The synthesis and reactivity of 7-azaindolizines.

KONG THOO LIN, P.V.S.

1986

The

SYNTHESES and REACTIVITY

of

7-AZAINDOLIZINES

by

PAUL VEE SIEW KONG THOO LIN

ROBERT GORDON'S INSTITUTE OF TECHNOLOGY

PhD

NOVEMBER 1986

The

SYNTHESES and REACTIVITY

of

7-AZAINDOLIZINES

by

PAUL VEE SIEW KONG THOO LIN

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

ROBERT GORDON'S INSTITUTE OF TECHNOLOGY

NOVEMBER 1986

To

Mum and dad

ACKNOWLEDGEMENT

I am particularly indebted to my supervisors, Dr M. Fraser and Dr R. Buchan, of Robert Gordon's Institute Of Technology for their excellent guidance and encouragement throughout the course of this work. I wish also to record my sincere appreciation to Dr N.F Elmore of ICI plc, Pharmaceutical Division in his capacity as external supervisor.

I would like to thank Dr O.C Musgrave of Aberdeen University for his permission to participate and attend post-graduate lectures and seminars at the university.

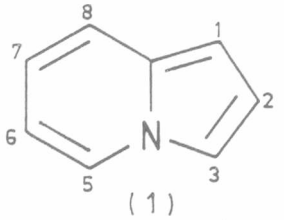
Thanks are also due to the technical staff(s) and my colleagues (especially Mr Eoin Cowie for his help in drawing the structures) of this institute. I would like to express gratitude to the Directors of Robert Gordon's Institute Of Technology, and to the past and present Heads of the Chemistry Department, Professor C.N.C Drey, and Professor I.W Nowell for the opportunity to carry out this research and for arranging financial support.

Thank also to my parents for their support and encouragement especially during my early education. Last, but by no means least, I would like to thank misses Fiona and Lesley MacLeod and Kam-Yee Wong for their help in typing this thesis.

CONTENTS

NOMENCLATURE

The Chemical Abstracts' names for 1-, 2-, 3-, 5-, 6-, 7- and 8-azaindolizines and the numbering for the indolizine system (1) is given below.

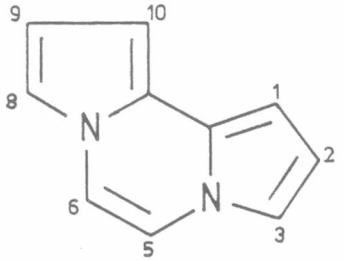


(1)

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

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

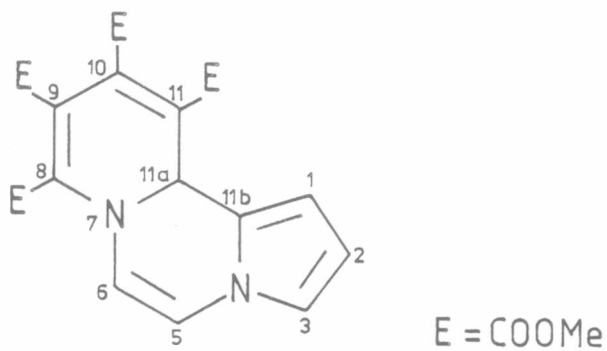
The 14π aromatic system (2) is named as dipyrrolo-[1,2-a:2,1-c]pyrazine and is numbered as shown below.



(2)

In chapter 6 (page 106), a number of angular poly-condensed systems were isolated from the reaction of

7-azaindolizines and dimethyl acetylenedicarboxylate. It is proposed in this thesis to name these poly-condensed structures using pyrazine as the base system. It is suggested to number these structures in such a way as to assign the two bridgehead nitrogens to occur at position 4- and 7 consistent with their assignment for the 7-aza-indolizine (or pyrrolo[1,2-a]pyrazine) system. For example compound (155) is named and numbered as follows:



(155)

Tetramethyl 11aH-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10,11-tetracarboxylate

Abbreviations

Throughout this thesis abbreviations and formula of certain chemicals are used and they are as follows:

CF_3COOH - Trifluoroacetic acid

CF_3COOD - Deuterated trifluoroacetic acid

$CDCl_3$ - Deuterated chloroform

DMAD - Dimethyl acetylenedicarboxylate

DEAD - Diethyl azodicarboxylate

$DMSO\text{-}d_6$ - Deuterated dimethyl sulphoxide

E - Carbomethoxy group

SUMMARY

Synthetic routes leading to 7-azaindolizines and the reactivity of this system together with other azaindolizines have been briefly reviewed.

A number of simple alkyl, aryl, carboethoxy, methoxy, chloro and amino substituted 7-azaindolizines have been synthesised via the Chichibabin reaction between suitably substituted methylpyrazines and α-bromoketones. The structures of the products obtained have been confirmed spectroscopically (mainly by pmr spectroscopy) and elemental analysis.

Examination of the pmr spectra of 7-azaindolizines in trifluoroacetic acid showed solely protonation at the non-bridgehead nitrogen. Similarly quaternisation was found to occur at the non-bridgehead nitrogen. Lithiation of 8-methyl-7-azaindolizine showed the 8-methyl group of 2,8-dimethyl-7-azaindoilzine to be acidic. Reaction between 2,3,8-trimethyl-7-azaindolizine and ethoxalyl chloride gave a diketodipyrrolo[1,2-a:2,1-c]pyrazine system. A number of electrophilic substitution reactions occurred at C-3 position. Nucleophilic replacement of chlorine by methoxide and amino from 8-chloro-2-methyl-7-azaindolizine occurred readily.

A number of simple alkyl, aryl, and carboethoxy substituted dipyrrolo[1,2-a;2,1-c]pyrazines have been obtained by the Chichibabin reaction between appropriate substituted 8-methyl-7-azaindolizines and α-bromoketones. The structures of these products have been established

spectroscopically.

An examination of the pmr spectra of dipyrrolo-[1,2-a:2,1-c]pyrazines in trifluoroacetic acid showed this system preferentially protonates at C-3 and C-8 postions. When positions 3 and 8 are substituted the C-3 conjugate acid cation predominates together with minor amounts of the C-1 cation. Dipyrrolo[1,2-a:2,1-c]pyrazines undergo electrophilic substitution preferentially at C-3(C-8) and when 3,8-disubstituted, substitution then occurs at C-1(C-10).

A brief survey of reaction between relevant nitrogen heteroaromatics and DMAD has been reviewed. The reaction between 7-azaindolizines and DMAD gave products involving bonding at the non-bridgehead nitrogen and the adjacent C-8 position or 8-substituent.

CHAPTER 1

INTRODUCTION

This thesis is concerned with the synthesis and reactions of 7-azaindolizines and of dipyrrolo[1,2-a:2,1-c]-pyrazines. This introductory chapter gives a survey of the methods used for the synthesis of these compounds together with their reported reactions. The reactions of other azaindolizines have also been included so that comparison can be made with the 7-azaindolizine system. The chemistry of indolizine and the azaindolizines has been reviewed by Borrows and Holland[1] (1948), Mosby[2](1961) Prostakov and Baktibaev[3](1975), Maury[4] (1977), Kuhla and Lambardino[5] (1977), and by Tisler[6](1980).

Synthesis of 7-azaindolizines

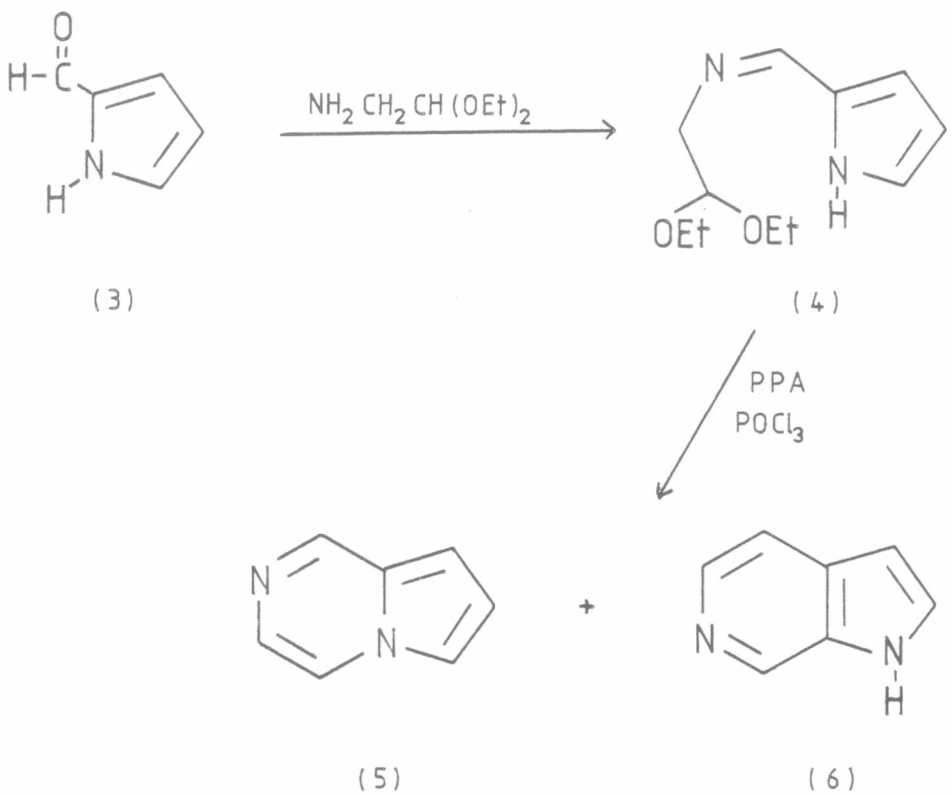
The methods used in the synthesis of 7-azaindolizines generally involve building a second ring onto a pyrrole or a pyrazine derivative. The methods may be classified under six general headings as detailed below.

1. From pyrrole derivatives

A number of syntheses have been developed which involve the condensation of a nitrogen-containing compound with a pyrrole which usually contains a carbonyl group at position 2:

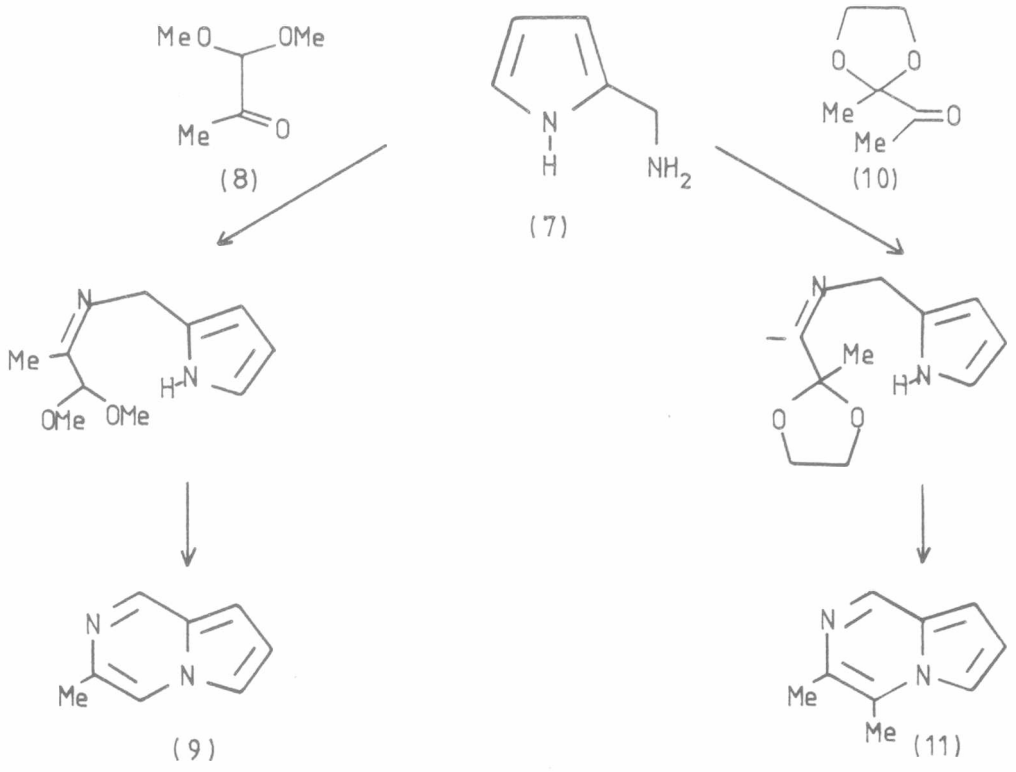
(a) 2-Pyrrole carboxyaldehyde (3) reacts with amino-acetaldehyde diethylacetal to give 2-pyrrole aldehyde amino-acetal (4) which may be cyclised in polyphosphoric acid and

phosphoryl chloride to give a mixture of the parent 7-aza-indolizine (5) as the major product(21%) and the azaindole (6)[7]. The 7-azaindolizine (5) is formed by cyclisation via the pyrrole nitrogen, whereas the azaindole (6) is formed by cyclisation at C-3. In a similar cyclisation reaction, 2-acetylpyrrole aminoacetal gave 8-methyl-7-azaindolizine in 23% yield[7].

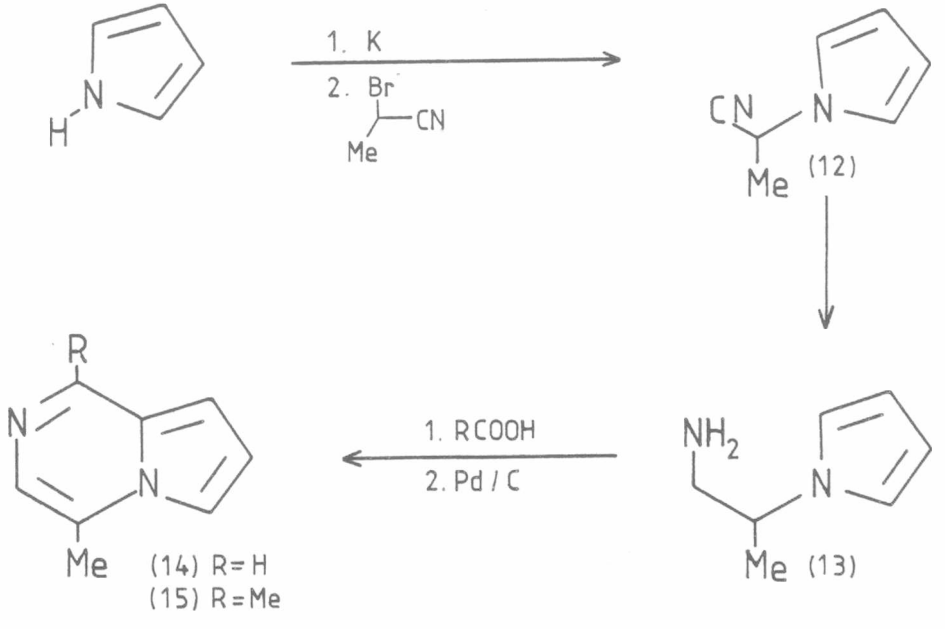


(3) (4) (5) (6)

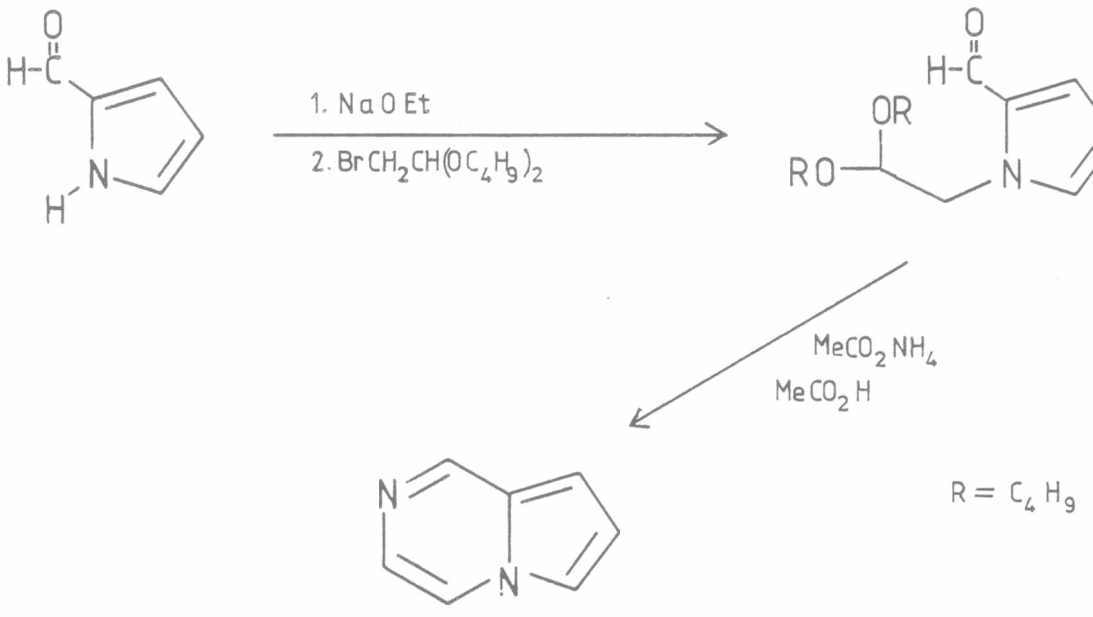
(b) The oxime of 2-pyrrole carboxyaldehyde on reduction[8,9,10] yielded the amine (7). Condensation of (7) with the dimethoxy propanone (8) gave 6-methyl-7-aza-indolizine (9), whilst the reaction with monoethylene acetal of butanedione (10) afforded 5,6-dimethyl-7-azaindolizine (11)[11].



(c) The potassium salt of pyrrole on alkylation gave the nitrile (12) which after reduction with lithium aluminium hydride yielded the amine (13). Cyclisation with formic acid afforded the dihydro derivative which on dehydrogenation gave 5-methyl-7-azaindolizine (14). Cyclisation with acetic acid similarly gave 5,8-dimethyl-7-azaindolizine (15)[12].



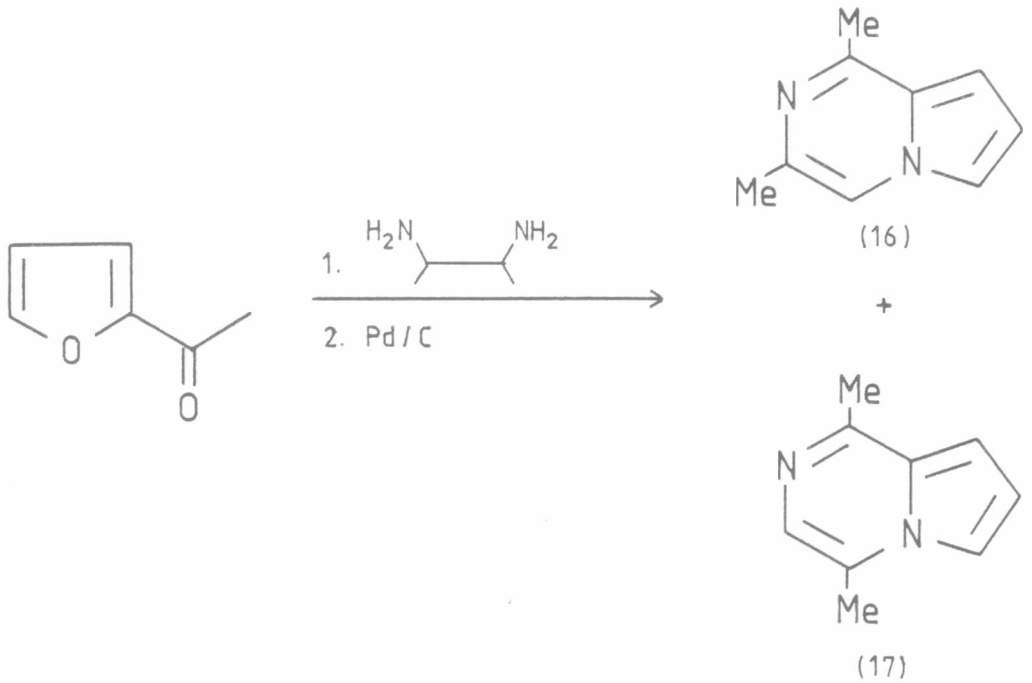
(d) The sodium salt of 2-pyrrole aldehyde reacts with the acetal of an α-halocarbonyl compound to give an N-alkyl derivative which cyclises in the presence of ammonium acetate to give 7-azaindolizine[13] as follows:



This method has also been applied to the synthesis of 1,3,8-trimethyl-2-carboethoxy-7-azaindolizine, 8-phenyl-7aza-indolizine and 6,8-dimethyl-7azaindolizine[13].

2. From Furfural

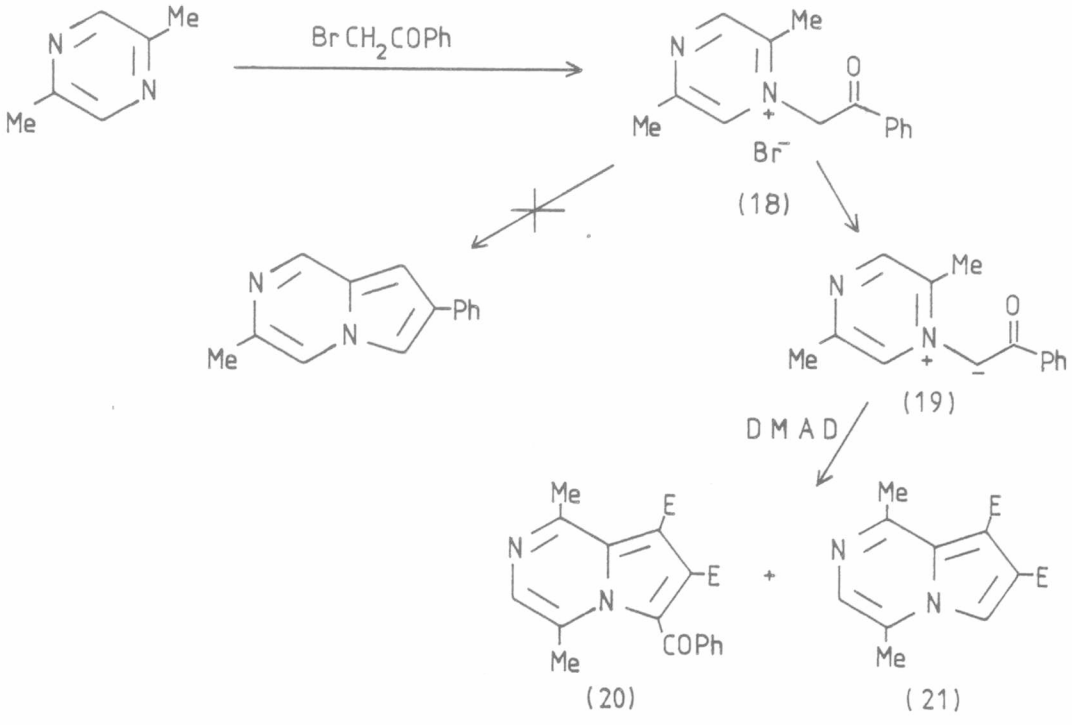
6,8-Dimethyl (16) and 5,8-dimethyl-7-azaindolizine (17) have been prepared from the condensation of 2-acetylfuran with 1,2-diaminopropane. The dihydro derivatives initially obtained were subsequently dehydrogenated by palladium on charcoal to afford (16) and (17) in very low yield[11].



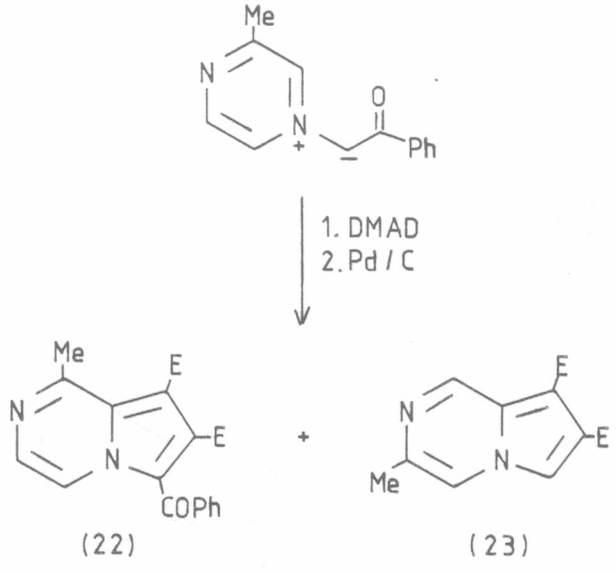
3. By the reaction of DMAD with pyrazinium ylides

A number of syntheses have been developed involving the addition of dimethyl acetylenedicarboxylate(DMAD) to a pyrazinium ylide.

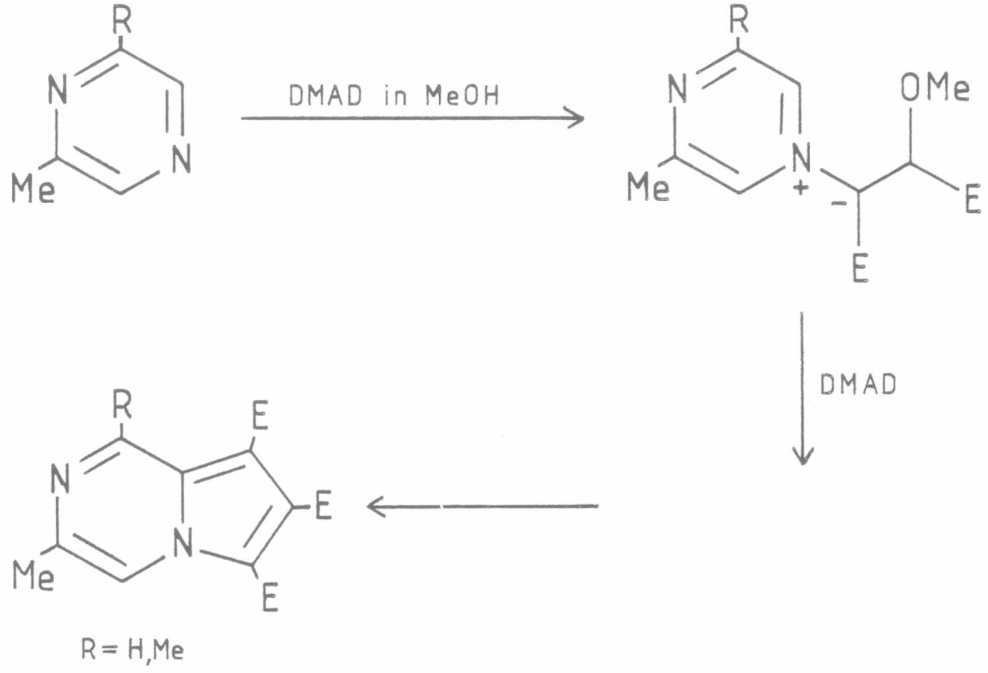
(a) Boekelheide et al[14]. attempted to prepare 6-methyl-2-phenyl-7-azaindolizine by a Chichibabin reaction in which 2,5-dimethylpyrazine was heated with phenacyl bromide to give the quaternary salt (18). This salt on reaction with base did not yield 6-methyl-2-phenyl-7-azaindolizine but gave an ylide (19) which on subsequent reaction with DMAD underwent cycloaddition to give the 7-azaindolizines (20) and (21)[14].



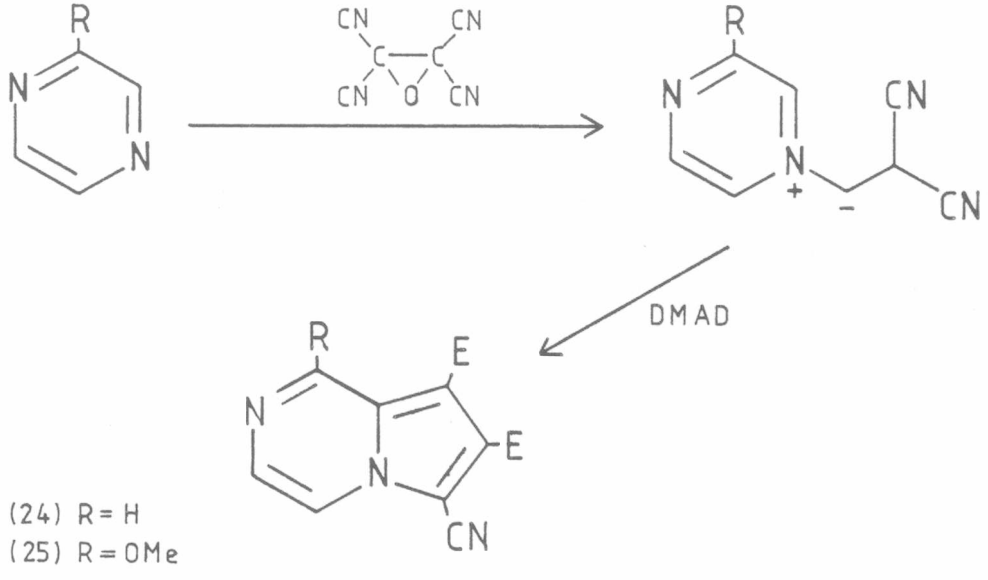
(b) In a similar reaction, Sasaki et al.[15] reacted 3-methylpyrazinium N-phenacylide with DMAD in acetonitrile at room temperature to give low yields(4-8%) of a mixture of the diesters (22) and (23) in the ratio of 2:1. The cyclisation has occurred at both C-2 and C-6 of the pyrazine ring.



(c) Other methyl esters of 7-azaindolizines have been obtained in low yield by reacting pyrazines with DMAD directly. It is suggested that the reaction proceeds with the formation of an ylide followed by the addition of a second molecule of DMAD as shown below[16].



(d) A pyrazinium ylide may also be formed by the reaction between a pyrazine and tetracyanoethylene oxide. The ylide will then react with DMAD to give the corresponding 3-cyano compound[17]:

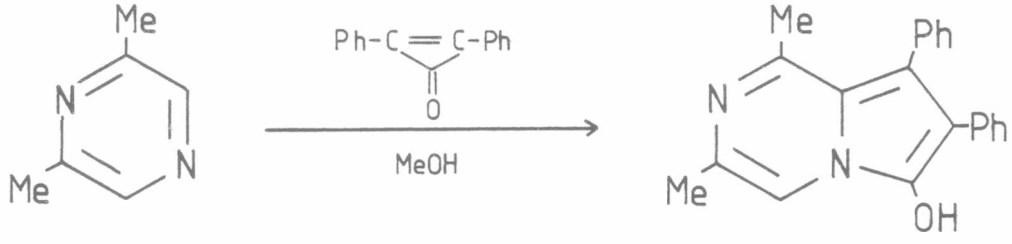


(24) R = H
(25) R = OMe

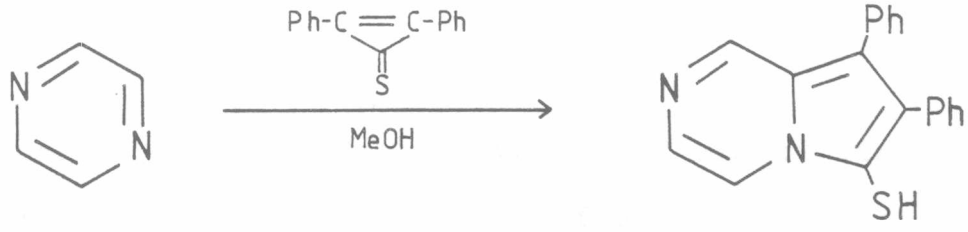
3-Cyano-1,2-dicarbomethoxy-7-azaindolizine (24) and 3-cyano-1,2-dicarbomethoxy-8-methoxy-7azaindolizine (25) were obtained in 62% and 43% yield respectively[17].

4. By the reaction of cyclopropene derivatives with pyrazines

2,6-Dimethylpyrazine reacts with diphenylcyclopropenone in methanol at room temperature to give 6,8-dimethyl-1,2-diphenyl-3-hydroxy-7-azaindolizine in 80% yield[18]:

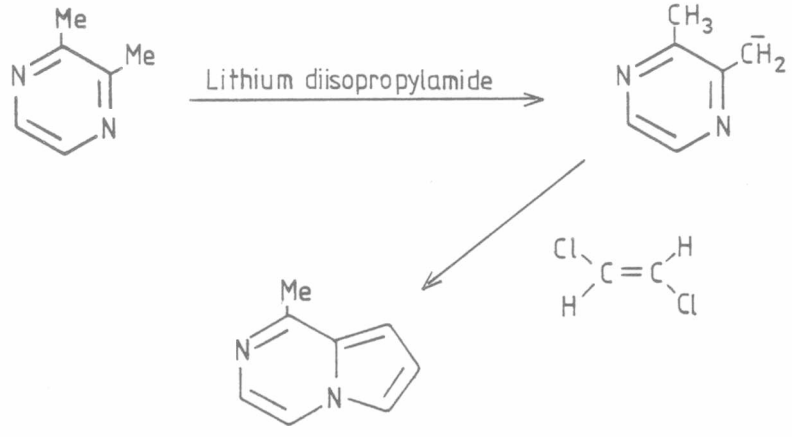


Analogously, the reaction under nitrogen of pyrazine with diphenylcyclopropenthione in methanol at room temperature afforded 1,2-diphenyl-3-thio-7-azaindolizine in 25% yield[19]:



5. By the reaction of alkylpyrazine anions with trans-1,2-dichloroethylene

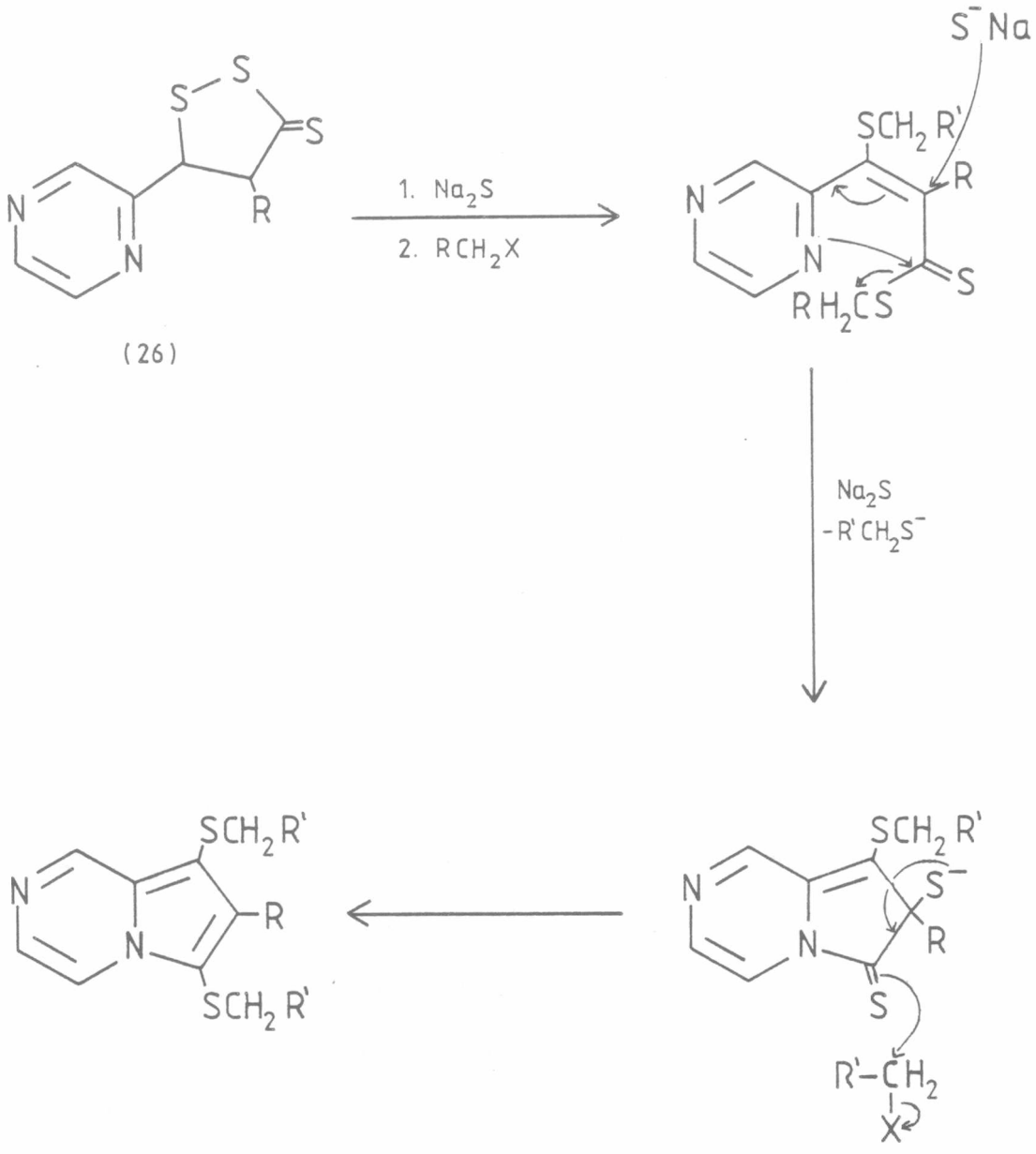
Alkyl pyrazines which have an α-hydrogen are easily converted into their anions by reaction with lithium diisopropylamide. Treatment of a suspension of these anions, in ether at 0°C, with one equivalent of trans-1,2-dichloroethylene resulted in the formation of the corresponding 7-azaindolizines[20] in varying yields:



This reaction has been applied to the synthesis of 8-methyl-7-azaindolizine(29%), 5-methyl-7-azaindolizine(15%) and 5,6,8-trimethyl-7-azaindolizine(less than 1%).

6. By the reduction of 5-(2-pyrazinyl)-1,2-dithiole-3-thiones

A number of thio derivatives of 7-azaindolizines have been prepared by the reduction of 5-(2-pyrazinyl)-1,2-dithiole-3-thiones (26) with sodium sulphide, followed by alkylation of the intermediate[21]. The mechanism suggested in this reaction is shown below.



(26)

R = Me, R' = H (53%)

R = H , R' = H (62%)

R = Me, R' = $(CH_2)_2N(CH_3)_2$ (23%)

R = Me, R' = COOEt (25%)

Reactions of azaindolizines

Azaindolizines can be formally classified as π-excessive heteroaromatic compounds in which there are 10π electrons over 9 ring centres and as such would be expected to characteristically bond to electrophiles. Experimentally they have been shown to bond to electrophiles at positions 1 and 3. These observations agree with theoretical calculations[22]. This section summarises the main aspects of the chemistry of azaindolizines.

