New Synthetic Approaches to Azapurines, Azapteridines and Related Polyazaheterocycles

by

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degree of Doctor of Philosophy
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To my parents

and

James and Elizabeth McGlashan

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 19th December 1985.

Acknowledgements

I would like to express my gratitude to my supervisor, Dr. G. Tennant, for his guidance and encouragement throughout the past three years.

I would also like to thank the University of Edinburgh for the provision of laboratory and library facilities. I am indebted to the technical staff of the Department of Chemistry and I am grateful to the Science and Engineering Research Council for the award of a studentship.

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Abstract

The subject matter of this thesis is concerned with investigations of new synthetic approaches to azapurines, azapteridines and related polyazaheterocycles. The description of the results obtained in these studies is preceded by a survey of the known syntheses and biological activity of aza- and diaza-analogs of purine and pteridine. Three approaches to such polyazaheterocycles are described.

Firstly, the use of 2*H*-1,2,3-triazoles and their N-oxides to synthesise 2*H*-aza- and diazapurines. The synthesis of appropriately functionalised 2*H*-1,2,3-triazole derivatives has been accomplished with moderate success. However attempted annulation of such 2*H*-1,2,3-triazoles to obtain 2*H*-aza- and diazapurines was unsuccessful.

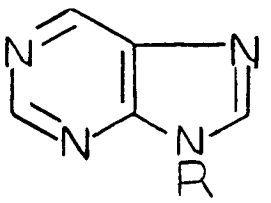
Secondly, the use of tosyl isocyanate to annulate *ortho* amino-azoheterocycles has been studied. It was found to be largely successful for a variety of *ortho*-aminoazopyrazoles and its mechanism has been elucidated. The reactivity of the resulting pyrazolo[3,4-*e*]-1,2,4-triazinones toward a variety of nucleophiles has been investigated. Extension of this tosyl isocyanate annulation to other *ortho* amino-azo heterocycles has had limited success. In particular, it was found that *ortho*-aminoazoisoxazoles undergo thermal rearrangements rather than annulation. The tosyl isocyanate annulation has also been studied as a general method of carbonylation in the formation of other heterocyclic systems.

The third and final approach to aza- and diaza-analogs of purine and pteridine which was investigated involved the use of bridgehead fused 1,2,3-triazoles. Appropriately functionalised 1,2,3-triazolo[5,1-c]-1,2,4-triazines were synthesised. These were subjected to orthodox annulation procedures which were largely unsuccessful. Disappointingly the unknown 1,2,3-triazolo[5,1-g]imidazo[4,5-c]-1,2,4-triazine failed to undergo triazole ring cleavage under the highly forcing conditions of refluxing trifluoroacetic acid. Some interesting rearrangements of 1,2,3-triazolo[5,1-c]-1,2,4-triazines were investigated.

CONTENTS

FOREWORD

The biological importance of derivatives of the imidazo[4,5-b]pyrimidine (purine) (1) and the pyrimido-[4,5-d]pyrazine (pteridine) (2) ring systems, is well known and the synthesis and biological activity of such



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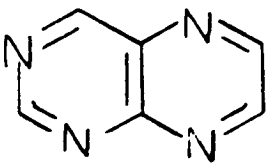

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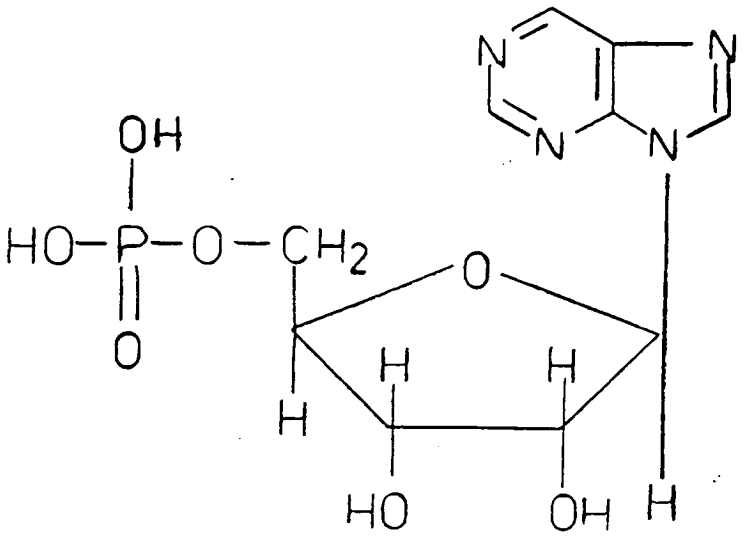
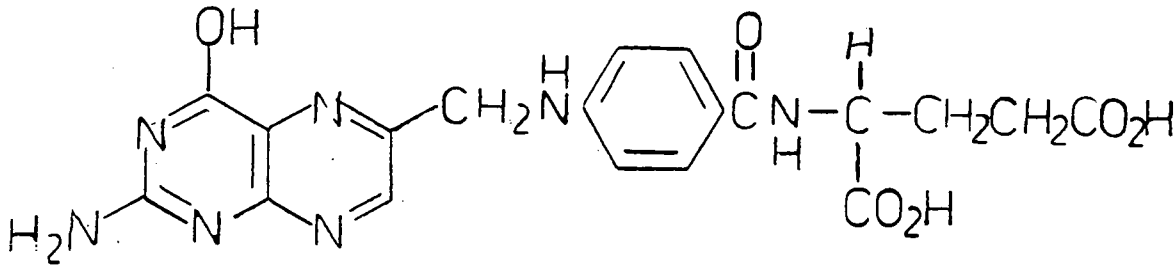
bicyclic polyazaheterocycles have been extensively studied. Purine derivatives are well known as monomer units of nucleic acids as exemplified by the ribonucleoside adenosine-5'-monophosphate (3). The pteridine nucleus is



(3)

also found in many natural products of which Folic acid (4) is physiologically the most important being involved in



(4)

vitamin and purine biosynthesis. Less is known about the biological activity of aza- and diaza-analogues of purines and pteridines and the following thesis is concerned with studies of new methods for the construction of certain aza and diaza purine and pteridine ring systems. By way of introduction the discussion of the results obtained in these studies is preceded by a survey of the currently available synthetic methods for such polyazaheterocycles and their more important biological properties.

CHAPTER 1

A Survey of the Biological Activity and Literature Methods for the Synthesis of Aza- and Diaza-Analogues of Purines and Pteridines

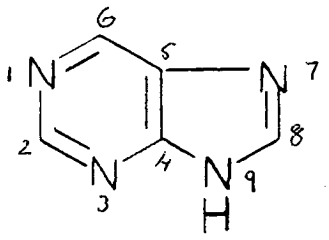
A Survey of the Biological Activity and Literature Methods for the Synthesis of Aza- and Diaza-Analogues of Purines and Pteridines

In the following survey of the currently available methods of synthesis and the biological activity of azapurines, diazapurines, azapteridines and diazapteridines, discussion is limited to bicyclic 6:5 and 6:6 polyazaheterocyclic ring systems derived by the insertion of one or two additional nitrogen atoms into the purine and pteridine frameworks without scrambling of the four ring-nitrogen atoms originally present. Aza and diaza purine and pteridine analogues incorporating bridgehead nitrogen atoms or tetrazine nuclei are also excluded from the survey.

1.1 AZAPURINES

Three distinct ring systems (Scheme 1) can be derived by replacing a single methine group in purine (1) by a nitrogen atom. These are the 1,2,3-triazolo[4,5-d]-pyrimidine ring system (2), the imidazo[4,5-e]-1,2,4-triazine ring system (3) and the imidazo[4,5-d]-1,2,3-triazine ring system (4), formally derived by inserting the circled nitrogen atoms into the purine framework. The systematic nomenclature and numbering (see Scheme 1) indicated for these ring systems is based on that used in Chemical Abstracts. However, the heterocyclic nuclei [(2) - (4)] can also be referred to as aza-analogues of purine (1) itself. Hence the 1,2,3-triazolo[4,5-d]-

pyrimidine ring system (2) can also be named as 8-azapurine and similarly 6-azapurine and 2-azapurine are alternative names for the imidazo[4,5-e]-1,2,4-triazine (3) and imidazo[4,5-d]-1,2,3-triazine (4) ring systems respectively.



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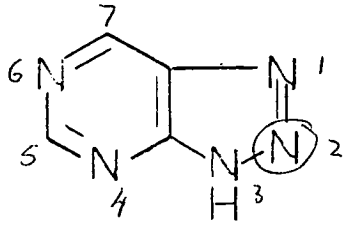

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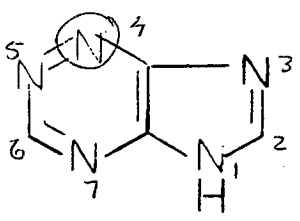

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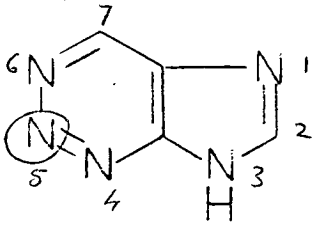

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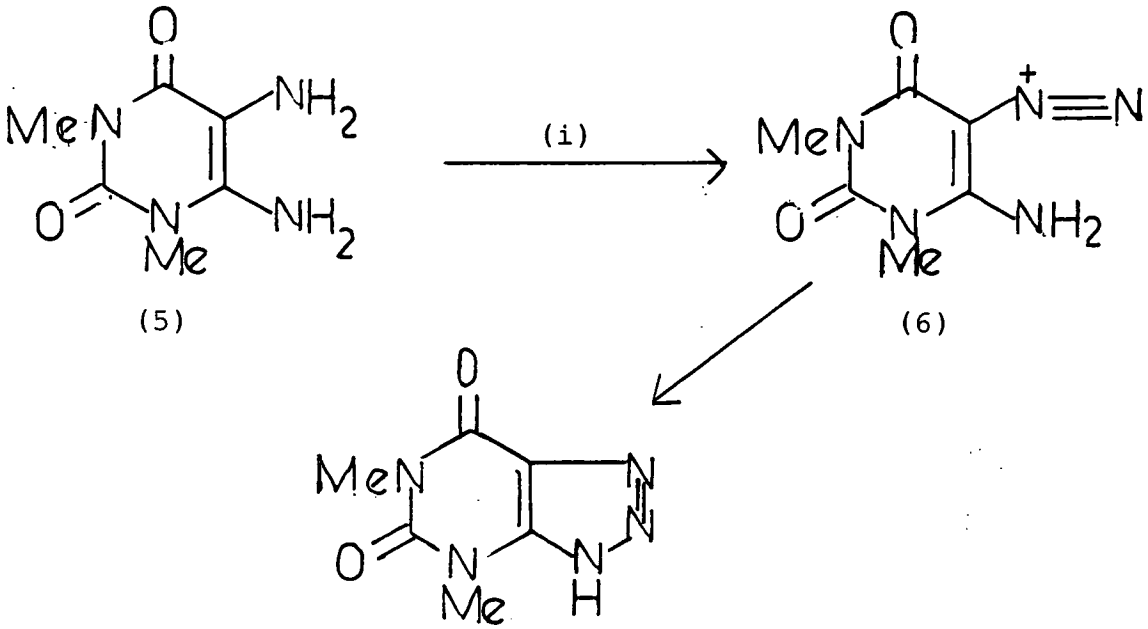
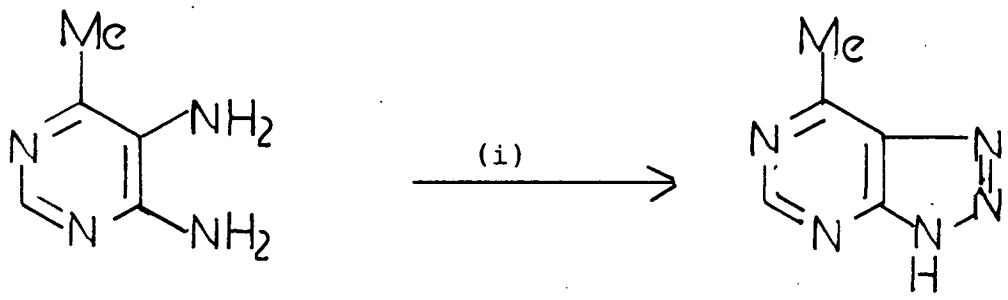
Scheme 1



(5) (6) (7)

(i) $NaNO_2$, HCl, 0°

Scheme 2



(8) (9)

(i) $NaNO_2$, HCl, 0°

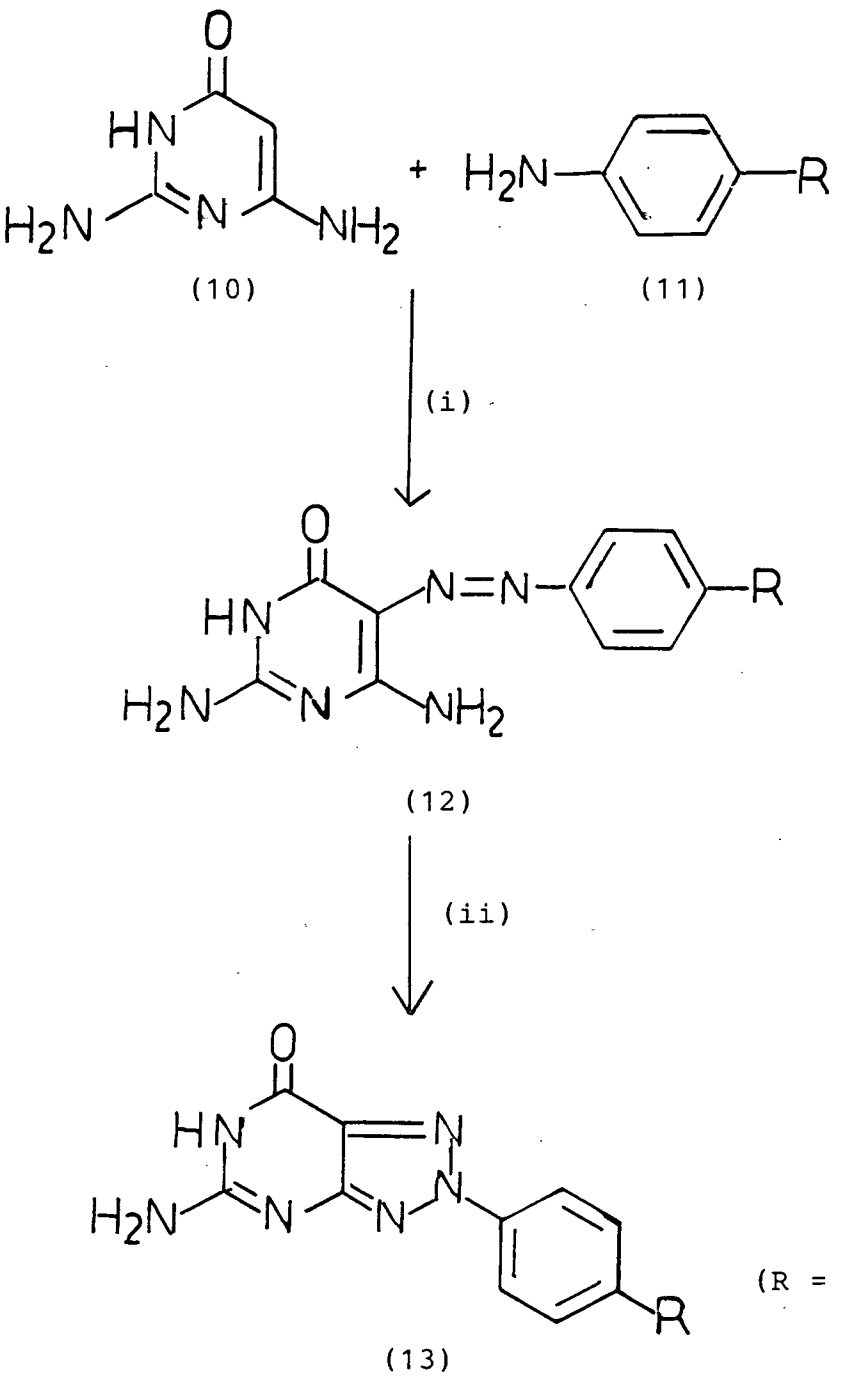
Scheme 3

1.1.1 1,2,3-Triazolo[4,5-d]pyrimidines (8-Azapurines)

1,2,3-Triazolo[4,5-d]pyrimidine derivatives have been the subject of extensive study largely because they exhibit a wide spectrum of biological activity[1] including antiallergic activity,[2] antiviral activity,[3] antitumor activity,[4] and antileukemic activity.[5] Three main synthetic strategies have been employed for the synthesis of 8-azapurines. Firstly from pyrimidine derivatives with subsequent formation of the 1,2,3-triazole ring.[1,6] Secondly, from 1,2,3-triazole derivatives with eventual ring closure of the pyrimidine ring.[1,6] Thirdly, by ring transformations of other heterocycles.[7]

8-Azapurine Synthesis Based on Ring-Closure Reactions of Pyrimidine Derivatives

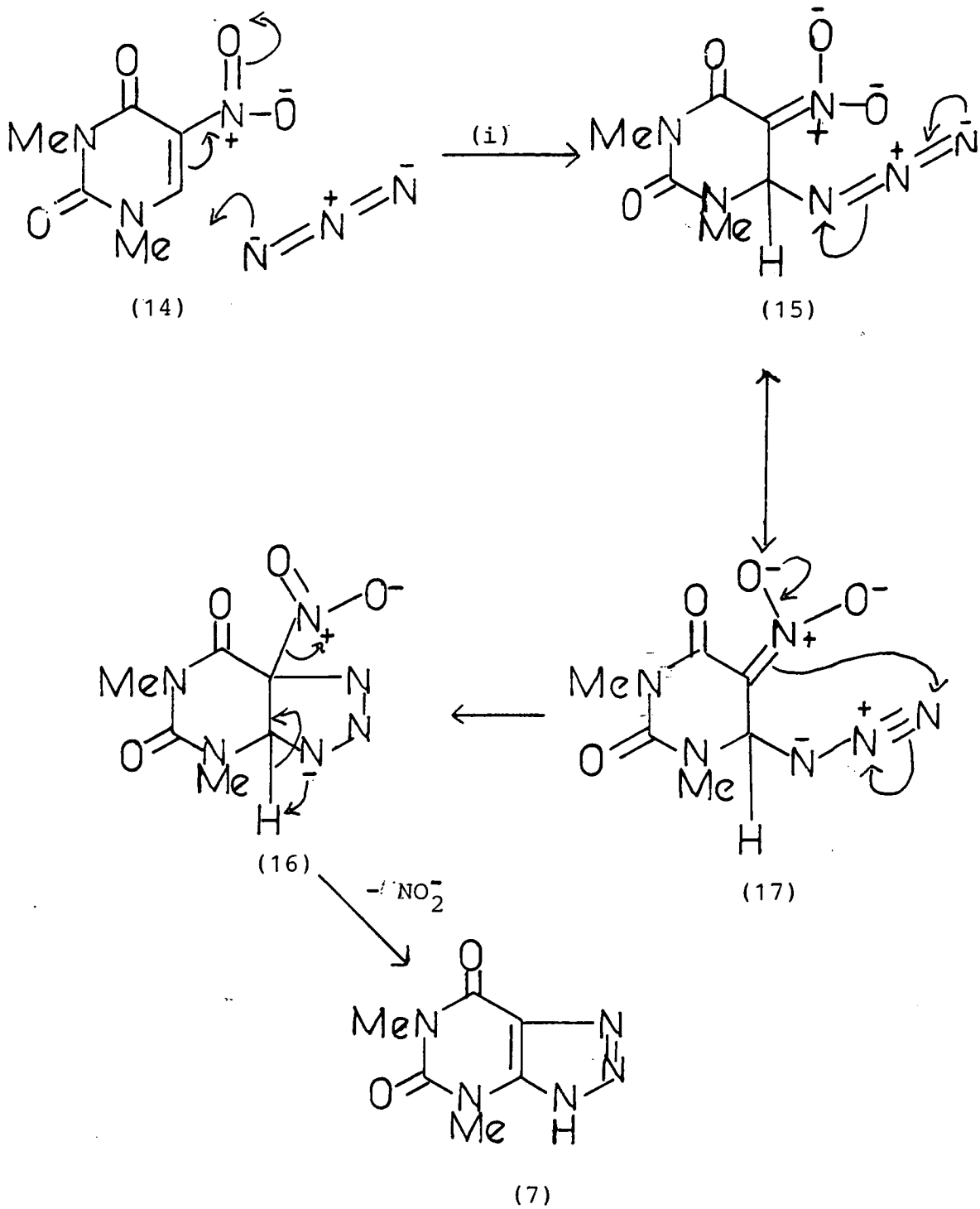
The first synthesis of an 8-azapurine (Scheme 2) appears to be that by Traube[8] in which the product he describes as an 'azimid', the 1,2,3-triazolo[4,5-d]-pyrimidine derivative (7) is synthesised by the diazotative cyclisation of the 4,5-diaminopyrimidinedione (5). Similarly (Scheme 3) Gabriel and Colman[9] treated 4,5-diamino-6-methylpyrimidine (8) with sodium nitrite and hydrochloric acid to obtain the 1,2,3-triazolo[4,5-d]-pyrimidine (9) which they called '4,5,6-methylazimido-pyrimidine'. This diazotative cyclisation procedure has been used for the synthesis of a large number of



(i) $NaNO_2$, HCl, NaOAc

(ii) $CuSO_4$, pyridine

Scheme 4



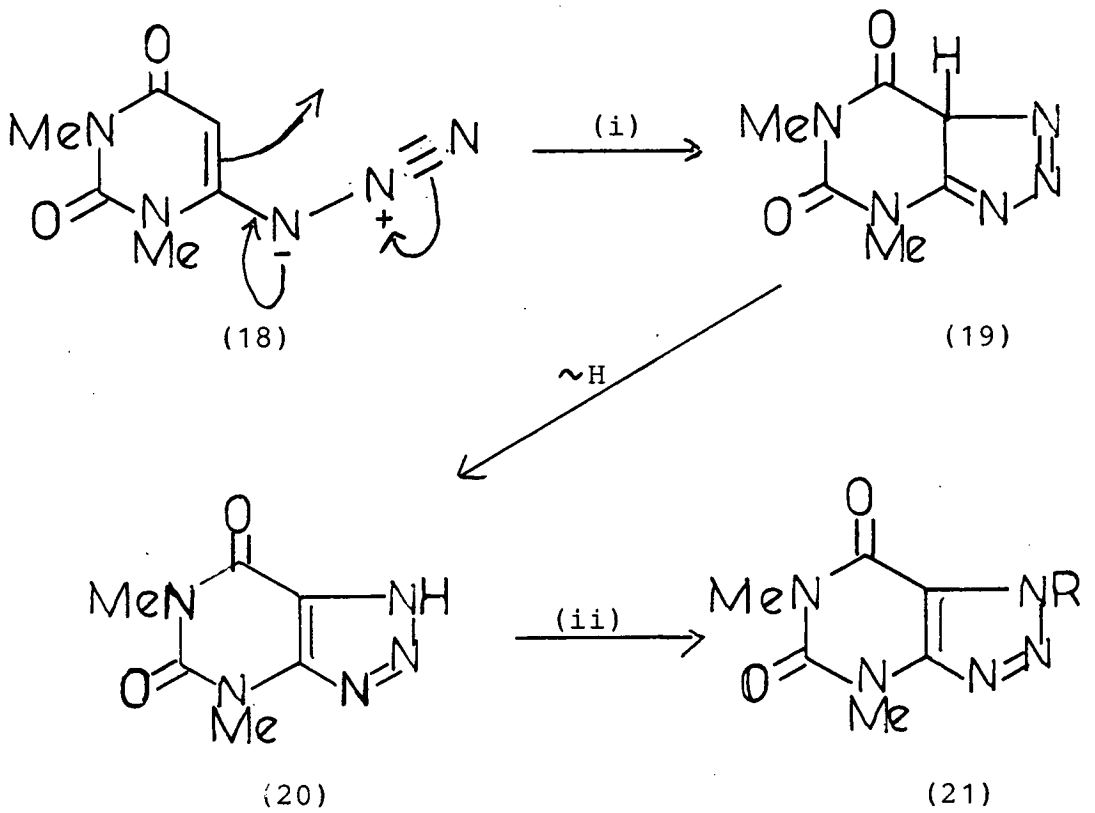
(i) $Me_2NCH{=}O$, heat

Scheme 5

8-azapurine derivatives[10-13] including 8-azapurinenucleosides.[14,15] The success of the diazotative ring-closure of 4,5-diaminopyrimidines to 8-azapurines in aqueous media appears to be dependent on the water solubility of the diaminopyrimidine starting material. Where the latter is insoluble in water the diazotative cyclisation can be carried out in an organic solvent using amyl nitrite as the diazotising agent.[16,17]

Another synthesis of 8-azapurine derivatives (Scheme 4) first described by Benson and his co-workers[18,19] involves oxidative closure of the triazole ring. These authors showed that the 2,6-diaminopyrimidine derivative (10) coupled readily with benzenediazonium chloride to give the 5-arylazo-derivative (12) which could be oxidatively cyclised using cupric sulphate in pyridine to yield the 1,2,3-triazolo[4,5-d]pyrimidine (13). The use of lead tetra-acetate for the oxidative cyclisation of ortho-amino-arylazopyrimidines is claimed[20] to result in improved yields of 8-azapurines.

Some interesting examples of the synthesis of 8-azapurine derivatives from pyrimidines with a single nitrogen substituent in the 4- or 5-position have been described. Thus Blank and his co-workers[21] have demonstrated the formation (Scheme 5) of 1,2,3-triazolo-[4,5-d]pyrimidines [e.g. (17)] from nitropyrimidines [e.g. (14)] by treatment with sodium azide in dimethylformamide. Reactions of this type can be explained by

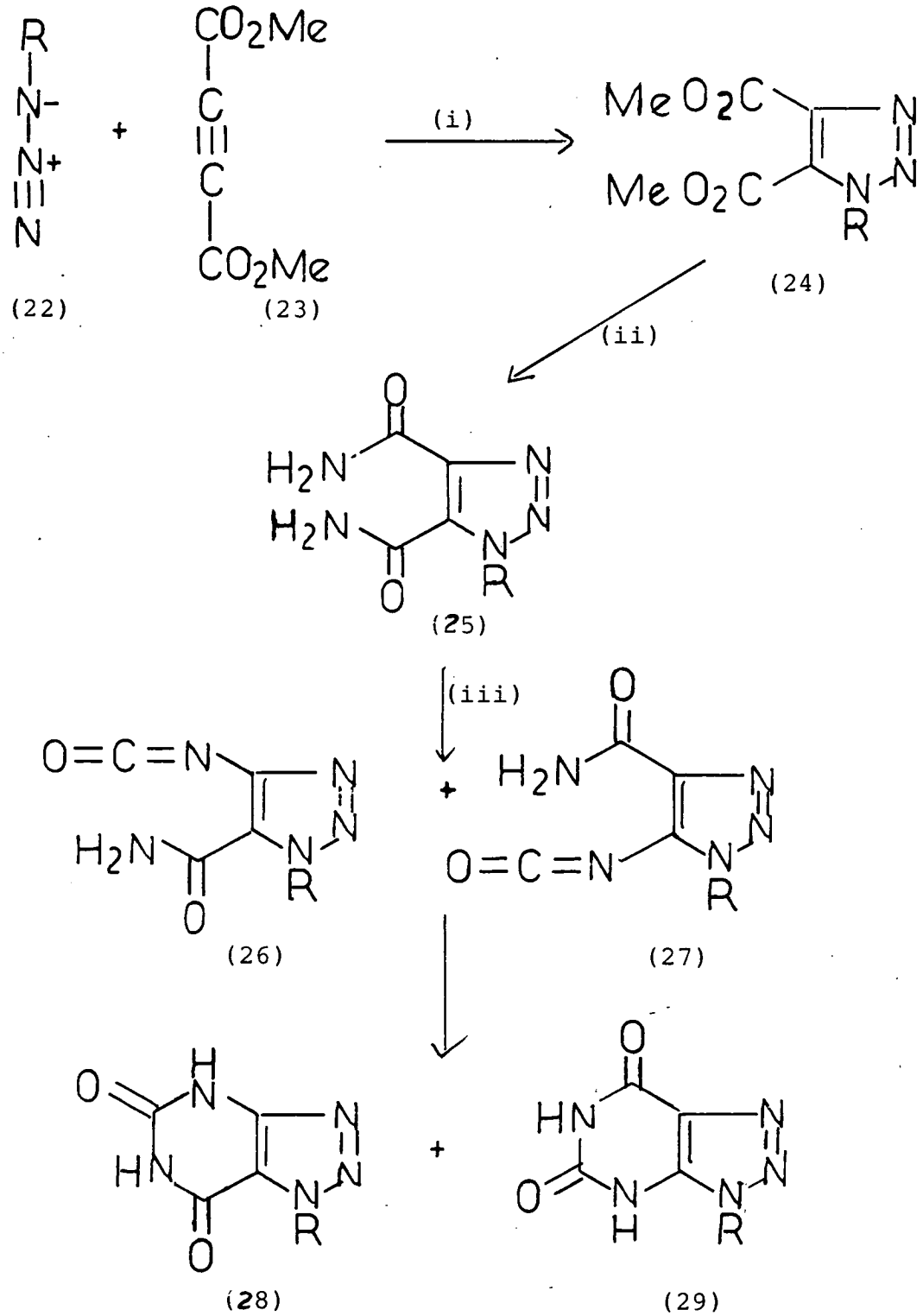


(R = Me, Et, $PhCH_2$)

(i) $Me_2NCH=O$, heat

(ii) RX, K_2CO_3 (X = Cl, Br, I)

Scheme 6



(i) benzene, heat

(ii) NH_3

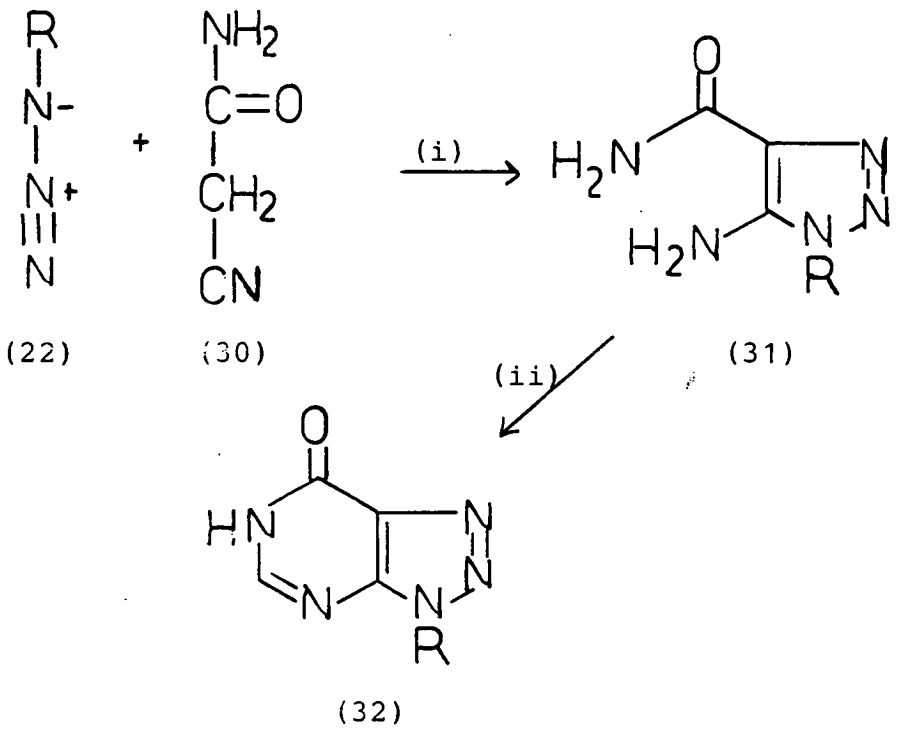
(iii) Br_2, NaOH

Scheme 7

initial Michael addition of azide ion to the nitropyrimidine (14) to give the adduct (15) which can cyclise as shown to afford the intermediate (16). Elimination of nitrous acid from the latter then gives the 1,2,3-triazolo[4,5-d]pyrimidine (7). 1,2,3-Triazolo[4,5-d]-pyrimidines are also the products of intramolecular cycloaddition reactions of certain azidopyrimidine derivatives. For example (Scheme 6)[22] heating 6-azido-1,3-dimethyluracil (18)[23] in dimethylformamide results in the formation of the 8-azapurine derivative (20). This transformation can be explained by electrocyclisation to give the unstable intermediate (19) which undergoes a spontaneous hydrogen shift to afford the more stable 1,2,3-triazolo[4,5-d]pyrimidine (20). Alkylation of the latter compound also provides a useful route to the corresponding 1-alkyl-1,2,3-triazolo[4,5-d]pyrimidines (21).

8-Azapurine Synthesis Based on Ring-Closure Reactions of 1,2,3-Triazole Derivatives

Baddiley and his co-workers[24,25] were the first to demonstrate the synthesis of 1,2,3-triazolo[4,5-d]pyrimidines (8-azapurines) from appropriately substituted triazoles. 8-Azapurine synthesis of this type is exemplified (Scheme 7) by the reaction of 1,2,3-triazole-4,5-dicarboxamides (25) with sodium hypobromite to give through the presumed intermediacy of the two possible isocyanato-1,2,3-

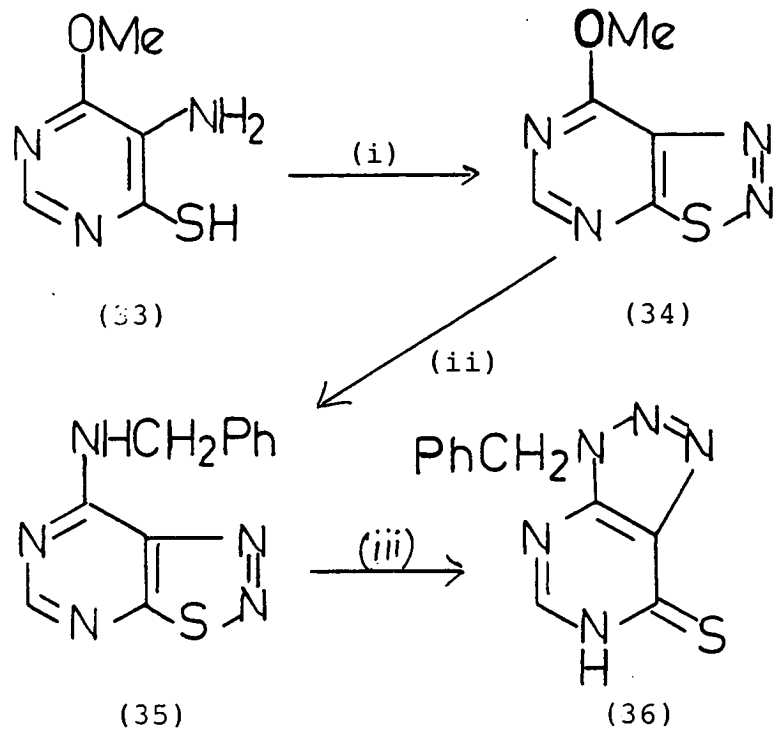


(22) (30) (31) (32)

(i) NaOEt, EtOH

(ii) $HC(OEt)_3$ or $HCONH_2$, heat

Scheme 8



(i) $NaNO_2$, HCl

(ii) $PhCH_2NH_2$

(iii) 2M NaOH, heat

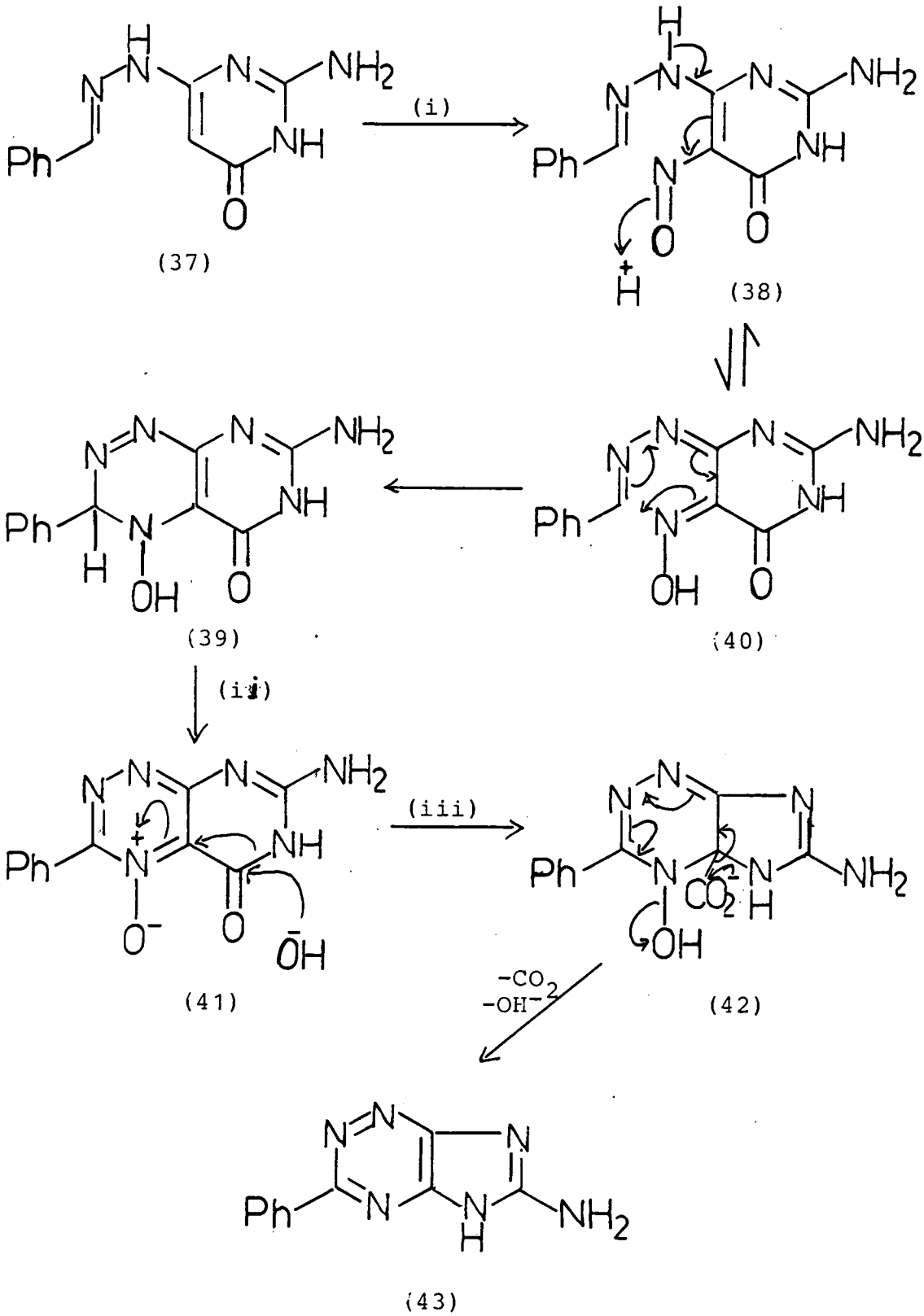
Scheme 9

triazolecarboxamides (26) and (27) a mixture of the corresponding isomeric 1,2,3-triazolopyrimidinediones (28) and (29). The 1,2,3-triazole-4,5-dicarboxamides required for this type of 8-azapurine synthesis are readily prepared (Scheme 7) by the cycloaddition of dimethyl acetylene-dicarboxylate (23) to azides (22) followed by the reaction of the resulting dimethyl 1,2,3-triazole-4,5-dicarboxylates (24) with ammonia.

1,2,3-Triazolo[4,5-d]pyrimidines have also been synthesised (Scheme 8) by more orthodox cyclisation reactions of 5-amino-1,2,3-triazole-4-carboxamides (31).[26] The latter are readily prepared by the base-catalysed condensation of azides (22) with cyanoacetamide (30) and are converted by reaction with triethyl orthoformate or formamide into the corresponding 1,2,3-triazolopyrimidines (32). Albert and his co-workers[27] have made extensive use of this type of synthesis to produce 1,2,3-triazolo-[4,5-d]pyrimidines with a wide variety of substituents.

8-Azapurine Synthesis Based on Ring Transformations of Other Heterocycles

Only a single example of the conversion of a different bicyclic heterocyclic system into an 8-azapurine derivative (Scheme 9) appears to be known.[7] The 4-benzylamino-1,2,3-thiadiazolo[5,4-d]pyrimidine (35) readily undergoes a Dimroth rearrangement in refluxing sodium hydroxide to give 1-benzyl-1H-1,2,3-triazolo[4,5-d]pyrimidine-4(5H)-thione (9-benzyl-6-mercapto-8-azapurine) (36). The

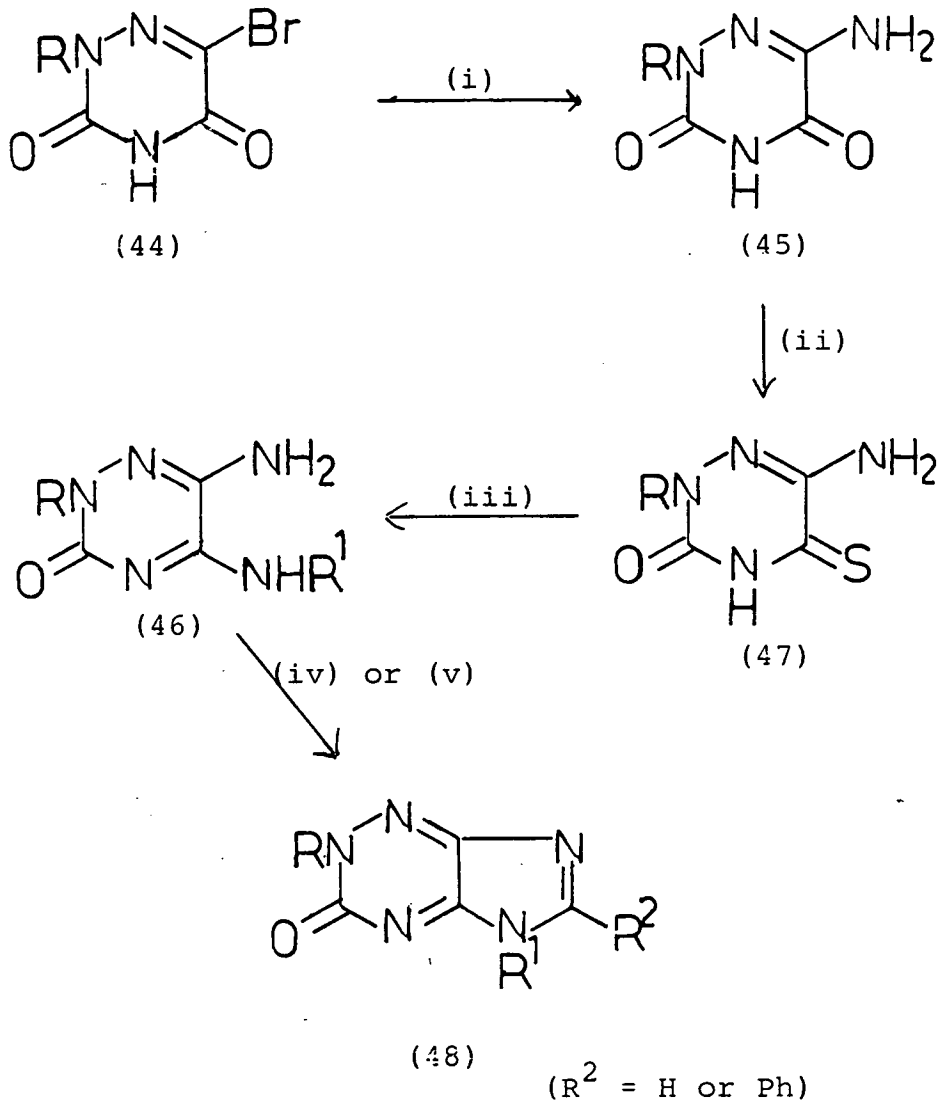


(i) $NaNO_2$, AcOH

(ii) $EtO_2CN{=}NCO_2Et$, fusion

(iii) NaOH, EtOH, heat

Scheme 10



(i) NH_3, heat

(ii) P_2S_5, heat

(iii) R^1NH_2, heat

(iv) PhCHO, heat

(v) $HC(OEt)_3$, heat

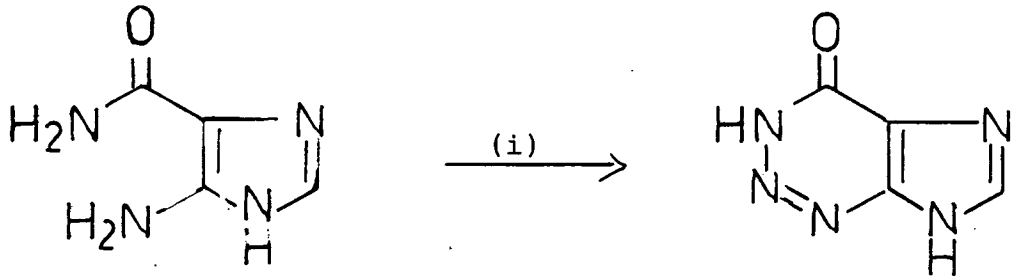
Scheme 11

thiadiazolo[5,4-d]pyrimidine (35) is readily available by diazotative cyclisation of 5-amino-6-mercapto-4-methoxypyrimidine (33) to give 4-methoxy-1,2,3-thiadiazolo-[4,5-d]pyrimidine (32)[28] followed by treatment with benzylamine.

1.1.2 Imidazo[4,5-e]-1,2,4-Triazines (6-Azapurines)

The first synthesis of 6-azapurines (Scheme 10) was reported by Yoneda and his co-workers[30] in 1976. These authors showed that treatment of pyrimido[5,4-e]-1,2,4-triazines [e.g. (41)] with ethanolic sodium hydroxide resulted in contraction of the pyrimidine ring to give through the presumed intermediate (42) the corresponding 6-azapurine derivative (43). This 6-azapurine synthesis is made general by the ready availability of the pyrimido-[5,4-e]-1,2,4-triazine starting materials [e.g. (41)] by nitrosative cyclisation of arylidene pyrimidylhydrazones [e.g. (37)] using sodium nitrite in acetic acid to give dihydropyrimido-1,2,4-triazines [e.g. (39)] followed by *in situ* oxidative aromatisation of the latter by treatment with diethylazodicarboxylate. Yoneda and his co-workers have used this route (Scheme 10) for the synthesis of a wide variety of 6-azapurine derivatives.[30-34]

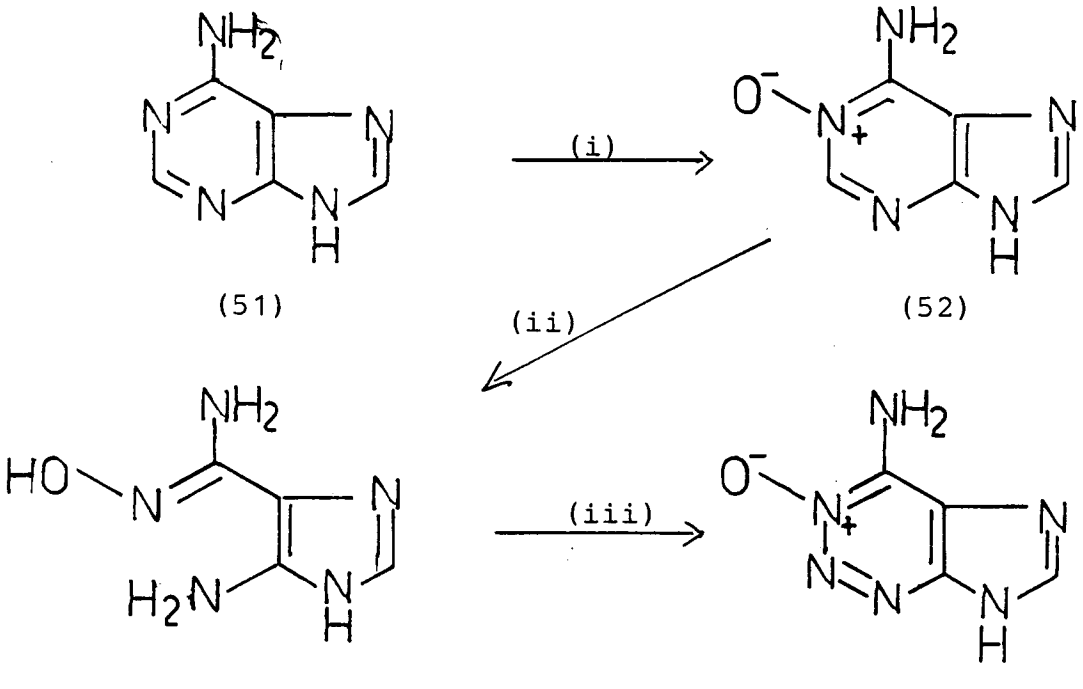
There would appear to be only one other route to 6-azapurine derivatives[35] (Scheme 11) involving the more orthodox procedure of the ring closure of 5,6-diamino-1,2,4-triazine derivatives [e.g. (46)]. These substrates are



(49) (50)

(i) $NaNO_2$, HCl

Scheme 12



(51) (52) (53) (54)

(i) H_2O_2-AcOH

(ii) conc. HCl

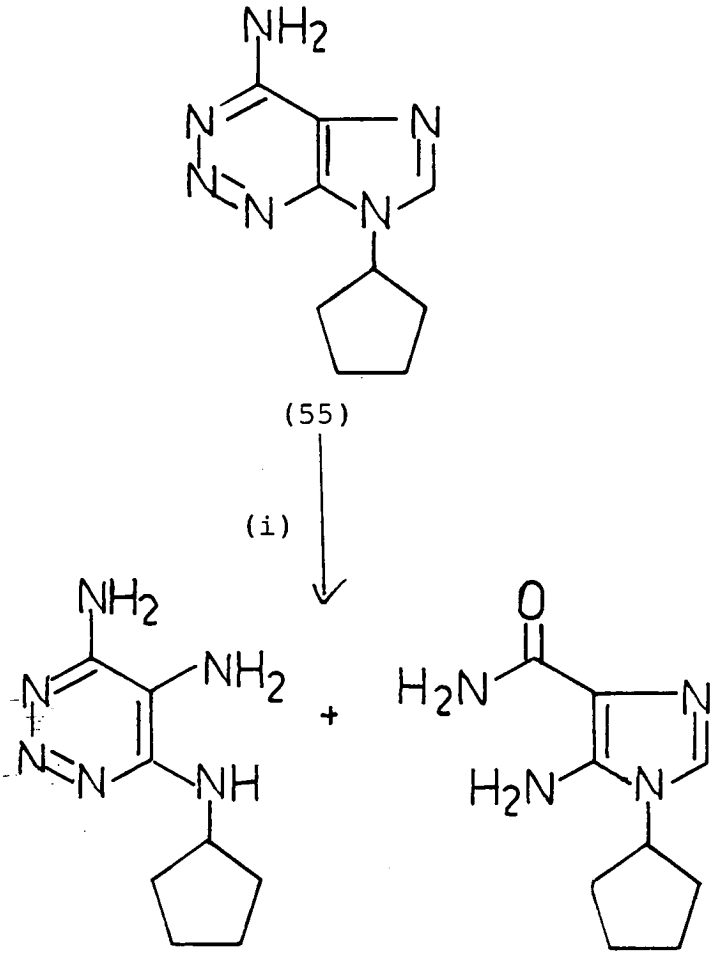
(iii) $NaNO_2$, HCl

Scheme 13

readily obtained from 6-bromo-1,2,4-triazine-3,5(2H-4H)-dione derivatives (44) by treatment with ammonia followed by reaction of the resulting amino-1,2,4-triazinediones (45) with phosphorus pentasulphide to give 1,2,4-triazinethiones (47) then treatment of the latter with amines. The 5,6-diamino-1,2,4-triazines (46) so obtained are readily ring closed to 6-azapurines (48) by heating with reagents such as ethyl orthoformate. The biological activity of 6-azapurine derivatives does not appear to have been investigated.

1.1.3 Imidazo[4,5-d]-1,2,3-triazines (2-Azapurines)

Only one synthetic approach (Scheme 12) to the 2-azapurine ring system has been described to date. This is based on the diazotative cylisation[36-40] of 4-amino-imidazole-5-carboxamides as demonstrated (Scheme 12) by the transformation of 4-amino-imidazole-5-carboxamide (49) itself on treatment with sodium nitrite in aqueous hydrochloric acid into 1H-imidazo[4,5-d]-1,2,3-triazin-4(5H)-one (50). 2-Azapurine N-oxides have also been reported[41] as products of the diazotative cyclisation (Scheme 13) of 5-aminoimidazole-4-caboxamidoximes as illustrated by the conversion of 5-aminoimidazole-4-carboxamidoxime (53) itself into 4-amino-1H-imidazo-[4,5-d]-1,2,3-triazine 5-N-oxide (54) by reaction with sodium nitrite in aqueous hydrochloric acid. 5-Amino imidazole-4-carboxamidoxime (53) is obtained by the



(56) (57)

(i) NaOH, heat

Scheme 14

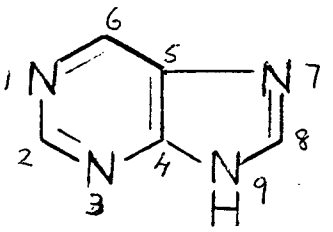
hydrochloric acid-catalysed degradation of the purine-N-oxide (52) which in turn can be synthesised by oxidation of 6-aminopurine (adenine) with peracetic acid.

The other obvious synthetic approach to 2-azapurines involving ring closure of 4,5-diamino-1,2,3-triazine precursors has not been reported to date presumably because such 1,2,3-triazine derivatives are only accessible by the hydrolysis of 2-azapurines themselves[42,43] as exemplified (Scheme 14) by the alkaline hydrolysis of the cyclopentyl derivative (55) to the triamino-1,2,3-triazine (56) and the 5-amino-imidazole-4-carboxamide derivative (57).

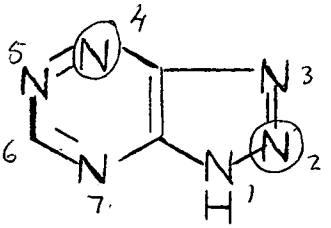
The biological properties of 2-azapurines have been investigated only to a limited extent to judge from the relatively few reports of their biological activity in the literature. 2-Azapurines are claimed[44] to possess antiviral and antitumor activity apparently related to their ability to inhibit cellular and viral methyl-transferase enzymes. In the form of sugar derivatives (nucleosides) they can act as substrates for the enzyme phosphodiesterase[45] an important enzyme in the metabolism of cylic AMP (adenosine-3',5'-monophosphate) a compound of pronounced biological and physiological significance.

1.2 DIAZAPURINES

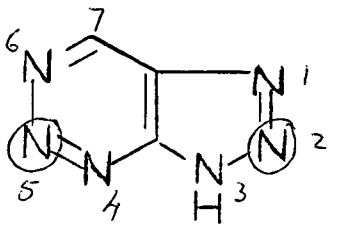
Two distinct diazapurine ring systems (Scheme 15) can in theory be derived by replacement of methine groups in the imidazole and pyrimidine rings of purine (1) by two nitrogen atoms. These are the 1,2,3-triazolo[4,5-e]-1,2,4-triazine ring system (58) and the 1,2,3-triazolo-[4,5-d]-1,2,3-triazine ring system (59), formally obtained by insertion of the circled nitrogen atoms (Scheme 15) into the single available site of the imidazole moiety and the two distinct sites in the pyrimidine nucleus of the purine framework (1).



(1)

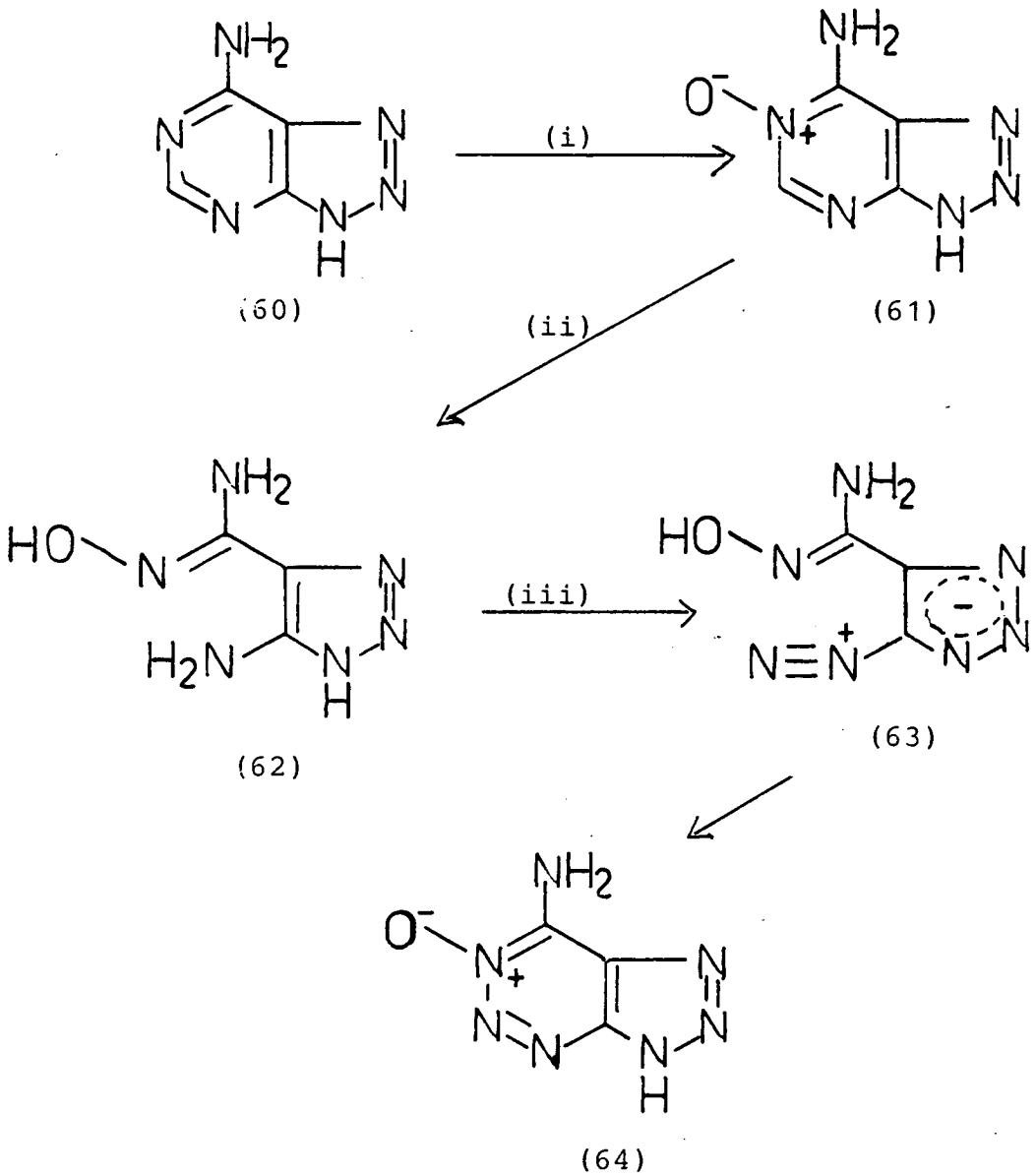


(58)



(59)

Scheme 15



(60) (61) (62) (63) (64)

(i) H_2O_2-AcOH

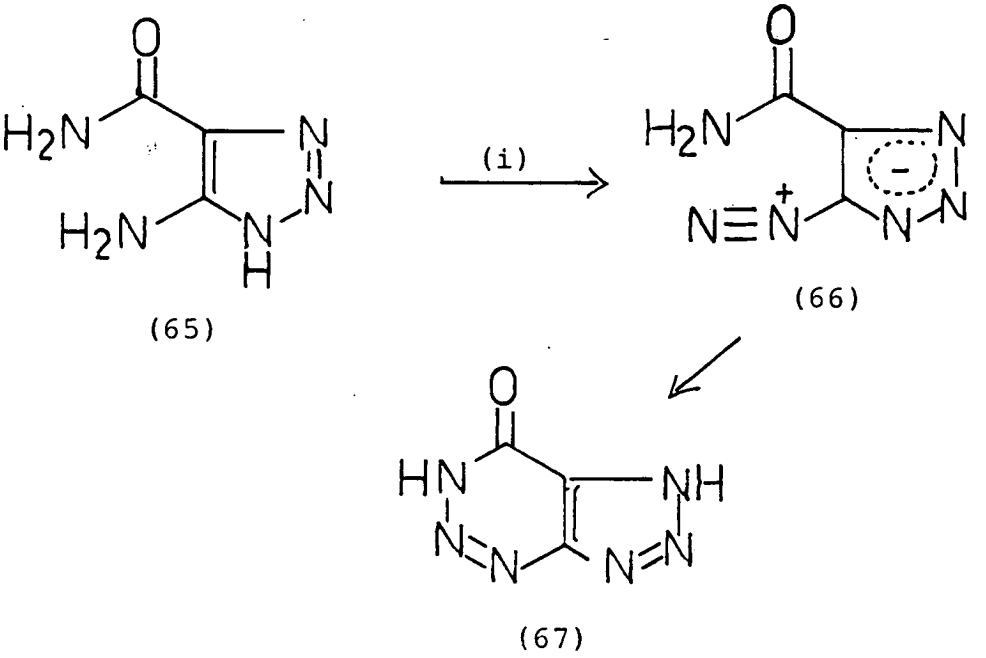
(ii) conc. HCl

(iii) $NaNO_2$, HCl

Scheme 16

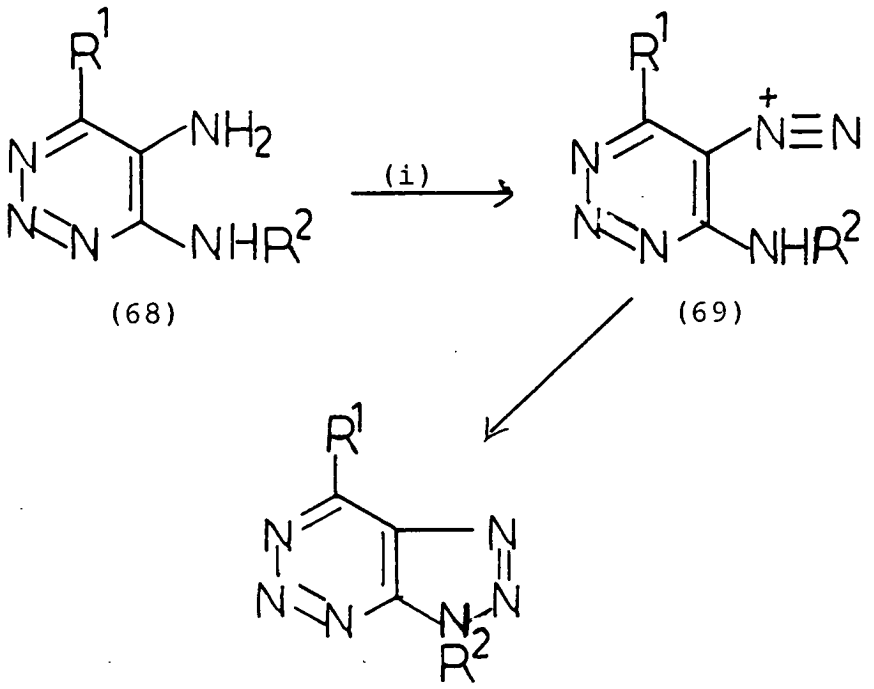
The systematic nomenclature and numbering (Scheme 15) indicated for these ring systems is based on that used in Chemical Abstracts. As in the case of azapurines (see before) the triazolotriazine ring systems (58) and (59) can also be named as diazapurines the former being 6,8-diazapurine and the latter 2,8-diazapurine respectively. Replacement of both methine groups in the pyrimidine nucleus of purine (1) by nitrogen atoms would lead to an imidazotetrazine structure consideration of which is outwith the scope of the present survey.

Of the two possible diazapurine ring systems under consideration only derivatives of the 1,2,3-triazolo[4,5-d]-1,2,3-triazine ring system (59) appear to have been described in the literature to date. Derivatives of the 1,2,3-triazolo[4,5-e]-1,2,4-triazine ring system (58) appear to be unknown. Moreover the few derivatives of the 1,2,3-triazolo[4,5-d]-1,2,3-triazine ring system that are known have received little attention. The first example of a 1,2,3-triazolo[4,5-d]-1,2,3-triazine derivative was described by Stevens and his co-workers[41] (Scheme 16) who showed that treatment of 5-amino-1H-1,2,3-triazole-4-carboxamidoxime (62) with sodium nitrite in aqueous hydrochloric acid afforded 7-amino-3H-1,2,3-triazolo[4,5-d]-1,2,3triazine 6-N-oxide (64) presumably through cyclisation of the transient diazonium intermediate (63). 5-Amino-1H-1,2,3-triazole-4-carboxamidoxime (62) is obtained by acid-catalysed degradation of the



(i) $NaNO_2$, HCl

Scheme 17



(68) (69) (70)

(i) HNO_2

Scheme 18

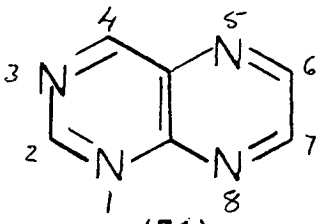
purine N-oxide (61) which in turn is readily accessible by peracid oxidation of the 8-azapurine (60). In a closely related 1,2,3-triazolo[4,5-d]-1,2,3-triazine synthesis (Scheme 17) Shealy and his co-workers[46,47] have shown that diazotisation of 5-amino-1H-1,2,3-triazole-4-carboxamide (65) gives an isolable diazonium betaine intermediate (66) which on standing in aqueous solution ring-closes to the triazolotriazine (67).

Synthetic routes to the 1,2,3-triazolo[4,5-d]-1,2,3-triazines other than those based on the cyclisation of 1,2,3-triazolediazonium intermediates (see before), appear to be unknown. In particular the obvious alternative method (Scheme 18) involving the diazotative ring closure of 4,5-diamino-1,2,3-triazines (68) is precluded by the inaccessibility of such 1,2,3-triazine derivatives. Due to the relatively few examples of diazapurine derivatives their biological properties have received only moderate attention. However they are known to possess antitumor activity[47] and the triazolo-triazinone (67) is a potent inhibitor of the enzyme uricase and appears to be of value in the treatment of kidney disorders.[48]

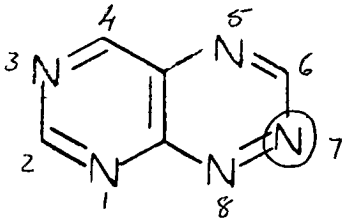
1.3 AZAPTERIDINES

Replacement (Scheme 19) of a single methine group in pteridine (71) by a nitrogen atom results in four possible azapteridine structures [(72)-(75)]. These are

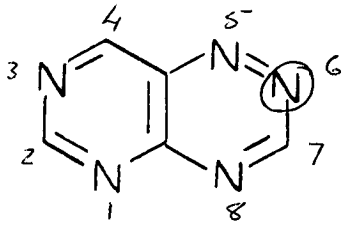
formally derived by insertion of the circled nitrogen atoms into the pteridine framework and are systematically named as the pyrimido[5,4-e]-1,2,4-triazine ring system (72), the pyrimido[4,5-e]-1,2,4-triazine ring system (73), the pyrazino[2,3-e]-1,2,4-triazine ring system (74) and the pyrazino[2,3-d]-1,2,3-triazine ring system (75). The systematic nomenclature and numbering indicated (Scheme 19) for these ring systems is based



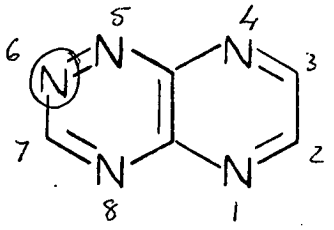
(71)



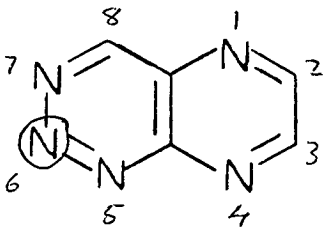
(72)



(73)

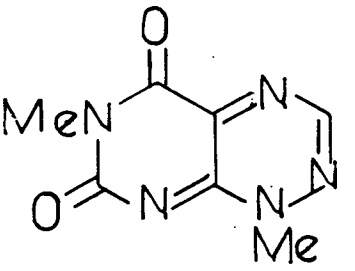


(74)

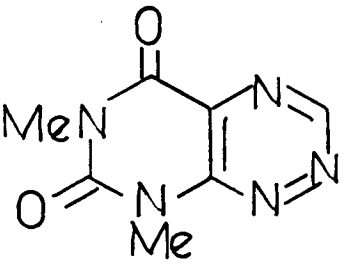


(75)

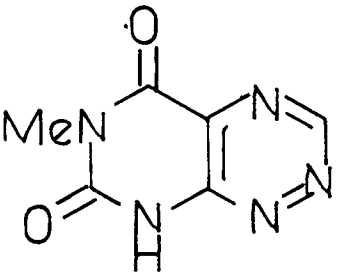
Scheme 19



(76)



(77)



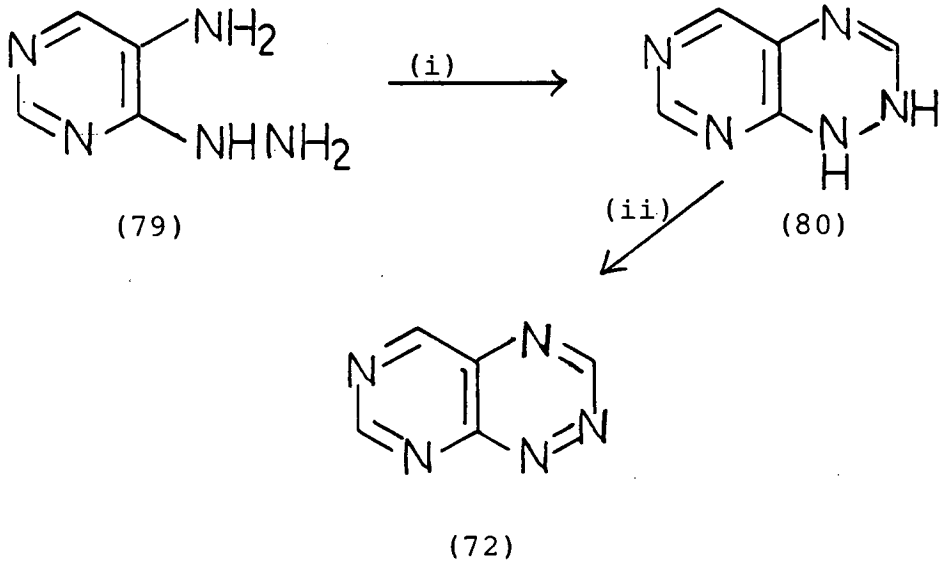
(78)

Scheme 20

on that used in Chemical Abstracts. However as in the case of azapurines (see before) the heterocyclic nuclei (72)-(75) can also be named in a trivial fashion as aza-analogues of pteridine (71) itself. Therefore the known pyrimido[5,4-e]-1,2,4-triazine ring system (72) is also named as 7-azapteridine, the known pyrimido-[4,5-e]-1,2,4-triazine ring system (73) as 6-azapteridine and the known pyrazino[2,3-e]-1,2,4-triazine ring system (74) as 4-azapteridine, while the apparently unknown pyrazino[2,3-d]-1,2,3-triazine ring system (75) would be called 2-azapteridine.

1.3.1 Pyrimido[5,4-e]-1,2,4-triazines (7-Azapteridines)

The first report of a compound containing the 7-azapteridine framework (72) was that of Van Veen and Mertens[49] who isolated a substance toxoflavin (Scheme 20) responsible for the toxicity of the bacterium Pseudomonas cocovenenans, and subsequently shown by Van Damme and his co-workers[50] to be the 7-azapteridine derivative (76). It was later found[51] that toxoflavin (76) and its close analogues fervenulin (77) isolated from Streptomyces fervens and reumycin (78) isolated from an Actomyces bacterium possessed considerable antibiotic activity. More recently it has been shown[52] that 7-azapteridine derivatives can inhibit the enzymes involved in vitamin biosynthesis. Due to their biological properties and in particular their



(79) (80)

(72)

(i) $HC(OEt)_3$, heat

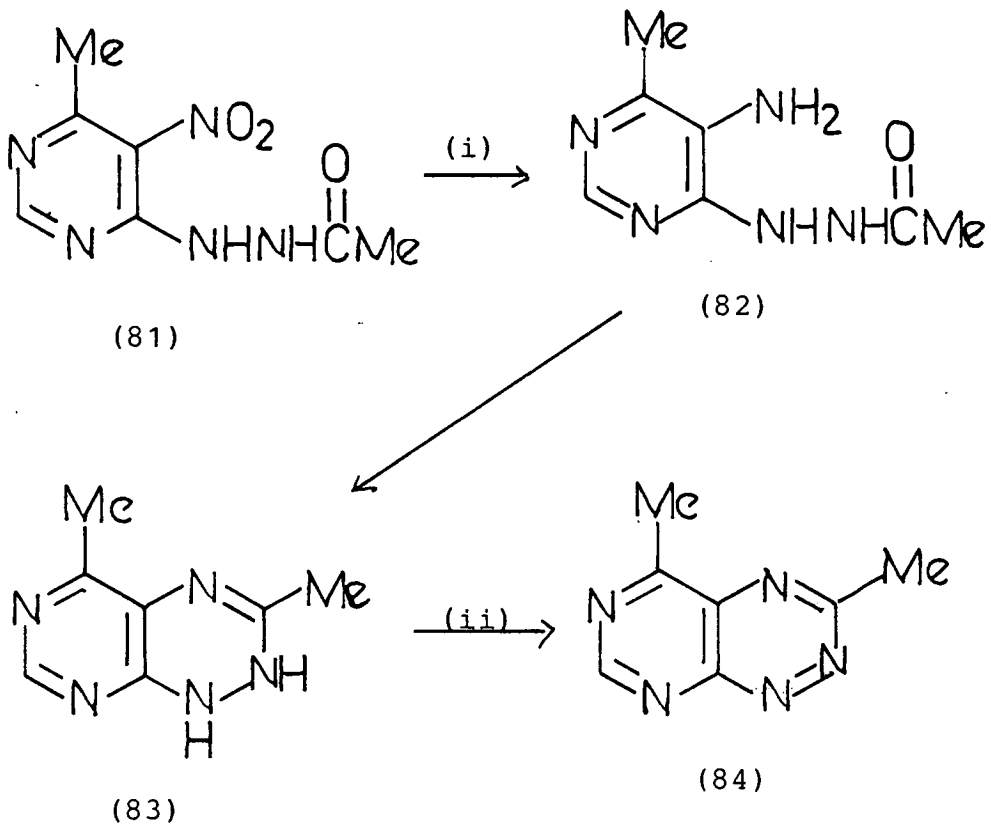
(ii) Ag_2O, BaO, THF, 11 h.

Scheme 21

significant antibiotic activity 7-azapteridines have been intensively investigated.[53] A comprehensive review of the synthesis and biological activity of such compounds is therefore outwith the scope of the present survey. In the following account discussion is restricted to the main synthetic methods for the construction of 7-azapteridine derivatives and their salient biological properties. Two main synthetic strategies have been employed for the synthesis of 7-azapteridines. Firstly starting from pyrimidine derivatives with subsequent ring closure to form the 1,2,4-triazine ring,[53] and secondly starting from 1,2,4-triazine precursors with eventual formation of the pyrimidine ring.[53]

7-Azapteridine Synthesis Based on Ring-Closure Reactions of Pyrimidine Derivatives

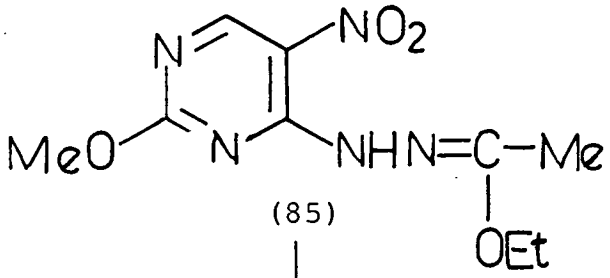
Routes to 7-azapteridine derivatives employing pyrimidine derivatives as the key starting materials have received the most attention. This type of synthetic approach to 7-azapteridines is illustrated (Scheme 21)[54] by the reaction of 5-amino-1,2,4-triazin-4-ylhydrazine (79) with triethyl orthoformate to afford the dihydropyrimido-[5,4-*e*]-1,2,4-triazine (80) which can be oxidised with silver oxide and barium oxide to yield the parent 7-azapteridine (72). In a variant of this type of 7-azapteridine synthesis *ortho*-acylhydrazino-nitropyrimidines undergo reductive cyclisation,[54] presumably through the corresponding ortho-acylhydrazino-amino-pyrimidines to afford dihydro-7-azapteridine derivatives which are readily oxidised to



(i) H_2, Pd-C

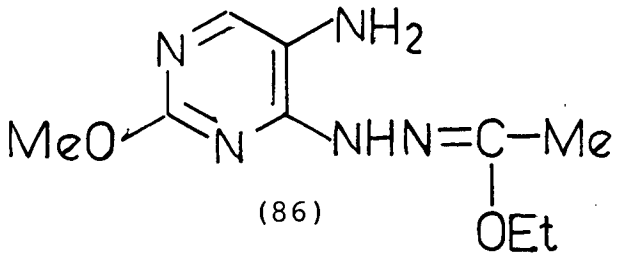
(ii) Ag_2O, MeOH, heat

Scheme 22

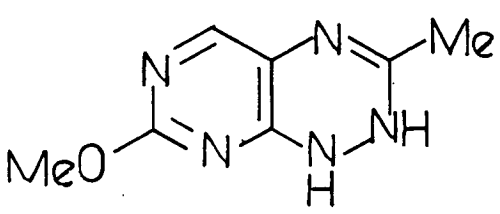


(85)

(i)

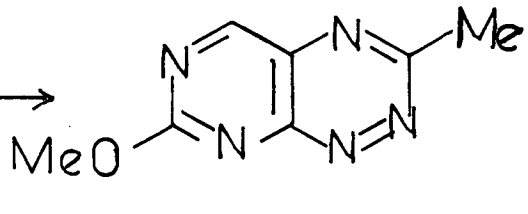


(86)



(87)

(ii)

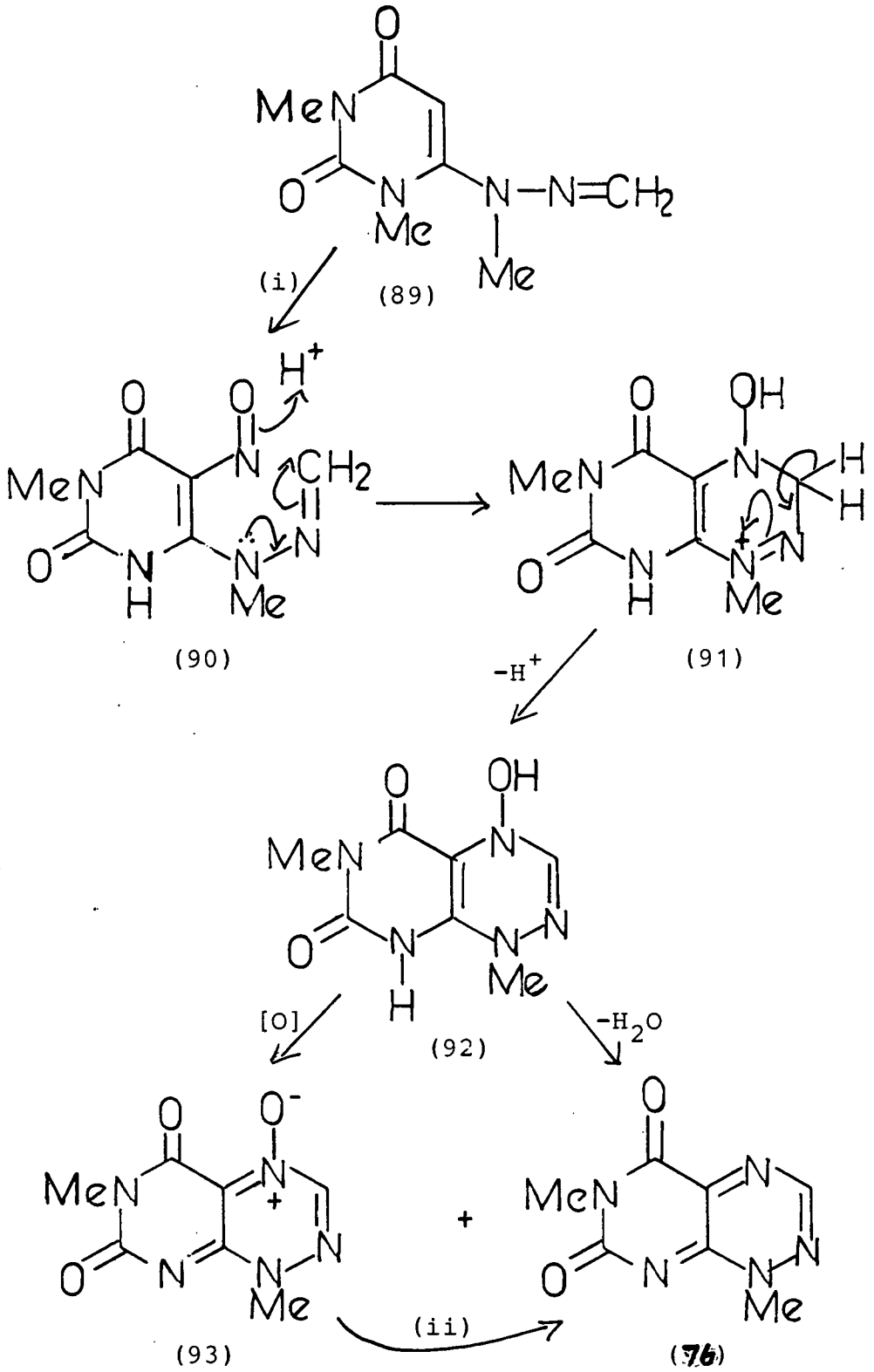


(88)

(i) H_2, Pd-C

(ii) Ag_2O, MeOH, heat

Scheme 23



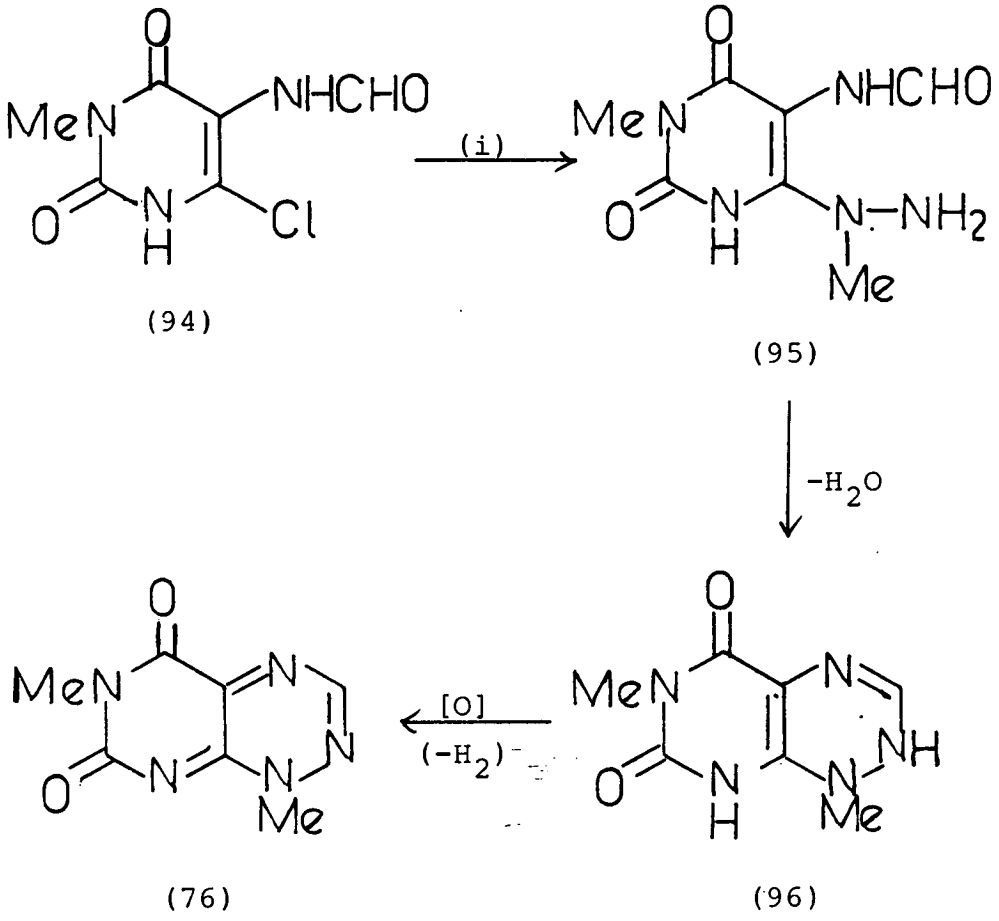
(i) $NaNO_2$, AcOH

(ii) PhSH, MeOH, room temp.

Scheme 24

the parent 7-azapteridines. A variety of reagents and conditions[53] have been used to oxidise dihydro-7-azapteridines to 7-azapteridines including silver oxide in methanol[53,54] and a combination of silver oxide-barium oxide in tetrahydrofuran.[53-54] However, manganese dioxide in tetrahydrofuran in the presence of magnesium sulphate fails to effect the dehydrogenation of dihydro-7-azapteridines to 7-azapteridines.[53,54] A 7-azapteridine synthesis based on ortho-acylhydrazino-nitropyrimidines is illustrated (Scheme 22)[54] by the reductive cyclisation of the nitropyrimidine derivative (81), through the amine (82) to give the dihydro-7-azapteridine (83), oxidation of which by silver oxide in refluxing methanol yields 4,6-dimethylpyrimido[5,4-e]-1,2,4-triazine (84). Hydrogenolysis (Scheme 23) of the 4-(2-alkoxymethylene)-hydrazonepyrimidine derivative (85) over 20% palladium-on-charcoal similarly results in reductive cyclisation to the dihydropyrimido[5,4-e]-1,2,4-triazine derivative (87) which on oxidation affords the 7-azapteridine (88).[55]

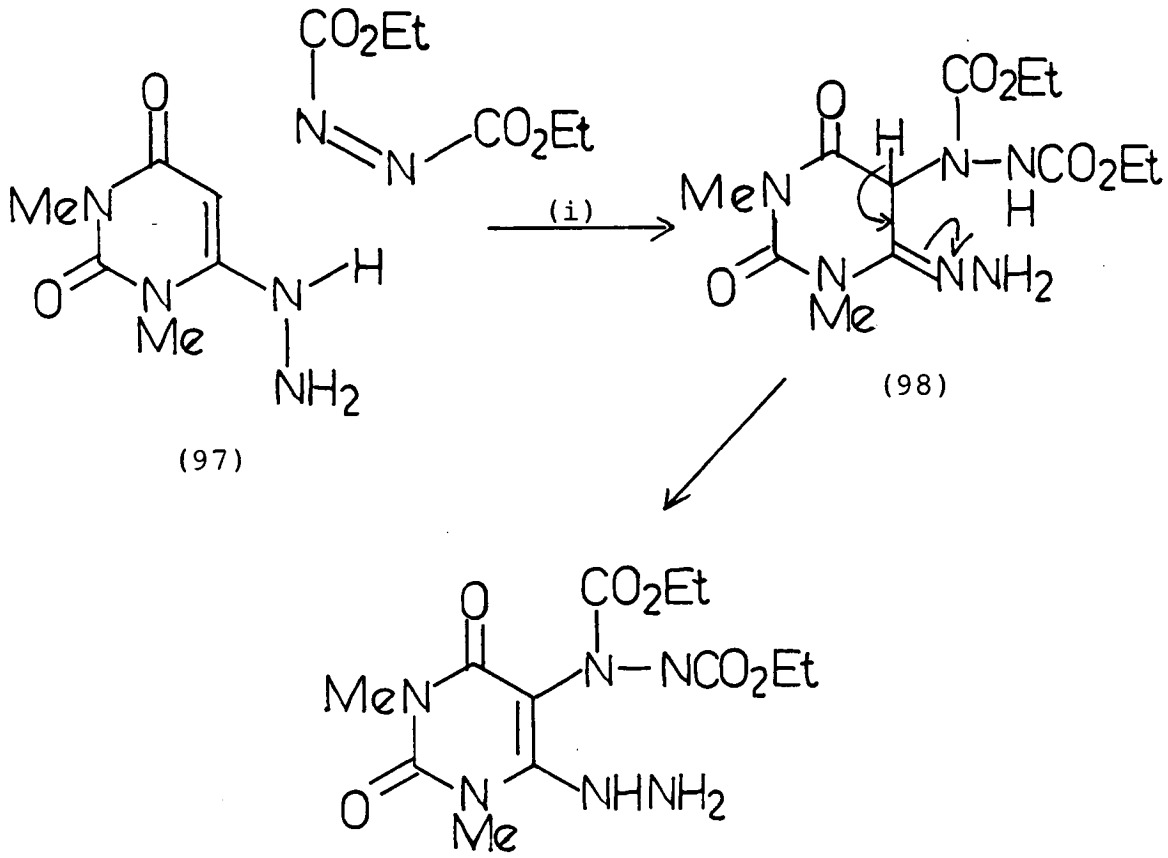
Pyrimido[5,4-e]-1,2,4-triazine derivatives can also be formed directly by the nitrosative cyclisation of 2-alkylidinehydrazinopyrimidines. An example of this type of synthetic procedure for 7-azapteridines is illustrated (Scheme 24) by the reaction[56] of the pyrimidine derivative (89) with sodium nitrite in acetic acid to afford a mixture of the 7-azapteridine, toxoflavin (76) and its 4-N-oxide (93). The latter compound can be



(94) (95) (76) (96)

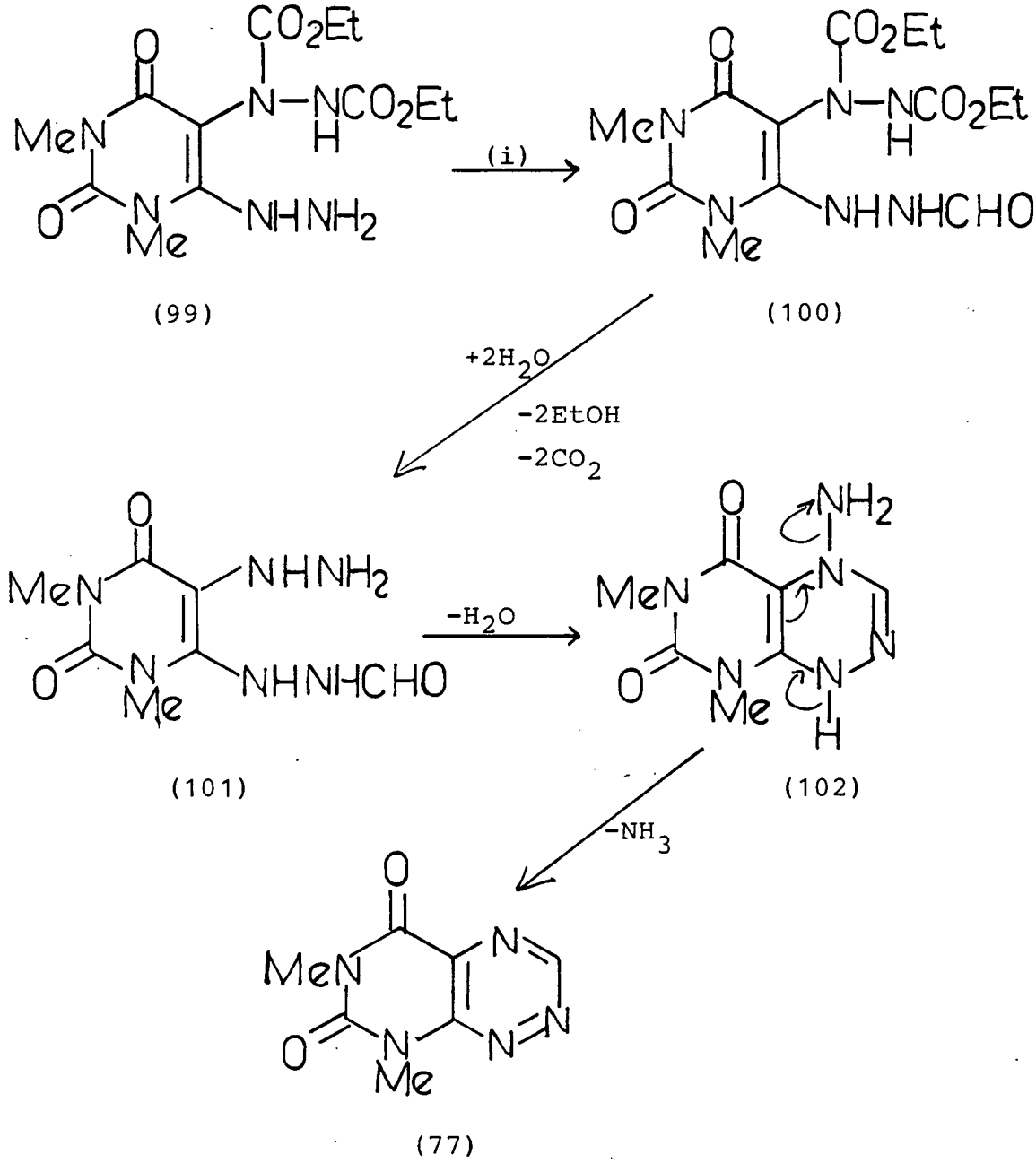
(i) $MeNHNH_2$, heat

Scheme 25



(i) $Me_2NCH=O$, heat

Scheme 26

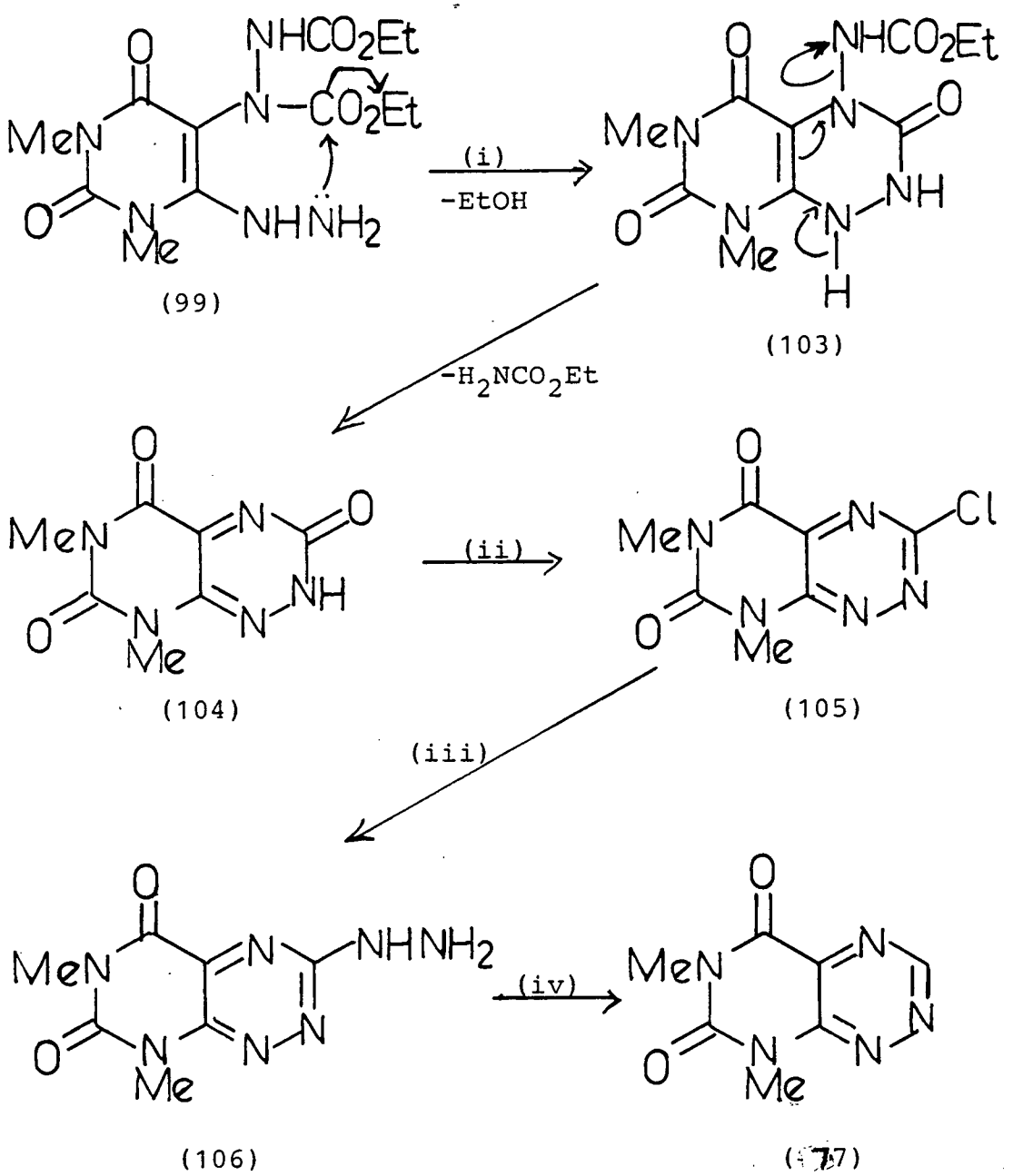


(i) $POCl_3$, $Me_2NCH{=}O$, heat

Scheme 27

readily reduced under mild conditions with benzenethiol to afford toxoflavin (76). These 7-azapteridine syntheses involve formation of the 1,2,4-triazine ring by closure of the 3,4-bond. 7-Azapteridine derivatives are also accessible by cyclisation of ortho-amino-hydrazino-pyrimidines involving formation of the 1,2,4-triazine ring through closure of the 2,3-bond. The first total synthesis[57] of toxoflavin (Scheme 25) provides a good example of this synthetic approach to 7-azapteridines. Thus reaction of 6-chloro-5-formamido-3-methylpyrimidine-2,4(1H, 3H)-dione (94) with methylhydrazine leads directly to toxoflavin (76) presumably through the intermediacy of the hydrazino-derivative (95) cyclisation of which yields the dihydro-7-azapteridine (96) and thence by oxidation toxoflavin (76).

A final variant of the use of pyrimidine derivatives, and in particular ortho-amino-hydrazinopyrimidines, for the construction of pyrimido[5,4-e]-1,2,4-triazines has been reported by Taylor and Sowinsky.[58] These authors have demonstrated the use of the highly functionalised pyrimidine derivative (99), synthesised by the reaction (Scheme 26) of the 4-hydrazinopyrimidine-2,6-(1H,3H)-dione (97) with diethyl azodicarboxylate in dimethyl-formamide presumably through the intermediate pyrimidine derivative (98), as the starting material in two synthetic routes to fervenulin (77). Firstly (Scheme 27) by the direct conversion of the pyrimidine derivative (99) under Vilsmeier-Hack formylation conditions (treatment with



(99) (103) (104) (105) (106) (107)

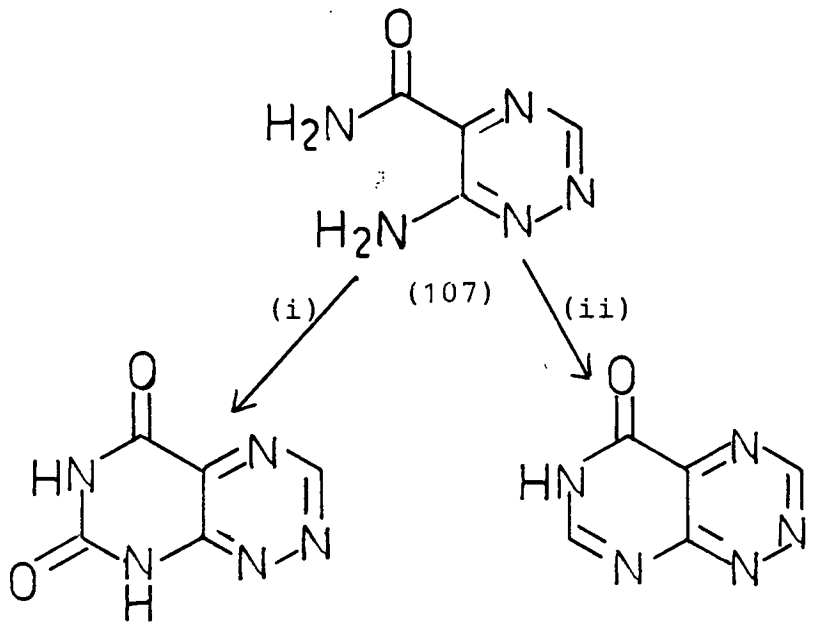
(i) NaOEt, EtOH

(ii) $POCl_3$

(iii) NH_2NH_2, EtOH

(iv) AgO, H_2O, 3 hr.

Scheme 28



(108) (109)

(i) $Cl_2C=O$, heat

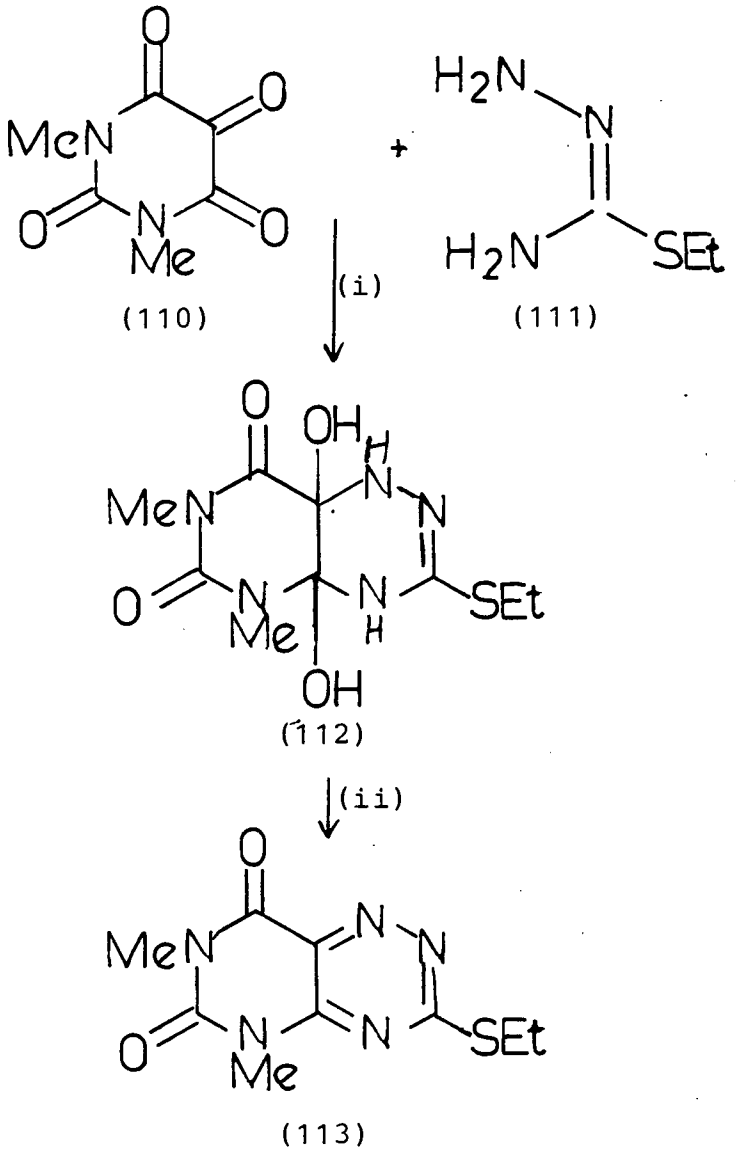
(ii) $CH(OEt)_3$, heat

Scheme 29

phosphoryl chloride in dimethylformamide), through the presumed intermediates [(100)-(102)] into fervenulin (77). Secondly (Scheme 28) by the reaction of the pyrimidine derivative (99) with sodium ethoxide to yield 1,3-dimethylpyrimido[5,4-e]-1,2,4-triazine-2,4,6(1H, 3H, 7H)-trione (104), followed by chlorination with phosphoryl chloride to afford 6-chloro-1,3-dimethylpyrimido[5,4-e]-1,2,4-triazine-2,4(1H, 3H)-dione (105) and reaction of the latter with hydrazine hydrate in ethanol to give the hydrazino 7-azapteridine derivative (106) oxidation of which with mercuric oxide in aqueous solution affords fervenulin (77).

7-Azapteridine Synthesis Based on Ring-Closure Reactions of 1,2,4-Triazine Derivatives

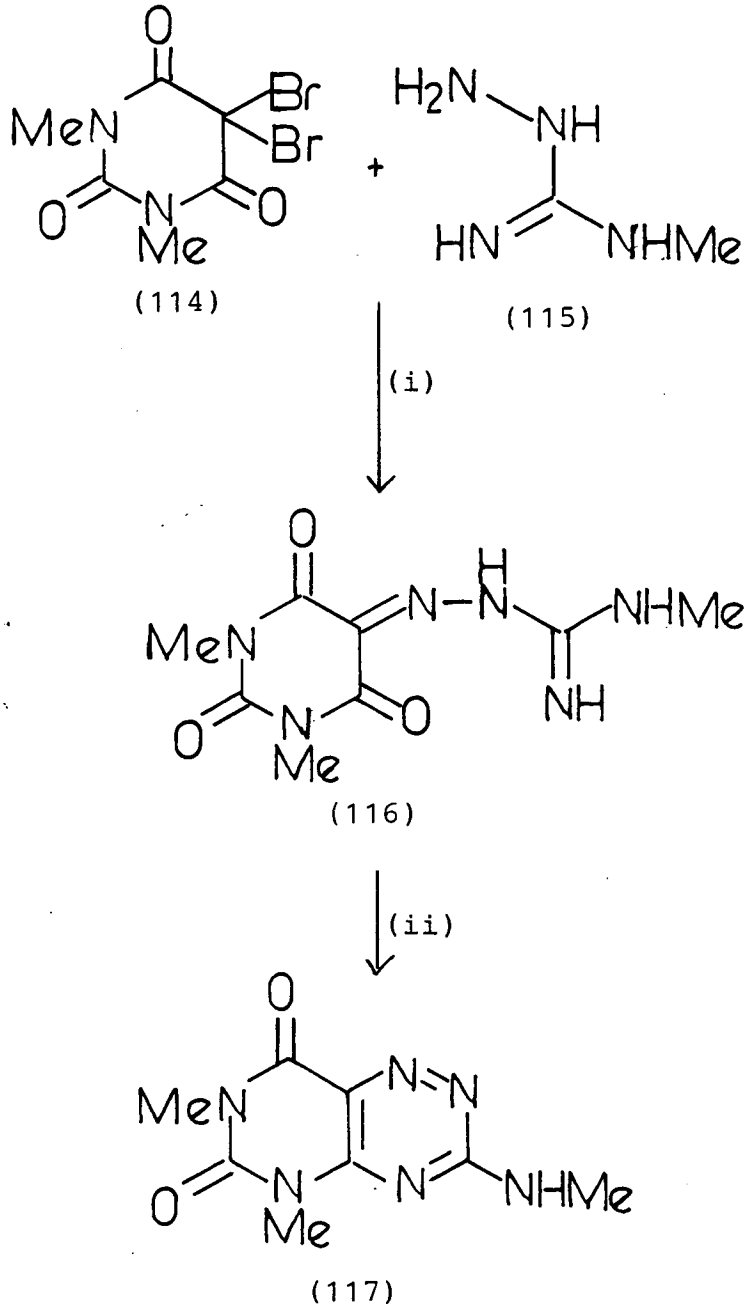
Few examples of the synthesis of pyrimido[5,4-e]-1,2,4-triazine derivatives from 1,2,4-triazine precursors are reported in the literature[59,60,61] and all involve (Scheme 29) 6-amino-1,2,4-triazine-5-carboxamide (107) as the key starting-material. Ring closure of this 1,2,4-triazine derivative (107) with one carbon condensation reagents such as phosgene or triethyl-orthoformate yields the 7-azapteridines (108) and (109) respectively.



(i) AcOH, room temp.

(ii) pyridine, heat

Scheme 30



(i) AcOH, room temp.

(ii) 1% aq. NH_3, heat

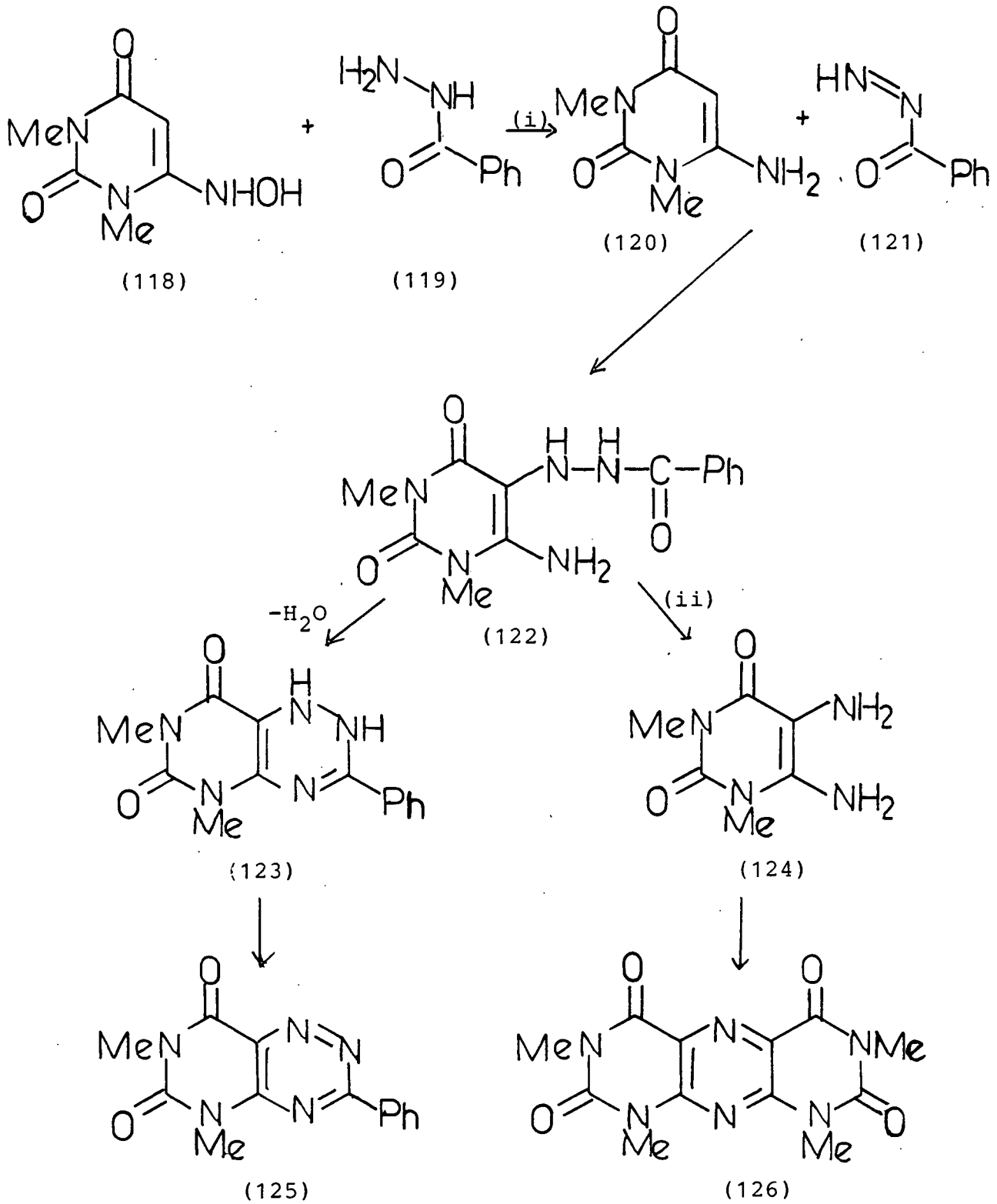
Scheme 31

1.3.2 Pyrimido[4,5-e]-1,2,4-triazines (6-Azapteridines)

As in the case of 7-azapteridines, 6-azapteridine derivatives may be constructed from pyrimidine derivatives with final ring closure of the 1,2,4-triazine ring or from 1,2,4-triazine derivatives with final ring closure of the pyrimidine ring.

6-Azapteridine Synthesis Based on Ring-Closure Reactions of Pyrimidine Derivatives

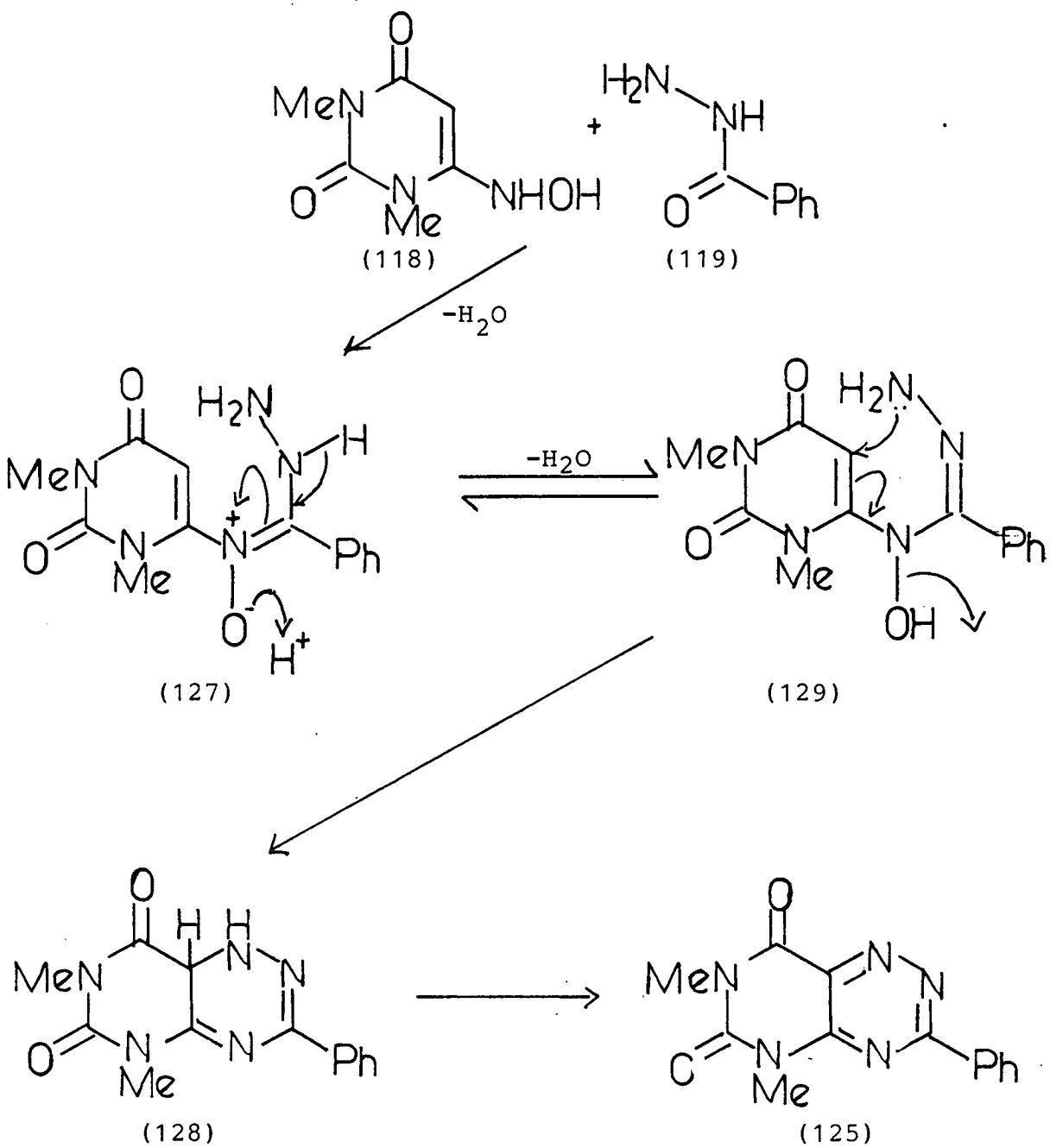
The first example of a 6-azapteridine derivative was synthesised by Heinisch and his co-workers[62] in 1964. These workers showed that the reaction of S-alkylisothiosemicarbazides with alloxan derivatives in acetic acid at room temperature yielded hydrated intermediates which readily underwent dehydration on refluxing in pyridine to afford 7-(alkylmercapto)pyrimido[4,5-e]-1,2,4-triazine-2,4(1H, 3H)-dione derivatives. This type of 6-azapteridine synthesis is exemplified (Scheme 30) by condensation of 1,3-dimethylalloxan (110), with S-ethylisothiosemicarbazide (111) to give the hydrated 6-azapteridine derivative (112) which on heating under reflux in pyridine yielded the parent 6-azapteridine (113). In a closely related condensation procedure (Scheme 31),[63] the 5,5-dibromopyrimidine derivative (114) on reaction with 1-amino-3-methylguanidine (115) in acetic acid afforded the guanyliminopyrimidine derivative (116) which readily undergoes cyclisation on heating in aqueous ammonia to yield the 6-azapteridine derivative (117).



(i) $Me_2NCH{=}O$, heat

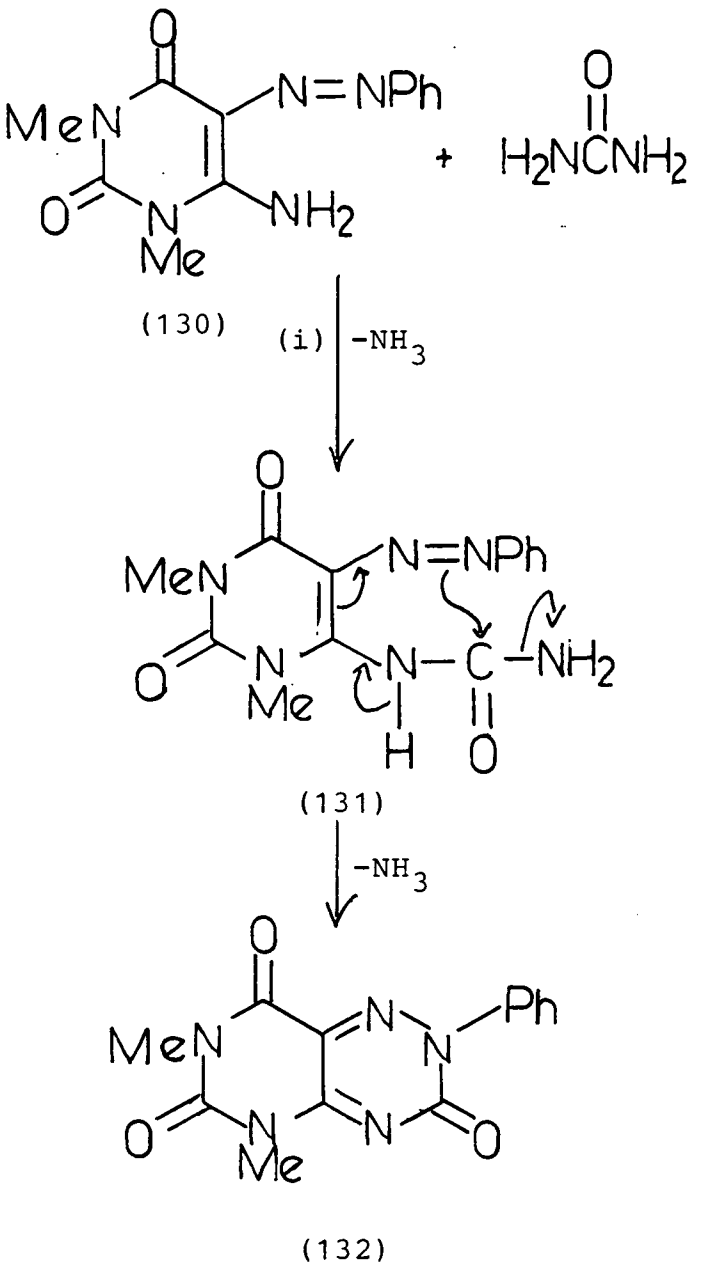
(ii) $PhC(O)NHNH_2$, $Me_2NCH{=}O$, heat

Scheme 32



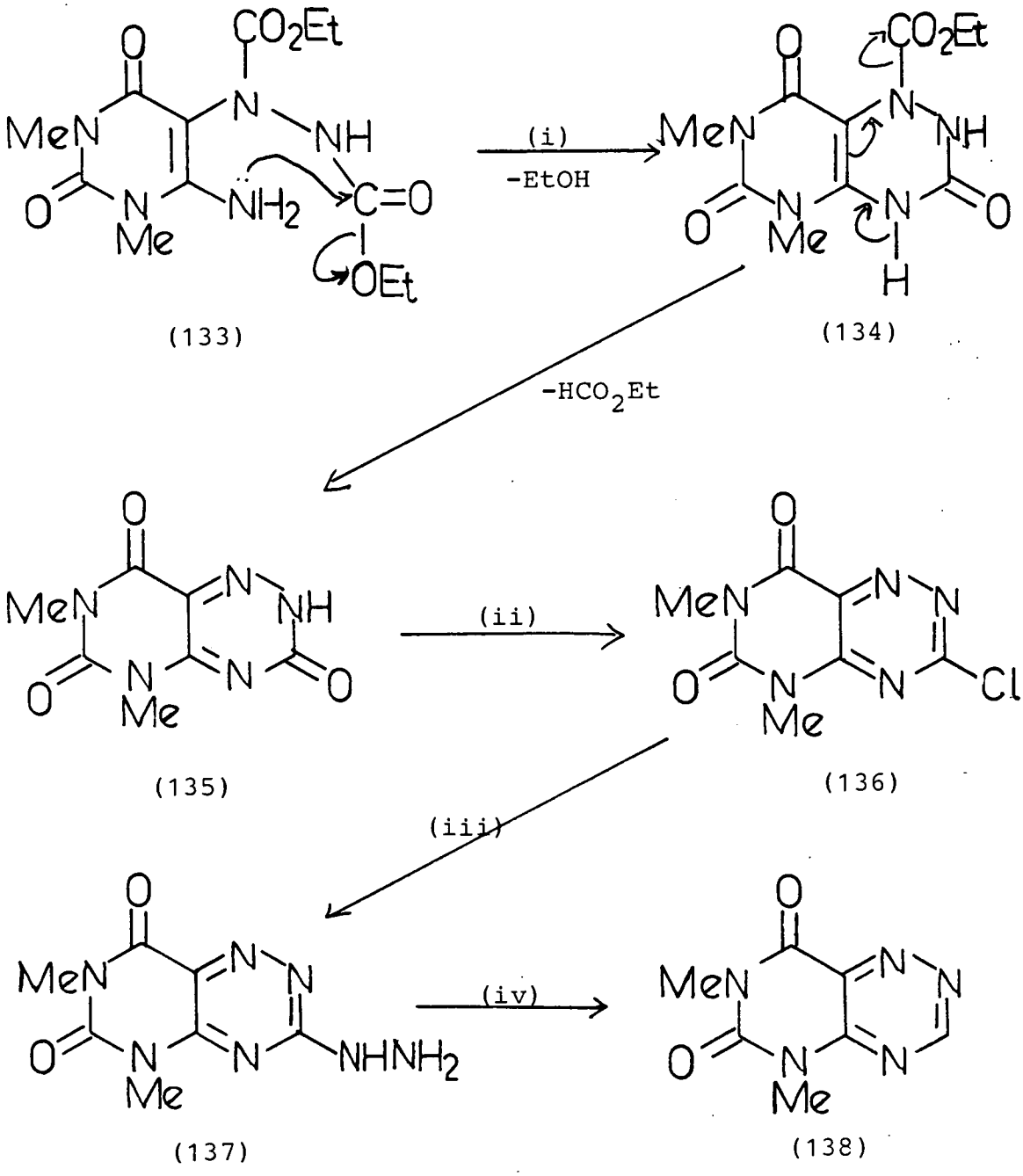
Scheme 33

6-Azapteridine derivatives have reportedly been synthesised from pyrimidine derivatives containing an amino-group or similar moiety in the 6-position, which eventually becomes part of the 1,2,4-triazine ring. 6-Azapteridine synthesis of this type is exemplified (Scheme 32) by the synthesis, described by Yoneda and his co-workers,[64] of 1,3-dimethyl-7-phenylpyrimido-[4,5-e]-1,2,4-triazine-2,4,(1H-, 3H)-dione (125) from 1,3-dimethyl-6-hydroxyaminopyrimidine-2,4,(1H, 3H)-dione (118) by treatment with an equimolar amount of benzoyl hydrazine (119) in dimethylformamide under reflux. 1,3,7,9-Tetramethylpyrimido[5,4-g]pteridine-2,4,6,8-(1H, 3H, 7H, 9H)-tetraone (126) was also isolated as a minor by-product in this reaction. Due to the fact that 1,3-dimethyl-6-hydroxyaminopyrimidine-2,4,(1H, 3H)-dione (118) was recovered unchanged on heating under reflux in dimethylformamide alone, the authors[64] explain the course of 6-azapteridine formation (Scheme 32) in terms of initial intramolecular oxidation-reduction to give intermediates (120) and (121) which combine to form a Michael-type adduct (122) cyclisation and dehydrogenation of which then givesthe 6-azapteridine derivative (125). Similarly the Michael adduct (122) can be reduced by benzoyl-hydrazine (119) to afford 5,6-diamino-1,3-dimethyl-pyrimidine-2,4,(1H, 3H)-dione (124) oxidative dimerisation of which accounts for the formation of the pyrimido-pteridine derivative (126). However an alternative course (Scheme 33) for the formation of the 6-azapteridine



(i) heat (200-220°)

Scheme 34



(133) (134) (135) (136) (137) (138)

(i) $Pb(OAc)_4$, AcOH

(ii) $POCl_3$

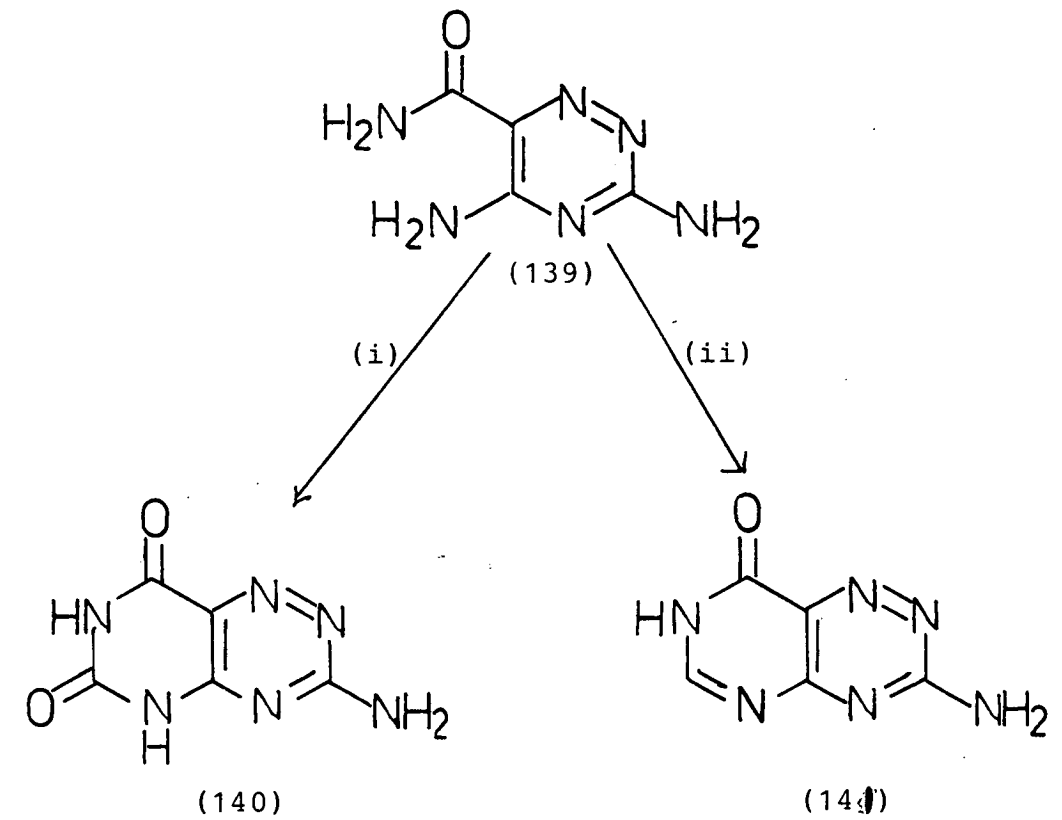
(iii) $NH_2NH_2.H_2O$, EtOH

(iv) HgO, H_2O, 14 h.

