The synthesis and reactivity of 6- and 8-azaindolizines.

SHAND, C.A.

1977

The

SYNTHESES and REACTIVITY

of

6- and 8-AZAINDOLIZINES

by

CHARLES ALEXANDER SHAND

A thesis presented in part fulfilment of the requirements for the degree of Doctor of Philosophy of the Council for National Academic Awards.

ROBERT GORDON'S INSTITUTE OF TECHNOLOGY

MAY 1977

ACKNOWLEDGEMENTS

I wish to record my sincere appreciation for the guidance and help given to me by my research supervisors, Dr. M. Fraser and Dr. R. Buchan, of Robert Gordon's Institute of Technology, and also by Dr. A. Murray of Dundee University in his capacity as external supervisor.

I would like to thank Dr. Youngson of the Institute for helpful discussions on the interpretation of infrared spectra, Dr. O.C. Musgrave of Aberdeen University for the use of hydrogenation apparatus, and Professor R.H. Thomson of Aberdeen University for his permission to attend post-graduate lectures and seminars.

Thanks are also due to the technical staff(s) of this Institute and of Aberdeen University, in particular to Mr. N. Faulkes for recording the 100 MHz NMR spectra.

I would like to express gratitude to the Directors of Robert Gordon's Institute of Technology, and to the past and present Heads of the Chemistry Department, Dr. M.B. Watson and Dr. C.N.C. Drey, for the opportunity to carry out this research, and for arranging financial support.

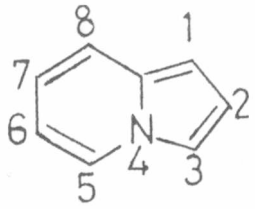
Last, but by no means least, I would like to thank Sheila, my wife, for typing this thesis and for her encouragement and help during all stages of this work.

C O N T E N T S

* * * *

NOMENCLATURE

The currently accepted Chemical Abstracts' names for the seven possible mono-aza derivatives of indolizine (1) are given below.



(1)

Azaindolizine	Chemical Abstracts' Name
1-Azaindolizine	Imidazo[1,2-a]pyridine
2- "	Imidazo[1,5-a]pyridine
3- "	Pyrazolo[1,5-a]pyridine
5- "	Pyrrolo[1,2-b]pyridazine
6- "	Pyrrolo[1,2-c]pyrimidine
7- "	Pyrrolo[1,2-a]pyrazine
8- "	Pyrrolo[1,2-a]pyrimidine

For simplicity, in this thesis these compounds will be named exclusively as azaindolizines and numbered as for indolizine(1).

SUMMARY

Synthetic routes leading to indolizine and its mono-aza derivatives and the reactivity of these systems have been briefly reviewed.

A number of simple alkyl, aryl, methoxy and chloro substituted 6- and 8- azaindolizines have been synthesised via the Chichibabin reaction between suitably substituted 2- or 4- methylpyrimidines and α-bromo ketones. The structures of the products obtained have been confirmed spectroscopically, principally by ^{1}H NMR spectroscopy, and by formylation procedures. The reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide has been shown to yield a 6-azaindolizine structure rather than an 8-azaindolizine structure as previously reported. The reaction between 2-methylpyrimidine and ethyl bromopyruvate gave 2-carbethoxy-8-azaindolizine which on hydrolysis and decarboxylation gave the parent 8-azaindolizine system.

Formylation of 6-azaindolizines bearing a C-5 methyl group gave along with their formyl derivatives, 5-azacycl[3,2,2]azine structures which were also synthesised by 1,3-dipolar addition reactions between dimethyl acetylenedicarboxylate and 6- or 8- azaindolizines.

An examination of the ^{1}H NMR spectra of 6- and 8- azaindolizines in trifluoroacetic acid showed both systems to have a preference for protonation at their non-bridgehead nitrogen atoms, although partial carbon protonation at C-3 was observed in a number of alkyl derivatives. The protonation of 6- and 8- azaindolizinones and 5-azacycl[3,2,2]azines was also investigated. Formylation of 6- and 8- azaindolizines occurred preferentially at C-3 and then at C-1. A number of other electrophilic substitution reactions on 2,7-dimethyl-8-azaindolizine also occurred at C-3. Nucleophilic replacement of chlorine by methoxide from a 5-chloro-6-azaindolizine and a 7-chloro-8-azaindolizine occurred readily. Ammonolysis and hydrolysis were however only successful in the case of the for-

mer compound. These experimentally determined sites of reactivity in 6- and 8- azaindolizines are in accord with those predicted from reported π-electron density calculations.

Formylation of 5-amino-7-methyl-2-phenyl-6-azaindolizine gave a 4,5-diazacycl[3,2,2]azine structure and refluxing a solution of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one in phosphoryl chloride gave a peri-condensed di(6-azaindolizino)pyrazine.

CHAPTER I

Introduction

This Chapter is a summary of the reported methods of syntheses and reactions of indolizine and its seven mono-aza derivatives. The reactions discussed include protonation, electrophilic and nucleophilic substitution, and addition type reactions.

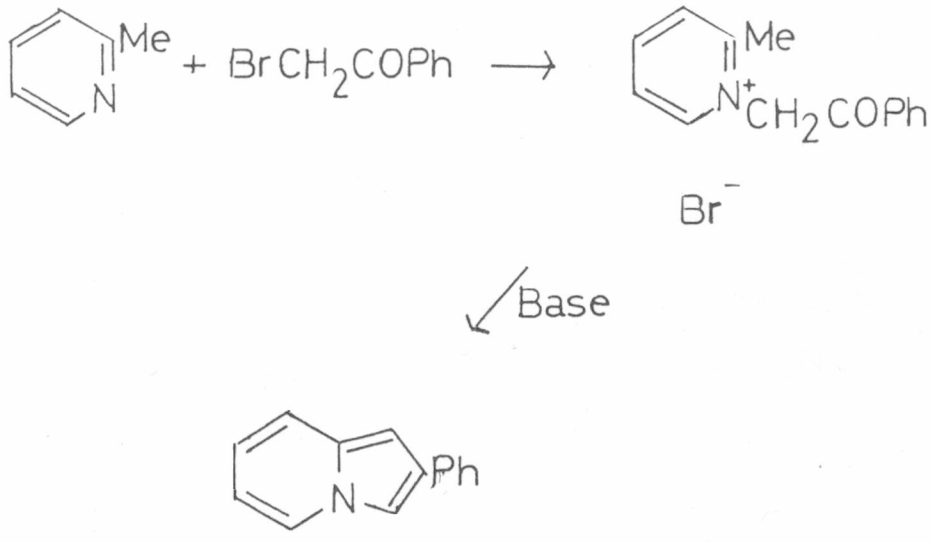
Synthesis of indolizines

The chemistry of indolizine has been reviewed by Borrows and Holland[1] (1948), by Mosby[2] (1961), and recently by Prostakov and Baktibaev[3] (1975).

The synthetic methods employed in the synthesis of the indolizine nucleus may be classified under four general headings.

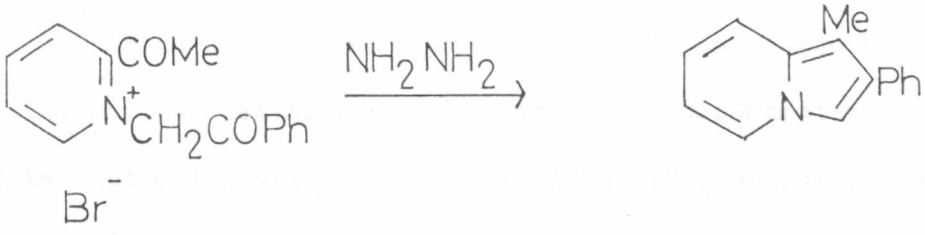
1. By cyclisation of pyridinium salts

(a) The majority of the simple alkyl and aryl derivatives of indolizine have been synthesised by the Chichibabin method[4], in which an α-methyl or α-methylene pyridine is quaternised with an α-halocarbonyl compound and the resulting quaternary salt cyclised with base. An example[5] is shown below.

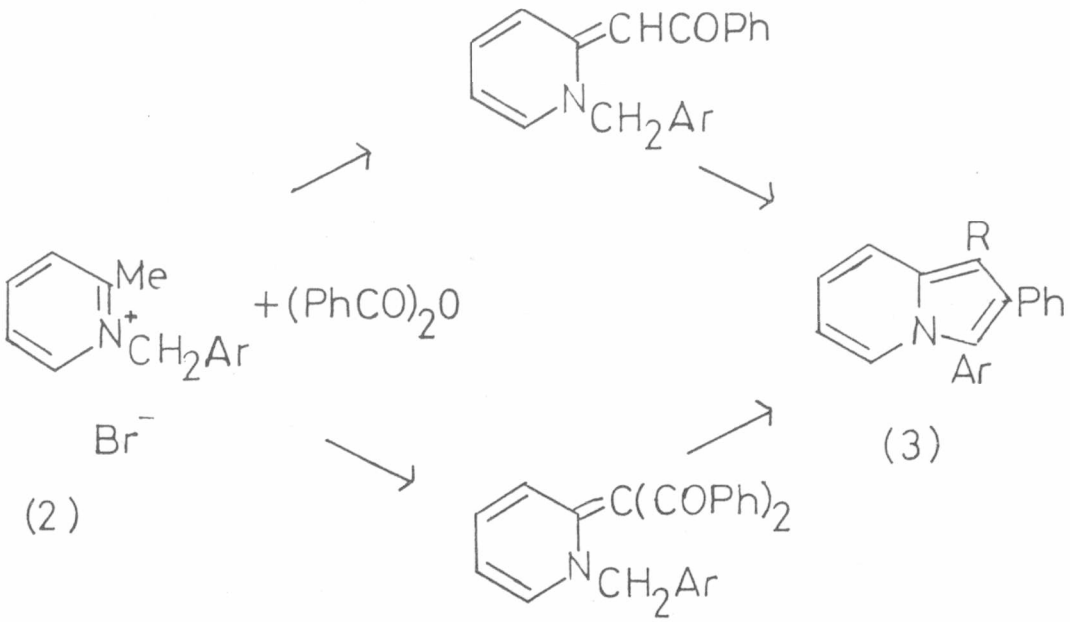


High yields of 2-alkyl and particularly 2-aryl derivatives have been obtained. α-Picoline and bromoacetaldehyde gives only 1% of indolizine itself but the parent base may be conveniently obtained from indolizine-2-carboxylic acid ester, itself prepared in 30% yield from the Chichibabin reaction between α-picoline and ethyl bromopyruvate[6]. The initial quaternisation in such Chichibabin reactions can be carried out in a variety of solvents[7]. Cyclisation is best achieved with aqueous bicarbonate and optimum yields are obtained with bromo rather than chloro carbonyl compounds[8] and when the halogen and carbonyl functions are unhindered[9]. The Chichibabin reaction has been extended to the preparation of indolizines containing aminoalkyl, carboxylic acid, cyano, ethoxy, hydroxy, nitro, nitroso and phenoxy substituents[3].

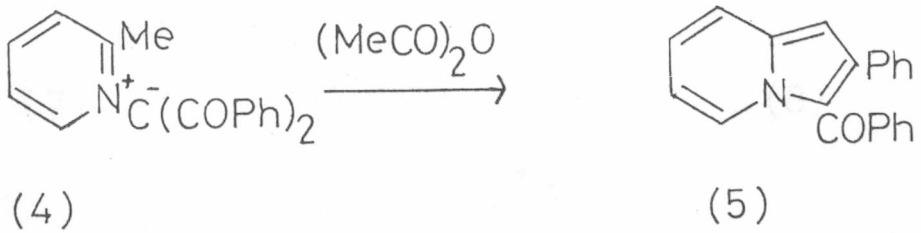
(b) A number of 1,2-disubstituted indolizines have been obtained by reacting 2-acyl-1-(β-oxoalkyl) pyridinium salts with hydrazine hydrate[10].



(c) 1,2-Disubstituted and 1,2,3-trisubstituted indolizines may be obtained by cyclisation of 2-alkyl-1-benzyl pyridinium salts by heating them with acid anhydrides. Thus the bromide (2), on heating with benzoic anhydride in the presence of triethylamine, gives (3)[11].



(d) Ylids, which are internal quaternary salts, may also be cyclised to indolizines. For example 2-methylpyridinium dibenzmethylid (4) on heating in acetic anhydride for a short time gives 3-benzoyl-2-phenyl-indolizine (5) as the main product [11,12].



(4) (5)

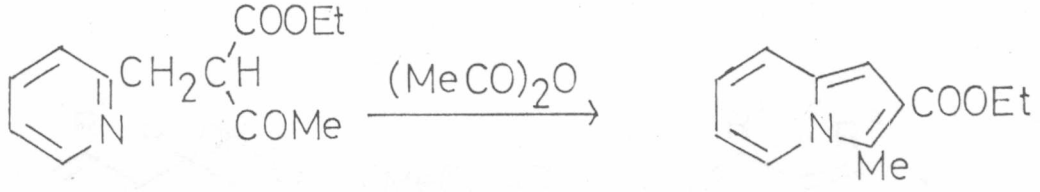
2. By cyclisation of 2-substituted pyridines

The common feature of this method is that the indolizines are formed by an intramolecular nucleophilic attack of the pyridine nitrogen on the δ-carbon atom of suitable side chains at C-2 and is illustrated by the following examples.

(a) An important example leading to indolizine itself in yields of up to 50% is the cyclisation of 3-(2-pyridyl)-1-propanol (6)[13,14,15].

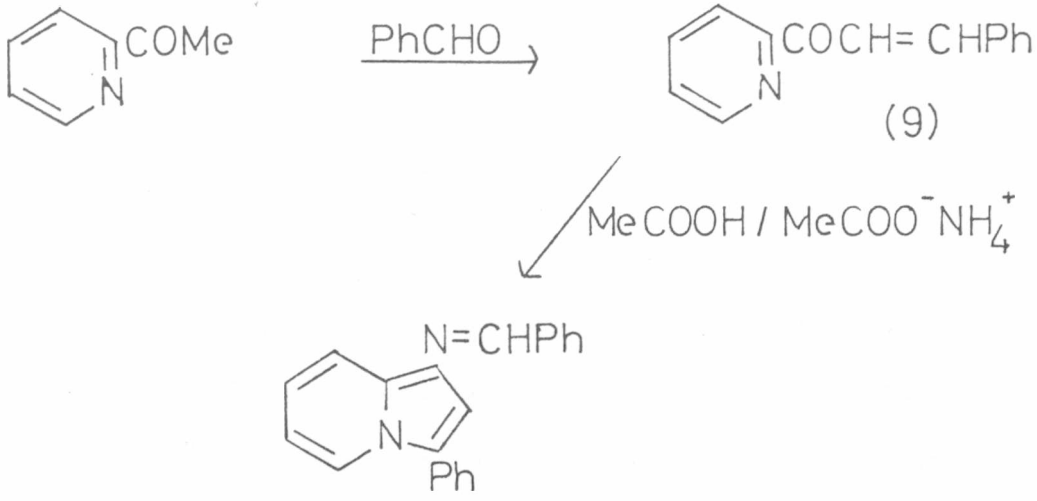
(6)

(b) 2-(γ-Oxoalkyl)pyridines may also be cyclised to indolizines. For example, compound (7) cyclises in acetic anhydride to 2-carbethoxy-3-methyl-indolizine (8). In this case cyclisation occurs via the more reactive ketone carbonyl function[16].



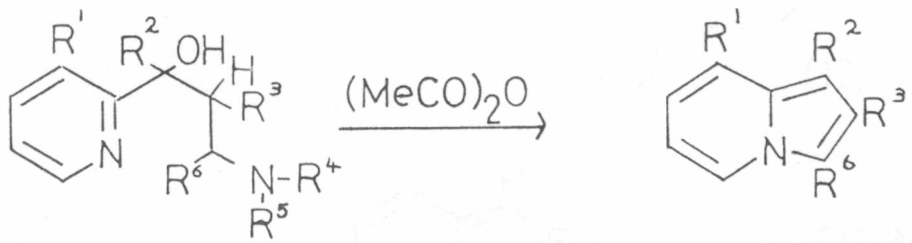
(7) (8)

(c) Cyclisation in this type of reaction is not restricted to side chains containing γ-hydroxy or γ-oxo functions. For example, the 2-cinnamoylpyridine (9) cyclises in an acetic acid/ammonium acetate mixture to give the azomethine (10). The azomethine function results from the reaction of the initially formed 1-hydroxy derivative with ammonia and then benzaldehyde[17].



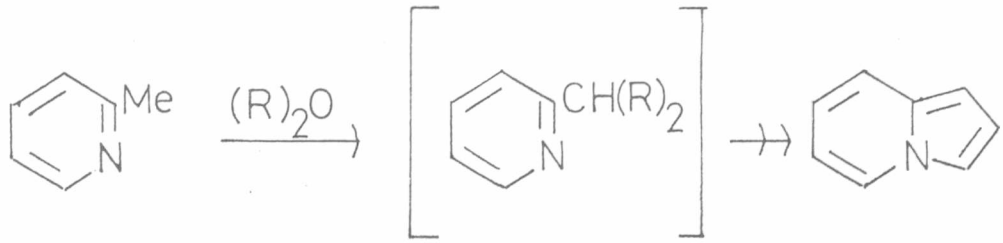
(10)

(d) 2-Lithiopyridines react with β-dialkylaminoketones to form amino alcohols (11) which may be converted in 60% yield to indolizines by heating in acetic anhydride[18, 19].



(11)

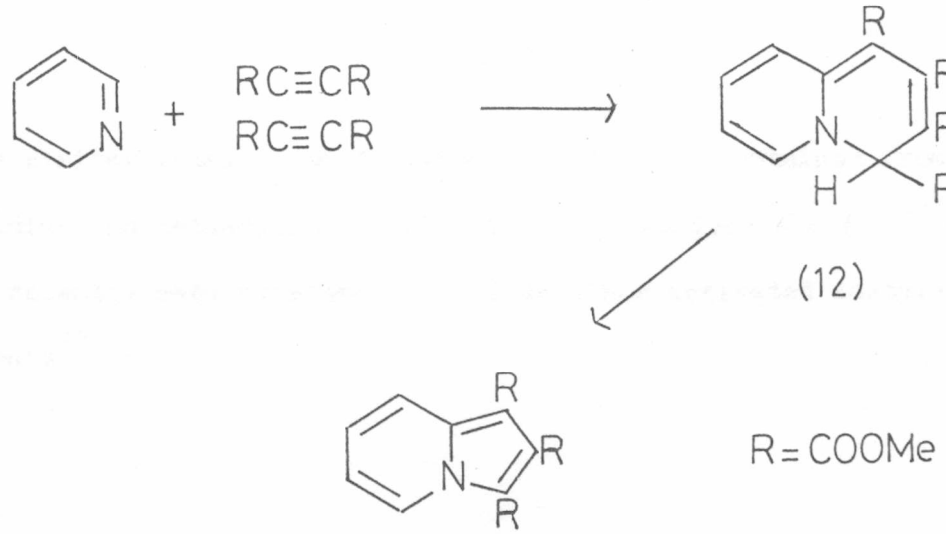
(e) The first reported synthesis of indolizine, by Scholtz[20], was from α-picoline and acetic anhydride. The mechanism of this reaction has been investigated and the intermediate shown below proposed[3].



R = MeCO

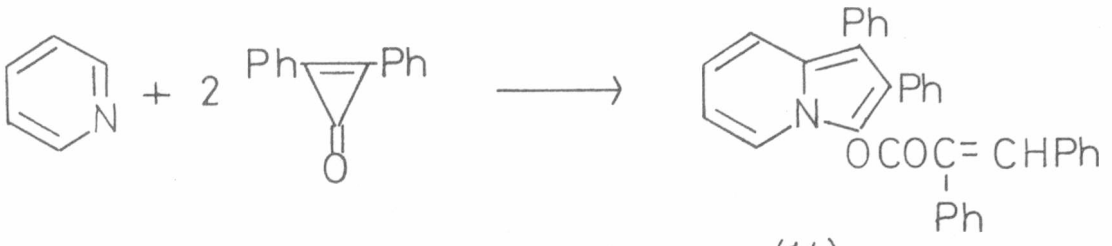
3. By addition reactions

(a) The structures of the products formed by reaction of pyridine and dimethyl acetylenedicarboxylate have received much attention[21,22]. One of these products (12), is converted readily to the trimethyl ester (13), either by treatment with bromine and subsequent hydrolysis of the product, or by oxidation with dilute nitric or chromic acids, or alternatively by irradiation with ultraviolet light.



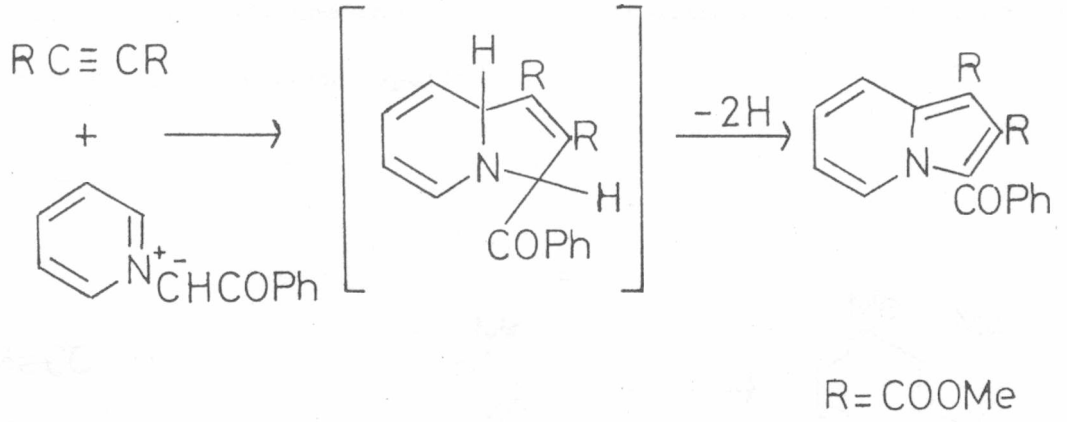
(13)

(b) Pyridine also reacts with two molar equivalents of diphenylcyclopropenone to give (14)[23].

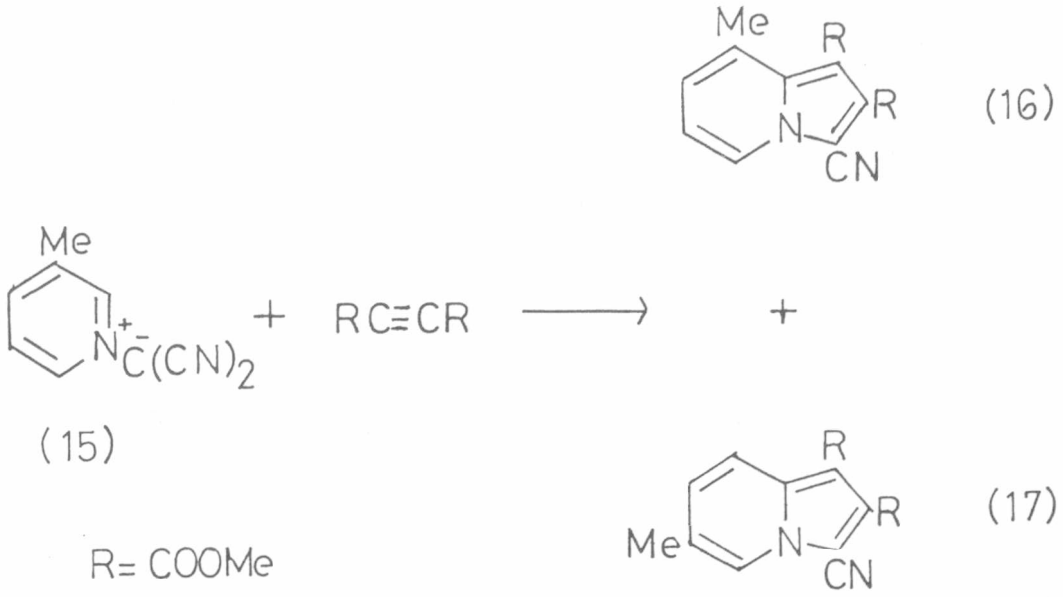


(14)

(c) Pyridinium phenacylid on reaction with acetylenic compounds such as dimethyl acetylenedicarboxylate, gives indolizines[24].

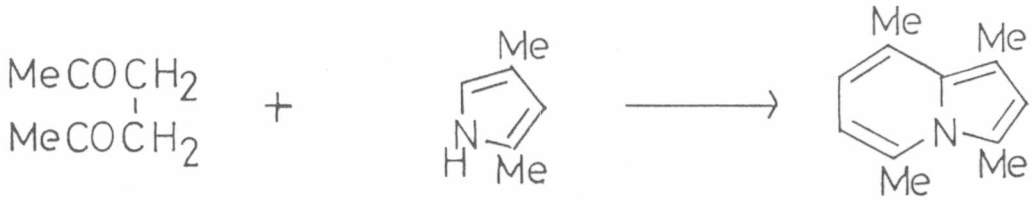


In a similar fashion the dicyanomethylid (15) obtained from 3-methylpyridine and tetracyanoethylene oxide[25] gives (16) and (17)[26]: this method has recently been extended to include other activated acetylenes and allenes[27].



4. From pyrroles

The tetramethylindolizine (18) has been obtained from 2,4-dimethylpyrrole and acetonylacetone[28]: few other examples of indolizines prepared by this route have been reported.



(18)

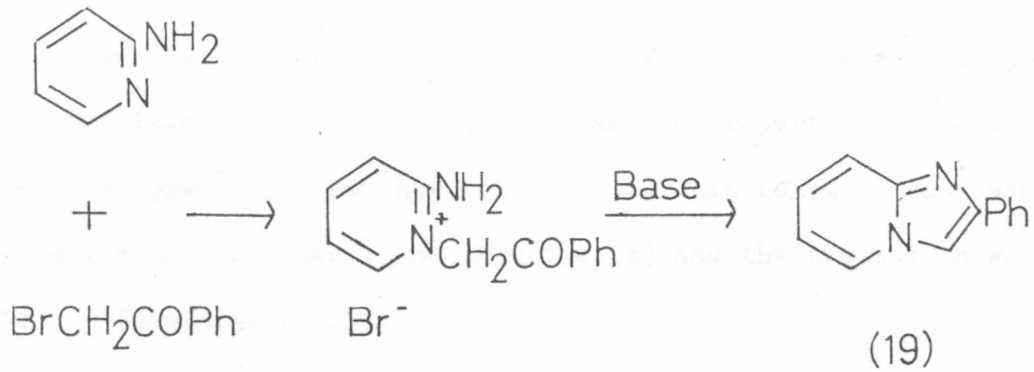
Synthesis of azaindolizines

The chemistry of azaindolizines has been reviewed by Mosby[2](1961), and updated in the cases of 6- and 8-azaindolizines by Amarnath and Madhav[29](1974). The brief review which follows deals primarily with 6- and 8-azaindolizines and in these cases additionally includes reference to their hydrogenated derivatives. The synthetic methods used resemble those leading to indolizines and are therefore classified under similar headings.

1. By cyclisation of pyridinium salts and aza analogues

1-,3-,5- and 6- azaindolizines may be obtained by this route.

(a) The Chichibabin reaction[30] between 2-aminopyridines and α-halocarbonyl compounds leads to 1-azaindolizines and is an important route to this system. In the particular example shown below, conclusive evidence for the 2-substituted structure (19) produced via quaternisation at the tertiary ring nitrogen, rather than a 3-substituted structure via quaternisation at the amino substituent, has been obtained[31]. Yields are generally good and is quantitative[32] in the example shown.

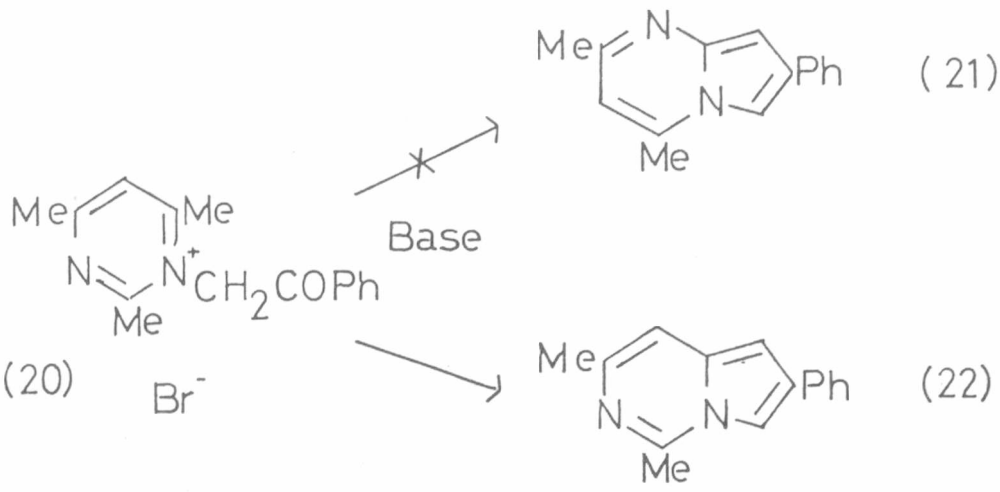


(19)

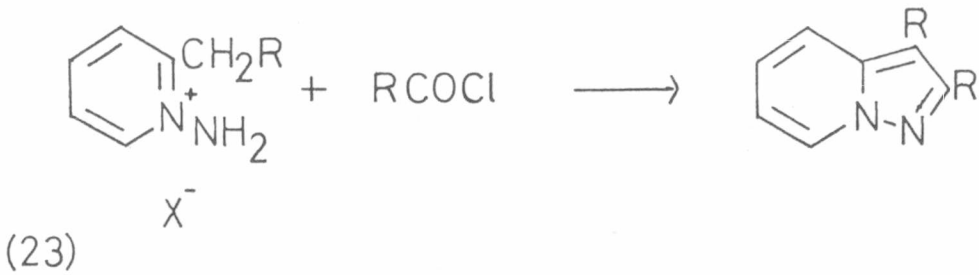
A similar reaction with 3,6-dimethylpyridazines leads to 5-azaindolizines[33, 34].

The Chichibabin reaction is also an important route to 6-azaindolizines. Thus 4,6-dimethylpyrimidine or 4-methyl-6-phenylpyrimidine reacts with α-haloketones to give 2,7-disubstituted-6-azaindolizines. In the latter case the bulky phenyl group directs quaternisation to occur at the least sterically hindered nitrogen[35, 36].

Cyclisation of the quaternary product (20) formed between 2,4,6-trimethylpyrimidine and phenacyl bromide has been reported by Ochiai and Yanai[37] to give the 8-azaindolizine (21). This reaction has been reinvestigated (see Chapter II of this thesis) and the product shown to be the 6-azaindolzine (22).

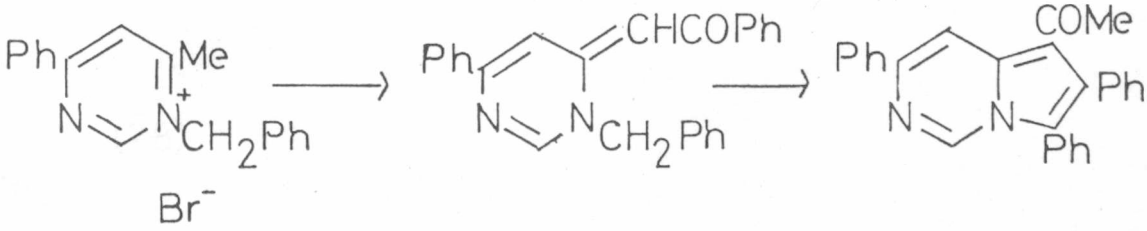


(b) 2-Alkyl-1-aminopyridinium salts (23), prepared from the corresponding alkyl pyridine and hydroxylamine-O-sulphonic acid, on reacting with acyl chlorides give 3-azaindolizines[38].



(23)

(c) Simultaneous benzoylation and dehalogenation of the quaternary bromide (24) gives (25), which on heating with acetic anhydride gives the 6-azaindolizine (26).



(24) (25) (26)

Expectations that this reaction would provide a general route to 6-azaindolizines were not realised due to difficulties at the quaternisation stage[36,39].

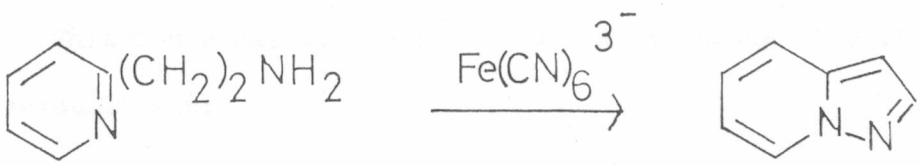
2. By cyclisation of 2-substituted pyridines and aza analogues

The essential features of this method are as previously described for indolizine. This route has been used to prepare 2-, 3- and 6-azaindolizines.

(a) Cyclisation of 2-(1'-acylamino)alkypyridines (27) using phosphoryl chloride gives 2-azaindolizine and its derivatives[40].

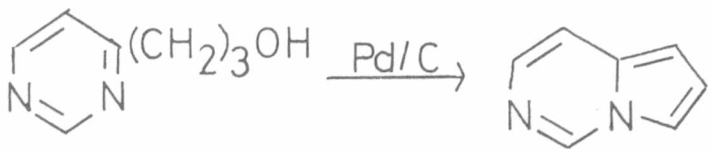
(27)

(b) Ferricyanide oxidation of 2-(2'-aminoethyl)pyridines (28) gives 3-azaindolizine and its derivatives[41].

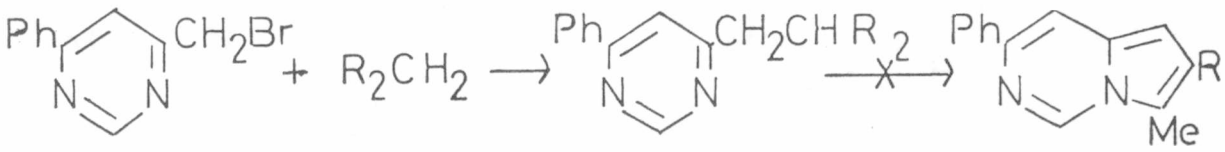


(28)

(c) Cyclisation of 3-(4-pyrimidyl)-1-propanol gives 6-azaindolizine in 5% yield[15].



Attempts to prepare substituted 6-azaindolizines, for example (31), by cyclisation of (30) failed[36]. Difficulties were also experienced at the earlier stage due to self-quaternisation of the bromide (29).



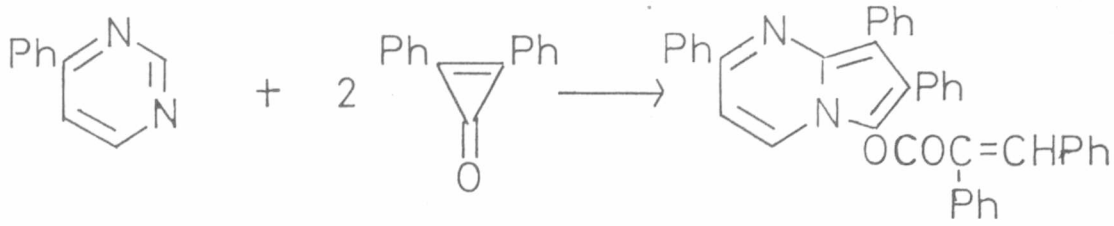
(29) (30) (31)

R = COMe

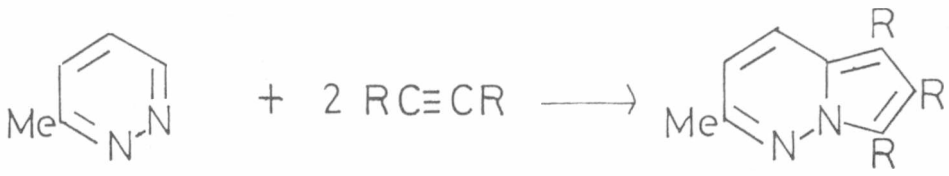
3. By addition reactions

This route has been applied to the syntheses of 3-, 5-, 7- and 8-azaindolizines.

(a) Pyridazines, pyrimidines and pyrazines react with diphenylcyclopropenone to give 1,2,3-trisubstituted 5-, 7-, and 8-azaindolizines[23]. The last case is illustrated below.

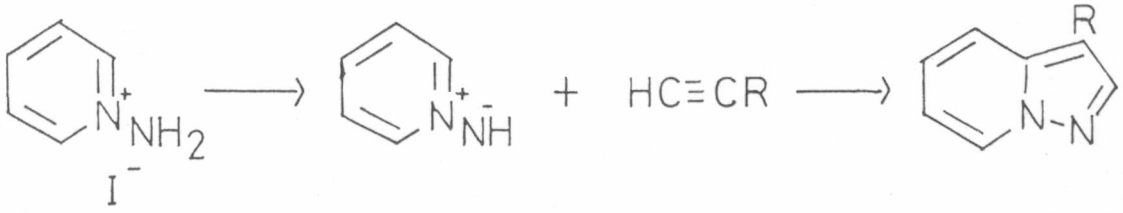


Pyridazines and pyrazines also react with dimethyl acetylenedicarboxylate to give the tricarboxylic acid esters of 5- and 7- azaindolizines[42,43].



R= COOMe

(b) Pyridinium and pyridazinium ylids react with activated acetylenes to give 3- and 5-azaindolizines[27,44,45]. For example, the ylid (32) derived from 1-aminopyridinium iodide reacts with ethyl propiolate to give (33).



(32) (33)

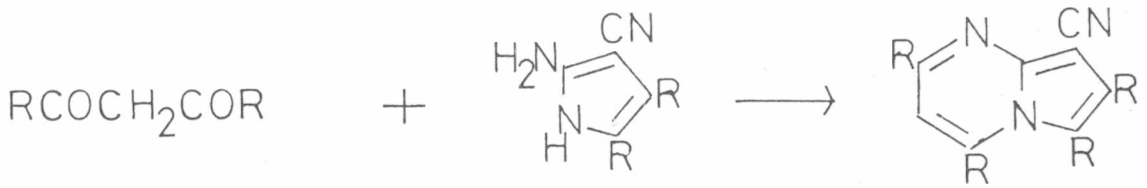
R= COOEt

One example of the synthesis of an 8-azaindolizine has also been recorded by this method: thus the 1-dicyanomethylid derived from 4-methoxypyrimidine reacts with dimethyl acetylenedicarboxylate to give 3-cyano-1,2-dicarbmethoxy-7-methoxy-8-azaindolizine[46].

4. From pyrroles

In contrast to their limited use in the synthesis of indolizines, pyrroles find general application in the synthesis of azaindolizines in which the additional nitrogen is in the six-membered ring.

(a) For example β-dicarbonyl compounds react with 1-aminopyrroles to give 5-azaindolizines[47-49], and with 2-aminopyrroles containing stabilising 3-cyano groups, to give 8-azaindolizines[50]. An example of the latter is shown below.

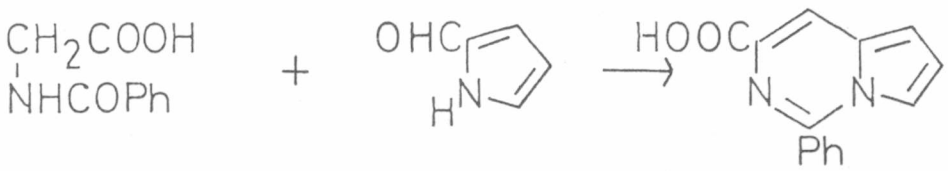


A number of hydrogenated 8-azaindolizines have also been prepared from 2-amino-1-pyrroline[51-54].

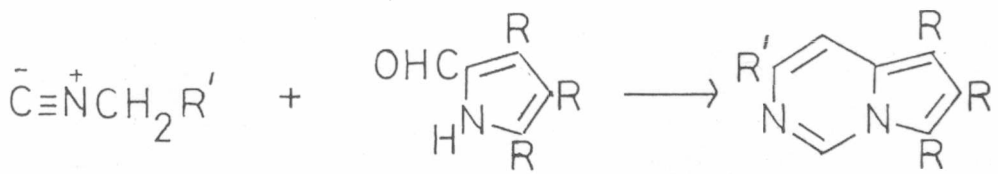
2-Amino-3-cyanopyrroles react with ring substituted phenacyl bromides to give products such as (34) which with strong base cyclise by a bimolecular process to yield highly substituted 8-azaindolizines[55].

(34)

(b) 2-Acylpyrroles give 6- and 7-azaindolizines. The example shown below is that of the first synthesised 6-azaindolizine[56].

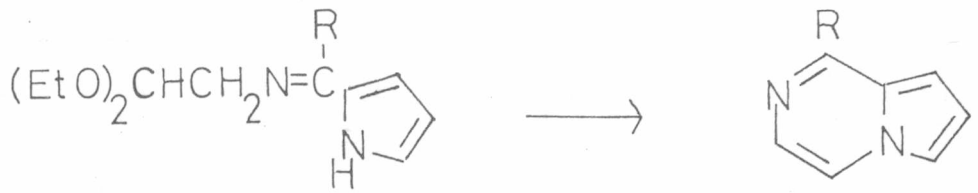


More recently a number of 6-azaindolizine-7-carboxylic acid esters have been obtained from 2-formylpyrroles and methyl isocyanoacetate[57].



R′ = COOMe

Alkylation of the sodium derivatives of 2-acylpyrroles with α-bromo-carbonyl compounds, followed by reaction with ammonium acetate in acetic acid gives 7-azaindolizines[58]. Similarly, 2-acylpyrroles on reaction with diethylaminoacetal gives compounds such as (35) which have been cyclised to 7-azaindolizines by heating in a polyphosphoric acid/phosphoryl chloride mixture as illustrated below[59].



(35)

Reactivity of Indolizine and its Aza-derivatives

Indolizine and its aza-derivatives are heteroaromatic, π-excessive systems. Theoretical π-electron densities[60-63,65-67] (Table I), frontier electron densities[64-67] (Table II), bond orders[60,62] and atom localisation energies[14] have been calculated.

TABLE I

π-Electron Densities[62]

Compound	1	2	3	4	5	6	7	8	9
Indolizine	1.134	1.016	1.238	1.387	1.120	0.981	1.049	0.949	1.124
1-Aza	1.360	0.885	1.277	1.372	1.109	0.991	1.024	0.966	1.015
2-Aza	0.994	1.257	1.099	1.397	1.133	0.963	1.065	0.929	1.162
3-Aza	1.193	0.863	1.476	1.338	1.076	1.006	1.011	0.981	1.055
5-Aza	1.111	1.040	1.193	1.342	1.400	0.779	1.121	0.852	1.160
6-Aza	1.145	0.996	1.251	1.409	0.928	1.246	0.927	1.015	1.083
7-Aza	1.109	1.029	1.212	1.365	1.186	0.863	1.302	0.769	1.164
8-Aza	1.154	0.994	1.263	1.406	1.025	1.045	0.858	1.228	1.027

TABLE II

Frontier Electron Densities

Compound	1	2	3	4	5	6	7	8	9
Indolizine[64]	0.454	0.031	0.527	0.033	0.289	0.141	0.191	0.218	0.086
1-Aza[65]	0.592	0.052	0.508	0.003	0.315	0.074	0.186	0.228	0.042
3-Aza[66]	0.46	0.02	0.61	0.01	0.33	0.10	0.18	0.26	0.04
5-Aza[67]	0.234	0.005	0.264	0.023	0.173	0.009	0.148	0.068	0.076
7-Aza[66]	0.45	0.00	0.46	0.04	0.35	0.17	0.30	0.13	0.10

Assuming a correlation between π-electron density and ease of electrophilic attack, electrophilic attack may be expected to occur preferentially at the non-bridgehead nitrogens, or at ring positions-3 or-1, and electrophilic substitution at C-3 or C-1. Electrophilic attack at the bridge-

head nitrogen is not considered as this would be expected to result in considerable distortion[68] of the molecule and loss of resonance energy. Frontier electron densities, where available, also support these predictions. In addition it has been pointed out that the species formed by attack of an electrophile at the 1- or 3- positions of indolizine are highly resonance stabilised since canonical forms containing 6π pyridinium rings can be drawn as shown[14].

E = Electrophile

Table I also indicates indolizine and its aza-derivatives to incorporate sites of electron deficiency although the degree of deficiency at these sites in azaindolizines is generally considerably greater than for indolizine. Indolizine and its aza-derivatives may therefore be expected to be vulnerable to nucleophilic attack and substitution.

The experimental results for indolizine and azaindolizines outlined below, are in good agreement with these predictions concerning the preferred sites of electrophilic attack and substitution. The reactivity of these systems towards nucleophiles has apparently received little attention.

1. Protonation

Protonation which is the simplest form of electrophilic attack occurs preferentially at C-3 for indolizines unsubstituted at this position; 3-alkyl substituted indolizines protonate at both C-1 and C-3[70-73]. Aza-indolzines with the additional nitrogen in the five membered ring protonate preferentially at the non-bridgehead nitrogen[34,72]. 5-Azaindolizines have

been shown to protonate at C-1, C-3 and N-5 depending on the substituents present and on the nature of the protonating media[34,74]. No systematic studies on the protonation patterns of 6-, 7- and 8- azaindolizines have been made.

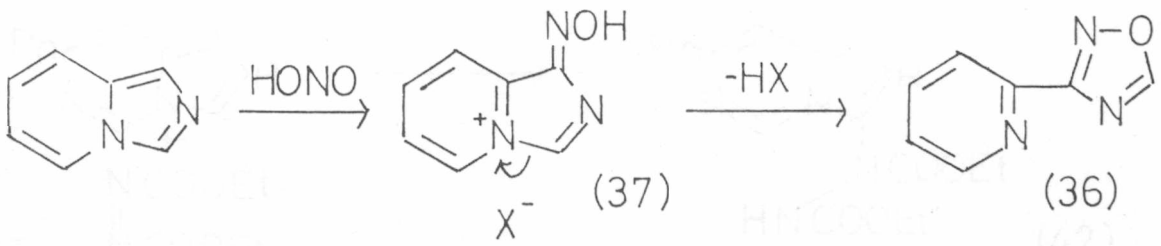
2. Electrophilic substitution

Little data is available for indolizine itself. However 2-methylindolizine has been shown to undergo a variety of electrophilic substitution reactions (e.g. alkylation, acetylation, azo-coupling, formylation and nitrosation) at C-3. Nitration is exceptional and occurs predominantly at C-1. In all of these reactions the use of more forcing conditions leads to 1,3-disubstituted products[3]. A summary of the most important electrophilic substitution reactions of azaindolizines is given below. Unless otherwise stated reference to a particular azaindolizine is to the unsubstituted system or to a simple derivative.

(a) Acylation 2- and 3- Azaindolizines acylate at C-1[40,75]. 5- and 6- Azaindolizines acylate at C-3[36,49].

(b) Formylation 1- and 6- Azaindolizines give 3-formyl derivatives[36,76,77]. The site of formylation of 2-azaindolizine is reagent dependent; with the Vilsmeier reagent, formylation occurs mainly at C-1, whereas with phenyllithium/dimethylformamide, formylation occurs at C-3[78]. 5-Azaindolizines with a methyl group at C-3, formylate at C-1[74].

(c) Nitrosation 1-, 5- and 6- azaindolizines give their respective 3-nitroso derivatives[36,49,76], whereas 3-azaindolizine gives a 1-nitroso derivative[75]. Attempted nitrosation of 2-azaindolizine gave 3-(2-pyridyl)-1,2,4-oxadiazole (36) thought to result from ring-opening of the intermediate (37)[79].



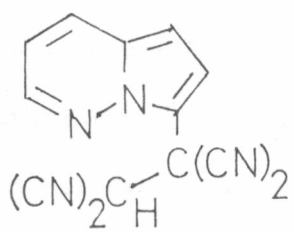
(37) (36)

(d) Nitration 1-Azaindolizine nitrates at C-3[80]. 3-Azaindolizine gives a 1-nitro or 1,8-dinitro derivative depending on reaction conditions[75,81]. 5-Azaindolizines give 1,3-dinitro derivatives[49].

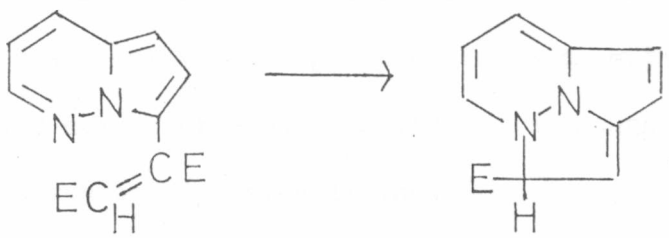
(e) Bromination Bromination of azaindolizines has been achieved using bromine, sodium hypobromite or N-bromosuccinimide and in some instances may occur via a free radical process. Thus bromination of 1-[65,80], 2-[82], 3-[66], 5-[49], 6-[36] and 7-[66] azaindolizines generally occurs at C-3 and/or C-1. In the cases of 1- and 5- azaindolizines bromination may additionally occur in their 6-membered rings at C-5 and C-7 respectively.

(f) Other electrophilic substitutions, and addition type reactions

The Mannich reaction[83] on 1-azaindolizine, and chloroformylation and diazonium coupling of 6-azaindolizines have been reported to occur at C-3[36]. Tetracyanoethylene and dimethyl acetylenedicarboxylate react with 5-azaindolizine at C-3 to give the addition products (38) and (39). The addition product (38) readily loses hydrogen cyanide to give a 3-vinyl derivative and the addition product (39) may be cyclised to (40) on heating with HCl[49]. 2,7-Disubstituted 6-azaindolizines similarly react with diethyl azodicarboxylate to give addition products such as (42)[36].

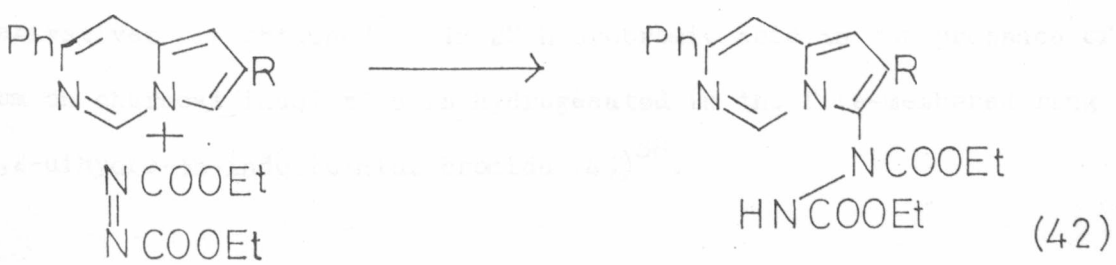


(38)



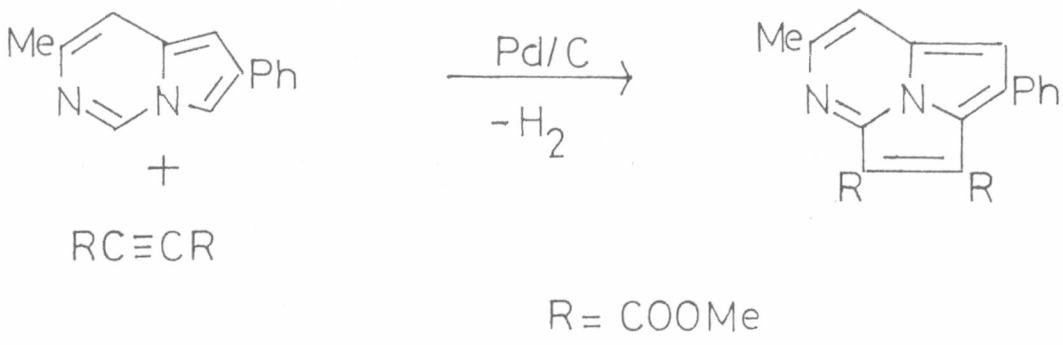
E=COOMe

(39) (40)



(42)

Like indolizine[14], 1-, 2- and 6- azaindolizines undergo 1,3-dipolar addition reactions with dimethyl acetylenedicarboxylate to give cycl[3,2,2]azines[35,84]. An example is shown below.



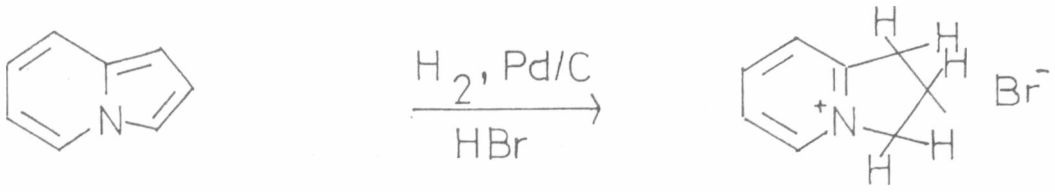
R= COOMe

3. Nucleophilic substitution

No successful nucleophilic substitution reactions on indolizine have been reported, even with sodamide[1], although the electron deficiency of the C-5 site has been demonstrated by the acidity of the methyl group in 5-methylindolizine[85]. 1-Azaindolizine is unique in that it is the only system in the mono-azaindolizine series to have been shown to undergo nucleophilic substitution reactions. Thus for example, the 5-chloro substituent in 5-chloro-[86] and hexachloro-1-azaindolizine[87] is substituted by a methoxy group on reaction with sodium methoxide and the 2-chloro substituent in 2-chloro-3-nitro-1-azaindolizine by a dimethylamino group on reaction with dimethylamine[80]. With piperidine, hexachloro-1-azaindolizine is thought to yield 5,7-dipiperidyl-2,3,6,8-tetrachloro-1-azaindolizine.

4. Redox reactions

Alkylindolizines may be selectively hydrogenated. With Raney nickel or Adams catalyst at room temperature, the six-membered ring is reduced to give 5,6,7,8-tetrahydro derivatives while at higher temperatures, octahydro derivatives are obtained[3]. In 2M hydrobromic acid in the presence of palladium on charcoal, indolizine is hydrogenated in the five-membered ring to give 1,2-dihydro-3H-indolizinium bromide (43)[88].



(43)

Little information in connection with the reduction of azaindolizines is available. Hydrogenation of 2-methyl-1-azaindolizine in acetic acid with a platinum catalyst gave a compound thought to be 5,6,7,8-tetrahydro-2-methyl-1-azaindolizine[89]. Similarly, sodium in liquid ammonia reduction of 3-azaindolizine has been reported to yield its 5,6,7,8-tetrahydro derivative[75]. 6-Azaindolizine is perhydrogenated in acid solution over a platinium catalyst[15], whereas in neutral conditions 2,7-dimethyl or 2,7-phenyl-3-nitro-6-azaindolizine may be reduced to 3-amino-2,7-dimethyl (or phenyl) -6-azaindolizine[90].

