New Synthetic Approaches to Nitroimidazoles, Nitro-1,2,5-oxadiazoles, and Nitrotriazoles

by

John Grant England B.Sc.

Thesis presented for the degree of

Doctor of Philosophy

University of Edinburgh

1988

To my parents

Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself and that it has not been submitted in any previous application for a higher degree.

The thesis describes the results of research carried out in the Department of Chemistry, University of Edinburgh, under the supervision of Dr. G. Tennant between October 1982 and September 1985.

Signed _____

Date 18/2/88

Acknowledgements

I would like to thank Dr. G. Tennant for his supervision and encouragement during the course of my research.

I would like to thank Dr. R.W. Millar (Ministry of Defence) for his helpful suggestions and the Ministry of Defence for the award of a Research Studentship.

I would also like to thank the University of Edinburgh for the provision of laboratory and library facilities.

I would also like to acknowledge the help and expertise of the technical staff of the Department of Chemistry, University of Edinburgh, notably Mr. L. Bell and Mr. J. Millar for the measurement of n.m.r. spectra, Mr. J. Grunbaum and Mrs. E. McDougall for the determination of microanalyses and Mr. A.T. Taylor and Mr. D. Thomas for the mass spectra recorded in this thesis.

Finally, I would like to express my indebtedness to Mrs. C.G. Ranken for her care and patience in typing the manuscript of this thesis.

Postgraduate Lecture Courses Attended between October 1982 and September 1985

"Medicinal Chemistry"

Dr. R.M. Paton (University of Edinburgh)

"The Chemistry of Photographic Processes"

Dr. L.A. Williams (Kodak Ltd.)

"1,3-Dipoles"

Drs. J.T. Sharp and R.M. Paton (University of Edinburgh)

"Current Topics in Organic Chemistry"

Dr. G. Tennant (University of Edinburgh)

"Silicon in Organic Chemistry"

Dr. E. Colvin (University of Glasgow)

"Current Topics in Organic Chemistry"

Dr. G. Tennant (University of Edinburgh)

"Synthetic Strategy"

Professor R. Ramage (University of Edinburgh)

"Current Topics in Organic Chemistry"

Dr. G. Tennant (University of Edinburgh)

Departmental Seminars

Departmental Colloquia

Abstract

The subject matter of this thesis is concerned with investigations of new synthetic approaches to nitroimidazole, nitro-1,2,5-oxadiazole, and nitrotriazole derivatives. The description of the results obtained in these studies is preceded in Chapter 1 by a survey of the known literature methods for the synthesis of monocyclic nitrogen heteroaromatic nitro-compounds.

Chapter 2 describes attempts to develop new synthetic routes to dinitro- and trinitroimidazoles based on appropriately functionalised acyclic precursors. Synthetic routes based on the oxidative cyclisation of ethane-1,2-dione monoimine monoxime derivatives were unsuccessful. Orthodox annulation reactions of nitroethane-1,2-dione dioxime to nitroimidazole derivatives were also unsuccessful as were approaches based on the conversion of ethane-1,2-dione dioxime into imidazole derivatives followed by nitration. The attempted cyclisation of 1,2-diaminoethane-1,2-dione dioxime to 4,5-diaminoimidazole derivatives led instead to 1,2,4-oxadiazolyl-1,2,4-oxadiazoles thus thwarting the intended further oxidative conversion into 4,5-dinitroimidazoles. Attempts to condense 1,2-dichloroethane-1,2-dione dioxime with amidines and related compounds to give aminoimidazoles suitable for further elaboration to nitroimidazoles were also unsuccessful.

In Chapter 3 investigations of new synthetic approaches to nitrofurazan and nitrofuroxan derivatives are described. The oxidative cyclisation of nitroethane-1,2-dione dioxime

was shown to afford a low yield of the previously unknown 4-nitro-1,2,5-oxadiazole 1-N-oxide. Interestingly, the oximation of 2-nitroacetamidoxime unexpectedly gave a low yield of a product whose properties are in accord with its formulation as 4-amino-5-nitro-1,2,5-oxadiazole.

In the final chapter synthesis of mononitro- and dinitro-1,2,3-triazole derivatives were investigated. The attempted synthesis of nitro-1H-1,2,3-triazole derivatives from 1,2-diaminoethane-1,2-dione dioxime was unsuccessful. A series of nitro-2H-1,2,3-triazole-1 N-oxide derivatives were successfully prepared from 1-nitroethane-1,2-dione hydrazone oxime derivatives using a variety of oxidising reagents. In contrast, the dehydrative cyclisation of nitroethane-1,2-dione hydrazone oxime derivatives, in some cases resulted in rearrangement giving good yields of nitro-1H-1,2,4-triazole derivatives.

Contents

Foreword

Nitro and in particular polynitro derivatives of nitrogen containing heteroaromatic compounds are of considerable interest because of their utility as synthetic intermediates and also because of their potentially unique physical and chemical properties. Thus the ready manipulation of the nitro-substituent by reduction as well as by nucleophilic displacement makes nitro-heteroaromatic compounds key intermediates for the synthesis of a variety of nitrogen heteroaromatic derivatives. Because of the powerful electron-withdrawing properties of the nitro-group, polynitro-heteroaromatic compounds should also exhibit unconventional physical and chemical properties. Certain nitro-heteroaromatic compounds also show interesting biological properties particularly as antibiotics and as radiosensitising agents in the treatment of cancer.

However despite all these interesting properties, compared with nitrobenzene derivatives, nitro-heteroaromatic compounds have been relatively little investigated principally because they are not readily synthesised. Thus, unlike most benzene derivatives, the electron-deficient nature of many nitrogen-containing heteroaromatic ring systems makes their nitro-derivatives inaccessible by the usual electrophilic nitration procedures. The following thesis is concerned with the development of new synthetic routes to nitro-derivatives of a variety of nitrogen-

containing heteroaromatic systems which avoid the inherent limitations of electrophilic nitration. By way of introduction the discussion of the results obtained in these studies is preceded by a survey of the scope and limitations of the main literature methods available for the synthesis of nitro-derivatives of nitrogen-containing heteroaromatic ring systems.

Chapter 1

A Survey of Synthetic Methods for Monocyclic Nitrogen Heteroaromatic Nitro-compounds

A Survey of Synthetic Methods for Monocyclic Nitrogen Heteroaromatic Nitro-compounds

The following survey is concerned with the scope and limitations of literature methods for the synthesis of nitro-derivatives of five and six-membered monocyclic heteroaromatic compounds containing only nitrogen and is organised according to reaction type rather than compound type. The reaction types are dealt with under three main headings namely, nitration, functional group modification of preformed heterocyclic derivatives and synthesis from acyclic nitro-compounds.

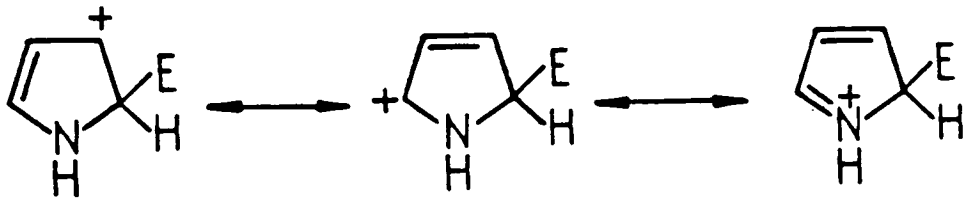
1.1 Synthetic Methods Involving Nitration

The nitration of nitrogen-heteroaromatic compounds presents difficulties depending on whether the heterocycle is π-electron-excessive or π-electron-deficient. A π-electron-excessive nitrogen heterocycle is one in which the nitrogen lone pair electrons are involved in the aromatic system making the ring susceptible to electrophilic nitration. All five-membered nitrogen-containing heteroaromatic ring systems are of the π-excessive type. Unfortunately, when mixed acid nitration conditions are used, protonation of the nitrogen lone pair results in the loss of aromaticity with consequent destruction of the ring system. The simplest example of this situation is encountered in the case of pyrrole which undergoes polymerisation under mixed acid conditions.

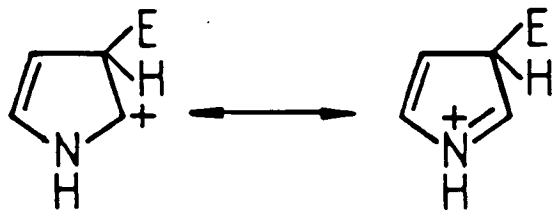
In π-electron-deficient nitrogen heterocycles the overall effect of the nitrogen atom is to reduce the electron density at the ring carbon atoms thus making the ring resistant to electrophilic nitration. All six-membered nitrogen-containing heteroaromatic ring systems are of the π-deficient type, the simplest example being pyridine which is essentially inert to electrophilic nitration under conditions in which benzene nitrates readily. The position(s) of the nitrogen atom(s) in both five- and six-membered nitrogen heteroaromatic rings also determines the site at which electrophilic substitution occurs, again limiting electrophilic nitration as a synthetic method.

1.1.1 Synthesis of Five-membered Heteroaromatic Nitro-compounds

Pyrrole undergoes electrophilic substitution predominantly at the positions α to the nitrogen atom although if these positions are blocked substitution will occur at the β-positions. The preference for α-substitution may be explained qualitatively by considering the Wheland intermediates for α- and β-substitution. For α-substitution it can be seen (Scheme 1) that the positive charge in the Wheland intermediate is more delocalised [(1)↔(2)↔(3)] than that in the Wheland intermediate for β-substitution [(4)↔(5)] and therefore the activation energy for α-substitution is lower thus explaining the preference for the latter.



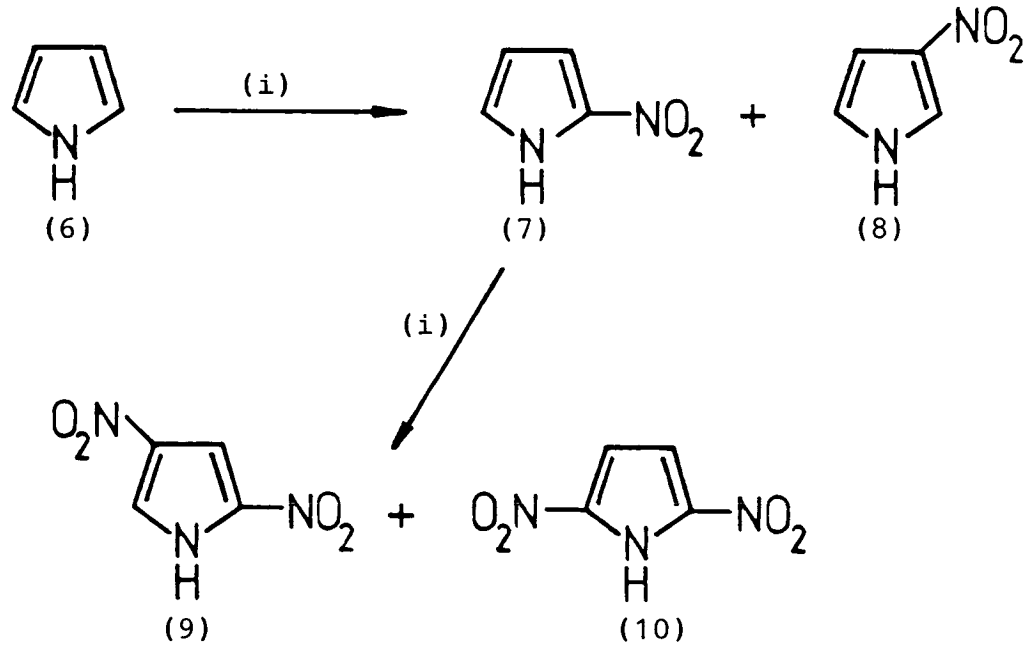
(1) (2) (3)



(4) (5)

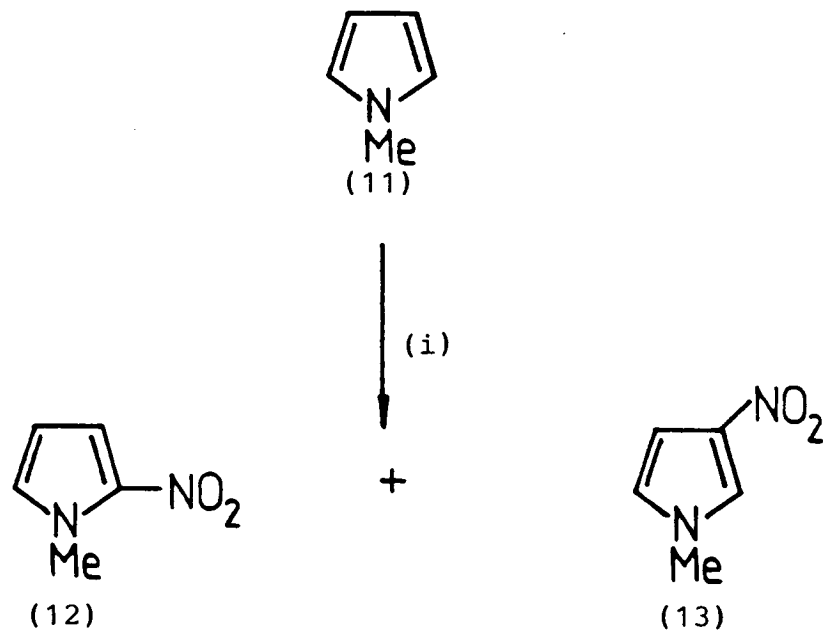
Scheme 1

Though pyrrole is formally activated towards electrophilic attack, under acidic conditions the pyrrole ring is destroyed due to loss of aromatic character resulting from protonation of the nitrogen atom, the lone pair of which is involved in the aromatic system. It follows that special conditions have to be used for the nitration of pyrrole and its derivatives. A useful reagent in this context is acetyl nitrate which is conveniently prepared in situ from a mixture of acetic anhydride and nitric acid. This reagent was first employed by Rinkes[1] (Scheme 2) for the nitration of pyrrole (6), the sole product isolated in relatively good yield being the 2-nitro-derivative (7). Rinkes[1,2] also showed in turn that nitration with fuming nitric acid-acetic anhydride converted 2-nitropyrrole (7) into a 3:1-mixture of 2,4-dinitropyrrole (9) and 2,5-dinitropyrrole (10).



(i) N_2O_4-HNO_3, Ac_2O, -15 to -10°

Scheme 2



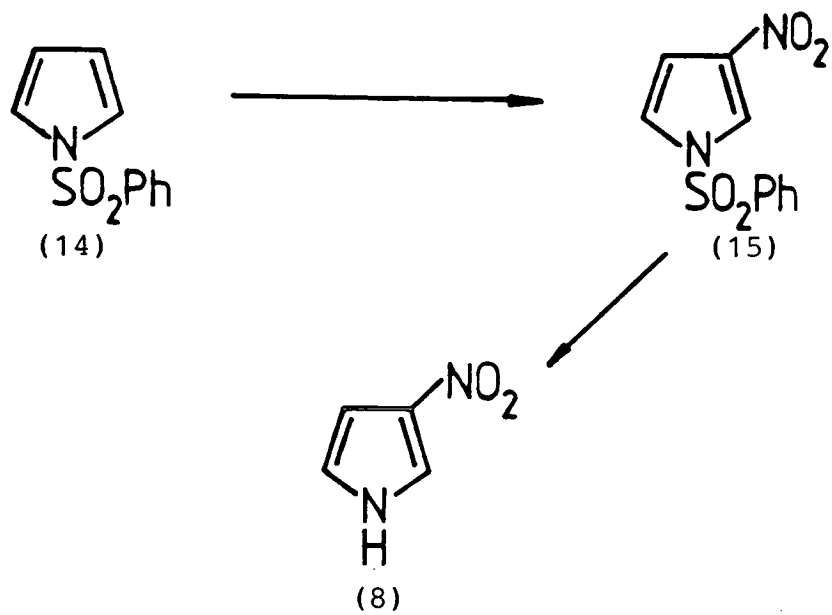
(i) N_2O_4-HNO_3, Ac_2O, -10 to 5°

Scheme 3

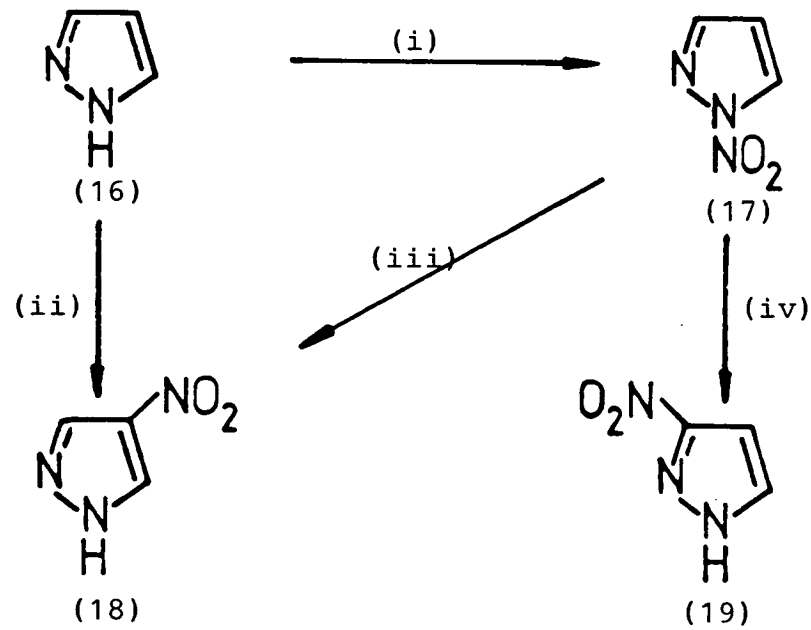
Anderson[3] found that in apparent contrast to pyrrole, nitration (Scheme 3) of 1-methylpyrrole (11) with fuming nitric acid-acetic anhydride though affording largely 1-methyl-2-nitropyrrole (12) also gave a low yield of the 3-nitro-derivative (13). It was subsequently shown (Scheme 2) by a reinvestigation[3] of the nitration of pyrrole (6) with fuming nitric acid-acetic anhydride that contrary to the result reported by Rinkes,[1] 2-nitropyrrole (7) was accompanied by the 3-nitro-isomer (8) albeit only in low yield (7%). However, though no experimental details were given, the latter compound has been reported[4] to be formed exclusively and in high yield (Scheme 4) by the nitration of 1-benzenesulphonyl pyrrole (14) followed by hydrolytic removal of the benzenesulphonyl group. This specific synthesis of 3-nitropyrrole (8) illustrates the use of the N-benzenesulphonyl substituent as a subsequently removeable directing group which deactivates the 2-position of the pyrrole ring towards electrophilic attack thus promoting nitration at the 3-position.

Pyrrole shows acidic properties, deprotonation of the NH-substituent giving a resonance-stabilised 6πe-aromatic anion. This anion should be more susceptible to electrophilic attack than pyrrole itself and indeed it has been shown[5,6] that treatment of pyrrole with sodium in ethereal solution followed by ethyl nitrate affords 3-nitropyrrole (8) though only in low yield.

The introduction of a second nitrogen atom into a five-membered π-excessive heteroaromatic ring reduces the



Scheme 4



(i) N_2O_4-HNO_3, Ac_2O, room temp.

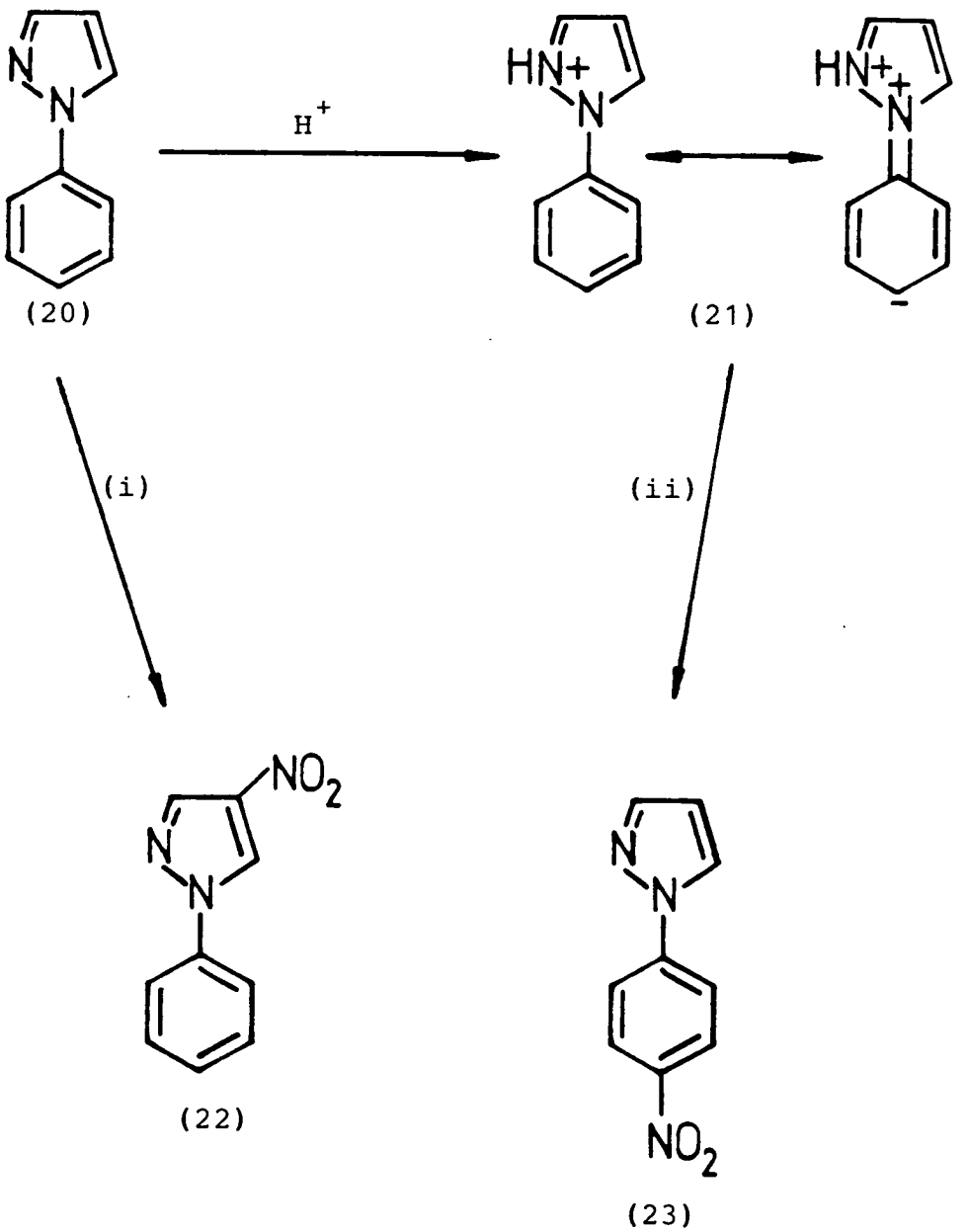
(ii) N_2O_4-HNO_3, SO_3-H_2SO_4, 110°

(iii) Conc. H_2SO_4, 0°

(iv) heat, 145°

Scheme 5

reactivity of the molecule to electrophilic attack and such heterocycles tend to require more forcing conditions for nitration than those successful for pyrrole and its derivatives. Thus the lower reactivity of pyrazole to electrophilic nitration is directly attributable to the presence of the second pyridine-like electron-withdrawing nitrogen atom. Hüttel[7] found (Scheme 5) that the nitration of pyrazole (16) using fuming nitric acid in the presence of acetic anhydride gave exclusively the 1-N-nitro-derivative (17) in good yield (70%). On the other hand 4-nitropyrazole (18) was obtained in high yield (80%) when pyrazole (16) was nitrated with a mixture of fuming nitric and fuming sulphuric acid at elevated temperature.[7] Furthermore, 4-nitropyrazole (18) was also obtained from the 1-N-nitro derivative (17) by treatment with concentrated sulphuric acid at low temperature.[7] Habraken[8] later studied the thermal isomerisation of 1-N-nitropyrazole (17) and showed that at high temperature 3(5)-nitropyrazole (19) was formed in near quantitative yield. Carrying out the rearrangement in the presence of anisole or phenol resulted in no nitration of these substrates and consequently proved that the formation of 3(5)-nitropyrazole (19) from the N-nitropyrazole (17) must occur by an intramolecular process. The re-investigation[8] of the formation of 4-nitropyrazole (18) using the conditions described by Hüttel but with the addition of anisole or phenol resulted in the nitration of these substrates and thus demonstrated that an intermolecular process was occurring in this case.



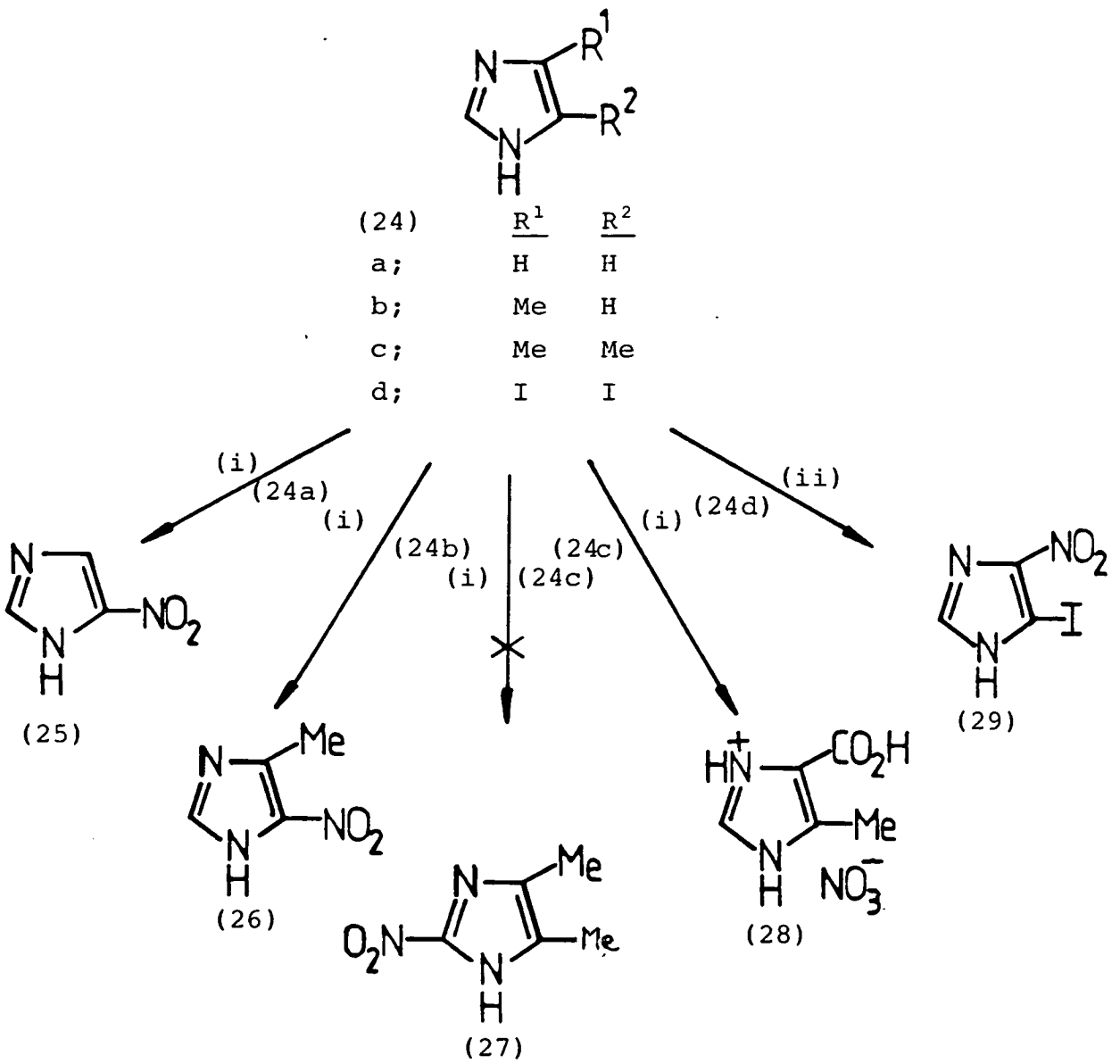
(i) N_2O_4-HNO_3, Ac_2O, -5°

(ii) Conc. HNO_3, conc. H_2SO_4, 12°

Scheme 6

The nitration (Scheme 6) of 1-phenylpyrazole (20) has been achieved[9] using fuming nitric acid and acetic anhydride the product being the 4-nitro derivative (22). However it was observed[10] that using a mixture of concentrated nitric acid and concentrated sulphuric acid, nitration occurs at the para-position of the phenyl ring giving 1-(4-nitrophenyl)pyrazole (23) in high yield (86%). It has been suggested by Khan and his co-workers[9] that the nitration of the phenyl substituent observed under 'mixed acid' conditions is the result of deactivation of the pyrazole ring due to initial protonation at N(2) to give the conjugate acid (21) the actual species undergoing nitration.

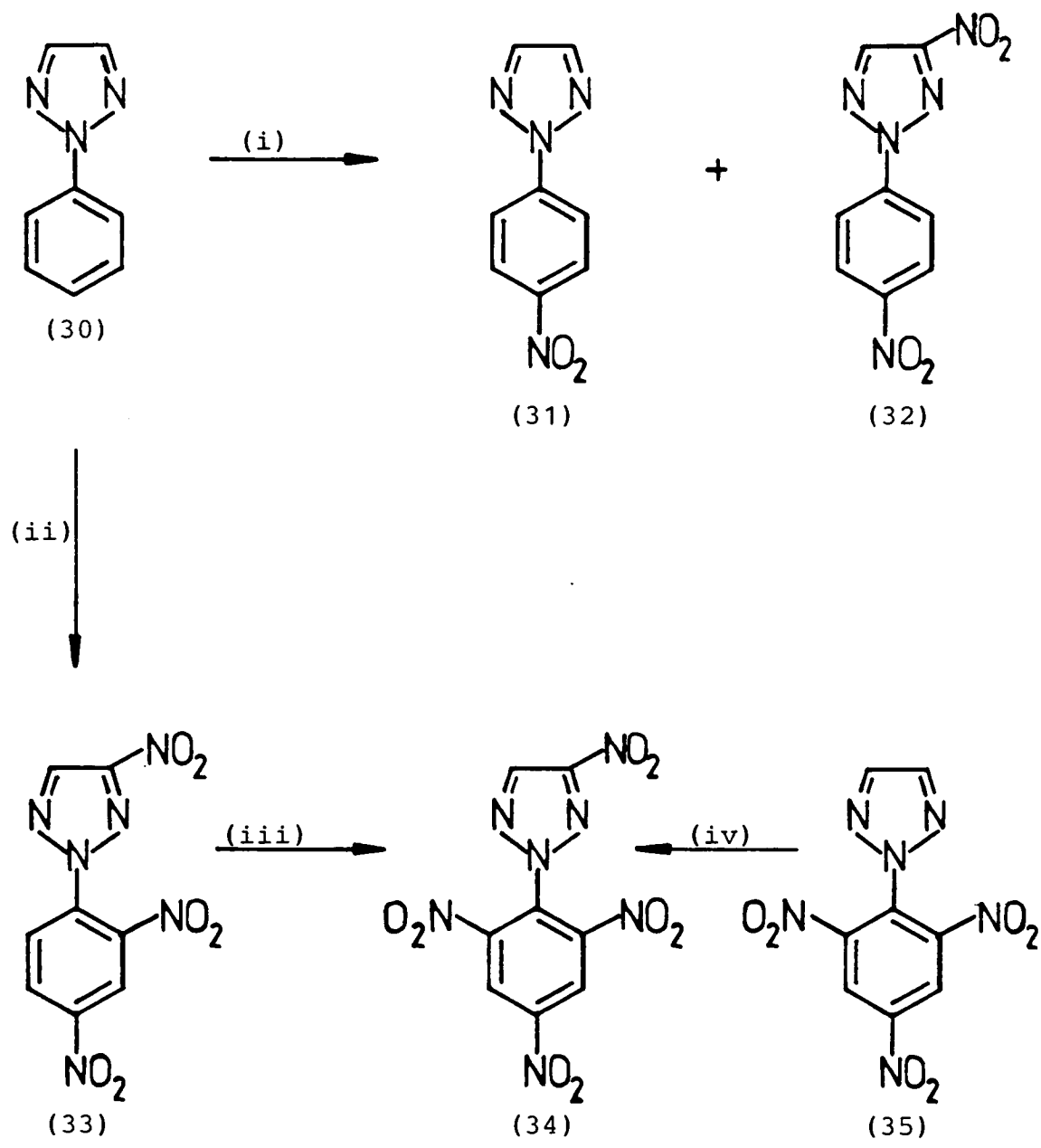
As in the case of pyrazole, the pyridine-like nitrogen atom in imidazole lowers the reactivity of the ring towards electrophilic substitution in general and nitration in particular. Generally electrophilic nitration of imidazole gives the 4(5)-nitro derivative with no substitution at the C(2)-position. It follows that the important antibiotic 2-nitroimidazole (azomycin) cannot be prepared by direct nitration.[11] A number of nitroimidazole derivatives have been prepared[12] by nitration under mixed acid conditions (concentrated nitric acid and concentrated sulphuric acid). Thus (Scheme 7) nitration of imidazole (24a) itself gives the 4(5)-nitro derivative (25) in good yield. When either the 4- or 5-position is blocked nitration tends to occur at the 5- or 4-position. Thus nitration of 4(5)-methylimidazole (24b) gives a high yield (90%) of 4-methyl-5-nitroimidazole (26). However, when



(i) Conc. HNO_3, conc. H_2SO_4, reflux

(ii) Conc. HNO_3, conc. H_2SO_4, 20°

Scheme 7



(i) Conc. HNO_3, conc. H_2SO_4, 20°

(ii) Conc. HNO_3, SO_3-H_2SO_4, 20°

(iii) $NaNO_3$, SO_3-H_2SO_4, 145°

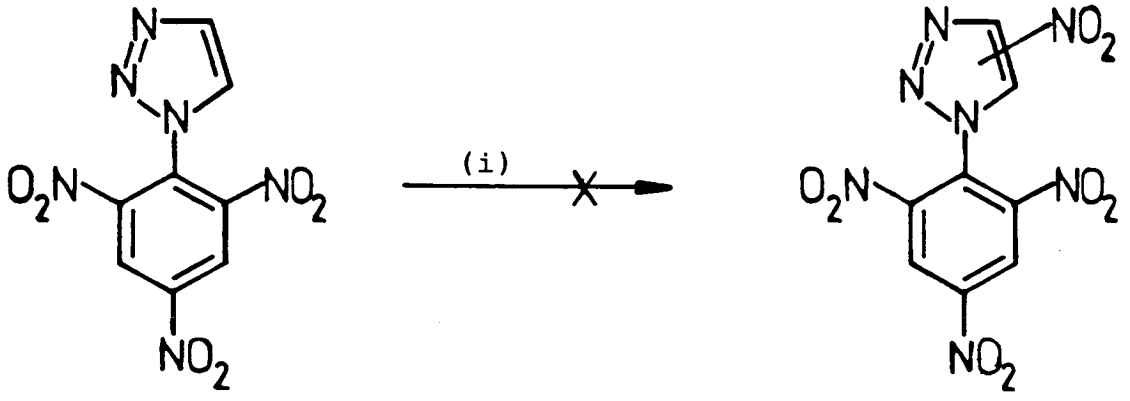
(iv) Conc. HNO_3, conc. H_2SO_4, 85°

Scheme 8

both the 4- and the 5-positions are blocked nitration at the available 2-position is resisted. For example, attempted nitration of 4,5-dimethylimidazole (24c) gave only unreacted starting-material and a low yield of the nitrate salt of 5-methylimidazole-4-carboxylic acid (28) formed by oxidation rather than the 2-nitro-derivative (27).

Nitroimidazole derivatives are also formed by nitrative dehalogenation of halogenoimidazoles. Hoffer[13] originally reported the nitrative deiodination of a diiodoimidazole, wrongly presumed[13] to be 2,4-diiodo-imidazole, to afford a product incorrectly formulated[13] as 2-iodo-4-nitroimidazole. However a reinvestigation[14] of Hoffer's work showed that the diiodoimidazole nitrated (Scheme 7) was in fact 4,5-diiodoimidazole (24d) and the nitration product 4(5)-iodo-5(4)-nitroimidazole (29).

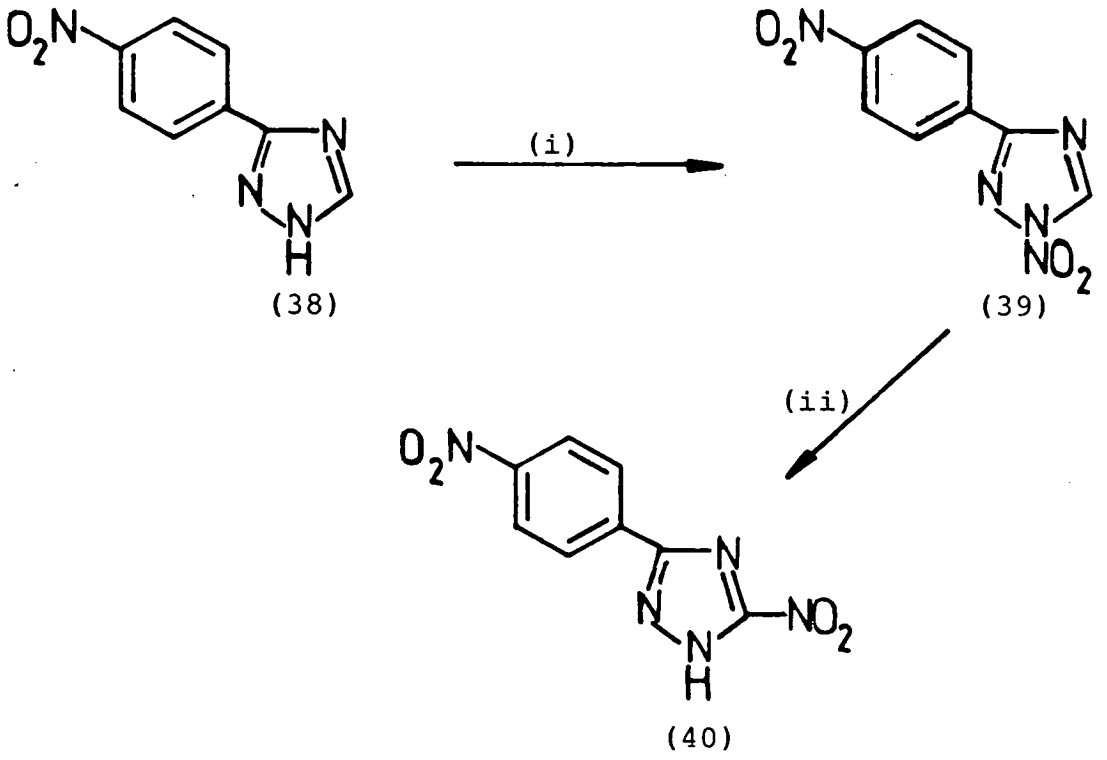
Electrophilic substitution reactions of 1,2,3- and 1,2,4-triazoles are not common since the electron density at the ring carbon atoms is depleted due to the presence of three electron-withdrawing nitrogen atoms. Riebsomer[15] investigated the nitration (Scheme 8) of 2-phenyl-2H-1,2,3-triazole (30) using concentrated nitric acid and concentrated sulphuric acid and formulated the two products obtained as the 2-nitrophenyl and 4-nitrophenyl derivatives. However a reinvestigation[16] of this work showed that though one of the products was indeed 2-(4-nitrophenyl)-2H-1,2,3-triazole (31) the other product was in fact 4-nitro-2-(4-nitrophenyl)-2H-1,2,3-triazole (32). Moreover the latter product was also formed by further nitration of 2-(4-nitrophenyl)-2H-



(36) (37)

(i) Conc. HNO_3, conc. H_2SO_4, 85°

Scheme 9



(38) (39) (40)

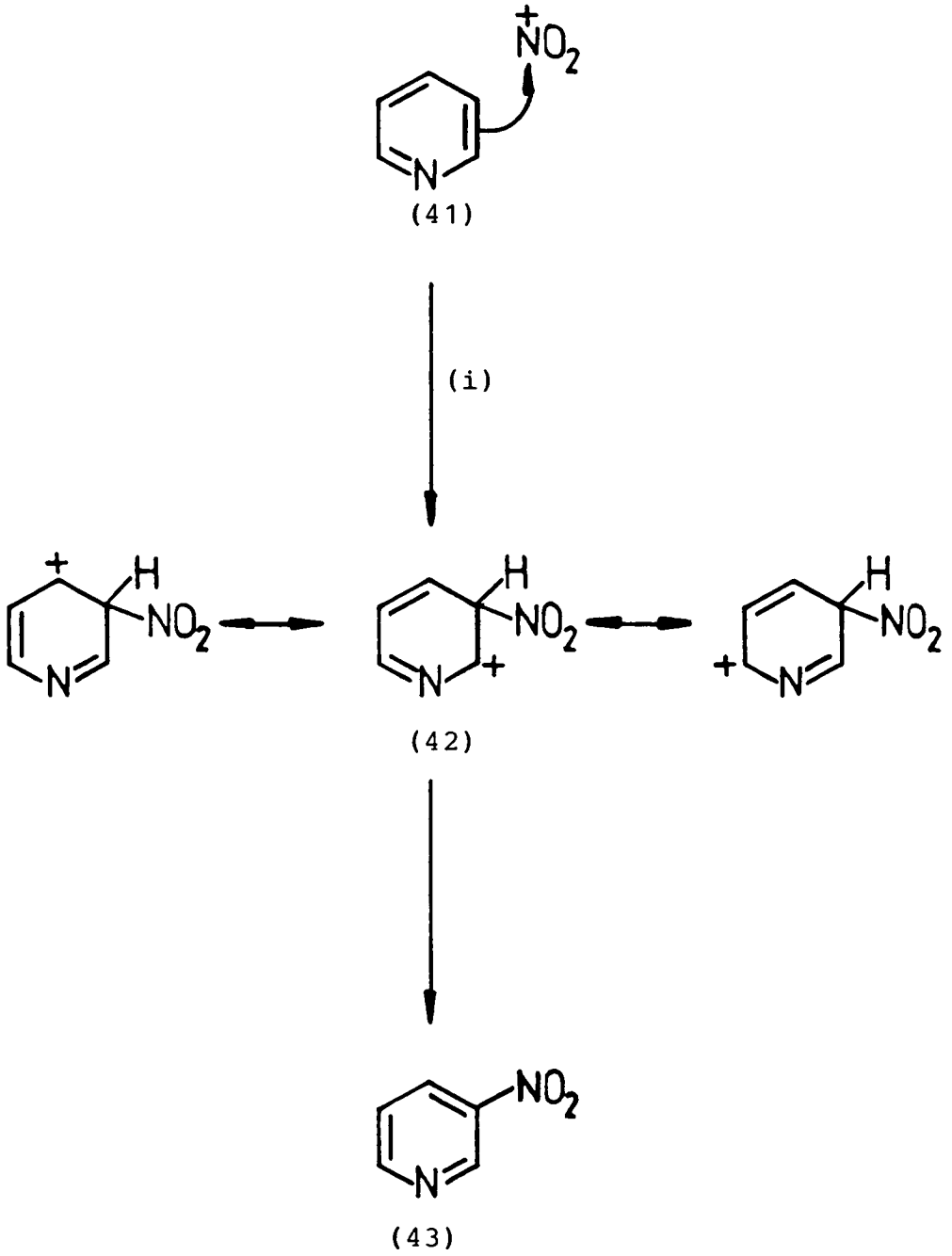
(i) N_2O_4-HNO_3, Ac_2O, room temp.

(ii) heat, 120°

Scheme 10

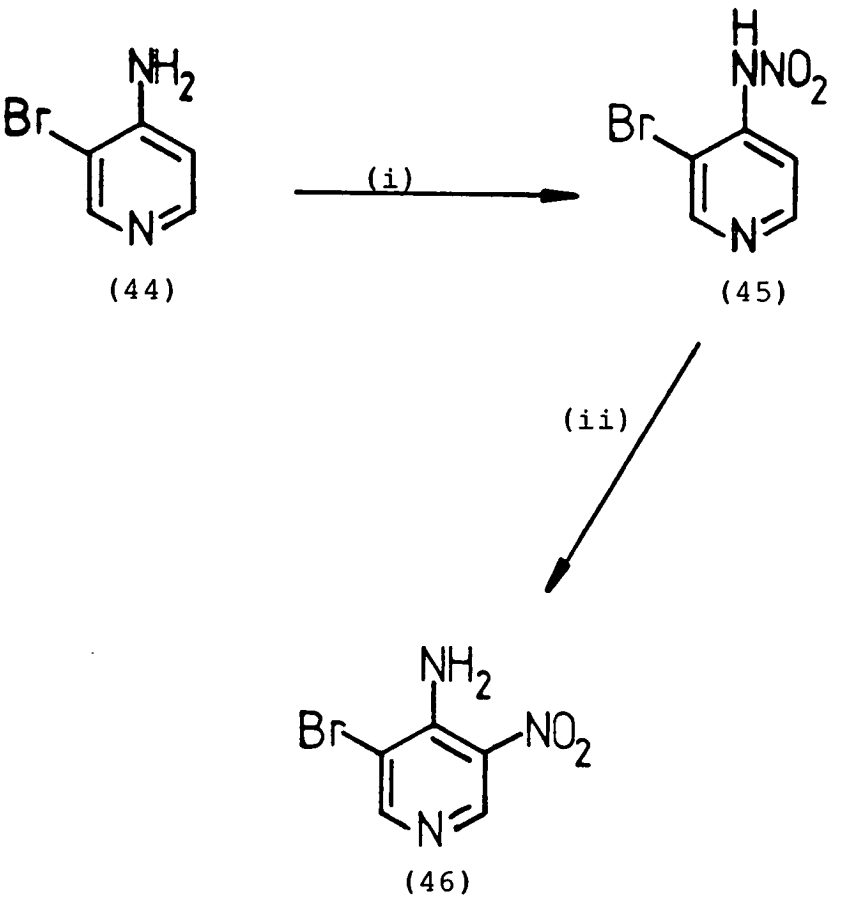
1,2,3-triazole (31)[16]. The nitration[16] of 2-phenyl-2H-1,2,3-triazole (30) under milder conditions using concentrated nitric acid and acetic anhydride gave 2-(4-nitrophenyl)-2H-1,2,3-triazole (31) as the sole product in high yield. The nitration (Scheme 8) of 2-phenyl-2H-1,2,3-triazole (30) was also investigated by Newman[17] using concentrated nitric acid and fuming sulphuric acid and was found to give 2-(2,4-dinitrophenyl)-4-nitro-2H-1,2,3-triazole (33) in low yield. Further nitration[17] of the latter compound using sodium nitrate and fuming sulphuric acid at high temperature was found only to effect further nitration of the phenyl ring rather than the triazole ring giving 4-nitro-2-(2,4,6-trinitrophenyl)-2H-1,2,3-triazole (34) in low yield. The tetranitro-1,2,3-triazole derivative (34) was also formed[17] in high yield by the nitration of 2-(2,4,6-trinitrophenyl)-2H-1,2,3-triazole (35) using concentrated nitric acid and concentrated sulphuric acid. In contrast the attempted nitration (Scheme 9) of 1-(2,4,6-trinitrophenyl)-1H-1,2,3-triazole (36) under identical conditions gave only unreacted starting material rather than the expected 4-nitro or 5-nitro-derivative (37).

1,2,4-Triazole and its C-monoalkyl derivatives resist nitration.[18] However Habraken and her co-workers have shown[19] (Scheme 10) that treatment of 3-(4-nitrophenyl)-1H-1,2,4-triazole (38) with fuming nitric acid and acetic anhydride affords the N-nitro-compound (39) which upon heating isomerises to 5-nitro-3-(4-nitrophenyl)-1H-1,2,4-triazole (40).



(i) KNO_3, conc. H_2SO_4, 350°

Scheme 11



(i) N_2O_4-HNO_3, conc. H_2SO_4, 0 to 10°

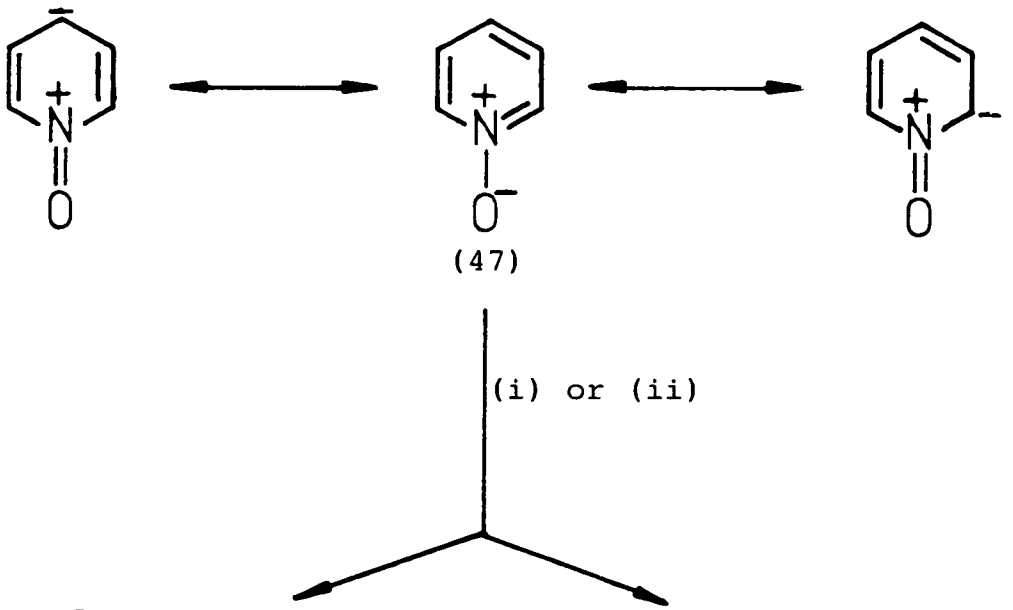
(ii) Conc. H_2SO_4, 100°

Scheme 12

1.1.2 Synthesis of Six-membered Heteroaromatic Nitro-compounds

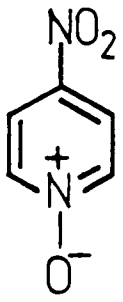
Electrophilic substitution of the unsubstituted pyridine ring is only accomplished with extreme difficulty.[20] Pyridine (41) shows roughly the same reactivity towards electrophilic substitution as nitrobenzene and in accordance with the formation (Scheme 11) of the most resonance stabilised Wheland intermediate (42) undergoes nitration at the 3-position.[20] Thus as early as 1912 Friedl[21] showed (Scheme 11) that treatment of pyridine (41) with potassium nitrate and concentrated sulphuric acid at high temperature resulted in nitration to 3-nitropyridine (43) in low yield (15%). The use of dinitrogen tetroxide[22] as the nitrating reagent in this reaction gave an even lower yield (10%) of 3-nitropyridine (43). In contrast nitration[23] (Scheme 12) of the more electron-rich pyridine ring in 4-amino-3-bromopyridine (44) with fuming nitric acid and concentrated sulphuric acid resulted in the formation of 3-bromo-4-nitraminopyridine (45) in high yield (85%). Heating the nitraminopyridine (45) resulted in its thermal isomerisation to 4-amino-3-bromo-5-nitropyridine (46) in high yield (93%).

In contrast to pyridine, pyridine N-oxide (Scheme 13), because of its resonance hybrid structure (47) exhibits enhanced reactivity towards electrophilic substitution and hence nitration at the 2- and 4-positions. Thus Ochiai[24] found that nitration of pyridine N-oxide (47) with potassium nitrate and fuming sulphuric acid gave 4-nitropyridine N-oxide (48) in high yield. Ochiai[24] also showed that the

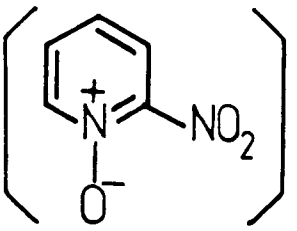


(47)

(i) or (ii)

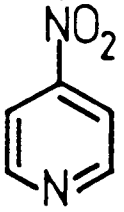


(48)

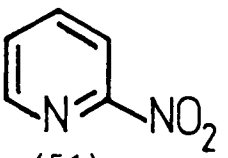


(49)

(iii) or (iv)



(50)



(51)

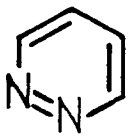
(i) KNO_3, SO_3-H_2SO_4, 100°

(ii) Conc. HNO_3, SO_3-H_2SO_4, 130°

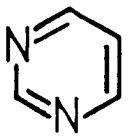
(iii) PCl_3, $CHCl_3$, 70 to 80°

(iv) KNO_3, conc. H_2SO_4, 160°

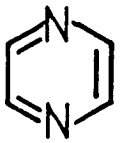
Scheme 13



(52)

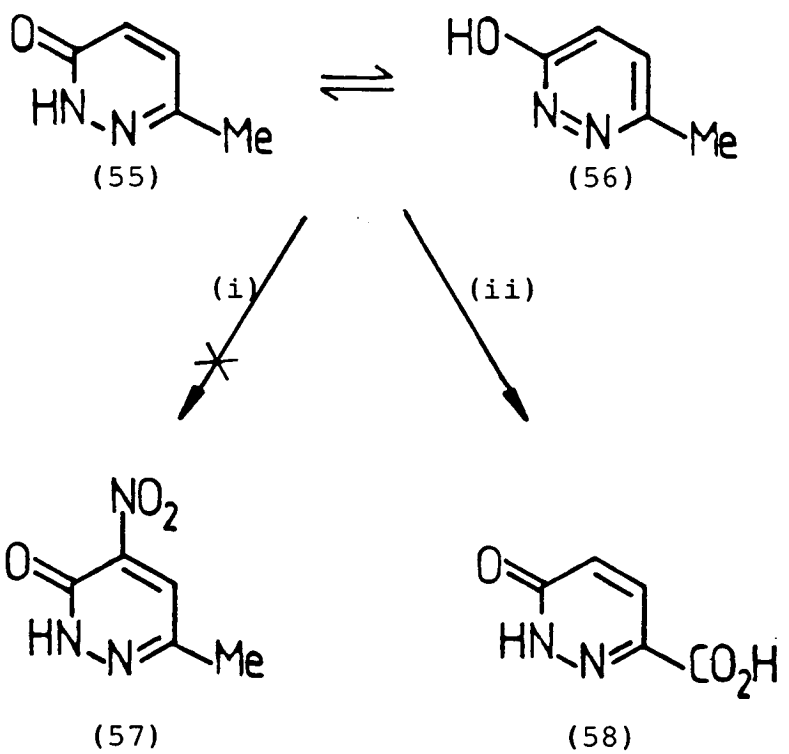


(53)



(54)

Scheme 14



(i) Conc. HNO_3, room temp.

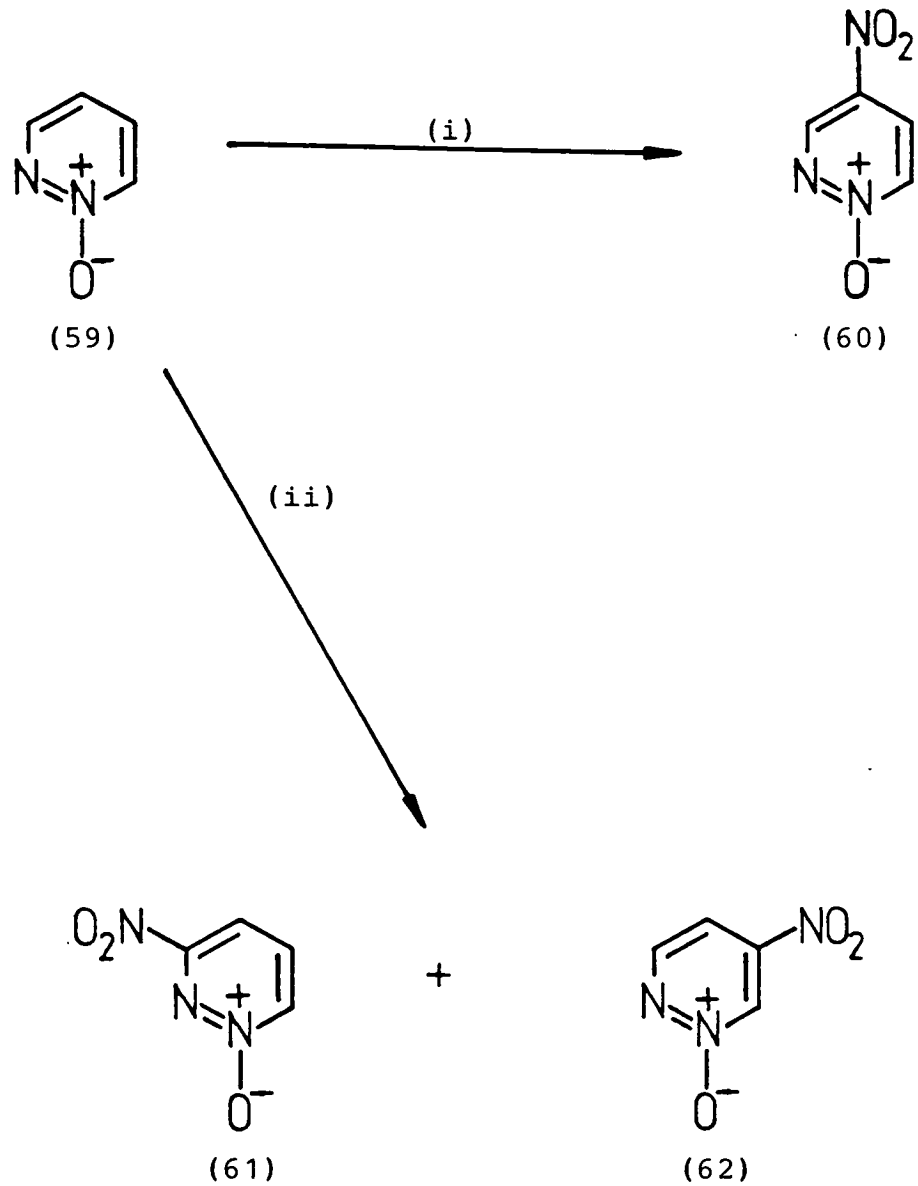
(ii) HNO_{3aq}, reflux

Scheme 15

N-oxide function in 4-nitropyridine N-oxide (48) so produced could be selectively reduced by treatment with phosphorus trichloride giving 4-nitropyridine (50). The nitration of pyridine N-oxide (47) with concentrated nitric acid and fuming sulphuric acid resulted in the simultaneous formation of three products identified as 4-nitropyridine N-oxide (48), 2-nitropyridine (51) and 4-nitropyridine (50). It was also observed that the treatment of 4-nitropyridine N-oxide (47) with potassium nitrate and concentrated sulphuric acid at high temperature, resulted in deoxygenation to 4-nitropyridine (50). It is likely therefore that the formation of 2-nitropyridine (51) in the nitration of pyridine N-oxide (47) with concentrated nitric acid and fuming sulphuric acid is due to the lower stability of 2-nitropyridine N-oxide (49) to deoxygenation compared with 4-nitropyridine N-oxide (48).

It follows from the observed reluctance of pyridine to undergo electrophilic substitution reactions that the introduction of a second azomethene nitrogen atom into the ring should reduce still further the reactivity of the resulting diazine ring towards electrophilic attack. Thus (Scheme 14) the diazines, pyridazine (52), pyrimidine (53), and pyrazine (54) would be expected to be more reluctant to undergo electrophilic substitution, and in particular nitration, than pyridine.

All of the ring positions in the pyridazine nucleus are electron deficient due to the electron-withdrawing effect of the nitrogen atoms.[25] Thus, pyridazine (52)



(i) N_2O_4-HNO_3, conc. H_2SO_4, 105 to 110°

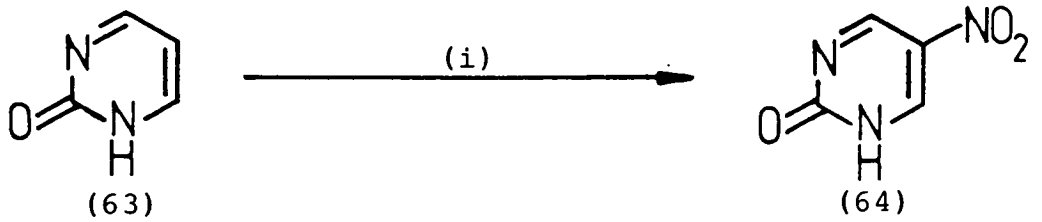
(ii) $AgNO_3$, $MeC(=O)Cl$, -10°

Scheme 16

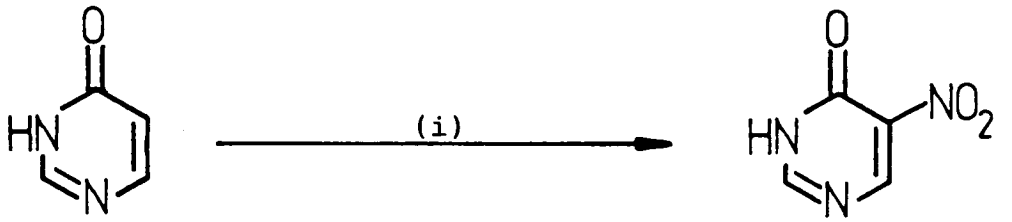
is stable to attempted nitration using potassium nitrate in concentrated sulphuric acid.[26] Even activation of the pyridazine ring by electron-donating substituents fails to promote nitration.[25] Thus the attempted nitration (Scheme 15) of the tautomeric 6-methylpyridazin-3(2H)-one [(55)⇌(56)] with concentrated nitric acid failed to afford any of the expected nitro-derivative (57).[26] Conversely heating 6-methylpyridazin-3(2H)-one (55) with dilute nitric acid resulted only in the oxidation of the methyl substituent giving the carboxylic acid derivative (58) with no apparent formation of the nitration product (57).[26]

In contrast (Scheme 16) to pyridazine but analogously to pyridine N-oxide (see before) pyridazine 1-N-oxide (59) undergoes nitration more readily. Thus, treatment[29] of pyridazine 1-N-oxide (59) with fuming nitric acid and concentrated sulphuric acid resulted in nitration at the 4-position giving 4-nitropyridazine 1-N-oxide (60) though in low yield (8%). The yield of the 4-nitro product (60) was improved (26%)[30] when the temperature of reaction was increased (Scheme 16). Nitration of pyridazine 1-N-oxide (59) with silver nitrate in the presence of acetyl chloride[31] gave as the major product (yield 17%) 3-nitropyridazine 1-N-oxide (61) together with a low yield (1%) of 5-nitropyridazine 1-N-oxide (62) as well as some unreacted starting-material.

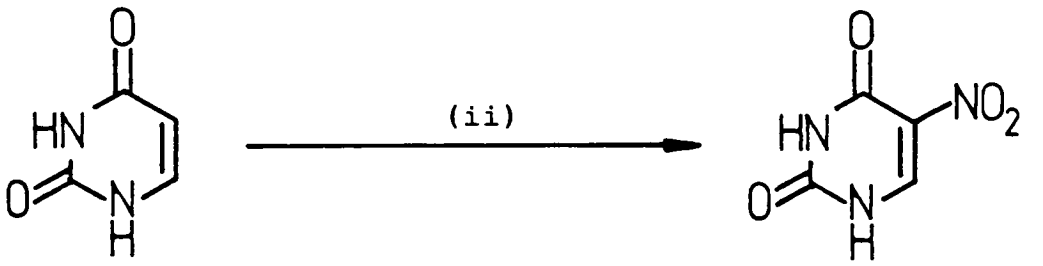
The successful electrophilic nitration of the pyrimidine ring requires activation by the presence of strongly electron-donating substituents. The nitration of pyrimidine



(63) (64)



(65) (66)

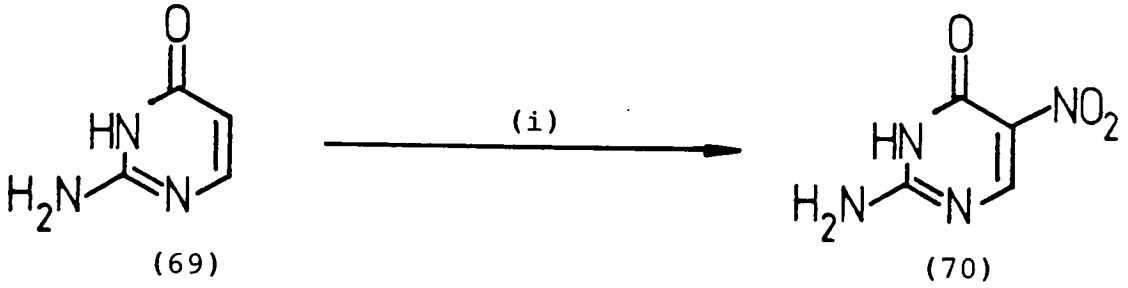


(67) (68)

(i) KNO_3, conc. H_2SO_4, 95°

(ii) N_2O_4-HNO_3, 50 to 60°

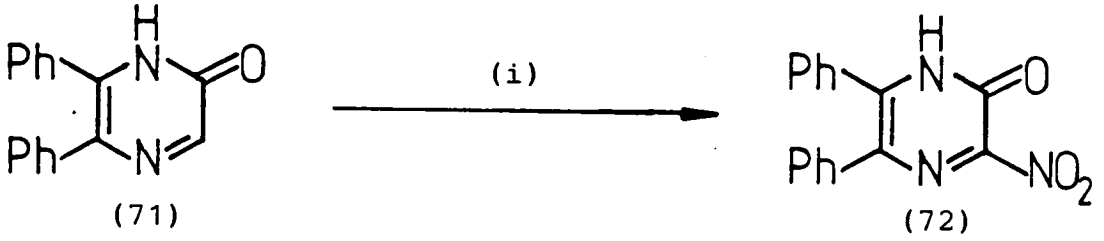
Scheme 17



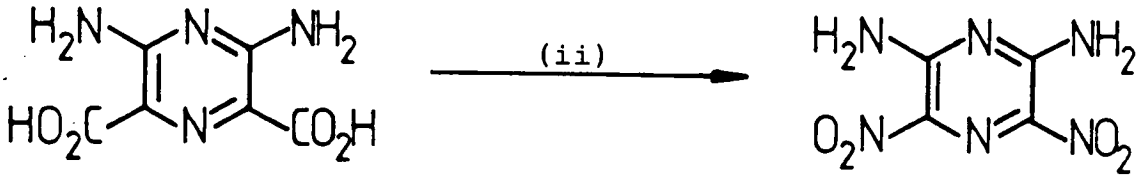
(69) (70)

(i) N_2O_4-HNO_3, conc. H_2SO_4, 100°

Scheme 18



(71) (72)

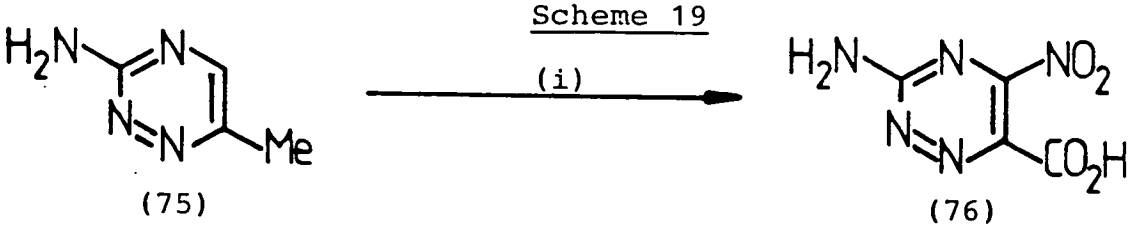


(73) (74)

(i) N_2O_4-HNO_3, AcOH, 25°

(ii) Conc. HNO_3, conc. H_2SO_4, 10°

Scheme 19



(75) (76)

(i) N_2O_4-HNO_3, conc. H_2SO_4, 50°

Scheme 20

itself and its alkyl derivatives cannot be achieved under the usual conditions.[30] However, the presence of even a single electron-releasing substituent promotes nitration which invariably occurs at the 5-position.[30] Fox and his co-workers[31] have shown (Scheme 17) that both pyrimidin-2(1H)-one (63) and pyrimidin-4(3H)-one (65) can be nitrated using potassium nitrate and concentrated sulphuric acid giving respectively 5-nitropyrimidin-2(1H)-one (64) and 5-nitropyrimidin-4(3H)-one (66) though only in moderate yield (38-49%). Not surprisingly in view of the presence of two electron-donating substituents, pyrimidine-2,4(1H,3H)-dione (67) undergoes nitration[32,33] under milder conditions (Scheme 17) giving 5-nitropyrimidine-2,4(1H,3H)-dione (68) in essentially quantitative yield. The presence of amino-substituents also facilitates nitration of the pyrimidine ring, as illustrated (Scheme 18) by the nitration of 2-aminopyrimidin-4(3H)-one (69) with fuming nitric acid and concentrated sulphuric acid to yield the 5-nitro-derivative (70) in quantitative yield.[34]

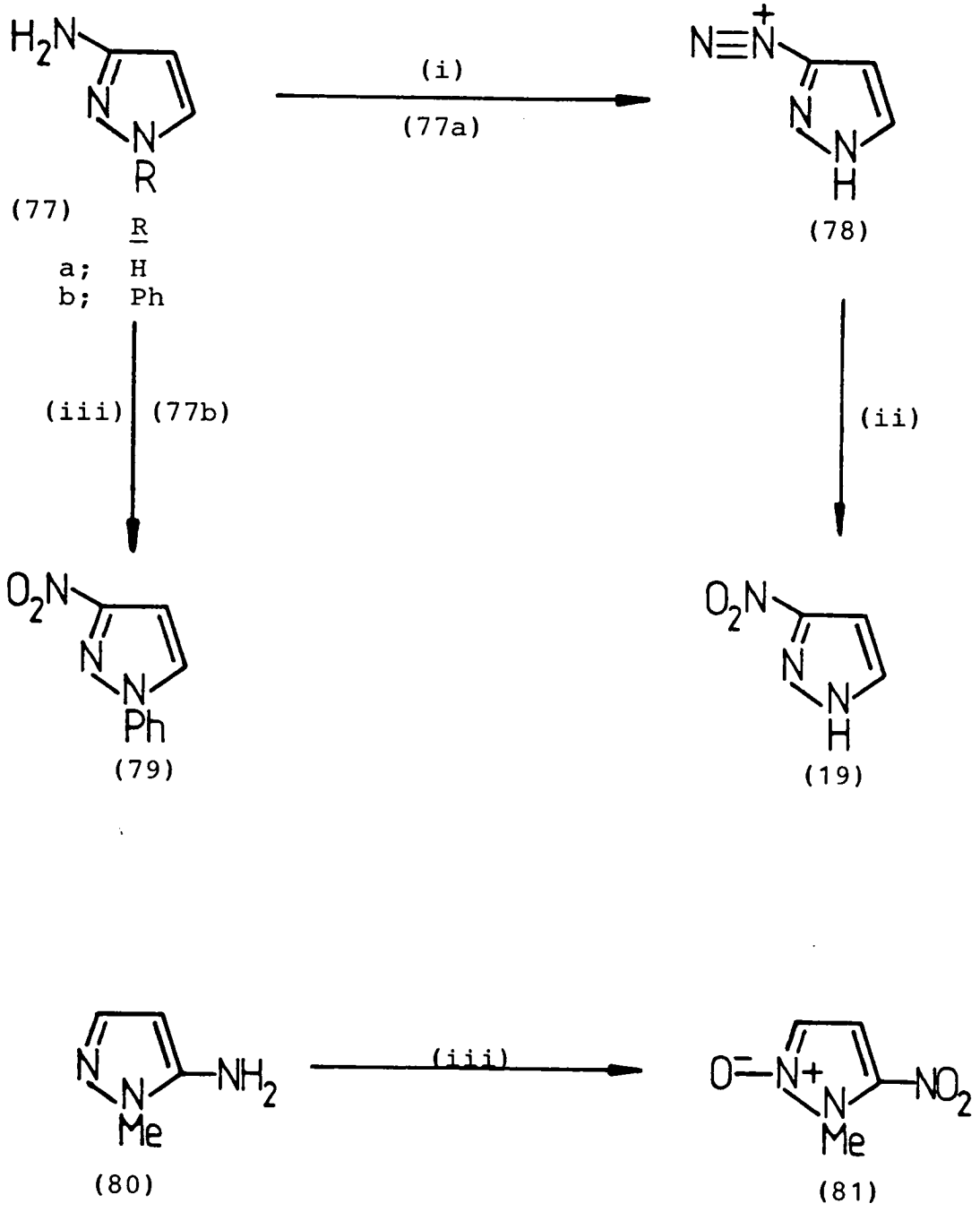
Pyrazines containing electron-donating substituents undergo nitration under relatively mild conditions (Scheme 19). Thus 5,6-diphenylpyrazin-2(1H)-one (71) reacts with fuming nitric acid in acetic acid to give 5,6-diphenyl-3-nitropyrazin-2(1H)-one (72) in good yield.[35] 2,6-Diamino-pyrazine-3,5-dicarboxylic acid (73) likewise undergoes nitrative decarboxylation to give the dinitropyrazine derivative (74) in high yield.[36]

1,2,3- And 1,3,5-triazines are hydrolysed under the

usual conditions used for electrophilic nitration which therefore cannot be used for the synthesis of nitro-derivatives of these heterocyclic ring systems. However an example of the nitration of the 1,2,4-triazine ring (Scheme 20), has been described by Hadacek and Kisa.[37] Thus treatment of 3-amino-6-methyl-1,2,4-triazine (75) with fuming nitric acid and concentrated sulphuric acid resulted in nitration at the 5-position with accompanying oxidation of the 6-methyl group giving 3-amino-5-nitro-1,2,4-triazine-6-carboxylic acid (76) in low yield.