1. Protonation

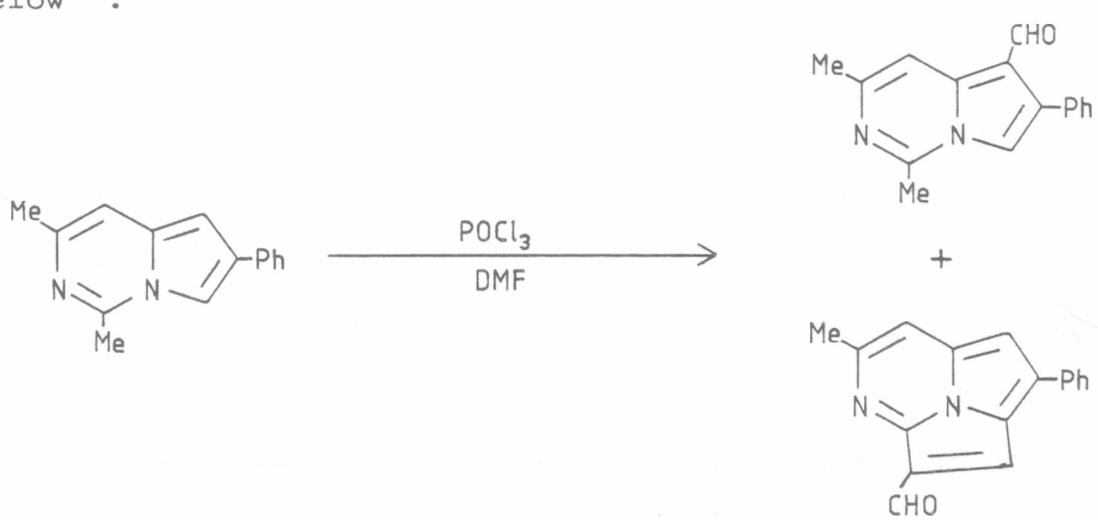
Azaindolizines with a nitrogen in the five membered ring i.e 1-, 2- and 3-azaindolizines protonate preferentially at the non-bridgehead nitrogen[23,24]. 5-Azaindolizines have been shown to protonate at C-1, C-3 and N-5 depending on the substituents present and the nature of the protonating media[23,25]. Alkyl and aryl 6- and 8-azaindolizines[26] have been shown to have a preference for N-protonation in trifluoroacetic 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 cases of 2,7-dimethyl-6- and 8-azaindolizines[26]. In contrast the methoxy-substituted 6- and 8-azaindolizines protonated solely at C-3. Protonation of the parent 7-azaindolizine occurs solely at the non-bridgehead nitrogen(N-7)[27,28]. The protonation of substituted 7-azaindolizines has not been investigated.

2. Electrophilic substitution

2-, 5-, 6-, 7- And 8-azaindolizines generally undergo electrophilic substitution at the 1- and 3- positions. A summary of the most important electrophilic substitution reactions of azaindolizines is given below.

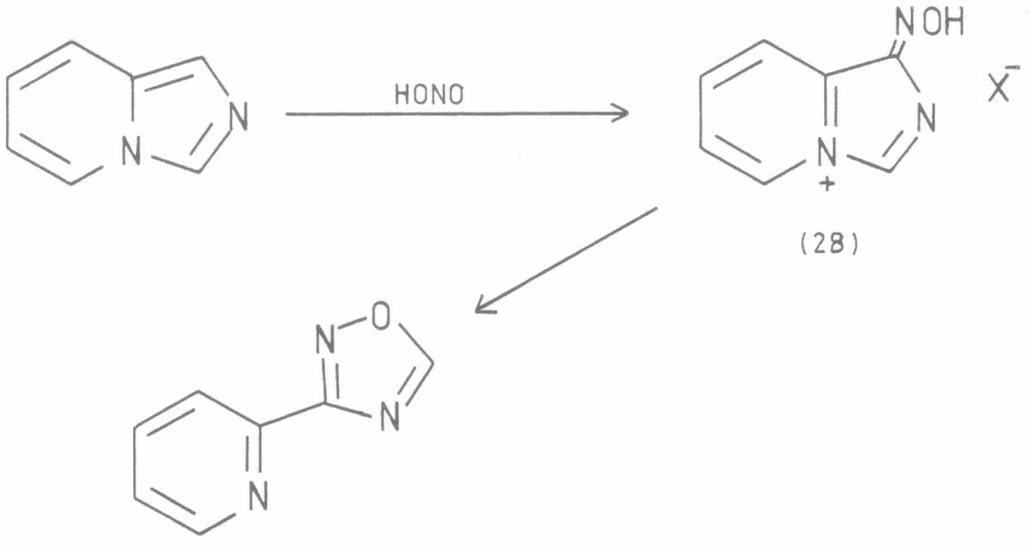
(a) Acetylation: 2- and 3-azaindolizines acetylate at C-1[29,30]. 5-, 6- and 8-azaindolizines acetylate at C-3 under mild conditions; under more severe conditions, substitution also occurs at C-1 giving rise to diacetyl derivatives[26,31,32].

(b) Formylation: 1-Azaindolizine gives 3-formyl derivatives[31,33,34]. 2-Azaindolizine undergoes a Vilsmeier reaction to give mainly the 1-formyl derivative. When phenyllithium/dimethylformamide[35] is reacted with 2-azaindolizine, formylation occurs by the anion development at C-3. 5-Azaindolizine formylates at both C-1 and C-3; 5-azaindolizines with a methyl group at position 3 formylate at C-1[25]. Similar observations were reported with 6- and 8-azaindolizines[26,36]. However, Vilsmeier formylation of 5,7-dimethyl-6-azaindolizine interestingly gave a formyl cyclazine as well as the 1-formyl derivative as shown below[37]:



(c) Diazonium coupling: 1-, 5-, 6- and 8-azaindolizines are all reported to undergo azo coupling at C-3[25,26,30,32,33].

(d) Nitrosation: 1-, 5- and 6-azaindolizines give their respective 3-nitroso derivatives[31,32,33], whereas 3-azaindolizine gives a 1-nitroso derivative[30]. Nitrosation of 2-azaindolizine, however, gave the 3-(2-pyridyl)-1,2,4-oxadiazole (27) thought to result from ring opening of the intermediate(28)[38].



(e) Nitration: Stronger electrophiles such as the NO_2^+ ion give either the mono or the disubstituted derivatives. 1-Azaindolizine nitrates at C-3[39] and 3-azaindolizine gives the 1-nitro or 1,8-dinitro derivative depending on the reaction conditions[30,40]. 5-, 6- and 8-Azaindolizines nitrate at C-3 and C-1 to give the disubstituted derivatives[26,32].

(f) Bromination: The bromination of azaindolizines has been exhaustively examined. The general procedure is to add the azaindolizine in ethanol to an aqueous solution of

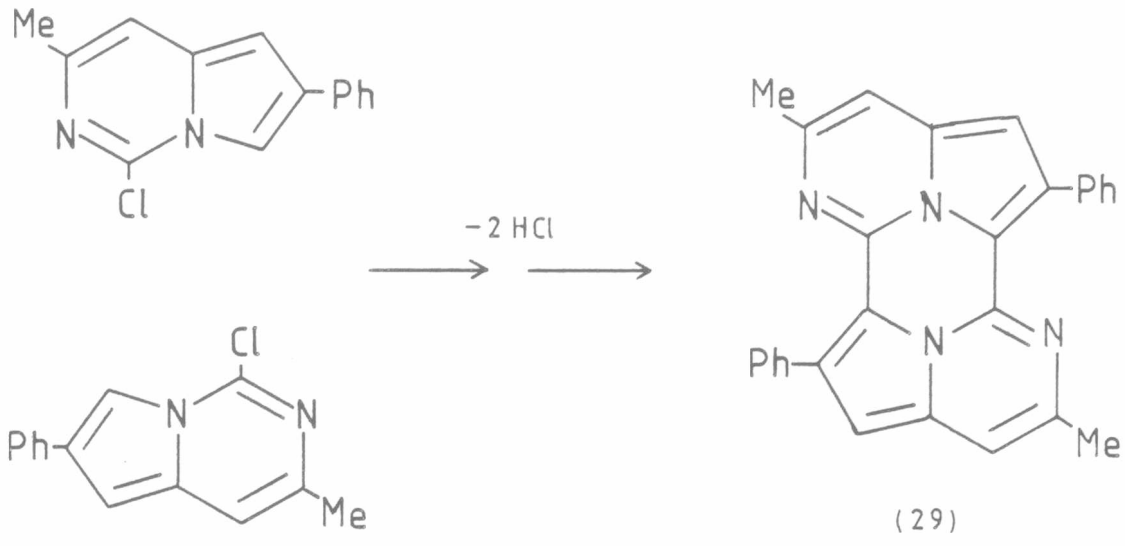
bromine. Thus the reaction between 1-azaindolizine and bromine yields the 3-bromo derivative[39,41]. 2-Azaindolizine brominates at C-3[42] and 3-azaindolizine brominates at C-1[43]. 5-, 6- And 7-azaindolizines brominate at both C-3 and C-1 to give the dibromo derivatives[32,43]. In the cases of 1- and 5-azaindolizine[44,45] bromination may also occur at the C-5 and C-7 positions respectively to give the corresponding tribromo derivatives.

3. Nucleophilic substitution

Although azaindolizines contain a -excessive system, the presence of the pyridine type non-bridgehead nitrogen would be expected to cause sites of electron deficiency. -Electron density calculations indicate the sites of greatest electron deficiency for 1-, 2-, 3-, 5-, 6-, 7-, and 8-azaindolizines are C-2, C-8, C-2, C-6, C-5, C-8 and C-7 respectively[22]. Despite the presence of these electron deficient carbon centres, only a few examples of nucleophilic substitution have been reported. The 5-chloro substituent in 5-chloro-[46] and hexachloro-1-azaindolizine[47] is substituted on reaction with sodium methoxide, and the 2-chloro substituent in 2-chloro-3-nitro-1-azaindolizine on reaction with dimethylamine[46]. The 5-chloro substituent in 5-chloro-7-methyl-2-phenyl-6-azaindolizine was successfully displaced by hydroxide, methoxide, and ammonia[48].

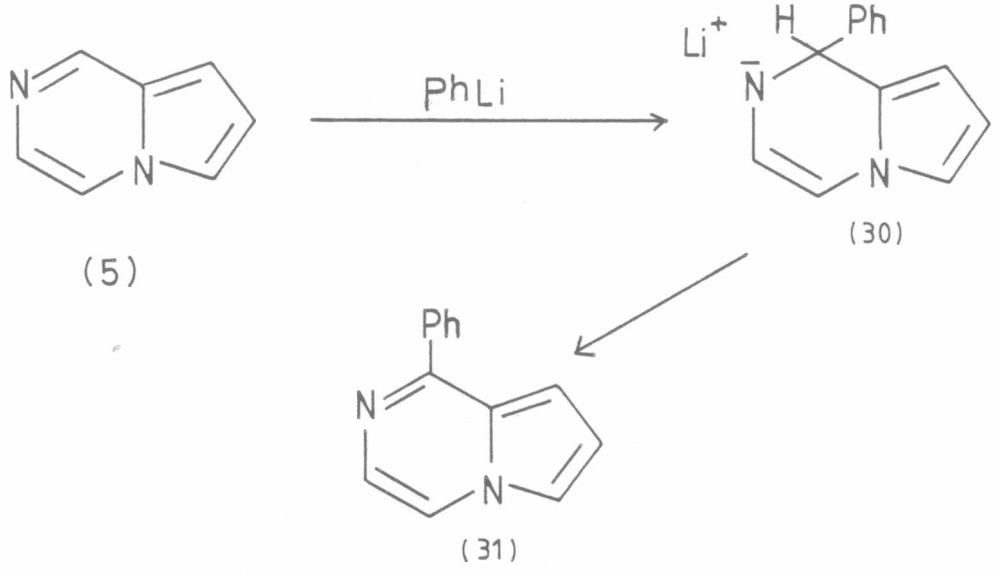
Reaction of 5-chloro-7-methyl-2-phenyl-6-azaindolizine with phosphoryl chloride gives the centrosymmetric structure (29) which is probably formed by a nucleophilic-electrophilic process involving two molecules of the

6-azaindolizine as shown below[48]:



(29)

7-Azaindolizine (5) reacts with phenyllithium to give the 8-phenyl derivative (31) via the intermediate (30)[42]:



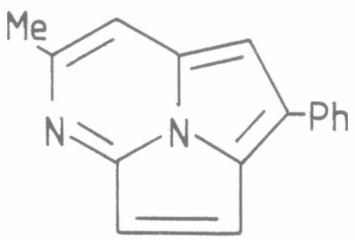
(5)

(30)

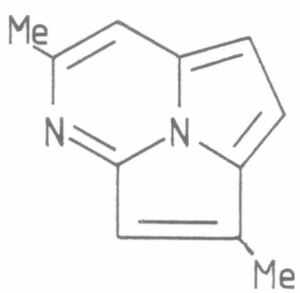
(31)

4. Reaction of azaindolizines with DMAD

Like indolizine[50], 1-, 2-, 6-, and 8-azaindolizines each react with DMAD in the presence of palladium on charcoal to give an azacycl[3.2.2]azine by a cycloaddition process followed by dehydrogenation[26,50,51]. Hence, 1-azaindolizine gives a 1-azacycl[3.2.2]azine, and 2-azaindolizine affords 2-azacycl[3.2.2]azine[51]. 6- and 8-azaindolizines both react with DMAD to give 5-azacycl[3.2.2]azines[26,52,53]; thus, 7-methyl-2-phenyl-6-azaindolizine reacts with DMAD to give an azacyclazine derivative, which on hydrolysis and decarboxylation gave 6-methyl-2-phenyl-5-azacycl[3.2.2]azine (32) in 25% yield. Similarly, 2,7-dimethyl-8-azaindolizine gives the corresponding 5-azacycl[3.2.2]azine (33).

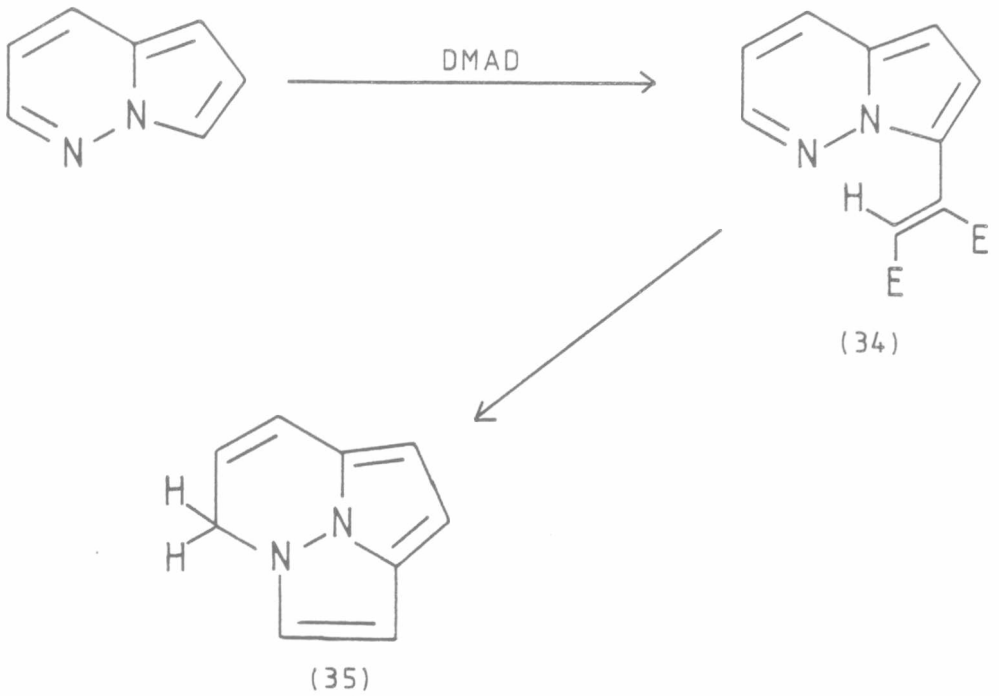


(32)



(33)

5-Azaindolizine with DMAD gave the diester (34) which can be cyclised under acid conditions to give the tricyclic diazacyclopentadiene derivative (35)[32,44,45].



(34)

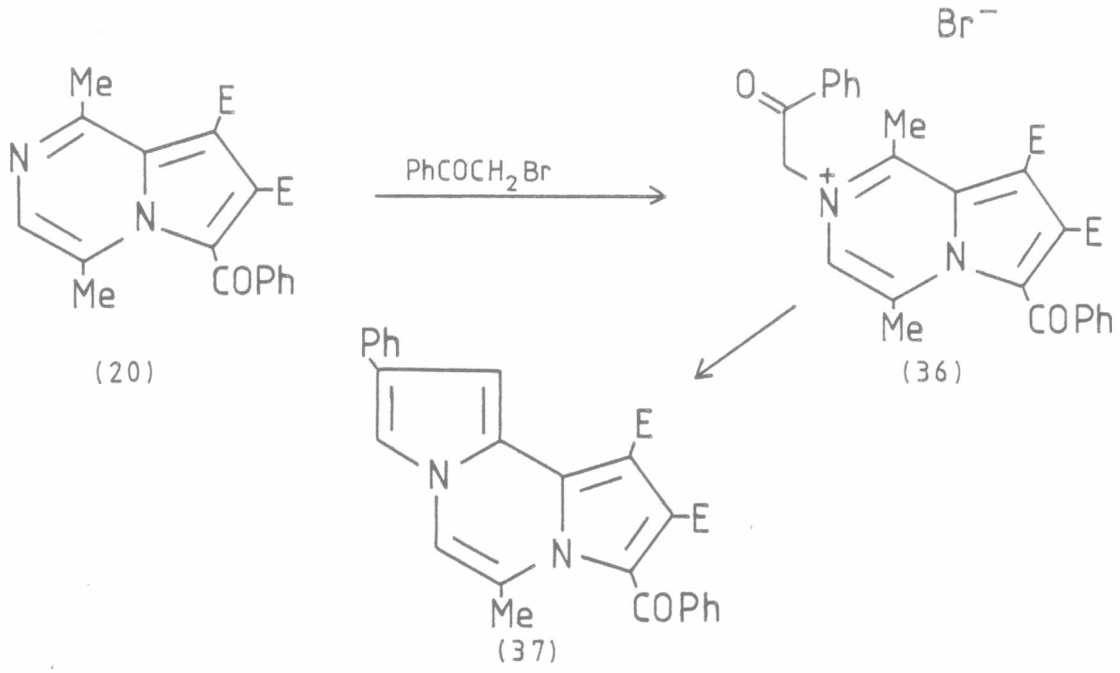
(35)

The reaction between 7-azaindolizine and DMAD has been attempted, but no identifiable products were isolated[27].

The synthesis and chemistry of cyclazines and azacyclazines have been reviewed by Taurins[54](1977), Flitsch[55](1978) and Lee[56](1983).

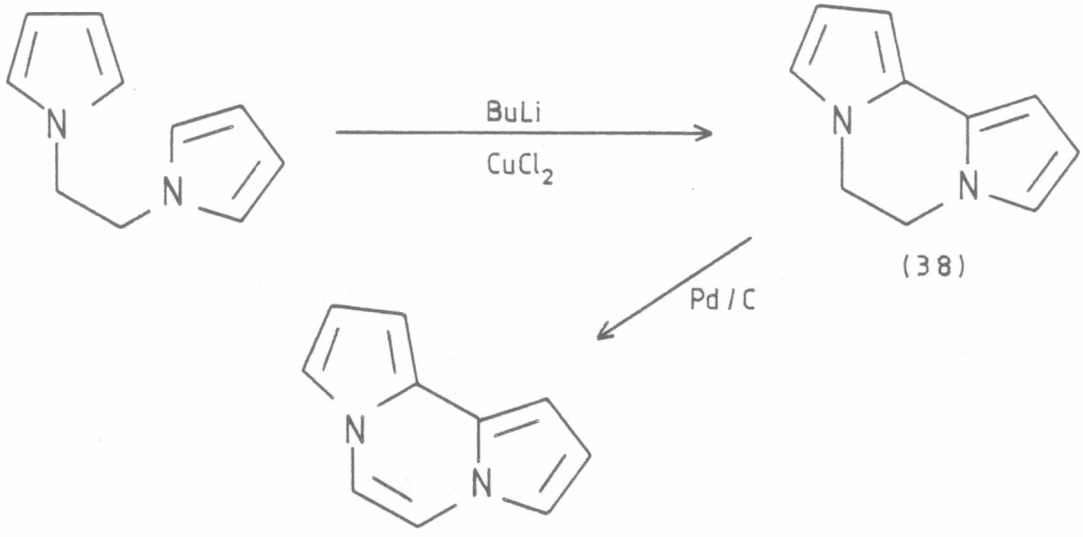
Synthesis and reactivity of dipyrrolo[1,2-a:2,1-c]-pyrazines

Boekelheide et al.[14] first reported the synthesis of a dipyrrolo[1,2-a:2,1-c]pyrazine in 1959. The 7-azaindolizine (20) reacted readily with phenacyl bromide to give a quaternary salt (36) which was not isolated as such but was treated with sodium carbonate to give the dipyrrolo-[1,2-a:2,1-c]pyrazine (37) in 55% yield.



(20) (36) (37)

More recently, the synthesis of the parent dipyrrolo-[1,2-a:2,1-c]pyrazine was reported by Burger et al.[57] This involved the cyclisation of 1,2-N,N'-dipyrrolylethane with n-butyllithium and copper(II)chloride in a mixture of benzene and tetramethylethylene diamine to give the dipyrrolo[1,2-a:2,1-c]-5,6-dihydropyrazine (38) in 34% yield. Dehydrogenation of (38) over palladium on charcoal in vacuo gave dipyrrolo[1,2-a:2,1-c]pyrazine (2) in 67% yield.

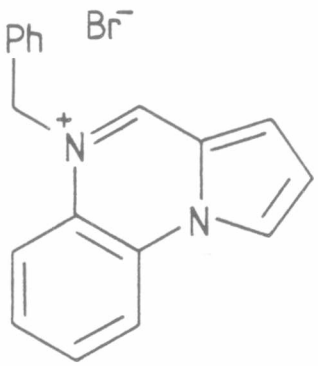


(38) (2)

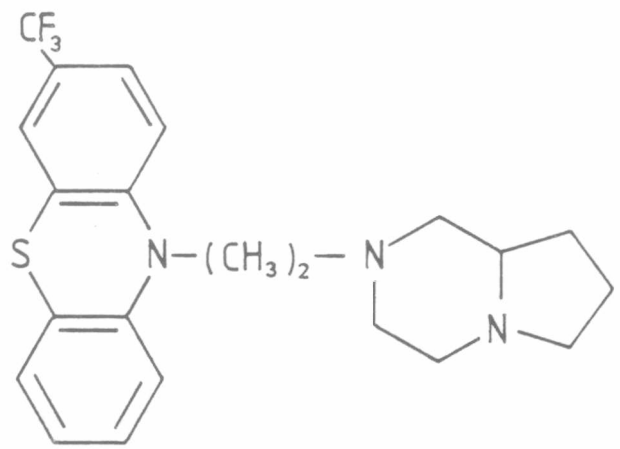
These are the only reported syntheses of dipyrrolo-[1,2-a:2,1-c]pyrazines and there has been no studies on the reactivity of this system.

Biological activity of 7-azaindolizines

Quaternary salts of 7-azaindolizines, for example the quaternary salt (39) are orally effective hypoglycemic agents useful in the reduction of blood sugar levels of diabetics[58].



(39)



(40)

There are many more reports of the biological activity of perhydro 7-azaindolizine derivatives. These have been shown to have activity on the central nervous system(CNS); for example, the phenothiazine (40) was found to be active in mouse amphetamine-induced hypermobility tests[59]. Other 7-substituted perhydro 7-azaindolizines have been patented as sympatholytics[60], antihistaminic, antichlinergic and antitremorine compounds[61], CNS depressants[62,63], antiarr-hythmics[59], coronary vaso-dilators[64] and anticonvulsants and analgesics[62].

CHAPTER 2

THE SYNTHESIS OF SUBSTITUTED 7-AZAINDOLIZINES

This chapter describes the syntheses of some methyl-, ethyl-, phenyl-, methoxy-, carboethoxy-, chloro- and amino-7-azaindolizines by the Chichibabin method[65]. The structures of the products were deduced by pmr, ir and occasionally by ^{13}cmr spectroscopy.

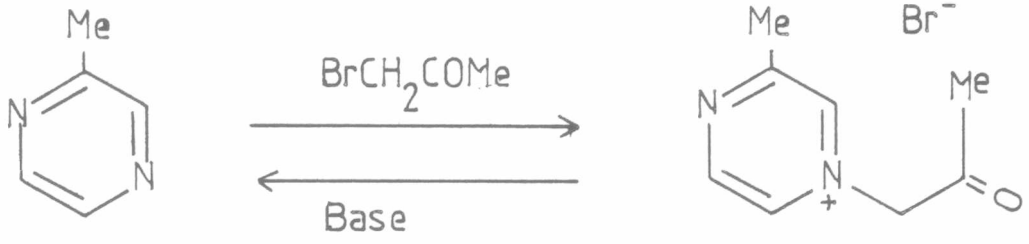
Synthesis of alkyl and aryl 7-azaindolizines

The Chichibabin reaction has been successfully applied in the syntheses of indolizine[66] and 5-[23], 6- and 8-azaindolizines[67,68]. In these syntheses, methyl- or ethyl-pyridines, pyridazines and pyrimidines were reacted with a variety of α-haloketones. An obvious extension of this reaction would be the synthesis of 7-azaindolizines. Here the starting azine would be a methyl or ethyl derivative of the less basic pyrazine system.

Reaction of 2-methylpyrazine and bromoacetone

2-Methylpyrazine reacts with bromoacetone to give a single quaternary salt (41) whose ir spectrum showed a strong carbonyl band at 1720 cm^{-1}. Its pmr spectrum showed singlets at δ2.38 and δ6.00 due to the methyl and methylene groups of the acetonyl moiety and a 3H singlet at δ2.80 due to the ring methyl group. At lower field 1H singlets at δ8.90, δ9.15 and δ9.50 were assigned to H-5, H-2 and H-6

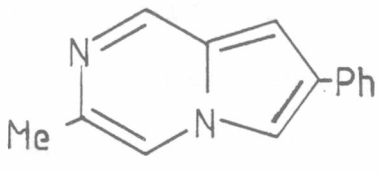
respectively. Quaternisation at N-1 is most likely because of steric hindrance of the methyl group at position 2. Treatment of the quaternary salt (41) with sodium bicarbonte gave back 2-methylpyrazine.



(41)

Reaction between 2,5-dimethylpyrazine and (a) phenacyl bromide and (b) bromoacetone

Boekelheide et al.[14] attempted the synthesis of 6-methyl-2-phenyl-7-azaindolizine (42) by reacting 2,5-dimethylpyrazine with phenacyl bromide. The resulting quaternary salt however did not cyclise when base was added; a zwitterionic intermediate was proposed which on subsequent reaction with DMAD gave the highly substituted 7-azaindolizines as described on page 9.

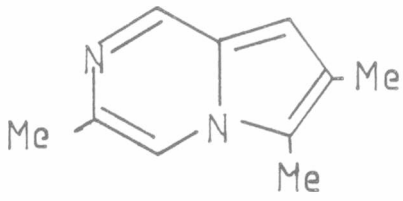


(42)

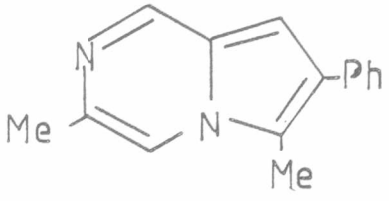
When the reaction between 2,5-dimethylpyrazine and phenacyl bromide was carried out, the resulting quaternary salt, on heating with base simply, gave back the starting dimethylpyrazine. Similar results were obtained when bromoacetone was used as the α-haloketone.

Reaction between 2,5-dimethylpyrazine and (a) 3-bromobutan-2-one and (b) bromopropiophenone

In contrast to the above reactions, treatment of 2,5-dimethylpyrazine with 3-bromobutan-2-one gave a salt which on reaction with base yielded a crude oil. Purification of the latter by tlc gave a low yield of a product which was analysed for $C_{10}H_{12}N_2$. The ir spectrum showed no carbonyl absorption, suggesting that cyclisation had occurred. The pmr spectrum showed three high field 3H singlets at δ2.28, δ2.36 and δ2.43 due to three methyl groups, and at lower field three 1H singlets at δ6.68, δ7.38 and δ8.60, indicating the presence of three aromatic protons. By comparing this pmr spectrum with that of the parent 7-azaindolizine spectrum[28,43], the signals at δ2.28, δ2.36 and δ2.43 were assigned to H-1, H-5 and H-8 respectively; the assignment of the methyl signals were based on their proximity to the nitrogen atoms. Hence, the peaks at δ2.28, δ2.36 and δ2.43 were due to the methyl groups at 2, 3 and 6 positions respectively. Therefore the above observations are consistent with the structure of 2,3,6-trimethyl-7-azaindolizine (43). Similarly, reaction of 3-bromopropiophenone with 2,5-dimethylpyrazine gave the corresponding 2-phenyl-3,6-dimethyl-7-azaindolizine (44) in low yield.

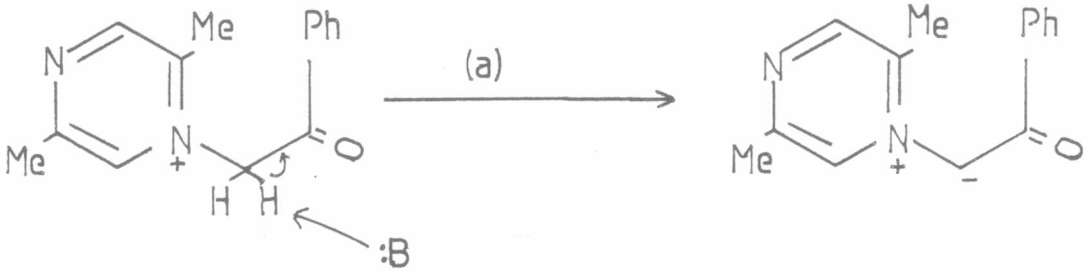


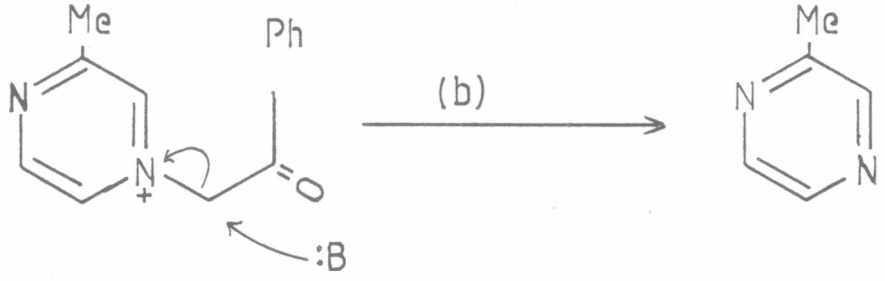
(43)

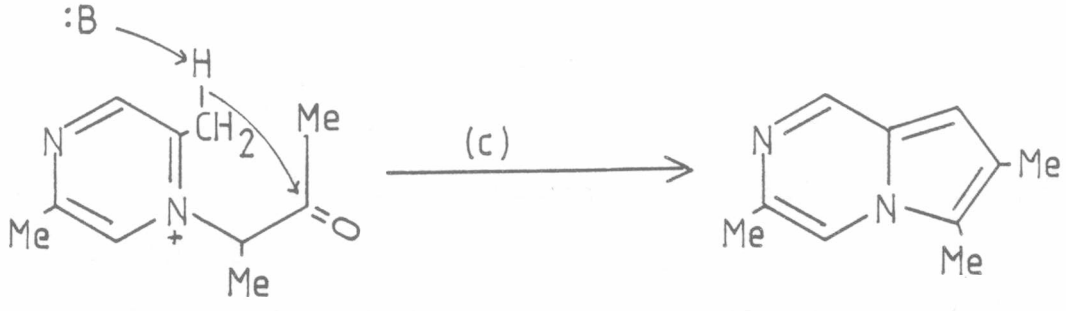


(44)

The reactions discussed above indicate that the pyrazinium salt may react with base (:B) by three possible pathways:







(a) The base could remove a proton from the acidic methylene group to form a zwitterion as proposed by Boekelheide[14].

(b) The base could act as a nucleophile and displace the pyrazine as a leaving group.

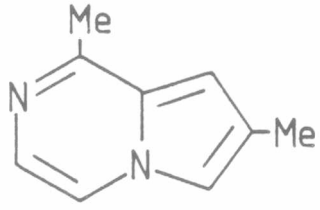
(c) The base could remove a proton from a ring methyl group and subsequently undergo cyclisation to give a 7-azaindolizine.

In the reactions between 2,5-dimethylpyrazine and bromobutan-2-one and bromopropiophenone, it appears that the methyl branching of the α-haloketone reduces the acidity of the methine hydrogen adjacent to the carbonyl function. It also sterically suppresses nucleophilic substitution sufficiently to allow some cyclisation to the 7-azaindolizine.

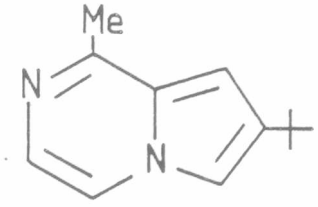
In the reactions discussed below, treatment of 2,3-dimethyl-, 2,3,5-trimethyl-, 2,3,5,6-tetramethyl-, 2,3-diethyl- and 2-ethyl-3-methylpyrazines with various α-haloketones gave the corresponding 7-azaindolizines (45-59) in yields generally between 10-75%. Thus, the cyclisation process (c) appears to be more favourable than displacement of the pyrazine as a leaving group (b), but in most of the reactions some of the starting pyrazine was obtained on treating the quaternary salt with base.

Reaction between 2,3-dimethylpyrazine and (a) bromoacetone (b) bromopinacolone (c) phenacyl bromide and (d) 3-bromobutan-2-one

The reaction between 2,3-dimethylpyrazine and bromoacetone gave 2,8-dimethyl-7-azaindolizine (45).



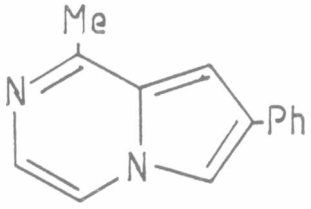
(45)



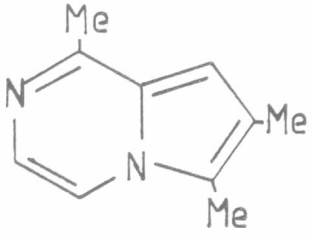
(46)

The pmr spectrum of (45) showed two 3H singlets at δ2.35 and δ2.60, an AB doublet centered at δ7.57 and δ7.32 (J=5.3Hz) and two weakly coupled singlets at δ6.55 and δ7.14. The lower field methyl signal at δ2.60 was assigned to the methyl at the 8 position since it is nearest to the electron attracting nitrogen atom. The ring protons were assigned by comparison with the pmr spectrum of the parent 7-azaindolizine. Hence peaks at δ6.55 and δ7.32 were due to H-1 and H-3 respectively while H-5 and H-6 showed signals at δ7.35 and δ7.57 respectively. The ^{13}cmr spectrum of (45) showed two high field singlets at δ10.79 and δ19.70 and at low field seven singlets between δ101.92 and δ150.00. The high field singlets were assigned to CH_3-2 and CH_3-8 respectively while the lower field singlets were due to the ring carbons.

The reaction between 2,3-dimethylpyrazine and bromopinacolone afforded 8-methyl-2-t-butyl-7-azaindolizine (46). The pmr spectrum of compound (46) was very similar to that of the dimethyl compound (45), except that the former showed a 9H singlet at δ1.40 which is ascribed to the t-butyl group at position C-2, and a 3H singlet at δ2.80 attributed to CH_3-8.



(47)

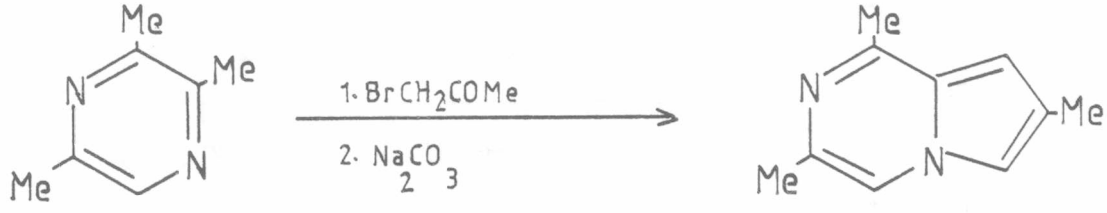


(48)

The reaction of 2,3-dimethylpyrazine with phenacyl bromide gave 8-methyl-2-phenyl-7-azaindolizine (47) and with 3-bromobutan-2-one yielded 2,3,8-trimethyl-7-azaindolizine (48) in 75% yield. The pmr spectra are summarised in Table I.

Reaction between 2,3,5-trimethylpyrazine and (a) bromoacetone (b) phenacyl bromide and (c) 3-bromobutan-2-one

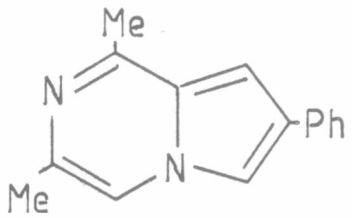
The reaction between 2,3,5-trimethylpyrazine and bromoacetone gave only 2,6,8-trimethyl-7-azaindolizine (49). The pmr spectrum of the product (49) showed three 3H singlets at δ2.28, δ2.30 and δ2.54 due to methyl groups at C-2, C-6 and C-8 and three 1H singlets at δ6.40, δ6.95 and δ7.28 assigned to H-1, H-3 and H-5 respectively.



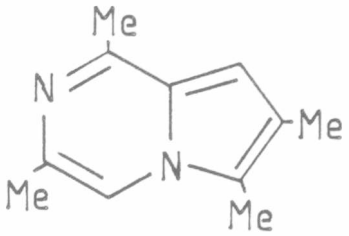
(49)

Analogously the reaction between 2,3,6-trimethylpyrazine and phenacyl bromide gave 6,8-dimethyl-2-phenyl-7-azain-

dolizine (50) and with 3-bromobutan-2-one 2,3,6,8-tetramethyl-7-azaindolizine (51).



(50)

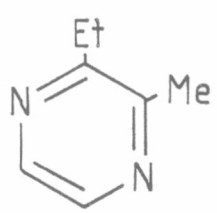


(51)

Formation of the 7-azaindolizines (49), (50) and (51), indicates that quaternisation has occurred solely at the least hindered nitrogen of the pyrazine system.

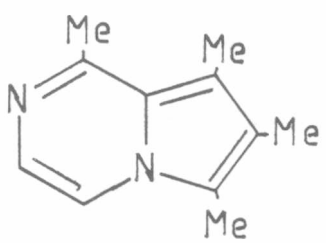
Reaction between 2-ethyl-3-methylpyrazine and 3-bromobutan-2-one

The reaction between 2-ethyl-3-methylpyrazine and 3-bromobutan-2-one can, in theory give two products (52) and (53) depending on which nitrogen the quaternisation has occurred.



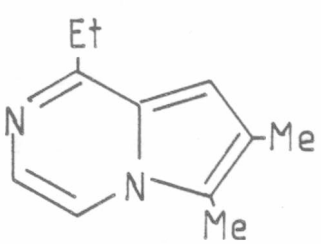
1. BrCHMeCOMe

2. Base



(52)

or



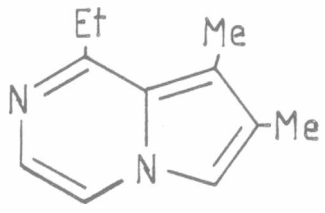
(53)

However, only one product (53) was isolated, together with some starting material. The pmr spectrum showed two 3H singlets at δ2.25 and δ2.30, indicating the presence of only two methyl groups; a triplet centered at δ1.35 and a quartet centered at δ2.90 implies the presence of an ethyl group showing that the product of the Chichibabin reaction is (53) rather than (52). The aromatic hydrogens of (53) occur as a 2H singlet at δ7.38; these are assigned to H-5 and H-6. The 1H singlet at δ7.38 is assigned to H-1. In this reaction the formation of (53) must have resulted from quaternisation at the nitrogen flanked by the methyl group.