Alkylindolizines are susceptible to oxidation even by air[20,91]. Peracetic acid or hydrogen peroxide oxidation of indolizines gives picolinic acid N-oxide and its homologues[92]. Selective oxidation of the nitroso group in 1-nitroso-3-azaindolizine to a nitro group may be achieved in acetic acid with hydrogen peroxide[81] whereas with permanganate, 3-azaindolizines give pyrazole-3-carboxylic acids[75]. The presence of electron withdrawing substituents in the 5-membered ring of indolizines stabilises them towards oxidation. Thus indolizine-1,2,3-tricarboxylic acid resists oxidation even by nitric or chromic acids[92-94].

CHAPTER II

Syntheses of 6- and 8-azaindolizines

This chapter describes the syntheses of some methyl and phenyl substituted 6-azaindolizines, some methyl, phenyl and methoxy substituted 8-azaindolizines and of the parent 8-azaindolizine by the Chichibabin method. The structures of the products obtained were deduced mainly by ^{1}H NMR spectroscopy. Signal assignments were made on the basis of the relative proximity of the protons to nitrogen[95], with the aid of double resonance, by a comparison of related spectra and by deuterium exchange[34,71].

Synthesis of 6-azaindolizines

Reaction between 4,6-dimethylpyrimidine and (a) phenacyl bromide (b) bromoacetone and (c) 3-bromo-2-butanone

(a) The Chichibabin reaction between 4,6-dimethylpyrimidine and phenacyl bromide gave 7-methyl-2-phenyl-6-azaindolizine (44) in good yield as reported[35].

(44)

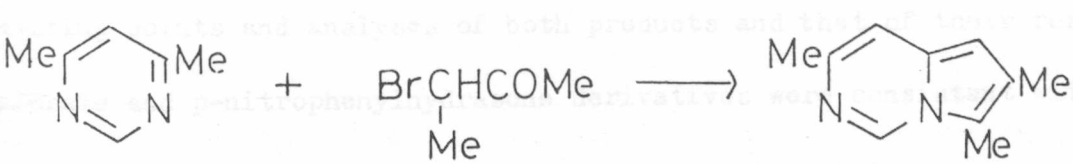
The NMR spectrum of (44) in deuterochloroform (see Table III, p34) showed four 1H singlets (δ 6.56, 7.00, 7.53 and 8.70), a complex phenyl signal at δ 7.30-7.70 and a 3H methyl signal at δ 2.40. Irradiation at the frequency of the methyl signal caused the signal at δ 7.00 to sharpen. The signal at δ 7.00 was therefore assigned to H-8. On the basis of their proximity to nitrogen H-1, H-3 and H-5 were assigned to the signals at δ 6.56, 7.53 and 8.70 respectively. This assignment was supported by the addition of a drop of deuterotrifluoroacetic acid to the azaindolizine (44) in deuterochloroform which resulted in a reduction in the intensities of the signals assigned to H-1 and H-3. Exchange at these positions is inferred from electron density calculations[62] and by comparison with indolizines which readily undergo exchange at C-1 and C-3[71].

(b) 4,6-Dimethylpyrimidine and bromoacetone reacted to give 2,7-dimethyl-6-azaindolizine (45) in 10% yield.

(45)

The NMR spectrum of (45) showed 3H methyl singlets at δ 2.25 and 2.29 and four lower field 1H singlets (δ 6.08, 6.90, 7.05 and 8.58). Irradiation at the frequency of the higher field methyl signal resulted in sharpening of the 1H singlets at δ 6.08 and δ 7.05, whereas irradiation at the lower field methyl signal resulted in sharpening of only the 1H singlet at δ 6.90. Since the protons of Me-2 would be expected to be weakly coupled to both H-1 and H-3, and those of Me-7 to H-8, the signals at δ 2.25 and 2.29 were assigned as Me-2 and Me-7 and those at 6.08, 6.90, 7.05 and 8.58 to H-1, H-8, H-3 and H-5 respectively. These signal assignments were supported by comparison with those of 7-methyl-2-phenyl-6-azaindolizine (44) and by deuterium exchange of the signals assigned to H-1 and H-3.

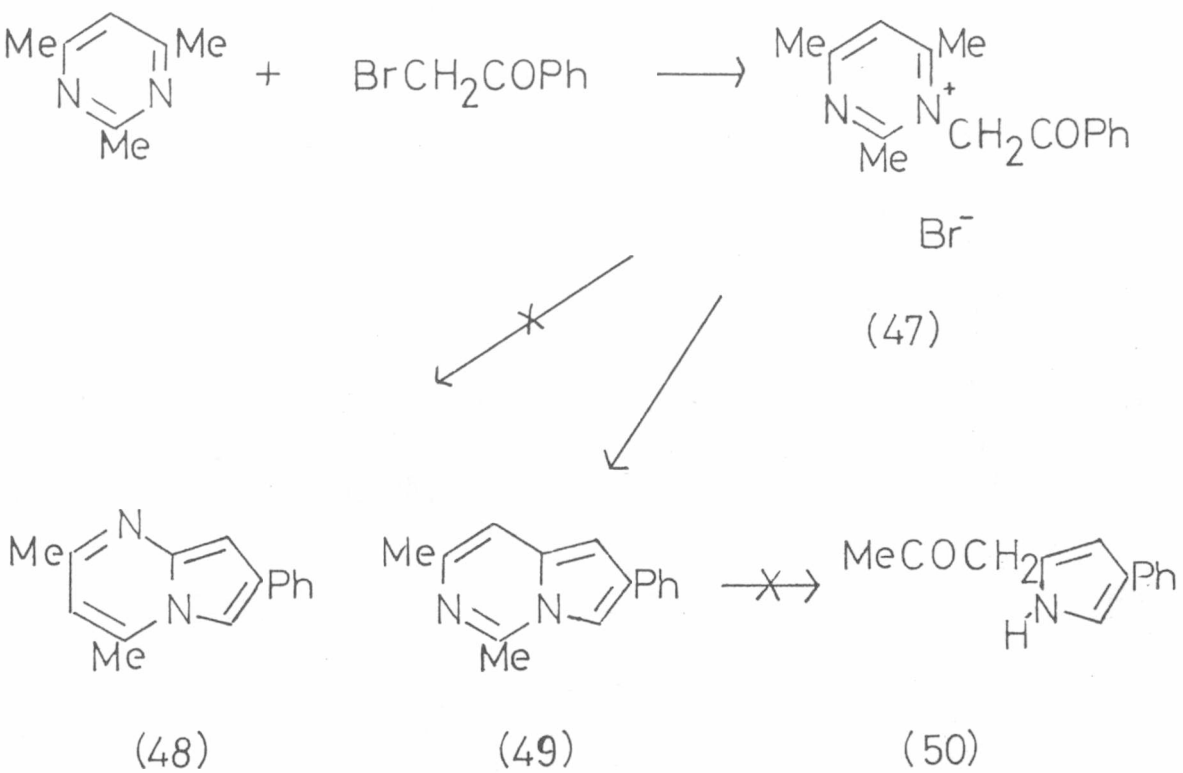
(c) 4,6-Dimethylpyrimidine and 3-bromo-2-butanone gave 2,3,7-trimethyl-6-azaindolizine (46) in 15% yield. The NMR spectrum was similar to that of 2,7-dimethyl-6-azaindolizine (45) except for the absence of a signal attributable to H-3 and the emergence of an additional 3H methyl singlet. The ring protons were assigned by a comparison with (45) and that due to H-1 confirmed by its deuterium exchange.



(46)

Reaction between 2,4,6-trimethylpyrimidine and (a) phenacyl bromide and (b) bromoacetone

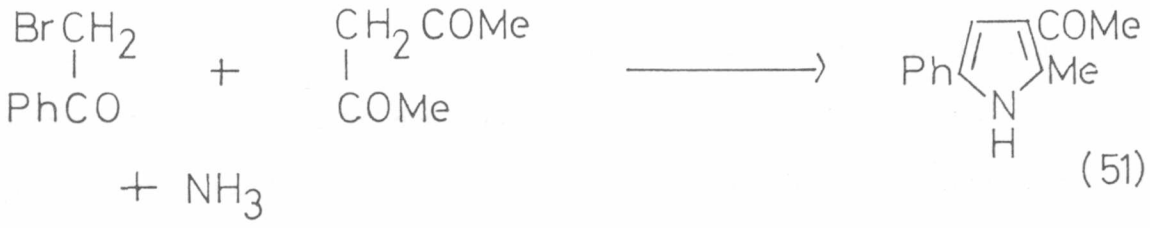
(a) The reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide was originally investigated by Ochiai and Yanai[37]. They isolated two products from this reaction. One was an azaindolizine and assigned the 8-azaindolizine structure (48) and assumed to be formed by cyclisation of the intermediate quaternary salt (47) via its 2-methyl group. The other product was a pyrrole derivative which was assigned structure (50) and was thought to be formed by degradation of the 6-azaindolizine (49) initially formed from (47) by cyclisation via its 4-methyl group.



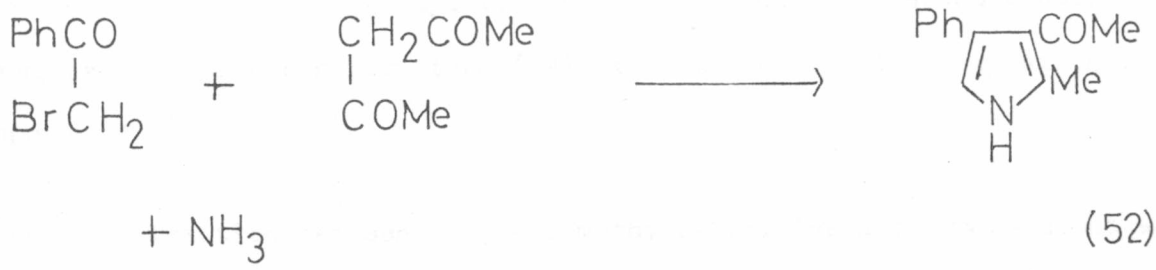
(48) (49) (50)

The structures assigned to these products have been reinvestigated. Thus 2,4,6-trimethylpyrimidine, prepared[96] from acetylacetone and acetamidine hydrochloride, on reaction with phenacyl bromide gave two products. The melting points and analyses of both products and that of their respective picrate and p-nitrophenylhydrazone derivatives were consistent with those

reported by Ochiai for compounds he assigned as (48) and (50). The infrared spectrum of the higher melting product whose analysis agreed with the pyrrole (50) showed N-H stretching at 3220 cm^{-1} and a carbonyl absorption at 1629 cm^{-1}. The NMR spectrum however showed no 2H methylene signal but significantly two 3H methyl singlets at δ 2.43 and 2.59. It also showed a complex phenyl signal, a broad exchangeable NH peak at δ 8.78 and a 1H doublet at δ 6.77 (J = ca 1.5 Hz). This suggested the compound to be an acetyl-methyl-phenylpyrrole. The positions of the substituents were determined by an alternative synthesis from acetylacetone, phenacyl bromide and ammonia[97]. This Hantzsch pyrrole synthesis can give two acetyl-methyl phenylpyrroles (51) and (52) although the former is more likely.



(51)



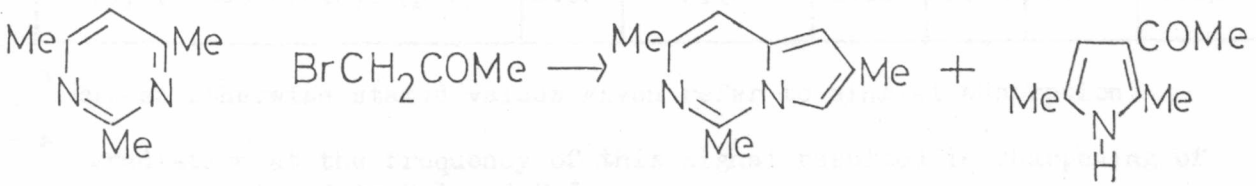
(52)

Only one pyrrole was isolated. It had a melting point and spectral characteristics (uv, ir and NMR) identical to those of the pyrrole isolated from the reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide. Since the melting point of this compound was 179-181° and the literature reports compounds (51) and (52) to have melting points [98,99] of 183° and 150° respectively, it was concluded that the pyrrole isolated from the reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide was 3-acetyl-2-methyl-5-phenylpyrrole (51). This pyrrole is presumably formed by a

similar Hantzsch synthesis between phenacyl bromide and a degradation product of 2,4,6-trimethylpyrimidine or its quaternary product and not by a breakdown of the 6-azaindolizine (49) as suggested by Ochiai. This is substantiated by the fact that the pyrrole (51) was present mainly in the crude quaternary product. After the addition of bicarbonate only much smaller quantities could be isolated.

The NMR spectrum of the lower melting product isolated from the reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide showed two features which were inconsistent with this compound having the 8-azaindolizine structure (48). Firstly, the chemical shifts of the two methyl singlets were significantly different (δ 2.34 and δ 2.64). Secondly after assigning H-3 and H-1 by deuterium exchange the remaining 1H singlet at δ 6.88 was shown by double resonance to be coupled to the protons of only one methyl group. In the 8-azaindolizine (48) the protons of both methyl groups would be expected to be observably coupled to H-6 and both to have similar chemical shifts. However these findings are consistent with the 6-azaindolizine (49). In this isomer the protons of only one methyl group would be expected to be coupled and the methyl groups to have significantly different chemical shifts. Unequivical proof for structure (49) was obtained by its formylation (see Chapter III).

(b) The reaction between 2,4,6-trimethylpyrimidine and bromoacetone was analagous to the above mentioned reaction involving phenacyl bromide, in that two products, a pyrrole and an azaindolizine, were isolated.



(54) (53)

The pyrrole was 3-acetyl-2,5-dimethylpyrrole (53) deduced by a comparison of its melting point and spectral characteristics (uv, ir and NMR) with those reported[100, 101].

The azaindolizine had a similar NMR spectrum to that of (49) provided allowances were made for the deshielding effect of the phenyl group. It was therefore assigned as 2,5,7-trimethyl-6-azaindolizine (54) and again further evidence for this structure was obtained by formylation.

Attempted reaction between 2,4,6-trimethylpyrimidine and 3-bromo-2-butanone

This reaction failed to give any characterisable products. Failure to obtain an azaindolizine may possibly be accounted for by steric blockage at the quaternisation stage.

Table III[a]

Chemical Shifts (δ) in the 100 MHz NMR spectra of 6-azaindolizines in $CDCl_3$

6-Azaindolizine	1	2	3	5	7	8
7-methyl-2-phenyl (44)	6.56	7.30-7.70 (complex)	7.53	8.70	2.40*	7.00*
2,7-dimethyl (45)	6.08	2.25[b]	7.05	8.58	2.29*	6.90*
2,3,7-trimethyl (46)	6.07	2.22	2.36	8.46	2.38	6.90
5,7-dimethyl-2-phenyl (49)	6.58	7.20-7.70 (complex)	7.34	2.64	2.34*	6.88*
2,5,7-trimethyl (54)	6.13	2.30[b]	6.94	2.62	2.36*	6.85*
2,3,5,7-tetramethyl (p67)	6.00*	2.16*	2.60	2.86	2.28*	6.69*

[a] Unless otherwise stated values given refer to singlet absorption.

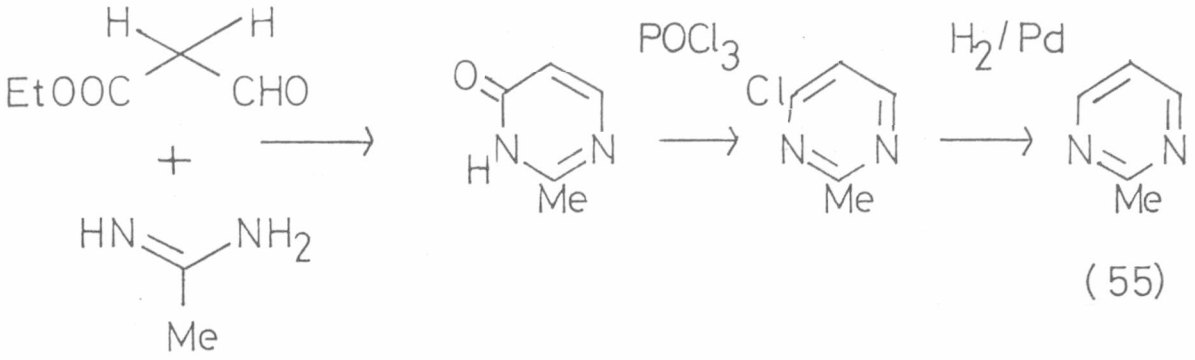
[b] Irradiation at the frequency of this signal resulted in sharpening of signals assigned to H-1 and H-3.

* Indicates pairs of signals found by double resonance to be weakly coupled to each other.

Synthesis of 8-azaindolizine(s)

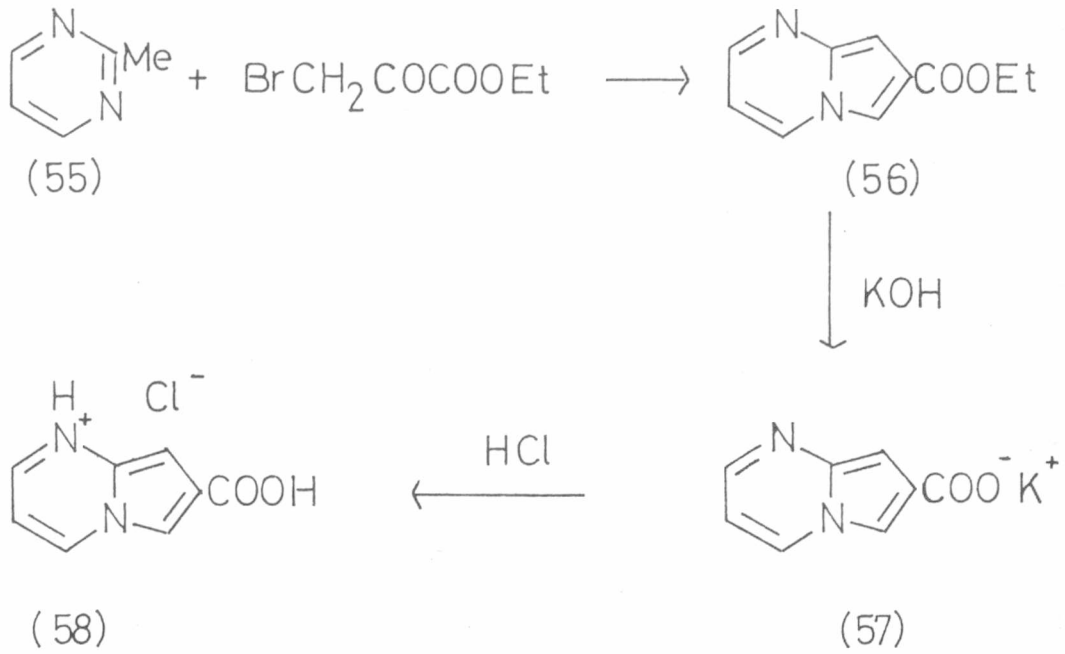
Reaction between 2-methylpyrimidine and ethyl bromopyruvate

2-Methylpyrimidine (55)[102] was prepared from acetamidine hydrochloride and the sodium salt of ethyl formylacetate by the route[103] shown.



(55)

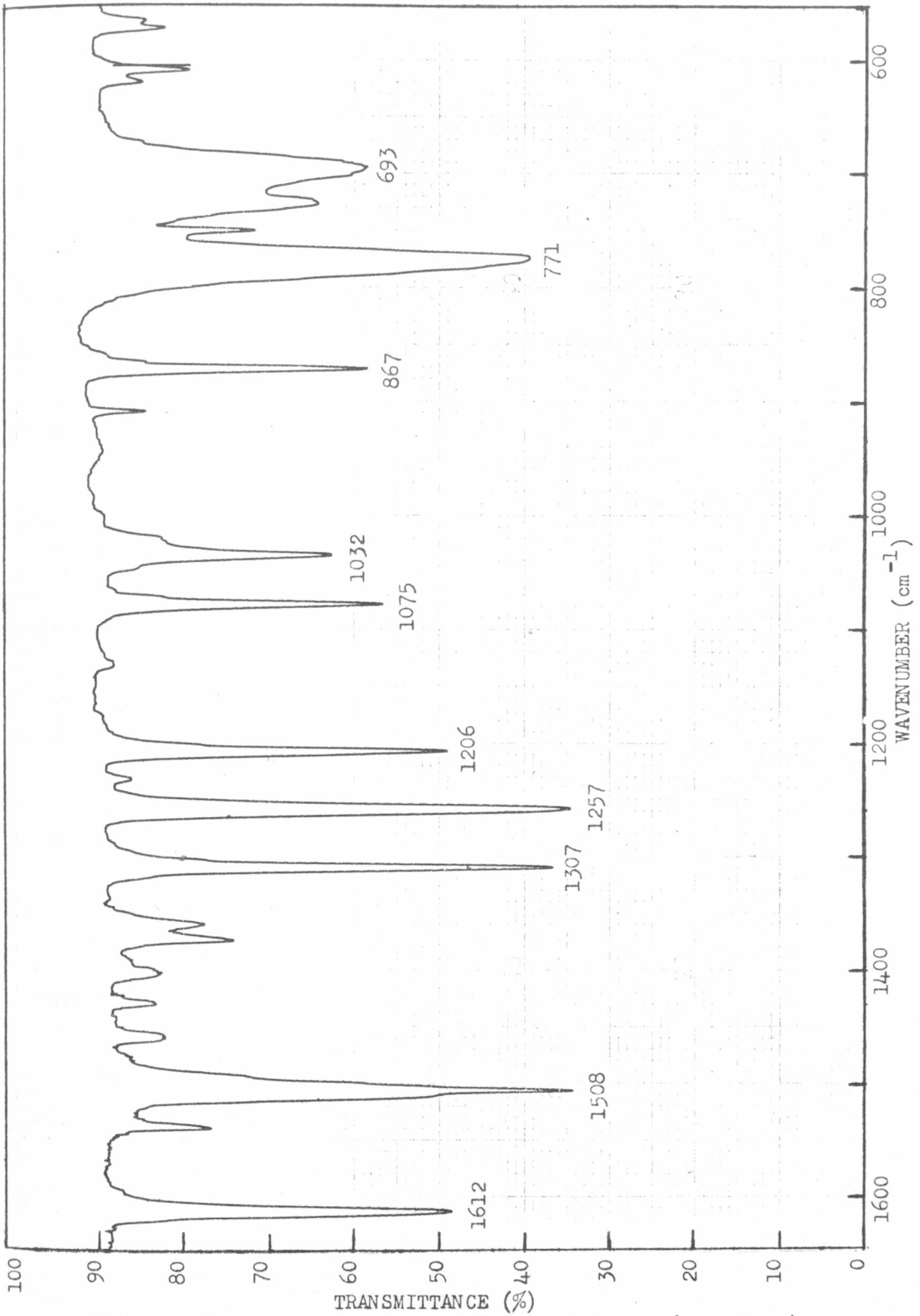
The pyrimidine (55) on reaction with ethyl bromopyruvate gave a low yield of 2-carbethoxy-8-azaindolizine (56). The NMR spectrum of this product (see Table IV p50) showed a 3H triplet at δ 1.37 and a 2H quartet at δ 4.38 due to the protons of the ethyl group, a 1H singlet at δ 7.03 assigned to H-1, a doublet at δ 7.71 (J = ca 1.5 Hz) assigned to H-3, a 1H multiplet at δ 6.58 approximating to a triplet, assigned to H-6, and a low field 2H apparent doublet at 8.14 (J = ca 5.5 Hz) assigned to H-5 and H-7. The infra-red spectrum showed an ester carbonyl absorption at 1700 cm^{-1}. Hydrolysis of the ester (56) with potassium hydroxide gave the potassium salt of 8-azaindolizine-2-carboxylic acid (57) which showed infra-red absorption at 1570 cm^{-1} due to its ionised carboxyl group. The addition of an approximately equimolar equivalent of hydrochloric acid to an aqueous solution of the salt (57) immediately precipitated a yellow solid. The infra-red spectrum of the solid showed a strong carbonyl absorption at 1698 cm^{-1}, two prominent broad absorptions at 1880 and 2590 cm^{-1} and a weaker band at 2750 cm^{-1} all of which suggested the compound to be 8-azaindolizine-2-carboxylic acid hydrochloride (58). Tentatively the absorption at 2590 cm^{-1} is



(55) (56) (58) (57)

assigned to the C = NH^+ group[104] and those at 1698 and 2750 cm^{-1} to the free carboxylic acid group. Insufficient sample was available for microanalysis. However the hydrochloride structure (58) was further supported by its NMR spectrum in deuterated dimethylsulphoxide which showed a multiplet at δ 8.18 due to H-7, a doublet at δ 8.68 (J = ca 7.5 Hz) due to H-5, a 2H multiplet at δ 6.77 due to H-1 and H-6, and a 1H doublet at δ 7.96 (J = ca 1.5 Hz) due to H-3. This is a closely similar pattern to that of the potassium salt (57) in deuterotrifluoroacetic acid where protonation on N-8 occurred (see Ch IV). Irradiation at the frequency of the 2H multiplet assigned to H-1 and H-6 simplified the spectrum. The signal assigned to H-3 now appeared as a sharp singlet and those assigned to H-5 and H-7 as broad singlets.

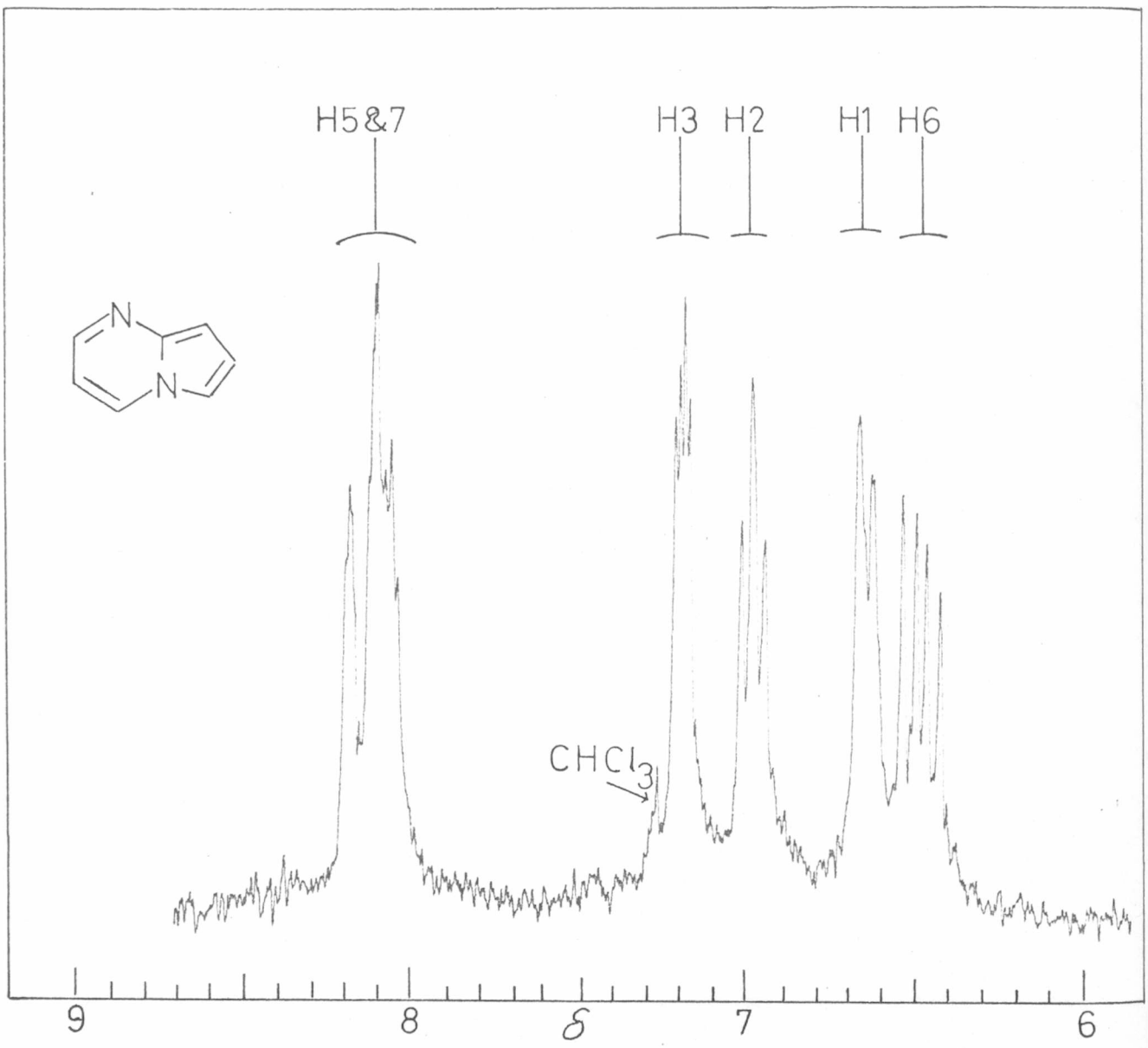
Figure I



Infrared Absorption Spectrum of 8-azaindolizine (Thin Film)

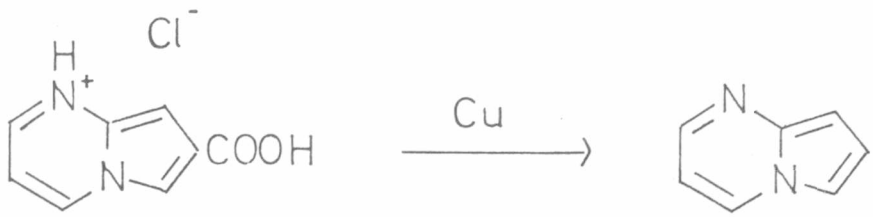
Figure II

100 MHz NMR spectrum of 8-azaindolzine in $CDCl_3$



Decarboxylation of 8-azaindolizine-2-carboxylic acid

When 8-azaindolizine-2-carboxylic acid hydrochloride (58) was heated with copper powder[105] under vacuum, it underwent decarboxylation to give the parent 8-azaindolizine (59) as a yellow liquid which darkened on exposure to light and air. The infra-red spectrum of (59) is shown in Figure I, p 37.



(58) (59)

NMR spectrum of 8-azaindolizine

The 100 MHz NMR spectrum of 8-azaindolizine (59) in deuterochloroform is shown in Figure II. The 1H apparent triplet at δ 6.98 was assigned to H-2, its multiplicity arising mainly through approximately equal coupling with H-1 and H-3. The multiplets at 6.64 and 7.19 were assigned to H-1 and H-3 respectively. The 1H apparent quartet centred at δ 6.48 was assigned to H-6, its multiplicity arising mainly through coupling with H-5 and H-7. The low field 2H multiplet at δ 8.00-8.24 was assigned to H-5 and H-7. These assignments were confirmed by double resonance. Thus irradiation at the frequency of signal assigned to H-2 simplified the multiplets assigned to H-1 and H-3 to a pair of broad singlets. Irradiation at the frequency of the signal assigned to H-6 simplified the 2H multiplet assigned to H-5 and H-7 to two broad singlets at δ 8.07 and 8.14. Addition of a small drop of deuterotrifluoroacetic acid to the sample in deuterochloroform resulted in a reduction in the intensity of the signal assigned to H-3, and to a lesser extent of the signal assigned to H-1, due to deuterium exchange; after a period of one hour, the spectrum showed the complete absence of the signals assigned to H-1 and H-3. The H-2 signal now appeared as a singlet at δ 7.41, and H-5 and

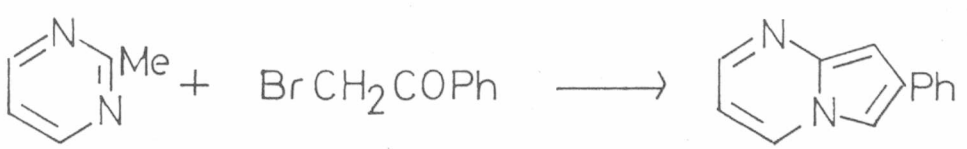
H-7 as a pair of doublets at δ 8.88 (J = ca 7.0 Hz) and 8.56 (J = ca 5.5 Hz): H-6 appeared as an apparent quartet at δ 7.08.

Reaction between 2-methylpyrimidine and (a) bromoacetone (b) phenacyl bromide and (c) 3-bromo-2-butanone

(a) Reaction between 2-methylpyrimidine and bromoacetone gave a low yield of 2-methyl-8-azaindolizine (60) as a low melting waxy solid which darkened on exposure to light and air. The NMR spectrum of (60) showed two deuterium exchangeable 1H singlets at δ 6.44 and δ 6.99 assigned to H-1 and H-3, a multiplet at 6.33-6.53 assigned to H-6 and, like the parent system (59), a 2H multiplet at δ 7.91-8.15 assigned to H-5 and H-7. The signal due to the protons of the 2-methyl group occurred as a 3H singlet at δ 2.34.

(60)

(b) Reaction between 2-methylpyrimidine and phenacyl bromide gave 2-phenyl-8-azaindolizine (61) in low yield as a relatively stable yellow solid. The NMR was similar to that of 2-methyl-8-azaindolizine (60). The absorption position of H-3 (δ 7.46) was obscured by the complex phenyl signal (δ 7.17-7.77) but was confirmed by double resonance through weak coupling with H-1.



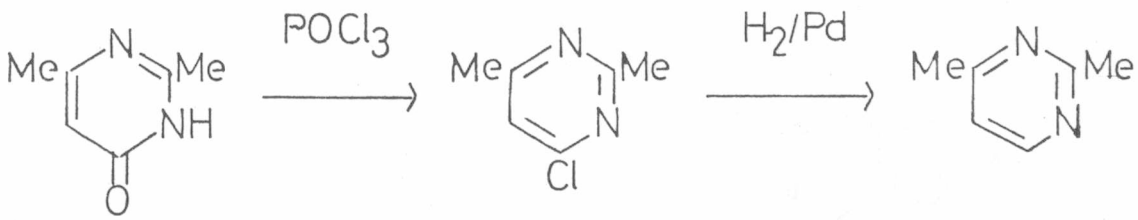
(61)

(c) Reaction between 2-methylpyrimidine and 3-bromo-2-butanone gave a low yield of 2,3-dimethyl-8-azaindolizine (62) as a yellow, crystalline solid. The lower field of the two 3H methyl signals (δ 2.32 and 2.36) in the NMR spectrum was assigned to the methyl group at C-3 and the higher to the methyl group at C-2. The deuterium exchangeable 1H singlet at δ 6.47 was assigned to H-1. The signals due to the protons of the 6-membered ring occurred at field positions similar to those of compounds (59), (60) and (61).

(62)

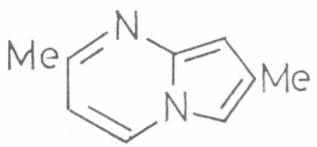
Reaction between 2,4-dimethylpyrimidine and (a) bromoacetone (b) 3-bromo-2-butanone

(a) 2,4-Dimethylpyrimidine (63) was obtained from 2,4-dimethyl-6-hydroxypyrimidine by chlorination[106] and subsequent catalytic dehalogenation[102] as shown below.



(63)

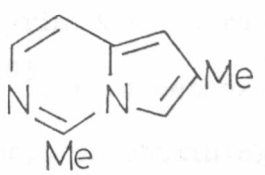
Unlike reactions with 2-methylpyrimidine which can give only one 8-azaindolizine, the Chichibabin reaction with 2,4-dimethylpyrimidine and bromoacetone can lead to three isomeric azaindolizines. Quaternisation of the pyrimidine (63) at N-1 followed by cyclisation via the 2-methyl group may give the 8-azaindolizine (64). Alternatively quaternisation at N-3 followed by cyclisation via the 2- or 4- methyl groups may give the 8-azaindolizine (65) or the 6-azaindolizine (66) respectively. The most likely to be formed is (64) as this results from quaternisation at the least hindered nitrogen. Only one azaindolizine was isolated from the reaction. It showed spectral characteristics (NMR and uv) consistent with structure (64). Proof for this structure was obtained from its products of formylation as discussed in Chapter III.



(64)

(63)

(65)



(66)

(b) As in the previous reaction involving bromoacetone the reaction between 2,4-dimethylpyrimidine and 3-bromo-2-butanone can give three products of which 2,3,7-trimethyl-8-azaindolizine (67) seems most likely. Proof for this structure via reductive formylation of the 8-azaindolizine (64) is given in Chapter III.

(67)

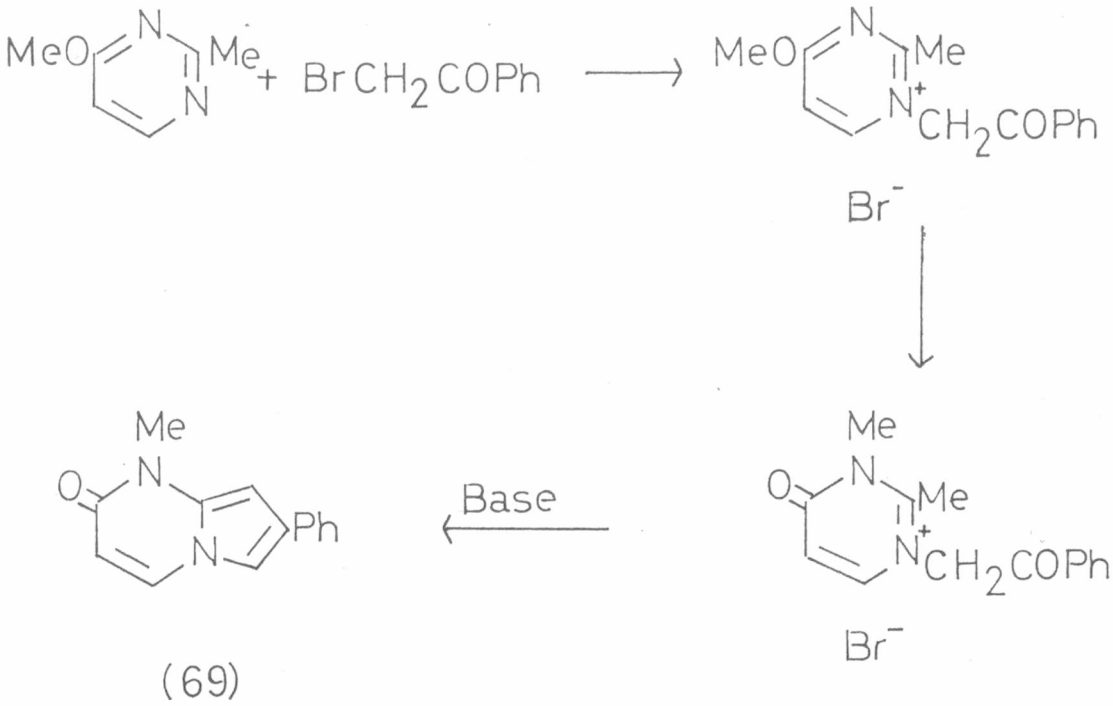
Reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide

The lower yields (less than 6%) of the 8-azaindolizines compared to the yields of 6-azaindolizines (6 to 89%[35,36]), and the preferential formation of 6-azaindolizines from 2,4,6-trimethylpyrimidine indicates that the 2-methyl group is less reactive than the 4(6)-methyl group in the cyclisation of methylpyrimidinium salts. The superior reactivity of the 4-methyl group of 2,4- and 2,4,6-trimethyl pyrimidines in condensation reactions with aromatic aldehydes has also been reported[107,108]. The introduction of a methoxy group at C-4 of the pyrimidine ring would be expected to aid quaternisation by increasing the basicity of N-1 (via +M effect) and also aid cyclisation by increasing the acidity of 2-methyl groups (via -I effect). As 4-methoxy-2-methylpyrimidine is readily available[109] from 4-chloro-2-methyl pyrimidine[103], this methoxy pyrimidine was reacted with phenacyl bromide, in the hope of obtaining good yields of 7-methoxy-2-phenyl-8-azaindolizine (68), at (a) room temperature and (b) 40°.

(a) 4-Methoxy-2-methylpyrimidine and phenacyl bromide, when quaternised without solvent at room temperature and then cyclised with bicarbonate, gave 7-methoxy-2-phenyl-8-azaindolizine (68) in 27% yield. The infra-red spectrum of (68) showed ether bands at 1232 and 1010 cm^{-1}. The NMR spectrum showed a 3H singlet at δ 3.94 due to the protons of the methoxy group, two weakly coupled 1H singlets at δ 6.54 and 7.20 assigned to H-1 and H-3 and a pair of doublets at δ 6.08 and 7.90 assigned to H-6 and H-5 respectively. The signal due to the phenyl protons appeared as a complex multiplet at δ 7.10-7.70 and obscured the H-3 signal.

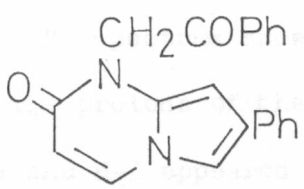
(68)

(b) When quaternisation between 4-methoxy-2-methylpyrimidine and phenacyl bromide was carried out at 40°, followed by the same bicarbonate cyclisation procedure, a different product which was isomeric with (68) was obtained in 58% yield. The infra-red spectrum of this compound showed a strong carbonyl absorption at 1668 cm^{-1}. The NMR spectrum was similar in pattern to (68) but showed a significant upfield shift in the resonance positions of the protons of the methyl group from δ 3.94 to 3.48. This shift to higher field suggested that the methyl group was now attached to a nitrogen rather than an oxygen atom and that the product isolated at 40° was 8-methyl-2-phenyl-8-azaindolizin-7(8H)-one (69). The formation of this indolizinone structure may be rationalised in terms of a rearrangement [110,111] at the quaternisation stage as shown overleaf.

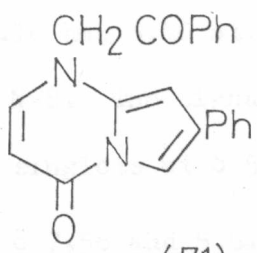


(69)

Two other products in low yields were isolated from this reaction. The mass spectra of these products showed both to have molecular compositions corresponding to $C_{21}H_{16}N_2O_2$ and to possess benzoyl functions since they displayed intense peaks at m/e 105 ($PhCO^+$). Both compounds showed two carbonyl absorptions in their infra-red spectra at approximately 1655 and 1690 cm^{-1}. They also had similar NMR spectra (see Table V p51) which when analysed showed them to contain two complex phenyl groups, one 2H midfield methylene singlet, two lower field weakly coupled singlets and a pair of doublets. The data is consistent with structures (70) and (71).

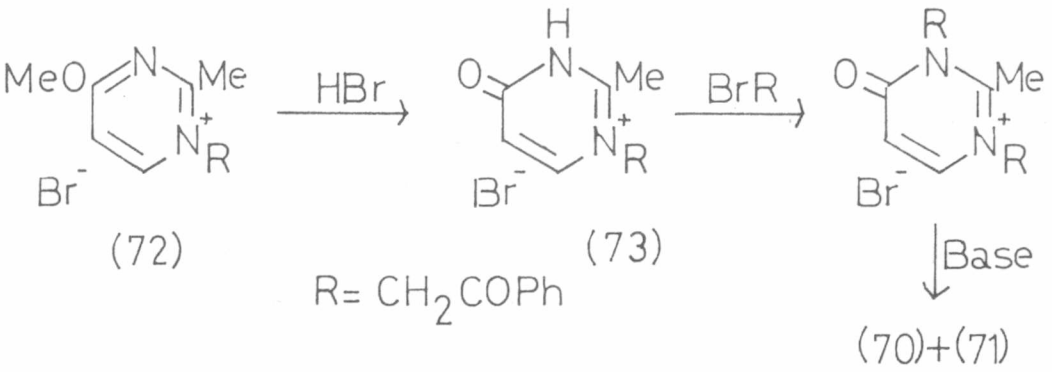


(70)



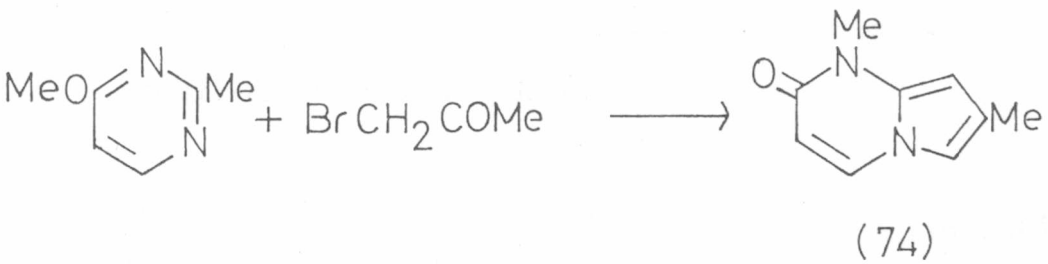
(71)

The isomer with the greater R_f value (on TLC) had a closely similar ultra-violet spectrum to that of compound (69) and was assigned structure (70). The other isomer which had quite a different ultra-violet spectrum and a lower field H-3 resonance in its NMR spectrum was assigned the structure (71). It is suggested that the methoxy group of the intermediate quaternary bromide (72) is cleaved by the action of hydrobromic acid produced as a side product. The demethylated salt (73) on reaction with more phenacyl bromide and then with bicarbonate leads to (70) and (71).



Reaction between 4-methoxy-2-methylpyrimidine and bromoacetone

This reaction gave mainly 2,8-dimethyl-8-azaindolizin-7(8H)-one (74) when quaternisation was carried out at room temperature and at 40°.

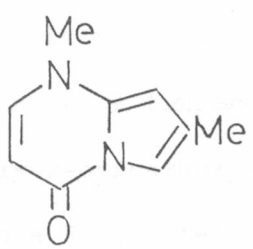


(74)

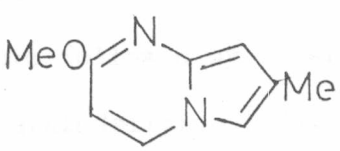
The infra-red spectrum of (74) showed a carbonyl absorption at 1660 cm^{-1}. The NMR spectrum showed two 3H singlets at δ 2.16 and 3.40 attributable to the protons of the methyl groups at C-2 and N-8. The signals due to H-1 and H-3 appeared as deuterium exchangeable singlets at δ 5.47 and 6.47, and H-5 and H-6 as a pair of doublets at δ 7.56 and 5.84 respectively.

A minor product isolated from the reaction was the isomer (75) which differed from (74) in that its H-3 proton absorption occurred at significantly lower field (Δ = 76 Hz) due to the effect of the peri-orientated carbonyl group.

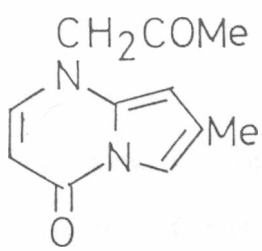
Two other products both in low yields were isolated. The first was 7-methoxy-2-methyl-8-azaindolizine (76). The NMR spectrum of this compound showed 3H singlets at δ 2.26 and 3.92 due to the protons of the 2-methyl and 7-methoxy groups, two 1H singlets at δ 6.07 and δ 6.75 assigned to H-1 and H-3 and a pair of doublets at δ 6.02 and δ 7.85 assigned to H-6 and H-5 respectively. The assignment of the 7-methoxy structure (76) for this compound is supported by a comparative examination of its NMR spectrum with those of 2-methyl-8-azaindolizine (60) and 7-methoxy-2-phenyl-8-azaindolizine (68). Furthermore this compound results from quaternisation at the least hindered N-1 pyrimidine site. The other minor product isolated showed carbonyl absorptions in the infra-red at 1660 and 1720 cm^{-1}. The NMR spectrum showed a 2H methylene singlet at δ 4.54, two 3H methyl singlets at δ 2.19 and 2.20 and at lower field, two 1H singlets at δ 5.53 and 7.22 and a pair of doublets at δ 5.62 and 7.09. This data, particularly the low field singlet at δ 7.22, compared with δ 7.23 for H-3 in 2,8-dimethyl-8-azaindolizin-5(8H)-one (75) and a close similarity in their ultra-violet spectra, suggested the compound to be 8-acetonyl-2-methyl-8-azaindolizin-5(8H)-one (77).



(75)

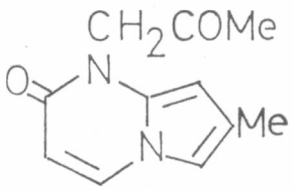


(76)

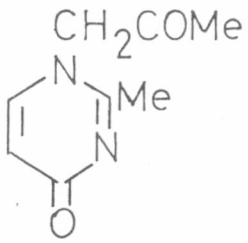


(77)

To confirm the 8-azaindolizin-5(8H)-one structure (77), the Chichibabin reaction between 4-hydroxy-2-methylpyrimidine[103] and bromoacetone was carried out. Bicarbonate cyclisation gave three products. The first product was identical with the 8-azaindolizinone (77). The second product was isomeric with it and was assigned as 8-acetonyl-2-methyl-8-azaindolizin-7(8H)-one (78). It had an NMR spectrum which was similar in pattern to (77) except that (78) had a significantly higher field H-3 signal (Δ = 76 Hz). The third product was an N-acetonyl pyrimidine with an NMR spectrum similar to that of 1-phenacyl-2-methyl-pyrimidin-4(1H)-one (178) (see Chapter V) except for the absence of a 5H phenyl signal and the emergence of an additional 3H methyl singlet. Consequently this compound was assigned the 1-acetonyl-pyrimidin-4(1H)-one structure (79) but was not further investigated.



(78)



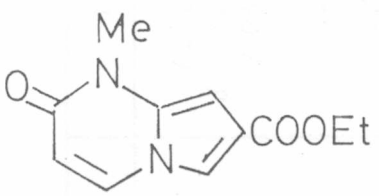
(79)

Reaction between 4-methoxy-2-methylpyrimidine and ethyl bromopyruvate

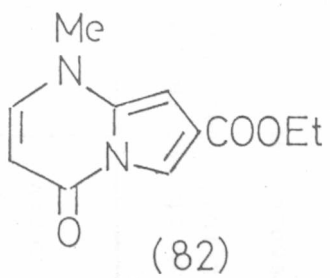
This reaction produced four products all in low yields. Quaternisation at room temperature followed by bicarbonate cyclisation gave 7-methoxy-2-carbethoxy-8-azaindolizine (80). The NMR spectrum of (80) showed a 2H quartet and a 3H triplet assigned to the protons of the ethoxy group, a 3H singlet at δ 3.94 assigned to the methoxy group and at lower field, two weakly coupled 1H signals at δ 6.61 and δ 7.49 assigned to H-1 and H-3 and a pair of aromatic doublets at δ 6.18 and 7.92 assigned to H-6 and H-5 respectively. Support for this structure was obtained by a comparison of its NMR spectrum with that of 2-carbethoxy-8-azaindoline (56).

(80)

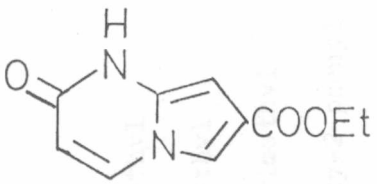
When quaternisation of the pyrimidine with ethyl bromopyruvate was carried out at 50°, extraction of the aqueous quaternary salt gave in addition to traces of (80), three other products. Two of these were isomeric with each other and had molecular formulae $C_{11}H_{12}N_2O_3$. Both exhibited carbonyl absorptions at approximately 1660 and 1700 cm^{-1}. This, and an examination of their NMR spectra indicated these compounds to have structures (81) and (82). The isomer with the lower field H-3 signal was assigned to structure (82). The NMR and infra-red spectra of the fourth compound isolated, showed the presence of an NH function. This, and the similarity of the NMR and ultra-violet spectra to those of 2-carbethoxy-8-methyl-8-azaindolizin-7(8H)-one (81) suggested the compound to be 2-carbethoxy-8-azaindolizin-7(8H)-one (83).



(81)



(82)



(83)

Table IV[a]

Chemical Shifts (δ) in the 100 MHz spectra of 8-azaindolizines in $CDCl_3$

8-azaindolizine	1	2	3	5	6	7
Unsubstituted (59)	6.64 dd[b] J = 1.5, 3.5	6.98 dd J = 3.0, 3.5	7.19 dd J = 1.5, 3.0	8.00-8.24 m	6.48 q J = 4.0, 7.5	8.00-8.24 m
2-Carbethoxy (56)	7.03	1.37 t, 4.38 q J = 7.0	7.71 d J = 1.5	8.14 d J = 5.5	6.58 dd J = 5.5, 5.5	8.14 d J = 5.5
2-methyl (60)	6.44	2.34	6.99	7.91-8.15 m	6.33-6.53 m	7.91-8.15 m
2-phenyl (61)	6.91*	7.17-7.77 m	7.46*	8.00-8.23 m	6.44-6.58 m	8.00-8.23 m
2,3-dimethyl (62)	6.47	2.32	2.36	7.80-8.04 m	6.42-6.60 m	7.80-8.04 m
2,7-dimethyl (64)	6.27	2.30*	6.87*	7.90 d J = 7.0	6.27 d J = 7.0	2.43
2,3,7-trimethyl (67)	6.27	2.28 (2.31)	2.31 (2.28)	7.76 d J = 7.5	6.34 d J = 7.5	2.45
7-methoxy-2-phenyl (68)	6.54*	7.10-7.70 m	7.20*	7.90 d J = 7.5	6.08 d J = 7.5	3.94
7-methoxy-2-methyl (76)	6.07	2.26	6.75	7.85 d	6.02 d	3.92
2-carbethoxy-7-methoxy (80)	6.61*	1.36 t, 4.34 q J = 7.0	7.49* d J = 1.5	7.92 J = 7.5	6.18 J = 7.5	3.94

[a] Unless otherwise stated values refer to singlet absorption d = doublet, dd = double doublet, t = triplet, q = quartet and m = complex multiplet absorption. Coupling constants (Hertz) are approximate and measured directly from the spectra.

[b] Under normal resolution this signal appeared as an apparent doublet (J = ca 4.0 Hz).

* Indicates pairs of signals found by double resonance to be weakly coupled to each other.