1.2 Synthetic Methods Involving Functional Group Modification

The direct introduction of nitro-groups into nitrogen heteroatomic compounds by electrophilic nitration has several limitations such as the relative lack of control over the position of nitration, low yield and in some cases the vigorous conditions necessary. An alternative synthetic approach to nitro-derivatives of nitrogen hetero-aromatic compounds involves the manipulation of functional groups such as amino or nitroso already present in the heteroaromatic compound. Two general methods are available for such nitro-group synthesis namely oxidation of other nitrogen substituents such as amino and nitroso and nitro-dediazoniation reactions of heteroaromatic diazonium salts.



(i) $NaNO_2$, conc. H_2SO_4, AcOH, -5 to 0°

(ii) $NaNO_2$, H_2O, 45 to 50°

(iii) 90% H_2O_2, F_3CCO_2H, CH_2Cl_2, reflux

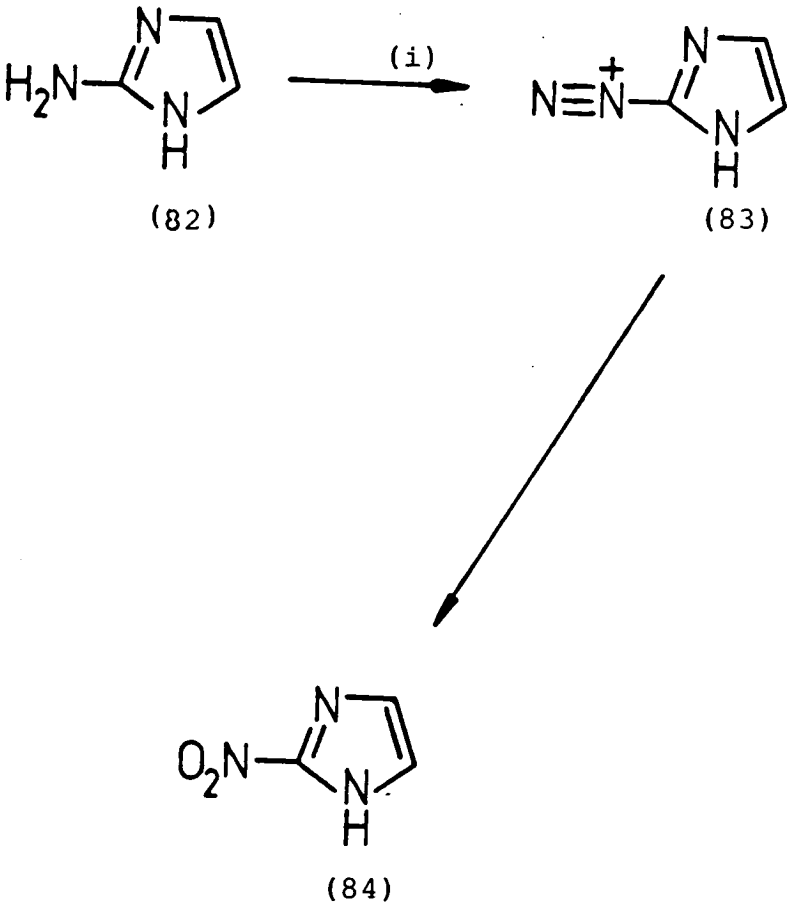
Scheme 21

1.2.1 Synthesis of Five-membered Heteroaromatic Nitro-compounds

3-Aminopyrazoles have been converted into their corresponding 3-nitro-derivatives by two methods (Scheme 21). Firstly by the non-catalytic replacement of a diazonium-group by a nitro-group and secondly by the oxidation of an amino-substituent to a nitro-group. Thus it has been shown[38] that diazotisation of 3-aminopyrazole (77a) with sodium nitrite in sulphuric acid affords 3-nitropyrazole (19) after nucleophilic replacement of the diazonium substituent in a diazonium intermediate (78) by nitrite ion. In comparison the direct nitration of pyrazole[8] gives a higher yield of 3-nitropyrazole (19) although the conditions to effect this transformation are more forcing.

Coburn[39] has reported the oxidative conversion of heterocyclic amino-compounds into their nitro-derivatives. Oxidation (Scheme 21) of 3-amino-1-phenylpyrazole (77b) with trifluoroperacetic acid gave 3-nitro-1-phenylpyrazole (79) in a yield comparable to that of direct nitration. Oxidation[39] of 3-amino-2-methylpyrazole (80) with trifluoroperacetic acid resulted in both N-oxidation and nitro-group formation giving 2-methyl-3-nitropyrazole 1-N-oxide (81) in low yield (10%).

It would appear that the only synthesis of nitro-imidazoles by functional group modification involves the catalytic displacement of a diazonium substituent by a nitro-group (Scheme 22). Thus, reaction[40,41] of



(82) (83) (84)

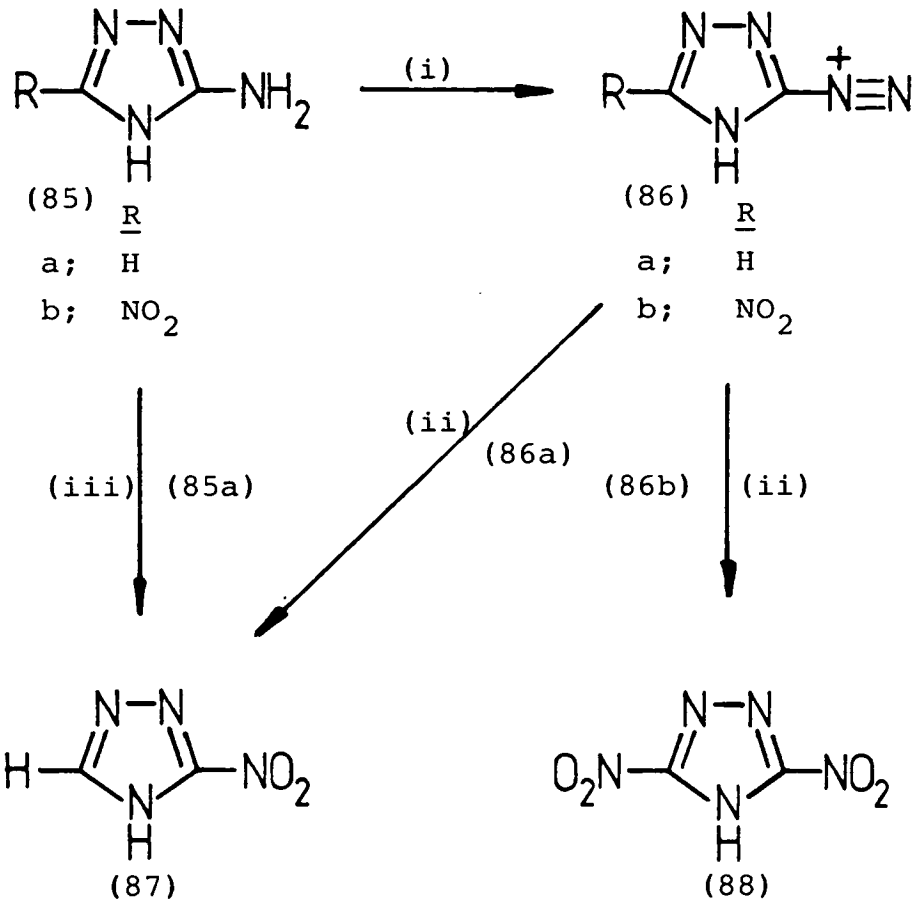
(i) $NaNO_2$, $CuSO_4$, HNO_3aq., room temp.

Scheme 22

2-amino-imidazole (82) with sodium nitrite and dilute nitric acid in the presence of copper sulphate affords 2-nitroimidazole (84) in moderate yield (40%) presumably *via* nitro-dediazoniation of the imidazole-diazonium intermediate (83). This synthetic method for nitro-imidazoles complements that of the direct nitration of imidazoles which results in the formation of 4- and 5-nitro-imidazoles even under forcing conditions (see section 1.1.1 before).

Nitro-1,2,4-triazoles are readily accessible (Scheme 23) by displacement of the diazonium group in 1,2,4-triazole-diazonium salts produced by diazotisation of readily available amino-1,2,4-triazoles and also by peracid oxidation of the latter. Bagal *et al* [38] have shown that treatment of 3-amino-(4*H*)-1,2,4-triazole (85a) and its 5-nitro-derivative (85b) with sodium nitrite in sulphuric acid followed by heating in aqueous sodium nitrite results in the formation of 3-nitro-(4*H*)-1,2,4-triazole (87) and 3,5-dinitro-(4*H*)-1,2,4-triazole (88) in good yield (60-80%). 3-Amino-(4*H*)-1,2,4-triazole (85a) is also oxidatively converted (Scheme 23) in moderate yield (45%) into 3-nitro-(4*H*)-1,2,4-triazole (87).[42] Since the 1,2,4-triazole ring is not susceptible to nitration nitro-dediazoniation and peracid oxidation of amino-1,2,4-triazoles represent valuable methods for the synthesis of nitro-1,2,4-triazoles.

The tendency for nitrotetrazoles to decompose under typical nitration conditions also makes nitro-dediazoniation the method of choice for the synthesis of such nitroazoles



(85) R
a; H
b; NO_2

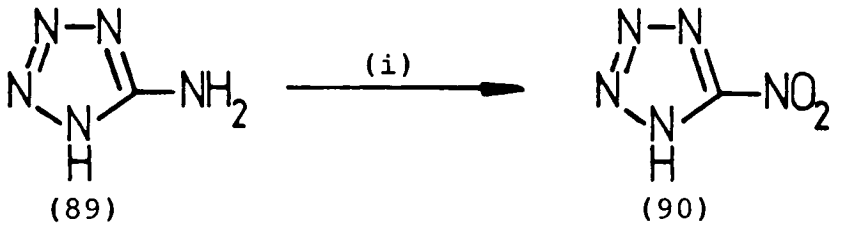
(86) R
a; H
b; NO_2

(i) $NaNO_2$, Conc. H_2SO_4, AcOH, -5 to 10°

(ii) $NaNO_2$, H_2O, 45 to 50°

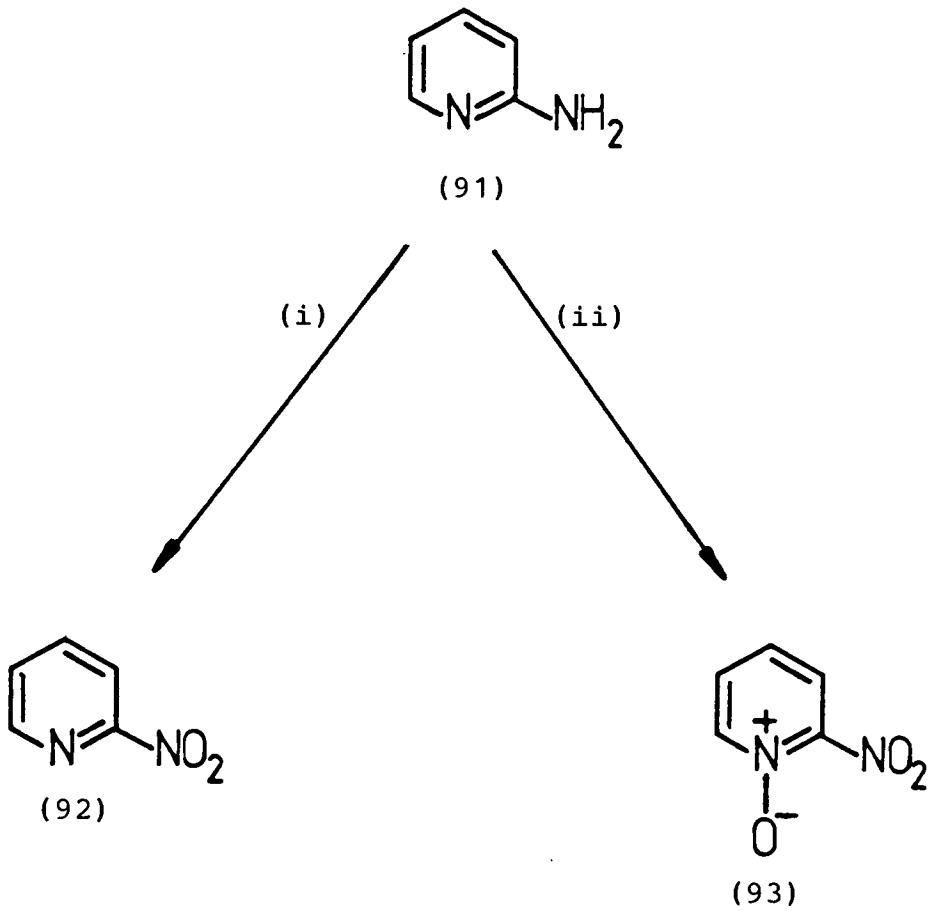
(iii) 90% H_2O_2, F_3CCO_2H, 70 to 80°

Scheme 23



(i) $NaNO_2$, $CuSO_4$, H_2SO_4aq., room temp.

Scheme 24



(i) 30% H_2O_2, Conc. H_2SO_4, room temp.

(ii) 90% H_2O_2, $(F_3CCO)_2O$, CH_2Cl_2, reflux

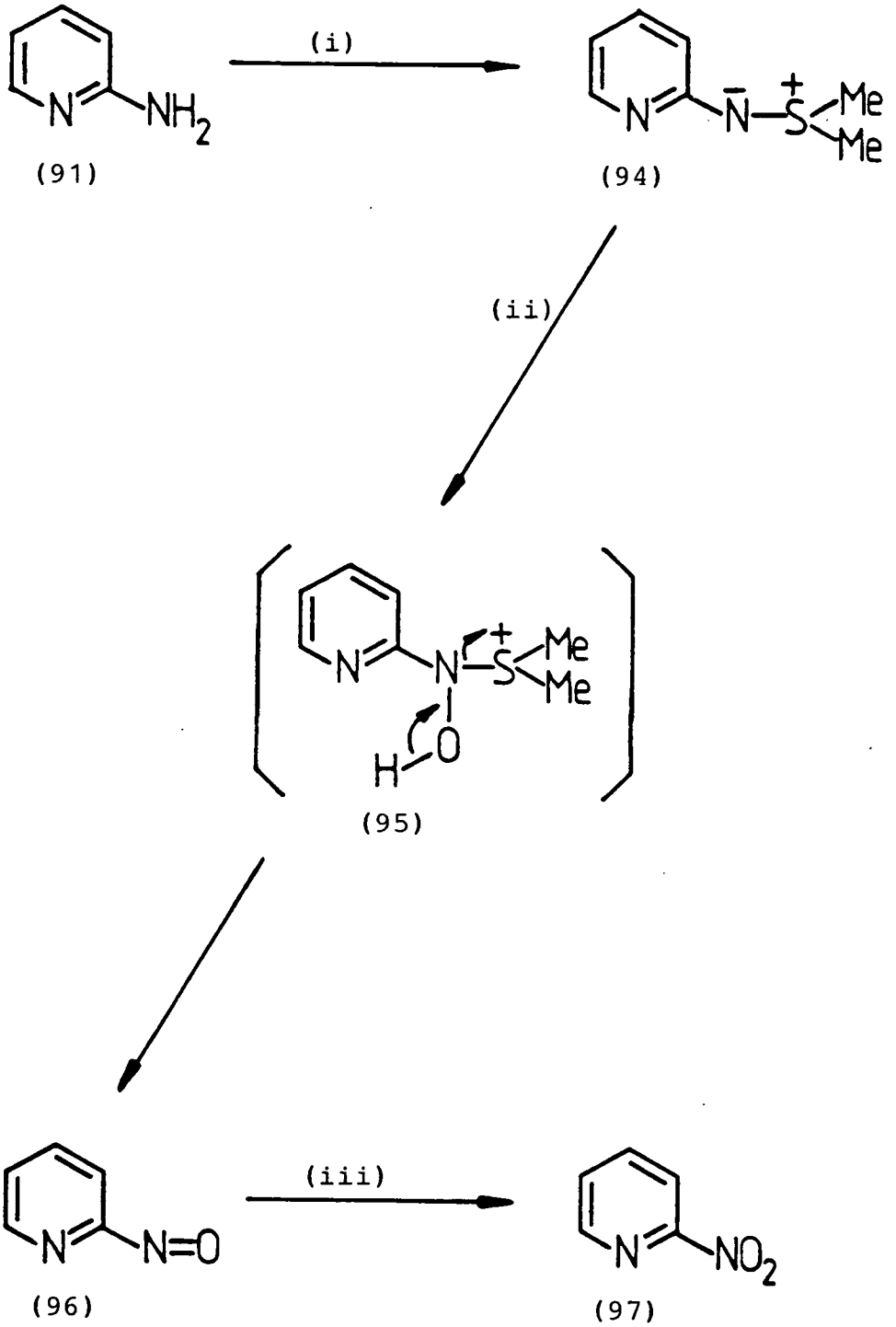
Scheme 25

(Scheme 24). Thus nitro-dediazoniation of 5-amino-tetrazole (89) under Sandmeyer conditions affords 5-nitrotetrazole (90) in high yield (90%).[43,44]

1.2.2 Synthesis of Six-membered Heteroaromatic Nitro-compounds

Because of the reluctance of the pyridine ring to undergo electrophilic nitration many nitropyridine derivatives are only accessible by the manipulation of other functional groups more readily introduced into the pyridine ring. The oxidation of amino- or nitroso-pyridines has been of particular value for the synthesis of nitropyridines. The oxidative conversion of an amino-pyridine into a nitropyridine (Scheme 25) was first reported in 1932 by Kirpal and Bohm[45] who showed that the reaction of 2-aminopyridine (91) with 30% hydrogen peroxide in sulphuric acid gave 2-nitropyridine (92) in good yield (75%). It was later shown by Coburn[39] that forcing oxidation of 2-aminopyridine (91) with trifluoroperacetic acid (Scheme 25) resulted in the oxidation of both the amino-substituent and the ring nitrogen atom affording 2-nitropyridine N-oxide (93) though only in low yield (20%).

2- and 4-Aminopyridines tend to react with electrophilic reagents at the ring nitrogen atom rather than at the amino-substituent, thus making the oxidative conversion of aminopyridines into nitropyridines by electrophilic oxidising agents (e.g. peracids) a relatively difficult process. Taylor[46] has circumvented this difficulty (Scheme 26) by



(i) Me_2S, N-chlorosuccinimide, CH_2Cl_2, -20°

(ii) m-$ClC_6H_4CO_3H$, CH_2Cl_2, 0 to 5°

(iii) O_3, CH_2Cl_2, 0°

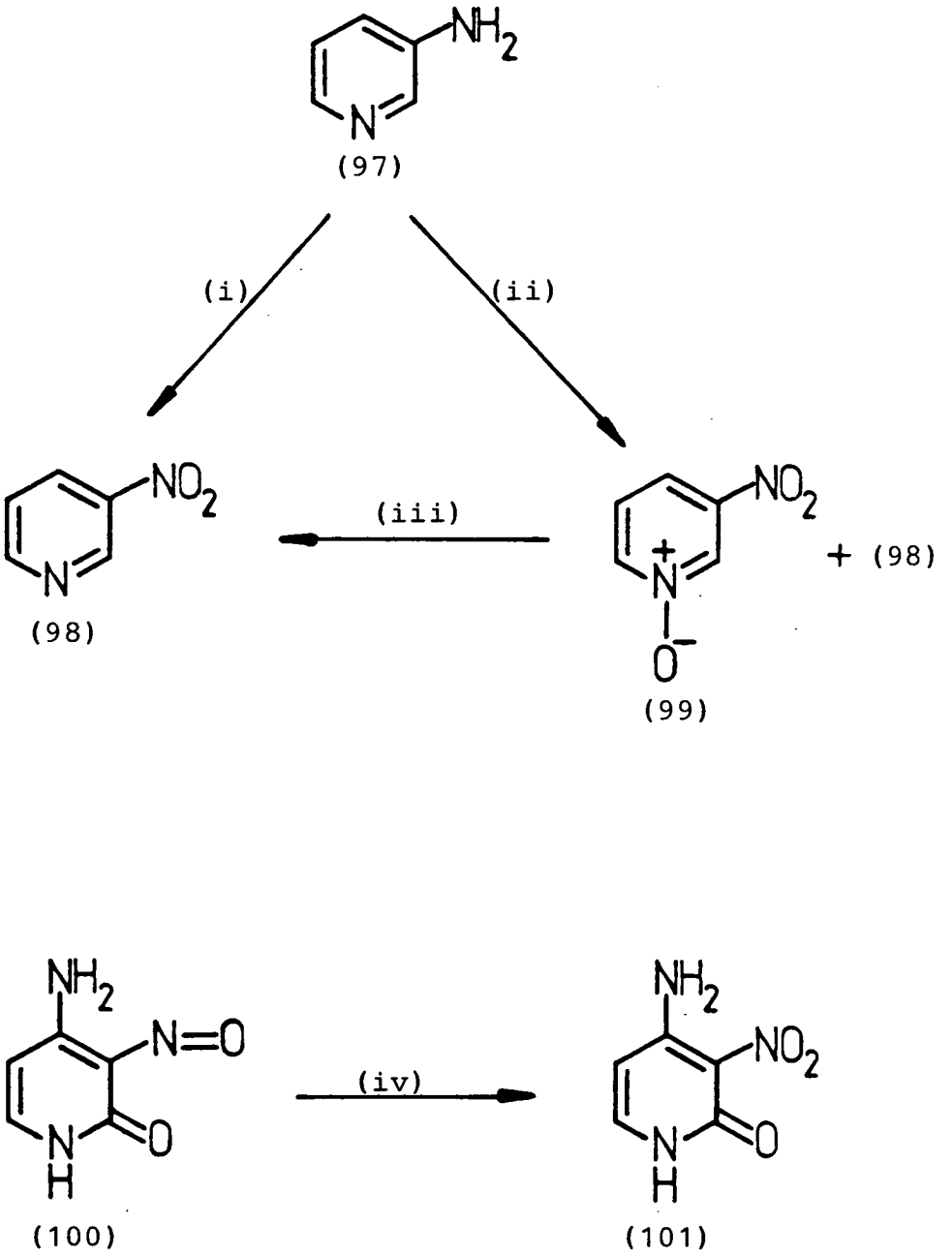
Scheme 26

converting the aminopyridine into the corresponding sulphilimine in which the nucleophilic character of the exocyclic nitrogen atom is enhanced thus making it more susceptible to electrophilic oxidation. Hence (Scheme 26) peracid oxidation of the S,S-dimethylsulphilimine (94) derived from 2-aminopyridine (91) gives by way of the intermediate (95) a moderate yield (44%) of 2-nitroso-pyridine (96) which in turn can be oxidised by ozone to afford 2-nitropyridine (92) in quantitative yield.

3-Nitropyridines have also been prepared by the oxidation of both 3-aminopyridines and 3-nitrosopyridines (Scheme 27). 3-Aminopyridine (97) is converted[47] in low yield into 3-nitropyridine (98) by treatment with hydrogen peroxide in concentrated sulphuric acid. In contrast when 3-aminopyridine (97) is oxidised with trifluoroperacetic acid[48] (Scheme 27) the result is a mixture of 3-nitro-pyridine (98) and 3-nitropyridine N-oxide (99). However the N-oxide (99) can be converted (Scheme 27) into 3-nitropyridine (98) by deoxygenation with phosphorus tri-chloride.[48] The yields of 3-nitropyridine (98) by either method (Scheme 27) are higher than can be obtained by direct nitration procedures (see section 1.1.2).

The oxidative conversion of a 3-nitrosopyridine into a 3-nitropyridine has also been described[49] (Scheme 27). Thus 4-amino-3-nitrosopyridin-2(1H)-one (100) is converted into the 3-nitro-derivative (101) in good yield by oxidation with hydrogen peroxide in sulphuric acid.

Simple nitropyrimidines and nitropyrazines cannot be obtained by direct nitration due to the inertness of the



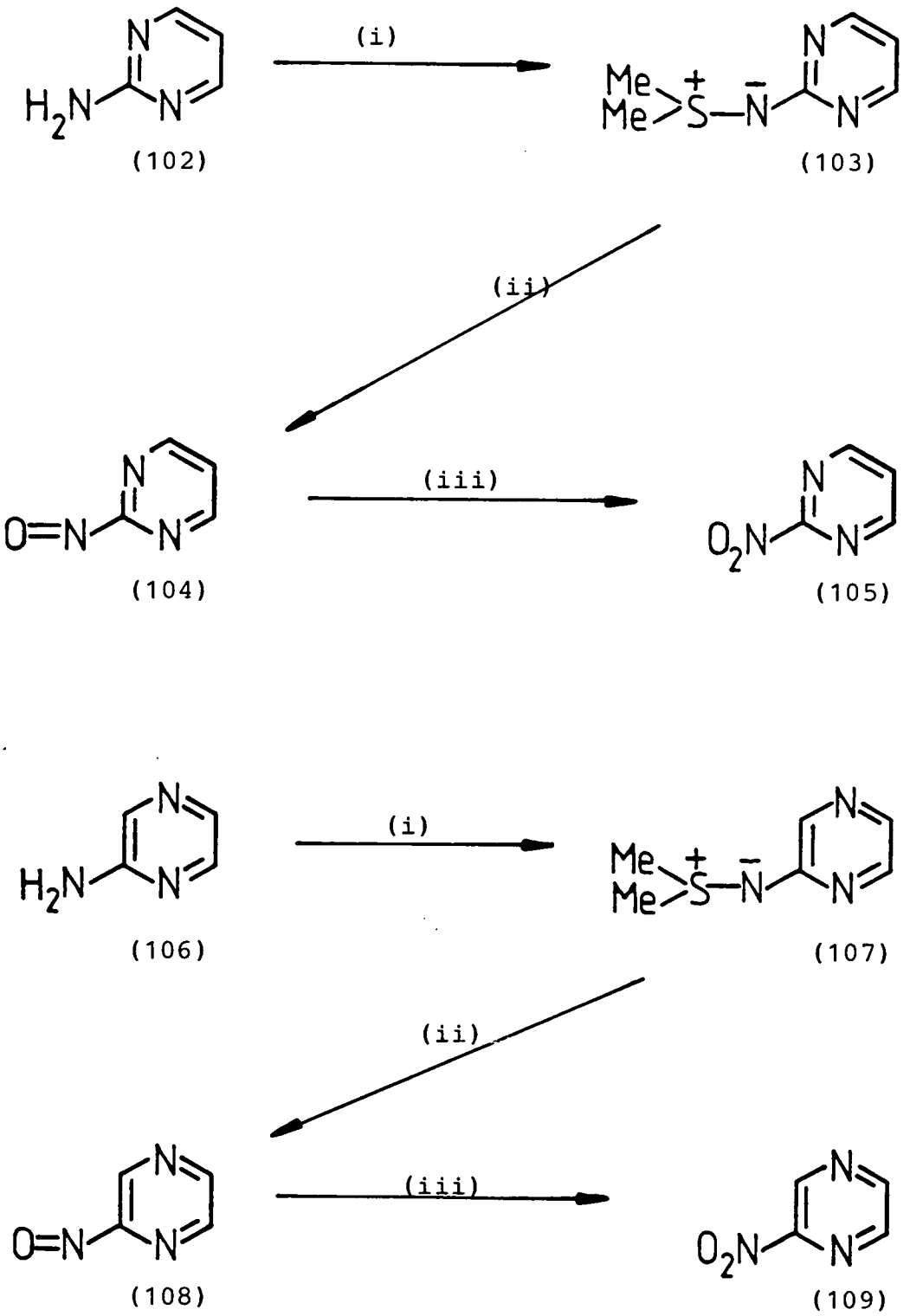
(i) 30% H_2O_2, conc. H_2SO_4, 60 to 70°

(ii) 90% H_2O_2, $(CF_3CO)_2O$, CH_2Cl_2, reflux

(iii) PCl_3, $CHCl_3$, 70 to 80°

(iv) 30% H_2O_2, conc. H_2SO_4, 60 to 70°

Scheme 27



(i) Me_2S, N-chlorosuccinimide, CH_2Cl_2, -20°

(ii) m-$ClC_6H_4CO_3H$, CH_2Cl_2, -7°

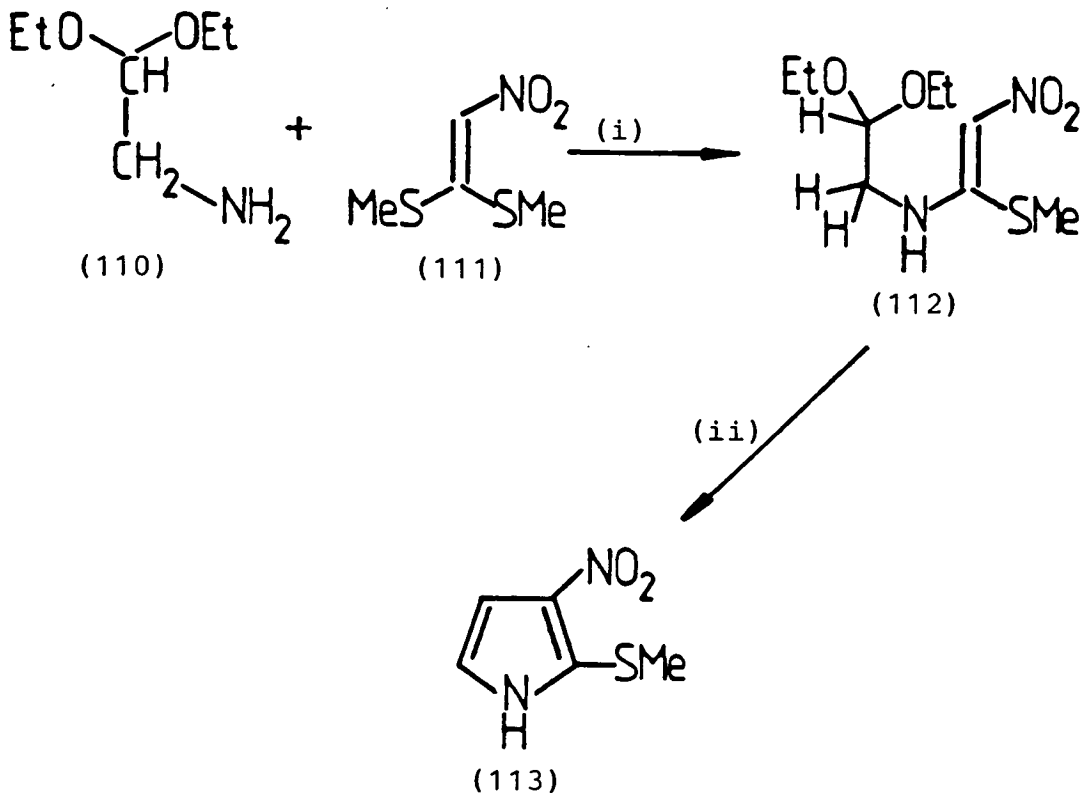
(iii) O_3, CH_2Cl_2, 0°

Scheme 28

pyrimidine and pyrazine rings to electrophilic substitution (see section 1.1.2). However both simple nitropyrimidines and nitropyrazines are indirectly accessible by oxidation of readily available sulphilimine derivatives (Scheme 28) as already described for the synthesis of nitropyridine derivatives (see Scheme 27). Thus S,S-dimethyl-N-(pyrimidin-2-yl) sulphilimine (103) is readily prepared[46] from 2-aminopyrimidine (102) and is oxidised by m-chloroperbenzoic acid to 2-nitrosopyrimidine (104) which on further oxidation with ozone ultimately yields[46] 2-nitropyrimidine (105). An analogous series of transformations (Scheme 28) allows the conversion of 2-aminopyrazine (106) into 2-nitropyrazine (109).[46]

1.3 Synthetic Methods Involving Acyclic Nitro-precursors

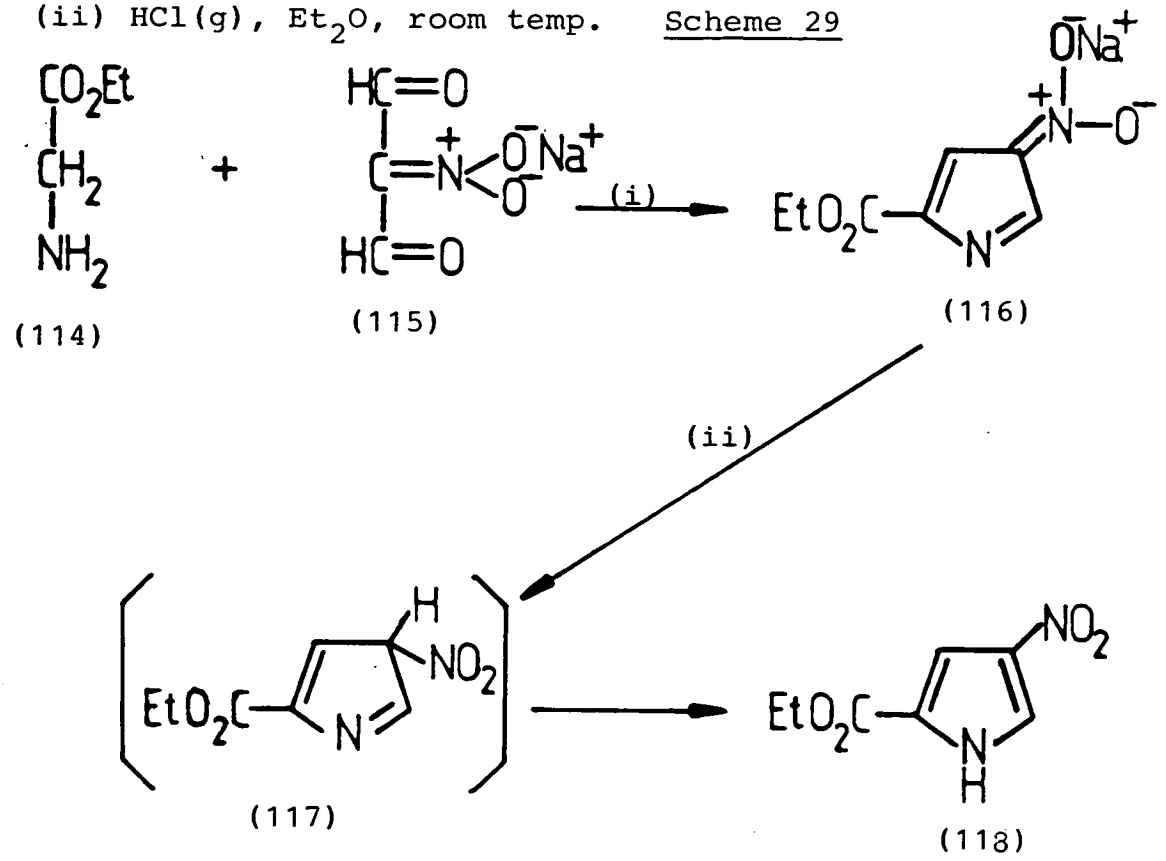
The only remaining general method for the synthesis of nitro-derivatives of nitrogen heteroaromatic compounds involves the use of acyclic nitro-precursors. The conversion of acyclic nitro-compounds into heteroaromatic nitro-derivatives broadly involves two types of cyclisation process namely intramolecular amine-carbonyl condensations or cycloaddition reactions either of the [4+2] Diels-Alder type or the [3+2] 1,3-dipolar type. The importance of such cyclisative methods is that they tend to complement syntheses of nitrogen heteroaromatic nitro-compounds based on direct nitration (Section 1.1) and functional group manipulation (Section 1.2).



(110) (111) (112) (113)

(i) EtOH, reflux

(ii) HCl(g), Et_2O, room temp. Scheme 29



(114) (115) (116) (117) (118)

(i) NaOH aq., EtOH, 50°

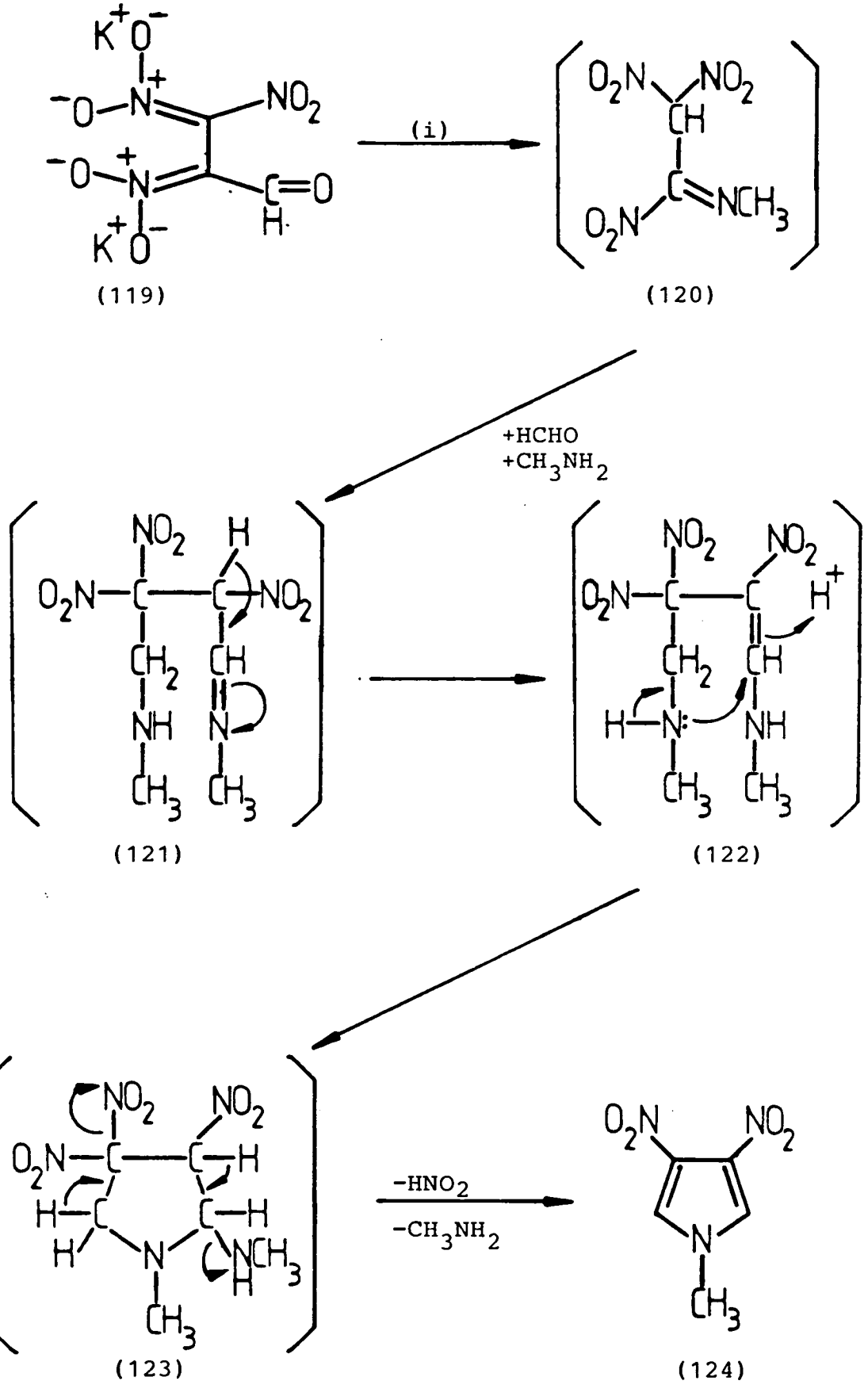
(ii) HCl aq., room temp.

Scheme 30

1.3.1 Synthesis of Five Membered Heteroaromatic Nitro-compounds

Procedures for the synthesis of 2-nitropyrroles involving cyclisation of acyclic nitro-precursors appear to be unknown but methods of this type have been used for the synthesis of 3-nitropyrroles (Schemes 29 to 31). A recent method (Scheme 29) for the synthesis of 2-methylthio-3-nitropyrrole (113) involves the condensation of 1,1-bis-methylthio-2-nitroethene (111) with aminoacetaldehyde diethyl acetal (110) to give the amino-nitroethene (112) followed by cyclisation of the latter with ethereal hydrogen chloride.[50] In an alternative synthesis of 3-nitropyrroles from acyclic nitro-compounds (Scheme 30) it has been shown[6,51] that the sodium salt of 2-nitromalondialdehyde (115) condenses with ethyl glycinate (114) in the presence of aqueous alkali to afford after acidification ethyl 4-nitropyrrole-3-carboxylate (118) in high yield (66-90%). 3,4-Dinitropyrrole (124) is the end product of the complex condensation reaction (Scheme 31) of the dipotassium salt of 2,3,3-trinitropropionaldehyde (119) with methylamine and formaldehyde.[52,53]

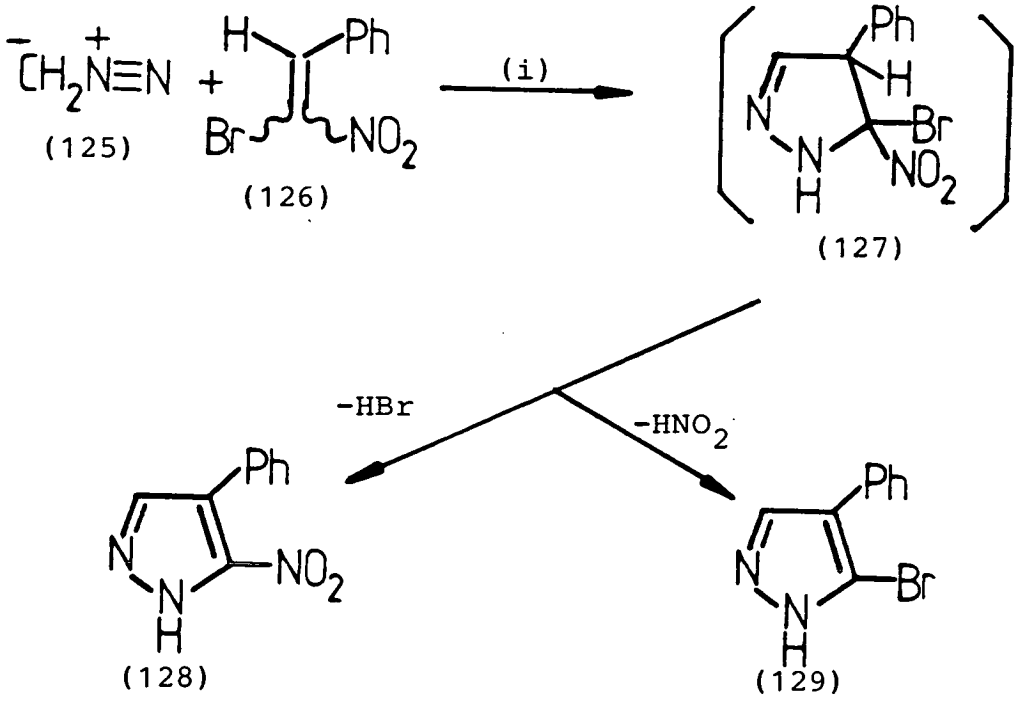
The formation of a 3-nitropyrazole derivative (Scheme 32) by 1,3-dipolar cycloaddition has been achieved[54] in relatively high yield (74%). Thus the reaction of diazomethane (125) with 1-bromo-1-nitro-2-phenylethene (126) in the presence of sodium hydrogen carbonate gave 3-nitro-4-phenylpyrazole (128) together with a small quantity (10%) of 3-bromo-4-phenylpyrazole (129). The



(119) (120) (121) (122) (123) (124)

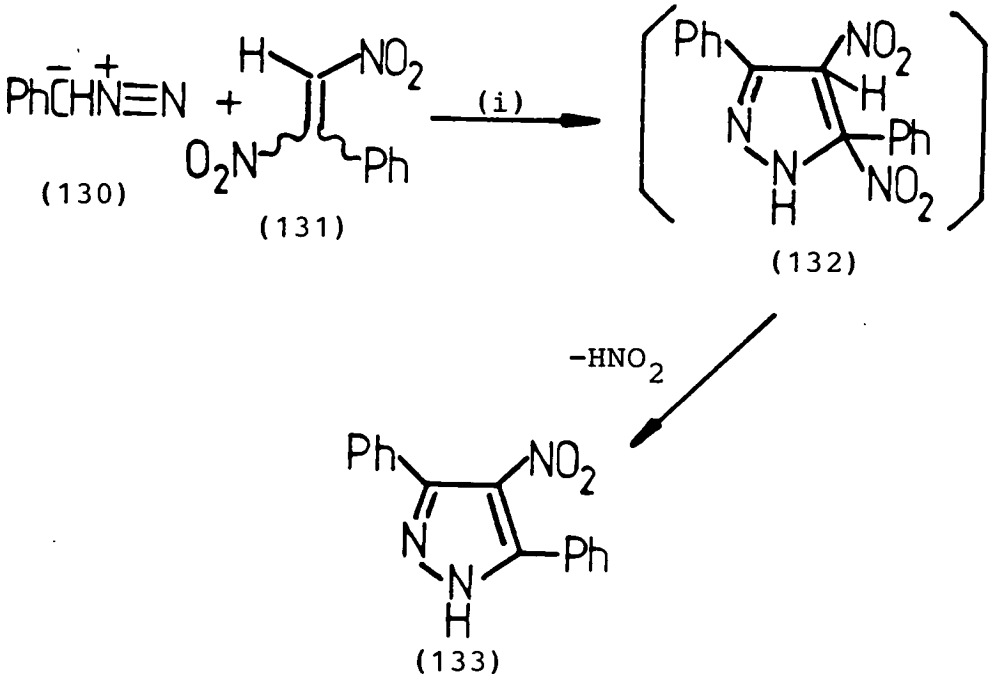
(i) $CH_3NH_3^+Cl^-$, HCHO, H_2O, room temp.

Scheme 31



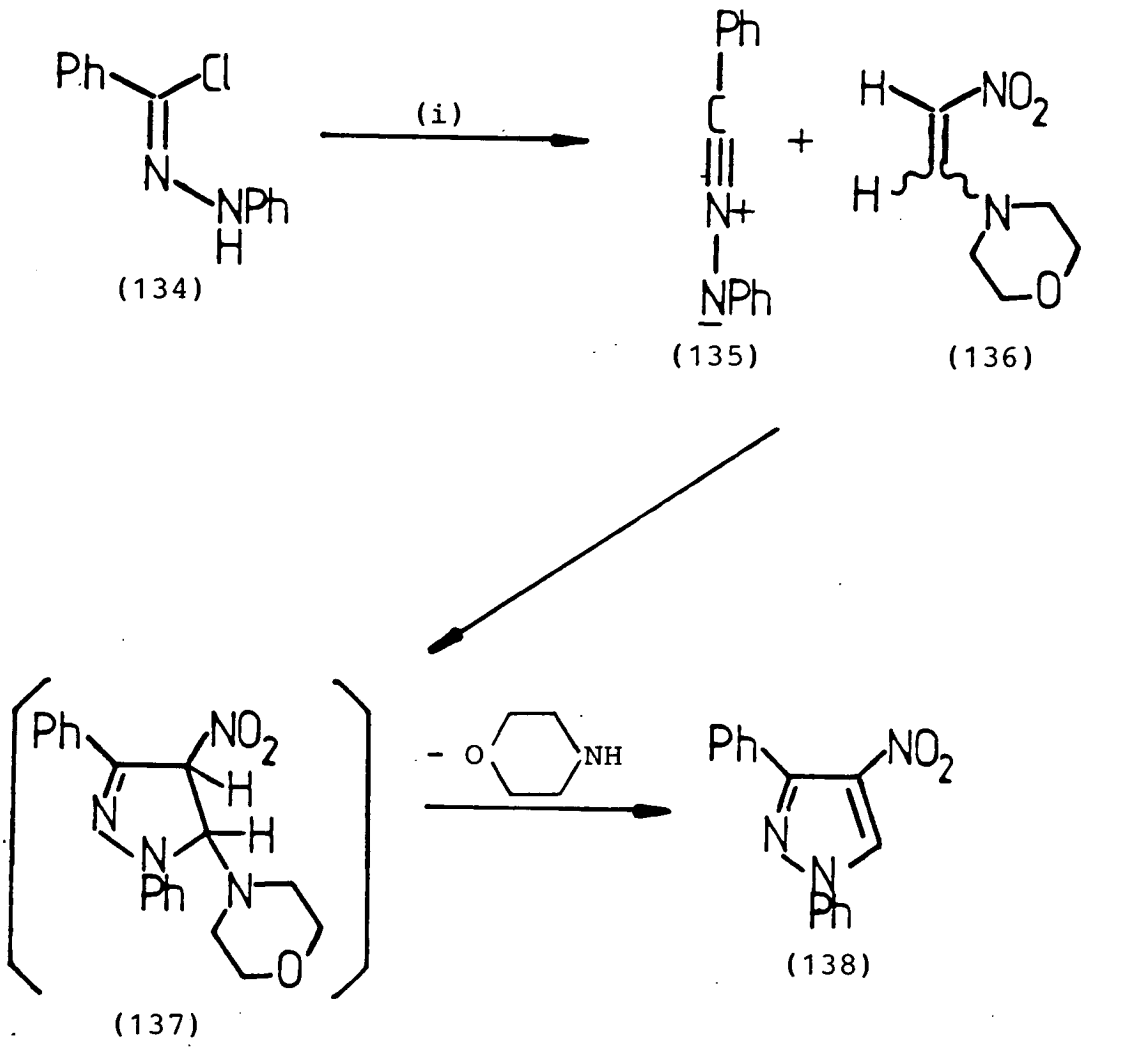
(i) $NaHCO_3$aq., Et_2O, room temp.

Scheme 32



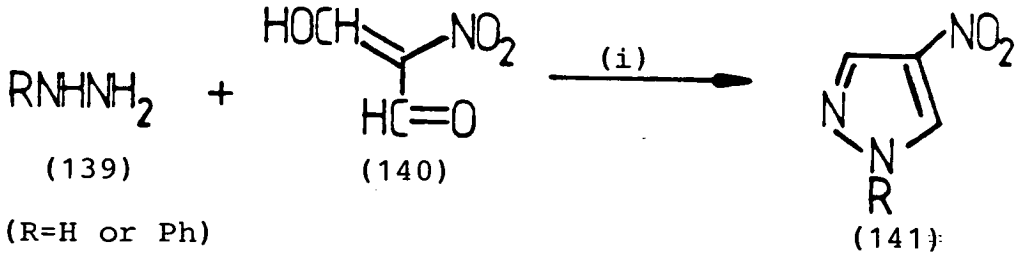
(i) Et_2O, 20 to 25°

Scheme 33



(i) Et_3N, $CHCl_3$, 60°

Scheme 34



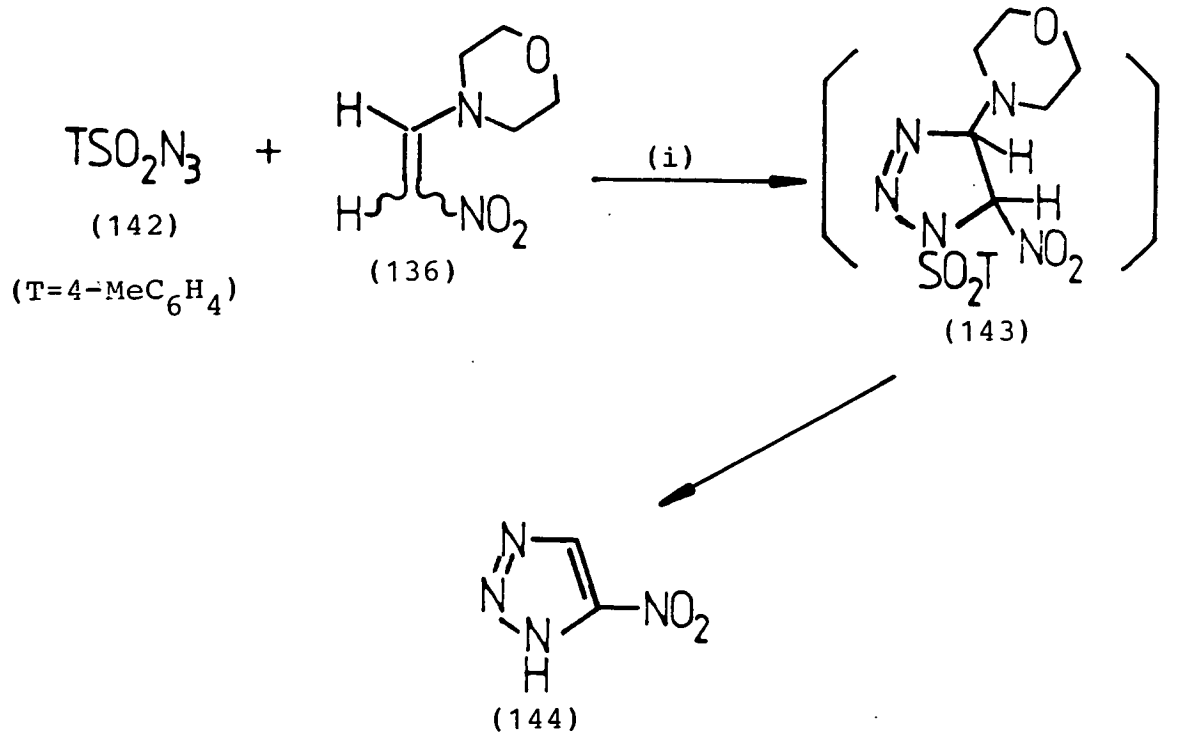
(i) H_2O, room temp.

Scheme 35

formation of the pyrazole products (128) and (129) are readily explained by competing elimination of hydrogen bromide and nitrous acid from the initially formed pyrazoline cycloadduct (127). Similar 1,3-dipolar cycloaddition (Scheme 33) can be used for the construction of 4-nitropyrazoles as exemplified[55] by the reaction of phenyldiazomethane (130) with 1,2-dinitrostyrene (131) to give through the intermediacy of the pyrazoline derivative (132) 3,5-diphenyl-4-nitropyrazole (133). The base-catalysed reaction[56] (Scheme 34) of benzoyl chloride N-phenylhydrazone (134) with 1-(4-morpholino)-2-nitroethene (136) to give 1,3-diphenyl-4-nitropyrazole (138) can be rationalised by the intermediate formation and 1,3-dipolar cycloaddition of the nitrileimine (135) to the alkene (136) to afford the pyrazoline cycloadduct (137) followed by elimination of morpholine from the latter.

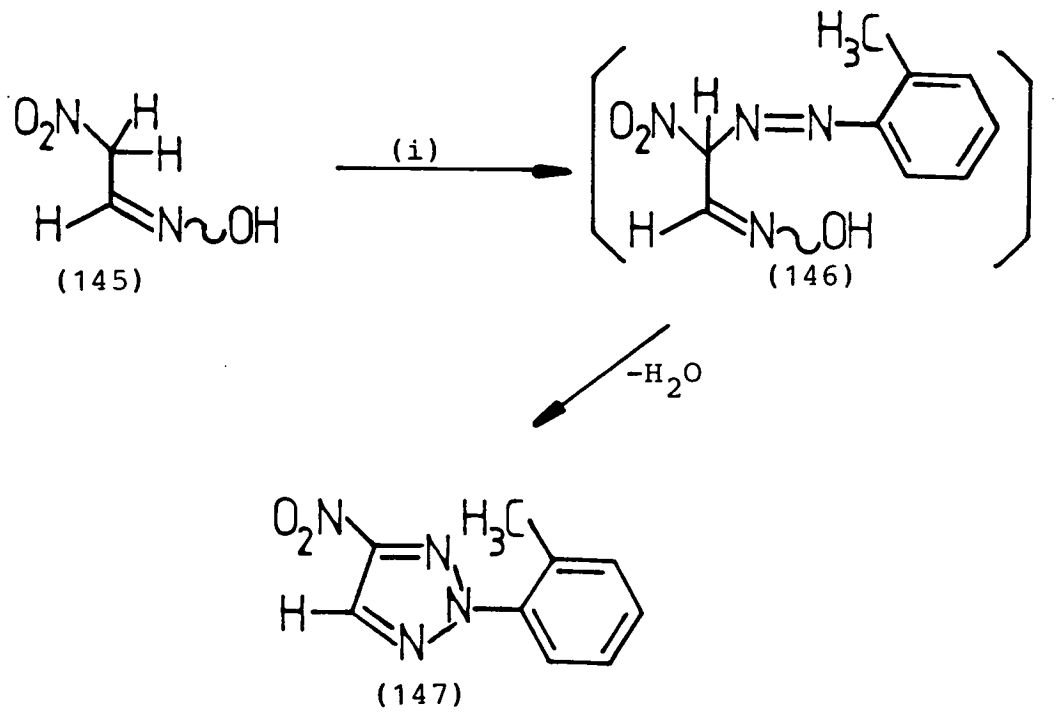
Amino-carbonyl condensation reactions have also been used in the construction of nitropyrazoles from acyclic nitro precursors. Cyclisation reactions of this type are illustrated (Scheme 35) by the reaction[57] of hydrazines (139) with nitromalondialdehyde (140) to afford the corresponding 4-nitropyrazole derivatives (141).

Cyclisation reactions of acyclic nitro precursors to nitro-1,2,4-triazoles do not appear to have been reported in the literature to date. However nitro-1,2,3-triazoles are accessible both by 1,3-dipolar cycloaddition and cyclodehydration reactions (Schemes 36 and 37). The 1,3-dipolar cycloaddition of toluene-4-sulphonyl azide



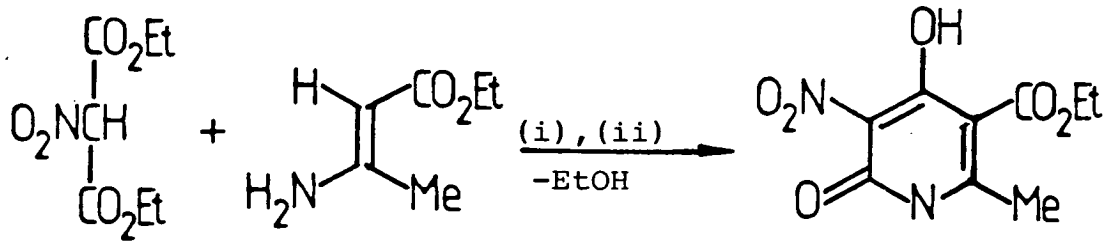
(i) EtOH, reflux

Scheme 36



(i) $2\text{-}CH_3C_6H_4N_2^+Cl^-$, NaOH, MeOH, then $SOCl_2$, 0 to 5°

Scheme 37

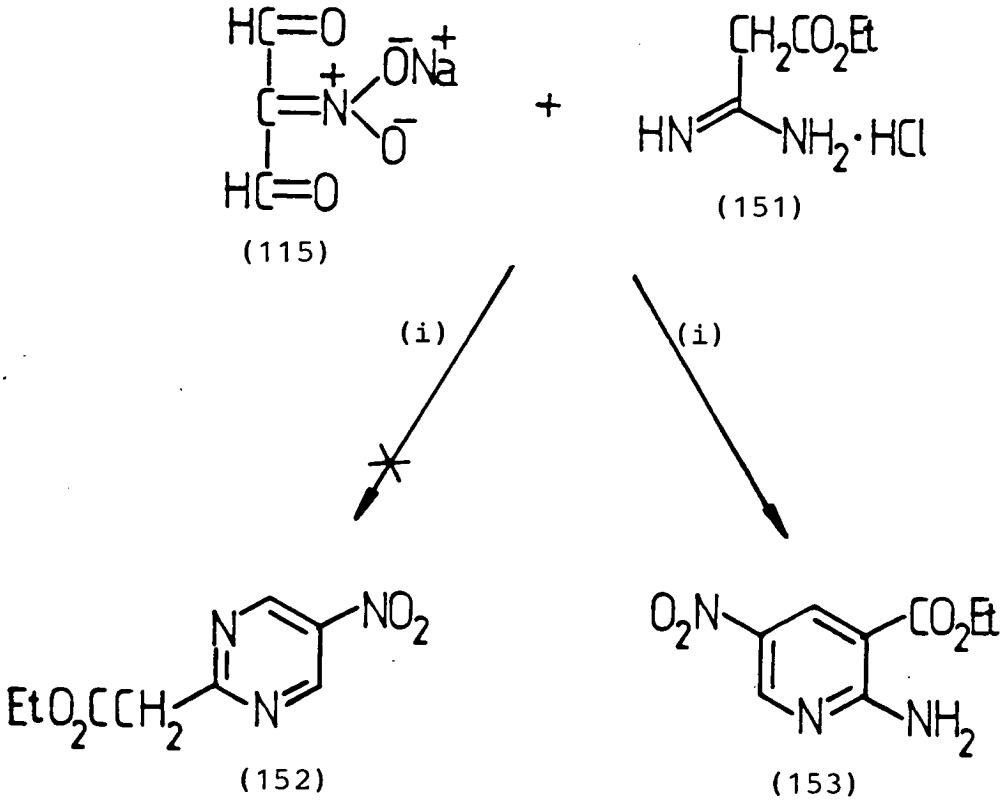


(148) (149) (150)

(i) Na, EtOH, 100°

(ii) HCl aq.

Scheme 38



(115) (151) (152) (153)

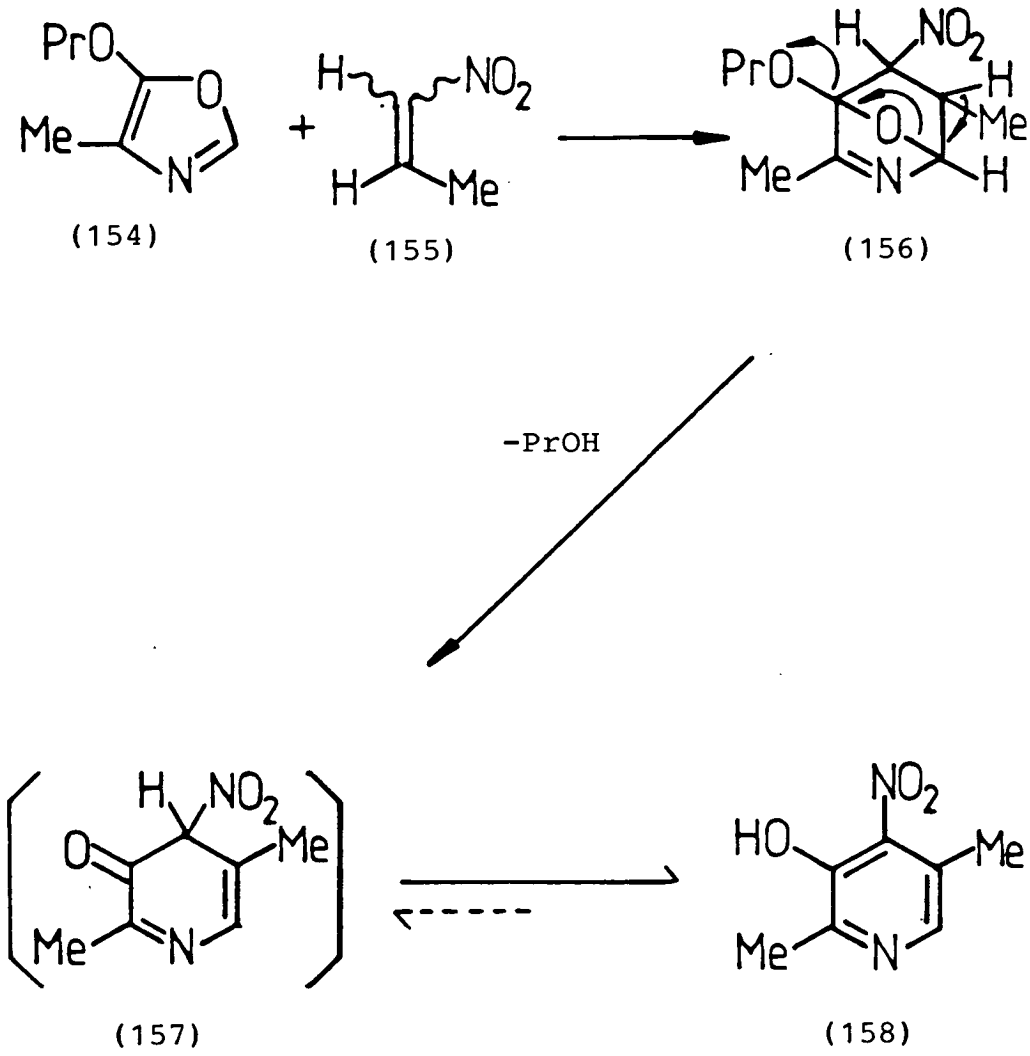
(i) piperidine, H_2O, room temp.

Scheme 39

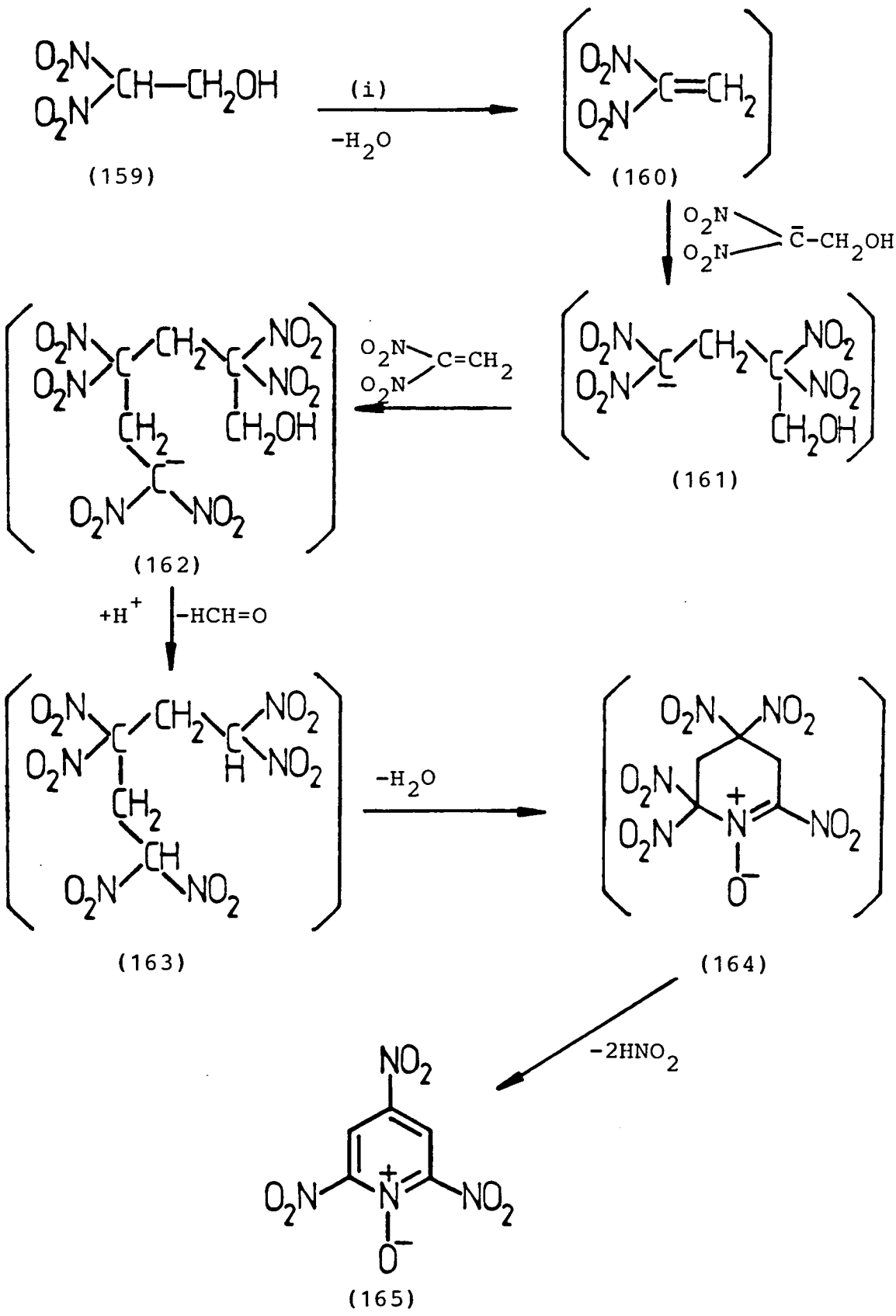
(142) to 1-(4-morpholino)-2-nitroethene (136) has been reported[58] to afford 5-nitro-(1H)-1,2,3-triazole (144) in good yield (80%) presumably via the intermediate formation and subsequent aromatisation and hydrolysis of the 1,2,3-triazoline derivative (143). The 4-nitro-2N-aryl-(2H)-1,2,3-triazole (147) (Scheme 37) has been reported[59] to be readily obtained by cyclodehydration of an azo-intermediate (146) which was prepared by coupling methazonic acid (145) with the corresponding aryldiazonium salt.

1.3.2 Synthesis of Six Membered Heteroaromatic Nitro-compounds

A series of nitropyridines have been prepared from acyclic nitro-precursors. Nitromalonic ester (148) (Scheme 38) has been used[60] to prepare a 3-nitropyridone derivative (150) in moderate yield (35%) by cyclocondensation with the enamino-ester (149) in the presence of base. In an attempt[61] (Scheme 39) to prepare a 5-nitropyrimidine derivative (152) by condensing the sodium salt of nitromalondialdehyde (115) with ethyl formamidinoacetate hydrochloride (151) the product actually obtained was 2-amino-5-nitronicotinate (153). A 4-nitropyridine derivative (158) (Scheme 40) has been prepared by reacting 1-nitropropene (155) with 4-methyl-5-propoxyoxazole (154).[62] This transformation presumably involves Diels-Alder cycloaddition followed by rearomatisation as shown in Scheme 40. Heating (Scheme 41) 2,2-dinitroethanol (157) in water has been reported[63,64] to afford 2,4,6-trinitropyridine N-oxide (165). The formation

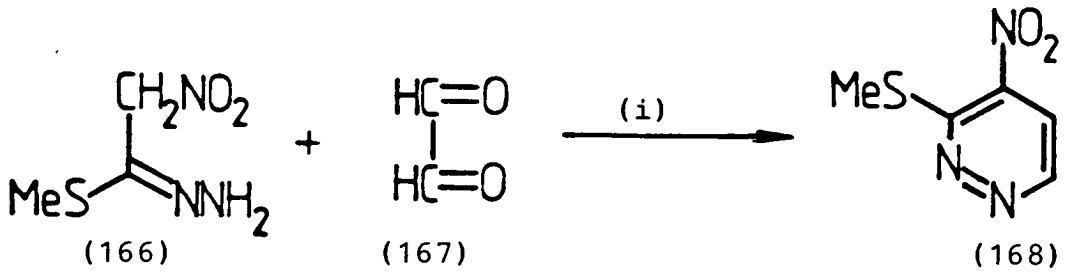

PrO
O
Me
N
(154)
+
H
NO2
H
Me
(155)
H
NO2
PrO
H
O
Me
Me
N
H
(156)
-PrOH
H
NO2
O
Me
Me
N
(157)
NO2
HO
Me
Me
N
(158)

Scheme 40



(i) H_2O, reflux

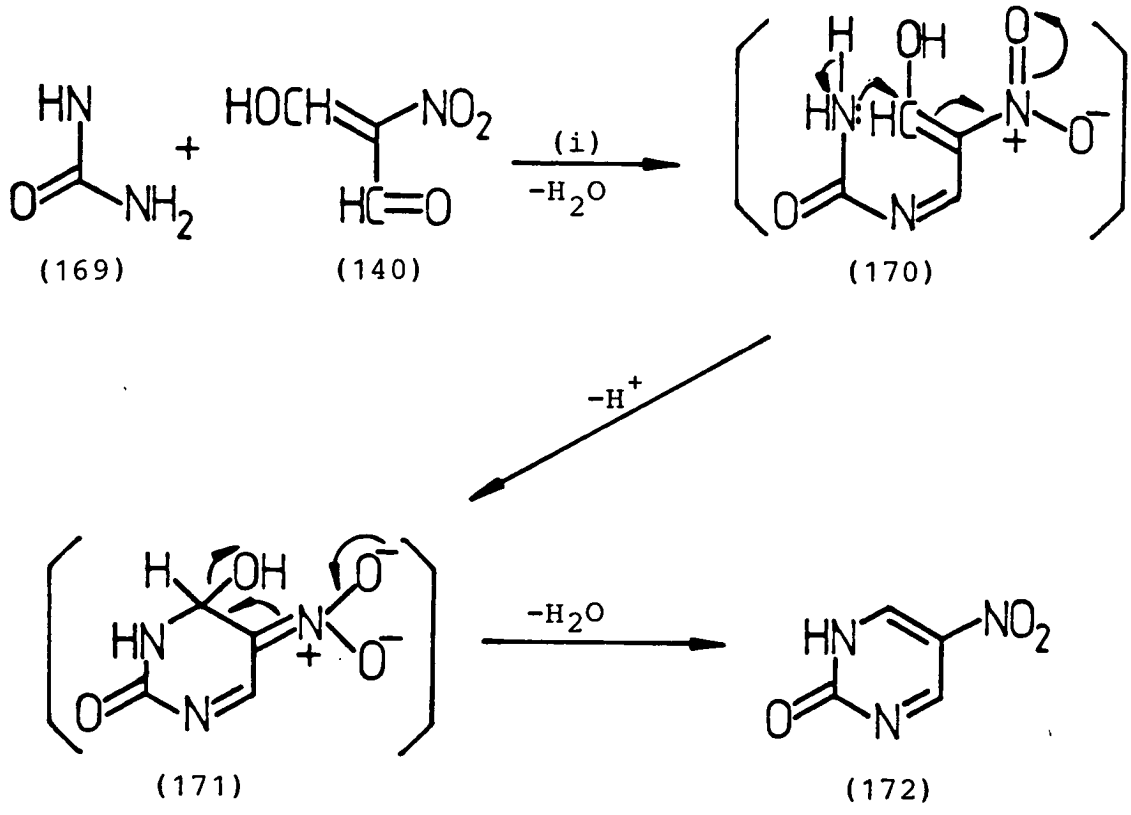
Scheme 41



(166) (167) (168)

(i) H_2O, EtOH, 10°

Scheme 42



(169) (140) (170) (171) (172)

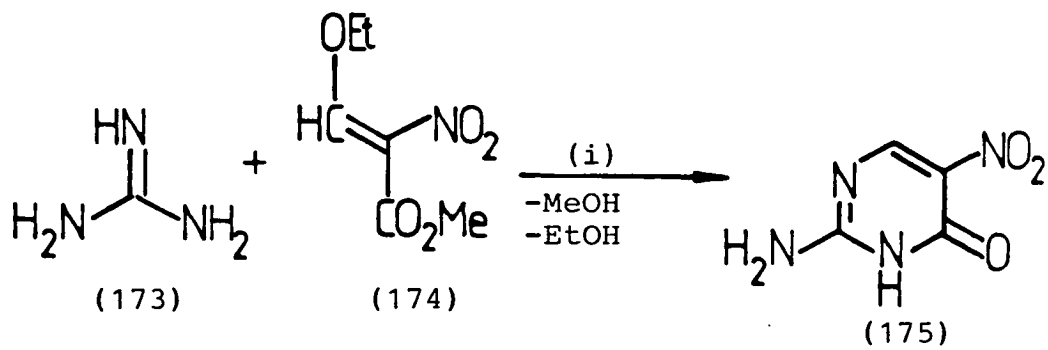
(i) NaOH aq., room temp.