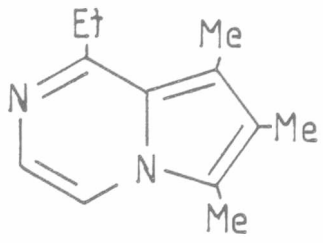
Reaction between 2,3-diethylpyrazine and (a) bromoacetone and (b) 3-bromobutan-2-one

Reaction between 2,3-diethylpyrazine and bromoacetone gave 1,2-dimethyl-8-ethyl-7-azaindolizine (54). The pmr of compound (54) showed two 3H singlets at δ2.21 and δ2.44 assigned to CH_3-1 and CH_3-2 respectively, a triplet at δ1.34(J=7.4Hz) and a quartet at δ3.06 due to the ethyl group at position 8. The 1H singlet at δ7.12 was assigned to H-3 and an AB doublet at δ7.40(J=4.7Hz) and δ7.48(J=4.7Hz) were assigned to H-6 and H-5 respectively.

The reaction between 2,3-diethylpyrazine and 3-bromobutan-2-one yielded 8-ethyl-1,2,3-trimethyl-7-aza-indolizine (55). The pmr of the above product (55) was similar to that of (54) except for the emergence of a 3H signal at δ2.48 assigned to CH_3-3 in the place of the 1H at δ7.12.



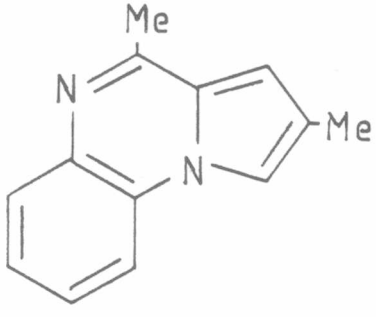
(54)



(55)

Reaction between 2,3-dimethylquinoxaline and bromoacetone

The reaction between 2,3-dimethylquinoxaline and bromoacetone, followed by treatment with base, gave 5,6-benzo-2,8-dimethyl-7-azaindolizine (56) in very low yield. The pmr of (56) consisted of two 3H singlets at δ2.35 and δ2.68 assigned to CH_3-2 and CH_3-8 respectively. The two 1H signals at δ6.68 and δ7.45 were weakly coupled and were assigned to H-1 and H-3. The benzo group showed four aromatic proton signals between δ7.25 and δ7.85.

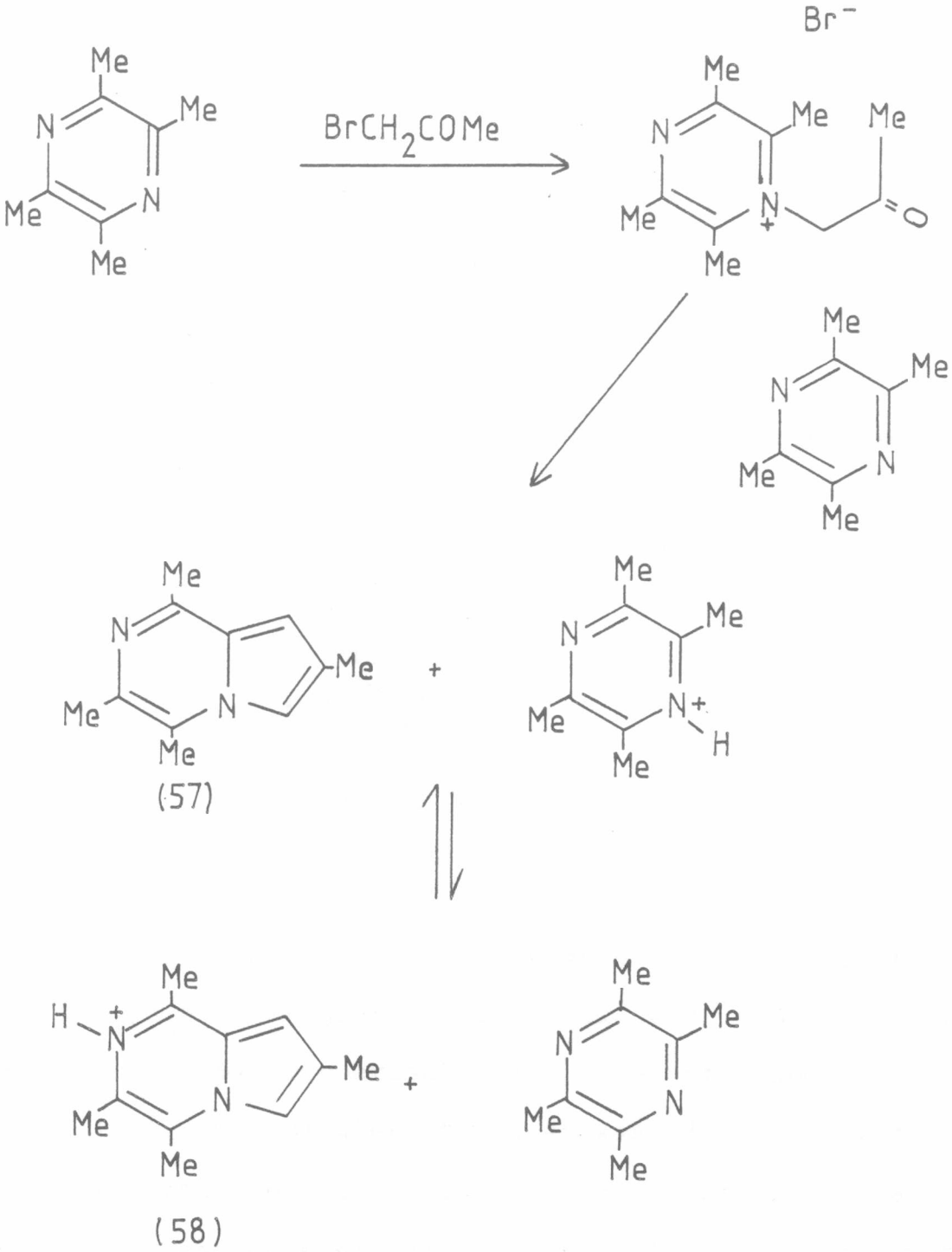


(56)

Reaction between 2,3,5,6-tetramethylpyrazine and (a) bromoacetone and (b) phenacyl bromide

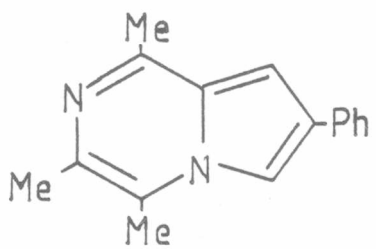
The reaction between 2,3,5,6-tetramethylpyrazine and bromoacetone followed by treatment with base gave 2,5,6,8-tetramethyl-7-azaindolizine (57) in 52% yield.

The pmr of compound (57) consisted of four 3H singlets at δ2.32, δ2.55, δ2.40 and δ2.48 and two 1H singlets at δ6.52 and δ7.01. When compared with spectrum of 2,6,8-trimethyl-7-azaindolizine (49), signals at δ2.32, δ2.40, δ2.48 and δ2.55 were assigned to CH_3-2, CH_3-5, CH_3-6 and CH_3-8. The weakly coupled signals at δ6.52 and δ7.01 were due to H-1 and H-3 respectively.



In this reaction some 2,5,6,8-tetramethyl-7-azaindolizinium hydrobromide (58) was isolated before the addition of sodium bicarbonate. The formation of salt (58) may be due to the tetramethylpyrazine acting as a base as shown above. The pmr of the 7-azaindolizinium hydrobromide salt (58) showed four 3H singlets at δ2.44, δ2.55, δ2.79 and δ3.10 assigned to CH_3-2, CH_3-5, CH_3-6 and CH_3-8 respectively, and two 1H signals at δ7.20 and δ7.50, due to H-1 and H-3 respectively. Addition of sodium bicarbonate to salt (58) gave 2,5,6,8-tetramethyl-7-azaindolizine whose pmr spectrum was identical to that of the previous compound (57).

Similarly the reaction between 2,3,5,6-tetramethylpyrazine and phenacyl bromide yielded 16% of 2-phenyl-5,6,8-trimethyl-7-azaindolizine (59). Again in this reaction, some of the 7-azaindolizinium hydrobromide was isolated before the addition of bicarbonate to the pyrazinium salt.



(59)

The pmr of compound (59) consisted of two singlets at δ2.48 and δ2.65 integrating for six and three protons respectively. By comparison with the pmr spectrum of compound (57), the singlet at δ2.48 was due to CH_3-5 and CH_3-6 while the one at δ2.65 was assigned to CH_3-8. At lower field, resonance signals at δ7.00 and δ7.30 were

ascribed to H-1 and H-3 respectively and a complex multiplet between δ7.35 and δ7.80 assigned to the phenyl protons at position C-2.

The pmr spectra of alkyl and aryl 7-azaindolizines

The detailed analysis of the parent 7-azaindolizine (5) was reported by Paudler et al.[43] They found that the ring protons were generally situated between δ6.85 and δ8.91. H-1 was found at δ6.85, H-2 at δ6.97, H-3 at δ7.46, H-5 at δ7.89, H-6 at δ7.58 and H-8 at δ8.91.

In this work, the ring protons resonances were found to occur at a progressively higher field in the order of H-8, δ ≃8.6; H-5, δ≃7.4; H-6, δ≃7.3; H-3, δ≃7.1 and H-1, δ≃6.6. These observations were found to be consistent with the values quoted by Paudler. The methyl groups were assigned by close comparative examination of related spectra and on the proximity to the nitrogen atom. Thus, the ring methyl absorptions were generally found to occur at progressively higher field in the order of CH_3-8, δ≃2.61; CH_3-6, δ≃2.50; CH_3-5, δ≃2.45; CH_3-3, δ≃2.37; CH_3-2, δ≃2.31 and CH_3-1, δ ≃2.20. The chemical shifts of the protons of the alkyl and aryl 7-azaindolizines are listed in Table I.

Table I. Chemical shifts (δ) in the 60 MHz spectra of alkyl and aryl 7-azaindolizines in $CDCl_3$.

7-Azaindolizine	1	2	3	5	6	8
Parent[27,28]	6.85	6.97	7.46	7.89	7.58	8.91
2,3,6-Trimethyl (43)	6.68	2.28	2.36	7.38	2.43	8.60
2-Ph-3,6-dimethyl (44)	6.83	7.43	2.45	7.35	2.52	8.70
2,8-Dimethyl (45)	6.55*	2.35	7.14*	7.32d (J=5.5Hz)	7.55d (J=5.5Hz)	2.60
8-Methyl-2-t-butyl (46)	6.55*	1.40	7.14*	7.35d (J=5.5Hz)	7.55d (J=5.5Hz)	2.80
8-Methyl-2-phenyl (47)	6.77	7.26-7.70m(8H,Ph-2,H-3,H-5,H-6)				2.66
2,3,8-Trimethyl (48)	6.55	2.27	2.32	7.55	7.55	2.60
2,6,8-Trimethyl (49)	6.40*	2.28	6.98*	7.28	2.30	2.54
6,8-Dimethyl-2-Ph (50)	7.00[7.29-7.77(7H,Ph-2,H-3&H-5)]				2.41	2.69
2,3,6,8-Tetramethyl (51)	6.54	2.28	2.32	7.25	2.60	2.60
2,3-Dimehtyl-8-ethyl (53)	6.58	2.25	2.30	7.38	7.38	2.90q 1.35t
1,2-Dimethyl-8-ethyl (54)	2.21	2.44	7.12	7.40 (J=4.7Hz)	7.48 (J=4.7Hz)	3.06q 1.34t
1,2,3-Trimethyl-8-ethyl (55)	2.19	2.34	2.48	7.33	7.33	3.08q 1.35t
2,8-Dimethyl-5,6-benzo (56)	6.69*	2.35	7.45*	7.25-7.95m		2.68
2,5,6,8-Tetramethyl (57)	6.52*	2.32	7.01*	2.40	2.48	2.55
2-Ph-5,6,8-trimethyl (59)	7.00	7.35-7.80m	7.30	2.48	2.48	2.65

Unless otherwise stated values given refer to singlet absorption.

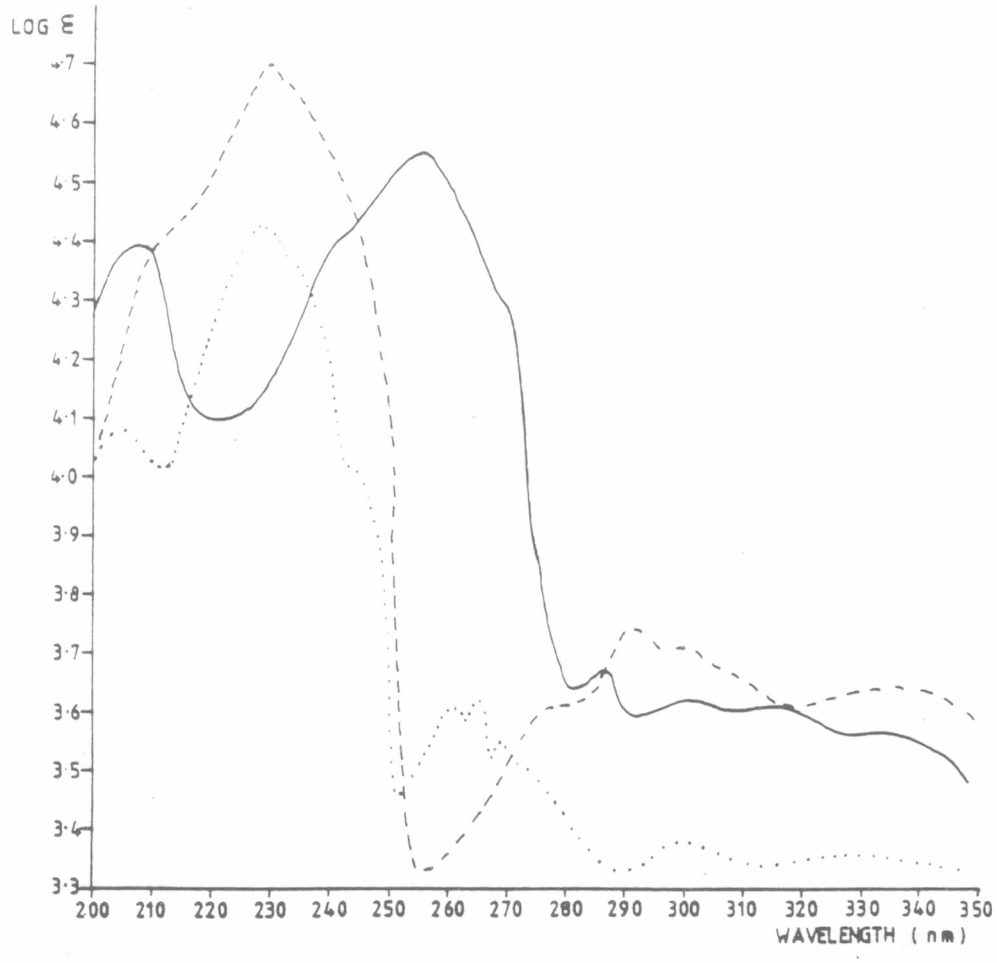
d = doublet; t = triplet; q = quartet; m = multiplet.

Coupling constants(Hz) are approximate and measured directly from spectra. Signals marked by asterisks are broadened and/or further split.

Ultra-violet spectra of alkyl and aryl 7-azaindolizines

The uv absorption spectrum of 7-azaindolizine is similar to that of indolizine and other azaindolizines[74]. In general the spectra consist of three main bands which are found at about 210-240nm, 250-280nm and 290-369nm respectively. As shown in Figure 1, simple alkyl substituents generally have little effect on the spectra. However, the presence of a phenyl group on the ring system induced a hypsochromic shift of about 15nm.

Figure 1. uv spectra of alkyl and aryl 7-azaindolizine



8-methyl-2-phenyl-7-azaindolizine (————)

2,8-dimethyl-7-azaindolizine (--------)

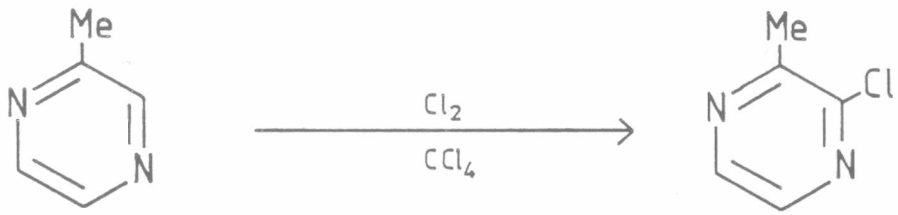
2,5,8-trimethyl-7-azaindolizine (.....)

Synthesis of chloro-, methoxy-, carboethoxy-, and amino-7-azaindolizines

In addition to the alkyl- and aryl- 7-azaindolizines, other substituted 7-azaindolizines have been successfully synthesised from appropriate pyrazines and α-haloketones.

Attempted synthesis of 8-chloro-2-methyl-7-azaindolizine

2-chloro-3-methylpyrazine[69] was prepared in good yield by reacting methylpyrazine with chlorine in carbon tetrachloride.



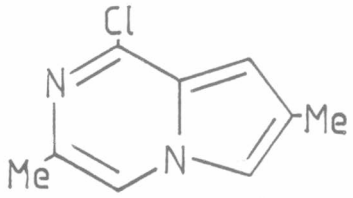
Reaction between 2-chloro-3-methylpyrazine and bromoacetone gave a salt which on treatment with base yielded an oil from which no identifiable products could be isolated.

Reaction between 3-chloro-2,5-dimethylpyrazine and (a) bromoacetone and (b) phenacyl bromide

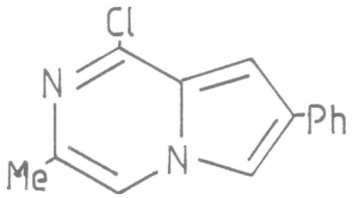
The reaction between 3-chloro-2,5-dimethylpyrazine and bromoacetone gave a crude oil which on separation by preparative tlc gave a colourless crystalline compound in low yield. The mass spectrum of the compound showed a base peak at m/e 180 and another peak at m/e 145 (25%) corresponding to the loss of a chlorine atom from the

molecular ion. The pmr spectrum consisted of two 3H singlets at δ2.33 and δ2.38 indicating the presence of two ring methyl groups and at lower field, signals at δ6.55, δ7.20 and δ7.48 showed three aromatic protons. These observations are therefore consistent with the structure of 8-chloro-2,6-dimethyl-7-azaindolizine (60).

Similarly, reaction between 3-chloro-2,5-dimethylpyrazine and phenacyl bromide gave 8-chloro-6-methyl-2-phenyl-7-azaindolizine (61) in 9% yield.



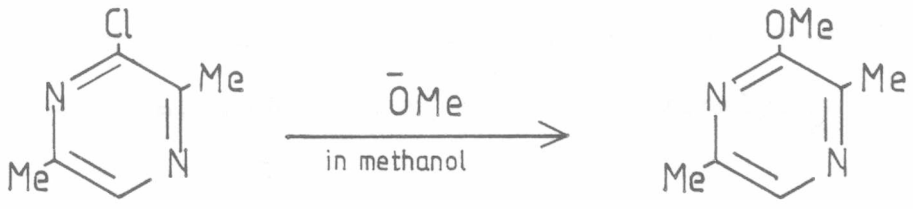
(60)



(61)

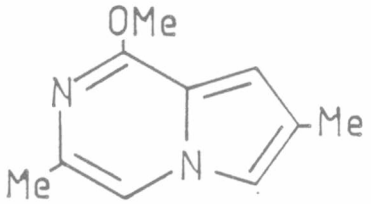
Reaction between 2,5-dimethyl-3-methoxypyrazine and (a) bromoacetone and (b) phenacyl bromide

The methoxypyrazines[70] were prepared by nucleophilic substitution of the chlorine by a methoxide ion. For example 2,5-dimethyl-3-methoxypyrazine was prepared by the action of sodium methoxide on 3-chloro-2,5-dimethylpyrazine in methanol.

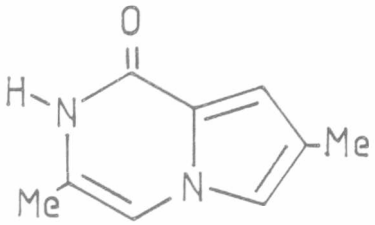


Reaction between 2,5-dimethyl-3-methoxypyrazine and bromoacetone gave an oil which, on fractional distillation gave a yellow oil and a colourless crystalline solid. The pmr spectrum of the yellow oil showed a 6H singlet at δ2.25, a 3H singlet at δ4.00 and three 1H signals at δ6.51, δ6.95 and δ7.14. These pmr signals are assigned to CH_3-2, CH_3-6, the methoxy methyl and the 1H aromatic field signals to H-1, H-3 and H-5 respectively. The above observations indicate the structure of the product to be 2,6-dimethyl-8-methoxy-7-azaindolizine (62). Solution of (62) in ethanol followed by addition of perchloric acid gave a monoperchlorate salt. The pmr spectrum of the perchlorate salt in DMSO-d_6 showed signals at lower field, but with a pattern similar to the free base (62).

The colourless crystalline solid showed strong C=O and N-H absorption bands at 1650 cm^{-1} and 3160 cm^{-1} respectively. The pmr spectrum showed two 3H singlets at δ2.16 and δ2.21 attributable to two methyl groups and two signals at δ6.61 and δ6.87 integrating for three protons indicating the presence of three aromatic type protons. The mass spectrum of this solid consisted of a base peak at m/e 162 and another strong peak at m/e 161 (50%). These spectral details indicate the compound to be 2,6-dimethyl-7-azaindolizin-8(7H)-one (63). A compound with identical spectral characteristics was produced when the 2,6-dimethyl-8-methoxy-7-azaindolizine (62) was hydrolysed with acid as shown in Chapter 3.

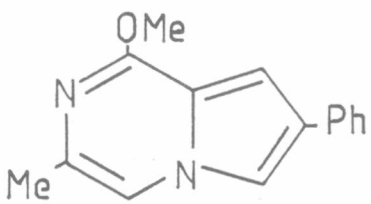


(62)



(63)

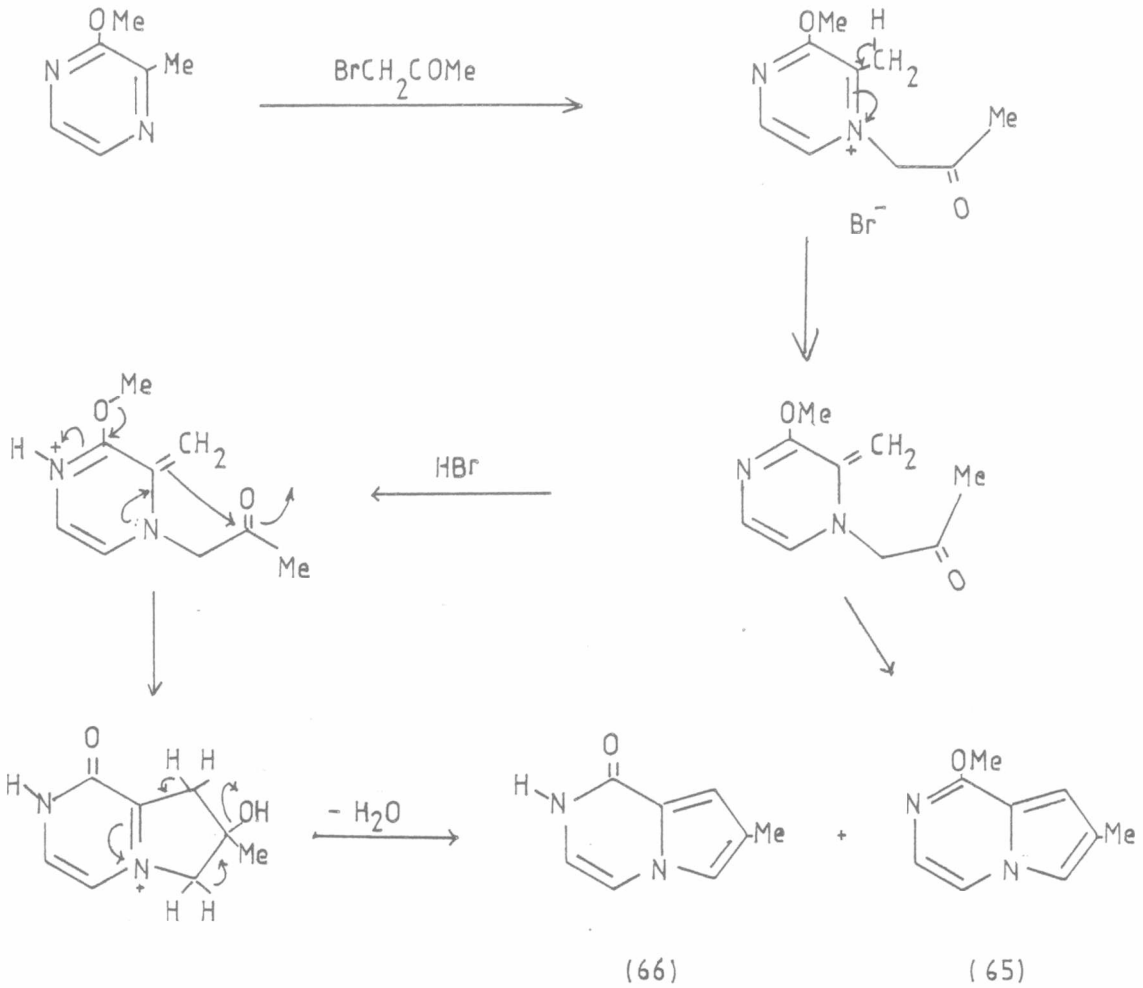
The reaction between 2,5-dimethyl-3-methoxypyrazine and phenacyl bromide afforded 8-methoxy-6-methyl-2-phenyl-7-azaindolizine (64); none of the azaindolizinone was isolated.



(64)

Reaction between 3-methoxy-2-methylpyrazine and bromoacetone

In an analogous reaction 3-methoxy-2-methylpyrazine with bromoacetone gave 8-methoxy-2-methyl-7-azaindolizine(65) and 2-methyl-7-azaindolizin-8(7H)-one (66). A possible mechanism for the formation of these products is shown below.

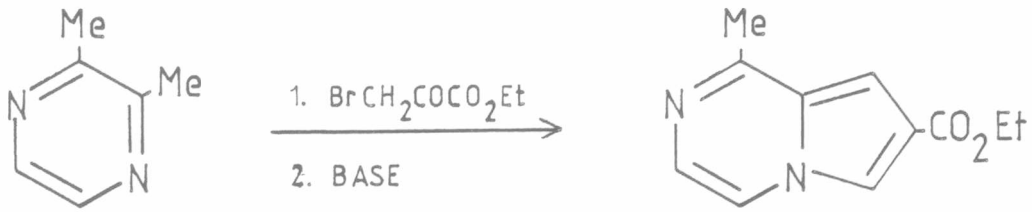


(66) (65)

Reaction between 2,3-dimethylpyrazine and ethylbromo pyruvate.

Treatment of 2,3-dimethylpyrazine with ethylbromo-pyruvate gave pale yellow crystals whose ir spectrum showed a strong carbonyl absorption at 1700 cm^{-1} indicating the presence of a carboethoxy group. The pmr spectrum of the product showed signals at δ1.35 as a triplet integrating for three protons and at δ4.35 as a quartet integrating for two protons. This set of signals confirms the presence of a carboethoxy group. At δ2.62 a 3H singlet was due to the methyl group. At lower field two 1H singlets at δ7.15 and δ7.81 and a 2H AB doublet centered at δ7.40 and δ7.60 were assigned to H-1, H-3, H-6 and H-5 respectively. Thus the

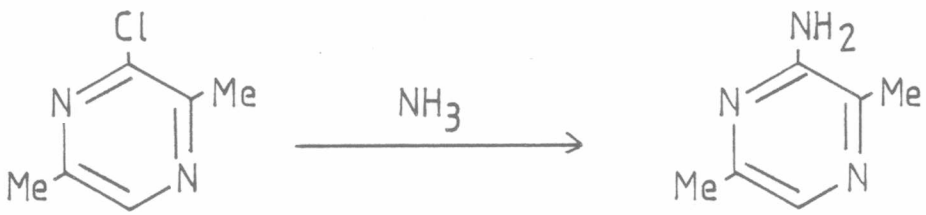
above observations are consistent with the structure of 2-carboethoxy-8-methyl-7-azaindolizine (67).



(67)

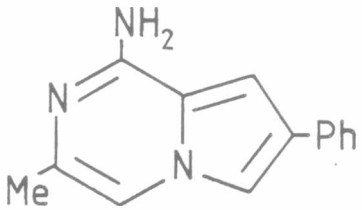
Reaction between 2-amino-3,6-dimethylpyrazine and (a) phenacyl bromide and (b) bromoacetone

2-Amino-3,6-dimethylpyrazine[70] was prepared by heating 2-chloro-3,6-dimethylpyrazine under pressure with ammonia whereupon direct displacement of chlorine by ammonia occurred:

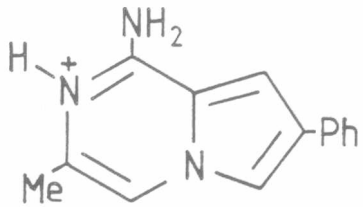


The reaction between 2-amino-3,6-dimethylpyrazine with phenacyl bromide gave a straw-coloured solid whose ir spectrum showed an N-H signal at 3160 cm^{-1}. The pmr spectrum consisted of a 3H singlet at δ2.24, a broad 2H signal at δ4.40, 1H singlet at δ6.78 and an 8H complex multiplet between δ7.30 and δ7.67 ascribed to a methyl group, an amino group, a phenyl group and three aromatic

ring protons. The structure of the compound is proposed to be 8-amino-6-methyl-2-phenyl-7-azaindolizine (68). Reaction with perchloric acid in ethanol gave the corresponding salt (69).



(68)



(69)

The pmr spectrum of the salt (69) in DMSO consisted of a singlet at δ2.25, a complex multiplet between δ7.30 and δ8.20 and a broad signal at δ8.60 which were attributed to CH_3-6, Ph-2, H-1, H-3 and NH_2-8 respectively. Further downfield at δ12.20 a broad signal integrating for one proton was assigned to the quaternary proton on N-7 hence confirming that protonation has occurred on the non-bridgehead nitrogen (N-7).

Reaction between 2-amino-3,6-dimethylpyrazine and bromoacetone gave a dark red salt which upon basification regenerated the starting 2-amino-3,6-dimethylpyrazine.

Conclusions

The Chichibabin reactions described in this Chapter provide convenient routes to a number of 7-azaindolizines. 2,3-Dimethyl, 2,3,5-trimethyl and 2,3,5,6-tetramethylpyrazines give alkyl and aryl 7-azaindolizines. 3-Chloro-2,5-dimethyl, 3-methoxy-2-methyl and 2-amino-3,6-dimethylpyrazines afford the corresponding 8-chloro-, 8-methoxy- and 8-amino-7-azaindolizines respectively. Generally the yields obtained were fair (more than 15%) except in the case for the 8-chloro-7-azaindolizines where the yields were very low (0.5-10%). 3-Methoxy-2-methylpyrazines also gave 7-azaindolizin-8(7H)-ones.

Chapter 3

CHEMICAL REACTIVITY OF 7-AZAINDOLIZINES

7-Azaindolizine is a 10π nitrogen heteroaromatic system with the seven sp^2 hybridised carbons and the non-bridgehead nitrogen contributing one electron each, and the bridgehead nitrogen two electrons to make up the aromatic dectet. The π-electron densities of the rings centres of the 7-azaindolizine system have been calculated[22,43] and are shown in Table II. The electron density calculations, while showing the two nitrogen centres to have the highest electron density, indicate electrophilic substitution to take place preferentially at C-3 and C-1 and nucleophilic substitution to most likely occur at the most electron deficient site. This chapter discusses the reactivity of 7-azaindolizine and its derivatives.

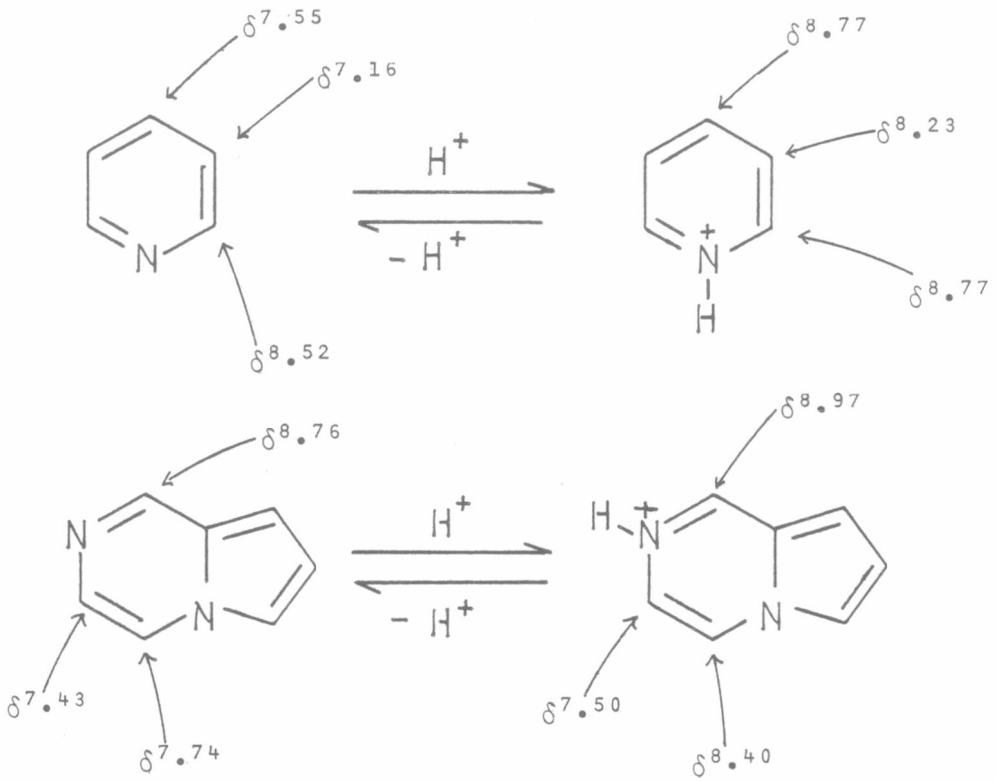
Table II. π-Electron Densities of 7-azaindolizine[43]

Position	Electron densities
1	1.13
2	1.07
3	1.10
4	1.50
5	0.98
6	1.02
7	1.27
8	0.88
9	1.04

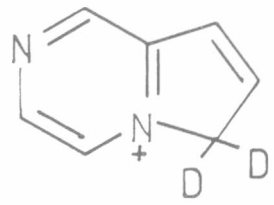
Deuterium exchange and protonation of 7-azaindolizine and its alkyl and aryl derivatives

The sites of protonation of the 7-azaindolizines were examined by studying their pmr spectra in CF_3COOH. These spectra indicate that the parent 7-azaindolizine (5) and its alkyl and aryl derivatives all protonate solely at the non bridgehead nitrogen and that there was no evidence of protonation occurring at a carbon atom. For example the pmr spectra of 7-azaindolizine (5) itself in CF_3COOH showed no resonances in the region between δ4.00 and δ6.00 which would have been expected if protonation had occurred at C-1 or C-3 (cf alkyl and aryl 5-azaindolizines and some of the 6- and 8-azaindolizines in CF_3COOH all showed a methine or a methylene signal in this region due to C-1 or C-3 protonation). The pattern of the pmr signals of 7-azaindolizine (5) in CF_3COOH was similar to that in $CDCl_3$

except that there had been a downfield shift of all the signals in the CF_3COOH solvent. The ring protons which experienced the smallest downfield shift are H-8 and H-6. These observations imply protonation to have occurred at N-7 by analogy with the chemical shift of pyridine[71,72] which on protonation at nitrogen shows a large downfield shift of its β- and γ- protons (Δδ relative to the free base was 1.07 and 1.22 ppm) but only a relatively small shift of its α-protons (Δδ 0.25ppm).



The pmr spectrum of 7-azaindolizine in CF_3COOD was identical to that in CF_3COOH and showed no evidence of the diminution of the signals due to ring protons. This indicates deuterium exchange to have occurred at N-7 and excludes even a low concentration of a carbon deuterated cation such as (70).



(70)

Table III shows the pmr resonances for some alkyl and aryl substituted 7-azaindolizines. All these compounds show the absence of signals between δ4.00 and δ6.00 and thus give evidence for protonation at the non-bridgehead nitrogen. 7-Azaindolizine and its alkyl and aryl derivatives therefore exclusively protonate at the non bridgehead nitrogen to give the corresponding 10π 7-azaindolizinium cation.

Table III. Chemical shift (δ) in the 60 MHz pmr spectra of 7-azaindolizines in CF_3COOH

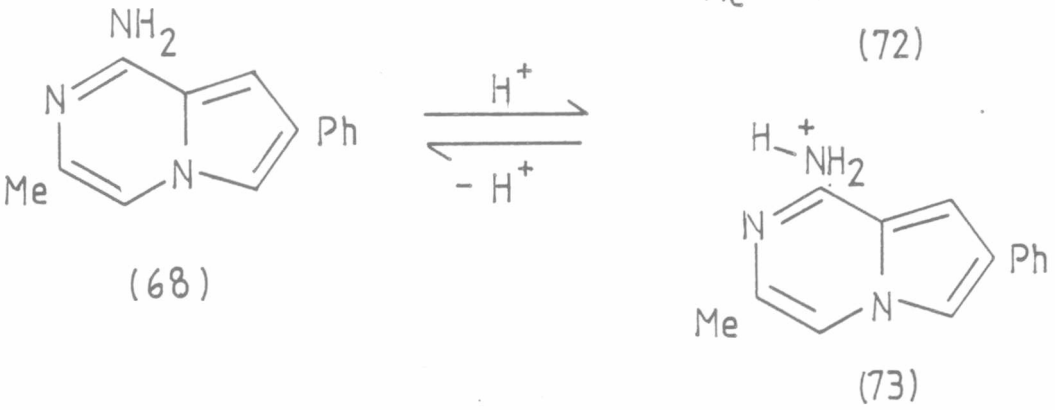
Structure	1	2	3	5	6	8
(45)	7.54*	2.54	7.95*	8.15d (J=5.3Hz)	7.32d (J=5.3Hz)	2.98
(48)	7.55	2.48	2.62	7.92d (J=5.7Hz)	7.38d (J=5.7Hz)	2.92
(49)	7.47*	2.49	7.88*	7.95	2.55	2.95
(57)	7.44*	2.52	7.84*	2.60	2.62	2.90
(56)	7.64*	2.55	8.42*	7.60-8.24m		2.68

Deuterium exchange and protonation of 2,6-dimethyl-8-methoxy-7-azaindolizine (62) and 8-methoxy-2-methyl-7-azaindolizine (65)

The deuterium exchange and protonation studies of both 2,6-dimethyl-8-methoxy-7-azaindolizine (62) and 8-methoxy-2-methyl-7-azaindolizine (65) paralleled that of the alkyl and aryl 7-azaindolizines. For example, the CF_3COOH pmr spectrum of compound (62) showed a general downfield shift of its signals relative to its $CDCl_3$ spectrum. It showed no 2H singlet in the region of δ4.00 and δ6.00 suggesting that protonation has occurred at N-7. The 6H singlet at δ2.25 was assigned to CH_3-3 and CH_3-6, a 3H singlet at δ4.40 was due to OCH_3-8 and three 1H singlets at δ7.30, δ7.40 and δ7.50 were attributed to H-1, H-3 and H-5 respectively. Also in marked contrast to 5- and 7- methoxy 6- and 8-azaindolizines, the 8-methoxy-7-azaindolizines (62) and (65) showed no exchange of protons at positions 3 and 1.

