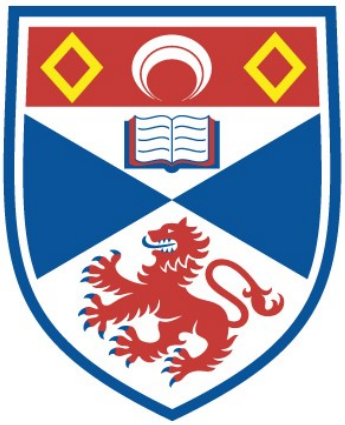
REACTIONS OF SOME SECONDARY AND TERTIARY O-NITROANILINE DERIVATIVES WITH BASES

Pamela Ann Collins

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



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A thesis presented to the University of St. Andrews

for the degree of Doctor of Philosophy

by

Pamela Ann Collins

February 1991

University of St. Andrews

DEDICATION

To My Parents

DECLARATION

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

Signed..... Date...27/2/91.....

I was admitted to the Faculty of Science of the University of St Andrews under Ordinance General No. 12 on 1st November 1987 and as a candidate for the degree of Ph.D. on 1st October 1988.

Signed ..... Date...27/2/91.....

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

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ACKNOWLEDGEMENTS

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ABSTRACT

In chapter **1**, a brief account of the chemical and physical properties of benzimidazole *N*-oxides is given. The scope and limitations of a method recently developed for the synthesis of the *N*-oxides from substituted *o*-nitroaniline derivatives are discussed.

Chapter **2** discusses the reactions in the literature which are relevant to those being investigated.

Chapter **3** describes the efforts made to investigate the involvement of the 'activating' groups of the *o*-nitroaniline derivatives in the reaction pathway.

In chapter **4** the reactions of *N*-(4 and/or 6-substituted *o*-nitrophenyl)glycine and sarcosine esters with bases are described. All of the 4-substituted glycine esters and those with fluorine, acetamido and methyl on C-6 cyclized 'normally' to the corresponding *NH*-benzimidazole *N'*-oxides whereas those with chlorine, trifluoromethyl, and nitro on C-6 reacted 'abnormally' to give, in addition, such products as 1-hydroxy-quinoxaline-2,3-diones and diaminoazoxybenzenes. All of the sarcosine esters reacted 'abnormally' producing none of the *N*-methylbenzimidazole *N'*-oxides. Surprisingly they did form products indicating loss of the *N*-methyl group, e.g. quinoxalin-2-ones.

The aldol-type condensation mechanism that has been previously applied to the syntheses of benzimidazole *N*-oxides does not explain these new results; they suggest that the presence of an amino-hydrogen in the starting material is necessary for *N*-oxide formation. An alternative mechanism is proposed which takes this possibility and the types of products formed into account. It involves the formation of an oxadiazine intermediate which can then react in a number of different ways to give the observed products. The reasons for some neighbouring substituents affecting the reaction pathway appears to be largely steric though there may also be an electronic factor.

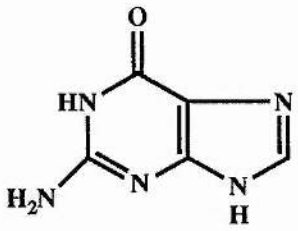
Chapter **5** contains a discussion of how the alternative mechanism could be applied to a number of other cyclizations of carbocyclic and heterocyclic compounds which involve interaction of a nitro group with a potentially nucleophilic *ortho*-substituent.

CONTENTS

CHAPTER 1

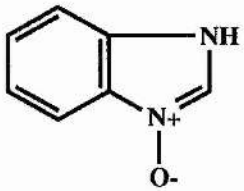
INTRODUCTION

Considerable research has been involved in the synthesis of compounds analogous to those natural products that possess useful biological properties. The hope is that such analogs will exhibit similar behaviour. Two such natural products are guanine and adenine. At St. Andrews, research has been conducted for the last 20 years on the synthesis of benzimidazole *N*-oxides which have an obvious structural similarity to these compounds.



Guanine

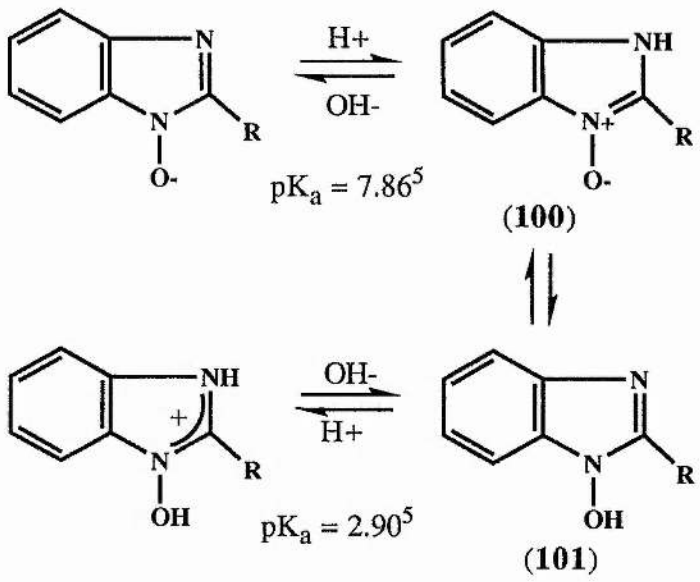
Adenine



Benzimidazole *N*-oxide

In the latter part of this research a synthesis of 1*H*-benzimidazole 3-oxides was devised[1]. The scope of the synthesis was investigated as to the range of derivatives that could be produced including the *N*-alkylbenzimidazole *N'*-oxides. However, some unexpected results were obtained especially in the latter case. This project was designed to try and characterize these results and to discover or propose the reasons behind them. First an overview of the *N*-oxides in general will be given, then the aims of the project will be laid out in more detail.

The first benzimidazole *N*-oxide was reported in 1887[2] and was thought to have a tricyclic structure. It was not until 1951[3] that the correct structure was assigned. In 1910 the parent and its 2-methyl derivative were reported[4]. The characteristics listed in the paper are typical of the *N*-oxides in general: white needles, high melting (>200^{o}C), light-fast, soluble in hot water and alcohols, mostly insoluble in acetone and insoluble in benzene and ether. Due to their being both acidic and basic (Scheme **1.1**), the *N*-oxides can be difficult to isolate, though for the most part they are insoluble in weakly acidic media.



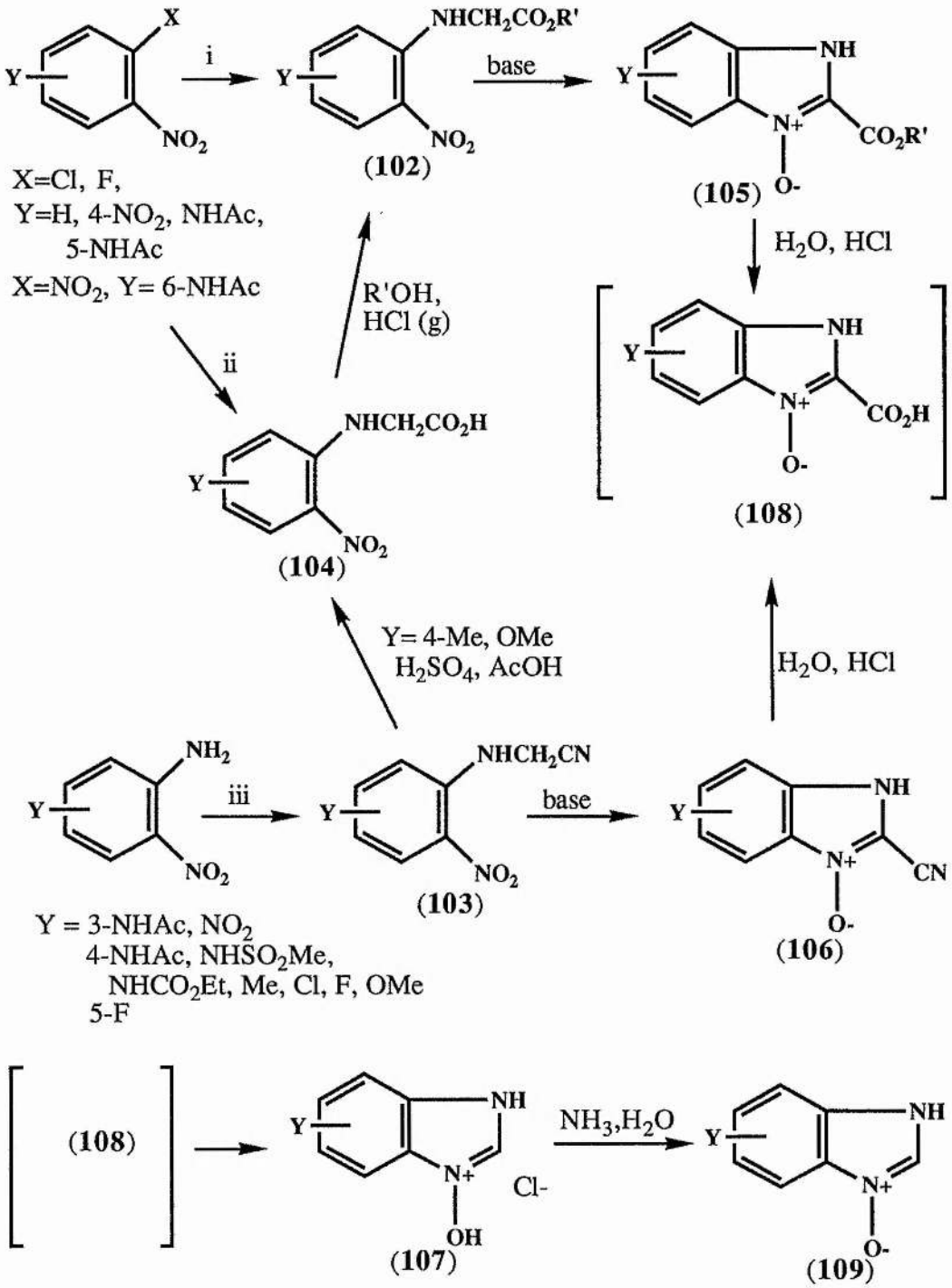
Scheme **1.1**

The 1*H*-benzimidazole 3-oxides (**100**) are tautomeric with *N*-hydroxy-benzimidazoles (**101**). A number of studies have shown that the position of equilibrium in solution depends on the solvent. One report[6] states that in non-polar media the hydroxy form predominates and in aqueous media the *N*-oxide. Another paper[7] based on ultraviolet spectra concluded similarly except to say that the hydroxy form predominates in ethanolic solution. Schilf[8] conducted a quantitative investigation of the tautomeric equilibria of two 1-hydroxybenzimidazoles using nitrogen-15 nmr. The observation of the N-3 signal gave a quantitative estimation of the position of equilibrium. The conclusion drawn matches general opinion on the subject, namely that the amount of OH present in solution depends proportionally on the pKa value of the solvent. Thus the concentration of the hydroxy form increases with decreasing solvent polarity or hydrogen-bonding power. However, there are exceptions, such as the 2-phenyl derivative which is known to exist in the hydroxy form even in polar media. Though it is recognized that an equilibrium exists in solution, the compounds in this thesis will be referred to as *N*-oxides.

Synthesis of the *N*-oxides has been hampered by the inability of the parent benzimidazoles to undergo direct oxidation. Only one[9] of many attempts has succeeded but the 10% yield was too low to be synthetically useful. Most attempts involved the use of peracids, which have been successful in the oxidation of similar bicyclic species, but gave only the benzimidazoles back unchanged[10,11,12,13]. One reported a residue which could not be purified or identified[14]. Other oxidizing reagents have been used on benzimidazoles giving interesting products. Russian researchers[15,16,17] have investigated the oxidative cleavage of benzimidazoles to 4,5-imidazole-dicarboxylic acids using $K_2Cr_2O_7$ and H_2SO_4. Benzimidazole has been oxidized by $Pb(OAc)_4$ to a mixture of the 2-acetoxy derivative, 2-benzimidazolone and *NN'*-diacetyl-*o*-phenylene-diamine[18]. Also, 5,6-dimethylbenzimidazole-4,7-dione was obtained in 2% yield from the oxidation of 5,6-dimethylbenzimidazole[19].

A good, general synthetic method was developed recently by Harvey, McFarlane, Moody, and Smith[1] for the production of 1*H*-benzimidazole 3-oxides (Scheme **1.2**). Unlike previous methods this one can be used to synthesize a variety of *N*-oxides singly substituted in the benzene ring. The starting materials are either *o*-halogenonitrobenzenes or *o*-nitroanilines. The esters (**102**) are obtained by reaction of the former directly with glycine ester or by reaction with glycine and subsequent esterification. The reaction of an *o*-nitroaniline with potassium cyanide, paraformaldehyde, and zinc chloride in acetic acid gives the nitriles (**103**). The esters can also be obtained by hydrolysis of the nitriles with sulphuric acid and esterification of the resulting free acid (**104**).

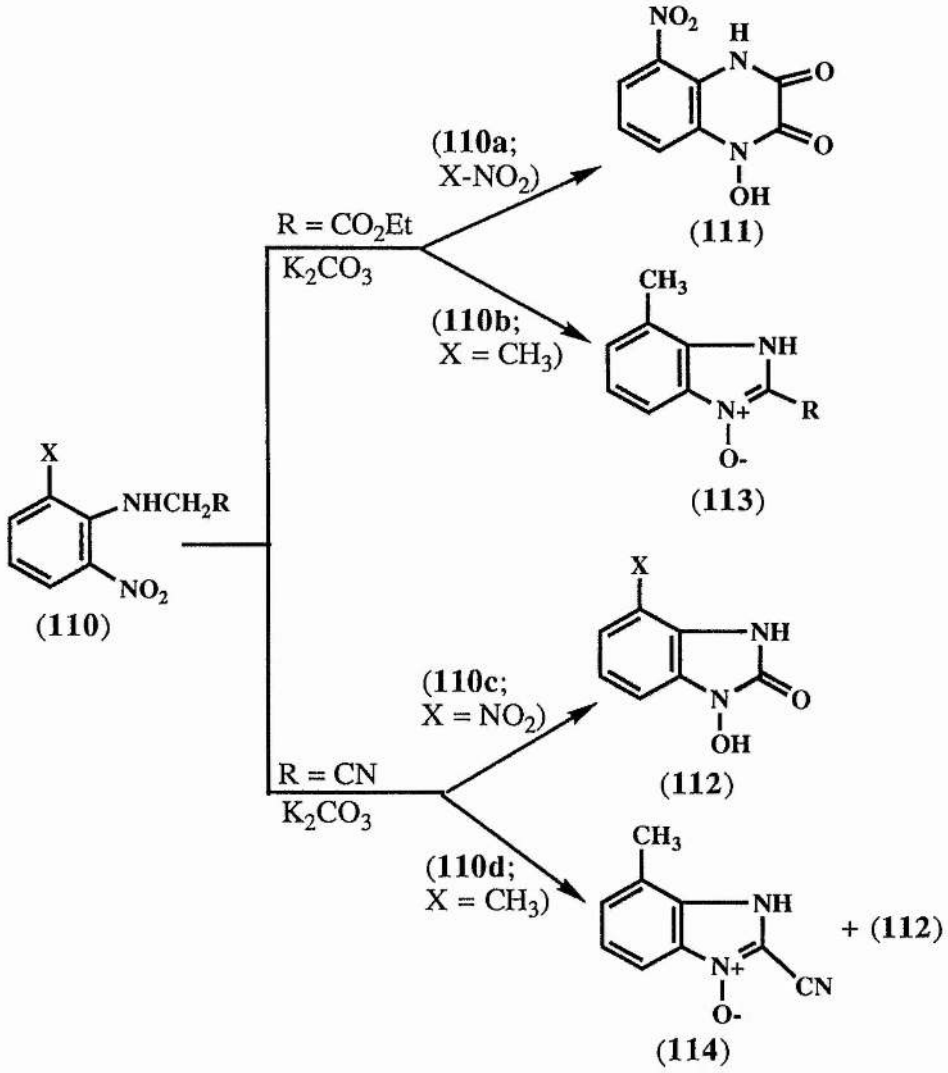
The esters and the nitriles are cyclized by reaction with base to their respective 2-substituted benzimidazole *N*-oxides (**105, 106**). These *N*-oxides are hydrolyzed in one step to the 2-unsubstituted products (**107**) with the presumed intermediate being the 2-carboxylic acid *N*-oxides (**108**): these are known to undergo facile decarboxylation under the conditions employed. Finally, the hydrochloride is removed using ammonia and water to give the *N*-oxides (**109**).



i = $NH_2CH_2CO_2Et$
ii = $NH_2CH_2CO_2H$
iii = KCN, $(CH_2O)_n$, $ZnCl_2$, AcOH

Scheme **1.2**

Interesting deviations from the pattern occurred, however, for some esters and nitriles containing a substituent in the position *ortho* to the amino side-chain and *meta* to the nitro group (**110a-d**). Products such as 1-hydroxyquinoxaline-2,3-diones (**111**) and benzimidazol-2-ones (**112**) were found instead of or in addition to the expected *N*-oxides (**113,114**) (Scheme **1.3**)[20].

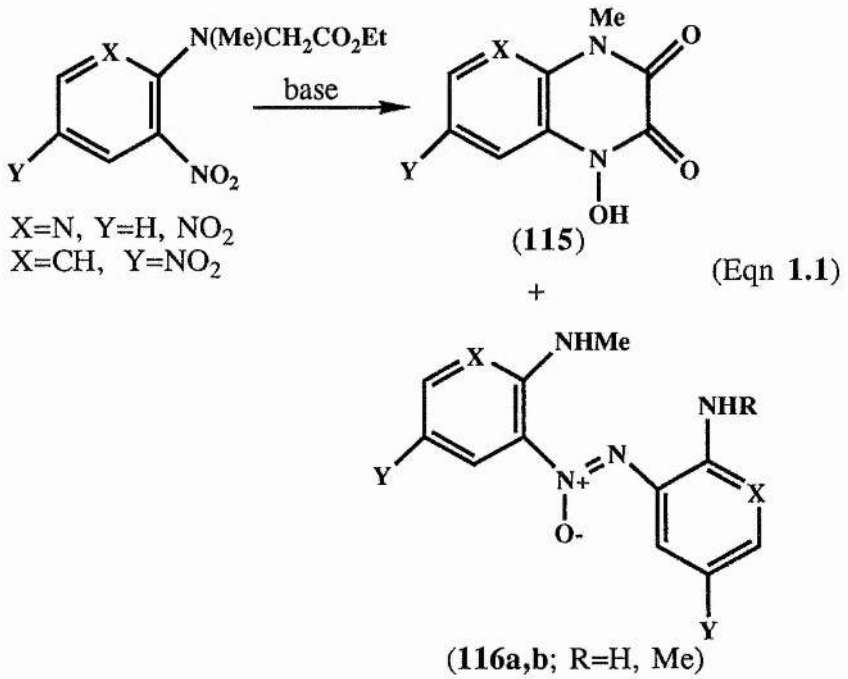


Scheme **1.3**

Not all of the glycine esters with substituents in this position gave these unexpected products. From the few reactions that had been performed, it seemed as though the electron-withdrawing substituents changed the reaction pathway, while the electron-donating ones effected no change. One goal of this project was to perform reactions of other glycine esters with a variety of substituents in this position in order that

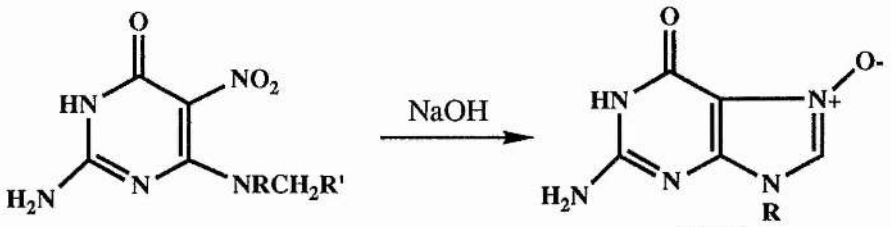
this relationship between the type of group and the effect caused could be more definitely characterized.

The other goal was to investigate anomalous reactions that occurred when McFarlane tried to extend the general method to synthesizing 1-methylbenzimidazole 3-oxides. In such cases as he tried, no *N*-oxides were found at all; instead, 1-hydroxy-quinoxaline-2,3-diones (**115**), 2,2′-bis(methylamino)- and/or 2-amino-2′-methylamino-azoxybenzenes (**116a,b**; R=H, Me) (or their pyridyl derivatives for the pyridyl series) were isolated (Eqn **1.1**)[20,21].



(Eqn **1.1**)

Exploration was therefore needed into the scope of these reactions to determine if other tertiary *o*-nitroanilines behave in the same way. In fact, similar starting materials (**117,118**) are cyclized under basic conditions to give 9-methylguanine 7-oxide (**119**) (Eqns **1.2**, **1.3**)[22,23].



(**117**; R=Me, CH_2CH_2Me, CH_2=$CHCH_2$, CH_2Ph, etc R'=COPh) (Eqn **1.2**)

(**118**; R=Me, R'=CHO) (Eqn **1.3**)

(**119**)

An attempt seemed justified therefore, to try and mimic the guanine synthesis by performing analogous reactions with the benzenoid system as a possible route to 1-methylbenzimidazole 3-oxides. Unfortunately the work never reached cyclization stage.

The reactions of the glycine and sarcosine esters with bases are more complex than initially supposed. There appear to be several factors which can change the course of the reactions. The results from an investigation into the effects caused by a tertiary nitrogen or a neighbouring substituent are presented in chapter **4**. The efforts made to mimic the guanine syntheses mentioned above are discussed in chapter **3**, and chapter **2** takes a look at the literature to see if parallel reactions of compounds analogous to the amino esters have been similarly effected.

CHAPTER 2

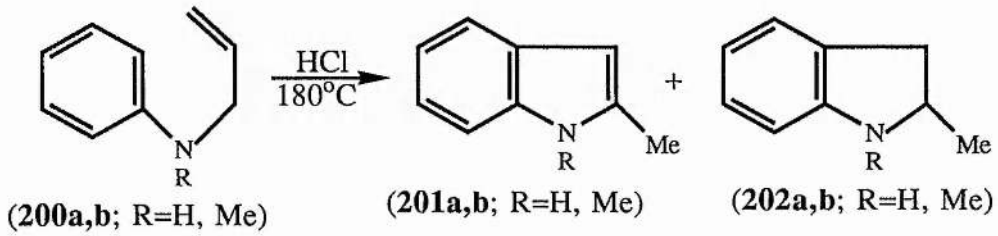
N-(2,4-Dinitrophenyl)sarcosine ethyl ester, *N*-(2,6-dinitrophenyl)glycine ethyl ester, and *N*-cyanomethyl-*N*-(6-methyl-2-nitrophenyl), and *N*-cyanomethyl-*N*-(2,6-dinitrophenyl)anilines all gave products other than, or in addition to, the expected benzimidazole *N*-oxides upon reaction with base (cf Eqn **1.1** and Scheme **1.3**). An investigation into the cyclization reactions of *NN*-disubstituted anilines has helped to put these abnormal reactions into historical perspective. The investigation is detailed in this chapter and focuses on answering two main questions:

1. Is there any literature precedent for derivatives giving such different results under the same conditions?
2. Are there any cases of tertiary anilines cyclizing to *N*-alkyl-benzimidazole *N'*-oxides under any conditions?

The information needed to answer both questions was obtained in several ways. One was by examining the syntheses of derivatives of bicyclic compounds such as indole, benzimidazole, quinoline, quinazoline, quinoxaline, and purine[24]. While looking at the cyclization of *NN*-disubstituted anilines to the *N*-alkyl derivatives of these compounds (including *N'*-oxides, where applicable), special attention was paid to any mention of anomalous reactions involving tertiary anilines, particularly where they reacted differently from the corresponding secondary derivatives under the same conditions. Also, the syntheses of compounds with substituents *ortho* to a group involved in cyclization were looked into to see if there was any evidence of the substituents affecting the cyclization pathway. The review of tertiary aniline reactions by Meth-Cohn and Suschitzky[25] was a useful source of information, particularly for reactions pertaining to question two.

For the most part the recorded syntheses of the bicyclic compounds mentioned did not provide many examples by way of the literature precedent . The *N*-alkyl derivatives are often made by ring closure on to the nitrogen of secondary anilines or by alkylation of

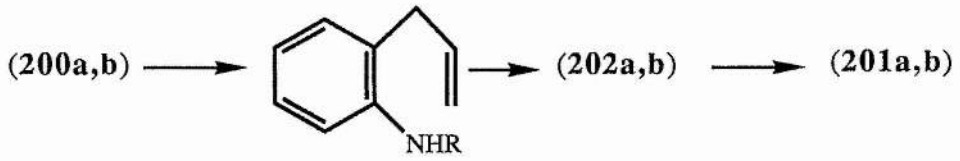
the corresponding *NH* compound, though there are some syntheses involving tertiary anilines. For the most part the secondary and tertiary anilines behaved similarly under the same conditions. The following is one example of those reactions found. *N*-Allylaniline (**200a**; R=H) and hydrochloric acid give a mixture of 2-methylindole (**201a**; R=H), 2-methylindoline (**202a**; R=H) and 2-methyl-3-propylindole (Eqn **2.1**)[26]. Several ring-substituted derivatives give similar results; the presence of the *ortho*-substituent in *N*-allyl-*o*-methylaniline apparently has no effect on the reaction. The reaction is thought to proceed with the Claisen rearrangement of *N*-allylaniline to *o*-allylaniline (**203a**; R=H), then the cyclization of the latter to 2-methylindoline and finally dehydrogenation to the indole (**201a**) (Scheme **2.1**). The individual steps are all known to occur[27]. The *N*-methyl derivative (**200b**; R=Me) reacts in the same way as (**200a**), but less vigorously.



(**200a,b**; R=H, Me) (**201a,b**; R=H, Me) (**202a,b**; R=H, Me)

+ 2-methyl-3-propylindole

Eqn **2.1**

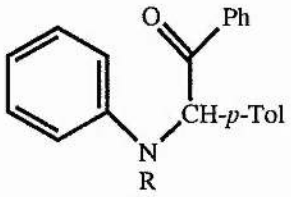


(**203a,b**; R = H, Me)

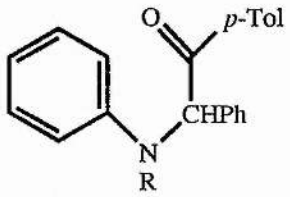
Scheme **2.1**

The following are the cases found in which secondary and tertiary aniline derivatives behaved differently under similar conditions. The formation of 2,3-diarylindoles from α-arylaminoketones has been studied extensively[28-30]. If the amino group is secondary, the aminoketones are stable at 200°C but in the presence of acid at moderate heat they isomerize readily and at higher heat they form indoles. If on the other

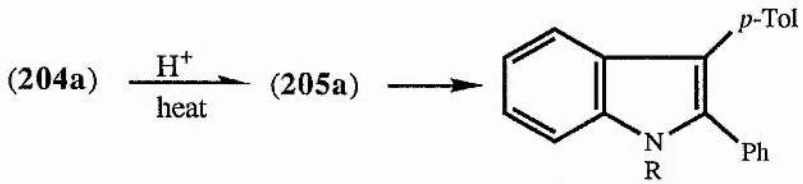
hand, the amino group is tertiary, the aminoketones are unaffected by heat alone or in the presence of acid. Both sets of ketones give indoles in reactions with zinc chloride. The isomer of indole formed seems to be determined partially by the ability of the ketone to isomerize. For example, in boiling alcoholic zinc chloride or fused with zinc chloride, the aminoketone (**204a**; R=H) isomerizes to (**205a**; R=H) (the reverse does not occur) which cyclizes to the indole (**206a**; R=H) (Eqn **2.2**)[28].



(**204a,b,c**; R=H, Me, Ph)



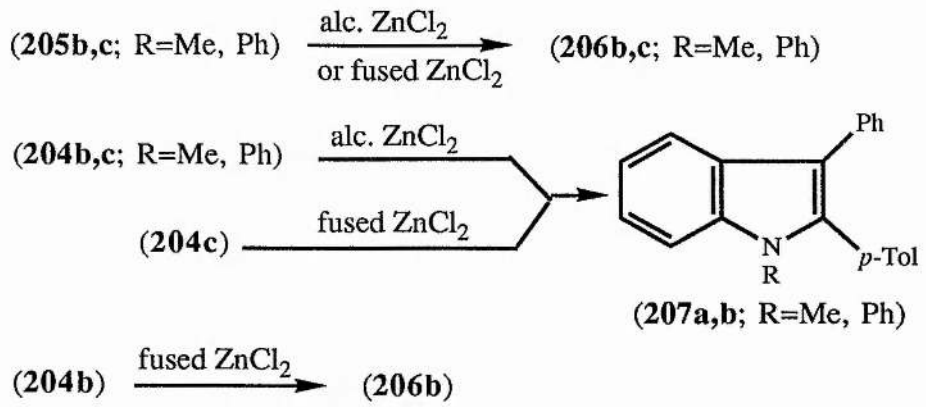
(**205a,b,c**; R=H, Me, Ph)



(**206a**; R=H)

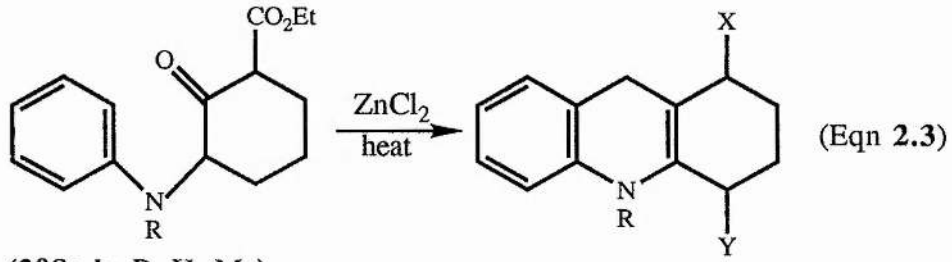
Eqn **2.2**

In the synthesis of *N*-substituted indoles there is a dependence on the nature of the *N*-substituent. Thus under both sets of conditions (**205b,c**; R=Me, Ph) give (**206b**; R=Me, Ph), (**204b,c**; R=Me, Ph) in boiling alcoholic zinc chloride and (**204c**) fused with zinc chloride give the indole (**207a,b**; R=Me, Ph) presumably by direct cyclization (Scheme **2.2**). However, (**204b**) when fused wtih zinc chloride gave only a small amount of (**206b**; R=Me) which would seem to indicate that at least some degree of isomerization took place[28]. It has been suggested that the other isomer was actually present in the reaction mixture but was perhaps more difficult to isolate.



Scheme **2.2**

One clear case of *NH* and *N*-substituted aminoketones cyclizing by different mechanisms in reactions with zinc chloride arose in the cyclization of the compounds (**208a,b**; R=H, Me). Compound (**208a**) in zinc chloride with heat gave a product (**209a**) which indicated that the ketone had isomerized before cyclizing whereas (**208b**) gave the product (**209b**) expected form direct cyclization (Eqn **2.3**)[31]. Thus the fact that the nitrogen was fully substituted affected the reaction pathway.

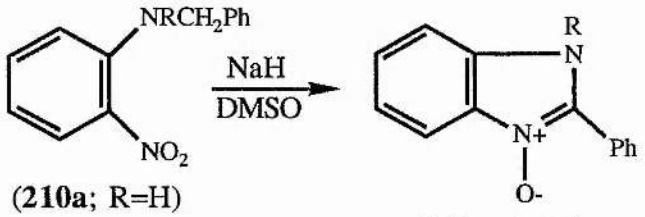


(**208a,b**; R=H, Me)

(Eqn **2.3**)

(**209a**; R=H, X=H, Y=CO_2Et)
(**209b**; R=Me, X=CO_2Et, Y=H)

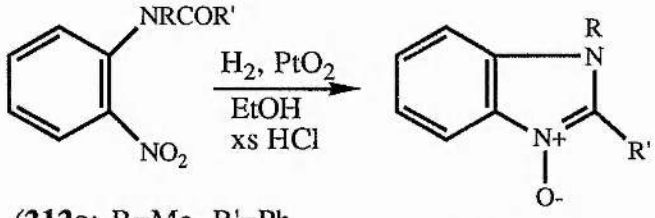
In 1966, Stacy *et. al.*[14] reported that while *N*-benzylaniline (**210a**; R=H) was cyclized by sodium hydride in dimethyl sulfoxide to 2-phenyl-1*H*-benzimidazole 3-oxide (**211a**; R=H) (Eqn **2.4**), the *N*-methyl derivative (**210b**; R=Me) was completely unreactive towards base (Eqn **2.5**).



(**210a**; R=H) (**211a**; R=H) (Eqn **2.4**)

(**210b**; R=Me) ⟶✕ (**211b**; R=Me) (Eqn **2.5**)

Several other methods were employed such as sodium hydroxide-methanol, sodium ethoxide-ethanol, and sodium hydroxide-dioxane-water and under some of these conditions pressure was applied using a sealed tube with heating. None of the methods when applied to compound (**210b**) produced the desired *N*-oxide (**211b**; R=Me). There was no indication that any alternative products had been formed as with *N*-(2,4-dinitrophenyl)sarcosine ester (cf Eqn **1.1**). The *N*-oxide (**211b**) was only synthesizable from *N*-benzoyl-*N*-methylaniline (**212a**; R=Me, R′=Ph) via a reductive cyclization method employed by Schulenberg[32] for the synthesis of the isomeric 1-phenyl-2-methyl-benzimidazole 3-oxide (**213**) from (**212b**; R=Ph, R′=Me) (Eqn **2.6**).

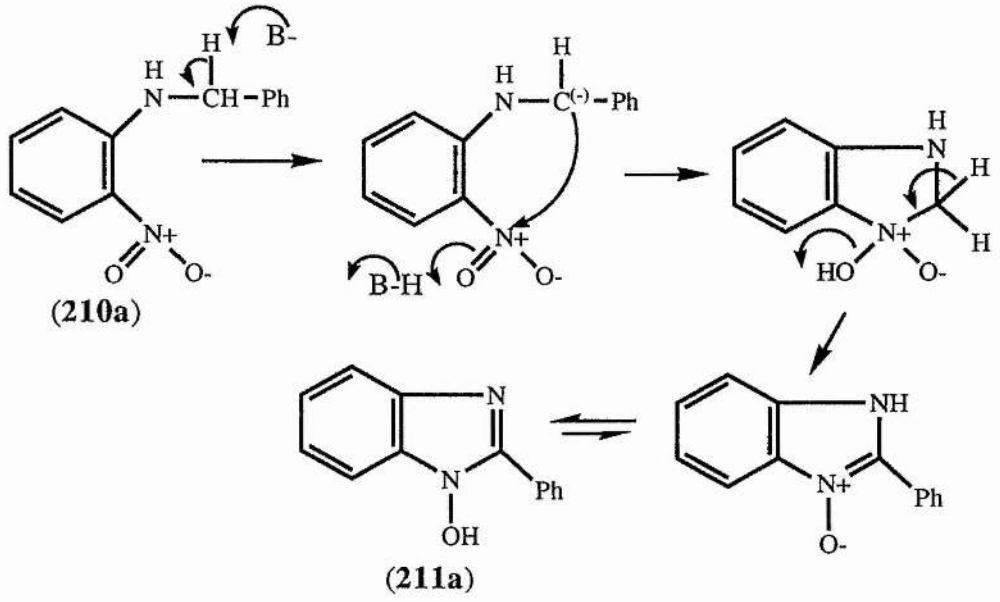


(**212a**; R=Me, R'=Ph
212b; R=Ph, R'=Me)

(**211b**; R=Me, R'=Ph
213; R=Ph, R'=Me)

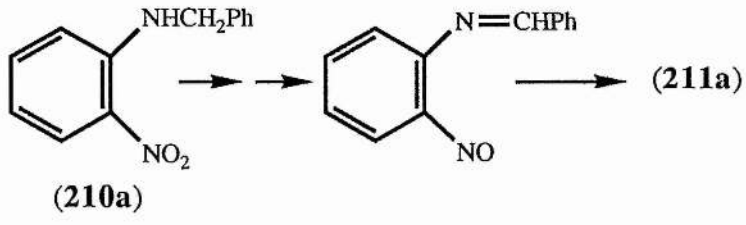
(Eqn **2.6**)

The mechanism for the cyclization of (**210a**) is proposed to be the attack of the hydride on the methylene group leading to a carbanion which then attacks the nitro group. Subsequent dehydration gives the *N*-oxide (**211a**) (Scheme **2.3**). However, according to this mechanism, the degree of substitution at the amino nitrogen should have no bearing on the success of cyclization, which is obviously not the case.



Scheme **2.3**

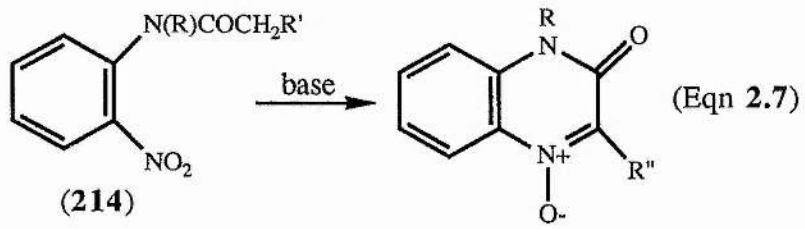
This example relates directly to the results McFarlane encountered with reactions of *N*-(2,4-dinitrophenyl)glycine and sarcosine esters with base. In both cases, tertiary aniline derivatives did not give the expected products, analogous to those which were formed from the corresponding secondary aniline derivatives. Initially the same mechanism outlined above was proposed for the formation of *NH*-benzimidazole *N'*-oxides from *N*-(substituted-*o*-nitrophenyl)glycine esters. McFarlane proposed an alternative mechanism in which a hydrogen on the amino nitrogen is necessary for the formation of the *N*-oxide. The mechanism involves the formation of a nitroso-anil intermediate which could also be formed from compound (**210a**) (Scheme **2.4**). The mechanism will be discussed in more detail in chapter **4**.



Scheme **2.4**

N-Acyl-*o*-nitroanilines (**214**) are used to synthesize quinoxalin-2-one 4-oxides (**215**)[33], as indicated by equation **2.7**. Unlike the previous example however, this cyclization occurs for either R=H or alkyl under a variety of basic conditions. Some of the results are in the table below.

Table **2.1** The products from the reactions of *N*-acyl-*o*-nitroanilines with bases



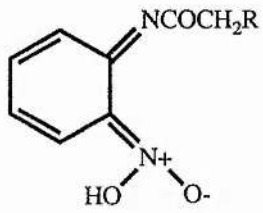
(**214**) (**215**) (Eqn **2.7**)

(**214**)			Conditions	(**215**)		
R	R′	Compd		R	R″	Compd
H	Ph	a	NaOEt, EtOH	H	Ph	a
Me	Ph	b	"	Me	Ph	b
H	CN	c	aq. NaCN	H	CN	c
Me	CN	d	"	Me	CN	d
H	CN	c	NaOEt	H	CN	c
Me	CN	d	"	Me	OH	e
H	CN	c	warm aq. alkali	H	OH	f
Me	CN	d	"	Me	OH	g

Whereas (**214b**; R=Me, R′=Ph) gave a good yield of the 4-oxide (**215b**), the corresponding *NH* compound (**214a**) gave only a small percentage of (**215a**). The researchers rationalized the result by stating that the *N*-methyl derivative (**214b**) would be less susceptible to hydrolysis. The two compounds (**214c,d**; R=H, Me, R′=CN) essentially gave the same products upon reaction with different bases. Both 3-cyano-1*H*- and 1-methylquinoxaline 4-oxides gave the 3-hydroxy derivatives upon hydrolysis,

thus the formation of 3-hydroxy-1-methylquinoxaline 4-oxide from (**214c**) in sodium ethoxide was assumed to involve the nitrile (**215d**) as an intermediate.

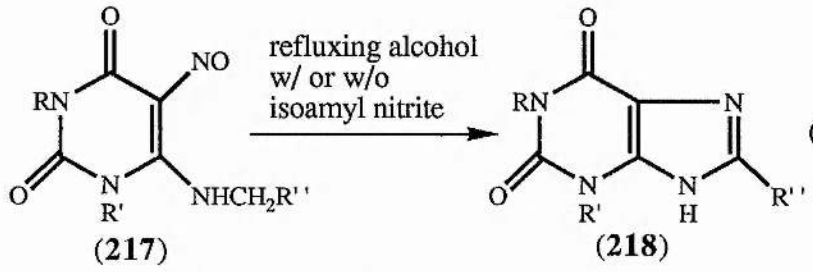
The reactions of the *N*-methylacetanilides were undertaken in part to try to solve a mechanistic question. Two mechanisms had been proposed for the cyclization of the *NH* derivatives to the quinoxaline 4-oxides. One involved a direct, aldol-type condensation again analogous to the mechanism in scheme **2.3**. The other proceeded through an *aci*-nitro intermediate (**216**) which could not be formed from the *N*-methylacetanilides. The results clearly show that the *N*-methyl compounds react in the same way as the *NH* derivatives and would then logically proceed by the same mechanism, i.e. the direct, aldol-type condensation.



(**216**)

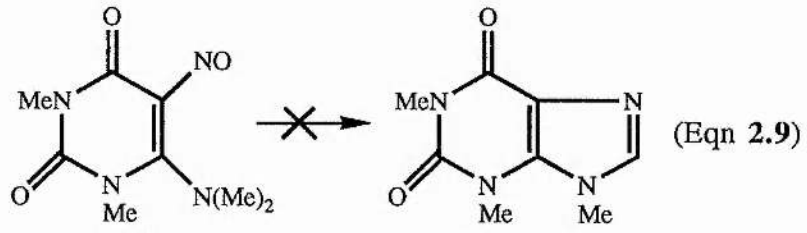
For the *N*-(substituted-*o*-nitrophenyl)amino esters, the presence of a hydrogen on the amino nitrogen appears to be crucial to cyclization to the benzimidazole *N*-oxides whereas for the *o*-nitroacetanilides, the hydrogen does not appear to play a part in the reaction. In the latter case the nitrogen and the methylene group are separated by a carbonyl group, thus it is more understandable why a substituent on nitrogen would not have any effect on the nature of the products formed.

Goldner *et. al.*[34] reported that the uracil derivatives (**217**) with a secondary amino nitrogen cyclized as expected to the xanthines (**218**) (Eqn **2.8**), but one with a tertiary amino nitrogen (**219**) did not (Eqn **2.9**).



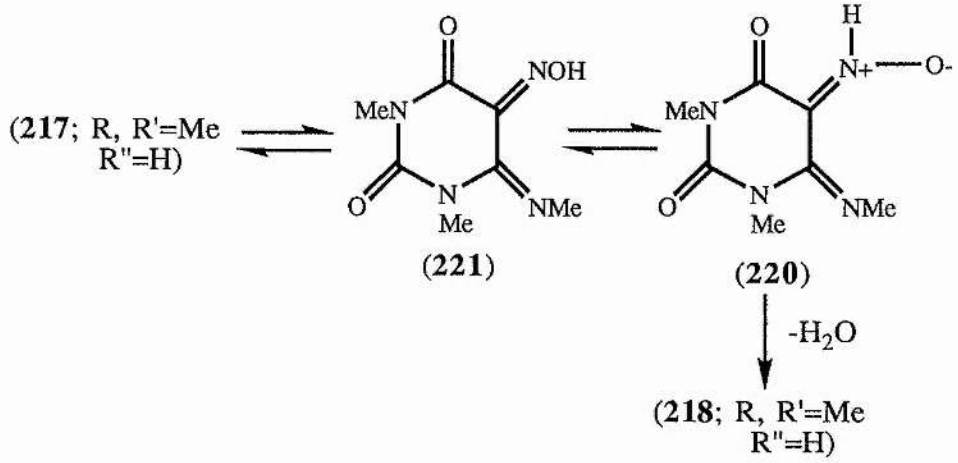
(217) (218)

R and / or R'=H, alkyl, aryl, or aralkyl
R''=H, alkyl, hydroxyalkyl, alkoxycarbonyl



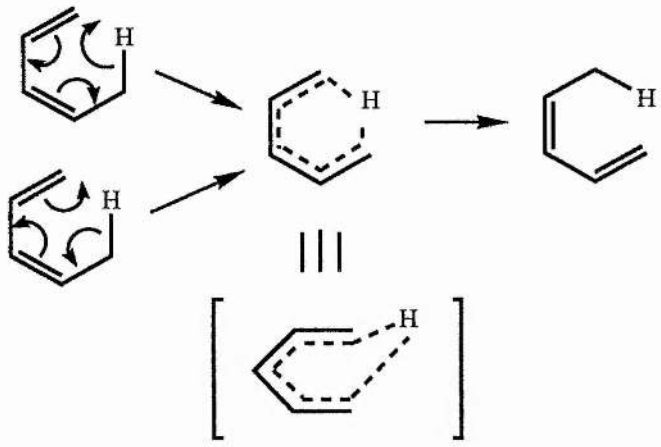
(219)

The explanation given was that the pyrimidine (**219**) could not isomerise to an *N*-oxide analogous to (**220**) necessary for achieving the product (Scheme **2.5**). However, we would like to propose an alternative mechanism which seems more plausible.



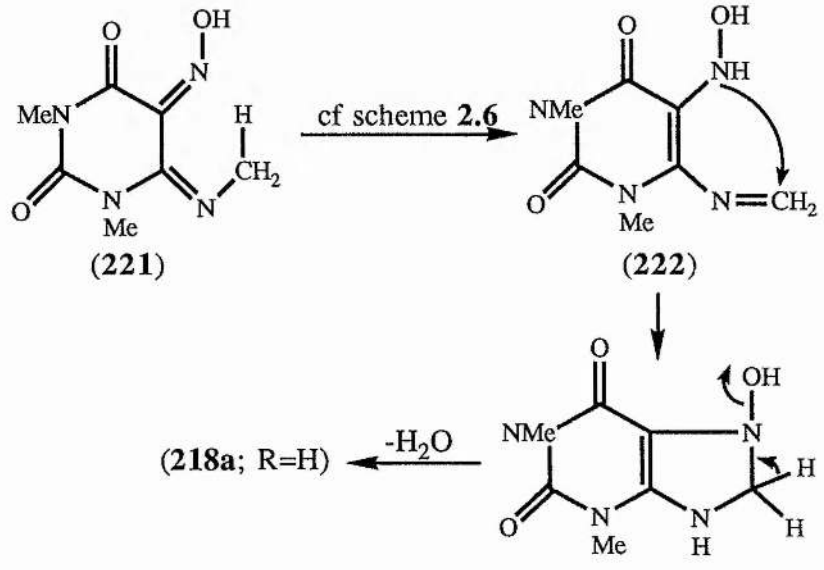
Scheme **2.5**

The alternative mechanism is one in which the oxime intermediate (**221**) undergoes an intramolecular hydrogen shift. This rearrangement can be called an intramolecular ene reaction or a sigmatropic [1,5] migration (Scheme **2.6**). Such rearrangements are widely known, particularly concerning 1,5 hydrogen shifts[35].



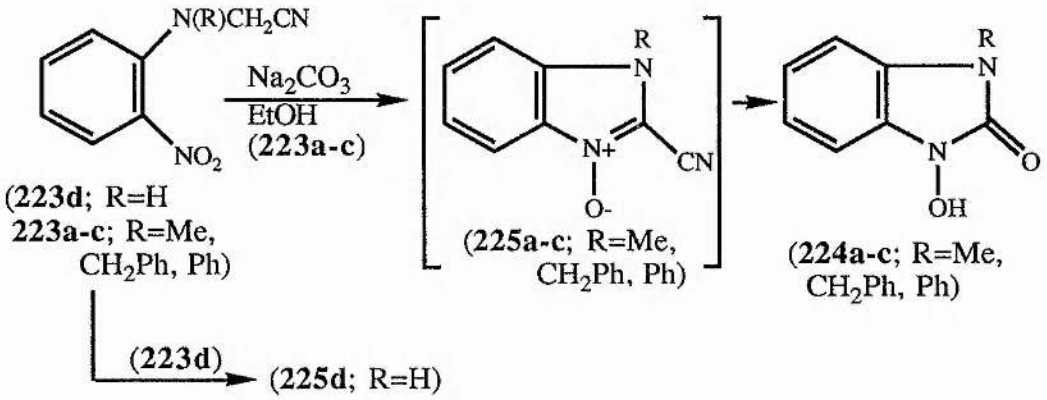
Scheme **2.6**

In the case of the intermediate (**221**), such migration would lead to formation of the hydroxylamino-anil (**222**). Cyclization and dehydration would then give the xanthine (Scheme **2.7**) A compound such as (**219**), in which the nitrogen was fully substituted could not form the anil intermediate necessary to give 7-methylxanthine. This mechanism is similar to the one proposed by McFarlane that was mentioned when the Stacy reaction was discussed (cf Scheme **2.4**). For the formation of benzimidazole *N*-oxides, the anil intermediate is the nitroso derivative, whereas for the formation of the xanthines, analogous to benzimidazoles, it is the hydroxylamino derivative.



Scheme **2.7**

In this thesis the argument is put forward that the *N*-(substituted-*o*-nitrophenyl)-sarcosine esters investigated do not form 1-methylbenzimidazole 3-oxides *at all* upon reaction with base. It is considered unlikely that the *N*-oxides were formed as intermediates which then reacted further to give the products isolated. Livingstone and Tennant[36] use this latter argument to explain why an *N*-substituted-*N*-cyanomethyl-*o*-nitroaniline (**223a-c**; R=Me, CH_2Ph, Ph) in a reaction with base gave only the *N*-substituted benzimidazol-2-one (**224a-c**; R=Me, CH_2Ph, Ph) while the *NH* derivative (**223d**; R=H) gave the corresponding *N*-oxide (**225d**; R=H) (Scheme **2.8**).

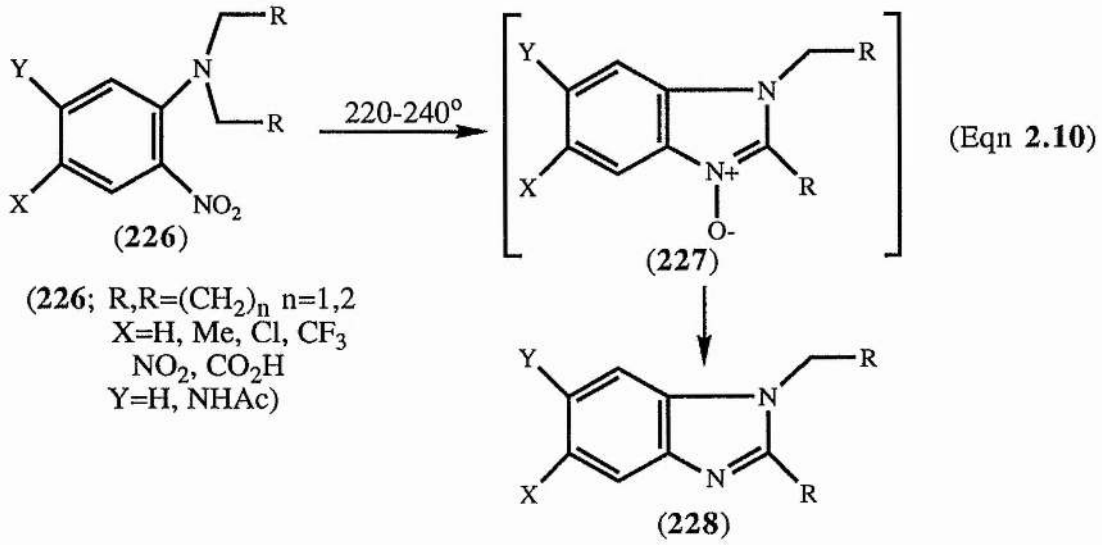


Scheme **2.8**

The researchers had apparently assumed that the compounds (**223a-c**) cyclized as dictated by the traditional mechanism analogous to the one outlined in scheme **2.3**, and that the *N*-substituted benzimidazole *N'*-oxides were formed and then converted by reaction with base into the benzimidazol-2-ones. There is an alternative explanation, namely that the cyano *N*-oxides were not formed at all but that the observed final product was formed directly. Both possible explanations are discussed in section **4.1** of chapter **4**.

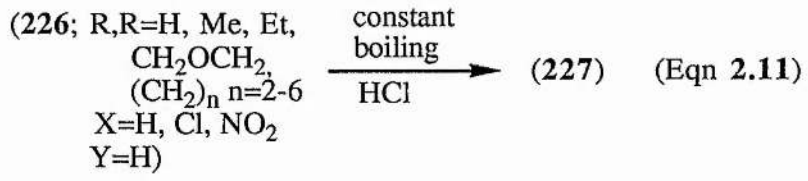
N-Alkylbenzimidazole *N'*-oxides have been the presumed and in some cases proven intermediates for several reactions of *NN*-disubstituted-*o*-nitroanilines. The thermal cyclization of the anilines (**226**) gave 1,2-disubstituted benzimidazoles with the corresponding *N*-oxides (**227**) as the presumed intermediates[37] (Eqn **2.10**). It was found that mineral acid facilitated the cyclization and allowed the reactions to be

performed at lower temperatures. When the anilines (**226**) were boiled in mineral acids, the reactions could be done at sufficiently low temperatures to give the *N*-oxides (**227**) themselves as the sole products[38] (Eqn **2.11**). The mechanism proposed for the acid-catalyzed cyclizations is shown in scheme **2.9**.



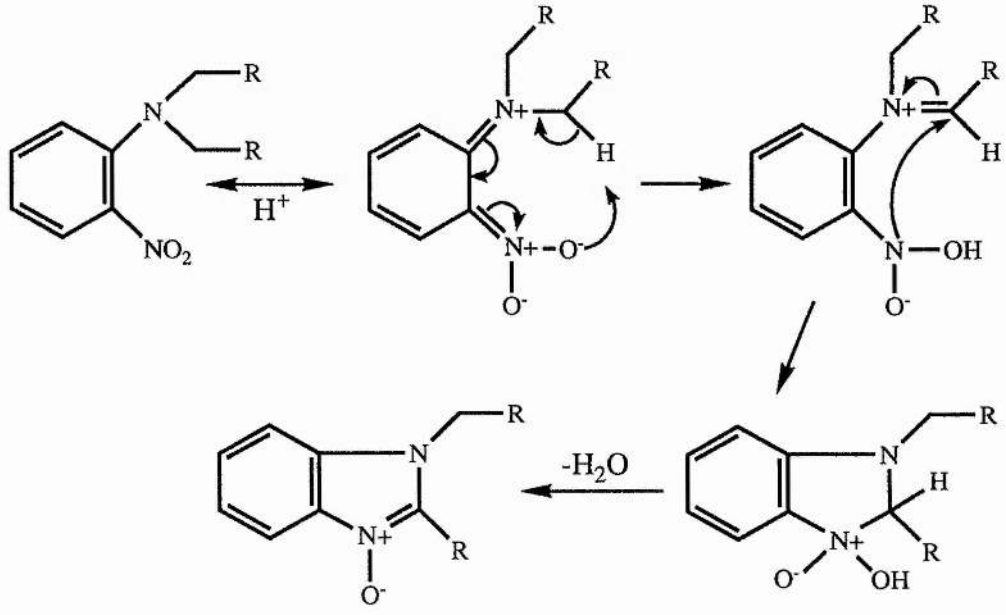
(**226**; R,R=$(CH_2)_n$ n=1,2
X=H, Me, Cl, CF_3
NO_2, CO_2H
Y=H, NHAc)

(Eqn **2.10**)



(**226**; R,R=H, Me, Et, CH_2OCH_2, $(CH_2)_n$ n=2-6
X=H, Cl, NO_2
Y=H)

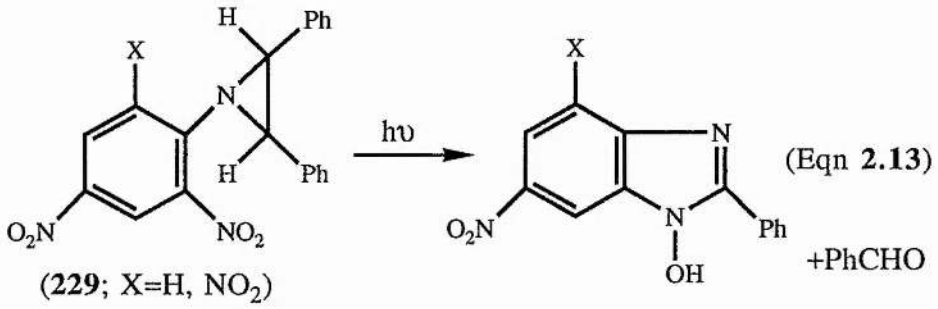
(Eqn **2.11**)



Scheme **2.9**

The photolysis of the anilines (**226**) gave either the benzimidazoles (**228**) or their *N*-oxides (**227**)[38] (Eqn **2.12**). Since a mixture of products was never isolated, it was put forth that the formation of the two products involved different mechanisms, and therefore, the *N*-oxide was not the intermediate in this case. One factor which appeared to determine which product was formed was ring size: (**226**; R=$(CH_2)_2$) formed the *N*-oxide while (**226**; R=$(CH_2)_n$ n=3,4) gave the benzimidazole. Along these lines, the photolysis of two aziridines (**229**; X=H, NO_2) containing a three membered ring gave only the *N*-oxide (Eqn **2.13**)[39].