Scheme 43

of the pyridine 1-oxide (163) was shown[65] to involve successive Michael-additions [(159)→→→(163)] and then cyclisation and loss of nitrous acid.

4-Nitropyridazine (168) (Scheme 42) was shown[66] to be the end product of the condensative cyclisation between glyoxal (167) and the hydrazone (166). Thus, this method provides a potential route to 5,6-disubstituted-4-nitropyridazines from the appropriate α-dicarbonyl compound.

Only 5-nitropyrimidine derivatives appear to have been synthesised from open-chain nitro-containing precursors. Thus, the reaction of nitromalondialdehyde (140) (Scheme 43) with urea (169) gave 5-nitro-(1H)-pyrimidinone (172).[67] This reaction was suggested to occur (Scheme 43) by successive condensations and then aromatisation to give the final product. The reaction (Scheme 44) of methyl 3-ethoxymethylene nitroacetate (174) with guanidine (173) has been shown[68] to afford a good yield (78%) of 2-amino-5-nitropyrimidin-6(1H)-one (175).



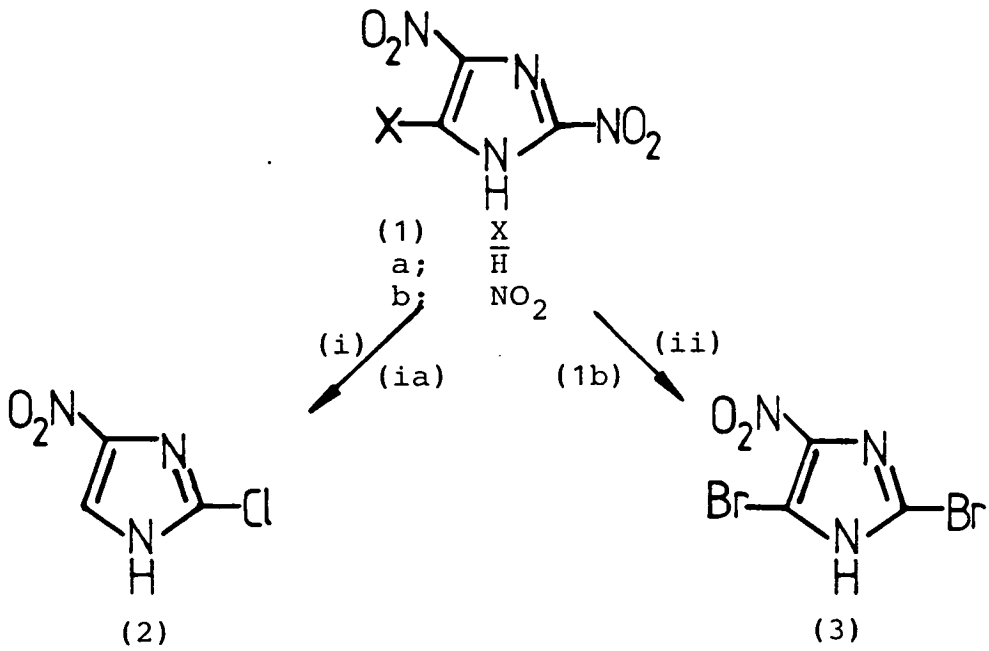
(173) (174) (175)

(i) EtOH, 2 to 5°

Scheme 44

Chapter 2

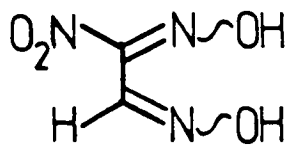
New Synthetic Approaches to Nitroimidazole Derivatives



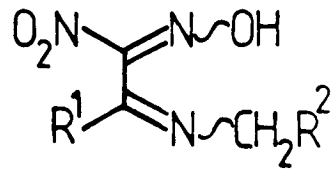
(i) $POCl_3$, Me_2NCHO, 80 to 85°

(ii) $POBr_3$, Me_2NCHO, reflux

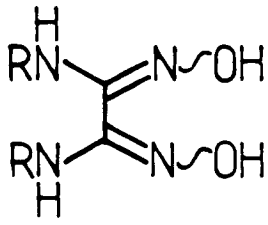
Scheme 1



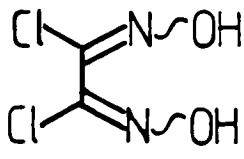
(4)



(5)



(6)



(7)

Scheme 2

New Synthetic Approaches to Nitroimidazole Derivatives

2.1 Introduction

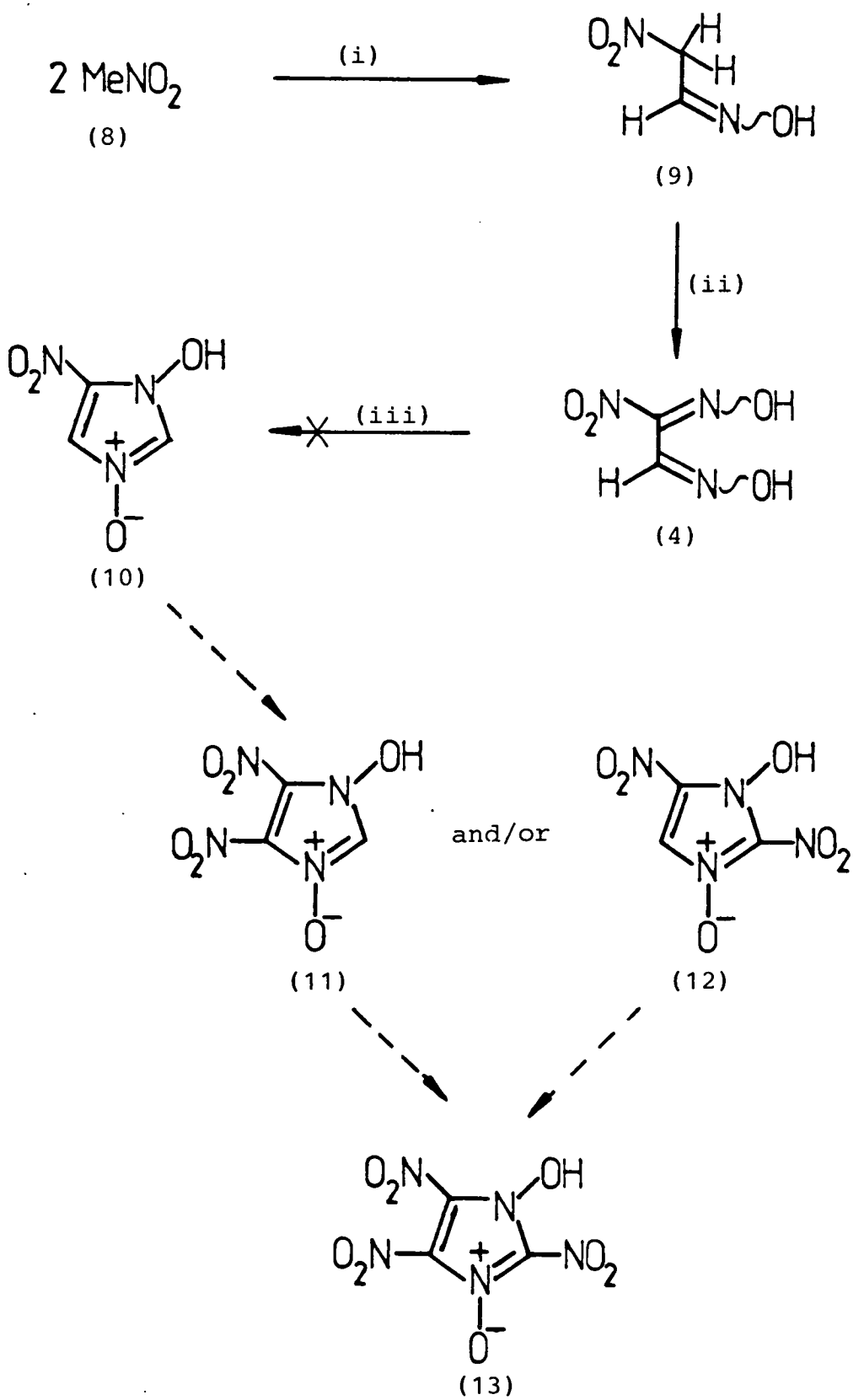
This chapter deals with new synthetic approaches to dinitro- and trinitroimidazoles. These molecules are of interest because of their potentially unique physical and chemical properties associated with the presence of the electron-withdrawing nitro-groups on an already electron-deficient nucleus. In particular the imidazole nucleus in dinitro- and trinitroimidazoles is, as might be expected particularly susceptible to nucleophilic attack. This situation is illustrated (Scheme 1) by the ready halogenative denitration reactions of dinitro- and trinitroimidazoles. Thus (Scheme 1) the action of phosphoryl chloride on 2,4(5)-dinitroimidazole (1a)[69] and of phosphoryl bromide on 2,4,5-trinitroimidazole (1b)[70] yields 2-chloro-4(5)-nitro-imidazole (2) and 2,4-dibromo-5-nitroimidazole (3) respectively.

The potential biological properties of nitroimidazoles have also stimulated much interest in recent years. 2-Nitro-imidazole (azomycin) (see Chapter 1, page 16 and Scheme 22) has been used in the treatment of trichomonas vaginalis and 2,4(5)-dinitroimidazole has been used as a radiosensitiser for hypoxic mammalian cells[71] and may therefore be of use for the treatment of solid tumours in humans.

To date the available methods for the synthesis of dinitro- and trinitritroimidazoles appear to be confined to direct sequential nitration of the parent imidazole or nitrodeiodination of iodoimidazoles. Both of these methods

have disadvantages. The direct nitration of imidazole[12,72] needs increasingly more forcing conditions to effect the second nitration and the yields tend to be only moderate. Also, direct nitration tends to be non-selective and occurs in both the 4- and 5-positions.[12,72] In the case of nitrodeiodination the iodoimidazole starting-materials are not particularly accessible and dinitrodeiodination and trinitrodeiodination are only achieved in moderate yields under forcing conditions.[73,74] There is therefore a need for alternative synthetic approaches to dinitro- and trinitro-imidazoles. The studies described in the present chapter are concerned with attempts to develop new synthetic routes to dinitro- and trinitroimidazoles based on the acyclic building-blocks (Scheme 2) nitroethane-1,2-dione dioxime (4), nitroethane-1,2-dione imine oximes (5), 1,2-diaminoethane-1,2-dione dioximes (6), and 1,2-dichloroethane-1,2-dione dioxime (7).

Nitroethane-1,2-dione imine oximes (5) have the advantage as nitroimidazole building-blocks that they already contain one nitro group. In the case of nitroethane-1,2-dione dioxime (4) it was intended to constrict the imidazole ring by bis-condensation reactions of the two oximino-groups with appropriate reagents, to give mononitroimidazole derivatives suitable for further nitration to dinitro- and trinitro-imidazoles. Correspondingly, it was hoped that oxidative cyclisation of nitroethane-1,2-dione imine oximes (5) would lead to mononitroimidazoles and thence by further nitration to dinitro and trinitroimidazole derivatives. It was



(i) NaOH, H_2O, 45 to 50°

(ii) KOH, EtOH, then $NaNO_2$, H_2SO_4, 0°

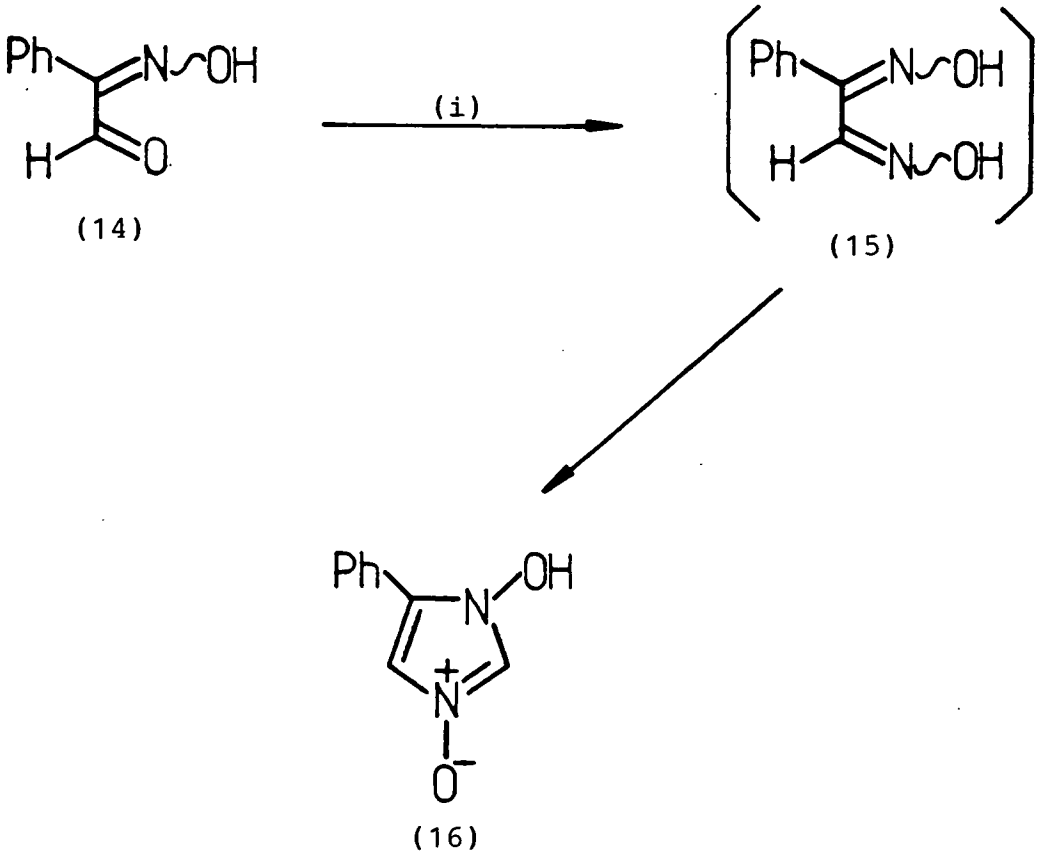
(iii) HCH=O, conc.HCl, MeOH, 45 to 55°

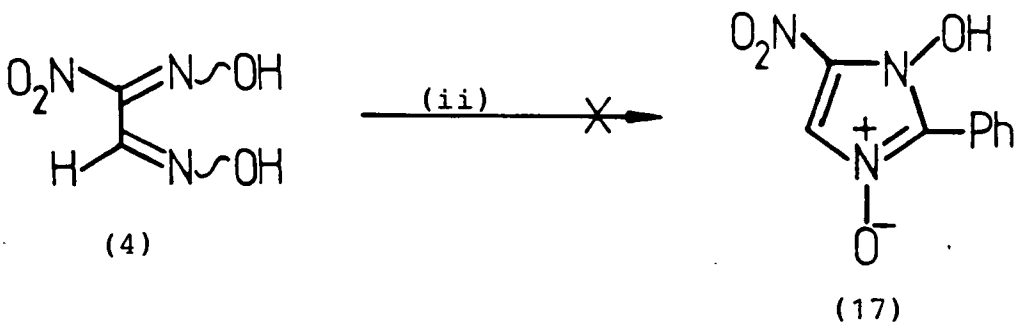
Scheme 3

proposed to convert 1,2-diaminoethane-1,2-dione dioximes (6) into 4,5-dinitroimidazoles by closure of the imidazole ring through the amino-groups followed by oxidation of the oximino-substituents in the resulting 4,5-dioximinoimidazoles. It was anticipated that the formation of 4,5-dinitroimidazoles from 1,2-dichloroethane-1,2-dione dioxime (7) could be achieved by construction of the imidazole ring through the oxime groups to give a 4,5-dichloroimidazole derivative followed by further transformations. Alternatively reaction of 1,2-dichloroethane-1,2-dione dioxime (7) with a suitable 1,3-diamino reagent should afford an alternative route to 4,5-dioximinoimidazoles and thence by oxidation to 4,5-dinitroimidazole derivatives as already discussed.

2.2 Synthetic Approaches to Dinitro- and Trinitroimidazoles Based on Nitroethane-1,2-dione Dioxime (Nitroglyoxime) Derivatives

The initial strategy (Scheme 3) for the synthesis of dinitro- and trinitroimidazoles involved the use of the readily available[75] nitroethane-1,2-dione dioxime (4) as the key starting-material. The intention was to convert this compound by acid-catalysed condensation with formaldehyde into the previously unknown 3-hydroxy-4-nitroimidazole 1-*N*-oxide (10), whose bis-*N*-oxygenated structure should be susceptible to further nitration to the corresponding dinitroimidazoles (11) and/or (12) than the trinitroimidazole (13). The proposed synthesis of the nitroimidazole derivative (10)





(i) HCH=O, $NH_2OH.HCl$, conc.HCl, MeOH

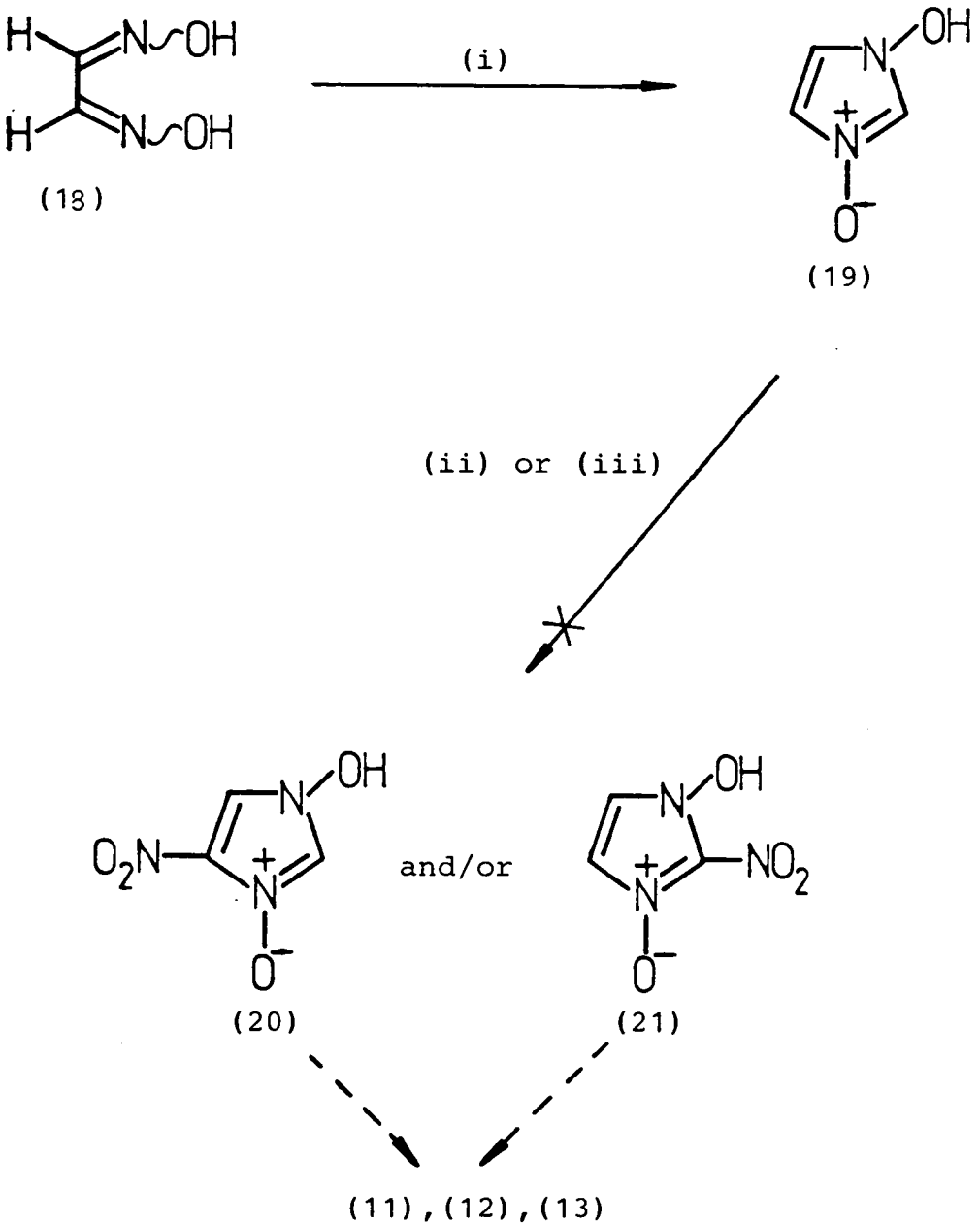
(ii) PhCH=O, HCl(g), EtOH, room temp.

Scheme 4

was based on previous work by Beger et al.[76] who showed (Scheme 4) that the reaction of 1-phenylethane-1,2-dione 1-oxime (14) with formaldehyde and hydroxylamine hydrochloride in the presence of concentrated hydrochloric acid affords 3-hydroxy-4-phenylimidazole 1-N-oxide (16) in high yield. Formation of the N-hydroxyimidazole N-oxide (14) is readily explained (Scheme 4) in terms of the intermediate formation of the dioxime (15) and its cyclisative condensation with formaldehyde.

The preparation (Scheme 3) of nitroethane-1,2-dione dioxime (4) was achieved in two stages in good overall yield by the sodium hydroxide catalysed self-condensation of nitromethane (8) to give[77] 2-nitroethanal monoxime (methazonic acid) (9), followed by oximation[75] of the latter. Disappointingly the attempted acid-catalysed reaction (Scheme 3) of nitroethane-1,2-dione dioxime (4) with formaldehyde gave no identifiable material. Since this result was possibly due to the difficulty of isolating the potentially water soluble N-hydroxyimidazole N-oxide product (10) an attempt was made (Scheme 4) to achieve the acid-catalysed condensation of nitroethane-1,2-dione dioxime (4) with benzaldehyde. It was expected that this reaction would give the previously unknown but potentially more readily isolated 3-hydroxyimidazole 1-N-oxide derivative (17). In practice the reaction of nitroethane-1,2-dione dioxime (4) with benzaldehyde in ethanol in the presence of hydrogen chloride gave only a complex mixture which yielded no identifiable product.

Having failed to synthesise the nitroimidazole derivative



(18) (19) (20) (21) (11), (12), (13)

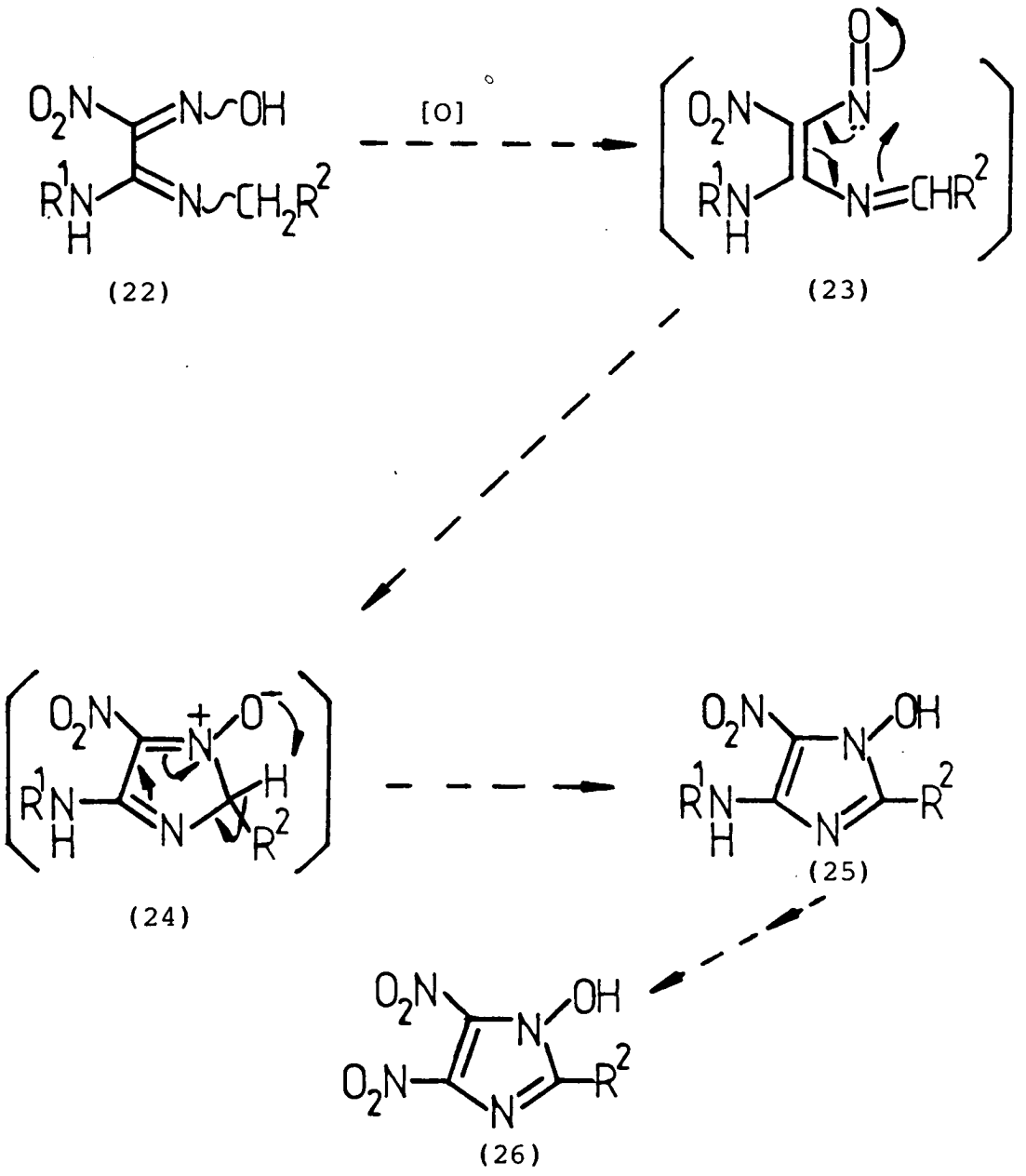
(i) HCH=O, Conc.HCl, MeOH, 45-50°

(ii) Conc.HNO_3 or N_2O_4-HNO_3, room temp.

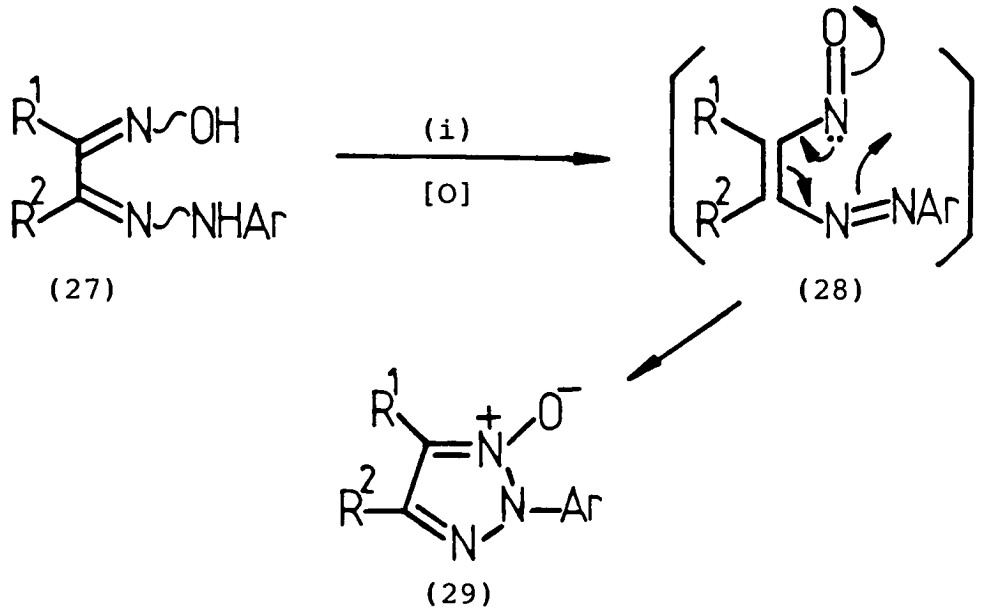
(iii) Cu $(NO_3)_2$, Ac_2O, room temp.

Scheme 5

(10) from acyclic starting-materials attempts (Scheme 5) were next made to obtain this potential precursor of the dinitroimidazoles (11) and (12) and the trinitroimidazole (13) by the previously uninvestigated nitration of 3-hydroxyimidazole N-oxide (19). The mononitration of the N-hydroxyimidazole N-oxide (19) can give two possible products (20) and/or (21) either of which is capable of further nitration to the dinitroimidazoles (11) and (12) and then to the trinitroimidazole (13). The known[79] 3-hydroxyimidazole 1-N-oxide (19) was readily prepared by the acid-catalysed condensation of ethane-1,2-dione dioxime (18) with formaldehyde as described in the literature. Ethane-1,2-dione dioxime[78] (18) was available by the reaction of commercially available disodium-1,2-dihydroxyethane-1,2-disulphonate monohydrate (glyoxal sodium bisulphite complex) with hydroxylamine. The attempted nitration of N-hydroxyimidazole N-oxide (19) at room temperature using fuming nitric acid resulted in the copious evolution of dinitrogen tetroxide accompanied by flame and hence this nitration procedure was hastily abandoned. The reaction of the N-hydroxyimidazole N-oxide (19) with concentrated nitric acid at room temperature was also hazardous. This reaction led to an oil whose spontaneous flammability in air resulted in the experiment being abandoned. The attempted nitration of the N-hydroxyimidazole N-oxide (19) with the milder[80] nitrating agent, acetyl nitrate, gave no isolable material.



Scheme 6



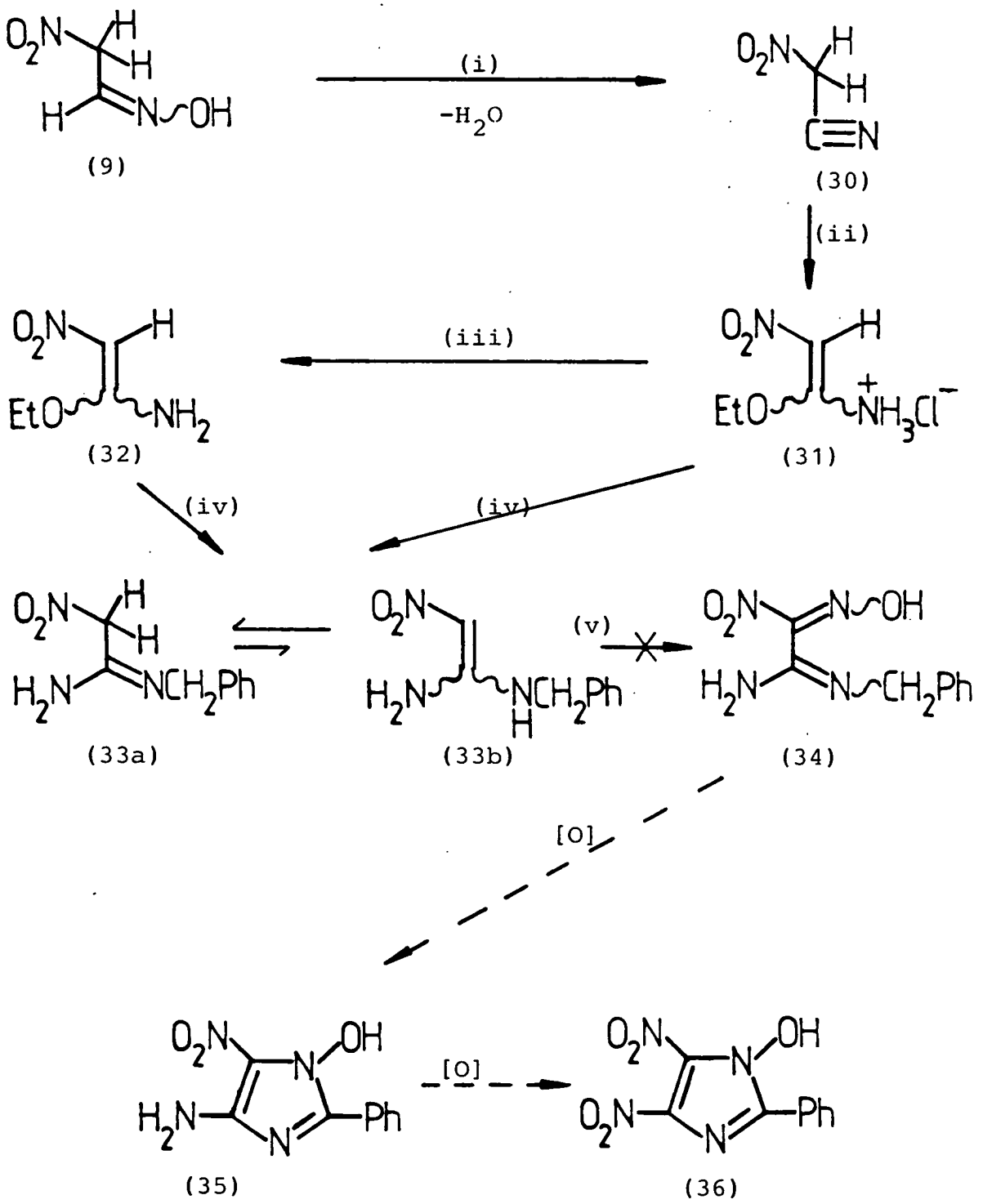
(i) $Cu(II)SO_4, H_2O$, pyridine, reflux

Scheme 7

2.3 Synthetic Approaches to Dinitroimidazoles Based on Nitroethane-1,2-dione Monoimine Monoxime Derivatives

Having failed to achieve the synthesis of nitroimidazole derivatives through nitroethane-1,2-dione dioxime (4) or the preformed N-hydroxyimidazole N-oxide (20) as synthetic intermediates it was decided to investigate an alternative strategy (Scheme 6) based on oxidative cyclisation reactions of 1-amino-2-nitroethane-1,2-dione-1-alkylimine 2-oxime derivatives (22) to 4-amino-1-hydroxy-5-nitroimidazoles (25), suitable for further conversion into 4,5-dinitroimidazoles (26). Heterocyclisation reactions of the type [(22)↠(25)] have not been described previously but would be analogous to the known[81,82] oxidative cyclisation (Scheme 7) of ethane-1,2-dione hydrazone oximes (27) to 2H-1,2,3-triazole 1-N-oxides (29). Hence the proposed oxidative conversion of the imine oximes (22) into the N-hydroxyimidazoles (25) can be envisaged to occur via the formation and electrocyclisation of nitroso-intermediates (23) followed by rearrangement of the 2H-imidazole intermediates (24) produced.

In order to test the validity of the proposed new nitroimidazole synthesis outlined in Scheme 6 it was decided to investigate the oxidative cyclisation of the benzylimine oxime (25; R^1=H, R^2=Ph). However it was first necessary to develop a synthesis of this previously unreported compound. The initial intention (Scheme 8) was to obtain the required imine oxime (34) by nitrosation of the unknown amidine derivative (33a) which was readily synthesised as outlined in Scheme 8. Dehydration of 2-nitroethanal monoxime (methazonic acid) (9)



(i) $SOCl_2$, Et_2O, reflux

(ii) HCl(g), EtOH, Et_2O, 0°

(iii) NH_3(g), EtOH or Et_2O, 0° or -20°

(iv) $PhCH_2NH_2$, EtOH, room temp.

(v) $NaNO_2$, AcOH, H_2O, room temp.

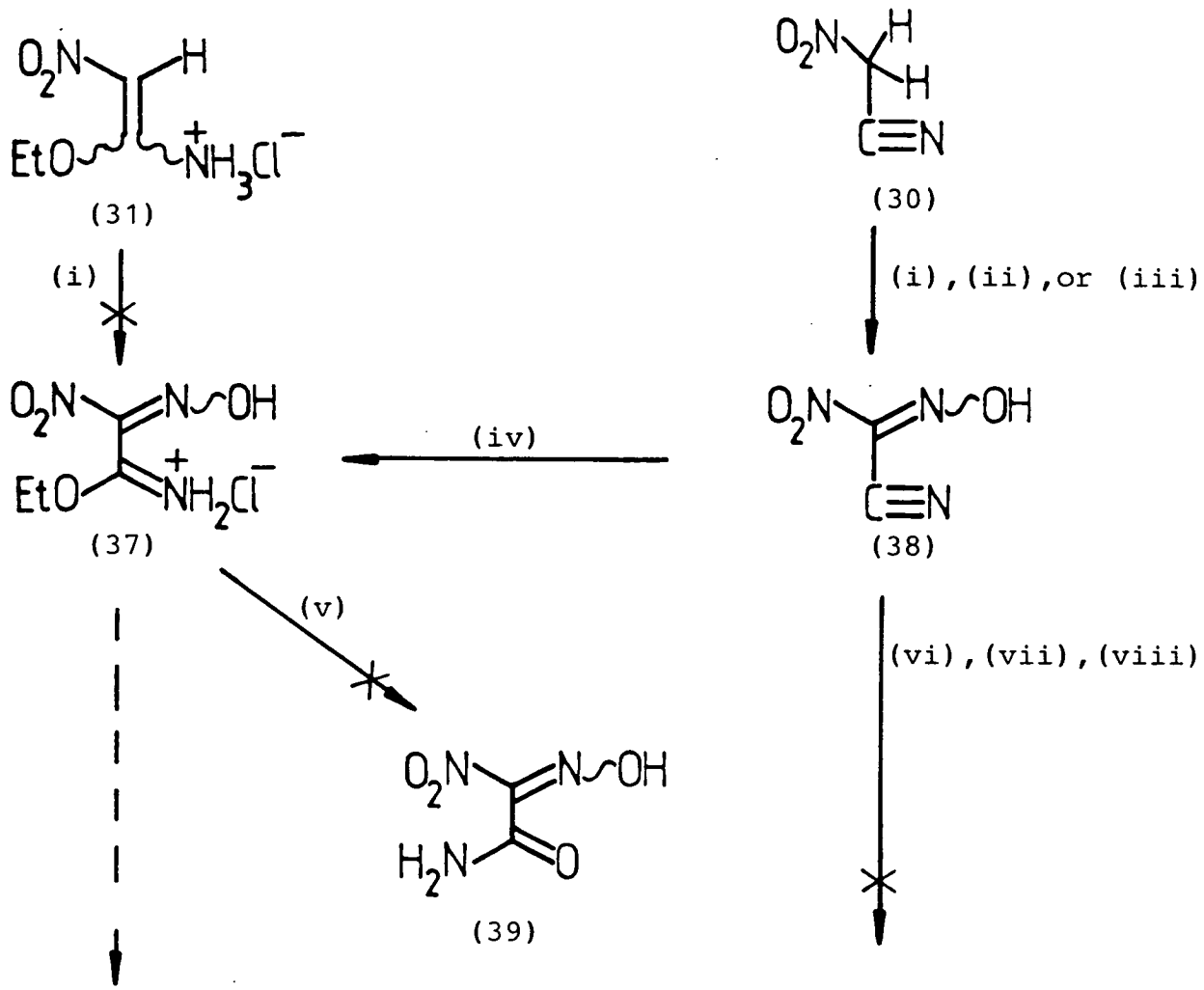
Scheme 8

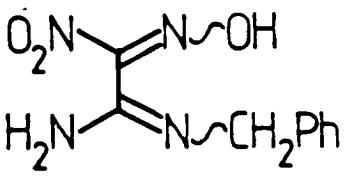
using thionyl chloride as described in the literature[83] gave nitroacetonitrile (30) in good yield. The nitrile (30) reacted in orthodox fashion with ethanol in the presence of hydrogen chloride to give a good yield of the expected imidate hydrochloride (31) which, due to its relative instability, could not be purified for combustion analysis. However the product was readily characterised by its i.r. and ^{1}H n.m.r. absorption. Thus its i.r. spectrum showed a broad band at 3200-2600 cm^{-1} attributable to the NH absorption of an ammonium group and bands at 1550 and 1350 cm^{-1} due to a nitro-group. In addition to a broad signal due to the protons of the ammonium group the ^{1}H n.m.r. spectrum of the product also showed a one proton singlet at δ6.54 assignable to the ethene proton and a two proton quartet and a three proton triplet at δ4.15 and 1.26 attributable to the protons of the ethoxy-group. Treatment of the imidate hydrochloride (31) with ethereal or ethanolic ammonia gave the free imidate (32) in good to excellent yield. The imidate (32) gave a combustion analysis and showed mass, i.r. and ^{1}H n.m.r. spectra fully in accord with its structure. The imidate (32) reacted with benzylamine in ethanol to give a low yield of a product which gave analytical and mass spectral data consistent with the amidine structure (33a) but showed spectroscopic properties more in accord with the tautomeric ene-diamine structure (33b). In particular its ^{1}H n.m.r. spectrum was at variance with the structure (33a) but consistent with the structure (33b). The spectrum showed signals due only to a single CH_2 group and contained a one proton singlet at δ6.44 attributable to the vinylic proton in the ene-diamine structure (33b). The ene-

diamine structure (33b) was formed in substantially improved yield by reacting the imidate hydrochloride (31) with benzylamine in ethanol. Despite its ene-diamine structure it was thought that nitrosation/oximation of the ene-diamine (33b) might still afford the required imine oxime product (34). However reaction of the ene-diamine (33b) with sodium nitrite in aqueous acetic acid gave only an intractable red oil which yielded no identifiable material.

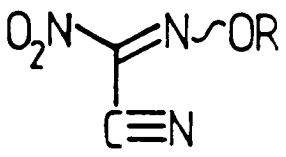
The failure of the ene-diamine (33b) to undergo nitrosation to give the required imine oxime (34) prompted the study of other routes to this compound (Scheme 9). Initially nitrosation/oximation of the imidate hydrochloride (31) was investigated in an attempt to obtain the oxime (37) and then by reaction with benzylamine the imine oxime (34). In practice the imidate hydrochloride (31) reacted with ethyl nitrite and hydrogen chloride in ethanol to give a good yield of an oil identical in all respects to an authentic sample of ethyl 2-nitroacetate. This product presumably arises by deamination rather than nitration/oximation of the imidate hydrochloride (31).

Attention was next directed to the synthesis of the imidate hydrochloride (37) [and hence the imine oxime (34)] by the acid-catalysed reaction of 2-oximinonitroacetonitrile (38) with ethanol (Scheme 9). The previously unknown 2-oximino-nitroacetonitrile (38) was readily prepared by the nitrosation/oximation of nitroacetonitrile (30). The use of ethyl nitrite-hydrogen chloride or sodium nitrite-acetic acid as the nitrosating agents gave only low yields (25-29%) of 2-oximino-nitroacetonitrile (38) whereas an essentially quantitative yield





(34)



(40) R

a; MeC=O

b; PhNC=O
H

c; 2,4-$(NO_2)_2C_6H_3$

(i) EtONO, HCl(g), 0°

(ii) $NaNO_2$, AcOH, 0°

(iii) $NaNO_2$, H_3PO_4, H_2O, 30-40°

(iv) HCl(g), EtOH, Et_2O, 0°

(v) 100°

(vi) $MeC(=O)Cl$, Et_3N, room temp.

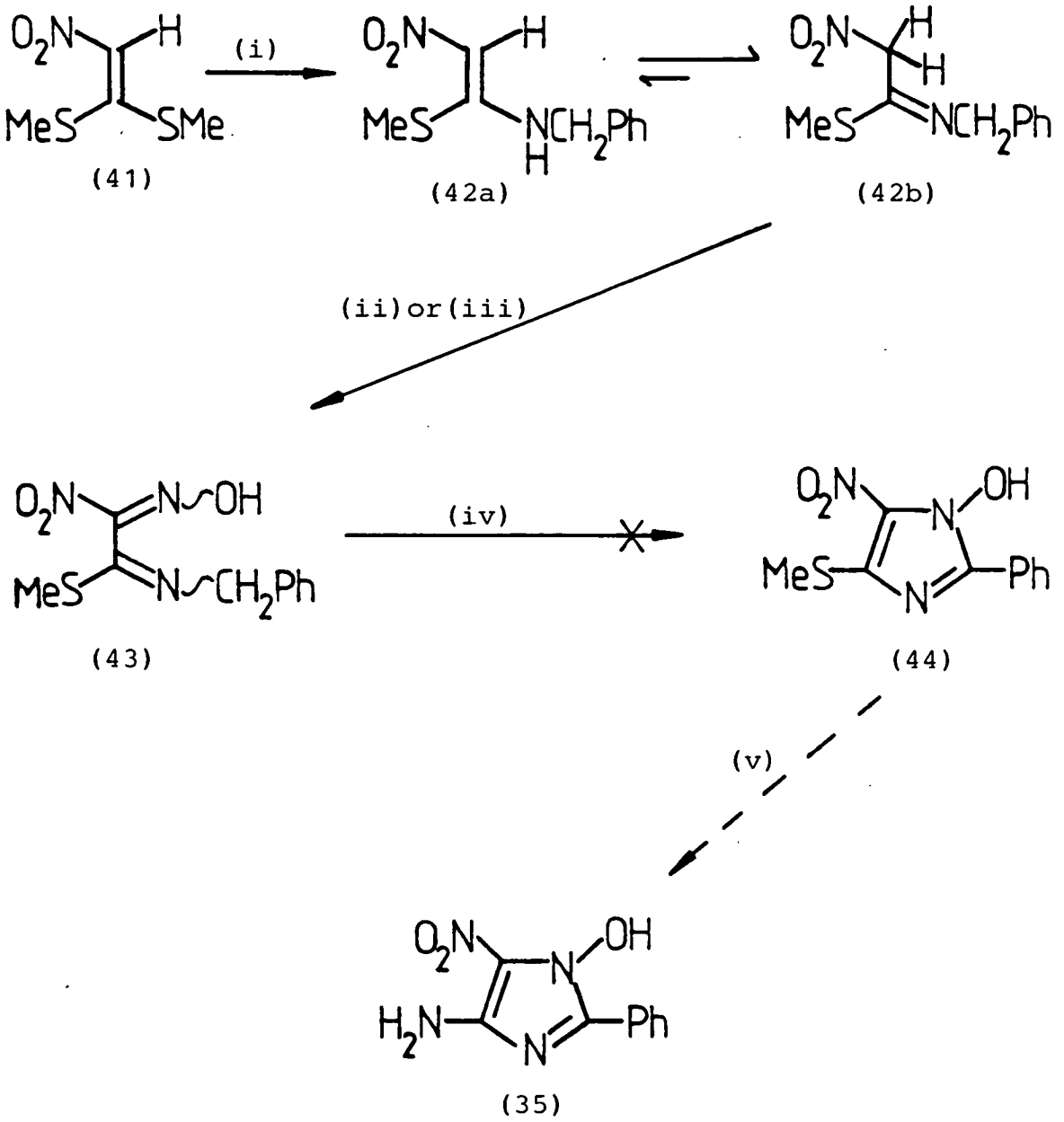
(vii) PhN=C=O, Et_2O, room temp.

(viii) 2,4-$(NO_2)_2C_6H_3Cl$, NaOH, room temp.

Scheme 9

of this product was obtained using sodium nitrite-phosphoric acid as the nitrosating agent. In all cases 2-oximino-nitroacetonitrile (38) was obtained as a yellow oil which could be chromatographed unchanged but was too unstable to purify for combustion analysis and failed to give an intelligible mass spectrum. However in accord with the assigned structure, the oximino-nitrile (38) showed broad i.r. absorption at 3650-3100 cm^{-1} due to the oxime OH-group and cyano-absorption at 2220 cm^{-1}. The structure of the oximino-nitrile (38) was also supported by its ^{13}C n.m.r. spectrum which contained only two signals at δ171.2 and 111.9 attributable to the carbon atoms of imino (C=N) and cyano-substituents. Attempts were made to further characterise 2-oximinonitroacetonitrile (38) by its conversion into a solid derivative (Scheme 9). However attempted reaction with acetyl chloride in the presence of triethylamine or with phenyl isocyanate gave only intractable oils rather than the expected O-acetyl derivative (40a) or the urethane (40b). The attempted sodium hydroxide catalysed reaction of 2-oximino-nitroacetonitrite (38) with 2,4-dinitrochlorobenzene resulted only in a high recovery of the latter with no evidence for the formation of the expected ether derivative (40c).

Despite the difficulty of fully characterising 2-oximino-nitroacetonitrile (38) it was decided to go ahead with its conversion into the imidate hydrochloride (37). However, reaction with ethanol in the presence of hydrogen chloride gave a hygroscopic product which was too unstable to be characterised directly. On the assumption that this product was the required imidate hydrochloride (37) an attempt was



(41) (42a) (42b) (43) (44) (35)

(i) $PhCH_2NH_2$, EtOH, reflux

(ii) KNO_2, AcOH, H_2O, room temp.

(iii) $NaNO_2$, AcOH, H_2O, 0°

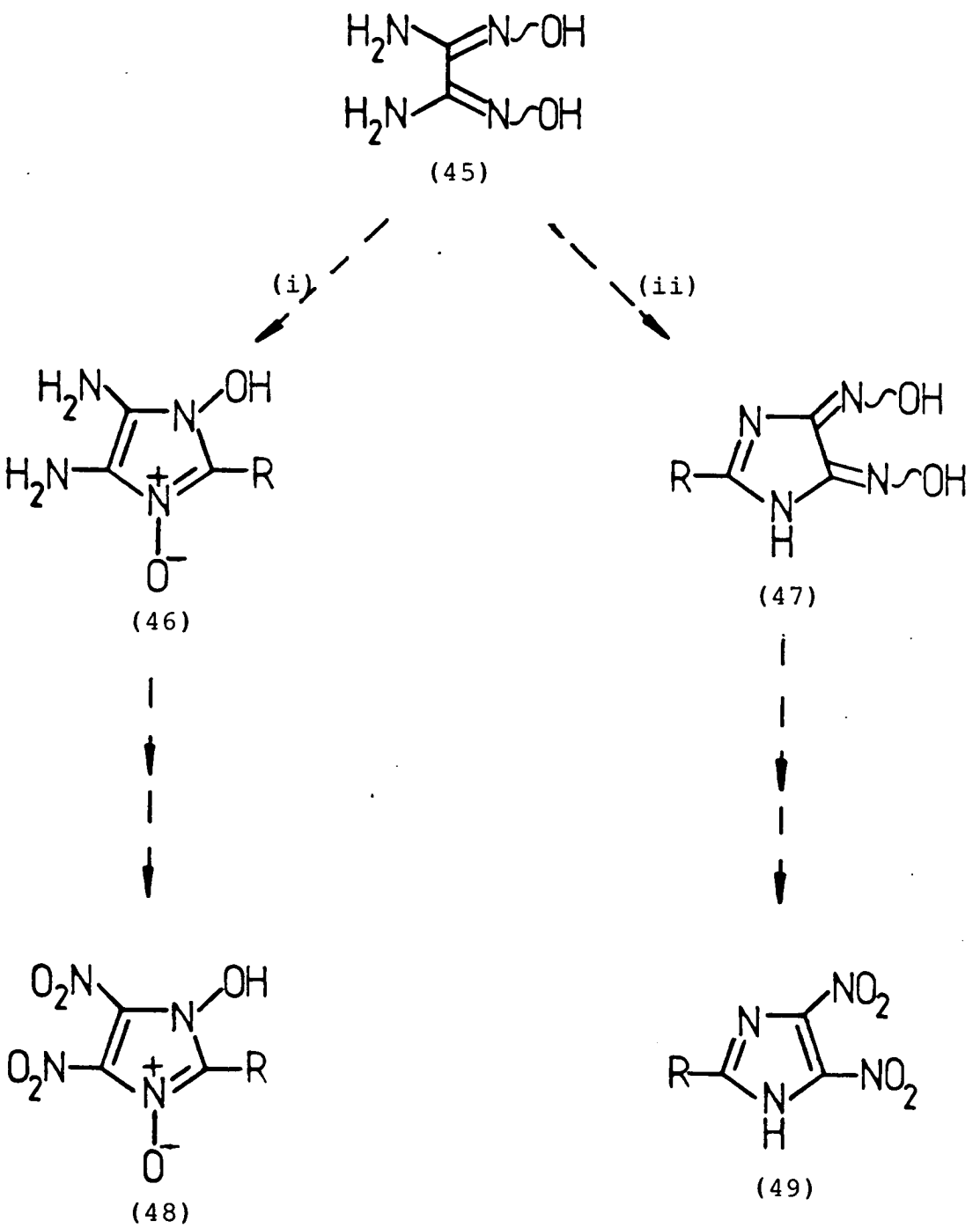
(iv) MnO_2, MeCN, room temp.

(v) NH_3

Scheme 10

made to characterise it by thermolysis to 2-nitro-2-oximinoacetamide (39). The conversion of imidate hydrochlorides into amides on heating is a well known process.[84] However heating the hygroscopic product in the absence of solvent gave only an intractable gum from which no identifiable material could be obtained.

The lack of a suitable synthesis of the imine oxime (34) prevented the study of its oxidative cyclisation to the nitroimidazole (35) and as an alternative it was next decided to investigate the synthesis and oxidative cyclisation (Scheme 10) of the methylthio-compound (43). It was anticipated that this previously unknown compound might be more readily synthesised than the imine oxime (34) and might also undergo oxidative cyclisation to the methylthio-nitroimidazole (44). Nucleophilic displacement of the methylthio-group in the latter compound by ammonia would then afford the required amino-nitroimidazole (35). In practice the methylthio-compound (43) was readily synthesised in two steps (Scheme 10) by reaction of the readily available[85] 1,1-bis-methylthio-2-nitroethene (41) with benzylamine to afford the known[86] 1-benzylamino-1-methylthio-2-nitroethene (42a). The enamine structure (42a) rather than the imine structure (42b) for this compound is supported by its ^{1}H n.m.r. spectrum which contains a vinylic proton singlet at δ6.67 and shows absorption due to the protons of only a single methylene group. Nitrosation/oximation of the enamine (42a) occurred readily on treatment with sodium nitrite in glacial acetic acid giving the desired imine oxime (43) in good yield. The analytical and spectroscopic properties of the product (43) were fully



(i) RCH=O, H^+

(ii) $RCCl$, $(RC)_2O$, RCO_2H or $RC(OEt)_3$

Scheme 11

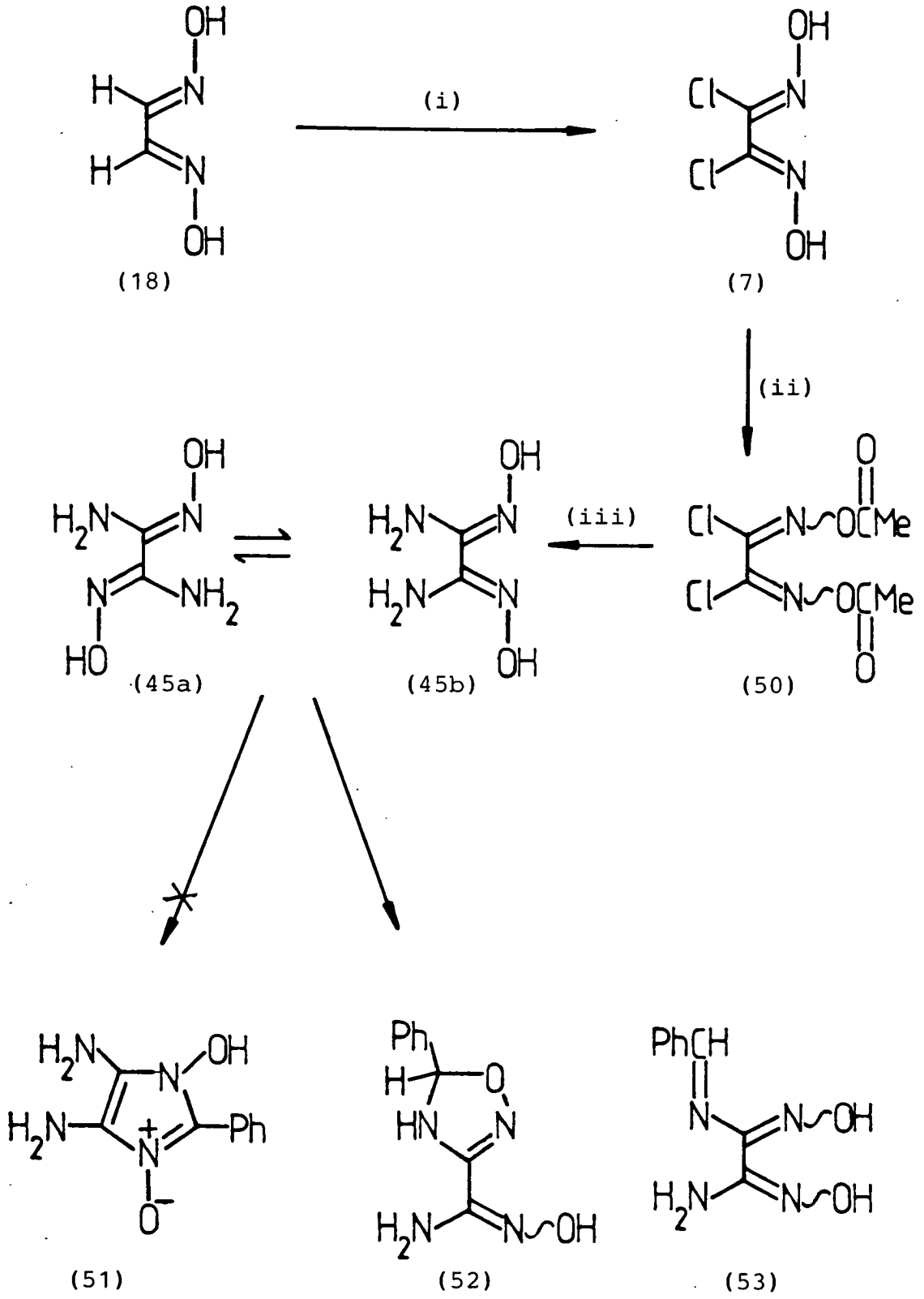
in accord with its assigned structure.

Unfortunately the attempted oxidative cyclisation of the imine oxime (43) to the nitroimidazole derivative (44) by treatment with activated manganese dioxide in 1,2-dimethoxyethane gave only an intractable gum which yielded no identifiable material. Lack of time prevented a more extensive study of the oxidative cyclisation of the imine oxime (43) to the nitroimidazole derivative (44) and this approach to the amino-nitroimidazole (35), and hence the dinitroamidazole (36), was abandoned at this stage.

2.4 Synthetic Approaches to Dinitro- and Trinitroimidazoles Based on 1,2-Diaminoethane-1,2-dione Dioxime (1,2-Diaminoglyoxime) Derivatives

Though the readily accessible[87] 1,2-diaminoethane dioxime (1,2-diaminoglyoxime) (45) has been widely used[88] as a chelating agent for the determination of metals it does not appear to have been used previously for the synthesis of imidazole derivatives. Its possible exploitation for the synthesis of polynitroimidazoles in particular is outlined in Scheme 11. Annulation through the oximino-groups (see Section 2.2, page 28) can potentially give 4,5-diamino-imidazole derivatives (46) suitable for further elaboration to dinitroimidazoles (48). Conversely more orthodox annulation via the amino-groups could lead to 4,5-dioximinoimidazoles (47) appropriate for further conversion into 4,5-dinitro-imidazoles (49) and 2,4,5-trinitroimidazole (49; $R=NO_2$).

By analogy with the well known[76,80] hydrochloric acid-



(i) Cl_2, Conc.HCl, 0°

(ii) Ac_2O, reflux

(iii) NH_3, EtOAc, room temp.

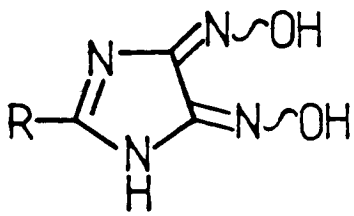
(iv) PhCH=O, HCl, MeOH, 45 to 55°

Scheme 12

catalysed condensation of ethane-1,2-dione dioximes with aldehydes to give 3-hydroxyimidazole 1-N-oxides it was expected that diaminoglyoxime (45) would condense with benzaldehyde in the presence of hydrochloric acid (Scheme 12) to afford the 4,5-diamino-3-hydroxy-2-phenylimidazole 1-N-oxide (51). Diaminoglyoxime (45) was readily synthesised (Scheme 12) as described in the literature[87] by chlorination[87,88] of ethane-1,2-dione dioxime (18) to give 1,2-dichloroethane-1,2-dione dioxime (7) then reaction[87] of the di-O-acetyl derivative (50) of the latter with ammonia.

There is evidence[88] that 1,2-diaminoethane-1,2-dione dioxime exists predominantly in the anti-trans configuration (45a). However the anti-cis configuration (45b) can be attained by simple bond rotation and since it is annulation reactions of this form which are of interest in the present studies, 1,2-diaminoethane-1,2-dione dioxime will be so formulated throughout.

The hydrochloric acid catalysed condensation of diaminoglyoxime (45b) with benzaldehyde afforded a low yield (44%) of a solid product which gave a combustion analysis and showed a parent ion at m/e 206 in its mass spectrum consistent with the molecular formula $C_9H_{10}N_4O_2$. In further accord with the expected imidazole structure (51) the compound showed i.r. absorption attributable to the presence of OH and NH groups. However the ^1H n.m.r. spectrum of the product contained a one-proton doublet at δ5.76 which collapsed to a singlet on exchange with D_2O allowing its assignment to the proton of a CH- group coupled to that of an NH-substituent.

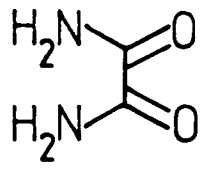


(47) R

a; H

b; Me

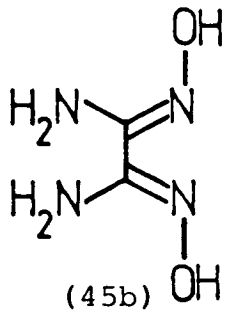
c; NH_2



(54)

(i)–(v)

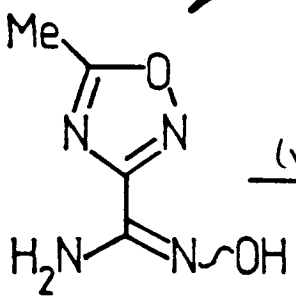
(i)



(45b)

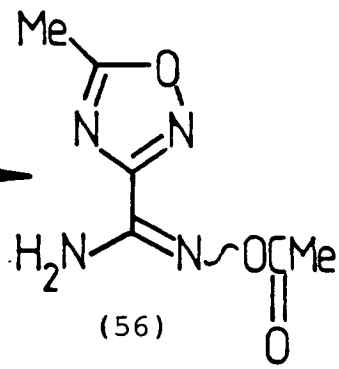
(ii)

(iii)

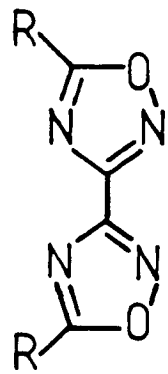


(55)

(vi)



(56)



(57) R

a; H

b; Me

(i) HCO_2H, reflux

(ii) AcOH, reflux

(iii) $RC(OEt)_3$, reflux

(iv) Ac_2O, reflux

(v) BrCN, $Me_2NCH{=}O$, reflux

(vi) AcCl, Et_3N, dioxane, room temp.

Scheme 13

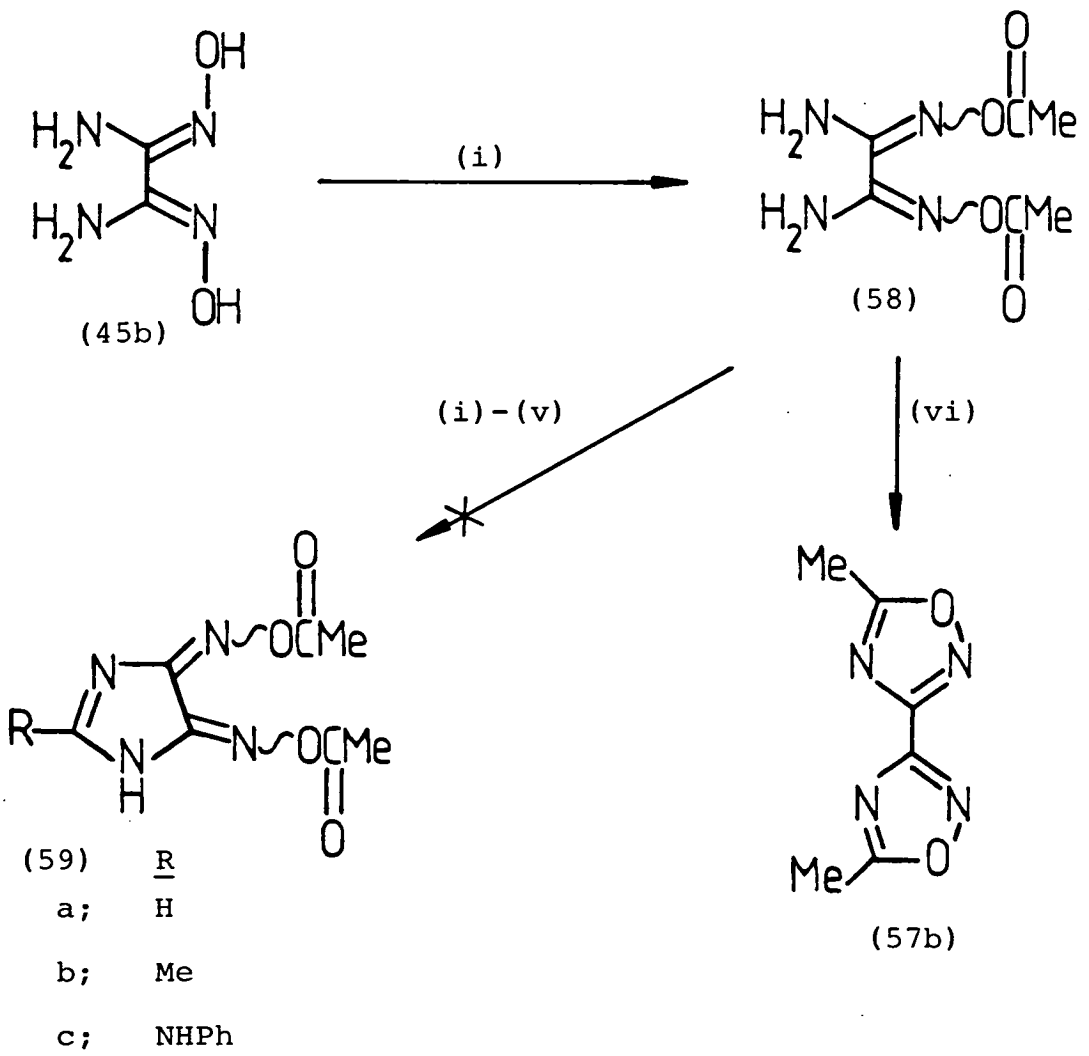
This ^1H n.m.r. absorption excludes the imidazole structure (51) or even the isomeric open-chain imine structure (53) in favour of the ring-tautomeric 1,2,4-oxadiazoline structure (52).

The formation of the oxadiazoline (52) in the acid-catalysed condensation of benzaldehyde with diaminoglyoxime (45b) indicates a preference for the latter to undergo annulation through an oxime and an amino substituent rather than via the two oximino-groups or the two amino-groups. Despite this it was decided to investigate the reactions of 1,2-diaminoglyoxime (45b) with various acylating agents (Scheme 13) in the hope that annulation through the two amino-groups would afford a general route to 4,5-dioximinoimidazoles (47) and hence to 4,5-dinitroimidazoles (49) (see Scheme 11). Heating 1,2-diaminoglyoxime (45b) with formic acid afforded none of the expected 4,5-dioximinoimidazole (47a; R=H) but only a low yield of a product identified by comparison with an authentic sample as oxamide (54). This product presumably arises by solvolysis of the starting 1,2-diaminoglyoxime (45b). In contrast to its behaviour with formic acid, heating 1,2-diaminoglyoxime (45b) with glacial acetic acid afforded a low yield of a product whose spectroscopic properties and chemical reactivity support its formulation as the 1,2,4-oxadiazole carboxamidoxime (55). Thus, it gave analytical and mass spectral data consistent with the molecular formula $C_4H_6N_4O_2$ and it showed i.r. absorption in the range 3470-3300 cm^{-1} assignable to the amino and hydroxyimino components of a carboxamidoxime group. In addition to a sharp singlet due to the three protons of a single methyl group the ^1H n.m.r.

spectrum of the product contained broad, exchangeable signals also attributable to the amino- and hydroxyimino protons of a carboxamidoxime group. The structure of the oxadiazole carboxamidoxime (55) was further confirmed by its conversion into a monoacetyl derivative which showed high frequency i.r. carbonyl absorption at 1755 cm^{-1} consistent with the oxime O-acetate structure (56).

In view of the failure of 1,2-diaminoglyoxime (45b) to undergo annulation with carboxylic acids to afford the corresponding 4,5-dioximinoimidazoles (47), attention was next turned to the use of orthoesters for this purpose. However heating 1,2-diaminoglyoxime (45b) with triethyl orthoformate converted it in quantitative yield into a product which gave a combustion analysis and showed spectroscopic properties fully in accord with its formulation as the known[89] 1,2,4-oxadiazolyl-1,2,4-oxadiazole derivative (57a). In contrast, heating 1,2-diaminoglyoxime (45b) with triethyl orthoacetate gave only a low recovery of the starting material (45b) rather than the expected oxadiazolyloxadiazole (57b). However this known[88] compound was obtained in low yield by heating 1,2-diaminoglyoxime (45b) with acetic anhydride. The analytical and spectroscopic properties of the oxadiazolyloxadiazole (57b) were fully in accord with its assigned structure.

In a final attempt to convert 1,2-diaminoglyoxime (45b) into a 4,5-dioximinoimidazole derivative, it was reacted with cyanogen bromide in anhydrous dimethylformamide. This reaction was expected to afford the aminoimidazole derivative (47c)



(i) AcCl, Et_3N, $Me_2NCH=O$, room temp.

(ii) $HC(OEt)_3$, reflux

(iii) HCO_2H, reflux

(iv) Ac_2O, reflux

(v) $PhN=C=O$, $Me_2NCH=O$, room temp.

(vi) AcOH or $EtCO_2H$, reflux

Scheme 14

but in practice gave only an intractable red oil which yielded no identifiable material.

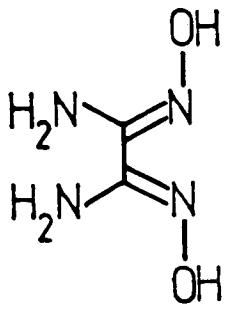
The foregoing results clearly demonstrate that 1,2-diaminoglyoxime (45b) undergoes annulation with acylating agents via the oxime and amino groups rather than exclusively through the amino groups giving 1,2,4-oxadiazole derivatives [eg (55) and (57a and b)] and not the required 4,5-dioximino-imidazoles [i.e. (47a and b)]. In an effort to prevent the unwanted annulation through the oxime groups it was decided to investigate the reactions (Scheme 14) of the known[88] 1,2-diaminoglyoxime O,O-diacetate (58) with acylating agents. It was hoped that these reactions would afford 4,5-dioximino-imidazole O,O-diacetates [eg (59a and b)] and by hydrolysis of the latter the required 4,5-dioximinoimidazoles [i.e. (47a and b)].

