THE CHEMISTRY OF IMIDAZO[5,1-c][1,2,4]TRIAZINES

By

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Chemistry of imidazo[5,1-c][1,2-4]triazine

SUMMARY

All possible imidazo-1,2,4-triazine ring systems containing a bridgehead nitrogen atom are described in the Introduction. Synthetic routes to, and properties of, imidazo[2,1-c][1,2,4]triazines and imidazo[5,1-c][1,2,4]triazines are reviewed in detail.

5-Aminoimidazole-4-carboxamide (4.1) was diazotised and coupled with active methylene compounds to form a series of hydrazones (4.6-4.15). The hydrazones were cyclised in acid or alkali to yield bicyclic imidazo-[5,1-c][1,2,4]triazines. Hydrazones with acetyl groups (4.6-4.9) underwent cyclodehydration to form imidazotriazines with 7-methylene substituents (4.29-4.32) whereas cyano hydrazones (4.13-4.15) cyclised in acid to yield 7-amino-imidazotriazines (4.45, 4.47 and 4.49). Hydrazones from diethyl acetonedicarboxylate (4.10) and ethyl benzoylacetate (4.11) underwent cyclo-dehydration with great reluctance to yield the corresponding imidazotriazines (4.51, 4.52).

In basic conditions hydrazones with reactive ester groups (4.6, 4.7 and 4.10-4.13) cyclised to imidazotriazin-7(4H)ones (4.55, 4.58-4.61) with loss of an alcohol moeity.

A new general route to the synthesis of pyrazolo[4,3-c]pyridazines was achieved by coupling 4-diazopyrazole-3-carboxamide (5.3) with reactive methylenicesters to yield the hydrazones (5.6-5.8). The hydrazones (5.6-5.7) underwent smooth cyclo-dehydration to yield the corresponding pyrazolopyridazines(5.14, 5.15)whereas hydrazone (5.8) cyclised with loss of ethanol to yield the pyrazolopyridazinone (5.16).

The 7-methylene (4.29) and 7-aminoimidazo[5,1-c][1,2,4]triazine (4.45) yielded mono-acetyl derivatives (6.1) and (6.2) respectively. Stepwise hydrolysis of the ethyl 7-aminoimidazotriazine-6-carboxylate (4.45) yielded the 3-carbamoyl-6-ethoxycarbonyl-imidazotriazin-7(4H)-one (4.60) or its sodium salt (6.4). The former compound was further hydrolysed to a 3-carbamoyl-4,7-dihydro-7-oxoimidazotriazine-6-carboxylic acid (6.5) and thence to 3-carbamoylimidazotriazin-7(4H)one (6.9). 7-Amino-3-carbamoyl-6-cyanoimidazo[5,1-c][1,2,4]triazine (4.47) was partially hydrolysed to yield the 3,6-dicarbamoylimidazotriazin-7(4H)-one (6.10).

Ethyl 7-aminoimidazo[5,1-c][1,2,4]triazine-6-carboxylate (4.45) reacted with hot secondary amines to yield amides (6.12-6.15). 7-Amino-3-carbamoyl-6-cyanoimidazo[5,1-c][1,2,4]triazine (4.47) was converted to 6-amino (or 6,8-diamino)-3-carbamoylpyrimido[4,5-e]imidazo[5,1-c][1,2,4]triazine (6.18 or 6.19) by heating in formamide or quanidine respectively.

The reactions of hydrazine derivatives with substituted imidazo-[5,1-c][1,2,4]triazines led to ring-fission and recyclisation to yield substituted imidazolylazopyrazoles.

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Key words: -

1. *5-Diazoimidazole-4-carboxamide*
2. *Imidazo[5,1-c][1,2,4]triazines*
3. *Pyrazolo[4,3-c]pyridazines*
4. *Pyrimido[4,5-e]imidazo[5,1-c][1,2,4]triazines*
5. *Hydrazinolysis*

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TO ABID AND MUZAFFER

CONTENTS

PART I INTRODUCTION

Part 1

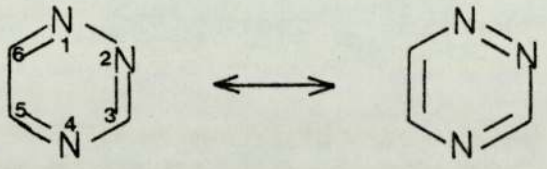
Introduction

Synthesis and properties of imidazo[1,2,4]triazines

Chapter 1

1.1 Nomenclature and definitions

The parent compound of the 1,2,4-triazine series has structure(1.1) and is numbered as indicated. In *Chemical Abstracts* the ring-system is called 1,2,4-triazine or as-triazine, where as denotes the asymmetric arrangement of the nitrogen atoms. In the old literature the name α-triazine or iso-triazine is also used.



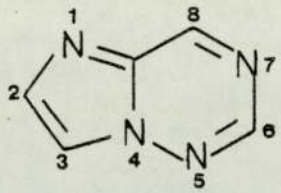
(1.1)

Numerous investigations of the synthesis and properties of 1,2,4-triazines fused with carbocycles and heterocycles have been reported. In the Introduction to this thesis all possible imidazo[1,2,4]triazine ring-systems with an imidazole ring fused to the triazine ring at a nitrogen bridgehead are listed; the synthesis and properties of imidazo[2,1-c][1,2,4]triazines(1.8) and imidazo[5,1-c][1,2,4] triazines(1.9) are reviewed in detail. An investigation of the synthesis and chemistry of the imidazo[5,1-c][1,2,4]triazines forms the substance of the Discussion of the thesis.

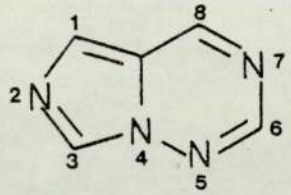
1.2 Imidazoles fused to N-1, N-2, or N-4 of the triazine ring with a bridgehead nitrogen

Theoretically eight different imidazo-triazines with a bridgehead nitrogen atom common to both the imidazole and the triazine ring are possible. These are listed below in structures (1.2) - (1.9).

Ring-Systems fused at N-1

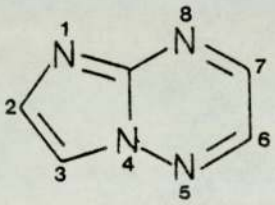


(1.2)
[2,1-f]*

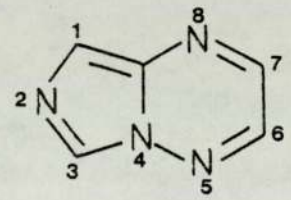


(1.3)
[5,1-f] [1-6]

Ring-systems fused at N-2



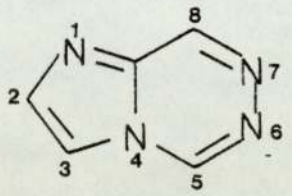
(1.4)
[1,2-b] [7-28]



(1.5) [29]
[1,5-b]

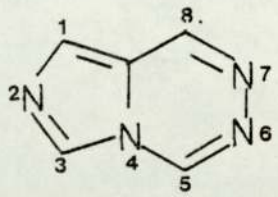
* The imidazo[2,1-f][1,2,4] triazine system has not been reported in the literature.

Ring systems fused at N-4



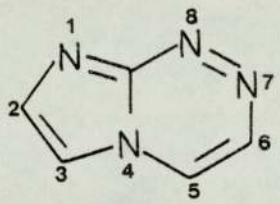
(1.6)

[1,2-d]



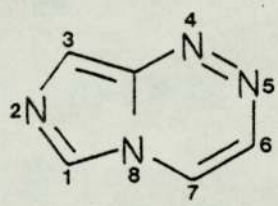
(1.7)

[1,5-d]



(1.8)

[2,1-c]



(1.9)

[5,1-c]

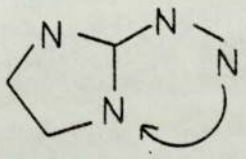
Of the structural arrangements which involve N-4 of the triazine ring the [1,2-d] and [1,5-d] systems are unknown, whereas examples of [2,1-c] and [5,1-c] fusion have been reported: these are described in Chapter 2 and 3.

Chapter 2

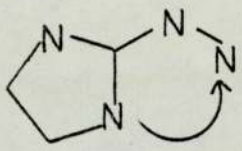
2.1 Synthesis of imidazo[2,1-c][1,2,4]triazines

The procedures which have been applied for the synthesis of the imidazo[2,1-c][1,2,4]triazine ring-system can be conveniently divided into two - those using substituted imidazoles as starting materials and those using triazine precursors. Synthetic routes using imidazoles have proved to be very versatile and numerous imidazotriazines have been made in this way.

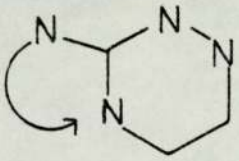
These cyclisations can be further sub-divided into four principal types (A-D) depending on the direction of ring cyclisation.



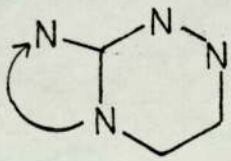
Type A



Type B



Type C



Type D

2.1.1 Syntheses of Type A

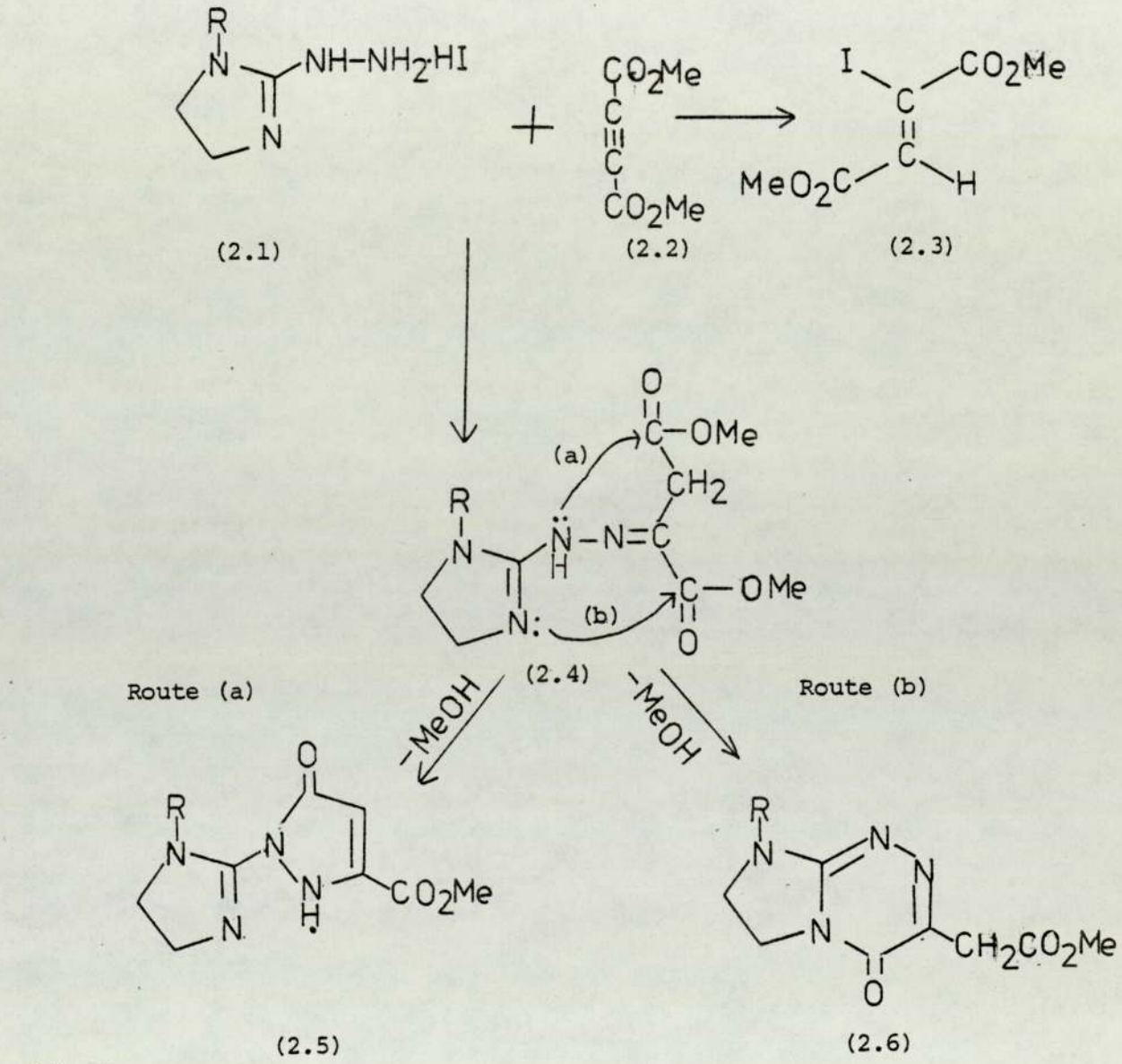
These syntheses invariably involve the cyclisation of 2-substituted imidazoles where ring closure is effected by attack of a nucleophilic imidazole ring nitrogen on an electron-deficient carbon atom on the 2-substituent.

From 2-hydrazinoimidazole derivatives

Although extensive research has been carried out on the reactions of hydrazones[30] and guanidines[31,32] with acetylenic carbonyl compounds, very little is known of the reactions of acetylenic compounds with aminoguanidine and amidrazones. Sasaki[31] made the first attempt to react aminoguanidine with dimethylacetylenedicarboxylate to form a 1,2,4-triazine ring. Similarly Wamhoff et al [33] discovered that the hydrazones obtained from the coupling reactions between heterocyclic amidrazones and unsaturated acetylenedicarboxylic esters, could undergo subsequent cyclocondensation yielding annelated triazines.

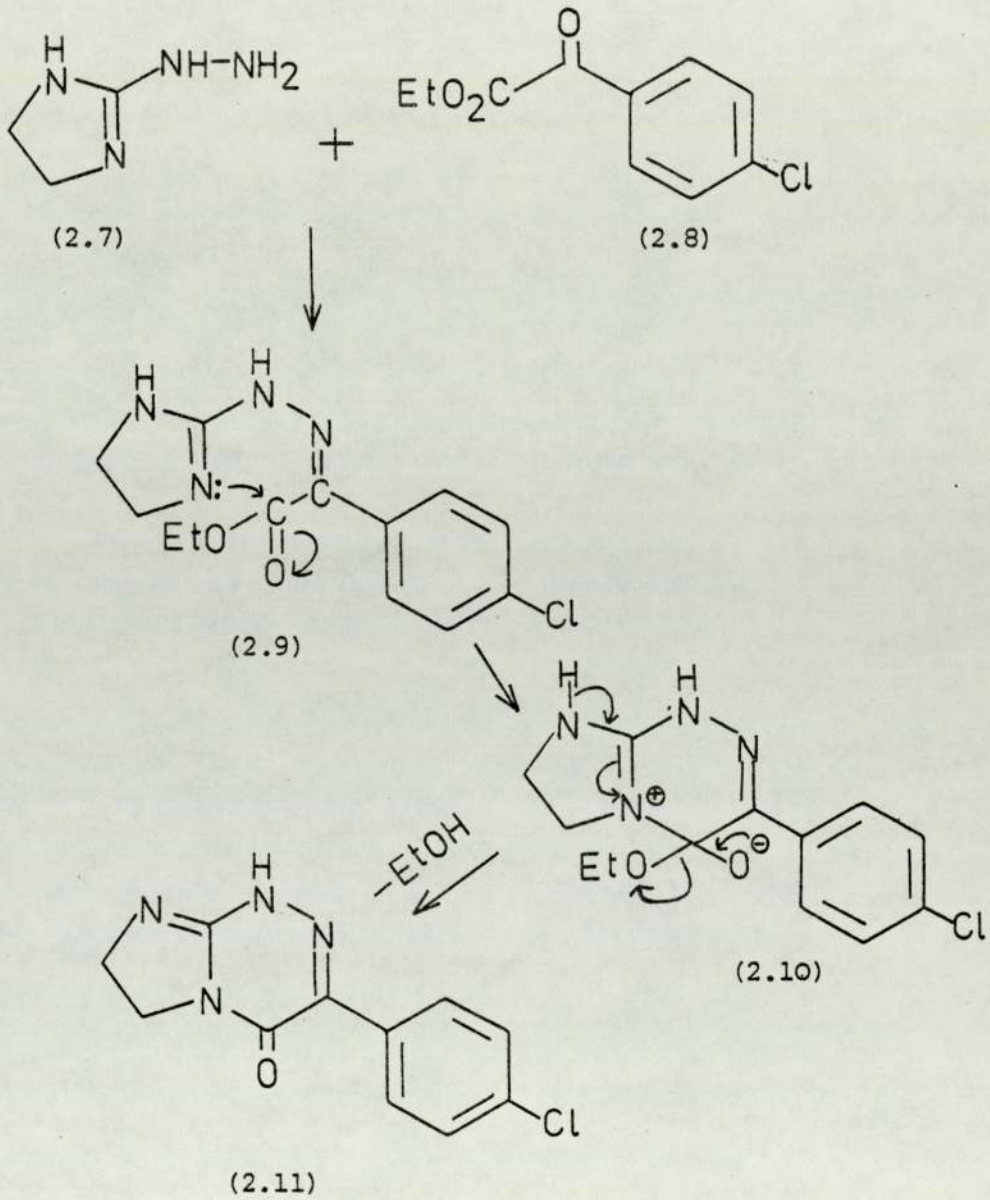
Based on the above findings[32,33] Le Count and co-workers[34,35] investigated the reactions of 2-hydrazinoimidazoline hydroiodides[36,37] (2.1; R = H, Me) with dimethyl acetylenedicarboxylate(2.2). When the reaction was attempted[35] in methanol the free base of the hydrazone(2.4) was isolated in low yield. Examination of the filtrate revealed that hydrogeniodide had reacted with the ester(2.2) to form the dimethyliodofumarate(2.3) as a major product. This side reaction was inhibited by employing water containing triethylamine as a solvent. However, the hydrazone cyclised under these conditions to the pyrazolin-5-one(2.5; R=H). The required triazinone(2.6; R=H) was obtained when the reaction was carried out in methanol containing triethylamine. The hydrazone(2.4; R=Me) did not cyclise to the

pyrazolin-5-one(2.5; R=Me) under any conditions: only the dihydro imidazotriazinone (2.6; R=Me) was formed, as illustrated by Scheme 2.1 .



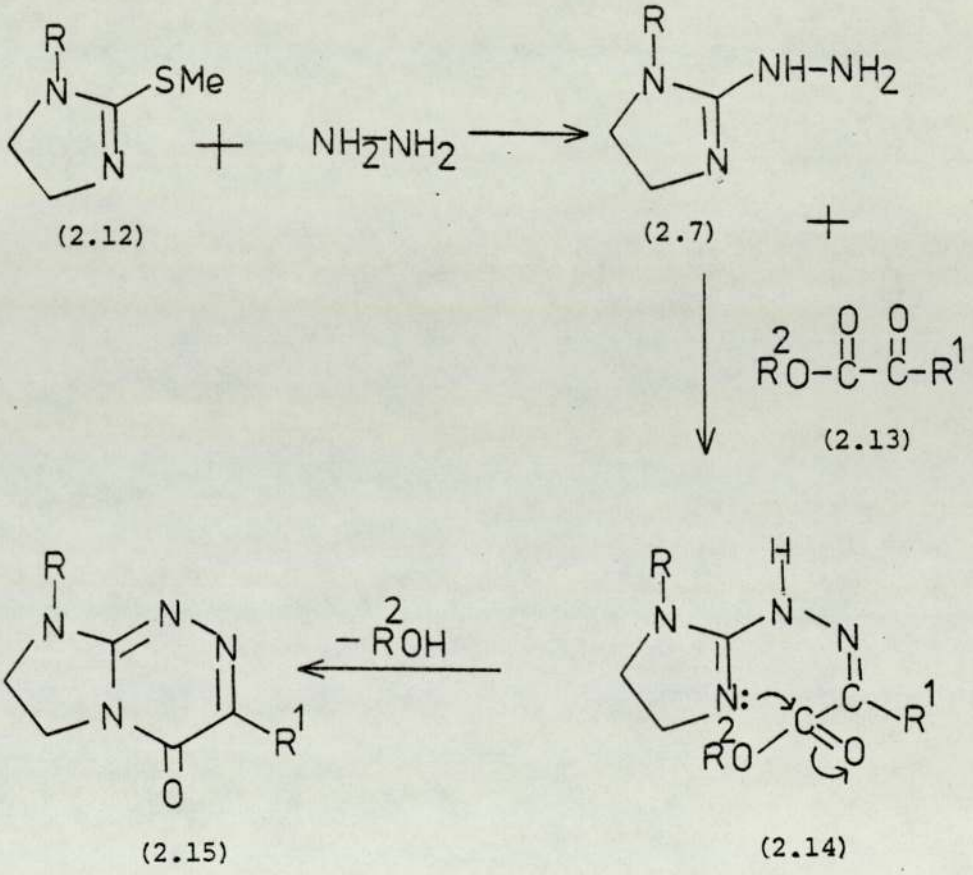
Scheme 2.1

The aryl substituted imidazotriazinone[38] (2.11) has been prepared by an analogous[34,35,36] reaction. The condensation of ethyl p-chlorobenzoyl formate (2.8) with 2-hydrazinoimidazoline (2.7) yielded the imidazotriazinone[39] (2.11) via an intermediate hydrazone (2.9) which was not isolated (scheme 2.2).



Scheme 2.2

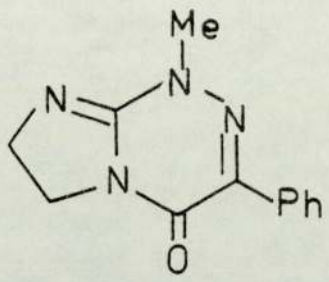
The 6-methylimidazotriazinone(2.15; R=H; R^1=Me) was first made by Lempert et al[40] in 1968 by a Type C synthesis from a 3-substituted-1,2,4-triazine (see section 2.1.3).Later in 1972 Brügger and Korte[41] adopted a Type A approach to achieve a synthesis of this compound and its 6-phenyl analogue. The reaction of hydrazine with 2-methylthio-imidazoline[42](2.12; R=H) afforded the 2-hydrazinoimidazoline(2.7; R=H). The latter when condensed with the α-ketoesters(2.13; R^1=Me,Ph; R^2=Et) yielded 6-methyl(orphenyl)-2,3-dihydroimidazotriazinones(2.15; R=H; R^1=Me or Ph) (Scheme 2.3).



R^1=Me, Ph

Scheme 2.3

Other derivatives of this series(2.15; R=R^1=Me or Ph) were synthesised by LeCount and Taylor[35] from 1-substituted-2-hydrazinoimidazoles(2.7; R=Me, Ph); these authors also prepared the 8-methyl-6-phenylimidazotriazinone(2.16).



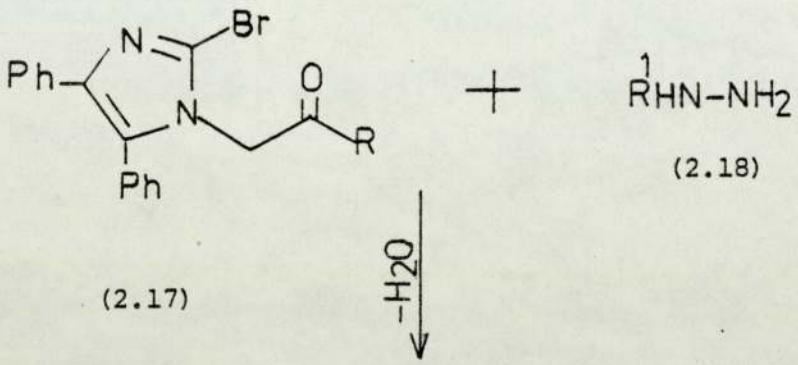
(2.16)

2.1.2 Syntheses of Type B

This type of synthesis involves the cyclisation of 1,2-disubstituted imidazoles which have an acyl group incorporated on the imidazole N-1 and a leaving group at C-2.

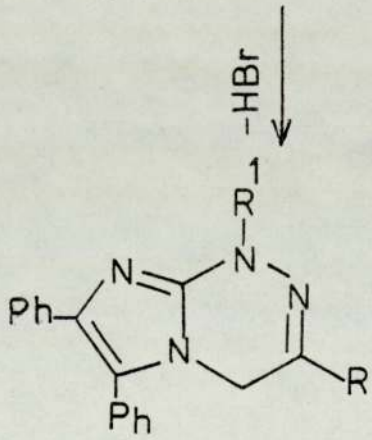
From 1,2-disubstituted imidazoles

The interaction of 1-aroylalkyl-2-haloimidazoles(2.17) with an appropriate hydrazine derivative(2.18) yields 6-aryl-dihydroimidazotriazines[43,44]. For example 6-p-bromophenyl-2,3-diphenyl-5,8-dihydroimidazotriazine(2.20a; R=C_6H_4Br-p, R^1=H) and 6-p-bromophenyl-2,3,8-triphenyl-5,8-dihydroimidazotriazine(2.20b; R=C_6H_4Br-p, R^1=Ph) are prepared *via* the intermediate hydrazones(2.19). Other examples of the products formed in this type of synthesis are listed in Table 2.1.



(2.17) (2.18)

(2.19)



(2.20)

R = see Table 2.1

R^1 = " " "

Scheme 2.4

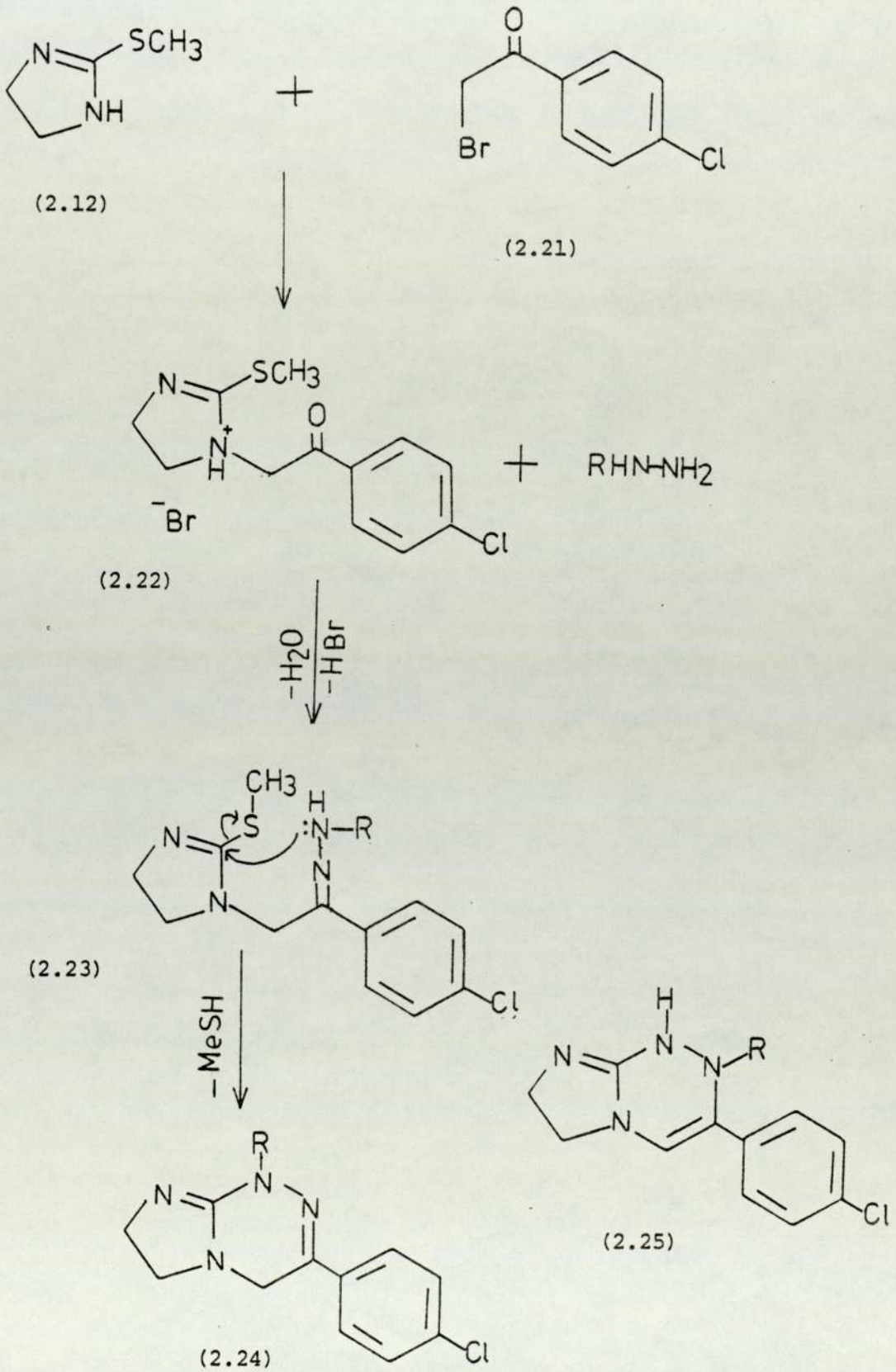
5,8-Dihydroimidazole[2,1-c][1,2,4]triazines

Table 2.1

Compound	R	R^1	% yield	References
2.20a	p-C_6H_4Br	H	70	43,44
2.20b	p-C_6H_4Br	Ph	69	"
2.20c	Ph	H	76	"
2.20d	Ph	Ph	65	"

Other substituted derivatives of phenacyl bromide[16,45] proved to be successful reagents for the synthesis of substituted imidazo-[2,1-c][1,2,4]triazines. This route has been explored by Eberle and Schrim[38] to prepare the substituted 6-phenyltetrahydroimidazo-triazines from the readily available 2-methylthioimidazoline[42] (2.12). This compound when condensed with p-chlorophenacyl bromide (2.21) in acetone afforded the hydrobromide salt (2.22). A marked acceleration with improved yield was noted when the reaction was carried out in dimethyl formamide. The tetrahydroimidazo[2,1-c][1,2,4]triazine (2.24; R=H) was obtained from the exothermic reaction between the hydrobromide salt and hydrazine with the evolution of methylmercaptan (scheme 2.5).

The chlorophenyltriazine (2.24; R=Me) was the only product obtained by the condensation of the hydrobromide salt (2.22) and methylhydrazine. Therefore it was envisaged that the hydrazone (2.23) was formed in the first stage of the reaction and the subsequent

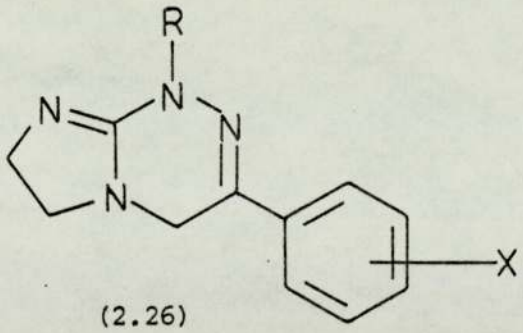


Scheme 2.5

cyclisation occurred with the elimination of methylmercaptan at the second stage. If the elimination of the methylmercaptan had occurred at the first stage then this mode of cyclisation would presumably yield two isomers(2.24; R=H and 2.25; R=Me).

The same procedure was adopted to prepare various analogues (2.26) by condensing different substituted phenacyl bromides with hydrazine derivatives(Table 2.2).

2,3,5,8-Tetrahydroimidazo[2,1-c][1,2,4]triazines

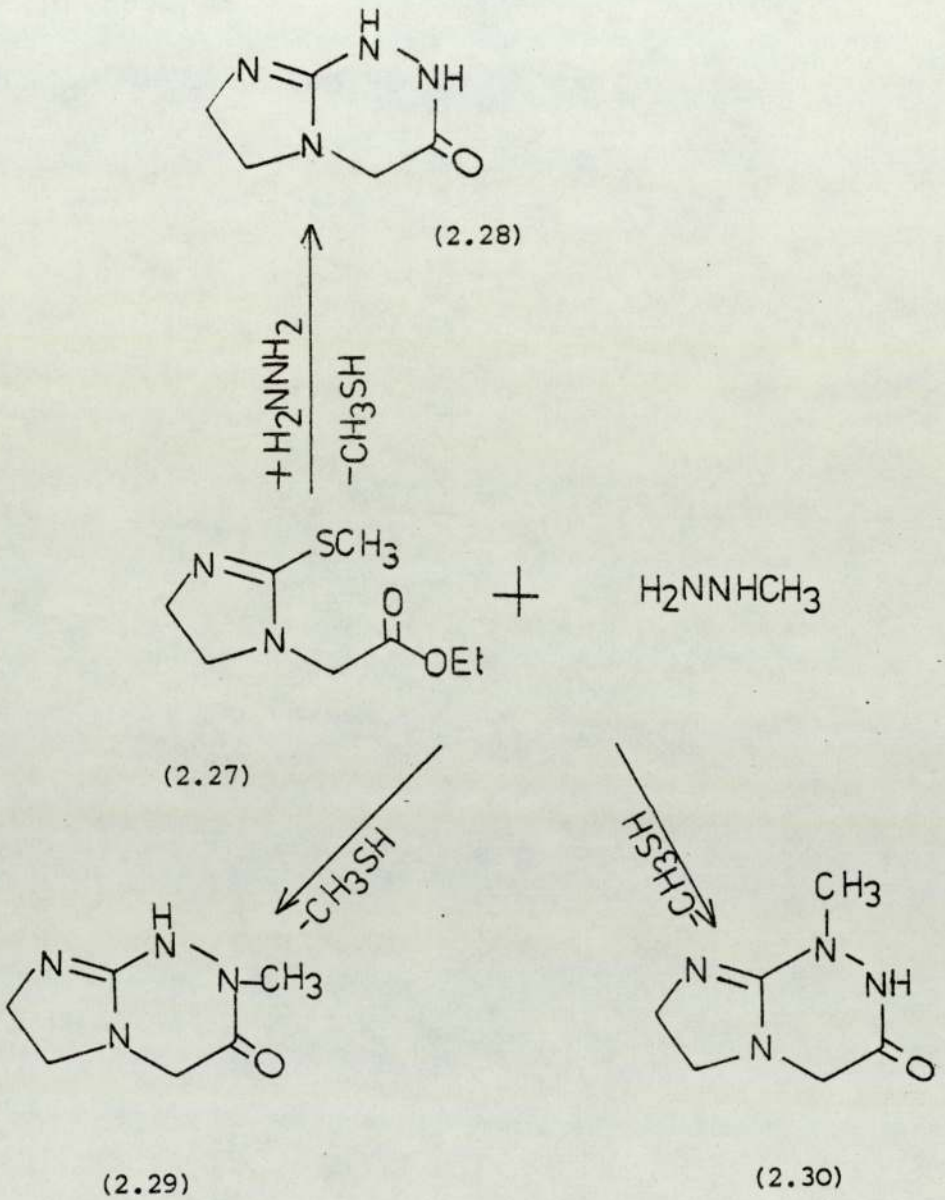


(2.26)

Table 2.2

Compound	R	x	Salt	% yield	Reference
2.24	H			70	38
2.25	Me			a	"
2.25	Me		HBr	90	"
2.26	H	p-OMe		60	"
2.26	Me	p-OMe	HBr	74	"
2.26	Me	p-OMe		a	"
2.26	H	H		70	"
2.26	Me	H	$HBr.H_2O$	39	"
2.26	Me	H		a	"
2.26	H	o,p-Cl_2		80	"
2.26	Me	o,p-Cl_2		63	"
2.26	H	p-F		52	"
2.26	Me	p-F	HBr	55	"
2.26	H	p-Me		41	"
2.26	Me	p-Me		a	"

a = % yields not quoted



Scheme 2.6

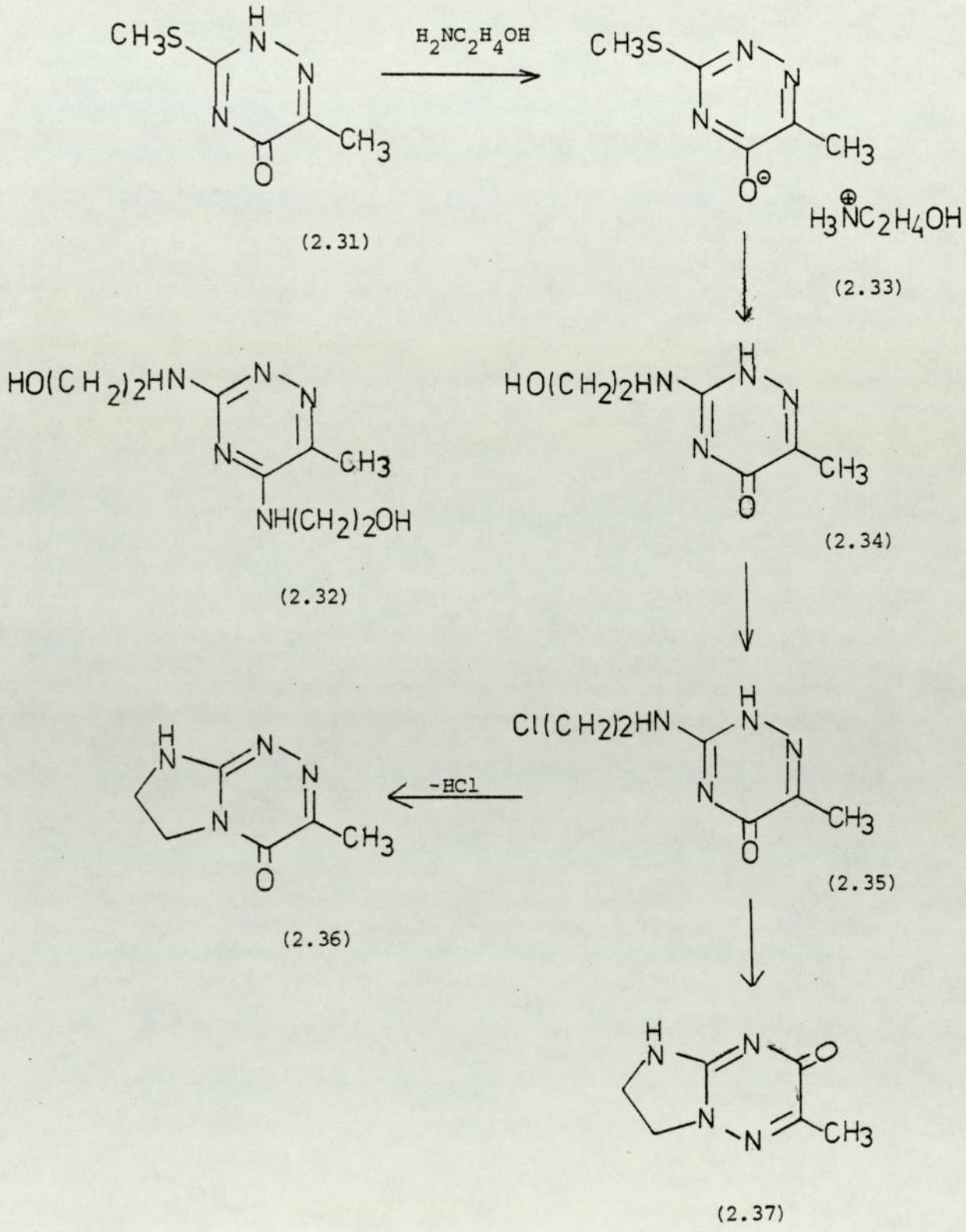
Similarly the reaction of methylthioimidazoline with ethyl-bromoacetate yielded the hydrobromide salt of 1-ethyl-2-methylthio-imidazoline acetate. When the free base of this compound(2.27) was condensed with hydrazine, the hexahydroimidazo[2,1-c][1,2,4]triazinone (2.28) was isolated in 90% yield[38] (scheme 2.6).

However, when compound(2.27) was reacted with methylhydrazine the 7-methyl(2.29) and 8-methylhexahydrotriazinone(2.30) were formed in approximately equal amounts[38]. The course of this reaction must be determined by the relative nucleophilicities of N-1 and N-2 of methyl-hydrazine: evidently this unsymmetrical hydrazine behaves as an ambident nucleophile in this reaction. In contrast only one isomer(2.24) is formed in the reaction between the phenacylimidazolinium salt(2.21) and methylhydrazine.

2.1.3 Syntheses of type C

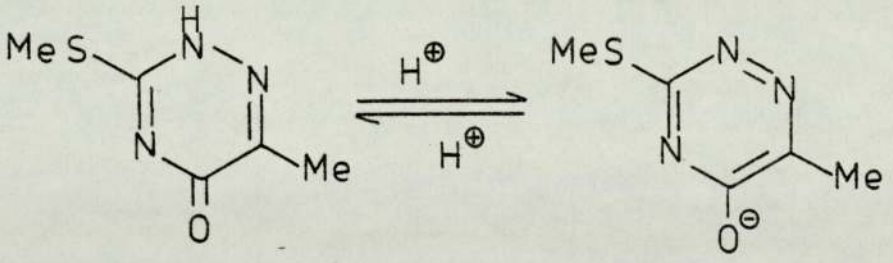
The methods described so far for the synthesis of imidazo-[2,1-c][1,2,4]triazine have utilised suitably substituted imidazoles to build the triazine ring fused through a nitrogen bridgehead. The same bicyclic system can alo be obtained from the cyclisation of substituted 3-amino-1,2,4-triazines by making use of an exocyclic alkylamino group at C-3 and ring nitrogen at position 4. The only example of this type is due to Lempert et al[40], who have also explored the synthesis of various substituted thiazolotriazines by this route from 3-mercapto-1,2,4-triazindiones[47,48].

3-(2-Hydroxyethylamino)-6-methyl-1,2,4-triazin-5(2H)-one(2.34) was prepared from the methylthio-1,2,4-triazinone (2.31) by heating the triazinone in excess of 2-aminoethanol. In addition to the selective aminolysis of the methylthio group, aminolysis at C-5 also occurred,


CH3S
H2NC2H4OH
CH3
(2.31)
H3⊕NC2H4OH
(2.33)
HO(CH2)2HN
NH(CH2)2OH
(2.32)
(2.34)
Cl(CH2)2HN
-HCl
(2.35)
(2.36)
(2.37)

Scheme 2.7

yielding a substituted 3,5-diamino-1,2,4-triazine derivative(2.32). This was due to the enhanced activity of the conjugated carbonyl group to nucleophilic attack - namely alcoholysis[49,50] and aminolysis[51] - as compared to the reactivity of ordinary amides. This undesirable side reaction was inhibited by using one molar equivalent of 2-aminoethanol. The only disadvantage of this method was that it yielded a salt (2.33), as indicated by the characteristic ultraviolet spectrum of this compound, which was comparable to the uv spectrum of the anion of 5-hydroxy-6-methyl-3-methylthio-1,2,4-triazine(2.38)[52,53].

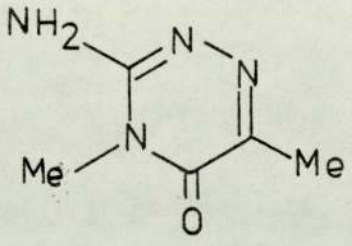


(2.31) (2.38)

The salt(2.33) was efficiently converted to 3-(2-hydroxyethylamino)-6-methyl-1,2,4-triazin-5(2H)-one (2.34) in tetralin at 150°C. Treatment of the alcohol with thionyl chloride yielded the corresponding 3-(2-chloroethylamino)-1,2,4-triazine derivative(2.35). Thermal cyclisation of the hydrochloride of the chloroethylamine yielded an imidazotriazinone hydrochloride salt. The free base of this compound (2.36) was obtained by treatment of the salt with diazomethane.

In contrast, when(2.35) was boiled in hot ethanolic sodium ethoxide ring closure took place to involve N-2 of the triazine ring and the isomeric imidazo[1,2-b][1,2,4]triazinone(2.37) was obtained. The direction of cyclisation was easily deduced from the uv spectra of these products(2.36 and 2.37). The uv spectrum of the product obtained

from thermal cyclisation, the imidazo[2,1-c][1,2,4]triazinone(2.36), showed two distinct absorption bands (Table 2.3). Similar bands are found in the electronic absorption spectrum of the 3-amino-1,2,4-triazinone(2.39)[54]. The isomeric compound (2.37) obtained from basic cyclisation contained only one peak at λmax 210nm and a shoulder at 244nm similar to the spectrum of the cross-conjugated 3-amino-1,2,4-triazin-5-one(2.34) (Table 2.3).



(2.39)

These structural assignments were also corroborated by the i.r. spectra of the products. The carbonyl band of the thermally-cyclised product(2.36) was found at higher frequency than that of its isomer (2.37) (Table 2.3). This marked difference in the frequencies is in complete agreement with earlier observations[47,48] which assert that the carbonyl band of the continuously conjugated system is always found at higher frequency than that of cross-conjugated system.

The cyclisation of (2.35) under basic conditions is the result of a direct intramolecular alkylation reaction at nitrogen N-2 which is known to be more nucleophilic than the nitrogen atom N-4, as observed in many similar triazinone syntheses[47,48,55-57]. The thermal cyclisation of (2.35) to yield (2.36) is an exception. Salt formation apparently inverts the order of nucleophilicity of the two nitrogen atoms. This can be explained by assuming that in the salt of (2.35) the nitrogen at N-2 is protonated and no longer nucleophilic; and the ring closure must of necessity proceed with participation of nitrogen N-4.

Table 2.3

Electronic and infrared spectra of the triazinones

Compound	λmax (nm) [log ε]	γa (cm^{-1})	Refs.
2.34	210 [4.42]; 240* [3.86]	1660,1600(vs),1555/45(d)1525,1480	40
2.36	220 [4.05]; 300 [3.79]	1680,1635(vs),1545,1490	40
2.37	210 [4.05]; 244* [3.86]	1660,1600(vs),1560-20(br)1480	40
2.39	220 [4.05]; 300 [3.79]	1680,1635(vs)1540,1490	54

a = characteristic bands of double bond region

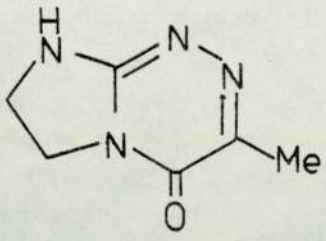
br= broad

d = doublet

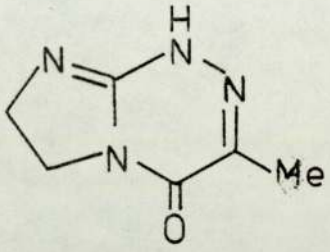
vs= very small

* = shoulder

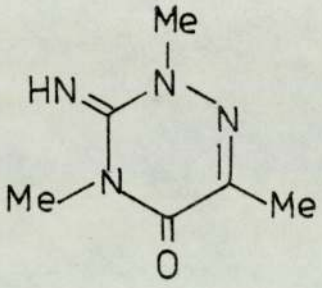
The compound (2.36) could potentially exist in another tautomeric form with a C=N fragment in an exocyclic position with respect to the triazine ring (2.36b). This possibility was excluded by comparison with the spectra of the known triazine (2.40)[54] containing the latter type of chromophore. However Le count and Taylor[35] disregard this assumption and claim that both forms (2.36a and 2.36b) are isolable in the solid state although no method has been developed to yield the tautomer of choice (see page 40).



(2.36a)



(2.36b)



(2.40)

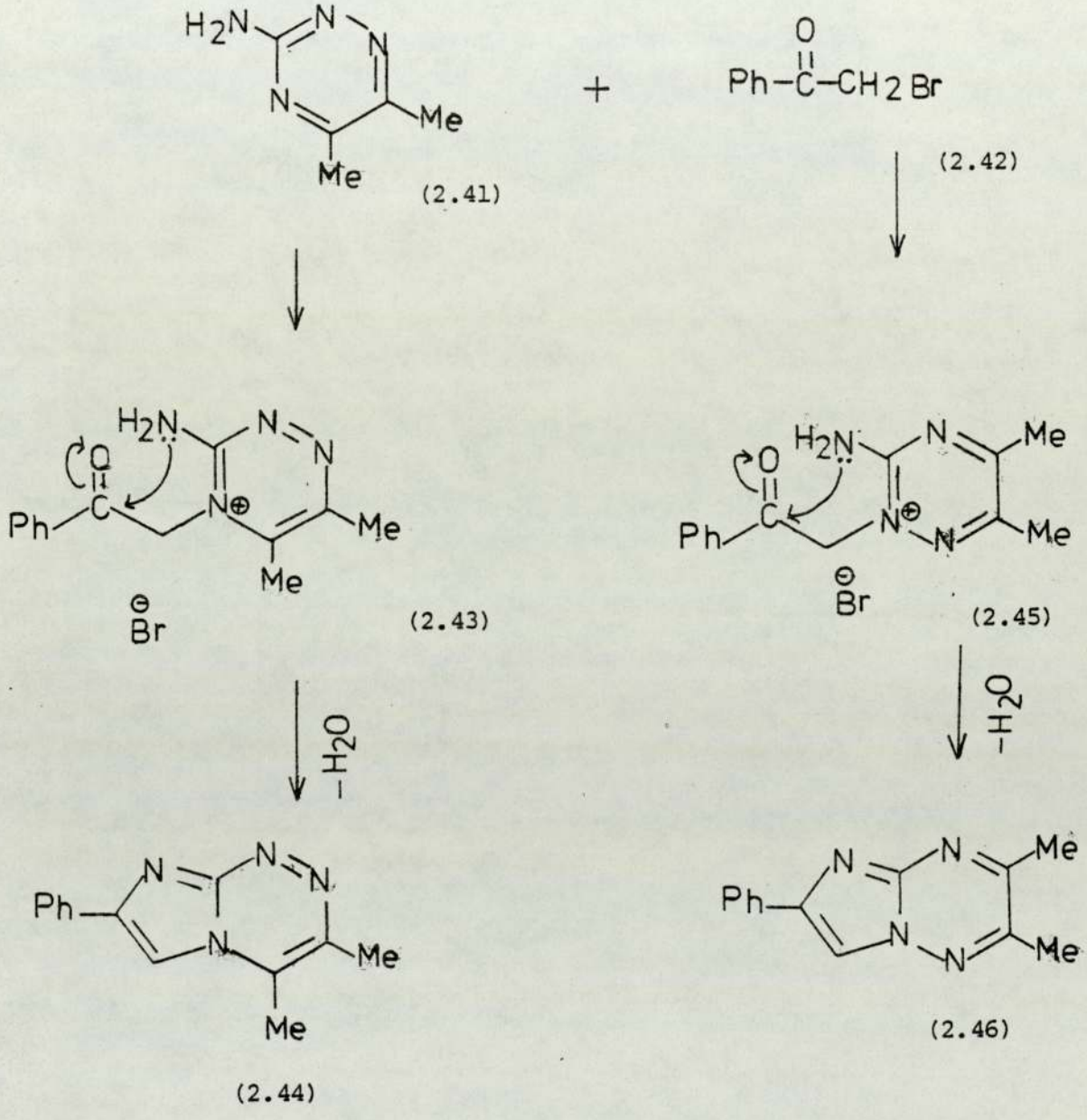
2.1.4 Syntheses of Type D

From 3,4-disubstituted 1,2,4-triazines

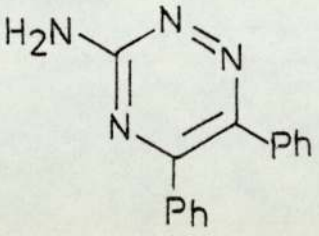
The first fully aromatic imidazo[2,1-c][1,2,4]triazine synthesized was 5,6-dimethyl-2-phenylimidazo[2,1-c][1,2,4]triazine (2.44)[16]. This compound was prepared in the search for pharmacologically useful imidazole derivatives.