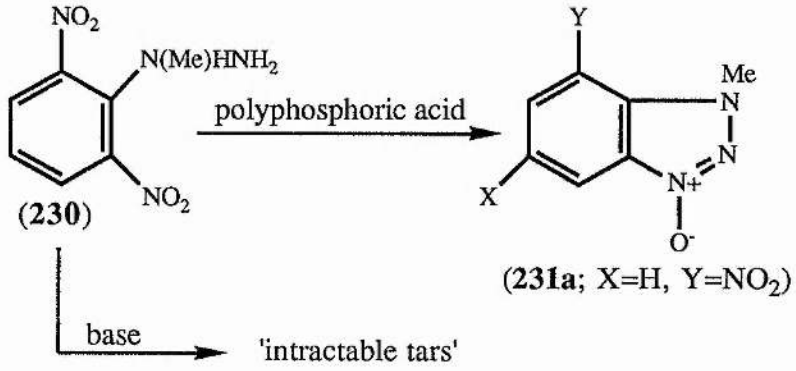
(**226**; X=Y=H, R,R=CH_2OCH_2, $(CH_2)_n$ n=2-4; X=Cl, Y=H, R,R=$(CH_2)_n$ n=2,4) $\xrightarrow{h\upsilon}$ (**227**) or (**228**) (Eqn **2.12**)



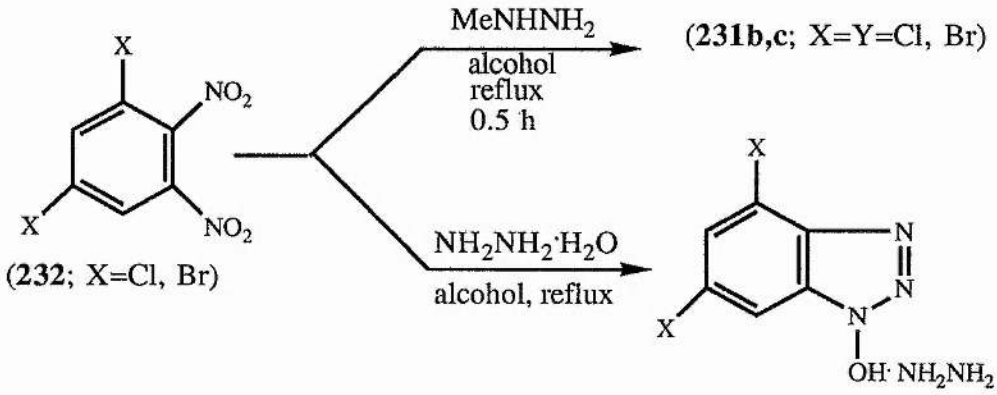
(**229**; X=H, NO_2) (Eqn **2.13**)

The cyclization of a 1-methyl-1-*o*-nitrophenylhydrazine (**230**) to 1-methylbenzotriazole 3-oxide (**231a**; R=Me, X=H, Y=NO_2) using polyphosphoric acid could also occur via the mechanism in scheme **2.9**. The researchers said that they used this method because attempts using base resulted in intractable tars (Scheme **2.10**)[40]. No details were given so it is not known if other products were formed. This result could be significant with respect to the failure of the sarcosine esters to be cyclized by base. However, the paper referred to an earlier report that included the syntheses of two derivatives of 1-methylbenzotriazole 3-oxide (**231b,c**; R=Me, X=Y=Cl, Br) by reaction of substituted *o*-dinitrobenzenes (**232**; X=Y=Cl, Br) with methylhydrazine in alcohol

(Scheme **2.11**)[41]. The 1-methyl-1-phenyl-2′,4′-dichloro- and dibromo-6′-nitrophenyl-hydrazines were the assumed intermediates.



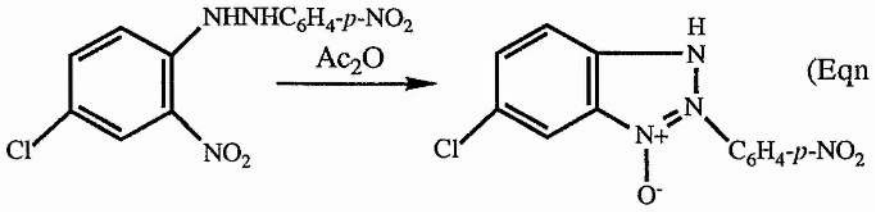
Scheme **2.10**



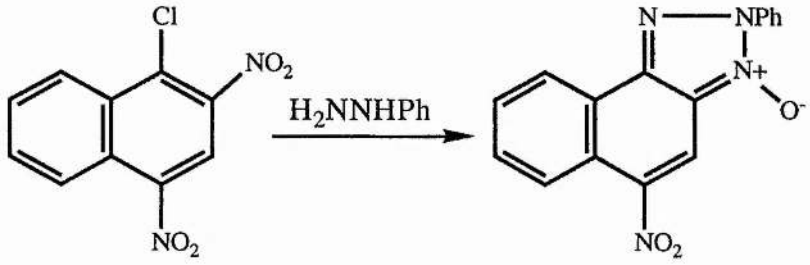
Scheme **2.11**

It is surprising that these compounds would cyclize in this case to the *N*-oxides in ~50% yield while the 6′-nitro derivative (**230**) would not react with base to give the analogous product (**231a**). These were the only syntheses of the 1-substituted benzotriazole 3-oxides using these methods found. Also reported was the reaction of the dinitrobenzenes with hydrazine hydrate which gave 1-hydroxybenzotriazoles (Scheme **2.11**).

The 1-unsubstituted benzotriazole 3-oxides are usually synthesized by reaction of a substituted phenylhydrazine with a reagent such as acetic anhydride[42] (Eqn **2.14**) or by *in situ* reactions such as that illustrated in eqn **2.15**[41,42].



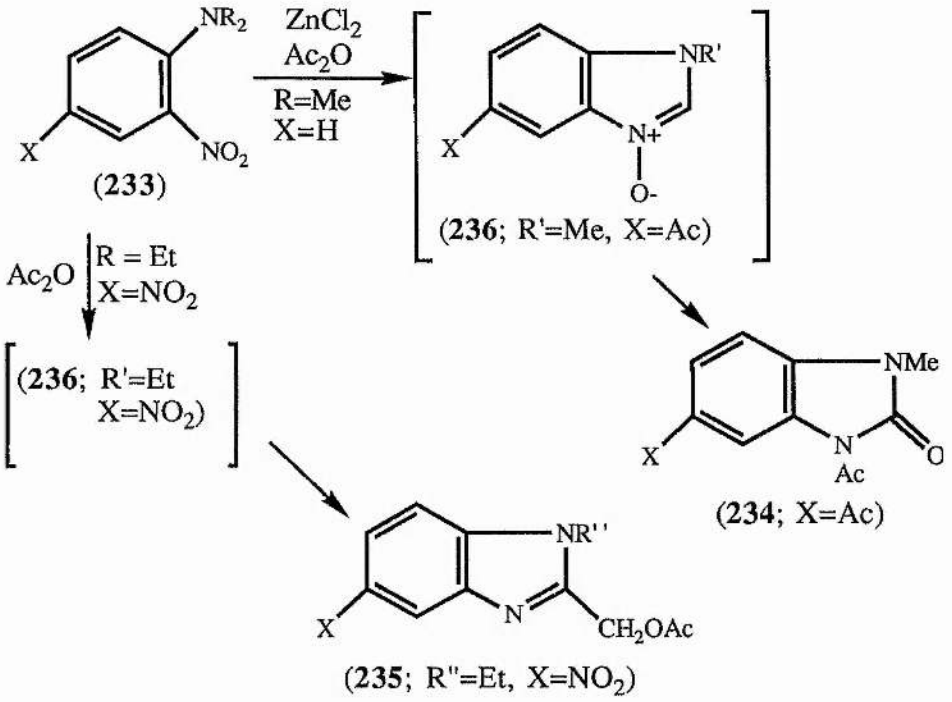
(Eqn **2.14**)



(Eqn **2.15**)

It is tempting to say that the 1-methyl-1-*o*-nitrophenylhydrazines upon reaction with base reacted 'abnormally' with base as the sarcosine esters did. However, the success of the *in situ* reactions indicate that further investigation is necessary before any conclusions can be drawn.

Returning to the benzimidazole *N*-oxides, another case in which the they were the presumed intermediates was the reaction of *NN*-dialkyl-*o*-nitroanilines (**233**) with zinc chloride in boiling acetic anhydride[43]. For R=methyl (X=H), the product was 3,5-diacetyl-1-methylbenzimidazol-2-one (**234**; X=Ac), and for R=ethyl ($X=NO_2$), the product was 2-acetoxymethyl-1-ethylbenzimidazole (**235**; R″=Et, $X=NO_2$). Though all attempts to trap the intermediate failed, the researchers supported their assignment by referring to two reactions conducted by Takahashi and Kano[44a,b]. The reactions show that the two *N*-oxides (**236**; X=H, R=Me, R′=H, Me), under similar, milder conditions, readily give the acetylbenzimidazoles (**234**; X=H, **235**; R″=Me, X=H) (Scheme **2.12**).

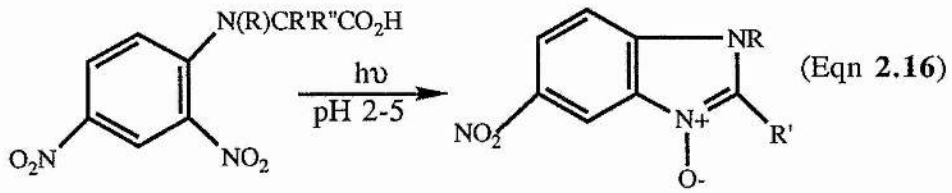


(**236**; R'=Me, X=H) $\xrightarrow{Ac_2O}$ (**234**; X=H)

(**236**; R'=Me, 2-Me) $\xrightarrow{Ac_2O}$ (**235**; R''=Me, X=H)

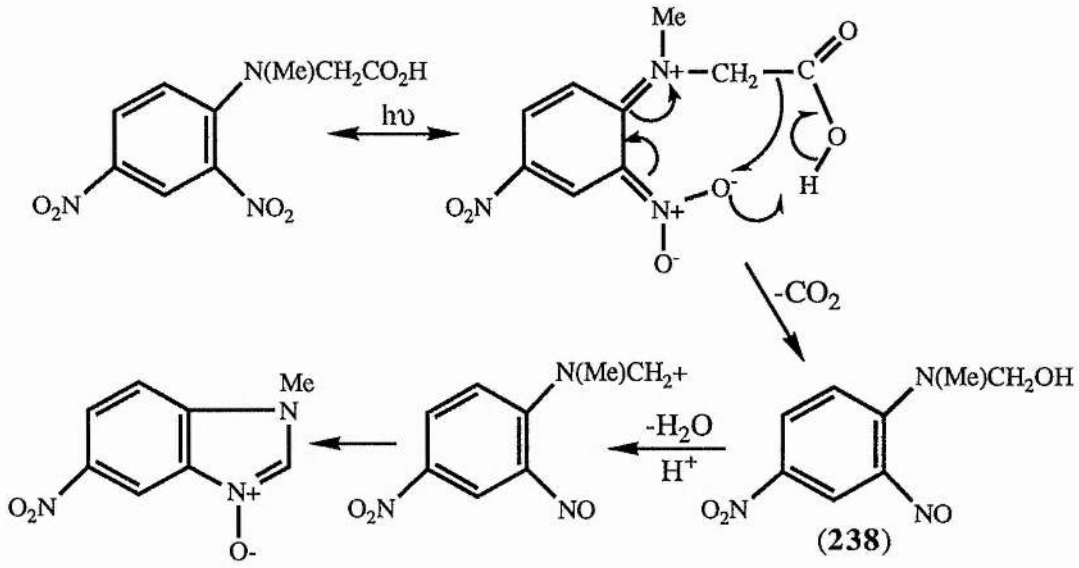
Scheme **2.12**

The photolysis of *N*-(2,4-dinitrophenyl)amino acids (**237**) gave the corresponding *N*-oxides when the pH of the solution was between 2 and 5[45] (Eqn **2.16**). This includes the one known case in which *N*-(2,4-dintrophenyl)sarcosine has been cyclized to 1-methyl-5-nitrobenzimidazole 3-oxide under any conditions. The mechanism involves the formation of an alcohol (**238**) (Scheme **2.13**).



(Eqn **2.16**)

(**237**; R, R', R''=H, Me
R' or R''=Me)

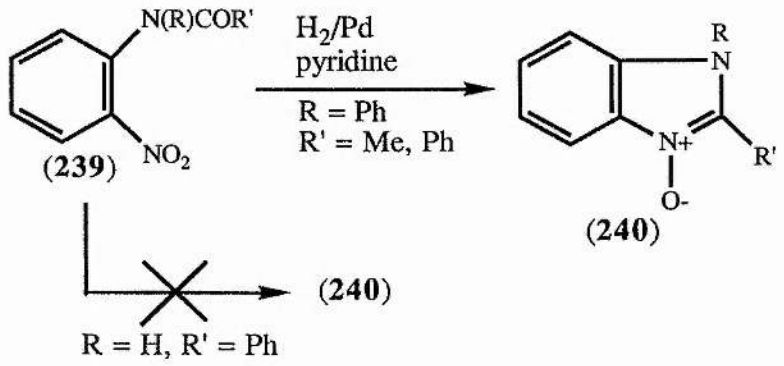


Scheme **2.13**

The mechanism for the cyclization of the secondary amino acids proceeds through a nitroso-anil and is thus analogous to the alternative one proposed for the afore-mentioned reactions of *N*-benzyl-*o*-nitroanilines, the glycine ester derivatives and the uracils.

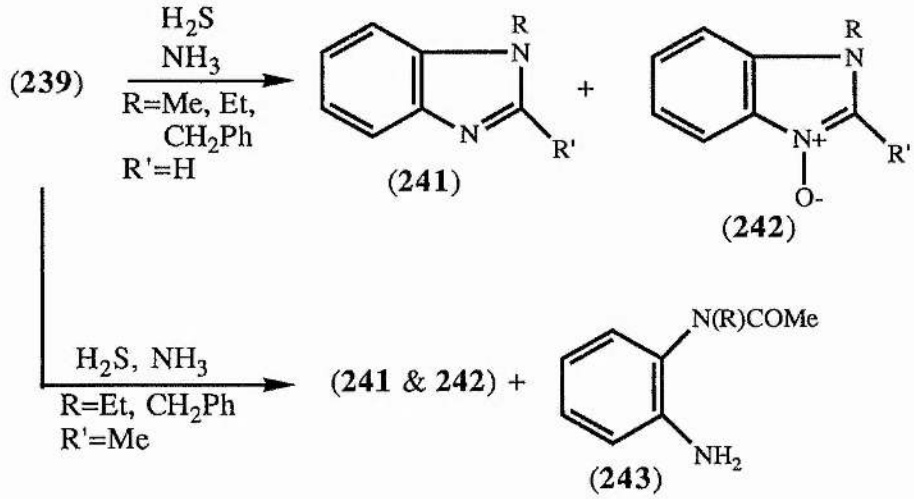
Pyrolysis of the amino acids gave mixtures of many products. The compound (**237**; R=R′=H, R″=Ph) was the only one to give an *N*-oxide[46].

N-Alkylbenzimidazole *N*′-oxides have been synthesized using a number of other methods. One method involves catalytic hydrogenation of *N*-alkyl-*o*-nitroacetanilides (**239**). Compound (**239**; R=Ph, R′=Me, Ph) was cyclized to the corresponding *N*-oxide (**240**) in good yield. However, (**239**; R=H, R′=Ph) did not give the corresponding *N*-oxide[47] (Scheme **2.14**). No explanation was given.

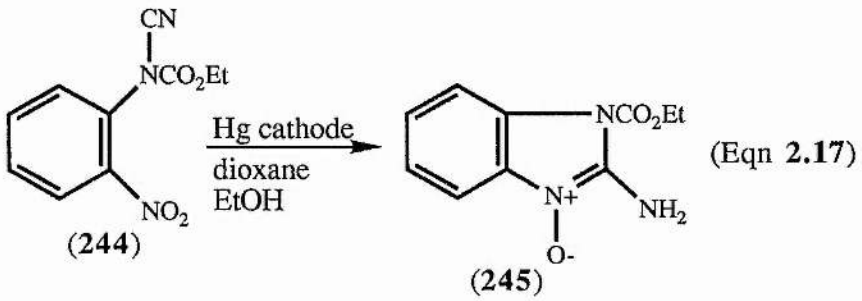


Scheme **2.14**

Reaction of the acetanilides (**239**; R=Me, Et, CH_2Ph, R′=H) with hydrogen sulfide and ammonia gives the the benzimidazole (**241**) and its *N*-oxide (**242**). *N*-alkyl-2′-nitroformanilides (**239**; R=Et, CH_2Ph, R′=Me) under the same conditions gave a mixture of the corresponding benzimidazoles, their *N*-oxides, and 2-aminoacetanilides (**243**) (Scheme **2.15**)[7]. Finally, the cyanocarbanilate (**244**) was electrochemically converted to the ethyl 2-aminobenzimidazole-1-carboxylate 3-oxide (**245**) (Eqn **2.17**)[48].



Scheme **2.15**

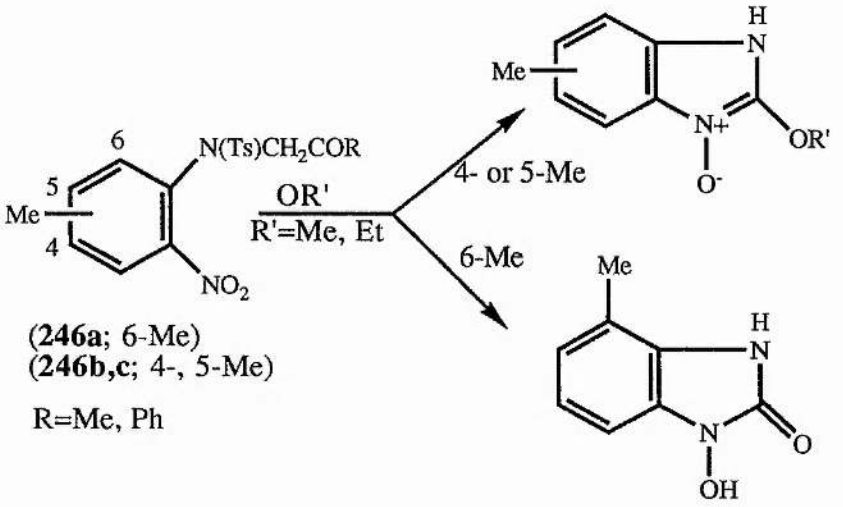


(Eqn **2.17**)

The cyclizations of tertiary anilines to the *N*-alkylbenzimidazole *N'*-oxides have been presented and thus, question two has been answered. For the most part the starting materials and/or the reaction conditions were sufficiently different from the reaction of the *N*-(substituted phenyl)sarcosine esters that they do not help to explain the anomalous results in the cyclization of the latter.

One part of question one has also been answered concerning the literature precedent for a tertiary aniline reacting differently from a secondary aniline under the same conditions. The catalytic hydrogenation of compounds (**239**; R=H, Ph, R'=Ph, R=Ph, R'=Me) was an interesting case in which a tertiary aniline gave the expected product and the secondary aniline did not. Several cases where the reverse occurred were found, such as the reactions of Stacy *et. al.*, Livingstone and Tennant, and Goldner *et. al.* that were discussed. They could all be explained by a mechanism in which an anil intermediate cyclizes to the *N*-oxides (cf Scheme **2.4**) which accounts for the *N*-substituted compounds not cyclizing to these compounds. Thus they and the reactions of the *N*-(substituted-*o*-nitrophenyl)amino esters could all be linked by an analogous mechanism.

To address the other part of the question, there were only a few cases found which indicated that a substituent was apparently impeding reaction involving a neighbouring group. *N*-phenacyl and *N*-acetonyl-*N*-tosyl-*o*-nitroanilines are for the most part cyclized by alkoxides to 2-alkoxybenzimidazole 3-oxides[49]. The 6-methyl derivative (**246a**) gave 1-hydroxy-4-methylbenzimidazol-2-one while the 4- and 5-methyl derivatives (**246b,c**) gave the *N*-oxides (Scheme **2.16**). It is interesting to note that the analogous 6-methylglycine ester cyclized 'normally' to the *N*-oxide.

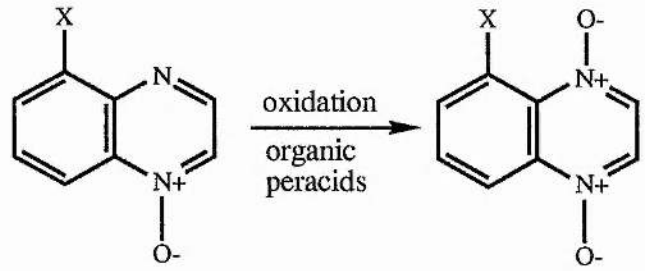


(**246a**; 6-Me)
(**246b,c**; 4-, 5-Me)

R=Me, Ph

(Scheme **2.16**)

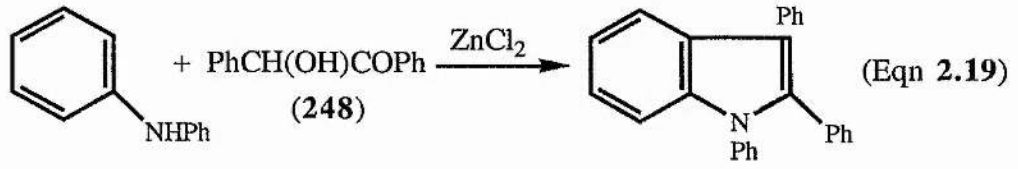
Landquist[50] reported that with the exception of 5-methoxyquinoxaline 1-oxide (**247**; X=OMe), the 5-substituted derivatives (**247**; X=Me, Cl, OEt, NHAc) were particularly resistant to further oxidation (Eqn **2.18**). The cause was thought to be the reduced electron-density at the nitrogen (due to the other nitrogen being positively charged) and the steric hindrance (which is smallest for methoxy) caused by the neighbouring group.



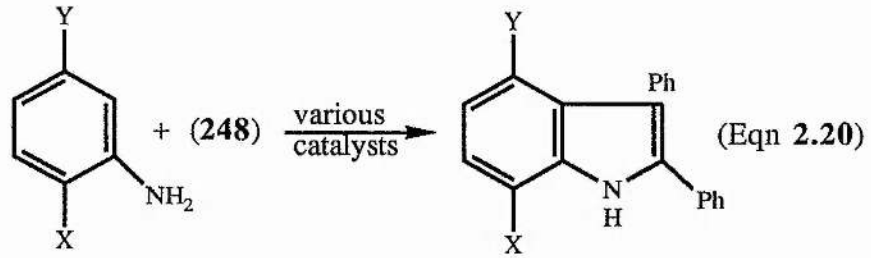
(Eqn **2.18**)

(**247**; X = OMe, Me, Cl, OEt, NHAc)

Another example was found in the synthesis of substituted indoles. In accordance to the Japp-Murray synthesis, diphenylamine and benzoin (**248**) react in the presence of zinc chloride to give 1,2,3-triphenylindole[51] (Eqn **2.19**). However, the similar 2- and 2,5-disubstituted anilines (**249**; X=Cl, Y=H, Me) under the same conditions give only very small percentages of the corresponding indoles or none at all[52] (Eqn **2.20**).



(Eqn **2.19**)

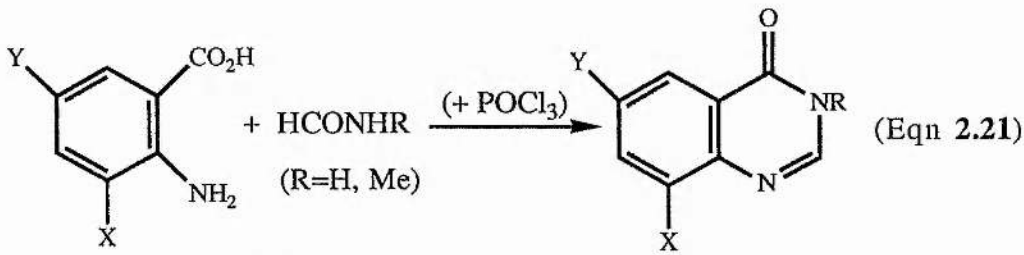


(**249**; X=Cl
Y=H, Me)

very small % or
no crystalline products

(Eqn **2.20**)

It is possible that the reason why the substituted anilines give poor yields of the indoles was that the rings were more electron-deficient making the nitrogen less nucleophilic. Another case which at first appeared to involve steric hindrance turned out to be a matter of increased elctron-deficiency causing decreased reactivity. Substituted anthranilic acids (**250**) react with formamide or *N*-methylformamide to form quinazolinones (Eqn **2.21**)[53]. For **250**; X=NO_2, if Y is also a strongly electron-withdrawing group, the amount of product formed is decreased. In some cases the decreased reactivity could be made up by addition of $POCl_3$, resulting in a boost in the yield of the products. However, for the extreme cases where Y=NO_2, only a trace amount of the quinazolines were isolated for both R=H and methyl.



(Eqn **2.21**)

(**250**; X=Cl, CH_3, NO_2
Y=H, OCH_3, Cl, NO_2)

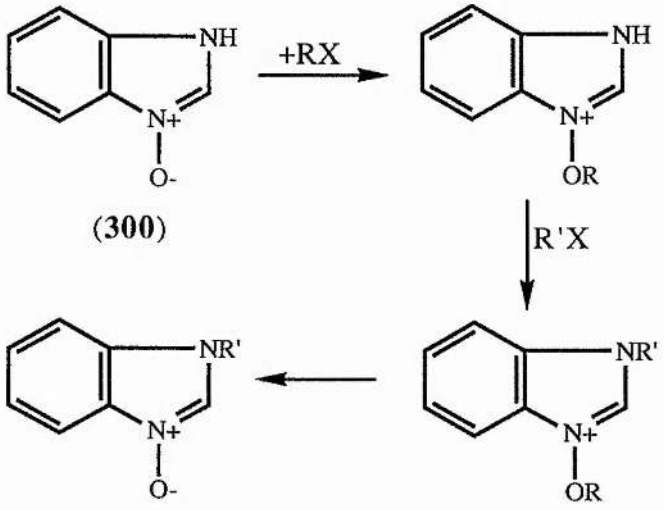
Thus, the literature search did uncover some cases providing precedent for a neighbouring substituent, on compounds similar to the esters, affecting the progress or direction of reaction. It is widely accepted that neighbouring groups in general can have

profound effects on the reactivities of one another. These effects may be either steric or electronic or both. The investigation in this project into neighbouring group effects was designed to explore both types of effect: the results are presented and discussed in section **4.2** of chapter **4.**

CHAPTER 3

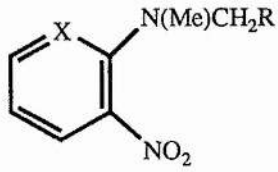
INTRODUCTION

When the general method detailed in scheme **1.2** failed to give the *N*-alkyl-benzimidazole *N'*-oxides, alternative methods were considered, such as alkylation of the *N*-unsubstituted benzimidazole *N'*-oxides (**300**). Although such a reaction is known to result in preferential alkylation of the oxygen[7,54]; by protecting the oxygen with a group that could be removed later, the desired *N*-alkylation should occur (Scheme **3.1**).



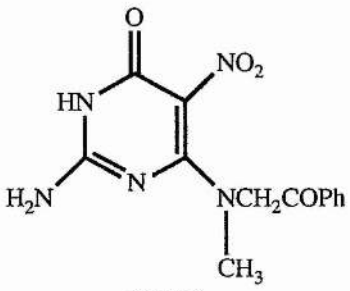
Scheme **3.1**

This possibility has not yet been investigated. Instead, another possible method which involved the mimicking of the guanine syntheses[22,23] discussed in chapter **1** was considered. The cyclization conditions used in these syntheses were very similar to those under which the *N*-(substituted phenyl and pyridyl)sarcosine esters (**301**) gave the unexpected azoxybenzenes and the *N*-hydroxyquinoxaline-2,3-diones (cf Eqn **1.1**). There could be a number of reasons why the reactions failed to give the *N*-alkyl-benzimidazole *N'*-oxides. The fact that the nitrogen in the starting materials was fully substituted is an obvious possibility but it could also have to do with the type of activating group, R, situated adjacent to the methylene group.

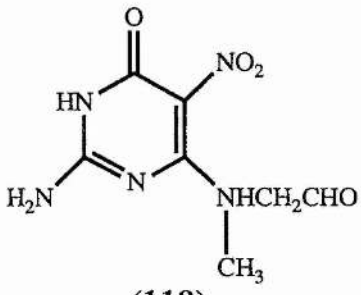


(**301**; X=CH, N
R=CO_2Et, the activating group)

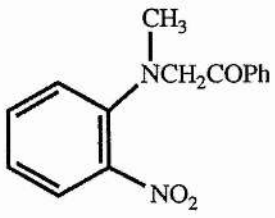
By trying to cyclize the benzene analogs of the 6-(dialkylamino)pyrimidine (**117**) and [*N*-(2-amino-6-hydroxy-5-nitropyrimidin-4-yl)-*N*-methylamino]acetaldehyde (**118**), the latter possibility could be investigated. With this idea in mind, attempts were made to synthesize the ketone (**302**) and the aldehyde (**303**). The compounds are the same as those McFarlane tried to cyclize except that the activating group is a ketone or an aldehyde, rather than an ester. Therefore, any difference in the cyclization products formed under the same conditions would be attributable to the difference in activating group.



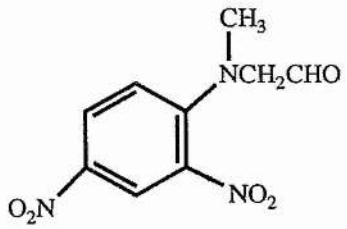
(**117**)



(**118**)



(**302**)

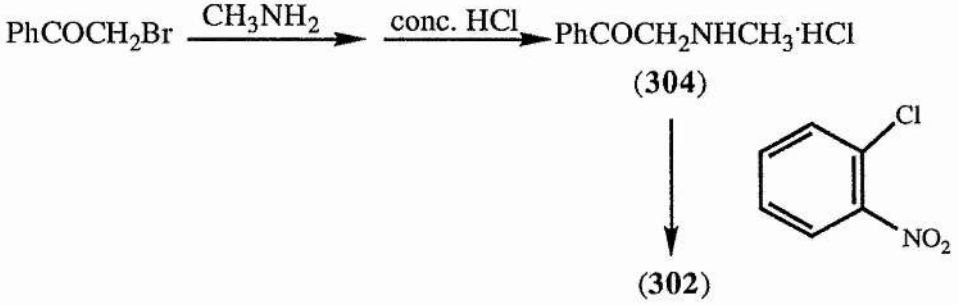


(**303**)

RESULTS

ATTEMPTED SYNTHESIS OF *N*-METHYL-*N*-(2-NITROPHENYLAMINO)-ACETOPHENONE (**302**)

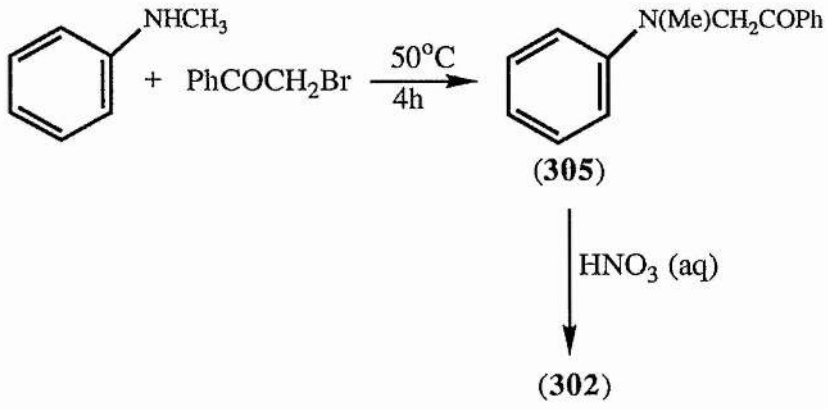
The route to this ketone that was to tried first involved making *N*-methylphenacylamine (**304**) by the method of Hyde and Browning[55] and then reacting that with an *o*-halogenonitrobenzene (Scheme **3.2**).



Scheme **3.2**

Attempts to synthesize the phenacylamine (**304**) were almost completely unsuccessful. The literature method[55] was repeated three times, each time under slightly different conditions. A small amount (4.5%) of the crude amine was obtained on only one occasion. Attempts were made to temper the reaction since the conditions seemed too harsh but the result could not be repeated, much less improved. Thus another approach to the ketone (**302**) was pursued.

It also seemed possible to synthesize the ketone by first making (*N*-methyl-*N*-phenyl-amino)acetophenone (**305**), followed by nitration (Scheme **3.3**).

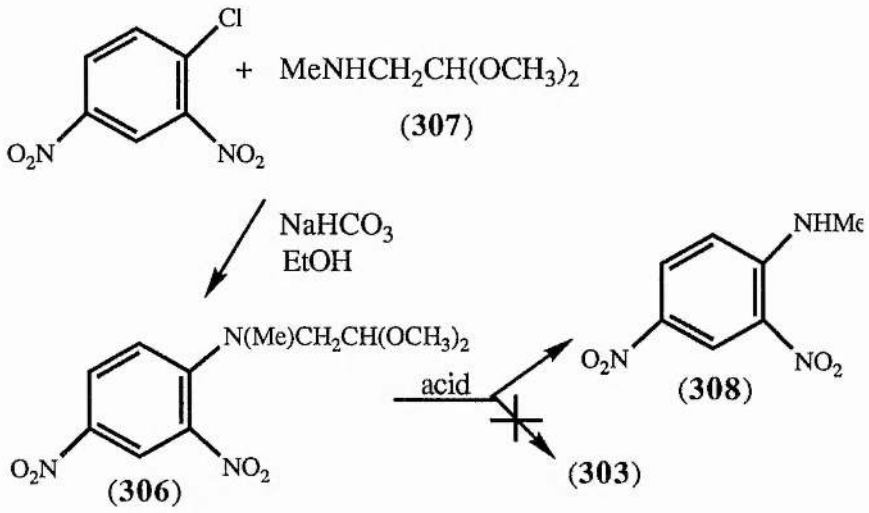


Scheme **3.3**

The first step is straightforward and by following the literature method[56], (**305**) is obtained in good yield. The method for the mono-nitration of a similar product, *N*-(4-methyl-2-nitrophenylamino)acetophenone[57], was applied to (**305**). Once again, several attempts were made but only complicated mixtures resulted. The conditions were modified but with no improvement.

ATTEMPTED SYNTHESIS OF [*N*-METHYL-*N*-(2,4-DINITROPHENYL-AMINO)]ACETALDEHYDE (**303**)

The acetal derivative (**306**) of the aldehyde was unknown. However, because it has a strong similarity to the ester analogs a similar synthetic method was employed. 2-(*N*-methylamino)acetaldehyde dimethyl acetal (**307**) and 1-chloro-2,4-dinitrobenzene were readily obtained and reaction of the two in ethanol in the presence of base gave the desired acetal in good yield and purity. The difficulty arose in converting the acetal into the aldehyde (Scheme **3.4**).



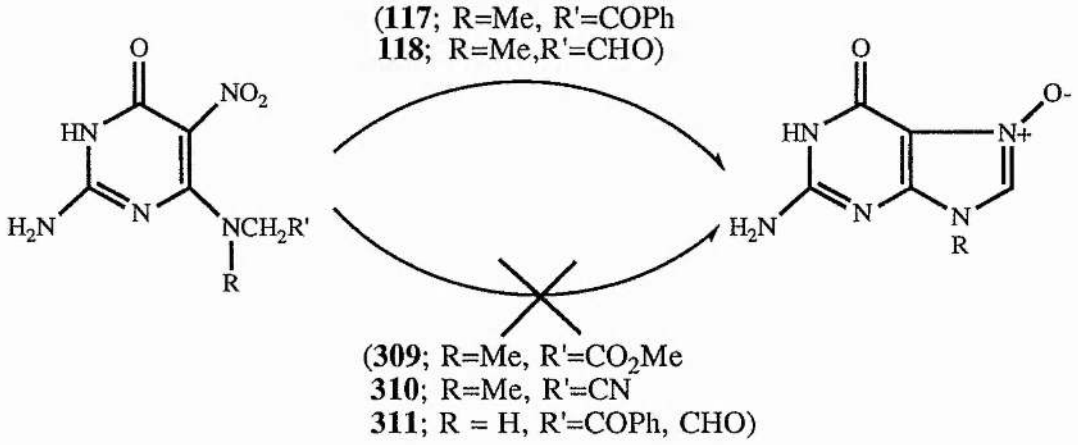
Scheme **3.4**

Brown *et. al.* reported[22] that the acetal derivative of (**118**) and concentrated hydrochloric acid with heating gave the aldehyde (**118**) in excellent yield. When the method was applied to (**306**), the result was cleavage of the side-chain to give a small amount of *N*-methyl-2,4-dinitroaniline (**308**). Several attempts using dilute hydrochloric acid and one using trifluoroacetic acid also gave the aniline. In all, thirteen attempts were

made using a variety of acids which gave either the aniline, the unreacted starting material or an inseparable mixture from which nothing could be identified. Thus all attempts at conversion to the aldehyde were unsuccessful. No attempt was made to cyclize the acetal (**306**) directly to the *N*-oxide.

DISCUSSION

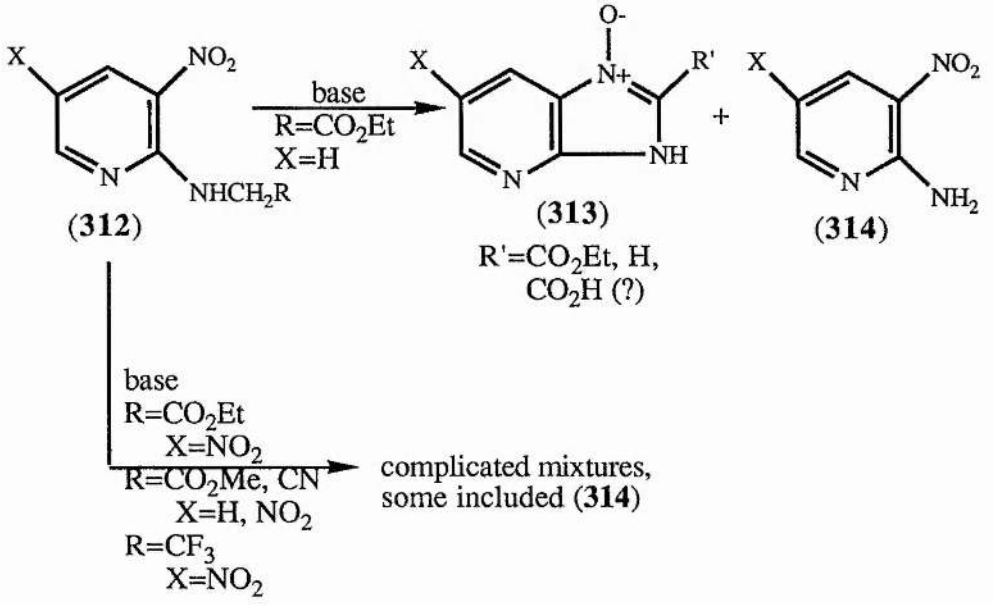
The attempted syntheses having failed, the intended comparison of the cyclization products could not be made. Thus the possible significance of the type of activating group is still uncertain. However, there is evidence supporting the idea that the nature of this group can have profound influence on the outcome or success of cyclization. Brown *et.al.* reported that while ketones and aldehydes cyclized to the *N*-oxides, esters (**309**) and nitriles (**310**) did not (Scheme **3.5**).



Scheme **3.5**

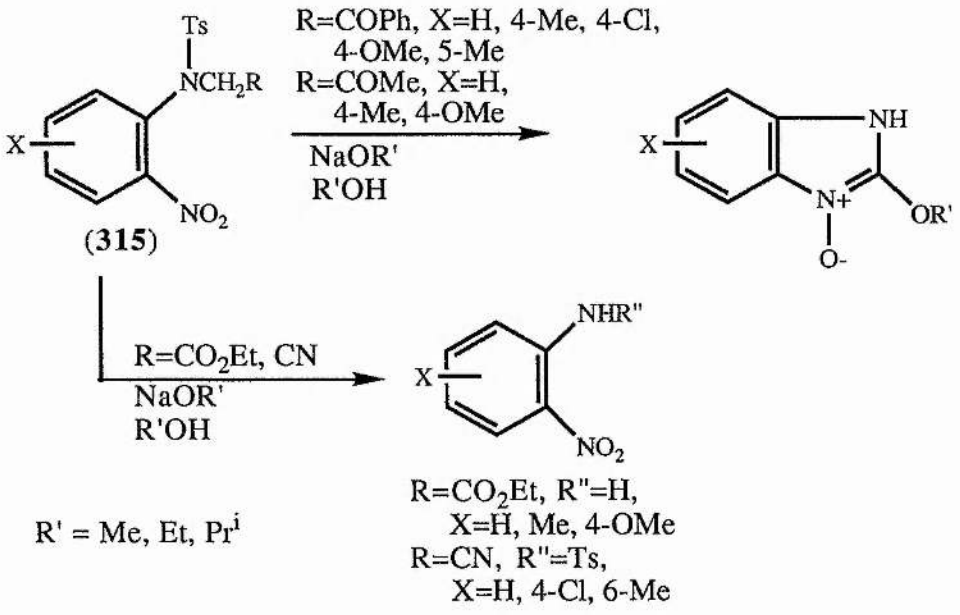
The paper included no discussion of these findings except to say that the structural requirements for the cyclization were specific. The reason for the difference in reactivity is not obvious. All of the activating groups are electron-acceptors adjacent to the methylene group, which is commonly accepted as a requirement for cyclization. The fact that Brown *et. al.* reported that esters did not cyclize suggests that the failure of *N*-(substituted phenyl and pyridyl)sarcosine esters to cyclize to the *N*-oxides could be due to the ester group. However, trying to draw conclusions from the reactions of the guanine

compounds and apply them directly to the reactions of the benzenoid analogs is too simplistic and most likely not valid. Analogous derivatives of the two sets of compounds can exhibit markedly different behaviour. One example is that both Brown *et. al.* and Nohara *et. al.* reported that the *NH* starting materials (**311**) would not cyclize under the same conditions as the *N*-methyl derivatives (**117, 118**) (Scheme **3.5**). (Nohara *et.al.* put forth that the NH group probably destabilized the phenacyl carbanion.) The general synthetic method described in chapter **1** shows that the *N*-(substituted *o*-nitrophenyl)glycine esters for the most part cyclize readily to 1*H*-benzimidazole 3 -oxides (the only exceptions being for those compounds indicated in scheme **1.3**). However, in the reactions of the pyridylglycine ester esters and derivatives (**312**) with bases, only one compound (**312**; R=CO_2Et, X=H) cyclized to the corresponding 1*H*-benzimidazole 3-oxide (and possibly its two 2-substituted derivatives) (**313**) (Scheme **3.6**)[1,58]. Aminonitropyridine (**314**; X=H) was also isolated. The other compounds gave complicated mixtures in which.none of the components could be identified; the only exceptions were the corresponding aminonitropyridines (**314**) in some cases (Scheme **3.6**). The pyridylsarcosine esters gave products analogous to those formed by the phenyl derivatives (Eqn **1.1**)[20].



Scheme **3.6**

The reactions of the pyridylglycine esters reinforce the possibility that there is an activating group effect. It is especially interesting to find such similar compounds as the glycine methyl and ethyl ester derivatives of (**312**) reacting so differently; it is not clear why this difference should affect the reaction pathway. The pyridine and pyrimidine series could also react differently than the benzene series because of the difference in electron distribution in the rings. Thus, as stated before, making assumptions based on comparison of these series may not be valid. Even so, this dependence on the functionality of the activating group has been reported for systems much more similar to the *NN*-disubstituted *o*-nitroaniline derivatives. Machin and Smith[49] in the course of investigating the ring-closures of *N*-phenacyl-*N*-*p*-tolylsulphonyl-substituted-*o*-nitroanilines (**315**) to 1*H*-benzimidazole 3-oxides, found that the corresponding esters and nitriles gave only primary or secondary anilines under the same conditions (Scheme **3.7**). These reactions can be accounted for mechanistically[49]; however, those of the pyridine and pyrimidine compounds that did not react or gave complicated mixtures are not so readily explained.



Scheme **3.7**

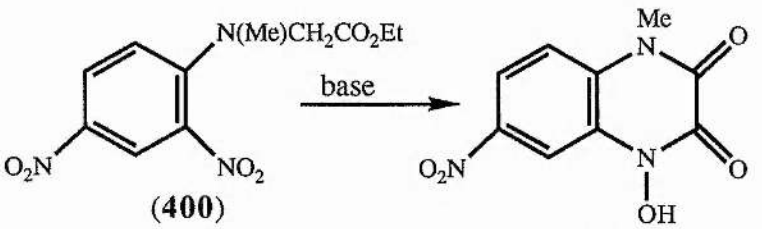
CONCLUSION

It is unfortunate that the attempts to synthesize the ketone and aldehyde starting materials failed. Both involved literature procedures that could not be duplicated so it may be that further trials may prove successful or that other approaches could be used. In any case further investigation into this aspect of the cyclization is warranted if the reaction as a whole is to be fully understood. Instead of proceeding with this investigation, given the failures encountered, it was decided to proceed to the question of the significance of having a tertiary rather than a secondary nitrogen in the starting materials.

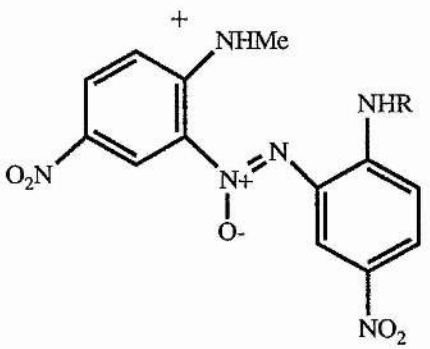
CHAPTER 4

INTRODUCTION

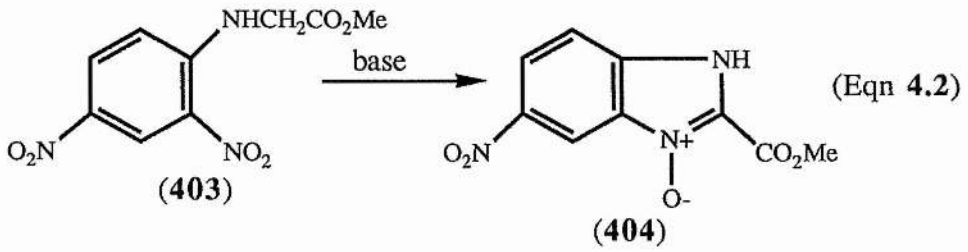
This chapter deals with the investigation into the two cases of anomalous reactions discovered by McFarlane. Both cases involved the reactions of *N*-(substituted-*o*-nitrophenyl)amino esters that gave products other than or in addition to the expected 1*H*-benzimidazole 3-oxides upon reaction with base. In one case, an *N*-(2,6-dinitrophenyl)-glycine ester (**110a**; R=CO_2Et, X=NO_2) reacted with base to give a 1-hydroxy-quinoxaline-2,3-dione (**111**) and possibly a 2,2′-diaminoazoxybenzene; this is discussed in section **4.2**. In the other case the *N*-(2,4-dinitrophenyl)sarcosine ester (**400**) reacted with a variety of bases to give 1-hydroxy-4-methyl-7-nitroquinoxaline-2,3-dione (**401**) and 2-amino-2′-methylamino or 2,2′-bis(methylamino)-5,5′-dinitro-azoxybenzene (**402a,b**) (Eqn **4.1**)[21]. Under similar conditions, the corresponding glycine ester (**403**) gave only methyl 5-nitro-1*H*-benzimidazole-2-carboxylate 3-oxide (**404**) (Eqn **4.2**)[1]. The only difference between these two esters is the substitution of the nitrogen, indicating that the presence of the methyl group was the reason for the sarcosine ester reacting 'abnormally'.



(**400**) (**401**) (Eqn **4.1**)[1]



(**402a,b**; R=H, Me)



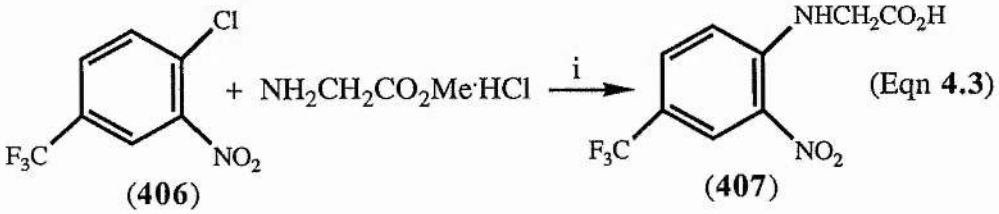
(403) (404) (Eqn **4.2**)

The reactions of other pairs of glycine and sarcosine esters had to be performed to see if they showed the same contrasting behaviour. Section **4.1** discusses the reactions of two such pairs of esters with base.

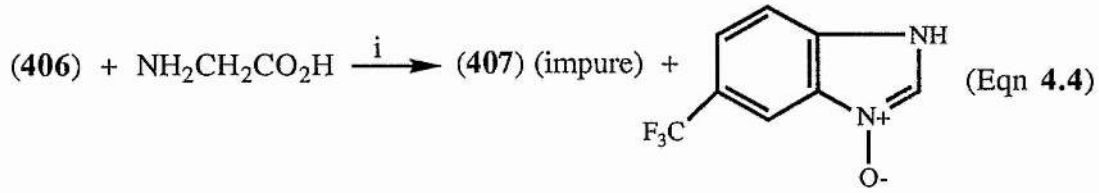
SECTION 4.1

A. *N*-(2-NITRO-4-TRIFLUOROMETHYLPHENYL)GLYCINE AND SARCOSINE ESTERS (**405**, **410**) AND THEIR REACTION WITH BASES

As was the case with many of the esters, the synthesis of the title esters proved to be tedious. Often several methods were attempted before a suitable one was found. The direct synthesis of the title glycine ester (**405**) presented difficulties. A method was adapted from that previously used in two similar reactions[59,60]. Unfortunately under the same conditions 4-chloro-3-nitrobenzotrifluoride (**406**) and glycine methyl ester hydrochloride gave only the free acid (**407**) (Eqn **4.3**). The reaction was repeated using glycine itself but the acid obtained was too impure to be used. Surprisingly, a small amount of the *N*-oxide (**408**) was also collected (Eqn **4.4**).



(**406**) (**407**) (Eqn **4.3**)

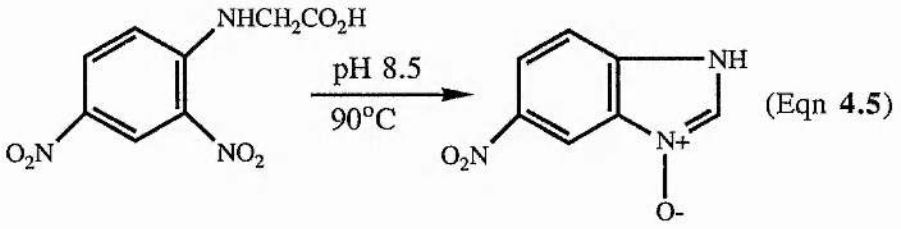


(Eqn **4.4**)

i = $NaHCO_3$, H_2O, ROH, reflux, 20 h

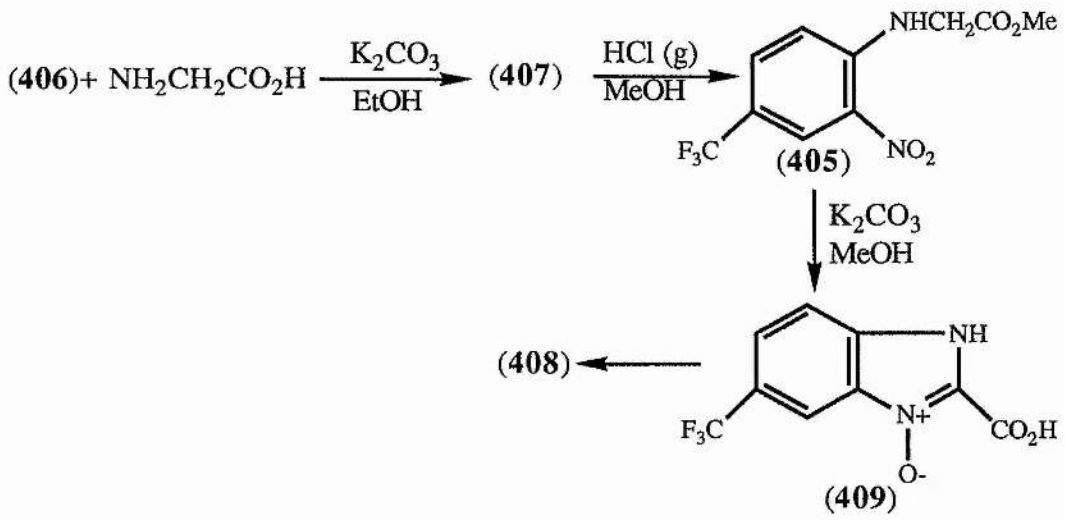
(**408**)

The cyclization of a carboxylic acid such as compound (**407**) is known, but nevertheless unexpected. Cyclizations of *N*-(2,4-dinitrophenyl)amino acids by photolysis have been studied extensively[38,45], but there are only a few cases reported to have occurred under basic conditions. Ljublinskaya and Stepanov[61] reported the cyclization of *N*-(2,4-dinitrophenyl)glycine to 5-nitro-1*H*-benzimidazole 3-oxide in a phosphate buffer solution (pH 8.5) at 90° (Eqn **4.5**). The formation of the *N*-oxide is surprising because the activating group adjacent to the methylene group needs to be electron-accepting. The carboxylic acid in basic solution would be in its anionic form and thus would not be expected to stabilize the carbanion intermediate necessary for *N*-oxide formation.