Table V[a]

Chemical Shifts (δ) in the 100 MHz NMR spectra of 8-azaindolizinones

8-Azaindolizin-7(8H)-one	1	2	3	5	6	8
8-methyl-2-phenyl (69)	5.92	7.10-7.66 m	6.98	7.66 d J = 7.5	5.95 d J = 7.5	3.48
8-phenacyl-2-phenyl (70)	5.74 d J = 1.5	7.19-8.19 m	6.97 d J = 1.5	7.73 d J = 8.0	5.97 d J = 8.0	5.40 (CH_2) 7.19-8.19 m (Ph)
2,8-dimethyl (74)	5.47	2.16	6.47	7.56 d J = 8.0	5.84 d J = 8.0	3.40
8-acetonyl-2-methyl (78)	5.30	2.10*	6.48*	7.62 d J = 8.0	5.86 d J = 8.0	2.17 (CH_3) 4.64 (CH_2)
2-carbethoxy-8-methyl (81)	6.05[b]	1.36 t, 4.34 q J = 7.0	7.31 d J = 2.0	7.68 d J = 7.5	6.06 d J = 7.5	3.45
2-carbethoxy[c] (83)	5.76 d J = 1.5	1.26 t, 4.20 q J = 7.0	7.54 d J = 1.5	8.21 d J = 8.0	5.91 d J = 8.0	11.5 (broad)

8-Azaindolizin-5(8H)-one	1	2	3	6	7	8
8-phenacyl-2-phenyl[c,d] (71)	6.56 d J = 2.0	7.11-8.24 m	-	5.60 d J = 8.0	-	5.78 (CH_2) 7.11-8.24 m (Ph)
2,8-dimethyl (75)	5.72 d J = 1.5	2.24	7.23 d J = 1.5	5.51 d J = 7.5	7.13 d J = 7.5	3.57
8-acetonyl-2-methyl (77)	5.53	2.19	7.22	5.62 d J = 8.0	7.09 d J = 8.0	2.20 (CH_3) 4.54 (CH_2)
2-carbethoxy-8-methyl (82)	6.30 d J = 2.0	1.36 t, 4.34 q J = 7.0	8.02 d J = 2.0	5.60 d J = 7.5	7.26 d J = 7.5	3.64

[a] See footnote 'a' Table IV. Unless otherwise indicated values refer to solutions in deuterochloroform.

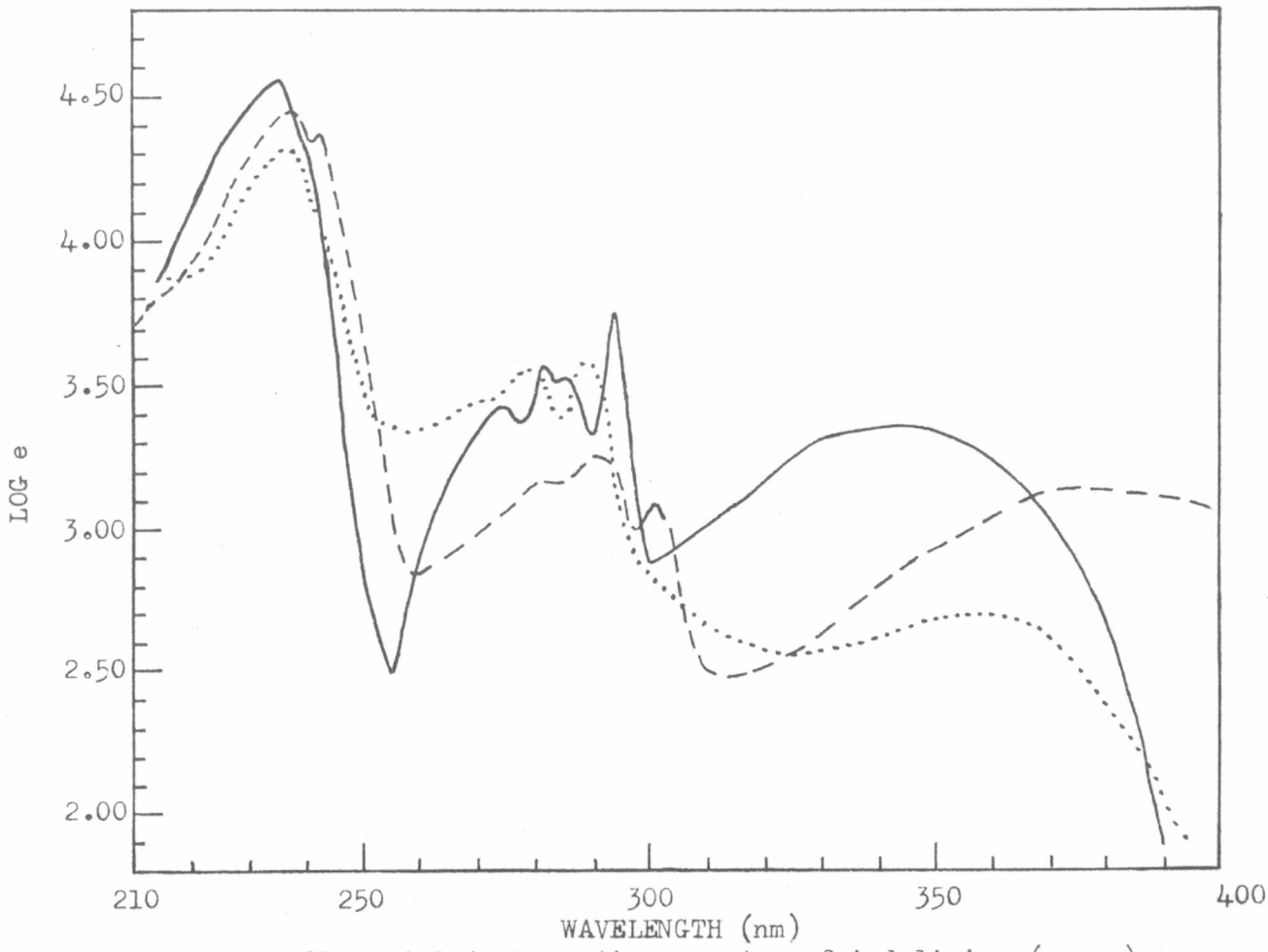
[b] This signal was obscured by H-6. [c] Recorded in deuterated dimethylsulphoxide.

[d] The signals due to H-3 and H-7 were obscured by the 10H phenyl complex at δ 7.11-8.24.

Ultraviolet absorption spectra of 6- and 8- azaindolizine and their methyl derivatives

The ultraviolet absorption spectrum of 8-azaindolizine is similar to that of indolizine[112] and both are shown in Figure III, along with that of 2,7-dimethyl-6-azaindolizine which was the simplest 6-azaindolizine obtained in this study. The ultraviolet absorption maxima for 6-azaindolizine in ethanol have been reported and occur at 229, 272, 283 and 345 nm with log e 4.44, 4.74, 3.77 and 3.03 respectively[15].

Figure III



Ultraviolet absorption spectra of indolizine (——), 8-azaindolizine (-----) and 2,7-dimethyl-6-azaindolizine (....) in ethanol.

The spectrum of 8-azaindolizine has two maxima in the band between 210 and 250 nm. It also displays its principal absorption at a slightly longer wavelength than indolizine, a result which is in contrast to those reported[62] for 1-, 2-, 3- and 7-azaindolizine which in cyclohexane, relative to indolizine in cyclohexane, show slight hypsochromic shifts of 10-20 nm. Spectra of methyl substituted 6- and 8- azaindolizines are similar to those of the unsubstituted systems but show bathochromic shifts. For example, the principal maxima in the spectrum of 8-azaindolizine is at 239 nm, whereas in the cases of its 2-methyl, 2,7-dimethyl and 2,3,7-trimethyl derivatives it is at 243, 245 and 249 nm respectively.

Figure IV

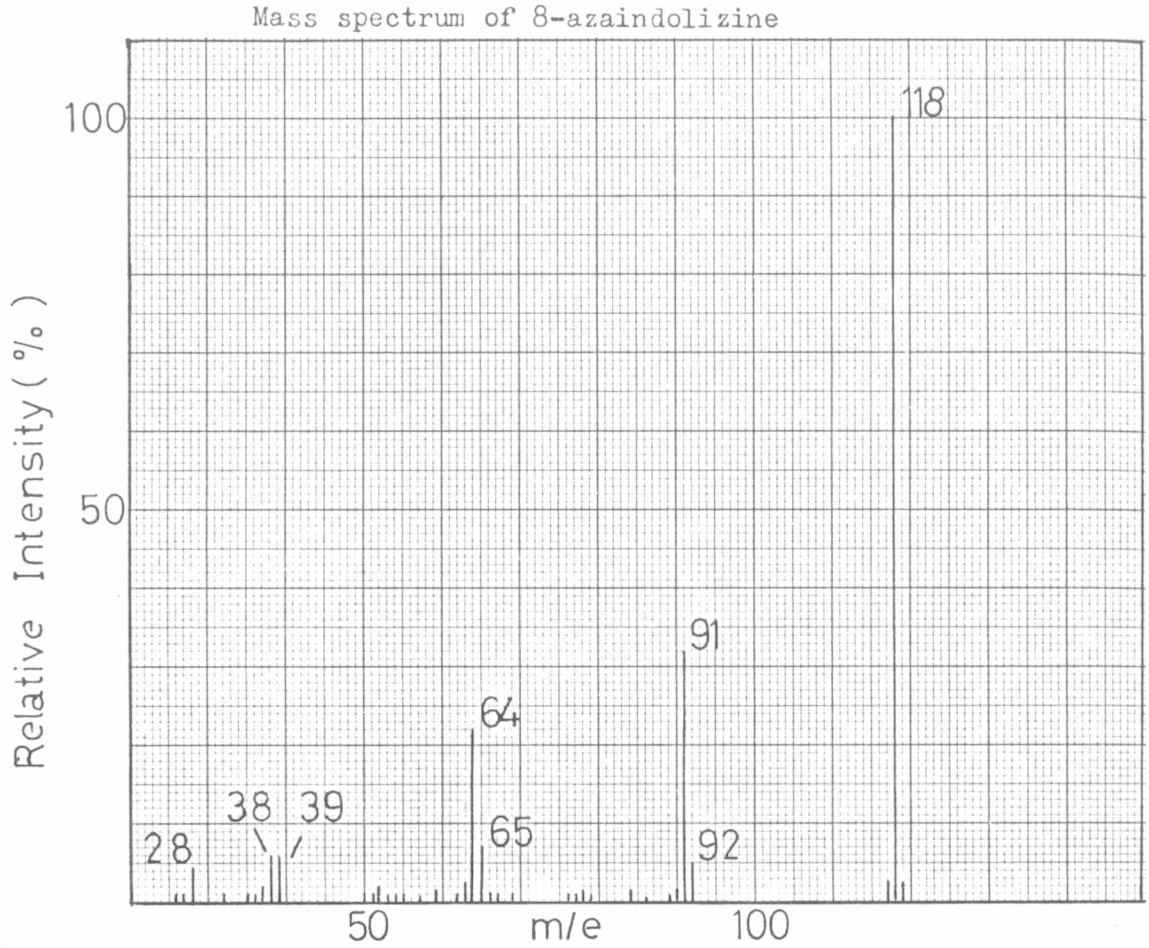
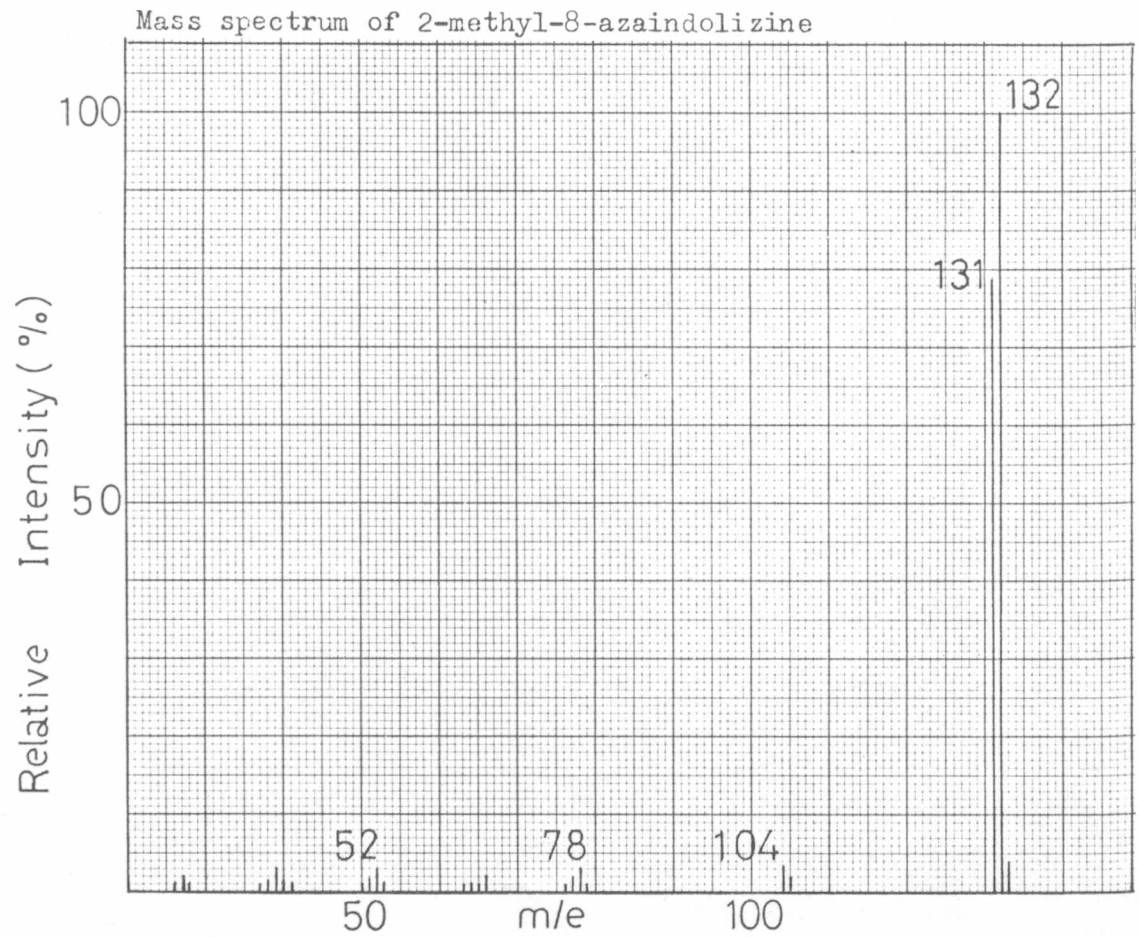
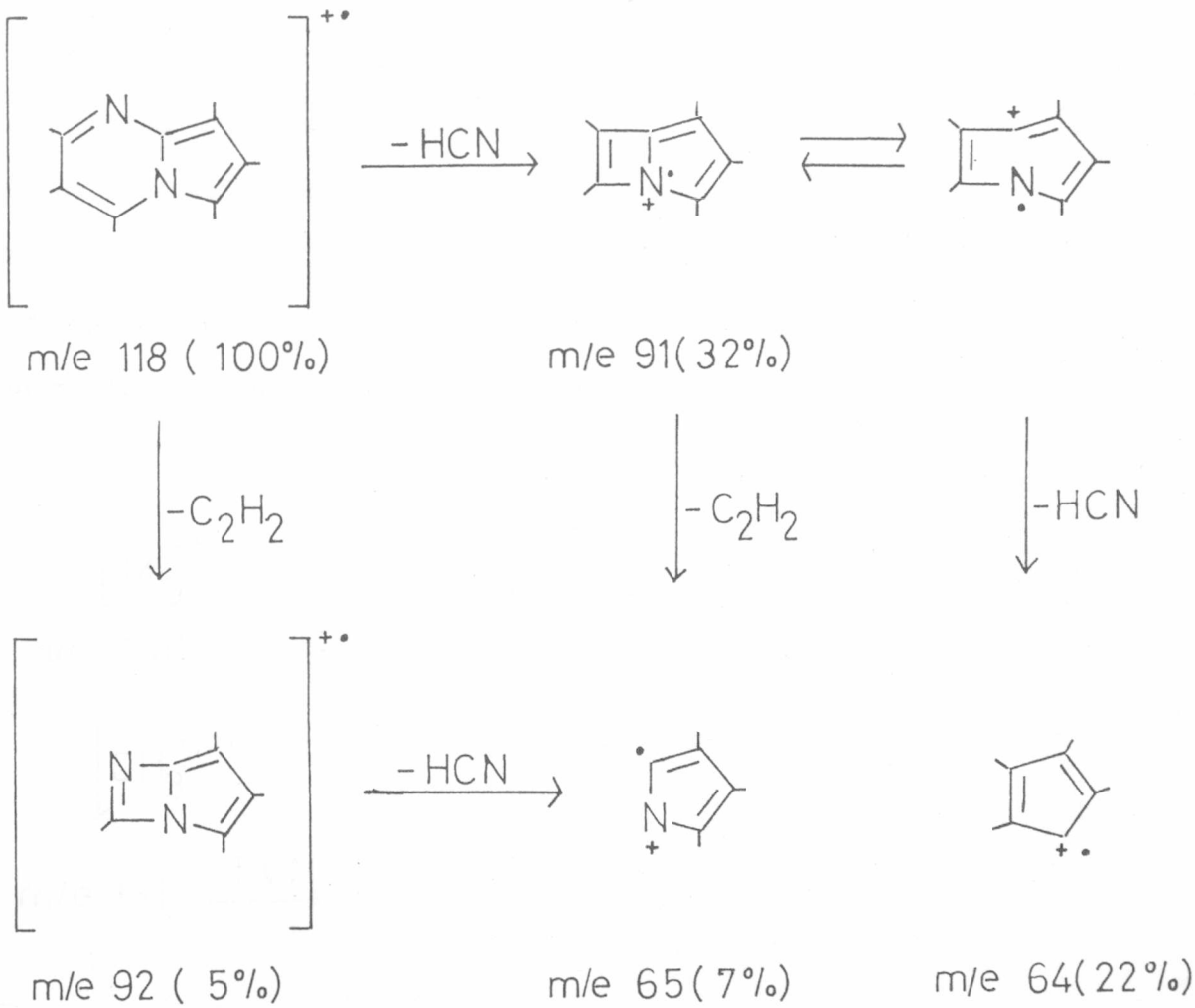


Figure V

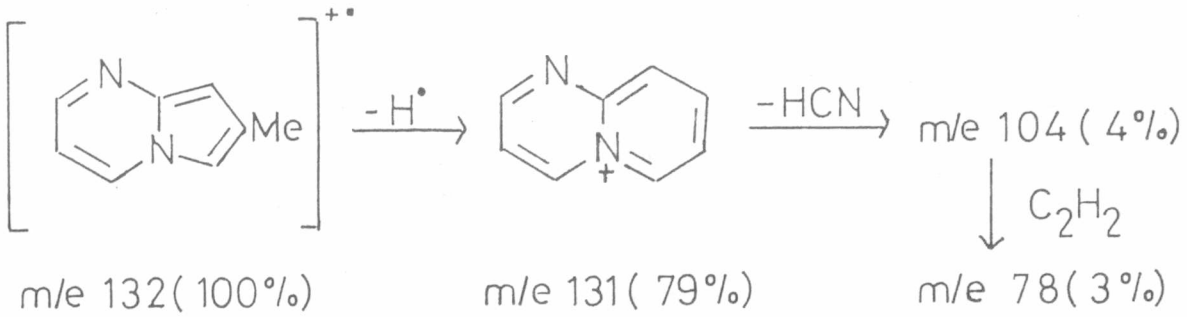


Mass spectra of 6- and 8- azaindolizines

The mass spectrum of 8-azaindolizine is shown in Figure IV. The intense peaks at m/e 91 (32%) and m/e 64 (22%) result from the consecutive losses of 27 mass units from the molecular ion at m/e 118 (100%). These transitions, m/e 118 → 91 and m/e 91 → 64, are accompanied by corresponding metastable peaks at m/e 70 and 45 and are most likely to be due to the expulsion of hydrogen cyanide. The next two most significant peaks at m/e 92 (5%) and 65 (7%) may be due to loss of acetylene from the molecular ion and from the fragment with m/e 91. A possible fragmentation scheme is shown below.



The mass spectrum of 2-methyl-8-azaindolizine is shown in Figure V. The main features are the intense molecular ion peak at m/e 132 (100%) and the loss of a hydrogen atom to give a large peak at m/e 131 (79%). The loss of a hydrogen atom which was accompanied by a metastable peak at m/e 130 suggests that ring expansion involving the carbon of the methyl group has occurred. This is supported by the absence of a peak at m/e 117 expected for loss of a methyl radical.



2,7-Dimethyl-6- and 8-azaindolizines and 2,3-dimethyl-8-azaindolizine also showed the loss of a hydrogen atom and a corresponding metastable peak but additionally showed the loss of a methyl radical from the molecular ion. The relative intensities of the main fragment ions in the spectra of these dimethyl azaindolizines are given in Table VI overleaf and may be accounted for by the scheme shown below.

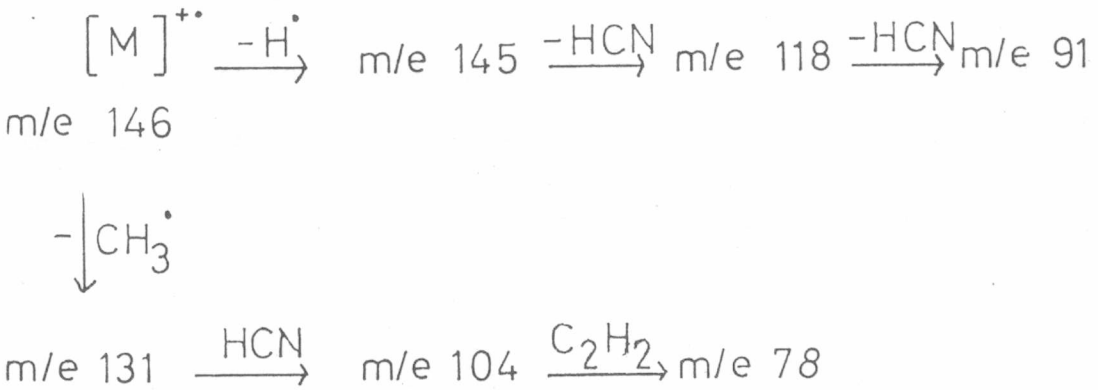


Table VI[a]

Relative intensities (%) in the mass spectra of dimethyl-6- and 8- azaindolizines

m/e	2,7-dimethyl-6-azaindolizine	2,7-dimethyl-8-azaindolizine	2,3-dimethyl-8-azaindolizine
146 (M^+)	100	100	71
145	28	50	100
131	3	3	3
118	20	4	1
104	8	6	0.5
91	4	2	0.5
78	1	8	1
73 (M^{2+})	2	5	2

[a] All other ions in the range studied had peaks with relative intensities less than 5%.

The mass spectra discussed in this section are consistent with those reported for indolizines[113] and 1- and 2- azaindolizines[114].

The Chichibabin reactions described in this Chapter provide convenient routes to a number of 6- and 8- azaindolizines from methylpyrimidines. 4,6-Dimethyl and 2,4,6-trimethylpyrimidines give 6-azaindolizines whereas 2-methyl and 2,4-dimethylpyrimidines give 8-azaindolizines. The parent 8-azaindolizine was isolated by hydrolysis and decarboxylation of its 2-carbethoxy derivative resulting from the Chichibabin reaction between 2-methylpyrimidine and ethyl bromopyruvate. The yields obtained were generally low ($<15\%$) particularly in the syntheses of the 8-azaindolizines. Exceptionally, the reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide gave 7-methoxy-2-phenyl-8-azaindolizine in 27% yield. 4-Methoxy-2-methylpyrimidine also gave a number of 8-azaindolizinones. In cases where the Chichibabin reaction can lead to isomeric products, formylation procedures described in the next Chapter confirmed the original assignments.

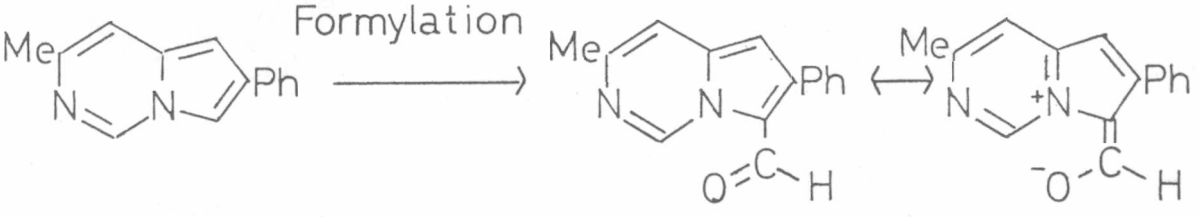
CHAPTER III

Formylation studies and cycloaddition reactions on 6- and 8- azaindolizines

Vilsmeier formylation was carried out firstly to confirm the structures of the 6- and 8- azaindolizines and 8-azaindolizinones isolated from the Chichibabin reactions described in Chapter II and secondly to determine their preferred site(s) of electrophilic substitution. 1,3-Dipolar addition reactions with dimethyl acetylenedicarboxylate, and a few other electrophilic substitution reactions are also described.

Formylation of (a) 7-methyl-2-phenyl-, (b) 2,7-dimethyl- and (c) 2,3,7-trimethyl-6-azaindolizine

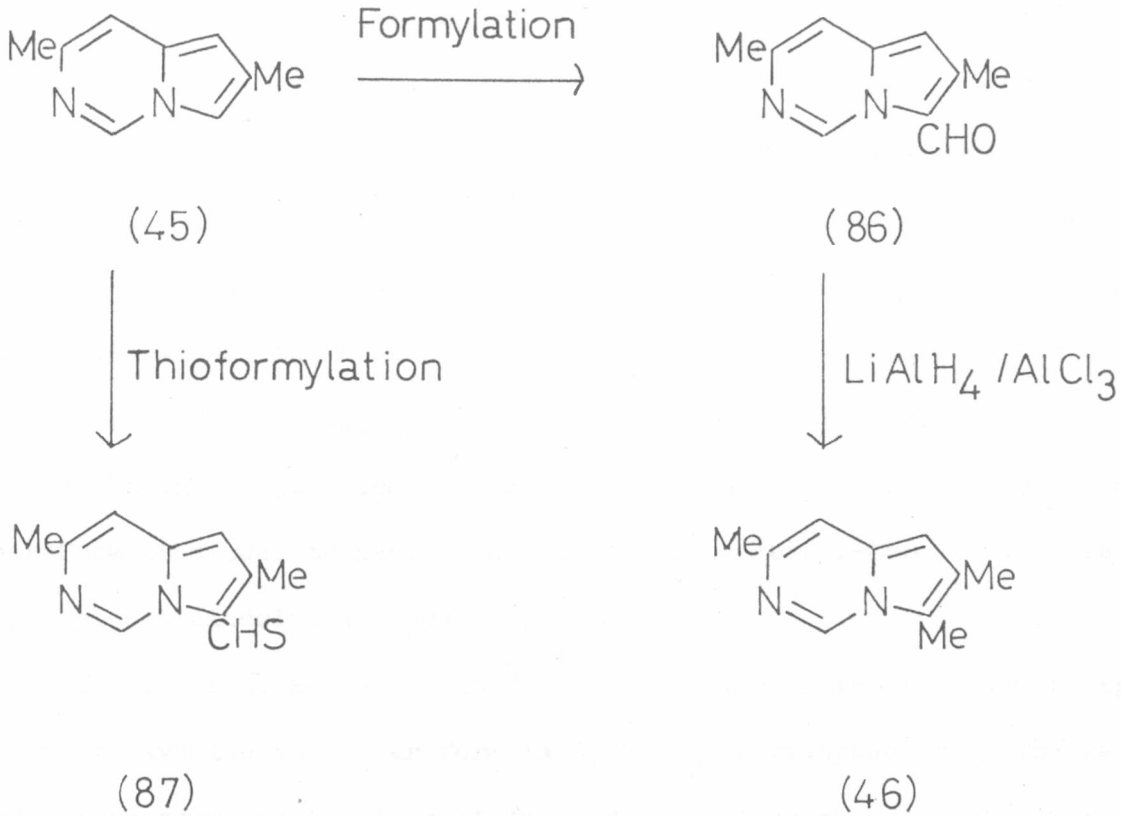
(a) Vilsmeier formylation [115] of 7-methyl-2-phenyl-6-azaindolizine (44) with a slight excess of phosphoryl chloride in dimethylformamide gave a mono-formyl derivative. The NMR spectrum of this aldehyde when compared with the parent compound (44) showed the absence of the signal attributed to H-3, the emergence of a 1H formyl singlet at δ 9.74 and a large down-field shift of 116 Hz in the absorption position of the singlet assigned to H-5 (see Table III p34 and Table VII p74). To account for these observations formylation must have occurred at C-3 to give the aldehyde (84). In this structure the formyl group would be expected to exert an anisotropic deshielding effect on the peri orientated H-5 proton [36, 116]. Addition of a drop of deuterotrifluoroacetic acid to the sample in deuterochloroform resulted in a slow reduction in the intensity of the signal assigned to H-1. The infra-red spectrum of the aldehyde (84) showed a low wavenumber carbonyl absorption at 1636 cm^{-1} and suggests canonical form (85) to make a significant contribution to the hybrid structure.



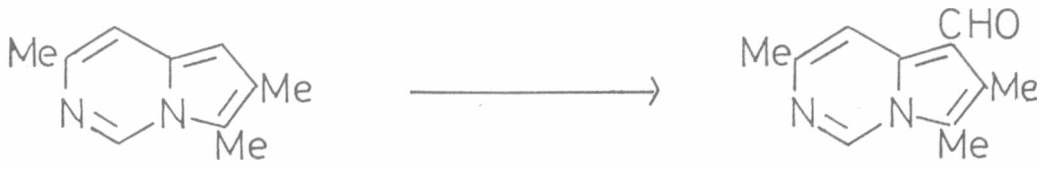
(44) (84) (85)

(b) Formylation of 2,7-dimethyl-6-azaindolizine (45) similarly gave a 3-formyl derivative (86). The NMR spectrum of this aldehyde when compared with (45) showed the signal assigned to H-5 to have undergone the peri shift of 168 Hz. By pouring the intermediate Vilsmeier salt into aqueous sodium hydrogen sulphide [116] rather than sodium hydroxide, the 6-azaindolizine (45)

gave a stable 3-thioformyl derivative (87). The NMR spectrum of the thioaldehyde showed the thioformyl proton to absorb at δ 10.71 and the signal assigned to H-5 to have undergone a peri shift of 305 Hz. Unequivocal proof that formylation had occurred at C-3 was obtained by lithium aluminium hydride/aluminium chloride reduction of the aldehyde (86). This gave 2,3,7-trimethyl-6-azaindolizine (46) which showed identical melting point and spectral characteristics to the product obtained from the Chichibabin reaction between 4,6-dimethylpyrimidine and 3-bromo-2-butanone.



(c) Formylation of 2,3,7-trimethyl-6-azaindolizine (46) also gave a mono-formyl derivative. The NMR spectrum of this aldehyde when compared with that of (46) showed the absence of the signal attributed to H-1, the emergence of a 1H formyl singlet at δ 10.06 and a peri shift of 90 Hz in the absorption positions of the signal assigned to H-8. Formylation must have occurred at C-1 to give (88).

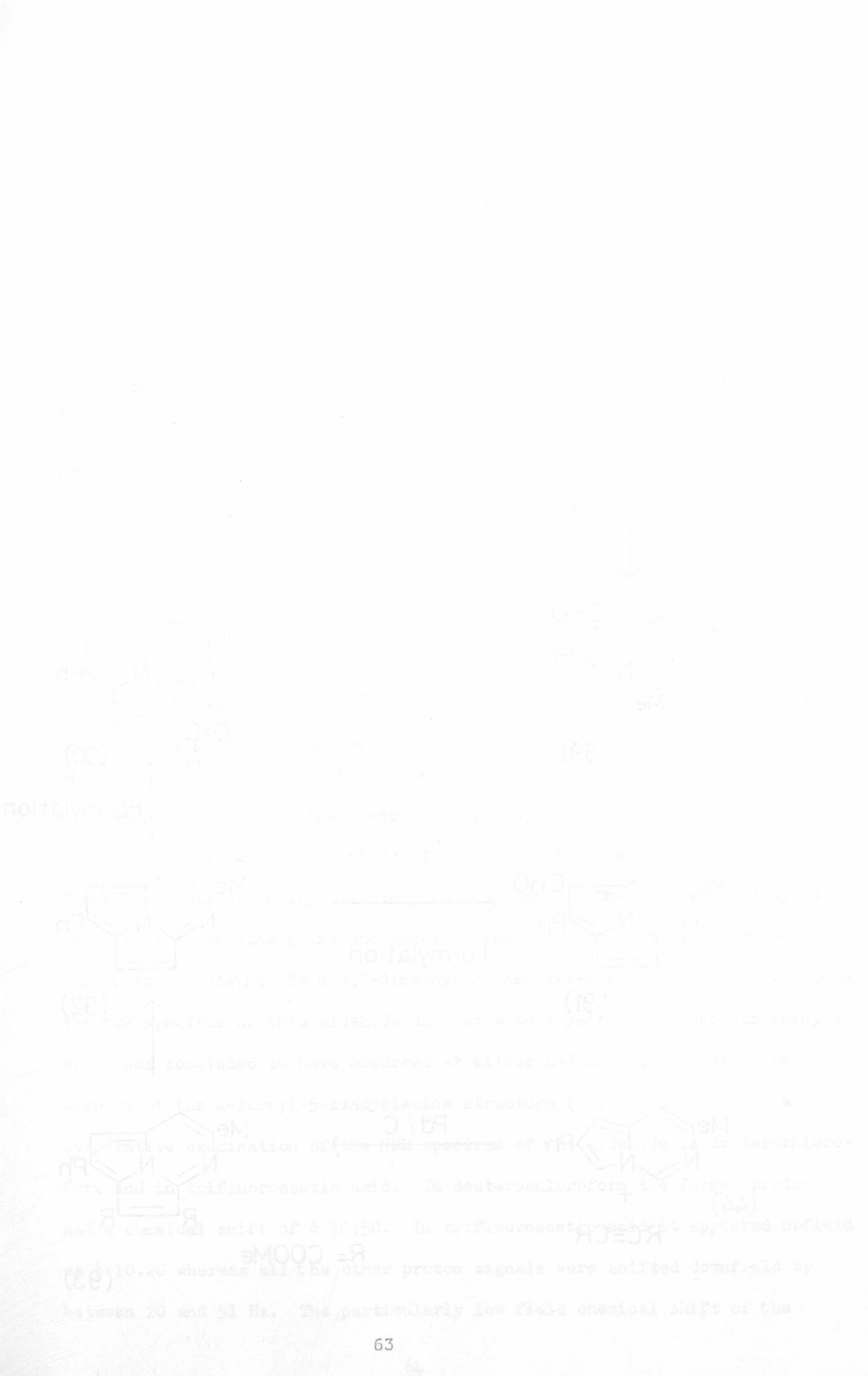


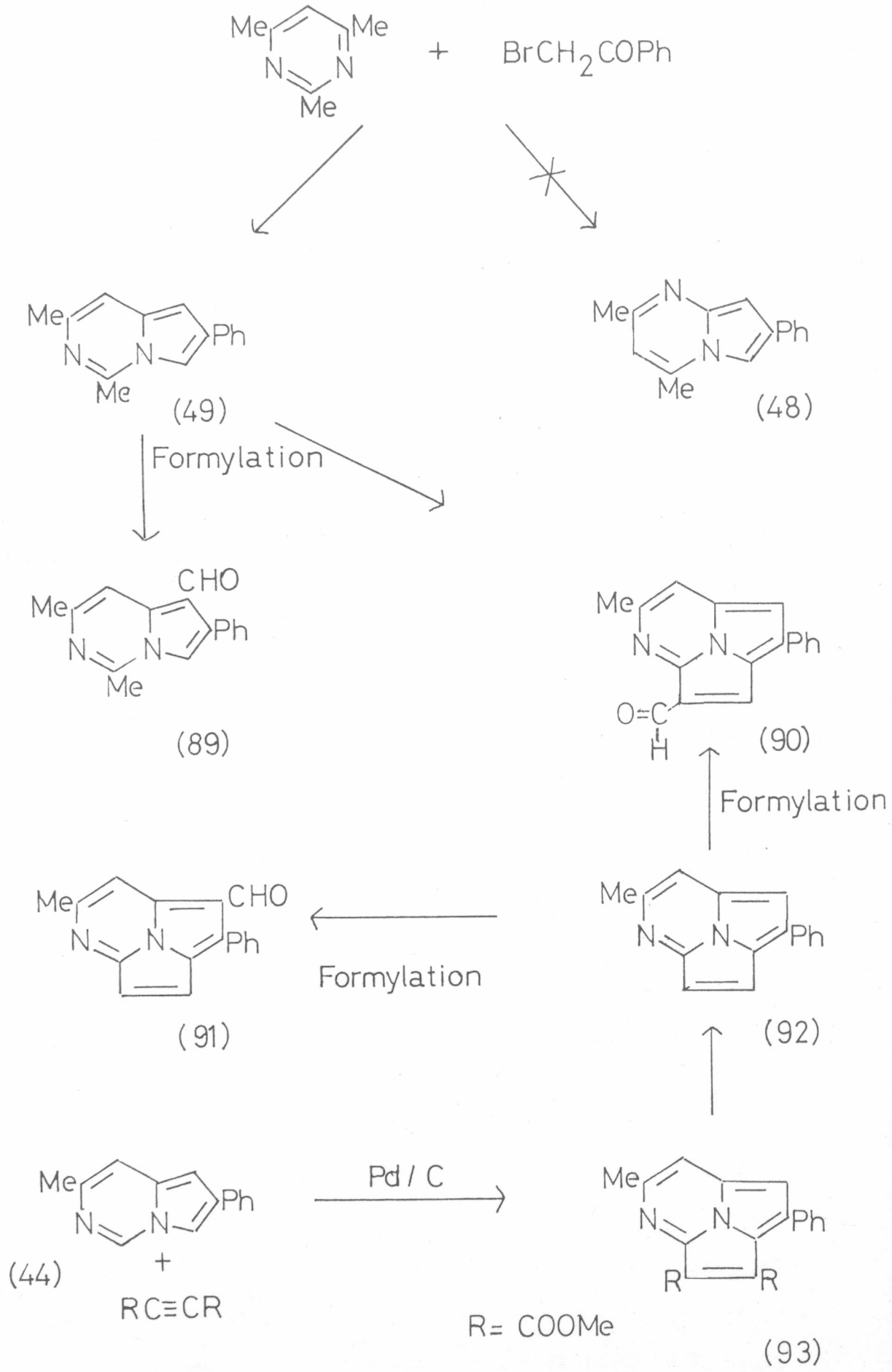
(46) (88)

Formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine

Vilsmeier formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (49) obtained from the reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide gave two mono-formyl products. The spectral characteristics of one of these indicated it to be a simple formyl derivative. The NMR spectrum of this aldehyde when compared with that of the parent 6-azaindolizine (49) showed the absence of the signal attributed to H-1, the emergence of a 1H formyl singlet at δ 9.98 and a downfield peri shift of 116 Hz in the absorption position of the signal assigned to H-8. Formylation was therefore concluded to have occurred at C-1 to give 1-formyl-5,7-dimethyl-2-phenyl-6-azaindolizine (89).

The other aldehyde isolated was shown by high resolution mass spectrometry to have the molecular formula $C_{17}H_{12}N_2O$ corresponding to the gain of one carbon atom and the loss of two hydrogen atoms when compared with the 1-formyl-6-azaindolizine (89). The NMR spectrum showed a 3H methyl singlet at δ 3.01, three 1H singlets (δ 7.42, 7.67, 8.37), a complex phenyl signal at δ 7.30-8.06, and a low field 1H formyl singlet at δ 10.50. This suggested the compound to be a formyl derivative of 6-methyl-2-phenyl-5-azacycl[3,2,2]-azine (92). Since the NMR spectrum did not show a pair of 1H doublets the formyl group must be located at either C-3 or C-4. Irradiation at the frequency of the methyl signal resulted in sharpening of the 1H singlet at δ 7.67. The signal at δ 7.67 was therefore assigned to H-7. The azacycl-




Me
Me
N
N
Me
+
BrCH2COPh
Me
N
Ph
N
Me
(49)
Me
N
N
Ph
Me
(48)
Formylation
CHO
Me
N
N
Ph
Me
(89)
Me
N
N
Ph
O=C
H
(90)
Formylation
Me
N
N
Ph
(92)
Me
N
N
Ph
CHO
(91)
Formylation
Me
N
N
Ph
(44)
+
RC≡CR
Pd / C
Me
N
N
Ph
R
R
R= COOMe
(93)

azine structure was confirmed by the alternative synthesis described below. Formylation of the alternative 8-azaindolizine structure (48) from the reaction between 2,4,6-trimethylpyrimidine and phenacyl bromide could in no way be expected to show a peri shift on formylation at any of its unsubstituted ring positions, or to yield a 6-methyl-2-phenyl-5-azacycl-[3,2,2]azine structure.

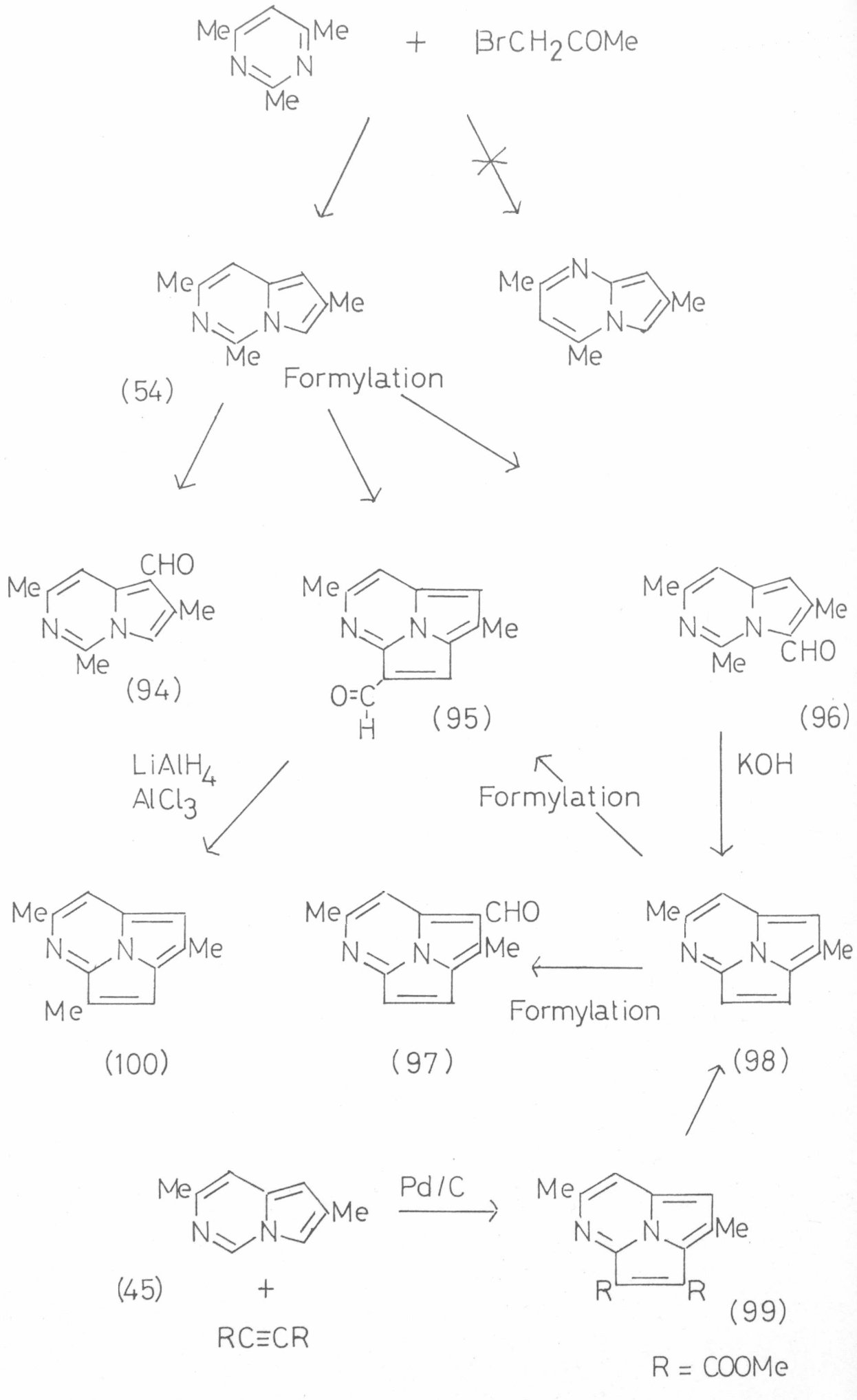
Synthesis and formylation of 6-methyl-2-phenyl-5-azacycl[3,2,2]azine

A 1,3-dipolar addition reaction between 7-methyl-2-phenyl-6-azaindolizine (44) and dimethyl acetylenedicarboxylate gave the 5-azacyclazine diester (93) which on hydrolysis and decarboxylation gave 6-methyl-2-phenyl-5-azacycl[3,2,2]azine (92)[35]. The NMR spectrum of this azacyclazine (92)(see Table VIII p82) consisted of a 3H methyl singlet at δ 2.93, two 1H singlets at δ 7.24 and 7.58, a pair of 1H doublets at δ 7.20 and 7.91 (J = ca 4.0 Hz), and a complex phenyl signal at δ 7.34-8.06. Irradiation at the frequency of the methyl signal resulted in sharpening of the 1H singlet at δ 7.58. The singlet at 7.58 was therefore assigned to H-7 and that at δ 7.24 to H-1. On the basis of a comparison with the NMR spectrum[117] of cycl[3,2,2]azine itself the higher field of the two 1H doublets (δ 7.20) was assigned to H-4 and the lower (δ 7.91) to H-3.

Vilsmeier formylation of the azacyclazine (92) gave two isomeric monoformyl derivatives in approximately equal amounts. One of these aldehydes had identical melting point and spectral characteristics to the formylazacyclazine obtained from 5,7-dimethyl-2-phenyl-6-azaindolizine (49). Since the NMR spectrum of this aldehyde did not show a pair of 1H doublets formylation was concluded to have occurred at either C-3 or C-4. Evidence in support of the 4-formyl-5-azacyclazine structure (90) was obtained by a comparative examination of the NMR spectrum of the aldehyde in deuterochloroform and in trifluoroacetic acid. In deuterochloroform the formyl proton had a chemical shift of δ 10.50. In trifluoroacetic acid it appeared upfield at δ 10.20 whereas all the other proton signals were shifted downfield by between 20 and 51 Hz. The particularly low field chemical shift of the

formyl proton in deuterochloroform and its anomalous upfield shift in trifluoroacetic acid can only be rationalised if the formyl group of the azacyclazine is at C-4. In this structure (90), the anisotropic deshielding effect [105,118] associated with the lone pair of electrons on N-5 results in a displacement of the formyl signal to lower field. In trifluoroacetic acid the formyl-azacyclazine (90) is protonated at N-5 and this effect is absent. The 4-formyl-azacyclazine structure was also supported by the observation that introduction of the formyl group into 6-methyl-2-phenyl-5-azacycl[3,2,2]azine (92) did not result in a significant shift in the resonance position of the phenyl protons.

The structure of the second aldehyde isolated was also deduced by NMR spectroscopy. The NMR spectrum of this aldehyde when compared with that of 6-methyl-2-phenyl-5-azacycl[3,2,2]azaine (92) showed the retention of the pair of doublets assigned to H-3 and H-4, the absence of the singlet attributed to H-1, the emergence of a 1H formyl singlet at δ 10.22, and a downfield shift of 62 Hz in the absorption position of the signal assigned to H-7. This aldehyde was therefore concluded to be 1-formyl-6-methyl-2-phenyl-5-azacycl[3,2,2]azine (91). The relatively small 62 Hz downfield peri shift in the absorption position of the H-7 signal in this 1-formyl-azacyclazine (91), compared with that of 90 Hz found for H-8 in 1-formyl-7-methyl-2-phenyl-6-azaindolizine, may be due to increased separation between the formyl group and the peri orientated proton in the azacyclazine (91). A similar small peri shift of 59 Hz has been reported for H-5 in 2-azacycl-[3,2,2]azine on formylation at its C-4 site[105]. In trifluoroacetic acid the 1-formyl azacyclazine (91) was also concluded to protonate at N-5. Here however, all the proton signals were displaced to lower field; in particular the 1-formyl proton signal which occurred at δ 10.22 in deuterochloroform occurred at δ 10.33 in trifluoroacetic acid.


Me
Me
N
N
Me
+ BrCH2COMe
Me
Me
N
N
Me
Me
N
Me
Me
N
Me
(54)
Formylation
CHO
Me
Me
N
N
Me
(94)
Me
N
N
Me
O=C
H
(95)
Me
Me
N
N
Me
CHO
(96)
LiAlH4
AlCl3
Formylation
KOH
Me
N
N
Me
Me
(100)
Me
CHO
N
N
Me
(97)
Formylation
Me
N
N
Me
(98)
Me
N
N
Me
(45)
+
RC≡CR
Pd/C
Me
N
N
Me
R
R
(99)
R = COOMe

Formylation of 2,5,7-trimethyl-6-azaindolizine

Vilsmeier formylation of 2,5,7-trimethyl-6-azaindolizine (54) obtained from the reaction between 2,4,6-trimethylpyrimidine and bromoacetone gave three aldehydes. The structures of two of these were analagous to the structures of the products obtained from formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (49) and were concluded to be 1-formyl-2,5,7-trimethyl-6-azaindolizine (94) and 4-formyl-2,6-dimethyl-5-azacycl[3,2,2]azine (95). The third aldehyde was isomeric with the 1-formyl-6-azaindolizine (94). Its NMR spectrum was similar to that of the parent 2,5,7-trimethyl-6-azaindolizine (54) except for the absence of the signal attributed to H-3 and the emergence of a 1H formyl singlet at δ 9.97. This aldehyde was therefore assigned as 3-formyl-2,5,7-trimethyl-6-azaindolizine (96). The NMR signal assignments of (96) were made with the assistance of double resonance and by deuterium exchange of H-1. Heating this aldehyde (96) with solid potassium hydroxide under vacuum resulted in the elimination of water between the 3-formyl group and the peri orientated C-5 methyl group to give 2,6-dimethyl-5-azacycl[3,2,2]azaine (98). The azacyclazine structures (95) and (98) were confirmed by their alternative synthesis as described overleaf. Hydride reduction of 3-formyl-2,5,7-trimethyl-6-azaindolizine (96) gave 2,3,5,7-tetramethyl-6-azaindolizine which on subsequent formylation gave 1-formyl-2,3,5,7-tetramethyl-6-azaindolizine.

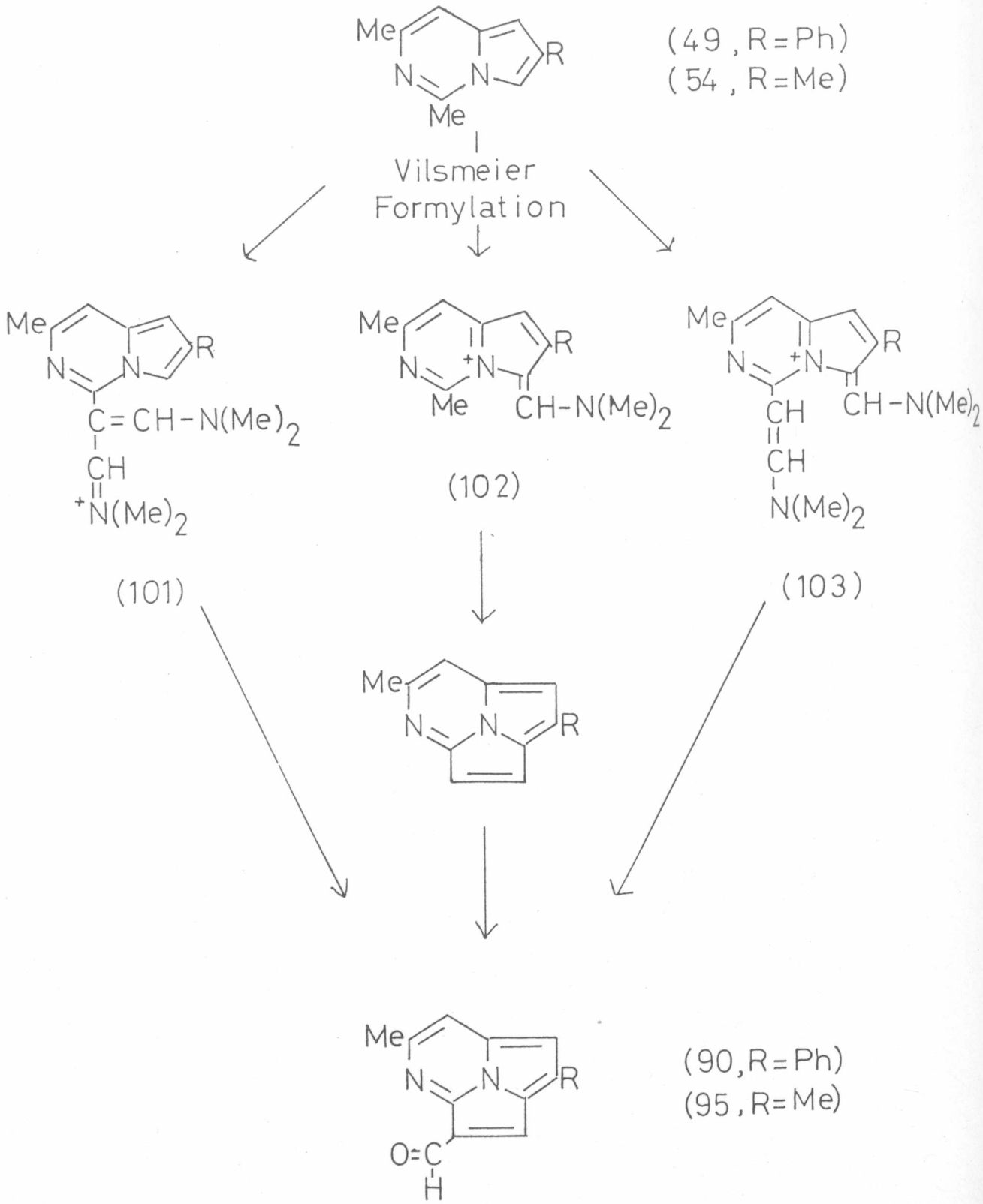
Synthesis and formylation of 2,6-dimethyl-5-azacycl[3,2,2]azine

A 1,3-dipolar addition reaction between 2,7-dimethyl-6-azaindolizine (45) and dimethyl acetylenedicarboxylate gave the 5-azacyclazine diester (99) which on hydrolysis and decarboxylation gave 2,6-dimethyl-5-azacycl[3,2,2]-azine (98) which had identical melting point and spectral characteristics to the sample obtained by the elimination of water from 3-formyl-2,5,7-trimethyl-6-azaindolizine (96). The NMR spectrum of the azacyclazine (98) consisted of two 3H methyl singlets at δ 2.70 and 2.93, two 1H singlets at δ 6.81 and 7.52, and a pair of 1H doublets at δ 7.10 and 7.70 (J = ca 4.0 Hz). The signal assignments were made on the basis of a comparison with 6-methyl-2-phenyl-5-azacycl[3,2,2]azine (92) and by double resonance.