There are several methods described in the literature[58-62] for the synthesis of an imidazole ring from various amino heterocycles. Werbel and Zomara[16] have used the Tschitschibabin method[63] to build the imidazole ring fused to a triazine ring. This method involves the reaction of phenacyl bromide(2.42) with 3-amino-5,6-dimethyl-1,2,4-triazine(2.41) at ring nitrogen to yield the quaternary salt (2.43). Thermal cyclisation of this salt by attack of the amino group at the electrophilic carbonyl furnished the imidazotriazine (2.44). The authors failed to determine the direction of cyclisation On the basis of the analogous compound made in the pyridine series[64-67] it was assumed that electrophilic attack of phenacyl bromide at N-2 of the triazine ring would yield the [1,2-b]isomer(2.46), while the participation of N-4 would yield the imidazo[2,1-c][1,2,4]triazine (2.44) (Scheme 2.8).

In the analogous reaction of 3-amino-5,6-diphenyl-1,2,4-triazine(2.47) with a range of acid halides(2.48) it was claimed[68,69] that the cyclisation occurred involving N-2 of the triazine ring in preference to N-4. The products in this case were formulated as imidazo[1,2,b]triazines(2.49 or 2.50). Since 3-hydrazine-5,6-diphenyl-1,2,4-triazine reacts with benzoyl chloride to yield the imidazo-[1,2-b]triazine(2.49; R^1=Ph, R^2=H)[70] this also suggests(2.46)

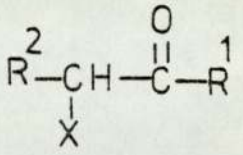


Scheme 2.8

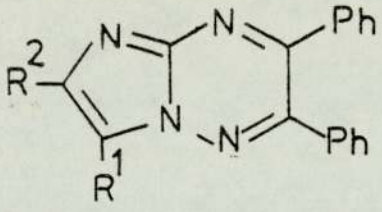


(2.47)

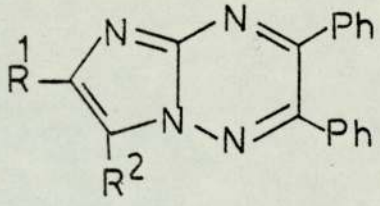
+



(2.48)



(2.49)



(2.50)

skeletal arrangement is to be preferred, although no structural proof was offered to support this assignment and to eliminate the alternative structure (2.44).

2.1.5 Syntheses of imidazo[2,1-c][1,2,4]triazines from miscellaneous heterocycles

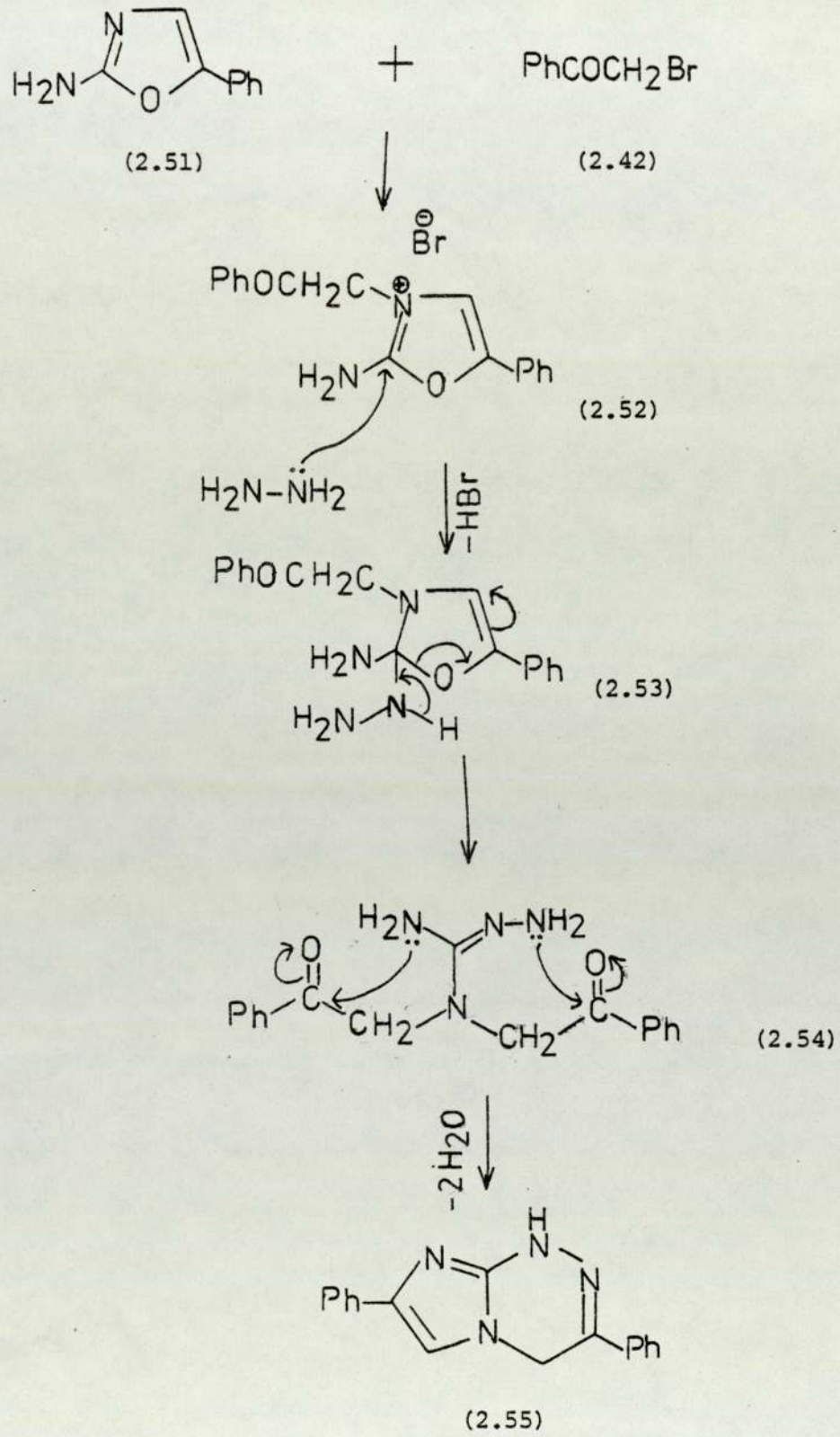
This route involves the ring-fission of other nitrogen heterocycles (containing oxygen or sulphur) by hydrazine derivatives, with subsequent recyclisation to form the expanded triazine ring.

2.1.5.1 From 2-aminooxazoles

The literature contains several references[70-76] regarding the replacement of oxygen in oxygen heterocycles by various substituted hydrazine derivatives. Different substituted 5,8-dihydroimidazo[2,1-c][1,2,4]triazines are claimed to be obtained by this intriguing reaction of hydrazines with 2-aminooxazoles,

For example, 2-amino-4-phenyloxazole (2.51) may be quaternised at the ring nitrogen with phenacyl bromide to yield 2-amino-3-phenacyl-5-phenyloxazolium bromide (2.52). This product, when treated with various hydrazines, apparently undergoes spontaneous ring expansion by fission and recyclisation to form 5,8-dihydro-2,6-diphenylimidazo[2,1-c][1,2,4]triazine (2.55)[45] (Scheme 2.10).

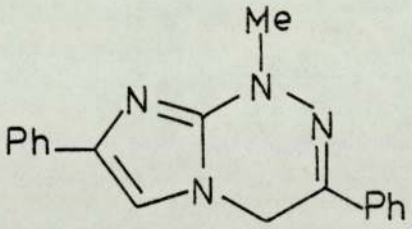
The mechanism of this reaction is obscure; obviously there can be no nucleophilic attack by hydrazine at the carbonyl carbon of the phenacyl group, which might have been expected. Instead, hydrazine probably initiates ring-opening by attack at C-2 of the oxazolium salt. This carbon has relatively high partial positive


PhCOCH2Br
(2.51)
(2.42)
Br⊖
PhOCH2C
H2N
Ph
(2.52)
H2N–NH2
-HBr
PhOCH2C
H2N
Ph
(2.53)
H2N
H
H2N
N–NH2
O
Ph
CH2
CH2
Ph
(2.54)
-2H2O
H
N
Ph
Ph
(2.55)

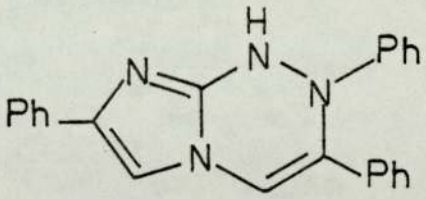
Scheme 2.10

charge because of the adjacent electropositive centre.

5,8-Dihydro-8-methyl-2,6-diphenylimidazo[2,1-c][1,2,4]-triazine(2.56) was the only product obtained from the reaction between the salt(2.52) and methylhydrazine. This imidazotriazine was also prepared by the methylation of compound(2.55) with dimethyl sulphate in sodium methoxide solution (see page 30). Phenylhydrazine behaved differently under the same conditions; apparently the 2,6,7-triphenyl isomer (2.57) was formed exclusively.

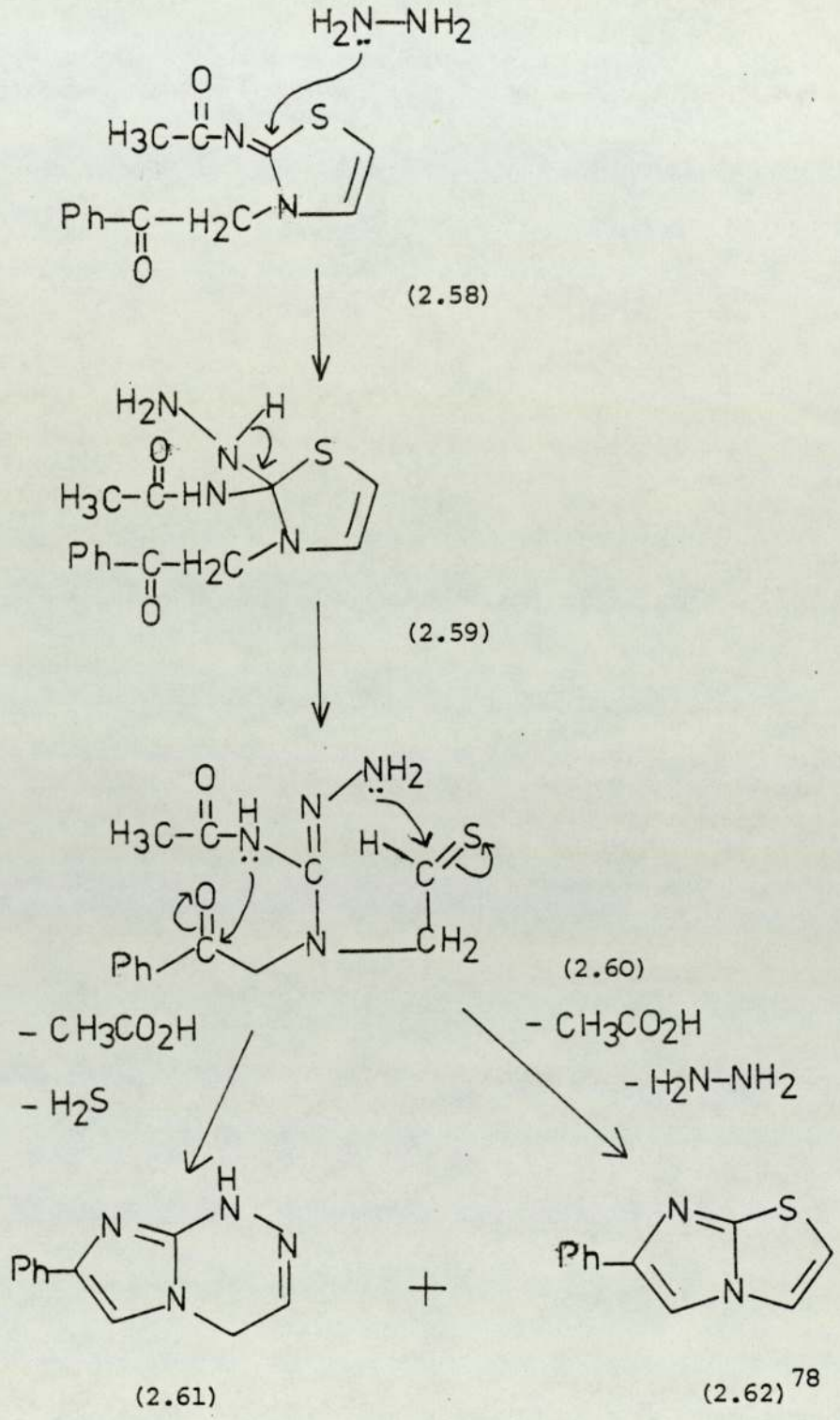


(2.56)



(2.57)

These results may be adequately explained by considering the electronic influence of the methyl and phenyl groups on the nucleophilicity of the nitrogen atoms of the respective substituted hydrazines. In the case of methylhydrazine, the electron-donating methyl group renders the methylamino group more nucleophilic and it is therefore the substituted amino group which initially participates in the ring cleavage. This is not the case with phenylhydrazine where (evidently) the unsubstituted amino group is the participating nucleophile.



Scheme 2.11

2.5.1.2 From 2,3-disubstituted thiazolines

Investigations[77] on the reactions of hydrazine with various substituted thiazolo[3,2-a]pyrimidin-5-ones led to the discovery of this ring-system.

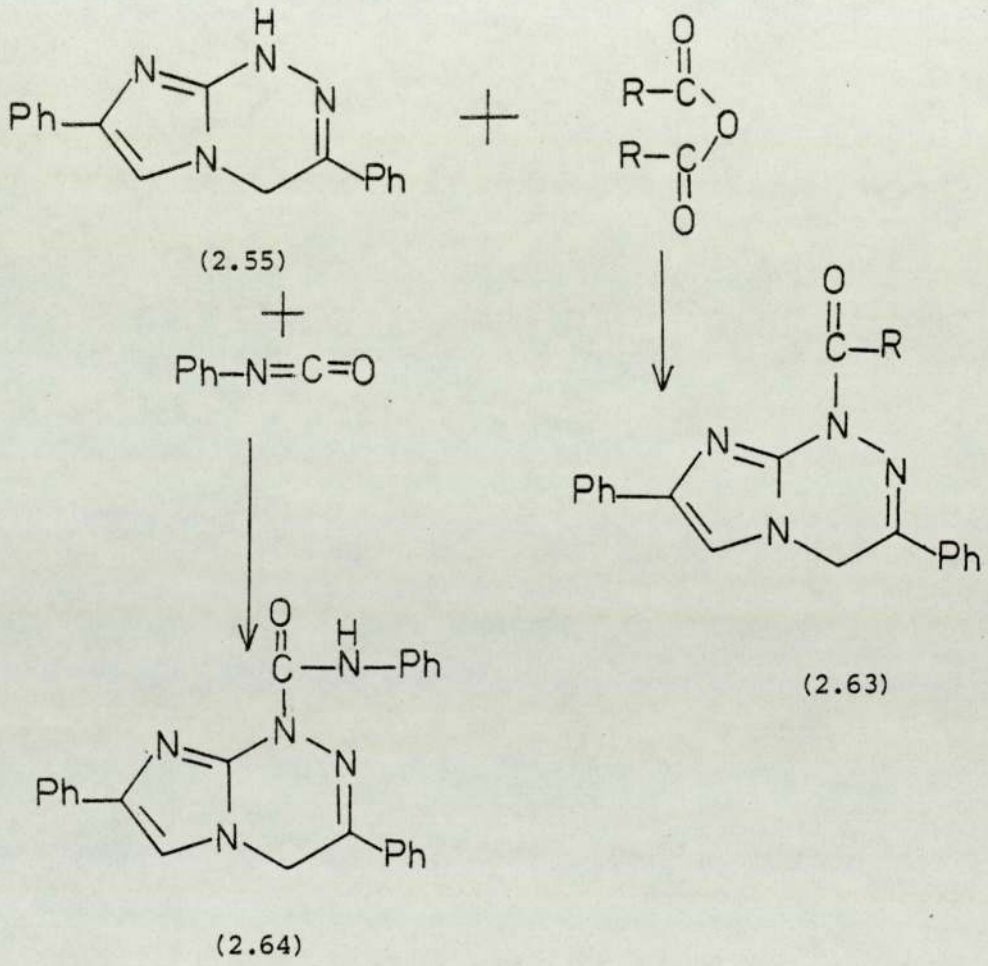
2-Acetylimino-3-phenacyl-4-thiazoline(2.58) which contains an electron-deficient centre at the C-2 position, forms an adduct with hydrazine. The ring-opened product(2.60) cyclises under heat with the loss of acetic acid and hydrogen sulphide to yield 5,8-dihydro-2-phenylimidazo[2,1-c][1,2,4]triazine(2.61)[77]. A small amount of 2-phenylimidazo[2,1-b]thiazole(2.62)[78] was also obtained (Scheme 2.11). The rate of reaction in this case is much slower than the analogous reaction in the oxazole series.[45]

2.2 Chemical properties of imidazo[2,1-c][1,2,4]triazines

The literature contains only few references pertaining to the chemical properties of imidazo[2,1-c][1,2,4]triazine. These reactions are summarised in this section.

2.2.1 Acylation

5,8-Dihydro-2,6-diphenylimidazo[2,1-c][1,2,4]triazine (2.55) has been acylated successfully with acid anhydrides in pyridine. Acylation occurred in the 8 position to yield the 8-acyl-5,8-dihydro-2,6-diphenylimidazo[2,1-c][1,2,4]triazines (2.63).[45,46] Similarly phenyl isocyanate in dioxan was employed to produce the 8-phenylcarbamoyl-2,6-diphenyl-5,8-dihydroimidazo[2,1-c][1,2,4]triazine (2.64).[45,46]



(2.55)

(2.63)

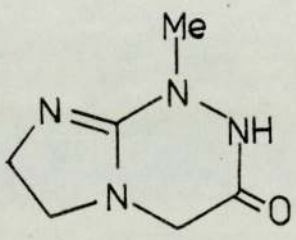
(2.64)

2.2.2 N-Methylation

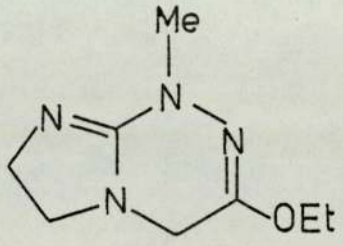
5,8-Dihydro-2,6-diphenylimidazo[2,1-c][1,2,4]triazine(2.55) was readily methylated with dimethylsulphate in sodium methoxide solution. It was found that N-8 of the triazine ring was the only methylated site.[45] The same imidazotriazine(2.56) was also obtained from the reaction of methylhydrazine with phenyloxazolium bromide (2.52) (see page 26).

2.3.3 O-Alkylation

When 8-methylhexahydroimidazo[2,1-c][1,2,4]triazin-6-one (2.30)[38] was reacted with triethyloxonium fluoroborate[79], a non polar liquid was isolated which was assigned the structure(2.65)[38] based on ^{1}H.n.m.r. spectroscopic evidence (see p. 45).



(2.30)



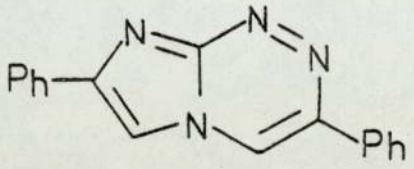
(2.65)

2.2.4 Oxidation

Mild oxidising agents such as N-bromosuccinimide or bromine oxidise the triazine ring alone[45], while drastic oxidising agents such as chromic oxide effect degradation of the imidazole ring and oxidation of the triazine ring[38].

(a) N-Bromosuccinimide

Oxidation of the imidazotriazine (2.55) with N-bromsuccinimide



(2.66)

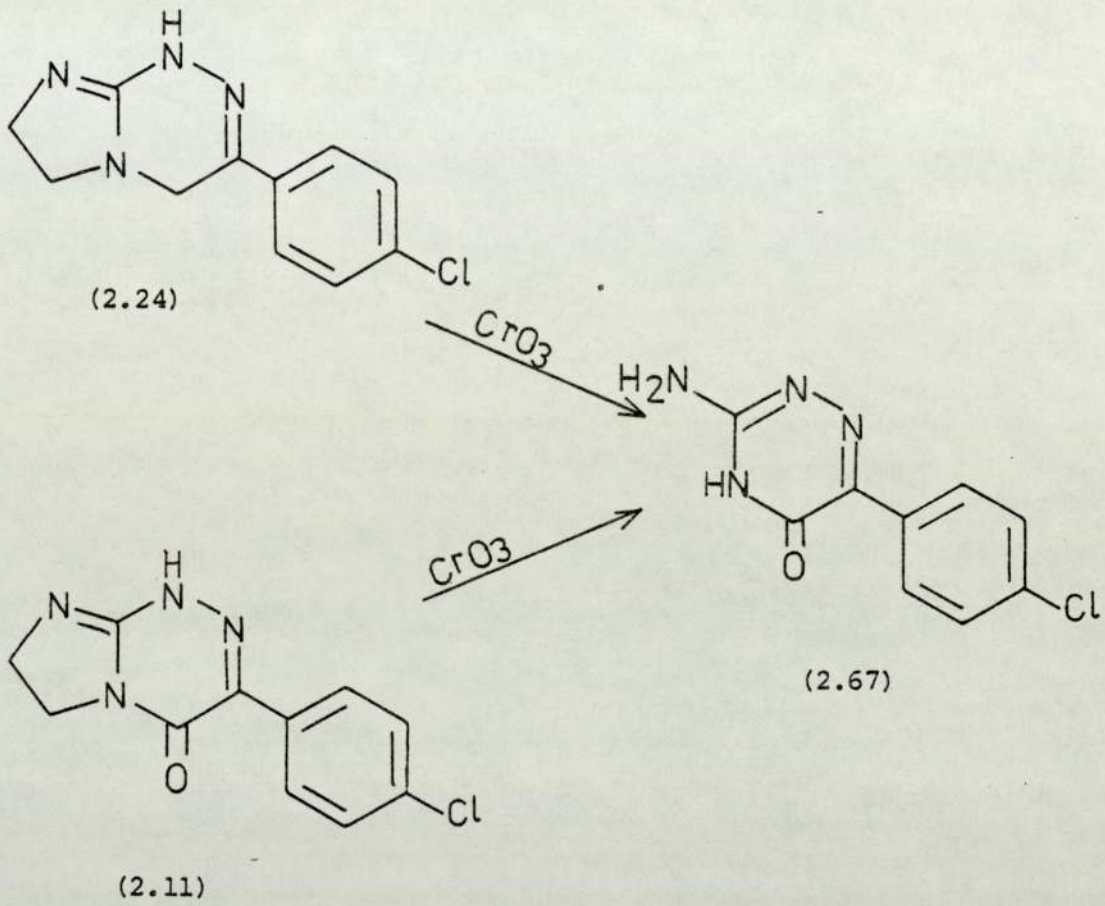
afforded the fully aromatic bicycle (2.66).[45]

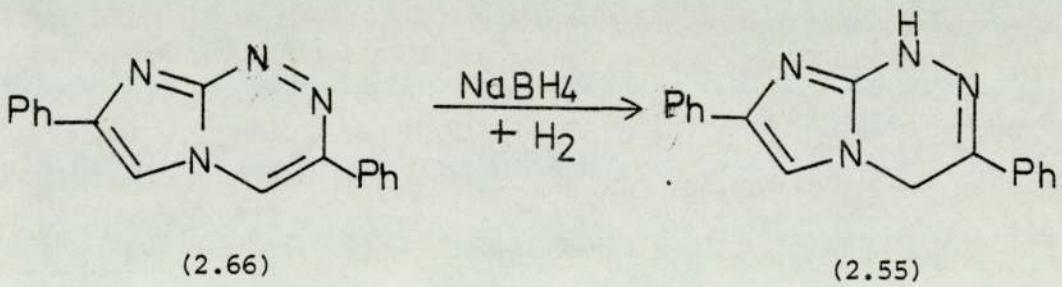
(b) Chromium trioxide

6-(4-Chlorophenyl)-2,3,5,8-tetrahydroimidazo[2,1-c][1,2,4]-triazine (2.24) when treated with chromium trioxide in glacial acetic acid underwent oxidative ring-fission to afford 3-amino-6-(4-chlorophenyl)-1,2,4-triazin-5(4H)-one (2.67).[38] This product was also obtained from the oxidation of 6-(4-chlorophenyl)-2,3-dihydro-imidazo[2,1-c][1,2,4]triazin-5(8H)-one (2.11) under the same conditions.[38]

2.2.5 Reduction

The fully aromatic imidazotriazine (2.66) was reduced to the 2,8-dihydro derivative (2.55) with sodium borohydride in hot dimethylformamide and pyridine.[45] This reaction indicates that the triazine ring is more susceptible to reducing agents generating hydride ions than the imidazole ring, as expected for a π-deficient heterocycle.


(2.24)
CrO3
(2.67)
CrO3
(2.11)


NaBH4
+ H2
(2.66)
(2.55)

2.3 Physical and spectral properties of imidazo[2,1-c]|1,2,4|-triazines.

All known physical and spectral properties of derivatives of this ring-system are summarised in Tables(1-8). The numbers used in the tables below for these compounds do not correspond to the number given in the earlier sections of this thesis.

2.3.1 Melting points.

The melting point of only aromatic imidazotriazine(2.44)[16] (M.pt 218-219°c) has been reported; the base is obtained in very poor yield (18%) from its hydrobromide salt.

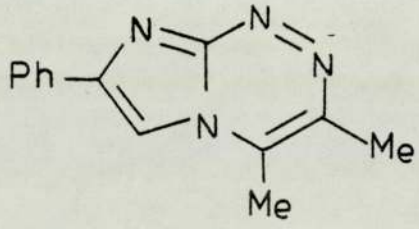
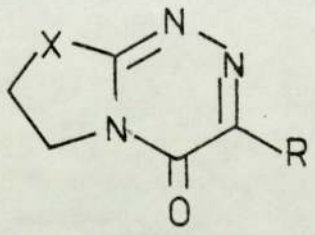


Table 1

2,3-Dihydroimidazotriazines



(2.68)

Compound	X	R	M.p. (°C)	References
2.68	NH	CH_2CO_2Me	202	34,35
2.68	NMe	CH_2CO_2Me	98- 99	"
2.68	NH	Me	291-292	40,41
2.68[a]	NH	Me	273-274	"
2.68[b]	NH	Me	142	35
2.68	NH	Ph	210	41
2.68[c]	NH	Ph	188-190	"
2.68	NMe	Me	102-103	35
2.68	NMe	Ph	184-185	"
2.68	NPh	Me	225-227	"

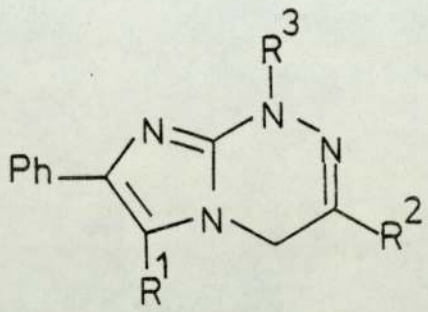
a = Hydrochloride salt

b = 8-Methyl-derivative

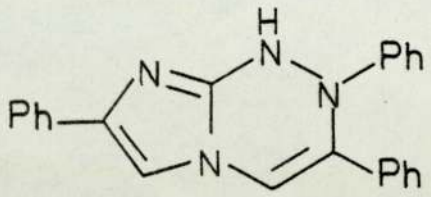
c = Hydrate

Table 2

5,8-Dihydroimidazotriazines and a 7,8-dihydro imidazotriazine



(2.69)



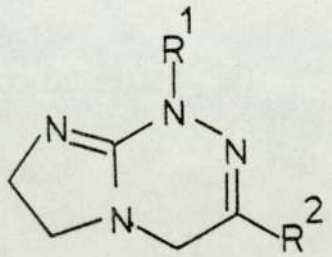
(2.70)

Compound	R^1	R^2	R^3	M.P. (°C)	References
2.69	Ph	p-C_6H_4Br	H	285-288	43,44
2.69	Ph	p-C_6H_4Br	Ph	256-258	"
2.69	Ph	Ph	H	268-270	"
2.69	Ph	Ph	Ph	248-250	"
2.69	H	Ph	H	295-297(dec)	45,46
2.69[a]	H	Ph	H	264-264(dec)	"
2.69	H	Ph	Me	160	"
2.69	H	H	H	259-260	77
2.69	H	Ph	Ac	195	45,46
2.69	H	Ph	Et.Co	218-219	"
2.69	H	Ph	Bz	219-220	"
2.69	H	Ph	Ph.NH.CO	289-291(dec)	"
2.70	-	-	-	184-185	"

a = Hydrochloride salt

Table 3

2,3,5,8-Tetrahydroimidazotriazines



(2.71)

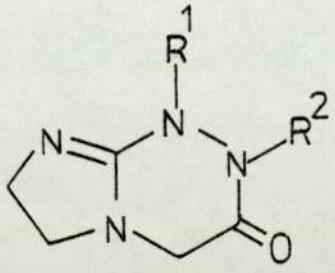
Compound	R^1	R^2	M.p. (°C)	Reference
2.71	H	p-C_6H_4Cl	263-265	38
2.71	Me	p-C_6H_4Cl	282-283	"
2.71[a]	Me	p-C_6H_4Cl	279-281	"
2.71	H	p-C_6H_4OMe	258-260	"
2.71	Me	p-C_6H_4OMe	111-112	"
2.71[a]	Me	p-C_6H_4OMe	235-237	"
2.71	H	Ph	228-230	"
2.71	Me	Ph	82-83	"
2.71[b]	Me	Ph	255-257	"
2.71	H	o,p-$C_6H_3Cl_2$	194-197	"
2.71	Me	o,p-$C_6H_3Cl_2$	105-106	"
2.71	H	p-C_6H_4F	254	"
2.71[a]	Me	p-C_6H_4F	274-275	"
2.71	H	p-Tolyl	266-268	"
2.71	Me	p-Tolyl	97-98	"

a = Hydrobromide salt

b = Hydrobromide hydrate

Table 4

Hexahydroimidazotriazines



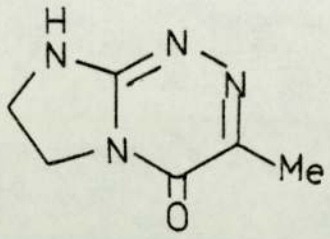
(2.72)

Compound	R^1	R^2	M.P. (°C)	Reference
2.72	H	H	282-284	38
2.72	Me	H	185-186	"
2.72	H	Me	317-318	"

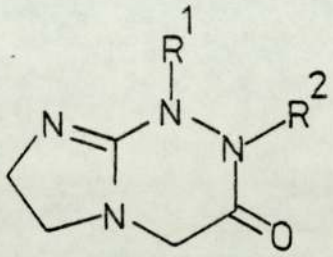
2.3.2 Electronic absorption spectra

Electronic absorption maxima of very few compounds have been recorded in the literature. Compound (2.73)[40,41] with a saturated imidazole ring and conjugated triazine ring showed uv absorption maxima at 220 nm and 300 nm[40,41], whereas compounds with a fully saturated triazine ring and partially saturated imidazole-ring as

in compound (2.72; R^1=R^2=H) showed an absorption band at λmax 268 nm; compounds (2.78; R^1=Me, R^2=H) and (2.78; R^1=H, R^2=Me) showed a uv maximum at λmax 265 nm.



(2.73)

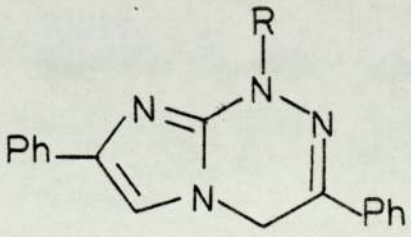


(2.72)

R=H, Me

R= H, Me

Some of the 5,8-dihydroimidazotriazines (2.74) have been reported[45] to exhibit fluorescence upon irradiation with uv light both as solids or in solution in dimethylformamide or dioxan. Colours varied from orange-violet. These triazines (2.74) otherwise showed great stability towards uv light and remained unphotolysed even after prolonged exposure to the irradiation. Compound (2.74; R=H) showed a yellowish



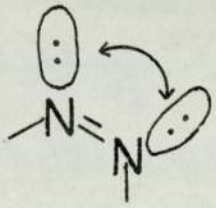
(2.74)

R = H, Ac, COEt, PhNH, Bz, Ph

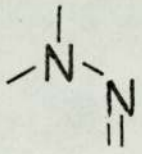
green fluorescence, and its hydrochloride salt a violet fluorescence when exposed to uv light of wavelengths 480 and 421 nm respectively. All the acyl derivatives of this compound (2.74; R=Ac, COEt, PhNHCO exhibit a blue colour on irradiation (λmax 460-440nm), except the benzoyl derivative (2.74; R=Bz) which showed a bluish green fluorescence. The compound (2.74; R=H) when substituted with a phenyl group at N-7 (2.70) showed a dark orange fluorescence.[45]

2.3.3 I.r. spectra

LeCount and Taylor[35] have studied the i.r. spectra of a number of fused 1,2,4-triazinones, and have discussed the possibility of amino⇌imino tautomerism in such a system. It is generally accepted that in most cases amino groups in heterocyclic compounds exist as such; imino-tautomers, if any exist in amounts too small to be detected[80]. Amino-triazinones which would otherwise require a formal N=N in their structure, are exempted from this rule as such a bond is avoided in these azines[81,82]. This behaviour has been explained by Pitha et al[81]. In plane lone pair interactions of



(2.75a)



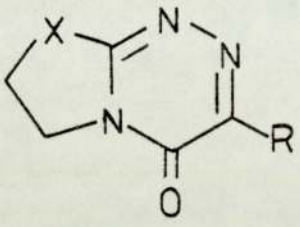
(2.75b)

sp^2-hybridised nitrogen atoms lead to the destabilisation of the conjugated system as illustrated (2.75a and b). The i.r. results

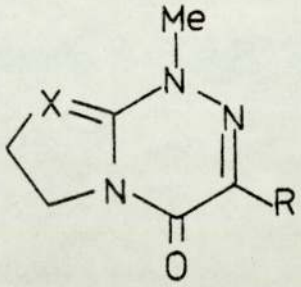
obtained by LeCount and Taylor agree with the above explanations[80-83] and these authors[35] suggested that two opposing factors operate in deciding the tautomeric state of amino-triazinones - namely on the one hand in-plane lone pair interactions of neighbouring sp^2 hybridised nitrogen atoms which favour (2.75b) and on the other the resonance stability of the conjugated system which would favour (2.75a). In such triazinones the latter effect is likely to be small since it is known that aza-substitution progressively reduces resonance stabilisation[83]. The balance of these factors critically influences the tautomeric populations. LeCount and Taylor[34] measured the difference in the frequencies of C=O and C=N of the triazinones (2.68; X=NH,NMe,NPh and R=CH_2CO2Me,Me,Ph) in the solid state, in nujol dispersion, and in solution in chloroform, and the results indicate that imino-tautomers of such systems are capable of existence (Table 5). In the fully conjugated systems, i.e. compounds (2.68; X=NMe, R=CH_2CO_2Me; or X=NMe, R=Me; or X=NMe, R=Ph), the difference in the frequencies is of the order of 83-92 cm^{-1} in chloroform solution. Where C=N is exocyclic to the triazinone ring e.g. the imino-form as in 8-methyl derivative (2.76; X=N, R=Me) the difference in these frequencies falls to 45 cm^{-1}. The compounds (2.68; X=NH, R=CH_2CO2Me and X=NH; R=Ph), although capable of amino-imino tautomerism, showed a difference of the order of 78-84 cm^{-1}, which suggests that the amino-tautomer is the preferred form. Only in compound (2.68, X=NH, R=Me) did both tautomeric forms exist in the solid state as indicated by $\Delta\gamma$ frequencies 48 and 78 cm^{-1} (Table 5) but in solution this compound existed exclusively in the amino-form. Alternative tautomeric forms for this compound (2.68; X=NH, R=Me) have also been discussed by Lempert et al[40] (See page 19).

Table 5

The infrared spectra of imidazotriazinones



(2.68)



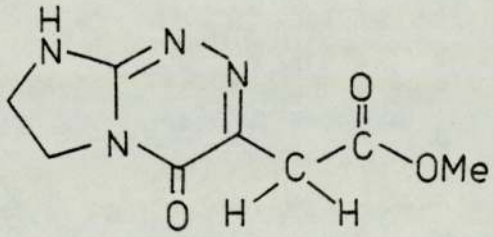
(2.76)

Compound	X	R	$\gamma_1 cm^{-1}$ C=O	$\gamma_2 cm^{-1}$ C=N	$\Delta\gamma cm^{-1}$ $\gamma_1-\gamma_2$	References
2.68	NMe	CH_2CO_2Me	1685*s 1681s	1593*vs 1625s	92 69	34,35
2.68	NMe	Me	1681*s 1685s	1598*vs 1575	83 93	35,41
2.68	NMe	Ph	1679*s 1672vs	1591*vs 1611vs	88 61	35
2.68	NH	CH_2CO_2Me	1684*s 1686s	1600*s 1606	84 80	34,35
2.68	NH	Me	1680*s 1670s 1682s	1602vs 1622vs 1604vs	78 48 78	35,40,41
2.68	NH	Ph	1681*s 1678s	1597* 1614vs	84 64	35
2.68	NPh	Me	1685*s 1690vs	1568* 1584	117 106	35
2.76	N	Me	1687*vs 1683s	1642*vs 1643	45 40	35

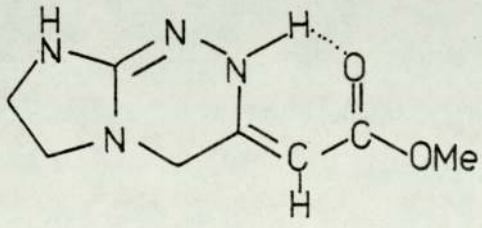
* Frequencies in chloroform

2.3.4. N.M.R. spectra

The ^{1}H.n.m.r. spectral data of only few imidazotriazine are recorded in the literature[34,38,41], in general they do not have any special significance. However, LeCount and Greer[34] observed the very interesting tautomeric interconversions of imidazotriazinone (2.77) in different solvents. For example the spectrum of compound (2.77) in DMso-d_6 showed two quartets centred at δ4.05 and δ3.65 for the imidazoline methylene protons, and singlet at δ3.60 which was attributed to the methylene protons at C-6 (2.77). These authors observed that the singlet resolved into a doublet when trifluoro-acetic acid was added to the solution. This splitting of the methylene resonance in acid could possibly be due to the protonation



(2.77)



(2.78)

of ring nitrogen N-7 by one of the protons of the exo-cyclic methylene group attached to the adjacent carbon atom (C-6) of the ring forming enimine tautomer (2.78). Analogous behaviour was also observed in the pyrrolo[2,1-c][1,2,4]triazines series.[33]

In ^{13}C.n.m.r. chemical shifts are generally the most useful parameters to elucidate the fine structural details as regard to *Sp* hybridised character of the carbon atoms, and also the position of the various substituents in the compounds. American authors[38] have utilised this technique to confirm the position of the methyl groups in compounds (2.82), (2.83) and the position of the double bonds and the methyl group in compound (2.84). The results are listed (Table 6). For example the compound (2.82) showed a peak at 161.1 ppm which is attributed to the lactam carbon.[84] The corresponding peak in compound (2.83) is observed at 157.2 ppm. [The value of C=O for compound (2.81) was not quoted.] Similarly the peak for the guanidine carbon in the 7-methylimidazotriazinone (2.83) is observed at 153.4 ppm. Substitution of methyl group on the guanidino nitrogen (2.82) shifts the corresponding guanidino carbon to 149.5 ppm. Compound (2.84) showed a peak at 62.7 for the carbon atom of the ethoxy group which is in agreement with the previous observations for the corresponding carbon of the ethyl ester.[85]

Table 6

^{13}C. n.m.r. spectra of hexahydroimidazotriazinones in deuterium oxide

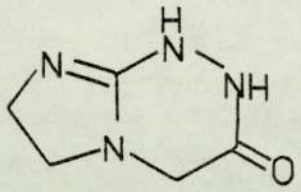
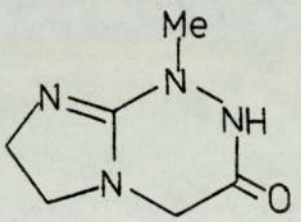
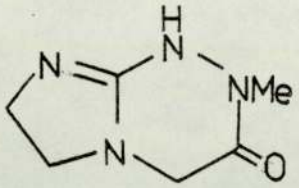
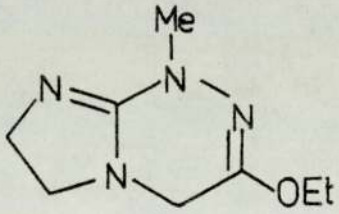
Compound	Standard	Chemical Shifts	Relative intensities	Assignment
 (2.81)	pyridine	46.9	132	$N-CH_2$
		45.4	64	$N-CH_2$
		39.6	125	$N-CH_2-C=O$
		147.6		pyridine
		135.8		
		122.9		
 (2.82)	pyridine	161.1	29	C=O
		149.5	14	N-C=N
		46.2	168	$N-CH_2$
		43.3	216	$N-CH_2$
		39.4	154	$N-CH_2-C=O$
		35.6	60	$N-CH_3$
		146.8		pyridine
		135.7		
		122.6		

Table 6 cont'd.

Compound	Standard	Chemical Shifts	Relative	Assignment
 (2.83)	pyridine	157.2	16	C=O
		153.4	8	N-C=N
		46.4	206	$N-CH_2$
		45.0	216	$N-CH_2$
		38.9	144	$N-CH_2-C=O$
		33.5	67	$N-CH_3$
		146.8		pyridine
		135.7		
		122.6		
 (2.84)	TMS	156.9	15	N=C-OEt
		149.9	23	N-C=N
		62.7	65	$O-CH_2$
		53.5	61	$N-CH_2$
		50.4	74	$N-CH_2$
		46.0	84	$N-CH_2$
		38.9	34	$N-CH_3$
		14.2	40	H_2C-CH_3

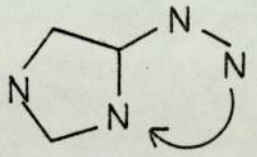
Chapter 3

3.1 Syntheses of imidazo[5,1-c][1,2,4]triazines

This is the least investigated of the ring-systems under examination; only five compounds have been reported[86-89], all prepared from substituted imidazoles by Type A or Type B syntheses.

3.1.1 Syntheses of Type A

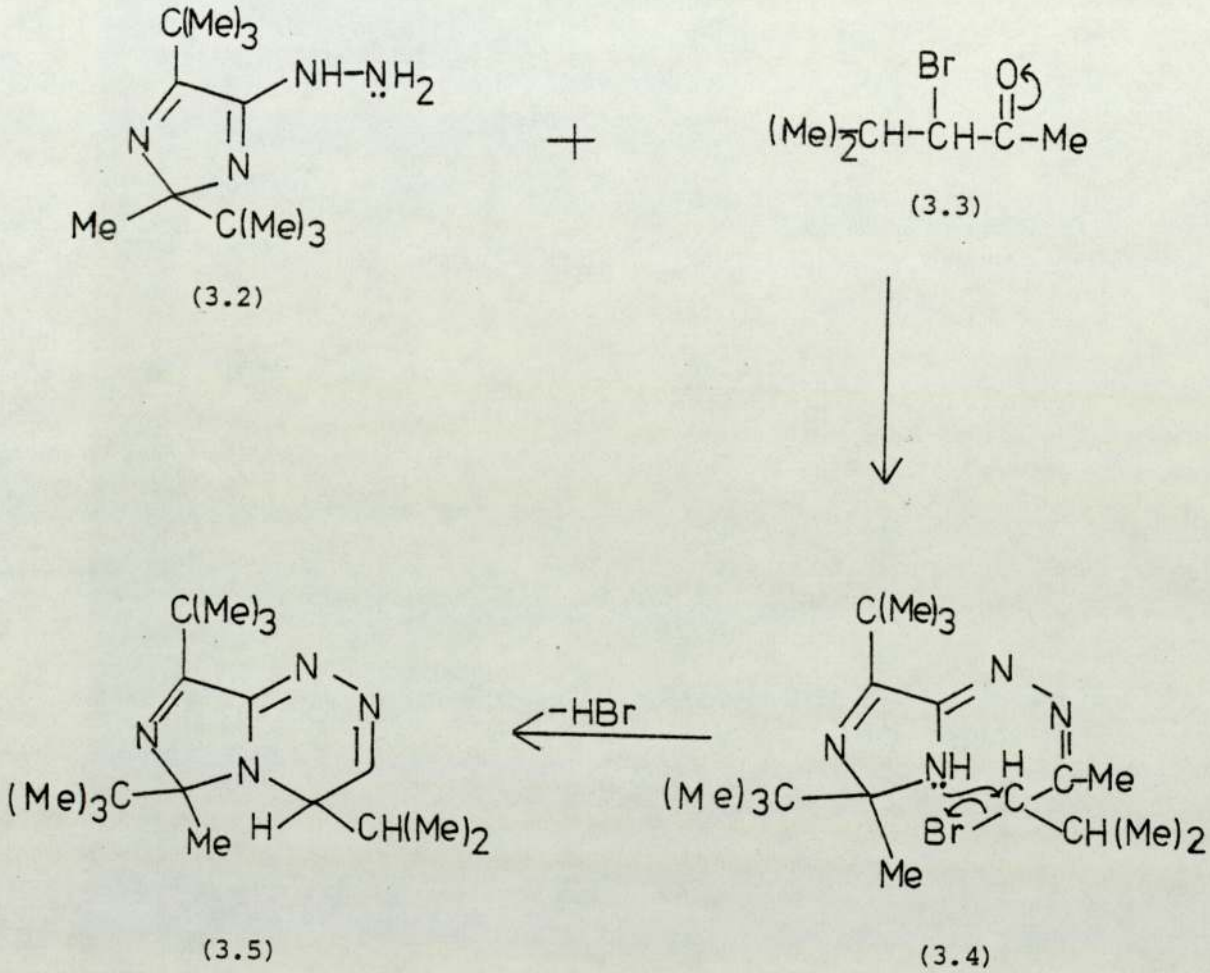
The four compounds known to be made from a Type A synthesis are prepared from the cyclisation of 5-hydrazinoimidazole[87] or 5-diazoimidazole[87,88] derivatives.



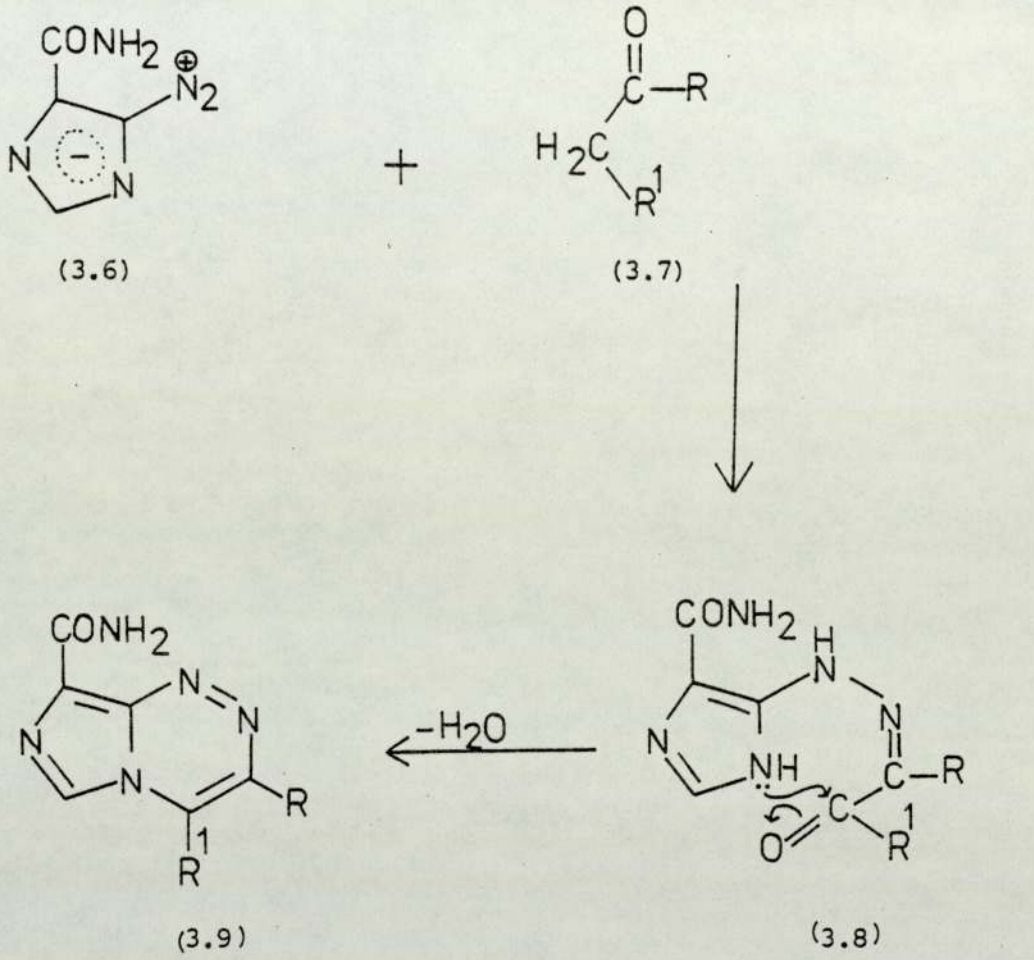
(3.1)

3.1.1.1 From 5-hydrazinoimidazoles

The first compound of this class (3.5), made by Asinger and co-workers[86] was prepared from the reaction of 5-hydrazino-2-methyl-2,4-di-t-butylimidazole (3.2) with 3-bromo-4-methyl-2-pentanone (3.3) via an intermediate non-isolable hydrazone (3.4) as illustrated by scheme (3.1). No spectral evidence was provided by the authors to support the assigned structure (3.5). Presumably this compound could be aromatised by the elimination of either methane or isobutane.