Scheme 35

derivative (125) is possible involving initial condensation of the 6-hydroxyamino-pyrimidine derivative (118) with benzoylhydrazine (119) to yield the N-oxide intermediate (127). Rearrangement of the latter to the N-hydroxy intermediate (129) followed by ring closure and subsequent oxidation would then afford the 6-azapteridine derivative (125).

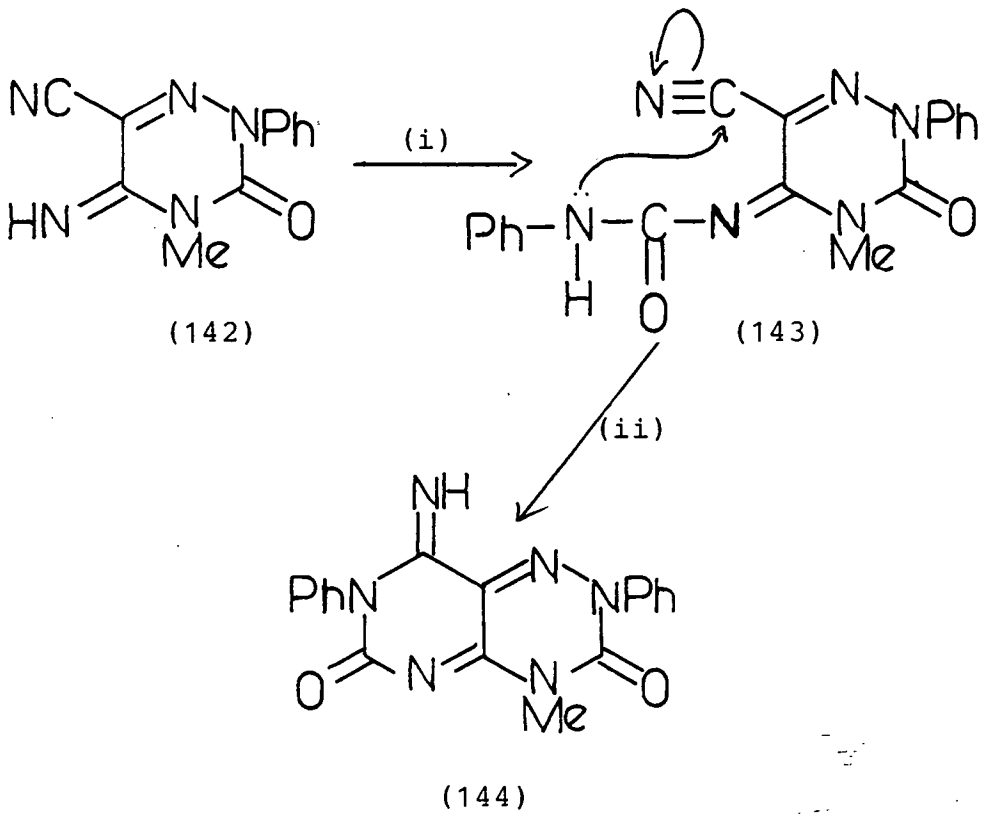
The remaining synthetic route to 6-azapteridines involving final closure of the 1,2,4-triazine ring utilises pyrimidine derivatives having nitrogen substituents which eventually contribute all three nitrogen atoms of the 1,2,4-triazine ring with closure of the latter being effected intermolecularly or intramolecularly. The former category of 6-azapteridine synthesis is exemplified (Scheme 34) by the reaction[65] of 1,3-dimethyl-5-phenylazo-pyrimidine-2,4(1H, 3H)dione (130) with urea at 200-220° to give the 6-azapteridine derivative (132). This transformation presumably involves the intermediate urea (131) which can undergo cyclisation with extrusion of ammonia to afford the 6-azapteridine derivative (132). The intramolecular ring-closure of an ortho-amino-hydrazinopyrimidine to a 6-azapteridine is represented (Scheme 35) by an extension of the annulation reaction utilised for the synthesis of the 7-azapteridine, fervenulin (see Scheme 27 before) by Taylor and Sowinsky.[58] These authors[58] have shown (Scheme 35) that treatment of 6-amino-1,2-dimethyl-5-(1,2-di-ethoxycarbonylhydrazino)-pyrimidine-2,4-(1H, 3H)-dione (133) with lead tetraacetate



(i) $(EtO)_2C=O$, NaOEt

(ii) $H_2NCH=O$, NaOEt

Scheme 36



(i) PhN=C=O, heat

(ii) Et_3N, EtOH, R.T.

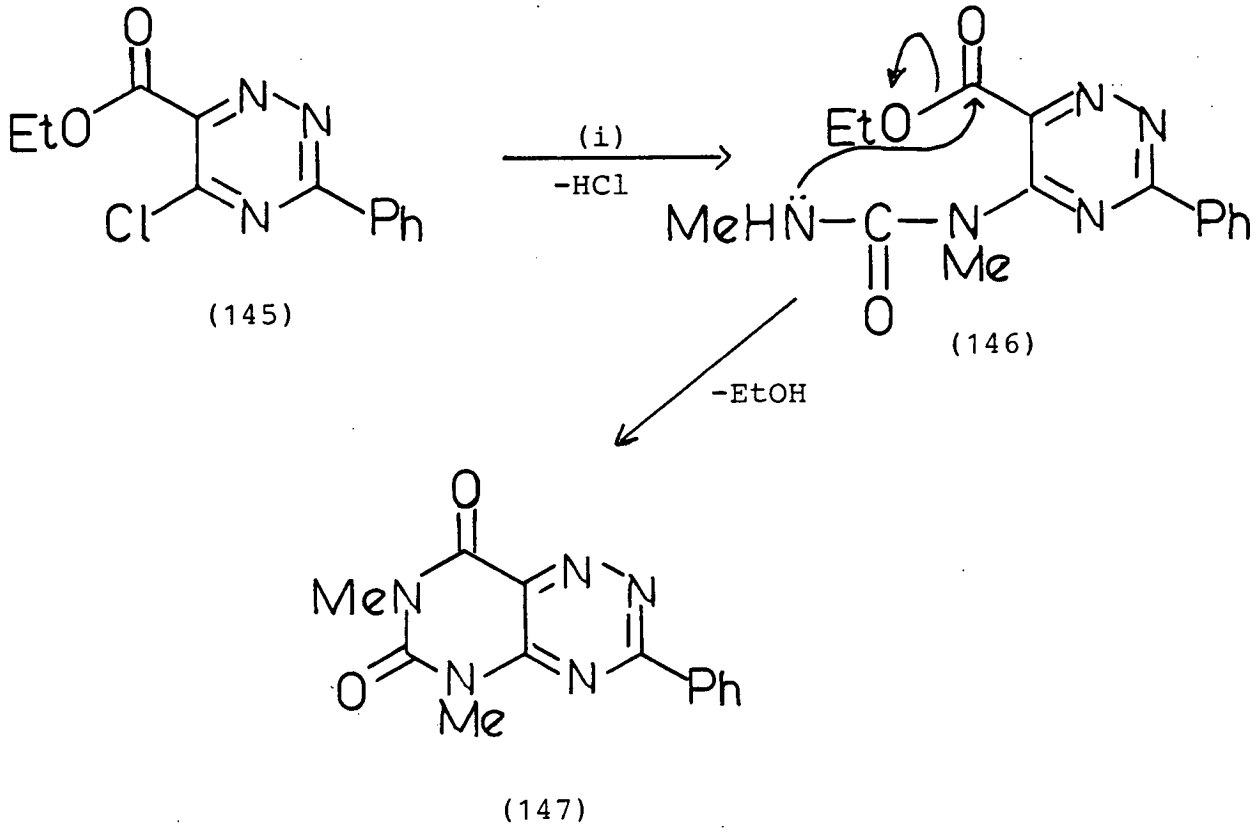
Scheme 37

affords the 6-azapteridine derivative (135) via the presumed intermediacy of the fused tetrahydrotriazinone (134). The 6-azapteridine derivative (135) can be further converted[58] into the 6-azapteridine analogue (138) of fervenulin by a procedure analoguous to that used in the synthesis of the latter, involving chlorination to give the chloro-derivative (136), followed by hydrazinolysis then oxidation of the resulting hydrazino-6-azapteridine (137).

6-Azapteridine Synthesis Based on Ring-Closure Reactions of 1,2,4-Triazine Derivatives

The first reported synthesis of pyrimido[4,5-e]-1,2,4-triazine derivatives from 1,2,4-triazine precursors was that of Taylor and Morrison[66,67] in which (Scheme 36) 3,5-diamino-1,2,4-triazine-6-carboxamide (139) was reacted with either diethylcarbonate or formamide in the presence of sodium ethoxide to yield the 6-azapteridine derivatives (140) and (141) respectively.

6-Azapteridine derivatives are also accessible by the ring closure of ortho-ammonated-cyano-1,2,4-triazine derivatives. Thus it has been shown[68] (Scheme 37) that the imino-1,2,4-triazinone (142) reacts with phenyl-isocyanate to yield the urea (143) which on treatment with a non-nucleophilic base such as triethylamine undergoes cyclisation to form the 6-azapteridine derivative (144). Closely related 6-azapteridine syntheses



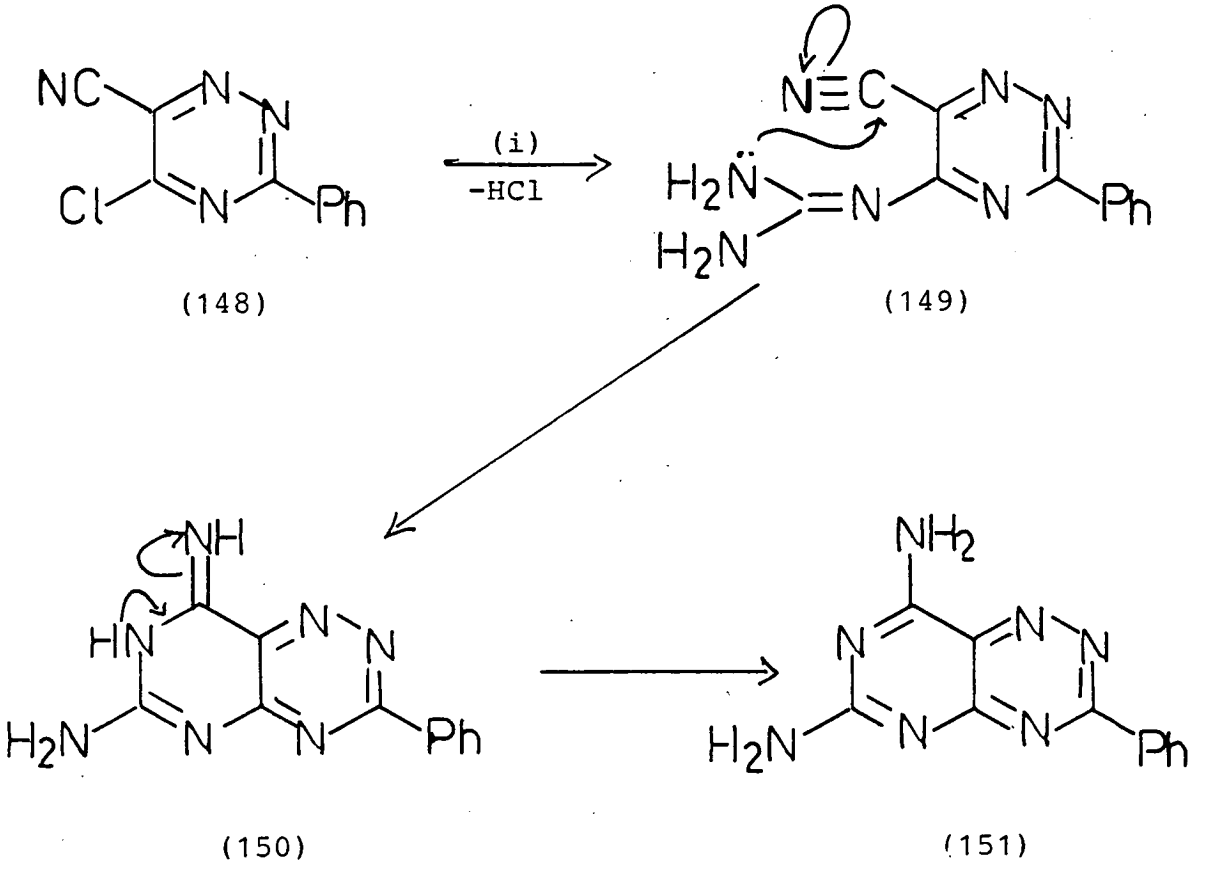
(145)

(146)

(147)

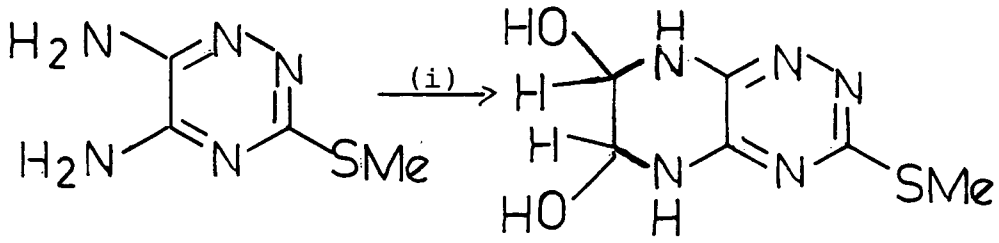
(i) $(MeNH)_2C=O$, heat

Scheme 38



(i) $(H_2N)_2C=NH$, heat

Scheme 39



(152) (153)

(i) O=CHCH=O, H_2O

Scheme 40

(Schemes 38 and 39) involve the *in situ* formation and ring closure of *ortho*-ureido- or *ortho*-guanidino-cyano-1,2,4-triazines. Thus (Scheme 38) heating the chloro-1,2,4-triazine-carboxylate (145) with *N*,*N*-dimethylurea affords the 6-azapteridine derivative (147) through the presumed intermediacy of the ureido-1,2,4-triazine (146).[69] Analogously, condensation (Scheme 39) of the chloro-cyano-1,2,4-triazine (148) with guanidine affords the diamino-6-azapteridine (151) via the formation and cyclisation of the *N*-(cyanotriazinyl)guanidine (149).[70]

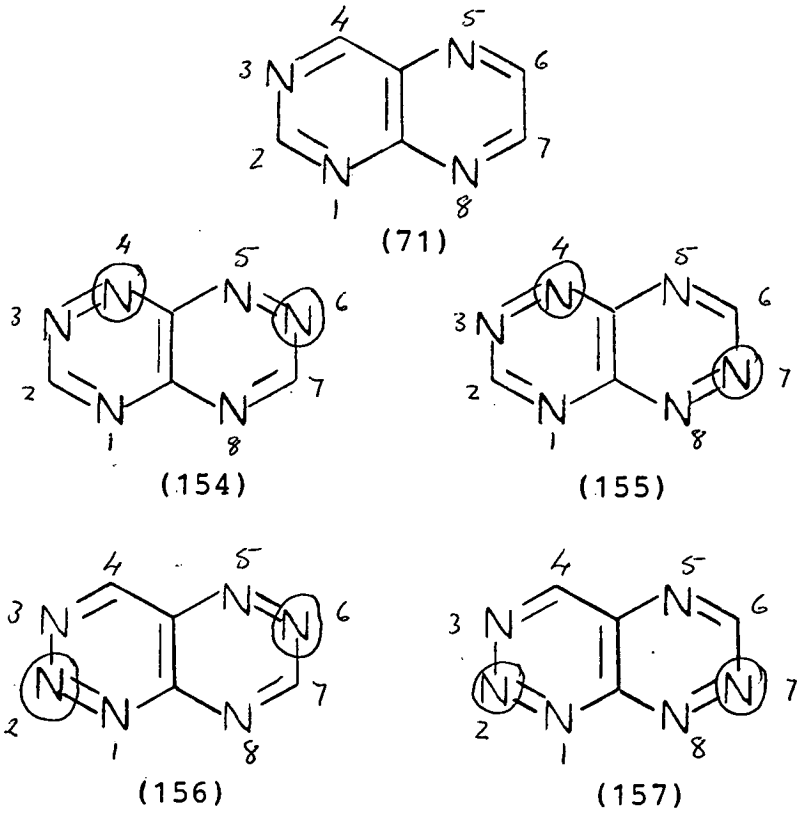
The biological properties of 6-azapteridines have been extensively investigated.[53] They are known to possess antibacterial and antiviral activity[71] and have also been reported to have analgesic and antiinflamatory properties.[72]

1.3.3 Pyrazino[2,3-*e*]-1,2,4-triazines (4-Azapteridines)

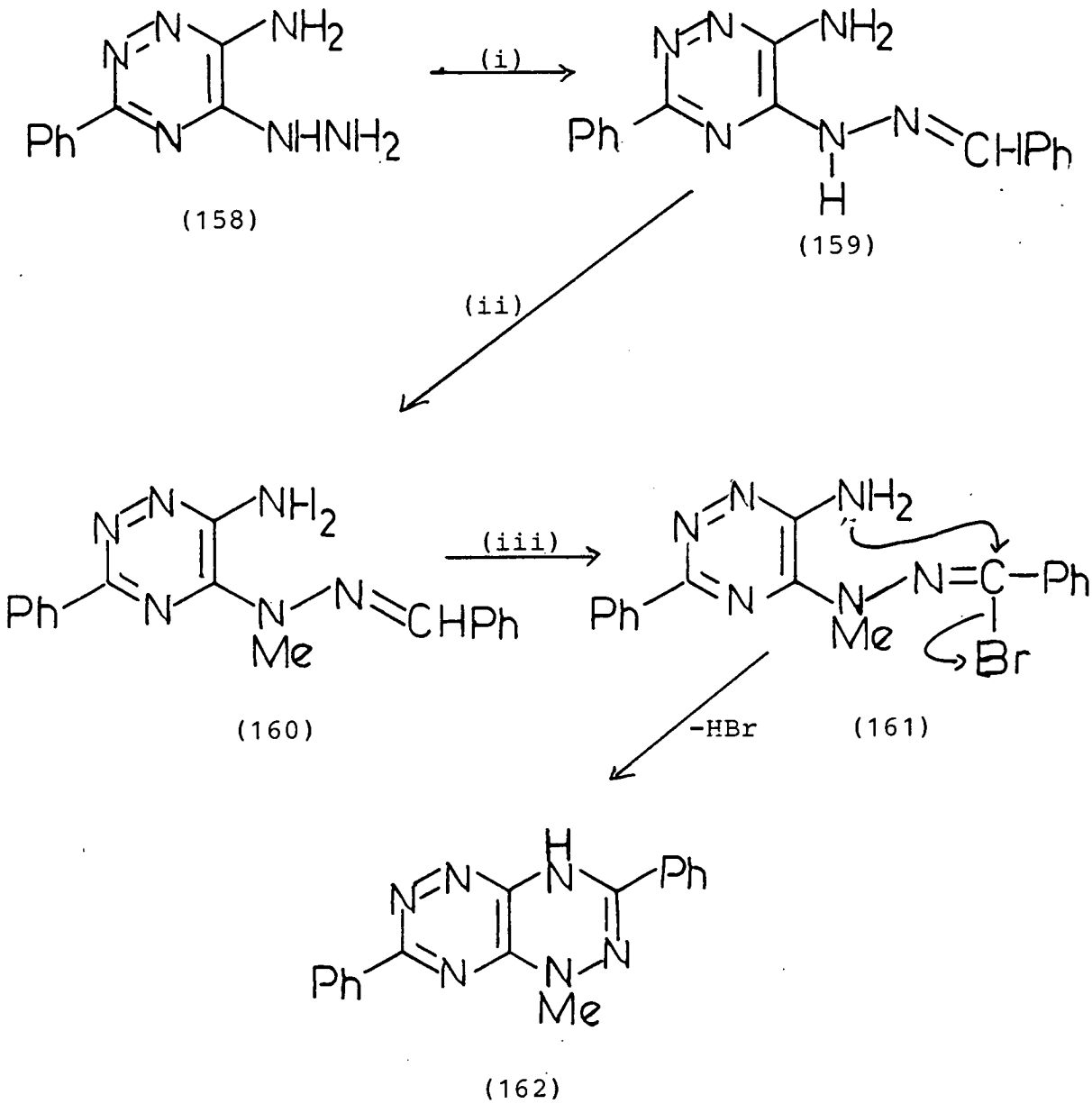
Until recently, derivatives of the 4-azapteridine ring system were apparently unknown. However in 1983 Panzica and his co-workers[73] reported the synthesis (Scheme 40) of 6,7-dihydroxy-3-methylthio-5,6,7,8-tetrahydropyrazino[2,3-*e*]-1,2,4-triazine (153) by the reaction of 5,6-diamino-3-methylthio-1,2,4-triazine (152) with aqueous glyoxal. This appears to be the only example of a 4-azapteridine derivative and it follows that the biological characteristics of such azapteridine derivatives have not as yet been investigated.

1.4 DIAZAPTERIDINES

Theoretically four diazapteridine ring systems can be constructed (Scheme 41) by replacement of two methine groups in pteridine (71), one methine group in the pyrimidine ring and one methine group in the pyrazine ring, by nitrogen atoms. These structures [(154)-(157)] are formally derived by inserting the



Scheme 41



(i) PhCH=O, heat

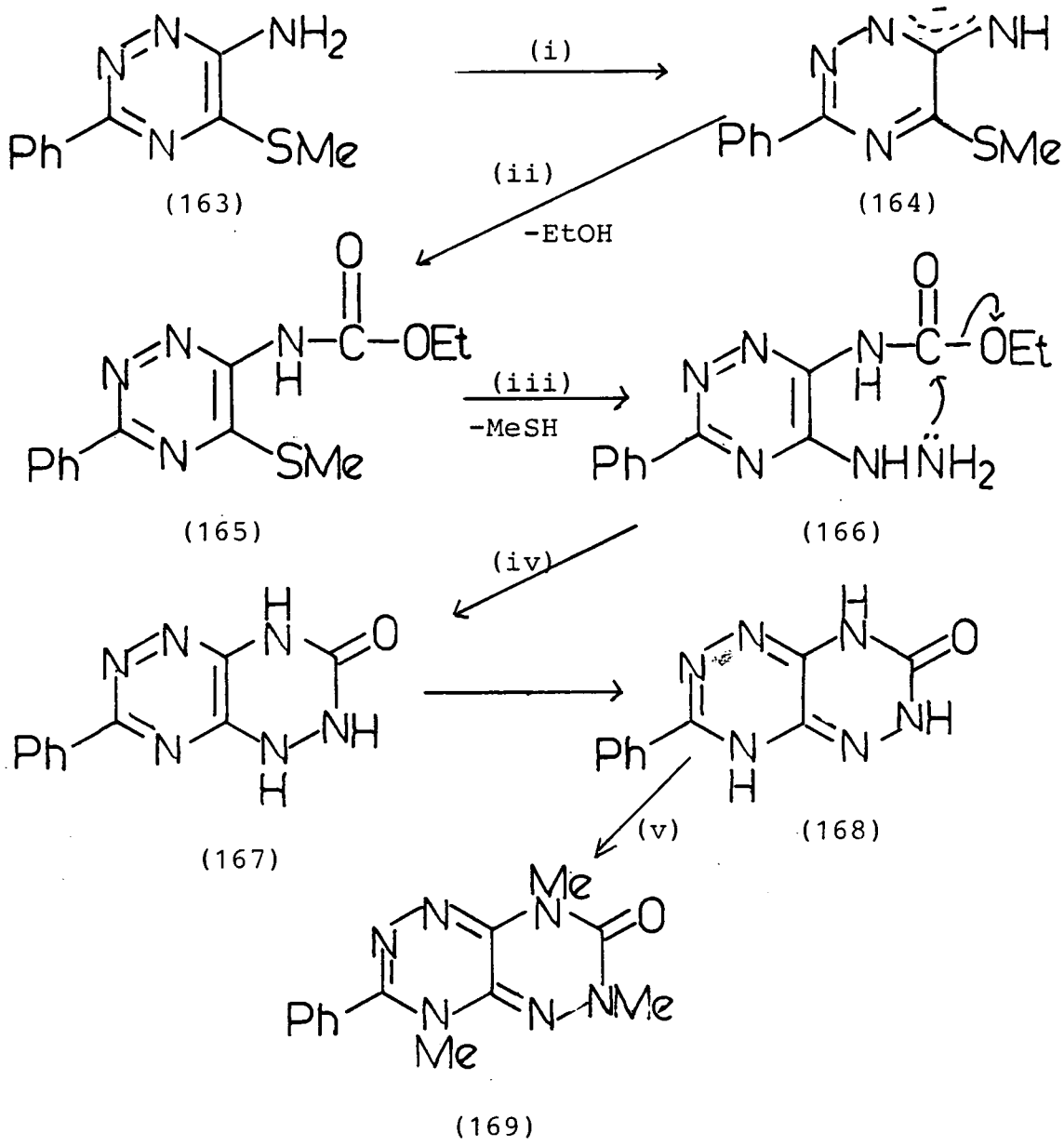
(ii) MeI, $KOBu^t$

(iii) Br_2, AcOH

Scheme 42

circled nitrogen atoms into the pteridine framework (71) and would systematically be named in accordance with Chemical Abstracts as the 1,2,4-triazino[5,6-e]-1,2,4-triazine ring system (154), the 1,2,4-triazino[6,5-e]-1,2,4-triazine ring system (155), the 1,2,3-triazino-[4,5-e]-1,2,4-triazine ring system (156) and the 1,2,3-triazino[5,4-e]-1,2,4-triazine ring system (157). The ring systems (154), (155), (156), and (157) can also be named trivially as 4,6-diazapteridine, 4,7-diaza-pteridine, 2,6-diazapteridine and 2,7-diazapteridine respectively. Only derivatives of the 1,2,4-triazino-[6,5-e]-1,2,4-triazine (4,7-diazapteridine) ring system (155) appear to be known to date.

The few derivatives of the 1,2,4-triazino[6,5-e]-1,2,4-triazine ring system that are known have been recently synthesised by Neunhoffer and Hummann[74] from ortho-amino-hydrazino-1,2,4-triazines. This type of synthesis is exemplified (Scheme 42) by the reaction of 5-amino-6-hydrazino-2-phenyl-1,2,4-triazine (158) with benzaldehyde to afford the 1,2,4-triazine derivative (159) which is subsequently methylated and treated with bromine in acetic acid to afford the hydrazonoyl bromide (161) elimination of hydrogen bromide from which gives the diazapteridine derivative (162).



(163) (164) (165) (166) (167) (168) (169)

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

(ii) $(EtO)_2C=O$, $Me_2NCH=O$, room temp.

(iii) $NH_2NH_2H_2O$, room temp.

(iv) heat

(v) NaH, MeI, $Me_2NCH=O$

Scheme 43

An alternative approach to 1,2,4-triazino[6,5-e]-1,2,4-triazines (Scheme 43) involves the thermal cyclisation of ortho-ethoxycarbonylamino-hydrazino-1,2,4-triazines. This type of 4,7-diazapteridine synthesis is exemplified[74] by the pyrolytic conversion of the hydrazinotriazinylurethane (166) into the tetrahydrotriazinotriazine (167) which apparently reacts predominantly in the alternative tautomeric form (168) since methylation affords the trimethyl derivative (169). The hydrazinotriazinylurethane (166) is readily synthesised from the amino-methylmercapto-triazine (163) by ethoxycarbonylation through the anionic species (164) to afford the urethane (165) followed by reaction of the latter with hydrazine. The examples shown in Schemes 42 and 43 illustrate the only synthetic methods for 1,2,4-triazino[6,5-e]-1,2,4-triazine(4,7-diazapteridine) derivatives.

The biological properties of the few 1,2,4-triazino[6,5-e]-1,2,4-triazine derivatives known do not appear to have been investigated as yet.

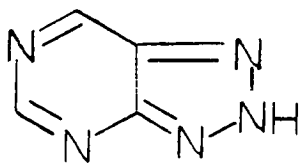
Chapter 2

Synthetic Approaches to Azapurines, Diazapurines and Related Polyazaheterocycles Based on Annulation Reactions of 4-Amino-2H-1,2,3-Triazole Derivatives

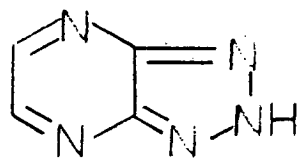
Synthetic Approaches to Azapurines, Diazapurines and Related Polyazaheterocylces Based on Annulation Reactions of 4-Amino-2H-1,2,3-Triazole Derivatives

2.1 Introduction

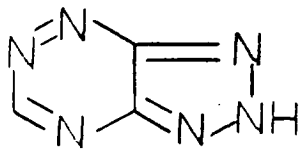
This chapter is concerned with the development of new synthetic routes to derivatives (Scheme 1) of the azapurine and diazapurine ring systems (1), (3) and (4) and the scrambled azapurine ring system (2). In contrast to the



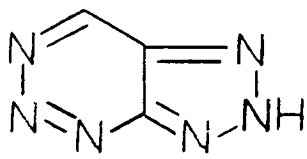
(1)



(2)



(3)

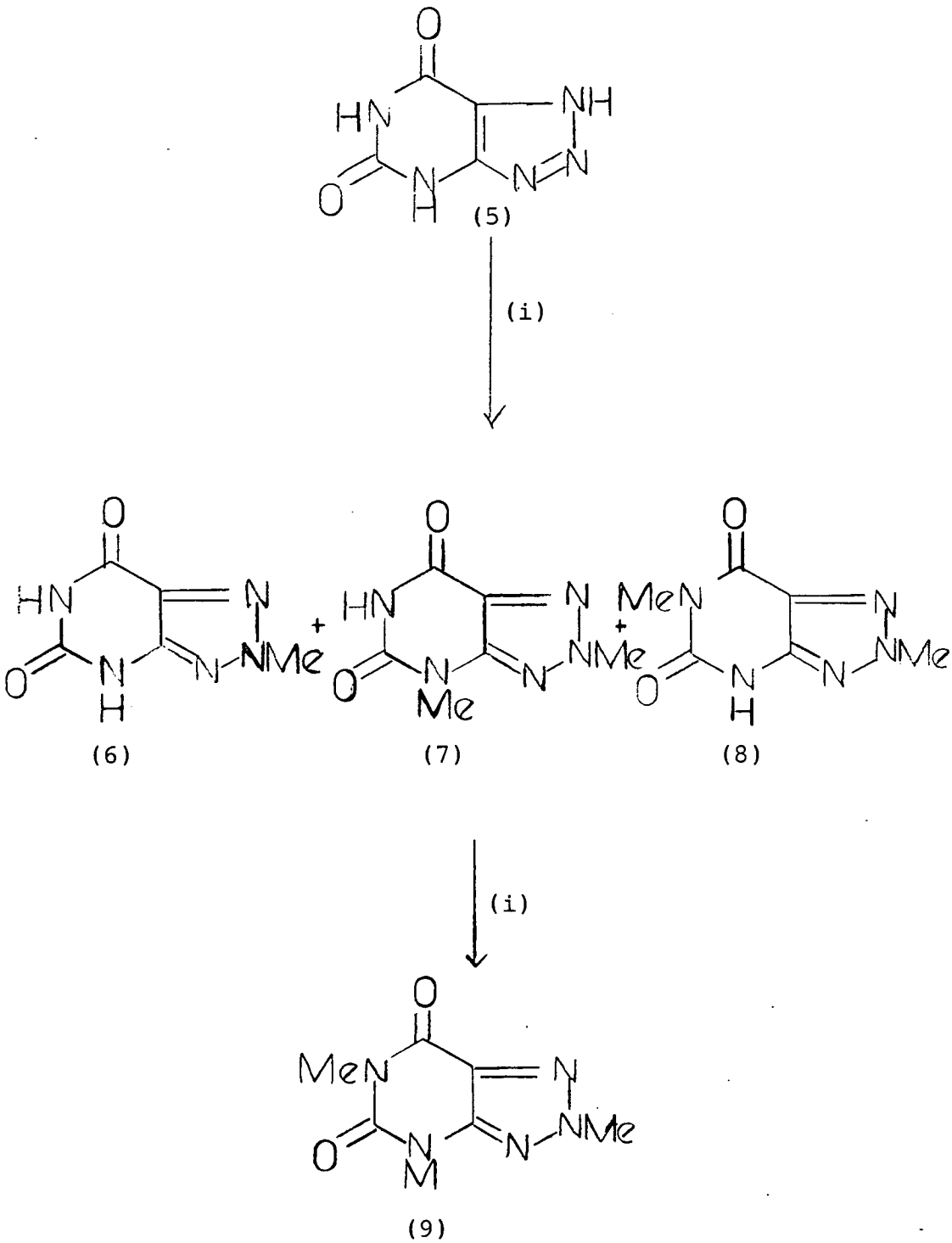


(4)

Scheme 1

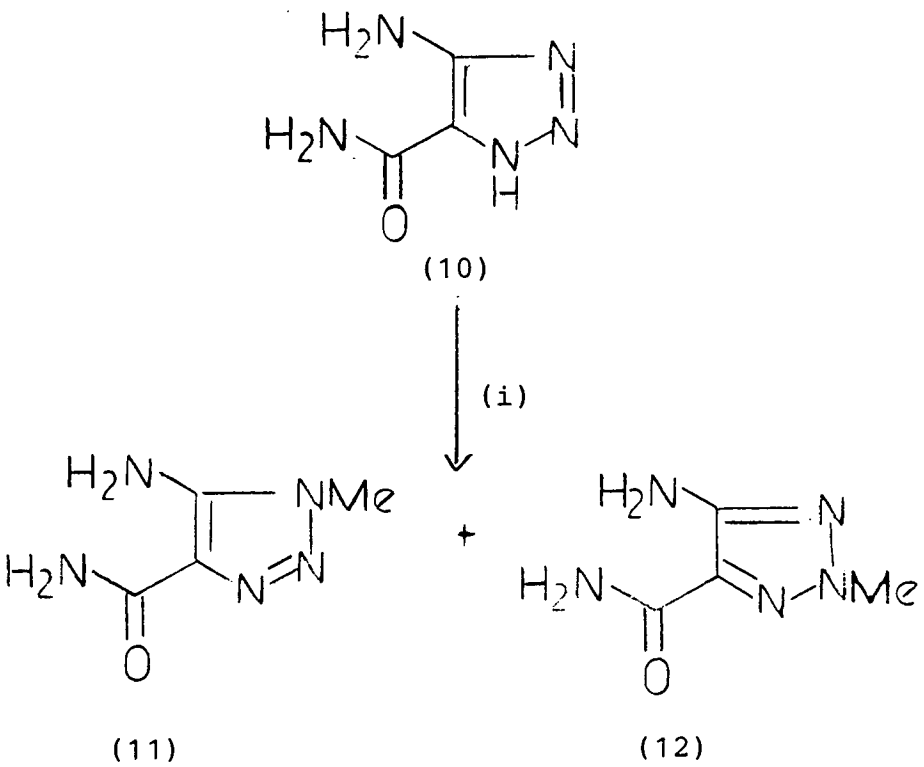
corresponding 1H- and 3H-8-azapurine ring systems which are well documented and have been previously described in Chapter 1, the 2H-8-azapurine ring system (1) has been little studied. The biological activity of 2H-8-azapurine derivatives would appear not to have been investigated to date. However one might expect that such derivatives would possess similar biological properties to other 8-azapurine derivatives which are responsible for a variety of physiological effects[1-5]. In general the 1,2,3-triazolo[4,5-b]pyrazine ring system (2) has also been little studied and only a single method for the synthesis of 2H-1,2,3-triazolo[4,5-b]pyrazine derivatives has been described[75]. The biological effects of such compounds are therefore unknown. Of the two diazapurine ring systems (3) and (4) only derivatives of the latter have been reported as already discussed in Chapter 1. However to date no 2H-derivative of this ring system has been described. Derivatives of the 1,2,3-triazolo[4,5-d]-1,2,4-triazine ring system (3) appear to be unknown. Therefore no information is available on the biological activity of derivatives of the diazapurine ring systems (3) and (4).

The potential biological activity of derivatives of the little investigated or previously unknown ring systems [(1)-(4)] prompted the studies described in the present chapter on a new general strategy for the synthesis of such polyazaheterocycles based on annulation reactions of 4-amino-2H-1,2,3-triazole derivatives as common synthetic precursors.



(i) Me_2SO_4, KOH

Scheme 2



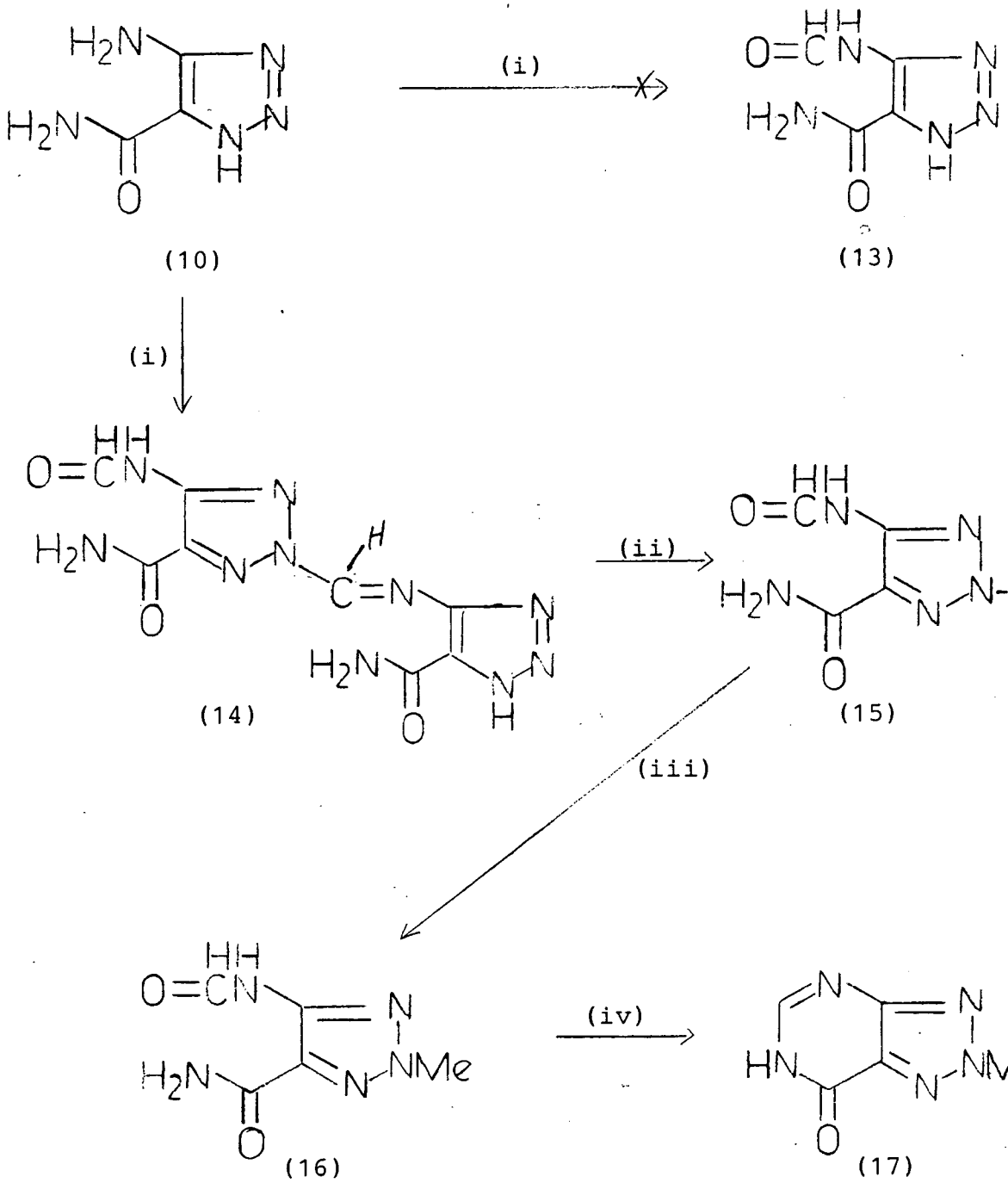
(i) Me_2SO_4, KOH

Scheme 3

2.2 General Synthetic Approaches to 2H-8-Azapurine and 2H-2,8-Diazapurine Derivatives from 4-Amino-2H-1,2,3-triazole Derivatives

2H-8-Azapurine derivatives have been synthesised previously by two procedures. Firstly by alkylation of 8-azapurine derivatives as illustrated (Scheme 2) by the methylation[76] of 8-azaxanthine (5) with dimethyl sulphate in alkaline solution to give a mixture containing the three isomers [(6)-(8)] further methylation of which afforded the fully methylated product, 2,5,7-trimethyl-2H-1,2,3-triazolo[4,5-d]pyrimidine-4,6(5H, 7H)-dione (9). Major difficulties encountered using this methodology, are the formation of several isomers many of which are not 2H-products and the consequent low yields of the desired 2H-1,2,3-triazolo[4,5-d]pyrimidine derivatives. Albert and his co-workers[77] have refined the foregoing methylation procedure but at best it only affords a 33% yield of the 8-methyl-8-azapurine (9).

The second procedure for the synthesis of 2H-8-azapurine derivatives involves preliminary alkylation of the 1,2,3-triazole precursor followed by cyclisation to the 8-substituted 8-azapurine derivative. Again however a disadvantage of this method is isomer formation at the triazole alkylation stage as illustrated (Scheme 3) by methylation[78] of 4-amino-1H-1,2,3-triazole-5-carboxamide (10) which affords a mixture of the isomers (11) and (12).



(i) HCO_2H, heat

(ii) KOH, H_2O

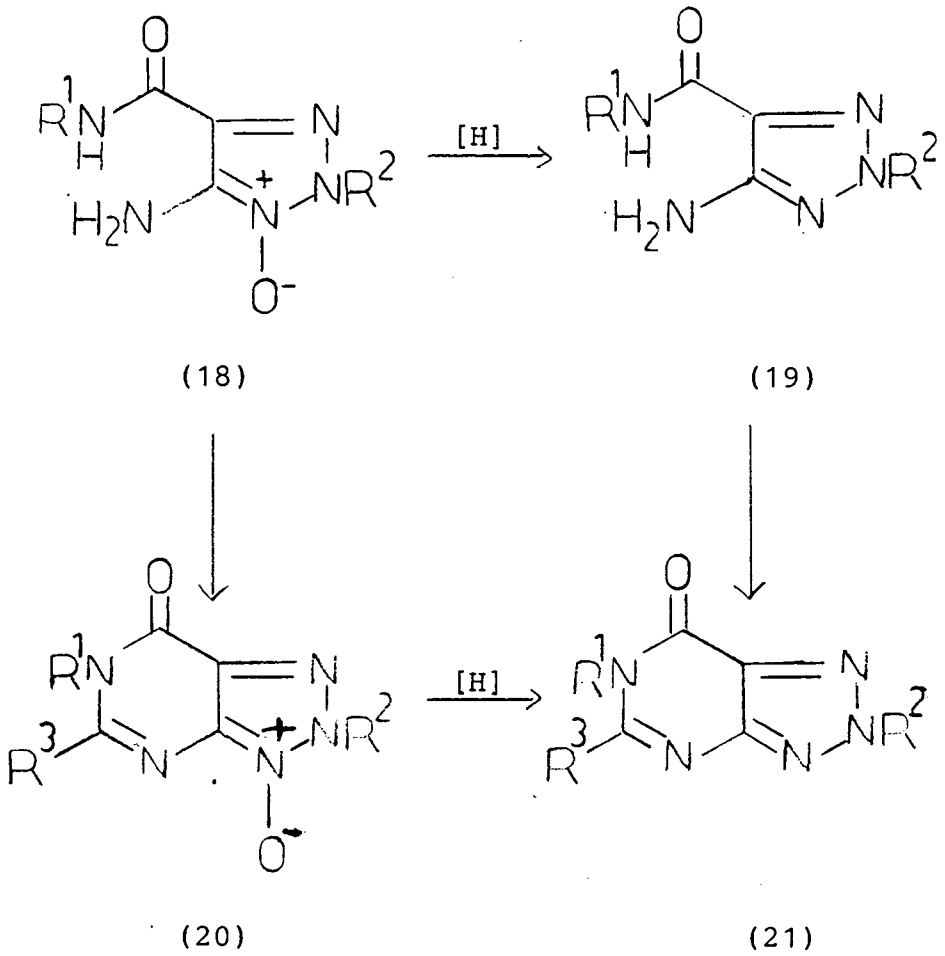
(iii) Me_2SO_4

(iv) $NH_2CH{=}O$, 220°

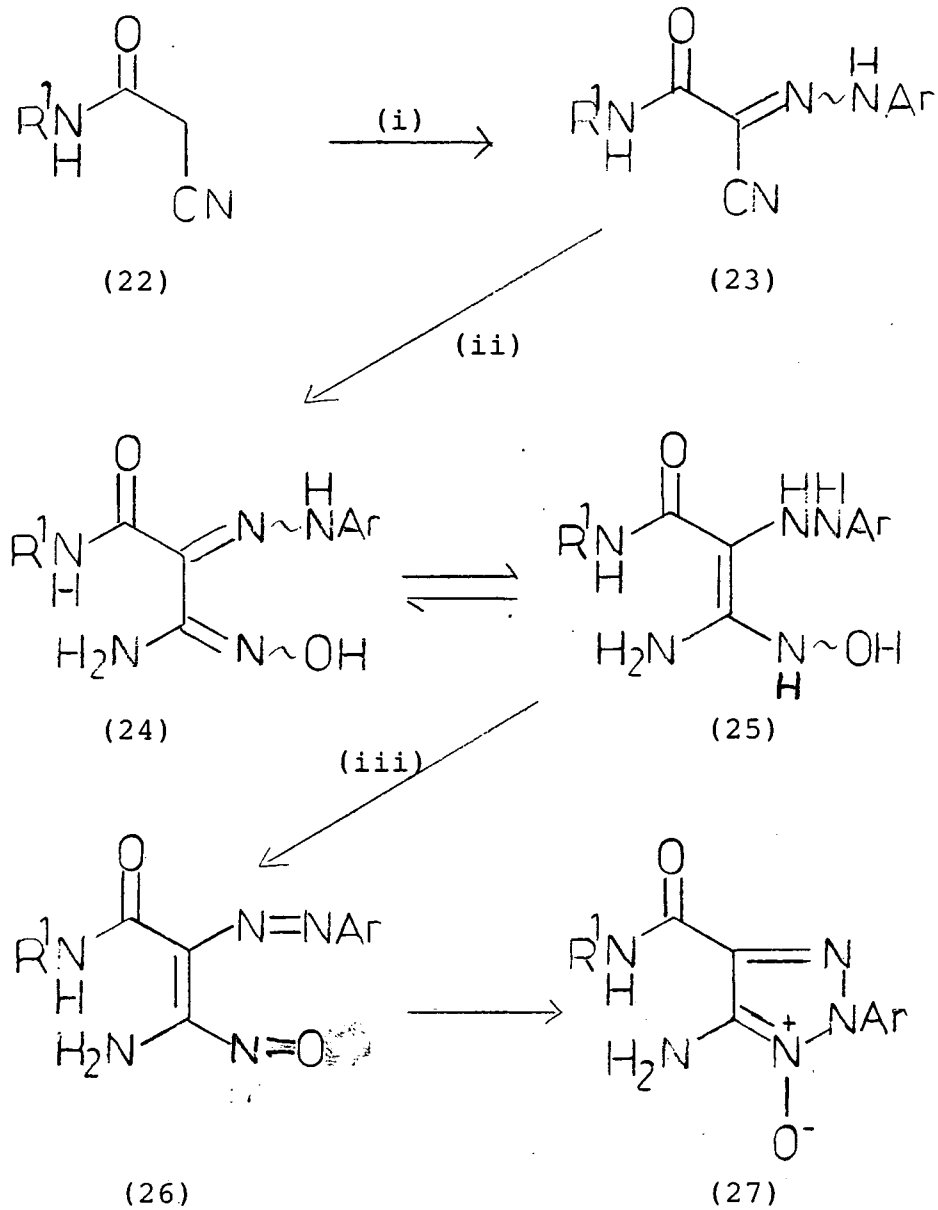
Scheme 4

A noteworthy feature of this reaction as pointed out by Albert et al[78,79] is the suppression of methylation at the 1-position of the triazole ring as a result of steric hindrance by the carboxamide substituent. These authors[78,79] concluded therefore that an increase in the size of the substituent at the 4-position of the 1,2,3-triazole precursor would promote exclusive methylation at the 2-position. Hence they investigated (Scheme 4) the synthesis of 4-formamido-1,2,3-triazole-5-carboxamide (13) as a suitable precursor for specific methylation to the 2-methyl-2H-1,2,3-triazole derivative (16) set up for cyclisation to the 8-methyl-8-azapurine derivative (17). However the product obtained[78,79] in the reaction of the aminotriazolecarboxamide (10) was not the formamido derivative (13) but rather the anhydro-dimer (14) formed by specific dimerisation through the 2-position of the triazole ring. However subsequent treatment[78] of the anhydro-dimer (14) with dimethyl sulphate in aqueous potassium hydroxide afforded the desired 4-formamido-2-methyl-2H-1,2,3-triazole-5-carboxamide (16) presumably through the intermediacy of the anionic species (15). Heating the 2H-1,2,3-triazole derivative (16) with formamide afforded the 8-methyl-8-azapurine derivative (17) in good yield.[78]

Since neither of the available methods for the synthesis of 8-substituted 8-azapurine derivatives was satisfactory for general synthesis of such compounds it was decided in the present studies to investigate a new general



Scheme 5

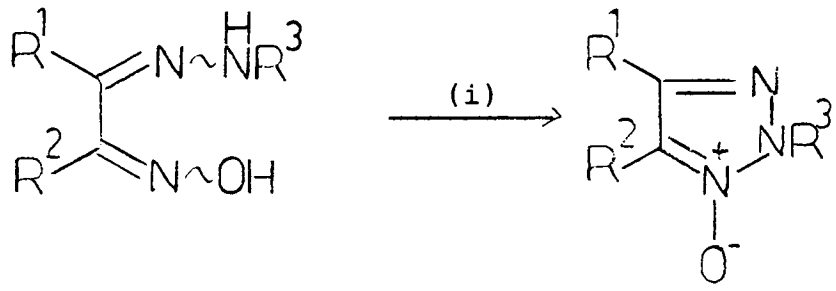


(i) ArN_2^+

(ii) H_2NOH

(iii) oxidation

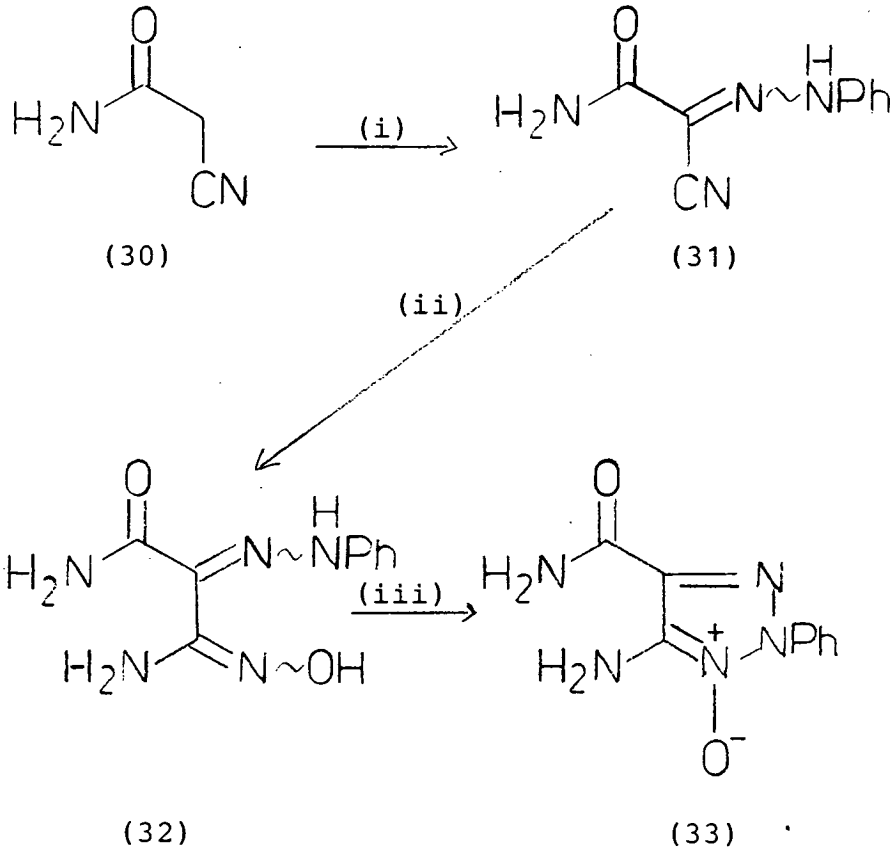
Scheme 6



(28) (29)

(i) $CuSO_4$, pyridine

Scheme 7



(30) (31) (32) (33)

(i) $PhN_2^+Cl^-$, NaOAc, 0°

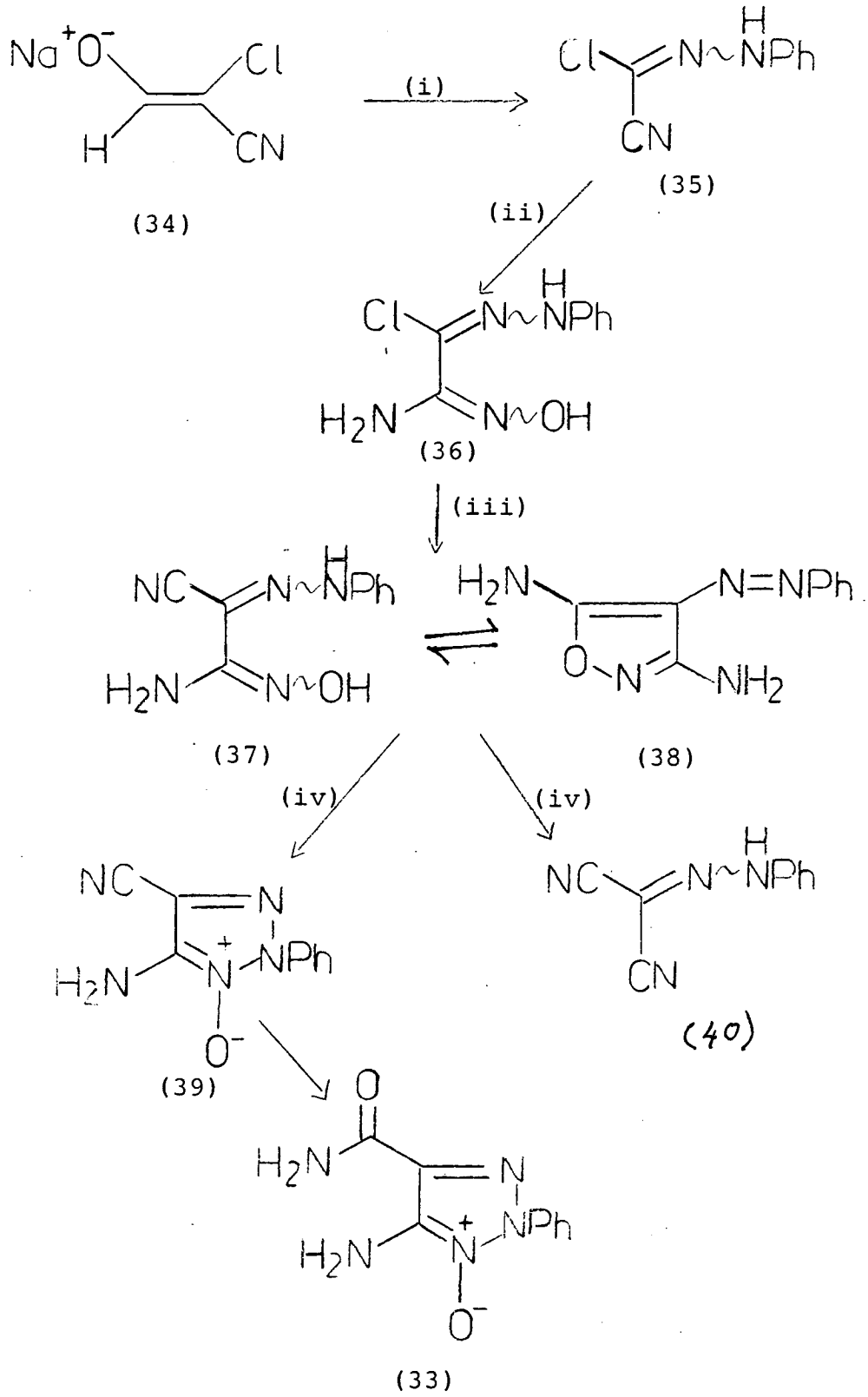
(ii) HCl, Na_2CO_3. EtOH, room temperature

(iii) MnO_2, MeCN, room temperature

Scheme 8

route to 8-substituted 8-azapurines (Scheme 5), based on the unambiguous synthesis of appropriate 2H-1,2,3-triazole 1-N-oxides (18) and the derived 2H-1,2,3-triazoles (19) and their subsequent annulation to 8-substituted 8-azapurine N-oxides (20) and the parent 8-substituted 8-azapurines (21). Since the ready availability of suitable functionalised 2H-1,2,3-triazole derivatives (18) and (19) was crucial for the success of this synthetic strategy it was initially important to develop a new synthetic method for such compounds which did not have the disadvantages of the alkylation method already discussed. The method chosen (Scheme 6) involved the known[80] coupling of cyanoacetamide derivatives (22) with aryldiazonium salts to afford hydrazono-nitriles (23) capable of reaction with hydroxylamine[81] to afford amidoximes (24) oxidative cyclisation of which would yield the required 2H-1,2,3-triazole 1-N-oxides (27), through the formation and electrocyclisation of nitroso-azo-intermediates (26). The oxidative cyclisations (Scheme 7) of simple α-diketone oxime hydrazones (28) to the corresponding 2H-1,2,3-triazole 1-N-oxides (29) are well documented[82] processes.

Initially the general strategy detailed in Scheme 6 was investigated (Scheme 8) starting with cyanoacetamide (30) which coupled readily with benzenediazonium chloride to yield the known[83] 2-cyano-2-phenylhydrazonoacetamide (31) in quantitative yield. The phenylhydrazonocyanoacetamide (31)



(i) $PhN_2^+Cl^-$, NaOAc, 0°

(ii) $H_2NOHHCl$, Na_2CO_3, EtOH, room temperature

(iii) NaCN, EtOH, room temperature

(iv) MnO_2, MeCN, room temperature

(v) base

Scheme 9

reacted readily with hydroxylamine hydrochloride in the presence of sodium carbonate to afford the previously unknown amidoxime derivative (32) in quantative yield. The compound (32) gave mass spectral data and showed other spectroscopic data consistent with the assigned structure. In particular its i.r. spectrum showed NH and OH absorptions due to the amidoxime and amide substituents the presence of the latter also being supported by carbonyl absorption at 1640 cm^{-1}. The ^1H n.m.r. spectrum of the amidoxime (32) contained the expected signals for four exchangable protons as well as proton resonances due to five aromatic hydrogen atoms. Disappointingly the attempted oxidation of the amidoxime derivative (32) with manganese dioxide under conditions successful for related cyclisations (see later) failed to afford the hoped for triazole N-oxide (33) only a low yield of an unidentified solid being obtained.

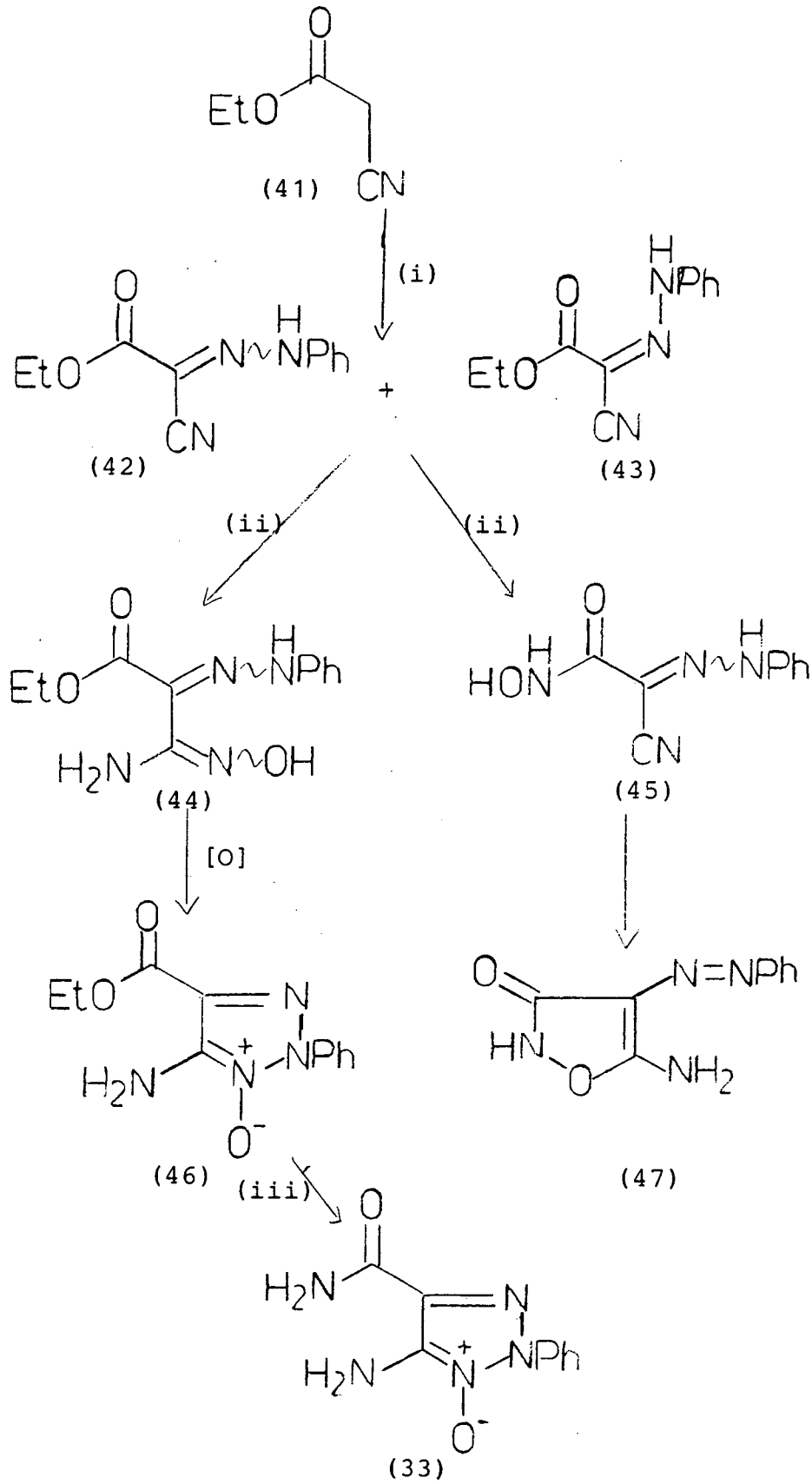
It is unclear why the oxidative cyclisation [(32)→(33)] was unsuccessful but the failure of this transformation may be due to the presence of the oxidatively sensitive primary amide group. On the basis of this assumption it was decided to seek a route (Scheme 9) to the corresponding nitrile (39) which should allow access to the amide (33) by hydrolysis.[84] The route envisaged for the cyanotriazole N-oxide (39) (Scheme 9) involved the oxidative cyclisation of the phenylhydrazonocyanoacetamidoxime (37) which it was anticipated would be readily accessible by reaction of the phenylhydrazonochloroacetamidoxime (36) with cyanide ion.

The previously unknown phenylhydrazonochloroacetamidoxime (36) was readily prepared in quantitative yield (Scheme 9) by coupling of sodio formylchloroacetonitrile[85] (34) with benzenediazonium chloride to afford the known[85] phenylhydrazonochloroacetonitrile (35) followed by reaction with hydroxylamine hydrochloride in the presence of sodium carbonate. The phenylhydrazonochloroacetamidoxime (36) gave a combustion analysis and mass spectrum and showed i.r., and ^{1}H and ^{13}C n.m.r. spectra consistent with the assigned structure. Subsequent reaction of the acetamidoxime derivative (36) with ethanolic sodium cyanide at room temperature afforded a product in quantitative yield which gave analytical data in agreement with either the phenylhydrazonocyanoacetamidoxime structure (37) or the isomeric diaminoisoxazole structure (38). However the absence of cyano-absorption in the infrared spectrum of the product and the presence of resonances in the ^{1}H n.m.r. spectrum due to two pairs of identical exchangable hydrogen atoms is in accord with the isoxazole structure (38) rather than the amidoxime derivative (37). The four exchangable protons in the latter compound would be expected to give rise to three distinct proton resonances. Perplexingly the ^{13}C n.m.r. spectrum contains only three resonances due to quaternary carbon atoms whereas both the acetamidoxime derivative (37) and the isomeric isoxazole derivative (38) possess four such carbon atoms. However due to the long relaxation

times of hetero-atom substituted quaternary carbon atoms, signals for such carbon atoms are not always observed in the ^{13}C n.m.r. spectrum.[86] This provides an explanation for the lack of a signal in the ^{13}C n.m.r. spectrum of the compound (37) or (38).

In conclusion the available evidence supports the isoxazole structure (38) as being the product of the reaction (Scheme 9) of 2-chloro-2-phenylhydrazono-acetamidoxime (36) which ethanolic sodium cyanamide. The diamino-isoxazole derivative (38) is presumably formed via the intermediacy of the acetamidoxime derivative (37) by cyclisation involving the cyano and oxime functionalities to form the isoxazole ring. A process which has been well documented[87] in the literature.

Despite the likelihood that the product described above is the isoxazole derivative (38) it could still lead by ring-opening to the phenylhydrazonocyanacetamid-oxime (37) and it was therefore decided to investigate the oxidation of the isoxazole derivative (38). The attempted oxidation (Scheme 9) of this compound with manganese dioxide gave in addition to a moderate recovery of starting material (38) a low yield of a product which gave accurate mass data consistent with its formulation as the known[88] phenylhydrazonomalononitrile (40). This structure is further supported by the melting point of the product which agrees with that of the phenylhydrazono-malononitrile (40) as reported in the literature.[88] The



(i) $PhN_2^+Cl^-$, NaOAc, 0°

(ii) NH_2OH HCl, Na_2CO_3, room temp. or NH_2OH HCl, NaOAc, heat

(iii) NH_3

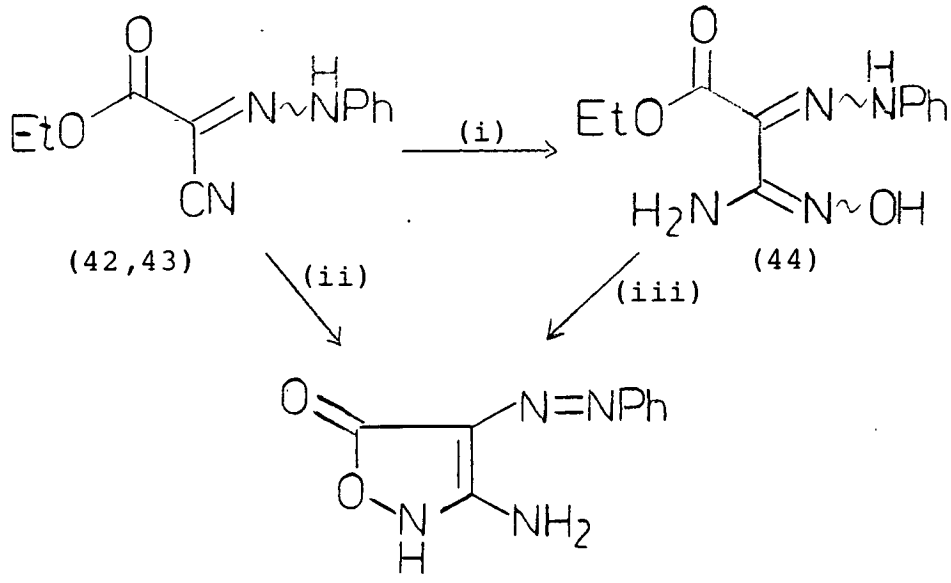
Scheme 10

identity of the product of the manganese dioxide oxidation of the isoxazole derivative (38) as phenylhydrazono-malononitrile (40) is further supported by the presence of a cyano-absorption at 2210 cm^{-1} in its i.r. spectrum and resonances in its ^{1}H and ^{13}C n.m.r. spectra due to one exchangable hydrogen atom and four quaternary carbon atoms. This product, phenylhydrazonomalonitrile (40) is presumably formed by initial ring opening of the isoxazole derivative (38) to the phenylhydrazocyano-acetamidoxime (37) which does not oxidise to the desired 2H-1,2,3-triazole derivative (39) but by a loss of hydroxylamine affords the phenylhydrazono-malonitrile (40).

The failure to obtain the cyanotriazole N-oxide (39) and hence by hydrolysis the key triazole N-oxide (33) prompted the investigation of an alternative synthetic strategy. It was therefore decided to seek a route (Scheme 10) to the ethoxycarbonyltriazole N-oxide (46) which was anticipated to be easily converted by reaction with ammonia under known conditions[89] to the amide (33). The route envisaged for the synthesis of the ethoxy-carbonyltriazole N-oxide (46) involved the oxidative cyclisation of the reported[90] phenylhydrazonoethoxy-carbonylacetamidoxime (44). It was anticipated that this compound would be readily accessible by reaction of either a mixture of (E) and (Z) ethyl 2-cyano-2-phenylhydrazonoacetates[91] (42) and (43) or of these isomers individually with hydroxylamine hydrochloride in the

presence of sodium acetate as reported.[90] A readily separated mixture of the known[91] (E) and (Z) ethyl 2-cyano-2-phenylhydrazonoacetates (42) and (43) was prepared in high yield by the coupling of ethyl cyanoacetate with benzenediazonium chloride. The (E)-isomer (42) was found to have a melting point of 106-107° which differs markedly from the literature value of 125°. However its combustion analysis and other spectroscopic data are consistent with it being (E)-ethyl 2-cyano-2-phenylhydrazonoacetate (42). In particular its i.r. spectrum has a carbonyl absorption at 1740 cm^{-1} characteristic of non-hydrogen bonded esters[92] and the ^1H n.m.r. has characteristic resonances for an ethyl group. The (Z)-isomer (43) however has a melting point of 86° which agrees with that reported in the literature,[91] and has a combustion analysis and spectroscopic data consistent with the assigned structure. Again of particular note is its i.r. spectrum which has a carbonyl absorption at 1680 cm^{-1} characteristic of hydrogen bonded esters.[92]

However reaction (Scheme 10) of a mixture of (E)- and (Z)-ethyl 2-cyano-2-phenylhydrazonoacetates (42) and (43) with hydroxylamine hydrochloride in the presence of sodium acetate as described by Elnagdi and his co-workers[90] failed to give 2-ethoxycarbonyl-2-phenylhydrazonoacetamidoxime (44) as reported. A product was obtained from this reaction in good yield which gave analytical data consistent



(42,43)

(44)

(48)

(i) NH_2OH HCl, NaOAc, EtOH, heat

(ii) NH_2OH HCl, Na_2CO_3, EtOH, heat

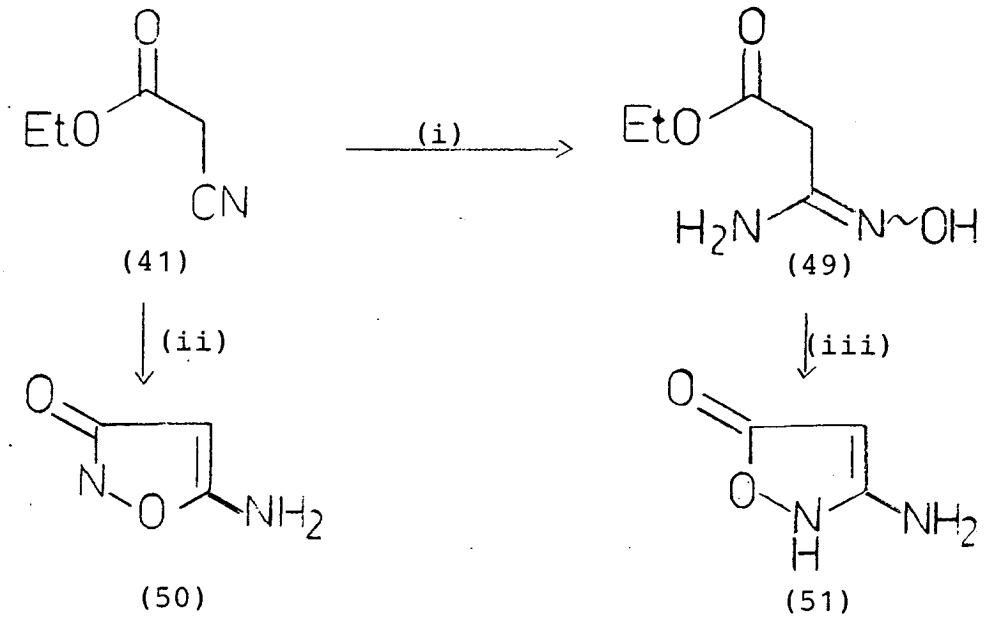
(iii) NaOMe, MeOH, heat

Scheme 11

with it being 5-amino-4-phenylazo-Δ^4-isoxazolino-3-one (47). This structure is further supported by carbonyl absorption in its i.r. spectrum at 1700 cm^{-1} characteristic of cyclic amides.[93] The ^1H n.m.r. spectrum of the isoxazolin-3-one (47) contained the expected signals for two exchangable protons and also resonances for five aromatic hydrogen atoms, and the ^{13}C n.m.r. contained signals for four quaternary carbon atoms.

In an attempt to obtain 2-ethoxycarbonyl-2-phenylhydrazonoacetamidoxime (44) by using conditions already shown to be successful for the conversion of nitriles into amidoximes the (E)- and (Z)-isomers (42) and (43) were individually treated with hydroxylamine hydrochloride in the presence of sodium carbonate. However again the isoxazolin-3-one (47) was obtained in good yield for both (E)- and (Z)-ethyl 2-cyano-2-phenylhydrazonoacetates (42) and (43). Presumably this isoxazolin-3-one derivative (47) is formed by initial reaction of hydroxylamine with the ethyl 2-cyano-2-phenylhydrazonoacetates (42) and (43) to give the N-hydroxyamide derivative (45) which then cyclises with loss of ethanol to afford the isoxazolin-3-one derivative (47). However the mechanism of this reaction still remains unclear.

Elnagdi and his co-workers[90] (Scheme 11) describe the synthesis of 2-ethoxycarbonyl-2-phenylhydrazonoacetamidoxime from (E)- and (Z)-ethyl 2-cyano-2-phenylhydrazonoacetate (42) and (43) and the conversion of all of these derivatives



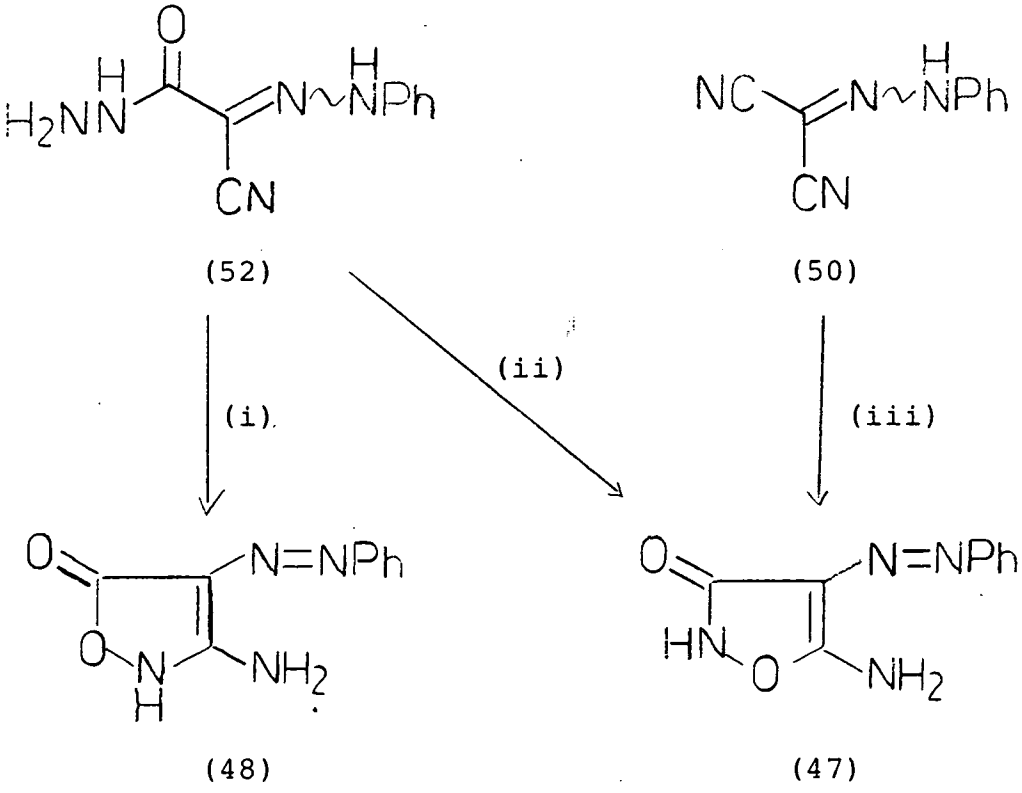
(i) $NH_2OH \cdot HCl$, NaOEt, 75°

(ii) $NH_2OH \cdot HCl$, NaOEt, room temperature

(iii) NaOH, H_2O, heat

Scheme 12

(42), (43) and (44) into a product they have assigned as 3-amino-4-phenylaza-Δ^3-isoxazolin-5-one (48). This isoxazolin-5-one derivative (48) is reported to have a melting point of 208° and a carbonyl absorption in its i.r. spectrum at 1700 cm^{-1}. It seems reasonable to suggest that this product is not the isoxazolin-5-one (48) but the isoxazolin-3-one (47) described above which has a melting point of 210-212° and a carbonyl stretching frequency in its i.r. spectrum at 1700 cm^{-1}. This conclusion is supported by the work of Bauer et al[94-96] in which these authors describe (Scheme 12) the synthesis and infrared spectral characteristics of the isoxazolin-3-one and isoxazolin-5-one derivatives (50) and (51). These authors reacted ethyl cyanoacetate (41) with hydroxylamine hydrochloride in the presence of sodium ethoxide to yield 5-amino-Δ^4-isoxazolin-3-one (50) which they report as having a carbonyl band in its i.r. spectrum at 1636 cm^{-1}. They also converted the acetamidoxime derivative (49), synthesised by the reaction of ethyl cyanoacetate with hydroxylamine hydrochloride in the presence of sodium ethoxide, into 3-amino-Δ^3-isoxazolin-5-one (51) which they report as having a carbonyl band in its i.r. spectrum at 1775 cm^{-1}. Hence it can be concluded that in general isoxazolin-3-one derivatives would be expected to have carbonyl stretching frequencies at 1700 cm^{-1} and below and that isoxazolin-5-one derivatives would have such carbonyl stretching frequencies at greater than 1700 cm^{-1}.



(i) NH_2OH . HCl, NaOAc, EtOH, room temperature

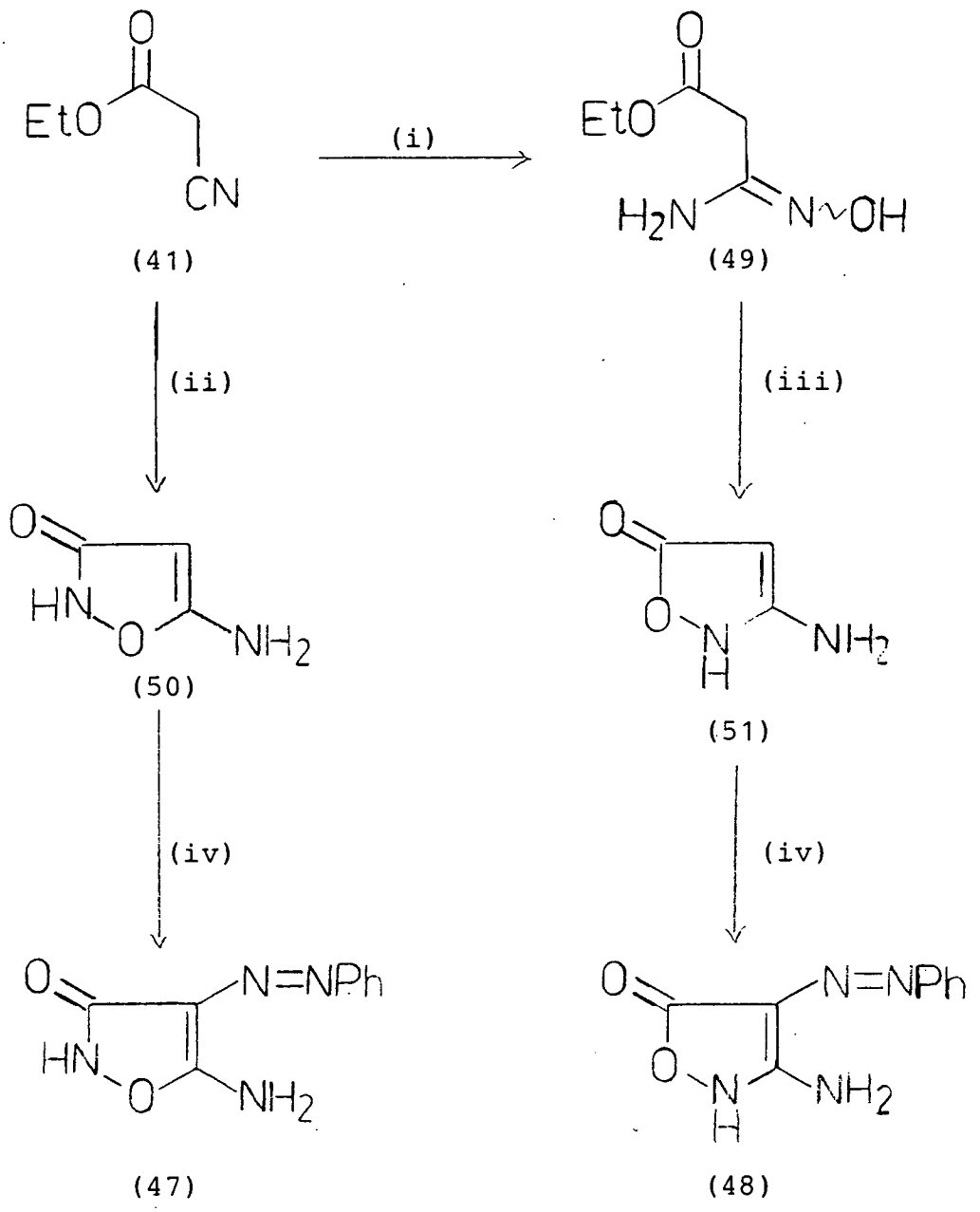
(ii) NH_2OH . HCl, NaOEt, EtOH

(iii) NH_2OH . HCl, Na_2CO_3, EtOH, reflux

Scheme 13

In an attempt to repeat (see Scheme 11) the conversion of (E)- and (Z)-ethyl 2-cyano-2-phenylhydrazonoacetate (42) and (43) into 3-amino-4-phenylazo-Δ^3-isoxazolin-5-one (48) the ethyl cyanophenylhydrazonoacetates (42) and (43) were reacted with hydroxylamine hydrochloride in the presence of sodium carbonate as described by Elnagdi and his co-workers.[90] The product obtained, which as yet is unidentified, has a melting point of 251° and a carbonyl stretching frequency in its i.r. spectrum at 1690-1695 cm^{-1}. This evidence conflicts with the reported melting point of 208° and a carbonyl stretching frequency in its i.r. spectrum at 1700 cm^{-1}.

In two later papers Elnagdi et al[97,98] describe the synthesis (Scheme 13) of 5-amino-4-phenylazo-Δ^4-isoxazolin-3-one (47) and 3-amino-4-phenylazo-Δ^3-isoxazolin-5-one (48). The reaction of the phenylhydrazonoacetonitrile derivative (52) with hydroxylamine hydrochloride in the presence of sodium ethoxide reported[97] affords 5-amino-4-phenylazo-Δ^4-isoxazolin-3-one (47). These authors claim that this product has a melting point of 238° in contrast to the melting point of 210-212° obtained for this product in the course of the present investigations. Similarly Elnagdi and his co-workers[97] reacted (Scheme 13) the phenylhydrazonoacetonitrile derivative (52) with hydroxylamine hydrochloride in the presence of sodium acetate and claim to obtain 3-amino-4-phenylazo-Δ^3-isoxazolin-5-one (48).



(i) $NH_2OH.HCl$, NaOEt, 75°

(ii) $NH_2OH.HCl$, NaOEt, room temperature

(iii) NaOH, H_2O, reflux, or Na_2CO_3, room temperature

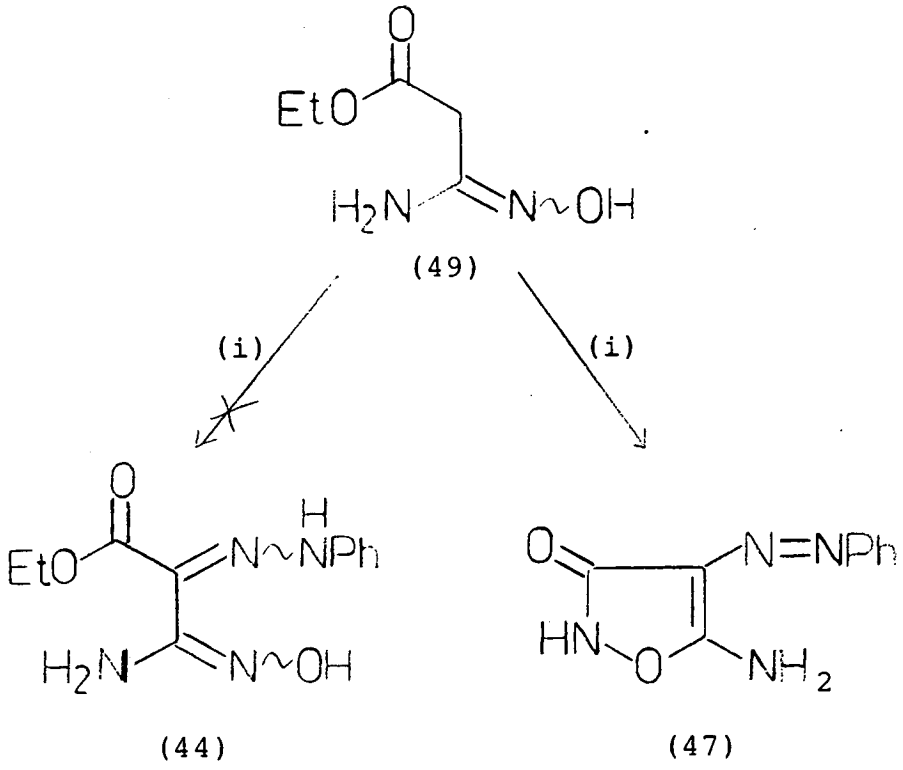
(iv) $PhN_2^+Cl^-$, NaOAc, 0°

Scheme 14

In contrast to previous work (see earlier) these authors claim that this isoxazolin-5-one (48) has a melting point of 196°. Elnagdi et al[98] have also reported (Scheme 13) the synthesis of 5-amino-4-phenylazo-Δ^4-isoxazolin-3-one (47) from phenylhydrazonomalononitrile (40) by its reaction with hydroxylamine hydrochloride in the presence of sodium carbonate. Again these authors[98] present conflicting evidence since they claim the isoxazolin-3-one derivative (47) to have a melting point of 245°.

The synthesis of 3-amino-4-phenylazo-Δ^3-isoxazolin-5-one (48) from (E)- and (Z)-ethyl 2-cyano-2-phenylhydrazonoacetates (42) and (43) (see Scheme 12) has also been reported by Dubenko and his co-workers.[99] These authors claim that this isoxazolin-5-one derivative (48) has a melting point of 231°.

The conflicting nature of the results obtained by various groups of workers prompted the investigation of the unambiguous synthesis of 5-amino-4-phenylazo-Δ^4-isoxazolin-3-one (47) and 3-amino-4-phenylazo-Δ^3-isoxazolin-5-one (48). The strategy envisaged (Scheme 14) was by coupling of the known[94,96] 5-amino-Δ^4-isoxazolin-3-one (50) and 3-amino-Δ^3-isoxazolin-5-one (51) with benzene diazonium chloride. However repetition of the reaction of ethyl cyanoacetate with sodium ethoxide failed to give 5-amino-Δ^4-isoxazolin-3-one (50) as reported[94] only a multi-component oil being obtained.



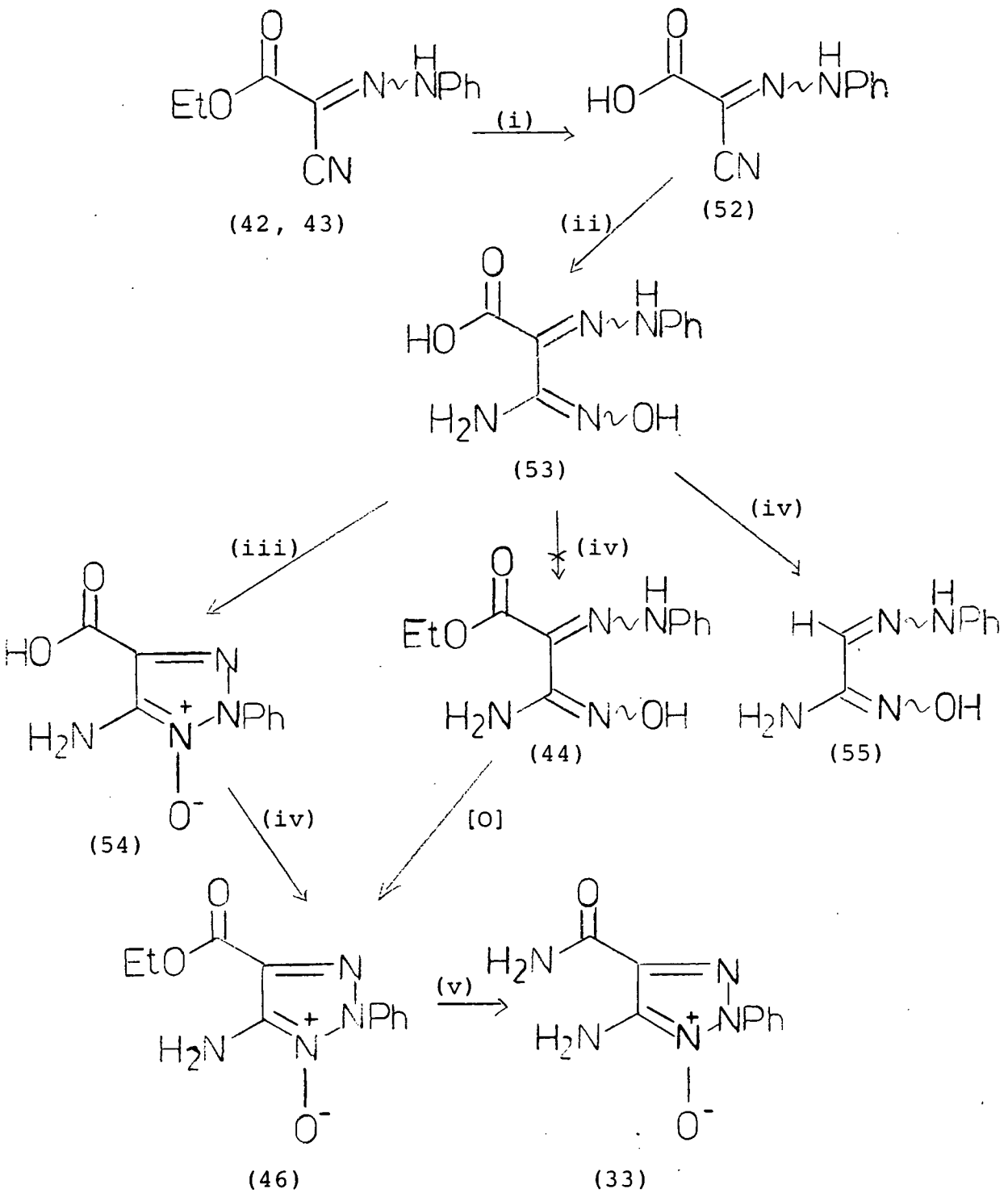
(i) $PhN_2^+Cl^-$, NaOAc, 0°

Scheme 15

The attempted preparation of 3-amino-Δ^3-isoxazolin-5-one (51) from 2-ethoxycarbonylacetamidoxime (49) also was unsuccessful, a multicomponent oil being obtained when the reaction was carried out in the presence of sodium hydroxide and a good yield of unreacted 2-ethoxycarbonylacetamidoxime (49) being obtained when the reaction was carried out in the presence of sodium carbonate. 2-Ethoxycarbonylacetamidoxime (49) was readily prepared by the procedure of England and Tennant[100] and whose melting point was identical to that reported.[96]

2-Ethoxycarbonylacetamidoxime (49) offers an alternative route (Scheme 15) to 2-ethoxycarbonyl-2-phenylhydrazonoacetamidoxime (44) which as described earlier in Scheme 10 is anticipated by oxidative cyclisation to afford the ethoxycarbonyltriazole N-oxide derivative (46) and thence by reaction with ammonia yield the key precursor, the triazole 1-N-oxide (33), in the overall strategy to 2H-8-azapurine derivatives. However coupling of 2-ethoxycarbonylacetamidoxime (49) with benzenediazonium chloride gave a good yield of 5-amino-4-phenylazo-Δ^3-isoxazolin-3-one (47). This product has identical melting point and i.r. spectrum to that described earlier. The mechanism of this transformation remains unclear.

The failure to obtain 2-ethoxycarbonyl-2-phenylhydrazonoacetamidoxime (44) prompted the design of a synthetic strategy in which the ester functionality could



(i) 20% w/v NaOH, H_2O, heat

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

(iii) MnO_2, MeCN, room temperature

(iv) conc. H_2SO_4, EtOH, reflux

(v) NH_3

Scheme 16

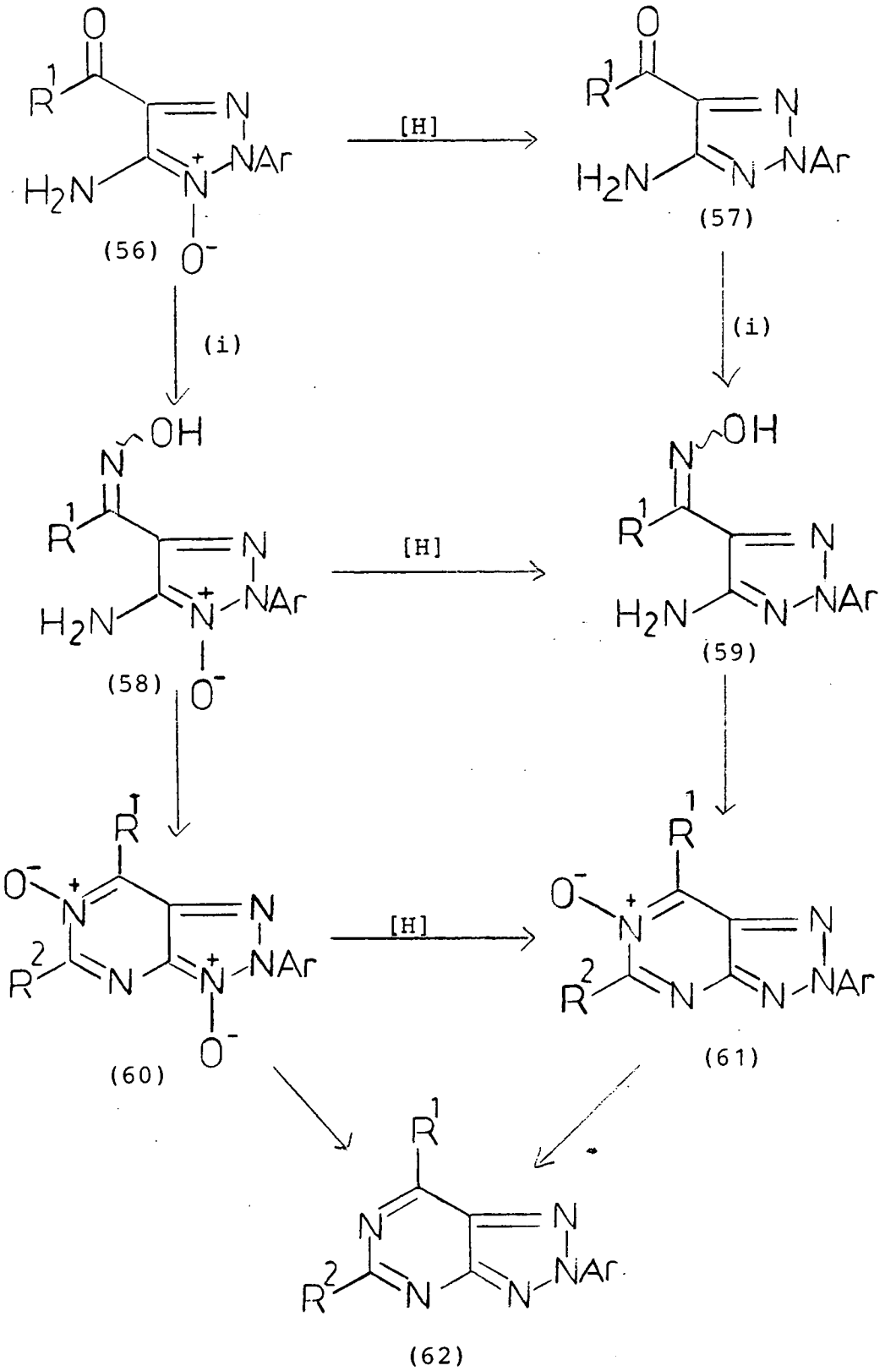
be introduced at a later stage of the overall synthesis (Scheme 16) to the key triazole 1-N-oxide (33). It was therefore decided to seek a route (Scheme 16) to 2-phenylhydrazonomalonamidoxime (53) which would offer two routes to the desired ethoxycarbonyltriazole derivative (46). Firstly by oxidative cyclisation of the malonamidoxime (53) to the triazole 1-N-oxide (54) which by esterification under standard conditions[101] would be anticipated to give the triazole derivative (46). Secondly by initial esterification[101] of the malonamidoxime (53) and consequent oxidative cyclisation of the acetamidoxime derivative (44) to give the desired ethoxycarbonyltriazole N-oxide (46).

The previously unknown 2-phenylhydrazonomalonamidoxime (53) was synthesised in good yield (Scheme 16) from (E)-2-cyano-2-phenylhydrazonoacetic acid (52)[91] by its treatment with hydroxylamine hydrochloride in the presence of sodium carbonate. The compound (53) has combustion analysis and other spectroscopic data consistent with the assigned structure. In particular its i.r. spectrum showed NH and OH absorptions due to the amidoxime and carboxylic acid substituents the presence of the latter being supported by a carbonyl absorption at 1680 cm^{-1}. The ^1H n.m.r. spectrum of the amidoxime (53) contained the expected signals for five exchangable protons and proton resonances due to five aromatic hydrogen atoms. (E)-2-cyano-2-phenylhydrazono-

acetic acid (52) was readily accessable by the hydrolysis of a mixture of (E)- and (Z)-ethyl 2-cyano-2-phenylhydrazonoacetates (42) and (43) with aqueous sodium hydroxide as described by Brecknell and his co-workers.[91]

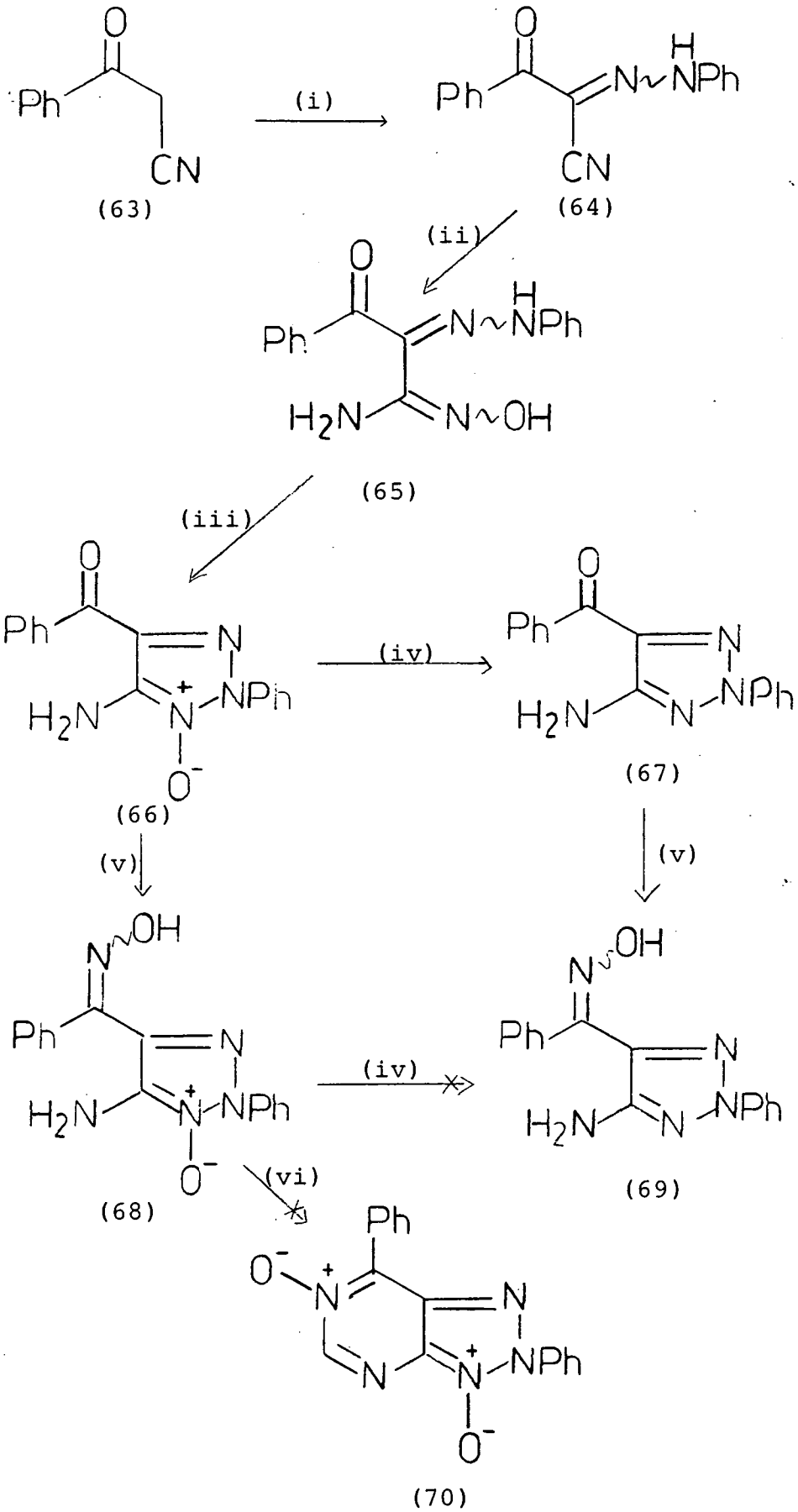
The oxidation of 2-phenylhydrazonomalonamidoxime (53) with manganese dioxide (Scheme 16) gave a low yield of 5-amino-2-phenyl-2H-1,2,3-triazole-4-carboxylic acid 1-N-oxide (54). The compound (54) has accurate mass spectral data consistent with the assigned structure. It has an i.r. spectrum containing a characteristic carboxylic acid OH absorption supported by a broad carbonyl band at ~1800 cm^{-1}. The ^1H n.m.r. of the triazole derivative (54) contains resonances due to five aromatic hydrogen atoms but perplexingly has an anomalous number of exchangable protons.

The low yield of the oxidation of 2-phenylhydrazonomalonamidoxime (53) to the triazole N-oxide (54) prompted investigation of the esterification of 2-phenylhydrazonomalonamidoxime (53). However reaction of 2-phenylhydrazonomalonamidoxime (53) with concentrated sulphuric acid in ethanol (Scheme 16) gave a good yield of the previously unknown 2-phenylhydrazonoacetamidoxime (55) none of the expected 2-ethoxycarbonyl-2-phenylhydrazonoacetamidoxime (44) could be detected. The compound (55) has accurate mass spectrum and other spectroscopic data consistent with it being the assigned structure. In particular the ^1H n.m.r. spectrum contains resonances for three exchangable protons and the ^{13}C spectrum has two signals for quaternary carbon atoms.



(i) NH_2OH.

Scheme 17



(i) $PhN_2^+Cl^-$, NaOAc, 0°
(ii) NH_2OHHCl, Na_2CO_3
(iii) MnO_2, CH_3CN
(iv) $Na_2S_2O_4$, ethanol, H_2O.
(v) NH_2OH.
(vi) $(EtO)_3CH$.

Scheme 18

The failure of this strategy to obtain the ethoxycarbonyltriazole 1-N-oxide (46) prompted investigation of a different strategy to 2H-8-azapurines from 4-amino-2H-1,2,3-triazole derivatives. Therefore it was decided to investigate (Scheme 17) the synthesis of 4-amino-5-acyl-2H-1,2,3-triazole 1-N-oxide derivatives (56) and the derived 2H-1,2,3-triazoles (57), their subsequent oximation[102] to the derivatives (58) and (59) and the annulation of these oximes to the 8-substituted-8-azapurine N-oxides (60) and (61) and thence by reduction ~~afford~~ the parent 8-substituted-8-azapurine derivatives (62).

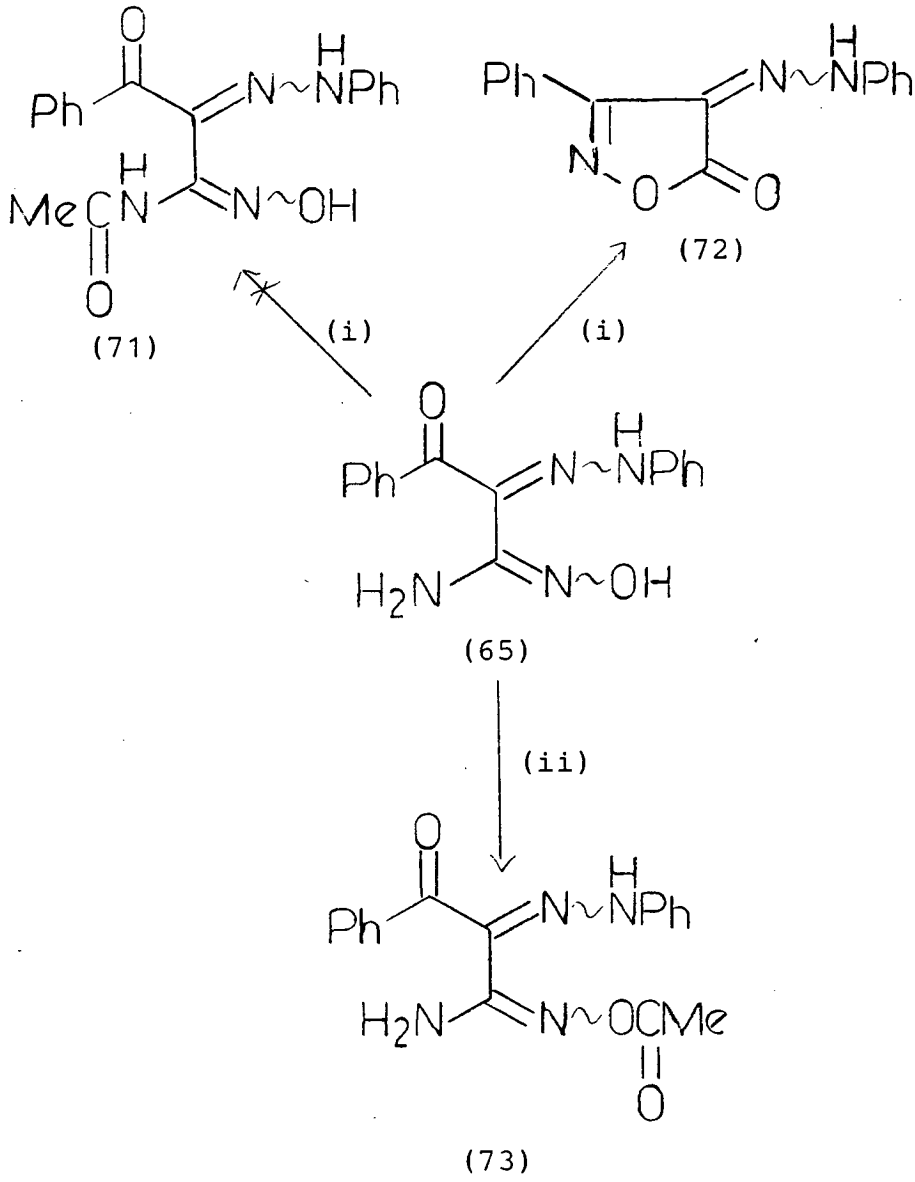
The general strategy outlined in scheme 17 was pursued (Scheme 18) starting with benzoylacetonitrile (63) which was readily prepared from 2-bromoacetophenone by reaction with potassium cyanide as described by Obregia.[105] Benzoylacetonitrile (63) coupled readily with benzenediazonium chloride to yield the known[104] 2-benzoyl-2-phenylhydrazonoacetonitrile (64) in high yield. The reaction of 2-benzoyl-2-phenylhydrazonoacetonitrile (64) with hydroxylamine hydrochloride in the presence of sodium carbonate gave a quantitative yield of the known[90] 2-benzoyl-2-phenylhydrazonoacetomidoxime (65). The functional group chemistry of this compound was investigated and is described later (see Scheme 19).

The phenylhydrazonoacetamidoxime (65) was smoothly oxidised (Scheme 18) in high yield with manganese dioxide to the previously unknown 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66). This triazole N-oxide (66) has combustion analysis and spectroscopic data consistent with the assigned structure. The i.r. spectrum of the triazole derivative (66) has a carbonyl absorption at 1650 cm^{-1}. The ^{1}H n.m.r. spectrum of this compound (66) contains resonances for ten aromatic hydrogen atoms and signals for two exchangeable hydrogen atoms. The ^{13}C n.m.r. spectrum perplexingly contains only four resonances due to the quaternary carbon atoms whereas the assigned structure (66) contains five such carbon atoms. However as stated earlier the long relaxation times of hetero-atom substituted quaternary carbon atoms can mean that signals for such carbon atoms are not always observed in the ^{13}C n.m.r. spectrum.[86] The functional group chemistry of this new compound (66) was investigated and is discussed later (see Schemes 20-24).

The 2H-1,2,3-triazole 1-N-oxide (66) was reacted with ethanolic hydroxylamine hydrochloride (Scheme 18) to afford the previously unknown 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide oxime (68) in quantitative yield. This compound (68) has accurate mass spectral data and other spectroscopic data consistent with the assigned structure. In particular the ^{1}H n.m.r. spectrum contains

resonances for ten aromatic hydrogen atoms and three exchangable protons. Disappointingly the attempted annulation (Scheme 18) of the 2H-1,2,3-triazole 1-N-oxide oxime (68) with triethyl orthoformate gave a multi-component gum none of the expected 2H-8-azapurine N-oxide derivative (70) being detected.

It is uncertain why this annulation [(68)→(70)] was unsuccessful but the failure of this reaction prompted the investigation of the reduction[106] (Scheme 18) of the 2H-1,2,3-triazole 1-N-oxide oxime (68) in an attempt to obtain the 2H-1,2,3-triazole derivative (69) which might be more amenable toward cyclisation to give a 2H-8-azapurine derivative. However attempted reduction of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide oxime (68) by reaction with sodium dithionite was unsuccessful, a good yield of unreacted starting material being recovered. The failure of this latter reduction step [(68)→(69)] prompted the investigation of the reduction of the 2H-1,2,3-triazole 1-N-oxide (66) to its parent 2H-1,2,3-triazole derivative (67) which was anticipated to yield the desired oxime derivative (69) on reaction with hydroxylamine hydrochloride. The reaction of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with sodium dithionite afforded a low yield of 4-amino-5-benzoyl-2-phenyl-2H-1,2,3-triazole (67). This compound (67) has combustion analysis and other spectroscopic data in agreement with the assigned structure. In particular it has a carbonyl absorption at 1635 cm^{-1} in its i.r. spectrum.



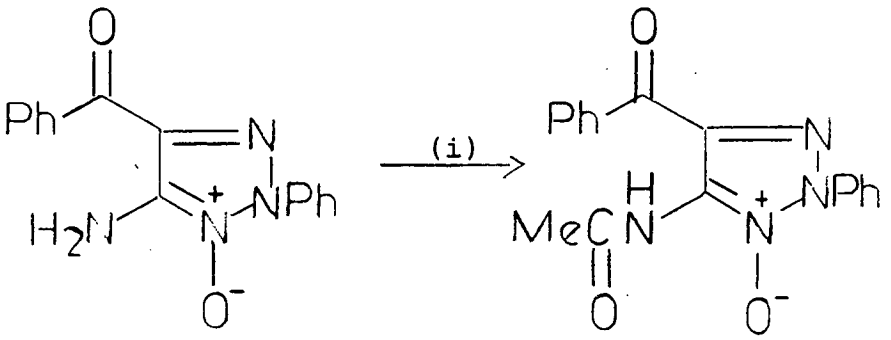
(i) Ac_2O, heat

(ii) AcCl, Et_3N, room temperature

Scheme 19

The triazole (67) contained resonances in its ^{1}H n.m.r. spectrum for ten aromatic hydrogen atoms and two exchangeable protons. Due to the low yield of the transformation [(66)→(67)] it was decided not to pursue the oximation of the 2H-1,2,3-triazole derivative (67) to the desired oxime derivative (69) and thence by cyclisation the 2H-8-azapurine ring system.

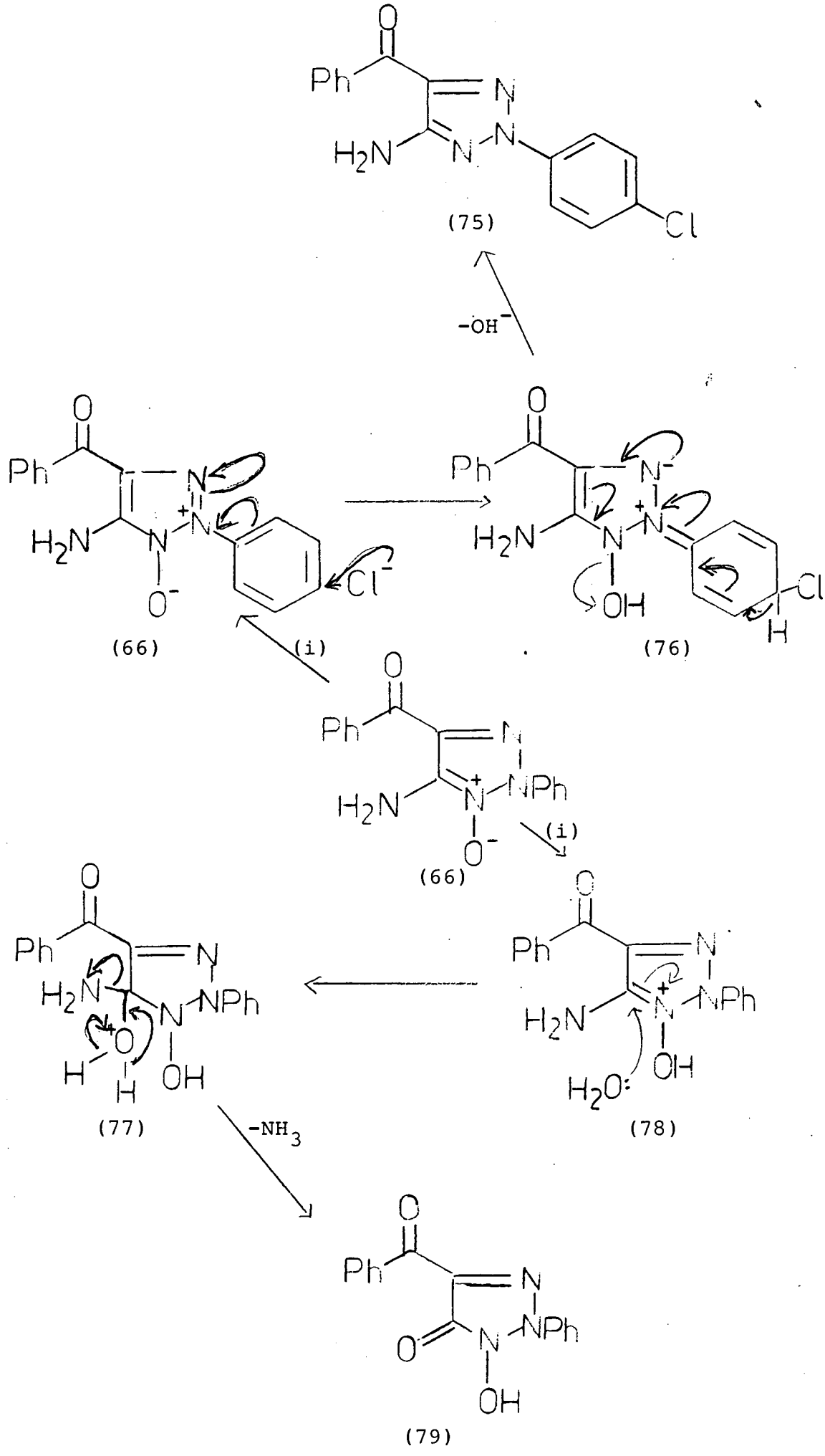
As stated earlier the functional group chemistry (Scheme 19) of 2-benzoyl-2-phenyl hydrazonoacetamidoxime (65) was investigated. The reaction of the phenylhydrazono-acetamidoxime (65) with acetic anhydride was expected to give the acetamide derivative (71). However in practice only a low yield of the known 3-phenyl-4-phenylhydrazono-Δ^{2}-isoxazolin-5-one (72)[107] was isolated. This compound (72) has a melting point of 168-169° which is in agreement with the literature.[107] It also has combustion analysis and spectroscopic data consistent with the assigned structure. In particular its i.r. spectrum contains a carbonyl absorption at 1720 cm^{-1} consistent with such an isoxazolin-5-one (see earlier). The ^{1}H n.m.r. spectrum contains resonances for ten aromatic hydrogen atoms and a single exchangable proton and the ^{13}C n.m.r. spectrum contains signals for five quaternary carbon atoms. The mechanism of this transformation [(65)→(72)] remains unclear.



(66) (74)

(i) Ac_2O, heat

Scheme 20



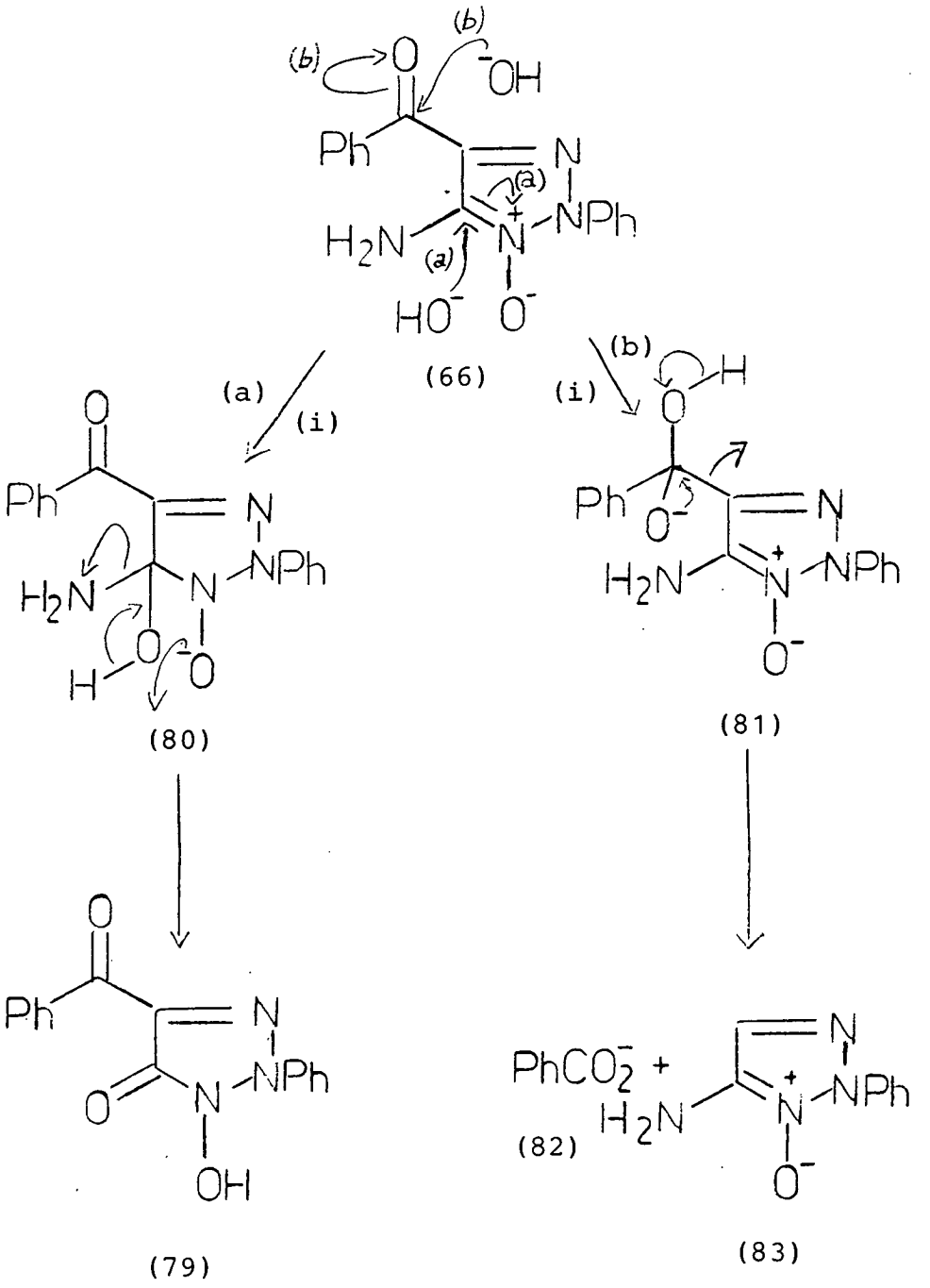
(i) conc. HCl, EtOH, heat

Scheme 21

In order to derivatise the oxime functionality 2-benzoyl-2-phenylhydrazonoacetamidoxime (65) was reacted with acetyl chloride in the presence of triethylamine, conditions known to acetylate oximes,[108] to give a quantitative yield of O-acetyl-2-benzoyl-2-phenylhydrazonoacetamidoxime (73). This phenylhydrazonoacetamidoxime (73) gave combustion analysis and spectroscopic data consistent with the assigned structure. In particular its i.r. spectrum contains a carbonyl absorption at 1750 cm^{-1} characteristic of an oxime acetate.[109] The ^{13}C n.m.r. spectrum contains six signals for quaternary carbon atoms, and a signal for a methyl carbon atom.