Vilsmeier formylation of the azacyclazine (98) gave two aldehydes which on the basis of a comparison of their NMR spectra with each other and with the NMR spectra of 1- and 4-formyl-6-methyl-2-phenyl-5-azacycl[3,2,2]azines (91) and (90) were concluded to be 1- and 4-formyl-2,6-dimethyl-5-azacycl-[3,2,2]azines (97) and (95). The 4-formyl-azacyclazine (95) was identical (mp, uv, ir and NMR) to the sample obtained from formylation of 2,5,7-trimethyl-6-azaindolizine. Lithium aluminium hydride/aluminium chloride reduction of the 4-formyl-azacyclazine (95) gave 2,4,6-trimethyl-5-azacycl-[3,2,2]azine (100). The NMR spectrum of this cyclazine consisted of three 3H methyl singlets (2.62, 2.70 and 2.94) and three 1H singlets (δ 6.87, 7.38 and 7.58). Signal assignments were made on the basis of a comparison with the NMR spectrum of 2,6-dimethyl-5-azacycl[3,2,2]azine and by irradiation at the frequency of each of the three methyl signals.

[illegible]

gave approximately equal amounts of [illegible] 4-formyl derivatives together with anthranilic [illegible] azacyclazine [illegible] route involving [illegible] (104) being operative then both the 1- and [illegible] derivatives [illegible] unformylated azacyclazines would have been expected products. Only their 4-formyl derivatives were isolated. Comparable cleavages have recently been reported[105,121] in the syntheses of the 4-formyl derivatives of 1- and 2-azacycl[3,2,2]azines


Me
R
N
N
Me
(49 , R=Ph)
(54 , R=Me)
Vilsmeier
Formylation
C=CH-N(Me)2
CH
+N(Me)2
(101)
CH-N(Me)2
(102)
CH
CH
N(Me)2
(103)
O=C
H
(90,R=Ph)
(95 , R=Me)

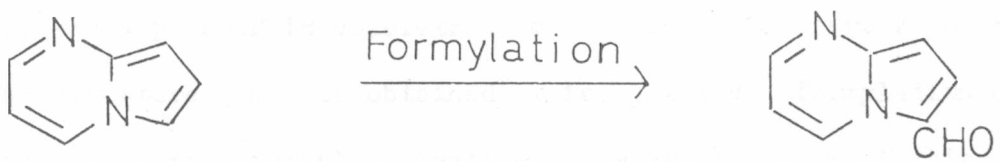
Mechanism of the formation of 4-formyl-azacycl[3,2,2]azines during Vilsmeier formylation of 5,7-dimethyl-2-phenyl- and 2,5,7-trimethyl-6-azaindolizines

There would appear to be three routes whereby the 4-formyl-5-azacycl-[3,2,2]azine structures (90) and (95) could be formed from the 6-azaindolizines (49) and (54) respectively. Firstly cyclisation could occur through an intermediate cation such as (102) formed by attack of the Vilsmeier electrophile[115] on the electron rich C-3 site of the azaindolizine followed by formylation of the resulting cyclazine. Secondly, attack by the electrophile on the active 5-methyl group of the 6-azaindolizine could give an intermediate such as (101) which on cyclisation and hydrolysis would be expected to yield a 4-formyl-5-azacycl[3,2,2]azine. Thirdly, attack by the electrophile at both the C-3 ring position and at the active 5-methyl group could give an intermediate such as (103) which on cyclisation and hydrolysis would also give a 4-formyl-azacyclazine. A similar intermediate to (101) has been suggested[119] to account for the formation of 3-formyl-4,7-diazaindole from 2-amino-3-methylpyrazine and in the conversion of hydrazones to pyrazoles[120]. The formation of 3-formyl-2,5,7-trimethyl-6-azaindolizine (96) from 2,5,7-trimethyl-6-azaindolizine would be expected to occur via the cation (102) so that the 4-formyl-azacyclazines could be formed via intermediates (102) and (103). However, formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine gave no 3-formyl derivative suggesting that the access of the Vilsmeier electrophile to the C-3 site is hindered, and yet the 4-formyl-azacyclazine (90) was isolated. This infers that the 4-formyl-azacyclazines (90) and (95) are most likely to be formed through intermediates such as (101). Furthermore formylation of 6-methyl-2-phenyl- and 2,6-dimethyl-5-azacycl[3,2,2]azines (92) and (98) gave approximately equal amounts of their 1- and 4-formyl derivatives together with unchanged azacyclazines. Had the route involving intermediate (102) been operative then both the 1- and 4-formyl derivatives together with unformylated azacyclazines would have been expected products. Only their 4-formyl derivatives were isolated. Comparable findings have recently been reported[105,121] in the syntheses of the 4-formyl derivatives of 1- and 2-azacycl[3,2,2]azines

from the 5-methyl derivatives of 1- and 2-azaindolizines respectively by the action of butyl-lithium and dimethylformamide.

Formylation of 8-azaindolizine

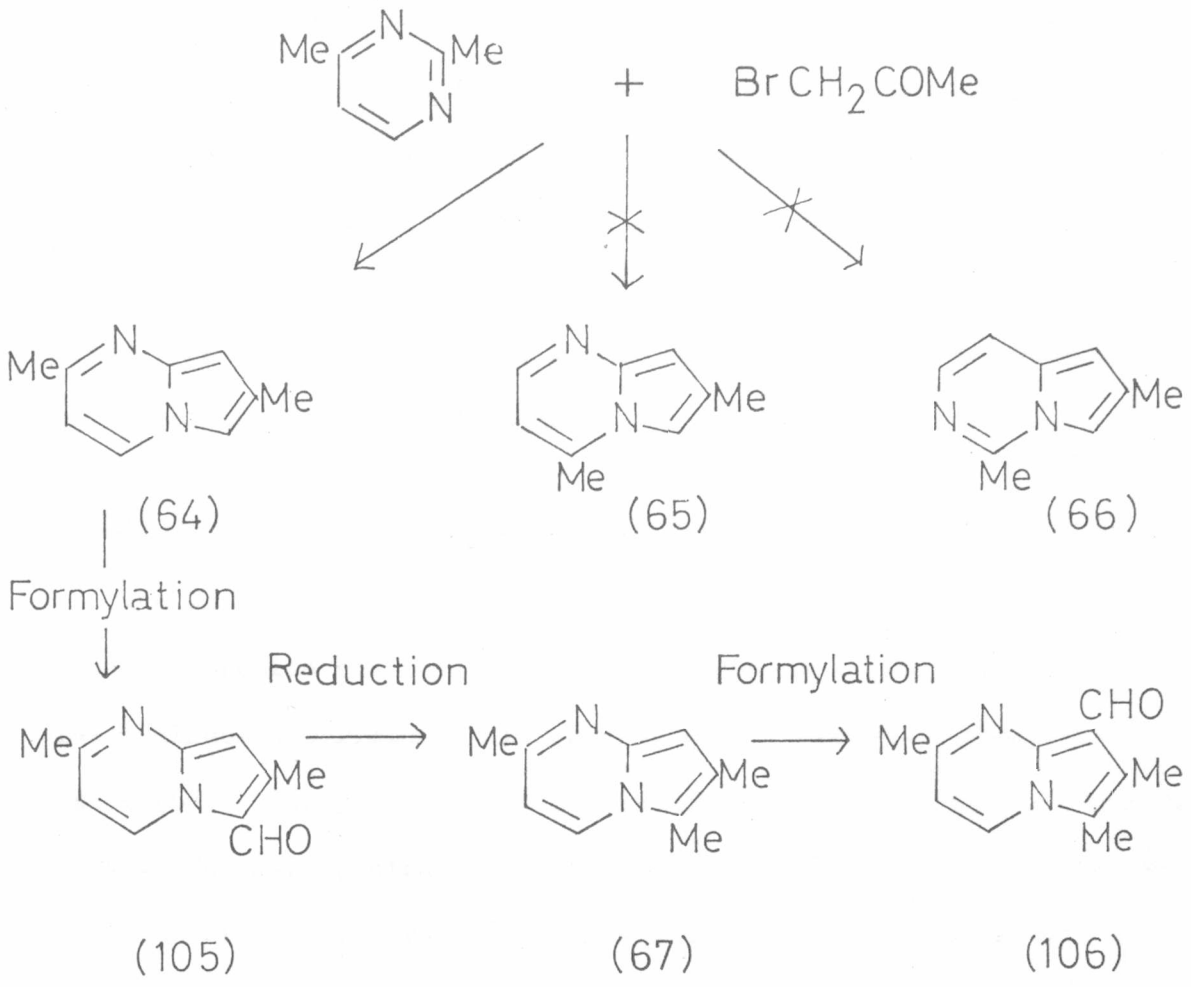
Formylation of the parent 8-azaindolizine (59) gave a mono-formyl derivative. The NMR spectrum of this aldehyde when compared with that of (59) showed the absence of the signal assigned to H-3, the emergence of a 1H formyl singlet at δ 9.73, and a peri shift of ca 170 Hz in the resonance position of the proton assigned to H-5. Formylation was therefore concluded to have occurred at C-3 to give 3-formyl-8-azaindolizine (104). The H-1 and H-2 proton signals appeared as a pair of doublets at δ 6.75 and 7.63, and the H-5, H-6 and H-7 signals as three 1H multiplets centred at δ 9.82, 6.93 and 8.47 respectively. Irradiation at the frequency of the signal assigned to H-7 simplified the two multiplets assigned to H-5 and H-6 to a pair of doublets (J = ca 7.0 Hz). The infra-red spectrum of the aldehyde(104) showed a low wavenumber carbonyl absorption at 1655 cm^{-1} indicating considerable polarisation of the carbon-oxygen double bond.



(59) (104)

Formylation of 2,7-dimethyl and 2,3,7-trimethyl-8-azaindolizine

The Chichibabin reaction between 2,4-dimethylpyrimidine and bromoacetone can lead to three isomeric azaindolizines (64), (65) and (66) of which 2,7-dimethyl-8-azaindolizine (64) is most likely on steric grounds (see Chapter II p42). The NMR spectrum of the azaindolizine which was isolated, consisted of two 3H methyl singlets at δ 2.30 and 2.43, two 1H singlets at δ 6.27 and



6.87, and a pair of 1H doublets at δ 6.27 and 7.90. Proof for the 8-azaindolizine structure (64) was obtained by formylation. Formylation of the azaindolizine gave a mono-formyl derivative. The NMR spectrum of this aldehyde when compared with that of the unformylated precursor showed the absence of the lower field 1H singlet, the emergenge of a 1H formyl singlet at δ 9.79 and a peri shift of 179 Hz in the chemical shift of the lower field component of the doublet system. Lithium aluminium hydride/aluminium chloride reduction of the aldehyde gave a trimethyl-azaindolizine identical to that obtained from the Chichibabin reaction between 2,4-dimethylpyrimidine and 3-bromo-2-butanone. Therefore the formyl group must have occupied a C-3,6- or 8-azaindolizine site. Of the three possible structures (64), (65) and (66) only (64) would be expected to show a large peri shift on formylation at C-3. The azaindolizine obtained from the reaction between 2,4-dimethylpyrimidine and bromoacetone

was therefore concluded to be 2,7-dimethyl-8-azaindolizine (64) and its formylation product to have structure (105). 2,7-Dimethyl-8-azaindolizine (64) also gave a stable 3-thioformyl derivative. Formylation of 2,3,7-trimethyl-8-azaindolizine (67) gave a 1-formyl derivative (106). The NMR spectrum of this aldehyde showed a particularly low field 1H formyl singlet at δ 10.43 due to the anisotropic deshielding effect of N-8 and its associated lone pair of electrons, and no large shifts in the resonance positions of any of the remaining protons.

Formylation of 7-methoxy-2-phenyl-8-azaindolizine

The Chichibabin reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide has been assumed to proceed via quaternisation at the least hindered pyrimidine nitrogen to give 7-methoxy-2-phenyl-8-azaindolizine (68). Formylation of this azaindolizine gave a mono-formyl derivative. The NMR spectrum of this aldehyde when compared with the NMR spectrum of its precursor (68) showed the absence of the signal attributed to H-3, the emergence of a 1H formyl singlet at δ 9.64 and a peri shift of 183 Hz in the resonance position of the signal assigned to H-5. Formylation must therefore have occurred at the C-3 site of the 8-azaindolizine (68) to give 3-formyl-7-methoxy-2-phenyl-8-azaindolizine (107). Formylation of the alternative 5-methoxy-2-phenyl-8-azaindolizine (108) would in no way be expected to show a peri shift.

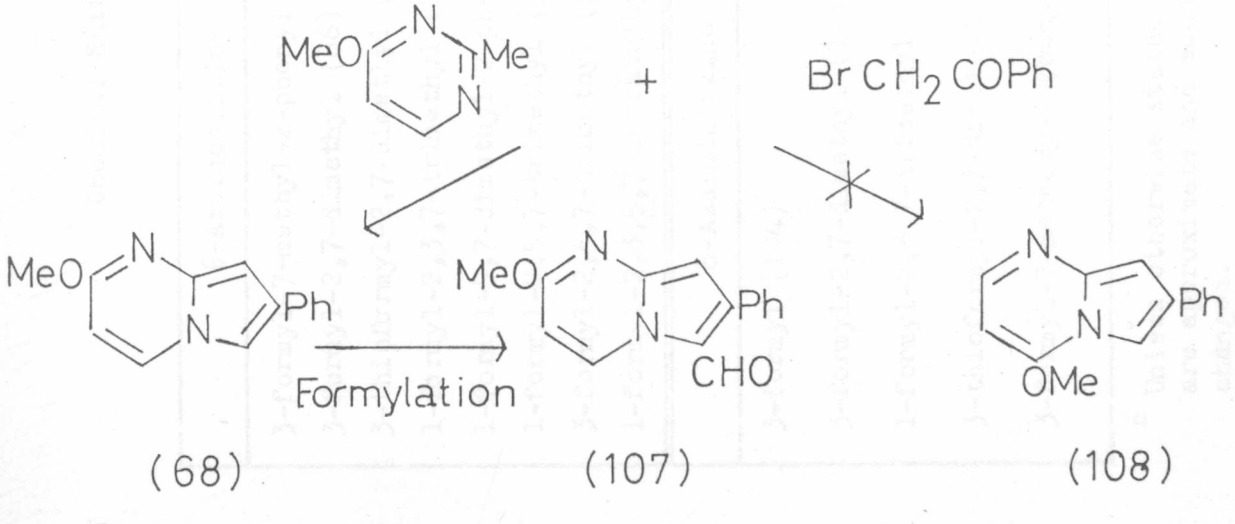


Table VII[a]

Chemical Shifts (δ) in the 100 MHz NMR spectra of formyl-6- and 8-azaindolizines in $CDCl_3$

6-Azaindolizine	1	2	3	5	7	8
3-formyl-7-methyl-2-phenyl (84)	6.48	7.40-7.62 m	9.74	10.36	2.54	7.25
3-formyl-2,7-dimethyl (86)	6.23	2.54	9.85	10.26	2.60	7.16
3-thioformyl-2,7-dimethyl (87)	6.35*	2.51*	10.71	11.63	2.53	7.24
1-formyl-2,3,7-trimethyl (88)	10.06	2.43	2.43	8.63	2.51	7.80
1-formyl-5,7-dimethyl-2-phenyl (89)	9.98	7.36-7.60 m	7.18	2.81	2.52*	8.04*
1-formyl-2,5,7-trimethyl (94)	10.06	2.51*	6.95*	2.74	2.49*	7.74*
3-formyl-2,5,7-trimethyl (96)	6.26*	2.59*	9.97	2.98	2.45*	7.00*
1-formyl-2,3,5,7-tetramethyl (p 67)	10.02	(2.39)	(2.66)	3.01	2.42*	7.73*
8-Azaindolizine	**1**	**2**	**3**	**5**	**6**	**7**
3-formyl (104)	6.75 d J = 5.0	7.63 d J = 5.0	9.73	9.82 dd J = 2.0, 7.0	6.93 dd J = 4.0, 7.0	8.47 dd J = 2.0, 4.0
3-formyl-2,7-dimethyl (105)	6.35	2.57	9.79	9.69 d J = 7.0	6.73 d J = 7.0	2.57
1-formyl-2,3,7-trimethyl (106)	10.43	(2.58)	(2.32)	7.91 d J = 7.0	6.70 d J = 7.0	(2.51)
3-thioformyl-2,7-dimethyl (p 73)	6.48*	2.54*	10.65	11.26 d J = 7.0	6.90 d J = 7.0	2.61
3-formyl-7-methoxy-2-phenyl (107)	6.45	7.32-7.72 m	9.64	9.73 d J = 7.0	6.45 d J = 7.0	4.04

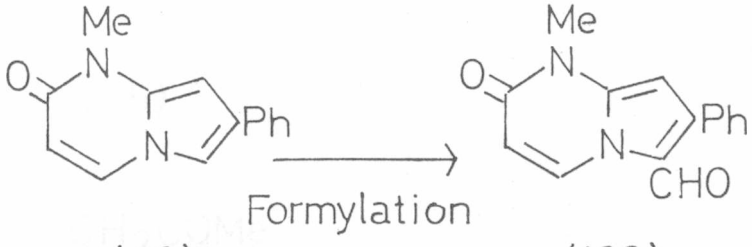
[a] Unless otherwise stated values refer to singlet absorption; d = doublet and m = multiplet. Coupling constants (Hertz) are approximate and measured directly from the spectra, Assignments in parenthesis are tentative and may be interchanged.

* Indicates pairs of signals found by double resonance to be weakly coupled to each other.

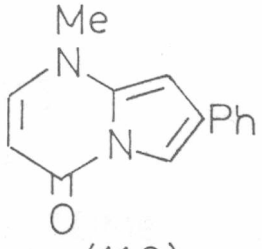
Formylation of 8-azaindolizin-7(8H)-ones

The main product obtained from the reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide at 40° has been assumed to be 8-methyl-2-phenyl-8-azaindolizin-7(8H)-one (69) formed via quaternisation at the least hindered pyrimidine nitrogen. Formylation of the azaindolizinone gave a mono-formyl derivative. The NMR spectrum of this aldehyde when compared with the NMR spectrum of the azaindolizinone (69) showed the absence of the signal attributed to H-3, the emergence of a 1H formyl singlet at δ 9.57, and a peri shift of 166 Hz in the resonance position of the signal attributed to H-5. Formylation is therefore concluded to have occurred at C-3 to give 3-formyl-8-methyl-2-phenyl-8-azaindolizin-7(8H)-one (109). Formylation of the alternative azaindolizinone (110) would not be expected to result in such a peri shift.

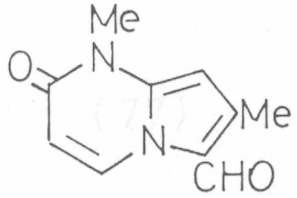
Similarly, formylation of 2,8-dimethyl-8-azaindolizin-7(8H)-one (74) and 8-acetonyl-2-methyl-8-azaindolizin-7(8H)-one (78) gave their 3-formyl derivatives (111) and (112) with peri shifts of 159 and 162 Hz respectively in the resonance positions of the signals attributed to their H-5 protons.



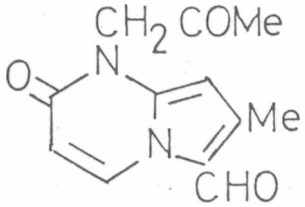
(69) (109)



(110)



(111)



(112)

Formylation of 8-azaindolizin-5(8H)-ones

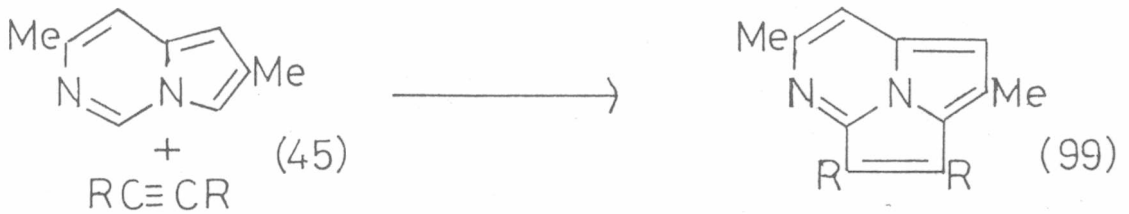
Two minor products isolated from the reaction between 4-methoxy-2-methylpyrimidine and bromoacetone have been assigned the azaindolizinone structures (75) and (77). Formylation of (75) gave a mono-formyl derivative. The NMR spectrum of this aldehyde when compared with that of (75) showed the absence of the signal attributed to H-3 and the emergence of a 1H formyl singlet at δ 11.00. Formylation was therefore concluded to have occurred at C-3 to give 3-formyl-2,8-dimethyl-8-azaindolizin-5(8H)-one (113). The particularly low field chemical shift of the formyl proton is presumably due to the combined anisotropic deshielding effect of the formyl and peri orientated ring carbonyl groups and possibly to hydrogen bonding between the formyl proton and the ring carbonyl. Similarly, formylation of the azaindolizine (77) gave its 3-formyl derivative (114) with a formyl signal at δ 10.95.

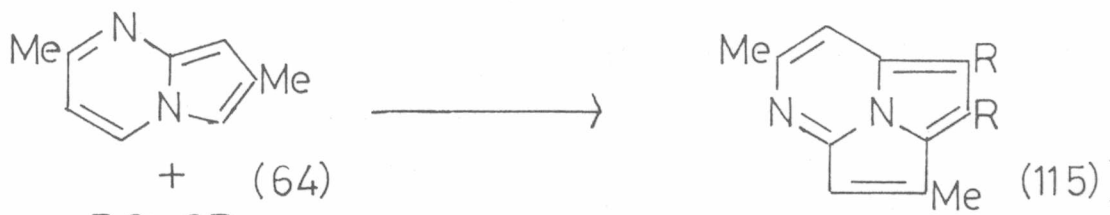
(75) (113)

(77) (114)

1,3-Dipolar addition reactions of (a) 2,7-dimethyl-8-azaindolizine and (b) 2,8-dimethyl-8-azaindolizin-7(8H)-one with dimethyl acetylenedicarboxylate

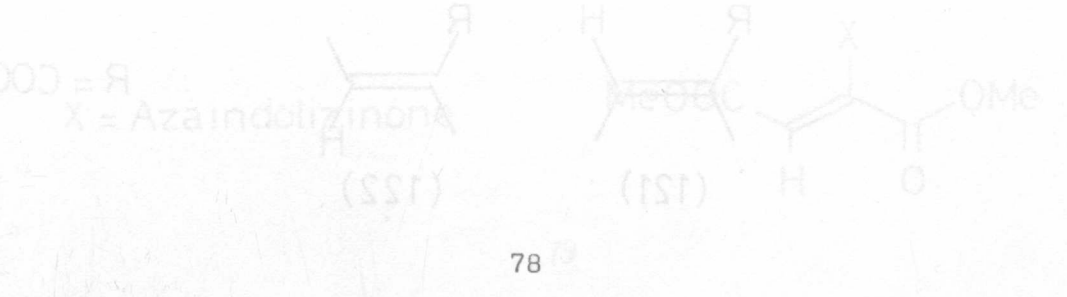
(a) 2,7-Dimethyl-6-azaindolizine (45) reacts with dimethyl acetylenedicarboxylate to give the 5-azacycl[3,2,2,]azine diester (99), see p 68. A similar reaction with 2,7-dimethyl-8-azaindolizine (64) gave the isomeric 5-azacycl[3,2,2]azine diester (115). The NMR spectrum of this diester consisted of two 3H singlets at δ 2.71 and 2.93 attributed to the protons of the methyl groups at C-3 and C-6 respectively, two 3H singlets at δ 3.99 and 4.07 attributed to the protons of the ester groups, and two 1H singlets at δ 7.04 and 7.99. Irradiation at the frequency of the signal at δ 7.04 resulted in sharpening of the signal attributed to Me-3. The signals at δ 7.04 and 7.99 were therefore assigned to H-4 and H-7 respectively.

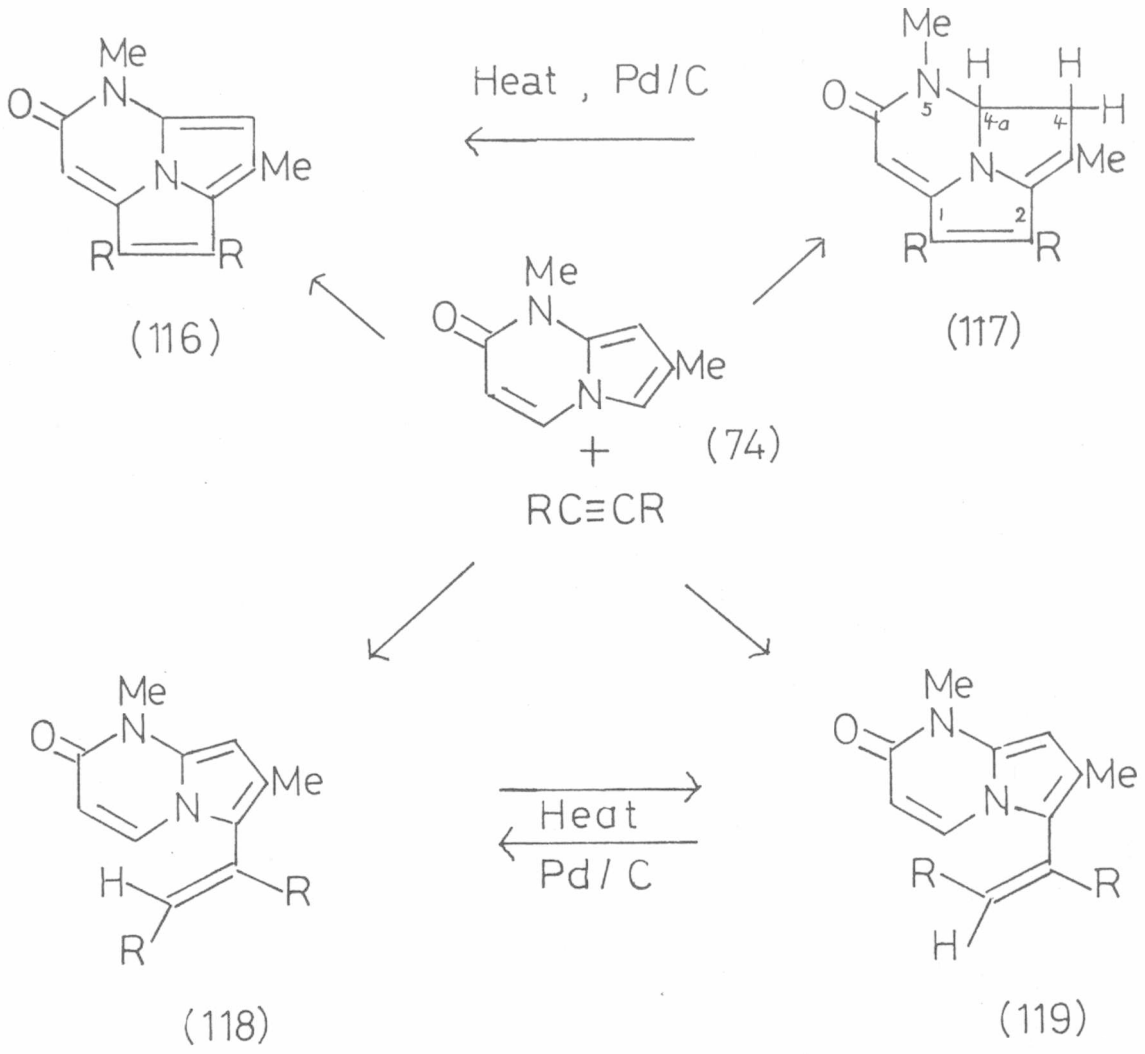


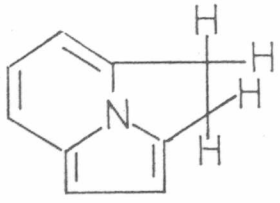


R= COOMe

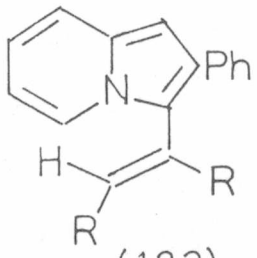
(b) 2,8-Dimethyl-8-azaindolizin-7(8H)-one (74) on reaction with dimethyl acetylenedicarboxylate gave four products. The main product was the azacycl[3,2,2] azin-6(5H)-one (116), as red crystals which exhibited a strong fluorescence in solution. The NMR spectrum showed two 3H singlets at δ 2.49 and 3.78 attributed to the protons of the methyl groups at C-3 and



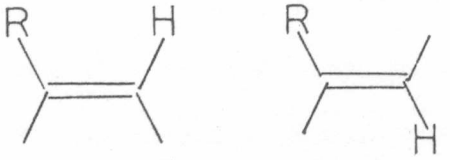




(120)



(123)



(121) (122)

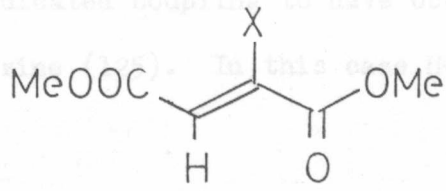
R = COOMe

N-5, two 3H singlets at δ 3.91 and 4.04 attributed to the protons of the ester groups, and two 1H singlets at δ 6.20 and 7.02. Irradiation at the frequency of the signal attributed to Me-3 resulted in sharpening of the singlet at δ 6.20. The signals at δ 6.20 and δ 7.02 were therefore assigned to H-4 and H-7.

The second product obtained was shown by mass spectrometry to have a molecular composition two mass units more than the azacyclazinone (116), and since it could be converted to (116) by heating in toluene in the presence of palladium on charcoal it was concluded to be a dihydro derivative of (116). The NMR spectrum of the dihydro derivative may be interpreted on the basis of the 4,4a-dihydro-azacyclazinone structure (117). The multiplicity of the signals at δ 2.47 and 3.12 attributed to the protons of the C-4 methylene function may be envisaged to arise mainly through coupling with each other (J = ca 15.5 Hz) and with the C-4a proton (J_{cis} = ca 14.5 Hz, J_{trans} = ca 15.5 Hz). Irradiation at the frequency corresponding to the centre of the multiplet assigned to the methine proton (δ 4.90) resulted in simplification of the signals attributed to the methylene protons to a pair of equally split doublets (J = ca 15.5 Hz). The reaction between indolizine and dimethyl acetylenedicarboxylate has also been reported to give a similar dihydrocyclazine (120)[14].

The other two products isolated were isomeric with the dihydro-azacyclazinone (117). The NMR spectra of these compounds indicated them to be the cis- and trans- stereoisomers (118) and (119). The vinyl proton of one stereoisomer absorbed at δ 5.93 whereas the vinyl proton of the other absorbed at δ 7.13. It is suggested that the vinyl proton of the trans isomer absorbs at lower field due to the anisotropic deshielding effect of the carbonyl group on the α-carbon atom of the C-3 side chain as shown in the conformation below[122].

X = Azaindolizinone



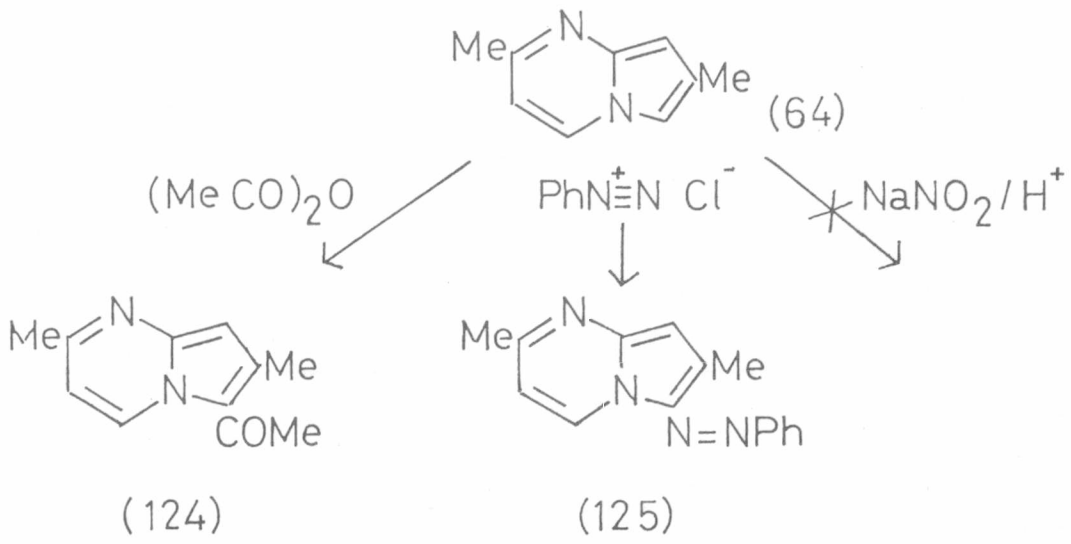
Differences between the chemical shifts of the β-olefinic protons in several pairs of cis- and trans-α:β-unsaturated carboxylic esters such as (121) and (122) have been reported in the range 0.5-0.9 ppm[123]. Heating solutions of either the cis- or trans- isomers in toluene in the presence of palladium on charcoal resulted in their partial interconversion but failed to yield any of the azacyclazinone structures (116) or (117). This suggests that the cis- and trans- isomers are not intermediates in the formation of (116) and (117) from the azaindolizinone (74). The reaction between 2-phenylindolizine and dimethyl acetylenedicarboxylate has similarly been reported to yield a vinyl derivative (123) although no stereochemical comment was made[124].

Acetylation, diazonium coupling and attempted nitrosation of 2,7-dimethyl-8-azaindolizine

In order to augment the formylation studies on 8-azaindolizines described earlier in this Chapter, and to complement the reported electrophilic substitution reactions of 6-azaindolizines[36], acetylation, diazonium coupling and nitrosation reactions were carried out on 2,7-dimethyl-8-azaindolizine (64).

(a) Acetylation Refluxing a solution of the 8-azaindolizine (64) in acetic anhydride gave an acetyl derivative. The NMR spectrum of this derivative when compared with the precursor (64) showed the absence of the signal attributed to H-3, the emergence of an additional 3H methyl singlet, and a downfield peri shift of 207 Hz in the position of the signal attributed to H-5. Acetylation was therefore concluded to have occurred at C-3 to give 3-acetyl-2,7-dimethyl-8-azaindolizine (124).

(b) Diazonium coupling The 8-azaindolizine (64) reacted with phenyldiazonium chloride to give an orange-red dye. The NMR spectrum of the dye when compared with the precursor indicated coupling to have occurred at C-3 to give the 3-phenylazo-8-azaindolizine (125). In this case H-5 underwent a peri shift of 197 Hz.



(124) (125)

(c) Attempted nitrosation Attempted nitrosation of the 8-azaindolizine (64) with sodium nitrite in aqueous acetic or hydrochloric acid gave dark coloured polymeric material from which no products or starting material could be isolated.

The results embodied in this Chapter show both 6- and 8- azaindolizines to undergo electrophilic substitution preferentially at C-3 and then at C-1. The parent 8-azaindolizine also underwent formylation at C-3 in agreement with the site expected from a consideration of theoretical π-electron density calculations (see Table I, p22). 8-Azaindolizinones also formylate preferentially at C-3.

Table VIII[a]

Chemical Shifts (δ) in the 100 MHz NMR spectra of 5-azacycl[3,2,2]azines in $CDCl_3$

5-Azacycl[3,2,2]azine	1	2	3	4	6	7
4-formyl-6-methyl-2-phenyl (90)	7.42	7.30-8.06 m	8.37	10.50	3.01*	7.67*
1-formyl-6-methyl-2-phenyl (91)	10.22	7.48-7.92 m	7.86 d J = 4.5	7.30 d J = 4.5	2.98*	8.20*
6-methyl-2-phenyl (92)	7.24	7.34-8.06 m	7.91 d J = 4.0	7.20 d J = 4.0	2.93*	7.58*
3,4-dicarbmethoxy-6-methyl-2-phenyl (93)	7.31	7.38-7.90 m	(4.06)	(3.98)	3.04*	7.70*
4-formyl-2,6-dimethyl (95)	6.98*	2.71*	8.10	10.45	2.99*	7.57*
1-formyl-2,6-dimethyl (97)	10.29	2.96	7.82 d J = 4.5	7.24 d J = 4.5	2.96	8.02
2,6-dimethyl (98)	6.81*	2.70*	7.70 d J = 4.0	7.10 d J = 4.0	2.93	7.52
3,4-dicarbmethoxy-2,6-dimethyl (99)	6.95*	2.71*	4.05	4.05	2.99	7.58
2,4,6-trimethyl (100)	6.87*	2.70*	7.38 *	2.62 *	2.94*	7.58*
1,2-dicarbethoxy-3,6-dimethyl (115)	(3.99)	(4.07)	2.71*	7.04*	2.93	7.99

[a] Unless otherwise stated values refer to singlet absorption; d = doublet and m = multiplet. Coupling constants (Hertz) are approximate and measured directly from the spectra. Assignments in parenthesis are tentative and maybe interchanged.

* Indicates pairs of signals found by double resonance to be weakly coupled to each other.

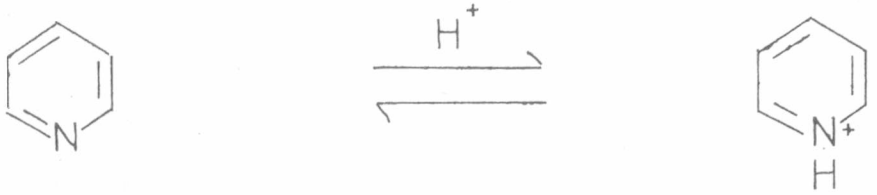
CHAPTER IV

Protonation studies on 6- and 8- azaindolizines and and azacyl[3,2,2]azines

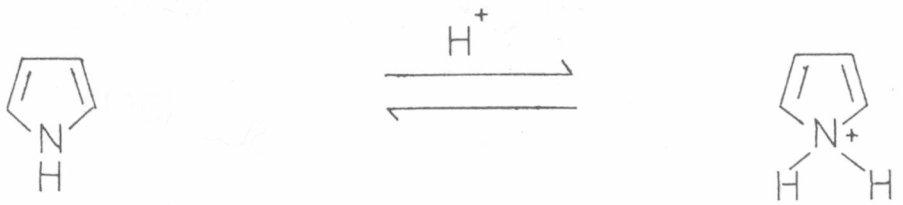
This Chapter discusses the protonation patterns of simple alkyl, aryl and alkoxy substituted 6- and 8- azaindolizines, the parent 8-aza-indolizine, 6- and 8- azaindolizinones, alkyl and aryl 5-azacycl[3,2,2]-azines, and 6-methyl-2-phenyl-4,5-diazacycl[3,2,2]azine. The sites of protonation were determined by a comparative examination of the NMR spectra recorded for solutions in deuterochloroform and trifluoroacetic acid. Proton assignments were made by a comparative examination of related spectra, by their proximity to nitrogen and with the aid of double resonance.

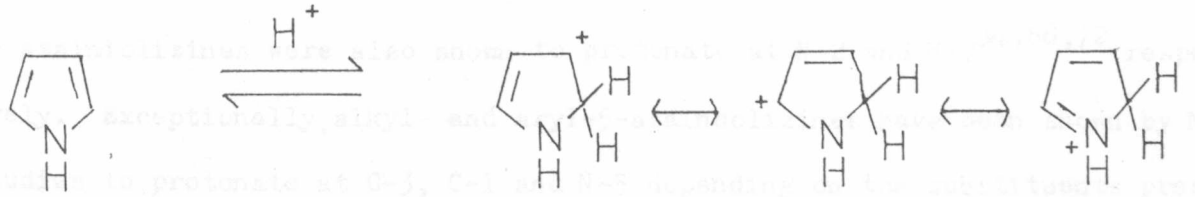
Introduction

Heteroaromatic nitrogen compounds may protonate at either nitrogen or carbon depending on the electronic arrangement of the nitrogen atoms[34]. If the nitrogen has its unshared pair of electrons in an sp^2 hybridised orbital as in pyridine then protonation generally occurs at nitrogen to give a conjugate acid which retains aromaticity.



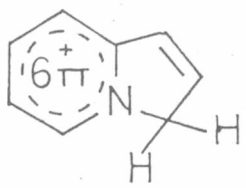
If the nitrogen has its unshared pair in a p-orbital as in pyrrole then protonation generally occurs at carbon. Protonation of pyrrole itself, whether at carbon or nitrogen, cannot give rise to an aromatic conjugate acid but occurs preferentially at C-2 to give the resonance stabilised cation (126)



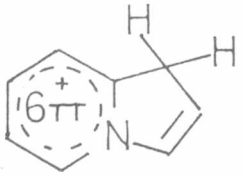


(126)

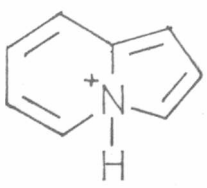
Indolizine which containes a bridgehead nitrogen of the pyrrole type has been shown to protonate preferentially at C-3 and then at C-1[70-73]. Here protonation at either C-3 or C-1 can lead to a conjugate acid (127) or (128) containing an aromatic pyridinium ring[69]. Protonation at the bridgehead nitrogen is not expected since this would lead to the formation of a non-aromatic conjugate acid (129).



(127)

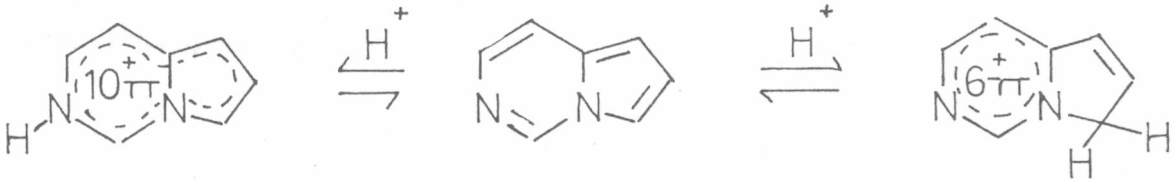


(128)



(129)

By analogy azaindolizines would be expected to offer three sites for protonation. Protonation at the non-bridgehead nitrogen can lead to a 10π-cation (130) whereas protonation at sites -1 or -3 can lead to a 6π-cation such as (131) as shown for 6-azaindolizine.



(130) (131)

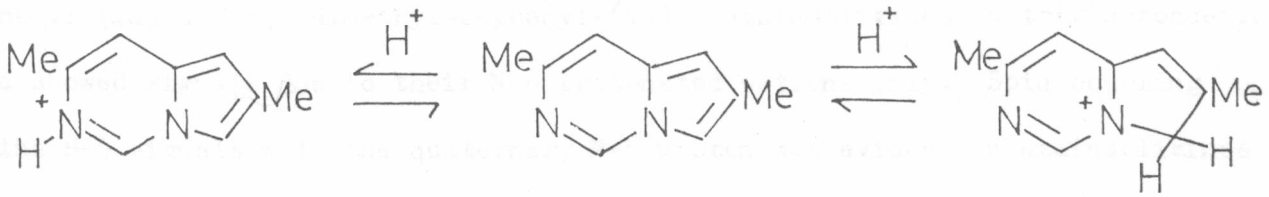
Ultra-violet and NMR studies on 1- and 3- azaindolizines have shown them to protonate at the non-bridgehead nitrogen. This is to be expected since the formation of both 6π- and 10π- cations is accommodated. The parent 2- and 7- azaindolizines were also shown to protonate at N-2 and N-7[34,68,72] respectively. Exceptionally, alkyl- and aryl-5-azaindolizines have been shown by NMR studies to protonate at C-3, C-1 and N-5 depending on the substituents present and the protonating media[34,74]. No systematic studies on the protonation patterns of 6- and 8- azaindolizines have been made.

π-Electron density calculations[62] (see Table I, p22) on azaindolizines

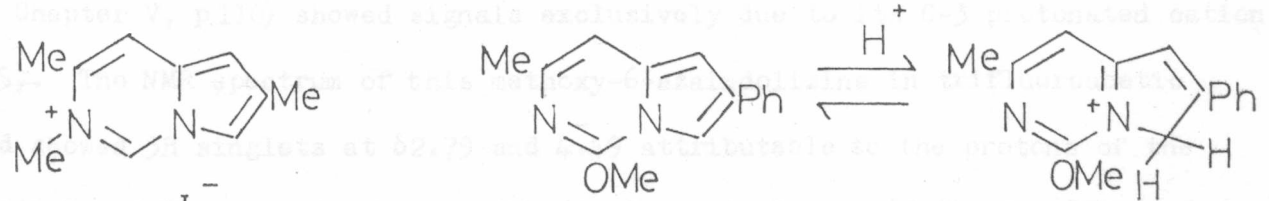
give the order of decreasing electron densities for 6-azaindolizine as N-4 ⟫ C-3 ⟩N-6 ⟫ C-1 and for 8-azaindolizine as N-4 ⟫ C-3 ⟩ N-8 ⟫ C-1. Assuming a correlations between these calculated π-electron densities and the preferred sites of electrophilic attack, and discounting the possiblility of protonation at the bridgehead nitrogens, protonation of both systems would be expected to occur firstly at their non-bridgehead nitrogens and/or at their C-3 sites and then at their C-1 sites.

Protonation of 6-azaindolizines

The least substituted 6-azaindolizine prepared in this work was 2,7-dimethyl-6-azaindolizine (45). The NMR spectrum of this compound in trifluoroacetic acid (see Table IX, p 92) indicated the presence of both N-protonated (85%) and C-protonated cations (15%). The NMR spectrum of the minor C-protonated species showed a midfield 2H methylene signal at δ5.60. Since the chemical shift of this methylene is within the range (δ5.36-5.91) reported for C-3 protonated indolizines in trifluoroacetic acid it is suggested that this species is the C-3 protonated cation (132). C-1 Protonated indolizines show corresponding methylene signals at significantly higher field (δ4.14-4.60)[71].



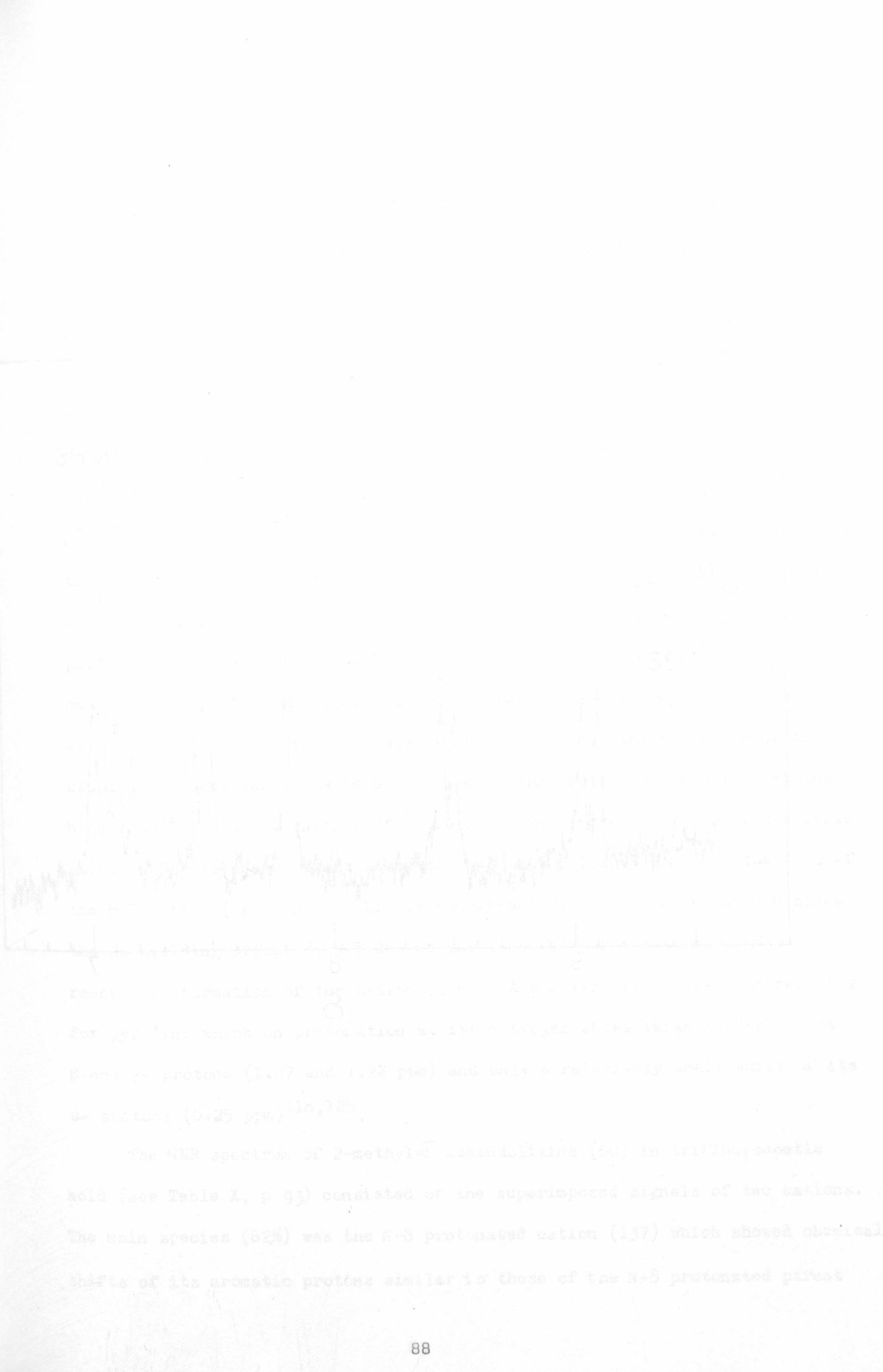
(133) (45) (132)



(134) (165) (135)

The NMR spectrum of the major N-protonated species (133) showed no direct evidence for a proton bound to quaternary nitrogen. Its presence was however implied by the multiplicity of the H-5 signal which appeared as a 1H doublet at δ9.45 (J = ca 6.0 Hz). The other aromatic 1H proton signals at δ6.72, 7.29 and 7.59 were assigned to H-1, H-8 and H-3 respectively. Further evidence for the N-protonated structure (133) was obtained by comparing its NMR spectrum with that of the quaternary methyl salt (134) in dimethylsulphoxide. These were closely similar apart from the presence of an additional 3H singlet at δ3.98 due to the quaternary methyl group and the absence of splitting of the signal attributed to H-5 in the spectrum of the latter. In addition, when the NMR spectrum of the perchlorate salt of 2,7-dimethyl-6-azaindolizine was recorded in deuterated dimethyl sulphoxide only the N-protonated cation (133) was observed with a spectral pattern similar to that of the main species generated from 2,7-dimethyl-6-azaindolizine in trifluoroacetic acid. However in the case of the perchlorate in dimethyl sulphoxide the quaternary proton was directly observed and appeared as a broad band centred at δ9.67.

The NMR spectra of 2,3,7-trimethyl-(46), 2,5,7-trimethyl-(54), 7-methyl-2-phenyl-(44) and 5,7-dimethyl-2-phenyl-(49) 6-azaindolizines in trifluoroacetic acid showed signals due to their N-6 protonated cations only. Spin coupling of the H-5 signals with the quaternary N-6 proton was evident in azaindolizines (44) and (46) even although the quaternary proton was not directly observed. In contrast to this preference for N-protonation in the cases of these alkyl- and aryl-6-azaindolizines, 5-methoxy-7-methyl-2-phenyl-6-azaindolizine (165, see Chapter V, p110) showed signals exclusively due to its C-3 protonated cation (135). The NMR spectrum of this methoxy-6-azaindolizine in trifluoroacetic acid showed 3H singlets at δ2.79 and 4.49 attributable to the protons of the 7-methyl and 5-methoxy groups, a 2H methylene singlet at δ5.55, two 1H singlets at δ7.25 and 7.38, and a complex phenyl absorption at δ7.45-7.85. Irradiation at the frequency of the methyl signal at δ2.79 resulted in sharpening of the signal at δ7.38. The signals at δ7.38 and 7.25 were therefore assigned to H-8

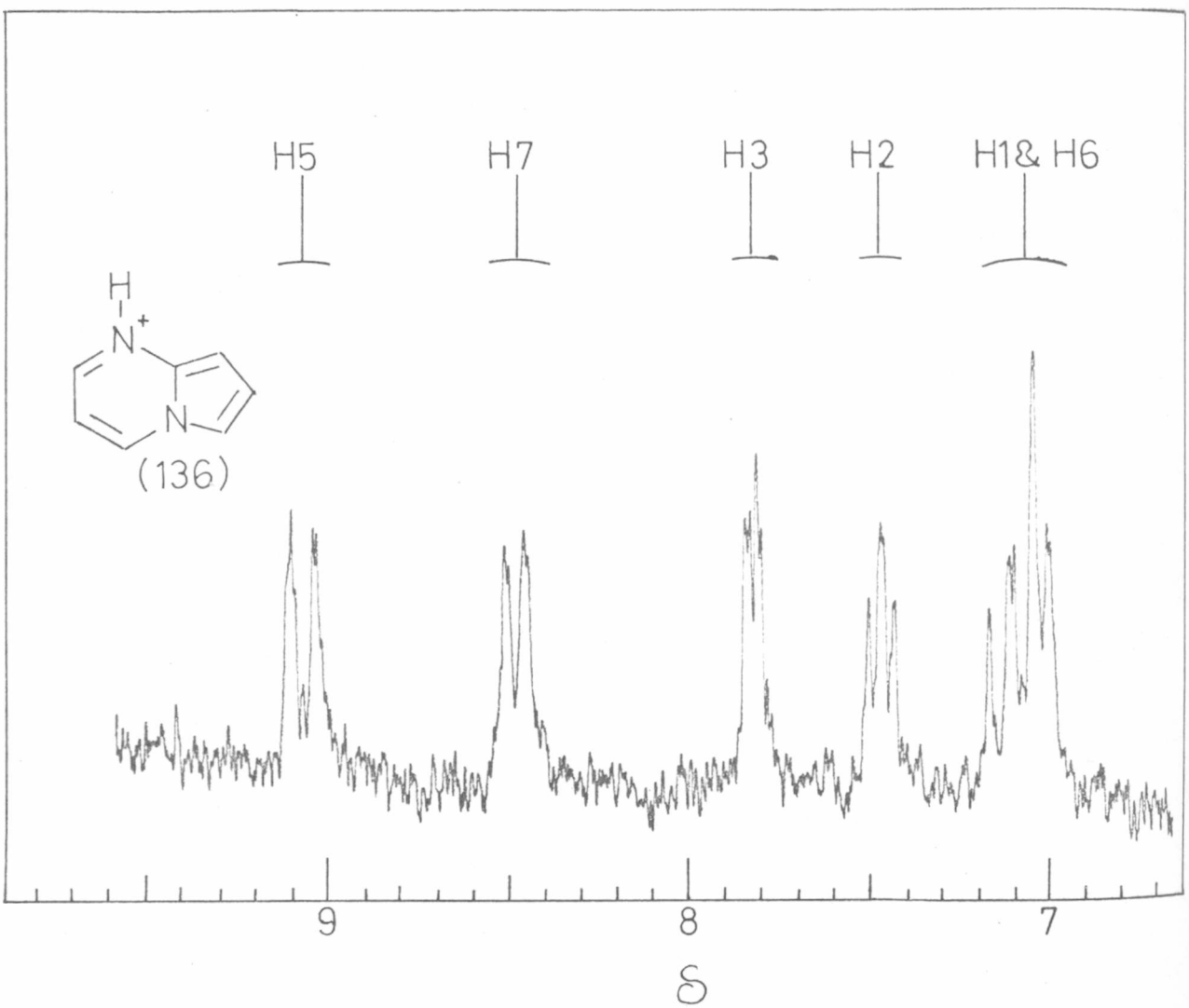


for pyridine which on protonation at its nitrogen shows large ... at the β- and γ- protons (1.07 and 1.22 ppm) and only a relatively small shift of the α- protons (0.25 ppm)[118,125].