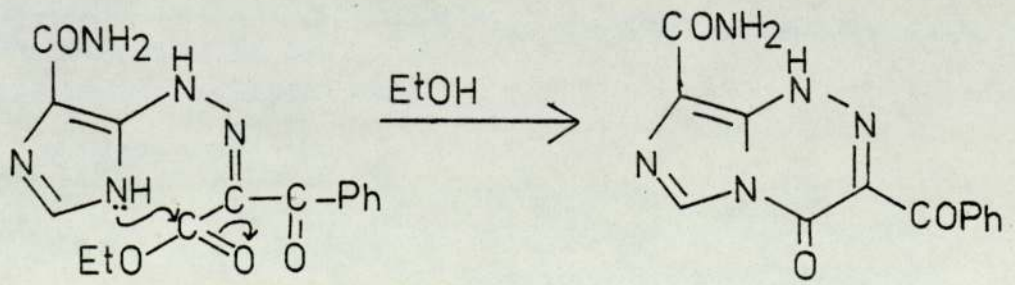

C(Me)3
NH-NH2
N
N
Me
C(Me)3
(3.2)
Br
O
(Me)2CH-CH-C-Me
(3.3)
C(Me)3
N
N
N
N
(Me)3C
Me
H
CH(Me)2
(3.5)
-HBr
C(Me)3
N
N
N
NH
H
C-Me
(Me)3C
Br
C
CH(Me)2
Me
(3.4)

Scheme 3.1



(3.6) (3.7) (3.9) (3.8)

Scheme 3.2



(3.10) (3.11)

Scheme 3.3

3.1.1.2 From 5-diazoimidazole-4-carboxamide

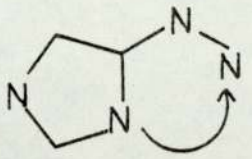
The second type of reaction utilised the following general route to the synthesis of imidazo[5,1-c][1,2,4]triazines.[87,88] 5-Diazoimidazole-4-carboxamide[90] (3.6) was coupled with reactive methylenic substrates (3.7) in sodium acetate buffer, to form the hydrazones (3.8). The latter then cyclised in acetic acid to yield the substituted triazines (3.9) (Scheme 3.2). The compounds were synthesised as potential anti-microbial agents, but selected examples (3.9; R=Me, Pr; R^1=Ac, CO.Pr) showed no biological activity.[88]

In a comparable cyclisation[88] the hydrazone (3.10), prepared by coupling diazoimidazole carboxamide (3.5) with ethyl-benzoylacetate was cyclised in hot acidified ethanol (Scheme 3.3). The desired imidazotriazinone (3.11) was isolated from the acidic solution upon neutralisation with potassium hydroxide.

The reactions outlined in schemes 3.2 and 3.3 appeared to offer a versatile synthesis to cyclic modifications of 5-amino-imidazole-4-carboxamide based on the imidazo[5,1-c][1,2,4]triazine nucleus, and the development of synthetic methods adapting this route forms the substantial topic discussed in following chapters of this thesis.

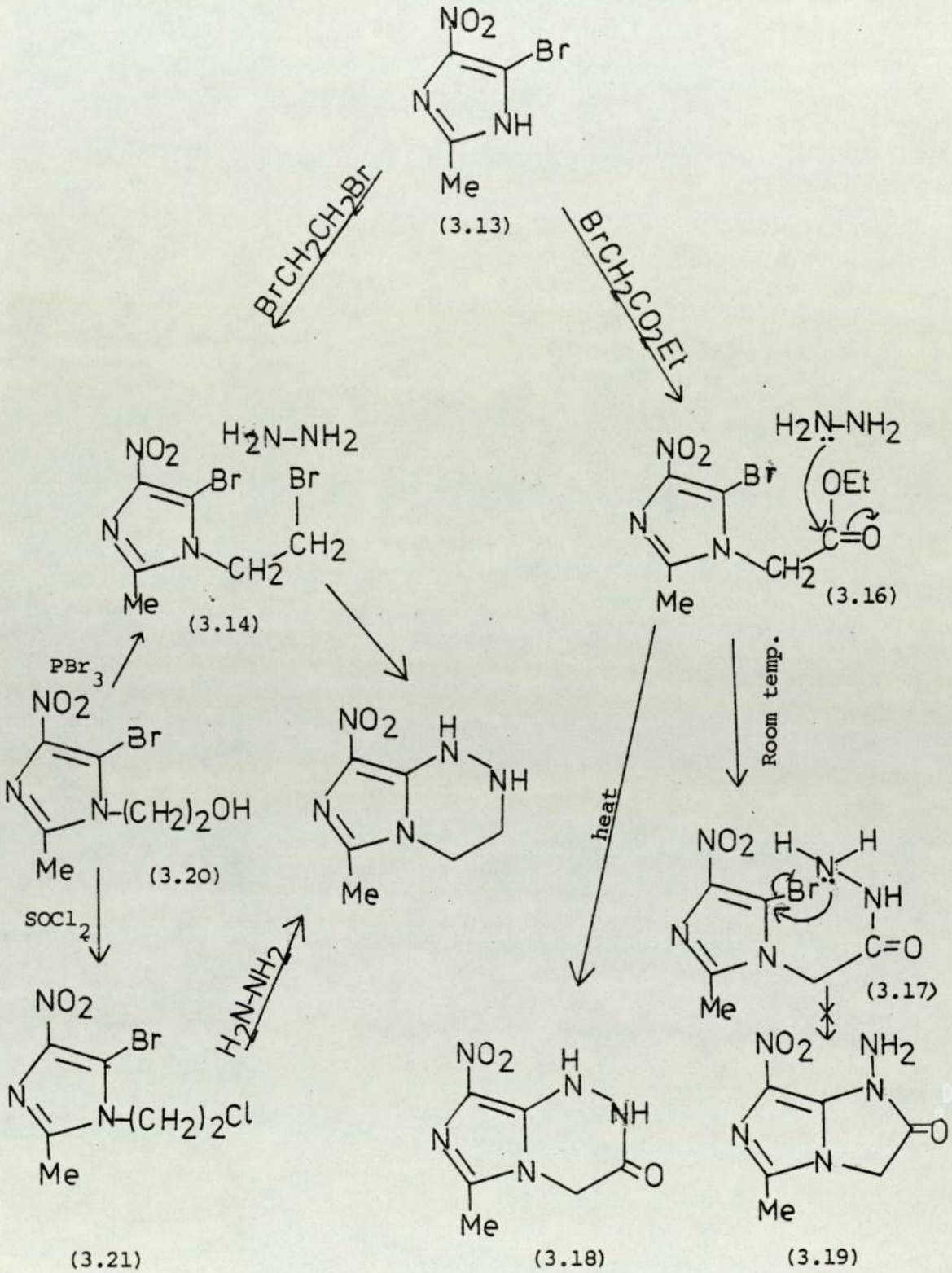
3.1.2 Syntheses of Type B

There are two examples only of this type of syntheses that have been reported recently by Russian authors.[89] The method involves the cyclisation of substituted imidazoles in which suitable leaving groups are incorporated on the imidazole ring at position 5.



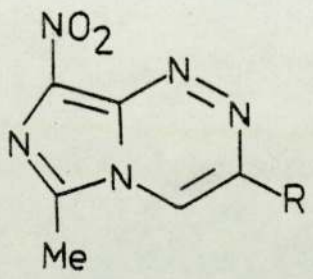
(3.12)

The first stage of the reaction is presumably a substitution at N-1 of the imidazole ring (3.13) with 1,2-dibromoethane or ethylbromoacetate to yield the corresponding 1-substituted compounds (3.14 or 3.16). The compound (3.21) was obtained by the chlorination of the hydroxyethyl derivative (3.20) with thionyl chloride; the hydroxyethyl derivative also furnished the dibromo-imidazole (3.14) when reacted with phosphorus tribromide. On treatment with hot hydrazine hydrate compounds (3.14 and 3.21) cyclised instantly to form the bicyclic imidazo[5,1-c][1,2,4]triazine (3.15). The compound (3.16) when treated with hydrazine hydrate at room temperature formed the corresponding carbohydrazide (3.17) which could be converted exclusively to the imidazotriazinone (3.18) at elevated temperatures. The same imidazotriazinone (3.18) could be prepared directly from (3.16) with hot hydrazine hydrate. The isomeric imidazoimidazolinone (3.19) was not isolated. The triazinone (3.18) showed i.r. absorptions at 3200 cm^{-1} and 1680 cm^{-1} for N-H and C=O groups respectively. No further spectroscopic details were supplied to corroborate the assigned structures (3.15) and (3.18).


NO2
Br
N
NH
Me
(3.13)
BrCH2CH2Br
BrCH2CO2Et
H2N-NH2
Br
CH2
(3.14)
PBr3
N-(CH2)2OH
(3.20)
SOCl2
N-(CH2)2Cl
(3.21)
H2N-NH2
(3.16)
OEt
C=O
Room temp.
heat
(3.17)
(3.18)
(3.19)
NH2

Scheme 3.4.

The other examples of this series (3.22; R=Ph, p-C_6H_4Cl) reported by the same authors[89a] were also synthesised by the above method, via the N-alkylation of compound (3.13) with phenacyl



R=Ph, p-C_6H_4Cl

(3.22)

bromide derivatives and subsequent cyclisation with hydrazine hydrate.

PART II DISCUSSION OF THE EXPERIMENTAL RESULTS

Part II

Discussion of the experimental results

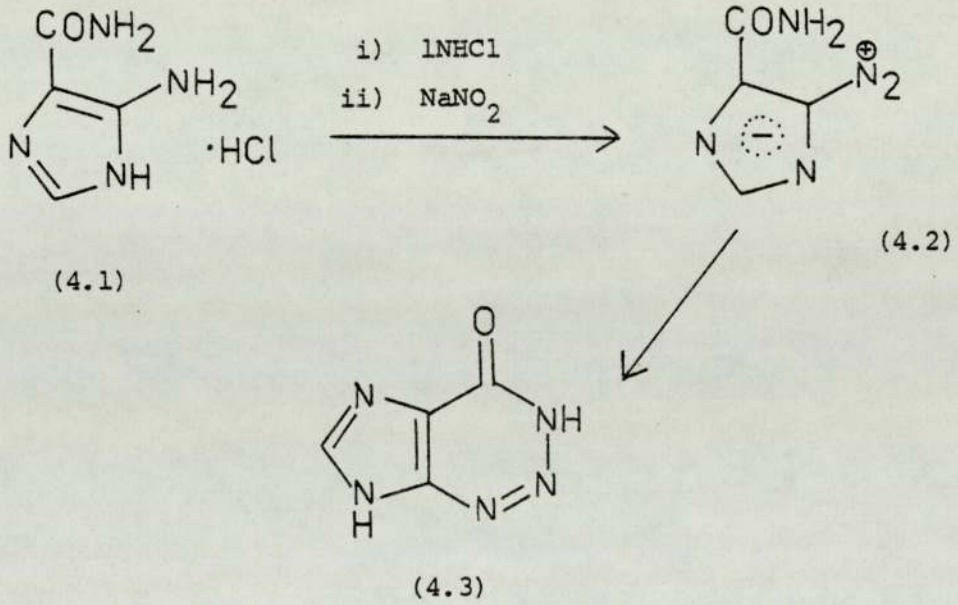
Chapter 4

4.1 Aims and objectives of the work

The hetero-fused imidazoles include many substances of both biological and chemical interest; those of special significance are the purines. In addition, certain 2-substituted imidazo[1,2-a]-pyridines are claimed to have diuretic[91,92] and anti-inflammatory activity[93], and 5-nitro-2-furyl-substituted imidazo[1,2-a]pyridines and imidazo[1,2-a]pyrimidines anti-bacterial and anti-protozoal properties.[94] The bronchodilator properties of 6-amino-1-methyl-3-propylimidazo[5,1-f][1,2,4]triazine have been explored recently.[95] In the introduction to this thesis all known syntheses of imidazo-[2,1-c][1,2,4]triazines have been reviewed, and their chemical and physical properties summarised. In view of the limited knowledge of imidazo[5,1-c][1,2,4]triazines it seemed desirable to investigage further the syntheses and properties of this ring-system. Therefore it was decided to synthesise imidazotriazines (3.9) with a carboxamide function at C-3, since these derivatives and their acyclic precursors, can be envisaged as structural modifications of 5-aminoimidazole-4-carboxamide (4.1); they are thus potential inhibitors of *de novo* purine biosynthesis.[96] Such considerations might have inspired previous workers[87,88] who prepared a limited number of compounds of this type. Little information as regard to their spectral and chemical properties was provided in these reports.

4.2 Synthesis and characterisation of hydrazones

5-Diazoimidazole-4-carboxamide (4.2)[90] which has been shown to have bacteriostatic and tumour-inhibitory properties[97,98,99] was obtained as a white crystlline solid[90] when a solution of 5-aminoimidazole-4-carboxamide (4.1)[100] in 1N-hydrochloric acid was added to an aqueous solution of sodium nitrite.



(4.1) (4.2) (4.3)

The diazoimidazole showed an intense infrared absorption band at 2190 cm^{-1} (N≡N) and a band at λ_{max} 317 nm in its ultraviolet spectrum. The compound (4.2) in aqueous solution has been reported[101] to furnish 2-azahypoxanthine (4.3) by intramolecular cyclisation. This can be demonstrated by observing the changes when a solution of (4.2) in water is monitored by u.v. spectroscopy.

Cyclisation of 5-diazoimidazole-4-carboxamide in water recorded at 10 minute intervals.

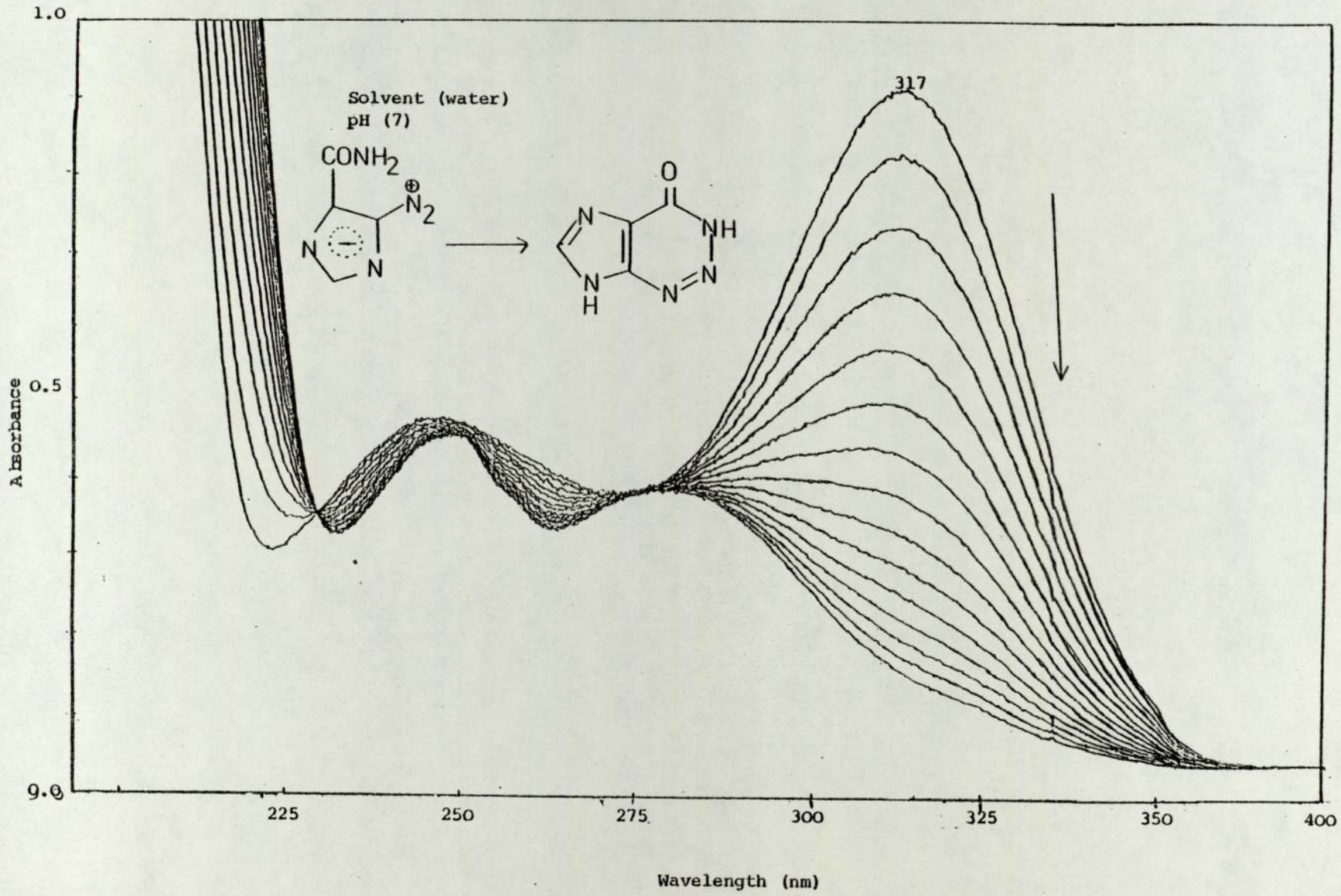
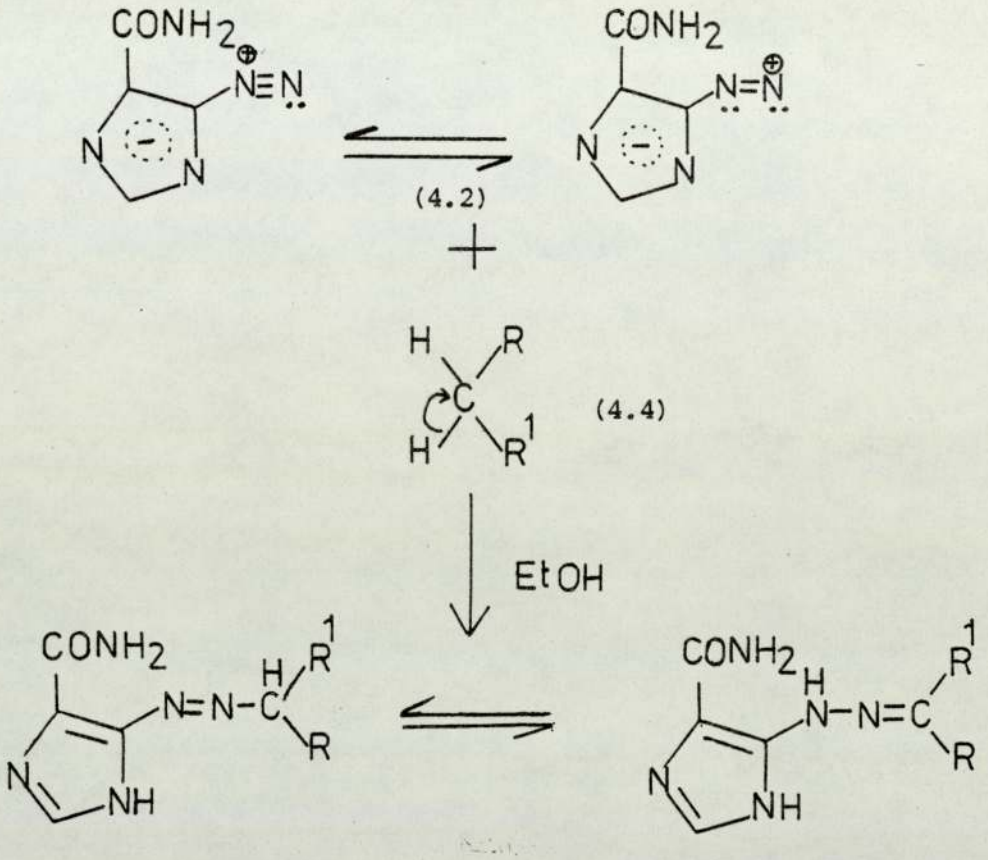


Figure (4.1)

The peak at λ_{max} 317 nm slowly disappears and two new peaks at λ_{max} 273 and 245 nm emerge (Fig. 4.1). The stability of the diazoimidazocarboxamide in the solid state depends mainly on charge delocalisation through the heterocyclic ring. It can couple with various amines to from triazenes[97]. Analogous coupling with reactive methylenic compounds to form hydrazones[87,88] was unreported at the commencement of this work. The coupling reactions were carried out by stirring a suspension of diazoimidazocarboxamide (4.2) with a range of reactive methylenic compounds (4.4) in ethanol in the dark to afford hydrazones (4.6 - 4.15). Some of these hydrazones have been recently described by Kocevar and co-workers[88]. The literature methods to obtain pure samples of these hydrazones in good yields proved difficult to reproduce. Therefore it was decided to monitor the coupling reactions by ultraviolet spectroscopy. The emergence of a new peak between λ_{max} 350-400 nm (Table 4.1) indicated the initiation of the coupling reactions. As the reaction proceeded the peak at λ_{max} 317 nm of compound (4.2) decreased, and ultimately disappeared. It is absolutely crucial to carry out these reactions in the dark as in the presence of light intramolecular cyclisation to 2-azahypoxanthine (4.3) takes place in preference to intermolecular coupling reactions. At the end of the reactions the hydrazones (yield $\sim$ 85-90%) were collected and characterised by analysis and spectroscopy. The reactions with benzoylacetone and diethyl malonate proceeded sluggishly and the hydrazones (4.9) and (4.12) were isolated in



(4.5) (4.6 - 4.15)

Compound	R	R^1
4.6	Ac	CO_2Me
4.7	Ac	CO_2Et
4.8	Ac	Ac
4.9	Ac	Bz
4.10	$COCH_2CO_2Et$	CO_2Et
4.11	Bz	CO_2Et
4.12	CO_2Et	CO_2Et
4.13	CN	CO_2Et
4.14	CN	CN
4.15	CN	$CONH_2$

Scheme 4.1

Table 4.1

Electronic absorption maxima of the hydrazones

Compound	Solvent	λ_{max} (nm)
4.6	A	342, 250*, 206
	B	335, 255, 227*, 205
	C	405, 257*, 207
4.7	A	342, 250*, 206
	B	337, 255*, 207
	C	408, 257, 207
4.8	A	346, 255*, 204
	C	405, 256*, 207
	D	425, 262*, 207
4.9	A	347, 254*, 208, 204
4.10	A	344, 252*, 206
4.11	A	345, 254*, 207
	B	335, 258*, 207
	C	426, 260*, 208
4.12	A	346, 276*, 255*, 235, 213
4.13	A	396, 240*, 209, 206
	B	
	C	408, 255*, 206
	D	407, 255*, 206
4.13^{P}	A	406, 263*, 257*, 250*,247*,204
4.14	A	387, 257*, 227*, 207
	B	395, 252*, 227*, 207
	C	406, 257*, 209, 206
4.15	A	408, 240*, 211

Solvents: A = 95% ethanol; B = 95% ethanol + 2N hydrochloric acid
C = 95% ethanol + saturated ferrous sulphate
D = 95% ethanol + 2N Sodium hydroxide
P = pyridinium salt

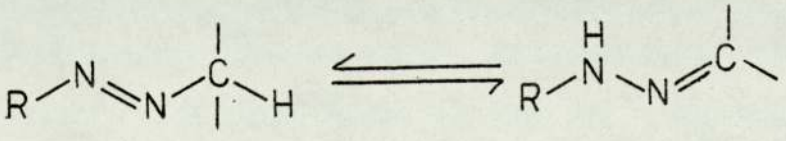
* inflection.

poor yields. Attempted coupling reactions with cyanoacetic acid and phenacylbromide proved unsuccessful. On both occasions 2-azahypoxanthine (4.3) was recovered.

4.2.1 Physical and spectral properties of hydrazones

All the hydrazones (4.6 - 4.15) are amorphous powders, varying in colour from cream to deep yellow. They all exhibit lime-green fluorescence when exposed to u.v. light, and decompose on melting. The hydrazones as such are insoluble in water. The metal salts (see page 62) of these compounds are soluble in water, but dissociate slowly back to free hydrazones in aqueous solution. All these hydrazones are soluble in a large excess of hot ethanol; however hydrazone (4.14) rapidly cyclises in hot ethanol.

All these compounds are characterised by absorption maxima in three bands at 205, 250 and 350-410 nm. The hydrazones with cyano groups (4.13-4.15) are intensely coloured and absorb at higher wavelengths (Table 4.1). Compounds of this type can exist as azo (4.16) or hydrazono (4.17) tautomeric forms.[102] The possible existence of the azo tautomeric form (4.16) was



(4.16) (4.17)

discounted on the basis of the u.v. and ^{1}H.n.m.r. spectral evidence. The absorption in the region of λ_{max} 350-410 nm is found to be a characteristic feature for many arylhydrazones[102-107], and in many related cases it has been shown that hydrazones, in general, are more stable than the corresponding azo compounds.[108] Each compound studied during this work was always obtained in one form only, namely the hydrazono form, which is characterised by a definite melting point and consistent spectral properties.

The i.r. spectra of these compounds show expected features due to N-H and C=O functions together with other characteristic absorptions, details of which can be found in the Experimental Section of this Thesis.

The ^{1}H.n.m.r. spectra of these hydrazones were also consistent with the proposed structures. In DMSO-d_6 the hydrazones showed a sharp singlet at δ7.8 for the imidazole proton and a broad singlet for NH_2 protons at δ7.1-7.2; they showed no evidence of any resonance which could be attributed to methine protons. This again strongly favours the hydrazono tautomeric form at least in solution.

4.2.2 Chemical properties

When ethanolic solutions of the hydrazones (4.6-4.15) were treated with alkali, the colour of the solution intensified considerably and the metal salts of the corresponding hydrazones were formed. This was evidenced by an increase in the intensity (Fig.4.2) of the peaks and pronounced bathochromic shifts of the main

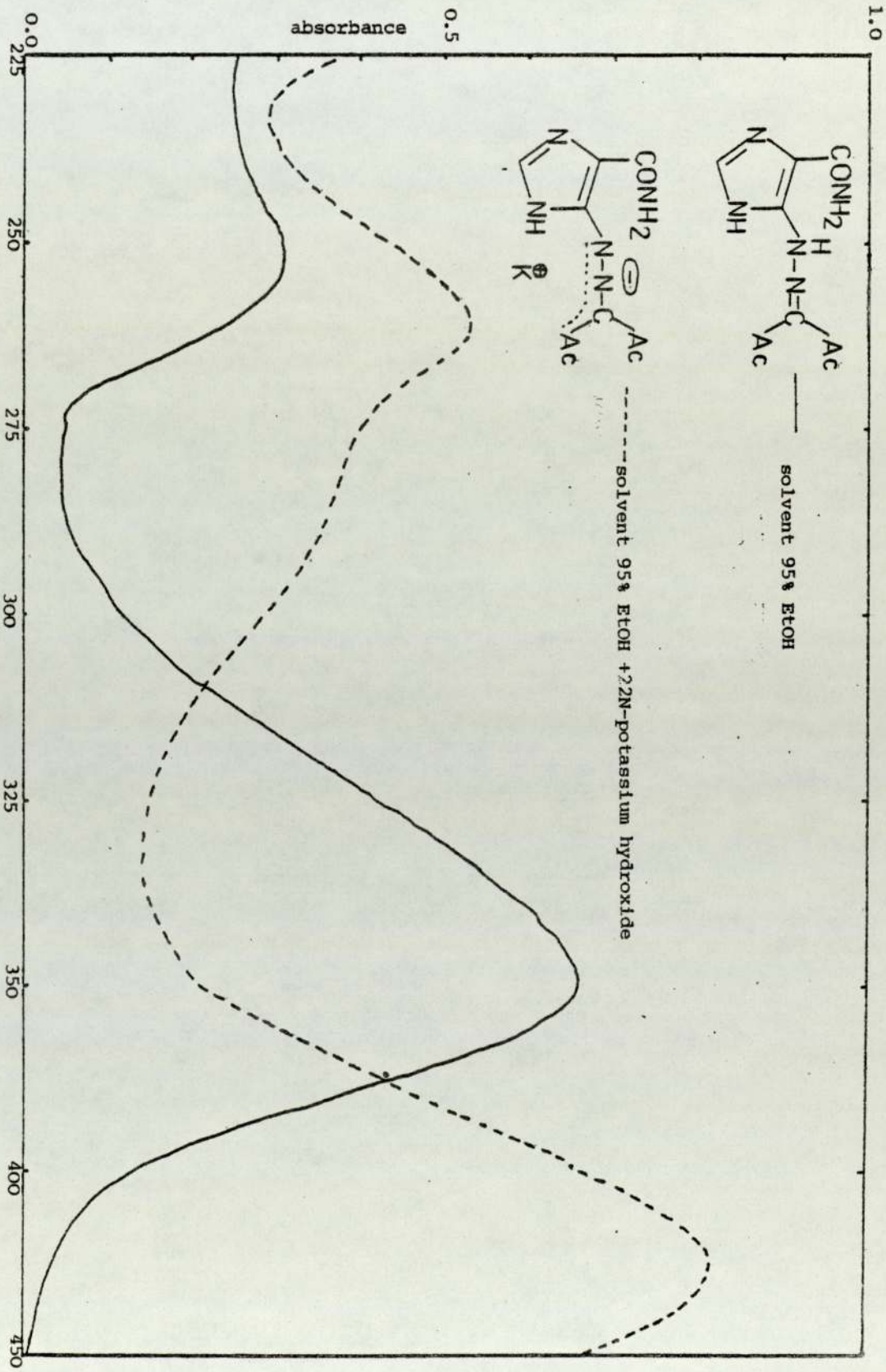
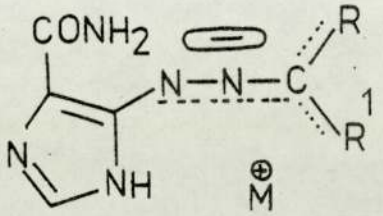

1.0
0.5
0.0
absorbance
225
250
275
300
325
350
400
450
wavelength (nm)
solvent 95% EtOH
------solvent 95% EtOH +2N-potassium hydroxide

Figure (4.2)

absorbtion bands in their ultraviolet spectra. This may be attributed to the contribution of the extensively delocalised hydrazone anions (4.18). Certain of the hydrazones rapidly cyclised in alkaline solution (see page 93), and further spectral changes ensued.



M = (K,Na,Fe)

(4.18)

However, this property of salt formation was demonstrated by employing neutral salts of transition metals, as these conditions do not initiate cyclisation. In contrast, addition of hydrochloric acid to ethanolic solutions of the hydrazones only produced a slight hyperchromic effect with no appreciable shift in the absorption maxima. Spectral characteristics of the hydrazones are recorded in Table (4.1).

The i.r. spectrum of the potassium salt of the diacetylhydrazone (4.8), which was obtained as a deep yellow solid by the addition of alcoholic potassium hydroxide to a suspension of the hydrazone in ethanol, showed striking differences from the spectrum of the free hydrazone. The carbonyl absorptions at 1688 and 1622 cm^{-1} (KBr) of the free hydrazone (Fig. 4.3) were absent and replaced by a band at 1640cm^{-1} and a slightly broader peak at 1590-1610 cm^{-1} (Fig. 4.4). An analytically pure sample

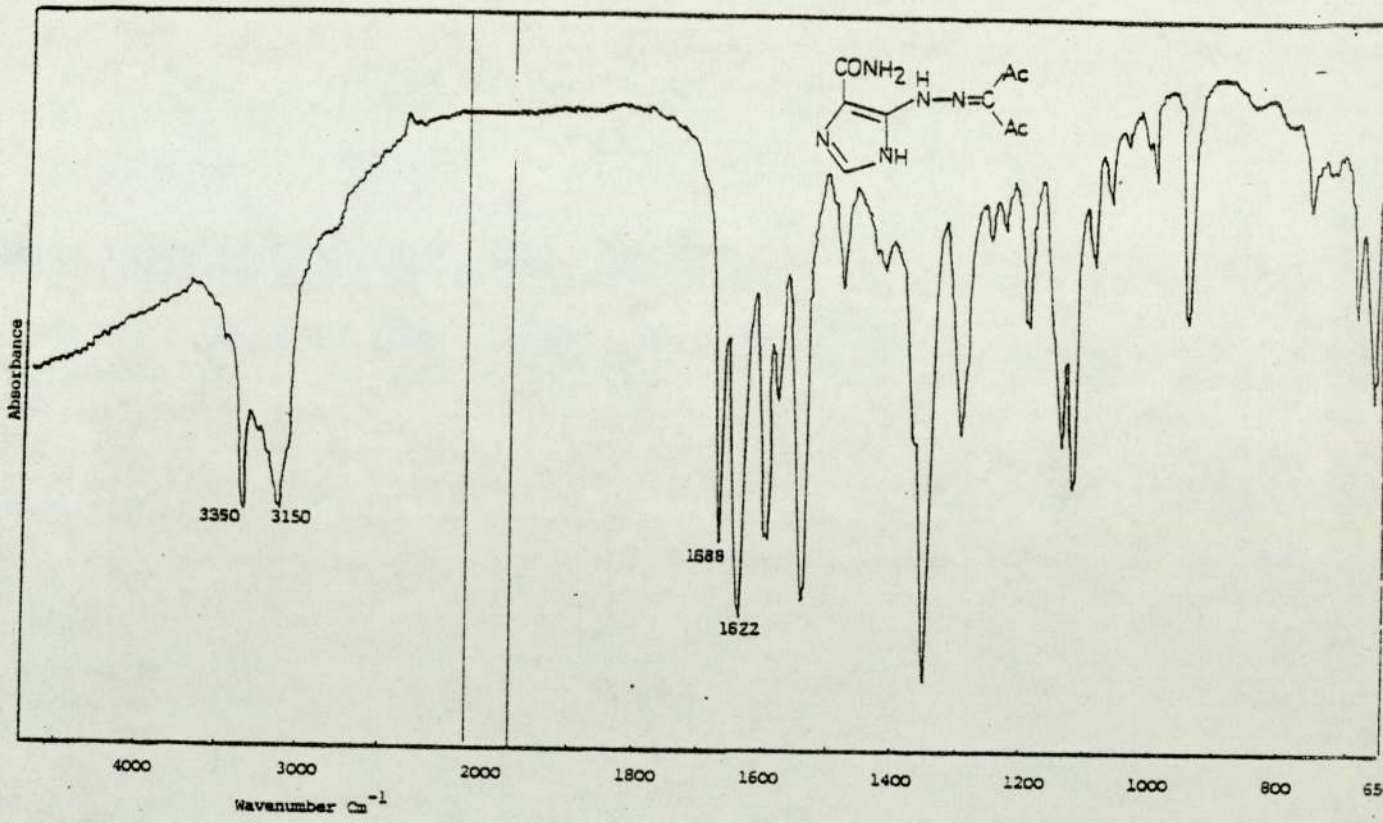


Figure (4.3)

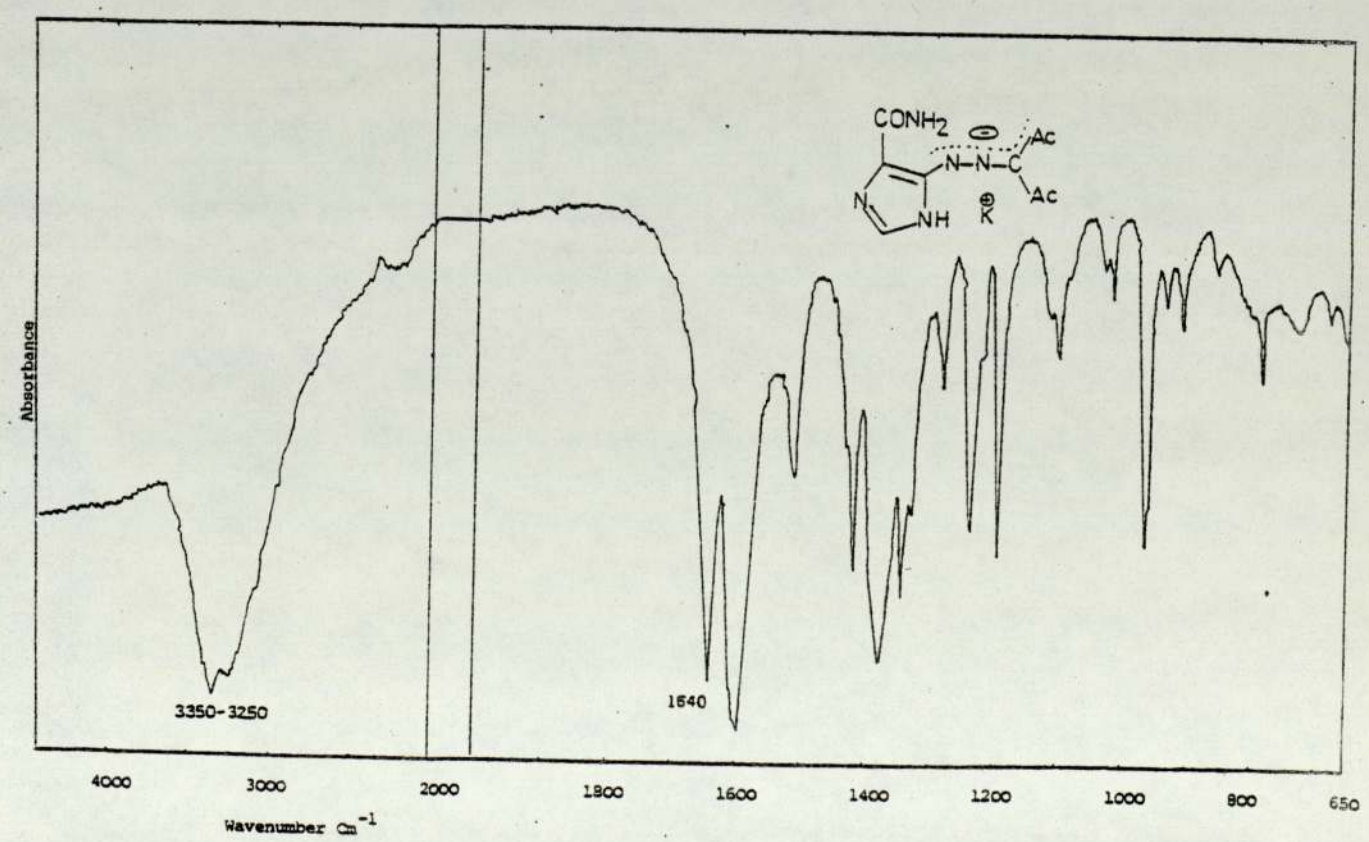


Figure (4.4)

of the salt was not obtained, as the salt readily dissociated to the free hydrazone. The same differences were found in the spectrum of hydrazone (4.13) and its potassium salt (4.19). The i.r. spectrum of the salt did not exhibit the carbonyl band at 1710 cm^{-1} and 1628 cm^{-1}, but instead showed an ill-defined doublet between 1620-1625 cm^{-1} (Fig. 4.5). It was interesting to observe that upon reacidification the potassium salt (4.19) was converted to a different modification of the original hydrazone possibly a different geometrical isomer. This was hardly surprising as *syn-anti* isomerism is a well documented phenomenon in hydrazone chemistry[108-111]. The new isomer exhibited a very sharp and intense band for C≡N absorption at slightly lower frequency (2200 cm^{-1}) than the original form (2220 cm^{-1}) and a less intense peak for ester carbonyl at 1708 cm^{-1}. An N-H streching absorption was also observed in the region 3100-3350 cm^{-1}. The low value of this band must be due to hydrogen bonding[106] (Fig. 4.8). On the basis of i.r. spectral evidence it can be speculated that the new isomer might have structure (4.13b), and the analytical data indicates that it is an hydrate. Unfortunately at present no strong evidence could be provided to further justify this speculation. The hydrazone (4.13) when boiled with pyridine yielded a yellowish-green solid which was correctly analysed as $C_{14}H_{15}N_7O_3$ (i.e. the hydrazone with one mole of pyridine). The i.r. spectrum of the solid exhibited similar features to that of the potassium salt (Fig. 4.7); namely showing a shift of the carbonyl absorption

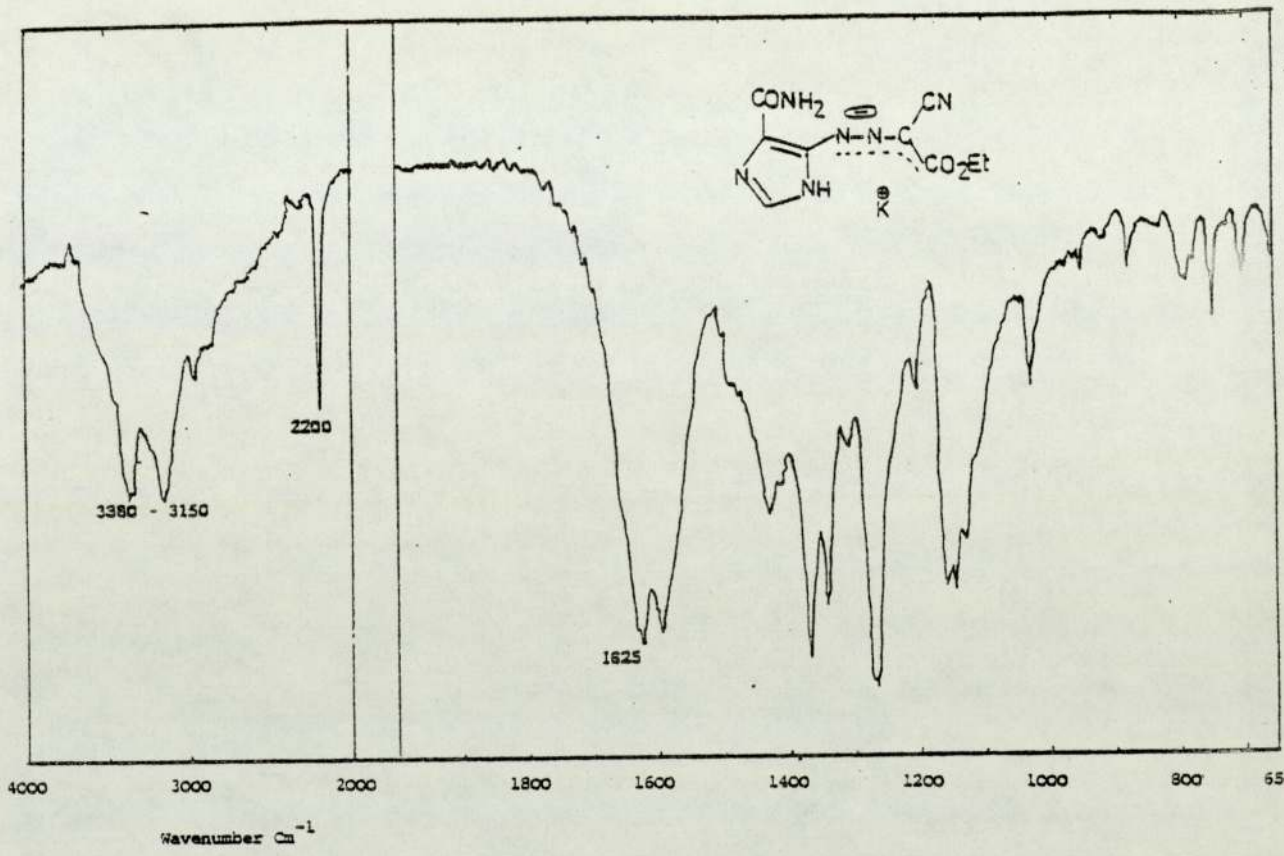


Figure (4.5)

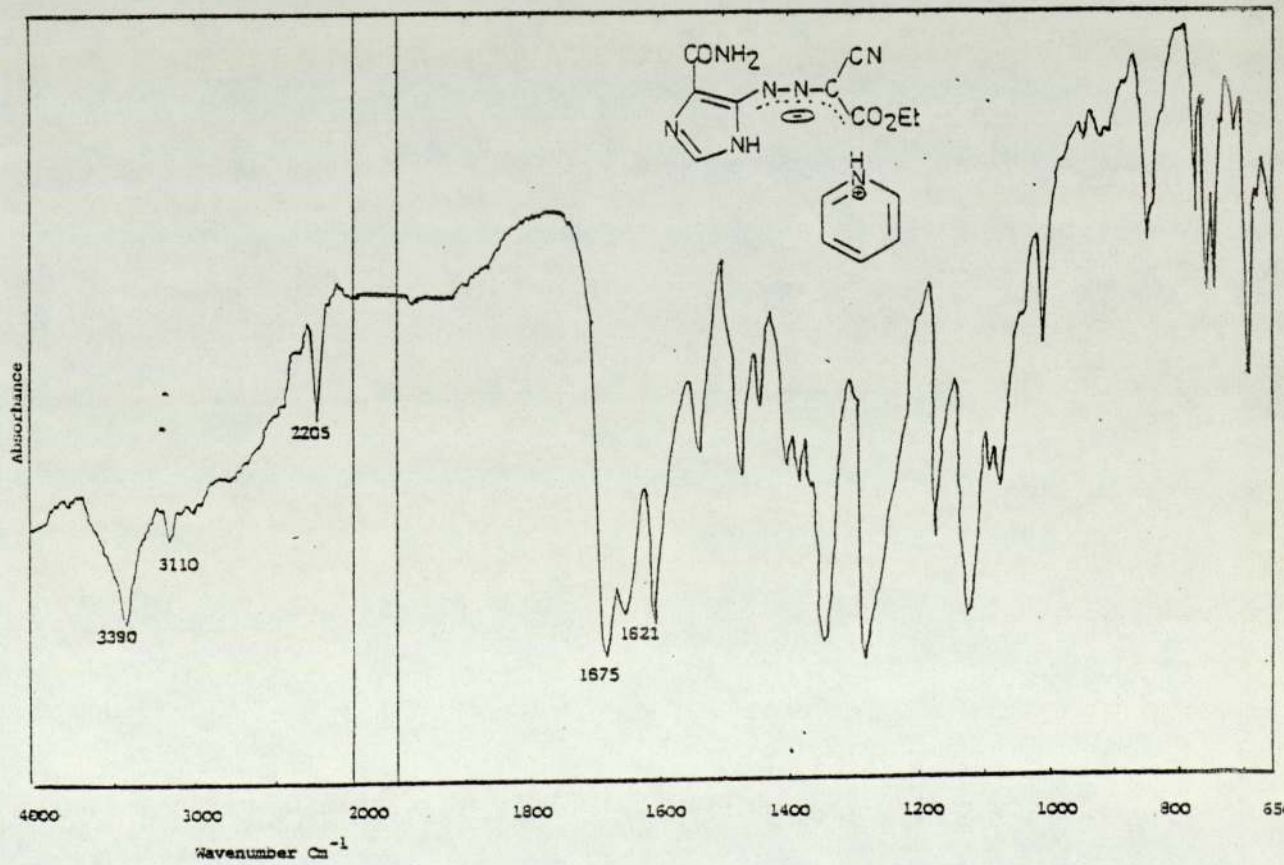


Figure (4.6)

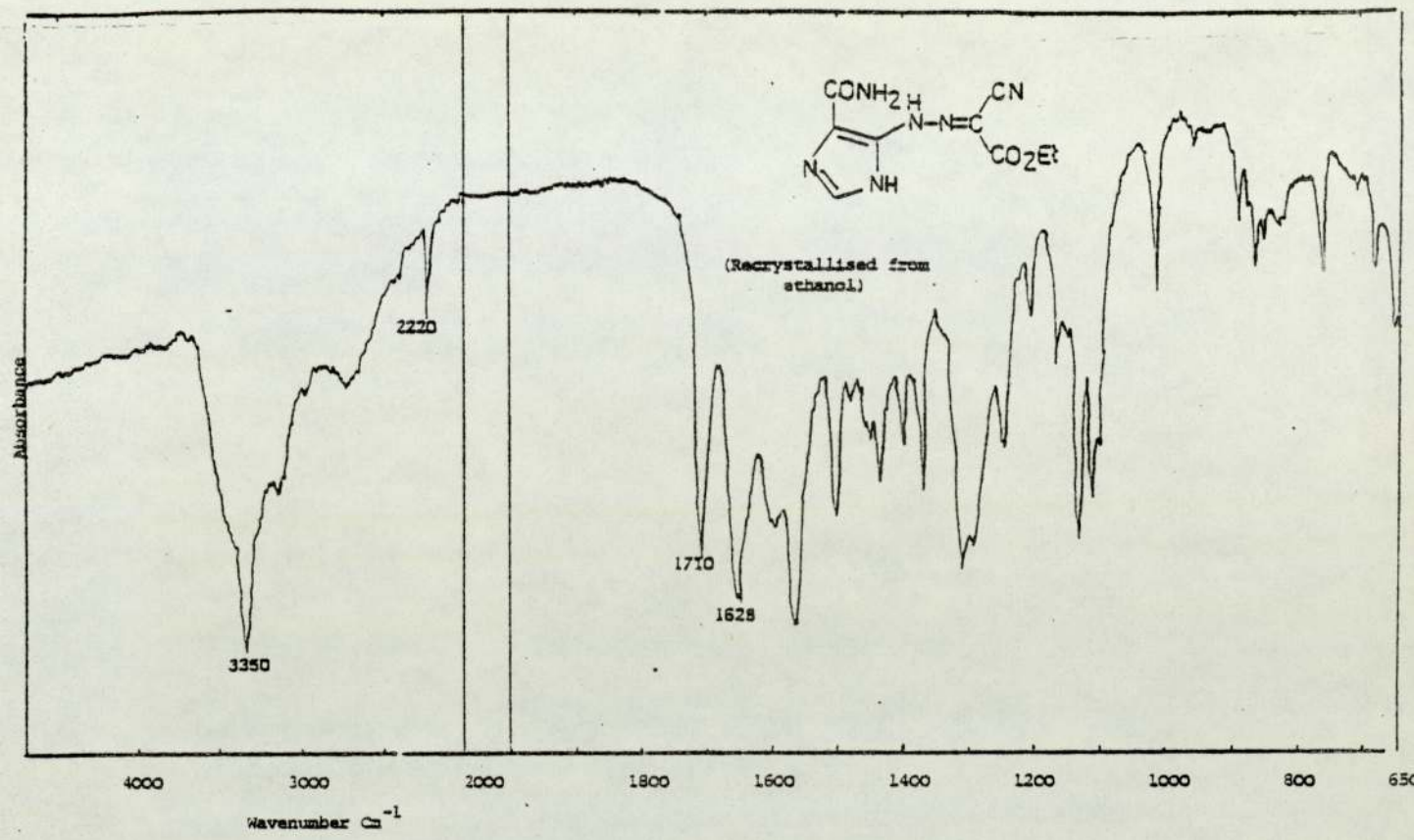


Figure (4.7)

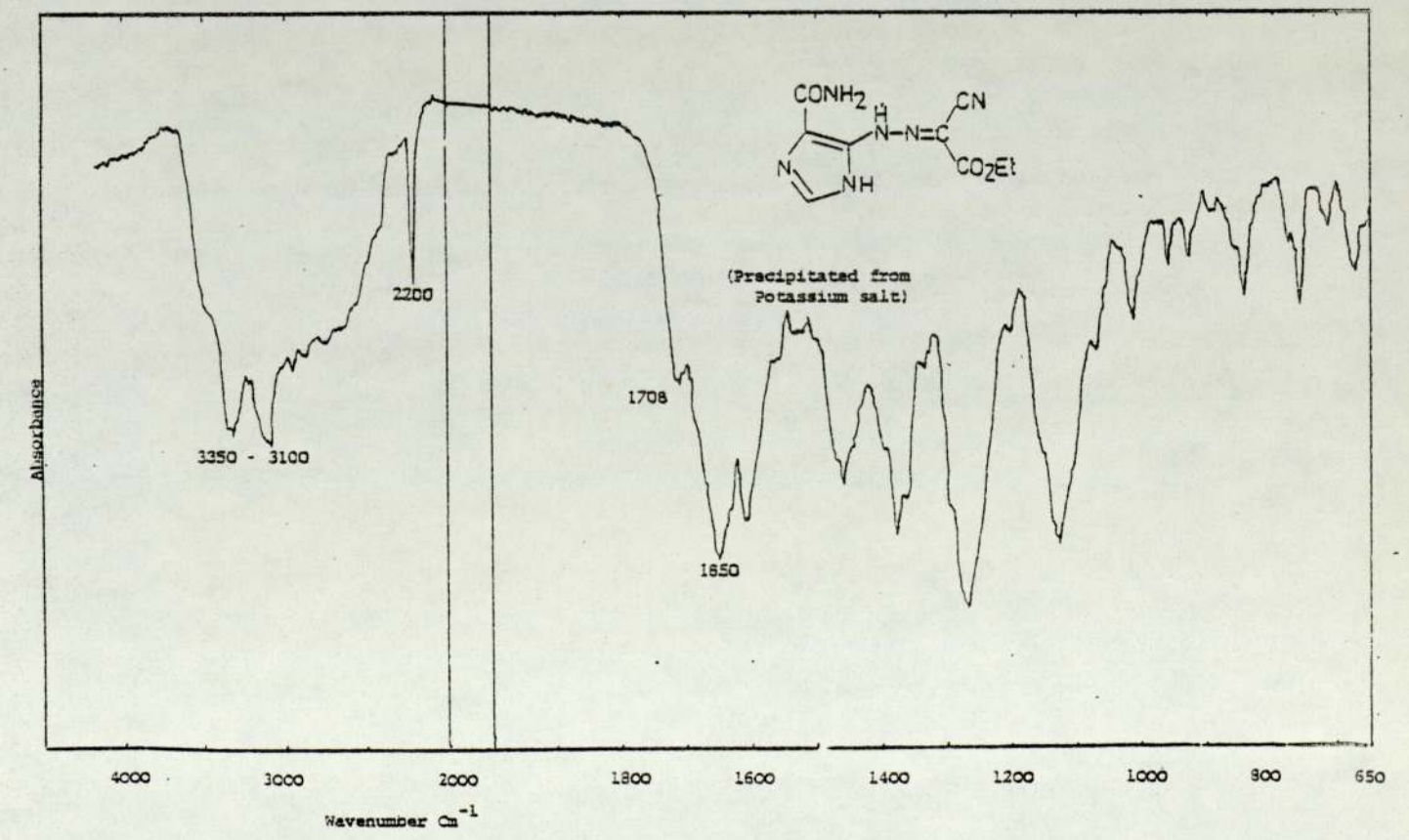
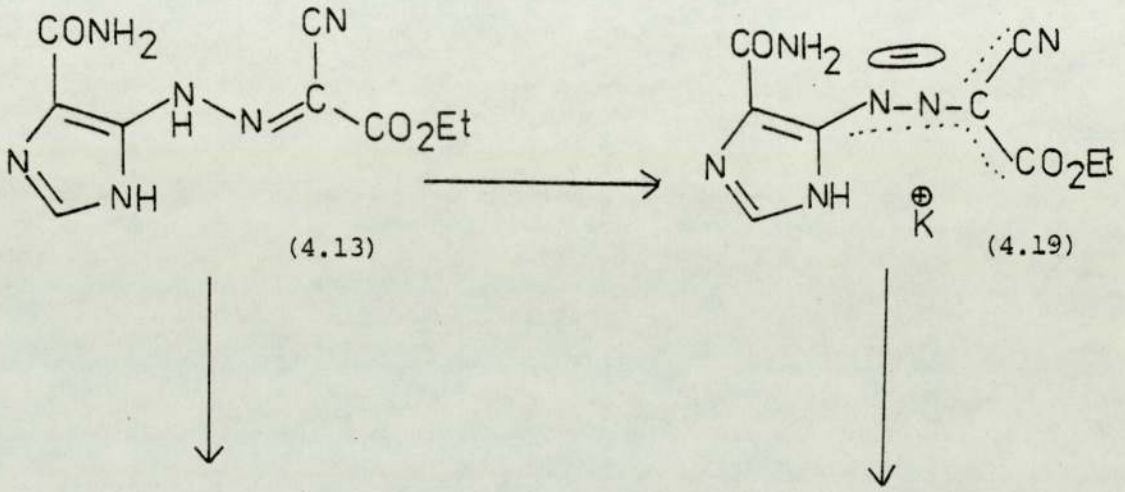
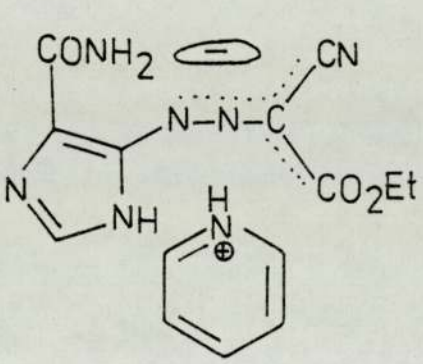


Figure (4.8)

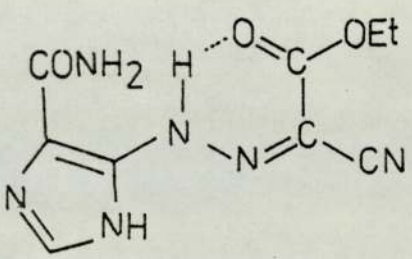


(4.13)

(4.19)



(4.20)



(4.13b)

to lower frequency compared to original hydrazone (Fig. 4·6). [Although the frequency shift is not as pronounced as that of potassium salt]. The u.v. spectrum of this compound also showed a bathochromic shift (10 nm) similar to that observed by the addition of sodium hydroxide or ferrous sulphate to an ethanol solution of the hydrazone (see Table 4.1). The presence of pyridine associated with the hydrazone was evidenced by series of inflections $\sim \lambda_{max}$ 265-250 nm region. The ^{1}H.n.m.r. spectrum also showed resonances for pyridine protons as a multiplet around δ7.5-7.8. On the basis of the spectroscopic evidence structure (4.20) was assigned to the yellowish-green salt.