Triethylamine catalysed the smooth condensation of 1,2-diaminoglyoxime (45b) with acetyl chloride giving a high yield of the O,O-diacetate derivative (58). This product gave a combustion analysis and showed spectroscopic properties consistent with the assigned structure. In particular the compound's i.r. spectrum lacked carbonyl absorption due to an amide substituent but showed bands at 3420-3160 cm^{-1} characteristic of primary amino-groups and high frequency carbonyl absorption typical[90] of oxime O-acetyl derivatives. The existence of the dioxime diacetate (58) as a single geometrical isomer is indicated by its ^1H n.m.r. spectrum in which the protons of the acetoxy groups absorb as a sharp singlet. However no attempt was made to establish the precise configuration of the 1,2-diaminoethane-1,2-dione

dioxime O,O-diacetate (58) used in the present studies. Disappointingly 1,2-diaminoglyoxime O,O-diacetate (58) failed to react with triethyl orthoformate or formic acid to give the expected imidazole product (59a). Instead the dioxime diacetate (58) was recovered unchanged in good yield after heating with triethyl orthoformate while heating with formic acid gave no identifiable material. The attempted conversion of the dioxime diacetate (58) into the imidazole derivative (59b) by heating with acetic anhydride was also unsuccessful giving only a low recovery of the unreacted starting-material (58) together with a complex gum.

Attempts to N-acetylate the dioxime diacetate (58) under milder conditions also failed. Thus it was recovered unchanged in good yield after treatment with acetyl chloride in dimethylformamide in the presence of triethylamine. In addition the attempted reaction of the dioxime diacetate (58) with phenyl isocyanate in dimethylformamide gave only a low yield of unreacted starting-material (58) with no evidence for the formation of a simple acyl derivative or of the ring-closed 2-aminoimidazole derivative (59c).

In contrast to its behaviour towards heating with acetic anhydride, heating the dioxime diacetate (58) with glacial acetic acid converted it in essentially quantitative yield into the oxadiazolyloxadiazole derivative (57b) identical in all respects to a sample obtained before. The oxadiazolyloxadiazole (57b) was also formed though in lower yield by heating the dioxime diacetate (58) in propionic acid. The lack of crossover in this reaction indicates the intramolecular nature of this type of heterocyclisation which is also demonstrated



(45b)

(i)

(60) R

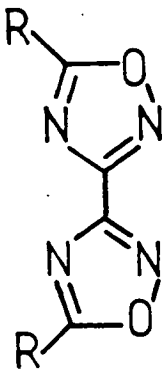
a; Et

b; CH_2Cl

c; CO_2Et

d; OEt

(ii)

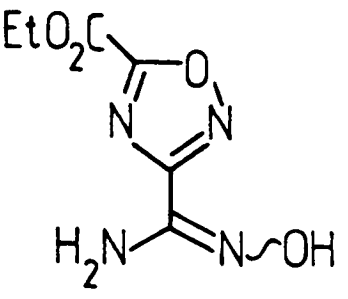


(61) R

a; Et

b; CH_2Cl

c; CO_2Et



(62)

(i) $RC(=O)Cl$, Et_3N, $Me_2NCH{=}O$, room temp.

(ii) AcOH, reflux

Scheme 15

by the reported[88] conversion of the dioxime diacetate (58) into the oxadiazolyloxadiazole (57b) simply on melting.

The thermal biscyclodehydration of the dioxime diacetate (58) to the oxadiazolyloxadiazole (57b) exemplifies an interesting type of 1,2,4-oxadiazole synthesis few examples[88,89] of which have been reported in the literature to date. It was therefore decided in passing to further investigate the scope of this type of 3-(1,2,4-oxadiazol-3-yl)-1,2,4-oxadizole synthesis (Scheme 15). 1,2-Diaminoethane-1,2-dione dioxime (45b) reacted smoothly with propionyl chloride in dimethylformamide in the presence of triethylamine affording the expected O,O-dipropionate derivative (60a) in moderate yield. The dioxime dipropionate (60a) gave analytical and spectroscopic data fully in accord with its assigned structure. The existence of the dioxime dipropionate (60a) as a single geometrical isomer is indicated by its ^{1}H n.m.r. spectrum in which the protons of the methylene and methyl components of the dipropionate groups absorb as a simple quartet and triplet respectively. No attempt was made to establish the actual configuration of the dioxime dipropionate (60a). Heating the dioxime dipropionate (60a) in glacial acetic acid resulted in its conversion in good yield (87%) into the oxadiazolyloxadiazole derivative (61a). This product gave analytical data and showed spectroscopic properties fully in accord with its assigned structure.

The triethylamine catalysed condensation of 1,2-diaminoethane-1,2-dione dioxime (45b) with chloroacetyl chloride afforded a good yield of a product for which accurate

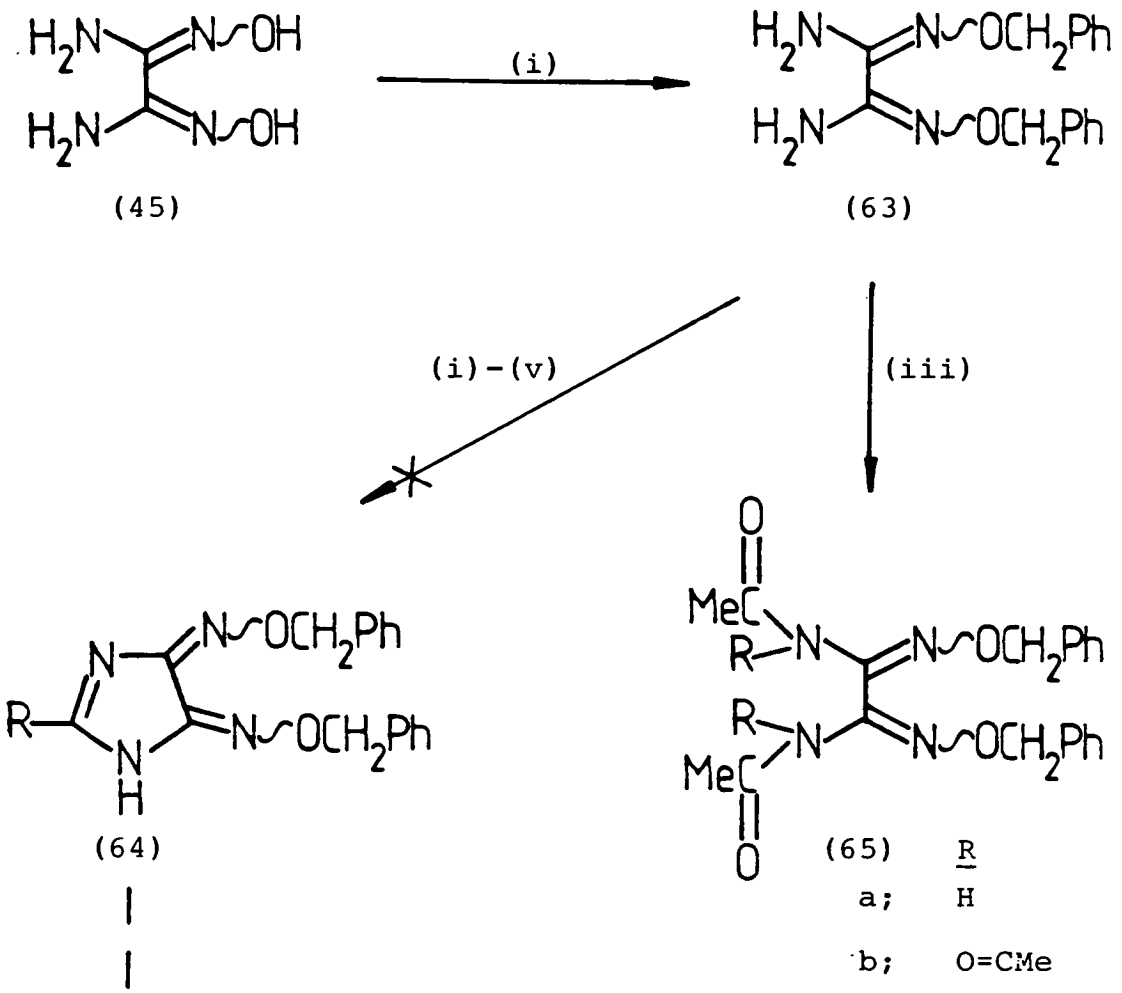
analytical data could not be obtained but whose mass, i.r. and ^1H n.m.r. spectra fully support the dioxime di-(2-chloroacetate) structure (60b). The existence of this compound as a single geometrical isomer is indicated by its ^1H n.m.r. spectrum which contains a single sharp singlet for the protons of the chloromethyl groups. No attempt was made to establish the precise configuration of the dioxime di-(chloroacetate) derivative (60b). However in accord with this structure heating the compound in glacial acetic acid afforded a quantitative yield of the expected chloromethylated oxadiazolyloxadiazole derivative (61b).

The reaction of 1,2-diaminoethane-1,2-dione dioxime (45b) with ethoxalyl chloride in the presence of triethylamine was more complex and less reproduceable than the analogous acylations with acetyl chloride, propionyl chloride, and chloroacetyl chloride. In one instance the triethylamine catalysed condensation of 1,2-diaminoethane-1,2-dione dioxime (45b) with ethoxalyl chloride afforded two products in moderate yield. The major product (yield 33%) analysed correctly for $C_{10}H_4N_4O_8$ and showed a parent ion at m/e 318 in its mass spectrum. These properties and the presence of amino-absorption at 3480-3180 cm^{-1} and high frequency carbonyl absorption at 1780 cm^{-1} in the compound's i.r. spectrum allow its formulation as the dioxime di-ethoxalate (60c). The methyl and methylene protons of the ethoxycarbonyl groups in this compound absorbed as multiplets in its ^1H n.m.r. spectrum indicating that it was a mixture of conformational or geometrical isomers. The minor product (yield 19%) gave

analytical and spectroscopic properties in accord with its formulation as the 1,2,4-oxadiazole carboxamidoxime derivative (62). The presence of the carboxamidoxime substituent in particular was indicated by the compound's i.r. spectrum which in addition to ester carbonyl absorption at 1755 cm^{-1} contained NH and OH bands at 3450-3140 cm^{-1} and C=N absorption at 1655 cm^{-1}.

In another instance the reaction of 1,2-diaminoethane-1,2-dione dioxime (45b) with ethoxalyl chloride in the presence of triethylamine gave the 1,2,4-oxadiazole carboxamidoxime (62) as the major product (yield 34%) together with a second compound (yield 24%) non-identical to the dioxime di-ethoxalate (60c). However, this new product was also obtained though in only low yield (36%) by heating the dioxime di-ethoxalate (60c) in glacial acetic acid. On this basis and its observed combustion analysis and i.r., ^1H n.m.r. and mass spectra it is formulated as the 1,2,4-oxadiazolyl-1,2,4-oxadiazole derivative (61c).

1,2-Diaminoethane-1,2-dione dioxime (45b) also reacted with ethyl chloroformate in the presence of triethylamine to afford a good yield of a compound which analysed correctly for $C_8H_{14}N_4O_6$, showed a parent ion in its mass spectrum at m/e 262 and i.r. amino and carbonyl absorption at 3490-3380 and 1770 cm^{-1} respectively. It is therefore formulated as the expected dioxime dicarbonate derivative (60d). Unlike the O,O-diacyl dioximes (58) and (60a-c), the dioxime O,O-dicarbonate (60d) was recovered in good yield after heating in glacial acetic acid with no evidence for the formation of


(i)
(i)-(v)
(iii)
(45)
(63)
(64)
(65) R
a; H
b; O=CMe
(47)
(i) HC(OEt)3, reflux
(ii) HCO2H, reflux
(iii) Ac2O, reflux
(iv) AcCl, NaH, Me2NCH=O, reflux
(v) BrCN, Me2NCH=O, reflux

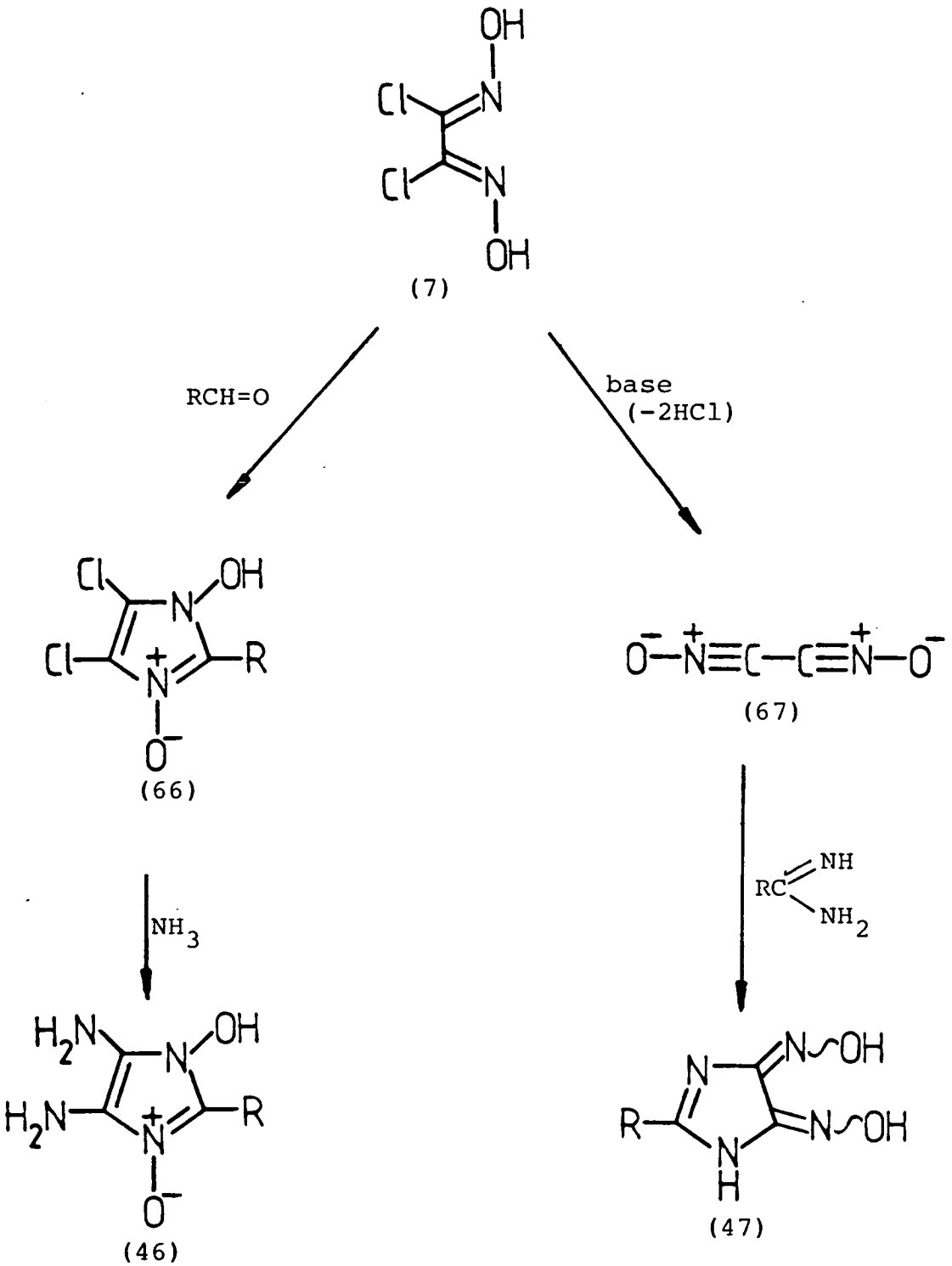
Scheme 16

the oxadiazolyloxadiazole derivative [i.e. (61; R=OEt)]. The failure of the dioxime O,O-dicarbonate (60d) to undergo cyclisation in glacial acetic acid can be attributed to the lower reactivity of the carbonate substituents towards cyclodehydrative condensation compared with the acyl-substituents in the compounds (60a-c).

The foregoing studies clearly demonstrate that due to their tendency to cyclodehydrate to 1,2,4-oxadiazolyl-1,2,4-oxadiazoles, O,O-diacyl compounds [i.e. (58) and (60a-c)] are unsuitable as protected derivatives of 1,2-diaminoethane-1,2-dione dioxime (45b). Attention was therefore turned (Scheme 16) to the previously unknown O,O-dibenzyl-1,2-diaminoethane-1,2-dione dioxime (63) as a protected 1,2-diaminoethane-1,2-dione dioxime suitable for annulation to imidazole derivatives (64) capable of conversion by catalytic hydrogenolysis into the 4,5-dioximinoimidazoles (47) needed as precursors of 4,5-dinitroimidazoles (see before). The O,O-dibenzyl dioxime (63) was readily prepared in high yield (73%) by reacting 1,2-diaminoethane-1,2-dione dioxime in dimethylformamide with sodium hydride followed by benzyl chloride. The O,O-dibenzyl dioxime (63) analysed correctly and gave mass, i.r. and ^{1}H n.m.r. spectra fully consistent with its structure. The ^{1}H n.m.r. spectrum of the O,O-dibenzyl dioxime (63) shows a sharp singlet at δ4.99 for the methylene protons of the benzyl group indicating the presence of a single geometrical isomer whose precise configuration was not established in the present studies.

In an attempt (Scheme 16) to obtain the imidazole derivative (64; R=H), the O,O-dibenzyl dioxime (63) was

heated under reflux with triethyl orthoformate. However this reaction gave only a low recovery of unreacted starting-material (63). Heating the O,O-dibenzyl dioxime (63) with formic acid also failed to yield the imidazole derivative (64; R=H), the starting-material (63) being recovered in low yield together with an intractable gum. Heating the O,O-dibenzyl dioxime (63) with acetic anhydride in an effort to induce ring-closure to the imidazole derivative (64; R=Me) was equally unsuccessful. A reaction time of one hour gave in addition to unreacted starting-material (63) (23%) a low yield (26%) of a product whose properties are consistent with the diacetamido-structure (65a). Thus it gave analytical and mass spectral data consistent with the molecular formula $C_{20}H_{22}N_4O_4$ and its i.r. spectrum contained bands at 3280 and 1680 cm^{-1} attributable to the NH and carbonyl absorption of the secondary amide groups in the structure (65a). The ^1H n.m.r. spectrum of the diacetamido-derivative (65a) contains sharp singlets at δ5.66 and 2.00 assignable to the protons of the methylene and methyl substituents and demonstrating a single geometrical configuration for the compound. Prolonging the reaction time in an attempt to improve the yield of the product (65a) gave instead a moderate yield (58%) of a new product which analysed correctly for $C_{24}H_{26}N_4O_6$ and showed a parent ion at m/e 466 in its mass spectrum indicating that it was the tetraacetamido derivative (65b). This structure was fully confirmed by the product's i.r. spectrum which lacked NH-absorption but contained two carbonyl bands at 1730 and 1700 cm^{-1}. The tetraacetamido compound's ^1H n.m.r.


OH
Cl
N
Cl
N
OH
(7)
RCH=O
base
(-2HCl)
Cl
OH
N
Cl
R
N
O
(66)
O
N
C
C
N
O
(67)
NH3
NH
RC
NH2
H2N
OH
N
H2N
R
N
O
(46)
N
OH
N
R
N
H
N
OH
(47)

Scheme 17

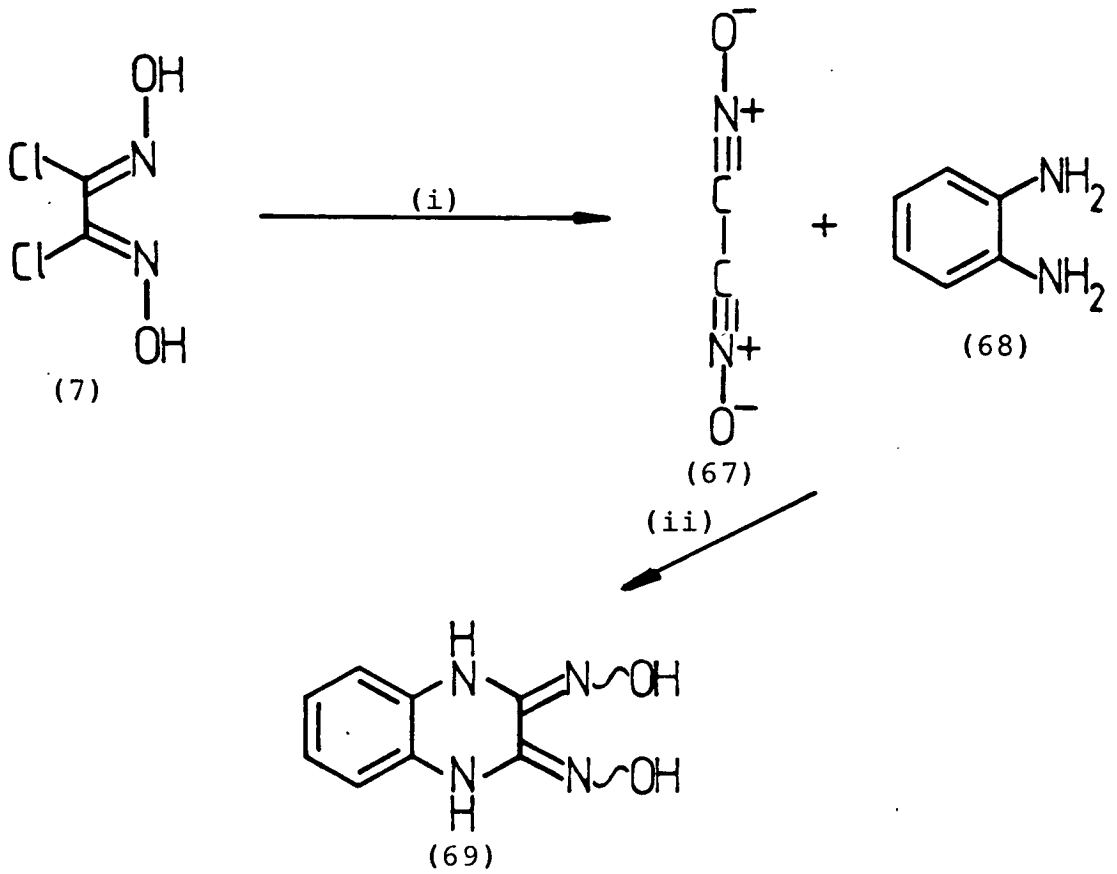
spectrum showed singlet absorption due to the methyl and methylene protons indicating that it exists predominantly as a single geometrical isomer.

The failure to effect direct imidazole formation from the O,O-dibenzyl dioxime (63) prompted the attempted monoacetylation of this compound with the intention of carrying out the controlled cyclisation of the resulting monoacetyl product to the required imidazole derivative (64; R=Me). However the sodium hydride catalysed condensation of the O,O-dibenzyl dioxime (63) with acetyl chloride in dimethylformamide gave only starting-material (35%) together with intractable gums.

In a final effort to achieve the annulation of the O,O-dibenzyl dioxime (63) to a 4,5-dioximinoimidazole derivative it was heated under reflux with cyanogen bromide in dimethylformamide. However, this reaction failed to afford the expected aminoimidazole derivative (64; $R=NH_2$) but gave instead only an intractable multicomponent red gum. At this stage synthesis of polynitroimidazoles based on 1,2-diaminoethane-1,2-dione dioxime (45) as the starting-material were not investigated further.

2.5 Synthetic Approaches to Dinitroimidazoles and Trinitroimidazoles Based on 1,2-Dichloroethane-1,2-dione Dioxime (1,2-Dichloroglyoxime) Derivatives

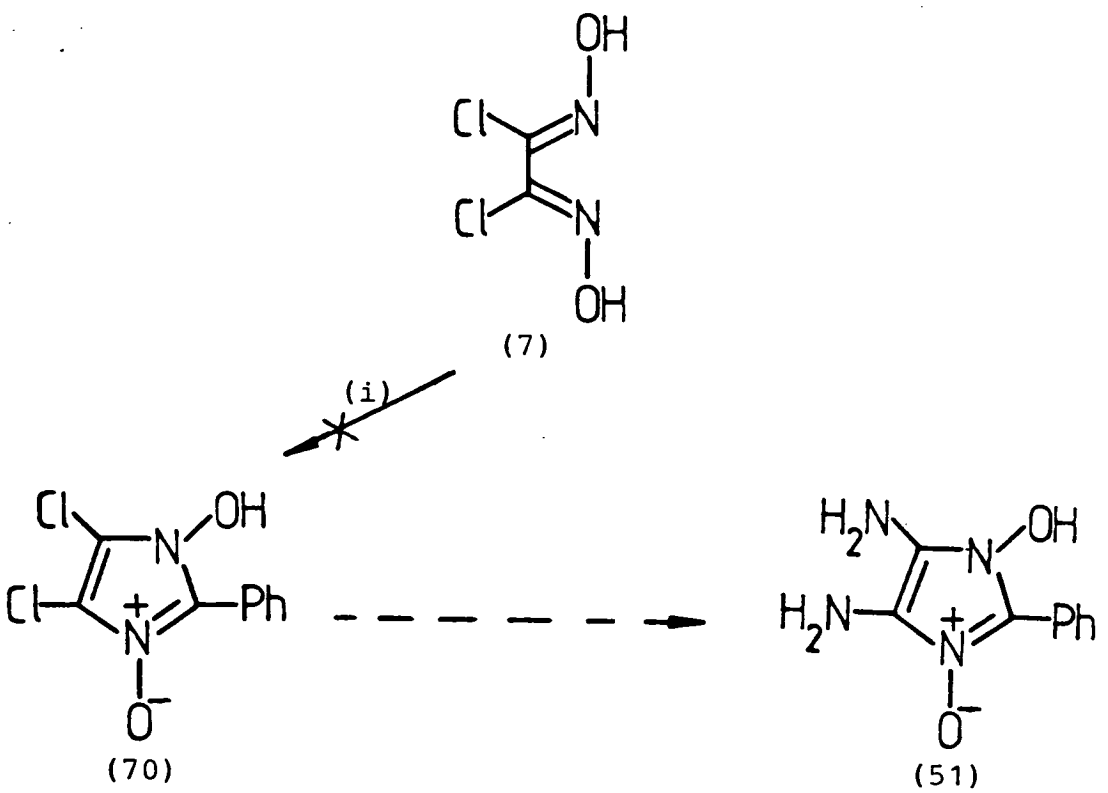
In parallel with the previously described work, studies were also carried out on 1,2-dichloroethane-1,2-dione dioxime (7) as a building block for the synthesis of polynitroimidazoles



(i) Na_2CO_3, CH_2Cl_2, 0°

(ii) CH_2Cl_2, 0°

Scheme 18



(i) PhCH=O, Conc.HCl, MeOH, 45 to 55°

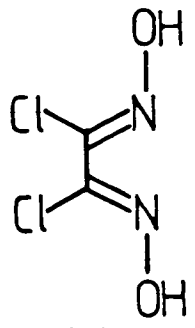
Scheme 19

(Scheme 17). It was anticipated that 1,2-dichloroethane-1,2-dione dioxime which is known[91] to exist in the anti-configuration (7), might, by analogy with ethane-1,2-dione dioxime (see Section 2.2, page 29), undergo acid-catalysed condensation with aldehydes to afford 4,5-dichloro-3-hydroxy-imidazole 1-N-oxides (66). Nucleophilic displacement of the halogen atoms in the latter with ammonia or amide ion would then lead to 4,5-diaminoimidazole derivatives (46) suitable for further conversion into polynitroimidazoles (see before, Sections 2.4, page 35). Alternatively (Scheme 17) it was expected that 1,2-dichloroethane-1,2-dione dioxime (7) might undergo annulation with amidines, either by direct nucleophilic displacement of both chloro-substituents or via the intermediacy of cyanogen di-N-oxide (67) to afford 4,5-dioximinoimidazoles (47) potential precursors of 4,5-di-nitroimidazoles (see before, Section 2.4, page 35). Reactions of 1,2-dichloroethane-1,2-dione dioxime (7) with nucleophiles involving cyanogen di-N-oxide (67) as an unstable intermediate have been described in the literature.[92,93] Thus (Scheme 18) the reaction of a methylene chloride solution of cyanogen di-N-oxide [prepared from the dichloro-dioxime (7)] reacts with ortho-phenylenediamine (68) to give 2,3-dioximino-1,2,3,4-tetrahydroquinoxaline (69).[93]

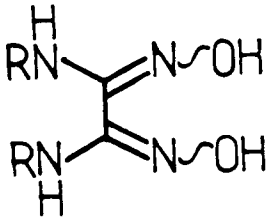
In practice (Scheme 19) the dichloro-dioxime (7) failed to react with benzaldehyde in the presence of hydrochloric acid, the starting-material (7) being recovered in good yield with no evidence for the formation of the expected dichloro-imidazole derivative (70). The failure of this reaction is

puzzling in view of the successful hydrochloric acid catalysed condensation of ethane-1,2-dione dioxime (18) with formaldehyde to give the N-hydroxyimidazole N-oxide (19) (see Section 2.2, page 29). The lack of formation of the dichloroimidazole derivative (70) precluded the investigation of its ammonolysis as a method for the synthesis of the diaminoimidazole derivative (51).

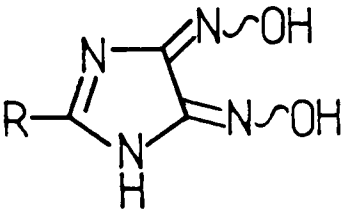
Attention was next directed (Scheme 20) to the investigation of the reactions of 1,2-dichloroethane-1,2-dione dioxime (7) with amidines as synthetic routes to the elusive 4,5-dioximinoimidazoles (47). It was first decided to investigate (Scheme 20) the reactions of 1,2-dichloroethane-1,2-dione dioxime with primary amines [(7)→(6)] as models for the proposed annulation reactions [(7)→(47)]. However the attempted conversion of the dichloro-dioxime (7) into the diamino-dioxime (6a) by reaction with ethylamine in dioxane at room temperature gave only a low recovery of starting-material (7). The failure of this reaction was probably due to the volatility of the ethylamine since the dichloro-dioxime (7) reacted smoothly with the less volatile benzylamine in dioxane at room temperature to afford a high yield of a product whose analytical and spectroscopic properties are fully in accord with the diamino-dioxime structure (6b). The simplicity of the ^{1}H n.m.r. absorption of the benzyl protons in this compound suggests that it exists largely as a single geometrical isomer. Since the proposed annulation reactions of the dichloro-dioxime with amidines [(7)→(47)] would ideally be carried out under aqueous conditions, the condensation of the dichloro-dioxime (7) with benzylamine in



(7)



(6) R
a; Et
b; CH_2Ph

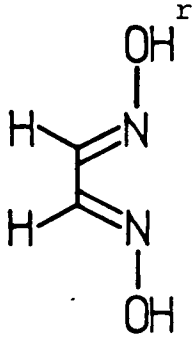


(47) R
a; Ph
b; NH_2

(i) RNH_2, dioxane or Na_2CO_3, H_2O, CH_2Cl_2, room temp.

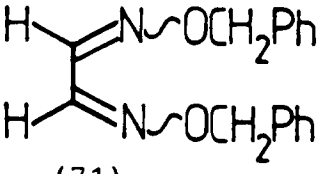
(ii) $RC(NH_2)=\overset{+}{N}H_2Cl^-$, Et_3N, dioxane or Na_2CO_3, H_2O, CH_2Cl_2, room temp.

Scheme 20



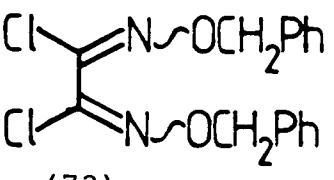
(18)

(i)

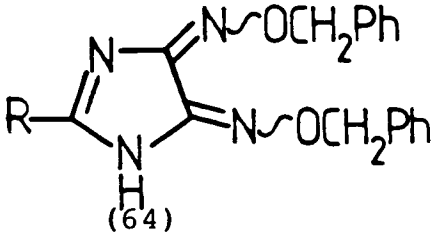


(71)

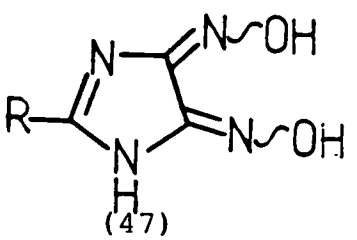
(ii)



(72)



(64)



(47)

(i) $PhCH_2Cl$, NaH, $Me_2NCH=O$, room temp.

(ii) Cl_2, CH_2Cl_2, 0°, or Cl_2, Conc.HCl, AcOH, H_2O, 0°

Scheme 21

methylene chloride in the presence of aqueous sodium carbonate was also investigated. The di-(benzylamino) dioxime (6b) was also formed under these conditions though in diminished yield (55%).

Having demonstrated the ready replacement of both chloro-substituents in the dichloro-dioxime (7) by amines attention was next turned to the previously uninvestigated reactions (Scheme 20) of the dichloro-dioxime (7) with amidines, with the expectation of obtaining the required 4,5-dioximinoimidazoles (47). However the attempted reaction of the dichloro-dioxime (7) with commercially available benzamidine hydrochloride in dioxane in the presence of triethylamine gave only an intractable red oil with no evidence for the formation of the 4,5-dioximinoimidazole (47a). The conversion of 1,2-dichloroethane-1,2-dione dioxime (7) into the aminoimidazole (47b) by reaction with guanidine was no more successful. Thus treatment of the dichloro-dioxime (7) with guanidine hydrochloride at room temperature in dioxane in the presence of solid sodium carbonate or at 0° in methylene chloride in the presence of aqueous sodium carbonate gave either a low recovery of unreacted dichloro-dioxime or no identifiable material.

The failure of 1,2-dichloroethane-1,2-dione dioxime (7) to react with benzamidine or guanidine to afford the 4,5-dioximinoimidazole derivatives (47a and b) is surprising in view of the ready base catalysed condensation (Scheme 18) of the dichloro-dioxime (7) with ortho-phenylenediamine (69) to afford the dioximinoquinoxaline derivative.[93] Since the

failure of the imidazole annulation reactions could be due to premature decomposition of the presumed cyanogen di-N-oxide intermediate (67) under the reaction conditions it was decided to investigate an alternative 1,2-dichloroethane-1,2-dione dioxime derivative whose annulation to 4,5-dioximinoimidazoles would not be dependent on initial cyanogen di-N-oxide (67) formation. The derivative chosen (Scheme 21) was the previously unknown O,O-dibenzyl-1,2-dichloroethane-1,2-dione dioxime (72). This compound cannot afford cyanogen di-N-oxide (67) but being a diimidoyl chloride should still be highly reactive towards amine nucleophiles and hence towards amidines to afford 4,5-di-(O-benzyl)-oximinoimidazoles (64). Catalytic hydrogenolysis of the latter would then afford the required parent 4,5-dioximino-imidazoles (47). It was considered unlikely that the reactivity of 1,2-dichloroethane-1,2-dione dioxime (7) would be compatible with the conditions needed to effect direct O-benzylation to the O,O-dibenzyl derivative (72), and it was therefore decided to synthesise the latter indirectly (Scheme 21) by the formation and chlorination of the previously undescribed O,O-dibenzyl ethane-1,2-dione dioxime (71). This compound was readily prepared in high yield by the sodium hydride catalysed reaction of ethane-1,2-dione dioxime (18) with benzyl chloride. The product (71) gave a combustion analysis and showed spectroscopic properties in accord with its assigned structure. Unfortunately, attempts to chlorinate the O,O-dibenzyl dioxime (71) under various conditions failed to afford the required dichloro-derivative

(72). In one attempt using chlorine in glacial acetic acid in the presence of hydrochloric acid the product obtained in low yield (39%) was benzyl acetate. The mode of formation of this product is not clear but it cannot be the result of solvolysis of the O,O-dibenzyl compound (71) which is stable to aqueous hydrochloric acid in glacial acetic acid in the absence of chlorine.

Due to the lack of time approaches to the synthesis of polynitroimidazoles based on 1,2-dichloroethane-1,2-dione dioxime and its derivatives were terminated at this point.

2.6 Experimental

2-Nitroethanal Monoxime (Methazonic Acid) (9)

A solution of sodium hydroxide (20.0 g; 0.5 mol) in water (40.0 ml) was stirred and treated dropwise at 45-50° (water bath) with nitromethane (20.0 g; 0.33 mol) at such a rate that the temperature remained within the range 45-50°. An exothermic reaction set in and the reaction temperature was maintained at 55° by periodic cooling in an ice-water slurry. The mixture was allowed to cool to room temperature with stirring then cooled to -10° (ice-salt bath) and acidified to pH 1 by the dropwise addition of concentrated hydrochloric acid (ca.45.0 ml) at such a rate that the temperature of the mixture remained <-5°. The precipitated solid was quickly collected, washed with water, dissolved in ether (250 ml) and the solution evaporated at room temperature to afford methazonic acid (9) as an orange crystalline solid (10.4 g; 61%) m.p. 56-62° (lit.,[77] 80°) which was stored in a freezer at <-5° until used.

Nitroethane-1,2-dione Dioxime (Nitroglyoxime) (4)

A solution of methazonic acid (9) (5.8 g; 0.056 mol) in ethanol (30.0 ml) was stirred and treated dropwise with a solution of potassium hydroxide (3.3 g; 0.058 g) in ethanol (25.0 ml) with cooling in an ice-water bath. The mixture was stirred for a further 0.5h and then the precipitated solid was filtered off, washed with ethanol and dried *in vacuo* to afford the potassium salt of methazonic acid (6.7 g; 77%).

A solution of the potassium salt of methazonic acid (6.0 g; 0.035 mol) in water (20.0 ml) was stirred and treated at 0-4° (ice-salt bath) with a solution of sodium nitrite (3.0 g; 0.043 mol) in water (10.0 ml) followed by the dropwise addition of aqueous 1M sulphuric acid until the dark orange colour of the mixture faded to light orange and no further colour change was apparent. The light orange aqueous mixture was then treated with sodium chloride, extracted with ether (5x20.0 ml) and the combined extracts washed with saturated aqueous sodium chloride solution (5x20.0 ml) then concentrated at room temperature to 5.0 ml then diluted with light petroleum (10.0 ml) and left stoppered at 0° for 0.5h. The precipitated solid was then filtered off, washed with light petroleum and combined with a second crop of solid obtained by concentrating the light petroleum mother liquor to afford nitroglyoxime (4) (3.5 g; 74%) m.p. 102-105° (decomp.) [Lit.,[75] 105° (decomp.)].

The Attempted Reaction of Nitroethane-1,2-dione Dioxime (Nitroglyoxime) (4) with Formaldehyde in the Presence of Hydrochloric Acid

A solution of nitroglyoxime (4) (0.68 g; 0.005 mol) and 35-40% w/v aqueous formaldehyde solution (0.47 g; 0.005 mol) in methanol (10.0 ml) was treated with concentrated hydrochloric acid (0.25 ml) and the mixture was stirred at 45-55° (oil bath) for 48h.

The mixture was brought to pH4 by the dropwise addition of 50% w/v aqueous sodium hydroxide solution, then evaporated, treated with water (2.0 ml), neutralised with aqueous

2M sodium hydroxide solution and glacial acetic acid, and extracted with methylene chloride to give only a negligible quantity of gum.

The Attempted Reaction of Nitroethane-1,2-dione Dioxime (Nitroglyoxime) (4) with Benzaldehyde in the Presence of Hydrogen Chloride

A solution of nitroglyoxime (4) (0.27 g; 0.002 mol) and benzaldehyde (0.21 g; 0.002 mol) in ethanol (15.0 ml) was treated with a slow stream of hydrogen chloride at 0° (ice-salt bath) until the mixture was saturated. The mixture was securely stoppered and left at room temperature for 24h.

The mixture was filtered to remove some inorganic material (0.03 g) then the filtrate was evaporated, and the residue treated with water (10.0 ml) and extracted with methylene chloride to give a red oil (0.17 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Ethane-1,2-dione Dioxime (Glyoxime) (18)

Ethane-1,2-dione dioxime (glyoxime) (18) was prepared by the reaction of disodium 1,2-dihydroxyethane-1,2-disulphonate monohydrate (glyoxal sodium bisulphite addition compound) with hydroxylamine hydrochloride in the presence of sodium acetate as described by Haaijman and Wibaut,[78] yield 60%, m.p. 180° (lit.,[78] 173°) and was used without further purification.

1-Hydroxyimidazole 3-N-Oxide (19)

A solution of ethane-1,2-dione dioxime (glyoxime) (18)

(9.3 g; 0.10 mol) and 35-40% w/v aqueous formaldehyde solution (10.3 g; 0.11 mol) in methanol (30.0 ml) was treated with concentrated hydrochloric acid (4.5 ml) and the mixture was stirred at 45-50° (oil bath) for 48h.

The mixture was brought to pH4 by the dropwise addition of 50% w/v aqueous sodium hydroxide solution, cooled in an ice bath and the precipitated solid was collected, washed with water and methanol and dried to afford the N-hydroxyimidazole N-oxide (19) (3.5 g; 35%) m.p. 180-182° (decomp.) (lit.,[79] 178-180°). Extraction of the aqueous mother liquor with methylene chloride gave no further material.

Attempted Nitration Reactions of 1-Hydroxyimidazole 3-N-Oxide (19)

(a) The N-hydroxyimidazole N-oxide (19) (0.40 g; 0.004 mol) was added in small portions with stirring at room temperature to fuming nitric acid (5.0 ml). This resulted in the copious evolution of dinitrogen tetroxide accompanied by flame and the experiment therefore had to be abandoned.

(b) The reaction described in (a) was repeated using concentrated nitric acid (5.0 ml). The resulting solution was stirred at room temperature for 1h then evaporated under reduced pressure to give an oil whose spontaneous flammability in air resulted in the experiment being abandoned.

(c) A mixture of powdered copper(II) nitrate trihydrate (0.60 g; 0.0025 mol) and acetic anhydride (2.0 g; 0.02 mol) was stirred at room temperature for 0.5h, then treated in portions with stirring with the N-hydroxyimidazole N-oxide

(19) (0.20 g; 0.002 mol) at such a rate that the temperature was <35°. The mixture was stirred at room temperature for 0.5h then diluted with water (10.0 ml) and extracted with methylene chloride. Evaporation of the washed (saturated aqueous sodium hydrogen carbonate solution) methylene chloride extract gave no identifiable material.

The acidic aqueous mother liquor was neutralised with aqueous 2M sodium hydroxide solution and glacial acetic acid and evaporated. Extraction of the resulting residue with boiling ethyl acetate gave no identifiable material.

Nitroacetonitrile (30)

A solution of 2-nitroethanal monoxime (methazonic acid) (9) (75.6 g; 0.73 mol) in anhydrous ether (350 ml) was stirred and heated under reflux (water bath) with the exclusion of atmospheric moisture. The heat source was removed and the mixture was treated dropwise with stirring with freshly distilled thionyl chloride (89.5 g; 0.75 mol) at such a rate that the mixture refluxed gently. The mixture was stirred and heated under reflux for 1h, filtered to remove some insoluble material and evaporated at 30°. The residue was then dissolved in fresh anhydrous ether (300 ml) and the solution was washed with water (2x80.0 ml) and evaporated to give a red oil (53.8 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded nitroacetonitrile[83] (30) (39.9 g; 64%) as an amber oil which was used without further purification and stored at <-5° in a freezer until required.

1-Amino-1-ethoxy-2-nitroethene Hydrochloride (31)

A solution of nitroacetonitrile (30) (8.4 g; 0.1 mol) in anhydrous ethanol (60.0 ml) and anhydrous ether (100 ml) was cooled to 0° (ice-salt bath) and treated with a slow stream of hydrogen chloride until the mixture was saturated. The mixture was securely stoppered and left at 0° in a refrigerator for 24h.

The precipitated solid was collected, washed with anhydrous ether and dried *in vacuo* to afford 1-amino-1-ethoxy-2-nitroethene hydrochloride (31) (12.0 g; 71%), m.p. 84-87°, ν_{max} 3200-2600 br ($\overset{+}{N}H$) and 1550 and 1350 (NO_2) (cm^{-1}), $\delta_H[(CD_3)_2SO]$ 9.13 (3H, brs, NH), 6.54 (1H, s, CH), 4.15 (2H, q, J7Hz, CH_2) and 1.26 (3H, t, J7Hz, CH_3) which decomposed on attempted purification for combustion analysis.

1-Amino-1-ethoxy-2-nitroethene (32)

(a) A suspension of 1-amino-1-ethoxy-2-nitroethene hydrochloride (31) (0.3 g; 0.002 mol) in anhydrous ether (4.0 ml) was stirred and cooled at -20° (ice and solid carbon dioxide bath) and treated with a slow stream of ammonia gas for 1.5h. The insoluble solid (0.2 g) was collected and extracted with boiling ethyl acetate (50.0 ml) leaving ammonium chloride insoluble. Evaporation of the combined ethyl acetate extract and ether mother liquor gave 1-amino-1-ethoxy-2-nitroethene (32) (0.1 g; 54%) which formed large colourless needles, m.p. 84-86° (from toluene) $\nu_{max.}$ 3360 (NH), 1630 (C=N), and 1500 and 1300 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 9.30-5.50 (br, NH) (removed by shaking with D_2O), 6.56 (1H, s, CH), 4.05 (2H, q,

J7Hz, CH_2) and 1.24 (3H, t, J7Hz, CH_3).

Found: C, 36.4; H, 6.0; N, 21.3%; M^+, 132.

$C_4H_8N_2O_3$ requires: C, 36.4; H, 6.1; N, 21.2%; M , 132.

(b) A solution of ammonia gas (0.07 g; 0.004 mol) in anhydrous ethanol (10.0 ml) was cooled to 0° (ice-salt bath) and treated with a single portion of 1-amino-1-ethoxy-2-nitroethene hydrochloride (31) (0.7 g; 0.004 mol). The mixture was securely stoppered and shaken on a mechanical shaker at room temperature for 2h and then left in a refrigerator at 0° for a further 22h.

The mixture was filtered to remove ammonium chloride and the ethanolic filtrate was evaporated to give 1-amino-1-ethoxy-2-nitroethene (32) (0.5 g; 96%) m.p. 81-83° identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

1-Amino-1-(N-benzylamino)-2-nitroethene (33b)

(a) A solution of benzylamine (0.65 g; 0.006 mol) in anhydrous ethanol (15.0 ml) was treated with a single portion of 1-amino-1-ethoxy-2-nitroethene (32) (0.8 g; 0.006 mol) and the mixture was left stoppered at room temperature for 19h.

The precipitated solid was collected, washed with ethanol and dried to afford 1-amino-1-(N-benzylamino)-2-nitroethene (33b) (0.16 g; 14%) which formed colourless crystals m.p. 224-226° (decomp.) (from aqueous methanol) ν_{max} 3350-3050 br (NH), 1650 (C=N), and 1550 and 1350 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 9.23 (1H, brs, NH) (removed by shaking with D_2O), 8.02 (2H, brs, NH_2) (removed by shaking with D_2O), 7.34 (5H, brs,

ArH), 6.44 (1H, s, CH), and 4.47 (2H, d, J6Hz, CH_2) (collapses to a singlet on shaking with D_2O).

Found: C, 55.5; H, 5.6; N, 21.5%; M^+, 193.0848.

$C_9H_{11}N_3O_2$ requires: C, 56.0; H, 5.7; N, 21.8%; M , 193.0851.

The combined ethanol mother liquor and washings were evaporated to give a gummy solid (0.8 g) from which no identifiable material could be obtained.

(b) A solution of 1-amino-1-ethoxy-2-nitroethene hydrochloride (31) (6.7 g; 0.04 mol) in anhydrous ethanol (100 ml) was stirred and treated dropwise at 0° (ice-salt bath) with benzylamine (8.6 g; 0.08 mol) and the mixture was stoppered and stored at 0° in a refrigerator for 24h.

The precipitated solid was collected and combined with a second crop obtained by evaporating the ethanolic mother liquor and treating the residue with water to afford 1-amino-1-(N-benzylamino)-2-nitroethene (33b) (5.4 g; 69%), identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Neutralisation of the aqueous mother liquor and extraction with methylene chloride gave no further identifiable material.

The Attempted Reaction of 1-Amino-1-(N-benzylamino)-2-nitroethene (33b) with Sodium Nitrite in Aqueous Acetic Acid

A solution of 1-amino-1-(N-benzylamino-2-nitroethene (33b) (1.2 g; 0.006 mol), in glacial acetic acid (15.0 ml) was stirred and treated dropwise at 5-8° (ice bath) with a solution of sodium nitrite (0.45 g; 0.0066 mol) in water (2.0 ml) over 15 min. The mixture was stirred at 5-8° for 2h

then evaporated and the residual cake treated with water (5.0 ml) and extracted with methylene chloride to give a red oil (0.84 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to methanol gave only small amounts of gums (total 0.17 g) whose t.l.c. in methylene chloride-ethyl acetate (2:1) over silica showed them to be unresolvable multicomponent mixtures which were not further investigated.

The Attempted Reaction of 1-Amino-1-ethoxy-2-nitroethene Hydrochloride (31) with Ethyl Nitrite in the Presence of Hydrogen Chloride

A suspension of 1-amino-1-ethoxy-2-nitroethene hydrochloride (31) (1.7 g; 0.01 mol) in anhydrous ethanol (25.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of hydrogen chloride (0.93 g; 0.025 mol) in anhydrous ethanol (5.0 ml) then dropwise with a solution of ethyl nitrite (0.73 g; 0.011 mol) in anhydrous ethanol (5.0 ml) at such a rate that the temperature remained <5°. The mixture was stirred at room temperature for 22h, filtered to remove ammonium chloride and the ethanolic filtrate was evaporated to give a gummy solid. This was washed with ether and the residue extracted with boiling ethyl acetate leaving ammonium chloride insoluble. The combined ethyl acetate and ether mother liquors were evaporated and the residue extracted with methylene chloride to give ethyl 2-nitroacetate (1.1 g; 83%) identical (i.r. spectrum) to an authentic sample.

2-Oximinonitroacetonitrile (38)

(a) A solution of nitroacetonitrile (30) (1.7 g; 0.02 mol) in anhydrous ethanol (20.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of hydrogen chloride (1.9 g; 0.05 mol) in anhydrous ethanol (10.0 ml) followed by a solution of ethyl nitrite (1.7 g; 0.022 mol) at such a rate that the temperature was <5°. The mixture was stirred at room temperature for 22h, then evaporated to give an oil (3.6 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave 2-oximinonitroacetonitrile (38) as an unstable oil (0.57 g; 25%), ν_{max} 3650-3100 br (NOH) and 2220 (C≡N) cm^{-1}, δ_C 171.2 (C=N) and 111.9 (C≡N).

Further elution with ethyl acetate through to methanol gave no other material.

(b) A solution of nitroacetonitrile (30) (1.4 g; 0.016 mol) in glacial acetic acid (20.0 ml) was stirred and treated dropwise at 0-10° (ice-bath) with a solution of sodium nitrite, (1.1 g; 0.016 mol) in water (8.0 ml) at such a rate that the temperature remained <10°. The mixture was stirred in the melting ice bath for 20h then diluted with water (40.0 ml) and extracted with ether. The ethereal extract was washed with saturated aqueous sodium hydrogen carbonate solution and evaporated to give 2-oximinonitroacetonitrile (38) as a yellow oil (0.5 g; 29%), identical (i.r. spectrum) to a sample prepared in (a) before.

(c) A solution of nitroacetonitrile (30) (4.3 g; 0.05 mol) and sodium nitrite (7.0 g; 1.0 mol) in water (50.0 ml) was

stirred and treated dropwise with a solution of 88% w/v aqueous phosphoric acid (5.0 g; 0.045 mol) over 0.5h and at such a rate that the temperature was 30-40° (cooling with water bath) and the pH remained constant at 4-5.

The mixture was stirred for a further 1h, acidified with concentrated hydrochloric acid (6.3 ml) and extracted with ether to give 2-oximinonitroacetonitrile (38) as a yellow oil (5.7 g, 100%) identical (i.r. spectrum) to a sample prepared in (a) before.

The Attempted Reaction of 2-Oximinonitroacetonitrile (38) with Acetyl Chloride in the Presence of Triethylamine

A solution of 2-oximinonitroacetonitrile (38) (0.23 g; 0.002 mol) and triethylamine (0.22 g; 0.0022 mol) in anhydrous dioxane (5.0 ml) was stirred and treated dropwise at room temperature with a solution of acetyl chloride (0.17 g; 0.0022 mol) in anhydrous dioxane (1.0 ml) and the mixture was stirred at room temperature for 1h. The mixture was filtered to remove triethylamine hydrochloride (0.28 g) and the filtrate was evaporated to afford a red oil (0.19 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (4:1) through to methanol gave no identifiable product.

The Attempted Reaction of 2-Oximinonitroacetonitrile (38) with Phenyl Isocyanate

A solution of 2-oximinonitroacetonitrile (38) (0.23 g; 0.002 mol) in anhydrous ether (5.0 ml) was stirred and treated

at room temperature with a solution of phenyl isocyanate (0.24 g; 0.002 mol) in anhydrous ether (5.0 ml) and the mixture was stirred at room temperature for 16h. The mixture was filtered to remove N,N-diphenylurea (0.07 g) identified by comparison (i.r. spectrum) with an authentic sample and the filtrate was evaporated to give an oil (0.31 g), whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture containing some starting-material which was not further investigated.

The Attempted Reaction of 2-Oximinonitroacetonitrile (38) with 2,4-Dinitrochlorobenzene in the Presence of Sodium Hydroxide

A solution of 2-oximinonitroacetonitrile (38) (0.70 g; 0.004 mol) in Analar acetone (10.0 ml) was stirred at room temperature and treated in one portion with a solution of sodium hydroxide (0.18 g; 0.0044 mol) in water (1.0 ml) then dropwise with a solution of 2,4-dinitrochlorobenzene (0.89 g; 0.0044 mol) in Analar acetone (5.0 ml). The mixture was stirred at room temperature for 1h then evaporated and the residue treated with water (5.0 ml) and extracted with methylene chloride to give unreacted 2,4-dinitrochlorobenzene as a yellow oil (0.78 g; 88%), identical (i.r. spectrum and t.l.c. in methylene chloride over silica) to an authentic sample.

Neutralisation of the aqueous mother liquor and extraction with methylene chloride gave only a negligible quantity of gum.

The Attempted Conversion of 2-Oximinonitroacetonitrile (38) into Ethyl 2-Nitro-2-oximinoacetimidate Hydrochloride (37) and 2-Nitro-2-oximinoacetamide (39)

A solution of 2-oximinonitroacetonitrile (38) (0.6 g; 0.005 mol) in anhydrous ethanol (3.0 ml) and anhydrous ether (5.0 ml) was treated at 0° (ice-salt bath) with a slow stream of hydrogen chloride until the mixture was saturated. The mixture was securely stoppered and stored in a refrigerator at 0° for 24h. The precipitated hygroscopic solid (0.18 g) was collected, washed with ether, dried and then heated at 100° (steam bath) for 2.5h.

The resulting residue was washed with ethanol leaving only a negligible amount of insoluble solid. Evaporation of the ethanolic filtrate gave an intractable gum from which no identifiable material could be obtained.

1,1-Bis-methylthio-2-nitroethene (41)

1,1-Bis-methylthio-2-nitroethene (41) was prepared by the reaction of dipotassium 2-nitrodithioacetic acid as described by Gompper and Schaeffer[85], yield 74% and had m.p. 124° (lit.,[85] 126°).

1-Benzylamino-1-methylthio-2-nitroethene (42a)

A solution of 1,1-bis-methylthio-2-nitroethene (41) (3.3 g; 0.02 mol) in ethanol (50.0 ml) was treated with benzylamine (2.2 g; 0.02 mol) and the mixture was heated under reflux for 4h. The solid which separated from the cooled mixture was collected and combined with further

material obtained by evaporating the ethanolic filtrate and triturating the residue with ether-ethanol to afford 1-benzylamino-1-methyl-thio-2-nitroethene (42a)[86] which formed cream crystals (3.8 g; 84%), m.p. 112° (from ethanol), ν_{max} 3100 (NH) and 1550 and 1350 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 10.5 (1H, br, NH) (removed by shaking with D_2O), 7.34 (5H, s, ArH), 6.67 (1H, s, vinylic CH), 4.66 (2H, d, J6Hz, CH_2) (becomes a singlet on shaking with D_2O) and 2.49 (3H, s, SMe).

Found: M^+, 224.0619.

$C_{10}H_{12}N_2O_2S$ requires: M , 224.0619.

Methyl N-Benzyl-2-nitro-2-oximinothioacetimidate (43)

A solution of 1-benzylamino-1-methylthio-2-nitroethene (42a) (1.1 g; 0.005 mol) in glacial acetic acid (20.0 ml) was stirred at 5-8° (ice-bath) and treated dropwise over 15 min with a solution of sodium nitrite (0.38 g; 0.0055 mol) in water (2.5 ml). The mixture was stirred at 5-8° for 2h and the precipitated solid was collected, washed with water and dried in vacuo to afford methyl N-benzyl-2-nitro-2-oximinothioacetimidate (43) (0.92 g; 73%), m.p. 108-110° (decomp.) which due to its thermally instability was purified by flash-chromatography in methylene chloride-ethyl acetate (9:1) over silica, ν_{max} 1635 (C=N) and 1540 and 1340 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 14.00 (1H, brs, NOH), 7.32 (5H, m, ArH), 4.63 (2H, s, CH_2), and 2.39 (3H, s, CH_3).

Found: C, 47.7; H, 4.4; N, 16.6%; M^+, 253.

$C_{10}H_{11}N_3O_3S$ requires: C, 47.4; H, 4.4; N, 16.6%; M , 253

The combined aqueous acetic acid mother liquor and

aqueous washings were evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give only a negligible quantity of gum.

The Attempted Oxidative Cyclisation of Methyl N-Benzyl-2-nitro-2-oximinothioacetimidate (43) using Manganese Dioxide

A solution of methyl N-benzyl-2-nitro-2-oximinothioacetimidate (43) (0.76 g; 0.003 mol) in anhydrous acetonitrile (20.0 ml) was treated with activated manganese dioxide (4.5 g) and the mixture was stirred at room temperature for 1h. The mixture was filtered to remove the manganese and the filtrate was evaporated to give an oil (0.5 g) which was treated with ethanol and filtered to remove a small amount of an unidentified solid. Evaporation of the ethanol filtrate gave a gum (0.4 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

1,2-Dichloroethane-1,2-dione Dioxime (7)

1,2-Dichloroethane-1,2-dione dioxime (7) was prepared by the chlorination of ethane-1,2-dione dioxime (18) in hydrochloric acid as described in the literature,[87,91] yield 52%, m.p. 202° (lit.,[87] 212°), which was used without further purification.

1,2-Dichloroethane-1,2-dione Dioxime O,O-Diacetate (50)

1,2-Dichloroethane-1,2-dione dioxime O,O-diacetate (50)

was prepared by heating 1,2-dichloroethane-1,2-dione dioxime (7) with acetic anhydride as described by Houben and Kauffmann,[87] yield 89%, m.p. 163° (lit.,[87] 163°), and was used without further purification.

1,2-Diaminoethane-1,2-dione Dioxime (1,2-Diaminoglyoxime) (45)

1,2-Diaminoethane-1,2-dione dioxime (45) was prepared by the reaction of 1,2-dichloroethane-1,2-dione dioxime O,O-diacetate (50) with ammonia in ethyl acetate as described by Houben and Kauffmann[87], yield 77%, m.p. 182° (decomp.) (lit.,[87] 198°), which was used without further purification.

5-Phenyl-Δ^2-1,2,4-oxadiazoline-3-carboxamidoxime (52)

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (0.72 g; 0.006 mol) and benzaldehyde (0.72 g; 0.0066 mol) in methanol (15.0 ml) containing concentrated hydrochloric acid (0.15 ml) was stirred at 45-55° (oil bath) for 48h. The precipitated solid was collected, washed with methanol and dried to afford 5-phenyl-Δ^2-1,2,4-oxadiazoline-3-carboxamidoxime (52) (0.54 g; 44%), m.p. 200-202° (from acetic acid-water), $\nu_{max.}$ 3350 br (NH and NOH) and 1660 br (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 10.00 (1H, brs, NOH), 7.75 (1H, d, J1Hz, NH), 7.37 (5H, m, ArH), 6.41 (2H, brs, NH_2), and 5.76 (1H, d, J1Hz, CH) (shaking with D_2O removes the signals at δ10.00, 7.75, and 6.41, and collapses the doublet at δ5.76 to a singlet δ5.76).

Found: C, 52.4; H, 4.8; N, 27.1%; M^+, 206.

$C_9H_{10}N_4O_2$ requires: C, 52.4; H, 4.9; N, 27.2%; M , 206.

Working up the combined methanolic filtrate and washings gave no further identifiable material.

The Reaction of 1,2-Diaminoethane-1,2-dione Dioxime (45b) with Formic Acid

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (0.48 g; 0.004 mol) in 98-100% formic acid (10.0 ml) was heated under reflux for 2h. The mixture was evaporated and the residue was azeotroped with toluene to remove any residual formic acid. The resulting gummy solid was washed with ethanol and dried *in vacuo* to afford oxamide (54) (0.02 g; 6%), m.p. >360° (sublim.) (lit.,[94] >350°), $\nu_{max.}$ 3300-2600 br (NH) and 1700 (C=O) cm^{-1}, identical (m.p. and i.r. spectrum) to an authentic sample.

Found: M^+, 88.

Calc. for $C_2H_4N_2O_2$: M , 88.

Evaporation of the ethanolic mother liquor gave only an intractable gum.

5-Methyl-1,2,4-oxadiazole-3-carboxamidoxime (55)

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (0.24 g; 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 1h. The mixture was evaporated, azeotroped with toluene to remove residual acetic acid, and the residue triturated with ethanol to afford a solid which was combined with a second crop obtained by flash-chromatography of the oil obtained by evaporating the ethanolic mother liquor in methylene chloride-ethyl acetate (1:1) over silica

to give 5-methyl-1,2,4-oxadiazole-3-carboxamidoxime (55) (0.08 g; 28%), m.p. 164-166° (from ethyl acetate), $\nu_{max.}$ 3470, 3370, and 3300 (NH and NOH) and 1660 and 1575 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 10.29 (1H, brs, NOH), 5.88 (2H, brs, NH_2), and 2.61 (3H, s, CH_3).

Found: C, 33.7; H, 4.3; N, 40.0%; M^+, 142.

$C_4H_6N_4O_2$ requires: C, 33.8; H, 4.2; N, 39.4%; M , 142.

5-Methyl-1,2,4-oxadiazole-3-carboxamidoxime O-acetate (56)

A solution of 5-methyl-1,2,4-oxadiazole-3-carboxamidoxime (55) (0.28 g; 0.002 mol) and triethylamine (0.66 g; 0.0066 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at room temperature with a solution of acetyl chloride (0.53 g; 0.0066 mol) in anhydrous dimethylformamide (1.0 ml). The mixture was stirred at room temperature for 1h and then filtered to remove triethylamine hydrochloride (0.6 g). The filtrate was evaporated and the residual gummy solid was triturated with ether to give the carboxamidoxime O-acetate (56) (0.34 g; 92%), m.p. 188-190° (from ethyl acetate), $\nu_{max.}$ 3410, 3320, and 3190 (NH), 1755 (C=O) and 1635 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.17 (2H, brs, NH_2), 3.11 (3H, s, CH_3), and 2.13 (3H, s, CH_3).

Found: C, 39.3; H, 4.7; N, 30.4%; M^+, 185.

$C_6H_8N_4O_3$ requires: C, 39.1; H, 4.4; N, 30.4%; M , 184.

3-(1,2,4-Oxadiazol-3-yl)-1,2,4-oxadiazole (57a)

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (3.2 g; 0.027 mol) in triethyl orthoformate (45.0 ml) was heated under reflux for 3h. The mixture was evaporated and

the residual gummy solid was triturated with ether to afford the known[89] oxadiazolyloxadiazole (57a) (3.7 g; 100%), m.p. 138-140° (lit.,[89] 136°), $\delta_H[(CD_3)_2SO]$ 9.98 (2H, s, CH), $\delta_C[(CD_3)_2SO]$ 168.6 (CH) and 158.8 (quat.).

Found: C, 34.8; H, 1.6; N, 40.4%; M^+, 138.

Calc. for $C_4H_2N_4O_2$: C, 34.8; H, 1.4; N, 40.6%; M , 138.

The Attempted Reaction of 1,2-Diaminoethane-1,2-dione Dioxime (45b) with Triethyl Orthoacetate

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (0.48 g; 0.004 mol) in triethyl orthoacetate (20.0 ml) was heated under reflux for 3h. The mixture was filtered to remove some insoluble material and then evaporated to give a red gum (0.6 g) which was flash-chromatographed over silica.

Elution with ethyl acetate gave only unreacted 1,2-diaminoethane-1,2-dione dioxime (45b) (0.15 g; 32%), m.p. 183°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Further elution with methanol gave no other material.

The Attempted Reaction of 1,2-Diaminoethane-1,2-dione Dioxime (45b) with Cyanogen Bromide

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (0.24 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at room temperature with a solution of cyanogen bromide (0.53 g; 0.005 mol) in anhydrous dimethylformamide (1.0 ml) and the mixture was stirred at room temperature for 15 min then heated under reflux for 4h.

The mixture was evaporated and the residue was treated with aqueous 1M sodium hydroxide (2.0 ml) and extracted with methylene chloride to give a red oil (0.23 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to methanol gave no identifiable product.

1,2-Diaminoethane-1,2-dione Dioxime O,O-Diacetate (58)

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (2.4 g; 0.02 mol) and triethylamine (4.4 g; 0.044 mol) in anhydrous dimethylformamide (40.0 ml) was stirred and treated dropwise at room temperature with a solution of acetyl chloride (3.5 g; 0.044 mol) in anhydrous dimethylformamide (2.0 ml). The mixture was stirred at room temperature for 1h, filtered to remove triethylamine hydrochloride (5.3 g) and the dimethyl-formamide filtrate evaporated to give a gummy solid which was washed with ethanol to afford the known[88] dioxime diacetate (58) (3.3 g; 82%) m.p. 197-199° (from ethanol) (lit.,[88] 194°), $\nu_{max.}$ 3420, 3320 and 3160 (NH), 1750 (C=O), and 1600 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 6.61 (4H, brs, NH_2) and 2.13 (6H, s, CH_3), $\delta_C[(CD_3)_2SO]$ 392.0 (CH_3), 336.2 (C=O), and 300.3 (quat.).

Found: C, 35.5; H, 5.0; N, 27.6%; M^+, 202.

Calc. for $C_6H_{10}N_4O_4$: C, 35.6; H, 5.0; N, 27.7%; M , 202.

Evaporation of the combined ethanolic filtrate and washings gave only a negligible quantity of gum.

The Attempted Reaction of 1,2-Diaminoethane-1,2-dione Dioxime O,O-Diacetate (58) with Triethyl Orthoformate

A suspension of 1,2-diaminoethane-1,2-dione dioxime O,O-diacetate (58) (0.40 g; 0.002 mol) in triethyl orthoformate (20.0 ml) was heated under reflux for 3h. The mixture was cooled to room temperature and filtered to afford unreacted dioxime diacetate (58) (0.23 g; 60%) m.p. 196-198°, identical (m.p. and i.r. spectrum) to an authentic sample.

The triethyl orthoformate mother liquor was evaporated to give a gum (0.1 g) whose t.l.c. in ethyl acetate over silica showed it to consist largely of unreacted dioxime diacetate (58).

The Attempted Reaction of 1,2-Diaminoethane-1,2-dione Dioxime O,O-Diacetate (58) with Formic Acid

A solution of 1,2-diaminoethane-1,2-dione dioxime O,O-diacetate (58) (0.40 g; 0.002 mol) in 98-100% formic acid (5.0 ml) was heated under reflux for 2h. The mixture was evaporated and the residual gum was treated with saturated aqueous sodium hydrogen carbonate solution and extracted with methylene chloride. Evaporation of the methylene chloride extract gave only a negligible quantity of gum.

The Attempted Reaction of 1,2-Diaminoethane-1,2-dione Dioxime O,O-diacetate (58) with Acetic Anhydride

A solution of 1,2-diaminoethane-1,2-dione dioxime O,O-diacetate (58) (0.40 g; 0.002 mol) in acetic anhydride (5.0 ml)

was heated under reflux for 0.5h. The mixture was cooled to room temperature and the precipitated solid was collected and washed with ether to afford the unreacted dioxime diacetate (58) (0.17 g; 43%) m.p. 178-181°, identical (i.r. spectrum) to an authentic sample prepared before.

The combined acetic anhydride filtrate and ethereal washings were evaporated to give a gum (0.24 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Attempted Reaction of 1,2-Diaminoethane-1,2-dione Dioxime O,O-Diacetate (58) with Acetyl Chloride in the Presence of Triethylamine

A solution of 1,2-diaminoethane-1,2-dione dioxime O,O-diacetate (58) (0.40 g; 0.002 mol) and triethylamine (0.22 g; 0.0022 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated at room temperature with a solution of acetyl chloride (0.18 g; 0.0022 mol) in anhydrous dimethylformamide (1.0 ml). The mixture was stirred at room temperature for 1h then filtered to remove triethylamine hydrochloride (0.2 g). The dimethylformamide filtrate was evaporated and the residue was treated with water (5.0 ml) and the insoluble solid was collected, washed with water and dried *in vacuo* to afford the unreacted dioxime diacetate (58) (0.27 g; 68%) m.p. 144-147°, identical (i.r. spectrum) to an authentic sample.

5-Methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)-1,2,4-oxadiazole (57b)

(a) A solution of 1,2-diaminoethane-1,2-dione dioxime (45b)

(1.2 g; 0.01 mol) in acetic anhydride (50.0 ml) was heated under reflux for 1h. The mixture was evaporated to give a brown gum (2.6 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (4:1) gave a gummy solid which was washed with ether to yield the known[88] 5-methyl-3-(5-methyl-1,2,4-oxadiazol-3-yl)-1,2,4-oxadiazole (57b) (0.25 g; 15%), m.p. 169-170° (from ethanol) (lit.,[88] 167°), $\nu_{max.}$ 1580 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 2.69 (6H, s, CH_3), $\delta_C[(CD_3)_2SO]$ 358.2 (quat.), 345.5 (quat.), and 241.5 (CH_3).

Found: C, 43.4; H, 3.7; N, 33.9%; M^+, 166.

Calc. for $C_6H_6N_4O_2$: C, 43.4; H, 3.6; N, 33.7%; M , 166.

Subsequent elution with ethyl acetate gave no further identifiable material.

(b) A solution of 1,2-diaminoethane-1,2-dione dioxime O,O-diacetate (58) (3.1 g; 0.015 mol) in glacial acetic acid (35.0 ml) was heated under reflux for 1h. The mixture was evaporated and the residue was azeotroped with toluene to remove residual acetic acid to afford the oxadiazolyloxadiazole (57b) (2.5 g; 99%), m.p. 169-170°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

(c) A solution of 1,2-diaminoethane-1,2-dione dioxime O,O-diacetate (58) (0.40 g; 0.002 mol) in propionic acid (5.0 ml) was stirred and heated at 116-118° (oil bath) for 1h. The mixture was evaporated and the residue was dissolved in ethyl acetate and the solution washed with saturated aqueous sodium hydrogen carbonate solution (5.0 ml) and evaporated to give the oxadiazolyloxadiazole (57b) (0.19 g; 58%) identified by

comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

The Attempted Reaction of 1,2-Diaminoethane-1,2-dione Dioxime O,O-Diacetate (58) with Phenyl Isocyanate

A solution of 1,2-diaminoethane-1,2-dione dioxime O,O-diacetate (58) (0.40 g; 0.002 mol) in anhydrous dimethylformamide (4.0 ml) was stirred and treated at room temperature with a solution of phenyl isocyanate (0.48 g; 0.004 mol) in anhydrous dimethylformamide (1.0 ml). The mixture was stirred at room temperature for 24h and then treated with further phenyl isocyanate (0.48 g; 0.004 mol) in anhydrous dimethylformamide (1.0 ml) and the mixture stirred at room temperature for 25h.

The mixture was evaporated to give a solid (0.53 g), m.p. 177-184°, which was flash-chromatographed over silica.

Elution with methylene chloride-ethylacetate (5:1) afforded diphenylurea (0.3 g) m.p. 244-246°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate afforded the unreacted dioxime diacetate (58) (0.11 g; 26%) m.p. 194-196°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

1,2-Diaminoethane-1,2-dione Dioxime O,O-Dipropionate (60a)

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (0.48 g; 0.004 mol) and triethylamine (0.88 g; 0.0088 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at room temperature with a solution of propionyl

chloride (0.82 g; 0.0088 mol) in anhydrous dimethylformamide (1.0 ml). The mixture was stirred at room temperature for 1h and the precipitated solid was collected, washed with water and combined with a second crop obtained by evaporating the dimethylformamide mother liquor and triturating the residue with ethanol to afford the dioxime dipropionate (60a) (0.51 g; 56%), m.p. 208-210°, (from dimethylformamide-water), $\nu_{max.}$ 3450, 3330, and 3160 (NH), 1760 (C=O), and 1610 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 6.60 (4H, brs, NH_2), 2.49 (4H, q, J7.5Hz, CH_2), and 1.08 (6H, t, J7.5Hz, CH_3).

