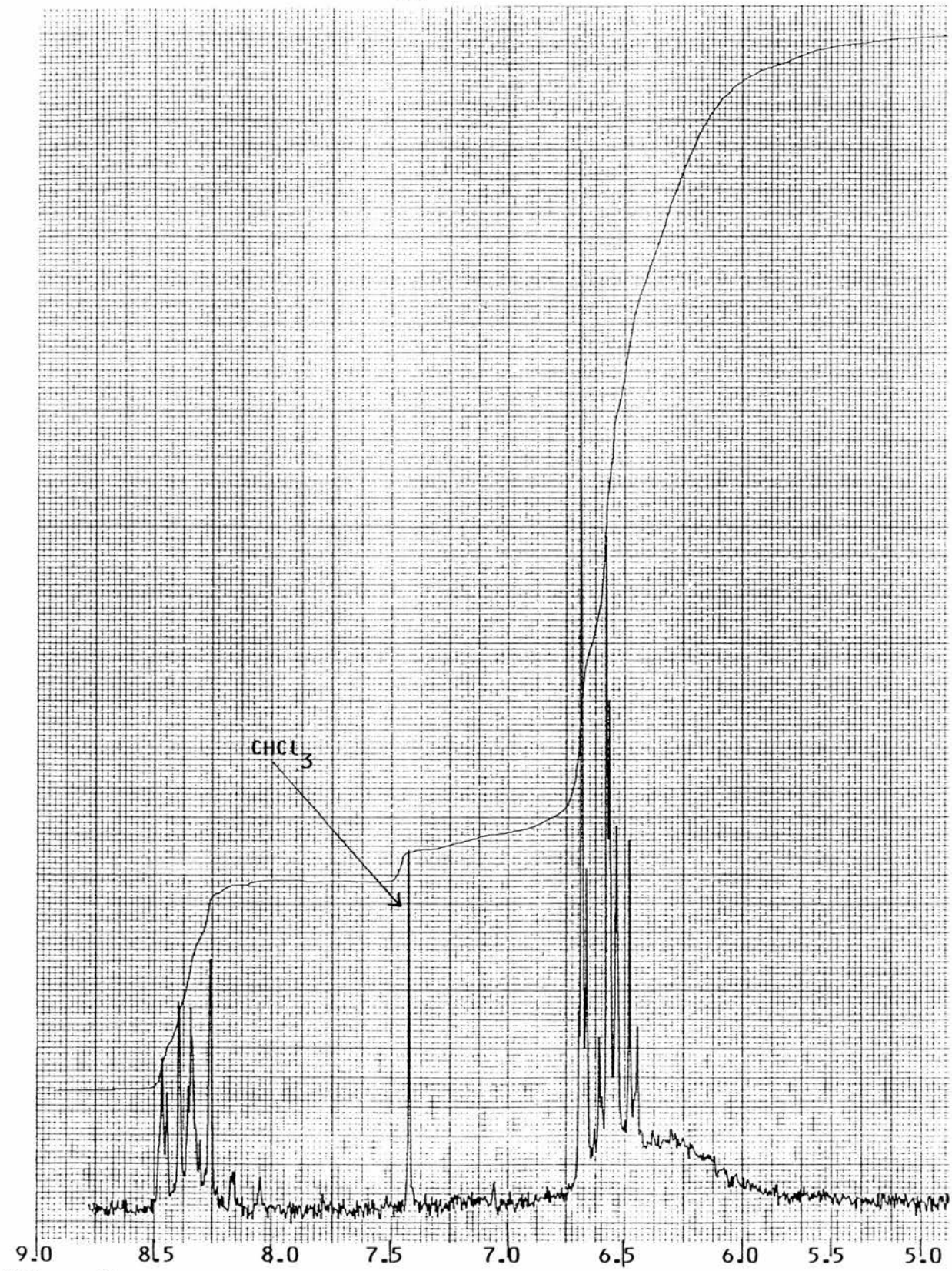


Atom	Chemical Shifts (Hz)		Couplings (Hz)	
	(80 MHz)	(300 MHz)		
H_c	518	1943	$J_{c,b} = 2.8$	$J_{b,F} = 8$
H_b	514.5	1930	$J_{c,a} = 0.0$	$J_{a,F} = 5.6$
H_a	653.5	2452	$J_{c,}F = 10.0$	
F	5000	5000	$J_{b,a} = 9.4$	

(Table 4)

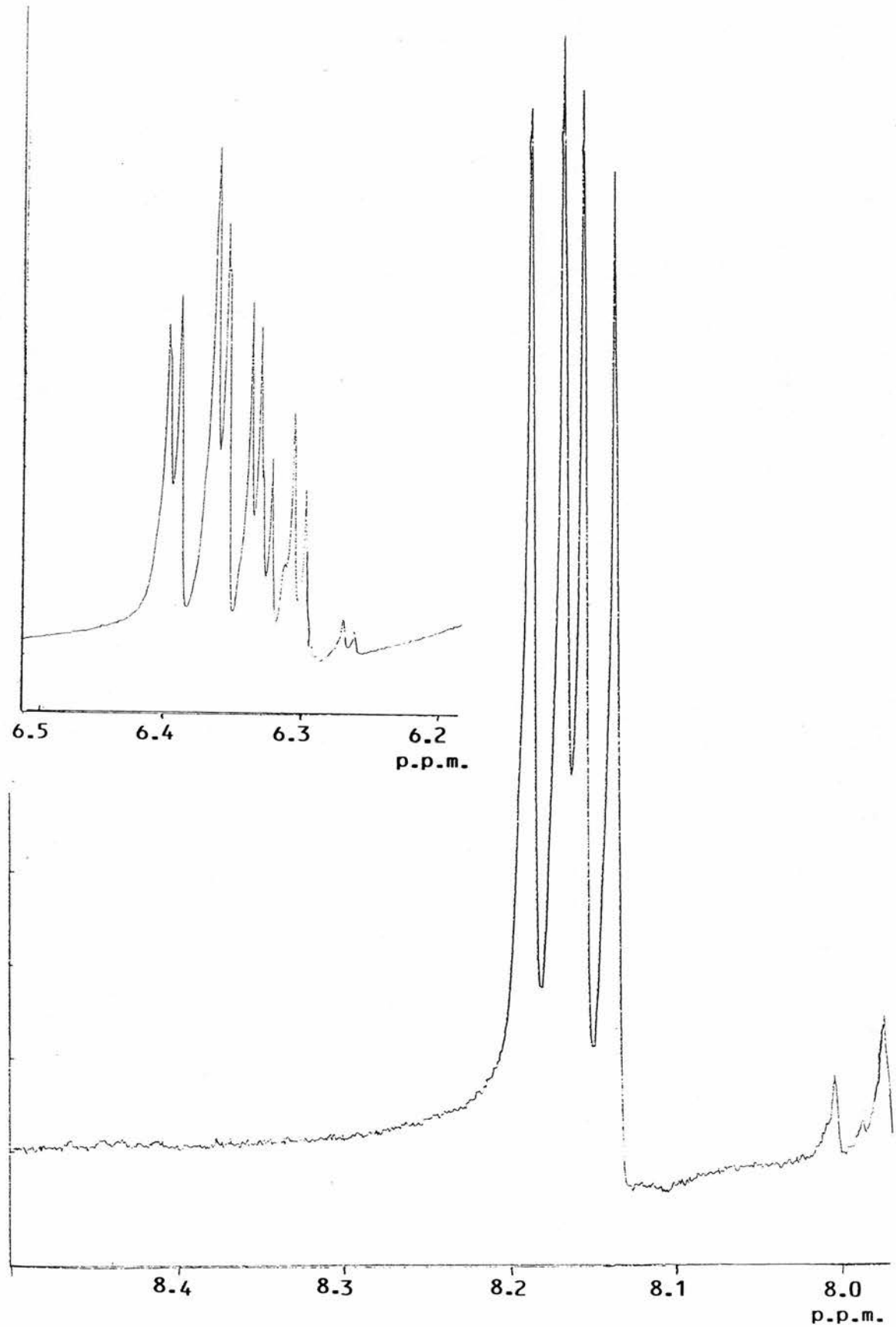
The original spectra are also illustrated for comparison (Figures 3, 8 and 9, pages 36, 43 and 44).

At 80 MHz the proton spectrum (Fig. 12) is clearly non-first-order while the fluorine spectrum at 75.3 MHz (Fig. 13) begins to show the ideal pattern of eight lines [observed for the 4-fluoro analogue (Figure 10 page 45)]. The ideal eight lines are only displayed at 282.3 MHz (Fig.13); interestingly the corresponding proton spectrum at 300 MHz (Fig. 11) is still slightly non-first-order. In theory a first order proton spectrum could only be obtained at an even higher frequency, e.g. 500 MHz.



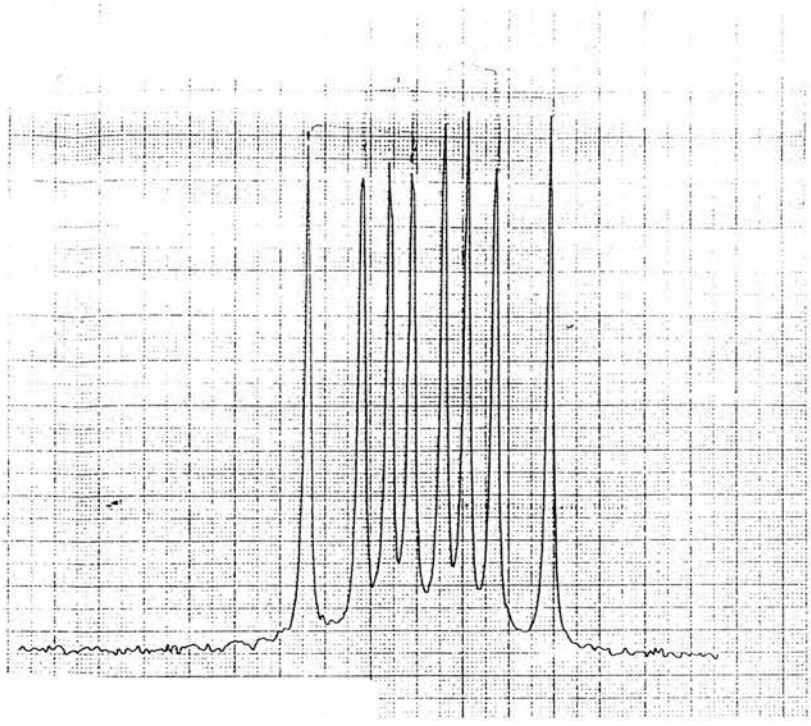
(Figure 8)

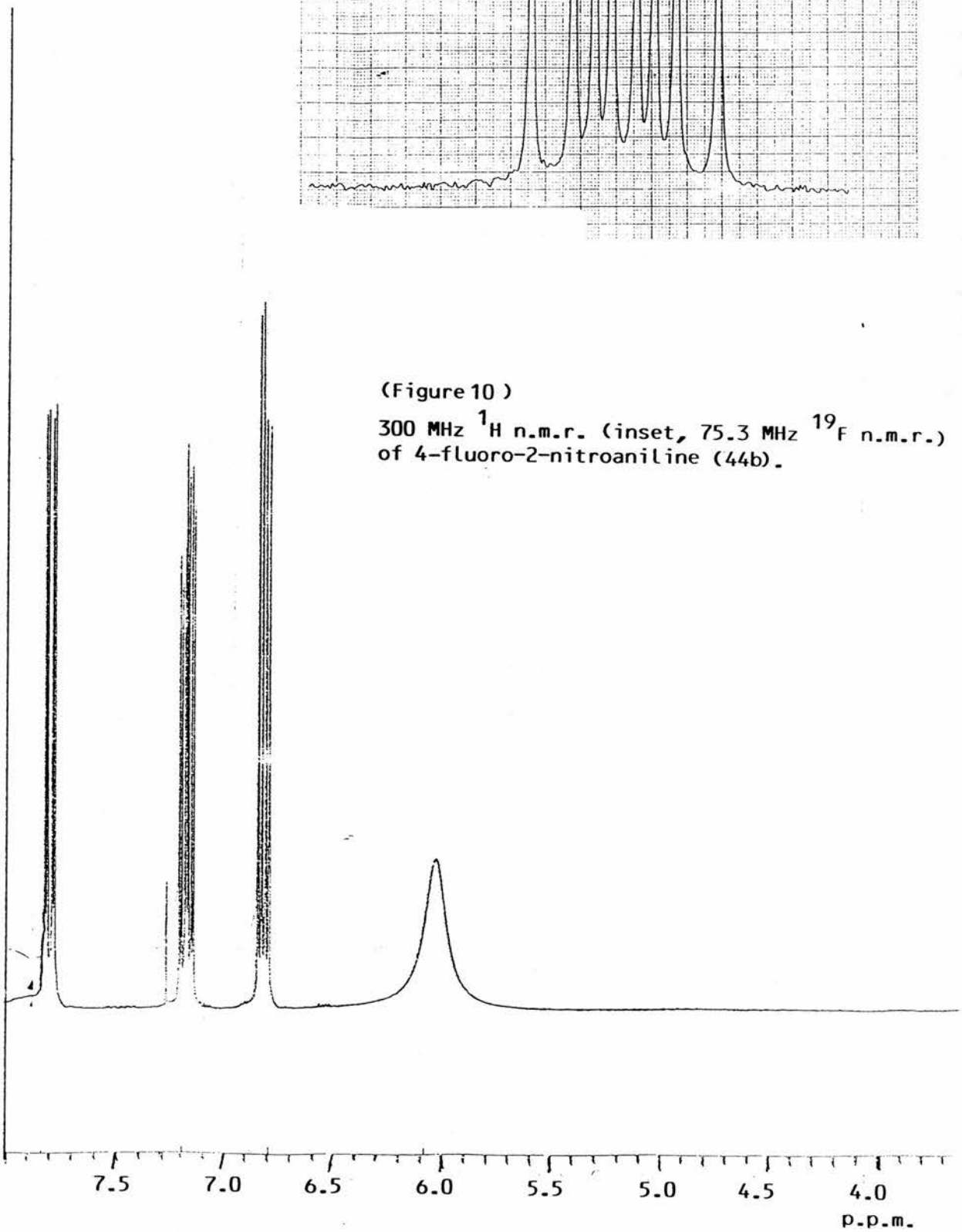
Experimentally obtained ^{1}H n.m.r. spectrum at 80 MHz of 5-fluoro-2-nitroaniline (44a).



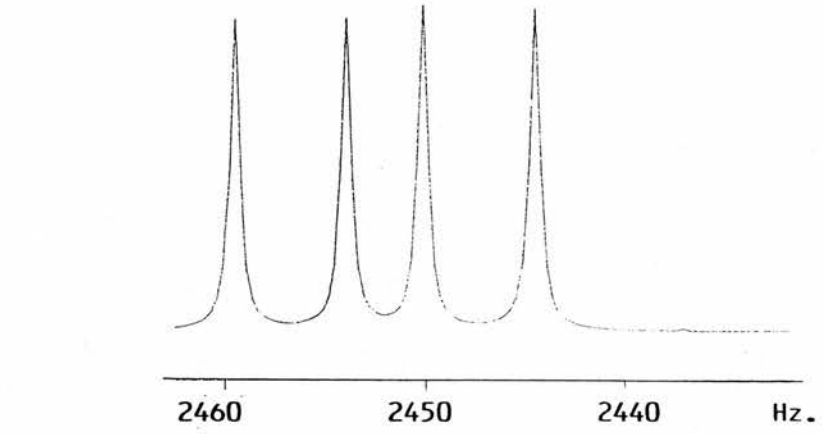
(Figure 9)

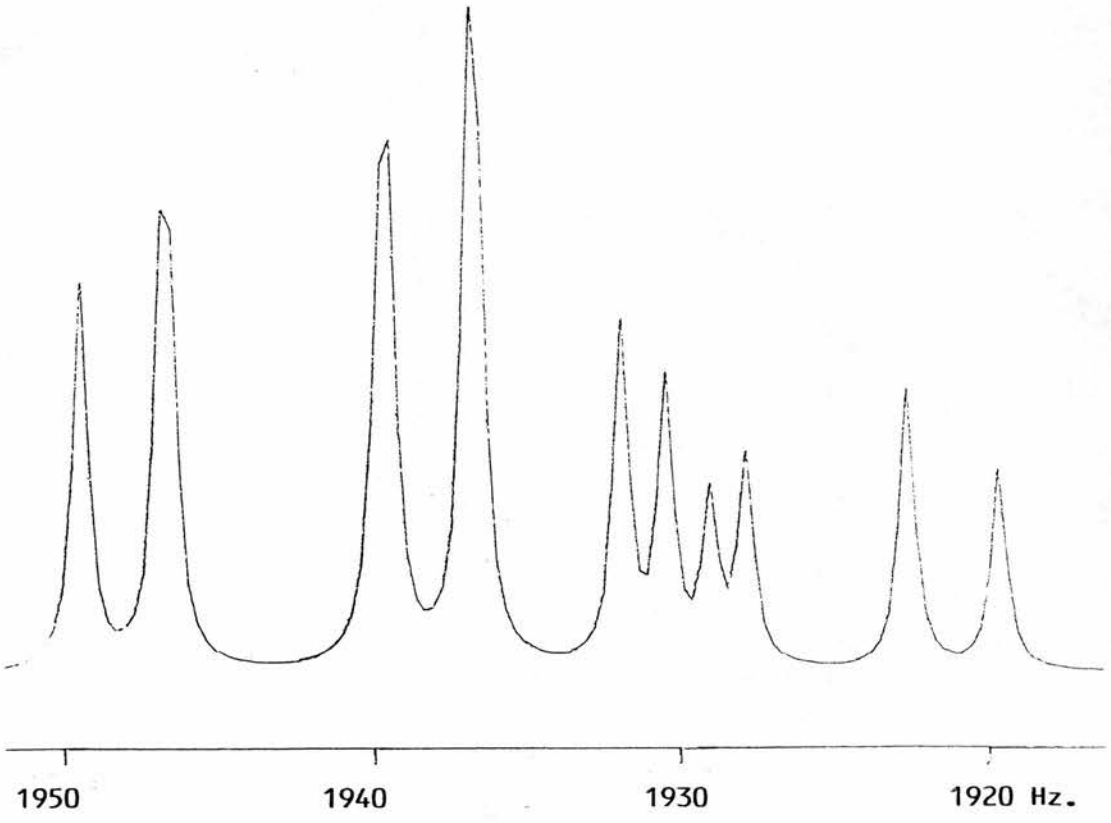
Authentic ^{1}H n.m.r. at 300 MHz of 5-fluoro-2-nitroaniline (44a).





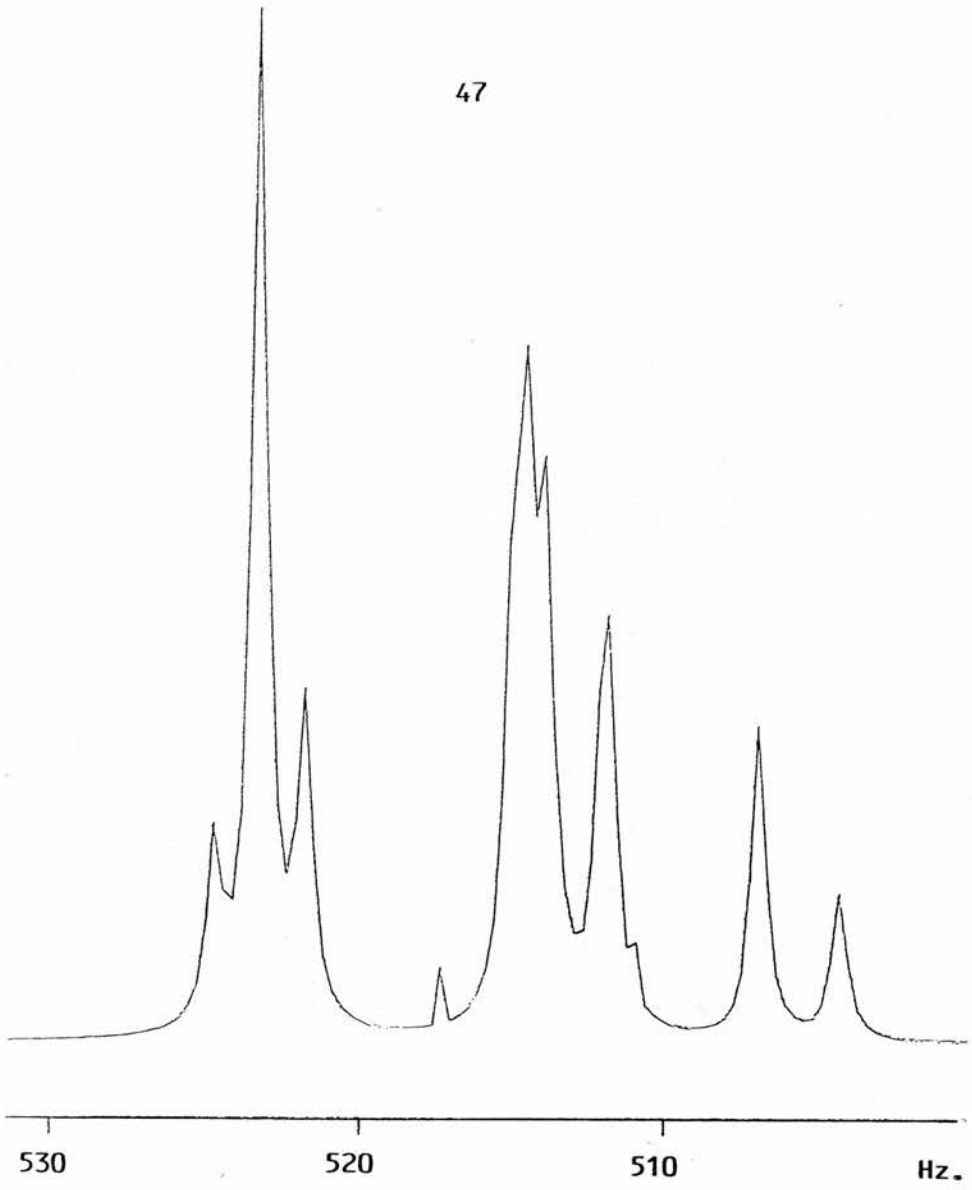
(Figure 10)
300 MHz ^{1}H n.m.r. (inset, 75.3 MHz ^{19}F n.m.r.) of 4-fluoro-2-nitroaniline (44b).

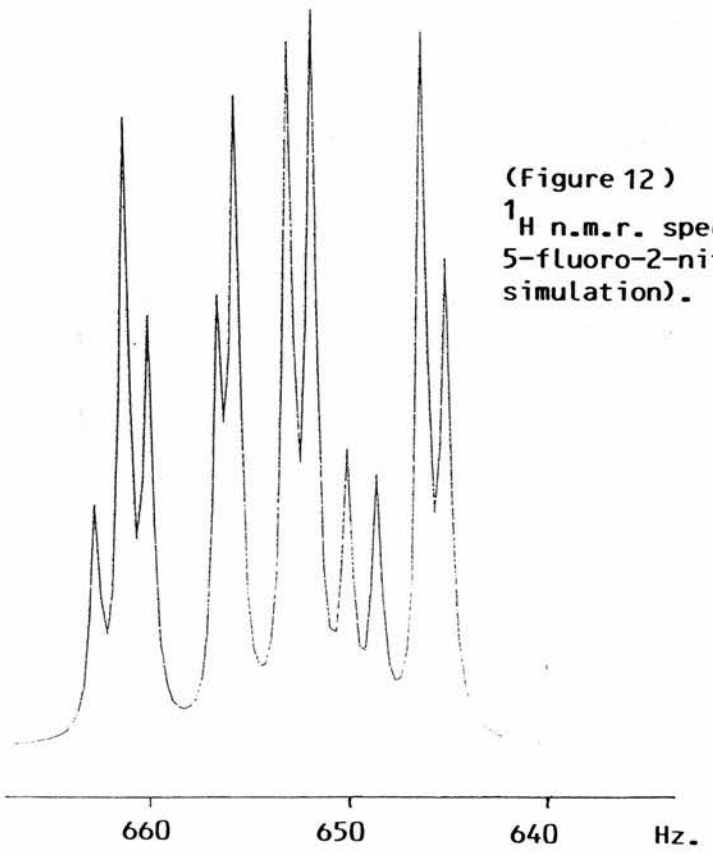




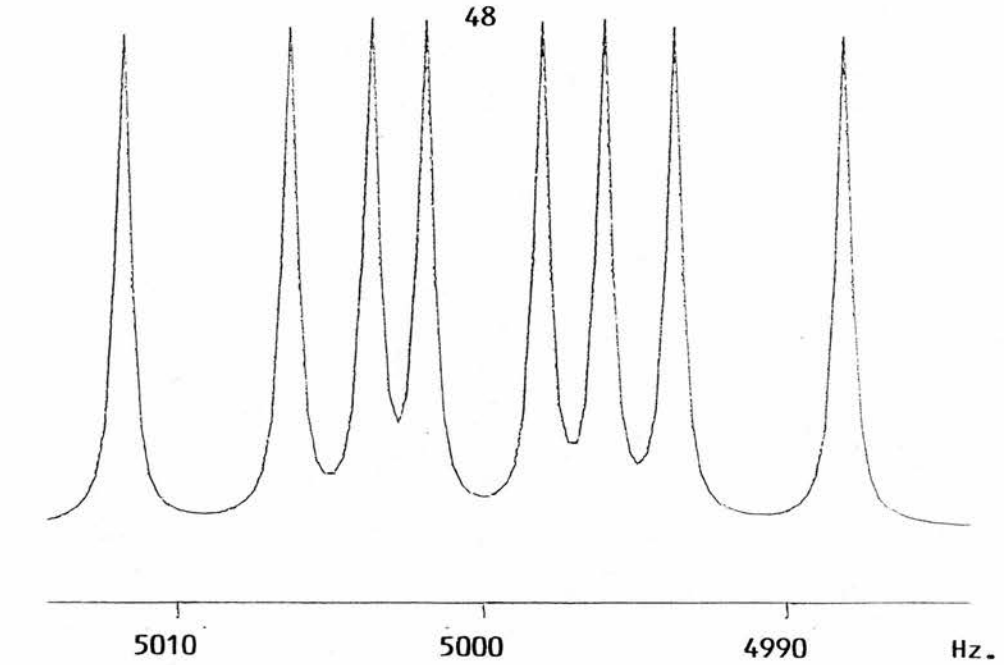
(Figure 11)

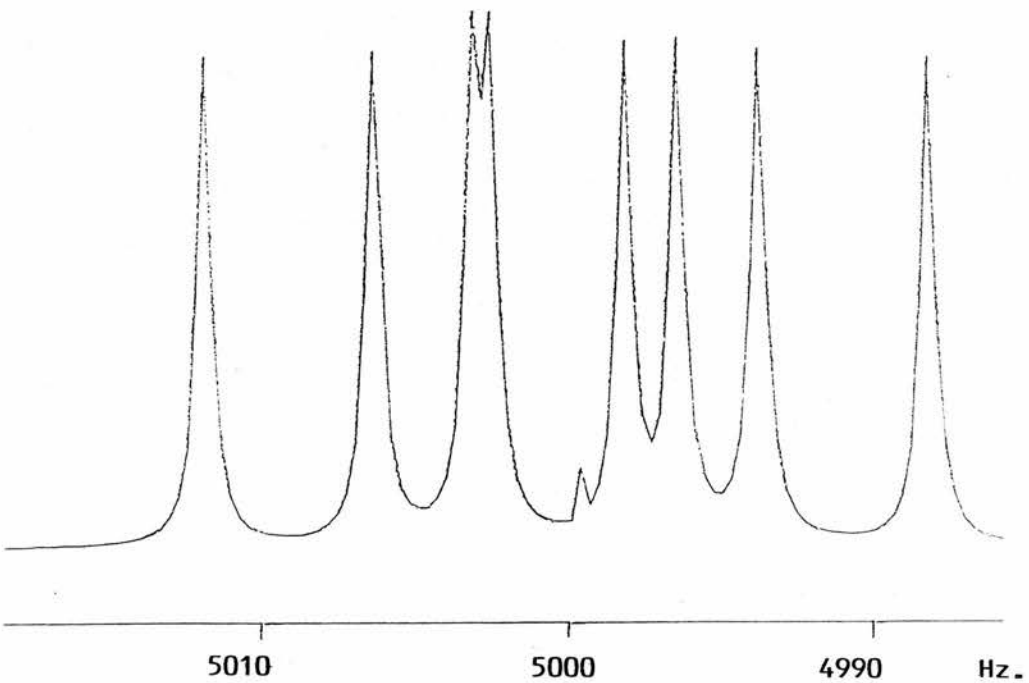
^{1}H n.m.r. at 300 MHz of 5-fluoro-2-nitroaniline (computer simulation).





(Figure 12)
^{1}H n.m.r. spectrum at 80 MHz of 5-fluoro-2-nitroaniline (computer simulation).





(Figure 13)

Top : ^{19}F n.m.r. spectrum, compound (44a) at 282.3 MHz (computer simulation)

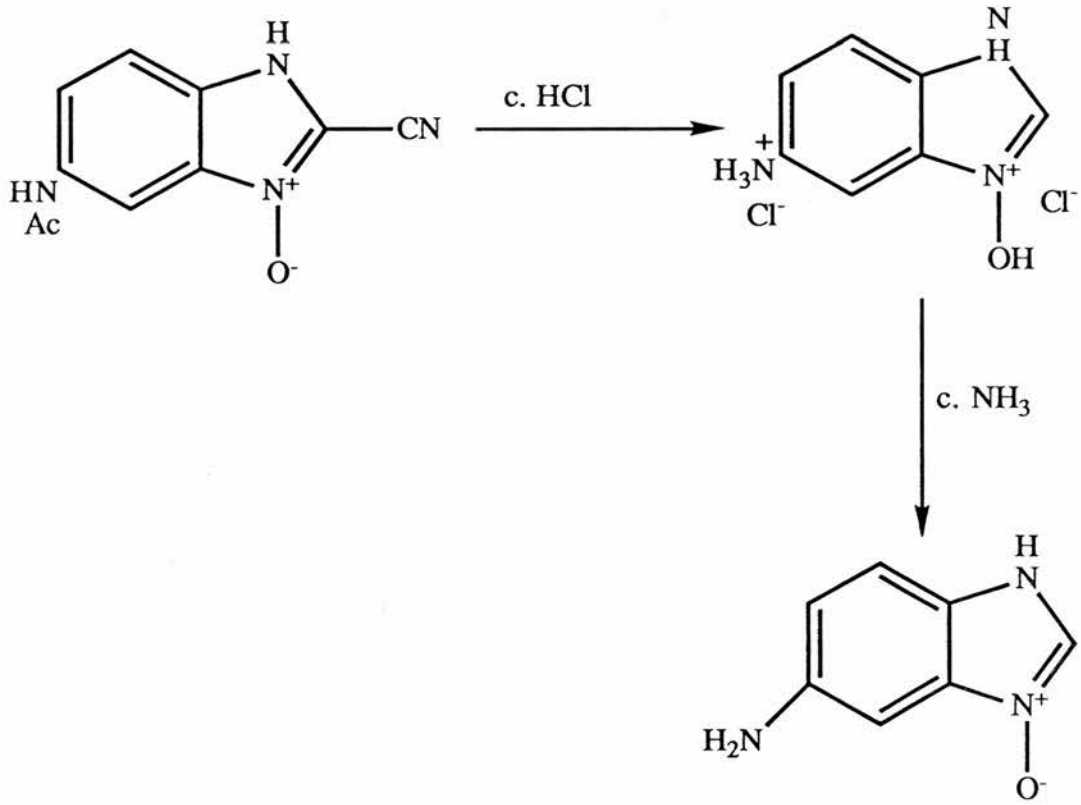
Bottom : ^{19}F n.m.r. spectrum, compound (44a) at 75.3 MHz (computer simulation).