Deuterium exchange and protonation of 8-amino-6-methyl-2-phenyl-7-azaindolizine (68) and 8-amino-2-methyl-7-azaindolizine (71)

The pmr spectrum of 8-amino-6-methyl-2-phenyl-7-azaindolizine (68) in CF_3COOH showed no midfield 2H singlet and this suggests protonation to occur either on N-7 or the exocyclic 8-amino group to give the corresponding conjugate acid (72) or (73).



(68) (72) (73)

The perchlorate salt of compound (68) was also prepared as described on page 45 and its pmr spectrum in DMSO-d_6 showed evidence of a broad 1H signal at δ12.20 which was attributed to the proton on the quaternary nitrogen at position 7. Similar observations were obtained when the pmr spectrum of 8-amino-2-methyl-7-azaindolizine (71) was recorded in CF_3COOH. Thus these 8-amino-7-azaindolizines are also believed to protonate at N-7.

(74) (75)

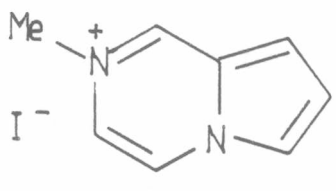
In contrast to alkyl, aryl, and methoxy substituted 7-azaindolizines, 8-amino-6-methyl-2-phenyl-7-azaindolizine

(68) and 8-amino-2-methyl-7-azaindolizine (71) when its pmr spectrum was recorded in CF_3COOD showed exchangeable protons at C-3 and C-1. This implies that compounds (68) and (71) establish a low equilibrium concentration of the corresponding conjugate acids(for example (74) and (75)).

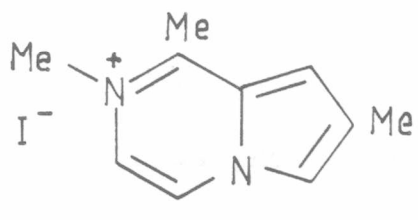
Quaternisation

Treatment of 7-azaindolizine (5) with methyl iodide in ethanol gave a quaternary salt as yellow crystals. The pmr spectrum of this salt in CF_3COOH showed a 3H singlet at δ4.12, the remaining signals in the spectrum occurred at lower field between δ7.30 and δ8.98 which integrated for six protons and were identical in pattern to the CF_3COOH spectrum of the parent base (5). This implies that quaternisation has taken place at the N-7 position to give the salt (76)

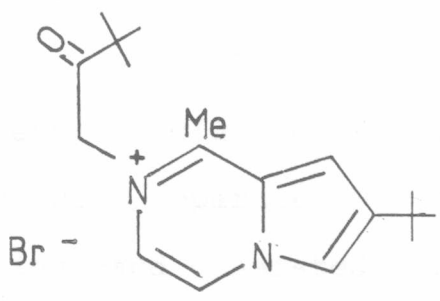
Similarly 2,8-dimethyl-7-azaindolizine (45) on reaction with methyl iodide gave the salt (77). Here again the quaternary methyl protons at N-7 were observed at δ4.08.



(76)



(77)



(78)

Quaternisation of 7-azaindolizines with various α-haloketones was used in the first step of the Chichibabin synthesis of dipyrrolo[1,2-a:2,1-c]pyrazines as described in Chapter 4. Generally these salts were not isolated but reacted with bicarbonate to give the dipyrrolo[1,2-a:2,1-c]-pyrazines. However the salt (78) resulting from the reaction of 8-methyl-2-t-butyl-7-azaindolizine (45) with bromopinacolone was isolated and characterised. Its pmr spectrum in CF_3COOH showed two 9H singlets at δ1.45 and δ1.48 due to the two tertiary butyl groups, a 3H singlet at δ2.85 assigned to CH_3-8, a 2H singlet at δ5.68 attributable to the methylene group of the α-haloketone. Further downfield, two 1H singlets at δ7.62 and δ8.08 were due to H-1 and H-3 respectively and a 2H AB doublet at δ7.20 and δ8.20 were assigned to H-5 and H-6 respectively.

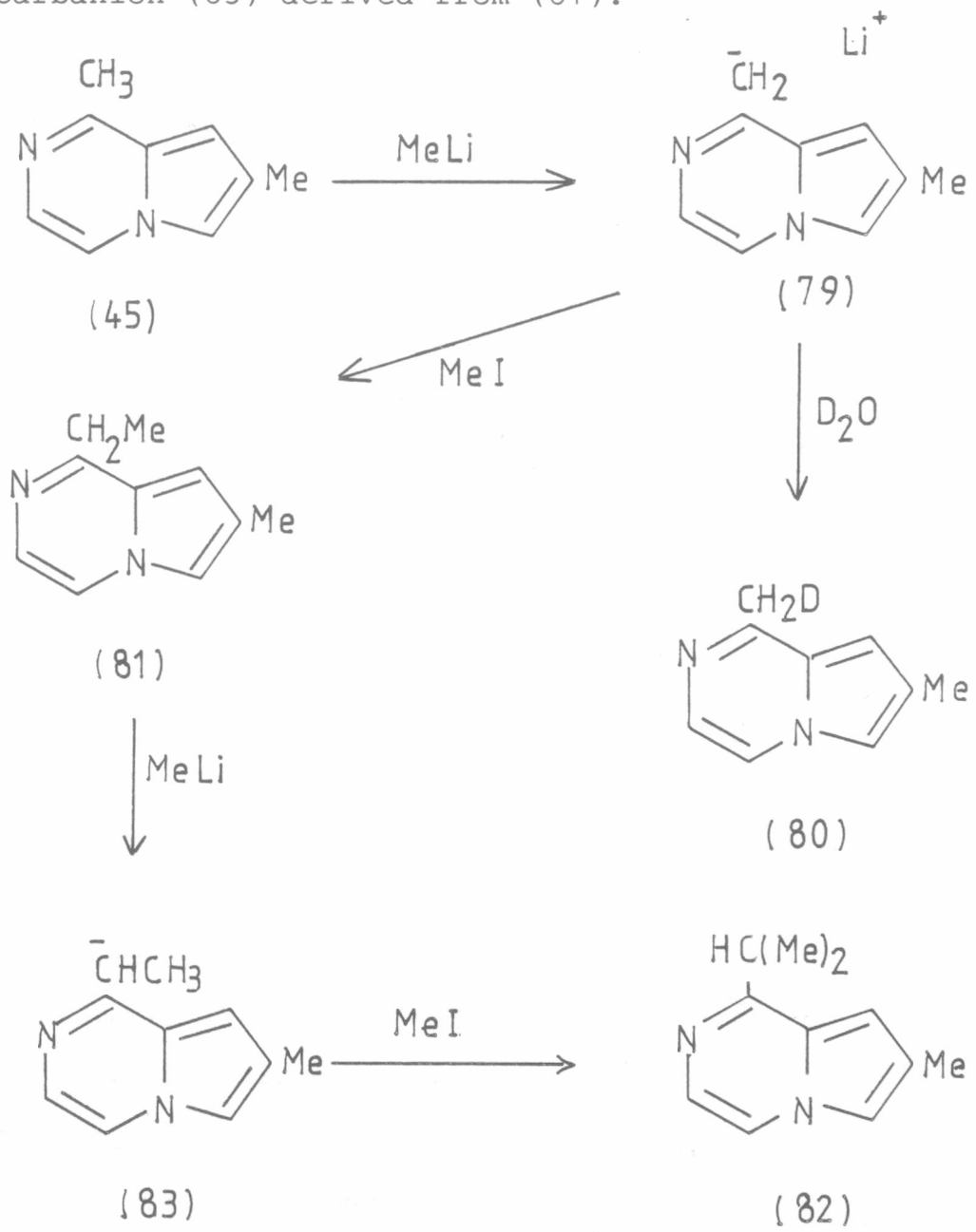
Lithiation

Treatment of 2,8-dimethyl-7-azaindolizine (45) with methyl lithium in dry ether gave a red solution due to the formation of the lithio salt (79). Addition of D_2O afforded a compound whose pmr spectrum differed from (45) only in the intensity of the singlet at δ2.52, attributed to CH_3-8. This signal now integrates for two protons, thus indicating the formation of the deutero compound (80).

Addition of methyl iodide to the lithio salt (79) gave two products which were separated by tlc. The pmr spectrum of the faster moving band consisted of a 3H methyl singlet at δ2.32, an ethyl group represented by a 2H quartet at

δ2.90 and a 3H triplet at δ1.35, and at lower field two 1H singlets at δ6.60 and δ7.14 and a 2H AB doublet centered at δ7.35 and δ7.55 attributable to ring protons. This evidence indicates the formation of 8-ethyl-2-methyl-7-azaindolizine (81).

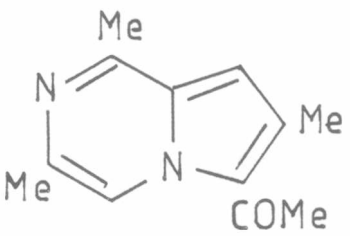
The slower moving band gave 8-isopropyl-2-methyl-7-azaindolizine (82). Its pmr spectrum showed a 6H doublet at δ1.28 and δ1.38 and a methine multiplet centered at δ3.22 due to the isopropyl group. This compound (82) is formed <u>via</u> the carbanion (83) derived from (81):



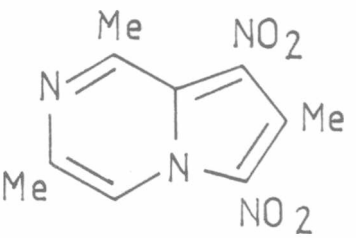
Reactions with electrophiles

Acetylation

Refluxing a solution of 2,8-dimethyl-7-azaindolizine (45) in acetic anhydride gave the mono acetyl derivative in low yield. The pmr spectrum of this compound when compared with that of the precursor (45) showed the absence of the signal attributed to H-3, the emergence of an additional 3H methyl singlet, and a downfield peri shift of 120Hz in the position of the signal attributed to H-5. Thus the resonance signals in the pmr of this compound are assigned as follows: the three 3H singlets at δ2.59, δ2.65 and δ2.70 were due to CH_3-2, CH_3-8 and the acetyl methyl at C-3, the 1H singlet at δ6.62 to H-1 and the AB doublet centered at δ7.72 and δ9.54 were assigned to H-6 and H-5(J=7.0Hz) respectively. From the above evidence, acetylation was concluded to have occurred at C-3 to give 3-acetyl-2,8-dimethyl-7-azaindolizine (84)



(84)



(85)

Nitration

When 2,6,8-trimethyl-7-azaindolizine (49) was added to a mixture of concentrated nitric and sulphuric acids at 0°C, a 1,3-dinitro derivative (85) was obtained. The pmr spectrum of this derivative showed a 3H singlet at δ2.60 due to

CH_3-2, a 6H singlet at δ2.80 attributed to CH_3-6 and CH_3-8 and a 1H singlet at δ9.18 due to H-5. The latter singlet showed a large downfield shift of about 115Hz when compared with the corresponding signal of the starting compound (49). This shift is due to the nitro group at position C-3 exerting an anisotropic deshielding effect on the peri oriented H-5 proton.

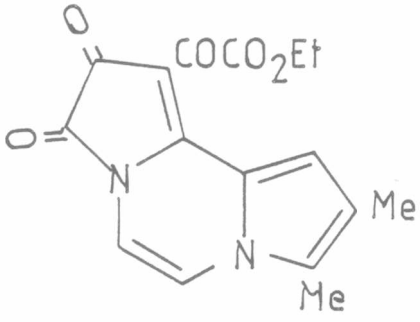
Attempted formylation

The reaction of 2,8-dimethyl-7-azaindolizine (45) with phosphoryl chloride and dimethylformamide at 40°C gave a dark green oil from which only starting material was recovered.

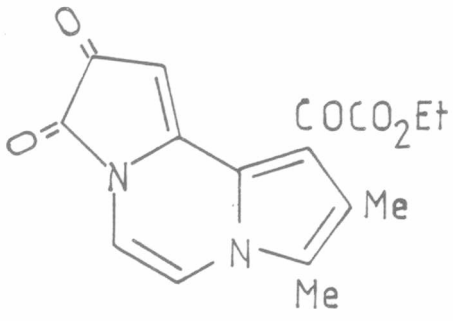
Reaction between 2,3,8-trimethyl-7-azaindolizine and ethoxalyl chloride

A mixture of 2,3,8-trimethyl-7-azaindolizine (48) and excess ethoxalyl chloride in dichloromethane afforded a red solid which melted at 250°C. The ir spectrum of this solid showed carbonyl absorptions at 1730 cm^{-1} and 1770 cm^{-1}. The mass spectrum consisted of a molecular ion at m/e 314(15%) and the base peak was found at m/e 241 resulting from the loss of a COOEt unit from the molecular ion. This evidence suggests that two molecules of ethoxalyl chloride were involved in the reaction with one molecule of 7-azaindolizine (48). The pmr spectrum of the product showed the presence of an ethyl group manifested by a 2H quartet at δ4.28 and a 3H triplet at δ1.28. It also showed only two methyl singlets at δ2.24 and δ2.52 suggesting that one of the methyl groups of the trimethyl-7-azaindolizine (48) may

have reacted with the ethoxalyl chloride. The only other pmr signals were a 2H AB doublet centered at δ7.40 and δ7.70 and a 1H singlet at δ8.49. These observations indicate the red product to be either (86) or (87).



(86)



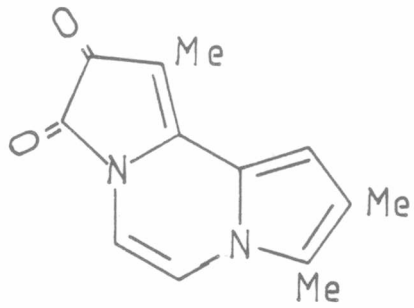
(87)

Further evidence from the cmr spectrum of the product supports the proposed structures. It consists of three singlets at δ13.20, δ14.50 and δ17.00 from the sp^3 hybrid carbons of the methyl groups and a singlet at δ64.00 from the carbon of the methylene group. There were also five quaternary carbons at δ106.00, δ122.00, δ132.00, δ124.50 and δ151.50, three methine carbons at δ112.00, δ114.50 and δ129.50 and four carbonyl carbons at δ177.20, δ177.50, δ180.18 and δ180.22.

Reaction between 2,3-dimethyl-8-ethyl-7-azaindolizine and ethoxalyl chloride

The reaction between 2,3-dimethyl-8-ethyl-7-aza-indolizine (53) and ethoxalyl chloride similarly gave a single product. Its mass spectrum showed a molecular ion at m/e 228(24%) followed by three other fragmentation ions at

m/e 200(28%), m/e 172(80%) and m/e 171(100%) which resulted from the consecutive loss of two CO units and one H atom respectively. The ir spectrum of this compound showed carbonyl absorption at 1745 cm^{-1}. The pmr spectrum indicated three 3H singlets at δ1.91, δ2.12 and δ2.29, a 2H AB doublet centered at δ6.47 and δ6.70 and a 1H singlet at δ6.91. These observations are consistent with structure (88). The resonance signals of compound (88) were assigned as follows: the three 3H singlets at δ1.91, δ2.12 and δ2.29 were due to CH_3-10, CH_3-2 and CH_3-3 respectively, the AB doublet at δ6.47 and δ6.70 to H-5 and H-6 and the 1H singlet at δ6.91 to H-1.

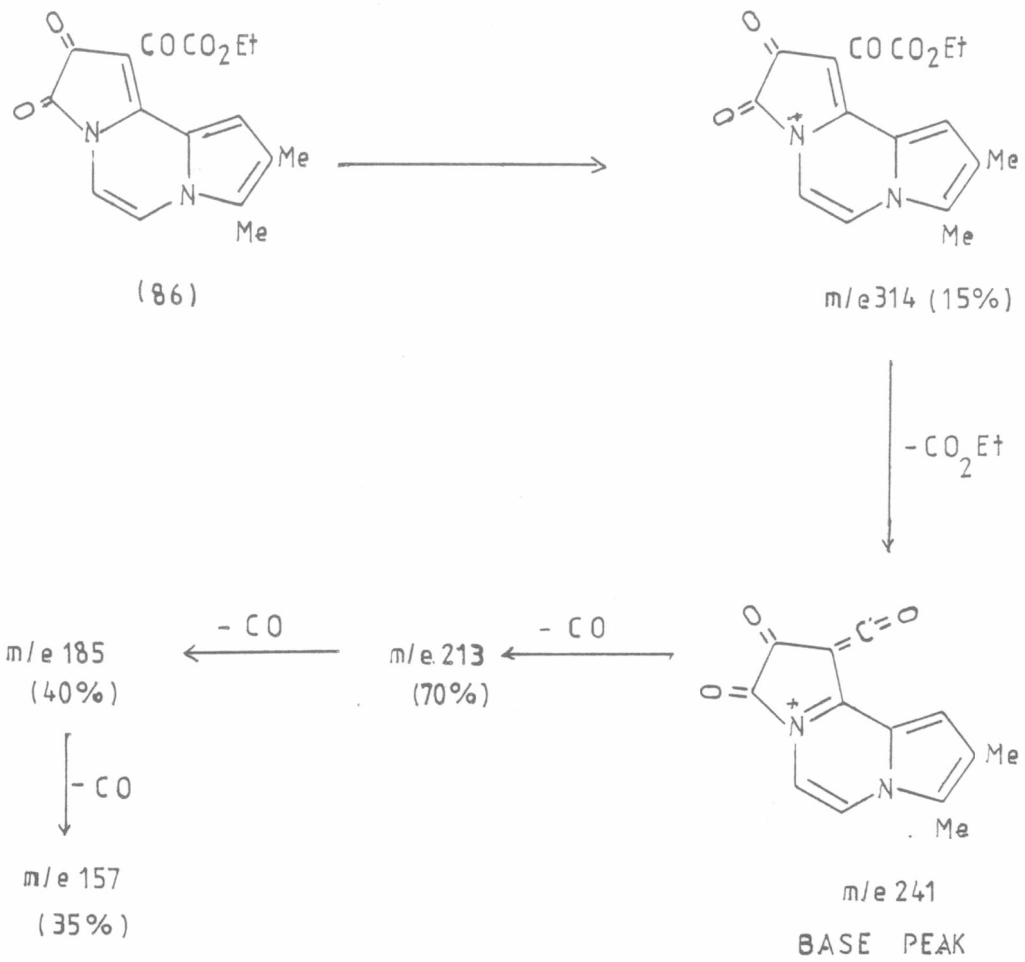


(88)

As this compound possesses no $COCOOCH_2CH_3$ at C-1, it implies that position 1 resists electrophilic attack with excess ethoxalyl chloride. Thus it is inferred that the structure of the red compound from the reaction of 2,3,8-trimethyl-7-azaindolizine (48) and ethoxalyl chloride is (86) rather than (87).

Mass spectrum of compounds (86) and (88)

The mass spectra of compounds (86) and (88) are shown in Figs. 2 and 3 respectively. Compound (86) showed a weak molecular ion at m/e 314(15%) and a base peak at m/e 241 due to the loss of COOEt. The three other significant ions were found at m/e 213(70%), m/e 185(40%) and m/e 157(35%) and were accounted for the consecutive loss of three molecules of CO from the base peak.



In contrast to compound (86), the mass spectrum of compound (88) showed no loss of ester group but the loss of two molecules of CO and a hydrogen atom from the molecular ion at m/e 228(24%) to give the base peak at m/e 171.

Figure 2. Mass spectrum of compound (86)

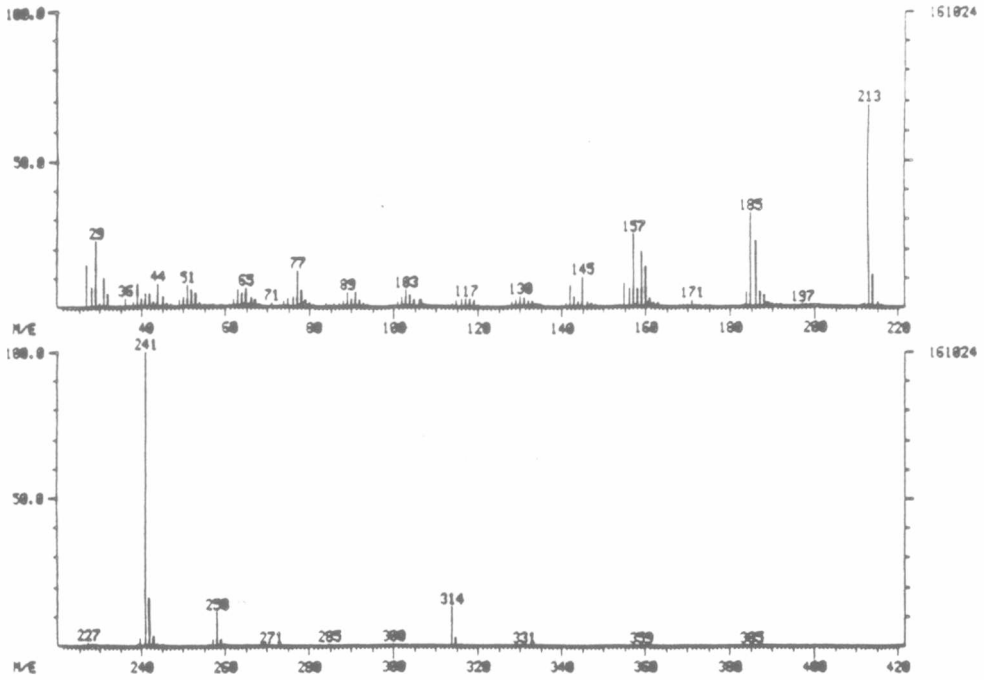
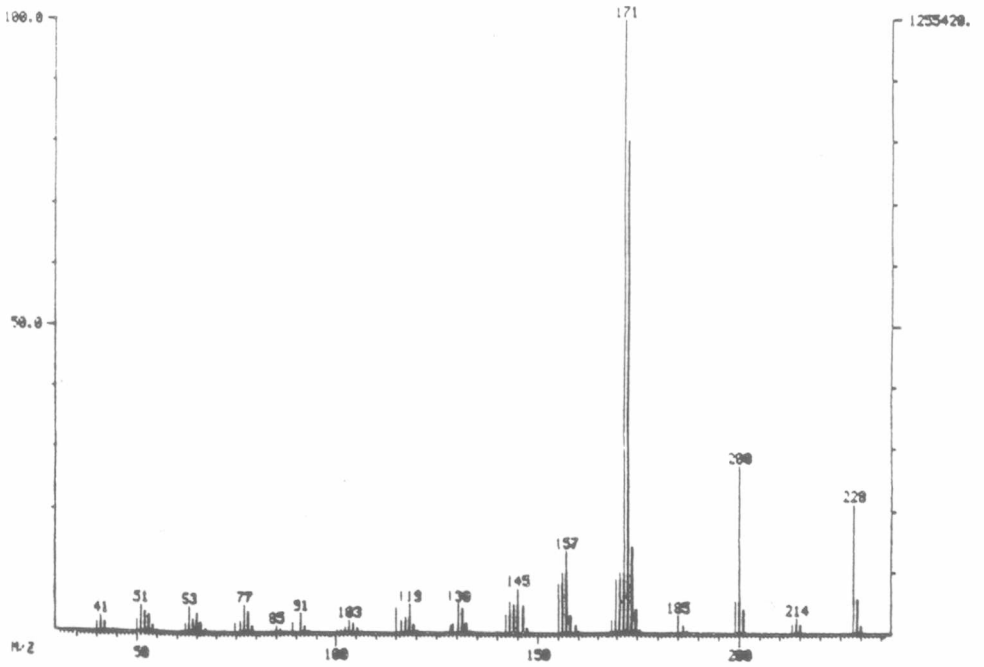


Figure 3. Mass spectrum of compound (88)

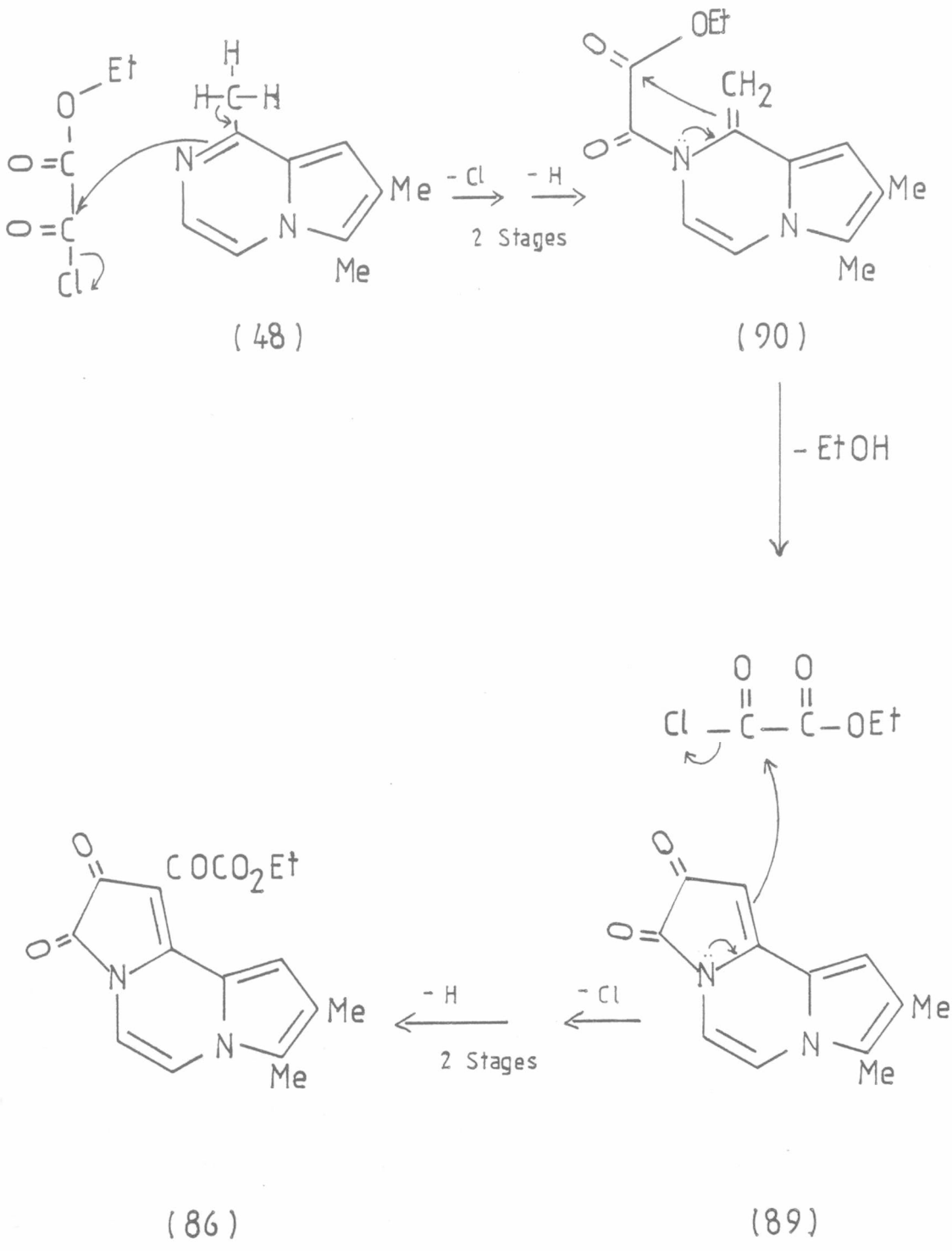


Suggested mechanisms for the formation of compound (86)

The suggested mechanism leading to compound(86) is shown in scheme 1. The first step involves the condensation of ethoxalyl chloride with the 8-methyl-7-azaindolizine (48) *via* the non-bridgehead nitrogen. Subsequent cyclisation followed by elimination of ethanol would lead to the formation of compound (89). The COCOOEt group leading to compound (86) may be incorporated as shown, or it may have been introduced at an earlier stage *via* intermediate (90).

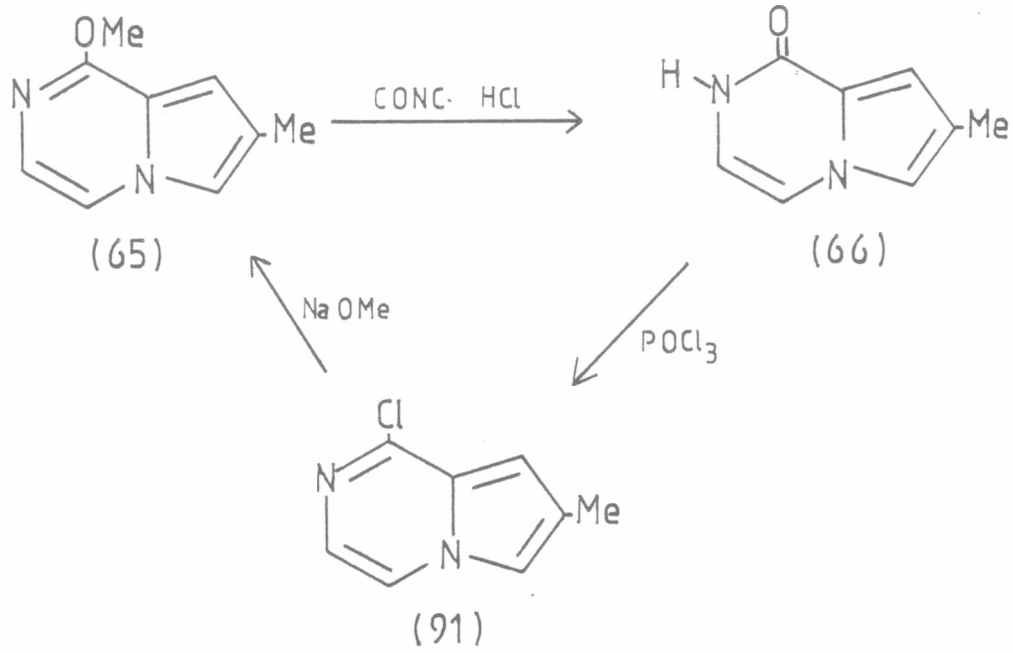
The results obtained from the reaction of 8-alkyl-7-azaindolizines with ethoxalyl chloride contrast with that of 5-methyl-2-phenylindolizine reported by Leaver[73]. He obtained a 1,3-diethoxalyl derivative which arises from direct electrophilic substitution at the C-3 and C-1 positions of the indolizine system. However 8-alkyl-7-aza-indolizines showed a propensity towards quaternisation at the electron rich non-bridgehead nitrogen followed by cyclisation to form a diketo dipyrrolopyrazine system *viz* (86) and (88).

Scheme 1. Suggested mechanism for the formation of compound (86)



Reaction of 8-chloro-2-methyl-7-azaindolizine with nucleophiles

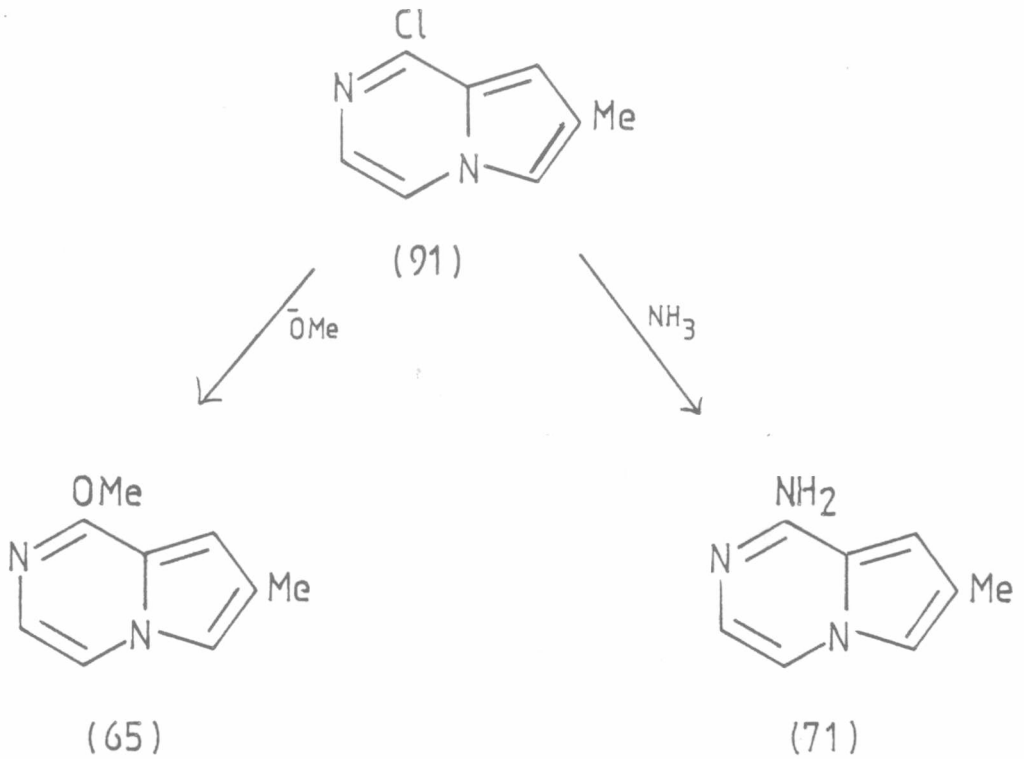
8-Chloro-2-methyl-7-azaindolizine (91) was obtained by chlorination of 2-methyl-7-azaindolizin-8(7H)-one (66). The latter (66) was prepared by demethylation of 8-methoxy-2-methyl-7-azaindolizine (65) using aqueous hydrochloric acid. Refluxing a solution of the 7-azaindolizinone (66) in phosphoryl chloride gave the 8-chloro-2-methyl-7-azaindolizine (91) in 93% yield.



The chloro-7-azaindolizine (91) reacted with sodium methoxide in refluxing methanol to yield 8-methoxy-2-methyl-7-azaindolizine (65) in 68% yield. It showed identical spectral characteristics to the sample obtained from the reaction between 3-methoxy-2-methylpyrazine and bromoacetone (see page 43).

Heating the chloro-7-azaindolizine (91) in an aqueous solution of ammonia at 180°C for 15 hours gave

8-amino-2-methyl-7-azaindolizine (71). The mass spectrum of this amino-7-azaindolizine (71) showed the molecular ion at m/e 148. Its pmr spectrum showed a 3H singlet at δ2.29 assigned to CH_3-2, a broad 2H signal at δ4.49 due to NH_2-8, two 1H singlets at δ6.37 and δ7.08 to H-1 and H-3 respectively and a 2H AB doublet centered at δ6.99 and δ7.28 attributed to H-5 and H-6 respectively.



Conclusions

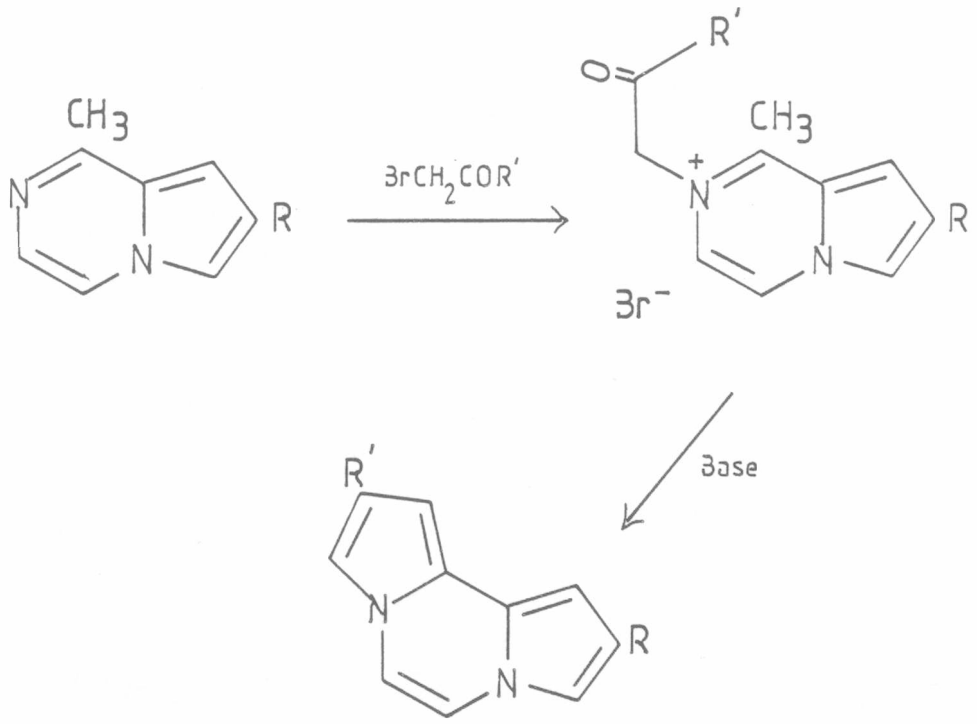
Protonation and deuterium exchange studies of 7-azaindolizine(s) unequivocally demonstrate the superior basicity of the non-bridgehead nitrogen relative to carbon for this system. The higher basicity of the non-bridgehead nitrogen and the lower electron density at position 1 and 3 of the 7-azaindolizine system is also apparent from its reactivity with electrophiles. In contrast to 5-, 6- and 8-azaindolizines which readily formylate and acetylate, 7-azaindolizines failed to formylate, and with boiling acetic anhydride gave only a low yield of the 3-acetyl-7-azaindolizine (84). Furthermore ethoxalyl chloride bonded to the non-bridgehead nitrogen rather than substituting at the 3- and/or 1- positions.

In common with 6- and 8- azaindolizines, 7-azaindolizines readily underwent nucleophilic displacement of chlorine from their most electron deficient carbon centres. Thus 8-chloro-7-azaindolizine (89) readily reacted with methoxide ion and ammonia to give the corresponding 8-methoxy- and 8-amino-7-azaindolizines (65) and (71). As a consequence of this marked electron deficiency at the 8-position, 8-alkyl-7-azaindolizines are acidic and this is shown in the formation of carbanions and in the formation of the diketo dipyrrolo-pyrazine systems (86) and (88). The basicity of the non-bridgehead nitrogen and the acidity of the 8-alkyl groups in 8-alkyl-7-azaindolizines are utilised in the synthesis of dipyrrolo[1,2-a:2,1-c]pyrazines and other angular condensed polycyclic systems described in Chapter 4 and Chapter 6 of this thesis.