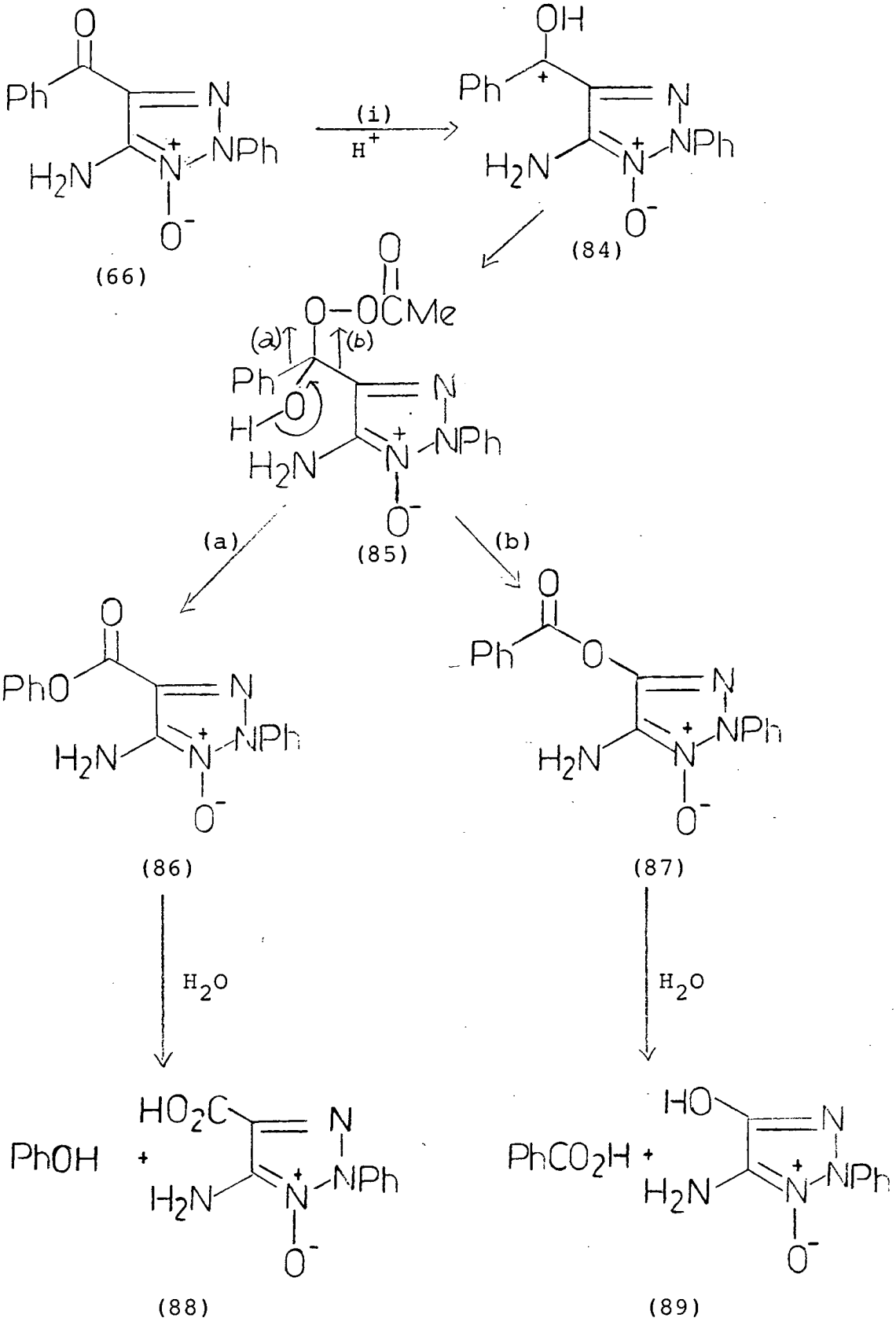
Also as stated earlier, the functional group chemistry (Schemes 20-24) of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) was investigated. Reaction (Scheme 20) of the 2H-1,2,3-triazole derivative (66) with acetic anhydride gave a low yield of the expected acetamide derivative (74). This compound has accurate mass spectral data in agreement with the assigned structure. Perplexingly however its i.r. spectrum contains a carbonyl band at 1760 cm^{-1}. This is too high for an amide carbonyl which would be expected to have a carbonyl stretching frequency at around 1650 cm^{-1}.

It is known that triazole N-oxides can react with hydrochloric acid to afford acyl substituted 1,2,3-triazole derivatives.[110] In the case (Scheme 21) where 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) is treated with hydrochloric acid two products might be



(i) 20% w/v KOH-H_2O, EtOH, heat

Scheme 22



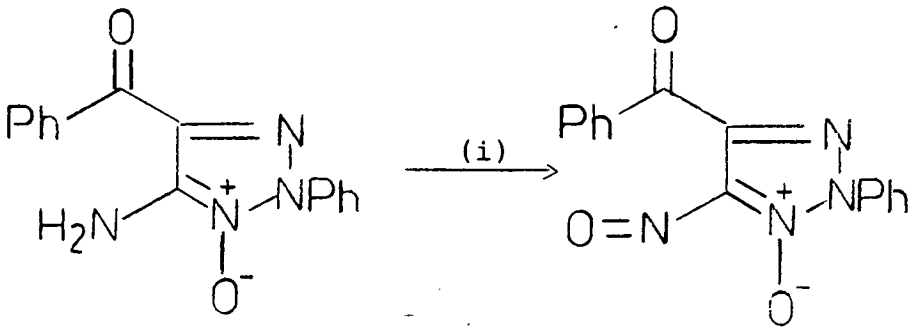
(i) H_2O_2, $MeCO_2H$

Scheme 23

expected. Firstly by rearrangement through the intermediate (76) to afford 4-amino-5-benzoyl-2-(4-chlorophenyl)-2H-1,2,3-triazole (75). Secondly by hydrolysis via the intermediates (78) and (79) to afford 4-benzoyl-1-hydroxy-2-phenyl-2H-Δ^2-1,2,3-triazolin-5-one (79). However in practice treatment of the 2H-1,2,3-triazole 1-N-oxide (66) with ethanolic hydrochloric acid gave a good yield of unreacted starting material none of the anticipated products (75) and (79) were detected.

Similarly treatment with alkali (Scheme 22) of the 2H-1,2,3-triazole 1-N-oxide (66) might be expected to give two products. Firstly the triazolin-5-one derivative (79) by hydrolytic elimination of ammonia through the intermediate (80). Secondly 5-amino-2-phenyl-2H-1,2,3-triazole 1-N-oxide (83) by elimination of benzoic acid (82) by the mechanism illustrated (Scheme 22) via the intermediate (81), a process which has been reported.[111] However treatment of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with potassium hydroxide yielded neither of the expected products, a low yield of starting material and an unidentified solid being isolated.

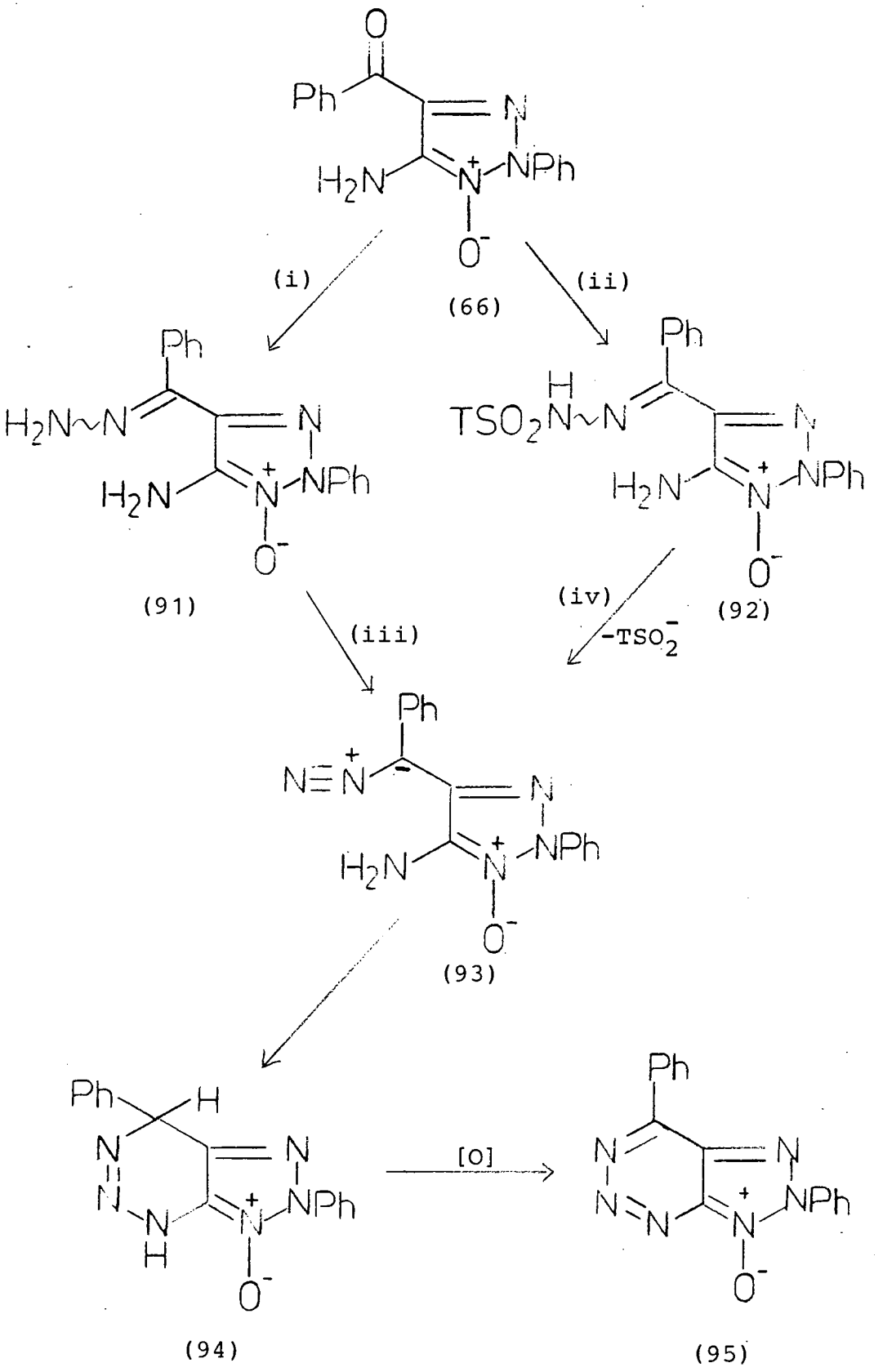
In further exploring the functional group chemistry of the 2H-1,2,3-triazole derivative (66) it was decided to investigate its behaviour toward hydrogen peroxide in acid. It was expected that these conditions would induce a Bayer-Villiger rearrangement[112] (Scheme 23) to yield the esters (86) and (87) by the mechanism illustrated. These



(66) (90)

(i) H_2O_2, $MeCO_2H$

Scheme 24



(i) $NH_2NH_2H_2O$ or NH_2NH_2HCl

(ii) TSO_2NHNH_2

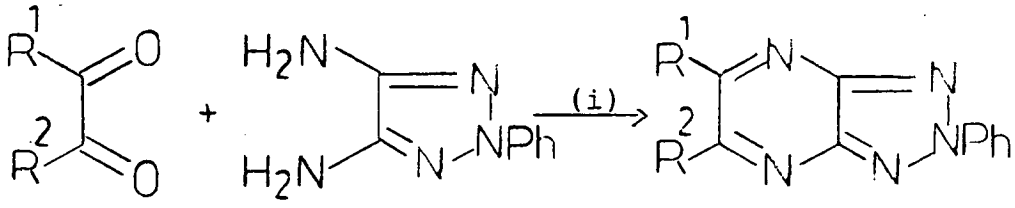
(iii) [O]

(iv) base

Scheme 25

esters (86) and (87) might then be anticipated to afford the triazole derivatives (88) and (89) by either loss of phenol and benzoic acid respectively. However reaction (Scheme 24) of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with hydrogen peroxide in acetic acid afforded 4-benzoyl-5-nitroso-2-phenyl-2H-1,2,3-triazole 1-N-oxide (90) in low yield along with a moderate yield of unreacted starting material. This product (90) is formed by oxidation of the amino substituent, a well documented process.[113,114] The 4-benzoyl-5-nitroso-2-phenyl-2H-1,2,3-triazole 1-N-oxide (90) has combustion analysis and spectroscopic data in agreement with the assigned structure. In particular its i.r. spectrum has a carbonyl band at 1680 cm^{-1} and the ^{13}C n.m.r. spectrum has signals for five quaternary carbon atoms.

The discussion in this section has so far been confined to the synthesis of 4-amino-2H-1,2,3-triazole derivatives which afford an approach to the synthesis of 2H-8-azapurines. However these 4-amino-2H-1,2,3-triazole derivatives can also be used in the synthesis of 2H-2,8-diazapurines. In particular (Scheme 25) 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) was anticipated to yield the hydrazone derivative (91) on reaction with hydrazine monohydrate[115] or hydrazine hydrochloride.[116] The hydrazone (91) was further anticipated to yield the 2H-2,8-diazapurine (95) by diazotative cyclisation[41,46,47] through the intermediacy of



(96) (97) (98)

(i) $MeCO_2H$, EtOH, heat or BF_3 etherate, room temp.

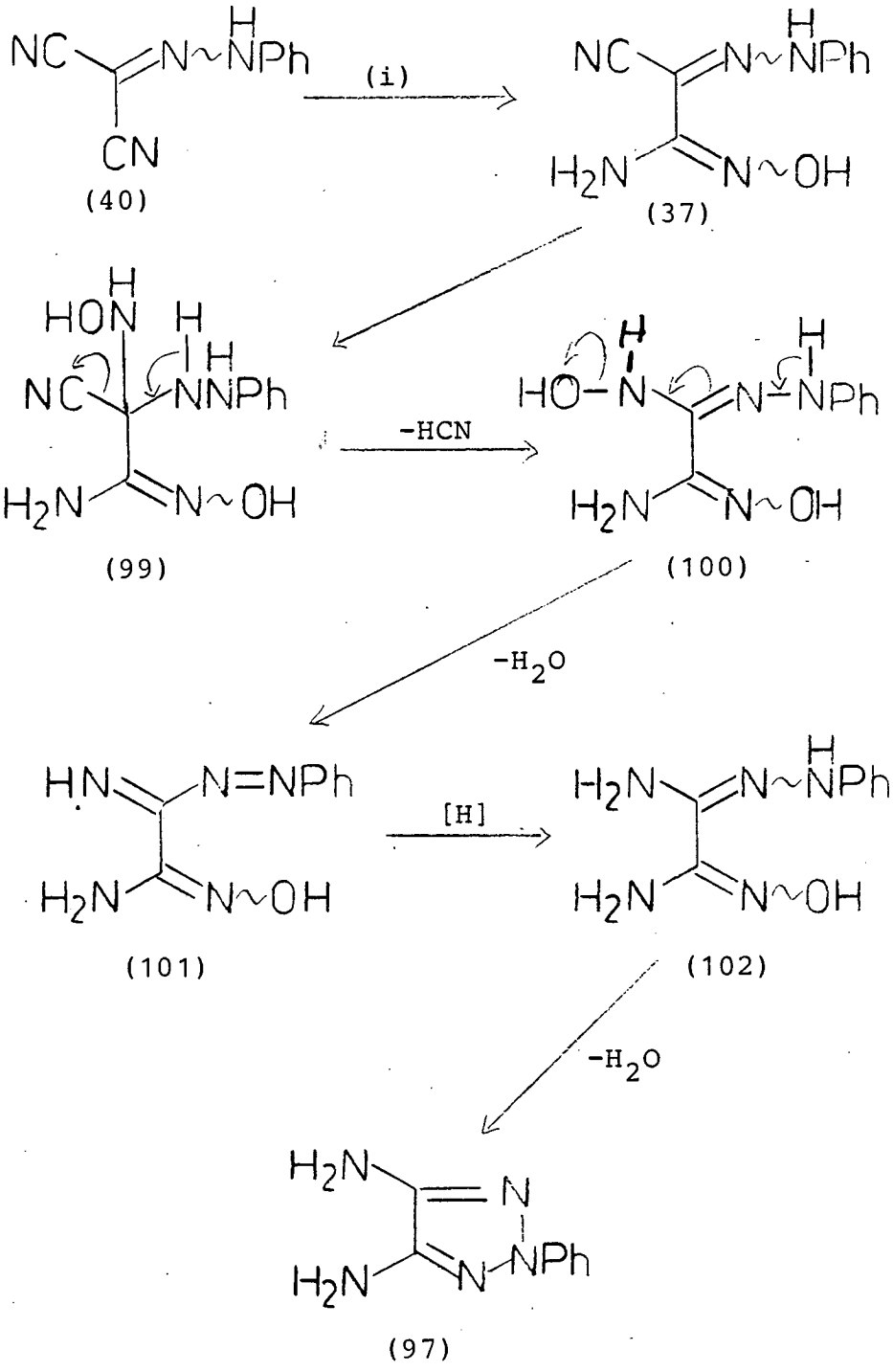
Scheme 26

the derivatives (93) and (94). The 2H-2,8-diazapurine derivative (95) was also the anticipated product of the tosylhydrazone derivate (92) on treatment with base,[117] presumably by the same mechanism. This tosylhydrazone derivative (92) was expected to be readily available by reaction of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with tosylhydrazine.[118]

Disappointingly reaction (Scheme 25) of the 2H-1,2,3-triazole derivative (66) with hydrazine monohydrate, hydrazine hydrochloride and tosylhydrazine failed to give any of the expected triazole products (91) and (92). Reaction of the triazole derivative (66) with hydrazine monohydrate and tosylhydrazine gave a good yield of unreacted starting material in both cases. Its reaction with hydrazine hydrochloride gave a low yield of unreacted starting material and a series of unidentified gums.

2.3 General Synthetic Approaches to 2H-1,2,3-Triazolo-[4,5-b]pyrazine Derivatives from 4-Amino-2H-1,2,3-Triazole Derivatives

Only a single method appears to have been described[75] for the synthesis of 2H-1,2,3-triazolo[4,5-b]pyrazine derivatives. This involves the condensation of a 4,5-diamino-2H-1,2,3-triazole with α-dicarbonyl compounds as illustrated (Scheme 26) by the condensation of 4,5-diamino-2-phenyl-2H-1,2,3-triazole (97)[119] with α-dicarbonyl compounds (96) to yield 2H-1,2,3-triazolo[4,5-b]pyrazine derivatives (98).



(40) (37) (99) (100) (101) (102) (97)

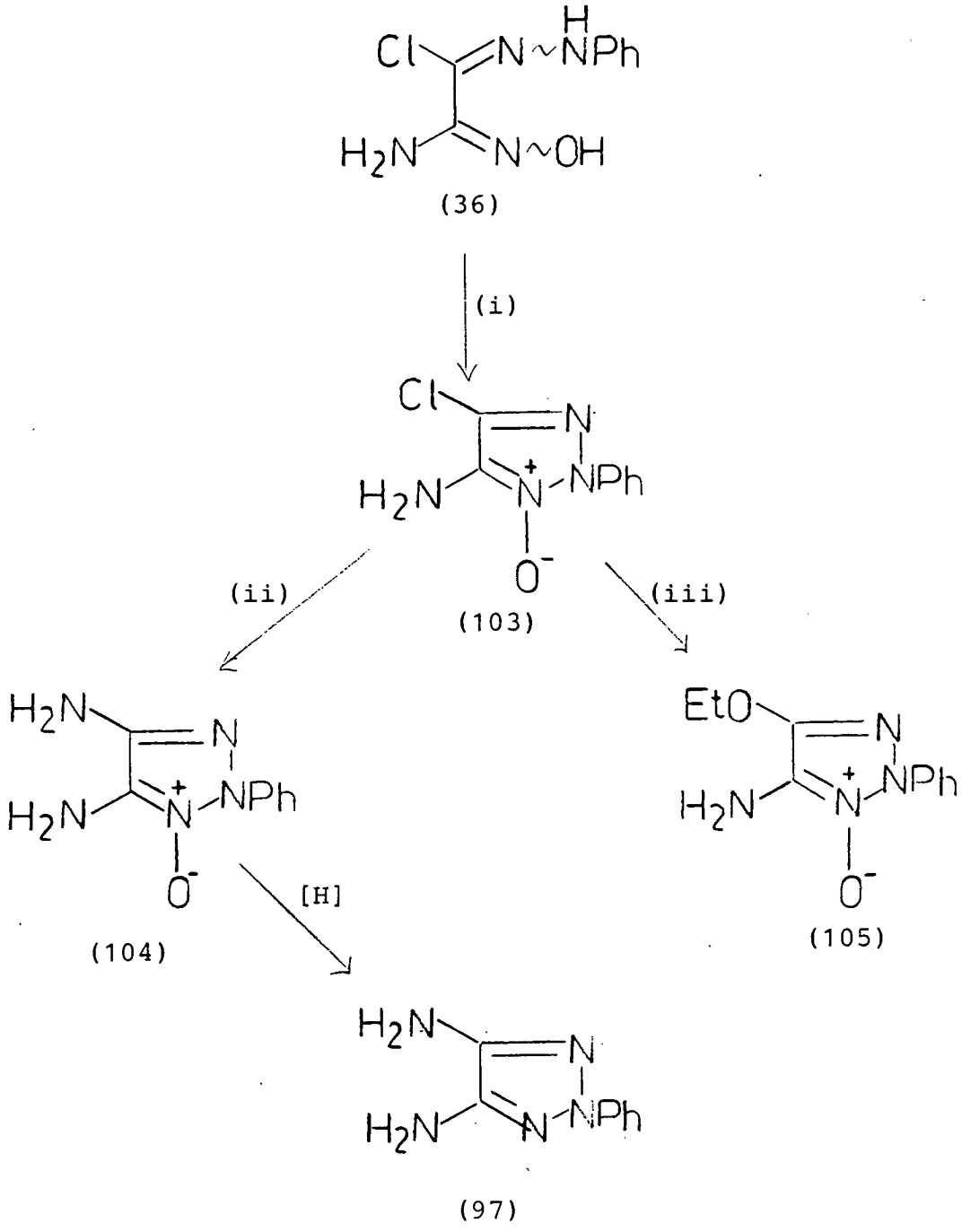
(i) NH_2OH . HCl, NaOH

(ii) H_2O, 150°, 25 atm.

Scheme 27

Indeed, 4,5-diamino-2-phenyl-2H-1,2,3-triazole (97) appears to be the only example of a 4,5-diamino-2H-1,2,3-triazole derivative. Its preparation has been described by Thiele and Schleusner[119] as illustrated (Scheme 27) in which phenylazomalonitrile (40) was treated with hydroxylamine hydrochloride in the presence of sodium hydroxide to afford 2-amino-2-phenylhydrazonoacetamidoxime (102). A mechanism for this reaction was not proposed by these authors however it would seem feasible that the reaction proceeds as follows. Reaction of phenylazomalonitrile with hydroxylamine gives the intermediate (37) which reacts further with hydroxylamine to give the intermediate (99). This product (99), by loss of hydrogen cyanide, can form the acetamidoxime derivative (100) which by dehydration and further reduction affords the isolated 2-amino-2-phenylhydrazonoacetamidoxime (102). This acetamidoxime (102) was dehydratively cyclised in water at high temperature and high pressure to yield 4,5-diamino-2-phenyl-2H-1,2,3-triazole (97).

Alternative routes to this 4,5-diamino-2-phenyl-2H-1,2,3-triazole (97) were investigated in order to examine the possibility of obtaining a general route to a variety of 4,5-diamino-2-aryl-2H-1,2,3-triazoles and hence further derivatives of the 2H-1,2,3-triazolo[4,5-b]pyrazine ring system. Initially this was investigated (Scheme 28) starting with 2-chloro-2-phenylhydrazonoacetamidoxime (36) whose preparation was described earlier (see Scheme 9) and which on treatment with manganese dioxide gave a



(i) MnO_2, MeCN, room temperature

(ii) NH_3, EtOH, room temperature

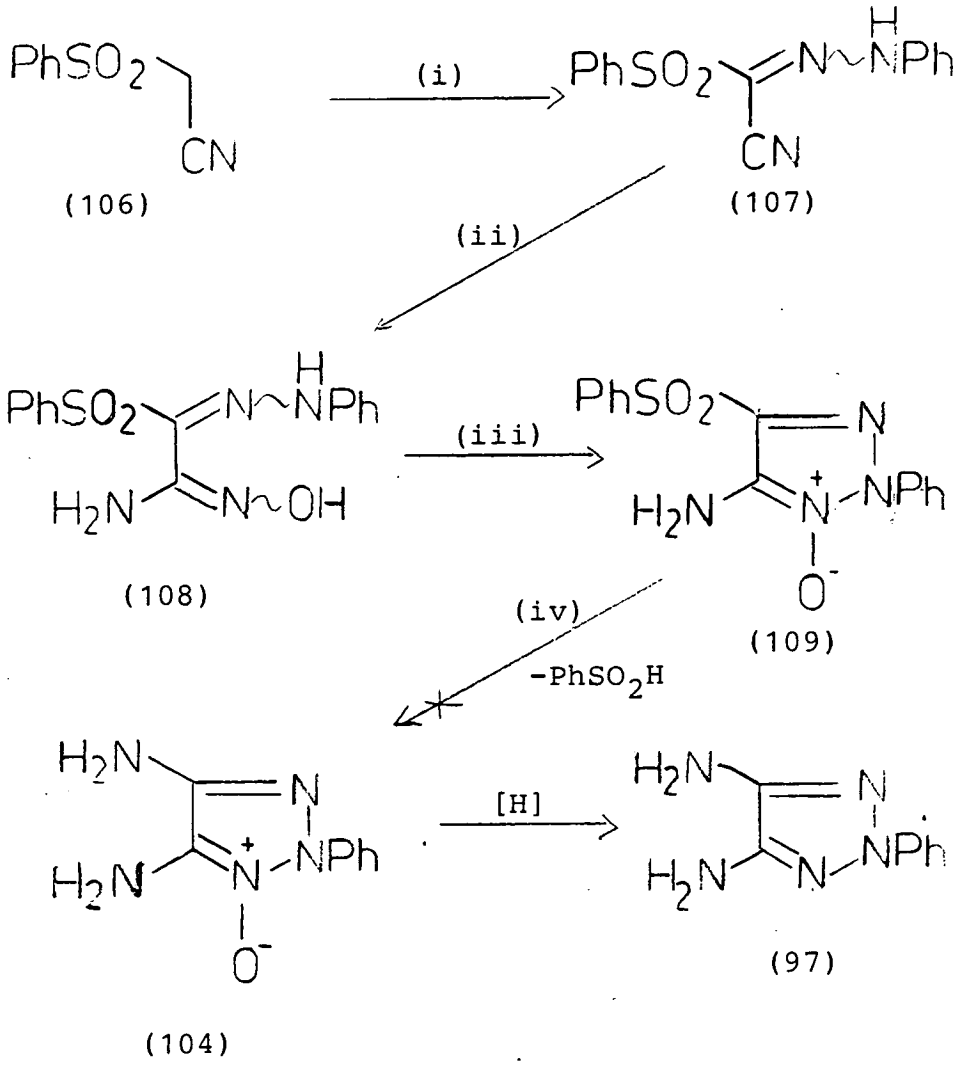
(iii) NaOEt, EtOH, heat

Scheme 28

high yield of 5-amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103). This previously unknown compound has combustion analysis and spectroscopic data consistent with the assigned structure. In particular the ^{1}H n.m.r. contained the expected signals for two exchangable protons as well as resonances for five aromatic hydrogen atoms. The ^{13}C n.m.r. exhibits, as expected, three signals for quaternary carbon atoms and the mass spectrum has two characteristic peaks at 212 and 210 corresponding to the two isotopes of chlorine.

It was anticipated that the chloro group of the 2H-1,2,3-triazole 1-N-oxide (103) would be readily displaced by reaction with ammonia to yield 4,5-diamino-2-phenyl-2H-1,2,3-triazole 1-N-oxide (104). This compound, by reduction, would afford 4,5-diamino-2-phenyl-2H-1,2,3-triazole and hence 2H-1,2,3-triazolo[4,5-b]pyrazine derivatives. However, treatment of the chlorotriazole N-oxide (103) with ammonia failed to afford the expected diamino-triazole derivative (104) only a high yield of unreacted starting material being isolated.

The unexpected inertness of the chloro group of the triazole N-oxide (103) to displacement by ammonia prompted the reaction (Scheme 28) of the triazole derivative (103) with ethoxide ion, a better nucleophile than ammonia.[120] It was anticipated that this reaction would afford 5-amino-4-ethoxy-2-phenyl-2H-1,2,3-triazole 1-N-oxide (105).



(i) $PhN_2^+Cl^-$, NaOAc, 0°C

(ii) $NH_2OH.HCl$, Na_2CO_3, room temperature

(iii) MnO_2, MeCN, room temperature

(iv) NH_3, EtOH, room temperature

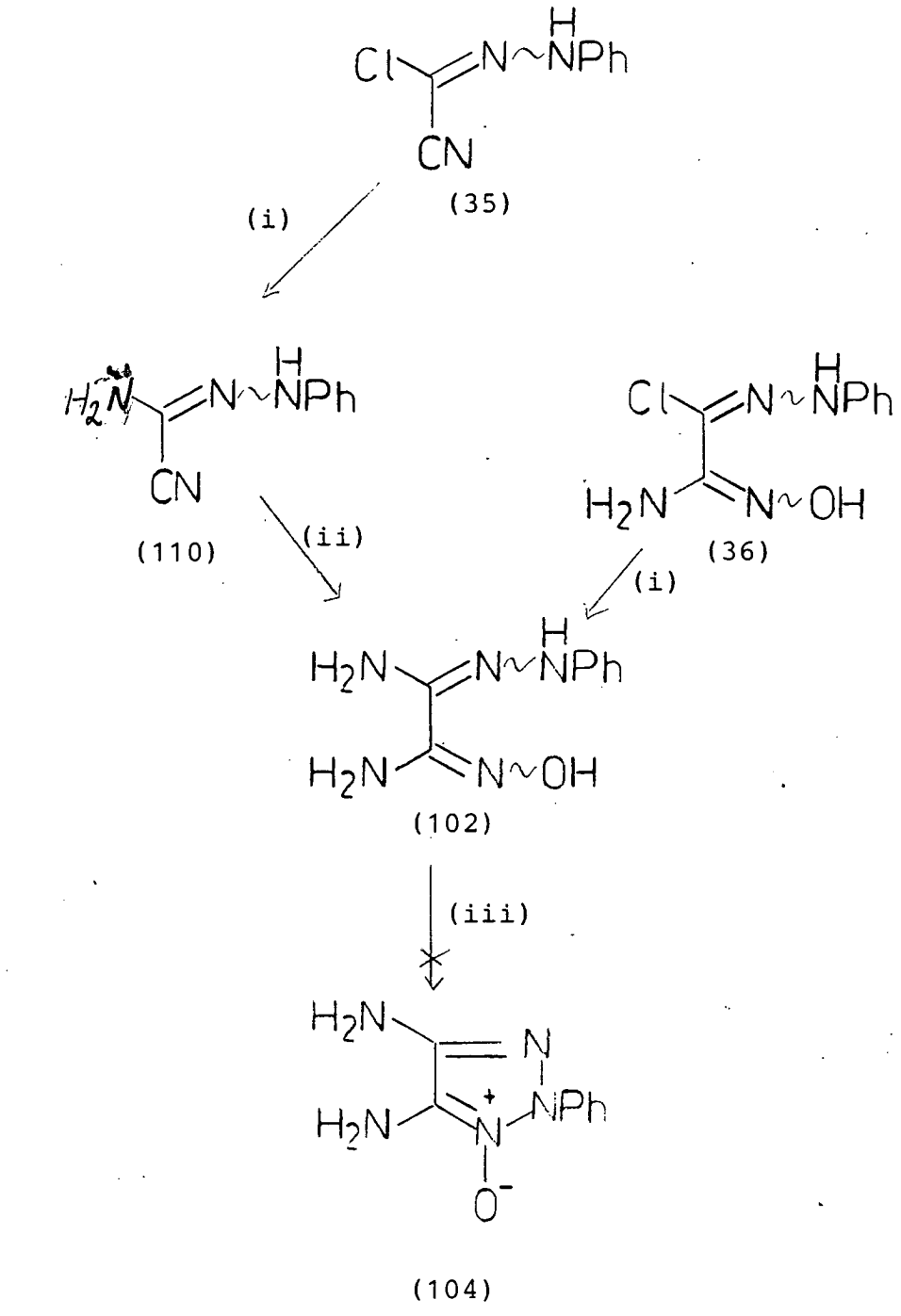
Scheme 29

However, treatment of 5-amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103) with sodium ethoxide yielded a multicomponent gum, none of the expected triazole derivative (105) was detected.

It is not certain why displacement of the chloro group of the triazole N-oxide derivative (103) should either be complicated or not proceed. However the failure of this transformation prompted the investigation of a route (Scheme 29) to 5-amino-4-phenylsulphonyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (109) since it has been reported[121] that the phenylsulphonyl moiety is a better leaving group than a chloro substituent. Hence the synthesis of the triazole derivative (109) was pursued starting with benzene sulphonylacetonitrile which was readily prepared by reaction of sodium benzenesulphinate with chloroacetonitrile as described by Troger and Hille[122] in good yield. Benzenesulphonylacetonitrile was coupled with benzenediazonium chloride to afford the previously unknown 2-benzenesulphonyl-2-phenylhydrazonoacetonitrile (107) in quantitative yield. This compound (107) has combustion analysis and spectroscopic data consistent with the assigned structure. In particular its i.r. spectrum has a nitrile absorption at 2200 cm^{-1}. The ^1H n.m.r. of the acetonitrile (107) contains resonances for ten aromatic hydrogen atoms and one exchangable proton.

2-Benzenesulphonyl-2-phenylhydrazonoacetonitrile (107) was readily converted (Scheme 29) into the previously unknown 2-benzenesulphonyl-2-phenylhydrazonoacetamidoxime (108) by treatment with hydroxylamine hydrochloride in the presence of sodium carbonate. This compound (108) has combustion analysis and spectroscopic data consistent with the assigned structure. In particular its ^{1}H n.m.r. spectrum contains signals for resonances of ten aromatic hydrogen atoms and four exchangeable protons. However, its ^{13}C n.m.r. spectrum contains only three resonances for quaternary carbon atoms whereas the compound (108) contains four such carbon atoms. However, as was stated earlier due to the long relaxation times of hetero-atom substituted quaternary carbon atoms, signals for such carbon atoms are not always observed in the ^{13}C n.m.r. spectrum.[86]

The oxidation of 2-benzenesulphonyl-2-phenyl-hydrazonoacetamidoxime (108) with manganese dioxide (Scheme 29) afforded a high yield of the previously unknown 5-amino-4-benzenesulphonyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (109). This product (109) has combustion analysis and spectroscopic data consistent with the assigned structure. In particular the ^{1}H n.m.r. spectrum exhibits resonances for ten aromatic hydrogen atoms and two exchangeable protons. The ^{13}C n.m.r. spectrum



(i) NH_3, EtOH, room temperature

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

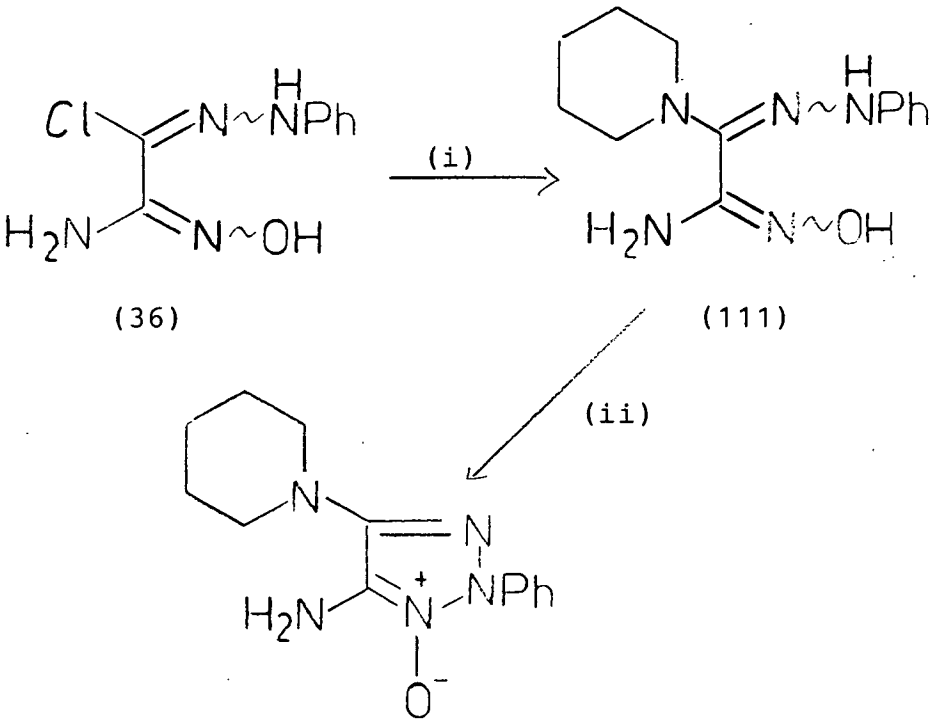
(iii) MnO_2, MeCN, room temperature

Scheme 30

contains four signals corresponding to the compound's four quaternary carbon atoms. ~~Disappointingly~~ Disappointingly however, reaction of this triazole N-oxide (109) with ammonia failed to give the desired 4,5-diamino-2-phenyl-2H-1,2,3-triazole 1-N-oxide (104) a quantitative yield of unreacted starting material being recovered.

The failure of the nucleophilic displacement of both the chloro moiety and benzenesulphonyl group in the triazole derivatives (103) and (109) respectively prompted the investigation of new synthetic routes to the acetamidoxime derivative (102) which has been described by Thiele and Schluessner.[119] It was anticipated that this derivative (102) would undergo oxidation with manganese dioxide to yield the diaminotriazole N-oxide (104) which in turn could be reduced to the desired parent triazole (97).

Therefore two new routes (Scheme 30) to 2-amino-2-phenylhydrazonoacetamidoxime (102) were investigated. Firstly 2-chloro-2-phenylhydrazonoacetamidoxime (36) whose synthesis has been previously described (see Scheme 9) on treatment with ammonia gave a moderate yield of the expected 2-amino-2-phenylhydrazonoacetamidoxime (102). This compound (102) has a melting point in agreement with that reported[119] and combustion analysis and spectroscopic data consistent with the assigned structure. Secondly, a better overall yielding route (Scheme 30) from 2-chloro-2-phenylhydrazonoacetonitrile (35), whose



(36) (111) (112)

(i) piperidine, EtOH, room temperature

(ii) MnO_2, MeCN, room temperature

Scheme 31

preparation has been discussed earlier (see Scheme 9), was investigated. The reaction of 2-chloro-2-phenylhydrazonoacetonitrile (35) with ammonia afforded the previously unknown 2-amino-2-phenylhydrazonoacetonitrile (110) in high yield. This compound has combustion analysis and spectroscopic data consistent with the assigned structure. In particular this acetonitrile derivative (110) has in its i.r. spectrum a cyano band at 2215 cm^{-1}. Its ^{1}H n.m.r. spectrum contains resonances for five aromatic hydrogen atoms and three exchangeable protons. Reaction of 2-amino-2-phenylhydrazonoacetonitrile (110) with hydroxylamine hydrochloride in the presence of sodium carbonate afforded a quantitative yield of 2-amino-2-phenylhydrazonoacetamidoxime (102) having melting point and i.r. spectrum identical to that discussed above.

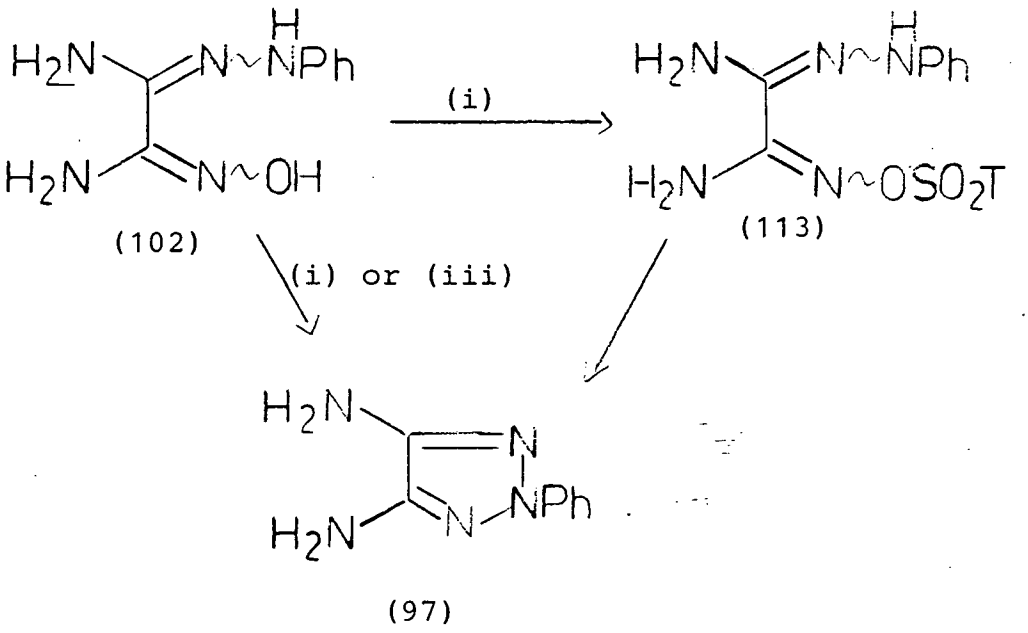
Disappointingly, treatment (Scheme 30) of the acetamidoxime (102) with manganese dioxide failed to give the expected 4,5-diamino-2-phenyl-2H-1,2,3-triazole 1-N-oxide (104). A series of multicomponent gums being isolated.

It is not clear why the oxidative cyclisation [(102)→(104)] was not successful but it is possible that it may be due to the 2-amino substituent being oxidatively sensitive. On the basis of this assumption it was decided to investigate (Scheme 31) the behaviour of an amino substitutent containing no oxidatively sensitive

hydrogen atoms. To this end, 2-phenylhydrazono-2-(piperidin-1-yl)acetamidoxime (111) was prepared by the reaction of 2-chloro-2-phenylhydrazonoacetamidoxime whose synthesis has been discussed earlier (see Scheme 9), with piperidine. The product (111) was obtained only in low yield but has combustion analysis and spectroscopic data consistent with the assigned structure. In particular the ^{1}H n.m.r. spectrum has resonances for five aromatic hydrogen atoms, ten hydrogen atoms of the piperidinyl group and four exchangable protons. The ^{13}C n.m.r. spectrum of the acetamidoxime (111) exhibits three signals for quaternary carbon atoms.

The treatment of the acetamidoxime derivative (111) with manganese dioxide perplexingly failed to yield the expected 2H-1,2,3-triazole N-oxide derivative (112), a multi-component gum being isolated. Hence it remains unclear why the oxidative cyclisation of 2-amino-2-phenylhydrazonoacetamidoxime (102) failed to give the desired triazole N-oxide (104).

The failure of this transformation [(102)→(104)] prompted the investigation of the cyclodehydration (Scheme 32) of 2-amino-2-phenylhydrazonoacetamidoxime (102) to 4,5-diamino-2-phenyl-2H-1,2,3-triazole (97). Since this transformation has been described by Thiele and Schlausner[119] as discussed earlier (see Scheme 27) it was decided to investigate new conditions for this transformation (Scheme 32). Firstly, the acetamidoxime



(i) TsCl, Et_3N, dioxane, room temperature

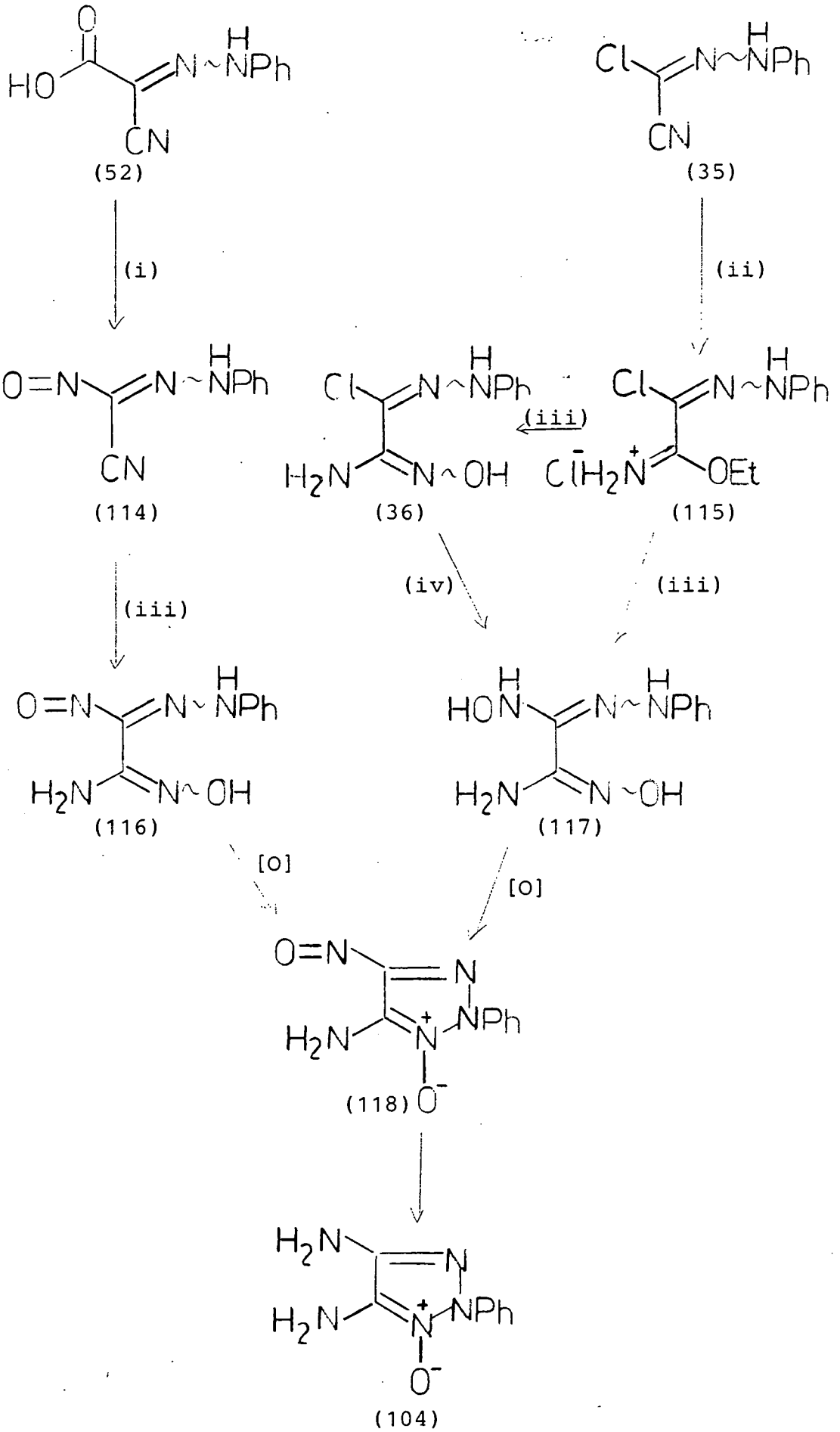
(ii) $SOCl_2$, dioxane, room temperature

(iii) TSO_3H, toluene, heat

Scheme 32

(102) was treated with thionyl chloride in an attempt to induce dehydrative cyclisation as is known to happen in similar systems.[123] However, this reaction afforded a dark multicomponent gum, none of the desired triazole derivative (97) being detected. Secondly, the acetamidoxime (102) was treated with toluene-4-sulphonic acid, conditions also known to cause cyclodehydration.[124] However, in this reaction a good yield of unreacted starting material was recovered. Finally it was anticipated that treatment of the acetamidoxime (102) with triethylamine and toluene-4-sulphonyl chloride (tosyl chloride)[125] would yield either the triazole derivative (97) directly or the tosylate derivative (113) which by further heating would afford the desired triazole derivative (97). However, reaction of 2-amino-2-phenylhydrazonoacetamidoxime (102) with triethylamine and tosyl chloride afforded a series of gums, none of the expected products being detected. It would appear that the method described by Thiele and Schleusner[119] (see Scheme 27) for the cyclodehydration of 2-amino-2-phenylhydrazonoacetamidoxime (102) remains the method of choice.

The failure to transform 2-amino-2-phenylhydrazono-acetamidoxime (102) to either the triazole N-oxide (104) by oxidation or the triazole (97) by cyclodehydration prompted the investigation of an alternative route to 4,5-diamino-2-phenyl-2H-1,2,3-triazole 1-N-oxide (104). It was



Scheme 33

(i) $NaNO_2$, AcOH, 0°

(ii) HCl, EtOH, 0°

(iii) $NH_2OH \cdot HCl$, Na_2CO_3, room temperature

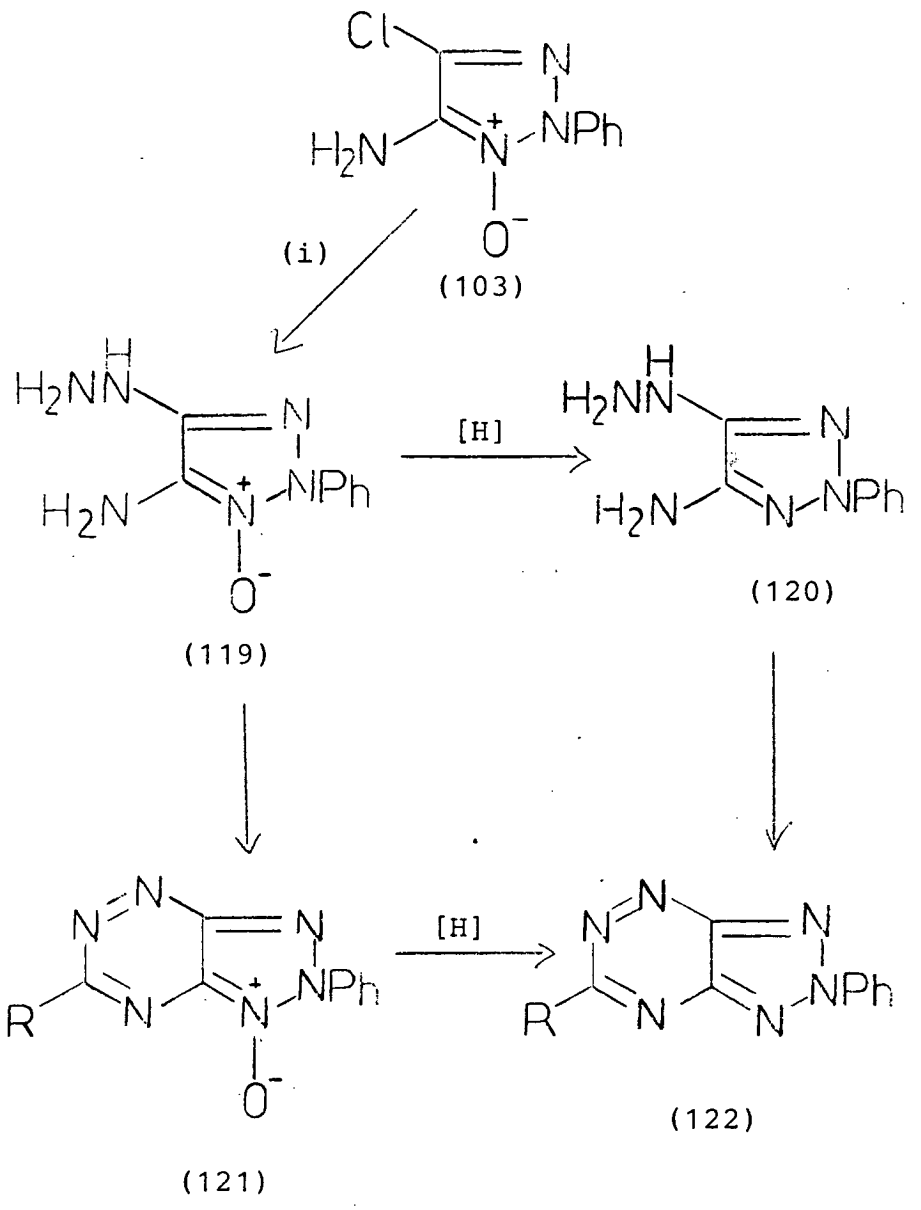
(iv) $NH_2OH \cdot HCl$, Na_2CO_3, reflux

therefore decided to seek a route (Scheme 33) to 5-amino-4-nitroso-2-phenyl-2H-1,2,3-triazole 1-N-oxide (118) which by reduction[126] might be expected to give the desired 4,5-diamino-2-phenyl-2H-1,2,3-triazole 1-N-oxide (104). In fact, three routes (Scheme 33) to the nitrosotriazole N-oxide (118) were investigated.

Firstly, treatment of (E)-2-cyano-2-phenylhydrazonoacetic acid (52), whose synthesis has been discussed earlier (see Scheme 16), with sodium nitrite in glacial acetic acid as described by Gewald and his co-workers[127] afforded a good yield of 2-nitroso-2-phenylhydrazonoacetonitrile (2-oximinino-2-phenylazoacetonitrile) (114). There is a discrepancy in the melting point of this product, in that it is reported[127] as 166-168°, whereas it has been found to be 156-157°. However it has combustion analysis and spectroscopic data consistent with the assigned structure. It was anticipated that treatment of this acetonitrile derivative (114) with hydroxylamine-hydrochloride in the presence of sodium carbonate would afford the acetamidoxime derivative (116) which by oxidation would give the desired nitrosotriazole N-oxide (118). However in practice reaction of 2-nitroso-2-phenylhydrazonoacetonitrile (114) with hydroxylamino-hydrochloride in the presence of sodium carbonate gave a moderate yield of starting material and a series of gums.

The failure of this transformation [(114)→(116)] prompted the investigation of a second route (Scheme 33) to the nitroso triazole N-oxide (118). It was expected that the acetamidoxime (117) would be oxidised to the desired triazole N-oxide (118) and that this acetamidoxime derivative (117) would be accessible from 2-chloro-2-phenylhydrazonoacetamidoxime (36), whose synthesis has been discussed earlier (see Scheme 9), by treatment with hydroxylamine. Reaction of 2-chloro-2-phenylhydrazono-acetamidoxime (36) with hydroxylamine hydrochlorile in the presence of sodium carbonate however gave a good recovery of unreacted starting material.

The failure of this reaction [(36)→(117)] prompted the investigation of another route (Scheme 33) to this acetamidoxime derivative (117) and hence by oxidation the nitroso-triazole N-oxide (118), i.e. the third route to this compound. 2-Chloro-2-phenylhydrazonoacetonitrile (35), whose preparation has been described earlier (see Scheme 9), was treated as a solution in ethanol with a slow stream of hydrogen chloride gas, standard conditions for the formation of imidates from nitriles,[128] to afford ethyl 2-chloro-2-phenylhydrazonoacetimidate hydrochloride (115) in high yield. This compound has accurate mass spectral data and other spectroscopic data consistent with the structure assigned. In particular, the ^{1}H n.m.r. spectrum has resonances for five aromatic protons and characteristic signals for the five hydrogen atoms of



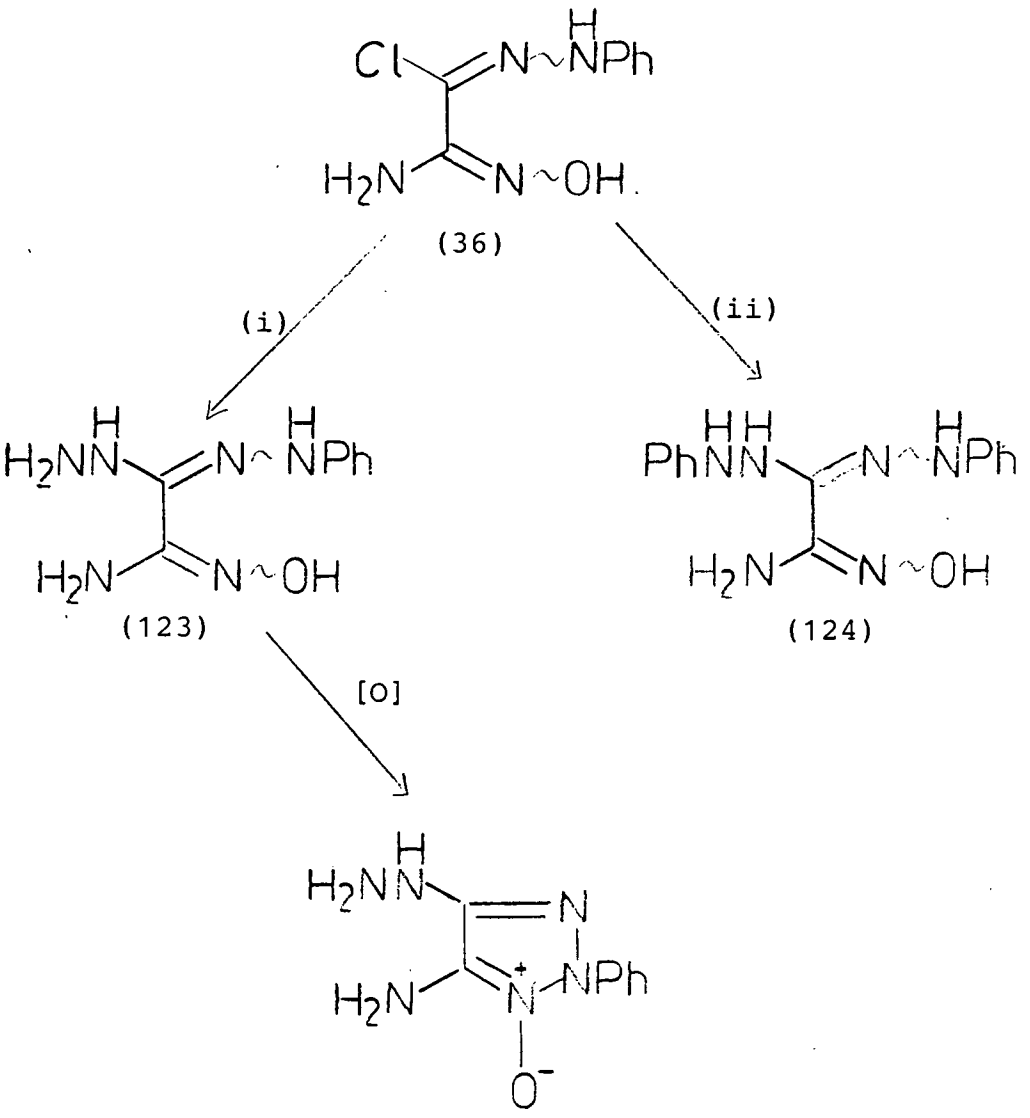
(i) $NH_2NH_2.H_2O$, EtOH, heat

Scheme 34

an ethyl group, as well as a single exchangeable proton. This imidate hydrochloride (115) was anticipated to yield the desired acetamidoxime derivative (117) on treatment with a large excess of hydroxylamine. However reaction of ethyl 2-chloro-2-phenylhydrazonoacetimidate hydrochloride (115) with a large excess of hydroxylamine hydrochloride in the presence of sodium carbonate gave a quantitative yield of 2-chloro-2-phenylhydrazono-acetamidoxime (36) having melting point and i.r. spectrum identical to a sample previously described.

2.4 General Synthetic Approaches to 2H-6,8-Diazapurine Derivatives from 4-Amino-2H-1,2,3-Triazole Derivatives

The 2H-6,8-diazapurine ring system is unknown and 4-amino-2H-1,2,3-triazole derivatives appear to offer a synthetic strategy toward the synthesis of derivatives of this unknown ring system. In particular (Scheme 34) 5-amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103) was anticipated on reaction with hydrazine monohydrate to afford 5-amino-4-hydrazino-2-phenyl-2H-1,2,3-triazole 1-N-oxide (119) and by subsequent reduction the parent triazole (120). These triazole derivatives (119) and (120) would be expected by standard cyclisations to afford the 2H-6,8-diazapurine derivatives (121) and (122). However, reaction of the chlorotriazole N-oxide (103) with hydrazine monohydrate gave a quantitative



(i) $NH_2NH_2.H_2O$, EtOH, heat

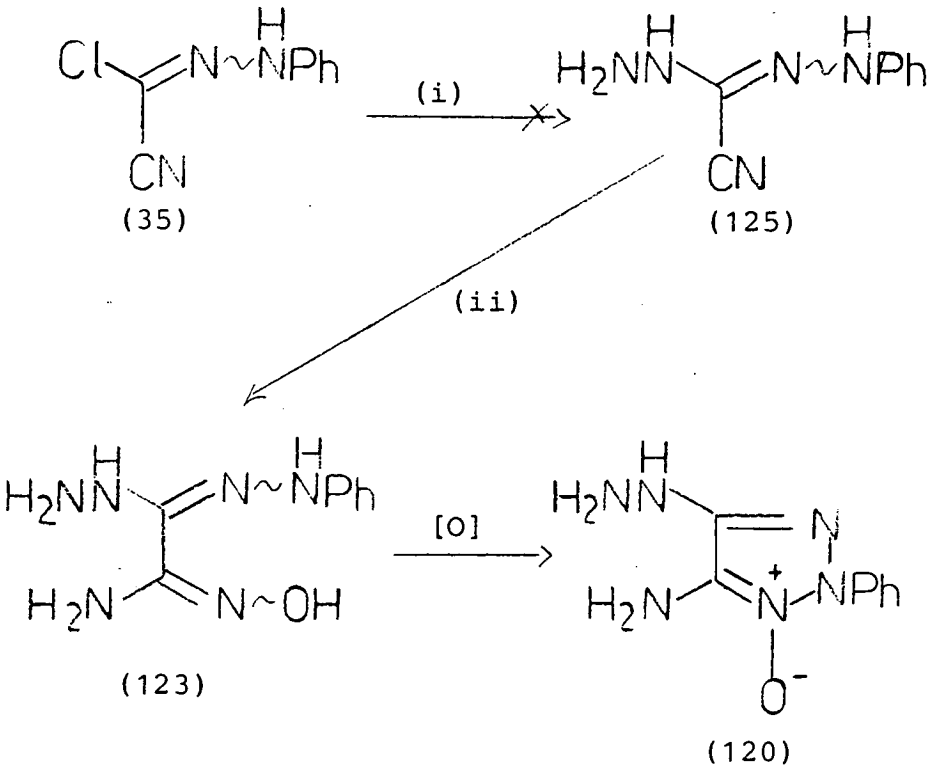
(ii) $PhNHNH_2$, EtOH, heat

Scheme 35

recovery of unreacted starting material. This result confirms the earlier observation concerning the inertness of the chloro group in this triazole derivative (103) to nucleophilic displacement.

The failure of this reaction [(103)→(119)] prompted the investigation (Scheme 35) of the reaction of 2-chloro-2-phenylhydrazonoacetamidoxime (36) with hydrazine monohydrate which would be expected to yield 2-hydrazino-2-phenylhydrazonoacetamidoxime (123) and thence by oxidation the desired 5-amino-4-hydrazino-2-phenyl-2H-1,2,3-triazole 1-N-oxide (120). However, treatment of the chlorophenylhydrazonoacetamidoxime (36) with hydrazine monohydrate gave a quantitative recovery of starting material. This is a surprising result since this acetamidoxime (36) reacts with other nucleophiles, such as ammonia, cyanide ion and piperidine, as described earlier. Therefore it was decided to react (Scheme 35) the acetamidoxime derivative (36) with phenylhydrazine to investigate if this derivative (36) will react with hydrazines. Again a quantitative yield of starting material was recovered on reaction of 2-chloro-2-phenylhydrazonoacetamidoxime (36) with phenylhydrazine. This result tends to indicate that the chloro substituent of the acetamidoxime (36) is inert to displacement by hydrazines.

The failure of hydrazines to displace the chloro group of the acetamidoxime (36) prompted the investigation (Scheme 36) of the displacement of the chloro group in



(i) $NH_2NH_2 \cdot H_2O$, EtOH, room temperature or heat

(ii) NH_2OH

Scheme 36

2-chloro-2-phenylhydrazonoacetonitrile (35), whose synthesis has been discussed earlier (see Scheme 9), by hydrazine monohydrate. It was anticipated that such a transformation would give the acetonitrile derivative (125) which by reaction with hydroxylamine hydrochloride in the presence of sodium carbonate would yield the acetamidoxime derivative (123) and thence by oxidation the triazole N-oxide (120), the key precursor in the strategy previously outlined (Scheme 34) to the unknown 2H-6,8-diazapurine ring system.

Disappointingly however, reaction of 2-chloro-2-phenylhydrazonoacetonitrile (35) with hydrazine monohydrate afford a series of gums. It remains unclear why this displacement reaction is complex whereas as discussed previously the chlorophenylhydrazonoacetonitrile (35) reacts smoothly with ammonia to yield 2-amino-2-phenylhydrazonoacetonitrile (110) (see Scheme 30).

In conclusion although no derivatives of 2H-aza- and 2H-diazapurines have been synthesised a variety of synthetic strategies in which 4-amino-2H-1,2,3-triazoles are the key precursor have been investigated. Particularly encouraging has been the success in synthesising a variety of phenylhydrazonoacetamidoxime derivatives which by oxidation have yielded the corresponding 5-amino-2H-1,2,3-triazole 1-N-oxide derivatives. It is hoped that future workers will continue to investigate these transformations and eventually produce a novel high yielding route to 2H-aza- and 2H-diazapurine derivatives from 4-amino-2H-1,2,3-triazole derivatives.

2.5 EXPERIMENTAL

2-Cyano-2-phenylhydrazonoacetamide (31)

A solution of redistilled aniline (20.0 g, 0.2 mol) in aqueous 5M hydrochloric acid (102 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (16.4 g, 0.22 mol) in water (20.0 ml). The resulting amber benzenediazonium chloride solution was stirred for a further 5 min. in the ice-bath, then added dropwise at 0-5° (ice-salt bath) to a stirred solution of cyanoacetamide (16.8 g, 0.2 mol) and anhydrous sodium acetate (42.0 g, 0.5 mol) in ethanol (400 ml) and water (50.0 ml), and the mixture was stirred for a further 1h. at room temperature. Filtration afforded 2-cyano-2-phenylhydrazonoacetamide (31) as an orange solid (37.0 g; quant.), m.p. 242-245°, (lit.,[83] 245°), ν_{max} 3480, 3360, 3200, 3180, 3120, and 3060 (NH), 2205 (CN), and 1650 (CO) cm^{-1}, which was used without further purification.

2-Phenylhydrazonooxamidoxime (32)

A solution of 2-phenylhydrazonocyanoacetamide (31) (1.9 g, 0.01 mol) in anhydrous ethanol (200 ml) was treated with stirring at room temperature with a solutionof hydroxylamine hydrochloride (1.8 g, 0.025 mol) in anhydrous ethanol (20.0 ml) followed by solid sodium carbonate (1.3 g, 0.013 mol) and the mixture was stirred at room temperature for 48 h. Evaporation of the mixture and treatment of the residual cake with water afforded 2-phenylhydrazonooxamidoxime (32) an an orange solid (2.2g; quant.) which

formed orange crystals, m.p. 150-151° (from ethylacetate), ν_{max} 3450, 3430, 3320, and 3140 (NH, OH) and 1640 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 10.18 (1H, S, NH or OH), 10.00 (1H, S, OH or NH), 7.89-6.94 (5H, m, ArH), 6.74 (2H, brs, NH_2), and 5.65 (2H, brs, NH_2), δ_C [$(CD_3)_2SO$] 168.02 (quat), 151.85 (quat), 142.78 (quat), 129.1, 122.48, 122.13, 119.92 (quat), 114.42 and 114.06.

Found: 221.0841.

$C_9H_{11}N_5O_2$ requires: 221.0913.

The Attempted Oxidation of 2-Phyenylhydrazonooxamidoxime (32) with Activated Manganese Dioxide

A solution of 2-phenylhydrazonooxamidoxime (32) (0.88 g, 0.004 mol) in anhydrous acetonitrile (50.0 ml) was treated with activated manganese dioxide (6.0 g) and the mixture was stirred at room temperature for 1h. The mixture was filtered and the residual manganese dioxide was subjected to soxhlet extraction with ethyl acetate to yield an unidentified solid (0.10 g) m.p. 215-216° (from ethanol-light petroleum), ν_{max} 3450, 3360, 3270 and 3160 (NH) and 1675 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 11.72 (brs, NH), 9.21 (brs, NH), 7.96-7.02 (m, ArH), and 5.84 (brs, NH), δ_C [$(CD_3)_2SO$] 162.21 (quat), 142.19 (quat), 134.79 (quat), 134.50 (quat), 129.21, 129.01, 125.86 (quat, 123.82 (quat), 123.45 (quat), 122.67, 115.85 and 115.09.

Found: C, 52.6; H, 4.5; N, 28.9%; M^+ 207,205

Further soxhlet extraction of the manganese dioxide residue with dimethylformamide gave a brown gum (0.40 g) which on flash chromatography in methylene chloride through ethylacetate to ethanol yielded a series of intractable gums (total, 0.28 g), none of which were further investigated.

Evaporation of the original acetonitrile mother liquor afforded only a small quantity (0.03 g) of brown gum which was not further investigated.

Sodio Formylchloroacetonitrile (34)[85]

A solution of sodium (23.0 g, 1.0 g atom) in anhydrous ethanol (100 ml) was evaporated by azeotroping with toluene to afford sodium ethoxide which was suspended in anhydrous diethyl ether (300 mls) and treated at 5-8° (ice bath) with redistilled anhydrous ethyl formate (74.0 g, 1.0 mol) in one portion followed dropwise by freshly distilled chloroacetonitrile (85.2 g, 1.1 mol) over a period of 1 h. The mixture was stirred at room temperature for a further 6 h and filtered to afford sodio formyl-chloroacetonitrile (34) as a colourless solid (125 g; quant.) m.p. > 350°, ν_{max} 2180 (CN) and 1590 (C=N) cm^{-1} which was used without further purification.

2-Chloro-2-phenylhydrazonoacetonitrile (35)[85]

A solution of redistilled aniline (14.0 g, 0.14 mol) in aqueous 5M hydrochloric acid (70.0 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a

solution of sodium nitrite (11.5 g, 0.15 mol) in water (35.0 ml). The resulting amber benzenediazonium chloride solution was stirred for a further 5 min. in the ice-salt bath, then added dropwise at 0-5° (ice-salt bath) to a stirred solution of sodio formylchloroacetonitrile (34) (17.6 g, 0.14 mol) and anhydrous sodium acetate (20.5 g, 0.25 mol) in water (100 ml). The mixture was stirred for a further 1 h. at room temperature then filtered to afford 2-chloro-2-phenylhydrazonoacetonitrile (35) (16.6 g; 66%) which formed orange needles, m.p. 130-132° (from ethanol-water) (lit.,[85] 132-134°), ν_{max} 3240 (NH) and 2210 (CN) cm^{-1}.

2-Chloro-2-phenylhydrazonoacetamidoxime (36)

A solution of 2-chloro-2-phenylhydrazonoacetonitrile (35) (7.2 g, 0.04 mol) in anhydrous ethanol (100 ml) was treated with stirring at room temperature with a solution of hydroxylamine hydrochloride (7.0 g, 0.1 mol) in anhydrous ethanol (100 ml) followed by sodium carbonate (5.3 g; 0.05 mol) and the mixture was stirred at room temperature for 48 h. Evaporation of the mixture and treatment of the residual cake with water yielded 2-chloro-2-phenylhydrazonoacetamidoxime (36) (8.5 g; quant.) which formed salmon pink prisms, m.p. 185-186° (from ethanol), $_{max}$ 3450 and 3340 (NH) and 3330-2500 (OH) cm^{-1}, δ_H [$(CD_3)_2SO$] 10.23 (1H, s, NH or OH), 9.84 (1H, s, OH or NH), 7.43-6.83 (5H, m, ArH) and 5.65 (2H, brs, NH), δ_C [$(CD_3)_2SO$] 146.98 (quat), 143.67 (quat), 128.83, 120.62, 117.05 (quat) and 113.78.

Found: C, 45.1; H, 4.2; N, 26.4%; M^+, 215, 214, 212

$C_8H_9ClN_4O$ requires: C, 45.2; H, 4.2; N, 26.4%; M, 212.5

3,5-Diamino-4-phenylhydrozonoisoxazole (38)

A solution of 2-chloro-2-phenylhydrazonoacetamidoxime (36) (3.2 g, 0.016 mol) in anhydrous ethanol (160 ml) was treated with a solution of sodium cyanide (0.86 g, 0.018 mol) in anhydrous ethanol (40.0 ml) and the mixture was stirred at room temperature for 2h. The mixture was evaporated and the residue was treated with water to afford 3,5-diamino-4-phenylhydrazonoisoxazole (38) (2.7 g; 82%), which formed irregular brown prisms, m.p. 136-137° (from toluene), ν_{max} 3420 and 3360 (NH), and 1640 (C=N) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.24 (2H, brs, NH), 7.79-7.24 (5H, m, ArH) and 6.16 (2H, brs, NH), δ_C [$(CD_3)_2SO$] 158.37 (quat), 152.91 (quat), 128.81, 127.81, 120.88 and 107.95 (quat).

Found: C, 53.1; H, 4.5; N, 34.3%; M^+, 203.

$C_9H_9N_5O$ requires: C, 53.2; H, 4.4; N, 34.5%; M, 203.

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid followed by extraction with methylene chloride yielded no further material.

The Reaction of 3,5-diamino-4-phenylhydrazonoisoxazole (38) with Activated Manganese Dioxide

A solution of 3,5-diamino-4-phenylhydrazonoisoxazole (38) (2.0 g, 0.01 mol) in anhydrous acetonitrile (150 ml) was treated with activated manganese dioxide (20 g) and the mixture was stirred at room temperature for 1h. The mixture was filtered through celite and the filtrate was evaporated to afford a dark gum (1.6 g) which was subjected to flash chromatography.

Elution with methylene chloride gave an orange gum (0.05 g) which was not further investigated followed by 2-phenylhydrazonomalononitrile (40),[88] (0.05 g, 3.0%) m.p. 139-141° (from toluene), (lit.,[88] 146-147°), ν_{max} 3230, 3200, 3160 and 3065 (NH) and 2210 (CN) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.99 (1H, brs, NH), and 7.50-7.17 (5H, m, ArH), δ_C [$(CD_3)_2SO$] 141.43 (quat), 129.45, 125.82 (quat), 116.49, 109.85 (quat), 84.45 (quat).

Found: 170.0579.

Calc. for $C_9H_6N_4$: 170.0592.

Elution with ethyl acetate afforded a series of dark gums (total, 0.21 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed them to be multicomponent mixtures which were not further investigated.

Further elution with ethyl acetate yielded unreacted starting material (38) (0.50 g; 25%) m.p. 133-136°, identical (m.p. and i.r. spectrum) to an authentic sample.

Final elution with ethanol gave a dark intractable gum (0.70 g) which was not further investigated.

(E) and (Z)-Ethyl 2-Cyano-2-phenylhydrazonoacetate (42) and (43)[91]

A solution of redistilled aniline (20.0 g, 0.2 mol) in aqueous 5M hydrochloric acid (102 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (16.4 g, 0.22 mol) in water (20.0 ml). The resulting amber benzenediazonium chloride solution was stirred for a further 5 min. in the ice-salt bath, then added dropwise at 0-5° (ice-salt bath) to a stirred solution of ethyl cyanoacetate (22.6 g, 0.2 mol) and anhydrous sodium acetate (42.0 g, 0.5 mol) in ethanol (150 ml) and water (50.0 ml). The mixture was stirred at room temperature for a further 1 h. then filtered to afford a yellow solid (43.0 g) which was crystallised from toluene-light petroleum to give (E)-ethyl 2-cyano-2-phenyl-hydrazonoacetate (42) (30.0 g; 70%) which formed yellow needles, m.p. 106-107° (from toluene), (lit.,[91] 125°), ν_{max} 3210, 3140 and 3060 (NH), 2205 (CN) and 1740 (CO) cm^{-1}, δ_H ($CDCl_3$) 9.90 (1H, brs, NH), 7.38-7.05 (5H, m, ArH), 4.36 (2H, q, J 7Hz, CH_2) and 1.36 (3H, t, J 7Hz, CH_3).

Found: C, 60.8; H, 5.0; N, 19.4%; M^+, 217

Calc. for $C_{11}H_{11}N_3O_2$: C, 60.8; H, 5.1; N, 19.4%; M, 217.

Evaporation of the toluene-light petroleum mother liquor gave an orange solid (10.0 g) which was subjected to flash chromatography.

Elution with methylene chloride yielded (Z)-ethyl 2-cyano-2-phenylhydrazonoacetate (43) (8.5 g; 20%) which formed orange crystals, m.p. 83-85° (from light petroleum (b.p. 80-100°)), (lit.,[91] 86°), ν_{max} 3160 (NH), 2210 (CN) and 1680 (CO) cm^{-1}, δ_H ($CDCl_3$), 13.05 (1H, brs, NH), 7.38-7.12 (5H, m, ArH), 4.32 (2H, q, J7Hz, CH_2) and 1.48-1.23 (3H, m, CH_3)

Found: C, 60.9; H, 5.0; N, 19.3%; M^+ 217.

Calc. for $C_{11}H_{11}N_3O_2$: C, 60.8; H, 5.1; N, 19.4%; M 217.

Further elution with methylene chloride afforded a yellow solid (1.4 g) whose t.l.c. in methylene chloride showed it to be a mixture of (E)- and (Z)-ethyl 2-cyano-2-phenylhydrazonoacetate (42) and (43).

5-Amino-4-phenylazo-Δ^4-isoxazolin-3-one (47)

(a) A solution of (E)-ethyl 2-cyano-2-phenylhydrazonoacetate (42) (21.7 g, 0.1 mol) in anhydrous ethanol (400 ml) was treated with stirring with a solution of hydroxylamine hydrochloride (17.5 g, 0.25 mol) in anhydrous ethanol (100 ml) followed by solid sodium carbonate (13.0 g, 0.125 mol) and the mixture was stirred at room temperature for 48 h. The mixture was evaporated and the residue was treated with water and extracted with methylene chloride to give a three-phase system. This was filtered and the orange solid obtained was combined with material obtained by evaporating the methylene chloride extract followed by flash chromatography in ethyl acetate of the resulting orange gum to yield

5-amino-4-phenylazo-Δ^4-isoxazolin-3-one (47), (total, 20.3 g, 99%) which formed orange prisms, m.p. 210-212° (from dimethylformamide-toluene), ν_{max} 3405, and 3200 (NH) and 1700 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.73-7.14 (5H, m, ArH) and 6.44 (2H, brs, NH) δ_C [$(CD_3)_2SO$] 162.48 (quat), 158.92 (quat), 141.62 (quat), 129.18, 125.33, 116.28 and 116.06 (quat).

Found: C, 52.8; H, 3.9; N, 27.4%; M^+, 204.

$C_9H_8N_4O_2$ requires: C, 52.9; H, 3.9; N, 27.5%; M, 204.

(b) A solution of (Z)-ethyl 2-phenylhydrazono-cyanoacetate (43) (0.87 g, 0.004 mol) in anhydrous ethanol (50.0 ml) was treated with stirring with a solution of hydroxylamine hydrochloride (0.7 g, 0.01 mol) in anhydrous ethanol (20.0 ml) followed by solid sodium carbonate (0.53 g; 0.005 mol) and the mixture was stirred at room temperature for 48 h. The mixture was evaporated and the residue was treated with water and extracted with methylene chloride to yield a yellow gum (1.0 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethylacetate (1:1) gave 5-amino-4-phenylazo-Δ^4-isoxazolin-3-one (47), (0.7 g; 85%) m.p. 208-210° identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Final elution with ethanol gave a small amount of a yellow gum (0.05 g) which was not further investigated.

(c) A suspension of a mixture of (E)- and (Z)-ethyl 2-phenylhydrazonocyanoacetate (42) and (43) (0.87 g, 0.004 mol) in anhydrous ethanol (20.0 ml) was treated with a solution of hydroxylamine hydrochloride (0.28 g, 0.004 mol) in water (2.0 ml) followed by solid anhydrous sodium acetate (0.41 g, 0.005 mol) and the mixture was stirred and heated under reflux for 3 h. The mixture was diluted with water and the precipitated orange solid (0.8 g) was subjected to flash chromatography.

Elution with methylene chloride-n-hexane (1:1) gave a yellow gum (0.05 g) which was not further investigated.

Elution with methylene chloride yielded 5-amino-4-phenylazo-Δ^4-isoxazolin-3-one (47), (0.61 g; 74%), m.p. 208-210°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Final elution with ethanol yielded no further material.

Extraction of the original aqueous ethanolic mother liquor with methylene chloride gave a small amount of a yellow gum (0.03 g) which was not further investigated.

(d) A solution of redistilled aniline (7.0 g, 0.075 mol) in aqueous 5M hydrochloric acid (38.0 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (5.7 g, 0.038 mol) in water (5.0 ml). The resulting amber benzenediazonium chloride solution was stirred for a further 5 min. in the ice-salt bath, then added dropwise at 0-5° (ice-salt bath) to a

stirred solution of 2-ethoxycarbonylacetamidoxime (49) (11.0 g, 0.075 mol) and anhydrous sodium acetate (15.6 g, 0.19 mol) in ethanol (50.0 ml) and water (30.0 ml) and the mixture was then stirred at room temperature for a further 1 h. The resulting suspension was concentrated to remove the ethanol and extracted with methylene chloride to afford a red gum (16.0 g) which was subjected to flash chromatography.

Elution with n-hexane followed by methylene chloride gave orange gums (total, 2.1 g) whose t.l.c. in methylene chloride or ethyl acetate over silica showed them to be multicomponent mixtures which were not further investigated.

Elution with ethyl acetate afforded 5-amino-4-phenylazo-Δ^4-isoxazolin-3-one (47) (12.2 g; 78%), m.p. 210-213°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Final elution with ethanol gave a dark intractable gum (2.0 g) which was not further investigated.

The Attempted Preparation of 3-Amino-4-phenylazo-Δ^3-isoxazolin-5-one (48)

A solution of hydroxylamine hydrochloride (0.28 g, 0.004 mol) in water (8.0 ml) was treated with sodium carbonate (0.21 g, 0.002 mol) and the resulting hydroxylamine solution was mixed with a solution of (E)- and (Z)-ethyl 2-cyano-2-phenylhydrazonoacetate (42) and (43) (0.87 g,

0.004 mol) in ethanol (40.0 ml) and the mixture heated under reflux for 4 h. The cooled mixture was diluted with water (50.0 ml), acidified with glacial acetic acid and left at room temperature overnight. Filtration afforded an orange solid (0.14 g) which was crystallised from dimethylformamide-glacial acetic acid to yield an unidentified solid, as orange crystals, m.p. 250-251°, ν_{max} 3460, and 3210 (NH) and 1695 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.76 (2H, brs, NH), 8.18 (1H, brs, NH) and 7.54-7.03 (5H, m, ArH), δ_C [$(CD_3)_2SO$] 165.78 (quat), 161.62 (quat), 142.16 (quat), 129.25, 123.48 (quat) and 115.21.

Found: C, 52.3; H, 4.9; N, 26.5%; M^+, no ion pressure.

The aqueous mother liquor was constantly extracted with methylene chloride to yield a brown gum whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Attempted Preparation of 5-Amino-Δ^4-isoxazolin-3-one (47)[94]

A solution of sodium (1.3 g, 0.055 g atom) in anhydrous ethanol (10.0 ml) was mixed with a solution of hydroxylamine hydrochloride (3.9 g, 0.055 mol) in anhydrous ethanol (100 ml) and the resulting hydroxylamine solution was cooled to 5-8° (ice bath) and treated with ethyl cyanoacetate (5.7 g, 0.05 mol). The mixture was then treated with a solution of sodium (1.2 g, 0.05 g atom) in anhydrous ethanol (30.0 ml) and left stoppered at room temperature for 18 h. The

mixture was evaporated to afford a red gummy residue which was washed with diethylether and light petroleum (b.p. 40-60°) then dissolved in ice water (50.0 ml) and the solution obtained neutralised with 25% w/v aqueous hydrochloric acid. Extraction with methylene chloride gave a red oil (0.25 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

2-Ethoxycarbonylacetamidoxime (49)[96,100]

(a) 2-Ethoxycarbonylacetamidoxime (49), m.p. 58-60°, was prepared (yield 75%) together with 2-(N-hydroxycarbamoyl)acetamidoxime, m.p. 155-158° (yield 11%) by reaction of ethyl cyanoacetate with hydroxylamine hydrochloride in ethanol in the presence of sodium carbonate as described by England and Tennant.[100]

(b) A solution of sodium (2.3 g, 0.1 g.atom) in anhydrous ethanol (20.0 ml) was mixed with a solution of hydroxylamine hydrochloride (7.7 g, 0. mol) in anhydrous ethanol (100 ml). The resulting ethanolic solution of hydroxylamine was treated with ethyl cyanoacetate (11.3 g, 0.1 mol) and heated at 75° for 2 h. Evaporation gave a red oil which was washed with light petroleum (b.p. 40-60°) (5 x 50.0 ml) and extracted with anhydrous diethyl ether (5 x 100 ml) to leave 2-(N-hydroxycarbamoyl)-acetamidoxime as an insoluble residue (1.2 g) m.p. 150-

155°, identical (m.p. and i.r. spectrum) to a sample obtained in (a) before. The combined ethereal extracts were evaporated to yield an orange gum (7.5 g) which was subjected to flash chromatography.

Elution with ethyl acetate-methylene chloride (1:1) yielded 2-ethoxycarbonylacetamidoxime (49) as a yellow liquid (5.8 g, 79%) identical (i.r. spectrum) to an authentic sample prepared in (a) before.

Final elution with ethanol gave an orange gum (1.2 g) which was not further investigated.

The Attempted Base-catalysed Cyclisation of 2-Ethoxycarbonylacetamidoxime (49) to 3-Amino-Δ^3-isoxazolin-5-one (51)[96]

(a) A solution of 2-ethoxycarbonylacetamidoxime (49) (1.5 g, 0.01 mol) in methanol (10.0 ml) was treated with a solution of sodium hydroxide (0.4 g) in water (0.5 ml) and the mixture was heated under reflux for 2½ min. The mixture was evaporated, the residue was treated with water (2.0 ml) and the solution was neutralised by the dropwise addition of concentrated hydrochloric acid. Extraction with methylene chloride gave a dark oil (1.1 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

(b) A solution of 2-ethoxycarbonylacetamidoxime (49) (0.58 g, 0.004 mol) in anhydrous ethanol (10.0 ml) was treated with solid sodium carbonate (0.21 g, 0.002 mol) and the mixture was stirred at room temperature for 24 h. The mixture was evaporated and the residue was treated with water and extracted with methylene chloride to afford the unreacted amidoxime (49) (0.55 g; 96%) m.p. 60-62°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(E)-2-Cyano-2-phenylhydrazonoacetic acid (52)[91]

(E)-2-Cyano-2-phenylhydrazonoacetic acid (52) was prepared (yield 94%) by the aqueous sodium hydroxide-catalysed hydrolysis of (E)/(Z) mixture of ethyl 2-cyano-2-phenylhydrazonoacetate (42) and (43) as described by Brecknell, Carman, Deeth and Kibby,[91] and had m.p. 151-152° (lit.,[91] 152°), ν_{max} 3300-2500 (OH), 2200 (CN), and 1675 (CO) cm^{-1}.

2-Phenylhydrazonomalonamidoxime (53)

A solution of 2-cyano-2-phenylhydrazonoacetic acid (52) (0.76 g, 0.004 mol) in anhydrous ethanol (20.0 ml) was treated at room temperature with stirring with a solution of hydroxylamine hydrochloride (0.7 g, 0.01 mol) in anhydrous ethanol (20.0 ml) followed by solid sodium carbonate (0.53 g, 0.005 mol) and the mixture was stirred at room temperature for 24 h. The mixture was evaporated and the residue was treated with water and

filtered to afford 2-phenylhydrazonomalonamidoxime (53) (0.63 g; 71%) which formed yellow prisms, m.p. 189-190 (from dimethylformamide), ν_{max} 3350, 3290 and 3110 (NH, OH) and 1680 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 14.90 (1H, brs, NH or OH), 12.50 (1H, brs, OH or NH), 8.30 (2H, brs, NH), 7.55-7.03 (5H, m, ArH) and 3.50 (1H, brs, NH or OH).

Found: C, 48.8; H, 4.6; N, 25.4%; M^+, 222

$C_9H_{10}N_4O_3$ requires: C, 48.7; H, 4.5; N, 25.2%; M, 222.

Extraction of the neutral aqueous mother liquor with methylene chloride afforded no further material.

5-Amino-2-phenyl-2H-1,2,3-triazole-4-carboxylic acid 1-N-oxide (54)

A solution of 2-phenylhydrazonomalonamidoxime (53) (0.33 g, 0.0015 mol) in anhydrous dimethylformamide (20.0 ml) was treated with activated manganese dioxide (2.5 g) and the mixture was stirred at room temperature for 1 h. The suspension was then filtered through celite and the filtrate was evaporated to give a brown solid (0.30 g) which was subjected to flash chromatography.

Elution with methylene chloride through to ethyl acetate gave a series of gums (total, 0.06 g) none of which were further investigated.

Elution with ethanol gave a brown gum (0.20 g) which was triturated with methylene chloride to yield 5-amino-2-phenyl-2H-1,2,3-triazole-4-carboxylic acid 1-N-oxide (54) (0.10 g; 30%), m.p. 216-217° (from glacial acetic acid), ν_{max} 3540, 3420 and 3310 (NH), 3100-2500 (OH), and 2000 - 1600 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 7.49 - 7.05 (5H, m, ArH) and 5.48 (<2H, brs, NH).

Found: 220.0591.

$C_9H_8N_4O_3$ requires: 220.0596.

Evaporation of the methylene chloride filtrate gave a dark intractable gum (0.08 g) which was not further investigated.

The Attempted Esterification of 2-Phenylhydrazono-malonamidoxime (53)

A suspension of 2-phenylhydrazonomalonamidoxime (53) (0.44 g, 0.002 ml) in anhydrous ethanol (10.0 ml) was treated with concentrated sulphuric acid (0.4 ml) and the mixture was heated under reflux for 6 h. The mixture was concentrated under reduced pressure to remove the ethanol and the residue was cooled (ice bath) and treated with water (5.0 ml), then extracted with methylene chloride to afford a small amount of a brown solid (0.02 g) which was not further investigated.

The aqueous mother liquor was neutralised with aqueous 2M sodium hydroxide solution and filtered to yield 2-phenylhydrazonoacetamidoxime (55) (0.28g; 80%) m.p. 173-174° (from ethylacetate - light petroleum), ν_{max} 3430, 3340 and 3230 (NH, OH) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 10.31 (1H, brs, NH or OH), 9.76 (1H, brs, OH or NH), 7.31-6.66 (6H, m, ArH and CH) and 5.38 (2H, brs, NH), δ_C $[(CD_3)_2SO]$ 150.11 (quat), 144.96 (quat), 130.13, 129.02, 119.12 and 112.23.

Found. 178.0821.

$C_8H_{10}N_4O$ requires: 178.0854.

Constant methylene chloride extraction of the aqueous filtrate gave no further material.

Benzoylacetonitrile (63)[105]

Benzoylacetonitrile (63) was prepared (yield quant.) by the reaction of 2-bromoacetophenone with aqueous ethanolic potassium cyanide as described by Obregiu[105] and had m.p. 77-80° (lit.,[105] 80-81°).

2-Benzoyl-2-phenylhydrazonoacetonitrile (64)[104]

A solution of redistilled aniline (16.0 g, 0.16 mol) in aqueous 5M hydrochloric acid (80.0 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (13.6 g, 0.176 mol) in water (40.0 ml). The resulting amber benzenediazonium chloride solution was stirred for a further 5 min. in the ice-salt bath, then added dropwise at 0-5° (ice-salt bath) to a stirred solution of benzoylacetonitrile (63) (23.2 g, 0.24 mol) in ethanol (200 ml) and water (100 ml). The mixture was stirred at room temperature for a further 1 h then filtered to afford 2-benzoyl-2-phenylhydrazonoacetonitride (64) (38.5 g; 95%) which formed yellow needles, m.p. 135-137° (from toluene) (lit.,[104] 135°) ν_{max} 3100 (NH), 2210 (CN) and 1650 (CO) cm^{-1}, $[(CD_3)_2SO]$ 9.39 (1H, brs, NH) and 8.07-7.17 (10H, m, ArH).

Found: 249.0882.

Calc. for $C_{15}H_{11}N_3O$: 249.0902.

2-Benzoyl-2-phenylhydrazonoacetamidoxime (65)[92]

A solution of 2-benzoyl-2-phenylhydrazonoacetonitrile (64) (12.5 g, 0.05 mol) in anhydrous ethanol (120 ml) was treated with stirring at room temperature with a solution of hydroxylamine hydrochloride (8.8 g, 0.13 mol) in anhydrous ethanol (60.0 ml) followed by solid sodium carbonate (6.6 g, 0.063 mol) and the mixture was stirred at room temperature for 48 h. Evaporation of the mixture and treatment of the residual cake with water afforded 2-benzoyl-2-phenylhydrazonoacetamidoxime (65) as a yellow solid (14.1 g; quant.) which formed yellow needles, m.p. 155-156° (from toluene), (lit.,[92] 156°), ν_{max} 3470, 3370 and 3100-2600 (NH, OH) and 1630 (CO) cm^{-1}, δ_H ($CDCl_3$) 13.46 (1H, brs, NH or OH), 7.81-7.02 (10H, m, ArH), 6.51 (2H, brs, NH) and 6.49 (1H, brs, OH or NH), δ_C [$(CD_3)_2SO$] 193.07 (quat), 151.23 (quat), 142.47 (quat), 139.35 (quat), 131.24, 129.86, 129.54, 128.79, 127.51, 126.30 (quat), 123.59, 114.86 and 113.41.

Found: C, 64.0; H, 5.1; N, 19.9%; M^+, 282.

Calc. for $C_{15}H_{14}N_2O_2$: C, 63.8; H, 5.0; N, 19.9%; M, 282.

The Reaction of 2-Benzoyl-2-phenylhydrazonoacetamidoxime (65) with acetic anhydride

A solution of 2-benzoyl-2-phenylhydrazonoacetamidoxime (65) (0.56 g, 0.002 mol) in acetic anhydride (10.0 ml) was heated under reflux for 1 h. The mixture was evaporated to afford a brown gum (0.60 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethyl acetate (10:1) afforded 3-phenyl-4-phenylhydrazono-Δ^2-isoxazolin-5-one (72)[107] (0.06 g, 12%) which formed yellow prisms, m.p. 168-169° (from glacial acetic acid), (lit.,[107] 168°), ν_{max} 3180 (NH) and 1720 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.98 (1H, brs, NH) 8.03-7.26 (10H, m, ArH), δ_C [$(CD_3)_2SO$] 163.04 (quat), 158.43 (quat), 141.15 (quat), 131.05 , 129.47, 128.81, 127.34, 126.84 (quat), 126.37, 118.95 (quat) and 116.92.

Found: C, 67.7; H, 4.2; N, 15.9%; M^+, 265.

Calc. for $C_{15}H_{11}N_3O_2$: C, 67.9; H, 4.0; N, 15.8%; M, 265.

Elution with cyclohexane-ethylacetate (5:1) through to ethanol gave a series of gums (total, 0.49 g) none of which were further investigated.

O-acetyl-2-benzoyl-2-phenylhydrazonoacetamidoxime (73)

A solution of 2-benzoyl-2-phenylhydrazonoacetamidoxime (65) (0.28 g, 0.001 mol) in anhydrous dioxane (20.0 ml) was treated with stirring at room temperature with triethylamine (0.11 g, 0.0011 mol) then dropwise with a solution of acetyl chloride (0.09 g, 0.0011 mol) in anhydrous dioxane (1.0 ml). The mixture was stirred at room temperature for 1h and filtered to remove precipitated triethylamine hydrochloride (0.16 g), the filtrate was then evaporated to yield O-acetyl-2-benzoyl-2-phenylhydrazonoacetamidoxime (73) (0.33 g; quant.) m.p. 131-132° (from toluene), ν_{max} 3450 and 3310 (NH) and 1750 (CO) cm^{-1}, δ_H ($CDCl_3$) 14.20 (1H, brs, NH), 7.84-7.03 (12H, m, ArH and NH) and 2.23 (3H, s, CH_3), δ_C ($CDCl_3$) 166.72 (quat), 154.35 (quat), 142.25 (quat), 139.44 (quat), 131.06, 130.13, 129.26, 127.29 (quat), 127.32, 124.52, 122.53 (quat), 115.94 and 19.12 (CH_3).

Found: C, 62.8; H, 4.9; N, 17.3%; M^+, 324.
$C_{17}H_{16}N_4O_3$ requires: C, 63.0; H, 4.9; N, 17.3%; M^+, 324.

5-Amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66)

A solution of 2-benzoyl-2-phenylhydrazonoacetamidoxime (65) (2.8 g, 0.01 mol) in anhydrous acetonitrile (75.0 ml) was treated with activated manganese dioxide (15.0 g) and the mixture was stirred at room temperature for 1 h. The mixture was filtered through celite and the filtrate was

was evaporated to afford a yellow solid which was combined with further material obtained by soxhlet extraction of the manganese dioxide residue with ethyl acetate to yield 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66), (total 2.3 g; 80%) which formed yellow prisms, m.p. 168-170° (from ethanol), ν_{max} 3450 and 3260 (NH and 1650 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.26 - 7.51 (10H, m, ArH) and 6.36 (2H, hrs, NH), δ_C [$(CD_3)_2SO$] 185.63 (quat), 135.94 (quat), 135.82 (quat), 134.36 (quat), 131.10, 129.65, 129.38, 129.06, 128.35 and 123.07.

Found: C, 64.7; H, 4.3; N, 20.3%; M^+, 280.

$C_{15}H_{12}N_4O_2$ requires: C, 64.3; H, 4.3; N, 20.0%; M, 280.

4-Amino-5-benzoyl-2-phenyl-2H-1,2,3-triazole (67)

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) (0.28 g, 0.001 mol) in 70% v/v aqueous ethanol (10.0 ml) was treated with sodium dithionite (0.28 g) and the mixture was heated under reflux for 1 h, a further portion of sodium dithionite (0.28 g) was then added and the mixture was heated under reflux for a further 1h. The mixture was evaporated and the residue was treated with water. Extraction of the resulting solution with methylene chloride afforded the unreacted triazole N-oxide (66) (0.1 g; 30%) m.p. 164-166°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The aqueous mother liquor was evaporated and the residual cake was soxhlet extracted with ethyl acetate to afford a yellow solid (0.2 g) which was subjected to flash chromatography.

Elution with methylene chloride yielded 4-amino-5-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (67) (0.08 g; 28%), which formed yellow prisms, m.p. 116-117° (from light petroleum (b,p. 80-100)), ν_{max} 3460 and 3305 (NH) and 1635 (CO) cm^{-1}, $\delta(CDCl_3)$ 8.44-7.35 (10H, m, ArH) and 5.44 (2H, brs, NH).

Found: C, 68.4; H, 4.6; N, 21.1%; M^+, 264. $C_{15}H_{12}N_4O$ requires: C, 68.2; H, 4.5; N, 21.2%; M, 264.

Final elution with ethanol gave a yellow gum (0.08 g) whose t.l.c. with ethyl acetate showed it to be a multi-component mixture which was not further investigated.

5-Amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide Oxime (68)

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) (0.28 g, 0.001 mol) in anhydrous ethanol (20.0 ml) was treated with a solution of hydroxylamine hydrochloride (0.7 g, 0.01 mol) in water (5.0 ml) and the mixture was heated under reflux for 17 h. Evaporation of the mixture and treatment of the residue with water afforded 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide oxime (68) (0.33 g; quant), which formed

colourless, irregular prisms, m.p. 185-186° (from dimethyl formamide-water), ν_{max} 3360 and 3295 (NH, OH) cm^{-1}, δ[$(CD_3)_2SO$] 11.81 (1H, s, OH), 7.79-7.38 (10H, m, ArH) and 5.78 (2H, s, NH).

Found: 295.1065.

$C_{15}H_{13}N_5O_2$ requires: 295.1069.

The Attempted Reduction of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide Oxime (68) with Ethanolic Sodium Dithionite

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide oxime (68) (0.89 g, 0.003 mol) in 70% aqueous ethanol (40.0 ml) was heated with sodium dithionite (0.89 g) and the mixture was heated under reflux for 1h, a further portion of sodium dithionite (0.89 g) was then added and the mixture was heated under reflux for a further 1 h. The mixture was evaporated and the residue was treated with water. Filtration afforded the unreacted 2H-1,2,3-triazole 1-N-oxide oxime (68) (0.87 g; 89%) m.p. 180-185°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Reaction of 5-Amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with Acetic Anhydride

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) (0.28 g, 0.001 mol) in acetic anhydride (5.0 ml) was heated under reflux for 1 h. The mixture was evaporated to afford a brown gum (0.30 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded an unidentified yellow solid (0.01 g), m.p. 94-96°, ν_{max} 1790 and 1685 (CO) cm^{-1}, m/e 226, followed by a yellow gum (0.18 g) whose t.l.c. in methylene chloride showed it to be a mixture of three close-running components and was not further investigated.

Elution with methylene chloride-ethyl acetate (10:1) afforded a brown gum (0.04 g) which was not further investigated, followed by 5-acetamido-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (74) (0.02 g; 3%), m.p. 110-113°, ν_{max} 3200 (NH), 1760 (CO) and 1660 (C=N) cm^{-1}.

Found: M^+, 322.1064

$C_{17}H_{14}N_4O_3$ requires: M, 322.1064

Final elution with ethanol afforded no further material.

The Attempted Reaction of 5-Amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with Concentrated Hydrochloric Acid

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) (0.56 g, 0.002 mol) in ethanol (10.0 ml) was treated with concentrated hydrochloric acid (5.0 ml) and the mixture was heated under reflux for 24 h. The mixture was evaporated and the residue was treated with water to afford unreacted 2H-1,2,3-triazole 1-N-oxide (66) (0.53 g; 98%), m.p. 164-166°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Reaction of 5-Amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with 20% w/v Aqueous Potassium Hydroxide

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) (0.56 g, 0.002 mol) in ethanol (10.0 ml) was treated with 20% w/v aqueous potassium hydroxide solution (5.0 ml) and the mixture was heated under reflux for 3 h. The mixture was evaporated, the residue was treated with water, and the resulting solution was extracted with methylene chloride to yield a brown gum (0.40 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (4:1) afforded a yellow gum (0.07 g) whose t.l.c. in methylene chloride showed it to be a mixture of three close-running components and was not further investigated.

Elution with methylene chloride-ethyl acetate (2:1) afforded an unidentified buff solid (0.17 g), m.p. 120-121° [from light petroleum (b.p. 80-100°)], ν_{max} 1570 (C=N) cm^{-1}, δ_H ($CDCl_3$) 8.86 (1H, d, J 5Hz), 8.46 (2H, q, J 10Hz), 8.24 (2H, q, J 10Hz) and 7.61-7.25 (5H, m, ArH), δ_C ($CDCl_3$) 152.91, 140.18 (quat), 139.90 (quat), 134.47 (quat), 129.92, 129.47, 129.33, 128.86, 128.81, 120.75 and 118.89.

Found: C, 75.3; H, 4.5; N, 18.2%; M^+, 273.

Elution with methylene chloride-ethyl acetate (1:1) afforded the unreacted 2H-1,2,3-triazole 1-N-oxide (66) (0.05 g; 9%), m.p. 164-166°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Final elution with ethanol gave an intractable brown gum (0.1 g) which was not further investigated.

The original aqueous mother liquor on neutralisation with 2M aqueous hydrochloric acid and extraction with methylene chloride afforded no further material.

The Reaction of 5-Amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with Hydrogen Peroxide

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) (0.56 g, 0.002 mol) in glacial acetic acid (10.0 ml), was treated at room temperature with 30% w/v aqueous hydrogen peroxide solution (5.0 ml)

and the mixture was stirred at 50° (oil bath) for 17 h. The mixture was diluted with water (20.0 ml) and the resulting solution was neutralised with anhydrous sodium acetate and extracted with methylene chloride (3 x 30.0 ml) to afford a brown gum (0.40 g) which was subjected to flash chromatography.

Elution with methylene chloride yielded 4-benzoyl-5-nitroso-2-phenyl-2H-1,2,3-triazole 1-N-oxide (90) (0.10 g; 17%), m.p. 128-129° (from light petroleum (b.p. 80-100°)), ν_{max} 1680 (CO) cm^{-1}, δ_H ($CDCl_3$) 8.17-7.24 (10H, m, ArH), δ_C ($CDCl_3$) 184.12 (quat), 140.78 (quat), 138.35 (quat), 135.26 (quat), 134.67, 130.07, 129.96, 129.70, 128.82 (quat) and 119.72.

Found: C, 61.4; H, 3.4; N, 18.8%; M^+, 294

$C_{15}H_{10}N_4O_3$ requires: C, 61.2; H, 3.4; N, 19.1%; M, 294.

Elution with methylene chloride-ethyl acetate (10:1) gave a small amount (0.06 g) of a brown gum which was not further investigated.

Elution with ethyl acetate afforded the unreacted 2H-1,2,3-triazole 1-N-oxide (66) (0.20 g; 40%), m.p. 164-166°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Final elution with ethanol yielded no further material.

The Attempted Reaction of 5-Amino-4-benzoyl-2-phenyl-2*H*-1,2,3-triazole 1-*N*-oxide Oxime (68) with Triethyl Orthoformate

A solution of 5-amino-4-benzoyl-2-phenyl-2*H*-1,2,3-triazole 1-*N*-oxide oxime (68) (0.30 g, 0.001 mol) in triethyl orthoformate (5.0 ml) was heated under reflux for 24 h. The solution was evaporated to give a brown gum (0.30 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (10:1) gave a yellow gum (0.25 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

The Attempted Reaction of 5-Amino-2-benzoyl-2-phenyl-2*H*-1,2,3-triazole 1-*N*-oxide (66) with Hydrazine Hydrate

A solution of 5-amino-4-benzoyl-2-phenyl-2*H*-1,2,3-triazole 1-*N*-oxide (66) (0.56 g, 0.002 mol) in methanol (10.0 ml) was treated with 100% hydrazine monohydrate (0.1 g, 0.002 mol) and the mixture was heated under reflux for 3 h. Evaporation of the mixture afforded a yellow gummy solid which was titrated with toluene to yield the unreacted 2*H*-1,2,3-triazole 1-*N*-oxide (66), which was combined with further material obtained by evaporation of the toluene filtrate (total, 0.54 g; 96%), m.p. 164-166°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 5-Amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with Hydrazine Hydrochloride

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) (0.56 g, 0.002 mol) in ethanol (30.0 ml) was treated with a solution of hydrazine hydrochloride (2.10 g, 0.02 mol) in water (10.0 ml) and the mixture was heated under reflux for 17 h. Cooling to room temperature afforded a yellow solid which was collected by filtration and washed with saturated aqueous sodium hydrogen carbonate solution to yield the unreacted 2H-1,2,3-triazole 1-N-oxide (66) (0.10 g; 18%) m.p. 164-166°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The ethanolic filtrate was evaporated, the residue was treated with water and the resulting solution was extracted with methylene chloride to afford an orange gum (0.2 g) which was subjected to flash chromatography.

Elution with methylene chloride through to ethanol gave a series of gums (total, 0.17 g) none of which were further investigated.

The Attempted Reaction of 5-Amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) with Tosylhydrazine

A solution of 5-amino-4-benzoyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (66) in methanol (20.0 ml) was treated with tosylhydrazine (0.37 g, 0.002 mol) and the mixture was heated under reflux for 2 h. Cooling to room temperature afforded a yellow solid, which was combined with further material obtained by evaporation of the methanolic filtrate and treatment of the resulting residue with aqueous 2M sodium hydroxide solution to yield the unreacted 2H-1,2,3-triazole 1-N-oxide (66) (total 0.50 g; 89%), m.p. 164-166°, identical (m.p. and i.r. spectrum) to a sample prepared before.

5-Amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103)

A solution of 2-chloro-2-phenylhydrazonoacetamidoxime (36) (4.3 g, 0.02 mol) in anhydrous acetonitrile (250 ml) was treated with activated manganese dioxide (30 g) and the mixture was stirred at room temperature for 1 h. The mixture was filtered through celite and the filtrate was evaporated to afford a buff solid which was combined with further material obtained by soxhlet extraction of the manganese dioxide residue with ethyl acetate to yield 5-amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103) (total 4.1 g; 98%), which formed colourless prisms, m.p. 118-119° (from toluene-light petroleum), ν_{max} 3380, 3295 and 3180 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.82-7.42 (5H, m, ArH) and 6.03 (2H, s, NH), δ_C [$(CD_3)_2SO$] 135.00 (quat),

131.52 (quat), 129.04, 128.45, 123.33 (quat) and 122.35.

Found: C, 45.4; H, 3.3; N, 26.1%; M^+, 212,210

$C_8H_7ClN_4O$ requires: C, 45.6; H, 3.3; N, 26.6%; M, 210.5

The Attempted Reaction of 5-Amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103) with Ethanolic Ammonia

A solution of 5-amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103) (0.42 g, 0.002 mol) in anhydrous ethanol (25.0 ml) was added to a saturated solution of ammonia in anhydrous ethanol (25.0 ml) and the mixture was left firmly stoppered at room temperature for 17 h. The mixture was evaporated to afford the unreacted 2H-1,2,3-triazole 1-N-oxide (103) (0.40 g; 95%), m.p. 116-119°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 5-Amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103) with Ethanolic Sodium Ethoxide

A solution of 5-amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103) (0.42 g, 0.002 mol) in ethanol (20.0 ml) was added to a solution of sodium (0.18 g, 0.008 g atom) in ethanol (5.0 ml) and the resulting red solution was heated under reflux for 1h. The mixture was evaporated and the dark solid residue was heated with water and extracted with methylene chloride to afford a brown gum (0.3 g) which was subjected to flash chromatography.

Elution with n-hexane-methylene chloride (1:1) through to ethanol yielded a series of gums (total, 0.28 g) none of which were further investigated.

The original aqueous mother liquor was acidified with aqueous 2M hydrochloric acid and extracted with methylene chloride to afford a brown gum (0.05 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

Benzenesulphonylacetonitrile (106)[122]

Benzenesulphonylacetonitrile (106) was prepared (yield 87%) by the reaction of sodium benzenesulphinate with chloroacetonitrile as described by Troger and Hille[122] and had m.p. 103-107° (lit.,[122] 112-114°).

2-Benzenesulphonyl-2-phenylhydrazonoacetonitrile (107)

A solution of redistilled aniline (10.0 g, 0.1 mol) in aqueous 5M hydrochloric acid (51.0 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (8.2 g, 0.11 mol) in water (10.0 ml). The resulting amber benzenediazonium chloride solution was stirred for a further 5 min. in the ice-salt bath, then added dropwise at 0-5° (ice-salt bath) to a stirred solution of benzenesulphonylacetonitrile (106) (19.1 g, 0.1 mol) and anhydrous sodium acetate (21.0 g, 0.25 mol) in ethanol (300 ml) and water (50.0 ml). The mixture was stirred for a further 1 h at room temperature then filtered to afford

2-benzenesulphonyl-2-phenylhydrazonoacetonitrile (107) (28.3 g; quant.), which formed yellow prisms, m.p. 163-164°, ν_{max} 3215, 3200, 3130 and 3060 (NH) and 2200 (CN) cm^{-1}, $\delta(CDCl_3)$ 11.93 (1H, brs, NH) and 8.08-7.05 (10H, m, ArH).

Found: C, 58.8; H, 3.9; N, 14.7%; M^+, 285

$C_{14}H_{11}N_3O$ requires: C, 59.0; H, 3.9; N, 14.7%; M, 285.

2-Benzenesulphonyl-2-phenylhydrazonoacetamidoxime (108)

A solution of 2-benzenesulphonyl-2-phenylhydrazonoacetonitrile (108) (14.25 g, 0.05 mol) in anhydrous ethanol (400 ml) was treated with stirring at room temperature with a solution of hydroxylamine hydrochloride (8.8 g, 0.13 mol) in anhydrous ethanol (100 ml) followed by sodium carbonate (6.5 g, 0.06 mol) and the mixture was stirred at room temperature for 48 h. Evaporation of the mixture and treatment of the residual cake with water afforded 2-benzenesulphonyl-2-phenylhydrazonoacetamidoxime (108), (15.5 g; quant.), which formed colourless prisms, m.p. 179-180° (from ethanol), ν_{max} 3460, 3390 and 3370 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.43 (1H, s, NH or OH), 10.56 (1H, s, OH or NH), 8.00-8.07 (10H, m, ArH) and 6.10 (2H, m, NH), δ_C [$(CD_3)_2SO$] 146.64 (quat), 139.89 (quat), 133.63, 129.34, 129.04 (quat)., 127.82, 123.26 and 114.40.

Found: C, 53.0; H, 4.4; N, 17.6%; M^+, 318

$C_{14}H_{14}N_4O_3S$ requires: C, 52.8; H, 4.4; N, 17.6%; M, 318

5-Amino-4-benzenesulphonyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (109)

A solution of 2-benzenesulphonyl-2-phenylhydrazono-acetamidoxime (108) (1.3 g, 0.004 mol) in anhydrous acetonitrile (50.0 ml) was treated with activated manganese dioxide (6.0 g) and the mixture was stirred at room temperature for 1 h. The mixture was filtered through celite and the filtrate was evaporated to afford 5-amino-4-benzenesulphonyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (109) (1.1 g; 90%), which formed colourless prisms, m.p. 162-163° (from ethanol), ν_{max} 3460 and 3280 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.16-7.51 (10H, m, ArH) and 6.31 (2H, brs, NH), δ_C [$(CD_3)_2SO$] 139.57 (quat), 134.51, 134.00 (quat), 133.30 (quat), 130.70 (quat), 129.76, 129.14, 127.31 and 123.26.

Found: C, 53.2; H, 3.7; N, 17.5%; M^+, 316

$C_{14}H_{12}N_4O_3S$ requires: C, 53.2; H, 3.8; N, 17.7%; M, 316.

The Attempted Reaction of 5-Amino-4-benzenesulphonyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (109) with Ethanolic Ammonia

A solution of 5-amino-4-benzenesulphonyl-2-phenyl-2H-1,2,3-triazole 1-N-oxide (109) (0.73 g, 0.002 mol) in anhydrous ethanol (25.0 ml) was added to a saturated solution of ammonia in anhydrous ethanol (25.0 ml). The mixture was left firmly stoppered at room temperature for 3 days then evaporated to afford the unreacted 2H-1,2,3-triazole 1-N-oxide (110) (0.73 g; quant), m.p. 160-163°, identical (m.p. and i.r. spectrum) to a sample prepared before.

2-Amino-2-phenylhydrazonoacetonitrile (110)

A solution of 2-chloro-2-phenylhydrazonoacetonitrile (35) (7.2 g, 0.04 mol) in anhydrous ethanol (200 ml) was added to a saturated solution of ammonia in anhydrous ethanol (200 ml). The mixture was left firmly stoppered at room temperature for 17 h. then evaporated to yield a solid residue which was treated with water and filtered to afford 2-amino-2-phenylhydrazonoacetonitrile (110), (6.1 g, 95%), m.p. 163-164° (from toluene), ν_{max} 3420 and 3340 (NH) and 2215 (CN) cm^{-1}, $\delta(CDCl_3)$ 7.32-6.92 (5H, m, ArH), 3.94 (1H, brs, NH) and 1.55 (2H, brs, NH).

Found: C, 60.0; H, 4.9; N, 35.2%; M^+, 160

$C_8H_8N_4$ requires: C, 60.0; H, 5.0; N, 35.0%; M, 160.

2-Amino-2-phenylhydrazonoacetamidoxime (102)[119]

(a) A solution of 2-amino-2-phenylhydrazonoacetonitrile (110) (0.64g, 0.004 mol) in anhydrous ethanol (20.0 ml) was treated with stirring at room temperature with a solution of hydroxylamine hydrochloride (0.70 g, 0.01 mol) in anhydrous ethanol (20.0 ml) followed by sodium carbonate (0.53 g, 0.005 mol) and the mixture was stirred at room temperature for 48 h. Evaporation of the mixture and treatment of the residual cake with water afforded 2-amino-2-phenylhydrazonoacetamidoxime (102)[119] (0.75; quant.), which formed salmon pink crystals, m.p. 168-169° (from ethanol), (lit.,[119] 174°), ν_{max} 3460, 3360, 3260 and 3240 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.63

(1H, brs, NH or OH), 8.30 (1H, brs, OH or NH), 7.25-6.56 (5H, m, ArH), 5.41 (2H, brs, NH) and 5.32 (2H, brs, NH), δ_C [$(CD_3)_2SO$] 146.78 (quat), 146.52 (quat), 136.30 (quat), 128.75, 117.68 and 112.14.

Found: C, 49.6; H, 5.7; N, 36.2%; M^+, 193

$C_8H_{11}N_5O$ requires: C, 49.7; H, 5.7; N, 36.3%; M, 193.

(b) A solution of 2-chloro-2-phenylhydrazonoacetamidoxime (36) in anhydrous ethanol (25.0 ml) was added to a saturated solution of ammonia in anhydrous ethanol (25.0 ml). The mixture was left firmly stoppered at room temperature for 17 h. then evaporated to yield a solid residue which was treated with water. The resulting solution was extracted with methylene chloride to afford a brown solid (0.5 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (4:1) yielded 2-amino-2-phenylhydrazonoacetamidoxime (102), (0.31 g, 41%), m.p. 165-168°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

Elution with ethyl acetate through to ethanol gave a series of gums (total, 0.10 g) none of which were further investigated.

Constant extraction with methylene chloride of the original neutral aqueous mother liquor afforded no further material.

The Attempted Reaction of 2-Amino-2-phenylhydrazono-acetamidoxime (102) with Activated Manganese Dioxide

A solution of 2-amino-2-phenylhydrazonoacetamidoxime (111) (0.39 g, 0.002 mol) in anhydrous acetonitrile (20.0 ml) was treated with activated manganese dioxide (3.0 g) and the mixture was stirred at room temperature for 1 h. The mixture was filtered through celite and the filtrate was evaporated to afford a brown gum (0.4 g) which was subjected to flash chromatography.

Elution with methylene chloride through to ethanol yielded a series of gums (total 0.20 g) none of which were further investigated.

2-Phenylhydrazono-2-(piperidin-1-yl)acetamidoxime (111)

A solution of 2-chloro-2-phenylhydrazonoacetamidoxime (36) (1.1 g, 0.005 mol) in anhydrous ethanol (50.0 ml) was treated with piperidine (0.94 g, 0.011 mol) and the mixture was stirred at room temperature for 1 h. The mixture was evaporated to afford a dark gum which was titrated with diethyl ether and filtered to afford piperidine hydrochloride (0.75 g), m.p. 240-245°, identical (m.p. and i.r. spectrum) to an authentic sample. The diethyl ether filtrate was evaporated to afford a red gum (0.85 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded a red gum (0.07 g) which was not further investigated, followed by

2-phenylhydrazono-2-(piperidin-1-yl)acetamidoxime (111) (0.38 g; 29%), which formed colourless needles, m.p. 135-136° (from toluene), ν_{max} 3420 and 3300 (NH, OH) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.90 (1H, brs, NH or OH), 9.21 (1H, brs, OH or NH), 7.22-6.64 (5H, m, ArH), 5.82 (2H, brs, NH), 3.00 (4H, brs, CH_2) and 1.55 (6H, brs, CH_2), δ_C [$(CD_3)_2SO$] 146.23 (quat), 145.43 (quat), 141.91 (quat), 128.85, 117.71, 111.75, 48.44 (CH_2), 24.90 (CH_2) and 24.10 (CH_2).

Found: C, 60.0; H, 7.3; N, 26.5%; M^+, 261

$C_{13}H_{19}N_5O$ requires: C, 59.8; H, 7.3; N, 26.8%; M , 261

Elution with methylene chloride-ethyl acetate (1:1) through to ethanol gave a series of gums (total, 0.37 g) none of which were further investigated.

The Attempted Reaction of 2-Phenylhydrazono-2-(piperidin-1-yl)acetamidoxime (111) with Activated Manganese Dioxide

A solution of 2-phenylhydrazono-2-(piperidin-1-yl)-acetamidoxime (111) (0.13 g, 0.0005 mol) in anhydrous acetonitrile (10.0 ml) was treated with activated manganese dioxide (0.75 g) and the mixture was stirred at room temperature for 1 h. The mixture was filtered through celite and the filtrate was evaporated to afford a red gum (0.1 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture and was therefore not further investigated.

Attempted Cyclodehydration Reactions of 2-Amino-2-phenylhydrazonoacetamidoxime (102)

(a) By reaction with thionyl chloride in dioxane

A solution of 2-amino-2-phenylhydrazonoacetamidoxime (102) (0.77 g, 0.004 mol) in anhydrous dioxane (5.0 ml) was treated dropwise with stirring at room temperature with thionyl chloride (0.4 ml, 0.0056 mol). The mixture was stoppered and stirred at room temperature for 16 h. Evaporation of the mixture and treatment of the residue with saturated aqueous sodium hydrogen carbonate solution followed by extraction of the resulting suspension with methylene chloride afforded a dark gum (0.10 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a complex mixture and was not further investigated.

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid followed by extraction with methylene chloride yielded no further material.

(b) By reaction with toluene-4-sulphonic acid in toluene

A solution of 2-amino-2-phenylhydrazonoacetamidoxime (102) (0.77 g, 0.004 mol) in anhydrous toluene (20.0 ml) was treated with toluene-4-sulphonic acid (0.40 g) and the mixture was heated under reflux in a Dean and Stark apparatus for 4 h. The mixture was cooled to room temperature and filtered to afford a solid which was

washed with saturated aqueous sodium hydrogen carbonate solution to give the unreacted 2-amino-2-phenylhydrazono-acetamidoxime (103) (0.44 g; 57%), m.p. 163-165°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The filtrate and combined washings were evaporated to afford a brown gum (0.10 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture and was not further investigated.

(c) By reaction with tosyl chloride in the presence of triethylamine

A solution of 2-amino-2-phenylhydrazonoacetamidoxime (102) (0.77 g, 0.004 mol) in anhydrous dioxane (40.0 ml) was treated with stirring at room temperature with triethylamine (0.44 g; 0.0044 mol) followed by dropwise addition of a solution of tosyl chloride (0.76 g, 0.0044 mol) in anhydrous dioxane (10.0 ml) and the mixture was then stirred at room temperature for 1 h. Filtration afforded triethylamine hydrochloride (0.20 g), m.p. 252-255°, identical (m.p. and i.r. spectrum) to an authentic sample. The dioxane filtrate was evaporated to afford a dark gum which was treated with water and extracted with methylene chloride to yield a brown gum (1.5 g) which was subjected to flash chromatography.