PART 6 AMINO-1H-BENZIMIDAZOLE 3-OXIDES

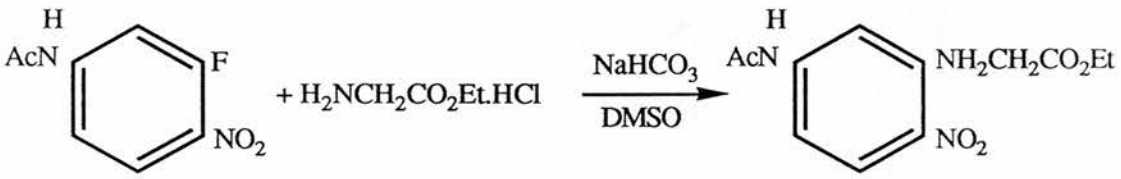
Having found a satisfactory general synthesis for the benzimidazole *N*- oxides described in part 3, the next aim was to obtain the N-oxides with the amino group as the only substituent in the carbocyclic ring. These compounds would therefore be even more closely related structurally to the naturally occurring molecules (12) and (13).

The pioneering work on these amino-substituted *N*- oxides was undertaken by McFarlane who made the 5- and 6- amino analogues[21].

The 5-amino compound was obtained by modification of Scheme 6, the amino moiety protected throughout by an acetyl group prior to hydrolysis. Loss of the protecting group was achieved on hydrolysis forming a dihydrochloride which on basification gave the desired *N*- oxide.



Likewise the 6-amino compound was obtained by slight alteration of Scheme 7, the ester equivalent of (49) being obtained directly as shown below.



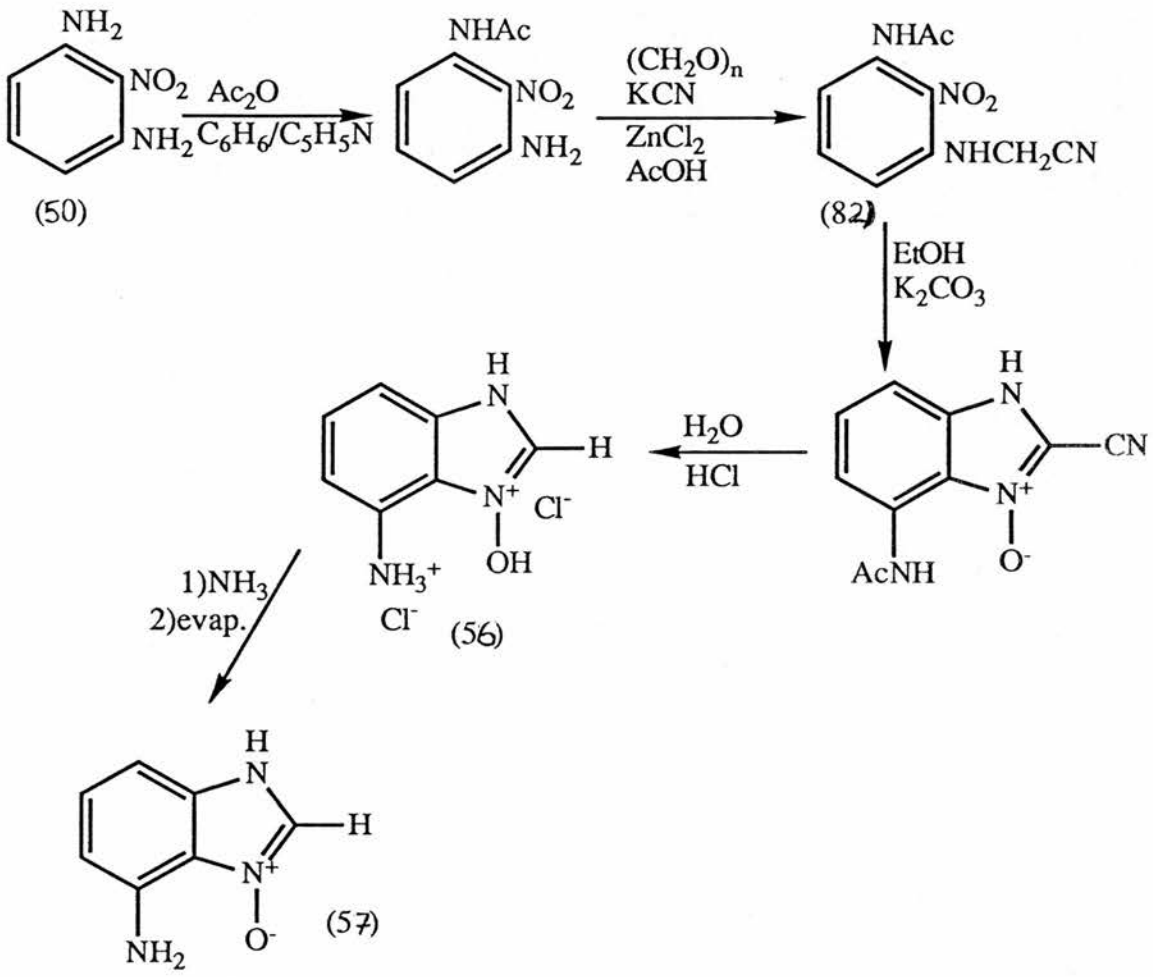
The acetyl protecting group was again lost on acid hydrolysis to give a dihydrochloride which gave the free *N*- oxide on basification.

The synthetic chemistry applied gave a worthwhile insight into ways of obtaining the 4- and 7- amino compounds, and a guide to their likely physical properties.

The synthetic approaches to the two compounds (57) and (58) were found to be so dissimilar that they warrant separate introductory discussions.

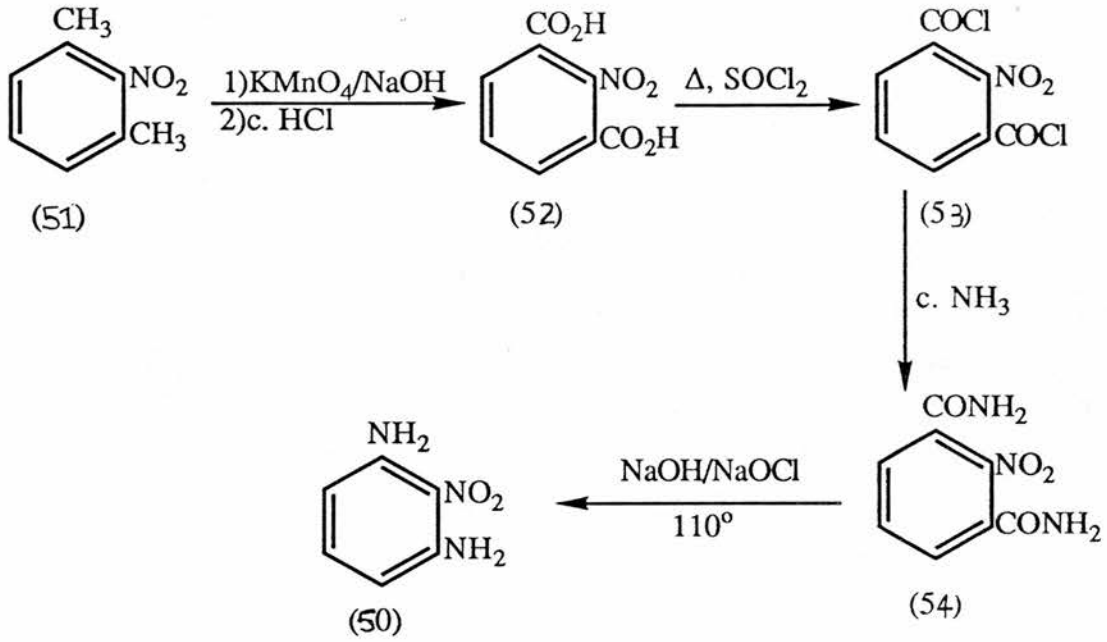
(1) 4-Amino-1H-benzimidazole-3-oxide (57)

Synthesis (Scheme 11)



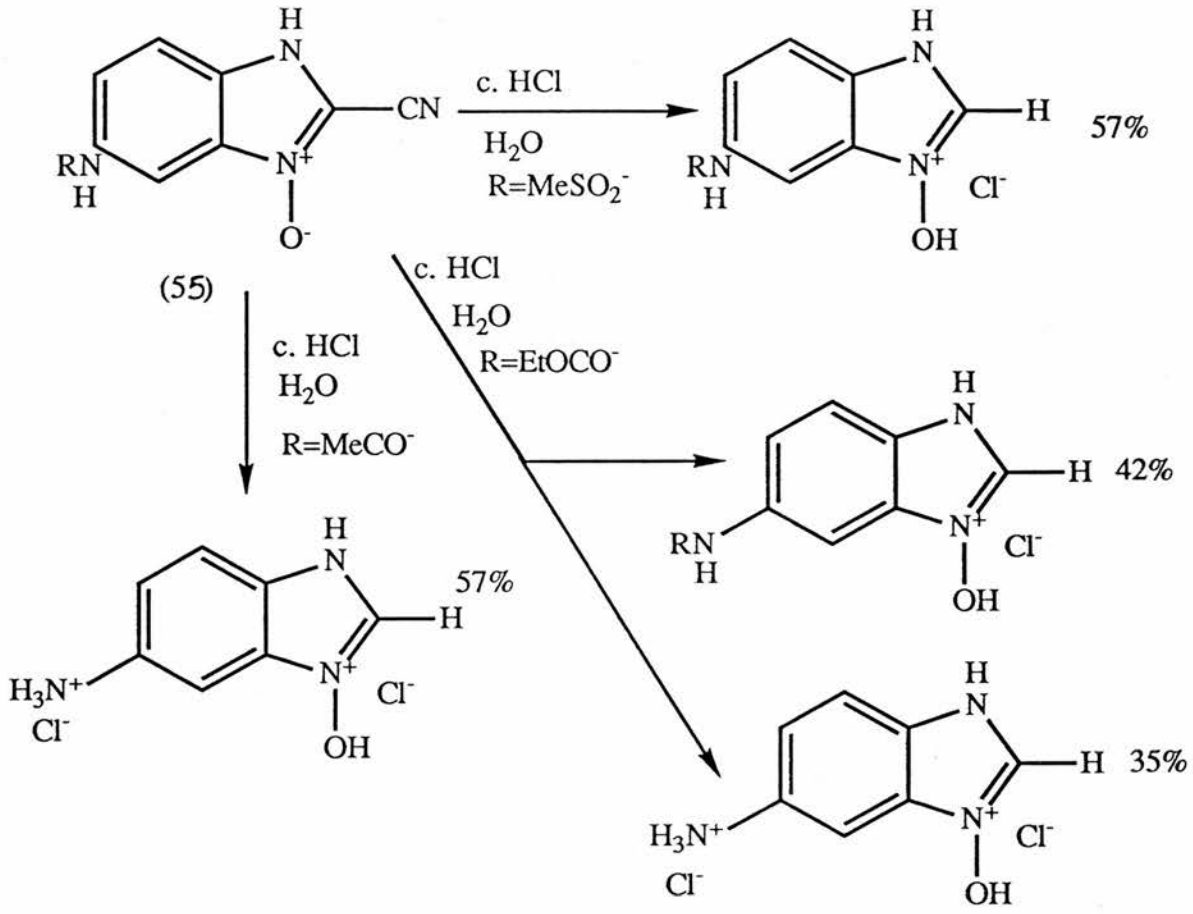
(Scheme 11)

To obtain the starting material (50) required a multiple-stage synthesis involving the oxidation of the two aromatic methyl groups in 2-nitro-m-xylene (51) to form the di-acid (52) and conversion via the di-acid chloride (53) to the diamide (54). The diamine (50) was then obtained by a carefully controlled double Hofmann degradation of (54) (Scheme 12).



(Scheme 12)

To effect the mono-cyanomethylation of the diamine (50) it was necessary to protect one of the amino functions. Acetylation was used to achieve this for the following reason: in the synthesis of the 5-amino analogue by McFarlane three different protecting groups were tried, *viz* acetyl, methylsulphonyl, and ethoxycarbonyl.



(Scheme 13)

However on acid hydrolysis of the various cyclisation products (55) (Scheme 13) the only one of the three to be totally removed was the acetyl group.

The cyanomethylation of the protected amine presented no problems. The amine required only three molar equivalents of zinc chloride at 50°C for 7 hours [*cf.* the 4-methoxy-analogue].

The basification of the dihydrochloride (56) is also worthy of note. The initial reaction must be conducted at between 0-5°C and the dihydrochloride added in portions to the ammonia solution, as following the usual procedure causes partial decomposition which results in an unpurifiable product. This behaviour was also noted with the 6-amino isomer but not with the 5-amino isomer which underwent basification under 'normal' conditions.

(2) 7-Amino-1H-benzimidazole-3-oxide (58)

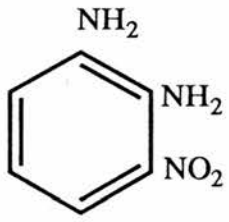
Synthesis (Scheme 17)

The synthesis of compound (58) was by far the most difficult to achieve, and the problem was finally solved by the utilisation of an unusual nucleophilic substitution reaction[26] which will be described later.

The attempted routes to (58)

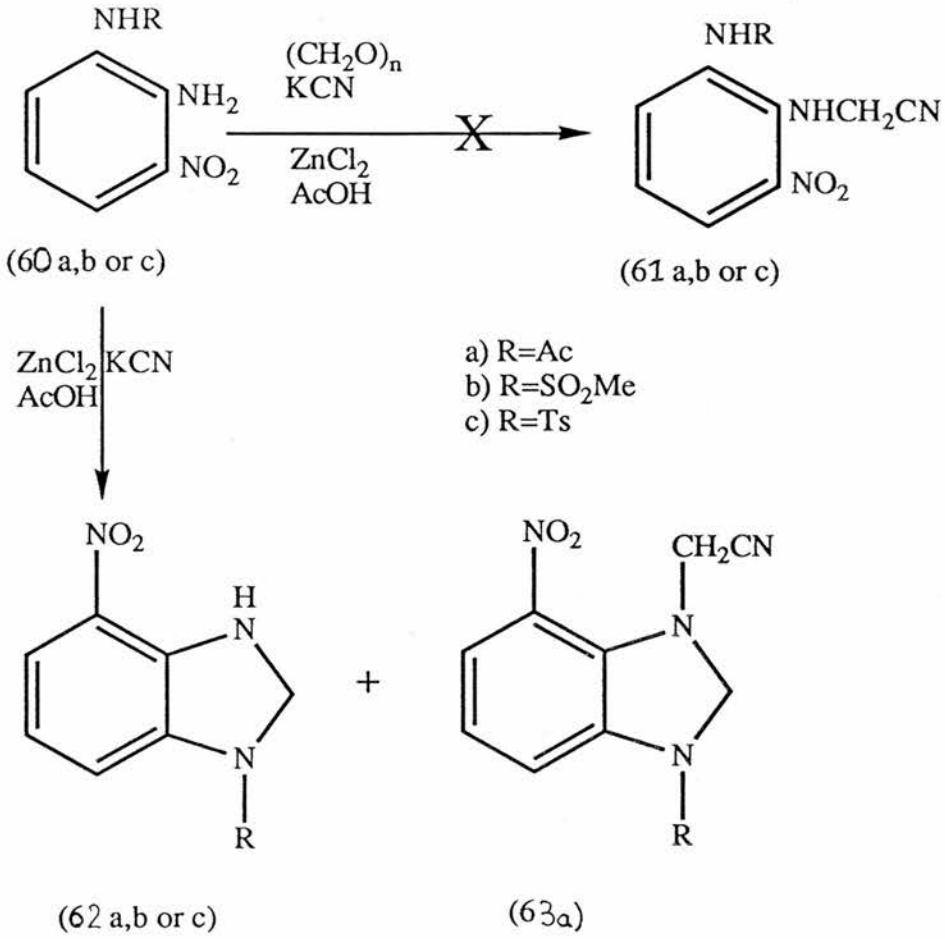
(a) By way of cyanomethylation of a protected amine

If the synthesis of the 4-amino isomer (57) (Scheme 11) was to be used as a model, then the diamine (59) would have to undergo a successful cyanomethylation reaction.



(59)

Previous work[13] had shown that tosyl- and methylsulphonyl-protected diamines (60b) and (60c) gave unexpected products on attempted cyanomethylation (Scheme 14).

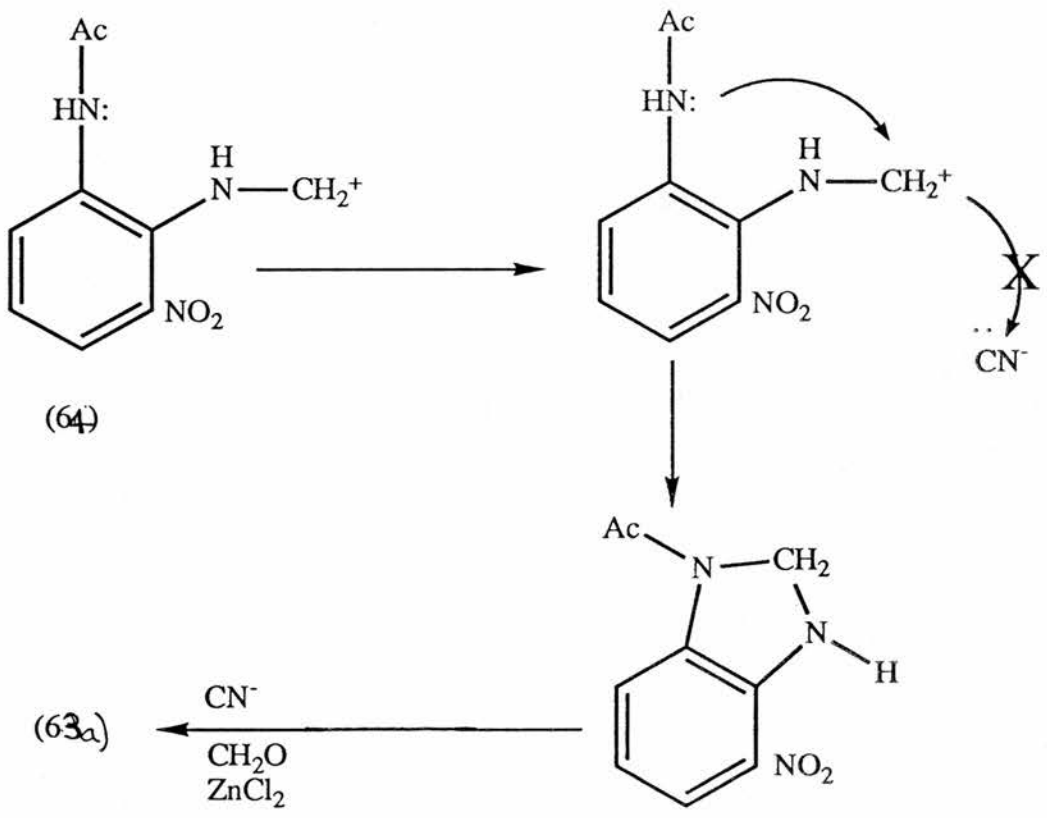


(Scheme 14)

Instead of the desired products (61b) and (61c) the dihydrobenzimidazoles (62b) and (62c) were formed.

The corresponding reaction of the acetyl analogue (60a) gave two products, neither of which was the cyanomethyl derivative (61a). The major product was identified, by elemental analysis and n.m.r., as 1-acetyl-2,3-dihydro-4-nitrobenzimidazole (62a). The minor product, similarly characterised, was identified as 1-acetyl-3-cyanomethyl-2,3-dihydro-4-nitrobenzimidazole (63a)

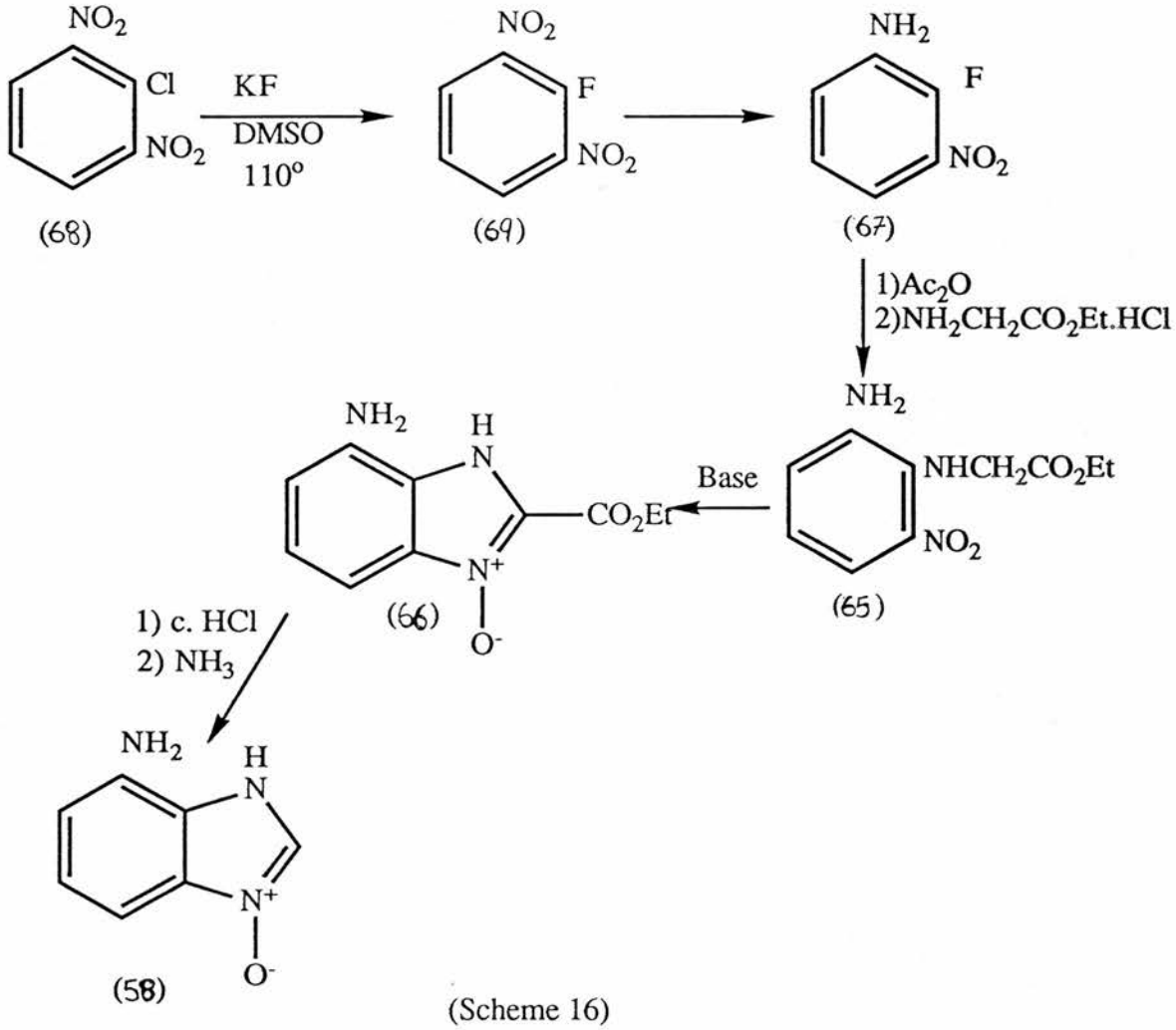
These results can be satisfactorily explained mechanistically (Scheme 15).



(Scheme 15)

The normal carbonium ion (64) is formed as expected; however, with the electron-rich acetylated nitrogen in close proximity to the carbonium ion an intramolecular reaction is possible which competes successfully with the intermolecular attack by the cyanide ion. The remaining free N-H in the product then undergoes cyanomethylation to form the secondary product (63a)

A second method using a protected amine was attempted by another group member. In principle the route (Scheme 16) used the proven displacement of a reactive fluorine atom by glycine ethyl ester to give the ester (65) which, once cyclised to give (66), could be subjected to hydrolysis and basification to form the product (58).



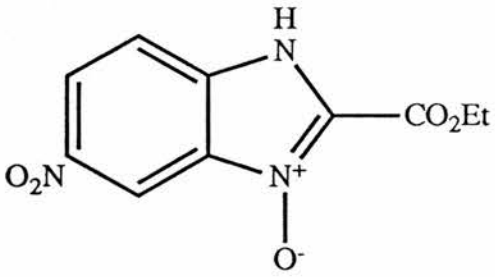
(Scheme 16)

Unfortunately the validity of this method could not be tested as the literature method for the preparation of 2-fluoro-3-nitroaniline[22] (67) could not be reproduced: the attempted displacement of the chlorine in (68) to form (69) failed, even after repeated attempts and modifications to the published method.

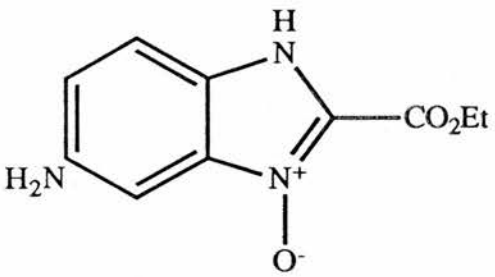
(b) <u>By way of reduction of a nitro group</u>

One of the most straightforward ways of obtaining an aminobenzimidazole oxide would be to reduce the corresponding nitrobenzimidazole *N*- oxide in such a way that the *N*- oxide function is unaffected. Indeed this method works to a limited degree, with McFarlane providing an alternative synthesis for (57)[23] by subjecting 4-nitrobenzimidazole *N*-oxide to hydrogenation using palladium-charcoal as

the catalyst. The same worker also synthesised the 5-amino analogue in a similar way by reducing the nitro group in (70) and immediately hydrolysing the unstable reduction product (71) with concentrated hydrochloric acid.

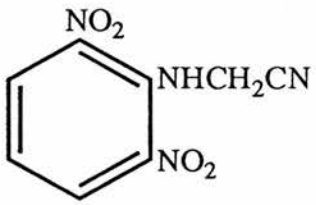


(70)

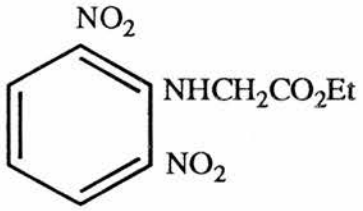


(71)

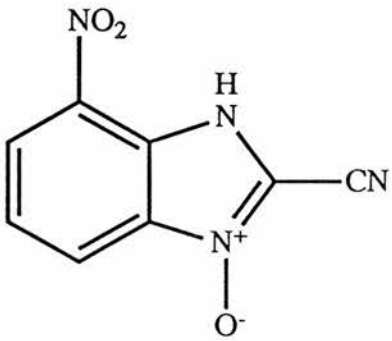
This "convenient" method proved inapplicable to the title compound (58), however, because of the failure of the precursors (72) and (73) to give the expected products (74) and (75) on attempted cyclisation.



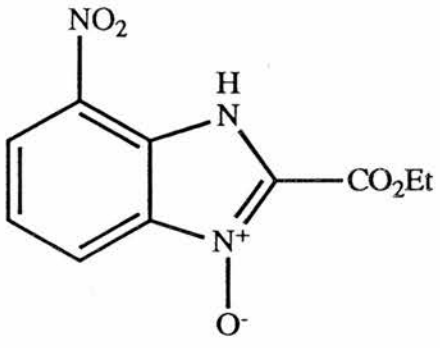
(72)



(73)

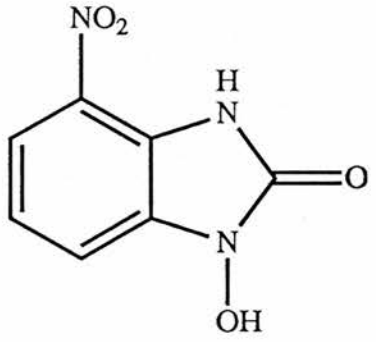


(74)

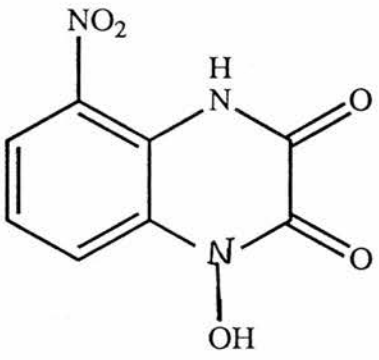


(75)

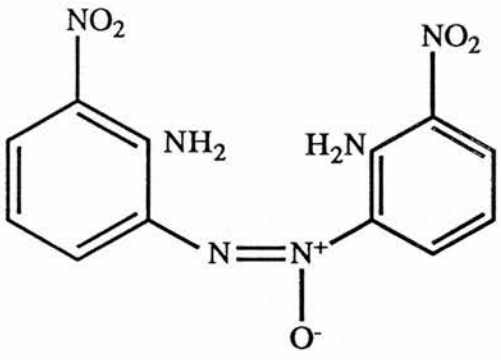
The actual products obtained[24] were a hydroxybenzimidazolone (76) from (74), while the dinitro-ester afforded two products (77) and (78).



(76)



(77)

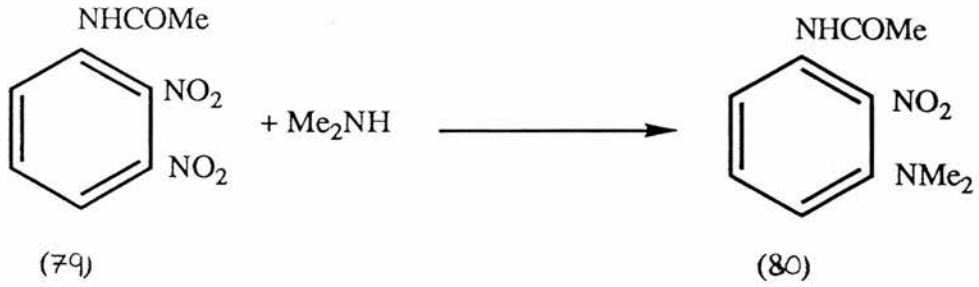


(78)

These unexpected results ruled out approaches to the title compound (58) by reductive methods.