Found: C, 41.5; H, 6.3; N, 24.6%; M^+, 230.

$C_8H_{14}N_4O_4$ requires: C, 41.7; H, 6.1; N, 24.4%; M , 230.

The ethanol mother liquor was evaporated to give a gum (0.6 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to methanol gave only gums (total 0.36 g) whose t.l.c. in ethyl acetate over silica showed them to be complex mixtures which were not further investigated.

5-Ethyl-3-(5-ethyl-1,2,4-oxadiazol-3-yl)-1,2,4-oxadiazole (61a)

A solution of 1,2-diaminoethane-1,2-dione dioxime O,O-dipropionate (60a) (0.51 g; 0.0022 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 1h. The mixture was evaporated and the residue was azeotroped with toluene to remove residual acetic acid and afford the oxadiazolyloxadiazole (61a) (0.37 g; 87%), m.p. 74-76° (from ethanol), $\nu_{max.}$ 1570 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 3.16 (4H, q, J7.5Hz, CH_2) and 1.35 (6H, t, J7.5Hz, CH_3).

Found: C, 49.0; H, 5.4; N, 29.5%; M^+, 194.0809.

$C_8H_{10}N_4O_2$ requires: C, 49.5; H, 5.2; N, 28.9%; M , 194.0804.

1,2-Diaminoethane-1,2-dione Dioxime O,O-di-(2-Chloroacetate) (60b)

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (0.72 g; 0.006 mol) and triethylamine (1.3 g; 0.013 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at room temperature with a solution of chloroacetyl chloride (1.5 g; 0.013 mol) in anhydrous dimethylformamide (1.0 ml). The mixture was stirred at room temperature for 1h and the precipitated solid was collected, washed with water and combined with a second crop obtained by evaporating the dimethylformamide mother liquor and then treating the residual gum with water to yield the dioxime di-(2-chloroacetate) (60b) (1.1 g; 68%), m.p. 184-186° (from dimethylformamide-water), $\nu_{max.}$ 3420, 3320 and 3160 (NH), 1760 (C=O), and 1600 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 6.90 (4H, brs, NH_2) and 4.55 (4H, s, CH_2).

Found: C, 27.3; H, 3.3; N, 21.2%; M^+, 274,272 & 270.

$C_6H_8Cl_2N_4O_4$ requires: C, 26.6; H, 3.0; N, 20.7%; M , 271.

Extraction of the combined aqueous mother liquors with methylene chloride gave only a negligible quantity of oil.

5-Chloromethyl-3-(5-chloromethyl-1,2,4-oxadiazol-3-yl)-1,2,4-oxadiazole (61b)

A solution of 1,2-diaminoethane-1,2-dione dioxime O,O-di-(2-chloroacetate) (60b) (0.54 g; 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 1h. The

mixture was evaporated and the residue was azeotroped with toluene to remove residual acetic acid to afford the oxadiazolyloxadiazole (61b) (0.49 g; 100%), m.p. 102-104° (from ethanol), $\nu_{max.}$ 1580 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 5.25 (4H, s, CH_2).

Found: C, 30.6; H, 1.7; N, 23.8%; M^+, 238,236 & 234.

$C_6H_4Cl_2N_4O_2$ requires: C, 30.6; H, 1.7; N, 24.1%; M , 135.

The Reaction of 1,2-Diaminoethane-1,2-dione Dioxime (45b) with Ethoxalyl Chloride in the Presence of Triethylamine

(a) A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (0.48 g; 0.004 mol) and triethylamine (0.88 g; 0.0088 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at room temperature with a solution of ethoxalyl chloride (1.2 g; 0.0044 mol) in anhydrous dimethylformamide (10.0 ml). The mixture was stirred at room temperature for 1h, then was filtered to remove triethylamine hydrochloride (1.4 g) and the dimethylformamide filtrate was evaporated to give a gummy solid which was washed with ethyl acetate to afford the dioxime di-(ethoxalate) (60c) (0.42 g; 33%), m.p. 145-147° (from ethanol), $\nu_{max.}$ 3480, 3360 and 3180 (NH), 1780 and 1750 (C=O), and 1630 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.20-6.00 (br, NH), 4.53-4.07 (4H, m, CH_2), and 1.46-1.09 (6H, m, CH_3).

Found: C, 37.6; H, 4.6; N, 17.7%; M^+, 318.

$C_{10}H_{14}N_4O_8$ requires: C, 37.7; H, 4.4; N, 17.6%; M , 318.

The ethyl acetate filtrate was evaporated to give a gum (0.9 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (2:1) gave a gummy solid which was washed with ethanol to give 5-ethoxy-

carbonyl-1,2,4-oxadiazole-3-carboxamidoxime (62) (0.15 g; 19%), m.p. 153-158° (from ethanol), ν_{max} 3450 br, 3270, 3230 and 3140 (NH and OH), 1755 (C=O) and 1655 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 10.50 (1H, brs, OH), 6.07 (2H, brs, NH), 4.53 (2H, q, J7Hz, CH_2) and 1.36 (3H, t, J7Hz, CH_3).

Found: C, 36.2; H, 4.1; N, 27.1%; M^+, 200.0535.

$C_6H_8N_4O_4$ requires: C, 36.0; H, 4.0; N, 28.0%; M , 200.0546.

Evaporation of the ethanolic mother liquor gave an oil (0.3 g) whose t.l.c. in ethyl acetate over silica showed it to be a unresolvable multicomponent mixture which was not further investigated.

(b) A solution of 1,2-diaminoethane-1,2-dione dioxime (45b) (1.9 g; 0.016 mol) and triethylamine (3.5 g; 0.035 mol) in anhydrous dimethylformamide (15.0 ml) was stirred and treated dropwise at room temperature with a solution of ethoxalyl chloride (4.8 g; 0.035 mol) in anhydrous dimethylformamide (2.0 ml). The mixture was stirred at room temperature for 1h, filtered to remove triethylamine hydrochloride (4.3 g) and the dimethylformamide filtrate was evaporated to give a gummy solid which was washed with ethyl acetate to afford the oxadiazolecarboxamidoxime (62) (0.88 g; 28%), m.p. 154-158°, identical (m.p. and i.r. spectrum) to an authentic sample obtained in (a) before.

The ethyl acetate mother liquor was evaporated and the residue was washed with ethyl acetate to give a solid which was combined with a second crop obtained by flash-chromatographing the gum from the ethyl acetate mother liquor in methylene chloride-ethyl acetate (2:1) over silica to afford 5-ethoxy-

carbonyl-3-(5-ethoxycarbonyl-1,2,4-oxadiazol-3-yl)-1,2,4-oxadiazole (61c) (1.1 g; 24%), m.p. 104-106°, identical (m.p. and i.r. spectrum) to an authentic sample prepared later.

Further elution with methanol afforded 5-ethoxycarbonyl-1,2,4-oxadiazole-3-carboxamidoxime (62) (0.2 g; 6%), m.p. 151-154°, identical (m.p. and i.r. spectrum) to an authentic sample obtained before.

5-Ethoxycarbonyl-3-(5-ethoxycarbonyl-1,2,4-oxadiazol-3-yl)-1,2,4-oxadiazole (61c)

A solution of 1,2-diaminoethane-1,2-dione dioxime di-(ethoxalate) (60c) (0.31 g; 0.001 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 1h. The mixture was evaporated and the residue was washed with ethanol to afford the oxadiazolyloxadiazole derivative (61c) (0.10 g; 36%) m.p. 108-110° (from ethanol), $\nu_{max.}$ 1750 (C=O) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 4.25 (4H, q, J7Hz, CH_2) and 1.39 (6H, t, J7Hz, CH_3).

Found: C, 42.6; H, 3.8; N, 19.9%; M^+, 282.

$C_{10}H_{10}N_4O_4$ requires: C, 42.6; H, 3.6; N, 19.9%; M , 282.

The ethanol mother liquor was evaporated to give an oil (0.13 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Diethyl 1,2-Diaminoethane-1,2-dione Dioxime O,O-dicarbonate (60d)

A solution of 1,2-diaminoethane-1,2-dione dioxime (45b)

(0.96 g; 0.008 mol) and triethylamine (1.8 g; 0.018 ml) in anhydrous dimethylformamide (20.0 ml) was stirred and treated dropwise at room temperature with a solution of ethyl chloroformate (1.9 g; 0.018 mol) in anhydrous dimethylformamide (4.0 ml). The mixture was stirred at room temperature for 1h and filtered to remove triethylamine hydrochloride (1.5 g). The filtrate was evaporated and the residue was washed with water (5.0 ml) and the insoluble solid was washed with water and dried in vacuo to afford the dioxime dicarbonate (60d) (1.3 g; 60%), m.p. 167-169° (from ethyl acetate), $\nu_{max.}$ 3490 and 3380 (NH), 1770 (C=O), and 1630 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 6.67 (4H, brs, NH_2), 4.19 (4H, q, J7Hz, CH_2), and 1.25 (6H, t, J7Hz, CH_3).

Found: C, 36.9; H, 5.3; N, 21.1%; M^+, 262.

$C_8H_{14}N_4O_6$ requires: C, 36.6; H, 5.3; N, 21.4%; M , 262.

The aqueous mother liquor was extracted with methylene chloride to give no further material.

The Attempted Cyclisation of Diethyl 1,2-Diaminoethane-1,2-dione Dioxime O,O-dicarbonate (60d) in Glacial Acetic Acid

A solution of the dioxime dicarbonate (60d) (0.52 g; 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 1h. The mixture was evaporated to give the unreacted starting material (60d) (0.37 g; 71%), m.p. 158-163°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

O,O-Dibenzyl-1,2-diaminoethane-1,2-dione Dioxime (63)

A suspension of sodium hydride (1.1 g; 0.0044 mol) in anhydrous dimethylformamide (20.0 ml) was stirred and treated in one portion at room temperature with a solution of 1,2-diaminoethane-1,2-dione dioxime (45) (2.4 g; 0.02 mol) in anhydrous dimethylformamide (10.0 ml). The mixture was stirred for 15 min then treated in one portion with a solution of benzyl chloride (5.6 g; 0.044 mol) in anhydrous dimethylformamide (10.0 ml). The mixture was stirred at room temperature for 21h with the exclusion of atmospheric moisture then treated with water (40.0 ml) and the precipitated solid was collected, washed with water and dried *in vacuo* to afford the dibenzyl derivative (63) (4.4 g; 73%), m.p. 118-120° (from ethanol), $\nu_{max.}$ 3460, 3340, and 3140 (NH), and 1610 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.36 (10H, brs, ArH), 5.55 (4H, brs, NH_2), and 4.99 (4H, s, CH_2).

Found: C, 64.2; H, 6.1; N, 18.9%; M^+, 298.
$C_{16}N_{18}N_4O_2$ requires: C, 64.4; H, 6.0; N, 18.8%; M , 298.

Working up the aqueous mother liquor gave no further characterisable material.

The Attempted Reaction of O,O-Dibenzyl-1,2-diaminoethane-1,2-dione Dioxime (63) with Triethyl Orthoformate

A solution of the O,O-dibenzyl dioxime (63) (0.30 g; 0.001 mol) in triethyl orthoformate (5.0 ml) was heated under reflux for 3h. The mixture was evaporated to give a gum (0.3 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded the unreacted

starting material (63) (0.14 g; 46%), m.p. 118-122°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate through to methanol gave no other material.

The Attempted Reaction of O,O-Dibenzyl-1,2-diaminoethane-1,2-dione Dioxime (63) with Formic Acid

A solution of the O,O-dibenzyl dioxime (63) (0.60 g; 0.002 mol) in 98-100% formic acid (10.0 ml) was heated under reflux for 19h. The mixture was evaporated and the residual gum was dissolved in methylene chloride and the solution was washed with saturated aqueous sodium hydrogen carbonate solution and water and evaporated to give a yellow gum (0.60 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded the unreacted O,O-dibenzyl dioxime (63) (0.22 g; 37%), m.p. 114-118°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Further elution with methylene chloride gave a gum (0.13 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

O,O-Dibenzyl-1,2-diacetamidoethane-1,2-dione Dioxime (65a)

A solution of the O,O-dibenzyl dioxime (63) (0.60 g; 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 1h. The mixture was evaporated and the residual gummy solid was washed with ether to afford the diacetamido-

derivative (65a) (0.15 g; 26%), m.p. 180-182° (from ethanol), $\nu_{max.}$ 3280 (NH), 1680 (C=O), and 1630 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 10.00 (2H, brs, NH), 7.35 (10H, brs, ArH), 5.66 (4H, s, CH_2), and 2.00 (6H, s, CH_3).

Found: C, 62.8; H, 5.8; N, 14.8%; M^+, 382.

$C_{20}H_{22}N_4O_4$ requires: C, 62.8; H, 5.8; N, 14.7%; M , 382.

The ether mother liquor was evaporated and the residual gum was triturated with ethanol to give unreacted starting material (63) (0.14 g; 23%), m.p. 106-108°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Working up the ethanolic mother liquor gave only an intractable gum.

O,O-Dibenzyl-1,2-di-(diacetamido)ethane-1,2-dione Dioxime (65b)

A solution of the O,O-dibenzyl dioxime (63) (0.30 g; 0.001 mol) in acetic anhydride (2.5 ml) was heated under reflux for 24h. The mixture was evaporated and the residual gummy solid was washed with ether to afford the tetraacetyl derivative (65b) (0.27 g; 58%), m.p. 158-161° (from ethanol), $\nu_{max.}$ 1730 and 1700 (C=O), and 1590 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.33 (10H, brs, ArH), 5.22 (4H, s, CH_2), and 2.15 (12H, s, CH_3).

Found: C, 61.8; H, 5.7; N, 12.0%; M^+, 466.

$C_{24}H_{26}N_4O_6$ requires: C, 61.8; H, 5.6; N, 12.0%; M , 466.

Evaporation of the ether mother liquor gave no further identifiable material.

The Attempted Reaction of O,O-Dibenzyl-1,2-diaminoethane-1,2-dione Dioxime (63) with Acetyl Chloride

A suspension of sodium hydride (0.14 g; 0.0055 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated in one portion at room temperature with a solution of the O,O-dibenzyl dioxime (63) (1.5 g; 0.005 mol) in anhydrous dimethylformamide (5.0 ml). The mixture was stirred at room temperature for 22h with the exclusion of atmospheric moisture then diluted with water (15.0 ml) and the precipitated solid collected and washed with ethanol to afford the unreacted starting material (63) (0.52 g; 35%), m.p. 104-106° identical (m.p. and i.r. spectrum) to an authentic sample.

The combined aqueous mother liquor and ethanolic washings were extracted with methylene chloride to give an oil (0.9 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (4:1) gave only gums (total 0.62 g) whose t.l.c. in methylene chloride-ethyl acetate (4:1) over silica showed them to be unresolvable multicomponent mixtures which were not further investigated.

The Attempted Reaction of O,O-Dibenzyl-1,2-diaminoethane-1,2-dione Dioxime (63) with Cyanogen Bromide

A solution of the O,O-dibenzyl dioxime (63) (0.60 g; 0.002 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated dropwise at room temperature with a solution of cyanogen bromide (0.53 g; 0.005 mol) in anhydrous dimethylformamide (1.0 ml). The mixture was stirred at room temperature

for 15 min then heated under reflux for 4h. The mixture was evaporated and the residue was treated with aqueous 1M sodium hydroxide solution (2.0 ml) and extracted with methylene chloride to give a dark red gum (0.73 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Attempted Reaction of 1,2-Dichloroethane-1,2-dione Dioxime (7) with Benzaldehyde

A solution of 1,2-dichloroethane-1,2-dione dioxime (7) (0.63 g; 0.004 mol) and benzaldehyde (0.48 g; 0.0044 mol) in methanol (10.0 ml) was treated with concentrated hydrochloric acid (0.1 ml) and the mixture was stirred at 45-55° (oil bath) for 48h. The mixture was evaporated and the residual gum was treated with water and methylene chloride and the three phase mixture filtered to afford the unreacted dichloro-dioxime (7) (0.38 g; 60%), m.p. 198-200°, identical (m.p. and i.r. spectrum) to an authentic sample.

Workup of the methylene chloride extract and aqueous mother liquor gave no further identifiable material.

The Attempted Reaction of 1,2-Dichloroethane-1,2-dione Dioxime (7) with Ethylamine

A solution of 1,2-dichloroethane-1,2-dione dioxime (7) (0.32 g; 0.002 mol) in anhydrous dioxane (10.0 ml) was treated at room temperature with ethylamine (0.36 g; 0.008 mol) and the mixture was stirred at room temperature for 2h.

The mixture was filtered to remove ethylamine hydrochloride (0.2 g) and the dioxane filtrate was evaporated to give a gum (0.31 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (3:1) gave a gummy solid which was triturated with methylene chloride to give unreacted starting material (7) (0.04 g; 13%), m.p. 196-198°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before. Evaporation of the methylene chloride mother liquor gave only a negligible quantity of gum.

1,2-Di-(N-benzylamino)ethane-1,2-dione Dioxime (6b)

(a) A solution of 1,2-dichloromethane-1,2-dione dioxime (7) (3.2 g; 0.02 mol) in anhydrous dioxime (100 ml) was stirred and treated at room temperature with benzylamine (8.6 g; 0.08 mol). The mixture was stirred at room temperature for 2h and the precipitated solid was collected, washed with water and washed with water and combined with further material obtained by flash-chromatographing the gum from the dioxane mother liquor in methylene chloride-ethyl acetate (4:1) over silica to afford 1,2-di-(N-benzylamino)ethane-1,2-dione dioxime (6b) (4.9 g; 83%), m.p. 162-164° (from ethyl acetate), $\nu_{max.}$ 3370 (NH), 3330-2100 br (OH), and 1610 (C=N) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 9.71 (2H, s, NOH), 7.25 (10H, s, ArH), 6.14 (2H, t, J6Hz, NH), and 4.12 (4H, t, J6Hz, CH_2)

Found: C, 64.3; H, 6.1; H, 18.7%; M^+, 298.

$C_{16}H_{18}N_4O_2$ requ: C, 64.4; H, 6.0; N, 18.8%; M , 298.

(b) A suspension of 1,2-dichloroethane-1,2-dione dioxime

(7) (0.63 g; 0.004 mol) in methylene chloride (20.0 ml) was stirred and treated in one portion at 0° (ice-salt bath) with aqueous 0.5M sodium carbonate solution (20.0 ml). The mixture was stirred at 0° for 5 min then treated in one portion with a solution of benzylamine (1.7 g; 0.008 mol) in methylene chloride (10.0 ml). The mixture was allowed to come to room temperature then stirred for 1h and the precipitated solid was collected, washed with water, and combined with further material obtained by flash-chromatographing the oil from the methylene chloride layer in methylene chloride-ethyl acetate (2:1) over silica to afford the dibenzylamino-derivative (6b) (0.65 g; 55%), m.p. 136-141° (decomp.), identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

The Attempted Reaction of 1,2-Dichloroethane-1,2-dione Dioxime (7) with Benzamidine.

A solution of benzamidine hydrochloride (0.94 g; 0.006 mol) and triethylamine (0.60 g; 0.006 mol) in anhydrous dioxane (5.0 ml) was stirred and treated at room temperature with a solution of 1,2-dichloroethane-1,2-dione dioxime (7) (0.32 g; 0.002 mol) in anhydrous dioxane (8.0 ml). The mixture was stirred at room temperature for 2h, filtered to remove some insoluble material and the filtrate evaporated to afford a red oil (0.25 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Attempted Reactions of 1,2-Dichloroethane-1,2-dione Dioxime (7) with Guanidine

(a) A suspension of guanidine hydrochloride (0.29 g; 0.003 mol) in anhydrous dioxane (5.0 ml) was stirred and treated at room temperature with anhydrous sodium carbonate (0.74 g; 0.007 mol) followed by a solution of 1,2-dichloroethane-1,2-dione dioxime (7) (0.32 g; 0.002 mol) in anhydrous dioxane (5.0 ml). The mixture was stirred at room temperature for 2h, then filtered to remove inorganic material and the dioxane filtrate evaporated to give a gummy solid which was washed with methylene chloride to afford unreacted starting-material (7) (0.13 g; 40%), m.p. 199-201°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

The methylene chloride mother liquor was evaporated to give a gum (0.13 g) whose t.l.c. in ethyl acetate showed it to be an unresolvable multicomponent mixture which was not further investigated.

(b) A suspension of 1,2-dichloroethane-1,2-dione dioxime (7) (0.63 g; 0.004 mol) and guanidine hydrochloride (0.38 g; 0.004 mol) in methylene chloride (20.0 ml) was stirred and treated at 0° (ice-salt bath) with aqueous 0.5M sodium carbonate solution (20.0 ml). The mixture was stirred at 0° for 1h and the methylene chloride layer was separated and evaporated to give no identifiable material.

The aqueous layer was neutralised with concentrated hydrochloric acid and anhydrous sodium acetate and extracted with methylene chloride to give no identifiable material.

O,O-Dibenzyl Ethane-1,2-dione Dioxime (71)

A suspension of sodium hydride (0.22 g; 0.0088 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated with ethane-1,2-dione dioxime (18) (0.37 g; 0.004 mol) and the mixture was stirred for 15 min then treated with benzyl chloride (1.1 g; 0.0088 mol) in anhydrous dimethylformamide (5.0 ml). The mixture was stirred at room temperature for 16h, treated with water (20.0 ml) and the precipitated solid was collected, washed with water and dried *in vacuo* to afford O,O-dibenzyl ethane-1,2-dione dioxime (71) (0.87 g; 82%), m.p. 69-71° (from ethanol), $\nu_{max.}$ 1565 (C=N) cm^{-1}, δ_H ($CDCl_3$) 7.83 (2H, s, CH), 7.37 (10H, s, ArH), and 5.18 (4H, s, CH_2).

Found: C, 71.7; H, 5.8; N, 10.5%; M^+, 268.

$C_{16}H_{16}N_2O_2$ requires: C, 71.6; H, 6.0; N, 10.4%; M , 268.

Extraction of the aqueous mother liquor with methylene chloride gave no further identifiable material.

Attempted Chlorination Reactions of O,O-Dibenzyl Ethane-1,2-dione Dioxime (71)

(a) A solution of O,O-dibenzyl ethane-1,2-dione dioxime (71) (0.54 g; 0.002 mol) in chloroform (10.0 ml) was stirred and treated at 0° (ice-salt bath) with a slow stream of chlorine for 2h.

The mixture was flushed with nitrogen for 15 min, then evaporated to give a gummy solid which was treated with ether and filtered to remove a small amount of insoluble material.

Evaporation of the ether filtrate gave a gum (0.5 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (2:1) gave only unreacted starting-material (71) (0.24 g; 36%), m.p. 65-67°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate through to methanol gave no other identifiable material.

(b) A solution of O,O- dibenzyl ethane-1,2-dione dioxime (71) (1.3 g; 0.005 mol) in glacial acetic acid (50.0 ml) was mixed with a solution of concentrated hydrochloric acid (2.0 ml) in water (10.0 ml) and the mixture was stirred and treated at 0° (ice-salt bath) with a slow stream of chlorine over 15 min. The gas flow rate was then increased and the mixture was stirred at 0° for 2h. The flow of gas was then stopped and the mixture was stirred for 15 min, flushed with nitrogen for 15 min then evaporated, and the residue treated with water (5.0 ml) and extracted with methylene chloride to give an oil (0.98 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloriee (2:1) gave benzyl acetate as an oil (0.58 g; 39%), identical (i.r. spectrum) to an authentic sample.

Further elution with ethyl acetate through to methanol gave no other identifiable material.

The Attempted Reaction of O,O-Dibenzyl Ethane-1,2-dione Dioxime (71) with Aqueous Hydrochloric Acid in Acetic Acid

A solution of O,O-dibenzyl ethane-1,2-dione dioxime (71) (1.3 g; 0.005 mol) in glacial acetic acid (50.0 ml) was mixed with a solution of concentrated hydrochloric acid (2.0 ml) in water (10.0 ml) and the mixture was stirred at 0° (ice-salt bath) for 2.5h. The precipitated solid was collected, washed with water and combined with a second crop obtained by evaporating the combined aqueous mother liquor and washings and treating the residue obtained with water to give the unreacted starting material (71) (0.96 g; 86%), m.p. 65-70°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Neutralisation of the aqueous mother liquor with aqueous 2M sodium hydroxide solution and glacial acetic acid followed by extraction with methylene chloride gave only a negligible quantity of gum.

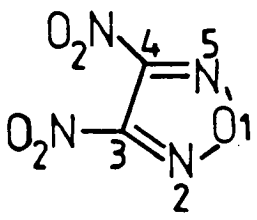
Chapter 3

Studies of New Synthetic Approaches to Nitro-1,2,5-oxadiazoles (Nitrofurazans) and Nitro-1,2,5-oxadiazole N-oxides (Nitrofuroxans)

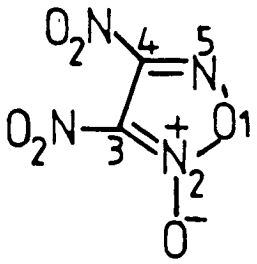
Studies of New Synthetic Approaches to Nitro-1,2,5-oxadiazoles (Nitrofurazans) and Nitro-1,2,5-oxadiazole N-Oxides (Nitrofuroxans)

3.1 Introduction

Though a number of mononitrofurazan[95] and furoxan[96,97] derivatives have been reported in the literature, the fully nitrated compounds, 3,4-dinitrofurazan (1) and 3,4-dinitrofuroxan (2) are to date unknown.



(1)

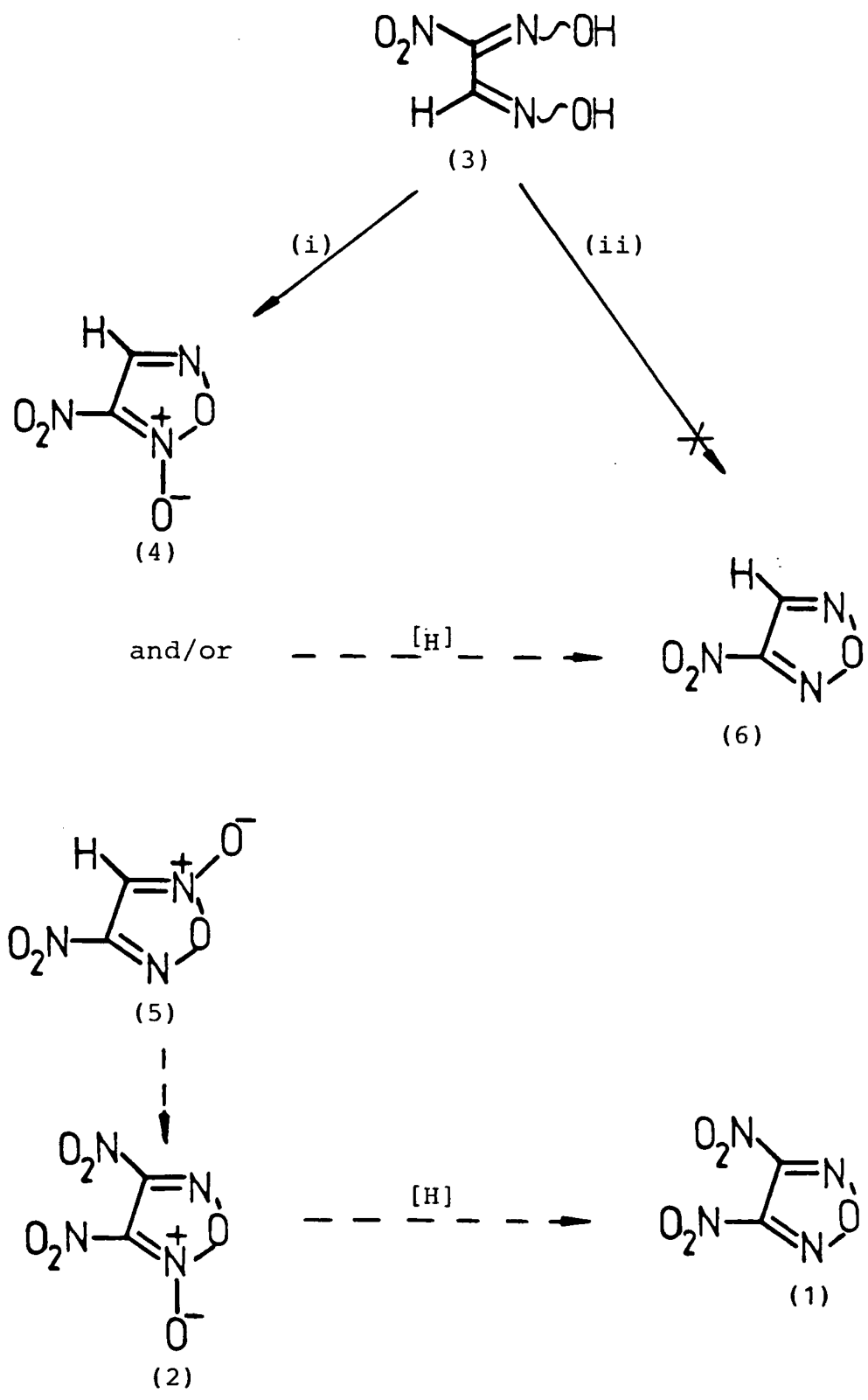


(2)

The dinitro-1,2,5-oxadiazole derivatives (1) and (2) are of considerable interest because the enhanced electron-deficiency conferred by the nitro-groups should result in unique physical and chemical properties. Moreover, despite their deceptively simple structures, the dinitrofurazan (1) and the dinitrofuroxan (2) pose a substantial synthetic challenge. These considerations were sufficient to provide the stimulous for the present investigations of new synthetic routes to nitrofurazans and nitrofuroxans.

3.2 Investigations of Synthetic Routes to Nitrofurazans and Nitrofuroxans Based on 1-Nitroethane-1,2-dione Dioxime (3)

The use (Scheme 1) of the readily available 1-nitroethane-1,2-dione dioxime (3) (see Chapter 2) as a key starting-material for the synthesis of nitrofurazans or nitrofuroxans



(i) $(NH_4)_2Ce(NO_2)_6$, AcOH, H_2O, 5°

(ii) Ac_2O, 100°

Scheme 1

does not appear to have been described in the literature hitherto. This is surprising since by analogy with the oxidative[98] and dehydrative[99] conversions of other ethane-1,2-dione dioxime derivatives into the corresponding furoxans and furazans respectively, 1-nitroethane-1,2-dione dioxime (3) should afford by oxidation the briefly previously described[100] 3- or 4-nitrofuroxan (4) or (5), and by dehydration the unknown 3-nitrofurazan (6). It was therefore decided to investigate the oxidative and dehydrative cyclisation of 1-nitroethane-1,2-dione dioxime (3) to 3-nitrofuroxan (4) and/or 4-nitrofuroxan (5) and 3-nitrofurazan (6) with a view to the further conversion of these molecules into 3,4-dinitrofuroxan (2) and/or 3,4-dinitrofurazan (1) as outlined in Scheme 1.

Initial attempts to oxidatively cyclise 1-nitroethane-1,2-dione dioxime (3) to the nitrofuroxans (4) and/or (5) were unsuccessful. The use of sodium hypochlorite, successfully applied as oxidant in cyclisations[98] of other ethane-1,2-dione dioxime derivatives to furoxans, when applied to 1-nitroethane-1,2-dione dioxime (3) under basic conditions (aqueous sodium hydroxide or pyridine) gave either intractable gums or resulted in the loss of the starting material. The attempted oxidation of 1-nitroethane-1,2-dione dioxime (3) to the nitrofuroxans (4) and/or (5) using nitric acid gave a multicomponent oil as the only product. This result contrasts with the successful cyclisation of 1,2-dichloroethane-1,2-dione dioxime to 3,4-dichlorofuroxan using nitric acid as described by Ungnade and Kissinger.[96]

Having failed to achieve the oxidative cyclisation

[(3)→(4)] using the usual oxidising agents, attention was next turned to less orthodox oxidants. However, treatment of 1-nitroethane-1,2-dione dioxime (3) in 1,2-dimethoxyethane with activated manganese dioxide gave only an intractable red oil from which no identifiable material could be obtained. In contrast, the dioxime derivative (3) reacted with cerric ammonium nitrate[101] in aqueous acetic acid at low temperature to afford a low yield (37%) of an unstable amber oil which did not give a satisfactory combustion analysis but did give a parent ion at m/e 131 in its mass spectrum consistent with either of the nitrofuroxan structures (4) or (5). In accord with its formulation as 4-nitrofuroxan (5) the amber oil showed bands at 1550 and 1335 cm^{-1} in its i.r. spectrum attributable to the presence of a nitro-group. In addition its ^{1}H and ^{13}C n.m.r. spectra contained a one proton singlet at $\delta_H 8.83$ and a CH-singlet at $\delta_C 125.7$ due to the presence of a single CH-group thus showing that the amber oil was not a mixture of the nitrofuroxan isomers (4) and (5). The carbon chemical shift of the CH-group in the nitrofuroxan product is akin to that in other 4-substituted furoxans and markedly different to that in 3-substituted furoxans.[102,103] Moveover the exceptional deshielding of the CH-proton can be attributed to its proximity to the anisotropic N-oxide group. On the basis of these n.m.r. features the amber oil is formulated as 4-nitrofuroxan (5) rather than 3-nitrofuroxan (4).

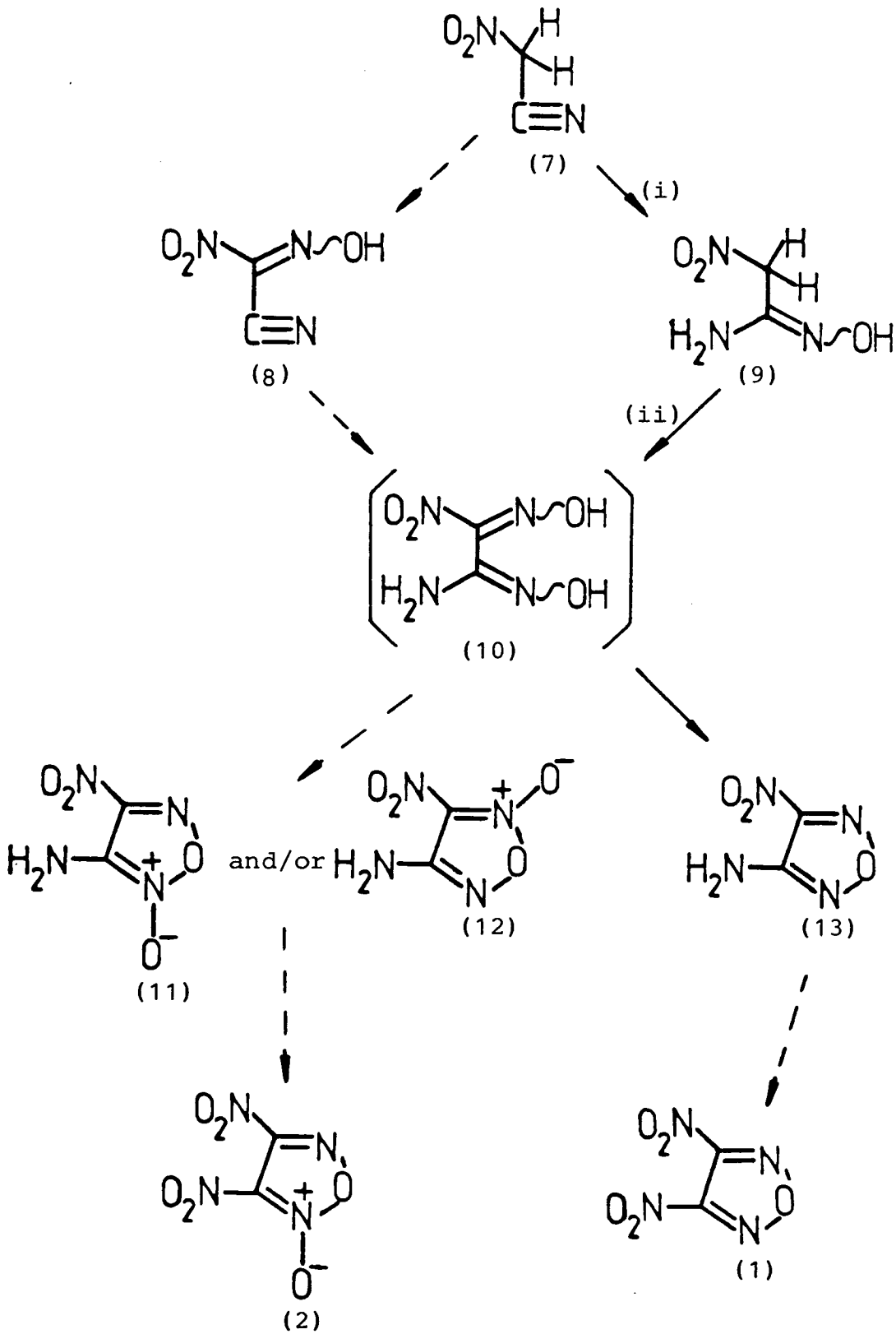
Having succeeded in the synthesis, albeit in low yield, of the nitrofuroxan (5) from 1-nitroethane-1,2-dione dioxime (3) attention was next turned to the dehydration of the

latter to 3-nitrofurazan (6). However, heating the dioxime (3) with acetic anhydride gave only a low yield of an intractable gum with no evidence for the formation of the nitrofurazan (6). Attempts to convert the dioxime (3) into activated esters which it was hoped might be more amenable to cyclisation to the nitrofurazan (6) were equally unsuccessful. Thus, the attempted triethylamine-catalysed reaction of the dioxime (3) with acetyl chloride gave only a complex mixture with no evidence for the formation of the required oxime diacetate (3; OAc for OH). 1-Nitroethane-1,2-dione dioxime (3) reacted with phenyl isocyanate in 1,2-dimethoxyethane at room temperature to give only a low yield of an unstable oil rather than the bis-carbamate derivative (3; $O\overset{O}{\overset{\|}{C}}NHPh$ for OH).

In view of the poor yield obtained in the oxidative cyclisation of 1-nitroethane-1,2-dione dioxime (3) to the nitrofuroxan (5) and the failure of the dioxime (3) to undergo cyclodehydration to the nitrofurazan (6) it was decided to terminate approaches to nitrofurazans and nitrofuroxans based on cyclisation reactions of the dioxime (3) in favour of alternative routes.

3.3 Investigations of Synthetic Routes to 3,4-Dinitrofurazan (1) and 3,4-Dinitrofuroxan (2) Based on 1-Amino-2-nitroethane-1,2-dione Dioxime

Having failed to develop synthetic routes to 3,4-dinitrofurazan (1) and 3,4-dinitrofuroxan (2) starting with 1-nitroethane-1,2-dione dioxime (3) attention was next turned to



(i) $NH_2OH.HCl$, Na_2CO_3, EtOH, room temp.

(ii) EtONO, HCl, EtOH, room temp, or $NaNO_2$, KOH, EtOH, 0 to 4°, or $NaNO_2$ or KNO_2, AcOH, H_2O, 4 to 8°

Scheme 2

routes (Scheme 2) based on 1-amino-2-nitroethane-1,2-dione dioxime (10). It was anticipated that this compound could be oxidatively cyclised to one or other or both of the aminonitrofuroxans (11) or (12) and cyclodehydrated to aminonitrofurazan (13). The amines (11) and/or (12) and (13) could then be elaborated to the dinitro heterocycles (1) and (2) by literature procedures[95] for the conversion of amino-groups into nitro substituents.

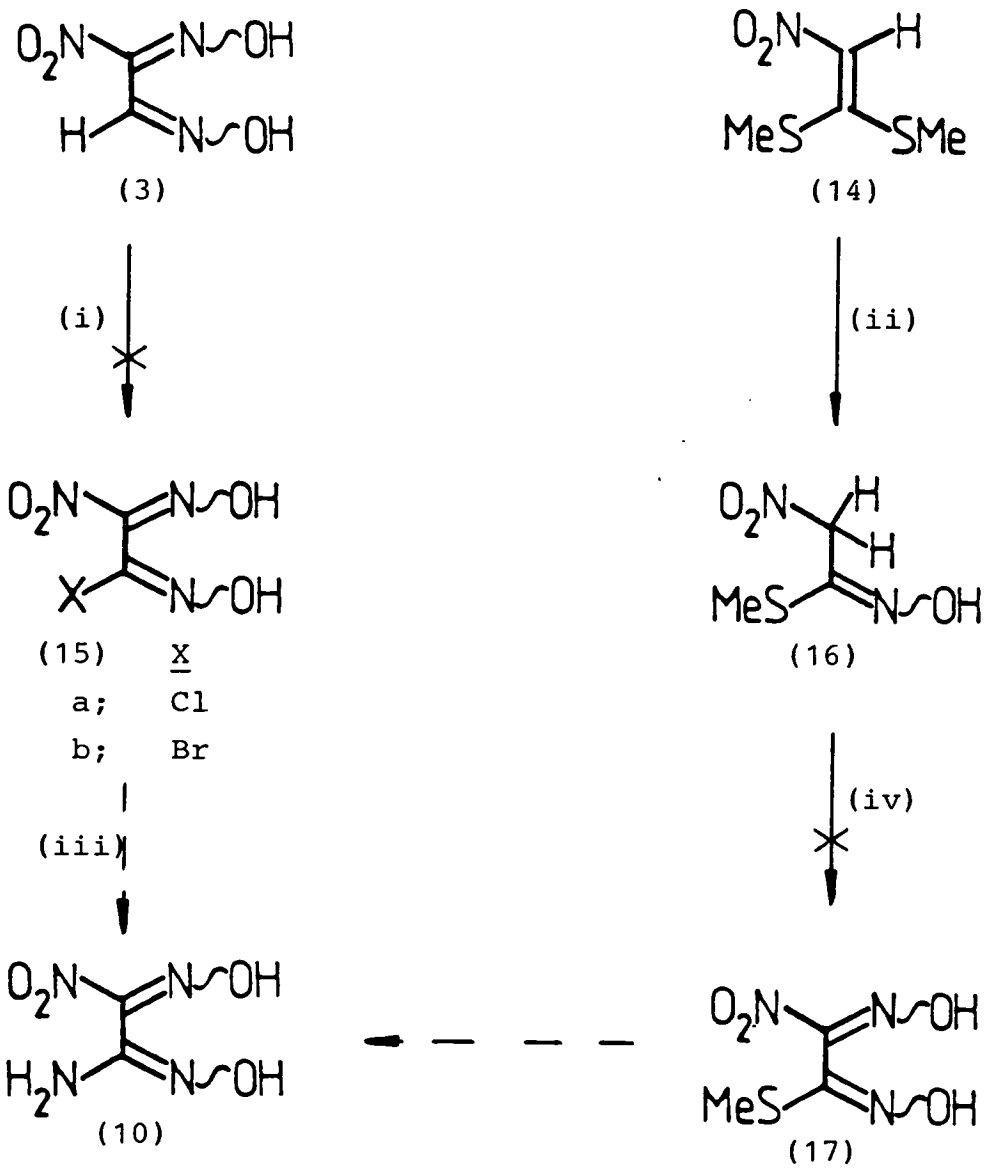
Two synthetic routes to the previously unknown 1-amino-2-nitroethane-1,2-dione dioxime (10) can be envisaged starting with the readily accessible nitroacetonitrile (7) (see Chapter 2). However, the route involving initial conversion into 2-oximinonitroacetonitrile (8) followed by the reaction of the latter with hydroxylamine was not considered because of the difficulty of characterising the unstable oxime (8) as already discussed in Chapter 2 (see page 38 and Scheme 9). The alternative approach (Scheme 2) involving the reaction of nitroacetonitrile (7) with hydroxylamine to give 2-nitro-acetamidoxime (9) then oximation of the latter was therefore investigated. 2-Nitroacetonitrile (7) reacted smoothly with hydroxylamine hydrochloride in the presence of sodium carbonate to give a good yield of a product which gave analytical and spectroscopic data fully consistent with its formulation as the required amidoxime derivative (9).

The oximation (Scheme 2) of 2-nitroacetamidoxime (9) was first attempted using amyl nitrite in the presence of sodium ethoxide. However this reaction gave no identifiable material. In contrast, the amidoxime (9) reacted with ethyl

nitrite in ethanolic hydrogen chloride to give a very low yield (3%) of a product which gave mass spectral data consistent with the molecular formula $C_2H_2N_4O_3$ rather than the expected dioxime structure (10). The unexpected product is formulated as the known[104] compound, 3-amino-4-nitro-furazan (13), on the basis of its melting point (123°) which agrees well with the literature[104] value (122.5°). This structure is further supported by the compound's i.r. spectrum which contains bands due to primary amino and nitro groups and the presence in its ^1H n.m.r. spectrum of a broad two proton singlet assignable to a primary amino group.

The formation of the aminonitrofurazan (13) in the course of the attempted oximation of 2-nitroacetamidoxime (10) most probably occurs by the intermediate formation of the dioxime (10) and its spontaneous dehydration under the reaction conditions. 3-Amino-4-nitrofurazan (13) was also formed in very poor yield (6%) when oximation of 2-nitroacetamidoxime (9) was attempted using sodium nitrite in alkaline solution. In contrast, 2-nitroacetamidoxime (9) reacted with sodium nitrite in acetic acid to give the aminonitrofurazan (13) in improved yield (27%). This yield was only marginally improved to 30% when potassium nitrite in glacial acetic acid was used as the oximating agent.

The poor yields of the aminonitrofurazan (13) and the failure of 2-nitroacetamidoxime (9) to undergo oximation to afford the required 1-amino-2-nitroethane-1,2-dione dioxime (10) prompted the investigation of alternative routes to this key starting-material. By analogy with the known chlorination of ethane-1,2-dione dioxime to 1,2-dichloroethane-1,2-dione



(i) Cl_2(g), Conc.HCl, 50°, or Cl_2(g), dioxane, 10° or Br_2, 1,2-dimethoxyethane, room temp.

(ii) NH_2OH, HCl, Na_2CO_3, EtOH, room temp.

(iii) NH_3

(iv) AmONO, EtOH, 0°, or EtONO, HCl, EtOH, 0 to 5°, or KNO_2, AcOH, H_2O, 4°, or $NaNO_2$, 10%aq HCl, AcOH, 0°

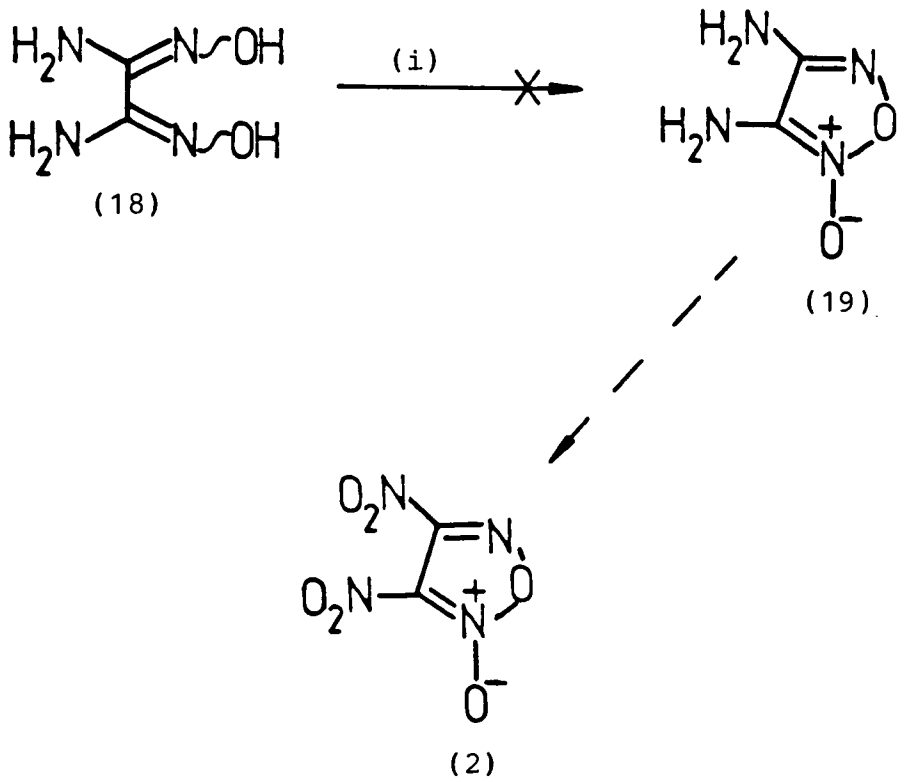
Scheme 3

dioxime (see Chapter 2, page 36 and Scheme 12) it was first decided to attempt the halogenation (Scheme 3) of 1-nitroethane-1,2-dione dioxime (3) in the expectation of obtaining the halogeno-derivatives (15a) or (15b). The intention was then to convert these compounds by amination into the required 1-amino-2-nitroethane-1,2-dione dioxime (10). In practice the attempted reaction of the dioxime (3) with chlorine in hydrochloric acid resulted in both chlorination and degradation of the molecule with the formation in good yield (60%) of chloropicrin which was identified by comparison with an authentic sample. Treatment of the dioxime (3) with chlorine in 1,4-dioxane on the other hand yielded a purple multicomponent oil from which no identifiable material could be obtained. The attempted bromination of 1-nitroethane-1,2-dione dioxime (3) was no more successful, treatment with bromine in 1,2-dimethoxyethane at room temperature affording only an intractable multi-component oil.

Having failed to achieve the synthesis of the halogeno-nitroethane-1,2-dione dioximes (15a and 15b) attention was next turned (Scheme 3) to the synthesis of the unknown 1-methylthio-2-nitroethane-1,2-dione dioxime (17) which should be convertible by amination into the required 1-amino-2-nitroethane-1,2-dione dioxime (10). The intention was to obtain 1-methylthio-2-nitroethane-1,2-dione dioxime (17) by oximation of methyl N-hydroxy-2-nitroethanimidothioate (16). The latter compound had not been described previously in the literature but was readily obtained in the present studies in

high yield (89%) by the reaction of the readily accessible 1,1-bis-methylthio-2-nitroethane (14) with hydroxylamine. The thiohydroximate derivative (16) tended to decompose at room temperature and did not give a satisfactory combustion analysis but did give mass, i.r. and ^1H n.m.r. spectral data fully in accord with its assigned structure. Disappointingly the attempted conversion of the thiohydroximate derivative (16) into 1-methylthio-2-nitroethane-1,2-dione dioxime (17) under a variety of conditions was unsuccessful. Attempted oximation using amyl nitrite in the presence of sodium ethoxide afforded in addition to a very low recovery (32%) of unreacted starting-material (16) an intractable gum containing further starting material (16). Reaction of the thiohydroximate derivative (16) with ethyl nitrite in ethanolic hydrogen chloride afforded only a low recovery of starting-material (17%). The attempted oximation of the thiohydroximate derivative (16) using potassium nitrite in glacial acetic acid or sodium nitrile in aqueous acetic acid or aqueous hydrochloric acid-acetic acid also resulted only in the isolation of low (10%) and high (79-85%) recoveries respectively of unreacted starting-material.

Because of the lack of success in developing routes to 3,4-dinitrofurazan (1) and 3,4-dinitrofuroxan (2) based on 1-amino-2-nitroethane-1,2-dione dioxime (10) as the key starting-material the investigation of these synthetic approaches was terminated at this point.



(18) (19) (2)

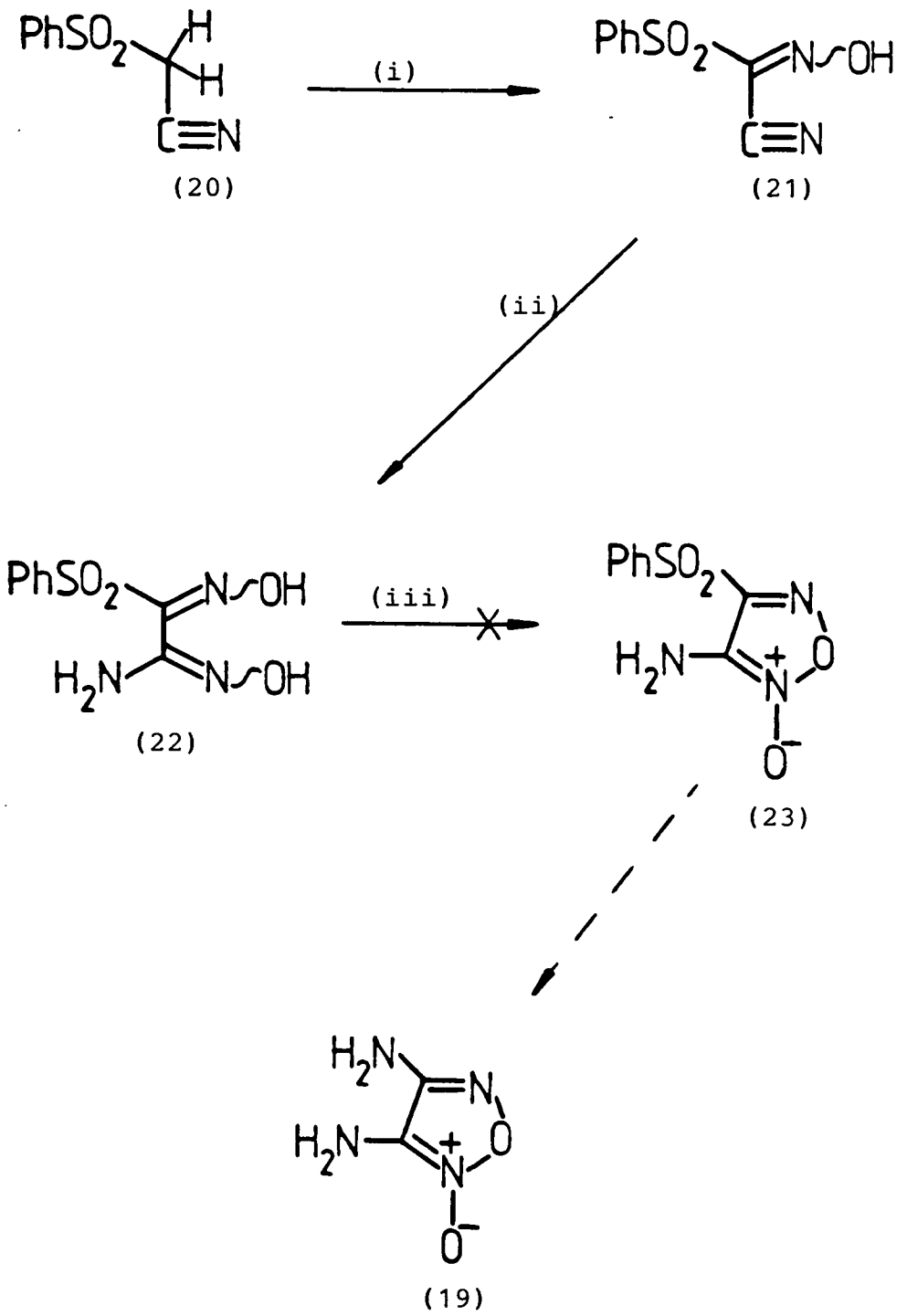
(i) MnO_2, $Me_2NCH{=}O$, room temp., or NaOCl, H_2O, C_5H_5N, room temp.

Scheme 4

3.4 Investigations of Synthetic Routes to 3,4-Dinitrofuroxan (2) Based on 3,4-Diaminofuroxan

In a final attempt to develop a practical synthetic route to 3,4-dinitrofuroxan (2) attention was focussed on the synthesis (Scheme 4) of the previously unreported 3,4-diaminofuroxan (19) and its conversion by known procedures into the dinitrofuroxan (2). Initial attempts to obtain 3,4-diaminofuroxan (19) (Scheme 4) were based on the oxidative cyclisation of the readily available compound 3,4-diaminoethane-1,2-dione dioxime (18) (see Chapter 2, page 36 and Scheme 12).[87] However the attempted conversion of the dioxime (18) into the furoxan derivative (19) by oxidation with activated manganese dioxide in dimethylformamide or with aqueous sodium hypochlorite in pyridine gave no identifiable material.

As an alternative approach to 3,4-diaminofuroxan (19) it was next decided to attempt the synthesis (Scheme 5) of the previously unknown 3-amino-4-phenylsulphonylfuroxan (23) in the expectation that the phenylsulphonyl substituent in the latter would undergo nucleophilic displacement by ammonia to afford the desired diaminofuroxan (19). It was anticipated that the aminophenylsulphonylfuroxan (23) would be readily accessible (Scheme 5) from the hitherto unknown 2-oximino phenylsulphonylacetamidoxime (22) by oxidative cyclisation. It was expected that 2-oximino-2-phenylsulphonylacetamidoxime (22) in turn could be prepared (Scheme 5) by reaction of the readily available[105] 2-oximinophenylsulphonylacetonitrile (21) with hydroxylamine. The latter compound (21) is readily prepared[105] by the oximation of the known[106] compound



(20) (21) (22) (23) (19)

(i) AmONO, NaOEt, EtOH, room temp.

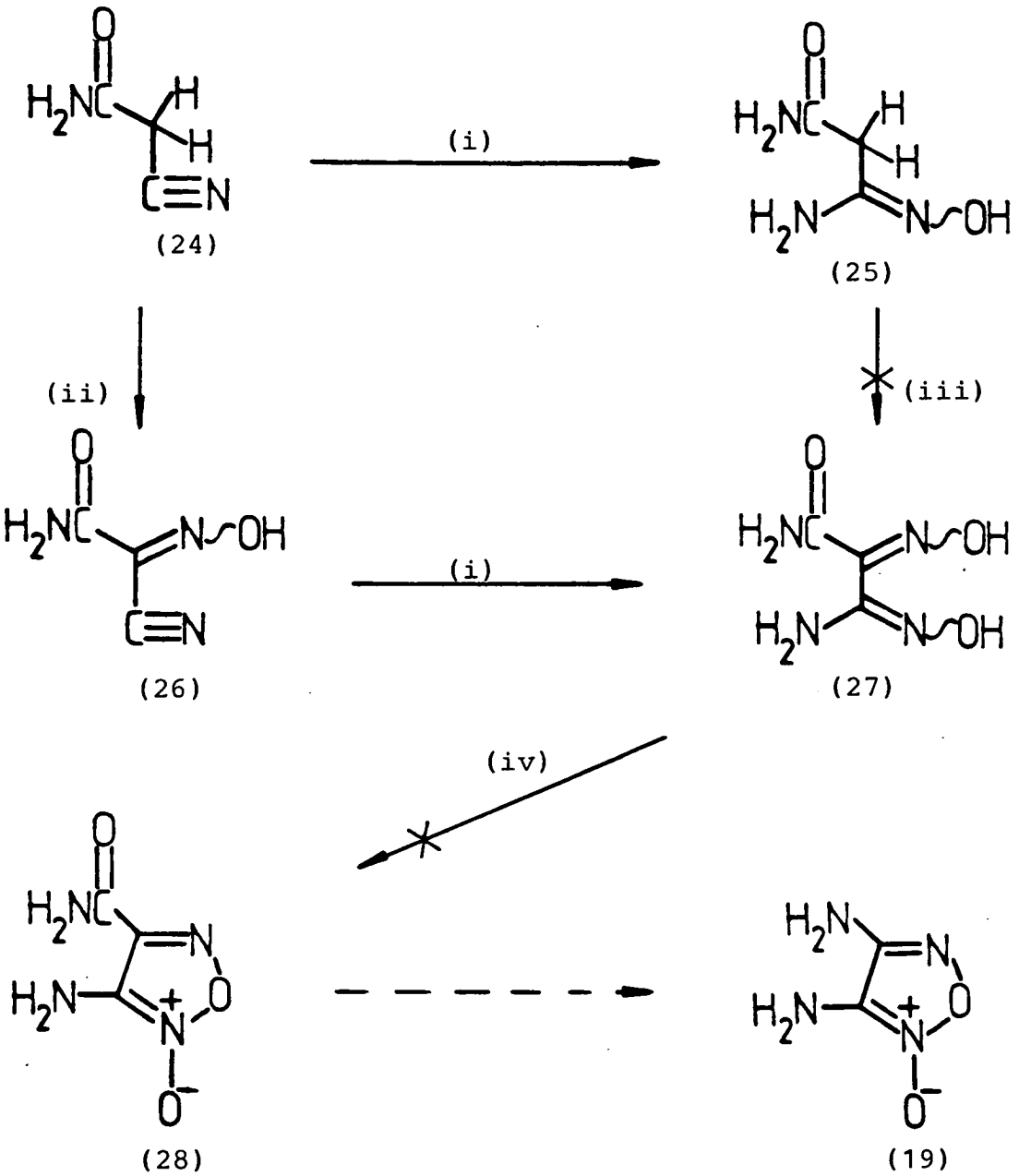
(ii) $NH_2OH.HCl$, Na_2CO_3, EtOH, room temp.

(iii) MnO_2, $CH_3C{\equiv}N$, room temp., or $CeNH_4(NO_2)_3$ 90% aq AcOH, 5°

Scheme 5

phenylsulphonylacetonitrile (20). The reaction of 2-oximino phenylsulphonylacetonitrile (21) with hydroxylamine hydrochloride in ethanol in the presence of sodium carbonate gave a good yield (58%) of the required acetamidoxime derivative (22) which gave analytical and mass spectral data consistent with its assigned structure. The attempted oxidative cyclisation (Scheme 5) of the oximino phenylsulphonylacetamidoxime (22) using either activated manganese dioxide or ceric ammonium nitrate failed to give any of the desired furoxan (23) giving in the former case no identifiable material and in the latter an intractable gum.

Because the preparation of the diaminofuroxan (19) could not be achieved through the phenylsulphonyl derivative (23) attention was next directed towards an alternative route (Scheme 6) involving the synthesis of the previously unreported 5-amino-4-carbamoylfuroxan (28) and its conversion by Hofmann degradation of the carbamoyl group into the diaminofuroxan (19). The intention was to obtain the furoxan-carboxamide (28) by oxidative cyclisation (Scheme 6) of the previously unreported 2-carbamoyl-2-oximinoacetamidoxime (27). Initially it was decided to obtain this compound (Scheme 6) by oximation of 2-carbamoylacetamidoxime (25). This compound had not been described previously in the literature but was readily prepared in the present studies in moderate yield (54%) by the reaction of cyanoacetamide (24) with hydroxylamine hydrochloride in the presence of sodium carbonate. 2-Carbamoylacetamidoxime (25) gave a combustion analysis and showed spectroscopic properties fully consistent with its assigned



(i) NH_2OH, HCl, Na_2CO_3, EtOH, room temp.

(ii) $NaNO_2$, AcOH, H_2O, 0 to 5°

(iii) KNO_2, AcOH, H_2O, 4°

(iv) MnO_2, $Me_2NCH{=}O$, room temp.

Scheme 6

structure. Disappointingly the amidoxime derivative (25) failed to undergo oximation to the required dioxamino-compound (27) using potassium nitrite in aqueous acetic acid this reaction giving no identifiable material.

The failure of 2-carbamoylacetamidoxime (25) to undergo oximation to 2-carbamoyl-2-oximinoacetamidoxime (27) prompted an alternative approach to this compound (Scheme 6) involving the reaction of the known[107] 2-oximinocyanoacetamide (27) with hydroxylamine. In practice 2-oximinocyamoacetamide (27) was readily prepared in moderate yield (54%) by the oximation of cyanoacetamide (24) as described by Conrad and Schulze.[107] Reaction of 2-oximinocyanoacetamide (27) with hydroxylamine hydrochloride in the presence of sodium carbonate gave a product albeit in only very low yield (5%) which analysed correctly for $C_3H_6N_4O_3$ and showed spectroscopic properties consistent with its formulation as the required 2-carbamoyl-2-oximinoacetamidoxime (27). In particular its i.r. spectrum showed bands in the range 3400-3000 cm^{-1} attributable to NH_2 and oxime substituents and a low frequency carbonyl band at 1650 cm^{-1} assignable to a primary amide group. The ^1H n.m.r. spectrum of the product showed three exchangeable one-proton singlets at δ12.78, 9.80, 7.32 and 7.00 attributable to the protons of the two oximino groups and those of the primary amide substituent and also an exchangeable two proton singlet at δ5.85 assignable to the NH-protons of the carboxamidoxime substituent. Unfortunately the attempted oxidative cyclisation of 2-carbamoyl-2-oximinoacetamidoxime (27) to the desired 5-amino-4-carbamoylfuroxan (28) using

manganese dioxide was unsuccessful. This reaction gave only an intractable gum which yielded no identifiable material. In view of this result and the inefficiency of the synthesis of the dioximino-compound (27) the investigation of the synthetic route to the diaminofuroxan (19) via the aminofuroxancarboxamide (28) was terminated at this point.

3.5 Experimental

The Reaction of 1-Nitroethane-1,2-dione Dioxime (3) with Sodium Hypochlorite in the Presence of Sodium Hydroxide

A solution of 1-nitroethane-1,2-dione dioxime (3) (0.27 g; 0.002 mol) in 10% w/v aqueous sodium hydroxide solution (4.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with aqueous sodium hypochlorite solution (containing 14% available chlorine) (10.0 ml) at such a rate that the temperature was <5°. The mixture was stirred at 0-5° for 0.5h and extracted with methylene chloride to give no identifiable material.

The aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and anhydrous sodium acetate and extracted with methylene chloride to give no material.

Evaporation of the aqueous mother liquor and extraction of the residual cake with boiling ethyl acetate also gave no material.

The Reaction of 1-Nitroethane-1,2-dione Dioxime (3) with Sodium Hypochlorite in the Presence of Pyridine

A solution of 1-nitroethane-1,2-dione dioxime (3) (0.27 g; 0.002 mol) in Analar pyridine (5.0 ml) was stirred at room temperature and treated dropwise with aqueous sodium hypochlorite solution (containing 14% available chlorine). The mixture was stirred at room temperature for 20 min, treated with water (5.0 ml), acidified with concentrated hydrochloric acid and extracted with methylene chloride to give a yellow gum (0.1 g) whose t.l.c. in methylene chloride

over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Attempted Oxidation of 1-Nitroethane-1,2-dione Dioxime (3) with Fuming Nitric Acid

A solution of fuming nitric acid (10.0 ml; d=1.52) was stirred and treated portionwise at room temperature with 1-nitroethane-1,2-dione dioxime (3) (0.81 g; 0.006 mol). The mixture was stirred at room temperature for 1h, poured onto cracked ice (40.0 g) and extracted with methylene chloride to afford an oil (0.8 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Attempted Oxidation of 1-Nitroethane-1,2-dione Dioxime (3) with Activated Manganese Dioxide

A suspension of activated manganese dioxide (3.0 g) in anhydrous 1,2-dimethoxyethane (5.0 ml) was stirred and treated dropwise at 10° (ice-water bath) with a solution of 1-nitroethane-1,2-dione dioxime (3) (0.27 g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (2.5 ml) over 10 min. The mixture was stirred in the melting ice bath for 1h, filtered to remove manganese dioxide and the dimethoxyethane mother liquor was evaporated to give a red oil (0.2 g) which was flash-chromatographed over silica.

Elution with methylene chloride-ethyl acetate (3:1) afforded a red oil (0.16 g) whose t.l.c. in methylene chloride-ethyl acetate (3:1) over silica showed it to be an unresolvable

multicomponent mixture which was not further investigated.

Further elution with ethyl acetate through to methanol gave no identifiable material.

4-Nitro-1,2,5-oxadiazole 1-N-Oxide (3)

A solution of 1-nitroethane-1,2-dione dioxime (3) (1.4 g; 0.01 mol) in 90% v/v aqueous acetic acid (25.0 ml) was stirred and treated dropwise at 5° (ice bath) with a solution of ceric ammonium nitrate (11.0 g; 0.02 mol) in water (10.0 ml). The mixture was stirred at 5° for 0.5h, treated with ice (25.0 g) and extracted with methylene chloride. The methylene chloride extract was then washed with saturated aqueous sodium hydrogen carbonate solution and evaporated to afford 4-nitro-1,2,5-oxadiazole 1-N-oxide (6) as an unstable amber oil (0.5 g; 37%), $\nu_{max.}$ 1620 (C=N), and 1550 and 1335 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 8.83 (1H, s, CH), $\delta_C(CDCl_3)$ 139.2 (quat.) and 125.7 (CH).

Found: M^+, 131.

$C_2H\ N_3O_4$ requires: M , 131.

The Attempted Reaction of 1-Nitroethane-1,2-dione Dioxime (3) with Acetic Anhydride

1-Nitroethane-1,2-dione dioxime (3) (0.27 g; 0.002 mol) and a few drops of acetic anhydride were heated at 100° (steam bath) for 10 min. The mixture was cooled to room temperature, treated with a few drops of water, neutralised with anhydrous sodium hydrogen carbonate and glacial acetic acid and extracted with methylene chloride to give only a

negligible quantity of gum,

The Attempted Reaction of 1-Nitroethane-1,2-dione Dioxime (3) with Acetyl Chloride in the Presence of Triethylamine

A solution of 1-nitroethane-1,2-dione dioxime (3) (1.4 g; 0.01 mol) and triethylamine (0.22 g; 0.022 mol) in anhydrous 1,4-dioxane (25.0 ml) was stirred and treated at room temperature with a solution of acetyl chloride (1.8 g; 0.022 mol) in anhydrous 1,4-dioxane (5.0 ml). The mixture was stirred at room temperature for 1h, filtered to remove triethylamine hydrochloride (2.6 g) and the dioxane filtrate was evaporated to give a red oil (1.0 g) which was flash-chromatographed over silica.

Elution with ethyl acetate gave only an intractable gum (0.2 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture from which no material could be obtained.

Further elution with methanol gave no other identifiable material.

The Attempted Reaction of 1-Nitroethane-1,2-dione Dioxime (3) with Phenyl Isocyanate

A solution of 1-nitroethane-1,2-dione dioxime (3) (1.1 g; 0.008 mol) in anhydrous 1,4-dioxane (10.0 ml) was stirred and treated at room temperature with a solution of phenyl isocyanate (1.92 g; 0.016 mol) in anhydrous 1,4-dioxane (10.0 ml). The mixture was stirred at room temperature for 16h, filtered to remove diphenyl urea (1.5 g) identical (i.r. spectrum)

to an authentic sample. The dioxane filtrate was evaporated to give an oil which upon trituration with ether yielded a further quantity of diphenylurea (0.2 g).

The ether mother liquor was evaporated to give an oil (1.0 g) which was flash-chromatographed over silica.

Elution with ethyl acetate afforded an unstable oil (0.1 g) which rapidly decomposed on standing at room temperature.

Further elution with methanol gave no other identifiable material.

2-Nitroacetamidoxime (9)

A solution of nitroacetonitrile (7) (10.3 g; 0.12 mol) in anhydrous ethanol (240 ml) was stirred and treated at room temperature with a solution of hydroxylamine hydrochloride (21.0 g; 0.3 mol) in anhydrous ethanol (300 ml) followed by anhydrous sodium carbonate (16.2 g; 0.16 mol). The mixture was stirred at room temperature for 24h, evaporated and the residual cake was treated with water (40.0 ml) and the insoluble solid was collected, washed with water and dried in vacuo to afford 2-nitroacetamidoxime (9) (8.4 g; 59%), m.p. 130-132° (decomp.) (from water), $\nu_{max.}$ 3320 and 3140 (NH and NOH), 1650 (C=N), and 1540 and 1305 (NO_2) cm^{-1}, δ_H[$(CO_3)_2$ SO] 9.63 (1H, brs, NOH), 5.80 (2H, brs, NH), and 5.04 (2H, s, CH_2).

Found: C, 20.3; H, 4.0; N, 35.3%; M^+, 119.

$C_2H_5N_3O_3$ requires: C, 20.2; H, 4.2; N, 35.3%; M , 119.

Extraction of the combined aqueous mother liquors with

methylene chloride gave no further identifiable material.

The Attempted Reaction of 2-Nitroacetamidoxime (9) with Amyl Nitrite in the Presence of Sodium Ethoxide

A suspension of 2-nitroacetamidoxime (9) (0.60 g; 0.005 mol) in anhydrous ethanol (5.0 ml) was stirred and treated at 0° (ice-salt bath) with a solution of sodium (0.12 g; 0.005 g.atm.) in anhydrous ethanol (5.0 ml) followed by the dropwise addition of amyl nitrite (0.59 g; 0.005 mol). The mixture was stirred in the melting ice bath for 24h, evaporated and the resulting residue was treated with water (5.0 ml) and extracted with methylene chloride to give only a negligible quantity of gum.

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate followed by extraction with methylene chloride gave no identifiable material.

The aqueous mother liquor was brought to pH1 by the dropwise addition of 2M hydrochloric acid and extracted with methylene chloride but gave no material.

4-Amino-5-nitro-1,2,5-oxadiazole (13)

(a) A suspension of 2-nitroacetamidoxime (9) (0.60 g; 0.005 mol) in anhydrous ethanol (10.0 ml) was stirred and treated at 0° (ice-salt bath) with a solution of hydrogen chloride (0.45 g; 0.012 mol) in anhydrous ethanol (1.5 ml) followed by the dropwise addition of a solution of ethyl nitrite (0.38 g; 0.005 mol) in anhydrous ethanol (0.75 ml) at such a rate that the temperature was <5°. The mixture was stirred in the

melting ice bath for 18h, evaporated and the residue was treated with water (2.0 ml), neutralised with 10% w/v aqueous sodium carbonate solution and extracted with methylene chloride to afford the known[104] 4-amino-5-nitro-1,2,5-oxadiazole (13) (0.02 g; 3%), m.p. 121-123° (from toluene) (lit.,[104] 122.5°), $\nu_{max.}$ 3470, 3440 and 3340 (NH) and 1530 and 1350 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 6.97 (2H, brs, NH).