Elution with methylene chloride through to ethanol gave a series of gums (total, 1.4 g) none of which were further investigated.

2-Oximino-2-phenylazoacetonitrile (115) [2-Nitroso-2-phenylhydrazonoacetonitrile (114)][127]

A solution of (E)-2-cyano-2-phenylhydrazonoacetic acid (52) (7.6 g, 0.04 mol) in glacial acetic acid (400 ml) was treated dropwise with stirring at room temperature at such a rate that the reaction temperature was maintained between 20-30° with a solution of sodium nitrite (4.0 g, 0.0055 mol) in water (20.0 ml) and the resulting red solution was stirred at room temperature for a further 10 minutes. The mixture was evaporated, the residue was treated with water, and the resulting solution was extracted with methylene chloride to afford 2-oximino-2-phenylazoacetonitrile (114) (6.1 g; 88%) which formed buff prisms, m.p. 156-157° (from toluene), (lit.,[127] 166-168°) ν_{max} 3240 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.90-7.60 (6H, m, ArH and NH), δ_C [$(CD_3)_2SO$] 151.28 (quat), 145.54 (quat), 133.37, 129.68, 123.07, and 106.44 (quat).

Found: C, 55.2; H, 3.5; N, 32.6%; M^+, 174.
Calc. for $C_8H_6N_4O$: C, 55.2; H, 3.5; N, 32.3%; M, 174.

The Attempted Reaction of 2-Oximino-2-phenylazoacetonitrile (114) [2-Nitroso-2-phenylhydrazonoacetonitrile (114)] with hydroxylamine Hydrochloride in the Presence of Sodium Carbonate

A solution of 2-oximino-2-phenylazoacetonitrile (114) (3.5 g, 0.02 mol) in anhydrous ethanol (200 ml) was treated with a solution of hydroxylamine hydrochloride (3.5 g, 0.05 mol) in anhydrous ethanol (200 ml) followed by solid sodium carbonate (2.7 g, 0.025 mol) and the mixture was stirred at room temperature for 24 h. The mixture was evaporated and the residual cake was treated with water and the resulting solution extracted with methylene chloride to afford a red gum (4.3 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded unreacted 2-oximino-2-phenylazoacetonitrile (114) (1.3 g; 36%), m.p. 150-152°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with methylene chloride-ethyl acetate (1:1) through to ethanol gave a series of gums (2.9 g) none of which were further investigated.

Ethyl 2-Chloro-2-phenylhydrazonoacetimidate Hydrochloride (115)

A solution of 2-chloro-2-phenylhydrazonoacetonitrile (35) (0.90 g, 0.005 mol) in anhydrous ethanol (6.0 ml) and anhydrous diethyl ether (10.0 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 then left stoppered in a refrigerator overnight, then diluted with an equal volume of anhydrous diethylether (16.0 ml) and filtered to afford ethyl 2-chloro-2-phenylhydrazono-acetimidate hydrochloride (115), (1.3 g; 96%), m.p. 158-159 (from ethanol-light petroleum), ν_{max} 3140 (NH) cm^{-1}, δ [$(CD_3)_2SO$] 11.34 (1H, brs, NH), 7.82-7.03 (5H, m, ArH), 4.69 (2H, q, J7Hz, CH_2) and 1.43 (3H, t, J7Hz, CH_3).

Found: 226.0876.

$C_{10}H_{12}ClN_3O$ requires: 226.0986.

The Reaction of Ethyl 2-Chloro-2-phenylhydrazonoacetimidate Hydrochloride (115) with Hydroxylamine Hydrochloride in the Presence of Sodium Carbonate

A solution of ethyl 2-chloro-2-phenylhydrazono-acetimidate hydrochloride (115) (0.26 g, 0.002 mol) in anhydrous ethanol (10.0 ml) was treated with stirring at room temperature with a solution of hydroxylamine hydro-chloride (0.18 g, 0.0025 mol) in anhydrous ethanol (10.0 ml) followed by sodium carbonate (0.14 g; 0.00125 mol) and the mixture was stirred at room temperature for 24 h. Evaporation of the mixture and treatment of the residual cake with water afforded 2-chloro-2-phenylhydrazonoacetamidoxime (36) (0.21; quant), m.p. 180-183°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 2-Chloro-2-phenylhydrazono-acetamidoxime (36) with Hydroxylamine Hydrochloride in the Presence of Sodium Carbonate

A solution of 2-chloro-2-phenylhydrazonoacetamidoxime (36) (0.43 g, 0.002 mol) in anhydrous ethanol (20.0 ml) was treated at room temperature with a solution of hydroxylamine hydrochloride (0.36 g, 0.005 mol) in anhydrous ethanol (10.0 ml) followed by sodium carbonate (0.28 g, 0.0025 mol) and the mixture was stirred and heated under reflux for 24 h. Evaporation of the mixture and treatment of the residual cake with water afforded unreacted 2-chloro-2-phenylhydrazonoacetamidoxime (36) (0.43 g; quant.), m.p. 180-183°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (103) with Hydrazine Hydrate

A solution of 5-amino-4-chloro-2-phenyl-2H-1,2,3-triazole 1-N-oxide (0.42 g, 0.002 mol) in ethanol (20.0 ml) was treated with 100% hydrazine monohydrate (0.40 g, 0.008 mol) and the mixture was heated under reflux for 24 h. Evaporation of the mixture afforded the unreacted 2H-1,2,3-triazole 1-N-oxide (104) (0.42 g; quant.), m.p. 115-119°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 2-Chloro-2-phenylhydrazono-acetamidoxime (36) with Hydrazine Hydrate

A solution of 2-chloro-2-phenylhydrazonoacetamidoxime (36) (0.43 g, 0.002 mol) in anhydrous ethanol (20.0 ml) was treated with 100% hydrazine monohydrate (0.11 g, 0.0044 mol) and the mixture was stirred at room temperature for 24 h., heated at 50° (oil bath) for 3 h., and then heated under reflux for a further 4 h. Evaporation of the mixture afforded unreacted 2-chloro-2-phenylhydrazonoacetamidoxime (36) (0.43 g; quant.), m.p. 180-185°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 2-Chloro-2-phenylhydrazono-acetamidoxime (36) with Phenylhydrazine

A solution of 2-chloro-2-phenylhydrazonoacetamidoxime (36) (0.85 g, 0.0004 mol) in anhydrous ethanol (40.0 ml) was treated with phenylhydrazine (0.24 g, 0.0088 mol) and the mixture was stirred at room temperature for 24 h., heated at 50° (oil bath) for 3 h., and then heated under reflux for a further 4 h. Evaporation of the mixture afforded a brown gum which was triturated with light petroleum to yield unreacted 2-chloro-2-phenylhydrazono-acetamidoxime (36) (0.83 g; 98%), m.p. 180-185°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 2-Chloro-2-phenylhydrazono-acetonitrile (35) with Hydrazine Hydrate

(a) A solution of 2-chloro-2-phenylhydrazonoaceto-nitrile (35) (0.36 g, 0.002 mol) in ethanol (20.0 ml) was treated with 100% hydrazine monohydrate (0.40 g, 0.008 mol) and the mixture was heated under reflux for 30 min. Evaporation of the mixture afforded a red gum (0.40 g) which was subjected to flash chromatography.

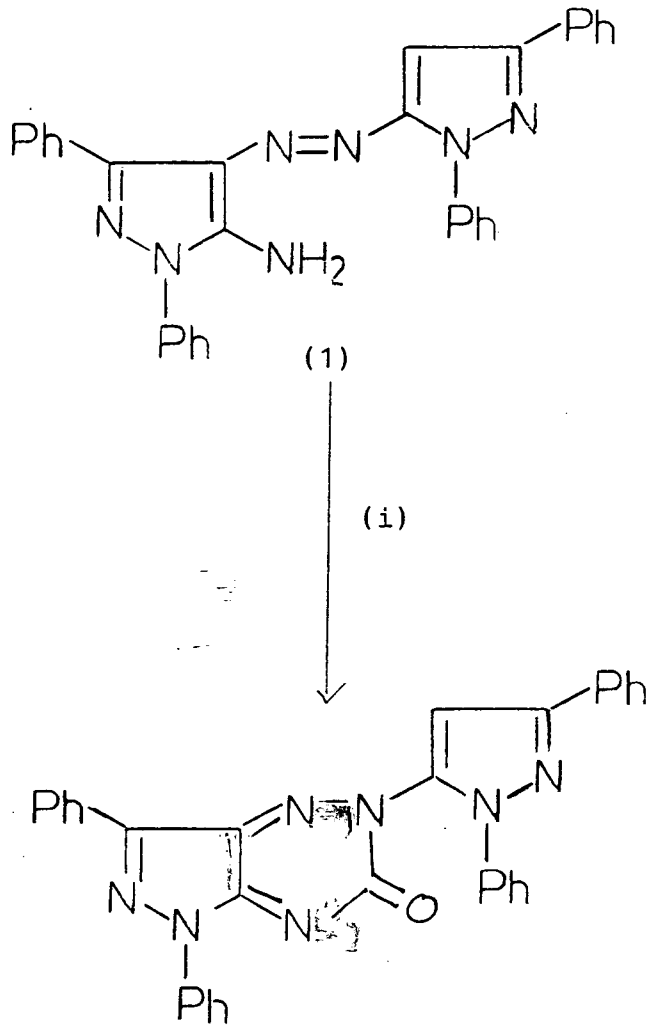
Elution with methylene chloride through to ethanol affords a series of gums (total, 0.33 g) none of which was further investigated.

(b) A solution of 2-chloro-2-phenylhydrazonoaceto-nitrile (35) (0.36 g, 0.002 mol) in ethanol (20.0 ml) was treated with 100% hydrazine monohydrate (0.40 g, 0.008 mol) and the mixture was stirred at room temperature for 1 h. Evaporation of the mixture afforded a brown solid (0.70 g) which was subjected to flash chromatography.

Elution with methylene chloride through to ethanol afforded a series of gums (total, 0.36 g) none of which was further investigated.

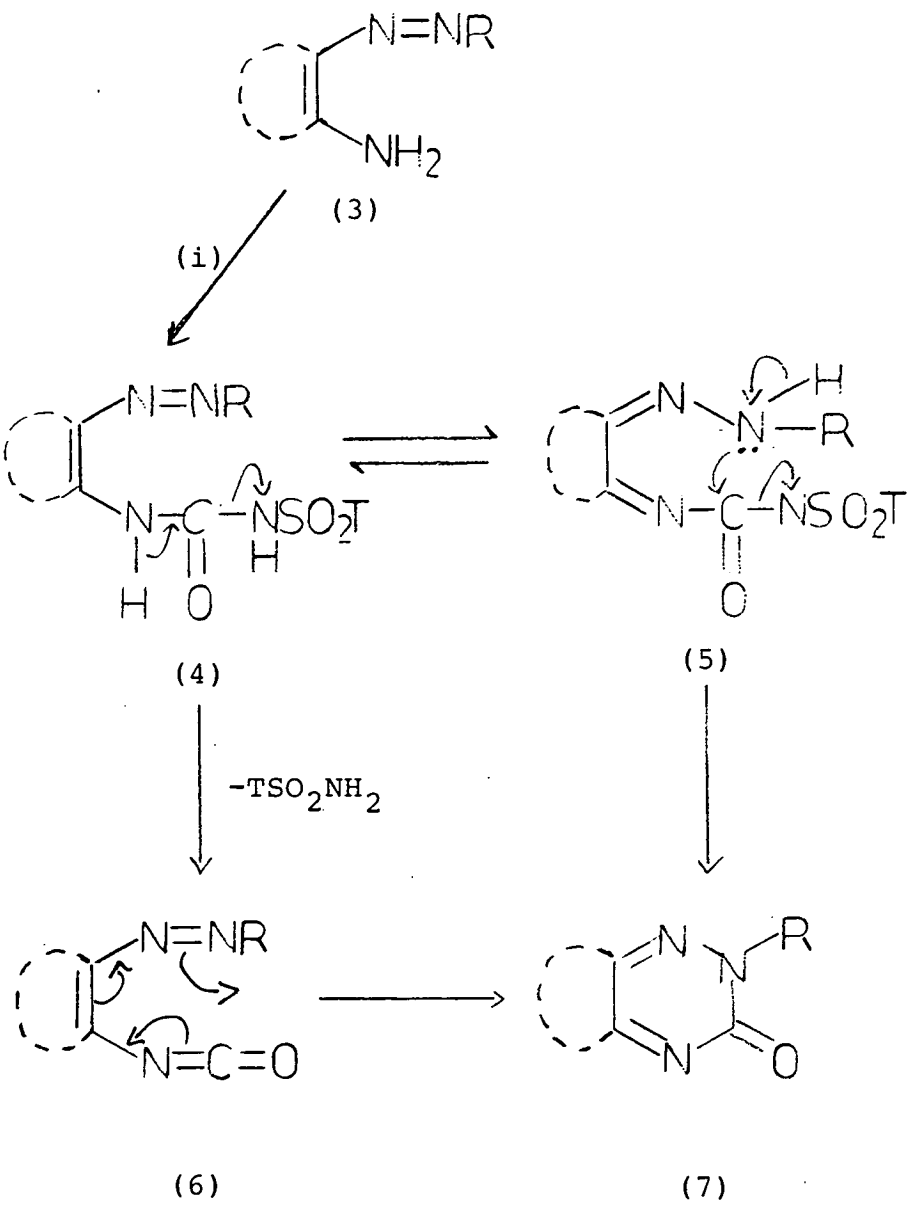
Chapter 3

Synthetic Approaches to Azapurines, Azapteridines and Related Polyazaheterocycles Based on Annulation Reactions with Tosyl Isocyanate



(i) $TSO_2N=C=O$, $MeOCH_2CH_2OMe$, reflux

Scheme 1



(i) $TSO_2N{=}C{=}O$, heat

Schème 2

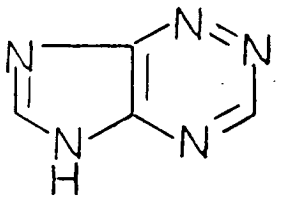
Synthetic Approaches to Azapurines, Azapteridines and Related Polyazaheterocycles Based on Annulation Reactions with Tosyl Isocyanate

3.1 Introduction

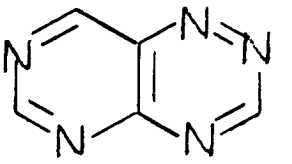
In the course of previous studies at Edinburgh[129] it was shown (Scheme 1) that the pyrazolylazopyrazole (1) reacts with tosyl isocyanate to afford the pyrazolo[3,4-e]-1,2,4-triazine derivative (2) in good yield. This appears to be the only previous example of such an annulation reaction using tosyl isocyanate for the formation of 1,2,4-triazines. It therefore represents a potentially general method for the annulation (Scheme 2) of ortho-amino-azo compounds to afford fused 1,2,4-triazine derivatives (7). There appear to be two conceivable mechanistic pathways for this transformation [(3)-(7)]. Firstly, by initial formation of the urea adduct (4) which in the tautomeric form (5) can give the triazinone (7) by direct nucleophilic elimination of toluene-4-sulphonamide. Secondly, the urea adduct (4) can initially eliminate toluene-4-sulphonamide to afford the isocyanate derivative (6) which by electrocyclisation yields the triazinone (7).

The studies described in this chapter are concerned with the investigation of the scope and mechanism of such fused triazine synthesis as well as the reactivity of the

fused triazine products. Of particular interest is the use of the tosyl isocyanate annulation procedure for the synthesis of the polyazaheterocycles illustrated in Scheme 3.



(8)



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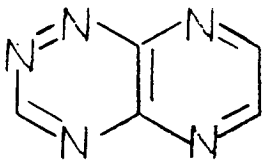

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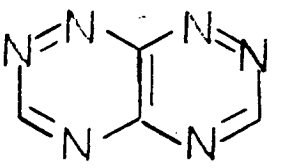

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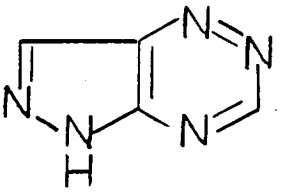
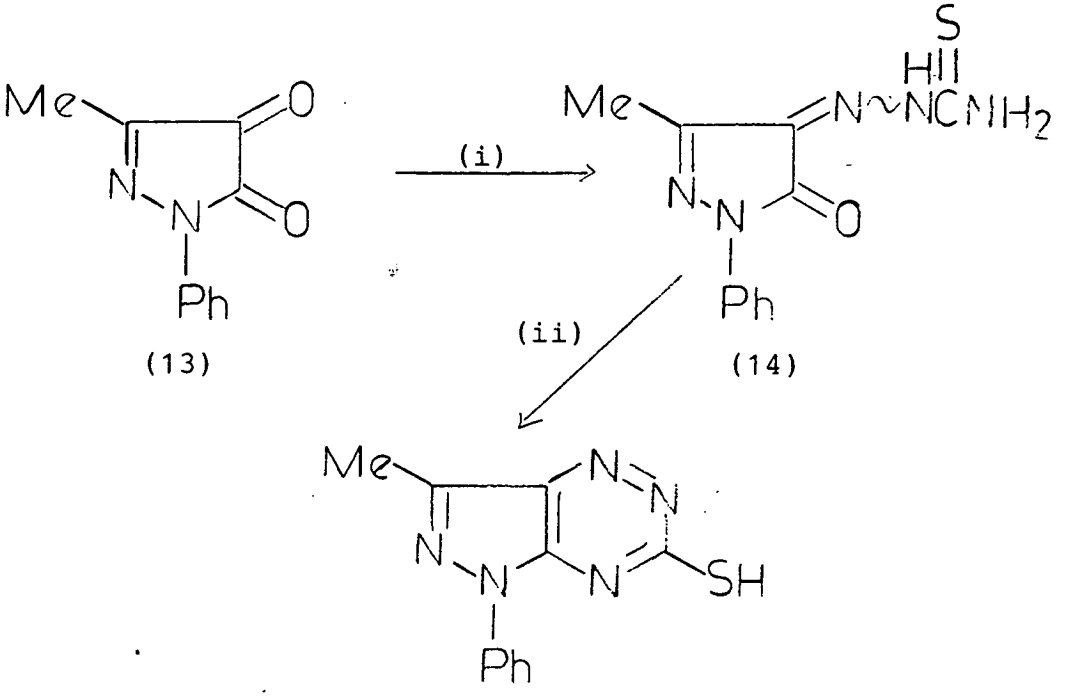


(12)

Scheme 3

The nomenclature of the ring systems [(8)-(11)] has already been discussed (see Chapter 1) and these heterocyclic nuclei are named as follows: the imidazolo-[4,5-e]-1,2,4-triazine ring system (6-azapurine) (8), the pyrimido[4,5-c]-1,2,4-triazine ring system (6-azapteridine) (9), the pyrazino[2,3-e]-1,2,4-triazine ring system (4-azapteridine) (10) and the 1,2,4-triazino[5,6-e]-1,2,4-triazine ring system (4,6-diazapteridine). The ring system (12) has not been described previously and is systematically named in accordance with Chemical Abstracts as the pyrazolo[3,4-e]-1,2,4-triazine ring system, formally a scrambled derivative of the 6-azapurine ring system (8).

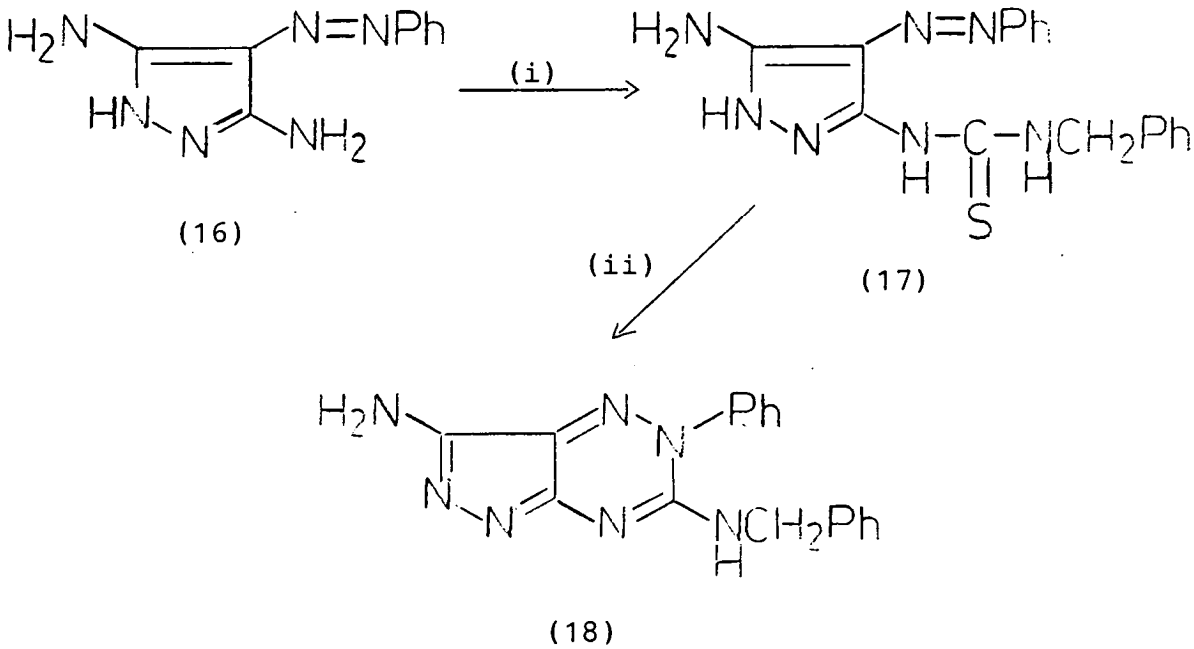
The biological activity of the ring systems [(8)-(11)] has also been discussed previously (see Chapter 1). The pyrazolo[3,4-e]-1,2,4-triazine ring system has been reported to have antiviral activity[130] and antitumor activity.[131] The known and potential biological activity of derivatives of these ring systems [(8)-(12)] prompted the present investigations of a general strategy for the synthesis of such polyazaheterocycles based on the annulation of ortho-amino-azo precursors with tosyl isocyanate.



(i) $H_2NCSNHNH_2$, ethanol, reflux

(ii) K_2CO_3, ethanol, reflux

Scheme 4

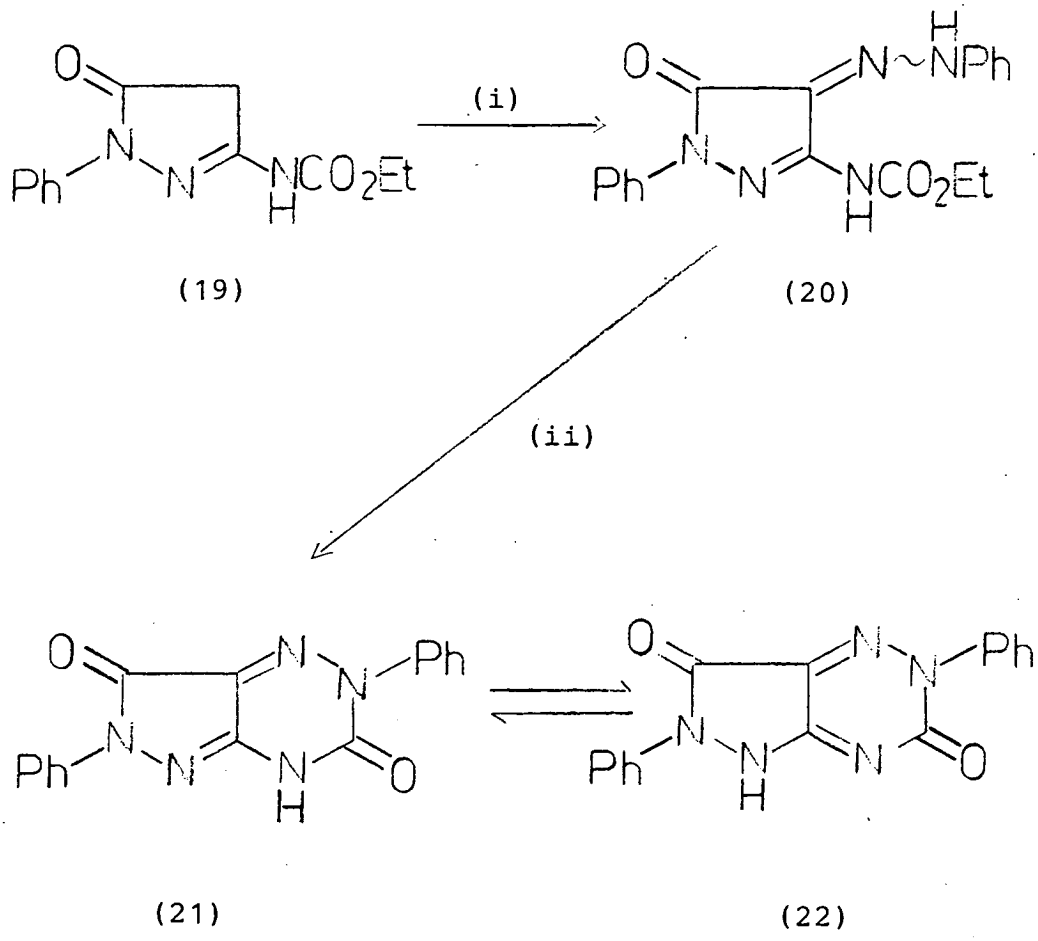


(16) (17) (18)

(i) $PhCH_2N=C=S$, room temperature

(ii) Pyridine, heat

Scheme 5



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

(i) $PhN_2^+Cl^-$, pyridine, 0°

(ii) cis-decalin, reflux

Scheme 6

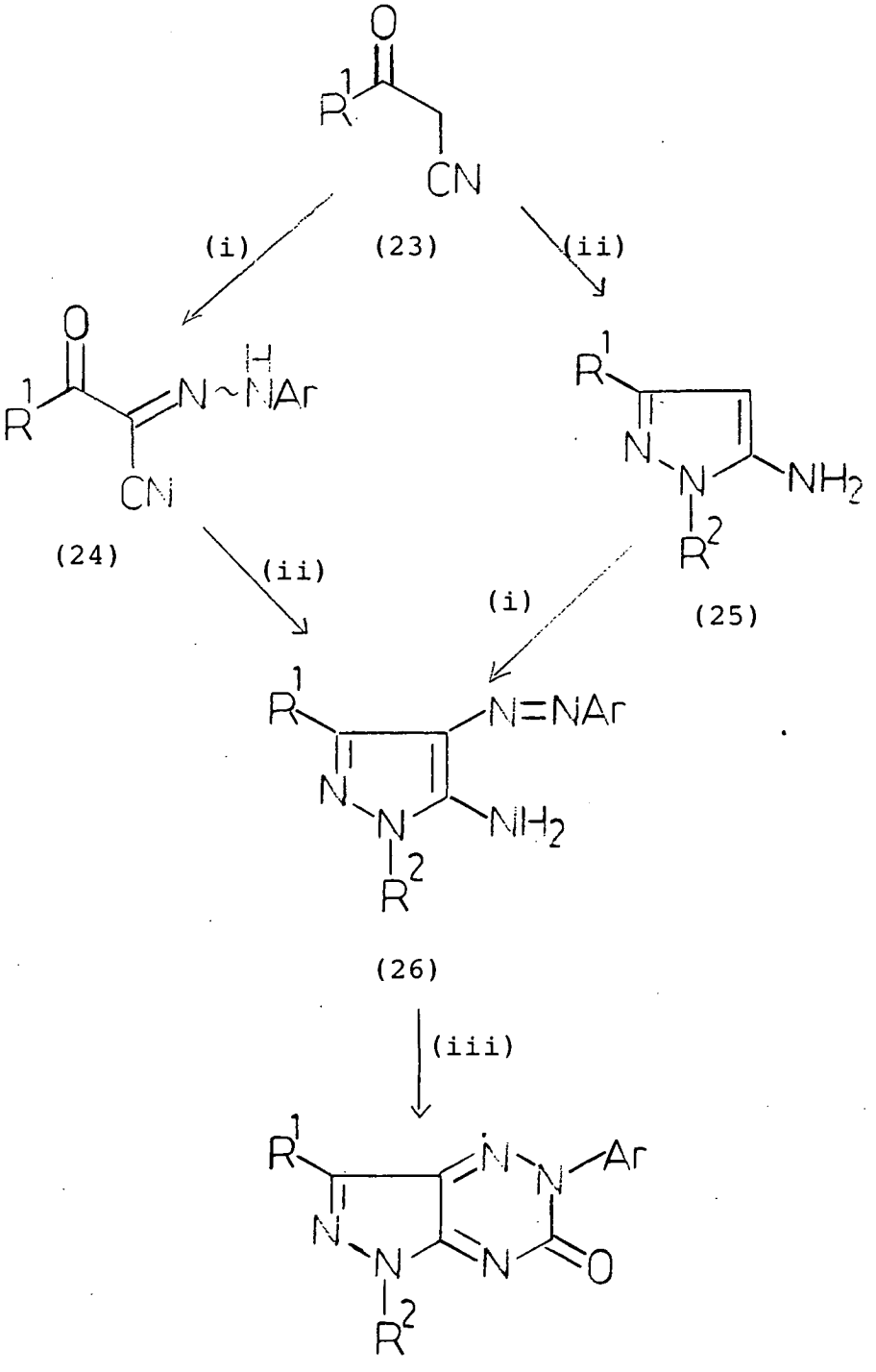
3.2 Studies on the Synthesis and Reactivity of Pyrazolo[3,4-e]-1,2,4-triazine Derivatives

3.2.1 A General Synthesis of Pyrazolo[3,4-e]-1,2,4-triazine Derivatives Based on Annulation Reactions of 5-Amino-4-arylazopyrazoles with Tosyl Isocyanate

Pyrazolo[3,4-e]-1,2,4-triazine derivatives have been synthesised previously by three procedures. Firstly from pyrazolinedione 4-thiosemicarbazone[130] as illustrated (Scheme 4) by the base-catalysed cyclisation of the compound (14) to afford the pyrazolo[3,4-e]-1,2,4-triazine (15). The pyrazolinedione thiosemicarbazide derivative (14) was readily synthesised by the reaction of 3-methyl-1-phenylpyrazoline-4,5-dione (13) with thiosemicarbazide.

A second procedure for the synthesis of derivatives of the pyrazolo[3,4-e]-1,2,4-triazine ring system is based on ortho-amino-azopyrazoles[132] as exemplified (Scheme 5) by reaction of 3,5-diamino-4-phenylazo-1H-pyrazole (16) with benzyl isothiocyanate to afford the pyrazole derivative (17) which by heating in pyridine is readily cyclised to the pyrazolo[3,4-e]-1,2,4-triazine derivative (18).

The third and final procedure used to synthesis derivatives of the pyrazolo[3,4-e]-1,2,4-triazine ring system utilises ortho-arylhydrazonopyrazolylurethane derivatives[133] as illustrated (Scheme 6) by the thermal



(i) $ArN_2^+Cl^-$, NaOAc, 0°

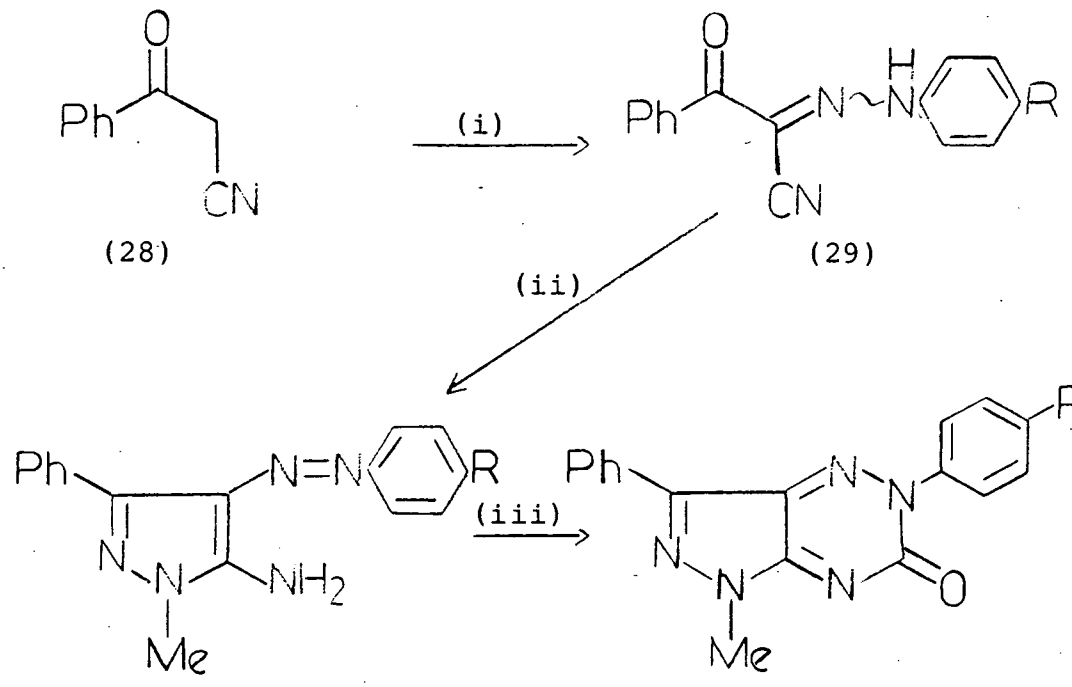
(ii) NH_2NHR^2, EtOH, heat

(iii) $TSO_2N=C=O$, diglyme, reflux

Scheme 7

cyclisation of the pyrazole derivative (20) to give the pyrazolotriazinone derivative (21) which readily tautomerises to its isomer (22). The arylhydrazono-pyrazolylurethane (20) was readily accessible by coupling of the pyrazolylurethane (18) with benzenediazonium chloride.

As an extension of the observation by Tennant and Torano[129] that ortho-amino-azopyrazoles can yield pyrazolo[3,4-e]-1,2,4-triazine derivatives as described earlier (see Scheme 1) it was decided to investigate the scope of this reaction. It was of particular interest to see if this type of reaction (Scheme 1) could be extended to provide a general route to pyrazolo[3,4-e]1,2,4-triazine derivatives (Scheme 7), based on the annulation of 5-amino-4-arylazopyrazoles (26) with tosyl isocyanate. Such 5-amino-4-arylazopyrazoles (26) are readily accessible by two routes, both starting from acylacetonitrile derivatives (23). Firstly, by coupling of the acylaceto-nitrile (23) with aryldiazonium salts to give 2-arylhydrazono-acetonitriles (24) which on reaction with hydrazines afford the 5-amino-4-arylazopyrazole derivatives (26). The second route to 5-amino-4-arylazopyrazole derivatives (25) involves the coupling of 5-aminopyrazoles (25) with aryldiazonium salts, the 5-aminopyrazoles (25) being readily available by reaction of acylacetonitrile derivatives (23) with hydrazines.



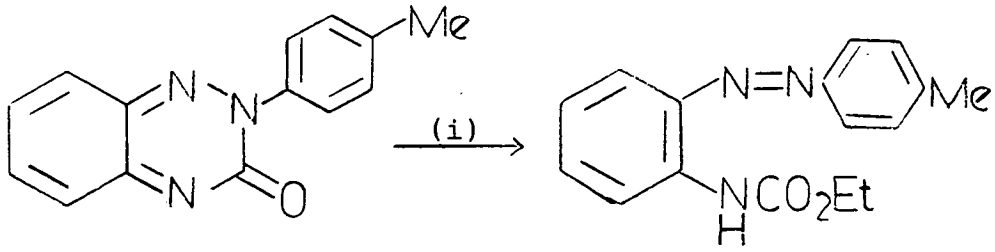
(28) (29) (30) (31)

			R
(i)	$4\text{-}RC_6H_4N_2^+Cl^-$, NaOAc, 0°	a;	H
(ii)	H_2NNHMe, EtOH, reflux	b;	Me
(iii)	$TSO_2N{=}C{=}O$, diglyme, reflux	c;	Cl
		d;	OMe
		e;	NO_2

Scheme 8

In pursuing this strategy (Scheme 8) benzoylacetonitrile (28)[105] was coupled with benzediazonium chloride to afford the known[104] 2-phenylhydrazonobenzoylacetonitrile (29a) as previously described in Chapter 2. This acetonitrile derivative (29a) was reacted with methylhydrazine under conditions known[134] to form pyrazoles and gave the previously unknown 5-amino-1-methyl-4-phenylazo-1-phenylpyrazole (30a) in good yield. This product has analytical and spectroscopic data consistent with the assigned structure. In particular, its ^{1}H n.m.r. spectrum exhibits resonances for ten aromatic hydrogen atoms, two exchangable protons and the three hydrogen atoms of an NCH_3 grouping. The ^{13}C n.m.r. spectrum of the pyrazole derivative (30a) contains the expected five signals for the quaternary carbon atoms of the assigned structure.

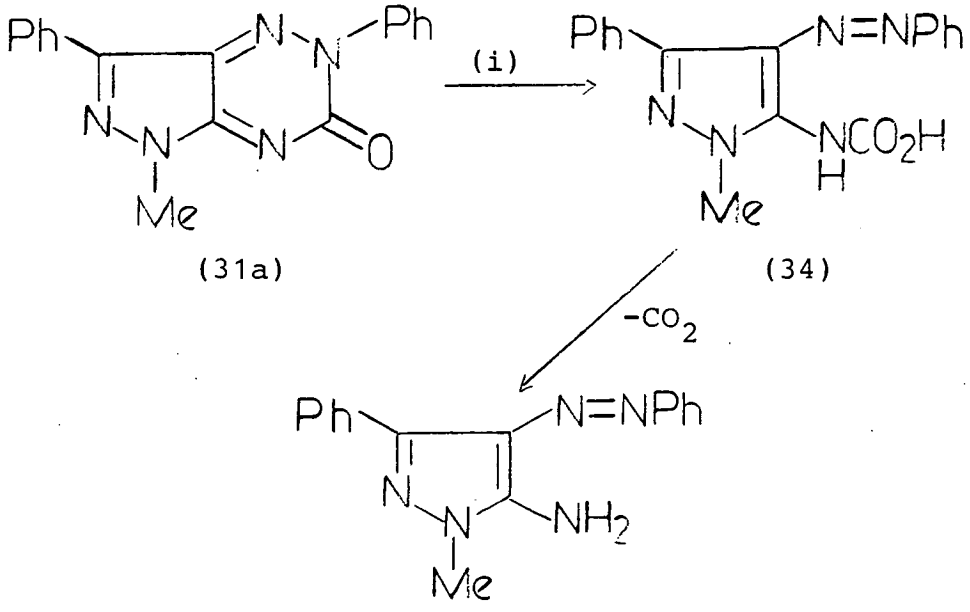
The annulation reaction of this pyrazole derivative (30a) with tosylisocyanate proceeded smoothly and in high yield to give 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) together with toluene-4-sulphonamide isolated in quantitative yield. The product (31) has analytical data and spectroscopic properties consistent with the assigned structure. In particular its i.r. spectrum shows a carbonyl band at 1690 cm^{-1}, and its ^{1}H n.m.r. spectrum exhibits resonances for ten aromatic hydrogen atoms and for the three hydrogen atoms of the NCH_3 group. Significantly no exchangable protons are observed in the ^{1}H n.m.r. spectrum. The ^{13}C n.m.r. spectrum contains the six expected signals for quaternary carbon atoms.



(32) (33)

(i) KOH, EtOH, heat

Scheme 9



(31a) (34) (30a)

(i) NaOH, heat, 5 min.

Scheme 10

Further evidence for the structure of the pyrazolotriazinone derivative (31a) is provided by its behaviour towards alkali. It is known[135] that fused triazinone systems can on treatment with alkali undergo ring-opening to give urethane derivatives as illustrated (Scheme 9) by the reaction of the benzotriazinone derivative (32) with potassium hydroxide to afford the urethane derivative (33). Therefore by analogy the pyrazolotriazinone derivative (31a) should undergo ring-opening in a similar fashion. Indeed brief heating (Scheme 10) of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) with aqueous sodium hydroxide afforded the pyrazole derivative (30a) presumably by initial ring-opening to the carbamic acid (34) followed by loss of carbon dioxide.

The foregoing procedure for the synthesis of the pyrazolotriazinone (31a) was successfully applied (Scheme 8) to the synthesis of the other 5-aryl-1-methyl-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-ones (31b and 31c). Benzoylacetonitrile (28) readily coupled with 4-methylbenzenediazonium chloride to afford the known[136] 2-(4-methylphenylhydrazono)benzoylacetonitrile (29b) in high yield. Similarly the known[135] 2-(4-chlorophenylhydrazono)-benzoylacetonitrile (29c) was readily prepared in good yield by coupling benzoylacetonitrile (28) with 4-chlorobenzenediazonium chloride. Both of the 2-arylhydrazono-benzoylacetonitriles (29b and 29c) gave on reaction with

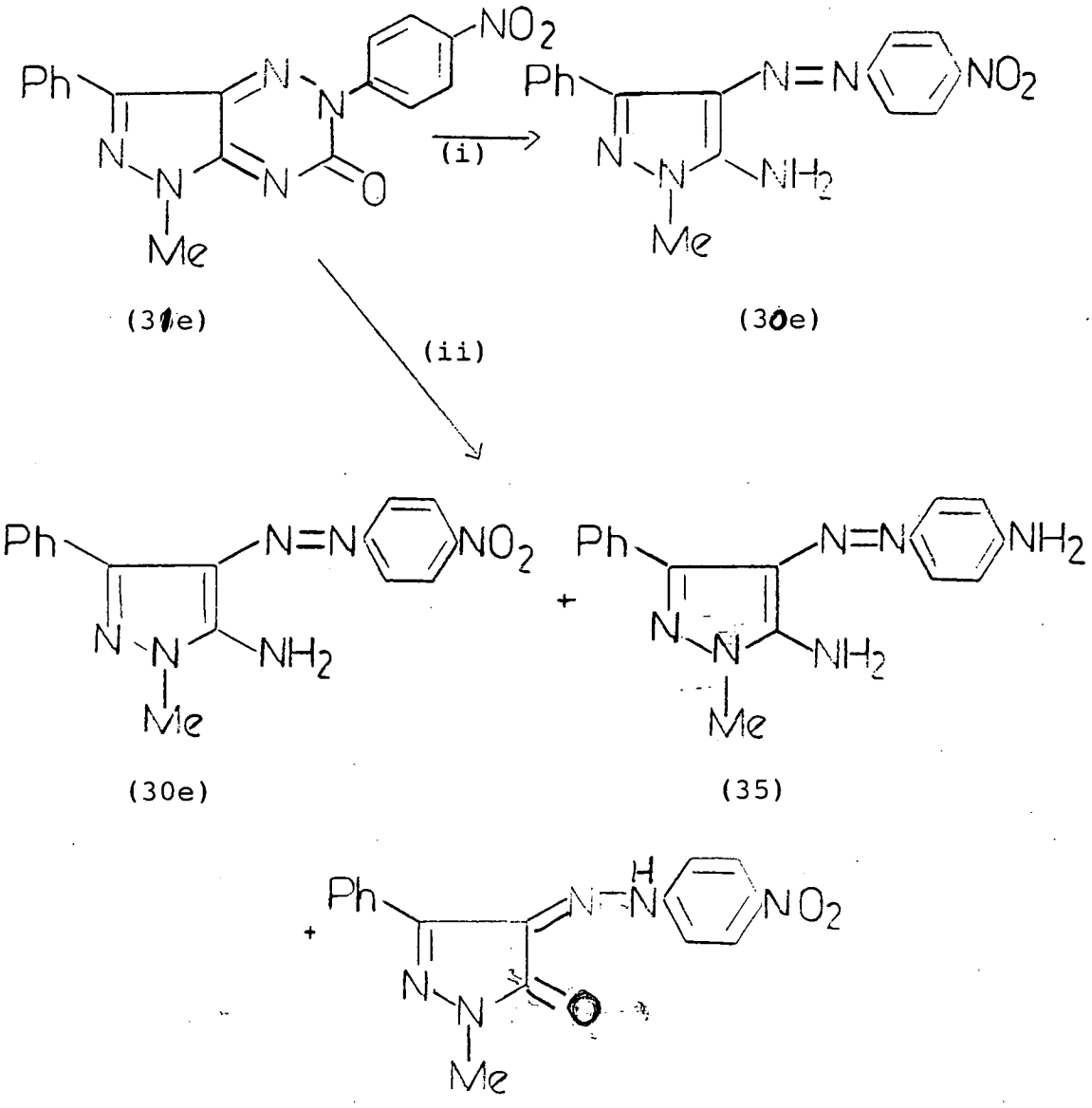
methylhydrazine the expected but previously unknown pyrazole derivatives, 5-amino-1-methyl-4-(4-methylphenylazo)-3-phenylpyrazole (30b) and 5-amino-4-(4-chlorophenylazo)-1-methyl-4-phenylpyrazole (30c), both of which gave combustion analysis and spectroscopic data consistent with the assigned structures. Subsequent reaction (Scheme 8) of the pyrazole derivatives (30b and 30c) with tosyl isocyanate gave as expected the pyrazolotriazinone derivatives (31b and 31c) in good yield. Both of these products (31b and 31c) gave analytical and spectroscopic data in agreement with the assigned structures.

In order to investigate the possibility that substituents in the 4-position of the arylazo grouping of the 5-amino-4-arylazo-1-methyl-3-phenylpyrazoles (30) might affect the course and/or yield of the annulation [(30)→(31)] (Scheme 8) the pyrazole derivatives, 5-amino-4-(4-methoxyphenylazo)-1-methyl-3-phenylpyrazole (30d) and 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) were synthesised. These derivatives (30d and 30e) having a strong electron-donating substituent and a strong electron-withdrawing substituent in the arylazo moiety might exhibit behaviour towards annulation with tosyl isocyanate which would provide information on the course of the latter process.

Coupling (Scheme 8) of benzoylacetonitrile (28) with 4-methoxybenzenediazonium chloride afforded a good yield of the previously unknown 2-(4-methoxyphenylhydrazono)benzoylacetonitrile (29d), which gave analytical and spectroscopic

proporties in agreement with the assigned structure. Similarly the previously unknown 2-(4-nitrophenylhydrazono)-benzoylacetonitrile (29e) was readily accessible by coupling of benzoylacetonitrile (28) with 4-nitrobenzene-diazonium chloride. Again the combustion analysis and spectroscopic properties of this product were fully consistent with the assigned structure. Both of the arylhydrazonobenzoylacetonitrile derivatives (29d and 29e) gave on reaction with methylhydrazine, the expected but previously unknown pyrazole derivatives, 5-amino-4-(4-methoxyphenylazo)-1-methyl-3-phenylpyrazole (30 ml) and 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e). Reaction of both of these pyrazole derivatives (30d and 30e) with tosyl isocyanate gave the corresponding pyrazolo-triazinone derivatives (31d and 31e) in good yield. The structures assigned to the pyrazolotriazinone derivatives (31d and e) were fully confirmed by their combustion analysis and spectroscopic properties. The uniformly good yields of the pyrazolotriazinones (31d and e) demonstrates an apparent lack of substituent effects at the <u>para</u>-position of the arylazo group of the pyrazole starting material on the course of the transformation [(30)→(31)] (Scheme 8).

As has been described earlier (Schemes 9 and 10) the behaviour of the pyrazolotriazinone derivatives (31) towards hydrolytic ring-opening in aqueous alkali can provide confirmatory evidence of their structure. It was

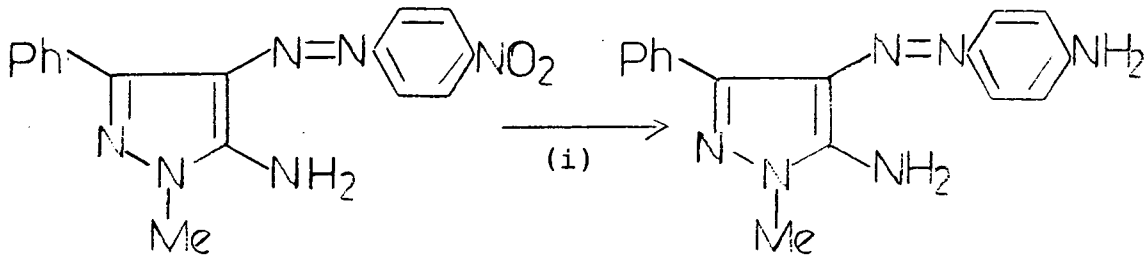


(i) NaOH, heat, 5 min.

(ii) NaOH, heat, 30 min.

Scheme 11

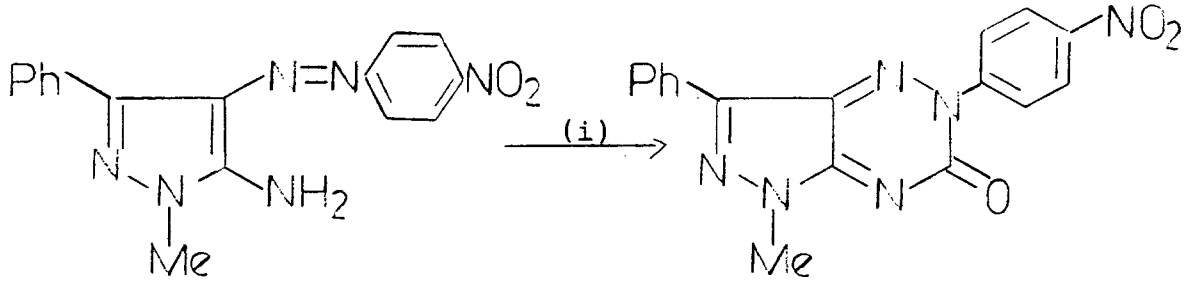
decided to investigate such behaviour in one further case (Scheme 11) namely that of 1-methyl-5-(4-nitrophenylazo)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31e). Brief heating of the pyrazolotriazinone (31e) with sodium hydroxide in aqueous ethane-1,2-diol as expected gave the pyrazole derivative (30e) in high yield. However, longer heating of the pyrazolotriazinone (31e) with sodium hydroxide in aqueous ethane-1,2-diol yielded a variety of products (Scheme 11). 5-Amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) was isolated in moderate yield and identified by comparison with an authentic sample prepared as described previously. A moderate yield of a product formulated as 5-amino-4-(4-aminophenylazo)-1-methyl-3-phenyl pyrazole (35) was also obtained and identified from its combustion analysis and spectroscopic properties. In particular, its i.r. spectrum showed NH absorption attributable to a primary amino group but significantly no absorption, due to a nitro-group. The structure of the (4-aminophenylazo)pyrazole derivative (35) was also supported by its ^1H n.m.r. spectrum which contained characteristic resonances for nine aromatic hydrogen atoms four of which were assignable to a para-substituted phenyl group, three hydrogen atoms corresponding to a NCH_3 group and four exchangable protons. A further product (Scheme 11) obtained in low yield from the prolonged heating of the pyrazolotriazinone (31e) with aqueous sodium hydroxide is tentatively formulated as 1-methyl-4-(4-nitrophenyl)azo-3-phenyl-Δ^2-pyrazolin-5-one (36) on spectroscopic evidence.



(30e) (35)

(i) NaOH, heat, or Fe, CH_3CO_2H, heat

Scheme 12



(30e) (31e)

(i) PhN=C=O, heat

Scheme 13

In particular, it has a parent ion in its mass spectrum at 323 a.m.u. corresponding to the molecular weight of the assigned structure. Also, the i.r. spectrum of the product (36) exhibited carbonyl absorption at 1670 cm^{-1} and nitro group absorption at 1550 and 1345 cm^{-1}.

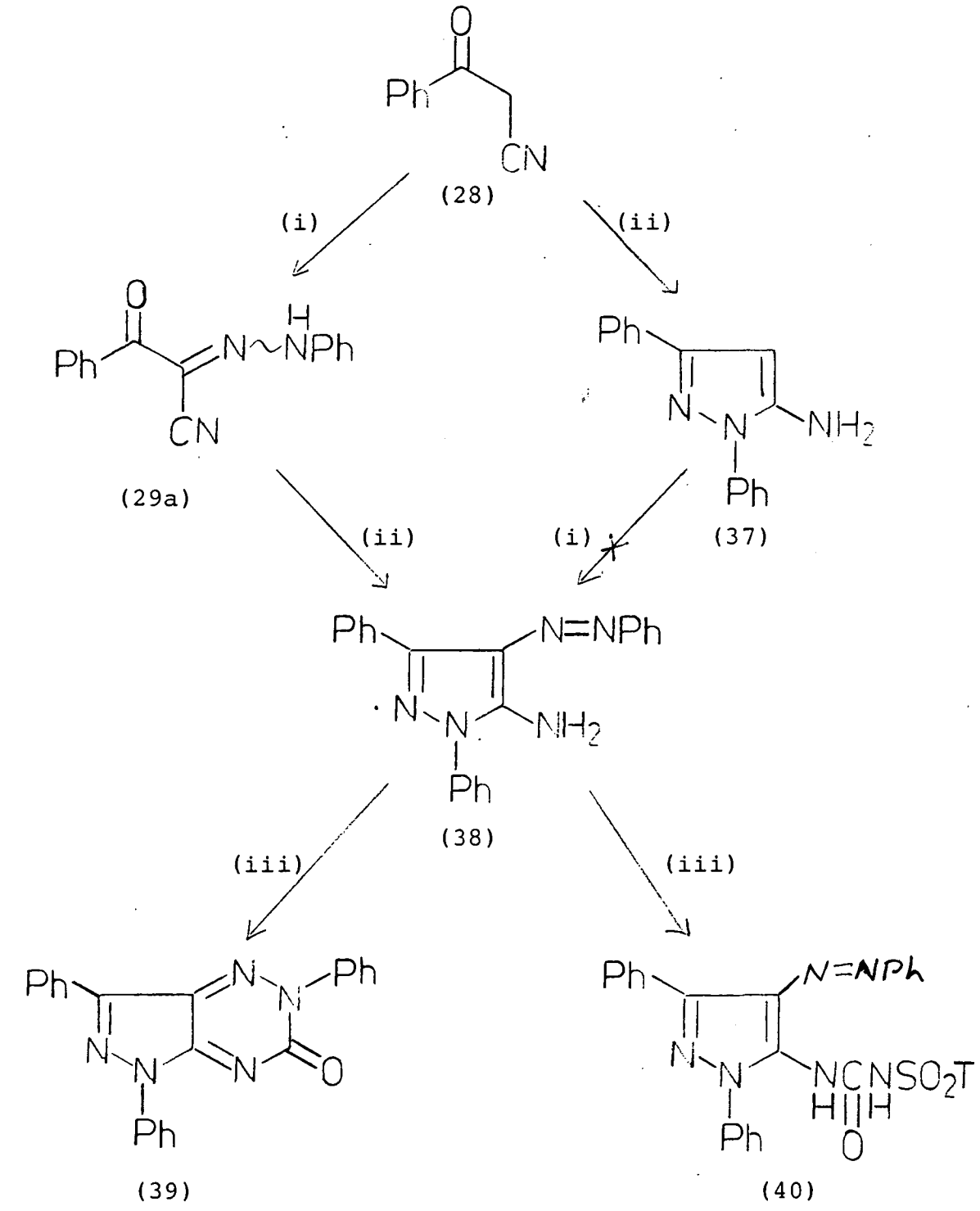
Since brief treatment of the pyrazolotriazinone derivative (31e) with aqueous sodium hydroxide affords only the pyrazole derivative (30e) it would seem reasonable to assume that the other products observed on prolonged treatment of the pyrazolotriazinone (31e) are in fact derived from the pyrazole derivative (30e). In order to investigate this hypothesis, 1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) was heated with sodium hydroxide in aqueous ethane-1,2-diol. It was anticipated that this reaction would give 1-methyl-4-(4-aminophenylazo)-3-phenylpyrazole (35) and the pyrazolinone derivative (36). However, in practice this reaction gave only a good recovery of the unreacted pyrazole (30e). This would suggest that the pyrazole derivative (30e) is not the direct precursor of the pyrazole derivatives (35) and (36) which must be formed by some other route which as yet remains unexplained.

In order to verify the structure of the (4-aminophenylazo)pyrazole (35) it was decided to synthesise it (Scheme 12) by deliberate reduction of the pyrazole derivative (30e) with iron in glacial acetic acid, conditions known[137] to reduce nitro to amino-groups. However reaction of 1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) with iron in

glacial acetic acid failed to give 1-methyl-4-(4-amino-phenylazo)-3-phenylpyrazole (35) only unreacted starting material being recovered in good yield. The resistance of the nitro-substituent in the arylazopyrazole (30e) to reduction is surprising and in turn makes the isolation of the (4-aminophenylazo)pyrazole in the reaction of the pyrazolotriazonone (31e) with aqueous alkali in ethylene glycol even more puzzling.

In further studying the scope of the annulation procedure outlined in Scheme 8 [(30)→(31)] it was decided to investigate the use of other isocyanates, in particular phenyl isocyanate and methyl isocyanate, in this transformation. 1-Methyl-4-(4-nitrophenylazo)-3-phenyl-pyrazole (31e) was arbitrarily chosen for study (Scheme 13) and as anticipated was found to react with phenyl isocyanate to afford a good yield of the pyrazolotriazinone (31e). In contrast, however, the attempted reaction of the nitrophenylazopyrazole (31e) with methyl isocyanate gave only a good recovery of the unreacted starting-material (31e). The failure of this reaction can be attributed to the enhanced volatility of methyl isocyanate and hence its loss from the reaction mixture in the course of the reaction.

In further studying the applicability of the general strategy detailed in Scheme 7 as a route to pyrazolo[3,4-e]-1,2,4-triazine derivatives it was decided to investigate



(i) $PhN_2^+Cl^-$, NaOAc, 0°

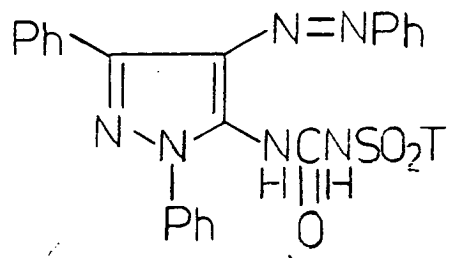
(ii) $PhNHNH_2$, EtOH, heat

(iii) $TSO_2N=C=O$, diglyme, heat

Scheme 14

whether the annulation process [(26)→(27)] would be influenced by the introduction of a bulky substituent at the 1-position of the pyrazole ring. Hence it was decided to investigate (Scheme 14) the annulation of the diphenylpyrazole (38) with tosyl isocyanate to give the pyrazolotriazinone derivative (39). The known[136,138] 5-amino-1,3-diphenyl-4-phenylazopyrazole (38) was readily synthesised by the reaction of the previously described 2-phenylhydrazonobenzoylacetonitrile (29a)[104] with phenylhydrazine. The alternative route from 5-amino-1,3-diphenylpyrazole (37)[139] by coupling with benzenediazonium chloride failed to give the phenylazopyrazole (38) only a good yield of the unreacted pyrazole (37) being obtained.

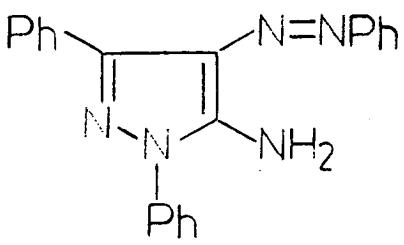
The reaction (Scheme 14) of the pyrazole derivative (38) with tosyl isocyanate failed to give the anticipated pyrazolotriazinone (39), a good yield of 1-(1,3-diphenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl)urea (40) being isolated instead. This compound (40) gave analytical data and spectroscopic properties consistent with the assigned structure. In particular its i.r. spectrum showed NH and carbonyl absorption consistent with the presence of the urea side-chain. Also the ^{1}H n.m.r. spectrum of the urea (40) contained the expected signals for two exchangeable protons as well as proton resonances for nineteen aromatic hydrogen atoms, four of which could be assigned to the 4-tolyl substituent whose presence also accounted for a three-proton singlet due to the 4-methyl substituent. The



(40)

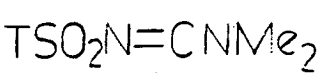
(i)

(ii)

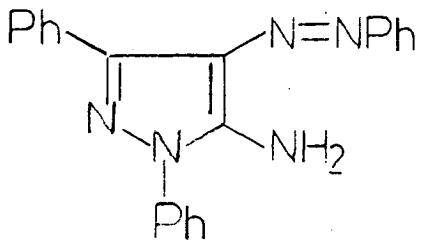


(38)

+

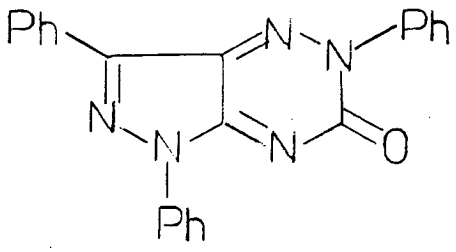


(41)



(38)

+



(39)

(i) $Me_2NCH=O$, heat

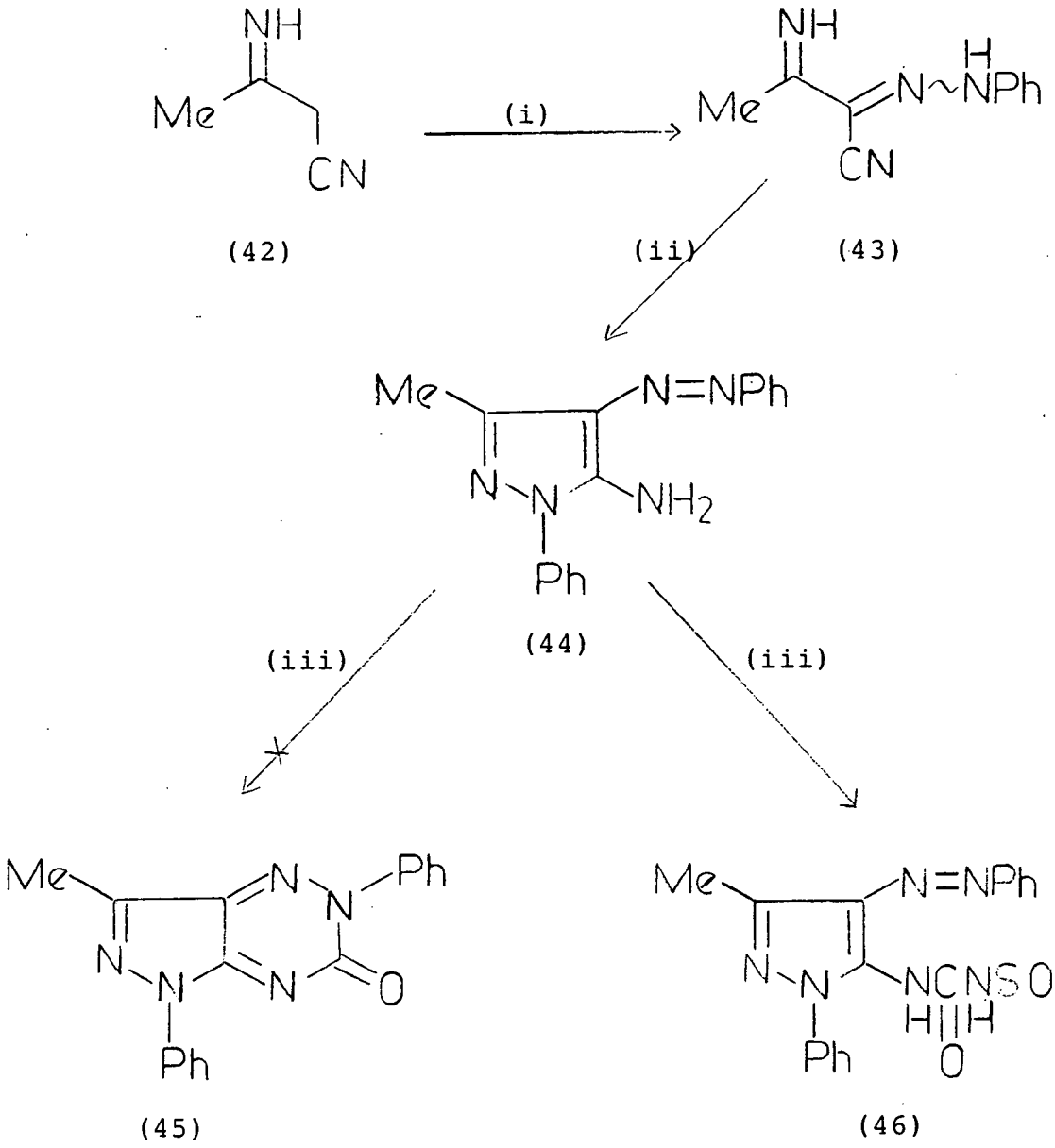
(ii) heat

Scheme 15

^{13}C n.m.r. spectrum of the urea derivative exhibited signals due to the four quaternary carbon atoms in the structure (40).

It has been postulated (see Scheme 2) that urea derivatives of the type (40) could be intermediates in the annulation of ortho-amino-arylazopyrazoles with tosyl isocyanate to give pyrazolo[3,4-e]-1,2,4-triazinones. It was therefore decided (Scheme 15) to investigate the possible cyclisation of the urea (40) under forcing conditions. In practice, heating the urea (40) in dimethylformamide yielded 5-amino-1,3-diphenyl-4-phenylazopyrazole (38) and 1,1-dimethyl-3-(toluene-4-sulphonyl)-formamidine (41). The latter compound (41) gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular, its ^{1}H n.m.r. spectrum contained resonances for four aromatic protons assignable to a 4-tolyl residue, a one proton singlet due to a CH group and three three-proton singlets due to the three methyl groups.

In a further attempt to induce the urea derivative (40) to undergo cyclisation it was heated at 200° under reduced pressure in a Kugelrohr apparatus. However, this procedure resulted only in the isolation of some toluene-4-sulphonamide together with the unreacted pyrazolylurea (40). However, the pyrazolylurea (40) was eventually successfully cyclised to the pyrazolotriazinone derivative (39) by heating it at 245° (Woods metal bath) under reduced pressure. 5-Amino-1,3-diphenyl-4-phenylazopyrazole (38) was also formed



(i) $PhN_2^+Cl^-$, NaOHc, 0°

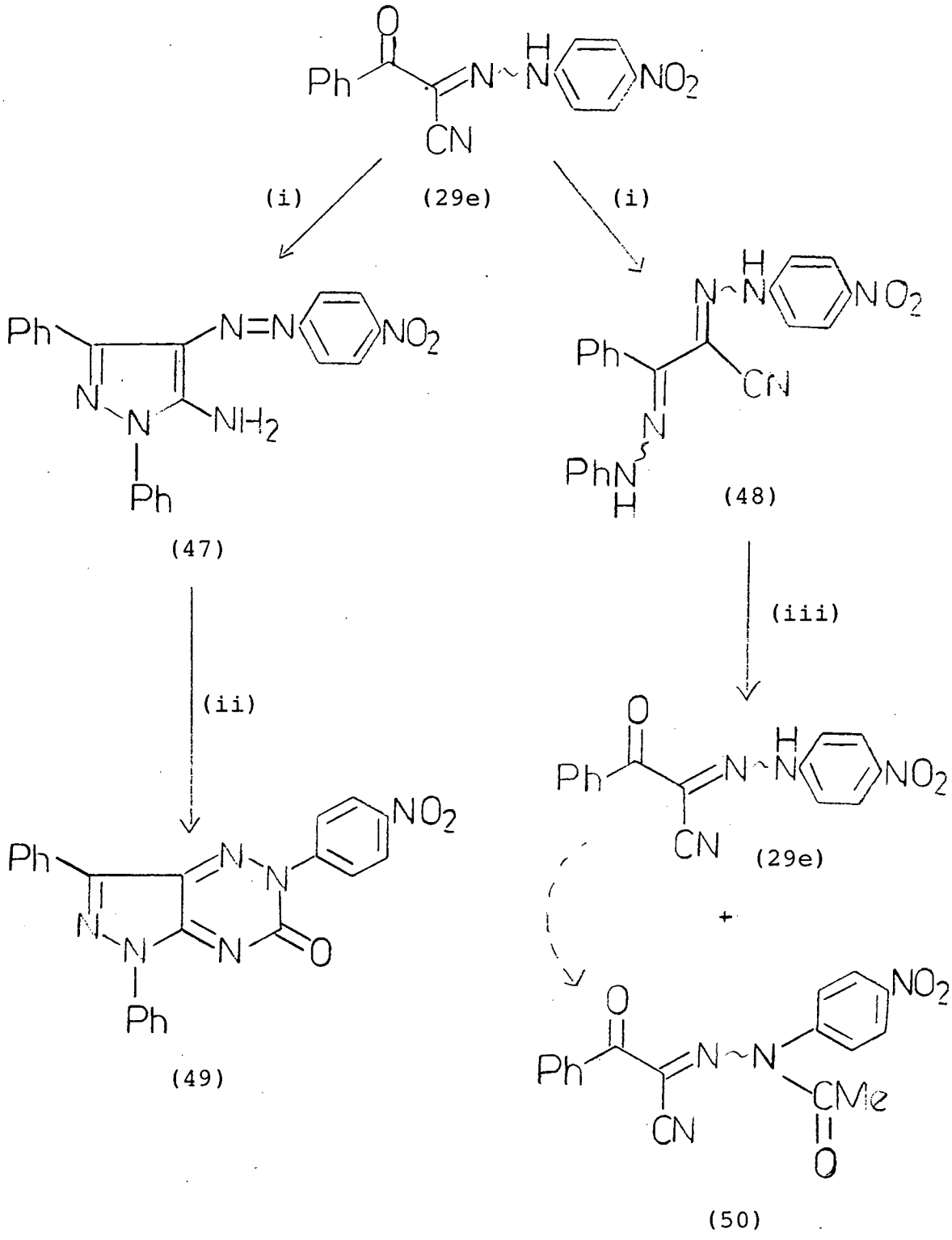
(ii) $PhNHNH_2$, EtOH, reflux

(iii) $TSO_2N=C=O$, diglyme, reflux

Scheme 16

in moderate yield as a by-product in this reaction. The pyrazolotriazinone (39) gave accurate mass data and showed spectroscopic properties consistent with the assigned structure. Of particular note is the presence in its i.r. spectrum, of a high frequency carbonyl absorption at 1720 cm^{-1} due to the triazinone carbonyl substituent.

The observation that reaction (Scheme 15) of the pyrazole derivative (38) with tosyl isocyanate does not directly yield the pyrazolotriazinone (39) but gives the intermediate urea adduct (40) instead may be explained in terms of the steric effect of the bulky phenyl group at the 1-position of the pyrazole ring. In order to further test this hypothesis it was decided to investigate the reaction (Scheme 16) of the pyrazole derivative (44) with tosyl isocyanate. The known[140] 5-amino-3-methyl-1-phenyl-4-phenylazopyrazole (44) was readily prepared starting with β-iminocrotononitrile (42) which coupled smoothly with benzenediazonium chloride to yield the known[141] 3-imino-2-phenylhydrazonobutanenitrile (43). The phenylhydrazonobutanenitrile (43) reacted readily with phenylhydrazine to afford 5-amino-3-methyl-1-phenyl-4-phenylazopyrazole (44) in good yield. Reaction (Scheme 16) of this pyrazole derivative (44) with tosyl isocyanate gave 1-(3-methyl-1-phenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl)urea (46) with no evidence for the formation of the pyrazolotriazinone derivative (45).



(i) $PhNHNH_2$, EtOH, heat

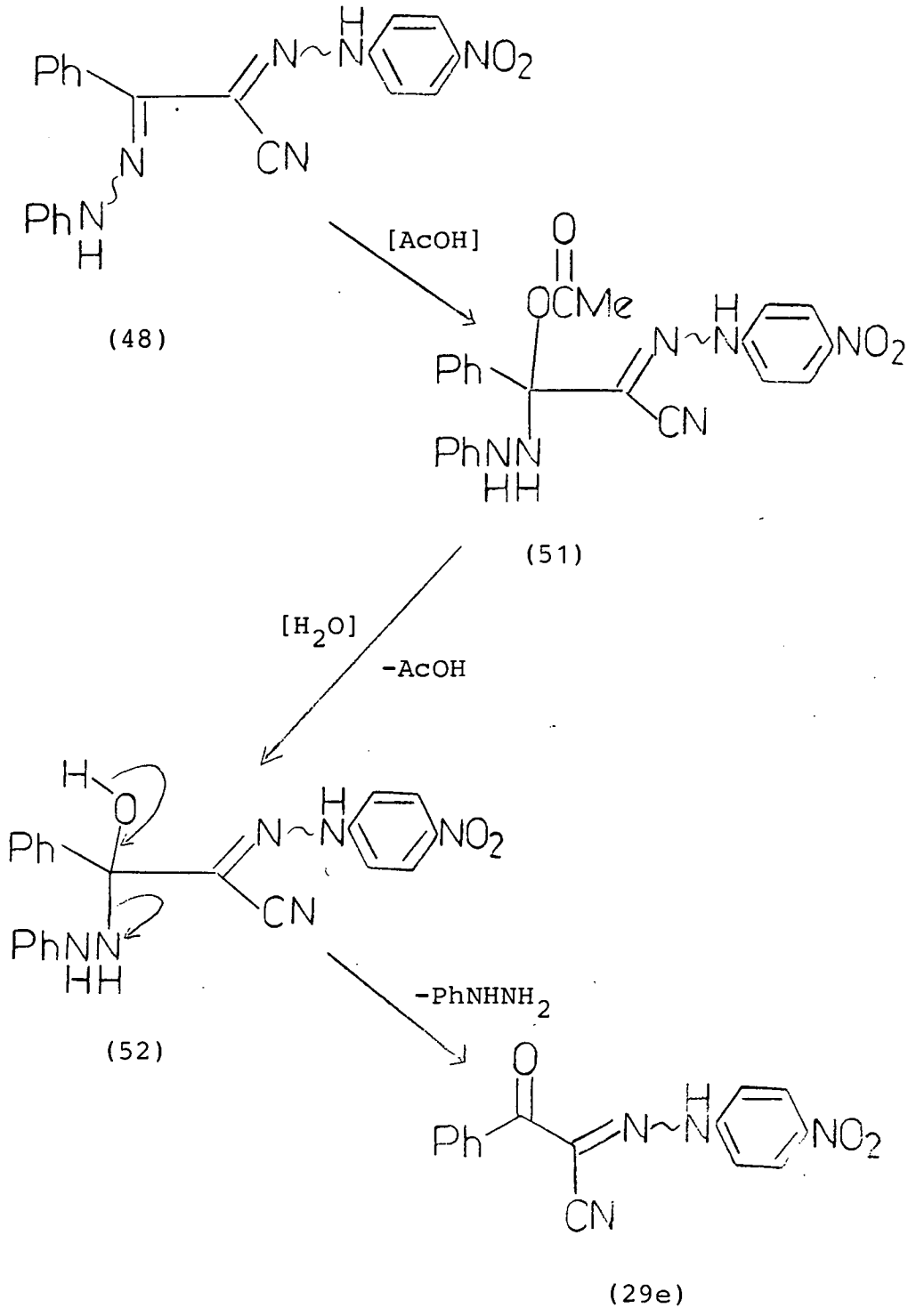
(ii) $TSO_2N=C=O$, diglyme, heat

(iii) Ac_2O, heat

Scheme 17

This observation supports the hypothesis that a bulky group in the 1-position of the pyrazole ring of ortho-amino-arylazopyrazoles sterically hinders tosyl isocyanate annulation to the corresponding pyrazolotriazinone derivative.

As shall be discussed later, there is good evidence that the tosyl isocyanate annulation of ortho-amino-arylazapyrazoles to pyrazolotriazinones proceeds via the intermediacy of toluene-4-sulphonylurea adducts which thermally eliminate toluene-4-sulphonamide to afford the corresponding pyrazolyl isocyanates. Electrocyclisation of the latter then affords the observed pyrazolotriazinone products. It could be argued therefore that an electron-withdrawing substituent at either the 1- or 4-position of the pyrazole ring by weakening the pyrazolyl substituted NH bond of the urea intermediate should promote elimination of toluene-4-sulphonamide to give the pyrazolyl isocyanate and hence the ultimate formation of the pyrazolotriazinone product. On the basis of this assumption it was decided (Scheme 17 to investigate the tosyl isocyanate annulation of the pyrazole derivative (47) having an electron-withdrawing substituent in the 4-position of the pyrazole ring. It was anticipated that the pyrazole derivative (47) would be readily available, by analogy with other ortho-amino-arylazo pyrazole synthesis [see Scheme 14 (29a)→(38)] from the phenylhydrazonoacetonitrile derivative (29e), whose synthesis has been described earlier (see Scheme 8).

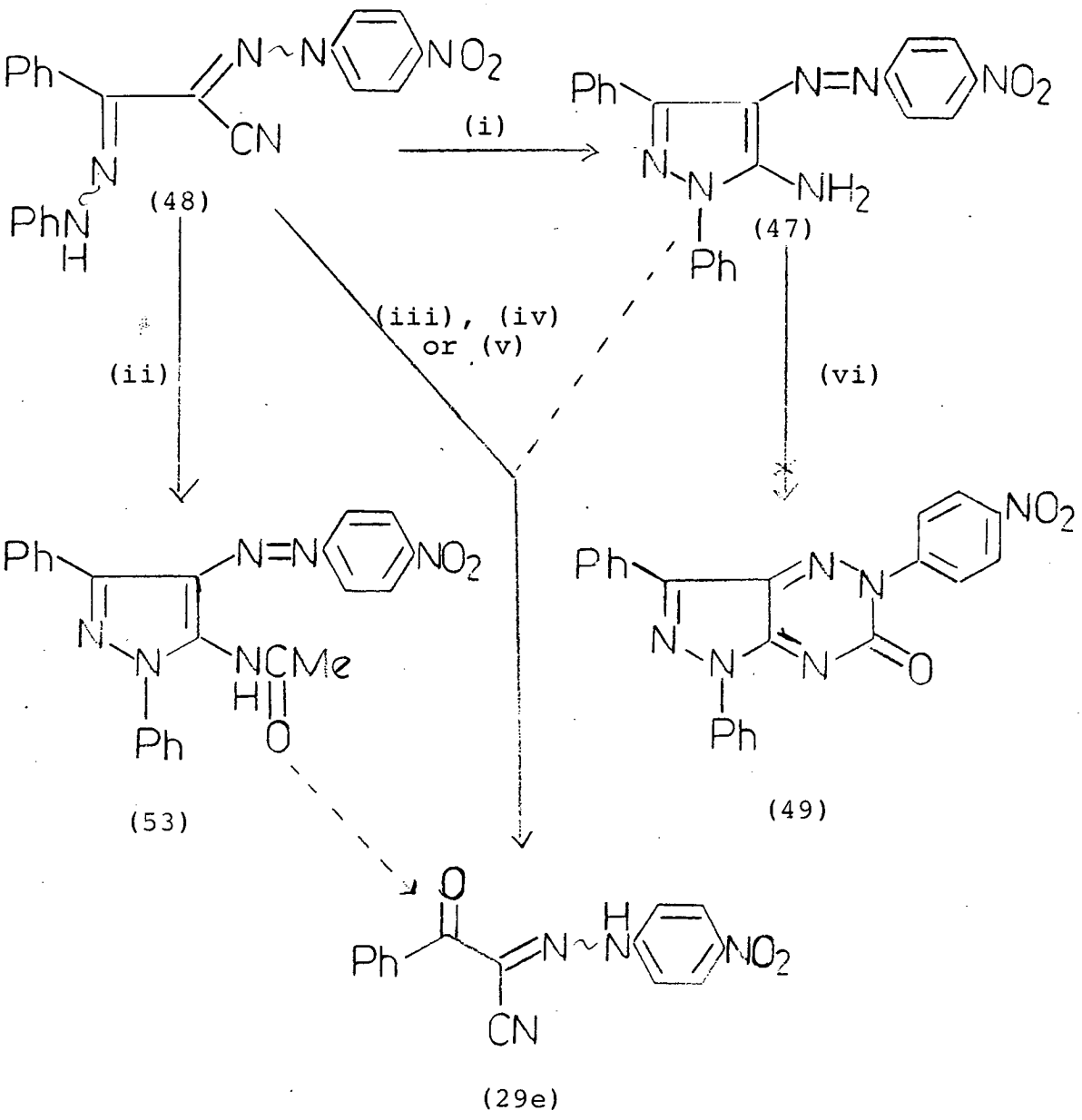

Ph
N
CN
PhN
H
N
H
NO2
(48)
[AcOH]
O
OCMe
Ph
PhNN
HH
N
H
N
NO2
CN
(51)
[H2O]
-AcOH
H
O
Ph
PhNN
HH
N
H
N
NO2
CN
(52)
-PhNHNH2
O
Ph
N
H
N
NO2
CN
(29e)

Scheme 18

However, in practice, reaction of 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29e) with phenylhydrazine gave a good yield of 2-(4-nitrophenylhydrazono)benzoylacetonitrile phenylhydrazone (48). This product gave analytical data and showed spectroscopic properties consistent with the assigned structure (48). Of particular note is the presence of a nitrile absorption at 2205 cm^{-1} in the i.r. spectrum of the bishydrazone (48).

In order to further substantiate the structure of the bishydrazone (48) it was decided to attempt its conversion into an acetyl derivative. However, unexpectedly, reaction of 2-(4-nitrophenylhydrazono)benzoylacetonitrile phenylhydrazone (48) with acetic anhydride gave 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29e) and 2-(N-acetyl-4-nitrophenylhydrazono)benzoylacetonitrile (50). The latter product is presumably formed by acetylation of the former. The N-acetyl product (50) gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular, its i.r. spectrum contains a carbonyl band at 1715 cm^{-1} but lacks cyano-absorption. The lack of cyano absorption in the i.r. spectrum of the pyrazole derivative (50) can be explained in terms of conjugation of the nitrile and "quenching" of the nitrile band by the adjacent carbonyl group.[142]

The formation of the hydrazonoacetonitrile (29e) from 2-(4-nitrophenylhydrazono)benzoylacetonitrile phenylhydrazone (48) is tentatively postulated to occur (Scheme 18) by the reaction of the bishydrazone derivative (48)



(i) AcOH, conc. HCl, heat 1h. or NaOEt, EtOH, heat, 1h.

(ii) AcOH, heat, 18 h.

(iii) AcOH, heat, 3 days

(iv) AcOH, conc. HCl, heat, 18 h.

(v) Trigol, conc. HCl, heat, 3 h.

(vi) $TSO_2N=C=O$, diglyme, heat

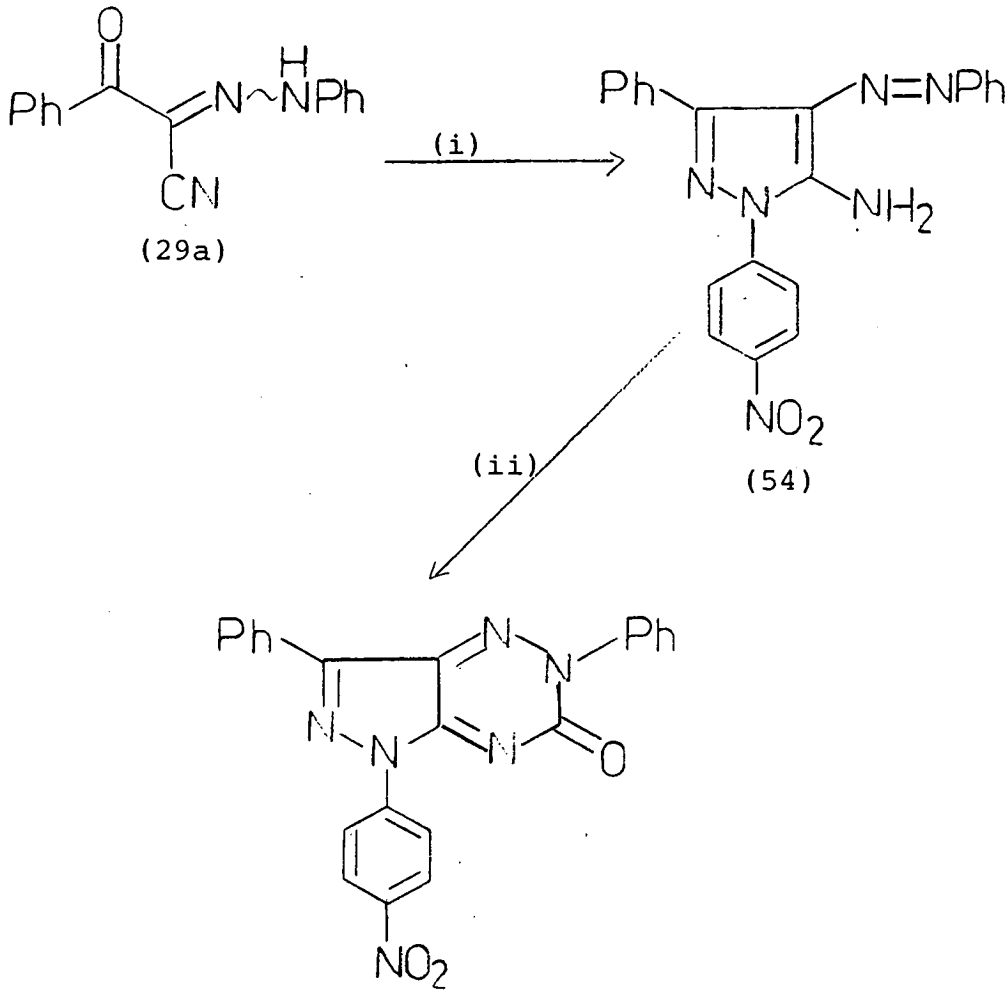
Scheme 19

with acetic acid (a small amount of which can be assumed to be present in the acetic anhydride) to give the intermediate (51). Hydrolysis of the latter followed by elimination of phenylhydrazine from the resulting hydroxy-compound (52) then accounts for the formation of the arylhydrazonobenzoylacetanitrile (29e).

In an attempt to induce the cyclisation (Scheme 19) of the bishydrazone derivative (48) to give the pyrazole (47) it was heated in acetic acid. Heating for 18 h. gave together with the unreacted bishydrazone (48), a moderate yield of 5-acetamido-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (53). This latter product (53) gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular its i.r. spectrum showed bands at 3220 and 1685 cm^{-1} attributable to the NH and carbonyl absorption of an amide substituent. The ^1H n.m.r. spectrum of the pyrazole derivative (53) showed resonances for 28 aromatic hydrogen atoms, eight of which are assignable to a para-substituted phenyl substituent. The ^1H n.m.r. spectrum of the pyrazole derivative (53) also contained a three-proton singlet due to the acetyl methyl substituent and signals for two exchangeable protons. As can be seen the ^1H n.m.r. spectrum of the contains twice the number of hydrogen atoms expected and this may indicate the presence of two conformational isomers.

In an attempt to increase the yield of the transformation [(48)→(53)] the bishydrazone (48) was heated in acetic acid for 3 days. However, none of the expected pyrazole derivative (53) was obtained, a quantitative yield of 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29e) being isolated. Presumably this latter product (29e) is formed via the previously obtained 5-acetamido-1,3-diphenyl-4(4-nitrophenylazo)pyrazole (53) by an as yet uncertain mechanism. It is possible that the acetamido-pyrazole derivative (53) is also involved as an intermediate in the conversion of the bishydrazone (48) by acetic anhydride into the arylhydrazonobenzoylacetonitrile derivative (29e) (see Schemes 17 and 18). However, further evidence is required before any definite mechanistic conclusion can be drawn regarding the course of this reaction.

In a further attempt to obtain (Scheme 19) the required pyrazole derivative (47), the bishydrazone (48) was heated in acetic acid containing concentrated hydrochloric acid. These conditions afforded a moderate yield of 5-amino-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (47) as well as a moderate yield of 2-(4-nitrophenylhydrazono)-benzoylacetonitrile (29e). The product (47) gave a combustion analysis and exhibited spectroscopic properties consistent with the assigned structure. In particular its ^{1}H n.m.r. spectrum contained resonances for 14 aromatic hydrogen atoms and two exchangable protons. Formation of the 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29e) from the bishydrazone (48) by heating with hydrochloric



(i) $4\text{-}NO_2C_6H_4NHNH_2$, TSO_3H, MeOH, reflux

(ii) $TSO_2N{=}C{=}O$, diglyme, reflux

Scheme 20

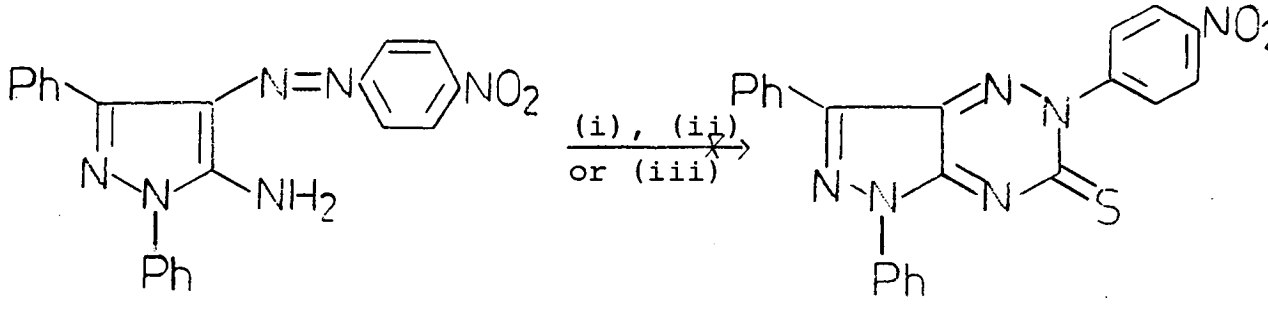
acid in acetic acid presumably occurs via hydrolytic ring-opening of the pyrazole derivative (47). This is supported by the quantitative formation of the benzoylacetonitrile derivative (29e) from 2-(4-nitrophenylhydrazono)benzoyl-acetonitrile phenylhydrazone (48) by prolonged heating with concentrated hydrochloric acid in acetic acid or trigol.

In an attempt to increase the yield of the transformation [Scheme 19; (48)→(47)] the bishydrazone (48) was heated under reflux with ethanolic sodium ethoxide. However a poorer yield of the desired pyrazole derivative (47) was obtained. Attempts to improve the yield of this reaction by increasing the reaction time were unsuccessful. Disappointingly the reaction (Scheme 19) of 5-amino-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (47) with tosyl isocyanate failed to give the expected pyrazolotriazinone derivative (49), a good yield of starting material being recovered.

Further to the previously stated hypothesis that an electron-withdrawing substitutent at the 1-position of the pyrazole ring would enhance the formation of a pyrazolyl-isocyanate intermediate and therefore the tosyl isocyanate promoted cyclisation of ortho-amino-arylazopyrazoles to the corresponding pyrazolotriazinones, it was decided to investigate the synthesis (Scheme 20) of 5-amino-1-(4-nitrophenyl)-3-phenyl-4-phenylazopyrazole (54) and its subsequent transformation by tosyl isocyanate into the pyrazolo[3,4-e]-1,2,4-triazinone (55). It was anticipated that 5-amino-1-

(4-nitrophenyl)-3-phenyl-4-phenylazopyrazole (54) would be readily accessible from 2-phenylhydrazonobenzoylacetonitrile (29a) by its reaction with 4-nitrophenylhydrazine. The reaction of the benzoylacetonitrile derivative (29a) with 4-nitrophenylhydrazine gave only quantitative yields of the unreacted starting-materials even when catalysed with concentrated hydrochloric acid. However when this reaction was catalysed by toluene-4-sulphonic acid a low yield of 5-amino-1-(4-nitrophenyl-3-phenyl-4-phenylazopyrazole (54) was obtained. This product (54) gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular its ^{1}H n.m.r. spectrum contains resonances due to fourteen aromatic hydrogen atoms and two exchangeable protons while its ^{13}C n.m.r. spectrum contains the expected signals for seven quaternary carbon atoms.

In contrast to the reaction of 5-amino-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (47) with tosyl isocyanate which failed to give the expected pyrazolotriazinone derivative (49), (see Scheme 19), 5-amino-1-(4-nitrophenyl)-3-phenyl-4-phenylazopyrazole (54) reacted smoothly with tosyl isocyanate to give 3,5-diphenyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (55) in quantitative yield. This compound (55) gave analytical and mass spectral data in agreement with the assigned structure. The i.r. spectrum of the pyrazolotriazinone (55) has a carbonyl band at 1685 cm^{-1}. No n.m.r. data could be obtained for the pyrazolotriazinone derivative (55) due to its insolubility in common n.m.r. solvents. It can be



(30e) (56)

(i) PhN=C=S, diglyme, reflux

(ii) CS_2, $MeOCH_2CH_2OMe$, reflux

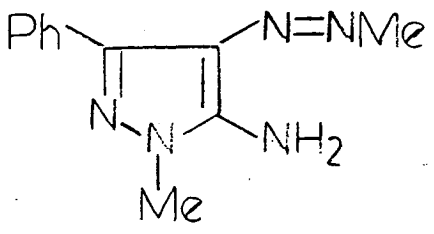
(iii) Cl_2CS, $MeOCH_2CH_2OMe$, room temperature

Scheme 21

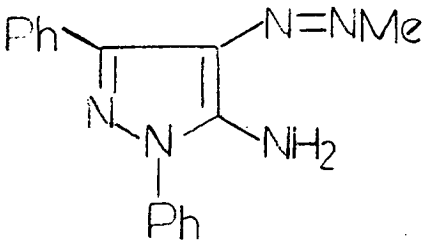
concluded from the ready formation of the pyrazolotriazinone derivative (55) that an electron-withdrawing substituent at the 1-position of the pyrazole ring in ortho-amino-arylazopyrazoles does enhance their tosyl isocyanate promoted cyclisation to pyrazolotriazinone derivatives. However an electron-withdrawing substituent at the 4-position seems to have no effect or indeed a suppressive effect upon this type of cyclisation.

In further studying, the scope of annulation reactions of the type [Scheme 7; (26)→(27)] it was decided to investigate whether ortho-amino-arylazopyrazoles (26) would undergo a similar transformation to yield the corresponding pyrazolotriazinethione, as illustrated (Scheme 21) by the reaction of the pyrazole derivative (30e) with phenyl isothiocyante to give the hoped-for product (56). This reaction however failed to give the anticipated pyrazolotriazinethione derivative (56) only a moderate yield of the unreacted starting pyrazole (30e) being isolated.

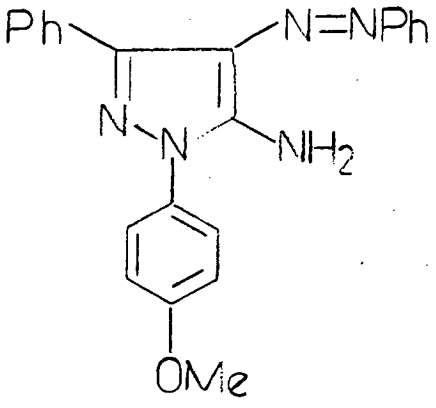
Assuming that the transformation [(30e)→(56)] involves a similar mechanism to that of the transformations [Scheme 7; (26)→(27)] as discussed later an isothiocyanate intermediate would be involved. It was therefore hoped that known conditions for the conversion of amino groups into isothiocyanates, such as reaction with carbon disulphide[143] or thiophosgene[144], when applied (Scheme 21), to the pyrazole derivate (30e) might afford the pyrazolotriazine-thione derivative (56). However, in practice, the attempted



(57)



(58)

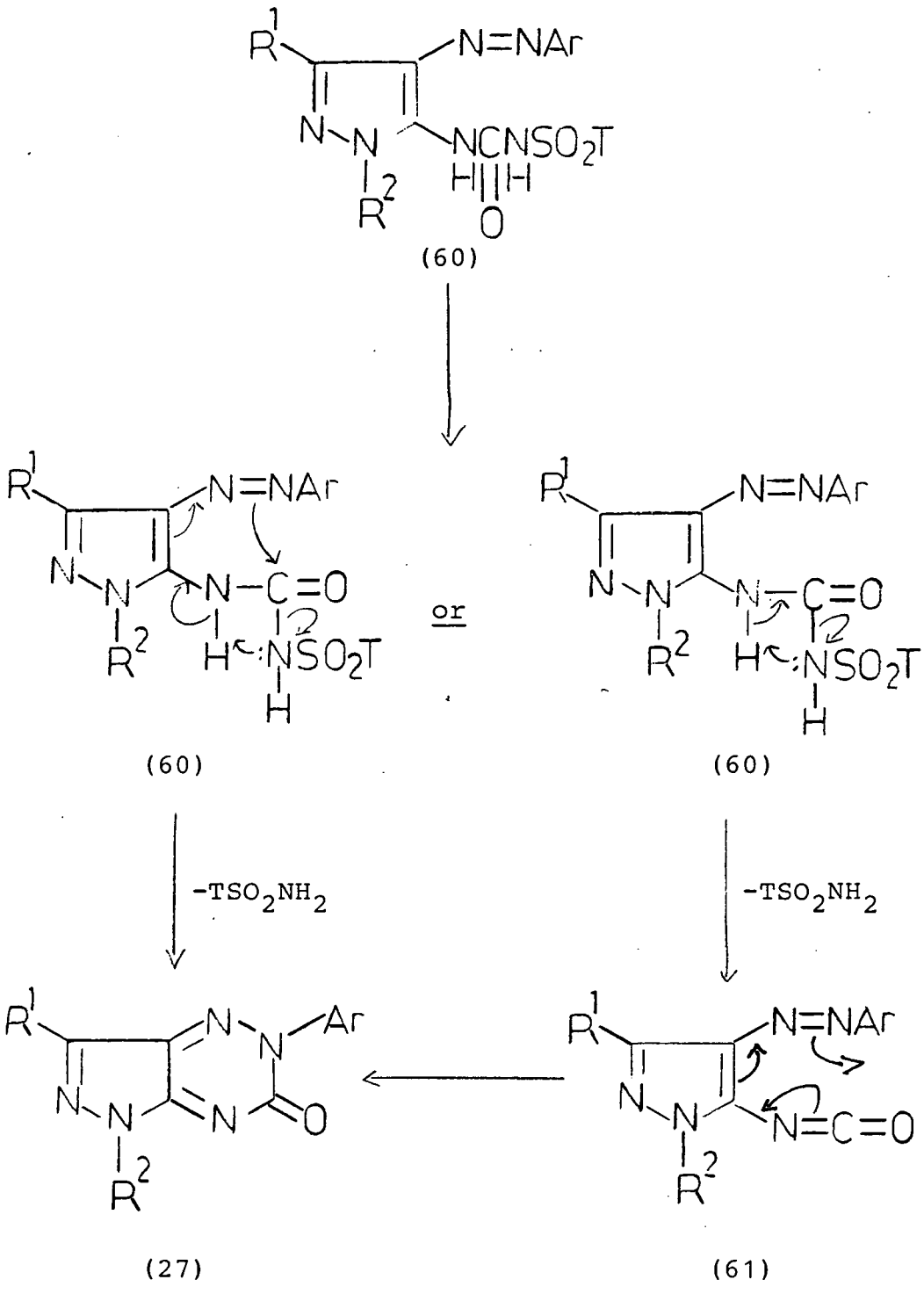


(59)

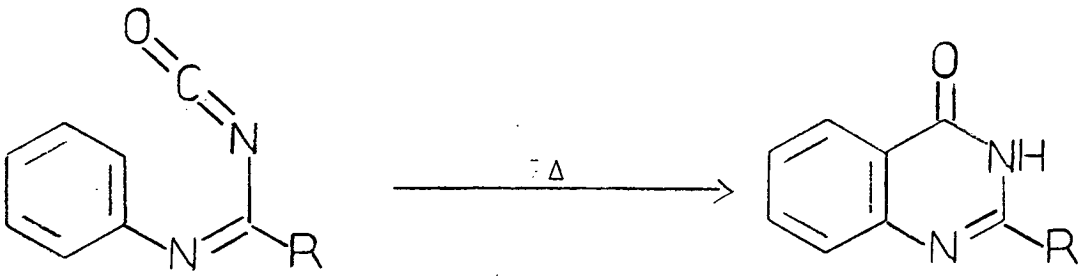
Scheme 22

reaction of the pyrazole derivative (30e) with either carbon disulphide or thiophosgene gave only high recoveries of the unreacted starting material.

In conclusion, in this section it has been shown that 5-amino-4-arylazopyrazoles can be converted into the potentially biologically active pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-ones by reaction with tosyl isocyanate, a previously little investigated process. It has also been shown that this annulation reaction of 5-amino-4-arylazopyrazoles to pyrazolotriazinones is influenced by steric and electronic effects of substituents on the pyrazole ring, particularly at the 1- and 4-positions. Further studies in this area are required and it is suggested that such studies should extend the presently described initial investigations of steric and electronic effects involved in the annulation of 5-amino-4-arylazopyrazoles with tosyl isocyanate. In particular (Scheme 22) the pyrazole derivatives (57) and (58) might provide further information on steric effects while the study of the tosyl isocyanate annulation of the pyrazole derivative (59) might provide information regarding the inhibiting effect of an electron-donating substituent at the 1-position of the pyrazole.

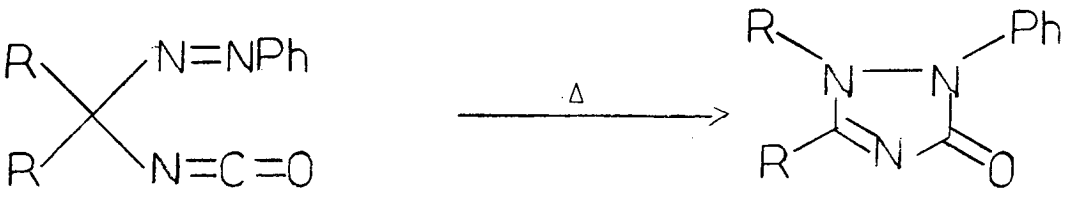


Scheme 23



(62) (63)

Scheme 24



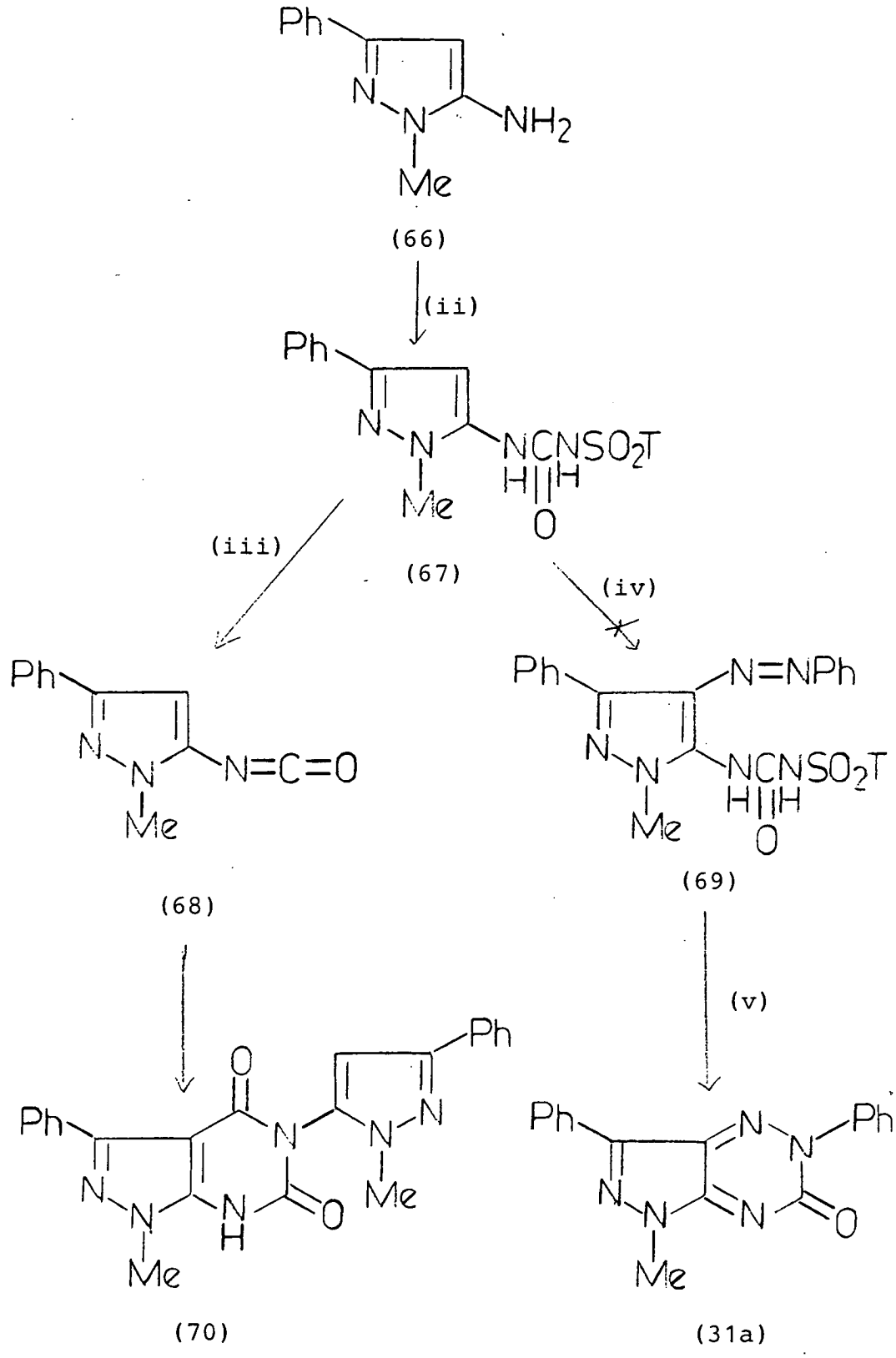
(64) (65)

Scheme 25

3.2.2 Investigations of the Mechanism of the Annulation of 5-Amino-4-arylazopyrazoles with Tosyl Isocyanate

As described earlier (see Scheme 2) there appear to be two plausible mechanistic pathways for the formation of 1,2,4-triazinones (7) from ortho-amino-azo derivatives (3) by reaction of such derivatives with tosyl isocyanate. Both mechanisms involve the urea adduct (4) as a common intermediate. This section describes studies on the elucidation of the precise course of the transformation of the urea adduct into the triazinone product in the case of the conversion of 5-amino-4-arylazopyrazoles into pyrazolo-[3,4-e]-1,2,4-triazinones as illustrated (Scheme 23) by the two mechanistic pathways from the pyrazolylurea adduct (60) to the pyrazolotriazinone (23). Firstly, by a concerted process involving loss of toluene-4-sulphonamide and cyclisation to yield the pyrazolotriazinone (27). Secondly, by a stepwise process involving initial loss of toluene-4-sulphonamide to give an isocyanate derivative (61) which gives the pyrazolotriazinone (27) by electro-cyclisation.

The former mechanistic pathway appears to have no literature precedent, however the latter pathway involving the isocyanate intermediate has two notable precedents. Firstly,[145,146] (Scheme 24) in the synthesis of ~~quinoxalines~~ quinazolines (63) for which these authors cite an isocyanate intermediate (62). Secondly[147] (Scheme 25) in which the isocyanate (64) is converted thermally into the 1,2,4-triazole derivative (65).



(i) $TSO_2N=C=O$, diglyme, heat

(ii) $TSO_2N=C=O$, $MeOCH_2CH_2OMe$, room temp.

(iii) diglyme, heat

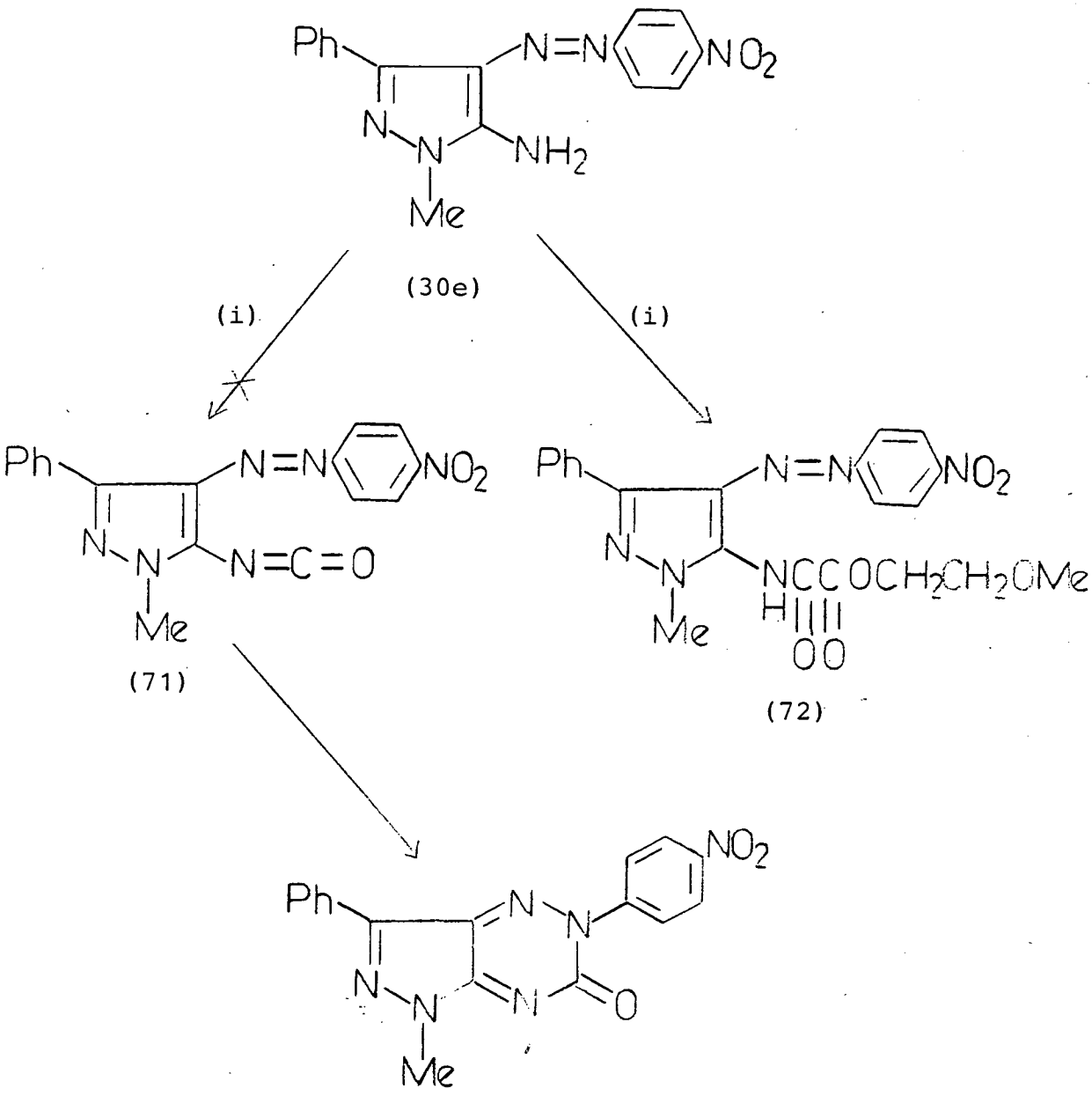
(iv) $PhN_2^+Cl^-$, NaOAc, 0°

(v) heat

Scheme 26

The remainder of this section shall be concerned with the presentation of evidence to support the latter mechanistic pathway. That is that the conversion of the urea adduct (60) in Scheme 23 proceeds via isocyanate intermediate (61) to give the pyrazolotriazinone (27).

In an attempt to study the cyclisation process (Scheme 26) of the urea adduct (69) to the pyrazolotriazinone (31a) the synthesis of this urea (69) was undertaken. As was observed earlier (see Scheme 8) reaction of the 5-amino-4-arylazopyrazole (30a) with tosyl isocyanate afforded the pyrazolotriazinone (31a) directly with none of the urea (69) being isolated. Therefore, it was decided to employ the alternative synthetic route (Scheme 26) to this urea (69) from the known[134] 5-amino-1-methyl-3-phenylpyrazole (66) which was anticipated to afford 1-(1-methyl-3-phenylpyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (67) by treatment with tosyl isocyanate. Subsequently, this urea derivative (67) was expected to yield on coupling with benzenediazonium chloride the desired urea derivative (69). However, treatment of 5-amino-1-methyl-3-phenylpyrazole (66) with tosyl isocyanate and heat gave only a small amount of the pyrazolo[3,4-d]pyrimidinedione (70), no other identifiable material being isolated. This product (70) has accurate mass spectral data consistent with the assigned structure and contains two carbonyl absorptions in its i.r. spectrum at 1730 and 1680 cm^{-1}. This product is also formed by the thermolysis (Scheme 26) of the pyrazolylurea derivative (67), this urea (67) being formed by



(i) $Cl-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-Cl$, $MeOCH_2CH_2OMe$, heat

Scheme 27

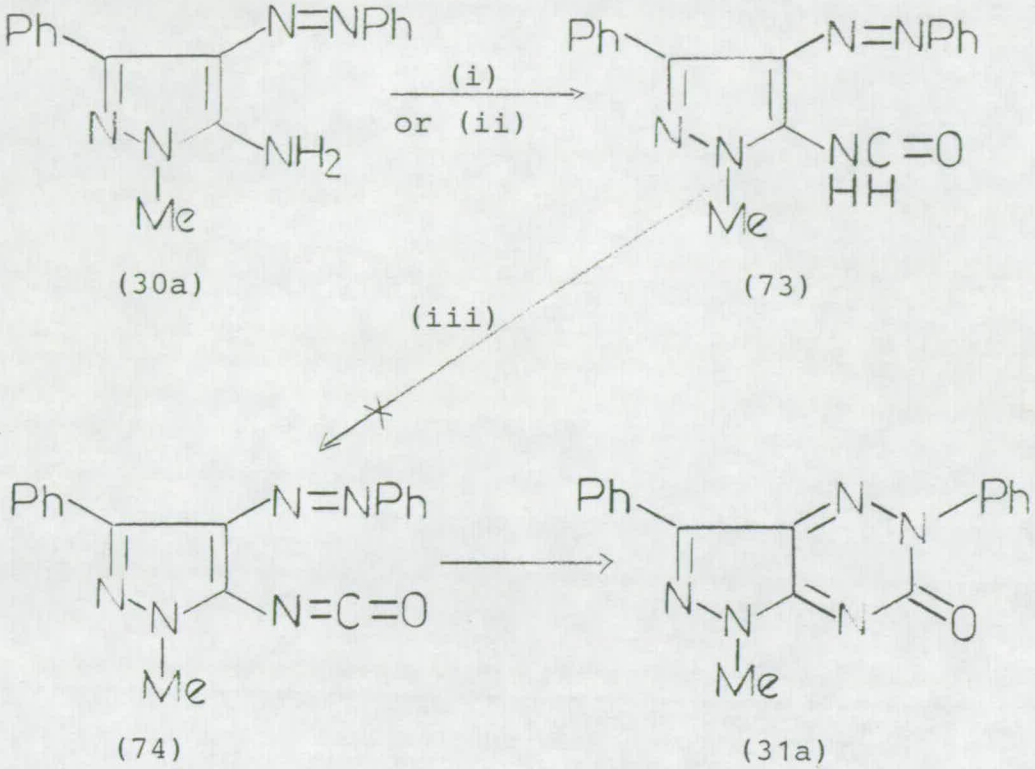
reaction of 5-amino-1-methyl-3-phenylpyrazole (66) with tosyl isocyanate at room temperature. This product (67) gave accurate mass spectral data and other spectroscopic data consistent with the assigned structure. In particular, the i.r. spectrum contained amide NH absorption at 3315 and 3305 cm^{-1} supported by a carbonyl band at 1680 cm^{-1}. The ^1H n.m.r. spectrum of this product (67) contained resonances for nine aromatic hydrogen atoms, two signals for the NCH_3 group and the tolyl CH_3 group and a characteristic pyrazole CH resonance.

Disappointingly, reaction of this pyrazolylurea (67) with benzene diazonium chloride failed to give the desired pyrazole derivative (69) a high yield of starting material being recovered. However, the evidence of formation of the pyrazolo[3,4-d]pyrimidinedione suggests that this is formed via the isocyanate derivative (68), which by reaction with itself gives the product (70).

Conditions were now applied to 5-amino-4-arylazo-pyrazoles that were known to convert amines into isocyanates and hence by the isolation of either the isocyanate or the pyrazolotriazinone give further evidence that such isocyanate derivatives were involved in the annulation of 5-amino-4-arylazopyrazoles with tosyl isocyanate. It is known[148] that amines can be converted to isocyanates by their reaction with oxalyl chloride. Therefore this was applied to 5-amino-4-arylazopyrazoles as illustrated (Scheme 27) by the reaction of the pyrazole derivative (30e) with oxalyl

chloride. However, none of the expected isocyanate derivative (71) or the pyrazolotriazinone (31e) were observed. A high yield of the pyrazole derivative (72) was obtained which seems to have been formed by reaction with oxalyl chloride and the 1,2-dimethoxyethane solvent by a mechanism which is unclear. This product (72) however has combustion analysis and spectroscopic data consistent with the assigned structure. In particular its i.r. spectrum contains a carbonyl absorption at 1730 cm^{-1} and two absorptions at 1520 and 1340 cm^{-1} for the nitro group. The ^{1}H n.m.r. spectrum contains resonances for nine aromatic hydrogen atoms, four of which are part of a para-substituted phenyl group. It also has resonances for two adjacent CH_2 groups and two signals for CH_3 groups and also a single exchangeable proton. The ^{13}C n.m.r. spectrum contains signals for eight quaternary carbon atoms, as expected for the assigned structure. Of note here is that the pyrazole derivative (30e) was specifically used to perform the transformation [(30e)→(71)] since it had been suggested that the annulation process may be enhanced by an electron withdrawing substituent in the 4-position of the pyrazole ring (see earlier). However, this has subsequently been shown not necessarily to be the case.

The failure of the transformation [Scheme 27: (30e)→(71)] prompted the investigation of another route to isocyanates. The oxidative conversion of formamides to isocyanates has been reported.[149] Hence it was decided to

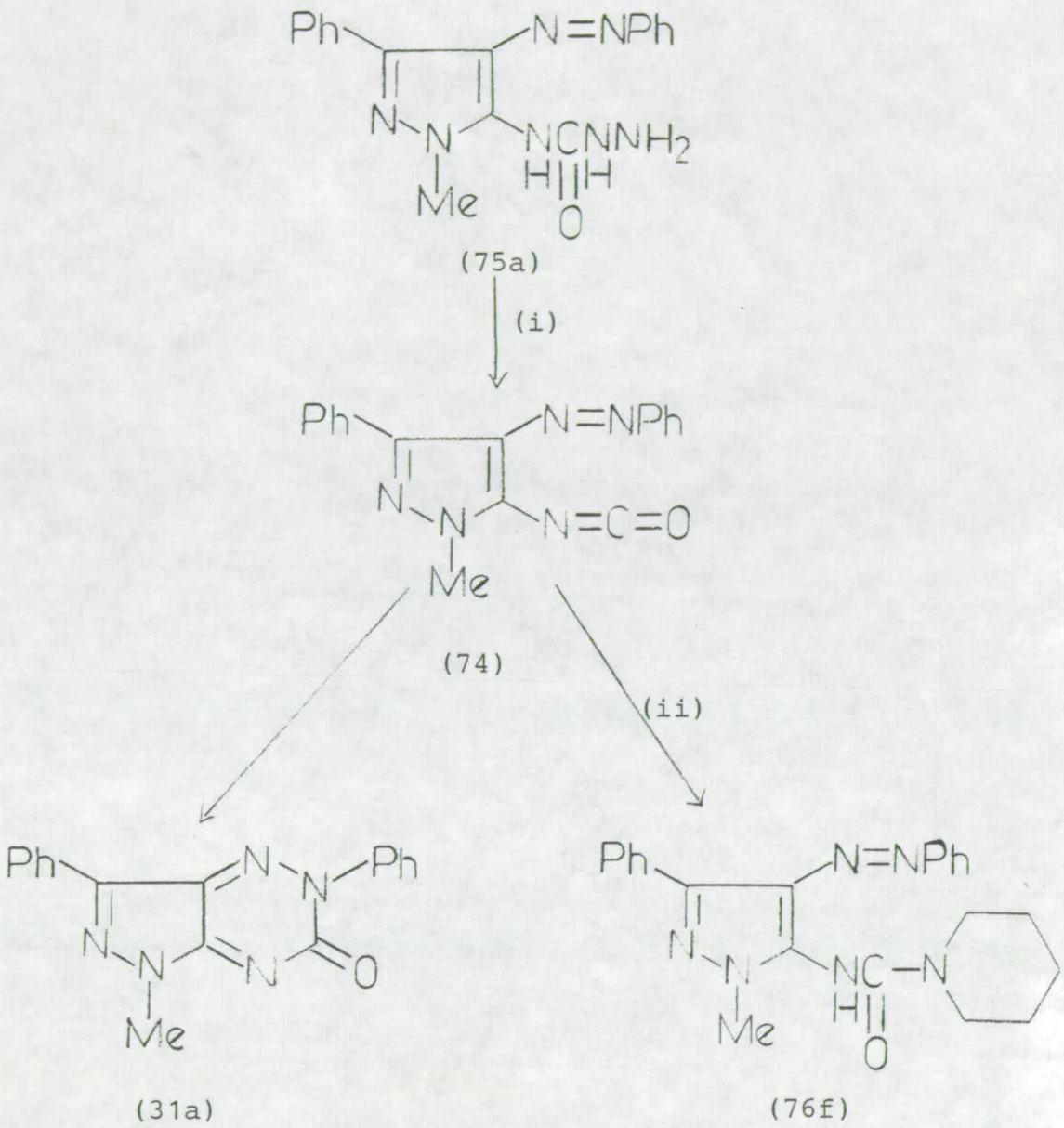


(i) HCO_2H, reflux

(ii) $(EtO)_3CH$, reflux

(iii) MnO_2, CH_3CN, R.T.

Scheme 28



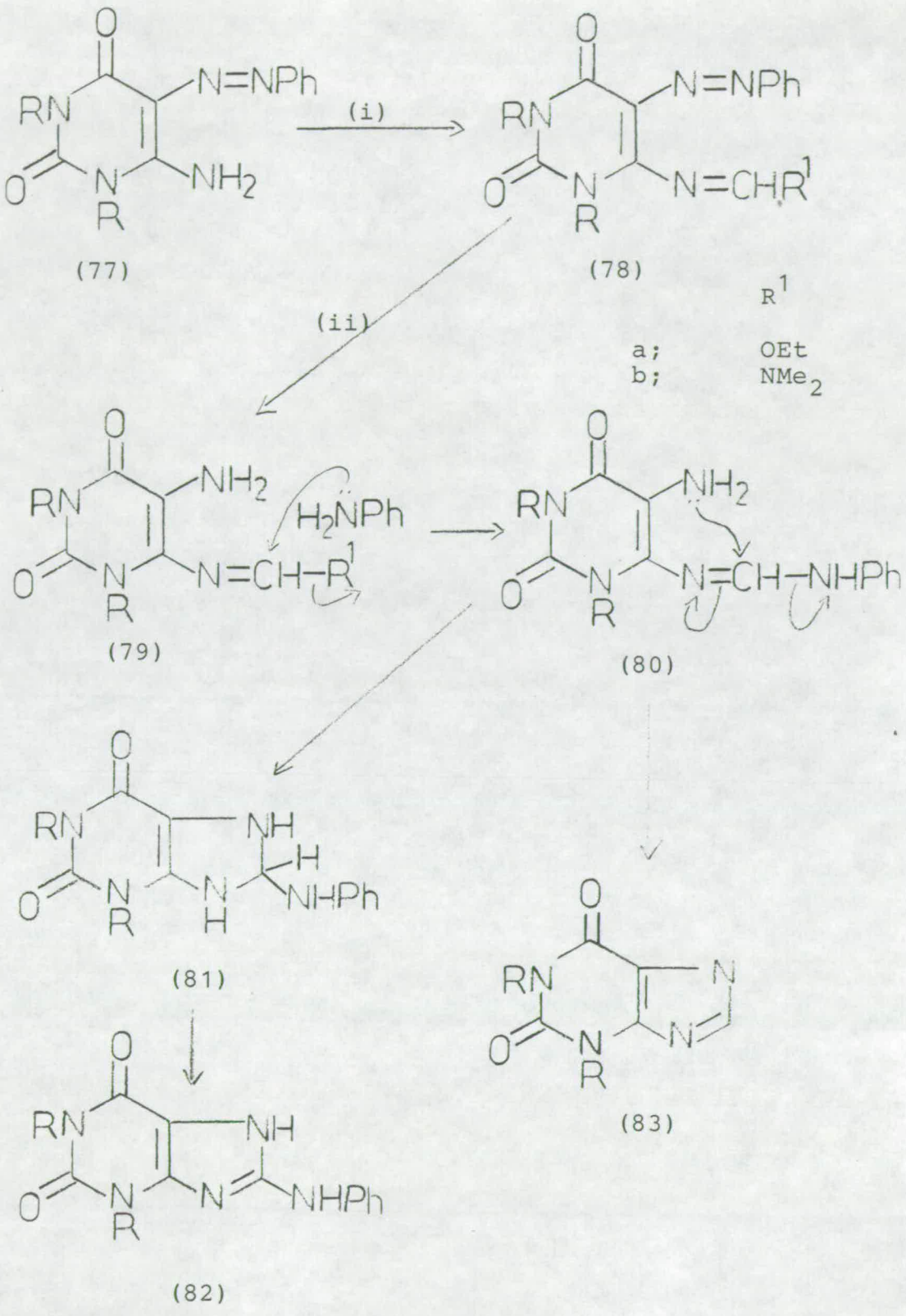
(i) MnO_2, CH_3CN, R.T.