4.3 Cyclic modifications of 5-Aminoimidazole-4-carboxamide

4.3.1 Acid-catalysed cyclisation

4.3.1.1 Acetylhydrazones

Recrystallisation attempts (from ethanol-acetic acid) to obtain an analytically pure sample of the hydrazone (4.6) resulted in the formation of a yellow shiny crystalline product. This process of recrystallisation was repeated successively until a compound with a consistent melting-point (250-260°C) was finally obtained.

A study of the i.r. and u.v. spectra of these two compounds suggested that they were distinctly different in their chemical structure. A bathochromic shift of the major absorption peak (252 nm) with prominent spectral changes in the region of 250-200 nm

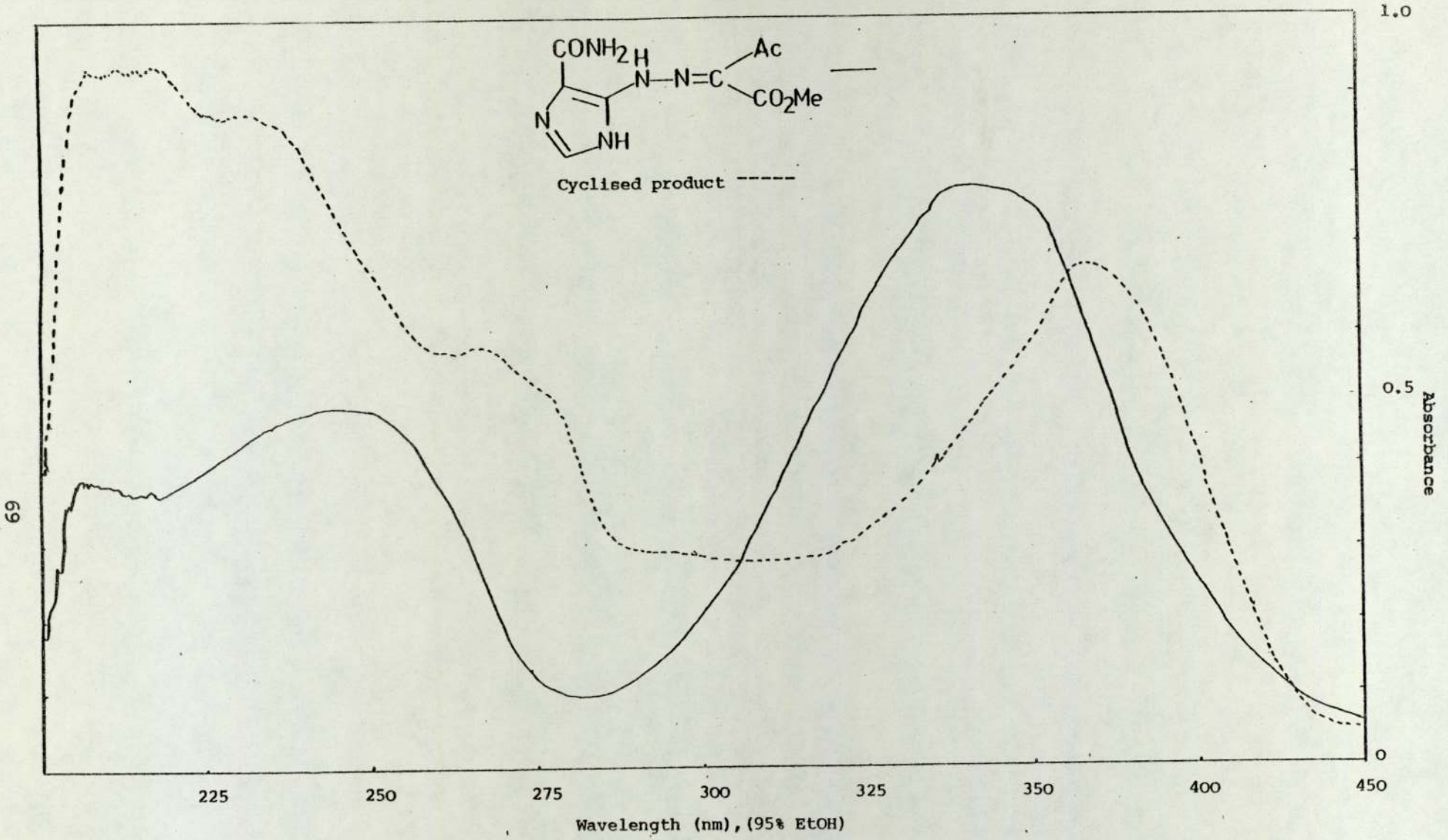
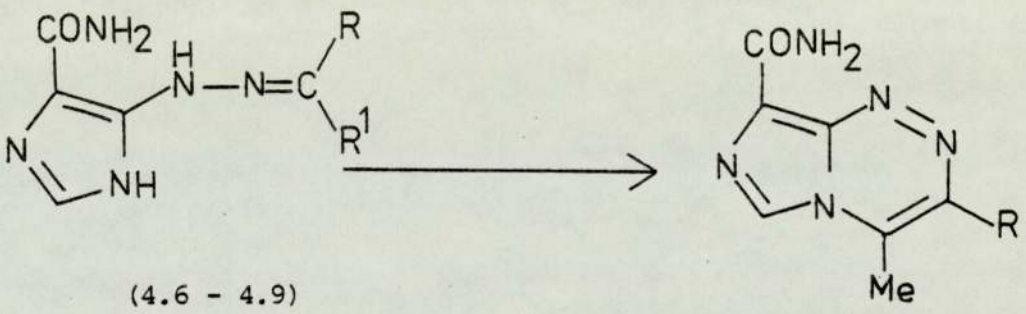

CONH2
H
N
N=C
Ac
CO2Me
N
NH
Cyclised product
1.0
0.5
0
Absorbance
225
250
275
300
325
350
400
450
Wavelength (nm), (95% EtOH)

Figure (4.9)

was noted in the u.v. spectrum of the crystalline product compared to the starting hydrazone (Fig. 4. 9). The i.r. spectrum also showed major differences in the finger-print region as well as in the carbonyl absorptions. For example a broad absorption band at 1630-1642 and a sharp peak at 1718 cm^{-1} were absent in the purified product and replaced by a sharp band at 1642 cm^{-1} and doublet at 1700 cm^{-1} and 1716 cm^{-1} . The mass spectrum of the purified product did not show a peak corresponding to molecular ion of the hydrazone (M/e 253). Instead an intense peak at M/e 235 was observed. On the basis of the spectroscopic and analytical data this product was assigned structure (4.21), an assignment subsequently changed when the tautomeric possibilities were examined (see page 76).

Similarly the other acetylhydrazones (4.7-4.9) were apparently smoothly converted to the bicyclic imidazo[5,1-c][1,2,4]triazines (4.22-4.24) in acetic acid-ethanol mixture. Analogous reactions for this type of cyclisation to yield azolo[5,1-c][1,2,4]triazines[111-120] have been reported previously.

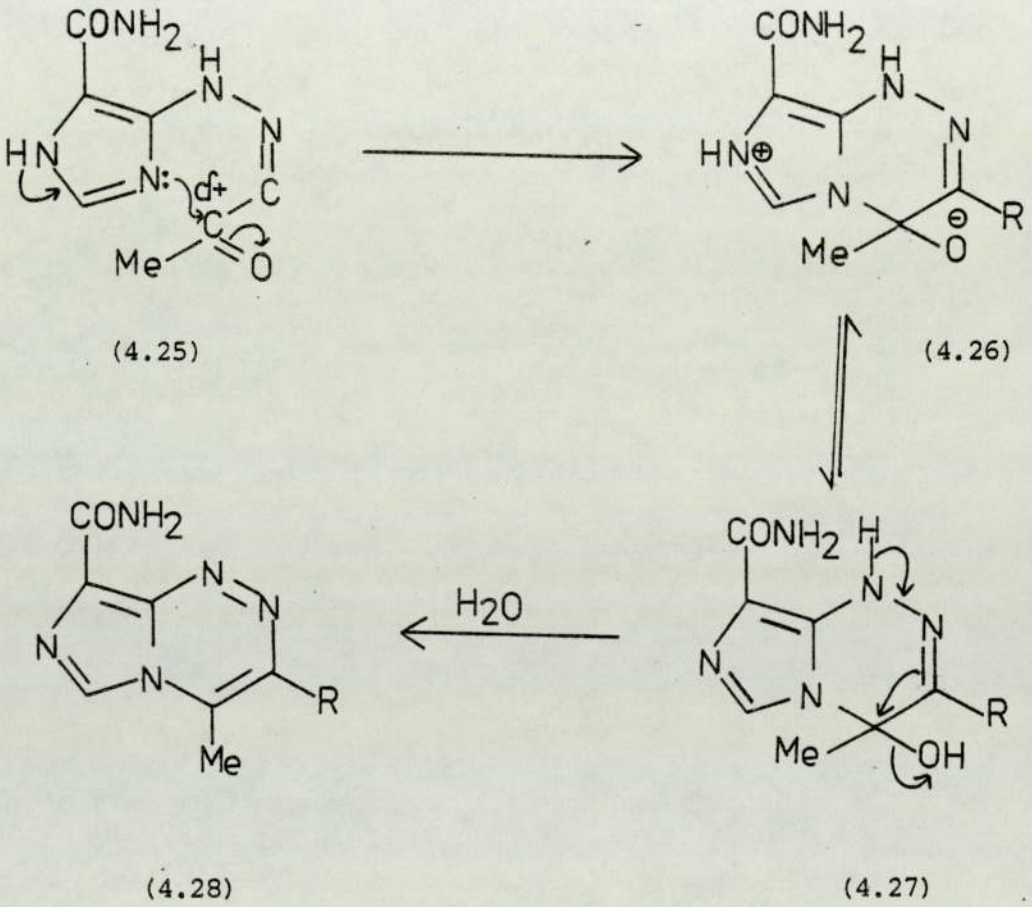
It was envisaged that the cyclisation in the acidic medium involves nucleophilic attack of the imidazole ring nitrogen at the electron-deficient ester carbonyl carbon to form a tetrahedral intermediate (4.26-4.27) which subsequently loses water to form the bicyclic compound (4.28) scheme (4.2). However, contrary to expectations the products were not the 7-methyl imidazotriazines (4.21-4.24) respectively since their ^{1}H.n.m.r. spectra showed no absorptions for the 7-methyl group. Instead hydrazone (4.6), which



(4.6 - 4.9)

(4.21 - 4.2)

Compound	R	R^1	Compound	R
4.6	CO_2Me	Ac	4.21	CO_2Me
4.7	CO_2Et	Ac	4.22	CO_2Et
4.8	Ac	Ac	4.23	Ac
4.9	Ac	Bz	4.24	Bz



(4.25) (4.26)

(4.28) (4.27)

Scheme 4.2

crystallised as an acetic acid solvate, showed an AB geminal splitting pattern (J=4Hz) integrating for two protons and also contained absorptions for two methyl protons at δ4.1 and δ2.24 (Fig. 4.10). The latter resonance was first mistaken for the 7-methyl protons but was later shown to be the methyl protons of acetic acid. This was proved by heating the solvate in ethanol; the spectrum of the dissociated product lacked the absorption at δ2.24. The same unsolvated triazine was also obtained in moderate yields after prolonged boiling of hydrazone (4.6) in ethanol alone. A compound formulated as (4.23) has been reported recently[87]. Apparently the ^{1}H.n.m.r. spectrum of this compound was not recorded and it should be reformulated as the methylene tautomeric form (4.31). The spectra of these compounds (4.23-4.26) were identical in both TFA and DMSO-d_6. The ^{1}H.n.m.r. of these compounds could not be recorded in $CDCl_3$ or deuteropyridine due to their lack of solubility in these solvents. However, the ^{1}H.n.m.r. spectrum of compound (4.22) in trifluoroacetic acid at 220 MHz showed a very small methyl peak at δ3.4 (Fig. 4.12) which may possibly be attributed to the methyl group at C-7. If so integration indicated the 7-methyl: 7-methylene ratios to be approximately 1:30.

The opposing factors which influence tautomer populations in 1,2,4-triazines (in particular amino - or imino-triazinones) have been discussed by LeCount and Taylor[35] (see Page 39). In-plane lone-pair interactions of the neighbouring sp^2 hybridised nitrogen

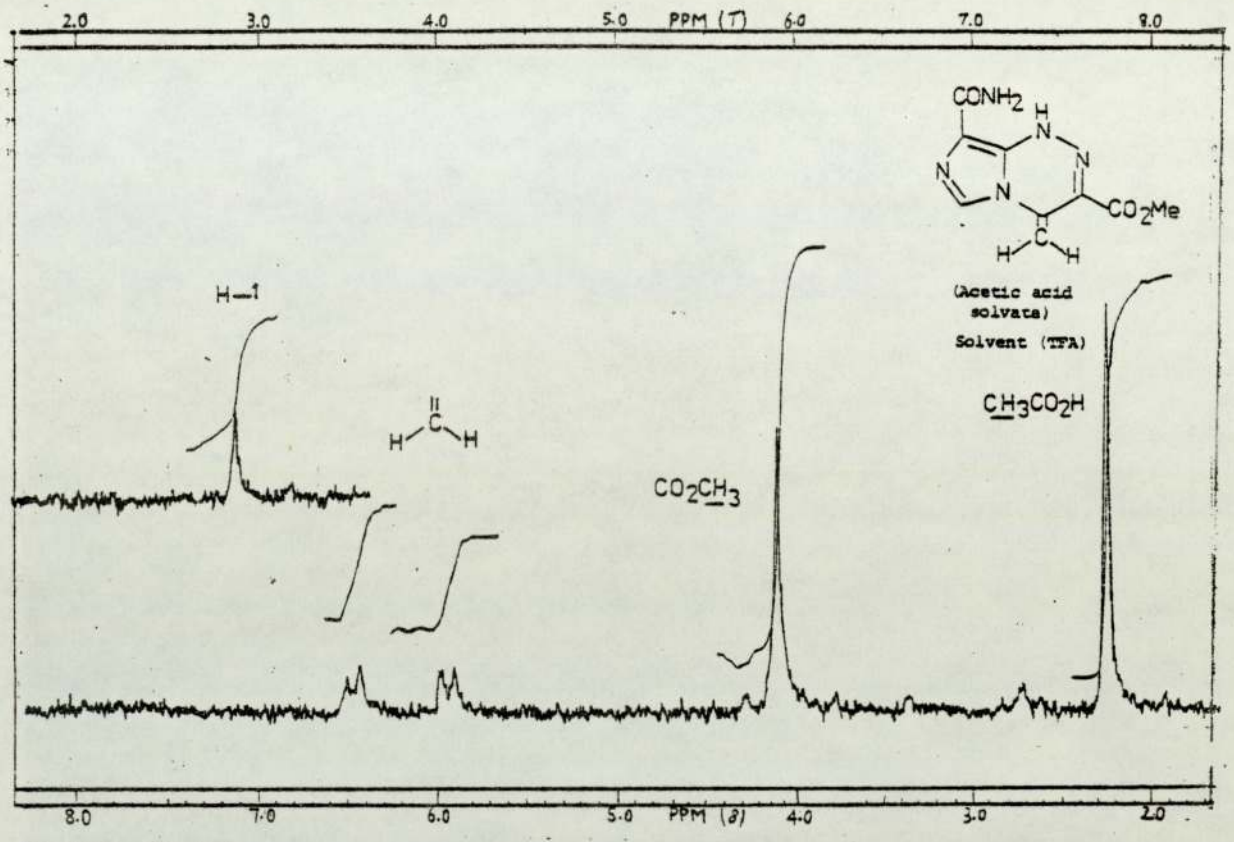


Figure (4.10)

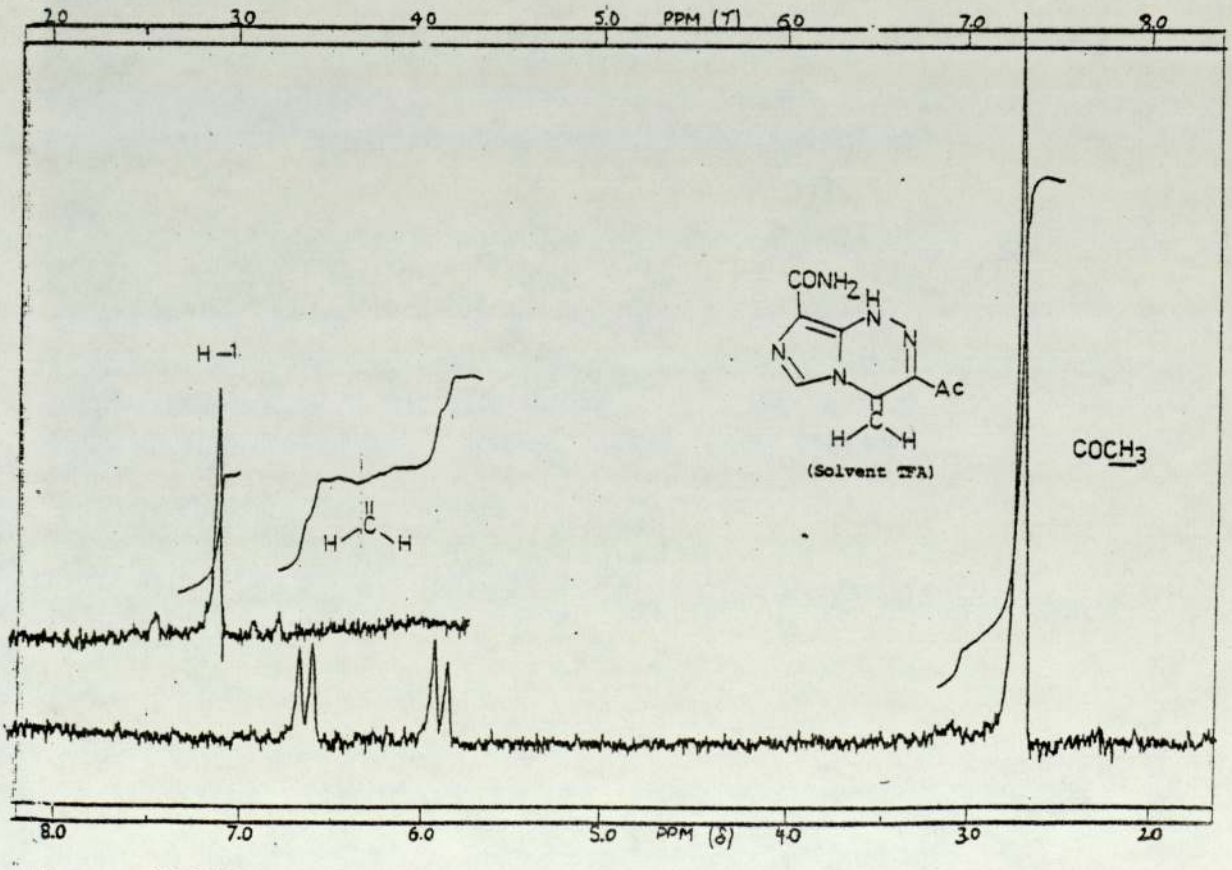
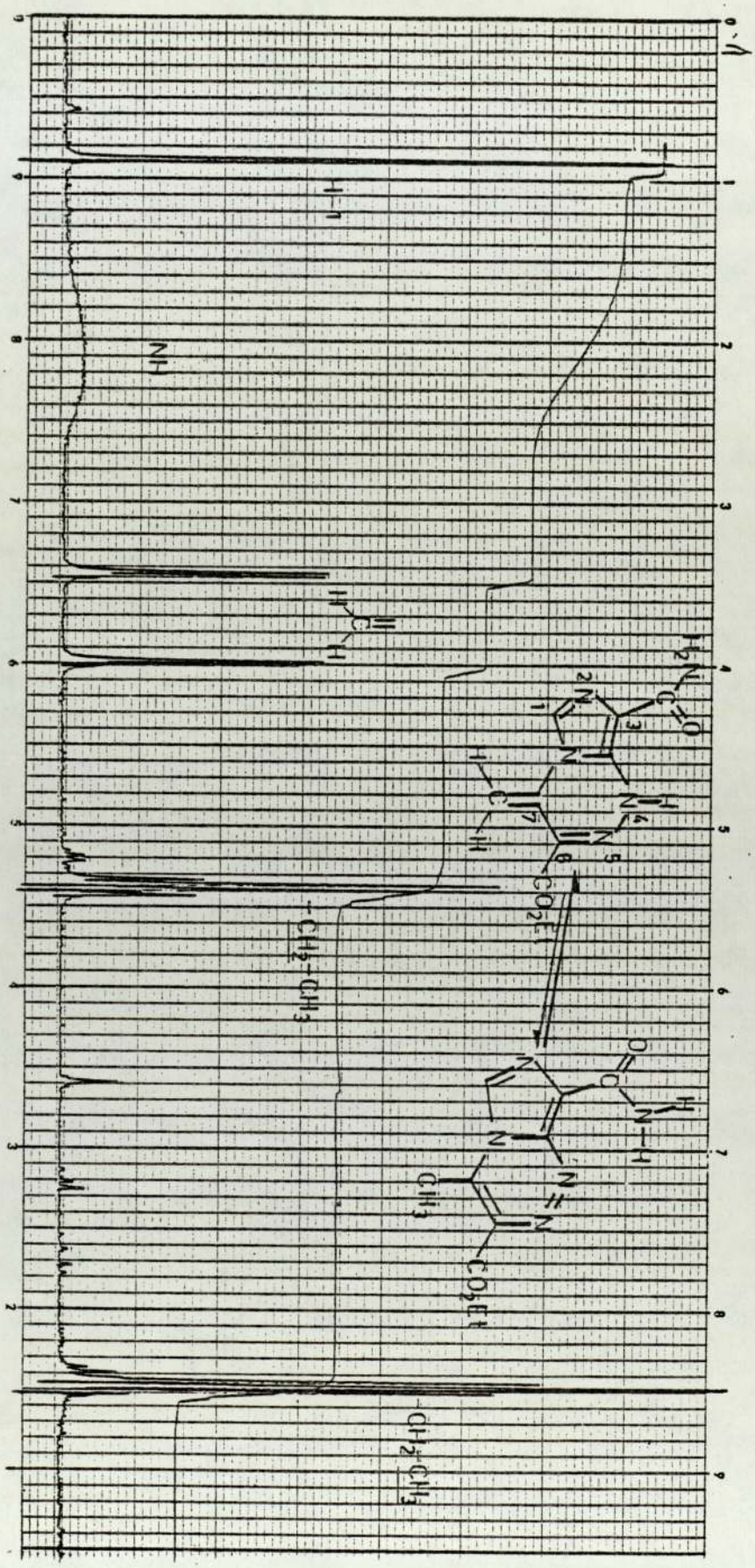


Figure (4.11)



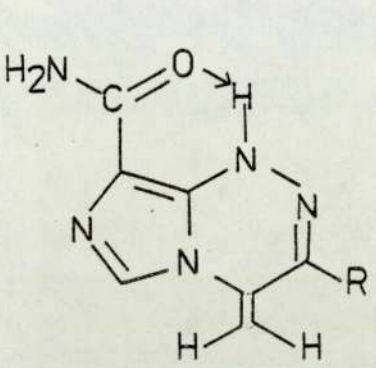
Recorded on 220 MHz, solvent (TFA)

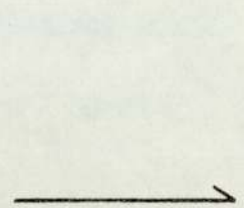
Figure (4.12)

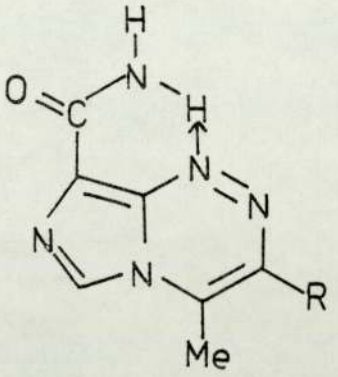
atoms of the triazine ring which destabilise a formal NN double bond would favour the methylene state (4.29-4.32): in contrast conjugation in the triazine ring imparting heteroaromatic stability on the bicyclic system would favour the 7-methyl arrangement (4.33-4.36). An additional feature - intramolecular hydrogen bonding involving the carboxamide group could also be important in stabilising these different tautomers. In the methylene forms (4.29-4.32) the oxygen atom of the carboxamide group could act as the hydrogen bond donor, whereas in the 7-methyl forms (4.33-4.36) the sp^2 lone-pair on N-4 would fulfil this function. As adjudged by ^{1}H.n.m.r. the balance of these forces overwhelmingly favours the methylene forms (at least in solution).

The ^{1}H.n.m.r. spectra in $CDCl_3$ of two pyrazolo[5,1-c][1,2,4]triazines[121] (4.37; R=Ac or CO_2Et) lacking a carboxamide group at C-3 show no evidence for methylene tautomers.

The analogous compound in pyrazolo[4,3-c]pyridazine series existed exclusively in the 7-methyl form as adjudged by their ^{1}H.n.m.r. spectra (see page 112) despite the favoured Juxtaposition of carboxamide and ring nitrogen common to the imidazotriazines. Therefore it is concluded that intramolecular hydrogen bonding involving the carboxamide group is not an important element in determining the tautomeric behaviour, but the loss of heteroaromatic stability occasioned by aza-substitution to produce the fused 1,2,4-triazine tips the balance in favour of the methylene forms of the imidazotriazines (4.29-4.32).







4.29 - 4.32

4.33 - 4.36

4.29; R = CO_2Me

4.30; R = CO_2Et

4.31; R = Ac

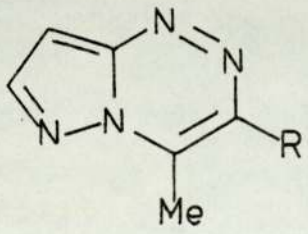
4.32; R = Bz

4.33; R = CO_2Me

4.34; R = CO_2Et

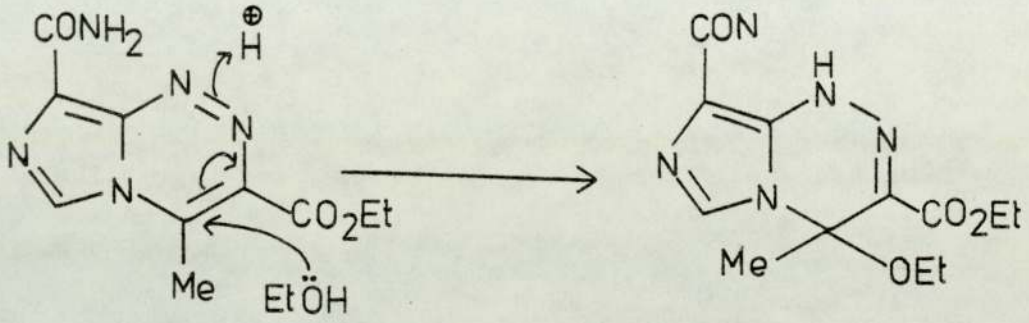
4.35; R = Ac

4.36; R = Bz

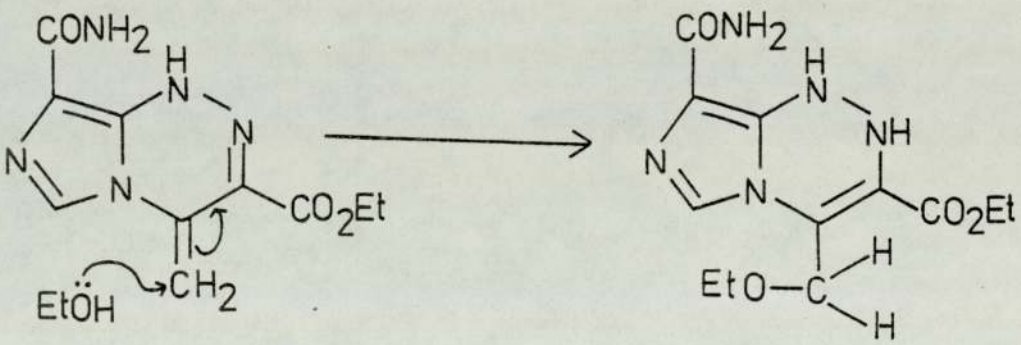


4.37

R = Ac, CO_2Et



(4.38) (4.39)

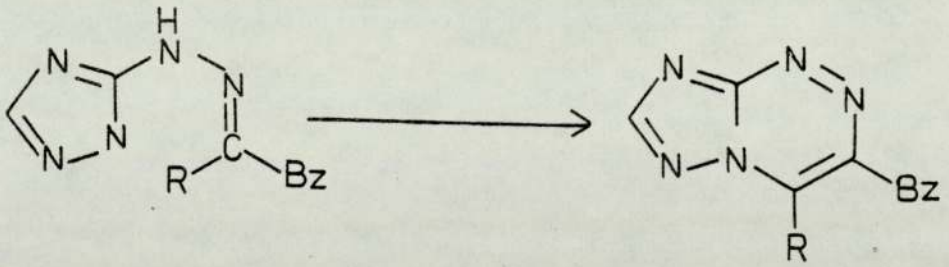


(4.40) (4.41)

Scheme 4.3

The hydrazone (4.7) upon boiling in acetic-acid ethanol mixture furnished the compound (4.30) in good yield (80-90%). From the acid filtrate a yellow crystalline product was isolated. This product melted sharply without decomposition at 175°C and the boiling oil re-solidified at 200°C and re-melted with decomposition at 235-240°C. The u.v. spectrum of this compound did not show the characteristic absorptions of the parent compound (4.30) but instead showed bands at 340, 252, 227 and 206 nm. The i.r. spectrum of this product was also different from the original compound (4.30) and showed absorptions for C-H at γ2980 cm^{-1} and also contained a sharp band at 1142 cm^{-1} (ether group). The precise structure of this compound has not been elucidated but may be tentatively formulated as (4.39 or 4.41) the presence of which is firmly established by its mass spectrum (molecular ion M/e M^{+} 295) and this assumption was also corroborated by the analytical data. It can be envisaged that the 7-methyl tautomer (4.38) might yield compound (4.39) and 7-methylene tautomer (4.40) would possibly give the isomeric compound (4.41) as illustrated by scheme (4.3). Unfortunately because of the small amount of material available a ^{1}H.n.m.r. spectrum of this compound was not recorded and structural proof for this product must await more detailed examination.

The hydrazone (4.9) from benzoylacetone underwent dehydrative cyclisation with the participation of the acetyl group rather than the electronically favoured benzoyl function to yield (4.32) isolated as a hemihydrate. The i.r. spectrum of this compound showed a carbonyl absorption at 1655 cm^{-1} slightly lower than that (1662 cm^{-1})



4.42

R = Ac, CN

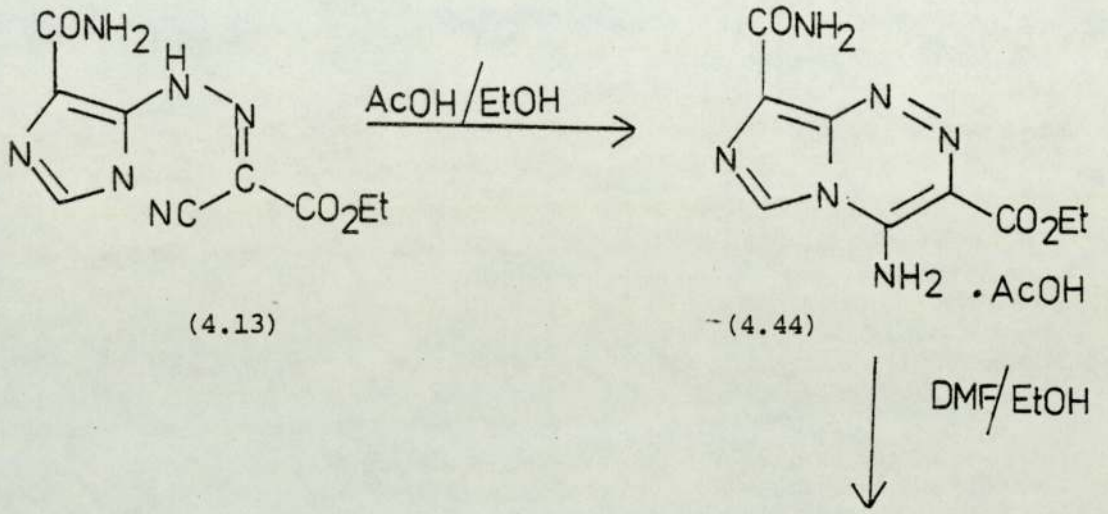
4.43

R = Me, NH_2

of the acetyltriazine (4.31) and also showed a very ill-defined band for bonded N-H. The presence of a 6-benzoyl moeity in the product was confirmed by an abundant phenylacylium ion at M/e 105 in the mass spectrum. The reluctance of a benzoyl group to participate in cyclo-dehydration was also encountered in the triazolo[5,1-c][1,2,4]-triazine series[112], where the hydrazones (4.42, R=Ac or CN) obtained from coupling of 1,2,4-triazole-5-diazonium nitrate with benzoyl-acetone or benzoylacetonitrile respectively, cyclised in glacial acetic acid to yield compound (4.43; R=Me or NH_2).

4.3.1.2 Cyano hydrazones

The cyclisation of compound (4.13) was accomplished easily by refluxing this hydrazone in 50% ethanolic acetic acid to afford an acetic acid solvate of the amine (4.44) as shiny pink crystals. That the cyclisation had involved the cyano rather than ester function was evidenced by the spectroscopic properties of the solvate (4.44). The i.r. spectrum of this compound showed no absorption at 2220 cm^{-1} (C≡N) but retained the ester carbonyl band (1690 cm^{-1}). The i.r. spectrum also showed absorptions at 3050, 3180 and 3390 cm^{-1} (N-H). The ^{1}H.n.m.r. spectrum (TFA) of the crystalline product (4.44) offered conclusive evidence for the presence of acetic acid by showing a three-proton singlet at δ2.24; and in accord with the formulation the spectrum also contained resonances for the ethyl protons of the ester group. A singlet for the imidazole H-1 proton was observed at slightly lower field (δ9.2) than the corresponding proton of the precursor (4.13).



(4.13)

(4.44)

(4.46)

(4.45)

Scheme 4.4

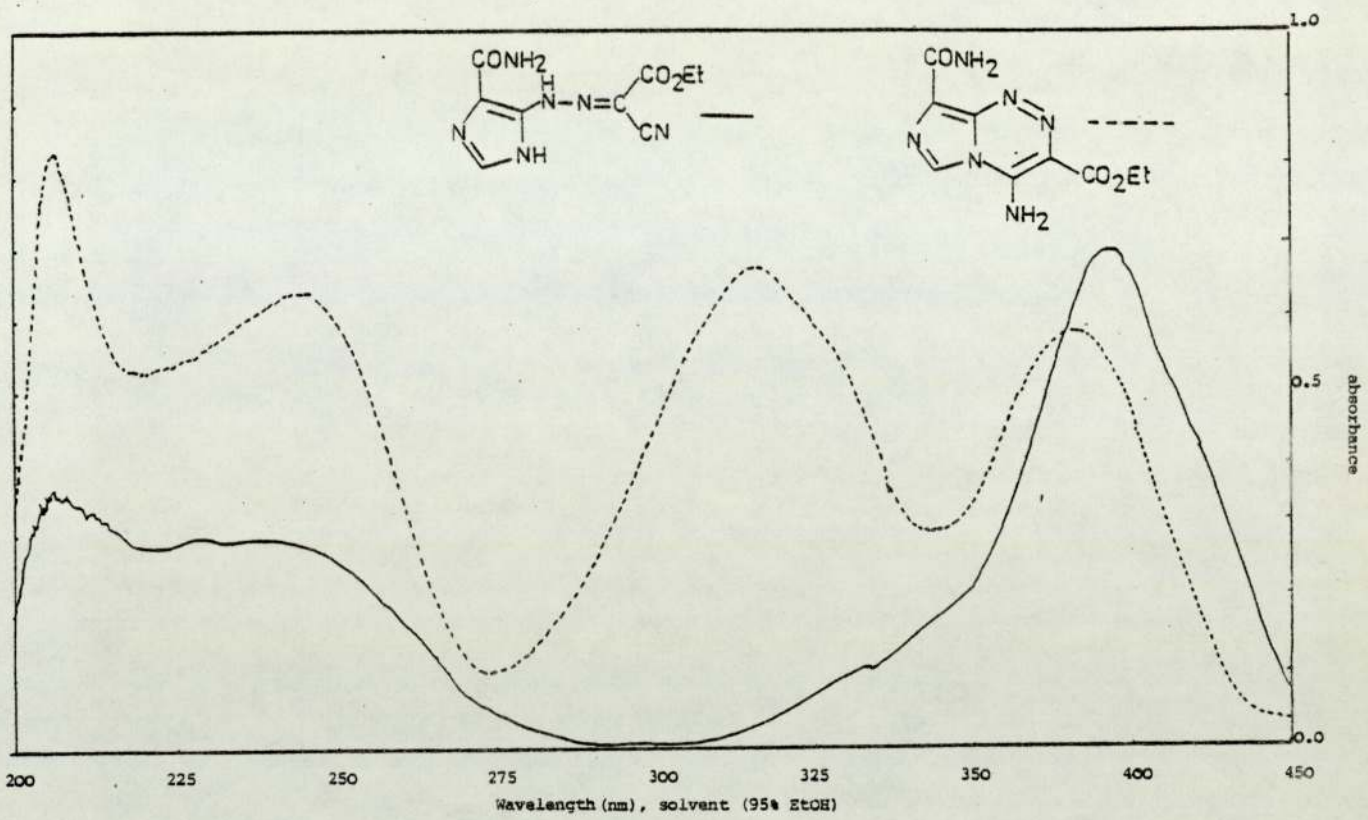


Figure (4.13)

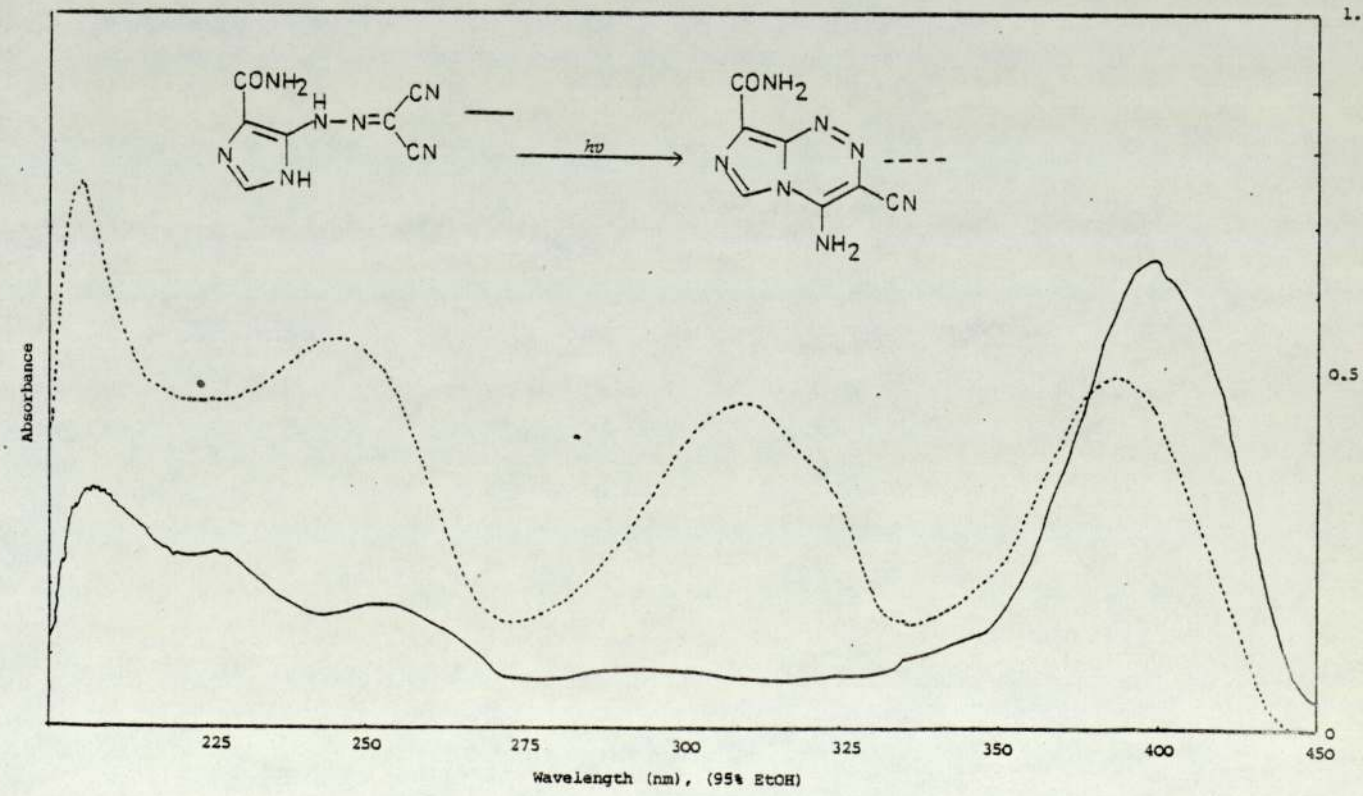


Figure (4.14)

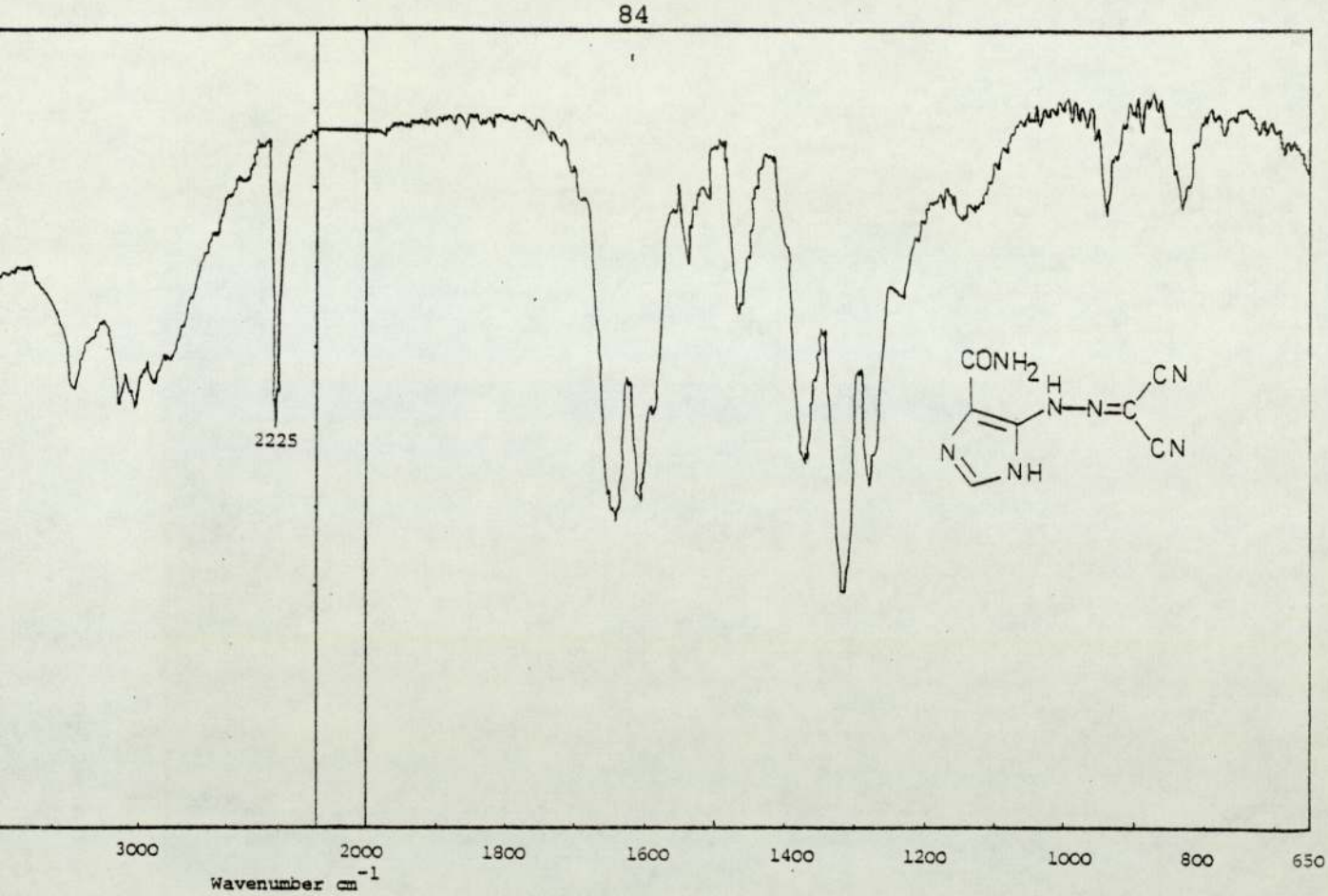


Figure (4.15)

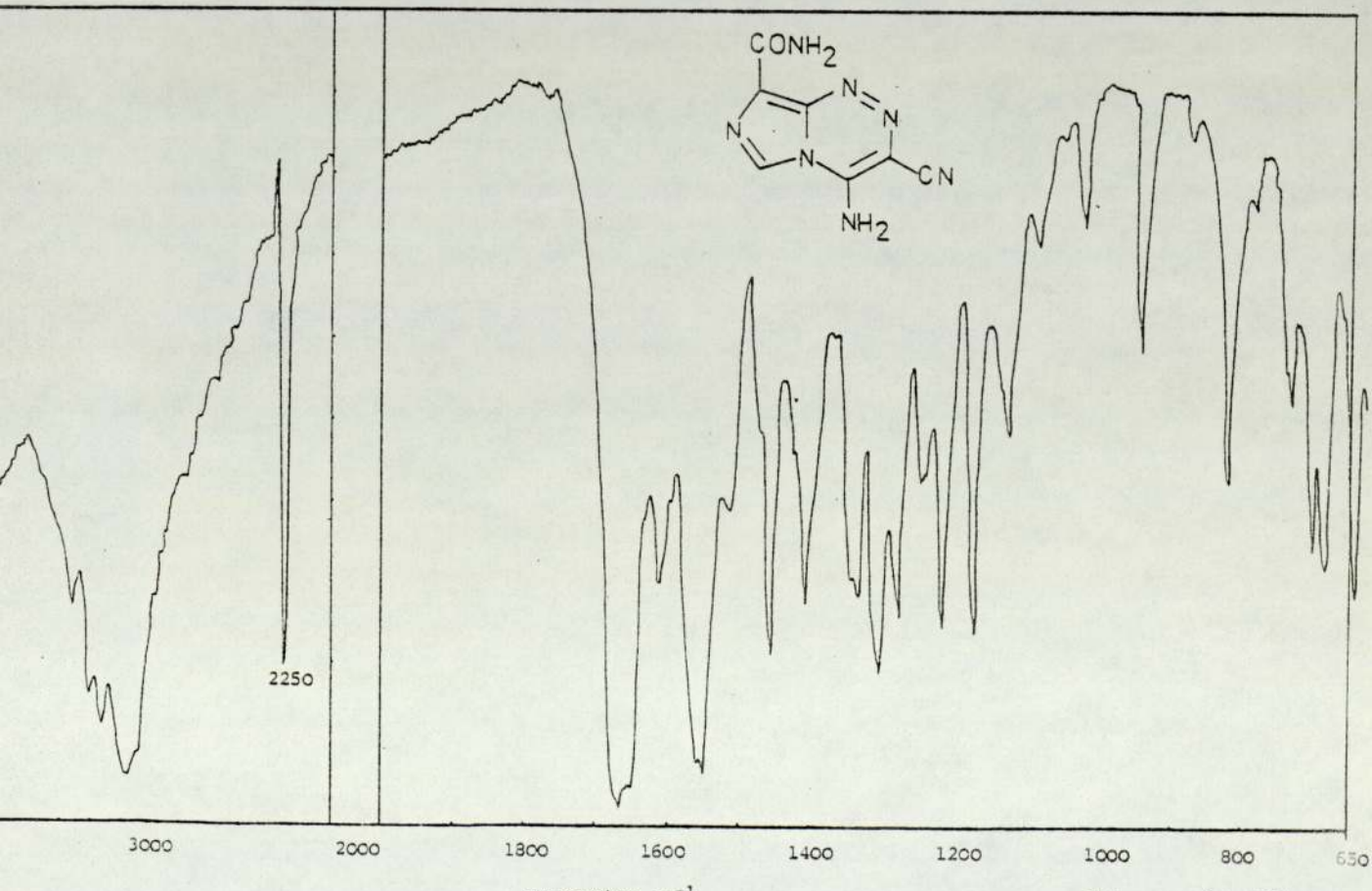
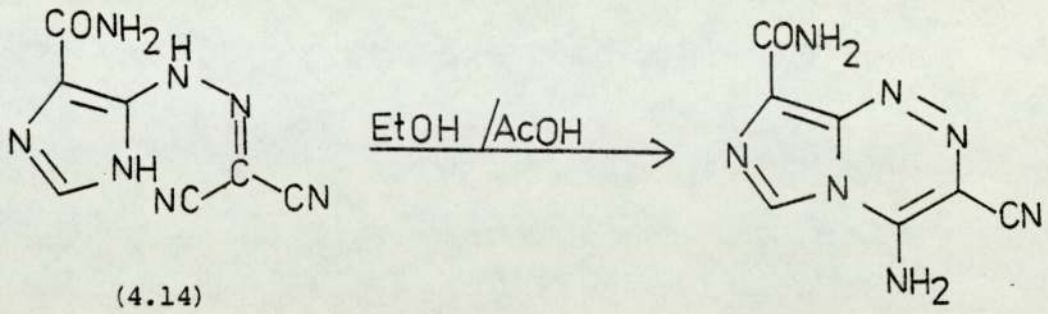


Figure (4.16)

Recrystallisation of the solvate (4.44) from dimethylformamide gave the unsolvated amine (4.45) as evidenced by the ^{1}H.n.m.r. spectrum of the product (4.45) which lacked an absorption for the methyl protons. This amine could be converted back to the solvate from (4.44) by recrystallisation from acetic acid. This compound is considered a solvate rather than an acetic acid salt (4.46) because related azolo[1,2,4]triazines[111,113] similarly prepared by cyclisation of hydrazones and which would be expected to be more basic than the amino-ester (4.45) do not form acetic acid salts under the same conditions. The ^{1}H.n.m.r. spectrum of the triazine methyl ester (4.29) which also crystallised as an acetic acid solvate also showed a resonance at δ2.24 for the methyl protons of acetic acid (see Fig. 4.10).