(Eqn **4.5**)

In the end the ester (**405**) was successfully synthesized by reaction of (**406**), glycine, and potassum carbonate in ethanol and esterified using gaseous hydrogen chloride and methanol (Scheme **4.1**). Cyclization of the ester using potassium carbonate in methanol (Scheme **4.1**) gave a buff coloured *N*-oxide which required several recrystallizations until a sample was obtained that gave n.m.r. spectra with good resolution. On the basis of these spectra, the product was characterized as the 2-unsubstitued 5-trifluoromethyl-1*H*-benzimidazole 3-oxide. The reason for the purification problem appeared to be that the *N*-oxide initially isolated (once acidified) was in fact the 2-carboxylic acid (**409**) rather than the expected methyl ester. Benzimidazole-2-carboxylic acid *N*-oxides and their salts are known to be unstable, readily decarboxylating under mild conditions[62]. Therefore, it was unexpected to find a sample stable enough to be isolated and identified. Only after several recrystallizations from aqueous hydrochloric acid, then aqueous methanol did the decarboxylation appear to be complete. No other products were isolated.



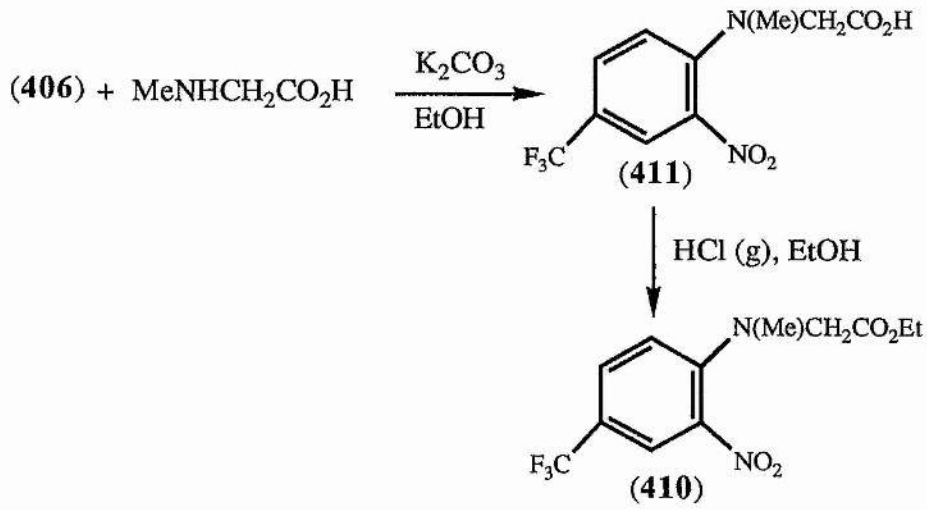
Scheme **4.1**

In comparison, the corresponding sarcosine ester (**410**) behaved quite differently under similar conditions. This ester was synthesized in the same manner as the glycine ester, i.e. via the free acid (**411**) (Scheme **4.2**). Compound (**410**) reacted with triethylamine in ethanol to give only the 1-hydroxy-4-methyl-7-trifluoromethyl-quinoxaline-2,3-dione (**412**) (Eqn **4.6**), the product being identified by comparison of its ^{13}C n.m.r. spectrum with that of the 7-nitro analog[20]. When potassium carbonate was used as the base, compound (**412**) was again formed, along with several additional products including the benzimidazole *N*-oxide (**408**), and the two isomeric quinoxalin-2-ones (**413**) and (**414**) (Eqn **4.7**). It should be noted that in all three of these, the *N*-methyl group of the starting material (**410**) is missing.

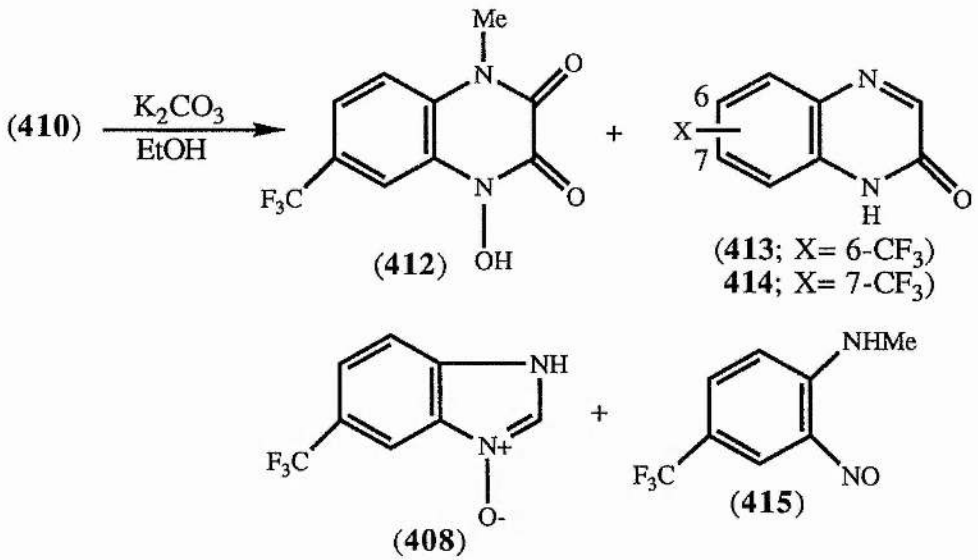
A dark green oil and a dark green oil-solid mixture were isolated which were found to contain unreacted ester (**410**) along with one other compound. The ^{1}H n.m.r. and the mass spectrum indicated that the compound could be *N*-methyl-2-nitroso-4-trifluoromethylaniline (**415**). The green colour of the mixtures reinforces this assignment. This is an important result because the aniline is proposed to be an intermediate in the formation of the quinoxalin-2-ones, the benzimidazole *N*-oxides (from sarcosine esters) and azoxybenzenes. This is the first instance in which this intermediate has thought to have been isolated in the reactions of the esters with bases.

The formation of the dione (**412**) parallels the reaction of the 4-nitro analog (**400**) under the same conditions, but in this case an azoxybenzene was not found. The

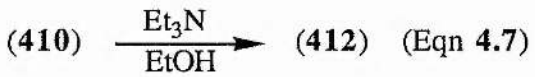
formation of the 1*H*-benzimidazole 3-oxide (**408**) is extraordinary, but comparison of the spectral data on the mixture with those for the pure samples makes the assignment irrefutable. There is no indication that the starting material contained any of the glycine ester so, unusual as it seems, the 1-unsubstituted benzimidazole 3-oxide must have formed from the sarcosine ester.



Scheme **4.2**



Eqn **4.6**



(Eqn **4.7**)

The two other products formed which resulted from loss of the methyl group, namely 6 and 7-trifluoromethylquinoxalin-2-one (**413, 414**) were produced in varying

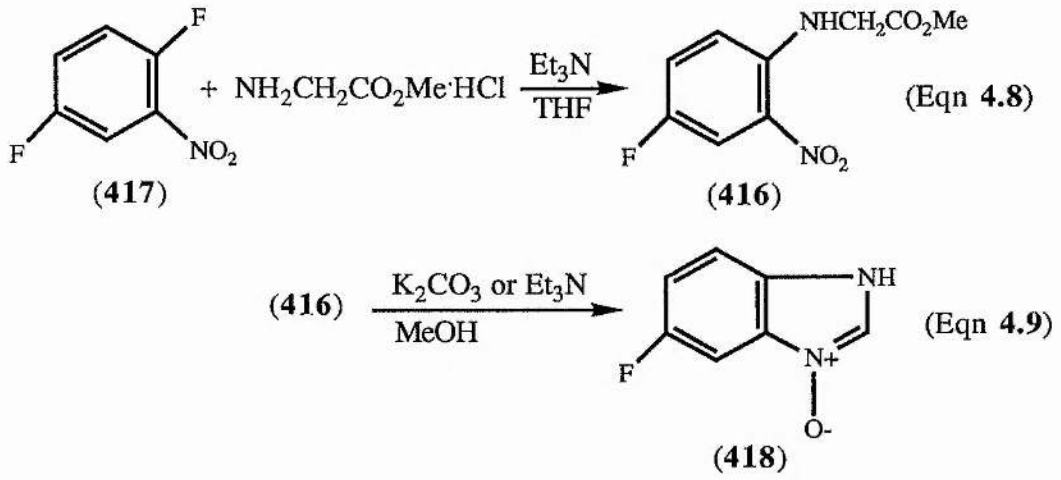
proportions. A seemingly equivalent combination of isomers was isolated in one case while another sample contained the isomers in a ratio of approximately 4:1. Unfortunately no assignment could be made as to which isomer was the more abundant in the product mixture over all. Quinoxalinones are typically formed from reaction of *o*-phenylenediamines with an α-aldehydo- or α-keto-ester, such as the esters of glyoxylic acid[63]. For unsymmetrically substituted diamines there are two ways in which the compounds can react and indeed in such cases two isomers are usually isolated. Since two isomers were isolated in this case it seems likely that they were formed from an *inter*- rather than an *intra*molecular process. The mechanism for their formation will be discussed at the end of the section.

Thus the glycine and sarcosine esters (**405**) and (**410**) gave very different products upon reaction with base. The principal compounds formed in each reaction, however, were for the most part analogous to those formed in the 2,4-dinitro series (Eqns **4.1**, **4.2**).

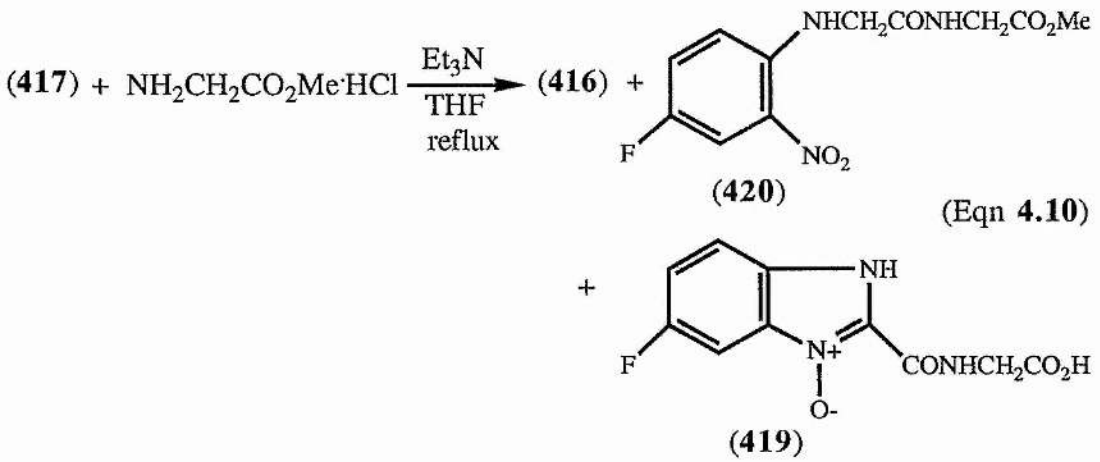
B. *N*-(4-FLUORO-2-NITROPHENYL)GLYCINE AND SARCOSINE ESTERS (**416**, **422**) AND THEIR REACTION WITH BASES

The synthesis of the glycine ester (**416**) was initially achieved by reaction of glycine methyl ester hydrochloride, 1,4-difluoro-2-nitrobenzene (**417**), and triethylamine in refluxing tetrahydrofuran (Eqn **4.8**). The ester (**416**) was cyclized to 5-fluoro-1*H*-benzimidazole 3-oxide (**418**) using potassium carbonate in methanol. The ester sample was also cyclized to the *N*-oxide (**418**) in the presence of triethylamine (Eqn **4.9**). The use of different bases affected the yield and the reaction time but not the products formed.

The reaction involving triethylamine was quite complicated; two products were isolated in addition to the ester (Eqn **4.10**). From work-up of the reaction solution, a precipitate was obtained that had similar colour and solubility to the 1*H*-benzimidazole *N*-oxide (**418**); however, the ^{1}H n.m.r. was distinctly different. The structure proposed for

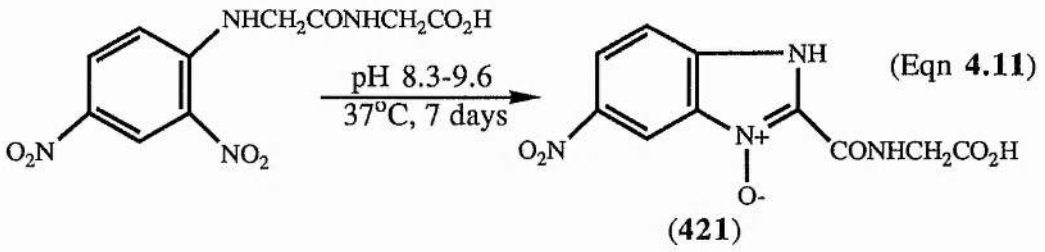


this compound is *N*-(5-fluoro-3-oxido-1*H*-benzimidazole-2-carbonyl)glycine (**419**). The second product was obtained when the impure ester initially isolated was purified by column chromatography. Elution and evaporation of the most polar fraction gave a bright reddish-orange solid that was identified as *N*-(4-fluoro-2-nitrophenyl)glycylglycine methyl ester (**420**).



This unusual ester (**420**) was most probably formed from the reaction of the desired ester (**416**) with glycine methyl ester. It also seems logical that the glycine (**419**) might have been formed from the glycylglycine ester. A reaction of the glycylglycine ester under the same conditions did not appear to give any of the glycine (**419**). However the reaction was on a very small scale (due to the minimal amount that was obtained) so it was not likely to prove anything. Still, the formation of an acid from an ester under these conditions has already been discussed (see discussion of Eqn **4.4**) and

Ljublinskaya and Stepanov[61] reported the "slow conversion" in phosphate buffer, of *N*-(2,4-dinitro-phenyl)glycylglycine methyl ester to *N*-(5-nitro-3-oxido-1*H*-benzimidazole-2-carbonyl)glycine (**421**) (Eqn **4.11**).



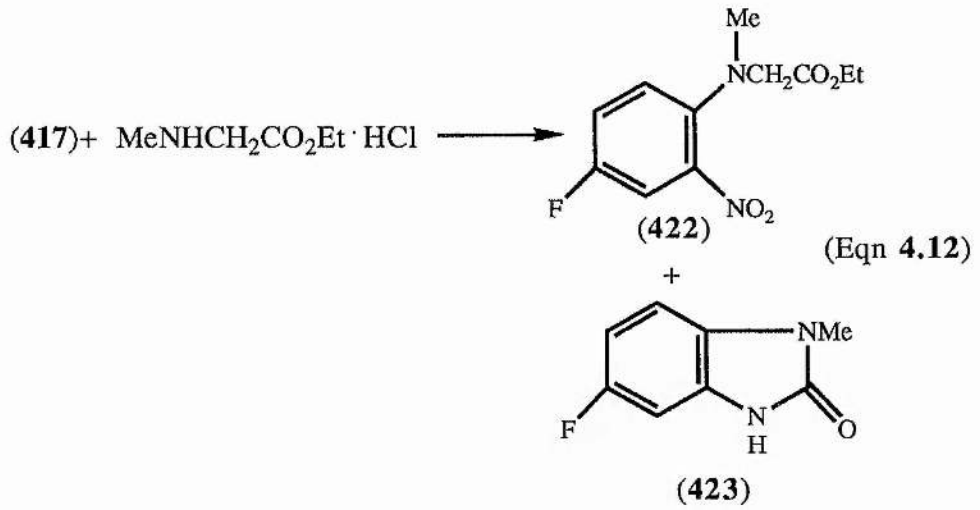
(Eqn **4.11**)

(**421**)

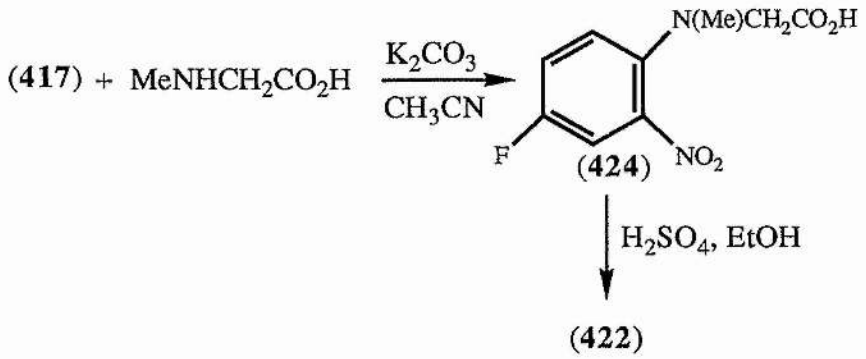
The formation of these unusual products was not thought to be due to the *para*-fluorine but to the propensity of amino esters to polymerize and for these products to cyclize. Thus their formation is not attributed to the nature of the substituents on the benzene ring. These results therefore do not threaten the hypothesis that glycine ester starting materials unsubstituted at C-6 cyclize 'normally' to the *N*-oxides.

As with the other two pairs of esters the sarcosine counterpart to the glycine ester just discussed gave different products upon reaction with base. The principal products formed were again analogous to those produced from *N*-(2-nitro-4-trifluoromethyl-phenyl)sarcosine ethyl ester.

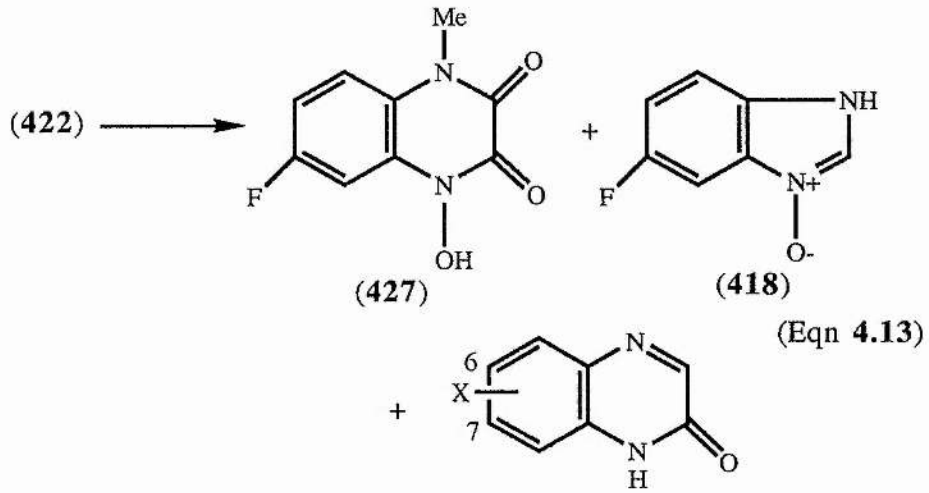
Direct synthesis of *N*-(4-fluoro-2-nitrophenyl)sarcosine ethyl ester (**422**) was difficult. A method was employed using triethylamine in acetonitrile. A pure sample of the ester was obtained, but the yield was mediocre (41%). An attempted cyclization reaction using this ester sample gave only a complicated mixture, none of the components of which could be identified. When the synthetic reaction was attempted again with potassium carbonate and acetonitrile, the ester (**422**) obtained was impure (Eqn **4.12**) Also isolated was a small amount of 5-fluoro-1-methylbenzimidazol-2-one (**423**) in a mixture with another compound that could not be identified.



Due to the low yields and formation of other products, the synthesis of the sarcosine ester via the free acid (**424**) was attempted and was completely successful. Esterification of the product was performed using sulfuric acid and ethanol (Scheme **4.3**). Reaction of the ester with base gave a number of interesting products (Eqn **4.13**). A mixture of 6-fluoroquinoxalin-2-one (**425**) with a small amount of the 7-fluoro isomer (**426**) was isolated. (A study of the ^{1}H and ^{13}C n.m.r.s allowed the signals arising from each isomer to be assigned.) In contrast to the 4-trifluoromethyl analog which gave the corresponding 1-hydroxyquinoxaline-2,3-dione (**412**) in 31% yield, only trace amounts of 7-fluoro-1-hydroxyquinoxaline-2,3-dione (**427**) were found. It was isolated alone and in a mixture with at least two other compounds. The major component of the mixture was 5-fluoro-1*H*-benzimidazole 3-oxide (**418**) and one of the minor ones was 6-fluoroquinoxalin-2-one (**425**). The presence of the 7-fluoro isomer (**426**) was indicated in the ^{1}H n.m.r. of the mixture. Thus this was another case in which a sarcosine ester gave a 1-unsubstituted benzimidazole 3-oxide . Once again there was no evidence that any of the glycine ester (**416**) had contaminated the original sarcosine ester sample.



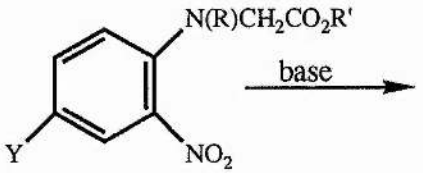
Scheme **4.3**



DISCUSSION

The results of the reactions discussed in this section are summarized in table **4.1**. The compounds are listed in pairs to allow comparison of the reactions of glycine and sarcosine esters in the same series. In all three pairs, the glycine esters gave only *NH*-benzimidazole *N'*-oxides and the sarcosine esters gave two or more products, none of which was the *N*-methylbenzimidazole *N'*-oxide.

Table **4.1** Summary of reactions of the esters with bases



Compd No.	R	Y	1*H*-Benzimidazole 3-oxides	1-OH-4-Me-Quinoxaline-2,3-diones	Benz-imidazol-2-ones	Azoxy-benzenes	Quinoxalin-2-ones
403	H	NO_2	56% 2-CO_2Me				
400[a]	Me	NO_2		14-35%		4-32%[b] 7, 16%[c]	
405	H	CF_3	73% 2-CO_2H				
410[f]	Me	CF_3	~5%[e]	~34%[e], 2%			X[d]
416[f]	H	F	24%, 72%				
422	Me	F	~10%[e]	X[d,e]	X[d]		X[d]

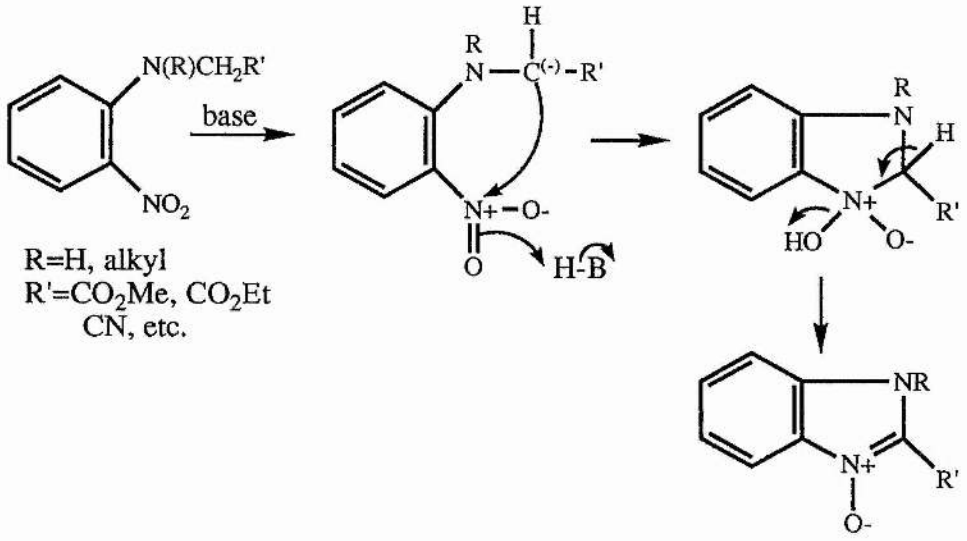
[a] reacted with a number of different bases, range of yields given.
[b] 2-amino-2'-methylamino derivative
[c] 2,2'-bis(methylamino) derivative
[d] (X) indicates that the yields could not be measured
[e] isolated as mixtures, approximate yields
[f] reacted with two different bases

The fact that some of the esters were reacted under slightly different conditions is not important because this was not found to affect whether an ester reacted 'normally' or 'abnormally'. In the 4-trifluoromethyl series, reaction of the sarcosine ester with triethylamine yielded only the quinoxaline-2,3-dione (**412**), but with potassium carbonate, the quinoxalin-2-ones (**413,414**) and the 1*H*-benzimidazole 3-oxide (**408**) were also isolated. However, the type of base did not change the fact that no 1-methyl-5-tirfluoromethylbenzimidazole 3-oxide was formed. As was also mentioned before, the reaction of *N*-(4-fluoro-2-nitrophenyl)glycine ester using potassium carbonate only

resulted in a higher yield and a shorter reaction time as compared to the reaction with triethylamine; the ester still only gave the expected *N*-oxide (**418**).

The fact that none of the *N*-methylbenzimidazole *N'*-oxides was isolated could be due to two reasons: one is that none was formed, the other is that they were formed as intermediates which then rearranged or reacted further with base to give the products found. Although the first reason is more likely, the second one must be addressed.

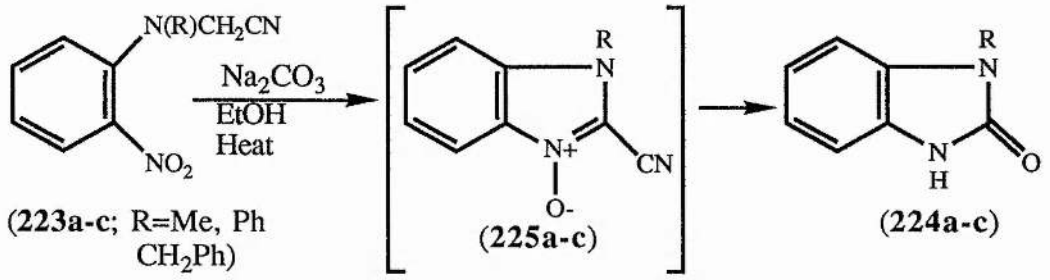
For many years a straightforward mechanism was accepted for the formation of benzimidazole *N*-oxides from *N*-(activated-alkyl)-2-nitroaniline derivatives[64] (Scheme **4.4**). It involved an intramolecular aldol-type condensation in which a carbanion forms and attacks the nitro group. Subsequent dehydration leads to the *N*-oxides. In chapter **2**, the failings of this type of mechanism were mentioned briefly, specifically with respect to the experimental observation (Stacy *et. al.*)[14] that if R=H and R'=Ph, the cyclization succeeds, but if R=Me and R'=Ph, the cyclization fails. However, the mechanism has been presented in support of other, similar work.



Scheme **4.4**

Livingstone and Tennant[36] reported in a preliminary communication that *N*-cyanomethyl-*N*-substituted-2-nitroanilines (**223a-c**; R=Me, CH_2Ph, Ph) reacted with aqueous ethanolic sodium carbonate with heating to give only 1-hydroxy-3-substituted

benzimidazol-2-ones (**224a-c**; R=Me, CH_2Ph, Ph) rather than the expected *N*-oxides (**225a-c**; R=Me, CH_2Ph, Ph) (Eqn **4.14**).



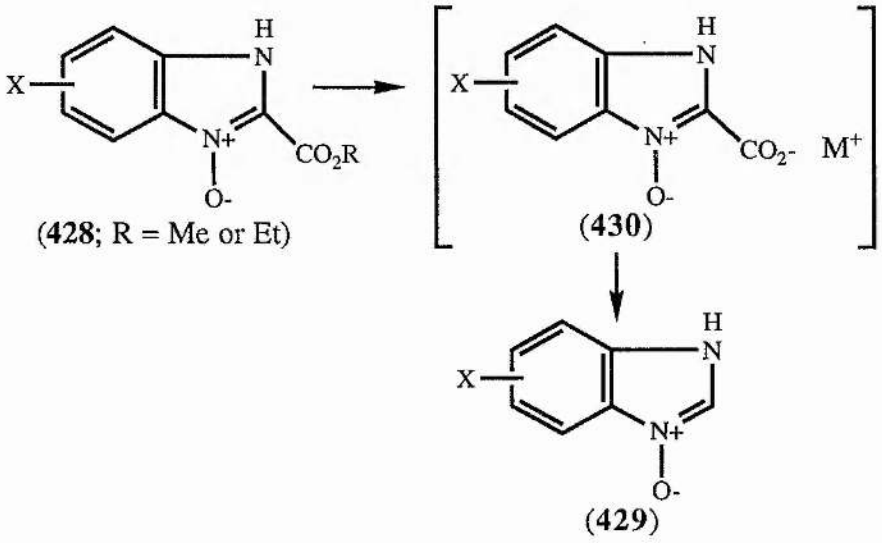
(**223a-c**; R=Me, Ph CH_2Ph) (**225a-c**) (**224a-c**)

(Eqn **4.14**)

They proposed that 1-methylbenzimidazole-2-carbonitrile 3-oxides (**225**) were formed according to the 'traditional' mechanism (cf Scheme **4.4**) and that these *N*-oxides were attacked by base to give (**224**): Takahashi and Kano[65] had reported that the latter reaction (**225** to **224** for R=Me) could be brought about by using potassium hydroxide in refluxing methanol for one hour. In the same paper the reactions of the *N*-oxide (**225a**; R=Me) and its alkyl 2-carboxylate derivative with a number of other reagents were also reported, illustrating the fact that 1-methyl-2-substituted-benzimidazole 3-oxides are reactive compounds towards nucleophilic attack at C-2. 1*H*-benzimidazole 3-oxides are able to isomerize to 1-hydroxybenzimidazoles (cf chapter **1**, p.2) and gain stability in solution against attack at C-2; however this is impossible for the *N*-substituted derivatives. On the basis of this evidence, it is a reasonable assumption that the *N*-oxides (**225**) could be the intermediates in the formation of the benzimidazol-2-ones (**224**). However, though such *N*-oxides are undoubtedly reactive they are by no means unstable. Livingstone and Tennant have not yet published the full paper so the full experimental details are not known. Still, the base they used was considerably milder than that used by Takahashi and Kano. The reaction time may have been longer (the time was not given in the communication), or the reaction may not need a base as strong as potassium hydroxide; but barring these possibilities, it would not be unreasonable to have expected that some of the *N*-oxide (**225**) could have been isolated from Livingstone and Tennant's reaction if it had been formed.

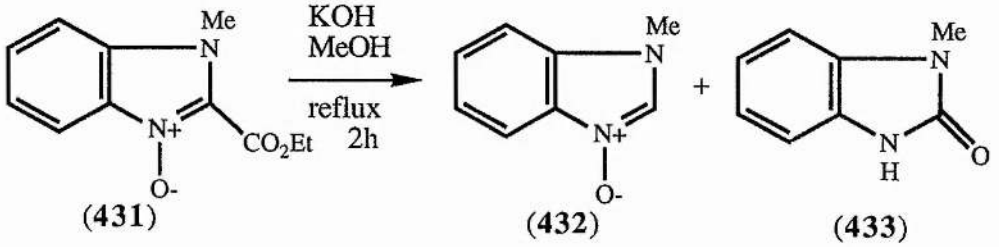
So far as it is known, no other reactions of *N*-cyanomethyl-*N*-methyl-2-nitroanilines with bases have been performed. *N*-Methylbenzimidazole *N'*-oxides have not been isolated from the reactions of *N*-(substituted-2-nitrophenyl)sarcosine esters. However, the direct comparison of sarcosine ester and nitrile reactions such as these may not be valid. The possibility that the type of activating group, whether it is a nitrile, an ester or something else, could influence the reaction pathway, and thus the products that are formed, has been discussed in chapter **3**. Even so, the fact that neither *N*-methylbenzimidazole N'-oxide nor any of its 2-substituted derivatives has ever been isolated from reaction of *N*-methyl-*N*-(activated-alkyl)-*o*-nitroaniline derivatives with base sheds considerable doubt on whether the 1-substituted benzimidazole-2-carbonitrile 3-oxides (**225**) were formed at all.

The presumed intermediates in the conversion of alkyl 1*H*-benzimidazole-2-carboxylate 3-oxides (**428**) to the 2-unsubstituted compounds (**429**) are the 1*H*-benzimidazole-2-carboxylic acid 3-oxides (**430**) (Eqn **4.15**). One derivative of the protonated form of (**430**) appears to have been isolated from reactions performed in this project. This is surprising considering that they were thought to be very unstable and too reactive; far more reactive than *N*-substituted benzimidazole *N'*-oxides. Thus again it seems unusual that the latter have not been isolated, even in trace amounts.



(Eqn **4.15**)

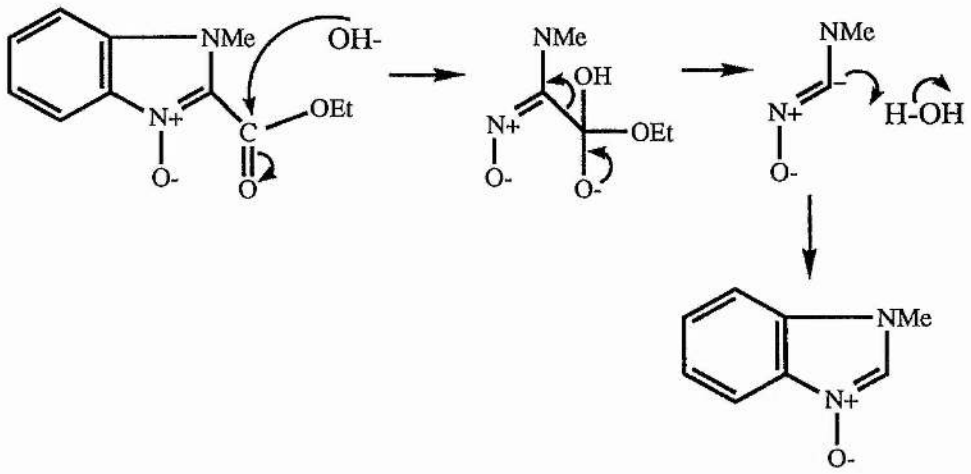
Takahashi and Kano found that whereas N-methylbenzimidazole-2-carbonitrile 3-oxide gave 1-methylbenzimidazol-2-one upon reaction with hydroxide, ethyl 1-methylbenzimidazole-2-carboxylate 3-oxide reacted under the same conditions to give the 2-unsubstituted compound (**432**) plus a small amount of 1-methylbenzimidazol-2-one (**433**) (Eqn **4.16**)[65].



(**431**) (**432**) (**433**)

Eqn **4.16**

The reaction could occur by two mechanisms. The first proceeds via the 2-carboxylic acid intermediate (as per eqn **4.15**), and the second is the ester hydrolysis mechanism detailed in scheme **4.5**. In both mechanisms the 2-unsubstituted *N*-oxide (**432**) presumably then reacts with base to give the small amount of benzimidazol-2-one (**433**) formed. In the present work, the sarcosine esters were not reacted with hydroxide, although it could be produced *in situ* by reaction of the base with water. Thus, if the ethyl 1-methylbenzimidazole-2-carboxylate 3-oxides were produced, the reaction in equation **4.16** suggests the 2-unsubstituted 3-oxides could have been produced. Neither of these products were detected. It would be worthwhile to perform a reaction of a sarcosine ester with hydroxide for, certainly, if no *N*-methylbenzimidazole *N'*-oxide was isolated, that would be a strong indication that the 2-carboxylate esters had not been formed, even as an intermediate.



Scheme **4.5**

When comparing the reactions of the sarcosine esters, it is interesting to see that neither the 4-fluoro nor 4-trifluoromethyl compounds produced an azoxybenzene, but did produce quinoxalin-2-ones. In the 4-nitro case it was the other way around. In fact, even including the sarcosine ester reactions to be discussed in section **4.3**, these two types of product were never isolated from the same reaction mixture. (One ester did give both products, but separately and under different conditions.) Due to the fact that their respective spectral characteristics are so distinctive, it is highly unlikely that the presence of either one, even in complicated mixtures, went undetected. The results suggest that perhaps there is a common intermediate which under some conditions gives a quinoxalin-2-one and under others gives an azoxybenzene. The mechanism McFarlane put forward for the formation of methylamino- and bis(methylamino)azoxybenzenes (see below) contains this feature.

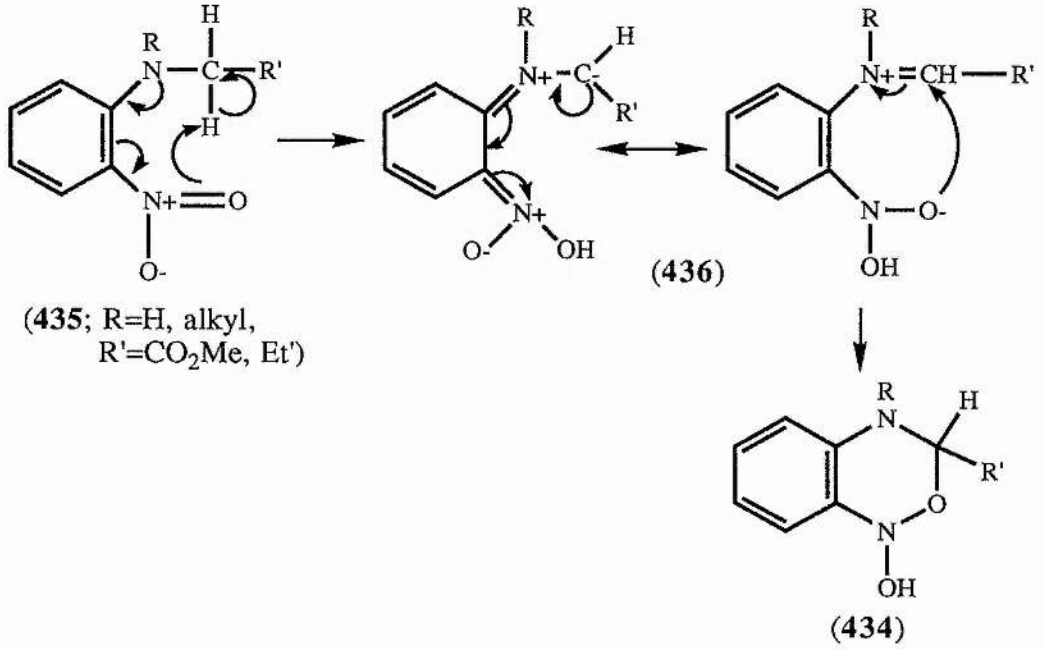
MECHANISM

An examination of the mechanism McFarlane proposed for the formation of the 2-amino-2′-methylamino- and 2,2′-bis(methylamino)azoxybenzenes provides possible explanations for the formation of the 1*H*-benzimidazole 3-oxides and the quinoxalin-2-ones from sarcosine esters.

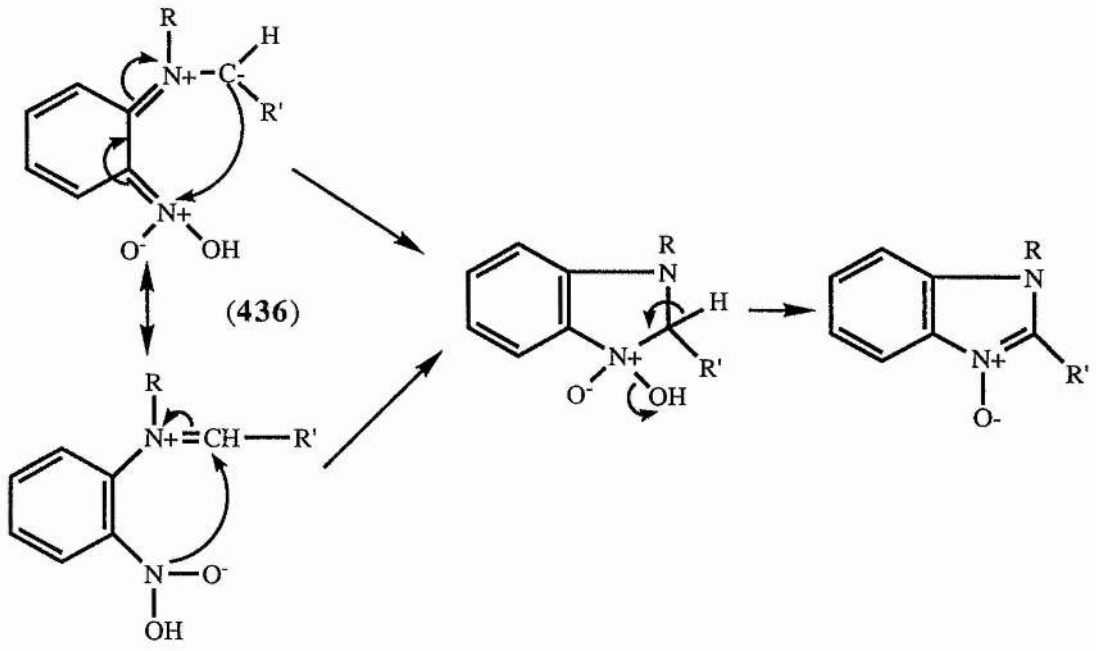
A key intermediate in the scheme is the oxadiazine (**434**) which could be formed in two ways from the amino esters (**435**). One way involves a proton being transferred

from the methylene group on to the nitro group giving an *aci*-nitro compound (**436**). The negatively charged oxygen attacks the carbon in the double bond of the iminium ion leading to cyclization and the oxadiazine intermediate (**434**) (Scheme **4.6**).

Analogous to the 'traditional' mechanism (cf Scheme **4.4**), is the possibility that the *aci*-nitro compound (**436**) could cyclize and dehydrate, forming the benzimidazole *N*-oxides (Scheme **4.7**). This could occur for either R=H or alkyl, but experimentally this does not seem to be the case; therefore this pathway is not representative of the reactions of the esters.



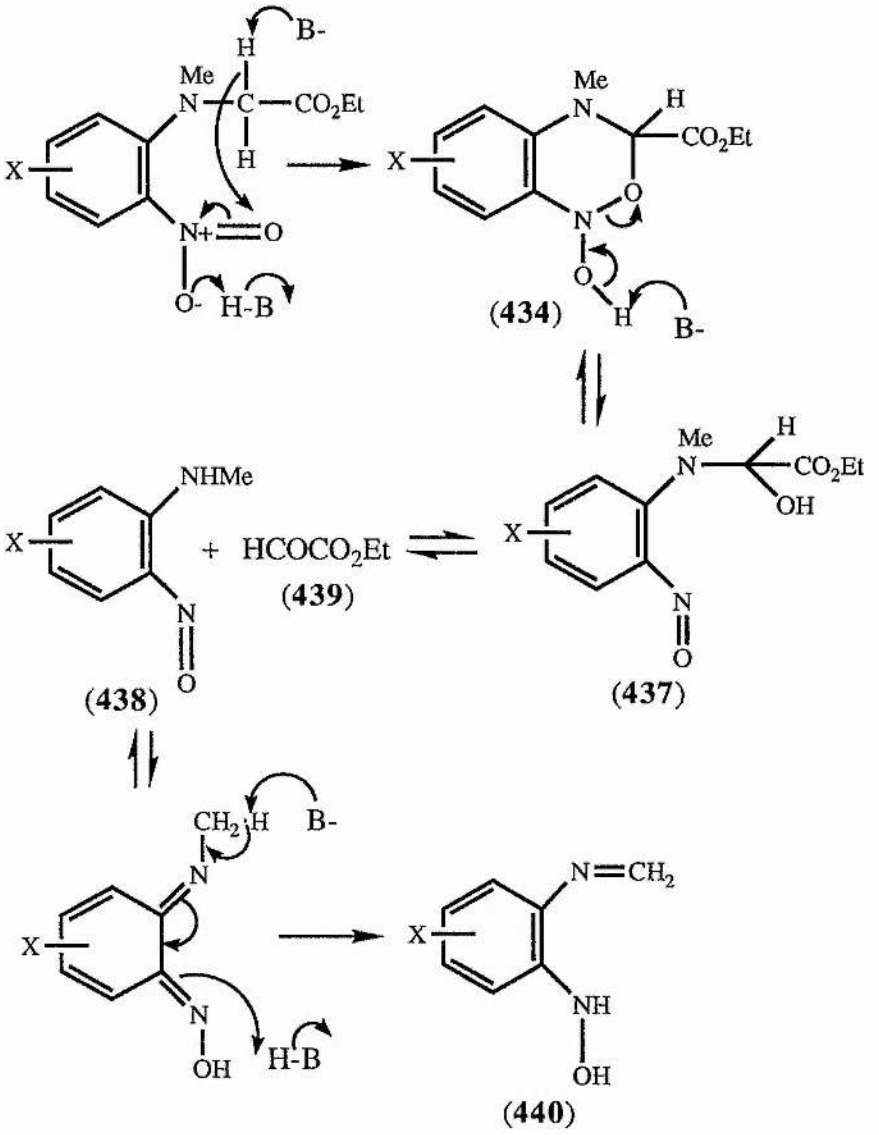
Scheme **4.6**



Scheme **4.7**

However, there is an alternative pathway from the amino esters (**435**) to (**434**) and the *N*-oxides involving deprotonation of the ester by base generating a carbanion which could attack a nitro-oxygen effecting cyclization and giving compound (**434**).

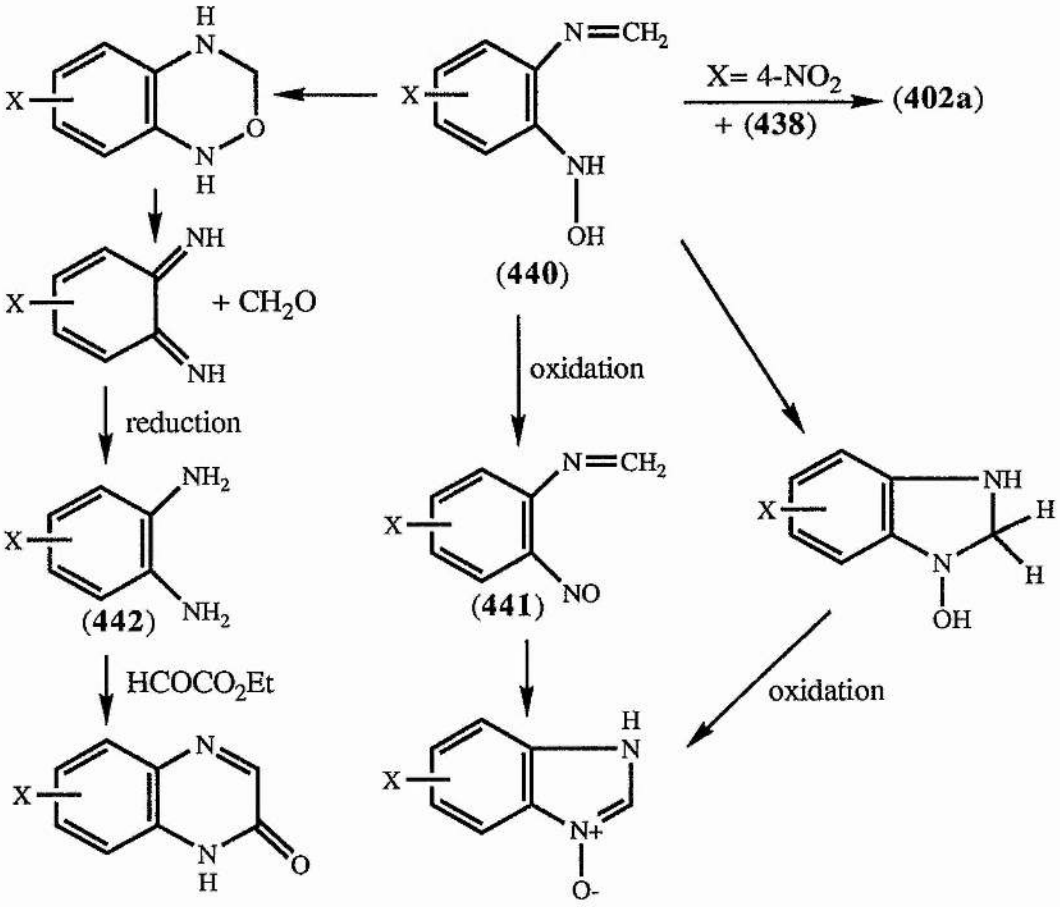
Focusing on the products formed from the sarcosine esters, the following pathway is envisaged. The oxadiazine intermediate ring-opens upon attack of base on the hydroxyl group to give the nitroso compound (**437**) which is, formally, the adduct of the nitrosoaniline (**438**) and ethyl glyoxylate (**439**). There is strong evidence that the 4-trifluoromethyl derivative (**415**) of the aniline was isolated in the reaction of the sarcosine ester (**410**) with potassium carbonate. Another derivative of (**438**) was also believed to have been isolated from a glycine ester (described in section **4.2**). Base attack on the *N*-methyl group of (**438**) gives another important intermediate, the hydroxylamino-anil (**440**) (Scheme **4.8**).



Scheme **4.8**

Hydroxylamines are known to be unstable, readily oxidizing or reducing to the more stable nitroso or amino derivatives respectively. Ring closure of the anil (**440**) and subsequent oxidation would give the 1*H*-benzimidazole 3-oxides. Alternatively the oxidation of the anil itself would first give the nitroso compound (**441**) which could cyclize to the *N*-oxide. Nitroso-anils have been proposed as intermediates in *N*-oxide formation though they have not been isolated[64]. This would explain how such 1-unsubstituted compounds could have formed from the sarcosine esters. The hydroxylamino-anil (**440**), with cyclization then loss of formaldehyde and reduction, could give the *o*-phenylenediamine (**442**) which could then react with ethyl glyoxylate

used to synthesize such compounds[63]. McFarlane proposed that a hydroxylamino-anil reacted with the nitrosoaniline (**438**) to give the 2-amino-2′-methylaminoazoxybenzene (**402a**) (Scheme **4.9**). Thus the anil (**440**) could be the 'common intermediate' mentioned earlier.



Scheme **4.9**

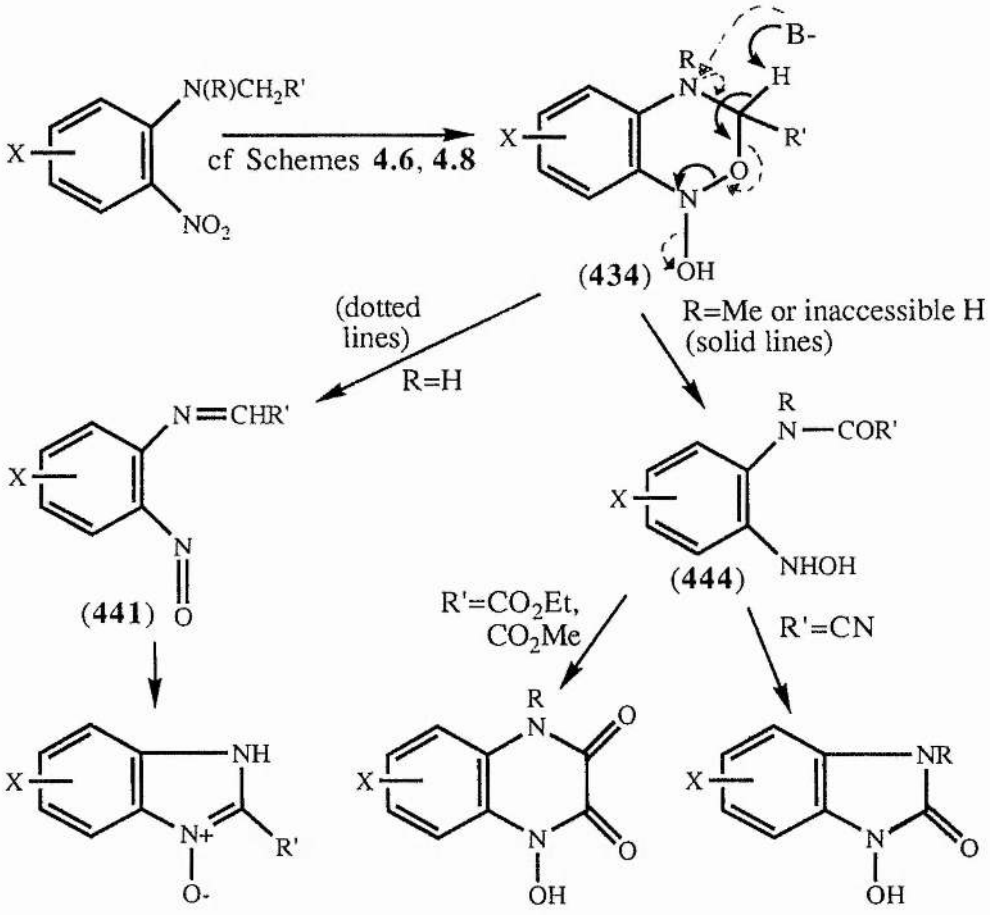
McFarlane, in attempting to prove the production of ethyl glyoxylate, added a molar equivalent of *o*-phenylenediamine to a reaction of *N*-(2,4-dinitrophenyl)sarcosine ethyl ester (**400**) with triethylamine. Quinoxalin-2-one (**443**) was produced in addition to a larger precentage of 2,2′-bis(methylamino)-5,5′-dinitroazoxybenzene (**402b**) than was isolated from a reaction without the diamine. A possible reason is that the reaction of *o*-phenylenediamine with ethyl glyoxylate (**439**) pushes the series of equilibria (cf Scheme **4.8**) in favour of (**439**) and the aniline (**438**). The azoxybenzene, formed from the reduction of the aniline would thus be expected to be produced in greater yield. In

this project, the diamine (**442**) must come from the starting material. The most logical way it may be formed is from the hydroxylamino-anil (**440**) which is also thought to go on to form the azoxybenzenes. Thus in this situation, it is expected that the percentage of azoxybenzenes formed should decrease or in the extreme be eliminated. No conclusions can be drawn, however, as to why the anil (**440**) should produce one compound in one situation and the other compound in the other. A case will be reported later of one sarcosine ester producing both compounds but separately, under different conditions so the behaviour does not appear to be determined by the structure of the ester.

McFarlane also proposed a mechanism explaining how 1-hydroxy-4-methyl-quinoxaline-2,3-diones and *N*-methylbenzimidazol-2-ones could be formed from *N*-(substituted phenyl)sarcosine esters. First it is necessary to consider the 'traditional' mechanism already mentioned for the formation of 1*H*-benzimidazole 3-oxides. There are several problems with this mechanism (cf Scheme **4.4**). One is that the amino hydrogen plays no part in the formation of the *N*-oxide therefore suggesting that a substituent on the nitrogen should be unimportant. The fact that sarcosine esters do not seem to cyclize to the corresponding *N*-methylbenzimidazole *N'*-oxides suggests that the availability of the amino hydrogen may be essential to *N*-oxide formation. Also according to the 'traditional' mechanism there is no obvious reason why an additional substituent *ortho* to the amino side-chain and *meta* to the nitro group should have any effect on the products formed. Evidence presented in section **4.2** indicates that certain types of substituent in this position have a significant effect on the reaction pathway, one similar to that induced by a methyl group on the amino nitrogen. Therefore the 'traditional' mechanism appears to be too simple to explain adequately the formation of all the various products formed. McFarlane proposed an alternative mechanism which accounts for the full complexity of the reactions (Scheme **4.10**).

Once again the oxadiazine is an important intermediate. Base could attack the intermediate at the NH or CH or both (not simultaneously). Attack at the NH would lead to a *o*-nitroso-anil which could then cyclize to the *N*-oxide, a reaction which, as mentioned previously, does have literature precedent. Attack at the CH would give an acyl intermediate (**444**). This intermediate could then do a number of things. The nitriles

that reacted 'abnormally' have all given 1-hydroxybenzimidazol-2-ones. This could be explained by the cyclization of (**444**) by attack of the hydroxylamino-nitrogen on the amido-carbonyl. The glycine esters investigated prior to this project gave quinoxaline-2,3-diones upon 'abnormal' cyclization. These products could result from attack on the more nucleophilic ester-carbonyl. In this project, a number of glycine and sarcosine esters were believed to give 1*H*- and 1-substituted-3*H*-benzimidazol-2-ones. The way in which the alternative mechanism could account for the formation of these compounds is discussed in section **4.2**.