The NMR spectrum of 2-methyl-1,8-naphthyridine (50) in trifluoroacetic acid (see Table X, p 93) consisted of the superimposed signals of two cations. The main species (62%) was the N-8 protonated cation (137) which showed chemical shifts of its aromatic protons similar to those of the N-8 protonated parent

Figure VI

100 MHz NMR spectrum of 8-azaindolizine in CF_3COOH



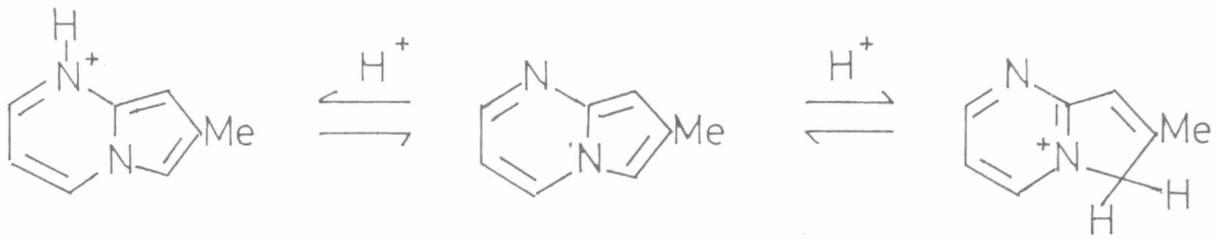
and H-1 respectively.

Protonation of 8-azaindolizines

The NMR spectrum of the parent 8-azaindolizine (59) in trifluoroacetic acid is shown in Figure VI. The absence of a midfield methylene signal discounts protonation at carbon. It is suggested therefore that protonation has occurred at N-8 to give cation (136). The high field 2H multiplet at δ6.96-7.22 was attributed to H-1 and H-6. The apparent 1H triplet at δ7.48 was attributed to H-2, the multiplicity arising mainly from approximately equal coupling with H-1 and H-3. The apparent 1H quartet at δ7.83 was attributed to H-3, the multiplicity arising mainly from coupling with H-1 and H-2. The low field doublets at δ8.48 and 9.07 were attributed to H-7 and H-5 respectively, the multiplicity arising mainly from coupling with H-6. Irradiation at the frequency corresponding to the centre of the high field 2H multiplet assigned to H-1 and H-6 simplified the two low field doublets assigned to H-5 and H-7 to a pair of broad singlets, and the multiplets assigned to H-2 and H-3 to a pair of equally coupled doublets (J = ca 3.5Hz). Coupling between the proton on N-8 and H-7 (J = ca 6.5 Hz) was only observed when a drop of perchloric acid was added to the trifluoroacetic acid solution. The emergence of this coupling is presumably due to a decrease in the proton exchange rate at the higher pH[125]. On protonation of 8-azaindolizine there is a greater downfield shift in the resonance position of the H-5 proton (ca 95 Hz) than there is of the H-7 proton (ca 36 Hz). This is consistent with protonation at N-8 since the deshielding effect on H-7 due to the lone pair of electrons on N-8 is removed on formation of the cation (136). A similar effect has been reported for pyridine which on protonation at its nitrogen shows large shifts of its β-and γ- protons (1.07 and 1.22 ppm) and only a relatively small shift of its α- protons (0.25 ppm)[118,125].

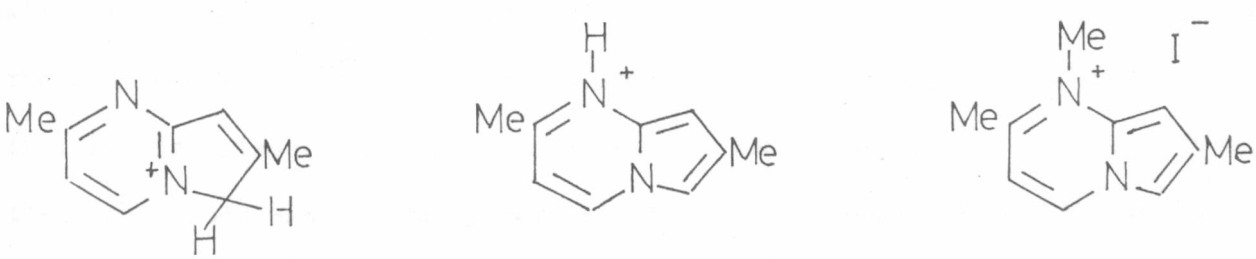
The NMR spectrum of 2-methyl-8-azaindolizine (60) in trifluoroacetic acid (see Table X, p 93) consisted of the superimposed signals of two cations. The main species (62%) was the N-8 protonated cation (137) which showed chemical shifts of its aromatic protons similar to those of the N-8 protonated parent

8-azaindolizine. The minor species (38%) was the C-3 protonated cation (138) with a 2H methylene signal at δ5.55, a 3H methyl singlet at δ2.54, a 1H singlet at δ7.11 attributed to H-1, an apparent 1H quartet at δ7.87 attributed to H-6, and a low field 2H multiplet at δ9.24-9.52 attributed to H-5 and H-7.



(137) (60) (138)

Similarly the NMR spectrum of 2,7-dimethyl-8-azaindolizine (64) in trifluoroacetic acid showed both C-3 and N-8 protonated cations (139) and (140) although here the percentage of the C-3 protonated species was considerably greater (63%). No measurable change in the relative proportions of the C- and N- protonated cations was observed after allowing the trifluoroacetic acid solution to stand for six hours, or by recording the spectrum at various temperatures in the range 0-40°. Evidence in support of the assignment of the minor species as the N-8 protonated cation (140) was obtained by a comparison of its NMR spectrum with that of the quaternary methyl salt (141).



(139) (140) (141)

The NMR spectra of both 2,3-dimethyl and 2,3,7-trimethyl-8-azaindolizines (62) and (67) in trifluoroacetic acid showed signals attributable to their N-8 protonated cations only. In the case of the cation derived from the 8-azaindolizine (62) the H-7 signal was considerably broadened presumably through coup-

ling with the proton at N-8.

The NMR spectra of 2-phenyl-and 2-methyl-7-methoxy-8-azaindolizines (68) and (76) in trifluoroacetic acid showed signals attributable to their C-3 protonated cations only with 2H methylene signals at 5.71 and 5.17 respectively.

Summary of the protonation patterns of 6- and 8- azaindolizines

The results obtained show alkyl and aryl 6- and 8- azaindolizines to have a preference for N- protonation in trifluoroaceitc acid. N- protonation occurs exclusively with the parent 8-azaindolizine and in 6- and 8- azaindolizines where the C-3 or C-5 sites are methyl substituted. Protonation at C-3 is most marked in the cases of 2,7-dimethyl-6- and 8- azaindolizines. In contrast the methoxy substituted 6- and 8- azaindolizines protonated solely at C-3. Increasing the pH of the protonating medium by the addition of approximately 5% of perchloric acid favoured C-3 protonation at the expense of the N-protonated cations (see Table XI) and in some cases showed only carbon protonation. Even 2,3,7-trimethyl-6-azaindolizine showed 35% of its C-3 protonated cation in the presence of perchloric acid. The parent 8-azaindolizine was unaffected by the addition of perchloric acid and still showed 100% N-8 protonation. All the 6- and 8- azaindolizines studies showed deuterium exchange of their H-1 and H-3 protons: recording the NMR spectra shortly after dissolving the samples in deuterotrifluoroacetic acid generally showed the complete absence of the signals attributed to the H-3 protons and a reduction in the intensity of the signals attributed to H-1 protons. Exchange of the H-1 protons was generally complete within one hour. Thus although no C-1 or in some cases C-3 protonated cations were directly observed in trifluoroacetic acid, their presence in a low equilibrium concentration is implied[71].

Table IX[a]

Chemical shifts (δ) in the 100 MHz NMR spectra of 6-azaindolizines in CF_3COOH

6-Azaindolizine	Cation	%	1	2	3	5	7	8
7-methyl-2-phenyl (44)	N-6	100	7.16	7.40-7.80 m	8.05	9.60 br $w_{\frac{1}{2}}$ = 6 Hz	2.60	7.37
2,7-dimethyl (45)	N-6	85	6.72	2.46	7.59	9.45 d J = 6.0	2.57	7.29
	C-3	15	6.95	2.91	5.60	9.71	2.91	7.92
2,3,7-trimethyl (46)	N-6	100	6.68	2.40	2.56	9.23 d J = 6.0	2.56	7.26
5,7-dimethyl-2-phenyl (49)	N-6	100	7.17	7.40-7.90 m	-[b]	3.15	2.56	7.34
2,5,7-trimethyl (54)	N-6	100	6.72	2.45	7.45	3.08	2.59	7.22
2,6,7-trimethyl-6-azaindolizinium iodide (134)[c]	-	-	6.66	2.34	7.74	10.27	2.51*	7.63*
5-methoxy-7-methyl-2-phenyl (165)	C-3	100	7.25	7.45-7.85 m	5.55	4.49	2.79*	7.38*

[a] Unless otherwise stated values refer to singlet absorption; br = broad, d = doublet, dd = double doublet, m = complex multiplet and q = quartet. Coupling constants (Hertz) are approximate and measured directly from the spectra. Pairs of signals found by double resonance to be weakly coupled to each other are marked with asterisks (*).

[b] Obscured by the complex phenyl signal at δ7.40-7.90

[c] Recorded in dimethylsulphoxide; Me-6 occurred at δ3.98.

Table X[a]

Chemical shifts (δ) in the 100 MHz NMR spectra of 8-azaindolizines in CF_3COOH

8-Azaindolizine	Cation	%	1	2	3	5	6	7
2-carboxylic acid, potassium salt (57)	N-8	100	7.50	-	8.45	9.17 d J = 7.0	7.29 dd J = 5.5, 7.0	8.75 d J = 5.5
Unsubstituted (59)	N-8	100	6.96-7.22 m	7.48 dd J = 3.5, 4.0	7.83 dd J = 1.5, 3.5	9.07 d J = 7.0	6.96-7.22 m	8.48 d J = 6.0
2-methyl (60)	N-8	62	6.86*	2.54	7.64*	8.94 d J = 7.0	7.03 dd J = 6.0, 7.0	8.35 d J = 6.0
	C-3	38	7.11	2.54	5.55	9.24-9.52 m	7.87 dd J = 6.0, 7.0	9.24-9.52 m
2,3-dimethyl (62)	N-8	100	6.86	2.50	2.59	8.74 d J = 7.0	7.08 dd J = 6.0, 7.0	8.27 br $w_{\frac{1}{2}}$ = 11.0 Hz
2,7-dimethyl (64)	N-8	37	6.62	2.46	7.45	8.74 d J = 6.5	6.81 d J = 6.5	2.58
	C-3	63	7.04	2.50	5.42	9.01 d J = 6.5	7.66 d J = 6.5	2.93
2,3,7-trimethyl (67)	N-8	100	6.62	2.42	2.52	8.54 d J = 7.0	6.83 d J = 7.0	2.81
7-methoxy-2-phenyl (68)	C-3	100	7.29	7.42-7.86 m	5.71	8.67 d J = 7.5	7.00 d J = 7.5	4.35
7-methoxy-2-methyl (76)	C-3	100	6.78	2.45	5.17	8.58 d J = 7.5	6.96 J = 7.5	4.30

[a] See footnote 'a' Table IX

Table XI[a]

Chemical shifts (δ) in the 100 MHz NMR spectra of 6- and 8- azaindolizines in CF_3COOH containing approximately 5% of perchloric acid

6-Azaindolizine	Cation	%	1	2	3	5	7	8
7-methyl-2-phenyl (44)	C-3	100	7.74	7.60-8.00 m	6.45	-[b]	3.10	8.25
2,7-dimethyl (45)	C-3	100	6.95	2.91	5.60	9.71	2.91	7.92
2,3,7-trimethyl (46)	N-6	65	6.68	2.38	2.56	9.25 J = 6.0	2.56	7.26
	C-3	35	7.26	2.64	2.08 d, 6.20 q J = 7.0	-[b]	3.16	8.35
5,7-dimethyl-2-phenyl (49)	C-3	100	-[c]	7.50-8.15 m	6.24	3.42	3.03	-[c]
2,5,7-trimethyl (54)	C-3	100	7.16	2.63	5.67	3.28	3.04	8.10

8-Azaindolizine	Cation	%	1	2	3	5	6	7
Unsubstituted (59)	N-8	100	6.96-7.22 m	7.44 dd J = 3.5, 4.0	7.82 dd J = 1.5, 3.5	9.07 d J = 7.0	6.96-7.22 m	8.50 dd J = 6.0, 6.5
2,7-dimethyl (64)	N-8	17	6.66	2.62	7.84	9.04 d J = 7.0	-[d]	2.89
	C-3	83	7.23	2.62	5.69	9.35 d J = 7.0	7.94 d J = 7.0	3.11

[a] See footnote 'a' Table IX

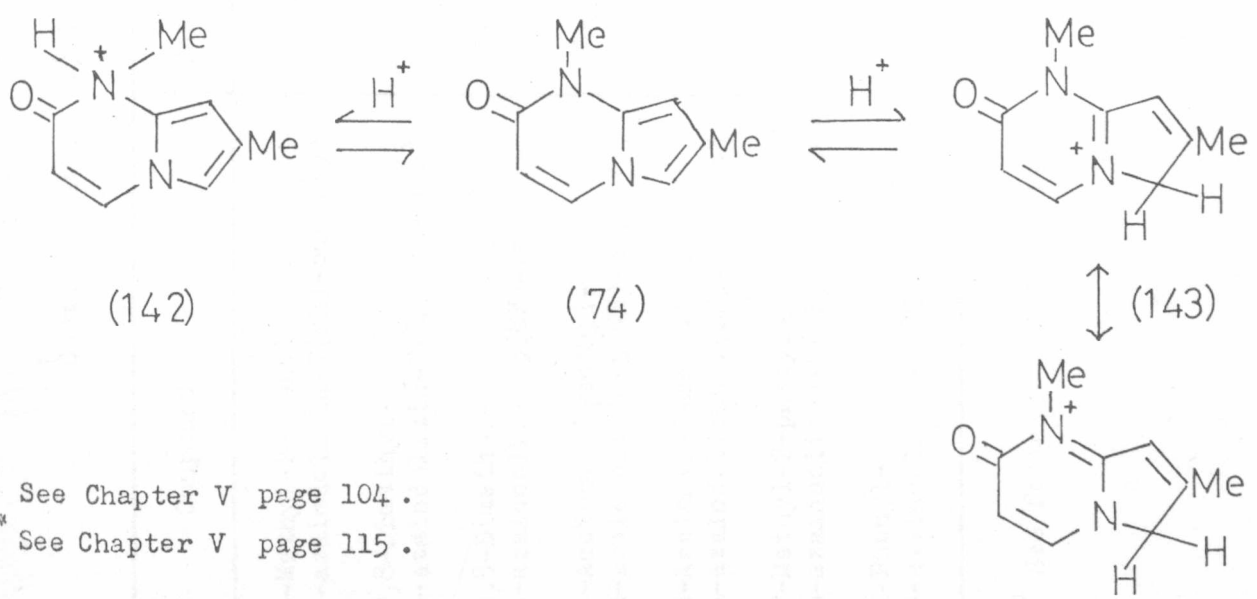
[b] Obscured by the base of the broad solvent peak (δ8.50)

[c] Obscured by the complex phenyl signal at δ7.50-8.15

[d] Obscured by the signal at δ7.23 attributed to H-1 of the C-3 protonated cation

Protonation of 6- and 8- azaindolizinones

The NMR spectra of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156)*; 8-methyl-2-phenyl (69), 2,8-dimethyl (74), 8-acetonyl-2-methyl (78) and 2-phenyl-(176)**-8-azaindolizin-7(8H)-ones; and 2,8-dimethyl(75) and 8-acetonyl-2-methyl (77)-8-azaindolizine-5(8H)-ones were examined in trifluoroacetic acid and the results recorded in Table XII. Unlike the fully aromatic 6- and 8-azaindolizines which generally gave orange-red coloured cations, these azaindolizinones gave pale coloured cations which in some cases were quite fluorescent. For example 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one emitted a particularly strong violet fluorescence. All the azaindolizinones examined showed signals due to their respective C-3 protonated cations only, with midfield 2H methylene signals in the range δ5.16-5.81. In deuterotrifluoroacetic acid no midfield methylene signals were observed. Deuterium exchange of the H-1 protons only occurred after 1-2 hours or on warming the deuterotrifluoroacetic acid solutions at 60° for a short period. Protonation of these azaindolizinones at carbon rather than at nitrogen is not surprising since protonation at the non-bridgehead 'amide' nitrogen would lead to a conjugate acid (142) with a localised positive charge whereas C-3 (or C-1) protonation leads to a conjugate acid (143) with a positive charge which can be delocalised over both ring nitrogens. This is illustrated for 2,8-dimethyl-8-azaindolizin-7(8H)-one (74).



(142) (74) (143)

* See Chapter V page 104.

** See Chapter V page 115.

Table XII[a]

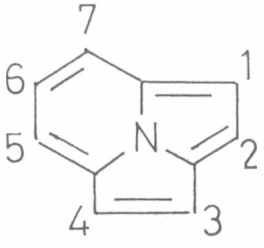
Chemical shifts (δ) in the 100 MHz NMR spectra of 6- and 8-azaindolizinones in CF_3COOH

Compound	Cation	%	1	2	3	5	6	7	8
8-Methyl-2-phenyl 8-azaindolizin-7(8H)-one (69)	C-3	100	7.46	7.39-7.95 m	5.81	8.30 d J = 8.0	6.81 d J = 8.0	-	3.95
2,8-Dimethyl- 8-azaindolizin-7(8H)-one (74)	C-3	100	6.96	2.55	5.29	8.22 d J = 8.0	6.78 d J = 8.0	-	3.85
2,8-Dimethyl- 8-azaindolizin-5(8H)-one (75)	C-3	100	6.99	2.58	5.16	-	6.82 d J = 8.0	7.99 d J = 8.0	4.09
8-Acetonyl-2-methyl- 8-azaindolizin-5(8H)-one (77)	C-3	100	6.82	2.52	5.18	-	6.84 d J = 8.0	7.90 d J = 8.0	2.52, 5.48
8-Acetonyl-2-methyl 8-azaindolizin-7(8H)-one (78)	C-3	100	6.81	(2.52)	5.32	8.24 d J = 8.0	6.82 d J = 8.0	-	(2.56), 5.38
7-Methyl-2-phenyl- 6-azaindolizin-5(6H)-one (156)	C-3	100	7.38	7.60-8.00 m	5.67	-	-	2.77	7.06
2-Phenyl- 8-azaindolizin-7(8H)-one (176)	C-3	100	7.33	7.43-7.98 m	5.78	8.34 d J = 8.0	6.75 d J = 8.0	-	-

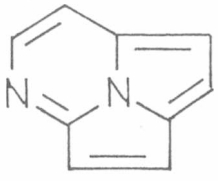
[a] See footnote 'a' Table IX

Protonation of azacycl[3,2,2]azines

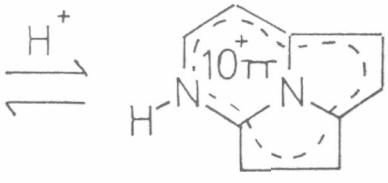
Cyclazine itself (144) is a heteroaromatic compound with 10π-electrons delocalised over its ten peripheral carbon atoms. Protonation of the parent system occurs at either of the equivalent C-1 or C-4 sites[117] rather than at the central nitrogen as might be expected from a consideration of the stability of their respective conjugate acids. With the introduction of an additional nitrogen at one of the non-bridgehead positions protonation may be expected to occur at this nitrogen with the formation of a 10π- cation (146) or at ring positions -1 or -4 with the formation of 6π- cations (148) and (149) as shown below for 5-azacycl[3,2,2]azine (145).



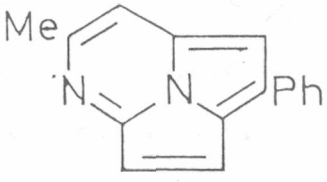
(144)



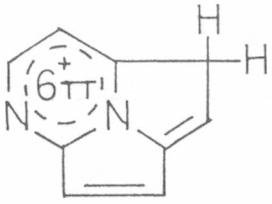
(145)



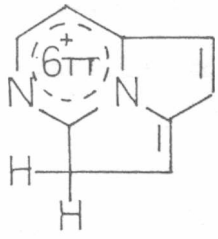
(146)



(147)



(148)

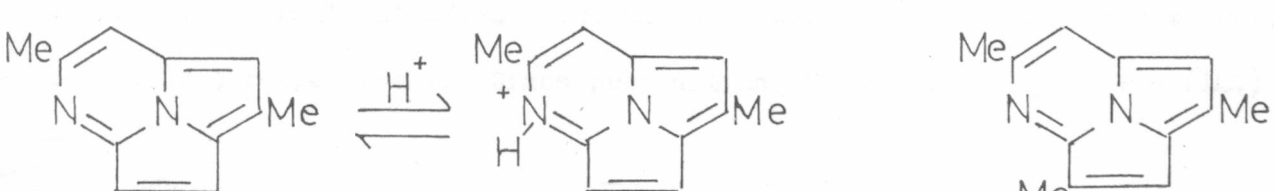


(149)

According to Boekelheide[35] who examined the ultra-violet spectrum of 6-methyl-2-phenyl-5-azacycl[3,2,2]azine (147) in ethanol and in aqueous hydrochloric acid this system protonated at the non-bridgehead nitrogen. He

also examined the NMR spectrum of (147) in concentrated sulphuric acid, and in addition to the signals from the main N-5 protonated cation, observed two smaller additional 'methyl' signals and attributed them to low concentrations of C-1 and C-4 protonated cations. A reinvestigation of the NMR spectrum of 6-methyl-2-phenyl-5-azacycl[3,2,2]azine in concentrated sulphuric acid (Reference H_2SO_4 = δ10.00) gave a surprisingly simple spectrum showing a 3H methyl signal at δ2.41, a 5H phenyl complex at δ6.67-7.30, and only two 1H singlets at δ7.69 and δ7.82. Attempted recovery of the free base by basification of the aqueous H_2SO_4 solution of the sample, followed by ether extraction failed; the yellow colour of the cyclazine was retained in the basic aqueous phase. These results suggested the azacyclazine (147) to have undergone sulphonation at both C-1 and C-4. This led to an investigation of the spectroscopically simpler 2,6-dimethyl-5-azacycl[3,2,2]azine (150).

The NMR spectrum of 2,6-dimethyl-5-azacycl[3,2,2]azine (150) in trifluoroacetic acid (see Table XIII) had a pattern similar to that of the base in deuterochloroform and consisted of two 3H singlets at δ2.92 and δ3.20 assigned to Me-2 and Me-6, two 1H singlets at δ7.32 and δ7.97 assigned to H-1 and H-7 and a pair of 1H doublets at δ7.31 and δ8.21 assigned to H-4 and H-3 respectively. Although no signal directly attributable to a proton attached to quaternary nitrogen was observed, the NMR spectrum suggests that protonation had occurred at N-5 to give the cation (151). Similarly, 2,4,6-trimethylcycl[3,2,2]azine (152) in trifluoroacetic acid was also concluded to protonate at N-5.

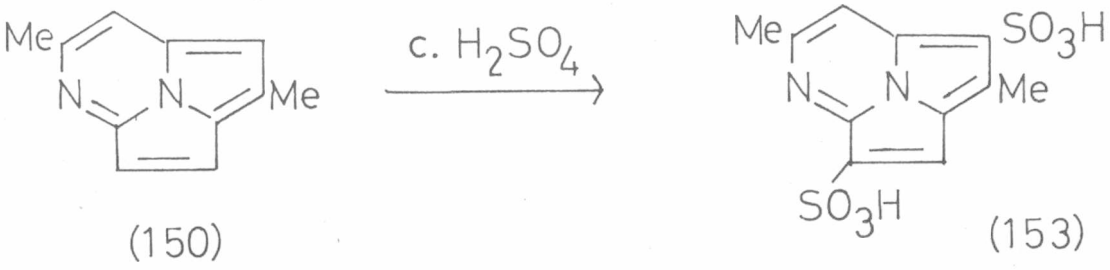


(150) (151) (152)

The NMR spectrum of the azacyclazine (150) in deuterotrifluoroacetic acid was initially identical to that in trifluoroacetic acid but after two hours

showed a 50% reduction in the intesity of the signals assigned to H-1 and H-4. After standing a further six hours deuterium exchange of the H-1 and H-4 protons was complete. Subsequent basification of the NMR sample with solid anhydrous sodium carbonate followed by the addition of water gave a quantitative recovery of the free base deuterated at C-1 and C-4.

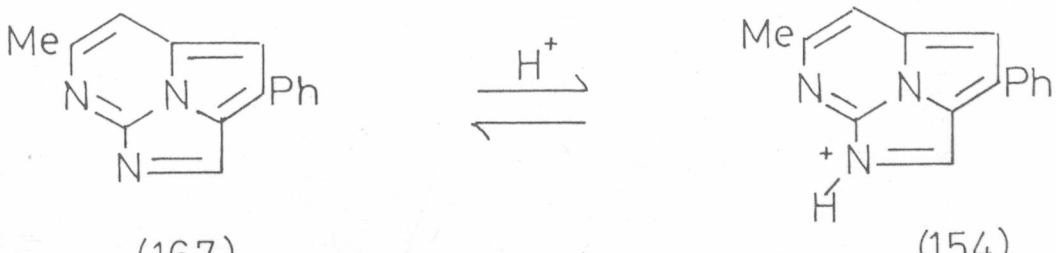
The NMR spectrum of the 5-azacyclazine (150) in concentrated sulphuric or deuterosulphuric acid like that of the phenyl-5-azacyclazine (147) was very simple and suggested sulphonation once again to have occurred at C-1 and C-4 to give the azacyclazine (153). Attempted recovery of the free base from the sulphuric acid solution failed.



(150) (153)

Protonation of 6-methyl-2-phenyl-4,5-diazacycl[3,2,2]azine

This yellow coloured cyclazine (167, see Chapter V) emitted a strong green fluorescence in trifluoroacetic acid. The NMR spectrum was similar in form to that of the base in deuterochloroform and showed a 3H singlet at δ3.20, three 1H singlets (δ7.94, 8.21 and 8.95) and a complex phenyl signal at δ7.58-8.18. The absence of any midfield methylene or methine signal discounts carbon protonation but points to protonation at nitrogen. Irradiation at the frequency of the methyl signal resulted in sharpening of the 1H singlet at δ8.21. The signals at δ7.94, 8.21 and 8.95 were therefore assigned to H-1, H-7 and H-3 respectively. Since protonation of the parent cyclazine (144)



(167) (154)

occurs at its C-1 or equivalent C-4 site protonation of the diazacyclazine (167) may be expected to occur at N-4 rather than N-5 to give the cation (154). However, since no coupling of the H-3 proton with the quaternary proton was observed protonation may have occurred at N-5. When the spectrum was recorded in deutertrifluoroacetic acid no apparent exchange occurred even after 24 hours at 60°

Table XIII[a]

Chemical shifts (δ) in the 100 MHz NMR spectra of azacycl[3,2,2]azines in CF_3COOH

Cycl[3,2,2]azine	Cation	%	1	2	3	4	6	7
6-methyl-2-phenyl-5-aza (147)	N-5	100	7.72[b]	7.49-8.24 m	8.41 d J = 4.0	7.39 d[b] J = 4.0	3.20*	8.01*
2,6-dimethyl-5-aza (150)	N-5	100	7.32[b]	2.92	8.21 J = 4.0	7.31[b] J = 4.0	3.20	7.97
2,4,6-trimethyl-5-aza (152)	N-5	100	7.08	2.89	(8.06)	2.74	3.16	(8.01)
6-methyl-2-phenyl-4,5-diaza (167)	N-5 or N-4	100	7.94	7.58-8.18 m	8.95	-	3.20*	8.21*

[a] See footnote 'a' Table IX

[b] The protons assigned to these signals underwent slow deuterium exchange in CF_3COOD

CHAPTER V

Nucleophilic substitution studies on 6- and 8- azaindolizines

This Chapter discusses an investigation into the propensity of the 6- and 8- azaindolizine systems towards nucleophilic displacement reactions. The possibility of direct nucleophilic displacement of hydride ion from 7-methyl-2-phenyl-6-azaindolizine was first investigated, and then the nucleophilic substitution of chlorine from 5-chloro-7-methyl-2-phenyl-6-azaindolizine and 7-chloro-2-phenyl-8-azaindolizine. The syntheses of the latter two chloro compounds are also discussed.

Introduction

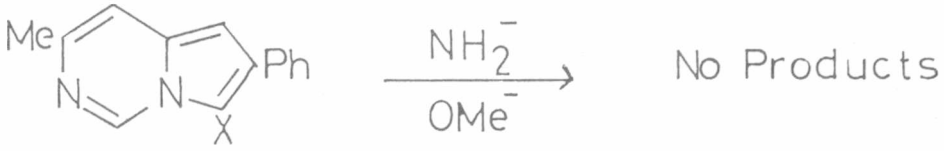
Pyrimidine is a π-deficient heterocycle and therefore expected to be vulnerable to attack by nucleophiles. In this ring system the two nitrogen atoms exert their electron withdrawing effects in unison so that the electron-deficiency at the α- and γ- positions is expected to be considerable and greater than in the isomers pyridazine and pyrazine. These predictions are borne out by experiment and in general pyrimidine undergoes nucleophilic substitution reactions more readily than pyridazine or pyrazine. However, only a few successful direct nucleophilic displacements of hydride ion from the pyrimidine nucleus are known[37,126]. In contrast the displacement of halogen from the 2-, 4- or 6- positions of pyrimidine is facile and many examples have been reported[127].

6- and 8- Azaindolizines contain both a pyrimidine and a pyrrole moiety but are formally classified as π-excessive heterocyclic systems. Despite the extra π-electron in excess of ring centres theoretical π-electron density calculations[62] (see Table I, p 22) predict both 6- and 8- azaindolizines to have π-deficient carbons. The calculations indicate the most electron deficient site(s) for 6-azaindolizine to be at C-5 and C-7, and for 8-azaindolizine to be at C-7. Therefore nucleophilic substitution reactions on 6- and 8-azaindolizines are likely to occur at the C-5 and C-7 sites respectively, though no such reactions have as yet been reported.

Attempted direct nucleophilic substitution on 7-methyl-2-phenyl-6-azaindolizine and its 3-formyl derivative

7-Methyl-2-phenyl-6-azaindolizine (44) was selected for this initial study since it has an unsubstituted C-5 site, is relatively stable and easily obtained[35]. Attempted ammination with sodamide[128] in N,N-dimethylaniline or in xylene at 110° gave only starting material; raising the temperature to 180° merely resulted in decomposition. Similarly, no reaction occurred when the 6-azaindolizine (44) was heated with sodium methoxide in refluxing methanol. Attempts to displace hydride ion by amide and methoxide from 3-formyl-7-methyl-2-phenyl-6-azaindolizine were equally unsuccessful despite the presence of the

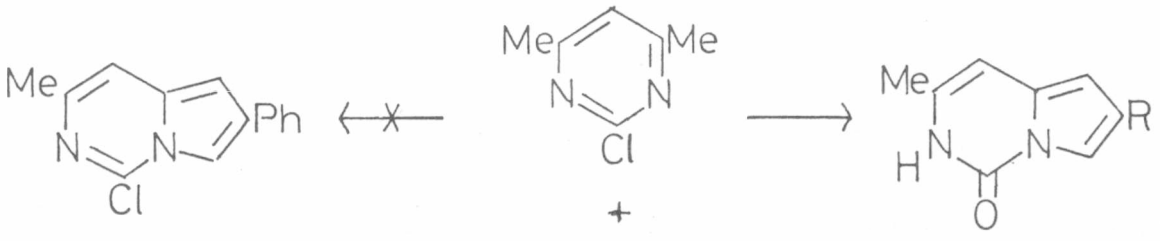
additional electron withdrawing formyl group.



(44, X=H)
(84, X=CHO)

Synthesis of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one

Attempts to prepare 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155) directly from 2-chloro-4,6-dimethylpyrimidine[129] and phenacyl bromide resulted in a low yield of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156). An even lower yield of the corresponding dimethyl-6-azaindolizinone (157) was obtained when phenacyl bromide was replaced by bromoacetone.

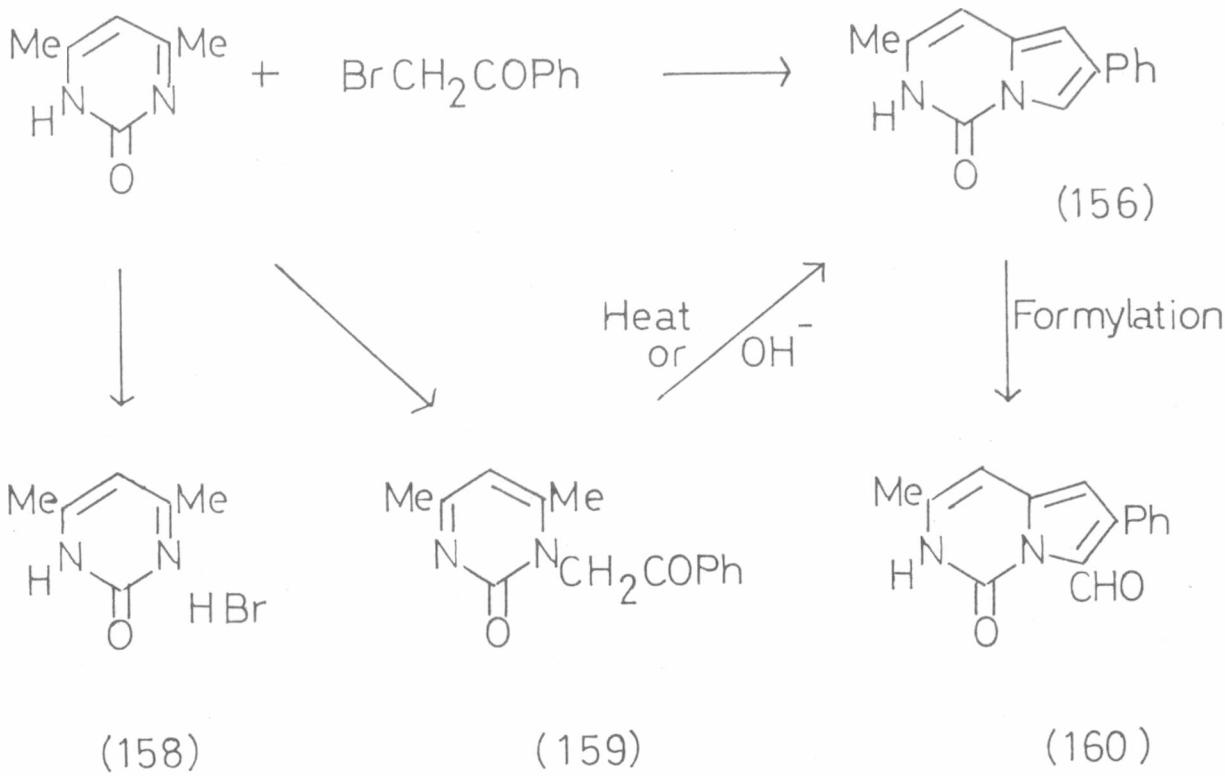


(155)

(156, R= Ph)
(157, R= Me)

Since these attempts to obtain 5-chloro-6-azaindolizines directly resulted in poor yields of the corresponding azaindolizinones, an alternative route to the chloro compounds was sought. A logical procedure would be to develop an improved synthesis of the indolizinones, for example (156), and then to convert the azaindolizinones to their corresponding chloro- compounds by the action of phosphoryl chloride as in the conversion of 'hydroxy' -pyrimidines to chloro-pyrimidines.

The reaction between 2-hydroxy-4,6-dimethylpyrimidine[130] and phenacyl bromide in boiling ethanol gave a brown solution from which separated crystals of 2-hydroxy-4,6-dimethylpyrimidine hydrobromide (158) with spectral characteristics (uv and NMR) virtually identical to those of the reported hydrochlor-



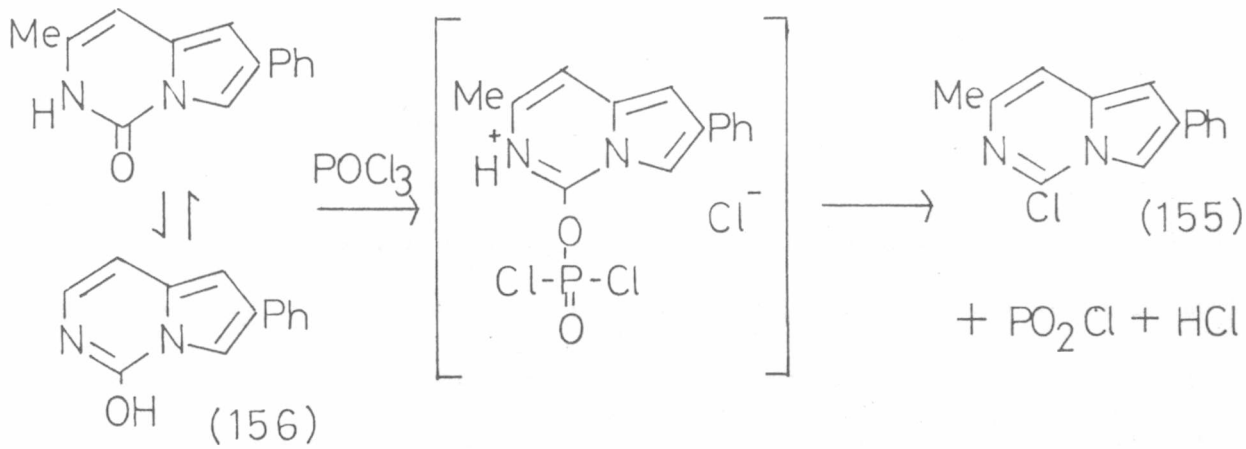
ide[130]. After removing these crystals by filtration, the ethanolic filtrate was evaporated and the residue dissolved in water. Addition of sodium bicarbonate to the aqueous solution gave two products. The minor product was 7-methyl-2-phenyl-6-azaindolizinone (156) readily identified by its infra-red and NMR spectra. The infra-red spectrum showed carbonyl absorption and NH absorption at 1693 and 3210 cm^{-1} respectively. The NMR spectrum in deuterated dimethyl sulphoxide showed a 3H methyl singlet at δ2.13, three 1H singlets (δ6.23, 6.58 and 7.83), a complex phenyl signal at δ7.20-7.78, and a broad NH signal at δ10.88. Irradiation at the frequency of the methyl signal resulted in sharpening of the 1H singlet at δ6.58. The signals at δ6.23, 6.58 and 7.83 were therefore attributed to H-1, H-8 and H-3 respectively. Formylation of this azaindolizinone occurred at C-3 to give an aldehyde (160) which showed a low field 1H formyl singlet at δ10.82.

The major product obtained in the reaction between 2-hydroxy-4,6-dimethyl-pyrimidine and phenacyl bromide could be converted to the azaindolizinone (156)

in good yield by heating it above the melting point, or with 2M aqueous sodium hydroxide. It also showed carbonyl absorptions at 1655 and 1690 cm^{-1} in the infra-red, and signals corresponding to two methyl groups, one methylene group, one aromatic proton and one phenyl group in its NMR spectrum and was concluded to be 1-phenacyl-4,6-dimethylpyrimid-2(1H)-one (159).

Reaction between 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one and phosphoryl chloride

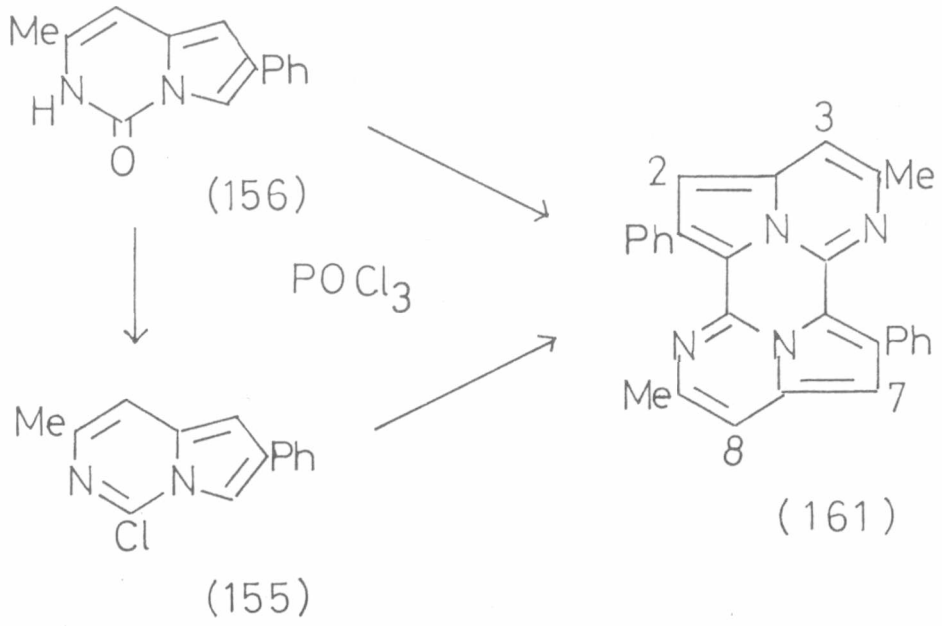
Refluxing a solution of 7-methyl-2-phenyl-6-azaindolizinone (156) in phosphoryl chloride readily gave 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155) in 75% yield. The mass spectrum of this product showed the expected $^{35}Cl/^{37}Cl$ isotope pattern. The NMR spectrum had a pattern closely similar to that of 7-methyl-2-phenyl-6-azaindolizine (44) except for the absence of its H-5 signal.



7-Methyl-2-phenyl-6-azaindolizin-5(6H)-one (156) is potentially tautomeric and its conversion to the chloro compound may occur via either tautomer by an intermediate of the type shown. Nucleophilic substitution may then be effected by chloride ion liberated in the first step (S_N2), or by a chlorine still attached to the phosphorus (S_Ni), by analogy to pathways envisaged for the conversion of hydroxypyridines to chloropyridines[131,132].

In addition to the chloro-6-azaindolizine (155), a dark red compound was isolated. Mass spectroscopy showed it to have a molecular ion at m/e 412 corresponding to the m/e value expected for a molecule constructed from two phenyl-methyl-azaindolizine nuclei less four hydrogen atoms. The NMR spectrum

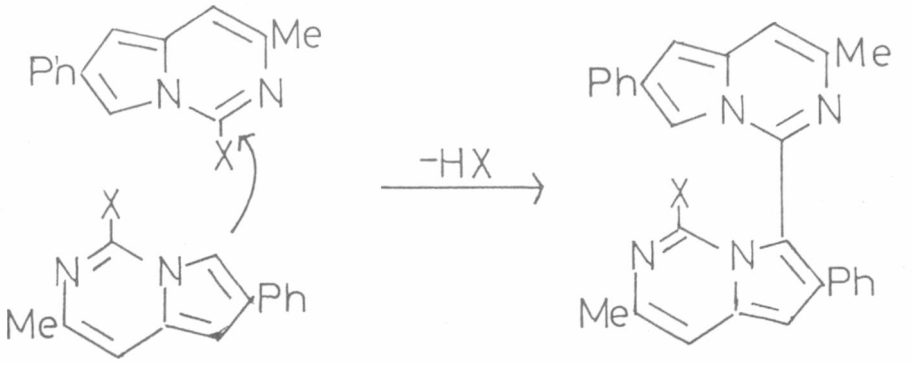
of this red compound was simple and apart from a complex phenyl absorption, showed only three other singlets. This suggested the compound to have the structure (161).



The NMR spectrum showed a 6H singlet at δ1.93 assigned to Me-4 and Me-9, two 2H singlets (δ5.96 and 6.08), and a 10H complex at δ7.20-7.88 assigned to Ph-1 and Ph-6. Irradiation at the frequency of the methyl signals resulted in sharpening of the singlet at δ6.08. The 2H signal at δ6.08 was therefore attributed to H-3 and H-8, and that at δ5.96 to H-2 and H-7.

The same red, dimeric compound was also obtained when 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155) was itself heated with phosphoryl chloride. The unsymmetrical bridging between the two 6-azaindolizine units leading to (161) can be envisaged to occur by the interaction of the electron rich C-3 site of one azaindolizine molecule with the electron deficient site of another followed by the elimination of either water or hydrogen chloride depending on whether it is formed from (156) or (155). Since no singly bridged dimeric structures such as (162) were isolated from these reactions, or in the reaction between 2-phenyl-8-azaindolizin-7(8H)-one (176) and phosphoryl chloride (see p115), the reaction leading to the dimer may involve the simultaneous elimin-

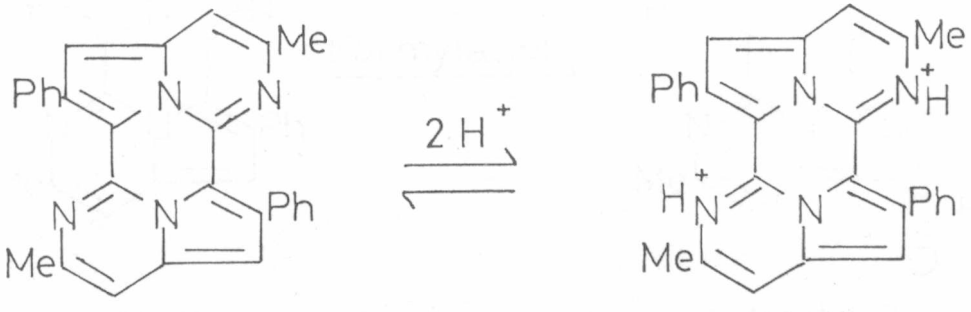
ation of two molecules of hydrogen chloride rather than two distinct steps.



(155, X=Cl)
(156, X=OH)

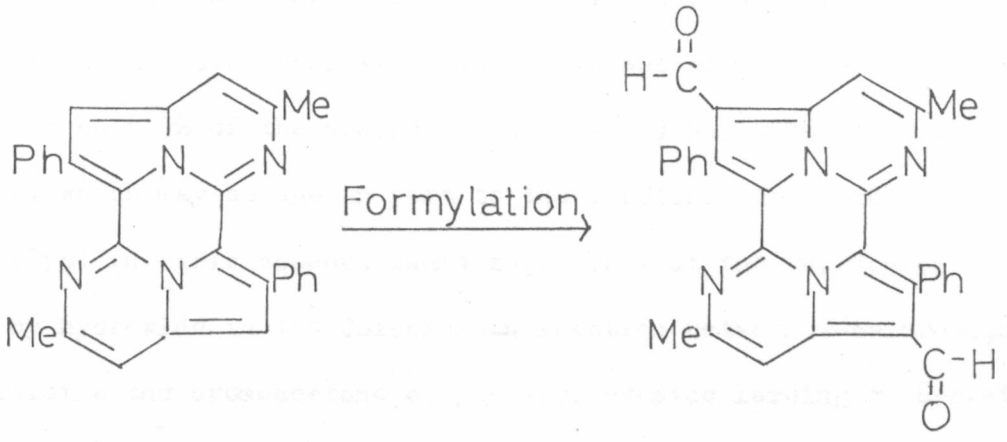
Protonation and formylation of 4,9-dimethyl-1,6-diphenyl-di(6-azaindolizino)[3,4,5-af:3',4',5'-dc]pyrazine (161)

The NMR spectrum of 4,9-dimethyl-1,6-diphenyl-di(6-azaindolizino)[3,4,5-af:3',4',5'-dc]pyrazine (161) in trifluoroacetic acid was similar in form to the free base in deuterochloroform and since it showed no midfield methylene or methine expected for protonation at carbon, this cation was deduced to be protonated at both of its non-bridgehead nitrogen atoms to give the dication (163).



The spectrum of (163) consisted of a 6H singlet at δ2.20 assigned to the methyl groups, a 10H singlet at δ7.70 attributed to the phenyl groups and two 2H singlets at δ6.69 and 6.78. Irradiation at the frequency of the methyl signal resulted in sharpening of the signal at δ6.69. This signal at δ6.69 was assigned to H-3 and H-8. The other 2H singlet which underwent slow deuterium exchange in deuterotrifluoroacetic acid was attributed to H-2 and H-7.

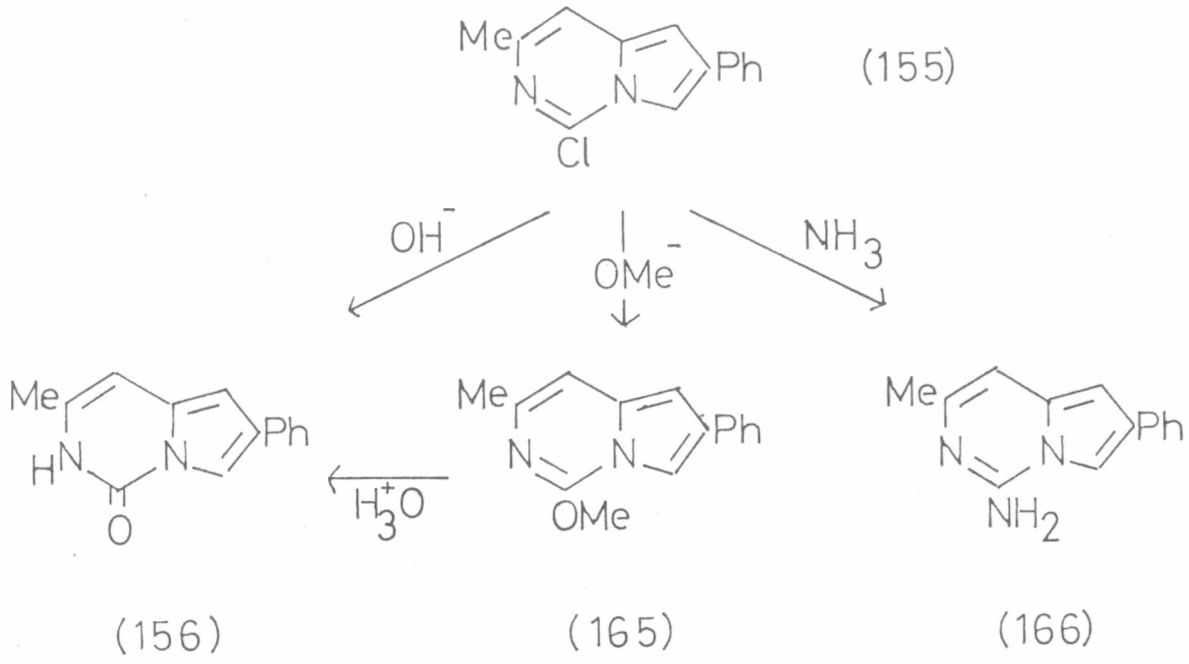
Vilsmeier formylation the the dimer (161) with 10% excess reagent at room temperature failed, but with a large excess of reagent at 70-90° a diformyl derivative was obtained which was practically insoluble in chloroform, dichloromethane, methanol, acetone, benzene and dimethyl sulphoxide. The NMR spectrum of this aldehyde in trifluoroacetic acid showed a 6H methyl singlet at δ2.28, a 2H singlet at δ7.58, a 10H phenyl singlet at δ7.72 and a broad 2H formyl singlet at δ9.72. Irradiation at the frequency of the methyl signal resulted in sharpening of the signal at δ7.58. This signal at δ7.58 was therefore attributed to H-3 and H-8, indicating formylation to have occurred at C-2 and C-7 to give the aldehyde (164). A comparison of the NMR spectrum of the aldehyde (164) with that of the parent compound (161) in trifluoroacetic acid showed the signal attributed to H-3 and H-8 to have undergone a peri shift of 89 Hz on formylation.



(161) (164)

Nucleophilic substitution reactions on 5-chloro-7-methyl-2-phenyl-6-azaindolizine

The 5-chloro substituent in 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155) was successfully replaced by hydroxide ion, methoxide ion and ammonia as described below.



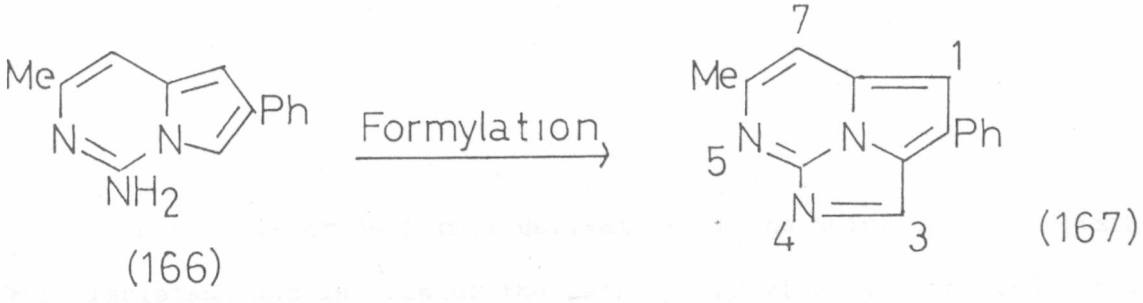
(a) Hydroxide ion Attempted hydrolysis of (155) with aqueous sodium bicarbonate at 100° gave unchanged starting material (ir, NMR) although TLC showed it to contain traces of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156). Even with 2M sodium hydroxide hydrolysis was slow and after a number of hours at 100° only 9% of the azaindolizinone (156) was obtained. This slow hydrolysis, which may be due in part to the insolubility of the chloro-azaindolizine (155) in basic aqueous media suggests that the replacement of the chlorine by hydroxide in the Chichibabin reaction between 2-chloro-4,6-dimethylpyrimidine and bromoacetone or phenacyl bromide leading to 6-azaindolizinones (see p 104) does not occur by replacement of the chlorine from the chloro-azaindolizine but occurs earlier from the intermediate pyrimidinium salt.