Hydrazone (4.14) cyclised to yield compound (4.47) on attempted crystallisation from hot ethanol or even in cold ethanol; in the latter case the rate could be greatly accelerated by exposure of the solution to sunlight ($t_{\frac{1}{2}} \sim$ 35 mins.) as indicated by the u.v. spectrum (Fig. 4.14). A few drops of acetic acid added to the hot ethanolic solution considerably enhanced the rate of reaction in the former case.

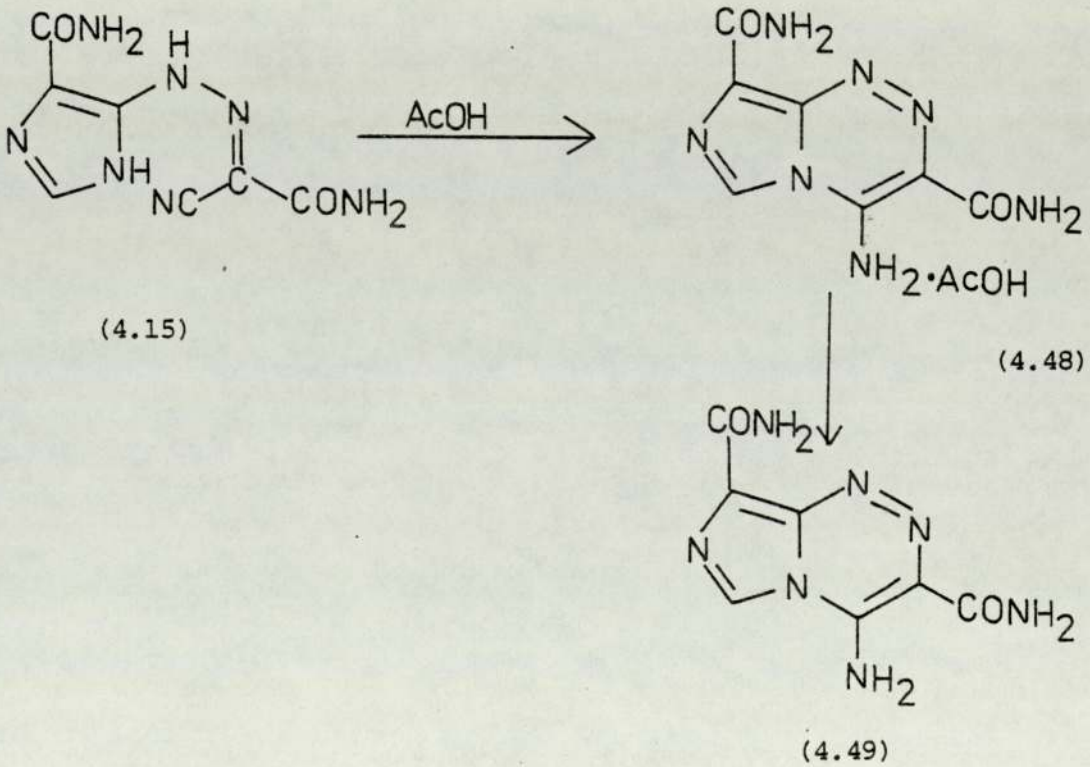
The i.r. spectrum of the cyclic product (4.47) was markedly different (Fig. 4.16) from the spectrum of the hydrazone (4.14) (Fig. 4.15) in the finger-print region and showed a sharp singlet at 2250 cm^{-1} for the C≡N absorption. In the hydrazone this band was centred at 2225 cm^{-1} and was broadened because of the presence



(4.14)

(4.47)

Scheme 4.5.



(4.15)

(4.48)

(4.49)

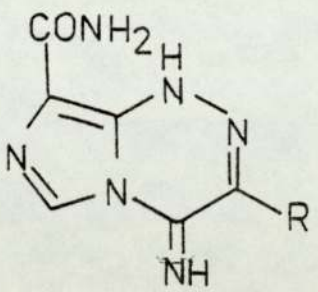
Scheme 4.6

of two cyano groups.

Cyclisation of hydrazone (4.15) on prolonged heating in glacial acetic acid yielded the acetic acid solvate of the amine (4.48). The unsolvated form (4.49) was obtained upon recrystallisation of the solvate from dimethylformamide - ethanol. The assigned structure (4.49) was corroborated by spectroscopic evidence and elemental analysis data. The mass spectrum of the bicyclic product showed the expected peak at M/e 221 for the molecular ion, and the i.r. spectrum of this compound lacked the absorption band at 2200 cm^{-1} (C≡N) and showed absorptions in the 3200-3450 cm^{-1} region (NH).

Electronic absorption spectra of the aminotriazines

The hydrazones (4.13-4.15) upon cyclisation showed a hypsochromic shift of the major peak in their u.v. spectra with the appearance of three more prominent peaks (Fig. 4.13 and 4.14). It is generally accepted that an amino group in π-deficient heterocycles exist as such[80] and the presence of an N=N grouping may be giving rise to the long wavelength absorption which may be associated with the $\eta \rightarrow \pi$ transition in the N=N chromophore.[122] However, the u.v.-visible spectra (Table 4.2) of the 7-aminoimidazotriazines (4.45,4.47, 4.49) are strikingly similar to those of the imidazotriazin-7(4H)-ones (cf. Table 4.3, Page 106) and the possibility of a substantial 7(4H)-imino (4.50) contribution can not be discounted.



R = CO_2Et, $CONH_2$, CN

(4.50)

Table 4.2

Electronic absorption spectra of 7-aminoimidazotriazines

Compound	λ_{max}(nm) solvent 95% EtOH
4.45	385, 317, 245*, 206
4.47	386, 324*, 312, 245*, 206
4.49	387, 314, 246*, 207

* shoulder

4.3.1.3 Miscellaneous hydrazones

The hydrazones from diethyl acetone dicarboxylate (4.9) and from ethyl benzoylacetate (4.10) cyclised only with great difficulty upon prolonged heating in acid conditions to yield compounds (4.51; R=CH_2CO_2Et) and (4.52; R=Ph). It was found that the proportion of the cyclised material was increased considerably when acetic acid alone was used as solvent. The

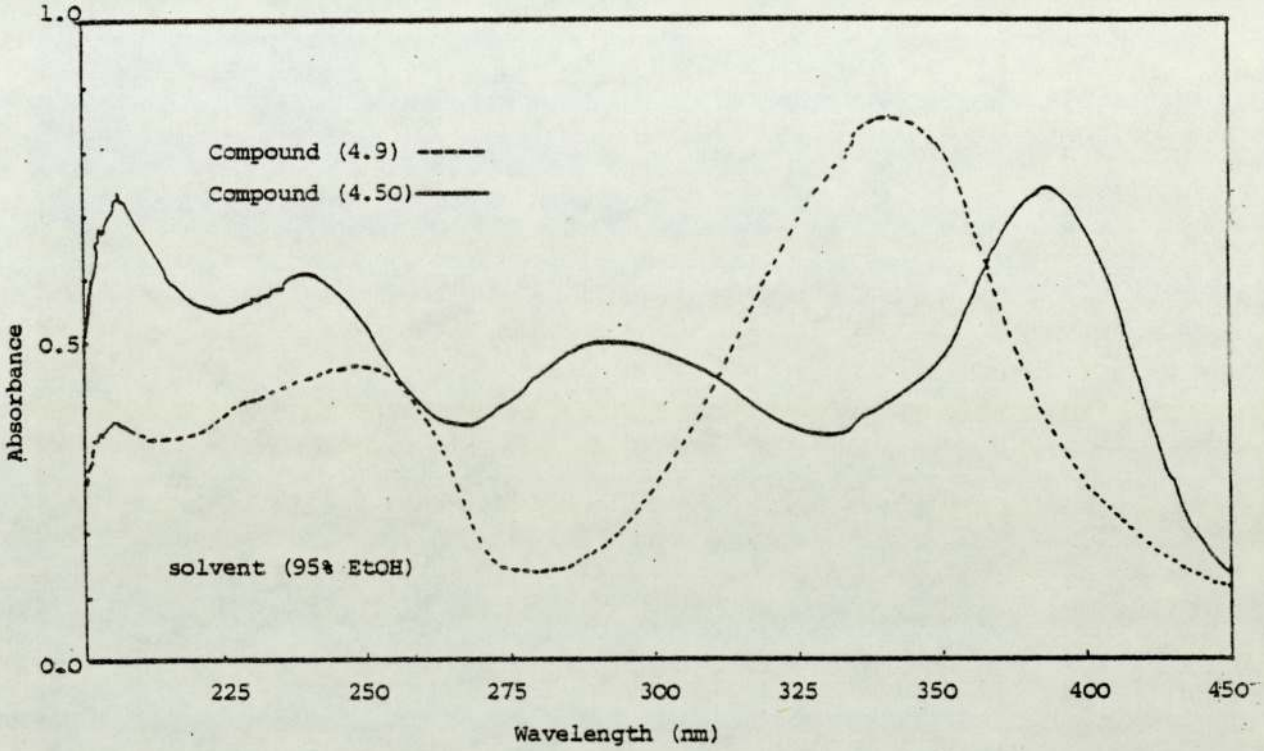
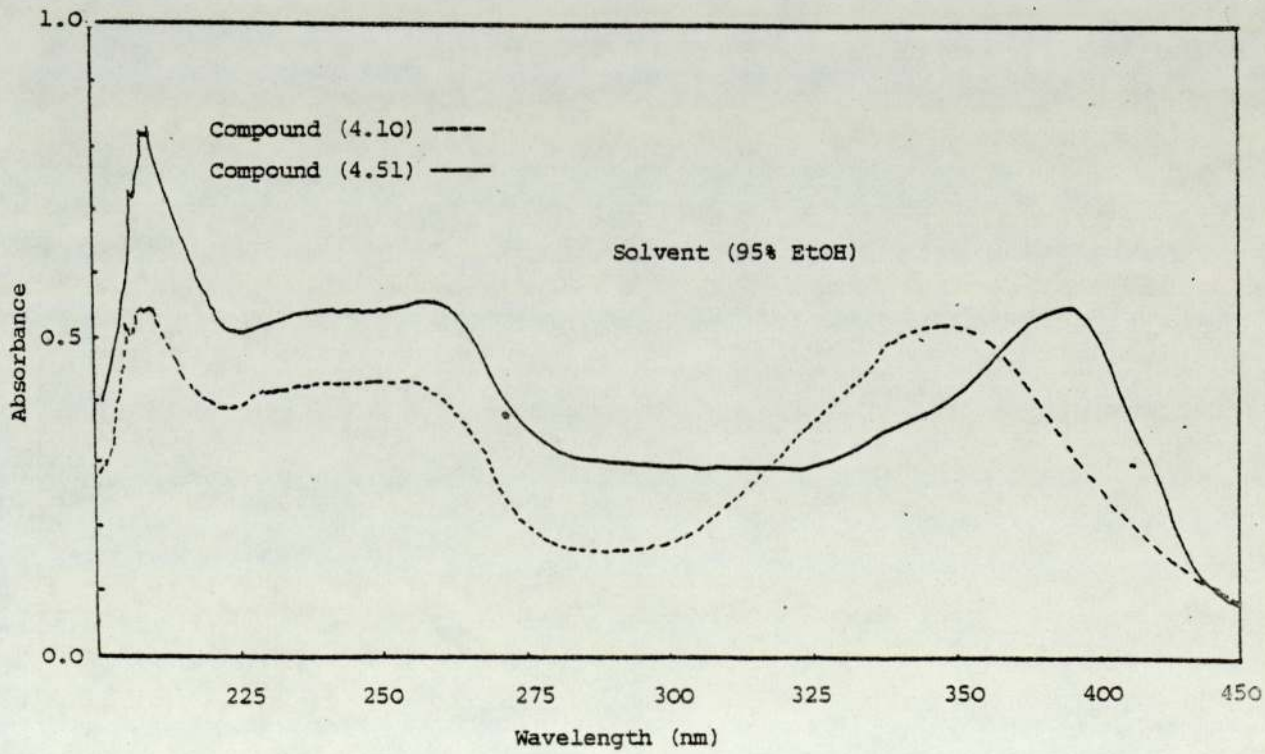
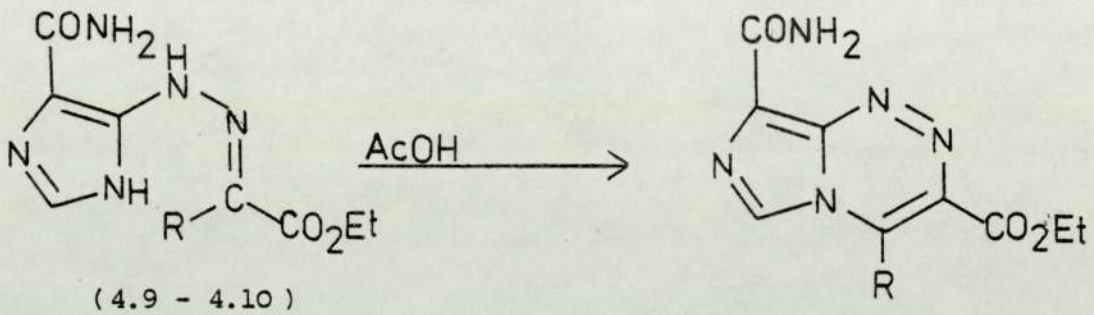


Figure (4.17)



(Figure (4.18)



(4.9 - 4.10)

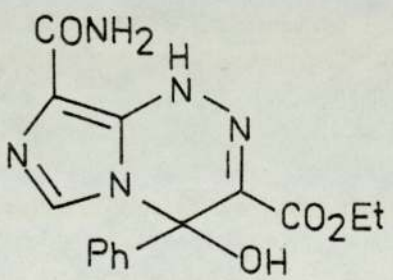
(4.51 - 4.52)

4.9, R = $COCH_2CO_2Et$

4.10, R = Bz

4.51, R = CH_2CO_2Et

4.52, R = Ph



(4.52a)

progress of the reactions was monitored by u.v. spectroscopy (Figs. 4.17 and 4.18). These products were further characterised by i.r., ^{1}H.n.m.r. and mass spectroscopy. The mass spectrum of compound (4.51) showed an appropriate molecular ion at M/e 321. The elemental analysis of this compound revealed that it was monohydrate. Similarly compound (4.52) was also obtained as a monohydrate, but in this case it was probably a covalent hydrate (4.52a). This conclusion was corroborated by examination of the mass spectrum of the compound which showed a peak at M/e 329 corresponding to the covalent hydrate (4.52). This type of adduct has been reported previously[123].

4.3.2 Base-catalysed cyclisations

When ethanolic solutions of the hydrazones (4.6 - 4.15) were treated with alkali some interesting colour changes were observed (see page 62). On one occasion these intriguing colour transformations were recorded by ultraviolet spectroscopy. Upon addition of alkali to the solution of hydrazone (4.11) in 95% ethanol the colour of the solution intensified to dark orange and then rapidly decolourised. These colour transformations were attended by swift spectral changes (Fig. 4.19). The u.v. spectrum of the solution showed an absorption at 440 nm for the intermediate orange anion (4.53) and also displayed peaks at 390, 330 (inflection) 252 and 207 nm. When the spectrum of the decolourised solution was re-run the absorption at 440 nm for the intermediate orange anion had disappeared as anticipated from the drastic colour change.

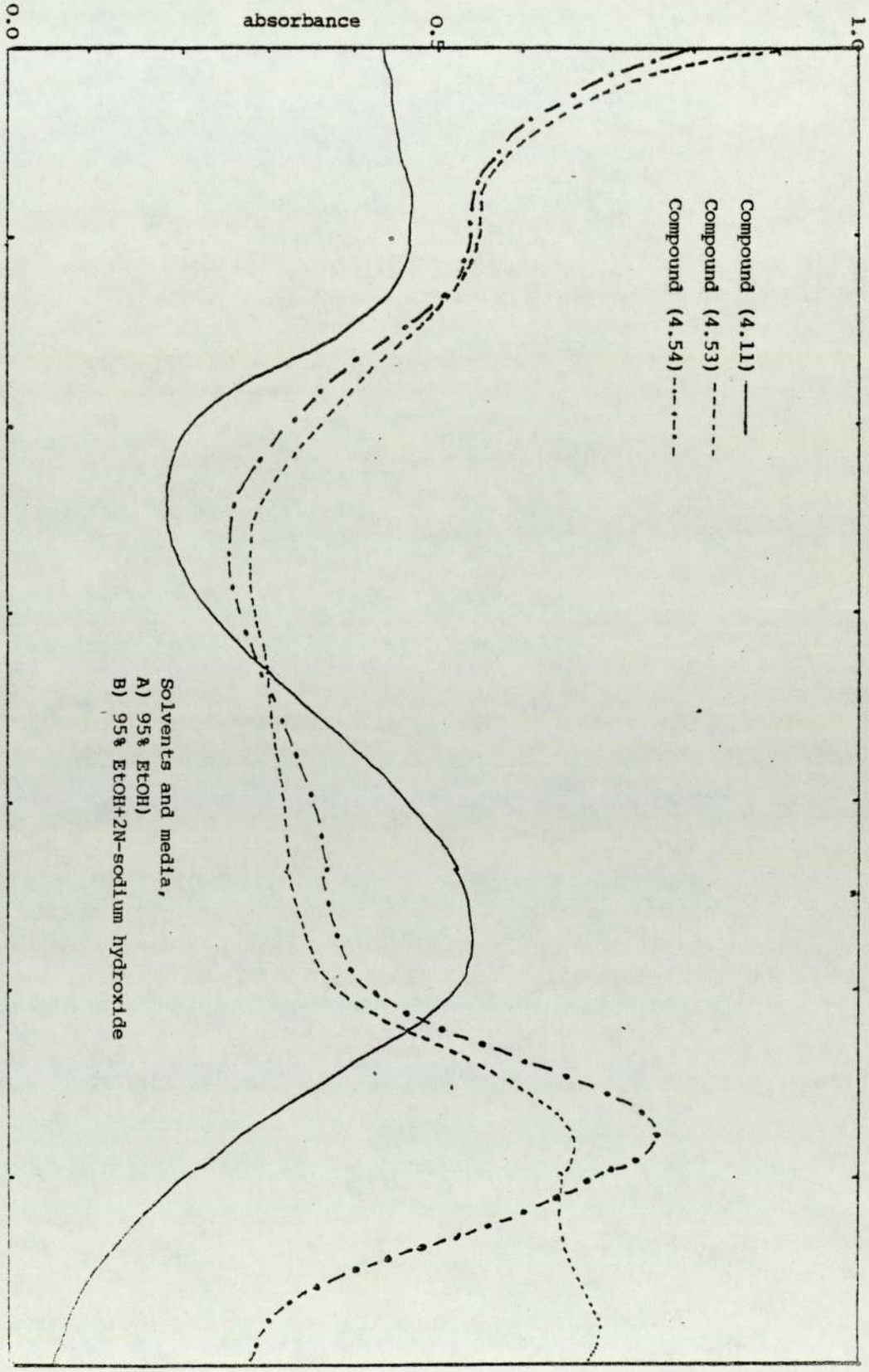
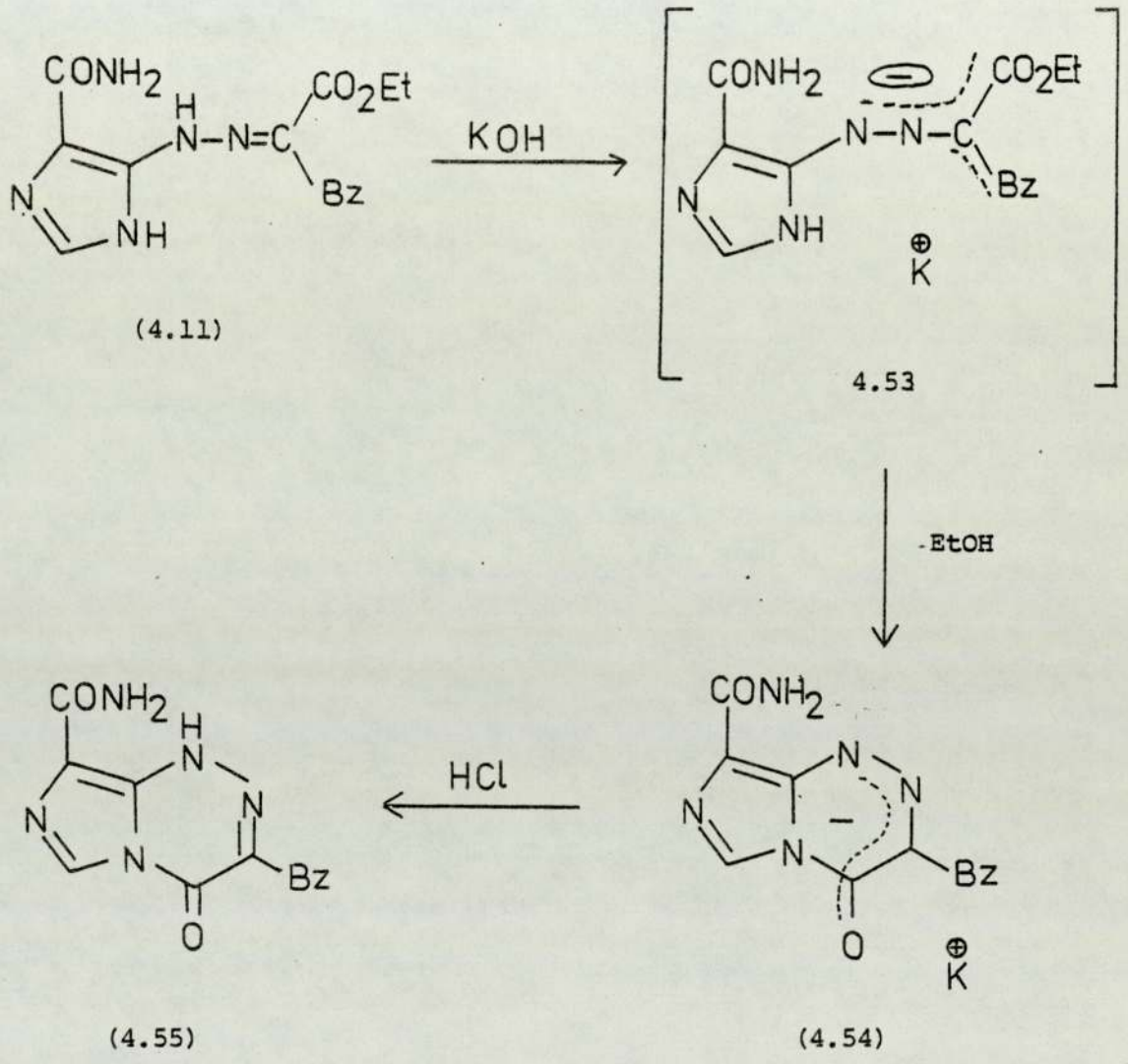

absorbance
0.0
0.5
1.0
225
250
275
300
325
350
400
450
wavelength (nm)
Compound (4.11) ——
Compound (4.53) ------
Compound (4.54) -·-·-·-
Solvents and media,
A) 95% EtOH)
B) 95% EtOH+2N-sodium hydroxide

Figure (4.19)



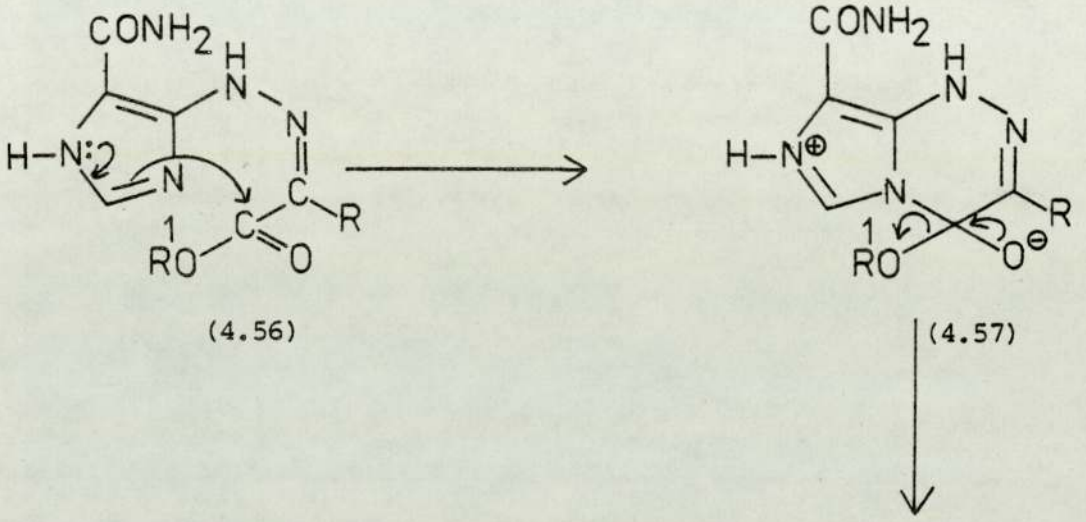
(4.11)

4.53

(4.54)

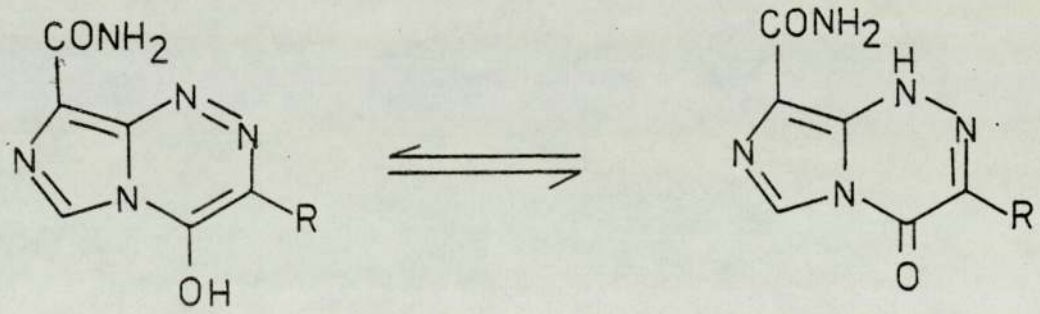
(4.55)

A preparative-scale transformation of the hydrazone (4.11) in alkali followed the same course and the hydrazone rapidly dissolved in ethanolic potassium hydroxide producing an orange solution; an insoluble orange solid (4.53) immediately precipitated but slowly changed colour from orange to yellow. The u.v. spectrum of this product showed absorptions at 390, 330 (inflection) 252 and 207 nm (Fig. 4.19). The i.r. spectrum of the free acidic product (4.55) obtained by acidification of the salt (4.54) with dilute acid did not show the absorption at 1718 cm^{-1} of the ethyl ester group. However the product retained the band at 1638 cm^{-1} of the ketonic carbonyl and also showed a new carbonyl peak at 1670 cm^{-1} which could be attributable to C=O at position 7[40]. The ^{1}H.n.m.r. spectrum of the product was consistent with structure (4.55) and showed a multiplet for the benzoyl protons but did not show the corresponding resonances of the ester protons. The singlet for the imidazole (H-1) was observed at lower field than the corresponding proton of the original hydrazone. This bicyclic triazinone has been reported[88] previously to be formed from hydrazone (4.11) and dilute hydrochloric acid. (The u.v. and i.r. spectral properties of this compound were not published[88]). When this previously described cyclisation was repeated it was found that at the end of the acid treatment the product was mainly unreacted hydrazone with traces of cyclic product (4.51) (as indicated by t.l.c. examination) and cyclisation with loss of ethanol only occurred when the mixture was basified with alkali.



(4.56)

(4.57)



(4.62)

(4.58 - 4.61)

4.58; R=Ac

4.59; R=$COCH_2CO_2Et$

4.60; R=CO_2Et

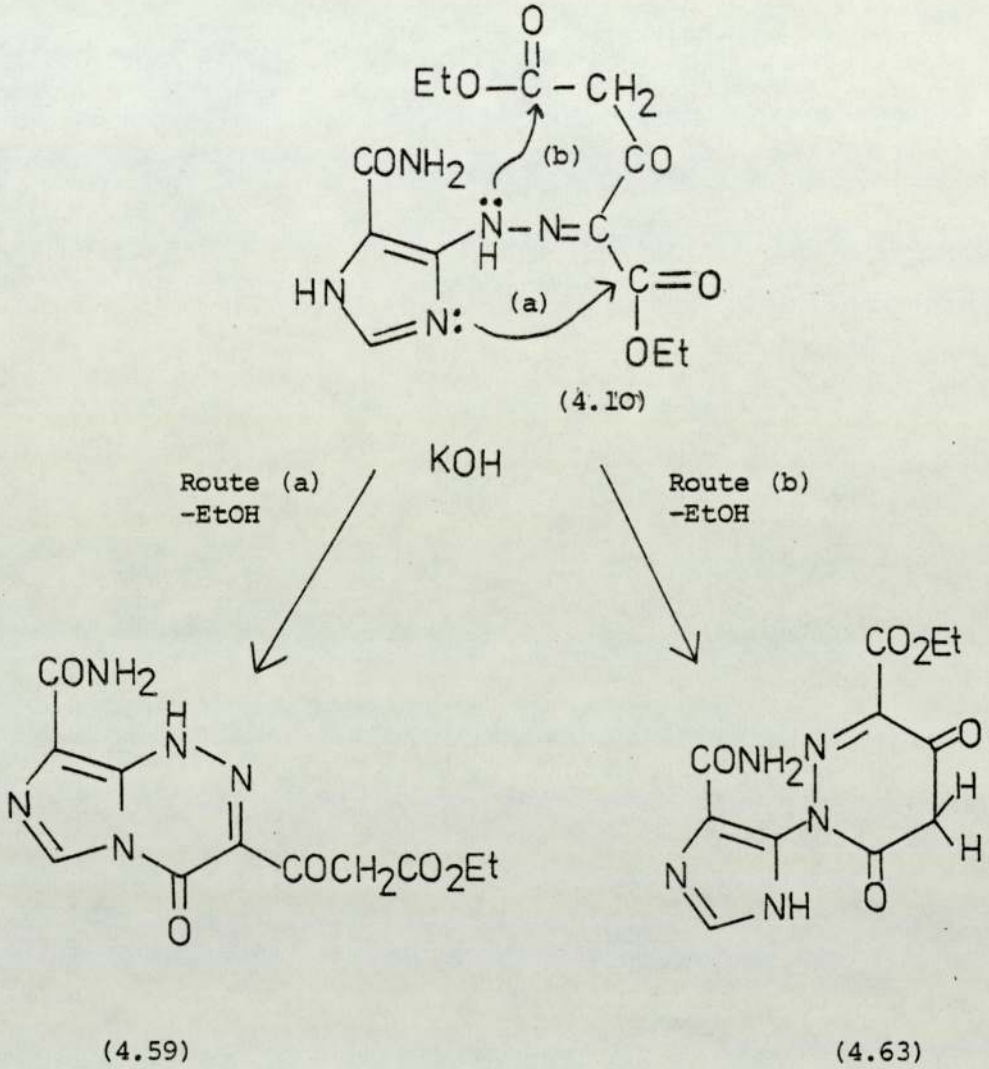
4.61; R=CN

Scheme 4.7

This procedure was extended to the cyclisation of other hydrazones bearing an ester group (4.6, 4.7, 4.10, 4.12, 4.13). These hydrazones responded similarly to the alkaline treatment but the reaction in many cases was so fast that it was impossible to record any intermediate changes by u.v. spectroscopy. These hydrazones underwent spontaneous cyclisation to yield the bicyclic triazinones (4.58 - 4.61). The general reaction of this type of cyclisation can be illustrated mechanistically by scheme (4.7).

The hydrazones (4.6 and 4.7) obtained by coupling diazo-imidazole carboxamide with methylacetoacetate or ethylacetoacetate cyclised to form the same 6-acetylimidazotriazine (4.58) with the loss of either methanol or ethanol respectively; the products had identical ^{1}H.n.m.r. spectra. The spectrum (TFA) in each case exhibited resonances for acetyl protons and an imidazole (H-1) ring proton. The mass spectrum showed a substantial peak for the molecular ion (M/e 221). The hydrazone (4.10) prepared by coupling diazoimidazocarboxamide with diethyl acetonedicarboxylate also cyclised in alkali with the loss of ethanol to yield a product tentatively assigned structure (4.59). (Scheme 4.8) on the grounds that its u.v. spectrum is nearly identical to that of the related triazinones (4.58, 4.60, 4.61). However, the isomeric pyridazin-dione structure (4.63) can not be excluded on the spectroscopic evidence.

Those hydrazones (4.8) and (4.9) with acyl groups did not cyclise at all under basic conditions. When treated with alkali compounds (4.8) and (4.9) dissolved rapidly and the insoluble

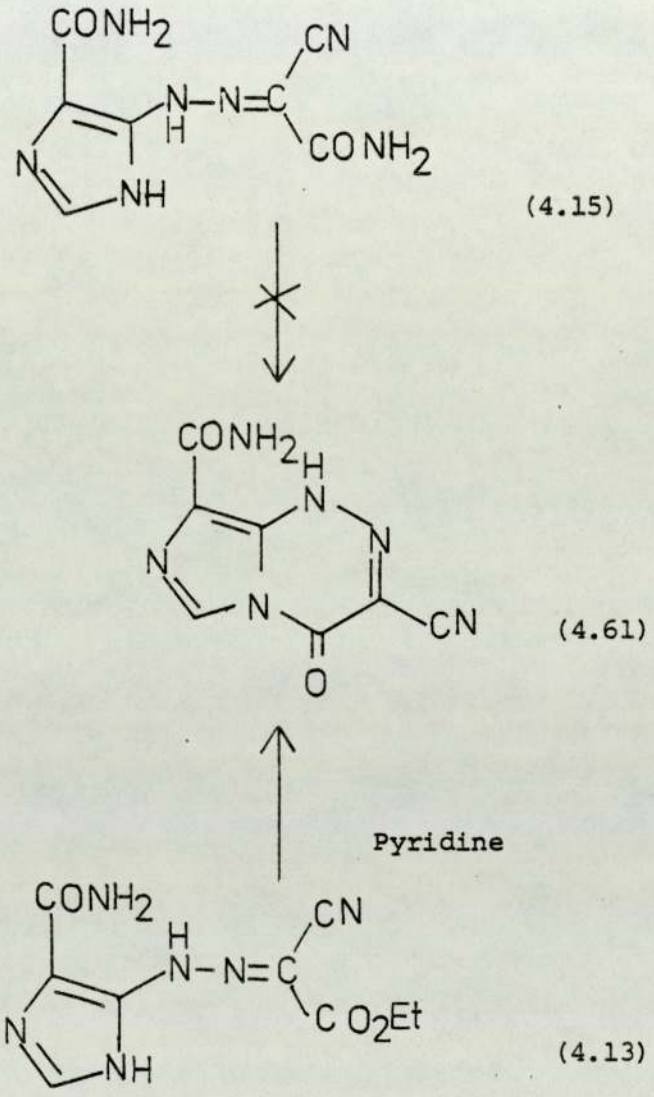


(4.10)

(4.59)

(4.63)

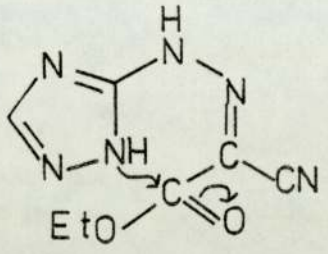
Scheme 4.8


CONH2
CN
N–N=C
H
CONH2
N
NH
(4.15)
CONH2
H
N
N
N
N
CN
O
(4.61)
Pyridine
CONH2
H
N–N=C
CN
N
NH
C O2Et
(4.13)

Scheme 4.9

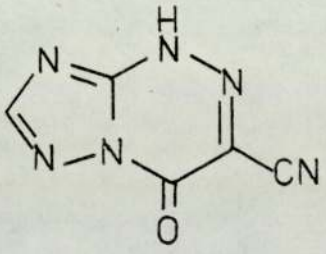
salts of the corresponding hydrazones were isolated (see page 62). The hydrazone (4.15) obtained from cyanoacetamide did not yield the expected triazinone (4.61) in alkali or in pyridine presumably because of the diminished propensity of the amido group to undergo nucleophilic addition (when compared with ester groups). However the triazinone (4.61) was prepared by the alternative route from the hydrazone (4.13). This hydrazone reacted slugglishly in cold alkali but cyclised rapidly in boiling ethanolic pyridine. Initially the insoluble pyridinium salt of the hydrazone (4.20) (see page 67) was formed and after prolonged heating the acidic triazinone (4.61) was isolated as an unstable pyridinium salt. The salt dissociated readily when stirred in ethanol. In a comparable reaction the triazolohydrazone (4.64) obtained by coupling the triazolyldiazonium salt with ethylcyanoacetate, cyclised in boiling pyridine to yield the triazolotriazinone (4.65) (Scheme 4.10). It has been claimed that this triazinone is very acidic[111] and obtained from reaction mixture as a stable pyridinium salt (4.66) which crystallised unchanged in boiling acetic acid. This contrast suggests that imidazotriazinone (4.61) is less acidic than the corresponding triazolotriazinone (4.65).

Since the cyclic product (4.61) was also recovered in small amounts from the filtrate of the acid-catalysed cyclisation of hydrazone (4.13) to aminotriazine ester (4.45) it was considered that the oxo-nitrile (4.61) might have originated from the amino-ester by a base-catalysed ring-opening reaction similar to that observed in 1,2,3-benzotriazin-4(3H)imines[107]. When the

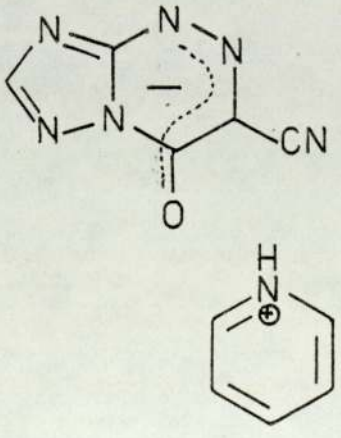


(4.64)

Pyridine

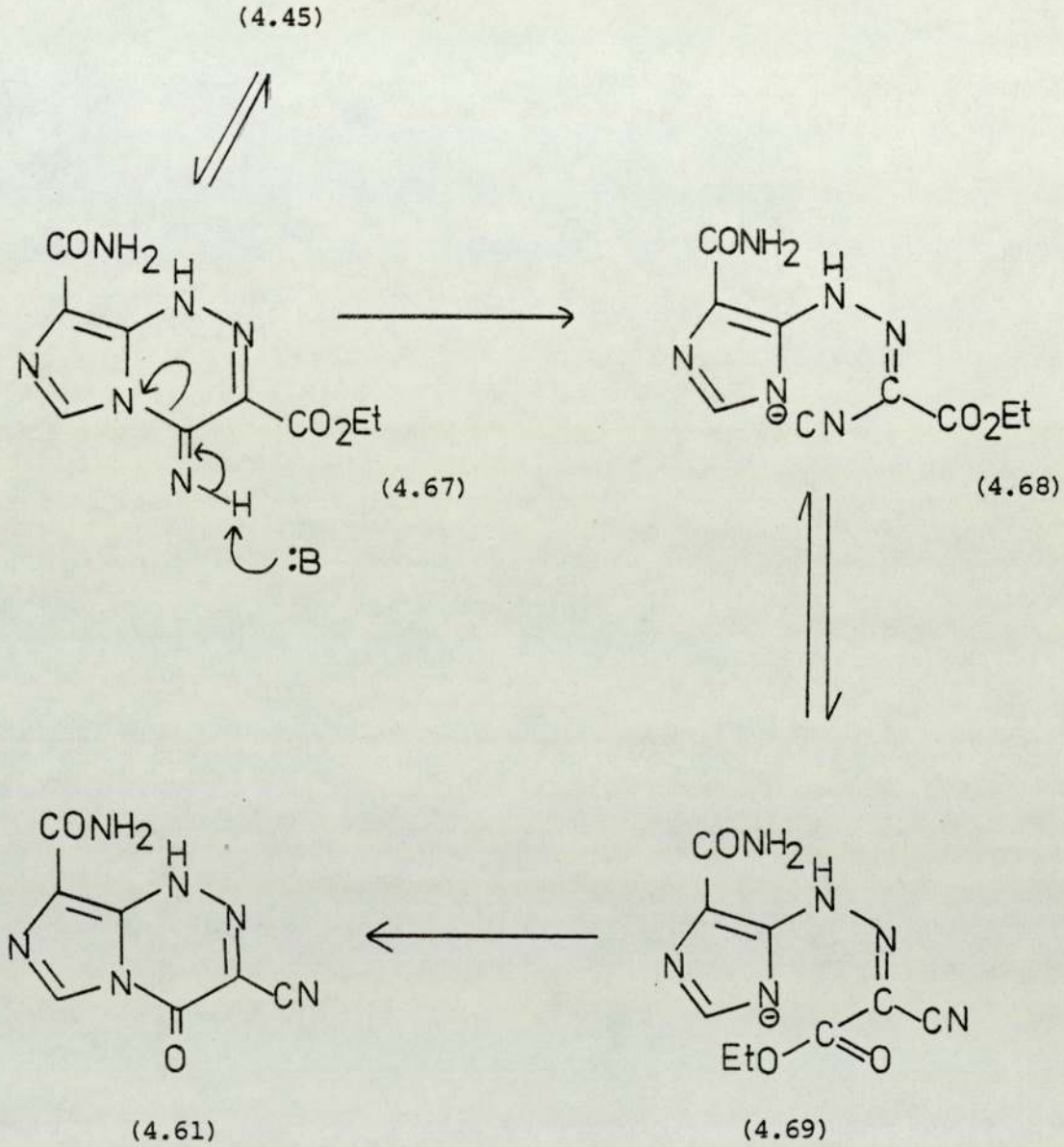


(4.65)

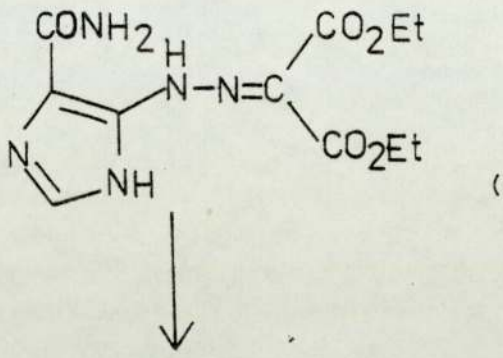


(4.66)

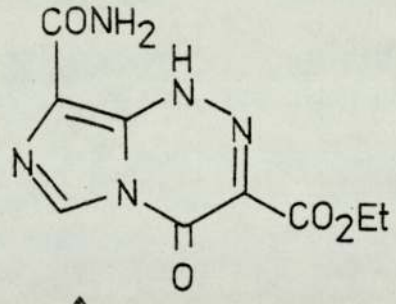
Scheme 4.10



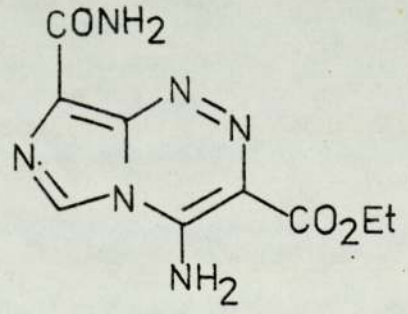
Scheme 4.11



(4.12)



(4.60)



(4.45)

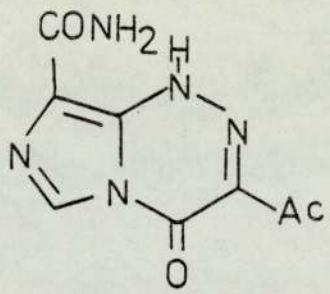
Scheme 4.12

experiment was attempted no evidence for such a mechanism (Scheme 4.11) was obtained: and the amino-ester (4.45) was recovered unchanged from boiling pyridine. This strongly supports the earlier observations made by Gray and co-workers[111] in the triazolotriazine series.

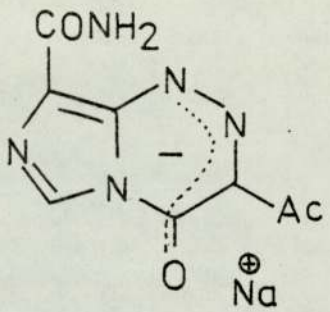
The hydrazone (4.12) obtained from diethylmalonate underwent spontaneous cyclisation in alkali and the product (4.60) was isolated. This product proved to be identical to that formed by the acidic hydrolysis of amino-ester (4.45) (see page 119).

Electronic and infrared spectra of imidazotriazinones

Imidazotriazinones show several prominent and well-defined peaks in their electronic absorption spectra. The general shape of the spectra of all these triazinones (4.58 - 4.61) are similar and show slight variations in the absorption maxima with different substituents at C-6. These characteristics are listed in Table (4.3). The triazinones are potentially tautomeric and also very acidic, as may be deduced by their u.v. spectral properties. For example the spectrum of compound (4.58) was profoundly changed in alkali. This spectral change could be attributable to the formation of the anion (4.70) Fig (4.20). Similarly all the other triazinones (4.55,4.59,4.60) showed the same characteristic differences in their u.v. spectra when treated with alkali. Compound (4.61) behaved differently and showed very little response to alkaline treatment (Table 4.3). In all cases addition of acid to the alkaline solutions restored the spectra to those of the starting triazinone free acids.