Scheme **4.10**

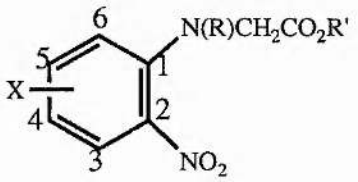
In the case of a sarcosine ester, attack on the nitrogen in the oxadiazine intermediate could not occur because it is fully substituted leaving, therefore, only the attack at the CH. This would then explain why none of the *N*-methylbenzimidazole *N'*-oxides were formed and why instead quinoxaline-2,3-diones and/or benzimidazol-2-ones

were found. For glycine esters such as those discussed in this section, the base could attack at either NH or CH or both. Because only the *N*-oxide was formed, the attack on NH is presumably preferable to attack on the CH to the total exclusion of the latter. The competition could be kinetically controlled such that the attack of base on NH is so much faster than the attack on CH, that only the *N*-oxide is formed and not the quinoxaline-2,3-dione or benzimidazol-2-one. For some glycine esters substituted in the benzene ring, *ortho* to the amino side-chain, and *meta* to the nitro group, several or all of these products were found to have formed. Section **4.2** details the study of the reactions of such esters and section **4.3**, the reactions of their *N*-methyl derivatives with bases.

SECTION 4.2

NOTE

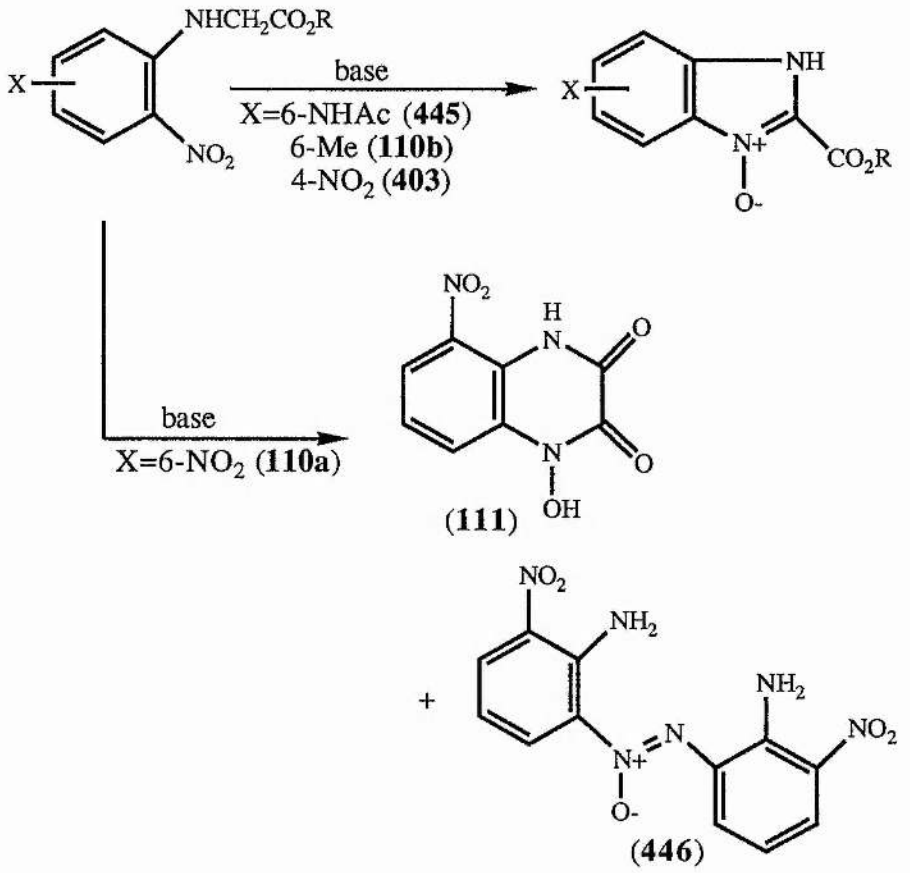
All of the esters described in this section have substituents at C-4 and C-6 as well as the nitro group at C-2. The substituent *ortho* to the amino side chain and *meta* to the nitro group is thought to have a significant effect on the reaction pathway in the reaction of such esters with base. [Following the rules of nomenclature, for some of the esters this substituent would be designated as being in position two and others position six. For the sake of clarity and to enable discussion and comparison among the esters, this substituent will be designated as being in position six in all cases. That is to say the first ester to be discussed will be called *N*-(6-chloro-2-nitro-4-trifluoromethylphenyl)glycine methyl ester rather than the strictly correct *N*-(2-chloro-6-nitro etc).]



INTRODUCTION

Background

Several interesting anomalies were discovered in the reactions of *N*-(substituted phenyl)glycine esters. *N*-(6-Acetamido-2-nitrophenyl)glycine ethyl ester (**445**) was successfully cyclized to ethyl 7-acetamido-1*H*-benzimidazole-2-carboxylate 3-oxide under basic conditions[66]. The *N*-(6-methyl-2-nitrophenyl)glycine ester (**110b**) also gave the corresponding 2-substituted *N*-oxide. However, the 6-nitro compound (**110a**) did not. Instead, only 1-hydroxy-5-nitroquinoxaline-2,3-dione (**111**) and small amounts of a by-product which is possibly 2,2′-diamino-3,3′-dinitroazoxybenzene (**446**) were formed[20]. The 4-nitro isomer (**403**), under the same conditions, gave only methyl 5-nitro-1*H*-benzimidazole-2-carboxylate 3-oxide (Scheme **4.11**)[1]. Thus it seems that it was the 6-nitro group specifically which was changing the reaction pathway. It is not clear from the results how these groups interfere; more examples are needed to clarify the picture.



Scheme **4.11**

Approach

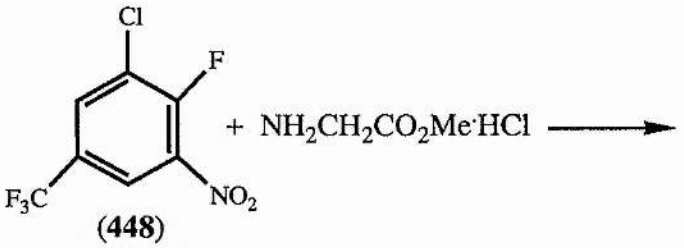
There were two ways in which the question of the 6-substituent could have been explored further. One was to compare the reactions of *N*-(6-substituted-2-nitrophenyl)-glycine esters with base to those of the 4-substituted isomers. Thus, any differences in products formed would be due to the position of the substituent. It was decided to try to synthesize esters from commercially available *o*-halogenonitrobenzenes (rather than *o*-nitroanilines). Thus 6-substituted-*o*-halogenonitrobenzenes were needed to make the desired *N*-(6-substituted-2-nitrophenyl)glycine esters. Unfortunately the benzene derivatives are difficult to make and are not, in general, commercially available.

The other way to explore the question was to use 2,4,6-trisubstituted esters where the 4-substituents corresponded to those in the 2,4-disubstituted esters that had already been examined or could be easily obtained. Thus the differences in the products formed in the presence of base would be due to the additional substituent. The starting materials required for three of the four trisubstituted esters discussed in this section were easily obtained and all of the substituents were electron-withdrawing groups. The fact that these trisubstituted esters had more electron-deficient benzene rings than the disubstituted esters with which they were compared, does not appear to have influenced the reactions in terms of the products formed, only to require that milder conditions be employed. The additional substituents in position six varied in electron-withdrawing power and size, enabling conclusions to be drawn about the connection between the nature of the substituent and the effect caused. The cases previously studied suggested that the effect was an electronic one rather than a steric one, so being able to compare the effects of NO_2, CF_3, Cl, and F would allow appropriate exploration into the hypothesis.

N-(4, 6-SUBSTITUTED-2-NITROPHENYL)GLYCINE ESTERS AND THEIR REACTION WITH BASES

N-(6-Chloro-2-nitro-4-trifluoromethylphenyl)glycine methyl ester (**447**) was the first of all the esters in this project to be synthesized. Several methods were applied to the task and the lessons learned from these applications were taken into consideration when making the analogs. Five methods in all were employed. The conditions and problems with each are listed in table **4.2**.

Table **4.2** Details of the methods used to synthesize (**447**) and the problems with each

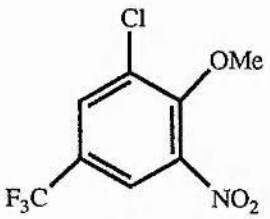


(**448**)

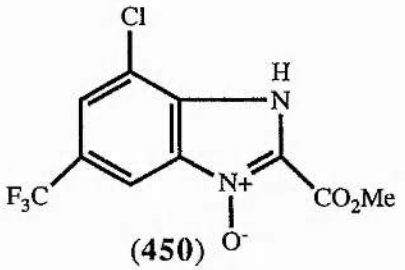
Method	Base	Solvent	Temp (°C)	Problems
A	Et_3N	MeOH	rt	(**447**) slightly contaminated[a], further reaction of (**447**)
B	Na_2CO_3	MeOH	reflux	
C[b]	Et_3N	toluene	65	impure (**447**), further reaction of (**447**)
D	Et_3N	toluene	~75	"
E	$Ba(OH)_2{\cdot}8H_2O$	THF	rt	further reaction of (**447**)

[a] Contamination was by a very small amount of 2-chloro-6-nitro-4-trifluoromethylanisole (**449**) or methyl 7-chloro-5-trifluoromethylbenzimidazole-2-carboxylate 3-oxide (**450**) (see experimental).

[b] The ester hydrochloride was neutralized with sodium hydroxide first and so only one equivalent of base was used. In all other cases, two equivalents were used.



(**449**)

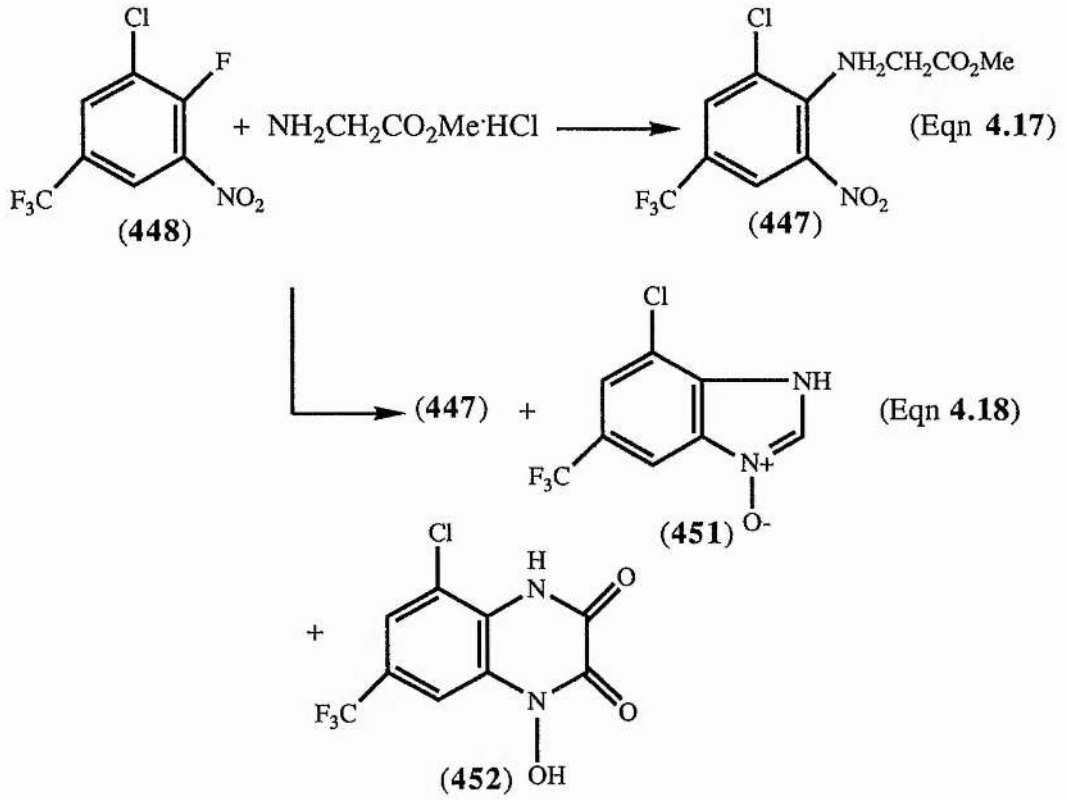


(**450**)

The first two times when method E was used, the purest product was obtained out of all the methods (Eqn **4.17**). Unfortunately, all subsequent attempts resulted in further reaction of (**447**) taking place simultaneously. The fact that this occurred is not surprising because as already discussed the esters react under basic conditions. Synthesis via the acid, as discussed for the previous series, would seem to be the obvious solution.

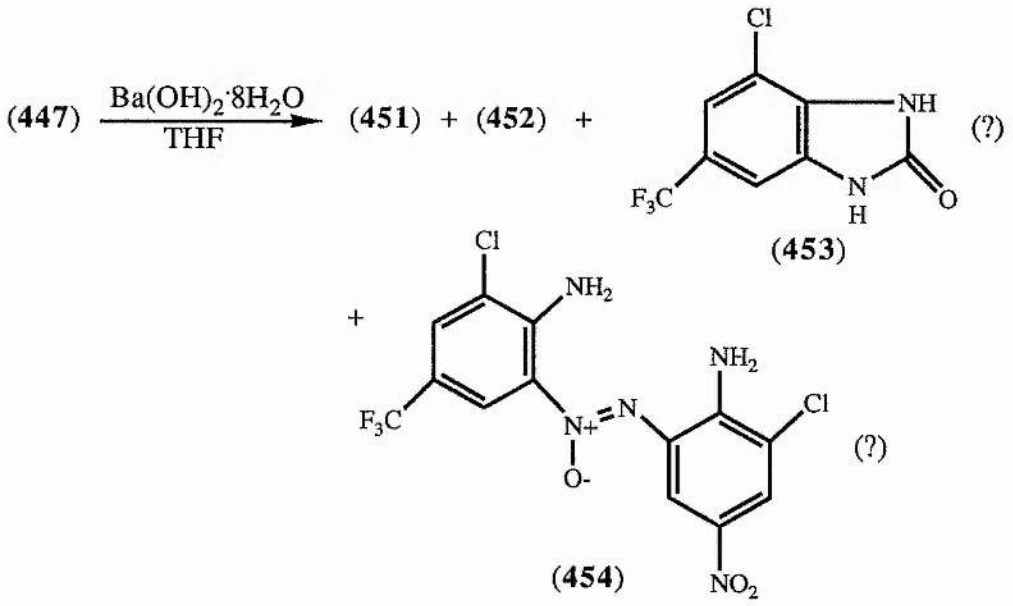
Nevertheless, it was not attempted because enough of the pure ester had already been obtained from some of the reactions using methods B and E. Also there was already considerable information about the products formed from reaction of the ester with base from the synthetic attempts in which further reaction had been observed.

The first bicyclic product to be isolated was from a synthetic reaction using method E. The sample was originally thought to be the pure 7-chloro-1*H*-5-trifluoromethylbenzimidazole 3-oxide (**451**). Recrystallization, microanalysis and a closer look at the spectral data, however, indicated that there was also present a small amount of a second product, which was identified by comparison of the spectral data with those from a pure sample of 5-chloro-1-hydroxy-7-trifluoromethylquinoxaline-2,3-dione (**452**) (Eqn **4.18**).



During another synthetic reaction using method E, t.l.c. showed that cyclization was already taking place so, to encourage cyclization, another molar equivalent of base was added to the two equivalents already present. An impure sample of the *N*-oxide (**451**) was isolated along with a mixture of (**451**) and the quinoxaline-2,3-dione (**452**).

A cyclization reaction performed under the conditions in method E gave even more interesting results (Eqn **4.19**). A sample containing a mixture of three main cyclic products was isolated. Two of the components were identified as the benzimidazole *N*-oxide (**451**) and the quinoxaline dione (**452**). The third was thought to be 7-chloro-5-trifluoromethyl-3*H*-benzimidazol-2-one (**453**). Also isolated was a solid containing a mixture of starting material with a small amount of 2,2′-diamino-3,3′-dichloro-5,5′-bis-(trifluoromethyl)azoxybenzene (**454**). As already mentioned, quinoxaline-2,3-dione (**111**) and possibly a diaminoazoxybenzene (**446**) were isolated from the reaction of *N*-(2,6-dinitrophenyl)glycine ester (**110a**) with base. A 1-hydroxybenzimidazol-2-one was found in the reaction of *N*-(2,6-dinitrophenyl)-*N*-cyanomethylaniline with base.



(Eqn **4.19**)

Most of the reactions which were performed under the conditions specified in the other methods (i.e A-D) also resulted in a mixture of the same products being obtained (Table **4.3**). Thus the ester (**447**) behaved similarly to the 6-nitro analog (**110a**) in the presence of base.

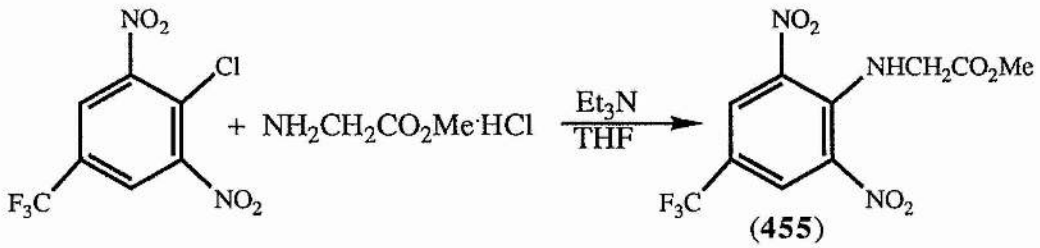
Table **4.3** Summary of the results for reaction of (**447**) with bases[a]

Method used (Table **4.5**)	Benzimidazole *N*-oxides	Quinoxaline-2,3-diones	Benzimidazol-2-ones	Diamino-azoxybenzenes
A	X	X		
C	(?)[b]			
D[c]		X		
D[c]		X		X
D	X	X		X
E[c]	X	X	(?)	X
E[d]	X	X		
E	X	X		
K_2CO_3, MeOH	X	X		

[a] X indiactes that the product was isolated from the reaction
[b] 2-CO_2Me derivative (**450**)
[c] reactions of the glycine ester under these conditions
[d] another equivalent of base added to the synthetic reaction

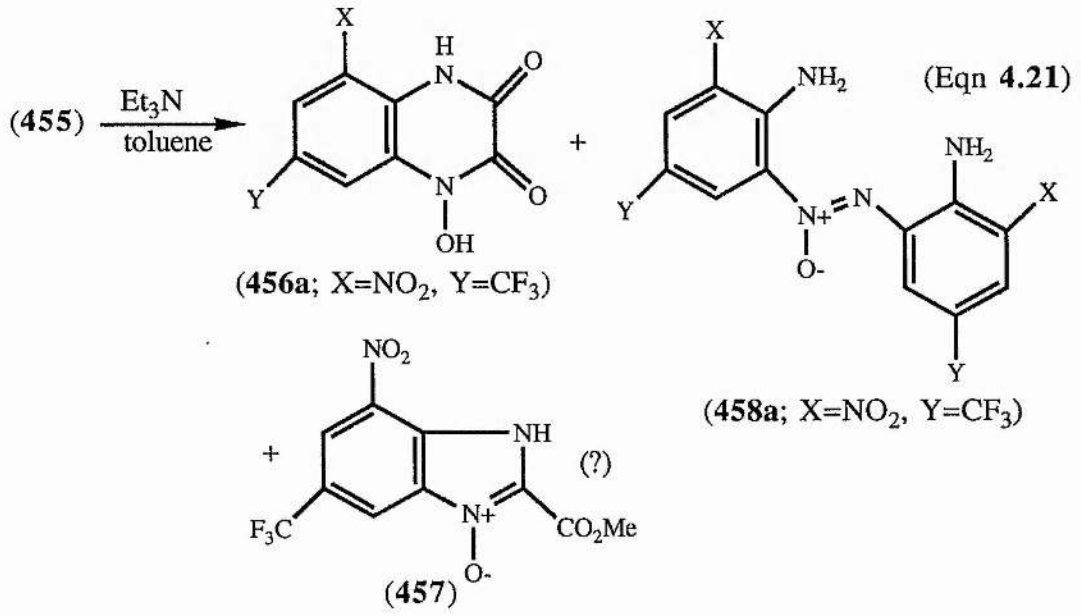
Two other trisubstituted esters were synthesized and both also gave 'abnormal' products in addition to the *NH*-benzimidazole *N'*-oxides when reacted with bases.

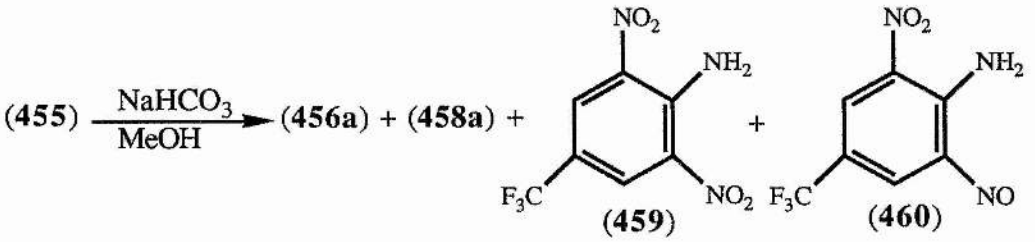
N-(2,6-Dinitro-4-trifluoromethylphenyl)glycine methyl ester (**455**) was made directly from 4-chloro-3,5-dinitrobenzotrifluoride, glycine methyl ester hydrochloride, and triethylamine in tetrahydrofuran (Eqn **4.20**).



(Eqn **4.20**)

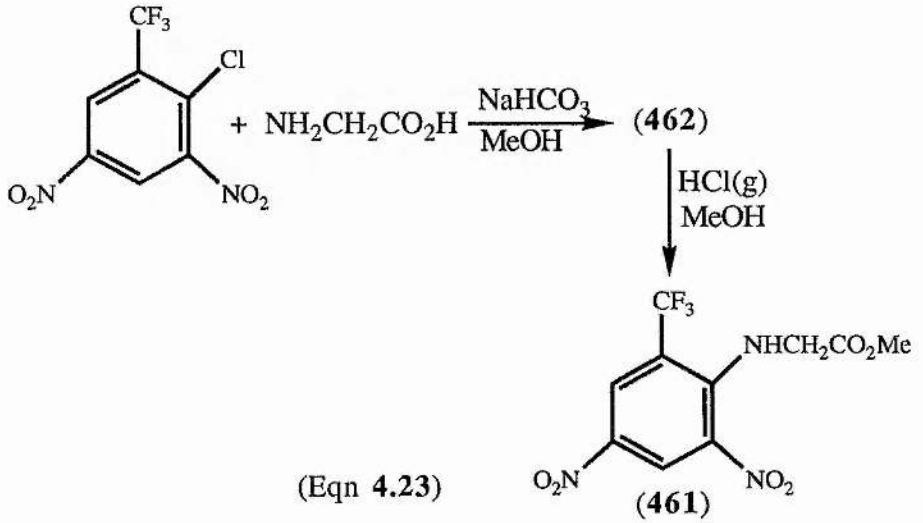
Cyclization of (**455**) occurred in toluene in the presence of triethylamine to give the pure 1-hydroxy-5-nitro-7-trifluoromethylquinoxaline-2,3-dione (**456a**; X=NO_2, Y=CF_3) and a mixture of this dione with what appeared to be methyl 7-nitro-5-trifluoromethyl-1*H*-benzimidazole-2-carboxylate 3-oxide (**457**) (Eqn **4.21**). Also isolated was 2,2′-diamino-3,3′-dinitro-5,5′-bis(trifluoromethyl)azoxybenzene (**458a**; X=NO_2, Y=CF_3). In another reaction, in methanol in the presence of sodium hydrogen carbonate, only a small amount of the quinoxaline-2,3-dione (**456a**) was isolated (Eqn **4.22**). An impure sample of the azoxybenzene (**458a**) was obtained and sublimed. Dark green spikes collected on the cold finger. The mass spectrum contained the molecular ions for both *N*-(2,6-dinitro-4-trifluoromethyl)aniline (**459**) (M^+ 251, 6%) and the 2-nitroso derivative (**460**) (M^+ 235, 53%). The mass spectrum of pure (**459**) contains only a small peak at m/z 235 (~3%)[67] so it seems that, taking into account the intensity of the peak at m/z 235 in the spectrum of the mixture and its green colour, a significant portion of the mixture was made up of the nitroso derivative (**460**). *N*-Methyl-2-nitroso-4-trifluoromethylaniline was thought to have been isolated from reaction of the corresponding sarcosine ester (**410**) with potassium carbonate. The nitrosoanilines are important intermediates in the proposed mechanisms for the formation of the quinoxalin-2-ones and the diaminoazoxybenzenes (cf Schemes **4.8, 4.9**).



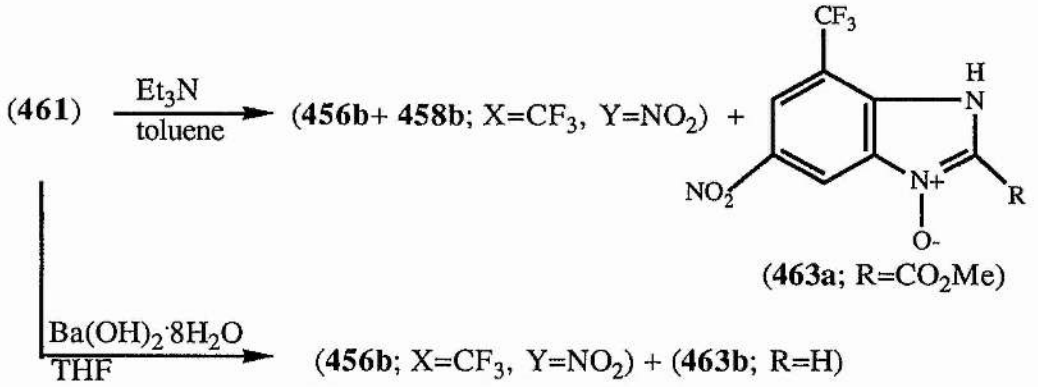


(Eqn **4.22**)

The isomeric *N*-(2,4-dinitro-6-trifluoromethylphenyl)glycine methyl ester (**461**) behaved similarly. The free acid (**462**) was made first using 2-chloro-3,5-dinitrobenzotrifluoride, glycine, sodium bicarbonate and methanol, then esterified in the normal way (Eqn **4.23**). Reaction of the ester with triethylamine and toluene gave 2,2′-diamino-5,5′-dinitro-3,3′-bis(trifluoromethyl)azoxybenzene (**458b**; X=CF_3, Y=NO_2) and 1-hydroxy-7-nitro-5-trifluoromethylquinoxaline-2,3-dione (**456b**; Y=CF_3, Z=NO_2) and samples containing mixtures of (**456b**) with what spectral evidence indicated was methyl 5-nitro-7-trifluoromethyl-1*H*-benzimidazole-2-carboxylate 3-oxide (**463a**; R=CO_2Me) (Scheme **4.12**). From the reaction of the glycine ester with barium hydroxide in tetrahydrofuran only small quantities of two solids were isolated. Spectral evidence showed that one contained mostly the 2-unsubstituted benzimidazole *N*-oxide (**463b**, R=H) and the other a mixture of the dione (**456b**) and the *N*-oxide (**463b**).

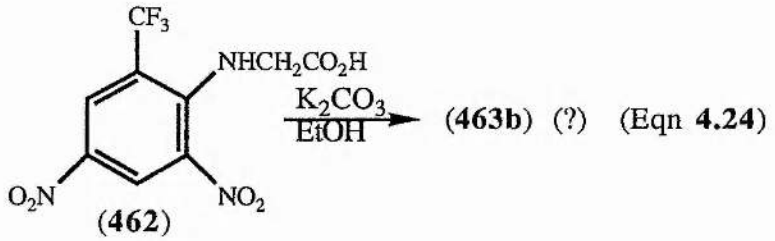


(Eqn **4.23**)

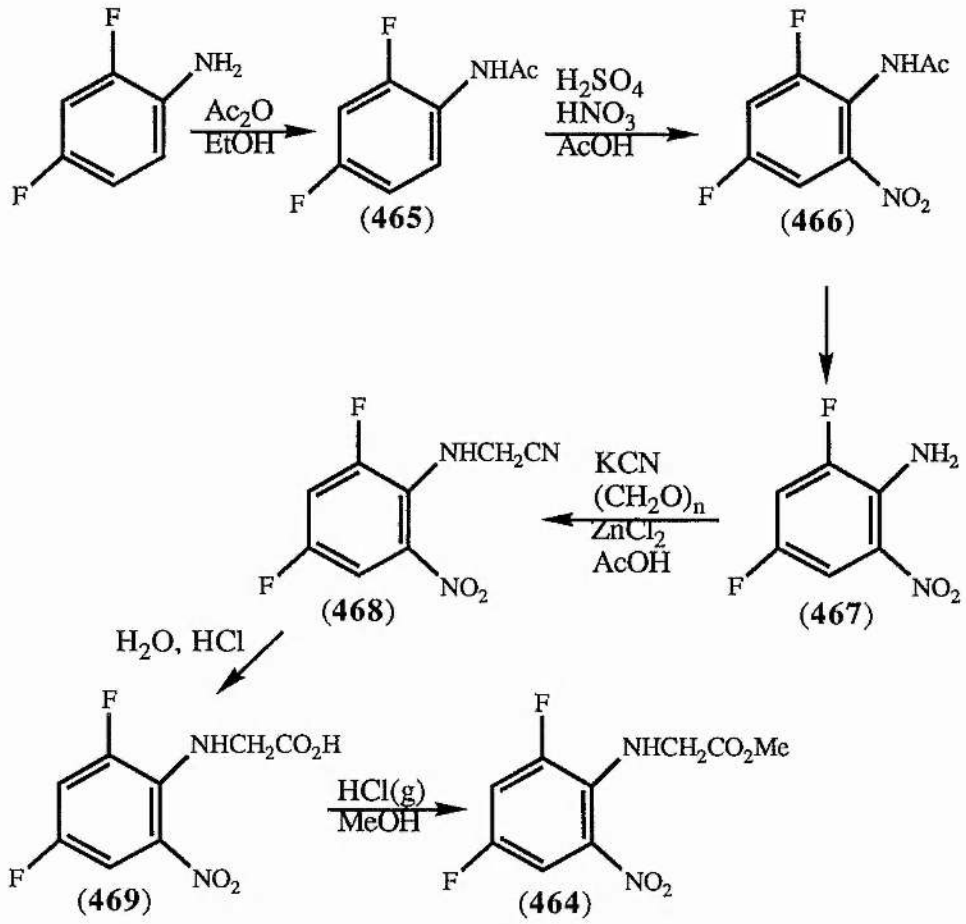


Scheme **4.12**

A sample of the *N*-oxide (**463b**) also appears to have been isolated from an attempt to synthesize the free acid (**462**) using potassium carbonate and refluxing ethanol (Eqn **4.24**); see section **4.1**, (p. 40) for the possible explanation of such an occurrence.



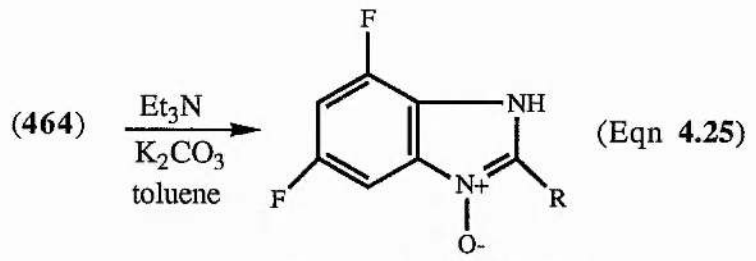
So far all of the glycine esters discussed which have given products instead of or in addition to the *N*-oxide have had substituents at C-6 which, taking into account both resonance and inductive effects, have been electron-withdrawing. Those that gave only the *N*-oxide have either been unsubstituted at C-6 or had an electron-donating substituent in that position. Therefore, the evidence thus far indicated that the effect was electronically and not sterically induced. The ideal test for this hypothesis was to attempt the cyclization of a glycine ester with fluorine in position six and see what products were formed; fluorine is the smallest substituent of those involved and has a strong electron-withdrawing power.



Scheme **4.13**

N-(4,6-Difluoro-2-nitrophenyl)glycine methyl ester (**464**) was made via the nitrile (**468**) as indicated by scheme **4.13**. The ester was reacted with triethylamine in toluene initially at room temperature, but because the conditions were too mild, an equivalent of potassium carbonate was added and the mixture heated under reflux (Eqn **4.25**). An extensive work-up involving several recrystallizations gave several solids which could not be identified immediately. Several mass spectra contained large peaks at m/z 154 which corresponds to the $(M-16)^+$ ion for 5,7-difluoro-1*H*-benzimidazole 3-oxide (**470a**; R=H); but only one spectrum showed the molecular ion. In the mass spectra of the *N*-oxides, the peaks for the $(M-16)^+$ ions are usually intense[68]. A peak at m/z 212 was also observed, which corresponds to the $(M-16)^+$ ion for the methyl 2-carboxylate ester (**470b**; R=CO_2Me). The molecular ion was not observed but the

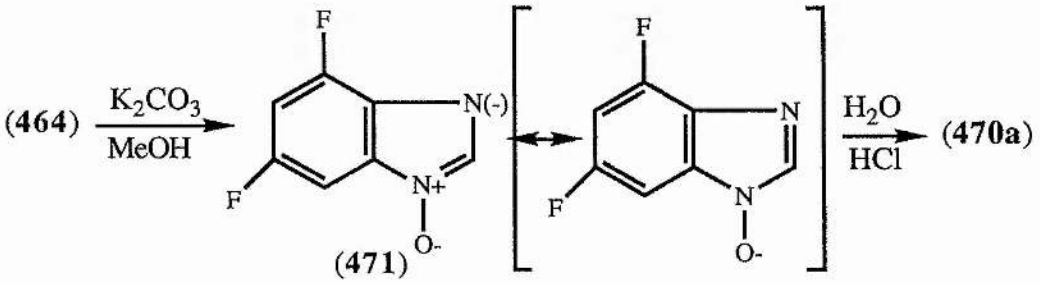
presence of a very small amount of the ester was indicated by a ^{13}C n.m.r. spectrum of the mixture. There was no indication that any other products had been formed.



(Eqn **4.25**)

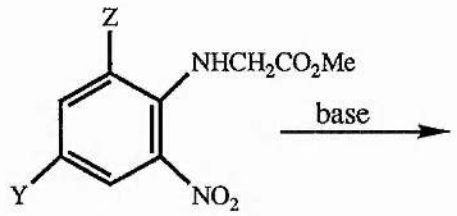
(**470a,b**; R=H, CO_2Me)

Since the result was contrary to expectations and because one molar equivalent of each of two bases had been employed, the reaction was repeated. (Most of the other cyclization reactions used ony one molar equivalent of one base.) Heating the ester (**464**) and potassium carbonate in methanol under reflux and stirring at room temperature gave a pale orange solution that was filled with a white precipitate. The solid was collected, dissolved (surprisingly easily) in water and the solution acidified. The precipitate was identified by ^{1}H and ^{13}C n.m.r. as the 2-unsubstituted benzimidazole *N*-oxide (**470a**) (Eqn **4.26**). (The ^{13}C n.m.r. assignments matched those made for (**470a**) in the spectrum of the mixture above.) The precipitate initially collected from the reaction solution was presumably the ion (**471**). Some 2-substituted 6-nitrobenzimidazole 3-oxides have also been isolated in this ionic form[69].



(Eqn **4.26**)

Table **4.4** The products formed from the reactions of *N*-(di- and tri-substituted phenyl)-glycine esters with bases[a]



Compd No.	Y	Z	Benzimidazole *N*-oxides	Quinoxaline-2,3-diones	Benzimidazol-2-ones	Diamino-azoxybenzenes
(405)	CF_3	H	2-CO_2H, 2-H			
(447)[a]	CF_3	Cl	~15%[b]	~2%[b]	(?)[b]	X[b]
(455)	CF_3	NO_2	trace amt of 2-CO_2Me	38%		15%
(110b)	H	Me	55% 2-CO_2Me			
(446)	H	NHAc	43% 2-CO_2Me			
(110a)	H	NO_2		39%		
(403)	NO_2	H	56% 2-CO_2Me			
(461)[c]	NO_2	CF_3	2-CO_2Me	25%		17%
(416)	F	H	74%			
(464)[d]	F	F	85% 2-H			

[a] This ester was reacted several times, the reaction most representative of the products formed is given.

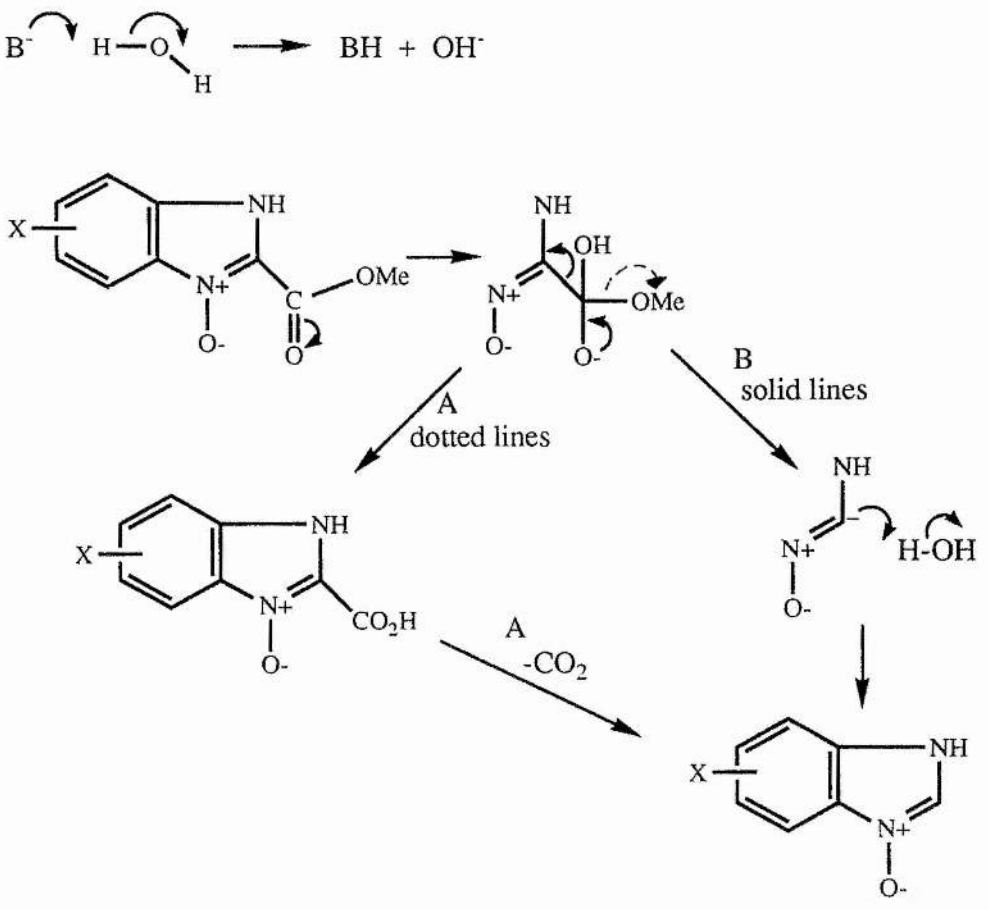
[b] The products were isolated in mixtures in this reaction though all but the benzimidazol-2-one were also isolated separately; X indicates that the yield could not be measured.

[c] This ester, when reacted with barium hydroxide in tetrahydrofuran instead of triethylamine and toluene, gave only trace amounts of the quinoxaline-2,3-dione and the 2-unsubstituted benzimidazole *N*-oxide.

[d] This ester, when reacted with triethylamine and potassium carbonate in toluene instead of just the latter in methanol, gave mixtures of the benzimidazole-2-carboxylate ester *N*-oxide and the 2-unsubstituted compound.

In one case, the benzimidazole *N*-oxide isolated was believed to be the 2-carboxylic acid derivative. In several others, the 2-unsubstituted *N*-oxides were isolated. The alkyl 2-carboxylate esters, the expected derivatives, were only found in very small amounts and often in mixtures. These results are in contrast to the fact that McFarlane and others isolated only the esters from analogous reactions. The compounds required hydrolysis before the parent *N*-oxides could be obtained. The hydrolyses are presumed to proceed through the 2-carboxylic acid intermediates, which are known to decarboxylate readily under mild conditions[62]. Analogously, compound (**405**) presumably cyclized to the 2-carboxylate ester and underwent hydrolysis in the reaction solution. Though McFarlane *et. al.*[1] used acid hydrolysis, base hydrolysis of methyl 1-methyl-benzimidazole-2-carboxylate 3-oxide using potassium hydroxide has also been reported[65] (Eqn **4.16**) in which a minor quantity of benzimidazol-2-one was isolated in addition to the 2-unsubstituted *N*-oxide. The mechanism for this hydrolysis (cf Scheme **4.5**) is particular to hydroxide as the base. Though hydroxide was not present in the reactions of the esters in this project, it could be generated by the bases that were used and water[70] (Scheme **4.14**). Compound (**405**) was cyclized in ethanol which would contain a small percentage of water.

N-(2-Nitro-4-trifluoromethylphenyl)glycine methyl ester (**405**) and the 4-nitro derivative (**403**) are very similar compounds, yet the former was believed to have given the benzimidazole-2-carboxylic acid 3-oxide and the latter the methyl carboxylate 3-oxide. This could be due to several factors. One is the different bases used, though this seems unlikely. Many different bases have been used in these reactions, one of the most common being potassium carbonate. If the base used was a significant factor then surely these results would have been encountered before this. Another factor could be the relative solubilities of the benzimidazole-2-carboxylate esters in the reaction solution. The 5-trifluoromethyl derivative could be more soluble in alcoholic solution and thus could be more susceptible to further reaction.



Scheme **4.14**

The same could be true for the other benzimidazole-2-carboxylate esters which hydrolyze in the reaction solution to give the 2-unsubstituted derivatives. However, these reactions did not necessarily occur through the 2-carboxylic acid intermediates. The intermediate in basic hydrolysis of an ester could do two things, it could eliminate alkoxide, as previously indicated to give the acid (Scheme **4.14**, pathway A) or it could eliminate the entire side chain leaving an electron pair (carbanion) on C-2 which could then abstract a proton to give the 2-unsubstituted benzimidazole (pathway B). According to this mechanism, methyl 5-trifluoromethylbenzimidazole-2-carboxylate 3-oxide reacted along pathway A, while the rest could have reacted according to either possibility. Both of the mechanisms rely on the presence of water in the solutions. Most of the cyclizations were performed in alcoholic solvents or toluene which would contain a small percentage of water. Some of the esters were reacted with barium hydroxide octahydrate in dry tetrahydrofuran. In these cases the water could have come from the base.

The glycine esters which gave the 2-unsubstituted products contained, with the exception of (**416**), three electron-withdrawing substituents on the ring including the *ortho* nitro group. The esters that have been investigated previously possessed only one substituent (electron-donating or -withdrawing) besides the *ortho* nitro group. This suggests that the added electron-deficiency of the ring could be the reason for the former compounds being hydrolyzed in the reaction solutions. Perhaps the added electron-deficiency makes the compounds more soluble. Alternatively (or in addition) electron-withdrawing groups are known to facilitate hydrolysis in general and particularly involving bases[70]; they help stablilize the ionic intermediate. The same is true for decarboxylation. Thus the benzimidazole-2-carboxylate esters with the more electron-deficient six-membered rings would be more readily hydrolyzed and decarboxylated (by either pathway) to the 2-unsubstituted compounds.

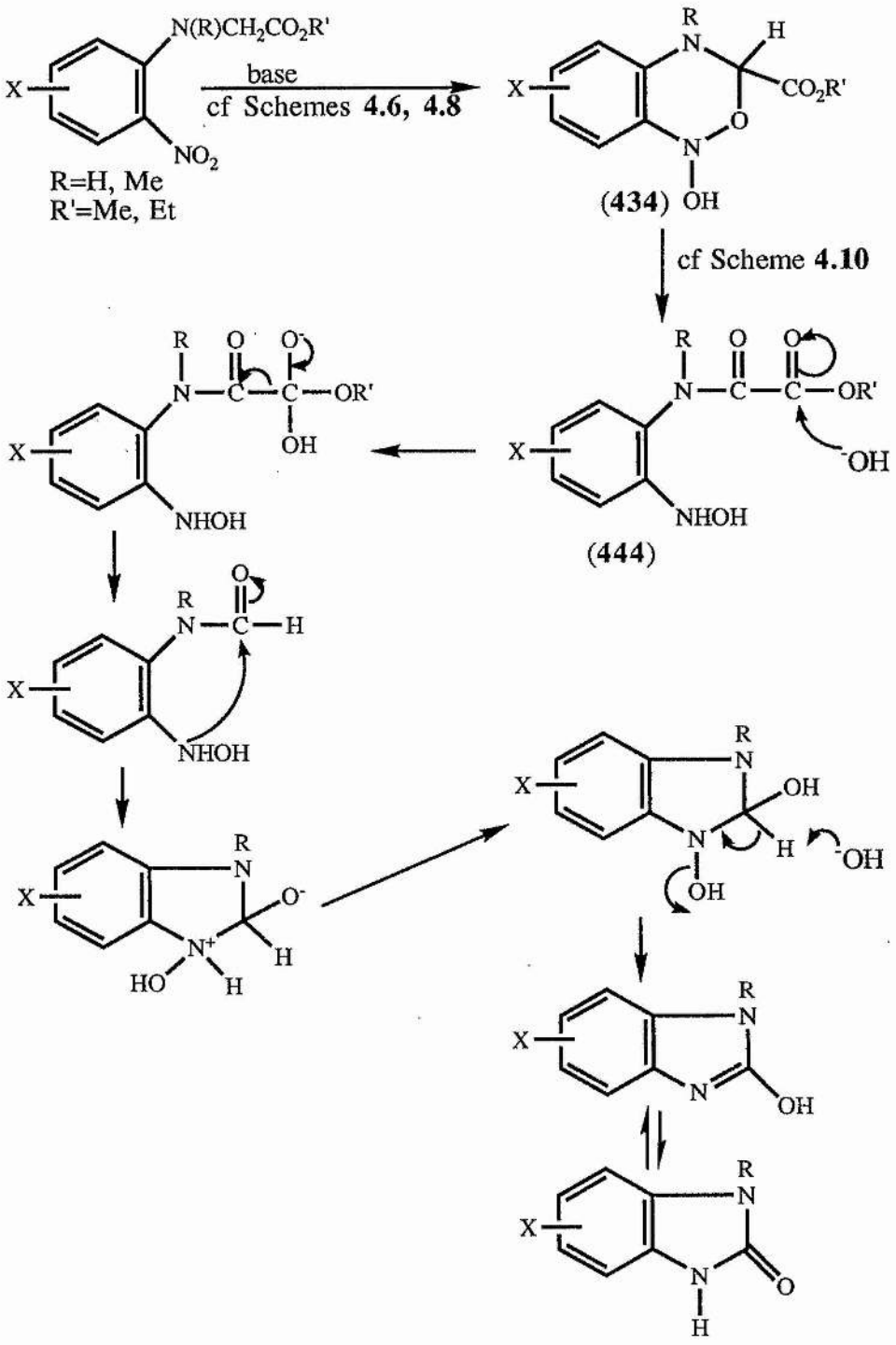
Takahashi and Kano[65] reported that base hydrolysis of methyl 1-methyl-benzimidazole-2-carboxylate 3-oxide gave the 2-unsubstituted-1-methylbenzimidazole 3-oxide and a small percentage of 3*H*-benzimidazol-2-one. Thus it is possible that it is through the reaction of 7-chloro-5-trifluoromethyl-1*H*-benzimidazole 3-oxide (**451**) with the hydroxide generated in solution that the corresponding benzimidazol-2-one (**453**) was formed. However, if this were the case it is strange that none of the benzimidazol-2-ones were isolated from the glycine esters which gave only the *N*-oxides. Another possibility, which incorporates this fact, is that they were formed from an intermediate which also could give the quinoxaline-2,3-diones. This intermediate is postulated to be formed only from the glycine esters having a particular type of substituent at position six.

This intermediate is the acyl compound (**444**) which is formed when base attacks the CH of the oxadiazine (**434**) (cf Scheme **4.10**). As described in section **4.1**, cyclization of acyl-esters (glycine or sarcosine) would give 1-hydroxyquinoxaline-2,3-diones and acyl-nitriles would give 1-hydroxybenzimidazoles both of which were found experimentally. To also account for the formation of 3*H*-benzimidazol-2-ones (from the esters) from the acyl intermediate (**444**) is not so straightforward. A simple reduction of the hydroxylamino group to amino would not be sufficient; the ester-carbonyl would still be the more reactive of the two. It is possible; however, that the ester group could be

cleaved off by attack of hydroxide (produced *in situ*). This attack on the acyl-ester (**444**) would result in a formamide (or its anion) which upon cyclization and elimination could give the 3*H*-benzimidazol-2-one (Scheme **4.15**). The reason why the acyl compounds derived from some of the esters would cyclize directly and those from other esters would also undergo cleavage is not clear. The strength of the base used does not seem to correlate with the results; the bases used in the reactions that gave both 1-hydroxy-quinoxaline-2,3-diones and benzimidazol-2-ones were generally weaker than those used in reactions giving only the former.

Most of the glycine esters cyclize 'normally' upon reaction with base to the corresponding benzimidazole *N*-oxides. These include all of the esters unsubstituted at C-6 and those with methyl, acetamido, and fluorine at C-6. In section **4.1** a mechanism was detailed for the synthesis of the *N*-oxides from these compounds (cf Schemes **4.6**, **4.8**, **4.10**). The mechanism also accounts for the formation of quinoxaline-2,3-diones and 3*H*-benzimidazol-2-ones from the glycine and sarcosine esters and 1-hydroxy-benzimidazol-2-ones from the nitriles. The glycine esters with chlorine, trifluoromethyl, or nitro on C-6 produced some or all of these compounds, though never the *N*-oxides alone. Due to the similarity in products formed, it seems reasonable to suggest that they were formed by the same mechanism. Table **4.4** shows some pairs of compounds which differ only in the substituent at C-6, but which behave differently when reacted with base. These comparisons indicate that the formation of the 'abnormal' products is directly related to the substitution at C-6. This being the case, it is necessary to consider what sort of role the substituents could have in the proposed mechanism.

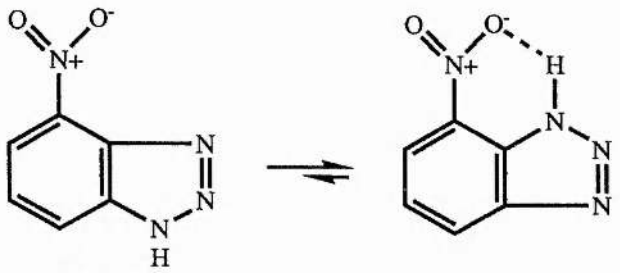
According to the mechanism outlined in scheme **4.10**, when base attacks the oxadiazine intermediate (**434**), it has the choice of abstracting a proton from the amino group or the α-CH. In the cases of 'normal' cyclization, only attack at NH occurs. This suggests that attack at NH is preferred over attack at CH, to the total exclusion of the latter. When the nitrogen is fully substituted, the base attacks at the CH and the 'abnormal' products are formed. For most of the glycine esters that also give 'abnormal' products, attack occurs at both sites, suggesting that somehow the attack at NH is made


N(R)CH2CO2R'
base
cf Schemes 4.6, 4.8
X
NO2
R=H, Me
R'=Me, Et
(434)
OH
CO2R'
cf Scheme 4.10
(444)
OR'
NHOH
-OH

Scheme **4.15**

less favourable and thus attack at CH more competitive. This could be how some of the substiutents on C-6 are involved; they could hinder the attack at NH. The interference could have to do with the resonance, inductive (and field), and/or steric effects that are associated with the substituents. Although this is undoubtedly a complicated issue, by looking at the substituents and the effects individually it might be possible to speculate why some of the substiutents seem to hinder the attack at NH and others do not.

First, it is necessary to mention what may be a special case among those compounds which gave 'abnormal' products. Two glycine esters (**455**, **110a**), both with nitro attached to C-6, gave products other than the expected benzimidazole *N*-oxide. The reason behind these results could be that one of the nitro-oxygens is hydrogen-bonded to the amino hydrogen thereby giving the more stable tautomer. This could prevent the NH from becoming involved in the reaction with base. A similar conclusion was made to explain why the amino nitrogen in the benzotriazole (**472**) was resistant to abstraction or to involvement in reaction[71]. If this explanation for the reactions of compounds (**455**, **110a**) is valid then it must follow that the acetamido-carbonyl in compound (**445**) lies away from the amino nitrogen because (**445**) did cyclize as expected. There is no evidence to suggest that there is any hydrogen bonding between the two.



(**472**)

It should be noted that this discussion focuses on the differences between the substituents that occupy position six in the glycine esters. Some of these esters also had different substiutents at C-4 but this is not thought to play a significant part in the 'normal' or 'abnormal' reaction of the esters with base. All of the esters in question were either unsubstituted at C-4 or had fluorine, trifluoromethyl or nitro in that position. In

reactions of *N*-(2-nitro-4-substiuted phenyl)glycine esters with bases the nature of the 4-substituent sometimes increased the reactivity and lessened the necessary reaction time, especially in the case of nitro. A variety of substituents were employed (Cl, F, CF_3, NO_2, OMe, Me, NHAc, etc.) that had definite effects on the basicity of the amino group (as judged by a comparison of pK_a values for the 4-substituted anilines[72]). However, the change in substituent did not result in a change in the products formed.

At first glance, the results seem to suggest that there may be an electronic factor determining which substituents affect the attack at NH. Except for fluorine, the substiutents which are said to interfere in the attack are all electron-withdrawing (over-all) and those that did not are electron-donating (over-all). By 'over-all' it is meant that both inductive and resonance effects are taken into account (Table **4.5**).

Table **4.5** : The substituents on C-6 according to whether they are electron-withdrawing (a negative sign) or electron-donating (a positive sign) with respect to resonance (M) and inductive (I) effects[73]

+M +I	+M -I	-M -I
CH_3	NHAc Cl F	CF_3 NO_2

Accordingly, methyl is clearly electron-donating and trifluoromethyl is electron-withdrawing. (The very weak electron-donation of the methyl group and the electron-attraction of trifluoromethyl group by resonance has been confirmed and is thought to be due to hyperconjugation[73,74].) Chlorine and fluorine while being electron-donating by resonance are more strongly inductively electron-withdrawing. The opposite is true for acetamido making it over-all electron-donating because of its lone-pair. Looking at the substituents according to their separate electronic effects does not match up as well with the results. Inductive effects would be expected to be an important consideration for a situation involving two groups *ortho* to one another. However, considering only inductive effects presents an added contradiction to the fluorine case because chlorine,

fluorine, and acetamido are inductively electron-withdrawing yet the compound containing the first at C-6 reacted 'abnormally' and the ones containing the other two in that position cyclized 'normally'. Considering just resonance effects also presents more discrepancies, whereas taking them both into account seems to offer the best fit to the results.