(b) Methoxide The chloro-6-azaindolizine (155) reacted with sodium methoxide in boiling methanol to give 5-methoxy-7-methyl-2-phenyl-6-azaindolizine (165) in 81% yield. The NMR spectrum of the methoxy compound showed 3H singlets at δ2.30 and 4.13 assigned to the Me-7 and MeO-5 groups, three 1H singlets (δ6.47, 6.65 and 7.55) and a complex phenyl signal at δ7.20-7.80. Irradiation at the frequency of the methyl signal at δ2.30 resulted in sharpening of the 1H singlet at δ6.65. The signals at δ6.47, 6.65 and 7.55 were therefore assigned to H-1, H-8 and H-3 respectively. Demethylation[133] of the methoxy group in (165) with hydrochloric acid gave 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156).

(c) Ammonia The chloro-6-azaindolizine (155) reacted with a solution of anhydrous ammonia in ethanol in a sealed tube at 130-150° to give 5-amino-7-methyl-2-phenyl-6-azaindolizine (166) in 71% yield which showed amine absorptions in the infra-red at 3450, 3340 and 1655 cm^{-1}. The NMR spectrum in deuterated dimethyl sulphoxide showed a 3H methyl signal at δ2.17, a 2H singlet at δ6.50 assigned to H-1 and H-8, a 1H singlet at δ7.89 assigned to H-3, and a complex phenyl signal at δ7.20-7.78 which overlapped with a broad 2H amine signal centred at δ7.14.

Formylation of 5-amino-7-methyl-2-phenyl-6-azaindolizine

Formylation of 5-amino-7-methyl-2-phenyl-6-azaindolizine (166) gave 6-methyl-2-phenyl-4,5-diazacycl[3,2,2]azine (167) which for consistency with the other cyclazines mentioned in this thesis is numbered as shown.

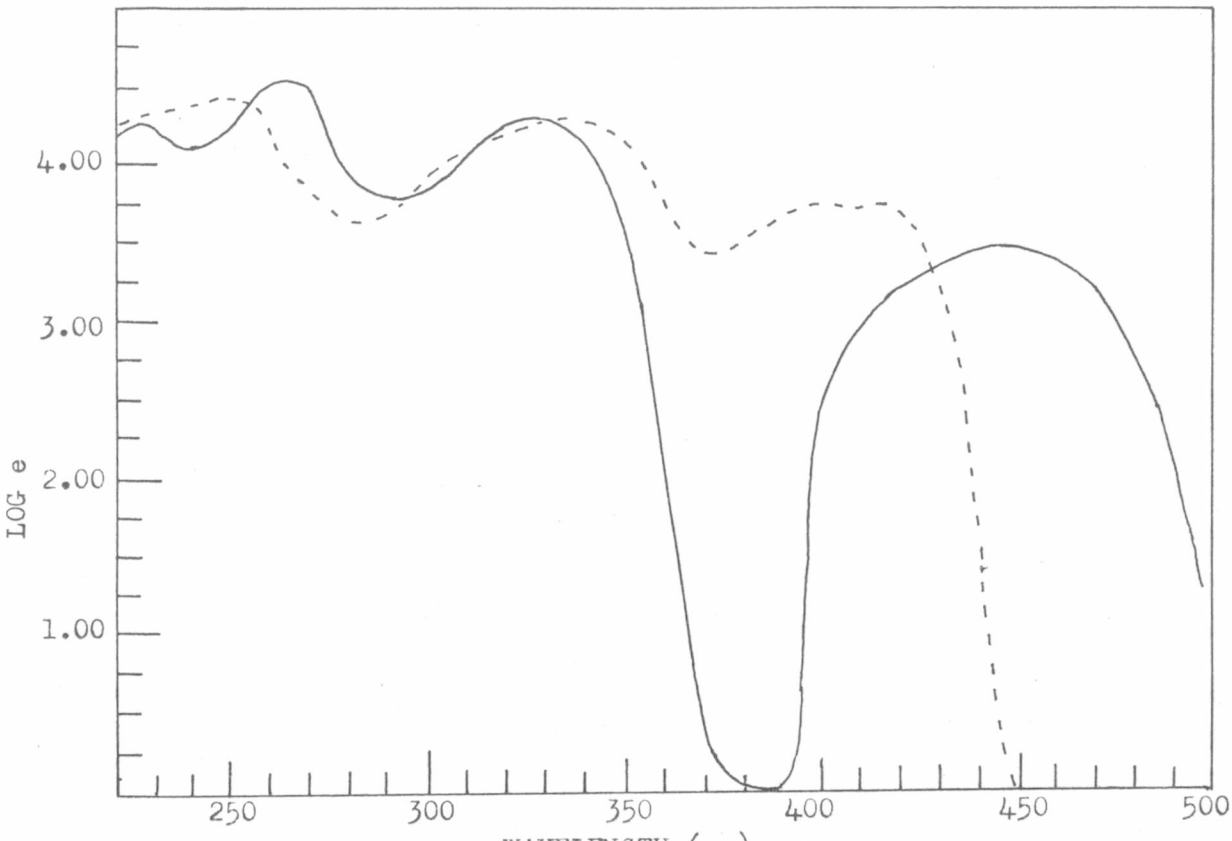


(166) (167)

The NMR spectrum of the diazacyclazine (167) showed a 3H methyl singlet at δ3.00, three 1H singlets (δ7.40, 7.65 and 8.83) and a complex phenyl absorption at δ7.33-8.11. By comparison with the NMR spectrum of 6-methyl-2-phenyl-5-azacycl[3,2,2]azine (92) the signals at δ7.40, 7.65 and 8.83 were assigned to

H-1, H-7 and H-3 respectively. The H-3 signal occurs at particularly low field due to its proximity to nitrogen. Irradiation at the frequency of the methyl signal resulted in sharpening of the 1H signal attributed to H-7. The ultra-violet spectra of the diazacyclazine (167) was similar to that of the corresponding 2-phenyl-azacyclazine (92) and both are shown in Figure VII.

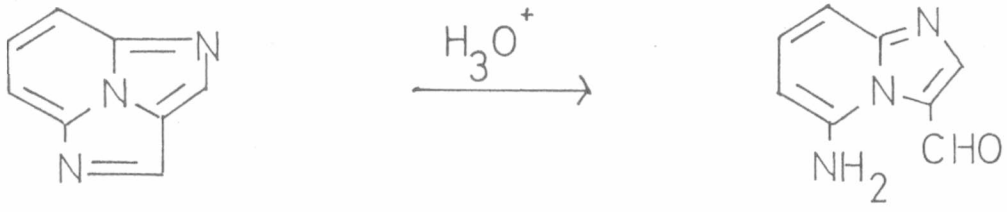
Figure VII



Ultraviolet absorption spectra of 6-methyl-2-phenyl-5-azacycl[3,2,2]azine (———) and 6-methyl-2-phenyl-4,5-diazacycl[3,2,2]azine (-----) in ethanol

Since no 1- or 3- formyl derivatives of the amino-6-azaindolizine (166) were isolated, and in view of the pathways previously discussed (see p 68) for the formation of 4-formyl-6-methyl-2-phenyl-5-azacycl[3,2,2]azine (90) in the Vilsmeier formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (49), it seems likely that formation of the diazacyclazine (167) results from attack

by the Vilsmeier electrophile at the 5-amino group[119] of the azaindolizine (166), rather than by attack at its C-3 ring carbon site. In contrast to the ready formylation of 5-azacycl[3,2,2]azines (92) and (98), formylation of the diazacyclazine (167) failed even at 60°, and points to considerable deactivation of the C-1 site by the additional N-4 nitrogen. Although the 1,4-diazacyclazine (168) has been reported to undergo acid catalysed hydrolysis to the amino-formyl-azaindolizine (169), no corresponding ring-opening reaction was observed for the 4,5-diazacyclazine (167) when it was similarly dissolved in methanolic hydrochloric acid[134].

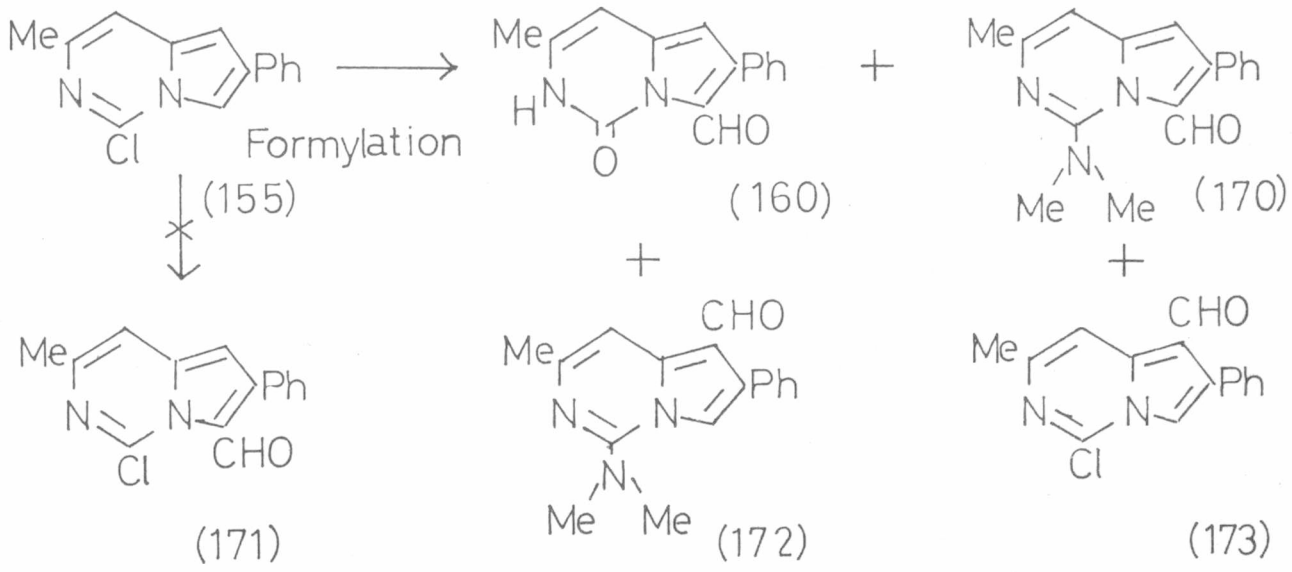


(168) (169)

Formylation of 5-chloro-7-methyl-2-phenyl-6-azaindolizine

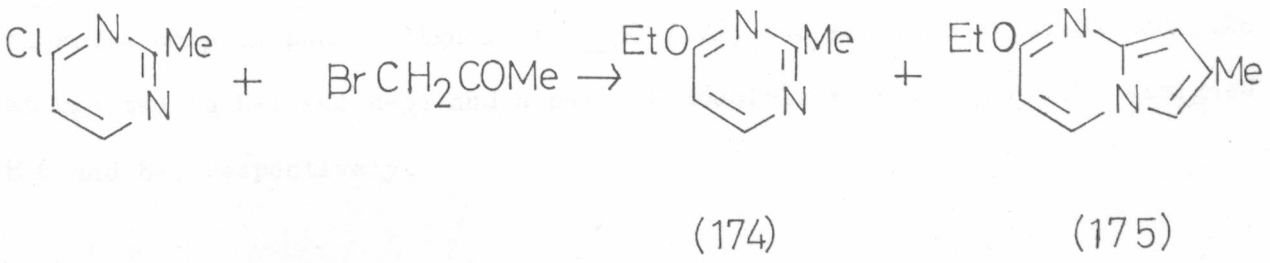
This formylation was carried out with a view to obtaining the 4,5-diazacyclazine (167) by an alternative route (viz. 5-chloro-3-formyl-6-azaindolizine ⟶ 5-amino-3-formyl-6-azaindolizine ⟶ 4,5-diazacyclazine). However no 5-chloro-3-formyl-7-methyl-2-phenyl-6-azaindolizine (171) was obtained and instead four other products were isolated. The main product was identical (ir, NMR) with 3-formyl-7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (160). The next two products obtained were isomeric formyl-N,N-dimethylamino-6-azaindolizines. A comparative examination of their NMR spectra and with that of 3-formyl-7-methyl-2-phenyl-6-azaindolizine (84) suggested these isomers to be the 6-azaindolizines (170) and (172). The NMR spectrum of the isomer assigned structure (172) showed a particularly low field H-8 signal (δ7.78) due to the deshielding effect of the peri orientated 1-formyl group. The fourth product was obtained in low yield. Its NMR spectrum when compared with that of the parent chloro compound (155) had no signal attributable to H-1 but a 1H formyl signal emerged at δ10.04, and a peri shift of 110 Hz in the

position of the signal attributed to H-8. This indicated this product to be 5-chloro-1-formyl-7-methyl-2-phenyl-6-azaindolizine (173). The N,N-dimethylamino products (170) and (172) are presumably formed by nucleophilic displacement of chlorine by N,N-dimethylamine formed from dimethylformamide in the course of formylation.



Attempted synthesis of 7-chloro-8-azaindolizines from 4-chloro-2-methylpyrimidine

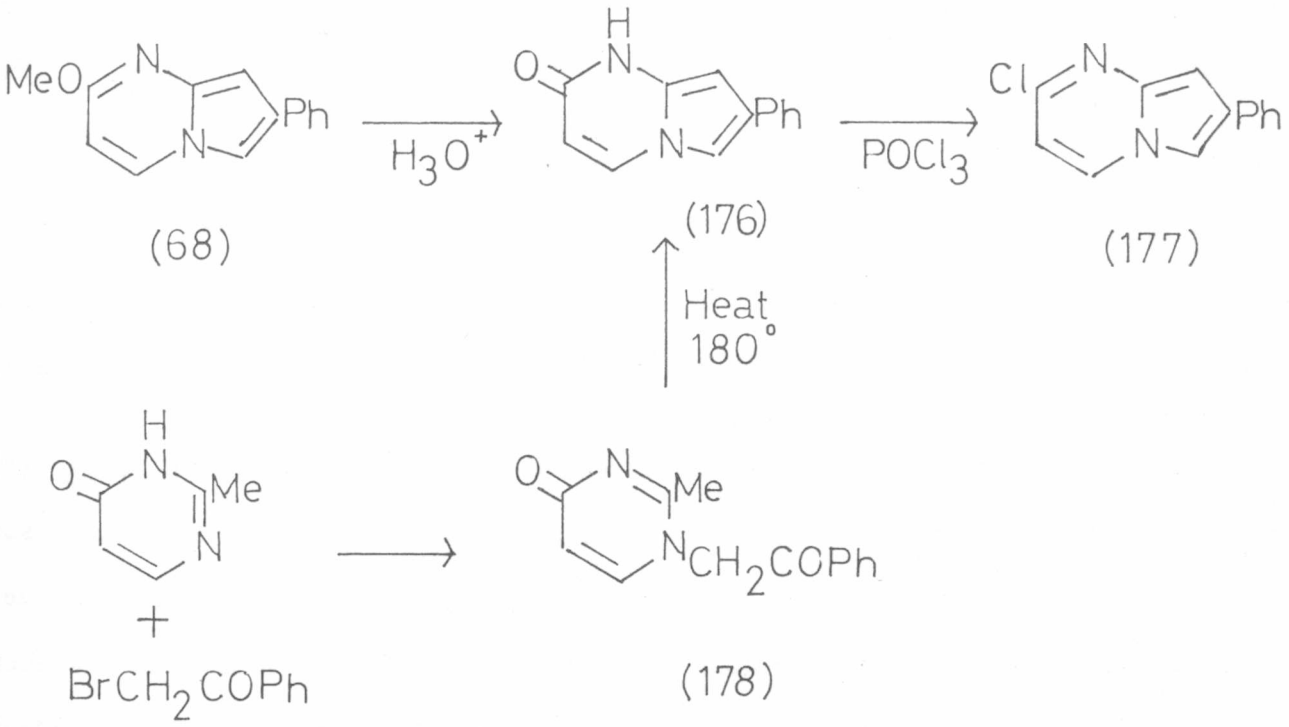
The reaction between 4-chloro-2-methylpyrimidine[103] and bromoacetone or phenacyl bromide, without solvent or in benzene, failed to yield any characterisable products. When the reaction between the pyrimidine and bromoacetone was carried out in ethanol followed by aqueous bicarbonate cyclisation, two products were isolated. The main product was 4-ethoxy-2-methylpyrimidine (174). The minor product obtained in low yield was 7-ethoxy-2-methyl-8-azaindolizine (175) with ultra-violet and NMR absorptions similar to those of 7-methoxy-2-methyl-8-azaindolizine (76).



(174) (175)

Synthesis of 7-chloro-2-phenyl-8-azaindolizine

Failure to obtain 7-chloro-2-phenyl-8-azaindolizine (177) directly from 4-chloro-2-methylpyrimidine led to an investigation into its synthesis by chlorination of 2-phenyl-8-azaindolizin-7(8H)-one (176). The 8-azaindolizinone (176) was obtained in 85% yield by demethylation of 7-methoxy-2-phenyl-8-azaindolizine (68) using aqueous hydrochloric acid. The 8-azaindolizinone (176) was also obtained from the reaction between 4-hydroxy-2-methylpyrimidine[103] and phenacyl bromide. This reaction gave the N-phenacylpyrimidone (178) in 27% yield which could be cyclised to (176) in quantitative yield by heating at 180°.



Refluxing a solution of the 8-azaindolizinone (176) in phosphoryl chloride gave 7-chloro-2-phenyl-8-azaindolizine (177) in 75% yield. The mass spectrum of the chloro compound showed the expected $^{35}Cl/^{37}Cl$ isotope pattern. Its NMR spectrum showed a complex phenyl signal at δ7.30-7.76, two singlets at δ6.84 and 7.26 attributed to H-1 and H-3, and a pair of doublets at δ6.50 and 8.07 assigned to H-6 and H-5 respectively.

Nucleophilic substitution reactions on 7-chloro-2-phenyl-8-azaindolizine

7-Chloro-2-phenyl-8-azaindolizine (177) was treated with methoxide, hydroxide and amide ion and with ammonia. The results are described below.

(a) Methoxide The chloro-8-azaindolizine (177) reacted with sodium methoxide in refluxing methanol to yield 7-methoxy-2-phenyl-8-azaindolizine (68) in quantitative yield. It showed identical spectral characteristics to the sample obtained from the reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide (see p 43).

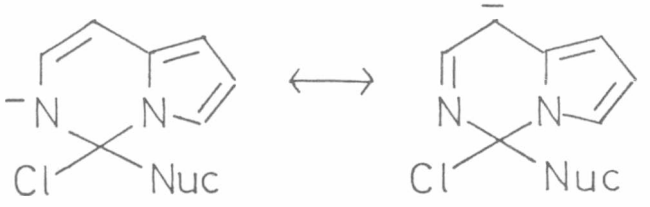
(b) Hydroxide Attempted hydrolysis of the chloro-8-azaindolizine (177) with aqueous 2M sodium hydroxide at 100° failed and the starting material was recovered unchanged. Increasing the temperature to 130° resulted in partial decomposition and only starting material (63%) was recovered.

(c) Amide Addition of the chloro-8-azaindolizine (177) to a suspension of sodamide in liquid ammonia at -33° gave a rapidly darkening, brown solution from which no characterisable products or starting material could be obtained.

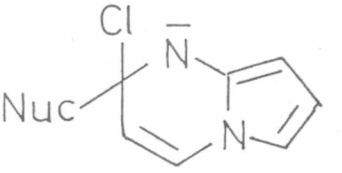
(d) Ammonia Heating the chloro-8-azaindolizine (177) in a solution of anhydrous ammonia in ethanol at 140° in a sealed tube for 5 hours failed to cause any reaction and all the starting material was recovered. Increasing the temperature to 200° resulted in darkening of the solution but no characterisable products could be isolated. Again starting material (64%) was recovered.

The reactions discussed in this Chapter although limited in scope demonstrate that nucleophilic substitution of chlorine from the C-5 site of 6-azaindolizine and the C-7 site of 8-azaindolizine is possible and in the instances of replacement by methoxide ion, occurs in high yield. However in the cases of ammonolysis and hydrolysis of the 7-chlorine from the 8-azaindolizine (177) no products were isolated and the bulk of the starting material recovered. This suggests that the 7-chlorine atom of the 8-azaindolizine (177) is less reactive

than the 5-chlorine atom of the 6-azaindolizine (155). This difference in reactivity although not anticipated from theoretical π-electron density calculations[62] (Table I p22), may possibly be rationised by a comparative examination of the transition intermediates resulting from an S_N2 attack. In the case of the 6-azaindolizine the negative charge on the intermediate (179) can be accommodated at two sites in the 6-membered ring, whereas in the case of the 8-azaindolizine the negative charge on the intermediate (180) can only be accommodated at one site in the 6-membered ring, keeping the pyrrole moiety intact.



(179)



(180)

Nuc = Nucleophile

CHAPTER VI

Experimental

Explanatory notes New compounds are underlined when first mentioned. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Light absorption data refers to solutions in ethanol unless otherwise stated and were measured using a Unicam SP800 spectrophotometer and 10 mm silica cells. Principal maxima are underlined and inflections are given in parenthesis. Infra-red spectra were obtained for Nujol mulls using a Unicam SP200 spectrophotometer unless otherwise stated. ^{1}H NMR data refers to solutions in deuterochloroform unless otherwise indicated and were obtained using a Varian HA-100D instrument operating at 100 MHz and 30° with tetramethylsilane (TMS) as internal standard. Values given are on the δ scale (TMS = δ 0.00) and refer to singlet absorptions unless otherwise stated. Apparent coupling constants in hertz, integration values (unless 1H) and signal assignments are given in parenthesis. For multiplets d = doublet, dd = double doublet, t = triplet, q = quartet and m = complex multiplet. Mass spectra were obtained using an AEI MS30 instrument operating at a ionisation potential of 70 eV. Metastable peaks are marked with asterisks. The apparent mass losses measured from the molecular ion and relative intensities (%) or in the case of metastable peaks the likely transitions are given in parenthesis. Elemental analyses were performed by the analytical laboratories of Aberdeen University.

Solvents, reagents and chromatographic materials Concentrated hydrochloric, sulphuric and perchloric acid (sg 1.70) were 'Analar' grade. Benzene, diethyl ether, petroleum ether, toluene and xylene were dried over sodium wire and filtered before use. Dimethylformamide for application in Vilsmeier formylation procedures was dried by allowing it to stand over molecular sieve material (Linde type 4A) and then passing it through a column of fresh alumina[135]. N,N-dimethylaniline was dried over sodium hydroxide pellets and distilled before use. Copper powder used for decarboxylation was the type reduced by hydrogen. Catalytic grade palladium on barium sulphate and palladium on char-

coal were commercial products obtained from Koch-Light Laboratories. Anhydrous ammonia (99.98%) was obtained from a cylinder. Sodamide was prepared immediately before use from sodium and anhydrous ammonia[128]. Column chromatography was carried out on Woelm neutral alumina (activity grade IV), and on silica gel as supplied by Hopkins and Williams Ltd. Thin layer chromatography (TLC) was carried out on Merck Kieselgel GF_{254}.

General procedures Organic solutions were dried over anhydrous magnesium sulphate and evaporated at reduced pressure on a rotary film evaporator. TLC plates were prepared by coating glass plates (20 x 20 cm) with a slurry of silica gel to a thickness of ca 0.8 mm. The plates were dried at 100° for 2 hours and left to cool overnight. Compounds to be chromatographed were applied as solutions in chloroform and the plates developed using benzene/ethyl acetate (3:1) unless otherwise stated. In the cases indicated, spraying a test plate firstly with a 10% solution of p-dimethylaminobenzaldehyde and then with 4M aqueous hydrochloric acid (Ehrlich's reagent)[136] aided band identification. Bands were marked whilst viewing under ultra-violet light (254 and 350 nm) and extracted with chloroform unless otherwise stated and are listed in the order of their speed of movement, the fastest being given first. Where the term 'steam distillation' is used it is implied that the distillation was continued until 400-1000 cm^3 of distillate was collected. The distillate was then extracted with ether (6 x 150 cm^3) and the combined extracts dried and evaporated to leave the stated crude product. Sealed tubes were made from thick walled pyrex glass - wall thickness 2.2 mm, outside diameter 14 mm, approximate length 20 cm. Compounds to be purified by distillation in glass tubes were transferred to the tubes, previously closed at one end, as solutions in ether (1-2 cm^3). In each case the solvent was evaporated at atmospheric pressure and the tube sealed under vacuum (0.01 mm). Subsequently, the tube was held in a horizontal position and the end containing the residue heated at the temperature specified.

In a few minutes the purified compound collected on the cold part of the tube, just outside the heating block. In cases where the identity of a compound was established by a comparison with an authenticated sample, this was by infra-red spectroscopy unless otherwise stated.

Sources of pyrimidines 4,6-Dimethylpyrimidine and 2,4-dimethyl-6-hydroxypyrimidine were commercial products. The following pyrimidines were synthesised by procedures similar to those given in the references cited.

2,4,6-Trimethylpyrimidine dihydrate[96] was obtained by the condensation of acetylacetone and acetamidine hydrochloride. The water of crystallisation was removed by azeotropic distillation with benzene until the theoretical quantity of water was collected. The benzene was then evaporated and the residue distilled. The fraction boiling at 160-164° gave 2,4,6-trimethylpyrimidine in 15% overall yield (lit bp 168-170°, 13%).

4-Hydroxy-2-methylpyrimidine[103] (mp 212-214°, 30%; lit 212.5-213°; 33%) was obtained by the condensation of the sodium salt of ethyl formylacetate[142] and acetamidine hydrochloride. The sodium salt of ethyl formylacetate prepared by the procedure published by Gabriel[143] was found unsatisfactory since the product obtained was dark brown in colour and contained unreacted sodium. Refluxing a solution of 4-hydroxy-2-methylpyrimidine in phosphoryl chloride gave crude 4-chloro-2-methylpyrimidine[103] (91%; lit 92%) which was recrystallised from petroleum ether (40-60°) and distilled at 80° (10 mm) to give the purified base as pale yellow crystals (mp 59-60°, lit[143] 59-60°). Catalytic dechlorination of 4-chloro-2-methylpyrimidine in a low pressure hydrogenation apparatus using a 5% palladium on barium sulphate catalyst gave 2-methylpyrimidine[102] (bp 130-132°, 83%; lit 129-133°). Attempts to dechlorinate crude samples of 4-chloro-2-methylpyrimidine were unsuccessful and purification of the pyrimidine by distillation at reduced pressure was essential before dechlorination would proceed. Refluxing a solution of 4-chloro-2-methylpyrimidine in methanol with sodium methoxide gave 4-methoxy-2-methylpyrimidine[109]. The product was worked up by filtering off the precipitated sodium chloride and distilling the filtrate. 4-Methoxy-2-methylpyrimidine was collected at 160-162° in a yield of 61% and gave a picrate which crystallised from ethanol. The picrate underwent a sudden change in

crystalline form at 117° and then melted at 152-159° (lit[109] 159°).

Similarly chlorination of 2,4-dimethyl-6-hydroxypyrimidine gave 2,4-dimethyl-6-chloropyrimidine[106] [bp 78° (18 mm), 86%; lit 182°, 67%] which on catalytic dechlorination[102] gave 2,4-dimethylpyrimidine (bp 150°, 74%; lit[144] 150°).

4,6-Dimethyl-2-hydroxypyrimidine hydrochloride[130] (67%; lit 71%) was obtained by the condensation of urea and acetylacetone in hydrochloric acid. 4,6-Dimethyl-2-hydroxypyrimidine (mp 205°; lit[145] 194-196°) was obtained by the addition of sodium bicarbonate to an aqueous solution of the hydrochloride followed by multiple extraction with chloroform. 2-Chloro-4,6-dimethylpyrimidine[129] (mp 37-39°; 91%; lit 38°, 90%) was obtained by refluxing a solution of 4,6-dimethyl-2-hydroxypyrimidine hydrochloride in phosphoryl chloride, and was further purified by distillation at 100° (15 mm).

The structures and purity of the pyrimidines prepared were confirmed by ir and NMR spectroscopy.

Chapter II

Reaction between 4,6-dimethylpyrimidine and phenacyl bromide[35]

The Chichibabin reaction between 4,6 -dimethylpyrimidine and phenacyl bromide by Boekelheide's procedure gave 7-methyl-2-phenyl-6-azaindolizine (44) as a yellow solid: mp 190° (dec), lit 180-190° (dec); NMR 2.40 (3H, Me), 6.56 (H-1), 7.00 (H-8), 7.30-7.70 (m, 5H, Ph), 7.53 (H-3), 8.70 (H-5).

Reaction between 4,6-dimethylpyrimidine and bromoacetone

Bromoacetone (13.7 g, 0.1 mol) was added to 4,6-dimethylpyrimidine (10.8 g, 0.1 mol). After two days at room temperature the red, glassy product was dissolved in water (300 cm^3) and extracted with ether. Sodium bicarbonate (20 g) was added to the aqueous extract and the resultant steam distilled to give a brown oil (3 g) which was fractionally distilled. 2,7-Dimethyl-6-azaindolizine (45) 2.08 g (14%) was collected at 90° (0.01 mm) as white crystals which darkened on standing: mp 69-70°; uv_{max} 239, (270), 280, 291, 335 (broad) nm, log e 4.31, 3.44, 3.57, 3.61, 2.70; ir 735, 780, 860, 1235, 1615 cm^{-1}; NMR 2.25 (3H, Me-2), 2.29 (3H, Me-7), 6.08 (H-1), 6.90 (H-8), 7.05 (H-3), 8.58 (H-5); mass spectrum m/e 146 (M, 100), 145 (M-1, 28), 118 (M-28, 20), 144* (146-145), see Table VI, p 57.

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N 19.16. Found: C, 73.8; H, 7.2; N, 19.0.

Reaction between 4,6-dimethylpyrimidine and bromobutanone

4,6-dimethylpyrimidine (21.6 g, 0.2 mol) and 3-bromo-2-butanone (30.2 g, 0.2 mol) in ethanol (25 cm^3) were gently refluxed for 30 minutes. The resultant brown gum was left overnight, the solvent evaporated, the product extracted into water (400 cm^3) and extracted with ether. Sodium bicarbonate (40 g) was added to the aqueous extract and the product steam distilled to yield a brown oil (5 g) which was fractionally distilled. 2,3,7-Trimethyl-6-azaindolizine (46), 4.17 g (15%) was collected at 100° (12 mm) as yellow waxy prisms which gradually darkened: mp 55-57°; uv_{max} (238), 240, (246), (272) 282, 293, 370 (broad) nm, log e 4.41, 4.43, 4.32, 3.64, 3.75, 3.76, 3.00; ir 760, 850, 1355, 1420, 1630 cm^{-1}; NMR 2.22 (3H, Me-2), 2.36 (3H, Me-3), 2.38 (3H, Me-7), 6.07 (H-1), 6.90 (H-8), 8.46 (H-5).

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.96; H, 7.55; N, 17.48. Found: C, 74.7; H, 7.7; N, 17.2.

Reaction between 2,4,6,-trimethylpyrimidine and phenacyl bromide

2,4,6-Trimethylpyrimidine[96] (12.2 g, 0.1 mol) and phenacyl bromide (19.9 g, 0.1 mol) in ethanol (5 cm^3) were gently warmed to boiling and the exothermic reaction which ensued moderated by the addition of ethanol (5 cm^3). After standing overnight, the solvent was evaporated and the resulting dark, brown gum extracted well with water (200 cm^3). The aqueous part was extracted with chloroform (4 x 75 cm^3) and the combined organic extracts dried and evaporated to give a brown, oily liquid (4 g). This was subjected to TLC with benzene/ethyl acetate (8:1).

The first band gave unchanged phenacyl bromide (1.2 g).

The next band gave a yellow solid which after recrystallisation from petroleum ether (60-80°) gave ω-hydroxyacetophenone (0.34 g) as

yellow needle clusters: mp 85-86°, lit[137] 89.5-90.5°; ir 1680, 3420 cm^{-1}; NMR 3.54 (OH), 4.87 (2H, CH_2), 7.20-8.00 (5H, m, Ph); mass spectrum m/e 136 (M^+, 4), 105 (M-31, 100), 77 (M-59, 45).

Anal. Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.7, H, 5.9.

The material from the band which gave a violet Ehrlich's test, after recrystallisation from petroleum ether/benzene (20:1) yielded 3-acetyl-2-methyl-5-phenylpyrrole (51), 28 mg as green needles: mp 179-181°, lit[98] 183°; uv_{max} (229), (236) 242, 288, (310), log e 4.22, 4.31, 4.34, 4.31, 4.06; ir 775, 812, 930, 952, 1238, 1561, 1600, 1629, 3220 cm^{-1}; NMR 2.43 (3H, Me-2) 2.59 (3H, Me of acetyl), 6.77 (d, J=2.5 Hz, H-4), 7.04-7.56 (m, 5H, Ph), 8.78 (broad and disappears on addition of D_2O, NH); mass spectrum m/e 199 (M, 56), 184 (M-15 , 100), 156(M-43, 10), 170* (199-184), 132* (184-156).

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.4; H; 6.5; N, 6.7.

This pyrrole gave a p-nitrophenylhydrazone derivative which crystallised from methanol: mp 235-237°; mass spectrum, calcd mass for $C_{19}H_{18}N_4O_2$: 334.1429, found m/e 334.1429 (M, 35), 197 (M-137, 100).

A pyrrole with identical characteristics was obtained by a Hantzsch[97] synthesis as follows. Excess concentrated aqueous ammonia sg 0.88 (20 cm^3) was slowly added to the mixture of phenacyl bromide (1.99 g, 0.01 mol) and acetylacetone (1.00 g, 0.01 mol) and the mixture gently warmed before refluxing for 15 minutes. The reaction mixture was evaporated to dryness and the residue extracted with chloroform (50 cm^3) and the chloroform extract evaporated to leave a red gum. This gum on TLC with benzene/ethyl acetate (8:1) gave the pyrrole (51), 84 mg (4%) with identical mp, uv, ir and NMR as cited above.

Sodium bicarbonate (20 g) was added to the aqueous quaternisation product and the solution heated on a boiling water bath for 30 minutes, cooled and extracted several times with ether (4 x 100 cm^3). The combined ether extracts were dried and evaporated to leave a dark brown liquid (ca 6 g) which was either (i) fractionally distilled or (ii) subjected to TLC.

(i) The first fraction collected at temperatures less than 130° (0.01 mm) was unchanged 2,4,6-trimethylpyrimidine (2.2 g) followed at 180-200° (0.01 mm) by 5,7-dimethyl-2-phenyl-6-azaindolizine (49), 1.50 g (7%) as a yellow oil which solidified: mp 89-92° (dec); uv_{max} 257, (290), 350 (broad) nm, log e 4.61, 3.81, 3.24; ir 690, 724, 765, 1408, 1620 cm^{-1}; NMR 2.34 (3H, Me-7), 2.64 (3H, Me-5), 6.52 (H-1), 6.88 (H-8), 7.20-7.70 (m, 5H, Ph), 7.34 (H-3); mass spectrum m/e 222 (M, 100), 221 (M-1, 22), 207 (M-15, 2), 181 (M-41, 6), 180 (M-42, 20), 220* (222-221), 193* (222-207), 179* (181-180), 147.5* (222-181).

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.1; H, 6.3; N, 12.3.

This 6-azaindolizine gave a picrate derivative which was recrystallised from ethanol: mp 220-223° (dec).

Anal. Calcd for $C_{21}H_{17}N_5O_7$: C, 55.88; H, 3.80. Found: C, 55.7; H, 3.80.

(ii) TLC was with benzene/methanol (20:1). The material from the pale yellow band which gave a bright yellow Ehrlich's test was extracted and the solid obtained recrystallised from petroleum ether to give (49), 1.35 g (6%) as pale green crystals mp 95-96° (dec) with identical ir and NMR spectra to the sample obtained by fractional distillation.

The material from the slower-moving band which gave a violet Ehrlich's test was extracted to give the pyrrole (51), 6 mg as white crystals with identical mp and spectral characteristics to the sample isolated previously from the crude quaternary product.

Ochiai[37] reports the pyrrole he isolated and its p-nitrophenylhydrazone derivative to have mp 178-180° and 233-235° respectively, and the picrate derivative of the azaindolizine to have mp 220-223° (dec).

Reaction between 2,4,6,-trimethylpyrimidine and bromoacetone

2,4,6-Trimethylpyrimidine (12.2 g, 0.1 mol) and bromoacetone (13.7 g, 0.1 mol) in ethanol (5 cm^3) were heated together until an exothermic reaction occurred. After the reaction had subsided the dark coloured solution was refluxed gently for 30 minutes and left overnight. Evaporation of the solvent left a brown gum which was extracted into water (300 cm^3). The aqueous part was extracted with ether (4 x 150 cm^3) and the combined ether extracts dried and evaporated to leave a brown oil (0.5 g). This was subjected to TLC with benzene/ethyl acetate (13:2). A number of bands developed.

The material from the band which slowly gave a red Ehrlich's test was extracted and recrystallised from petroleum ether to give 3-acetyl-2,5-dimethylpyrrole (53), 92 mg as white needles: mp 93-94°, lit[100] 94°; uv_{max} (Et_2O) 235, 282 nm, log e 3.98, 3.87, lit[101] (Et_2O) 233, 281 nm, log e 3.97, 3.70; ir ($CHCl_3$) 1640, 3300, 3450 cm^{-1}, lit[101] ($CHCl_3$) 1640, 3250, 3400 cm^{-1}; NMR 2.19 (3H, Me-5), 2.35 (3H, Me-2), 2.48 (3H, acetyl Me), 6.15 (m, H-4), 8.60 (broad and disappears on addition of D_2O, NH), lit[101] 2.22 (d, J=0.5 Hz, 3H), 2.37 (3H), 2.50 (3H), 6.12 (m); mass spectrum m/e 137 ($M^{\cdot}$, 50), 122 (M-15, 100), 94 (M-43, 9), 108.5* (137-122), 72.5* (122-94).

Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08. Found: C, 69.9; H, 8.4.

Sodium bicarbonate (20 g) was added to the aqueous quaternisation product and the resultant steam distilled to yield a brown liquid (6 g) which was fractionally distilled. The first fraction at 70-90° (10 mm) was unchanged 2,4,6-trimethylpyrimidine (3.0 g) followed at 110° (2 mm)

by 2,5,7-trimethyl-6-azaindolizine (54), 0.86 g (5%) as a yellow liquid which gradually became blue-green: uv_{max} 235, (273), 279, 290, 345 (broad) nm, log e 4.59, 3.97, 3.89, 3.92, 3.26; ir (liquid film) 1290, 1410, 1440, 1530, 1624 cm^{-1}, NMR 2.30 (3H, Me-2), 2.35 (3H, Me-7), 2.62 (3H, Me-5), 6.13 (H-1), 6.87 (H-8), 6.95 (H-3).

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.8; H, 7.6; N, 17.3.

Attempted reaction between 2,4,6-trimethylpyrimidine and 3-bromo-2-butanone

2,4,6-Trimethylpyrimidine (1.22 g, 0.01 mol), 3-bromo-2-butanone (1.51 g, 0.01 mol) and ethanol (0.5 cm^3) were heated under reflux for $2\frac{1}{2}$ hours. The dark coloured gum produced was extracted into water (100 cm^3) and the solution extracted with ether. Sodium bicarbonate (5 g) was added to the aqueous part and the resultant steam distilled to afford a small quantity of yellow oil. This was subjected to TLC with benzene/ethyl acetate (9:1) along with a reference spot of 2,3,5,7-tetramethyl-6-azaindolizine obtained by reductive formylation of 2,5,7-trimethyl-6-azaindolizine as described on pages 147 and 153. A number of minor bands developed, none of which corresponded to 2,3,5,7-tetramethyl-6-azaindolizine.

Reaction between 2-methylpyrimidine and ethyl bromopyruvate

Ethyl bromopyruvate (10.4 g, 53 m mol) was added to a solution of 2-methylpyrimidine[102] (5.0 g, 53 m mol) in ethanol (3 cm^3). After standing overnight the ethanol was removed under vacuum and the brown viscous residue dissoved in water (350 cm^3) and extracted with ether (3 x 100 cm^3). Sodium bicarbonate (20 g) was added to the aqueous part and the solution heated on a boiling water bath for 10 minutes, cooled and extracted with ether (3 x 100 cm^3). After drying, this ether extract was evaporated to leave a yellow oil (1 g) which on TLC with benzene/ethyl acetate gave a number of bands. The material from the yellow band which gave a blue Ehrlich's test on heating the plate at 100° was extracted and further chromatographed using petroleum ether/ethyl acetate (1:1). The faster moving of the two yellow bands which developed afforded 2-carbethoxy-8-azaindolizine (56), 94 mg (1.0%) as a yellow oil which crystallised on cooling: mp 48-60°; uv_{max} 225, 235, 242, (249), (258), 282, 292, 303, 370 (broad) nm, log e 4.37, 4.35, 4.33, 4.10, 3.95, 3.48, 3.52, 3.37, 3.22; ir (melt) 770, 1198, 1230, 1700 cm^{-1}; NMR - see Table IV p 50 ; mass spectrum, calcd mass for $C_{10}H_{10}N_2O_2$: 190.0742, found m/e 190.0742 (M, 100), 162 (M-28, 15), 145 (M-45, 56), 118(M-72, 63), 117 (M-73, 19), 130* (162-145), 95* (145-117).

Hydrolysis of the ester (56), 80 mg with potassium hydroxide (180 mg) in boiling ethanol (3 cm^3) gave a yellow precipitate. This was filtered from the cold solution, washed with a few drops of ethanol and dried to give the potassium salt of 8-azaindolizine-2-carboxylic acid (57), 79 mg (94%) which did not melt below 350°: uv_{max} (water) 218, (237), 241, (247), (256), 283, 292, 304 372 (broad) nm, log e 4.33, 4.29, 4.30, 4.02, 3.91, 3.40, 3.47, 3.37, 3.11; ir 770, 3122, 1570 cm^{-1}; NMR (CF_3COOH) 7.29 (dd, J = 5.0 and 7.0 Hz, H-6), 7.50 (H-1), 8.45 (H-3), 8.75 (d, J = 5.0 Hz, H-7), 9.17 (d, J = 7.0 Hz, H-5).

Neutralisation of the potassium salt (57), 35 mg (0.175 m mol) dissolved in a few drops of water with 1M HCl (0.175 cm^3) gave a yellow precipitate. This was filtered off, washed with a little water and dried to give 8-aza-

indolizine-2-carboxylic acid hydrochloride (58), 22 mg (63%) as a yellow powder which decomposed 290°: uv_{max} 219, (238), 242, (247), 282, 292, 303, 374 (broad) nm, log e 4.50, 4.45, 4.50, 4.45, 3.61, 3.67, 3.54, 3.37; ir 734, 790, 1250, 1495, 1698, 1880 (broad), 2590 (broad), 2750 cm^{-1}; NMR [$(CD_3)_2SO$] 6.77 (m, 2H, H-1 and H-6), 7.96 (d, J = 2.0 Hz, H-3), 8.18 (m, H-7), 8.68 (d, J = 7.0 Hz with some additional fine splittings, H-5); mass spectrum m/e 162 (M^a, 100), 145 (M-17, 28), 117 (M-45, 25), 130* (162-145), 94.5* (145-117).

Decarboxylation of 8-azaindolizine-2-carboxylic acid

An intimate mixture of 8-azaindolizine-2-carboxylic acid hydrochloride (58), 32 mg and copper powder (1 g)[105] was placed at one end of a sealed, evacuated (0.01 mm) glass tube and heated in a block maintained at 260°. After a few minutes a band of yellow liquid collected on the cold part of the tube just outside the heating block. This liquid was further distilled at 90° to the end of the tube immediately before opening to give 8-azaindolizine (59), 15 mg (79%) as a yellow oil: uv_{max} - see Figure III p 52 , (234), 239, 244, (285), 291, 302, 374 (broad) nm, log e 4.35, 4.43, 4.37, 3.18, 3.26, 3.08, 3.08; ir - see Figure I p 37 ; NMR - see figure II p 39 and Table IV p 50 ; mass spectrum - see Figure IV, p 55 , calcd mass for $C_7H_6N_2$: 118.0530, found m/e 118.0529 (M, 100).

For elemental analysis see formyl derivative p 150.

Reaction between 2-methylpyrimidine and bromoacetone

A solution of 2-methylpyrimidine (0.94 g, 0.01 mol) and bromoacetone (1.37 g, 0.01 mol) was allowed to stand at 35° for 2 days. The glassy mass produced was dissolved in water (50 cm^3) and washed with ether (3 x 50 cm^3). Sodium bicarbonate (5 g) was added to the aqueous part and the resultant steam distilled to give a few milligrams of a yellow oil which was subjected to TLC firstly with benzene/ethyl acetate (10:1) and then with ether. The material from the yellow band was extracted with ether and distilled at 90° (0.01 mm) in a sealed glass tube to give 2-methyl-8-azaindolizine (60), 7 mg

[a] Free amino acid

(0.5%) as a yellow oil which crystallised on cooling: mp 43-43.5°; uv_{max} (238), 243, 250, (291), 301, 313, 347 (broad) nm, log e 4.28, 4.35, 4.29, 3.12, 3.27, 3.30, 3.07; ir 747, 773, 799, 1254, 1506, 1615 cm^{-1}; NMR - see Table IV p 50; mass spectrum - see Figure V p 55, calcd mass for $C_8H_8N_2$: 132.0687, found m/e 132.0683 (M, 100).

Reaction between 2-methylpyrimidine and phenacyl bromide

A solution of 2-methylpyrimidine (0.82 g, 8.7 m mol) and phenacyl bromide (1.73 g, 8.7 m mol) was heated at 60° for 4 hours. The red orange glassy solid produced was dissolved in water (100 cm^3) and washed with ether (3 x 100 cm^3). Sodium bicarbonate (5 g) was added to the aqueous phase and the resultant heated on a boiling water bath for 15 minutes, cooled and extracted with ether (3 x 100 cm^3). After drying, evaporation of this ether extract gave a red oil (0.1 g) which was subjected to TLC with benzene/ethyl acetate (4:1). The material from the pale yellow band which slowly gave a blue Ehrlich's test was extracted to give 2-phenyl-8-azaindolizine (61), 9 mg (0.5%) as pale yellow crystals: mp 138-141°; uv_{max} 253, 325, 371 (broad) nm, log e 4.54, 3.78, 3.37; ir (KBr) 738, 768, 1198, 1267, 1370, 1510, 1600, 1618 cm^{-1}; NMR - see Table IV p 50; mass spectrum, calcd mass for $C_{13}H_{10}N_2$: 194.0843, found m/e 194.0846 (M, 100), 193 (M-1, 6), 167 (M-27, 2), 166 (M-28, 3), 192* (194-193).

Reaction between 2-methylpyrimidine and 3-bromo-2-butanone

A solution of 2-methylpyrimidine (0.94 g, 0.01 mol) and 3-bromo-2-butanone (1.51 g, 0.01 mol) was allowed to stand for 2 weeks. The orange brown solid produced was taken up in water (100 cm^3) and washed with ether (3 x 100 cm^3). Sodium bicarbonate (5 g) was added to the aqueous part and the resultant steam distilled to give a yellow solid (12 mg) which was subjected to TLC. The material from the yellow band was extracted with ether and distilled at 100° (0.01 mm) in a sealed glass tube to give 2,3-dimethyl-8-azaindolizine (62), 4 mg (0.3%) as yellow prisms: mp 93-94°; uv_{max} (228),

232, 249, 256, (295), 302, 315, 390 (broad) nm, log e 4.25, 4.28, 4.44, 4.37, 3.29. 3.37, 3.37, 3.24; ir 771, 1268, 1502, 1614 cm^{-1}; NMR - see Table IV p 50 ; mass spectrum - see p 56 , calcd mass for $C_9H_{10}N_2$: 146.0843, found m/e 146.0841 (M, 71).

Reaction between 2,4-dimethylpyrimidine and bromoacetone

A solution of 2,4-dimethylpyrimidine[102, 106] (5.4 g, 0.05 mol) and bromoacetone (6.85 g, 0.05 mol) was warmed at 35° overnight. The red glassy mass produced was dissolved in water (400 cm^3) and washed with ether (4 x 100 cm^3). Sodium bicarbonate (10 g) was added to the aqueous phase and the resultant steam distilled to give a yellow oil (1.1 g) which was subjected to TLC with ether. The material from the fast moving yellow band was extracted with ether and distilled at 100° (0.01 mm) in a sealed glass tube to give 2,7-dimethyl-8-azaindolizine (64), 406 mg (6%) as a yellow oil which subsequently crystallised: mp 33-49°; uv_{max} (239), 245, 252, (291), 296, (306), 370 (broad) nm; log e 4.33, 4.42, 4.40, 3.54, 3.56, 3.39, 3.06; ir (melt) 780, 1143, 1253, 1521, 1622 cm^{-1}; NMR - see Table IV p 50 ; mass spectrum - see p 56, calcd mass for $C_9H_{10}N_2$: 146.083, found m/e 146.0842 (M, 100).

Anal. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.89. Found: C, 74.2; H, 7.2.

Reaction between 2,4-dimethylpyrimidine and 3-bromo-2-butanone

A solution of 2,4-dimethylpyrimidine (4.32 g, 0.04 mol) and 3-bromo-2-butanone (6.04 g, 0.04 mol) was heated just below reflux for fifteen minutes. The dark coloured viscous mass produced was dissolved in water (100 cm^3) and washed with ether (3 x 100 cm^3). Sodium bicarbonate (10 g) was added to the aqueous phase and the resultant steam distilled to give a yellow oil (0.15 g) which was subjected to TLC with benzene/ethyl acetate. The material from the yellow band was extracted with ether and distilled at 100° (0.01 mm) to give 2,3,7-trimethyl-8-azaindolizine (67), 18 mg (0.3%) as an oil which subsequently crystallised: mp 64-65°; uv_{max} (237), 250, (255), 299, 313, 386 (broad) nm, log e 4.37, 4.55, 4.50, 3.56, 3.41, 3.26; ir 780, 1268, 1620 cm^{-1}; NMR - see Table IV p 50; mass spectrum, calcd mass for

$C_{10}H_{12}N_2$: 160.1000, found m/e 160.1000 (M, 71), 159 (M-1, 100), 158* (160-159).

A compound with identical mp, uv, ir and NMR spectra to (67) was obtained by reductive formylation of 2,7-dimethyl-8-azaindolizine (64), see pages 150 and 153.

Reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide

(a) A solution of 4-methoxy-2-methylpyrimidine (0.31 g, 2.5 m mol) and phenacyl bromide (0.50 g, 2.5 m mol) was left at room temperature for 2 days. The brown solid produced was dissolved in water (50 cm^3) and washed with chloroform (3 x 50 cm^3). Sodium bicarbonate (2.5 g) was added to the aqueous phase and the resultant heated on a boiling water bath for 10 minutes. The buff coloured solid which separated was filtered from the cold solution, washed with a little water and dried. This solid (165 mg) was subjected to TLC, recrystallised from petroleum ether/benzene and finally distilled at 160° (0.01 mm) to give 7-methoxy-2-phenyl-8-azaindolizine (68), 150 mg (27%) as pale yellow crystals: mp 147-148°; uv_{max} 251, (255), 301, (310), 347 (broad) nm, log e 4.62, 4.61, 3.95, 3.88, 3.31; ir 705, 763, 1015, 1232, 1307, 1627 cm^{-1}; NMR - see Table IV p 50 ; mass spectrum m/e 224 (M, 100), 223 (M-1, 1), 209 (M-15, 6), 195 (M-29, 6), 182 (M-42, 6), 222* (224-223), 195* (224-209).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.8; H, 5.7; N, 12.2.

(b) A solution of 4-methoxy-2-methylpyrimidine (0.31 g, 2.5 m mol) and phenacyl bromide (0.50 g, 2.5 m mol) was heated carefully over a flame to start the exothermic reaction and then maintained at 40° for 6 hours. The yellow glassy product was dissolved in water (50 cm^3) and extracted with chloroform (3 x 50 cm^3). Sodium bicarbonate (2.5 g) was added to the aqueous part and the resultant heated on a boiling water bath for 10 minutes. The sand coloured crystals which separated were filtered from the cold solution, washed with a little water and dried (yield 360 mg). Distillation of this

product at 160-170° (0.01 mm) followed by recrystallisation from benzene gave 8-methyl-2-phenyl-8-azaindolizin-7(8H)-one (69), 324 mg (58%) as yellow crystals: mp 158.5-160.5°; uv_{max} 243, (289), 301, (329) nm, log e 4.52, 4.09, 4.12, 3.55; ir 740, 1220, 1548, 1668 cm^{-1}; NMR - see Table V p 51; mass spectrum m/e 224 (M, 100), 195 (M-29, 4), 181 (M-43, 3).

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.8; H, 5.6; N, 12.3.

The chloroform extract of the aqueous quaternary salt solution was dried and evaporated to give a yellow solid (50 mg) which on TLC gave a number of bands. The material from the band which gave a green Ehrlich's test and had the same R_f value as the azaindolizinone (69) was recrystallised from ethanol to give 8-phenacyl-2-phenyl-8-azaindolizin-5(8H)-one (71), 11 mg (1.3%) as white needles: mp 244.5-246.5; uv_{max} 247, (278), (297), 347 nm, log e 4.64, 4.05, 3.85, 3.76; ir 748, 1218, 1590, 1638, 1658, 1688 cm^{-1}; NMR-see Table V; mass spectrum, calcd mass for $C_{21}H_{16}N_2O_2$: 328.1211, found m/e 328.1213 (M, 32), 223 (M-105, 28), 195 (M-133, 1), 105 (PhCO, 100), 77 (Ph, 25), 56.5* (105-77).

(c) Quaternisation of 4-methoxy-2-methylpyrimidine (0.62 g, 5 m mol) with phenacyl bromide (1.0 g, 5 m mol) by warming gently with a flame for 15 minutes gave a yellow glass. This was dissolved in water (100 cm^3) and washed with ether (3 x 100 cm^3). Sodium bicarbonate (5 g) was added to the aqueous part and the resultant heated on a boiling water bath for 10 minutes. Chloroform extraction (3 x 100 cm^3) of the cold product gave a brown oil (0.8 g) which on TLC gave a number of bands. The material from the pale yellow band which had an R_f value greater than the azaindolizinone (69) and gave a blue-green Ehrlich's test was extracted and recrystallised from ethanol to give 8-phenacyl-2-phenyl-8-azaindolizin-7(8H)-one (70), 19 mg (1.2%) as yellow crystals: mp 209-213°; uv_{max} 243, 300, (331) nm, log e 4.62, 4.12, 3.56; ir 750, 1224, 1554, 1655, 1688 cm^{-1}; NMR - see Table V p 51; mass spectrum, calcd mass for $C_{21}H_{16}N_2O_2$: 328.1211, found m/e 328.1210 (M, 94), 223 (M-105, 100), 195 (M-133, 18), 105 (PhCO, 35), 77 (Ph, 10). The material from the band with the same R_f value as (69) was extracted and gave a yellow solid (320 mg). Fractional crystallisation

from benzene containing a little ethanol gave the 8-azaindolizin-5(8H)-one (71), 21 mg (1.3%) followed by the 8-azaindolizin-7(8H)-one (69), 213 mg (19%).