(ii) piperidine

Scheme 29

investigate (Scheme 28) the oxidation of 5-formamido-1-methyl-3-phenyl-4-phenylazopyrazole (73) which was anticipated would either give the pyrazolylisocyanate (74) or more probably the pyrazolotriazinone (31a). The formamidopyrazole (73) was synthesised only in low yield from the reaction of the aminopyrazole (30a) with formic acid or with triethyl orthoformate. Disappointingly, the subsequent oxidation of 5-formamido-1-methyl-3-phenyl-4-phenylazopyrazole (73) with manganese dioxide gave only a good yield of unreacted starting material.

It is not clear why the oxidation [(73)→(74)] was unsuccessful but the failure of this transformation prompted the investigation of the novel oxidative formation of isocyanates from semicarbazides as illustrated (Scheme 29). 4-N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)semicarbazide (75a), whose synthesis is discussed later (see section 3.2.3), was treated with manganese dioxide and gave a quantitative yield of the pyrazolotriazinone (31a) in either anhydrous or aqueous acetonitrile. However, if piperidine is included in the reaction of the semicarbazide (75a) with manganese dioxide a quantitative yield of N-[N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)carbamoyl]-piperidine (76f) was obtained. The compound (76f) gave combustion analysis and spectroscopic data consistent with the assigned structure. In particular the ^{1}H n.m.r. spectrum contains resonances for ten aromatic hydrogen atoms, for ten hydrogen atoms corresponding to the five CH_2 groups of the



(i) $(EtO)_3CH$, Me_2NCHO, heat or $Me_2NCH(OEt)_2$, Me_2NCHO, heat

(ii) $Na_2S_2O_4$, heat

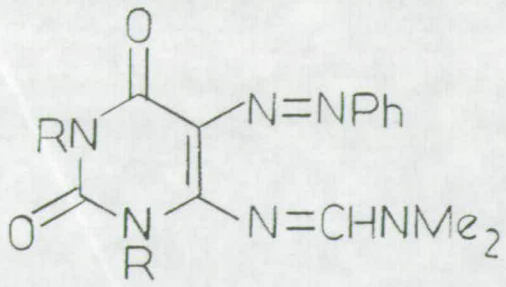
Scheme 30

piperidyl substituent, for the three hydrogen atoms of the NCH_3 group, and a single exchangeable proton. The compound (76f) has a ^{13}C n.m.r. spectrum containing only signals for five quaternary carbon atoms and not, as expected, six. This can be explained in terms of the long relaxation times of hetero-atom substituted quaternary carbon atoms and hence such carbon atoms are not always observed in the ^{13}C n.m.r. spectrum.[86]

This product (76f) is not formed by the reaction of the semicabazide (75a) with piperidine alone. Therefore it can be concluded that the piperidine reacts with an oxidation product most probably the isocyanate derivative (74) and it would hence seem reasonable that the pyrazolotriazinone (31a) is also formed via the isocyanate derivative (74). This evidence would therefore suggest that the annulation of such 5-amino-4-arylazopyrazoles with tosyl isocyanate to give pyrazolo[3,4-d]-1,2,4-triazinones proceeds via a pyrazolylisocyanate derivative.

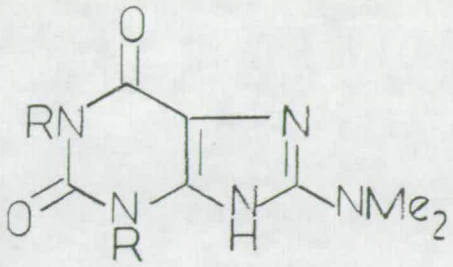
Since, in essence, the cyclisation (Scheme 29) of the isocyanate derivative (74) to the pyrazolotriazinone is an electrocyclic process, it was decided to investigate whether other double bonded derivatives such as imines would undergo similar transformations.

It has been shown by Senga and his co-workers[150,151] (Scheme 30) that ortho-amino-arylazouracil derivatives (77) can react with triethyl orthoformate or N,N-dimethylformamide dimethylacetal to give the imines (78a) and (78b) respectively which by reaction with sodium bisulphite give



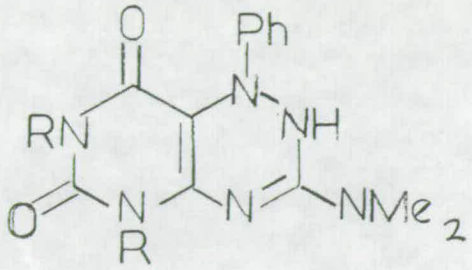
(78b)

(i)



(84)

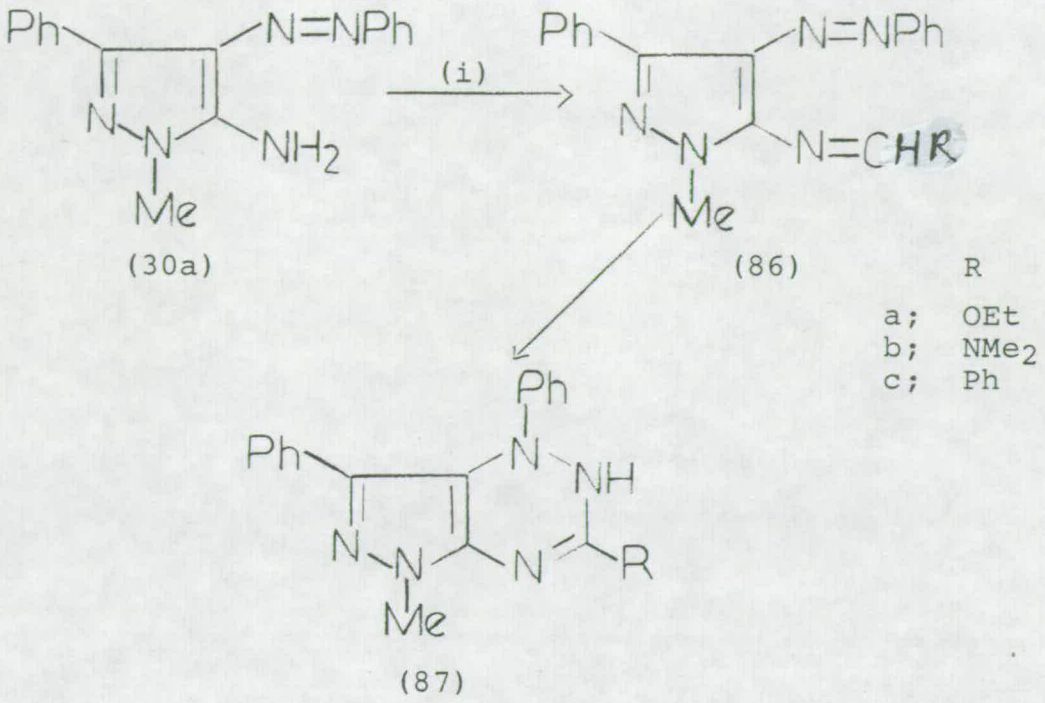
+



(85)

(i) 220°

Scheme 31



(30a) (86) (87)

R
a; OEt
b; NMe_2
c; Ph

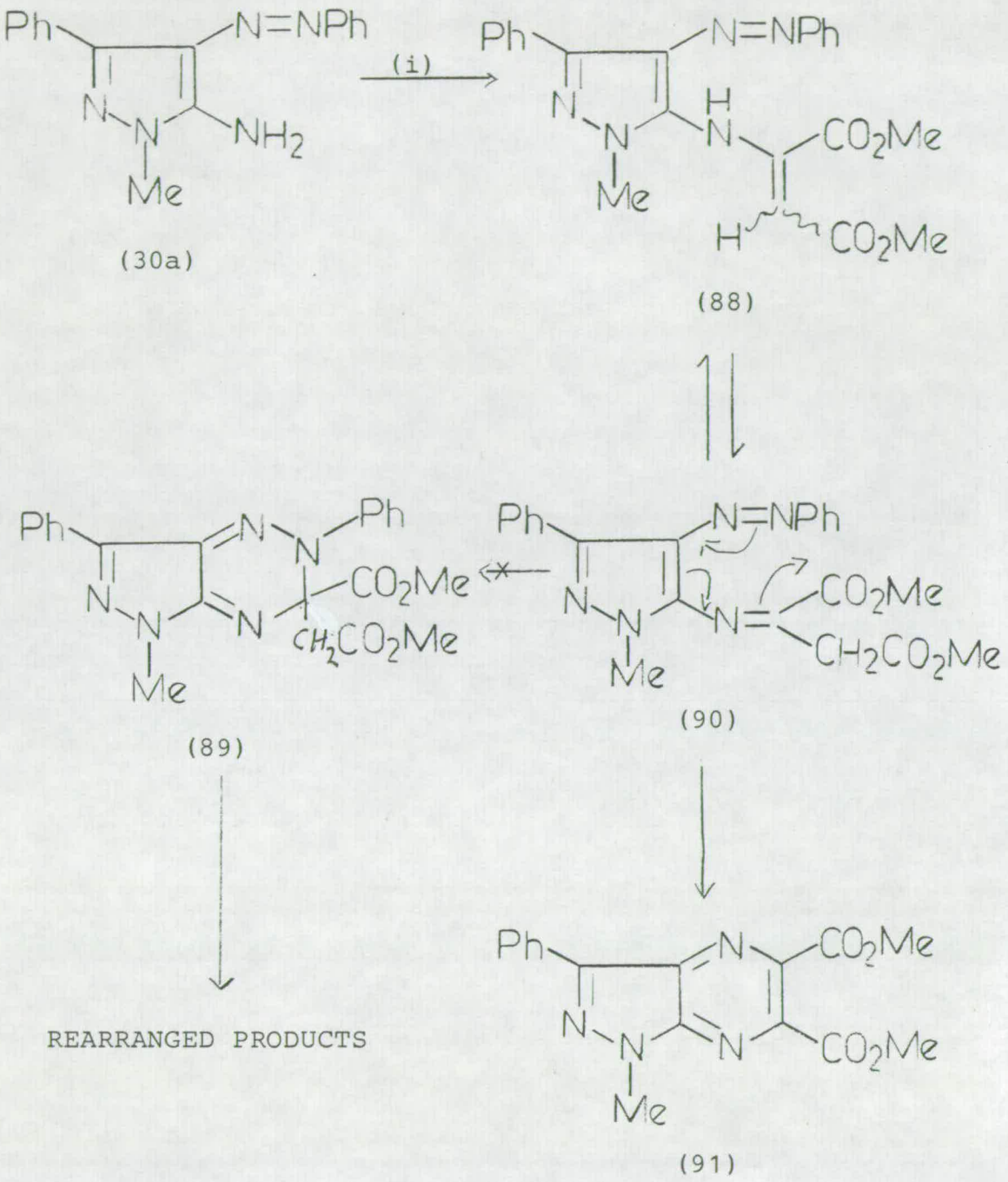
(i) $(EtO)_3CH$, heat, or $Me_2N\overset{H}{C}(OEt)_2$, heat or PhCHO, heat

Scheme 32

the purine derivatives (82) and (83). Yoneda and his co-workers[152] have also shown (Scheme 31) that the imine derivative (78b) on fusion gives the products (84) and (85).

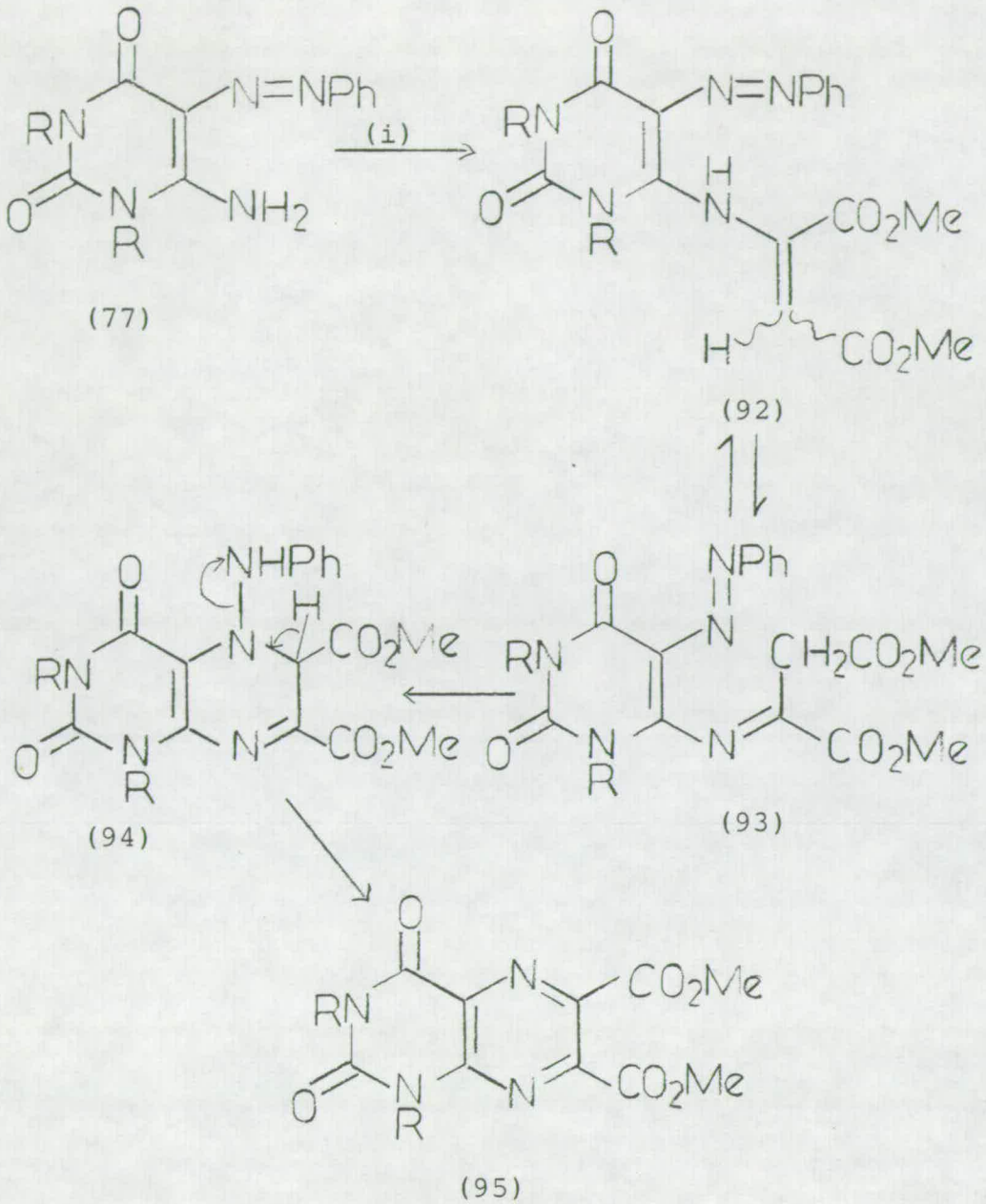
In an attempt to apply some of the above described chemistry to ortho-amino-arylazopyrazoles (Scheme 32) the pyrazole derivative (30a) was reacted with a number of reagents known to form imines. Firstly, reaction of the pyrazole (30a) with triethylorthoformate failed to give the expected imine derivative (86a), only a low yield of 5-formamido-1-methyl-3-phenyl-4-phenylazopyrazole (73) as described in Scheme 28 was isolated. Reaction of the pyrazole derivative (30a) with N,N-dimethylformamide dimethylacetal gave a good yield of 1,1-dimethyl-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) formamidine (86b). This compound (86b) gave combustion analysis and spectroscopic data consistent with the assigned structure. In particular, the ^1H n.m.r. spectrum contains resonances for ten aromatic hydrogen atoms and has three signals corresponding to the three NCH_3 groups of the illustrated structure. Disappointingly, however, thermolysis of this imine derivative (86b) gave only a quantitative recovery of unreacted starting material.

In an attempt (Scheme 32) to obtain another imine derivative which might be more susceptible to thermal cyclisation to yield a derivative (87), the pyrazole (30a) was reacted with benzaldehyde. However the expected imine (86c) was not obtained, only a good yield of unreacted starting material being recovered.



(i) $MeO_2CC{\equiv}CCO_2Me$, Me_2NCHO, heat

Scheme 33

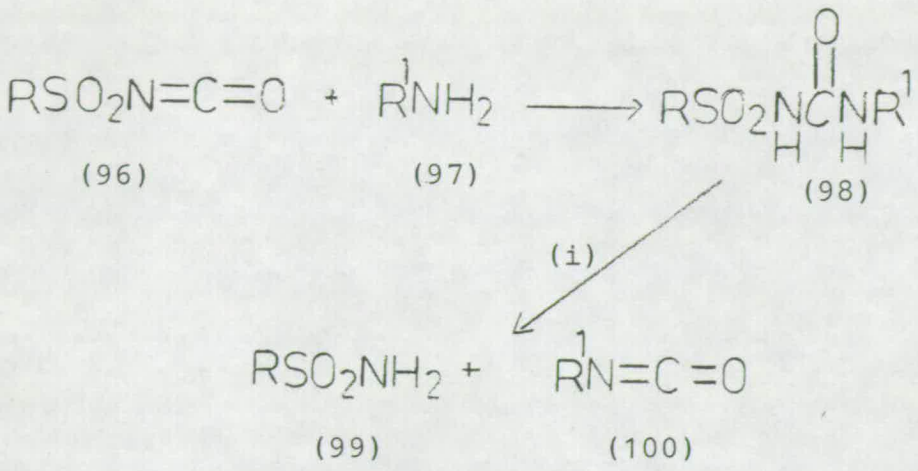


(i) $MeO_2CC{\equiv}CCO_2Me$, MeNCHO, heat

Scheme 34

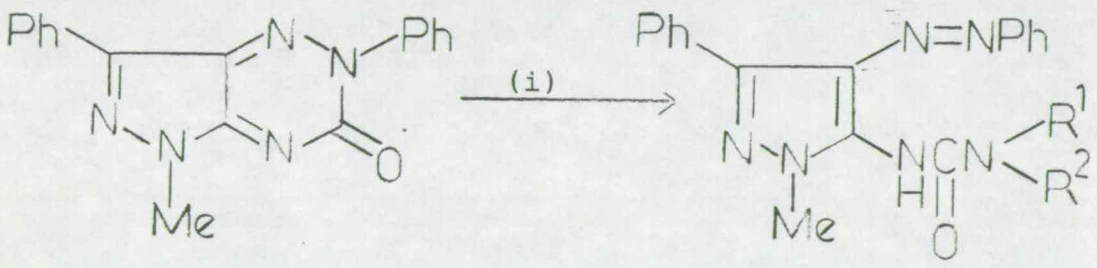
The failure of the imine derivative (86b) to cyclise prompted the investigation of the reaction (Scheme 33) of the pyrazole derivative (30a) with dimethylacetylene dicarboxylate which would be anticipated to give on tautomerism the imine derivative (88). This derivative might be expected to give a variety of products as illustrated. The transformation [(90)→(91)] has been described by Yoneda and his co-workers[153,154] as illustrated (Scheme 34) by the reaction of the ortho-amino-arylazouracils (77) with dimethylacetylene dicarboxylate which by the mechanism shown affords the pteridine derivatives (95). However disappointingly reaction (Scheme 33) of the pyrazole (30a) with dimethylacetylene dicarboxylate gave a low yield of unreacted starting material, no other identifiable material being isolated.

In conclusion, it has been shown that the literature and experimental evidence for the mechanism of the transformation (Scheme 23) of the pyrazolyl urea (60) to the pyrazolo-triazinone (27) favours the pathway via the isocyanate derivative (61). Although it does not seem possible to extrapolate the cyclisation of imine derivatives of other ortho-amino-anylazo compounds to 5-amino-4-arylazopyrazoles further work is encouraged in this area as it should be possible for a multiple bond functionality to undergo the electrocyclisation as described for the conversion of the isocyanate (61) into the pyrazolotriazinone (27). Hence there is the possibility of many other fused pyrazolo heterocyclic systems being formed.



(i) heat

Scheme 35



(31a)

(76)	R^1	R^2
a;	H	H
b;	H	Me
c;	H	CH_2Ph
d;	H	Ph
e;	Me	Me
f;	$-(CH_2)_5-$	

(i) R^1NHR^2, $MeOCH_2CH_2OMe$, room temp. or EtOH, heat

Scheme 36

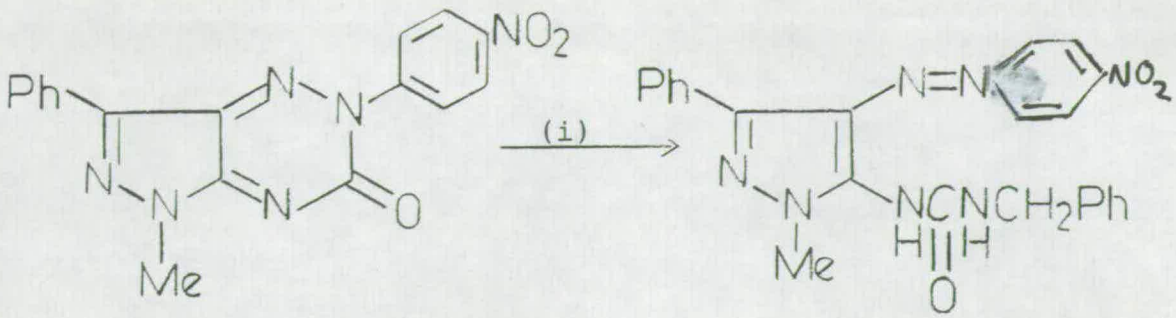
Since the annulation of 5-amino-4-arylazopyrazoles by tosyl isocyanate appears to proceed through a pyrazolyl-isocyanate intermediate it is suggested that the overall transformation can be regarded as an isocyanate transfer. Indeed, such a process has been described by Ulrich and Sayigh[155] and is illustrated (Scheme 35) by the reaction of sulphonyl isocyanates (96) with amines (97). This yields the urea derivative (98) which on heating gives the sulphonyl amide (99) and the isocyanate (100).

3.2.3 Studies of Ring-Opening Reactions of Pyrazolo[3,4-e]-1,2,4-triazinones with Nucleophilic Reagents

As has been discussed earlier (see section 3.2.1) the pyrazolo[3,4-e]-1,2,4-triazinone (31a) has been shown (see Scheme 10) to react in a ring-opening fashion with sodium hydroxide to yield 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a). Busch has reported[135] the reaction of fused 1,2,4-triazinone derivatives with nucleophilic reagents. Therefore, this evidence prompted the investigation of the behaviour of pyrazolo[3,4-e]-1,2,4-triazinones toward a variety of nucleophilic reagents.

(1) Ring-opening reactions with amines

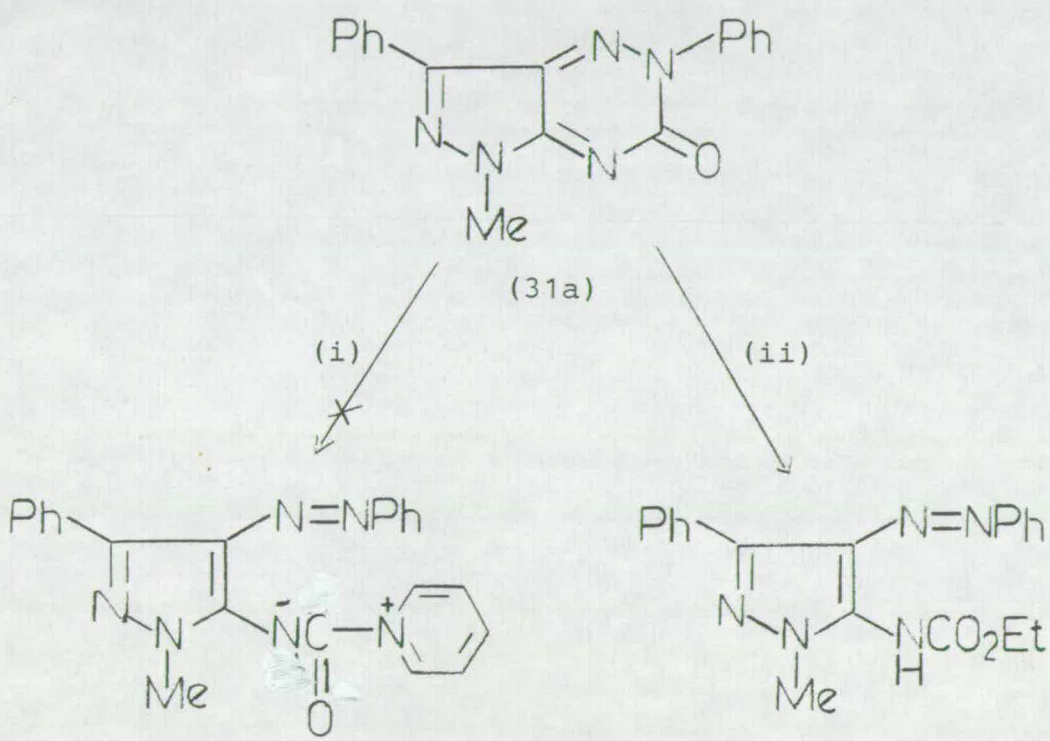
In extending the ring-opening reactions of pyrazolo-[3,4-e]-1,2,4-triazinones it was decided to investigate the reaction of such derivatives with a variety of amines, as illustrated (Scheme 36) by the reaction of the pyrazolo-



(31e) (101)

(i) $PhCH_2NH_2$, EtOH, heat

Scheme 37



(31a)

(102) (103)

(i) pyridine, $MeOCH_2CH_2OMe$, room temp. or heat

(ii) pyridine, EtOH, heat

Scheme 38

triazinone derivative (31a) with ammonia to afford 1-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)urea (76a). This compound (76a) gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular the i.r. spectrum contains amide NH absorptions at 3400 and 3200 cm^{-1}, supported by a carbonyl band at 1680 cm^{-1}. The ^{1}H n.m.r. spectrum of this urea derivative (76a) exhibits resonances for ten aromatic hydrogen atoms and three hydrogen atoms of the NCH_3 group, as well as three exchangable protons. The ^{13}C n.m.r. spectrum has the expected six signals for quaternary carbon atoms.

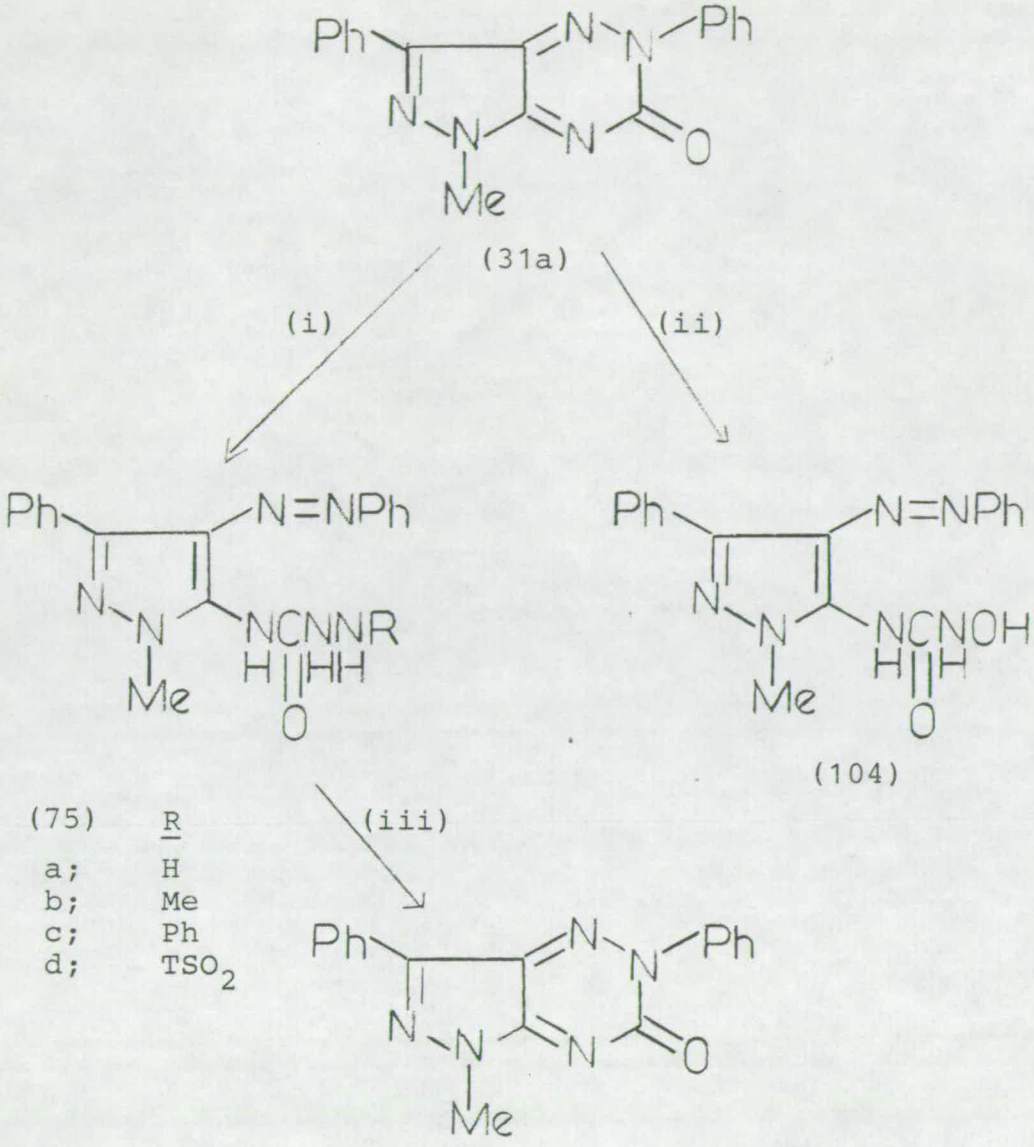
Similarly (Scheme 36), the pyrazolo[3,4-e]-1,2,4-triazinone (31a) reacted with the primary amines methylamine and benzylamine to give quantitative yields of the urea derivatives (76b) and (76c) respectively. Both compounds have combustion analysis, mass spectral data and other spectroscopic data consistent with the assigned structures. Also of note (Scheme 37) here is that the pyrazolotriazinone (31e) afforded a moderate yield of the corresponding urea derivative (101) on reaction with benzylamine. This product (101) gave analytical data and exhibited spectroscopic properties consistent with the assigned structure. However, the mass spectrum exhibited no parent ion, a loss of benzylamine being indicated.

In further exploring the reaction of pyrazolo-triazinones with amines it was decided to investigate the

reaction of such derivatives with arylamines. This is illustrated (Scheme 36) by the reaction of the pyrazolo-[3,4-e]-1,2,4-triazinone (31a) with aniline, which afforded a good yield of unreacted starting material plus a small amount of a product which has been tentatively assigned as the urea derivative (76d) on the basis of its i.r. spectrum which contains a carbonyl band at 1675 cm^{-1}, consistent with an amide carbonyl absorption. However, attempted crystallisation of this product gave pyrazolo-triazinone starting material (31a).

The reaction (Scheme 36) of the pyrazolotriazinone (31a) with dimethylamine was investigated as an example of such pyrazolotriazinone derivatives with secondary amines. This reaction gave the urea derivative (76e) in quantitative yield and had combustion analysis and spectroscopic data consistent with the assigned structure. In an extension of such ring-opening reactions of pyrazolotriazinones with secondary amines it was decided to investigate the reaction (Scheme 36) of the pyrazolo[3,4-e]-1,2,4-triazinone (31a) with the cyclic secondary amine piperidine. This reaction gave the expected urea derivative (76f) which was shown to have identical melting point and i.r. spectrum to the compound described earlier (see Scheme 29).

In further investigating the ring-opening reactions of pyrazolotriazinone derivatives with amines it was decided to look at the reaction of such derivatives with tertiary amines. This was illustrated (Scheme 38) by the



(i) $RNHNH_2$, EtOH, heat

(ii) $NH_2OH.HCl$, NaOMe, $MeOCH_2CH_2OMe$, room temp.

(iii) heat

Scheme 39

reaction of the pyrazolotriazinone (31a) with pyridine. However, the expected product (102) was not detected, a good yield of unreacted starting material being recovered along with a small amount of the urethane (103) when the reaction was carried out using ethanol as the solvent. This product (103) has accurate mass spectral data and other spectroscopic data consistent with the assigned structure. In particular the urethane derivative (103) has a carbonyl band at 1740 cm^{-1} in its i.r. spectrum. The ^1H n.m.r. spectrum has resonances for ten aromatic hydrogen atoms and signals for a $-NCH_3$ group and the ethyl group of the ester moiety and also a single exchangeable proton. This result would suggest that the pyridine is acting as a base and that the ethoxide ion formed is acting as the nucleophile.

(ii) Ring-opening reactions with hydrazines and hydroxylamine

In continuing the studies of ring-opening reactions of pyrazolo[3,4-e]-1,2,4-triazinones it was decided to investigate the reaction (Scheme 39) of the pyrazolotriazinone derivative (31a) with hydrazine monohydrate. This reaction afforded a quantitative yield of the semicarbazide derivative (75a) whose combustion analysis and spectroscopic data is consistent with the assigned structure. In particular the i.r. spectrum shows amide NH absorptions at 3310 and 3210 cm^{-1} supported by a carbonyl band at 1685 cm^{-1}.

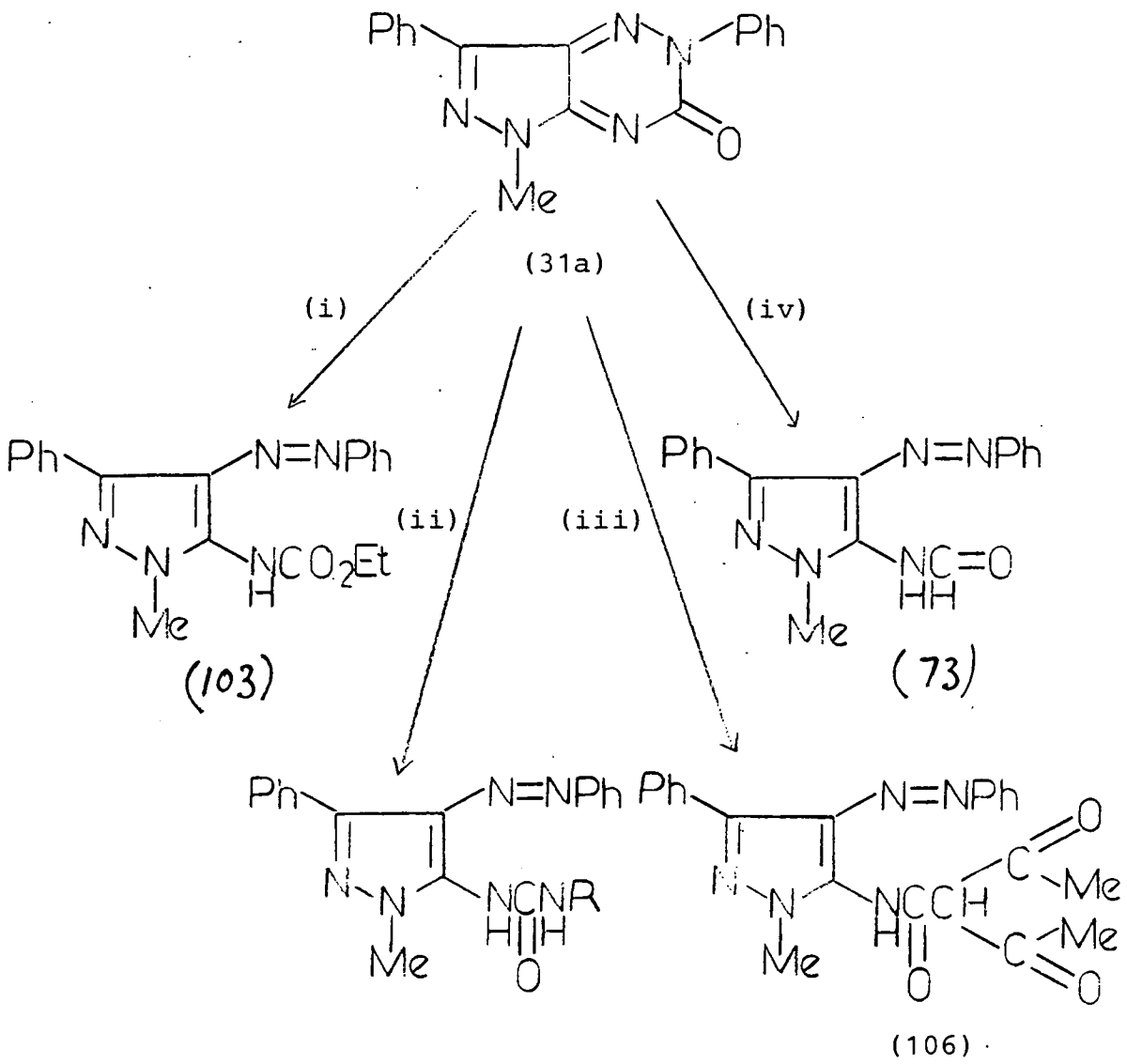
The ^{1}H n.m.r. spectrum of the semicarbazide derivative (75a) exhibits resonances for ten aromatic hydrogen atoms, three hydrogen atoms of the NCH_3 group and four exchangeable protons. The ^{13}C n.m.r. has the expected six signals for quaternary carbon atoms.

Similarly (Scheme 39) the hydrazines, methylhydrazine and phenylhydrazine on reaction with the pyrazolotriazinone derivative (31a) gave good yields of the corresponding semicarbazide derivatives (75b) and (75c) respectively. Both these products gave analytical data and showed spectroscopic properties in agreement with the assigned structures. Of note is the fact that both these compounds do not show parent ions in their mass spectra, the major ions being that of the starting material, the pyrazolo-triazinone (31a). This is consistent with loss of methylhydrazine and phenylhydrazine respectively in the mass spectrometer.

A further extension of the ring-opening reactions (Scheme 39) of the pyrazolo[3,4-e]-1,2,4-triazinone (31a) with hydrazine derivatives is the reaction of the pyrazolotriazinone (31a) ~~was treated~~ with tosylhydrazine to afford a low yield of the semicarbazide derivative (75d), whose structure has been tentatively assigned on the basis of its i.r. spectrum as a reasonable combustion analysis was impossible to obtain.

In a similar ring-opening reaction to that described for hydrazines (Scheme 34) the pyrazolo[3,4-e]-1,2,4-triazinone (31a) was treated with hydroxylamine hydrochloride in the presence of sodium methoxide. This reaction gave a quantitative yield of ~~the expected~~ a product which has been tentatively assigned as 1-hydroxyl-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) urea (104) ~~has been tentatively assigned~~ on the basis of its i.r. and mass spectra, its combustion analysis being inconclusive. In particular, the i.r. spectrum contains OH and amide NH absorption at 3200 cm^{-1} the latter being supported by a carbonyl band at 1700 cm^{-1}.

A point of note with many of the aforementioned products is their double melting points. For instance, the semicarbazide derivative (75a) exhibits a phase change at 172° and a further melting point at 228-230° which is consistent with the pyrazolotriazinone starting material (31a). This observation would seem to indicate that these derivatives can be converted into the pyrazolo-triazinone starting material by heating. To test this hypothesis the semicarbazide derivative (75a) was heated under vacuum in a kugelrohr apparatus (see Scheme 39). This reaction afforded a quantitative yield of the pyrazol[3,4-e]-1,2,4-triazinone (31a). Therefore it can be concluded that such semicarbazide derivatives are indeed capable of thermal transformation into pyrazolo-[3,4-e]-1,2,4-triazinone derivatives.



(105) R

a; TSO_2

b; CN

(i) NaOEt, EtOH, room temp.

(ii) NaNHR, EtOH, heat

(iii) $Na^+ Me\overline{C}C(=O)CHC(=O)Me$, $Me_2NCH=O$, heat

(iv) $NaBH_4$, dioxane, room temp.

Scheme 40

(iii) Ring-opening reactions with anionic reagents

In further studying the ring-opening reactions of pyrazolo[3,4-e]-1,2,4-triazinones with nucleophilic reagents it was decided to investigate the reactions of such derivatives with anionic reagents. This was illustrated (Scheme 40) by the reaction of the pyrazolotriazinone (31a) with a variety of anionic reagents. The reaction of the pyrazolotriazinone derivative (31a) with sodium ethoxide afforded a low yield of the urethane derivative (103) which has been described earlier (see Scheme 38). Reaction of the pyrazolotriazinone (31a) with sodium toluene-4-sulphonamide afforded a low yield of the expected urea derivative (105a). This product 1-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonamide)urea (105a) has combustion analysis in agreement with a monohydrate of the product. The mass spectrum of this product shows a molecular ion for a loss of toluene-4-sulphonamide.

In further exploring the reactions (Scheme 40) of the pyrazolotriazinone (31a) it was decided to react this derivative with sodium cyanamide. This reaction afforded a low yield of a product which has been tentatively assigned the structure illustrated (105b) on the basis of its spectroscopic data as it has been unable to obtain accurate combustion analysis. The i.r. spectrum of this urea derivative (105b) has amide NH absorptions at 3620, 3510 and 3300 cm^{-1} supported by a carbonyl

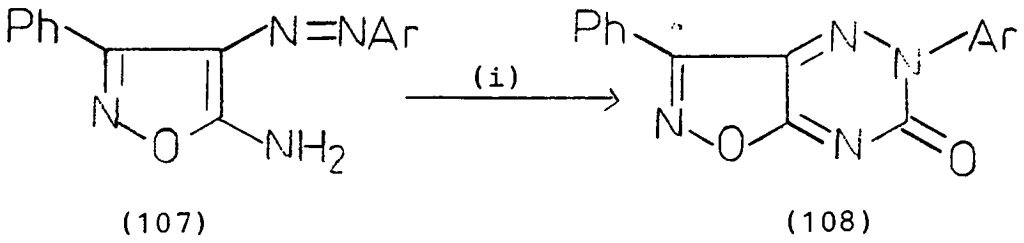
band at 1690 cm^{-1}, and the spectrum also contains a cyano band at 2180 cm^{-1}. The ^{1}H n.m.r. spectrum of this product (105b) exhibits resonances for ten aromatic hydrogen atoms, a signal for the three hydrogen atoms of the NCH_3 group and two exchangeable protons. The ^{13}C n.m.r. spectrum only contains signals for six quaternary carbon atoms where seven such signals are expected. However, as has been explained previously, hetero-atom substituted carbon atoms have long relaxation times in the ^{13}C n.m.r. spectrum and hence such carbon atoms are not always visible in the ^{13}C spectrum.[86]

Another interesting reaction (Scheme 40) of the pyrazolotriazinone (31a) was its treatment with the sodium salt of acetylacetone. This afforded a low yield of a product which has combustion analysis in agreement with the amide derivative (106). The i.r. spectrum contains an amide NH absorption at 3270 cm^{-1} supported by a carbonyl band at 1655 cm^{-1}. This product was only obtained by isolation of the sodium salt of acetylacetone and its subsequent reaction with the pyrazolotriazinone (31a) in dimethylformamide. Other conditions such as reaction of the pyrazolotriazinone (31a) with triethylamine and acetylacetone in dioxane gave a quantitative yield of starting material. Also reaction of the pyrazolotriazinone (31a) with acetylacetone and sodium ethoxide in ethanol yielded unreacted starting material

and 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a). The latter presumably being formed via the ring opening of the pyrazolotriazinone (31a) with sodium ethoxide to the urethane which readily forms the amino-arylazo-pyrazole.

A final reaction in investigating the ring-opening (Scheme 40) of the pyrazolo[3,4-e]triazinone (31a) with anionic reagents was its reaction with sodium boro-hydride. This was expected to yield the formamido derivative (73) which has been previously described. However the reaction proved to be unsuccessful, a good yield of the pyrazolotriazinone starting material (31a) being obtained.

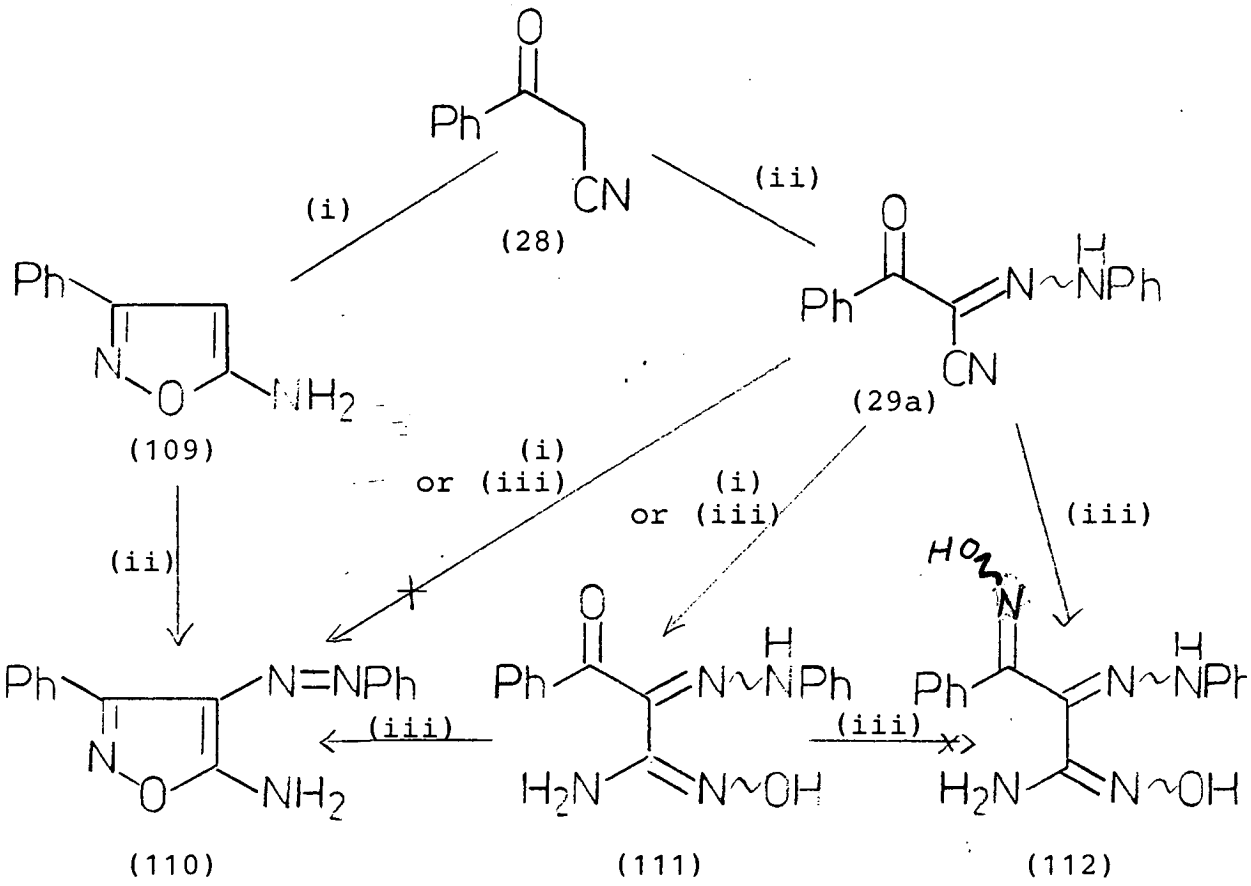
In conclusion, it has been shown that the pyrazolo-[3,4-e]-1,2,4-triazinone derivative (31a), and most probably all such derivatives, undergoes ring-opening reactions with a variety of nucleophilic reagents. It is suggested that future workers should concentrate efforts in perfecting the ring-opening reactions of hydroxylamine and anionic reagents as the products of such transformations would appear to be potential substrates for further reaction. In particular the derivatives from the reaction of hydroxylamine and sodium cyanamide with the pyrazolo triazinone (31a), i.e. compounds (104) and (105b) might afford other heterocyclic ring systems under suitable conditions.



(107) (108)

(i) $TSO_2N=C=O$

Scheme 41



(109) (28) (29a) (110) (111) (112)

(i) $NH_2OH.HCl$, NaOH, room temp.

(ii) $PhN_2^+Cl^-$, NaOAc, 0°

(iii) $NH_2OH.HCl$, NaOMe, heat

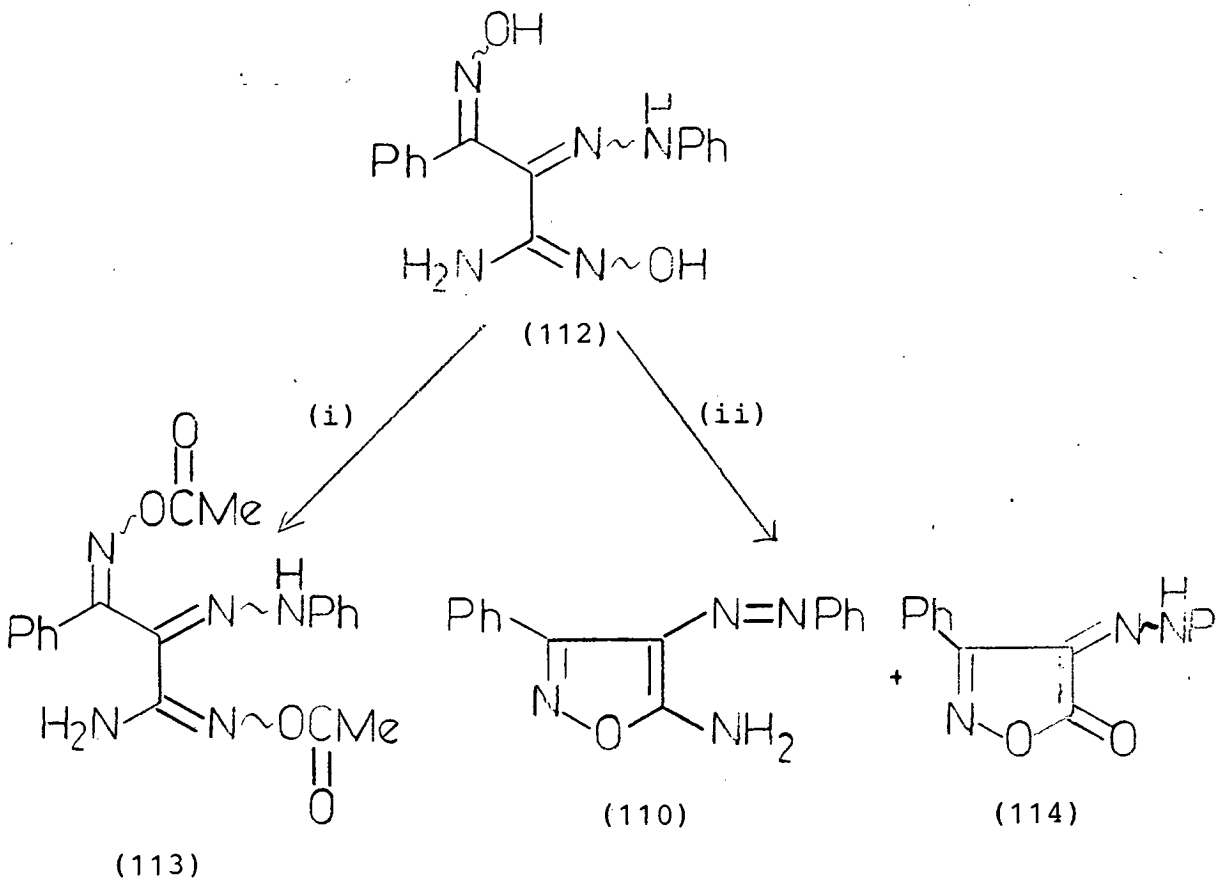
Scheme 42

3.3 Studies on the Synthesis and Reactivity of 3(5)-Amino-4-phenylazoisoxazoles and 5-Amino-4-nitroso-3-phenylisoxazole

3.3.1 Studies on the Reactivity of 3(5)-Amino-4-phenylazoisoxazoles

In the course of investigating the scope of the annulation of ortho-amino-azo compounds with tosyl isocyanate it was decided to investigate the extension of this annulation (Scheme 41) to 5-amino-4-arylazo-isoxazoles (107). This is a potential synthesis of the unknown ring system isoxazolo[3,4-e]-1,2,4-triazin-6(5H)-one (108).

In order to investigate the transformation [(107)→(108)] it was decided to synthesise (Scheme 42) the known[90] isoxazole derivative, 5-amino-3-phenyl-4-phenylazoisoxazole (110). The synthesis of this isoxazole has been reported[90] by two routes both starting from benzoylacetonitrile (28).[105] Firstly by the coupling of benzoylacetonitrile (28) with benzenediazonium chloride to afford the known[104] and previously described 2-phenylhydrazonobenzoylacetonitrile (29a). 2-Phenylhydrazonobenzoylacetonitrile (29a) has been reported[90] to afford the desired 5-amino-3-phenyl-4-phenylazoisoxazole (110) on treatment with hydroxylamine hydrochloride in the presence of sodium methoxide. However by following the reported procedure only a high yield of unreacted 2-phenylhydrazonobenzoylacetonitrile (29a) was isolated.



(i) Ac_2O, heat

(ii) AcOH, heat

Scheme 43

It seems conceivable that these authors[90] had not taken into account the volatility of the free hydroxylamine generated in the reaction mixture. Therefore it was decided to have present in the reaction mixture a large excess of free hydroxylamine by using a large excess of hydroxylamine and sodium methoxide. However, these conditions also failed to give the desired 5-amino-3-phenyl-4-phenylazoisoxazole (110) a high yield of 2-benzoyl-2-phenylhydrazonoacetamidoxime (111) being recovered. This product (111) has been previously described in Chapter 2, page 48 . Repetition of this reaction on a larger scale gave a low yield of unreacted starting material and a moderate yield of 2-benzoyl-2-phenylhydrazonoacetamidoxime oxime (112). This product (112) gave combustion analysis and spectroscopic data consistent with the assigned structure. In particular the ^{1}H n.m.r. spectrum contained resonances for ten aromatic hydrogen atoms and five exchangable protons. The ^{13}C n.m.r. spectrum exhibited the expected five signals for quaternary carbon atoms.

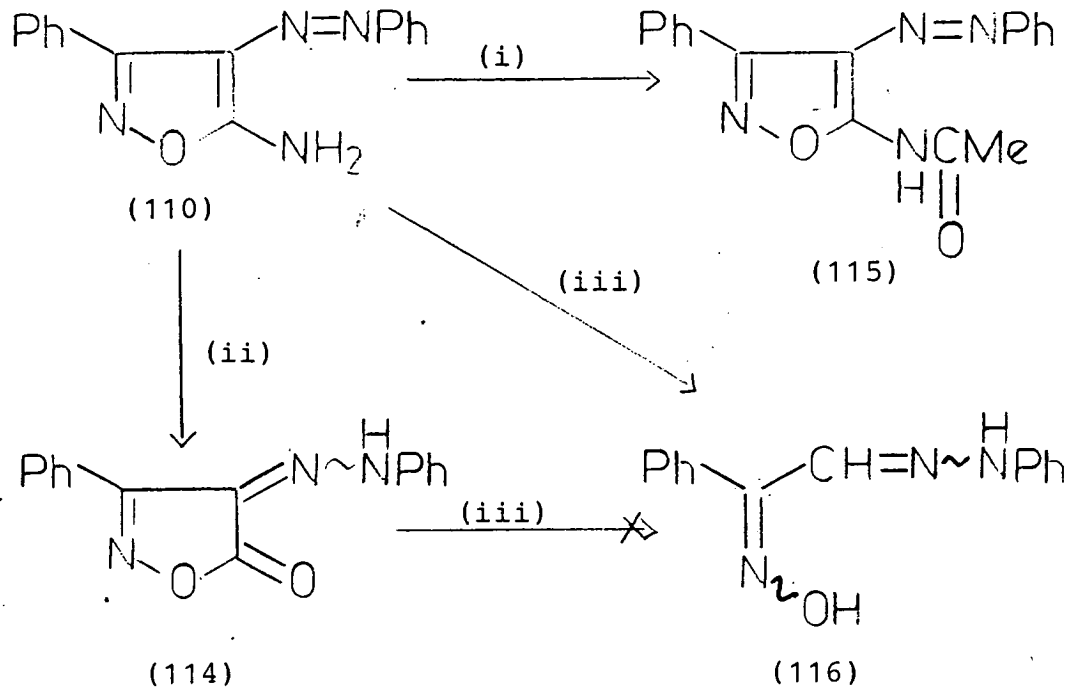
In an attempt to support the structure of the acetamidoxime (112) it was reacted (Scheme 43) with acetic anhydride in an attempt to afford the bis-acetoxy derivative (113). However, in practice a series of intractable gums was isolated. Similarly in a further attempt to derivatise the acetamidoxime (112) it was reacted with acetic acid. However instead of forming an acetate derivative, two products were isolated. These were shown to be 5-amino-3-phenyl-4-phenylazoisoxazole (110)[90] and

3-phenyl-4-phenylazo-Δ^2-isoxazolin-5-one (114), both of which have been unambiguously synthesised (see later), the latter also being a known compound.[156]

It would seem reasonable to assume that the bisoxime derivative (112) is formed by oximation of the acetamidoxime (111). However, reaction (Scheme 42) of 2-benzoyl-2-phenylhydrazonoacetamidoxime (111) with hydroxylamine hydrochloride in the presence of sodium methoxide yielded a small amount of 5-amino-3-phenyl-4-phenylazoisoxazole (110) which, as stated earlier, has been unambiguously synthesised (see later).

In continuing the investigation (Scheme 42) of the synthesis of 5-amino-3-phenyl-4-phenylazoisoxazole (110) from the hydrazonoacetonitrile (29a) it was decided to use conditions known[105] to form isoxazoles from acylacetonitriles. Hence, 2-benzoyl-2-phenylhydrazonoacetonitrile (29a) was reacted with hydroxylamine hydrochloride in the presence of sodium hydroxide. However this failed to afford the expected 5-amino-3-phenyl-4-phenylazoisoxazole (110), moderate yields of unreacted starting material and 2-benzoyl-2-phenylhydrazonoacetamidoxime (111) being isolated.

A final and successful route (Scheme 42) to 5-amino-3-phenyl-4-phenylazoisoxazole (110) as described by Elnagdi and his co-workers[90] was investigated. Benzoylacetonitrile (28)[105] was treated with hydroxylamine hydrochloride in the presence of sodium hydroxide as described by Obregia[105] to afford the known 5-amino-3-



(i) Ac_2O, heat

(ii) 20% w/v aq. H_2SO_4, heat

(iii) 2M NaOH, heat

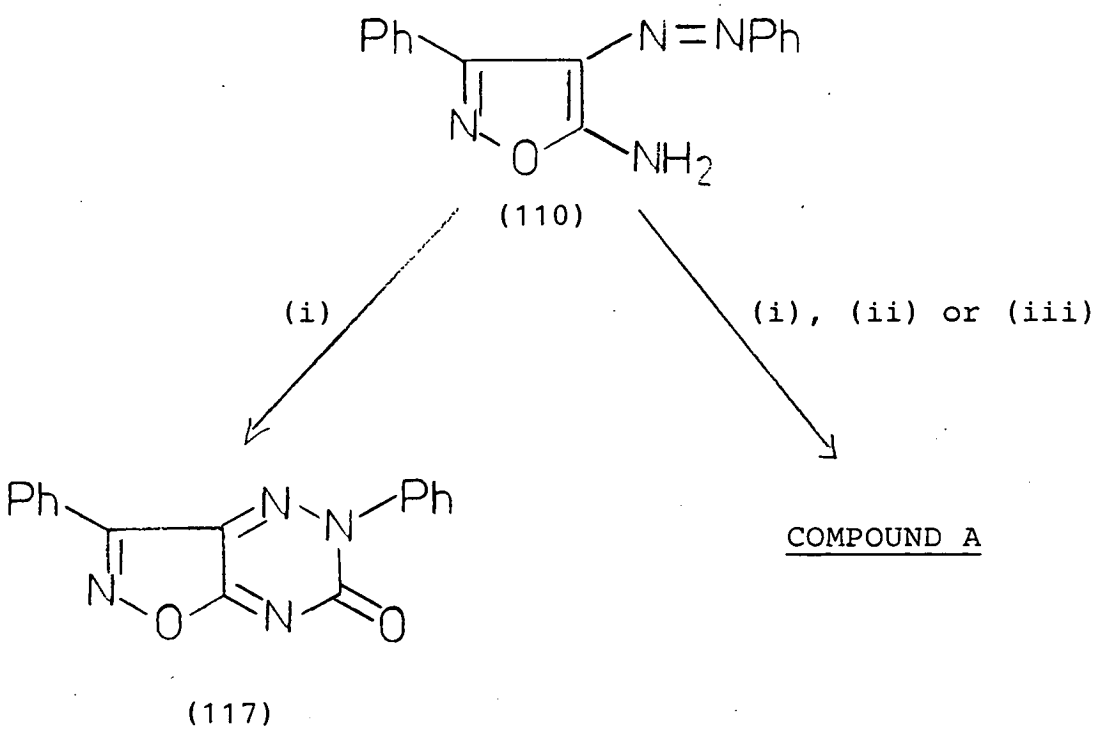
Scheme 44

phenylisoxazole (109) in high yield. This isoxazole (109) was readily coupled with benzenediazonium chloride as described by Elnagdi et al[90] to give a high yield of 5-amino-3-phenyl-4-phenylazoisoxazole (110) which had a melting point in agreement with that reported, and also gave a combustion analysis and showed spectroscopic properties consistent with the assigned structure.

Further evidence to support the structure of 5-amino-3-phenyl-4-phenylazoisoxazole (110) is provided by the characteristic reactions (Scheme 44) of its amino functionality. Reaction (Scheme 44) of 5-amino-3-phenyl-4-phenylazoisoxazole with acetic anhydride gave a moderate yield of the previously unknown 5-acetamido-3-phenyl-4-phenylazoisoxazole (115). This product had combustion analysis and spectroscopic data consistent with the assigned structure. In particular the i.r. spectrum of the isoxazole (115) showed amide NH absorption at 3270 cm^{-1} supported by a carbonyl band at 1695 cm^{-1}. The ^{1}H n.m.r. spectrum contains resonances for ten aromatic hydrogen atoms, a signal for the three hydrogen atoms of the acetyl CH_3 group and a single exchangeable proton. The ^{13}C n.m.r. spectrum shows resonances for only five quaternary carbon atoms where six such carbon atoms are contained in the structure. However as has been stated previously, due to the long relaxation times of hetero-atom substituted quaternary carbon atoms such carbon atoms are not always visible in the ^{13}C n.m.r. spectrum.

In continuing the structure proof of the isoxazole (110) such 5-aminoisoxazoles are known[157] to form the corresponding isoxazolin-5-one derivatives on treatment with acid or alkali. Reaction (Scheme 44) of 5-amino-3-phenyl-4-phenylazoisoxazole (110) with aqueous 20% sulphuric acid afforded a quantitative yield of the known[156] 3-phenyl-4-phenylazo-Δ^2- isoxazolin-5-one (114). This product (114) had a melting point in agreement with that reported,[156] and gave combustion analysis and other spectroscopic data consistent with the assigned structure. However reaction (Scheme 44) of 5-amino-3-phenyl-4-phenylazoisoxazole (110) with aqueous 2M sodium hydroxide did not give the isoxazolinone derivative (114) as expected but afforded a good yield of 1-oximino-1-phenyl-2-phenylhydrazonoethane (116). This product gave combustion analysis and showed spectroscopic properties consistent with the assigned structure. In particular the ^1H n.m.r. spectrum exhibited resonances for ten aromatic hydrogen atoms, a signal for a single hydrogen atom consistent with a CH proton and two exchangeable protons. The ^{13}C n.m.r. spectrum contained signals for the expected three quaternary carbon atoms.

It seems reasonable to assume that 1-oximino-1-phenyl-2-phenylhydrazonoethane (116) is formed via the isoxazolinone derivative (114). However, reaction of the isoxazolinone (114) with aqueous 2M sodium hydroxide gave a moderate yield of unreacted starting material and an

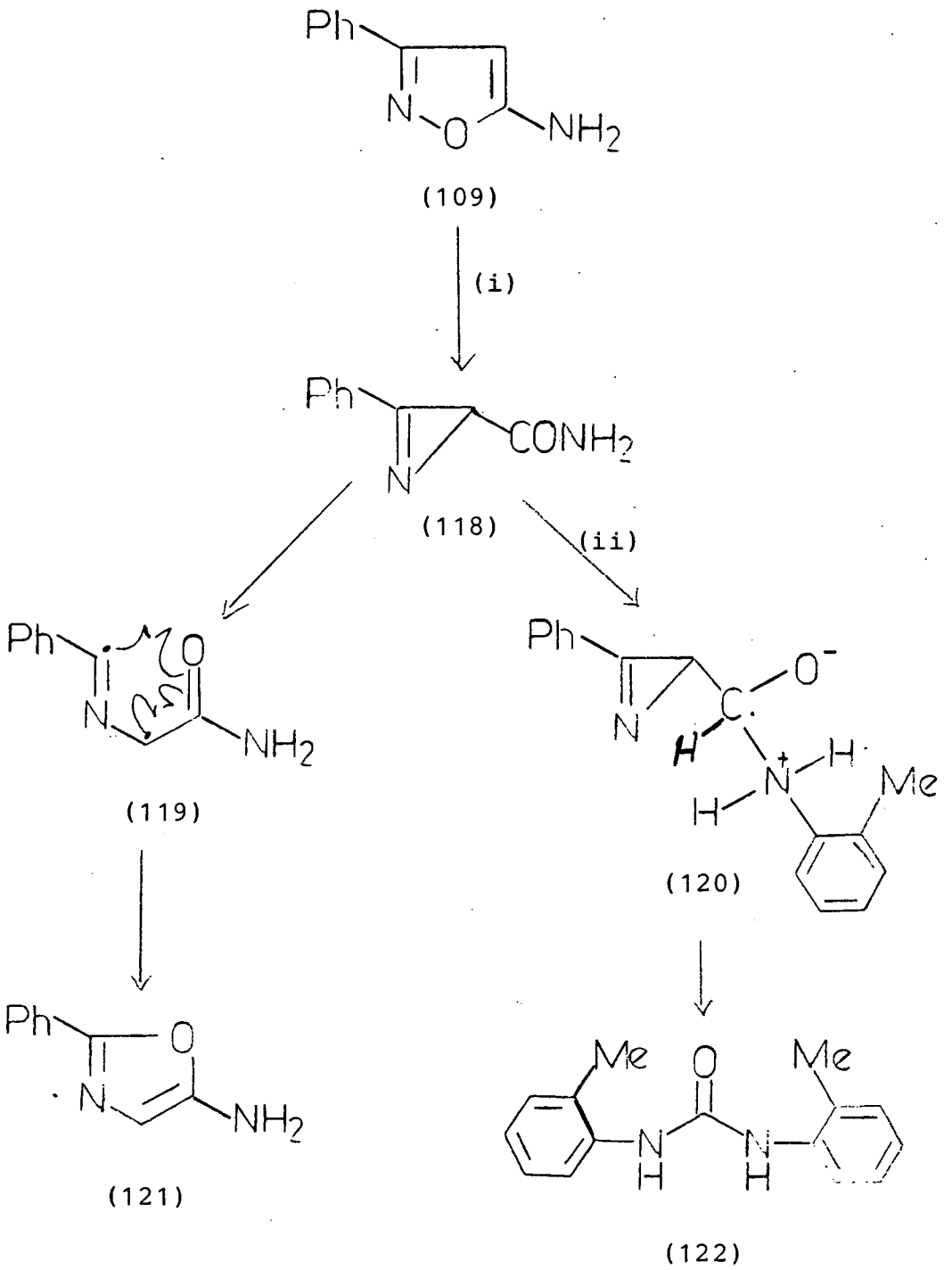


(i) $TSO_2N=C=O$, diglyme, heat

(ii) AcOH, heat

(iii) Diglyme, heat

Scheme 45



(i) heat

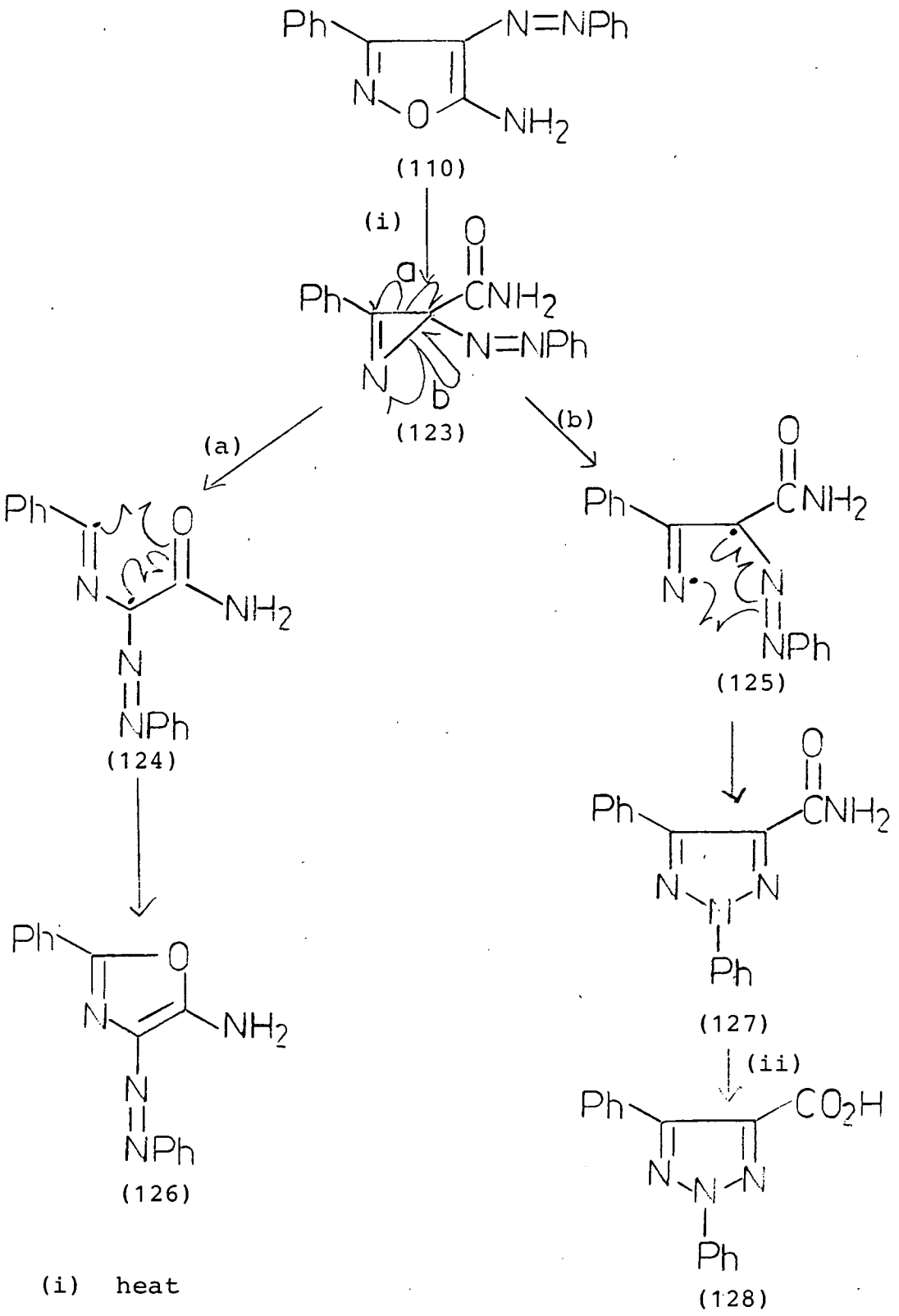
(ii) ortho-$MeC_6H_4NH_2$

Scheme 46

unidentified solid. None of the expected derivative (116) was detected. This would suggest that 1-oximino-1-phenyl-2-phenylhydrazonoethane (116) is formed directly from 5-amino-3-phenyl-4-phenylazoisoxazole (110) by a mechanism which is unclear.

The evidence would support 5-amino-3-phenyl-4-phenylazoisoxazole (110) having the assigned structure and in continuing the investigation of the annulation of such ortho-amino-arylazo heterocycles with tosyl isocyanate it was decided to investigate the reaction (Scheme 45) of the isoxazole derivative (110) with tosyl isocyanate. However reaction of 5-amino-3-phenyl-4-phenylazoisoxazole (110) with tosyl isocyanate failed to give the expected isoxazolo[3,4-e]-1,2,4-triazinone derivative (117) a quantitative yield of compound A being obtained. This compound was also obtained by simply heating the isoxazole (110) in diglyme or acetic acid indicating that the formation of the compound A from the isoxazole (110) was a thermal process and that tosyl isocyanate was not involved.

It is well documented[158] that isoxazoles rearrange thermally via azirines to oxazoles. This is illustrated (Scheme 46) by the thermal rearrangement[159] of 5-amino-3-phenylisoxazole (109) to the oxazole (121) via the azirine (118) whose existence was shown by "trapping" with ortho-toluidine to yield the urea derivative (122). Hence it would seen reasonable to suggest that compound A (see Scheme 45) is formed by a similar process to that described in Scheme 46. This would yield two possible



(i) heat

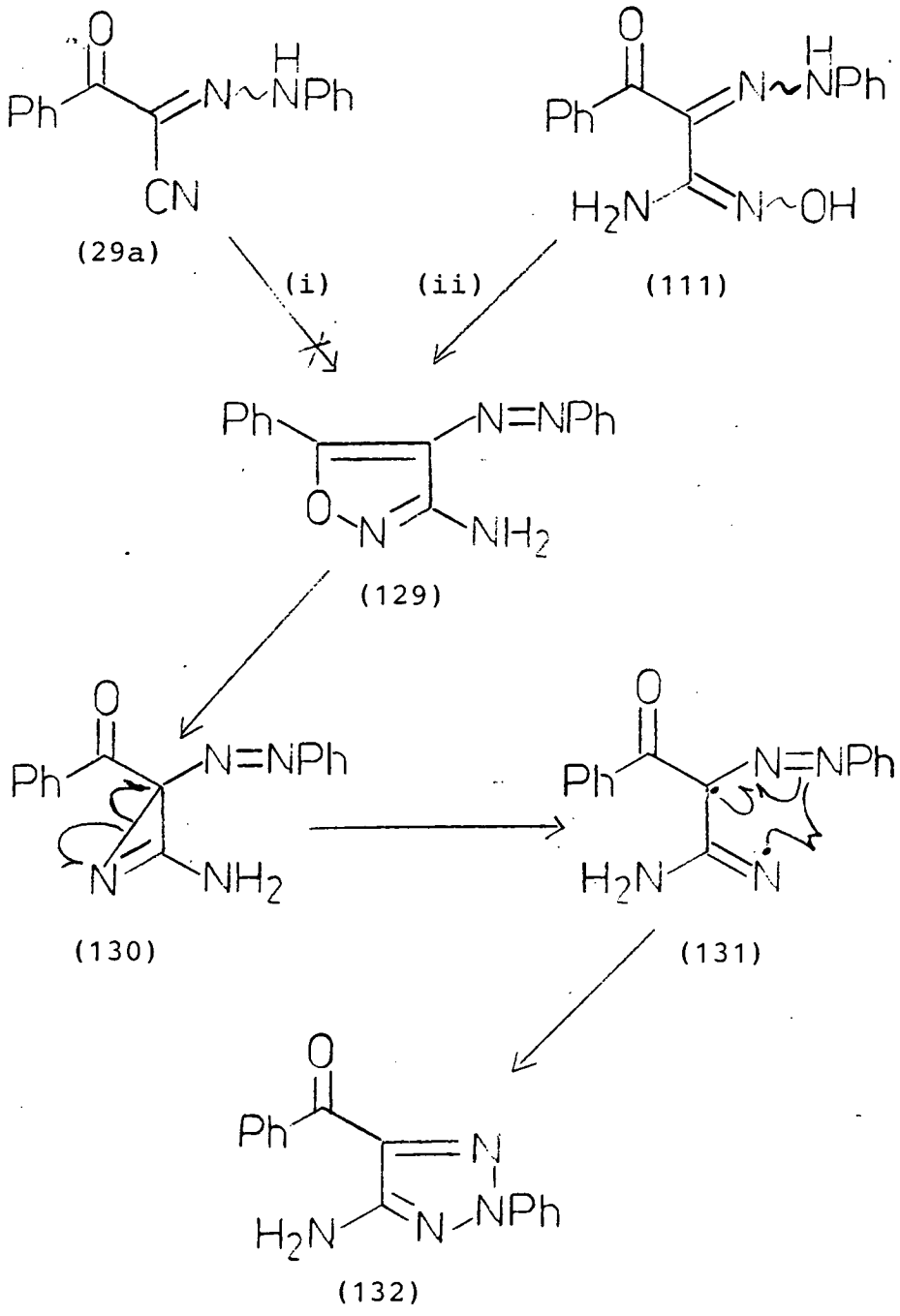
(ii) 2M NaOH, heat

Scheme 47

products as illustrated in Scheme 47, derivatives (126) and (127).

Both of these isomeric products are unknown and a combustion analysis and mass spectral data for compound A gave a molecular formula in agreement with both such products (126) and (127). However, other spectroscopic evidence would support the structure of compound A being that of 2,4-diphenyl-2H-1,2,3-triazole-5-carboxamide (127). In particular the i.r. spectrum exhibited absorptions at 3350 and 3150 cm^{-1} assignable as amide NH and supported by a carbonyl band at 1650 cm^{-1}. The ^{1}H n.m.r. spectrum contained resonances for ten aromatic hydrogen atoms and two exchangeable protons. The ^{13}C n.m.r. spectrum exhibited, as expected, five signals corresponding to five quaternary carbon atoms.

The structure of compound A being the triazole derivative (127) is further supported (Scheme 47) by the reaction of compound A with aqueous 2M sodium hydroxide to yield 2,4-diphenyl-2H-1,2,3-triazole-5-carboxylic acid (128). This product (128) gave combustion analysis and other spectroscopic data consistent with the assigned structure. In particular the i.r. spectrum shows a broad messy carboxylic acid OH band at 3200-2500 cm^{-1} supported by a carbonyl absorption at 1690 cm^{-1}. The ^{13}C n.m.r. spectrum only exhibits signals for four quaternary carbon atoms where five such signals are expected. However, as has been stated before, due to the long relaxation times



(i) $NH_2OH.HCl$, Na_2CO_3, EtOH, heat

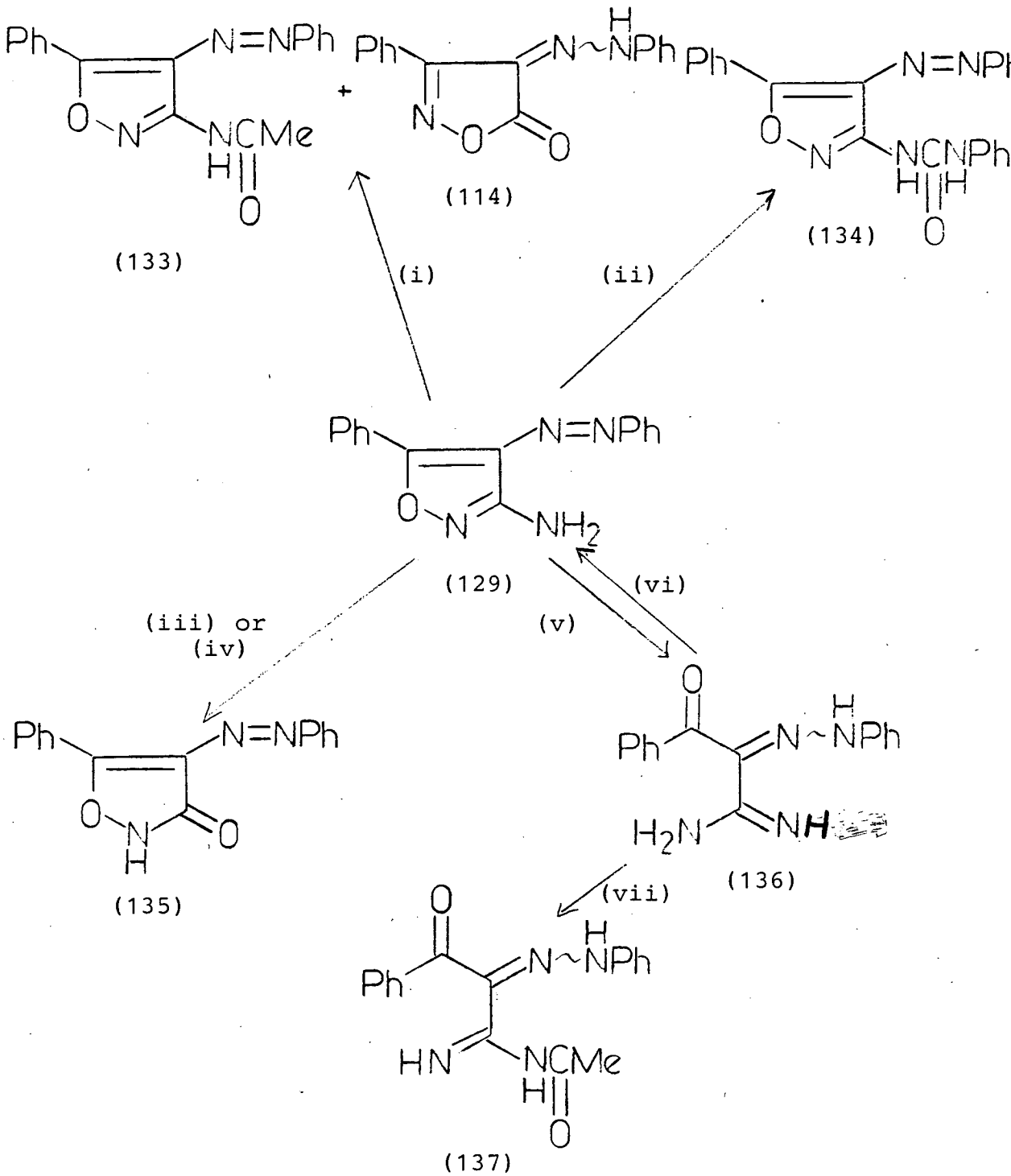
(ii) AcOH, heat

Scheme 48

of hetero-atom substituted quaternary carbon atoms such carbon atoms are not always visible in the ^{13}C n.m.r. spectrum.[86] The conversion of amides into carboxylic acids has also been reported[160] by treatment with acid. However, reaction of the triazole derivative (127) with aqueous sulphuric acid gave only a high recovery of unreacted starting material.

The unusual thermal behaviour of the isoxazole derivative (110) (Scheme 47) prompted the investigation of the thermal behaviour of other similar isoxazole derivatives. In particular (Scheme 48) the known[90] 3-amino-5-phenyl-4-phenylazoisoxazole (129) might be anticipated to undergo an analogous thermal rearrangement to give as illustrated the previously described (see Chapter 2, page 50) 4-amino-5-benzoyl-2-phenyl-2H-1,2,3-triazole (132). This isoxazole derivative (129) has been synthesised by Elnagdi and his co-workers[90] (Scheme 48) from 2-benzoyl-2-phenylhydrazonoacetonitrile (29a) by its reaction with hydroxylamine hydrochloride in the presence of aqueous sodium carbonate. However, repetition of these conditions only afforded a quantitative yield of unreacted acetonitrile (29a).

The isoxazole derivative (129) appears to have been successfully synthesised (Scheme 48) from 2-benzoyl-2-phenylhydrazonoacetamidoxime (111) by reaction with acetic acid by a mechanism which seems unclear. Since this reaction was carried out under reflux it might be presumed that if



(i) Ac_2O, heat

(ii) PhN=C=O

(iii) 20% w/v aq. H_2SO_4, EtOH, heat

(iv) 2M NaOH, EtOH, heat

(v) H_2, Pd-C

(vi) MnO_2

(vii) Ac_2O, 100°, 10 min.

Scheme 49

the isoxazole (129) was going to thermally rearrange then one should be able to detect the triazole derivative (132). However none of this triazole was isolated, a quantitative yield of 3-amino-5-phenyl-4-phenylazoisoxazole (129) being obtained. This product although not having a melting point in agreement with the reported[90] melting point, gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular the ^{1}H n.m.r. spectrum has resonances for ten aromatic hydrogen atoms and two exchangeable protons. The ^{13}C n.m.r. spectrum exhibited only signals for four quaternary carbon atoms. However, as has been stated before, due to the long relaxation times of hetero-atom substituted quaternary carbon atoms such carbon atoms are not always visible in the ^{13}C n.m.r. spectrum.[86]

The discrepancy in the melting point of 3-amino-5-phenyl-4-phenylazoisoxazole (129) reported here and as reported by Elnagdi and his co-workers[90] prompted the investigation (Scheme 49) of derivatisation of this isoxazole (129). Reaction of the isoxazole (129) with acetic anhydride afforded a small amount of 3-phenyl-4-phenylazo-Δ^{2}-isoxazolin-5-one (114) which has been described earlier (see Scheme 44) and a small amount of 3-acetamido-5-phenyl-4-phenylazoisoxazole (133). This product gave combustion analysis and spectroscopic data consistent with the assigned structure. In particular, the isoxazole (133) has amide NH absorption at 3220 cm^{-1} in its i.r. spectrum supported by a carbonyl band at 1690 cm^{-1}.

The ^{1}H n.m.r. spectrum contains resonances for ten aromatic hydrogen atoms, three hydrogen atoms of an acetyl CH_3 and a single exchangeable proton. Again, however, the ^{13}C n.m.r. spectrum has one signal less than expected for the number of quaternary carbon atoms contained in the product (133) in that five signals are visible whereas six are expected. This again can be explained in terms of the long relaxation times of hetero-atom substituted quaternary carbon atoms, such atoms are not always visible in the ^{13}C n.m.r. spectrum.[86]

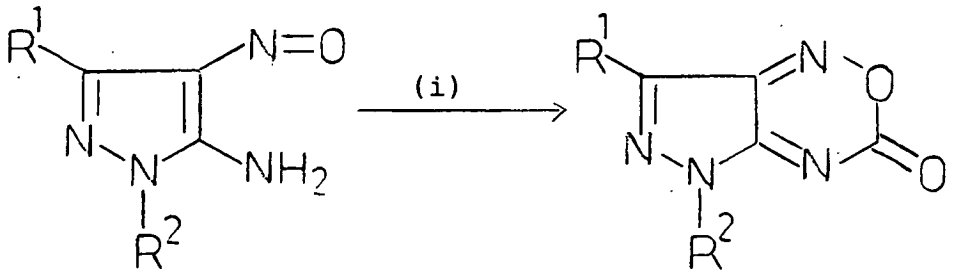
Continuing the investigation of the derivatisation of the isoxazole derivative (129) it was decided to attempt the synthesis (Scheme 49) of the urea derivative (134). Such derivatives are known[161] to be readily accessible by reaction with phenylisocyanate. Disappointingly, however, reaction of the isoxazole (129) with phenylisocyanate gave only a high yield of unreacted starting material.

It is known[157] and has been shown earlier that 5-aminoisoxazoles can be converted into isoxazolin-5-ones by treatment with acid or alkali. However treatment (Scheme 49) of the isoxazole derivative (129) with 20% w/v aqueous sulphuric acid or aqueous 2M sodium hydroxide failed to give the expected isoxazolinone derivative (135) only good yields of unreacted starting material being obtained.

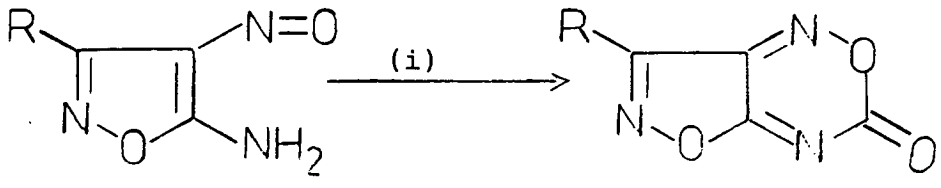
In further studying the derivatisation of the isoxazole derivative (129) it is known[162] that isoxazoles can undergoe catalytic hydrogenation to yield ring opened compounds. The catalytic hydrogenation (Scheme 49) of

3-amino-5-phenyl-4-phenylazoisoxazole (129) gave a good yield of the previously unknown 2-benzoyl-2-phenylhydrazono-acetamidine (136). This product gave analytical data and showed spectroscopic properties in agreement with the assigned structure. In particular the ^{1}H n.m.r. spectrum of the compound (136) exhibits resonances for ten aromatic hydrogen atoms and four exchangeable protons. The ^{13}C n.m.r. spectrum shows five signals for quaternary carbon atoms which is consistent with the assigned structure. This latter product (136) was not converted into the isoxazole (129) by oxidation with manganese dioxide only a good yield of unreacted 2-benzoyl-2-phenylhydrazonoacetamidine (136) being obtained. Also reaction of 2-benzoyl-2-phenylhydrazono-acetamidine (136) with acetic anhydride gave a good yield of 2-benzoyl-2-phenylhydrazono-N-acetylacetamidine ~~acetate~~ (137). This product gave combustion analysis and spectroscopic data consistent with the assigned structure. In particular, the ^{1}H n.m.r. spectrum contains resonances for ten aromatic hydrogen atoms, exhibits a signal for the three hydrogen atoms of an acetyl CH_3 group and contains resonances for three exchangeable protons. The ^{13}C n.m.r. spectrum also supports the assigned structure of the compound (137) in that it contains signals for six quaternary carbon atoms.

In conclusion, it has been shown that 5-amino-4-phenyl-azoisoxazoles do not undergo annulation with tosylisocyanate but prefer to rearrange to 2H-1,2,3-triazole derivatives.



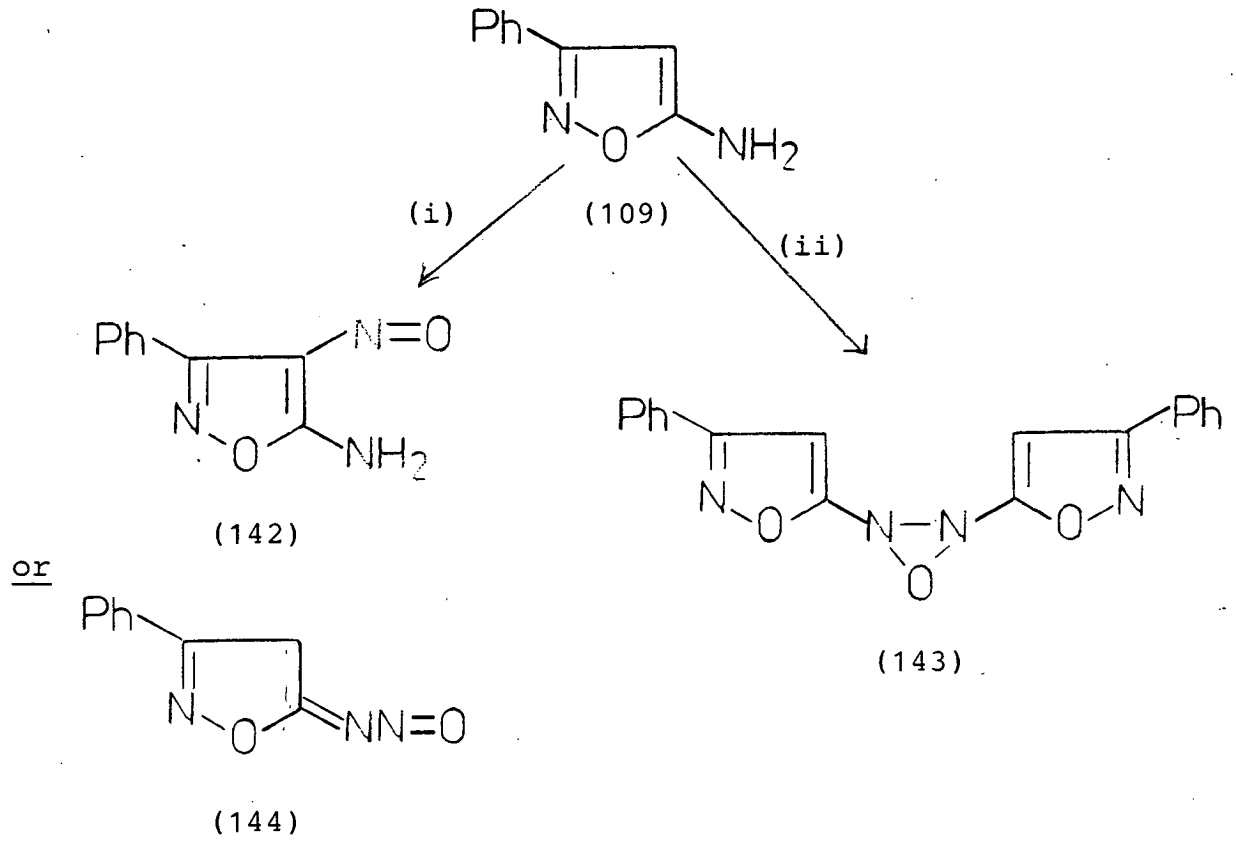
(138) (139)



(140) (141)

(i) $TSO_2N=C=O$

Scheme 50



(i) Amyl nitrite

(ii) HNO_2

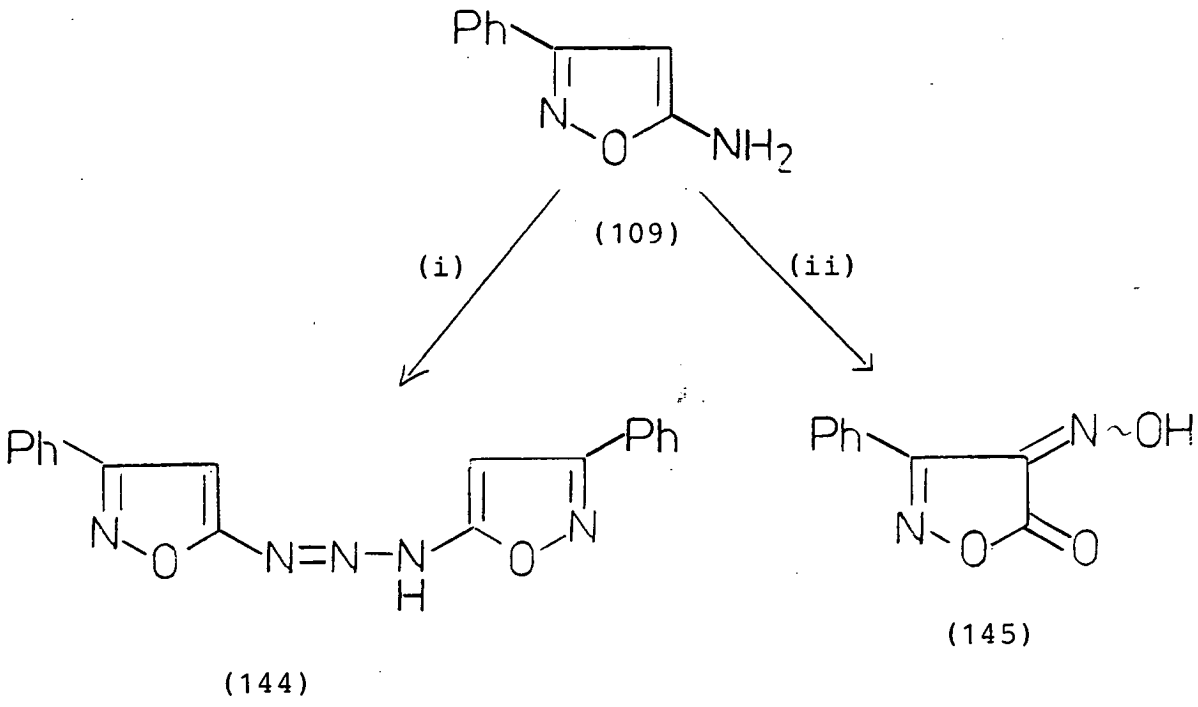
Scheme 51

It is suggested that this transformation be further investigated as it might lead to a general synthesis of 2H-1,2,3-triazole derivatives which, as has been described in Chapter 2, are useful precursors to 8-azapurines and other closely related polyazaheterocycles.

3.3.2 Studies on the Synthesis of 5-Amino-4-nitroso-5-phenylazoisoxazole

Previous studies at Edinburgh[129] have shown (Scheme 50) that 5-amino-4-nitrosopyrazoles (138) react with tosyl-isocyanate to afford the pyrazolooxadiazinone system (139). Therefore in continuing the investigation of the synthesis of polyazaheterocycles by annulation reactions of tosyl isocyanate it was decided to investigate the possible extension of the tosyl isocyanate annulation of amino-nitroso compounds to 5-amino-4-nitrosoisoxazoles as illustrated (Scheme 50) by the reaction of the 5-amino-4-nitrosoisoxazole (140; R=H) with tosyl isocyanate. This would by analogy be anticipated to yield the isoxazolo-oxadiazinone (141; R=H).

Such 5-amino-4-nitrosoisoxazoles have been reported[164] as illustrated (Scheme 51) by the reaction of 5-amino-3-phenylisoxazole (109) with amyl nitrite to give a product which has been assigned either as 5-amino-4-nitroso-3-phenylisoxazole (142) or as the N-nitrosoisoxazole derivative (144). However, this is the only report of the nitrosoisoxazole (142) and other workers have been unable to repeat this result. For instance, Moureau and Lazennec[163] have reacted (Scheme 51) 5-amino-4-phenylisoxazole (109)



(144)

(145)

(i) $NaNO_2$, CH_3CO_2H, 0°

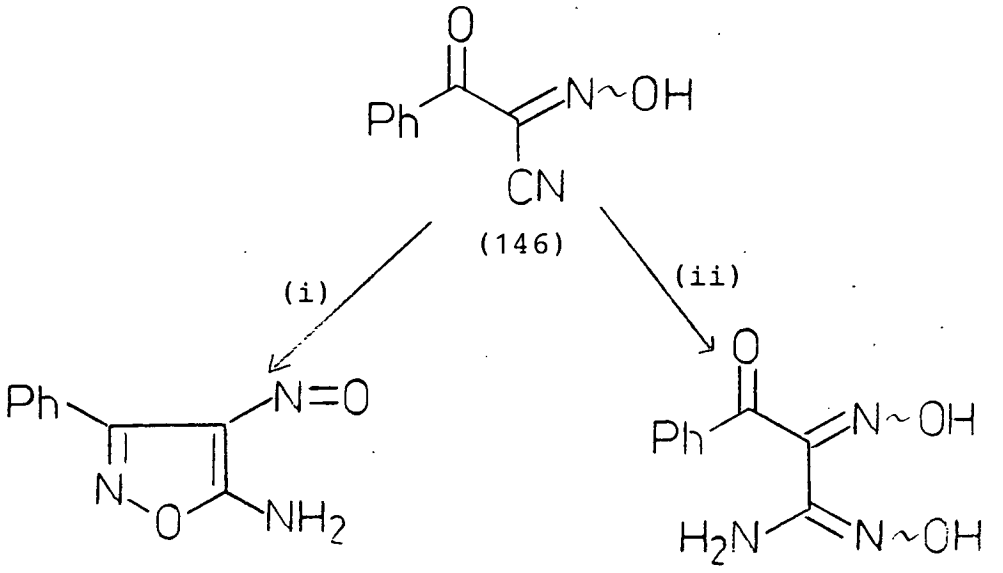
(ii) $EtNO_2$, HCl, ethanol, 0°

Scheme 52

with nitrous acid to afford a product they have assigned as the isoxazole dimer (143).

The ambiguity of the identity of the products of the nitrosation of 5-amino-3-phenylisoxazole (109) prompted the investigation of the nitrosation of this compound in the hope of obtaining the required 5-amino-4-nitroso-3-phenylisoxazole (142) as reported by Lublin.[164] Reaction (Scheme 52) of 5-amino-3-phenylisoxazole (109) under the standard conditions of nitrosation[165] of sodium nitrite in glacial acetic acid did not however yield the desired 5-amino-4-nitroso-3-phenylisoxazole (142), a low yield of 1,3-di-(phenylisoxazol-5-yl)triazene (144) being recovered along with a series of intractable gums. This product (144) had accurate mass spectral data and other spectroscopic data consistent with the assigned structure. In particular the ^{1}H n.m.r. spectrum exhibited resonances for ten aromatic hydrogen atoms, a signal for two characteristic isoxazole hydrogen atoms and a single exchangeable proton.

It is known that ethyl nitrite is a useful reagent of nitrosation.[166] The failure of the conditions described above prompted (Scheme 52) the reaction of 5-amino-3-phenylisoxazole (109) with ethyl nitrite. However, ~~this~~ of the isoxazole (109) with ethyl nitrite reaction failed to afford the desired 5-amino-4-nitroso-3-phenylisoxazole (142), a low yield of the known[167] 4-oximino-3-phenyl-Δ^{2}-isoxazolin-5-one (145) and an



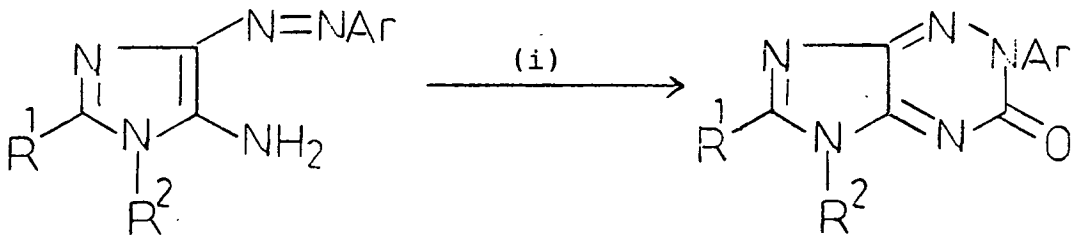
(i) $H_2NOH.HCl$, NaOH

(ii) $H_2NOH.HCl$, NaOMe

Scheme 53

intractable gum. This product (145) gave combustion analysis and had spectroscopic data consistent with the assigned structure. However, the mass spectrum exhibits no parent ion at 191 a.m.u., a peak being observed at 145 a.m.u. which can be explained by the loss of a nitro group.

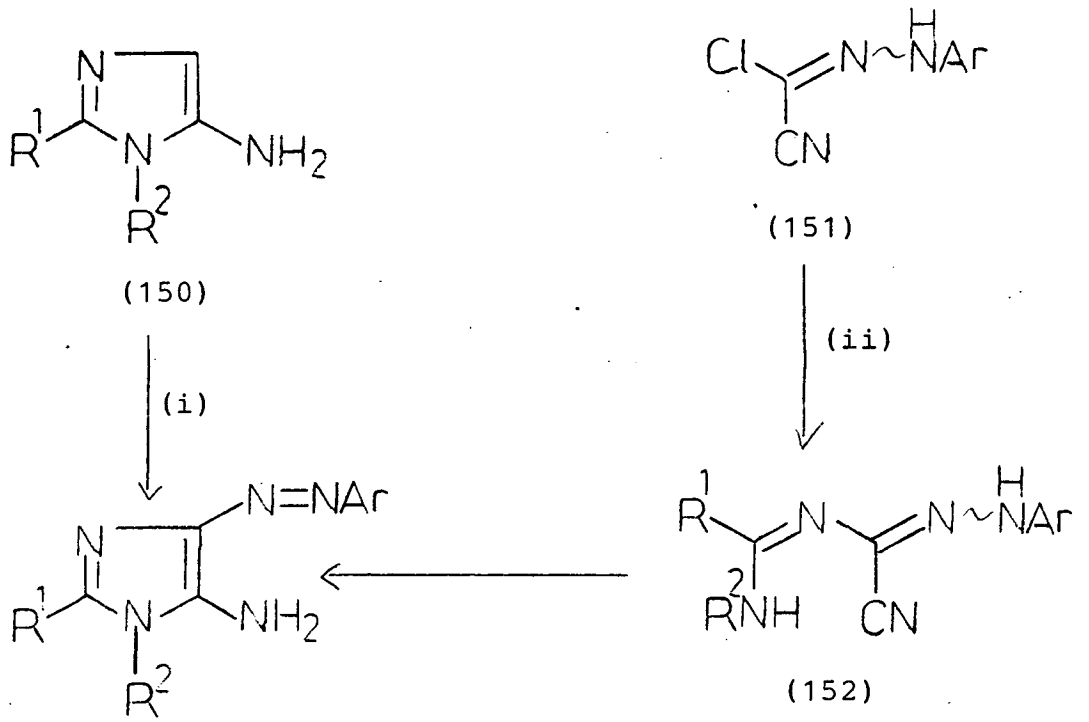
The failure of direct nitrosation to afford 5-amino-4-nitroso-3-phenylisoxazole (142) prompted the investigation of an alternative strategy (Scheme 53) It was anticipated that the known[168] 2-oximino-benzoyl-acetonitrile (146) readily prepared by reaction of 2-benzoyl-acetonitrile (28)[105] with sodium nitrite in glacial acetic acid would on reaction with hydroxylamine hydrochloride and sodium hydroxide yield the desired 5-amino-4-nitroso-3-phenylisoxazole (142) as similar nitriles are known[105] to form isoxazoles under these conditions. However, reaction of 2-benzoyl-2-oximinoacetonitrile (146) with hydroxylamine hydrochloride in the presence of sodium hydroxide gave a series of intractable solids, none of the desired nitrosoisoxazole being detected. In changing the conditions of reaction to hydroxylamine hydrochloride in the presence of sodium methoxide a moderate yield of the previously unknown 2-benzoyl-2-oximinoacetamidoxime (147) was recovered. This product (147) gave combustion analysis and spectroscopic data consistent with the assigned structure. In particular, the i.r. spectrum showed NH and OH absorption due to the amidoxime and oxime substituents, and a carbonyl band at 1645 cm^{-1}. The mass spectrum exhibits a parent ion at 207 a.m.u.



(148) (149)

(i) $TSO_2N=C=O$

Scheme 54



(150) (151) (152) (148)

(i) $ArN_2^+Cl^-$

(ii) $R^1C(=NH)NHR^2$

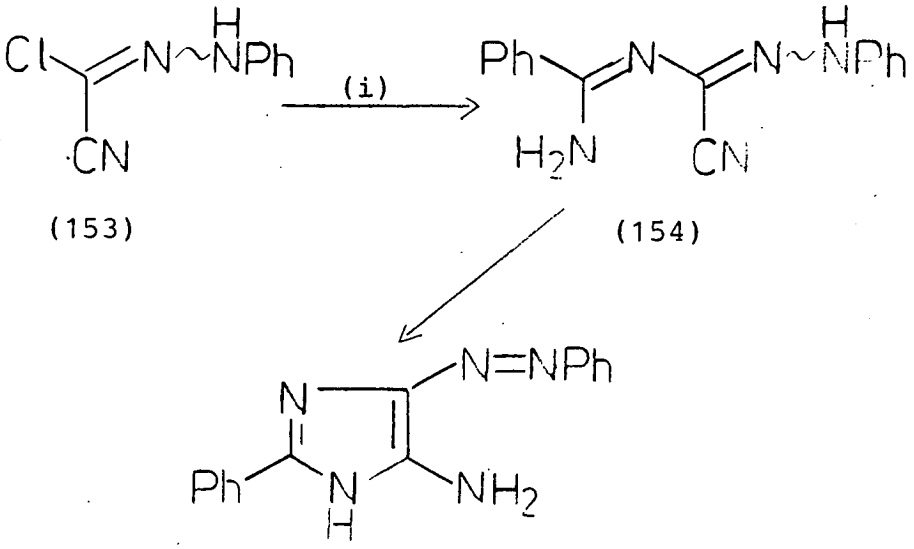
Scheme 55

In conclusion it has not been possible to synthesise the desired precursor 5-amino-4-nitroso-3-phenylisoxazole (142) in order to investigate its reaction with tosyl isocyanate. It is suggested that future workers in this area seek a radically new approach to the synthesis of this isoxazole derivative.

3.4 Synthetic Approaches to 5-Amino-4-arylazo-imidazoles

In continuing the investigation of the scope of the annulation of ortho-amino-arylazo heterocycles with tosyl isocyanate it was decided to investigate the application of this annulation (Scheme 54) to 5-amino-4-arylazoimidazoles (148). Such compounds on reaction with tosyl isocyanate would be expected to yield imidazolo[4,5-e]-1,2,4-triazine (6-azapurine) derivatives (149).

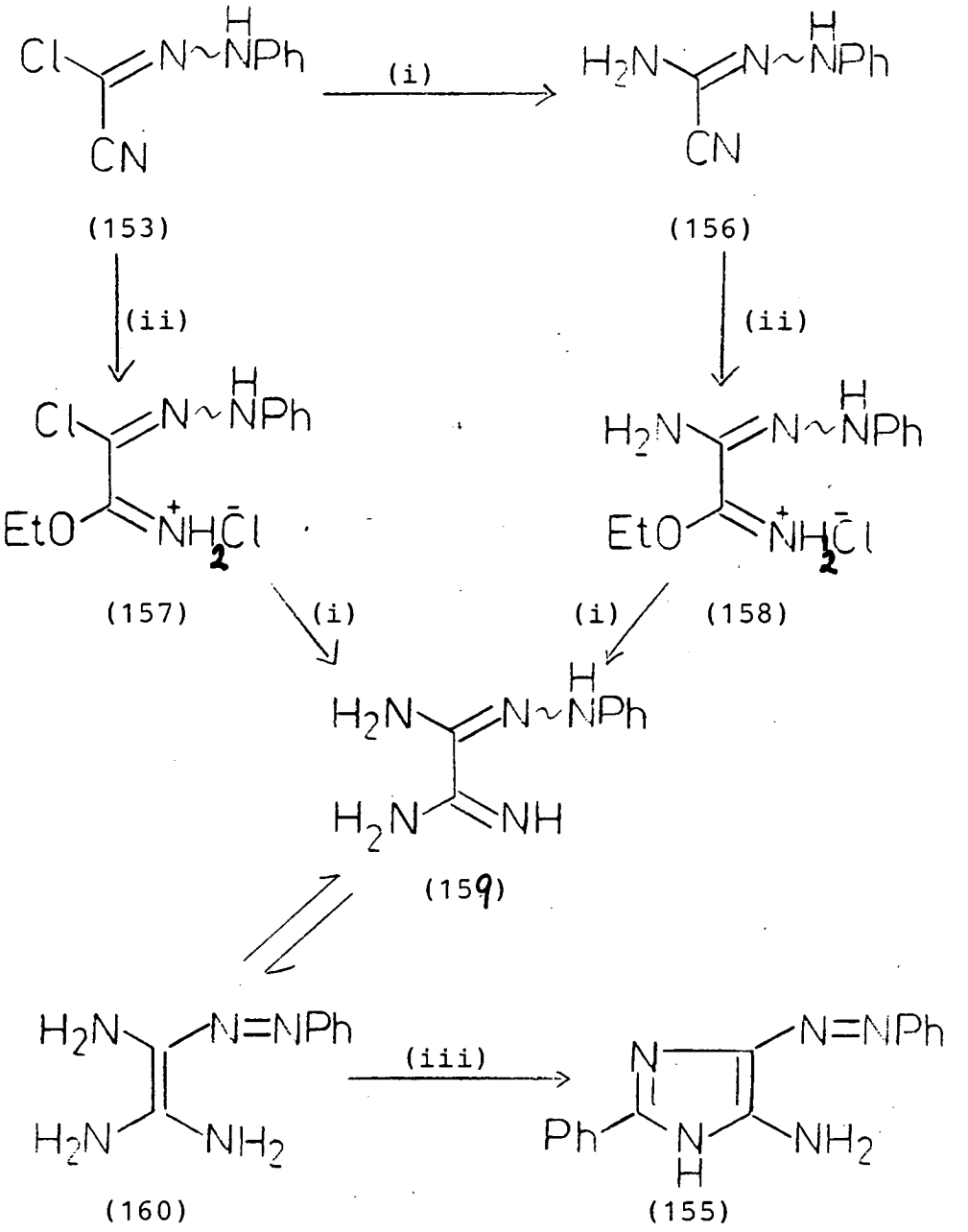
5-Amino-4-arylazoimidazoles are not known therefore it was necessary to devise a high yielding and unambiguous route to such systems. Two approaches to 5-amino-4-arylazo imidazoles are illustrated in Scheme 55. Firstly, by direct coupling of an aryldiazonium chloride with a 4(5)-amino imidazole (150). However 4(5)-amino imidazoles have been sparsely reported and are of dubious stability. Indeed 4(5)-amino imidazole itself has never been isolated being highly unstable.[169]



(153) (154) (155)

(i) $Ph-C(=NH)-NH_2.HCl$, NaOEt, EtOH, room temp.

Scheme 56



(i) NH_3, EtOH, room temp.

(ii) HCl, EtOH, 0°

(iii) PhCH=O, oxidation

Scheme 57

The second approach outlined (Scheme 55) is from 2-chloro-2-arylhydrazonoacetonitrile (151) which on reaction with an amidine derivative was anticipated to give 5-amino-4-arylazoimidazoles (148) directly, presumably through the intermediate (152).

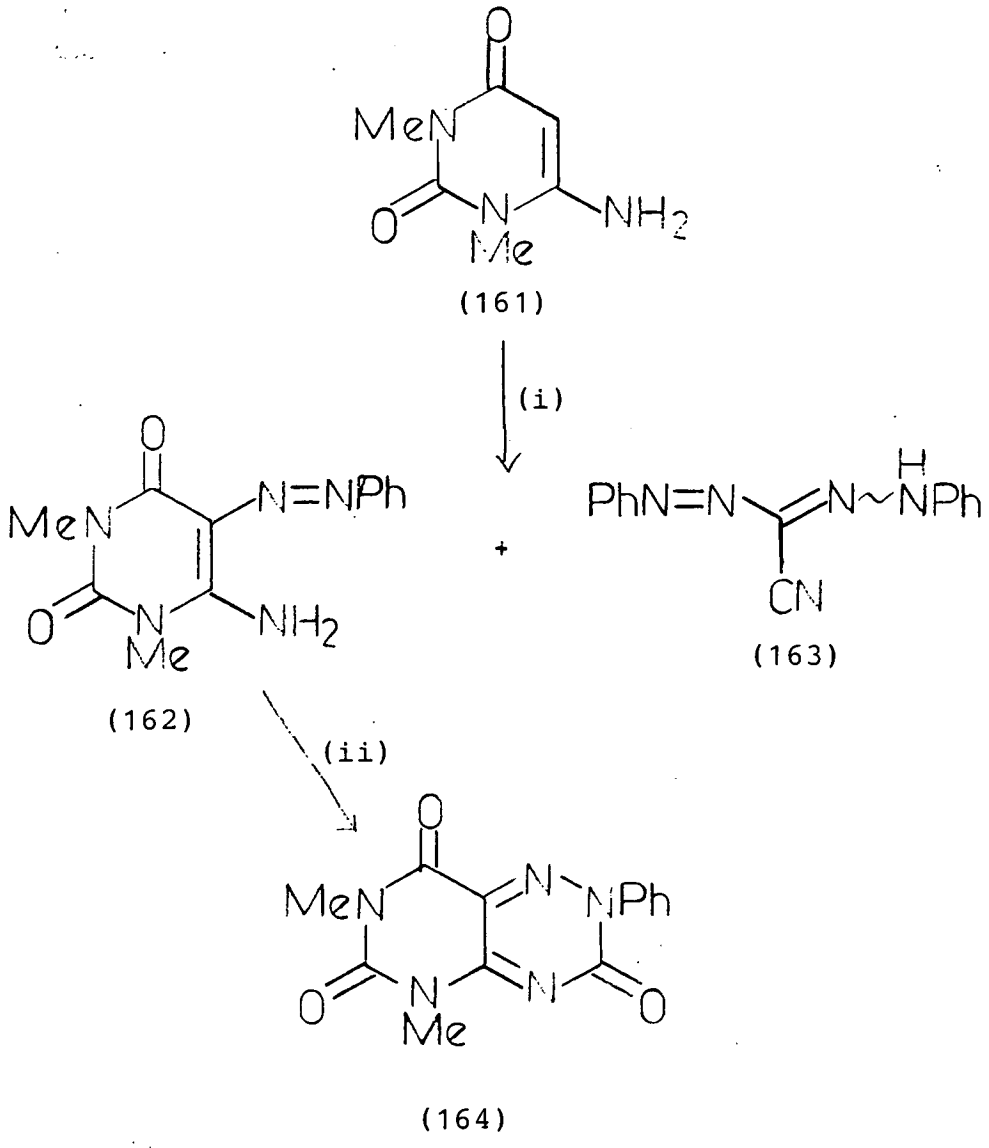
The latter approach is exemplified (Scheme 56) by the reaction of the previously described 2-chloro-2-phenylhydrazonoacetonitrile (153) (see Chapter 2, page 37) which on treatment with benzamidine hydrochloride in the presence of sodium ethoxide gave a moderate yield of 5-amino-4-phenylazo-2-phenyl-1H-imidazole (155) and a moderate yield of unreacted 2-chloro-2-phenylhydrazonoacetonitrile. The product (155) gave analytical data and showed spectroscopic properties consistent with the assigned structure. Unfortunately, repetition of this reaction on a larger scale failed to give any identifiable material. This prompted the investigation of an alternative strategy to 5-amino-4-arylazoimidazole derivatives, as illustrated (Scheme 57) by the reaction of the amidine derivative (160) with benzaldehyde which would be anticipated to yield the imidazole derivative (155) presumably after oxidation.

The amidine derivative (160) and its tautomer (159) were anticipated to be accessible by two routes (Scheme 57). Firstly, by reaction of the 2-chloro-2-phenylhydrazonoacetimidate hydrochloride (157), whose

synthesis from 2-chloro-2-phenylhydrazonoacetonitrile (153) has been described before (see Chapter 2, page 37), with ethanolic ammonia. However, reaction of O-ethyl 2-chloro-2-phenylhydrazonoacetimidate hydrochloride (157) with ethanolic ammonia gave a series of intractable gums and solids.

The failure of this reaction [(157)→(159)] prompted the investigation of the second route (Scheme 57) to the amidine derivative (159). 2-Amino-2-phenylhydrazono-acetonitrile (156), whose synthesis from 2-chloro-2-phenylhydrazonoacetonitrile (153) has been described earlier (see Chapter 2, page 37), was readily converted into O-ethyl 2-amino-2-phenylhydrazonoacetimidate hydro-chloride (158) by reaction with ethanolic hydrogen chloride. This product was highly unstable and has been assigned in terms of its mass spectrum and ^{1}H n.m.r. spectrum which exhibits resonances for five aromatic hydrogen atoms, contains signals for an ethyl group and has resonances for four exchangeable protons. However, subsequent reaction of this imidate derivative (158) with ethanolic ammonia failed to afford the desired amidine (159), a series of intractable solids and gums being obtained.

Therefore, in conclusion, the previously unknown 5-amino-4-phenylazo~~isoxazole~~ imidazole ring system has been synthesised. However, in insufficient yield to continue the investigation



(161)

(i)

(162)

(163)

(ii)

(164)

(i) $PhN_2^+Cl^-$, NaOAc, 0°

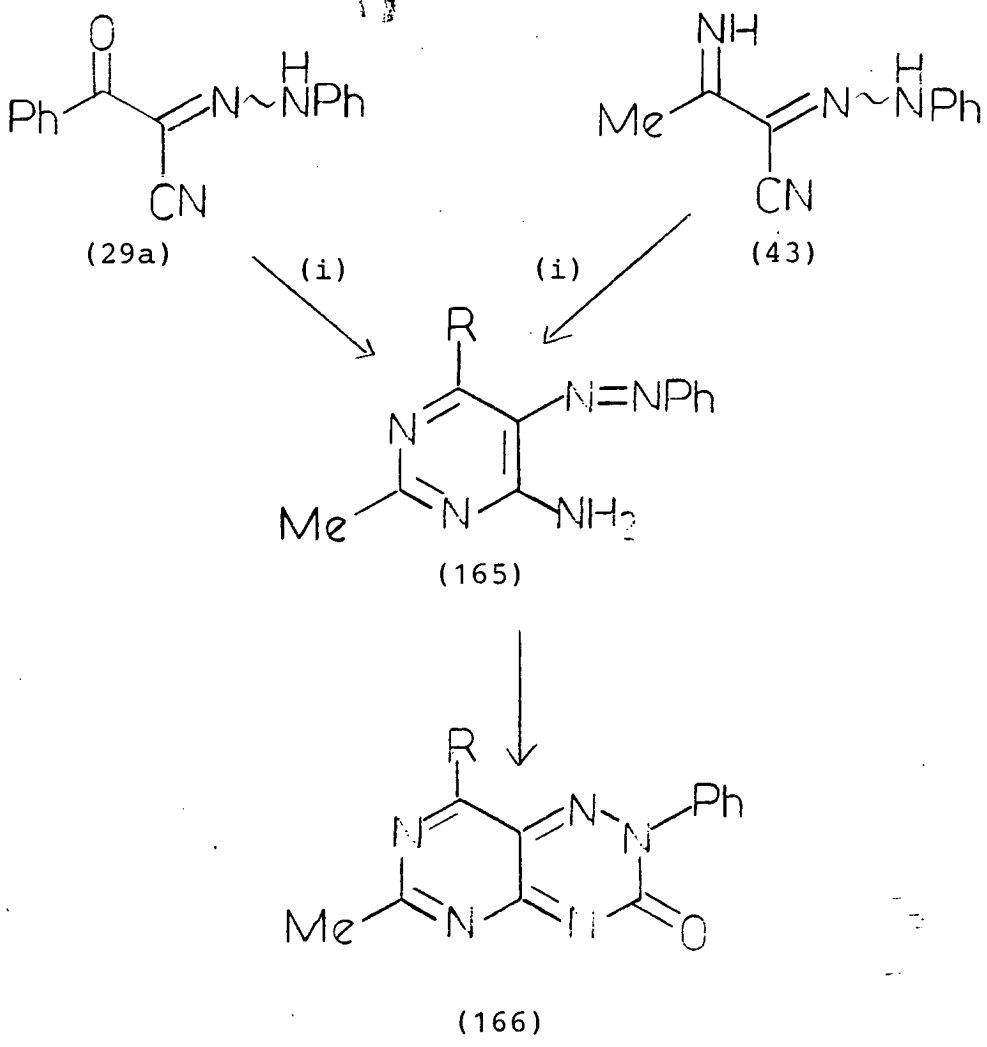
(ii) $TSO_2N=C=O$, diglyme, heat

Scheme 58

of its reaction with tosyl isocyanate. Further work has yet to be carried out in order to establish high yielding and reproducible reaction conditions for the synthesis of 5-amino-4-arylazoimidazoles.

3.5 Studies of the Synthesis and Tosyl Isocyanate Annulation of 4-amino-5-arylazopyrimidines

So far discussion of the annulation of ortho-amino-arylazo and ortho-amino-nitroso compounds has been limited to 5-membered heterocyclic systems containing two hetero-atoms, usually nitrogen. Hence synthetic approaches to azapurines and closely related polyazaheterocycles have been described. In extending the applicability of the tosyl isocyanate annulation it was decided to investigate the reaction of 4-amino-5-arylazopyrimidines with tosyl isocyanate. This was illustrated (Scheme 58) by the reaction of 4-amino-1,3-dimethyl-5-phenylazouracil (162) with tosyl isocyanate, which afforded a moderate yield of the known[65,170] 6-azapteridine derivative (164). The known[171,172] 4-amino-5-phenylazouracil (162) was readily available by coupling of 4-amino-1,3-dimethyluracil (161) with benzenediazonium chloride. This latter reaction also afforded a moderate yield of the known[172] 1,5-diphenyl-3-formazancarbonitrile (163). The 6-aza-pteridine derivative (164) gave combustion analysis and spectroscopic data in agreement with the assigned structure.



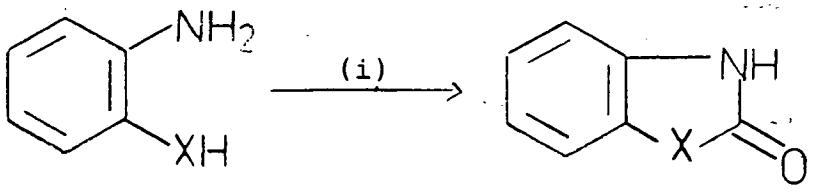
	R
a;	Ph
b;	Me

(i) $MeC(=NH)-NH_2.HCl$, NaOEt, EtOH, heat

Scheme 59

In order to extend this synthesis of 6-azapteridines it is necessary to develop a high yielding and unambiguous synthesis of 4-amino-5-arylazopyrimidines. It is well known that β-ketonitriles react with amidines and similar compounds to yield pyrimidines.[173,174] Therefore it was anticipated (Scheme 59) that the previously described acetonitrile derivatives (29a) and (43a) would react with acetamidine hydrochloride in the presence of sodium ethoxide to yield 4-amino-5-phenylazopyrimidines (165a) and (165b) respectively. These derivatives would in turn be expected to react with tosyl isocyanate to give the 6-azapteridine derivatives (166a) and (166b). However reaction of the acetonitrile derivatives (29a) and (43) with acetamidine hydrochloride in the presence of sodium ethoxide disappointingly gave only high yields of unreacted starting material.