Assuming for (only) a moment that electron-withdrawing power is one cause for the interference with attack at NH, it does not appear to be a matter of degree, for the effect is weaker for chlorine than for fluorine. Though this theory does explain almost all of the results, it is not immediately evident why it should be that electron-withdrawing power should hinder attack at NH in the first place. Theoretically, the opposite should be true. Electron-withdrawing substituents make the ring more electron-deficient, forcing the amino nitrogen to contribute more of the electron-density of its lone-pair. Thus the nitrogen would be less basic than in the absence of the substituent and the hydrogen more susceptible to attack by base, not less. For electron-donating substituents the opposite would be true, the attack would be made less likely. This is supported by the fact that electron-donating substituents suppress the reactivity of *N*-(substituted-2-nitrophenyl)-glycine esters while electron-withdrawing groups facilitate reaction[58]. Therefore the fact that the results seem to indicate that the electronic effect plays a major part in the reaction seems to be misleading. These reactions are complicated, however, and no explanation is easily available to explain the results. It is most likely that a combination of factors is involved. It could be that the electronic nature of the substituents is important in more subtle ways that are not evident at this time.

Another possibility is that there is a steric factor involved. Table **4.6** lists the Van der Waals and covalent radii[75] for the atoms making up the substituents including a value for the methyl group itself. Using these values it is possible to estimate the relative sizes of the substituents in question.

Table **4.6**

atom or group	van der Waals radii (pm)	covalent radii (pm)
H	120-145	37
C	165-170	77
F	150-160	71
Cl	170-190	99
CH_3	200*	

* ref 76

For example, if a methyl group has a van der Waals radius 200 pm and a covalent C-F bond is longer (~148 pm) than a C-H bond (~114 pm) then it stands to reason that the trifluoromethyl group is larger than a methyl group. The deductions made allowed the following trend with respect to increasing size to be estimated: $F < Cl < CH_3 < CF_3$. (It is difficult to access the size of the acetamido group, though being planar the steric hindrance would probably be minimal. The nitro group is not included because it is most likely hydrogen-bonded to NH.) The possible steric factor alone does not explain all of the results obtained; however, the fact that the smallest substituent did not interfere in the attack on NH and the larger chlorine and trifluoromethyl ones did could be significant.

As opposed to the possible electronic influence, it is easy to understand why a bulky substituent might influence attack at a neighbouring site. Returning to the discussion of the overlap of the lone-pair on nitrogen with the ring, a bulky substituent could force the amino group out of the necessary orientation, thus limiting or in fact eliminating the overlap altogether. The nitrogen would then be more basic than in the absence of the substituent and would be made less favourable for base attack. In addition there is the obvious possibility that the substituent could physically hinder the attack.

Even though this theory is easy to rationalize it does not explain why the methyl group, larger than chlorine, would not hinder the attack while the chlorine apparently does. As it was emphasized before, the question of why some of the glycine esters cyclize as expected to the benzimidazole *N*-oxides and some give additional products is

obviously a complicated one which can not be easily explained. Futher research in this area may help to clarify the picture. For instance, it would be interesting to see how a compound with a bulky electron-donating substituent on C-6 would behave under basic conditions. The methyl case could be used as a comparison for the reactions of analogous compounds with larger alkyl groups in the same position. Also, it would be enlightening to see what products were formed from a basic reaction of a glycine ester having a methoxy group in that position.

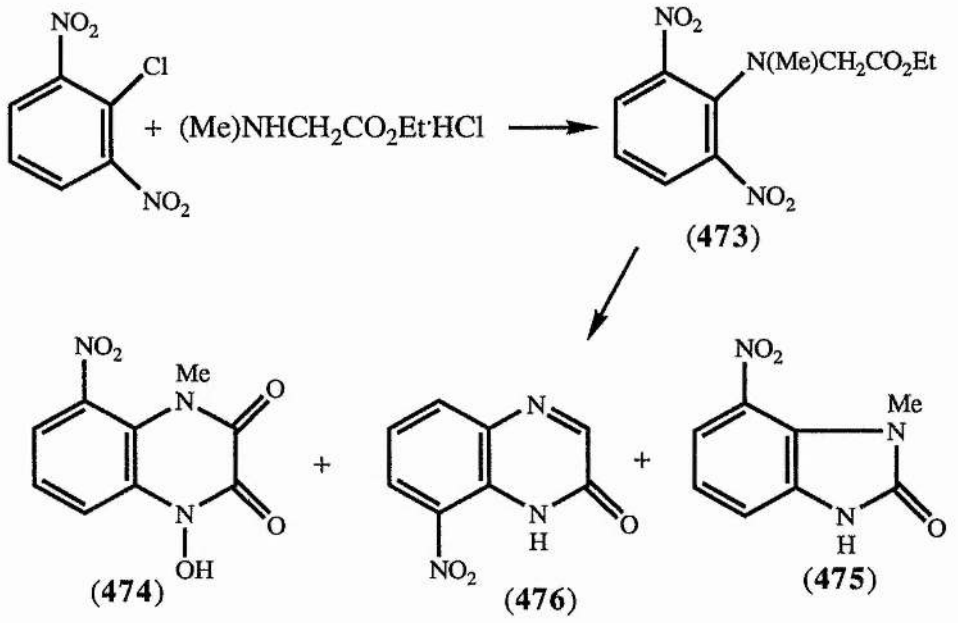
SECTION 4.3

INTRODUCTION

The sarcosine esters corresponding to the glycine esters discussed in section **4.2** were also synthesized. The reaction of these esters with base did not provide any more information about the effects of the *N*-methyl group or of the substituent in position six because they were both present in the compounds. The reactions were, however, interesting in their own right. As expected, no *N*-methylbenzimidazole *N'*-oxides were isolated. This would be due to the *N*-methyl group because even the glycine esters with the larger substituents such as CF_3 or NO_2 in position six, gave trace amounts of the corresponding 1*H*-benzimidazole 3-oxides. Thus these sarcosine esters behaved as the others did and gave only the 'abnormal' products upon reaction with base.

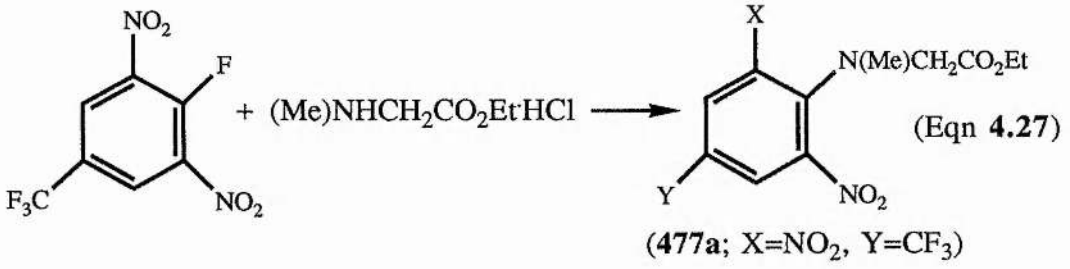
N-(4,6-DISUBSTITUTED-2-NITROPHENYL)SARCOSINE ESTERS AND THEIR REACTION WITH BASES

The esters were difficult to synthesize. Attempts to make *N*-(2,6-dinitrophenyl)-sarcosine and esterify it failed. Direct synthesis from sarcosine ethyl ester with extensive purification, finally gave the pure ester (**473**). 1-Hydroxy-4-methyl-5-nitroquinoxaline-2,3-dione (**474**) was isolated from a reaction of the ester with potassium carbonate along with mixtures of 1-methyl-7-nitro-3*H*-benzimidazol-2-one (**475**) and 8-nitroquinoxalin-2-one (**476**) (Scheme **4.16**). The position of the nitro group was determined from a study of the ^{1}H and ^{13}C n.m.r. spectra on that compound and other quinoxalin-2-ones isolated. The 5-nitro isomer of (**476**) did not appear to have been formed.



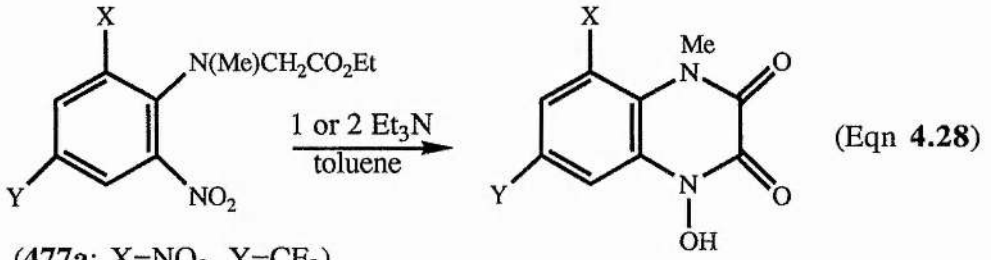
Scheme **4.16**

Attempts to obtain pure samples of *N*-(2,6-dinitro-4-trifluoromethylphenyl)-sarcosine ethyl ester (**477a**; X=NO_2, Y=CF_3) failed, in addition to one attempt at making the free acid. The same method used to make the corresponding glycine ester was applied (Eqn **4.27**). The sarcosine ester obtained was impure. In the end an ester sample which had been chromatographed twice, but was still slightly impure, was used in reactions with base.

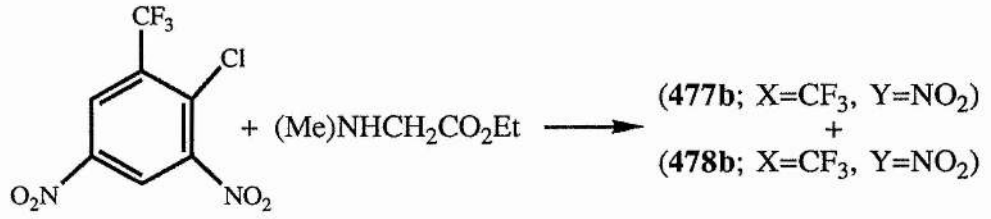


The ester (**477a**) was combined with triethylamine in toluene and stirred at room temperature (Eqn **4.28**). Under these conditions, the glycine ester (**455**) needed to be reacted for 4.5 hours before t.l.c. indicated a considerable amount of reaction had taken place. Interestingly enough, the sarcosine ester reacted much more slowly. Even after 22 hours the reaction mixture was still relatively uncomplicated. A small amount of

1-hydroxy-4-methyl-5-nitro-7-trifluoromethylquinoxaline-2,3-dione (**478a**; X=NO_2, Y=CF_3) was identified in addition to the starting material. The same compounds were isolated when the reaction was repeated using two equivalents of triethylamine. When the isomeric *N*-(2,4-dinitro-6-trifluoromethylphenyl)sarcosine methyl ester (**477b**; X=CF_3, Y=NO_2) was synthesized directly, an oily film was also isolated which gave a mass spectrum containing the molecular ion and expected fragmentation ions for the corresponding quinoxaline-2,3-dione (**478b**; X=CF_3, Y=NO_2) (Eqn **4.29**). No further reactions of the ester were performed because detection of (**478b**) was an indication that the sarcosine ester behaved as the others had done.



(**477a**; X=NO_2, Y=CF_3) (**478a**; X=NO_2, Y=CF_3) (Eqn **4.28**)

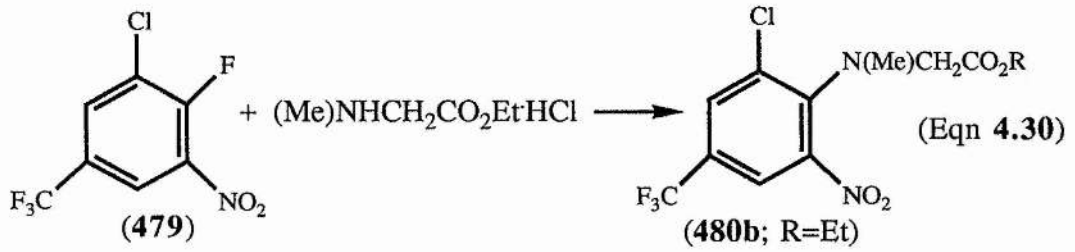


(Eqn **4.29**)

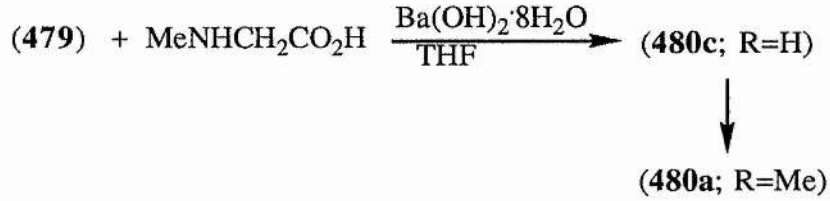
The reactions of *N*-(6-chloro-2-nitro-4-trifluoromethylphenyl)sarcosine methyl and ethyl esters (**480a,b**; R=Me, Et) with base were much more complicated than the reactions of the three esters discussed thus far in this section.

Attempts to synthesize the sarcosine ester (**480b**) directly (Eqn **4.30**) were the same as those used to make the corresponding glycine methyl ester (**448**) and similar problems were encountered (cf Table **4.2**, p.64). In particular, methods D (triethylamine, toluene), and E (barium hydroxide, tetrahydrofuran) and potassium carbonate in tetrahydrofuran produced impure ester samples. By the time a pure sample was obtained, the yields of the ester were greatly diminished. Synthesis via the acid

(**480c**) proved to be the best method considering yield and purity (Scheme **4.17**). The methyl ester was synthesized in this manner, and both derivatives were reacted with bases.



(Eqn **4.30**)

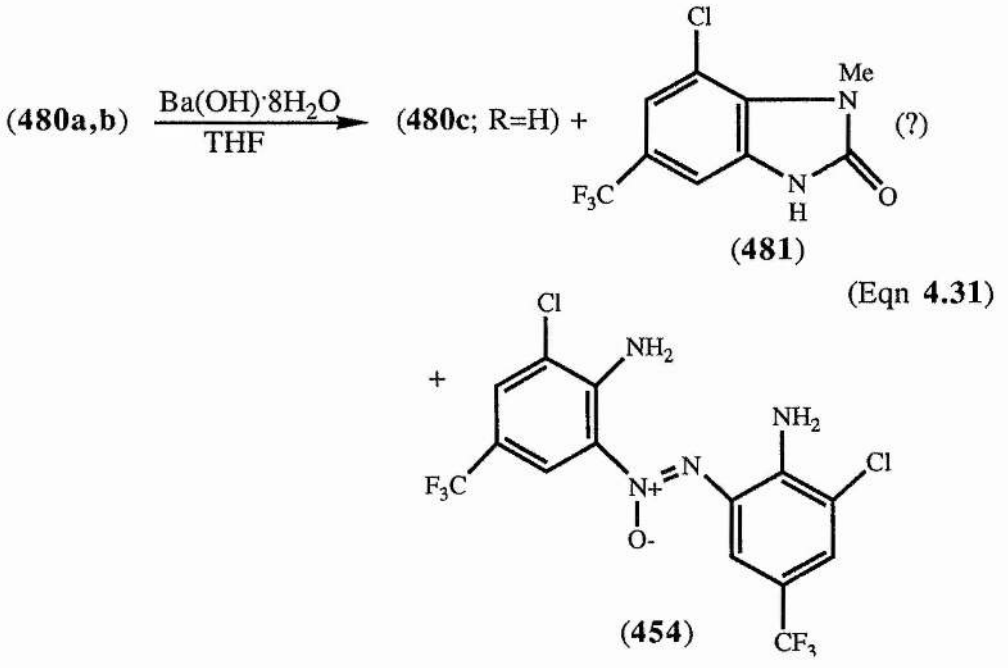


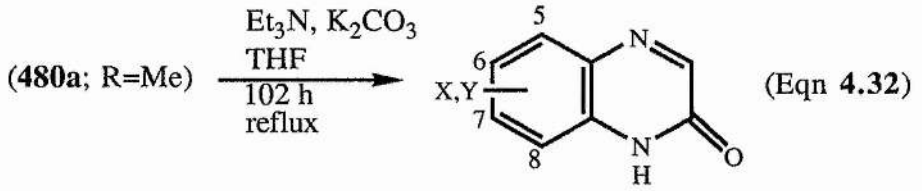
Scheme **4.17**

Several reactions of the esters (**480a,b**) with base resulted in complex mixtures from which nothing could be identified. As was the case with the cyclization reactions involving sarcosine esters discussed in section **4.1**, the reactions were stopped before all of the starting material had reacted because t.l.c. showed that many components had already formed. It was decided to allow one reaction of this ester with triethylamine in toluene to go to completion. The result was that none of the components could be separated for identification. The same result was obtained when the ester was reacted with potassium carbonate in refluxing ethanol, the conditions under which *N*-(2,4-dinitrophenyl)sarcosine ester gave the corresponding 1-hydroxyquinoxaline-2,3-dione and 2-amino-2′-methylamino- and 2,2′-bis(methylamino)azoxybenzenes (cf Eqn **4.1**). Fortunately by tempering the conditions the products from several reactions could be characterized.

As with the glycine ester parent, the reaction of the sarcosine esters (**480a,b**) with barium hydroxide in tetrahydrofuran gave the widest range of products and aptly illustrated the complexity of the reaction. Two such reactions performed under these

conditions, one on each of the methyl and ethyl esters, produced the same results (Eqn **4.31**). Substantial amounts of the free acid (**480c**) were isolated, in addition to 2,2′-diamino-3,3′-dichloro-5,5′-bis(trifluoromethyl)azoxybenzene (**454**). A buff-coloured solid was also collected which appeared to be 7-chloro-1-methyl-5-trifluoromethyl-benzimidazol-2-one (**481**). The fact that the azoxybenzene was the diamino derivative and not the methylamino or bis(methylamino) derivative was very surprising, although some of the sarcosine esters already discussed have also given products that do not contain the *N*-methyl group. One such product, the 1*H*-benzimidazole 3-oxide, was not isolated in any of the reactions. The corresponding derivatives of the other two products, the quinoxalin-2-one isomers (**482a,b**), were the only products identified from the reaction of this ester with triethylamine (Eqn **4.32**). ^{1}H n.m.r. spectra of the reaction solution were taken throughout the 102 hour reflux to see if the order of formation of the products could be determined. No conclusions could be drawn.





(Eqn **4.32**)

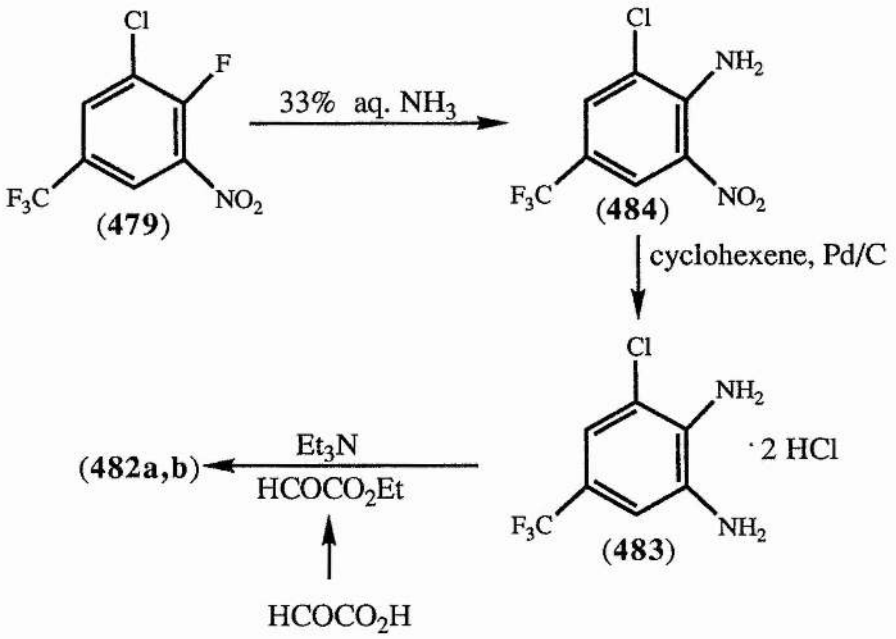
(**482a**; X= 5-Cl, Y= 7-CF_3)
(**482b**; X= 8-Cl, Y= 6-CF_3)

As explained previously, if the quinoxalin-2-one was formed by reaction of an unsymmetrically substituted *o*-phenylenediamine and ethyl glyoxylate, two isomers could form. In this case, a solid was obtained which appeared to contain a mixture. The solid was purified which left predominantly one isomer. It was not until the product was synthesized independently that the orientation of that isomer was determined. (The independent synthesis would also confirm the identity of the product since microanalysis could not be obtained for any of the derivatives isolated.)

INDEPENDENT SYNTHESIS OF TWO ISOMERIC QUINOXALIN-2-ONE DERIVATIVES

The dihydrochloride of the *o*-phenylenediamine (**483**) needed was made from the 3-chloro-4-fluoro-5-nitrobenzotrifluoride according to scheme **4.18**. The addition of triethylamine to a solution of the diamine and ethyl glyoxylate in ethanol rapidly induced reaction (Scheme **4.18**). Interestingly enough, in the mixture of the quinoxalin-2-one isomers (**482a,b**) isolated, the predominant form was the one that was in the lesser abundance in the purified sample obtained from the sarcosine ester reaction. This was quite fortunate in that it allowed for the positive identification of both isomers. They had distinctly different spectral characteristics allowing logical assignment of the orientations. Thus the main isomer formed from the independent synthesis was 8-chloro-6-trifluoromethylquinoxalin-2-one (**482b**) and that from the sarcosine ester was the 5-chloro-7-trifluoromethyl isomer (**482a**). The crude sample that was obtained from the sarcosine ester reaction was found to have contained a more equal mixture of the isomers. It is difficult to say which one was produced in the greater abundance overall from the reaction. The product mixture was so complicated, because the reaction had been allowed

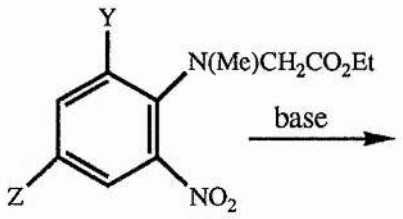
to run for so long, that more of one or both of the isomers could have been present but could not be isolated.



Scheme **4.18**

The *N*-(2,6-dinitrophenyl)sarcosine ester (**473**) was the only one to produce solely one isomer of the quinoxalin-2-one. The remainder seem to have produced almost equivalent amounts of both. The nucleophilicity of an amino nitrogen would be considerably reduced by the presence of an *ortho*-nitro group, thus the attack on that nitrogen would be disfavoured. The nitro group may also sterically hinder the attack. Both effects would result in the preferential formation of the 8-nitro isomer, which was indeed the isomer isolated.

Table **4.7**: The products from the reactions of the 6-substituted sarcosine esters with base



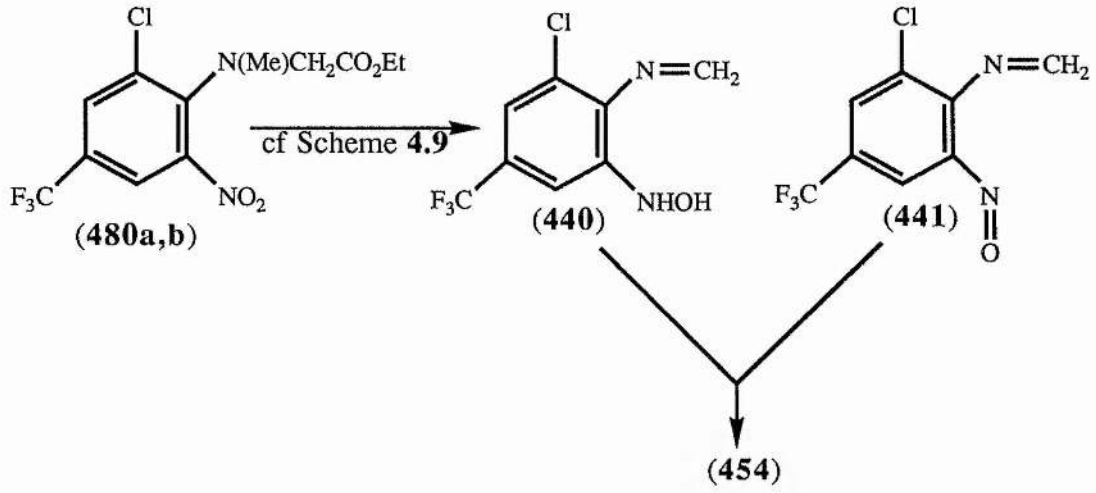
Compd. No.	Y	Z	Quinoxalin-2-ones	Benzimidazol-2-ones	Diamino-azoxybenzene	Quinoxaline-2,3-diones
(473)	NO_2	H	X	X		X
(477a)	NO_2	CF_3				X
(477b)	CF_3	NO_2				X
(480a,b)	Cl	CF_3	X	(?)	X	

X indicates that the product was formed from reaction of that ester

For most of the glycine and sarcosine esters, 1-hydroxyquinoxaline-2,3-diones were produced in higher percentage yields than the benzimidazol-2-ones; the latter have not been isolated in sufficient amount and purity to be confirmed by microanalysis. However, 1-hydroxy-4-methyl-5-chloro-7-trifluoromethylquinoxaline-2,3-dione was not isolated from any of the reactions of (**480a,b**), though the glycine ester analog (**447**) gave up to 10% of the corresponding quinoxaline-2,3-dione and a small amount of the benzimidazol-2-one. Both products are proposed to form from the acyl intermediate (**444**) (cf Scheme **4.15**); the former by direct cyclization, the latter by attack of base with elimination of the keto-group and subsequent cyclization. It is puzzling why in this particular series, direct cyclization should occur for the glycine ester and not for the sarcosine ester.

The mechanisms for the formation of 1-hydroxy-4-methylquinoxaline-2,3-diones, quinoxalin-2-ones, and *N*-methylbenzimidazol-2-ones from *N*-(substituted phenyl) sarcosine esters have already been detailed in section **4.1**. In that section it was stated

that quinoxalin-2-ones and azoxybenzenes have not been isolated from the same reaction mixture, and thus the two mechanisms involved may have a common intermediate, namely the hydroxylamino-anil (**440**). The sarcosine esters are one case in point (**480a,b**). The anil could react with ethyl glyoxylate to give the quinoxalin-2-one (cf Scheme **4.9**), or it could be partially oxidized up to the nitroso derivative and the two could react to give the azoxybenzene (**454**) (Scheme **4.19**).



Scheme **4.19**

The mechanism in scheme **4.19** is a reasonable one for the formation of the diaminoazoxybenzene (**454**) from the sarcosine esters (**480a,b**). The combination of hydroxylamino and nitroso compounds is an established method for synthesizing azoxybenzenes. However, several problems arise when trying to apply the same mechanism to the glycine esters (**447**,**455**,**461**) which also gave diamino-azoxybenzenes. These esters all cyclized 'abnormally' giving several products in addition to the benzimidazole *N*-oxides. The mechanism for the formation of these products involves base attacking at the NH or CH of an oxadiazine intermediate (cf Scheme **4.10**). Attack at NH leads to a nitroso-anil intermediate analogous to the one proposed in the formation of the azoxybenzenes. (This intermediate cyclizes to give the benzimidazole *N*-oxide.) The problem comes from trying to explain why the azoxybenzenes are not formed then from the glycine esters that cyclize 'normally'. According to the mechanism, these esters are only attacked at NH to give the nitroso-anils and thus the *N*-oxides. Why

should it be that in such cases the anils readily give the benzimidazole *N*-oxides but in the others go on to form the azoxybenzenes in addition to the *N*-oxides? The question is especially pertinent considering that the nitroso-anils are proposed intermediates in a number of reactions giving benzimidazole *N*-oxides[64]. Is it possible that the substituents on C-6 affect not only the site of attack on the oxadiazine but the cyclization of the nitroso-anil to the *N*-oxides? This seems unlikely but so do the alternative explanations.

The glycine esters that cyclized 'abnormally' for the most part gave significantly reduced yields of the *N*-oxides. This may be due to the hindrance of base attack on NH and which would cause less of the anil intermediates to be formed, thus reduucing the yields of the *N*-oxides. However, considering the mechanism in scheme **4.19**, the possibility arises that the reduced yield could also be because the nitroso-anils give a second compound, the diaminoazoxybenzenes. Thus a competing reaction may be responsible for the low yields of the *N*-oxides.

Though the azoxybenzenes are typically formed from compounds such as the nitroso-anils, the theory of a 'competing reaction' is in some doubt. Considering compounds (**110a**, **455**) with a nitro group on C-6, the hydrogen-bonding of a nitro group to NH might be expected to stabilize the 1*H*-benzimidazole 3-oxide tautomer. Such an interaction might be expected to impede attack on NH more than steric interference. This being the case, the amount of the anil formed would be less, and indeed compounds (**110a**, **455**) with a nitro group on C-6 produced little or none of the benzimidazole *N*-oxides. However, compound (**455**) did produce a 15% yield of the diaminoazoxybenzene (**458a**). Along this line of reasoning, then, it would seem unlikely that if the amount of the nitroso-anil formed was greatly reduced, that the intermediate went on to form as much as 15% of a diaminoazoxybenzene.

One alternative is that the glycine ester formed the azoxybenzene through an intermediate which is formed only from the esters that have particular types of substituents at C-6. The acyl intermediate (**444**) could be oxidized up to the nitroso compound, but the reaction of the two would give an azoxybenzene and ethyl glyoxylate. This creates a different problem. In the reactions of the esters, it is proposed that ethyl glyoxylate reacts with an *o*-phenylenediamine formed from a hydroxylamino-anil. If

ethyl glyoxylate was formed in the reactions of the glycine esters, why were none of the quinoxalin-2-ones found? The *o*-phenylenediamine could be generated from reduction of the nitroso-anil (**441**).

Another alternative is that the proposed mechanisms for the formation of the azoxybenzenes and the *N*-oxides (and others) are wrong. However, even though the mechanisms do not seem to account for how the azoxybenzenes were formed from the glycine esters, they do provide reasonable explanations, most of which have literature precedent, for the other products that were found in the reactions of both the glycine and sarcosine esters. Also, in two cases, it was thought that a key intermediate in those mechanisms was isolated; namely a nitrosoaniline. In one instance it was isolated from a reaction of a sarcosine ester which produced two isomeric quinoxalin-2-ones and a 1-hydroxyquinoxaline-2,3-dione. In the other it was detected in the product mixture from reaction of a glycine ester which gave a 1-hydroxyquinoxaline-2,3-dione, a diamino-azoxybenzene and a trace amount of a methyl 1*H*-benzimidazole-2-carboxylate 3-oxide. Though the identification of the nitrosoanilines has not been confirmed, the evidence for the assignments is strong. Nitrosoanilines play an important part in the mechanisms for the formation of azoxybenzenes and quinoxalin-2-ones. On the basis of these findings and on evidence in the literature, the mechanisms are perfectly reasonable.

So, the issue of the formation of diaminoazoxybenzenes from glycine esters is more complicated than would be expected. In general, it seems more likely that the nitroso-anils do cyclize readily to give the *N*-oxides as supported by the literature and that the diaminoazoxybenzenes were formed by some other mechanism which is not obvious at this time. However, there is no positive proof to discount the 'competing reaction' theory.

CHAPTER 5

RETROSPECTIVE AND PROSPECTIVE

Many 1*H*-benzimidazole 3-oxides can be produced in good yield using the general synthetic method outlined in scheme **1.2**. It is unfortunate that an analogous method cannot be applied to the synthesis of the 1-methyl derivatives and that when using the method the yields of some of the 7-substituted derivatives are low due to substituent effects. However, attempts to apply the method to the syntheses of these compounds have led to fascinating results which in turn have forced a review of the previously accepted mechanism for the formation of benzimidazole *N*-oxides. This mechanism involves the straightforward aldol-type condensation with subsequent dehydration (cf Scheme **4.4**). The question remains, given the 'abnormal' cyclizations discussed in this project: does this mechanism still have any credibility with regard to the syntheses of the benzimidazole *N*-oxides?

In general, a mechanism must account for all of the known facets of a reaction in order to be applicable to it. These facets include the products that are formed, the way in which factors like substituents and solvent influence the reaction, and the formation of any intermediates that may have been detected. The 'traditional' mechanism covers all of these points for the reactions of substituted *o*-nitroaniline derivatives with bases that gave only the benzimidazole *N*-oxides. It accounts for the fact that stronger bases, protic solvents, and electron-withdrawing groups tend to facilitate the reactions while electron-donating ones retard, and in some cases prevent, it. However, the mechanism does not seem to accommodate the deviant reactions of some of the 6-substituted esters and nitriles nor those of the *N*-methyl derivatives; according to the mechanism there is no obvious reason why substituents in these positions should affect what products are formed. Also, the mechanism does not account for any nitrosoaniline intermediates which appear to have been isolated in some of the reactions. (These intermediates are thought to go on to form the azoxybenzenes and the quinoxalin-2-ones, although the formation of the products could, however, involve a completely separate mechanism.) It also seems possible that the alternative mechanism via an oxadiazine intermediate (**434**), which does explain most

of the facets of these reactions, may also be applied to the reactions of the *NH* derivatives that cyclize 'normally'.

The *N*-methyl and the 6-substituted *o*-nitroaniline derivatives that cyclized 'abnormally' produced some of the same types of compounds so it seems probable that these, at least, can react along similar pathways. The crucial issue is that some of the 6-substituted derivatives represent 'borderline' cases, giving some products formed by the *NH* derivatives that cyclized 'normally' and some typical of the *N*-methyl compounds. The question is then, are these results to be explained by two competing mechanisms or is one mechanism with several variants adequate? A mechanism for the reaction of the 6-substituted derivatives that cyclized 'abnormally' must include pathways to the benzimidazole *N*-oxides, 1-hydroxyquinoxaline-2,3-diones and benzimidazol-2-ones. There is no apparent reason why these pathways could not also be applied to the *NH* derivatives that cyclized only to the *N*-oxides and to the *N*-methyl derivatives that gave one or both of the other two products. Thus it would seem that one branched mechanism, such as the alternative mechanism, would be more appropriate for these reactions.

Having said that, can this mechanism be used to explain the reactions of other *o*-nitroaniline derivatives for which the 'traditional' mechanism was also thought to be adequate? There are several cases in which this appears to be possible. The reactions of the *N*-cyanomethyl-*o*-nitroanilines are one case in point. The full applicability of this mechanism to those reactions of *NH*- and *N*-substituted derivatives with base that were reported by Livingstone and Tennant[36] has already been discussed (see section **4.1**). The two reactions of the 6-substituted derivatives (**110c**, **110d**) were also discussed in that section. The alternative mechanism is fully adequate in explaining the reaction of the 6-nitro compound with base forming 1-hydroxy-4-nitrobenzimidazol-2-one and also possibly a diaminoazoxybenzene. It could account for the formation of the benzimidazole *N*-oxide and the 1-hydroxy-4-methylbenzimidazol-2-one from the 6-methyl derivative, but does not explain why they were formed. The corresponding ester in the 6-methyl series cyclized 'normally' so the 'abnormal' cyclization of the nitrile does not appear to be due to the methyl group. Thus the 6-methyl-substituted nitrile reaction could be one case

in which the nature of the activating group affects the reaction pathway in a way which at this point is not understood. In any case, the 'traditional' mechanism, in so far as the activating group is an electron-acceptor, does not explain the effect nor can it account for the formation of the products.

The 'traditional' mechanism adequately explains the cyclization of *N*-benzyl-*o*-nitroanilines but fails to account for why the *N*-methyl derivative does not react at all with base[14]. The alternative mechanism provides a plausible explanation. An *NH* derivative would form an *NH* oxadiazine intermediate (cf Schemes **4.6**, **4.8**). Abstraction by base of the amino-hydrogen, and cyclization of the nitroso-anil then formed, would give the benzimidazole *N*-oxide in accordance with the experimental results. The *N*-methyl derivative would give the *N*-methyloxadiazine which could not form the nitroso-anil, due to lack of the amino-hydrogen, and thus would not give the 1-methylbenzimidazole 3-oxides. The only problem is explaining why *N*-benzyl-*N*-methyl-*o*-nitroaniline gave no reaction at all upon treatment with base. Base could attack the CH of the *N*-methyl-oxadiazine to give other products such as *N*-hydroxyquinoxaline-2,3-diones and benzimidazol-2-ones. It may be that the activation of the CH in this case is not sufficient to make it reactive enough towards base attack.

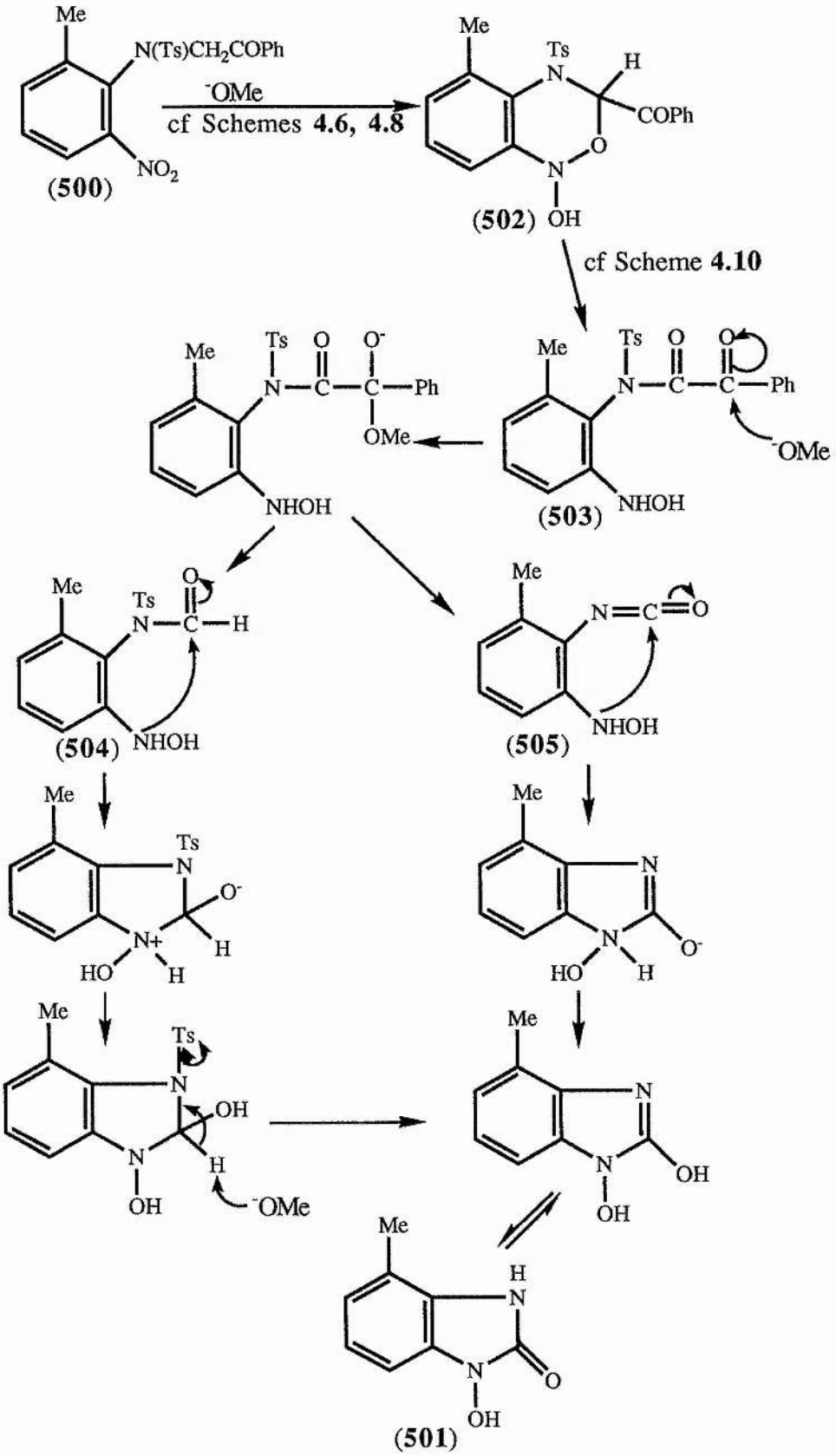
It is difficult to present one mechanism which will account for all known facets of the reactions of *N*-acyl-*N*-(activated-alkyl)-*o*-nitroanilines because there were many anomalous results which illustrated the delicate balance between different effects. By focusing on a few aspects of the reactions it is possible to show how the alternative mechanism provides (other) explanations for the results .

N-*p*-nitrobenzyl-*N*-*p*-tolylsulphonyl-*o*-nitroaniline was found to cyclize faster than the *NH* derivative, *N*-*p*-nitrobenzyl-*o*-nitroaniline[49]. This observation could be accounted for by either the 'traditional' or the alternative mechanism. In terms of the former, the tosyl group with an electron-deficient sulphur would make the attached nitrogen less basic and thus the β-methylene group more reactive towards attack by base. In terms of the latter mechanism, the *NH* and the *N*-tosyloxadiazine intermediates would be formed. Base attack on the tosyl group would be faster than attack on hydrogen, again because of the electron-deficient sulphur, thus the formation of the nitroso-anil and the *N*-

oxide would also be faster in the tosyl case. There is not much to choose between the two explanations, though it is possible that if the difference in rates were large the alternative mechanism could be more applicable because it involves the tosyl group directly.

In chapter **2**, the reaction of the *N*-tosyl-*N*-phenacyl-6-methyl-2-nitroaniline (**500**) was mentioned because it seemed to be an example of a neighbouring group affecting the reaction pathway; the cyclization with alkoxide gave 1-hydroxy-4-methylbenzimidazol-2-one (**501**) rather than the expected benzimidazole[49]. The alternative mechanism could account for the product formed (Scheme **5.1**). Spectroscopy has shown that there is severe restriction of rotation about the aryl-nitrogen bond causing non-equivalence of the methylene protons. It was concluded that methyl and tosyl groups could only be eclipsed in a configuration of high energy. Due to the presence of the *ortho*-methyl group, the attack of base on the tosyl group of the oxadiazine inermediate (**502**) could be sterically hindered. This being the case, methoxide would preferentially attack the CH of the intermediate leading to formation of the corresponding acyl intermediate (**503**). Methoxide could attack the ketonic-carbonyl carbon and elimination could take place in either of two ways. Analogous to scheme **4.15** in section **4.2**, the keto-group only could be eliminated leaving an formamide (**504**). Cyclization followed by abstraction of a proton on C-2 and the removal of the tosyl group would give the 1-hydroxybenzimidazol-2-one. Alternatively, because tosyl is a good leaving group, it could be eliminated earlier at the same time as the keto-group to give an isocyanate (**505**) which would also cyclize to give the product (**501**).

The base-catalyzed reactions of *o*-nitroaniline derivatives expected to give the benzimidazole *N*-oxides in general can be more suitably explained by the alternative mechanism, due to its versatility, than the 'traditional' mechanism. In this thesis the reactions of similar carbocyclic and heterocyclic compounds have been described. In all cases these reactions were initially assumed to proceed by a mechanism analogous to the 'traditional' one. However, in some cases anomalous aspects of the reactions have arisen that could not be explained by that mechanism. Thus the question now is: can the applicability of the alternative mechanism be broadened to include these reactions?


Me
N(Ts)CH2COPh
NO2
(500)
-OMe
cf Schemes 4.6, 4.8
Ts
H
COPh
(502) OH
cf Scheme 4.10
(503)
NHOH
OMe
(504)
(505)
HO
(501)

Scheme **5.1**

In chapter **2**, the reactions of phenylhydrazines designed to form 1*H*-benzotriazole 3-oxides were discussed (cf pp. 20-22). Though the alternative mechanism is not conclusively involved overall it could explain why an *N*-methyl derivative did not cyclize under basic conditions[40]. Also, the cyclizations of the uracils via a hydroxylamino anil were described (cf p.17) which accounted for the failure of a tertiary uracil to cyclize to the corresonding xanthine[34]. In the 9-methylguanine 7-oxide-forming reactions, substituted pyrimidines similar to the uracils reacted in an opposite manner; the secondary derivatives did not cyclize while the tertiary ones did[22,23]. Neither mechanism is able to account for these results. It was also reported that the tertiary esters and nitriles did not cyclize either. As with the sarcosine esters, the alternative mechanism could explain why these compounds did not cyclize to the *N*-oxides. This would mean, however, that the amino-ketones and amino-aldehydes react by a different mechanism.

Though the alternative mechanism does seem to be more applicable to the reactions discussed thus far, there is nothing to suggest that the 'traditional' mechanism is less than adequate for the formation of the quinoxalin-2-one 4-oxides from *N*-acyl-*o*-nitroanilines. These reactions occur for either *NH*- or *N*-substituted derivatives, although the paper in which the work was reported did not include the reactions of any ring substituted starting materials[33]. Interestingly enough, an alternative mechanism had been previously proposed for the cyclization of the *NH* compounds via an *aci*-nitro intermediate (**216**). Since Tennant showed, however, that the *NH* and the *N*-methyl derivatives both cyclized to the quinoxalin-2-one 4-oxides, the direct aldol-type condensation mechanism was favoured because the other could not be applied to the *N*-methyl derivatives; it relied on the amino nitrogen being secondary.

These results suggest that it is the proximity of the NH (α) to the acidic CH that is complicating the reactions of the *o*-nitroaniline derivatives that cyclized 'abnormally'. The explanation given for the formation of the 'abnormal' products in the alternative mechanism relies on this hypothesis. The *ortho*-nitro group must be a significant factor as well. The formation of many possible reduction products such as nitroso, hydroxylamino, and amino is thought to be vital to the formation of some of these products. Though it seems as if many reactions previously assumed to proceed by the

'traditional' mechanism can be better explained by the alternative one, the former one is still needed in some cases.

Speaking in more general terms, these are few examples of *inter*molecular reactions between methylene and nitro groups in comparison with the number of *intra*molecular reactions that occur when the groups are *ortho* to one another. This indicates that the mechanism by which the groups react is dependent upon the *ortho* configuration. The 'traditional' mechanism does not account for this observation. The methylene-derived carbanion could attack an *ortho* nitro group or one on another molecule. In the alternative mechanism, there are two routes to the oxadiazine intermediate, one of which could account for the observation because it involves an *intra*molecular ene-type reaction requiring *ortho* configuration (cf Scheme **4.6**). Several additional pieces of information are also relevant: the observation has been made that labile α-amino hydrogens are necessary for the cyclization of compounds with feebly activated β-methylene groups, the cyclizations of some *o*-nitroaniline derivatives have been likened to cyclizations of compounds with α,β-unsaturation, and the cyclizations of some compounds to benzimidazole *N*-oxides via nitroso-anil intermediates has been proposed and commonly accepted for some time. It was not until McFarlane put together the alternative mechanism that all of these observations and proposals have been combined in one mechanism. The discussions in this chapter indicate that not only is it vital in helping to explain the attempted and successful syntheses of benzimidazole *N*-oxides but that it could also have real applications to the reactions used to synthesize other, similar bicyclic compounds. Though there is much to be determined about the many factors governing these reactions and how the mechanism could account for them, it is certain that the full scope of this mechanism has yet to be fully realized.

EXPERIMENTAL

MATERIALS AND APPARATUS

Melting points were determined on a Riechert hot-stage microscope and are uncorrected.

The infra-red spectra were recorded as Nujol mulls.

Unless otherwise indicated, n.m.r. spectra were recorded in d_6-dimethyl sulfoxide.

Unless otherwise indicated, ^1H n.m.r. spectra were recorded at 80 MHz on a Bruker WP80 spectrometer or at 300 MHz on a Bruker AM300 spectrometer with tetramethylsilane as an internal reference.

^{13}C n.m.r. spectra were recorded at 75.5 MHz on a Bruker AM300 spectrometer with tetramethylsilane as an internal reference.

^{19}F n.m.r. spectra were recorded at 75.3 MHz on a Bruker WP80 spectrometer with trichlorofluoromethane as an internal reference

Mass spectra were generated on a Finnagen mat. Incos 50 mass spectrometer.

SYMBOLS AND ABBREVIATIONS

n.m.r.	nuclear magnetic resonance
δ	chemical shift (ppm)
s	singlet
d	doublet
dd	double doublet
dt	double triplet
t	triplet
td	triple doublet
m	multiplet
J	spin-spin coupling constant
D.E.P.T.	Distortionless Enhancement by Polarization Transfer

i.r.	infrared
υ	wave number
s	strong
w	weak
br	broad
sl. br.	slightly broad
m/z	mass to charge ratio
M^+	molecular ion
t.l.c.	thin-layer chromatography
m.p.	melting point
b.p.	boiling point
dec.	decomposition
d	density
Ac	acetyl
Me	methyl
DMSO	dimethyl sulfoxide
D	deuterium

EXPERIMENTAL FOR CHAPTER 3

ATTEMPTED SYNTHESIS OF *N*-METHYLPHENACYLAMINE HYDROCHLORIDE (**304**)

A literature procedure[55] was repeated three times each time slight modifications were made in the method. The first time, though the method called for the addition of phenacyl bromide directly to methylamine (33% in ethanol) at room temperature, the bromide was added as a solution in ethanol. Thus a solution of the bromide (19.91 g, 0.1 mol) in ethanol (200 ml) was added dropwise over 1.5 h to the amine (7.77 g, 0.25 mol) cooled in an ice-water bath. The solution was stirred for 40 minutes. Cold concentrated hydrochloric acid was added along with cracked ice until the pH was about 2. The work-up described in the method gave only 0.34 g (3%) of the crude product, m.p.181-184°C (lit.[55] 219°C) (from ethanol, acetone); δ_H 2.80 (3H, s, N-CH_3), 4.95 (2H, s, CH_2), 7.60-8.25 (5H, m, arom. H), and 9.20 (br s, NH).

In the second attempt (using the same scale), the bromide was added directly to a concentrated solution of the amine in ethanol (25 ml). Following the work-up in the literature procedure, only 5% of the impure product was obtained.

The third time the procedure was initially followed to the letter. However, once the starting materials had been combined, the mixture once again formed a tar. The reaction was stopped and the work-up from another synthesis[77] of the ketone (**304**) from sarcosine anhydride and phenylmagnesium bromide was implemented but none of the product was obtained.

(*N*-METHYL-*N*-PHENYLAMINO)ACETOPHENONE (**305**)

The compound (**305**) was prepared according to the literature[56]. Phenacyl bromide (9.95 g, 0.05 mol) was added in two portions to a solution of of *N*-methylaniline (10.75 g, 0.10 mol) in ethanol (40 ml) and stirred at 50°C for 4 h. Green flakes were filtered off, dissolved in hot ethanol (60 ml), the solution was hot filtered (nothing collected) and the filtrate cooled. The ketone (**305**) was collected as a green precipitate, yield 8.11 g (72 %), m.p. 120-121°C (lit[56].122-123°C) (from methanol);

δ_H* 3.02 (3H, s, N-CH_3), 4.98 (2H, s, CH_2), 6.50-6.75 (3H, m, H-2',4',6'), 7.00-7.25 (2H, m, H-3', 5'), 7.40-7.80 (3H, m, H-3, 4, 5), 7.95-8.10 (2H, m, H-2, 6).

* ' refers to Ph-N; not first order

ATTEMPTED NITRATION OF (**305**) TO THE 2-NITRO DERIVATIVE (**302**)

The procedure[57] for the mono-nitration of a similar material, *N*-(4-methylphenyl)aminoacetophenone was applied. Thus, 22% aqueous nitric acid (30 ml) was added slowly to (**305**) (1.00 g, 0.0044 mol) over 16 h. A remarkable succession of colour changes was displayed ending with a black tar. The work-up from the literature method yielded only a black solid which gave four spots on t.l.c. The use of column chromatography was ineffective; the fractions collected still showed two spots. The ^1H n.m.r. spectrum for one fraction contained a complicated aromatic region (more so than could be accounted for by the desired product). The reaction had obviously been too forceful, leading to formation of several nitration products. Therefore, the procedures used in other trials were modified towards encouraging gentler reactions.

For the second attempt, all was the same except that the solution was chilled in an ice-water bath. There was no apparent reaction. The solution was allowed to warm to 25°C and still no reaction occurred. N_2 (g) was blown into the flask until the red colour persisted. The reaction was then quenched by addition to water. The work-up yielded only 0.21 g of material giving two spots on t.l.c. and a complicated ^1H n.m.r. spectrum.

The third attempt involved starting with 5.8% aqueous nitric acid, added with stirring at room temperature and increasing the concentration of the acid and the temperature until reaction took place. Once again only samples containing several components could be obtained.

N-(2,4-DINITROPHENYL)-*N*-METHYLAMINOACETALDEHYDE DIMETHYL ACETAL (**306**)

N-Methylaminoacetaldehyde dimethyl acetal (5.50 g, 0.052 mol) and sodium hydrogen carbonate (5.00 g, 0.059 mol) were added portionwise to 1-chloro-2,4-dinitrobenzene (10.94 g, 0.054 mol) in ethanol (100 ml). The mixture was heated under

reflux for 5 h then added to H_2O. The insoluble acetal (**306**) was collected, yield 3.57 g (72%); m.p. 56°C (from ethanol, water); (Found: C, 46.5; H, 5.2; N, 14.7. $C_{11}H_{15}N_3O_6$ requires C, 46.3; H, 5.3; N, 14.7%); δ_H 2.99 (3H, s, N-CH_3), 3.38 (6H, s, (O-Me)$_2$), 3.57 (2H, d, CH_2), 4.66 (1H, t, CH), 7.50 (1H, d, H-6), 8.27 (1H, dd, H-5), and 8.60 (1H, d, H-3) ($J_{CH2,CH}$ 5, $J_{3,5}$ 2, $J_{5,6}$ 10 Hz).

ATTEMPTED SYNTHESES OF *N*-(2,4-DINITROPHENYL)-*N*-METHYL-ACETALDEHYDE (**303**) FROM (**306**)

Brown *et. al.*[22] reported that a solution of [*N*-(2-amino-6-hydroxy-5-nitro-pyrimidin-4-yl)-*N*-methylamino]acetaldehyde dimethyl acetal in conentrated hydrochloric acid was stirred for 15 minutes at 80°C yielding a near quantitative yield of the corresponding aldehyde (**118**). Application of these conditions to the acetal (**306**) resulted in cleavage of the side-chain to give a small amount of impure *N*-methyl-2,4-dinitroaniline (**308**), m.p. ~150°C (lit.[78] 178°C); δ_H 3.20 (3H, d, CH_3), 7.28 (1H, d, H-6), 8.42 (1H, dd, H-5), 9.0 (1H, d, H-3), and 9.0 (1H, br s, NH) ($J_{3,5}$ 2, $J_{5,6}$ 9 Hz). The sample was identified by comparison of the ^{1}H n.m.r. spectrum with that for a synthesized sample (following).

Several other acids were employed under various conditions, none of which gave the aldehyde (**303**). Other acids were employed under various conditions; the details are presented in table **T.1**. Experiments (B), (C), and possibly (D) also resulted in the formation of the aniline. Nothing could be identified from the reaction solutions in experiments (E-G) and the rest effected no reaction at all. Thus all attempts at conversion to the aldehyde were unsuccessful. No attempt was made to cyclize the acetal directly to the *N*-oxide.

Table **T.1**: The conditions used in attempts to convert (**306**) to (**303**) and the results obtained.

Expt.	Acid used	Solvent	Temp (°C)	Time (min.)	Results
A	conc. HCl	---------	80	8	*N*-methyl-2,4-dinitroaniline
B	50% (aq)HCl	EtOH	heated[a]	5	"
C	TFA	"	reflux	5	"
D	3M HCl	"	"	10	"(?)
E	conc. HCl	---------	"	5	nothing identified
F	conc. HCl	---------	"	20	"
G	50% (aq)HCl	---------	heated[a]	5	"
H	50% (aq)HCl	EtOH	0	5	starting mat.
I	50% (aq)HCl	EtOH	rt	5	"
J	1M HCl	"	45	5	"
K	NaOAc	AcOH	reflux	1	"
L	Oxalic[b]	EtOH	"	30	"
M	Formic	EtOH	"	30	"

[a] The solution was heated until it was homogeneous.