Reaction between 4-methoxy-2-methylpyrimidine and bromoacetone

(a) A solution of 4-methoxy-2-methylpyrimidine (0.31 g, 2.5 m mol) and bromoacetone (0.35 g, 2.5 m mol) was left for 3 days. The yellow glass produced was dissolved in water (50 cm^3) and washed with chloroform (3 x 50 cm^3). Sodium bicarbonate (2.5 g) was added to the aqueous phase and the resultant heated on a boiling water bath for 15 minutes, cooled and extracted with chloroform (3 x 50 cm^3). After drying, evaporation of this chloroform extract gave a brown oil (205 mg) which was subjected to TLC with benzene/ethyl acetate (5:1). Three main bands developed.

The material from the fastest band which additionally gave a blue Ehrlich's test, on extraction gave 7-methoxy-2-methyl-8-azaindolizine (76), 6 mg (1.5%) as an oil which crystallised on cooling to a waxy solid: mp gradual up to 54°; uv_{max} 242, 249, 274, 285, 297, 352 (broad) nm, log e 4.36, 4.36, 3.37, 3.34, 3.16, 3.04; ir 785, 1025, 1232, 1315, 1635 cm^{-1}; NMR - see Table IV p 50; mass spectrum, calcd mass for $C_9H_{10}N_2O$: 162.0793, found m/e 162.0794 (M, 100), 161 (M-1, 8), 147 (M-15, 18), 133 (M-29, 16), 120 (M-42, 20), 160* (162-161), 98* (147-120).

The material from the following broad yellow band was recrystallised from benzene/petroleum ether to give 2,8-dimethyl-8-azaindolizin-7(8H)-one (74), 159 mg (39%) as yellow needles: mp 122-124°, uv_{max} 239, 287, 335 (broad) nm, log e 4.18, 3.85, 3.02; ir 740, 1502, 1558, 1628, 1660 cm^{-1}; NMR - see Table V, p 51; mass spectrum m/e 162 (M, 100), 161 (M-1, 13), 147 (M-15, 13), 133 (M-29, 20), 160* (162-161), 133* (162-147).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.64; H, 6.22; N, 17.27. Found: C, 66.4; H, 6.5; N, 17.0.

The material from the next band which had a blue fluorescence on the plate under the uv light, was distilled at 110° (0.01 mm) to give 2,8-dimethyl-8-azaindolizin-5(8H)-one (75), 3 mg (0.7%) as a white waxy solid: mp 78-83.5°;

uv_{max} 226, (255), 345 nm, log e 4.36, 3.68, 3.63; ir (mulled under dry nitrogen to prevent absorption of moisture) 732, 782, 1600, 1658 cm^{-1}; NMR - see Table V, p 51; mass spectrum, calcd mass for $C_9H_{10}N_2O$: 162.0793, found m/e 162.0794 (M, 100), 161 (M-1, 40), 147 (M-15, 10), 133 (M-29, 13), 119 (M-43, 16), 166* (162-161), 133* (162-147).

(b) A solution of 4-methoxy-2-methylpyrimidine (1.00 g, 8.1 m mol) and bromoacetone (1.11 g, 8.1 m mol) was heated at 40° for two days. The dark coloured solid produced was dissolved in water (100 cm^3) and washed with ether (3 x 100 cm^3). Sodium bicarbonate (5 g) was added to the aqueous phase and the solution heated on a boiling water bath for 15 minutes, cooled and extracted with ether (3 x 100 cm^3). After drying, this ether extract was evaporated to leave a red-brown oil (1 g) which was subjected to TLC as in the previous reaction. This gave in addition to the 8-azaindolizin-7(8H)-one (74) and the 8-azaindolizin-5(8H)-one (75) in yields of 22% and 0.5% respectively, a slower moving band with blue fluorescence on the plate under uv light. Chloroform extraction of this band gave 8-acetonyl-2-methyl-8-azaindolizin-5(8H)-one (77), 12 mg (0.7%) as white needles: mp 170.5-174.5°; uv_{max} 225, (255), 347 (broad) nm, log e 4.39, 3.74, 3.58; ir 782, 1598, 1660, 1720 cm^{-1}; NMR - see Table V, p 51; mass spectrum m/e 204 (M, 50), 161 (M-43, 100), 127* (204-161).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.6; H, 6.2; N, 14.0.

Reaction between 4-hydroxy-2-methylpyrimidine and bromoacetone

4-Hydroxy-2-methylpyrimidine[103] (3.0 g, 27 m mol) and bromoacetone (3.74 g 27 m mol) in dimethylformamide (30 cm^3) were heated at 60° for 8 hours. The bulk of the solvent was removed at ca 80° (15 mm) and the dark coloured residue taken up in water (100 cm^3) and washed with chloroform (3 x 100 cm^3). Sodium bicarbonate (10 g) was added to the aqueous part and the resultant heated on a boiling water bath for 30 minutes, cooled and extracted with chloroform (3 x 100 cm^3). After drying this chloroform extract

was evaporated to leave a small volume of a brown liquid which was subjected to TLC with benzene/ethyl acetate (3:2). Three main bands developed. The fastest moving band gave a violet Ehrlich's test. Chloroform extraction of this band gave 8-acetonyl-2-methyl-8-azaindolizin-7(8H)-one (78), 84 mg (1.5%) as a yellow oil which subsequently crystallised: mp 100°; uv_{max} 238, 287, 340 (broad) nm, log e 4.29, 3.80, 2.84; ir 768, 1169, 1351, 1549, 1641, 1720 cm^{-1}; NMR - see Table V p 51; mass spectrum m/e 204 (M, 89), 161 (M-43, 100), 133 (M-71, 50), 127* (204-161), 110* (161-133).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.09; H, 5.92; N, 13.72. Found: C, 64.4; H, 6.0; N, 13.5.

Chloroform extraction of the middle band gave 8-acetonyl-2-methyl-8-azaindolizin-5(8H)-one (77), 63 mg (1.1%) with identical mp and spectral characteristics to the sample obtained from the reaction between 4-methoxy-2-methylpyrimidine and bromoacetone.

The material from the slowest moving band,was further chromatographed on a short column of silica gel. Elution with chloroform gave 1-acetonyl-2-methyl-pyrimidin-4(1H)-one (79), 134 mg (3.0%) as pale purple crystals: mp 121°; uv_{max} 277, log e 3.71; ir 842, 1530, 1662, 1712 cm^{-1}; NMR 2.30 (3H, Me), 2.38 (3H, Me), 4.85 (2H, CH_2), 6.33 (d, J = 7.0 Hz, H-5), 7.80 (d, J = 7.0 Hz, H-6); mass spectrum m/e 166 (M, 7), 151 (M-15, 3), 124 (M-42, 100), 96 (M-70, 11).

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.8; H, 6.1; N, 16.7.

Continued elution of the column with methanol gave unchanged 4-hydroxy-2-methylpyrimidine (140 mg, 4.7%).

Reaction between 4-methoxy-2-methylpyrimidine and ethyl bromopyruvate

(a) Ethyl bromopyruvate (0.98 g, 5 m mol) was added to 4-methoxy-2-methyl-pyrimidine (0.62 g, 5 m mol) and the solution left for 2 days at room temperature to give a crystalline mass which was dissolved in water (100 cm^3) and washed with chloroform (3 x 100 cm^3). Sodium bicarbonate (5 g) was added to

the aqueous part and the solution heated on a boiling water bath for 5 minutes, cooled and extracted with chloroform (3 x 100 cm^3). After drying, this chloroform extract was evaporated to leave a brown oil (0.1 g) which was subjected to TLC. The material from the fast moving band which gave a blue Ehrlich's test was recrystallised from petroleum ether to give 2-carbethoxy-7-methoxy-8-azaindolizine (80), 19 mg (1.7%) as yellow needle clusters: mp 117.5-119°; uv_{max} 231, 239, 256, 264, (277), (287), 343 (broad) nm, log e 4.58, 4.51, 4.04, 4.02, 3.66, 3.45, 3.11; ir 1020, 1220, 1640, 1695 cm^{-1}; NMR - see Table IV, p 50; mass spectrum, calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847, found m/e 220.0844 (M, 100), 192 (M-28, 10), 175 (M-45, 20), 148 (M-72, 63).

(b) Repeating the above procedure with ethyl bromopyruvate (0.98 g, 5 m mol) and 4-methoxy-2-methylpyrimidine (0.62 g, 5 m mol) at a quaternisation temperature of 50° for 6 hours gave only a trace of the 8-azaindolizine (80). However the chloroform washings of the quaternary salt solution gave a brown liquid (0.6 g) which on TLC gave four bands.

The fastest was 2-carbethoxy-7-methoxy-8-azaindolizine (80), 4 mg (0.4%).

The material from the next band which gave a purple Ehrlich's test was recrystallised from benzene/petroleum ether to give 2-carbethoxy-8-methyl-8-azaindolizin-7(8H)-one (81), 14 mg (1.3%) as pale yellow crystals: mp 207-207.5°; uv_{max} 226, (232), (271), 275, 286, 328 (broad) nm, log e 4.51, 4.42, 4.05, 4.10, 3.98, 3.18; ir 1213, 1658, 1705 cm^{-1}; NMR - see Table V, p 51; mass spectrum, calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847, found m/e 220.0844 (M, 100), 192 (M-28, 13), 175 (M-45, 6), 148 (M-72, 14).

The material from the following band which gave a turquoise Ehrlich's test was recrystallised from benzene/petroleum ether to give 2-carbethoxy-8-methyl-8-azaindolizin-5(8H)-one (82), 5 mg (0.5%) as white needles: mp 178.5-179.5°; uv_{max} 231, (239), (256), (277), 347 nm, log e 4.48, 4.37, 3.52, 3.12, 3.47; ir 1190, 1208, 1660, 1705 cm^{-1}; NMR - see Table V, p 51; mass spectrum, calcd mass for $C_{11}H_{12}N_2O_3$: 220.0847, found m/e 220.0844 (M, 100), 192 (M-28, 6); 175 (M-45, 9), 148 (M-72, 14).

The material from the slowest band which gave a blue Ehrlich's test was recrystallised from benzene/ethanol to give 2-carbethoxy-8-azaindolizin-7(8H)-one (83), 16 mg (1.6%) as a pale yellow solid: mp 260° (dec); uv_{max} 226, (233), (272), 276, 286, 328 (broad) nm, log e 4.49, 4.37, 4.08, 4.12, 3.97, 3.09; ir 1228, 1424, 1700, 2740 cm^{-1}; NMR - see Table V, p 51; mass spectrum, calcd mass for $C_{10}H_{10}N_2O_3$: 206.0691, found m/e 206.0688 (M, 100), 178 (M-28, 20), 163 (M-45, 40), 134 (M-72, 56).

6-Methyl-2-phenyl-5-azacycl[3,2,2]azine (92)

This azacyclazine (92) was prepared[35] from 7-methyl-2-phenyl-6-azaindolizine (44) and dimethyl acetylenedicarboxylate: mp 147.5-148.5°; uv - see Figure VII, p112; NMR - see Table VIII, p 82.

2,6-Dimethyl-5-azacycl[3,2,2]azine (98)

A solution of dimethyl acetylenedicarboxylate (3.00 g, 21 m mol) in nitrobenzene[138] (20 cm^3) was added to a solution of 2,7-dimethyl-6-azaindolizine (45), 1.00g (4.81 m mol) in nitrobenzene (20 cm^3) and the resulting red solution refluxed for 1 hour. The solvent was removed at reduced pressure on a rotary film evaporator at 90° (ca 0.1 mm) and the dark coloured residue subjected to TLC with benzene/ethyl acetate (20:3). The slow moving bright yellow band was extracted and the solid obtained distilled at 160-180° (0.1 mm) and recrystallised from ethyl acetate to give 3,4-dicarbmethoxy-2,6-dimethyl-5-azacycl[3,2,2]azine (99), 0.21g (11%) as orange prisms: mp 143.5-145°; uv_{max} 239, 263, 315, 438 nm, log e 4.51, 4.36, 4.07, 3.93; ir 792, 1060, 1131, 1153, 1190, 1229, 1261, 1700, 1726 cm^{-1}; NMR - see Table VIII, p 82; mass spectrum m/e 286 (M, 79), 255 (M-31, 100), 225 (M-61, 6), 196 (M-90, 7), 170 (M-116, 10), 227.5* (286-255), 198.5* (255-225).

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.8; H, 5.1; N, 10.0.

A solution of potassium hydroxide (5.2 g) in methanol (13 cm^3) was added to a solution of the diester (99), 100 mg in warm methanol (2 cm^3). A yellow precipitate was formed and the mixture was heated at 50° for 1 hour to ensure complete hydrolysis. The precipitate of the potassium salt was filtered off, dissolved in water (5 cm^3) and the solution acidified with 6M HCl. The diacid which separated (64 mg, 71%) was filtered off, dried and heated for 2 hours in refluxing aniline (50 cm^3) containing copper powder (250 mg)[35]. The copper powder was removed by filtration and the bulk of the aniline removed on a rotary film evaporator at 80° (ca 0.1 mm). The dark coloured residue was subjected to TLC firstly with benzene/ethyl acetate (25:1) and then with petroleum

ether (60-80°)/ethyl acetate (10:1). Chloroform extraction of the bright yellow band gave 2,6-dimethyl-5-azacycl[3,2,2]azine (98), 8 mg (19%) as an oil which crystallised on cooling: mp 40.5-43°; uv_{max} 249,291,306,433 nm, log e 4.62, 4.61, 3.75, 3.54; ir 710, 719, 741, 1332, 1515, 1525, 1590 cm^{-1}; NMR - see Table VIII, p 82 ; mass spectrum, calcd mass for $C_{11}H_{10}N_2$: 170.0843, found m/e 170.0843 (M, 100), 169 (M-1, 40), 168* (170-169).

The azacyclazine (98) was also obtained by heating 3-formyl-2,5,7-trimethyl-6-azaindolizine (96) with potassium hydroxide as described on p 148.

1,2-Dicarbmethoxy-3,6-dimethyl-5-azacycl[3,2,2]azine (115)

Dimethyl acetylenedicarboxylate (150 mg, 1.06 m mol) was added to 2,7-dimethyl-8-azaindolizine (64), 100 mg (0.68 m mol) in toluene (25 cm^3) and the solution refluxed under nitrogen with 5% palladium on charcoal (150 mg) for 20 hours[35]. The catalyst was filtered off, the solvent evaporated and the residue subjected to TLC with benzene/ethyl acetate (6:1). The material from the bright yellow band was extracted, recrystallised from ethanol and finally distilled at 170° (0.01 mm) to give 1,2-dicarbmethoxy-3,6-dimethyl-5-azacycl-[3,2,2]azine (115), 129 mg (66%) as yellow crystals which had a green fluorescence in solution: mp 137°; uv_{max} 250, (280), (294), (317), 434 nm, log e 4.39, 4.03, 3.93, 3.68, 3.80; ir 1120, 1195, 1310, 1598, 1700, 1730 cm^{-1}; NMR - see Table, VIII p 82 ; mass spectrum m/e 286 (M, 84), 255 (M-31, 100), 254 (M-32, 13), 196 (M-90, 11).

Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.2; H, 5.2; N, 9.5.

Reaction between 2,8-dimethyl-8-azaindolizin-7(8H)-one and dimethyl acetylene-dicarboxylate

Dimethyl acetylenedicarboxylate (145 mg, 1.02 m mol) was reacted with 2,8-dimethyl-8-azaindolizin-7(8H)-one (74), 110 mg (0.68 m mol) in the presence of 5% palladium on charcoal (150 mg) as in the above case with 2,7-dimethyl-8-azaindolizine (64). TLC gave four coloured bands. Chloroform extraction of the fast moving yellow band gave 4,4a-dihydro-1,2-dicarbmethoxy-3,5-dimethyl-5-aza-cycl[3,2,2]azin-6(5H)-one (117), 8 mg (4%) as orange crystals: mp 128-131°; uv_{max}

240 (broad), 280 (broad), 420 nm, log e 4.00, 3.71, 4.02; ir 805, 1130, 1280, 1680, 1733 cm^{-1}; NMR 2.11 (d, J = 1.5 Hz, 3H, Me-3), 2.47 (dd, J = 14.5 and 15.5 Hz, H of C-4 methylene), 3.12 (dd, J = 5.5 and 15.5 Hz, H of C-4 methylene), 3.25 (3H, Me-N), 3.75 (3H, MeO), 3.96 (3H, MeO), 4.77-5.03 (m, C-4a methine), 5.63 (H-7); mass spectrum m/e 304 (M, 63), 273 (M-31, 14), 245 (M-59, 94), 217 (M-87, 100), 186 (M-119, 10), 245* (304-273), 197.5* (304-245), 192.5* (245-217), 158* (217-185).

Anal. Calcd for $C_{15}H_{16}N_2O_5$: C, 59.21; H, 5.30; N, 9.21. Found: C, 59.4; H, 5.1; N, 9.2.

The next yellow band gave 3-(cis-dicarbmethocyethenyl)-2,8-dimethyl-8-azaindolizin-7(8H)-one (118), 28 mg (13.6%) as an oil which crystallised slowly: mp 116-118°; uv_{max} 240, 285, 370 nm, log e 4.13, 3.78, 4.03; ir 1240, 1650, 1718 cm^{-1}; NMR 2.20 (3H, Me-2), 3.43 (3H, Me-N), 3.78 (3H, MeO), 3.88 (3H, MeO), 5.65 (H-1), 5.93 (vinyl H), 5.96 (d, J = 8.0 Hz, H-6), 7.96 (d, J = 8.0 Hz, H-5); mass spectrum, calcd mass for $C_{15}H_{16}N_2O_5$: 304.1059, found m/e 304.1056 (M, 71), 245 (M-59, 100), 186 (M-118, 20), 197.5* (304-245).

The following orange band gave 3-(trans-dicarbmethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8H)-one (119), 37 mg (18%) as an oil which crystallised slowly: mp 106-110°; uv_{max} 240, 284, 420 nm, log e 4.38, 3.83, 3.48; ir 1240, 1660, 1706 cm^{-1}; NMR 2.01 (3H, Me-2), 3.44 (3H, Me-N), 3.68 (3H, MeO), 3.82 (3H, MeO), 5.63 (H-1), 5.89 (d, J = 8.0 Hz, H-6), 7.13 (vinyl H), 7.33 (d, J = 8.0 Hz, H-5); mass spectrum, calcd mass for $C_{15}H_{16}N_2O_5$: 304.1059, found m/e 304.1056 (M, 79), 245 (M-59, 100), 186 (M-118, 16), 197.5* (304-245).

The material from the slow moving red band was recrystallised from ethyl acetate to give 1,2-dicarbmethoxy-3,5-dimethyl-5-azacycl[3,2,2]azin-6(5H)-one (116), 121 mg (59%) as dark red needle clusters with a strong fluorescence in solution: mp 179.5-180°; uv_{max} 231, (240), 278, (287), (298), 362, (498), 526, (552) nm, log e 4.32, 4.27, 4.18, 4.13, 3.60, 3.66, 3.81, 3.99, 3.66; ir 1083, 1290, 1658, 1689, 1716 cm^{-1}; NMR 2.49 (3H, Me-3), 3.78 (3H, Me-N), 3.91 (3H, MeO), 4.04 (3H, MeO), 6.20 (H-4), 7.02 (H-7), mass spectrum m/e 302 (M, 100), 271 (M-31, 35), 270 (M-32, 20), 241 (M-61, 4), 212 (M-90, 7), 184 (M-118, 6), 241.5* (302-270), 167* (270-212), 160* (212-184).

Anal. Calcd $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.4; H, 4.5; N, 9.5.

Dehydration of 4,4a-dihydro-1,2-dicarbmethoxy-3,5-dimethyl-5-azacycl[3,2,2]azin-6(5H)-one (117)

A solution of the dihydro-azacyclazinone (117), 30 mg in toluene (15 cm^3) was refluxed for 20 hours under nitrogen with 5% palladium on charcoal (25 mg). The catalyst was removed by filtration, the solution evaporated and the residue subjected to TLC. Chloroform extraction of the slow moving red band gave 1,2-dicarbmethoxy-3,5-dimethyl-5-azacycl[3,2,2]azin-6(5H)-one (116), 13 mg (43%) as crystals with identical spectral characteristics to the sample obtained directly from 2,8-dimethyl-8-azaindolizin-7(8H)-one (74) and dimethyl acetylene-dicarboxylate.

Attempted cyclisation of 3-(cis-dicarbmethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8H)-one (118)

A solution of the cis isomer (118), 12 mg in toluene (15 cm^3) was refluxed for 4 hours under nitrogen with 5% palladium on charcoal (20 mg). The catalyst was removed by filtration and the orange coloured solution evaporated. The residue was subjected to TLC with benzene/ethyl acetate (6:1) and gave two bands. Chloroform extraction of the faster moving yellow band gave unchanged starting material 10 mg (83%). Extraction of the slower moving orange band gave 3-(trans-dicarbmethoxyethenyl)-2,8-dimethyl-8-azaindolizin-7(8H)-one (119), 2 mg (17%). No red band corresponding to the azacyclazinone (116) was observed.

Similarly, the trans isomer (119), 20 mg when subjected to the same treatment, gave unchanged starting material 15 mg (75%) and the cis isomer (118), 3 mg (15%).

Formylation[74,115] of 6- and 8- azaindolizines, 5-azacyclo[3,2,2]azines and 8-azaindolizinones

Formylation of 7-methyl-2-phenyl-6-azaindolizine

A solution of phosphoryl chloride (337 mg, 2.2 m mol) in dimethylformamide (2 cm^3) was added dropwise to a magnetically stirred solution of 7-methyl-2-phenyl-6-azaindolizine (44), 416 mg (2 m mol) in dimethylformamide (3 cm^3) and the resultant left in a closed vessel at 40° for 16 hours. The product was then poured into 2M aqueous sodium hydroxide (30 cm^3), diluted with water (30 cm^3) and the brown solid which separated filtered off and dried. Recrystallisation of this solid from benzene/petroleum ether (1:4) gave 3-formyl-7-methyl-2-phenyl-6-azaindolizine (84), 295 mg (63%) as buff coloured needles: mp 197-199°; uv_{max} 247, (261), 369 nm, log e 4.34, 4.19, 4.09; ir 768, 1258, 1430, 1636 cm^{-1}; NMR - see Table VII, p 74; mass spectrum m/e 236 (M, 100), 235 (M-1, 71), 208 (M-28, 5), 207 (M-29, 7), 234* (236-235), 182.5* (235-207).

Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.0; H, 5.0; N, 11.9.

Formylation and thioformylation[116] of 2,7-dimethyl-6-azaindolizine

A solution of phosphoryl chloride (1.69 mg, 11 m mol) in dimethylformamide (5 cm^3) was added dropwise to a magnetically stirred solution of 2,7-dimethyl-6-azaindolizine (45), 1.46 g (10 m mol) in dimethylformamide (5 cm^3) and the resultant left for 3 hours in a closed vessel at room temperature. The product was then poured into 2M aqueous sodium hydroxide (100 cm^3) and the aqueous solution extracted with chloroform (4 x 75 cm^3). The chloroform extract was washed with water (4 x 75 cm^3), dried and evaporated. The brown solid obtained was chromatographed on a short column of alumina (50 g) with benzene, and recrystallised from benzene/petroleum ether to give 2,7-dimethyl-3-formyl-6-azaindolizine (86), 1.08 g (62%) as straw coloured needles: mp 109-110°; uv_{max} 228, 247, (253), 264, (360), 367 nm, log e 4.27, 4.07, 4.01, 3.97, 4.17, 4.22; ir 720, 780, 960, 1130, 1260,

1625, 1645 cm^{-1}; NMR - see Table VII, p 74.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.79. Found C, 69.2; H, 6.1.

A solution of phosphoryl chloride (287 mg, 1.88 m mol) in dimethylformamide (2 cm^3) was added dropwise to a stirred solution of the azaindolizine (45), 250 mg (1.71 m mol) in dimethylformamide. After 3 hours the product was poured into 2M aqueous sodium hydrogen sulphide[139] (30 cm^3) and extracted with chloroform (4 x 30 cm^3). The chloroform extract was dried and evaporated and the residue chromatographed on a column of alumina (80 g) using benzene for absorption and elution. The solid obtained from the red band was recrystallised from benzene/cyclohexane (1:5) to give 2,7-dimethyl-3-thioformyl-6-azaindolizine (87), 190 mg (58%) as red needles: mp 175-176°; uv_{max} 227, (238), (253), (300), 308, 370, (420), (433), 439 nm, log e 4.20, 4.02, 3.91, 3.72, 3.76, 3.65, 3.98, 4.15, 4.20; ir 870, 980, 1135, 1258, 1318, 1510, 1610 cm^{-1}; mass spectrum m/e 190 (M, 63), 189(M-1, 100), 188(M-2, 3), 175 (M-15, 2), 145 (M-45, 2), 188* (190-189).

Anal. Calcd for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30; N, 14.72; S, 16.85. Found: C, 63.0; H, 5.4; N, 15.0; S, 16.9.

Formylation of 2,3,7-trimethyl-6-azaindolizine

Formylation of 2,3,7-trimethyl-6-azaindolizine (46), 1.60 g (10 m mol) by a procedure similar to that employed in the formylation of 2,7-dimethyl 6-azaindolizine gave 1-formyl-2,3,7-trimethyl-6-azaindolizine (88), 1.28 g (68%) as straw coloured needles: mp 143-146°; uv_{max} 240, (264), (274) 340 nm, log e 4.41, 3.71, 3.37, 4.10; ir 780, 870, 1045, 1250, 1360, 1510, 1615, 1660 cm^{-1}; NMR - see Table VII, p 74.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43. Found: C, 70.2; H, 6.7.

Formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine

Phosphoryl chloride (169 mg, 1.1 m mol) in dimethylformamide (2 cm^3) was added dropwise to a magnetically stirred solution of 5,7-dimethyl-2-phenyl-6-azaindolizine (49), 222 mg (1 m mol) in dimethylformamide (2 cm^3) and the solution warmed at 40° for 16 hours. The product obtained was

poured into 2M aqueous sodium hydroxide (20 cm^3), extracted with ether (4 x 30 cm^3) and the ether extract washed with water (6 x 15 cm^3), dried and evaporated. The green oily residue (0.2 g) was subjected to TLC: a number of bands developed. The material from the band which had a blue fluorescence on the plate under uv light was extracted and recrystallised from benzene/petroleum ether to give 5,7-dimethyl-1-formyl-2-phenyl-6-azaindolizine (89), 10 mg (4.0%) as pale green needles: mp 167-169°; uv_{max} 242, (282), 348 nm, log e 4.50, 3.79, 4.19; ir 719, 1490, 1508, 1610, 1641 cm^{-1}; NMR - see Table VII, p 74; mass spectrum, calcd mass for $C_{16}H_{14}N_2O$: 250.1106, found m/e 250.1107 (M, 100), 249 (M-1, 94), 222 (M-28, 1), 221 (M-29, 1), 248* (250-249), 196* (249-221).

The material from the bright yellow band was extracted and recrystallised from benzene/petroleum ether to give 4-formyl-6-methyl-2-phenyl-5-azacycl[3,2,2]azine (90), 5 mg (1.9%) as orange needles: mp 178.5-179°; uv_{max} (230), 245, (253), 283, 342, 454 nm, log e 4.46,4.59,4.52,4.22,4.36, 3.98; ir 685, 770, 1150, 1410, 1505, 1528, 1591, 1659 cm^{-1}; NMR - see Table VIII, p 82; mass spectrum, calcd mass for $C_{17}H_{12}N_2O$: 260.0949, found m/e 260.0946 (M, 71), 259 (M-1, 35), 232 (M-28, 100), 231 (M-29, 5), 230* (232-231).

Formylation of 2,5,7-trimethyl-6-azaindolizine

Formylation of 2,5,7-trimethyl-6-azaindolizine (54), 1.00 g (6.3 m mol) by a procedure similar to that used in the formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine gave a brown oil (ca 1 g). TLC with benzene/ethyl acetate (10:1) gave three main bands. The fastest band gave unchanged starting material (170 mg, 17%).

The material from the middle band was extracted and recrystallised from petroleum ether to give 3-formyl-2,5,7-trimethyl-6-azaindolizine (96) 190 mg (16%) as pale pink prisms: mp 100-101°; uv_{max} 228, 246, (253), (260), (355), 365 nm; log e 4.26, 4.06, 4.03, 3.99, 4.23, 4.29; ir 790, 850, 1263, 13.9, 1410, 1518, 1630 cm^{-1}; NMR - see Table VII, p 74; mass spectrum m/e 188 (M, 94), 187 (M-1, 18), M-17 (171, 100), 159 (M-29, 9), 155.5* (188-

171), 135* (187-159).

Anal. Calcd for $C_{11}N_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.1; H, 6.5; N, 15.2.

Chloroform extraction of the slowest moving band gave an orange solid (127 mg) which on fractional crystallisation from petroleum ether/benzene (10:1) gave 4-formyl-2,6-dimethyl-5-azacycl[3,2,2]azine (95), 72 mg (6%) as long yellow needles: mp 202.5°; uv_{max} 224, 249, 281, 309, 315, 428, (435) nm, log e 4.33, 4.47, 4.20, 4.01, 4.01, 3.99, 3.98; ir 870, 1139, 1410, 1534, 1592, 1664 cm^{-1}; NMR - see Table VIII, p 82; mass spectrum m/e 198 (M, 100), 197 (M-1, 100), 170 (M-28, 79), 169 (M-29, 5).

Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.9; H, 5.0; N, 14.3 .

The mother liquor from the above fractional crystallisation was evaporated and the residue subjected to TLC with acetone/petroleum ether, 60-80° (5:2). Two overlapping bands developed. Chloroform extraction of the lower portion of the slower moving colourless band gave 1-formyl-2,5,7-trimethyl-6-azaindolizine (94), 22 mg (1.9%) as flesh coloured prisms; mp 127.5-129°; uv_{max} 232, (261), 338 nm, log e 4.39, 3.60, 4.16; ir 961, 1278, 1441, 1523, 1610, 1649 cm^{-1}; NMR - see Table VIII, p 82; mass spectrum, calcd mass for $C_{11}H_{12}N_2O$: 188.0949, found m/e 188.0949 (M, 94), 187 (M-1, 100), 159 (M-29, 2), 186* (188-187).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43. Found: C, 70.4; H, 6.5.

Fusing a mixture of the aldehyde (96) and solid potassium hydroxide (2.0 g) in a sealed evacuated (0.01 mm) glass tube over a free flame gave a yellow vapour which condensed on the cold parts of the tube. After thorough cooling the tube was opened and the condensate extracted with ether and subjected to TLC. Ether extraction of the bright yellow band which developed gave 2,6-dimethyl-5-azacycl[3,2,2]azine (98), 12 mg (27%) which showed identical mp and spectral characteristics to the sample obtained by hydrolysis and decarboxylation of 3,4-dicarbmethoxy-2,6-dimethyl-5-azacycl-[3,2,2]azine (99).

The following aldehydes were prepared by the dropwise addition of a 10% molar excess of phosphoryl chloride in dimethylformamide (1 cm^3) to a magnetically stirred solution of the azaindolizine, azaindolizinone or azacyclazine in dimethylformamide (1 cm^3). After 2-4 hours in a sealed vessel the resultant was poured into 2M NaOH (30 cm^3) or 2M NaSH in the case of thioformylation and extracted with chloroform. Evaporation of the dried chloroform extract [and any residual dimethylformamide at ca 30-60° (0.01 mm)] gave the crude aldehyde which was purified by TLC.

2,3,5,7-Tetramethyl-6-azaindolizine (p67), 32 mg gave 1-formyl-2,3,5,7-tetramethyl-6-azaindolizine (2 mg, 5%) as white needles from petroleum ether: mp 166°; uv_{max} 239, (267), (279), 349 nm; log e 4.40, 3.60, 3.30, 4.14; ir 965, 1438, 1519, 1510, 1647 cm^{-1}; NMR - see Table VII, p 74; mass spectrum, calcd mass for $C_{12}H_{14}N_2O$: 202.1106, found m/e 202.1104 (M, 100), 201 (M-1, 71), 187 (M-15, 3), 173 (M-29, 11), 200* (202-201), 173* (202-187).

6-Methyl-2-phenyl-5-azacycl[3,2,2]azine (92), 16 mg gave three yellow bands. Chloroform extraction of the fastest gave unchanged starting material (3 mg, 19%). The material from the middle band was recrystallised from petroleum ether to give 2,6-dimethyl-1-formyl-2-phenyl-5-azacycl[3,2,2]azine (91), 4 mg (22%) as orange needles: mp 163-164°; uv_{max} 225, (233), (284), 297, (315), 438 nm; log e 4.40, 4.33, 4.42, 4.46, 4.27, 3.97; ir 709, 760, 794, 1362, 1529, 1588, 1643 cm^{-1}; NMR - see Table VIII, p 82; mass spectrum, calcd mass for $C_{17}H_{12}N_2O$: 260.0949, found m/e 260.0946 (M, 84), 259 (M-1, 100), 232 (M-28, 2), 231 (M-29, 6), 230 (M-30, 5), 258* (260-259), 206* (259-231). The material from the slowest moving band was recrystallised from petroleum ether to give 4-formyl-6-methyl-2-phenyl-5-azacycl[3,2,2]azine (90), 4 mg (22%) with identical mp and spectral characteristics as the sample obtained from formylation of 5,7-dimethyl-2-phenyl-6-azaindolizine (49).

2,6-Dimethyl-5-azacycl[3,2,2]azine (98), 17 mg gave three yellow bands after TLC with benzene/ethyl acetate (50:3). Chloroform extraction of the fastest gave unchanged starting material 4 mg (24%). The material

from the middle band was recrystallised from petroleum ether to give 2,6-dimethyl-1-formyl-5-azacycl[3,2,2]azine (97), 3 mg (15%) as yellow crystals: mp 152-160°; uv_{max} 227, 258, (267), (286), 312, 424 nm, log e 4.38, 4.45, 4.33, 4.03, 4.00, 3.92; ir 720, 781, 1324, 1365, 1422, 1518, 1533, 1590, 1640 cm^{-1}; NMR - see Table VII p 74; mass spectrum, calcd mass for $C_{12}H_{10}N_2O$: 198.0793, found m/e 198.0791 (M, 75), 197 (M-1, 100), 170 (M-28, 1), 169 (M-29, 7), 168 (M-30, 2), 196* (198-197), 145* (197-169).

The material from the slowest moving band was recrystallised from petroleum ether to give 2,6-dimethyl-4-formyl-5-azacycl[3,2,2]azine (95) 4mg (20%) with identical mp and spectral characteristics to the sample obtained from formylation of 2,5,7-trimethyl-6-azaindolizine (54).

8-Azaindolizine (59), 15 mg gave 3-formyl-8-azaindolizine (104), 8 mg (43%) as pale yellow needles from petroleum ether; mp 121-122°; uv_{max} 222, (267), 270, 343 nm, log e 4.17, 4.43, 4.44, 4.03; ir 786, 1408, 1604, 1655 cm^{-1}; NMR - see Table VII, p 74; mass spectrum m/e 146 (M, 100), 145 (M-1, 45), 117 (M-29, 25), 144* (146-145), 94.5* (145-117).

Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14. Found: C, 65.7; H, 4.2.

2,7-Dimethyl-8-azaindolizine (64), 40 mg gave 3-formyl-2,7-dimethyl-8-azaindolizine (105), 22 mg (46%) as pale yellow needles from petroleum ether: mp 110°; uv_{max} (227), 230, (266), (276), 282, 352 nm, log e 4.21, 4.22, 4.22, 4.36, 4.43, 4.11; ir 720, 1438, 1630 cm^{-1}; NMR - see Table VII, p 74; mass spectrum, calcd mass for $C_{10}H_{10}N_2O$: 174.0793, found m/e 174.0792 (M, 100), 173 (M-1, 60), 145 (M-29, 18), 172* (174-173), 121.5* (173-145).

Similarly by pouring the intermediate Vilsmeier salt solution into 2M aqueous sodium hydrogen sulphide[139] 2,7-dimethyl-8-azaindolizine gave 3-thioformyl-2,7-dimethyl-8-azaindolizine (p 73), 26 mg (50%) as red needle clusters from benzene/petroleum ether: mp 168.5-169°; uv_{max} 227, 275, (310), 317, 418, 429 nm, log e 4.38, 4.01, 3.95, 4.06, 4.47, 4.50; ir 977, 1422, 1500, 1530, 1607 cm^{-1}; NMR - see Table VII, p 74; mass spectrum, calcd mass for $C_{10}H_{10}N_2S$: 190.0563, found m/e 190.0561 (M, 67), 189 (M-1, 100), 188

(M-2, 5), 145 (M-45, 4), 188* (190-189), 187* (189-188).

Anal. Calcd for $C_{10}H_{10}N_2S$: C, 63.13; H, 5.30. Found: C, 63.4; H, 5.2.

2,3,7-Trimethyl-8-azaindolizine (67), 12 mg gave 1-formyl-2,3,7-trimethyl-8-azaindolizine (106), 4 mg (28%) as pale yellow needles from benzene/petroleum ether: mp 140°; uv_{max} 235, 242, 255, 280, 289, 324, 360 nm, log e 4.14, 4.13, 3.92, 3.80, 3.80, 3.79, 3.24; ir 786, 1278, 1342, 1535, 1643 cm^{-1}; NMR - see Table VII, p 74; mass spectrum, calcd mass for $C_{11}H_{12}N_2O$: 188.0949, found m/e 188.0946 (M, 100), 187 (M-1, 56), 160 (M-28, 67), 159 (M-29, 94), 158* (160-159), 136.5* (188-160).

7-Methoxy-2-phenyl-8-azaindolizine (68), 31 mg gave 3-formyl-7-methoxy-2-phenyl-8-azaindolizine (107), 22 mg (63%) as white needles from petroleum ether: mp 143-143.5°; uv_{max} 230, 249, 277, 350 nm, log e 4.24, 4.10, 4.43, 4.13; ir 810, 1240, 1410, 1625, 1649 cm^{-1}; NMR - see Table VII, p 74; mass spectrum m/e 252 (M, 100), 251 (M-1, 56), 223 (M-29, 3), 250* (252-251), 198.5* (251-223).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.1; H, 5.1; N, 11.1.

8-Methyl-2-phenyl-8-azaindolizin-7(8H)-one (69), 31 mg gave 3-formyl-8-methyl-2-phenyl-8-azaindolizin-7(8H)-one (109), 28 mg (80%) as white needles from benzene: mp 218.5°; uv_{max} 226, 239, 295, 340 nm, log e 4.21, 4.23, 4.39, 4.05; ir 840, 1542, 1618, 1694 cm^{-1}; NMR 3.57 (3H, Me-N), 5.95 (H-1), 6.17 (d, J = 7.5 Hz, H-6), 7.48 (5H, Ph), 9.32 (d, J = 7.5 Hz, H-5), 9.57 (CHO); mass spectrum m/e 252 (M, 100), 251 (M-1, 50), 223 (M-29,3), 250* (252-251), 198.5* (251-223).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.1; H, 4.9; N, 11.2.

2,8-Dimethyl-8-azaindolizin-7(8H)-one (74), 280 mg gave 2,8-dimethyl-3-formyl-8-azaindolizin-7(8H)-one (111), 228 mg (69%) as sand coloured prisms from benzene/petroleum ether: mp 212°; uv_{max} (220), (229), (226), 283, (287), 312, 336 nm, log e 3.92, 3.76, 3.95, 4.19, 4.16 4.09, 4.06; ir 890, 1288,

1501, 1620, 1637, 1678 cm^{-1}; NMR 2.45 (3H, Me-2), 3.48 (3H, Me-N), 5.68 (H-1), 6.06 (d, J = 8.0 Hz, H-6), 9.15 (d, J = 8.0 Hz, H-5), 9.61 (CHO); mass spectrum m/e 190(M, 100), 189 (M-1, 16), 161 (M-29, 14), 188* (190-189), 137.5* (189-161).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.2; H, 5.4; N, 14.8.

8-Acetonyl-2-methyl-8-azaindolizin-7(8H)-one (75), 25 mg gave 8-acetonyl-3-formyl-2-methyl-8-azaindolizin-7(8H)-one (112) as glassy needles from benzene: mp 196-197°; uv_{max} (220), (229), (267), 283, 288, 311, 335 nm, log e 3.97, 3.76, 3.98, 4.22, 4.20, 4.12, 4.07; ir 818, 1642, 1665, 1720 cm^{-1}; NMR 2.27 (3H, Me of acetonyl), 2.42 (3H, Me-2), 4.77 (2H, methylene), 5.48 (H-1), 6.11 (d, J = 8.0 Hz, H-6), 9.24 (d, J = 8.0 Hz, H-5), 9.66 (CHO); mass spectrum m/e 232 (M, 75), 190 (M-42, 18), 189 (M-43, 14), 161 (M-71, 100), 188* (190-189), 155.5* (232-190).

Anal. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21. Found: C, 62.2; H, 5.5.

2,8-Dimethyl-8-azaindolizin-5(8H)-one (75), 20 mg gave 2,8-dimethyl-3-formyl-8-azaindolizin-5(8H)-one (113), 21 mg (90%) as white needles from benzene: mp 247.5°; uv_{max} 225, 247, 338, 343 nm, log e 4.41, 4.12, 4.32, 4.32; ir 800, 1022, 1505, 1580, 1633, 1680 cm^{-1}; NMR 2.57 (3H, Me-2), 3.68 (3H, Me-N), 5.79 (d, J = 8.0 Hz, H-6), 5.89 (H-1), 7.24 (d, J = 8.0 Hz, H-7), 11.00 (CHO); mass spectrum, calcd mass for $C_{10}H_{10}N_2O_2$: 190.0742, found m/e 190.0740 (M, 100), 189 (M-1, 4), 162 (M-28, 28), 161 (M-29, 45), 147 (M-43, 14), 160* (162-161), 138.5* (190-162), 133* (162-147).

Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30. Found: C, 63.3; H, 5.7.

8-Acetonyl-2-methyl-8-azaindolizin-5(8H)-one (77), 15 mg gave 8-acetonyl-3-formyl-2-methyl-8-azaindolizin-5(8H)-one (114), 11 mg (64%) as white needle clusters from benzene/ethanol: mp 201-202°; uv_{max} 225, 247, 337, 343 nm, log e 4.38, 4.05, 4.28. 4.28; ir 782, 803, 1342, 1500, 1580, 1632, 1671, 1722 cm^{-1}; NMR 2.29 (3H, Me of acetonyl), 2.52 (3H, Me-2), 4.66 (2H, methylene), 5.64

(H-1), 5.85 (d, J = 8.0 Hz, H-6), 7.13 (d, J = 8.0, H-7), 10.95 (CHO); mass spectrum, calcd mass for $C_{12}H_{12}N_2O_3$: 232.0847, found m/e 232.0846 (M, 40), 204 (M-28, 2), 161 (M-71, 100), 179.5* (232-204).

Reduction[74] of 3-formyl-6- and 8- azaindolizines and 4-formyl-2,6-dimethyl-5-azacycl[3,2,2]azine

A solution of 3-formyl-2,7-dimethyl-6-azaindolizine (86), 500 mg (2.9 m mol) in ether (15 cm^3) was added slowly to a stirred solution of lithium aluminium hydride (550 mg, 14.5 m mol) and aluminium chloride (3.87 g, 29 m mol) in ether (60 cm^3). The reaction mixture was stirred for 1 hour and poured into ice cold 0.05M sulphuric acid (200 cm^3). The solution was made basic by the addition of potassium carbonate and extracted with ether (4 x 100 cm^3). The ether extract was washed with water (4 x 50 cm^3), dried and evaporated to leave a brown oil (0.2 g) which was subjected to TLC with benzene/ethyl acetate (5:1). The material from the band which slowly turned blue-green on exposure to the atmosphere was extracted with ether to give 2,3,7-trimethyl-6-azaindolizine (46), 10 mg (2%) as a pale brown solid with identical spectral characteristics (uv, ir, NMR) to the sample obtained from the Chichibabin reaction between 4,6-dimethylpyrimidine and 3-bromo-2-butanone.

Similarly 3-formyl-2,5,7-trimethyl-6-azaindolizine (96), 200 mg gave 2,3,5,7-tetramethyl-6-azaindolizine (50 mg, 27%) as pale green needles: mp 64-67°; uv_{max} 240, (277), 284, 295, 358 (broad) nm, log e 4.39, 3.71, 3.83, 3.82, 3.15; ir 868, 1287, 1363, 1530, 1630 cm^{-1}; NMR - see Table III, p 34; mass spectrum, calcd mass for $C_{11}H_{14}N_2$: 174.1156, found m/e 174.1157 (M, 100), 173 (M-1, 79), 159 (M-15, 14), 132 (M-42, 20), 118 (M-56, 8), 172* (174-173), 145* (174-159).

A solution of 3-formyl-2,7-dimethyl-8-azaindolizine (105), 30 mg (0.17 m mol) in ether (5 cm^3) was added slowly to a stirred solution of lithium aluminium hydride (32 mg, 0.85 m mol) and aluminium chloride (230 mg,

1.7 m mol) in ether (15 cm^3). The reaction mixture was stirred for 1 hour and poured into cold 0.05M sulphuric acid (50 cm^3). The solution was made basic by the addition of potassium carbonate and extracted with ether (4 x 15 cm^3). The ether extract was washed with water (4 x 15 cm^3), dried and evaporated to leave a yellow oil (16 mg) which on TLC with benzene/ethyl acetate (5:1) gave 2,3,7-trimethyl-8-azaindolizine (67), 5 mg (18%) as a yellow solid with identical spectral characteristics to the sample obtained from the Chichibabin reaction between 2,4-dimethylpyrimidine and 3-bromo-2-butanone.

Reduction of 4-formyl-2,6-dimethyl-5-azacycl[3,2,2]azine (95), 10 mg (0.05 m mol) by a procedure similar to that used in the reduction of the 3-formyl-8-azaindolizine (105) gave 2,4,6-trimethyl-5-azacycl[3,2,2]azine (100), 7 mg (75%) as yellow needles which were further purified by distillation at 100° (10 mm): mp 64-67°; uv_{max} 252, (264), 304 (broad), 310, 317, 453 nm, log e 4.43, 4.00, 3.64, 3.64, 3.54, 3.49; ir 705, 780, 921, 1192, 1430, 1520, 1593 cm^{-1}; NMR - see Table VIII, p 82; mass spectrum, calcd mass for $C_{12}H_{12}N_2$: 184.100, found m/e 184.1000 (M, 63), 183 (M-1, 100), 182 (M-2, 7), 169 (M-15, 2).

Acetylation, diazonium coupling and attempted nitrosation of 2,7-dimethyl-8-azaindolizine[36]

(a) Acetylation A solution of 2,7-dimethyl-8-azaindolizine (64), 150 mg in acetic anhydride (5 cm^3) was refluxed for 3 hours, cooled and poured into water (20 cm^3). The solution was basified with 2M sodium hydroxide and extracted with chloroform (4 x 25 cm^3). After drying the brown chloroform extract was evaporated and the crystalline residue subjected to TLC with benzene/ethyl acetate (4:1) and recrystallised from petroleum ether to give 3-acetyl-2,7-dimethyl-8-azaindolizine (124), 151 mg (78%) as straw coloured crystals; mp 122-123°; uv_{max} (225), 228, (263), (273), 278, 326 nm, log e 4.27, 4.30, 4.25, 4.39, 4.45, 4.07; ir 838, 968, 1330, 1410, 1518, 1610 cm^{-1};

NMR 2.55 (6H, Me-2 and Me-7), 2.63 (3H, Me of acetyl), 6.37 (H-1), 6.67 (d, J = 7.5 Hz, H-6), 9.97 (d, J = 7.5 Hz, H-5).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.3; H, 6.7; N, 14.7.

(b) Diazonium Coupling Sodium nitrite (100 mg, 1.5 m mol) was added to a cold solution (0°) of aniline hydrochloride (130 mg, 1.0 m mol) in 2M hydrochloric acid (2 cm^3). The cold solution was adjusted to pH 8 [140] by the addition of 2M sodium hydroxide and added dropwise to a cold solution of 2,7-dimethyl-8-azaindolizine (64), 50 mg (0.34 m mol) in water (5 cm^3) containing a few drops of ethanol. The orange suspension produced was allowed to stand at 0° for 15 minutes and then extracted with chloroform (4 x 15 cm^3). The chloroform extract was dried and evaporated and the orange residue subjected to TLC with benzene/ethyl acetate(5:1). The material from the orange band was extracted and recrystallised from petroleum ether to give 2,7-dimethyl-3-phenylazo-8-azaindolizine (125), 58 mg (68%) as red needles: mp 89-90°; uv_{max} 246, 282, 319, 418, 439 nm, log e 4.18, 3.93, 4.05, 4.40, 4.42; ir 761, 1186, 1249, 1415, 1608 cm^{-1}; NMR 2.52 (3H, Me), 2.63 (3H, Me), 6.51 (H-1), 6.64 (d, J = 7,5 Hz, H-6), 7.20-7.90 (m, 5H, Ph), 9.87 (d, J = 7.5 Hz, H-5).

Anal. Calcd for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.9; H, 5.7; N, 22.6.

(c) Attempted nitrosation A cold solution of sodium nitrite (250 mg, 3.6 m mol) in water (1 cm^3) was added dropwise to a cold solution of 2,7-dimethyl-8-azaindolizine (64), 110 mg(0.76 m mol) in 4M hydrochloric acid (6 cm^3) and the temperature maintained at 0-5° for 15 minutes[36]. The orange-red solution was made basic by the addition of sodium bicarbonate, diluted with a little water, and extracted with chloroform (4 x 20 cm^3). The green chloroform extract was dried and evaporated to give a brown gum (ca 0.1 g). Attempted crystallisation of the gum from benzene/ethanol or ethyl acetate failed and the product was not further investigated.

A similar reaction with the 8-azaindolizine (64), 73 mg and sodium

nitrite (50 mg) in acetic acid[141] ($3\ cm^3$) also gave a brown gum. In this instance the gum was subjected to TLC with benzene/ethyl acetate (4:1). A number of bands containing only traces of products developed and the bulk of the reaction product remained at the origin.

2,6,7-Trimethyl-6-azaindolizinium iodide (134)

A solution of 2,7-dimethyl-6-azaindolizine (45), 50 mg in methyl iodide (2 cm^3) contained in a sealed glass tube was heated on a boiling water bath for 5 minutes and left at room temperature overnight. The yellow crystals which formed were collected by filtration and washed with a little methyl iodide to give 2,6,7-trimethyl-6-azaindolizinium iodide (134), 78 mg (79%): mp 256° (dec); uv_{max} 220, 244, (288), 293, (300), (310) nm, log e 4.27, 4.42, 3.75, 3.79, 3.70, 3.55; ir 720, 802, 1145, 1378, 1560, 1660 cm^{-1}; NMR - see Table IX, p 92.

Anal. Calcd for $C_{10}H_{13}N_2I$: C, 41.68; H, 4.55; N, 9.72. Found: C, 41.7; H, 4.6; N, 9.8.

2,7,8-Trimethyl-6-azaindolizinium iodide (141)

By a procedure similar to that used to prepare the 6-azaindolizinium iodide (134), 2,7-dimethyl-8-azaindolizine (45), 50 mg gave 2,7,8-trimethyl-8-azaindolizinium iodide (141), 84 mg (85%) as yellow crystals: mp 227° (dec); uv_{max} 225, 243, 327 nm, log e 4.43, 4.23, 3.86; ir 770, 1280, 1340, 1562, 1620 cm^{-1}; NMR [$(CD_3)_2SO$] 2.36 (3H, Me-2), 2.80 (3H, Me-7), 4.10 (3H, Me-8), 6.89 (H-1), 7.15 (d, J = 7.0 Hz, H-6), 7.71 (H-3), 9.17 (d, J = 7.0 Hz, H-5).

Anal. Calcd for $C_{10}H_{13}N_2I$: C, 41.68; H, 4.55; N, 9.72. Found: C, 41.8; H, 4.8; N, 9.7.

2,7-Dimethyl-6-azaindolizinium perchlorate

Perchloric acid (0.2 cm^3, 1.4 m mol) was added to a solution of 2,7-dimethyl-6-azaindolizine (45), 146 mg (1 m mol) in ethanol (10 cm^3)[70]. The yellow needles which formed were collected by filtration, washed with a little cold ethanol and dried to give 2,7-dimethyl-6-azaindolizinium perchlorate (230 mg, 93%): mp 198-199°; ir 802, 1050, 1120, 1402, 1662, 3090, 3230 cm^{-1}; NMR [$(CD_3)_2SO$] 2.32 (3H, Me-2), 2.40 (3H, Me-7), 6.55 (H-1), 7.40 (H-8),

7.64 (H-3), 9.66 (broad, N-H).

Anal. Calcd for $C_9H_{11}ClN_2O_4$: C, 43.83; H, 4.50; Cl, 14.37; N, 11.36. Found: C, 44.1; H, 4.6; Cl, 14.6; N, 11.3.

Attempted recovery of 6-methyl-2-phenyl-5-azacycl[3,2,2]azine and 2,6-dimethyl-5-azacycl[3,2,2]azine from their solutions in concentrated sulphuric acid

6-Methyl-2-phenyl-5-azacycl[3,2,2]azine (147) 10 mg was dissolved in concentrated sulphuric acid (0.3 cm^3) at room temperature and the NMR spectrum recorded (H_2SO_4 = δ10.00). The spectrum obtained was consistent with that expected for 6-methyl-2-phenyl-5-azacycl[3,2,2]azine-1,4-disulphonic acid: δ 2.41 (3H, Me), 6.67-7.30 (m, 5H, Ph), 7.69 (H-7), 7.82 (H-3). The orange-red sulphuric acid solution was then poured into water (25 cm^3) and the solution made basic by the addition of sodium bicarbonate. Ether extraction (3 x 25 cm^3) of the resulting yellow solution gave a colourless ether extract and the yellow colour of the azacyclazine was retained in the aqueous phase. The ether extract was dried and evaporated but left no residue.

Similarly 2,6-dimethyl-5-azacycl[3,2,2]azine (150) in concentrated sulphuric or deuterosulphuric acid gave an NMR spectrum consistent with that expected for its 1,4-disulphonic acid derivative: δ 2.16 (3H, Me), 2.32 (3H, Me-6), 7.55 (H-7), 7.80 (H-3). Again attempted recovery of the azacyclazine failed.