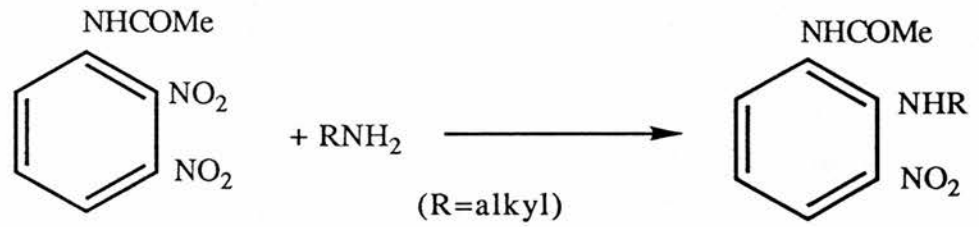
(c) <u>By way of displacement of a nitro group</u>

The reaction of 2,3-dinitroacetanilide (79) with dimethylamine has been known for many years[25] to give 3-(N,N-dimethylamino)-2-nitroacetanilide (80) by displacement of the nitro-group at position 3.



(79) (80)

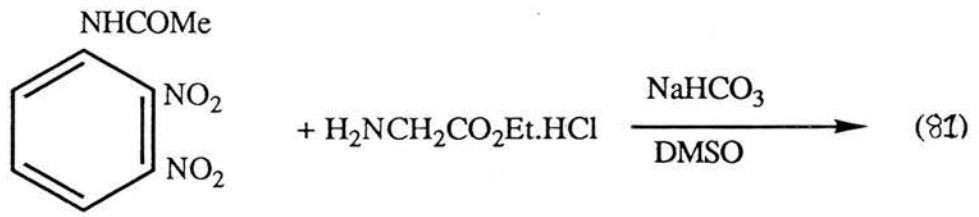
However later work[26] by Piotrovskii showed that reaction of (79) with a primary amine caused the displacement of the nitro-group at position 2 leaving position 3 unaffected.

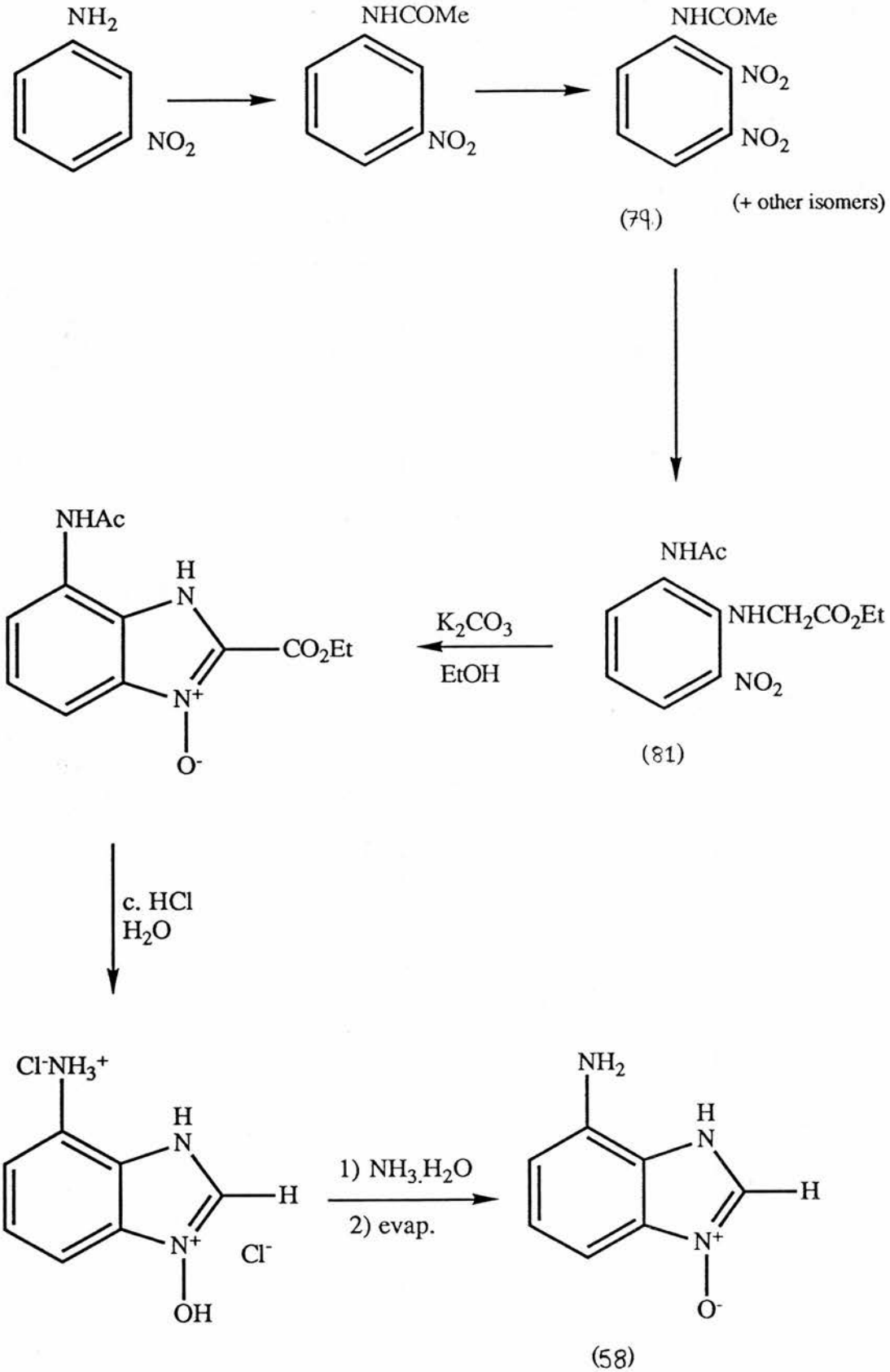


(79)

Both of the aforementioned reactions can be explained in terms of steric factors. Only the less bulky primary amine can enter between the acetamido- and 3-nitro group to attack the 2-nitro group, a secondary amine being too bulky to do this.

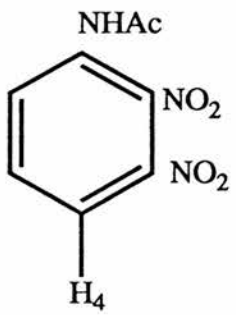
Therefore since glycine ethyl ester is a type of primary amine, the possibility of the displacement reaction (below) to give the nitro ester (81) was envisaged.



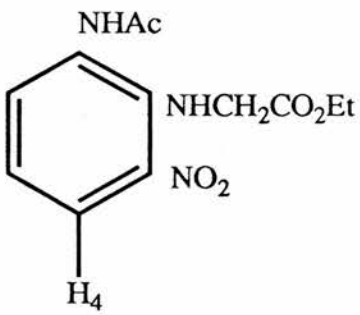

NH2
NO2
NHCOMe
NO2
NHCOMe
NO2
NO2
(+ other isomers)
(79)
NHAc
NHCH2CO2Et
NO2
(81)
K2CO3
EtOH
NHAc
H
N
CO2Et
N+
O-
c. HCl
H2O
Cl-NH3+
H
N
H
N+
Cl-
OH
1) NH3.H2O
2) evap.
NH2
H
N
H
N+
O-
(58)

(Scheme 17)

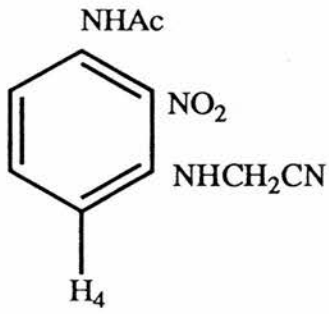
The reaction was successful in practice. Confirmation that the substitution had occurred at position 2 rather than position 3 was obtained by comparing the n.m.r. spectra of the product (81) with those of (79) and (82).



(79)



(81)

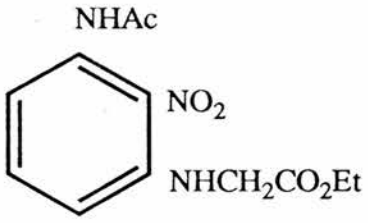


(82)

compound	δ_H (p.p.m.) H-4
(79)	7.62 - 7.74
(81)	7.57 - 7.91
(82)	6.7 - 6.95

If as in (82) the nitro in the meta position has been replaced, H-4 would have become less deshielded due to the removal of the electron withdrawing group and would as a result have shown a shift upfield relative to its value in the starting material (79). As the shift in the product (81) is almost unchanged we can assume the continued presence of the meta nitro group.

The subsequent synthetic steps confirmed this initial spectral evidence for ortho substitution. If the displacement reaction had given (83), this on completion of the synthesis would have given the 4-amino analogue (57).



(83)

The remaining steps in the synthesis proceeded as expected; the final basification with ammonia was again carried out using the low-temperature method (*cf* page 53).

(3) Observations on aminobenzimidazole *N*- oxides

Now that all four isomeric aminobenzimidazole *N*- oxides have been synthesised for the first time some physical and spectral properties common to these compounds are recorded.

(a) Physical properties

The polar nature of these compounds is evident by an appreciable solubility in water and crystallisation is always accompanied by the incorporation of at least one molecule of water of crystallisation.

They are all colourless and crystalline solids with distinct melting points in their purest form but tend to darken on standing and if left in solution decompose completely in a few days. The more stable hydrochlorides, however, provide a convenient method for storage over an extended period.

(b) Spectral properties

All the mass spectra show an M^+ peak and have loss of oxygen followed by hydrogen cyanide as the principal breakdown pattern.

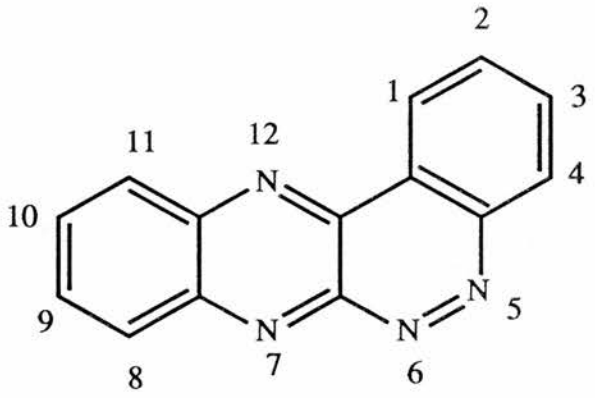
In the infra-red spectra the expected N-H stretching patterns do not show up due to extensive hydrogen bonding and the presence of the water of crystallisation.

The ^{1}H n.m.r. spectra are seldom first order, the only noticeable distinctive feature being the low field singlet caused by H-2 (δ 8.0 - 8.23 for the free *N*- oxides and δ 9.78 - 9.96 for the hydrochlorides).

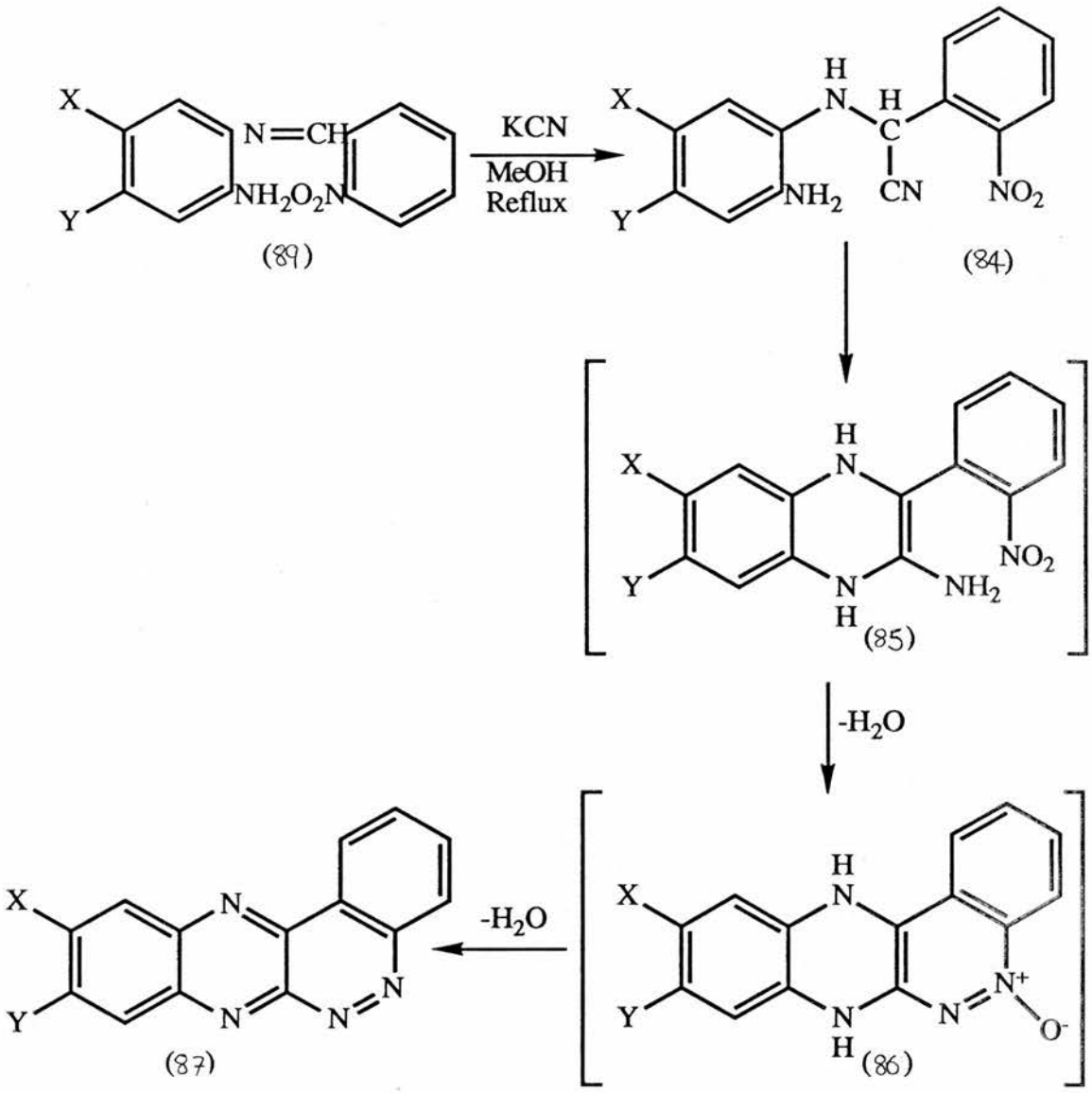
QUINOXALINO[2,3-c]CINNOLINES

PART 1 INTRODUCTION

Quinoxalino[2,3-c]cinnoline is a tetracyclic ring system comprising a quinoxaline fused to a cinnoline molecule through positions 3 and 4 of the cinnoline and positions 2 and 3 of the quinoxaline molecule, thus:-



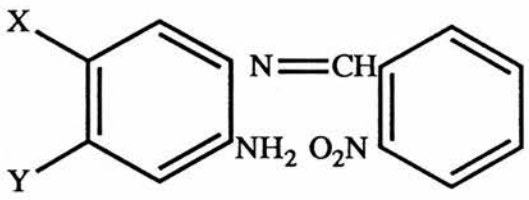
The synthesis of quinoxalino[2,3-c]cinnolines is achieved most readily by the method illustrated in Scheme 18



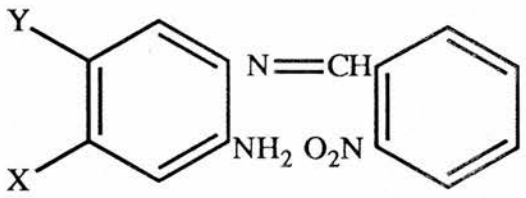
(Scheme 18)

The reaction consists of a cyanide-induced cyclisation of an o-amino-N-o-nitrobenzylideneaniline. It is believed to proceed as follows: cyanide addition gives rise to (84) and the *ortho* - located amino group acts as an internal nucleophile to form the aminodihydroquinoxaline (85). This may then undergo base-catalysed cyclisation to the tetracyclic N-oxide (86), which on dehydration gives the quinoxalino[2,3-c]cinnoline (87).

A problem occurs if the substituents X and Y are dissimilar, as the initial Schiff base formed from the diamine can be either (88) or (89) or a mixture of both, which when cyclised could produce a mixture of two quinoxalino-

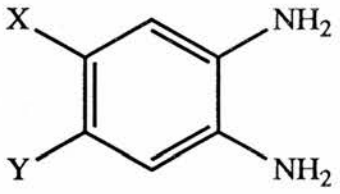


(89)



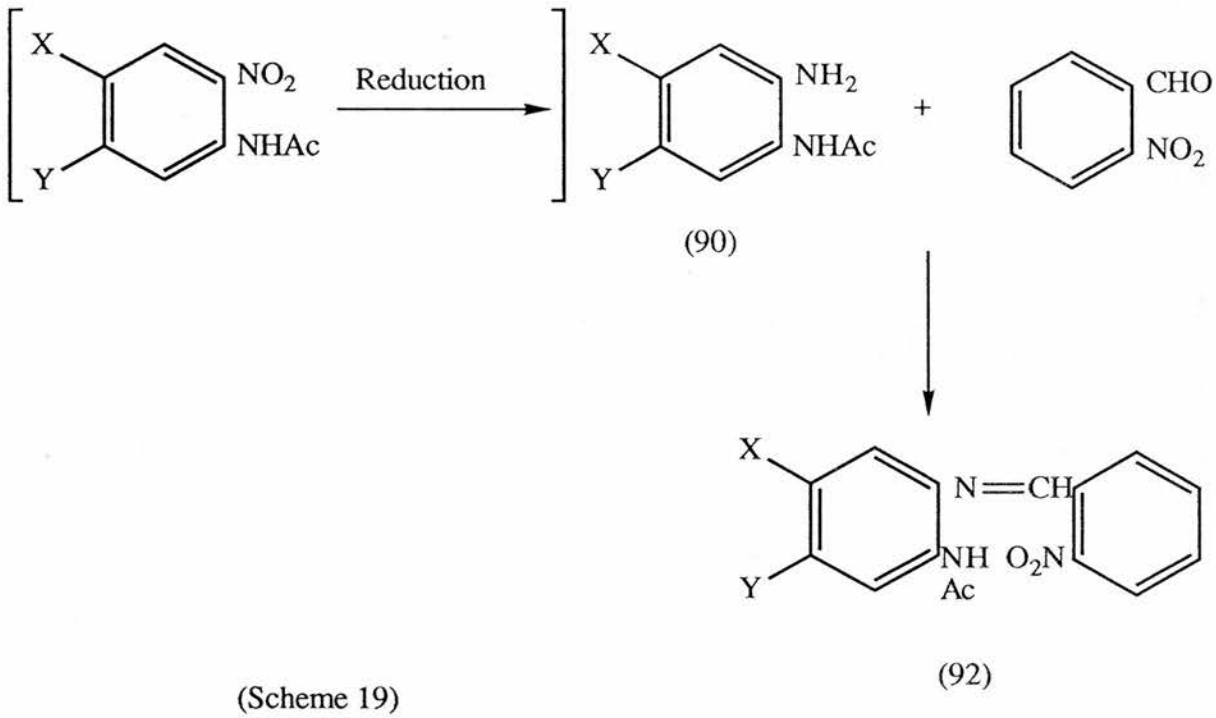
(88)

[2,3-c]cinnolines. This problem was overcome by Shepherd[27] by synthesis of a mono-acetylated derivative (90) of the diamine (91).



(91)

Thus to prepare only compound (87) the synthesis of the Schiff base (92) would proceed according to Scheme 19.



(Scheme 19)

The Schiff base (92) can then be cyclised to (87) directly. There is no need to deprotect the amino-group in a separate step prior to cyclisation.

The ^1H n.m.r. spectra of quinoxalino[2,3-c]cinnolines display one interesting feature, namely that protons H-1 and H-4 are heavily deshielded with respect to similar protons in the simple bicyclic heterocycle, i.e. H-5 and H-8 in cinnoline (see Table 5).

Compound	Proton	δ p.p.m.	Proton	δ p.p.m.	Solvent
Cinnoline	H-5	7.57	H-8	8.30	CCl_4
quinoxalino [2,3-c]cinnolines	H-1	9.02-9.22 m	H-4	8.72-8.39 m	$CDCl_3$

(Table 5)

In addition two features of the chemistry of quinoxalinocinnolines deserve a mention at this point. Neither of these reactions is known to occur in the simple quinoxaline system.

(i) Halogenation using hydrogen halides

When quinoxalino[2,3-c]cinnoline is reacted with hydrogen chloride gas, a blue solid results, and the blue solid when reacted with sodium hydroxide gives 10-chloroquinoxalino[2,3-c]cinnoline in high yield.

No previous reports of halogenation of a benzo-fused heteroaromatic system by hydrogen halides had been published.

(ii) Nucleophilic substitution of 10-chloroquinoxalino [2,3-c]cinnoline

Shepherd[28] observed a difference between 9-chloroquinoxalino[2,3-c]cinnoline and its 10-chloro analogue with regard to nucleophilic displacement. While the former compound is unreactive towards methoxide the latter reacts to give 10-methoxyquinoxalino[2,3-c]cinnoline in high yield.

These two features are now considered in greater detail.

(i) Halogenation using hydrogen halides

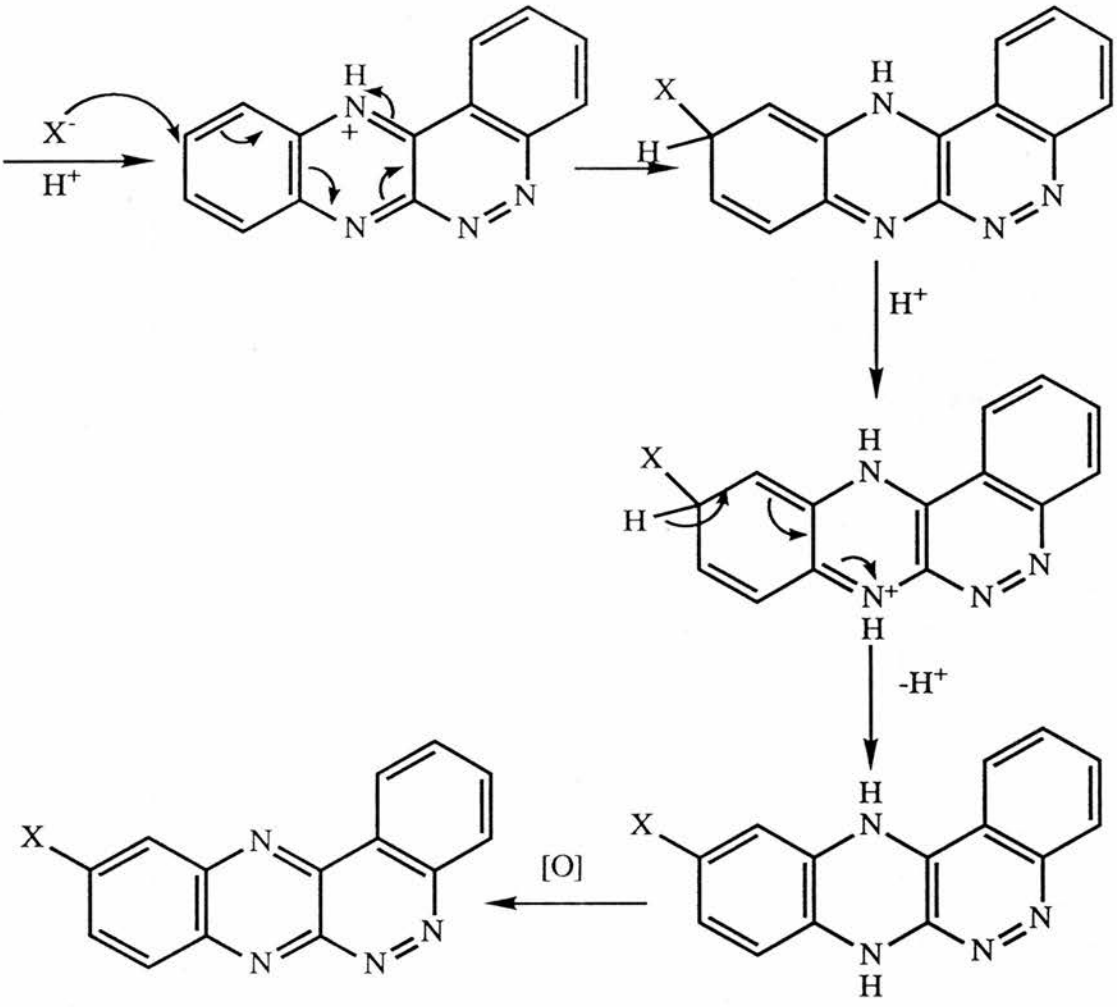
A theoretical insight into the likely reactivity and geometry of this ring system was obtained by MNDO calculations[29] (such calculations are approximations, applying to isolated molecules in the gas phase). The geometry was established as being substantially planar with the lone pair on each nitrogen atom co-planar with the molecule. Table 6 shows the charge values obtained for the four nitrogen atoms in the parent compound.

Atom	Charge
N-12	-0.157
N-7	-0.101
N-6	-0.004
N-5	-0.034

(Table 6)

The reaction with hydrogen halides is assumed to involve protonation as the first step. The charge values imply that the most likely site for initial protonation would be N-12.

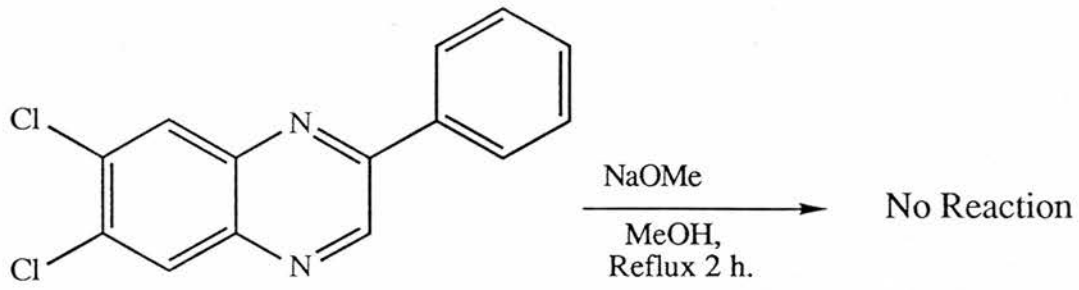
When N-12 is protonated, addition of the chloride ion may follow at C-10, and the eventual outcome is a 10-substituted quinoxalino[2,3-c]cinnoline as shown in Scheme 20.



(Scheme 20)

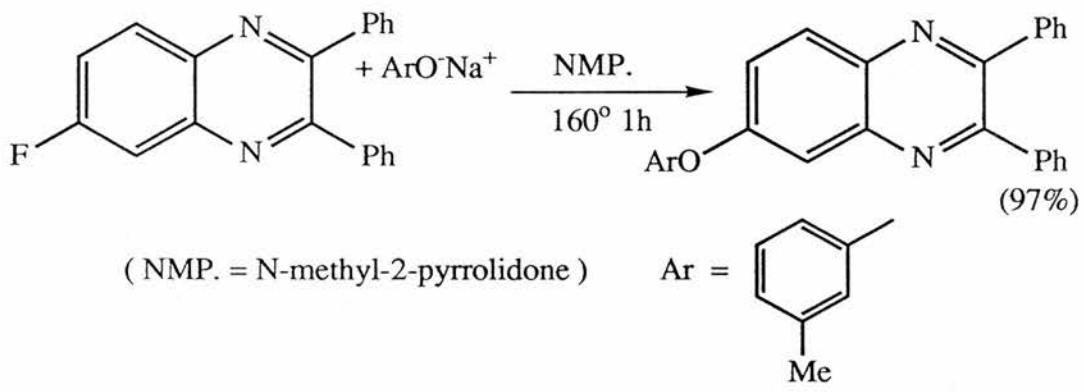
(ii) Nucleophilic substitution of 10-chloroquinoxalino-[2,3-c]cinnoline

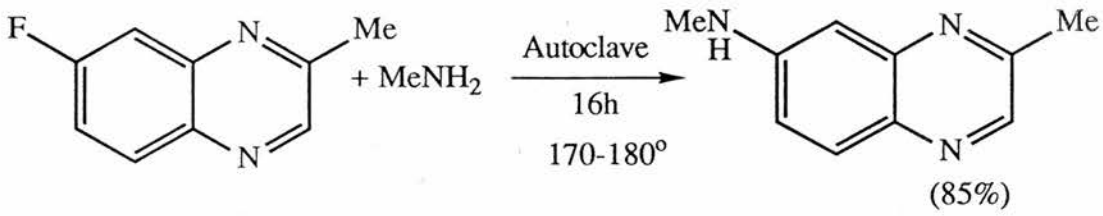
Halogeno-substituents in simple quinoxalines are relatively stable towards nucleophilic displacement. 6,7-Dichloro-2-phenylquinoxaline was recovered unchanged after being reacted with methoxide under the conditions shown[30] in the first reaction on the next page.



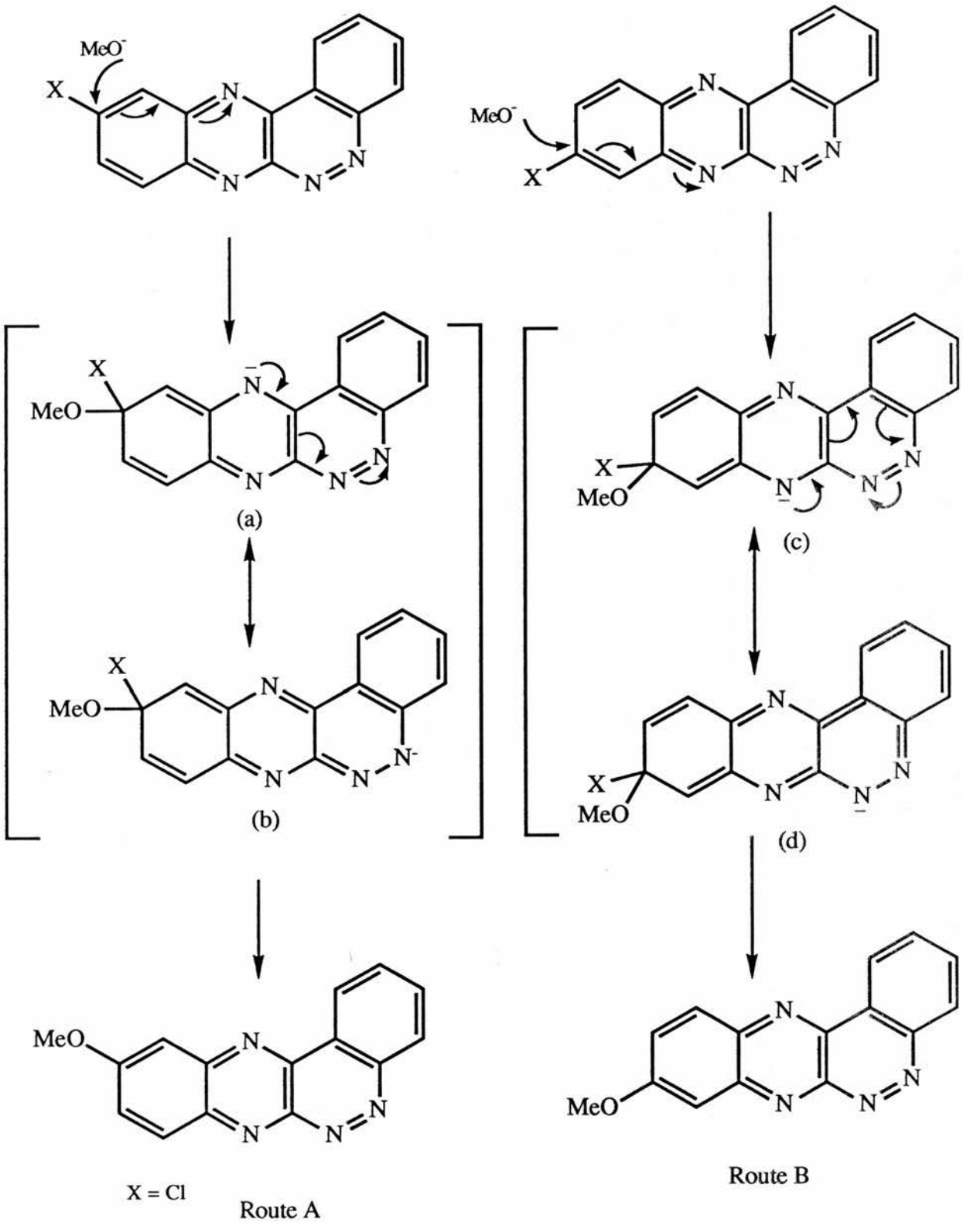
(Figure 20)

Even fluoro-quinoxalines require severe conditions to undergo nucleophilic displacement and only very recently have reports of such displacements been published[31,32] as shown below.