[b] dissolved in water

N-METHYL-2,4-DINITROANILINE (**308**)

A literature procedure[78] was implemented. Thus methylamine (0.63 g, 0.02 mol) (33% in ethanol) was added to a stirred solution of 1-chloro-2,4-dinitrobenzene (2.33 g, 0.01 mol) in ethanol (10 ml) and heated under reflux for 2 h. The reaction was not complete but it was stopped anyway. Filtration gave a fluffy, bright yellow solid. The ^{1}H n.m.r spectrum showed it was a mixture of the starting material and the desired aniline (**308**). The following peaks were assigned to (**308**); δ_H 3.07 (3H, d, CH_3), 7.25 (1H, d, H-6), 8.25 (1H, dd, H-5), 8.85 (1H, d, H-3) ($J_{3,5}$ 3, $J_{5,6}$ 9).

EXPERIMENTAL-CHAPTER 4

SECTION 4.1A

REACTION OF 4-CHLORO-3-NITROBENZOTRIFLUORIDE (406) WITH GLYCINE AND ITS METHYL ESTER

A procedure was adapted from two similar reactions of the benzotrifluoride (**406**) with phenylglycine[59] and the 4-fluoro analog of (**406**) with γ-aminobutyric acid (GABA)[60]. Thus compound (**406**) (2.26 g, 0.01 mol) in methanol (50 ml) was added to a stirred solution of glycine methyl ester hydrochloride (1.88 g, 0.015 mol) and sodium hydrogen carbonate (2.25 g, 0.03 mol) in water (20 ml). The solution was heated under reflux for 20 h and evaporated *in vacuo* to a rubbery orange gel with yellow solid. Treatment with 3M sodium hydroxide, ether and water only resulted in a small amount being dissolved. Treatment of the rest with hot water and saturated sodium hydrogen carbonate solution (400 ml) finally dissolved all of the material. The layers were separated, the aqueous layer acidified (conc. HCl) and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated to give 0.83 g of impure *N*-(2-nitro-4-trifluoromethyl-phenyl)glycine (**407**) as a yellow solid; υ_{max} 3350, 3305 (NH), 3300-2500br (OH), 1710br cm^{-1} (CO); the ^1H n.m.r. spectrum contained the peaks that were in a spectrum of the pure sample (see p.109); m/z 264 (M^+), 246, 219 [$(M-CO_2H)^+$, 100%], 202, etc.

The same procedure was applied to a reaction with glycine itself and (**406**). Accidentally, two molar equivalents of base were also used in this reaction when only one was required. The mixture was boiled for 20 h and the solvent evaporated *in vacuo*. The residue was treated with 3M sodium hydroxide and extracted with ether. The aqueous layer was acidified (conc. HCl) and extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated, giving a gummy yellow solid with thick orange oil. T.l.c. showed a yellow spot at the origin (the acid (**407**)) plus two mobile spots. The pH of the acidic aqueous solution was adjusted to ~6 (5M HCl) and a precipitate was collected. By comparison of the spectral data with those of a known sample, the main component in the precipitate was identified as 5-trifluoromethylbenzimidazole 3-oxide (**408**); mp 192-

193°C (pure (**408**) had m.p. 196°C, see p. 110); δ_H (300 MHz) 7.54 (1H, dd, H-6), 7.83-7.93 (2H, d & s, H-4 & H-7)* ($J_{4,6}$ 2, $J_{6,7}$ 9 Hz, J_{CF3} could not be measured); m/z 202 (M^+, 100%), 185, 183, 173, 158, etc. The ^{13}C n.m.r. spectra matched that for a pure sample obtained in a later experiment except that the n.m.r. for the present sample showed the C-4 and C-6 resonances as quartets whereas the other spectrum only showed the two central lines. (Most of the other ^{13}C n.m.r. spectra of CF_3-containing compounds in this project also only showed the two central lines.) See Table **T.2** (p.158) for the ^{13}C n.m.r. data.

* See Figure **E.1** and **E.2** (pp. 164, 165) for the aromatic regions of the 300 MHz and 80 MHz ^1H n.m.r. spectra for (**408**). The former is first order with overlapping peaks, the latter, taken on the sample obtained later, is not.

N-(2-NITRO-4-TRIFLUOROMETHYLPHENYL)GLYCINE (**407**)

Potassium carbonate (3.46 g, 0.025 mol) and glycine (1.88 g, 0.025 mol) were added to a solution of (**406**) (4.51 g, 0.02 mol) in ethanol (60 ml) and the mixture heated under reflux for 24 h. The resulting solution was acidified (5M HCl). The yellow precipitate was filtered off and recrystallized from toluene to give the acid (**407**) (3.06 g, 58%), m.p. 161-162°C (Found: C, 40.8; H, 2.5; N, 10.45. $C_9H_7F_3N_2O_4$ requires C, 40.9; H, 2.7; N, 10.6%); δ_H (d_6-acetone) 4.30 (2H, d, CH_2), 7.27 (1H, d, H-6), 7.80 (1H, dd, H-5), 8.37-8.50 (1H, m*, H-3), 8.75 (1H, br s, NH), and 9.70 (1H, br s, CO_2H) ($J_{CH2,NH}$ 5, $J_{3,5}$ 2, $J_{5,6}$ 10 Hz); m/z 264 (M^+), 245, 219 (100%).

* this double doublet appears as a multiplet due to small couplings to CF_3 and H-5

N-(2-NITRO-4-TRIFLUOROMETHYLPHENYL)GLYCINE METHYL ESTER (**405**)

Gaseous hydrogen chloride (1.50 g, 0.04 mol) was bubbled into a solution of the acid (**407**) (2.1 g, 0.008 mol) in methanol (40 ml). The solution was heated under reflux for 5 h. Filtration of the cooled reaction solution gave the ester (**405**) as bright yellow needles, yield 2.08 g (94%), m.p. 129-130°C (from methanol) (Found: C, 43.1; H, 3.1; N, 10.0. $C_{10}H_9F_3N_2O_4$ requires C, 43.2; H, 3.3; N, 10.1%); δ_H ($CDCl_3$) 3.90 (3H, s,

CH_3), 4.20 (2H, d, CH_2), 6.90 (1H, d, H-6), 7.75 (1H, dd, H-5), 8.60 (1H, d, H-3), and 8.75 (1H, br s, NH) ($J_{CH2,NH}$ 6, $J_{3,5}$ 2, $J_{5,6}$ 9 Hz)

5-TRIFLUOROMETHYL-1*H*-BENZIMIDAZOLE 3-OXIDE (**408**)

A mixture of the ester (**405**) (1.50 g, 0.0054 mol) and potassium carbonate (1.52 g, 0.011mol) in methanol (30 ml) was heated under reflux for 1.5 h. The solvent was evaporated and the residue partitioned between methylene chloride and water. Dropwise acidification (5M HCl) of the aqueous solution gave a precipitate which when washed with chloroform left a buff-coloured solid [0.97 g (73% based on (**409**); υ_{max} 3000-3700br (OH), 1650br cm^{-1} (CO)]. The sample was difficult to purify. Several recrystallizations were attempted from water giving solids with the correct mass spectra but for which the ^1H n.m.r. spectrum showed no signal for H-2. The reason for this appeared to be that the *N*-oxide initially isolated was the 2-carboxylic acid derivative (**409**). Repeated recrystallizations from aqueous hydrochloric acid, then twice from ethanol-water appear to have completed the decarboxylation to give an analytically pure sample of the 2-unsubstituted *N*-oxide (**408**), m.p. 196°C (Found: C, 47.85; H, 2.4; N, 13.9. $C_8H_5F_3N_2O$ requires C, 47.5; H, 2.5; N, 13.9%). The i.r. spectrum was distinctly different from that for what is proposed to be (**409**) and contains some interesting absorptions that could not be readily explained; υ_{max} 3140 (NH), 2000-2900, 1650-1900; δ_H (80 MHz) 7.63 (1H, d, H-6), 7.90-8.10 (2H, unsymm. m, H-4 and H-7)*, and 8.75 (1H, s, H-2) ($J_{4,6}$ 2, $J_{6,7}$ 9Hz); δ_F -59.0. See Table **T.2** (p.158) for the ^{13}C data.

* Not first order, see Figures **E.1** and **E.2** (pp. 164, 165) for the aromatic regions of the 300 and 80MHz ^1H n.m.r. spectra for (**408**).

N-(2-NITRO-4-TRIFLUOROMETHYLPHENYL)SARCOSINE (**411**)

To a solution of the benzotrifluoride (**406**) (1.13 g, 0.005 mol) in ethanol (25 ml) was added potassium carbonate (0.83 g, 0.006 mol) and sarcosine (0.53 g, 0.006 mol). The mixture was boiled for 5 h, filtered, and evaporated to dryness *in vacuo*. The residue

was treated with ether (25 ml) and extracted with 5M hydrochloric acid, then with 3M sodium hydroxide. The basic extracts were combined, acidified (conc. HCl) and extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated to give the crude acid as a light green powder (1.05 g, 76%), m.p. 120-121°C (from toluene) (Found: C, 43.2; H, 3.0; N, 9.8. $C_{10}H_9F_3N_2O_4$ requires C, 43.2; H, 3.3; N, 10.1%); δ_H (d_6-acetone) 3.07 (3H, s, N-CH_3), 4.27 (2H, s, CH_2), 7.42 (1H, d, H-6), 7.75 (1H, br s, NH), 7.90 (1H, dd, H-5), and 8.17-8.25 (1H, m, H-3) ($J_{3,5}$ 2, $J_{5,6}$ 9 Hz)

N-(2-NITRO-4-TRIFLUOROMETHYLPHENYL)SARCOSINE ETHYL ESTER (**410**)

The crude acid (**411**) (11.80 g, 0.042 mol) was dissolved in ethanol (120 ml) and gaseous hydrogen chloride (4.00 g, 0.11 mol) was bubbled into the solution. After being heated at reflux for 4.5 h, the solvent was evaporated *in vacuo* to give the crude product (11.66 g, 91%). The sample was purified by column chromatography (silica gel in CH_2Cl_2). The mobile yellow fraction was collected and evaporated to give waxy bright yellow needles. The ester (**410**) had m.p. 44-44.5°C (from ethanol-water) (Found: C, 47.3; H, 4.3; N, 9.2. $C_{12}H_{13}F_3N_2O_4$ requires C, 47.1; H, 4.3; N, 9.15%); δ_H (d_6-acetone) 1.25 (3H, t, CH_2*Me*), 3.07 (3H, s, N-Me), 4.27 (2H, s, N-CH_2), 4.32 (2H, q, *CH_2*Me), 7.45 (1H, d, H-6), 7.92 (1H, dd, H-5), and 8.23 (1H, d, H-3) ($J_{CH2,NH}$ 7, $J_{3,5}$ 2, $J_{5,6}$ 10 Hz); m/z 306 (M^+, 5%), 287, 272, 261, 245, 233 (100), etc.

CYCLIZATION OF *N*-(2-NITRO-4-TRIFLUOROMETHYLPHENYL)SARCOSINE ETHYL ESTER (**410**)

a.) With potassium carbonate

The ester (2.14 g, 0.007 mol) and potassium carbonate (0.97 g, 0.007 mol) were stirred at room temperature in ethanol (50 ml) for 4.5 h. The solution was filtered, a brown solid was collected and this was partitioned between water and methylene chloride. The organic layer was dried (Na_2SO_4) and evaporated to a dark green oil. T.l.c. showed one mobile spot with a similar R_f to the starting material, but the ^1H n.m.r. spectrum indicated that actually only a small amount of the ester was present. The main component gave δ_H (d_6-acetone) 3.10 d (*J* 5 Hz), 7.35 d (*J* 9 Hz), 7.88 dd (*J* 2 Hz),

8.97-9.10 m, and 10.75 br s; m/z 306 (M^+ (**410**), 3%), 287, 233 (60), 215, 204 (75), 187 (100), etc. The multiplicities, intensities and chemical shifts in the ^1H n.m.r. spectrum and the intense peak at m/z 204 indicate the other component could be *N*-methyl-2-nitroso-4-trifluoromethylaniline (**415**) (M^+ 204). The identification was reinforced by the fact that the mixture was distinctly green.

The aqueous layer was acidified slowly with 5M hydrochloric acid and a cream coloured precipitate was filtered off. The *N*-hydroxy-4-methyl-7-trifluoromethyl-quinoxaline-2,3-dione hemihydrate (**412**) had a yield of 0.40 g (22%); m/z 260 (M^+), 244, 242, 232, 25, 215, 187 (100%). The filtrate was acidified further and a second crop was collected as white needles. Yield 0.16 g (9%, total of 31%), m.p. 218.5°C (from water) (Found: C, 44.4; H, 3.1; N, 10.4. $C_{10}H_7F_3N_2O_3 \cdot 0.5\ H_2O$ requires C, 44.6; H, 3.0; N, 10.4%); υ_{max} 3650w (N-Me), 3460-3100br (OH), 1680br, 1700br cm^{-1} (CO); δ_H 3.60 (~3H, s, N-Me), 7.60-7.70 (2H, m, H-5 and 6), 7.75 (1H, s, H-8), and 12.0 (1H, br s, OH). See Table **T.3** (p.159) for the ^{13}C n.m.r. data.

The mother liquor was evaporated and partitioned between methylene chloride and water. The organic solution was extracted with 5M hydrochloric acid and then with 3M sodium hydroxide. The organic layer was dried (Na_2SO_4) and evaporated to a wet dark green solid for which the spectra were very similar to the supposed mixture of the starting material and the nitrosoaniline (**415**). The basic extracts were acidified slowly (conc. and 5M HCl). A light brown precipitate was collected, 0.10 g; m/z 216 (38%), 214 (100), 201, 197, 195, 187 (32), 186 (79), 167 (45). 6- and 7-trifluoromethylquinoxalin-2-ones (**413, 414**) have a molecular ion at m/z 214 and give rise to high field resonances (8.5 δ) found in the (complicated) ^1H n.m.r. spectrum . There was a water signal at 3.5 δ which could have overlapped with *N*-methyl signal in *N*-methyl-5-trifluoromethylbenzimidazol-2-one (M^+ 216). The 3,4-dihydro derivatives of (**413, 414**) also have a molecular ion at m/z 214, but there were no signals between 3.55-7.40 δ in the spectrum of the mixture.

The filtrate was extracted with methylene chloride and the extracts were dried (Na_2SO_4) and evaporated. More of the mixtures of quinoxalin-2-ones (**413, 414**) were isolated; the ^1H n.m.r. matched that for the one above; m/z 214 (M^+, 39%), 195, 186, 167, 159, etc.

The aqueous solution (from the partition of the mother liquor) was acidified with 5M hydrochloric acid and a light coloured precipitate was filtered off [υ_{max} 3660s, 3300br (OH), 3100 (NH), 1680br cm^{-1} (CO)]. The ^1H n.m.r. contained peaks at 7.80 δ and 7.92 δ which resembled those in the 1-hydroxyquinoxaline-2,3-dione (**412**) ^1H n.m.r. spectrum and some considerably smaller multiplets underneath and near by that could not be identified at once. There was also a singlet at 8.82 δ at considerably higher field than the rest of the resonances, which is typical for H-2 in a 2-unsubstituted benzimidazole *N*-oxide (and which is too high for H-3 in the quinoxalin-2-ones), and a methyl peak (overlapping with the water resonance arising from d_6-DMSO). The ^{13}C n.m.r. spectrum gave conclusive evidence that the sample was a mixture of the quinoxaline-2,3-dione (**412**) and the 1-unsubstituted-5-trifluoromethylbenzimidazole 3-oxide (**408**); m/z 260 (M^+(**412**)) 244, 232, 225, 215, 202 (M^+, (**408**)), 187, 174, etc.

b.) With triethylamine

The reaction was repeated on the same scale except that triethylamine (1 mol.eq.) was used instead and the solution heated under reflux for 7 h. The solution was evaporated (no solid was present) and partitioned between methylene chloride and water. Acidification of the aqueous layer eventually resulted in the 1-hydroxyquinoxaline-2,3-dione (**412**) precipitating out as white needles; yield 0.03 g (2%); m.p. 217.5-218°C. The ^1H n.m.r. and the mass spectra matched those for the sample above. The methylene chloride solution was extracted with 5M hydrochloric acid, then with more water to see if more of the dione (**412**) could be collected. The water extracts were combined, acidified, saturated with sodium chloride and extracted with ethyl acetate. The dried (Na_2SO_4) organic extracts were evaporated to an oily film. The ^1H n.m.r. spectrum was complicated but the mass spectrum indicated that the film contained some of the quinoxaline-2,3-dione (**412**); m/z 260 (M^+, 9%), 244, 232, 215, 202, 187, etc. A mass spectrum of the residual methylene chloride solution indicated that it was starting material with no azoxybenzene present.

SECTION 4.1B

N-(4-FLUORO-2-NITROPHENYL)GLYCINE METHYL ESTER (**416**)

1,4-Difluoro-2-nitrobenzene (**417**) (0.94 g, 0.006 mol), glycine methyl ester hydrochloride (0.82 g, 0.0065 mol), and triethylamine (1.52 g, 0.015 mol) were combined in tetrahydrofuran (40 ml) and heated under reflux. After 13 h more of the ester (0.75 g, 0.006 mol) and base (0.66 g, 0.0065 mol) were added. Heating was continued for another 6 h. The solution was filtered and the filtrate evaporated to dryness. The residue was treated with 5M HCl and filtered to give the ester (**416**) (0.74 g, 54 %), m.p. 106-108°C (from methanol) (m.p. for analytically pure sample obtained later 107.5-108°C); δ_H ($CDCl_3$) 3.90 (3H, s, O-CH_3) 4.28 (2H, d, CH_2), 6.78 (1H, dd, H-6), 7.25-7.35 (1H, symm. 7-line m, H-5)*, 8.05 (1H, dd, H-3), and 8.38 (1H, br s, NH) ($J_{CH2,NH}$ 7, $J_{3,5}$ 3, $J_{5,6}$ 9 Hz); δ_F -99.36 (8-line symm. m) ($J_{3,F}$ 7, $J_{5,F}$ 11, $J_{6,F}$ 4 Hz).

* the center line is twice the height of the others in the multiplet, it appears to be two overlapping lines which would give the eight-line multiplet expected

CYCLIZATION OF *N*-(2-NITRO-4-FLUOROPHENYL)GLYCINE METHYL ESTER (**416**) USING TRIETHYLAMINE

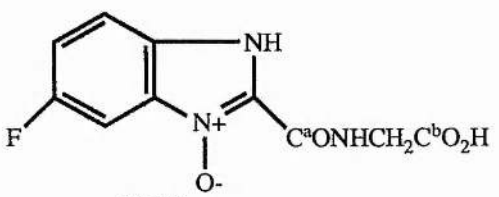
The ester (1.44 g, 0.0063 mol) and triethylamine (1.52 g, 0.015 mol) in methanol (40 ml) were heated under reflux for 6 h. The solution was evaporated to dryness, treated with ether and extracted with 5M hydrochloric acid. (Work up of the ether layer layer gave no useful information.) The aqueous extracts were basified (NaOH) and reacidified (5M HCl). 5-Fluoro-1*H*-benzimidazole 3-oxide (**418**) was collected as light brown sheets (0.23 g, 24 %). (Another crop was collected when the solution was slightly basic but this sample contained a high percentage of salt.) The assignment was confirmed by comparison of data with those of a known sample[3]. Though the ^1H n.m.r. shifts were a bit different (7.15, 7.40, 7.70, 8.50 δ as compared to 7.03, 7.3, 7.65, 8.38 δ), there was no doubt that the precipitate was the *N*-oxide (**418**) m.p.225-227°C (lit 227-229°C); δ_H 4.90 (-, br s, NH), 7.15 (1 H, dt, H-6), 7.40 (1H, dd, H-4), 7.70 (1

H, dd, H-7), and 8.50 (1 H, s, H-2) ($J_{4,6}$ 2, $J_{6,7}=J_{4,F}=J_{6,F}=9$, $J_{7,F}$ 5 Hz); m/z 152 (M^+), 136, 123, 108 etc.

REACTION OF (**417**) WITH GLYCINE METHYL ESTER

To a solution of 1,4-difluoro-2-nitrobenzene (**417**) (4.77 g, 0.03 mol) in dry tetrahydrofuran (150 ml), glycine methyl ester hydrochloride (7.53 g,0.06 mol) and triethylamine (10.10 g, 0.10 mol) were added. After 6 h at reflux temperature, t.l.c. showed there was still a considerable amount of reactant left so more of the ester and base were added. This procedure was continued for a total period of 40 h. A total of 17.58 g (0.14 mol) of the ester and 19.02 g (0.188 mol) of base was added, not including the initial amounts used. Even after 70 h, t.l.c. still showed that starting material was present in addition to the product and there was also one orange spot at the origin which appeared after 21 h.

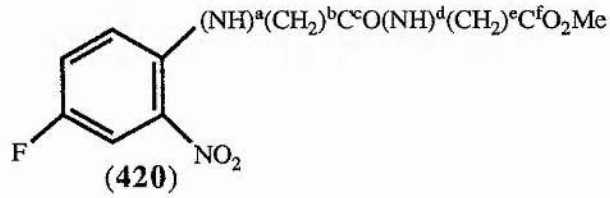
The reaction solution was filtered and the filtrate evaporated to dryness. The residue was treated with ether (50 ml) and 5M hydrochloric acid (20 ml). The insoluble orange solid was filtered off and recrystallized from methanol to give the still impure ester (**416**) (3.55 g, 52%). The two immiscible liquids in the filtrate was separated and extraction of the acidic phase with ether was continued. Further work-up of the ether extracts (base extraction, etc.) gave no useful information. The acidic phase was neutralized (3M NaOH) and extracted with methylene chloride. A brown precipitate appeared at the interface which was filtered off with each extraction (0.17 g). Another 0.40 g appeared after the aqueous solution had sat covered overnight. From the ^1H and ^{13}C n.m.r. spectra obtained for the first crop, the main component is suggested to be the *N*-(5-fluoro-3-oxido-1*H*-benzimidazole-2-carbonyl)glycine (**419**), though the ^{19}F n.m.r. spectrum indicates there were three fluorine containing compounds in the sample.



(**419**)

It was insoluble in acetone and small quantities of 5M hydrochloric acid, soluble in 3M sodium hydroxide and in excess 5M hydrochloric acid. (This behaviour is typical of the bicyclic products isolated in this project.) υ_{max} 3300-2700 (NH/OH), 1600-1750 (CO) cm^{-1}; δ_H 4.05 (2H, d, CH_2), 7.24 (1H, td, H-6), 7.43 (1H, dd, H-4), and 7.75 (1H, dd, H-7) ($J_{CH2,NH}$ 6, $J_{4,6}$ 3, $J_{6,7}$ 9, $J_{4,F} = J_{6,F} = 9$, $J_{7,F}$ 5 Hz); δ_C 40.8 (CH_2), 96.8 (d, J_F 27, C-4), 112.8 (d, J_F 26, C-6), 120.7* (s, J_F 9, C-7), 132.9, 133.0 (C-3a,7a), 157.1 (C-2), 158.6 (d, J_F 240, C-5), and 170.5 (CO^b) (The CO^a resonance was not observed but may coicide with the C-2 or C-5 resonance.); DEPT confirmed all CH and CH_2 assignments; δ_F -115.9 (*J*'s 5, 9, 10 Hz), -119.9 (*J*'s 6, 9, 10, Hz), -122.1 (*J*'s 6, 9.6, 10.4 Hz),all were eight line multiplets with the one at -199.9 ppm being the most intense; m/z 253 (M^+), 236, 208,192, 178, 163, 153, 152, etc

The impure ester in methylene chloride was chromatographed on a silica gel column in petrol (b.p. 40/60°C) and eluted initially with a mixture of petrol and methylene chloride. The main band was collected and evaporated to give the pure ester (**416**) as a light orange solid (2.07 g, 30%), m.p. 107.5-108°C (from methanol) (Found: C, 47.3; H, 3.8; N, 12.3. $C_9H_9FN_2O_4$ requires C, 47.4; H, 4.0; N, 12.3%). The more polar band was eluted (CH_2Cl_2/MeOH, ~50/50), and upon evaporation gave a bright reddish-orange solid (0.13 g, 1.3%) which analyses indicated was <u>*N*-(2-nitro-4-fluoro-phenyl)glycylglycine methyl ester</u> (**420**); m.p. 152°C (from methanol);



(420)

* This signal appeared in one spectrum taken as a singlet and in another as a doublet; the former was a better spectrum so it is described while the coupling value was taken from the latter.

(Found: C, 46.1; H, 3.8; N, 15.0. $C_{11}H_{12}FN_3O_5$ requires C, 46.3; H, 4.2; N, 14.7%); δ_H (d_6-acetone) 3.65 (3H, s, CH_3), 3.91 (2H, m*, CH_2[b]), 4.10 (2H, m*, CH_2[e]), 6.88 (1H, dd, H-6), 7.46-7.58 (1H, symm. 8-line m, H-5), 7.87 (1H, dd, H-3), 8.36 (1H, br t*, NH[a])^, and 8.51 (1H, br t*, NH[d])^ ($J_{CH2,NH}$ 6, $J_{3,5}$ 3, $J_{5,6}$ 9, $J_{3,F}$ 9, $J_{5,F}$ 11, $J_{6,F}$ 5); δ_C 40.71 (d, J_D 8, C[b])*, 45.69 (d, J_D 6, C[e])*, 51.82 (Me), 111.14 (d, J_F 27, C-3), 116.58 (d, J_F 6, C-6), 125.10 (d, J_F 24, C-5), 130.37 (d, J_F 9, C-2), 141.87 (d, J_D 8, C-1)*, 152.10 (d, J_F 236, C-4), 169.08 (d, J_D 3, C[c])*, and 170.22 (C[f]).

*Due to partial H-D exchange between the NH's and the solvent, the CH_2 signals appeared as singlets superimposed on doublets, the acetone signal as a singlet superimposed on a septet and the intensities of the NH_2 signals were reduced. A spectrum taken at a later time showed the singlets in the CH_2 signals to be more pronounced. An 80 MHz spectrum of another sample showed no NH peaks at all and two singlets for the CH_2 signals.

^ provisional assignments

REACTION OF (**420**) WITH TRIETHYLAMINE

Compound (**420**) (0.03 g, 0.00011 mol) and triethylamine (0.02 g, 0.0002 mol) in tetrahydrofuran (10 ml) was heated under reflux for 48 h and evaporated down to an orange-red solid. In the ^1H n.m.r. spectrum of this material there were no new peaks corresponding to (**419**). There were two triplets at 2.75 δ and 3.60 δ which could not be explained. Aside from another few small singlets the spectrum was the same as that for the starting material.

CYCLIZATION OF THE ESTER (**416**) WITH POTASSIUM CARBONATE

Potassium carbonate (2.76 g, 0.02 mol) was added to a solution of the ester (2.10 g, 0.009 mol) in methanol (50 ml) causing a change from yellow to red. The mixture was heated under reflux for 3 h, and the solvent evaporated off *in vacuo*. The residue was treated with methylene chloride and water, filtered and the two immiscible liquids in the filtrate separated. The aqueous layer was acidified dropwise (5M HCl) and the light brown precipitate was collected by filtration and washed with chloroform to give

the crude 5-fluoro-1*H*-benzimidazole 3-oxide (**418**) (1.01 g, 72%); m.p. 225.5-227°C (lit 227-229°C)[1]; the ^{1}H n.m.r. matches with that for the first sample obtained (see p.114); the ^{13}C n.m.r. was not quoted in the literature so the one taken of this sample is included in Table **T.2** (p. 158).

The filtrate from collection of the *N*-oxide was acidified further and another crop of the *N*-oxide was collected, yield 0.77 g (there was presumably some salt in the sample, because the total yield would be well over 100%); m/z 152 (M^+), 123, 108 (100%).

REACTION OF (**417**) WITH SARCOSINE ETHYL ESTER

Sarcosine ethyl ester hydrochloride (1.69 g, 0.011 mol) was added to a solution of (**417**) (1.59 g, 0.01 mol) in HPLC grade acetonitrile (30 ml) containing a small amount of triethylamine. Then the rest of the base was added (total 2.53 g, 0.025 mol). The solution was heated under reflux for 19 h during which time more of the ester and base were added (0.025 mol of each). The solution was filtered and the solvent was evaporated *in vacuo*. The liquid residue was treated with 5M hydrochloric acid and extracted with ether. The ether extracts were combined and extracted with 3M sodium hydroxide. The organic layer was dried (Na_2SO_4) and evaporated to give 1.05 g (41%) of the ester (**422**) as an oil; bp 168°C (Kugelrohr, ~1 mmHg); δ_H (80 MHz; $CDCl_3$) 1.28 (2H, t, CH_2Me), 3.02 (3H, s, N-Me), 3.95 (2H, s, N-CH_2), 4.27 (2H, q, CH_2 Me), 7.35 (2H, dd, H-3 & H-6), and 7.65 (1H, dt, H-5) ($J_{CH2,CH3}$ 7 Hz)*; δ_F -178.41 (6-line symm. m, $J_{3,F}$ 8.1, $J_{5,F}$ 6.0$J_{6,F}$ 5.0 Hz)

The basic extracts were combined, acidified (conc. HCl) and extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated to give 0.67 g (29%) of impure *N*-(4-fluoro-2-nitrophenyl)sarcosine (**424**). The acid was positively identified by comparison with a pure sample described latter.

* A 300 MHz ^{1}H n.m.r. spectrum of the ester [δ_H 7.15-7.26 (2H, unsymm. m, H-5 & 6), 7.52 (1H, dd, H-3)] and a computer simulation of the 300 MHz spectrum were used to confirm the fluorine-proton quoted, and the proton-proton couplings as $J_{3,5}$ 3.3, $J_{5,6}$ 9.0 Hz (See Figures **E.3**, **E.4**, pp. 166, 167).

REACTION OF (**417**) WITH SARCOSINE ESTER RESULTING IN CYCLIZATION

Sarcosine ethyl ester hydrochloride (2.00 g, 0.013 mol) and potassium carbonate (3.59 g, 0.026 mol) were added to (**417**) (1.59 g, 0.01 mol) in HPLC grade acetonitrile (50 ml). The mixture was heated under reflux for 20 h, during which time an addition of 0.01 mol of each of the ester and the base was made. The reaction solution was filtered, the filtrate evaporated *in vacuo* and the residue partitioned between methylene chloride and water. The aqueous layer was slowly acidified (5M HCl). No precipitate appeared. The solution was extracted with methylene chloride and the extracts were dried (Na_2SO_4) and evaporated to give an oily film of the acid (**424**).

The methylene chloride layer was extracted with 5M hydrochloric acid, then with 3M sodium hydroxide. The organic layer was dried (Na_2SO_4) and evaporated to give the impure ester (**422**). The basic extracts were acidified and extracted with methylene chloride which was dried (Na_2SO_4) and evaporated to an oily film. An n.m.r. sample of the film in d_6-acetone was made up. The insoluble light-coloured residue was used for an n.m.r. sample in d_6-dimethyl sulfoxide. The ^1H n.m.r. spectra indicate the presence of 5-fluoro-1-methylbenzimidazol-2-one (**423**) along with mainly one other unidentifiable compound; δ_H 3.27 (3H, s, N-Me), 6.77-6.88 (2H, m, H-4 & 6), 7.04 (1H, dd, H-7), 10.9 (1H, br s, NH/OH) [($J_{6,7}$ 9, $J_{7,F}$ 5 Hz (the rest cannot be measured because of the overlapping peaks)]; m/z 210, 183, 166 (M^+, 88%), 151, 137, 124, etc. See Table **T.4** (p.160) for the ^{13}C resonances corresponding to (**423**). The corresponding quinoxaline-2,3-dione could be an impurity, giving rise to m/z 210 (M^+), 183, in the mass spectrum.

A mass spectrum of the d_6-acetone solution gave m/z 291 (18%), 256 (3), 245 (17), 217, 203, 190, 183, 178, 166 (M^+ for (**423**), 100), 151, 137, etc. The molecular ion for the starting material is 256, and that for the corresponding 2,2′-bis(methylamino)-azoxybenzene is 292, however there is nothing in the ^1H n.m.r. spectrum to suggest the presence of an azoxybenzene. Only three aromatic multiplets were left unaccounted for, not the six required for a 2,2′,4,4′-substituted azoxybenzene. There were two possible *N*-methyl peaks in the d_6-acetone spectrum and one in the d_6-DMSO spectrum but they were not nearly intense enough to correspond with the aromatic signals. The latter

spectrum showed no other alkyl peaks. The spectral data does not match that of any compound isolated in this project.

ATTEMPTED CYCLIZATION OF (**422**) WITH POTASSIUM CARBONATE

A mixture of the ester (1.38 g, 0.004 mol) and potassium carbonate (1.52 g, 0.011 mol) in ethanol (25 ml) was heated under reflux for 50 minutes. Even after an extensive work-up involving extraction, acidification and column chromatography, none of the components could be identified.

N-(4-FLUORO-2-NITROPHENYL)SARCOSINE (**424**)

1,4-Difluoro-2-nitrobenzene (12.70 g, 0.08 mol) in HPLC grade acetonitrile (250 ml), sarcosine (8.90 g, 0.10 mol) and potassium carbonate (13.80 g, 0.10 ml) were combined and heated under reflux for 22 h in an apparatus fitted with a drying tube ($CaCO_3$). The solution was filtered, treated with saturated sodium hydrogen carbonate solution and extracted with methylene chloride. The aqueous layer was acidified and the light orange precipitate was filtered off to give the crude acid (**424**) (83%). Recrystallization from methanol gave large, clear crystals; m.p. 132°C (Found: C, 47.4; H, 4.0; N, 12.3. $C_9H_9FN_2O_4$ requires C, 47.4; H, 4.0; N, 12.3%); δ_H (80 MHz; d_6-acetone) 3.00 (3H, s, Me), 4.10 (2H, s, CH_2), 7.50 (2H, dd, H-5, H-6), 7.75 (1H, dt, H-3), and 8.20 (1H, br s, OH). The spectrum contained the same aromatic pattern as the 80 MHz spectrum of the ester (**422**) (see Figure **E.3**, p.166).

N-(2-NITRO-4-FLUOROPHENYL)SARCOSINE ETHYL ESTER (**422**)

Concentrated sulfuric acid (0.88 g, 0.009 mol) was added to a solution of the acid (**424**) (3.0 g, 0.013 mol) in ethanol (50 ml). The solution was heated under reflux for 2 h and 45 minutes, and the solvent was evaporated. The residue was treated with methylene chloride and extracted with saturated sodium hydrogen carbonate solution until the extracts were colorless. The organic layer was dried (Na_2SO_4) and evaporated to give the ester as an orange oil (3.20 g, 96 %). The 80 MHz ^1H n.m.r. spectrum was the same as for the sample described earlier (see Figure **E.3**, p.166).

CYCLIZATION OF (**422**) WITH POTASSIUM CARBONATE

Potassium carbonate (1.38 g, 0.01 mol) was added to a solution of the ester (2.28 g, 0.009 mol) in ethanol (30 ml) and stirred at room temperature for 4.5 h. The solution was filtered. The solid collected was dissolved in hot water and acidified slowly with 5 M hydrochloric acid. The precipitate was collected and washed with a little acetone. The insoluble solid was soluble in water (salt) and thus disgarded. The acetone washings were evaporated to give grey needles, which were then washed with ethyl acetate. The insoluble solid gave an extremely weak ^{1}H n.m.r. and could not be identified. The washings were evaporated to a thin oily film of what spectral evidence indicated was 7-fluoro-1-hydroxy-4-methylquinoxaline-2,3-dione (**427**); δ_H 3.60 (3H, s, N-Me), 7.13 (1H, td, H-6), 7,32 (1H, dd, H-8), 7.47 (1H, dd, H-5), and 12.0 (1H, br s, OH) ($J_{5,F}$ 4, $J_{6,F}$=$J_{5,6}$ 8, $J_{6,8}$ 2, $J_{7,8}$ 8 Hz); m/z 364, 210 (M^+, 11%), 165, 137 (100%), 123, etc. See Table **T.3** for the ^{13}C n.m.r. data (p. 159).

The mother liquor was treated with methylene chloride and water and filtered. A reddish precipitate was collected (0.05 g) which by comparison to a sample collected next was identified (^{1}H n.m.r. and i.r.) as 6-fluoroquinoxalin-2-one (**425**). The two immiscible layers in the filtrate were separated. The organic layer was concentrated to small volume and filtered. The filtrate was evaporated and identified as starting material. A red film that was left on the filter was removed using acetone and the solution evaporated. The residue was identified as 6-fluoroquinoxalin-2-one (**425**) with a very small amount of the 7-fluoro isomer (**426**); δ_H (**425**) 7.36 (1H, dd, H-8), 7.45 (1H, td, H-7), 7.59 (1H, dd, H-5), 8.21 (1H, s, H-3) ($J_{5,F}$ 8, $J_{5,7}$ 2, $J_{7,F}$=$J_{7,8}$=8, $J_{8,F}$ 5 Hz); (**426**) 7.06 (1H, dd, H-8), 7.14 (1H, m, H-6), 7.835 (1H, dd, H-5), 8.11 (1H, s, H-3) ($J_{5,F}$ 6, $J_{6,F}$=$J_{5,6}$=9, $J_{7,8}$ 9, $J_{6,8}$ 3 Hz). See Table **T.5** (p. 161) for the ^{13}C n.m.r. data.

The aqueous solution was acidified until weakly acidic and a powdery reddish-brown precipitate (0.21 g) was collected. The solid contained three, possibly four components. The major component was 5-fluoro-1*H*-benzimidazole 3-oxide (**418**) (~10%) which was positively identified by comparison of the ^{1}H and ^{13}C n.m.r. spectra with those for a pure sample. The signals of H-4, H-6, and H-7 obscured those for the other minor components but two high field singlets in addition to the H-2 signal for

(**418**) were visible. The shifts corresond to those for the H-3 signals in the quinoxalin-2-ones (**425**, **426**). Only most of the carbon signals corresponding to (**425**) were visible in the ^{13}C n.m.r. of the mixture, the ones for the other isomer were presumably too small to be seen (the peaks in the ^{1}H n.m.r. spectrum were very small). The signals left unaccounted for were as follows; δ_H 3.60 s, 12.0 br s; δ_C 99.97 (d, *J* 29), 110.48 (d, *J* 26), 116.60 (d, *J* 9), 122.00, 150.36, 154.50. The carbon resonances match those in the spectrum for the quinoxaline-2,3-dione (**427**) (see Table **T.3**, p.159), and its molecular ion was in the mass spectrum ; υ_{max} 3100-3700br (NH/OH), 1670 cm^{-1} (CO); m/z 210 (M^+ (**427**), 20 %), 194, 165, 152 (M^+ (**418**), 65), 137 (100), etc.

The filtrate was saturated with sodium chloride and 0.02 g of one or both of 6- and 7-fluoroquinoxalin-2-ones (**425**, **426**) was collected by filtration; m/z 164 (M^+), 136 (100%), 109, 94, etc. The filtrate was extracted with ethyl acetate, the extracts were evaporated and the residue washed with methylene chloride. A ^{1}H n.m.r. spectrum of the insoluble tan solid was very complicated but it was clear that it contained both quinoxalin-2-one isomers (**425**, **426**). A mass spectrum indicated that some of the 1-hydroxyquinoxaline-2,3-dione (**427**) could also be present.

SECTION 4.2

N-(6-CHLORO-2-NITRO-4-TRIFLUOROMETHYLPHENYL)GLYCINE METHYL ESTER (**447**)

The following methods were used to prepare samples of the ester (**447**). The problems with each are described. The reactants in each case are glycine methyl ester hydrochloride and 3-chloro-4-fluoro-5-nitrobenzotrifluoride (**448**). Some of the reactions resulted in the ester (**447**) reacting further. For these reactions, only the synthetic methods are described below. The full details of the work-ups, the products formed and in some cases the reaction times and temperatures are given in separate descriptions to follow, along with the reactions of (**447**) with bases.

A.) Equimolar amounts of the reactants (0.01 mol) and two molar equivalents of triethylamine in methanol were stirred for 45 minutes. The solution was evaporated to give the ester as light orange needles, yield 1.82 g (58%) m.p. 46°C (from methanol); δ_H ($CDCl_3$) 3.80 (3H, s, OMe), 4.25 (2H, d, CH_2), 7.95 (1H, br s, NH), 7.97 (1H, d, H-5), 8.22 (1H, d, H-3) ($J_{3,5}$ 2 Hz). The n.m.r. spectrum also showed a very small singlet at 4.10 δ which could correspond to either methyl 2-chloro-6-nitro-4-trifluoromethyl-anisole (**449**) or methyl 7-chloro-5-trifluoromethylbenzimidazole-2-carboxylate 3-oxide (**450**). Another reaction definitely resulted in further reaction of the ester (**447**) (see pp.127-128)

B.) This method is the same as method A except that sodium hydrogen carbonate was used instead of triethylamine and the mixture was heated under reflux for 2 h. The solution was cooled (4°C) overnight, then added to ice-water. The ester was filtered off to give yellow needles, yield 2.89 g (93%), m.p. 48-49.5°C (from methanol) (Found: C, 38.4; H, 2.1; N, 8.9. $C_{10}H_8ClF_3N_2O_4$ requires C, 38.4; H, 2.6; N, 9.0%); δ_F -62.9. The ^1H n.m.r. was the same as that reported above except that there was no small singlet at 4.1 δ. Though this reaction produced a pure sample of the ester, it was decided to investigate other methods because of the possibility that methanol could act as a competitive nucleophile.

C.) Glycine methyl ester hydrochloride (2.51 g, 0.02 mol) was dissolved in water (10 ml) and the solution neutralized with sodium hydroxide (23 ml). The solution was then extracted with chloroform. The organic extracts were dried (Na_2SO_4) and evaporated to give glycine methyl ester, yield 1.18 g (66%). The ester (1.00 g, 0.011 mol) was added portionwise over 1 h to a solution of (**448**) (2.45 g, 0.01 mol) and triethylamine (1.11 g, 0.011 mol) in toluene (30 ml). During this time the temperature was raised to 65°C and maintained for 3 h after the additions were complete. More of the ester (0.20 g, 0.0022 mol) was added and heating continued for another 2 h. One problem with this method was that the initial extraction of glycine methyl ester into chloroform only gives an average yield (66%). Also, further reaction of the ester occurred (see pp.128-129).

D.) Two molar equivalents of triethylamine were added to a solution of the reactants in toluene and the mixture heated. Further reaction of the ester also occurred (see pp. 129-131).

E.) Glycine methyl ester (0.73 g, 0.003 mol) was added to a solution of the benzotrifluoride (**448**) (1.90 g, 0.066 mol) in dry tetrahdyrofuran (10 ml). The mixture was stirred for 22 h at room temperature and filtered. The filtrate was evaporated *in vacuo* to a orange-yellow liquid. With addition of methanol (0.5 ml) and with scratching, the liquid crystallized to give the ester (**447**) as waxy yellow needles; yield 0.91 g (89%), m.p. 48.5-49°C (from methanol) (Found: C, 38.1; H, 2.3; N, 8.8. $C_{10}H_8ClF_3N_2O_4$ requires C, 38.4; H, 2.6; N, 9.0%). The ^1H n.m.r. spectrum matches the one quoted in method A. The first two times the procedure was used it gave the pure ester but subsequent attempts resulted further reaction of the ester (**447**) taking place (see pp. 125-126).

Note: Only the pure ester (**447**) samples obtained by using methods B and E were used in reactions with bases.

ATTEMPTED SYNTHESES OF THE ESTER (**447**) USING METHOD E

a.) Barium hydroxide (6.94 g, 0.022 mol) was added to a solution of 3-chloro-4-fluoro-5-nitrobenzotrifluoride (**448**) (2.44 g, 0.01 mol) and glycine methyl ester hydrochloride (1.38 g, 0.011 mol) in tetrahydrofuran (30 ml). After stirring at room temperature for 18 h, t.l.c. showed that starting material was still present, so more of the ester and base were added (0.002 and 0.004 mol respectively). The solution was stirred for another 3 h, then evaporated and treated with ether, 1M hydrochloric acid and methanol until two clear layers were obtained. The layers were separated and extraction of the aqueous layer was continued with ether. The ether extracts were combined and extracted with 1M sodium hydroxide. The basic extracts were acidified (conc HCl) and a light-brown precipitate (1.04 g) was filtered off. The ether solution was dried (Na_2SO_4) and evaporated to a green viscous liquid (1.01 g). The ^1H n.m.r. spectrum identified it as the impure ester (**447**). The presence of a peak at 8.9 δ suggested that one of the contaminants could be the 7-chloro-5-trifluoromethyl-benzimidazole 3-oxide (**451**). The precipitate was identified as containing the *N*-oxide and a small amount of 5-chloro-1-hydroxy-7-trifluoromethylquinoxaline-2,3-dione (**452**). Treatment with a small amount of boiling water left about half of the solid insoluble. The soluble portion was acidified. Microanalysis of the precipitate was far off for the*N*-oxide but the carbon/nitrogen ratio was very close to that in the quinoxaline-2,3-dione (**452**). A pure sample of the *N*-oxide was obtained by treatment of the mixture with successive amounts of boiling water and recrystallization of the insoluble solid twice from ethanol. The *N*-oxide (**451**) was collected as pale brown needles; m.p. 217-218°C, (Found: C, 40.5; H, 1.5; N, 11.7. $C_8H_4ClF_3N_2O$ requires C, 40.6; H, 1.7; N, 11.8%); (the following spectra are for the mixture) υ_{max} 3440, 3080w (NH), 2600-2100 (OH), 1700s (CO); δ_H 7.75 (1H, d, H-6), 7.95 (1H, d, H-4), and 8.85 (1H, s, H-2); δ_F* -59.3 (**451**), 60.7 ppm (**452**); m/z 280 (M^+ (**452**), 1%), 263, 236 (M^+ (**451**), 220, 219, 217,
207, 190, 187, 181, 173, etc. The presence of (**452**) was also indicated by resonances

*assignments were made by comparison to a ^{19}F spectrum of the pure quinoxaline-2,3-dione (**452**)

at 151.25 (CO) and 155.20 (CO) in the ^{13}C n.m.r. spectrum. See Table **T.2** (p.158) for the ^{13}C n.m.r. data for the *N*-oxide (**451**).

b.) Method E was used again with 2 mol. eq. of barium hydroxide and 1 mol. eq. of each of the reactants. After stirring at room temperature for 2.5 h, t.l.c. indicated that cyclization was taking place before all of the starting material had reacted. Another mol. eq. of base was added to encourage the reaction on towards cyclization. Stirring continued for another 6 h. T.l.c. showed that starting material was still present but there seemed to be very little change from a t.l.c. taken 2 h earlier so the reaction was stopped.

The solution was evaporated, treated with methanol (10 ml) and water (50 ml) and filtered. The filtrate was acidified (conc. HCl) and extracted with ether. The ether layer was dried (Na_2SO_4) and evaporated to a mustard yellow solid (0.34 g) which was identified (^1H n.m.r.) as the impure *N*-oxide (**451**). The insoluble solid from the initial filtration was treated with ether and extracted with 5M hydrochloric acid, then with 2M sodium hydroxide. The ether layer was dried (Na_2SO_4) and evaporated to a thin orange film, 0.22 g. The ^1H n.m.r. spectrum suggested that it is a mixture of the *N*-oxide (**451**) and the quinoxaline-2,3-dione (**452**). Further work-up of the basic extracts gave no additional information.

REACTION OF THE ESTER (447) WITH BARIUM HYDROXIDE

The ester (1.56 g, 0.005 mol) and barium hydroxide (1.89 g, 0.006 mol) in dry tetrahydrofuran (20 ml) were stirred at room temperature for 19 h. The reaction solution was evaported *in vacuo* and treated with methanol and water and an orange precipitate was filtered off. The solid was treated with ether and extracted with 1M hydrochloric acid, water, and 2M sodium hydroxide. The ether layer was dried (Na_2SO_4) and evaporated to a yellow-orange solid weighing 0.17 g. T.l.c. showed many components but the ^1H n.m.r. and mass spectra indicated that it was mostly a mixture of the ester (**447**) and 2,2′-diamino-3,3′-dichloro-5,5′-bis(trifluoromethyl)azoxybenzene (**454**). The latter identification was supported by a comparison of the spectral data with that for the azoxybenzenes isolated later in this project and by McFarlane[21]; δ_H (60 MHz; $CDCl_3$)

(resonances arising from **454***) 5.20 (2H, br s, NH_2), 6.45 (2H, br s, NH_2), 7.55-7.75 (1H, m, H-4′), 7.75-7.90 (m, H-4)^, 8.20-8.35 (m, H-6)^, and 8.75-9.10 (1H, m, H-6′); m/z 432 (M^+ **454**), 415,..., 253, 224, 208, 194, 173 (100%).

The water extract was acidified and extracted with ether. The extracts were combined, dried (Na_2SO_4) and evaporated to a solid (0.59 g). T.l.c. showed only one spot at the origin. The solid was washed with chloroform. A ^1H n.m.r. spectrum of the evaporated washings was too complicated to be interpreted. The insoluble solid (0.28 g) was identified as a mixture of the *N* -oxide (**451**) (~15%), the quinoxaline-2,3-dione (**452**) (~2%) and mainly one other compound; υ_{max} 3120 (NH), 1680, 1720br (CO), 1275, 1290 cm^{-1}. Comparison of the ^1H, ^{13}C, and ^{19}F n.m.r. spectra with those taken of more pure samples of (**451**) and (**452**) allowed the peaks corresponding to those compounds to be discounted, leaving those arising from the third compound including, δ_H** 7.28 s, 7.42 s, 11.25br s, 11.60br s, 12.21br s; δ_F -59.5. Based on the spectral evidence, the third main compound is proposed to be 7-chloro-5-trifluoromethyl-benzimidazol-2-one (**453**); m/z (236 (M^+ (**451**, **453**)), the molecular ion for (**452**) was not observed. See Table **T.3** (p.159) for the ^{13}C n.m.r. resonances attributed to (**453**). Several more derivatives of benzimidazol-2-one were thought to have been isolated in this project and all of them gave some high field aromatic signals (~7 δ) in the ^1H n.m.r. and a carbonyl resonance at about 150 ppm in the ^{13}C n.m.r.(see Table **T.3**, p.159).

The filtrate from collection of the mixture was acidified and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated to give an orange solid. T.l.c. showed two spots, one slightly mobile and the other one unmoved. The solid was treated with a little ether and filtered. A crop of the *N*-oxide (**451**) was collected, 0.02 g (2%); m/z 236 (M^+, 100%), 220 (M-16), 217, 201, 193, 187, 181, 173, etc.

*assignments were made on the basis of a spin-spin decoupling experiment on an n.m.r. run on a sample obtained from a reaction described in section **4.3**

^overlapping with the resonances for the ester.

** The spectrum also showed two much smaller singlets at 7.21 δ and 7.35 δ but no corresponding ones in the ^{13}C n.m.r. were visible. In this 300 MHz spectrum, none of the aromatic signals showed coupling.

ATTEMPTED SYNTHESES OF THE ESTER (**447**) USING OTHER METHODS

a.) Using method A

Glycine methyl ester hydrochloride (1.26 g, 0.01 mol) was added to a solution of triethylamine (2.02 g, 0.02 mol) and the benzotrifluoride (**448**) (2.46 g, 0.01 mol) in methanol (30 ml) and stirred for 30 minutes. More of the ester was added (0.30 g, 0.002 mol) and stirring was continued for another 1.3 h. The solution was evaporated *in vacuo* to a residue which was dissolved in ether and extracted with 1M hydrochloric acid. Then, extraction of the ether layer with 1M sodium hydroxide with subsequent drying (Na_2SO_4) and evaporation gave 2.80 g (89%) of the crude ester (**447**). T.l.c. indicated that it was contaninated by a small amount of another less polar compound, possibly the anisole (**449**). The drying agent (Na_2SO_4) was stained orange and the colour could not be removed by ether. It was washed with methanol, and the filtrate evaporated to leave an oily film of the *N*-oxide (**451**) (m.s.).

The basic extracts were combined, acidified and extracted with ether. The ether extracts were dried (Na_2SO_4) and evaporated to give a small amount of (**451**) seemingly contaminated by the quinoxaline-2,3-dione (**452**); m/z 280 (M^+ (**452**), 236 (M^+ (**451**)), 220, 207, 201, 187, 181, 178, 173, etc. (There are also many very small peaks (1-2%) up to m/z 355 that could not be assigned.)

b.) Using method C

The method was carried out as described in the beginning of this section. The reaction solution was filtered and the solvent evaporated. The oily residue was treated with a little methanol and ether and extracted with 1M hydrochloric acid. The ether layer was dried (Na_2SO_4) and evaporated to give a mixture of solid and oil. T.l.c. indicated that several polar and non-polar components were present. The mixture was chromatographed (silica gel in petrol) and eluted with a mixture of petrol and ether. The most mobile fractions were identified as mixtures of the unreacted benzotrifluoride (**448**), the anisole (**449**) (presumably resulting from the use of methanol in the work-up) and the ester (**447**). Another mobile fraction upon evaporation produced yellow needles which gave one spot on t.l.c.. At first glance the ^1H n.m.r. spectrum resembled that for

the anisole (**449**). However, an independent synthesis of (**449**) gave the product as a liquid giving rise to a ^{1}H n.m.r. (4.08 s, 8.35-8.40 m in d_6-DMSO) different from that obtained in this reaction. Methyl 7-chloro-5-trifluoromethyl-1*H*-benzimidazole-2-carboxylate 3-oxide (**450**) has a structure which is consistent with the ^{1}H n.m.r.spectrum and its molecular ion appears in the mass spectrum; δ_H 4.02 (3H, s, CH_3), 7.80-7.90 (1H, m, H-4), and 8.00-8.08 (1H, m, H-6); m/z 294 (M^+), 275, 278, 262, 253, 247.

6-CHLORO-2-NITRO-4-TRIFLUOROMETHYLANISOLE (**449**)

Triethylamine (0.51 g, 0.005mol) was added to a solution of the benzotrifluoride (**448**) (1.27 g, 0.005 mol) in methanol (20 ml) and the mixture stirred at room temperature for 16 h, then heated under reflux for 2.5 h. The solution was evaporated, the residue treated with ether and extracted with 1M hydrochloric acid. The ether layer was filtered through celite, dried (Na_2SO_4) and evaporated to give a yellow liquid; δ_H (d_6-DMSO) 4.08 (3H, s, CH_3), and 8.35-8.40 (2H, m, arom. H); δ_H ($CDCl_3$) 4.12 (3H, s, CH_3), 7.90-8.10 (2H, 2 overlapping m, H-3 & H-5) ($J_{3,5}$ could not be measured).

ATTEMPTED SYNTHESES OF THE ESTER (**447**) USING METHOD D

a.) The benzotrifluoride (**448**) (7.31 g, 0.03 mol) and triethylamine (6.66 g, 0.066 mol) were combined in toluene (150 ml) and heated to between 70-75°C. Glycine methyl ester hydrochloride (4.14 g, 0.033 mol) was added portionwise over 1 h and the heating continued for another 2 h. The solution was filtered and the solvent evaporated. The resulting oil was treated with ether and extracted with 1M hydrochloric acid. The ether layer was dried (Na_2SO_4) and evaporated to an orange liquid which with scratching and chilling partially solidified. The precipitate was filtered off and washed thoroughly with ether leaving the 1-hydroxyquinoxaline-2,3-dione (**452**) as a light yellow powder (0.16 g, 2%); m/z 280 (M^+), 264, 263, 252, 237, 235, 208, 173 (100%). The filtrate and the ether washings were evaporated to give an oil. With addition of a small amount of methanol, scratching and cooling the crude ester (**447**) appeared as orange needles (1.4 g) (^{1}H n.m.r.).

b.) Glycine methyl ester hydrochloride was added portionwise over 1.5 h to a solution of the benzotrifluoride (**448**) and triethylamine in toluene at 75°C. Initially only half of the necessary two mol. eq. of base was added but this was later rectified when additions of base and the ester were made. The total amounts used were as follows: the ester (4.82 g, 0.0384 mol), the base (6.90 g, 0.0684 mol) and the benzotrifluoride (3.77 g, 0.03 mol) in 80 ml toluene. The mixture was heated for a total of 4 h at 70°C and then 2 h at 100°C.