CHAPTER 4

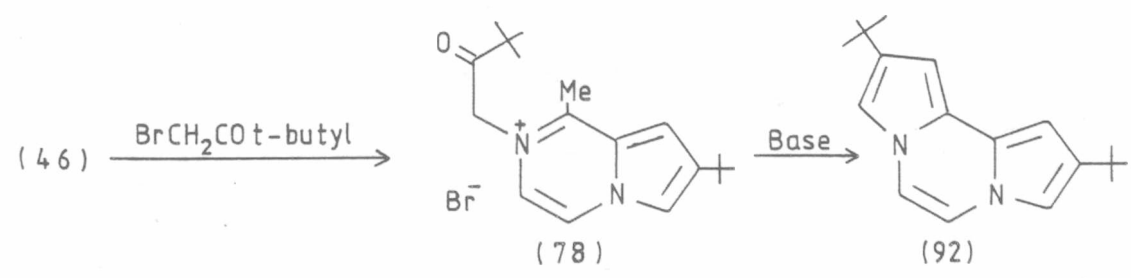
SYNTHESIS OF DIPYRROLO[1,2-a:2,1-c]PYRAZINES

The synthesis of a variety of 7-azaindolizines by the Chichibabin quaternisation-cyclisation of methylpyrazines with an α-haloketone is described in Chapter 2. This chapter discusses how some of these 7-azaindolizines have been used as starting materials for the synthesis of dipyrrolo[1,2-a:2,1-c]pyrazines. As discussed in Chapter 3, 7-azaindolizines protonate solely at N-7 and resist deuterium exchange; furthermore the α-hydrogens attached to an 8-alkyl group of 7-azaindolizines are acidic. Thus these factors would suggest that 8-methyl-7-azaindolizines should readily undergo a Chichibabin quaternisation-cyclisation reaction with an α-haloketone to give derivatives of the dipyrrolo[1,2-a:2,1-c]pyrazine system as shown below.



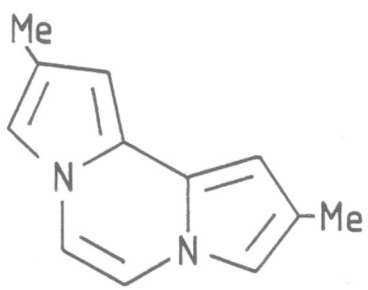
Reaction between 8-methyl-2-t-butyl-7-azaindolizines and bromopinacolone.

The reaction between 8-methyl-2-t-butyl-7-azaindolizine (46) and bromopinacolone gave the bromide salt (78) which was isolated and characterised as described in Chapter 3. When sodium bicarbonate was added to an aqueous solution of this salt (78) and the mixture refluxed, a crystalline solid was obtained which showed no C=O absorption band in its ir spectrum. The mass spectrum showed an intense molecular ion peak at m/e 268 and elemental analyses indicated a molecular formula of $C_{18}H_{24}N_2$. The pmr spectrum was very simple showing only four singlets at δ1.30, δ6.40, δ6.74 and δ6.92 thus reflecting symmetry of the molecule. The above observations would suggest the structure to be 2,9-di-t-butyldipyrrolo[1,2-a:2,1-c]pyrazine (92). In the pmr spectrum, the singlet at δ1.30 integrating for 18 protons was assigned to the two t-butyl groups at positions C-2 and C-9. The assignments of the aromatic protons were made on the basis of their proximity to the nitrogen atoms. Thus, signals at δ6.40, δ6.74 and δ6.92 each integrating for two protons were ascribed to H-1(H-10), H-3(H-8) and H-5(H-6) respectively. These assignments were confirmed by comparative examinaton of the pmr spectra of related compounds (see Table IV) and by deuterium exchange studies.



Reaction between 2,8-dimethyl-7-azaindolizine and bromoacetone.

The reaction of 2,8-dimethyl-7-azaindolizine (45) with bromoacetone gave a salt which on subsequent basification with sodium bicarbonate gave a product in 60% yield. The pmr spectrum of this compound showed only four singlets at δ2.25 due to two methyl groups at δ6.40, δ6.75 and δ6.88 due to the aromatic protons thus indicating the symmetry of the molecule. This symmetry was also reflected in the cmr spectrum which consisted of six signals; the non-quaternary ring carbons occurring at δ100.49, δ110.65 and δ112.72. The mass spectrum of this compound showed molecular ion at m/e 184 and a base peak at m/e 183 corresponding to the loss of a hydrogen atom from the molecular ion. The similarity of the pmr, ir and uv spectra to those of 2,9-di-t-butyl-dipyrrolo[1,2-a:2,1-c]pyrazine (92) suggested the compound to be 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93). Deuterium exchange studies showed two exchangeable protons at δ6.75 assigned to H-3(H-8) followed by diminution of the singlet at δ6.40 due to H-1(H-10). The singlet at δ6.88 was therefore due to H-5(H-6) and at high field, the singlet at δ2.25 was attributed to CH_3-2(CH_3-9).



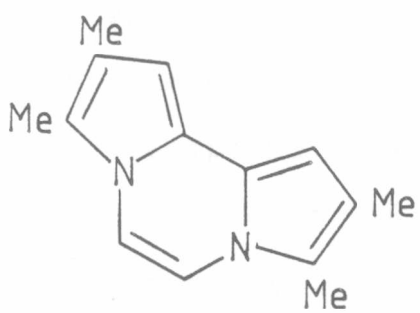
(93)

Reaction between 2,3,8-trimethyl-7-azaindolizine and 3-bromobutan-2-one

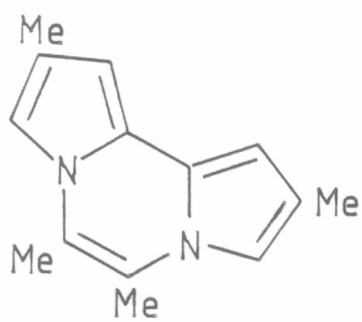
2,3,8-Trimethyl-7-azaindolizine (48) reacted with bromobutan-2-one to give 2,3,8,9-tetramethyldipyrrolo-[1,2-a:2,1-c]pyrazine (94). Its pmr spectrum consisted of four singlets at δ2.16, δ2.28, δ6.22 and δ6.87 which when compared with spectra (92) and (93) were assigned to CH_3-2(CH_3-9), CH_3-3(CH_3-8), H-1(H-10) and H-5(H-6) respectively.

Reaction between 2,5,6,8-tetramethyl-7-azaindolizine and bromoacetone.

The reaction between 2,5,6,8-tetramethyl-7-azaindolizine (57) and bromoacetone gave a salt which on subsequent addition of sodium bicarbonate yielded 2,5,6,9-tetramethyl-dipyrrolo[1,2-a:2,1-c]pyrazine (95). The pmr spectrum of (95) was similar to that of compound (94), showing only four singlets at δ2.20, δ2.28, δ6.30 and δ6.72 due to CH_3-2(CH_3-9), CH_3-5(CH_3-6), H-1(H-10) and H-3(H-8) respectively.



(94)

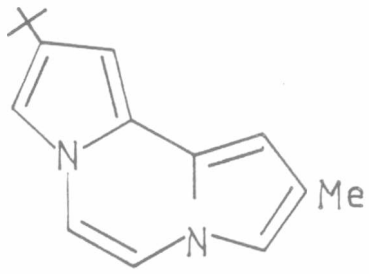


(95)

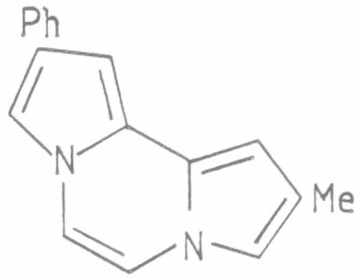
Reaction between 2,8-dimethyl-7-azaindolizine and (a) bromopinacolone and (b) phenacyl bromide.

The reation between 2,8-dimethyl-7-azaindolizine (45) and bromopinacolone gave after addition of base 2-methyl-9-t-butyldipyrrolo [1,2-a:2,1-c]pyrazine (96) as colourless crystals. The pmr spectrum of (96) showed six signals at δ1.30, δ 2.21, δ6.27, δ6.35, δ6.72 andδ6.87. By comparison with spectrum of compound (92), signals at δ1.30 and δ2.21 were attributed to t-butyl-9 and CH_3-2 respectively. Deuterium exchange showed the disappearance of the 2H signal at δ6.72 suggesting that this signal was due to H-3 and H-8 while diminution of the peaks at δ6.27 and δ6.35 indicated these to be due to H-10 and H-1 respectively. Finally the 2H signal at δ6.87 was attributed to H-5 and H-6.

Reaction between 2,8-dimethyl-7-azaindolizine (45) and phenacyl bromide gave a salt which after addition of base yielded 2-methyl-9-phenyldipyrrolo[1,2-a:2,1-c]pyrazine (97). Since compound (97) is unsymmetrical and contains a phenyl group at C-9 position, it gave a more complex pmr spectrum which showed signals at δ2.25, δ6.37 and a complex multiplet between δ6.75 and δ7.80. By comparison with the spectrum of compound (93), the singlet at δ2.25 was assigned to CH_3-2, the one at δ6.37 was due to H-1 and the complex multiplet between δ6.73 and δ7.80 incorporate H-3, H-5, H-6, H-8, H-10 and the protons of the phenyl group at position C-9.



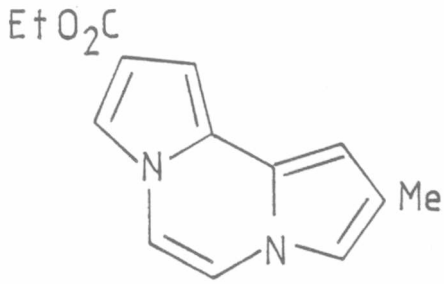
(96)



(97)

Reaction between 2-carboethoxy-8-methyl-7-azaindolizine and bromoacetone.

The reaction between 2-carboethoxy-8-methyl-7-azaindolizine (67) and bromoacetone gave a salt which upon basification afforded 9-carboethoxy-2-methyldipyrrolo-[1,2-a:2,1-c]pyrazine (98) as pale orange crystals. The ir spectrum of compound (98) showed a strong absorption band at 1710 cm^{-1} due to the C=O of the ester group. Its pmr spectrum consisted of a 3H singlet at δ2.21 assigned to CH_3-2, four 1H singlets at δ6.38, δ6.73, δ6.81 and δ6.93 due to H-1, H-10, H-8 and H-3 respectively and a 2H AB doublet system centered at δ6.49 and δ6.94 were attributed to H-5 and H-6 respectively. The carboethoxy group at C-9 was represented by a triplet centered at δ1.36 (J=7.2Hz) and a quartet centered at δ4.21 (J=7.2Hz).



(98)

Pmr spectra of dipyrrolo[1,2-a:2,1-c]pyrazines

The chemical shifts of the dipyrrolo-pyrazines in $CDCl_3$ are given in Table IV. Compounds (92-95) all show only four singlets, this simplicity reflects the symmetry of these compounds and of the dipyrrolo[1,2-a;2,1-c]pyrazine ring system. The ring proton absorptions were found to occur at chemical shifts corresponding to that of the parent (2)[57] occurring at progessively lower field in the order H-1(H-10), H-3(H-8), H-5(H-6) . For example 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) showed in addition to its high field methyl signal at δ2.25, three lower field singlets at δ6.40, δ6.75 and δ6.88 assigned respectively to H-1(H-10), H-3(H-8) and H-5(H-6). The ring methyl groups generally occur between the region of δ2.15 and δ2.30 with CH_3-3(CH_3-8) and CH_3-5(CH_3-6) occurring at lower field because of their proximity to the bridgehead nitrogen.

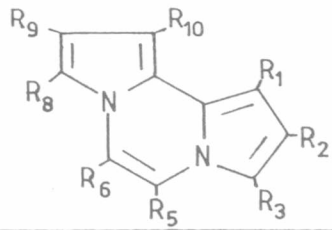
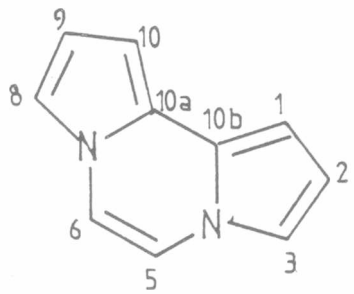


Table IV pmr Spectra of dipyrrolo[1,2-a : 2,1-c]pyrazines in $CDCl_3$ (δ values)

	R_1	R_2	R_3	R_5	R_6	R_8	R_9	R_{10}
2	6.50	6.55	6.98	7.05	7.05	6.98	6.55	6.50
92	6.40*	1.30(9H)	6.74*	6.92	6.92	6.74*	1.30(9H)	6.40*
93	6.40*	2.25(3H)	6.75*	6.88	6.88	6.75*	2.25(3H)	6.40*
94	6.22	2.16(3H)	2.28(3H)	6.87	6.87	2.28(3H)	2.16(3H)	6.22
95	6.30*	2.20(3H)	6.72*	2.28(3H)	2.28(3H)	6.72*	2.20(3H)	6.30*
96	6.35*	2.21(3H)	6.72*	6.87	6.87	6.72*	1.30(9H)	6.27*
97	6.37	2.25(3H)	6.73	6.94	6.94	7.11 to 7.63 6H complex H-8 and Ph-9		6.73
98	6.38	2.21(3H)	6.81	6.94d J=1.4Hz	7.49d J=1.4Hz	6.93	1.36 t(3H,CH_3-2) J = 7.2Hz 4.21 q(2H,CH_2-2)	6.73

Signals marked by asterisk are broadened and/or weakly split.

Cmr spectra of symmetrical alkyl substituted dipyrrolo-[1,2-a:2,1-c]pyrazines



(2)

The chemical shifts of compounds (92), (93) and (95) in their respective cmr spectrum are recorded in Table V. All the examined spectra were simple, again reflecting the symmetry of these molecules by showing equivalent carbon signals. For example the cmr spectrum of 2,9-di-t-butyl (92) and 2,5,6,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazines (95) both showed only seven resonance signals.

Generally the carbon resonances occur in the following regions: C-1 and C-10 between δ97.30 and δ100.49, C-2 and C-9 between δ121.14 and δ124.22, C-3 and C-8 between δ109.71 and δ112.72, C-5 and C-6 between δ110.65 and δ121.68 and C-10a and C-10b between δ124.00 and δ138.96. Quaternary carbons at positions C-2, C-9, C-10a and C-10b generally show resonance signals further downfield and are of lower intensity.

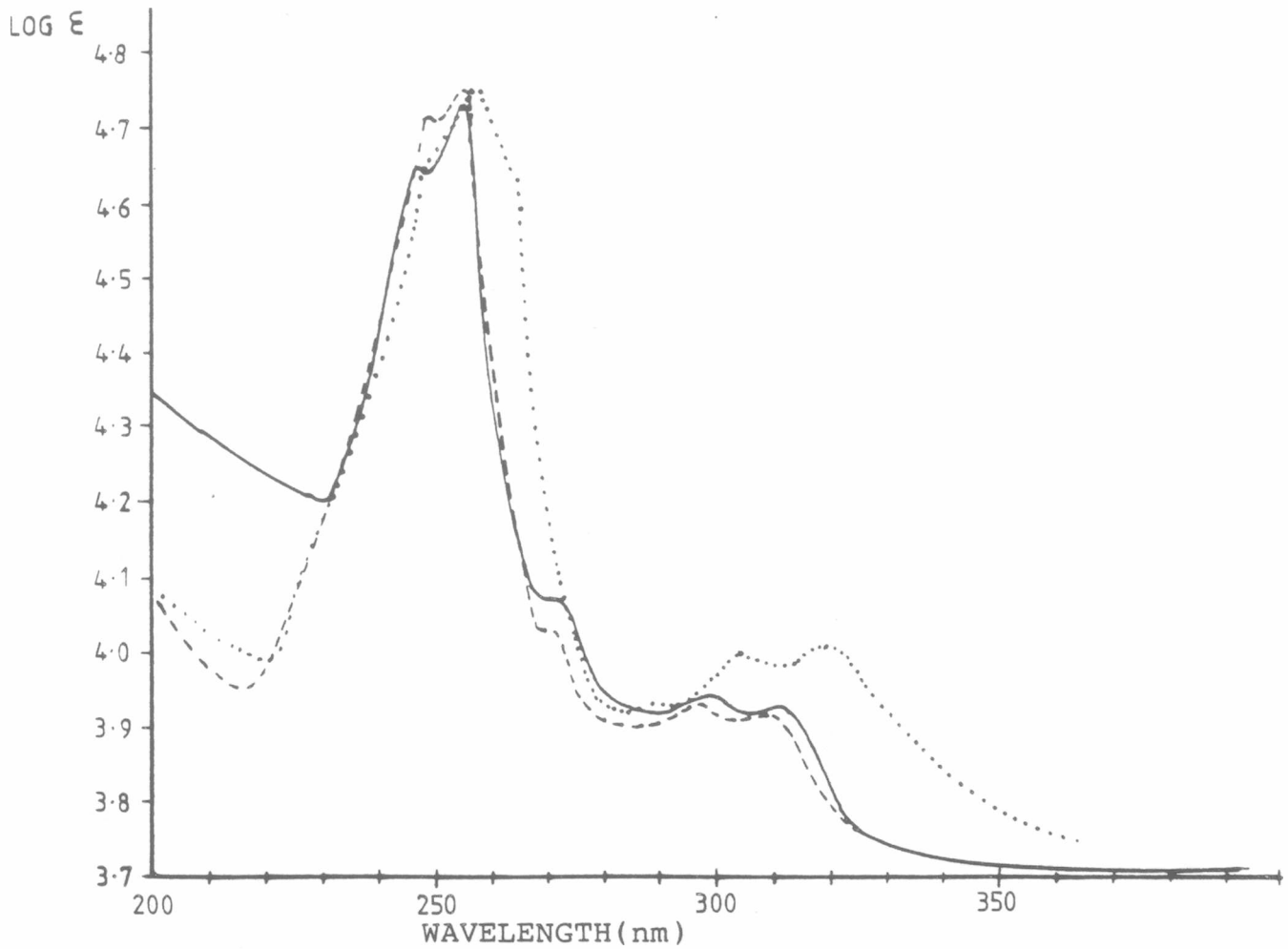
Table V Cmr spectra of dipyrrolo[1,2-a:2,1-c]pyrazines in $CDCl_3$ (δ Values)

Dipyrrolo[1,2a:2,1-c]pyrazines	C-1(C-10)	C-2(C-9)	C-3(C-8)	C-5(C-6)	C-10a(C-10b)
2,9-Di-t-butyl-(92)	97.30	124.22 30.83, 31.70 (t-butyl-2, t-butyl-9)	109.92	110.84	138.96
2,9-Dimethyl-(93)	100.49	122.29 12.01 (Me-2,Me-9)	112.72	110.65	124.00
2,5,6,9-Tetramethyl-(95)	99.85	121.14 12.14 (Me-2,Me-9)	109.71	121.68 13.44 (Me-5,Me-6)	124.12

Uv spectra of alkyl substituted dipyrrolo[1,2-a:2,1-c]-pyrazines

The uv spectra of alkyl dipyrrolo[1,2-a:2,1-c]pyrazines (92), (93) and (94) are shown in Figure 4. They all showed a closely similar pattern with λ_{max} occurring at about 254 nm. When these spectra were compared with that of alkyl 7-azaindolizines (Figure 1), they demonstrated some similarities in the pattern and also exhibited a hypsochromic shift (about 20nm) of the major bands due to the extra nitrogen in the system.

Figure 4. Uv spectrum of alkyl dipyrrolo[1,2-a:2,1-c]pyrazines



2,9-Di-t-butyldipyrrolo[1,2-a:2,1-c]pyrazine (-------)

2,9-Dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (————)

2,3,8,9-Tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine(.....)

Figure 5. Mass spectrum of compound (94)

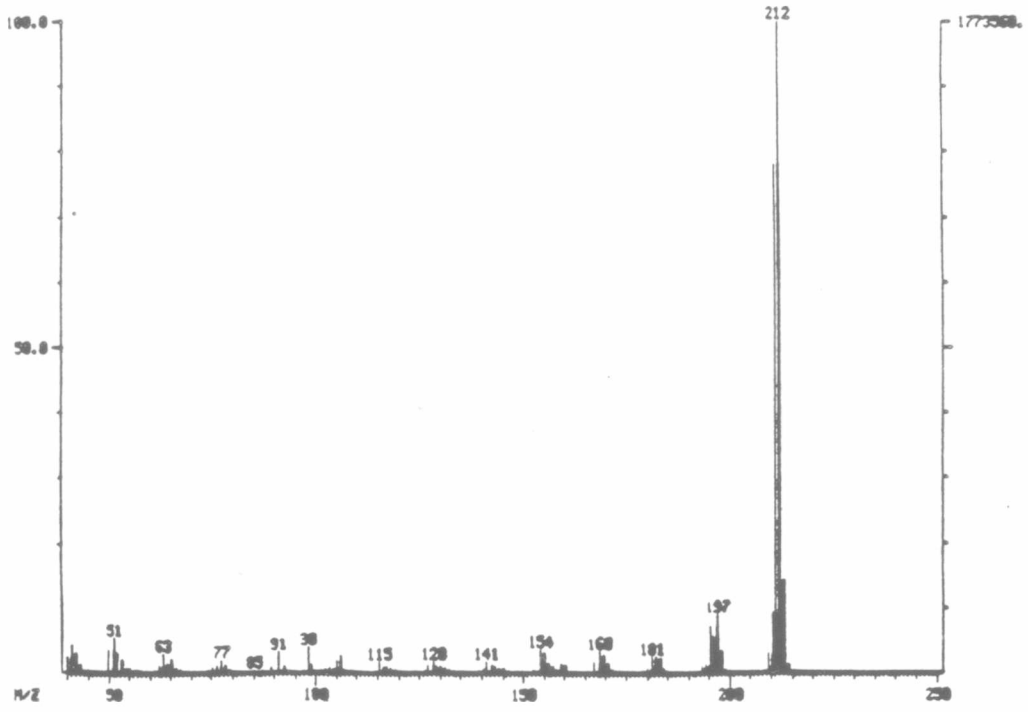
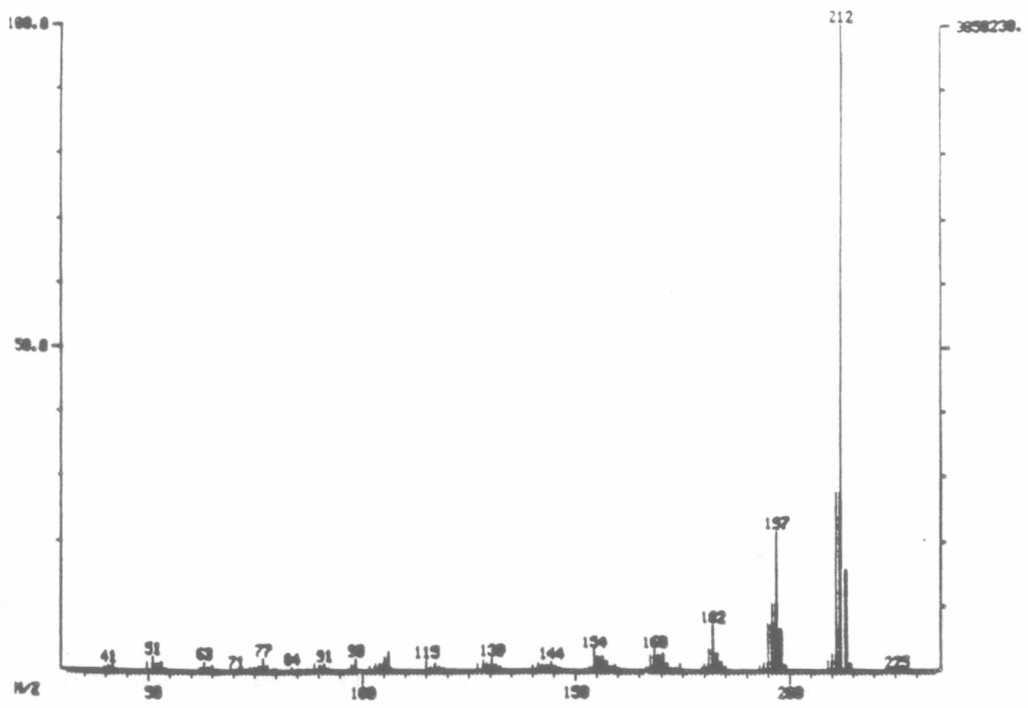
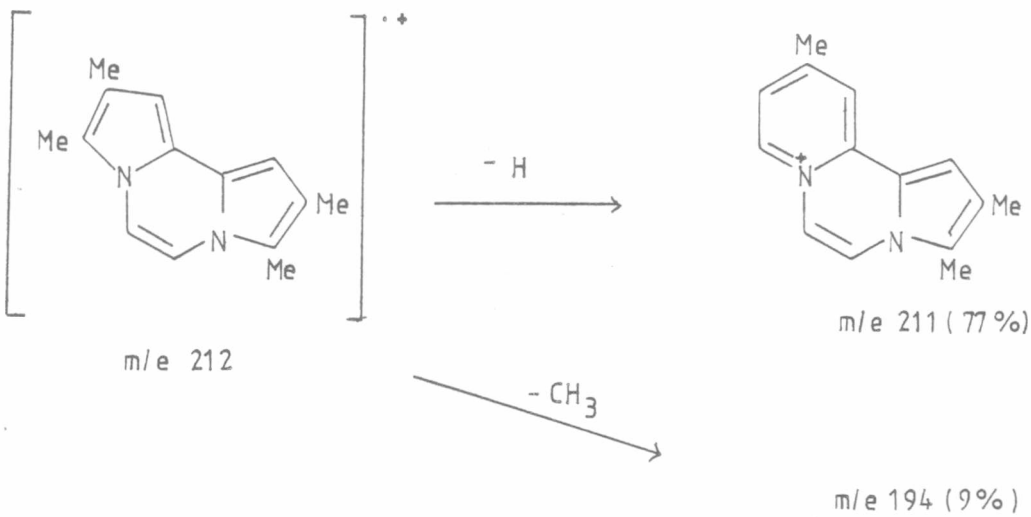


Figure 6. Mass spectrum of compound (95)



Mass spectrum of alkyl dipyrrolo[1,2-a:2,1-c]pyrazines

The mass spectrum of 2,3,8,9-tetramethyl (94) and 2,5,6,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazines (95) are shown in Figures 5 and 6. The main features in the spectrum of compound (94) are the intense molecular ion at m/e 212(100%) which is also the base peak, a loss of a hydrogen atom to give a large peak at m/e 211(77%) and a loss of a methyl group from the molecular ion to give a weak peak at m/e 197(9%). Like in 2-methyl-8-azaindolizine[26], the loss of hydrogen from the alkyl dipyrrolo[1,2-a:2,1-c]pyrazines (94) and (95) may have occurred from the methyl attached to the ring carbons at positions 3(8) or 2(9) as shown below.



Mass spectrum of compound (95) although showing closely similar fragmentation pattern consisted of peaks with different intensities relative to compound (94). The molecular ion was found at m/e 212(100%) and the other main fragments were found at m/e 211(28%) and m/e 197(7%) due to the loss of a hydrogen atom and a methyl group respectively. The intense molecular ions produced by compounds (94) and

(95) reflects the stability of the dipyrrolo-pyrazine system.

Conclusions

The reactions discussed in this chapter indicate that dipyrrolo[1,2-a:2,1-c]pyrazines may be formed readily by a Chichibabin reaction on 8-methyl-7-azaindolizines in yields varying from 13 to 60%. Generally, the formation of these dipyrrolo-pyrazines from 7-azaindolizines proceeded more easily than the formation of 7-azaindolizines from methylpyrazines. The simplicity of the nmr spectra of the symmetrical substituted compounds indicate the symmetry and planarity of the dipyrrolo-pyrazine system. The mass spectra showed close similarities to those of indolizine and azaindolizines by exhibiting a very intense molecular ion, thus reflecting stability of the dipyrrolo-pyrazine system.

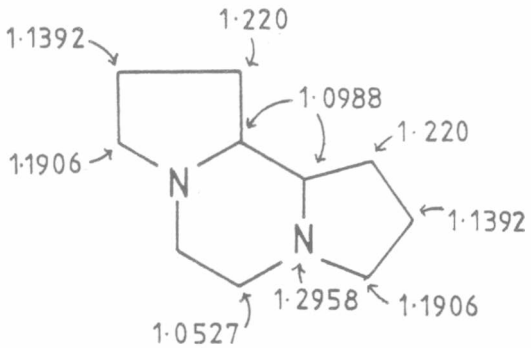
CHAPTER 5

REACTIVITY OF DIPYRROLO[1,2-a:2,1-c]PYRAZINES

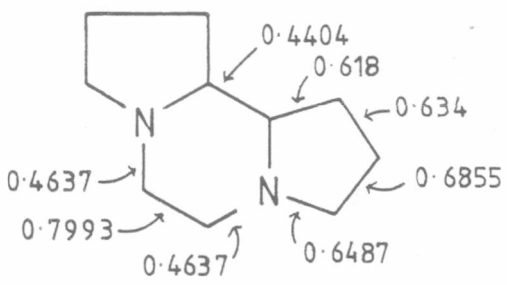
Dipyrrolo[1,2-a:2,1-c]pyrazine (2) can be considered to be a π-excessive heteroaromatic system with 14 peripheral electrons delocalised over twelve ring centres, the two sp^2 hybridised bridgehead nitrogens each furnishing two electrons, and ten electrons arising from the ten sp^2 hybridised ring carbons. An alternative model would be to consider the dipyrrolo[1,2-a:2,1-c]pyrazine system to be constituted of two bridged pyrrole rings linked through an ethylenic double bond. Simple Huckel molecular orbital calculations, nmr and mass spectral data all point to the dipyrrolo[1,2-a:2,1-c]pyrazine system behaving as a 14 π heteroaromatic rather than two linked 6 systems. As shown on page 82, the 5-6 bond order of the dipyrrolo-pyrazine system is calculated to be slightly greater than that of an ethylenic double bond and the 10a-10b bond order lies between that for benzene and ethane. The cmr chemical shifts of the non quaternary carbons of 2,9-dimethyldipyrrolo-[1,2-a:2,1-c]pyrazine (93) (see page 75) occurred at δ100, δ112, δ122 and δ113, these values are comparable to ring carbon resonances of other electron rich heteroaromatic compound[75]. Also as an indicator of the stability of dipyrrolo[1,2-a:2,1-c]pyrazine system, the molecular ion in the mass spectrum of compound (94) is also the base peak (see page 79) and the intensity of the other fragment ions is low (less than 10%). This chapter discusses the

HMO calculations on the dipyrrolo[1,2-a:2,1-c]pyrazine system

Calculated electron densities[76]



Calculated partial bond orders[76]

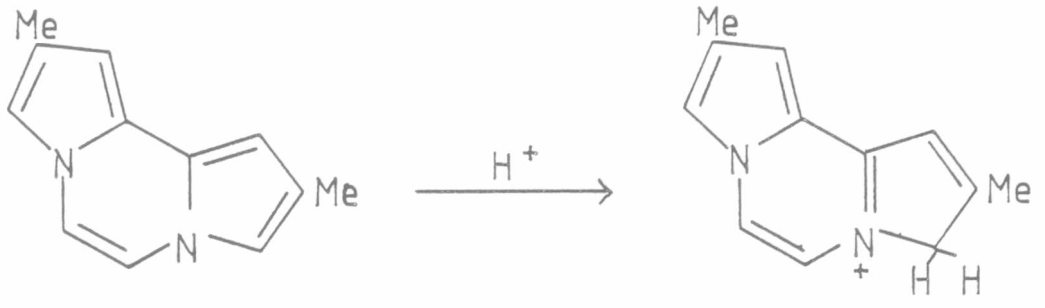


reactivity of the π-excessive dipyrrolo[1,2-a:2,1-c]pyrazine system.

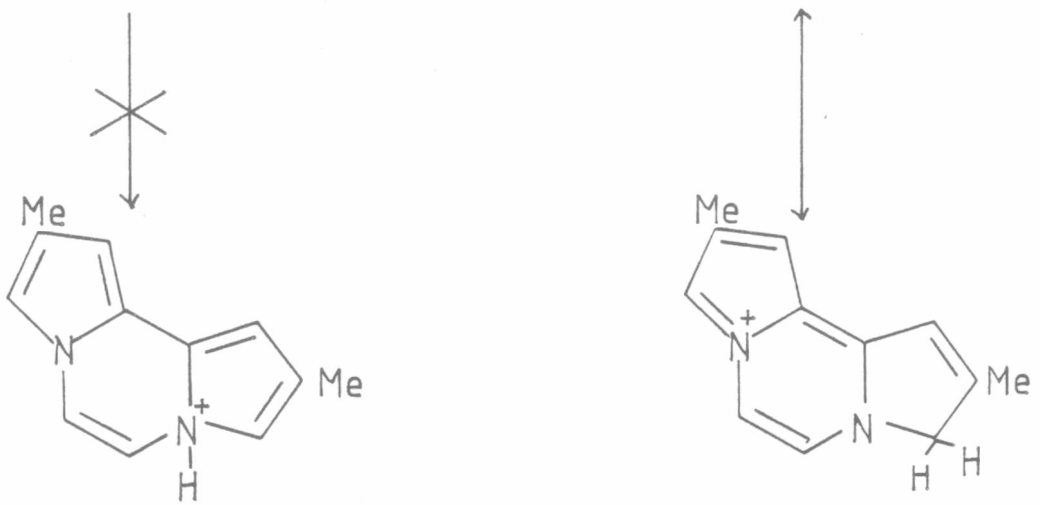
Protonation

The site of protonation of the prepared dipyrrolo-[1,2-a:2,1-c]pyrazines was determined by comparing the pmr spectra of the unprotonated base in $CDCl_3$ (see Table IV) with the corresponding spectra in CF_3COOH and also by reference to the CF_3COOOH spectra of indolizines and other azaindolizines.

The least substituted dipyrrolo-pyrazines prepared in this work were 2,9-dimethyl and 2,9-di-t-butyldipyrrolo-[1,2-a:2,1-c]pyrazines (93) and (92). The CF_3COOH spectrum of (93) (see Table VI) was more complex and showed a general downfield shift compared to the simple spectrum of (93) in $CDCl_3$. This implies the formation of an unsymmetrical monocation and the emergence of a 2H singlet at δ5.26 suggests C-3 protonation to have occurred as C-3 protonation of indolizine shows the methylene proton signals between δ5.26 and δ5.91 whereas when C-1 protonation occurs, the methylene signals appear between δ4.00 and δ5.00[23,24]. As in indolizine the dipyrrolo-pyrazine (93) would be expected to protonate on carbon rather than on nitrogen since carbon protonation would result in the resonance stabilised aromatic cation (99) whereas protonation on nitrogen would give the non planar conjugate acid (100) containing a localised bridgehead quaternary nitrogen.



(93) (99)

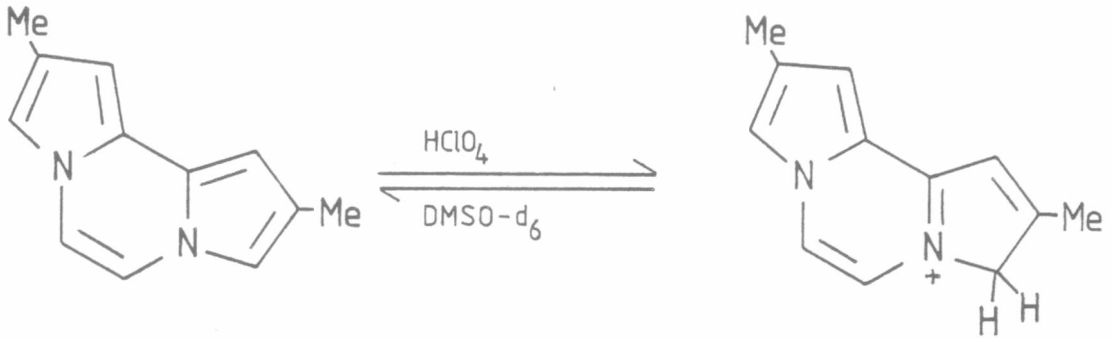


(100)

In the spectrum of compound (93) in CF_3COOH, the 2H AB doublet at δ7.50 and δ8.00 was attributed to H-6 and H-5 and the 1H singlets at δ7.00, δ7.50 and δ7.85 to H-10, H-1 and H-8 respectively.

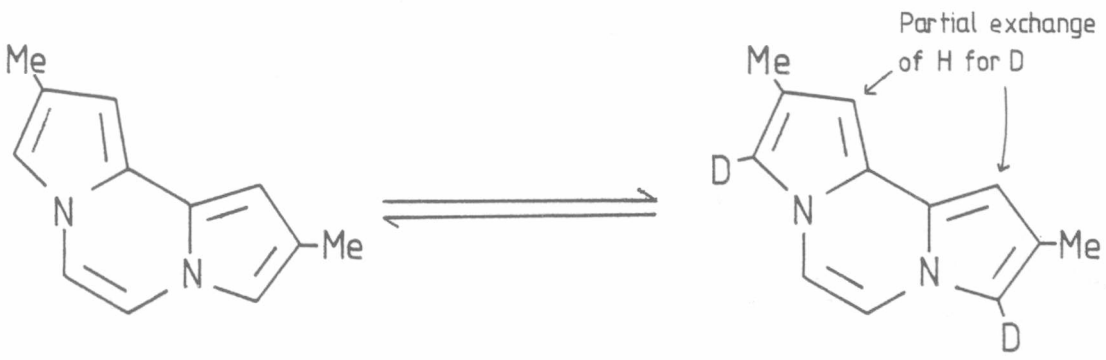
The CF_3COOH spectrum of the perchlorate salt of (93) showed an identical pmr spectrum to that of (93) in CF_3COOH. However when the pmr spectrum of the perchlorate salt was recorded in DMSO-d_6, a spectrum identical to (93) in $CDCl_3$ was observed. This implies the DMSO-d_6 solvent to be

sufficiently basic to deprotonate the cation (101) and indicates dipyrrolo-pyrazines to have lower base strength than DMSO-d_6 and to be weaker bases than the 7-azaindolizines since their perchlorate salts in DMSO-d_6 were that of their conjugate acid cations.



(93) (101)

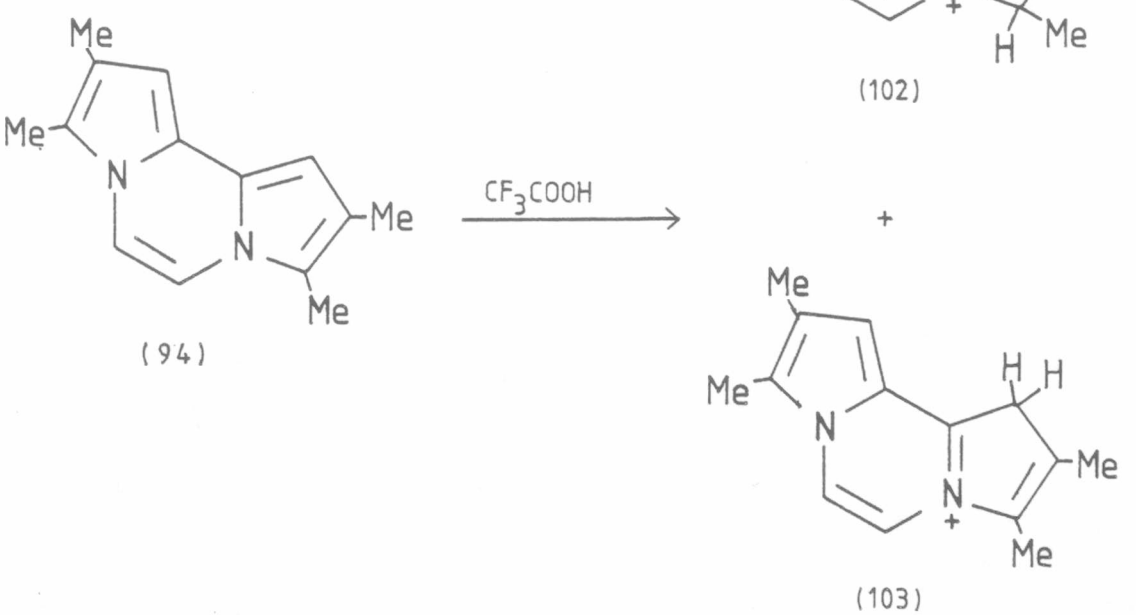
When the $CDCl_3$ solution of compound (93) was triturated with a drop of CF_3COOD the signals assigned to H-3(H-8) disappeared and those assigned to H-1(H-10) were reduced. This implies that in addition to the formation of the C-3 cation (99), a lower equilibrium concentration of the C-1 cation is also formed.