1,4-Dideutero-2,6-dimethyl-5-azacycl[3,2,2]azine

2,6-Dimethyl-5-azacycl[3,2,2]azine (150), 10 mg, was dissolved in deuterotrifluoroacetic acid (0.3 cm^3). After 8 hours the solution was poured onto anhydrous soldium carbonate (2.5 g) and the resultant dissolved in water (25 cm^3) and immediately extracted with ether (3 x 25 cm^3). The ether extract was dried and evaporated to leave 2,6-dimethyl-5-azacycl[3,2,2]azine (10 mg) deuterated at C-1 and C-4: NMR ($CDCl_3$) 2.70 (3H, Me-2), 2.93 (3H, Me-6), 7.52 (H-7), 7.70 (H-3).

Chapter V

Attempted reaction between 7-methyl-2-phenyl-6-azaindolizine and (a) sodamide and (b) sodium methoxide

(a) 7-Methyl-2-phenyl-6-azaindolizine (44), 500 mg (2.4 m mol) was added to a suspension of sodamide (0.5 g, 12.8 m mol) in dry N,N-dimethylaniline (20 cm^3)[128]. The brown mixture was heated at 110° with stirring on an oil bath and protected from the atmosphere by a blanket of nitrogen and a calcium chloride drying tube. No evolution of gas was observed and heating was continued for 5 hours. After cooling, water (10 cm^3) was added to the dark brown suspension to destroy unreacted sodamide and the resultant extracted with chloroform (2 x 100 cm^3). The chloroform extract was washed with water (3 x 20 cm^3), dried and then evaporated at reduced pressure, firstly at 15 mm to remove the chloroform and secondly at ca 100° (0.01 mm) to remove the N,N-dimethylaniline. The brown solid obtained was subjected to TLC. Only one significant band developed. The material from this band was extracted to give unchanged 7-methyl-2-phenyl-6-azaindolizine (44), 177 mg (35%). Raising the reaction temperature from 110° to 180° resulted in complete decomposition and no characterisable products or starting material were isolated. The reaction at 110° was repeated with xylene in place of N,N-dimethylaniline. In this case starting material 327 mg (65%) was isolated.

(b) 7-Methyl-2-phenyl-6-azaindolizine (44), 1 g (4.8 m mol) was added to a solution of sodium methoxide prepared from methanol (20 cm^3) and sodium (1 g, 43.5 m mol) and the resultant refluxed for 8 hours during which time it was protected from moisture by a drying tube containing silica gel. The solvent was then removed at reduced pressure and the brown residue treated with water (20 cm^3) and extracted with chloroform (5 x 20 cm^3). The chloroform extract was washed with water (3 x 20 cm^3), dried and evaporated to give unchanged starting material 0.93 g (93%).

Attempted reaction between 3-formyl-7-methyl-2-phenyl-6-azaindolizine and (a) sodamide and (b) sodium methoxide

(a) 3-Formyl-7-methyl-2-phenyl-6-azaindolizine (84), 0.5 g (2.12 m mol) was added to a suspension of sodamide (0.5 g, 21.7 m mol) in N,N-dimethylaniline (40 cm^3) and the mixture heated at 140° and worked up as in the attempted reaction between 7-methyl-2-phenyl-6-azaindolizine and sodamide and the brown residue obtained subjected to TLC with benzene/ethyl acetate (5:1). A large number of minor bands developed. The main band gave unchanged aldehyde (26 mg, 5%). Chloroform extraction of the other bands gave very small quantities of material which were not further investigated.

(b) 3-Formyl-7-methyl-2-phenyl-6-azaindolizine (84), 400 mg (1.69 m mol) was added to a solution of sodium methoxide prepared from methanol (30 cm^3) and sodium (400 mg, 17.4 m mol) and the suspension refluxed for 8 hours and worked up as in the attempted reaction between 7-methyl-2-phenyl-6-azaindolizine and sodium methoxide. The aldehyde (84), 377 mg (94%) was recovered unchanged.

Reaction between 2-chloro-4,6-dimethylpyrimidine and phenacyl bromide

A solution of 2-chloro-4,6-dimethylpyrimidine[129] (5.0 g, 35 m mol) and phenacyl bromide (8.0 g, 40 m mol) was heated on an oil bath for 3 hours at 130°. The black solid obtained was extracted with water (250 cm^3) and the aqueous extract washed with ether (3 x 100 cm^3). Sodium bicarbonate (10 g) was added to the aqueous part and the resultant heated on a boiling water bath for 30 minutes, cooled and extracted with ether (5 x 75 cm^3). After drying this ether extract was evaporated and the resulting brown residue (0.15 g) subjected to TLC with benzene/ethyl acetate (4:1). The material from the slow moving band which gave a blue-green Ehrlich's test was extracted with chloroform and the solution concentrated. The yellow needles which separated were filtered off and dried to give 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156), 52 mg (0.7%): mp 275° (dec); uv_{max} 253, (277), (305) nm, log e 4.69, 4.09, 3.72; ir 730, 832, 1200, 1410, 1640, 1693, 3100, 3210 cm^{-1};

NMR [$(CD_3)_2SO$] 2.13 (3H, Me-7), 6.23 (H-1), 6.58 (H-8), 7.20-7.78 (m, 5H, Ph), 7.83 (H-3), 10.88 (broad, NH); mass spectrum m/e 224 (M, 100), 223 (M-1, 2), 155 (M-69, 5), 154 (M-70, 11).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.1; H, 5.3; N, 12.8.

Reaction between 2-chloro-4,6-dimethylpyrimidine and bromoacetone

2-Chloro-4,6-dimethylpyrimidine (5.0 g, 35 m mol) and bromoacetone (4.8 g, 35 m mol) were heated together and the product cyclised as in the previous synthesis of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one. The crude material obtained (0.13 g) was subjected to TLC with benzene/ethyl acetate (5:1). Two main bands developed. Extraction of the faster moving band gave unchanged 2-chloro-4,6-dimethylpyrimidine (61 mg). The material from the slower moving band which gave a green Ehrlich's test was extracted and recrystallised from benzene/petroleum ether to give 2,7-dimethyl-6-azaindolizin-5(6H)-one (157), 20 mg (0.4%) as pale pink needles: mp 198-200°; uv_{max} (229), (237), 285 nm, log e 3.70, 3.47, 4.14; ir 775, 820, 1420, 1650, 1700, 3100, 3210 cm^{-1}; NMR 2.20 (6H, Me-2 and Me-7), 6.00 (H-1), 6.06 (H-8), 7.27 (H-3), 9.78 (broad, NH), irradiation at the frequency of the signal attributed to H-1 resulted in sharpening of the signal attributed to H-3; mass spectrum m/e 162 (M, 100), 161 (M-1, 11), 93 (M-69, 40), 160* (162-161).

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.9; H, 6.5; N, 17.2.

Reaction between 2-hydroxy-4,6-dimethylpyrimidine and phenacyl bromide

A solution of 2-hydroxy-4,6-dimethylpyrimidine[130] (17.5 g, 0.14 mol) and phenacyl bromide (28.1 g, 0.14 mol) in ethanol (200 cm^3) was refluxed on a water bath for $1\frac{1}{2}$ hours. The solid which separated was filtered from the hot solution, washed with a little boiling ethanol and dried under vacuum to give 2-hydroxy-4,6-dimethylpyrimidine hydrobromide (158), 9.1 g (31%) as a pale orange solid which did not melt below 300°: uv max 305 nm, log e 3.79; ir 847,

1627, 1735, 2500-3300 (broad and obscured by nujol) cm^{-1}; NMR [$(CD_3)_2SO$] 2.44 (6H, Me-4 and Me-6), 6.74 (H-5).

Anal. Calcd for $C_6H_9N_2BrO$: C, 35.14; H, 4.42; N, 13.66; Br, 38.97. Found: C, 35.4; H, 4.5; N, 13.8; Br, 39.0.

The ethanolic solution was refluxed for a further $1\frac{1}{2}$ hours and the ethanol removed at reduced pressure. The brown solid obtained was dissolved in water (400 cm^3) and extracted with ether (4 x 100 cm^3). Sodium bicarbonate (25 g) was added to the aqueous part and the solution heated for 15 minutes on a boiling water bath. The buff coloured solid (4.4 g) which separated was collected by filtration and dried. The uv and NMR spectrum of this solid indicated it to be a mixture of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156) and 4,6-dimethyl-1-phenacylpyrimidin-2(1H)-one (159) with a molar ratio of 1:4 respectively.

The residual aqueous bicarbonate phase was extracted with chloroform (5 x 200 cm^3) and the chloroform extract dried and evaporated to leave a pale yellow solid which was recrystallised from chloroform to give 4,6-dimethyl-1-phenacylpyrimidin-2(1H)-one (159) as white needles: mp 166.5°; uv_{max} 243, 305 nm, log e 4.17, 3.89; ir 760, 1225, 1608, 1655, 1690 cm^{-1}; NMR 2.11 (3H, Me), 2.35 (3H, Me), 5.51 (2H, methylene), 6.16 (H-5), 7.33-8.13 (m, 5H, Ph); mass spectrum m/e 242 (M, 40), 224 (M-18, 22), 137 (M-105, 89), 105 (PhCO, 100).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.83; N, 11.56. Found: C, 69.2; H, 5.7; N, 11.8.

Cyclisation of 4,6-dimethyl-1-phenacylpyrimidin-2(1H)-one

(a) 4,6-Dimethyl-1-phenacylpyrimidin-2(1H)-one (159), 50 mg was heated at 200° under vacuum (10 mm) for 15 minutes to give 7-methyl-2-phenyl-6-azaindolizine-5(6H)-one (156), 47 mg (100%) as a buff coloured solid.

(b) A suspension of the pyrimidone (159), 70 mg in 2M aqueous sodium hydroxide (10 cm^3) was heated on a boiling water bath for 2 hours, cooled and the grey coloured solid obtained collected by filtration and dried to give the azaindolizinone (156), 60 mg (93%).

In both these cases the ir and NMR spectra of the cyclisation products were identical to those of the sample of the azaindolizinone (156) obtained directly from the Chichibabin reaction between 2-hydroxy-4,6-dimethylpyrimidine and phenacyl bromide.

Formylation of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one

Formylation of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156), 100 mgs by the general procedure outlined on p149, gave 3-formyl-7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (160), 58 mg (52%) as pale yellow crystals from chloroform: mp 258° (dec); uv_{max} 225, 272, (293), 365 nm, log e 4.12, 4.28, 3.86, 4.19; ir 791, 838, 1360, 1638, 1690, 3110, 3250 cm^{-1}; NMR [$(CD_3)_2SO$] 2.22 (3H, Me), 6.46 (H-8), 6.49 (H-1), 7.28-7.74 (m, 5H, Ph), 10.82 (CHO), irradiation at the frequency of the methyl signal resulted in sharpening of the signal attributed to H-8; mass spectrum m/e 252 (M, 100), 251 (M-1, 71), 237 (M-15, 10), 235 (M-17, 18), 224 (M-28, 22), 250* (252-251).

Anal. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79. Found: C, 71.3; H, 4.9.

Reaction between 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one and phosphoryl chloride

A solution of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156), 300 mg in phosphoryl chloride (45 cm^3) was refluxed for 4 hours and the bulk of the phosphoryl chloride removed at ca 60° (10 mm). The dark coloured residue was poured onto crushed ice (30 g), basified by the addition of 2M sodium hydroxide and immediately extracted with chloroform (4 x 50 cm^3). The brown chloroform extract was dried and evaporated and the gum obtained subjected to TLC with benzene. Two main bands developed. The material from the fast moving orange coloured band was extracted with chloroform and the extract concentrated to approximately 5 cm^3 and cooled in ice. 4,9-Dimethyl-1,6-diphenyl-di(6-azaindolizino)[3,45-af:3',4',5'-dc]pyrazine (161), 8 mg (3.1%) separated as dark red prisms; mp 262.5-265° (dec); uv_{max} (CH_2Cl_2) 268, (288), (410), (438), 460, 486 nm, log e 4.80, 4.55, 3.47, 3.87, 4.09, 4.17; ir 698, 760, 839, 1387, 1541, 1615 cm^{-1}; NMR 1.93 (6H, Me-4 and

Me-9), 5.96 (2H, H-2 and H-7), 6.08 (2H, H-3 and H-8), 7.20-7.88 (m, 10H, Ph-1 and Ph-6); mass spectrum m/e 412 (M, 100), 411 (M-1, 5), 206 (M-206, 3), 410* (412-411).

Anal. Calcd for $C_{28}H_{20}N_4$: C, 81.53; H, 4.89; N, 13, 13.58. Found: C, 81.7; H, 4.7; N, 13.8.

The material from the slower moving band which gave a green Ehrlich's test was extracted and recrystallised from petroleum ether to give 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155), 243 mg (75%) as white flakes: mp 144.5-145°; uv_{max} 254, (256), (283), (300), 358 (broad) nm, log e 4.71, 4.71, 3.95, 3.57, 3.45; ir 728, 768, 1245, 1407, 1620 cm^{-1}; NMR 2.39 (3H, Me-7), 6.70 (H-1), 7.00 (H-8), 7.10-7.75 (m, 5H, Ph), 7.70 (H-3), irradiation at the frequency of the methyl signal resulted in sharpening of the signal attributed to H-8 and irradiation at the frequency of the signal attributed to H-1 resulted in sharpening of the signal attributed to H-3; mass spectrum (^{35}Cl), m/e 242 (M, 100), 241 (M-1, 4), 207 (M-35, 2), 180 (M-62, 10), 240* (242-241), 244 (M for ^{37}Cl, 20).

Anal. Calcd for $C_{14}H_{11}N_2Cl$: C, 69.28; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.3; H, 4.3; N, 11.5; Cl, 14.9.

Reaction between 5-chloro-7-methyl-2-phenyl-6-azaindolizine and phosphoryl chloride

A solution of 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155), 5 mg in phosphoryl chloride (10 cm^3) was refluxed for 4 hours and the product worked up using a procedure similar to that given in the previous reaction between 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one and phosphoryl chloride. TLC gave the di(6-azaindolizino)pyrazine (161), 3 mg (70%) with identical mp and ir absorptions to the sample obtained from 7-methyl-2-phenyl-6-azaindolizine and phosphoryl chloride. No other products were isolated although TLC indicated traces of the starting chloro-6-azaindolizine to be present in the crude product.

Formylation of 4,9-dimethyl-1,6-diphenyl-di(6azaindolizino)[3,4,5-af:3',4',5'-dc] pyrazine

A solution of the di(6-azaindolizino)pyrazine (161), 20 mgs (0.05 m mol) in dimethylformamide (1.5 cm^3) was added to a solution of phosphoryl chloride (100 mg, 0.65 m mol) in dimethylformamide (1.5 cm^3) and the resultant heated for 4 hours at 70-90° on an oil bath. The red solution obtained was poured into 2M aqueous sodium hydroxide (50 cm^3) and extracted with chloroform (6 x 100 cm^3). The chloroform extract was washed with water (4 x 50 cm^3), dried and evaporated. The brown residue was subjected to TLC with benzene/ethyl acetate (10:1). The material from the slow moving orange-yellow band was extracted to give 2,7-diformyl-4,9-dimethyl-1,6-diphenyl-di(6-azaindolizino)[3,4,5-af:3',4',5'-dc]pyrazine (164), 22 mgs (97%) as a maroon coloured solid which did not melt below 350°: uv_{max} (CH_2Cl_2) 274, 370, (452), 467 nm, log e 4.72, 4.12, 4.19, 4.28; ir 702, 830, 1200, 1500, 1545, 1608, 1645 cm^{-1}; NMR (CF_3COOH) 2.28 (6H, Me-4 and Me-9), 7.58 (2H, H-3 and H-8), 7.72 (10H, Ph-1 and Ph-6), 9.72 (2H, broad, $w_{\frac{1}{2}}$ = 10 Hz, CHO-2 and CHO-7); mass spectrum, calcd mass for $C_{30}H_{20}N_4O_2$: 468.1586, found m/e 4.68,1585 (M, 100), 440 (M-28, 9), 412 (M-56, 32), 234 (M^{2+} or M-234, 2).

Attempted formylation of (161), 20 mg by the general procedure given on p149 gave a quantitative yield of unchanged starting material.

Reaction between 5-chloro-7-methyl-2-phenyl-6-azaindolizine and (a)hydroxide ion (b) methoxide ion and (c) ammonia

(a) A suspension of 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155), 20 mg in aqueous sodium bicarbonate (20 cm^3 water and 1 g $NaHCO_3$) was heated on a boiling water bath for 30 minutes, cooled and extracted with chloroform (4 x 30 cm^3). The chloroform extract was dried and evaporated and the residue subjected to TLC with benzene and then with benzene/ethyl acetate (4:1). The fast moving band gave unchanged 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155), 12 mg (60%). TLC indicated the crude hydrolysis product to contain only traces of 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156).

A suspension of the chloro-6-azaindolizine (155), 35 mg in 2M aqueous sodium hydroxide was heated on a boiling water bath for 6 hours and the hydrolysis product worked up as in the attempted hydrolysis using sodium bicarbonate. The fast moving band gave unchanged 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155), 15 mg (43%). The slower moving band gave 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (156), 3 mg (9%) with identical NMR and ir spectra to the sample obtained from 2-hydroxy-4,6-dimethylpyrimidine and phenacyl bromide.

(b) A suspension of 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155), 40 mg (0.16 m mol) in a methanolic solution of sodium methoxide obtained from methanol (20 cm^3) and sodium (0.3g) was refluxed for 30 minutes. The methanol was evaporated and the residue dissolved in water (20 cm^3) and extracted with chloroform (3 x 20 cm^3). The chloroform extract was washed with water (2 x 20 cm^3), dried and evaporated. The residue obtained was subjected to TLC with benzene. Only one band developed. The material from this band was extracted and recrystallised from petroleum ether to give 5-methoxy-7-methyl-2-phenyl-6-azaindolizine (165), 32 mg (81%) as pale green needles: mp 87°; uv_{max} 253, (276), (289), 322 nm, log e 4.67, 4.02, 3.78, 3.46; ir 700, 758, 1570, 1630 cm^{-1}; NMR - see Table IX, p 92.

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.8; H, 5.8; N, 11.8.

(c) 5-Chloro-7-methyl-2-phenyl-6-azaindolizine (155), 100 mg was heated at 140° for 4 hours in a sealed glass tube containing ethanol (10 cm^3) saturated with anhydrous ammonia at 0°. After cooling the tube was opened and the solvent evaporated. The residue was subjected to TLC with benzene/ethyl acetate (2:1). Only one main band developed. The material from this band was extracted and recrystallised from benzene containing a small percentage of ethanol to give 5-amino-7-methyl-2-phenyl-6-azaindolizine (166), 65 mg (71%) as small white crystals which decomposed at temperatures greater than 215°: uv_{max} 257, 301, 331 (broad) nm, log e 4.61, 3.82, 3.49; ir 699, 765, 1540, 1610, 1655, 3050, 3340,

3450 cm^{-1}; NMR [$(CD_3)_2SO$] 2.17 (3H, Me), 6.50 (2H, H-1 and H-8), 7.14 (2H, broad, NH_2), 7.20-7.78 (m, 5H, Ph), 7.89 (H-3); NMR ($CDCl_3$) 2.32 (3H, Me), 6.52 (H-1), 6.65 (H-8), 7.12-7.74 (m, 5H, Ph), 7.22 (H-3), irradiation at the frequency of the methyl group resulted in sharpening of the signal attributed to H-8, irradiation at the frequency of the signal attributed to H-1 resulted in sharpening of the signal attributed to H-3; mass spectrum m/e 223 (M, 100), 222 (M-1, 9), 181 (M-42, 5), 180 (M-43, 6), 221* (223-222).

Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.3; H, 5.9; N, 18.6.

Formylation of 5-amino-7-methyl-2-phenyl-6-azaindolizine

Formylation of 5-amino-7-methyl-2-phenyl-6-azaindolizine (166), 50 mg was carried out using the general procedure given on p149. TLC with petroleum ether/ethyl acetate (1:1) gave two bands. Extraction of the material from the faster moving band gave unchanged 5-amino-7-methyl-2-phenyl-6-azaindolizine (6 mg, 12%). The material from the following yellow band was extracted and recrystallised from benzene/petroleum ether to give 6-methyl-2-phenyl-4,5-diazacycl[3,2,2]azine (167), 16 mg (31%) as khaki coloured needles: mp 155-157°; uv_{max} (see Figure VII, p112) (238), 247, 332, 404, 416 nm, log e 4.34, 4.43, 4.30, 3.72, 3.69; ir 700, 778, 1133, 1540, 1595 cm^{-1}; NMR 3.00 (3H, Me), 7.33-8.11 (m, 5H, Ph), 7.40 (H-1), 7.65 (H-7), 8.83 (H-3); mass spectrum, calcd mass for $C_{15}H_{11}N_3$: 233.0952, found m/e 233.0952 (M, 100), 232 (M-1, 16), 205 (M-28, 5), 231* (233-232).

Attempted formylation of 6-methyl-2-phenyl-4,5-diazacycl[3,2,2]azine

A solution of phosphoryl chloride (30 mg, 0.20 m mol) in dimethylformamide (0.5 cm^3) was added to a solution of the diazacyclazine (5 mg, 0.02 m mol) in dimethylformamide (0.5 cm^3) and the resulting solution heated for 1 hour at 80° protected from the atmosphere by a blanket of nitrogen. The red solution obtained was cooled and poured into 2M aqueous sodium hydroxide (25 cm^3)

and extracted with chloroform (4 x 25 cm^3). The chloroform extract was evaporated to dryness and the residue subjected to TLC with petroleum ether/ethyl acetate (3:4). Only one significant band developed. Extraction of this band gave unchanged diazacyclazine (167), 3 mg (60%).

Attempted formylation of the diazacyclazine (167), 5 mg by the general procedure outlined on p 149 gave a quantitative recovery of the starting material.

Attempted ring opening[134] of 6-methyl-2-phenyl-4,5-diazacycl[3,2,2]azine

6-Methyl-2-phenyl-4,5-diazacycl[3,2,2]azine (167), 5 mg was dissolved in methanol (2 cm^3) containing concentrated hydrochloric acid (0.2 cm^3) and left at room temperature for 24 hours. The solution was concentrated at reduced pressure, basified by the addition of 2M aqueous sodium hydroxide and extracted with ether (3 x 10 cm^3). The ether extract was dried and evaporated to give unchanged starting material in quantitative yield. TLC with petroleum ether/ethyl acetate (1:1) indicated the recovered material to be homogenous.

Formylation of 5-chloro-7-methyl-2-phenyl-6-azaindolizine

Formylation of 5-chloro-7-methyl-2-phenyl-6-azaindolizine (155), 58 mg by the general procedure outlined on p 149 gave four products. Chloroform extraction of the material from the fastest moving band gave 5-chloro-1-formyl-7-methyl-2-phenyl-6-azaindolizine (173), 2 mg (3.1%): mp 169.5-170.5°; uv_{max} (243), 249, (276), 339 nm, log e 4.27, 4.29, 3.71, 3.92; ir 700, 728, 1220, 1420, 1609, 1650 cm^{-1}; NMR 2.55 (3H, Me), 7.47 (H-3), 7.50 (5H, Ph), 8.10 (H-8), 10.04 (CHO), irradiation at the frequency of the methyl signal resulted in sharpening of the signal attributed to H-8; mass spectrum, calcd mass for $C_{15}H_{11}{}^{35}Cl\,N_2O$: 270.0559, found m/e 270.0555 (M, 79), 269 (M-1, 100), 253 (M-17, 2), 241 (M-29, 2), 268* (270-269), 272 (M for ^{37}Cl, 19).

Chloroform extraction of the material from the next band followed by recrystallisation from benzene/petroleum ether gave 5-(N,N-dimethylamino)-1-

formyl-7-methyl-2-phenyl-6-azaindolizine (172), 4 mg (6.0%) as white needles: mp 208.5°; uv_{max} 240, 367 nm, log e 4.54, 4.24; ir 757, 850, 1410, 1510, 1648 cm^{-1}; NMR 2.47 (3H, Me-7), 3.07 (6H, $N(Me)_2$), 7.22 (H-3), 7.32-7.64 (m, 5H, Ph), 7.78 (H-8), 9.98 (CHO), irradiation at the frequency of the methyl signal at δ 2.47 resulted in sharpening of the signal attributed to H-8; mass spectrum, calcd mass for $C_{17}H_{17}N_3O$: 279.1371, found m/e 279.1369 (M, 100), 278 (M-1, 8), 264 (M-15, 4), 250 (M-29, 10), 236 (M-43, 16), 277* (279-278), 224.5* (278-250).

The material from the next yellow band was extracted and recrystallised from benzene/petroleum ether to give 5-(N,N-dimethylamino)-3-formyl-7-methyl-2-phenyl-6-azaindolizine (170), 17 mg (25%) as glassy, yellow crystals: mp 178°; uv_{max} 246, 272, 330 (broad), 407 nm, log e 4.48, 4.16, 3.70, 4.05; ir 702, 795, 1170, 1352, 1530, 1610, 1645 cm^{-1}; NMR 2.38 (Me-7), 3.05 (6H, $N(Me)_2$), 6.37 (H-1), 6.68 (H-8), 7.30-7.72 (m, 5H, Ph), 9.80 (CHO), irradiation at the frequency of the methyl signal at δ 2.38 resulted in sharpening of the signal attributed to H-8; mass spectrum, calcd mass for $C_{17}H_{17}N_3O$: 279.1371, found m/e 279.1369 (M, 35), 262 (M-17, 100), 261 (M-18, 5), 250 (M-29, 4), 246* (279-262).

The material from the slowest moving band was extracted to give 3-formyl-7-methyl-2-phenyl-6-azaindolizin-5(6H)-one (160), 17 mg (28%).

Reaction between 4-chloro-2-methylpyrimidine and bromoacetone

A solution of 4-chloro-2-methylpyrimidine[103] (1.28 g, 10 m mol) and bromoacetone (1.37 g, 10 m mol) in ethanol (5 cm^3) was refluxed for 18 hours and the solvent evaporated. The brown solid obtained was dissolved in water (100 cm^3) and washed with ether (3 x 100 cm^3). Sodium bicarbonate (5 g) was added to the aqueous part and the solution heated on a boiling water bath for 5 minutes, cooled and extracted with ether (3 x 100 cm^3). After drying this ether extract was evaporated and the residue subjected to TLC. Two main bands developed. The material from the fast moving band which gave a violet Ehrlich's test was extracted and distilled at 100° (0.01 mm) to give 7-ethoxy-2-methyl-8-azaindolizine (175), 6 mg (0.3%) as yellow crystals: mp 69-72°; uv_{max} 243, 250, 275, 285, 298, 350 (broad) nm, log e 4.51, 4.50, 3.39,

3.42, 3.29, 3.02; ir 750, 780, 1038, 1235, 1313, 1535, 1630 cm^{-1}; NMR 1.37 (t, J = 7.0 Hz, 3H, ethoxy methyl), 2.26 (3H, Me-2), 4.37 (q, J = 7.0 Hz, 2H, ethoxy methylene), 6.00 (d, J = 7.5 Hz, H-6), 6.04 (H-1), 6.74 (H-3), 7.84 (d, J = 7.5 Hz, H-5); mass spectrum, calcd mass for $C_{10}H_{12}N_2O$: 176.0949, found m/e 176.0945 (M, 45), 148 (M-28, 100), 147 (M-29, 25), 120 (M-56, 16), 119 (M-57, 18), 146* (148-147), 124.5* (176-148).

The material from the other band was extracted and distilled at 100° (10 mm) to give 4-ethoxy-2-methylpyrimidine (174), 117 mg (8.5%) as a colourless liquid; ir (thin film) 827, 1040, 1315, 1450, 1572 cm^{-1}; NMR 1.37 (t, J = 7.0 Hz, 3H, ethoxy methyl), 2.58 (3H, Me-2), 4.38 (q, J = 7.0 Hz, 2H, ethoxy methylene), 6.46 (d, J = 6.0 Hz, H-5), 8.26 (d, J = 6.0 Hz, H-6). The pyrimidine (174) gave a picrate which was recrystallised from ethanol: mp 148-149°.

Anal. Calcd for $C_{13}H_{13}N_5O_8$: C, 42.52; H, 3.54; N, 19.08. Found: C, 42.4; H, 3.4; N, 19.4.

The reaction between 4-chloro-2-methylpyrimidine and bromoacetone was repeated with benzene as solvent instead of ethanol, and without solvent at 40°. In both instances no products were isolated.

Demethylation of 7-methoxy-2-phenyl-8-azaindolizine

A solution of 7-methoxy-2-phenyl-8-azaindolizine (68), 100 mg in concentrated hydrochloric acid (20 cm^3) was heated on a boiling water bath for 30 minutes and then evaporated to dryness at reduced pressure. The solid obtained was dissolved in water (20 cm^3), the solution made basic by the addition of sodium bicarbonate and extracted with chloroform (6 x 50 cm^3). The chloroform extract was dried and evaporated and the residue sublimed at 200° (0.01 mm) to give 2-phenyl-8-azaindolizin-7(8H)-one (176), 80 mg (85%) as a pale yellow solid which decomposed at 270°:

uv_{max} 243, (249), 290, 299, (329) nm, log e 4.50, 4.47, 4.12, 4.13, 3.54; ir 828, 860, 711, 968, 1219, 1440, 1680, 2800, 3140 cm^{-1}; NMR [$(CD_3)SO$] 5.78 (d, J = 8.0 Hz, H-6), 5.89 (d, J = 1.5 Hz, H-1), 7.06-7.70 (m, 5H, Ph), 7.36 (H-3), 8.17 (d, J = 8.0 Hz, H-5), 11.52 (broad, NH, disappears on addition of D_2O); mass spectrum m/e 210 (M, 100), 182 (M-28, 3), 181 (M-29, 7), 155 (M-55, 4), 180* (182-181).

Anal. Calcd for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.32. Found: C, 74.0; H, 5.0; N, 13.3.

Reaction between 4-hydroxy-2-methylpyrimidine and phenacyl bromide

4-Hydroxy-2-methylpyrimidine[103] (5.5 g, 50 m mol) and phenacyl bromide (10 g, 50 m mol) were heated together at 60° for 8 hours in dimethylformamide (10 cm^3). The dark red, partially solid product was dissolved in water (150 cm^3) and washed with chloroform (3 x 100 cm^3). Sodium bicarbonate (5 g) was added to the aqueous part and the white needles which separated collected by filtration, washed with a little water and dried at 50° (0.01 mm) to give hydrated 2-methyl-1-phenacyl-pyrimidin-4(1H)-one (178), 3.2 g (27%): uv_{max} 248, log e 4.47; ir 750, 1210, 1520, 1590, 1639, 1690, 3430 (broad) cm^{-1}; NMR [$(CD_3)_2SO$] 2.22 (3H, Me), 5.72 (2H, methylene), 5.97 (d, J = 7.5 Hz, H-5), 7.40-8.20 (m, 5H, Ph), 7.59 (d, J = 7.5 Hz, H-6).

Anal. Calcd for $C_{13}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$: C, 65.81; H, 5.62. Found: C, 65.7; H, 5.6.

Heating the hydrated pyrimidinone (178) at 110° (0.01 mm) for 30 minutes gave the anhydrous pyrimidinone: mp 172-182° followed by the formation of new crystals at 184° which decomposed at 270°; uv_{max} 248 nm, log e 4.48; ir 759, 1228, 1528, 1627, 1643, 1692 cm^{-1}; NMR ($CDCl_3$) 2.25 (3H, Me), 5.50 (2H, methylene) 6.05 (d, J = 7.5 Hz, H-5), 7.32 (d, J = 7.5 Hz, H-6), 7.40-8.17 (m, 5H, Ph), the NMR spectrum in $(CD_3)_2SO$ was identical to that of the above hydrated derivative; mass spectrum 228 (M, 1), 210 (M-18, 100), 182 (M-46, 5), 181 (M-47, 11), 155 (M-73, 6).

Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.1; H, 5.4; N, 12.3.

Cyclisation of 2-methyl-1-phenacylpyrimidin-4(1H)-one

2-Methyl-1-phenacylpyrimidin-4(1H)-one (178), 100 mg was heated at 180° under vacuum (15 mm) for 30 minutes and the product sublimed at 200° (0.01 mm) to give 2-phenyl-8-azaindolizin-7(8H)-one (176), 92 mg (100%) with identical spectral characteristics to the sample obtained by demethylation of 7-methoxy-2-phenyl-8-azaindolizine.

7-Chloro-2-phenyl-8-azaindolizine (177)

A solution of 2-phenyl-8-azaindolizin-7(8H)-one (176), 100 mg in phosphoryl chloride (10 cm^3) was gently refluxed for 4 hours and the product worked up as in the reaction between 7-methyl-2-phenyl-6-azaindolizin-5(6H)-one and phosphoryl chloride (see p163). TLC with benzene/ethyl acetate (20:1) gave a fast moving yellow band. The material from this band was extracted and recrystallised from benzene to give 7-chloro-2-phenyl-8-azaindolizine (177), 82 mg (75%): mp 212° (dec); uv_{max} 254, 325, 370 (broad) nm, log e 4.60, 3.88, 3.47; ir 737, 770, 1090, 1132, 1510, 1609 cm^{-1}; NMR 6.50 (d, J = 7.0 Hz, H-6), 6.84 (H-1), 7.26 (H-3), 7.30-7.76 (m, 5H, Ph), 8.07 (d, J = 7.0 Hz, H-5); mass spectrum (^{35}Cl), m/e 228 (M, 100), 193 (M-35, 2), 192 (m-36, 3), 166 (M-62, 3), 191* (193-192), 163* (228-193), 230 (M for ^{37}Cl, 19).

Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.28; H, 3.97; N, 12.25; Cl, 15.50. Found: C, 68.5; H, 4.1; N, 12.0; Cl, 15.4.

Reaction between 7-chloro-2-phenyl-8-azaindolizine and methoxide ion

7-Chloro-2-phenyl-8-azaindolizine (177), 14 mg (0.06 m mol) in hot methanol (2 cm^3) was added to a solution of sodium methoxide obtained from methanol (4 cm^3) and sodium (50 mg, 2.2 m mol) and the resulting yellow solution refluxed for 2 hours. The solvent was evaporated and the residue treated with water (25 cm^3) and extracted with chloroform (3 x 25 cm^3). The chloroform extract

was washed with water (25 cm^3), dried and evaporated to leave 7-methoxy-2-phenyl-8-azaindolizine (68), 14 mg (100%) as a yellow solid (mp 139-143°) with identical spectral characteristics (ir, NMR) to the sample obtained from the reaction between 4-methoxy-2-methylpyrimidine and phenacyl bromide.

Attempted reaction between 7-chloro-2-phenyl-8-azaindolizine and (a) hydroxide ion and (b) amide ion and (c) ammonia

(a) A suspension of 7-chloro-2-phenyl-8-azaindolizine (177), 10 mg in 2M aqueous sodium hydroxide (5 cm^3) was heated on a boiling water bath for 6 hours, cooled and extracted with chloroform (4 x 10 cm^3). The chloroform extract was dried and evaporated to give unchanged starting material (177) in quantitative yield.

The same procedure was repeated with the suspension contained in a sealed tube at a reaction temperature of 130°. A sample of the crude orange coloured product was subjected to TLC with benzene/ethanol (10:1). No band corresponding (R_f) to 2-phenyl-8-azaindolizin-7(8H)-one (176) developed. The remainder of the crude product was subjected to TLC with benzene. Chloroform extraction of the fast moving yellow band gave unchanged starting material (177), 6.3 mg (63%).

(b) 7-Chloro-2-phenyl-8-azaindolizine (177), 20 mg (0.08 m mol) was added to a stirred suspension of sodamide (100 mg, 2.6 m mol) in liquid ammonia (10 cm^3) at -33° and the mixture protected from atmospheric moisture by a soda-lime drying tube. The suspension gradually darkened and after 30 minutes the ammonia was allowed to evaporate and the residue treated with water and extracted with chloroform (6 x 25 cm^3). The chloroform extract was evaporated and the brown amorphous solid obtained subjected to TLC with benzene/ethyl acetate (10:1). The bulk of the material remained at the origin. The material from the four minor bands which developed was extracted but yielded insignificant quantities which were not further investigated. TLC also indicated all the starting chloro-8-azaindolizine (177) to have been completely consumed.

(c) 7-Chloro-2-phenyl-8-azaindolizine (177), 30 mg was heated at 140° for 4 hours in a sealed glass tube containing ethanol (10 cm^3) which had been saturated with anhydrous ammonia at 0°. After cooling the tube was opened and the solvent evaporated to give unchanged 7-chloro-2-phenyl-8-azaindolizine (TLC, ir) in quantitative yield.

The procedure was then repeated at a temperature of 200°. In this case the reaction solution became quite dark. TLC with benzene/ethyl acetate (10:1) gave unchanged starting material (177), 19 mg (64%). No other significant bands developed.

REFERENCES*

(1) E.T. Borrows and D.O. Holland, Chem. Rev., 42, 611 (1948).

(2) W.L. Mosby, 'Heterocyclic Systems with Bridgehead Nitrogen Atoms', Part 1, Interscience Publishers Inc., New York, 1961.

(3) N.S. Prostakov and O.B. Baktibaev, Russ. Chem. Rev., 44, 748, (1975).

(4) A.E.Tschitschibabin, Chem. Ber., 60, 1607 (1927).

(5) E.T. Borrows, D.O. Holland and J. Kenyon, J. Chem. Soc., 1069 (1946).

(6) E.T. Borrows and D.O. Holland, J. Chem. Soc., 672 (1947).

(7) G.F. Duffin, 'Advances in Heterocyclic Chemistry', Vol 3, Ed A.R. Katritzky, Academic Press, New York and London, 1964, p 1.

(8) E.T. Borrows, D.O. Holland and J. Kenyon, J. Chem. Soc., 1083 (1946).

(9) N.P. Buu-Hoi, P. Jacquignon, N.D. Xuong and D. Lavit, J. Org. Chem., 19, 1370 (1954).

(10) F. Krohnke and W. Weiss, Justus Liebigs Ann. Chem., 679, 136 (1964).

(11) F.W. Krock and F. Krohnke, Chem. Ber., 102, 659 and 669 (1969).

(12) I. Dainis, Aust. J. Chem., 25, 1003 (1972).

(13) V. Boekelheide and R.J. Windgassen (Jr), J. Am. Chem. Soc., 81, 1456 (1959).

(14) A. Galbraith, T. Small, R.A. Barnes and V. Boekelheide, J. Am. Chem. Soc., 83, 453 (1961).

(15) W.J. Wong, M.S. Brown and H. Rapoport, J. Org. Chem., 30, 2398 (1965).

(16) J. Hurst, T. Melton and D.G. Wibberley, J. Chem. Soc., 2948 (1965).

(17) F.W. Krock and F. Krohnke, Chem. Ber., 104, 1629 (1971).

(18) P.A. Barrett, J. Chem. Soc., 325 (1958).

(19) P.A. Barrett and K.A. Chambers, J. Chem. Soc., 338 (1958).

(20) M. Scholtz, Chem. Ber., 45, 734 (1912).

(21) R.M. Acheson, 'Advances in Heterocyclic Chemistry', Vol 1, Ed A.R. Katritzky, Academic Press, New York and London 1963, p 125.

(22) R.M. Acheson, S.T. Hodgson and R. Wright, J. Chem. Soc., Perkin Trans. 1, 1911 (1976).

(23) J.W. Lown and K. Matsumoto, Can. J. Chem., 49, 1165 (1971).

(24) V. Boekelheide and K. Fahrenholtz, J. Am. Chem Soc., 83, 458 (1961).

* Journal abbreviations are those used in "The Journal of Organic Chemistry" and "Chemical Abstracts".

(25) W.J. Linn, O.W. Webster and R.E. Benson, J. Am. Chem. Soc., 87, 3651 (1965).

(26) T. Sasaki, K. Kanematsu, Y. Yukimoto and S. Ochiai, J. Org. Chem., 36, 813, (1971).

(27) R.M. Acheson, M.G. Bite and M.W. Cooper, J. Chem. Soc., Perkin Trans. 1, 1901, (1976).

(28) J.E. Saxton, J. Chem. Soc., 3239 (1951).

(29) V. Amarnath and R. Madhav, Synthesis, 837 (1974).

(30) A.E. Tschitschibabin, Chem. Ber., 58, 1704 (1925).

(31) F. Krohnke, B. Kickhofen and C. Thoma, Chem. Ber., 88, 1117 (1955).

(32) I.A. Kaye, C.L. Parris and W.J. Burlant, J. Am. Chem. Soc., 75, 746 (1953).

(33) R.L. Letsinger and R. Lasco, J. Org. Chem., 21, 764 (1956).

(34) M. Fraser, J. Org. Chem., 36, 3087 (1971).

(35) V. Boekelheide and S.S. Kertelj, J. Org. Chem., 28, 3212 (1963).

(36) J. Taylor and D.G. Wibberley, J. Chem. Soc. C, 2693 (1968).

(37) E. Ochiai and M. Yanai, J. Pharm. Soc. Jpn., 59, 18 and 97 (1939); see Brit. Chem. Abstr., A II, 451 (1939) and Chem. Abstr., 33, 3791 (1939).

(38) K.T. Potts, U.P. Singh and T. Bhattacharyya, J. Org. Chem., 33, 3766 (1968).

(39) T. Melton, J. Taylor and D.G. Wibberley, J. Chem. Soc., Chem. Commun., 151 (1965).

(40) J.D. Bower and G.R. Ramage, J. Chem. Soc., 2834 (1955).

(41) J.D. Bower and G.R. Ramage, J. Chem. Soc., 4506 (1957).

(42) R.L. Letsinger and R. Lasco, J. Org. Chem, 21, 764 (1956).

(43) R.M. Acheson and M.W. Foxton, J. Chem. Soc. C, 2218 (1966).

(44) R. Huisgen, R. Grashey and R. Krischke, Tetrahedron Lett., 387 (1962).

(45) V. Boekelheide and N.A. Fedoruk, J. Org. Chem., 33, 2062 (1968).

(46) Y. Kobayashi, T. Kutsuma and K. Morinaga, Chem. Pharm. Bull., 19, 2106 (1971).

(47) W. Flitsch and U. Kramer, Tetrahedron Lett., 1479 (1968).

(48) W. Flitsch and U. Kramer, Justus Liebigs Ann. Chem., 735, 35 (1970).

(49) M. Zupan, B. Stanovnik and M. Tisler, J. Heterocycl. Chem., 8, 1 (1971).

(50) V.I. Shvedov, I.A. Kharizomenova, L.B. Altukhova and A.N. Grinev, Khim. Geterotsikl. Soedin., 428 (1970); see Chem. Abstr., 73, 25403d (1970).

(51) A. Etienne, A. Le Berre and C. Renault, Compt. Rende., Ser. C, 262, 365 (1966).

(52) A. Le Berre and C. Renault, Compt. Rende., Ser. C, 265, 249 (1967).

(53) A. Le Berre and C. Renault, Bull. Soc. Chim. Fr., 3133 (1969).

(54) A. Le Berre and C. Renault, Bull. Soc. Chim. Fr., 3146 (1969).

(55) J.W. Sowell (Sr) and C. DeWitt Blanton (Jr), J. Heterocycl. Chem., 10, 287 (1973).

(56) W. Herz, J. Am. Chem. Soc., 71, 3982 (1949).

(57) M. Suzuki and N. Yoneda, J. Org. Chem., 41, 1482 (1976).

(58) V.I. Shvedov, L.B. Altukhova and A.N. Grinev, Khim. Geterotsikl. Soedin., 1048 (1970); see Chem. Abstr., 74, 125628v (1971).

(59) W. Herz and S. Tocker, J. Am. Chem. Soc., 77, 6355 (1955).

(60) H.C. Longuet-Higgins and C.A. Coulson, Trans. Faraday Soc., 43, 87 (1947).

(61) W.W. Paudler and H.L. Blewitt, Tetrahedron, 21,353 (1965).

(62) V. Galasso, G. De Alti and A. Bigotto, Theor. Chim. Acta, 9, 222 (1968).

(63) E. Kleinpeter, R. Borsdorf, G. Fischer and H.J. Hofmann, J. Prakt. Chem., 314, 515 (1972).

(64) F. Fukui, T. Yonezawa, C. Nagata and H. Shingu, J. Chem. Phys., 22, 1433 (1954).

(65) W.W. Paudler and H.L. Blewitt, J. Org. Chem., 30, 4081 (1965).

(66) W.W. Paudler and D.E. Dunham, J. Heterocycl. Chem., 2, 410 (1965).

(67) M. Zupan, B. Stanovnik and M. Tisler, J. Heterocycl. Chem., 8, 1 (1971).

(68) W.L.F. Armarego, J. Chem. Soc., 2778 (1965).

(69) E.D. Rossiter and J.E. Saxton, J. Chem. Soc., 3654 (1953).

(70) M. Fraser, A. Melera, B.B. Molloy and D.H. Reid, J. Chem. Soc., 3288 (1962).

(71) M. Fraser, S. McKenzie and D.H. Reid, J. Chem. Soc. B, 44 (1966).

(72) W.L.F. Armarego, J. Chem. Soc., 4226 (1964).

(73) W.L.F. Armarego, J. Chem. Soc. B, 191 (1966).

(74) M. Fraser, J. Org. Chem., 37, 3027 (1972).

(75) I.I. Grandberg, S.B. Nikitina, V.A. Moskalenko, and V.I. Minkin, Khim. Geterotsikl. Soedin., 1076 (1967); see Chem. Abstr., 69, 52067w (1968).

(76) L. Pentimalli and S. Bozzini, Boll. Sci. Fac. Chim. Ind. Bologna, 23, 181 (1965); see Chem. Abstr. 63, 14848e (1965).

(77) L. Almirante, A. Mugnaini, L.P. Fritz and E. Provinciali, Boll. Chim. Farm., 105, 32 (1966); see Chem. Abstr., 65, 699h (1966).

(78) O. Fuentes and W.W. Paudler, J. Heterocycl. Chem., 12, 379 (1975).

(79) W.W. Paudler and J.E. Kuder, J. Org. Chem., 32, 2430 (1967).

(80) J.P. Paolini and R.K. Robins, J. Org. Chem., 30, 4085 (1965).

(81) B.M. Lynch and B.P. Lem, J. Heterocycl. Chem., 11, 223 (1974).

(82) E.E. Glover, K.D. Vaughan and D.C. Bishop, J. Chem. Soc., Perkin Trans. 1, 2595 (1973).

(83) J.G. Lombardino, J. Org. Chem., 30, 2403 (1965).

(84) V. Boekelheide and A. Miller, J. Org. Chem., 26, 431 (1961).

(85) R.J. Windgassen (Jr), W.H. Saunders (Jr) and V. Boekelheide, J. Am. Chem. Soc., 81, 1459 (1959).

(86) J.P. Paolini and R.K. Robins, J. Heterocycl. Chem., 2, 53 (1965).

(87) W.W. Paudler, D.J. Pokorny and J.J. Good, J. Heterocycl. Chem., 8, 37 (1971).

(88) O.G. Lowe and L.C. King, J. Org. Chem., 24, 1200 (1959).

(89) H. Kondo and Y. Mitugi, J. Pharm. Soc. Jpn., 57, 397 (1937); see Chem. Abstr., 33, 2139 (1939).

(90) W.J. Irwin and D.G. Wibberley, J. Chem. Soc. C, 3237 (1971).

(91) M. Scholtz, Chem. Ber., 45, 1718 (1912).

(92) O. Diels and K. Alder, Justus Liebigs Ann. Chem., 498, 16 (1932).

(93) E.T. Borrows and D.O. Holland, J. Chem. Soc., 672 (1947).

(94) O. Diels, K. Alder, W. Friedrichsen, H. Klare, H. Winkler and H. Schrum, Justus Liebigs Ann. Chem., 505, 103 (1933).

(95) T.J. Batterham, "NMR Spectra of Simple Heterocycles", John Wiley and Sons, New York, 1973, Chapter 10, p 514.

(96) J.C. Roberts, J. Chem. Soc., 3065 (1952).

(97) A. Hantzsch, Chem. Ber., 23, 1474 (1890).

(98) V. Sprio and E. Ajello, Ann. Chim. (Rome), 56, 858 (1966); see Chem. Abstr., 66, 18636j (1966).

(99) J.M. Tedder and B. Webster, J. Chem. Soc., 1638 (1962).

(100) R.W. Guy and R.A. Jones, Aust. J. Chem., 19, 107 (1966).

(101) J. Streith and C. Sigwalt, Bull. Soc. Chim. Fr., 1157 (1970).

(102) R.H. Wiley and S.C. Slaymaker, J. Am. Chem. Soc., 79, 2233 (1957).

(103) H.J. Den Hertog, H.C. Van Der Plas, M.J. Pieterse and J.W. Streef, Recl. Trav. Chim. Pays-Bas, 84, 1569 (1965).

(104) L.J. Bellamy, "The Infra-red Spectra of Complex Molecules", Vol. 1, 3rd ed, Chapman and Hall, London, 1975, p 290.

(105) O. Fuentes and W.W. Paudler, J. Org. Chem., 40, 1210 (1975).

(106) K.F.M.J. Schmidt, Chem. Ber., 35, 1575 (1902).

(107) H.R. Sullivan and W.T. Caldwell, J. Am. Chem. Soc., 77, 1559 (1955).

(108) A. Fujita, T. Yamamoto, S. Minami and H. Takamatsu, Chem. Pharm. Bull., 13, 1183 (1965).

(109) S. Mizukami and E. Hirai, J. Org. Chem., 31, 1199 (1966).

(110) T.B. Johnson and G.E. Hilbert, Science, 69, 579 (1929).

(111) D.J. Brown, "The Pyrimidines", Interscience Publishers, New York, 1962, p 371, and "The Pyrimidines Supplement 1", Wiley - Interscience, New York, 1970, p 276.

(112) V. Boekelheide and W. Feely, J. Org. Chem., 22, 589 (1957).

(113) G. Jones and J. Stanyer, Org. Mass Spectrom., 3, 1489 (1970).

(114) W.W. Paudler, J.E. Kuder and L.S. Helmick, J. Org. Chem., 33, 1379 (1968).

(115) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis", John Wiley and Sons, Inc., New York, 1967, p 284.

(116) S. McKenzie and D.H. Reid, J. Chem. Soc. C, 145 (1970).

(117) V. Boekelheide, F. Gerson, E. Heilbronner and D. Meuche, Helv. Chim. Acta, 46, 1951 (1963).

(118) See ref 95, p 14.

(119) S. Klutchko, H.V. Hansen and R.I. Meltzer, J. Org. Chem., 30, 3454 (1965).

(120) M.A. Kira, M.O. Abdel-Raeman, Tetrahedron Lett., 109 (1969).

(121) M. DePompei and W.W. Paudler, J. Org. Chem., 41, 1661 (1976).

(122) L.M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry", Pergamon Press, Oxford, 1959, Chapter 7, p 112.

(123) L.M. Jackman and R.H. Wiley, J. Chem. Soc., 2886 (1960).

(124) C.M. Gupta and N. Anand, Indian J. Chem., 11, 427 (1973).

(125) I.C. Smith and W.G. Schneider, Can. J. Chem., 39, 1158 (1961).

(126) See ref 111, "The Pyrimidines", p 12.

(127) See ref 111, "The Pyrimidines", p 183, and "The Pyrimidines Supplement 1", p 126.

(128) M.T. Leffler, Org. React., 1, 91 (1942).

(129) T. Matsukawa and B. Ohta, J. Pharm. Soc. Jpn., 69, 489 (1949); see Chem. Abstr., 44, 3455h (1950).

(130) G.M. Kosolapoff and C.H. Roy, J. Org. Chem., 26, 1895 (1961).

(131) K. Schofield, "Hetero-Aromatic Nitrogen Compounds, Pyrroles and Pyridines" Butterworths, London, 1967, p 232.

(132) J.A. Joule and G.F. Smith, "Heterocyclic Chemistry", Van Nostrand Reinhold Company, London, 1972, p 63.

(133) See ref 111, "The Pyrimidines", pp 169-170.

(134) W.W. Paudler, R.A. VanDahm and Y.N. Park, J. Heterocycl. Chem., 9, 81 (1972).

(135) M. Fieser and L.F. Fieser, "Reagents for Organic Synthesis", Vol. 2, Wiley-Interscience, New York, 1969, p 153.

(136) K.G. Krebs, D. Heusser and H. Wimmer, "Thin-Layer Chromatography", 2nd ed, E. Stahl, Ed., George Allen and Unwin, London, 1969, p 868.

(137) "Dictionary of Organic Compounds", 4th ed, Vol. 3, I. Heilbron et al Eds., Eyre and Spottiswoode Publishers Ltd., London, 1965, p 1639.

(138) R.P. Cunningham, D. Farquhar, W.K. Gibson and D. Leaver, J. Chem. Soc. C, 239 (1969).

(139) R.G. Webster, M.Sc. Thesis, University of St. Andrews, 1972, p 90.

(140) D.O. Holland and J.H.C. Nayler, J. Chem. Soc., 1504 (1955).

(141) E.T. Borrows, D.O. Holland and J. Kenyon, J. Chem. Soc., 1075 (1946).

(142) W. Deuschel, Helv. Chim. Acta, 35, 1587 (1952).

(143) S. Gabriel, Chem. Ber., 37, 3638 (1904).

(144) See ref 111, "The Pyrimidines", p 504.

(145) See ref 111, "The Pyrimidines", p 528.

PUBLICATIONS

The results of some of the work described in this thesis have been published in a paper entitled "Azaindolizines 3. Formylation Studies on 6-Azaindolizines": see R. Buchan, M. Fraser and C. Shand, 'Journal of Organic Chemistry, 41, 351 (1974).

A second paper entitled "Azaindolizines 4. Synthesis and Formylation of 8-Azaindolizines" by the same authors has also been accepted for publication and is scheduled to appear in the 'Journal of Organic Chemistry' during June 1977. 42, 2448 (1977).

POST-GRADUATE STUDIES

In addition to attending the Third and Fourth Scottish Perkin Symposia at the Universities of Stirling and St. Andrews, I have attended a number of lectures and seminars at the University of Aberdeen and at Robert Gordon's Institute of Technology.

OTHER WORK

During 1973-74 I contributed to the writing of a paper entitled "The Determination of Mercury in Soils and Related Materials by Cold-Vapour Atomic Absorption Spectrometry" incorporating work which I carried out at The Macaulay Institute for Soil Research, Aberdeen, during 1971-72, as part of my first degree course; see A.M. Ure and C.A. Shand, Analytica Chimica Acta 72, 63 (1974).