The mixture was filtered, the toluene was removed under vacuum from the filtrate and the residual oil treated with ether. Extraction with 1M hydrochloric acid resulted in a precipitate at the interface which was removed using a small volume of the aqueous layer and added to ice. The solid was collected by filtration (see below). The extraction was continued. The ether was dried (Na_2SO_4) and evaporated to an oil which eventually gave some crystals. A small portion containing some crystals was recrystallized from methanol giving only 0.04 g. All of this was used to make up a ^1H n.m.r. sample. The spectrum indicated that it was the diaminoazoxybenzene (**454**); δ_H (60 MHz; $CDCl_3$) 5.2 (2H, br s, NH_2)*, 6.45 (2H, br s, NH_2')*, 7.65 (1H, s, H-4′), 7.75 (1H, s, H-4), 8.25 (1H, s, H-6), and 9.0 (1H, s, H-6′) (The resolution was not good enough to show coupling.)

The rest of the oil was put down a column of silica gel in petrol and eluted with increasing proportions of ether to petrol. The main fraction contained a mixture of the azoxybenzene (**454**) and the ester (**447**).

The solid collected from the extraction solution was treated with hot methanol and filtered upon cooling to room temperature. A small amount of solid was collected and identified as the quinoxaline-2,3-dione (**452**) (^1H**, ^{13}C n.m.r., m.s., i.r.). The filtrate was evaporated and treated with small portions of chloroform. The soluble material was identified as the ester (**447**) along with some impurities. The insoluble material was more of the quinoxaline-2,3-dione (**452**); total yield 0.80 g (10%); m.p. 247-249°C

* provisional assignments

** This spectrum, including an expansion of the aromatic region, showed only one aromatic signal at 7.65 δ.

[from water with acidification (5M HCl)] (Found: C, 38.3; H, 1.2; N, 9.8. $C_9H_4ClF_3N_2O_3$ requires C, 38.5; H, 1.4; N, 10.0%); υ_{max} 3000-3300br (NH/OH), 1750br, 1670br cm^{-1} (CO); δ_H^ 7.64 (1H, d, H-8), 7.68 (1H, d, H-6), and 11.95 (~2H, br s, NH/OH); δ_F -60.5; m/z 280 (M^+), 261, 252, 235, 216, 208, 173 (100%) etc. See Table **T.3** for the ^{13}C n.m.r. data (p.159).

^ An expansion of the aromatic region showed a very small (< 1 Hz) CF_3 coupling that could not be measured accurately.

REACTION OF THE ESTER (**447**) WITH BASES

a.) With triethylamine

A solution of the ester (1.56 g, 0.005 mol) and triethylamine (0.56 g, 0.0055 mol) in toluene (20 ml) was stirred for 2 h at room temperature. The temperature was then raised to 75°C for 1 h, then to between 80-90°C for 4 h. The solution was evaporated and the residue treated with ether and a little methanol and extracted with 1M hydrochloric acid. The aqueous extracts were combined and filtered and a powdery orange solid collected that was identified as a mixture of the ester (**447**) and the quinoxaline-2,3-dione (**452**) (^1H n.m.r., m.s., i.r.)

The ether layer was extracted with 3M sodium hydroxide. The extracts were combined, acidified, and extracted with ether. The organic extracts were dried (Na_2SO_4) and evaporated to give 0.36 g (31%) of the *N* -oxide (**451**) (t.l.c., i.r., ^1H n.m.r.).

The surviving ether solution was dried (Na_2SO_4) and evaporated *in vacuo* to a dark orange film. T.l.c. showed many components but the ^1H n.m.r. spectrum indicated that the azoxybenzene (**454**) was the major one. This compound was isolated several times in the project and could not be purified well enough to pass microanalysis. This particular sample was sublimed at 110°C but still gave a wide melting-point range, m.p. 155-162°C. The most pure sample had m.p. 171-175°C.

b.) With potassium carbonate

The procedure for the reaction and the work-up were taken from McFarlane for the cyclization of *N*-(3-nitro-2-pyridyl)glycine ethyl ester[1].

The ester (0.63 g, 0.002 mol) and potassium carbonate (0.28 g, 0.002 mol) in methanol (20 ml) was heated under reflux for 5.5 h. The solution was filtered. The white solid collected was dissolved in water, decolourized with charcoal and acidified. The precipitate was dissolved in water, evaporated to dryness and the residue washed with ether to give 0.01 g of white needles containing a mixture of the quinoxaline-2,3-dione (**452**) and the *N*-oxide (**451**) (m.s.).

Work-up of the mother liquor according to the procedure gave a solid which only gave unidentifiable peaks at m/z 149 and m/z 104 in the mass spectrum.

N-(2,6-DINITRO-4-TRIFLUOROMETHYLPHENYL)GLYCINE METHYL ESTER (**455**)

Glycine methyl ester hydrochloride (3.01 g, 0.024 mol) and sodium hydrogen carbonate (4.62 g, 0.055 mol) were added to a solution of 4-fluoro-3,5-dinitro-benzotrifluoride (5.08 g, 0.02 mol) in dry tetrahydrofuran (30 ml) and heated under reflux for 40 minutes in an apparatus fitted with a drying tube ($CaCl_2$). The reaction solution was filtered and evaporated to give a thick red oil. A little methanol was added and the oil crystallized with scratching to give red-stained yellow needles. The needles were carefully washed on a filter with small amounts of cold methanol to give the crude ester (**455**) as yellow needles, 3.40 g (53%); m.p. 78.5-79°C (from methanol); (Found: C, 37.0; H, 2.35; N, 12.9. $C_{10}H_8F_3N_3O_6$ requires C, 37.2; H, 2.5, N, 13.0%); δ_H (d_6-acetone) 3.85 (3H, s, CH_3), 4.05 (2H, m*, CH_2), 8.75 (2H, s, H-3 & H-5), and 9.40 (>1H, br s, NH).

The filtrate including the methanol washings was evaporated to give a sticky red solid which was recrystallized from methanol to give 2.14 g of an impure second crop of the ester (**455**) (t.l.c.). This solid was purified by column chromatography (silica gel in methylene chloride). The mobile yellow fraction was collected to give an additional 1.21 g (19%, total 71%) of the ester, m.p. 78-79°C ; the ^1H n.m.r. spectrum was identical to the one already described.

*doublet and singlet superimposed; due to partial H-D exchange of NH.

REACTION OF THE ESTER (**455**) WITH BASES

a.) With triethylamine

Triethylamine (0.61 g, 0.006 mol) was added to the ester (1.94 g, 0.006 mol) in toluene (30ml) and the mixture stirred at room temperature for 4.5 h. No solid was present in the reaction solution so it was evaporated directly to leave a dark oil which was then partitioned between methylene chloride and water. The aqueous solution was acidified slowly (5M HCl) and a light coloured precipitate was collected and washed with methylene chloride. The crude 1-hydroxy-5-nitro-7-trifluoromethylquinoxaline-2,3-dione (**456a**) was obtained with a yield of 0.22 g (13%). Treatment of this with hot water and recrystallization of the insoluble portion gave a light-coloured powder, m.p. 247°C dec. (Found: C, 36.8; H, 1.2; N, 14.3. $C_9H_4F_3N_3O_5$ requires C, 37.1; H, 1.4; N, 14.4%) ; υ_{max} 3100-3240w (NH/OH), 1760br, 1690w cm^{-1} (CO); δ_H 8.28 (1H, d, H-8), 8.40 (1H, d, H-6), and 11.50 (br s, NH/OH) ($J_{6,8}$ 2 Hz). See Table **T.3** (p.159) for the ^{13}C n.m.r. data.

The methylene chloride solution was extracted with water, and the extracts were acidified to give more of the quinoxaline-2,3-dione (**456a**), 0.45 g (26%) [total yield 0.67 g (38%)]; the infrared spectrum matches that for the first sample; m/z 291(M^+), 275, 273, 263, 257, 247, 236, etc.

The organic phase was extracted with saturated aqueous sodium hydrogen carbonate solution. The basic extracts were acidified and extracted with methylene chloride. The extracts were dried (Na_2SO_4) and evaporated. The spectra suggest that the residue is a mixture of (**456a**) and methyl 7-nitro-5-trifluoromethylbenzimidazole-2-carboxylate-3-oxide (**457**); υ_{max} (in d_6-DMSO) 3000-3700 (NH/OH), 1600-1750cm^{-1} (CO); δ_H (60 MHz) 4.0 s (OCH_3), 8.0 s, 8.25s, 8.45 s, and 8.75 s; m/z 305 (M^+ (**457**), 27%), 291 (M^+ (**456a**), 84), 289 [(M (**457**)-16)$^+$, 9], 275, 273, 263, etc. The 8.25 and 8.45 ppm resonances match those in the spectrum above for the quinoxaline-2,3-dione. However, that would mean that the *N* -oxide signals would be the two that are about 0.8 ppm apart. In the specrtra of other *N*-oxides, the aromatic signals are considerably closer together. Nonetheless, both molecular ions appear in the mass spectrum and the ^{13}C n.m.r. spectrum, though weak, shows the main quinoxaline-2,3-dione peaks plus those

consistent with a 2-substituted benzimidazole *N*-oxide structure. See Table **T.2** (p.158) for the resonances thought to arise from the 2-substituted *N*-oxide (**457**).

The organic phase which survived the base extraction was evaporated. T.l.c. showed that it contained many components. The residue was treated with a small portion of methylene chloride and an orange solid was filtered. The 2,2′-diamino-3,3′-dinitro-5,5′-bis(trifluoromethyl)azoxybenzene (**458a**) had a yield of 0.21 g (15%), m.p. 193°C (from ethanol) (Found: C, 37.1; H, 18.4; N, 1.5. $C_{14}H_8F_6N_6O_5$ requires C, 37.0; H, 18.5; N, 1.8%); δ_H 8.30 (4H, br s, 2xNH_2), 8.36 (1H, d, H-4′)*, 8.51 (1H, d, H-4)*, 8.54 (1H, d, H-6)*, and 9.04 (1H, d, H-6′)* ($J_{3,5}$=$J_{3',5'}$=2 Hz, J_{CF3} estimated at 0.5 Hz); m/z 454 (M^+, 100%), 438, 435,..., 235, 219, etc.

* provisional assignments

b.) With sodium hydrogen carbonate

Sodium hydrogen carbonate (0.34 g, 0.004 mol) was added to the ester (**455**) (1.30 g, 0.004 mol) in methanol (30 ml) and stirred at room temperature for 2.5 h. The solution was filtered, the salt collected and washed with methanol. The filtrate was evaporated to a dark film. Equal amounts of petrol and ether were added and filtered. The solid collected was treated with 5 ml portions of each petrol and ether. After 100 ml (total) had been added, a t.l.c. of the solid left showed a predominant spot that was unmoved and a faint one with the same R_f as the azoxybenzene (**458a**). The solid was washed thoroughly with methylene chloride on the filter, work-up of the solid is decribed below. The combined filtrates were evaporated, treated with a little petrol and filtered. The filtrate was evaporated to give a film composed mostly of the ester (**455**) and a little of the diaminoazoxybenzene (**458a**), m/z 454 (M^+(**458a**), 5%), 323 (M^+(**455**), 6), 304, 294, 277, 264 (100), etc.

The insoluble solid was sublimed. Dark green spikes of what appears to be a mixture of 2,6-dinitro-4-trifluoromethylaniline (**459**) and the 2-nitroso derivative (**460**) crystallized on the cold finger; m.p. 98-99°C; υ_{max} 3800, 3400 cm^{-1} (NH); m/z 251 (M^+ (**459**), 6%), 235 (M^+ (**460**), 53), 217, 189, 171, 159 (100), etc. A mass spectrum of

the nitro compound (**459**) contains a peak at m/z 235 but it is only ~3%[67]. Thus the mixture, especially considering the deep green colour, appeared to be comprised mostly of the nitroso derivative (**460**).

The material left at the bottom of the tube was removed using ethanol and identified as a mixture of the ester (**455**) and the azoxybenzene (**458a**) (^{1}H n.m.r.).

The insoluble solid was dissolved in water and made just acidic (5M HCl). The solid collected appeared to be the quinoxaline-2,3-dione (**456a**), yield 0.10 g (9%); υ_{max} 3100-3300 (NH/OH), 1760s cm^{-1} (CO). The filtrate was saturated with sodium chloride and extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and evaporated to give more (**456a**) as a powdery buff coloured solid, 0.03 g (total 11%); i.r. and ^{1}H n.m.r. spectra identical to those for a pure sample (see previous reaction); m/z 291 (M^+, 90%), 275, 272, 263, 256, 247, etc.

N-(2,4- DINITRO-6-TRIFLUOROMETHYLPHENYL)GLYCINE (**462**)

Glycine (2.63 g, 0.035 mol) and sodium hydrogen carbonate (5.04 g, 0.06 mol) were added to a solution of 2-chloro-3,5-dinitrobenzotrifluoride (8.12 g, 0.03 mol) in methanol (150 ml) and the mixture heated under reflux for 5 h. The reaction solution was filtered and the solvent evaporated *in vacuo*. The orange solid residue was treated with methylene chloride (30 ml) and 5M hydrochloric acid (20 ml) and stirred well. The yellow solid was collected and washed with water to give the acid (**462**), 9.15 g (99%); m.p. 161.5-162°C (from methanol-water) (Found: C, 34.8; H, 1.75; N, 13.35. $C_9H_6F_3N_3O_6$ requires C, 35.0; H, 2.0; N, 13.4%); δ_H (d_6-acetone) 4.25 (2H, s, CH_2), 8.80 (1H, m*, H-5), and 9.27 (1H, d, H-3) ($J_{3,5}$ 3 Hz).

* doublet with additional coupling to CF_3

N-(2,4-DINITRO-6-TRIFLUOROMETHYLPHENYL)GLYCINE METHYL ESTER (**461**)

The acid (**462**) (3.09 g, 0.01 mol) was dissolved in methanol (50 ml) and gaseous hydrogen chloride (1.3 g, 0.03 mol) was bubbled into the solution. The solution was heated under reflux for 7 h, reduced to small volume under vacuum and the precipitate filtered off. T.l.c. indicated the presence of some polar material which was not removed by base extraction, indicating it was something other than starting material (**462**). The solid was dissolved in methylene chloride and purified by column chromatography (silica gel in methylene chloride). Evaporation of the mobile yellow fractions gave waxy yellow needles, 2.03 g (63%), m.p. 77-78°C (from methanol); (Found: C, 37.2; H, 2.4; N, 13.0. $C_{10}H_8F_3N_3O_6$ requires C, 37.2; H, 2.5; N, 13.0%); δ_H (d_6-acetone) 3.82 (3H, s, Me), 4.25 (2H, d, CH_2), 8.20 (1H, br s, NH), 8.75 (1H, d, H-5), and 9.10 (1H, d, H-3) ($J_{CH2,NH}$ 5, $J_{3,5}$ 2 Hz).

REACTION OF THE ESTER (**461**) WITH BASES

a.) With triethylamine

A solution of the ester (1.62 g, 0.005 mol) and triethylamine (0.51 g, 0.005 mol) in toluene (30 ml) was stirred at room temperature for 4.5 h. The solution was filtered though all of the solid remained behind. The mother liquor was evaporated. The solid was treated with methylene chloride and water and filtered. (The filtrate was combined with the evaporated mother liquor.) A light orange solid was collected and identified as 2,2′-diamino-5,5′-dinitro-3,3′-bis(trifluoromethyl)azoxybenzene (**458b**), 0.13 g (11%), m.p. 292-293°C. Recrystallization was difficult: attempts from aqueous and neat alcohols and in combination with dimethylformamide resulted in the material remaining in solution or forming a suspension. However, one treatment with hot ethanol and filtration gave a solid which nearly passed microanalysis; (Found: C, 36.6; H, 1.5; N, 18.1. $C_{14}H_8F_6N_6O_5$ requires C, 37.0; H, 1.8; N, 18.5%); υ_{max} 3320w, 3400w, 3500w cm^{-1} (NH); δ_H 7.20 (2H, br s, NH_2), 7.67 (2H, br s, NH_2), 8.30 (1H, d, H-4′)*, 8.42 (1H, d, H-4)*, 8.92 (1H, d, H-6), and 9.48 (1H, d, H-6′) ($J_{3,5}$=$J_{3',5'}$ 3 Hz); m/z 454 (M^+,

*provisional assignments

100%), 438 (M-16), 417, 408, 388, 371..., 235, 215, 205, etc. See Table **T.6** (p.162) for the ^{13}C n.m.r. data.

The filtrate-mother liquor solution was separated into its organic and aqueous phases. The latter was acidified dropwise (5M HCl) causing long white needles slowly appeared. The precipitate was collected and washed with acetone which surprisingly dissolved it (most of the other quinoxaline-2,3-diones isolated were relatively insoluble in acetone). The solution was evaporated to give the 1-hydroxy-7-nitro-5-trifluoromethyl-quinoxaline-2,3-dione (**456b**), 0.10 g (7%), m.p. 244.5°C (from water), (Found: C, 35.1; H, 1.7; N, 13.7. $C_9H_4F_3N_3O_5 \cdot H_2O$ requires C, 35.0; H, 2.0; N, 13.6%); υ_{max} 3000-3600br (OH), 3110w (NH), 1680s, 1730s cm^{-1} (CO); δ_H (d_6-acetone) 6.75 (~1H, br s, NH/OH), 8.55 (1H, d, H-8), and 8.81 (1H, d, H-6) ($J_{6,8}$ 3 Hz); m/z 291 (M^+), 275, 263, 247, etc. See Table **T.3** (p.159) for the ^{13}C n.m.r. data.

The organic phase was extracted with water. The extracts were filtered and another crop of the diaminoazoxybenzene (**458b**) was obtained, yield 0.06 g (total of 17%); m/z 454 (M^+, 100%), 438, etc. The aqueous filtrate was acidified in two batches to give light brown needles, 0.18 g, m/z 305 (41%), 291 (22), 275 (27),273 (30), 258 (35), 247 (70), etc and 0.02 g, m/z 319 (10%), 305 (60), 300, 291 (5), 289, 286, 273 (40), 258 (50), 247 (90), etc. The peak at m/z 319 does not make sense; the starting material (**461**) and the acid (**462**) have molecular ions at m/z 323 and m/z 309 respectively. The peak at m/z 305 is the molecular ion for methyl 5-nitro-7-trifluoromethylbenzimidazole-2-carboxylate 3-oxide (**463a**), and the quinoxaline-2,3-dione (**456b**) has a molecular ion at m/z 291.

The filtrate was saturated with sodium chloride, extracted with ethyl acetate and washed with methylene chloride leaving a buff coloured solid, the quinoxaline-2,3-dione (**456b**) 0.02 g (total of 25%), m.p. 242-243°C; υ_{max} 3000-3400br (NH/OH), 1680br, 1750br cm^{-1} (CO); m/z 291(M^+, 60%), 275(22), 273 (10), 263, etc.

b.) With barium hydroxide

Barium hydroxide (1.58 g, 0.005 mol) was added to the ester (**461**) (1.62 g, 0.005 mol) in tetrahydrofuran (30 ml) and stirred at room temperature for 35 minutes. The solution was allowed to settle and the liquid was carefully decanted. The residual solid was treated repeatedly with ether and decanted and added to the mother liquor. The solution was evaporated to a red film, treated with methylene chloride and water and filtered. Hot water was added to the red solid collected. Analysis of the insoluble solid gave only an uninterpretable ^1H n.m.r. spectrum. The filtrate was acidified (5M HCl) and extracted with methylene chloride. The organic extracts contained a mixture of products; the ^1H n.m.r. spectrum has an interesting doublet or two singlets at 4.0 δ but a complicated aromatic region. The aqueous solution was saturated with sodium chloride and extracted with ethyl acetate. The extracts were dried (Na_2SO_4) and evaported to a thin powdery film, all of which was used to make up an n.m.r. sample. The spectral data indicated it contained the quinoxaline-2,3-dione (**456b**) and the 5-nitro-7-trifluoromethyl-benzimidazole 3-oxide (**463b**); δ_H 8.10 d, 8.25 d, 8.37 d, 8.47 dd, 9.08 s, 11.75 (br s), and 12.3 (br s); m/z 291 (M^+ (**456b**), 13%), 275, 263, 247 (M^+ (**463b**) 80), 231, 228, 217, 212, 201, etc.

The immiscible liquids in the filtrate were separated. The organic solution contained mostly starting material (**461**) (0.60 g) (^1H n.m.r.). The aqueous solution was acidified and extracted with methylene chloride. The evaporated extracts gave an ^1H n.m.r. spectrum with mostly non-aromatic peaks. The aqueous solution was saturated with sodium chloride. Extraction with ethyl acetate, drying (Na_2SO_4) and evaporation of the extracts gave a powdery film. The ^1H n.m.r. spectrum was the same as for the mixture above except for an extra peak at 8.45 δ, and one less peak at 8.55 δ. However the mass spectrum indicated only the presence of the *N*-oxide (**463b**); m/z 247 (M^+, 36%), 231 [$(M-16)^+$, 12], 201, 185, 165, etc.

ATTEMPTED SYNTHESIS OF (462) RESULTING IN CYCLIZATION

Potassium carbonate (0.69 g, 0.005 mol) was added to a solution of 2-chloro-3,5-dinitrobenzotrifluoride (1.08 g, 0.004 mol) and glycine (0.38 g, 0.005 mol) in

ethanol (25 ml). The solution was heated under reflux for 2 h and filtered. The filtrate was evaporated, treated with ether and extracted with 5M hydrochloric acid. The ether solution was then extracted with 3M sodium hydroxide. The basic extracts were acidified and extracted with ether. The extracts were dried (Na_2SO_4) and evaporated to a powder, 0.30 g. Spectral evidence indicated that the powder contained the *N*-oxide (**463b**); δ_H (60MHz; d_6-acetone) 8.30-8.55 m, 8.60-8.75 m, 9.00 s; m/z 264 [(M (**462**)-$CO_2H)^+$, 45%)], 263 (47), 247 (M^+(**463b**), 90), 231 [$(M-16)^+$, 50], 217, 212, 201, etc. There were also some very small (1%) peaks up to m/z 447.

4,6-DIFLUORO-2-NITROANILINE (**467**)

a.) Acetylation of 4,6-difluoroaniline

Acetic anhydride (9.18 g, 0.09 mol) was added dropwise to the aniline (3.93 g, 0.03 mol) over 10 minutes. The solution was stirred at room temperature for 1 h, filtered and the white precipitate collected. The filtrate was added to ice-water and more of the *N*-acetyl-4,6-difluoroaniline (**465**) appeared to give a total of 4.45 g, (87%), m.p.119-120°C (from ethanol) (lit[79] m.p. 120.9°C).

b.) Nitration of (**465**)

A literature procedure was employed[80]. Thus concentrated sulfuric acid (4 ml) and acetic acid (1.4 ml) were combined and added to (**465**) (3.20 g, 0.02 mol). Contrary to the literature method, the aniline did not dissolve completely despite vigorous stirring. The procedure was continued by cooling the mixture to 18°C and adding mixture of concentrated sulfuric acid (1.4 ml) and concentrated nitric acid (1.4 ml) dropwise over 15 minutes. The temperature was allowed to rise to between 40-50°C and stirred for 1.5 h. The red, homogeneous solution was added to ice and *N*-acetyl-4,6-difluoro-2-nitroaniline (**466**) was filtered off and recrystallized from ethanol to give 3.60 g, (83%), m.p. 132-134°C (lit[80] 142-143°C); δ_H (d_6-acetone) 2.20 (3H, s, Ac), 7.52-7.92 (2H, m, arom. H)*; m/z 216 (M^+, 2%), 201, 175, 174, etc.

* not first order

c.) Deacetylation of (**466**)

Compound (**466**) (2.34 g, 0.011 mol) and concentrated sulfuric acid (4 ml) were combined and heated on a steam bath for 2 h (in accordance with the literature method[80]). The solution was poured on to ice and 4,6-difluoro-2-nitroaniline (**467**) was collected as a mustard yellow precipitate, yield 1.50 g (78%), m.p. 81-82°C (from ethanol) (lit[80] 85.5-86.5°C); δ_H (60 MHz, $CDCl_3$) 5.90 (2H, br s, NH_2), 7.00-7.10 (1H, symm. 7-line m, H-5), and 7.50 (1H, td, H-3) ($J_{3,5}$ 3, $J_{3,F-4}$ 9, $J_{3,F-6}$ 3, $J_{5,F-4\&F-6}$ 7,10 Hz)

N-CYANOMETHYL-4,6-DIFLUORO-2-NITROANILINE (**468**)

The same procedure was used as for the cyanomethylation of 4-fluoro-2-nitroaniline[1]. The aniline (**467**) (2.61 g, 0.015 mol), paraformaldehyde (1.35 g, 0.045 mol), zinc chloride (15.54 g, 0.114 mol), and potassium cyanide (2.93 g, 0.045 mol) were combined and concetrated sulfuric acid (2 drops) in acetic acid (40 ml) was added. After the mixture was heated at 50°C for 6 h and was stirred at room temperature overnight, an aliquot was taken and added to ice-water. An i.r spectrum of the precipitate indicated the reaction was complete. The rest of the solution was poured on to ice-water and the product (**468**) was filtered off, yield 2.88 g (90%), m.p. 121-122°C (from methanol), (Found: C, 44.9; H, 2.2; N, 19.6. $C_8H_5F_2N_3O_2$ requires C, 45.1; H, 2.4; N, 19.7%); δ_H (d_6-acetone) 4.65 (2H, dd, CH_2), 7.68 (1H, symm. m*, H-3), 7.75 (1H, br s, NH)^, and 7.93 (1H, M, H-5) ($J_{5,NH}$ 0.4, $J_{CH2,NH}$ 7.2, $J_{CH2,F-6}$ 4, $J_{3,5}$ 3.2 Hz); δ_F -119.6 (F-6), -122.0 (F-4) ($J_{F,F}$ 2.0, $J_{5,F-4}$ 9.0, $J_{5,F-6}$ 2.0, $J_{3,F-4}$ 8.0, $J_{3,F-6}$ 13.4 Hz).

* See Figures **E.5**, **E.6** (pp.168, 169) for the ^1H and ^{19}F n.m.r. spectra.
^underneath the aromatic signals

N-(4,6-DIFLUORO-2-NITROPHENYL)GLYCINE (**469**)

The procedure was taken from that used on *N*-cyanomethyl-4-methyl-2-nitroaniline[2]. The nitrile (**468**) (4.10 g, 0.019 mol), 50% (v/v) sulfuric acid (220 ml) and acetic acid (90 ml) were combined and heated at 100°C for 2.5 h. The solution was

added to ice and the bright orange precipitate was collected, yield 3.10 g (70%), m.p. 156-158°C (from ethanol); (Found: C, 41.2; H, 2.3; N, 11.9. $C_8H_6F_2N_2O_4$ requires C, 41.4; H, 2.6; N, 12.1%); υ_{max} 3390w (NH), 1710br cm^{-1} (CO); δ_H (d_6-acetone) 4.45 (2H, d, CH_2), 7.55 (1H, symm. m*, H-5), and 7.87 (1H, symm. m*, H-3) ($J_{NH,CH2}$ 5, $J_{3,5}$ 3.2, $J_{3,F-4}$ 9.2, $J_{3,F-6}$ 2.0, $J_{5,F-4}$ 8.0, $J_{5,F-6}$ 14.0 Hz).

* The multiplets were of the same pattern as those in the spectrum of the ester (see Figure **E.7**, p.170) except there was no small coupling between NH and H-5.

N-(4,6-DIFLUORO-2-NITROPHENYL)GLYCINE METHYL ESTER (**464**)

The acid (**469**) (2.70 g, 0.012 mol) was dissolved in methanol (65 ml) and gaseous hydrogen chloride (1.10 g, 0.03 mol) was bubbled in. The solution was heated under reflux for 3.5 h and poured on to ice. The ester (**464**) was collected as a light orange precipitate, 2.52 g (88%), m.p. 73.5°C (from methanol); (Found: C, 44.0; H, 3.1; N, 11.4. $C_9H_8F_2N_2O_4$ requires C, 43.9; H, 3.3; N, 11.4%); δ_H (d_6-acetone) 3.80 (3H, s, OMe), 4.45 (2H, dd, CH_2), 7.50 (1H, symm. m*, H-5), 7.85 (1H, symm. m*, H-3), and 8.00 (1H, br s, NH) ($J_{CH2,NH}$ 6, $J_{5,NH}$ 0.6, $J_{3,5}$ 3.2 Hz); δ_F -121.1 (m, F-6), -124.9 (m, F-4) ($J_{NH,F-6}$ 2.3, $J_{F,F}$ 1, $J_{3,F-4}$ 9.4, $J_{3,F-6}$ 2, $J_{5,F-4}$ 8.0, $J_{5,F-6}$ 14 Hz).

*The ^1H and ^{19}F n.m.r. spectra were simulated, see Figures **E.7-E.10** (pp. 170-173) for all of the experimental and simulated spectra.

REACTION OF THE ESTER (**464**) WITH BASES

a.) Triethylamine and potassium carbonate (in the same reaction)

The ester was expected to be as reactive as the other trisubstiuted glycine esters (**455**, **461**). Accordingly, the reaction conditions at first were very mild. The ester (1.97 g, 0.008 mol) was dissolved in toluene (50 ml) to which triethylamine (0.81 g, 0.008 mol) was added. After stirring at room temperature for 2.5 h and at 50°C for 2 h, t.l.c. indicated that reaction had not yet taken place. Even after 4.5 h at reflux temperature, t.l.c. showed that the ester was still mostly unreacted. Potassium carbonate

(1.11 g, 0.008 mol) was added to the solution, the reflux was continued for 2 h, and the solution was stirred overnight at room temperature. The solution was filtered and the solid collected washed with methylene chloride. The filtrate was evaporated to an oily orange film containing unreacted ester (**464**) (^{1}H n.m.r., m.s.). The solid was treated with hot water and filtered. The filtrate was acidified (5M HCl) and a light brown precipitate was collected and recrystallized from water with hot filtration. A greyish solid was collected; υ_{max} 1740br cm^{-1} (CO). A light coloured precipitate appeared in the filtrate and was filtered off; υ_{max} 1735br cm^{-1} (CO); δ_H 3.95 s, 5.50 br s, 6.95-7.45m, 8.52 s; m/z 154 [(M (**470a**)-16)$^+$, 100%)*, 127, etc; m/z (two mass spectra were recorded at different temperatures) 212* (M(**470b**)-16)$^+$, 180, 154 (100%), etc. The mass spectrum and the shifts of the two singlets suggested the precipitate was a mixture of 5,7-difluoro-1*H*-benzimidazole 3-oxide (**470a**) and its methyl 2-carboxylate ester (**470b**). The assignments were confirmed by comparison of the ^{1}H n.m.r. to that of another mixture of (**470a, 470b**) for which a ^{13}C n.m.r. was obtained.

The filtrate was acidified and the precipitate was collected (work-up of the filtrate is described below) and recrystallized from water with hot filtration. A powdery solid was collected from the filtrate and recrystallized from water; m.p.159-162°C (with dec. at 157°C); υ_{max} 2900-2000 (OH), 1740br cm^{-1} (CO); m/z 154*, 134, 127, 125, etc. Microanalysis for this sample did not match the values calculated for any of the possible products including the corresponding quinoxaline-2,3-dione, the benzimidazol-2-one, the benzimidazole *N*-oxide (**470a**) or either of its possible 2-substituted derivatives (the carboxylic acid or the ester (**470b**)).

The filtrate was saturated with sodium chloride and extracted with ethyl acetate to give a thin powdery film; υ_{max} (d_6-DMSO) 1730w (CO); δ_H 4.00 s, 7.05 (1H, t d, H-6), 7.25 (1H, dd, H-4), 7.35 dd, 8.45 (1H, s, H-2), 12.25 br s. The ^{1}H and ^{13}C n.m.r. spectra indicated that the 2-unsubstituted *N*-oxide (**470a**) was the major component; the major resonances match those for the pure sample of (**470a**) isolated from the next

* The mass spectra of benzimidazole *N*-oxides typically have an intense M$^+$-16 peak[68].

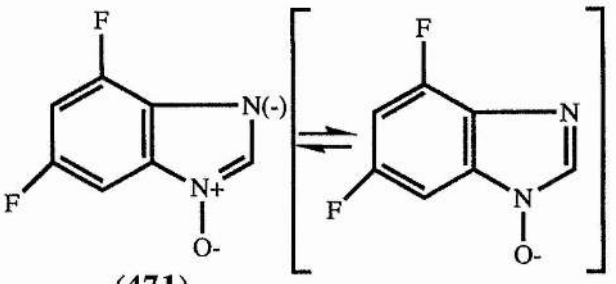
reaction. Also present was a very small amount of another compound which is believed to be the corresponding methyl benzimidazole-2-carboxylate (**470b**). The signals at 4.00 δ and 7.35 δ, along with a multiplet that is almost completely hidden by the H-4 signal of (**470a**), are consistent with this identification. In the ^{13}C n.m.r. spectrum, the main set of signals corresponds well to those found in the spectrum of the 2-unsubstituted benzimidazole *N*-oxide (**470a**) (see Table **T.2**, p.158). Of the minor set, only three resonances (Me, C-4, and C-6) were large enough for their shifts to be detected by the computer. These are also included in the table. The rest of the peaks were visible though very small, including a possible carbonyl peak at ~158 ppm which corresponds well with that for another such derivative (see Table **T.2**, p.158).

b.) With potassium carbonate

The ester (**464**) (0.40 g, 0.0016 mol) was added to a solution of potassium carbonate (0.22 g, 0.0016 mol) in methanol (15 ml). The mixture was stirred at room temperature for 18 h and heated under reflux for 5 h. The white precipitate was filtered off, dissolved in water and acidified. The precipitate was collected by filtration and treated with hot water. The insoluble cream-coloured solid was wasshed with hot water and vacuum dried to give 5,7-1*H*-difluorobenzimidazole 3-oxide (**470a**); 0.23 g (85%), m.p. 192°C dec.; υ_{max} 3660w (NH), 1700br cm^{-1}; δ_H 6.94 (1H, t d, H-6), 7.03 (1H, dd, H-4), 8.28 (1H, s, H-2) ($J_{4,6}$ 2, $J_{4,F-5}$ 8, $J_{6,F-5}=J_{6,F-7}=11$ Hz, $J_{4,F-7}$ could not be measured). See Table **T.2** (p.158) for the ^{13}C data.

The *N*-oxide first isolated appears to be a salt because of its solubility in water and because the solubility disappears once it was acidified. Considering the amount of

recrystallization it took to decarboxylate the 5-trifluoromethylbenzimidazole-2-carboxylic acid 3-oxide thought to have been isolated, it seems unlikely that the salt was this derivative of (**470a**). Instead it is possible that the anion was in fact (**471**), which has literature precedent[69].



(**471**)

SECTION 4.3

N-(2,6-DINITROPHENYL)SARCOSINE ETHYL ESTER (**473**)

1-Chloro-2,6-dinitrobenzene (4.37 g, 0.022 mol), sarcosine ethyl ester hydrochloride (4.61 g, 0.03 mol) and potassium carbonate (8.29 g, 0.06 mol) were combined in HPLC grade acetonitrile (100 ml) and heated at 70-90°C for 1.3 h. Heating was continued for another 1.3 h after more of the ester (2.15 g, 0.014 mol) and the base (4.15 g, 0.03 mol) were added. The solution was filtered, and the solvent evaporated. The dark oily residue solidified when treated with a little ether and chilled. The solid was filtered off and washed with cold ethanol to give a dirty yellow solid. A second crop was obtained from the washings to give a total of 4.31 g (69%) of the ester (**473**), m.p. 77°C (from ethanol) (Found C, 46.7; H, 4.4; N, 14.9. $C_{11}H_{13}N_3O_6$ requires C, 46.7; H, 4.6; N, 14.8%); δ_H (300 MHz; d_6-acetone) 1.25 (3H, t, CH_2CH_3), 2.92 (3H, s, N-Me), 3.80 (2H, s, CH_2), 4.15 (2H, q, CH_2CH_3), 7.60 (1H, t, H-4), and 8.10 (2H, d, H-3 & H-5) (J_{CH2CH3} 7, $J_{4,(3,5)}$ 8 Hz).

REACTION OF THE ESTER (**473**) WITH POTASSIUM CARBONATE

Potassium carbonate (0.69 g, 0.005 mol) was added portionwise over 1 h to a solution of the ester (**473**) (1.42 g, 0.005 mol) in ethanol (50 ml) and stirred at room temperature for a further 3.5 h. The reaction solution was filtered. The solid collected was washed thoroughly with water. Only a black film was left insoluble which could not be identified. The washings were acidified slowly with 5M hydrochloric acid until cloudiness persisted and cooled (4°C) for 48 h. The light coloured precipitate was collected (0.23 g, 19%) and washed with two small portions of acetone. Both the insoluble solid and the solid from evaporation of the acetone washings were identified as 1-hydroxy-4-methyl-5-nitro-quinoxaline-2,3-dione hemihydrochloride (**474**), m.p. 160°C dec. (from water) (Found C, 42.3; H, 2.95; N, 16.5. $C_9H_7N_3O_5 \cdot 0.5$ HCl requires C, 42.3; H, 3.0; N, 16.45%); υ_{max} 3190, 3200-3600 (OH), 1665, 1690br cm^{-1} (CO); δ_H 3.25 (3H, s, N-CH_3), 7.45 (1H, t, H-7), 7.70 (1H, dd, H-8), and 7.84 (1H, dd, H-6) ($J_{6,7}$=$J_{7,8}$ 8, $J_{6,8}$ 2 Hz); m/z 237 (M^+), 221 (M-16), 209, 204, 193, 176, etc. See Table **T.3** (p. 159) for the ^{13}C n.m.r. data.

The mother liquor was evaporated and the residue partitioned between methylene chloride and water. The aqueous solution was acidified with 5M hydrochloric acid; no precipitate appeared. Further work-up proved to be worthless. The methylene chloride solution was extracted with 5M hydrochloric acid then with 3M sodium hydroxide. The surviving methylene chloride solution was dried (Na_2SO_4), evaporated and the residue identified as unreacted starting material (**473**). The basic extracts were acidified and a brown precipitate was filtered off which spectral evidence indicated to be 1-methyl-7-nitro-benzimidazol-2-one (**475**); υ_{max} 1700br cm^{-1} (CO); δ_H * 7.27-7.84 (2H, m (t & dd), H-4 & H-5)^, 7.75 (1H, dd, H-6), and 11.80 (1H, br s, NH) ($J_{4,5}$=$J_{5,6}$=8, $J_{4,6}$ 2 Hz); m/z 193 (M^+), 191(6%), 176 (M-17), 164, 163, 159, etc. See Table **T.4** (p. 160) for the ^{13}C n.m.r. data.

The filtrate containing the acidified extracts was extracted with methylene chloride. The organic extracts were dried (Na_2SO_4) and evaporated. The ^1H and ^{13}C n.m.r. spectra of the residue indicated a small amount of (**475**) was present but the main component contained similar spectral characteristics to the quinoxalin-2-ones isolated in the project. The mass spectrum did contain the molecular ion for a nitro derivative. The sample contained one isomer which by comparison to the other quinoxalin-2-one spectra was identified as 8-nitroquinoxalin-2-one (**476**); υ_{max} (in d_6-DMSO) 1600-1750br cm^{-1} ($CO+H_2O$); δ_H 7.63 (1H, t, H-6), 8.35 (1H, dd, H-5) 8.50, 8.55 (2H, s & dd, H-2 & H-7 (resp))**, and 11.75 (1H, br s, NH) ($J_{5,6}$=$J_{6,7}$= 8 $J_{5,7}$ 2 Hz); (two mass spectra were taken at different temperatures) m/z 191 (M^+ (**476**), 60%), 117 (100%); m/z 264, 256, 243, 236, 193 (M^+ (**475**),43%), 191 (M^+ (**476**), 15), 185, 176, 171, 164, 163, etc. See Table **T.5** (p. 161) for ^{13} C n.m.r. data for (**476**).

* large water resonance at 3.4 δ was thought to obscure the N-Me signal; a small singlet at 8.53 δ and several small multiplets at 8.34, 8.45, and 8.64 δ indicated the presence of the quinoxalin-2-one (**476**)

^ see Figure **E.11** (p. 174) for an expansion of the aromatic region

** the higher field doublet is obscured by the H-2 singlet

N-(2,6-DINITRO-4-TRIFLUOROMETHYLPHENYL)SARCOSINE ETHYL ESTER (**477a**)

Sodium hydrogen carbonate (4.62 g, 0.055 mol) was added to 4-fluoro-3,5-dinitrobenzotrifluoride (5.08g, 0.02 mol) and sarcosine ethyl ester hydrochloride (3.69 g, 0.024 mol) in dry tetrahydrofuran (100 ml). Both the base and the ester were dried (Na_2SO_4) in a vacuum desiccator for 48 h. The mixture was heated under reflux for 30 minutes. The solution was filtered and the filtrate evaporated. The residue was treated with ethanol (~15 ml) and poured on to ice. An orange and yellow precipitate (6.68 g) was collected. T.l.c. of the solid showed two mobile spots and one spot unmoved besides the main product spot. The sample was chromatographed (silica gel in methylene chloride) but the combined fractions of the main band still showed several mobile components. A second column in petrol with elution by an increasing ratio of ether to petrol still did not separate the desired ester from impurities (the possibility that the compound was reacting on the column was not ruled out). The main fractions were evaporated to give the slightly impure ester (**477a**) as a light orange solid; m.p. 41-43°C; δ_H ($CDCl_3$) 1.30 (3H, t, CH_2CH_3), 3.03 (3H, s, N-Me), 3.85 (2H, s, N-CH_2), 4.28 (2H, q, CH_2 CH_3), 8.27 (2H, s, H-3 & H-5) ($J_{CH2,CH3}$ 7 Hz); δ_C 14.10 (CH_2CH_3), 41.51 (N-CH_2), 56.57 (N-Me), 61.61 (CH_2 CH_3), 122.06 (q, J_F 272, CF_3), 124.85 (q, J_F 36, C-4), 168.21 (CO), 141.60 (C-1), 146.94 (C-2 & C-6), 126.26 (*, J_F 3, C-3 & C-5).

* poorly resolved quartet, only the two middle lines were visible

REACTION OF (**477a**) WITH BASE

a.) Triethylamine (1 mol. eq.)

Triethylamine (0.51 g, 0.005 mol) was added to the ester (**477a**) (1.75 g, 0.005 mol) in of toluene (25 ml) and the mixture stirred at room temperature for 22 h. The solution was evaporated under vacuum and the residue taken up in methylene chloride. Extraction with water and acidification of the extracts did not induce precipitation. The aqueous solution was saturated with sodium chloride, extracted wtih ethyl acetate and the extracts dried (Na_2SO_4) and evaporated. The resulting film was washed with a little

methylene chloride and the insoluble part gave a mass spectrum with the molecular ion for 1-hydroxy-4-methyl-5-nitro-7-trifluoromethylquinoxaline-2,3-dione (**478a**); m/z 305 (M^+, 18%), 289, 287, 278, 277,..., 186 (100), etc.

The original methylene chloride solution gave three spots on t.l.c., two mobile and one unmoved. Very small samples of each component were obtained by preparative t.l.c.. The fraction with the smallest R_f gave a mass spectrum with the molecular ion for 2,6-dinitro-4-trifluoromethylphenol; m/z 252 (M^+, 32%), 233, 231, 194, 189, 185, etc. The one with the next highest R_f was starting material and the sample of the component that was unmoved were too weak to be analyzed. (The phenol was assumed to be an impurity in the starting material.)

b.) Triethylamine (2 mol. eq.)

The ester (**477a**) (1.75 g, 0.005 mol) and triethylamine (1.01 g, 0.01 mol) were stirred together at room temperature in toluene (25 ml) for 6.5 h. The solution was evaporated, taken up in methylene chloride and extracted with water. The extracts were acidified and, since no precipitate appeared, extracted with methylene chloride. The organic extracts were dried (Na_2SO_4) and evaporated. The residue was treated with chloroform and the insoluble portion used to make up an n.m.r. sample. The ^1H and ^{13}C n.m.r. spectra were similar to those for the other derivatives of the 1-hydroxy-quinoxaline-2,3-diones. Thus this sample was identified as the 1-hydroxyquinoxaline-2,3-dione (**478a**) δ_H 3.30 (3H, s, N-CH_3), 8.08 (1H, d, H-8), and 8.28 (1H, d, H-6) ($J_{6,8}$ 2 Hz); m/z 305 (M^+), 289, 286, 278, 261, 250, etc. See Table **T.3** (p.159) for the ^{13}C n.m.r. data.

The aqueous solution was saturated with sodium chloride and extracted with ethyl acetate to give another sample of (**478a**) (^1H n.m.r., m.s.). The original methylene chloride solution was extracted with 5M hydrochloric acid. Saturation of the extracts with sodium chloride, extraction with ethyl acetate and drying and evaporation of the extracts gave a film which appeared to contain mostly 2,6-dinitro-4-trifluoromethyl-phenol; δ_H (60 MHz; d_6-acetone) 8.7 s; m/z 278 (M (**277a**)-$CO_2Et)^+$, 252 (M^+, 62%), 233, 222, 205, 194, etc.

The methylene chloride solution was extracted with saturated sodium hydrogen carbonate solution. The organic solution was evaporated to an oil, treated with several portions of petrol and the liquid decanted. The ^1H n.m.r. identified the liquid as some unreacted ester (**477a**). The insoluble oil gave the following; m/z 332 [(M (**477a**)-F)$^+$, 4%], 278 [M (**477a**)-$CO_2Et)^+$, 100], 262, 248, 232, etc. The basic extracts were acidified and extracted with methylene chloride. T.l.c. showed only a spot unmoved by the eluant; δ_H (60 MHz; d_6-acetone) 7.60-7.80 m, and 7.80-8.35 m; m/z 261 (28%), 232 (40), 216, 215, 201, 187 (100), etc. M/z 261 is the molecular ion for the corresponding *N*-methylbenzimidazol-2-one but there did not appear to be an *N*-methyl resonance intense enough in the ^1H n.m.r. spectrum to correspond to the aromatic signals.

ATTEMPTED SYNTHESIS OF *N*-(2,4-DINITRO-6-TRIFLUOROMETHYL-PHENYL)SARCOSINE ETHYL ESTER (**477b**)

Sarcosine ethyl ester hydrochloride (6.91 g, 0.045 mol) and triethylamine (4.55 g, 0.045 mol) in dry toluene (10 ml) were stirred at room temperature for 30 minutes. The mixture was added to 2-chloro-3,5-dinitrobenzotrifluoride (4.1 g, 0.015 mol) in dry toluene (30 ml). The method was adapted from the reactions of the benzotrifluoride with dialkylamines[81]. The mixture was heated at 90-110°C for just over 5 h. The solution was filtered and the filtrate was treated with methylene chloride and extracted with water. T.l.c. of the organic solution showed it contained a complex mixture of components. The largest spot had an R_f similar to that for (**477a**), isomeric with the desired ester (**477b**). Half of the solution was applied to a silica gel column in methylene chloride. Fractions of the least polar component were combined and evaporated to give what could be 2,4-dinitro-6-trifluoromethylphenol, giving; δ_H ($CDCl_3$) 2.38 s, 7.33 s (ratio 1:2).

The main component, the ester (**477b**), was collected, evaporated and crystallized by cooling in liquid N_2 then an ice-salt bath, yield 1.10 g (21%), m.p. 31-33°C; δ_H (d_6-acetone) 1.25 (3H, t, CH_2*Me*), 3.05 (3H, s, N-CH_3), 3.92 (2H, s, N-CH_2), 4.20 (2H, q, *CH_2* CH_3), 8.87 (1H, d, H-5), and 9.02 (1H, d, H-3) ($J_{CH2,CH3}$ 7, $J_{3,5}$ 3 Hz).

The aqueous extracts were combined and acidified dropwise with 5M hydrochloric acid and extracted with methylene chloride. The extracts were dried (Na_2SO_4) and evaporated. The residue was treated with a little methylene chloride. Both the solution and the insoluble solid gave mass spectra with the molecular ion for 1-hydroxy-4-methyl-7-nitro-5-trifluoromethylquinoxaline-2,3-dione (**478b**); m/z 305 (M^+, 18%), 289, 277, 261, 260, etc. (There was not enough to make up an n.m.r. sample.)

SYNTHESES OF *N*-(6-CHLORO-2-NITRO-4-TRIFLUOROMETHYLPHENYL)-SARCOSINE ETHYL ESTER (**480b**)

a.) Using method D (see experimental section **4.2**)

Triethylamine (2.33 g, 0.02 mol) was added to a warm (50°C) solution of 3-chloro-4-fluoro-5-nitrobenzotrifluoride (**479**) (2.43 g, 0.01 mol) in toluene (35 ml). Sarcosine ethyl ester hydrochloride (1.69 g, 0.011 mol) was added portionwise over 1.5 h while the temperature was increased to 70°C. Heating was continued for another 5 h during which time more of the ester (1.08 g, 0.007 mol) and the base (1.01 g, 0.01 mol) were added. The solution was filtered and the filtrate reduced *in vacuo* to an oil. Dissolution in ether and extraction with 1M hydrochloric acid then drying (Na_2SO_4) and evaporation of the ether layer gave an orange oil. T.l.c. showed the presence of several minor, more polar components other than the ester (**480b**). The oil was treated with a small amount of methylene chloride and was chromatographed (silica gel in petrol (b.p. 40/60°C). The first band was collected and evaporated to give the ester (**480b**) as an oil (all attempts to crystallize the oil failed), yield 0.69 g (20%), b.p. 150°C (Kugelrohr, ~1 mm Hg); δ_H (300 MHz; $CDCl_3$) 1.30 (3H, t, CH_2CH_3), 2.98 (3H, s, N-Me), 3.83 (2H, s, N-CH_2), 4.22 (2H, q, CH_2CH_3), 7.80-7.85 (1H, m, H-5), and 7.85-7.90 (1H, m, H-3) ($J_{CH2,CH3}$ 7 Hz; $J_{3,5}$ could not be measured; at lower frequencies the aromatic signals appear as a singlet.)

b.) Using method E

Sarcosine ethyl ester hydrochloride (0.46 g, 0.003 mol) was added to a mixture of the benzotrifluoride (**479**) (0.38 g, 0.003 mol) and barium hydroxide (1.90 g, 0.006 mol) in dry tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 70 h. Filtering the solution was a problem because the base made a fine suspension. Filtering through celite did not help so a column of silica gel in petrol was used instead. Elution with an increasing ratio of ether to petrol gave the pure ester (**480b**), 0.34 g (33%) (t.l.c., ^{1}H n.m.r). The polar component was the acid derivative (**480c**) (^{1}H n.m.r.).

c.) Using potassium carbonate in tetrahydrofuran

Potassium carbonate (0.91 g, 0.0066 mol) was dried (Na_2SO_4) at 100°C for 5 h and added to a mixture of the benzotrifluoride (**479**) (0.38 g, 0.003 mol) and sarcosine ethyl ester hydrochloride (0.51 g, 0.0033 mol) in dry tetrahydrofuran (10 ml). The apparatus was fitted with a drying tube and the solution was stirred at room temperature for 24 h. More of the ester (0.09 g, 0.0006 mol) and the base (0.17 g, 0.0012 mol) were added and stirring continued for another 5 h. The solution was filtered and the solvent evaporated off *in vacuo*. T.l.c. of the residue indicated that it was mostly the ester with a small amount of another polar component. Treatment with ether and extraction with 5M hydrochloric acid then with 3 M sodium hydroxide gave an organic solution which when dried (Na_2SO_4) and evaporated gave the ester (**480b**) as an oil, 0.57 g (56%) (^{1}H n.m.r.). Acidification of the basic extracts, exctraction with ether and drying (Na_2SO_4) and evaporation of the ethereal extracts gave an oily film which crystallized to give the acid (**480c**); δ_H ($CDCl_3$) 2.97 (3H, s, N-Me), 3.93 (2H, s, CH_2), 7.99 (2H, s, H-3 & H-5), and 9.85 (1H, br s, OH).

N-(6-CHLORO-2-NITRO-4-TRIFLUOROMETHYLPHENYL)SARCOSINE (**480c**)

Barium hydroxide (3.15 g, 0.01 mol) was added to 3-chloro-4-fluoro-5-nitro-benzotrifluoride (4.87 g, 0.02 mol) and sarcosine (1.96 g, 0.022 mol) in tetrahydrofuran (45 ml) and the mixture stirred at room temperature. Two more additions of the base (2 x

0.005 mol) were made after 6 h and 14 h. After 18.5 h the solution was allowed to settle, the liquid was decanted and the tetrahydrofuran removed under vacuum. The residue was taken up in methylene chloride and extracted with saturated sodium hydrogen carbonate solution. The extracts were acidified and extracted with methylene chloride. The dried (Na_2SO_4) extracts were evaporated to an oil that crystallized into yellow blooms. Recrystallization twice from methanol gave the acid (**480c**) 4.60 g (74%); m.p.122-123°C (Found C, 38.7; H, 2.5; N, 9.0. $C_{10}H_8ClF_3N_2O_4$ requires C, 38.4; H, 2.6; N, 9.0%); δ_H ($CDCl_3$) 3.00 (3H, s, N-Me), 3.97 (2H, s, CH_2), and 8.00 (~3H, sl br s, H-3 & H-5, OH).

N-(6-CHLORO-2-NITRO-4-TRIFLUOROMETHYLPHENYL)SARCOSINE METHYL ESTER (**480a**)

The acid (**480c**) (8.60 g, 0.028 mol) and gaseous hydrogen chloride (3.00 g, 0.06 mol) in methanol (200 ml) were heated under reflux for 5 h. The solvent was evaporated under reduced pressure. The residue was taken up in methylene chloride and extracted with saturated sodium hydrogen carbonate solution. The methylene chloride solution was dried (Na_2SO_4) and evaporated to give the ester (**480a**) as an oil; the yield was near quantitative; b.p. 150°C (Kugelrohr ~1mm Hg); δ_H ($CDCl_3$) 3.00 (3H, s, N-CH_3), 3.82 (3H, s, OCH_3), 3.92 (2H, s, CH_2), 8.00 (2H, s, H-3 & H-5).