Found: M^+, 130.

Calc. for $C_2H_2N_4O_3$: M, 130.

The aqueous mother liquor was brought to pH1 by the dropwise addition of aqueous 2M hydrochloric acid and extracted with methylene chloride but gave no identifiable material.

(b) A suspension of 2-nitroacetamidoxime (9) (0.60 g; 0.005 mol) in anhydrous ethanol (20.0 ml) was stirred and treated at 10° (ice-water bath) with a solution of potassium hydroxide (0.29 g; 0.0052 mol) in anhydrous ethanol (5.0 ml). The mixture was stirred in the melting ice bath for 0.5h and the precipitated solid was collected and washed with anhydrous ethanol to afford the potassium salt of 2-nitroacetamidoxime (0.65 g; 82%), m.p. 136-140° (decomp.).

A solution of the potassium salt (0.63 g; 0.004 mol) and sodium nitrite (0.35 g; 0.005 mol) in water (6.0 ml) was stirred and treated dropwise at 0-4° (ice-salt bath) with aqueous 1M sulphuric acid (4.5 ml) and extracted with methylene chloride to give 4-amino-5-nitro-1,2,5-oxadiazole (13) (0.03 g; 6%), m.p. 63-66° (decomp.) identical (i.r. spectrum) to an authentic sample prepared in (a) before.

The aqueous mother liquor was brought to pH1 by the

dropwise addition of aqueous 1M sulphuric acid and extracted with methylene chloride but gave no further material.

(c) A solution of 2-nitroacetamidoxime (9) (0.24 g; 0.002 mol) in glacial acetic acid (10.0 ml) was stirred and treated dropwise at 5-8° (ice bath) with a solution of sodium nitrite (0.15 g; 0.0022 mol) in water (1.0 ml) over 15 min. The mixture was stirred at 5-8° for 2h, evaporated and the residue treated with water (2.0 ml) and extracted with methylene chloride to give 4-amino-5-nitro-1,2,5-oxadiazole (13) (0.07 g; 27%), m.p. 121-123°, identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

(d) A suspension of 2-nitroacetamidoxime (9) (4.8 g; 0.04 mol) and potassium nitrite (4.1 g; 0.048 mol) in water (40.0 ml) was stirred and treated in one portion at 4° (ice bath) with glacial acetic acid (4.8 ml). The mixture was removed from the ice bath and an exothermic reaction set in. The mixture was stirred for 1h at room temperature and then constantly extracted with methylene chloride to give 4-amino-5-nitro-1,2,5-oxadiazole (13) (1.6 g; 30%), m.p. 112-115°, identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

<u>The Attempted Chlorination of 1-Nitroethane-1,2-dione Dioxime (3)</u>

(a) A solution of 1-nitroethane-1,2-dione dioxime (3) (0.27 g; 0.002 mol) in concentrated hydrochloric acid (1.0 ml) in water (10.0 ml) was stirred and warmed to 50° (water bath)

for 5 min, cooled to 0° (ice-salt bath) and treated with a slow stream of chlorine gas for 2.5h.

The mixture was extracted with methylene chloride to give a yellow oil (0.4 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave only chloropicrin (0.19 g; 60%) as a green oil.

Found: M^+, 164.5.

CCl_3NO_2 requires: M , 164.5.

(b) A solution of 1-nitroethane-1,2-dione dioxime (3) (0.27 g; 0.002 mol) in anhydrous 1,4-dioxane (10.0 ml) was stirred and treated at 10° (ice bath) with a slow stream of chlorine gas (2.31 g; 0.033 mol) for 0.5h. The mixture was securely stoppered and left in the melting ice bath for 16.5h, then purged with nitrogen gas for 1h and evaporated to give a purple oil (1.5 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Attempted Bromination of 1-Nitroethane-1,2-dione Dioxime (3)

A solution of 1-nitroethane-1,2-dione dioxime (3) (0.27 g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) was stirred and treated with a solution of bromine (3.2 g; 0.02 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml). The mixture was stirred at room temperature with the exclusion of atmospheric moisture for 20h.

The mixture was evaporated to give a red oil which was

dissolved in methylene chloride and the solution washed with water (2x5.0 ml) and evaporated to give an oil (0.6 g) whose t.l.c. in methylene chloride-ethyl acetate (4:1) over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

1,1-Bis-methylthio-2-nitroethene (14)

1,1-Bismethylthio-2-nitroethene (14) was prepared as described in Chapter 2, page 64.

Methyl N-Hydroxy-2-nitroethanimidothioate (16)

A solution of 1,1-bis-methylthio-2-nitroethene (14) (3.3 g; 0.02 mol) in anhydrous ethanol (150 ml) was treated with a solution of hydroxylamine hydrochloride (3.5 g; 0.05 mol) in anhydrous ethanol (75.0 ml) followed by anhydrous sodium carbonate (2.2 g; 0.026 mol) and the mixture was heated under reflux for 17h.

The mixture was evaporated to give a residual cake which was treated with water (15.0 ml) and the solution extracted with methylene chloride to give methyl N-hydroxy-2-nitro-ethanimidothioate (16) (2.7 g; 89%) which was purified by bulb-to-bulb distillation, m.p. 64-69°, $\nu_{max.}$ 1600 (C=N), and 1540 and 1310 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 8.14 (1H, brs, NOH), 5.27 (2H, s, CH_2), and 2.44 (3H, s, CH_3).

Found: M^+, 150.

$C_3H_6N_2O_3S$ requires: M , 150.

Neutralisation of the aqueous mother liquor with 10% w/v aqueous sodium hydrogen carbonate solution and extraction with methylene chloride gave no further material.

The Attempted Reaction of Methyl N-Hydroxy-2-nitroethanimidothioate (16) with Amyl Nitrite in the Presence of Sodium Ethoxide

A solution of methyl N-hydroxy-2-nitroethanimidothioate (16) (0.75 g; 0.005 mol) in anhydrous ethanol (5.0 ml) was stirred and treated at 0° (ice-salt bath) with a solution of sodium (0.12 g; 0.005 g.atm.) in anhydrous ethanol (5.0 ml), then dropwise with amyl nitrite (0.59 g; 0.005 mol). The mixture was stirred in the melting ice bath for 24h, evaporated and the residual cake was treated with water (5.0 ml) and extracted with methylene chloride to give only a negligible quantity of gum.

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate followed by extraction with methylene chloride afforded only unreacted methyl N-hydroxy-2-nitroethanimidothioate (16) (0.24 g; 32%), m.p. 58-65°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

The aqueous mother liquor was brought to pH1 by the dropwise addition of aqueous 2M hydrochloric acid and extracted with methylene chloride to give a gum (0.28 g) whose t.l.c. in methylene chloride over silica showed it to be largely unreacted methyl N-hydroxy-2-nitroethanimidothioate (16).

The Attempted Reaction of Methyl N-Hydroxy-2-nitroethanimidothioate (16) with Ethyl Nitrite in the Presence of Hydrogen Chloride

A solution of methyl N-hydroxy-2-nitroethanimidothioate

(16) (0.75 g; 0.005 mol) in anhydrous ethanol (10.0 ml) was stirred and treated at 0° (ice-salt bath) with a solution of hydrogen chloride (0.45 g; 0.012 mol) in anhydrous ethanol (1.5 ml) then dropwise with a solution of ethyl nitrite (0.38 g; 0.005 mol) in anhydrous ethanol (0.75 ml) at such a rate that the temperature was <5°. The mixture was stirred in the melting ice bath for 18h, evaporated and the residue was treated with water (2.0 ml) and extracted with methylene chloride to give a yellow oil (0.42 g) which was flash-chromatographed over silica.

Elution with methylene chloride through to methanol gave only unreacted methyl N-hydroxy-2-nitroethanimidothioate (16) (0.13 g; 17%), m.p. 46-56°, identical (i.r. spectrum) to an authentic sample.

The aqueous mother liquor was neutralised with 10° w/v aqueous sodium hydrogen carbonate and extracted with methylene chloride to give no further material.

The Attempted Reaction of Methyl N-Hydroxy-2-nitroethanimidothioate (16) with Potassium Nitrite in Aqueous Acetic Acid

A suspension of methyl N-hydroxy-2-nitroethanimidothioate (16) (0.75 g; 0.005 mol) and potassium nitrite (0.51 g; 0.006 mol) in water (5.0 ml) was stirred and treated in one portion at 4° (ice bath) with glacial acetic acid (0.60 ml). The mixture was removed from the ice bath and an exothermic reaction set in. The mixture was then stirred at room temperature for 1h, cooled to 0° (ice-salt bath) and extracted with methylene chloride to give an oil (0.12 g) which was flash-chromatographed over silica.

Elution with methylene chloride through to methanol gave only unreacted methyl N-hydroxy-2-nitroethanimidothioate (16) (0.07 g; 10%), m.p. 52-56°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

The aqueous mother liquor was brought to neutrality with anhydrous sodium acetate and extracted with methylene chloride to give only a negligible quantity of gum.

The Attempted Reaction of Methyl N-Hydroxy-2-nitroethanimidothioate (16) with Sodium Nitrite in Aqueous Acetic Acid

A solution of methyl N-hydroxy-2-nitroethanimidothioate (16) (0.75 g; 0.005 mol) in glacial acetic acid (5.0 ml) was stirred and treated dropwise at 5-8° (ice bath) with a solution of sodium nitrite (0.15 g; 0.0022 mol) in water (1.0 ml) over 15 min. The mixture was stirred at 5-8° for 2h, then evaporated, and the residue was treated with water (5.0 ml) and extracted with methylene chloride to afford only unreacted methyl N-hydroxy-2-nitroethanimidothioate (16) (0.64 g; 85%), m.p. 57-62°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

The Attempted Reaction of Methyl N-Hydroxy-2-nitroethanimidothioate (16) with Sodium Nitrite in the Presence of Hydrochloric Acid

A solution of methyl N-hydroxy-2-nitroethanimidothioate (16) (0.75 g; 0.002 mol) in 10% w/v aqueous hydrochloric acid (2.5 ml) and glacial acetic acid (5.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of

sodium nitrite (0.17 g; 0.0025 mol) in water (1.0 ml) at such a rate that the temperature was <5°. The mixture was stirred at 0-5° for 1h, concentrated to one third of the original volume, treated with water (5.0 ml) and extracted with methylene chloride to give only unreacted methyl N-hydroxy-2-nitroethanimidothioate (16) as a yellow oil (0.59 g; 79%) identical (i.r. spectrum) and t.l.c. over silica in methylene chloride to an authentic sample prepared before.

The Attempted Oxidation of 1,2-Diaminoethane-1,2-dione Dioxime (18) with Activated Manganese Dioxide

A solution of 1,2-diaminoethane-1,2-dione dioxime (18) (0.24 g; 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was stirred and treated at room temperature with activated manganese dioxide (2.0 g). The mixture was stirred at room temperature for 2h, filtered to remove manganese dioxide and evaporated to give a gum (0.24 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to methanol gave no identifiable material.

The Attempted Reaction of 1,2-Diaminoethane-1,2-dione Dioxime (18) with Sodium Hypochlorite in the Presence of Pyridine

A solution of 1,2-diaminoethane-1,2-dione dioxime (18) (0.24 g; 0.002 mol) in Analar pyridine (5.0 ml) was stirred and treated at room temperature with aqueous sodium hypochlorite solution (containing 14% available chlorine) (5.0 ml). The mixture was stirred at room temperature for 20 min, diluted

with water (10.0 ml) and brought to pH1 by the dropwise addition of concentrated hydrochloric acid and extracted with methylene chloride to give no identifiable product.

Phenylsulphonylacetonitrile (20)

Phenylsulphonylacetonitrile (20) was prepared by the reaction of sodium benzenesulphinate with chloroacetonitrile as described by Tröger and Hille,[106] yield 83% and had m.p. 112-114° (lit.,[106] 112-114°).

2-Oximino 2-Phenylsulphonylacetonitrile (21)

A solution of phenylsulphonylacetonitrile (20) (18.1 g; 0.1 mol) in anhydrous ethanol (150 ml) was mixed with a solution of sodium (2.3 g; 0.1 g atm) in anhydrous ethanol (100 ml) and the mixture was stirred, cooled to 0° (ice salt bath) and treated dropwise with amyl nitrite (11.7 g; 0.1 mol). The mixture was stirred at room temperature for 24h.

The precipitated solid was collected, washed with ethanol, dried *in vacuo* and combined with a second crop of solid obtained by evaporating the combined ethanolic mother liquors. The combined solids were dissolved in water (50.0 ml), brought to pH1 with concentrated hydrochloric acid and the precipitated solid collected, washed with water and dried *in vacuo* to afford the known[105] 2-oximino 2-phenylsulphonylacetonitrile (21) (12.0 g; 58%), m.p. 137-141° (lit.,[105] 140°).

2-Oximino 2-Phenylsulphonylacetamidoxime (22)

A solution of 2-oximino 2-phenylsulphonylacetonitrile

(21) (10.5 g; 0.005 mol) and hydroxylamine hydrochloride (8.7 g; 0.125 mol) in anhydrous ethanol (375 ml) was stirred and treated in one portion at room temperature with anhydrous sodium carbonate (6.9 g; 0.065 mol). The mixture was stirred at room temperature for 24h, evaporated, the residue treated with water (25.0 ml) and the insoluble solid collected and dried in vacuo to afford 2-oximino-2-phenylsulphonyl-acetamidoxime (22) (7.0 g; 58%), m.p. 120-123° (from water), $\nu_{max.}$ 3100-3560 br (NOH, NH), δ_H[$(CD_3)_2SO$] 13.00 (1H, brs, NOH, exchanged with D_2O), 9.95 (1H, brs, NOH, exchanged with D_2O), 7.60-7.97 (5H, m, ArH), and 5.85 (2H, s, NH_2, exchanged with D_2O).

Found: M^+, 243.0318.

$C_8H_9N_3O_4S$ requires: M , 243.0314.

The aqueous mother liquor was extracted with methylene chloride to give no further identifiable material.

The Attempted Oxidative Cyclisation of 2-Oximino-2-phenyl-sulphonylacetamidoxime (22)

(a) Using activated manganese dioxide

A solution of 2-oximino-2-phenylsulphonylacetamidoxime (22) (0.61 g; 0.0025 mol) in anhydrous acetonitrile (10.0 ml) was stirred and treated at room temperature with a single portion of activated manganese dioxide (3.8 g). The mixture was stirred at room temperature for 2h, filtered through celite to remove the manganese dioxide, and the filtrate evaporated to give no identifiable material.

Soxhlet extraction of the manganese dioxide-celite residue with ethyl acetate gave no further material.

(b) Using ceric ammonium nitrate

A solution of 2-oximino-2-phenylsulphonylacetamidoxime (22) (0.24 g; 0.001 mol) in 90% v/v aqueous acetic acid (5.0 ml) was stirred and treated dropwise at 5° (ice bath) with a solution of ceric ammonium nitrate (1.1 g; 0.002 mol) in water (1.3 ml). The mixture was stirred at 5° for 0.5h, treated with ice (2.5 g) and extracted with methylene chloride to give only a gum (0.2 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

2-Carbamoylacetamidoxime (25)

A solution of cyanoacetamide (24) (8.4 g; 0.1 mol) and hydroxylamine hydrochloride (17.4 g; 0.25 mol) in anhydrous ethanol (600 ml) was stirred and treated at room temperature with a single portion of anhydrous sodium carbonate (13.8 g; 0.13 mol). The mixture was stirred at room temperature for 24h, evaporated, and the residue treated with water (50.0 ml) to give a solid which was collected, washed with water and dried in vacuo to afford 2-carbamoylacetamidoxime (25) (6.3 g; 54%), m.p. 147-151° (decomp.) (from water), $\nu_{max.}$ 3500-3100 br (NH, OH) and 1650 (C=O) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 8.99 (1H, brs, NOH, exchanged with D_2O), 7.36 (1H, s, NH, exchanged with D_2O), 7.00 (1H, s, NH, exchanged with D_2O), 5.38 (2H, s, NH_2, exchanged with D_2O), and 2.79 (2H, s, CH_2), $\delta_C[(CD_3)_2SO]$ 171.5 (C=O), 149.9 (C=N), and 39.6 (CH_2 reversed by dept $3\pi/4$).

Found: C, 30.6; H, 6.2; N, 36.3%; M^+, 117.

$C_3H_7N_3O_2$ requires: C, 30.8; H, 6.0; N, 35.9%; M , 117.

Extraction of the neutral aqueous mother liquor gave no further material.

The Attempted Reaction of 2-Carbamoylacetamidoxime (25) with Potassium Nitrite in the Presence of Acetic Acid

A suspension of 2-carbamoylacetamidoxime (25) (0.59 g; 0.005 mol) in a solution of potassium nitrite (0.51 g; 0.006 mol) in water (5.0 ml) was stirred at 4° (ice bath) and treated with a single portion of glacial acetic acid (0.60 ml). The mixture was removed from the ice bath and a slight exothermic reaction set in. The mixture was then allowed to cool to room temperature, stirred for 1h, cooled to 0° (ice-salt bath) and extracted with methylene chloride to give no identifiable material.

Further workup of the aqueous mother liquor gave no other identifiable material.

2-Oximinocyanoacetamide (26)

2-Oximinocyanoacetamide (26) was prepared by the reaction of cyanoacetamide (24) with sodium nitrite in aqueous acetic acid as described by Conrad and Schulze,[107] yield 54%, and had m.p. 174-176° (lit.,[107] 184°).

2-Carbamoyl-2-oximinoacetamidoxime (27)

A solution of 2-oximinocyanoacetamide (26) (4.5 g; 0.04 mol) and hydroxylamine hydrochloride (7.0 g; 0.1 mol) in

anhydrous ethanol (300 ml) was stirred and treated with a single portion of anhydrous sodium carbonate (5.5 g; 0.052 mol). The mixture was stirred at room temperature for 24h, evaporated and the residue treated with water and extracted with methylene chloride to give 2-carbamoyl-2-oximinoacetamidoxime (27) (0.3 g; 5%), m.p. 133-135° (decomp.)(from water), $\nu_{max.}$ 3460-3000 br (NH, NOH) and 1650 (C=O) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 12.78 (1H, s, NOH, exchanged with D_2O), 9.80 (1H, s, NOH, exchanged with D_2O), 7.32 (1H, s, NH, exchanged with D_2O), 7.00 (1H, s, NH, exchanged with D_2O), and 5.85 (2H, s, NH_2, exchanged with D_2O).

Found: C, 24.5; H, 4.0; N, 38.4%; M^+, 146.

$C_3H_6N_4O_3$ requires: C, 24.7; H, 4.1; N, 38.4%; M , 146.

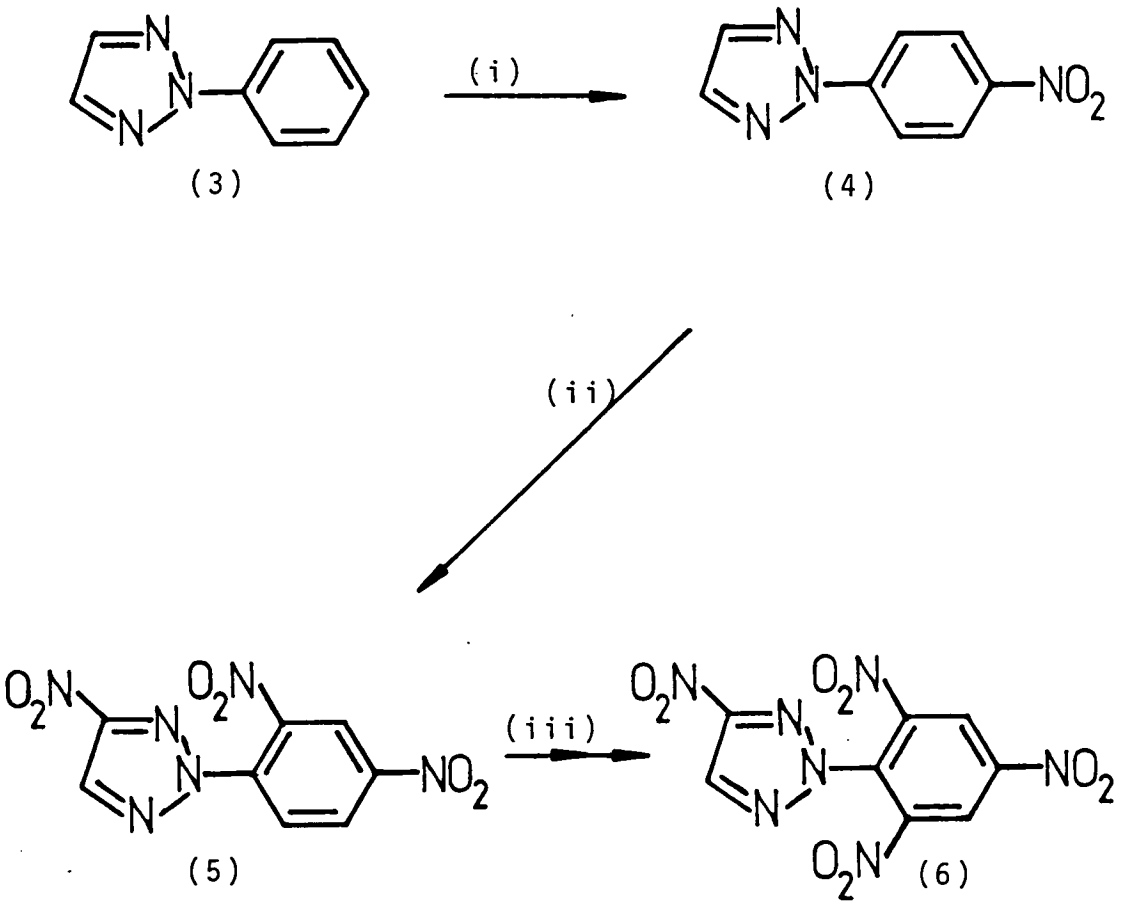
Evaporation of the aqueous mother liquor and extraction of the residue with boiling ethyl acetate gave no further identifiable material.

The Attempted Oxidative Cyclisation of 2-Carbamoyl-2-oximinoacetamidoxime (27) using Activated Manganese Dioxide

A solution of 2-carbamoyl-2-oximinoacetamidoxime (27) (1.0 g; 0.007 mol) in anhydrous dimethylformamide (40.0 ml) was stirred and treated at room temperature with a single portion of activated manganese dioxide (10.5 g). The mixture was stirred at room temperature for 1h, filtered through celite to remove residual manganese dioxide and evaporated to give a gum (0.2 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Chapter 4

New Synthetic Approaches to Mononitro- and Dinitro-1,2,3-triazole Derivatives



(i) Conc.HNO_3, Conc. H_2SO_4, 20°

(ii) Conc.HNO_3, Conc. H_2SO_4, 80°

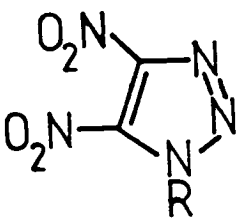
(iii) $NaNO_3$, SO_3-H_2SO_4, 145°

Scheme 1

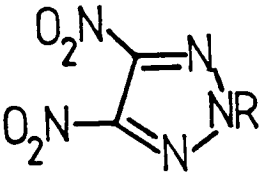
New Synthetic Approaches to Mononitro- and Dinitro-1,2,3-triazole Derivatives

4.1 Introduction

4,5-Dinitro-1H-1,2,3-triazoles (1) and the corresponding 2H-analogues (2) are of interest as synthetic intermediates for the construction of fused 1,2,3-triazole derivatives. Like other π-excessive heteroaromatic nitro compounds (see Chapter 1) they also have potential as antibacterial and

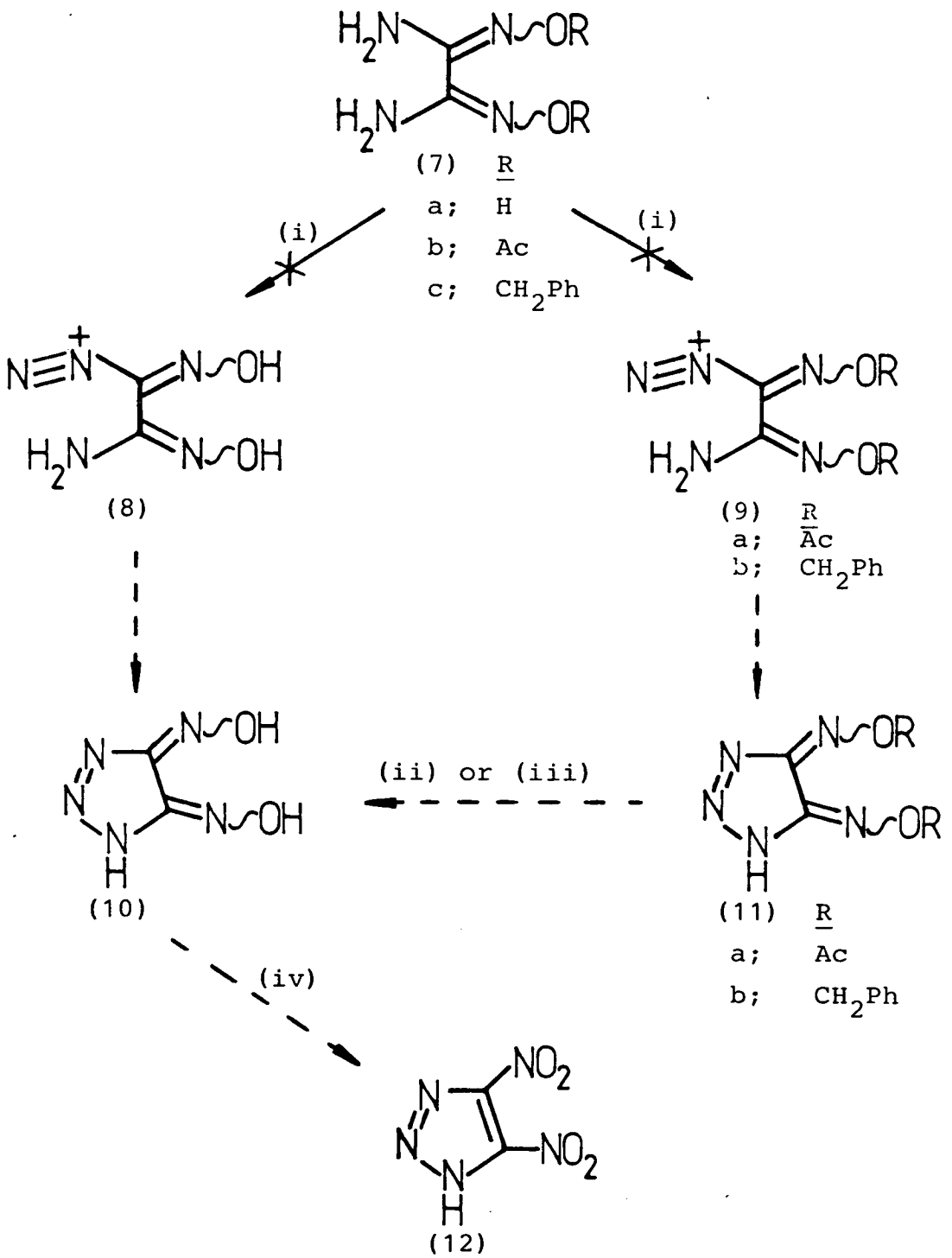


(1)



(2)

radiosensitising agents. To date no example of a 4,5-dinitro-1,2,3-triazole derivative (1) or (2) has been reported in the literature. The fact that 4,5-dinitro-1,2,3-triazole derivatives have not been described hitherto can be attributed largely to the reluctance of the 1,2,3-triazole nucleus to undergo nitration. Thus, 1H-1,2,3-triazole itself resists nitration even under forcing conditions.[17] Also (Scheme 1) though 2-phenyl-2H-1,2,3-triazole (3) can be nitrated[15-17] to give 4-nitro-2-(2,4-dinitrophenyl)-2H-1,2,3-triazole (5) this is achieved only after initial nitration of the phenyl substituent to give 2-(4-nitrophenyl)-2H-1,2,3-triazole (4). Moreover the dinitrotriazole (5) resists further nitration of the heterocyclic nucleus even under conditions[17] which



(i) $NaNO_2$, AcOH, H_2O

(ii) hydrolysis

(iii) hydrogenolysis

(iv) [O]

Scheme 2

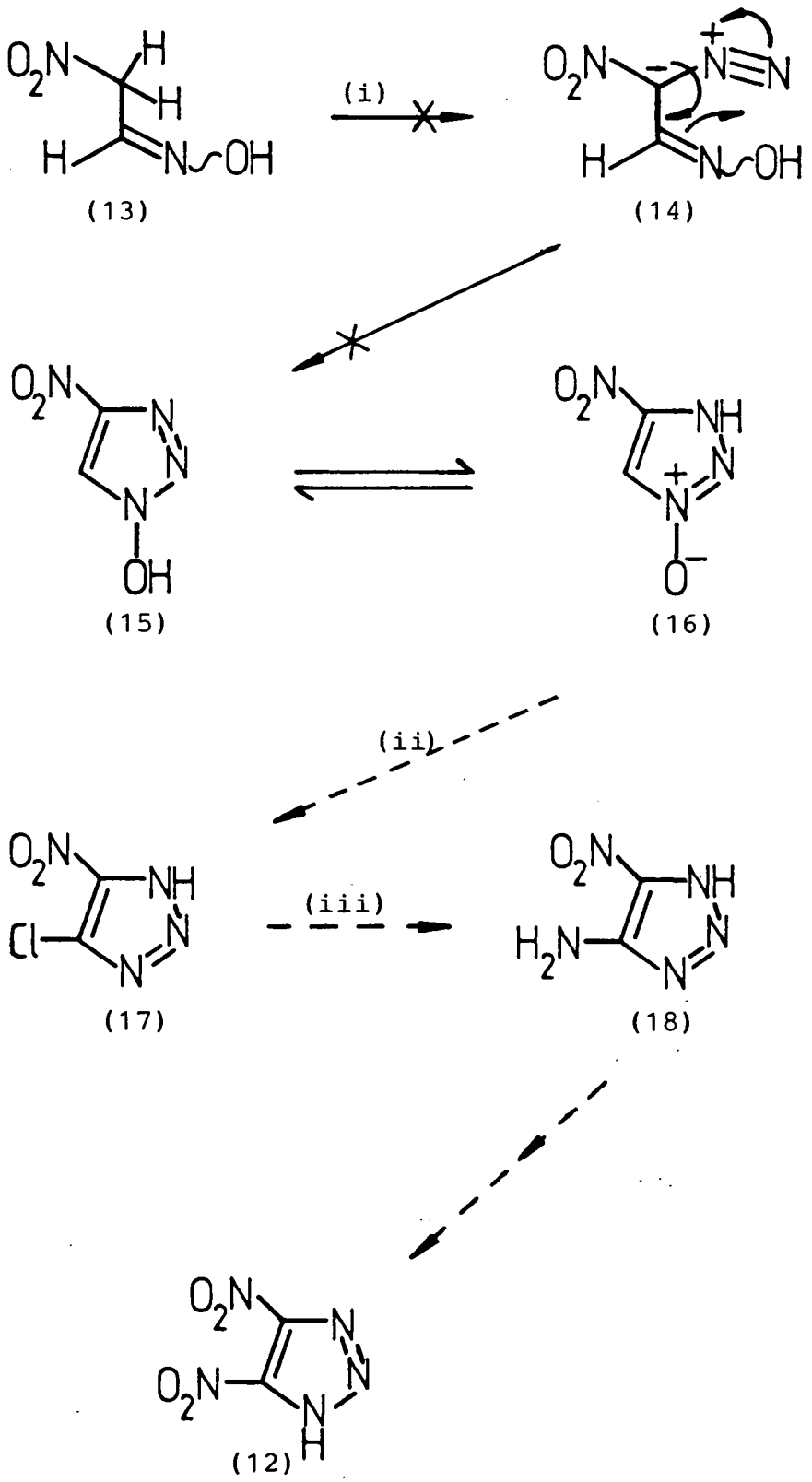
result in complete nitration of the phenyl substituent to give 4-nitro-2-(2,4,6-trinitrophenyl)-2H-1,2,3-triazole (6).

The following account describes studies aimed at developing viable general synthetic routes to 4,5-dinitro-1H-1,2,3-triazole derivatives (1) and their 2H-analogues (2).

4.2 Synthetic Approaches to 4,5-Dinitro-1H-1,2,3-triazole Based on Cyclisation Reactions of 1,2-Diaminoethane-1,2-dione Dioxime Derivatives

The initial strategy for the synthesis of a 4,5-dinitro-1,2,3-triazole derivative (Scheme 2) was aimed at 4,5-dinitro-1H-1,2,3-triazole (12) and was based on the use of the readily available[87] 1,2-diaminoethane-1,2-dione dioxime (7a) as the key starting material. It was hoped that this compound might undergo diazotisation to a transient diazonium species (8) which would immediately cyclise to the novel dioximino-1H-1,2,3-triazole derivative (10). Oxidation of the latter would then afford 4,5-dinitro-1H-1,2,3-triazole (12). In practice the attempted diazotisation of 1,2-diaminoethane-1,2-dione dioxime (7a) using sodium nitrite in aqueous acetic acid gave only a low yield of an intractable solid which could not be purified for characterisation. There was no evidence for the formation of the required derivative (10).

Since the low recovery of material in the attempted diazotisation of 1,2-diaminoethane-1,2-dione dioxime (7a) could have been due to involvement by the free oxime substituents it was next decided to investigate the behaviour of the



(13) (14) (15) (16) (17) (18) (12)

(i) TSO_2N_3 Et_3N, room temp. (T = 4-tolyl)

(ii) HCl or AcCl

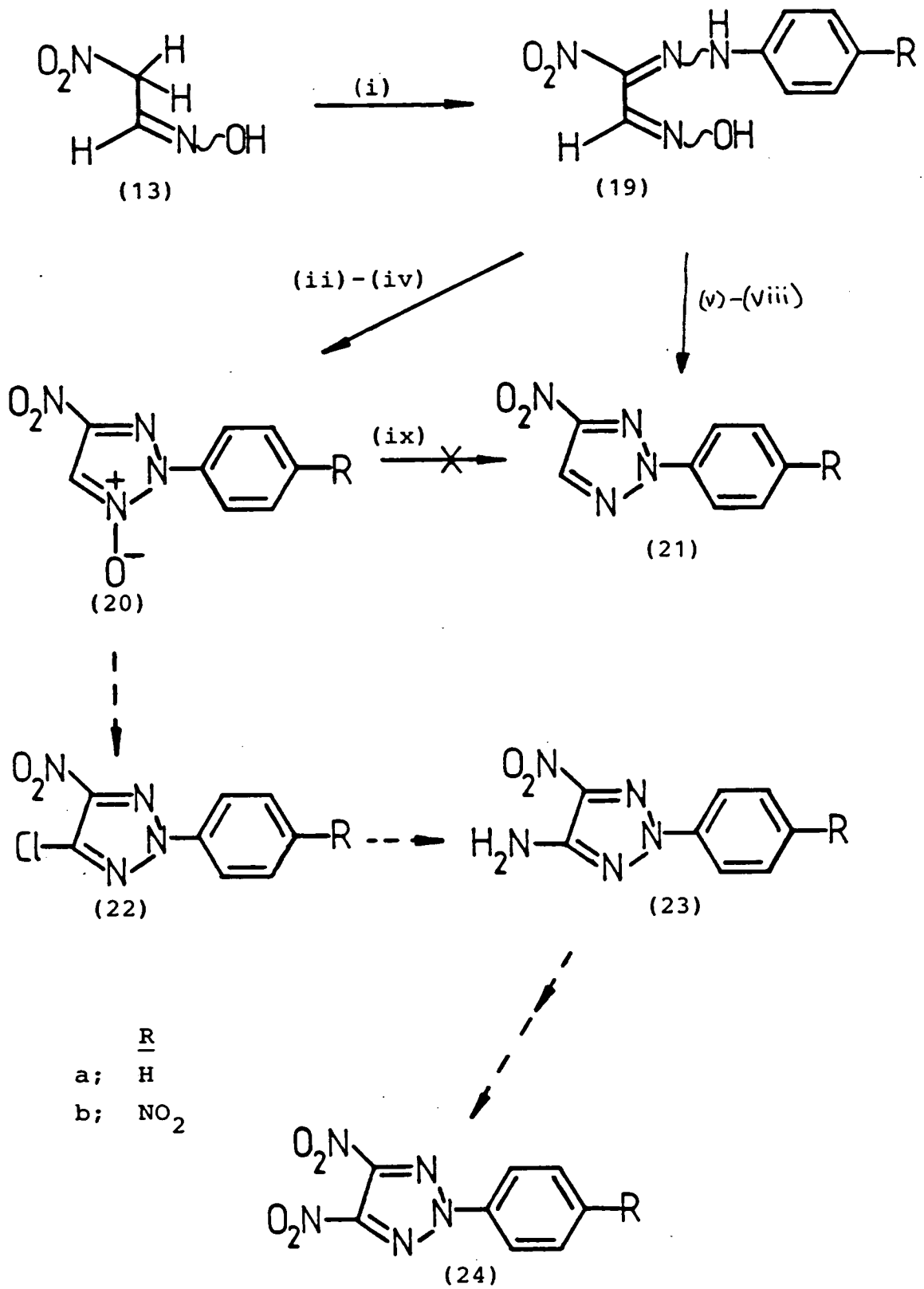
(iii) NH_3

Scheme 3

protected derivatives (7b) and (7c) towards diazotisation. These compounds were readily available by acylation and benzylation respectively of 1,2-diaminoethane-1,2-dione dioxime (7a) as described in Chapter 2 and it was hoped that on diazotisation they would afford diazonium intermediates (9a) and (9b) capable of efficient cyclisation to the 1,2,3-triazole derivatives (11a) and (11b). Deprotection would then give the required dioximino-1,2,3-triazole (10). However the attempted reaction of the diacetyl derivative (7b) with sodium nitrite in aqueous acetic acid gave only a good recovery of the unreacted starting material. Similar treatment of the dibenzyl derivative on the other hand afforded a complex gum which yielded no identifiable material.

4.3 Synthetic Approaches to 4,5-Dinitro-1,2,3-triazole Derivatives Based on Cyclisation Reactions of 2-Nitroethanal Monoxime (Methazonic Acid) Derivatives

Having been unable to exploit 1,2-diaminoethane-1,2-dione dioxime (7a) and its simple derivatives (7b) and (7c) as key starting material for the synthesis of 4,5-dinitro-1H-1,2,3-triazole (12) attention was next turned (Scheme 3) to 2-nitroethanal monoxime (methazonic acid) (13) as the key building block. The preparation of this compound has already been described in Chapter 2. The anticipation was that methazonic acid (13) would undergo diazo-transfer on reaction with toluene-4-sulphonyl (tosyl) azide in the presence of triethylamine to afford a diazo-intermediate (14) electro-



(i) $4\text{-R-C}_6\text{H}_4\overset{+}{\text{N}}_2\text{Cl}^-$, NaOAc, EtOH, H_2O, 0°

(ii) NaOCl, NaOH or pyridine, H_2O, 0-5°

(iii) 30% w/v H_2O_2 aqu., NaOH, H_2O, room temp.

(iv) MnO_2, MeCN, room temp.

(v) Ac_2O, heat

(vi) AcCl or ClCO_2Et, Et_3N, room temp.

(vii) O_2, $\text{Me}_2\text{S=O}$, reflux

(viii) SOCl_2 or PCl_3, 1,4-dioxane or 1,2-dimethoxyethane, room temp.

(ix) $\text{Na}_2\text{S}_2\text{O}_4$, EtOH, H_2O room temp. or reflux or H_2, 10% Pd-C, 1,4-dioxane

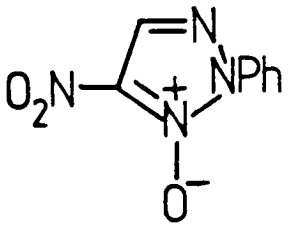
Scheme 4

cyclisation of which would yield the previously unknown 1-hydroxy-4-nitro-1H-1,2,3-triazole (15). Elaboration of this tautomeric compound (Scheme 3) by chlorination[107,81] then ammonolysis and further manipulation would provide a potential route to 4,5-dinitro-1H-1,2,3-triazole (12). Unfortunately, methazonic acid (13) failed to react with tosyl azide in the presence of triethylamine to give the nitro-N-hydroxytriazole (15). Instead this reaction gave only a poor yield of a red multicomponent oil.

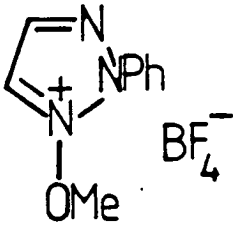
Despite the failure of the synthetic strategy outlined in Scheme 3, it was decided to investigate an analogous approach (Scheme 4) to 2-aryl-4,5-dinitro-2H-1,2,3-triazoles (24). It is well known[60,108] that methazonic acid (13) couples in alkaline solution with arene diazonium salts to afford high yields of the corresponding 1-nitroethane-1,2-dione 1-arylhydrazone 2-oximes. In the present studies it was found that methazonic acid (13) coupled smoothly with benzenediazonium chloride in aqueous ethanol in the presence of sodium acetate to afford a high yield (98%) of the known[108] compound, 1-nitroethane-1,2-dione 1-phenylhydrazone 2-oxime (19a). The melting-point of the product obtained in the present studies was significantly higher than that quoted[108] in the literature. However, it analysed correctly and showed mass, i.r., and ^{1}H n.m.r. spectral properties consistent with its formulation as the required hydrazone-oxime (19a). Methazonic acid (13) was also found to couple smoothly in weakly alkaline solution with 4-nitrobenzene-diazonium chloride to afford the 4-nitrophenyl derivative

(19b) in high yield (97%). This compound had been previously prepared[109] by oximation of the corresponding aldehyde (19a; O for NOH) and the melting point of the product obtained in the present studies agreed closely with the literature value.[109]

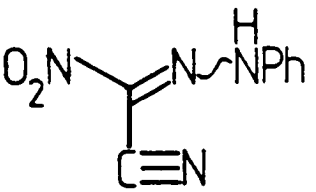
With the hydrazone-oximes (19a) and (19b) readily available in high yield attention was next directed to their oxidative cyclisation to the respective 4-nitro-2-aryl-2H-1,2,3-triazole 1-N-oxides (20a) and (20b). Related ethane-1,2-dione hydrazone oximes are reported[81,82] to be smoothly cyclised to the corresponding 2H-1,2,3-triazole 1-N-oxides by heating with copper(II) sulphate in aqueous pyridine. However, heating the nitro-compound (19a) with copper(II) sulphate in aqueous pyridine resulted in the consumption of the starting material with no apparent formation of any product. Fuming nitric acid, which smoothly cyclises ethane-1,2-dione dioximes to the corresponding furoxans[96] (see Chapter 3) converted the hydrazone-oxime (19a) into an unstable solid which immediately decomposed to a tar thus preventing its characterisation. Ceric ammonium nitrate in aqueous acetic acid, which also readily cyclises[101] ethane-1,2-dione dioximes to furoxans (see Chapter 3), decomposed the starting-material (19a) to water soluble products which could not be isolated for characterisation. The attempted oxidative cyclisation of the hydrazone-oxime (19a) to the triazole N-oxide (20a) using potassium ferricyanide in alkaline solution gave only a low yield of a solid whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture. In contrast 30% w/v aqueous hydrogen peroxide in



(25)



(26)



(27)

Scheme 5

aqueous sodium hydroxide converted the hydrazone-oxime (19a) into a product in low yield (20%) which analysed correctly and showed spectral properties consistent with the expected triazole N-oxide structure (20a). In particular its i.r. spectrum contained absorption due to a nitro-group but lack bands assignable to NH or OH substituents. Its ^{1}H n.m.r. spectrum contained a one proton singlet at δ9.13 which is substantially deshielded compared to the alkene proton in the starting hydrazone-oxime (19a) and can therefore be assigned to H-5 in the structure (20a). Significant deshielding of H-5 in the latter structure is a consequence of the anisotropic effect of the N-oxide substituent. The presence of the latter in the product of the oxidative cyclisation of the hydrazone-oxime (19a) is substantiated by a fragment ion at (M^+-16) in its mass spectrum.

The previously unreported 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) had a melting-point (146-149°) which differed substantially from the melting-point (114-120°) reported for the known 5-nitro isomer [Scheme 5; (25)]. Attempts to further verify the structure of the nitrotriazole N-oxide (20a) by reduction to the known[110] compound 4-nitro-2-phenyl-2H-1,2,3-triazole (21a) were unsuccessful. Thus, treatment of the N-oxide (20a) with sodium dithionite in aqueous ethanol under reflux gave no characterisable material while at room temperature only a low yield of a multicomponent gum was obtained. Hydrogenation over palladium-on-charcoal was without effect on the N-oxide (20a) which under

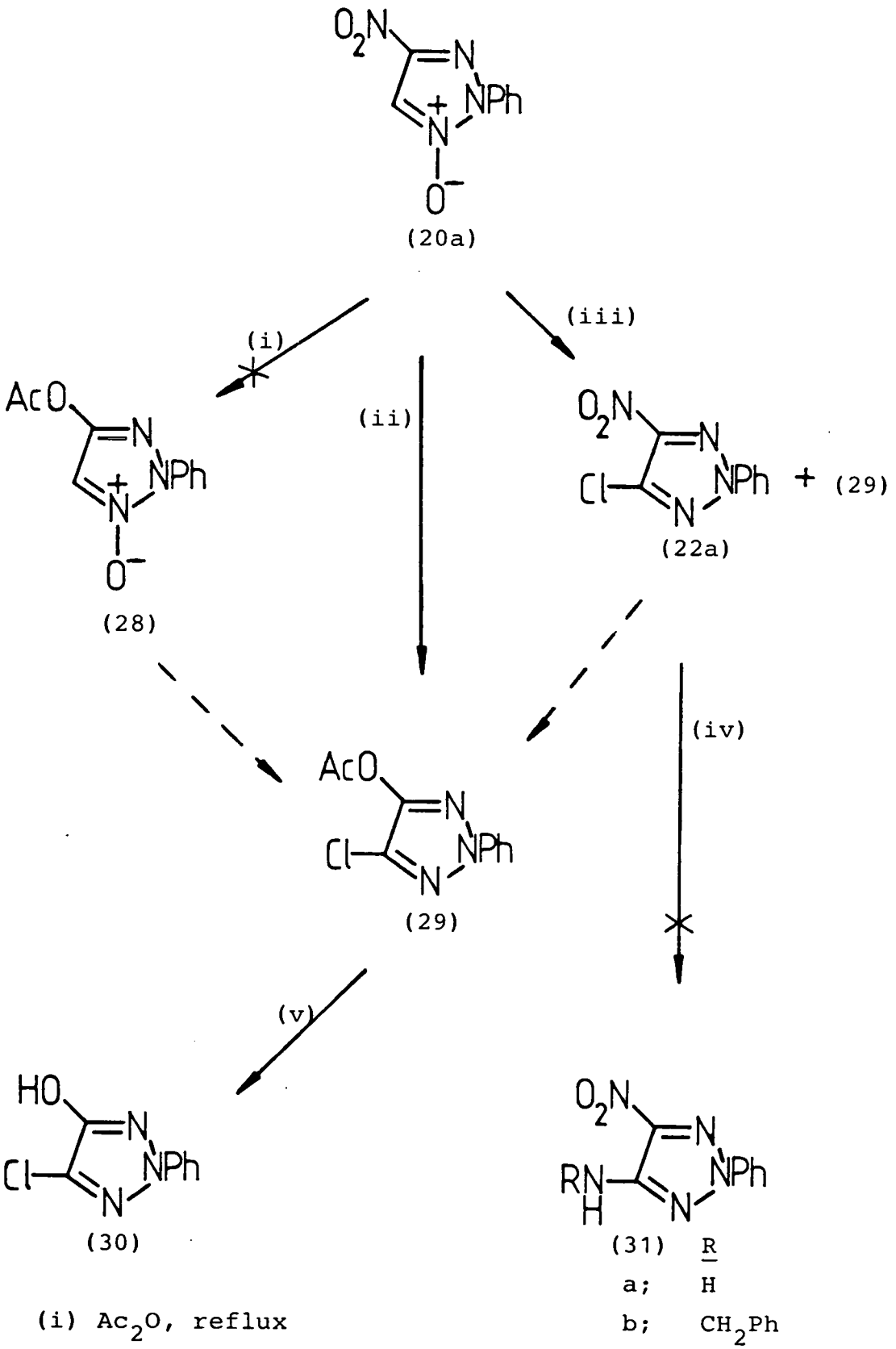
these conditions was recovered unchanged in good yield (73%). In contrast the nitro N-oxide (20a) was smoothly converted in high yield (91%) into the hydrazone-oxime (19a). This result demonstrates the ready reductive cleavage of the N(1)-N(2) bond in the N-oxide (20a) and explains the lack of formation of the parent nitrotriazole (21a) using reducing agents (e.g. sodium dithionite) which normally effect deoxygenations of this type.

In order to exclude the possibility that the lack of product formation observed in the dithionite reduction of the nitro N-oxide (20a) was not due to the instability of the expected nitrotriazole product (21a) it was decided to synthesise this compound by an alternative route. 4-Nitro-2-phenyl-1H-1,2,3-triazole (21a) has been obtained in low yield[110] (18-23%) by the reaction of 1-methoxy-2-phenyl-2H-1,2,3-triazolium tetrafluoroborate [Scheme 5; (26)] with nitrite ion and has also been briefly reported[111] as the product of phenyl isocyanate catalysed dehydration of the hydrazone-oxime (19a). In the present studies an attempt was first made to cyclodehydrate the hydrazone-oxime (19a) to the nitrotriazole (21a) by heating with acetic anhydride. This reaction gave a low yield (18%) of a product which analysed correctly for the nitrotriazole structure (21a) and had a melting-point which agreed closely with the literature value[110] for this compound. The mass, i.r. and ^{1}H n.m.r. spectra of the product further confirmed its identity as 4-nitro-2-phenyl-2H-1,2,3-triazole (21a). In an attempt to improve the yield of this compound the cyclisation of the hydrazone-

oxime (19a) using other acylating agents was also investigated. Treatment of the hydrazone-oxime (19a) with acetyl chloride in the presence of triethylamine at room temperature resulted in the formation of the nitrotriazole (21a) in only marginally improved yield (20%). In contrast, room temperature reaction of the hydrazone-oxime (19a) with ethyl chloroformate-triethylamine resulted in extensive dehydration without cyclisation to give the known[112,113] compound 2-nitro-2-oxoacetonitrile phenylhydrazone [Scheme 5; (27)], the nitrotriazole (21a) being in only low yield (10%).

Phosphorus pentachloride and thionyl chloride have been shown[99] to be useful reagents for the cyclodehydration of ethane-1,2-dione hydrazone oximes and dioximes to 2H-1,2,3-triazoles and furazans respectively. It was therefore decided to apply these reagents to the cyclodehydration of the hydrazone-oxime (19a) in the hope of obtaining a better yield of the nitrotriazole (21a). However, thionyl chloride in 1,4-dioxane at room temperature largely dehydrated the hydrazone-oxime (19a) to the nitrile (27), cyclodehydration to the nitrotriazole (21a) being only a minor pathway under these conditions. In contrast, treatment of the hydrazone-oxime (19a) with phosphorus pentachloride in 1,2-dimethoxyethane at room temperature gave a significantly improved yield (34%) of the nitrotriazole (21a) together with a low yield (16%) of the nitrile (27).

In order to pursue further the synthetic strategy for 4,5-dinitro-2H-1,2,3-triazoles outlined in Scheme 4 it was necessary to develop a method for the oxidative cyclisation



(i) Ac_2O, reflux
(ii) AcCl, reflux
(iii) AcCl, AcOH, reflux
(iv) $PhCH_2NH_2$, EtOH, reflux
(v) NaOH, H_2O, reflux

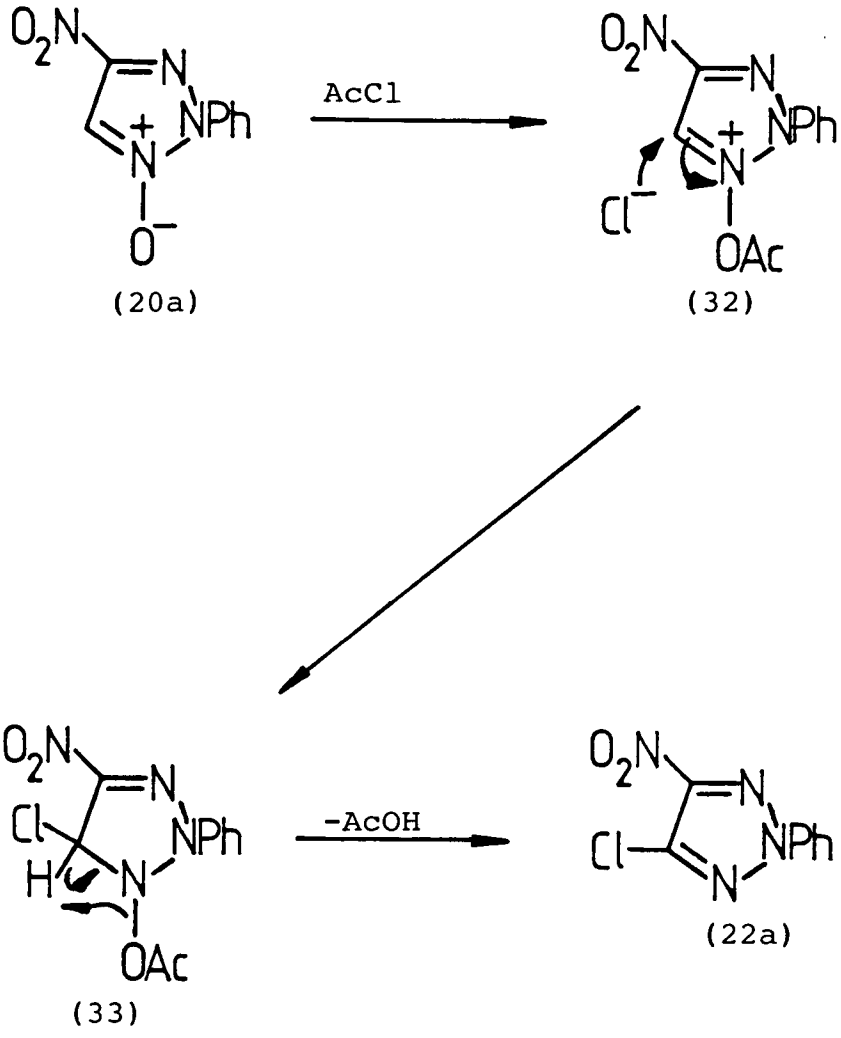
Scheme 6

of the hydrazone-oximes (19) which would give improved yields of nitrotriazole N-oxides such as (20a). As a first step in this direction the oxidative cyclisation of the hydrazone-oxime (19a) by oxygen in dimethyl sulphoxide at room temperature was investigated. Surprisingly this reaction gave only a low yield (20%) of the nitrotriazole (21a) rather than the N-oxide (20a). The use of activated manganese dioxide as the oxidising agent in acetonitrile solution at room temperature was more successful and gave the nitrotriazole N-oxide (20a) in improved though not high yield (42%). In contrast, under the same conditions, the nitrophenylhydrazone-oxime (19b) afforded only a good recovery (88%) of unreacted starting-material. Sodium hypochlorite in cold aqueous alkali converted the hydrazone-oxime (19a) only in low yield (25%) into the desired N-oxide (20a) while the same reaction using triethylamine instead of sodium hydroxide as the catalyst afforded only a complex mixture. On the other hand the use of sodium hypochlorite as the oxidant in conjunction with pyridine led to the formation of the nitrotriazole N-oxide (20a) in acceptable yield (63%). Unfortunately these conditions did not extend to the nitrophenylhydrazone-oxime (19b) which treated with sodium hypochlorite-pyridine gave a complex mixture which yielded no identifiable material.

Having developed a suitable method for the synthesis of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) attention was next turned (Scheme 6) to its chlorinative deoxygenation to the previously undescribed compound 4-chloro-5-nitro-2-

phenyl-2H-1,2,3-triazole (22a). 2-Aryl-2H-1,2,3-triazole 1-N-oxides unsubstituted at the 5-position are known[107,81] to undergo chlorinative deoxygenation on treatment with hydrogen chloride[107] or concentrated hydrochloric acid,[81] or acetyl chloride[81] to afford the corresponding 2-aryl-4-chloro-2H-1,2,3-triazoles. In the present studies treatment of the nitrotriazole N-oxide (20a) with hydrogen chloride in glacial acetic acid afforded only a good recovery (66%) of the unreacted starting-material with no evidence for the formation of the required chloro-nitrotriazole (22a). On the other hand heating the N-oxide (20a) with acetyl chloride gave a low yield (36%) of a product which gave analytical and mass spectral data consistent with the molecular formula $C_{10}H_8ClN_3O_2$. The formation of this product as 4-acetoxy-5-chloro-2-phenyl-2H-1,2,3-triazole (29) is based on its spectroscopic and chemical properties. In particular its i.r. spectrum lacked bands due to a nitro-group but contained high frequency carbonyl absorption at 1780 cm^{-1} assignable to an enol acetate substituent. The presence of the latter was further confirmed by alkaline hydrolysis of the compound to give a high yield of the corresponding hydroxytriazole (30). This product gave analytical and mass spectral data and showed spectroscopic properties fully consistent with the assigned structure.

In contrast to the result using acetyl chloride alone, heating the nitrotriazole N-oxide (20a) with acetyl chloride in glacial acetic acid gave a readily separated mixture of two products that formed in minor amount (yield 42%) being

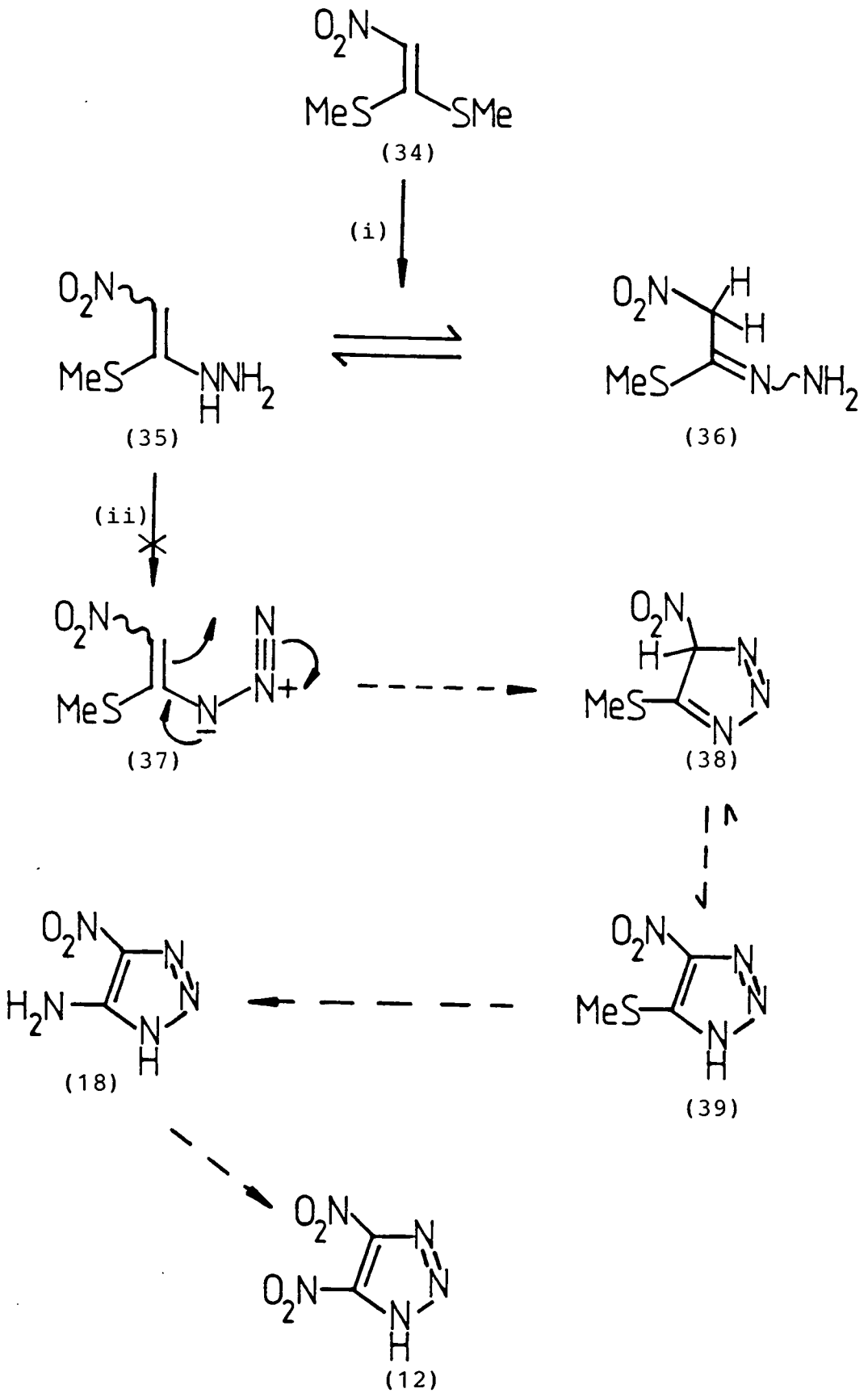


Scheme 7

identical in every respect to the acetoxy-chlorotriazole (29) obtained before. The major product (yield 56%) gave analytical and spectral data in accord with its identity as the required 4-chloro-5-nitro-2-phenyl-2H-1,2,3-triazole (22a). The formation of this product can be explained in terms of a mechanism (Scheme 7) involving the initial reaction of the N-oxide (20a) with acetyl chloride to afford a salt-like intermediate (32). Nucleophilic attack by chloride ion at the 5-position in this intermediate would then give an intermediate adduct (33) loss of the elements of acetic acid from which affords the observed product (22a). The reason for the apparent lack of formation of this product in the reaction of the N-oxide (20a) with acetyl chloride alone is not clear. Nor is it clear how the acetoxy-chlorotriazole (29) is formed from the nitrotriazole N-oxide (20a). A route (Scheme 6) involving initial nucleophilic displacement of the nitro-group in the N-oxide (20a) by an acetoxy-group under conditions of acetylation followed by chlorinative deoxygenation of the resulting acetoxytriazole N-oxide [(28)→(29)] is excluded by the stability of the nitro-triazole N-oxide (20a) to acylation under forcing conditions. Thus, the nitro-triazole N-oxide (20a) was largely unaffected (recovery 56%) after prolonged heating in acetic anhydride. In addition it was recovered in good yield (78%) after treatment with cold aqueous alkali though hot aqueous alkali converted it into complex gums which yielded no identifiable material. Complex mixtures also resulted on attempted reaction of the nitro-triazole N-oxide (20a) with ethanolic sodium ethoxide both at

room temperature and under reflux. Formation of the acetoxy-chlorotriazole (29) by initial chlorinative deoxygenation of the nitrotriazole N-oxide (20a) to the chloro-nitrotriazole (22a) followed by nucleophilic displacement of the nitro-group in the latter can also be excluded. Thus the chloro-nitrotriazole (22a) was recovered unchanged in high yield (91%) after heating under reflux with sodium acetate in glacial acetic acid. In contrast to its ready reaction with acetyl chloride, the nitrotriazole N-oxide (20a) was largely unaffected (recovery 60%) by heating under reflux with toluene-4-sulphonyl (tosyl) chloride in 1,4-dioxane.

With 4-chloro-5-nitro-2-phenyl-2H-1,2,3-triazole (22a) readily available its reactivity towards ammonolysis was investigated with a view to the synthesis of 4-amino-5-nitro-2-phenyl-2H-1,2,3-triazole (31a) a key intermediate in the proposed synthetic strategy for 4,5-dinitro-2-phenyl-2H-1,2,3-triazole (24a) (see Scheme 4). As a model for the more practically complicated formation of the amino-nitrotriazole (31a) from the chloro-nitrotriazole (22a), the attempted reaction of the latter with benzylamine was first investigated. However the chloro-nitrotriazole (22a) was recovered unchanged in good yield (78%) after heating under reflux with benzylamine in ethanol. This inertness of the potentially reactive chlorine atom in the chloro-nitrotriazole (22a) to nucleophilic displacement was surprising and prompted the investigation of other routes to 4-amino-2-aryl-5-nitro-2H-1,2,3-triazoles.



(i) NH_2NH_2, EtOH, reflux

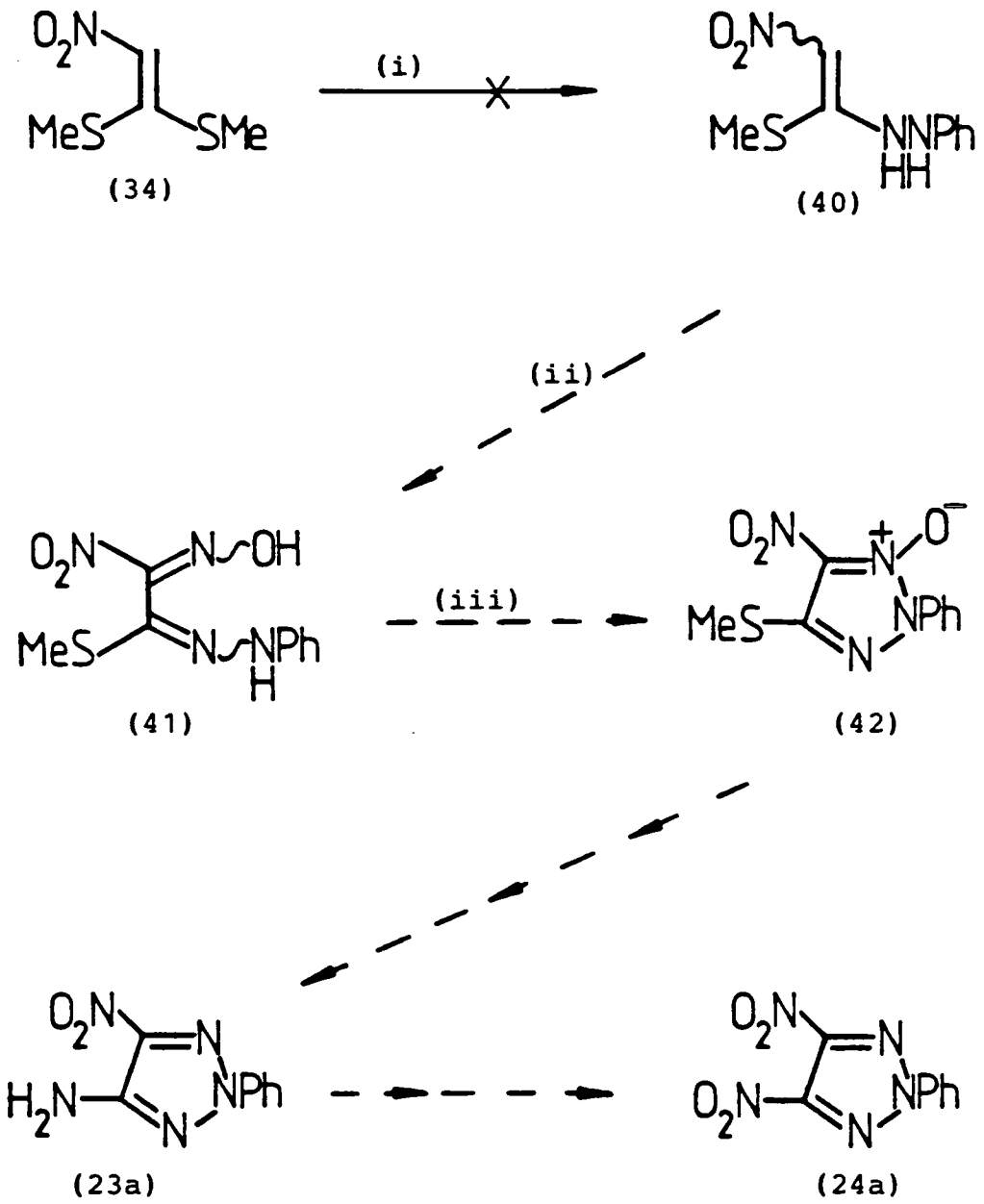
(ii) $NaNO_2$, HCl, 0-5°

Scheme 8

4.4 Synthetic Approaches to 4,5-Dinitro-1,2,3-triazole Derivatives Based on Cyclisation Reactions of Methyl 2-Nitroethanimidothioate Derivatives

In view of the inertness of the chlorine substituent in the chloro-nitrotriazole (22a) to nucleophilic displacement it was decided to develop synthetic routes to 4-nitro-5-methylthio-1,2,3-triazole derivatives in the hope that the methylthio substituent would be more amenable to ammonolysis thus allowing access to 4-amino-5-nitro-1,2,3-triazoles and hence the target 4,5-dinitro-1,2,3-triazoles. No example of a 4-methylthio-5-nitro-1,2,3-triazole derivative has been reported in the literature to date and it was decided initially to investigate the route to the parent compound 4-methylthio-5-nitro-1*H*-1,2,3-triazole (39) as outlined in Scheme 8. This involved the reaction of the readily available 1,1-bis-methylthio-2-nitroethene (34) with hydrazine to afford the known, tautomeric, 1-hydrazino-1-methylthio-2-nitroethene [(35)⇌(36)] followed by treatment of the latter with sodium nitrite in aqueous hydrochloric acid. However, this reaction afforded no characterisable material.

In an alternative approach (Scheme 9) to a 4-methylthio-5-nitro-1,2,3-triazole derivative suitable for further elaboration to a 4,5-dinitro-1,2,3-triazole attempts were made to synthesise 1-(2-*N*-phenylhydrazino)-1-methylthio-2-nitroethene (40). The intention was then to nitrosate this compound to give the oximino-derivative (41) which it was hoped could be oxidatively cyclised to 4-methylthio-5-nitro-2-phenyl-2*H*-1,2,3-triazole 1-*N*-oxide (42). However, this synthetic



(34) (40) (41) (42) (23a) (24a)

(i) $PhNHNH_2$, 1,4-dioxane, room temp., or EtOH, or 1,4-dioxane, reflux

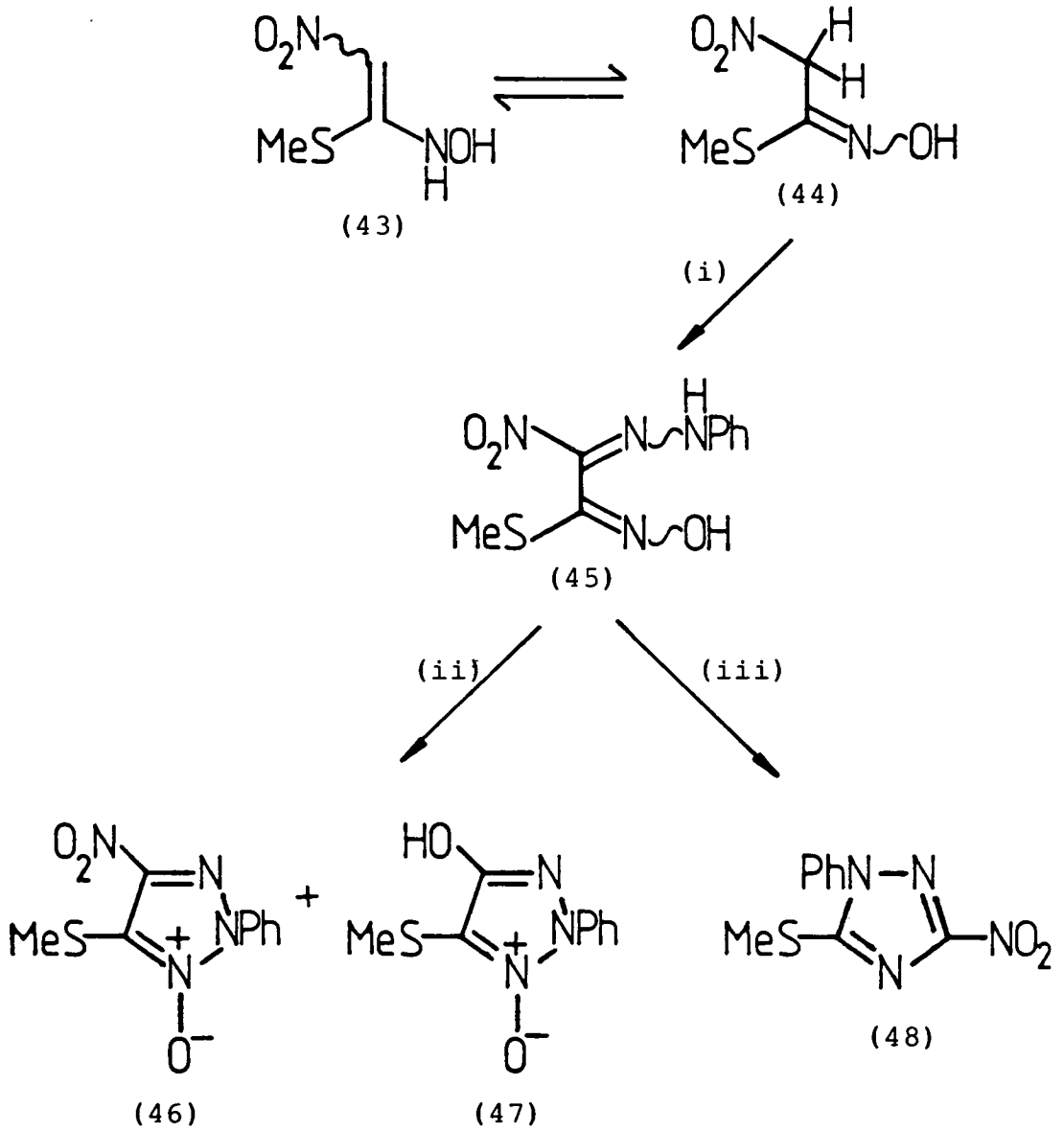
(ii) HNO_2

(iii) [O]

Scheme 9

approach was thwarted by the failure of 1,1-bis-methylthio-2-nitroethene (34) to react with phenylhydrazine to yield the hydrazino-methylthio-nitroethene (40). Thus, heating the nitroethene derivative (34) with phenylhydrazine in ethanol or 1,4-dioxane under reflux led only to intractable gums which in 1,4-dioxane at room temperature the starting-material (34) was recovered in high yield (89%).