To explain the different behaviour of 10-chloroquinoxalino[2,3-c]cinnoline compared to its 9-chloro counterpart towards methoxide a mechanism is given (Scheme 21) showing attack by methoxide at both positions 9 and 10.

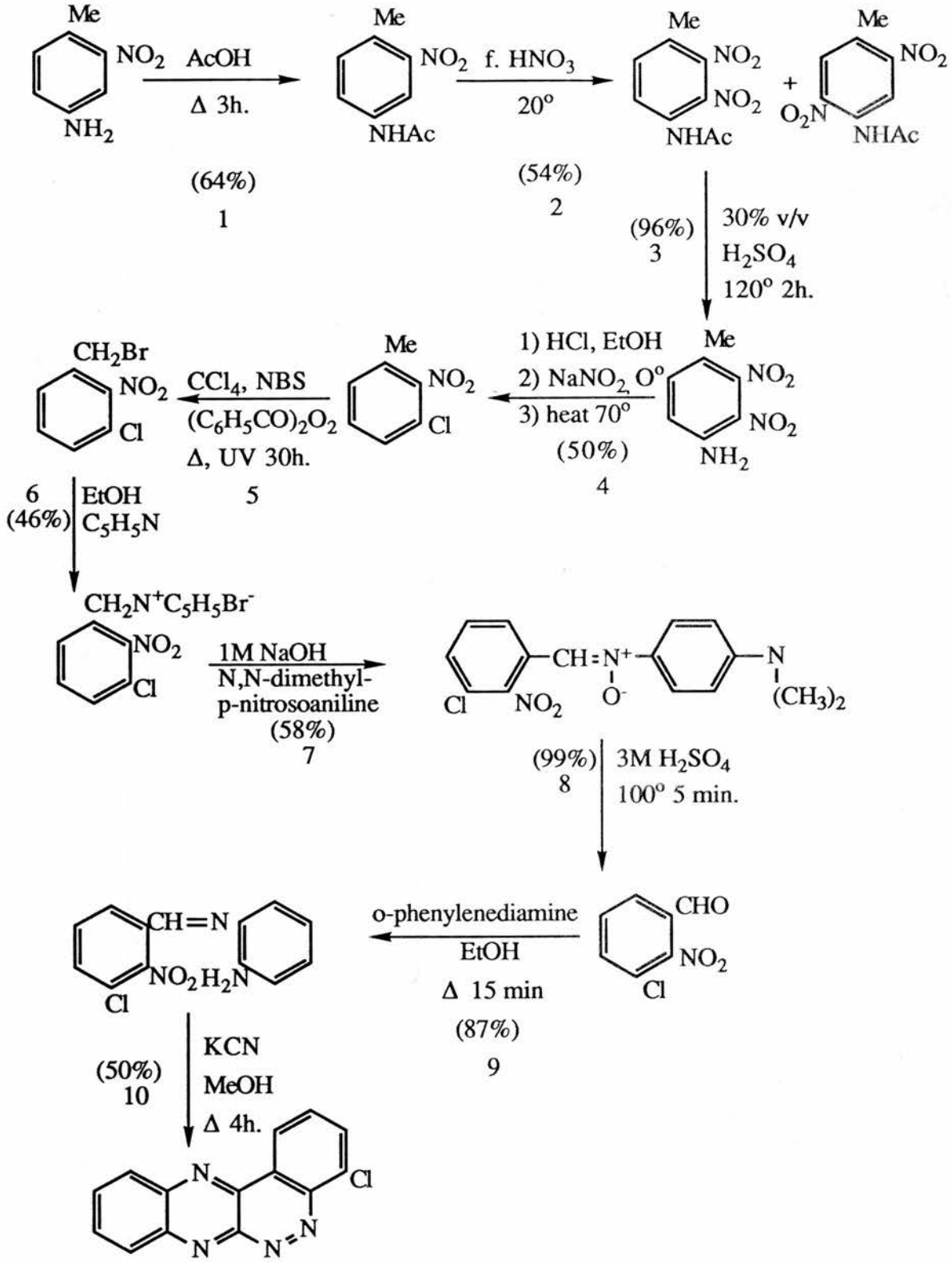


(Scheme 21)

The difference in the reactivity of the two compounds may be explained by the different degree of stabilisation of the negative charge in the intermediate. When the negative charge is shifted outwith the quinoxaline portion of the molecule, as in canonical forms (b) and (d), the 6π system of the cinnoline derived carbocyclic ring remains intact in route.A only (structure (b)) while in route B it is destroyed (structure (d)).

Shepherd also reported that chlorine atoms at positions 2 and 8 were unreactive towards methoxide and subsequently Dunbar[33] noted the same unreactive nature of chlorine at positions 1 and 3. Thus all that remained to investigate was the reactivity of chlorine at positions 4 and 11.

The 4-chloro isomer was synthesised according to Scheme 22 overleaf. The aldehyde required was synthesised using this lengthy route for the following reasons. The route although involving eight steps begins with a cheap, readily available amine thus enabling a large quantity of the starting material to be used. The yields obtained throughout are sufficiently high to allow the use of 250 g of starting material to provide 4 g of the aldehyde, an adequate quantity for the synthesis of the 4-chloroquinoxalino[2,3-c]cinnoline. Finally all the steps 1-8 had been reported in the literature.

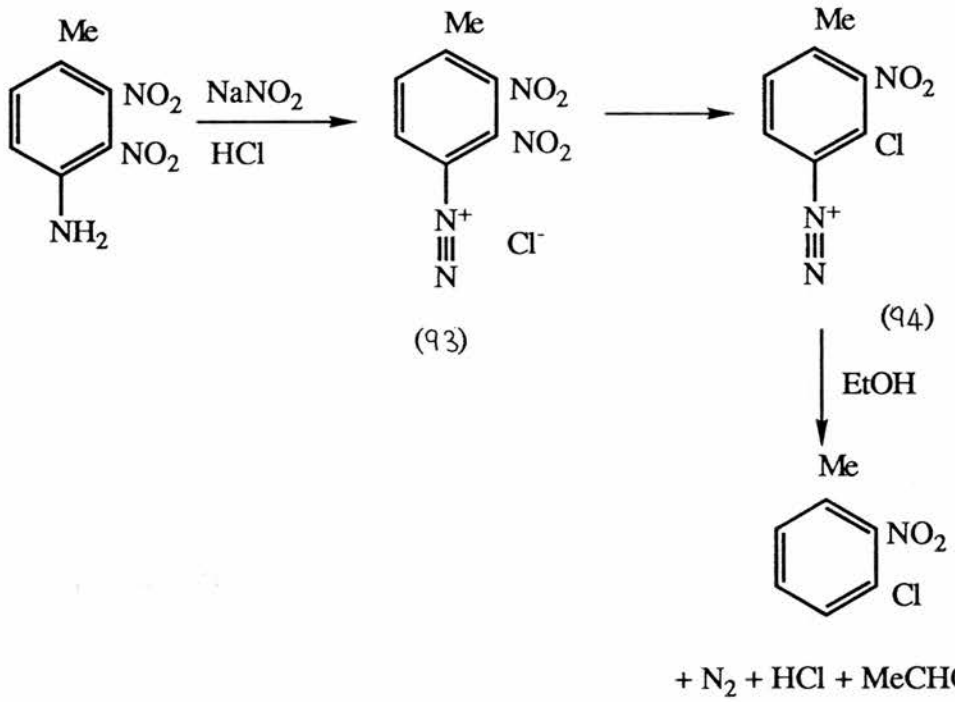


(Scheme 22)

The route also incorporates three interesting features that merit additional discussion, namely the nitration (step 2), the method used to obtain 3-chloro-2-nitrotoluene (step 4) and its subsequent oxidation via Kröhnke's method (steps 5-8).

The nitration, as expected, produces a mixture of isomers. The desired isomer is obtained as the major product and is also the more readily isolated, by steam distillation and recrystallisation.

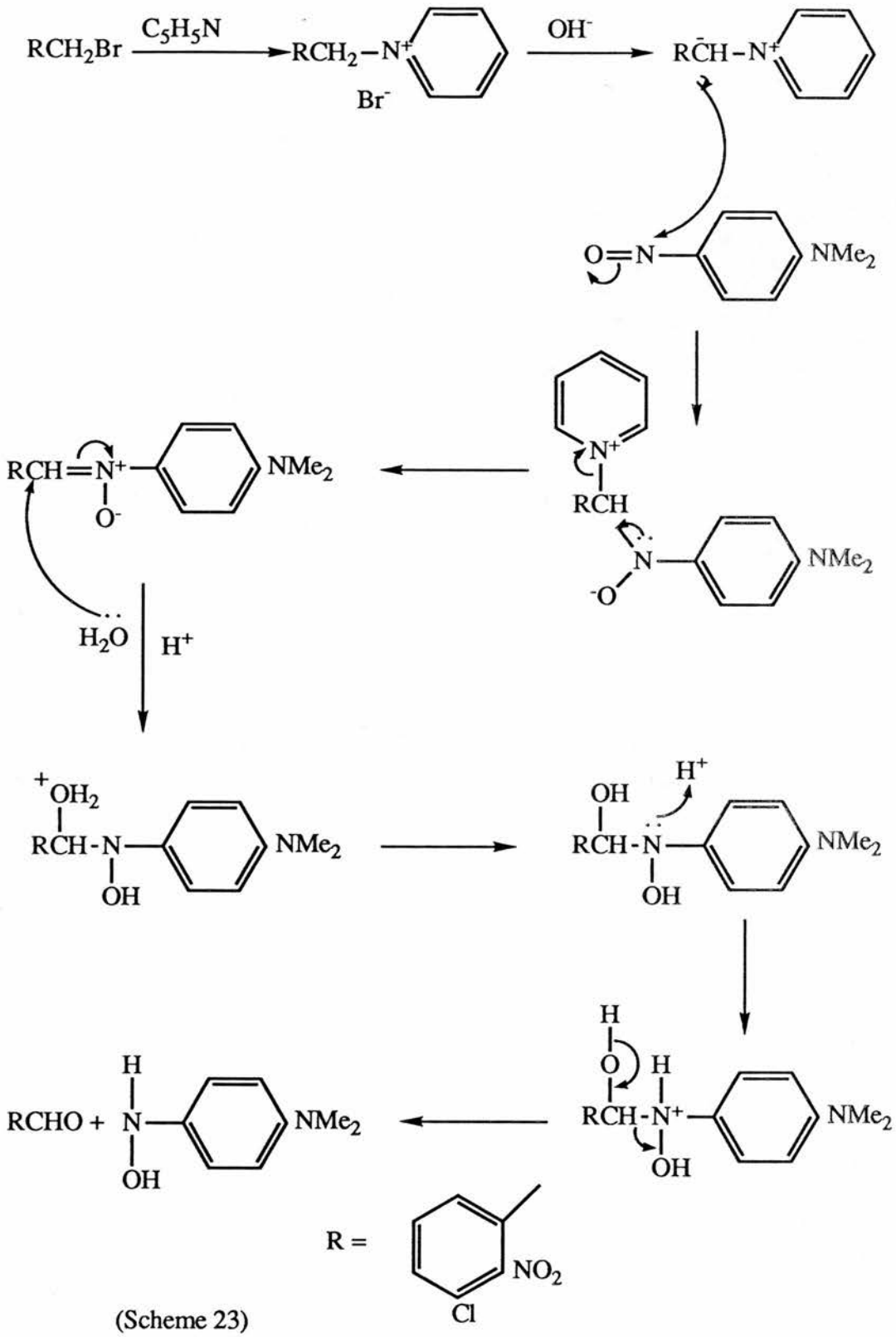
The conversion of 4-methyl-2,3-dinitroaniline into 3-chloro-2-nitrotoluene is shown in a stepwise form as shown.



The initial reaction is the formation of the diazonium salt (93), which has in it a nitro-group at position 2. This is highly activated, by having two electron withdrawing groups adjacent to it; therefore it is an excellent leaving group. So when the nucleophilic attack occurs it is this nitro-group that is displaced, producing the second diazonium salt (94); on heating in the presence of ethanol this salt decomposes forming the products as shown.

The mechanism of the Kröhnke oxidation is shown in Scheme 23 on page 78. This versatile method of oxidising a suitable methyl group to the corresponding aldehyde was first reported by Kröhnke in 1936[34].

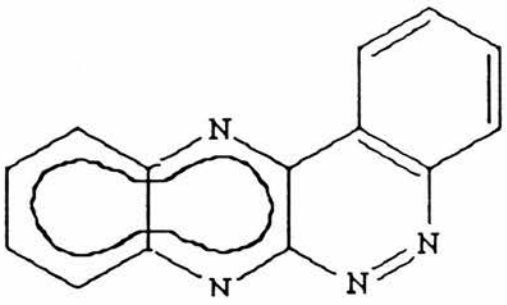
The attempt to displace the chlorine in 4-chloroquinoxalino[2,3-c]cinnoline by refluxing with sodium methoxide for 12 hours was unsuccessful, the starting material being recovered unchanged.


RCH2Br
C5H5N
RCH2–N+
Br-
OH-
R̄CH–N+
O=N
NMe2
N+
RCH
N
-O
NMe2
RCH=N+
O-
NMe2
H2O
H+
+OH2
RCH-N
OH
NMe2
H+
OH
RCH-N
OH
NMe2
H
O
H
RCH-N+
OH
NMe2
RCHO +
H
N
OH
NMe2
R =
NO2
Cl

(Scheme 23)

This result served to confirm the overall lack of reactivity of chlorine substituted in the cinnoline derived carbocyclic ring of the quinoxalino[2,3-c]cinnoline system.

The MNDO calculations serve to support the observations concerning the overall lack of reactivity displayed by chlorine at positions 1-4 as they show the pattern of electron delocalisation in the quinoxalino[2,3-c]cinnoline system thus:-

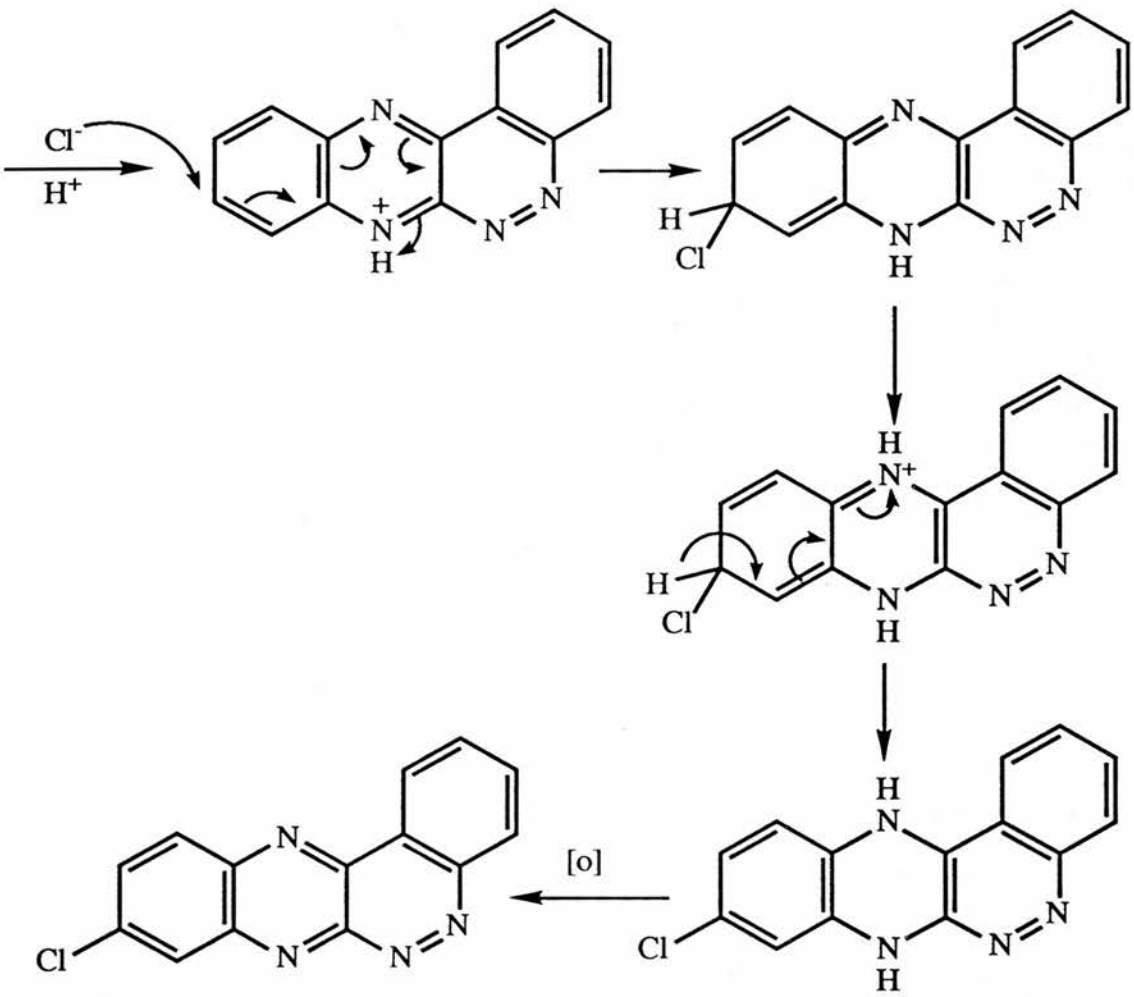


The quinoxaline part of the molecule has a delocalised 10π system whereas the cinnoline portion is comprised of one complete double bond and a normal 6π benzene ring. At the present time only position 11 remains to be examined, however it is not unreasonable to speculate that it will behave in the same way as position 9 and display no reaction with methoxide.

PART 2 ALTERING THE INITIAL SITE OF PROTONATION IN QUINOXALINO[2,3-c]CINNOLINE

As already described (page 69) the reaction of HCl gas and quinoxalino[2,3-c]cinnoline gives only 10-chloroquinoxalino[2,3-c]cinnoline because of preferential initial protonation at N-12. When the heats of formation of the protonated quinoxalinocinnolines were calculated (using MNDO), it was somewhat surprising that the molecule protonated at N-7 (not N-12) gave rise to the lowest heat of formation: 22.3 kJ mol^{-1} lower than the N-12-protonated species. The conclusion to be drawn from the above is that although initial protonation at N-12 is favoured in terms of electron density (see page 70), initial protonation at N-7 is thermodynamically favoured. The fine balance between the two possible reaction pathways is apparent when one considers that 10-methoxyquinoxalino[2,3-c]cinnoline undergoes chlorination at position 9 (presumably via protonation at N-7) despite the fact that N-12 is still the site of highest electron density. This is why an attempt to alter the site of protonation was deemed a worthwhile exercise.

If by some means the initial protonation could be forced to occur at N-7 the final product expected would be a quinoxalino[2,3-c]cinnoline substituted at position 9 in accordance with the mechanism in scheme 24.



(Scheme 24)

The strategy employed to attempt this change was one of spatial shielding of the lone pair of N-12 by having a large atom at position 1 thus hindering initial protonation at N-12. The atoms chosen to occupy position 1 were the halogens chlorine, bromine and iodine and their sizes and bond lengths to carbon are given in Table 7.

Atom	Covalent Radius (Å)	Bond Length(Å) C-X
Cl	0.99	1.77
Br	1.14	1.94
I	1.33	2.14

(Table 7)

Figure 14 shows the parent quinoxalino[2,3-c]cinnoline drawn to scale (distances provided by MNDO calculations) along with each chosen halogen to highlight its size relative to the cinnoline.

For each halogen the following steps were followed:

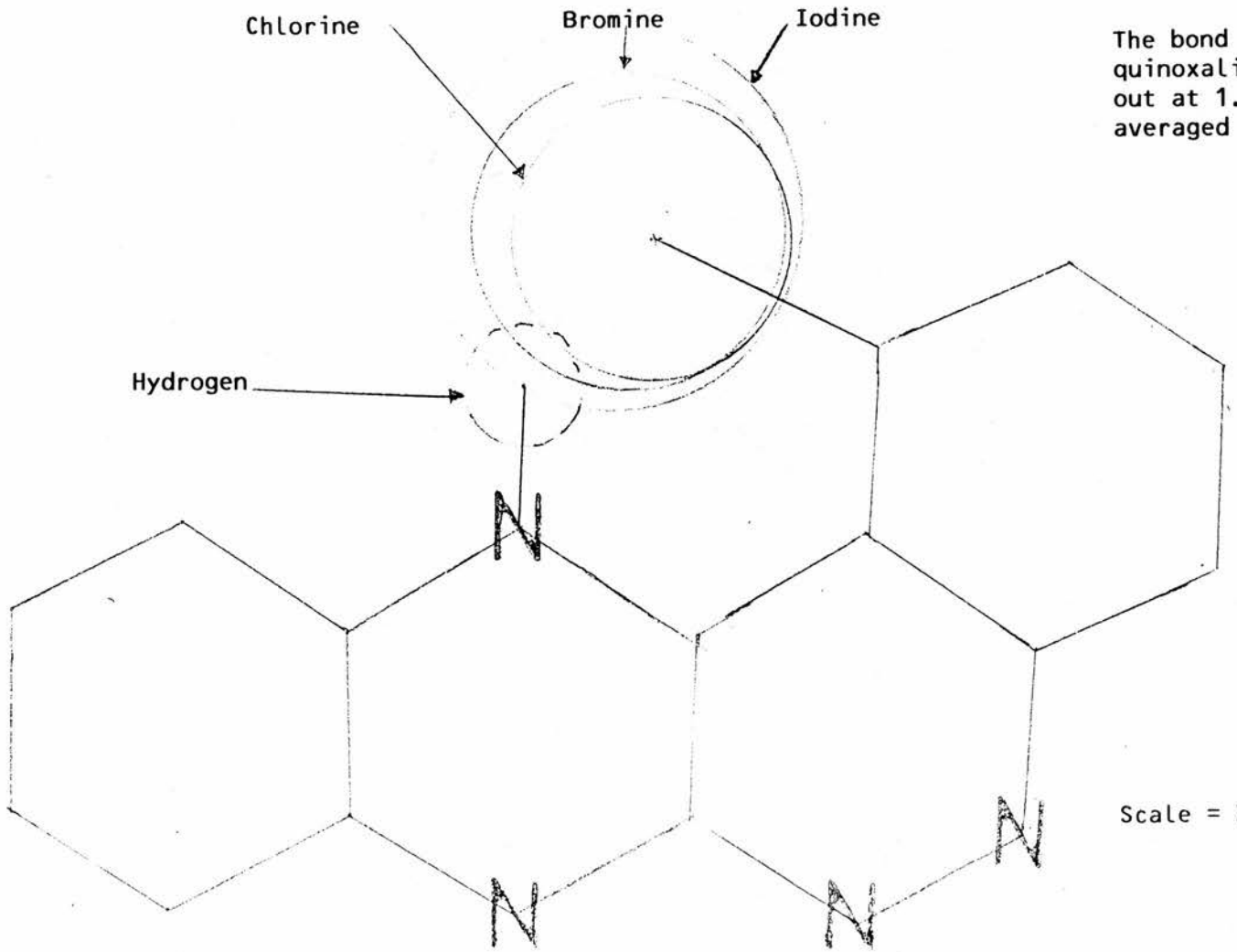
(i) The synthesis of the 1-halogenoquinoxalino[2,3-c]cinnoline and its reaction with HCl gas.

(ii) The synthesis of authentic samples of 1-halogeno-9-chloroquinoxaline[2,3-c]cinnoline and 1-halogeno-10-chloroquinoxalino[2,3-c]cinnoline, for comparison with the product or products obtained from (i).

A co-worker had previously investigated the reaction of 1-chloroquinoxalino[2,3-c]cinnoline with HCl^{35}, preliminary results obtained indicating that substitution still occurred at position 10. This has now been verified, demonstrating that chlorine is of insufficient size to inhibit protonation at N-12; thus the need to study the 1-bromo analogue.

The synthesis of 1-bromoquinoxalino[2,3-c]cinnoline (95) was achieved in two stages: firstly the synthesis of 6-bromo-2-nitrobenzaldehyde (96)

(Figure 14) Scale diagram of quinoxalino[2,3-c]cinnoline along with the chosen halogens.

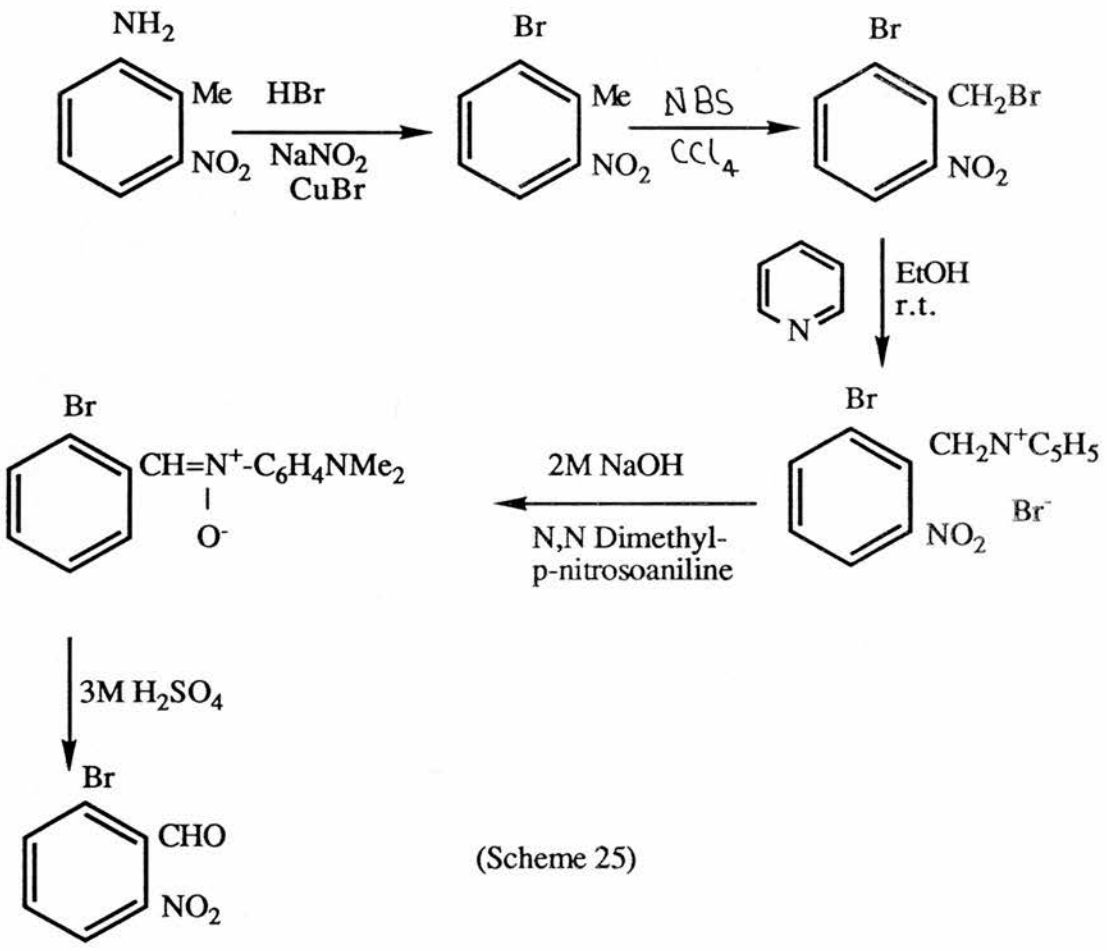


The bond lengths of the parent quinoxalino[2,3-c]cinnoline are averaged out at 1.4 Å and the bond angle averaged at 120°.

Scale = 20 mm/Å

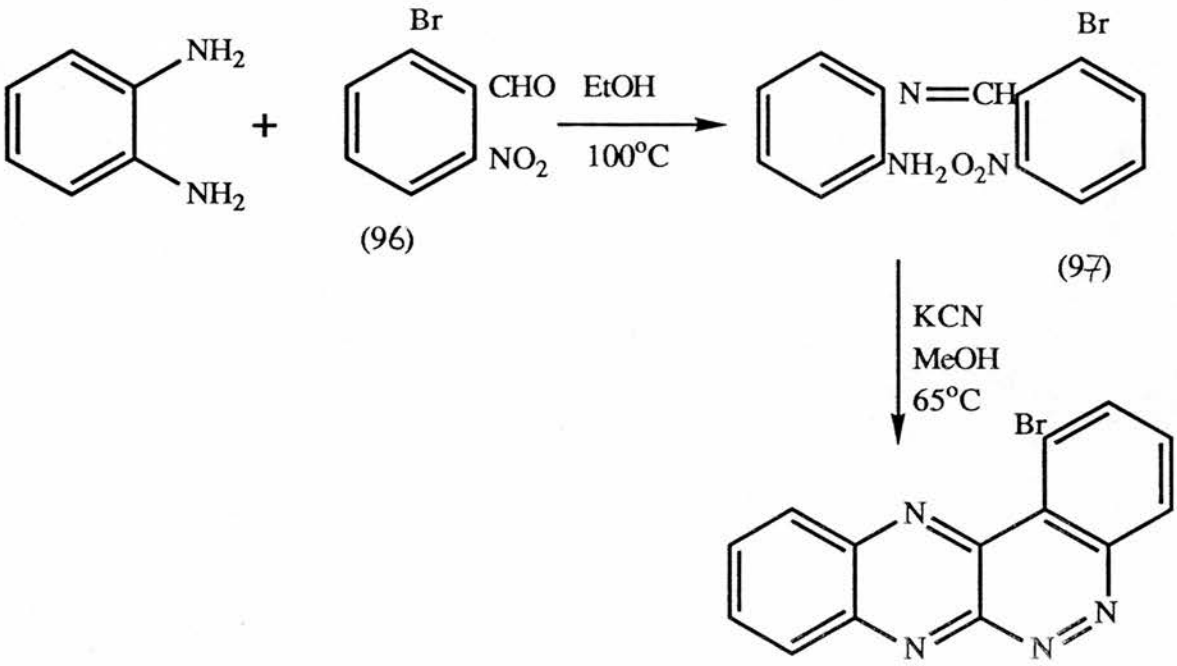
(Scheme 25), followed by formation and cyclisation of the anil (97) (Scheme 26).