REACTIONS OF THE ESTERS (**480a,b**) WITH BASES

a.) With triethylamine

The ester (**480a**; R=Me) (3.27 g, 0.01 mol) was added to a solution of triethylamine (2.02 g, 0.02 mol) in toluene (60 ml). The solution was heated at approximately 100°C for 18 h, and at reflux temperature for 53 h. Additions of more base were made because reaction proceeded slowly even at the elevated temperatures. It was intended to allow the reaction to go to completion, but it was stopped when t.l.c. showed that very little of the ester (**480a**) was left and many other components were present. An extensive work-up did not succeed in separating the components; a few

solids were obtained but they contained complex mixtures. One ^{19}F n.m.r. spectrum had 10 signals and a ^{13}C n.m.r. spectrum had no less than 42 signals.

b.) With potassium carbonate

The ester (**480b**) (2.42 g, 0.007 mol) and potassium carbonate (1.00 g, 0.007 mol) were heated under reflux in ethanol (35 ml) for 5 h. An extensive work-up was performed but none of the components could be identified; the conditions were apparently too harsh. Even when the reaction time was reduced to 2 h, still only complex mixtures were isolated the components of which could not be identified.

c.) With barium hydroxide

The ester (**480b**) (2.04 g, 0.006 mol) and barium hydroxide (2.52 g, 0.008 mol) in tetrahydrofuran (30 ml) were stirred at room temperature for 24.5 h. The solution was decanted and the solvent evaporated at reduced pressure. The residue was treated with methanol and water and filtered. The solid collected was taken up in ether and extracted with 5M hydrochloric acid and 3M sodium hydroxide. The latter extracts were filtered and a pale orange precipitate was collected which was thought to be 7-chloro-1-methyl-5-trifluoromethyl-3*H*-benzimidazol-2-one (**481**). The ^{1}H and ^{13}C n.m.r. and i.r. spectra were similar to those for the 1*H* derivative (**453**) that was thought to have been isolated from the corresponding glycine ester (**448**). Yield 0.18 g (18%); m.p. 280°C dec.; υ_{max} 1670br (CO), 3060 cm^{-1} (NH); δ_H 3.60 (3H, s, N-Me), 7.00-7.08 (1H, m, H-4), and 7.10-7.20 (1H, m, H-6); m/z 250 (M^+, 89%), 231, 221 (89), 201, 192, 187, 185, etc. See Table **T.4** (p. 160) for the ^{13}C n.m.r. data.

The filtrate was acidified and extracted with ether. The dried (Na_2SO_4) ethereal extracts were evaporated to an oil which crystallized to give 0.33 g of the acid (**480c**). The ^{1}H n.m.r. matched that for the pure sample; m/z 312 (M^+), 267 (100%).

The ether layer was dried (Na_2SO_4) and evaporated to give 0.11g (4%) of 2,2′-diamino-3,3′-dichloro-5,5′-bis(trifluoromethyl)azoxybenzene (**454**). A small amount of the sample was sublimed. Some of the impurities condensed on the cold

finger but could not be identified; m.p. 171-175°C (after sublimation); δ_H* ($CDCl_3$) 5.22 (2H, br s, NH_2)^, 6.50 (2H, br s, NH_2')^, 7.72 (1H, d, H-4′), 7.82 (1H, dd, H-4), 8.25-8.40 (1H, m, H-6), and 9.00-9.10 (1H, m, H-6′); m/z 432 (M^+), 416,..., 224, 216, 209, 207, 196, 194 (100%), 181, 173 (100),etc.

The methanol in the methanol-water filtrate was removed under vacuum. The same work-up to that described above was performed on the solution. Impure samples of the diaminoazoxybenzene (**454**) and the acid (**480c**) were obtained.

The same results were obtained when the methyl ester (**480a**) was reacted (on the same scale) under these conditions.

* The assignments were based on a spin-spin decoupling experiment; irradiation of the 9.00-9.10 δ resonance resulted in enhancement of the 7.72 δ resonance. The CF_3 coupling was too small to be measured

^ provisional assignments

d.) With triethylamine and potassium carbonate

The ester (**480a**) (2.48 g, 0.0087 mol) and triethylamine (2.02 g, 0.02 mol) were combined in dry tetrahydrofuran (50 ml) and heated under reflux. ^1H n.m.r. spectra were used in attempts to monitor the progress of the reaction, and to determine the order of formation of the products, but no such conclusions could be made. The reaction was very slow even after more triethylamine (total 6.06 g, 0.06 mol) was added so potassium carbonate (2.76 g, 0.02 mol) was added also. The solution was heated under reflux for a total of 102 h. The solution was filtered and the filtrate evaporated. The residue was partitioned between methylene chloride and water and the layers separated. The aqueous solution was acidified dropwise with 5M hydrochloric acid. The brown precipitate was filtered off and washed with small amounts of acetone to give 0.21 g of 5-chloro-7-trifluromethylquinoxalin-2-one (**482a**) with a small amount of the 8-chloro-6-trifluoromethyl isomer (**482b**) as a buff coloured solid (The exact orientations of the components were determined by comparison of the ^1H and ^{13}C n.m.r. spectra with a synthesized sample that also contained both isomers.); m.p. 180-184°C (152°C dec.); υ_{max} 1695br (CO), 3550-3200w cm^{-1} (NH); δ_H 7.62 (1H, s, H-8), 7.78 (1H, s, H-6),

and 8.40 (1H, s, H-3); δ_F* (relative intensities in brackets after the shifts are given with respect to the smallest resonance) -53.8 (1.3), -54.4 (2.8), -54.6 (1.0), -55.1 (1.1), -55.3 (1.3), -55.5 (20.5), -57.4 (1.3); m/z 248 (M^+). See Table **T.5** (p.161) for the ^{13}C n.m.r. data for both isomers.

Work up of the methylene chloride solution gave only very complicated, uninterpretable ^1H n.m.r.s.

* The spectrum was run on the purified sample, therefore, the resonance at -55.5 was thought to arise from the CF_3 fluorines in the 5-chloro-7-trifluoromethyl isomer and probably the one at -54.4 from those in the 8-chloro-6-trifluoromethyl isomer.

3-CHLORO-5-TRIFLUOROMETHYL-*o*-PHENYLENEDIAMINE (**483**)

a.) 2-Chloro-6-nitro-4-trifluoromethylaniline (**484**)

A solution of 3-chloro-4-fluoro-5-nitrobenzotrifluoride (**479**) (2.44 g, 0.01 mol) and 33% aq. ammonia solution (d. 0.88, 10 ml) was stirred at room temperature for 30 minutes and poured on to ice. The aniline (**484**) was collected as a bright yellow solid, yield 2.3 g (95%), m.p. 80-82°C; δ_H (60MHz; $CDCl_3$) 7.00 (2H, br s, NH_2), 7.85 (1H, s, H-3), 8.50 (1H, s, H-5); m/z 240 (M^+, 85%), 221, 210, 194, , 158 (100), etc; (Found 239.9914. $C_7H_4ClF_3N_2O_2$ requires 239.9913).

b.) Reduction of the aniline (**484**)

A literature method[82] was employed. Cyclohexene (25 ml) was added to the aniline (**484**) (2.00 g, 0.0083 mol) in ethanol (100 ml). Palladium-charcoal (10%, 2.5 g) was added and the solution was heated under reflux for 1 h and 10 minutes. The solution was filtered by gravity and the filtrate evaporated. The residue was treated with a small amount of methylene chloride and 5M hydrochloric acid and filtered. The diamine (**483**) was collected as a silvery solid, yield 0.75 g (43%), m.p. 201°C dec.; δ_H (60MHz) 7.35 (4H, br s, 2xNH_2), 7.50 (2H, s, H-3 & H-5); m/z 210 (M^+), 191, 182, 175, 163, etc; (Found 210.0173. $C_7H_6ClF_3N_2O_4$ requires 210.0172).

REACTION OF THE DIAMINE (**483**) WITH ETHYL GLYOXYLATE (**439**)

The procedure was taken from that used to react *o*-phenylenediamine with compound (**439**)[83]. The diamine (**483**) (0.55 g, 0.0023 mol) in ethanol (20 ml) was cooled in an ice-wter bath for a few minutes. Ethyl glyoxylate (prepared from the acid[84]) (0.35 g, 0.0034 mol) was added. There was no vigorous reaction as described in the literature procedure[3]. The solution was heated under reflux for 30 minutes. T.l.c. indicated the reaction was very slow. Departing from the prescribed method, triethylamine was added (0.35 g, 0.0035 mol) was added. The solution fumed and immediately became red. The solution was heated at the reflux temperature for 3 h. The solution was evaporated, treated with methylene chloride and water and filtered. A cream-coloured precipitate was collected, 0.30 g (53%), and was identified as 8-chloro-6-trifluoromethylquinoxalin-2-one (**482b**) with a very small amount of the 5-chloro-7-trifluoromethyl isomer (**482a**) contaminated by some ethyl glyoxylate; m.p.189-192°C [from dissolution in 3M NaOH, acidification (5M HCl) and successive treatment with hot acid (5M HCl)], (Found C, 43.1; H, 1.2; N, 11.0. $C_9H_4ClF_3N_2O$ requires C, 43.5; H, 1.6; N, 11.3%); υ_{max} 3260br (NH), 1710s cm^{-1} (CO); δ_H (poor resolution, resonances corresponding to **482b**) 8.20 (2H, sl br s, H-5 & H-7), 8.50 (1H, sl. br s, H-3); (**482a**) 7.6-7.9, two overlapping multiplets, the H-3 resonance is presumably incorporated with the one at 8.50 δ from (**482b**) that has a broad base; m/z 248 (M^+, 49%), 229 (14), 220 (100), 201, 192, 185, 170, etc. The ^1H n.m.r. data and the fragmentation pattern in the mass spectrum match those for the sample obtained from the sarcosine ester (**480b**) reaction. See Table **E.5** (p. 161) for the ^{13}C n.m.r. data for both isomers.

TABLES OF ^{13}C N.M.R. DATA

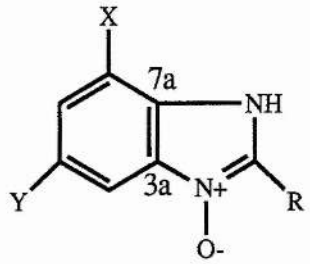


Table **T.2**: ^{13}C N.m.r. spectra for 5- and/or 7-substituted 1*H*-benzimidazole 3-oxides[a]

Compd. No.	R	X	Y	2	R	3a	4	5	6	7	7a	CF_3
(408)	H	H	CF_3	142.59	—	130.88[b]	106.84 ([c], 4)	123.00 (q, 32)	118.21 ([c], 3)	120.80	141.42[b]	124.88 (q, 271)
(418)	H	H	F	140.88	—	131.65 (d, 14)	95.58 (d, 28)	159.09 (d, 238)	110.04 (d, 25)	120.87 (d, 10)	135.60	—
(451)	H	Cl	CF_3	143.12	—	132.05	106.28 ([c], 4)	124.00 (q, 33)	117.68 ([c], 3)	124.80	138.12	124.01 (q, 272)
(457)[d]	CO_2Me	NO_2	CF_3	142.61	53.23 (Me) 157.47 (CO)	125.06	114.85 ([c], 4)	~123[e]	116.78 ([c], 3)	135.10	131.68	~123[e]
(470a)[d,f]	H	F	F	141.10	—	133.82 (dd) (16, 11)	92.04 (dd) (28, 4)	158.02 (dd) (11,239)	96.70 (dd) (30,22)	152.69 (dd) (15,254)	124.46 (d) (18)[g]	—

[a] multiplicities and coupling constants (in Hz) are given below the shifts [b] provisional assignments [c] poorly resolved quartets, only the two middle lines were visible [d] CH, CH_3 assignments were confirmed by DEPT [e] isolated as a mixture with the corresponding quinoxaline-2,3-dione (**456a**), the quartets arising from the two compounds overlapped preventing these shifts from being assigned [f] for all shifts couplings are given in the order (F-5, F-7) [g] carbon coupled only to F-7

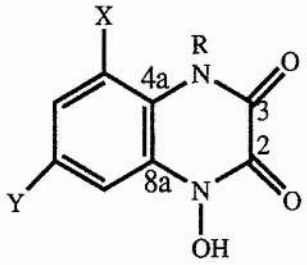


Table **T.3**: ^{13}C N.m.r. spectra for the 5- and/or 7-substituted 1-hydroxyquinoxaline-2,3-diones[a]

Compd. No.	R	X	Y	2	3	4 (R)	4a	5	6	7	8	8a	CF_3
(452)	H	Cl	CF_3	154.89	151.00	—	129.23	119.34	120.81 (b, 4)	123.83 (q, 33)	108.32 (b, 3)	124.41	123.29 (q, 272)
(456a)	H	NO_2	CF_3	154.22	150.55	—	122.44	134.80	117.00 (b, 3)	122.94 (q, 35)	114.07 (b, 4)	130.89	122.98 (q, 272)
(456b)	H	CF_3	NO_2	155.05	151.09	—	130.49[c]	116.42 (q, 33)	117.54 (b, 6)	143.31	112.93	127.45[c]	123.60 (q, 272)
(474)[d]	Me	NO_2	H	156.17	149.82	34.53	119.73	139.15	120.21	123.61	116.77	130.10	—
(427)	Me	H	F	154.46	150.33	30.20	121.99	116.64 (d, 9)	110.47 (d, 23)	158.45 (d, 240)	99.92 (d, 29)	128.63 (d, 11)	—
(412)[d]	Me	H	CF_3	155.11	150.17	30.19	128.50	115.83	120.65 (b, 3)	123.96 (q, 33)	109.39 (b, 4)	127.94	124.01 (q, 272)
(478a)[d]	Me	NO_2	CF_3	156.09	149.67	34.19	123.05	138.92	117.02 (b, 4)	123.41 (q, 34)	112.28 (b, 3)	131.26	122.81 (q, 272)

[a] multiplicities and coupling constants (in Hz) are given below the shifts [b] poorly resolved quartets, only the two center lines were visible [c] resonance for C-4a should be split by CF_3 but no other multiplet was present, therefore these assignments are only provisional [d] CH assignments were confirmed by DEPT

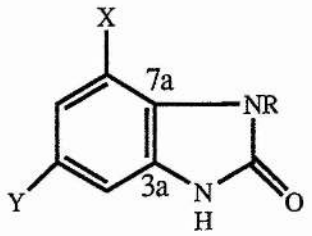


Table **T.4**: ^{13}C N.m.r. spectra for the 5- and/or 7-substituted benzimidazol-2-ones[a]

Compd. No.	R	X	Y	1(R)	2	3a	4	5	6	7	7a	CF_3
(423)	Me	H	F	26.42	154.70	128.88 (d, 13)	96.62 (d, 29)	157.78 (d, 234)	106.49 (d, 24)	107.80 (d, 10)	127.44	___
(453)	H	Cl	CF_3	___	151.69	117.94	101.68 ([b], 3)	123.34 ([c], 32)	117.85 ([b], 5)	113.84	130.63	123.97 ([c], 272)
(481)	Me	Cl	CF_3	28.88	152.02	123.68	100.67 ([b], 4)	121.21 ([c], 32)	115.99[c]	112.44	132.07	124.05 (q, 272)
(475)	Me	NO_2	H	29.99	154.57	124.41	116.69	113.64	120.67	133.30	131.31	___

[a] multiplicities and coupling constants (in Hz) are given below the shifts [b] poorly resolved quartets, only the two center lines visible [c] some resonances of the quartets were missing or were too small to be computed [d] the peak had the same intensity as the signals for C-4 but registered only as a singlet

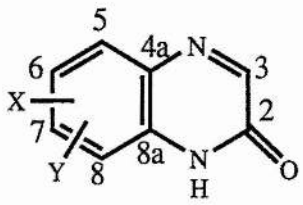


Table **T.5**: ^{13}C N.m.r. spectra for quinoxalin-2-one and its derivatives[a]

Compd. No.	X	Y	2	3	4a	5	6	7	8	8a	CF_3
(443)	H	H	154.80	151.50	131.80[b]	130.61	123.12	128.69	115.64	132.01[b]	—
(425)	6-F	H	154.84	153.18	132.49 (d, 12)	118.86 (d, 24)	157.94 (d, 240)	114.04 (d, 22)	117.33 (d, 9)	128.93	—
(426)[c]	7-F	H	153.18 ?			131.34 (d, 11)	111.30 (d, 23)		101.74 (d, 27)		
(476)	8-NO_2	H	153.82	152.47[d]	129.85	135.90	122.56	127.22	133.32	127.42	—
(482a)[e]	5-Cl	7-CF_3	154.44	154.91	133.97[b]	130.42	119.57 (f, 3)	130.52 (q, 33)	112.23 (f, 4)	134.06[b]	122.84 (q, 273)
(482b)[e]	8-Cl	6-CF_3	155.49	153.55	132.81[b]	125.08[b] (f, 3)	123.97 (q, 34)	126.66[b] (f, 3)	120.74	133.03[b]	123.26 (q, 272)

[a] multiplicities and coupling constants (in Hz) are given below shifts, all CH resonances were confirmed by DEPT [b] provisional assignments [c] a minor component in the sample of (**425**), only some of the more intense resonances were visible [d] broad resonance [e] both spectra contained several of the larger resonances of the other isomer [f] poorly resolved quartets, only the middle two lines were visible

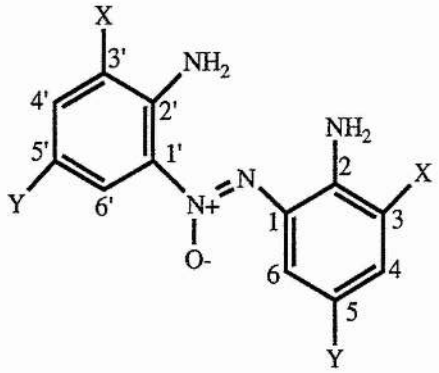


Table **T.6**: ^{13}C N.m.r. spectra for the diaminoazoxybenzenes[a]

No.	X	Y	1	1′	2	2′	3	3′	4[b]	4′[b]	5[b]	5′[b]	6	6′	CF_3[b]	CF_3′[b]
(**458a**)	NO_2	CF_3	131.18	131.84	144.32	141.53	132.97	137.28	124.02 (c, 3)	124.45 (c, 4)	~113.6[d]	~113.6[d]	128.22[e]	126.30 (c, 4)	123.70 (q,271)	123.73 (q,271)
(**458b**)	CF_3	NO_2	128.25	133.63	147.59	144.58	113.31 (q, 32)	111.07 (q, 32)	124.14 (c, 5)	125.16 (c, 5)	133.82	134.11	125.85	121.50	122.96 (f, 273)	~123[f]

[a] The multiplicities and coupling constants (in Hz) are given below the shifts [b] provisional assignments [c] poorly resolved multiplets, only the center two lines were visible [d] only five of the eight peaks were visible, none of them could be assigned to the same quartet (the difference in shifts did not correspond to reasonable couplings) [e] the intensity was comparable to the C-6′ multiplet but was only assigned a single shift by the computer [f] only four of the eight resonances were visible, three for one carbon, one for the other

FIGURES

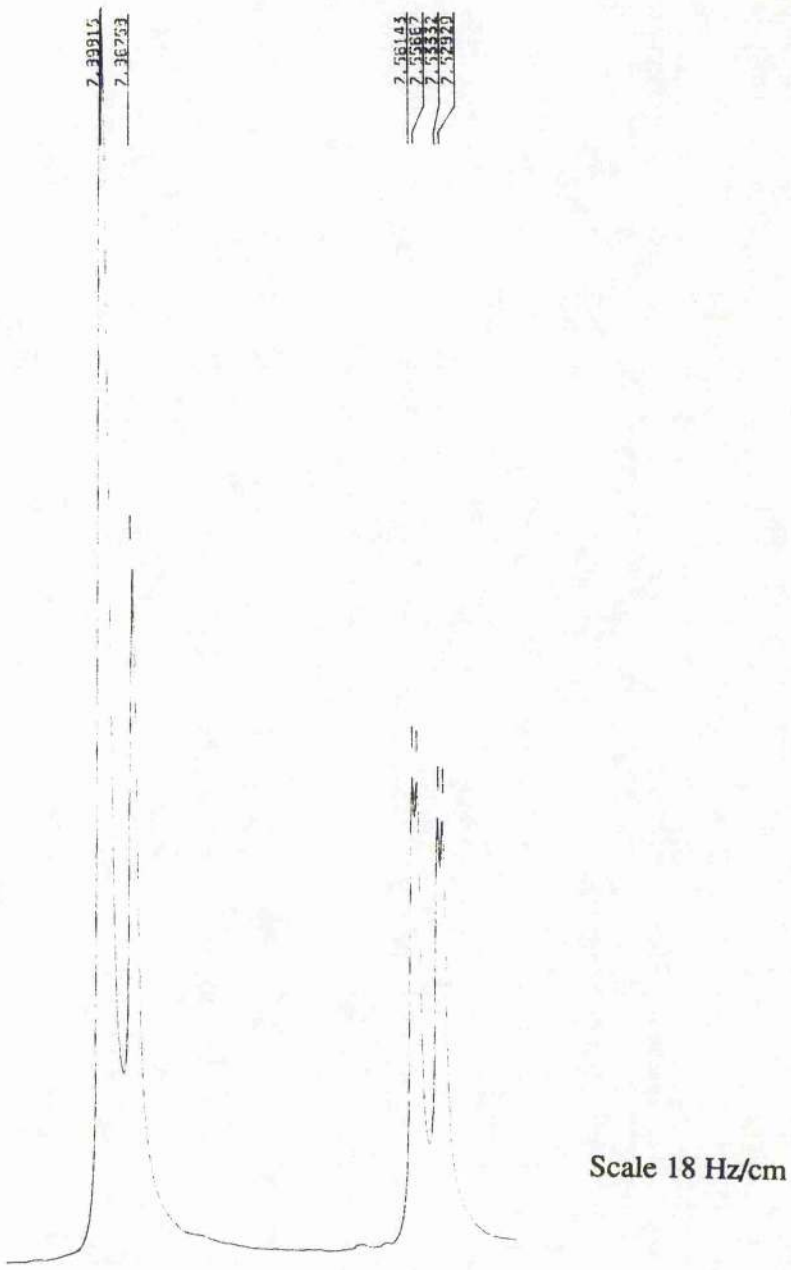


Figure **E.1**: The aromatic region (7.4-8.2 δ) of the 300 MHz ^{1}H n.m.r. spectrum for 5-trifluoromethyl-1*H*-benzimidazole 3-oxide (**408**).

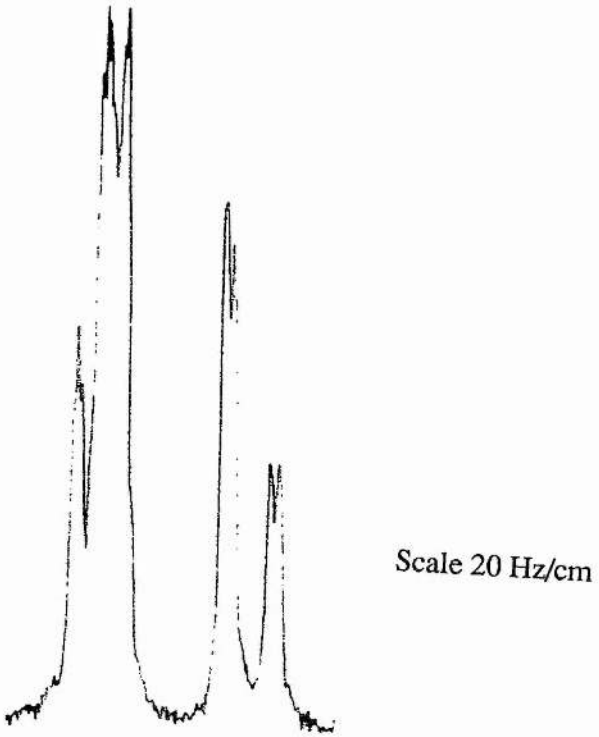


Figure **E.2**: The aromatic region (7.4-8.2 δ) of the 80 MHz ^{1}H n.m.r. spectrum for 5-trifluoromethyl-1*H*-benzimidazole 3-oxide (**408**).

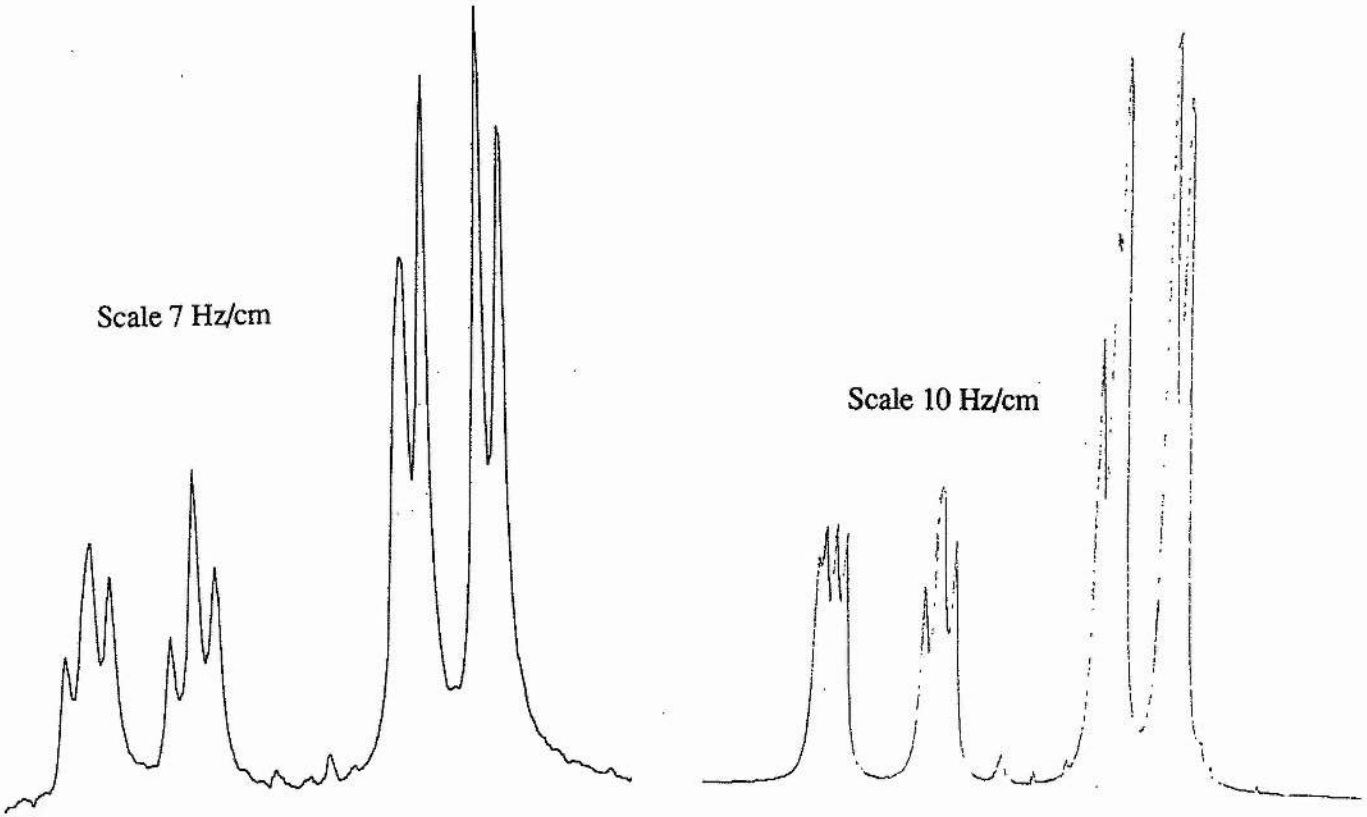


Figure **E.3**: The aromatic signals (7.65 δ, 7.35 δ) in the experimental (left) and the computer simulated (right) 80 MHz ^{1}H n.m.r. spectra for *N*-(4-fluoro-2-nitrophenyl)sarcosine ethyl ester (**422**).

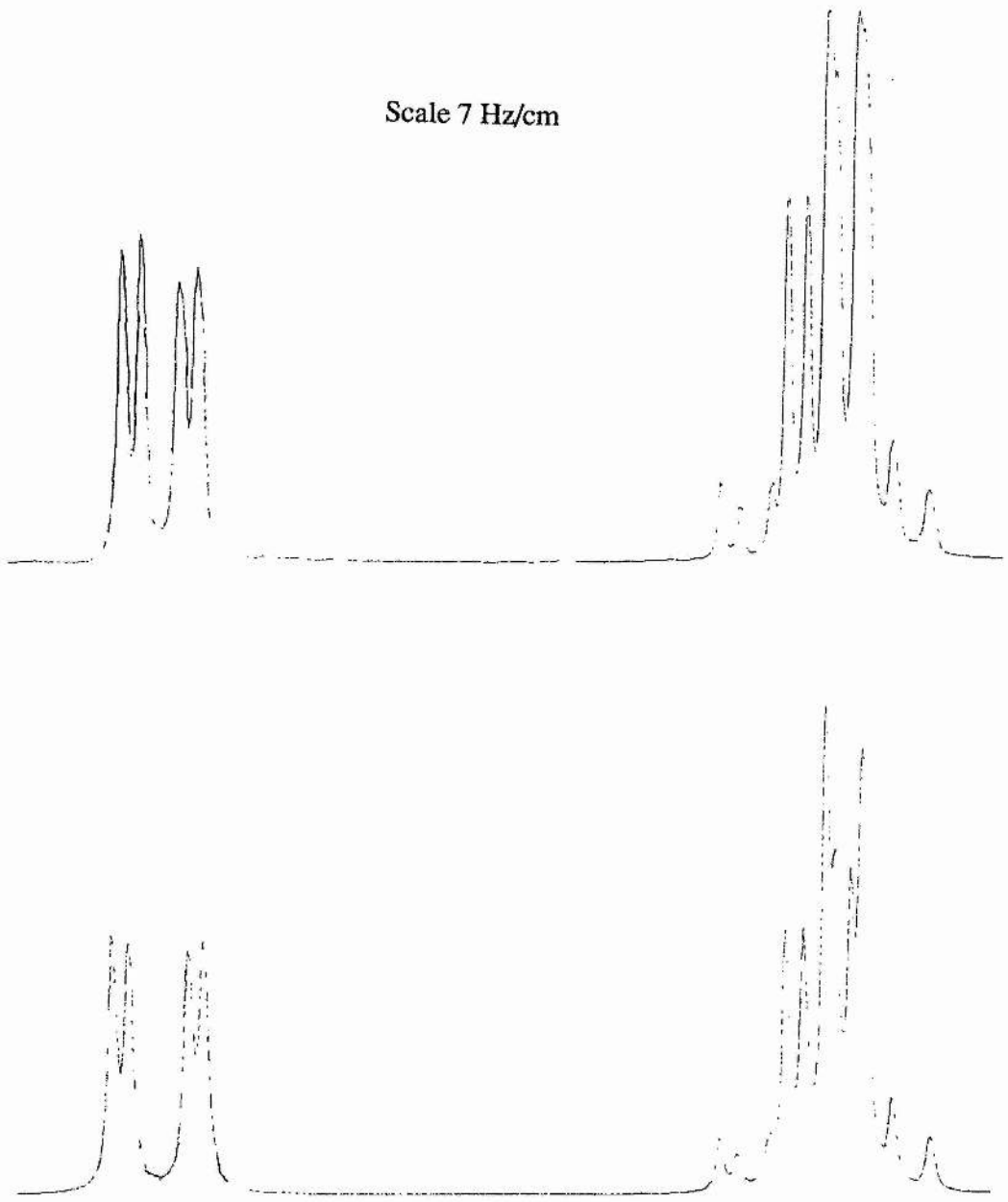


Figure **E.4**: The aromatic signals (7.52, 7.15-7.26 δ) in the experimental (above) and the computer simulated (below) 300 MHz ^{1}H n.m.r. spectra for *N*-(4-fluoro-2-nitrophenyl)-sarcosine ethyl ester (**422**).

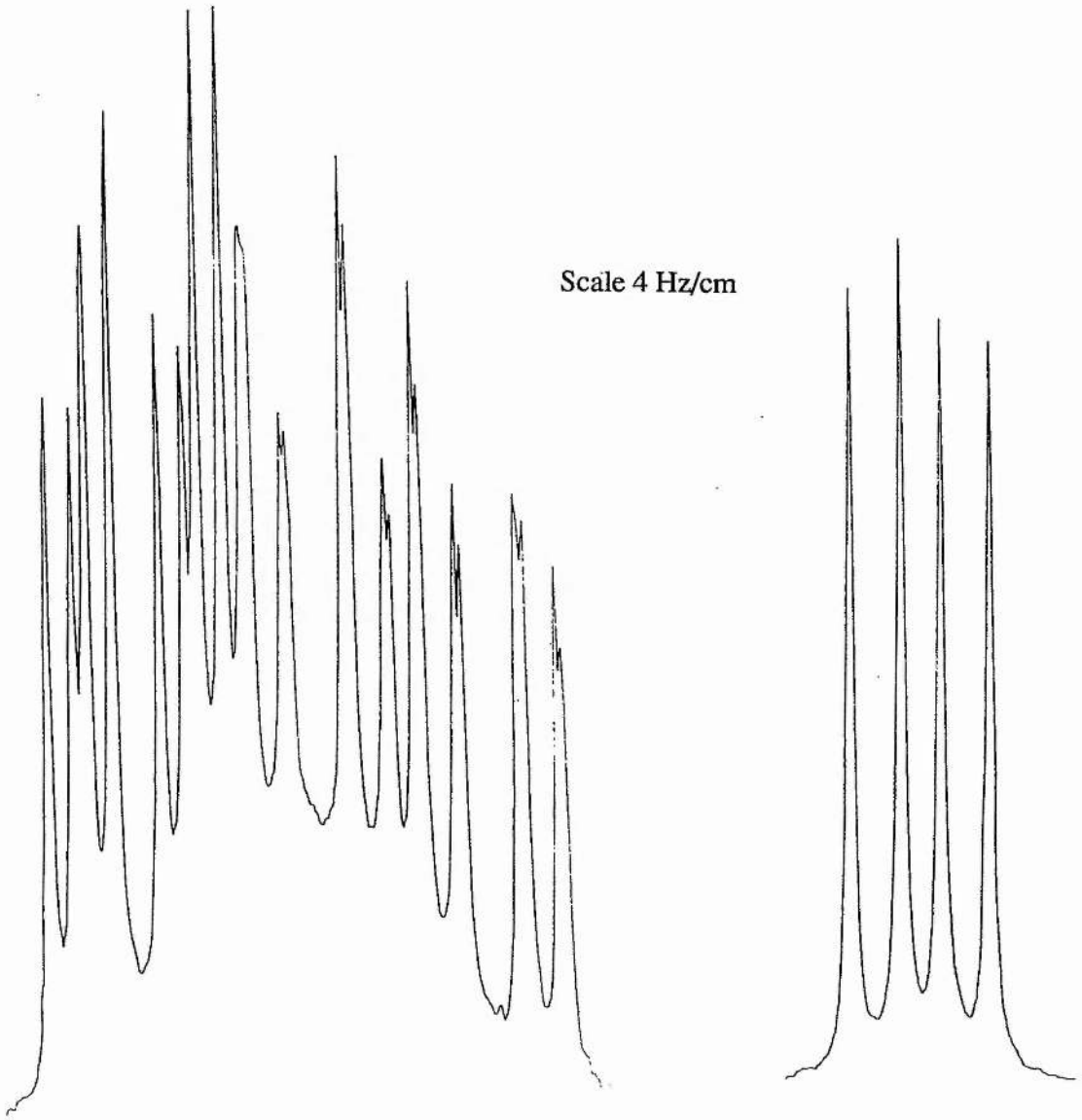


Figure **E.5**: The aromatic region (8.0-7.6 δ) (left) and the methylene signal (4.65 δ) in the ^{1}H n.m.r. spectrum of *N*-cyanomethyl-4,6-difluoro-2-nitroaniline (**468**).

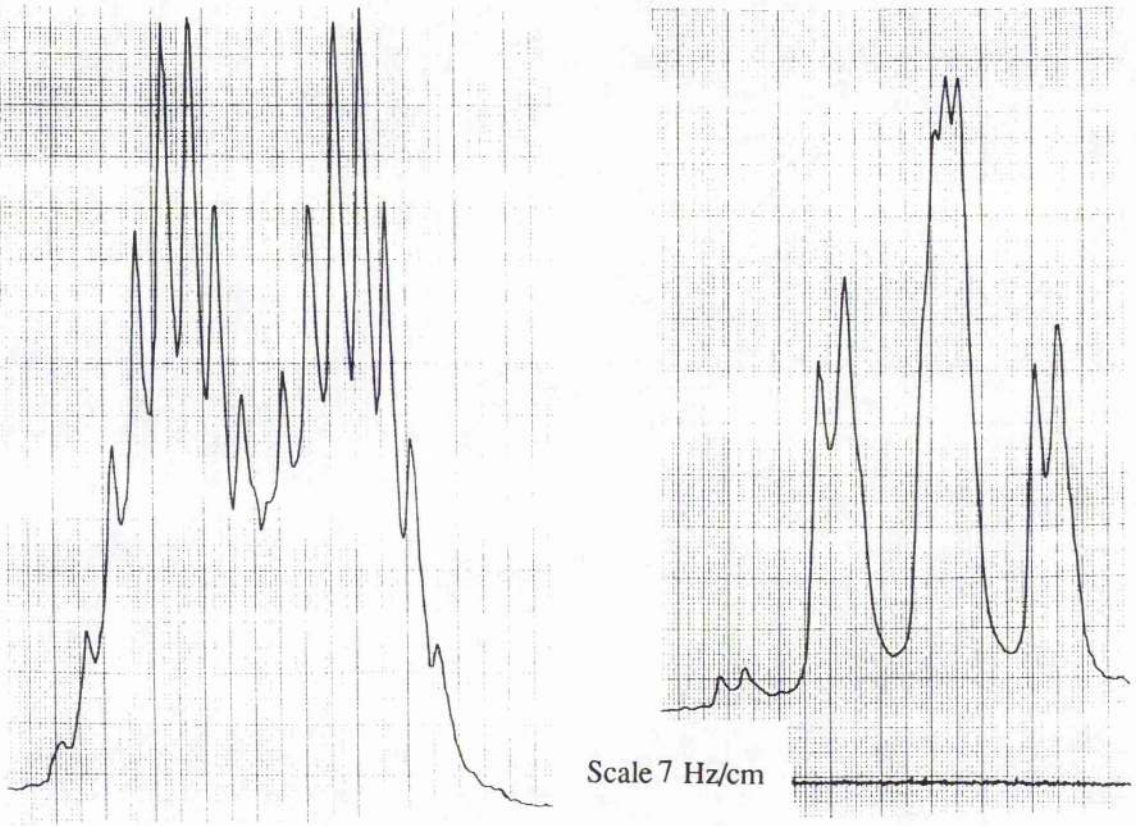


Figure **E.6**: The F-6 (left, -119.6 ppm) and F-4 (right, -122.0 ppm) signals in the ^{19}F n.m.r. spectrum of *N*-cyanomethyl-4,6-difluoro-2-nitroaniline (**468**)

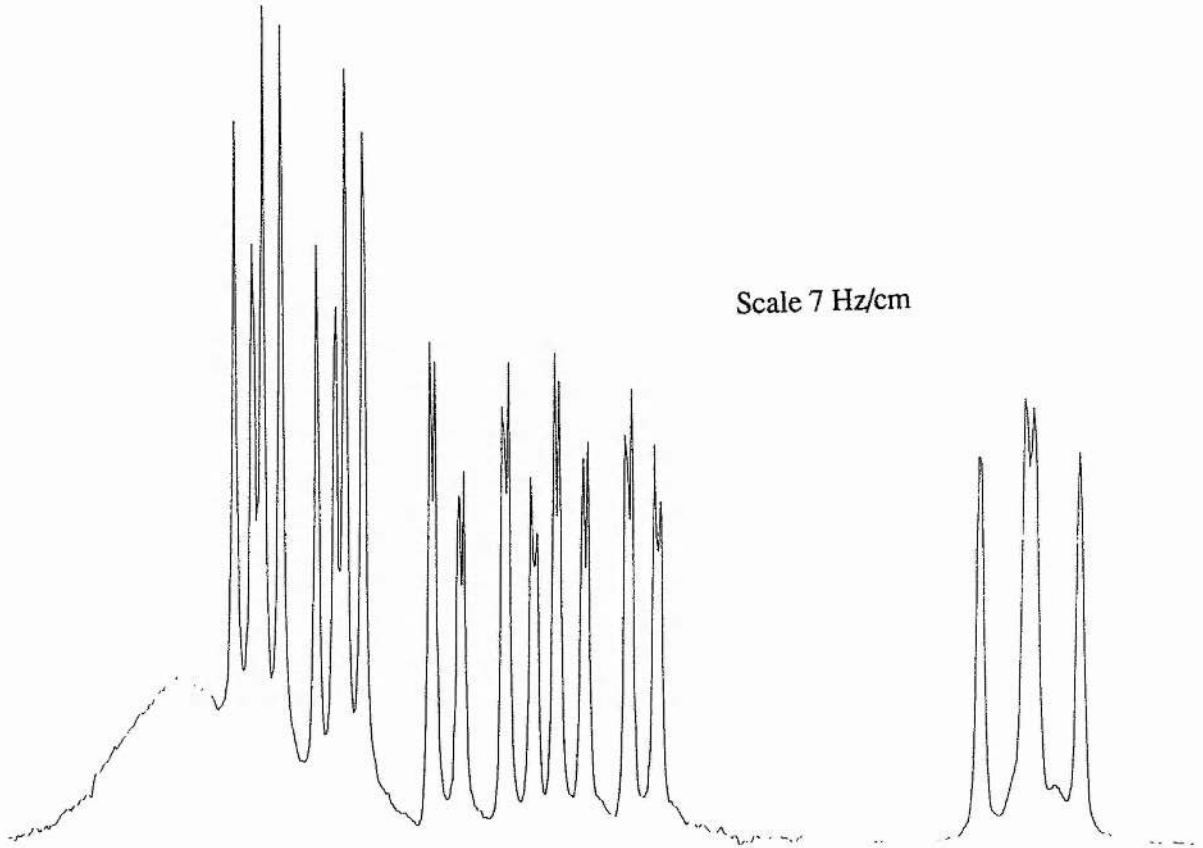


Figure **E.7**: The aromatic region (8.1 δ-7.4 δ) and the methylene signal (4.45 δ) in the experimental ^{1}H n.m.r. spectrum of *N*-(4,6-difluoro-2-nitro-phenyl)glycine methyl ester (**464**)

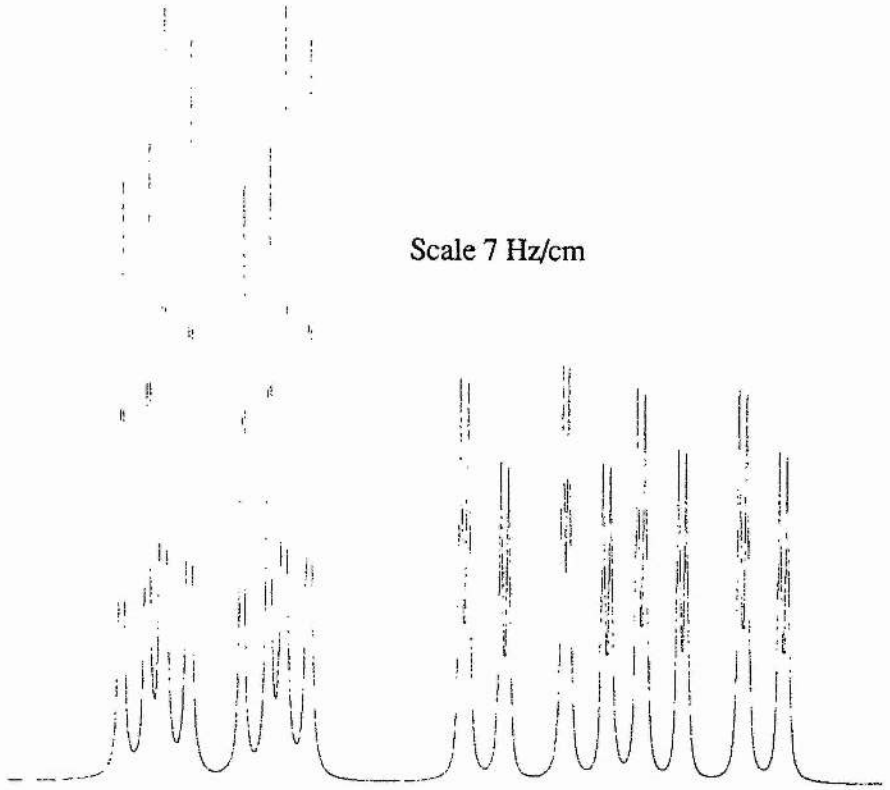


Figure **E.8**: The aromatic signals (7.50 δ, right; 7.85 δ, left) in the computer simulated ^{1}H n.m.r. spectrum of *N*-(4,6-difluoro-2-nitrophenyl)glycine methyl ester (**464**)

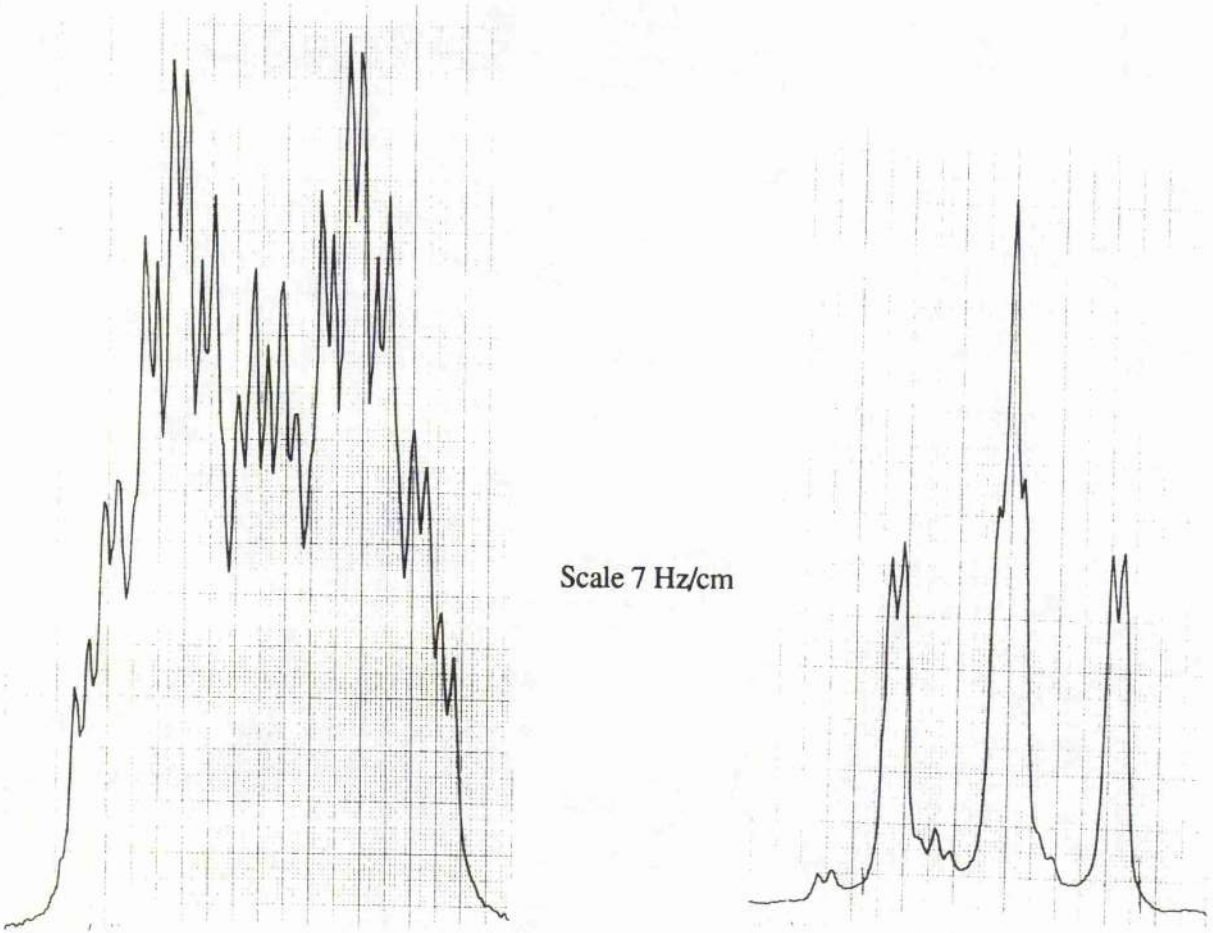


Figure **E.9**: The F-6 (left, -121.1 ppm) and F-4 (right, -124.9 ppm) signals in the experimental ^{19}F n.m.r. spectrum of *N*-(4,6-difluoro-2-nitrophenyl)-glycine methyl ester (**464**).

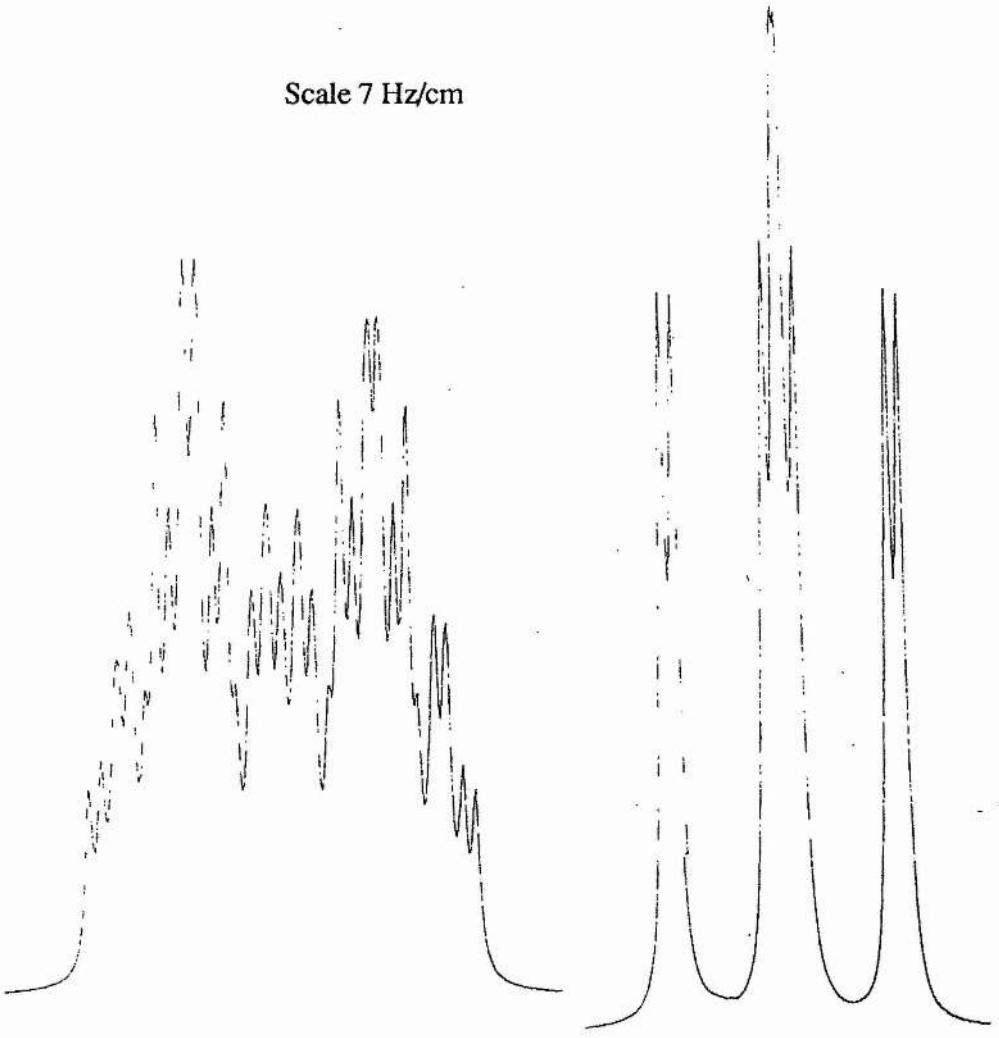


Figure **E.10**: The F-6 (left, -121 ppm) and F-4 (right, -124.9 ppm) signals in the computer simulated ^{19}F n.m.r. spectrum of *N*-(4,6-difluoro-2-nitrophenyl)glycine methyl ester (**464**).

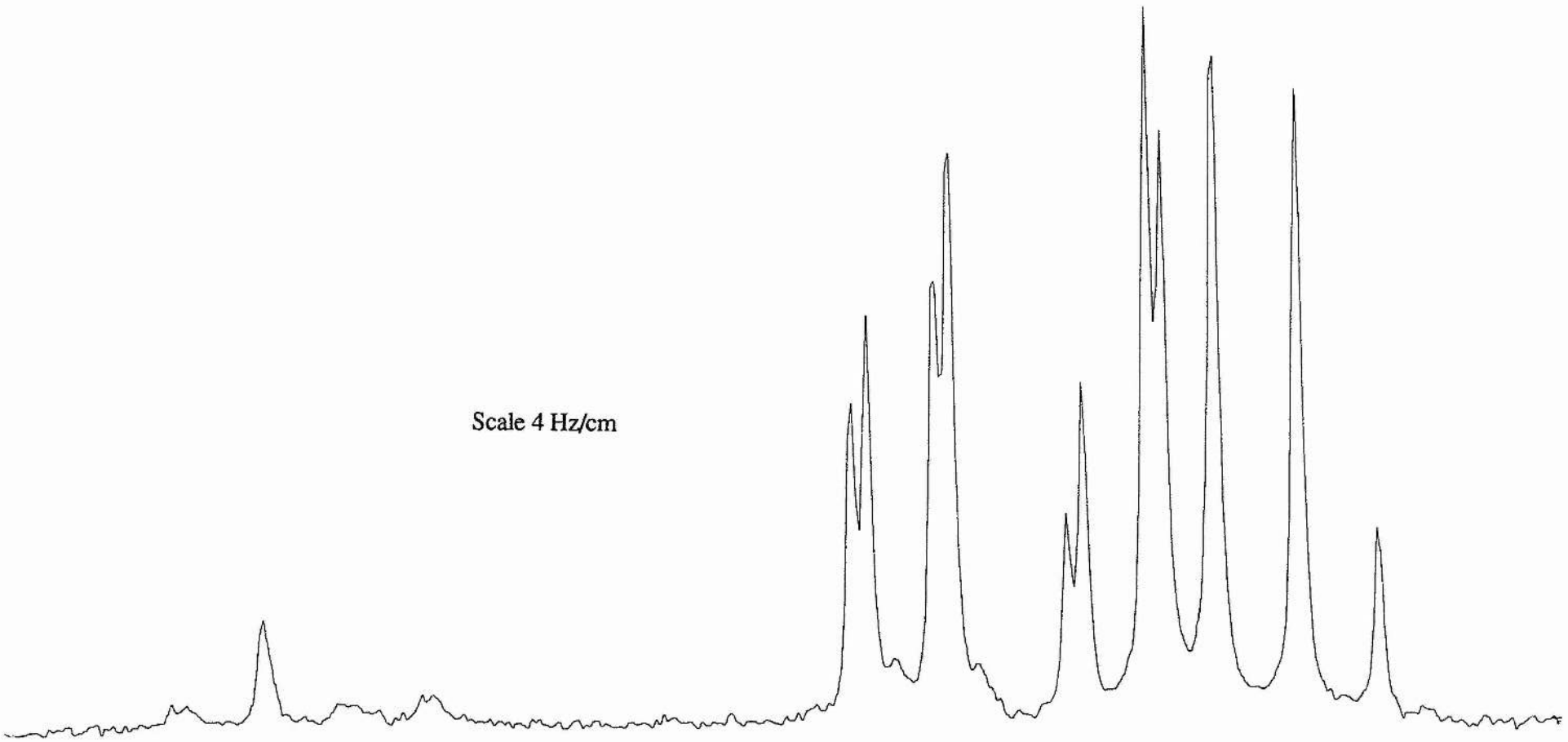


Figure **E.11**: The aromatic region (8.7-7.2 δ) in the ^{1}H n.m.r. spectrum of a mixture of 1-methyl-7-nitro-3*H*-benzimidazole (**475**) and a small amount of 8-nitroquinoxalin-2-one (**476**).

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