Having failed to synthesise the methylthio-nitrotriazole N-oxide (42) using the synthetic route outlined in Scheme 9 attention was turned to the synthesis (Scheme 10) of the isomeric triazole N-oxide (46) and the parent methylthio-nitrotriazole (48). The tautomeric N-hydroxy-2-nitroethan-imidothioate [(43)⇌(44)], readily prepared as described in Chapter 3 , reacted smoothly with benzenediazonium chloride in the presence of sodium acetate to afford a high yield (88%) of the expected methyl N-hydroxy-2-nitro-2-oxoethanimido-thioate phenylhydrazone (45). This product analysed correctly and showed mass, i.r., and ^{1}H n.m.r. spectral properties consistent with the assigned structure. In an initial attempt to effect the oxidative cyclisation [(45)→(46)], the hydrazone-oxime (45) was stirred with manganese dioxide in acetonitrile at 0°. However this reaction gave only unreacted starting-material (45) (53%). In contrast, repetition of this reaction at room temperature gave low yields of an unstable yellow product and a stable colourless product. The unstable yellow product decomposed on attempted purification but showed a parent ion at m/e 252 and a fragment ion at m/e 236 corresponding to (M^+-16) in its mass spectrum which allow its



(i) $PhN_2^+Cl^-$, NaOAc, EtOH, H_2O

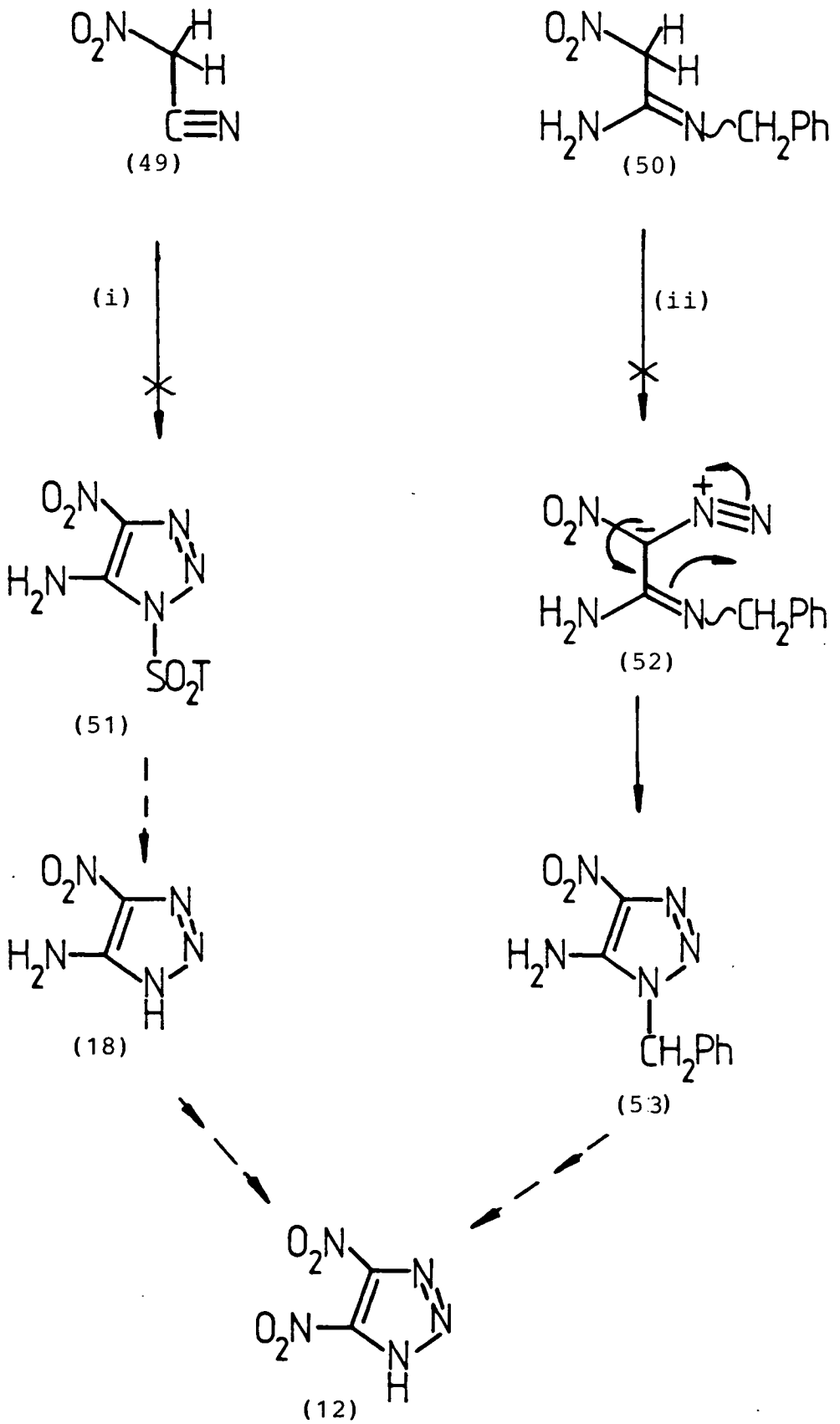
(ii) MnO_2, MeCN, room temp.

(iii) $SOCl_2$, 1,4-dioxane, 10-20°

Scheme 10

tentative formulation as the required 5-methylthio-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (46). The stable colourless product analysed correctly for $C_9H_9N_3O_2S$ and is formulated as 4-hydroxy-5-methylthio-2-phenyl-2H-1,2,3-triazole 1-N-oxide (47) on the basis of its spectral properties. Thus its i.r. spectrum lacked bands due to nitro-group but contained broad absorption at 3200-2300 cm^{-1} assignable to a hydroxyl group. Its ^1H n.m.r. spectrum showed a three proton singlet at δ2.38 demonstrating the presence of a methylthio-substituent while its mass spectrum showed a fragment ion at m/e 207 corresponding to (M^+-16) diagnostic for the presence of an N-oxide substituent. Treatment of 4-nitro-2-aryl-2H-1,2,3-triazole 1-N-oxide with aqueous acetic acid results in replacement of the nitro-group by a hydroxyl substituent.[114] Similar displacement of the nitro-group in the triazole N-oxide (46) by traces of water in the reaction mixture would account for the formation of the hydroxytriazole N-oxide (47) in the oxidative cyclisation of the hydrazone-oxime by manganese dioxide.

The very low yield of the methylthio-nitrotriazole N-oxide (46) obtained in the oxidative cyclisation of the hydrazone-oxime (45) prevented its use as a starting-material for the synthesis of the required amino-nitro-1,2,3-triazole (23a) and hence the dinitro-1,2,3-triazole (24a). The alternative route to these two compounds through the intermediacy of 4-methylthio-5-nitro-2-phenyl-2H-1,2,3-triazole (48) was also impractical. Thus, though treatment of the hydrazone-oxime (45) with thionyl chloride in 1,4-dioxane at



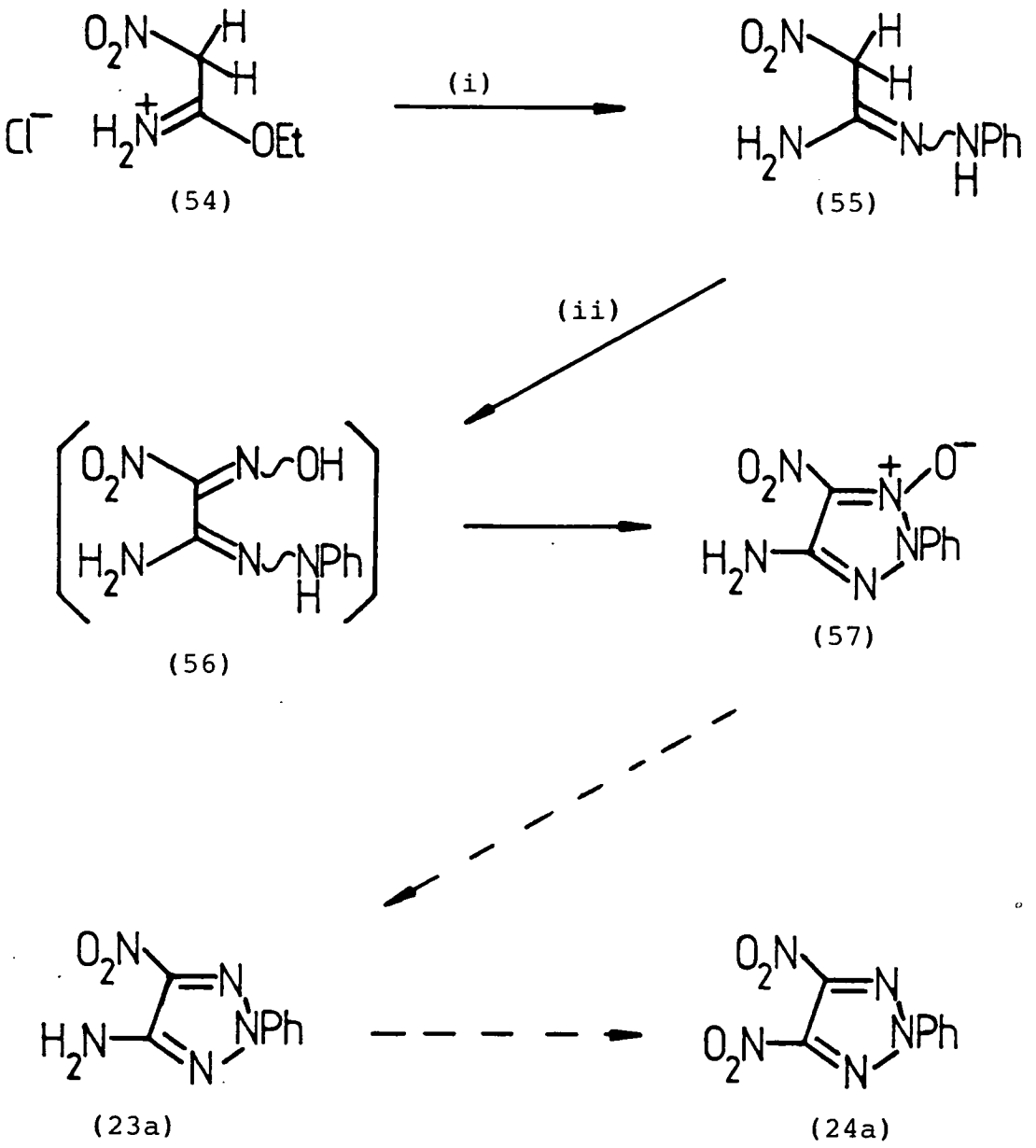
(i) TSO_2N_3, Et_3N, MeCN, room temp. (T = 4-tolyl)
(ii) TSO_2N_3, Et_3N, MeCN, 0°

Scheme 11

room temperature gave a product which analysed correctly and showed mass, i.r. and ^{1}H n.m.r. spectra consistent with the 1,2,4-triazole structure (48) the yield obtained (23%) was insufficient to justify its use as the precursor of the 1,2,4-triazole derivatives (71) and (75) (Scheme 16, see later).

4.5 Synthetic Approaches to 4,5-Dinitro-1,2,3-triazole Derivatives Based on Cyclisation Reactions of 2-Nitroacetamidine, 2-Nitroacetamidrazone, and 2-Nitroacetamidoxime Derivatives

Because of the inefficiency or impracticality of synthetic routes to 4-amino-5-nitro-1,2,3-triazoles (and hence 4,5-dinitro-1,2,3-triazoles) from 4-chloro-5-nitro-1,2,3-triazoles or 4-methylthio-5-nitro-1,2,3-triazoles (see Sections 4.3 and 4.4) more direct synthesis of 4-amino-5-nitro-1,2,3-triazole derivatives were sought. To this end the base-catalysed reaction (Scheme 11) of 2-nitroacetonitrile (see Chapter 2) with toluene-4-sulphonyl (tosyl) azide was investigated. It is well known[115] that acetonitrile derivatives undergo base-catalysed reaction with tosyl azide to afford amino-1,2,3-triazole derivatives and in the case of nitroacetonitrile (49) 5-amino-4-nitro-1-(toluene-4-sulphonyl)-1H-1,2,3-triazole (51) was the expected product. Hydrolytic removal of the tosyl substituent in this compound would allow access to 5-amino-4-nitro-1H-1,2,3-triazole (18) and further 4,5-dinitro-1H-1,2,3-triazole (12). In practice the reaction of nitroacetonitrile (49) with tosyl



(i) $PhNHNH_2$, EtOH, 0°

(ii) KNO_2 or $NaNO_2$, AcOH, H_2O, 4-8°

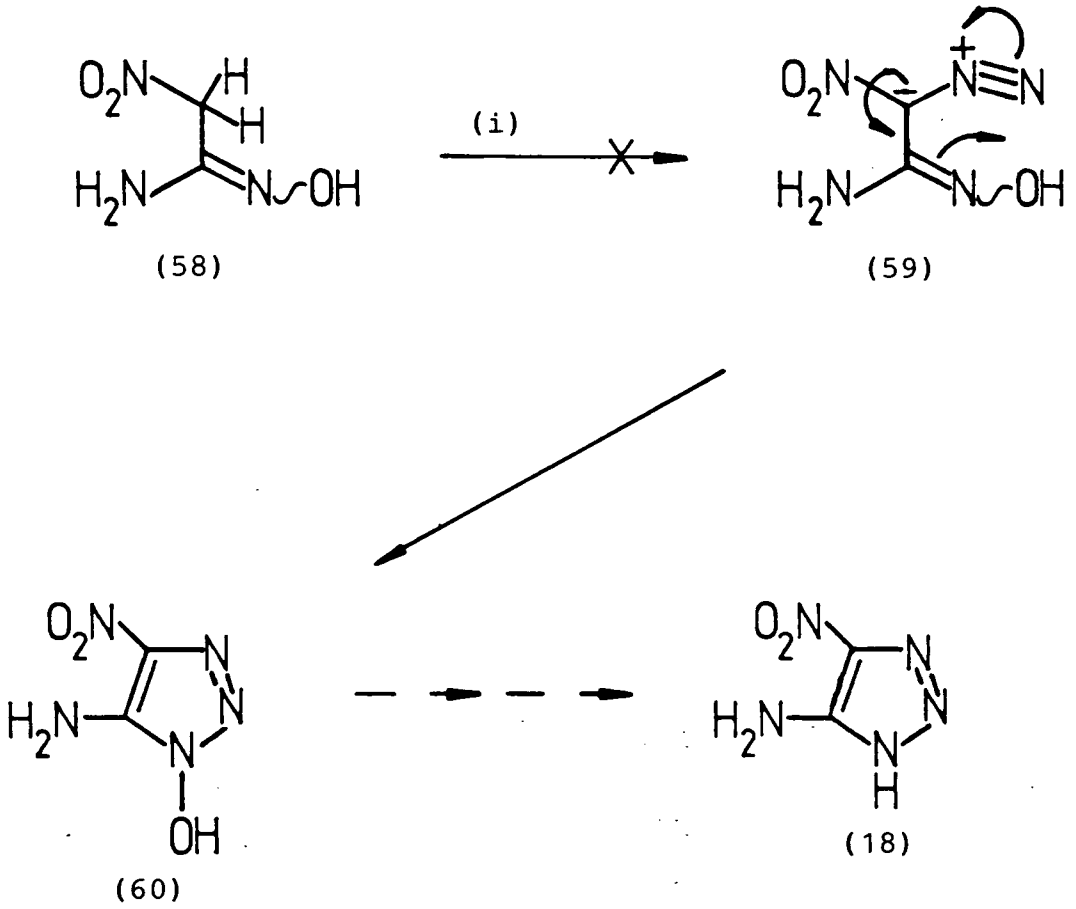
Scheme 12

azide in the presence of triethylamine gave in addition to toluene-4-sulphonamide and unreacted tosyl azide, only intractable gums which yielded no other identifiable material.

Having failed to convert nitroacetonitrile (49) into the amino-nitro-1,2,3-triazole derivative (51), attention was next turned to the base catalysed diazo-transfer reaction[115] of N-benzyl-2-nitroacetamidine (50) whose synthesis has already been described in Chapter 2. By analogy with related diazo-transfer processes[116] the base catalysed reaction of the acetamidine derivative (50) with tosyl azide was expected to afford, via the spontaneous cyclisation of the initially formed diazo-intermediate (52), 5-amino-1-benzyl-4-nitro-1H-1,2,3-triazole (53). The intention was then to use this compound as a source of the dinitrotriazole derivative (12). Disappointingly, attempts to effect the base-catalysed reaction of the acetamidine derivative (50) with tosyl azide to give the amino-nitro-triazole (53) were unsuccessful. The use of triethylamine as the basic catalyst in this reaction at 0° afforded only a good recovery (77%) of the unreacted starting-material (50), while in the presence of piperidine at 0-20° the only product formed (yield 75%) was N-tosylpiperidide.

In view of the failure of 5-amino-4-nitro-1H-1,2,3-triazole derivatives outlined in Scheme 11, it was next decided to investigate an approach (Scheme 12) to the required amino-nitro-triazole and dinitrotriazole derivatives (23a) and (24a) from the previously unknown compound 4-amino-5-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (57). Reaction of 1-amino-1-ethoxy-2-nitroethane hydrochloride (54), readily

prepared as described in Chapter 2, with phenylhydrazine afforded a high yield (89%) of the expected amidrazone (55) which analysed correctly and showed spectroscopic properties consistent with its assigned structure. Initially the nitrosation of the amidrazone (55) to give the required hydrazone-oxime (56) was attempted using potassium nitrite in aqueous acetic acid at low temperature. However this reaction yielded a product in low yield (25%) which gave combustion analysis and mass spectrum corresponding to the molecular formula $C_8H_7N_5O_3$, rather than $C_8H_9N_5O_3$ expected for the hydrazone-oxime (56). In addition it lacked the acidity expected for the hydrazone-oxime (56). The compound showed i.r. absorption at 3470-3300 cm^{-1} and 1560 and 1350 cm^{-1} demonstrating the presence of a primary amino group and a nitro-substituent respectively. In addition the presence of an N-oxide substituent was indicated by a fragment ion peak at m/e 205, corresponding to (M^+-16). On the basis of the spectroscopic evidence and the product's molecular formula it is assigned the amino-nitrotriazole N-oxide structure (57). This product presumably arises from the acetamidrazone derivative (55) by formation and spontaneous *in situ* oxidation of the hydrazone-oxime (56). In an attempt to improve the yield of 4-amino-5-nitro-2-phenyl-2H-1,2,3-1N-oxide (57), the acetamidine (55) was reacted with sodium nitrite in aqueous acetic acid. The use of one equivalent of sodium nitrite raised the yield of the N-oxide (57) to 37% while two equivalents of sodium nitrite marginally improved the yield to 44%. However,



(58) (59) (60) (18)

(i) TSO_2N_3, Et_3N, Me_2NCHO, 0°, (T = 4-tolyl)

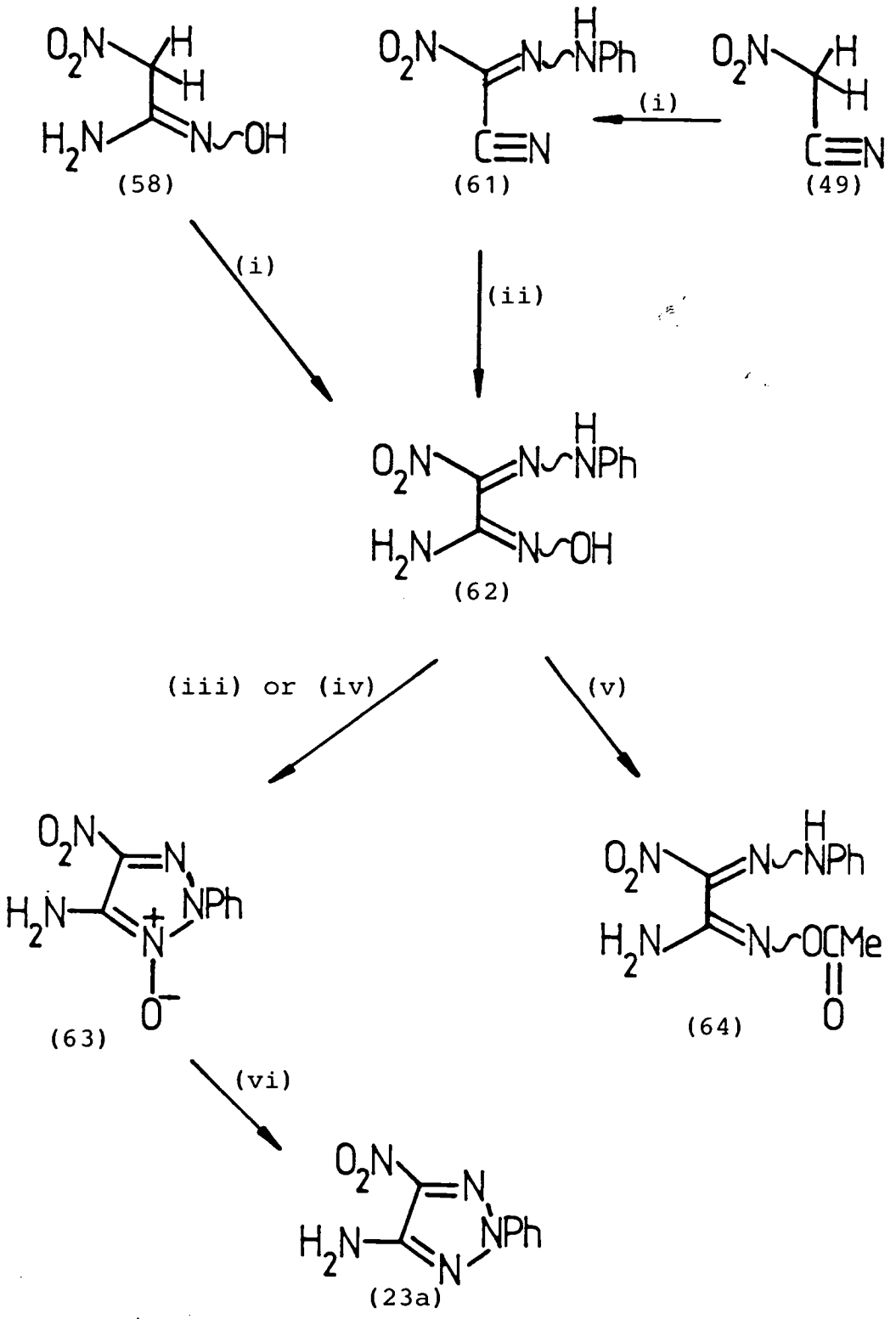
Scheme 13

despite this improvement in yield it was considered that the triazole N-oxide (57) was not a viable precursor of the required amino-nitrotriazole (23a). Yet other routes to this compound and 5-amino-4-nitro-1H-1,2,3-triazole (18) (Schemes 13 and 14) were therefore investigated using 2-nitroacetamidoxime (58) (see Chapter 3) as the key starting-material.

Initially an attempt was made (Scheme 13) to effect the base-catalysed diazo-transfer[115,116] reaction of 2-nitro-acetamidoxime (58) with tosyl azide to afford through the intermediacy of the diazo-species (59), 5-amino-1-hydroxy-4-nitro-1H-1,2,3-triazole (60) a potential precursor of the required amino-nitro-1,2,3-triazole (18). However the reaction of the amidoxime (58) with tosyl azide in the presence of triethylamine at room temperature led to an intractable oil which yielded no identifiable material.

Having failed to synthesise the amino-nitrotriazole (18) from 2-nitroacetamidoxime (58) attention was next turned to the exploitation of this compound for the synthesis (Scheme 14) of 5-amino-2-aryl-4-nitro-2H-1,2,3-triazole 1-N-oxides (62) and hence by deoxygenation 4-amino-5-nitro-2-aryl-2H-1,2,3-triazoles such as (64). The initial strategy was to couple 2-nitroacetamidoxime (58) with benzenediazonium chloride to give the hydrazone-oxime (62) then oxidatively cyclise this compound to the desired 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63).

In practice the amidoxime derivative (58) coupled smoothly with benzenediazonium chloride in aqueous ethanol containing sodium acetate at 0-5° to afford a good yield (82%) of a



(i) $PhN_2^+Cl^-$, NaOAc, EtOH, H_2O, 0-10°

(ii) $NH_3^+OHCl^-$, Na_2CO_3, EtOH, room temp.

(iii) NaOCl, pyridine, H_2O, room temp.

(iv) MnO_2, MeCN, room temp.

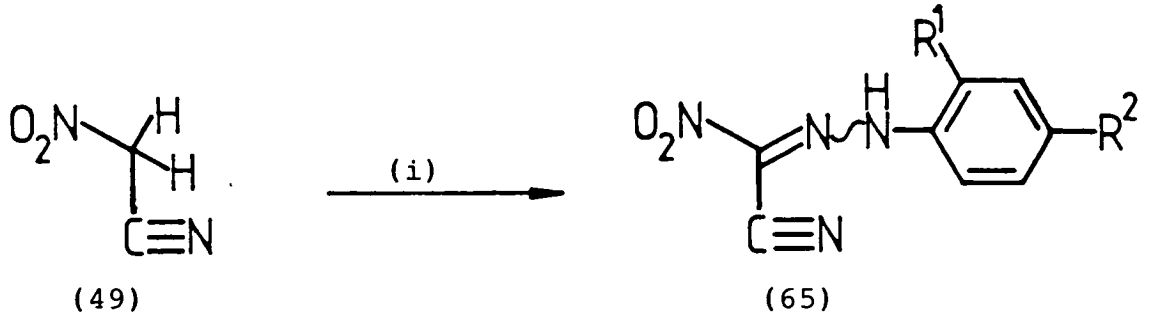
(v) $MeC(=O)Cl$, Et_3N, 1,4-dioxane, room temp.

(vi) PCl_3, 1,4-dioxane, reflux

Scheme 14

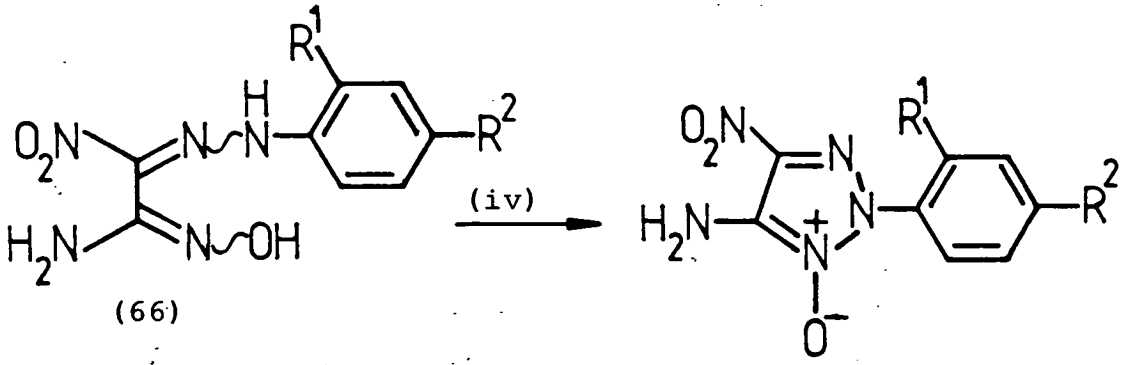
product which analysed correctly and showed spectroscopic and chemical properties consistent with the expected hydrazone-oxime structure (62). Thus, its i.r. spectrum, in addition to nitro absorption at 1540 and 1300 cm^{-1}, and C=N absorption at 1640 and 1615 cm^{-1}, contained a series of bands at 3500-3320 cm^{-1} consistent with the amino and oximino components of an amidoxime substituent, and the amino component of a hydrazone group. Four exchangeable protons in the product's ^1H n.m.r. spectrum are likewise attributable to the NH and OH protons in the structure (62). Treatment of the compound with acetyl chloride in the presence of triethylamine afforded a high yield (93%) of a monoacetyl derivative whose i.r. spectrum showed high frequency carbonyl absorption at 1760 cm^{-1} consistent with the oxime acetate structure (64). The structure of the hydrazone-oxime (62) was fully confirmed by its alternative synthesis (Scheme 14) by coupling 2-nitroacetonitrile (49) with benzenediazonium chloride to afford the known[115] compound, 2-nitro-2-oxoacetonitrile phenylhydrazone (61). The latter reacted smoothly with hydroxylamine to afford a high yield (90%) of the hydrazone-oxime (62) identical in every respect to the product derived from 2-nitroacetamidoxime (58).

With 2-nitro-2-oxoacetamidoxime phenylhydrazone (62) readily available its oxidative cyclisation to the amino-nitrotriazole N-oxide (63) was next investigated. Initially this cyclisation was attempted using aqueous sodium hypochlorite in the presence of triethylamine as the basic catalyst. However these conditions merely afforded an



(49) (65)

(ii) or (iii)



(66) (67)

	R^1	R^2
a;	H	Me
b;	H	Cl
c;	H	NO_2
d;	NO_2	NO_2

(i) $Ar\overset{+}{N}_2Cl^-$, NaOAc, EtOH, H_2O, 0-20°

(ii) 2,4-$(NO_2)C_6H_3\overset{+}{N}_2$, AcOH, H_2O, 0-20°

(iii) $\overset{+}{N}H_3OHCl^-$, Na_2CO_3, EtOH, room temp.

(iv) MnO_2, MeCN, room temp.

Scheme 15

intractable solid. The use of aqueous sodium hypochlorite in conjunction with pyridine on the other hand was more successful and led to a moderate yield (48%) of a solid product which analysed correctly for the expected 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide structure (63). This structure for the product was fully confirmed by its i.r. spectrum which showed bands typical of amino and nitro-substituents. The mass spectrum of the product in addition to a strong parent ion peak, contained a peak at m/e 205 due to the fragment ion (M^+-16) a feature typical of N-oxide structures. A much improved yield (84%) of the triazole N-oxide (63) was obtained when the oxidative cyclisation of the hydrazone-oxime (62) was carried out using activated manganese dioxide in acetonitrile.

The route outlined in Scheme 14 for the synthesis of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide [(49)→(61)→(63)] proved to be applicable in general to the synthesis of 5-amino-2-aryl-4-nitro-2H-1,2,3-triazole N-oxides (Scheme 15) a hitherto unknown class of 1,2,3-triazole derivatives. Thus, 2-nitroacetonitrile (49) coupled smoothly with a variety of arenediazonium salts in the presence of sodium acetate to give uniformly good yields (66-84%) of the corresponding 2-nitro-2-oxoacetonitrile arylhydrazones (65), the only exception being the 4-chloro derivative (65b) which was obtained in only 42% yield together with intractable gums. In the synthesis of the 2,4-dinitrophenyl derivative (65d), the diazotisation of the insoluble and weakly basic 2,4-dinitroaniline had to be carried out in glacial acetic acid

and the coupling accomplished in the same solvent. The analytical and spectroscopic properties of the aryl-hydrazone (65a-d) were fully in accord with the assigned structures. The 4-methyl derivative (65a) and the 4-nitro derivative (65c) were already described in the literature having been prepared by an alternative route.[117] However, though the melting-point (126°) of the 4-methyl derivative (65a) obtained in the present studies agreed closely with that (126°) reported in the literature,[117] the melting-point (158°) of the 4-nitro derivative (65c) was substantially higher than the literature value (148°).[117] The reason for this discrepancy is not clear but in view of its further transformation into the hydrazone-oxime (66c), the structure of the 4-nitrophenylhydrazone (65c) obtained in the present studies is not considered to be in any doubt.

All of the 2-nitro-2-oxoacetonitrile arylhydrazones (65a-d) reacted smoothly with hydroxylamine hydrochloride in ethanol at room temperature in the presence of sodium carbonate to give good to excellent yields (58-94%) of the corresponding and previously unreported 2-nitro-2-oxoacetamidoxime arylhydrazones (66a-d) all of which analysed correctly and showed spectroscopic properties fully consistent with the assigned structures. Stirring the hydrazone-oximes (66a-d) in acetonitrile with activated manganese dioxide at room temperature resulted in their ready cyclisation to the 5-amino-2-aryl-4-nitro-2H-1,2,3-triazole 1-N-oxides (67a-d) in good to excellent yield (67-97%). All of the triazole N-oxides (67a-d) analysed correctly and showed the i.r. and

^{1}H n.m.r. absorption expected for these structures. In addition the mass spectra of all of the triazole N-oxides (67a-d) as well as exhibiting the respective parent ion peaks contained fragment ion peaks corresponding to (M^+-16) and characteristic of N-oxide structures.

The poor nucleophilicity of the amino-substituent in the triazole N-oxide (63) expected from the adjacency of the nitro and N-oxide substituents was born out by its reluctance to undergo acylation reactions. Heating under reflux in acetic anhydride or treatment with acetyl chloride in the presence of triethylamine at room temperature gave only uncharacterisable gums while phenyl isocyanate at room temperature was without effect, the starting-material (63) being recovered in quantitative yield.

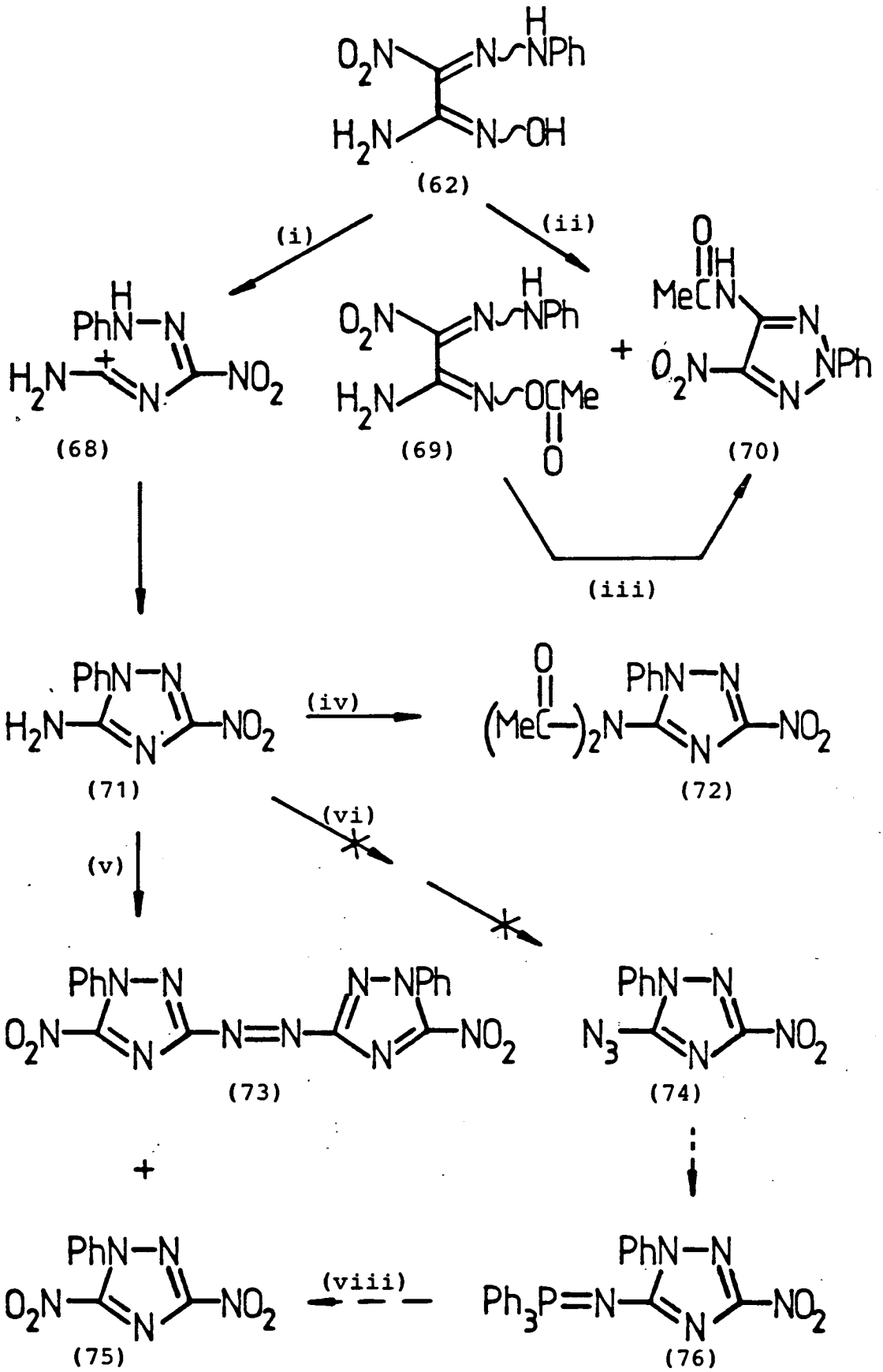
Attempts to deaminate the amino-nitrotriazole N-oxide (63) either hydrolytically or under diazotisation conditions were also unsuccessful. Thus, heating the N-oxide (63) with aqueous sodium hydroxide resulted in the destruction of the molecule whereas after similar treatment with aqueous sulphuric acid the starting-material was recovered unchanged in quantitative yield. The attempted diazotisation of the amino-nitrotriazole N-oxide (63) using sodium nitrite and hydrochloric acid in glacial acetic acid followed by hydrolytic decomposition of the diazotisation mixture gave only an intractable gum which yielded no well defined material. An attempt to diazotise the amino-nitrotriazole (63) with sodium nitrite and hydrochloric acid in glacial acetic acid then couple with β-naphthol in aqueous sodium hydroxide afforded

only a low recovery (36%) of the starting N-oxide (63).

Since the original intention was to use the amino-nitrotriazole N-oxide as a source of the parent amino-nitrotriazole (23a) the behaviour of the former compound towards reduction was next investigated. Disappointingly the attempted hydrogenolysis of the N-oxide (63) over 10% palladium-on-charcoal in 1,2-dimethoxyethane gave only a high recovery (86%) of starting-material while the use of glacial acetic acid as the solvent in this reaction afforded an intractable red oil. Heating the N-oxide (63) with sodium dithionite in aqueous ethanol gave only a small amount of an uncharacterisable gum rather than the expected amino-nitrotriazole (23a). Treatment with sodium borohydride in aqueous 1,4-dioxane at room temperature left the N-oxide (63) largely unchanged (recovery 82%). In contrast, deoxygenation of the amino-nitrotriazole N-oxide (63) by heating with phosphorus trichloride in 1,4-dioxane afforded a very low yield (8%) of a product which gave analytical and mass spectral data consistent with its formulation as the required 4-amino-5-nitro-2-phenyl-2H-1,2,3-triazole (23a). However, the very low yield of this product obtained in the deoxygenation of the N-oxide (63) excluded the latter as a practical precursor of the amino-nitrotriazole (23a). It was therefore decided at this stage to seek an alternative synthesis of the amino-nitrotriazole (23a) involving cyclodehydration of the hydrazone-oxime (62).

Treatment of the hydrazone-oxime (62) with thionyl chloride in 1,4-dioxane at low temperature afforded a good

yield (68%) of a product which analysed correctly for the expected amino-nitro-1,2,3-triazole (23a) but had a melting-point (210-211°) markedly higher than that (168-170°) of the product derived by deoxygenation of the amino-nitrotriazole N-oxide (63). The i.r. spectrum of the product derived from the hydrazone-oxime (62) showed bands at 3430-3150 cm^{-1} and at 1560 and 1310 cm^{-1} consistent with the presence of an amino and a nitro-substituent respectively. However its ^{1}H and ^{13}C n.m.r. absorption differed significantly from that of 4-amino-5-nitro-2-phenyl-2H-1,2,3-triazole (23a). On the basis of the analytical and spectroscopic evidence the product derived by cyclodehydration of the hydrazone-oxime (62) is therefore formulated as 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71). This structure was further substantiated by the conversion of the compound on heating in acetic anhydride into a diacetyl derivative which analysed correctly and gave mass, i.r. and ^{1}H n.m.r. spectra in accord with the structure (72). In contrast the amino-substituent in the amino-nitro-1,2,4-triazole (71) was inert to other acylating agents. Thus, the amino-nitro-1,2,4-triazole (71) was recovered unchanged in 98% and 86% yields after heating under reflux with formic acid and triethyl orthoformate respectively. The amino-nitrotriazole (71) was also recovered unchanged in high yield (88%) after heating under reflux with aqueous sulphuric acid in ethanol demonstrating the stability of its amino-group to hydrolysis. Surprisingly, the attempted catalytic hydrogenation of the amino-nitro-1,2,4-triazole (71) gave only a low yield of a gum whose t.l.c. showed it to consist largely



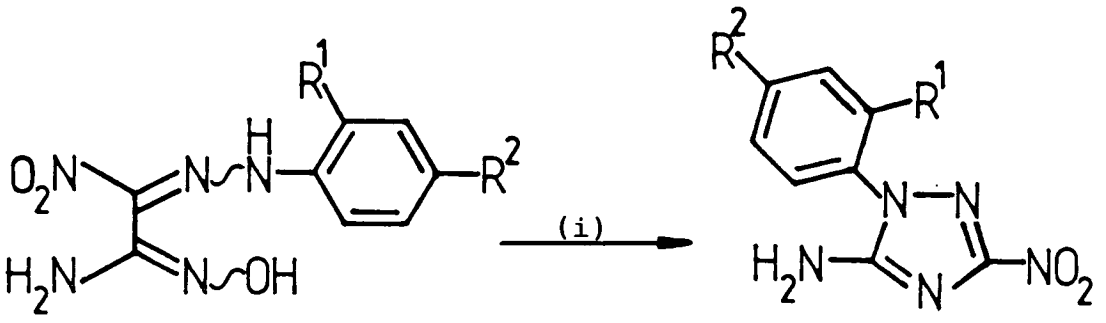
(i) $SOCl_2$, 1,4-dioxane, 10-20°
(ii) Ac_2O, reflux
(iii) AcOH, reflux
(iv) Ac_2O, reflux
(v) CF_3CO_2H, 90% v/v H_2O_2, room temp.
(vi) $NaNO_2$, HCl aqu, then NaN_3, H_2O, 0-15°
(vii) Ph_3P
(viii) O_3

Scheme 16

of unreacted starting-material.

The formation of the 1,2,4-triazole derivative (71) from the hydrazone-oxime (62) can be rationalised by a course (Scheme 16) involving initial Beckmann-type rearrangement to give a carbocation intermediate (68), cyclisation of which accounts for the observed product. A 1,2,4-triazole synthesis of this type does not appear to have been described previously in the literature,[118] and it was therefore of interest to investigate its generality (Scheme 17). It was found that all of the hydrazone-oximes (66a-c) reacted with thionyl chloride in 1,4-dioxane at low temperature to give moderate to good yields (49-67%) of products which gave combustion analyses and showed mass, i.r. and ^{1}H n.m.r. absorption fully in accord with 5-amino-1-aryl-3-nitro-1H-1,2,4-triazole structures (77a-c).

Because of the relatively low yields obtained in the cyclisation reactions [(62)→(71)] and [(66)→(77)] attempts were made to improve the efficiency of such 1,2,4-triazole syntheses using cyclodehydration agents other than thionyl chloride. However, the use of toluene-4-sulphonyl (tosyl) chloride in conjunction with triethylamine for the cyclisation of the hydrazone-oxime (62) gave a reduced yield (42%) of the 1,2,4-triazole derivative (71) in comparison with the same cyclisation using thionyl chloride. Cyclodehydration of the hydrazone-oxime (62) by heating with acetic anhydride in addition to giving the O-acetyl derivative (69) (see before) in low yield (9%) also afforded a product (yield 18%) which gave a combustion analysis and showed spectroscopic properties



(66) (77)

	R^1	R^2
a;	H	Me
b;	H	Cl
c;	H	NO_2

(i) $SOCl_2$, 1,4-dioxane, 10-20°

Scheme 17

consistent with the acetylamino-1,2,3-triazole structure (70) rather than the alternative 1,2,4-triazole structure. In particular it showed a mass-spectral fragmentation pattern different to that of the diacetylamino derivative (72) obtained by acylating 5-amino-3-nitro-1-phenyl-1,2,4-triazole (71) (see before). The acetylamino-1,2,3-triazole derivative (70) was also formed in low yield (36%) when the O-acetyl hydrazone-oxime (69) was heated under reflux in glacial acetic acid. It is possible therefore, that the O-acetyl hydrazone-oxime (69) is an intermediate in the conversion of the hydrazone-oxime (62) in acetic anhydride into the acetylamino-1,2,3-triazole (70) via simple dehydrative cyclisation.

Having been thwarted in attempts to obtain an efficient alternative route to 4-amino-5-nitro-2-phenyl-2H-1,2,3-triazole (23a) it was decided to investigate the suitability of the readily available isomeric amino-nitro-1,2,4-triazole derivative (71) as a precursor (Scheme 16) of the previously undescribed 3,5-dinitro-1-phenyl-1H-1,2,4-triazole (75). Initially the peracid oxidation[39] of the amino-nitrotriazole (71) to the dinitrotriazole (75) was studied. However treatment of the amine (71) with trifluoroperacetic acid at room temperature gave only a high recovery of the unreacted starting-material. Repetition of this reaction at elevated temperature (60-70°) gave in addition to unreacted starting-material (24%), low yields (4-5%) of two readily separated products tentatively identified on the basis of their mass spectra as the dinitro-1,2,4-triazole (75) and the azo-derivative (73). Amino-1,2,4-triazoles are known[119] to be

converted by oxidising agents into the corresponding azotriazole derivatives.

In view of the inefficiency of the transformation [(71)→(75)] a final attempt was made to achieve the synthesis of the dinitro-1,2,4-triazole (75) by firstly converting the amino-nitro-1,2,4-triazole by azide dediazonation into the azide (74) then reaction of this compound with triphenylphosphine to give the phosphineimino-1,2,4-triazole (76) and finally ozonolysis of the latter. Corey and his co-workers[120] have recently shown that the ozonolysis of phosphineimines provides a viable route to nitro-compounds. In the present studies the attempted conversion of the amino-nitro-1,2,4-triazole (71) into the azide (75) by diazotisation followed by reaction with sodium azide was unsuccessful, no identifiable material being obtained. The failure of this reaction is presumably due to the instability of the diazonium species derived from the amino-nitro-1,2,4-triazole (71) since diazotisation of the latter followed by attempted coupling with β-naphthol in alkaline solution gave only a multicomponent gum which yielded no identifiable material. Lack of time prevented further attempts to effect the conversion of the amino-nitro-1,2,4-triazole (71) into 3,5-dinitro-1-phenyl-1H-1,2,4-triazole (75).

4.6 Experimental

1,2-Diaminoethane-1,2-dione Dioxime (7a)

1,2-Diaminoethane-1,2-dione dioxime (7a) was prepared as described in Chapter 2, Section 2.6, page 67.

The Reaction of 1,2-Diaminoethane-1,2-dione Dioxime (7a) with Sodium Nitrite and Acetic Acid

A solution of 1,2-diaminoethane-1,2-dione dioxime (7a) (0.48 g; 0.004 mol) in glacial acetic acid (15.0 ml) was stirred and treated dropwise at 5-8° (ice bath) over 15 min with a solution of sodium nitrite (0.30 g; 0.0044 mol) in water (1.0 ml). The mixture was stirred at 5-8° for 2h, evaporated to dryness, the residue treated with water (1.0 ml) and the insoluble solid collected, washed with water and dried in vacuo to afford an unidentified product (0.12 g), m.p. 138-143° (decomp.), ν_{max} 3450, 3400, and 3300-2700 br (NH,OH), 1750 br (CO), and 1670 br (C=N) cm^{-1}, M^+, 145.

1,2-Diaminoethane-1,2-dione Dioxime O,O-Diacetate (7b)

1,2-Diaminoethane-1,2-dione dioxime O,O-diacetate (7b) was prepared as described in Chapter 2, Section 2.6, page 71.

The Reaction of 1,2-Diaminoethane-1,2-dione Dioxime O,O-Diacetate (7b) with Sodium Nitrite and Acetic Acid

A suspension of 1,2-diaminoethane-1,2-dione dioxime O,O-diacetate (7b) (0.40 g; 0.002 mol) in glacial acetic acid (15.0 ml) was stirred and treated dropwise at 5-8° (ice

bath) over 15 min with a solution of sodium nitrite (0.15 g, 0.0022 mol) in water (1.0 ml). The mixture was stirred at 5-8° for 2h then evaporated. The residue was treated with water and the insoluble solid was collected, washed with water and combined with further material obtained by extracting the combined aqueous mother liquor and washings with ethyl acetate to afford the unreacted starting-material (7b) (0.24 g; 60%), m.p. 195-196°, identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Further workup of the aqueous mother liquor by evaporation and extraction of the residual inorganic cake with boiling ethyl acetate gave no other material.

O,O-Dibenzyl-1,2-diaminoethane-1,2-dione Dioxime (7c)

O,O-Dibenzyl-1,2-diaminoethane-1,2-dione (7c) was prepared as described in Chapter 2, Section 2.6, page 82.

The Attempted Reaction of O,O-Dibenzyl-1,2-diaminoethane-1,2-dione Dioxime (7c) with Sodium Nitrite and Acetic Acid

A solution of O,O-dibenzyl-1,2-diaminoethane-1,2-dione dioxime (7c) (0.60 g; 0.002 mol) in glacial acetic acid (10.0 ml) was stirred and treated dropwise at 5-8° (ice bath) over 15 min with a solution of sodium nitrite (0.15 g; 0.0022 mol) in water (1.0 ml). The mixture was stirred at 5-8° for 2h, treated with water (10.0 ml) and extracted with methylene chloride to give a yellow gum (0.6 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to

methanol gave only intractable gums (total 0.4 g) which were not further investigated.

2-Nitroethanal Monoxime (13)

2-Nitroethanal monoxime (13) was prepared as described in Chapter 2, Section 2.6, page 52.

The Attempted Reaction of 2-Nitroethanal Monoxime (13) with Toluene-4-sulphonyl Azide in the Presence of Triethylamine

A solution of 2-nitroethanal monoxime (13) (1.0 g; 0.01 mol) and triethylamine (2.2 g; 0.022 mol) in anhydrous acetonitrile (5.0 ml) was stirred and treated at room temperature in one portion with toluene-4-sulphonyl azide (2.0 g; 0.01 mol). The mixture was stirred at room temperature for 1.5h, evaporated and the residual gum treated with aqueous 2M hydrochloric acid (10.0 ml) and extracted with methylene chloride. The methylene chloride extract was washed with aqueous 2M sodium hydroxide solution (10.0 ml) and evaporated to give a red oil (0.4 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Neutralisation of the aqueous acid mother liquor with aqueous 2M sodium hydroxide solution and glacial acetic acid and extraction with methylene chloride gave only a negligible quantity of gum.

The aqueous alkaline mother liquor was neutralised with aqueous 2M hydrochloric acid and anhydrous sodium acetate and the resulting precipitate was collected, washed with water

and dried in vacuo to afford toluene-4-sulphonamide (0.15 g; 9%) m.p. 100-108° (decomp.), identical (i.r. spectrum) to an authentic sample. Extraction of the neutralised aqueous mother liquor with methylene chloride gave no further identifiable material.

1-Nitroethane-1,2-dione 1-Arylhydraze 2-Oximes (19)

Solutions of redistilled aniline or 4-nitroaniline (0.063 mol) in aqueous 5M hydrochloric acid (30.0 ml) were stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (4.5 g; 0.063 mol) in water (8.0 ml) at such a rate that the reaction temperature was <5°. The resulting amber diazonium chloride solutions were stirred at <5° for 5 min and then added dropwise at 0° (ice-salt bath) to a stirred solution of 2-nitroethanol monoxime (13) (6.3 g; 0.06 mol) and anhydrous sodium acetate (7.8 g; 0.093 mol) in ethanol (30.0 ml) and water (30.0 ml). The mixture was stirred in the melting ice bath for 1h then worked up as described for the individual reactions below.

(a) The mixture from aniline was filtered and the solid was washed with water and dried in vacuo to afford the known[108] 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (12.3 g; 98%), m.p. 173-175° (decomp.) (from toluene) (lit.,[108] 164°), $\nu_{max.}$ 3300 and 3260 (NH) and 1530 and 1325 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 8.56 (1H, s, CH), 7.85-7.50 (1H, brs, NOH), and 7.45-7.38 (5H, m, ArH).

Found: C, 46.1; H, 3.9; N, 27.2%; M^+, 208

Calc. for $C_8H_8N_4O_3$: C, 46.2; H, 3.8; N, 26.9; M, 208

Extraction of the aqueous mother liquor with ethyl acetate gave no further identifiable material.

(b) The mixture from 4-nitroaniline was filtered and the solid was washed with water and dried *in vacuo* to afford the known[111] 1-nitroethane-1,2-dione 1-(4-nitrophenyl)hydrazone 2-oxime (19b) (14.7 g; 97%), m.p. 181-184° (decomp.) (from ethanol-water) (lit.,[111] 185°), $\nu_{max.}$ 3480-3220 br (NH) and 1580 and 1330 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 12.77 (1H, brs, NOH, exchanged with D_2O), 12.19 (1H, brs, NH; exchanged with D_2O), 8.50 (1H, s, CH), 8.31 (2H, d J9.3Hz, ArH), and 7.53 (2H, d J9.3Hz, ArH).

Found: C, 38.5; H, 2.7; N, 27.1%; M^+, 253.0441

Calc.for $C_8H_7N_5O_5$: C, 37.9; H, 2.7; N, 27.7%; M, 253.0447

Extraction of the aqueous mother liquor with methylene chloride gave no further identifiable material.

Attempted Oxidative Cyclisation Reactions of 1-Nitroethane-1,2-dione 1-Arylhydrazone 2-Oximes (19)

(a) Using copper sulphate in the presence of pyridine

A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) in 15% v/v aqueous pyridine (10.0 ml) was stirred and treated dropwise at room temperature over 15 min with a solution of copper(II) sulphate pentahydrate (0.8 g; 0.0032 mol) in water (4.0 ml). The mixture was heated under reflux for 4h then cooled to room temperature, brought to pH2 with 25% v/v aqueous sulphuric acid and extracted with methylene chloride. The methylene chloride

extract was washed with aqueous 2M sodium hydroxide solution (10.0 ml) and evaporated to give a gum (0.2 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to methanol gave no identifiable material.

Neutralisation of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate and extraction with methylene chloride gave no identifiable material.

(b) Using sodium hypochlorite in the presence of triethylamine

A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) and triethylamine (0.20 g; 0.002 mol) in anhydrous 1,4-dioxane (10.0 ml) was stirred and treated at room temperature with aqueous sodium hypochlorite solution (14% in available chlorine) (5.0 ml). The mixture was stirred at room temperature for a further 20 min then evaporated and the residual gummy solid treated with water (5.0 ml) and extracted with methylene chloride to give a gummy solid (0.4 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable mixture which was not further investigated.

(c) Using sodium hypochlorite in the presence of pyridine

A solution of 1-nitroethane-1,2-dione 1-(4-nitrophenyl)-hydrazone 2-oxime (19b) (0.51 g; 0.002 mol) in Analar pyridine (5.0 ml) was stirred and treated at room temperature with aqueous sodium hypochlorite solution (14% in available

chlorine) (5.0 ml). The mixture was stirred at room temperature for 20 min, diluted with water (10.0 ml), brought to pH1 with concentrated hydrochloric acid and extracted with methylene chloride to give a gum (0.23 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(d) Using activated manganese dioxide

A solution of 1-nitroethane-1,2-dione 1-(4-nitrophenyl)-hydrazone 2-oxime (19b) (1.3 g; 0.005 mol) in anhydrous 1,4-dioxane (35.0 ml) was stirred and treated at room temperature with activated manganese dioxide (7.5 g). The mixture was stirred at room temperature for 1h, then filtered through celite to remove the manganese dioxide and the filtrate evaporated to afford an oil. This was triturated with methylene chloride to give unreacted starting-material (19b) (1.1 g; 88%), m.p. 180-181° (decomp.) identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Evaporation of the methylene chloride mother liquor gave a brown gum (0.12 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(e) Using ceric ammonium nitrate

A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenyl-hydrazone (19a) (0.42 g; 0.002 mol) in 90% v/v aqueous acetic acid (10.0 ml) was stirred and treated dropwise at 5° (ice bath) with a solution of ceric ammonium nitrate (2.2 g;

0.004 mol) in water (2.5 ml). The mixture was stirred at 5° for 0.5h then treated with cracked ice (5.0 g) and extracted with methylene chloride. The methylene chloride extract was washed with saturated aqueous sodium hydrogen carbonate solution and water, and evaporated to give no identifiable material.

Neutralisation of the aqueous alkaline mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate and extraction with methylene chloride gave only a negligible quantity of gum.

The aqueous acidic mother liquor was neutralised with aqueous 2M sodium hydroxide solution and glacial acetic acid and extraction with methylene chloride gave no identifiable material.

(f) Using potassium ferricyanide in the presence of sodium hydroxide

A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) and sodium hydroxide (0.50 g; 0.0125 mol) in water (5.0 ml) was stirred and treated at room temperature over 15 min with a solution of potassium ferricyanide (1.3 g; 0.004 mol) in water (5.0 ml). The mixture was stirred for a further 15 min at room temperature then neutralised with aqueous 2M hydrochloric acid and anhydrous sodium acetate to give a solid (0.24 g) m.p. 67-76° (decomp.) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Extraction of the aqueous mother liquor with methylene

chloride afforded only a negligible quantity of gum.

(g) Using fuming nitric acid

1-Nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) was added in portions with stirring to fuming nitric acid (d=1.52) (5.0 ml). The mixture was stirred at room temperature for 1h then poured onto cracked ice (15.0 g) and the precipitated solid collected, washed with water and dried *in vacuo* to afford an unstable solid which decomposed rapidly at room temperature to an intractable tar.

4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a)

(a) A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (8.4 g; 0.04 mol) in 10% w/v aqueous sodium hydroxide solution (80.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with aqueous sodium hypochlorite solution (14% in available chlorine) (200 ml) at such a rate that the reaction temperature was <5°. The mixture was stirred at 0-5° for 0.5h and the precipitated solid was then collected, washed with water and dried *in vacuo* to afford 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (2.1 g; 25%), m.p. 146-149° (from ethanol), $\nu_{max.}$ 1510 and 1340 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 9.13 (1H, s, CH) and 7.95-7.48 (5H, m, ArH).

Found: C, 46.4; H, 2.9; N, 27.1%; M^+, 206 (M^+-16), 190

$C_8H_6N_4O_3$ requires: C, 46.6; H, 2.9; N, 27.2%; M, 206.

The aqueous mother liquor was neutralised with concentrated hydrochloric acid and anhydrous sodium acetate

and extracted with ethyl acetate to give a gum (1.3 g) whose t.l.c. in methylene chloride-ethyl acetate (4:1) over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(b) A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) in Analar pyridine (5.0 ml) was stirred and treated dropwise at room temperature with aqueous sodium hypochlorite solution (14% in available chlorine) (5.0 ml). The mixture was stirred at room temperature for a further 20 min, diluted with water (10.0 ml) and the precipitated solid was collected, washed with water and dried in vacuo to afford 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.26 g; 63%), m.p. 136-142° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared in (a) before.

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate and extraction with methylene chloride gave no further identifiable material.

(c) A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.21 g; 0.001 mol) in aqueous 1M sodium hydroxide solution (2.5 ml) was stirred and treated at room temperature with 30% w/v aqueous hydrogen peroxide solution (0.5 ml). The mixture was stirred at room temperature for 18h and the precipitated solid was collected, washed with water and dried in vacuo to afford 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.04 g; 20%), m.p. 134-139° (decomp.), identified by comparison (m.p. and i.r.

spectrum) with an authentic sample prepared in (a) before.

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate and extraction with methylene chloride gave a gum (0.2 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(d) Using activated manganese dioxide

A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (2.1 g; 0.01 mol) in anhydrous acetonitrile (75.0 ml) was stirred and treated at room temperature with activated manganese dioxide (15.0 g). The mixture was stirred at room temperature for 2h, filtered to remove manganese dioxide, and the acetonitrile mother liquor evaporated to give a solid (1.2 g), m.p. 94-99° which was flash-chromatographed over silica.

Elution with methylene chloride afforded 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.8 g; 42%) m.p. 142-144°, identified by comparison (m.p. and i.r. spectrum) with a sample prepared in (a) before.

Subsequent elution with methylene chloride-ethyl acetate (1:1) through ethyl acetate to methanol gave only small amounts of uncharacterised gums and oils.

Attempted Reduction of 4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (20a)

(a) Using sodium dithionite

(i) A solution of 4-nitro-2-phenyl-2H-1,2,3-triazole

1-N-oxide (20a) (0.41 g; 0.002 mol) in 70% v/v aqueous ethanol (25.0 ml) was treated with sodium dithionite (0.41 g) and the mixture was stirred at room temperature for 0.5h. A second portion of sodium dithionite (0.41 g) was added and stirring continued at room temperature for 0.5h.

The mixture was evaporated and the residue was treated with water (5.0 ml) and extracted with ethyl acetate. Evaporation of the ethyl acetate extract gave a gum (0.15 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

(ii) Repetition of reaction (i) but with heating under reflux for a total of 2h gave after workup no identifiable material.

(b) Using catalytic hydrogenation

4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.41 g; 0.002 mol) in anhydrous 1,4-dioxane (10.0 ml) was hydrogenated over 10% palladium-on-charcoal (0.04 g). The mixture was filtered through celite, the filtrate was evaporated and the residue was taken in ethyl acetate and filtered to remove some insoluble material. Evaporation of the ethyl acetate filtrate afforded impure starting-material (20a) (0.30 g; 73%), m.p. 124-127° (decomp.) identified by comparison (i.r. spectrum) with an authentic sample prepared before.

The Reduction of 4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) with Sodium Borohydride

A solution of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.41 g; 0.002 mol) in anhydrous 1,4-dioxane (10.0 ml) and water (5.0 ml) was stirred and treated at room temperature with a solution of sodium borohydride (0.30 g; 0.0088 mol) in water (4.0 ml). The mixture was stirred at room temperature for 3h, then evaporated and the residue treated with water and extracted with methylene chloride to afford a solid which was combined with a second crop obtained by neutralising the basic mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate and extraction with methylene chloride to yield 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.44 g; 91%), m.p. 166-170° (decomp.) identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

5-Nitro-2-phenyl-2H-1,2,3-triazole (21a)

(a) A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 1h. The mixture was evaporated and residual acetic anhydride was removed by co-evaporation with anhydrous toluene to yield a gum (0.5 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded the known[110] 4-nitro-2-phenyl-2H-1,2,3-triazole (21a) (0.07 g; 18%) m.p. 128-129° (from ethanol) (lit.,[110] 130°), $\nu_{max.}$ 1530 and 1350 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 8.36 (1H, s, CH) and 8.20-7.48 (5H, m, ArH).

Found: C, 50.7; H, 3.2; N, 29.4%; M^+, 190

Calc.for $C_8H_6N_4O_2$: C, 50.5; H, 3.2; N. 29.5%; M , 190

Further elution with ethyl acetate through to methanol gave no other identifiable material.

(b) A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenyl hydrazone (19a) (0.42 g; 0.002 mol) and triethylamine (0.22 g; 0.0022 mol) in anhydrous 1,4-dioxane (5.0 ml) was stirred and treated at room temperature with a solution of acetyl chloride (0.18 g; 0.0022 mol) in anhydrous 1,4-dioxane (1.0 ml). The mixture was stirred at room temperature for 1h, filtered to remove triethylamine hydrochloride and evaporated to give a gummy solid which was flash-chromatographed over silica.

Elution with methylene chloride afforded 4-nitro-2-phenyl-2H-1,2,3-triazole (21a) (0.10 g; 26%), m.p. 114-120°, identified by comparison (i.r. spectrum) with an authentic sample prepared in (a) before.

Further elution with ethyl acetate through to methanol gave no other material.

(c) A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) in dimethyl sulphoxide (2.5 ml) was aspirated with a slow stream of atmospheric oxygen and heated under reflux for 16h. The mixture was diluted with water (10.0 ml) and extracted with ether to give a gummy solid (0.3 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1) afforded 4-nitro-2-phenyl-2H-1,2,3-triazole (21a) (0.08 g;

20%), m.p. 118-121°, identified by comparison (i.r. spectrum) with an authentic sample prepared in (a) before.

Further elution with ethyl acetate through to methanol gave no other identifiable material.

The Reaction of 1-Nitroethane-1,2-dione 2-Oxime 1-Phenylhydrazone (19a) with Ethyl Chloroformate in the Presence of Triethylamine

A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) and triethylamine (0.22 g; 0.0022 mol) in anhydrous 1,4-dioxane (5.0 ml) was stirred and treated dropwise at room temperature with a solution of ethyl chloroformate (0.24 g; 0.0022 mol) in anhydrous 1,4-dioxane (1.0 ml). The mixture was stirred at room temperature for 1h, filtered to remove triethylamine hydrochloride, and the filtrate evaporated to give a gummy red solid (0.5 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1) afforded 4-nitro-2-phenyl-2H-1,2,3-triazole (21a) (0.04 g; 10%) m.p. 118-122°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with cyclohexane-methylene chloride (1:1) gave the known[112,113] 2-nitro-2-oxoacetonitrile phenylhydrazone (27) (0.09 g; 24%), m.p. 127-130° (decomp.) (from toluene-light petroleum) [lit.,[112] 108° (decomp.); lit.[113] 148°], $\nu_{max.}$ 3200 (NH), 2230 (C≡N), and 1550 and 1330 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 7.75-7.15, (5H, m, ArH) and 3.60 (1H, brs, NH, exchanged with D_2O).

Found: C, 50.8; H, 3.1; N, 30.0%; M^+, 190.0490

Calc.for $C_8H_6N_4O_2$: C, 50.5; H, 3.3; N, 29.5%; M , 190.0491

Identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared later.

Further elution with ethyl acetate through to methanol gave no other identifiable material.

The Reaction of 1-Nitroethane-1,2-dione 2-Oxime 1-Phenylhydrazone (19a) with Thionyl Chloride

A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (35.4 g; 0.17 mol) in anhydrous 1,4-dioxane (200 ml) was stirred and treated dropwise at room temperature with freshly distilled thionyl chloride (17.0 ml; 0.24mol). The mixture was securely stoppered and stirred at room temperature for 19h. A second portion of freshly distilled thionyl chloride (17.0 ml; 0.24 mol) was added and the mixture was securely stoppered and stirred at room temperature for a further 16h. The mixture was then evaporated to give a gummy solid which was triturated with ether to afford 2-nitro-2-oxoacetonitrile phenylhydrazone (27) (23.2 g; 72%), m.p. 126-129° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared later.

Evaporation of the ether mother liquor gave a gummy brown solid (6.5 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1) afforded 4-nitro-2-phenyl-2H-1,2,3-triazole (21a) (3.5 g; 11%) m.p. 87-92°, identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Further elution with methylene chloride through ethyl acetate to methanol gave no other identifiable material.

The Reaction of 1-Nitroethane-1,2-dione-2-oxime 1-Phenylhydrazone (19a) with Phosphorus Pentachloride

A solution of 1-nitroethane-1,2-dione 2-oxime 1-phenylhydrazone (19a) (0.42 g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml) was stirred and treated portionwise at 0° (ice-salt bath) with phosphorus pentachloride (0.5 g; 0.0024 mol). The mixture was securely stoppered and stirred at room temperature for 2h, then poured into ice-water (5.0 ml) and extracted with methylene chloride. The methylene chloride extract was washed with saturated aqueous sodium hydrogen carbonate solution (10.0 ml) and evaporated to give a solid (0.2 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1) afforded 4-nitro-2-phenyl-2H-1,2,3-triazole (21a) (0.13 g; 34%), m.p. 94-97°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Further elution with ethyl acetate through to methanol gave no other identifiable material.

The aqueous alkaline mother liquor was neutralised with aqueous 2M hydrochloric acid and anhydrous sodium acetate and the precipitated solid was collected, washed with water and dried in vacuo to afford 2-nitro-2-oxoacetonitrile phenylhydrazone (27) (0.06 g; 16%), m.p. 122-126° (decomp.), identified by comparison (m.p. and i.r. spectrum) to an authentic sample prepared before.

Extraction of the aqueous mother liquor with methylene chloride gave no further material.

The Reaction of 4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (20a) with Acetyl Chloride

(a) A solution of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (1.6 g; 0.008 mol) in acetyl chloride (30.0 ml) and glacial acetic acid (10.0 ml) was heated under reflux for 3h. The mixture was evaporated to give a gummy solid which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (3:1) afforded 4-chloro-5-nitro-2-phenyl-2H-1,2,3-triazole (22a) (1.0 g; 56%), m.p. 128-130° (from ethanol), $\nu_{max.}$ 1540 and 1315 (NO_2) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.11-7.54 (5H, m, ArH).

Found: C, 42.6; H, 2.1; N, 24.9%; M^+, 226 and 224

$C_8H_5ClN_4O_2$ requires: C, 42.8; H, 2.2; N, 24.9%; M , 224.5

Found: M^+, 224.0108

$C_8H_5{}^{35}ClN_4O_2$ requires: M, 224.0101

Found: M^+, 226.0080

$C_8H_5{}^{37}ClN_4O_2$ requires: M , 226.0072

Further elution with cyclohexane-methylene chloride (3:1) afforded 4-acetoxy-5-chloro-2-phenyl-2H-1,2,3-triazole (29) (0.8 g; 42%), m.p. 74-76° (from light petroleum), $\nu_{max.}$ 1780 (C=O) cm^{-1}, $\delta_H(CDCl_3)$ 8.00-7.25 (5H, m, ArH) and 2.39 (3H, s, CH_3).

Found: C, 50.2; H, 3.3; N, 17.9%; M^+, 234 and 237

$C_{10}H_8ClN_3O_2$ requires: C, 50.5; H, 3.4; N, 17.7%; M , 237.5

Elution with ethyl acetate through to methanol gave no further identifiable material.

(b) A solution of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.41 g; 0.002 mol) in acetyl chloride (10.0 ml) was heated under reflux for 3h. The mixture was evaporated to give a red oil (0.46 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1) afforded 4-acetoxy-5-chloro-2-phenyl-2H-1,2,3-triazole (29) (0.17 g; 36%), m.p. 61-62°, identified by comparison (i.r. spectrum) with a sample obtained in (a) before.

Elution with ethyl acetate through to methanol gave no further identifiable material.

4-Chloro-5-hydroxy-2-phenyl-2H-1,2,3-triazole (30)

A solution of 4-acetoxy-5-chloro-2-phenyl-2H-1,2,3-triazole (29) (0.48 g; 0.002 mol) in ethanol (10.0 ml) was treated with aqueous 2M sodium hydroxide (5.0 ml) and heated under reflux for 1h. The mixture was evaporated and the residue was dissolved in water (5.0 ml) and the solution brought to pH6 with aqueous 2M hydrochloric acid to give a solid which was collected, washed with water, and dried in vacuo to afford 4-chloro-5-hydroxy-2-phenyl-2H-1,2,3-triazole (30) (0.33 g; 85%), m.p. 154-155° (from toluene), $\nu_{max.}$ 3100-2700 br (OH), $\delta_H(CDCl_3)$ 9.54 (1H, brs, OH, exchanged with D_2O) and 7.87-7.50 (5H, m, ArH).

Found: C, 48.9; H, 3.0; N, 21.5%; M^+, 197 and 195

$C_8H_6ClN_3O$ requires: C, 49.1; H, 3.1; N, 21.5%; M , 195.5

The Attempted Reaction of 4-Chloro-5-nitro-2-phenyl-2H-1,2,3-triazole (22a) with Sodium Acetate in Glacial Acetic Acid

A solution of 4-chloro-5-nitro-2-phenyl-2H-1,2,3-triazole (22a) (0.48 g; 0.002 mol) and anhydrous sodium acetate (0.20 g; 0.0022 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 1h. The mixture was evaporated and the residue treated with water (5.0 ml) to give a solid which was washed with water and dried in vacuo to afford only unreacted starting material (22a) (0.44 g; 91%) m.p. 122-126°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Extraction of the aqueous mother liquor with methylene chloride gave no further material.