The authentic samples of 1-bromo-9-chloroquinoxalino[2,3-c]cinnoline (98) and 1-bromo-10-chloroquinoxalino[2,3-c]cinnoline (99) were synthesised according to Scheme 27 by condensation of 6-bromo-2-nitrobenzaldehyde (96) with the appropriate mono-acetylated diamines *cf.* pages 67–68), which in this case are 2-amino-4-chloroacetanilide (100) and 2-amino-5-chloroacetanilide (101).



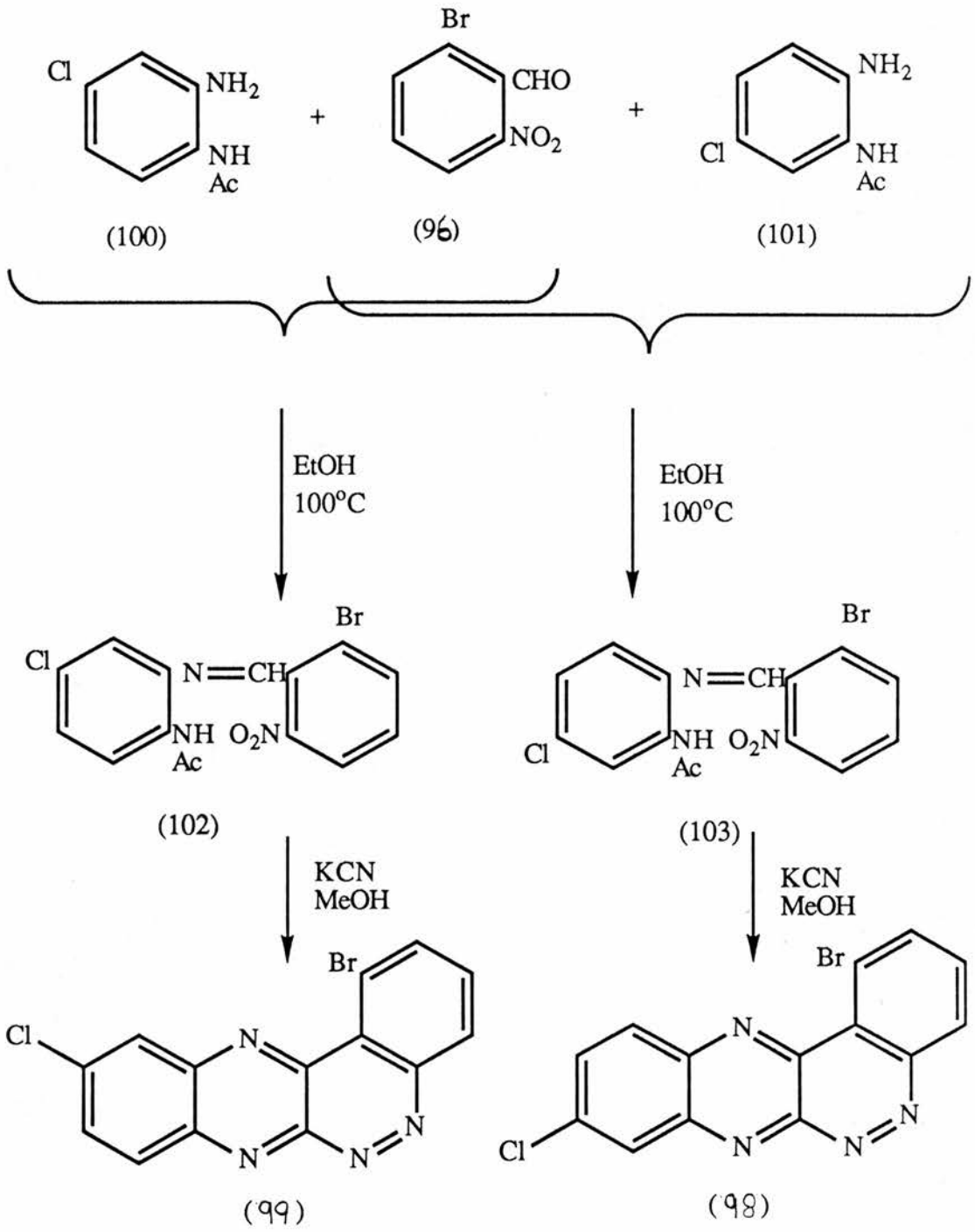
(Scheme 25)

(96)



(Scheme 26)

The respective anils (102) and (103), on subsequent condensation give the two authentic quinoxalino[2,3-c]cinnolines (99) and (98) (Scheme 27).

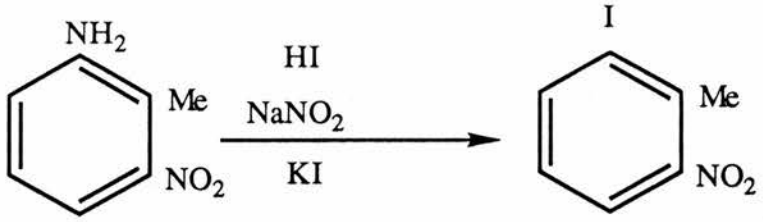


(Scheme 27)

The product formed on reaction of (95) with HCl gas was found to be identical (n.m.r., m.p. and elemental analysis) with (99). This meant that

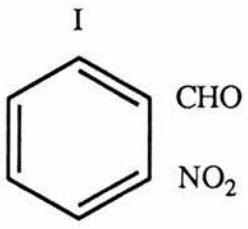
bromine, although 15% larger in radius and possessing a slightly longer bond length to carbon than chlorine, was still unable to prevent initial protonation occurring at N-12.

The final option of locating iodine at C-1 was now pursued, using the same synthetic pathways as described for the bromine analogue on page 84. The synthesis of 6-iodo-2-nitrotoluene (104) was accomplished by a straightforward diazotization reaction as shown below.

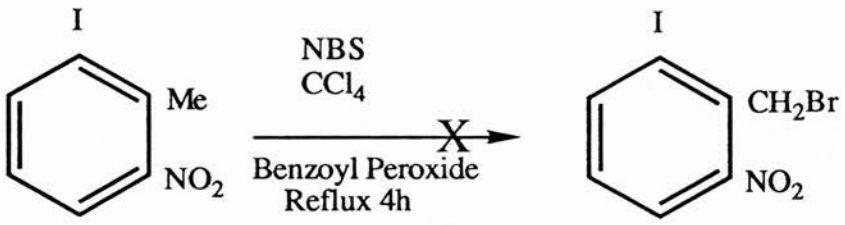


(104)

The continuation of this synthesis in accordance with Scheme 25 to produce the required aldehyde below was, however, unsuccessful due to the failure to form 6-iodo-2-nitrobenzyl bromide (105) despite repeated attempts using different methods.

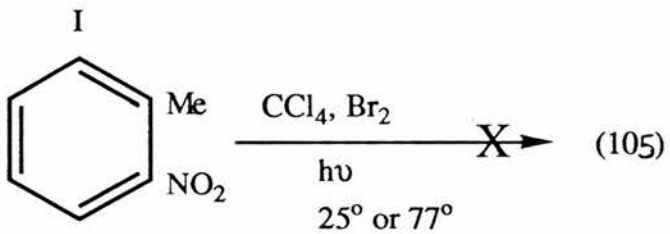


(i) Using the method that had previously worked for the bromine analogue



(104) (105)

(ii) Using elemental bromine as the brominating agent and illuminating with light, both at room temperature and under reflux in carbon tetrachloride.

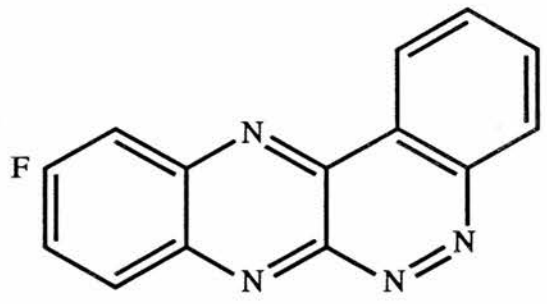


(104)

The explanation arrived at for the failure of the bromination of (104) was somewhat ironic since it appears that the large iodine atom adjacent to the site of the reaction is sterically hindering the entry of the brominating agents to the methyl group. So whether the iodine atom is large enough to prevent N-12 protonation is still not known at the present time.

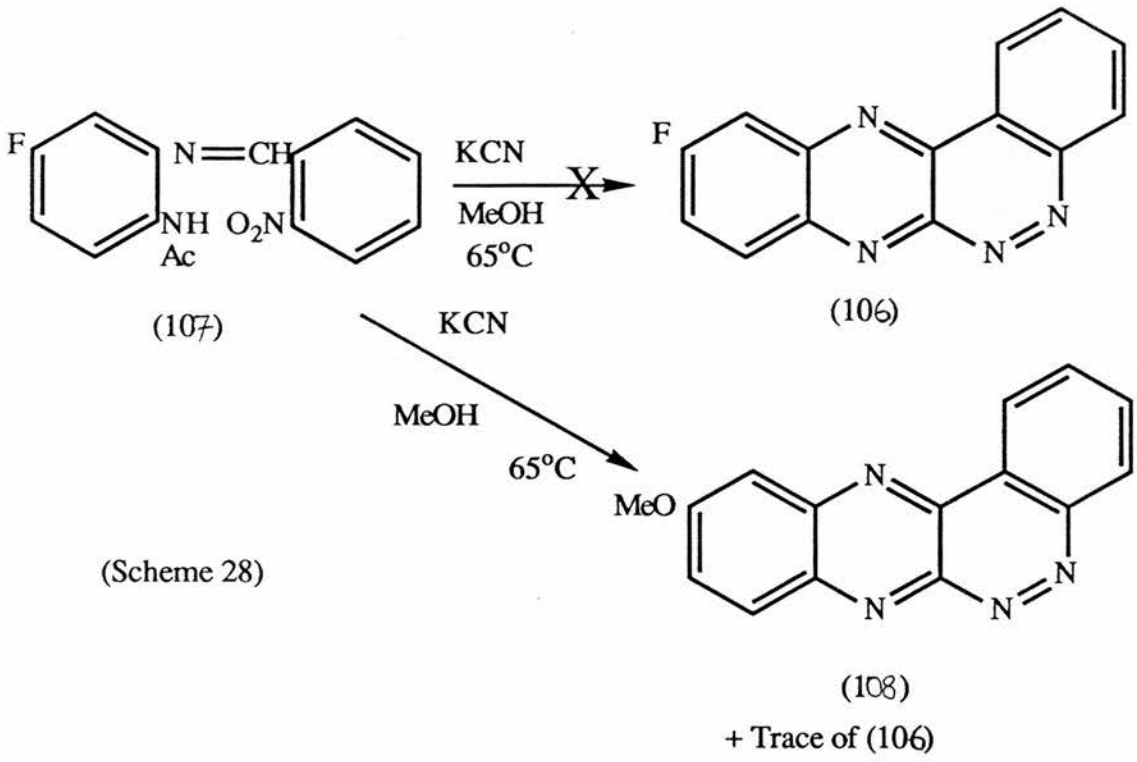
PART 3 THE STUDY OF FLUORINE-SUBSTITUTED QUINOXALINO[2,3-c]CINNOLINES

Numerous examples of quinoxalino[2,3-c]cinnolines are known having chlorine, bromine, methyl or methoxy as the substituents in a variety of positions around either carbocyclic ring. Very little was known about the chemistry of fluorine-substituted quinoxalino[2,3-c]cinnolines, except for Green's[36] attempted synthesis of 10-fluoroquinoxalino[2,3-c]cinnoline (106).



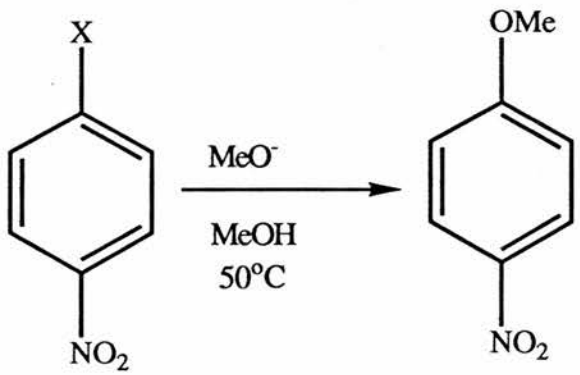
(106)

However, in this, the cyclisaton of the anil (107) did not proceed as expected; instead the methoxide ion displaced the fluorine giving 10-methoxyquinoxalino[2,3-c]cinnoline (108) as by far the major product (Scheme 28) with only a trace of (106) being detected in the mass spectrum.



(Scheme 28)

Arriving at an explanation for the reaction above is simple. The ease of nucleophilic displacement of fluorine in aromatic systems has been extensively reported[37] and measured. By considering the reaction below and the data (obtained from it) in Table 8 the ease with which fluorine undergoes displacement in a protic solvent (compared to the other three halogens) is self-evident.



X = F, Cl, Br or I

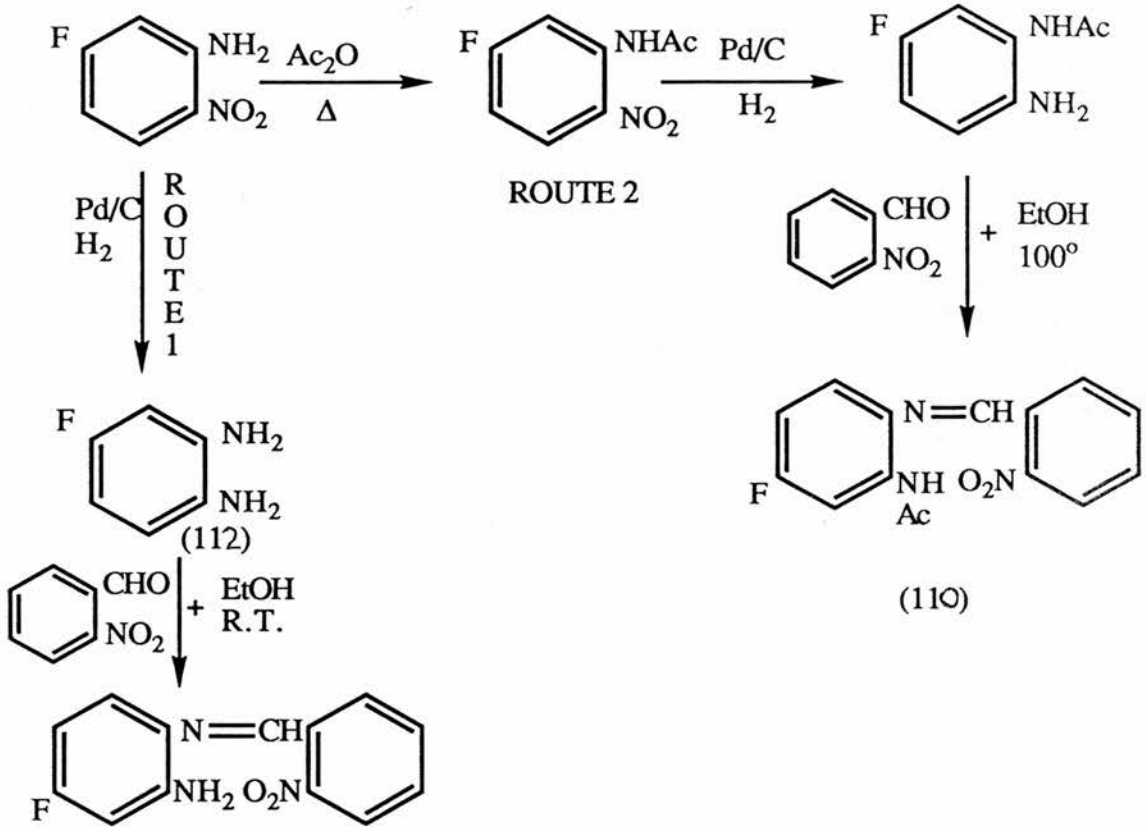
X	Rate Constant (k_2) ($mole^{-1}$ sec^{-1})
F	2.64×10^{-3}
Cl	8.47×10^{-6}
Br	7.16×10^{-6}
I	3.05×10^{-6}

(Table 8)

Also Shepherd found[28] that 10-chloroquinoxalino[2,3-c]cinnoline can be converted into the 10-methoxy derivative by heating the former under reflux for one hour in a solution of sodium methoxide in methanol, with dimethylformamide as co-solvent. It can therefore be understood how the more reactive fluoro-analogue underwent displacement under the milder cyclisation conditions.

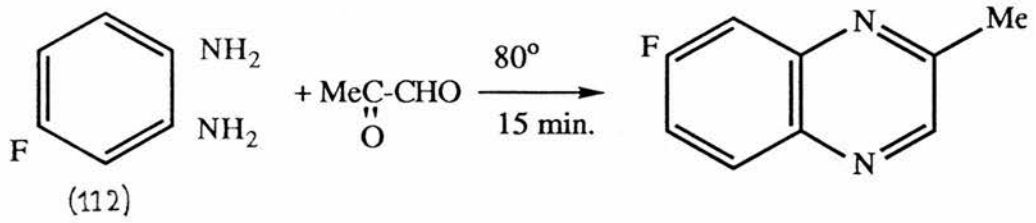
In view of the failure to synthesise (106) attention was turned to obtaining 9-fluoroquinoxalino[2,3-c]cinnoline (109). This stood a better chance of success because 9-chloroquinoxalino[2,3-c]cinnoline is known[28] to be inert to nucleophilic attack by methoxide. If this trend was mirrored by the fluoro system then the 9-fluoro-analogue likewise might also be less reactive towards methoxide than its 10-fluoro-isomer.

Two methods (Scheme 29) were used to obtain the anils (110) and (111) which are the precursors of the desired 9-fluoroquinoxalino[2,3-c]cinnoline.



(Scheme 29)

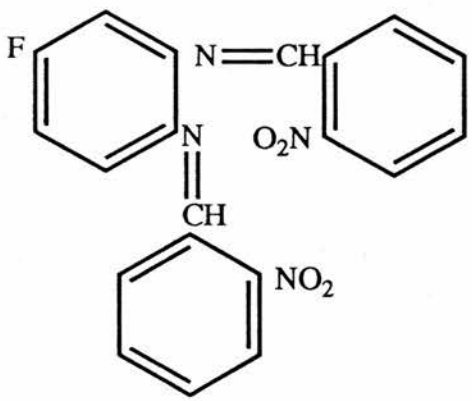
Although route 1 is shorter than route 2 the former pathway holds the possibility of forming one or both of two isomeric anils, which would give a 9- or 10- substituted quinoxalinocinnoline or an isomeric mixture of the two. Fortunately the results obtained proved that both anils (110) and (111) gave only 9- substituted quinoxalino[2,3-c]cinnolines. This means that under the conditions in Scheme 29 only the amino group *para-* to the fluorine (in the diamine (112) condenses with the aldehyde thereby giving the anil (111) as the sole product. The same behaviour was encountered by Loriga[38]. Grivas and Olsson[32] also experienced it with the reaction between 4-fluoro-o-phenylenediamine and pyruvic aldehyde to give 7-fluoro-methylquinoxaline as the main product as shown.



(112)

The more reactive carbonyl (aldehyde) reacts with the amino group situated *para-* to the fluorine atom.

A point to note is the reactivity of the diamine (112) in comparison to diamines containing chlorine and bromine. These form their anils at 100°C with no adverse effects, while the diamine (112) condenses with two molecules of the aldehyde at that temperature forming the compound below; hence the need to carry out the formation of anil (111) at room temperature.



In the attempt to synthesise 9-fluoroquinoxalino[2,3-c]cinnoline the cyclisations of the anils (111) and (110) were performed under three different conditions. Table 9 shows the conditions and the products obtained from each reaction.

Reaction of anils (111) and (110) with KCN in methanol

Anil	Reaction	Time (min)	Temp (°C)	Products from Insoluble ppte	Yield (%)	Products from $CHCl_3$ extract	Yield (%)
110	A	35	65	9-OCH_3–QC 9-F-QC	61 Trace	-	-
111	B	35	65	9-OCH_3–QC 9-F-QC	40 Trace	-	-
110	C	10	65	9-OCH_3–QC 9-F-QC	24 15.5	9-OCH_3-QC 9-F-QC Starting material	37
111	D	10	65	9-OCH_3–QC Starting material	16	9-OCH_3QC Starting material	60 15
110	E	30	RT	9-F–QC	24	9-OCH_3-QC Starting material	75
111	F	1440	RT	Starting material	3	9-F-QC Starting material	Trace 84

QC = quinoxalino[2,3-c]cinnoline

(Table 9)

The work-up procedures for reactions A, B, and E are described fully in the experimental section (pages 134 – 136). The work-up of the remaining reactions was the same except that the mother liquor from the initial filtration was treated in the following way. The methanol was evaporated under reduced pressure at room temperature and the residue dissolved in a mixture of chloroform and water. The organic layer was separated and the products recovered by the usual methods. The products obtained were identified as

far as was possible by n.m.r. and mass spectral analysis. The results clearly demonstrate that as the severity of the reaction conditions is moderated, the displacement of the fluorine atom is significantly reduced until the point is reached at which the anil (110) undergoes cyclisaton and 9-fluoroquinoxalino[2,3-c]cinnoline can be isolated free from the 9-methoxy adduct albeit with a yield of only 24%.

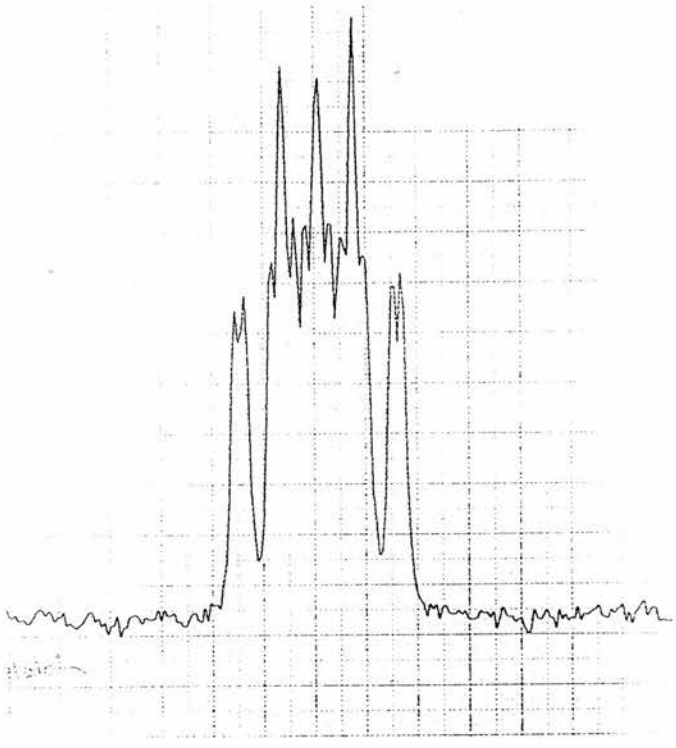
The complete characterisation of the 9-fluoroquinoxalino[2,3-c]cinnoline was essential as this was the first occasion that a fluoro-substituted quinoxalino[2,3-c]cinnoline had been synthesised and isolated. All the spectra discussed are shown in Figures 15-18, pages 96 and 97.

In the ^{1}H n.m.r. spectrum each proton was identified and the spectrum also displayed a pattern consistent with a quinoxalino[2,3-c]cinnoline, namely the presence of two highly deshielded protons (H-1 and H-4).

The ^{19}F n.m.r. spectrum compared with the precursor clearly showed the fluorine atom to have undergone a change in its environment, coupling to protons H-8, H-10 and H-11 giving an almost symmetrical pattern of 8 lines.

The mass spectrum gave the correct molecular ion at m/z 250 and also fragments of molecular weight 222 and 195 which correspond to loss of N_2 followed by HCN; a fragmentation pattern in keeping with a quinoxalino[2,3-c]cinnoline.

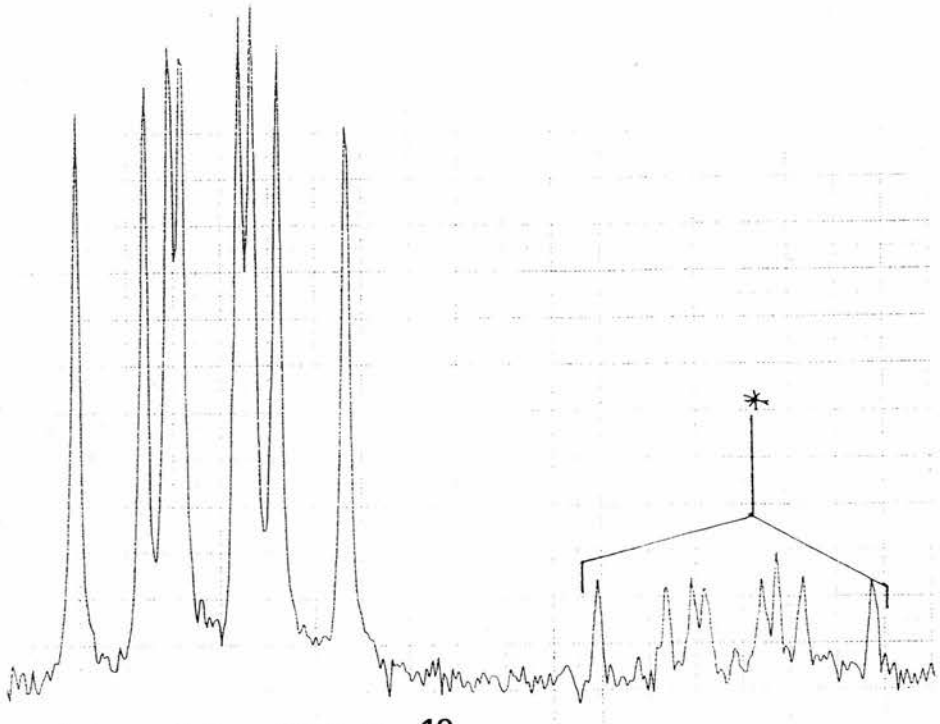
The elemental analysis however gave an unexpected result, namely a low carbon value although the hydrogen and nitrogen were within acceptable error (± 0.3%). The explanation lies in the product being contaminated by approximately 25% of 9-fluoroquinoxalino[2,3-c]cinnoline 5-oxide (see overleaf) and once the set of required values were adjusted to take the



Scale 8Hz/cm

δ_F = -110.6 p.p.m.

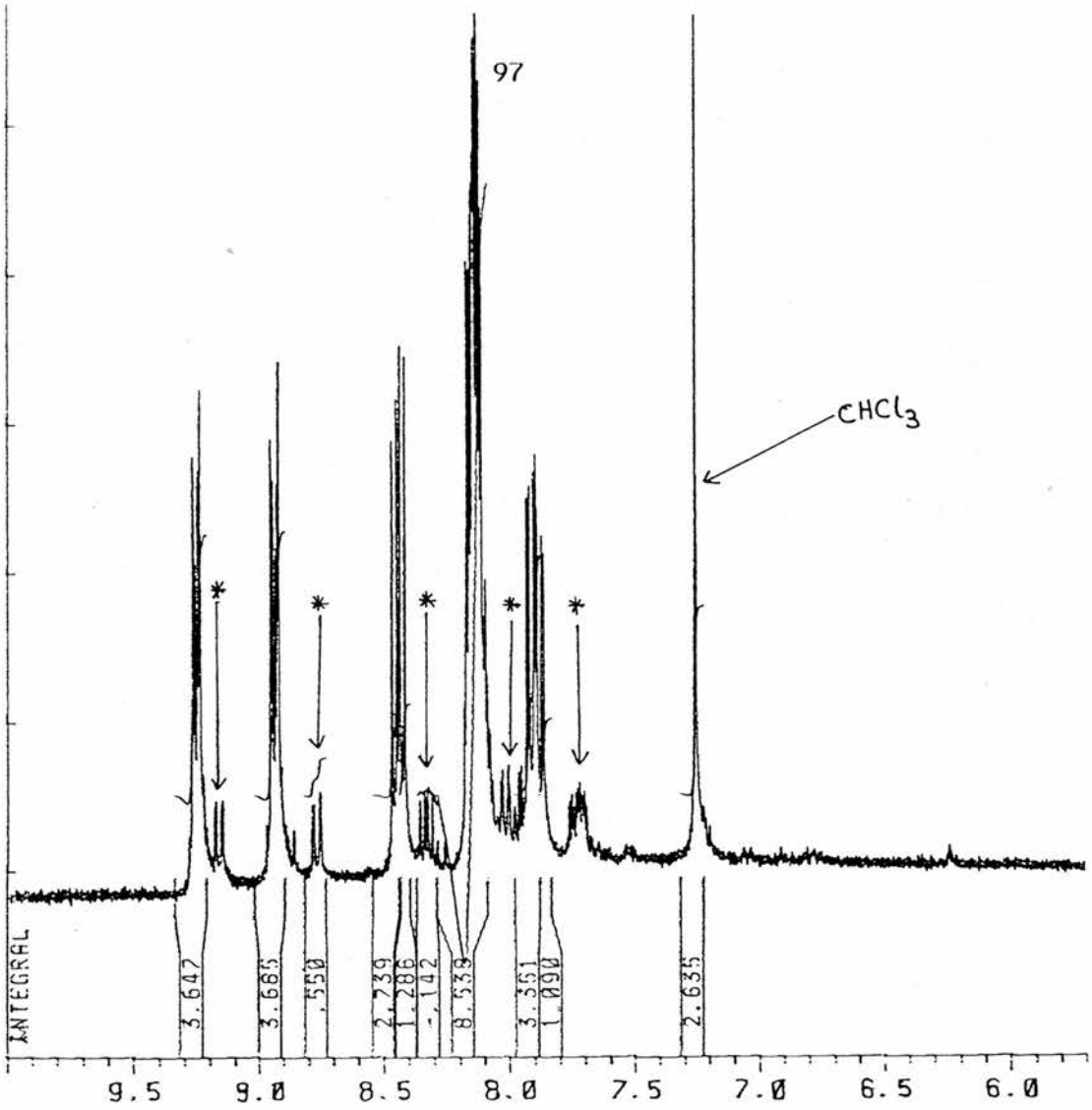
(Figure 15) 75.3 MHz ^{19}F n.m.r. of 2-acetamido-4-fluoro-N-(2-nitrobenzylidene)aniline.