(4.58)



(4.70)

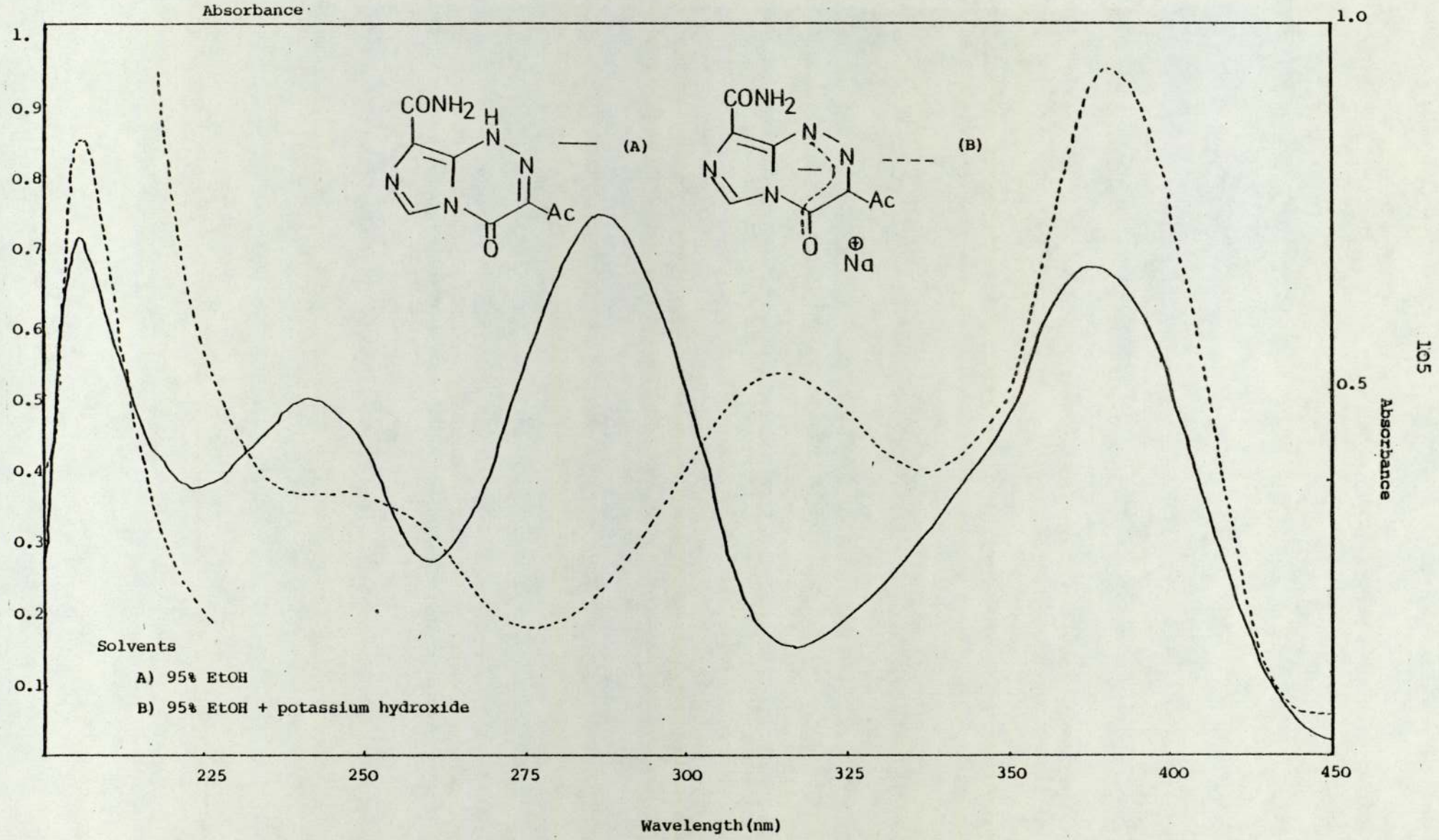

Absorbance
1.
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
1.0
0.5
Absorbance
225
250
275
300
325
350
400
450
Wavelength (nm)
CONH2
H
N
N
N
N
Ac
O
(A)
CONH2
N
N
N
N
Ac
O
⊕
Na
(B)
Solvents
A) 95% EtOH
B) 95% EtOH + potassium hydroxide

Figure (4.20)

Table 4.3

Electronic absorption maxima of imidazotriazinones

Compound	Solvent	$\lambda_{max.}$ (nm)
4.55	A	378, 296, 257, 240*
	B	390, 328, 255
4.58	A	376, 287, 243*
	B	382, 315, 250
4.59	A	385, 295, 240*
	B	398, 320, 267
4.60	A	373, 279, 239*
	B	382, 301, 250
4.61	A	382, 310*, 298, 283*, 244
	B	380, 310*, 293, 245
6.13[C]	A	376, 286, 250*, 240
	B	381, 310, 300, 242

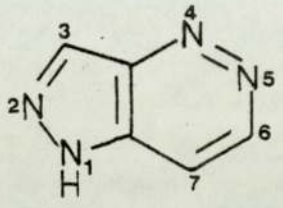
Solvent: A=95% EtOH
B=95% EtOH+2N-NaOH
C=obtained from the hydrolysis of (4.61) (p.123)
*=inflection

The i.r. spectra of the above triazinones showed a band at 1660-1670 cm^{-1} attributable to the carbonyl group at C-7. These values are in agreement with published values for 1,2,4-triazinones.[40] The imidazotriazinones (4.55, 4.58-4.61) also showed broad absorption for bonded N-H between 3100-3500 cm^{-1}.

Chapter 5

5.1 1H-Pyrazolo[4,3-c]pyridazines

A new general route has been discovered to the synthesis of substituted 1H-pyrazolo[4,3-c]pyridazines(5.1) by thermal cyclisation of precursor hydrazones.

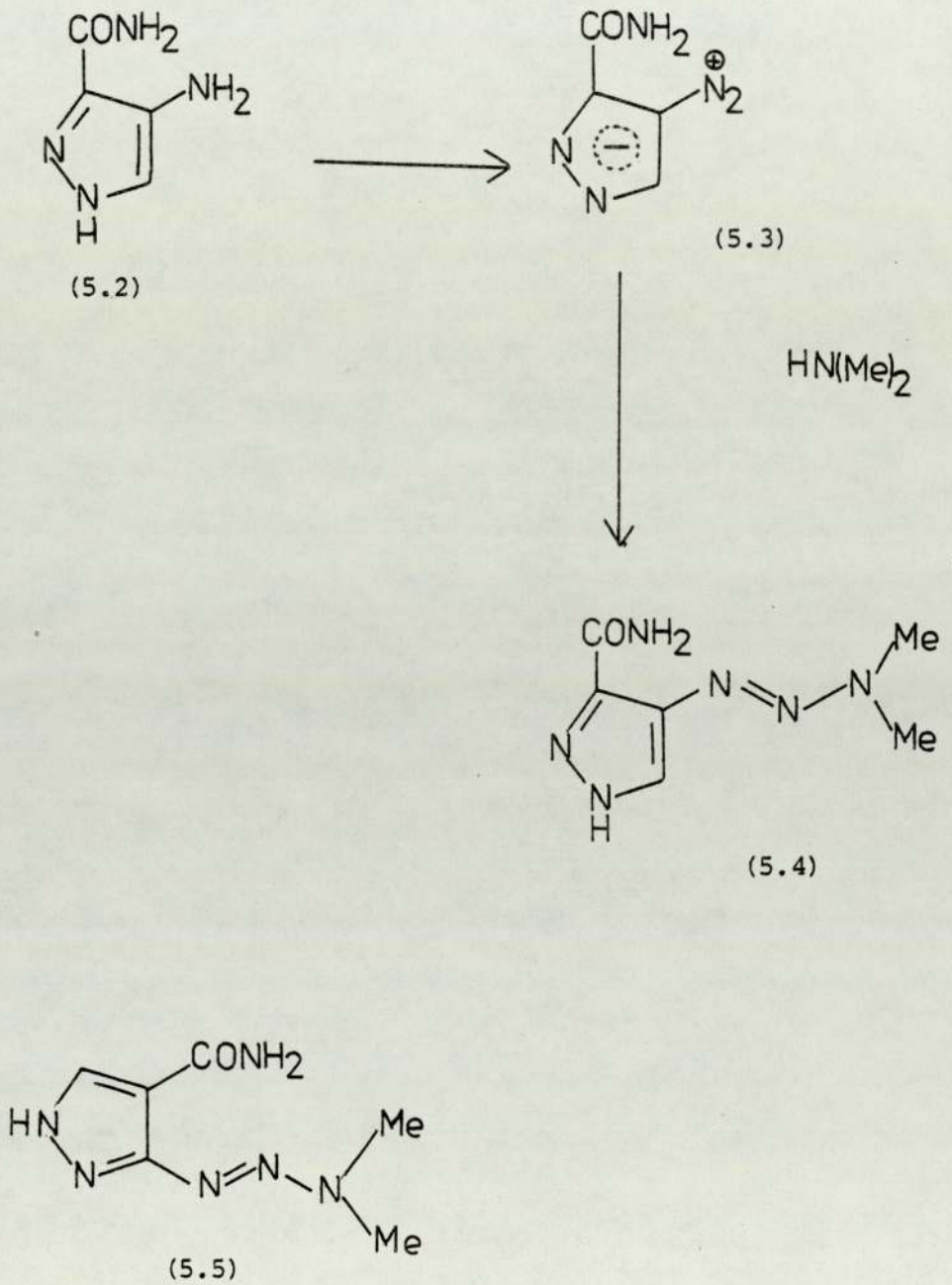


(5.1)

5.2 Synthesis of pyrazololylhydrahydrazones

In previous studies 4-aminopyrazole-3-carboxamide(5.2)[124] has been diazotized[125] and coupled with dimethylamine to achieve a synthesis of 4-(3,3-dimethyltriazen-1-yl)pyrazole-3-carboxamide(5.4). This compound was required in the search for anti-leukaemic analogues of the isomeric 3-(3,3-dimethyltriazen-1-yl)pyrazole-4-carboxamide[126,127] (5.5) scheme (5.1).

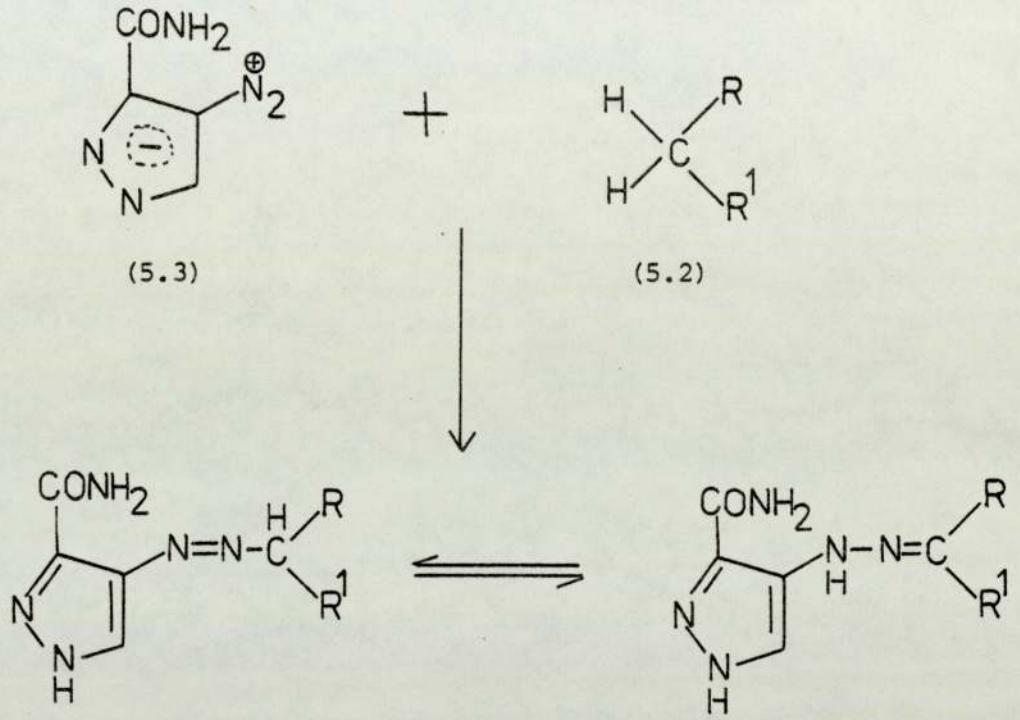
4-Diazopyrazole-3-carboxamide (5.3) is less prone to intramolecular cyclisation than the analogous 5-diazoimidazole-4-carboxamide (4.1). Coupling reactions were therefore initiated in situ by the addition of reactive methylene compounds to a buffered solution of diazopyrazole (5.3) in sodium acetate at 0°-5°. After stirring for a few hours the coupled products were collected. The crude products (5.6 - 5.8) could not be analysed because of their instability but were characterised by spectroscopy (u.v., i.r; ^{1}H.n.m.r.) and their constitutions were confirmed by mass spectroscopy.


CONH2
NH2
N
N
H
(5.2)
CONH2
⊕
N2
N
N
(5.3)
HN(Me)2
CONH2
N
N
Me
N
Me
N
N
H
(5.4)
CONH2
HN
N
N
N
N
Me
Me
(5.5)

Scheme 5.1

The coupling reactions between diazopyrazole (5.3) and ethyl acetoacetate or methyl acetoacetate in sodium acetate buffer furnished the hydrazones (5.6 or 5.7) as pink solids. The u.v. spectra of these products were similar to those of the hydrazones (4.6 - 4.8) obtained from the coupling reaction between diazoimidazole carboxamide and reactive methylene compounds and showed absorptions at λmax 342 nm and 242 nm (cf. Table 4.1). The i.r. spectra of these compounds were consistent with proposed structures and showed the presence of three different cabronyl groups (see Experimental Section) and also showed absorptions between 3100 - 3400 cm^{-1} (bonded N-H). Their ^{1}H.n.m.r. spectra showed resonances for the corresponding ester protons and methyl protons (see Experimental Section). These spectra also showed a sharp one proton singlet at δ8.22 (compound 5.6) or δ8.16 (compound 5.7) which was assigned to H-5 of the pyrazole ring. (The NH proton was not observed). The absence of any other C-H resonance in the ^{1}H.n.m.r. spectra exclude the possibility for the presence of azo-tautomers. The assigned structures (5.6) and (5.7) were further confirmed by their mass spectra which showed an intense peak for the corresponding molecular ions at M/e 267 and M/e 253 respectively.

The coupling reaction between diazopyrazole (5.3) and ethyl cyanoacetate furnished a yellow solid (5.8) (scheme 5.2). This hydrazone was intensely coloured and had characteristic u.v. absorptions in three bands at λ_{max} 405, 204 and 207 nm comparable with the absorption maxima of the related imidazolylhydrazones (4.13 - 4.15) Table (4.1) (see page 58). The ^{1}H.n.m.r. spectrum

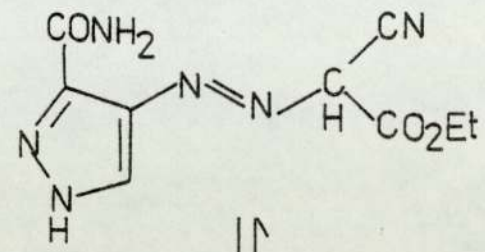


(5.3) (5.2)

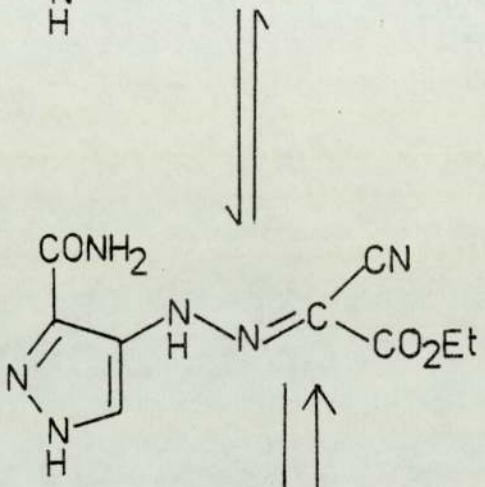
(5.6 - 5.8)

Compound	R	R^1
5.6	CO_2Et	Ac
5.7	CO_2Me	Ac
5.8	CO_2Et	CN

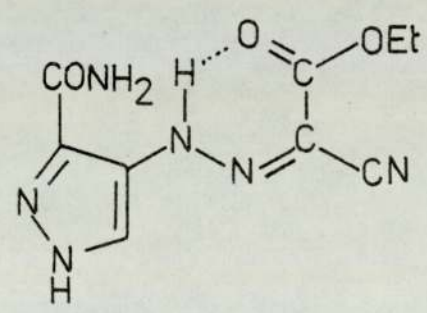
Scheme 5.2



(5.9)



(5.10a)

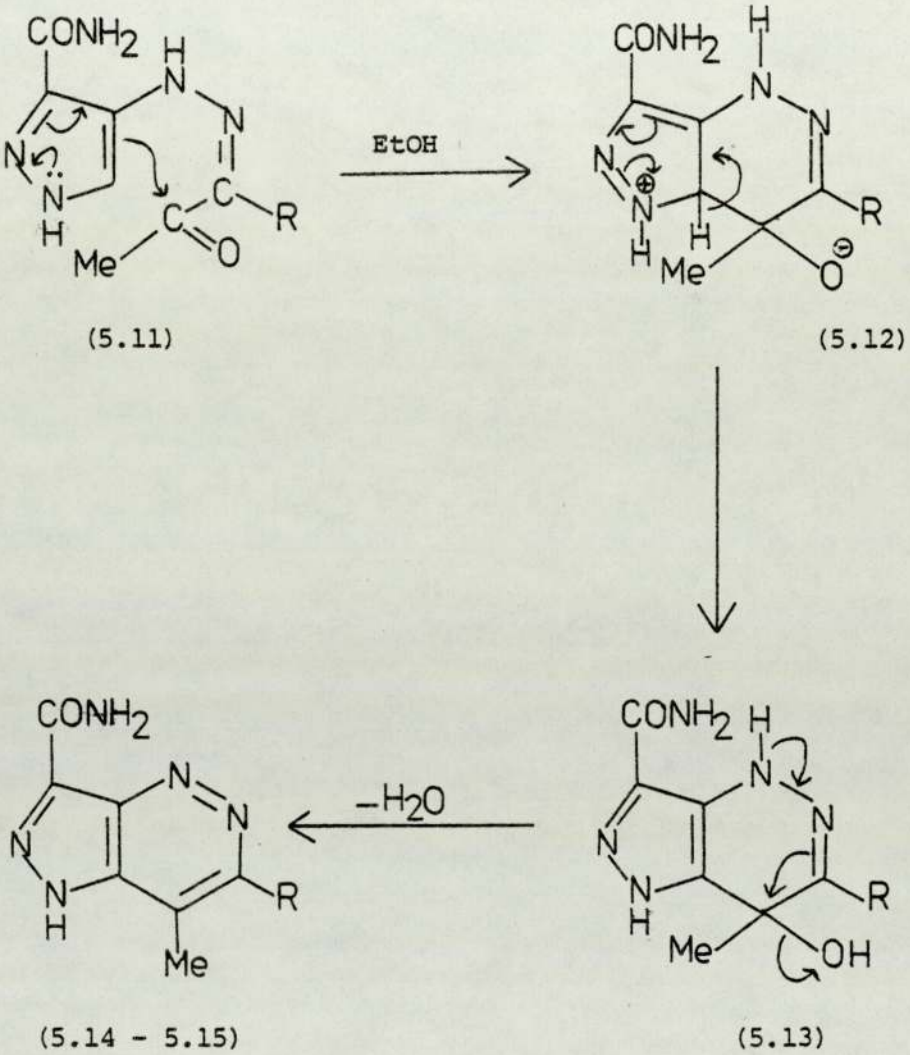


(5.10b)

of the hydrazone (5.8) in DMSO-d_6 showed a one proton singlet at δ8.24 assigned to H-5 of the pyrazole ring and also showed the presence of two quartets centred at δ4.3 and δ3.5 and also contained an overlapping double triplet centred at 1.4. The multiplicities of these absorptions suggest the possible co-presence of two geometrical isomers (5.10a, 5.10b).

5.3 Cyclisation of pyrazolylhydrazones

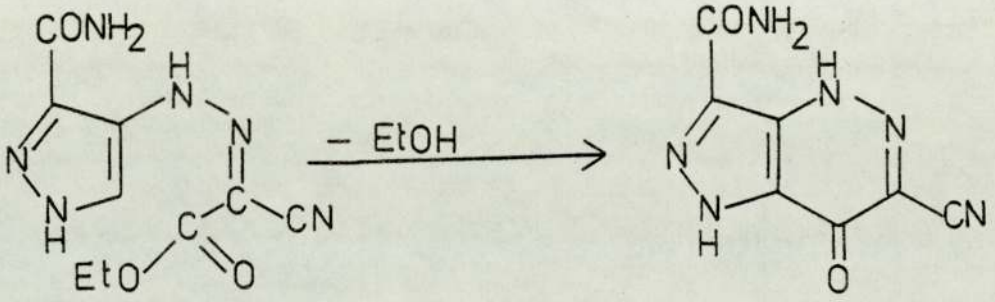
The pyrazolylhydrazones were very unstable in hot ethanol (cf. imidazolyhydrazones page 59). The Acetyl-hydrazones (5.6 - 5.7) were found to be more unstable than hydrazone (5.8) and underwent spontaneous dehydrative cyclisation to yield the corresponding 1H-pyrazolo[4,3-c]pyridazines (5.14 and 5.15). A mechanism for this cyclisation is advanced in scheme (5.3). These formulations (5.14 and 5.15) were derived from a consideration of their spectral and analytical properties. The u.v. spectra of the cyclic products (5.14, 5.15) showed obvious changes compared to the starting materials with absorptions at λ_{max} 313, 245 and 215 nm. Their i.r. spectra were also different and showed absorptions for two carbonyl groups and N-H bands. The ^{1}H.n.m.r. spectra of both compounds (5.14) and (5.15) did not show a resonance for the pyrazole C-H proton observed in the hydrazones; the only CH protons were those of the respective ester groups (see Experimental Section) and 7-methyl protons. As adjudged by their ^{1}H.n.m.r. spectra compounds (5.14) and (5.15) in DMSO-d_6 exist exclusively as 7-methyl tautomers in contrast with the analogous substituted imidazotriazines (see page 74) where the 7-methylenic forms (4.29 - 4.32) are preferred.



(5.11) (5.12) (5.13) (5.14 - 5.15)

Compound	R
5.14	CO_2Et
5.15	CO_2Me

Scheme 5.3



(5.9) (5.16)

Scheme 5.4

The hydrazone (5.9) surprisingly also cyclised thermally on prolonged boiling in ethanol with the involvement of the ester carbonyl group and a creamy crystalline product (5.16) was isolated. Evidently the pyrazole ring carbon is very highly susceptible to electrophilic attack due to its π-excessive character.

The i.r. spectrum of the product showed a sharp absorption at 2238 cm^{-1} (C≡N) and also carbonyl absorptions at 1670 cm^{-1} and 1660 cm^{-1}. The electronic absorption spectra of the product displayed maxima at 360, 282, 224 and 208 nm (cf hydrazone (5.9)). The H.n.m.r. spectrum showed no resonances for pyrazole C-H or N-H. The mass spectrum showed an appropriate molecular ion (M/e 204) and the product analysed as a hydrate.

Chapter 6

Properties of imidazo[5,1-c][1,2,4]triazines

6.1 Physical properties

All imidazotriazines made during the course of this work are yellow solids with melting-points usually greater than 250°C; 7-methylene derivatives have comparatively lower melting points than the 7-amino or 7-oxo analogues which generally melted over 300°C. The triazinones are weak acids and can form salts with alkali: the aminotriazines are very weak bases and do not form salts with acids. These structural types can exist in different tautomeric forms (see page 74 and 87); detailed study on the tautomerism is beyond the scope of this work. The electronic absorption spectra of all these compounds (in 95% ethanol) showed absorptions between 390-360 nm which is in agreement with the u.v. absorptions of many other monocyclic and bicyclic 1,2,4-triazines[111, 113, 128-136] in addition the triazinones and aminotriazines also showed absorption bands between 295-260 nm[128-135, 137, 138]. The first absorption has been attributed to an $\eta \rightarrow \pi^*$ transition whereas the latter band is due to $\pi \rightarrow \pi^*$ transition[134,135].

All imidazotriazines are insoluble in water and only sparingly soluble in ethanol. Purification by recrystallisation proved to be difficult due to their lack of solubility in many conventional organic solvents. Many of these compounds crystallised as hydrates, and some showed a tendency to form solvates with protic solvents such as acetic acid or ethanol.

6.2 Chemical properties

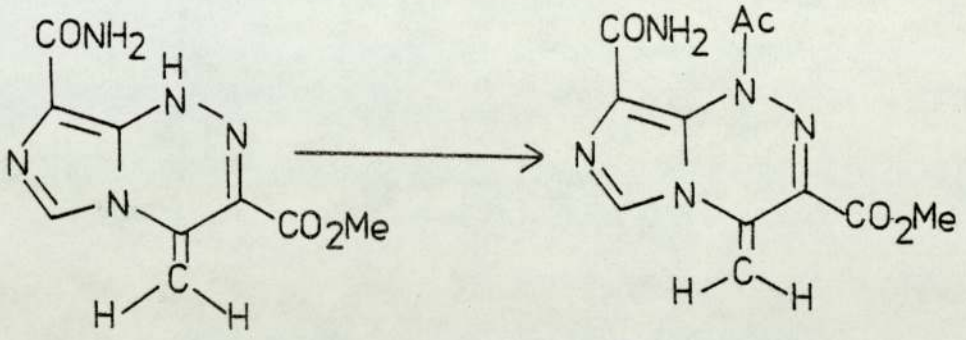
6.2.1 Acetylation

The 7-methyleneimidazotriazine (4.29) was readily acetylated when heated in an acetic anhydride-acetic acid mixture at 95°C. The product analysed as a mono-acetyl derivative. The mass spectrum was consistent with the analysis and showed a peak at M/e 277 for the molecular ion. The compound is tentatively assigned structure (6.1) although a C-acetyl structure cannot be excluded. The spectral properties of this compound are recorded in the Experimental section.

The 7-Aminoimidazotriazine ester (4.45) was also successfully acetylated in boiling acetic anhydride-acetic acid and yielded a mono-acetylated product. The u.v. spectrum of this compound was nearly identical to that of the starting amine (4.45) and is tentatively formulated as the 7-acetylaminoimidazotriazine (6.2). However, the u.v. spectra of all the 7-aminotriazines are strikingly similar to those of the triazin-7(4H)-ones and the possibility that this derivative is the 4-acetyltriazine (6.3) cannot be excluded. The mono-acetyl compound was characterised by spectroscopy (u.v., i.r. and ^{1}H.n.m.r.) and an appropriate peak at M/e 292 for the molecular ion was observed in the mass spectrum.

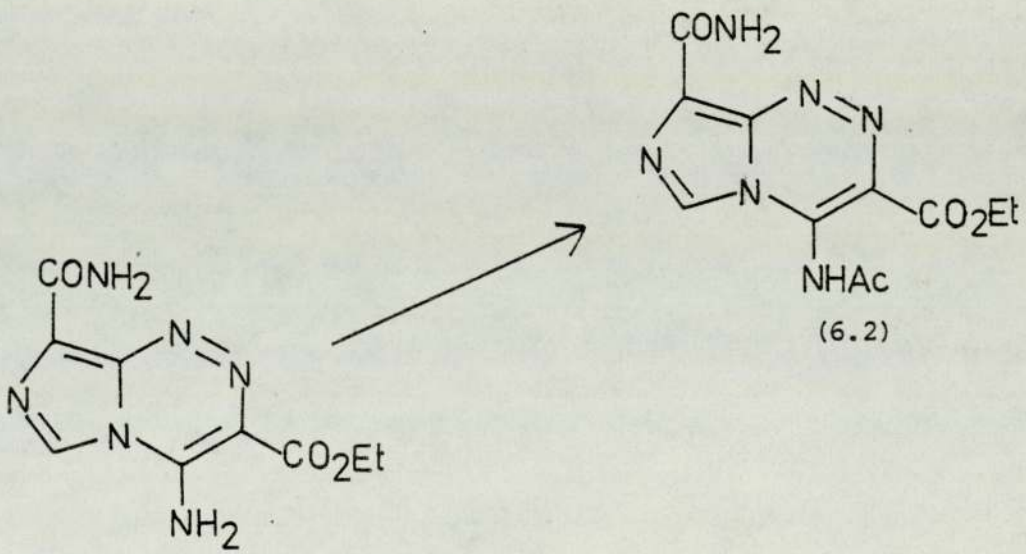
6.2.2 Acid Hydrolysis

The aminoimidazotriazine ester (4.45) when treated with hot 6N-hydrochloric acid gave a yellow solution from which no solid separated even after prolonged cooling. Evaporation of the



(4.29) (6.1)

Scheme 6.1

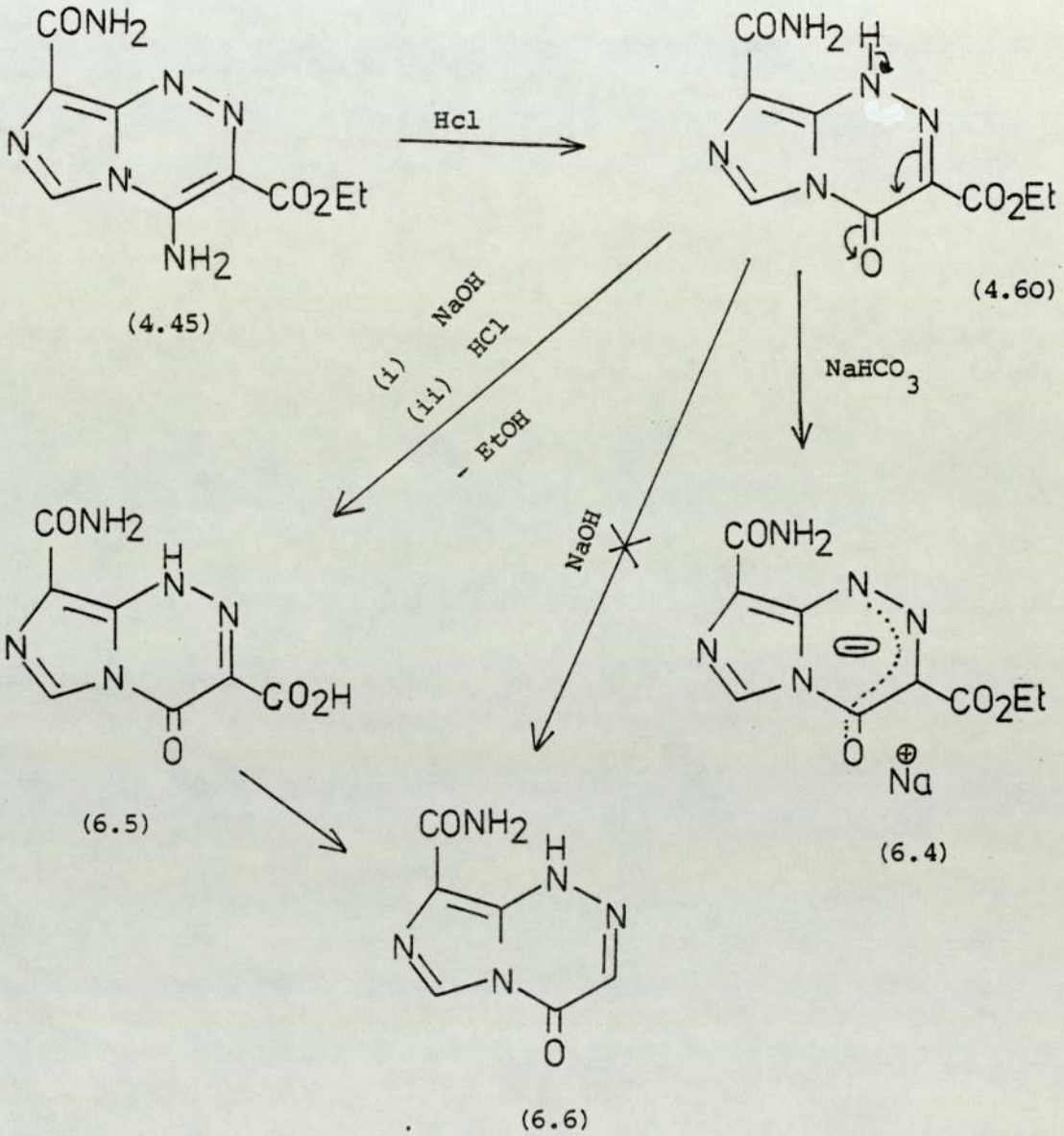


(4.45) (6.2) (6.3)

Scheme 6.2

hydrochloric acid under reduced pressure yielded an impure gum. T.l.c. analysis of this product revealed the presence of four poorly separated components. However, the amino ester (4.45) was selectively hydrolysed with hot 2N-hydrochloric acid and furnished a feathery cream-coloured crystalline product which was assigned structure (4.60). (Scheme 6.3). The structure assignment was corroborated by the spectral evidence. The u.v. absorption band of this product acquired the general shape of related triazinones (Fig. 6.1) (Table 4.3)(see page 106). The i.r. spectrum (Fig. 6.2) showed absorptions for ester carbonyl at 1713 cm^{-1} and also the triazinone carbonyl at 1663 cm^{-1}; this latter absorption is a common feature of the various substituted triazinones (see Experimental section). The ^{1}H.n.m.r. spectrum of this product in DMSO-d_6 showed the presence of characteristic resonances of an ethyl group. The presence of a peak at M/e 251 for the molecular ion further confirmed the assigned structure (4.60)which analysed as a monohydrate. The hydrolysed product was also identical to the triazinone obtained from the alkaline cyclisation of hydrazone (4.12) (see page 103).

The oxo-ester (4.60) like all triazinones of this series was strongly acidic, and dissolved in sodium bicarbonate (without effervescence); a sodium salt (6.4) separated from the clear solution. This salt (6.4) also analysed as a monohydrate. The extensively delocalised ionic charge on the nucleus of (6.4) elicited a considerable change in the electronic absorption properties of the anion when compared to the free acid. For


CONH2
N
N
N
N
CO2Et
NH2
(4.45)
Hcl
CONH2
H
N
N
N
N
CO2Et
O
(4.60)
(i) NaOH
(ii) HCl
- EtOH
NaHCO3
NaOH
CONH2
H
N
N
N
N
CO2H
O
(6.5)
CONH2
N
N
N
N
CO2Et
O
⊕
Na
(6.4)
CONH2
H
N
N
N
N
O
(6.6)

Scheme 6.3

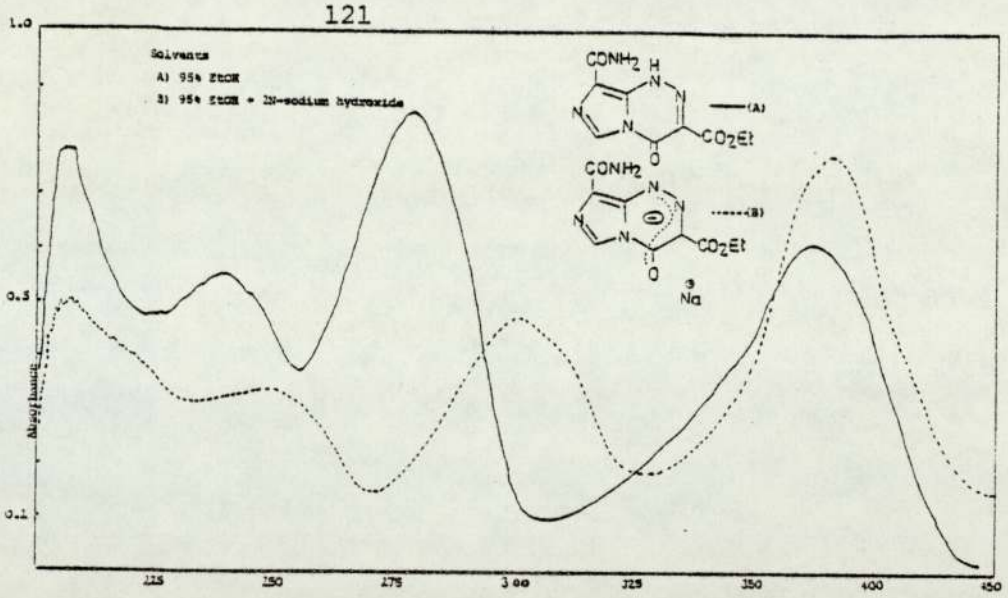


Figure (6.1)

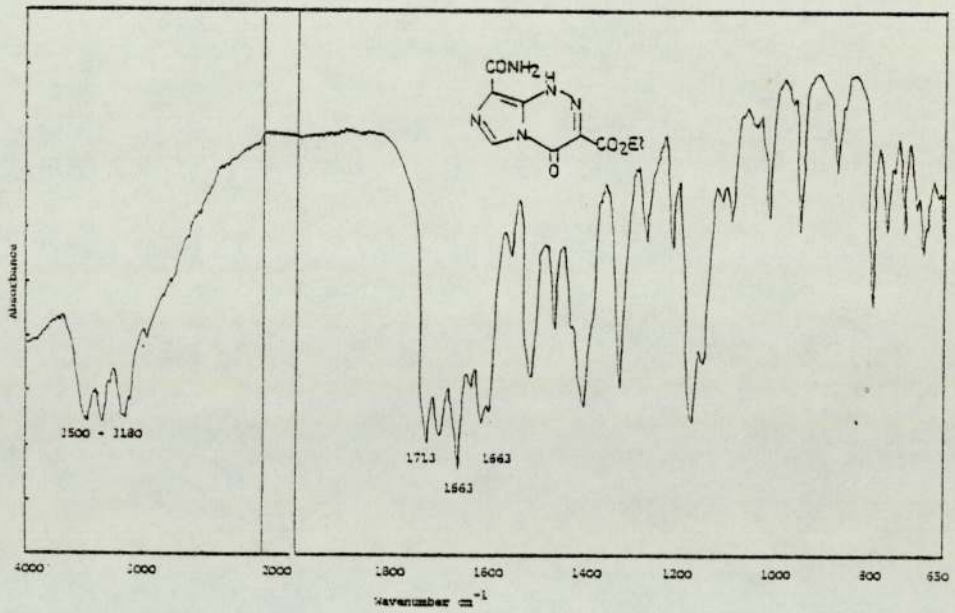


Figure (6.2)

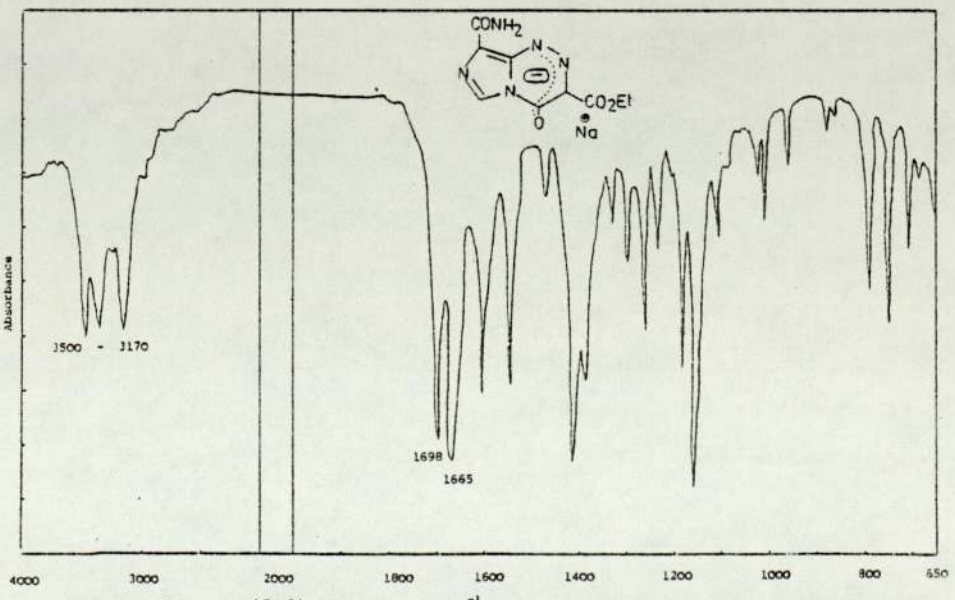
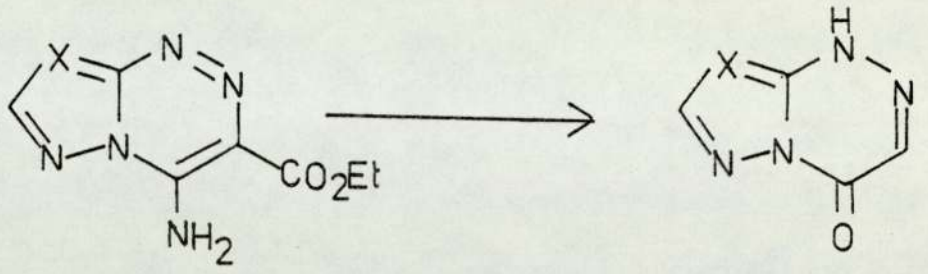


Figure (6.3)

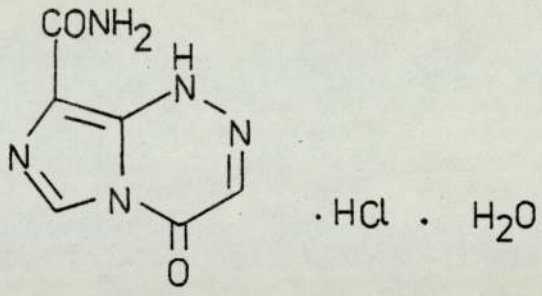
example the u.v. absorption peak at λ_{max} 279 nm. for the free acid (4.60) was shifted to λ_{max} 300 nm and the peak at 372 nm to 382 nm in the sodium salt (Fig. 6.1). The carbonyl band (ester) at γ1713 cm^{-1} of the triazinone (4.60) was observed at lower frequency (1698 cm^{-1}) in the i.r. spectrum of the salt (Fig. 6.3). The u.v. and i.r. spectra of the compound (4.60) and its salt (6.4) conclusively indicated that these transformations were reversible- addition of acid liberated the free triazinone (4.60) while treatment with alkali regenerated the salt (6.4).

The oxo-ester (4.60) was hydrolysed smoothly when treated with sodium hydroxide at room temperature to form the sodium salt of the imidazotriazine carboxylic acid (6.5). Contrary to expectations the salt when acidified with 2N-hydrochloric acid yielded a stable cyclic β-ketoacid (6.5) and not the expected imidazotriazinone (6.6). It is worth noting that in an analogous hydrolysis the pyrazolo-[1,2,4]triazine amino-ester (6.7; X=CH) and triazolo[1,2,4]-triazine amino-ester (6.7; X=N) underwent spontaneous decarboxylation to yield the corresponding triazinones (6.8; X=CH)[116] and (6.8; X=N)[111] respectively. In contrast acid (6.5) was found to be reasonably stable in acids at room temperatures and also in hot ethanol, although it underwent thermal decarboxylation at elevated temperature. This was indicated by a peak at M/e 179 ($M\pm CO_2$) when the mass spectrum was recorded with an inlet temperature of 300°C. No trace of the peak at M/e 222 was observed. Acid (6.7) analysed as a monohydrate.

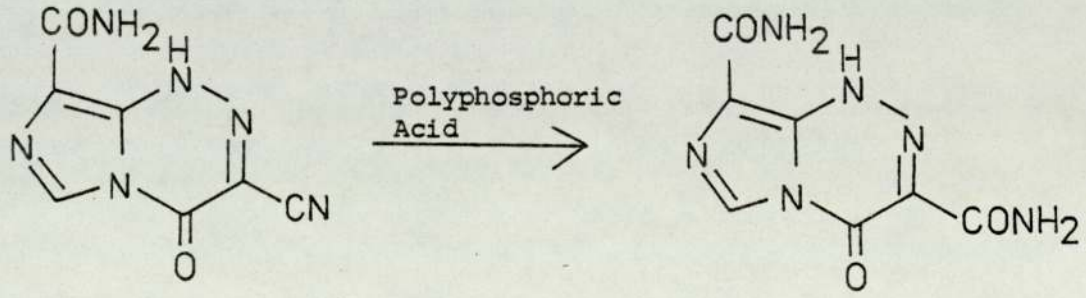


(6.7) (6.8)

X = CH,N



(6.9)



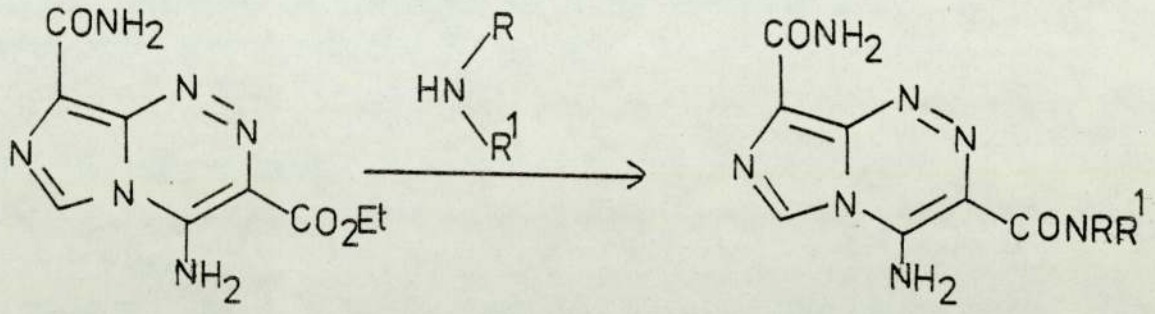
(4.61) (6.10)

When the acid (6.5) was heated in 5N-hydrochloric acid a yellow solid was obtained from the reaction mixture. The mass spectrum of this product again showed a peak at M/e 179 consistent with the formulation $C_6H_5N_5O_2$ and the elemental analysis tentatively suggested that this new product was possibly the imidazotriazinone monohydrochloride hydrate (6.9).

The oxo-nitrile (4.61) hydrolysed in hot polyphosphoric acid to yield the amide (6.10). The i.r. spectrum of the product showed no absorption for a cyano group, and its u.v. spectrum was nearly identical to those of related triazinones. (See table 4.3, Page 106). The structure assignment was confirmed by mass spectrometry and microanalysis.

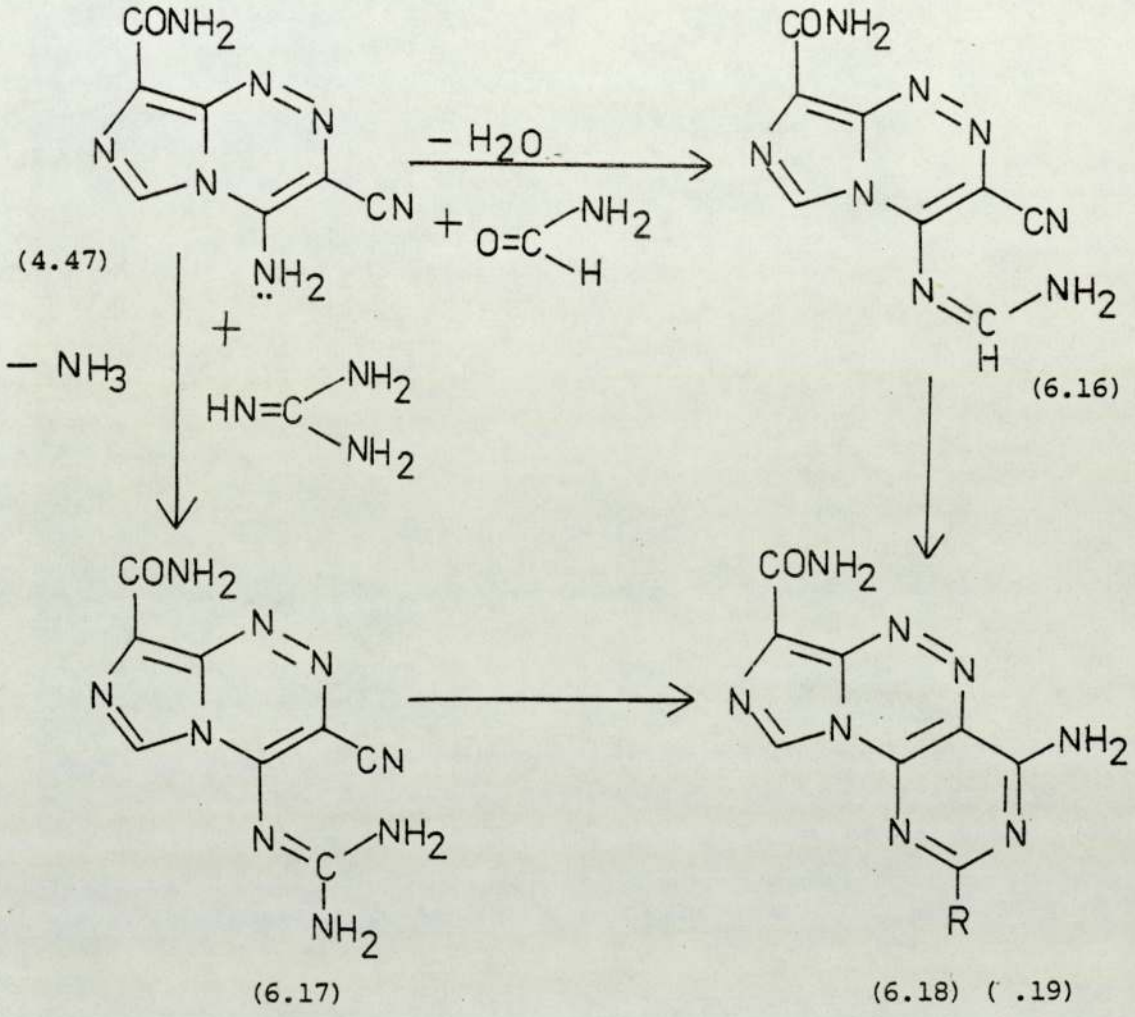
6.2.3 Reactions with amino nucleophiles

Although the amino ester (4.45) failed to ammonolyse in saturated ethanolic ammonia to yield the corresponding amide (6.11), it reacted readily with hot secondary amines such as piperidine, pyrrolidine, morpholine, and N-methylpiperazine to furnish compounds (6.12-6.15). The reaction of (4.45) with hot 2,6-dimethylpiperidine was unsuccessful and the amino ester (4.45) was recovered unchanged. All amides (6.12-6.15) (scheme 6.3) showed nearly identical u.v. spectra and retained the typical absorption bands of amino ester (4.45) attributable to the N=N Chromophore[122]. The addition of 2N-hydrochloric acid to the amino ester (4.45) produced very little hypsochromic shift whereas this effect on protonation was quite pronounced in the amides (Table 6.1).