It has however been demonstrated that 6-azapteridines can be synthesised by methodology based on tosyl isocyanate annulation and it is hoped that future workers will employ this in the synthesis of other azapteridines and diazapteridines.



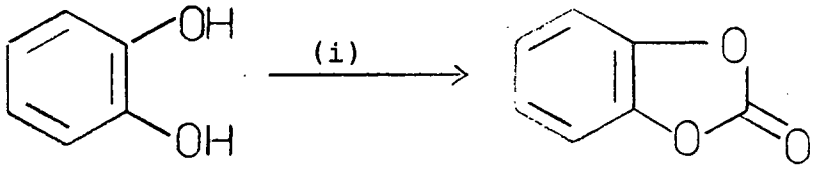
(167) (168)

X

a; NH

b; O

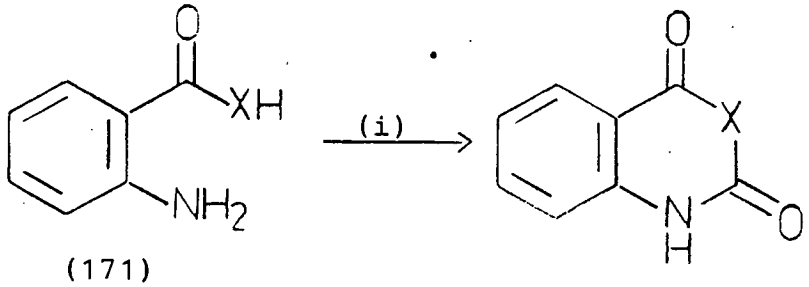
c; S



(169) (170)

(i) $TSO_2N=C=O$, diglyme, heat

Scheme 60



(171) (172)

X

a; NH

b; O

(i) $TSO_2N=C=O$, diglyme, heat

Scheme 61

3.6 Miscelleaneous Heterocyclic Syntheses Based on Tosyl Isocyanate Annulation Reactions

As can be readily seen, all the previously discussed annulation reactions with tosyl isocyanate involve cyclisation by introduction of a carbonyl group. In order to investigate the possibility that tosyl isocyanate might be a useful carbonylating reagent and also provide a general synthesis of heterocycles it was decided to investigate the reaction (Schemes 60 and 61) of a variety of ortho disubstituted benzene derivatives.

The reaction (Scheme 60) of ortho-phenylene diamine with tosyl isocyanate (167a) gave a good yield of the known[175] benzimidazolinone (168a). This compound gave combustion analysis and spectroscopic data consistent with the assigned structure. Similarly reaction of ortho-aminophenol (167b) with tosyl isocyanate gave a moderate yield of the known[176] benzisoxazolinone (168b) again having spectroscopic properties and analytical data in agreement with the assigned structure. However, inexplicably, reaction of ortho-amino-benzenethiol (167c) with tosyl isocyanate gave only a poor yield of the expected previously reported[177] benzthiazolinone derivative (168c). A high yield of toluene-4-sulphonamide being isolated. The product (168c) showed mass spectral data and other spectroscopic data in agreement with the assigned structure.

In extending this carbonylation process to ortho-benzene derivatives without an amine substitutent (Scheme 60) catechol (169) was reacted with tosyl isocyanate. This gave a moderate yield of the expected and known[178] 1,3-benzodioxol-2-one (170) which had a melting point in agreement with that reported. It also gave combustion analysis and spectroscopic data in agreement with the assigned structure.

Further extension of this annulation by tosyl isocyanate of ortho-disubstituted benzene derivatives is exemplified (Scheme 61) by the reaction of derivatives such as anthranilamide (171a) and anthranalic acid (171b), which on reaction with tosyl isocyanate would be expected to give the quinazolindione derivative (172a) and isatoic anhydride (172b). However in practice reaction of anthranilamide (171a) with tosyl isocyanate afforded only a low yield of the known[179] quinazolinone (172a), a high yield of toluene-4-sulphonamide being obtained. The product (172a) had combustion analysis and spectroscopic data consistent with the assigned structure.

Disappointingly reaction of anthranilic acid (171b) with tosyl isocyanate did not afford the expected product isatoic anhydride. In practice the reaction gave a moderate recovery of unreacted starting material and a quantitative yield of toluene-4-sulphonamide.

It would therefore appear that tosyl isocyanate can be used, albeit with varying degrees of success, as a carbonylating reagent to form a variety of heterocycles. Since this is a purely thermal process it might find application in generating such heterocycles where the more orthodox conditions of diethylcarbonate and base cannot be used, for example where the substrate contains a base sensitive protecting group.

3.7 EXPERIMENTAL

2-Phenylhydrazonobenzoylacetonitrile (2-Benzoyl-2-phenylhydrazonacetonitrile (29a)

2-Phenylhydrazonobenzoylacetonitrile (2-benzoyl-2-phenylhydrazonoacetonitrile) (29a) was prepared as described in Chapter 2.

2-Arylhydrazonobenzoylacetonitriles

A solution of the corresponding arylamine (0.05 mol) in aqueous 5M hydrochloric acid (50.0 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrile (4.3 g, 0.055 mol) in water (25.0 ml). The resulting aryldiazonium chloride solution was stirred for a further 5 min in the ice-salt bath, then added dropwise at 0-5° (ice-salt bath) to a stirred solution of benzoylacetonitrile (7.3 g, 0.05 mol) and anhydrous sodium acetate (6.3 g, 0.075 mol) in ethanol (150 ml) and water (150 ml), and the mixture was stirred in the melting ice-salt bath for a further 1 h. The mixture was then worked up as described for the individual reactions below.

(a) The mixture from 4-methylbenzenediazonium chloride was filtered to afford a yellow solid which was crystallised from toluene to yield 2-(4-methylphenylhydrazono)benzoylacetonitrile (29b),[135] (91%), as yellow prisms, m.p. 160-161°, (lit,[136] 156°) ν_{max} 3200 (NH), 2200 (CN) and 1630 (CO) cm^{-1}, δ ($CDCl_3$) 11.96 (1H, brs, NH), 9.41 (1H, brs, NH), 8.07-7.07 (18H, m, ArH), 2.38 (3H, s, CH_3) and 2.35 (3H, s, CH_3).

Found: 263.1059

Calc. for $C_{16}H_{13}N_3O$: 263.1059

The aqueous mother liquor on neutralisation with aqueous 2M sodium hydroxide solution and subsequent extraction with methylene chloride afforded no further material.

(b) The mixture from 4-nitrobenzenediazonium chloride was filtered to afford a yellow solid which was crystallised from dimethyl formamide-water to yield 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29e), (95%), as yellow needles, m.p. 232-233°, ν_{max} 3125 (NH), 2215 (CN), 1640 (CO), and 1540 and 1340 (NO_2) cm^{-1}, δ [$(CD_3)_2SO$] 13.00-12.00 (1H, brs, NH), 8.27 (2H, d, J9Hz ArH), 7.98-7.61 (5H, m, ArH) and 7.91 (2H, d, J9Hz ArH).

Found: C, 61.0; H, 3.4; N, 19.1%, M^+, 294.

$C_{15}H_{10}N_4O_3$ requires: C, 61.2; H, 3.4; N, 19.1%; M, 294.

The aqueous mother liquor on neutralisation with aqueous 2M sodium hydroxide and subsequent extraction with methylene chloride afforded no further material.

(c) The mixture from 4-methoxybenzenediazonium chloride was filtered to afford 2-(4-methoxyphenylhydrazono)benzoylacetonitrile (29d), (94%), m.p. 144-145° (from toluene), ν_{max} 3220 (NH), 2205 (CN) and 1690 (CO) cm^{-1}, δ ($CDCl_3$) 8.05-6.86 (9H, m, ArH), 3.83 (3H, s, OCH_3) and 1.56 (1H, brs, NH).

Found: 279.1007

$C_{16}H_{13}N_3O_2$ requires: 279.1008

The aqueous mother liquor on neutralisation with aqueous 2M sodium hydroxide and subsequent extraction with methylene chloride afforded no further material.

(d) The mixture from 4-chlorobenzenediazonium chloride was filtered to afford 2-(4-chlorophenylhydrazono)-benzoylacetonitrile (29c)[136] (59%) m.p. 175-176° (from toluene), (lit,[136] 171°), ν_{max} 3210 (NH), 2210 (CN) and 1640 (CO) cm^{-1}, δ ($CDCl_3$) 9.55 (1H, brs, NH) and 8.05-7.24 (9H, m, ArH).

Found: C, 63.2; H, 3.6; N, 14.7%; M^+, 285,283

Calc. for $C_{15}H_{10}N_3OCl$: C, 63.5; H, 3.5; N, 14.8%; M, 283.5

The aqueous mother liquor was neutralised with aqueous 2M sodium hydroxide solution and extracted with methylene chloride to afford a red gum (2.2 g) which was subjected to flash chromatography.

Elution with methylene chloride-n-hexane (2:1) through to ethylacetate and then ethanol afforded a series of intractable gums and solids (total, 2.2 g) which were not further investigated.

5-Amino-4-arylazo-1-methyl-3-phenybpyrazoles

A solution of the corresponding 2-arylhydrazonobenzoylacetonitrile (0.01 mol) in ethanol (50.0 ml) was treated with methylhydrazine (0.46 g, 0.01 mol) and the mixture was heated under reflux for 17 h. The mixture was then worked up as described for the individual reactions below.

(a) The mixture from 2-benzoyl-2-phenylhydrazo-acetonitrile (29a) was cooled and evaporated to afford a red-brown gum which was subjected to flash chromatography.

Eluting with methylene chloride-ethylacetate (8:1) yielded 5-amino-1-methyl-4-phenylazo-1-phenylpyrazole (30a) as an orange solid (12.1 g; 87%) which formed yellow crystals, m.p. 132-133° (from toluene-light petroleum), ν_{max} 3470 and 3310 (NH) cm^{-1}, δH ($CDCl_3$) 8.20-7.32 (CO, m, ArH), 6.00 (2H, brs, NH) and 3.68 (3H, s, NCH_3), δ_C[$(CD_3)_2SO$)] 153.09 (quat), 146.34 (quat), 140.46 (quat), 132.56 (quat), 129.06, 128.25, 127.95, 127.40, 121.55 (quat), 120.85 and 34.29 (NCH_3)

Found: 277.1318

$C_{16}H_{15}N_5$ requires: 277.1327

Final elution with ethanol afforded an intractable brown gum (0.01 g) which was not further investigated.

(b) The mixture from 2-(4-methylphenylhydrazone)-benzoylacetonitrile (29b) was cooled and evaporated to afford a brown gum which was subject to flash chromatography.

Elution with methylene chloride-cyclohexane (2:1) followed by methylene chloride-ethylacetate (10:1) gave unidentified gums (total, 0.6 g).

Elution with methylene chloride-ethylacetate (5:1) yielded 5-amino-1-methyl-4(4-methylphenylazo)-3-phenyl-pyrazole (30b) as a yellow solid (39%) m.p. 158-159° (from toluene), ν_{max} 3340 and 3175 (NH) cm^{-1}, δ_H ($CDCl_3$) 8.20-8.15 (2H, m, ArH), 7.66-7.62 (2H, d, J8Hz ArH), 7.49-7.37 (3H, m,

ArH), 7.27-7.23 (2H, d, J8H_3 ArH), 5.95 (2H, brs, NH), 3.64 (3H, s, NCH_3) and 2.40 (3H, s, CH_3), δ_c ($CDCl_3$) 151.29 (quat), 148.07 (quat), 138.64 (quat), 138.52 (quat), 132.53 (quat), 129.52, 128.13, 128.03, 122.15 (quat), 121.21, 33.64 (NCH_3) and 21.23 (CH_3).

Found: C, 70.2; H, 5.6; N, 24.4%; M^+, 290

$C_{17}H_{17}N_5$ requires: C, 70.1; H, 5.8; N, 24.1%; M , 291

Further elution with ethyl acetate through to ethanol gave a series of gums (total, 0.5 g) whose t.l.c. in methylene chloride showed them to be multicomponent mixtures which were not further investigated.

(c) The mixture from 2-(4-nitrophenolhydrazono)-benzoylacetonitrile (29c) was cooled and filtered to afford a red solid which was combined with a second crop obtained by evaporating the ethanolic filtrate and triturating the resulting red gum with ethanol to give 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30c) (86%) which formed red needles, m.p. 226-227° (from glacial acetic acid-water), ν_{max} 3420 (NH) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 8.28 (2H, d, J9H_3 ArH) 8.11-8.05 (2H, m, ArH), 7.90 (2H, d, J9Hz ArH), 7.82 (2H, brs, NH), 7.51-7.38 (3H, m, ArH) and 3.67 (3H, s, NCH_3), $\delta_C[(CD_3)_2SO]$ 157.48 (quat), 147.08 (quat), 145.51 (quat), 140.57 (quat), 131.89 (quat), 128.22, 127.46, 124.74, 123.53 (quat), 121.70, and 34.26 (NCH_3).

Found: C, 59.3; H, 4.3; N, 25.9%; M^+, 322.

$C_{16}H_{14}N_6O_2$ requires: C, 59.6; H, 4.4; N, 26.1%; M, 322.

The ethanolic filtrate was evaporated to afford a red gum (0.01 g) which was not further investigated.

(d) The mixture from 2-(4-methoxyphenylhydrazono)-benzoylacetonitrile (29d) was cooled and evaporated to afford a brown solid which was subjected to flash chromatography.

Elution with ethylacetate-cyclohexane (1:1) yielded 5-amino-4-(4-methoxyphenylazo)-1-methyl-3-phenylpyrazole (30d) (80%) m.p. 136-137° [from toluene-light petroleum (b.p. 40-60°)], ν_{max} 3380 and 3280 (NH) cm^{-1}, δ_H ($CDCl_3$) 8.22-8.10 (2H, m, ArH), 7.71 (2H, d, J9Hz ArH), 7.46-7.25 (3H, m, ArH), 6.95 (2H, d, J9Hz ArH), 5.88 (2H, brs, NH), 3.86 (3H, s, OCH_3) and 3.69 (3H, s, NCH_3), δ_C[$(CD_3)_2SO$] 159.38 (quat), 147.14 (quat), 146.00 (quat), 139.77 (quat), 132.75 (quat), 128.13, 127.71, 127.28, 122.18, 120.96 (quat), 114.29, 55.37 (OCH_3) and 34.23 (NCH_3).

Found: C, 66.3; H, 5.7; N, 22.7%, M^+, 307

$C_{17}H_{17}N_5O$ requires: C, 66.5; H, 5.5; N, 22.8%; M, 307

Further elution with ethylacetate-cyclohexane (1:1) through ethyl acetate to ethanol yield a series of gums (total, 0.1 g) which were not further investigated.

(e) The mixture from 2-(4-chlorophenylhydrazono)-benzoylacetonitrile (29c) was cooled and evaporated to afford a brown gum which was subjected to flash chromatography.

Elution with methylene chloride-ethylacetate (10:1) yielded 5-amino-4-(4-chlorophenylazo)-1-methyl-3-phenylpyrazole (30c) (80%) m.p. 151-152° (from toluene) ν_{max} 3350 and 3190 (NH) cm^{-1}, δ_H ($CDCl_3$) 8.16-8.11 (2H, m, ArH), 7.63 (2H, d, J11H_3 ArH), 7.49-7.42 (3H, m, ArH), 7.39 (2H, d, J11Hz ArH),

5.97 (2H, brs, NH) and 3.62 (3H, s, NCH_3), δ_C ($CDCl_3$) 151.74 (quat), 148.34 (quat), 138.79 (quat), 133.75 (quat), 132.26 (quat), 129.02, 128.18, 128.00, 122.39 and 33.61 (NCH_3).

Found: C, 61.5; H, 4.4; N, 22.3%; M+ 313, 311

$C_{16}H_{14}N_5Cl$ requires: C, 61.5; H, 4.5; N, 22.4%; M, 311.5.

Elution with ethylacetate through to ethanol gave a series of brown gums (total, 0.1 g) which was not further investigated.

5-Aryl-1-methyl-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-ones

A solution of the corresponding 5-amino-4-anylazo-1-methyl-3-phenylpyrazole (0.002 mol) in anhydrous diglyme (30.0 ml) was treated in one portion with redistilled tosyl isocyanate (0.43 g, 0.0022 mol) and the mixture was heated under reflux for 4-24 h. The mixture was cooled and evaporated and the solid residue dissolved in methylene chloride (200) resulting solution was subsequently washed with aqueous 2M sodium hydroxide and the methylene chloride extract was worked up as described for in individual reactions below.

(a) The methylene chloride extract from 5-amino-1-methyl-4-phenylazo-3-phenylpyrazole (30a) was evaporated to yield 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (96%) which formed orange needles m.p. 240-241° (from toluene), ν_{max} 1690 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.15-7.46 (10H, m, ArH) and 3.79 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 151.76

(quat), 149.97 (quat), 143-96 (quat), 142.24 (quat), 131.69 (quat), 130.77, 128.97, 128.92 (quat), 128.68, 126.30, 125.90 and 32.89 (NCH_3).

Found: C, 67.4; H, 4.3; N, 22.8%; M^+, 303

$C_{17}H_{13}N_5O$ requires: C, 67.3; H, 4.1; N, 23.1%; M, 303

The aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and extracted with methylene chloride to afford toluene-4-sulphonamide (quant.), m.p. 132-135%, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) The methylene chloride extract from 5-amino-1-methyl-4(4-methylphenylazo)-3-phenylpyrazole (30b) was evaporated to yield 1-methyl-5(4-methylphenyl)-3-phenyl-1H pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31b) (68%) which formed orange needles m.p. 223-224° (from toluene), ν_{max} 1690 (CO) cm^{-1}, $\delta_H[(CD_3)_2SO]$ 8.16-7.30 (9H, m, ArH), 3.80 (3H, s, NCH_3) and 2.41 (3H, s, CH_3), $\delta_C[(CD_3)_2SO]$ 151.89 (quat), 149.99 (quat), 143.93 (quat), 139.91 (quat), 138.49 (quat), 131-62 (quat), 130.24, 129.17, 129.06, 128.92 (quat), 126.36, 125.74, 32.97 (NCH_3) and 20.68 (CH_3).

Found: C, 67.8; H, 4.5; N, 21.9%; M^+, 318

$C_{18}H_{15}N_5O$ requires: C, 67.9; H, 4.7; N, 22.0%; M, 318

The aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and extracted with methylene chloride to afford toluene-4-sulphonamide (quant.), m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

(c) Themethylene chloride extract from 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) was

evaporated to yield 1-methyl-5-(4-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31e) (93%) which formed red needles m.p. 288-289° (from dimethylformamide), ν_{max} 1695 (CO), and 1520 and 1370 (NO_2) cm^{-1}, δ_H[$(CD_3)_2SO$] 8.43 (2H, d, J9Hz ArH), 8.15-8.04 (2H, m, ArH), 8.02 (2H, d, J9Hz ArH), 7.53-7.51 (3H, m, ArH) and 3.82 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 151.58 (quat), 150.13 (quat), 147.08 (quat), 146.92 (quat), 144.28 (quat), 132.77 (quat), 130.48, 129.16, 128.65 (quat), 127.28, 126.45, 124.18 and 33.07 (NCH_3).

Found: C, 58.7; H, 3.4; N, 24.3%, M^+, 348

$C_{17}H_{12}N_6O_3$ requires: C, 58.6; H, 3.4; N, 24.1%; M, 348

The aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and extracted with methylene chloride to afford toluene-4-suphonamide (quant.) m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

(d) The methylene chloride extract from 5-amino-4-(4-methoxyphenylazo)-1-methyl-3-phenylpyrazole (30d) was evaporated to afford a brown solid which was subjected to flash chromatography.

Elution with methylene chloride gave toluene-4-sulphonamide (50%) m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride-ethylacetate (10:1) yielded 5-(4-methoxyphenyl)-1-methyl-3-phenyl-1H-pyrazolo-[3,4-e]-1,2,4-triazin-6(5H)-one (31d) (84%) which formed orange crystals m.p. 232-233° (from dimethylformamide) ν_{max} 1680 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.12-7.04 (9H, m, ArH) 3.85 (3H, s, OCH_3) and 3.80 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 159.49

(quat), 152.08 (quat), 150.05 (quat), 144.01 (quat), 135.36 (quat), 131.56 (quat), 130.33, 129.16, 129.07 (quat), 127.34, 126.48, 114.03, 55.64 (OCH_3) and 33.06 (NCH_3).

Found: C, 64.5; H, 4.5; N, 20.9%; M^+, 333

$C_{18}H_{15}N_5O_2$ requires: C, 64.9; H, 4.5; N, 21.0%; M, 333

Final elution with ethanol gave an intractable gum (0.2 g) which was not further investigated.

The original aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and extracted with methylene chloride to afford toluene-4-sulphonamide (50%), m.p. 132-135° identical (m.p. and i.r. spectrum) to an authentic sample.

(e) The methylene chloride extract from 5-amino-4-(4-chlorophenylazo)-1-methyl-3-phenylpyrazole (30c) was evaporated to yield 5(4-chlorophenyl)-1-methyl-3-phenyl-1H-pyrazolo-[3,4-e]-1,2,4-triazin-6(5H)-one (31c) (67%) which formed orange crystals (67%) m.p. 264-265° (from dimethylformamide-toluene), ν_{max} 1690 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.17-7.49 (9H, m, ArH) and 3.81 (3H, s, NCH_3).

Found: C, 60.0; H, 3.6; N, 20.8%; $M,^+$ 339, 337

$C_{17}H_{12}N_5OCl$ requires: C, 60.0; H, 3.6; N, 21.0%; M, 337.5

The aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and extracted with methylene chloride to afford toluene-4-sulphonamide (quant.) m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of 3,5-Diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) with Sodium Hydroxide in Aqueous Ethane-1,2-diol

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a), (0.30 g, 0.001 mol) in ethane-1,2-diol (5.0 ml) was treated with aqueous 2M sodium hydroxide solution (1.0 ml) and the mixture was heated gently for 5 min. The mixture was cooled and filtered to afford 5-amino-1-methyl-4-phenylazo-3-phenylpyrazole)30a) (0.25 g; 92%) m.p. 128-130°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Neutralisation of the mother liquor with aqueous 2M hydrochloric acid followed by extraction with methylene chloride yielded no further material.

The Reaction of 1-Methyl-5(4-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) with Sodium Hydroxide in Aqueous Ethane-1,2-diol

(a) A solution of 1-methyl-5(4-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31e) (0.35 g, 0.001 mol) in ethane-1,2-diol (5.0 ml) was treated with aqueous 2M sodium hydroxide solution (1.0 ml) and the mixture was heated under reflux for 0.5 h. The mixture was cooled to room temperature, neutralised by the addition of aqueous 2M hydrochloric acid then extracted with methylene chloride to afford a dark red gum (0.28 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethylacetate (10:1) afforded an unidentified solid (0.03 g; 9%) m.p. 218-220°,

ν_{max} 1670 (CO) and 1550 and 1345 (NO_2) cm^{-1}, m/e 323, followed by 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenyl/-pyrazole (30e) (0.07 g, 20%) m.p. 224-226°, identical (m.p. and i.r. spectrum) to a sample prepared before, then 5-amino-4-(4-amino-phenylazo)-1-methyl-3-phenylpyrazole (35), (0.10 g; 34%) which formed yellow prisms m.p. 178-179° (from toluene), ν_{max} 3440, 3310 and 3195 (NH) cm^{-1}, δ ($CDCl_3$) 8.23-8.11 (2H, m, ArH), 7.62 (2H, d, J12Hz ArH), 7.51-7.21 (3H, m, ArH), 6.73 (2H, d, J12Hz ArH), 5.81 (2H, brs, NH), 3.84 (2H, brs, NH) and 3.68 (3H, s, NCH_3).

Found: C, 65.9; H, 5.5; N, 28.5%; M^+, 292

$C_{16}H_{16}N_6$ requires: C, 65.8; H, 5.5; N, 28.8%; M, 292

Elution with methylene chloride-ethylacetate (5:1) and finally ethanol gave brown gums (total 0.05 g) whose t.l.c. in methylene chloride-ethylacetate (1:1) showed to them to be multicomponent mixtures which were not further investigated.

(b) A solution of 1-methyl-5(4-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31e) (0.35 g, 0.001 mol) in ethane-1,2-diol (5.0 ml) was treated with aqueous 2M sodium hydroxide solution (1.0 ml) and the mixture was heated gently for 5 min. The mixture was cooled and filtered to afford 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e), as a red solid (0.28 g; 87%) m.p. 224-225°, identical (m.p. and i.r. spectrum) to an authentic sample.

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

The Attempted Reaction of 5-Amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) with Sodium Hydroxide in Aqueous Ethane-1,2-diol

A solution of 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.64 g, 0.002 mol) in ethane-1,2-diol (10.0 ml) was treated with aqueous 2M sodium hydroxide solution (2.0 ml) and the mixture was heated under reflux for 0.5 h. The mixture was cooled and filtered to afford unreacted starting material (30e) (0.63 g; 98%) m.p. 223-226°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reduction of 5-Amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole)30e) with Iron in Acetic Acid

A suspension of iron filings (0.90 g, 0.016 mol) in glacial acetic acid (10.0 ml) was stirred at room temperature and treated dropwise with a solution of 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) (1.3 g, 0.004 mol) in glacial acetic acid (40.0 ml) over a period of 15 min. The mixture was stirred for a further 2 h at 100° (steam bath), then hot filtered to remove unreacted iron filings and ferric acetate. The filtrate was evaporated and the residue was treated with water to afford the unreacted starting material (30e) (1.3 g; 97%) m.p. 220-225°, identical (m.p. and i.r. spectrum) to a sample prepared before.

1-Methyl-5-(4-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31e)

A solution of 5-amino-1-methyl-4(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.64 g, 0.002 mol) in anhydrous dry diglyme (30.0 ml) was heated in one portion with phenyl isocyanate (0.24 g, 0.0022 mol) and the resulting mixture was heated under reflux for 24 h. The mixture was cooled and evaporated to give a red gum (0.75 g) which was triturated with methylene chloride to give a red solid. This was combined with further material obtained by evaporating the methylene chloride mother liquor followed by flash chromatography of the resulting red gum (0.5 g) in methylene chloride-ethylacetate (5:1) to yield 1-methyl-5-(4-nitrophenylazo)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31e) (total 0.6 g; 86%) m.p. 284-286°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 5-Amino-5-(4-nitrophenylazo)-3-phenylpyrazole (30e) with Methyl Isocyanate

A solution of 5-amino-5-(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.64 g, 0.002 mol) in anhydrous diglyme (30.0 ml) was treated in one portion with methyl isocyanate (0.12 g, 0.0022 mol) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated to afford a brown gum (0.75 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethylacetate (10:1) yielded the unreacted starting material (30e) as a red solid (0.48 g; 70%) m.p. 220-223°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethylacetate followed by ethanol yielded dark intractable gums (total, 0.22 g) which were not further investigated.

5-Amino-1,3-diphenyl-4-phenylazopyrazole (38)[137]

A solution of 2-benzoyl-2-phenylhydrazonoacetonitrile (29a) (2.5 g, 0.01 mol) in ethanol (25.0 ml) was treated with phenylhydrazine (1.1 g, 0.01 mol) and the mixture was heated under reflux for 17 h. Hot filtration afforded the aminophenylazopyrazole (38) as yellow crystals (2.0 g; 55%) m.p. 255-258° (lit.,[137] 257°), ν_{max} 3410 and 3270 (NH) cm^{-1}.

On cooling the filtrate deposited unreacted starting material (29a), (0.2 g; 8%) m.p. 132-135, identical (m.p. and i.r. spectrum) to an authentic sample.

Evaporation of the ethanolic mother liquor afforded a brown gum (0.8 g), whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a multicomponent mixture which was not further investigated.

5-Amino-1,3-diphenylpyrazole (37)[139]

5-Amino-1,3-diphenylpyrazole (37) was prepared (yield 73%) by reaction of benzoylacetonitrile with phenylhydrazine as described by Seidel,[139] and had m.p. 124 (lit.,[139] 129°), ν_{max} 3425, 3300 and 3180 (NH) cm^{-1}.

The Attempted Reaction of 5-amino-1,3-diphenylpyrazole (37) with Benzenediazonium Chloride

A solution of redistilled aniline (0.2 g, 0.002 mol) in aqueous 5M hydrochloric acid (1.0 ml) was treated dropwise

with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.17 g; 0.0022 mol) in water (0.5 ml). The resulting amber benzenediazonium chloride solution was stirred for a further 5 min in the ice-salt bath, then added dropwise to a stirred solution of 5-amino-1,3-diphenylpyrazole (37) (0.47 g, 0.002 mol) in glacial acetic acid (15.0 ml) at 0-5° (ice-salt bath), and the mixture was stirred in the melting ice-salt bath for a further 1 h.

The mixture was co-evaporated with toluene to give a red gummy residue. This was treated with water (10.0 ml) and extracted with methylene chloride to afford a dark red gum (0.48 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethylacetate (4:1) gave the unreacted starting material (37) (0.4 g; 85%) m.p. 115-117°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with ethanol yielded only a small amount of brown solid (0.03 g) which was not further investigated.

1-(1,3-Diphenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphenyl) urea (40)

(a) A solution of 5-amino-1,3-diphenyl-4-phenylazo-pyrazole (38) (0.68 g, 0.002 mol) in anhydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.43 g, 0.002 mol) and the mixture was heated under reflux for 4 h. The mixture was cooled and evaporated to afford a red gummy solid (1.1 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethylacetate (10:1) yielded 1-(1,3-diphenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (40) as a yellow solid (0.95; 93%), m.p. 224-225°, ν_{max} 3150 (NH) and 1715 (CO) cm^{-1}, δ_H ($CDCl_3$) 11.16 (1H, brs, NH), 9.64 (1H, brs, NH), 802 (2H, d, J8Hz ArH), 7.69 (2H, d, J8Hz ArH), 7.48-7.31 (15H, m, ArH) and 2.42 (3H, s, CH_3), δ_C ($CDCl_3$) 152.04 (quat), 148.86 (quat), 144.44 (quat), 143.97 (quat), 139.78 (quat), 138.43 (quat), 136.21 (quat), 130.51, 129.70, 129.22, 128.98, 128.48, 128.32, 128.22, 126.77 (quat), 124.92 (quat), 124.77, 122.05 and 21.48 (CH_3).

Found: C, 64.5; H, 4.6; N, 15.4; M^+-TSO_2NH_2, 303
$C_{29}H_{24}N_6O$ requires: C, 64.9; H, 4.5; N, 15.7, M, 536

Final elution with ethanol gave a dark intractable gum (0.05 g) which was not further investigated.

(b) A suspension of 5-amino-1,3-diphenyl-4-phenylazopyrazole (38) (0.68 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (50.0 ml) was treated with redistilled tosyl isocyanate (0.43 g, 0.0022 mol) and the mixture was heated under reflux for 24 h after which period a further portion of tosyl isocyanate (0.43 g, 0.0022 mol) was added and heating under reflux continued for a further 2 h. The mixture was cooled and evaporated to afford a yellow gummy solid which was triturated with a little 1,2-dimethoxyethane to yield 1-(1,3-diphenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (40) (1.1 g; quant.) m.p. 220-224°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Thermolysis Reactions of 1-(1,3-Diphenyl-4-phenylazo-pyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (40)

(a) A solution of 1-(1,3-diphenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (40) (0.53 g, 0.001 mol) in anhydrous dimethylformamide (10.0 ml) was heated under reflux for 3 h. The mixture was evaporated to afford a yellow solid (0.52 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethylacetate (2:1) yielded 5-amino-1,3-diphenyl-4-phenylazopyrazole (38) (0.26 g; 77%) m.p. 250-255°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with ethyl acetate afforded 1,1-dimethyl-3-(toluene-4-sulphonyl)formamidine (41) (0.17 g; 64%), m.p. 133-134° (from toluene), δ ($CDCl_3$) 8.12 (1H, s, CH), 7.76 (2H, d, J8Hz ArH), 7.25 (2H, d, J8Hz ArH), 3.11 (3H, s, NCH_3), 3.00 (3H, s, NCH_3) and 2.39 (3H, s, CH_3).

Found: C, 52.7; H, 6.2; N, 12.3%, M^+, 226

$C_{10}H_{14}N_2O_2S$ requires: C, 53.1; H, 6.2; N, 12.4%; M, 226

Final elution with ethanol afforded only a small amount of an intractable brown gum (0.05 g) which was not further investigated.

(b) 1-(1,3-Diphenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (40) (0.53 g, 0.002 mol) was heated under vacuum in a Kugelrohr apparatus at 200°/2.0 mm Hg for 3 h. A pale yellow sublimate was collected and shown to be toluene-4-sulphonamide (0.16 g; 50%) m.p. 133-135°,

identical (m.p. and i.r. spectrum) to an authentic sample.

The residue was unreacted 1-(1,3-diphenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (40) (0.26 g; 50%) m.p. 245-250°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(c) 1-(1,3-Diphenyl-4-phenylazopyrazol-5-yl)-3-toluene-4-sulphonyl) urea (40) (0.53 g, 0.002 mol) was heated under vacuum in a 'cold finger' sublimation apparatus at 245°/0.5 mm Hg (Woods metal bath) for 10 min. The resulting sublimate and residue were combined (0.38 g) and subjected to flash chromatography.

Elution with methylene chloride afforded 5-amino-1,3-diphenyl-4-phenylazopyrazole (38) (0.20 g; 36%) m.p. 245-250°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with methylene chloride-ethylacetate (5:1) gave an orange solid (0.10 g; 27%) which was crystallised from dimethylformamide-water to yield 1,3,5-triphenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (39), m.p. 270-271°, ν_{max} 1720 (CO) cm^{-1}.

Found: C, 72.2; H, 4.4; N, 19.4%; M^+, 365

$C_{22}H_{15}N_5O$ requires: C, 72.3; H, 4.1; N, 19.2%; M, 365

Further elution with methylene chloride-ethyl acetate then ethanol gave no other identifiable material.

2-(4-Nitrophenylhydrazono)benzoylacetonitrile Phenylhydrazone (48)

A solution of 2-benzoyl-2-(4-nitrophenylhydrazono)-

acetonitrile (29e) (2.9 g, 0.01 mol) in ethanol (25.0 ml) was treated with redistilled phenylhydrazine (1.1 g, 0.01 mol) and the mixture was heated under reflux for 17 h. The mixture was cooled and filtered to afford 2-(4-nitrophenylhydrazono)benzoylacetonitrile phenylhydrazone (48) (2.4 g; 63%) m.p. 214-215° (from glacial acetic acid), ν_{max} 3420 and 3250 (NH) and 2205 (CN) cm^{-1}.

Found: 384.1331

$C_{21}H_{16}N_6O_2$ requires: 384.1335

The ethanolic filtrate was evaporated to give a red gum (1.4 g) whose t.l.c. in toluene showed it to be an unresolvable multicomponent mixture which was not further investigated.

5-Amino-1,3-diphenyl-4(4-nitrophenylazo)pyrazole (47)

(a) A solution of 2-(4-nitrophenylhydrazono) benzoylacetonitrile phenylbydrazone (48) (0.38 g, 0.001 mol) in glacial acetic acid (2.5 ml) was treated with concentrated hydrochloric acid (2.5 ml) and the mixture was heated under reflux for 1 h. The mixture was cooled and filtered to afford 2-(4-nitrophenylhydrazono) benzoylacetonitrile (29e) (0.20 g; 53%) m.p. 235-240°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The glacial acetic acid mother liquor was evaporated to afford 5-amino-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (48) (0.17 g; 45%) m.p. 234-235° (from glacial acetic acid) ν_{max} 3420 and 3150 (NH) cm^{-1}, δ [$(CD_3)_2SO$] 8.36-7.28 (14H, m, ArH) and 6.37 (2H, brs, NH).

Found: C, 63.8; H, 3.9; N, 21.2%; M^+, 384

$C_{29}H_{16}N_6O_2$ requires: C, 64.0; H, 4.1; N, 21.3%; M, 384

(b) A solution of 2-(4-nitrophenylhydrazono)benzoyl-acetonitrile phenylhydrazone (48) (0.38 g, 0.001 mol) in anhydrous ethanol (10.0 ml) was mixed with a solution of sodium (0.09 g, 0.004 g atom) in anhydrous ethanol (5.0 ml) and the mixture was heated under reflux for 1 h. The mixture was cooled and evaporated and the residue treated with water. The resulting solution was extracted with methylene chloride to yield 5-amino-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (47) (0.09 g; 24%) m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The aqueous mother liquor was acidified with aqueous 2M hydrochloric acid and extracted with methylene chloride to yield the unreacted starting material (48) (0.21 g; 55%) m.p. 210-215°, identical (m.p. and i.r. spectrum) to a sample prepared before.

5-Acetamido-1,3-diphenyl-4-(4-nitrophenlazo)pyrazole (53)

A solution of 2-(4-nitrophenylhydrazono)benzoyl-acetonitrile phenylhydrazone (48) (0.38 g, 0.001 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 18 h. The solution was cooled and filtered to afford unreacted starting material (0.16 g; 42%) m.p. 210-215°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The acetic acid filtrate was evaporated to give a red gum which was triturated with light petroleum (b.p. 40-60°) to afford 5-acetamido-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (53), as an orange solid (0.17 g; 40%) m.p. 234-235° (from glacial acetic acid) ν_{max} 3220 (NH), and 1685(10) cm^{-1}, δ [$(CD_3)_2SO$] 10.12 (1H, brs, NH), 8.37 (4H, d, J9Hz ArH), 7.84 (4H, d, J9Hz ArH), 7.46-7.36 (20H, m, ArH), 6.72 (1H, brs, NH) and 2.21 (6H, s, CH_3).

Found: 426.1444

$C_{23}H_{18}N_6O_3$ requires: 426.1440

Acid-catalysed Conversions of 2-(4-Nitrophenylhydrazono)-benzoylacetonitrile Phenylhydrazone (48) into 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29c)

(a) A solution of 2-(4-nitrophenylhydrazono)benzoylacetonitrile phenylhydrazone (48) (0.38 g, 0.001 mol) in glacial acetic acid (5.0 ml) was treated with concentrated hydrochloric acid (5.0 ml) and the mixture was heated under reflux for 17 h. Hot filtration afforded a yellow solid which was treated with saturated sodium hydrogen carbonate solution to give 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29e) which was combined with further material obtained from the filtrate on cooling (total 0.3 g; quant.) m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(b) A solution of 2-(4-nitrophenylhydrazono)benzoylacetonitrile phenylhydrazone (48) (0.38 g, 0.001 mol) in triethylene glycol (20.0 ml) was treated with concentrated hydrochloric acid (5.0 ml) and the mixture was heated under

reflux for 3 h. The mixture was cooled and filtered to afford a yellow solid which was combined with further material obtained by diluting the filtrate with water (20.0 ml) to give 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29e) (0.30 g; quant.), m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(c) A solution of 2-(4-nitrophenylhydrazono)benzoylacetonitrile phenylhydrazone (48) (0.38 g, 0.001 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 3 days. Evaporation of the solvent afforded a red gum which was triturated with light petroleum to afford 2-(4-nitrophenylhydrazono)benzoylacetonitrile (29e) (0.30 g; quant.) m.p. 230-232, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Reaction of 2-(4-Nitrophenylhydrazono) (48) with Acetic Anhydride

A solution of 2-(4-nitrophenylhydrazono)benzoylacetonitrile phenylhydrazone (48) (0.38 g, 0.001 mol), in acetic anhydride (10.0 ml) was heated under reflux for 1 h, then cooled to room temperature and filtered 2-(N-acetyl-4-nitrophenylhydrazono)benzoylacetonitrile (50) (0.15 g; 0.001 mol) m.p. 218-129° (from dimethylformamide-water), ν_{max} 1715 (CC), 1655 (C=N) and 1530 and 1380 (NO_2) cm^{-1}, δ [$(CD_3)_2SO$] 8.51-7.45 (H, m, ArH) and 2.27 (3H, s, CH_3).

Found: C, 60.9; H, 3.5; N, 16.6%; M^+-COCH_3, 294

$C_{16}H_{12}N_4O_4$ requires: C, 60.7; H, 3.5; N, 16.7%; M, 336

The acetic anhydride filtrate was evaporated to give

2-(4-nitrophenylhydrozono)benzoylacetonitrile (29e), (0.20 g; 64%) m.p. 231-232°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 5-Amino-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (47) with Tosyl Isocyanate

A solution of 5-amino-1,3-diphenyl-4-(4-nitrophenylazo)pyrazole (47) (0.77 g, 0.002 mol) in anhydrous diglyme (40.0 ml) was treated with redistilled tosyl isocyanate (0.44 g, 0.0022 mol) and the mixture was heated under reflux for 2 h. The mixture was evaporated and the resulting brown gum (1 hg) was subjected to flash chromatography.

Elution with methylene chloride afforded a brown gum (1.1 g) which was treated with aqueous 2M sodium hydroxide solution to yield the unreacted pyrazole derivative (47) (0.57 g; 74%) m.p. 230-233°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and extracted with methylene chloride to afford toluene-4-sulphonamide (0.34; quant.) m.p. 132-135° identical (m.p. and i.r. spectrum) to an authentic sample.

Fianl elution with ethyl acetate gave a red gum (0.2 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

Attempted Reactions of 2-Phenylhydrazoneobenzoylacetonitrile (29a) with 4-Nitrophenylhydrazine

(a) A solution of 2-phenylhydrazonobenzoylacetonitrile (29a) (1.0 g, 0.004 mol) in ethanol (50.0 ml) was treated with 4-nitro-phenylhydrazine (0.61 g, 0.004 mol) and the mixture was heated under reflux for 17 h. The mixture was cooled and evaporated to afford a brown gummy solid which was treated with aqueous 2M hydrochloric acid (20.0 ml) and filtered to yield the unreacted nitrile (29a) (1.0 g, quant.) m.p. 130-135°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The aqueous acidic filtrate was neutralised with aqueous 2M sodium hydroxide solution and extracted with methylene chloride to afford unreacted 4-nitrophenylhydrazine (0.61 g; quant.) m.p. 140-145°, identical (m.p. and i.r. spectrum) to an authentic sample.

(b) A solution of 2-phenylhydrazonobenzoylacetonitrile (29a) (0.50 g, 0.002 mol) in methanol (30.0 ml) was treated with 4-nitrophenylhydrazine (0.31 g, 0.002 mol) followed by concentrated hydrochloric acid (0.2 ml), and the mixture was heated under reflux for 3 h. The mixture was cobled and evaporated to afford a brown solid (0.75 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethylacetate (5:1) yielded unreacted 2-phenylhydrazonobenzoylacetonitrile (29a) (0.37 g; 74%) m.p. 136-138°, identical (m.p. and i.r. spectrum) to a sample prepared before, followed by unreacted 4-nitrophenyl-hydrazine (0.31 g; quant.) m.p. 142-145°, identical (m.p. and i.r. spectrum) to an authentic sample.

5-Amino-1-(4-nitrophenyl)-3-phenyl-4-phenylazopyrazole (54)

A solution of 2-phenylhydrazonebenzoylacetonitrile (29a) (2.5 g, 0.01 mol) in methanol (100 ml) was treated with 4-nitrophenylhydrazine (1.5 g, 0.01 mol) followed by toluene-4-sulphonic acid (0.1 g) and the mixture was heated under reflux for 3 h. The mixture was cooled and evaporated to afford a yellow solid (4.3 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethyl acetate (10:1) gave an unidentified red oil (0.16 g) ν_{max} (film) 2110 and 2085 (CN) cm^{-1}, m/e 279. 275, followed by unreacted 2-phenylhydrazono-benzoylacetonitrile (29a) (1.7 g, 68%) m.p. 130-135°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with cyclohexane-ethyl acetate (5:1) yielded 5-amino-1-(4-nitrophenyl)-3-phenyl-4-phenylazopyrazole (54) (0.58 g; 15%) m.p. 190-191° (from toulene), ν_{max} 1510 and 1335 (NO_2) cm^{-1}, δ_H ($CDCl_3$) 8.44-7.33 (14H, m. ArH) and 6.57 (2H, brs, NH), δ_C ($CDCl_3$) 153-90 (quat), 151.19 (quat), 146.22 (quat), 143.20 (quat), 138.41 (quat), 131.63 (quat), 129.05, 128.44, 128.31 (quat), 125.31, 122.73 and 121.52.

Found: 384.1338

$C_{21}H_{16}N_6O_2$ requires: 384.1335

Elution with cyclohexane-ethyl acetate (2:1) through to ethanol gave a series of gums and solids (total, 1.5 g) whose t.l.c. in ethyl acetate showed them to be multicomponent mixtures which were not further investigated.

3,5-Diphenyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (55)

A solution of 5-amino-1-(4-nitrophenyl)-3-phenyl-4-phenylazopyrazole (54) (0.38 g, 0.001 mol) in anhydrous diglyme (10.0 ml) was treated with redistilled tosyl isocyanate (0.22 g, 0.0011 mol) and the mixture was heated under reflux for 24 h. The solvent was removed under reduced pressure to give a dark gum (0.68 g) which was subjected to flash chromatography.

Elution with methylene chloride-n-hexane (3:1) yielded 3,5-diphenyl-1-(4-nitrophenyl)-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (55) (0.41 g; quant.), as an orange solid, m.p. 288-289° (from dimethylformamide-ethanol), ν_{max} 1685 (CO) cm^{-1}.

Found: C, 64.1; H, 3.3; N, 20.5%; M^+, 410

$C_{22}H_{14}N_6O_3$ requires: C, 64.4; H, 3.4; N, 20.5%; M, 410

3-Imino-2-phenylhydrazonobutanenitrile (43)[140]

A solution of redistilled aniline (8.0 g, 0.08 mol) in aqueous 5M hydrochloric acid (40.0 ml) was heated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (6.8 g, 0.088 mol) in water (20.0 ml). The resulting amber benzenediazonium solution was stirred for a further 5 min in the ice-salt bath, then added dropwise at 0-5° (ice-salt bath) to a stirred solution of aminocrotonitrile (42), (6.56 g, 0.08 mol) and anhydrous sodium acetate (10.0 g, 0.12 mol) in ethanol (100 ml) and water (50.0 ml),

and the mixture was stirred in the melting ice-salt bath for a further 1 h.

The mixture was filtered to afford 3-imino-2-phenylhydrazonebutanenitrile (43) (14.0 g; 94%), m.p. 158-161° (lit.,[140] 166-167°), ν_{max} 3415 (NH) and 2195 (CN) cm^{-1}.

The aqueous mother liquor on neutralisation with aqueous 2M sodium hydroxide solution and subsequent extraction with methylene chloride afforded no further material.

5-Amino-3-methyl-1-phenyl-4-phenylazopyrazole (44)[139]

A solution of 3-imino-2-phenylhydrazonobutanenitrile (43) (1.86 g, 0.01 mol) in ethanol (25.0 ml) was treated with redistilled phenylhydrazine (1.1 g, 0.01 mol) and the mixture was heated under reflux for 17 h. The mixture was coated and evaporated to afford a red gum (3.0 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded a dark intractable gum (0.4 g) which was not further investigated.

Elution with methylene chloride-ethyl acetate (10:1) yielded 5-amino-3-methyl-1-phenyl-4-phenylazopyrazole (44)[139] as a yellow solid (1.8 g; 65%), m.p. 137-140° (lit.,[139] 140°) ν_{max} 3400 and 3285 (NH) and 1600 (C=N) cm^{-1}.

Final elution with ethyl acetate gave a further intractable gum (0.1 g) which was not further investigated.

1-(3-methyl-1-phenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (46)

A solution of 5-amino-3-methyl-1-phenyl-4-phenylazopyrazole (44) (0.55 g, 0.002 mol) in anhydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.43 g, 0.0022 mol) and the mixture was heated under reflux for 7 h. The mixture was cooled and evaporated to afford a brown gummy solid (1.0 g) which was subjected to flash chromatography.

Elution with methylene chloride yielded toluene-4-sulphonamide (0.15 g; 36%) m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample, followed by 1-(3-methyl-1-phenyl-4-phenylazopyrazol-5-yl)-3(toluene-4-sulphonyl) urea (46) (0.60 g; 62%) m.p. 155-156° (from toluene), ν_{max} 3350 and 3260 (NH) and 1685 (CO) cm^{-1}, δ_H ($CDCl_3$) 8.18 (2H, d, J8Hz ArH), 7.76 (2H, d, J8Hz ArH), 7.68-725 (10H, m, ArH), 5.06 (2H, brs, NH), 2.58 (3H, s, CH_3) and 2.38 (3H, s, CH_3), δ_C ($CDCl_3$) 152.51 (quat), 148.78 (quat), 146.82 (quat), 144.32 (quat), 141.81 (quat), 139.26 (quat), 137.28 (quat), 133.88 (quat), 129.47 (quat), 129.10, 128.89, 126.31, 125.42, 119.68, 21.30 (CH_3) and 11.22 (CH_3).

Found: C, 60.6; H, 4.9; N, 17.8%; M^+, 474

$C_{24}H_{22}N_6O_3$ requires: C, 60.8; H, 4.6; N, 17.7%; M, 474

The Reaction of 5-Amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) with Phenyl Isothiocyanate

A solution of 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.64 g, 0.02 mol) in anhydrous diglyme

(30.0 ml) was treated with phenyl isothiocyanate (0.30 g, 0.0022 mol) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated to afford a brown gum (0.90 g) which was subjected to flash chromatography.

Elution with methylene chloride gave a small amount of an intractable solid (0.10 g) which was not further investigated.

Elution with methylene chloride-ethyl acetate (5:1) yielded unreacted starting material (0.35 g; 55%) m.p. 220-225°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Final elution with ethanol gave an intractable solid (0.40 g) from which no identifiable material could be obtained.

The Attempted Reaction of 5-Amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) with Carbon Disulphide

A solution of 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.64 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (10.0 ml) was treated with carbon disulphide (4.0 ml) and the mixture heated under reflux for 17 h. The mixture was cooled and evaporated to afford the unreacted 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.63 g; 98%) m.p. 220-225°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 5-Amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) with Thiophosgene

A solution of 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.64 g, 0.002 mol) in 1,2-dimethoxyethane (10.0 ml) was treated with a solution of sodium hydrogencarbonate (0.34 g, 0.004 mol) in water (4.0 ml) and the resulting suspension was treated dropwise with vigorous stirring at room temperature with a solution of thiophosgene (0.23 g, 0.002 mol) in 1,2-dimethoxyethane (5.0 ml). The mixture was stirred at room temperature for 2 h, then evaporated and the residue was treated with water to give the unreacted 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.60 g, 94%) m.p. 220-225°, identical (m.p. and i.r. spectrum) with a sample prepared before.

5-Amino-1-methyl-3-phenylpyrazole (66)

5-amino-1-methyl-3-phenylpyrazole (66) was prepared (yield 70%) by reaction of benzoylacetonitrile with methylhydrazine as described by Gaurneri, Ferroni and Fiorini,[134] and had m.p. 129° (lit., 132°), ν_{max} 3425, 3300 and 3180 (NH) cm^{-1}.

1-(1-Methyl-3-phenylpyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (67)

A solution of 5-amino-1-methyl-3-phenylpyrazole (66) (1.73 g, 0.01 mol) in anhydrous 1,2-dimethoxyethane (50.0 ml) was treated with redistilled tosyl isocyanate (2.15 g, 0.011 mol) and the mixture was stirred at room temperature for 2 h.

The mixture was evaporated to give 1-(-methyl-3-phenyl-pyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (67), (3.7 g; quant.) which formed colourless crystals, m.p. 230-231° [from light petroleum (b.p. 40-60°)], ν_{max} 3315 and 3305 (NH), and 1680 (CO) cm^{-1}, δ (CDl_3) 8.30 (1H, brs, NH), 7.86-7.69 (4H, m, ArH), 7.40-7.27 (5H, m, ArH), 6.50 (1H, s, CH), 3.69 (3H, s, NCH_3) and 2.45 (3H, s, CH_3).

Found: 370.1115

$C_{18}H_{18}N_4O_3S$ requires: 370.1098

1-Methyl-3-phenyl-6-(1-methyl-3-phenylpyrazol-5-yl)-1H-pyrazolo[3,4-e]pyrimidine-5,7(6H, 8H)-dione (70)

(a) A solution of 5-amino-1-methyl-3-phenylpyrazole (66) (0.35 g, 0.002 mol) in anhydrous diglyme (10.0 ml) was treated with tosyl isocyanate (0.43 g, 0.0022 mol) and the mixture was cooled and evaporated to afford a brown gum (0.60 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethylacetate (3:1) yielded 1-methyl-3-phenyl-6-)1-methyl-3-phenylpyrazol-5-yl)-1H-pyrazolo[3,4-d]pyrimidine-5,7(6H, 8H)-dione (70), (0.10 g; 27%), m.p. 140-145°, ν_{max} 1730 and 1680 (CO) cm^{-1}.

Found: M^+, 398.1470

$C_{22}H_{18}N_6O_2$ requires: M, 398.1491

Elution with ethyl acetate through to ethanol gave a series of gums and solids (total, 0.15 g) which were not further investigated.

(b) A solution of 1-(1-methyl-3-phenylpyrazol-5-yl)-3-(toluene-4-sulphonyl)urea (67) (0.74 g, 0.002 mol) in anhydrous diglyme (10.0 ml) was heated under reflux for 6 h. The mixture was cooled and evaporated to afford a brown gum (0.60 g) which was subject to flash chromatography.

Elution with methylene chloride acetate (10:1) yielded toluene-4-sulphonamide (0.40 g; 50%) m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride-ethyl acetate (5;1) through to methylene chloride-ethyl acetate (1:1) yielded a series of gums (total, 0.5 g) which were not further investigated.

Final elution with ethyl acetate gave 1-methyl-3-phenyl-6-(1-methyl-3-phenylpyrazol-5-yl)-1H-pyrazolo[3,4-d]-pyrimidine-5,7(6H, 8H)-dione (70) (0.04 g; 12%, identical (i.r. spectrum) to a sample prepared in (a) before.

The Attempted Reaction of 1-(1-Methyl-3-phenylpyrazo(5-yl)-3-(toluene-4-sulphonyl) urea (67) with Benzenediazonium Chloride

A solution of redistilled aniline (0.08 g, 0.00075 mol) in aqueous 5M hydrochloric acid (1.0 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (0.06 g, 0.00082 mol) in water (1.0 ml). The resulting amber benzenediazonium chloride solution was stirred in the ice bath for a further 5 min, then added dropwise at 0-5° (ice-salt bath) to a stirred solution of 1-(1-methyl-3-phenylpyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (67) (0.28 g. 0.00075 mol) and anhydrous sodium acetate (0.09 g, 0.0011 mol) in ethanol (10.0 ml) and water (2.0 ml) and the mixture was stirred at room temperature for a further 1 h. The mixture was evaporated and the gummy residue was treated with water and the resulting suspension was extracted with methylene chloride to yield unreacted 1-(1-methyl-3-phenylpyrazol-5-yl)-3-(toluene-4-sulphonyl) urea (67) (0.27 g; 96%) m.p. 220-225°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Reaction of 5-Amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) with Oxalyl Chloride

A solution of 5-amino-1-methyl-4-(4-nitrophenylazo)-3-phenylpyrazole (30e) (0.64 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (40.0 ml) was treated with stirring at 0-5° (ice-salt bath) with a solution of oxalyl chloride (0.28 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (5.0 ml). The

mixture was allowed to warm to room temperature and then heated under reflux for 24 h. The mixture was cooled to room temperature, filtered to remove some insoluble material and the filtrate was evaporated to afford an orange solid (0.82 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethyl acetate (1:1) yielded 2-methoxyethyl-N-(1-methyl-4-nitrophenylazo-3-phenylpyrazol-5-yl)oxamate (72) (0.75 g; 83%) m.p. 172-173° (from toluene) ν_{max} 1730 (CO) and 1520 and 1340 (NO_2) cm^{-1}, δ_H [$(CD_3)_2SO$] 11.1 (1H, brs, NH), 8.38 (2H, d, J12Hz ArH), 8.07-8.02 (2H, m, ArH), 7.85 (2H, d, J12Hz ArH), 7.57-7.45 (3H, m, ArH), 4.47 (2H, t, J4Hz $-CH_2\underline{\underline{C}}H_2O-$), 3.85 (3H, s, OCH_3), 3.68 (2H, t, J4Hz $-\underline{\underline{C}}H_2CH_2O-$) and 3.32 (3H, s, NCH_3), δ_C[$(CD_3)_2SO$], 159.34 (quat), 156.17 (quat), 155-87 (quat), 148.33 (quat), 147.76 (quat), 131.49 (quat), 129.54 (quat), 128.68, 128.52, 127.99, 126.39 (quat), 124.97, 122.45, 69.27 ($-CH_2\underline{\underline{C}}H_2O-$), 65.50 ($-\underline{\underline{C}}H_2CH_2O-$), 58.06 ($OCH_3$) and 36.61 ($NCH_3$).

Found: C, 55.7; H, 4.3; N, 18.6%; M^+, 452

$C_{21}H_{20}N_6O_6$ requires: C, 55.8; H, 4.4; N, 18.6%; M, 452

Elution with ethyl acetate-ethanol afforded no further material.

5-Formamido-1-methyl-3-phenyl-4-phenylazopyrazole (73)

A solution of 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) (0.56 g, 0.002 mol) in triethyl orthoformate (5.0 ml) was heated under reflux for 24 h and left stoppered at room temperature for a further 24 h. The mixture was evaporated to afford a dark gum (0.75 g) which was subject to flash chromatography.

Elution with methylene chloride-ethyl acetate (10:1) yielded 5-formamido-1-methyl-3-phenyl-4-phenylazopyrazole (73), (0.25 g; 35%) which formed yellow needles, m.p. 175-176° (from toluene), ν_{max} 3250 (NH) and 1670 (CO) cm^{-1}, δ [$(CD_3)_2SO$] 10.41 (1H, brs, NH), 8.39 (1H, s, CH), 8.02-7.41 (10H, m, ArH) and 3.79 (3H, s, NCH_3).

Found: C, 67.0; H, 4.8; N, 22.6%; M^+, 305

$C_{17}H_{15}N_5O$ requires: C, 66.9; H, 4.9; N, 23.0%; M, 305

Further elution with methylene chloride-ethyl acetate (10:1) gave a rbown gum (0.25 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

Final elution with ethyl acetate afforded an intractable brown solid (0.20 g) from which no identifiable material could be obtained.

The Reaction of 5-Amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) with Formic Acid

A solution of 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) (1.11 g, 0.004 mol) in formic acid (10.0 ml) was heated under reflux for 6 h. The mixture was cooled and evaporated to afford a red gum (1.3 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (10:1) gave an orange gum (0.38 g) whose t.o.c. in methylene chloride showed it to be a mixture of four close running components, followed by a further orange gum (0.20 g) which was triturated with ethyl acetate-light petroleum to yield 5-formamido-1-

methyl-3-phenyl-4-phenylazopyrazole (73), (0.16 g; 13%), m.p. 171-174°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with ethyl acetate afforded a yellow solid (0.72 g) which was treated with a saturated solution of sodium hydrogen carbonate to afford unreacted starting material (30a) (0.60 g; 54%), m.p. 130-132°, identical (m.p. and i.r. spectrum to a sample prepared before.

Final elution with ethanol gave a brown gum (0.02 g) which was not further investigated.

The Attempted Oxidation of 5-Formamido-1-methyl-3-phenyl-4-phenylazopyrazole (73) with Activated Manganese Dioxide

A solution of 5-formamido-1-methyl-3-phenyl-4-phenylazopyrazole (73) (0.15 g, 0.0005 mol) in anhydrous acetonitrile (20.0 ml) was treated in one position with activated manganese dioxide (0.75 g) and the mixture was stirred at room temperature for 1 h. The mixture was then filtered to remove the manganese dioxide and the filtrate was evaporated to afford the unreacted 5-formamido-1-methyl-3-phenyl-4-phenylazopyrazole (73) (0.15 g; quant.) m.p. 165-169°, identical (m.p. and i.r. spectrum) to an authentic sample.

The odixation of 4-N-(1-Methyl-3-phenyl-4-phenylazopyrazol-5-yl) semicarbazide (75a) with Activated Manganese Dioxide

(a) A solution of 4-N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) semicarbazide (75a) (0.67 g, 0.002 mol) in

anhydrous acetonitrile (50.0 ml) was treated with stirring with activated manganese dioxide (3.0 g) and the mixture was stirred at room temperature for 1 h. The mixture was filtered to remove manganese dioxide and the acetonitrile filtrate was evaporated to afford 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.6 g; quant.), m.p. 238-241°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(b) A solution of 4-N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) semicarbazide (75a) (0.34 g, 0.001 mol) in acetonitrile (20.0 ml) and water (10.0 ml) was treated with stirring at room temperature with activated manganese dioxide (1.5 g) and the mixture was stirred at room temperature for 1 h. Filtration of the mixture to remove the manganese dioxide and evaporation of the filtrate afforded 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g; quant.), m.p. 238-241°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Reaction of 4N-(1-Methyl-3-phenyl-4-phenylazopyrazol-5-yl)-semicarbazide (75a) in Anhydrous Acetonitrile

A solution of 4-N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yll) semicarbazide (75a) (0.17 g, 0.0005 mol) in anhydrous acetonitrile (20.0 ml) was stirred at room temperature for 1 h and then evaporated to afford 1-N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) semicarbazide (75a) unchanged (0.17 g; quant) m.p. 183-185°, identical (m.p. and i.r. spectrum) to a sample prepared before.

N-[N-(1-Methyl-3-phenyl-4-phenylazopyrazol-5-yl)carbamoyl]-piperidine (76f)

A solution of 4-N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) semicarbazide (75a) (0.67 g, 0.002 mol) in anhydrous acetonitrile (50.0 ml) was treated with piperidine (0.68 g, 0.008 ml) and activated manganese dioxide (3.0 g). The mixture was stirred at room temperature for 1 h and then filtered to remove the manganese dioxide. The acetonitrile filtrate was evaporated to give an orange gum which on treatment with aqueous 2M hydrochloric acid yielded N-[N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)carbamoyl]piperidine (76f) (0.76 g; quant) m.p. 236-237° (phase change at 131-132°)(from ethanol), ν_{max} 1675 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.95 (1H, brs, NH). 8.11-7.37 (10H, m, ArH), 3.78 (3H, s, NCH_3), 3.44 (4H, s, CH_2) and 1.67 (6H, s, CH_2), δ_C[$(CD_3)_2SO$] 153.60 (quat), 152.6 (quat), 146.69 (quat), 132.26 (quat), 130.75 (quat), 129.79, 129.21, 128.65, 128.27, 128.06, 128.63. 121.40, 44.76 (CH_2), 36.69 (NCH_3), 25.37 (CH_2).

Found: C, 67.6; H, 6.2; N, 21.7%; M^+, 388

$C_{22}H_{24}N_6O$ requires: C, 68.0; H, 6.2; N, 21.7%; M, 388

The Reaction of 4-N-(1-Methyl-3-phenyl-4-phenylazopyrazol-5-yl) semicarbazide (75a) with Piperidine in Anhydrous Acetonitrile

A solution of 4-N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) semicarbazide (75a) (0.34 g, 0.001 mol) in anhydrous acetonitrile (25.0 ml) was treated with piperidine (0.34 g,

0.004 mol) and the mixture stirred at room temperature for 2 hr. The mixture was evaporated to give a yellow gum which on treatment with aqueous 2M hydrochloric acid afforded unreacted 4-N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)-semicarbazide (75a) (0.33 g; 97%) m.p. 183-185°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 5-Amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) with Benzaldehyde

A solution of 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) (0.56 g, 0.002 mol) in anhydrous toluene (30.0 ml) was treated with benzaldehyde (0.24 g, 0.002 mol) and toluene-4-sulphoric acid (0.01 g) and the mixture was heated under reflux (Dean and Stark Apparatus) for 4 h. The mixture was cooled and evaporated to give a red oil (0.80 g) which was subject to flash chromatography.

Elution with methylene chloride afforded benzaldehyde (0.18 g, 75%) identical (i.r. spectrum) to an authentic sample.

Elution with methylene chloride-ethyl acetate (10:1) afforded an orange gum (0.45 g) which was triturated with toluene-light petroleum (b.p. 40-60°) to yield the unreacted 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) (0.25 g; 40%) m.p. 120-123°, identical (m.p. and i.r. spectrum) to a sample prepared before. The toluene filtrate was evaporated to give an orange gum (0.2 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a multicomponent mixture.

Final elution with ethanol afforded an unidentified brown solid (0.06 g) m.p. >350° which was not further investigated.

1,1-Dimethyl-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5yl)-formamidine (86b)

A solution of 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (86b) (0.56 g, 0.002 mol) in N,N-dimethylformamide dimethylacetal (5.0 ml) was heated under reflux for 6 h. The mixture was cooled and evaporated to afford an orange solid (0.68 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethylacetate (10:1) yielded 1,1-dimethyl-3-(1-methyl-3-phenyl-4-phenyazopyrazol-5-yl)formamidine (86b) (0.60 g; 91%) m.p. 138-139° (from ethanol), ν_{max} 1620 (C=N) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.63 (1H, s, CH9, 7.94-7.32 (10H, m, ArH), 3.70 (3H, s, NCH_3), 3.18 (3H, s, NCH_3) and 3.06 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 158.16 (CH), 152.97 (quat), 145.32 (quat), 144.79 (quat), 133.38 (quat), 129.05, 128.49, 128.23, 127.66, 127.51, 125.39 (quat), 121.14, 35.03 (NCH_3), 34.29 (NCH_3) and 33.55 (NCH_3).

Found: C, 68.8; H, 6.1; N, 25.0%; M^+, 322

$C_{19}H_{20}N_6$ requires: C, 68.7; H, 6.0; N, 25.3%; M, 322

The Attempted Pyrolysis 1,1-Dimethyl-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)formamidine (86b)

1,1-Dimethyl-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)formamidine (86b) (0.32 g, 0.001 mol) was heated under vacuum in a Kugelrohr apparatus at 220°/0.6 mmltg for 1 hr.

The dark orange distillate on cooling afforded the unreacted 1,1-dimethyl-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)-formamidine (86b) (0.3 g; 94%) m.p. 130-134°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 5-Amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) with Dimethylacetylene Dicarboxylate

A solution of 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) (0.56 g, 0.002 mol) in anhydrous dimethylformamide (20.0 ml) was treated with dimethylacetylene dicraboxylate (0.28 g, 0.002 mol) and the mixture heated under reflux for 3 h. The mixture was cooled and evaporated to afford a brown gum (0.80 g) which was subjected to flash chromatography.

Elution with methylene chloride yielded the unreacted 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) (0.20 g; 36%) m.p. 120-123°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with methylene chloride-ethylacetate (4:1) through to ethanol gave a series of gums (total, 0.53 g) which were not further investigated.

The Reaction of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) with Amines

(a) With ammonia

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g, 0.001 mol) in anhydrous

1,2-dimethoxyethane (20.0 ml) was saturated with ammonia gas at 0° (ice-salt bath) and the resulting solution was left tightly stoppered at room temperature for 24 h. The mixture was evaporated to afford 1-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) urea (76a) (0.32 g, quant.) which formed yellow needles, m.p. 235-236° (from dimethylformamide-water), ν_{max} 3400 and 3200 (NH) and 1680 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.06-8.02 (1H, brs, NH), 7.94-7.36 (10H, m, ArH), 6.70 (2H, s, NH) and 3.76 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 155.19 (quat), 152.67 (quat), 146.54 (quat), 132.29 (quat), 130.28 (quat), 129.99, 129.77, 129.23, 128.39, 128.19, 127.71, 127.41 (quat), 121.69 and 37.26 (NCH_3).

Found: 320.1385

$C_{17}H_{16}N_6O$ requires: 320.1385

(b) With Methylamine

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g, 0.001 mol) in anhydrous 1,2-dimethoxyethane (30.0 ml) was treated with a 33% w/v solution of methylamine in ethanol (0.37 g, 0.004 mol) and the mixture was stirred at room temperature for 1 h. The mixture was filtered to afford 1-methyl-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) urea (76b), (0.33 g; quant.), m.p. 232-234 (phase change at 192-194°) (from ethanol), ν_{max} 3330 (NH), and 1660 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.84 (1H, s, NH), 8.10-7.36 (10H, m, ArH), 7.21 (1H, q, J2Hz $\underline{\underline{N}}\underline{\underline{H}}\underline{\underline{C}}H_3$), 3.75 (3H, s, NCH_3) and 2.68 (3H, d, J2Hz $NH\underline{\underline{C}}\underline{\underline{H}}_3$), δ_C [$(CD_3)_2SO$] 154.83 (quat), 152.53 (quat), 146.48 (quat), 132.21 (quat),

130.30 (quat), 129.87, 129.15, 128.30, 128.10, 127.61, 127.13, 127.57 (quat), 37.23 (NCH_3) and 26.28 ($NHCH_3$).

Found: C, 65.0; H, 5.5; N, 25.3%; M^+, 334

$C_{18}H_{18}N_6O$ requires: C, 64.7; H, 5.4; N, 25.2%; M, 334

(c) With benzylamine

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g, 0.001 mol) in anhydrous ethanol (30.0 ml) was treated with benzylamine (0.11 g, 0.001 mol) and the mixture was heated under reflux for 2 h. The mixture was cooled and evaporated to afford 1-benzyl-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) urea (76c) (0.41 g; quant.) which formed yellow needles, m.p. 235-236° (from dimethylformamide-ethanol), ν_{max} 3290 (NH) and 1655 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.89 (1H, s, NH), 8.08-723 (16H, m, Arh and NH), 4.34 (2H, d, $\underline{CH}_2$ NH), and 3.78 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 154.60 (quat), 152.61 (quat), 146.58 (quat), 139.59 (quat), 132.24 (quat), 130.00, 129.22, 128.40, 128.27, 127.61, 127.44 (quat), 126.98, 126.81, 121.65, 43.10 (NCH_2) and 37.18 (NCH_3).

Found: C, 70.2; H, 5.3; N, 20.4%; M^+, 410

$C_{24}H_{22}N_6O$ requires: C, 70.2; H, 5.4; N, 20.5%; M, 410

(d) With aniline

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g, 0.001 mol) in anhydrous ethanol (30.0 ml) was treated with redistilled aniline (0.09 g, 0.001 mol) and the mixture was heated under reflux for 24 h. The mixture was cooled and filtered to afford the unreacted

pyrazolotriazinone (31a) (0.20 g; 67%) m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The ethanolic mother liquor was evaporated to give an orange gum (0.20 g) which was subjected to flash chromatography.

Elution with methylene chloride-cyclohexane (1:1) gave an orange gum (0.11 g) whose t.l.c. showed it to be an unresolvable multicomponent mixture which was not further investigated.

Elution with methylene afforded the unreacted pyrazolotriazinone (31a) (0.03 g; 10%) m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Final elution with ethanol yielded a yellow solid 1-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)-3-phenylurea (76d) (0.05 g, 17%) m.p. 200-210°, ν_{max} 3340 and 3100 (NY) and 1675 (CO) cm^{-1}, which on attempted crystallisation from dimethylformamide-water gave the starting pyrazolotriazinone (31a) m.p. 236-237°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(e) With dimethylamine

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g, 0.001 mol) in anhydrous 1,2-dimethoxyethane (30.0 ml) was treated with a 33% w/v solution of dimethylamine in ethanol (0.55 g, 0.004 mol) and the mixture was stirred at room temperature for 24 h. The mixture was evaporated to afford 1,1-dimethyl-3-(1-methyl-3-

phenyl-4-phenylazopyrazol-5-yl)urea (76e) (0.40 g, quant.) which formed orange prisms, m.p. 148-150° (from ethanol), ν_{max} 1690 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.94 (1H, brs, nH), 8.11-7.40 (10H, m, ArH), 3.77 (3H, s, NCH_3) and 3.02 [6H, s, $N(CH_3)_2$], δ_C [$(CD_3)_2SO$] 154.74 (quat), 152.48 (quat), 146.78 (quat), 132.25 (quat), 130.59 (quat), 130.22, 129.97, 129.35, 129.02, 128.75, 128.39, 128.20, 127.69, 127.50 (quat), 126.37, 125.98, 121.51, 36.87 (NCH_3) and 36.61 [$N(CH_3)_2$].

Found: C, 65.6; H, 5.6; N, 23.6%; M^+, 348

$C_{19}H_{20}N_6O$ requires: C, 65.5; H, 5.8; N, 24.1%; M, 348

(f) With piperidine

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo-[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.61 g, 0.002 mol) in anhydrous ethanol (30.0 ml) was treated with piperidine (0.17 g; 0.002 mol) and the mixture was stirred at room temperature for 3 h. The mixture was evaporated to afford N-[N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)carbamoyl]-piperidine (76f) as a yellow solid (0.77 g; quant) m.p. 130-132°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 3,5-Diphenyl-1-methyl-1H-pyrazolo [3,4-e]-1,2,4-triazin-6(5H)-one (31a) with Piperidine in Ethanol Under Reflux

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g; 0.001 mol) in anhydrous

ethanol (30.0 ml) was treated with piperidine (0.09 g, 0.001 mol) and the mixture was heated under reflux for 48 h. The mixture was cooled and evaporated to afford an orange gum (0.40 g) which was subjected to flash chromatography.

Elution with methylene chloride-cyclohexane (2:1) gave the unreacted pyrazolotriazinone (31a) (0.30 g; quant.) m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

1-Benzyl-3-[1-methyl-3-phenyl-4-(4-nitrophenylazo)pyrazol-5-yl]urea (101)

A solution of 1-methyl-5-(4-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31e) (0.35 g, 0.001 mol) in anhydrous diglyme (10.0 ml) was treated with benzylamine (0.11 g, 0.001 mol) and the mixture was heated under reflux for 0.5 h. The mixture was cooled and filtered to afford 1-benzyl-3-[1-methyl-3-phenyl-4-(4-nitrophenylazo)-pyrazol-5-yl]urea (101) (0.15 g; 33%), which formed orange needles m.p. 258-259° (from dimethylformamide), ν_{max} 3330 and 3260 (NH) and 1660 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$], 9.35 (1H, brs, NH), 8.45-7.23 (14H, m, ArH), 4.33 (2H, d, $NHC\underline{H}_2$) and 3.77 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 156.18 (quat), 154.11 (quat), 147.64 (quat), 147.33 (quat), 140.05 (quat), 131.70 (quat), 131.50 (quat), 123.38, 128.22, 127.79, 126.97, 126.77 (quat), 124.86, 122.30, 43.13 (CH_2) and 37.43 (NCH_3).

Found: C, 62.7; H, 4.4; N, 21.7%; M^+-$PhCH_2NH_2$, 348

$C_{24}H_{21}N_7O_3$ requires: C, 63.3; H, 4.6; N, 21.5%; M, 455

The diglyme filtrate was evaporated to give a red gum (0.27 g) which was triturated with methylene chloride to yield the unreacted pyrazolotriazinone (31e) (0.23 g; 66%) m.p. 285-287°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The methylene chloride filtrate was evaporated to give a small amount of intractable red gum (0.04 g) which was not further investigated.

The Reaction of 3,5-Diphenyl-1-methyl-1H-pyrazole[3,4-e]-1,2,4-triazin-6(5H)-one (31a) with Hydrazines

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo-[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g, 0.001 mol) in anhydrous ethanol (30.0 ml) was treated with the corresponding hydrazine (0.001 mol) and heated under reflux for 2 - 24 h.

(a) The mixture from hydrazine monohydrate was cooled and evaporated to afford 4-N(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)semicarbazide (75a) (quant.) which formed yellow crystals m.p. 228-230° (phase change at 172°) (from dimethylfromamide-ethanol), ν_{max} 3310 and 3210 (NH) and 1685 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.22 (1H, s, NH), 8.09-7.40 (11H, m, ArH and NH), 4.85 (2H, brs, NH) and 3.83 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 156.49 (quat), 152.43 (quat), 146.75 (quat), 132.51 (quat), 130.49 (quat), 129.92, 129.29, 128.42, 128.23, 127.64, 126.44 (quat), 121.72 and 38.33 (NCH_3).

Found: C, 60.4; H, 5.0; N, 29.3%; M^+, 335

$C_{17}H_{17}N_7O$ requires: C, 60.9; H, 5.1; N, 29.3%; M, 335

(b) The mixture from methylhydrazine was cooled and evaporated and the resulting orange gum (0.35 g) was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate yielded 1-N-methyl-4-N]-1(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)]-semicarbazide (75b) (92%) m.p. 228-230° (phase change at 138-140°) (from ethanol-water), ν_{max} 3600-3350, 3310, 3290 and 3210 (NH), and 1665 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.60 (1H, brs, NH), 9.20 (1H, brs, NH), 8.09 (1H, brs, NH), 7.87-7.37 (10H, m, ArH), 3.85 (3H, s, NCH_3), 3.34 (s, $NHCH_3$) and 3.31 (s, NH, CH_3), δ_C [$(CD_3)_2SO$] 155.55 (quat), 146.79 (quat), 132.14 (quat), 130.78 (quat), 130.21 (quat), 129.95, 129.33, 128.78, 128.45, 128.27, 127.65, 126.58, 126.21, 121.71, 121.62 and 37.28 (NCH_3 and $NHCH_3$).

Found: C, 62.1; H, 5.5; N, 27.3%; M^+-$MeNNNH_2$, 303

$C_{16}H_{19}N_7O$ requires: C, 61.9; H, 5.4; N, 28.0%; M, 349

Final elution with ethanol afforded a small amount of dark gum whose t.l.c. in ethyl acetate showed it to be a multicomponent mixture which was not further investigated.

(c) The mixture from phenylhydrazine was cooled and filtered to afford 4-[N(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)]-1-(N-phenyl)semicarbazide (75c) as a yellow solid (85%) m.p. 228-230° (phase change at 172-174°) (from dimethylformamide-ethanol), ν_{max} 3340, 3270, 3180 and 3090 (NH), and

1675 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.61 (1H, brs, NH), 8.95 (1H, s, NH), 8.08-6.83 (15H, m, ArH), 3.84 (3H, s, NCH_3) and 3.29 (1H, s, NH), δ_C [$(CD_3)_2SO$] 162.23 (quat), 155.93 (quat), 152.29 (quat), 148.67 (quat), 146.79 (quat), 132.10 (quat), 129.82, 129.07, 128.92, 128.77, 128.39, 128.24, 127.67, 126.75 (quat), 121.52, 119.77, 112.79 and 35.69 (NCH_3).

Found: C, 64.3; H, 5.5; N, 23.0%; M^+-$PhNHNH_2$, 303
$C_{23}H_{21}N_7O$-
$[(CH_3)_2NCHO]$ requires: C, 64.5; H, 5.8; N, 23.1%; M-$(CH_3)_2NCHO$, 411

The ethanolic mother liquor was evaporated to give a brown gum (0.1 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

(d) The mixture from toluene-4-sulphonylhydrazine was cooled and evaporated to afford an orange gum which was triturated with toluene to yield the unreacted pyrazolotriazinone (31a) (27%) m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The toluene filtrate was evaporated to afford an orange gum (0.30 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethylacetate (2:1) gave 4-[N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)-1-[N-(toluene-4-sulphonyl)]semicarbazide (75d), (49%) which formed yellow crystals m.p. 234-236° (from ethyl acetate) ν_{max} 3275 (NH) and 1665 (CO) cm^{-1}.

Found: C, 61.7; H, 4.8; N, 20.1%; M^+-TSO_2NH_2, 303
$C_{24}H_{23}N_7O_3S$ requires: C, 58.9; H, 4.7; N, 20.0%; M, 489

Final elution with ethanol gave a brown gum (0.06 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

The Thermal Cyclisation of 4-[N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)]semicarbazide (75a) to 3,5-Diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a)

4-[N-(1-Methyl-3-phenyl-4-phenylazopyrazol-5-yl)]-semicarbazide (75a) (0.16 g, 0.0005 mol) was heated under reduced pressure at 180°/0.3 mm Hg (Woods metal bath) for 5 min. The mixture was cooled to afford 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.15 g; quant.) m.p. 238-240°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted REactions of 3,5-Diphenyl-1-methyl-1H-pyrazolo [3,4-e]-1,2,4-triazin-6(5H)-one (31a) with Pyridine

(a) In ethanol

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g, 0.001 mol) in anhydrous ethanol (30.0 ml) was treated with pyridine (0.08 g, 0.001 mol) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated to afford an orange gum (0.40 g) which was subjected to flash chromatography.

Elution with methylene chloride yielded Ethyl N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)carbamate (103) (0.30 g; 86%), ν_{max} 3290 (NH) and 1740 (CO) cm^{-1}, δ ($CDCl_3$) 8.93 (1H, brs, NH), 8.18-7.25 (10H, m, ArH9, 4.25 (2H, q,

J7Hz, $\underline{CH_2}CH_3$), 3.93 (3H, s, NCH_3) and 1.34 (3H, t, J7Hz $CH_2\underline{CH_2}$).

Found: 349.1538

$\underline{C_{19}H_{19}N_5O_2}$ requires: 349.1538

Elution with methylene chloride-ethyl acetate (10:1) gave the unreacted pyrazolotriazinone (31a) (0.09 g; 30%) m.p. 235-237°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(b) In 1,2-dimethoxyethane

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo [3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.61 g, 0.002 mol) in anhydrous 1,2-dimethoxyethane (30.0 ml) was treated with pyridine (0.16 g, 0.002 mol) and the mixture was stirred at room temperature for 6 h, then heated under reflux for a further 17 h. The mixture was cooled and evaporated to afford unreacted pyrazolotriazinone (31a) (0.60 g; 98%) m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Ethyl N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)carbamate (103)

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo [3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.61 g, 0.002 mol) in anhydrous ethanol (30.0 ml) was mixed with a solution of sodium (0.05g; 0.002 g-atom) in anhydrous ethanol (3.0 ml) and the mixture stirred at room temperature for 1 h. The

mixture was filtered to afford unreacted pyrazolotriazinone (31a) (0.50 g; 82%) m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The mixture was evaporated and the residue was treated with water and extracted with methylene chloride to yield Ethyl N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)carbamate (103) as an orange gum (0.05 g; 14%) identical (i.r. and n.m.r. spectra) to a sample prepared before.

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

The Reaction of 1-Methyl-5-(4-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31e) with Sodium Ethoxide

A solution of 1-methyl-5-(4-nitrophenyl)-3-phenyl-1H-pyrazolo]3,4-e]-1,2,4-triazin-6(5H)-one (31e) (0.35 g, 0.001 mol) in anhydrous diglyme (10.0 ml) was mixed with a solution of sodium (0.09 g, 0.004 g-atom) in anhydrous ethanol (5.0 ml) and the mixture was heated under reflux for 15 min. The mixture was cooled and evaporated to afford a dark residue which was treated with water (10.0 ml) and extracted with methylene chloride to give a red oil (1.2 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (5:1) through to ethanol gave intractable red oils (total 1.1 g) which were not further investigated.

1-Hydroxy-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl) urea (104)

A solution of sodium (0.23 g, 0.01 g-atom) in methanol (10.0 ml) was mixed with a solution of hydroxylamine hydrochloride (0.70 g, 0.01 mol) in methanol (10.0 ml) and the mixture was filtered to remove sodium chloride and the methanolic filtrate added to a solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.30 g, 0.001 mol) in anhydrous 1,2-dimethoxyethane (20.0 ml). The resulting solution was left at room temperature for 17 h then evaporated and the residue treated with water and filtered to afford 1-hydroxy-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)urea (104) (0.34 g; quant.), which formed yellow crystals m.p. 237-239° (phase change 120-130°) (from ethanol), ν_{max} 3200 (NH) and 1700 (CO) cm^{-1}.

Found: C, 60.3; H, 4.8; N, 22.4%; M^+-NH_2OH, 303

$C_{17}H_{16}N_6O_2$ requires: C, 60.7; H, 4.8; N, 25.0%; M, 336

1-Cyano-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)urea (105b)

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.61 g, 0.002 mol) in ethanol (50.0 ml) was treated with a solution of sodium cyanamide (0.13 g, 0.002 mol) in water (1.0 ml) and the mixture was heated under reflux for 8 h. The mixture was cooled and evaporated and the residue treated with water (20.0 ml) and extracted with methylene chloride to afford an orange gum (0.60 g). Trituration of this gum with ethyl acetate yielded

1-cyano-3-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)urea (105b) (0.20 g; 29%), which formed yellow crystals m.p. 151-153° (from ethyl acetate-light petroleum), ν_{max} 3620, 3510 and 3300 (NH), 2180 (CN) and 1690 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.69 (2H, brs, NH), 8.07-7.39 (10H, m, ArH) and 3.79 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$], 161.49 (quat), 152.55 (quat), 146.38 (quat), 132.88 (quat), 132.34 (quat), 129.44, 129.19, 128.91, 128.24, 127.98, 127.57, 125.80 (quat) and 121.32.

Found: C, 53.6; H, 4.5; N, 25.3%; M^+, 374

$C_{18}H_{15}N_7O$ requires: C, 62.6; H, 4.4; N, 28.1%; M, 345

The ethyl acetate mother liquor was evaporated to afford a brown gum (0.4 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (10:1) gave the unreacted pyrazolotriazinone (31a) (0.20 g; 33%) m.p. 230-235° identical (m.p. and i.r. spectrum) to an authentic sample.

Final elution with ethanol afforded a dark intractable gum (0.10 g) which was not further investigated.

1-(1-Methyl-3-phenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl)urea (105a)

A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.61 g, 0.002 mol) in anhydrous ethanol (30.0 ml) was mixed with a solution of sodium (0.05 g, 0.002 g-atom) in anhydrous ethanol (3.0 ml)

which had been mixed with a solution of toluene-4-sulphonamide (0.38 g, 0.0022 mol) in anhydrous ethanol (7.0 ml), and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated and the residue (0.9 g) was subjected to flash chromatography.

Elution with methylene chloride yielded 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) (0.45 g; 81%), m.p. 130-133°, identical (m.p. and i.r. spectrum) to a sample prepared before, followed by the unreacted pyrazolo-triazinone (31a) (0.05 g; 8%), m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with ethanol gave a yellow solid (0.25 g) which was slurried with aqueous 2M hydrochloric acid to afford 1-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)-3-(toluene-4-sulphonyl)urea (105a) (0.20 g; 18%), m.p. 268-269° (from glacial acetic acid), ν_{max} 1715 (CO) cm^{-1},

Found: C, 58.2; H, 4.7; N, 16.6%; $M^+-TSO_2NH_2$, 303

$C_{30}H_{22}N_6O_3H_2O$ requires: C, 58.5; H, 4.9; N, 17.0%; $M-H_2O$, 546

The Reactions of 3,5-Diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) with Acetylacetone

(a) A solution of 3,5-diphenyl-1-methyl-1H-pyrazolo [3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.61 g, 0.002 mol) and acetylacetone (0.20 g, 0.002 mol) in anhydrous dioxane (30.0 ml) was treated with triethylamine (0.20 g, 0.002 mol) and the mixture was stirred at room temperature for 1 h, then heated under reflux for a further 3 h.

The mixture was evaporated to afford the unreacted pyrazolotriazinone (31a) (0.61 g; quant.) m.p. 235-238°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(b) A solution of sodium (0.05 g, 0.002 g-atoms) in anhydrous ethanol (3.0 ml) was treated with acetylacetone (0.22 g, 0.002 mol) in anhydrous ethanol (7.0 ml). The resulting ethanolic sodium acetylacetonate solution was mixed with a solution of 3,5-diphenyl-1-methyl-1H-pyrazolo-[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.61 g, 0.002 mol) in anhydrous ethanol (30.0 ml) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated to afford a brown gum (0.60 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (10:1) yielded 5-amino-1-methyl-3-phenyl-4-phenylazopyrazole (30a) (0.28 g; 51%) m.p. 130-133°, identical (m.p. and i.r. spectrum) to a sample prepared before, followed by the unreacted pyrazolotriazinone (31a) (0.20 g; 33%) m.p. 235-238°, identical (m.p. and i.r. spectrum) to an authentic sample.

Final elution with ethanol afforded a dark intractable gum (0.08 g) which was not further investigated.

(c) A solution of sodium (0.05 g, 0.002 g-atoms) in anhydrous ethanol (3.0 ml) was treated with acetylacetone (0.22 g, 0.0022 mol) and the resulting solution was evaporated by azeotroping with toluene to yield sodium acetylacetonate

as a cream solid. This was suspended in anhydrous dimethylformamide (2.5 ml) and the suspension treated with a solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (0.61 g, 0.002 mol) in anhydrous dimethylformamide (2.5 ml) then stirred at room temperature for 1 h, heated at 50° (water bath) for 1 h and finally heated at 70° for 4 h. The mixture was evaporated to give a brown solid which was treated with water and filtered to afford the unreacted pyrazolotriazinone (31a) (0.41 g; 67%), m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid to afford N-(1-methyl-3-phenyl-4-phenylazopyrazol-5-yl)-2-acetylacetoacetamide (106) (0.12 g; 14%) which formed yellow crystals m.p. 155-156° (from ethanol), ν_{max} 3270 (NH) and 1655 (CO) cm^{-1}.

Found: C, 65.3; H, 5.4; N, 17.5%; M^+, 403

$C_{22}H_{21}N_5O_3$ requires: C, 65.5; H, 5.2; N, 17.4%; M, 403

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

The Attempted Reaction of 3,5-Diphenyl-1-methyl-1H-pyrazolo-[3,4-e]-1,2,4-triazin-6(5H)-one (31a) with Sodium Borohydride

A stirred solution of 3,5-diphenyl-1-methyl-1H-pyrazolo[3,4-e]-1,2,4-triazin-6(5H)-one (31a) (0.61 g, 0.002 mol) in dioxane (50.0 ml) was treated with a solution of sodium borohydride (0.33 g, 0.008 mol) in water (5.0 ml) and the mixture was stirred at room temperature for 3 h. The

mixture was evaporated and the residue was treated with water to afford an orange solid (0.65 g) which was washed with ethyl acetate to yield the unreacted pyrazolotriazinone (31a) (0.52 g; 85%) m.p. 235-238°, identical (m.p. and i.r. spectrum) to a sample prepared before. The ethyl acetate filtrate was evaporated to afford a white solid (0.1 g) m.p. 7350° which was not further investigated.

The Reaction of 2-Phenylhydrazonobenzoylacetonitrile (29a) with Hydroxylamine Hydrochloride in Methanol in the Presence of Sodium Methoxide

(a) A suspension of 2-phenylhydrazonobenzoylacetonitrile (29a) (2.5 g, 0.01 mol) and hydroxylamine hydrochloride (0.70 g, 0.01 mol) in anhydrous methanol (10.0 ml) was treated with a solution of sodium (0.5 g, 0.02 mol) in methanol (10.0 ml) and the mixture was heated under reflux for 14 h. The mixture was cooled and evaporated and the residue treated with water, then filtered to afford a yellow solid which was combined with a second crop obtained by neutralisation of the aqueous mother liquor with glacial acetic acid to yield unreacted 2-phenylhydrazonobenzoyl-acetonitrile (29a) (total 2.2g; 89%) m.p. 136-128°, identical (m.p. and i.r. spectrum) to an authentic sample

(b) A suspension of 2-phenylhydrazonobenzoylacetonitrile (29a) (2.5 g, 0.01 mol) and hydroxylamine hydrochloride (2.80 g, 0.04 mol) in anhydrous methanol (10.0 ml) was treated with a solution of sodium (0.92 g, 0.04 g-atoms) in methanol (10.0 ml) and the mixture was heated under reflux for 17 h.

The mixture was cooled and evaporated and the residue treated with water and filtered to afford 2-benzoyl-2-phenylhydrazonoacetamidoxime (111) (2.4 g; 91%) m.p. 150-152°, identical (m.p. and i.r. spectrum) to an authentic sample as described in chapter 2.

(c) A suspension of 2-phenylhydrazonobenzoylacetonitrile (29a) (4.98 g, 0.02 mol) and hydroxylamine hydrochloride (5.6 g, 0.008 mol) in anhydrous methanol (20.0 ml) was treated with a solution of sodium (1.84 g, 0.08 g-atoms) in methanol (20.0 ml) and the mixture heated under reflux for 17 h. The mixture was cooled and evaporated and the residue treated with water. The resulting suspension was extracted with methylene chloride to afford a brown solid (4.6 g) which was subjected to flash chromatography.

Elution with toluene afforded 2-phenylhydrazonobenzoylacetonitrile (29a) (1.8 g; 36%) m.p. 136-138°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with ethyl acetate yielded 2-benzoyl-2-phenylhydrazonoacetamidoxime oxime (112) (1.8 g; 60%) which formed colourless crystals m.p. 171-172°, ν_{max} 3470, 3360 and 3180 (NH) 1650 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$], 11.54 (1H, brs, NH or OH), 9.76 (1H, s, OH or NH), 9.23 (1H, s, NH or OH), 7.49-6.76 (10H, m, ArH) and 5.44 (2H, brs, NH), δ_C [$(CD_3)_2SO$], 149.10 (quat), 148.67 (quat), 144.73 (quat), 133.93 (quat), 131.27 (quat), 128.67, 128.26, 125.72, 119.72 and 113.28.

Found: C, 60.6; H, 5.1; N, 23.6%; M^+, 297

$C_{15}H_{15}N_5O_2$ requires: C, 60.6; H, 5.1; N, 23.6%; M, 297

Final elution with ethanol afforded an intractable brown gum (0.6 g) which was not further investigated.

The original aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and extracted with methylene chloride to give a small amount of yellow solid (0.07 g), m.p. 118-122°, whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Reaction of 2-Benzoyl-2-phenylhydrazonoacetamidoxine Oxime (112) with Glacial Acetic Acid

A solution of 2-benzoyl-2-phenylhyrazonoacetamidoxime oxime (112) (0.30 g, 0.001 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 1 h. The mixture was cooled and evaporated to give an orange solid (0.24 g) which was subjected to flash chromatography.

Elution with methylene chloride-cyclohexane (1:1) yielded 3-phenyl-4-phenylazo-Δ^2-isoxazolin-5-one (114)[156] (0.03 g; 10%) m.p. 165-166°; (lit.,[156] 168°) identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride yielded 5-amino-3-phenyl-4-phenylazoisoxazole (110) (0.06 g; 20%) m.p. 143-145°, identical (m.p. and i.r. spectrum) to a sample prepared before, followed by an unidentified yellow solid (0.03 g) m.p. 150-155°, ν_{max} 3350 and 3160 (NH), and 1650 (CO) cm^{-1}, m/e 279.

Elution with methylene chloride-ethyl acetate (5:1) gave a colourless solid (0.03 g) m.p. 195-200°, ν_{max} 3360 and 3170 (NH) and 1650 (CO) cm^{-1}, m/e 340.

Further elution with ethyl acetate through to ethanol gave a series of intractable gums (total, 0.06 g) which were not further investigated.

The Attempted Reaction of 2-Benzoyl-2-phenylhydrazonoacetamidoxime oxime (112) with Acetic Anhydride

A solution of 2-benzoyl-2-phenylhydrazonoacetamidoxime oxime (112) (0.30 g, 0.001 mol) in acetic anhydride (5.0 ml) was heated under reflud for 1 h. The mixture was cooled and evaporated to give a brown gum (0.3 g) which when subjected to flash chromatography in cyclohexane through to ethyl acetate afforded a series of intractable gums (total, 0.28 g) none of which were further investigated.

The Reaction of 2-Phenylhydrazonobenzoylacetonitrile (29a) with Hydroxylamine Hydrochloride in the Presence of Aqueous Sodium Hydroxide

(a) A solution of 2-phenylhydrazonobenzoylacetonitrile (29a) (25.0 g, 0.1 mol) in ethanol (150 ml) was treated with aqueous 2M sodium hydroxide solution (100 ml) followed by a solution of hydroxylamine hydrochloride (56.0 g, 0.8 mol) in water (100 ml) which had been neutralised by the addition of aqueous 2M sodium hydroxide solution (400 ml). The resulting solution was stirred at room temperature for 24 h, then evaporated and the residue was treated with water and filtered

to afford a yellow solid which was slurried with aqueous 2M hydrochloric acid and filtered to afford the unreacted 2-phenylhydrazonebenzoylacetonitrile (29a) (20.0 g; 80%) m.p. 136-138°, identical (m.p. and i.r. spectrum) with an authentic sample.

The combined aqueous mother liquor and acidic washings were neutralised by addition of aqueous 2M hydrochloric acid and the solution extracted with methylene chloride to afford a dark gum (3.0 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

(b) A solution of 2-phenylhydrazonobenzoylacetonitrile (29a) (2.5 g, 0.01 mol) in ethanol (50.0 ml) was treated with aqueous 2M sodium hydroxide solution (10.0 ml) followed by a solution hydroxylamine hydrochloride (5.6 g, 0.08 mol) in water (25.0 ml) which had been neutralised by the addition of aqueous 2M sodium hydroxide solution (25.0 ml). The resulting yellow suspension was stirred at room temperature for 24 h and filtered to afford a yellow solid (2.2 g) which was subjected to flash chromatography.

Elution with methylene chloride-cyclohexane (1:1) yielded unreacted 2-phenylhydrazonobenzoylacetonitrile (29a) (0.98 g; 39%) m.p. 135-138°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride yielded 2-benzoyl-2-phenylhydrazonoacetamidoxime (111) (0.8 g; 28%) m.p. 155-156°, identical (m.p. and i.r. spectrum) to a sample prepared before as described in Chapter 2.

Final elution with ethanol afforded a brown gum (0.25 g) which was not further investigated.

The original aqueous mother liquor on neutralisation with aqueous 2M hydrochloric acid and subsequent extraction with methylene chloride yielded no further material.

The Reaction of 2-Benzoyl-2-phenylhydrazonoacetamidoxime (111) with Hydroxylamine Hydrochloride in the Presence of Sodium Methoxide

A suspension of 2-benzoyl-2-phenylhydrazonoacetamidoxime (111) (1.10 g, 0.004 mol) and hydroxylamine hydrochoride (1.10 g, 0.016 mol) in methanol (10.0 ml) was treated with a solution of sodium (0.37 g, 0.016 g-atoms) in methanol (5.0 ml) and the mixture was heated under reflux for 17 h. The mixture was cooled and evaporated and the residue treated with water. The resulting solution was extracted with methylene chloride to afford a brown gum (0.5 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded 5-amino-3-phenyl-4-phenylazoisoxazole (110)[90] (0.2 g, 18%) m.p. 135-138°, (lit.,[90] 140°) identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethyl acetate followed by ethanol gave gums (total, 0.11 g) whose t.l.c. in ethyl acetate showed them to be complex mixtures which were not further investigated.

Benzoylacetonitrile (28)[105]

Benzoylacetonitrile (28) was prepared as described in Chapter 2.

5-Amino-3-Phenylisoxazole (109)[105]

5-Amino-3-phenylisoxazole (109) was prepared by the reaction of benzoylacetonitrile (28) with hydroxylamine hydrochloride as described by Obregia[105] (90%) m.p. 107-109° (lit.,[105] 110-112°).

5-Amino-3-phenyl-4-phenylazoisoxazole (110)[90]

A solution of redistilled aniline (2.5 g, 0.025 mol) in aqueous 5M hydrochloric acid (13.0 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (2.1 g, 0.025 mol) in water (6.0 ml). The resulting amber benzenediazonium chloride solution was stirred for a further 5 min in the ice-salt bath, then added in one portion at 0-5° (ice-salt bath) to a stirred solution of 5-amino-3-phenylisoxazole (109) (4.0 g, 0.025 mol) and anhydrous sodium acetate (1.4 g, 0.0375 mol) in glacial acetic acid (25.0 ml) and water (7.0 ml) and the mixture was stirred at room temperature for a further 1 h.

The mixture was filtered to afford an orange solid which was crystallised from toluene-light petroleum (b.p. 40-60°) to yield 5-amino-3-phenyl-4-phenylazoisoxazole (110) (5.7 g; 86%), as yellow prisms, m.p. 143-144° (lit.,[90] 140°) ν_{max} 3390 and 3100 (NH) cm^{-1}, δ ($CDCl_3$) 8.24-7.20 (10H, m, ArH) and 7.07 (2H, brs, NH).

Found: C, 68.3; H, 4.5; N, 21.5%; M^+, 264

Calc. for $C_{15}H_{12}N_4O$: C, 68.2; H, 4.6; N, 21.2%; M, 264

The glacial acetic acid filtrate was evaporated and the residue was treated with water and extracted with

methylene chloride to afford a red gum (0.2 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

5-Acetamido-3-phenyl-4-phenylazoisoxazole (115)

A solution of 5-amino-3-phenyl-4-phenylazoisoxazole (110) (0.53 g, 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 1 h. The mixture was cooled and evaporated to afford a dark solid (0.5 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (5:1) yielded 5-acetamido-3-phenyl-4-phenylazoisoxazole (115) (0.2 g; 33%) m.p. 199-201° (from toluene), ν_{max} 3270 (NH) and 1695 (CO) cm^{-1}, $\delta_H(CDCL_3)$, 9.39 (1H, brs, NH), 8.17-7.44 (10NH, m, ArH) and 2.61 (3H, s, CH_3), δ_C ($CDCl_3$), 171.90 (quat), 158.47 (quat), 150.85 (quat), 138.84 (quat), 137.61 (quat), 129.72, 129.46, 129.32, 128.91, 128.24, 119.34 and 25.39 (CH_3).

Found: C, 66.6; H, 4.5; N, 18.4%, M^+, 306

$C_{17}H_{14}N_4O_2$ requires: C, 66.7; H, 4.6; N, 18.3%; M, 306

Further elution with methylene chloride-ethyl acetate (5:1) afforded a brown gum (0.1 g) which decomposed on attempted purification by Kugelrohr distillation at 190°/0.5 mmHg.

Final elution with ethanol gave a brown gum (0.16 g) whose t.l.c. in ethyl acetate showed it to be a multi-component mixture which was not further investigated.

1-Oximino-1-phenyl-2-phenylhydrazonoethane (116)

A solution of 5-amino-3-phenyl-4-phenylazoisoxazole (110) (0.53 g, 0.002 mol) in ethanol (10.0 ml) was treated with aqueous 2M sodium hydroxide solution (5.0 ml) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated and the residue treated with water (10.0 ml) and the resulting solution extracted with methylene chloride to afford a brown gum (0.55 g) which was subject to flash chromatography.

Elution with methylene chloride-cyclohexane (1:1) gave a small amount of an orange gum (0.05 g) which was not further investigated.

Elution with methylene chloride afforded 1-oximino-1-phenyl-2-phenylhydrazonoethane (116) (0.3 g; 63%) m.p. 154-155° (from toluene), ν_{max} 3305 (NH), and 3175 (OH) cm^{-1}, δ_H [$(CD_3)_2SO$] 11.53 (1H, s, NH or OH), 10.81 (1H, s, OH or NH) 8.34 (1H, s, CH), 7.66-6.74 (10H, m, ArH), δ_C [$(CD_3)_2SO$] 153.34 (quat), 144.47 (quat), 134.72 (quat), 129.74, 129.14, 128.88, 128.59, 128.39, 127.79, 127.64, 119.86, 118.90, and 112.48 (CH).

Found: C, 70.4; N, 5.2; N, 17.5%; M^+, 239

$C_{14}H_{13}N_3O$ requires: C, 70.3; H, 5.4; N, 17.6%; M, 239

Final elution with ethanol gave an intractable brown gum (0.17 g) which was not further investigated.

Neutralisation of the original aqueous mother liquor with aqueous 2M hydrochloric acid and extraction with methylene chloride yielded no further material.

3-Phenyl-4-Phenylazo-Δ^2-isoxazolin-5-one (114)[156]

A solution of 5-amino-3-phenyl-4-phenylazoizoxazole (110) (0.53 g, 0.002 mol) in ethanol (10.0 ml) was treated with aqueous 20% w/v sulphuric acid (5.0 ml) and the mixture heated under reflux for 0.5 h. The mixture was cooled and filtered to afford 3-phenyl-4-phenylazo-Δ^2-izoxazolin-5-one (114) (0.53 g; quant.) which formed yellow needles m.p. 168-169° (from glacial acetic acid) (lit.,[156] 168°), ν_{max} 3180 (NH), and 1720 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 12.97 (1H, brs, NH) and 8.03-7.26 (10H, m, ArH), δ_C [$(CD_3)_2SO$] 163.04 (quat), 158.43 (quat), 141.15 (quat), 131.05, 126.47, 128.81, 127.38, 126.84 (quat), 126.37, 118.95 (quat) and 116.92.

Found: C, 67.7; H, 4.0; N, 15.8%; M^+, 265

Calc. for $C_{15}H_{11}N_3O_2$: C, 67.9; H, 4.2; N, 15.9%; M, 265

The Attempted Reaction of 3-Phenyl-4-Phenylazo-Δ^2-isoxazolin-5-one (114) with Aqueous Sodium Hydroxide

A solution of 3-phenyl-4-phenylazo-4-isoxazolin-5-one (114) (0.26 g, 0.001 mol) in ethanol (20.0 ml) was treated with aqueous 2M sodium hydroxide solution (2.5 ml) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated and the residue treated with water and filtered to afford unreacted 3-phenyl-4-phenylazo-Δ-isoxazolin-5-one (114) (0.1 g; 40%), m.p. 168-169°, identical (m.p. and i.r. spectrum) to an authentic sample.

The original aqueous mother liquor was neutralised with aqueous 2M hydrochloric acid and extracted with methylene chloride to give a small amount of an unidentified solid (0.03 g), m.p. 130-135°, ν_{max} 3300 and 3180 (NH) cm^{-1}. Constant extraction of the aqueous mother liquor with methylene chloride yielded no further material.

2,4-Diphenyl-2H-1,2,3-triazole-5-carboxamide (127)

(a) A solution of 5-amino-3-phenyl-4-phenylazoisoxazole (1) (1.30 g; 0.005 mol) in anhydrous diglyme (50.0 ml) was treated with redistilled tosyl isocyanate (1.10 g, 0.005 mol) and the mixture was heated under reflux for 3h. The mixture was cooled and evaporated to give a brown gum (1.90 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (5:1) yielded 2,4-diphenyl-2H-1,2,3-triazole-5-carboxamide (127) (1.3 g; quant.), m.p. 200-203° (from toluene), ν_{max} 3350 and 3150 (NH), and 1650 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.17-8.01 (5H, m, ArH), 7.79 (2H, brs, NH) and 7.66-7.45 (5H, m, ArH), δ_C [$(CD_3)_2SO$] 162.29 (quat), 147.49 (quat), 140.57 (quat), 138.71 (quat), 129.73, 129.24 (quat), 129.11, 128.59, 128.46, 128.27 and 178.89.

Found: C, 68.4; H, 4.5; N, 21.3%, M^+, 264

$C_{15}H_{12}N_4O$ requires: C, 68.2; H, 4.6; N, 21.2%, M, 264.

Elution with ethyl acetate through to ethanol afforded a series of intractable gums (total, 0.5 g) which were not further investigated.

(b) A solution of 5-amino-3-phenyl-4-phenylazoisoxazole (110) (0.53 g, 0.002 mol) in anhydrous diglyme (20.0 ml) was heated under reflux for 2 h. The mixture was cooled and evaporated to afford a brown gummy solid which was triturated with toluene to yield 2,4-diphenyl-2H-1,2,3-triazole-5-carboxamide (127) (0.20 g; 38%), m.p. 203-204°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

The toluene mother liquor was evaporated to give a brown gum (0.3 g) which on flash chromatography in methylene chloride through to ethanol gave a series of gums (total, 0.23 g) none of which were further investigated.

(c) A solution of 5-amino-3-phenyl-4-phenylazoisoxazole (110) (0.53 g, 0.002 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 1 h. The mixture was cooled and evaporated to afford a brown solid (0.53 g) which was subjected to flash chromatography.

Elution with methylene chloride-cyclohexane (1:1) afforded the unreacted 5-amino-3-phenyl-4-phenylazoisoxazole (110) (0.33 g; 62%), m.p. 144-148°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Final elution with ethyl acetate yielded 2,4-diphenyl-2H-1,2,3-triazole-5-carboxamide (127) (0.12 g; 23%), m.p. 202-203° (from toluene), identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

The Attempted Reaction of 2,4-Diphenyl-2H-1,2,3-triazole-5-carboxamide (127) with Aqueous Sulphuric Acid

A solution of 2,4-diphenyl-2H-1,2,3-triazole-5-carboxamide (127) (0.46 g, 0.001 mol) in ethanol (15.0 ml) was treated with aqueous 20% w/v sulphuric acid (5.0 ml) and the mixture heated under reflux for 0.5 h. The mixture was cooled and filtered to afford the unreacted 2,4-diphenyl-2H-1,2,3-triazole-5-carboxamide (127) (0.45 g; 98%), m.p. 200-203°, identical (m.p. and i.r. spectrum) to a sample prepared before.

2,4-Diphenyl-2H-1,2,3-triazole-5-carboxylic Acid (128)

A solution of 2,4-diphenyl-2H-1,2,3-triazole-5-carboxamide (127) (0.46 g, 0.001 mol) in ethanol (15.0 ml) was treated with aqueous 2M sodium hydroxide (2.5 ml) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated and the residue treated with water to give a solid which was slurried with aqueous 2M hydrochloric acid to give a colourless solid which was combined with further material obtained by neutralisation of the aqueous alkaline filtrate with aqueous 2M hydrochloric acid to yield 2,4-diphenyl-2H-1,2,3-triazole-5-carboxylic acid (128) (0.27 g; quant.), m.p. 231-232° (from ethanol), ν_{max} 3200-2500 (OH), and 1690 (CO) cm^{-1}, δ_C [$(CD_3)_2SO$] 161.94 (quat), 149.51 (quat), 138.66 (quat), 138.03 (quat), 129.84, 129.27, 129.12, 128.78, 128.18 and 119.06.

Found: C, 67.6; H, 4.1; N, 15.8%; M^+, 265

$C_{15}H_{11}N_3O_2$ requires: C, 67.9; H, 4.2; N, 15.9%; M, 265.

The Attempted Preparation of 3-Amino-5-phenyl-4-phenylazoisoxazole (129)[90]

A solution of 2-phenylhydrazonobenzoylacetonitrile (29a) (1.0 g, 0.004 mol) in ethanol (20.0 ml) was treated with a solution of hydroxylamine hydrochloride (0.28 g, 0.004 mol) in water (2.0 ml) which had been neutralised by addition of sodium carbonate (0.42 g, 0.004 mol) and the mixture was

heated under reflux for 4 h. The mixture was cooled and treated with water (10.0 ml) then acidified with acetic acid and filtered to afford the unreacted 2-phenylhydrazono-benzoylacetonitrile (29a) (1.0 g; quant.), m.p. 134-137° identical (m.p. and i.r. spectrum) to a sample prepared before.

3-Amino-5-phenyl-4-phenylazoisoxazole (129)[90]

A solution of 2-benzoyl-2-phenylhydrazonoacetamidoxime (29a) (7.05 g, 0.025 mol) in glacial acetic acid (100 ml) was heated under reflux for 1 h. The mixture was cooled and evaporated and the residue triturated with light petroleum to yield 3-amino-5-phenyl-4-phenylazoisoxazole (129) (6.6 g; quant.), m.p. 171-172° (from toluene) (lit.,[90] 186°), ν_{max} 3440, 3260 and 3160 (NH), and 1625 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.22-7.55 (10H, m, ArH) and 6.61 (2H, brs, NH), δ_C [$(CD_3)_2SO$] 166.85, 156.21 (quat), 152.22 (quat), 131.36, 130.99, 129.41, 129.20, 127.63, 126.67 (quat), 124.23 (quat) and 122.20.

Found: 264.1012.

$C_{15}H_{12}N_4O$ requires: 264.1011.

The Reaction of 3-amino-5-phenyl-4-phenylazoisoxazole (129) with Acetic Anhydride

A solution of 3-amino-5-phenyl-4-phenylazoisoxazole (129) (0.26 g, 0.001 mol) in acetic anhydride was heated under reflux for 1 h. The mixture was evaporated to give a brown gum (0.28 g) which was subjected to flash chromatography.

Elution with methylene chloride-cyclohexane (1:1) yielded 3-phenyl-4-phenylazo-Δ^2-isoxazolin-5-one (114) (0.02 g, 1%), m.p. 160-165°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with methylene chloride through to methylene chloride-ethyl acetate (10:1) yielded two gums (total, 0.13 g) which were not further investigated. Further elution with methylene chloride-ethyl acetate (10:1) afforded 3-acetamido-5-phenyl-4-phenylazoisoxazole (133) (0.05 g; 2%), m.p. 142-143° [from toluene-light petroleum (b.p. 40-60°)], ν_{max} 3220 (NH), 1690 (CO) and 1625 (C=N) cm^{-1}, δ_H [$(CD_3)_2SO$] 9.83 (1H, brs, NH), 8.46-7.41 (10H, m, ArH) and 2.41 (3H, c, CH_3). δ_C [$(CD_3)_2SO$] 148.72 (quat), 139.14 (quat), 135.21 (quat), 133.61, 133.03 (quat), 132.66 (quat), 130.32, 129.30, 128.45, 119.44 and 26.43 (CH_3)

Found: C, 66.2; H, 4.4; N, 18.6%; M^+, 306.
$C_{17}H_{14}N_4O_2$ requires: C, 66.7; H, 4.6; N, 18.3%; M, 306.

Final elution with ethanol gave a brown intractable gum (0.08 g) which was not further investigated.

The Attempted Reaction of 3-Amino-5-phenyl-4-phenylazoisoxazole (129) with Phenyl Isocyanate

A solution of 3-amino-5-phenyl-4-phenylazoisoxazole (129) (0.53 g, 0.002 mol) in anhydrous dioxane (20.0 ml) was treated with stirring at room temperature with a solution of phenyl isocyanate (0.24 g, 0.002 mol) in anhydrous dioxane (2.0 ml) and the mixture stirred at room temperature for 16 h.

The mixture was evaporated to give an orange gum which was triturated with diethyl ether to afford unreacted 3-amino-5-phenyl-4-phenylazoisoxazole (129) (0.5 g; 94%), m.p. 170-172°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The ethereal mother liquor was evaporated to give a small amount of an orange gum (0.04 g) which was not further investigated.

The Attempted Reaction of 3-Amino-5-phenyl-4-phenylazoisoxazole (129) with Aqueous Sulphuric Acid

A solution of 3-amino-5-phenyl-4-phenylazoisoxazole (129) (0.53 g, 0.002 mol) in ethanol (10.0 ml) was treated with aqueous 20% w/v sulphuric acid (5.0 ml) and the mixture was heated under reflux for 0.5 h. The mixture was cooled and filtered to afford the unreacted 3-amino-5-phenyl-4-phenylazoisoxazole (129) (0.53 g; quant.), m.p. 170-171°,identica (m.p. and i.r. spectrum) with an authentic sample.

The Attempted Reactionof 3-Amino-5-phenyl-4-phenylazoisoxazole (129) with Aqueous Sodium Hydroxide

A solution of 3-amino-5-phenyl-4-phenylazoisoxazole (129) (0.53 g, 0.002 mol) in ethanol (10.0 ml) was treated with aqueous 2M sodium hydroxide solution (5.0 ml) and the mixture was heated under reflux for 24 h. The mixture was evaporated and the residue treated with water to afford the unreacted 3-amino-5-phenyl-4-phenylazoisoxazole (129)

(0.49 g; 93%), m.p. 170-172° (from toluene), identical (m.p. and i.r. spectrum) to a sample prepared before.

2-Benzoyl-2-phenylhydrazonoacetamidine (136)

A solution of 3-amino-5-phenyl-4-phenylazoisoxazole (129) (0.53 g, 0.002 mol) in ethanol (50.0 ml) was hydrogenated at atmospheric pressure and room temperature with agitation over palladium-charcoal (10%, 0.11 g). After 7 h. of agitation no more hydrogen appeared to be taken up. The mixture was filtered through 'celite' and the filtrate was evaporated to afford a yellow gum which was triturated with diethyl ether to yield 2-benzoyl-2-phenylhydrazono-acetamidine (136) (0.42 g; 80%), m.p. 200-202° (from ethyl acetate), ν_{max} 3440 and 3260 (NH) cm^{-1}, δ_H [$(CD_3)_2SO$] 10.52 (2H, brs, NH), 7.62 (2H, brs, NH) and 7.55-7.08 (10H, m, ArH), δ_C [$(CD_3)_2SO$] 192.62 (quat), 158.15 (quat), 152.75 (quat), 142.45 (quat), 128.92, 128.59, 126.66, 125.66, 119.95 and 118.01 (quat).

Found: 266.1162.

$C_{15}H_{14}N_4O$ requires: 266.1167.

The Attempted Oxidation of 2-Benzoyl-2-phenylhydrazono-acetamidine (136) with Activated Manganese Dioxide

A solution of 2-benzoyl-2-phenylhydrazonoacetamidine (136) (0.27 g, 0.001 mol) in anhydrous acetonitrile (20.0 ml) was treated with activated manganese dioxide (1.5 g) and the suspension stirred at room temperature for 1 h. The mixture was filtered through 'celite' and the filtrate

evaporated to afford the unreacted 2-benzoyl-2-phenylhydrazonoacetamidine (136) (0.24 g; 89%), m.p. 195-200°, identical (m.p. and i.r. spectrum) to a sample prepared before.

2-Benzoyl-2-phenylhydrazonoacetamidine Acetate (137)

A solution of 2-benzoyl-2-phenylhydrazonoacetamidine (136) (0.53 g, 0.002 mol) in acetic anhydride (2.0 ml) was heated at 100° (steam bath) for 10 min. The mixture was cooled and evaporated to afford 2-benzoyl-2-phenylhydrazonoacetamidine acetate (137) (0.55 g, 88%), m.p. 119-120° [from light petroleum (b.p. 100-120°)] ν_{max} 3300 (NH) and 1710 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 14.10 (1H, brs, NH), 11.90 (1H, brs, NH), 10.90 (1H, brs, NH), 7.60-7.17 (10H, m, ArH) and 2.31 (3H, s, CH_3), δ_C [$(CD_3)_2SO$] 194.50 (quat), 174.23 (quat), 153.41 (quat), 151.46 (quat), 140.96 (quat), 129.72, 129.12, 128.96, 127.23, 127.04, 120.29, 116.94 (quat) and 25.39 (CH_3).

Found: C, 66.5; H, 5.2; N, 17.5%; M^+, 308.
$C_{17}H_{16}N_4O_2$ requires: C, 66.2; H, 5.2; N, 18.2%; M, 308.

1,3-Di(3-phenylisoxazol-5-yl)triazene (144)

A solution of 5-amino-3-phenylisoxazole (109) (0.80 g, 0.005 mol) in glacial acetic acid (5.0 ml) was treated dropwise with stirring at 5-8° (ice-bath) with a solution of sodium nitrite (0.40 g, 0.006 mol) in water (2.0 ml) and

the mixture was stirred at room temperature for 1 h. The mixture was then treated with water (8.0 ml) and the resulting solution extracted with methylene chloride. The methylene chloride extract was washed with saturated aqueous sodium bicarbonate and evaporated to give a red oil (0.75 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethyl acetate (4:1) yielded 1,3-di(phenylisoxazol-5-yl)triazene (144) (0.29 g; 18%), m.p. 169-170° (from ethanol), ν_{max} 1685 (C=N) cm^{-1}, δ[$(CD_3)_2SO$] 9.25 (1H, brs, NH), 8.13-7.47 (10H, m, ArH) and 7.05 (2H, s, CH).

Found: 331.1060.

$C_{18}H_{13}N_5O_2$ requires: 331.1069.

Further elution with cyclohexane-ethyl acetate (4:1) through to ethanol gave a series of gums and solids (total, 0.27 g) none of which were further investigated.

4-Oximino-3-phenyl-Δ^2-isoxazolin-5-one (145)[167]

A solution of 5-amino-3-phenylisoxazole (109) (0.64 g, 0.004 mol) in anhydrous ethanol (10.0 ml) was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of hydrogen chloride (0.37 g, 0.01 mol) in anhydrous ethanol (2.5 ml), the mixture was then further treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of ethyl nitrite (0.33 g, 0.0044 mol) in absolute ethanol (2.5 ml) and the resulting mixture was stirred at room temperature for 18 h. The mixture was evaporated

and the residue treated with saturated aqueous sodium bicarbonate and extracted with methylene chloride to afford a brown gum (0.20 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded a yellow solid which was combined with further material obtained by neutralisation of the alkaline aqueous mother liquor with aqueous 2M hydrochloric acid followed by filtration to yield 4-oximino-3-phenyl-Δ^2-isoxazolin-5-one (145)[167] (total 0.19 g; 24%), which formed colourless crystals, m.p. 162-163° (from toluene) (lit.,[167] 156°), ν_{max} 3150 (OH) and 1785 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.93-7.50 (5H, m, ArH), and 3.50 (1H, brs, OH), δ_C [$(CD_3)_2SO$] 158.21 (quat), 156.61 (quat), 138.39 (quat), 131.42, 128.83, 127.75 and 126.36 (quat).

Found: C, 56.5; H, 3.2; N, 14.3%; M^+-NO_2 145.
$C_9H_6N_2O_3$ requires: C, 56.8; H, 3.2; N, 14.7%; M, 191.

Final elution with ethanol afforded a brown gum (0.72 g) whose t.l.c. in ethyl acetate showed it to be a multi-component mixture which was not further investigated.

2-Oximinobenzoylacetonitrile (146)[168]

2-Oximinobenzoylacetonitrile (146) was prepared (yield 37%) by reaction of benzoylacetonitrile with sodium nitrite in the presence of glacial acetic acid as described by Wolff and Oneto,[168] and had m.p. 117-120° (lit.,[168] 116-118), ν_{max} 3270 (OH) and 1645 (CO) cm^{-1}.

The Attempted Reaction of 2-Oximinobenzoylacetonitrile (146) with Hydroxylamine Hydrochloride in the Presence of Aqueous Sodium Hydroxide

A solution of 2-oximinobenzoylacetonitrile (146) (0.35 g, 0.002 mol) in aqueous 2M sodium hydroxide solution (2.0 ml) was treated with a solution of hydroxylamine hydrochloride (1.12 g, 0.016 mol) in water (20.0 ml) which had been neutralised by the addition of aqueous 2M sodium hydroxide solution (20.0 ml). The mixture was firmly stoppered and left at room temperature for 17 h. The mixture was then neutralised by addition of aqueous 2M hydrochloric acid and extracted with methylene chloride to afford a green solid (0.11 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a complex mixture which was not further investigated.

The aqueous mother liquor on standing afforded a colourless solid (0.11 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a multi-component mixture which was not further investigated.

2-Benzoyl-2-oximinoacetamidoxime (147)

A solution of 2-oximinobenzoylacetonitrile (146) (0.35 g, 0.002 mol) was treated with a solution of hydroxylamine hydrochloride (0.56 g, 0.008 mol) in methanol (10.0 ml) followed by a solution of sodium (0.18 g, 0.008 g-atom) in methanol (10.0 ml) and the mixture was stirred at room temperature for 1 h and then heated under reflux for

a further 17 h. The mixture was cooled and evaporated to give a yellow residue which was treated with water and filtered to afford a buff solid (0.30 g). This solid was slurried with aqueous 2M hydrochloric acid and filtered to remove a small amount of an insoluble material.

The acidic aqueous mother liquor was neutralised by addition of solid anhydrous sodium acetate and the solution evaporated. The resulting residue was soxhlet extracted with ethyl acetate to yield 2-benzoyl-2-oximino-acetamidoxime (147) (0.20 g; 80%), m.p. 178-179°(from ethanol-light petroleum), ν_{max} 3480, 3370 and 3180 (NH OH) and 1645 (CO) cm^{-1}.

Found: C, 52.8; H, 4.5; N, 19.9%; M^+, 207.

$C_9H_9N_3O_3$ requires: C, 52.2; H, 4.4; N, 20.2%; M, 207.