Scale 4Hz/cm

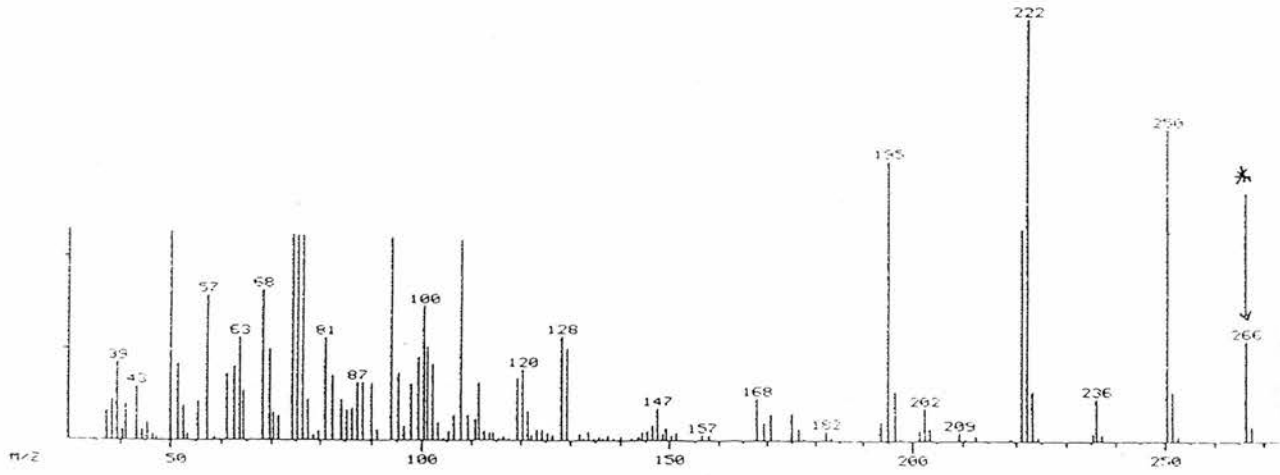
δ_F = -103.7 p.p.m.

(Figure 16) 73.5 MHz ^{19}F n.m.r. of 9-fluoroquinoxalino(2,3-c)cinnoline.



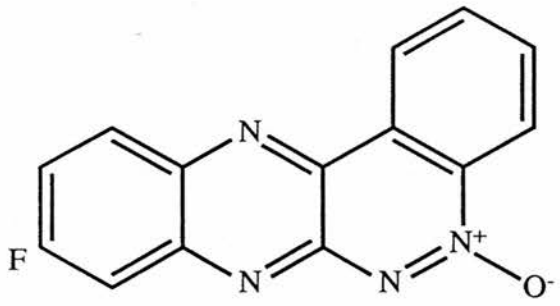
(Figure 17)

300 MHz ^{1}H n.m.r. of 9-fluoroquinoxaline[2,3,c]cinnoline.



(Figure 18)

Mass spectrum of 9-fluoroquinoxalino[2,3-c]cinnoline.



contamination into account the 'found' values for all the elements were now within acceptable error. All the figures for the analysis are in Table 10.

Source	% C	% H	% N
9-F-QC required	67.2	2.8	22.4
9-F-QC found	66.3	2.65	22.4
9-F-QC-5-oxide required	63.2	2.65	21.0
9-F-QC with 25% 5-oxide required	66.2	2.8	22.1

(Table 10)

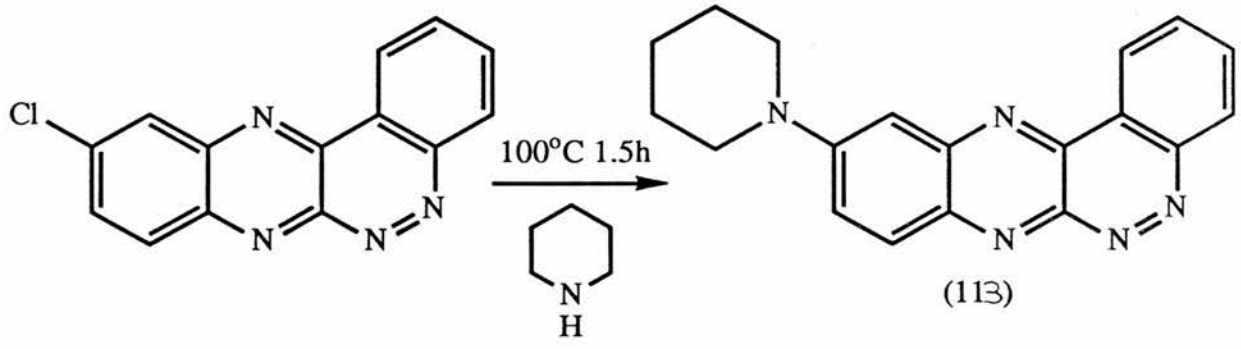
The presence of the 5-oxide was deduced from the peak at m/z 266 in the mass spectrum and the percentage of the contaminant estimated by the relative heights of the two molecular ions. (This assumes that both compounds are equally volatile in the mass spectrometer probe). The contaminant is also noticeable in both n.m.r. spectra (peaks labelled*).

Finally it is well known[27] that the 5-oxides of quinoxalino[2,3-c]cinnolines are frequently formed as by-products in such cyclisations,

possibly by atmospheric oxidation of the intermediate dihydrocompound (85) (Scheme 18, page 66).

Of equal importance was the similarity of behaviour shown towards methoxide of 9-fluoroquinoxalino[2,3-c]cinnoline and its 10-chloro counterpart (page 69). The comparable reactivity of the aforementioned compounds was found to continue with respect to a nitrogen nucleophile.

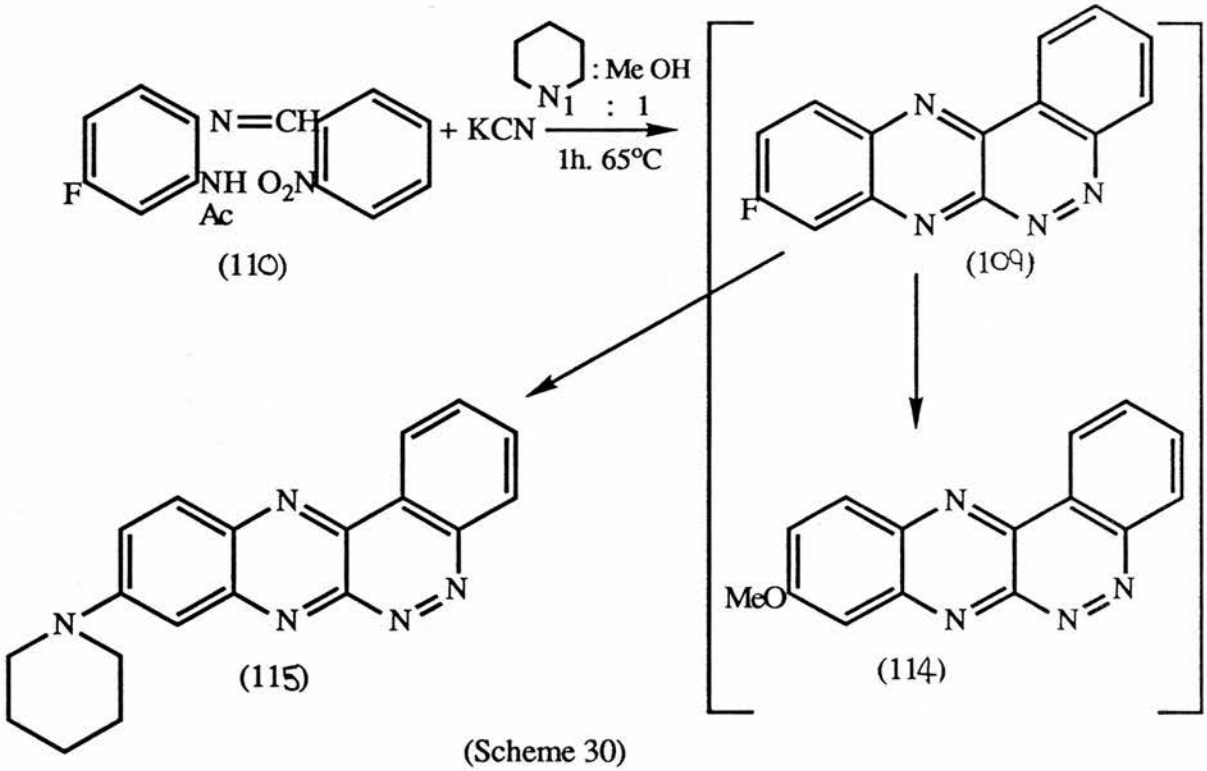
Previous work by Shepherd[28] provided some evidence for the formation of 10-piperidinoquinoxalino[2,3-c]cinnoline (113) in the reaction below



(113)

The assumption was based entirely on the mass spectrum of (113) which had the correct molecular ion and showed a breakdown consistent with the quinoxalinocinnoline structure which is loss of N_2 followed by HCN. The reaction has now been repeated and Shepherd's initial assumption of the nature of the product was validated.

The 9-fluoro analogue behaved in an identical manner as shown in Scheme 30.



(110) (109) (114) (115)

(Scheme 30)

In applying this reaction to the fluoro system it was necessary to cyclise the anil (110) in methanol with piperidine present as a co-solvent to obtain (115) in high yield. The reaction pathway via (109) and (114) was elucidated by mass spectral analysis of samples of the reaction mixture taken throughout the duration of the experiment. The product (115) was obtained as a dark purple solid, very similar in appearance to its 10-piperidino isomer.

9-fluoroquinoxalino[2,3-c]cinnoline was only made in poor yield (25%); the more positive aspect of this exercise was the usefulness of the fluorine in activating position 9 in the quinoxalino[2,3-c]cinnoline system, the reactivity being comparable to that of the 10-chloro analogue. This creates the situation of the anil (110) on cyclisation providing a useful substrate for nucleophilic substitutions at position 9, opening up a route to 9-substituted quinoxalino[2,3-c]cinnolines that otherwise would be difficult or impossible to obtain by direct means.

EXPERIMENTAL

Materials and Apparatus

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

The infra-red spectra were recorded as Nujol mulls or liquid thin films.

^1H n.m.r. spectra were recorded either at 80 MHz on a Bruker WP80 spectrometer or at 300 MHz on a Bruker AM300 spectrometer in $CDCl_3$ with tetramethylsilane as internal reference unless indicated otherwise.

^{19}F n.m.r. spectra were recorded at 75.3 MHz on a Bruker WP80 spectrometer for solutions in $CDCl_3$ with trichlorofluoromethane as internal reference unless indicated otherwise. Mass spectra were generated on a A.E.I. MS-902 spectrometer, operating at 70 eV with a source temperature of 200°C or on a Finnigan MAT. Incos 50 mass spectrometer.

Symbols and Abbreviations

n.m.r.	nuclear magnetic resonance
δ	chemical shift
s	singlet
d	doublet
dd	double doublet
t	triplet
q	quartet
m	multiplet
symm	symmetrical
J	spin-spin coupling constant
i.r.	infra-red
υ	wave number
br	broad

sh	shoulder
w	weak
M^+	molecular ion
mol eq	molar equivalent
dec	decomposition
m.p.	melting point
b.p.	boiling point
d	density
Ac	acetyl
Ms	methanesulphonyl
DMF	dimethylformamide
DMSO	dimethyl sulphoxide

Starting Materials

Three of the starting amines were commercially obtained namely 4-methyl and 4-methoxy-2-nitroaniline and 4-chloro-2-nitroaniline.

5-Fluoro-2-nitroaniline (44a)

The above amine (44a) was obtained by modification of the literature method of Hodgson and Nicholson[39].

Acetic anhydride (114 ml) was added slowly, with stirring, to 3-fluoroaniline (50 g) in such a way as to keep the temperature below 40°C. After completion of the addition, the mixture was stirred at 50°C for 3 h, cooled, and poured on to crushed ice (2 kg). The resultant white solid was collected by filtration. The 3-fluoroacetanilide (56.1 g, 81%) had m.p. 85-87°C (from propan-2-ol-water; lit.,[39] 85° C).

A nitration mixture of fuming nitric acid (d. 1.5; 15 ml) and concentrated sulphuric acid (110 ml) was added dropwise with stirring to an ice-cooled mixture of 3-fluoroacetanilide (37.5 g) in concentrated sulphuric acid (110 ml) in such a way as to maintain the temperature below 5°C. After completion of the addition the mixture was poured on to ice and the solid was then collected by filtration, washed with water and dried.

This mixture of nitration products was then hydrolysed in a mixture of ethanol (370 ml) and 50% aq. by wt. sulphuric acid (370 ml) and the resulting fluoronitroanilines separated by steam distillation according to the literature method. The steam-volatile 5-fluoro-2-nitroaniline was obtained in a yield of 19 g (50%), m.p. 93-95°C (from aqueous ethanol; lit.,[39] m.p. 98°C). The steam-involatile residue, worked up again according to the literature method, gave 3-fluoro-4-nitroaniline (11.4 g, 30%), m.p. 146-148°C (from ethanol-water; lit.,[39] 153°C).

2-Nitro-m-phenylenediamine (50)

Stage 1

2-Nitroisophthalic acid (52)

A solution of potassium permanganate (126 g, 0.79 mol), potassium hydroxide (26 g, 0.46 mol) and 2-nitro-m-xylene (30 g, 0.198 mol) in water (1200 ml) was heated under reflux and mechanically stirred for 15 h. The manganese dioxide formed was filtered off and the filtrate acidified with concentrated hydrochloric acid which gave the product as a white precipitate. The 2-nitroisophthalic acid (26.3 g, 63%) had m.p. 308-310°C (from aqueous methanol; lit.,[40] 315°C).

Stage 2

2-Nitroisophthalic diamide (54)

The di-acid (52) (26 g, 0.12 mol), thionyl chloride (80 ml), and dimethylformamide (1.5 ml) were heated under reflux for 4-5 h. After cooling, the excess thionyl chloride was removed *in vacuo* and the residue filtered off and washed with petroleum (b.p. 40-60°C). The crude di-acid chloride (53) (28 g, 90%) had m.p. 126-128°C.

The unpurified di-acid chloride (28 g, 0.11 mol) was then added in several portions, with stirring, to ammonia (d. 0.88,680 ml). After the final addition the mixture was stirred for an additional 4 h. The solid was then filtered off and recrystallised from water to give (54) (17.2 g, 73%), m.p. 276-278°C (lit.,[41] 278-280°C).

Stage 3

2-Nitro-m-phenylenediamine (50)

To a solution of sodium hydroxide (72 g, (1.8 mol) in water (100 ml) was added ice (400 g) and a stream of chlorine passed through the mixture until 55.3 g had been absorbed. The solution was made up to 570 ml to give aqueous sodium hypochlorite (1.35 M).

The finely ground diamide (54) (17 g, 0.086 mol) was added slowly with stirring, to the freshly prepared sodium hypochlorite solution (126 ml), diluted with water to 750 ml at 0°C. When all the diamide had dissolved the solution was diluted with sodium hydroxide (1%, 504 ml).

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 half-way through the spiral. The product (50) which crystallised from the cooled solution was filtered, washed with water and recrystallised from aqueous ethanol. Yield 9.3 g (71%), m.p. 137-139°C (lit.[41], 141°C).

3-Nitro-1,2-phenylenediamine (59)

Stage 1

2,1,3-Benzoselenadiazole

To a solution of 1,2-phenylenediamine (30 g, 0.28 mol) in hot ethanol (175 ml) was added a filtered aqueous solution of selenium dioxide (33.9 g, 0.3 mol) and the resultant solution boiled for 10 min. The mixture was cooled and a white solid filtered off. Recrystallisation from water gave the selenadiazole (37.2 g, 75%), m.p. 70-73°C (lit.[42] 75°C).

Stage 2

4-Nitro-2,1,3-benzoselenadiazole

A solution of 2,1,3-benzoselenadiazole (35 g) in concentrated sulphuric acid (77 ml) was added to a mixture of nitric acid (d. 1.4, 19.1 mol) and concentrated sulphuric acid (38.5 ml), with cooling and stirring at 0-10°C. On completion of the addition, the mixture was allowed to come to room temperature and then poured on to crushed ice to give a yellow precipitate. The precipitate was filtered off, washed with water, and recrystallised from

dimethylformamide to give the product (32.5 g, 75%), m.p. 217-218°C (lit.[43] 219-221°C, from ethanol).

Stage 3

3-Nitro-1,2-phenylediamine (59)

4-Nitro-2,1,3-benzoselenadiazole (25 g, 0.11 mol) was added to hydriodic acid (d. 1.7, 275 ml) and the mixture stirred and heated at 50°C for 1.5 h. The cooled mixture was treated with sodium bisulphite solution (40% w/w, 438 ml) and basified with sodium hydroxide (30%, 394 ml). The red precipitate was filtered off and washed with water. Recrystallisation from propan-2-ol (charcoal) gave (59) (11.7 g, 70%), m.p. 157-158°C (lit.[44] 158-159°C).

3-Amino-2-nitroacetanilide

The diamine (50) (5.11 g, 0.033 mol), acetic anhydride (7.7 g, 0.075 mol) benzene (600 ml), and pyridine (10 ml) were heated together, under reflux, for 4 h. More acetic anhydride (3.0 g) was then added and heating continued for another 3 h. The solvents were then evaporated *in vacuo* , and the residue extracted with chloroform. The insoluble material was identified as 1,3-bis-acetamido-2-nitrobenzene (0.72 g, 9%), m.p. 252-255°C (lit.[41] 256-258°C), and the extract on evaporation gave 3-amino-2-nitroacetanilide (4.82 g, 74%), m.p. 113-114°C (from propan-2-ol; lit.,[41] 114-114.5°C). ν_{max} 3445, 3290, 3160 (NH and NH_2), 1690 (CO), 1540 and 1315 cm^{-1} (NO_2); δ_H 2.00 (3H, s, Me), 6.38 (2H, brs, NH_2), 6.6-6.85 (2H, m, H-4 and H-6), 7.1-7.35 (1H, 4 lines, H-5), 9.89 (1H, s, NHAc).

2-Amino-3-nitroacetanilide (60a)

The diamine (59) (5 g, 0.033 mol) was heated under reflux in a mixture of acetic anhydride (3.4 g, 0.033 mol) and benzene (300 ml) for 30 minutes. After cooling to room temperature the yellow solid was filtered off and

recrystallised from ethanol. Yield 4.61 g (72%), m.p. 158-160°C (lit.,[26] 165-167°C); ν_{max} 3435 (NH), 3325 and 3300 (NH_2), 1670 (CO), 1520 and 1325 cm^{-1} (NO_2); δ_H 2.10 (3H, s, Me), 6.67 (1H, dd, H-5), 7.08 (2H, brs, NH_2), 7.51 (1H, brd, H-6), 7.92 (1H, dd, H-4), 9.32 (1H, s, NHAc); $J_{4,5}$ = 8Hz, $J_{5,6}$ = 7.5Hz, $J_{4,6}$ = 1.5 Hz.

Cyanomethylation of the o-nitroanilines

Cyanomethylation was carried out according to the general procedure below which was based on that of Dimroth and Aurich[18]. Individual conditions and spectral details and analyses are contained in Tables 11 and 12.

The cyanomethylation procedure

Acetic acid, containing a few drops of concentrated sulphuric acid, was added to a mixture of the amine (1 mol eq), paraformaldehyde (3 mol eq), potassium cyanide (3 mol eq), and zinc chloride (see Table 11). The mixture was then stirred at the stated temperature for the stated time (see Table 11). The cooled mixture was then poured on to crushed ice, filtered and the solid product washed well with water and then recrystallised.

Bis(4-chloro-2-nitroanilino) methane (43)

4-Chloro-2-nitroaniline (8.63 g, 0.05 mol), potassium cyanide (9.75 g, 0.15 mol), paraformaldehyde (4.5 g, 0.15 mol), and anhydrous zinc chloride (25 g, 0.18 mol) were heated at 50°C for 6 h. in acetic acid (250 ml) containing concentrated sulphuric acid (four drops). The mixture was then allowed to cool to room temperature and poured on to crushed ice (1 kg).

The bright yellow precipitate was filtered off and washed well with water. The solid (3.37 g, 39%) was recrystallised from dimethylformamide m.p. 266-268°C (lit.[45] 266°C).

(Found C, 43.5; H, 2.7; N, 15.7. Calc. for $C_{13}H_{10}Cl_2N_4O_4$: C, 43.7; H, 2.8; N, 15.7%). ν_{max} 3360 cm^{-1} (NH); δ_H (T.F.A.) 4.07 (2H, s,

CH_2), 5.92 (2H, brs, 2 x NH), 7.58 (2H, d, 2 x 6-H) 7.82 (2H, dd, 2 x 5-H), and 8.39 (2H, d, 2 x 3-H); $J_{3,5}$ 2.5 Hz and $J_{5,6}$ 8.5 Hz.

1-Acetyl-2,3-dihydro-4-nitrobenzimidazole (62a) and 1-Acetyl-3-cyanomethyl-2,3-dihydro-4-nitrobenzimidazole (63a)

2-Amino-3-nitroacetanilide (2g, 0.01 mol), paraformaldehyde (0.92 g), potassium cyanide (1.99 g, 0.03 mol), and zinc chloride (5.04 g, 0.03 mol) were heated in acetic acid (50 ml) containing a few drops concentrated sulphuric acid for 7 h. at 50°C. After the usual initial work-up the solid was fractionally crystallised from acetic acid. The less soluble fraction was identified as compound (63a) (0.91 g, 43%), m.p. 244-246°C.
(Found: C, 52.1; H, 4.35; N, 19.9. $C_9H_9N_3O_3$ requires C, 52.2; H, 4.4; N, 20.3%); $M^{+\cdot}$ 207; ν_{max} 3340 br (NH), 1665 (CO), 1510 and 1325 cm^{-1} (NO_2); δ_H 2.13 (3H, s, Me), 5.60 (2H, s, ring CH_2), 6.56 (1H, dd, H-6), 7.43 (1H, dd, H-5), 7.85 (1H, dd, H-7), 8.51 (1H, brs, NH); $J_{5,6}$ 9Hz, $J_{6,7}$ 7Hz, $J_{5,7}$ 1.5 Hz.

The more soluble fraction (0.2 g, 20%), m.p. 179- 180°C (from D.M.F.) was identified as compound (62a)
(Found: C, 54.0; H, 4.1; N, 22.4. $C_{11}H_{10}N_4O_3$ requires C, 53.7; H, 4.1; N, 22.7%. $M^{+\cdot}$ 246; ν_{max} 1670 (CO), 1515 and 1335 cm^{-1} (NO_2), no C≡N observed. δ_H 2.18 (3H, s, Me), 4.53 (2H, s, CH_2CN), 5.54 (2H, s, ring CH_2), 6.98 (1H, dd, H-6), 7.60 (1H, dd, H-5), 8.10 (1H, dd, H-7); $J_{5,6}$ 9Hz, $J_{6,7}$ 7.5 Hz, $J_{5,7}$ 1.5 Hz.

Cyclisation of N-cyanomethyl-2-nitroanilines

The following general procedure was followed to obtain the cyclised products.

The nitrile (1 mol eq) was heated with anhydrous potassium carbonate (1 mol eq) in ethanol (C 50 ml/g of nitrile) for the time and at the temperature stated in Table 13 The solvent was then removed *in vacuo* to leave a water

soluble residue. The free N-oxide was then precipitated from an aqueous solution of the residue using concentrated hydrochloric acid, and recrystallised from the solvent(s) shown (Table 13)

2-Cyano-5-methoxy-1H-benzimidazole 3-oxide

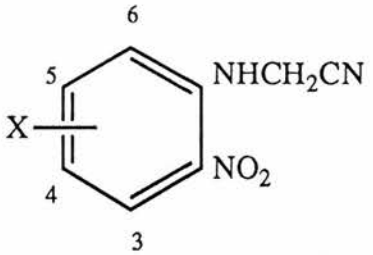
m.p. 276-277°C.

Found: C, 55.6; H, 3.7; N, 25.7. $C_{10}H_8N_3O_2$ requires C, 55.6; H, 3.7; N, 25.9%). ν_{max} 2230 cm^{-1} (CN), δ_H 3.90 (3H, s, OMe), 6.9-7.1 (2H, m, 4- and 6-H), 7.6-7.75 (1H, m 7-H), and 12.9 (1H, vbr, NH/OH).

5-Chloro-2-cyano-1H-benzimidazole 3-oxide

m.p. 216-218°C.

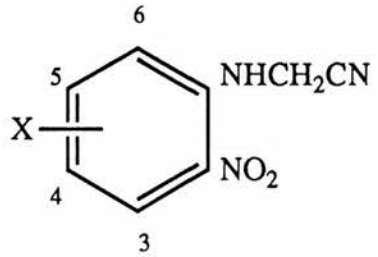
(Found: C, 49.3; H, 2.0; N, 21.5. C_8H_4ClN3O requires C, 49.6; H, 2.1; N, 21.7%). ν_{max} 2220 cm^{-1} (CN); δ_H 7.43 (1H, dd, 6-H), and 7.7-7.9 (2H, m, 4- and 7-H); $J_{4,6}$ 2.5Hz and $J_{6,7}$ 8Hz.



Compound x =	$ZnCl_2$(Mol eq w.r.t. amine)	Time (h)	Temp (°C)	m.p. (°C)	Recryst Solvent	Yield %	Analyses Found C	H	N	Formula	Required C	H	N
4-OMe	3.6	8	50	176-178	EtOH	85	52.1	4.35	20.3	$C_9H_9N_3O$	52.2	4.4	20.8
4-Cl	7.7	10	50	156-158	EtOH	72	45.3	2.8	19.9	$C_8H_6N_3ClO_2$	45.4	2.9	19.9
5-F	7.7	10	50	129-131	EtOH/H_2O	76	49.4	3.1	21.1	$C_8H_6N_3FO_3$	49.2	3.1	21.5
3-NHAc	3.6	7	50	222-224	AcOH	56	51.65	4.4	23.8	$C_{10}H_{10}N_4O_3$	51.3	4.3	23.9
* 4-Me	3.6	8	50	146-147	EtOH	75							
* H	3.6	8	50	136-138 Lit 139-140.5[18]	EtOH	76							
* 4-F	7.7	10	50	163-164	EtOH	52							

* Prepared by D. Moody

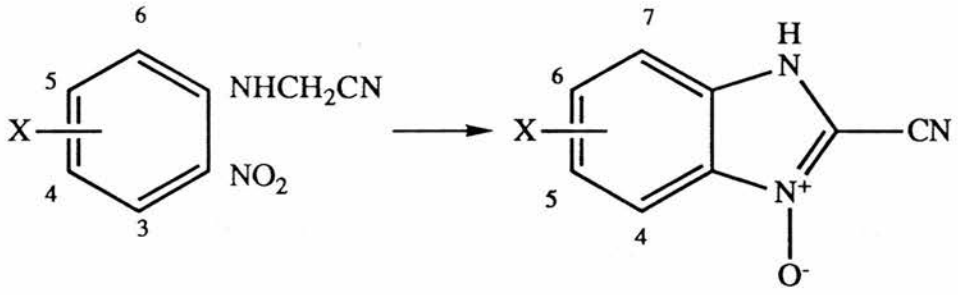
(Table 11)



Compound x =	Chemical Shifts 3-H	5-H	6-H	δ_H (p.p.m.) $-CH_2$	NH	OTHER	J/Hz		I.R. ν_{max} (cm^{-1}) NH	CN	NO_2	
4-OMe	7.63 d	7.44 dd	7.19 d	4.59 d	8.10 brt	OMe 3·82s	5,6 CH_2NH 3,5	9·0 6.5 2.5	3375	2240 w	1505 1340	
4-Cl	8.15 d	7.77 d	7.23 d	4.60 d	8.33 brt		CH_2NH 3,5 5,6	6.0 2.0 9.0	3385		1510 1335	
5-F	8.26 dd		7.04 d	4.60 d	8.47 brt	4-H 6.73 ddd	CH_2NH 3,4 4,6	6.5 9.5 2.5	3380	2245 w	1505 1340	
3-NHAc		*	*	4.38 d	*	NHAc 10.0 s 2.0s	CH_2NH	6.0	3270		1340	(CO) 1660

* Occur between 7.35 - 7.6 (unresolved multiplet)

Table 12



Compound x =	Temp (°C)	Time (h)	2-Cyanobenzimidazole-N-oxide Recryst Solvent	Yield %
4-OMe	Reflux	4.5	DMF/H2O	51
4-Cl	50	2	DMF/H2O	58
5-F	Reflux	1.5	DMF/H2O	71
3-NHAc	Reflux	1.5	MeOH	78
*H	Reflux	4	EtOH/H2O	54
*4-Me	Reflux	9	DMF/H2O	53
*4-F	Reflux	1.5	EtOH	52

(Table 13)

* Prepared by D.J. Moody

2-(4-Chloro-2-nitroanilino) acetamide

This compound was a water-insoluble by-product isolated in 23% yield from the cyclisation of the nitrile It had m.p. 211-213°C (from methanol).

(Found: C, 41.8; H, 3.5; N, 18.3. $C_8H_8ClN_3O_3$ requires C, 41.85; H, 3.5; N, 18.3%); ν_{max} 3390 and 3145 (NH), 1660 (CO) and 1505 and 1340 cm^{-1} (NO_2); δ_H 3.98 (2H, d, CH_2), 6.81 (1H, d, 6-H), 7.35 (1H, brs, amide NH), 7.60 (2H, overlapping dd and br s, 5-H and amide NH), 8.06 (1H, d, 3-H), and 8.47 (1H, brt, NH-CH_2); JCH_2NH 6Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9Hz.

2-Cyano-6-fluoro-1H-benzimidazole 3-oxide (46a)

m.p. 233-235°C (decomp) (from aqueous dimethylformamide)

(Found: C, 54.1; H, 2.3; N, 23.25. $C_8H_4FNO_3$ requires C, 54.2; H, 2.3; N, 23.7%); ν_{max} 2235 cm^{-1} (CN); δ_H 7.3-7.85 (unresolved multiplet); δ_F -117.3 p.p.m. (dt); $J_{4,F}$ 5Hz and $J_{5,F} = J_{7,F}$ 9.5Hz.

4-Acetamido-2-cyano-1H-benzimidazole 3-oxide

m.p. 220°C (decomp).

(Found: C, 57.45; H, 3.65; N, 22.3. $C_9H_7N_3O_2$ requires C, 57.1; H, 3.7; N, 22.2%); ν_{max} 3310 (NH), 2240 (CN), 1670 cm^{-1}(CO); δ_H 2.11 (3H, s, Me), 7.25-7.9 (3H, m, H-5, 6, 7), 9.70 (1H, brs, NHAc).

Benzimidazole N-oxide hydrochlorides

The general procedure to obtain the hydrochlorides was as follows:-

The cyanobenzimidazole N-oxide or benzimidazole-2-carboxylic ester N-oxide was heated under reflux with concentrated hydrochloric acid (20-25 ml per g of substrate) for 4 h. The solution was then cooled in ice which facilitated the precipitation of the hydrochloride. This was then filtered off and recrystallised.