(93)

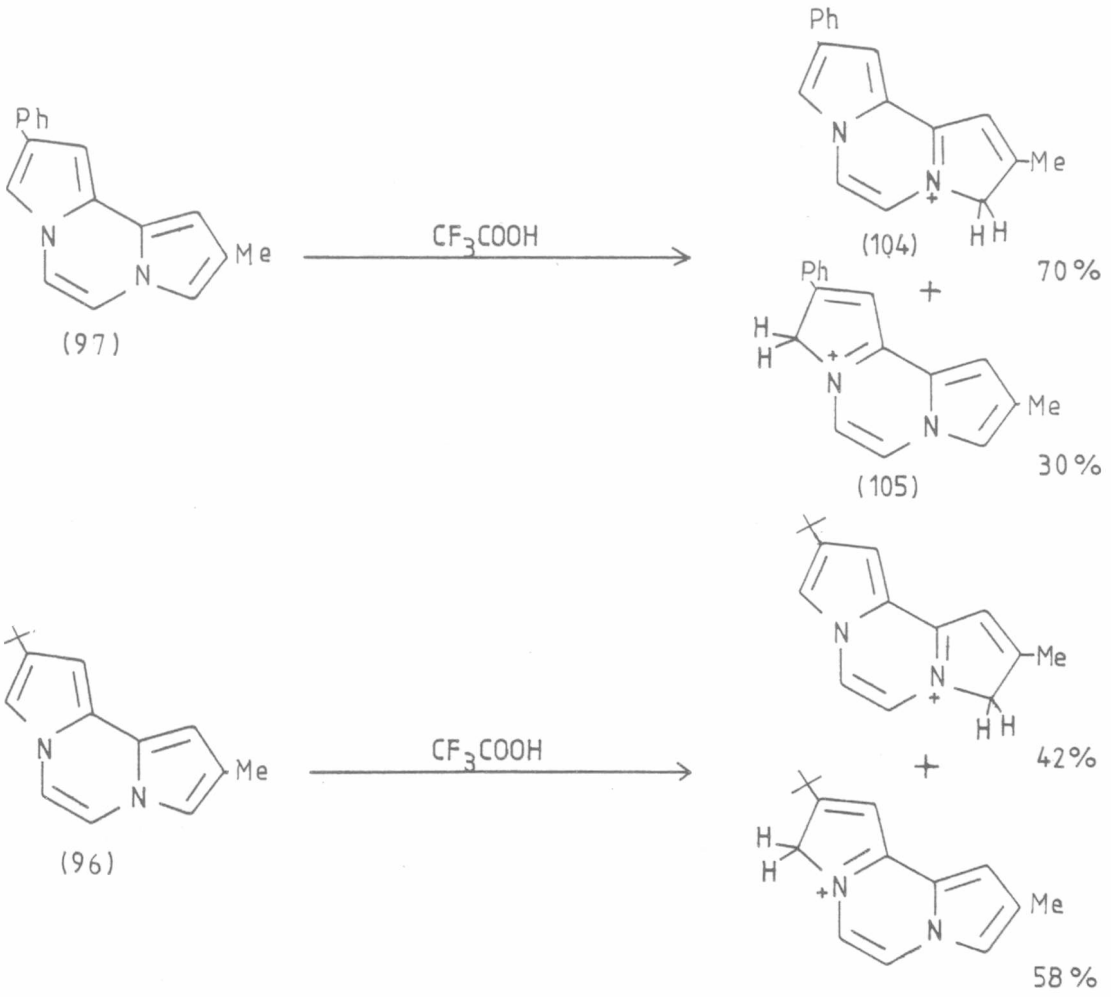
Similarly the symmetrically substituted 2,9-di-t-butyl- and 2,5,6,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazines (92) and (95) both showed C-3 protonation as shown in Table VI.

The pmr spectrum of 2,3,8,9-tetramethyldipyrrolo-[1,2-a:2,1-c]pyrazine (94) (Table VI) indicated the presence of both C-3 (60%) and C-1 (40%) conjugate acid cations (102) and (103). The spectrum of the minor C-1 protonated species showed a midfield 2H methylene signal at δ4.20 which lies within the range δ4.14 and δ4.60 reported for C-1 protonated indolizines and 5-azaindolizines[23,24]. The pmr spectrum of the major C-3 protonated species consisted of three 3H singlets at δ2.40, δ2.47 and δ2.60 attributed to CH_3-9, CH_3-8 and CH_3-2 respectively. The doublet at δ1.78 and the quartet centered at δ5.10 are assigned to the coupled C-3 methyl and methine protons.



The unsymmetrical dipyrrolo[1,2-a:2,1-c]pyrazines (96) and (97) gave a mixture of both C-3 and C-8 conjugate acid cations. For example 2-methyl-9-phenyldipyrrolo-[1,2-a:2,1-c]pyrazine (97) gave cations (104) (70%) and (105) (30%) (see Table VI). The CF_3COOH pmr of compound (97) showed superimposed signals of both these cations. The main species was the C-3 protonated cation (104) which showed a methylene signal at δ5.22 and in the minor species, the C-8 (105) protonated cation showed a 2H methylene signal at δ5.70.

Similarly, 2-methyl-9-t-butyl dipyrrolo[1,2-a:2,1-c]-pyrazine (96) showed both C-3 and C-8 protonated cations in 42% and 58% proportions respectively.



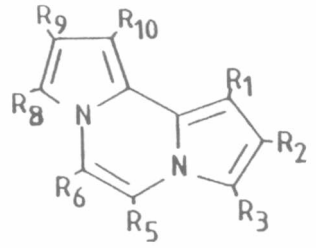


Table VI pmr Spectra of dipyrrolo[1,2-a : 2,1-c]pyrazines in CF_3COOH (δ values)

Structure	Cation	%	R_1	R_2	R_3	R_5	R_6	R_8	R_9	R_{10}
92	C-3	100	7.55	1.48(9H)	5.35(2H)	8.00d J = 6.0Hz	7.48d J = 6.0HZ	7.95	1.48(9H)	7.05
93	C-3	100	7.5	2.48(3H)	5.26(2H)	8.00d J = 6.0Hz	7.50d J = 6.0Hz	7.85	2.40(3H)	7.00
94	C-3	60	6.93	2.40(3H)	1.78d (3H) J = 7.5Hz 5.10q (1H) J = 7.5HZ	7.45d J = 6.6Hz	7.80d J = 6.6Hz	2.60(3H)	2.47(3H)	7.40
	C-1	40	4.2(2H)	2.18(3H)	2.58(3H)	7.50d J = 6.6Hz	8.00d J = 6.6Hz	2.18(3H)	2.58(3H)	7.40
95	C-3	100	7.30	2.60(3H)	5.10(2H)	2.60(3H)	2.35(3H)	7.65	2.35(3H)	7.00
96	C-3	42	7.40	2.49(3H)	5.34(2H)	8.00d J = 6.0Hz	7.50d J = 6.0Hz	7.40	1.48(9H)	7.00
	C-8	58	7.02	2.45(3H)	7.80	7.50d J = 6.0Hz	8.00d J = 6.0Hz	5.24(2H)	1.48(9H)	7.40
97	C-3	70		2.45(3H)	5.22(2H)	signals between 7.10-8.30(10H)				
	C-8	30		2.48(3H)	signals between 7.10-8.30(10H)			5.70(2H)		

Summary

The above results show that alkyl and aryl dipyrrolo-[1,2-a:2,1-c]pyrazines preferentially protonate at C-3(C-8). When positions 3 and 8 are substituted the C-3 conjugate acid cation predominates together with minor amounts of the C-1 cation. The formation of the C-3 and to the lesser extent C-1 protonated cations is also inferred from deuterium exchange studies. In CF_3COOD rapid chemical exchange occurs at C-3 and C-8 and slower exchange at C-1 and C-10. No deuterium exchange was observed at C-5 and C-6 positions pointing to a lower electron surplus at these positions despite the presence of enamine type character. These deuterium exchange and protonation studies are essentially in accord with Huckel molecular orbital electron density calculations which indicate sites at C-1(C-10) and C-3(C-8) to be the sites of highest electron density[76].

Electrophilic Substitution

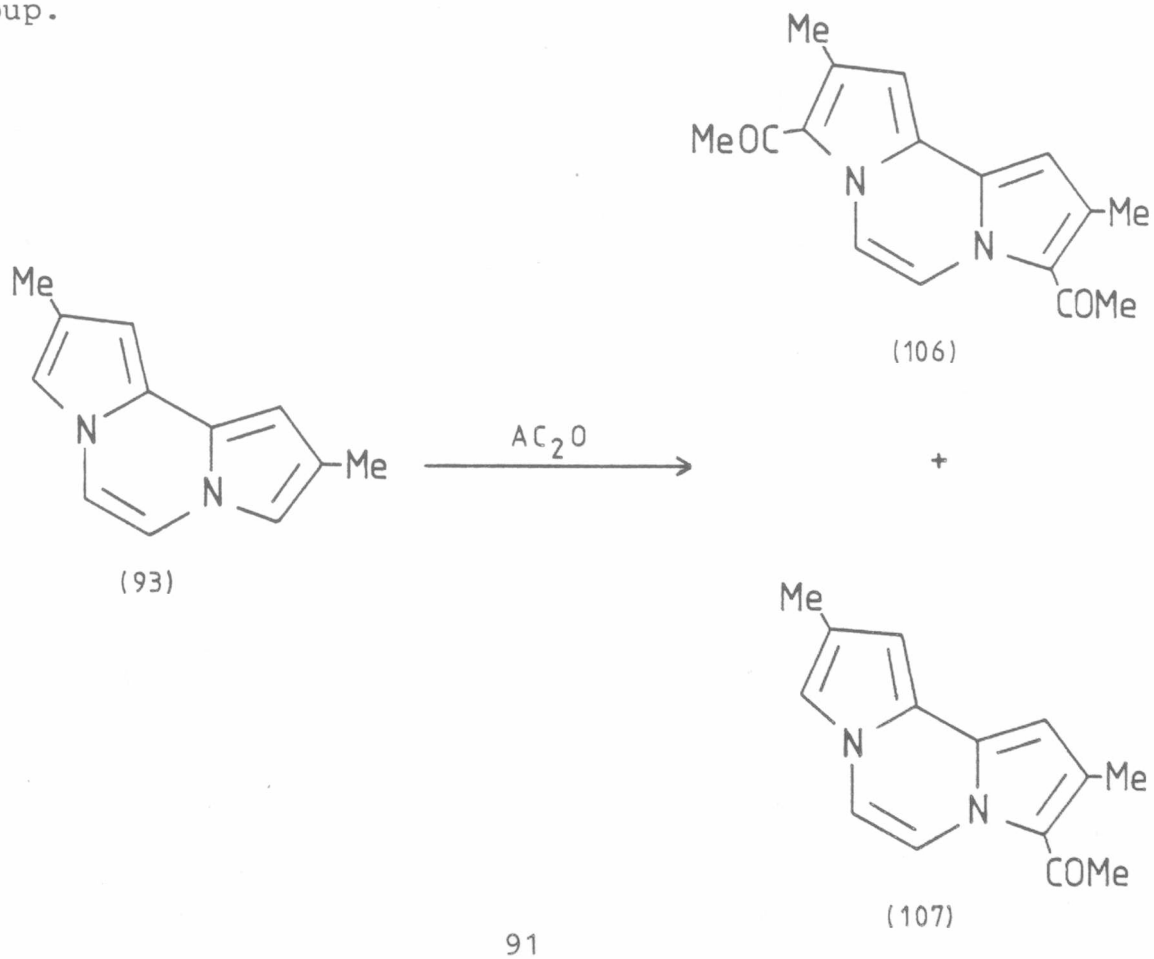
There is no reported study in the literature of the chemistry of the dipyrrolo[1,2-a:2,1-c]pyrazine system. Being π-excessive it would be expected to characteristically undergo electrophilic substitution. Huckel molecular orbital calculations and the protonation studies discussed, indicate the preferred sites of substitution to be at C-3(C-8) and C-1(C-10).

Acetylation

The reaction between 2,9-dimethyldipyrrolo[1,2-a:2,1-c] pyrazine (93) and acetic anhydride gave the diacetyl- and monoacetyl- derivatives both of which showed carbonyl absorption around 1700cm^{-1}. The mass spectrum of the diacetyl derivative exhibited an intense molecular ion peak at m/e 268 (100%) and fragmentation ions at m/e 253 (70%) and 225 (30%) resulting from the loss of 15 and 43 mass units from the molecular ion, this suggests the loss of a methyl and an acetyl group. The pmr spectrum of this compound was simple, showing only four peaks at δ2.55, δ2.58, δ6.55 and δ9.00 indicating a symmetrically substituted structure. The above spectroscopic data suggests the compound to be 3,8-diacetyl-2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (106). The methyl groups at positions 2 and 9 and the acetyl methyl protons were assigned to singlets at δ2.55 and δ2.58 respectively. The aromatic singlets at δ6.55 and δ9.00 were attributed to H-1(H-10) and H-5(H-6) respectively. The H-5(H-6) resonance signal of compound

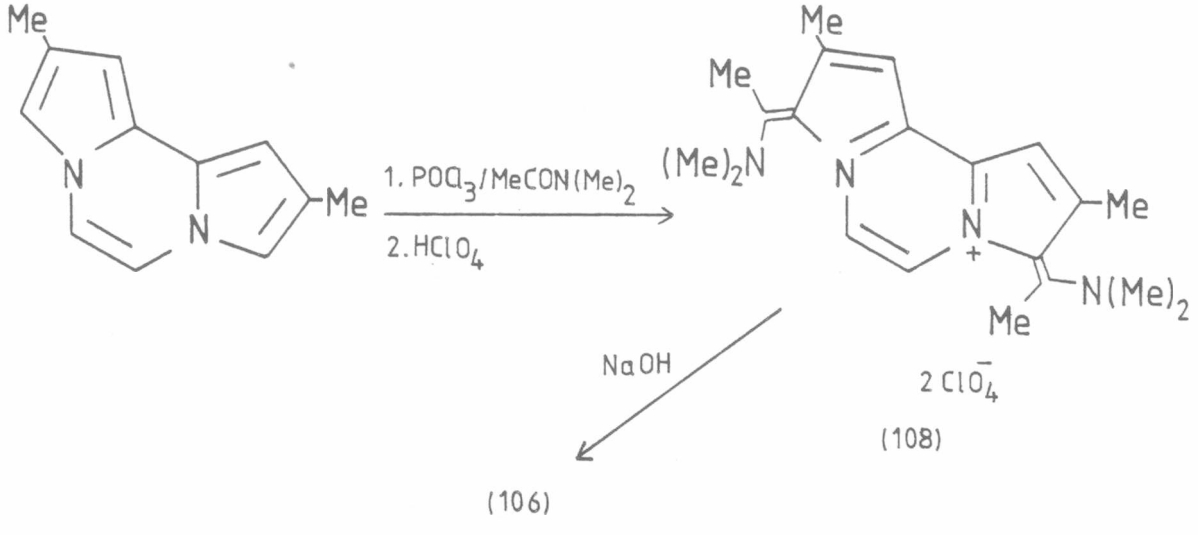
(106) occurs at 117 Hz downfield from the H-5(H-6) signal of (93), this is ascribed to the anisotropic deshielding caused by the carbonyl groups of the peri-oriented C-3 and C-8 acetyl groups. Addition of a drop of CF_3COOD to the $CDCl_3$ sample of (106) resulted in the slow diminution of the intensity of the signal at δ6.55 assigned to H-1(H-10).

The mass spectrum of the monoacetyl derivative (107) showed a molecular ion at m/e 226 (100%) and fragmentation ions at m/e 211 (50%) and m/e 183 (45%) corresponding to the loss of a methyl and an acetyl unit. Its pmr spectrum showed three 3H singlets at δ2.22, δ2.44 and δ2.46 assigned to CH_3-9, CH_3-2 and $COCH_3$-3 respectively. Further downfield, singlets at δ6.30, δ6.46, δ6.88 and an AB doublet centered at δ7.05 and δ8.82 were attributed to H-10, H-1, H-8, H-6 and H-5 respectively, H-5 giving the lowest field resonance due to the peri-oriented acetyl group.

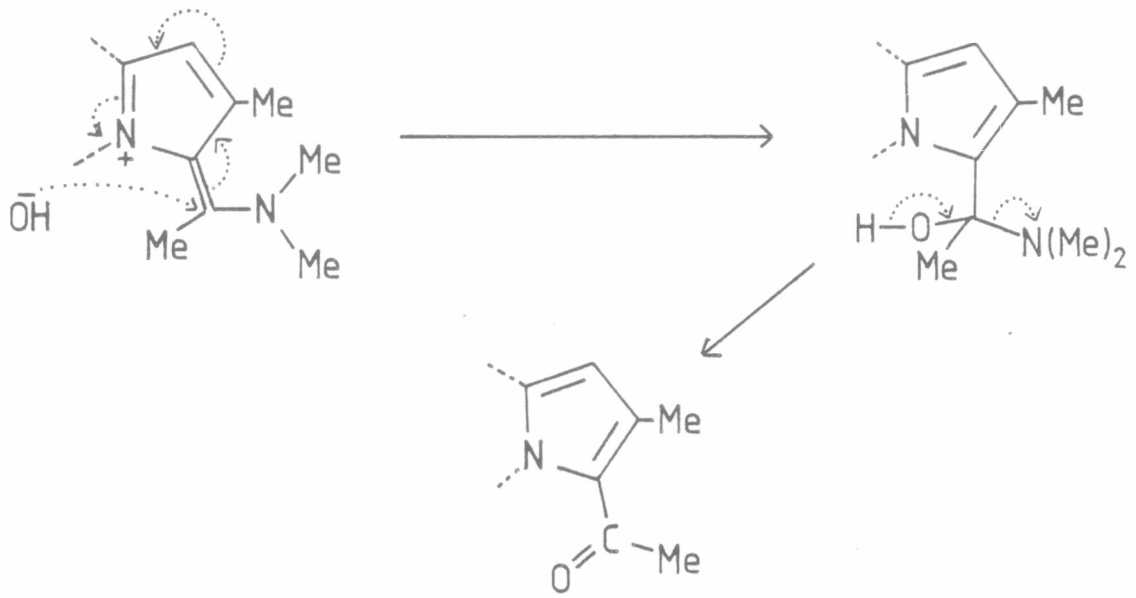


Indirect acetylation via a Vilsmeier Salt

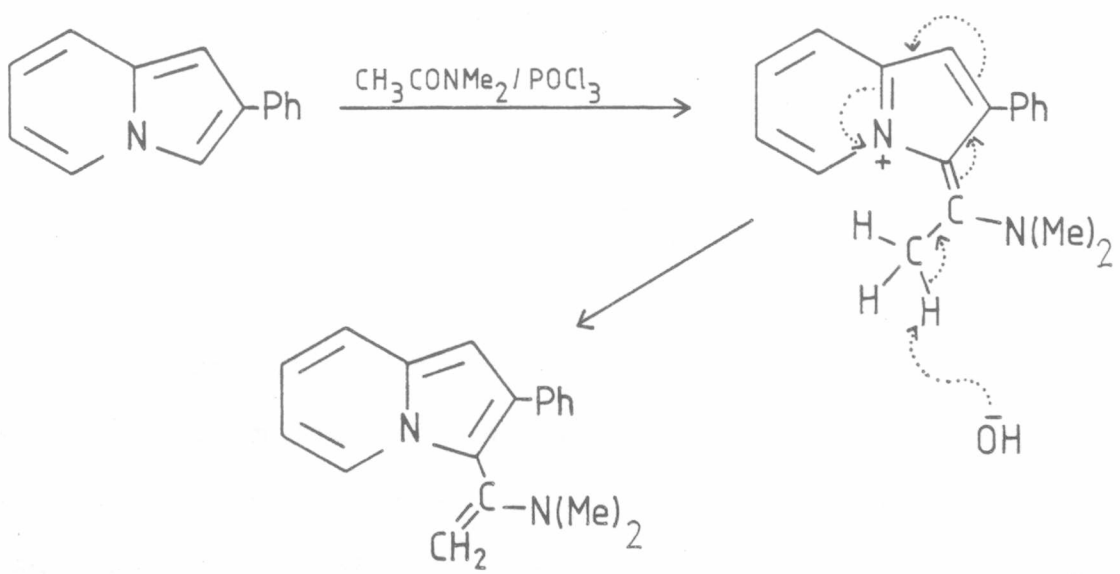
A mixture of 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) and phosphoryl chloride and dimethylacetamide at 0°C in benzene gave a Vilsmeier salt (108) which was isolated as the perchlorate. The pmr spectrum of this salt was very simple showing six singlets at δ2.48, δ3.04, δ3.80, δ3.92, δ7.00 and δ7.58 indicating it to be the symmetrical 3,8-dimethylaminoethylidenedipyrrolo[1,2-a:2,1-c]pyrazinium dication (108). Thus the singlets at δ2.48, δ3.04, δ3.80, and δ3.92 were assigned to CH_3-2(CH_3-9), the ethylene methyls and the four methyls attached to nitrogens respectively. The non equivalency of the latter methyls is ascribed to slow bond rotation. This reaction parallels the reaction[77] of indolizine and phosphoryl chloride and dimethylacetamide. Treatment of the perchlorate salt (108) with sodium hydroxide gave the diacetyl derivative (106) in good yield (89%).



The mechanism leading to the diacetyl compound (106) in this reaction probably involves nucleophilic bonding of a hydroxide ion at the vinyl carbon followed by elimination of dimethylamine, as shown:



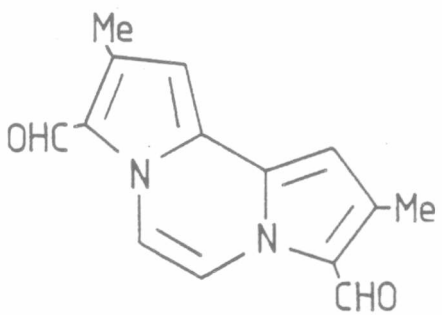
This reaction pathway contrasts with that of the reaction of hydroxide ion on the Vilsmeier salt of 2-phenyl indolizine[77] where the hydroxide ion acts as a base rather than a nucleophile to give the enamine derivative (109).



(109)

Formylation

When 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) was gently warmed with phosphoryl chloride and dimethylformamide, two products were isolated. The spectral characteristics of these products indicated the diformyl derivative (110) and the triformyl derivative (111). The ir spectrum of the diformyl compound (110) showed a low carbonyl absorption at 1660 cm^{-1}.

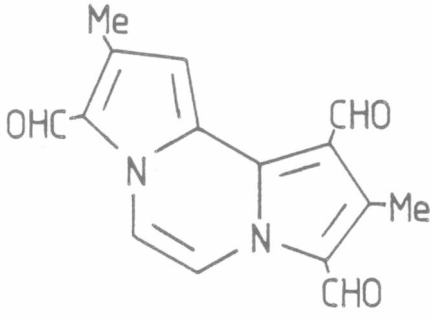


(110)

Its mass spectrum showed an intense molecular ion at m/e 240(100%). The presence of fragmentations at m/e 239 and m/e 211 are consistent with the loss from the molecular ion of a formyl group. The pmr spectrum of the compound comprised of only four singlets which were assigned as follows: the 6H singlet at δ2.54 was assigned to CH_3-2(CH_3-9), the 2H singlet at δ6.58 was due to H-1(H-10), the formyl protons arose at δ9.88 and the 2H singlet at δ8.81 was assigned to H-5(H-6) which are deshielded by the peri-oriented formyl groups.

The mass spectrum of the triformyl derivative (111) consisted of a molecular ion at m/e 268 (100%) and other fragmentation ions at m/e 240(30%) and m/e 212(25%) due to the successive loss of two molecules of CO. The pmr spectrum

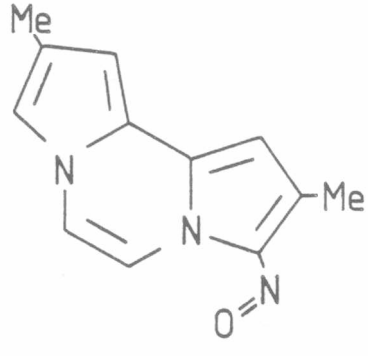
was more complex than that of compound (110) showing two 3H singlets at δ2.61 and δ2.81 attributable to CH_3-9 and CH_3-2 respectively. Further downfield a 1H singlet at δ7.76 and an AB doublet centered at δ8.50 and δ9.10 were assigned to H-10, H-6 and H-5 respectively. The 1H singlets at δ10.01, δ10.04 and δ10.32 were assigned to the three formyl protons.



(111)

Nitrosation

The addition of nitrous acid to 2,9-dimethyldipyrrolo-[1,2-a:2,1-c]pyrazine (93) gave 2,9-dimethyl-3-nitroso-dipyrrolo[1,2-a:2,1-c]pyrazine (112). The pmr spectrum of



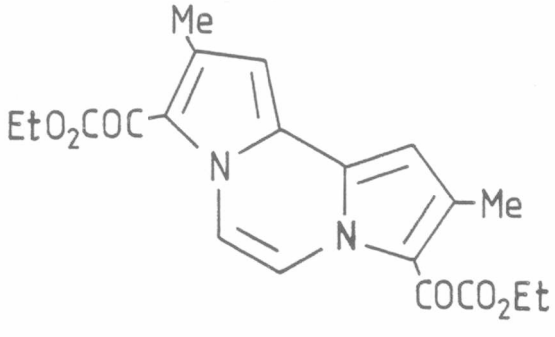
(112)

this compound consisted of two 3H singlets at δ2.32 and δ2.80 which were assigned to the methyl groups at C-9 and C-2 respectively, three 1H singlets at δ6.65, δ6.94 and

δ7.30 were due to H-10, H-1 and H-8 and the 2H AB doublet at δ7.35 and δ8.90 were attributed to H-6 and H-5 respectively. The significantly lower field absorption of H-5 was attributed to the anisotropic deshielding effect of the peri-oriented 3-nitroso group.

Reaction between dipyrrolo[1,2-a:2,1-c]pyrazine and ethoxalyl chloride

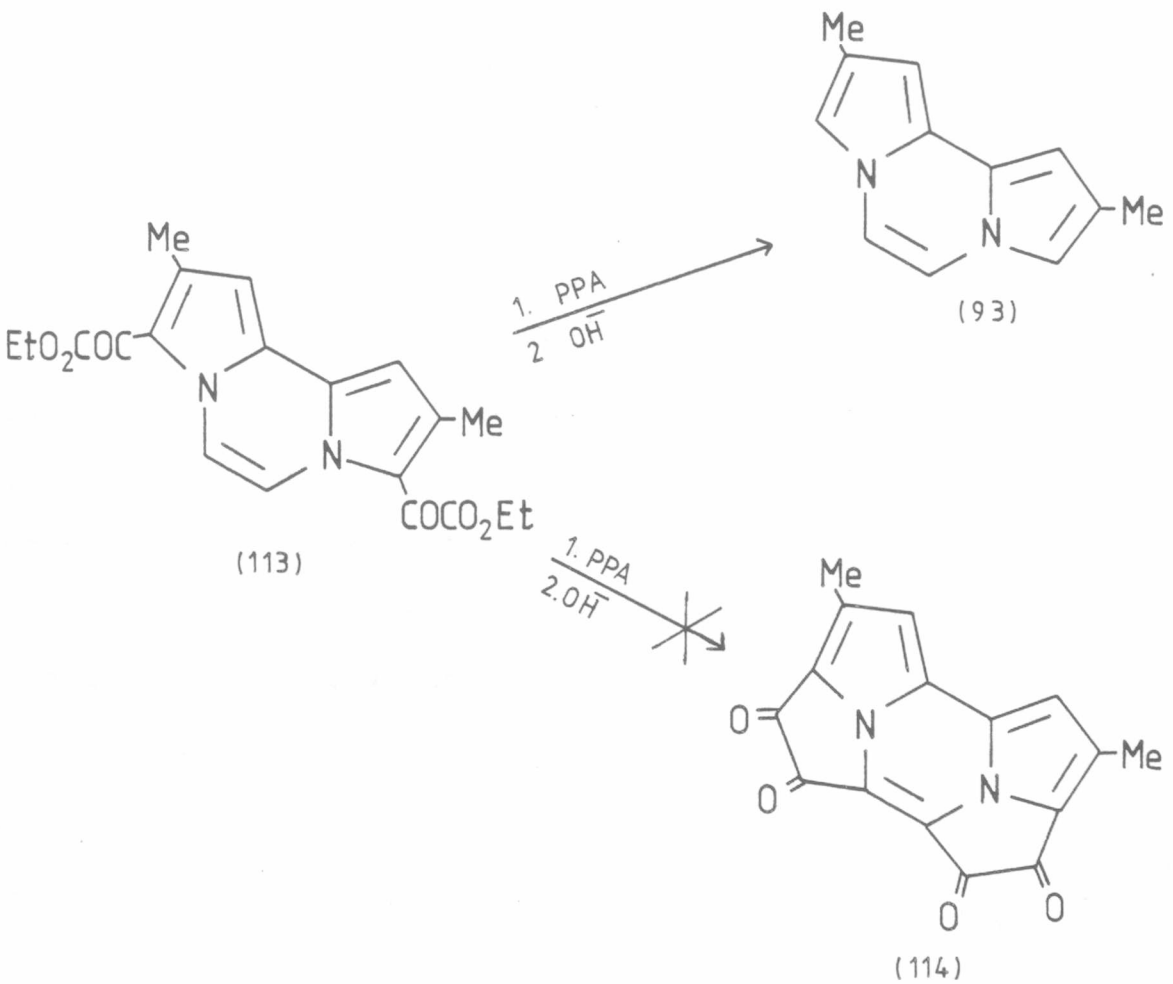
2,9-Dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) reacted with excess ethoxalyl chloride in dichloromethane to give a green solid whose ir spectrum showed two carbonyl absorption bands at 1730 cm^{-1} and 1745 cm^{-1}. The simplicity of the pmr spectrum suggested a symmetrical structure. It showed a 6H singlet at δ2.40, two 2H singlets at δ6.65 and δ9.00, a 4H quartet at δ4.45 and a 6H triplet centered at δ1.45. These observations indicate the structure of the compound to be 3,8-diethoxalyl-2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (113).



(113)

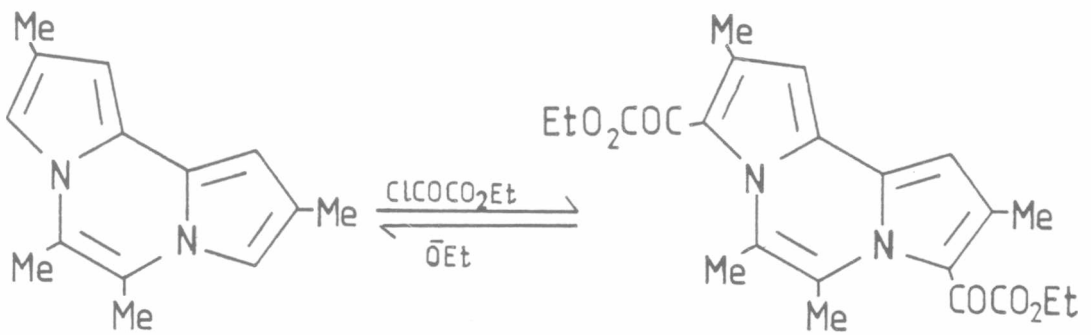
The pmr signals are assigned as follows: the 6H singlet at δ2.40 is attributed to CH_3-2(CH_3-9), the quartet at δ4.45 and the triplet at 1.45 to the ethyl groups and the 2H singlet at δ6.65 to H-1(H-10) and the 2H singlet at δ9.00 assigned to H-5(H-6). The latter signal showed a downfield shift of 117Hz relative to the corresponding signal of compound (93). This is attributed to the anisotropic deshielding effect of the carbonyl peri-oriented C-3 and C-8 ethoxalyl groups.

The diethoxalyl compound (113) was heated with polyphosphoric acid and then with base in an attempt to cyclise it to the tetracyclic compound (114). However, spectroscopic examination of the reaction products showed only starting material together with some 2,9-dimethyl-dipyrrolo[1,2-a:2,1-c]pyrazine (93).



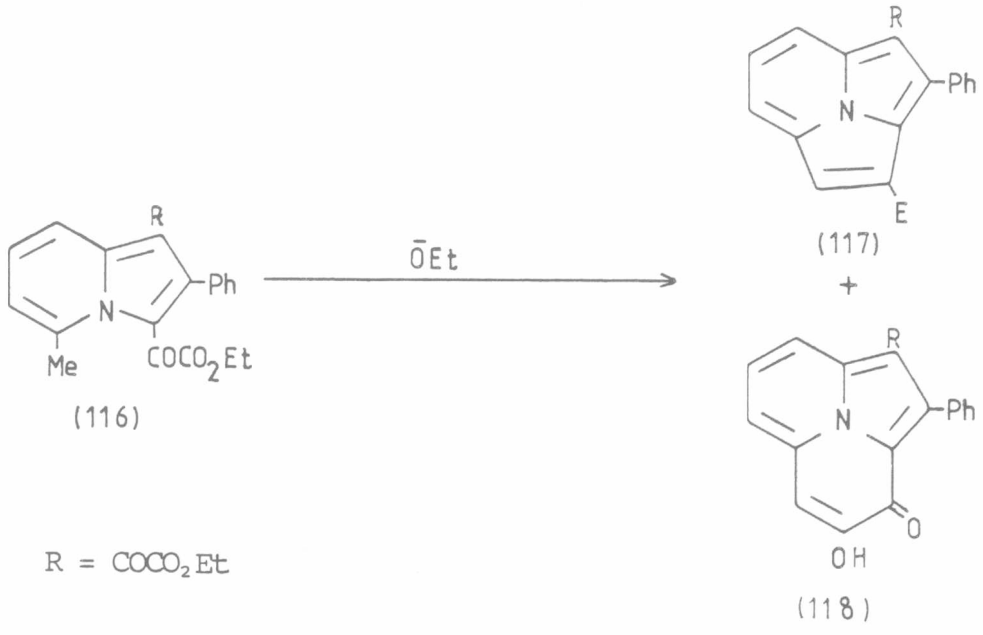
Reaction between 2,5,6,9-tetramethyldipyrrolo-[1,2-a:2,1-a]pyrazine and ethoxalyl chloride

Similarly compound (95) reacted with ethoxalyl chloride to give the diethoxalyl derivative (115). The pmr spectrum of compound (115) was simple and showed the presence of two ethyl groups as a quartet at δ4.43 and a triplet at δ1.42 and four methyl groups as a singlet at δ2.39 and a 2H singlet at δ6.63 attributed to H-1(H-10). These assignments infer electrophilic substitution to have occurred at C-3 and C-8.



(95) (115)

Treatment of the 3,8-diethoxalyl derivative (115) with ethoxide ion resulted in the removal of the COCOOEt groups to give 2,5,6,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (95). This reaction with ethoxide ion contrasts with the corresponding reaction of the ethoxalyl indolizine compound (116) which gives (117) and (118) by cyclisation involving the acidic methyl group at the C-5 position[73].

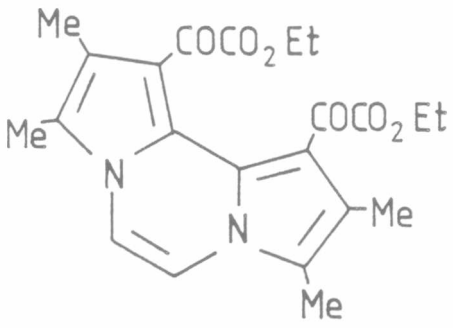


R = $COCO_2Et$

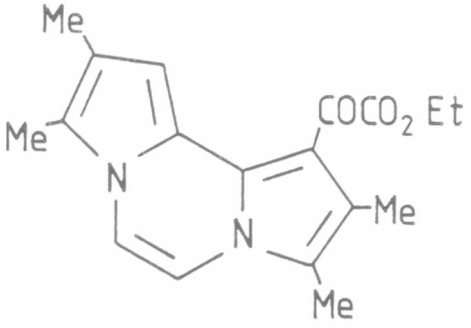
Reaction between 2,3,8,9-tetramethyldipyrrolo-[1,2-a:2,1-c]pyrazine and ethoxalyl chloride

The reaction between 2,3,8,9-tetramethyldipyrrolo [1,2-a:2,1-c]pyrazine (94) and ethoxalyl chloride gave the di- and the mono- ethoxalyl derivatives (119) and (120). The pmr spectrum of the diethoxalyl derivative (119) showed two 6H singlets at δ2.19 and δ2.24 assigned to CH_3-2(CH_3-9) and CH_3-3(CH_3-8) respectively, a 4H quartet centered at δ4.28 and a 6H triplet centered at δ1.34 were assigned to the ethyl groups and a 2H singlet at δ7.10 due to H-5(H-6).

The pmr spectrum of the mono derivative (120) showed the presence of the four methyl groups as singlets at δ2.17, δ2.23, δ2.25 and δ2.33 and one ethyl group as a quartet at δ4.40 and a triplet at δ1.40. Further downfield, a 2H doublet centered at δ7.16 and δ6.94 was assigned to H-5 and H-6 respectively. The 1H singlet at δ7.84 was assigned to H-10 since it is deshielded by the peri-oriented ethoxalyl group.



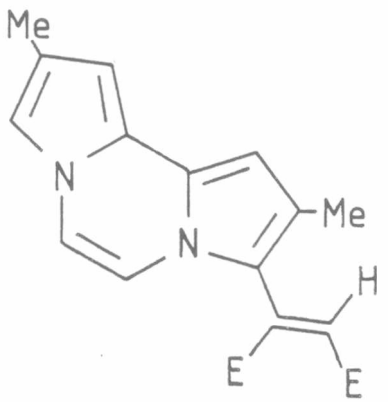
(119)



(120)

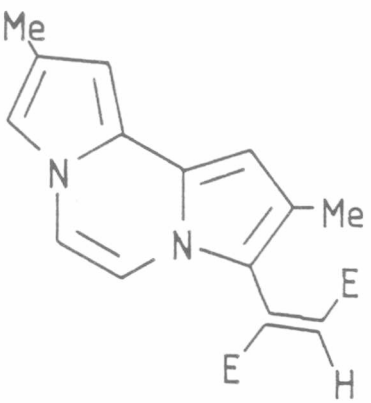
Reaction between 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine and DMAD.