5-Amino-2-phenyl-4-phenylazo-1H-imidazole (155)

(a) A solution of sodium (0.05 g, 0.002 g-atom) in anhydrous ethanol (5.0 ml) was added to a solution of benzamidine hydrochloride (0.31 g, 0.002 mol) in anhydrous ethanol (5.0 ml). The resulting suspension was filtered to remove sodium chloride and the filtrate, an ethanolic solution of benzamidine was added to a solution of 2-chloro-2-phenylhydrazonoacetonitrile (153) (0.36 g, 0.002 mol) in anhydrous ethanol (15.0 ml) and the mixture was stirred

at room temperature for 4 h. The mixture was evaporated to afford a brown solid (0.50 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded the unreacted 2-chloro-2-phenylhydrazonoacetonitrile (153) (0.10 g; 28%), m.p. 130-132°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Further elution with methylene chloride through to ethyl acetate yielded a series of solids and gums (total, 0.1 g), none of which were further investigated.

Final elution with ethanol gave a red gummy solid which was triturated with toluene to afford 5-amino-2-phenyl-4-phenylazo-1H-imidazole (155) (0.25 g; 47%) which formed orange crystals, m.p. 213-215° (from toluene), ν_{max} 3450 and 3300 (NH) cm^{-1}.

Found: 263.1168.

$C_{15}H_{13}N_5$ requires: 263.1170.

(b) Repetition of (a) on a larger scale (0.015 mol) afford a brown gum (5.0 g) which when subjected to flash chromatography yielded no identifiable material.

2-Chloro-2-phenylhydrazonoacetonitrille (153)

2-Chloro-2-phenylhydrazonoacetonitrile (153) was prepared as described in Chapter 2.

2-Amino-2-phenylhydrazonoacetonitrile (156)

2-Amino-2-phenylhydrazonoacetonitrile (156) was prepared as described in Chapter 2.

O-ethyl 2-chloro-2-phenylhydrazonoacetimidate Hydrochloride (157)

O-ethyl 2-chloro-2-phenylhydrazonoacetimidate hydrochloride (151) was prepared as described in Chapter 2.

O-ethyl 2-Amino-2-phenylhydrazonoacetimidate Hydrochloride (158)

A solution of 2-amino-2-phenylhydrazonoacetonitrile (156) (0.64 g, 0.004 mol) in anhydrous ethanol (5.0 ml) and anhydrous diethyl ether (10.0 ml) was cooled to 0° (ice-salt bath) and treated with a slow stream of hydrogen chloride gas until the solution was saturated. The resulting mixture was firmly stoppered and left in a refrigerator for 17 h and then filtered to afford O-ethyl 2-amino-2-phenylhydrazonoacetimidate hydrochloride (158) (0.92 g; 95%), m.p. 150-160°, ν_{max} 3200 (NH) and 1660 (C=N) cm^{-1}, δ [$(CD_3)_2SO$] 8.90 (4H, brs, NH), 7.46-6.84 (5H, m, ArH), 4.34 (2H, q, J7H_3, $\underline{CH_2}CH_3$) and 1.32 (3H, t, J7Hz $-CH_2\underline{CH_3}$), m/e 207.

The Reaction of O-ethyl 2-Chloro-2-phenylhydrazonoacetimidate Hydrochloride (157) with Ethanolic Ammonia

A solution of O-ethyl 2-chloro-2-phenylhydrazonoacetimidate hydrochloride (157) (0.52 g, 0.002 mol) in anhydrous ethanol (20.0 ml) was treated with a saturated solution of ammonia in anhydrous ethanol (20.0 ml). The mixture was firmly stoppered and left for 17 h. at room temperature then evaporated to give a red gum (0.5 g) which was triturated with methylene chloride to afford an intractable brown solid (0.25 g).

The methylene chloride mother liquor was evaporated to yield a red gum (0.25 g) which when subjected to flash chromatography gave a series of gums and solids (total, 0.25 g), none of which were further investigated.

The Reaction of O-ethyl 2-Amino-2-phenylhydrazonoacetimidate Hydrochloride (158) with Ethanolic Ammonia

A solution of O-ethyl 2-amino-2-phenylhydrazonoacetimidate hydrochloride (158) (0.49 g, 0.002 mol) in anhydrous ethanol (10.0 ml) was treated with a saturated solution of ammonia in anhydrous ethanol (10.0 ml). The mixture was firmly stoppered and left for 17 h. at room temperature. The mixture was evaporated and the residue treated with methylene chloride to afford an intractable brown solid (0.28 g).

The methylene chloride mother liquor was evaporated to yield a brown gum (0.20 g) which when subjected to flash chromatography gave a series of gums and solids (total, 0.16 g), none of which were further investigated.

The Attempted Reaction of 2-Phenylhydrazonobenzoyl-acetonitrile (29a) with Acetamidine

A solution of acetamidine hydrochloride (1.40 g, 0.015 mol) in anhydrous ethanol (20.0 ml) was treated with a solution of sodium (0.35 g, 0.015 g-atom) in anhydrous ethanol (10.0 ml) and the mixture was stirred at room temperature for 0.5 h. and filtered to remove sodium chloride. The filtrate, a solution of acetamidine was treated with a solution of 2-phenylhydrazonobenzoyl-acetonitrile (29a) (2.5 g, 0.01 mol) in anhydrous ethanol (100 ml) and the mixture was heated under reflux for 4 h. The mixture was cooled and evaporated and the resulting residue treated with water (20.0 ml) and the solution there form neutralised by the addition of aqueous 2M hydrochloric acid to afford on filtration the unreacted 2-phenylhydrazonobenzoylacetonitrile (29a) (2.25 g; 90%), m.p. 130-135°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Extraction of the aqueous filtrate with methylene chloride afforded no further material.

The Attempted Reaction of 3-Imino-2-phenylhydrazono-butanenitrile (43) with Acetamidine

A solution of acetamidine hydrochloride (1.40 g, 0.015 mol) in anhydrous ethanol (20.0 ml) was treated with a solution of sodium (0.35 g, 0.015 g-atom) in anhydrous ethanol (10.0 ml) and the mixture was stirred at room temperature for 0.5 h. and filtered to remove sodium chloride. The filtrate, a solution of acetamidine was treated with a solution of 3-imino-2-phenylhydrazono-butanenitrile (43) (1.9 g, 0.01 mol) in anhydrous ethanol (100 ml) and the mixture was heated under reflux for 48 h. The mixture was cooled and evaporated and the resulting residue treated with water (50.0 ml) and filtered to afford a yellow solid which was combined with further material obtained by neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid and extraction with methylene chloride to yield unreacted 3-imino-2-phenylhydrazono-butanenitrile (43) (total 1.6 g, 87%), m.p. 158-160°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Reaction of 4-Amino-1,3-dimethyluracil (161) with Benzenediazonium Chloride

A mixture of N,N-dimethylurea (22.0 g, 0.25 mol) and cyanoacetic acid (21.3 g, 0.25 mol) in acetic anhydride (31.0 ml) was heated at 60° (oil bath) for 3 h. and the excess acetic anhydric and acetic acid were removed under

reduced pressure. The residual liquid was treated dropwise with stirring at 0-5° (ice-salt bath) with 5% w/v aqueous sodium hydroxide solution (750 ml). The resulting 4-amino-1,3-dimethyluracil (161) suspension was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of benzenediazonium chloride [prepared from a solution of redistilled aniline (23.3 g, 0.25 mol) in aqueous 5M hydrochloric acid (125 ml) which was treated dropwise with stirring at 0-5° (ice-salt bath) with a solution of sodium nitrite (19.3 g, 0.28 mol) in water (63.0 ml), the resulting amber benzendiazonium chloride solution being stirred in the melting ice-salt bath for a further 5 min.] at such a rate that the temperature of the reaction mixture remained between 0-5° and then stirred in the melting ice-salt bath for a further 1 h.

The mixture was then filtered to afford an orange solid which was washed with water and ethyl acetate to yield 4-amino-1,3-dimethyl-5-phenylazouracil (162)[171] (26.5 g, 41%) which formed yellow crystals, m.p. 247-248° (from dimethylformamide-ethanol) (lit.,[171,172] 252-254°), ν_{max} 3300 (NH), 1705 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 11.70 (2H, brs, NH), 7.66-7.24 (5H, m, ArH), 3.35 (3H, s, NCH_3) and 3.23 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 159.05 (quat), 152.20 (quat), 149.76 (quat), 148.95 (quat), 128.82, 127.29, 120.48, 110.10 (quat), 28.88 (NCH_3) and 27.54 (NCH_3).

Found: 259.1064.

Calc. for $C_{12}H_{13}N_5O_2$: 259.1069.

The combined aqueous mother liquor, and aqueous washings were extracted with ethyl acetate to yield 1,5-diphenyl-3-formazancarbonitrile (163)[172] (5.1 g; 8%) which formed red platelets, m.p. 159-160° (from toluene) (lit.,[172] 159°), ν_{max} 3400 and 3210 (NH), and 2210 (CN) cm^{-1} $\delta(CDCl_3)$ 12.83 (1H, brs, NH) and 7.71-7.24 (10H, m, ArH).

Found: 249.1014.

Calc. for $C_{14}H_{11}N_5$: 249.1014.

The ethyl acetate washings were evaporated to afford a brown gum (25.0 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

1,3-Dimethyl-6-phenylpyrimido[4,5-e]-1,2,4-triazine-2,4,7(1H, 3H, 6H)-trione (164)

A solution of 4-amino-1,3-dimethyl-5-phenylazouracil (162) (0.78 g, 0.003 mol) in anhydrous diglyme was treated with redistilled tosyl isocyanate (0.65 g, 0.0033 mol) and the mixture heated under reflux for 21 h. The mixture was cooled and evaporated to afford a brown gum (1.30 g) which was subjected to flash chromatography.

Elution with methylene chloride-n-hexane (1:1) afforded toluene-4-sulphonamide (0.40 g; 78%), m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride yielded 1,3-dimethyl-6-phenylpyrimido[4,5-e]-1,2,4-triazine-2,4,7-(1H, 3H, 6H)-trione (164), (0.25 g; 29%), m.p. 209-210° (lit.,[170] 210), ν_{max} 1705 and 1680 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.64-7.51 (5H, m, ArH), 3.44 (3H, s, NCH_3) and 3.30 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 156.68 (quat), 153.84 (quat), 151.62 (quat), 150.24 (quat), 140.70 (quat), 129.02, 128.93, 125.39, 124.04 (quat), 28.85 (NCH_3) and 28.28 (NCH_3).

Found: C, 54.7; H, 3.9; N, 24.8%; M^+, 285

Calc. for $C_{13}H_{11}N_5O_3$: C, 54.7; H, 3.9; N, 24.6%; M, 285.

Final elution with ethanol afforded a brown gum (0.60 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

1,3-Dihydro-2H-Benzimidazol-2-one (168a)[175]

A solution of o-phenyldiamine (167a) (0.43 g, 0.004 mol) in anhydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.86 g, 0.0044 mol) and the mixture was heated under reflux for 3 h. The mixture was cooled and evaporated to afford a yellow gum (1.3 g) which was subjected to flash chromatography.

Elution with ethyl acetate-cyclohexane (1:1) gave a brown gum (0.1 g) which was not further investigated.

Elution with ethyl acetate yielded 1,3-dihydro-2H-benzimidazol-2-one (168a) (0.52 g; 88%), which formed colourless platelets, m.p. 320-321° (from ethanol-toluene) (lit.,[175] 310°), ν_{max} 3150 (NH) and 1755 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 10.52 (2H, brs, NH) and 6.91 (4H, s, ArH).

Found: C, 62.5; H, 4.5; N, 20.7%; M^+, 134

Calc. for $C_7H_6N_2O$: C, 62.7; H, 4.5; N, 20.9%; M, 134

Final elution with ethanol gave a yellow gum (0.2 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

2(3H)-Benzoxazolone (168b)[176]

A solution of o-aminophenol (167b) (0.55g, 0.004 mol) in anhydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.86 g, 0.0044 mol) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated to afford a dark solid (1.2 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (10:1) gave a colourless solid (1.1 g), m.p. 88-90°, ν_{max} 3350 and 3255 (NH) and 1750 (CO) cm^{-1} which was crystallised from toluene to afford toluene-4-sulphonamide (0·80 g; quant.), m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

The toluene filtrate was evaporated to give 2(3H)-benzoxazolone (168b) (0.20 g; 37%), m.p. 124-126° [from light petroleum (b.p. 80-100°)] (lit.,[176] 138°), ν_{max} 3360, 33260 and 3200 (NH) and 1750 (CO) cm^{-1}, ($CDCl_3$) 8.40 (1H, brs, NH) and 7.25-7.04 (4H, m, ArH).

Found: C, 62.5; H, 3.8; N, 10.4%; M^+, 135.
Calc. for $C_7H_5NO_2$: C, 62.2; H, 3.7; N, 10.4%; M^+, 135.

Further elution with methylene chloride-ethyl acetate (10:1) through to ethanol gave a series of gums and solids (total, 0.11 g) none of which were further investigated.

2(3H)-Benzthiazolone (168c)[177]

A solution of o-aminobenzenethiol (167c) (0.50 g, 0.004 mol) in anhydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.86 g, 0.0044 mol) and the mixture was heated under reflux for 3 h. The mixture was cooled and evaporated to give a brown solid (0.70 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded a buff solid (0.57 g), m.p. 100-105°, ν_{max} 3355 and 3260 (NH) and 1665 (CO) cm^{-1}, m/e 284, which was crystallised from toluene to give toluene-4-sulphonamide (0.52 g; 70%), m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

The toluene filtrate was evaporated to give 2(3H)-benthiazolone (168c) (0.04 g; 7%), m.p. 120-125° (lit.,[177] 136°), ν_{max} 3150 and 3100 (NH) and 1660 (CO) cm^{-1}, m/e 151.

Final elution with ethanol gave an intractable gum (0.1 g) which was not further investigated.

1,3-Benzodioxol-2-one (170)[178]

A solution of catechol (169) (0.44 g, 0.004 mol) in anhydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.86 g, 0.0044 mol) and the mixture was heated under reflux for 2 h. The mixture was cooled and evaporated to afford a buff solid (1.45 g) which was subjected to flash chromatography.

Elution with methylene chloride-cyclohexane (1:1) gave 1,3-benzodioxol-2-one (170) (0.23 g; 43%) which formed colourless crystals, m.p. 116-117° (lit.,[178] 118°), ν_{max} 1820 (CO) cm^{-1}.

Found: C, 61.8; H, 3.2; N, - %; M^+, 136.
Calc. for $C_7H_4O_3$: C, 61.8; H, 2.9; N, - %; M, 136.

Elution with methylene chloride afforded toluene-4-sulphonamide (0.80 g; quant.), m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

Final elution with ethanol gave no further material.

2,4(1H, 3H)-Quinazolinedione (172a)[179]

A solution of anthranilamide (171a) (0.54 g; 0.004 mol) in anhydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.86 g, 0.004 mol) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated to give a brown gum (1.3 g) which was subjected to flash chromatography.

Elution with methylene chloride-ethyl acetate (10:1) afforded toluene-4-sulphonamide (0.62 g; 83%), m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with methylene chloride-ethyl acetate (10:1) through to ethyl acetate afforded a series of gums and solids (total, 0.32 g) which were not further investigated.

Final elution with ethanol gave 2,4(1H, 3H)-quinazolinedione (172a) (0.20 g; 31%), m.p. 334-335° (from glacial acetic acid) (lit.,[179] 348°), ν_{max} 3160 (NH) and 1700 and 1665 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 11.19 (2H, brs, NH) and 7.95-7.08 (4H, m, ArH).

Found: C, 59.2; H, 3.7; N, 16.8%; M^+, 162.
Calc. for $C_8H_6N_2O_2$: C, 59.3; H, 3.7; N, 17.3%; M, 162.

The Attempted Reaction of Arthranilic Acid with Tosyl Isocyanate

A solution of anthranilic acid (171b) (0.55 g, 0.004 mol) in anhydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.86 g, 0.004 mol) and the mixture was heated under reflux for 24 h. The mixture was cooled and evaporated to afford a dark solid (1.4 g) which was subjected to flash chromatography.

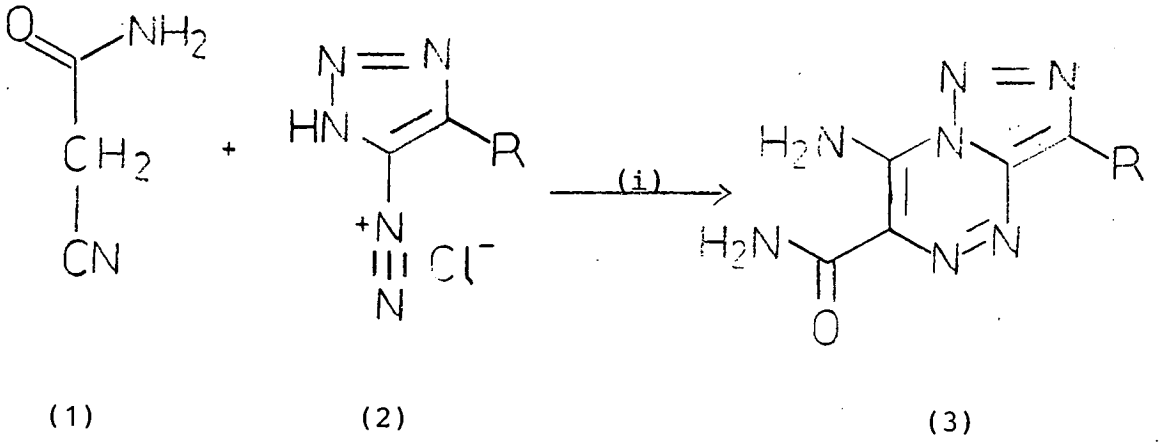
Elution with n-hexane-methylene chloride (2:1) afforded unreacted anthranilic acid (0.24 g; 54%), m.p. 125-130°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride-ethyl acetate (2:1) afforded toluene-4-sulphonamide (0.80 g, quant.), m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

Final elution with ethanol gave an intractable gum (0.25 g) which was not further investigated.

Chapter 4

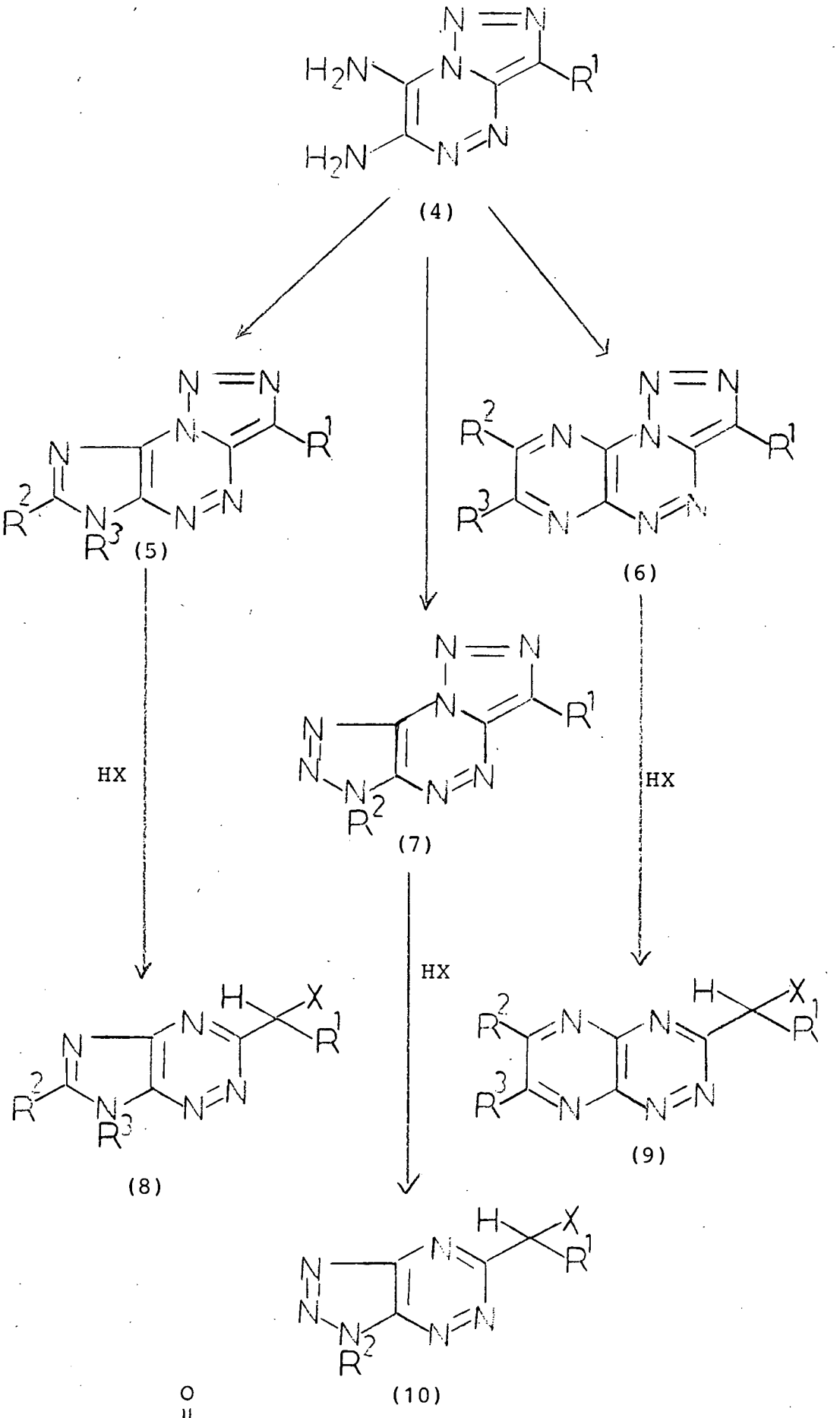
Synthetic Approaches to Aza and Diaza Analogues of Purines and Pteridines Based on Aminated 1,2,3-Triazolo[5,1-c]-1,2,4-triazine Derivatives



(1) (2) (3)

(i) NaOAc, EtOH, room temperature

Scheme 1



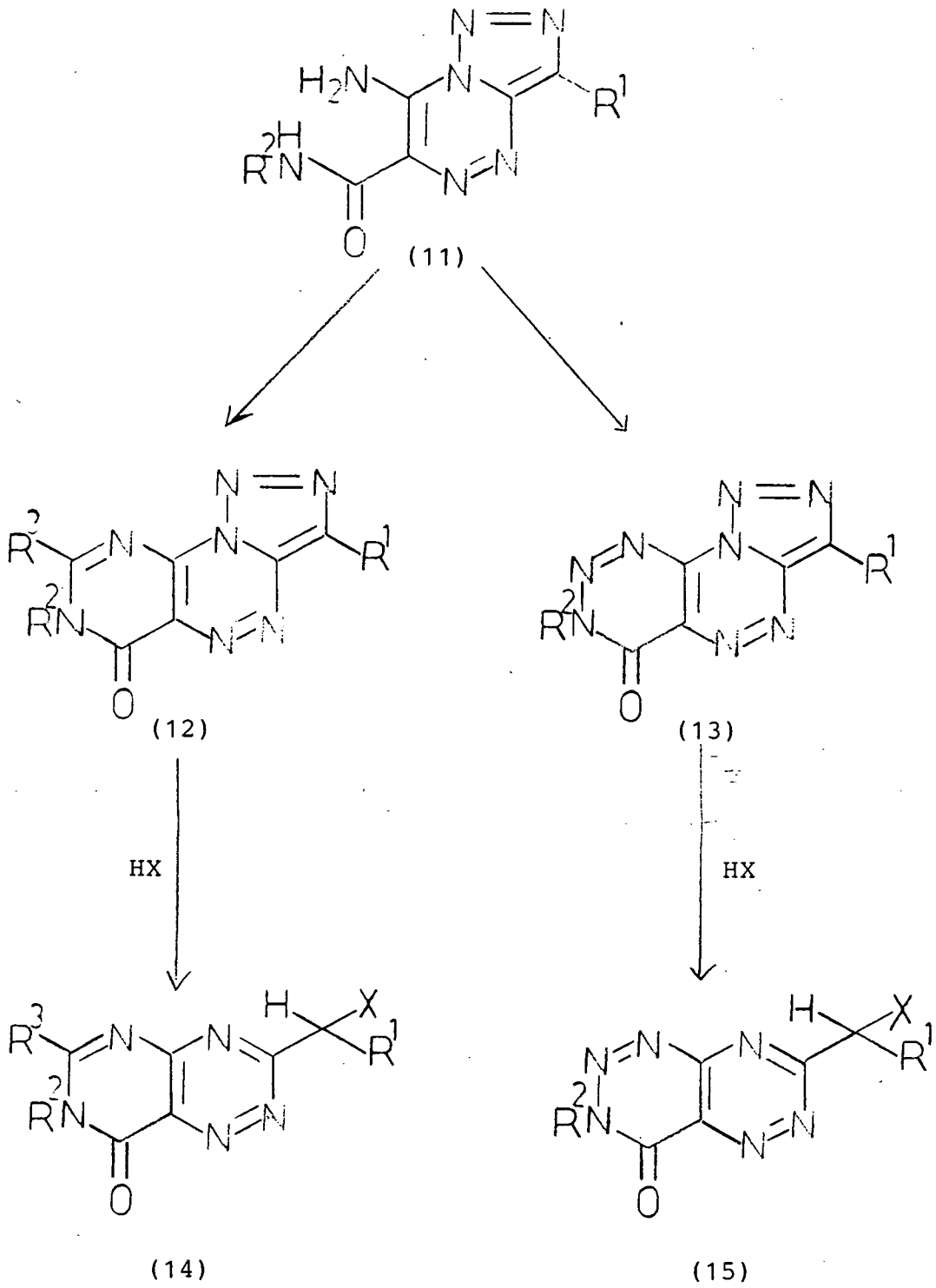
Scheme 2

Synthetic Approaches to Aza and Diaza Analogues of Purines and Pteridines Based on Aminated 1,2,3-Triazolo[5,1-c]-1,2,4-triazine Derivatives

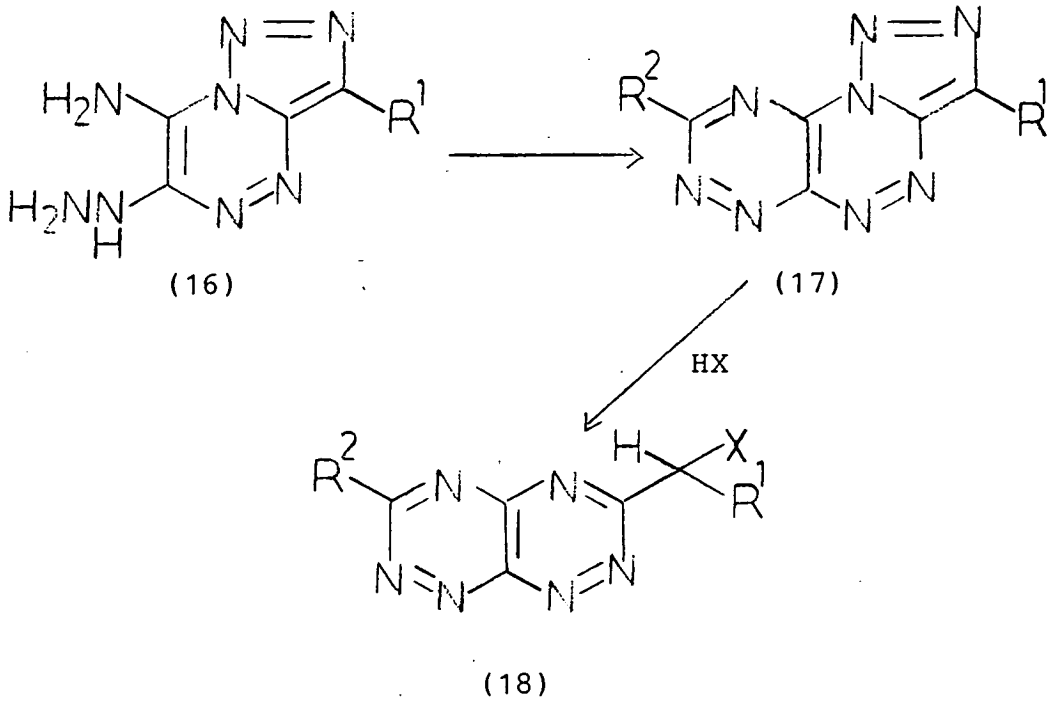
4.1 Introduction

Suitably aminated 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives are readily available by the coupling[180] of 1H-1,2,3-triazole-5-diazonium derivatives with substituted acetonitriles as illustrated (Scheme 1) by the reaction of the 1H-1,2,3-triazole-5-diazonium salts (2) with cyanoacetamide (1) to give the triazolo[5,1-c]-1,2,4-triazines (3). The acid-catalysed triazole scission of bridgehead-fused 1,2,3-triazole derivatives is well documented[181] and it could be anticipated that such aminated 1,2,3-triazolo[5,1-c]-1,2,4-triazines would readily cyclise and then undergo acid catalysed scission to yield aza- and diaza-analogues of purine and pteridine, (see Schemes 2-4).

On the basis of this strategy (Scheme 2) imidazo[4,5-e]-1,2,4-triazines (6-azapurines) (8), pyrazino[2,3-e]-1,2,4-triazines (4-azapteridines) (9) and 1,2,3-triazolo[4,5-e]-1,2,4-triazines (6,8-diazapurines) (10) are the anticipated products of the annulation by appropriate reagents of 6,7-diamino-1,2,3-triazolo[5,1-c]-1,2,4-triazines (4) to give the tricyclic systems (5), (6) and (7) followed by acid-catalysed triazole scission. Similarly (Scheme 3) the



Scheme 3

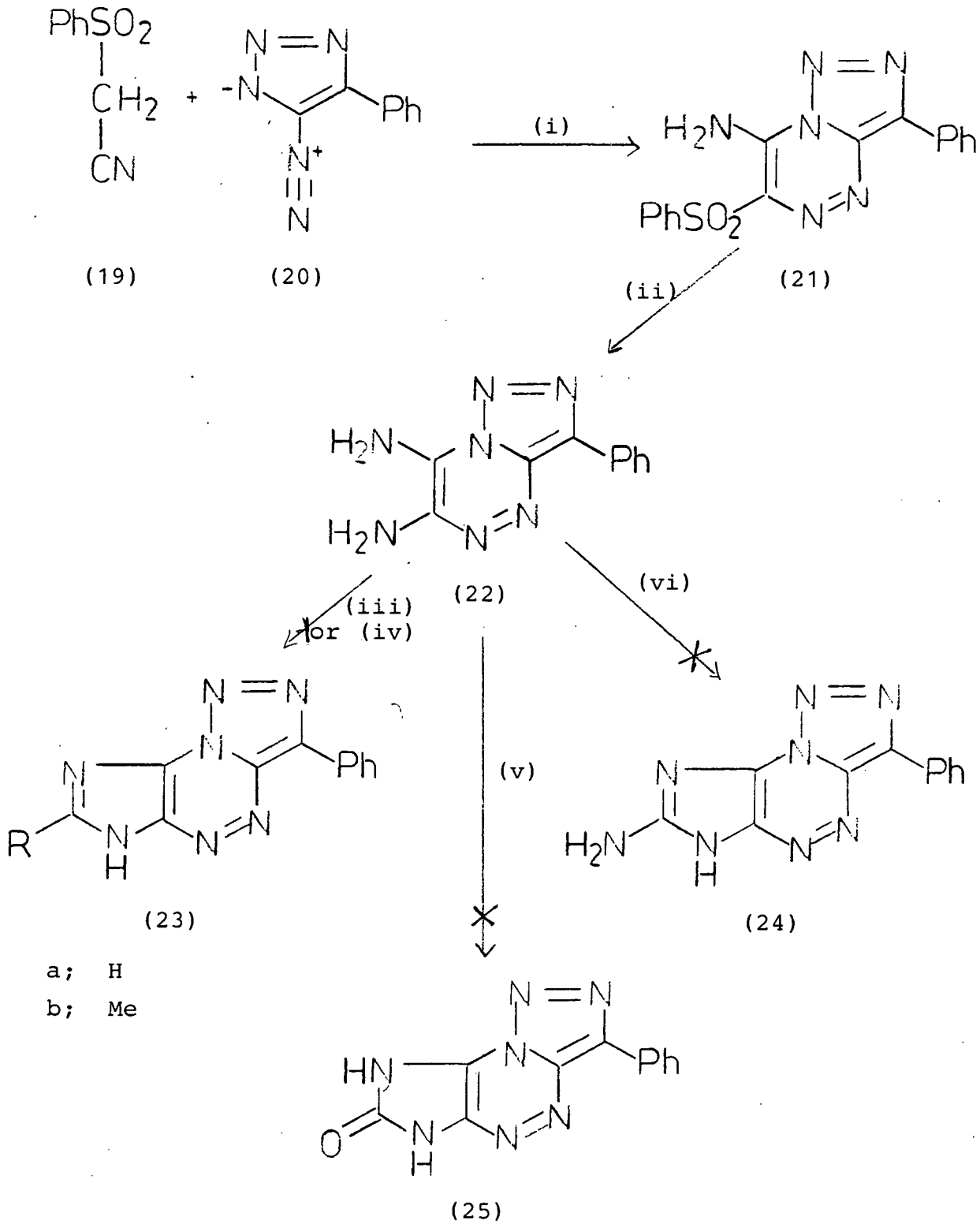


[X = OH, $\overset{O}{\overset{\|}{O}}CR$, Cl, Br]

Scheme 4

7-amino-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide derivatives (11) would be expected to give pyrimido[5,4-e]-1,2,4-triazines(6-azapteridines) (14) and 1,2,3-triazino[5,4-e]-1,2,4-triazines (2,6-diazapteridines) (15) by initial annulation to give the tricyclic systems (12) and (13) then acid-catalysed triazole scission of the latter. Finally (Scheme 4) 1,2,4-triazino[6,5-e]-1,2,4-triazines(4,6-diazpteridines) (18) are the ultimate products of the annulation of 7-amino-6-hydrazino-1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives (16) to give the tricyclic system (17) followed by its acid-catalysed triazole scission.

Derivatives of all of the aza- and diaza-analogues of purine and pteridine whose synthesis by annulation of aminated 1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives followed by acid-catalysed triazole scission is proposed are known and have been discussed in terms of their known syntheses and biological properties in Chapter 1. However, the synthetic stragegies outlined in Schemes 2-4 represent a novel unified approach to such potentially bioactive polyazaheterocycles.



(i) NaOAc, EtOH, H_2O, 0°

(ii) NH_3 liq.

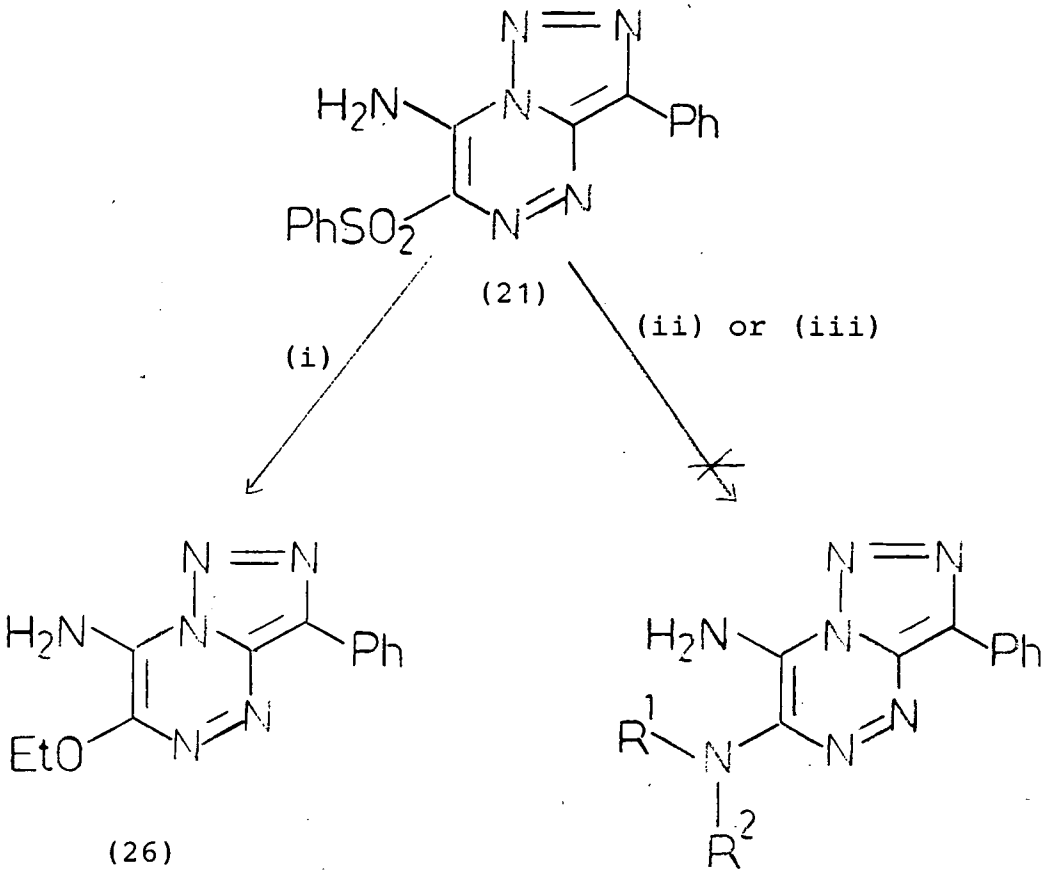
(iii) $HC(OEt)_3$, heat

(iv) Ac_2O, heat

(v) $TSO_2N=C=O$, diglyme, heat

(vi) BrCN, MeOH, room temp.

Scheme 5



(i) $PhCH_2NH_2$, EtOH, heat

(ii) $PhCH_2NH_2$, dioxane, heat

(iii) C_5H_9N, BuOH, heat

Scheme 6

4.2 Investigations of 6,7-Diamino-1,2,3-triazolo[5,1-c]-1,2,4-triazine Derivatives as Synthetic Precursors of 6-Azapurines, 6,8-Diazapurines and 4-Azapteridines

As outlined in the introduction to this chapter (see Scheme 2) it was anticipated that 6,7-diamino-1,2,3-triazolo[5,1-c]-1,2,4-triazine derivatives would afford on annulation and subsequent acid-catalysed scission of the bridgehead fused triazole moiety, 6-azapurines, 6,8-diazapurines and 4-azapteridines. This strategy generalised in Scheme 2 was investigated (Scheme 5) starting with benzenesulphonylacetonitrile (19), whose synthesis has been described previously (Chapter 2, page number 58). Benzenesulphonylacetonitrile coupled readily with 4-phenyl-1H-1,2,3-triazole-5-diazonium betaine (20)[182] to yield the known[182] 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (21) in good yield. This product (21) readily reacted with liquid ammonia with displacement of the phenylsulphonyl moiety to give a high yield of the previously unknown 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22). The compound (22) gave combustion analysis and exhibited spectroscopic properties consistent with the assigned structure.

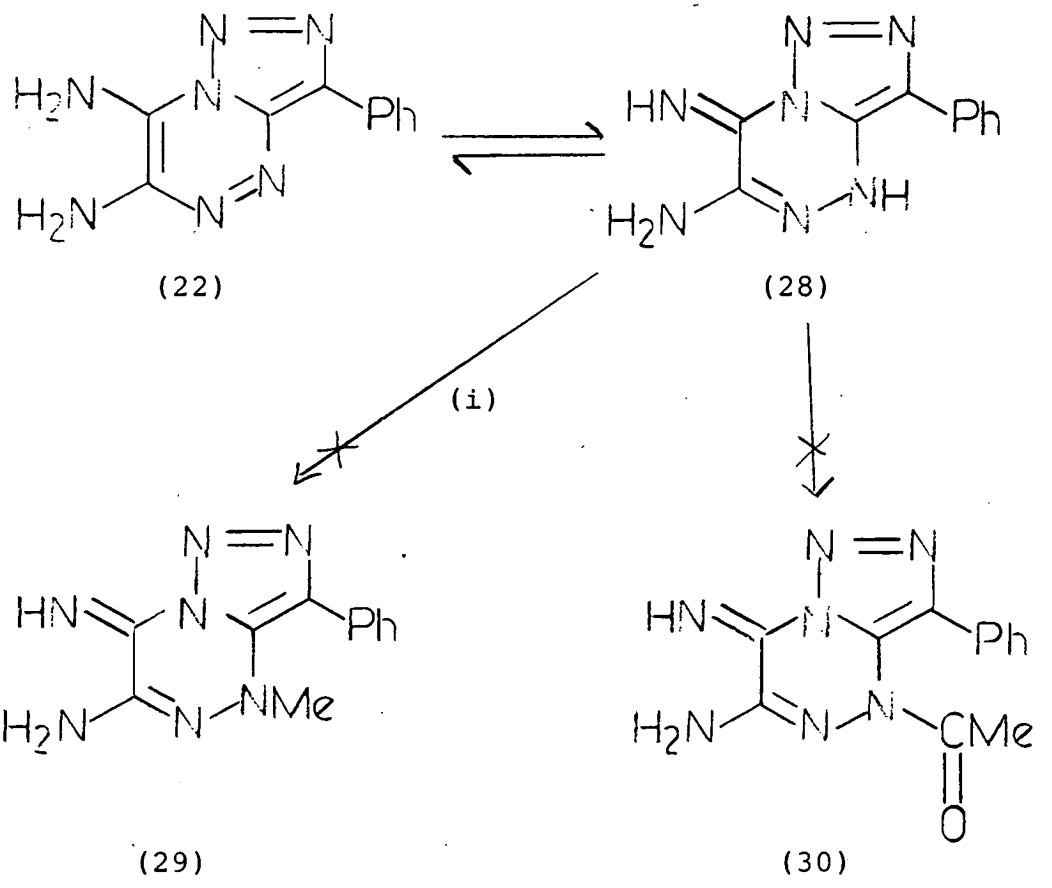
In an attempted extension (Scheme 6) of the nucleophilic displacement of the phenylsulphonyl moiety of the triazolotriazine derivative (21) by ammonia, 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) was reacted with benzylamine and pyrrolidine. However

reaction of the triazolotriazine (21) with these amines in dioxane gave no identifiable products. The reaction of the triazolotriazine (21) with benzylamine in ethanol gave a low yield of 7-amino-6-ethoxy-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (26). This product (26) gave analytical data and showed spectroscopic properties in agreement with the assigned structure. In particular its ^{1}H n.m.r. spectrum exhibited resonances for five aromatic hydrogen atoms, a two-proton quartet and a three-proton triplet attributable to the protons of the ethoxy-substituent, and also two exchangeable resonances due to the protons of the amino-group. Presumably, the ethoxytriazolotriazine is formed by the benzylamine acting as a base and so releasing ethoxide ion which is a better nucleophile than benzylamine.[120] Also of note in terms of the nucleophilic displacement of the benzenesulphonyl moiety of the triazolotriazine (21) is the observation that the attempted reaction of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazole[5,1-c]-1,2,4-triazine (21) with aqueous ammonia gave only a little unreacted starting-material and several intractable solids. None of the expected diaminotriazolotriazine (22) was isolated under these conditions. The contrasting behaviour of the benzenesulphonyl substituent in the triazolotriazine derivative (21) towards nucleophilic displacement by ammonia on the one hand and amines such as benzylamine and pyrrolidine on the other warrants further detailed studies of such nucleophilic displacements.

The 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) would be expected on annulation (Scheme 5) to afford the tricyclic systems (23), (24) and (25) which on acid-catalysed scission of the bridgehead fused triazole ring would be anticipated to yield 6-azapurine derivatives. Thus the reaction of 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (21) with triethyl orthoformate was expected to yield the triazoloimidazotriazine derivative (23a). In practice however, only a quantitative recovery of the unreacted triazolotriazine (21) was obtained after prolonged heating with ethyl orthoformate. Similarly the attempted reaction of the triazolotriazine (21) with acetic anhydride failed to give the expected tricyclic product (23b) only an intractable brown solid being obtained.

As has been described in Chapter 3, tosyl isocyanate can be used to annulate ortho-diamino derivatives. It was therefore hoped that reaction of 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) with tosyl isocyanate would give the tricyclic product (25). However the attempted reaction of the triazolotriazine (21) with tosylisocyanate in dioxane disappointingly gave only a good recovery of the unreacted triazolotriazine (21).

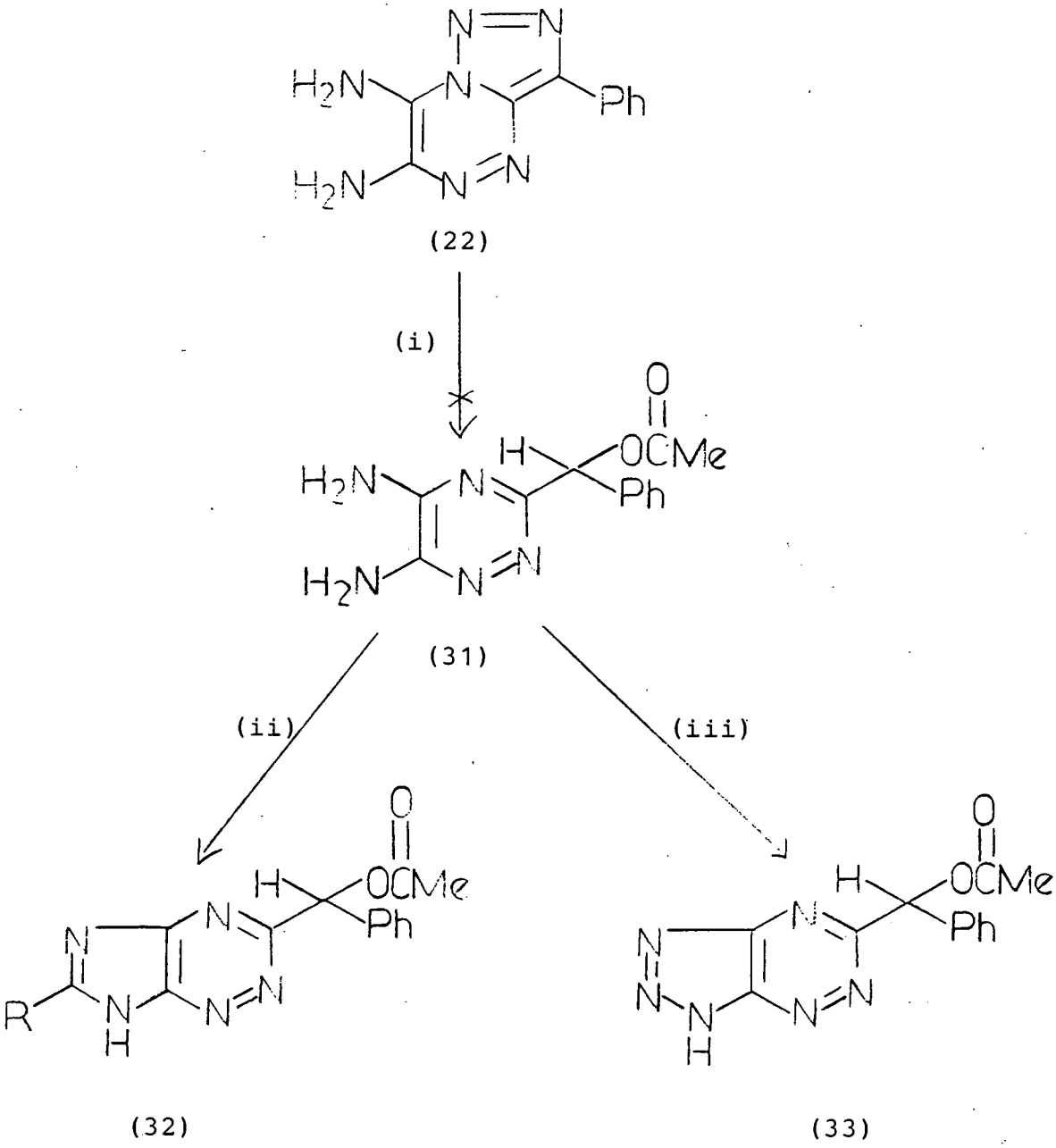
In a final attempt to annulate the triazolotriazine (21) it was reacted with cyanogen bromide. Cyanogen bromide is known to react with ortho-diamino derivatives to give amino-imidazoles. Hence it was anticipated that reaction of 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) with cyanogen bromide would give triazoloimidazo-triazine derivative (24). However the unreacted diamino-



(i) Me_2SO_4, K_2CO_3, acetone, heat

(ii) AcCl, Et_3N, $MeO(CH_2)_2OMe$, room temperature

Scheme 7



(i) $MeCO_2H$, heat

(ii) $RC(OEt)_3$, heat or RCH=O, heat

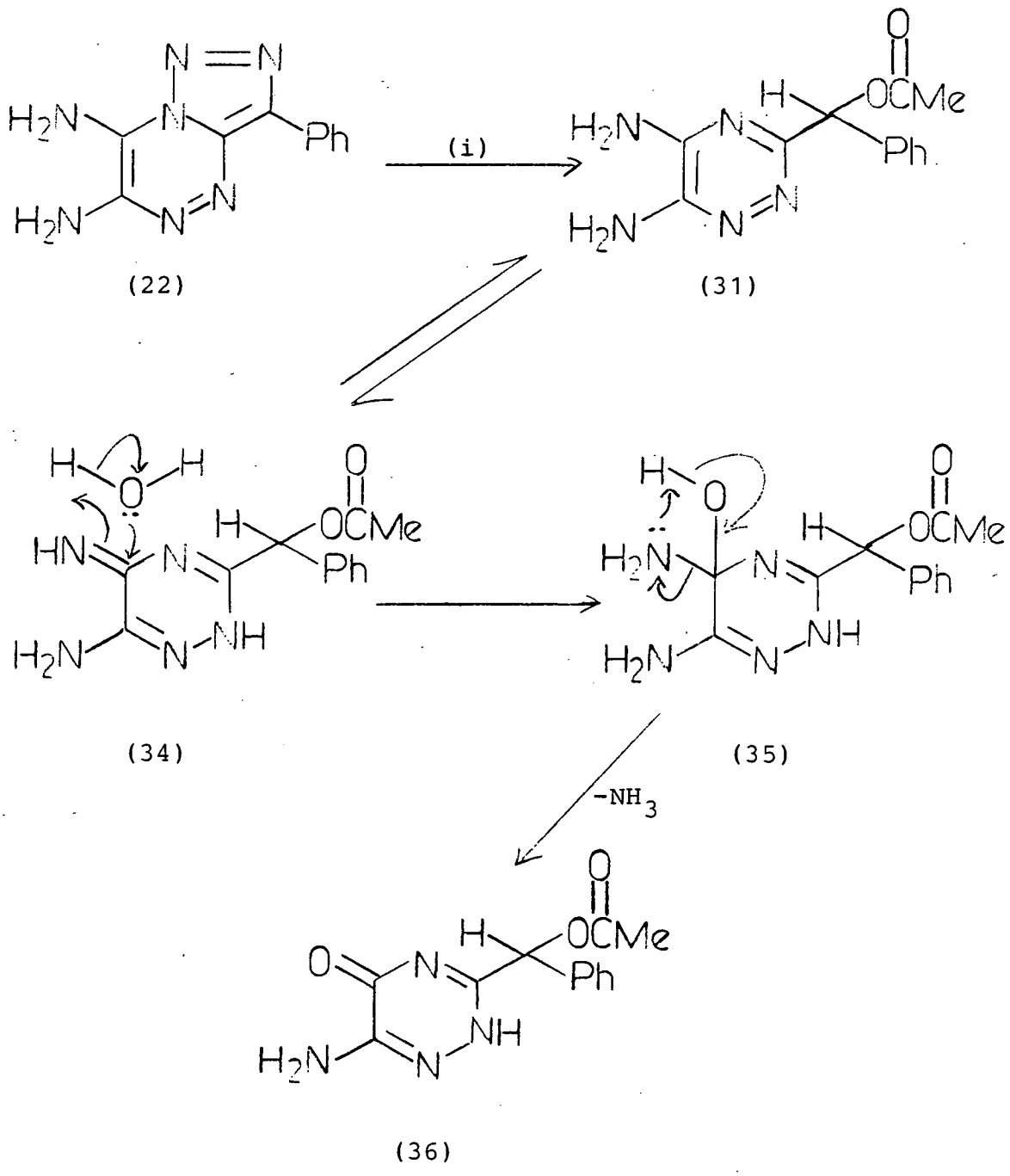
(iii) HNO_2

Scheme 8

triazolotriazine (21) was again recovered unchanged after heating with cyanogen bromide in methanol.

The apparent lack of reactivity of the 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) towards acylation as illustrated by the failure of the foregoing reactions may be accounted for by tautomerism (Scheme 7) in which the triazolotriazine (22) in fact exists predominantly as its imino tautomer (28). The hypothesis of tautomerism in the triazolotriazine (22) is supported by its acidic character as shown by its complete solubility in alkali. The acidity of the diaminotriazolotriazine (22) prompted the investigation (Scheme 7) of its reactions with dimethyl sulphate and acetyl chloride in which the derivatives (29) and (30) are the expected products. However, reaction of the triazolotriazine (22) with dimethylsulphate in the presence of potassium carbonate gave only a series of intractable gums. Similarly reaction of the triazolotriazine (22) with acetyl chloride in the presence of triethylamine gave a moderate recovery of the unreacted triazolotriazine (22) together with a complex gum. Therefore, no concrete evidence that the triazolotriazine (22) does exist predominantly as the imine tautomeric form (28) is available and further study of this aspect of the behaviour of the diaminotriazolotriazine (22) is warranted.

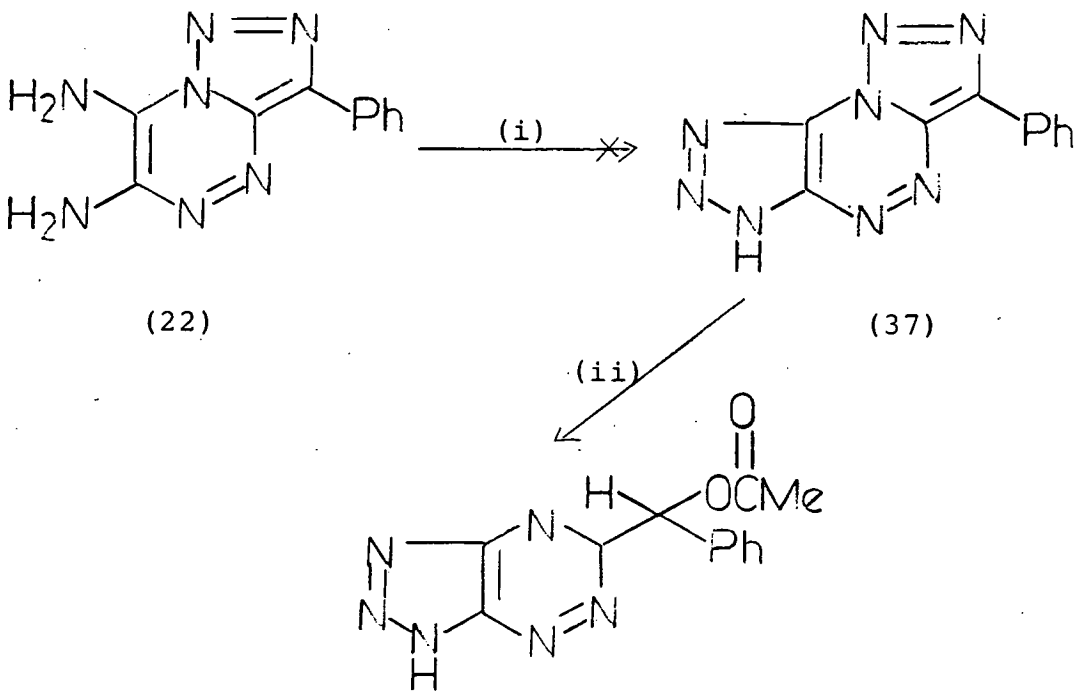
The failure of the triazolotriazine derivative (22) to undergo annulation (see Scheme 5) prompted the investigation of an alternative route to 6-aza- and 6,8-diazapurines as illustrated (Scheme 8) by the annulation



(22) (31) (34) (35) (36)

(i) $MeCO_2H$, heat

Scheme 9



(22) (37) (33)

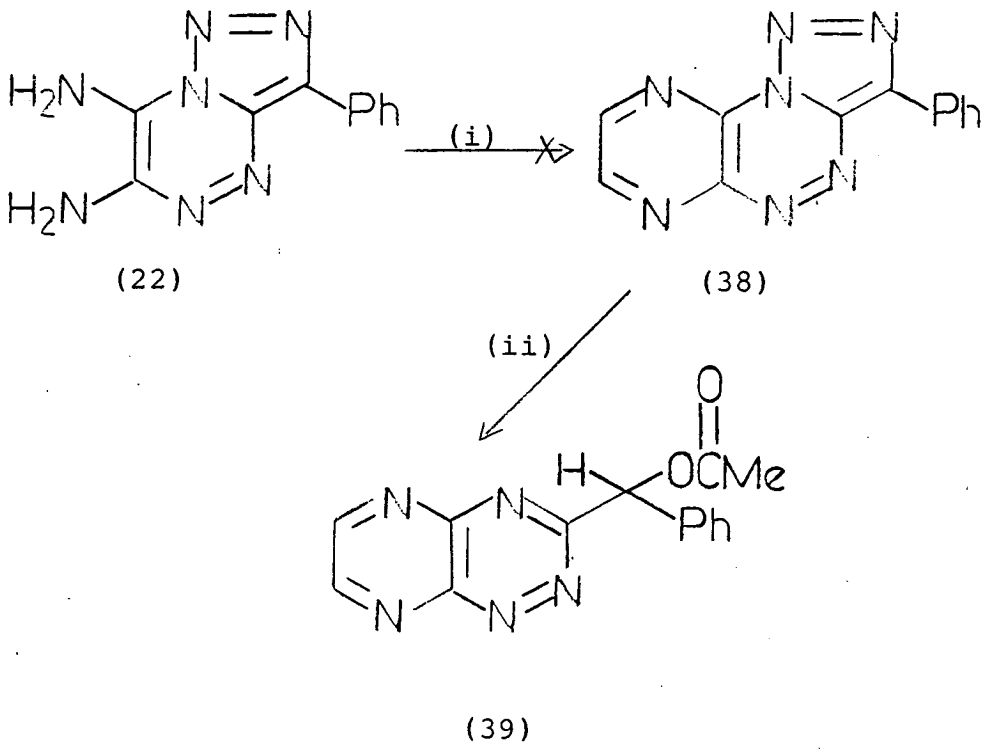
(i) $NaNO_2$, 10% w/v HCl, $MeCO_2H$

(ii) $MeCO_2H$, heat

Scheme 10

or diazotative cyclisation of the 5,6-diamino-1,2,4-triazine derivative (31) to give 6-azapurines (32) and 6,8-diazapurines (33) respectively. It is known[181] that bridgehead-fused triazole derivatives undergo acid-catalysed scission of the triazole ring and it was therefore anticipated that treatment of 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with glacial acetic acid would afford the 2-(α-acetoxybenzyl)-5,6-diamino-1,2,4-triazine (31). However, in practice (Scheme 9) the reaction of the diaminotriazolotriazine (22) with glacial acetic acid gave a low yield of the 1,2,4-triazine derivative (36), which is presumably formed by cleavage of the triazolotriazine (22) to give the expected diamino-triazine (31) which then undergoes hydrolytic deamination by the mechanism shown (Scheme 9) to afford the triazine (36). This product gave analytical data and showed spectroscopic properties consistent with the assigned structure (36). In particular its i.r. spectrum contained NH-absorption and bands due to two carbonyl groups. The ^1H n.m.r. spectrum showed resonances for five aromatic protons, a characteristic signal for a benzylic proton, a three-proton singlet attributable to the protons of the acetoxy methyl substituent and three exchangeable protons.

In a further attempt (Scheme 10) to cyclise the diaminotriazolotriazine (22) it was decided to investigate its reaction with nitrous acid. It was anticipated that the

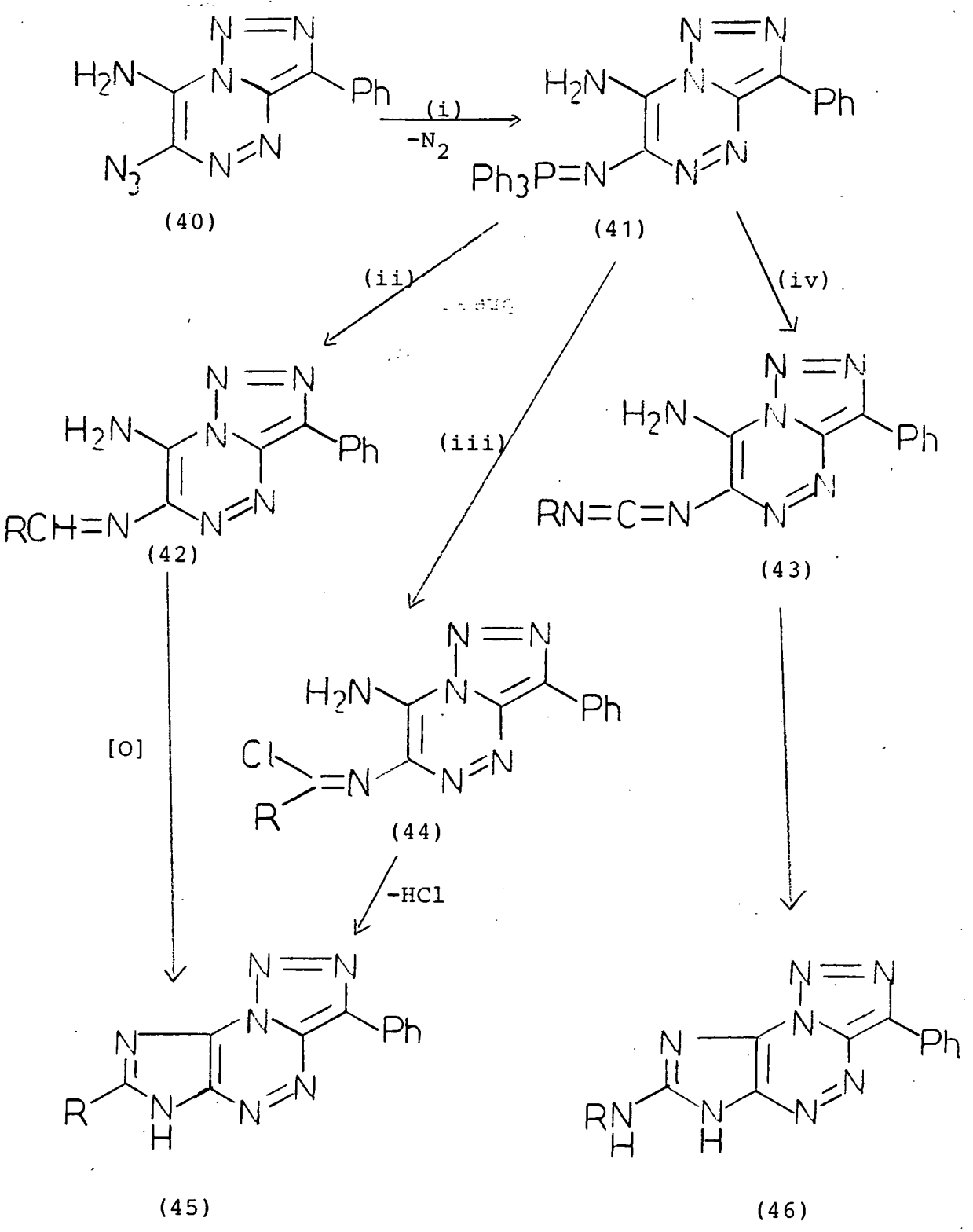


(22) (38) (39)

(i) O=CHCH=O, heat

(ii) $MeCO_2H$, heat

Scheme 11



(i) Ph_3P (iii) RCOCl

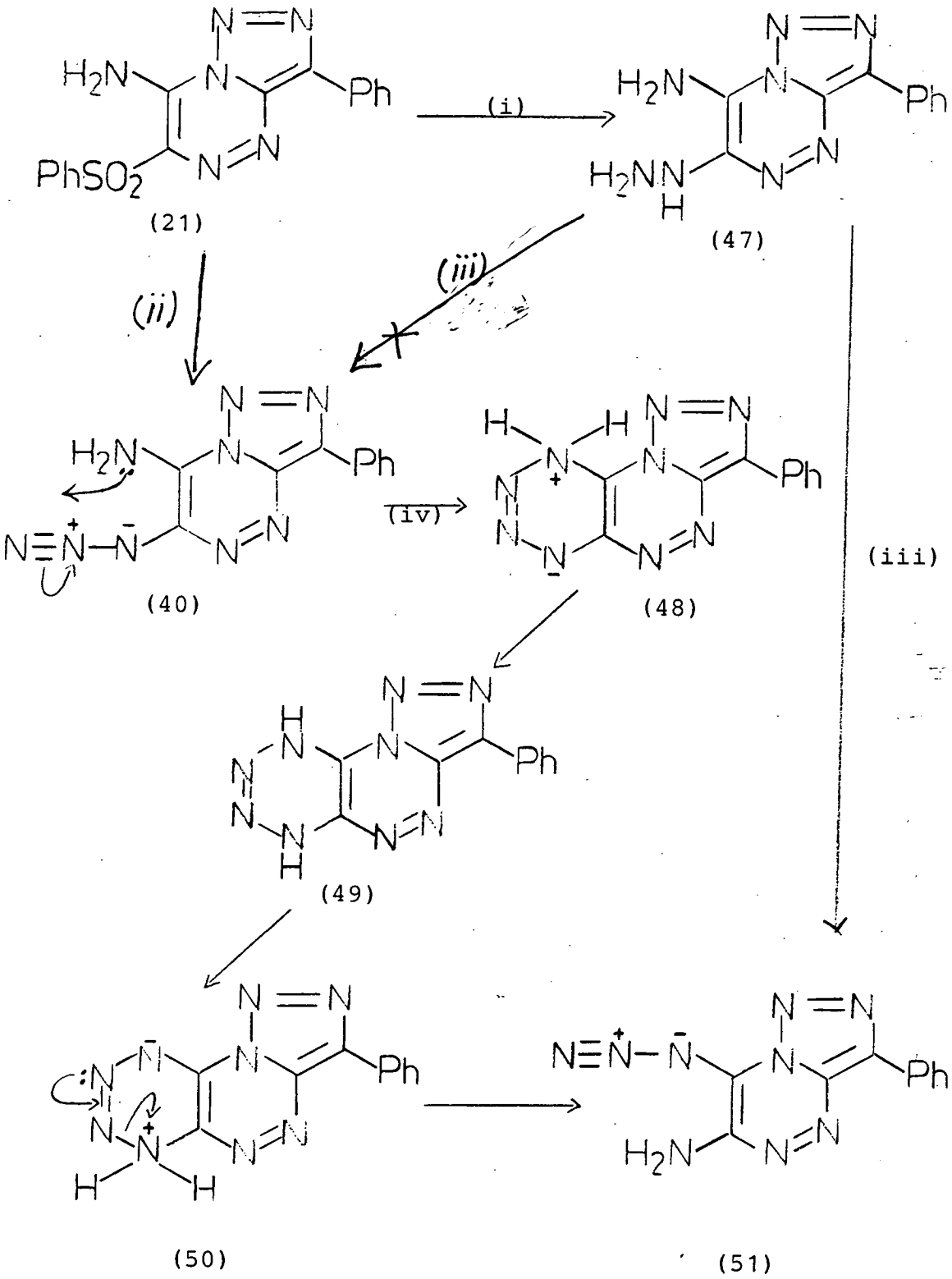
(ii) RCH=O (iv) RN=C=O

Scheme 12

tricyclic structure (37) resulting from diazotative cyclisation would be prone to undergo acid-catalysed scission of the bridgehead-fused triazole ring in glacial acetic acid to yield the 6,8-diazapurine derivative (33). In practice the reaction of the diaminotriazolotriazine (22) with sodium nitrite in the presence of hydrochloric acid afforded only a quantitative recovery of the unreacted triazolotriazine (22).

In a final attempt to cyclise the diaminotriazolotriazine (22) it was decided to investigate its reaction with glyoxal (Scheme 11). This reaction was expected to give the tricyclic system (38) glacial acetic acid-catalysed triazole scission of which, it was hoped, would yield the 4-azapteridine derivative (39). However, heating the 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with glyoxal again gave only a quantitative yield of the unreacted triazolotriazine (22).

The disappointing lack of reactivity of 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) towards annulation prompted the investigation of amino-functionalised 1,2,3-triazolo[5,1-c]-1,2,4-triazines. It is known that imines[183], imino chlorides[184] and carbodimides[185] ortho to an amino group will undergo cyclisation to yield imidazole derivatives. Hence it was anticipated as shown in Scheme 12 that the triazolotriazine derivatives (42), (43) and (44) would cyclise under the appropriate conditions to afford the tricyclic systems (45) and (46). The triazolotriazine derivatives (42), (43) and (44) were expected to be readily



(i) $NH_2NH_2.H_2O$, dioxane, room temperature

(ii) NaN_3, H_2O, dioxane, room temperature

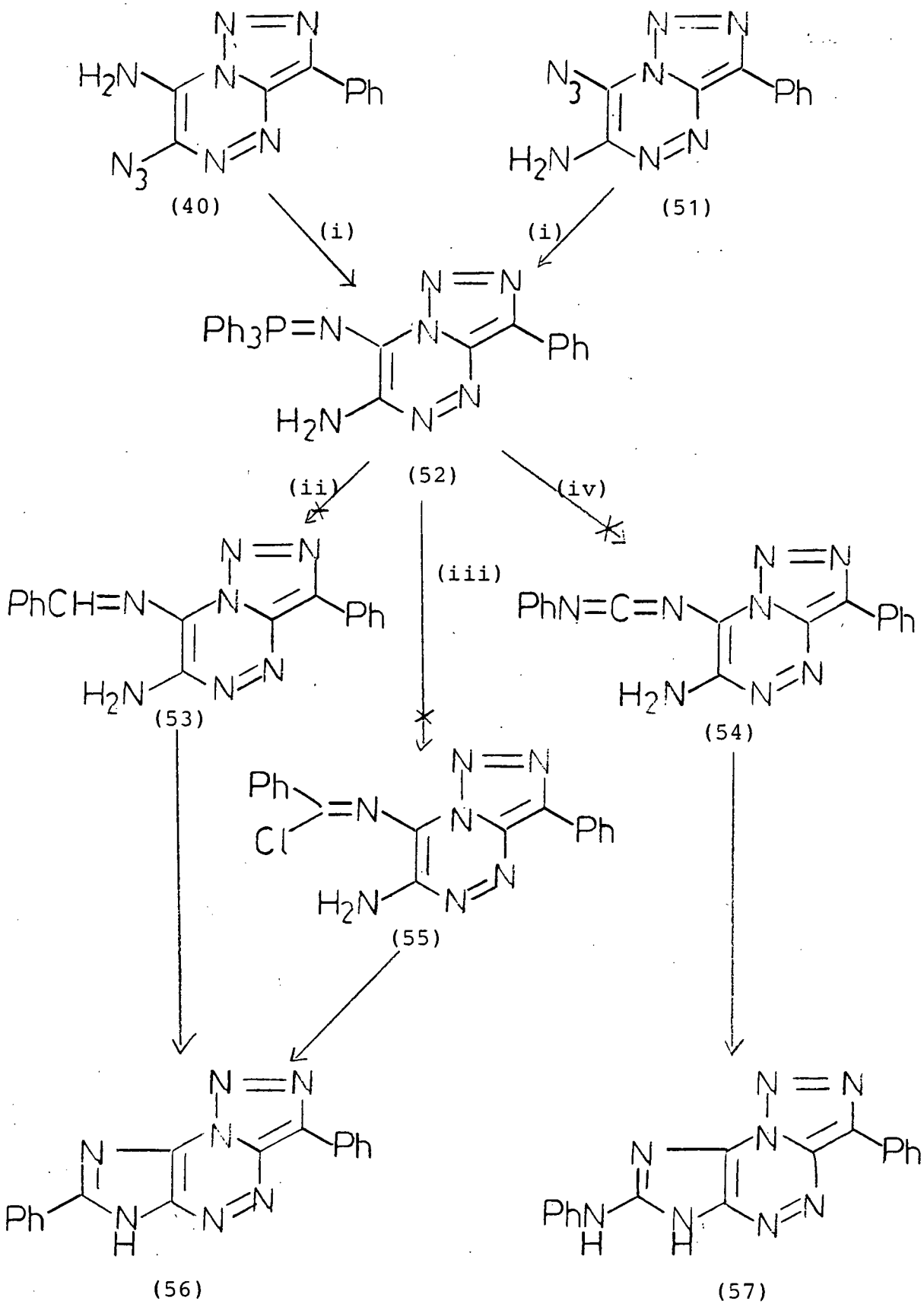
(iii) $NaNO_2$, HNO_3, H_2O, 0°

(iv) $Me_2NCH{=}O$, heat

Scheme 13

available from the triphenylphosphineiminotriazolotriazine (41) by reaction with aldehydes,[186] isocyanates,[187] and acid chlorides,[188] respectively. The phosphineimine (41) in turn was anticipated to be readily available from the reaction of the azidotriazolotriazine (40) with triphenylphosphine. It is known[189] that azides in general react with triphenylphosphine by loss of nitrogen to yield phosphineimines.

The general strategy detailed in Scheme 12 was investigated (Scheme 13) starting with the benzenesulphonyltriazolotriazine (21) which was reacted with sodium azide in aqueous dioxane at room temperature to afford a good yield of a product which is assigned the azidotriazolotriazine structure (40) on the basis of its i.r. spectrum which shows absorption at 2140 cm^{-1} and NH absorption at 3310, 3230 and 3180 cm^{-1}. The lack of other spectroscopic evidence and analytical data for this compound is due to its thermal instability. Thus on brief heating in dimethylformamide the azide (40) rearranges to the isomeric azidotriazolotriazine (51). This product gave analytical data and showed spectroscopic properties consistent with the assigned structure. Its i.r. spectrum contained an azide band at 2080 cm^{-1} and also exhibited NH absorption at 3350 and 3190 cm^{-1}. The novel rearrangement involved in the transformation of the azidotriazolotriazine (40) into the isomeric azide (51) is considered to proceed via a ring-closure/ring-opening sequence (Scheme 13) involving the tetrazine



(i) Ph_3P, dioxane, heat

(ii) PhCH=O, Me_2C=O, heat

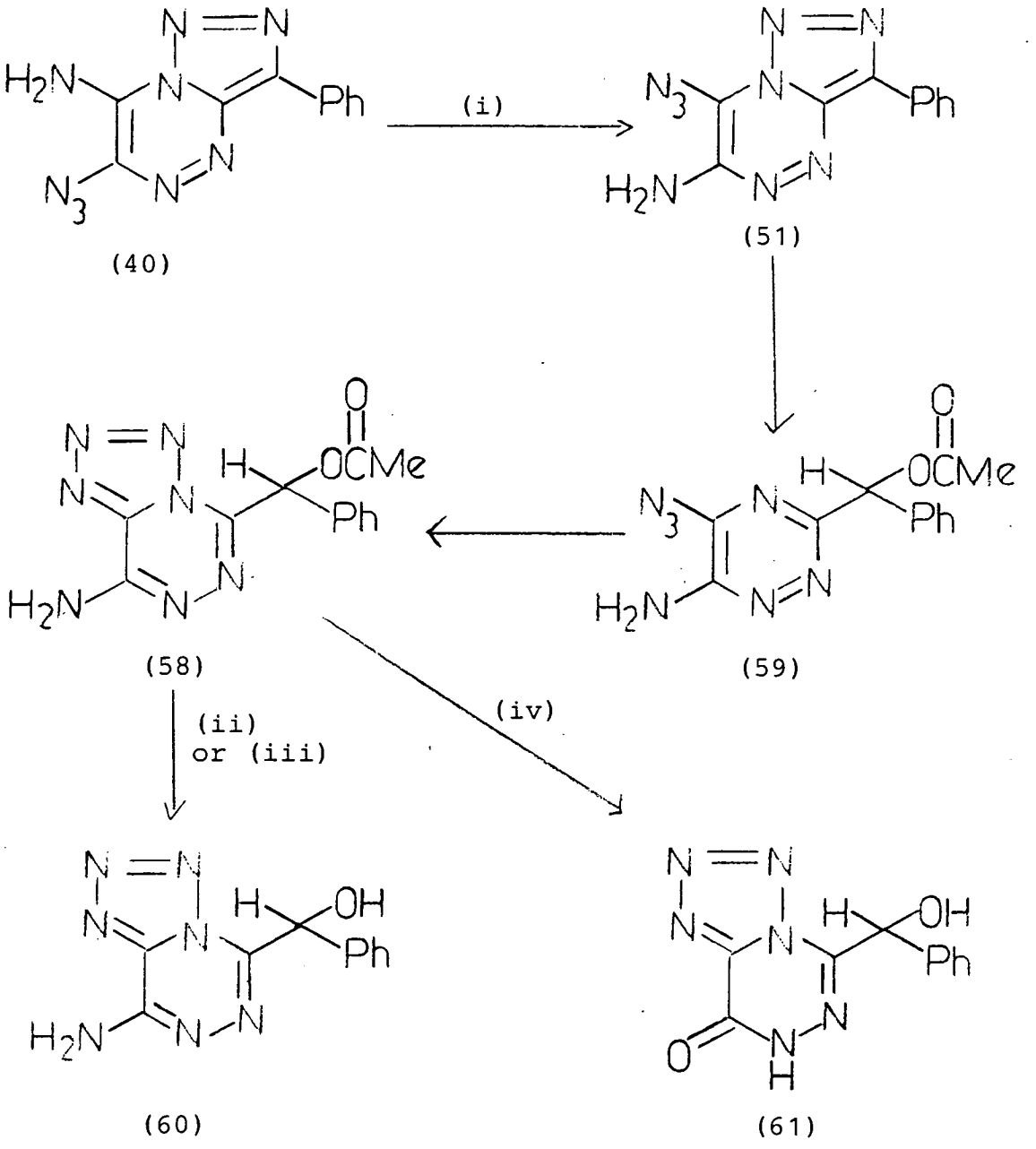
(iii) PhCOCl, dioxane, heat

(iv) PhN=C=O, dioxane, heat

Scheme 14

derivatives (48), (49) and (50). Interestingly, it was further found that treatment of the known[182] hydrazino-triazolotriazine (47) with sodium nitrite in concentrated nitric acid, conditions known[190] to diazotatively convert hydrazines to azides, also gave the isomeric azidotriazolo-triazine (51). This result is surprising in that diazotisation of the hydrazine (47) at low temperature would have been expected to afford the azide-derivative (40). Regrettably, lack of time prevented further studies of the interesting rearrangements [(21)→(51)] and [(47)→(51)] whose precise courses will require further detailed investigation.

Continuing with the investigation of the general synthetic-strategy outlined in Scheme 12 both azidotriazolo-triazines (40) and (51) were reacted (Scheme 14) with triphenylphosphine to give the same phosphineimine (52). This product gave analytical data and showed spectroscopic properties fully consistent with the assigned structure. In particular its ^{13}C n.m.r. spectrum exhibited as expected signals for eight quaternary carbon atoms. Also its ^{31}P n.m.r. spectrum showed a signal at δ18.43 characteristic of a P=N resonance. The assignment of the structure (52) to the triphenylphosphine imine derivative obtained from the azides (40) and (51), rather than the alternative 6-iminophosphorane structure [(40); $Ph_3P{=}N$ for N_3] is based on the expectation that treatment with triphenylphosphine would result in initial rearrangement to the thermally stable azide (51) prior to iminophosphorane formation.



(i) $MeCO_2H$, heat

(ii) 1M Na_2CO_3, EtOH, heat, 30 min.

(iii) 2M HCl, EtOH, heat, 30 min.

(iv) 2M HCl, EtOH, heat, 2h.

Scheme 15

Disappointingly, reaction of the phosphine-iminotriazolotriazine (52) with benzaldehyde in dimethylformamide gave a good recovery of the unreacted iminophosphorane (52) and reaction with benzaldehyde, in the absence of a solvent gave only intractable gums. The attempted reactions of the phosphiniminotriazolotriazine (52) with either benzoyl chloride or phenylisocyanate, also gave only good recoveries of the unreacted triazolotriazine (52).

The surprising lack of reactivity of the phosphine-iminotriazolotriazine (52) (see Scheme 14) prompted the investigation of the acid-catalysed triazole-scission (Scheme 15) of the azidotriazolotriazine (40) with glacial acetic acid. It was assumed that this reaction would initially result in thermal rearrangement to the isomeric azidotriazolotriazine (51) which would subsequently cleave to yield the azidotriazine derivative (59). It was hoped that further reaction of the azidotriazine (59) with triphenylphosphine would afford a phosphoimine derivative more susceptible to reaction with aldehydes, acid chlorides and isocyanates to yield 6-azapteridine derivatives. However, reaction of the azidotriazolotriazine (40) with glacial acetic acid afforded a good yield of the tetrazolotriazine (58). The structure of this product was supported by its combustion analysis and the lack of azide absorption in its i.r. spectrum which does contain carbonyl absorption at 1730 cm^{-1} characteristic of an acetoxy carbonyl group.

The ^{1}H n.m.r. spectrum of the product (58) showed the expected resonances due to five aromatic protons, a signal indicative of a benzylic CH substituent and a three proton singlet due to the methyl moiety of the acetoxy-group as well as two exchangeable hydrogen atoms. The ^{13}C n.m.r. spectrum of the tetrazolotriazine derivative (58) showed signals for the expected five quaternary carbon atoms. The tendency of azido-heterocycles to exist entirely as cyclic tetrazole structures is a well-documented[191] phenomenon.

The tetrazolotriazine derivative (58) also underwent chemical transformations which further supported its assigned structure. Thus, heating the tetrazolotriazine derivative (58) with aqueous sodium carbonate or hydrochloric acid for 30 minutes gave low yields of the hydroxybenzyl-tetrazolotriazine (60) thus confirming the presence of the acetoxybenzyl substituent in the tetrazolotriazine (58). The product (60) gave analytical data* and showed spectroscopic properties entirely consistent with the assigned structure. In particular its ^{1}H n.m.r. spectrum exhibited resonances assignable to five aromatic protons, a signal due to a benzylic CH group and three exchangeable protons. The ^{13}C n.m.r. spectrum contained signals for the expected four quaternary carbon atoms. Prolonged treatment of the tetrazolotriazine derivative (58) with hydrochloric acid gave a high yield of the tetrazolotriazinone derivative (61). The formation of this product not only supports the presence of an acetoxy-group in the tetrazolotriazine (58) but also the presence of the amino-group in the latter.

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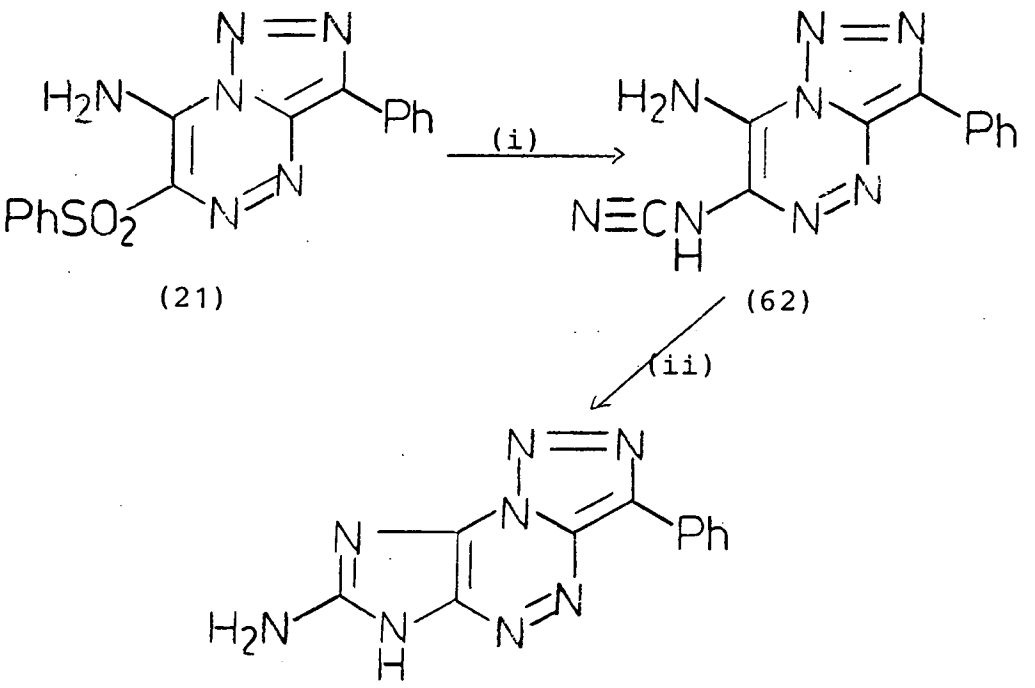
*corresponds to a hemi-hydrate



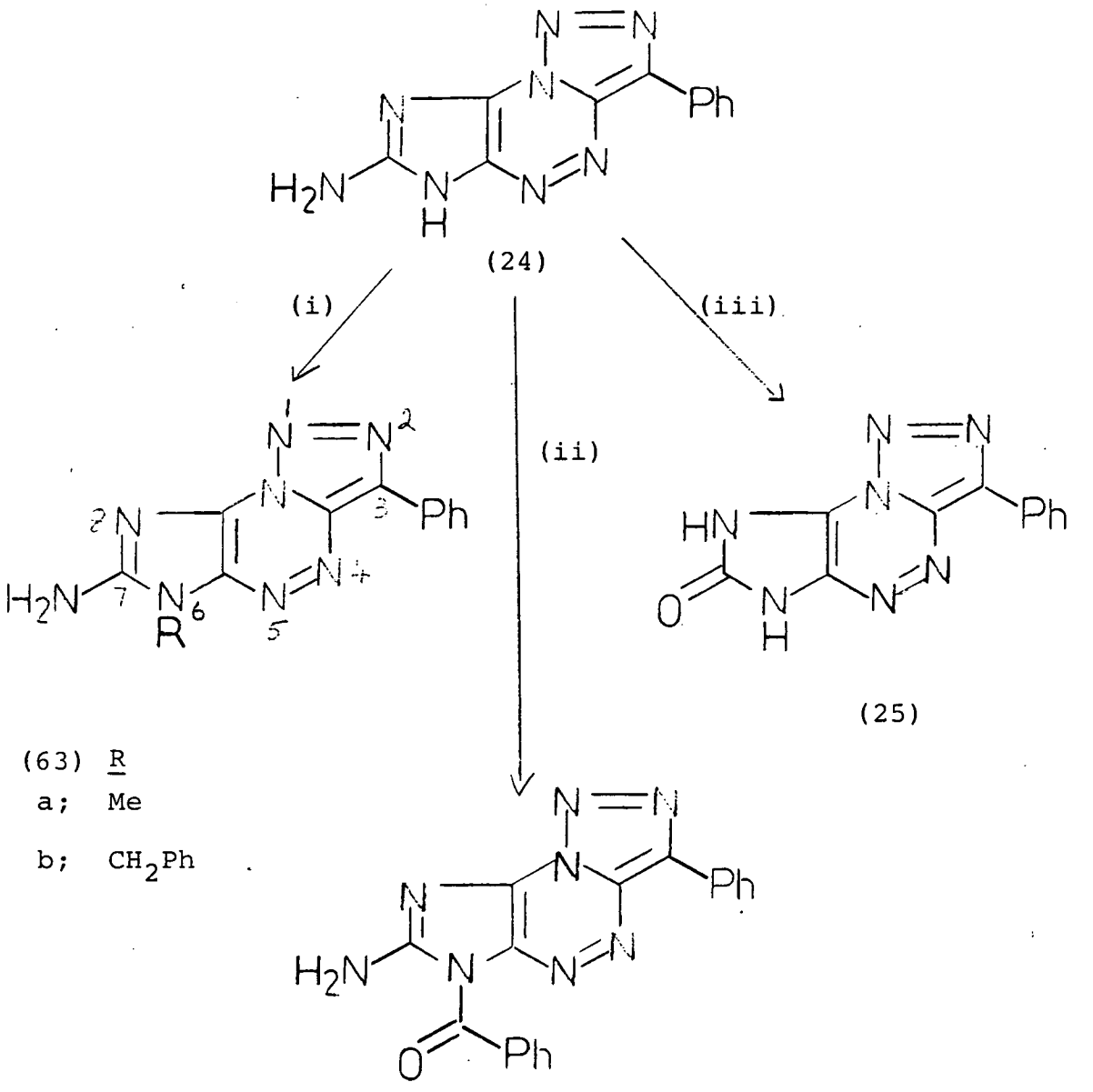
(i) $Na\overset{+}{\underset{-}{N}}HCN$, dioxane, room temp.

(ii) heat

Scheme 16

The tetrazolotriazinone derivative (61) gave analytical data and exhibited spectroscopic properties consistent with the assigned structure. In particular its i.r. spectrum showed the presence of a band due to a hydroxy-group and NH and carbonyl absorption characteristic of a lactam (i.e. triazinone) structure. The ^{1}H n.m.r. spectrum of the triazinone derivative (61) shows resonances for five aromatic protons, a one-proton singlet due to a benzylic CH-group and signals due to two exchangeable hydrogens. The ^{13}C n.m.r. spectrum showed signals for the expected four quaternary carbon atoms.

In a final attempt (Scheme 16) to develop a synthesis of 1,2,3-triazolo-6-azapurines suitable for acid-catalysed triazole-scission to 6-azapurine derivatives it was decided to investigate the synthesis and cyclisation of ortho-amino-cyanamide derivatives such as (62). In practice reaction of the benzenesulphonyltriazolotriazine (21) with sodium cyanamide afforded a good yield of the tricyclic product 7-amino-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (24). The formation of this product is presumed to proceed through the 7-amino-6-cyanoamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine intermeidate (62). This is supported by the co-formation in the reaction of a small amount of a yellow product having cyano absorption in its i.r. spectrum and a parent ion in its mass spectrum of m/e 252, which is tentatively assigned the cyanamidotriazolotriazine structure (62). The attempted crystallisation of this product resulted in its conversion



(i) MeI or $PhCH_2Cl$, NaH, $Me_2NCH{=}O$, room temp.

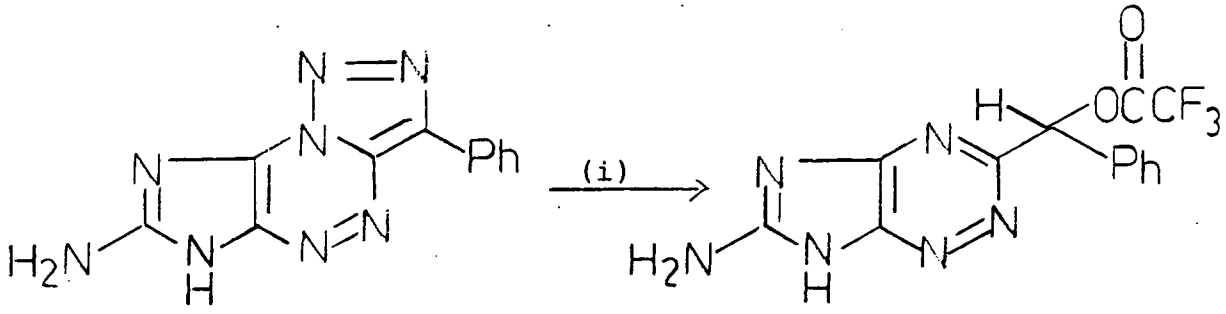
(ii) PhCOCl, 10% w/v NaOH, room temp.

(iii) 20% w/v KOH, 2-ethoxyethanol, heat

Scheme 17

into the tricyclic compound (24). The latter gave a combustion analysis and showed spectroscopic properties consistent with the assigned structure. In particular, its i.r. spectrum showed NH absorption but lacked a band due to a cyano-group. Its ^{13}C n.m.r. spectrum also showed signals due to the expected six quaternary carbon atoms. The mass spectrum of the triazolo-6-azapurine (24) did not show the expected parent ion at m/e 252 the ion of highest mass being at m/e 226 corresponding to loss of CN from the parent ion.

The structure of the tricyclic product (24) was further confirmed by its simple chemical transformations (Scheme 17). Thus reaction with methyl iodide and benzyl chloride in the presence of sodium hydride afforded good yields of the derivatives (63a) and (63b) respectively. Both of these products gave analytical data and showed spectroscopic properties consistent with the assigned structures. In particular the product (63a) exhibited signals in its ^{1}H n.m.r. spectrum assignable to five aromatic protons, a three-proton singlet due to an NCH_3 group and signals due to two exchangeable hydrogen atoms. Also the ^{13}C n.m.r. spectrum of the derivative (63a) shows signals for the six quaternary carbon atoms of the assigned structure. Likewise, the product (63b) showed resonances in its ^{1}H n.m.r. spectrum due to ten aromatic protons, a two-proton singlet due to a benzylic CH_2 group and signals due to two exchangeable hydrogen atoms. However, the ^{13}C n.m.r. spectrum of the benzyl derivative (63b) showed



(24) (65)

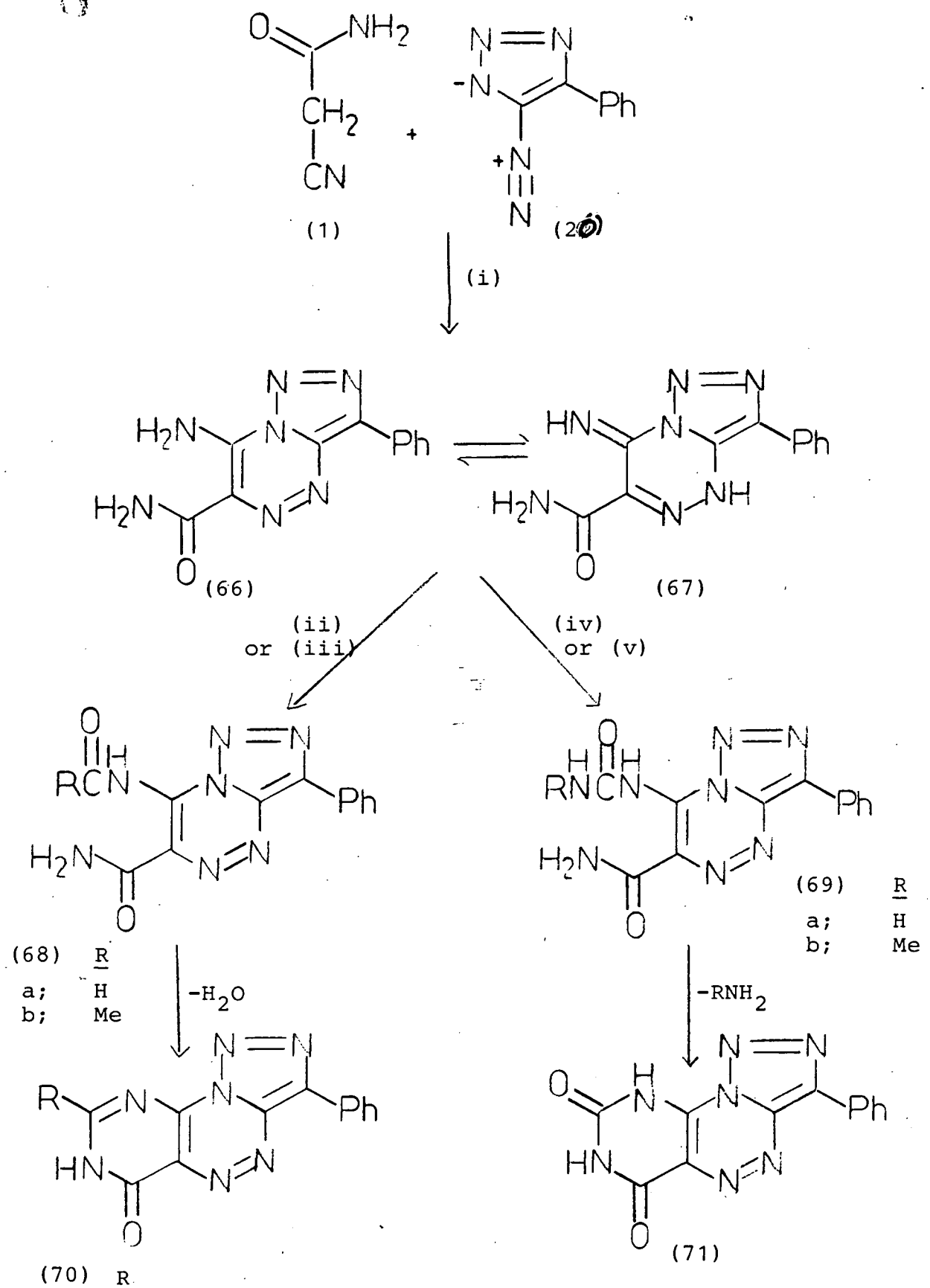
(i) CF_3CO_2H, heat

Scheme 18

signals for only six quaternary carbon atoms instead of the seven present in the structure (63b). This feature can be explained in terms of the long relaxation times of hetero-atom substituted quaternary carbon atoms which are not always observable in ^{13}C n.m.r. spectra.[86] The assignment of the 6-alkylated structures (63a) and (63b) to the products of the methylation or benzylation of the tricyclic product (24) rather than alternative 8-alkylated structures is based on the assumption of greater steric hindrance to reaction at N-8 compared with N-6.

In an attempt to obtain the benzoyl derivative (64) the tricyclic product (24) was reacted with benzoyl chloride in the presence of aqueous sodium hydroxide solution. However, this reaction gave only a good recovery of the unreacted triazoloimidazotriazine derivative (24). Similarly the attempted reaction of the tricyclic product (24) with 20% w/v potassium hydroxide solution gave only a good yield of the unreacted starting material (24), instead of the expected fused imidazolone product (25).

7-Amino-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo-[4,5-c]-1,2,4-triazine (24) is highly insoluble only being totally soluble in trifluoroacetic acid. However trifluoro-acetic acid should be a good reagent for the acid catalysed cleavage of the bridgehead-fused triazole moiety in the compound (24). Therefore it was anticipated (Scheme 18) that heating the tricyclic product (24) in trifluoroacetic acid would afford the 6-azapurine derivative (65). Disappointingly, however, heating a solution of the tricyclic compound (24) in trifluoroacetic



(i) NaOAc, EtOH, H_2O, 0°

(ii) $HC(OEt_3)$ or HCO_2H heat

(iii) AC_2O, heat or AcCl, conc. H_2SO_4, room temp.

(iv) $(H_2N)_2C{=}O$, 200°

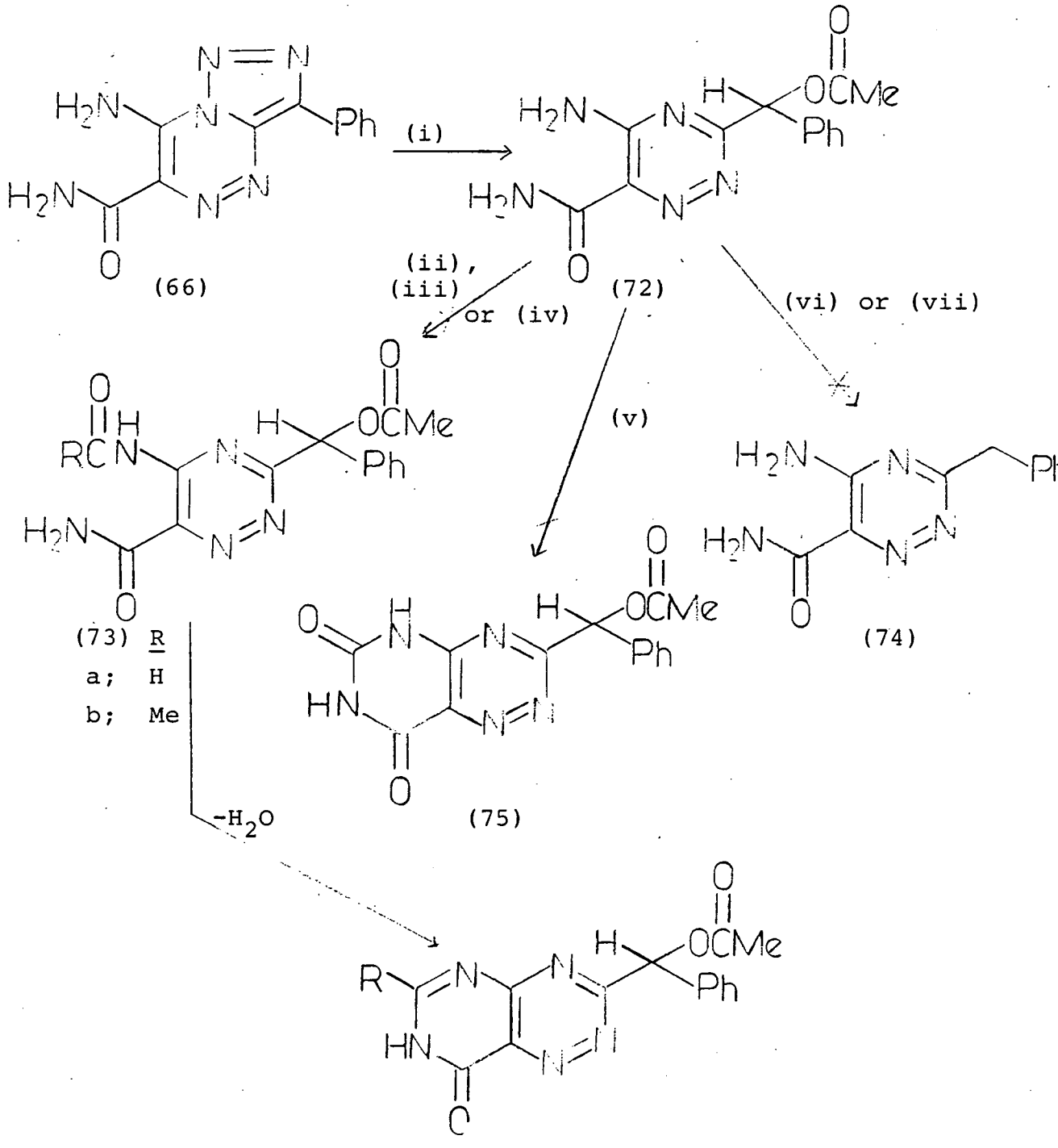
(v) $PhN{=}C{=}O$, $Me_2NHC{=}O$, room

Scheme 19

acid gave only a quantitative recovery of the unreacted triazoloimidazotriazine (24).

4.3 Investigations of 6-Acyl-7-amino-1,2,3-triazolo-[5,1-c]-1,2,4-triazines as Synthetic Precursors of 6-Azapteridines and 2,6-Diazapteridines

As has been outlined in the introduction to this chapter (see Scheme 3) it was anticipated that 6-azapteridines could be synthesised by the acid-catalysed triazole scission of 1,2,3-triazolopyrimido-1,2,4-triazines [(12)-(14)]. Tricyclic polyazaheterocycles of the type (12) were expected to be readily synthesised by the annulation of 7-amino-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide derivatives. This synthetic strategy was investigated (Scheme 19) by examining the annulation reactions of the known[180] 7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) which was readily prepared by the reaction of 4-phenyl-1H-1,2,3-triazole-5-diazonium betaine (20) with cyanoacetamide (1). It was anticipated that reaction of the triazolotriazine (66) with triethylorthoformate or formic acid would yield the tricyclic system (70a). In practice however, reaction of the triazolotriazine (66) with triethyl orthoformate gave only a good yield of the unreacted triazolotriazine (66), while reaction of the triazolotriazine (66) with formic acid afforded an intractable solid from which no identifiable material could be isolated.



(i) $MeCO_2H$, heat

(ii) $HC(OEt)_3$ or HCO_2H, heat

(iii) $H_2NCH{=}O$, NaOEt, heat

(iv) Ac_2O, heat

(v) $TSO_2N{=}C{=}O$, dajlyme heat

(vi) H_2, 10% Pd-C

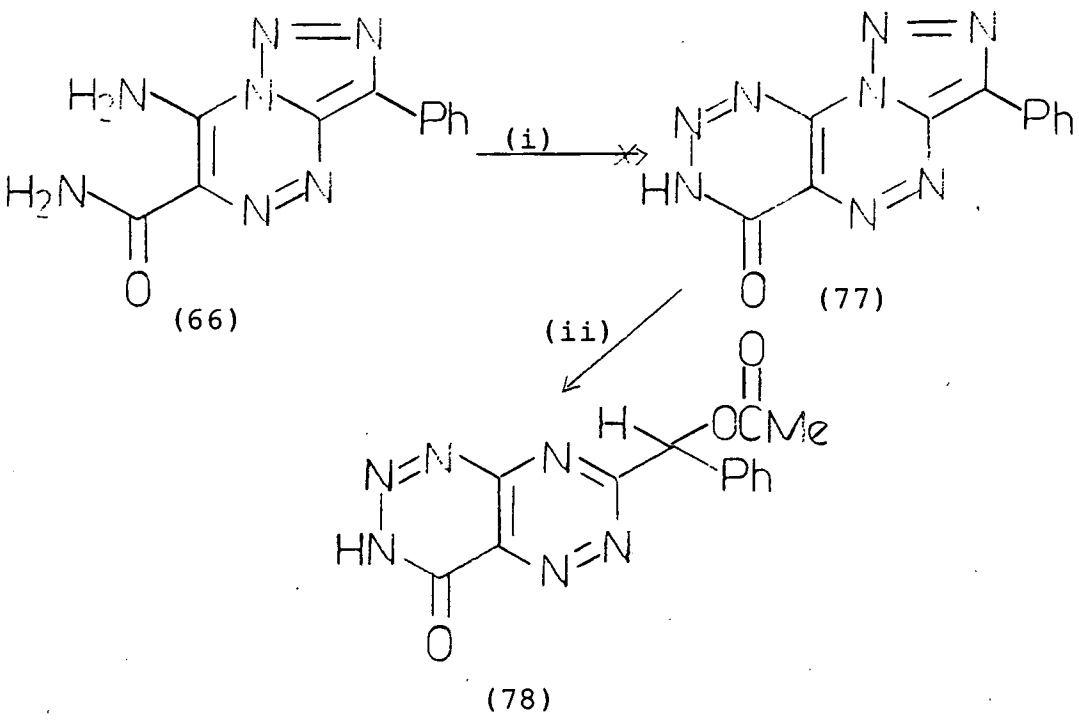
(vii) $NaBH_4$, 10% Pd-C, room temp.

Scheme 20

In an attempt to acetylate the triazolotriazine derivative (66) it was reacted with acetic anhydride and also acetyl chloride in the presence of concentrated sulphuric acid. However, none of the expected acetamido-derivative (68b) was isolated only complex mixtures being obtained.

In further pursuing the annulation reactions of the triazolotriazine (66) it was decided to investigate its reactions with urea and phenylisocyanate both of which were expected to lead to the tricyclic product (71). However, these reactions gave only low yields of the unreacted starting material (66) with no evidence for the formation of the required product (71). The surprising lack of reactivity of 7-amino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) towards acylation may be due to its existence predominantly as the imino-tautomer (67). Tautomerism of this type has already been discussed in connection with 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) (see Scheme 7).

The failure of the triazolotriazinecarboxamide (66) to undergo the desired annulation reactions prompted the investigation (Scheme 20) of the corresponding annulation reactions of the known[180] 1,2,4-triazine derivative (72) which was readily prepared by the acid-catalysed cleavage of the triazolotriazine (66) in glacial acetic acid. It was hoped that the 1,2,4-triazine derivative (72) would prove to be more amenable to annulation thus allowing access to the 6-azapteridine derivatives (75), (76a) and (76b). However the attempted reactions of the 1,2,4-triazine derivative (72) with triethyl ortho formate,



(66) (77) (78)

(i) $NaNO_2$, 10% w/v HCl, $MeCO_2H$, 0°

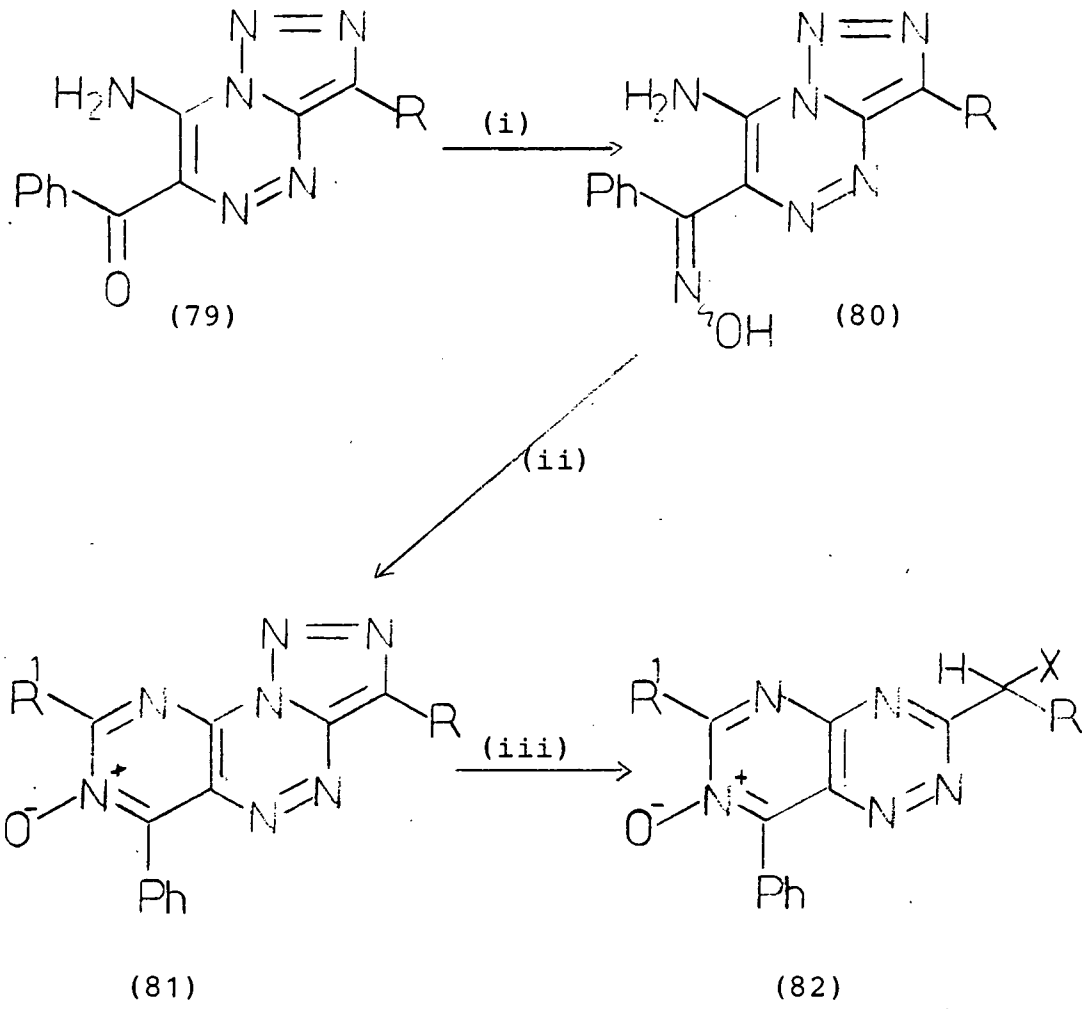
(ii) $MeCO_2H$, heat

Scheme 21

acetic anhydride, formamide in the presence of sodium ethoxide or tosyl isocyanate all gave complex mixtures, while its reaction with formic acid gave only a quantitative recovery of the unreacted 1,2,4-triazine derivative (72).

The complexity of the product mixtures from the attempted annulation reactions of the 1,2,4-triazine derivative (72) might at least in part, be due to side-reactions resulting from the presence of the acetoxy-group. It is known[192] that acetoxy-groups can be hydrogenolysed and in the case of the 1,2,4-triazine derivative (72) it was anticipated that hydrogenolysis (Scheme 20), would yield the benzyl-1,2,4-triazine derivative (74). It was hoped that this compound would cyclise more smoothly to yield 6-azapteridines. However, the attempted hydrogenolysis, under a variety of conditions, of the acetoxybenzyl-1,2,4-triazine derivative (72) afforded only good yields of the unreacted 1,2,4-triazine derivative (72), thus precluding the study of the annulation reactions of the benzyl-1,2,4-triazine (74).

In an attempt (Scheme 21) to synthesise the 2,6-diazapteridine derivative (78) it was anticipated that the triazolotriazine (66) would diazotatively cyclise to give the bicyclic product (77) which was then expected to undergo acid-catalysed, triazole-scission in glacial acetic acid to give the 2,6-diazapteridine derivative (78). However,

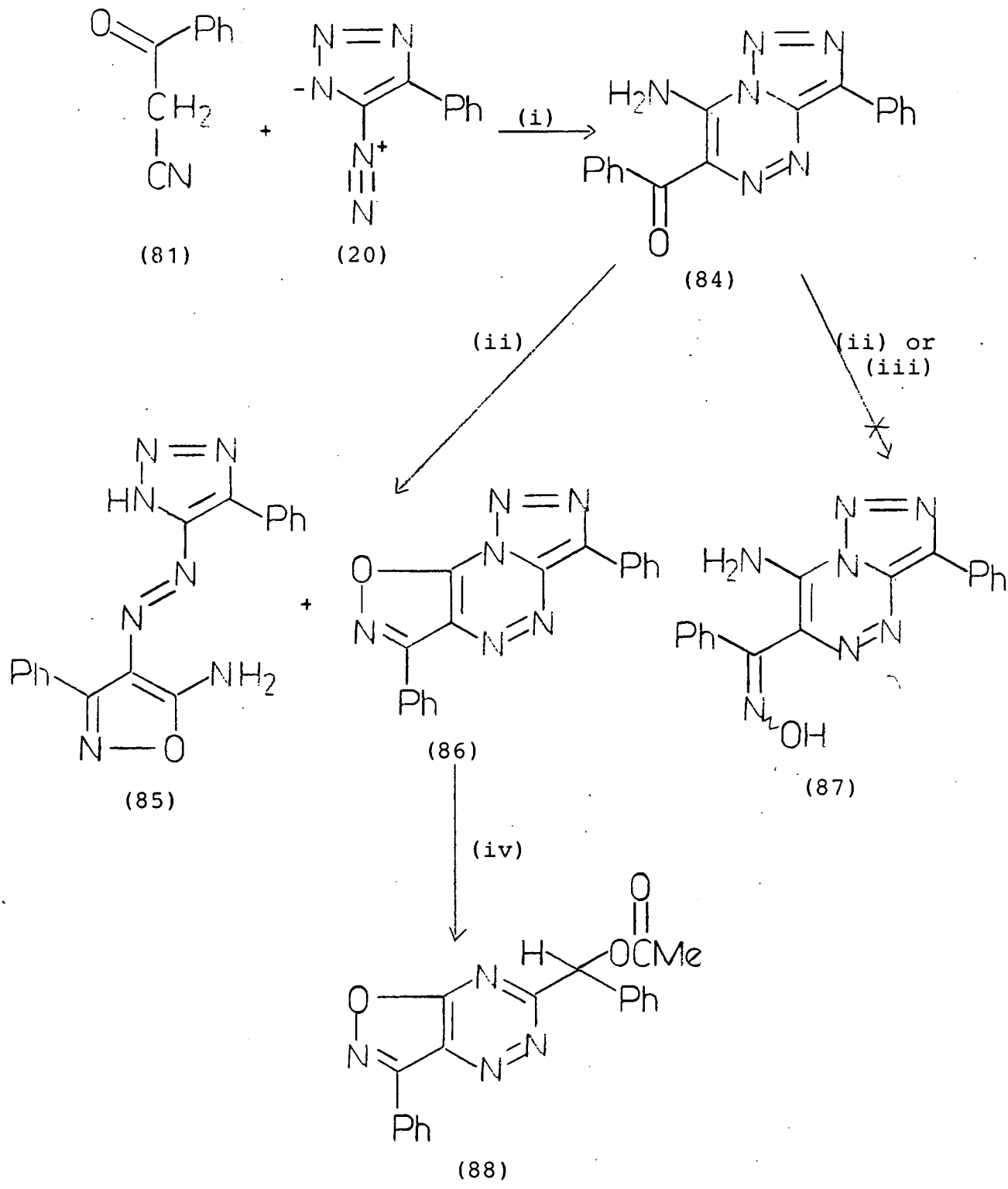


(i) H_2NOH HCl, EtOH, heat

(ii) $(EtO)_3CR^1$, heat

(iii) HX (X = H, OH, $\overset{O}{\overset{\|}{O}}CR$, Cl, Br)

Scheme 22



(81) (20) (84) (85) (86) (87) (88)

(i) NaOAc, EtOH, H_2O, 0°

(ii) $NH_2OH.HCl$, EtOH, heat

(iii) $NH_2OH.HCl$, NaOAc, EtOH, heat

(iv) $MeCO_2H$, heat

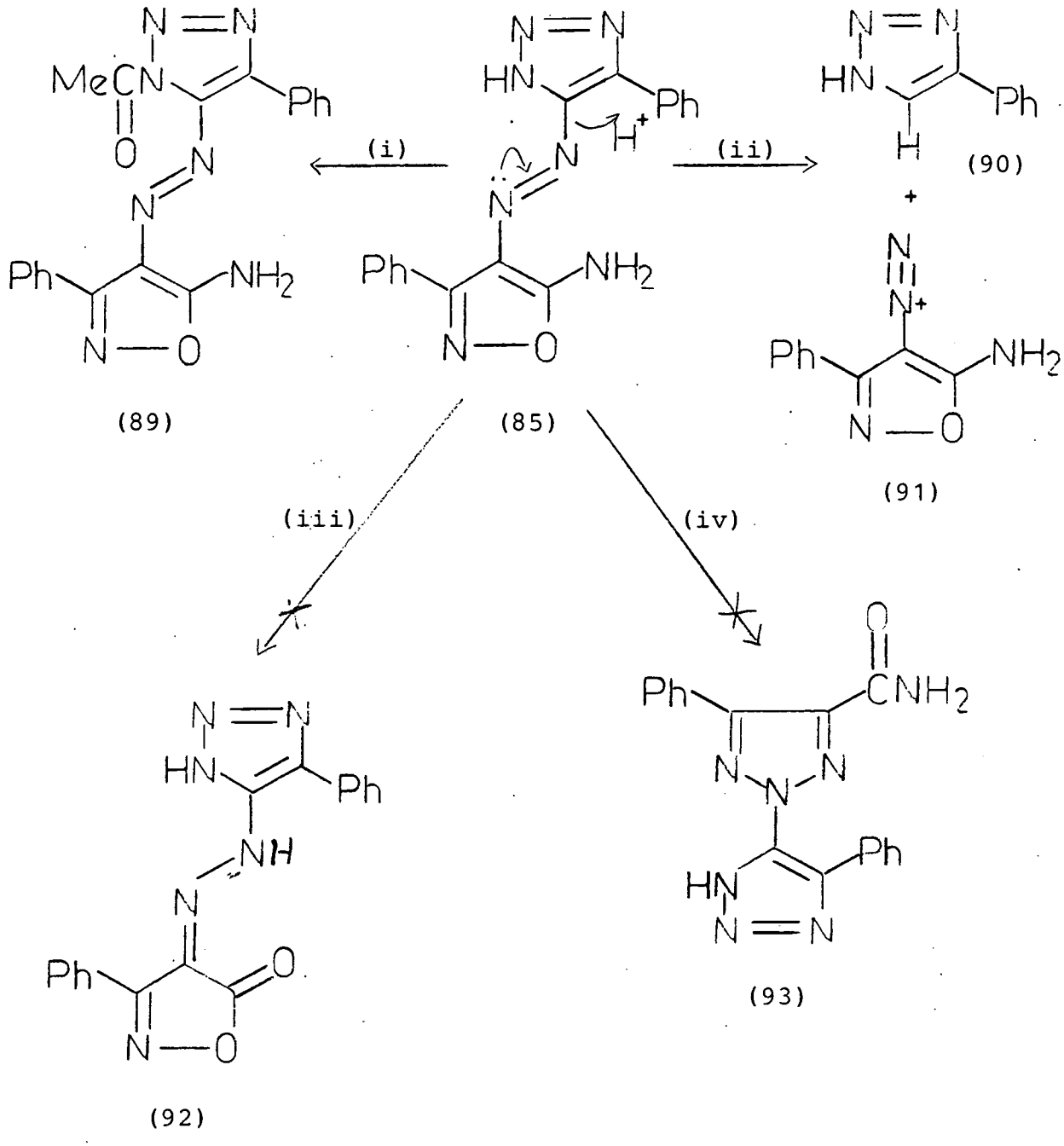
Scheme 23

disappointingly, the reaction of the triazolotriazine (66) with sodium nitrite in the presence of hydrochloric acid gave only a moderate yield of the unreacted triazolotriazine (66) and a complex brown gum which yielded no identifiable material.

In continuing the investigation of 6-acyl-7-amino-1,2,3-triazolo[5,1-c]-1,2,4-triazines as potential precursors of 6-azapteridine derivatives it was decided to study the synthetic utility (Scheme 22) of 7-amino-6-benzoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine oxime derivatives (80) since it is known[103] that structurally related compounds undergo cyclisation reactions of the required type [(80)→(81)]. It was then anticipated (Scheme 22) that acid-catalysed scission of the resulting tricyclic product would be expected to yield the corresponding 6-azapteridine N-oxide derivative [(81)→(82)]. It was further anticipated that the required oxime derivative (80) would be readily prepared from the known[197] 7-amino-6-benzoyl-1,2,3-triazolo[5,1-c]-1,2,4-triazines (79). This synthetic strategy was investigated (Scheme 23) by initially studying the oximation of the known[180] 7-amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (84) which was readily synthesised by the reaction of benzoylacetonitrile (81)[185] with 4-phenyl-1H-1,2,3-triazole-5-diazonium betaine (20). The reaction of the triazolotriazine (84) with hydroxylamine hydrochloride in the presence of sodium acetate however failed to give the expected oxime derivative (87) only a good yield of the unreacted triazolotriazine (84) being

obtained. Reaction of the benzoyltriazolotriazine (84) with a large excess of hydroxylamine hydrochloride also failed to give the expected oxime derivative (87), two products being obtained. These products ~~have~~ has been assigned as the isoxazoloazotriazole derivative (85) and the tricyclic system, the triazoloisoxazolotriazine (86). The latter product (86) can only be tentatively assigned as the illustrated structure, being a highly insoluble compound and subsequent purification after isolation was therefore not possible. However, this product (86) does have mass spectral data in agreement with the assigned structure. In an attempt to gain supportive evidence that this product (86) is indeed a fused triazole system it was reacted with glacial acetic acid (Scheme 23) which was expected to cause acid catalysed cleavage of the bridge-head fused triazole and yield the isoxazolotriazine derivative (88). However in practice a complex mixture was obtained.

The other product, the isoxazoloazotriazole derivative (85) from the reaction of hydroxylamine hydrochloride with the triazolotriazine (84) has been assigned the illustrated structure (85) on the basis of its analytical data and its chemical reactivity. In particular it does not undergo the Beckmann rearrangement on reaction with polyphosphoric acid as would be expected for the isomeric oxime derivative (87). Also it does not undergo acid



(i) Ac_2O, heat

(ii) 20% w/v H_2SO_4, EtOH, heat

(iii) 2M NaOH, heat

(iv) Diglyme, heat

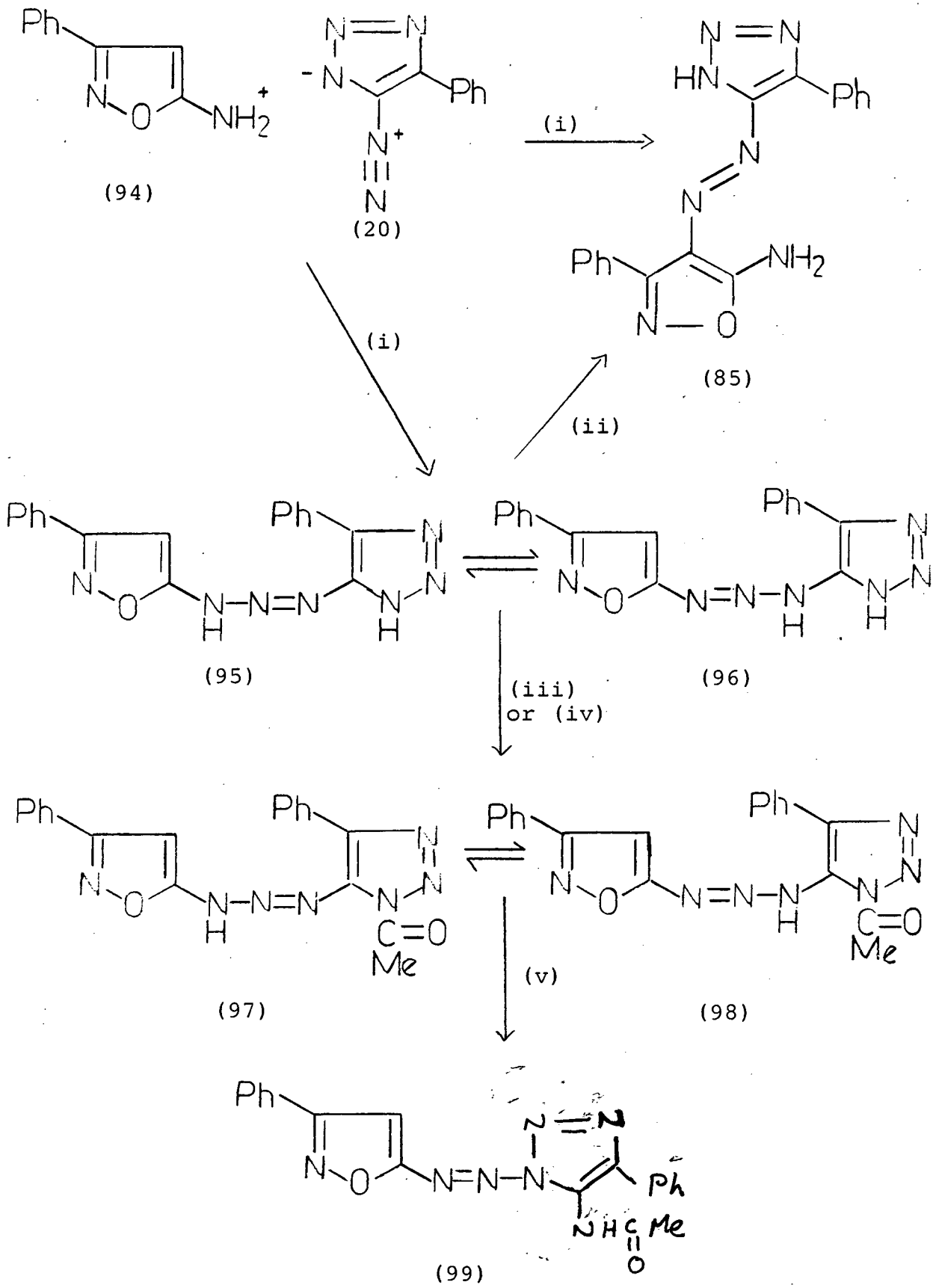
Scheme 24

catalysed triazole cleavage on reaction with glacial acetic acid as would be expected again for the oxime derivative (87).