Ethyl 5-methoxy-1H-benzimidazole-2-carboxylate 3-oxide was also hydrolysed and decarboxylated to the hydrochloride using the above method.

5-Methoxy-1H-benzimidazole 3-oxide hydrochloride

m.p. 215-216° (dec) (from ethanol).

(Found: C, 48.0; H, 4.6; N, 14.0. $C_8H_9ClN_2O_2$ requires C, 47.9; H, 4.5; N, 14.0%). δ_H 3.91 (3H, s, OMe), 7.1-7.35 (2H, m, 4- and 6-H), 7.77 (1H, d, 7-H) 9.74 (1H, s, 2-H), $J_{6,7}$ 8Hz.

5-Chloro-1H-benzimidazole 3-oxide hydrochloride

51% m.p. 224-226°C (dec) (from ethanol).

(Found: C, 41.2; H, 2.9; N, 13.6. $C_7H_6Cl_2N_2O$ requires C, 41.0; H, 2.9; N, 13.7%), δ_H 7.63 (1H, dd, H-6), 7.9 (1H, d, H-7), 7.96 (1H, d, H-4), 9.81 (1H, s, H-2). $J_{6,7}$ 9 Hz, $J_{4,6}$ 2Hz.

5-Fluoro-1H-benzimidazole 3-oxide hydrochloride (47b)

m.p. 240-242°C (decomp). Yield 88% (from 5-fluoro-2-cyano-1H-benzimidazole 3-oxide, synthesis by D. Moody)[13]. Recrystallised from concentrated hydrochloric acid.

(Found: C, 44.3; H, 3.1, N, 14.7. $C_7H_6ClFN_2O$ requires C, 44.6; H, 3.2; N, 14.85%). δ_H 7.46 (1H, dt, H-6), 7.73 (1H, dd, H-4), 7.88 (1H, dd, H-7), 9.85 (1H, s, H-2). δ_F -114.0 $J_{6,7}$ 9 Hz, $J_{4,6}$ 2 Hz, $J_{4,F}$ 8.4 Hz, $J_{6,F}$ 9Hz, $J_{7,F}$ 4.4Hz.

6-Fluoro-1H-benzimidazole 3-oxide hydrochloride (47a)

m.p. 194-196°C (from c.HCl) yield 79% from (46a),

(Found: C, 44.8; H, 3.2; H, 15.0. $C_7H_6ClFN_2O$ requires C, 44.6; H, 3.2; N, 14.85%). δ_H 7.50 (1H, dt, H-5), 7.73 (1H, ddd, H-7), 7.90 (1H, ddd, H-4) 9.78 (1H, s, H-2). δ_F -114.4, $J_{4,5}$ 9.2 Hz, $J_{5,7}$ 2.4 Hz, $J_{4,7}$ 0.6 Hz, $J_{5,F} = J_{7,F}$ 9.3 Hz, $J_{4,F}$ 6.7 Hz.

4-Amino-1H-benzimidazole 3-oxide dihydrochloride (56)

78% from 4-acetamido-2-cyano-1H-benzimidazole 3-oxide, m.p. 190-192°C (decomp) (from c.HCl).

(Found: C, 38.2; H, 4.1, N, 19.1. $C_7H_7N_3O.2HCl$ requires C, 37.9; H, 4.1; N, 18.9%). δ_H 7.00 and 7.18 (2H, 8 lines, H-5 and H-7), 7.46 (1H, t, H-6), 8.60 (broad, NHs and OH), 9.85 (1H, s, H-2).

Benzimidazole N-oxides

The following general procedure was followed to give the N-oxides from their hydrochlorides.

The hydrochloride was dissolved in ammonia (d 0.88; 40 ml per g) and the solution concentrated by evaporation under reduced pressure at 50°C until solid began to be deposited. The mixture was then cooled and the N-oxide collected by filtration and recrystallised.

5-Fluoro-1H-benzimidazole 3-oxide (48b)

Yield 57% m.p. 227-229°C (from water).

(Found: C, 55.1; H, 3.2; N, 18.5. $C_7H_5FN_2O$ requires C, 55.3; H, 3.3; N, 18.4%). δ_H 7.03 (1H, ddd, 6-H), 7.30 (1H, dd, 4-H), 7.65 (1H, dd, 7-H), 8.38 (1H, s, 2-H); δ_F -118.7, $J_{6,7}$ 9 Hz, $J_{4,6}$ 2.6 Hz, $J_{6,7}$ 10 Hz, $J_{4,F}$ 8.6 Hz, $J_{7,F}$ 4.9 Hz.

6-Fluoro-1H-benzimidazole 3-oxide (48a)

Yield 64% m.p. 229-231°C (dec) (from water).

(Found: C, 55.2; H, 3.0; N, 18.5. $C_7H_5FN_2O$ requires C, 55.3; H, 3.3; N, 18.4%). δ_H 7.14 (1H, ddd, 5-H), 7.43 (1H, dd, 7-H), 7.41 (1H, dd, 4-H), 8.41 (1H, s,2-H); δ_F -121.6. $J_{4,5}$ 8.8 Hz, $J_{5,7}$ 2.4 Hz, $J_{5,F}$ 9.7 Hz, $J_{7,F}$ 9.7 Hz, $J_{4,7}$ 5.9 Hz.

5-Methoxy-1H-benzimidazole 3-oxide

Yield 75% m.p. 176-177°C (from ethanol).

(Found: C, 58.1; H, 5.0; N, 17.2. $C_8H_8N_2O_2$ requires C, 58.5; H, 4.9; N, 17.1%). δ_H 3.80 (3H, s, Me), 6.80 (1H, dd, 6-H), 6.96 (1H, d, 4-H), 7.50 (1H, d, 7-H), 8.20 (1H, s, 2-H). $J_{6,7}$ 8.5 Hz, $J_{4,6}$ 2Hz.

5-Chloro-1H-benzimidazole 3-oxide

Yield 76% m.p. 224-226°C (from water).

(Found: C, 49.5; H, 2.9; N, 16.3; $C_7H_5ClN_2$ requires C, 49.9; H, 3.0; N, 16.6%). δ_H 7.21 (1H, dd, 6-H), 7.55 (1H, d, 4-H), 7.65 (1H, d, 7-H), 8.42 (1H, s, 2-H). $J_{6,7}$ 8.5 Hz, $J_{4,6}$ 2Hz.

4-Amino-1H-benzimidazole 3-oxide (57)

The dihydrochloride (0.3 gm.) was added in portions to ammonia (d 0.88; 6 ml per g) at 0°C with stirring, which was then continued for half an hour after the last addition of the solid. The solution was then evaporated under reduced pressure at 50°C, the residue triturated with a little ice-water, and the N-oxide collected by filtration (0.1 g, 44%).

This was found to be spectroscopically identical to the N-oxide prepared by McFarlane by catalytic hydrogenation[23] of 4-nitro-1H-benzimidazole-3-oxide.

N-(4-Methoxy-2-nitrophenyl) glycine

N-Cyanomethyl-4-methoxy-2-nitroaniline (4.3 g, 0.02 mol) was dissolved in acetic acid (100 ml) at 80°C. To the stirred suspension was added aqueous sulphuric acid (50% v/v; 240 ml). The resultant solution was then stirred at 80°C for 5 h. After cooling the solution was poured on to crushed ice and the crude product was collected by filtration and washed with water.

Yield 2.17 g (45%), m.p. 188-190°C (from ethanol).

(Found: C, 47.8; H, 4.4; N, 12.3. $C_9H_{10}N_2O_5$ requires C, 47.8; H, 4.5; N, 12.4%). ν_{max} 3345 (NH) and 1720 cm^{-1} (CO); δ_H 3.75 (3H, s, OMe) 4.14 (2H, d, CH_2), 6.89 (1H, d, 6-H), 7.27 (1H, dd, 5-H), 7.51 (1H, d, 3-H), and 8.20 (1H, brt, NH); J_{CH_2NH} 5Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9 Hz.

N-(4-Methoxy-2-nitrophenyl) glycine ethyl ester

N-(4-Methoxy-2-nitrophenyl) glycine (1.96 g, 0.008 mol) was dissolved in ethanol (100 ml) and hydrogen chloride (3% by wt w.r.t the alcohol) was added at room temperature. The solution was then heated under reflux for 5 h. After cooling to room temperature the solvent was evaporated at reduced pressure. The crude solid product remaining was then recrystallised from ethanol.

Yield 1.93 g (87%), m.p. 76-78°C.

(Found: C, 52.1; H, 5.55; N, 11.0. $C_{11}H_{14}N_2O_5$ requires C, 52.0; H, 5.55; N, 11.0%). ν_{max} 3345 (NH), 1730 (CO), and 1510 and 1345 cm^{-1} (NO_2). δ_H 1.32 (3H, t, $MeCH_2$), 3.81 (3H, s, OMe), 4.09 (2H, s, CH_2NH), 4.30 (2H, q, CH_2Me), 6.68 (1H, d, 6-H), 7.17 (1H, dd, 5-H), and 7.68 (1H, d, 3-H); J_{MeCH_2} 7 Hz, $J_{3,5}$ 2.5 Hz, and $J_{5,6}$ 9Hz.

Ethyl 5-methoxy-1H-benzimidazole-2-carboxylate 3-oxide

N-(4-Methoxy-2-nitrophenyl) glycine ethyl ester (1.49, 0.006 mol) was added to a mixture of ethanol (54 ml) and dimethylformamide (3 ml) and the solution cooled to 0°C. A solution of sodium ethoxide (0.138 g, 0.006 mol sodium in ethanol, 12 ml) was then added dropwise, the temperature throughout being kept below 5°C. After completion of the addition, the resultant suspension was allowed to warm to room temperature and was stirred for a further 2 h. The solvent was removed under reduced pressure and the residue dissolved in the minimum amount of water; acidification of

this solution with concentrated hydrochloric acid precipitated the N-oxide which was collected by filtration.

Yield 0.94 g (68%), m.p. 98-99°C (DMF/H_2O).

(Found: C, 51.7; H, 5.5, N, 11.0. $C_{11}H_{12}N_2O_4.H_2O$ requires C, 52.0; H, 5.55; H, 11.0%). ν_{max} 1700 cm^{-1} (CO); δ_H 1.35 (3H, t, $MeCH_2$), 3.85 (3H, s, OMe), 4.39 (2H, q, CH_2Me), 6.8-7.0 (2H, m, 4- and 6-H), and 7.65 (1H, m, 7-H); J_{MeCH_2} 7 Hz.

N-(6-Acetamido-2-nitrophenyl)glycine Ethyl Ester (81)

2,3-Dinitroacetanilide (7 g, 0.031 mol), glycine ethyl ester hydrochloride (3.92 g, 0.028 mol), sodium bicarbonate (4.76 g, 0.056 mol), and dimethyl sulphoxide (120 ml) were heated, with stirring, for 1.5 h. at 60° C. A further portion of glycine ethyl ester hydrochloride (3.92 g) was then added, and heating continued for 2.5 h. Two further portions of hydrochloride (each 3.92 g) were then added at 2 h. intervals. After a total reaction time of 8.5 h. the mixture was poured on to ice and the product collected by filtration.

Yield 5.0 g. (57%), m.p. 118-119°C (from ethanol).

(Found: C, 51.35; H, 5.3; N, 15.0. $C_{12}H_{15}N_3O_5$ requires C, 51.2; H, 5.4; N, 14.9%). ν_{max} 3355, 3220 (NH), 1740 (ester CO), 1650 (amido CO), and 1540, 1340 cm^{-1} (NO_2). δ_H 1.16 (3H, t, $MeCH_2$), 2.08 (3H, s, MeCO), 4.10 (4H, overlapping d and q, 2 x CH_2), 6.92 (1H, t, H-4), 7.35 (1H, brt, $NHCH_2$), 7.57 and 7.91 (2H, H-3 and H-5), 9.55 (1H brs, NHAc); $J_{CH_3CH_2}$ 7 Hz, $J_{3,4} = J_{4,5} = 8$ Hz.

Ethyl 7-acetamido-1H-benzimidazole-2-carboxylate 3-oxide

The nitro-ester (81) (4.53 g, 0.016 mol), potassium carbonate (2.26 g, 0.016 mol), and ethanol (170 ml) were refluxed together for 2 h. The solvent was then removed by evaporation under reduced pressure and the residue extracted with water. Acidification (c.HCl) of the extract gave the

product (1.83 g, 43%), m.p. 98-99°C (from aqueous ethanol). The product had a great affinity for water and as a result required prolonged drying.

(Found: C, 54.5; H, 5.0; N, 15.9. $C_{12}H_{13}N_3O_4$ requires C, 54.75; H, 5.0; N, 16.0%). ν_{max} 3340 (NH), 1730 (ester CO), 1665 cm^{-1} (amido CO). δ_H (3H, t, $MeCH_2$), 2.27 (3H, s, MeCO), 4.47 (2H, q, CH_2Me), 7.2-7.55 (2H, m, H-4 and H-5), 8.07 (1H, 4 lines, H-5); $J_{CH_3CH_2}$ 7 Hz.

7-Amino-1H-benzimidazole 3-oxide dihydrochloride

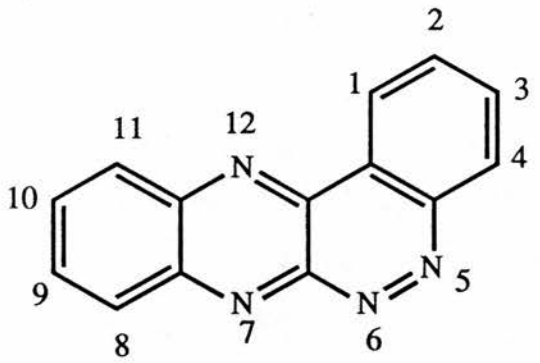
The acetamido-N-oxide ester (2g) was heated under reflux with concentrated hydrochloric acid (20 ml) for 4 h. The solution was then concentrated under reduced pressure and the brown residue recrystallised from concentrated hydrochloric acid (with charcoal), giving the dihydrochloride (1.15 g, 68%) m.p. 224-226°C.

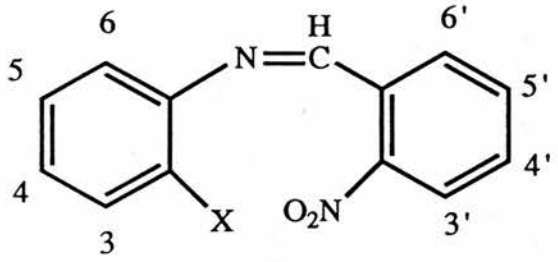
(Found: C, 38.0; H, 4.1; N, 18.95. $C_7H_7N_3O.2HCl$ requires C, 37.9; H, 4.1; N, 18.9%). δ_H 6.75-7.15 (2H, m), 7.37 (1H, approx. t), 9.50 br (NHs and OH) 9.79 (1H, s, H-2)

The dihydrochloride (0.2 g) was then reacted with ammonia under the same conditions for the dihydrochloride (56) to give 7 amino-1H-benzimidazole 3-oxide (58) yield 0.091 g, (61%), m.p. 118-120°C (from water).

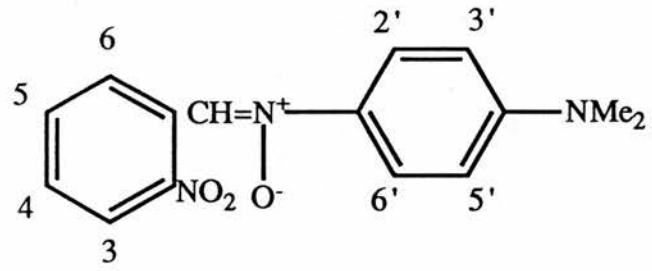
(Found: C, 50.5; H, 5.4; N, 25.2. $C_7H_7N_3O.H_2O$ requires C, 50.3; H, 5.4; N, 25.1%). ν_{max} 3500 sh, 3400, 3310, 3210 sh, 3115, 3075 cm^{-1} (NH and OH). δ_H 5.70 (broad, NH's and H_2O) 6.42 and 6.70 (2H, 2 x brd, H-4 and H-6), 7.01 (1H, t, H-5) 8.17 (1H, s, H-2).

The following compound types are numbered thus:-





X = NH_2 or NHAc



4-Methyl-3-nitroacetanilide

4-Methyl-3-nitroaniline (15.2 g, 0.1 mol) in acetic acid (55 ml) was heated under reflux for 3 h. The dark brown solution was then cooled to room temperature and poured on to ice. The precipitate was collected, washed with water and recrystallised from aqueous ethanol to give

4-methyl-3-nitroacetanilide (12.4 g, 64%), m.p. 143-144°C (lit.,[55] 144.5°C).

4-Methyl-2,3-dinitroacetanilide

4-Methyl-3-nitroacetanilide (30.0 g, 0.15 mol) was added portionwise to stirred fuming nitric acid (d: 1.5, 120 ml) in such a way as to maintain the temperature below 20°C. On completing the addition the solution was stirred at 20°C for 45 min, and then poured into water (1000 ml) with stirring and cooling. The lemon precipitate was immediately collected by filtration and washed well with water. The solid after recrystallisation from acetic acid (twice) gave the product as off-white needles (20.0 g, 54%), m.p. 172°C (lit.,[56] 174.5°C).

4-Methyl-2,3-dinitroaniline

4-Methyl-2,3-dinitroacetanilide (35.4 g, 0.15 mol) was added to a stirred mixture of sulphuric acid (131 ml) and water (262 ml) at room temperature. The suspension was then heated at 120°C for 2 h. After cooling the mixture in ice the solid orange product was collected and recrystallised from ethanol to give 27.7 g (96%) of 4-methyl-2,3-dinitroaniline as orange prisms, m.p. 123-124°C (lit.,[57] 124°C).

3-Chloro-2-nitrotoluene

A stirred mixture of 4-methyl-2,3-dinitroaniline (27.7 g, 0.15 mol), ethanol (200 ml) and hydrochloric acid (200 ml) was cooled to -5°C and to this was added, dropwise a solution of sodium nitrite (22.5 g, 0.33 mol) in water (30 ml), the temperature throughout was kept below 0°C. Once all the sodium nitrite was added the mixture was slowly heated to 70° C and held there for 30 min. The solution was then steam distilled and the pale yellow oil that distilled over was extracted into ether. The organic layer was separated, washed with 1M sodium hydroxide and then water, dried over

anhydrous calcium chloride and the solvent evaporated to obtain the product (13.0 g, 50%) as a yellow oil.

3-Chloro-2-nitrobenzyl bromide

3-Chloro-2-nitrotoluene (13.0 g, 0.076 mol), N-bromosuccinimide (13.5, 0.07 mol) and benzoyl peroxide (0.2 g), in carbon tetrachloride (25 ml) was heated at 80°C under u.v. light for 30 h. During this time a further two portions of benzoyl peroxide (0.2 g) after 8 h and 20 h were added to the reaction mixture.

After cooling to room temperature the mixture was filtered and the solid collected and washed with carbon tetrachloride. Both the washings and the initial filtrate were combined and evaporated under reduced pressure to leave the product as a pale brown oil. The product was then used directly to form the pyridinium salt.

1-(3-Chloro-2-nitrobenzyl)pyridinium bromide

The unpurified benzyl bromide was cooled to 0°C and stirred while a mixture of dry pyridine (5.0 ml, 0.063 mol) and dry ethanol (5 ml) was slowly added. The solution was then allowed to stir at room temperature for 1 h and then chilled in ice for 4 hours. The precipitated salt was collected by filtration and recrystallisation from ethanol gave the product (5.71 g, 46%), m.p. 201-203°C (lit.,[58] 205°C).

3-Chloro-2-nitrophenyl-N-(p-dimethylaminophenyl)nitrone

To a stirred solution at 0°C of 1-(3-chloro-2-nitrobenzyl)pyridinium bromide (5.71 g, 0.023 mol) and freshly prepared[59] N,N-dimethyl-p-nitrosoaniline (3.44 g, 0.023 mol) in ethanol (85 ml) was added dropwise 1M sodium hydroxide (50 ml); the temperature was kept below 2°C during the addition. After stirring at room temperature for 4 h the mixture was diluted with water (40 ml) and chilled in ice. The brown product was collected by filtration and washed with water.

Yield 3.2 g (58%), m.p. 178-179°C (from acetone).

(Found: C, 56.1; H, 4.0; N, 13.5. $C_{15}H_{14}ClN_3O_3$ requires C, 56.35; H, 4.4; N, 13.1%); δ_H 3.05 (6H, s, 2 x Me), 6.62 (2H, d, H-3' and H-5'), 7.44-7.61 (5H, m, H-2', H-6', H-6, H-5 and H-4), 7.72 (1H, s, CH=N).

3-Chloro-2-nitrobenzaldehyde

3-Chloro-2-nitrophenyl-N-(p-dimethylaminophenyl)nitrone (4.0 g, 0.0125 mol) was added, with stirring, to 3M sulphuric acid (70 ml) at room temperature for 1.5 h. The mixture was then heated at 50°C and held at this temperature for 50 minutes before finally being heated to 100°C for 5 min. After cooling, the solution was extracted three times with chloroform and the organic layer separated and washed with water, dried over anhydrous sodium sulphate and the solvent removed to obtain the crude aldehyde as a pale brown oil (2.12 g, 99%). No further purification was attempted but the spectral evidence, i.e. ^1H n.m.r. and i.r. obtained indicated the product had been made, and so the crude material was used for the next stage.

N-(3-Chloro-2-nitrobenzylidene)-o-phenylenediamine

The crude 3-chloro-2-nitrobenzaldehyde (2.13 g, 0.0124 mol) and o-phenylenediamine (1.29 g, 0.0124 mol) were both dissolved separately in the minimum volume of ethanol. The two solutions were then combined and a few crystals of toluene-p-sulphonic acid added. The mixture was then heated under reflux for 15 min, and after cooling to room temperature the solvent was removed under reduced pressure, thus giving the product as an orange solid. This was then collected on a filter funnel and washed with water.

Yield 3.03 g (87%), m.p. 194-196°C (from propan-2-ol).

(Found: C, 56.6; H, 3.4; N, 15.2. $C_{13}H_{10}ClN_3O_3$ requires C, 56.6; H, 3.65; N, 15.2%). υ_{max} 3420 and 3330 (NH_2), 1530 and 1330 cm^{-1}(NO_2); δ_H 4.2 (2H, brs, NH_2), 6.6-6.8 (4H, m, H-3, H-4, H-5 and H-6), 6.95-7.13

(1H, m, H-4'), 7.41-7.58 (1H, m, H-5'), 7.73 (1H, d, H-6'), 8.37 (1H, s, CH=N); $J_{5',6'}$ 7.2 Hz and $J_{4',6'}$ 1.8 Hz.

4-Chloroquinoxalino[2,3-c]cinnoline

Methanol (120 ml) was heated under reflux in an atmosphere of nitrogen gas for 45 min. To the degassed methanol was added N-(3-chloro-2-nitrobenzylidene)-o-phenylenediamine (2.5 g, 0.009 mol) and potassium cyanide (1.2 g, 0.018 mol) and the resultant solution was heated under reflux in an atmosphere of nitrogen for 4 h. The reaction mixture was then chilled in ice and the orange product was collected by filtration and washed with water.

Yield 1.20 g (50%), m.p. 323-325°C (from DMF).

(Found: C, 62.9; H, 2.3; N, 20.9. $C_{14}H_7ClN_4$ requires C, 63.05; H, 2.65; N, 21.0%); δ_H 8.03 (1H, t, H-2), 8.10 (2H, 2 x 8 lines, H-9 and H-10), 8.18 (1H, dd, H-3) 8.44 (1H, m, H-11), 8.61 (1H, m, H-8), 9.26 (1H, dd, H-1); $J_{1,3}$ 1.3 Hz., $J_{2,3}$ 7.7 Hz, $J_{8,9}$ 8.5 Hz, $J_{8,10} = J_{9,11}$ 1.8 Hz, and $J_{10,11}$ = 8.0 Hz.

Reaction of 4-Chloroquinoxalino[2,3-c]cinnoline with sodium methoxide

Sodium metal (0.1 g, 0.004 mol) was dissolved in methanol (50 ml) at room temperature. To the resultant solution was added 4-chloroquinoxalino[2,3-c]cinnoline (0.5 g, 0.0019 mol) and the suspension heated under reflux for 12 h. After cooling to room temperature the solvent was then removed under reduced pressure and the residue was collected on a sinter funnel, washed with water and dried. The solid 4.2 g (84%) was on characterisation found to be unchanged starting material.

6-Bromo-2-nitrotoluene

2-Methyl-3-nitroaniline (5 g 0.033 mol) was heated under reflux with a mixture of water (40 ml) and hydrobromic acid (48%; 16 ml). The solution

was then cooled to 0°C and stirred while a solution of sodium nitrite (2.3 g 0.033 mol) in water (12 ml) was added dropwise, the temperature throughout kept at 3-5°C. The solution was then allowed to warm to room temperature and a solution of copper(I) bromide (5.1 g, 0.033 mol) in hydrobromic acid (11 ml) and water (26 ml) was added with caution. After being heated on a steam bath, the mixture was steam distilled, and the product extracted from the distillate with ether. Removal of the solvent yielded the product as a pale cream solid (5.31 g, 75%), m.p. 35-37°C (lit[46] 42°C).

6-Bromo-2-nitrobenzyl bromide

6-Bromo-2-nitrotoluene (5.31 g, 0.025 mol),N-bromosuccinimide (4.39 g, 0.025 mol), benzoyl peroxide (1.24 g, 0.005 mol), and carbon tetrachloride (400 ml) were heated together under reflux for 4 h. The mixture was then cooled to room temperature and filtered and the filtrate evaporated to give the product as an orange oil. No attempt was made to purify the product which was used directly to form the pyridinium salt.

N-(6-Bromo-2-nitrobenzyl)pyridinium bromide

The unpurified benzyl bromide was cooled to 0°C. Dry pyridine (3.03 ml, 0.038 mol) in dry ethanol (4 ml) was added and the solution was left overnight at room temperature.

The resultant solid was filtered off and washed with ether. The salt (6.3 g, 64%), had m.p. 204-206°C (lit.,[47] 210°C).

6-Bromo-2-nitrophenyl-N-(p-dimethylaminophenyl)nitrone

A solution of 1-(6-bromo-2-nitrobenzyl)pyridinium bromide (3.0 g, 0.008 mol) and N,N-dimethyl-p-nitrosoaniline (1.5 g, 0.008 mol) in ethanol (37 ml) was cooled to 0°C and 1M sodium hydroxide (23 ml) added with stirring, the temperature being kept below 2°C during the addition. After stirring at room temperature for 3 h the solution was diluted with water (50 ml), then cooled in ice, and the solid filtered off and washed with water.

Recrystallisation from ethyl acetate gave the product as red needles (2.24 g, 76%) m.p. 160-162°C (lit.,[47] 162°C).

6-Bromo-2-nitrobenzaldehyde (96)

6-Bromo-2-nitrophenyl-N-(p-dimethylaminophenyl)nitrone (22.12 g, 0.06 mol) was added in small portions to 3M sulphuric acid (335 ml) with stirring at room temperature. Stirring was continued for 30 minutes after the final addition. Cooling in ice and filtration gave the product as pale cream needles with recrystallisation from ethanol (12.5 g, 89%), m.p. 81-82°C (lit.,[47] 82°C).

N-(6-Bromo-2-nitrobenzylidene)-o-phenylenediamine (97)

6-Bromo-2-nitrobenzaldehyde (0.5 g, 0.002 mol) and o-phenylenediamine (0.24 g, 0.002 mol) were added to ethanol (8 ml) along with a few crystals of toluene-p-sulphonic acid. After heating on a steam bath for 10 min., the solution was allowed to cool and the solvent evaporated to obtain the product as an orange solid (0.24 g, 60%) m.p. 101-103°C (from ethanol).

(Found: C, 48.5; H, 3.1; N, 12.9. $C_{13}H_{10}BrN_3O_3$ requires C, 48.8; H, 3.15; N, 13.1%, υ_{max} 3460 and 3380 (NH_2), 1510 and 1330 cm^{-1} (NO_2); δ_H 3.85 (2H, brs, NH_2), 6.57-6.80 (2H,m, H-5 and H-6), 6.97-7.17 (2H, symm. m, H-3 and H-4), 7.40 (1H, t, H-4'), 7.60 (1H, dd, H-5'), 7.80 (1H, dd, H-3'), 8.75 (1H, s, CH=N); $J_{3',4'}$, 8.0 Hz, $J_{3',5'}$, 2 0 Hz and $J_{4',5'}$ 8.2 Hz.

1-Bromoquinoxalino[2,3-c]cinnoline (95)

N-(6-Bromo-2-nitrobenzylidene)-o-phenylenediamine (1.6 g, 0.005 mol) and potassium cyanide (0.65 g, 0.01 mol) in methanol (100 ml) were heated under reflux for 4 h. The reaction mixture was then cooled in ice and the orange precipitate filtered off and washed with water. The product (1.0 g, 64%) had m.p. 237-238°C (from DMF).

(Found: C, 54.1; H, 2.2; N, 18.1. $C_{14}H_7BrN_4$ requires C, 54.0; H, 2.3; N, 18.0%); δ_H 7.87 (1H, t, H-3), 8.15 (2H, m, H-9 and H-10), 8.29 (1H, d, H-2), 8.39 (1H, m, H-11), 8.50 (1H, m, H-8), 8.84 (1H, dd, H-4); $J_{2,3}$ and $J_{3,4}$ = 6 Hz, $J_{2,4}$ = 2 Hz.

Reaction of 1-Bromoquinoxalino[2,3-c]cinnoline with hydrogen chloride gas.

1-Bromoquinoxalino[2,3-c]cinnoline (0.3 g 0.003 mol) was dissolved in chloroform to produce an orange solution into which hydrogen chloride gas was passed for 15 minutes. On filtration a blue solid was obtained which was shaken with a mixture of 5M sodium hydroxide and chloroform. The organic layer was separated and dried over anhydrous sodium sulphate.

Evaporation of the solvent gave the product as an orange solid (0.1 g, 30%) that was identified as 1-bromo-10-chloroquinoxalino[2,3-c]cinnoline by comparison with an authentic sample (see page 131).

2-Iodo-6-nitrotoluene (104)

2-Methyl-3-nitroaniline (3.0 g, 0.002 mol) was heated under reflux for 1 h with water (25 ml) while hydrobromic acid (40%) (9.6 ml) was added carefully. The resultant pale yellow solution was cooled to c. 0°C and a solution of sodium nitrite (1.38 g, 0.02 mol) in water (8 ml) was added dropwise at such a rate that the temperature remained around 2°C. The pale brown solution was then added to a stirred solution of potassium iodide (19.7 g, 0.118 mol) in water (25 ml) at room temperature. Finally the mixture was heated for 2.5 h on a steambath. The solution was then steam distilled and the product extracted from the distillate with methylene chloride. The methylene chloride was washed with saturated sodium bisulphite solution then with water, dried (Na_2SO_4) and evaporated; the product (3.21 g, 62%) was recovered as a pale cream solid and was recrystallised from ethanol. M.p. 38-39°C (lit.,[48] 34-36°C).