When a mixture of 2,9-dimethyldipyrrolo[1,2-a:2,1-c]-pyrazine (93) and DMAD was allowed to react at room temperature for 48 hours, a crude product was obtained. Separation by tlc afforded two isomers. These proved to be the cis and trans isomers (121) and (122).



cis-isomer

(121)



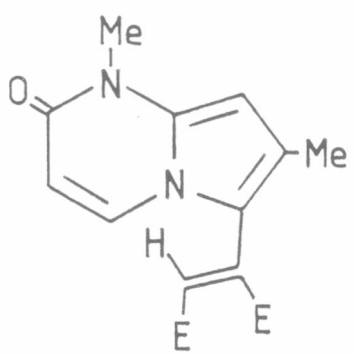
trans-isomer

(122)

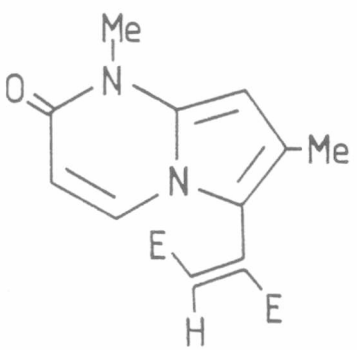
The pmr spectrum of the trans isomer (122) showed two 3H singlets at δ2.06 and δ2.23 due to the methyl groups at

C-9 and C-2 and another two 3H singlets at δ3.62 and δ3.79 due to the ester methyl groups, a 2H singlet at δ6.36 was attributed to H-1 and H-10 and a 1H singlet at δ6.76 to H-8. An AB doublet centered at δ6.70 and δ6.90 was attributed to H-5 and H-6. The only other signal was a very sharp 1H singlet at δ7.07 which was attributed to the vinyl proton of the ethene unit.

The pmr spectrum of the cis isomer (121) was similar to that of the trans isomer (122) except that the vinyl proton appeared as a sharp singlet at δ5.99. The vinyl proton of the trans isomer (122) occurs at considerably lower field (δ7.07) than that of the cis isomer (δ5.99) because of the anisotropic deshielding of the ester carbonyl on the adjacent α-carbon. A similar difference has been observed



(123)

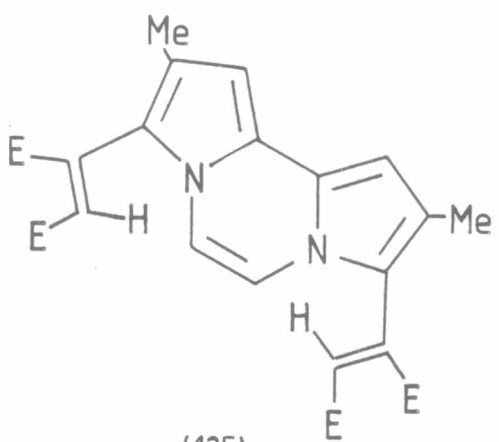


(124)

with other cis and trans isomers, for example in the reaction of 2,8-dimethyl-8-azaindolizin-7(8H)-one with DMAD the cis- and trans- stereoisomers (123) and (124) were isolated among the products[26]. The vinyl proton of the cis isomer absorbed at δ5.93 whereas the vinyl proton of the

trans isomer absorbed at δ7.13.

When 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) was treated with an excess of DMAD only one product was isolated which proved to be the 3,8-disubstituted compound (125). Its pmr spectrum showed a 6H singlet at δ2.25 due to CH_3-2(CH_3-9), two 6H singlets at δ3.79 and δ3.89 assigned to the presence of four ester methyl groups, two 2H singlets at δ6.48 and δ7.31 due to H-1(H-10) and H-5(H-6) respectively. The remaining sharp 2H singlets are attributed to the vinyl protons and since these resonances occur at δ6.04, it is suggested that the di-substituted derivative is the cis-cis isomer (125).

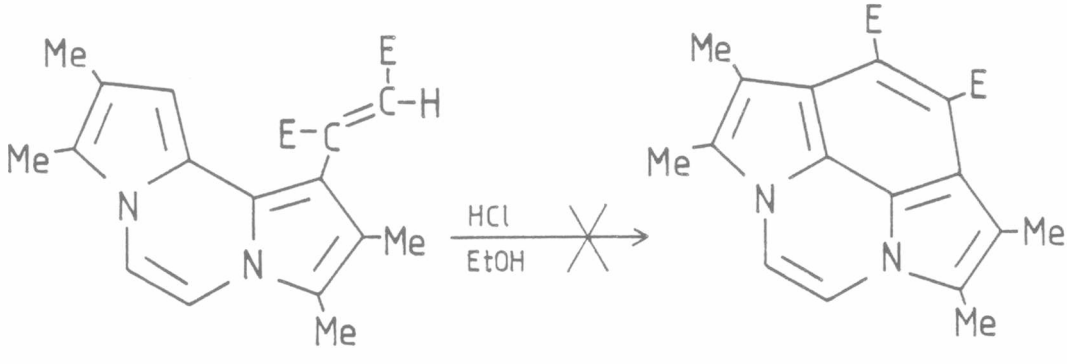


(125)

Reaction between 2,3,8,9-tetramethyldipyrrolo[1,2-a:-2,1-c]pyrazine and DMAD.

Since DMAD readily substitutes at the 3- and 8-positions of dipyrrolo-pyrazines, an attempt was made to effect reactions at position 1 and 10 by blocking the 3- and 8- positions. Thus 2,3,8,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (94) was treated with DMAD in toluene. This reaction gave the mono substituted dipyrrolo-pyrazine (126).

Its pmr spectrum showed the presence of two methyl groups at δ2.12 and δ2.18 which are attributed to the groups at C-9 and C-2, two methyl groups at δ2.28 due to the groups at C-3 and C-8 and two ester methyl groups occurred at δ3.84. The 1H singlet at δ6.55 is attributed to H-10 and the AB doublet at δ6.85 and δ6.95 to H-5 and H-6 respectively. The vinyl proton appeared as a singlet at δ6.20 and its resonance value suggests the compound to be the cis isomer.



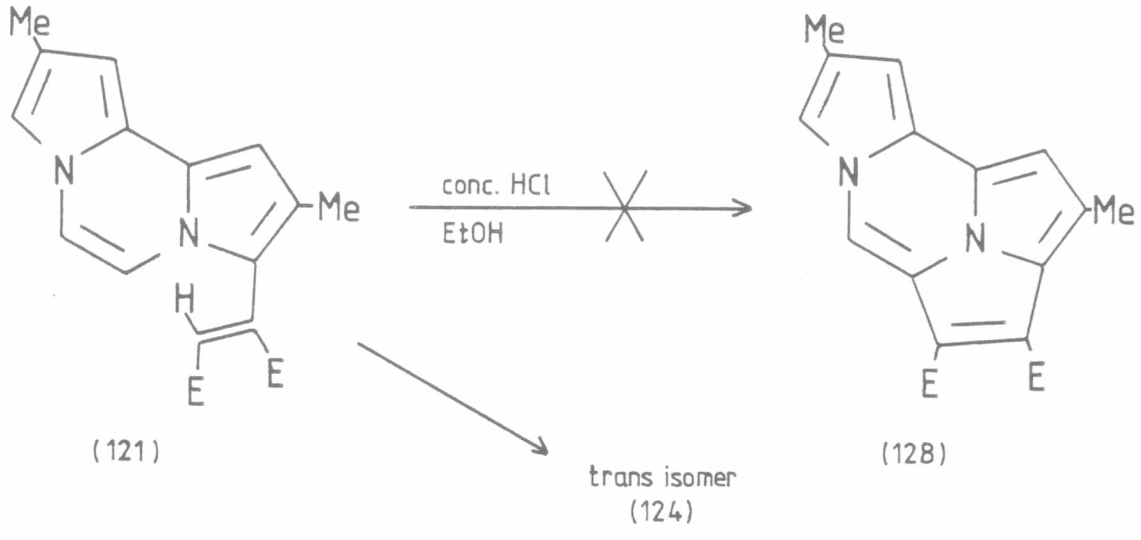
(126) (127)

When compound (126) was refluxed in ethanol with concentrated hydrochloric acid in an attempt to cyclise it to the tetracyclic structure (127), no characterisable product could be isolated.

Attempted cyclisation of the cis dimethyl ethylene-dicarboxylate dipyrrolo-pyrazine (125)

The 3-dicarbomethoxyethene-5-azaindolizine derivative has been successfully cyclised to a tricyclic compound (33) under acidic conditions (see Chapter 1, page 21). Thus an attempt was made to cyclise compound (121) to the corresponding tetracyclic compound (128). The reaction

between compound (121) and concentrated hydrochloric acid in ethanol gave a crude product. The tlc examination of this showed only the presence of the starting material together with traces of trans isomer (122).



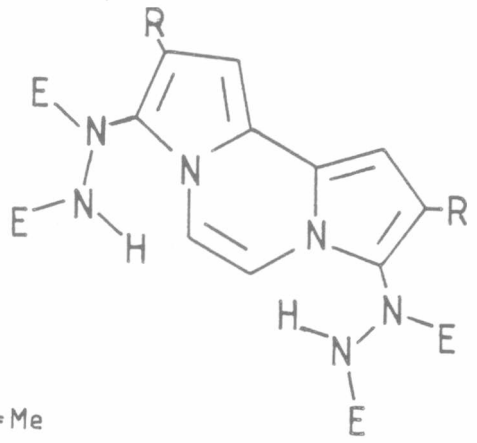
(121) (128)

Reaction between 2,9-dimethyl dipyrrolo[1,2-a:2,1-c]-pyrazine and diethyl azodicarboxlate (DAD)

A mixture of 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) and DAD in toluene gave a solid whose melting point was 227°C. This solid was found to be sparingly soluble in most solvents. The analytical data of this compound indicated a molecular formula of $C_{24}H_{32}N_6O_8$ which showed that 2 moles of DAD had reacted with 1 mole of the dipyrrolo-pyrazine. The pmr spectrum was simple and showed a methyl, ethyl, two aromatic proton signals and a broad N-H signal. Thus the product from this reaction is assigned to structure (129).

The pmr spectrum of this compound is as follows: the 6H singlet at δ2.15 is due to CH_3-2(CH_3-9), the quartet-triplet system centered at δ4.21 and δ1.27 is attributed to the

four ethyl groups, the 2H singlets at δ6.29 and δ7.12 are assigned to H-1(H-10) and H-5(H-6) respectively, the 2H broad signal at δ7.55 is due to the N-H groups. Similarly, 2,9-di-t-butyldipyrrolo[1,2-a:2,1-c]pyrazine (92) reacted with DAD to give the 3,8-disubstituted derivative (130).



(129) R=Me
(130) R=t-butyl

Conclusions

Dipyrrolo[1,2-a:2,1-c]pyrazines readily react with electrophiles to undergo electrophilic substitution, reaction taking place preferentially at C-3(C-8) and when 3,8-disubstituted, substitution occurs at C-1(C-10). In this respect the dipyrrolo[1,2-a:2,1-c]pyrazine system behaves analogously to indolizine(s). However, unlike indolizine(s) which undergo 1,3-dipolar addition with DMAD, dipyrrolo[1,2-a:2,1-c]pyrazines resist dipolar addition and reaction with dienophiles such as DMAD and DAD simply result in their substitution at C-3(C-8) and/or C-1(C-10). This preference for substitution to the exclusion of addition points to the π-excessive heteroaromatic nature and marked integral stability of the symmetrical dipyrrolo-[1,2-a:2,1-c]pyrazine system.

CHAPTER 6

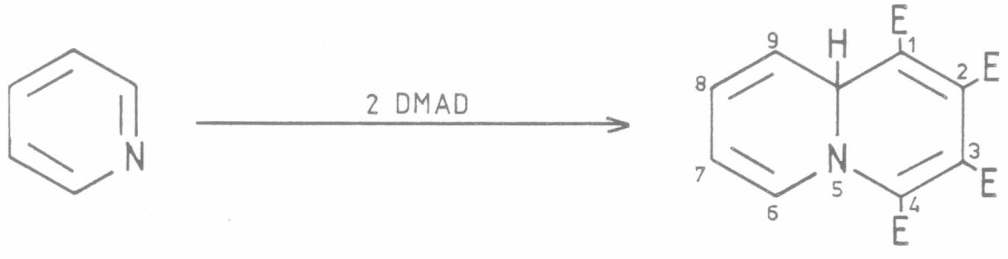
REACTIONS OF 7-AZAINDOLIZINES WITH DIMETHYL ACETYLENE-DICARBOXYLATE (DMAD)

Indolizine and its 1-, 6-, and 8-aza derivatives have been reported to undergo 1,3-dipolar addition reactions with DMAD to give cycl[3.2.2]azine and azacycl[3.2.2]-azines[26,50,78,79,80]. These reactions are normally carried out in boiling toluene in the presence of palladium on charcoal. Using similar conditions Dunham[27] reacted 7-azain-dolizine with DMAD but did not obtain an azacycl[3.2.2]azine or any characterisable product.

Initially in the work for this thesis the reaction between 7-azaindolizine and DMAD using similar conditions to Dunham was repeated, but again no characterisable compounds could be isolated. However, when this reaction was repeated at room temperature in the absence of palladium on charcoal, a single product was obtained and characterised. Furthermore, 8-methyl-, 8-ethyl- and 8-amino derivatives of 7-azaindolizine also readily react with DMAD in the absence of palladium on charcoal to yield a variety of polycyclic products. This chapter describes these reactions and it seems appropriate to give as an introduction a brief survey of some related reactions previously reported.

Some reported reactions of pyridines and quinolines with DMAD

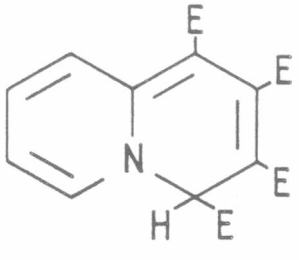
At temperatures between 0^{o} and $25^{o}C$, pyridine and many alkyl pyridines react with 2 moles of DMAD in various solvents[81,82,83,84] to give 9aH-quinolizines. For example pyridine gives (131). These quinolizines could be formed by



(131)

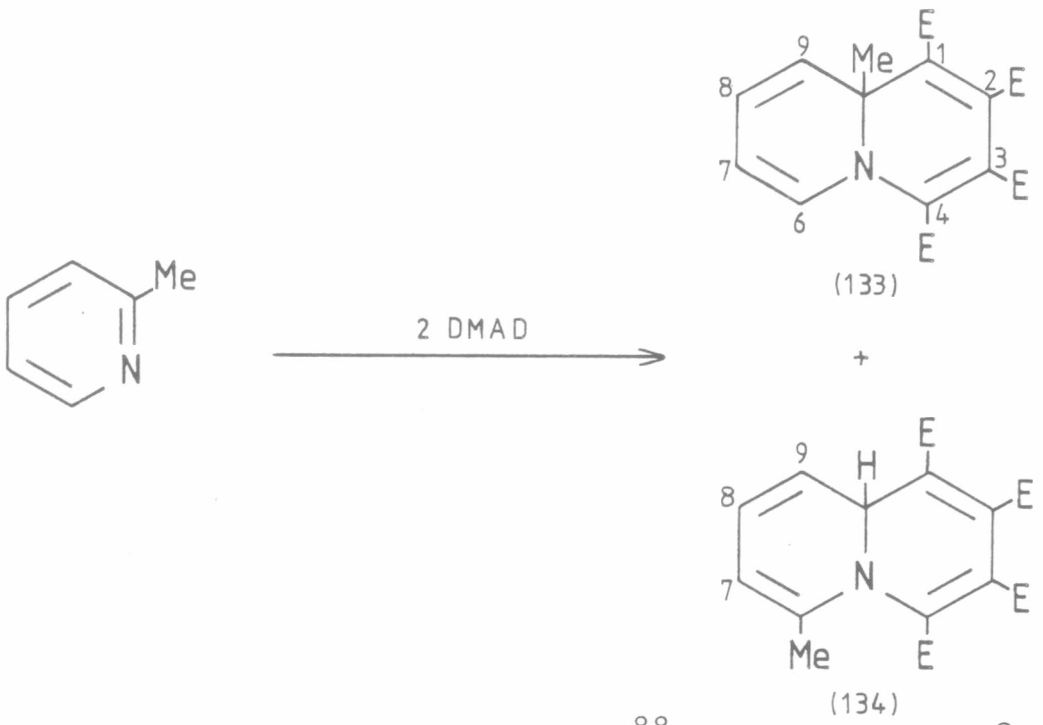
$E = COOCH_3$

either a stepwise or concerted cycloaddition process. The 9aH-quinolizine (131) readily rearranges at room temperature to the 4H-isomer (132) by a 1,5 sigmatropic shift[85]. The presence of alkyl groups can greatly stabilize the 9aH-quinolizine system, but rearrangement to the 4H-isomer takes place in hot toluene[85].

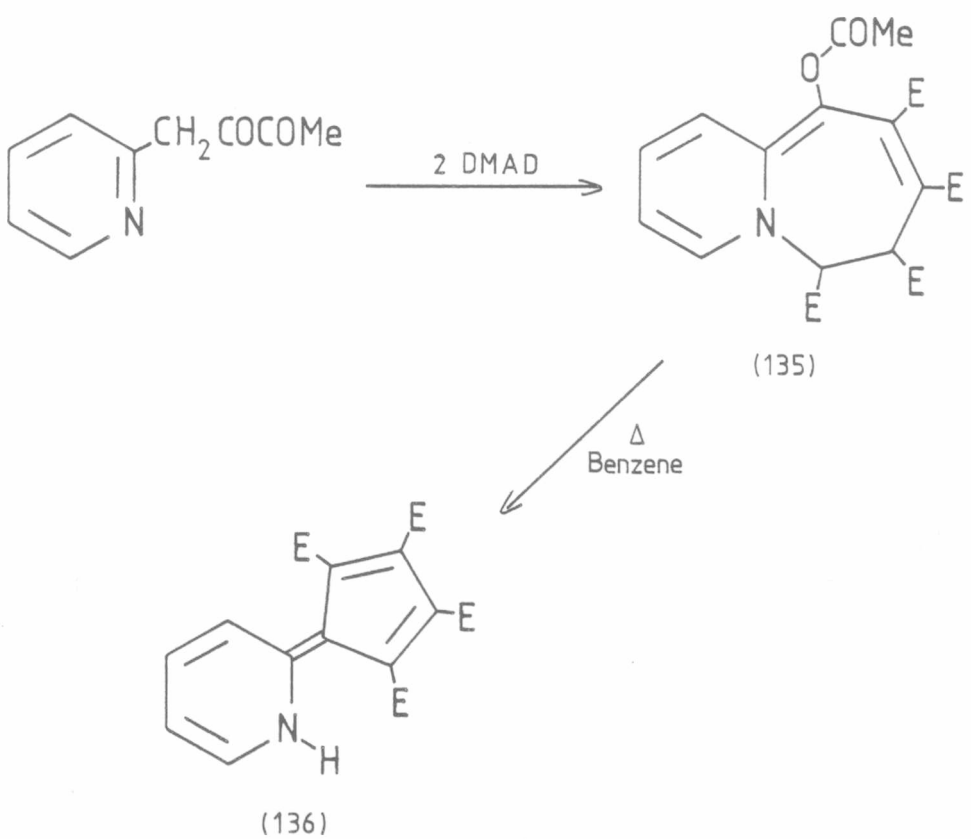


(132)

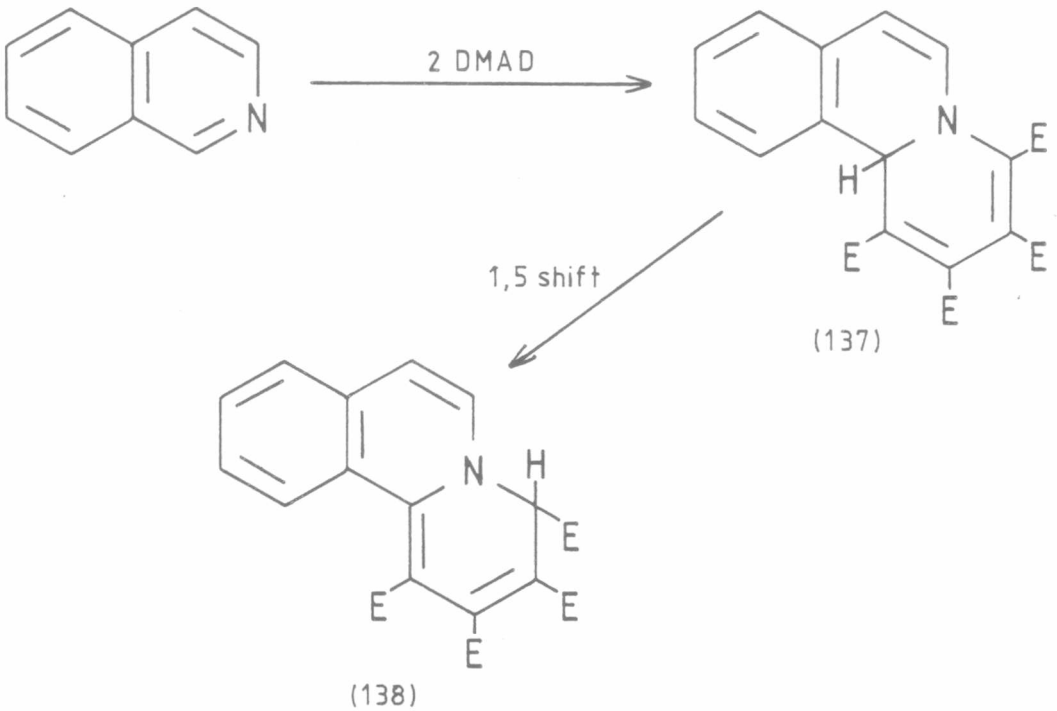
2-Methylpyridine[86,87] reacts with DMAD to give a mixture of 9a-methyl- and 6-methyl-9aH derivatives (133) and (134).



However 2-acetoxymethyl pyridine[88] with DMAD at 0°C in dry ether gives the pyrido[1,2-a]azepine (135) which can be converted to (136) on heating in benzene.



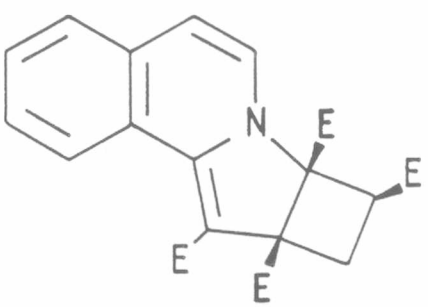
Isoquinoline reacts with DMAD in the absence of carbon dioxide or other trapping agents[89] to give the benzoquinolizine (137) which isomerises in the presence of acid or on heating to compound (138). This reaction is analogous to the corresponding reaction with pyridine.



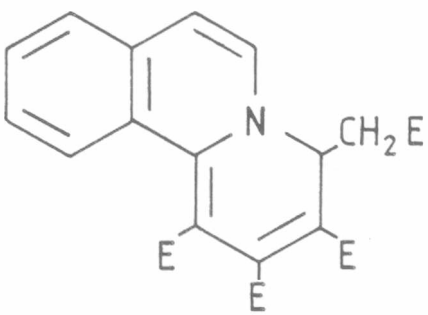
(137)

(138)

However 1-methylisoquinoline reacts with DMAD to give products which are usually quite different from those obtained from 2-methylpyridines. For example 1-methylisoquinoline with DMAD in ether gives a cyclobutapyrroloisoquinoline (139) and a benzoquinolizine[90] (140).

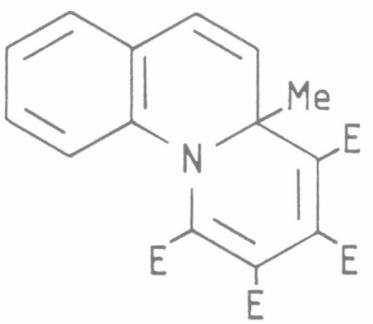


(139)

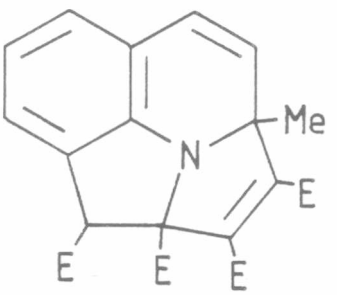


(140)

The reaction of 2-methylquinoline with DMAD has been extensively studied. In the initial work carried out by Diels and Alder[91,92,93], yellow, red and colourless adducts were obtained. The yellow adduct was identified as the 4a-methyl-4aH-benzo[c]quinolizine (141) from its nmr spectrum[94]. The red compound was originally considered to have structure (141), but later, structure (142) was suggested[93]. Johnson et al.[95] considered the dipolar structure (143) to best accommodate the pmr spectrum of the red compound but this was incompatible with its low dipole moment[96].

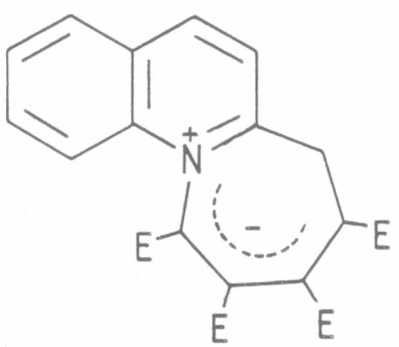


(141)

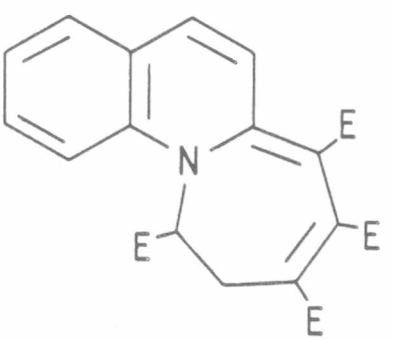


(142)

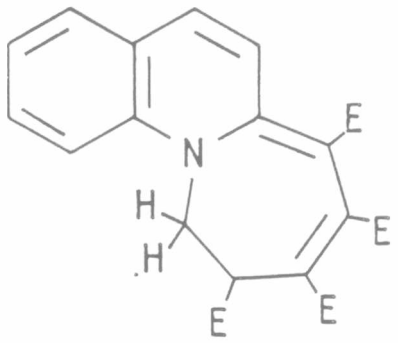
Acheson and co-workers[90,97,98] studied and extended this reaction. They obtained three types of adducts to which they originally gave the structures (144), (145) and (146)



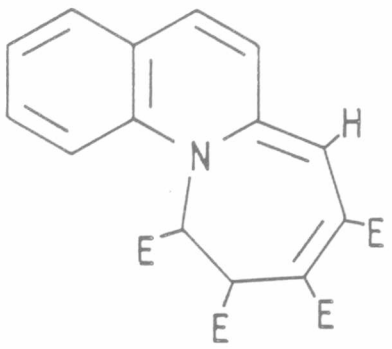
(143)



(144)

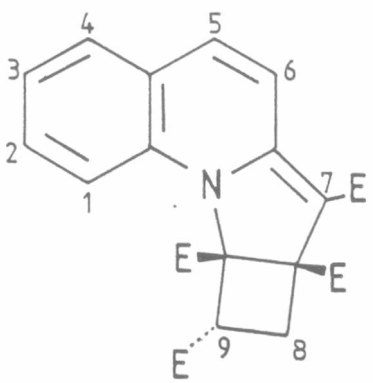


(145)

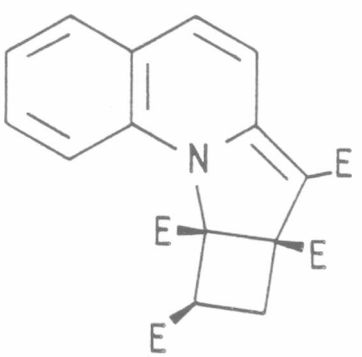


(146)

Subsequent x-ray crystal structure determinations[99] and cmr studies[100] showed that the compound which was proposed to be (144) had in fact structure (147) and the compound which was given structure (145) was (148). Compounds (147) and (148) differ only in the stereochemical arrangement of the ester group about the cyclobutane ring. The stereoisomers (147) and (148) could be distinguished by



(147)

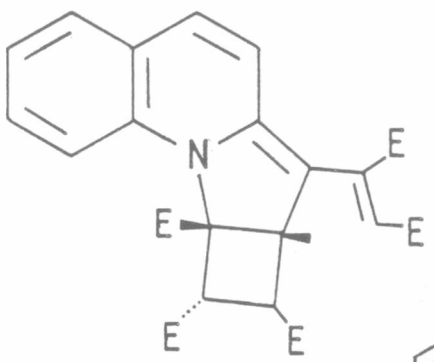


(148)

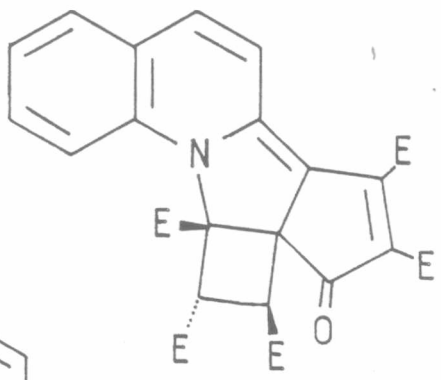
their pmr spectra[97]. Compound (147) showed one high field aromatic proton and one high field ester methyl group

whereas isomer (148) showed ester methyl and aromatic proton resonances in the normal positions. These differences are due to the fact that the trans ester methyl group at position 9 of of compound (147) is in the shielding region of the aromatic carbocyclic ring, and the 1-proton of the aromatic system is in the shielding region of the 9-ester carbonyl group, thus accounting for their high field resonances in their nmr spectra.

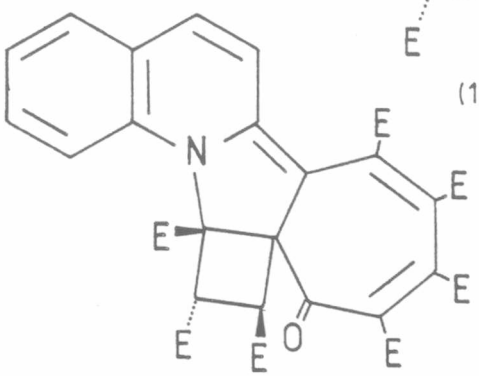
Additional adducts[101] have also been obtained from the reaction of DMAD and 2-methylquinoline and these adducts[99,100,102] were formulated as (149), (150) and (151). These three compounds incorporate more than 2 moles of DMAD for each mole of 2-methylquinoline. Thus, six compounds viz. (141), (147), (148), (149), (150) and (151) have been isolated from the reaction between 2-methylquinoline and



(149)



(150)

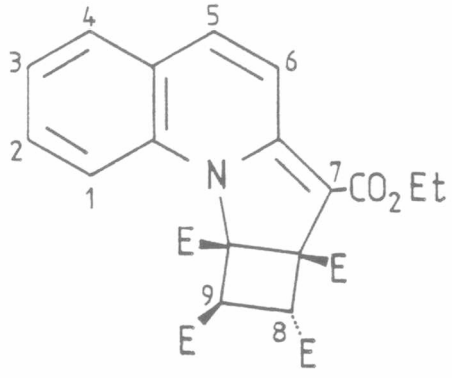


(151)

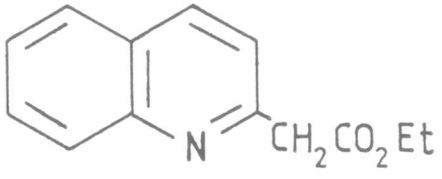
DMAD and the relative proportions of these compounds vary

with the solvent[90,95,99].

Ethylquinoline-2-acetate (152) reacts with DMAD in acetonitrile or methanol to give the 1:2 adducts[103] (153) and (154). The pmr spectra for both compounds showed similar AB doublet systems for the 8- and 9- protons, but (153) showed normal field ester methyl and aromatic proton resonances, whereas (154) possessed both a high field 9-ester methyl group and a H-1 high field aromatic proton resonance. These observations indicate the stereochemistry at position 9.



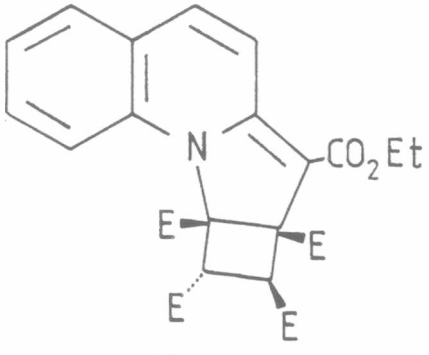
(153)



(152)

DMAD →

\+

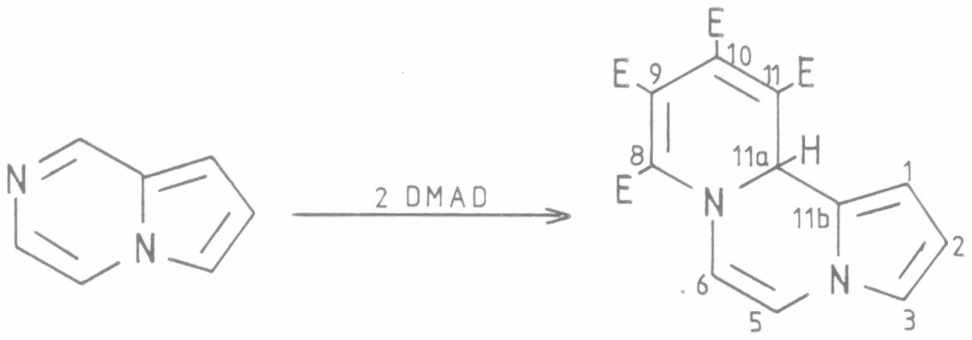


(154)

The above reactions therefore indicate that heterocycles possessing a 'pyridine type' sp^2 hybridised nitrogen readily react with DMAD to give a variety of products involving the nitrogen and the adjacent site or substituent. The structures of the products vary with the structure of the starting heterocycle and with the solvent used in the reaction.

Reaction between 7-azaindolizine and DMAD

7-Azaindolizine[7] (see page 5) was prepared by reacting pyrrole-2-carboxyaldehyde with aminoacetaldehyde diethyl-acetal followed by cyclisation with polyphosphoric acid. The freshly prepared 7-azaindolizine was reacted with excess DMAD at room temperature for 24 hours. Evaporation of the solvent and trituration of the residual oil with methanol gave a solid which on recrystallisation from methanol yielded a single compound which melted at 176°C. The elemental analysis of this compound, together with the molecular ion (m/e 402) in its mass spectrum indicated a molecular formula of $C_{19}H_{18}N_2O_8$. The ir spectrum showed ester carbonyl bands at 1700 cm^{-1} and 1730 cm^{-1}, and the pmr spectrum showed the presence of four carbomethoxy methyl groups at δ3.62, δ3.68 and δ3.85 the latter singlet integrating for six protons and a complex pattern of signals between δ5.80 and δ6.80 integrating for six protons was also observed thus suggesting the interaction of two molecules of DMAD with one molecule of 7-azaindolizine to give a 2:1 adduct. Comparison of the pmr spectrum of this compound with that of the parent 7-azaindolizine (5) showed the disappearence of the aromatic H-8 signal (this proton occurred at δ8.75 in the parent 7-azaindolizine). These observations suggested that the two molecules of DMAD had reacted at sites N-7 and C-8 of the parent 7-azaindolizine and the pmr spectrum is consistent with the structure (155) showing the angular proton as a singlet at δ6.20. Further evidence for this structure is obtained from its cmr spectrum. This showed four methyl carbons at δ55.88,

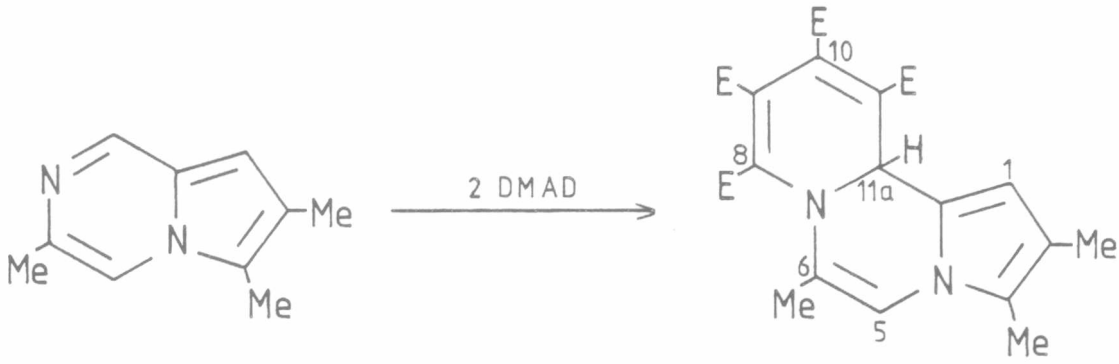


(5) (155)

δ55.99, δ56.34 and δ67.15 and four carbonyl carbons at δ166.69, δ167.51, δ168.28 and δ171.13 confirming the presence of four carbomethoxy groups in the molecule. The only other high field signal at δ58.00 was attributed to the remaining sp^3 hybridised carbon. The ten signals between δ99.42 and δ151.91 were assigned to the sp^2 hybridised carbons of the ring system, five of them at δ99.42, δ114.96, δ129.56, δ141.47 and δ151.91 were of lower intensity than the others and are assigned to the five quaternary carbons.

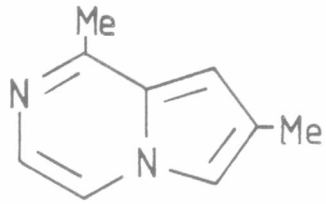
Reaction between 2,3,6-trimethyl-7-azaindolizine and DMAD

The reaction of 2,3,6-trimethyl-7-azaindolizine (43) with DMAD in toluene at room temperature again afforded a single product. The spectral characteristics of this compound i.e ir, pmr and mass spectra showed common patterns to those of compound (155) suggesting it to be the corresponding pyrido[2,1-c]pyrrolo[1,2-a]pyrazine (156). The pmr spectrum of compound (156) showed four carbomethoxy methyl singlets at δ3.60, δ3.72, δ3.80 and δ3.90 and three other methyl



(43) (156)

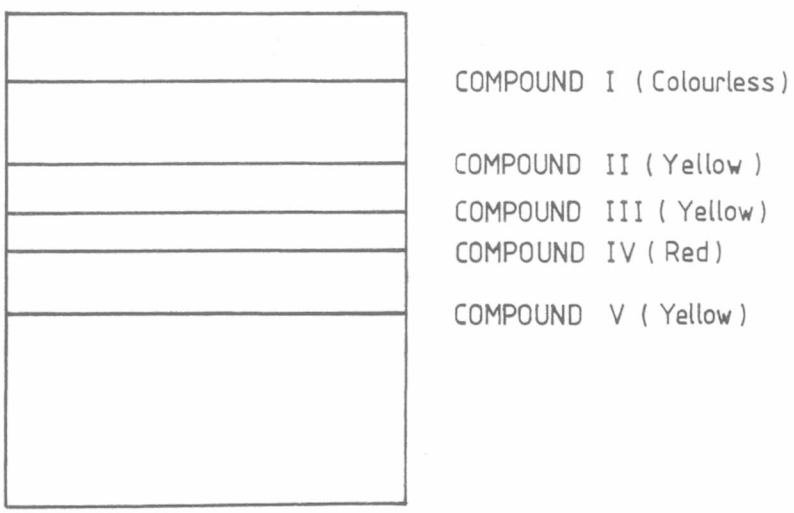
signals at δ1.95 integrating for 6 protons and at δ2.12 integrating for 3 protons. These latter signals are assigned to CH_3-2, CH_3-3 and CH_3-6 respectively. Further downfield, three 1H singlets at δ5.58, δ5.70 and δ6.65 were attributed to H-11a, H-1 and H-5 respectively, H-5 being the lowest field ring proton due to its proximity to one of the bridgehead nitrogen atoms. Further evidence for the structures of compounds (155) and (156) was obtained from the mass spectra of these compounds and will be discussed later in this chapter (see page 143).