(4.45) (6.14 - 6.17)

	R	R^1
(6.11)	H	H
(6.12)	$-(CH_2)_5-$	
(6.13)	$-(CH_2)_4-$	
(6.14)	$-(CH_2)_2O(CH_2)_2-$	
(6.15)	$-(CH_2)NMe(CH_2)_2-$	


CONH2
N
N
N
N
CN
NH2
(4.47)
− H2O
+ O=C
NH2
H
(6.16)
− NH3
+
HN=C
NH2
NH2
(6.17)
(6.18) (6.19)
R
6.18; R = H
6.19; R = NH2

Scheme 6.4

The peaks at 310-312 nm underwent a hypsochromic shift upon addition of acid and observed at 278-281 nm whereas the peaks at higher wavelength remain unaltered. The main absorptions in the i.r. spectra of the amides were also similar and they all showed carbonyl absorptions between 3050-3400 for C-H and N-H groups.

6.2.4 Reactions of aminonitriles with formamide and guanidine

An old but still widely employed method for accomplishing the overall conversion of o-aminonitrile to a fused aminopyrimidine is achieved by heating the former compound with formamide or guanidine[139].

The aminonitrile (4.47) failed to react with formamide when heated on a water-bath. However, the aminonitrile reacted in boiling formamide to yield the fused tricyclic aminopyrimidine (6.18) via an intermediate formamidine (6.16). The product was most efficiently purified by vacuum sublimation.

Analogously, interaction of guanidine and aminonitrile[140] (4.47) yielded the diaminopyrimidoimidazotriazine (6.19). This procedure for the synthesis of hetero-fused diaminopyrimidines has considerable applications because of the many biological properties of such systems, (e.g. diuretic[141,142] and antileukaemic[143,144] activities). Some difficulty was encountered in attempting to optimise the conditions for reaction. The aminonitrile (4.47) was eventually reacted at elevated temperature with excess of free guanidine base to yield the tricyclic diaminopyrimidine (6.19) (Scheme 6.4) in 50% yield.

The reactions of imidazotriazines with hydrazine derivatives are described in the following chapter.

Table 6.1

Electronic absorption spectra of 7-aminoimidazo[5,1-c][1,2,4]-triazine-6-carboxamides

Compound	Solvent	λ_{max}(nm)
6.12	A	383, 310,
	B	380, 277
6.13	A	384, 312
	B	380, 278
6.14	A	383, 311,
	B	381, 281,
6.15	A	382, 310
	B	380, 274

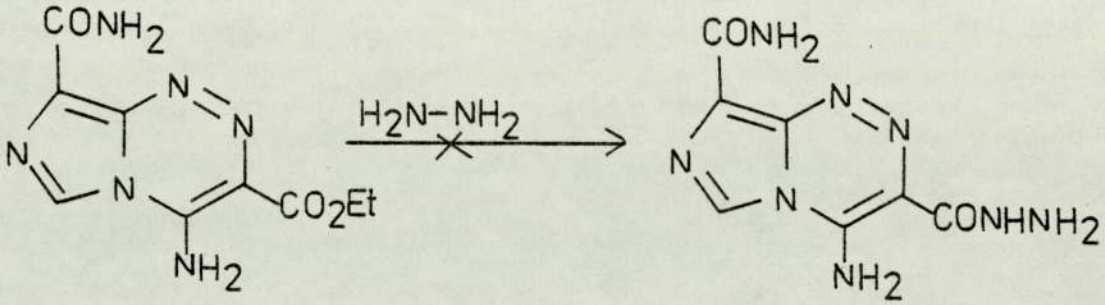
A = 95% EtOH

B = 95% EtOH+2N-Hcl.

Chapter 7

7.1 Reactions of hydrazine derivatives with imidazo[5,1-c][1,2,4]-triazines.

The reactions of hydrazine derivatives with various heterocycles leading to ring-fission and recyclisation have been reported in the literature on various occasions[45,70-77,113,145]. Reaction



(4.45) (7.1)

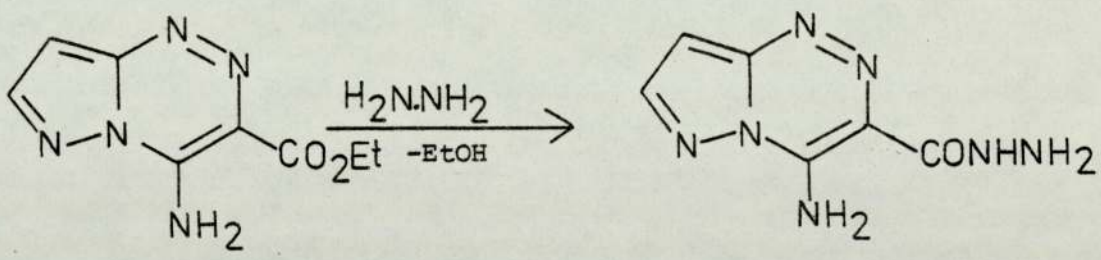
of the aminoimidazotriazine ester (4.45) with hydrazine hydrate in an apparently straightforward attempt to obtain the corresponding hydrazide (7.1) led to the isolation of an orange product. Spectroscopic examination of the orange compound suggested that it was not the expected hydrazide (7.1). The u.v. spectrum of this compound lost all characteristic absorptions of the precursor amino-ester (4.45) and showed a main absorption at 425 nm; the shape of the spectrum suggested that it was no longer a bicyclic triazine and it was assigned the structure (7.6) on the basis of analogous reactions in the pyrazolotriazine series[145]. The i.r. spectrum was consistent with the assigned structure and showed a strong carbonyl absorption at 1665 cm^{-1} which is in close agreement with the values (1665-1685 cm^{-1}) observed in 4-arylazo-3-methylpyrazolin-5-ones[146]

and pyrazol-3-ylazopyrazolones[145] for the endocyclic carbonyl group. The i.r. spectrum also indicated that bonded NH/OH groups were present.

Two possible mechanistic routes could be envisaged for this reaction.

Route a

Ethyl-7-aminopyrazolo[5,1-c][1,2,4]triazine-6-carboxylate (7.2) yielded an isolable pyrazolotriazine carbohydrazide (7.3) by the interaction with hydrazine hydrate. In contrast apparently the



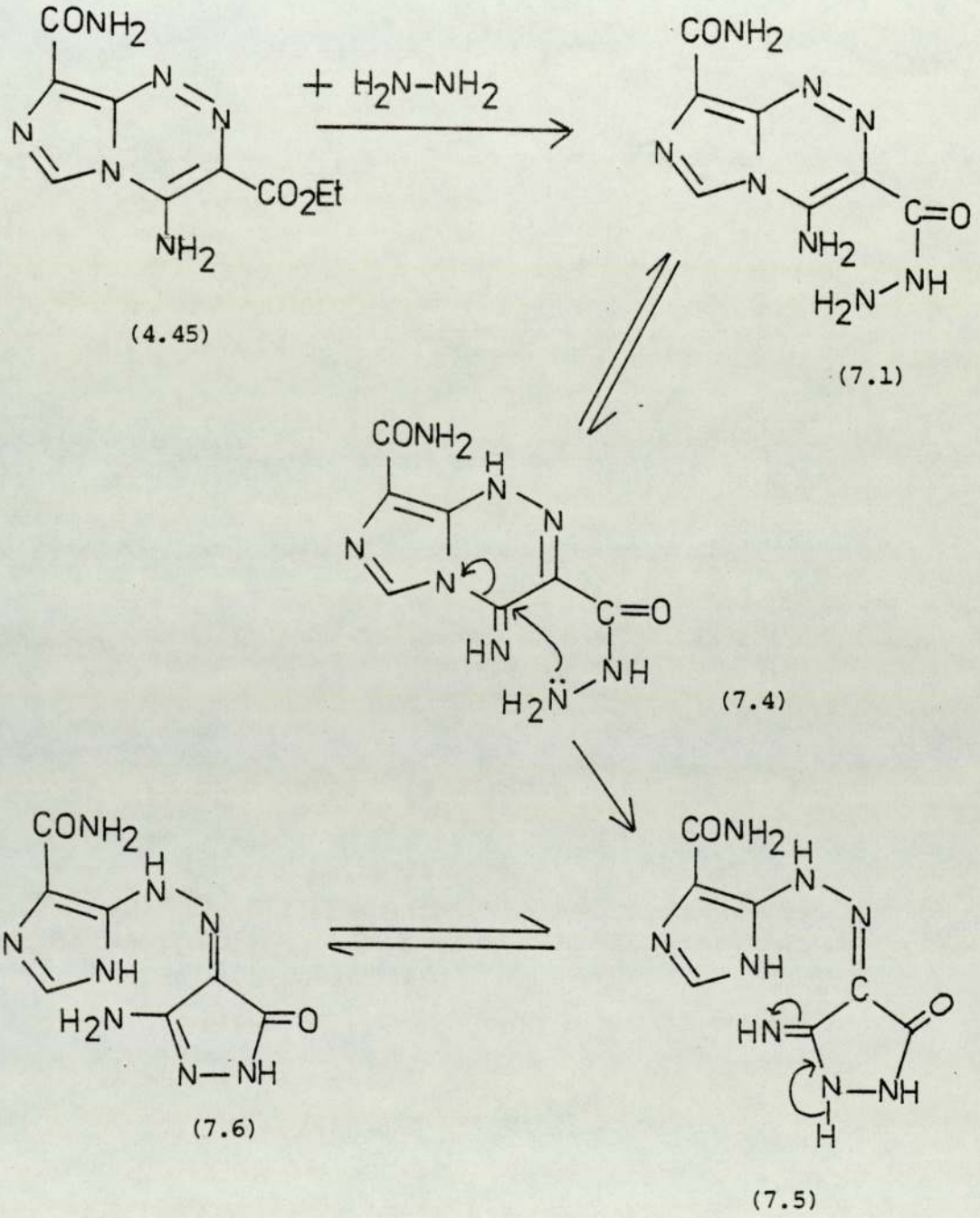
(7.2) (7.3)

reaction of hydrazine hydrate in the case of aminoimidazotriazine ester (4.45) did not stop at the carbohydrazide stage (7.1). It could be envisaged that the carbohydrazido group underwent further reaction involving intramolecular nucleophilic attack at the electrophilic C-7 position (Scheme 7.1).

Route b

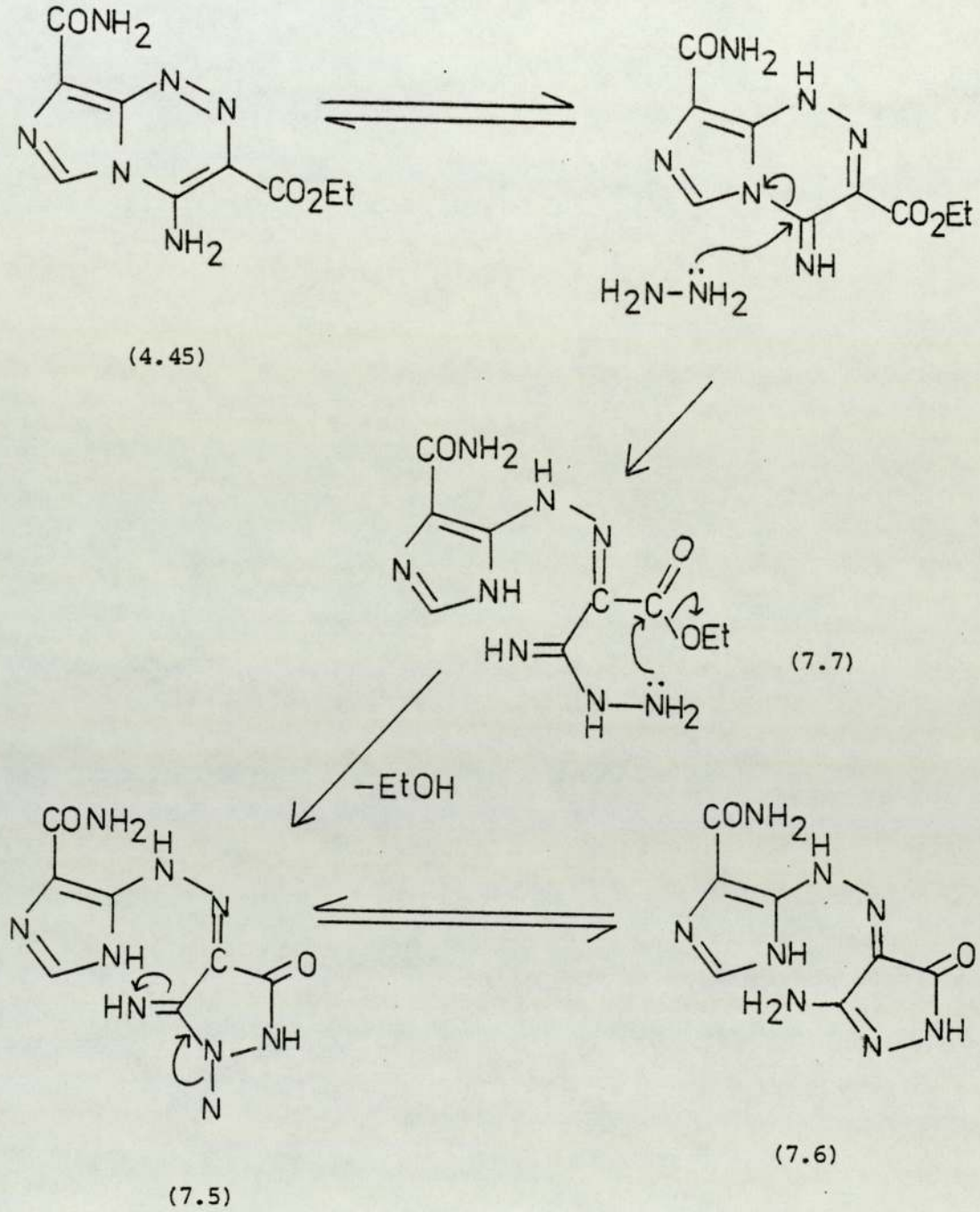
This alternative mechanism implies that the reaction may follow a different course and it appeared possible that the hydrazine did not react initially with the ester carbonyl but at C-7 of the triazine ring. The ring-opened amidrazone then

Route a



Scheme 7.1

Route b



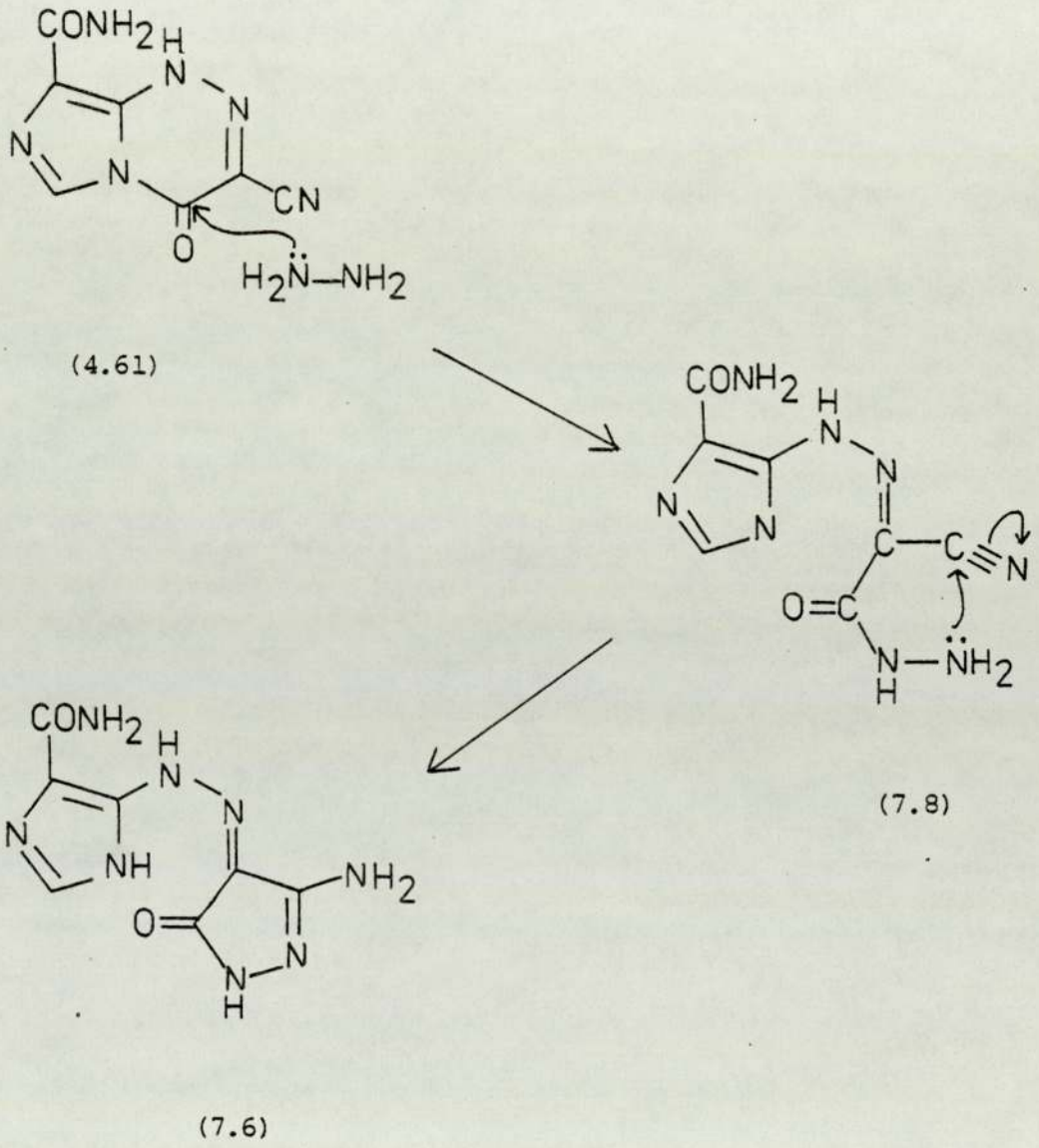
(4.45)

(7.7)

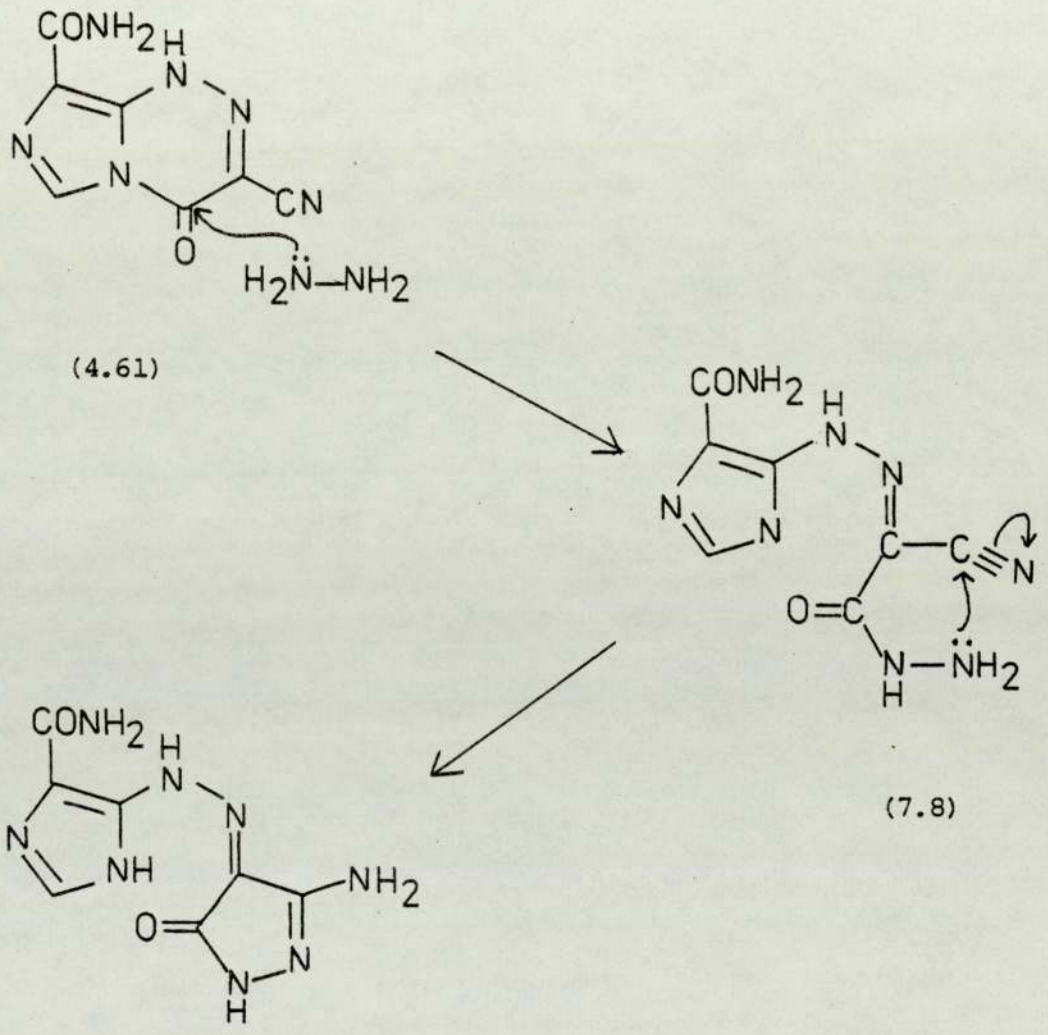
(7.5)

(7.6)

Scheme 7.2


CONH2
H
N
N
N
N
CN
O
H2N—NH2
(4.61)
CONH2
H
N
N
N
C
C
N
O=C
N—NH2
H
(7.8)
CONH2
H
N
N
N
NH
NH2
O
N
N
H
(7.6)

Scheme 7.3


CONH2
H
N
N
N
N
CN
O
H2N—NH2
(4.61)
CONH2
H
N
N
N
N
C
C
N
O=C
N
H
NH2
(7.8)
CONH2
H
N
N
N
NH
NH2
O
N
N
H
(7.6)

Scheme 7.3

re-cyclised with the elimination of ethanol to yield the orange product (7.6) (Scheme 7.2).

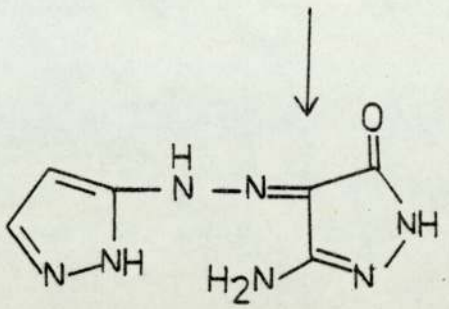
Analogously the interaction of hydrazine hydrate and the imidazotriazinone (4.61) yielded the same imidazoazopyrazolone (7.6) as outlined in (Scheme 7.3) via an intermediate carbohydrazide (7.8).

The reaction of hydrazine hydrate with pyrazolotriazine ester (7.2) was re-examined[145] in the light of present findings; but every time the corresponding carbohydrazide (7.3) was isolated. When the reaction was conducted under forcing conditions by heating in a slight excess of hydrazine hydrate the compound degraded and very small amount of an orange solid deposited on the side of glass vessel. The u.v. spectrum of the product (Table 7.1) suggested that it might have undergone the same type of reaction as shown by schemes (7.1 and 7.2) to yield the pyrazol-3-ylazopyrazolones (7.9)(Scheme 7.4). The i.r. spectrum of this compound (7.9) showed absorption bands at 3450-3150 cm^{-1} (N-H) and 1665 cm^{-1} (C=O).

The amino-ester (4.45) and triazinone (4.61) did not react with phenylhydrazine and only the starting materials were recovered unchanged.

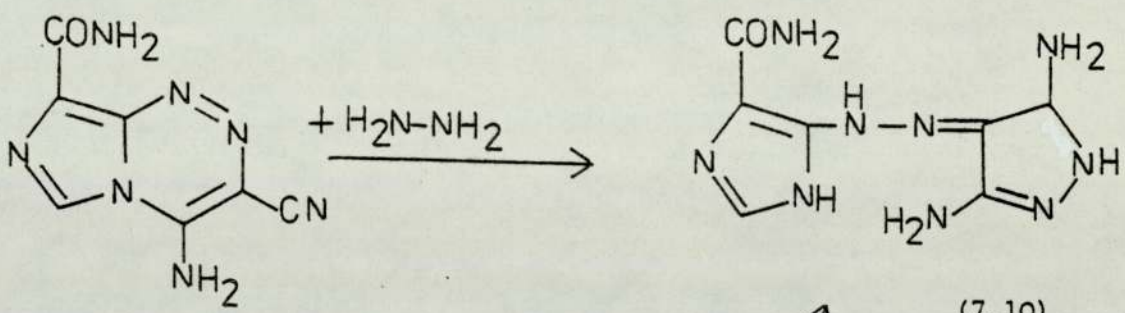
The cyano-aminotriazine (4.47) reacted very smoothly with hydrazine hydrate to yield the imidazo-5-ylazodiaminopyrazole (7.10) (Scheme 7.5). An alternative route to obtain the same compound (7.10) from the coupling of diazoimidazole carboxamide

(7.2) $\xrightarrow{H_2N\ NH_2}$ (7.3)

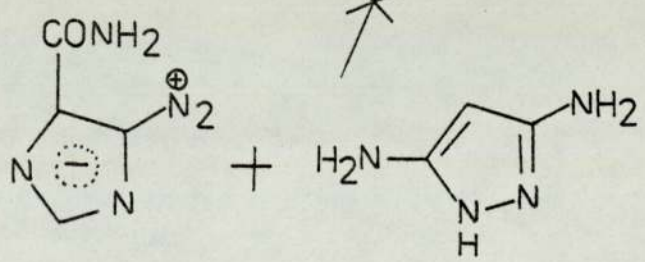


(7.9)

Scheme (7.4)



(4.47) (7.10)



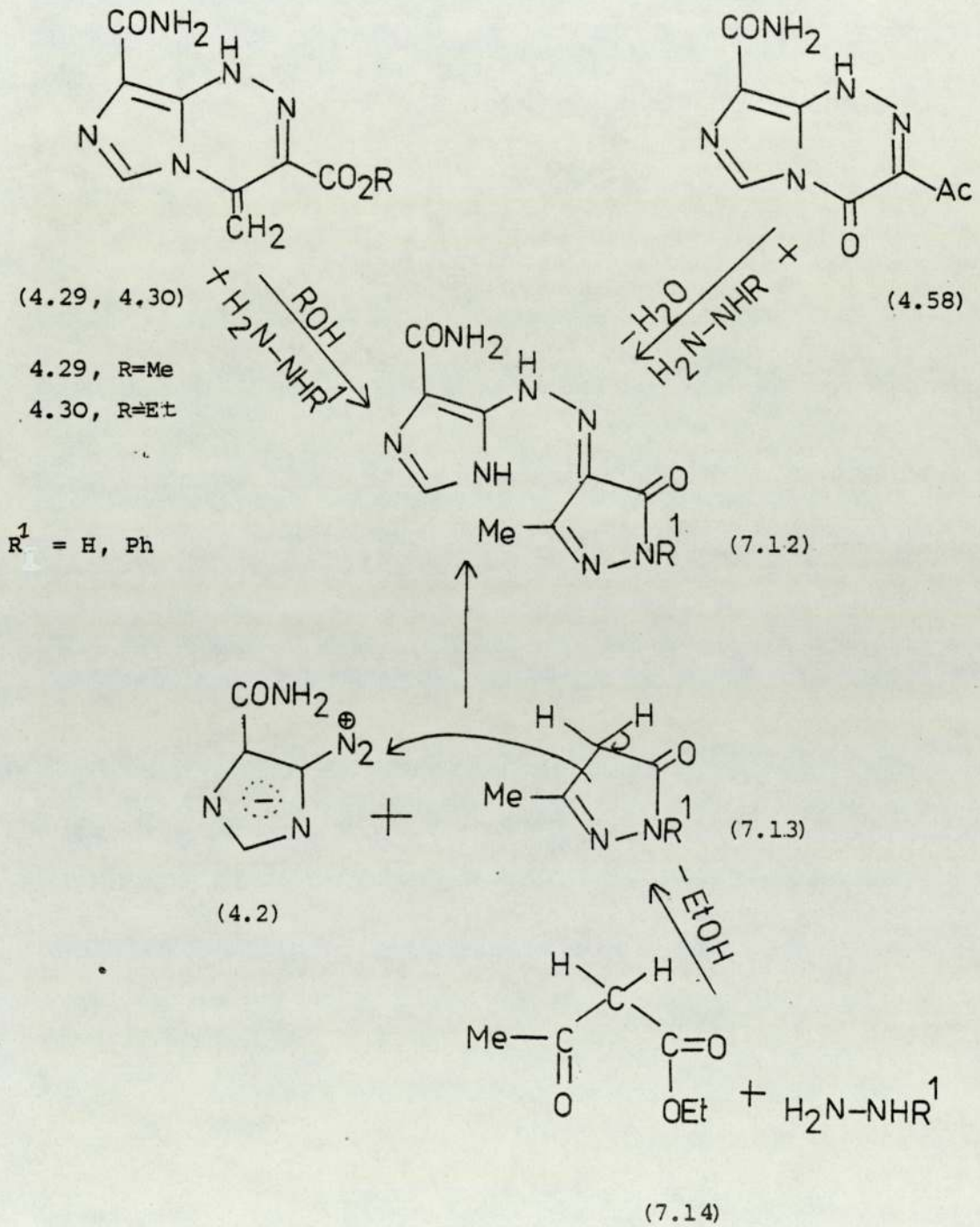
(4.2) (7.11)

Scheme 7.5

(4.2) with 3,5-diaminopyrazole (7.11) proved unsuccessful. The compound (7.10) was characterised by spectroscopy (i.r. and u.v.) and its constitution confirmed by mass spectrometry (M^+ 235) and analytical data.

Analogous products were obtained by the ring fission of other imidazotriazines having an ester or keto substituent at position C-6. Thus imidazotriazine ester (4.29 or 4.30) or 6-acetyltriazinone reacted with hydrazine hydrate to yield the same imidazol-5-ylazomethylpyrazolone (7.12 R^1=H). Similarly interaction of the compounds (4.29 or 4.30) or (4.58) with phenylhydrazine furnished the imidazol-5-ylazomethyl-N-phenylpyrazolone (7.12; R^1=Ph). Both compounds are highly coloured; compound (7.12; R^1=H) is deep orange and showed an absorption at λ_{max} 408 nm and compound (7.12; R^1=Ph) is deep red λ_{max} 425 nm). The i.r. spectrum of compound (7.12; R^1=H) showed a absorptions at 3300 cm^{-1} (N-H) and at 1678 cm^{-1} (N-H) and at 1678 cm^{-1} (C=O). The ^{1}H.n.m.r. spectrum (TFA) was consistent with the formulation (7.12; R^1=H) and showed resonances for methyl proton (δ2.72) and the imidazole H-2 proton (δ8.98). The N-phenyl analogue (7.12; R^1=Ph) showed a carbonyl absorption band at 1650 cm^{-1} and N-H/oH absorptions at 3100, 3400 cm^{-1}. The ^{1}H.n.m.r. spectrum (TFA) of this compound was also in accord with the structure assignment and showed resonance as singlets at δ2.58, δ7.58 and δ8.92 for methyl, phenyl and imidazole protons respectively.

Further support for the assigned structures (7.12; R^1=H and

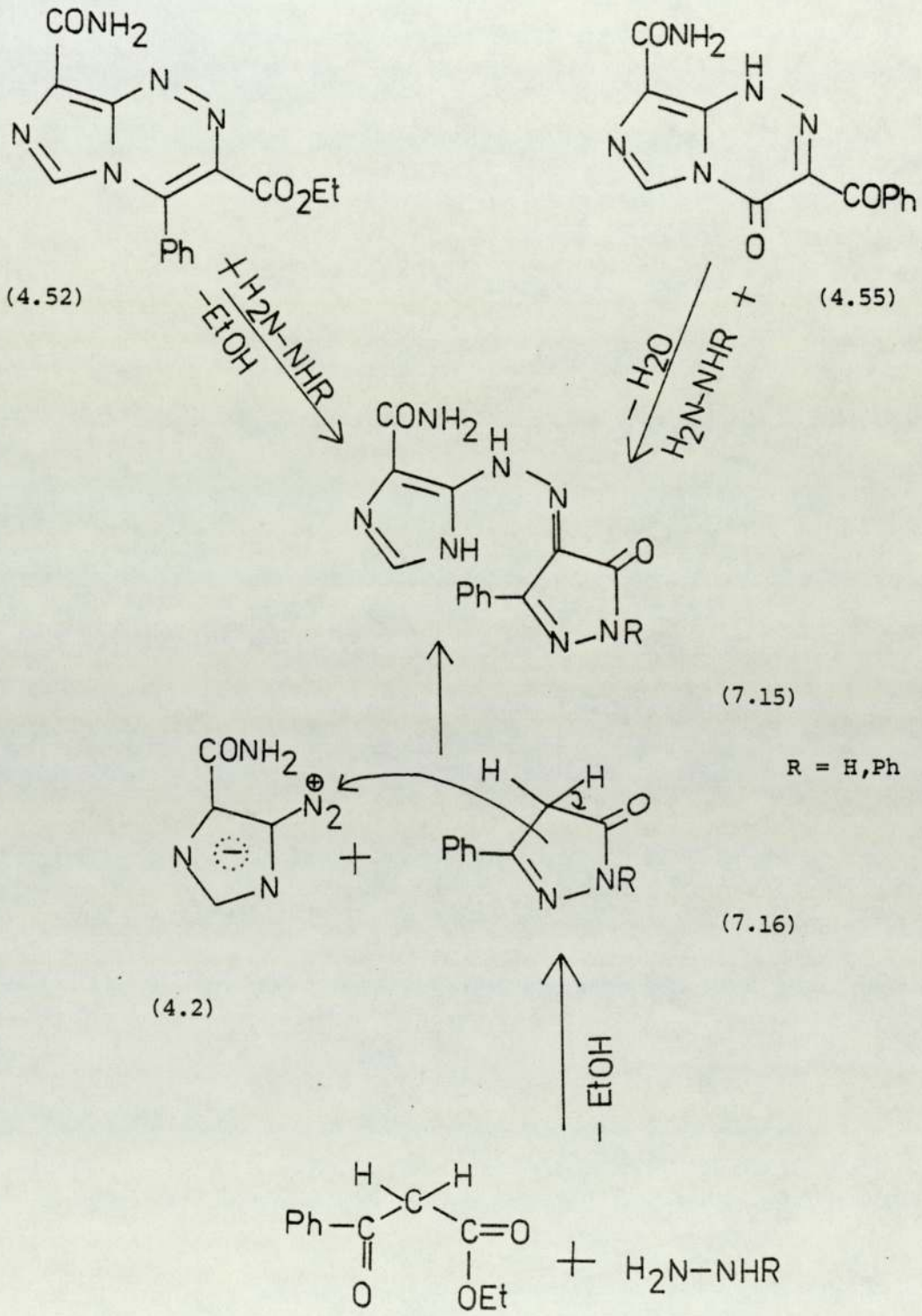

CONH2
CO2R
CH2
(4.29, 4.30)
4.29, R=Me
4.30, R=Et
+H2N-NHR1
ROH
CONH2
Ac
O
(4.58)
-H2O
H2N-NHR +
CONH2
NH
Me
O
NR1
(7.12)
R1 = H, Ph
CONH2
N2
(4.2)
+
H
H
O
Me
NR1
(7.13)
- EtOH
H
H
C
Me
C
C=O
O
OEt
+ H2N-NHR1
(7.14)

Scheme 7.6

R^1=Ph) was provided from their identity with the products obtained by the coupling reactions of diazoimidazocarboxamide (4.2) with methyl-pyrazolone (7.13; R^1=H) and methyl-N-phenylpyrazolone (7.13; R^1=Ph). The compounds (7.13; R^1=H or Ph) were themselves synthesised from the reaction of ethylacetoacetate with the corresponding hydrazine derivatives (Scheme 7.6).

The 3-phenyl (7.15; R=H) and 1,3-diphenylazopyrazolones (7.15; R=Ph) were prepared in the same fashion as described previously by heating the ethyl 7-phenylimidazotriazine-6-carboxylate (4.52) or the 6-benzoyltriazinone (4.55) with hydrazine derivatives (scheme 7.7). The same two compounds (7.15; R=H or Ph) were alternatively prepared from the coupling reaction between diazoimidazocarboxamide (4.2) and the substituted phenylpyrazolones (7.16; R=H or Ph). The latter two compounds were synthesised by the interaction of ethylbenzoylacetate (7.17) with hydrazine derivatives (Scheme 7.7).

These two compounds (7.15; R=H or Ph) were very similar in their physical appearance to the compounds (7.12; R^1=H or Ph). Compound (7.15; R=H) was obtained as a deep orange solid and its N-phenyl isomer obtained as a deep red powder. The close similarity in the u.v. spectra (Table 7.1) with other imidazolyl-azopyrazolones conclusively categorises these compounds as being in the same class. The i.r. spectra of the compounds (7.15; R=H or Ph) also showed an absorption band at 1600 cm^{-1} (C=O) and also absorptions between 3100-3450 cm^{-1} for multiple N-H groups. The ^{1}H.n.m.r. and mass spectra and analytical data



Scheme 7.7

were in accord with the assigned structures.

Table 7.1

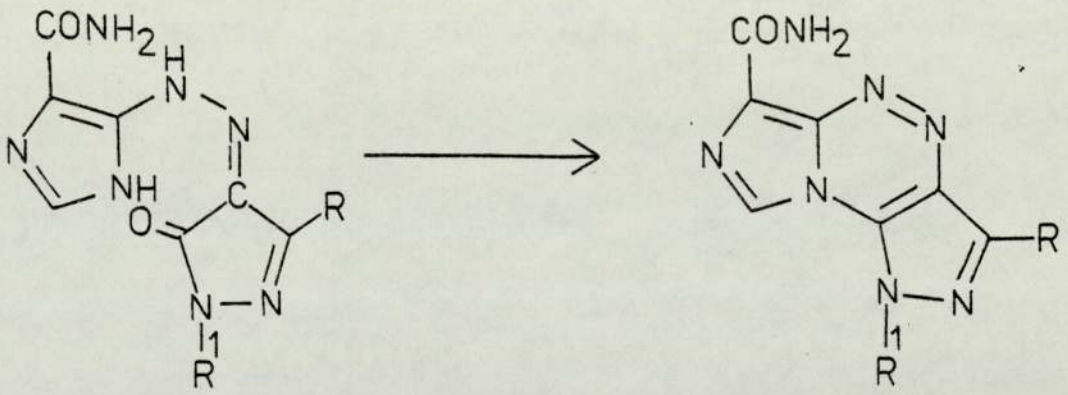
Electronic absorption spectra of azoloazoazoles

Compound	R	λ_{max} (nm, solvent 95% EtOH
7.6		425, 257*
7.9		386, 275*, 247*, 227
7.10		417, 265*, 257
7.12	H	427, 247*
7.12	Ph	405, 247*
7.15	H	415, 275*, 237
7.15	Ph	425, 275*, 247, 227

* inflection

7.2 Attempted cyclisations of imidazolylazo pyrazolones

Attempts to effect the cyclodehydration of imidazolyazo pyrazolones (7.18; R=Me, Ph; R^1=H, Ph) to obtain pyrazoloimidazotriazines (7.19; R=Me, Ph; R^1=H, Ph) by heating the compounds in glacial acetic acid were unsuccessful. Treatment with hot 2N-hydrochloric acid which has proven successful on other occasions[145] failed to effect cyclisation of these compounds and the products were recovered unchanged.



(7.18) (7.19)

R = Me, Ph

R^1=H, Ph

Scheme 7.8

PART III EXPERIMENTAL

Part III

Experimental

1. I.r. spectra were recorded as potassium bromide discs on a Unicam SP 200 spectrophotometer.

2. U.v. spectra were recorded on a Unicam SP 8000 spectrophotometer (in 95% EtOH; asterisk indicates inflection).

3. ^{1}H.n.m.r. spectra were recorded on a Varian A60-A spectrometer, with tetramethyl silane as internal standard. All the peaks are assigned in terms of δ values. Abbreviations used in the interpretation of the n.m.r. spectra are: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; J = coupling contstant (Hz).

4. Mass spectra were measured at 70 eV on a V.G. Micromass 12B single focusing spectrometer with a source temperature in the range 300°C; M^{+} signifies the molecular ion peak observed.

5. Melting points are uncorrected.

Chapter 8

Experimental

5-Diazoimidazole-4-carboxamide (4.2)

A solution of 5-aminoimidazole-4-carboxamide (10.g) in 1N. hydrochloric acid (80 ml) was added dropwise to a solution of sodium nitrite (4.7g) in water (120 ml) at 0°C. A crystalline precipitate began to form after a small portion of the amino-imidazole solution has been added; after about 90% of the amino-imidazole solution has been added the reaction mixture began to assume a pink colour. The addition was discontinued and the solid (85%) was removed by filtration, washed three times with 20 ml portions of water, dried in vacuo over Phosphorous pentoxide m.p. 207-210°C (decomposed explosively) (Lit.[91] 210°C); γmax, 3450, 3350 (N-H), 2210 cm^{-1} (C≡N).

Methyl 2-(4-carbomylimidazol-5-ylhydrazono)acetoacetate (4.6)

5-Diazoimidazole-4-carboxamide (1.37g) in absolute ethanol (25 ml) was stirred with methylacetoacete (1.5g) in the dark at room temperature for 2 days. The pink solid was collected by filtration and washed with ethanol; yield (2.1g), m.p. 230-235°C (Found: C,42.3; H,4.4; M^+, 253.081097. $C_9H_{11}N_5O_4$ requires C, 42.6; H, 4.3%; M,253.08093); λ_{max}. 342, 250* 205 nm; γmax 3500 (N-H) 3300, 3250 (bonded N-H) 1718 (CO_2Me) 1620-1625 cm^{-1} (C=O, Keto/amide); δ (DMSO-d_6) 2.16(3H,s,CH_3-CO), 3.80 (3H,s,-CH_3-CO_2), 7.16(2H,NH_2), 7.9(1H,s,imidazo H-2).

The above method was used to prepare the following hydrazones from 5-diazoimidazole-4-carboxamide and reactive methylenic compounds (1.5 mol. equiv.) in ethanol.

Ethyl 2-(4-carbamoylimidazol-5-ylhydrazono)acetoacetate (4.7) Obtained as a pink solid (88%) after stirring for 3 days, m.p. 145-146°C (from ethanol) (Lit.[89], m.p. 145°C). λ_{max} 342, 250*, 206 nm; γ_{max} 3480 (N-H) 3300, 3150 cm^{-1} (bonded N-H), 1705 (CO_2Et), 1625 cm^{-1} (C=O).

3-(4-Carbomylimidazol-5-ylhydrazone)pentan-2-4-dione (4.8) pink solid obtained after 3 days (80%), m.p. 193-196°C (Lit[89] 196°C) λ_{max}. 346, 255*, 204 nm; γ_{max}. 3400 (free N-H), 3320, 3190 (bonded N-H), 1688, 1650 cm^{-1} (C=O).

A suspension of hydrazone (4.8) (0.5g) in ethanol (10 ml) formed a deep yellow solution when 1% ethanolic potassium hydroxide (3 ml) was added. The precipitated potassium salt of (4.8) was recovered in 70% yield, m.p.>250°C. λ_{max}.425, 262* 207 nm.γ_{max}. 3350-3250 (bonded N-H), 1640, 1620 cm^{-1}) (C=O).

3-(4-carbamoylimidazol-5-ylhydrazono)benzoylacetone (4.9) Yellow solid (90%) obtained after stirring for 2 weeks, m.p. 156-160°C; λ_{max}. 347, 254*, 208, 204 nm; γ_{max}: 3450 (free N-H), 3320, 3250 (bonded N-H), 1670, 1640, 1620 cm^{-1} (C=O), after washing with ethanol (Found: M^+, 299.$C_{14}H_{13}N_5O_3$ requires M,299).

Diethyl 2-(4-carbamoylimidazol-5-ylhydrazono)acetonedicarboxylate (4.10) buff crystalline solid obtained after two days (90%), m.p. 182-184° (Lit[89], m.p. 180-182°C); λ_{max}.344, 252*, 206 nm; γ_{max}. 3450 (free N-H), 3350, 3180, 3150 (bonded N-H), 2995 (C-H), 1722, 1700 (C=O, ester), 1640 cm^{-1} (C=O, amide).

Ethyl 2(4-carbamoylimidazol-5-ylhydrazono)benzoylacetate (4.11) pink solid (88%) obtained after 4 days, m.p. 145-146°C (from ethanol) (Lit[89], m.p. 180-182°C); λ_{max}.345, 254*, 207 nm; γ_{max}. 3460 (free N-H), 3250 (bonded N-H), 1718 (C=O), ester), 1630 cm^{-1} (C=O, $CONH_2$).

Diethyl 2-(4-carbamoylimidazol-5-ylhydrazono) malonate (4.12), solid (20%) obtained after stirring for 3-4 weeks, m.p. 180-190°C; after washing with ethanol (Found: M^+ 297.10731.$C_{11}H_{15}N_5O_5$ requires M, 297.10644); λ_{max}.345, 235, 212 nm; γ_{max}. 3450 (free N-H) 3120 (bonded N-H), 2950, 2800 (CH), 1700 (CO_2Et) 1662 (C=O, $CONH_2$).

Ethyl 2-(4-carbamoylimidazol-5-ylhydrazono)cyanoacetate (4.13) yellow solid (85%) obtained after 5 days stirring, m.p. 230°C (Lit[89], m.p. 230°C); λ_{max}.396, 240*, 209, 206 nm; γ_{max}.3350, 3150 (bonded N-H), 2220 (C≡N), 1710 (C=O, ester) 1628 cm^{-1} (C=O, amide). The hydrazone (4.13) afforded a pyridinium salt from boiling pyridine, m.p.>320°C (decomp.) Found: C,51.5; H,4.5; N,29.2 $C_9H_{10}N_6O_3$. C_6H_6N requires C,51.1; H,4.6; N,29.8%), λ_{max}.406, 263*, 250*, 250*, 247*, 207 nm, γ_{max}.3380 (free N-H), 3110 (bonded N-H), 2205 (C≡N), 1675 (C=O), ester), 1620 cm^{-1} (C=O, amide); δ(DMSO-d_6) 1.36 (3H triplet, J=7Hz. CH_2-$\underline{CH_3}$),

4.3(2H,q,J=8Hz$\underline{CH_2}.CH_3$), 7.7(5H,m,pyridine), 8.75(1H,s,imidazole H-2). The hydrazone (4.13) also formed potassium salt (60%) by the method described (hydrazone 4.8). Careful neutralisation of the salt with 1N-hydrochloric acid liberated a different hydrazone, (Found: C,40.2; H,4.2.$C_9H_{10}N_6O_3.H_2O$ requires C,40.3; H,4.4%); λ_{max} 407, 255*, 205 nm; γ_{max}. 3350, 3100 (bonded N-H), 2220 (C≡N), 1708 (small) (CO_2Et), 1650 cm^{-1} (C=O).

2-(4-Carbamoylimidazol-5-ylhydrazono)malononitrile (4.14) obtained as deep yellow solid by stirring overnight (85%), m.p. 240-245°C (decomp). The unstable hydrazone washed with excess ethanol (Found: M^+ 203.$C_7H_5N_7O$ requires M,203); λ_{max}.385, 257*, 227*, 207 nm, γ_{max} 3380 (free N-H) 3200, 3100 (bonded N-H), 2225 (C≡N), 1640 cm^{-1} (C=O, $CONH_2$).

2-(4-Carbamoylimidazol-5-ylhydrazono)cyanoacetamide (4.15) obtained as deep yellow solid (90%) after 24 hours, m.p. 190-195°C. Re-crystallised from ethanol-dimethylformamide (Found: C,38.1; H,3.3; N,42.8; M^+,221.06611. $C_7H_7N_7O_2$ requires C,38.0; H,3.2; N,44.3% M,221.06607), λ_{max} 408, 240, 211 nm; γ_{max} 3380, 3290, 3120 (N-H) 2200 (C≡N), 1705, 1650 cm^{-1} (C=O, $CONH_2$).

Acid-catalysed cyclisations of hydrazones

Methyl 3-carbamoyl-4,7-dihydro-7-methyleneimidazo[5,1-c][1,2,4]-triazine-6-carboxylate (4.29). Hydrazone (4.6) (1.0g) was heated under reflux in ethanol (10 ml) and acetic acid (10 ml for 3 hours. The cooled solution deposited golden crystals of the methyl triazine - carboxylate acetic acid solvate (88%) which crystallised

from acetic acid with m.p. 250°C (decomp). (Found: C,44.8; H,4.3 M^+ 235. $C_9H_9N_5O_3$. CH_3CO_2H requires C,44.8; H 4.4% M,235; λ_{max}. 367, 296*, 278*, 267, 232 nm; γ_{max}. 3370, 3300 (N-H), 3200 (br N-H) 2600-2400 (br bonded OH), 1710 (CO_2Me) 1695 (Ac), 1642 ($CONH_2$). δ(TFA)2.23(3 H,S, $\underline{CH_3}COOH$), 4.1 (3 H,S,$CO\underline{CH_3}$), 5.92 (2 H,d, J=4Hz, CH_2), 6.48 (2 H,d, J=4Hz, CH_2), 9.1 (1 H,s, imidazole H-1). The acetic acid solvate decomposed in boiling ethanol (2 hours). The unsolvated methyl triazine-carboxylate precipitated as a yellow powder, m.p. 250°C (decomp.) (Found: C,45.6; H,4.4; N,29.4; M^+, 235.08176. $C_9N_5O_3$ requires C,45.8; H3.8; N, 29.5%; M,235.08168). The same unsolvated methyltriazine carboxylate (85%) was formed when hydrazone (4.6) was boiled in ethanol alone. λ_{max}. 367 296*, 278*, 267, 232 nm; $\gamma_{max.}$ 3360 (N-H), 3150(br N-H), 1722(CO_2Me), 1665($CONH_2$); δ(TFA)4.1(3 H,S,$CO_2\underline{CH_3}$),5.92(2 H,d,J=4Hz,CH_2)6.48(2 H,d,J=4Hz, $C\underline{H_2}$)9.12(1-H,s,imidazole H-1).

The methyl triazine-carboxylate (4.29) formed a mono-acetyl derivative (6.1) when it was boiled in acetic anhydride for 0.5 hour. The product (75%) crystallised from ethanol-dimethyl-formamide with m.p. 240-245°C (decomp). (Found: C,47.4; H,4.1; M^+,277.08097. $C_{11}H_{11}N_5O_4$ requires C,47.4; H,4.1%; M,277.08083); λ_{max}. 372, 295*, 268 nm; γ_{max} 3350, 3280 (N-H), 1729 and 1715 (CO_2Me), 1685 cm^{-1} (Ac).