3-Chloroacetanilide

3-Chloroaniline (29.9 g, 0.23 mol) and acetic anhydride (50 ml, 0.49 mol) were heated under reflux for 2 h. The pale yellow solution was cooled to room temperature and poured on to crushed ice (400 g). This precipitated the product as a white solid (39.13 g, 98%) which was then collected by filtration, washed with water and dried. The solid was checked for purity by N.M.R. and I.R. spectroscopy and then used without further purification for the nitration.

5-Chloro-2-nitroacetanilide

3-Chloroacetanilide (39 g, 0.23 mol) was dissolved in a mixture of acetic anhydride (46 g) and acetic acid (20.7 g). This solution was then cooled to 0° C and stirred while a mixture of acetic acid (20.7 g) and fuming nitric acid (d 1.52 : 23 g) was added dropwise. During the additions the temperature was maintained between 0-5°C. The solution was then left at room temperature overnight.

Pouring the solution on to crushed ice (700 g) precipitated the nitration products which were filtered off and washed well with water. The orange solid was then extracted with benzene (400 ml) and the brown filtrate evaporated to give crude 5-chloro-2-nitroacetanilide. Recrystallisation from ethanol produced the product as pale cream needles (27 g, 55%), m.p. 117-118° C (lit.,[49] 118°C). The residual solid, after recrystallisation from ethanol, gave 3-chloro-4-nitroacetanilide (9.8 g, 20%) as brown needles. M.p. 144-145°C (lit.,[49] 145°C).

2-Amino-5-chloroacetanilide (101)

Using the same method as described for 2-amino-4-chloroacetanilide, (page 130) 5-chloro-2-nitroacetanilide (19 g, 0.089 mol) was reduced with iron powder and acetic acid to give, after recrystallisation from water,

2-amino-5-chloroacetanilide as pale cream needles (8.9 g, 55%), m.p. 143°C (lit.,[50] 130-132°C).

2-Acetamido-4-chloro-N-(6-bromo-2nitrobenzylidene)aniline (103)

Using the method described for the preparation of (102), 2-amino-5-chloroacetanilide (1.32 g, 0.007 mol) and 6-bromo-2-nitrobenzaldehyde (1.64 g, 0.007 mol) gave the product (2.14 g, 75%), m.p. 219-220° C (from butanone).

(Found: C, 45.4; H, 2.7; N, 10.04. $C_{15}H_{11}BrClN_3O_3$ requires C, 45.4; H, 2.8; N, 10.6%), υ_{max} 3380 (NH), 1700 (CO), 1520 and 1360 cm^{-1} (NO_2); δ_H (DMSO-d_6) 2.14 (3H, s, Me), 7.23 (1H, dd, H-5), 7.93 (1H, d, H-6), 7.70 (1H, t, H-4'), 8.10 (1H, d, H-5') 8.13 (1H, dd, H-3')* , 8.29 (1H, d, H-3), 8.73 (1H, brs, NHAc) and 8.91 (1H, s, CH=N); $J_{4,5}$, = $J_{3,4}$, 8.1 Hz, $J_{5,6}$ 8.5 Hz and $J_{3,5}$ 2.4 Hz.

* Not first-order

1-Bromo-9-chloroquinoxalino[2,3-c]cinnoline (98)

The anil (103) (2.21 g, 0.006 mol) and potassium cyanide (0.78 g, 0.012 mol) were heated under reflux in methanol (100 ml) for 5 h. The reaction mixture was then cooled in ice and the orange product filtered off and washed with water; yield 0.70 g (37%), m.p. 277°C (from DMF).

(Found: C, 48.9; H, 1.7; N, 16.0. $C_{14}H_6BrClN_4$ requires C, 48.7; H, 1.75; N, 16.2%); δ_H 7.94 - H-8.0 (2H,m,H-3 and H-10), 8.37-8.55 (3H,m,H-2, H-8 and H-11), 8.95 (1H, d, H-4); $J_{3,4}$ 7.7 Hz.

4-Chloro-2-nitroacetanilide

4-Chloro-2-nitroaniline (10 g, 0.058 mol) was added to acetic acid (15 ml). The suspension was stirred at room temperature while acetic anhydride (15 ml) was added dropwise. The solution was then heated at 100°C for 1 h then cooled to room temperature and poured on to crushed ice.

The resultant precipitate was filtered off, washed with water, and recrystallised from ethanol which gave the product (10.41 g, 80%) as bright yellow needles, m.p. 102°C (lit.,[51] 103°C).

2-Amino-4-chloroacetanilide (100)

Water (120 ml) was kept at 80°C while iron powder (15.3 g, 0.28 mol) was added along with acetic acid (2.6 ml). To the stirred mixture was added 4-chloro-2-nitroacetanilide (13.9 g, 0.065 mol) in portions over 15 minutes. After the completion of the additions the mixture was then stirred for 10 minutes and the calcium carbonate (4.15 g) added to render the solution neutral. The mixture was then stirred for 10 minutes and then filtered hot through 'Hyflo' celite.

The solid filter cake was washed with boiling ethanol, and the ethanol then evaporated to leave the solid product. This recrystallised from water as pale cream needles (6.95 g, 53%) m.p. 144°C (lit.,[52] 144°C).

2-Acetamido-5-chloro-N-(6-bromo-2-nitrobenzylidene)aniline (102)

2-Amino-4-chloroacetanilide (1.32 g, 0.007 mol) and 6-bromo-2-nitrobenzaldehyde (1.64 g, 0.007 mol) were mixed together in ethanol (25 ml) with a few crystals of toluene-p-sulphonic acid. The mixture was heated for 15 minutes on a steam bath and then left to cool. The product, a bright yellow precipitate, was then filtered off and recrystallised from ethanol giving small yellow needles (2.21 g, 77%), m.p. 214°C.

(Found: C, 45.4; H, 2.7; N, 10.6. $C_{15}H_{11}BrClN_3O_3$ requires C, 45.4; H, 2.8; N, 10.6;), υ_{max} 3300 (NH),1690(CO), 1510 and 1300 $cm^{-1}(NO_2)$; δ_H(DMSO-d_6) 2.11 (3H, s, Me), 7.37 (1H, dd, H-4), 7.40 (1H, d, H-6), 7.71 (1H, t, H-4'), 8.07 (1H, d, H-3), 8.12-8.20 (2H, m, H-3' and H-5'), 8.71 (1H, brs, NHAc), 8.95 (1H, s, CH=N); $J_{4,5} = J_{3,4}$, 8.5 Hz and $J_{3,4}$ 7.5 Hz.

1-Bromo-10-chloroquinoxalino[2,3-c]cinnoline (99)

Using the same procedure as for the cyclisation of the anil(103) the anil (102) (2.14 g, 0.005 mol) and potassium cyanide (0.7 g, 0.012 mol) in methanol (80 ml) gave the product (0.94 g, 50%), m.p. 288-289°C (from DMF).

(Found: C, 48.2, H, 1.6; N, 16.1. $C_{14}H_6BrClN_4$ requires C, 48.7; H, 1.75; N, 16.2%); δ_H 7.94-7.98 (2H, m, H-3 and H-9), 8.37 (1H, dd, H-2), 8.47-8.49 (2H, m, H-8 and H-11) and 8.93 (1H, dd, H-4); $J_{3,4} = J_{2,3}$ 8 Hz, $J_{2,4}$ 1.2 Hz.

The following syntheses [(i)-(v)] were carried out in association with Mr. R. Wong and Miss L. Dunbar

(i) **2-Acetamido-4-chloro-N-(6-chloro-2-nitrobenzylidene) aniline**

To ethanol (15 ml) was added 2-amino-5-chloroacetanilide (0.42 g, 0.002 mol) and 6-chloro-2-nitrobenzaldehyde (0.4 g, 0.002 mol) and a few crystals of toluene-p-sulphonic acid. The mixture was then heated on a water bath for 10 minutes and after cooling the precipitate was collected by filtration.

Yield 0.61 g (76%), m.p. 221-223°C (from ethanol).

(Found: C, 51.0; H, 3.1; N, 11.8. $C_{15}H_{11}Cl_2N_3O_3$ requires C, 51.2; H, 3.15; N, 11.9%); υ_{max} 3370 (N-H), 1695 (C=O), 1500 and 1365 cm^{-1}(NO_2); δ_H 2.32 (3H, s, Me), 7.05 (1H, dd, H-5), 7.19 (1H, d, H-6), 7.53-7.59 (2H, m, H-4' and H-5'), 7.69 (1H, dd, H-3'), 8.62 (1H, d, H-3), 8.25 (1H, brs, NHAc), 8.92 (1H, s, CH=N); $J_{3',4'}$ 6.2 Hz, $J_{3,5}$ 2.4 Hz and $J_{5,6}$ 8.6 Hz.

(ii) 2-Acetamido-5-chloro-N-(6-chloro-2-nitrobenzylidene) aniline

This was prepared by the method described for 2-acetamido-4-chloro-N-(6-chloro-2-nitrobenzylidene)aniline (page 131) starting from 2-amino-4-chloroacetanilide (1.49 g 0.007 mol) and 6-chloro-2-nitrobenzaldehyde (1.5 g 0.007 mol).

Yield 2.19 g (72%), m.p. 201-203°C (from ethanol).

(Found: C, 51.0; H, 3.05; N, 11.9. $C_{15}H_{11}Cl_2N_3O_3$ requires C, 51.2; H, 3.15; N, 11.9%); υ_{max} 3350 (N-H), 1700 (C=O), 1510 and 1350 cm^{-1} (NO_2); δ_H 2.32 (3H, s, Me), 7.24 (1H, d, H-6), 7.31 (1H, dd, H-4), 7.55-7.65 (2H, m, H-4' and H-5'), 7.66-7.75 (1H, m, H-3'), 8.17 (1H, brs, NHAc), 8.50 (1H, d, H-3), 8.85 (1H, s, CH=N); $J_{3,4}$ 8.9 Hz and $J_{4,6}$ 2.0 Hz.

(iii) 1,9-Dichloroquinoxalino[2,3-c]cinnoline

Potassium cyanide (0.3 g, 0.004 mol) was added to a mixture of 2-acetamido-4-chloro-N-(6-chloro-2-nitrobenzylidene)aniline (0.61 g 0.002 mol) in methanol (45 ml). The mixture was then heated under reflux in a nitrogen atmosphere for 3 h. The reaction mixture was then cooled in ice and the precipitate filtered off.

Yield 0.3 g (58%), m.p. 270-272°C (from DMF).

(Found: C, 55.6; H, 2.0; N, 18.6. $C_{14}H_6Cl_2N_4$ requires C, 55.8; H, 2.0; N, 18.6%); δ_H 8.0-8.1 (2H, m, H-10 and H-3), 8.16 (1H, dd, H-2), 8.43 (1H, d, H-11), 8.53 (1H, d, H-8), 8.9 (1H, dd, H-4); $J_{3,4}$ 8 Hz; $J_{2,4}$ 1.4 Hz, $J_{8,10}$ 2 Hz, $J_{10,11}$ 9 Hz, and $J_{2,3}$ 7 Hz.

(iv) 1,10-Dichloroquinoxalino[2,3-c]cinnoline

Using the method as described for 1,9-dichloroquinoxalino-[2,3-c]cinnoline (above), 2-acetamido-5-chloro-N-(2-nitro-6-chlorobenzylidene)aniline (1.5 g, 0.004 mol) underwent cyclisation to yield

0.8 g (63%) of 1,10-dichloroquinoxalino[2,3-c]cinnoline m.p. 274-276°C (from DMF).

(Found: C, 55.8; H, 1.9; N, 18.7. $C_{14}H_6Cl_2N_4$ requires C, 55.8; H, 2.0; N, 18.6%; δ_H 7.95-8.18 (3H, m, H-2, H-3 and H-9), 8.44-8.51 (2H, m, H-8 and H-11), 8.90 (1H, dd, H-4); $J_{2,4}$ 1.0 Hz, and $J_{3,4}$ 8.0 Hz.

(v) Reaction of 1-chloroquinoxalino[2,3-c]cinnoline with hydrogen chloride gas

A solution of 1-chloroquinoxalino[2,3-c]cinnoline (0.026 g, 0.0008 mol) in chloroform (50 ml) underwent the reaction with hydrogen chloride gas according to the method previously described on page 127. The product (0.2 g, 66%) was on characterisation found to be 1,10-dichloroquinoxalino[2,3-c]cinnoline.

5-Fluoro-2-nitroacetanilide

5-Fluoro-2-nitroaniline (5.0 g, 0.03 mol); prepared as described on page 103) was added to acetic anhydride (8 ml) with stirring. The mixture was then heated under reflux for 1 h. and after cooling, the solution was poured on to ice. The precipitate was collected by filtration and washed with water. Recrystallisation from water gave the product as pale cream needles (5.0 g, 79%), m.p. 84-85°C (lit.,[53] 85°C).

2-Amino-5-fluoroacetanilide

5-Fluoro-2-nitroacetanilide (4.7 g, 0.02 mol) dissolved in ethanol (750 ml), was hydrogenated in presence of 5% palladium-charcoal (0.6 g). The catalyst was removed by filtration through 'Hyflo' celite and the red filtrate evaporated to dryness. This gave a dark solid (3.4 g, 85%), m.p. 89-100°C. Further attempts at purification were unsuccessful but the spectral evidence, i.e. ^1H n.m.r. and i.r., obtained indicated that the product had been made, and so the crude material was used for the next stage.

2-Acetamido-4-fluoro-N-(2-nitrobenzylidene)aniline (110)

2-Amino-5-fluoroacetanilide (1.5 g, 0.009 mol) in ethanol (15 ml) was added to a solution of o-nitrobenzaldehyde (1.35 g, 0.009 mol) in ethanol (15 ml) along with a few crystals of toluene-p-sulphonic acid. The solution was then heated at 100°C for 15 min. After cooling the solution in ice water the product was precipitated as a bright lemon solid.

Yield 2.15 g (79%), m.p. 145-146°C (from propan-2-ol).

(Found: C, 59.4; H, 4.0; N, 14.0. $C_{15}H_{12}FN_3O_3$ requires C, 59.8; H, 4.0; N, 13.95%). υ_{max} 3350 (NH), 1670(CO), 1510 and 1360 cm^{-1} (NO_2); δ_H 2.25 (3H, s, Me), 6.75 (1H, ddd, H-5), 7.2 (1H, dd, H-6), 7.6-7.8 (2H, dt, H-4' and H-5', 7.9 (1H, dd, H-6'), 8.02 (1H, dd, H-3'), 8.30 (1H, dd, H-3), 8.57 (1H, brs, NHAc), 8.8 (1H, s, CH=N); δ_F -110.5 p.p.m.; $J_{5,6}$ 9.0 Hz, $J_{3,5}$ 2.7 Hz, $J_{4',5'}$, 5 Hz, $J_{4',6'}$ 1.2 Hz, $J_{3',4'}$ 8.4 Hz, $J_{3',5'}$ 1.5 Hz, $J_{6,F}$ 5.7 Hz, $J_{5,F}$ 8.0 Hz, and $J_{3,F}$ 10.5 Hz.

Attempted preparation of 9-fluoroquinoxalino[2,3-c]cinnoline (109)

(Reaction A)

To a mixture of 2-acetamido-4-fluoro-N-(2-nitro-benzylidene)aniline (1.2 g, 0.004 mol) and methanol (80 ml) was added potassium cyanide (0.52 g, 0.008 mol). The mixture was then heated under reflux for 35 minutes and then cooled in ice and a golden yellow precipitate was filtered off. Spectral analysis showed the solid to be almost totally 9-methoxyquinoxalino[2,3-c]cinnoline. Yield 0.64 g (61%).

4-Fluoro-o-phenylenediamine (112)

5-Fluoro-2-nitroaniline (1.5 g, 0.009 mol), dissolved in ethanol (120 ml), was hydrogenated over 5% palladium-charcoal (0.2 g). When the expected hydrogen uptake was achieved the catalyst was removed by filtration through 'Hyflo' celite and the dark red filtrate evaporated to

dryness to give the solid product (1.17 g, 96%), m.p. 87-89°C (lit.,[54] 88-89°C). No further purification was attempted. Spectral evidence, i.e. ^{1}H n.m.r., i.r. and mass spectrum, also indicated that the desired product had been made.

4-Fluoro-N-(o-nitrobenzylidene)-o-phenylenediamine (111)

4-Fluoro-o-phenylenediamine (0.5 g, 0.004 mol) was dissolved in the minimum volume of ethanol. A solution of 2-nitrobenzaldehyde (0.59 g, 0.004 mol), in the minimum amount of ethanol, and a few crystals of toluene-p-sulphonic acid were added, and the mixture was then left to stand at room temperature for 48 h. The product was obtained as copper coloured crystals and these were collected by filtration. Yield 0.73 g (71%), m.p. 130-132°C (from ethanol).

(Found: C, 60.0, H, 3.8; H, 16.1. $C_{13}H_{10}FN_3O_2$ requires C, 60.2; H, 3.9; N, 16.2%); υ_{max} 3480 and 3390 (NH_2), 1520 and 1340 cm^{-1}(NO_2); δ_H 4.50 (2H, brs, NH_2), 6.42-6.53 (2H, m, H-3 and H-5), 7.14 (1H, d, H-6), 7.55-7.77 (2H, 2 x m, H-3' or H-6' and H-4' or H-5'), 8.01 (1H, d, H-4' or H-5') 8.27 (1H, d, H-3' or H-6'), 8.95 (1H, s, CH=N); ^{1}H n.m.r. spectrum non-first order, δ_F -113.6 p.p.m. (fluorine spectrum non-first order).

N.B. When the same reaction was carried out at 100°C the product was a red tar which was identified from the mass spectrum (M$^+$392) as the bis-anil (see page 93).

Attempted preparation of 9-fluoroquinoxalino[2,3-c]cinnoline (Reaction B)

To a mixture of 4-fluoro-N-(o-nitrobenzylidene)-o-phenylenediamine (1 g, 0.004 mol) in methanol (75 ml) was added potassium cyanide (0.5 g, 0.008 mol). The mixture was then heated under reflux for 35 minutes. After cooling in ice the precipitate was filtered off. Spectral analysis confirmed the product as 9-methoxyquinoxalino[2,3-c]cinnoline.

Yield 0.6 g (60%).

Reaction of sodium methoxide with the product from reaction A (page 134) and reaction B

To a solution of sodium metal (0.2 g, 0.009 mol) in methanol was added the product of reaction A (0.4 g, 0.001 mol) at room temperature. The suspension was then heated under reflux for 8 h and then cooled and the solvent removed under reduced pressure. The solid residue was collected and washed with distilled water. The product (0.33 g) was identified as 9-methoxyquinoxalino[2,3-c]cinnoline, m.p. 285-286°C dec (from DMF).
(Found: C, 69.1; H, 3.8; N, 21.5. $C_{15}H_{10}N_4O$ requires C, 68.7; H, 3.8; N, 21.5%); δ_H 4.1 (3H, s, Me), 7.70 (2H, m, H-8 and H-10), 8.08 (2H, m, H-2 and H-3), 8.28 (1H, dd, H-11), 8.89 (1H, m, H-4), 9.23 (1H, m, H-1); $J_{8,11}$ 1.0 Hz, and $J_{10,11}$ 10 Hz.

Identical treatment using the product from reaction B also gave as the product 9-methoxyquinoxalino[2,3-c]cinnoline.

9-Fluoroquinoxalino[2,3-c]cinnoline (109)

(Reaction E)

The anil (1.0 g, 0.003 mol) was stirred at room temperature in methanol (100 ml) and potassium cyanide (0.43 g, 0.006 mol) added. After 20 min a golden yellow precipitate appeared in the red solution, after another 15 min the reaction mixture was chilled in ice for 45 min before collecting the product by filtration.

Yield (0.2 g, 24%).

(Found: C, 66.3; H, 2.65; N, 22.4. $C_{14}H_7FN_4$ requires C, 67.2; H, 2.8; N, 22.4%) (contaminated by *ca.* 25% 9-fluoroquinoxalino[2,3-c]cinnoline 5-oxide (ref. page 98); δ_H 7.7-7.8 (1H, m, H-10), 8.2-8.2 (3H, m, H-2, H-3 and H-8), 8.41 (1H, dd, H-11), 8.90 (1H, m, H-4), 9.23 (1H, m, H-1); δ_F = -103.7 p.p.m. (8 lines), $J_{10,11}$ 9.7 Hz, $J_{10,F} = J_{8,F}$ 8.7 Hz, and $J_{11,F}$ 5.7 Hz; m/z 266

(11%), 250 ($M^{+\bullet}$, 35%), 222 (46%), 195 (31%), 128 (12%), 108 (29%), 94 (100%), 75 (32%), 68 (15%), 57 (15%), 50 (42%), etc.

9-Piperidinoquinoxalino[2,3-c]cinnoline (115)

To a mixture of methanol (30 ml) and piperidine (30 ml) was added 2-acetamido-4-fluoro-N-(2-nitrobenzylidene)aniline (1.0 g, 0.0033 mol) and potassium cyanide (0.43 g, 0.0066 mol). The mixture was then heated under reflux for 6 h. Within 5 minutes of the start of the reaction the solution passed through three distinct colour changes, orange to wine red and finally purple.

After cooling, the solvent was removed at reduced pressure, the purple residue was triturated with water at 0°C, and the solid (0.93 g, 88%) filtered off. The product was unable to be purified further but on the spectral evidence obtained the structure assigned was 9-piperidinoquinoxalino[2,3-c]cinnoline.

δ_H 1.77 (6H, brs, 3 x piperidine CH_2), 3.59 (4H, m, 2 x piperidine CH_2), 7.50 (1H, d, H-8), 7.87 (1H, dd, H-10), 7.95-8.05 (2H, symm. m, H-2 and H-3), 8.15 (1H, d, H-11), 8.80-8.87 (1H, m, H-4), 9.11-9.18 (1H, m, H-1); $J_{8,10}$ 3.0 Hz, and $J_{10,11}$ 9.5 Hz. The mass spectrum obtained is illustrated in Figure 19 on page 139.

10-Piperidinoquinoxalino[2,3-c]cinnoline (113)

(with T. Shepherd)

10-Chloroquinoxalino[2,3-c]cinnoline (0.8 g, 0.003 mol) in piperidine (90 ml) was heated on a steam bath for 1.5 h. After cooling to room temperature the solution was filtered and the piperidine evaporated under reduced pressure as much as possible.

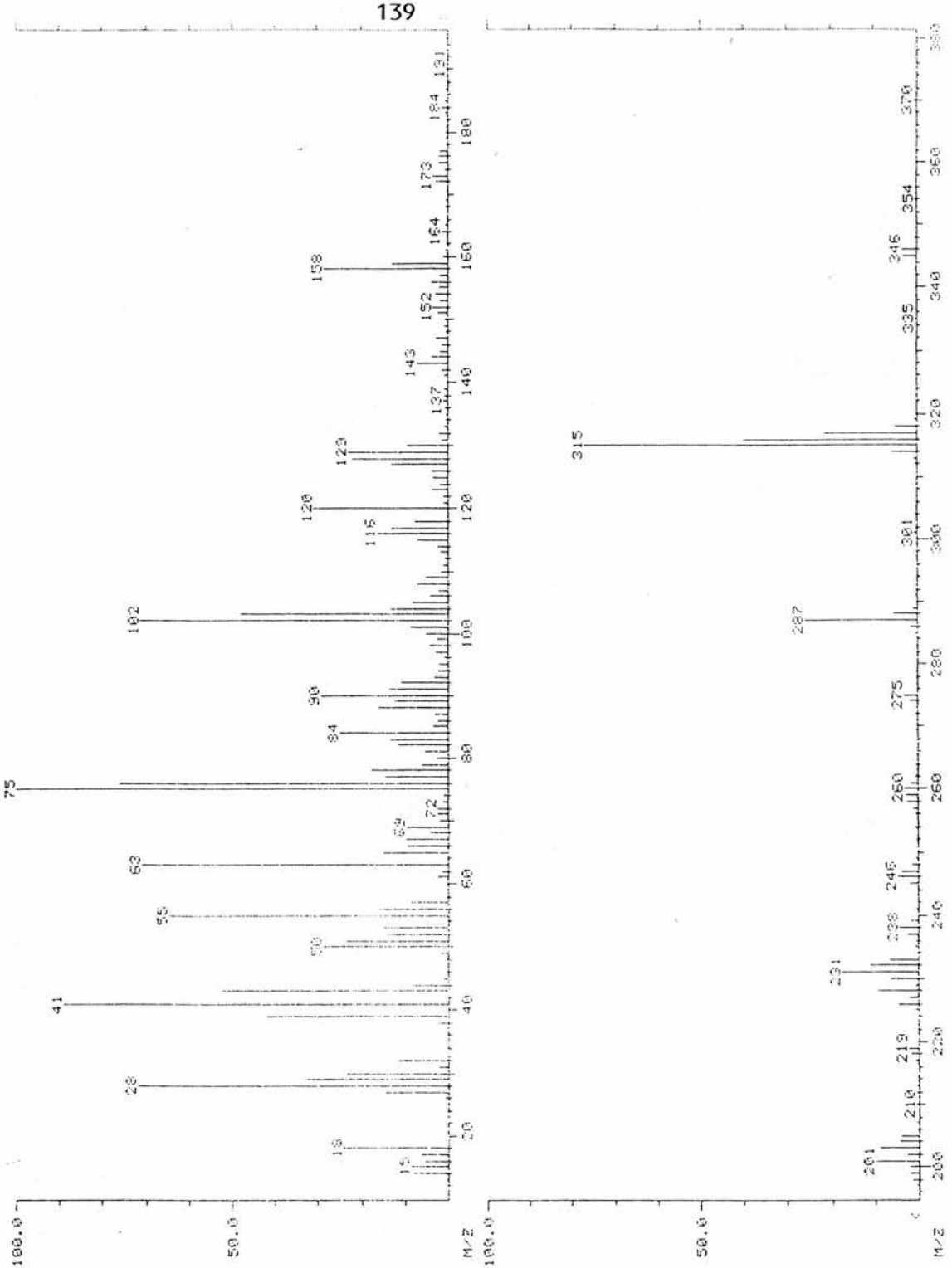
50% aqueous ethanol was then added to the residue and the solvent evaporated until the solid product began to precipitate. Before collecting the product by filtration the mixture was first chilled in ice. The product

(0.82 g, 87%) was obtained as a dark maroon solid m.p. 119-121°C; further attempts at purification were not successful.

δ_H 1.75 (6H, brs, 3 x piperidine CH_2), 3.60 (4H, brs, 2 x piperidine CH_2), 7.26 (1H, d, H-11), 7.73 (1H, dd, H-9), 7.90-8.06 (2H, symm. m, H-2 and H-3), 8.22 (1H, d, H-8), 8.75-8.81 (1H, m, H-4), 9.08-9.13 (1H, m, H-1); $J_{11,9}$ 3.0 Hz, and $J_{8,9}$ 9.7 Hz. The mass spectrum obtained is illustrated in Figure20 on page 140 .

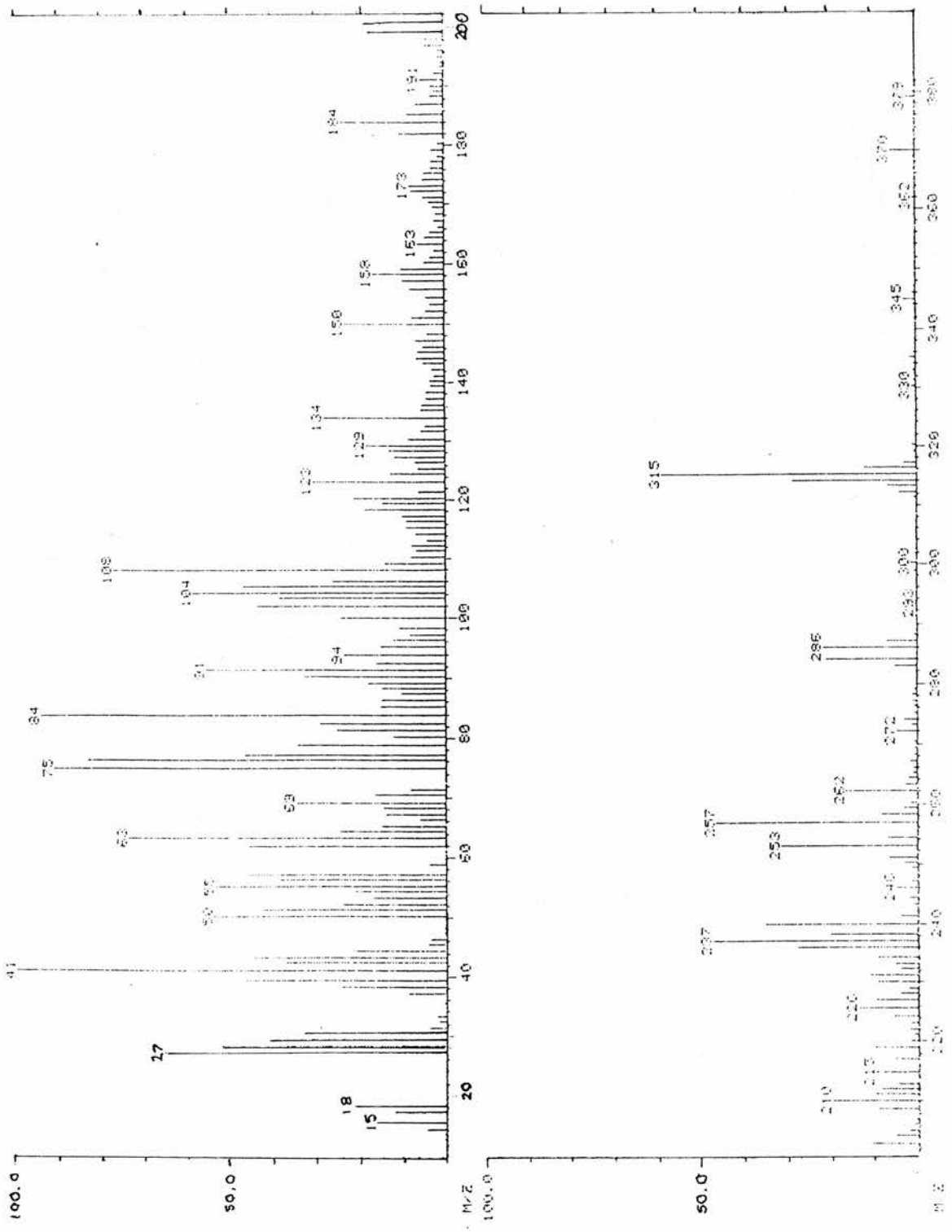
(Figure 19)

Mass spectrum of 9-piperidinoquinoxalino[2,3-c]cinnoline



(Figure 20)

Mass spectrum of 10-piperidinoquinoxalino[2,3-c]cinnoline



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