The Attempted Reaction of 4-Chloro-5-nitro-2-phenyl 2H-1,2,3-triazole (22a) with Benzylamine

A solution of 4-chloro-5-nitro-2-phenyl-2H-1,2,3-triazole (22a) (0.48 g; 0.002 mol) and benzylamine (0.47 g; 0.0044 mol) in ethanol (5.0 ml) was heated under reflux for 1h. The mixture was cooled to room temperature and the precipitated solid was collected, washed with ethanol and combined with further material obtained by evaporating the combined ethanolic mother liquor and washings, dissolving the resulting gum in methylene chloride, washing the solution with aqueous 2M hydrochloric acid, and evaporating the methylene chloride layer to give unreacted starting material (22a) (0.38 g; 78%), m.p. 122-126°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

The Attempted Reaction of 4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) with Hydrogen Chloride in Glacial Acetic Acid

A solution of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.41 g; 0.002 mol) in glacial acetic acid (10.0 ml) was treated at 5-8° (ice-water bath) with a slow stream of hydrogen chloride until saturated. The mixture was securely stoppered and left in the melting ice bath for 16h, then evaporated and the residual gum treated with water to give a solid which was collected, washed with water and dried in vacuo to afford only unreacted starting material (20a) (0.27 g; 66%), m.p. 147-149°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Extraction of the aqueous mother liquor with methylene chloride gave no further identifiable material.

The Attempted Reaction of 4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) with Toluene-4-sulphonyl Chloride.

A solution of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.41 g; 0.002 mol) and toluene-4-sulphonyl chloride (0.42 g; 0.0022 mol) in anhydrous 1,4-dioxane (10.0 ml) was heated under reflux for 1h. The mixture was evaporated to give a gum which was triturated with ethyl acetate to afford only unreacted 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.25 g; 60%), m.p. 144-147° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

Evaporation of the ethyl acetate mother liquor gave only unreacted toluene-4-sulphonyl chloride (0.42 g; 100%), m.p.

58-61°, identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Reaction of 4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) with Acetic Anhydride

A solution of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.41 g; 0.002 mol) in acetic anhydride (10.0 ml) was heated under reflux for 3h. The mixture was evaporated and the residue was co-evaporated with anhydrous toluene to remove residual acetic anhydride. Trituration of the gum obtained with methanol afforded only unreacted starting material (20a) (0.23 g; 56%), m.p. 132-139° (decomp.), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

Evaporation of the methanolic mother liquor gave a black oil (0.2 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

The Reaction of 4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (20a) with Sodium Hydroxide

(a) A suspension of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.41 g; 0.002 mol) in aqueous 2M sodium hydroxide (2.5 ml) was stirred at room temperature for 0.5h. The insoluble solid was collected, washed with water and dried in vacuo to afford unreacted starting material (20a) (0.32 g; 78%), m.p. 138-142° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample

prepared before.

The combined aqueous mother liquor and washings were brought to pH5 with aqueous 2M hydrochloric acid and extracted with ethyl acetate to give no further identifiable material.

(b) Repetition of reaction (a) but with heating under reflux for 1h in ethanol as co-solvent gave only low yields of gums whose t.l.c. in methylene chloride over silica showed them to be multicomponent mixtures which were not further investigated.

The Attempted Reaction of 4-Nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (20a) with Ethanolic Sodium Ethoxide

(a) A suspension of 4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (20a) (0.41 g; 0.002 mol) in anhydrous ethanol (10.0 ml) was stirred and treated at room temperature with a solution of sodium (0.09 g; 0.004 g.atom) in anhydrous ethanol (5.0 ml). The mixture was stirred at room temperature for 1h then evaporated and the residue treated with water (5.0 ml) and extracted with methylene chloride to give a red gum (0.16 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate gave a solid (0.1 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multicomponent mixture which was not investigated further.

(b) Repetition of reaction (a) but with heating under reflux for 1h afforded only intractable red gums which yielded no identifiable material.

1,1-Bis-methylthio-2-nitroethene (34)

1,1-Bis-methylthio-2-nitroethene (34) was prepared as described in Chapter 2, Section 2.6, page 64.

Methyl 2-Nitroethanehydrazonothioate (35)

Methyl 2-nitroethanehydrazonothioate (35) was prepared by the reaction of 1,1-bis-methylthio-2-nitroethene (34) with 100% hydrazine hydrate as described by Hamberger, Reinshager, Schulz and Sigmund,[66] yield 97%, obtained as an amber oil and was used without further purification.

The Attempted Reaction of Methyl 2-Nitroethane Hydrazonothioate (35) with Sodium Nitrite in the Presence of Hydrochloric Acid

A solution of methyl 2-nitroethanehydrazonothioate (35) (0.6 g; 0.004 mol) and concentrated hydrochloric acid (0.8 ml) in water (13.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.31 g; 0.0045 mol) in water (2.0 ml) at such a rate that the reaction temperature was <5°. The mixture was stirred at <5° for 0.5h then extracted with methylene chloride to give a red oil (0.6 g) which was flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1) through to methanol gave no identifiable material.

Attempted Reactions of 1,1-Bis-methylthio-2-nitroethene (34) with Phenylhydrazine

(a) A solution of 1,1-bis-methylthio-2-nitroethene (34) (0.66 g; 0.0044 mol) and phenylhydrazine (0.43 g; 0.004 mol) in ethanol (50.0 ml) was heated under reflux for 5.5h. The mixture was evaporated to give a gum which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) through to methanol gave only gums (total 1.1 g) whose t.l.c. in methylene chloride over silica showed them to be complex mixtures which were not further investigated.

(b) Repetition of reaction (a) in 1,4-dioxane at room temperature for 48h gave only unreacted starting-material (89%), m.p. 121-124° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(c) Repetition of reaction (b) but with heating under reflux for 4h gave only an intractable gum (0.86 g) from which no identifiable material could be obtained.

Methyl N-Hydroxy-2-nitroethanimidothioate (44)

Methyl N-hydroxy-2-nitroethanimidothioate (44) was prepared as described in Chapter 3, Section 3.5, page 115.

Methyl N-Hydroxy-2-nitro-2-oxoethanimidothioate Phenylhydrazone (45)

A solution of redistilled aniline (3.9 g; 0.042 mol) in aqueous 5M hydrochloric acid (20.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium

nitrite (2.9 g; 0.042 mol) in water (5.0 ml) at such a rate that the reaction temperature was <5°. The resulting benzenediazonium chloride solution was stirred at <5° for 5 min then added dropwise at 0° (ice-salt bath) to a stirred solution of methyl N-hydroxy-2-nitroethanimidothioate (44) (6.0 g; 0.04 mol) and anhydrous sodium acetate (5.3 g; 0.062 mol) in ethanol (20.0 ml) and water (20.0 ml). The mixture was stirred in the melting ice bath for 1h and the precipitated solid was collected, washed with water and dried *in vacuo* to afford methyl N-hydroxy-2-nitro-2-oxoethanimidothioate phenylhydrazone (45) (8.9 g; 88%), which formed orange needles, m.p. 127-129° (decomp.) (from toluene), $\nu_{max.}$ 3350 br (NOH) and 3200 (NH), and 1540 and 1370 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 9.66 (1H, brs, OH, exchanged with D_2O), 7.43-7.02 (5H, m. ArH), and 2.27 (3H, s, CH_3).

Found: C, 42.9; H, 3.9; N, 21.8%; M^+, 254

$C_9H_{10}N_4O_3S$ requires: C, 42.5; H, 3.9; N, 22.0%; M , 254

Extraction of the aqueous mother liquor with methylene chloride gave no further identifiable material.

Reactions of Methyl N-Hydroxy-2-nitro-2-oxoethanimidothioate Phenylhydrazone (45) with Activated Manganese Dioxide

(a) A solution of methyl N-hydroxy-2-nitro-2-oxoethanimidothioate phenylhydrazone (45) (2.0 g; 0.008 mol) in anhydrous acetonitrile (60.0 ml) was stirred and treated at room temperature with a single portion of activated manganese dioxide (12.0 g). The mixture was stirred at room temperature for 1h then filtered through celite to remove the manganese dioxide. Evaporation of the filtrate

gave a red oil (1.2 g) which was flash-chromatographed over silica.

Elution with methylene chloride gave an oil which was triturated with ether to afford an unstable solid tentatively formulated as 5-methylthio-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (46) (0.03 g; 2%), m.p. 112-116°, $\nu_{max.}$ 1550 and 1375 (NO_2) cm^{-1}.

Found: M^+, 252, (M^+,-16), 236

$C_9H_8N_4O_3S$ requires: M, 252

Elution with methylene chloride-ethyl acetate (4:1) gave a gummy solid which was triturated with methylene chloride to afford 4-hydroxy-5-methylthio-2-phenyl-2H-1,2,3-triazole 1-N-oxide (47) (0.09 g; 5%), which formed colourless prisms, m.p. 141-143° (from ethyl acetate, $\nu_{max.}$ 3200-2300 br (OH) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.80-7.75 (2H, m, ArH), 7.59-7.44 (3H, m. ArH), and 2.38 (3H, s, CH_3).

Found: C, 47.9, H, 3.9, N, 18.1%; M^+,223.0419 (M^+-16), 2.07.

$C_9H_9N_3O_2S$ requires : C, 48.4; H, 4.0; N, 18.8%; M , 223.0415.

(b) A solution of methyl N-hydroxy-2-nitro-2-oxoethanimidothioate phenylhydrazene (45) (1.0 g; 0.004 mol) in anhydrous acetonitrile (30.0 ml) was stirred and treated at 0° (ice-salt bath) with a single portion of activated manganese dioxide (6.0 g). The mixture was stirred at 0° for 1h, then filtered through celite to remove the manganese dioxide and the filtrate evaporated to give a red gum (0.76 g) which was flash-chromatographed over silica.

Elution with methylene chloride furnished only unreacted

starting-material (45) (0.55 g; 53%), m.p. and i.r. spectrum) to an authentic sample prepared before.

Further elution with ethylacetate through to methanol gave no other identifiable material.

5-Methylthio-3-nitro-1-phenyl-1H-1,2,4-triazole (48)

A solution of methyl N-hydroxy-2-nitro-2-oxoethanimidothioate phenylhydrazone (45) (1.0 g; 0.004 mol) in anhydrous 1,4-dioxane (10.0 ml) was stirred and treated at 10° (ice-water bath) with freshly distilled thionyl chloride (0.66 g; 0.0056 mol). The mixture was stirred in the melting ice bath for 19h then filtered to remove some insoluble solid and the filtrate evaporated. The resulting gum was treated with 10% w/v aqueous sodium hydrogen carbonate solution (5.0 ml) and extracted with methylene chloride to give a red gum (0.96 g) which was flash-chromatographed over silica.

Elution with hexane-methylene chloride (1:1) afforded 5-methylthio-3-nitro-1-phenyl-1H-1,2,4-triazole (48) (0.22 g; 23%), which formed colourless plates, m.p. 120-122° (from light petroleum b.p. 80-100°), $\nu_{max.}$ 1550 and 1375 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 7.68-7.46 (5H, m, ArH) and 2.78 (3H, s, CH_3), $\delta_C[(CD_3)_2SO]$ 161.9 (quat.), 157.4 (quat.), 135.5 (quat.), 130.6 (CH), 130.0 (CH), 124.7 (CH), and 15.6 (CH_3).

Found: C, 45.8, H, 3.3; N, 23.9%; M^+, 236

$C_9H_8N_4O_2S$ requires: C, 45.8; H, 3.4; N, 23.7%; M , 236

Further elution with ethyl acetate through to methanol gave no other identifiable material.

1-Amino-1-ethoxy-2-nitroethene Hydrochloride (54)

1-Amino-1-ethoxy-2-nitroethene hydrochloride (54) was prepared as described in Chapter 2, Section 2.6, page 57.

1-Amino-1-(2-N-phenylhydrazino)-2-nitroethene (55)

A solution of 1-amino-1-ethoxy-2-nitroethene hydrochloride (54) (1.7 g; 0.01 mol) and phenylhydrazine (2.2 g; 0.02 mol) in anhydrous ethanol (25.0 g) was securely stoppered and left in a refrigerator at 0° for 19h. The mixture was evaporated and the residue was treated with water and the solid collected and dried in vacuo to yield 1-amino-1-(2-N-phenylhydrazino)-2-nitroethene (55) (1.7 g; 89%), which formed pale yellow prisms, m.p. 273-275° (decomp.) (from ethanol), $\nu_{max.}$ 3350, 3250 and 3160 (NH), 1630 (C=N), and 1550 and 1375 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 9.86 (1H, brs, NH, exchanged with D_2O), 8.24 (2H, brs, NH, exchanged with D_2O), 7.97 (1H, s, NH, exchanged with D_2O), 7.33-6.70 (5H, m, ArH), and 6.46 (1H, s, CH).

Found: C, 49.9; H, 5.3; N, 29.2%; M^+, 194.0799

$C_8H_{10}N_4O_2$ requires: C, 49.5; H, 5.2; N, 28.9%; M , 194.0804

Extraction of the aqueous mother liquor gave no further identifiable material.

4-Amino-5-nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (57)

(a) A suspension of 1-amino-1-(2-N-phenylhydrazino)-2-nitroethene (55) (0.39 g; 0.002 mol) in a solution of potassium nitrite (0.20 g; 0.0024 mol) in water (5.0 ml) was stirred and treated at 4° (ice bath) with glacial acetic acid (0.24

ml). The mixture was removed from the ice bath and an exothermic reaction set in. The mixture was stirred at room temperature for 1h then extracted with methylene chloride to give a gum which was flash-chromatographed over silica.

Elution with methylene chloride afforded 4-amino-5-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (57) (0.11 g; 25%), which formed orange prisms, m.p. 194-196° (decomp.) (from toluene), $\nu_{max.}$ 3470 and 3300 (NH), 1630 (C=N), and 1560 and 1375 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 7.86-7.79 (2H, m, ArH), 7.67-7.55 (3H, m, ArH), and 6.99 (2H, s, NH, exchanged with D_2O).

Found: C, 43.0; H, 3.1; N, 31.5%; M^+, 221

(M^+-16), 205

$C_8H_7N_5O_3$ requires : C, 43.4; H, 3.2; N, 31.7%; M , 221

Further elution with ethyl acetate through to methanol gave no other identifiable material.

(b) A solution of 1-amino-1-(2-N-phenylhydrazino)-2-nitroethene (55) (0.39 g; 0.002 mol) in glacial acetic acid (10.0 ml) was stirred and treated dropwise at 5-8° (ice-bath) with a solution of sodium nitrite (0.15 g; 0.0022 mol) in water (1.0 ml) over 15 min. The mixture was stirred at 5-8° for a further 2h and the precipitated solid was then collected, washed with water, dried in vacuo, and combined with further material obtained by flash-chromatography of the gum obtained by evaporating the aqueous acetic acid mother liquor, treating the residue with water and extracting the solution with methylene chloride, to afford 4-amino-5-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (57) (0.15 g; 37%), m.p.

194-196° (decomp.), identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

(c) Repetition of reaction (b) but using twice the amount of sodium nitrite raised the yield of the 1,2,3-triazole 1-N-oxide (57) to 44%.

Nitroacetonitrile (49)

Nitroacetonitrile (49) was prepared as described in Chapter 2, Section 2.6, page 56.

The Attempted Reaction of Nitroacetonitrile (49) with Toluene-4-sulphonyl Azide in the Presence of Triethylamine

A solution of nitroacetonitrile (49) (0.86 g; 0.01 mol) and triethylamine (1.1 g; 0.011 mol) in anhydrous acetonitrile (5.0 ml) was stirred and treated at room temperature with a single portion of toluene-4-sulphonyl azide (2.0 g; 0.01 mol). The mixture was stirred at room temperature for 1.5h, then evaporated to give a gum. This was treated with aqueous 2M hydrochloric acid (10.0 ml) and extracted with methylene chloride to give an oil (3.0 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded only unreacted toluene-4-sulphonyl azide (0.11 g; 6%), identical (i.r. spectrum) to an authentic sample.

Further elution with methylene chloride gave toluene-4-sulphonamide (0.46 g; 29%), m.p. 116-120°, identical (i.r. spectrum) to an authentic sample.

Subsequent elution with ethyl acetate through to methanol

gave only intractable gums (total 1.7 g), from which no identifiable material could be obtained.

1-Amino-1-(N-benzylamino)-2-nitroethene (50)

1-Amino-1-(N-benzylamino)-2-nitroethene (50) was prepared as described in Chapter 2, Section 2.6, page 58.

The Attempted Reaction of N-Benzyl-2-nitroacetamidine (50) with Toluene-4-sulphonyl Azide

(a) In the presence of triethylamine

A solution of N-benzyl-2-nitroacetamidine (50) (0.40 g; 0.002 mol) and triethylamine (0.22 g; 0.0022 mol) in anhydrous acetonitrile (10.0 ml) was stirred and treated at 0° (ice-salt bath) with a single portion of toluene-4-sulphonyl azide (0.40 g; 0.002 mol). The mixture was stirred at 0° for 3h then evaporated to give a gum (0.8 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to methanol gave only unreacted starting-material (50) (0.3 g; 77%), m.p. 174-182°, identified by comparison (i.r. spectrum) with an authentic sample.

(b) In the presence of piperidine

A solution of N-benzyl-2-nitroacetamidine (50) (0.4 g; 0.002 mol) and piperidine (0.20 g; 0.0022 mol) in anhydrous acetonitrile (10.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of toluene-4-sulphonyl azide (0.44 g; 0.0022 mol) in anhydrous acetonitrile (2.5 ml). The mixture was stirred in the melting ice bath for

2h, then evaporated and the residue treated with aqueous 2M sodium hydroxide solution (10.0 ml) and extracted with methylene chloride to give a gummy solid (0.6 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to methanol gave only toluene-4-sulphonyl piperidide (0.4 g; 75%), m.p. 98-100°, identical (m.p.) to an authentic sample.

2-Nitroacetamidoxime (58)

2-Nitroacetamidoxime (58) was prepared as described in Chapter 3, Section 3.5, page 109.

The Attempted Reaction of 2-Nitroacetamidoxime (58) with Toluene-4-sulphonyl Azide in the Presence of Triethylamine

A solution of 2-nitroacetamidoxime (58) (0.24 g; 0.002 mol) in triethylamine (0.44 g; 0.0044 mol) in anhydrous dimethylformamide (5.0 ml) was stirred and treated at 0° (ice-salt bath) with a single portion of toluene-4-sulphonyl azide (0.40 g; 0.002 mol). The mixture was stirred at 0° for 3h and evaporated to give an amber oil (0.8 g) which was flash-chromatographed over silica.

Elution with methylene chloride through ethyl acetate to methanol gave no identifiable material.

2-Nitro-2-oxoacetonitrile Arylhydrazones (61) and (65)

(a) A solution of the corresponding aniline derivative (0.042 mol) in aqueous 5M hydrochloric acid (20.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a

solution of sodium nitrite (2.9 g; 0.042 mol) in water (5.0 ml) at such a rate that the reaction temperature was <5°. The resulting amber arenediazonium chloride solution was stirred at <5° for 5 min then added dropwise at 0° (ice-salt bath) to a stirred solution of nitroacetanitrile (49) (3.4 g; 0.04 mol) and anhydrous sodium acetate (12.3 g; 0.15 mol) in ethanol (20.0 ml) and water (20.0 ml). The mixture was stirred in the melting ice bath for 1h, then worked up as described for the individual reactions below.

(i) The mixture from aniline gave a solid which was collected, washed with water, and dried in vacuo to afford 2-nitro-2-oxoacetonitrile phenylhydrazone (61) (7.4 g; 98%), m.p. 130-134° (decomp.), identified by comparison (m.p. and i.r. spectrum) with a sample prepared before.

(ii) The mixture from 4-methylaniline gave a solid which was collected, washed with water and dried in vacuo to afford the known[117] 2-nitro-2-oxoacetonitrile 4-methylphenylhydrazone (65a) (5.9 g; 73%), m.p. 124-126° (decomp.) (from ethanol) (lit.,[117] 126°), $\nu_{max.}$ 3200 (NH), 2230 (C≡N), 1530 and 1320 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 9.20-7.20 (1H, brs, NH, exchanged with D_2O), 7.14 (2H, d J8.7Hz, ArH), 6.92 (2H, d J8.7Hz, ArH) and 1.98 (3H, s, CH_3).

Found: C, 53.2; H, 3.9; N, 27.3%; M^+, 204

Calc. for $C_9H_8N_4O_2$: C, 57.9; H, 4.0; N, 27.4%; M , 204

(iii) The mixture from 4-chloroaniline gave a solid which was collected, washed with water, dried in vacuo then flash-chromatographed over silica.

Elution with cyclohexane-methylene chloride (1:1)

afforded 2-nitro-2-oxoacetonitrile 4-chlorophenylhydrazone (65b) (4.0 g; 42%), m.p. 130-132° (from ethanol), $\nu_{max.}$ 3160 (NH), 2230 (C≡N), and 1530 and 1310 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.51 (4H, brs, ArH) and 4.34 (1H, brs, NH, exchanged with D_2O).

Found: C, 43.0; H, 2.3; N, 24.4%; M^+, 226 and 224

$C_8H_5ClN_4O_2$ requires: C, 42.8; H, 2.2; N, 24.9%; M , 224.5

Elution with ethyl acetate gave an intractable gum (1.6 g) from which no identifiable material could be obtained.

(iv) The mixture from 4-nitroaniline gave a solid which was collected, washed with water and dried in vacuo to afford the known[117] 2-nitro-2-oxoacetonitrile 4-nitrophenylhydrazone (65c) (8.3 g. 84%) m.p. 155-158° (decomp.) (from ethanol-water) (lit.,[117] 148°) $\nu_{max.}$ 3200 (NH), 2240 (C≡N), and 1520 and 1350 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 9.42 (1H, brs, NH), 8.29 (2H, d J9.3Hz, ArH), and 7.64 (2H, d J9.3Hz, ArH).

Found: C, 41.3; H, 7.1; N, 29.7%; M^+, 235.0342

Calc.for $C_8H_5N_5O_4$: C, 40.9; H, 2.1; N, 29.8%; M , 235.0342

(b) A solution of 2,4-dinitroaniline (0.40 g; 0.0022 mol) in concentrated sulphuric acid (1.6 ml) and glacial acetic acid (5.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.15 g; 0.0022 mol) in water (1.0 ml) at such a rate that the temperature was <5°. The resulting diazonium solution was stirred at <5° for 5 min then added dropwise at <10° (ice bath) to a stirred solution of nitroacetonitrile (61) (0.17 g; 0.002 mol) in 70% v/v aqueous acetic acid (5.0 ml). The mixture was stirred in the melting ice bath for 1h, then concentrated

to one half of its original volume, treated with water (5.0 ml) and extracted with methylene chloride to give a gum (0.4 g) which was flash-chromatographed over silica.

Elution with methylene chloride yielded 2-nitro-2-oxoacetonitrile 2,4-dinitrophenylhydrazone (65d) (0.37 g; 66%), m.p. 140-142° (from toluene), $\nu_{max.}$ 3200 (NH), 2240 (C≡N), and 1520 and 1310 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 12.16 (1H, brs, NH, exchanged with D_2O), 8.62 (1H, d J_{meta} 2.6Hz, ArH), 8.35 (1H, dd J_{ortho} 9.2Hz, ArH) and 7.76 (1H, d J_{ortho} 9.2Hz, ArH).

Found: C, 34.5; H, 1.3; N, 30.1%; M^+, 280

$C_8H_4N_6O_6$ requires: C, 34.3; H, 1.4; N, 30.0%; M , 280

Further elution with ethyl acetate through to methanol gave no other identifiable material.

2-Nitro-2-oxoacetamidoxime Arylhydrazones (62) and (66)

A solution of the respective 2-nitro-2-oxoacetonitrile arylhydrazone (61) and (65) (0.02 mol) and hydroxylamine hydrochloride (3.5 g; 0.05 mol) in anhydrous ethanol (200 ml) was stirred and treated at room temperature with a single portion of anhydrous sodium carbonate (2.7 g; 0.025 mol). The mixture was stirred at room temperature for 24h, then evaporated and the residual cake treated with water (25.0 ml) to give a solid which was washed with water, dried in vacuo and further purified as described for the individual reactions below.

(i) The solid from 2-nitro-2-oxoacetonitrile phenylhydrazone (61) was crystallised from toluene to give 2-nitro-

2-oxoacetamidoxime phenylhydrazone (62) as orange prisms (4.1 g; 90%), m.p. 134-135° (decomp.), $\nu_{max.}$ 3500, 3400, and 3320 (NH_n and OH), 1640 and 1615 (C=N), and 1540 and 1300 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$, 12.88 (1H, brs, NOH, exchanged with D_2O), 7.30 (5H, m, ArH, 6.05 (2H, brs, NH, exchanged with D_2O).

Found: C, 43.2; H, 4.0; N, 31.3%; M^+, 223

$C_8H_9N_5O_3$ requires: C, 43.1; H, 4.0; N, 31.4%; M , 223

(ii) The solid from 2-nitro-2-oxoacetonitrile 4-methylphenylhydrazone (65a) was crystallised from toluene to give 2-nitro-2-oxoacetamidoxime 4-methylphenylhydrazone (66a) as orange crystals (4.5 g; 94%), m.p. 133-136°, $\nu_{max.}$ 3500, 3380 br, and 3330 (NH, OH), 1650 (C=N), and 1550 and 1370 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 12.88 (1H, brs, NOH, exchanged with D_2O), 7.52 (2H, d J8.7Hz, ArH), 7.29 (2H, d J8.7Hz, ArH), 6.04 (1H, brs, NH, exchanged with D_2O), 5.13 (2H, NH, exchanged with D_2O), and 2.38 (3H, s, CH_3).

Found: C, 45.8; H, 4.6; N, 29.8%; M^+, 237

$C_9H_{11}N_5O_3$ requires: C, 45.6; H, 4.6; N, 29.5%; M , 237

(iii) The solid from 2-nitro-2-oxoacetonitrile 4-chlorophenylhydrazone (65b) was crystallised from toluene to give 2-nitro-2-oxoacetamidoxime 4-chlorophenylhydrazone (66b) as orange prisms (4.7 g; 90%), m.p. 158° (decomp.), $\nu_{max.}$ 3500 and 3390 br (NH,OH), 1640 (C=N), and 1550 and 1375 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 11.50 (1H, brs, NOH, exchanged with D_2O), 10.26 (1H, brs, NH, exchanged with D_2O), 7.48 (4H, brs, ArH) and 6.18 (2H, brs, NH, exchanged with D_2O).

Found: C, 37.5; H, 3.1; N, 27.1%; M^+, 259 & 257

$C_8H_8ClN_5O_3$ requires: C, 37.3; H, 3.1; N, 27.2%; M , 257.5

(iv) The solid from 2-nitro-2-oxoacetonitrile 4-nitrophenylhydrazone (65c) was flash-chromatographed over silica.

The elution with methylene chloride gave a small amount of unreacted starting-material (65c) (0.05 g; 1%), m.p. 148-155° (decomp.), identified by comparison (m.p. and i.r. spectrum) to an authentic sample prepared before.

Elution with ethyl acetate afforded 2-nitro-2-oxo-acetamidoxime 4-nitrophenylhydrazone (66c) as red-brown prisms (3.1 g; 58%), m.p. 170-172° (decomp.) (from toluene-ethyl acetate), ν_{max}.3510 and 3380 (NH,OH), 1640 (C=N), and 1500 and 1340 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 11.70 (1H, brs, NOH, exchanged with D_2O), 10.50 (1H, brs, NH, exchanged with D_2O), 8.27 (2H, d J9.1Hz, ArH), 7.60 (2H, d J9.1Hz, ArH), and 6.22 (2H, brs, NH, exchanged with D_2O).

Found: C, 36.1; H, 3.0; N, 31.4%; M^+, 268

$C_8H_8N_6O_5$ requires: C, 35.8; H, 3.0: N, 31.3%; M , 268

(v) The solid from 2-nitro-2-oxoacetonitrile 2,4-dinitrophenylhydrazone (65d) was crystallised from glacial acetic acid and to give 2-nitro-2-oxoacetamidoxime 2,4-dinitrophenylhydrazone (66d) as orange prisms (4.3 g; 68%), m.p. 175-177°, $\nu_{max.}$3510 and 3400 (NH,OH), 1650 and 1610 (C=N), and 1525 and 1340 (NO_2) cm^{-1}.

Found: C, 30.7; H, 2.2; N, 30.7%; M^+, 313.0422

$C_8H_7N_7O_7$ requires: C, 30.6; H, 2.2; N, 31.3%l M , 313.0407

2-Nitro-2-oxoacetamidoxime Phenylhydrazone (62)

A solution of redistilled analine (0.20 g; 0.0021 mol) in aqueous 5M hydrochloric acid (1.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.15 g; 0.0021 mol) in water (0.5 ml) at such a rate that the reaction temperature was <5°. The resulting amber benzenediazonium chloride solution was stirred at <5° for 5 min and then added dropwise at 0° (ice-salt bath) to a stirred solution of 2-nitroacetamidoxime (58) (0.23 g; 0.002 mol) and anhydrous sodium acetate (0.66 g; 0.008 mol) in ethanol (7.0 ml) and water (5.0 ml). The mixture was stirred in the melting ice bath for 1h and the precipitate solid was then collected, washed with water and dried in vacuo to afford 2-nitro-2-oxoacetamidoxime phenylhydrazone (62) (0.37 g; 82%), m.p. 139-142° (decomp.), identified by comparison (m.p. and i.r. spectrum) with an authentic sample prepared before.

2-Nitro-2-oxoacetamidoxime Phenylhydrazone O-Acetate (64)

A solution of 2-nitro-2-oxoacetamidoxime phenylhydrazone (62) (1.1 g; 0.005 mol) and triethylamine (0.55 g; 0.0055 mol) in anhydrous 1,4-dioxane (10.0 ml) was stirred and treated at room temperature with a solution of acetyl chloride (0.43 g; 0.0055 mol) in anhydrous 1,4-dioxane (1.0 ml). The mixture was stirred at room temperature for 1h then filtered to remove triethylamine hydrochloride. The filtrate was evaporated and the residue was treated with water (5.0 ml) to give a solid which collected, washed with water and dried

in vacuo to afford 2-nitro-2-oxoacetamidoxime phenylhydrazone O-acetate (64) (1.2 g; 93%) which formed yellow needles, m.p. 129-132° (from ethanol), $\nu_{max.}$ 3480 and 3360 (NH), 1760 (C=O), 1625 (C=N), and 1540 and 1360 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 11.61 (1H, brs, NH, exchanged with D_2O), 7.44-7.11 (7H, m, ArH and NH partly exchanged with D_2O), and 2.21 (3H, s, CH_3).

Found: C, 45.5; H, 4.2; N, 26.7%; M^+, 265

$C_{10}H_{11}N_5O_4$ requires: C, 45.3; H, 4.2; N, 26.4%; M , 265

5-Amino-2-aryl-4-nitro-2H-1,2,3-triazole 1-N-Oxides (63) and (67)

(a) A solution of the corresponding 2-nitro-2-oxoacetamidoxime arylhydrazone (62) and (66) (0.03 mol) in anhydrous acetonitrile (22.5 ml) was stirred and treated at room temperature with a single portion of activated manganese dioxide (45.0 g). The mixture was stirred at room temperature for 1h, filtered through celite to remove manganese dioxide, and the filtrate evaporated to afford the corresponding 5-amino-2-aryl-4-nitro-2H-1,2,3-triazole 1-N-oxides (63) and (67).

(i) 2-Nitro-2-oxoacetamidoxime phenylhydrazone (62) afforded 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) which formed orange needles (5.6 g; 84%), m.p. 194-196° (decomp.) (from ethanol), $\nu_{max.}$ 3380, 3250, and 3180 (NH), 1650 (C=N) and 1590 and 1315 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 8.01-7.88 (2H, m, ArH), 7.71-7.58 (3H, m, ArH) and 6.95 (2H, brs, NH, exchanged with D_2O).

Found: C, 43.5: H, 3.1; N, 31.7%; M^+, 221

(M^+-16), 205

$C_8H_7N_5O_3$ requires. C, 43.4; H, 3.2; N, 31.7%; M , 221

(ii) 2-Nitro-2-oxoacetamidoxime 4-methylphenylhydrazone (66a) gave 5-amino-2-(4-methylphenyl)-4-nitro-2H-1,2,3-triazole 1-N-oxide (67a) which formed yellow needles (3.2 g; 68%), m.p. 170-172° (from ethanol), $\nu_{max.}$ 3270, 3220 and 3140 (NH), 1665 (C=N), and 1510 and 1310 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 7.81 (2H, d J8.6Hz, ArH), 7.42 (2H, d J8.6Hz, ArH), 6.90 (2H, brs, NH), and 2.40 (3H, s, CH_3).

Found: C, 45.7; H, 4.2; N, 29.0%; M^+, 235.0708

(M^+-16), 219

$C_9H_9N_5O_3$ requires: C, 46.0; H, 3.9; N, 29.8%; M , 235.0705

(iii) 2-Nitro-2-oxoacetamidoxime 4-chlorophenylhydrazone (66b) gave 5-amino-2-(4-chlorophenyl)-4-nitro-2H-1,2,3-triazole 1-N-oxide (67b) which formed yellow needles (4.0 g; 79%), m.p. 195-196° (decomp.) (from ethanol), $\nu_{max.}$ 3440, 3280, 3220, and 3150 (NH), 1675 br (C=N), and 1500 and 1300 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 8.01 (2H, d J9.1Hz, ArH), 7.70 (2H, d J9.1Hz, ArH), and 6.98 (2H, brs, NH).

Found: C, 37.7; H, 2.3; N, 27.2%; M^+, 257 and 255

(M^+-16), 241 and 239

$C_8H_6ClN_5O_3$ requires: C, 37.6; H, 2.3; N, 27.4%; M , 255.5

(iv) 2-Nitro-2-oxoacetamidoxime 4-nitrophenylhydrazone (66c) gave 5-amino-4-nitro-2-(4-nitrophenyl)-2H-1,2,3-triazole 1-N-oxide (67c) which formed orange needles (5.1 g; 97%), m.p. 215-217° (decomp.) (from ethanol), $\nu_{max.}$ 3370, 3250, and

3180 (NH), 1660 (C=N), and 1500 and 1300 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 8.50 (2H, d J9.6Hz, ArH), 8.32 (2H, d J9.6Hz, ArH), and 7.07 (2H, brs, NH, exchanged with D_2O).

Found: C, 36.0; H, 2.2; N, 31.7%; M^+, 266

(M^+-16), 250

$C_8H_6N_6O_5$ requires : C, 36.1; H, 2.3; N, 31.5%; M , 266

(v) 2-Nitro-2-oxoacetamidoxime 2,4-dinitrophenylhydrazone (66d) afforded 5-oximo-2-(2,4-dinitrophenyl)-4-nitro-2H-1,2,3-triazole 1-N-oxide (67d) as orange prisms (4.2 g; 67%), m.p. 214-215° (decomp.) (from methanol), $\nu_{max.}$ 3480 and 3300 (NH), 1660 (C=N), and 1530 and 1350 (NO_2) cm^{-1}.

Found: C, 30.7; H, 1.6; N, 31.1%; M^+, 311

(M^+-16), 295

$C_8H_5N_7O_7$ requires. C, 30.9; H, 1.6; N, 31.2%, M, 311

(b) A solution of 2-nitro-2-oxoacetamidoxime phenylhydrazone (62) (0.45 g; 0.002 mol) in Analar pyridine (5.0 ml) was stirred and treated at room temperature with aqueous sodium hypochlorite solution (14% in available chlorine) (5.0 ml). The mixture was stirred at room temperature for 20 min, diluted with water (10.0 ml), cooled to 10° (ice bath), brought to pH1 with concentrated hydrochloric acid, and extracted with methylene chloride. The methylene chloride extract was washed with aqueous 2M hydrochloric acid and water and evaporated to afford a gummy solid which was triturated with ether to yield 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.21 g; 48%), m.p. 194-

196° (decomp.) (from ethanol), identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

Evaporation of the ether mother liquor gave a gum (0.13 g) whose t.l.c. in methylene chloride over silica showed it to be a complex mixture which was not further investigated.

(c) Repetition of reaction (b) but using triethylamine in 1,4-dioxane gave only a gummy solid (0.4 g) whose t.l.c. in methylene chloride over silica showed it to be a close-running multicomponent mixture which was not further investigated.

Attempted Acylation Reactions of 5-Amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (63)

(a) Using acetic anhydride

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.22 g; 0.001 mol) in acetic anhydride (2.5 ml) was heated under reflux for 1h then evaporated and the residue co-evaporated with anhydrous toluene to remove traces of acetic anhydride. Flash-chromatography of the resulting gum (0.22 g) over silica eluting with cyclohexane through methylene chloride to methanol gave no identifiable material.

(b) Using acetyl chloride in the presence of triethylamine

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) and triethylamine (0.22 g; 0.0022 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml) was stirred and treated dropwise at room temperature with a solution of acetyl chloride (0.17 g; 0.0022 mol) in anhydrous

1,2-dimethoxyethane (1.0 ml). The mixture was stirred at room temperature for 1h, filtered to remove triethylamine hydrochloride and the filtrate evaporated to give an intractable gum (0.5 g) which yielded no identifiable material.

(c) Using phenyl isocyanate

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml) was stirred and treated at room temperature with a solution of phenyl isocyanate (0.2 g; 0.002 mol) in anhydrous 1,2-dimethoxyethane (1.0 ml). The mixture was stirred at room temperature for 22h then evaporated to give a gummy solid (0.7 g) which was flash-chromatographed over silica in methylene chloride-ethyl acetate (4:1) to give only unreacted starting-material (63) (0.44 g; 100%), identified by comparison (m.p. and i.r.spectrum) to an authentic sample prepared before.

4-Amino-5-nitro-2-phenyl-2H-1,2,3-triazole (23a)

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) in anhydrous 1,4-dioxane (5.0 ml) was treated with phosphorus trichloride (0.3 g; 0.0022 mol) and the mixture was heated under reflux for 1h. The mixture was diluted with water (5.0 ml), brought to pH8 with aqueous 2M sodium hydroxide solution and extracted with methylene chloride to give a dark red gum (10.3 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded 4-amino-5-nitro-

2-phenyl-2H-1,2,3-triazole (23a) (0.03 g; 8%), m.p. 168-170° (from toluene), $\nu_{max.}$ 3480 and 3380 (NH), 1625 (C=N), and 1570 and 1310 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 7.99-7.92 (2H, m, ArH), 7.72-7.41 (3H, m, ArH, and 6.99 (2H, brs, NH, exchanged with D_2O), δ_C 149.4 (quat.), 139.6 (quat.), 138.2 (quat.), 129.7 (CH), 129.0 (CH), and 118.8 (CH).

Found: C, 46.8; H, 3.4; N, 34.0%; M^+, 205

$C_8H_7N_5O_2$ requires: C, 46.8; H, 3.4; N, 34.1%; M , 205

Further elution with ethyl acetate through to methanol gave no other identifiable material.

The Attempted Reduction of 5-Amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (63)

(a) Using catalytic hydrogenation

(i) A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) in 1,2-dimethoxyethene (20.0 ml) was hydrogenated over 10% palladium-on-charcoal at atmospheric pressure and temperature for 7h. The mixture was filtered through celite and the filtrate was evaporated to give unreacted starting-material (63) (0.38 g; 86%), m.p. 176-180° (decomp.), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

(ii) Repetition of reaction (i) but using acetic acid as the co-solvent gave only an intractable red oil from which no identifiable material could be obtained.

(b) Using sodium dithionite

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole

1-N-oxide (63) (0.44 g; 0.002 mol) and sodium dithionite (0.44 g) in 70% v/v aqueous ethanol (20.0 ml) was heated under reflux for 1h. The mixture was then treated with a second portion of sodium dithionite (0.44 g) and heating under reflux continued for a further 1h. The mixture was evaporated and the residue was treated with water (5.0 ml) and extracted with methylene chloride to give only a small amount of an uncharacterisable gum.

(c) Using sodium borohydride

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) in 1,4-dioxane (10.0 ml) and water (5.0 ml) was stirred and treated at room temperature with a solution of sodium borohydride (0.3 g; 0.0088 mol) in water (4.0 ml). The mixture was stirred at room temperature for 3h, then evaporated, and the residue treated with water (10.0 ml) to give unreacted starting-material (63) (0.4 g; 82%), m.p. 189-193° (decomp.), identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Hydrolysis of 5-Amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (63)

(a) Using aqueous sodium hydroxide

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) in aqueous 2M sodium hydroxide solution (5.0 ml) was heated under reflux for 5 min.

Extraction of the mixture with methylene chloride gave only a small amount of a gum (0.1 g) whose t.l.c. in methylene chloride over silica showed it to be an unresolvable multi-

component mixture which was not further investigated.

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid and anhydrous sodium acetate and extraction with methylene chloride gave no further material.

(b) Using aqueous sulphuric acid in ethanol

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) in ethanol (30.0 ml) and 20% w/v aqueous sulphuric acid (5.0 ml) was heated under reflux for 0.5h.

The mixture was cooled to room temperature and the precipitated solid was collected, washed with ethanol and combined with a second crop obtained by evaporating the ethanolic mother liquor, treatment of the residue with water and extraction with methylene chloride, to give only unreacted starting-material (63) (0.44 g; 100%), m.p. 194-196° (decomp.), identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

The Attempted Diazotisation of 5-Amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-Oxide (63)

A solution of 5-amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) in aqueous 5M hydrochloric acid (1.0 ml) and glacial acetic acid (15.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.14 g; 0.002 mol) in water (1.0 ml) at such a rate that the temperature was <5°. The resulting inhomogeneous diazonium chloride solution was stirred at <5°

for 5 min then heated at 100° (steam bath) for 0.5h. The mixture was concentrated to one fifth of its original volume, treated with water (5.0 ml) and extracted with methylene chloride to give only an intractable gum (0.3 g) from which no identifiable material could be obtained.

(b) 5-Amino-4-nitro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (63) (0.44 g; 0.002 mol) was treated with sodium nitrite in aqueous hydrochloric acid and acetic acid as described in (a) before and the resulting mixture was added dropwise at 0° (ice-salt bath) to a solution of β-naphthol (0.29 g; 0.002 mol) in aqueous 2M sodium hydroxide solution (5.0 ml). The mixture was stirred in the melting ice bath for 0.5h and extracted with methylene chloride to give a gum which was flash-chromatographed in ethyl acetate over silica to afford only unreacted starting-material (63) (0.16 g; 36%), m.p. 180-183° (decomp.), identified by comparison (i.r. spectrum) with an authentic sample prepared before.

5-Amino-1-aryl-3-nitro-1H-1,2,4-triazoles (71) and (77)

(a) A solution of the corresponding 2-nitro-2-oxoacetamidoxime arylhydrazone (62) and (66) (0.015 mol) in anhydrous 1,4-dioxane (50-100 ml) was stirred and treated dropwise at 10° (ice-water bath) with freshly distilled thionyl chloride (2.5 g; 0.021 mol). The mixture was stirred in the melting ice bath for 24h during which time a solid separated. The mixture was evaporated and the residue was treated with 10% w/v aqueous sodium hydrogen carbonate solution and extracted with methylene chloride to give the crude product which was

purified as described for the individual reactions below.

(i) The product from 2-nitro-2-oxoacetomidoxime phenylhydrazone (62) was flash-chromatographed over silica.

Elution with methylene chloride gave 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (68%) which formed buff crystals, m.p. 210-211° (decomp.) (from ethanol), $\nu_{max.}$ 3430, 3280 and 3150 (NH), 1630 (C=N), and 1560 and 1310 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.59 (5H, s, ArH) and 7.20 (2H, brs, NH, exchanged with D_2O), $\delta_C[(CD_3)_2SO]$ 160.3 (quat.), 155.8 (quat.), 135.7 (quat.), 129.7 (CH), 129.0 (CH), and 124.2 (CH).

Found: C, 46.6; H, 3.4; N, 33.8%; M^+, 205

$C_8H_7N_5O_2$ requires: C, 46.8; H, 3.4; N, 34.1%; M , 205

Further elution with ethyl acetate through to methanol gave no other material.

(ii) The product from 2-nitro-2-oxoacetamidoxime 4-methylphenylhydrazone (66 a) was flash-chromatographed over silica.

Elution with methylene chloride afforded unreacted 2-nitro-2-oxoacetamidoxime 4-methylphenylhydrazone (66 a) (0.14 g; 5%), m.p. 129-131° (decomp.), identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Elution with methylene chloride-ethyl acetate (4:1) yielded 5-amino-1-(4-methylphenyl)-3-nitro-1H-1,2,4-triazole (77 a) (49%) which formed cream crystals, m.p. 219-220° (decomp.) (from ethanol), $\nu_{max.}$ 3470, 3410, 3370, 3280, and 3140 (NH), 1630 (C=N), and 1560 and 1320 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.44 (4H, m, ArH), 7.13 (2H, brs, NH, exchanged with D_2O), and 2.39 (3H, s, CH_3).

Found: C, 49.5; H, 4.0; N, 32.2%; M^+, 219

$C_9H_9N_5O_2$ requires: C, 49.3; H, 4.1; N, 32.0%; M , 219

Further elution with ethyl acetate through to methanol yielded no other material.

(iii) The product from 2-nitro-2-oxoacetamidoxime 4-chlorophenylhydrazone (66b) was triturated with methylene chloride to afford 5-amino-1-(4-chlorophenyl)-3-nitro-1H-1,2,4-triazole (77b) (67%), which formed colourless needles, m.p. 241-244° (decomp.) (from ethanol), $\nu_{max.}$ 3430, 3290, 3230, 3160 (NH), 1640 (C=N), and 1520 and 1310 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 7.64 (4H, s, ArH) and 7.26 (2H, brs, NH, exchanged with D_2O).

Found: C, 40.4; H, 2.4; N, 29.2%; M^+, 234 and 241

$C_8H_6ClN_5O_2$ requires: C, 40.1; H, 2.5; N, 29.2%; M , 239.5

Evaporation of the methylene chloride mother liquor afforded an intractable black gum from which no identifiable material could be obtained.

(iv) The product from 2-nitro-2-oxoacetamidoxime 4-nitrophenylhydrazone (66c) was crystallised from glacial acetic acid to give 5-amino-3-nitro-1-(4-nitrophenyl)-1H-1,2,4-triazole (77c) (54%) which formed tan crystals, m.p. 203-205° (decomp.), $\nu_{max.}$ 3500 and 3320 (NH), 1620 (C=N) and 1510 and 1320 (NO_2) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 8.44 (2H, d, J9Hz, ArH), 8.18 (2H, d, J9Hz, ArH), and 7.12 (2H, brs, NH, exchanged with D_2O).

Found: C, 38.4; H, 2.3; N, 33.3%; M^+, 250

$C_8H_6N_6O_4$ requires: C, 38.4; H, 2.4; N, 33.6%; M , 250

(b) A solution of 2-nitro-2-oxoacetamidoxime phenylhydrazone (62) (0.45 g; 0.002 mol) and triethylamine (0.22 g; 0.0022 mol) in anhydrous 1,4-dioxane (5.0 ml) was treated dropwise at room temperature with a solution of toluene-4-sulphonyl chloride (0.42g; 0.0022 mol) in anhydrous 1,4-dioxane (1.0 ml). The mixture was stirred at room temperature for 1h, filtered to remove triethylamine hydrochloride (0.13 g) and evaporated to give an oil which was flash-chromatographed over silica.

Elution with methylene chloride gave 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.17 g; 42%), m.p. 210-211° (decomp.) (from ethanol), identical (m.p. and i.r. spectrum) to an authentic sample prepared in (a) before.

Further elution with ethyl acetate through to methanol gave only a series of gums (total 0.43 g) whose t.l.c. in ethyl acetate over silica showed them to be unresolvable multicomponent mixtures which were not further investigated.

4-Acetylamino-5-nitro-2-phenyl-2H-1,2,3-triazole (70)

(a) A solution of 2-nitro-2-oxoacetamidoxime phenylhydrazone (62) (0.45 g; 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 1h. The mixture was evaporated and the residue was co-evaporated with anhydrous toluene to remove residual acetic anhydride. The red gum (0.52 g) obtained was flash-chromatographed over silica.

Elution with cyclohexane-ethyl acetate (2:1) gave 2-nitro-2-oxoacetamidoxime phenylhydrazone O-acetate (69) (0.05 g; 9%), m.p. 144-149°, identical (i.r. spectrum) to an

authentic sample prepared before.

Elution with methylene chloride-ethyl acetate (3:1) gave a gummy solid (0.38 g) which was triturated with ether to yield 4-acetylamino-5-nitro-2-phenyl-2H-1,2,3-triazole (70) (0.09 g; 18%), which formed colourless needles, m.p. 184-186° (from ethanol), $\nu_{max.}$ 3320 (NH), 1700 (C=O), and 1530 and 1330 (NO_2) cm^{-1}, $\delta_H(CDCl_3)$ 8.81 (1H, brs, NH), 8.19-8.07 (2H, m, ArH), 7.60-7.42 (3H, m, ArH), and 2.44 (3H, s, CH_3).

Found: C, 48.6; H, 3.5; N, 28.6%; m/e 247 (M^+), 217, 205

$C_{10}H_9N_5O_3$ requires: C, 48.6; H, 3.6; N, 28.3%; M, 247

Further elution with ethyl acetate through to methanol gave no other material.

(b) A solution of 2-nitro-2-oxoacetamidoxime phenylhydrazone O-acetate (69) (0.53 g; 0.002 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 1h. The mixture was evaporated and the residue was co-evaporated with anhydrous toluene to remove traces of acetic acid. The resulting gummy solid (0.42 g) was flash-chromatographed over silica.

Elution with methylene chloride afforded 4-acetylamino-5-nitro-2-phenyl-2H-1,2,3-triazole (70) (0.18 g; 36%), m.p. 170-173°, identical (i.r. spectrum) to an authentic sample prepared in (a) before.

Attempted Acylation Reactions of 5-Amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71)

(a) Using acetic anhydride

A solution of 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.41 g; 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 6h. The mixture was evaporated and the residue was co-evaporated with anhydrous toluene to remove traces of acetic anhydride. The resulting gum (0.5 g) was flash-chromatographed over silica.

Elution with methylene chloride afforded 5-(N,N-diacetylamino)-3-nitro-1-phenyl-1H-1,2,4-triazole (72) (0.21 g; 49%) which formed colourless needles, m.p. 105-107° (from ethanol), $\nu_{max.}$ 1760 and 1720 (C=O) and 1520 and 1310 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 7.62 (5H, s, ArH), and 2.32 (6H, s, 2xCH_3).

Found: C, 49.6; H, 3.7; N, 24.2%; m/e 289 (M^+), 247 (M^+-42), 232, 205

$C_{12}H_{11}N_5O_4$ requires : C, 49.8; H, 3.8; N, 24.2%; M, 289

Elution with methylene chloride-ethyl acetate (9:1) afforded only unreacted starting-material (71) (0.10 g; 29%), m.p. 168° (decomp.), identical (i.r. spectrum) to an authentic sample prepared before.

Further elution with methanol gave no other material.

(b) Using formic acid

A solution of 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.41 g; 0.002 mol) in 98-100% formic acid (5.0 ml) was heated under reflux for 3h. The mixture was evaporated and

the residue was co-evaporated with anhydrous toluene to remove traces of formic acid leaving only unreacted starting-material (71) (0.4 g; 98%), m.p. 200-203° (decomp.), identical (i.r. spectrum) to an authentic sample prepared before.

(c) Using triethyl orthoformate

A solution of 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.41 g; 0.002 mol) in triethyl orthoformate (10.0 ml) was heated under reflux for 3h. The mixture was evaporated and the residue was triturated with ether to afford only unreacted starting-material (71) (0.35 g; 86%), m.p. 188-193° (decomp.), identical (i.r. spectrum) to an authentic sample prepared before.

The Attempted Acid-catalysed Hydrolysis of 5-Amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71)

A solution of 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.41 g; 0.002 mol) in ethanol (10.0 ml) was treated with 20% w/v aqueous sulphuric acid (5.0 ml) and the mixture was heated under reflux for 0.5h. The mixture was concentrated to one third of the original volume then diluted with water (5.0 ml) and the precipitated solid was collected and washed with ethanol to afford unreacted starting-material (71) (0.36 g; 88%), m.p. 203-206° (decomp.), identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

The Attempted Catalytic Reduction of 5-Amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71)

5-Amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.41 g; 0.002 mol) was hydrogenated in ethanol (25.0 ml) over 10% palladium-on-charcoal (0.04 g) at room temperature and atmospheric pressure for 6h. No hydrogen was absorbed and the mixture was therefore treated with glacial acetic acid (0.1 ml) and hydrogenation continued for a further 1.5h. The mixture was filtered through celite and the filtrate was evaporated to give a gum (0.19 g; 46%) whose t.l.c. in ethyl acetate over silica showed it to be predominantly unreacted starting-material (71).

The Attempted Peracid Oxidation of 5-Amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71)

(a) A solution of 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.41 g; 0.002 mol) in trifluoroacetic acid (4.0 ml) was stirred and treated at room temperature with 90% v/v aqueous hydrogen peroxide solution (0.76 ml; 0.02 mol). The mixture was stirred at room temperature for 1h then poured into ice-water (10.0 ml) and the precipitated solid was collected, washed with water, and dried in vacuo to afford the unreacted starting-material (71) (0.33 g; 82%), m.p. 207-210° (decomp.), identical (m.p. and i.r. spectrum) to an authentic sample prepared before.

Extraction of the aqueous mother liquor with methylene chloride gave only a negligible quantity of gum.

(b) Reaction (a) was repeated at 60-70° (water bath)

for 15 min and the mixture was poured into (ice-water) (10.0 ml), extracted with methylene chloride and the extract washed with 10% w/v aqueous sodium hydrogen carbonate and water, and evaporated to give a gummy solid (0.23 g) which was flash-chromatographed over silica.

Elution with methylene chloride afforded 3,5-dinitro-1-phenyl-1H-1,2,4-triazole (75) (0.02 g; 4%), m.p. 95-97°.

Found: M^+, 235.0338

$C_8H_5N_5O_4$ requires: M , 235.0342

Further elution with methylene chloride gave 5-(3-nitro-1-phenyl-1H-1,2,4-triazol-5-yl)azo-3-nitro-1-phenyl-1H-1,2,4-triazole (73) (0.02 g; 5%), m.p. 129-135° (decomp.).

Found: M^+, 406

$C_{16}H_{10}N_{10}O_4$ requires: M , 406

Elution with ethyl acetate gave unreacted starting-material (71) (0.10 g; 24%), m.p. 194-198° (decomp.), identical (i.r. spectrum) to an authentic sample prepared before.

Final elution with methanol gave no other identifiable material.

The Attempted Azido-dediazonation of 5-Amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71)

A solution of 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.41 g; 0.002 mol) in aqueous 5M hydrochloric acid (1.0 ml) and glacial acetic acid (10.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.14 g; 0.002 mol) in water (1.0 ml) at such

a rate that the temperature was <5°. The resulting diazonium chloride solution was stirred at <5° for 5 min then added dropwise at 0° (ice-salt bath) to a stirred solution of sodium azide (0.13 g; 0.002 mol) in water (2.5 ml). The mixture was stirred in the melting ice-bath for 0.5h, poured onto crushed ice and extracted with methylene chloride. The methylene chloride extract was washed with saturated aqueous sodium hydrogen carbonate solution and water, and evaporated to give a gum (0.2 g) which was flash-chromatographed over silica but gave no identifiable material.

The Attempted Diazotisation of 5-Amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) and Azo-coupling with β-Naphthol

A solution of 5-amino-3-nitro-1-phenyl-1H-1,2,4-triazole (71) (0.41 g; 0.002 mol) in aqueous 5M hydrochloric acid (1.0 ml) and glacial acetic acid (10.0 ml) was stirred and treated dropwise at 0° (ice-salt bath) with a solution of sodium nitrite (0.14 g; 0.002 mol) in water (1.0 ml) at such a rate that the reaction temperature was <5°. The resulting diazonium chloride solution was stirred at <5° for 5 min then added dropwise at 0° (ice-salt bath) to a stirred solution of β-naphthol (0.29 g; 0.002 mol) in aqueous 2M sodium hydroxide solution (5.0 ml). The mixture was stirred in the melting ice bath for 0.5h and extracted with methylene chloride to give a gum (0.64 g) whose t.l.c. in ethyl acetate over silica showed it to be an unresolvable multicomponent mixture which was not further investigated.

APPENDIX

General Experimental Data

Infrared spectra were recorded for nujol suspensions or thin films using a Perkin-Elmer 781 spectrophotometer. I.r. bands were strong and sharp unless specified as w (weak) or br (broad).

^{1}H and ^{13}C N.m.r. spectra were measured in the stated solvent at 80 MHz or 200 MHz using Bruker WP-80SY and WP-200SY spectrometers. Signals were sharp singlets unless specified as br (broad); d = doublet; d,d = double doublet; t = triplet; q = quartet; m = multiplet.

Mass spectral and accurate mass data were obtained using A.E.I. MS-902 and Kratos MS 50TC instruments.

Microanalyses were determined on a Carlo-Erba Strumentazione Elemental Analyser MOD 1106. Melting points (m.p.) of all analytical samples were determined on a Kofler hot-stage and are uncorrected.

All yields are based on unrecovered starting-material and all organic extracts were dried over anhydrous magnesium sulphate prior to evaporation under reduced pressure. Solvents were of technical grade, unless otherwise specified and unless otherwise indicated light petroleum had m.p. 60-80°.

Bibliography

1. I.J. Rinkes, Recl.Trav.Chim.Pays-Bas, 1934, 53, 1167 (Chem.Abstr., 1935, 29, 2532).
2. I.J. Rinkes, Recl.Trav.Chim.Pays-Bas, 1941, 60, 650 (Chem.Abstr., 1943, 37, 1123).
3. H.J. Anderson, Can.J.Chem., 1957, 35, 21 (Chem. Abstr., 1957, 51, 17878).
4. R. Xun Xu, H.J. Anderson, N.J. Gogan, C.E. Loader and R. McDonald, Tetrahedron Lett., 1981, 22, 4899.
5. L. Alessandri and A. Angeli, Rend.Accad.Sci.Fis.Mat., Naples, 1911, 20, 311; (Chem.Abstr., 1911, 5, 3403).
6. W.J. Hale and W.V. Hoyte, J.Am.Chem.Soc., 1915, 37, 2538.
7. R. Hüttel, F. Büchele, and P. Jochum, Chem.Ber., 1955, 88, 1577.
8. C.L. Habraken and J.W.A.M. Janssen, J.Org.Chem., 1971, 36, 3081.
9. M.A. Khan, B.M. Lynch, and Y. Hung, Can.J.Chem., 1963, 41, 1540.
10. I.L. Finar and R.J. Hurlock, J.Chem.Soc., Perkin Trans.1, 1957, 3024.
11. M.R. Grimmett in Comprehensive Heterocyclic Chemistry, Vol.5, eds. A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984, p.373.
12. R.G. Farger and F.L. Pyman, J.Chem.Soc., Perkin Trans.1, 1919, 217.
13. M. Hoffer, V. Toome, and A. Brossi, J.Heterocycl.Chem., 1966, 3, 454.

14. J.P. Dickens, R.L. Dyer, B.J. Hamill, and T.A. J.Org.Chem., 1981, 46, 1781.

15. J.L. Riebsomer, J.Org.Chem., 1948, 13, 815.

16. B.M. Lynch and T.L. Chan, Can.J.Chem., 1963, 41, 274.

17. P.N. Newman, J.Heterocyclc.Chem., 1971, 8, 51.

18. J.B. Polya in Comprehensive Heterocyclic Chemistry, Vol.5, eds. A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984, p.752.

19. C.L. Habraken and P. Cohen-Fernandes, J.Chem.Soc., Chem.Commun., 1972, 37.

20. A.J. Boulton and A. McKillop in Comprehensive Heterocyclic Chemistry, Vol.2, eds. A.R. Katritzky and C.W. Rees, Pergamon Press, Oxford, 1984, p.35.

21. F. Friedl, Chem.Ber., 1912, 45, 428.

22. P. Schorigin and A.V. Topchiev, Chem.Ber., 1936, 69, 1874.

23. J.S. Wieczorek and T. Talik, Roczniki Chem., 1962, 36, 976; (Chem.Abstr., 1963, 58, 5675).

24. E. Ochiai, J.Org.Chem., 1953, 18, 534.

25. M. Tisler in Comprehensive Heterocyclic Chemistry, Vol.3, eds. A.R. Katrizky and C.W. Rees, Pergamon Press, Oxford, 1984, p.20.

26. S. Dixon and L.F. Wiggins, J.Chem.Soc., 1950, 3236.

27. T. Nakagome, Yakugaku Zasshi., 1962, 82, 253; (Chem.Abstr., 1963, 58, 3426).

28. T. Itai and S. Natsume, Chem.Pharm.Bull., 1963, 11, 83; (Chem.Abstr., 1963, 59, 6402).

29. T. Itai and S. Natsume, Chem.Pharm.Bull., 1963, 11, 342; (Chem.Abstr., 1963, 59, 8733).

30. D.J. Brown in Comprehensive Heterocyclic Chemistry, Vol.3, eds. A.R. Katrizky and C.W. Rees, Pergamon Press, Oxford, 1984, p.69.

31. I. Wempen, H. Ulrich Blank, and J.J. Fox, J.Heterocycl. Chem., 1969, 6, 593.

32. T.B. Johnson and I. Matsuo, J.Am.Chem.Soc., 1919, 41, 782.

33. D.J. Brown, J.Appl.Chem.Biotechnol., 1952, 2, 239.

34. T.B. Johnson and C.O. Johns, J.Am.Chem.Soc., 1905, 34, 554.

35. G. Karmas and P.E. Spoererri, J.Am.Chem.Soc., 1953, 75, 5517.

36. D.S. Donald, U.S. Pat., 3,808,209 (Chem.Abstr., 1975, 83, 81219).

37. J. Hadacek and E. Kisa, Sb.Ved.Pr.,Vys.SR.Chemickotechnol., Pardubice, 1963, 439, 1; (Chem.Abstr., 1964, 60, 8031).

38. L.I. Bagal, M.S. Pevzner, A.N. Frolov, and N.I. Sheludyakova, Khim.Geterotsikl.Soedin., 1970, 6, 259; (Chem.Abstr., 1970, 72, 111383).

39. M.D. Coburn, J.Heterocycl.Chem., 1970, 7, 455.

40. A.G. Beaman, W. Tautz, T. Gabriel, and R. Duschinsky, J.Am.Chem.Soc., 1965, 87, 389.

41. H.P. Burchfield and D.K. Gullstrom, U.S.Pat., 3,054,800; (Chem.Abstr., 1963, 58, 10220).

42. J.T. Witkowski and R.K. Robins, J.Org.Chem., 1970, 35, 2635.

43. E.V. Herz, Ger.Pat., 562,511; (Chem.Abstr., 1933, 27, 1013).

44. E.V. Herz, Brit.Pat., 384,608; (Chem.Abstr., 1933, 27, 4253).

45. A. Kirpal and W. Bohm, Chem.Ber., 1932, 65, 680.

46. E.C. Taylor, C. Tseng, and J.B. Rampal, J.Org.Chem., 1982, 47, 552.

47. O.V. Schikh, A. Binz, and A. Schulz, Chem.Ber., 1936, 69, 2593.

48. E.C. Taylor and J.S. Driscoll, J.Org.Chem., 1960, 25, 1716.

49. T. Talik and Z. Talik, Roczniki.Chem., 1963, 37, 75; (Chem.Abstr., 1963, 59, 8698).

50. H. Junjappa, S.M.S. Chauhan, A. Kumar, and R.R. Rastogi, J.Chem.Soc., Chem.Commun., 1976, 593.

51. K.J. Morgan and D.P. Morrey, Tetrahedron, 1966, 22, 57.

52. S.S. Novikov and V.M. Belikov, Izv.Akad.Nauk., SSSR, Otdel.Khim.Nauk., 1959, 1098; (Chem.Abstr., 1960, 54, 1487).

53. S.S. Novikov, E.N. Safonova, and V.M. Belikov, Izv.Akad.Nauk.,SSSR., Otdel.Khim.Nauk., 1960, 1053; (Chem.Abstr., 1960, 54, 24641).

54. W.E. Parham and J.L. Bleasdale, J.Am.Chem.Soc., 1951, 73, 4664.

55. F.A. Gabitov, O.B. Kremleva, and A.L. Fridman, Zh.Org.Khim., 1977, 13, 1117; (Chem.Abstr., 1977, 87, 84885).

56. D. Pocar, S. Maiorana, P. Dalla Groce, Gazz.Chim.Ital., 1968, 98, 949; (Chem.Abstr., 1969, 70, 37725).

57. H.B. Hill and J. Torrey, J.Am.Chem.Soc., 1899, 22, 89.

58. D. Pocar, S. Maiorana, and P. Dalla Groce, Tetrahedron Lett., 1966, 6043.

59. R. Mohr and M. Zimmerman, Ger.Pat., 1,168,437; (Chem.Abstr., 1964, 61, 1873).

60. A.Dornow and H. Plessen, Chem.Ber., 1966, 99, 244.

61. D.J. Collins, J.Chem.Soc., 1963, 1337.

62. S.V. Stepanova, S.D.L'vova, B.S. El'yanov, and V.I. Gunar, Khim.Form.Zh., 1977, 11, 92; (Chem. Abstr., 1977, 87, 117803).

63. P. Duden and G. Pondorf, Chem.Ber., 1905, 38, 2031.

64. K.D.Gundermann and H.U. Alles, Angew.Chem.Int.Ed.Engl., 1966, 5, 846.

65. L.I. Bagal, I.V. Tselinskii, and I.N. Shokhov, Zh.Org.Khim., 1969, 5, 2016; (Chem.Abstr., 1970, 72, 55180).

66. H. Hamberger, H. Reinshagen, G. Schulz, and G. Sigmund, Tetrahedron Lett., 1977, 3619.

67. H.C. Brill and W.J. Hale, J.Am.Chem.Soc., 1912, 34, 82.

68. E. de la Cuesta and C. Avendano, J.Heterocycl.Chem., 1985, 22, 337.

69. G.P. Sharnin, R. Kh.Fassakhov, T.A. Eneikina, and P.P. Orlov, Khim.Geterotsikl.Soedin., 1977, 653; (Chem.Abstr., 1977, 87, 84886).

70. G.P. Sharnin, R. Kh. Fassakhov, and T.A. Eneikina, Khim.Geterotsikl.Soedin., 1977, 1666; (Chem.Abstr., 1978, 88, 121050).

71. K.C. Agrawal, B.C. Millar, and P. Neta, Radiat.Res., 1979, 78, 532; (Chem.Abstr., 1979, 91, 83079).

72. E.J.J. Grabowski, T.M. Lui, V.J. Grenda, and J.S. Amoto, J.Heterocycl.Chem., 1979, 16, 1153.

73. S.S. Novikov, L.I. Khmel'nitskii, O.V. Lebedev, and L.V. Epishina, Khim.Geterotsikl.Soedin., 1970, 5, 664; (Chem.Abstr., 1970, 73, 56028).

74. M.D. Coburn, H.H. Cady, B.W. Harris, and R.N. Rogers, Energy Res.Abstr., 1977, 2, 52829; (Chem.Abstr., 1978, 88, 152497).

75. E. Bamberger and U. Suzuki, Chem.Ber., 1912, 45, 2790.

76. J. Beger, J.Prakt.Chem., 1964, 311, 746.

77. W. Steinkopf, J.Prakt.Chem., 1910, 81, 203.

78. P.W. Haaijman and J.P. Wibaut, Recl.Trav.Chim.Pays-Bas, 1941, 60, 853.

79. K. Hayes, J.Heterocycl.Chem., 1974, 11, 615.

80. J.G. Buchanan, A. Stobie, and R.H. Wightman, Can.J.Chem., 1980, 58, 2624.

81. M. Begtrup and J. Holm, J.Chem.Soc., Perkin Trans.1, 1981, 503.

82. G. Kabas and H. Schlapfer, Ger.Pat., 2,031,819; (Chem.Abstr., 1971, 75, 22479).

83. W. Steinkopf and L. Bohrmann, Chem.Ber., 1908, 41, 1048.

84. R. Roger and D.G. Neilson, Chem.Rev., 1961, 61, 179.

85. R. Gompper and H. Schaefer, Chem.Ber., 1967, 100, 591.

86. M. Sone, Y. Tominaga, Y. Matsuda, and G. Kobayashi, Yakugaku.Zasshi, 1977, 97, 262; (Chem.Abstr., 1977, 87, 53195).

87. J. Houben and H. Kauffmann, Chem.Ber., 1913, 46, 2821.

88. H.E. Ungnade, L.W. Kissinger, A. Norath, and B.C. Borham, J.Org.Chem., 1963, 28, 134.

89. R. Lenaers, G. Moussebois, and F. Eloy, Helv.Chim. Acta, 1962, 45, 441.

90. J.D. Loudon and G. Tennant, J.Chem.Soc., 1960, 3466.

91. H.E. Ungnade, G. Fritz, and L.W. Kissinger, Tetrahedron, 1963, 19 (Suppl.1), 235.

92. C. Grundmann, V. Mini, J.M. Dean, and H.D. Frommeld, Justus.Liebigs.Ann.Chem., 1965, 687, 191.

93. N.E. Alexandrou and D.N. Nicolaides, J.Chem.Soc., Perkin Trans.1, 1969, 2319.

94. Heilbron, Dictionary of Organic Compounds, Vol.4, eds. J.R.A. Pollock and R. Stevens, Eyre and Spottiswood, London, 1965, p.2582.

95. M.D. Coburn, J.Heterocycl.Chem., 1986, 23, 421; M.D. Coburn, H.H. Haydon, C.L. Coori, and A.R. Mitchell, Synthesis, 1986, 490.

96. H.E. Ungnade and L.W. Kissinger, Tetrahedron, 1963, 19, 143.

97. A. Gasco, V. Mortanni, G. Rua, and A. Serafino, J.Heterocycl.Chem., 1973, 10, 587; R. Calvino, A. Gasco, A. Serafino, and D. Viterbo, J.Chem.Soc., Perkin Trans.1, 1973, 1240.

98. H. von Dobeneck, E. Weil, E. Brunner, H. Deubel, and D.G.G. Wolkenstein, Justus Liebigs Ann.Chem., 1978, 1428.

99. P. Pollet and S. Gelin, Synthesis, 1979, 977.

100. V.G. Andrianov, M.A. Shokhen, A.V. Eremeen, and S.V. Barmina, Khim.Geterotsikl.Soedin., 1986, 264; (Chem.Abstr., 1986, 105, 114403).

101. R. Calvino, A. Gasco, E. Menziani, and A. Serafino, J.Heterocycl.Chem., 1983, 20, 783.

102. A. Gasco, V. Mortanni, G. Rua, and A. Serafino, J.Heterocycl.Chem., 1973, 10, 587.

103. R. Calvino, A. Gasco, A. Serafino, and D. Viterbo, J.Chem.Soc., Perkin Trans.1, 1973, 1240.

104. G.D. Solodyuk, M.D. Boldyren, B.V. Gidaspov, and V.D. Nikolaen, J.Org.Chem. USSR, 1981, 17, 861; (Chem.Abstr., 1981, 95, 80839).

105. J. Tröger and A. Prochnow, J.Prakt.Chem., 1908, 78, 123.

106. J. Tröger and W. Hille, J.Prakt.Chem., 1905, 71, 201.

107. A.E. Sigrist, G. Kormany, G. Kabas, and H. Schlapfer, Helv.Chim.Acta, 1977, 60, 2334.

108. C. Kimich, Chem.Ber., 1877, 10, 140.

109. V.V. Maksimov, S.M. Kvitko, and V.V. Perekalin, Zh.Org.Khim., 1972, 8, 332; (Chem.Abstr., 1972, 76, 126544).

110. M. Begtrup and N.O. Knudsen, Acta Chem.Scand.,Ser.B, 1983, 37, 97.

111. U. Claussen, H. Gold, and J. Schroeder, Ger.Pat. 2,210,261; (Chem.Abstr., 1973, 79, 137160).

112. W. Steinkopf and L. Bohrmann, Chem.Ber., 1908, 41, 1044).

113. L.S. Pupko, A.I. Dychenko, and P.S. Pelkis, Zh.Org. Khim., 1972, 8, 39; (Chem.Abstr., 1972, 76, 112852).

114. H. Lind and H. Kristinsson, Synthesis, 1974, 198.

115. M. Regitz, Angew.Chem.Int.Ed.,Engl., 1967, 6, 746.

116. J. Schawartz, M. Hornyak, and T. Suts, Chem.Ind. (London), 1970, 92.

117. L.S. Pupko, A.I. Dychenko, and P.S. Perkis, Zhur. Org.Khim., 1972, 8, 39; (Chem.Abstr.,

118. C. Temple in '1,2,4-Triazoles', The Chemistry of Heterocyclic Compounds, Vol.37, ed. J.A. Montgomery, Wiley-Interscience, New York, 1981.

119. C. Temple in '1,2,4-Triazoles', The Chemistry of Heterocyclic Compounds, Vol.37, ed. J.A. Montgomery, Wiley-Interscience, New York, 1981, Chapter 8, p.226.

120. E.J. Corey, B. Samuelsson, and F.A. Luzzio, J.Am.Chem. Soc., 1984, 106, 3682.