The structure of the isoxazoloazotriazole derivative (85) is further supported by (Scheme 24) its reaction with acetic anhydride to give a moderate yield of the acetyl derivative (89). This product gave analytical data and showed other spectroscopic properties consistent with the assigned structure. In particular it exhibited a carbonyl band at 1760 cm^{-1} in its i.r. spectrum characteristic of a acetyl group attached to the ring nitrogen of a 1,2,3-triazole.[193] Its ^{1}H n.m.r. spectrum showed resonances for ten aromatic hydrogen atoms and two exchangeable protons. The ^{1}H n.m.r. spectrum of this product (89) also contained a signal at 2.8 p.p.m. for the three hydrogens of an acetyl CH_3 group, this chemical shift value being characteristic of an acetyl group attached to a ring nitrogen of a 1,2,3-triazole.[193]

In continuing the chemical degradation (Scheme 24) of the isoxazoloazotriazole derivative (85) it was reacted with sulphuric acid. This afforded a moderate yield of the known[194] 4-phenyl-1H-1,2,3-triazole (90) plus a complex gum. None of the other expected product, the isoxazole diazonium betaine (91) could be detected.

Both of these later reactions would support the existence of a 1,2,3-triazole moiety in the supposed isoxazoloazotriazole derivative (85). In an attempt to



(i) CH_2Cl_2, room temp.

(ii) 2M HCl, EtOH, heat

(iii) Ac_2O, heat

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

(v) heat

Scheme 25

show the existence of the isoxazole grouping in the structure (85) two further reactions (Scheme 24) were attempted. It is known[157] that amino-isoxazoles can be hydrolysed to isoxazolinones by treatment with aqueous sodium hydroxide. Therefore it was anticipated that the reaction (Scheme 24) of the isoxazole derivative (85) with sodium hydroxide would afford the isoxazolinone derivative (92). However, in practice only a complex mixture was obtained.

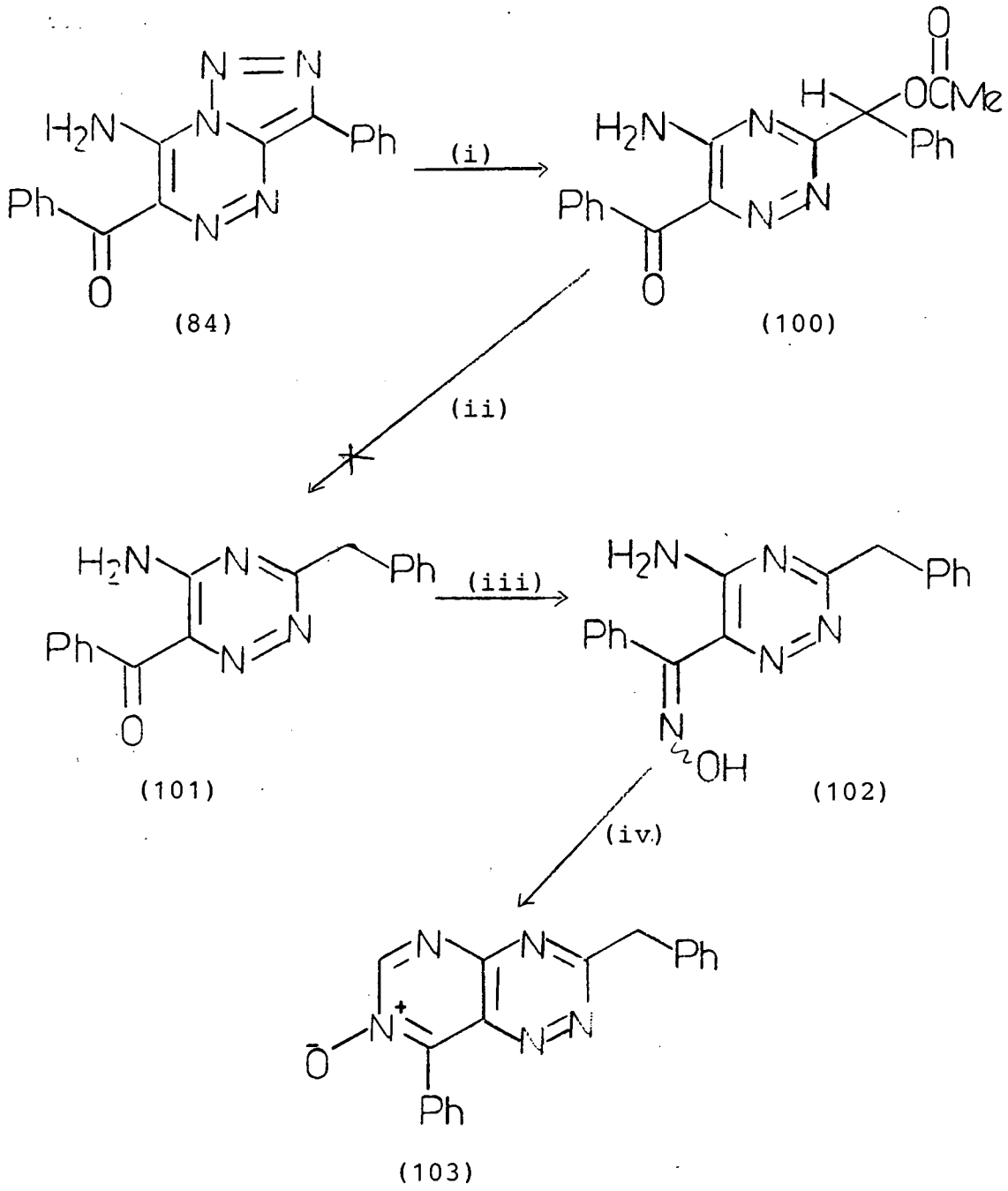
As has been previously described (see Chapter 3, page 163) isoxazoles can undergo characteristic thermal rearrangements. Therefore by analogy it was expected that heating a solution of the isoxazole derivative (85) in diglyme would yield the derivative (93). Disappointingly however a complex mixture was again obtained.

The ambiguity surrounding the structure of the compound (85) prompted investigation of its unambiguous synthesis. It was expected (Scheme 25) that coupling of the 4-phenyl-1H-1,2,3-triazole-5-diazonium betaine (20) with 5-amino-3-phenylisoxazole (94)[105] would afford the desired isoxazoloazotriazole derivative (85). However, in practice the triazene derivative (95) was obtained in good yield. This product (95) gave analytical data and showed spectroscopic properties consistent with the assigned structure. The ^{1}H n.m.r. spectrum exhibits resonances for ten aromatic hydrogen atoms and three exchangeable protons.

It has been observed[195] that triazene derivatives can rearrange to amino-azo derivatives. Therefore it was anticipated that the reaction of the triazene derivative (95) with hydrochloric acid would afford the desired isoxazoloazotriazolo derivative (85). However, reaction of the triazene (95) with hydrochloric acid in practice gave a good yield of the unreacted triazene derivative (95).

The attempted acetylation (Scheme 25) of the triazene (95) with acetic anhydride afforded a series of intractable gums and solids. However, treatment of the triazene (95) with acetyl chloride in the presence of triethylamine gave a good yield of the acetyl derivative (97) which on attempted crystallisation gave the acetyl derivative (99) presumably by a Dimroth rearrangement of the tautomer (98). Such rearrangements of 1,2,3-triazoles have been previously observed.[196]

The product (97) has been assigned the illustrated structure on the basis of its i.r. spectrum which has a carbonyl absorption at 1730 cm^{-1} characteristic of an acetyl group sited adjacent to a ring nitrogen of a 1,2,3-triazole.[193] The product (99) of the Dimroth rearrangement of the acetyl derivative (97) gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular the i.r. spectrum of the product (99) exhibited a carbonyl absorption at 1695 cm^{-1}, characteristic of the NH acetyl group attached to a 1,2,3-triazole.[193] The ^1H n.m.r.



(84) (100) (101) (102) (103)

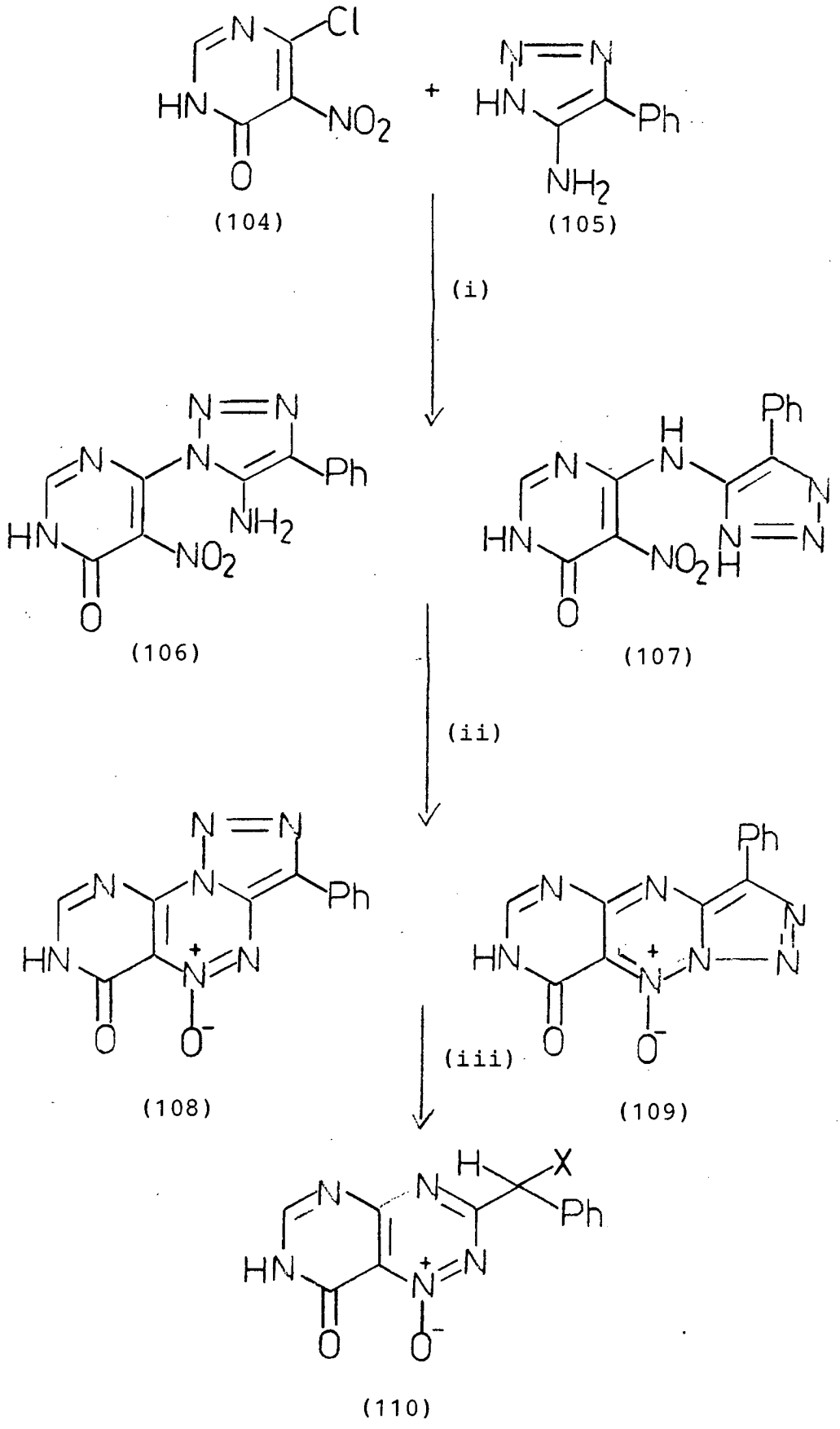
(i) $MeCO_2H$, heat

(ii) H_2, 10% Pd-C, room temp., atmos. press.

(iii) $NH_2OH.HCl$, EtOH, heat

(iv) $CR(OEt)_3$, heat

Scheme 26



(104) (105)

(i)

(106) (107)

(ii)

(108) (109)

(iii)

(110)

(i) KOAc, EtOH, room temp.

(ii) NaOEt, EtOH, reflux

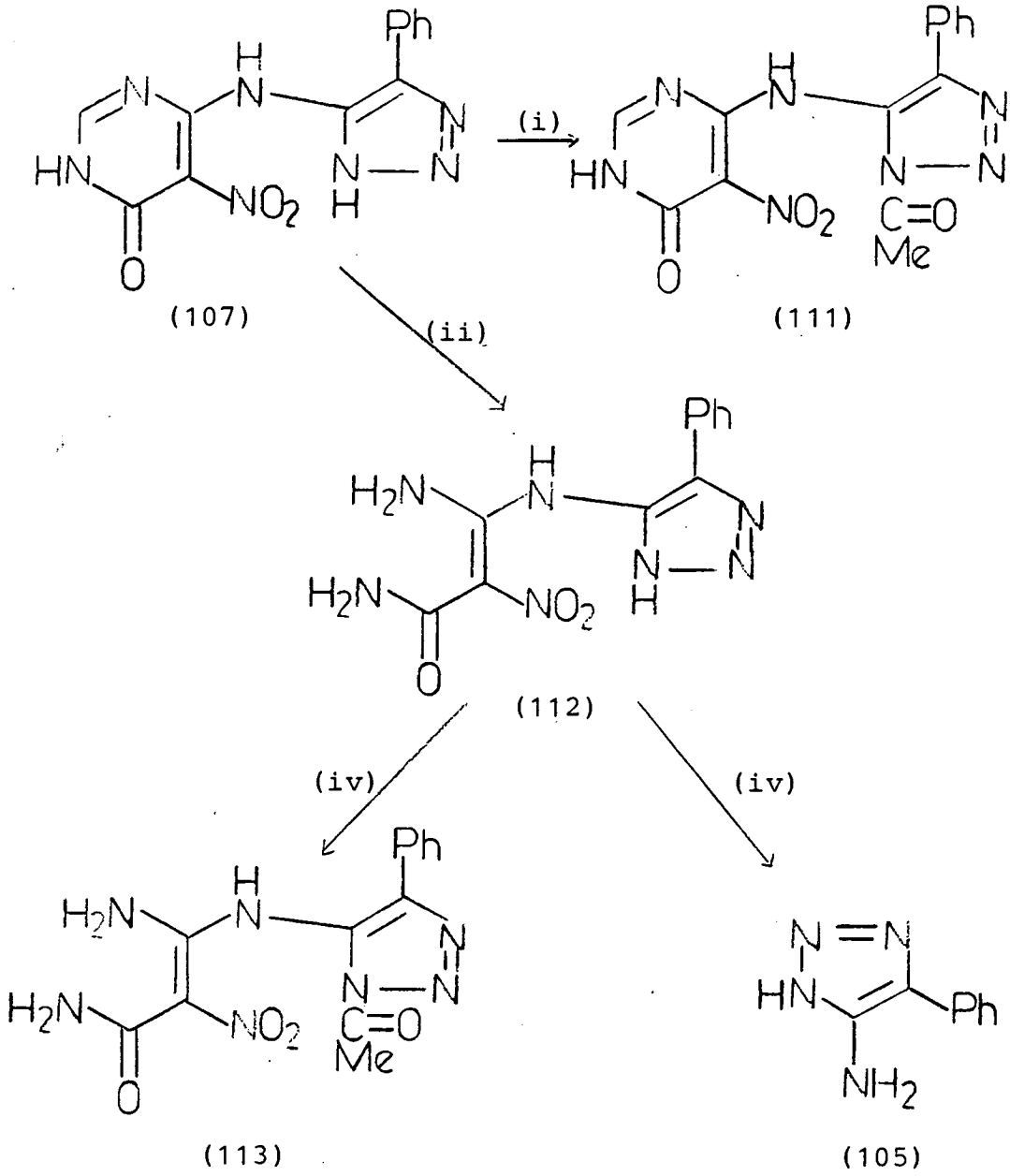
(iii) HX (X = H, OH, $O\overset{O}{\overset{\|}{C}}R$, Cl, Br)

Scheme 27

spectrum shows resonances for ten aromatic hydrogen atoms and a CH group, and also a signal at 2.17 p.p.m. for the CH_3 group of an NH acetyl moiety. This chemical shift value is characteristic of an NH acetyl group attached to a 1,2,3-triazole.[193]

The failure of the transformation [Scheme 23: (84)→(87)] prompted the investigation (Scheme 26) of the acid catalysed cleavage of the triazolotriazine (84) with glacial acetic acid to give the known[180] 1,2,4-triazine derivative (100). It was hoped that hydrogenolysis of this acetoxy-1,2,4-triazine (100) derivative would yield the 1,2,4-triazine (101) which would be anticipated to smoothly oximate to give the oxime derivative (102) and thence by subsequent annulation the 6-azapteridine derivative (103). Disappointingly however, the acetoxy-1,2,4-triazine derivative (100) failed to hydrogenolyse, a good yield of the unreacted 1,2,4-triazine (100) being recovered.

The lack of success in obtaining a tricyclic derivative which would potentially undergo acid catalysed cleavage to give a 6-azapteridine derivative prompted investigation of an alternative route (Scheme 27) to such tricyclic derivatives (108) or (109). These derivatives (108) or (109) would be expected to undergo acid catalysed cleavage of the fused triazole to afford the 6-azapteridine derivatives (110). It was anticipated that reaction of the chloronitropyrimidinone (104)[197] with the aminotriazole



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

(ii) NaOEt, EtOH, heat

(iii) Ac_2O, heat

(iv) 2M HCl, EtOH, heat

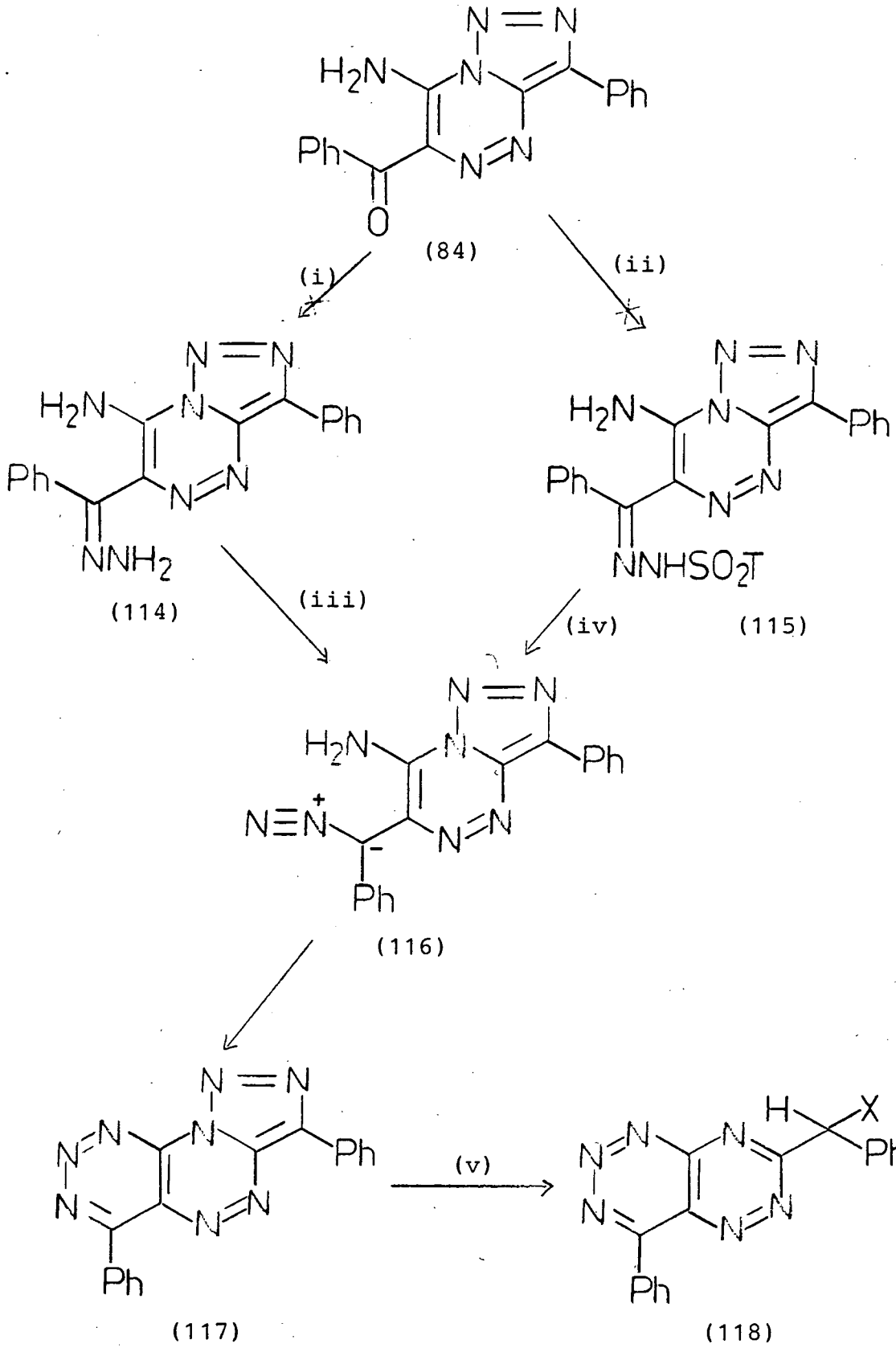
Scheme 28

(105)[198] would give either of the pyrimidine derivatives (106) or (107) which in turn could be induced to undergo base catalysed cyclisation to yield the tricyclic system (108) or (109) and thence by acid catalysed scission of the fused bridgehead triazole the 6-azapteridine ring system (110).

The reaction of the chloronitropyrimidinone (104) and the aminotriazole (105) gave a good yield of the nitropyrimidinone derivative (107). This product gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular the i.r. spectrum exhibited absorptions for NH stretching and a carbonyl band at 1690 cm^{-1}. The ^{1}H n.m.r. spectrum gave resonances for three exchangeable protons each having an individual signal whereas the other possible isomer (106) might be expected to show two signals for the three exchangeable protons it posseses.

Further support for the structure of this foregoing product (107) is that it forms (Scheme 28) an acetyl derivative (111) on reaction with acetyl chloride in the presence of triethylamine. This derivative (111) exhibits a carbonyl band in its infrared spectrum at 1770 cm^{-1} consistent with an acetyl group on a ring nitrogen of a 1,2,3-triazole.[193]

Disappointingly, however, the attempted base catalysed cyclisation (Scheme 27) of the nitropyrimidinone derivative (107) failed to give the expected tricyclic system (109) a good yield (Scheme 28) of the triazole



(i) $NH_2NH_2 . H_2O$, MeOH, heat

(ii) TSO_2NHNH_2, MeOH, heat

(iii) [O]

(iv) Base, heat

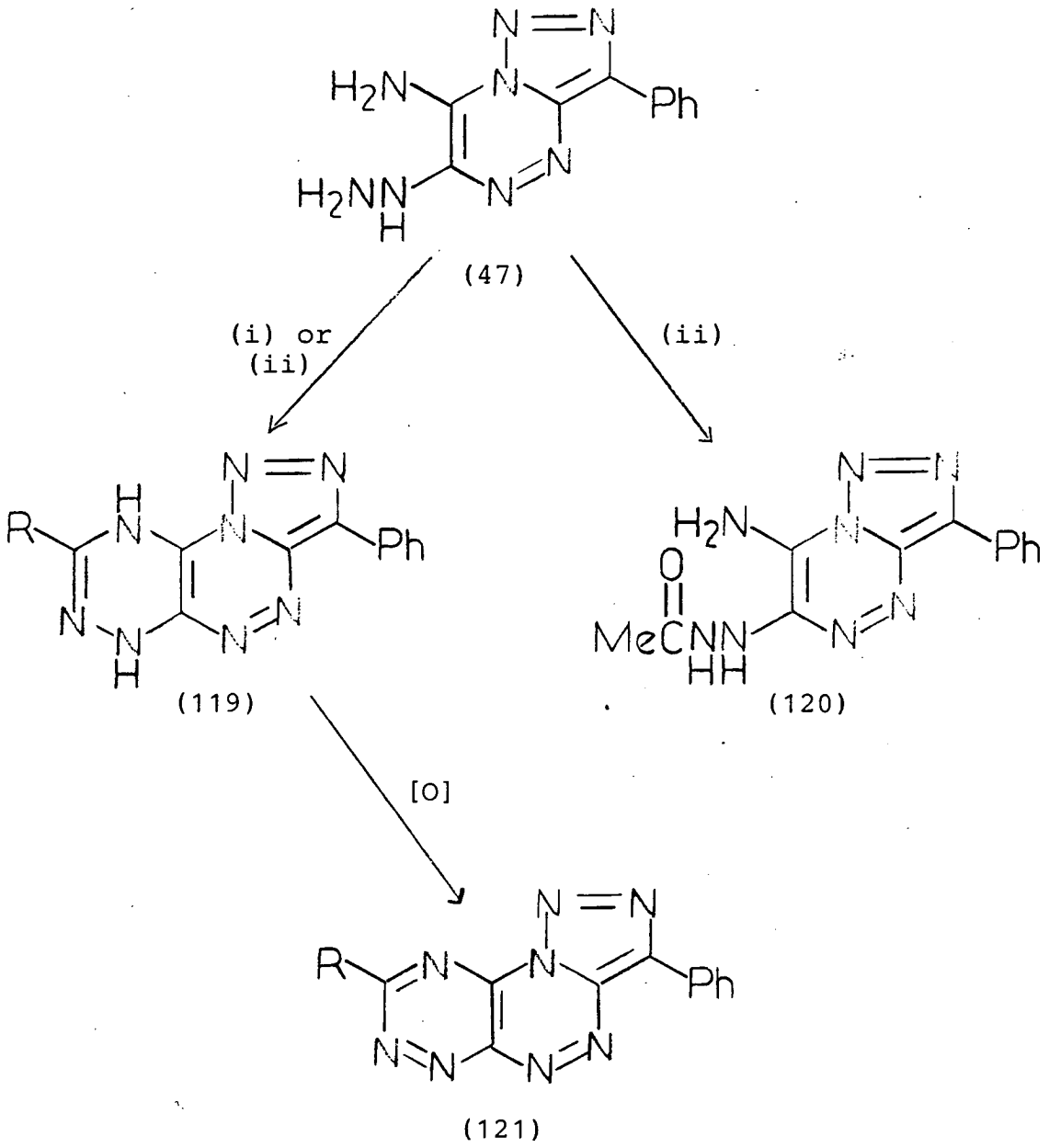
(v) HX (X = H, OH, OCR (with O), Cl, Br)

Scheme 29

derivative (112) being obtained. This product (112) showed spectroscopic properties and exhibit the correct analytical data for the illustrated structure. In particular, the ^{1}H n.m.r. spectrum gave resonances for five aromatic hydrogen atoms and exhibited signals for five exchangeable protons.

The structure of this product (112) is further supported by its hydrolysis with hydrochloric acid to afford a quantitative yield of the aminotriazole derivative (105). Disappointingly however its attempted acylation with acetic anhydride afforded no identifiable products.

In an attempt to synthesise (Scheme 29) the 2,6-diazapteridine derivatives (118) the benzoyl triazolotriazine derivative (84) was reacted with hydrazine monohydrate and tosylhydrazine in anticipation of forming the hydrazone derivatives (114) and (115) respectively. These hydrazones were subsequently expected to diazotatively cyclise to give the tricyclic system (117) through the intermediacy of the diazo species (116). This tricyclic derivative (117) in turn was expected to yield the 2,6-diazapteridine derivatives (118) on acid catalysed cleavage of the fused bridgehead triazole. However, in practice reaction of the triazolotriazine (84) with hydrazine monohydrate or tosylhydrazine failed to afford the desired hydrazones (114) and (115), good yields of the unreacted triazolotriazine (84) being recovered in both cases.



R

a; H

b; Me

(i) $HC(OEt)_3$, heat

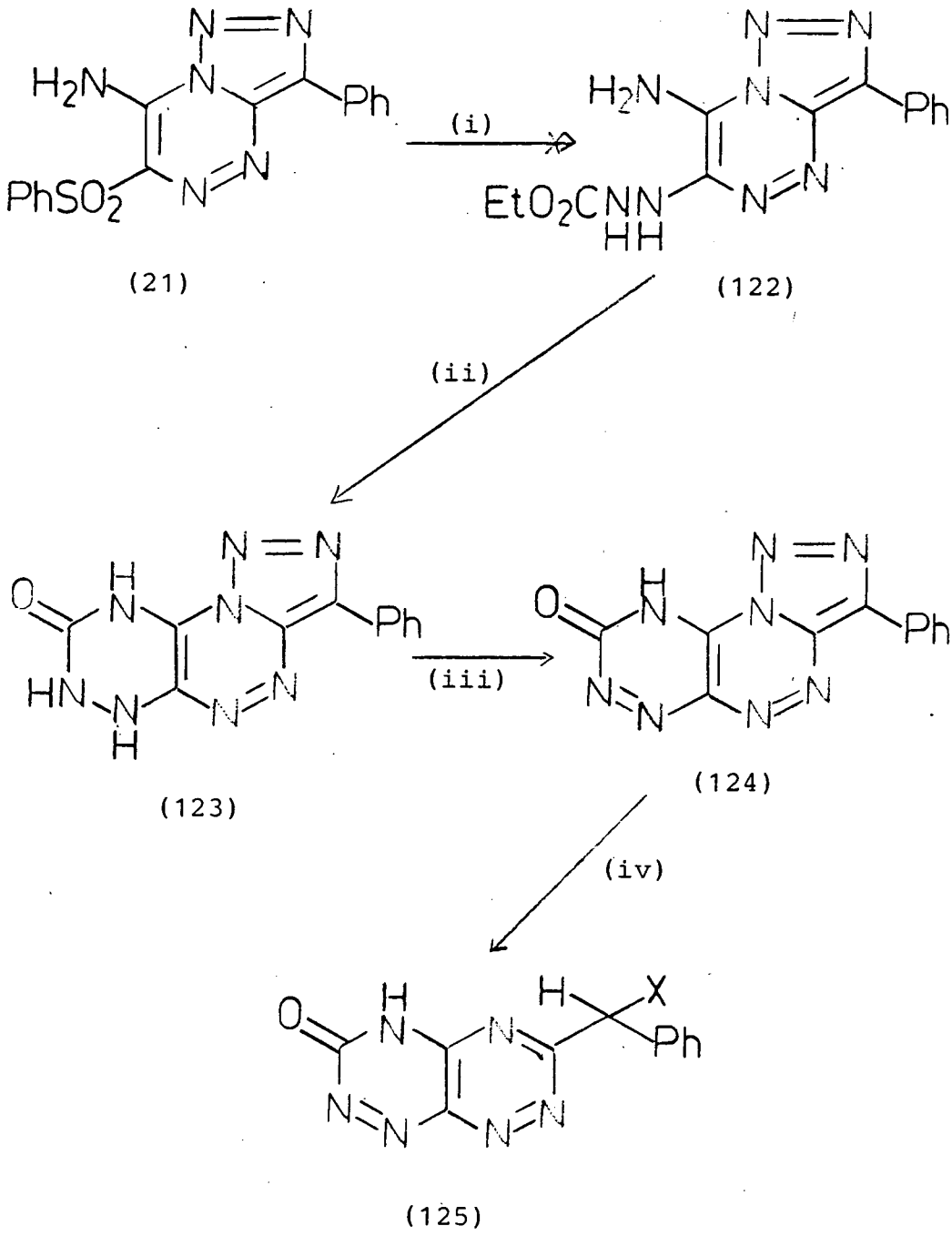
(ii) AC_2O, heat

Scheme 30

4.4 Investigation of 7-Amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine Derivatives as Synthetic Precursors of 4,6-Diazapteridines

As has been described in the introduction to this chapter (see Scheme 4) 4,6-diazapteridines were anticipated to be available by the annulation of 7-amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47) and the subsequent acid catalysed cleavage of the resulting tricyclic system. In pursuing this strategy (Scheme 30) 7-amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47), whose synthesis was described earlier (see Scheme 13) was heated with triethyl orthoformate in anticipation of forming the tricyclic system (119a) which by oxidation would lead to the key intermediate (121a). However in practice reaction of the triazolotriazine (47) with triethylorthoformate gave a moderate yield of the unreacted triazolotriazine (47) and an intractable gum.

The reaction of the triazolotriazine (47) with acetic anhydride failed to give the expected annulated product (119b) a good yield of the acetyl derivative (120) being obtained. This product (120) gave analytical data and showed spectroscopic properties consistent with the assigned structure. In particular the i.r. spectrum of the product (120) contains absorptions for NH and a carbonyl band at 1645 cm^{-1} characteristic of an amide. The ^1H n.m.r. spectrum exhibits resonances for five aromatic hydrogen atoms, a signal for a methyl group and four exchangeable protons.



(i) EtO_2CNHCN_2, dioxane, heat

(ii) heat

(iii) [O]

(iv) HX (X = H, OH, $O\overset{O}{\overset{\|}{C}}R$, Cl, Br)

Scheme 31

The failure of the transformation [Scheme 30; (47)→(119)] prompted the investigation (Scheme 31) of the displacement of the benzenesulphonyl moiety from the triazolotriazine (21) with ethyl carbazate. This was expected to yield the triazolotriazine derivative (122) which was anticipated would readily cyclise to the tricyclic system (123) which on subsequent oxidation and acid catalysed scission of the fused bridgehead triazole was expected to give the 4,6-diazapteridine (125). However, in practice, reaction of the benzenesulphonyltriazolotriazine (21) with ethyl carbazate gave a small amount of the unreacted triazolotriazine (21) and a series of intractable gums and solids.

4.5 EXPERIMENTAL

Benzenesulphonylacetonitrile (19)[122]

Benzenesulphonylacetonitrile (19) was prepared as described in Chapter 2.

Benzoylacetonitrile (81)[105]

Benzoylacetonitrile (81) was prepared as described in Chapter 2.

Benzylazide[199]

Benzylazide was prepared (yield 90%) by the reaction of benzyl chloride and sodium azide as described by Curtius and Erhart.[199]

5-Amino-1-benzyl-4-phenyl-1H-1,2,3-triazole[200]

5-Amino-1-benzyl-4-phenyl-1H-1,2,3-triazole was prepared (yield 90%) by the reaction of benzylazide and benzylacetonitrile as described by Day and Hoover[200] and had m.p. 151-153° (lit.,[200] 155°).

4-Amino-5-phenyl-1H-1,2,3-triazole (105)[198]

4-Amino-5-phenyl-1H-1,2,3-triazole (105) was prepared (yield 90%) by the reaction of 5-amino-1-benzyl-4-phenyl-1H-1,2,3-triazole with sodium in the presence of liquid ammonia as described by Sutherland and Tennant[198] and had m.p. 118-121° (lit.,[198] 124).

4-Phenyl-1H-1,2,3-triazole-5-diazonium Betaine (20)[182]

4-Phenyl-1H-1,2,3-triazole-5-diazonium betaine (20) was prepared (yield quant.) by the treatment of 4-amino-5-phenyl-1H-1,2,3-triazole with aqueous sodium nitrite in the presence of aqueous 2M sulphuric acid as described by Barnes and Tennant[182] and had m.p. 115-117° (lit.,[182] 126°).

7-Amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (21)[182]

A solution of 4-phenyl-1H-1,2,3-triazole-5-diazonium betaine (21) (9.9 g, 0.06 mol) in ethanol (75.0 ml) and water (75.0 ml) was added in small portions to a stirred solution of benzenesulphonylacetonitrile (19) (10.9 g, 0.06 mol) and anhydrous sodium acetate (7.5 g, 0.09 mol) in ethanol (200 ml) and water (100 ml) at 0-5° (ice-salt bath) and the mixture was stirred in the ice-salt bath for a further 1 h., then at room temperature for a further 2 h. The mixture was evaporated and the residue treated with water to yield 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (19.5 g; 94%), m.p. 203-205° (lit.,[182] 205°), ν_{max} 3450 and 3350 (NH) cm^{-1}, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 7-Amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) with Aqueous Ammonia

A solution of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (0.70 g, 0.002 mol) in anhydrous dioxane (40.0 ml) was treated in one portion with concentrated aqueous ammonia (S.Gr. 0.88) (0.40 g, 0.008 mol) and the mixture was stirred at room temperature for 3 h. after which time further concentrated aqueous ammonia (S.Gr. 0.88) (0.40 g, 0.008 mol) was added. The flask was then stoppered and left at room temperature for 17 h. The mixture was evaporated and the resulting gum was triturated with toluene to afford a dark solid (0.70 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethyl acetate (1:1) yielded the unreacted triazolotriazine (21) (0.06 g; 9%) m.p. 192-196°, identical (m.p. and i.r. spectrum) to an authentic sample.

Further elution with cyclohexane - ethyl acetate (1:1) through to ethanol yielded a series of solids (total, 0.47 g) whose t.l.c. in ethyl acetate showed them to be complex mixtures which were not further investigated.

6,7-Diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22)

The triazolotriazine (21) (0.70 g, 0.002 mol) was added in portions to liquid ammonia at -72° (acetone-solid CO_2 bath) so that the ammonia did not boil and the resulting mixture was stirred in the acetone-CO_2 bath for 1 h., then left to evaporate at room temperature for 17 h. The residue was treated with water (20.0 ml) and filtered to afford 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22), (0.43 g; 95%), m.p. 268-269° (from ethanol), ν_{max} 3400, 3320, 3240 and 3180 (NH) cm^{-1}.

Found: C, 52.8; H, 4.1; N, 43.0%; M^+, 227.

$C_{10}H_9N_7$ requires: C, 52.9; H, 4.0; N, 43.2%; M, 227.

The Reaction of 7-Amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) with Benzylamine in Ethanol

A solution of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (1.4 g, 0.004 mol) in ethanol (40.0 ml) was treated with benzylamine (0.43 g, 0.004 mol) and the mixture was heated under reflux for 1 h. The mixture was evaporated and the residue was triturated with toluene-light petroleum to afford a dark solid (1.5 g). This was treated with aqueous 2M sodium hydroxide solution (30.0 ml) and extracted with methylene chloride to give a red solid (0.67 g) which was crystallised from toluene-light petroleum to afford 7-amino-6-ethoxy-3-phenyl-1,2,3-

triazolo[5,1-c]-1,2,4-triazine (26), (0.34 g; 33%), m.p. 192-194°, ν_{max} 3480 and 3370 (NH) cm^{-1}, δ [$(CD_3)_2SO$] 8.22-7.26 (5H, m, ArH), 4.51 (2H, q, J8Hz CH_2CH_3), 3.74 (2H, brs, NH) and 1.53 (3H, t, J8Hz CH_2CH_3).

Found: 256.1073

$C_{12}H_{12}N_6O$ requires: 256.1073

The original toluene filtrate was evaporated to afford a dark intractable gum (0.3 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

The aqueous alkaline mother liquor was neutralised with aqueous 2M hydrochloric acid and constantly extracted with methylene chloride for 24 h. to afford a red gum (0.35 g) which was subject to flash chromatography.

Elution with ethyl acetate through to ethanol yielded only a series of solids and gums (total 0.25 g) whose t.l.c. in methylene chloride showed them to be complex mixtures which were not further investigated.

The Attempted Reaction of 7-Amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) with Benzylamine in Dioxane

A solution of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (0.70 g; 0.002 mol) in anhydrous dioxane was treated with benzylamine (0.21 g, 0.002 mol) and the mixture was stirred at room temperature

for 4 h. then heated at 50° for a further 17 h. The mixture was filtered to remove a small amount of orange residue and the filtrate was evaporated to afford a red solid (1.0 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethyl acetate (2:1) gave the unreacted triazolotriazine (21) (0.16 g; 23%), m.p. 198-202°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethyl acetate-cyclohexane (1:1) through to ethanol gave a series of intractable brown solids (total, 0.47 g) whose t.l.c. in methylene chloride showed them to be complex mixtures which were not further investigated.

The Attempted Reaction of 7-Amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) with Pyrrolidine in Butan-1-ol

A solution of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (0.70 g, 0.002 mol) in butan-1-ol (10.0 ml) was treated with pyrrolidine (0.14 g, 0.002 mol) and the mixture was heated under reflux for 0.5 h. The mixture was evaporated to give a brown gum whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 6,7-Diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with Triethyl Orthoformate

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol) in triethyl orthoformate (5.0 ml) was heated under reflux for 24 h. The mixture was evaporated to give the unreacted diamino-triazolotriazine (22) (0.45 g, quant.), m.p. 260-265°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of 6,7-Diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with Acetic Anhydride

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol), in acetic anhydride (5.0 ml) was heated under reflux for 3 h. The mixture was evaporated to give an intractable brown solid (0.59 g) from which no identifiable material could be obtained.

The Attempted Reaction of 6,7-Diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22) with Dimethyl Sulphate in the Presence of Potassium Carbonate

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol) in acetone (50.0 ml) was treated with anhydrous potassium carbonate (1.5 g) and dimethyl sulphate (1.0 ml) and the mixture was heated under reflux with exclusion of atmospheric moisture

for 4 h. The mixture was evaporated and the residue treated with water. The resulting solution was neutralised by addition of aqueous 2M hydrochloric acid to give an oily suspension which was extracted with methylene chloride to yield a dark gum (0.70 g). This was subjected to flash chromatography with methylene chloride through to ethanol to give a series of gums (total, 0.59 g) none of which were further investigated.

The Attempted Reaction of 6,7-Diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with Acetyl Chloride in the Presence of Triethylamine

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol) in 1,2-dimethoxyethane (20.0 ml) was treated in one portion with triethylamine (0.23 g, 0.0022 mol) then dropwise with acetyl chloride (0.17 g, 0.0022 mol) and the mixture was stirred at room temperature for 4 h. The mixture was filtered and the colourless solid was washed with water to remove triethylamine hydrochloride and combined with further material obtained by evaporating the dimethoxyethane filtrate and triturating the resulting gum with ethanol to yield the unreacted diamino-triazolotriazine (22) (total 0.28 g; 52%), m.p. 265-270°, identical (m,p. and i.r. spectrum) to an authentic sample.

The ethanol filtrate was evaporated to give a brown gum (0.25 g) whose t.l.c. in ethyl acetate showed it to

be a complex mixture containing the starting diamino-triazolotriazine (22) which was not further investigated.

The Attempted Reaction of 6,7-Diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with Tosyl Isocyanate

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol) in anhydrous dioxane (10.0 ml) was treated with a solution of tosyl isocyanate (0.43 g, 0.0022 mol) in anhydrous dioxane (5.0 ml) and the mixture was stirred with exclusion of atmospheric moisture at room temperature for 1 h. The mixture was filtered to afford the unreacted diaminotriazolotriazine (22) (0.44 g; 98%), m.p. 258-265°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 6,7-Diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with Cyanogen Bromide

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol) in methanol (10.0 ml) was stirred at room temperature and treated dropwise with a solution of cyanogen bromide (0.53 g, 0.005 mol) in methanol (5.0 ml) and the mixture was stirred at room temperature for 15 min. then heated under reflux for a further 4 h. The mixture was evaporated and the residue treated with aqueous 1M sodium hydroxide solution (2.0 ml) to afford the diaminotriazolotriazine (22) (0.37 g; 87%), m.p. 260-265°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The aqueous mother liquor was neutralised with aqueous 2M hydrochloride acid to give only a small amount of dark solid (0.05 g) which was not further investigated.

Extraction of the neutral aqueous filtrate with methylene chloride yielded no further material.

The Reaction of 6,7-Diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with Glacial Acetic Acid

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol) in glacial acetic acid (50.0 ml) was heated under reflux for 24 h. The mixture was evaporated to give a dark gum (0.46 g) which was subjected to flash chromatography.

Elution with ethyl acetate yielded 2-(α-acetoxybenzyl)-5-amino-1,2,4-triazin-6(1H)-one (36), (0.05 g; 10%), m.p. 249-250° (ethanol-light petroleum), ν_{max} 3380 and 3160 (NH), 1740 and 1680 (CO) and 1635 (C=N) cm^{-1}, δ [$(CD_3)_2SO$] 12.56 (1H, brs, NH), 8.16 (1H, brs, NH), 7.77 (1H, brs, NH), 7.41-7.31 (5H, m, ArH), 6.27 (1H, s, CH) and 2.10 (3H, s, CH_3).

Found: C, 55.6; H, 4.6; N, 21.6%; M^+, 259.

$C_{12}H_{11}N_4O$ requires: C, 55.5; H, 4.6; N, 21.3%; M, 259.

Further elution with ethanol gave an intractable brown gum (0.32 g) from which no identifiable material could be obtained.

The Attempted Reaction of 6,7-Diamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with Sodium Nitrite in the Presence of Aqueous Hydrochloric Acid

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol) in glacial acetic acid (10.0 ml) was treated with 10% aqueous hydrochloric acid (5.0 ml). The solution was cooled to 0° (ice-salt bath) and further treated with stirring with a solution of sodium nitrite (0.17 g, 0.0025 mol) in water (1.0 ml) and the mixture was then stirred at 0° (ice-salt bath) for 1h. The mixture was evaporated and the residue treated with water and filtered to afford the unreacted diaminotriazolotriazine (22) (0.45 g; quant.) m.p. 260-265° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 6,7-Diamino3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (22) with Glyoxal

A solution of 6,7-diamino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (22) (0.45 g, 0.002 mol) in ethanol (10.0 ml) was treated with a 40% ethanolic solution of glyoxal (0.32 g) and the mixture was heated under reflux for 1 h. The mixture was evaporated to give a brown gum which was triturated with toluene to give the unreacted triazolotriazine (22) (0.45 g; quant.), m.p. 200-203°, identical (m.p. and i.r. spectrum) to a sample prepared before.

7-Amino-6-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (40) and 6-Amino-7-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (51)

(a) A solution of 7-amino-6-phenylsulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (7.0 g, 0.02 mol) in dioxane (100 ml) was treated with a solution of sodium azide (5.2 g, 0.08 mol) in water (20.0 ml) and the mixture was stirred at room temperature for 1 h. The mixture was filtered to afford 7-amino-6-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (40) (5.1 g; quant.), m.p. 175° (explosive decomp.), ν_{max} 3310, 3230 and 3180 (NH) and 2140 (N_3) cm^{-1}, which was converted by crystallisation from dimethylformamide-water into 6-amino-7-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (51), m.p. 200° (decomp.), ν_{max} 3350 and 3190 (NH) and 2080 (N_3) cm^{-1}.

Found: 253.0815

$C_{10}H_7N_9$ requires: 253.0824

(b) A solution of 7-amino-6-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (40) (0.26 g, 0.001 mol) in dimethylformamide (5.0 ml) was heated for 5 min. The solid which separated from the filtrate on cooling was collected to afford 6-amino-7-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (51) (0.23g; 92%), m.p. 200°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

(c) A suspension of 7-amino-6-hydrozino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47) (0.48 g, 0.002 mol) in concentrated nitric acid (S.Gr. 1.42) (0.4 ml) and water (1.5 ml) was treated dropwise with stirring at 0° (ice-salt bath) with a solution of sodium nitrite (0.12 g, 0.004 mol) in water (4.0 ml). The resulting suspension was stirred at 0° (ice-salt bath) for 15 min. then filtered to yield 6-amino-7-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (51) (0.47 g; 96%), m.p. 190-195° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

7-Amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47)[182]

A solution of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (1.4 g, 0.004 mol) in anhydrous dioxane (40.0 ml) was treated with hydrazine monohydrate (0.80 g, 0.016 mol) and the mixture was stirred at room temperature for 0.5 h. The mixture was evaporated and the residue treated with aqueous 2M sodium hydroxide and the solution neutralised with aqueous 2M hydrochloric acid and then filtered to yield 7-amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47) (0.63 g, 66%), m.p. 250-253° (from dimethylformamide-water) (lit.,[182] 252-255°), ν_{max} 3430, 3280, 3200 and 3100 (NH) and 1660 (C=N) cm^{-1}, identical (m.p. and i.r. spectrum) to an authentic sample.

The aqueous filtrate was extracted with methylene chloride to give a red gum (0.40 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

6-Amino-3-phenyl-7-(triphenylphosphorarylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52)

(a) A solution of 6-amino-7-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (51) (0.25 g, 0.001 mol) in anhydrous dimethylformamide (20.0 ml) was mixed with a solution of triphenylphosphine (0.26 g, 0.001 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was left stoppered at room temperature for 0.5 h. then heated at 60° for 1 h. The mixture was evaporated to give a (0.72 g) which was subjected to flash chromatography.

Elution with ethyl acetate gave a small amount of an unidentified yellow solid (0.07 g), m.p. 200° (decomp.), ν_{max} 3420 and 3215 (NH) cm^{-1}, followed by 6-amino-3-phenyl-7-(triphenylphosphorarylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) (0.42 g; 84%), m.p. 260° (decomp.), (from dimethylformamide), ν_{max} 3420 and 3300 (NH) cm^{-1}, δ_C [$(CD_3)_2SO$] 150.88 (quat), 150.49 (quat), 146.79 (quat), 146.66 (quat), 137.29 (quat), 132.95, 132.76, 132.30, 131.38 (quat), 129.12, 128.87, 128.33, 128.12, 127.48 (quat), 126.06, 125.47 (quat), 125.23 and 124.24, δ_P [$(CD_3)_2SO$] 18.43 (P=N).

Found: C, 69.6; H, 4.6; N, 20.2%; M^+, 487.

$C_{28}H_{22}N_7P$ requires: C, 69.3; H, 4.5; N, 20.1%; M, 487.

Final elution with ethanol gave only a small amount of brown gum (0.04 g) which was not further investigated.

(b) A solution of 7-amino-6-azido-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (40) (0.51 g, 0.002 mol) in anhydrous dimethylformamide (20.0 ml) was treated with a solution of triphenylphosphine (0.50 g, 0.002 mol) in anhydrous dimethylformamide (5.0 ml) and the mixture was left stoppered at room temperature for 0.5 h., then heated at 60° for 1 h. The mixture was evaporated to afford 6-amino-3-phenyl-7-(triphenylphosphoranylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) (0.99 g; quant.), m.p. 263-264°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

The Attempted Reaction of 6-Amino-3-phenyl-7-(triphenylphosphorarylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) with Benzaldehyde

(a) A solution of 6-amino-3-phenyl-7-(triphenylphosphorarylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) (0.73 g, 0.0015 mol) in anhydrous dimethylformamide (15.0 ml) was treated with freshly distilled benzaldehyde (0.16 g, 0.0015 mol) and the mixture was heated under reflux for 1 h. The mixture was evaporated to give a buff solid (0.72 g) which was subjected to flash chromatography.

Elution with ethyl acetate-cyclohexane (1:1) gave a small amount of an unidentified yellow solid which was not further investigated.

Further elution with ethanol gave the unreacted triazolotriazine derivative (52) (0.45 g; 60%), m.p. 250-255° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared before.

(b) An intimate mixture of 6-amino-3-phenyl-7-(triphenylphosphorarylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) (0.98 g, 0.002 mol) and benzaldehyde (0.21 g, 0.002 mol) was heated under reduced pressure at 180°/2 mm Hg (Woods metal bath) and the resulting solution was maintained at this temperature and pressure for 15 min. The mixture was cooled to afford a dark gum whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a complex mixture containing the unreacted phosphorarylideneiminotriazolotriazine (52) which was not further investigated.

The Attempted Reaction of 6-Amino-3-phenyl-7-(triphenylphosphorarylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) with Benzoyl Chloride

A solution of 6-amino-3-phenyl-7-(triphenylphosphorarylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) (0.98 g, 0.002 mol) in anhydrous dimethylformamide (20.0 ml) was treated with benzoyl chloride (0.29 g, 0.002 mol) and the mixture was stirred with the exclusion of atmospheric

moisture at room temperature for 17 h. The mixture was evaporated to afford the unreacted triphenylphosphoraryl-ideneiminotriazolotriazine (52) (0.98 g; quant.), m.p. 256-259 (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 6-Amino-3-phenyl-7-(triphenyl-phosphorarylideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) with Phenyl Isocyanate

A solution of 6-amino-3-phenyl-7-(triphenylphosphoraryl-ideneimino)-1,2,3-triazolo[5,1-c]-1,2,4-triazine (52) (0.98 g, 0.002 mol) in anhydrous dimethylformamide (20.0 ml) was treated with phenyl isocyanate (0.23 g, 0.002 mol) and the mixture was stirred at room temperature for 17 h. The mixture was evaporated to give the unreacted triphenyl-phosphorarylideneiminotriazolotriazine (52) (0.98 g, quant.), m.p. 256-259° (decomp.), identical (m.p. and i.r. spectrum) to a sample prepared before.

6-(α-Acetoxybenzyl)-4-amino-tetrazolo[5,1-f]-1,2,4-triazine (58)

A solution of 7-amino-6-azido-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (40) (2.2 g, 0.008 mol) in glacial acetic acid (10.0 ml) was heated under reflux for 24 h. The mixture was evaporated and the resulting gum triturated with light petroleum (b.p. 40-60°) to give 6-(α-acetoxy-benzyl)-4-aminotetrazolo[5,1-f]-1,2,4-triazine (58)

(2.1 g; 93%) which formed colourless crystals, m.p. 187-188° [from light petroleum (b.p. 80-100°)], ν_{max} 3380, 3320 and 3160 (NH), 1730 (CO) and 1660 (C=N) cm^{-1}, δ_H ($CDCl_3$) 7.60-7.35 (5H, m, ArH), 7.25 (1H, brs, NH), 6.62 (1H, s, CH), 6.30 (1H, brs, NH) and 2.25 (3H, s, CH_3), δ_C [$(CD_3)_2SO$], 169.63 (quat), 161.70 (quat), 153.72 (quat), 136.49 (quat), 134.60 (quat), 128.67, 128.47, 127.90, 75.57 (CH_3) and 20.71 (CH).

Found: C, 50.8; H, 3.9; N, 34.5%; M^+, 285.

$C_{12}H_{11}N_7O_2$ requires: C, 50.5; H, 3.9; N, 34.4%; M, 285.

4-Amino-6-(α-hydroxybenzyl)tetrazolo[5,1-f]-1,2,4-triazine (60)

(a) A solution of 6-(α-acetoxybenzyl)-4-amino-tetrazolo[5,1-f]-1,2,4-triazine (58) (0.60 g, 0.002 mol) in ethanol (10.0 ml) was treated with aqueous 1M sodium carbonate solution (5.0 ml) and the mixture was heated under reflux for 0.5 h. The mixture was evaporated and the residue treated with water to afford 4-amino-6-(α-hydroxy-benzyl)-tetrazolo[5,1-f]-1,2,4-triazine (60) (0.16 g; 29%) which formed colourless crystals, m.p. 235-236° (from glacial acetic acid) ν_{max} 3370, 3300, 3240 and 3180 (NH, OH), δ_H [$(CD_3)_2SO$] 9.26 (2H, brs, NH), 7.56-7.25 (5H, m, ArH), 6.10 (1H, brs, CH) and 5.65 (1H, brs, OH), δ_C [$(CD_3)_2SO$] 165.56 (quat), 153.50 (quat), 141.64 (quat), 134.37 (quat), 127.93, 127.36, 126.85 and 74.23 (CH).

Found: C, 47.5; H, 3.8; N, %; M^+, 202.

$C_{10}H_9N_7O.\frac{1}{2}H_2O$ requires: C, 47.6; H, 4.0; N, %; M $-\frac{1}{2}H_2O$, 243

Neutralisation of the aqueous mother liquor with aqueous 2M hydrochloric acid followed by constant extraction with methylene chloride yielded no further material.

(b) A solution of 6-(α-acetoxybenzyl)-4-amino-tetrazolo[5,1-f]-1,2,4-triazine (58) (0.60 g, 0.002 mol) in ethanol (10.0 ml) was treated with aqueous 2M hydrochloric acid (5.0 ml) and the mixture was heated under reflux for 0.5 h. The mixture was evaporated and the residue treated with water to give a buff solid (0.48 g) which was hot filtered from methanol to afford 4-amino-6-(α-hydroxybenzyl)-tetrazolo[5,1-f]-1,2,4-triazine (60) (0.12 g; 22%), m.p. 230-235°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

The methanolic filtrate was evaporated to yield the unreacted tetrazolotriazine derivative (58) (0.34 g; 53%) m.p. 180-185°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Neutralisation of the aqueous mother liquor with solid anhydrous sodium acetate and extraction with methylene chloride afforded no further material.

6-(α-Hydroxybenzyl)tetrazolo[5,1-f]-1,2,4-triazin-4(5H)-one (61)

A solution of 6-(α-acetoxybenzyl)tetrazolo[5,1-f]-1,2,4-triazin-4(5H)-one (58) (1.3 g, 0.004 mol) in ethanol (20.0 ml) was treated with aqueous 2M hydrochloric acid and the mixture was heated under reflux for 2 h. The mixture was evaporated to afford 6-(α-hydroxybenzyl)-tetrazolo[5,1-f]-1,2,4-triazine-4(5H)-one (61) as a buff solid (0.96 g, 98%), m.p. 226-227° (from dimethylformamide-water), ν_{max} 3450 and 3130 (NH, OH) and 1750 (CO) cm^{-1}, δ_H [$(CD_3)_2SO$] 7.60-7.28 (5H, m, ArH), 6.80 (1H, brs, NH or OH), 5.70 (1H, s, CH) and 3.30 (1H, brs, OH or NH), δ_C [$(CD_3)_2SO$] 157.63 (quat), 151.65 (quat), 141.21 (quat), 139.32 (quat), 128.12, 126.96 and 71.27 (CH).

Found: C, 49.0; H, 3.3; N, 34.1%; M^+, 244.

$C_{10}H_8N_6O_2$ requires: C, 49.2; H, 3.3; N, 34.4%; M, 244.

7-Amino-3-phenyl-6H-1,2,3-triazolo[5,1-g]imidazo[4,5-c]-1,2,4-triazine (24)

(a) A solution of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (7.0 g, 0.02 mol) in dioxane (100 ml) was treated with a solution of sodium cyanamide (5.1 g, 0.08 mol) in water (20.0 ml) and the mixture was stirred at room temperature for 6 h. The mixture was evaporated and the residue was treated with water (50.0 ml) acidified with aqueous 2M hydrochloric

acid. The precipitated yellow solid was collected, heated under reflux in ethanol (100 ml) for 15 min., and the solid obtained on cooling, collected to afford 7-amino-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (24) (3.1 g; 70%) which formed yellow crystals, m.p. >350° (from dimethylsulphoxide-water) ν_{max} 3320 (NH) and 1695 (C=N) cm^{-1}, δ_C [$(CD_3)_2SO$] 164.89 (quat), 150.53 (quat), 149.86 (quat), 132.07 (quat), 131.47 (quat), 130.75 (quat), 128.57, 126.93, 124.70.

Found: C, 52.1; H, 3.3; N, 44.5%; M^+-CN, 226.

$C_{11}H_8N_8$ requires: C, 52.4; H, 3.2; N, 44.4%; M, 252.

The ethanolic filtrate was evaporated to give a brown gum (0.3 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

(b) A solution of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (0.70 g, 0.002 mol) in dioxane (10.0 ml) was treated with a solution of sodium cyanamide (0.51 g, 0.008 mol) in water (5.0 ml) and the mixture was stirred at room temperature for 4 h. The mixture was evaporated and the residue treated with water (20.0 ml). The mixture was filtered and the resulting buff solid was slurried with aqueous 2M hydrochloric acid to yield a small amount of 7-amino-6-cyanoamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (62) (0.06 g, 12%),

m.p. 260° (decomp.), ν_{max} 3460, 3430 and 3215 (NH) and 2145 (CN) cm^{-1}, m/e 252.

This small amount of 7-amino-6-cyanoamino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (62) was converted on crystallisation to 7-amino-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (24) which was combined with further material obtained by acidifying the alkaline filtrate with aqueous 2M hydrochloric acid and treating the yellow solid obtained with aqueous saturated sodium hydrogen carbonate and subsequently heating the obtained solid in dimethylformamide, (total 0.34 g; 67%), m.p. >350°, identical (m.p. and i.r. spectrum) to a sample prepared in (a) before.

7-Amino-6-methyl-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (63a)

A suspension of 7-amino-3-phenyl-6H-1,2,3-triazolo-[5,1-g]imidazo[4,5-c]-1,2,4-triazine (24) (0.50 g, 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was treated with a suspension of sodium hydride (0.05 g, 0.0022 mol) in anhydrous dimethylformamide (2.0 ml) and the mixture was stirred at room temperature for 15 min. then treated with methyl iodide (0.28 g, 0.002 mol) and stirring was continued at room temperature for 17 h. Dilution with water (15.0 ml) gave a yellow solid which was collected to give 7-amino-6-methyl-3-phenyl-6H-1,2,3-triazolo[5,1-g]imidazo[4,5-c]-1,2,4-triazine (63a), which formed yellow crystals, (0.35 g;

66%), m.p. >350° (from dimethylformamide), ν_{max} 3600-3000 (NH) and 1695 and 1640 (C=N) cm^{-1}, δ_H [$(CD_3)_2SO$] 8.74 (2H, brs, NH), 8.28-7.31 (5H, m, ArH), and 3.55 (3H, s, NCH_3), δ_C [$(CD_3)_2SO$] 164.7 (quat), 152.41 (quat), 145.73 (quat), 131.25 (quat), 131.11 (quat), 130.92 (quat), 128.56, 127.03, 124.67 and 27.43 (NCH_3).

Found: C, 50.4; H, 3.9; N, 40.2%; M^+, 266.

$C_{12}H_{10}N_8.H_2O$ requires: C, 50.7; H, 4.2; N, 39.4%; $M-H_2O$, 266.

The aqueous dimethylformamide mother liquor was neutralised by addition of aqueous 2M hydrochloric acid and the resulting solution extracted with methylene chloride to give a brown gum (0.10 g) whose t.l.c. in methylene chlorate showed it to be complex mixture which was not further investigated.

7-Amino-6-benzyl-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (63b)

A suspension of 7-amino-3-phenyl-6H-1,2,3-triazolo-[5,1-g]imidazo[4,5-c]-1,2,4-triazine (24) (0.50 g, 0.002 mol) in anhydrous dimethylformamide (10.0 ml) was treated with a suspension of sodium hydride (0.05 g, 0.0022 mol) in anhydrous dimethylformamide (2.0 ml) and the mixture was stirred at room temperature for 15 min. and then heated with benzyl chloride (0.36 g, 0.0028 mol) and stirring was continued at room temperature for 17 h. Dilution with water (15.0 ml) gave a yellow solid which was collected

to give 7-amino-6-benzyl-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (63b), which formed yellow crystals, (0.45 g; 66%), m.p. >350° (from dimethylformamide), ν_{max} 3430 (NH) and 1675 (C=N), δ_H [$(CD_3)_2SO$] 8.95 (1H, brs, NH), 8.21 (2H, s, CH_2) 7.49-7.32 (10H, m, ArH) and 5.31 (1H, brs, NH), δ_C [$(CD_3)_2SO$] 163.90 quat), 152.23 (quat), 145.42 (quat), 134.91 (quat), 131.16 (quat), 131.10 (quat), 128.59, 128.49, 127.70, 127.46, 127.09, 124.67 and 43.98 (CH_2).

Found: C, 60.2; H, 4.4; N, 30.7%; M^+, 342.
$C_{18}H_{14}N_8H_2O$ requires: C, 60.0; H, 4.4; N, 31.3%; M-H_2O, 342.

The aqueous dimethylformamide mother liquor was neutralised by addition of aqueous 2M hydrochloric acid and the resulting solution extracted with methylene chloride to give a brown gum (0.05 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 7-Amino-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo-[4,5-c]-1,2,4-triazine (24) with Benzoyl Chloride in the Presence of Aqueous Sodium Hydroxide

A suspension of 7-amino-3-phenyl-6H-1,2,3-triazolo-[5,1-g]imidazo[4,5-c]-1,2,4-triazine (24) (0.50 g, 0.002 mol) in 10% w/v aqueous sodium hydroxide (10.0 ml) was treated dropwise with stirring with benzoyl chloride (0.36 g, 0.002 mol) at room temperature. The mixture was then stirred at

room temperature for 2 h. and filtered to afford a yellow solid which was treated with hot water and recollected to give a yellow solid which on acidification with aqueous 2M hydrochloric acid gave an orange solid (0.26 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

The alkaline hot water washings were acidified with aqueous 2M hydrochloric acid to afford the unreacted triazoloimidazotriazine (24) (0.22 g; 44%), m.p. >350°, identical (m.p. and i.r. spectrum) to an authentic sample.

The original alkaline filtrate on treatment with aqueous 2M hydrochloric acid afforded benzoic acid (0.25 g, quant.), m.p. 210-215°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 7-Amino-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (24) with Aqueous Potassium Hydroxide

A suspension of 7-amino-3-phenyl-6H-1,2,3-triazolo-[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (24) (0.50 g, 0.002 mol) in 2-ethoxyethanol (30.0 ml) was treated with aqueous 20% potassium hydroxide solution (10.0 ml) and the resulting solution was heated under reflux for 8 h. The mixture was evaporated and the residue was treated with water (10.0 ml). The resulting solution was acidified with

aqueous 2M hydrochloric acid to afford the unreacted triazoloimidazotriazine (24) (0.35 g; 70%), m.p. >350° identical (m.p. and i.r. spectrum) to a sample prepared before.

Extraction of the acidic mother liquor with methylene chloride afforded no further material.

The Attempted Reaction of 7-Amino-3-phenyl-6H-1,2,3-triazolo[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (24) with Trifluoroacetic Acid

A solution of 7-amino-3-phenyl-6H-1,2,3-triazolo-[5,1-g]-imidazo[4,5-c]-1,2,4-triazine (24) (0.25 g, 0.001 mol) was heated under reflux for 24 h. The mixture was evaporated to give unreacted triazoloimidazotriazine (24) (0.25 g; quant.), m.p. >350°, identical (m.p. and i.r. spectrum) to a sample prepared before.

7-Amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66)[180]

A solution of 4-phenyl-1H-1,2,3-triazole-5-diazonium betaine (20) (6.6 g, 0.04 mol) in ethanol (80.0 ml) and water (50.0 ml) was added in small portions to a stirred solution of cyanoacetamide (1) (3.36 g, 0.04 mol) and anhydrous sodium acetate (5.0 g, 0.06 mol) in ethanol (100 ml) and water (50.0 ml) at 0° (ice-salt bath) and the mixture was stirred in the melting ice bath for a further 2 h. The mixture was evaporated and the residue

treated with water to yield 7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) (8.56 g; 87.0%), m.p. 228-231° (lit.,[180] 245°), ν_{max} 3475, 3420 and 3310 (NH), and 1675 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 7-Amino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) with Triethyl-orthoformate

A solution of 7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) (0.26 g, 0.001 mol) in triethyl orthoformate (5.0 ml) was heated under reflux for 17 h. The mixture was cooled and filtered to afford unreacted triazolotriazine (0.17 g; 65%), m.p. 235-240°, identical (m.p. and i.r. spectrum) to an authentic sample.

The filtrate was evaporated to give a red gum (0.06 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 7-Amino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) with Formic Acid

A solution of 7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) (0.26 g, 0.001 mol) in formic acid (5.0 ml) was heated under reflux for 3 h. The mixture was evaporated to yield a dark intractable solid (0.23 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 7-Amino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) with Acetic Anhydride

A solution of 7-amino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) (0.26 g, 0.001 mol) in acetic anhydride (5.0 ml) was heated under reflux for 3 h. The mixture was evaporated to afford a dark intractable solid (0.25 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 7-Amino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) with Acetyl Chloride in the Presence of Concentrated Sulphuric Acid

A suspension of 7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) (0.26 g, 0.001 mol) in acetyl chloride (2.0 ml) was cooled to 0° (ice-salt bath) and treated dropwise with concentrated sulphuric acid (0.3 ml). The resulting solution was stirred at room temperature for 17 h., poured onto ice (10.0 g) and filtered to afford a brown solid (0.14 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

The aqueous mother liquor was neutralised by addition of solid anhydrous sodium acetate and extracted with methylene chloride to yield a red oil (0.10 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 7-Amino-3-phenyl-3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) with Urea

An intimate mixture of 7-amino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) (1.01 g, 0.004 mol) and urea (0.24 g, 0.004 mol) was heated at 200° (Woods metal bath) for 1 h. The mixture was cooled and treated with warm aqueous 2M sodium hydroxide and filtered to remove a small amount of a dark solid. The filtrate was acidified with aqueous 2M hydrochloric acid and filtered to yield the unreacted triazolotriazine (65) (0.21 g; 21%), m.p. 245-250°, identical (m.p. and i.r. spectrum) to an authentic sample.

The acidic aqueous mother liquor afforded no further material on extraction with methylene chloride.

The Attempted Reaction of 7-Amino-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine-6-carboxamide (66) with Phenyl Isocyanate

A solution of 7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) (0.26 g, 0.001 mol) in dimethylformamide (25.0 ml) was treated in one portion with phenyl isocyanate (0.12 g, 0.001 mol) and the resulting mixture was stirred at room temperature for 16 h. The mixture was then diluted with water (20.0 ml) allowed to stand for 15 min. and filtered to afford a red solid (0.27 g) which was subjected to flash chromatography.

Elution with ethyl acetate-cyclohexane (1:4) yielded diphenyl urea (0.16 g, 75%), m.p. 229-234°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethyl acetate-cyclohexane (1:1) gave the unreacted triazolotriazine (0.07 g; 27%), m.p. 230-234°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with ethyl acetate through to ethanol afforded no further material.

3-(α-Acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72)[180]

A solution of 7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) (3.83 g, 0.015 mol) in glacial acetic acid (50.0 ml) was heated under reflux for 24 h. The mixture was evaporated to afford a brown gum which was triturated with toluene to afford 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72), as colourless crystals, (2.7 g; 63%), m.p. 105-108° (lit.,[180] 105°), ν_{max} 3375, 3275 and 3170 (NH) and 1740 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of 3-(α-Acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) with Triethyl Orthoformate

A solution of 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) (0.28 g, 0.001 mol) in triethyl orthoformate (5.0 ml) was heated under reflux for 6 h. The mixture was evaporated to give a dark gum (0.25 g) whose t.l.c. in ethyl acetate showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 3-(α-Acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) with Formic Acid

3(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) (0.57 g, 0.002 mol) in formic acid (5.0 ml) was heated under reflux for 1 h. The mixture was evaporated and the resulting gummy residue was triturated with light petroleum to afford the unreacted triazine (72) (0.57 g; quant.), m.p. 100-105°, identical (m.p. and i.r. spectrum) to an authentic sample.

The Reaction of 3-(α-Acetoxybenzyl)-5-amino-1,2,4-triazine (72) with Acetic Anhydride

A solution of 3-(α-acetoxylbenzyl)-5-amino-1,2,4-triazino-6-carboxamide (72) (0.57 g, 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 3 h. The mixture was evaporated to give a brown gum (0.63 g) which was subjected to flash chromatography.

Elution with methylene chloride through ethanol gave a series of solids and gums (total, 0.61 g) none of which were further investigated.

The Reaction of 3-(α-Acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) with Formamide in the Presence of Sodium Ethoxide

A solution of sodium (0.23 g, 0.01 g.atom) in anhydrous ethanol (20.0 ml) was treated with 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) (0.57 g, 0.002 mol) and formamide (0.8 ml) and the mixture was heated under reflux for 3 h. Hot filtration of the mixture afforded a brown solid which was treated with ice water and the filtrate acidified with glacial acetic acid and the resulting acidic solution was extracted with methylene chloride to give a small amount of yellow gum which was not further investigated.

The aqueous mother liquor was evaporated and the residue soxhlet extracted to give a small amount of a yellow gum which was not further investigated.

The Reaction of 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) with Tosyl Isocyanate

A solution of 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) (0.55 g, 0.002 mol) in anydrous diglyme (30.0 ml) was treated with redistilled tosyl isocyanate (0.44 g, 0.0022 mol) and the mixture was heated

under reflux for 24 h. A further portion of tosyl isocyanate (0.44 g, 0.0022 mol) was added and the mixture heated under reflux for a further 2h. The mixture was cooled and evaporated to give a dark gum (1.0 g) which was subjected to flash chromatography.

Elution with methylene chloride gave toluene-4-sulphonamide (0.52 g), m.p. 132-135°, identical (m.p. and i.r. spectrum) to an authentic sample.

Elution with methylene chloride-ethyl acetate (1:1) through to ethanol afforded a series of gums (total, 0.46 g) none of which were further investigated.

The Attempted Hydrogenolysis 3-(α-Acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72)

(a) A solution of 3-(α-acetoxybenzyl)-5-benzyl)-amino-1,2,4-triazine-6-carboxamide (72) (0.55 g, 0.002 mol) in ethanol (50.0 ml) was treated with 10% Palladium on charcoal (0.06 g) and the mixture hydrogenated at atmospheric pressure at room temperature until no further hydrogen was taken up. Filtration through a celite pad and evaporation of the filtrate gave the unreacted triazine (72) (0.44 g; 80%), m.p. 100-103°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(b) A solution of 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) (0.55 g, 0.002 mol) in ethanol (50.0 ml) containing glacial acetic acid (0.1 ml) was

treated with 10% palladium on charcoal (0.06 g) and the mixture was hydrogenated at atmospheric pressure and room temperature until no further hydrogen was taken up. Filtration through celite and evaporation of the filtrate gave the unreacted triazine (72) (0.53 g; 96%), m.p. 100-102° identical (m.p. and i.r. spectrum) to an authentic sample.

(c) A solution of 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) (0.55 g, 0.002 mol) in ethanol (100 ml) was treated with 10% palladium on charcoal (0.06 g) and the mixture was hydrogenated under pressure (3 atmospheres) at room temperature for 5 h. The mixture was filtered through celite and the filtrate evaporated to yield the unreacted triazine (72) (0.55 g; quant.), m.p. 101-103°, identical (m.p. and i.r. spectrum) to an authentic sample.

(d) Nitrogen was bubbled through a stirred suspension of 10% palladium on charcoal (0.005 g) in water (1.0 ml) and a solution of sodium borohydride (0.08 g, 0.002 mol) in water (1.5 ml) was added in one portion. The passage of nitrogen was continued and the mixture treated dropwise with stirring with a solution of 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) (0.28 g, 0.001 mol) in methanol (5.0 ml), then stirred for a further 10 min. at room temperature. The mixture was filtered to remove the catalyst and the filtrate was acidified with aqueous 2M hydrochloric acid and the solution concentrated to remove

the methanol. The mixture was filtered to give the unreacted triazine (72) (0.28 g; quant.), m.p. 101-103°, identical (m.p. and i.r. spectrum) to a sample prepared before.

(e) A solution of 3-(α-acetoxybenzyl)-5-amino-1,2,4-triazine-6-carboxamide (72) (0.55 g, 0.002 mol) in 70% aqueous ethanol (10.0 ml) was treated with sodium dithionite (0.55 g) and the mixture heated under reflux for 1 h. then a further portion of sodium dithionite (0.55 g) was added and the mixture heated under reflux for a further 1 h. The mixture was evaporated and the residue treated with water. The resulting solution was extracted with methylene chloride to give the unreacted triazine (72) (0.53 g; 96%), m.p. 101-103°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 7-Amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) with Sodium Nitrite in the Presence of Hydrochloric Acid

A solution of 7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine-6-carboxamide (66) in glacial acetic acid (15.0 ml) was treated with 10% w/v aqueous hydrochloric aic (5.0 ml). The resulting solution was cooled to 0° (ice-salt bath) and treated dropwise with a solution of sodium nitrite (0.17 g, 0.0025 mol) in water (1.0 ml) and the mixture was stirred in the melting ice bath for 1 h.

The mixture was filtered to give the unreacted triazolo-triazine (66) (0.23 g, 54%), m.p. 218-221°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The aqueous mother liquor was neutralised with aqueous 2M sodium hydroxide solution which was extracted with methylene chloride to give a brown gum (0.14 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

7-Amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (84)[180]

A solution of 4-phenyl-1H-1,2,3-triazole-5-diazonium betaine (20) (5.8 g, 0.034 mol) in ethanol (70.0 ml) and water (50.0 ml) was added in small portions to a stirred solution of benzoylacetonitrile (81) (4.90 g, 0.034 mol) and anhydrous sodium acetate (4.20 g, 0.051 mol) in ethanol (100 ml) and water (50.0 ml) at 0° (ice-salt bath). The mixture was stirred for 2 h. in the melting ice bath and then heated under reflux for a further 16 h. Cooling afforded a red solid which was combined with further material obtained by evaporating the ethanolic filtrate and treating the residue with water to yield 7-amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (84), which formed red needles, (9.6 g, 90%), m,p. 195-197° (lit.,[180] 214°) ν_{max} 3450 and 3340 (NH) and 1670 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) to an authentic sample.

The Attempted Reaction of 7-Amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (84) with Hydroxylamine Hydrochloride in the Presence of Sodium Acetate

A solution of 7-amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (84) (0.61 g, 0.002 mol) in ethanol (80.0 ml) was treated with hydroxylamine hydrochloride (1.39 g, 0.02 mol) and a solution of anhydrous sodium acetate (1.64 g, 0.02 mol) in water (10.0 ml). The resulting suspension was heated under reflux for 1 h. and the mixture was evaporated and the residue treated with water to afford the unreacted triazolotriazine (84) (0.48 g; 80%), m.p. 192-196°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Reaction of 7-Amino-6-benzoyl-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (84) with Hydroxylamine Hydrochloride

A solution of 7-amino-6-benzoyl-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (84) (3.16 g, 0.01 mol) in ethanol (250 ml) was treated with a solution of hydroxylamine hydrochloride (6.95 g, 0.1 mol) in water (20.0 ml) and the mixture was heated under reflux for 17 h. The mixture was cooled and filtered to give 3,6-diphenyl-1,2,3-triazolo[5,1-g]-isoxazolo[5,4-c]-1,2,4-triazine (86) (0.49 g; 16%), m.p. 244° (explosive decomp.), ν_{max} 1600 (C=N) cm^{-1}.

Found: C, 64.4; H, 3.1; N, 26.2%; M^+, 314

$C_{17}H_{10}N_6O$ requires: C, 65.0; N, 3.2; N, 26.8%; M, 314.

The filtrate was evaporated and the residue treated with water to yield 5-amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) (2.21 g; 72%), m.p. 255° (decomp.) (from glacial acetic acid), ν_{max} 3440 and 3317 (NH) and 1670 (C=N) cm^{-1}.

Found: C, 60.8; H, 3.9; N, 29.2%; M^+, 331.
$C_{17}H_{13}N_7O$ requires: C, 61.6; H, 3.9; N, 29.6%; M, 331.

The aqueous mother liquor was extracted with methylene chloride however no further material was obtained.

The Reaction of 5-Amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) with Polyphosphoric Acid

A solution of 5-amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) (0.33 g, 0.001 mol) in polyphosphoric acid (5.0 ml) was stirred and heated at 80° (oil bath) for 0.5 h. The mixture was then cooled and treated with ice and the resulting solution was neutralised with solid anhydrous solid acetate. The resulting neutral suspension was extracted with methylene chloride to give a red oil (0.3 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Reaction of 5-Amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) with Glacial Acetic Acid

A solution of 5-amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) (0.33 g, 0.001 mol) in glacial acetic acid was heated under reflux for 24 h. The mixture was evaporated to give a dark intractable gum (0.30 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

4-(1-Acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)azo-5-amino-3-phenylisoxazole (89)

A solution of 5-amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) (0.33 g, 0.001 mol) in acetic anhydride (2.0 ml) was heated at 100° for 10 min. and then left at room temperature for 20 min. The mixture was filtered to afford 4-(1-acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)azo-5-amino-3-phenylisoxazole (89), which formed orange crystals, (0.23 g; 62%), m.p. 210-211° (from glacial acetic acid), ν_{max} 3420 and 3320 (NH) and 1760 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 8.29-7.23 (10H, m, ArH), 3.46 (2H, brs, NH) and 2.80 (3H, s, CH_3).

Found: 373.1006

$C_{19}H_{15}N_7O_2$ requires: 373.1008

The acidic anhydride filtrate was diluted with water, neutralised with solid anhydrous sodium acetate. However, extraction of the resulting solution with methylene chloride afforded no further material.

The Reaction of 5-Amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) with Aqueous Sodium Hydroxide

A solution of 5-amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) (1.30 g, 0.004 mol) in 2M aqueous sodium hydroxide solution (25.0 ml) was heated under reflux for 10 min. The mixture was then acidified with concentrated hydrochloric acid and filtered to afford a yellow solid (1.10 g) which was subjected to flash chromatography.

Elution with cyclohexane-ethyl acetate (1:1) through to ethanol gave a series of intractable solids (total, 1.0 g) whose t.l.c. showed in methylene chloride showed them to be complex mixtures none of which were further investigated.

The Reaction of 5-Amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) with Aqueous Sulphuric Acid

A solution of 5-amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) (0.66 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 30 min. The mixture was cooled and concentrated to remove the ethanol and the resulting gummy suspansion was extracted with methylene chloride to give a yellow gum (0.60 g) which was subjected to flash chromatography.

Elution with methylene chloride afforded 4-phenyl-1H-1,2,3-triazole (90) (0.12 g; 41%), m.p. 140-145°, identical (m.p. and i.r. spectrum) to an authentic sample.[194]

Elution with methylene chloride-ethyl acetate (1:1) through to ethanol gave a series of gums (total, 0.36 g) whose t.l.c. in methylene chloride showed them to be multicomponent mixtures none of which were further investigated.

The Thermolysis of 5-Amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) in Anhydrous Diglyme

A solution of 5-amino-3-phenyl-4-(4-phenyl-1H-1,2,3-triazol-5-yl)azoisoxazole (85) (0.66 g, 0.002 mol) in anhydrous diglyme (20.0 ml) was heated under reflux for 2 h. The mixture was evaporated to give a dark gum (0.65 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a complex mixture which was not further investigated.

The Attempted Reaction of 3,6-Diphenyl-1,2,3-triazolo[5,1-g]-isoxazolo[5,4-e]-1,2,4-triazine (86) with Glacial Acetic Acid

A suspension of 3,6-diphenyl-1,2,3-triazolo[5,1-g]-isoxazolo[5,4-e]-1,2,4-triazine (86) (0.31 g; 0.001 mol) in glacial acetic acid (5.0 ml) was heated under reflux for 24 h. The mixture was evaporated to afford a dark intractable solid (0.23 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture which was not further investigated.

5-Amino-3-phenylisoxazole (94)[105]

5-Amino-3-phenylisoxazole (94) was prepared as described in Chapter 3.

1-(3-Phenylisoxazol-5-yl)-3-(4-phenyl-1H-1,2,3-triazol-5-yl)-triazene (95)

A solution of 5-amino-3-phenylisoxazole (94) (1.30 g, 0.008 mol) in methylene chloride (30.0 ml) was treated with a solution of 4-phenyl-1H-1,2,3-triazole-5-diazonium betaine (20) (1.30 g, 0.008 mol) in methylene chloride (20.0 ml) and the mixture was stirred at room temperature for 1 h. The mixture was filtered to give a yellow solid which was combined with further material obtained by evaporation of the filtrate and triturating the resulting gum with methylene chloride to yield 1-(3-phenylisoxazol-5-yl)-3-(4-phenyl-1H-1,2,3-triazol-5-yl)triazene (95) which formed yellow crystals

(2.2 g; 84%), m.p. 143-145° (from ethanol), ν_{max} 3370 (NH) and 1660 (C=N) cm^{-1}, δ[$(CD_3)_2SO$] 8.80 (2H, brs, NH), 8.40-7.40 (10H, m, ArH) and 5.75 (1H, s, CH).

Found: 331.1183

$C_{17}H_{13}N_3O$ requires: 331.1182

The methylene chloride mother liquor was evaporated to give a brown gum (0.86 g) whose t.l.c. in methylene chloride showed it to be a multicomponent mixture, containing the unreacted isoxazole (94) and triazole (20), which was not further investigated.

The Attempted Reaction of 1-(3-Phenylisoxazol-5-yl)-3-(4-phenyl-1H-1,2,3-triazol-5-yl)triazene (95) with Aqueous Hydrochloric Acid

A solution of 1-(3-phenylisoxazol-5-yl)-3-(4-phenyl-1H-triazol-5-yl)triazene (95) (0.66 g, 0.002 mol) in ethanol (10.0 ml) was treated with aqueous 2M hydrochloric acid and the mixture heated under reflux for 1 h. The mixture was concentrated to remove ethanol and filtered to afford the unreacted triazene derivative (95) (0.64 g, 97%) m.p. 140-145°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Reaction of 1-(3-Phenylisoxazol-5-yl)-3-(4-phenyl-1H-1,2,3-triazol-5-yl)triazene (95) with Acetic Anhydride

A solution of 1-(3-phenylisoxazol-5-yl)-3-(4-phenyl-1H-1,2,3-triazol-5-yl)triazene (95) (0.66 g, 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 1 h. The mixture was evaporated to give a dark gum (0.93 g) which was subjected to flash chromatography.

Elution with cyclohexane through to ethanol gave a series of gums and solids (total, 0.54 g) none of which were further investigated.

3-Acetyl-1-(3-phenylisoxazol-5-yl)-3-(4-phenyl-1H-1,2,3-triazol-5-yl)triazene (99)

A solution of 1-(3-phenylisoxazol-5-yl)-3-(4-phenyl-1H-1,2,3-triazol-5-yl)triazene (95) (0.66 g, 0.002 mol) in anhydrous dioxane (10.0 ml) was treated with stirring with triethylamine (0.22 g, 0.0022 mol) followed by dropwise addition of a solution of acetyl chloride (0.18 g, 0.0022 mol) in anhydrous dioxane (1.0 ml) and the resulting mixture was stirred at room temperature for 1 h. The mixture was filtered to remove triethylamine hydrochloride, m.p. 252-255°, identical (m.p. and i.r. spectrum) to an authentic sample. The dioxane filtrate was evaporated to give 3-(1-acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)-1-(3-phenylisoxazol-5-yl)triazene (97) (0.59 g; 79%), m,p. 162-165° ν_{max} 3140 (NH) and 1730 (CO) cm^{-1}, which on crystallisation from glacial acetic acid gave 3-acetyl-1-(3-phenylisoxazol-

5-yl)-3-(4-phenyl-1H-1,2,3-triazol-5-yl)triazene (99) as yellow crystals, m.p. 162-164°, ν_{max} 3385 and 3140 (NH) and 1695 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 8.00-7.58 (11H, m, ArH and CH) and 2.17 (3H, s, CH_3).

Found: C, 58.4; H, 4.2; N, 25.0%; M^+, 373

$C_{19}H_{15}N_7O_2 H_2O$ requires: C, 58.3; H, 4.3; N, 24.5%; $M-H_2O$, 373.

The methylene chloride filtrate was evaporated to yield a small amount of an intractable solid (0.04 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

3-(α-Acetoxybenzyl)-5-amino-6-benzoyl-1,2,4-triazine (100)[180]

A solution of 7-amino-6-benzoyl-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (84) (3.0 g, 0.01 mol) in glacial acetic acid was heated under reflux for 48 h. The mixture was evaporated to give a dark gum which was triturated with toluene-light petroluem to give 3-(α-acetoxybenzyl)-5-amino-6-benzoyl-1,2,4-triazine (100), (2.1 g; 66%), m.p. 118-120° (lit.,[180] 125°) ν_{max} 3420, 3300 and 3200 (NH) and 1720 and 1690 (CO) cm^{-1}, identical (m.p. and i.r. spectrum) to an authentic sample.

The toluene filtrate was evaporated to give a dark gum (0.8 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Attempted Hydrogenolysis of 3-(α-Acetoxybenzoyl)-5-amino-6-benzoyl-1,2,4-triazine (100)

A solution of 3-(α-acetoxybenzoyl)-5-amino-6-benzoyl-1,2,4-triazine (100) (0.70 g, 0.002 mol) in ethanol (50.0 ml) was treated with 10% palladium on charcoal (0.11 g) and the mixture was hydrogenated at atmospheric pressure and room temperature until no more hydrogen was taken up. The mixture was then filtered through celite and the filtrate evaporated to give the unreacted triazine (100) (0.65 g; 95%), m.p. 116-118°, identical (m.p. and i.r. spectrum) to a sample prepared before.

5-Hydroxy-5-nitropyrimidin-4-(3H)-one[201]

6-Hydroxy-5-nitropyrimidin-4-(3H)-one was prepared (yield quant.) by the nitration of 6-hydroxypyrimidine-4-(3H)-one as described by Boon, Jones and Ramage[201] and had m.p. >300° (lit.,[201] >300°).

4,6-Dichloro-5-nitropyrimidine[201]

4,6-Dichloro-5-nitropyrimidine was prepared (yield quant.) by the reaction of 6-hydroxy-5-nitropyrimidin-4-(3H)-one with phosphoryl chloride as described by Boon. Jones and Ramage[201] and had m.p. 95-98° (lit.,[201] 99°).

6-Chloro-5-nitropyrimidin-4-(3H)-one (104)[197]

6-Chloro-5-nitropyrimidin-4-(3H)-one (104) was prepared (yield 78%) by the reaction of 4,6-dichloro-5-nitropyrimidine with formic acid as described by Khromov-Borisov and Kheifets[197] and had m.p. 199° (lit.,[197] 199°).

5-Nitro-6-N-(4-phenyl-1H-1,2,3-triazol-5-ylaminopyrimidin-4-(3H)-one (107)

A solution of 6-chloro-5-nitropyrimidin-4-(5H)-one (104) (7.02 g, 0.04 mol) in anydrous ethanol (100 ml) was treated with stirring with a solution of 4-amino-5-phenyl-1H-1,2,3-triazole (105) (6.4 g, 0.04 mol) in anydrous ethanol (100 ml) followed by solid anhydrous potassium acetate (4.0 g, 0.04 mol) and the mixture was stirred at room temperature for 1 h. Evaporation and treatment of the residue with water afforded a yellow solid which was combined with further material obtained by allowing the aqueous filtrate to stand overnight to yield 5-nitro-6-N-(4-phenyl-1H-1,2,3-triazol-5-yl)aminopyrimidin-4-(3H)-one (107) (10.75 g; 90%), m.p. 270° (from dimethylformamide-water), ν_{max} 3300 and 3240 (NH) and 1690 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 12.70 (1H, bts, NH), 12.68 (1H, brs, NH), 10.57 (1H, brs, NH) and 7.48-7.24 (6H, m, ArH and CH).

Found: C, 47.9; H, 3.3; N, 32.8%; M^+, 299.
$C_{12}H_9N_7O_3$ requires: C, 48.2; H, 3.0; N, 32.8%; M, 299.

The neutral aqueous mother liquor on extraction with methylene chloride afforded no further material.

6-N-(1-Acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)amino-5-nitropyrimidin-4-(3H)-one (111)

A solution of 5-nitro-6-N-(4-phenyl-1H-1,2,3-triazol-5-yl)aminopyrimidin-4-(3H)-one (107) (0.60 g, 0.002 mol) in anhydrous dimethylformamide (20.0 ml) was treated with triethylamine (0.44 g, 0.0044 mol) and stirred at room temperature for 15 min., then acetyl chloride (0.36 g, 0.0044 mol) was added dropwise and the mixture stirred at room temperature for a further 1 h. The mixture was filtered to give triethylamine hydrochloride (0.50 g; 83%), m.p. 252-255°, identical (m.p. and i.r. spectrum) to an authentic sample.

The dimethylformamide filtrate was evaporated and the resulting residue treated with water to yield 6-N-(1-acetyl-4-phenyl-1H-1,2,3-triazol-5-yl)amino-5-nitropyrimidin-4-(3H)-one (111) (0.55 g, 81%), m.p. 205-206°, which could not be purified by crystallisation, ν_{max} 3315 (NH) and 1770 and 1680 (CO) cm^{-1}.

Found: 341.0874

$C_{14}H_{10}N_7O_4$ requires: 341.0872

3-Amino-2-nitro-3-N-(4-phenyl-1H-1,2,3-triazol-5-yl)-aminoacrylamide (113)

A solution of sodium (0.18 g, 0.008 g.atom) in anhydrous ethanol (5.0 ml) was added to a suspension of 5-nitro-6-N-(4-phenyl-1H-1,2,3-triazol-5-yl)aminopyrimidin-4-(3H)-one (107) (0.6 g, 0.002 mol) in anhydrous ethanol (5.0 ml) and the mixture was heated under reflux for 1 h. The mixture was evaporated and the residue treated with water (10.0 ml) and the resulting solution was extracted with metylene chloride to yield a small amount of brown gum (0.04 g) which was not further investigated.

The aqueous mother liquor was acidified with 2M hydrochloric acid to give 3-amino-2-nitro-3-N-(4-phenyl-1H-1,2,3-triazol-5-yl)aminoacrylamide (113) (0.38 g; 65%), m.p. 230-231° (from dimethylformamide-water), ν_{max} 3405, 3320 and 3120 (NH) and 1650 (CO) cm^{-1}, δ[$(CD_3)_2SO$] 14.46 (2H, brs, NH), 10.57 (1H, brs, NH), 9.13 (2H, brs, NH), 8.08 (1H, brs, NH) and 7.94-7.34 (5H, m, ArH).

Found: C, 45.5; H, 3.9; N, 33.6%; M^+, 289.
$C_{11}H_{11}N_7O_3$ requires: C, 45.7; H, 3.8; N, 33.9%; M, 289.

The acidic filtrate was extracted with methylene chloride but no further material was obtained.

The Reaction of 3-Amino-2-nitro-3-N(4-phenyl-1H-1,2,3-triazol-5-yl)aminoacrylamide (113) with Acetic Anhydride

A solution of 3-amino-2-nitro-3-N-(4-phenyl-1H-1,2,3-triazol-5-yl)aminoacrylamide (113) (1.1 g, 0.004 mol) in acetic anhydride (10.0 ml) was heated under reflux for 1 h. The mixture was evaporated to give a brown gum (1.0 g) whose t.l.c. in methylene chloride-ethyl acetate (1:1) showed it to be a complex mixture which was not further investigated.

The Reaction of 3-Amino-2-nitro-3-N-(4-phenyl-1H-1,2,3-triazole-5-yl)aminoacrylamide (113) with Aqueous Hydrochloric Acid

A solution of 3-amino-2-nitro-3-N-(4-phenyl-1H-1,2,3-triazol-5-yl)aminoacrylamide (113) (1.1 g, 0.004 mol) in ethanol (10.0 ml) was treated with aqueous 2M hydrochloric acid (5.0 ml) and the mixture was heated under reflux for 1h. The mixture was evaporated and the residue treated with water to afford 4-amino-5-phenyl-1H-1,2,3-triazole (105) (0.60 g; quant.), m.p. 120-124°, identical (m.p. and i.r. spectrum) to a sample prepared before.

No further material was obtained on extraction of the aqueous mother liquor with methylene chloride.

The Attempted Reaction of 7-Amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (84) with Hydrazine Monohydrate

A solution of 7-amino-6-benzoyl-3-phenyl-1,2,3-triazolo-[5,1-c]-1,2,4-triazine (84) (0.61 g, 0.002 mol) in methanol

(80.0 ml) was treated in one portion with hydrazine monohydrate (0.1 g, 0.002 mol) and the mixture was heated under reflux for 3h. The mixture was evaporated and the residue triturated with light petroleum to give the unreacted trizolotriazine (84) (0.5 g; 82%), m.p. 200-204°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 7-Amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (84) with Toluene-4-sulphonylhydrazide

A solution of 7-amino-6-benzoyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (84) (0.3 g, 0.001 mol) in methanol (50.0 ml) was treated with toluene-4-sulphonyl-hydrazide (0.19 g, 0.001 mol) and the mixture was heated under reflux for 3h. The mixture was evaporated to afford a red gum which was triturated with light petroleum to yield the unreacted triazolotriazine (84) (0.29 g; 97%), m.p. 200-203°, identical (m.p. and i.r. spectrum) to a sample prepared before.

The Attempted Reaction of 7-Amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47) with Triethyl Orthoformate

A solution of 7-amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47) (0.48 g, 0.002 mol) in triethyl orthoformate (20.0 ml) was heated under reflux

for 30 min. and hot filtered to give the unreacted triazolo-triazine (47) (0.28 g; 58%), m.p. 248-253°, identical (m.p. and i.r. spectrum) to an authentic sample. The filtrate was evaporated to give a brown gum (0.18 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Reaction of 7-Amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47) with Acetic Anhydride

(a) A solution of 7-amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (47) (0.48 g, 0.002 mol) in acetic anhydride (5.0 ml) was heated under reflux for 3 h. The mixture was evaporated to give a dark gum (0.50 g) whose t.l.c. in ethyl acetate showed it to be a multicomponent mixture which was not further investigated.

(b) A solution of 7-amino-6-hydrazino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-trazine (47) (0.24 g, 0.001 mol) in acetic anhydride (2.0 ml) was heated at 100° (steam bath) for 10 min. and then left at room temperature for 20 min. The mixture was filtered to afford 1-acetyl-2-(7-amino-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazin-6-yl)hydrazine (120) (0.24 g; 85%), m.p. 306-307°, ν_{max} 3420, 3300, 3180 (NH) and 1645 (CO) cm^{-1}, $\delta[(CD_3)_2SO]$ 10.25 (1H, brs, NH), 9.32 (1H, brs, NH), 8.22-8.10 (2H, m, ArH), 7.80 (2H, brs, NH), 7.56-7.25 (3H, m, ArH) and 2.03 (3H, s, CH_3).

Found: C, 50.4; H, 4.5; N, 38.5%; M^+-N_2, 256.

$C_{12}H_{12}N_8O$ requires: C, 50.7; H, 4.2; N, 39.4%; M, 284.

The acetic anhydride filtrate was evaporated to give a brown gum (0.1 g) whose t.l.c. in methylene chloride showed it to be a complex mixture which was not further investigated.

The Reaction of 7-Amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) with Ethyl Carbazate

A solution of 7-amino-6-benzenesulphonyl-3-phenyl-1,2,3-triazolo[5,1-c]-1,2,4-triazine (21) (0.70 g, 0.002 mol) in anhydrous dioxane (10.0 ml) was treated with a solution of ethyl carbazate (0.23 g, 0.002 mol) and the mixture was heated under reflux for 24 h. The mixture was evaporated to give a red gum (1.2 g) which was subjected to flash chromatography.

Elution with methylene chloride gave unreacted triazolotriazine (21) (0.14 g; 20%), m.p. 200-203°, identical (m.p. and i.r. spectrum) to a sample prepared before.

Elution with methylene chloride-ethyl acetate (4:1) through to ethanol gave a series of gums (total, 0.93 g) whose t.l.c. in ethyl acetate showed them to be complex mixtures none of which were further investigated.

General Experimental Data

Infrared spectra were measured for nujol suspensions using a Perkin-Elmer 781 Spectrophotometer. Bands were strong and sharp unless otherwise stated.

^{1}H Nuclear magnetic resonance spectra were measured at 80 MHz using a Brucker WP80 SY spectrometer and 200 MHz using a Brucker WP200SP spectrometer. Signals were sharp unless otherwise specified: (br) as broad; s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. T.M.S. as internal standard.

^{13}C Nuclear magnetic resonance spectra were measured at 200 MHz using a Brucker WP200SY spectrometer, were fully decoupled and accompanied by a DEPT $\Pi/2$ pulse sequence spectrum. Signals were sharp and quat = quaternary carbon atom.

Mass spectra were measured at 70 eV using an A.E.I. MS902 instrument.

Microanalysis were carried out by Mr. J. Grunbaum and Mrs E. McDougall, Department of Chemistry, University of Edinburgh. Melting points of all analytical samples were determined using a Koffler hot-stage microscope and are uncorrected.

All yields were based on unrecovered starting material. All organic extracts were dried over anhydrous magnesium sulphate. Solvents were of technical grade unless otherwise stated. Light-petroleum had b.p. 60-80°.

Flash chromatography was carried out over silica (Merk Kiesgel 60 GF_{254}).

Thin layer chromatography was carried out over silica (Merk Kiesgel 60 GF_{254}).

Bibliography

1. R.K. Robins, "The Purines and Related Ring Systems", Heterocyclic Compounds, Vol. 8, Ed. R.C. Elderfield.
2. K.R.H. Woolridge, B.J. Broughton, P. Chaplen, P. Knowles, E. Lunt, S.M. Marshall and D.L. Pain, J.Med.Chem., 1975, 18, 1117.
3. R.L. Tolman, C.W. Smith, R.W. Sidewell and R.K. Robins J.Med.Chem., 1972, 15, 883.
4. R.L. Tolman, W. Hatzenlaub and R.K. Robins, J.Med.Chem., 1972, 15, 879.
5. Y.F. Shealy and J.D. Clayton, J.Pharm.Sci., 1973, 62, 858.
6. J. Gut, Adv.Heterocyclic Chem., 1963, 1, 189.
7. A. Albert, J.Chem.Soc. (C), 1969, 152.
8. W. Traube, Chem.Ber., 1900, 33, 3035.
9. S. Gabriel and J. Colman, Chem.Ber., 1901, 34, 1234.
10. R.O. Roblin, J.O. Lampen, J.P. English, Q.P. Cole and J.R. Vaughan, Jr., J.Am.Chem.Soc., 1945, 67, 290.
11. J.H. Lister and G.M. Timmis, J.Chem.Soc., 1960, 765.
12. R. Weiss, R.K. Robins and C.W. Noell, J.Org.Chem., 1960, 25, 765.
13. H.C. Kopel, D.E. O'Brien and R.K. Robins, J.Am.Chem.Soc., 1959, 81, 3046.
14. J. Davol and D.D. Evans, J.Chem.Soc., 1960, 5041.
15. D.L. Ross, C.G. Skinner and W. Shive, J.Org.Chem., 1961, 26, 3582.

16. G.M. Timmis, D.G.I. Felton, H.O.J. Collier and P.L. Huskinson, J.Pharm. and Pharmacol., 1957, 9, 46. Chem.Abstr., 1957, 51, 10531.

17. P. Bitterli and H. Erlenmeyer, Helv.Chim.Acta., 1951, 34, 835.

18. F.R. Benson, L.W. Hartzell and W.L. Savell, J.Am.Chem.Soc., 1950, 72, 1816.

19. F.R. Benson and L.W. Hartzel, J.Am.Chem.Soc., 1954, 76, 2263.

20. Y. Maki and E.C. Taylor, Chem.Pharm.Bull., 1972, 20, 605.

21. H.U. Blank, I. Wempen and J.J. Fox, J.Org.Chem., 1970, 35, 1131.

22. K. Senga, M. Ichiba and S. Nishigaki, Heterocycles, 1977, 6, 1915.

23. W. Pfleiderer and K.H. Schündehütte, Justus.Leibigs.Ann.Chem., 1958, 612, 158.

24. J. Baddiley, J.G. Buchanan and G.O. Osborne, J.Chem.Soc., 1958, 1651.

25. J. Baddiley, J.G. Buchanan and G.O. Osborne, J.Chem.Soc., 1958, 3606.

26. A. Dornow and J. Helberg, Chem.Ber., 1960, 93, 2001.

27. A. Albert, J.Chem.Soc., Perkin 1, 1981, 2344 (and references cited therein).

28. E.C. Taylor and E.E. Garcia, J.Org.Chem., 1964, 29, 2121.

29. E.C. Taylor, J.W. Barton and W.W. Paudler, J.Org.Chem., 1961, 26, 4961.

30. F. Yoneda, T. Nagamura and M. Kawamura, J.Chem.Soc., Chem.Comm., 1976, 658.

31. F. Yoneda, M. Kawamura, T. Nagamatsu, K. Kuretani, A. Hoshi and N. Iigo, Heterocycles, 1976, 6, 1503.

32. F. Yoneda, M. Noguchi, M. Noda and Y. Nitta, Chem.Pharm. Bull., 1978, 26, 3154.

33. F. Yoneda, T. Kametani, M. Higuchi, M. Noguchi and Y. Hushiguchi, Heterocycles, 1980, 14, 1295.

34. F. Yoneda, M. Higuchi and Y. Nitta, J.Heterocyclic Chem., 1980, 17, 869.

35. K. Kaji and M. Kawase, Chem.Pharm.Bull., 1976, 24, 2274.

36. D.W. Wooley, E. Shaw, N. Smith and E.A. Singer, J.Biol.Chem., 1951, 189, 189.

37. D.W. Wooley and E. Shaw, J.Biol.Chem., 1952, 194, 641.

38. G. Shaw, R.N. Naylor, D.V. Wilson and D.N. Butler, J.Chem.Soc., 1961, 4845.

39. J.A. Montgomery, J.F. Shealy and J.D. Clayton, J.Org.Chem., 1962, 27, 2150.

40. Z.V. Pashkarera, V.I. Ofitserov, K.V. Aglitska, V.S. Mokrushin, Khim.Geterotsikl.Soedin., 1975, 1141. Chem.Abstr., 1976, 84, 4916k.

41. M.A. Stevens, H.W. Smith and G.B. Brown, J.Am.Chem.Soc., 1960, 82, 3189.

42. H. Neunhoeffer, "The Chemistry of 1,2,3-Triazines", Heterocyclic Compounds, Ed. E.C. Taylor and A. Weissberger, Wiley-Interscience, New York, 1978, p. 5-12.

43. J.A. Montgomery and H.J. Thomas, J.Med.Chem., 1972, 15, 182.

44. A.M. Wertheimer, Y.S. Chen, R.T. Borchardt and Y. Furuichi, J.Biol.Chem., 1980, 255, 5924.

45. R.K. Robins, T.S. Yagura, R.B. Meyer, Jr., and J.P. Miller, J.Carbohydr. Nucleosides, Nucleotides, 1980, 167.

46. Y.F. Shealy, R.F. Struck, L.B. Holum and J.A. Montgomery, J.Org.Chem., 1961, 26, 2396.

47. Y.F. Shealy and C.A. O'Dell, J.Med.Chem., 1966, 9, 733.

48. H. Iwata, I. Yamamoto, E. Gohdu, K. Morida, M. Nakamura and K. Sumi, Biochem.Pharmacol., 1973, 2237.

49. W.K. Merteens and A.G. van Veen, Rec.Trav.Chim., 1934, 53, 257.

50. P.A. van Damme, A.G. Johannes, A.C. Cox and W. Berends, Rec.Trav.Chim., 1960, 79, 255.

51. R.K. Robins, G.D. Daves, Jr., and C.C. Cheng, J.Org.Chem., 1961, 26, 5256.

52. H.C.S. Wood, S.S. Al-Hassan and I. Stirling, J.Chem. Research (S), 1980, 278.

53. D.J. Brown and R.K. Lynn, "Chemistry and Biology of Pteridines", Ed. W. Pfliederer, Walter de Gruyter, New York, 1975, p. 575-601.

54. M.E.C. Biffin, D.J. Brown and T. Sugimoto, J.Chem.Soc., 1970, 139.

55. D.J. Brown and T. Sugimoto, Aust.J.Chem., 1971, 24, 633.

56. F. Yoneda, K. Shinomura and S. Nishiguki, Tetrahedron Lett., 1971, 13, 851.

57. R.K. Robins, G.D. Daves, Jr., and C.C. Cheng, J.Am.Chem.Soc., 1961, 83, 3905.

58. E.C. Taylor and F. Sowinsky, J.Am.Chem.Soc., 1968, 90, 1374.

59. C. Temple, Jr., C.L. Kussner and J.A. Montgomery, J.Org.Chem., 1969, 34, 2102.

60. C. Temple, Jr., C.L. Kussner and J.A. Montgomery, J.Heterocyclic Chem., 1968, 2, 581.

61. D.J. Brown and R.K. Lynn, Aust.J.Chem., 1974, 27, 1781.

62. L. Heinisch, W. Ozegowski and M. Muehlstedt, Chem.Ber., 97, 5.

63. T. Sugimoto and S. Matsura, Bull.Chem.Soc. Jpn., 1975, 48, 1679.

64. F. Yoneda, M. Kanahori and S. Nishigaki, J.Heterocyclic Chem., 1971, 8, 523.

65. F. Yoneda, M. Higuchi and Y. Nitta, Heterocycles, 1978, 9 , 1387.

66. E.C. Taylor and R.W. Morrison, Jr., Angew.Chemie., 1964, 76, 342.

67. E.C. Taylor and R.W. Morrison, Jr., J.Am.Chem.Soc., 1965, 87, 1976.

68. P. Winternitz, Helv.Chim.Acta, 1978, 61, 1175.

69. E.C. Taylor and S.F. Martin, J.Org.Chem., 1972, 37, 3958.

70. M. Brugger, H. Wamhoff and K. Friedhelm, Justus. Liebigs. Ann.Chem., 1972, 758, 173.

71. C. Temple, Jr., C.L. Kussner and J.A. Montgomery, J.Org.Chem., 1971, 36, 1099.

72. Y.A. Azev, I.Y. Postovski, E.L. Pidemski and A.F. Goleneva, Khim-Farm. Zh., 1980, 39. Chem.Abstr., 1980, 93, 71719.

73. R.P. Panzica and C.C. Tzeng, J.Heterocyclic Chem., 1983, 20, 1123.

74. A. Neunhoffer and H. Hummann, Tetrahedron Lett., 1983, 24, 1767.

75. N. Sato and J. Adachi, J.Org.Chem., 1978, 43, 341.

76. G. Nabel and W. Pflieder, Chem.Ber., 1965, 98, 1060.

77. A. Albert, N. Pflieder and D. Thacker, J.Chem.Soc.(C), 1969, 1084.

78. A. Albert, J.Chem.Soc.(C), 1968, 2076.

79. A. Albert and D. Thacker, J.Chem.Soc., Perkin Trans. 1, 1972, 468.

80. B. Eistert and M. Regitz, Chem.Ber., 1963, 96, 2290.

81. F. Eloy and R. Lenaers, Chem.Revs., 1962, 62, 155.

82. M. Begtrap and J. Holm, J.Chem.Soc., Perkin Trans. 1, 1981, 503.

83. H. von Pechmann and K. Wehsurg, Chem.Ber., 1888, 21, 2994.

84. A.L.J. Beckwith, "Synthesis of Amides", in The Chemistry of Amides, Ed., J. Zabicky, Interscience, New York, 1970, p. 119.

85. M.O. Lozinskii and A.A. Gershkovich, Zh.Org. Khim., 1974, 10, 1482. Chem.Abstr., 1974, 81, 104915r.

86. Dr. I. Sadler, University of Edinburgh, personal communication.

87. N.K. Kochetov and S.D. Sokolov, Adv. Heterocyclic Chem., 1962, 2, 365.

88. A. Hantzsch and K.J. Thomson, Chem.Ber., 1905, 38, 2666.

89. A.L.J. Beckwith, "Synthesis of Amides", in the Chemistry of Amides, Ed. J. Zabicky, Interscience, 1970, p. 96.

90. M.H. Elnagdi, M.R.H. Elmoghayer, E.H.A. Hafez and H.A. Alnima, J.Org.Chem., 1975, 40, 2064.

91. D.J. Brecknell, K.M. Carman, H.C. Deeth and J.J. Kibby, Aus.J.Chem., 1969, 22, 1915.

92. L.J. Bellamy, "The Infra-red Spectra of Complex Molecules", Methuen and Co. Ltd., 1954, p. 153.

93. Ibid, p. 183.

94. L. Bauer and C.N.V. Namburg, J.Org.Chem., 1961, 26, 4917.

95. L. Bauer, C.N.V. Namburg and C.L. Bell, J.Org.Chem., 1961, 26, 4923.

96. L. Bauer, C.N.V. Namburg and C.L. Bell, Tetrahedron, 1964, 20, 165.

97. M.H. Elnagdi, E.M. Kandseel and K.M. Sudek, Z.Naturforsch B., 1980, 35B, 91.

98. M.H. Elnagdi, M.A.E. Khalifu, E.A.E. Hafez and S.K.A. Guda, Z.Naturforsch B., 1980, 35B, 485.

99. R.G. Dubenko, E.F. Gorbenko, V.D. Panchenko and P.S. Pel'kis, Khim.Geterotsikl.Soedin., 1969, 5, 740.

100. J.G. England and G. Tennant, unpublished results.

101. F.A. McDermott, Org.Synthesis, 1943, 2, 365.

102. H. Hantzsch, Chem.Ber., 1892, 25, 702.

103. W.L.F. Armarego, "Fused Pyrimidines, Part 1, Quinazolines", Heterocyclic Compounds, Eds. E.C. Taylor and A. Weisberger, Wiley Interscience, New York, 1977, p. 451.

104. E. von Meyer, J.Prakt.Chem., 1895, 52, 107.

105. A. Obregia, Justus.Leibigs.Ann.Chem., 1891, 266, 324.

106. M.J. Haddadin and C.H. Issidorides, Tetrahedron Lett., 1965, 36, 3253.

107. L. Claisen and W. Zeidel, Chem.Ber., 1891, 24, 140.

108. O. Exner, Collection Czechoslov.Chem.Commun., 1956, 20, 202.

109. O. Exner, Collection Czechoslov.Chem.Commun., 1956, 21, 1500.

110. G. Ponzio, J.Prakt.Chem., 1899, 29, 280.

111. G. Tennant and A.A. Sandison, unpublished results.

112. J.B. Lee and B.C. Uff, Q.Rev.Chem.Soc., 1967, 21, 429.

113. R.R. Holmes and R.P. Bayer, J.Am.Chem.Soc., 1960, 82, 3454.

114. J.W. Gorrod, Tetrahedron Lett., 1968, 6155/

115. E.G.R. Ardagh and J.G. Williams, J.Am.Chem.Soc., 1925, 47, 2976.

116. W.P. Jencks, J.Am.Chem.Soc., 1959, 81, 475.

117. M.P. Cava, R.L. Little and D.K. Napier, J.Am.Chem.Soc., 1958, 80, 2257.

118. J. Meinwald, J.C. Shelton, G.L. Buchanan and A. Courtin, J.Org.Chem., 1968, 33, 99.

119. J. Thiele and K. Schleussner, Justus Leibigs Ann.Chem., 1897, 295, 138.

120. J.F. Bunnett, Ann.Rev.Phys.Chem., 1963, 14, 271.

121. J.F. Bunnett, Q.Rev.Chem.Soc., 1958, 12, 1.

122. J. Troger and W. Hille, J.Prakt.Chem., 1905, 71, 201.

123. P. Pollet and S. Gelin, Synthesis, 1979, 977.

124. H. Wynberg and H. Bantjes, Org.Synthesis, 1963, 4, 534.

125. G. Tennant and J.G. England, unpublished results.

126. L.F. Fieser, Org.Synthesis, 1943, 2, 39.

127. K. Gewald, P. Bellman and H.J. Jänsch, Justus. Leibigs. Ann.Chem., 1980, 10, 1623.

128. R. Roger and D.G. Neilson, Chem.Revs., 1961, 61, 179.

129. G. Tennant and R. Torano, unpublished results.

130. J.H. Lister, D.S. Manners and G.M. Timmis, J.Chem.Soc.(C), 1970, 9, 1313.

131. R.W. Baldwin, M.W. Partridge and M.F.G. Stevens, J.Pharm.Pharmacol.Suppl., 1966, 18, 1.

132. M.H. Elnagdi, E.M. Kandseel and K.U. Sadek, Z.Naturforsch B. 1979, 34B, 275.

133. J. Slouka and P. Pec, Monatsh.Chem., 1972, 103, 1444.

134. M. Guarneri, R. Ferroni and F. Fiorini, Gazetta, 1968, 98, 569.

135. M. Busch, Chem.Ber., 1899, 32, 2959.

136. M.H. Elnagdi, M.R.H. Elmoghayer and D.H. Flieta, J.Prakt.Chem., 1974, 316, 975.

137. K. Johnson and E.F. Degering, J.Am.Chem.Soc., 1939, 61, 3194.

138. A.K. Fateen, A.I. Hashem and E.E. Eid, J.Prakt.Chem., 1979, 321, 127.

139. O. Seidel, J.Prakt.Chem., 1898, 58, 137.

140. M.H. Elnagdi, M.M.M. Sallam, H.M. Fahmy, S.A.M. Ibrahim and M.A.M. Elias, Helv.Chim.Acta., 1976, 59, 551.

141. E.von Meyer, J.Prakt.Chem., 1895, 52, 94.

142. L.T. Bellamy, "The Infra-red Spectra of Complex Molecules", Methan and Co. Ltd., 1954, p. 225.

143. J.E. Hodgkins and W.P. Reeves, J.Org.Chem., 1965, 30, 2465.

144. D.C. Schroeder, Chem.Rev., 1955, 55, 181.

145. L.I. Samuraj, V.H. Border and G.I. Darkatsch, Angew.Chem.Internat.Ed., 1967, 6, 864.

146. L.I. Samuraj, V.A. Border and G.I. Derkatsch, Zhur.Obsch.Khim., 1969, 5, 119.

147. H. Schildknecht and G. Hatzmann, Angew.Chem., 1969, 81, 469.

148. L.I. Samaraj, V.A. Bondar and G.I. Derkatsch, Zhur. Obsch.Khim., 1965, 1, 2004.

149. R. Richter and H. Ulrich, "Synthesis and Preparative Applications of Isocyanates", in The Chemistry of Cyanates and their Thio Derivatives, Part 2, Ed. S. Patai, Wiley, New York, 1977, p. 656.

150. K. Senga, M. Ichiba, H. Kanazawa and S. Nishigaki, Synthesis, 1977, 264.

151. K. Senga, F. Yoneda, M. Higachi, M. Ichiba, H. Kanazawa and S. Nishigaki, J.Heterocyclic Chem., 1978, 15, 641.

152. F. Yoneda, M. Higuchi and T. Nagamatsu, J.Am.Chem.Soc., 1974, 96, 5607.

153. F. Yoneda, K. Senga, R. Koga, T. Ueno, S. Ogusu, K. Matsuyma, S. Nishigaki, K. Fukami, M. Ichiba, H. Kanazawa and K. Matsuyma, Heterocycles, 1981, 15, 757.

154. F. Yoneda and R. Koga, J.Heterocyclic Chem., 1982, 19, 949.

155. H. Ulrich and A.A.R. Sayigh, Angew.Chem. Internat.Edn., 1966, 5, 704.

156. C. Parkanyi and H.S. Shawli, J.Heterocyclic Chem., 1980, 17, 897.

157. A. Quilico in "Chemistry of Heterocyclic Compounds", Ed. R.H. Wiley, Interscience, New York, 1962, Part 1, p. 143.

158. S.A. Long, Jr., and Y. Lin, "Isoxazoles and their Benzo Derivatives", Comprehensive Heterocyclic Chemistry, Eds. A.R. Katritzky and C.W. Rees, Pergamon Press, 1984.

159. T. Nishiwaki, J.Chem.Soc., Chem.Comm., 1970, 945.

160. B.C. Challis and J.A. Challis, "Reactions of the Carboxamide Group" in The Chemistry of Amides, Ed., J. Zabicky, Interscience, 1970, p. 824.

161. R. Richter and H. Ulrich, "Synthesis and Preparative Applications of Isocyanates" in the Chemistry of Cyanates and Their Thio Derivatives, Part 2, Ed. S. Patai, Wiley New York, 1977, p. 747.

162. G. Shaw and G. Sugowdz, J.Chem.Soc., 1954, 665.

163. C. Maureau and I. Lazennec, Bull.Soc.Chim. France, 1907, 1, 1086.

164. J. Lublin, J.Prakt.Chem., 1906, 74, 531.

165. B. Eistert, D. Gireiber and I. Caspari, Justus. Leibigs. Ann. Chem., 1962, 659, 64.

166. H. Weiland, Chem.Ber., 1904, 37, 1145.

167. G. Ponzio, Gazetta, 1931, 61, 943.

168. M.E. Wolf and J.F. Oneto, J.Am.Chem.Soc., 1956, 78, 2615.

169. K. Hoffman, "Imidazole and its Derivatives, Part 1", Heterocyclic Compounds, Ed. A. Weisberger, Wiley, Interscience, New York, 1953, p. 142.

170. F. Yoneda and M. Higuchi, J.Heterocyclic Chem., 1980, 17, 1365.

171. M. Ishidate, M. Sekiya, Y. Osaki and Y. Hanada, Yakugaku Zusshi, 1956, 76, 1107. Chem.Abstr., 1957, 51, 3614a.

172. M. Ishidate, M. Sekiya, Y. Osaki and I. Kurita, Pharm.Bull., 1955, 3, 244. Chem.Abstr., 1956, 50, 9430h.

173. P.B. Russel and G.H. Hitchings, J.Am.Chem.Soc., 1951, 73, 3763.

174. C.W. Whitehead and J.J. Traverso, J.Am.Chem.Soc., 1956, 78, 5294.

175. St. v. Neimentowski, Chem.Ber., 1910, 43, 3012.

176. C. Craebe and S. Rotovzeff, Chem.Ber., 1902, 35, 2752.

177. A.W. Hoffmann, Chem.Ber., 1879, 12, 1126.

178. G. Bender, Chem.Ber., 1880, 13, 697.

179. P. Griess, Chem.Ber., 1869, 2, 415.

180. H. Mackie and G. Tennant, Tetrahedron Lett., 1972, 46, 4719.

181. D.R. Sutherland and G. Tennant, J.Chem.Soc., Perkin Trans. 1, 1974, 534.

182. G.K. Barnes and G. Tennant, unpublished results.

183. J.G. Smith and I. Ho, Tetrahedron Lett., 1971, 3541.

184. G. Simdien and G. Entenmann, Angew.Chem.Internat.Edn., 1973, 12, 119.

185. F. Kurzer and K. Douraghi-Zadeh, Chem.Rev., 1967, 67, 107.

186. P. Appel and P. Volz, Chem.Ber., 1975, 108, 623.

187. E. Zbiral and E. Bauer, Phosphorus, 1972, 2, 35. Chem.Abstr., 1973, 78, 43599.

188. G. Aksnes and P. Froyan, Acta.Chem.Scand., 1969, 23, 2697.

189. J.I.G. Cadogan, K.T. Scott, R.D. Gee and I. Gosney, J.Chem.Soc., Perkin Trans. 1, 1974, 1694.

190. T. Curtius, Chem.Ber., 1893, 26, 1263.

191. J.H. Boyer and E.J. Miller, J.Am.Chem.Soc., 1959, 81, 4649.

192. G. Tennant, J.Chem.Soc.(C), 1967, 2658.

193. D.R. Sutherland and G. Tennant, J.Chem.Soc.(C), 1971, 706.

194. E. Oliveri-Mundala and A. Coppola, Gazetta, 1910, 40, 435.

195. H. Zollinger, "Diazo and Azo Chemistry", Intersience, New York, 1963, p. 182.

196. D.R. Sutherland, G. Tennant and R.J.S. Vevers, J.Chem.Soc., Perkin 1, 1973, 943.

197. N.V. Khromov-Borisov and G.M. Kheifets, Zh.Obsch.Khim., 1964, 34, 1321. Chem.Abstr., 1965, 62, 6480f.

198. D.R. Sutherland and G. Tennant, J.Chem.Soc.(C), 1971, 2156.

199. T. Curtius and G. Ehrhart, Chem.Ber., 1922, 55, 1559.

200. H.R. Day and J.E. Hoover, J.Am.Chem.Soc., 1956, 78, 5832.

201. W.K. Boon, W.G.M. Jones and G.R. Ramage, J.Chem.Soc., 1951, 96.