Ethyl 3-carbamoyl-4,7-dihydro-7-methyleneimidazo[5,1-c][1,2,4]-triazine-6-carboxylate (4.30). Hydrazone (4.7) (1.0g) was boiled

in ethanol (10 ml) and acetic acid (10 ml) for 4 hours. The cooled mixture deposited yellow crystals of the ethyl triazine-carboxylate (0.8g), m.p. 270°C (decomp). Recrystallised from ethanol-acetic acid (Found: C,47.7; H,4.4; N,27.7; M^+, 249.086183. $C_{10}H_{11}N_5O_3$ requires C,48.2; H,4.4; N,28.1%; M,249.08675); λ_{max} 367, 298, 278*, 267, 235 nm; γ_{max} 3330 (NH), 3180) (br, N-H), 1720 (CO_2Et), 1699 cm^{-1} ($CONH_2$); δ(TFA), 1.5 (3 H, t, J=6Hz, CH_2-$\underline{CH_3}$), 4.5 (2 H, q, J=8Hz, $\underline{CH_2}$-CH_3), 5.9(2 H,d, J=5Hz, CH_2), 6.5 (2 H, d, J=5Hz, CH_2), 6.5 (2 H, d, J=5Hz), 9.12 (1 H, s, imidazole H-1). From the acidic filtrate of the above compound (4.30) orange crystals of the covalent ethanolate (4.39) of imidazotriazine ester (4.30) obtained. The ethanolate had m.p. 175°C (with resolidification at 190°C, finally melts at 245° (decomp). (Found: C,46.3; H,6.3; N, 23.1; M^+ 295.$C_{12}H_{17}N_5O_4.H_2O$ requires C,46.0; H,6.1; N,22.5%; M,295); λ_{max} 338, 246, 225 nm; γ_{max} 3495; 3390, 328 (N-H); 3150 (br N-H), 1700 (CO_2Et), 1650 ($CONH_2$), 1140 cm^{-1} (OEt).

6-Acetyl-3-carbamoyl-4,7-dihydro-7-methyleneimidazo[5,1-c][1,2,4]-triazine (4.31).

Cyclisation of 3-(4-carbamoylimidazol-5-ylhydrazono)pentan-2,4-dione (4.8) in boiling acetic acid and ethanol as above yielded the acetyltriazine (85%) m.p. 250°C (decomp). recrystallised from acetic acid-ethanol [Lit[87] m.p. 226-227°C for the compound claimed to be (4.23)]. (Found: C,49.2; H,4.3; M^+219.$C_9H_9N_5O_2$ requires C,49.3; H,4.1; M^+219); λ_{max} 366, 279*, 270*, 253, 242 nm; γ_{max} 3460 (N-H) 3220-3120 (br N-H), 1670 cm^{-1} (br AC and $CONH_2$);

δ(TFA) 2.7 (3 H, s, $COCH_3$), 5.9 (2 H, d, J=4Hz, CH_2), 6.62 (2 H, d, J=4Hz, CH_2), 9.14 (1 H, s, imidazole H-1).

6-Benzoyl-3-Carbamoyl-4,7-dihydro-7-methyleneimidazo[5,1-c][1,2,4]-triazine (4.32).

3-(4-Carbamoylimidazol-5-ylhydrazono)benzoylacetone (4.11) (1.0g) was heated under reflux in acetic acid - ethanol mixture (1:1) (20 ml) for 4 hours. The volume of the reaction mixture was reduced by half under vacuum. The crystals of the yellow benzoyltriazine (65%) were deposited when the mixture was diluted with water, recrystallised from acetic acid-ethanol, m.p. 260-265°C (decomp). (Found: C,58.3; H,5.0; M^+, 281,091268.$C_{14}H_{11}N_5O_2.H_2O$ requires C,57.9; H,4.5%; M,281.09151); λ_{max} 364, 258, 226 nm; γ_{max} 3460, 3400 (N-H), 3200 (br,N-H), 1650 cm^{-1} (Bz and $CONH_2$); δ)TFA) 5.94 (2 H, s, CH_2), 7.8(5 H, m, $C_6H_5.CO$), 9.14(1 H, s, imidazole H-1).

Ethyl 7-amino-3-carbamoylimidazo[5,1-c][1,2,4]triazine-6-carboxylate (4.45).

A solution of hydrazone (4.13) (1.0g) in ethanol (10m) and acetic acid (10 ml) was boiled for 0.5h. Pink crystals of the aminoimidazotriazine acetic acid solvate (4.44) deposited from hot solution, m.p. 360°C (decomp). Recrystallised from acetic acid (Found: C,42.4; H,4.7; N,26.8; M^+250.$C_9H_{10}N_6O_3.CH_3CO_2H$ requires C,42.6; H,4.5; N.27.0%; M,310-60 (M-CH_3COOH) λ_{max} 382, 330*, 316, 307*, 244, 206 nm, γ_{max}. 3398 (N-H), 3180, 3020, (N-H, bonded), 1695 (CO_2Et), 1630 cm^{-1} ($CONH_2$); δ(TFA)1.5(3 H, t,

J=8Hz, $\underline{CH_3}$-CH_2), 4.56 (2 H, q, J=7Hz, CH_3-$\underline{CH_2}$), 9.22 (1H , s, imidazole H-1). The acetyl-derivative (6.3) was formed in 80% yield when the aminoimidazotriazine (4.45) (0.5g) was boiled in acetic anhydride-acetic acid (1:1) (10 ml) for 2 hours. The light yellow product had m.p. 350°(decomp). (Found: C,44.8; H,4.0; N,28.9; M^+292.$C_{11}H_{12}N_6O_4$ requires C,45.2; H,4.1; N,28.8%; M,292); λ_{max}. 386, 328*, 314, 240*, 206 nm; γ_{max} 3400, 3340 (N-H), 3070 (NHAC), 1720 (CO_2Et), 1685 (NHAC), 1635 cm^{-1}($CONH_2$); δ (TFA) 1.5 (3 H, t, J=6Hz, CH_2-$\underline{CH_3}$), 2.62(3 H, s, N-CO.$\underline{CH_3}$), 4.58 (2 H, q, J=7Hz, $\underline{CH_2}$-CH_3), 9.13 (1H, s, imidazole H-1).

7-Amino-3-Carbamoyl-6-cyanoimidazo[5,1-c][1,2,4]triazine (4.47).

Cyclisation of hydrazone (4.14) (1.0g) in a mixture of boiling ethanol and acetic acid (10:1) (15 ml) for 0.5 hour afforded the deep yellow aminonitrile (95%), m.p. 350-360°C (decomp.), recrystallised from dimethylformamide-ethanol (Found: C,41.2; H,2.5% N,48.0; M^+, 203.05555.$C_7H_5N_7O$ requires C,41.4; H,2.5; N,48.3% M,203.05501) λ_{max} 390, 325*, 312, 305*, 205 nm; γ_{max}. 3440, 3330, 3260 (N-H), 3130 (br N-H) 2250 (C≡N), 1660 cm^{-1} ($CONH_2$); δ (TFA) 9.12 (1H,s,imidazole H-1).

7-Amino-3-carbamoylimidazo[5,1-c][1,2,4]triazine-6-carboxamide (4.49)

Hydrazone (4.15) (1.0g) was boiled in glacial acetic acid (15 ml) for 2 hours. The precipitated yellow solid was collected, stirred in aqueous 1N-sodium hydroxide and washed with water. The triazine-carboxamide (85%) which could not be crystallised

had m.p. 320°C (decomp.) Found C,38.0; H,3.0 M^+, 221.$C_7H_7N_7O_2$ requires C,38.0; H,3.2%; M,221); λ_{max} 390, 325*, 313, 246, 206 nm; 3400, 3350, 3250 (N-H), 3150 (br N-H) 1680 and 1660 ($CONH_2$).

Ethyl-3-Carbamoyl-4,7-dihydro-7-ethoxycarbonylmethyleneimidazo-[5,1,c][1,2,4]triazine-6-carboxylate. (4.50)

The hydrazone (4.10) (1.0g) was heated under reflux in glacial acetic acid (20 ml) for 48 hours. A yellow microcrystalline solid (0.75g) was deposited from the solution on cooling. Recrystallised from glacial acetic acid, M.p. 220 (decomp). (Found: C,46.1; H,5.1; M^+, 321.10731.$C_{13}H_{15}N_5O_5.H_2O$ requires C, 46.0; H,5.0%; M,321.10687); λ_{max}. 385, 297, 241, 206 nm; γ_{max} (hydrate) 3340 (br N-H), 3150 (br N-H), 1700 (CO_2Et) 1650 cm^{-1} ($CONH_2$).

Ethyl-3-carbamoyl-7-phenylimidazo[5,1-c][1,2,4]triazine-6-carboxylate (4.51).

Ethyl 2-(4-carbamoylimidazol-5-ylhydrazono)benzoylacetate (4.11) (1.0g) was boiled in ethanolic acetic acid (1:1, 20 ml) for 24 hours. The crude precipitated product, possibly the triazine-carboxylate (4.51) had m.p. 295°C(decomp.) (c.f. m.p. 145°C for starting material) and could not be further purified (Found: M^+ 311.10183 $C_{15}H_{13}N_5O_3$ requires M,311.10119 λ_{max}. 368, 290* 253 nm; γ_{max}. 3300-3100 (br N-H), 1705 (CO_2Et) 1630 ($CONH_2$).

Base-catalysed cyclisations of hydrazones

6-Benzoyl-3-carbamoylimidazo [5,1-c] [1,2,4] triazin-7-(4H)-one (4.55)

The hydrazone (4.11) (1.0g) was stirred at room temperature in 1% alcoholic potassium hydroxide (15 ml). The orange product immediately precipitated out and slowly changed into deep yellow solid. The stirring was continued for 5 hours. The yellow product was acidified with 1N-hydrochloric acid and the product (85%) was collected by filtration. Recrystallised from dimethylformamide-ethanol; m.p. >300°C (Lit.[88], m.p.>250°C). The same triazinone (55%) was obtained from hydrazone (4.11) in boiling ethanolic pyridine. (Found: C,55.3; H,3.29; N,24.49; M+ 283. $C_{13}H_9O_3N_5$ requires C 55.12; H 3.20; N,24.7%; M,283); λ_{max} 378, 296, 257, 240, 207 nm; γ_{max} 3400, 3270 (N-H), 1670 (Bz and C=O) 1635 cm^{-1} ($CONH_2$).

6-Acetyl-3-carbamoylimidazo[5,1-c] [1,2,4] triazin-7(4H)-one. (4.58)

A solution of hydrazone (4.6) (1.0g) in 1% alcoholic potassium hydroxide was stirred (5 hr) and the mixture was acidified with 1N-hydrochloric acid. The precipitated benzoyltriazinone (85%) crystallised from dimethylformamide-ethanol with m.p.>300°C (decomp.) (Found: C,41.8; H,3.55; N,29.9; M^+,221. $C_8H_7N_5O_3.0.5H_2O$ requires C,41.7; H,3.5; N,30.4: M,221). The same triazinone (4.58) was prepared from hydrazone (4.7) and 1% alcoholic potassium hydroxide (as above) in 70% yield or by boiling hydrazones (4.6) or (4.7) in 50% ethanolic pyridine for 2 hours, yield 45%; λ_{max} 376, 289, 250*, 207 nm; γ_{max}. (hemihydrate) 3500, 3450, 3350 (N-H), 3150

(br N-H) 1710(AC), 1665 cm^{-1}(C=O and $CONH_2$; δ(TFA) 2.82(3 H,s,CH_3.CO), 9.02(1 H,s,imidazole H 1).

Ethyl 2-{3-Carbamoyl-4,7-dihydro-7-oxoimidazo[5,1-c][1,2,4]triazin-6-carbonyl}acetate (4.59).

Hydrazone (4.10) (1.0g) was stirred in 10% alcoholic potassium hydroxide (25 ml) for 5 hours and the precipitated yellow salt (95%) was acidified with 1N-hydrochloric acid crystallised from dimethylformamide-ethanol with m.p.320°C (decomp.) (Found: C,44.0; H,4.1; N,23.3; M^+,293.076011. $C_{11}H_{11}N_5O_5.0.5H_2O$ requires C,43.7; H,4.0; N.23.2%; M,293.07574); λ_{max} 385, 295, 240, 207 nm; γ_{max}. 3380(N-H), 3200(br N-H/O-H), 1700 (CO_2Et), 1670 cm^{-1} (C=O and $CONH_2$); δ (TFA) 1.4 (3 H,t,J=7H_3,CH_2-$\underline{CH_3}$), 4.5(2H,q,J=8Hz,$\underline{CH_2}$-CH_3), 4.35(2 H,s,CH_2), 9.02(1 H,s,imidazole H-1).

3-Carbamoyl-6-cyanoimidazo[5,1-c][1,2,4]triazin-7(4H)-one (4.61).

Hydrazone (4.13) (1.0g) was boiled in pyridine (10 ml) and ethanol (15 ml) for 4 hours. The precipitated yellow solid was collected and recrystallised from dimethylformamide-ethanol and afforded the triazinone (0.8g), m.p.>300°C (decomp.) Found: C,41.3; H,2.2; N,41.2; M^+,204.$C_7H_4N_6O_2$ requires C,41.2; H,2.0; N,41.2%; M,204); λ_{max} 384, 310*, 298, 288*, 244, 206 nm; γ_{max} 3410(N-H) 2220(C≡N), 1673 cm^{-1} (C=O and $CONH_2$).

3,6-Dicarbamoylimidazo[5,1-c][1,2,4]triazin-7(4H)-one (6.10)

Cyanoimidazotriazinone (4.61) (0.5g) was boiled in polyphosphoric acid (3 ml) for 4 hours. The cooled diluted solution was neutralised with sodium carbonate and the yellow product

collected (0.4g). Crystallisation from dimethylformamide-ethanol afforded yellow crystalline product, m.p. 340-345°C (decomp). (Found: N,36.3, M^+ 222.$C_7N_6O_3$ requires N,36.5%; M,222); γ_{max} 379, 286, 250*, 240, 208 nm; γ_{max} 3400 (N-H) 3220 (br N-H) 1695 ($CONH_2$), 1660 cm^{-1} (C=O,$CONH_2$).

3-Carbamoyl-6-ethoxycarbonylimidazo[5,1-c][1,2,4]triazin-7(4H)-one (4.60).

(i) Hydrazone (4.12) (0.5g) was stirred in 1% alcoholic potassium hydroxide (10 ml) for 10-15 mins. Acidification of the precipitated yellow salt with 1N-hydrochloric acid liberated the the free triazinone (4.60) (70%), m.p. 280°C (decomp.). (Found: M^+ 251 $C_9H_9N_5O_4$ requires M 251). The product was identical (i.r., uv) to a sample obtained by the hydrolysis of amino-ester (see below).

(ii) Hydrolysis of aminotriazine ester (4.45) (0.4g) in refluxing 2N-hydrochloric acid (15 ml) (0.5 hr) deposited a cream solid (0.35g) when cooled. The product was identical (i.r., u.v.) to a sample of the hydrate of triazinone (4.60) prepared by base-catalysed cyclisation of hydrazone (4.12). (Found: C,39.8; H,4.1; N,26.4 M^+ 251.$C_9H_9N_5O_4.H_2O$ requires C,40.1; H,4.1; N,26.0%; M,251); λ_{max} 375, 279, 239, 207 nm; γ_{max} 3500, 3370, 3150 (N-H), 1725(CO_2Et), 1665 cm^{-1} (C=O and $CONH_2$); δ(TFA) 1.32 (3 H,t, J=7Hz, $CH_3.CH_2$), 4.25(2 H,q,J=7Hz,$CH_3-\underline{CH_2}$), 7.5(2 H,$CONH_2$), 8.5 (1 H,s,imidazole H-1).

A solution of the triazinone (4.60) in 50% aqueous sodium bicarbonate rapidly deposited cream crystals of the sodium salt

(6.5), m.p.>350°C (decomp). (Found: C,36.7; H,3.5; N,23.6 $C_9H_8N_5NaO_4.H_2O$ requires C,36.9; H,3.7; N,23.9%); λ_{max} 382, 301, 250, 207 nm; ν_{max} 3498, 3370, 3150 (N-H), 1700 (CO_2Et), 1665 cm^{-1} (CO and $CONH_2$).

3-Carbamoyl-4,7-dihydro-7-oxoimidazo[5,1-c] [1,2,4]triazin-6-carboxylic acid (6.5).

3-Carbomyl-6-ethyoxycarbonylimidazo [5,1-c] [1,2,4]triazin-7(4H)-one (4.60) (0.4g) was stirred in 5N-sodium hydroxide for 0.5hr. The precipitated solid was collected, acidified with 1N-hydrochloric acid, and the crude product (0.3g) crystallised from aqueous ethanol to afford the carboxylic acid, m.p. 265-270°C (efferv.) (Found: C,34.7; H,2.9; N,29.4; M^+, 179.$C_7H_5N_5O_4.H_2O$ requires C,34.8; H,2.9; N,29.0%; M,233-44[CO_2]); λ_{max}, 375, 279, 250*, 239 nm; ν_{max} 3380 (NH) 3200 (br NH/OH, 1700 (CO_2Et), 1670 cm^{-1} (C=O and $CONH_2$).

3-Carbamoylimidazo[5,1-c] [1,2,4]triazin-7(4H)-one (6.9)

The triazine carboxylic acid (6.5) (0.49) when boiled (2 hr) in 5N-hydrochloric acid a deep yellow solid (65%) was obtained. which was further purified by boiling in 5N-hydrochloric acid, m.p.>260°C (decomp.) (Found: C,30.8; H,3.7; M^+179 $C_7H_5O_2N_5$. HCl.H_2O requires C,30.9; H,3.4%; M,179; λ_{max} 374, 312, 252*, 210 nm; ν_{max} 3420 (N-H) 3180 (br N-H), 1670 cm^{-1} (C=O and $CONH_2$)

Ethyl 2-(3-carbamoylpyrazol-4-ylhydrazon)acetoacetate (5.6)

A suspension of finely divided 4-aminopyrazole-3-carboxamide (1.26g) in 1N-Hydrochloric acid (10 ml) was cooled to 0°-5° and treated with sodium nitrite (1 mol. equiv) in water (3 ml). A

tan coloured precipitate was gradually formed. The mixture was neutralised with excess sodium acetate trihydrate and stirred at 0^{o}-5^{o}C with ethyl acetoacetate (1.3g) for 2 hours. The crude pink solid was collected by filtration and washed with water; yield (95%); M.p. 235-240^{o}C) (crude). Cyclised upon attempted crystallisation from ethanol (Found: M^{+} 267.$C_{10}H_{13}N_5O_4$ requires M,267); λ_{max} 345, 244 nm; ν_{max}.3500, 3400, 3250 (N-H) 1730 (C=O, ester), 1670 cm^{-1} (C=O, Ac and $CONH_2$); δ(DMSO-d_6) 1.25 (3H,t,J=7H,$\underline{CH_3}.CH_2$), 2.1(3H,s,CO.$\underline{CH_3}$),4.12(2H,q,J=8Hz, $CH_3.\underline{CH_2}$), 8.24 (1H,s,pyrazol,H-5).

The following hydrazones were prepared by the similar method.

Methyl 2-(3-carbamoylpyrazol-4-ylhydrazono)acetoacetate (5.7). The product obtained as a pink solid (90%) from the coupling reaction between 4-diazopyrazole-3-carboxamide and methyl acetoacetate; M.p. (crude) 235^{o}C. (Found: M^{+}, 253.$C_9H_{11}N_5O_4$ requires M,253); λ_{max}.345, 243 nm; ν_{max}. 3420, 3350, 3200 (N-H) 1720 (CO_2Me) 1660 cm^{-1} (br) (AC and $CONH_2$); δ(DMSO-d_6) 1.96(3H, s,CO2$\underline{CH_3}$), 3.34 (3H,s,$COCH_3$), 8.2 (1H,s,pyrazole $\underline{H}$-5.

Ethyl 2-(3-carbomylpyrazol-4-ylhydrazono)cyanoacetate . (5.8) The hydrazone obtained as an isomeric mixture (see page 111) from 4-diazopyrazole-3-carboxamide and ethyl cyanoacetate, in 78% yield. The hydrazone crystallised from ethanol as yellow microcrystals m.p. 240-245^{o}C (decomp.) (Found: C,41.2; H,4.0; M^{+}250.$C_9H_{10}N_6O_3$.0.5H_2O requires C,41.6; H,4.2%, M,250); ν_{max}.404, 290*, 281, 238, 207 nm; ν_{max}.3460, 3400, 3340(N-H) 3150(br N-H), 2207(C≡N), 1720 (C=O,ester), 1640 cm^{-1} ($CONH_2$); δ (DMSO-d_6)

1.25 (6H double,t,J=6Hz, 2X$\underline{CH_3}$-CH_2), 3.4(2H,q,J=7Hz,CH_3-$\underline{CH_2}$), 4.25(2H,q,J=7Hz, CH_3-$\underline{CH_2}$), 8.25(1H,s,pyrazole H-5).

Ethyl-3-carbamoyl-1H-7-methylpyrazolo[4,3-c]pyridazine-6-carboxylate (5.14).

A solution of hydrazone (5.6) (1.0g) in ethanol was refluxed for 2 hr. and cooled. The precipitated pyrazolopyridazine (0.8g), recrystallised from ethylacetate, m.p. 250°C (decomp.) (Found: C,48.2; H,4.8; N,28.3; M^+,249.$C_{10}H_{10}N_5O_3$ requires C,48.0; H,4.8; N,28.0%, M,249); λ_{max}.313, 246, 215 nm; ν_{max}.3450, 3200(N-H), 1715(CO_2Et), 1670 cm^{-1} ($CONH_2$); δ(DMSO-d_6), 1.35(3H,t,J=7Hz, $\underline{CH_3}$-CH_2), 2.18(3H,s,$\underline{CH_3}$), 4.26(2H,q,J=7Hz,CH_3-$\underline{CH_2}$).

Methyl-3-carbamoyl-1H-7-methylpyrazolo[4,3-c]pyridazine-6-carboxylate (5.15).

This pyrazolopyridazine (90%), similarly prepared from hydrazone (5.7) in boiling ethanol, had m.p. 250°C(decomp.) (Found: C,45.4; H,4.05; N,29.7; M^+,235.$C_9H_8N_5O_3$ requires C,45.8; H,3.8; N,29.6% M,235; λ_{max} 312, 246, 215 nm; ν_{max}.3500-3200 (br N-H), 1710(CO_2Me), 1640 cm^{-1} ($CONH_2$); δ(DMSO-d_6), 2.1 (3H,s,$\underline{CH_3}$), 3.38(3H,s,$CO_2\underline{CH_3}$).

3-Carbamoyl-6-cyano-1H-pyrazolo[4,3-c]pyridazin-7(4H)-one (5.16)

Hydrazone (5.8) (1.0g) was boiled in 70% aqueous ethanol for 8 hours. The cooled solution deposited crystals of the pyrazolopyridazinone(0.8g), m.p. 25°C (decomp.). Found: C,36.1; H,2.9; M^+,204.$C_7H_4N_6O_2$.1.5H_2O requires C,36.4; H,3.0% M,204);

λ_{max}.361, 290*, 285, 228, 208 nm; ν_{max}.3460(N-H), 3330-3100 (br NH/OH), 2230(C≡N), 1695(C=O), 1675, 1660 cm^{-1} ($CONH_2$).

Reactions of ethyl-7-amino-3-carbamoylimidazo[5,1-c][1,2,4]-triazine-6-carboxylate and secondary heteroalicyclic amines.

i) Piperidino-amide (6.12)

Aminotriazine ester (4.45) (0.5g) and piperidine (3 ml) were refluxed in benzene (20 ml) for 16 hr. The yellow product (0.38g) was recrystallised from dimethylformamide-ethanol, m.p. 290° (decomp.) (Found: C,49.5; H,5.3; N,33.6 M^+,289,12871.$C_{12}H_{15}N_7O_2$ requires C,49.8; H,5.2; N,33.9%; M,289.12793); λ_{max} 382, 309 250*, 211 nm; ν_{max} 3365 (N-H), 3250 (br N-H), 1660, 1635 cm^{-1} (C=O and $CONH_2$); δ(TFA) 1.95 br (6H,m,$\underline{CH_2}$), 3.8 br(4H,m,$\underline{CH_2}$), 7.70 br (2H,NH), 8.78 (1H,s,imidazole H-1).

ii) The pyrrolidino-amide (6.13) (89%), similarly prepared from aminoester (4.45) and pyrrolidine had m.p. 280°C (decomp) (Found: C,46.1; H,4.6; N,34.2; M^+,275.11306.$C_{11}H_{13}N_7O_2.0.5H_2O$ requires C,46.4; H,4.9; N,34.5%; M,275.11265); λ_{max} 382, 310, 250*, 212 nm; ν_{max} 3370(N-H), 3290(N-H), 3150(Br N-H/OH), 1675, 1625 cm^{-1} (C=O and $CONH_2$) δ(TFA), 2.30 br (4H,m,$\underline{CH_2}$), 4.0 br(4H,m,CH_2), 8.90(1H,s,imidazole H-1).

iii) The morpholino-amide (6.14) was similarly prepared from aminoester (4.45) and morpholine in refluxing benzene (70% yield). The product crystallised from dimethylformamide-ethanol with m.p. 280°C (decomp). (Found: C,45.1; H,4.5; N,33.6; M^+,291.10798. $C_{11}H_{13}N_7O_3$ requires C,45.36; H,4.5; N,33.6%, M,291.10883);

λ_{max} 383, 314, 250*, 211 nm; ν_{max} 3440 (N-H , 3280(br N-H), 1675, 1625 cm^{-1} (C=O and $CONH_2$); δ(TFA) 4.4-3.8br (8H,m,CH_2), 8.2 br (2H,NH), 8.70 (1H,s,imidazole H-1).

(iv) N-methylpiperazine-amide. (6.15).

Interaction of aminoester (4.45) and N-methylpiperazine furnished the amide as a light yellow solid (82%) recrystallised from dimethylformamide ethanol, m.p. 285°C(decomp). (Found: C,47.4; H,5.5; N,36.4; M^+,304.13961.$C_{12}H_{16}N_8O_2$ requires C,47·4; H,5.3; N,36.8%; M,304.14031); ν_{max} 382, 311, 250*, 211 nm; ν_{max} 3360, 3290, 3150(NH), 1670, 1635 cm^{-1} (C=O and $CONH_2$).

6-Amino-3-carbamoylpyrimido[4,5-e]imidazo[5,1-c][1,2,4]triazine (6.18)

A solution of 7-amino-3-carbamoyl-6-cyanoimidazo[5,1,c]-[1,2,4]triazine (4.47) (0.5g) in refluxing formamide (5 ml) for 1.5 hr deposited brown cyrstals (0.37g) when the mixture was cooled. Purified by vacuum sublimation, m.p.>350°C (decomp). (Found: C,41.3; H,2.7; N,48.0; M^+,230.06645,$C_8H_6N_8O$ requires C,41.7; H,2.6; N,48.7%; M,230.0663); ν_{max} 400, 302, 244, 207 nm; ν_{max} 3400 (N-H), 3150, 3050(br N-H), 1680 cm^{-1}($CONH_2$; δ(TFA 8.81 (1 H,s,pyrimidine H-2), 9.20 (1 H,s,imidazole H-1).

6,8-Diamino-3-carbamoylpyrimido[4,5-e]imidazo[5,1-c][1,2,4]-triazine (6.19)

Guanidine hydrochloride (5.2g) was dissolved in sodium ethoxide [prepared from sodium (1.3g) in absolute ethanol (40 ml.)]. Sodium chloride was removed and 7-amino-3-carbamoyl-6-cyano-imidazo[5,1-c][1,2,4]triazine (4.47) (0.6g) added to the filtrate.

Ethanol was volatilised from the mixture and the residue heated at 180°C for 2 hr. The cooled solid was sublimed under reduced pressure to yield the pyrimidoimidazotriazine (0.36g) m.p. 350°C (decomp). (Found N,51.4; M^+,245.07735.$C_8H_nN_9O$ requires N,51.0%; M,245.07755); λ_{max}.428, 325*, 313, 260, 209 nm; ν_{max} 3400-3200 (br N-H), 1660 cm^{-1} ($CONH_2$).

Reactions of hydrazine derivatives with imidazotriazines

3-Amino-4-(4-carbamoylimidazol-5-ylazo)pyrazolin-5-one (7.6)

Aminotriazine ester (4.45) or 6-cyanoimidazotriazinone (4.61) (0.50g) was heated under reflux with hydrazine hydrate (1ml) in ethanol (15 ml) for 0.5 hr. The reaction mixture when cooled deposited the orange crystals (65%), m.p. 280°C (decomp.)(from dimethylformamide-ethanol/3:1) (Found: C,35.25; H,3.5; M^+,236.07701 $C_7H_7N_8O_2$ requires C,35.6; 3.4; M,236.07636); λ_{max}.425, 257*, 208 nm; ν_{max}.3280, 3120 (bonded N-H), 1670 cm^{-1} (C=O and $CONH_2$).

3,5-Diamino-4-(4-carbamoylimidazol-5-ylazo)pyrazole (7.10)

When 7-amino-6-cyanoimidazotriazine (4.47) (0.50g) was heated in ethanol and hydrazine hydrate as above yielded the orange product (60%), m.p. 335-345°C (decomp.) (from dimethylformamide-ethanol) (Found: C,35.9; H,4.0; N,52.9; M^+, 235.09300 $C_7H_9N_9O$ requires C,35.74; H,3.82; N,53.6; M,235.09251); λ_{max}.417, 265*, 257*, 208 nm; ν_{max}.3350 (N-H), 3250, 3150 (bonded N-H), 1680 cm^{-1}($CONH_2$).

3-Methyl-4-(4-carbamoylimidazol-5-ylazo)pyrazolin-5-one) (7.12; R^1=H)

(i) The imidazotriazine ester (4.29 or 4.30) or the imidazotriazine (4.58) (0.5g) and hydrazine hydrate (1 ml) when refluxed in ethanol (15 ml) for 3 hr., deposited the pyrazolinone (70%) as orange needles, m.p. 260-265°C (decomp.).

(ii) The same pyrazolinone (95%) was obtained when 5-diazoimidazo-4-carboxamide (4.2) (0.69g) was stirred with 5-hydroxy-3-methyl-pyrazole (7.13; R=H) (0.41g) in absolute ethanol (15 ml) in the dark for 3 hr; m.p. 260, recrystallised from dimethylformamide-ethanol (1:3) (Found: C,40.5; H,3.8; N,41.7; M^+,235.08176 $C_8H_9O_2N_7$ requires C,40.85; H,3.8; N,41.7%, M,235.08168); λ_{max}.427, 247*, 212 nm; ν_{max}.3320-3300 (br N-H), 1665 cm^{-1} (C=O, $CONH_2$); δ(TFA) 2.72(3H,s,CH_3), 8.98(1H,s,imidazole H-2).

3-Methyl-1-phenyl-4-(4-carbamoylimidazol-5-ylazo)pyrazolin-5-one (7.12; R=Ph).

(i) The imidazotriazine (4.29 or 4.30) or (4.58) (0.5g) when heated in phenylhydrazine (1 ml) in ethanol (15 ml) for 3 hr. yielded deep red crystals of the phenylpyrazolinone (70% yield), m.p. 320°C (decomp.).

(ii) The above deep red azo compound (7.12; R=Ph) (96%) was also obtained by coupling 5-diazoimidazole-4-carboxamide (4.2) (0.68g) with 5-hydroxy-3-methyl-1-phenyl-pyrazolone (7.13; R=Ph) (0.90g), m.p. 320°C (decomp.), recrystallised from dimethylformamide-ethanol (1:3)(Found: C.54.7; H,4.18; N,31.51; M^+,311.11306 $C_{14}H_{13}N_7O_2$ requires

C,54.01; H,4.18; N,31.51; M,311.11293); λ_{max}.405, 247, 209 nm; ν_{max}.3400 (N-H) 3200, 3100 (N-H), 1645 cm^{-1}(C=O, $CONH_2$) δ(TFA) 2.58(3H,s,CH_3), 7.56 (5H,s,C_6H_5), 8.92 (1H, imidazole H-2).

3-Phenyl-4-(4-carbamoylimidazol-5-ylazo)pyrazolin-5-one (7.15; R=H)

(i) Orange crystals (65%) were obtained by boiling (3 hr) the triazine (4.52) or (4.55) (0.5g) and hydrazine hydrate (1 ml) in ethanol (15 ml) m.p. 280°C (decomp).

(ii) The same compound was also obtained from coupling diazoimidazole (4.2) (0.68g) with 5-hydroxy-3-phenylpyrazole (7.16; R=H) (0.80g). Recrystallised from dimethylformamide-ethanol) (3:1), m.p. 280-282°C (decomp). (Found; M^+,297.09741 $C_{13}H_{11}O_2N_7$ requires M,297.09741; λ_{max}.415, 275*, 237, 210 nm; ν_{max}.3320, 3280 (N-H), 1660, 1638 cm^{-1} (C=O, $CONH_2$), δ(TFA) 7.62-7.98 (5H,m,C_6H_5), 8.98 (1H,s,imidazole 1-H).

1,3-Diphenyl-4-(4-carbamoylimidazol-5-ylazo)pyrazolin-5-one (7.15; R=Ph)

(i) The imidazotriazines (4.52 or 4.55) (0.5g) when boiled in ethanol (15 ml) with phenylhydrazine (1.5 ml) for 6 hr. afforded the deep red product (7.15; R=Ph) (60%) m.p. 345-350°C (decomp).

(ii) The deep red crystals of the same pyrazolinone (7.15; R=Ph) was also obtained in 95% yield by coupling the diazoimidazole (4.2) (0.69g) with 1,3-diphenylpyrazolin-5-one (7.16; R=Ph) (1.14g). The product was recrystallised from dimethylformamide-ethanol (3:1) m.p. 345-350°C (decomp.) (Found: C,61.7; H,4.0; N,25.95; M^+,373

$C_{19}H_{15}N_7O_2$ requires C,61.14; H,4.0; N,26.27; M,373) λ_{max}.425, 275*, 255, 208 nm; ν_{max}.3350 (N-H), 3180 (bonded N-H), 1670 cm^{-1} (C=O and $CONH_2$); δ(TFA) 7.52-8.08 (10H,m,2xPh), 8.82 (1H,s, imidazole H-2).

BIBLIOGRAPHY

1. A. Kreutzberger and R. Schüker, Arch. Pharm., 1973, 306, 801.

2. A. Kreutzberger and R. Schüker, Arch. Pharm., 1973, 306, 697.

3. A. Kreutzberger and R. Schüker, Arch. Pharm., 1973, 306, 730.

4. A. Kreutzberger and R. Schüker, Tetrahedron, 1973, 29, 1413.

5. A. Kreutzberger and R. Schüker, Arch. Pharm., 1973, 306, 561.

6. R.W. Clarke, S.C. Garside, L.H.C. Lunts, D. Hartley, R. Hornby and A.W.Oxford, J.C.S. Perkin 1, 1979, 1120.

7. Brit., 1,001,064; Chem.Abs. 1966; 65, 20152b.

8. J. Hadacek, Spisp. Prirodovectie Tak. Univ. Brne., 1960, 417, 373.

9. B. Loev, U.S., 3; 631, 040; Chem. Abs., 1972, 76, 85845w.

10. B. Loev, U.S., 3, 422, 194; Chem. Abs., 1969, 70, 87859d.

11. J. Hadacek and E. Kisa, Pharmazie, 1962, 17, 211.

12. R. Fusco and S. Rossi, U.S., 2837, 520; Chem. Abs., 1965, 52, 16388c.

13. R. Fusco and S. Rossi, Ital., 536, 121; Chem. Abs, 1959, 53 2264f.

14. Gevaert Photo-Producten N.V; Belg., 594, 974; Chem. Abs., 1963, 58, 2460a.

15. B. Mariani and S. Sgarbi, Chimica e Industria, 1964, 46, 630.

16. L.M. Werbel and M.L. Zomara, J. Heterocyclic Chem., 1965, 2, 287.

17. W.W. Paudler, C.I.P. Chao and L.S. Helmic, J. Heterocyclic Chem., 1972, 9, 1157.

18. N. Saldabols, S. Hillers, L.N. Alekseeva and B. Brizga, Khim-Farm-Zh., 1967, 1, 27; Chem.Abs., 1968, 68, 2856m.

19. R. Fusco and S. Rossi, Rend. ist. lombardo. Sci. Pt.1. Classe Sci. mat e nat., 1955, 88, 194. Chem. Abs., 1956, 50, 10743d.

20. B. Loev and M.M. Goodman, Tetrahedron, 1968, 789.

21. B. Mariani and S. Sgarbi, Ital., 752, 234; Chem. Abs., 1968,

22. A. Hetzheim and Pusch and H. Beyer, Chem. Ber., 1970, 103, 3533.

22. A. Hetzheim and Pusch and H. Beyer, Chem. Ber., 1970, 103, 3533.

23. I. Lalezari and y. Levi, J. Heterocyclic Chem., 1974, 11, 327.

24. H. Beyer, A. Hetzheim and H. Honeck, Chimia, 1968, 22, 86.

25. H. Beyer and T. Pyl, Angew. Chem., 1956, 68, 374.

26. H. Beyer and T. Pyl, Annalen, 1957, 605, 50.

27. B. Loev, U.S., 3,719,677; Chem. Abs., 1973, 78, 148007p.

28. Belg, 657, 084; Chem. Abs., 1966, 64, 17760c.

29. P. Guerret, R. Jacquier, H. Lopez and G. Maury, Bull. Soc. Chim. France, 1974, 1453.

30. R. Turner "Pyrazoles, Pyrazolines, Indazoles and condensed Rings" ed. R.H. Wiley, Interscience publishers, New York, 1967, p.3.

31. H. Sasaki, H. Sakata and Y. Iwanami, J. Chem.Soc.Japan, 1964, 85, 704.

32. A.A. Katner and E.A. Ziege, Chem.Comm., 1971, 864.

33. M. Brüger, H. Warnhoff and F. Korte, Annalen, 1972, 757, 100.

34. D.J. LeCount and A.T. Greer, J.C.S. Perkin 1, 1974, 297.

35. D.J. LeCount and P.J. Taylor, Tetrahedron, 1975, 31, 433.

36. W.G. Finnegan, R.A. Henry and E. Lieber, J. Org. Chem., 1953, 18, 779.

37. A.F. McKay and M.E. Kreling, J. Org. Chem., 1957, 22, 1581.

38. M.K. Eberle and Paul Schrim, J. Heterocyclic Chem., 1977, 14, 59.

39. M. Julia and M. Baillarge, Bull. Soc. Chim. France, 1959, 850.

40. Gy. Hornyak, K. Lempert and K. Zauer, Acta.Chim.Acad.Sci. Hung., 1969, 61, 181.

41. M. Brügger and F. Korte, Annalen, 1972, 764, 112.

42. S.R. Aspinall and E.J. Bianco, J.Amer.Chem.Soc., 1951, 73, 602.

43. M.V. Povstyanoi and P.M. Kochergin, Ukrain.Khim.Zhur., 1974, 80, 82902J.

44. P.M. Kocherginand, M.V. Povstyanoi, U.S.S.R., 374, 308; Chem.Abs., 1973, 79, 53378S.

45. A. Hetzheim and H. Pusch, Chimia, 1969, 23, 303.

46. A. Hetzheim and H. Pusch, Ger(East); 77,495; Chem.Abs., 1971, 75, 98597w.

47. J. Nyitari, S. Bekassy, K. Lempert, Acta.Chim.Acad.Sci.Hung., 1967, 53, 395.

48. G. Doleschall, Gy. Hornyak-Hamori, K. Lempert and W. Wolfner, Acta.Chim.Acad.Sci.Hung., 1967, 53, 385.

49. G. Doleschall, Acta. Chim.Acad.Sci.Hung., 1967, 53, 395.

50. G. Doleschall, M. Hornyak-Hamori and K. Lempert, Acta.Chim. Acad.Sci.Hung., 1968, 55, 319.

51. G. Doleschall, K. Lempert, unpublished results.

52. G. Doleschall, Gy.Hornyak-Hamori, L.Lang, K. Lempert and K. Zauer, Acta.Chim.Acad.Sci.Hung., 1968, 57, 191.

53. K. Szivos, Thesis, University of Budapest, 1967.

54. J. Pitha, P. Fiedler and J. Gut, Coll. Czech.Chem.Comm., 1966, 31, 1864.

55. J. Gut, "Advances in Heterocyclic Chemistry", Vol.1, ed. A.R. Katrizky, Academic press New York and London, 1963, pp. 223-228.

56. A.Dornow, W. Abele and H. Manzel, Chem.Ber., 1964, 97, 2179.

57. A. Dornow, H. Menzel and P. Marx, Chem.Ber., 1964, 97, 2185.

58. B. Kichhofen, Arch.Pharm., 1955, 288, 473.

59. G. Morgan and J. Stewart, J. Chem.Soc., 1938, 1292.

60. F. Krohnke and W. Zecher, Chem.Ber., 1962, 95, 1128.

61. J. Mandereu, P. Reynaud, and R.C. Moreau, Compt. rend., 1963, 257, 3434.

62. C.W. Noel and R.K. Robins, J. Heterocyclic Chem. 1964, 1, 34.

63. A.E. Tschitschibabin, Chem. Ber., 1925, 58, 1704.

64. A.E. Tschitschibabin, Chem.Ber., 1926, 59, 2048.

65. D. Djerassi and G. Pettit, J. Amer.Chem.Soc., 1954, 76, 4470.

66. F. Krönke, B. Kickhöffen and C. Thoma, Chem.Ber., 1955, 88 1117.

67. R. Adams and J.S. Dix, J.Amer.Chem.Soc., 1958, 80, 4618.

68. R. Fusco and S. Rossi, Rend. ist. lombardo. sci. Pt.1. Classe Sci. mat e nat. 1955, 88, 173.

69. W. Mosby "Systems with bridgehead nitrogen" Part II, Interscience Publishers, New York, 1961, pp.903-905.

70. A. Mustafa and A.E.A.A. Hassan, J.Amer.Chem.Soc., 1967, 79, 3846.

71. C. Ainsworth and R.G. Jones, J.Amer.Chem.Soc., 1954, 76, 3172.

72. R.G. Jones and M.J. Mann, J.Amer.Chem.Soc., 1953, 75, 4048.

73. E. Koenigs and J. Freund, Chem.Ber., 1974, 80, 143.

74. W. Baker, J.B. Harborne and W.D. Ollis, J.Chem.Soc., 1952, 1303.

75. E.J. Browne, E.E. Nunn and J.B. Polya, J.Chem.Soc., 1967, 79, 3846.

76. B.Jägersten, Arkiv Kemi., 1969, 30, 261.

77. D.W. Dunwell and D. Evans, J.Chem.Soc (C)., 1971, 1615.

78. B. Kickhöffen and F. Kröhnke, Chem.Ber., 1955, 88, 1109.

79. M. Meerwein Org. Synth., 1966, 46, 113.

80. A.R. Katritzky and A.P. Ambler "Physical methods in Heterocyclic Chemistry" Vol. II ed. A.R. Katritzky, Academic Press, New York, 1963, p.323.

81. J. Pitha, P. Fiedler and J. Gut, Coll. Czech. Chem. Comm., 1966, 31, 1864.

82. A.R. Katritzky, Chimia (Switz.), 1970, 24, 134.

83. D.W. Davis, Trans. Farad. Soc., 1955, 51, 449.

84. G.C. Levy and G.L. Nelson "Carbon-13 Nuclear Magnetic resonance for organic chemists" ed. Wiley, Interscience publishers, New York 1972, p.120.

85. J.B. Slothers "Carbon-13 NMR spectroscopy" Vol. 24, Academic Press, New York 1972 p.150.

86. F. Asinger, W. Leuchtenberger and V. Gerber, Monatsh., 1974, 105, 38.

87. T. Novison, T. Okabe, R.K. Robins and T.R. Matthews, J.Med. Chem., 1976, 19 (No. 4), 517.

88. M. Kocevar, D. Kolman, H. Krajne, S. Polanc, B. Porovne, B. Stanovnik, and M. Tisler, Tetrahedron, 1976, 32, 725.

89. M.V. Poustyanoi, M.A. Klykov, N.M. Gorban and P.M. Kochergin, Khim. Geterotsikl Soedin., 1979, (No. 11), 1540-1542).

89a. M.V. Povstyanoi, M.A. Klykov, N.M. Gorban and P.M. Kochergin, Khim. Geterotsikl Soedin., 1975, 855; Chem. Abs., 1975, 83, 206189r.

90. Y.F. Shealy, R.F. Struck, L.B. Holum and J.A. Montgomery, J. Org. Chem., 1961, 26, 2396.

91. Brit., 955, 353.

92. G. Ferrari and C. Casagrande, Farmaco. Ed.Sci., 1962, 17, 611.

93. U.M. Teotino, L.P. Friz, A. Gandini and D.D. Bella, Farmaco. Ed. Sci., 1962, 17, 988.

94. Belg., 955, 353.

95. R.W. Clarke, S.C. Garside, L. Lunts, D. Hartley, R. Hornby and and A.W Oxford, J.C.S. Perkin 1, 1979, 1120.

96. J.A. Montgomery, Progr. Medicin. Chem., 1970, 7 (Pt. 1), 69.

97. Y.F. Shealy, C.A. Krauth and J.A. Montgomery, J. Org. Chem., 1962, 27, 2150.

98. I. Yamamoto, Biochem.Pharmacol., 1969, 18, 955.

99. P.P. Saunders and G.A. Schultz, Biochem. Pharmacol., 1970, 19, 911.

100. E. Shaw and D. Wooley, Biochem. J., 1951, 189, 401.

101. E. Shaw and D. Wooley, Biochem. J.,1952, 194, 641.

102. J. Buckingham, Quart. Rev., 1969, 23, 37.

103. F. Ramirez and A.F. Kirby, J. Amer.Chem.Soc., 1953, 75, 6026.

104. F. Ramirez and A.F. Kirby, J. Amer.Chem.Soc., 1954, 76, 1037.

105. R. Wiley and C.H. Jarboe, J.Amer.Chem.Soc., 1955, 77, 403

106. V.P. Chacko, K.C. Kalia and A. Chakravorty, J. Indian Chem. Soc., 1975, 13, 41.

107. M.S.S. Siddiqui and M.F.G. Stevens, J.C.S. Perkin 1, 1974, 2482.

108. H.C. Yao and P. Resnick, J. Amer.Chem.Soc., 1962, 84, 3514.

109. C.G. McCarty in "The Chemistry of the Carbon-Nitrogen Double Bond", ed. S. Patai, Interscience Publishers, London, 1970, pp. 343-464.

110. H. Katsuki, C. Tanegashima, M.Tokushige and S.Tanaka, Bull.Chem.Soc.Japan, 1972, 45 (3) 813).

111. E.J. Gray, M.F.G. Stevens, G. Tennant and R.J.S. Vevers, J.C.S. Perkin 1, 1976, 1496.

112. G. Tennant and R.J.S. Vevers. J.C.S. Perkin 1, 1976, 421.

113. G.R. Bedford, F.C. Cooper, M.W. Partridge and M.F.G. Stevens, J.Chem.Soc., 1963, 5901.

114. D. Fortuna, B. Stanovnik and M. Tisler, J.Org.Chem., 1974, 39, 1833.

115. R. Allmann, T.Debaerdemaeker, W. Grahn and C. Reichardt, Chem.Ber., 1974, 107, 1555.

116. M.W. Partridge and M.F.G. Stevens, J.Chem.Soc. (C), 1966, 1127.

117. J. Slouka, V. Bekarek and J. Kubata Monatsh., 1974, 105, 535.

118. H. Reimlinger, A. Van. Overstraeten, and H.G. Viehe, Chem.Ber., 1961, 94, 1036.

118. H. Reimlinger, A. van. Overstraeten, and H.G. Viehe, Chem.Ber., 1961, 94, 1036.

119. H. Reimlinger and A. van Overstraeten, Chem.Ber., 1966, 99, 3350.

120. H. Mackie and G. Tennant, Tetrahedron, 1972, 4719.

121. M.F.G. Stevens, unpublished results.

122. J.M. Hearn, R.A. Morton and J.C.E. SImpson, J. Chem.Soc., 1959, 3318.

123. C. Temple, Jr, R.L. McKee and J.A. Montgomery, J.Org.Chem., 1965, 30, 829.

124. R.K. Robins, F.W. Furcht, A.D. Grauer and J.W. Jones, J.Amer. Chem.Soc., 1956, 78, 2418.

125. C.W. Noell and C.C. Cheng, J. Medicin.Chem., 1971, 14, 1245.

126. C.W. Noell and C.C. Cheng, J. Medicin. Chem., 1969, 12, 545.

127. C.C. Cheng, R.K. Robins, K.C. Cheng and D.C. Lin, J.Pharm.Sci., 1968, 57, 1044.

128. H. Neunhoeffer, H.W. Fraühauf, H. Hennig and M. Mutlerer, Tetrahedron, 1969, 3147.

129. H. Neunhoeffer and H. Hennig, Chem.Ber., 1968, 101, 3952.

130. H. Neunhoeffer and F. Weisehedel, Annalen, 1971, 749, 16.

131. H. Neunhoeffer and H.W. Fraühauf, Annalen, 1972, 760, 102.

132. H. Neunhoeffer and G. Frey, Annalen, 1973, 1963.

133. A.E. Siegrist, Helv.Chim.Acta., 1967, 50, 906.

134. S.F. Mason, J.Chem.Soc., 1959, 1247.

135. S.F. Mason, J.Chem.Soc., 1959, 1240.

136. C.M. Atkinson and H.D. Cossey, J.Chem.Soc., 1962, 1805.

137. T.K. Sevastynova and L.B. Volodarskii, Khim. Geterotsikl Soedin., 1973, 134.

138. A. MacColl, J.Chem.Soc., 1946, 670.

139. E.C. Taylor and A. McKillop "The Chemistry of cyclic Enamino-nitriles and o.aminonitriles", Interscience Publishers, New York, 1970, p.270.

140. E.C. Taylor and A. McKillop "The Chemistry of cyclic Enamino-nitriles and o-aminonitriles", Interscience Publishers, New York, 1970, p.272.

141. E.C. Taylor, R.J. Knopf, R.F. Meyer, A. Holmes and M.L. Hoefle, J.Amer.Chem.Soc., 1960, 82, 5711.

142. H. Graboyes, G.E. Jaffe, I.J. Pachter, J.P. Rosenbloom, A.J. Villani, J.W. Wilson and J. Weinstock, J. Medicin.Chem., 1968, 11, 568.

143. R.J. Schnitzer and F. Hawking "Experimental Chemotherapy" Vol. IV, Pt.1, Academic Press, New York, 1966.

144. L.F. Larino "Cancer Chemotherapy", Pergamon Press, Oxford, 1965.

145. M.W. Partridge and M.F.G. Stevens, J.Chem.Soc. (C), 1967, 1828.

146. F.A. Snavely, W.S. Trahanovsky and F.H. Suydam, J.Org.Chem., 1962, 27, 994.