(45)

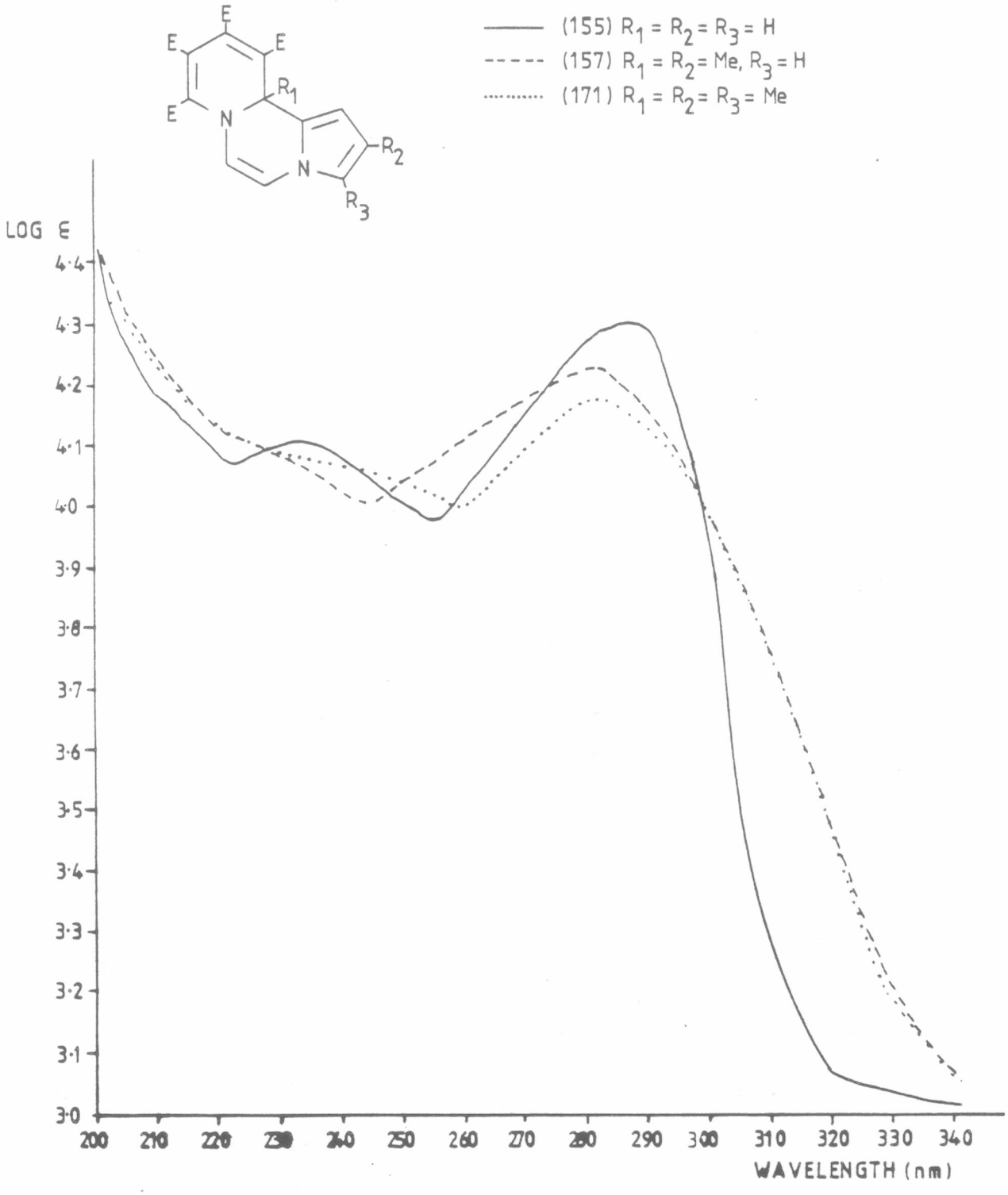
2,8-Dimethyl-7-azaindolizine (45) was allowed to react with excess DMAD in toluene at room temperature for 24 hours. The solvent was removed to give an oil which was separated into five compounds by preparative tlc. Two of these compounds occurred as bright yellow bands, one showed as a red band and the other two were fluorescent under uv light. The elution order in which these compounds appeared on tlc plates is shown in Figure 7. Each of these bands

Figure 7. Tlc separation of products in the reaction between 2,8-dimethyl-7-azaindolizine and DMAD



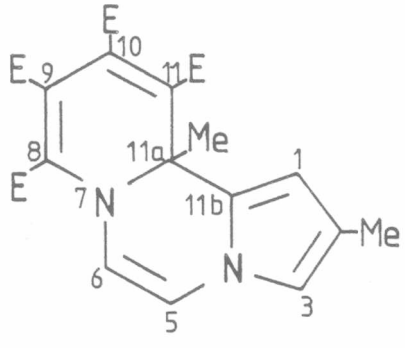
was removed from the plates to give five crystalline compounds. The order in which these compounds is discussed has been chosen to assist the reader to appreciate the relationship between the compounds isolated.

Figure 8. Uv spectra of compounds (155), (157) and (171)



Structure of compound II

The mass spectrum of this compound showed a molecular ion at m/e 430 and the elemental analysis data indicated the compound to have a molecular formula of $C_{21}H_{22}N_2O_8$. This would suggest the compound to be a 2:1 adduct of DMAD and 2,8-dimethyl-7-azaindolizine (45). There was close similarity between the uv (see Figure 8) and the ir spectra of this compound and that of compound (155). The pmr spectrum showed the presence of four carbomethoxy methyl protons at δ3.69, δ3.74, δ3.76 and δ3.93, one methyl group at δ2.02 and at higher field another methyl group at δ1.82, the other four protons showed as a 2H AB doublet centered at δ5.85 and δ6.38 and two 1H singlets at δ5.86 and δ6.38. These observations are consistent with the pyrido[2,1-c]-pyrrolo[1,2-a]pyrazine structure (157). The singlets at δ1.82



(157)

and δ2.02 in the pmr spectrum were assigned to the methyl groups at C-11a and C-2 respectively, the weakly coupled signals at δ5.85 and δ6.38 to the protons at C-1 and C-3 and the AB doublet at δ5.75 and δ6.25 to the protons at C-5 and C-6, respectively. The cmr spectrum of compound (157) is

Figure 9. cmr spectrum of compound (157)

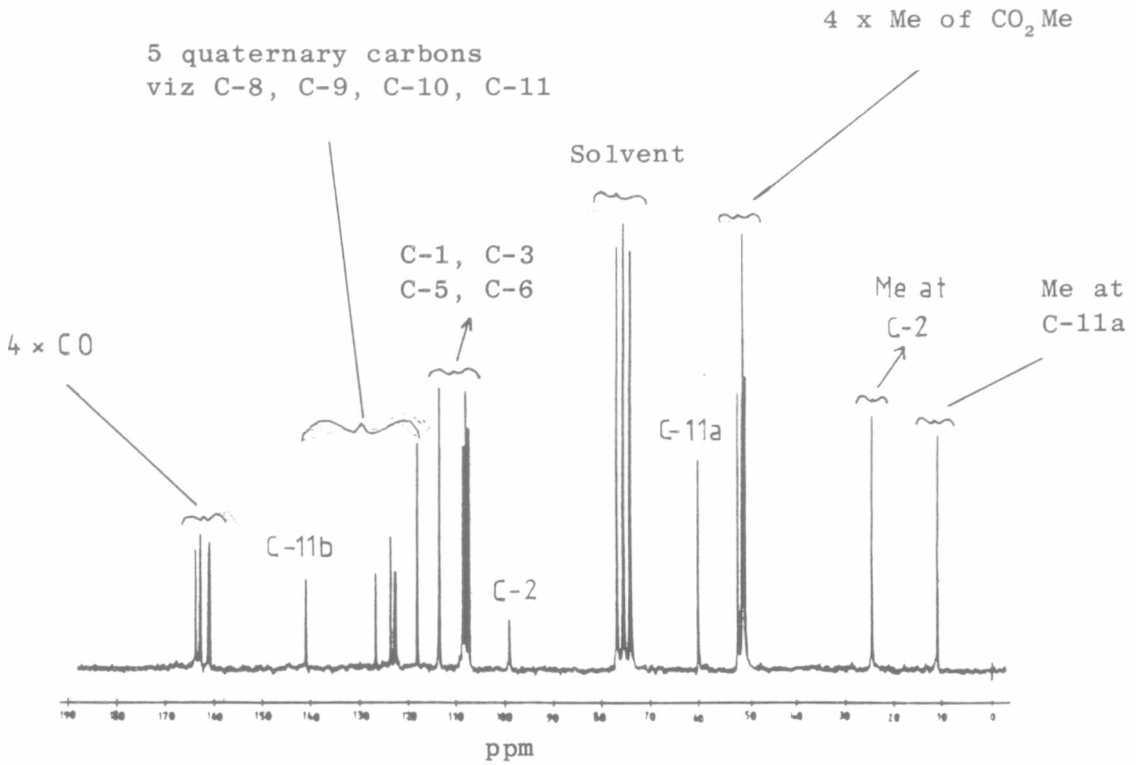
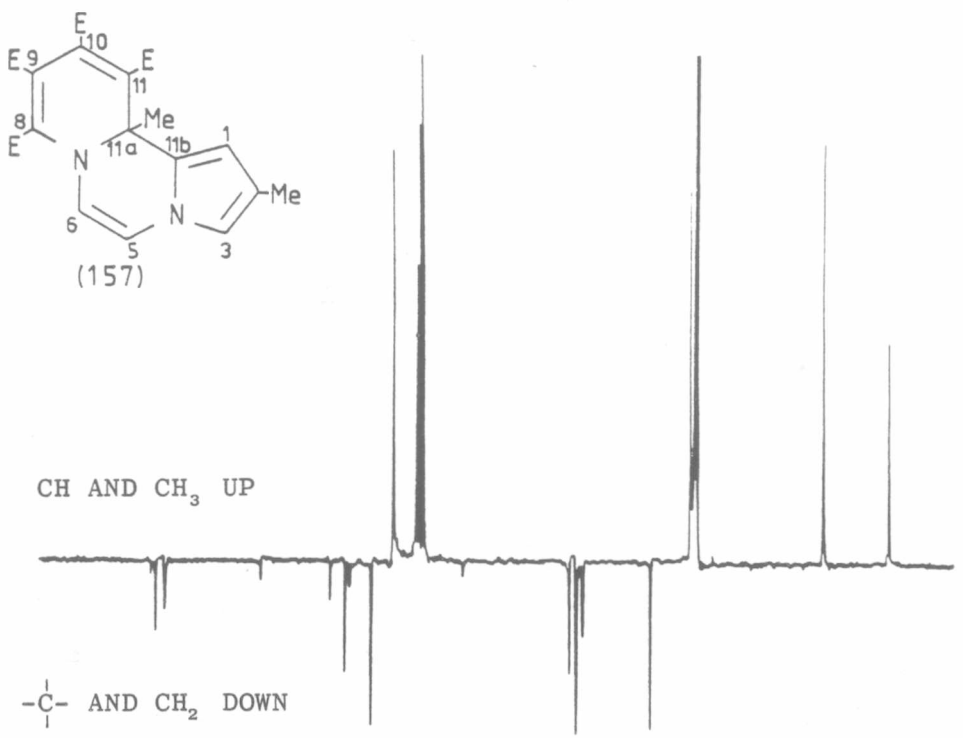


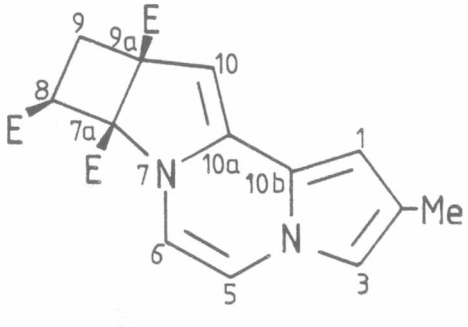
Figure 10. Spin Echo cmr spectrum of compound (157)



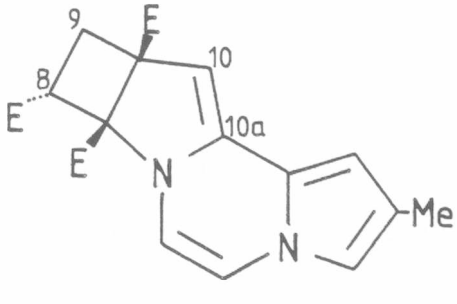
shown in Figure 9 and the assignments of different types of carbon as indicated in this figure have been made with the help of the spin echo cmr spectrum (Figure 10, page 120).

Structure of compound III

Elemental analysis of this compound indicated it to be isomeric with compound (157). The ir spectrum also showed strong ester carbonyl absorption bands at 1700 cm^{-1} and 1740 cm^{-1}. Its pmr spectrum consisted of a high field 3H singlet at δ2.20 assigned to a methyl group, four 3H singlets at δ3.63, δ3.66, δ3.70 and δ3.76 due to four carbomethoxy methyl groups, two weakly coupled 1H signals at δ6.87 and δ8.02 and a 2H AB doublet system centered at δ6.49 and δ6.73. The most significant difference between the pmr spectrum of this compound and that of compound (157) was a complex 3H multiplet in the region between δ2.64 and δ3.87 inferring the presence of a CH_2CH system in the molecule. These spectral characteristics suggested a cyclobutane structure such as (158) or (159) analogous to that of the compounds isolated from the reaction of 2-methylquinoline[100] with DMAD (see page 111).

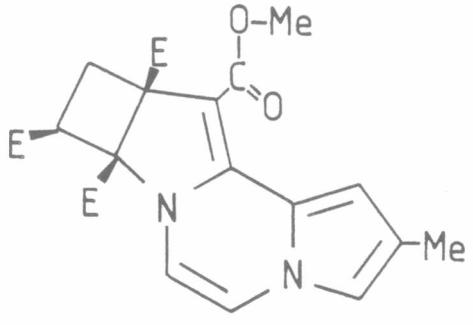


(158)

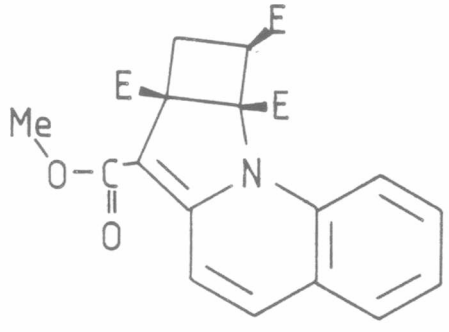


(159)

The stereochemical assignment of the 8-ester group follows from the pmr spectrum which showed a normal 8-ester methyl signal at approximately δ3.70 and not a high field ester methyl signal at around δ3.37. Therefore compound III is suggested to be stereoisomer (158) rather than (159). One of the weakly coupled protons occurred at δ8.02. This relatively low field resonance is attributed to H-1 which is deshielded by the ester carbonyl group at C-10. A similar observation[90] was reported for the benzocyclobutanquinoline system (148). The other weakly coupled proton at δ6.87 was attributed to H-3 and the AB doublet centered at δ6.49



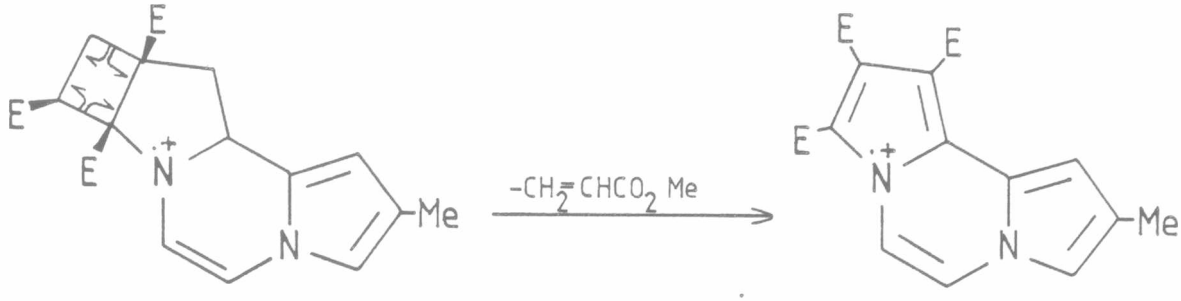
(158)



(148)

and δ6.73 were ascribed to H-5 and H-6 respectively.

The mass spectrum of compound III confirmed the cyclobutane structure (158). This showed only three significant fragmentation ions at m/e 430(45%), m/e 344(100%) and m/e 313(20%). The base peak (m/e 344) arises through the loss of methyl acrylate from the molecular ion to give the stable ion (160).

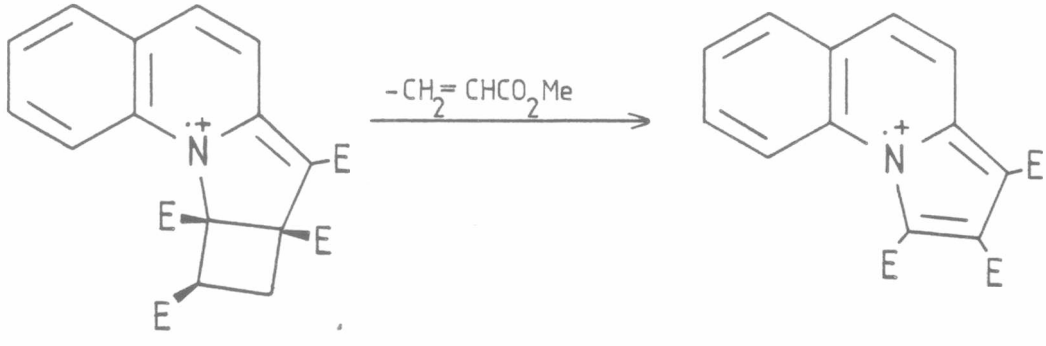


m/e 430 (50%)

(160)

m/e 344 (100%)

A similar fragmentation pattern was observed for the pyrrolocyclobutanquinolizine system[104]. For example structure (161) gave ion (162) as its base peak.



(161)

(162)

Structure of compound V

This compound was also isomeric with compounds (157) and (158) and its pmr spectrum again indicated the presence of four carbomethoxy groups, one methyl group and seven other protons. However the spectrum did not show a 3H complex multiplet in the region between δ2.64 and δ3.87 as did

Figure 11. cmr spectrum of compound (163)

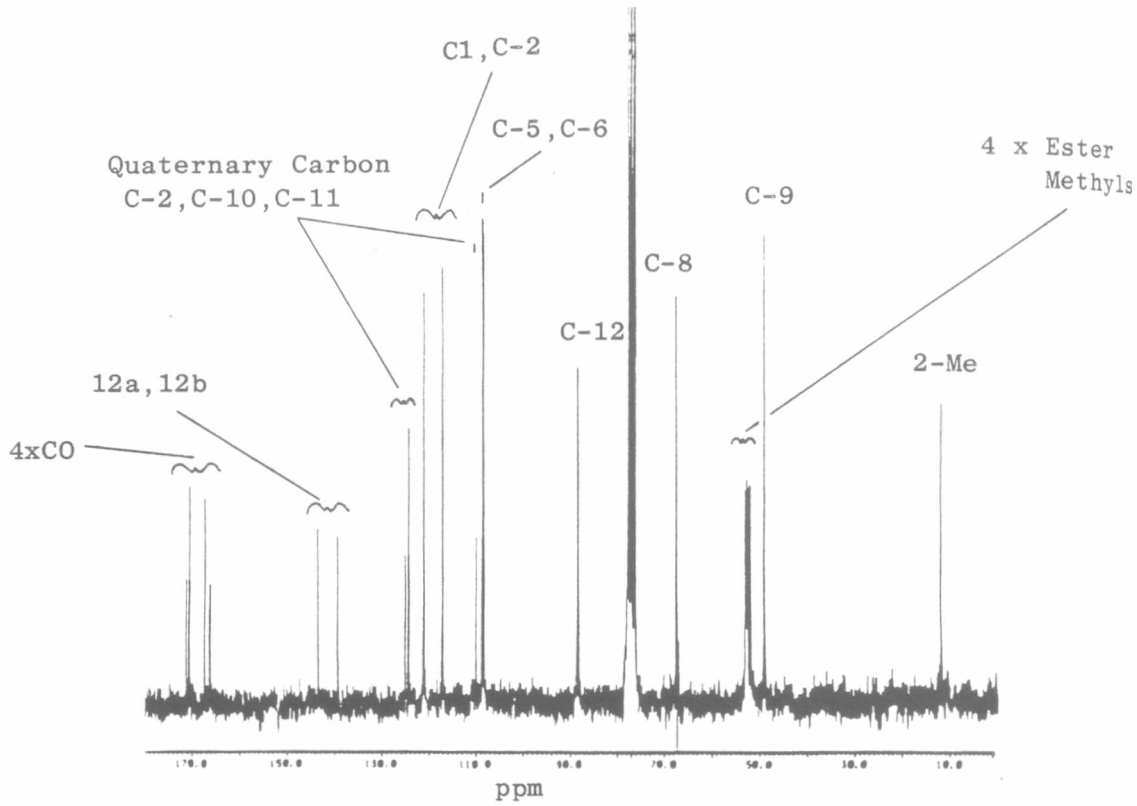
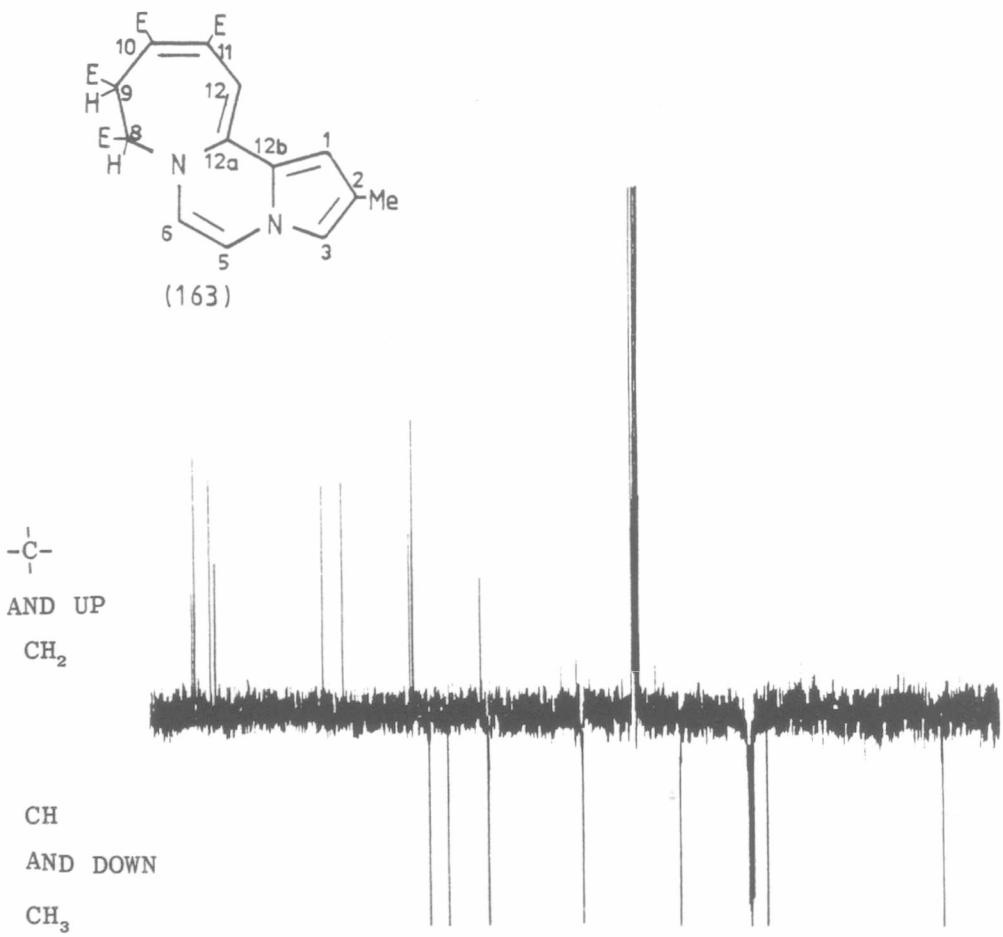
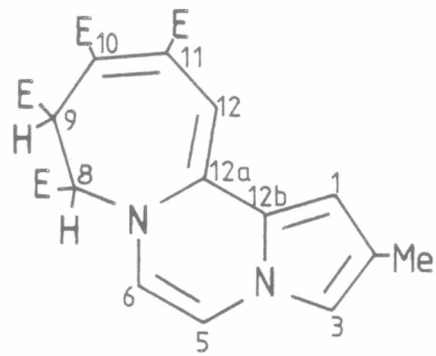


Figure 12. Spin echo cmr spectrum of compound (163)



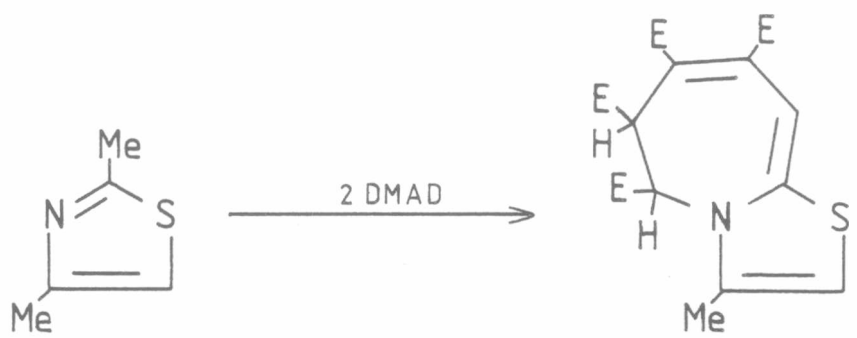
compound (158) neither did it show a low field proton resonance around δ8.02. Thus compound V cannot have a cyclobutane type of structure such as compound (158). The pmr spectrum indicated the presence of two AB doublet systems, one at δ5.25 and δ5.35 and the other one at δ6.18 and δ6.68, and three other 1H singlets at δ5.32 , δ6.56 and δ6.75. These observations are consistent with the azepinopyrrolo[1,2-a]pyrazine structure (163) where the AB doublet at δ5.25 and δ5.35 (J=6.0Hz) was attributed to the



(163)

protons at C-8 and C-9, the other doublet at δ6.18 and δ6.68 to the protons at C-5 and C-6 and the 1H singlets at δ5.32, δ6.18 and δ6.75 are due to H-12, H-1 and H-3 respectively. The cmr spectrum of compound V (Figure 11) was also consistent with structure (163) and showed resonance at δ11.97 due to the 2-methyl carbon. Further signals at δ52.06, δ52.41, δ52.65. δ52.96, δ166.12, δ167.20, δ170.45 and δ171.10 are due to the carbons of the carbomethoxy groups at C-8, C-9, C-10 and C-11. With the help of the spin echo cmr spectrum (see Figure 12), the

presence of seven carbons attached to one proton were confirmed at resonances δ48.90, δ67.49, δ88.38, 2 x δ108.59, δ117.01 and δ120.94. The first two signals are attributed to the two sp^3 hybridised carbons at positions 8 and 9 respectively while the rest are sp^2 hybridised carbons at positions 1,3,5,6 and 12. The presence of five quaternary carbons at δ109.89, δ124.10, δ124.82, δ139.04 and δ143.25 due to carbons at positions 2, 10, 11, 12a and 12b were also established. Similar azepine structures e.g (165) have been obtained from the reaction of DMAD with dimethyl thiazole (164)[105].

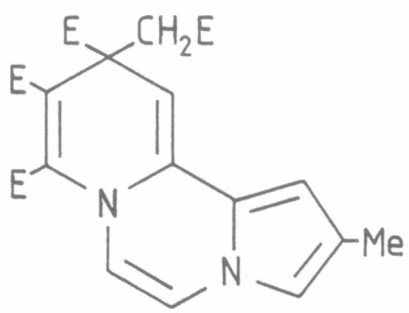


(164) (165)

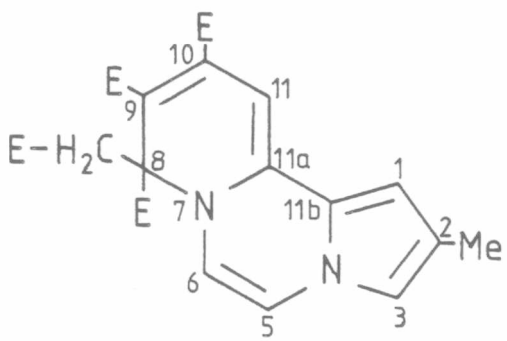
Structure of Compound IV

Analyses of compound IV indicated it to be isomeric with the compounds already discussed viz. (157), (158) and (163). This red compound with mp 191^{0}C again showed in its ir spectrum characteristic ester carbonyl bands at 1700 cm^{-1} and 1740 cm^{-1}. The uv spectrum of this compound showed a similar pattern to that of compounds (155), (156) and (157) except that the former exhibited a bathochromic shift. Its pmr spectrum indicated the presence of four ester groups and showed some similarities to the pmr spectra of (158) and

(163), however the absence of a complex multiplet between δ2.60 and δ4.00 indicated that the compound did not possess a cyclobutane structure similar to that of (158) and the absence of an AB doublet around δ5.30 would suggest that compound IV did not have an azepine stucture similar to that of (163). The significant features of the pmr spectrum of compound IV was the presence of an aliphatic 2H singlet at δ3.12 and an alkene 1H singlet at δ5.05. Its mass spectrum showed a weak molecular ion at m/e 430 (15%) and the base peak at m/e 357 corresponding to the loss of a $CH_2CO_2CH_3$ fragment from the molecular ion. The other significant ion at m/e 371 (15%) corresponds to the loss of CO_2CH_3 from the molecular ion. These mass spectral characteristics suggest compound IV to have either structure



(166)



(167)

(166) or (167). On the basis of structure (167), the pmr spectrum is interpreted as follows: the 3H singlet at δ2.20 was attributed to CH_3-2, the 2H singlets at δ3.12 due to CH_2 at C-8, the four 3H signals at δ3.60 , δ3.70, δ3.82 and δ3.85 were assigned to the four ester methyl groups.

The three 1H singlets at δ5.05, δ6.55 and δ6.84 were due to H-11, H-1 and H-3 respectively, and the AB doublet at δ6.20 and δ6.80 was attributed to H-5 and H-6 respectively. It is suggested that compound IV has structure (167) rather than (166) on the basis of the chemical shift of the proton at C-6(δ 6.82). This value is very close to the value of the C-6 proton(δ6.68) of the dihydroazepine structure (163). Had the structure been (166) the C-6 proton would have been deshielded by the peri-oriented ester group (compound (189) mentioned later shows H-6 to occur at δ8.10).

Further evidence from the cmr spectrum of compound IV as shown in Figure 13 confirms structure (167). The cmr spectrum showed resonances at δ11.81 and δ40.96 assigned to CH_3-2 and the methylene group at C-8 respectively. The presence of four ester methyl groups were confirmed by the resonances at δ51.41, δ51.99, δ52.17, δ53.41 and at δ164.30, δ169.35, δ170.10 and δ170.38. With the help of the spin echo cmr spectrum of compound (167) (see Figure 14), six quaternary carbons at δ69.53, δ100.00. δ121.89, δ124.98, δ138.15 and δ142 and five carbons attached to one hydrogen at δ84.79, δ121.89, δ124.98, δ138.15 and δ142.82 were established.

Figure 13. cmr spectrum of compound (167)

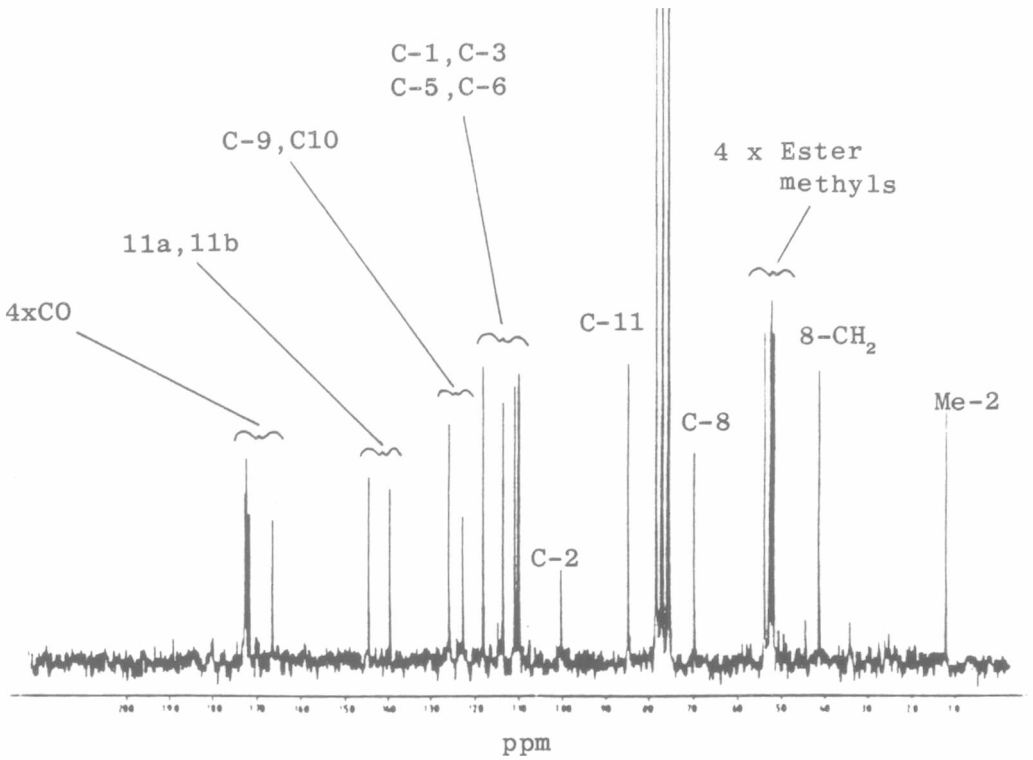
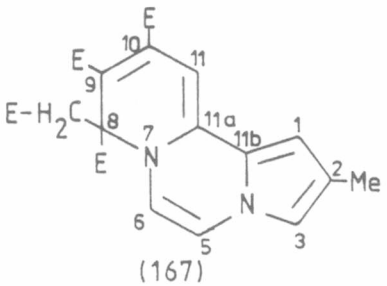
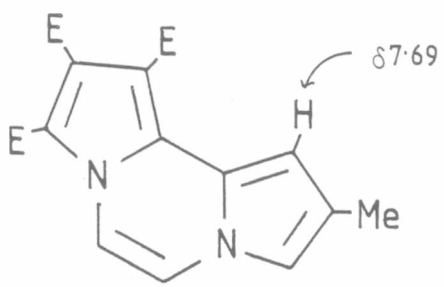


Figure 14. Spin echo cmr spectrum of compound (167)

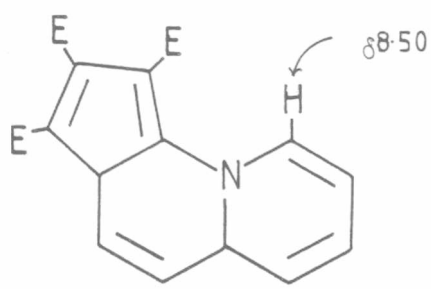


Structure of Compound I

Compound I was obtained from the fastest moving band on the tlc plates; it had a melting point of 142°C. In contrast to compounds (157), (158), (163) and (167), the mass spectrum of compound I showed a strong molecular ion at m/e 344 which was also the base peak. The only significant fragmentation ion was at m/e 313 due to the loss of a OCH_3 unit while the other ions were of low intensity (less than 8%). Analysis of this compound indicated that it is not isomeric with compounds (157), (158), (163) and (167) but had a molecular formula of $C_{17}H_{16}N_2O_6$. The pmr spectrum of compound I showed the presence of only three ester methyl groups at δ3.88 (6H) and δ3.95 (3H), the other signals being a 3H singlet at δ2.30, two weakly split 1H doublets at δ7.34 and δ8.50. Thus the spectral data indicated compound I to be 2-methyl-8,9,10-tricarbomethoxydipyrrolo[1,2-a:2,1-c]pyrazine (168). The resonances in the pmr spectrum were assigned as follows: the 3H singlet at δ2.30



(168)



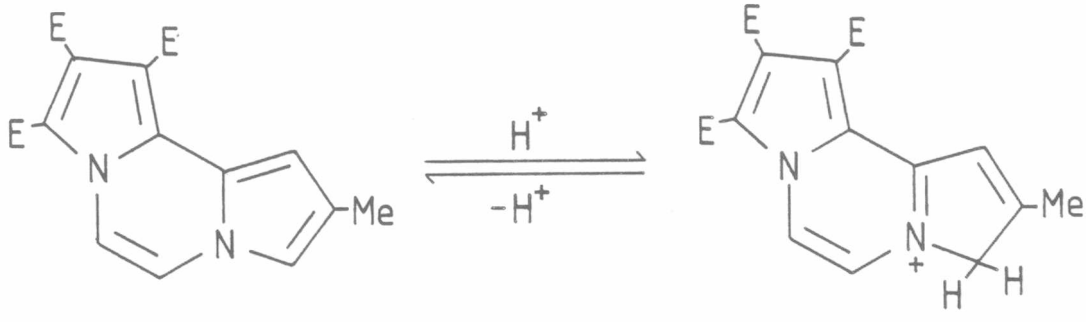
(169)

was due to the methyl group at C-2; the 6H singlet at δ3.88 to the ester methyl groups at C-9 and C-10; the 3H singlet at δ3.95 to the ester group at C-8; the 1H signals at

δ7.06 and δ7.69 were attributed to the protons on C-3 and C-1 respectively, and the AB doublet at δ7.34 and δ8.50 to the protons on C-5 and C-6 respectively. It is noteworthy that both H-1 and H-6 are strongly deshielded by the presence of the peri-oriented ester groups at C-10 and C-8. A similar deshielding effect is observed for the H-9 proton (δ8.50) of the cyclopenta[c]quinolizine[106] (169).

Protonation and deuterium exchange of the dipyrrolopyrazine (168)

The pmr spectrum of compound (168) was examined in neat CF_3COOH. When compared to the pmr spectrum of (168) in $CDCl_3$, it showed the emergence of a methylene signal at δ5.60, the disappearance of the 1H singlet due to H-3 and a general downfield shift of all the other resonances. These observations confirm C-3 protonation and the formation of conjugate acid (170). Also, when a drop of CF_3COOD was



(168) (170)

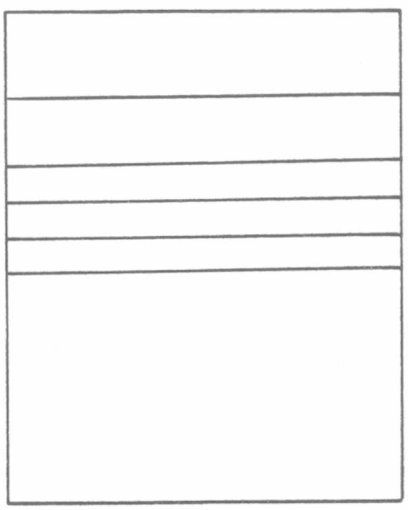
added to a solution of compound (168) in $CDCl_3$, the pmr spectrum of this solution showed firstly the disappearence of the 1H signal at δ7.06, due to H-3, followed by the

signal at δ7.69 due to H-1. This protonation and deuterium exchange behaviour of compound (168) are similar to that observed for the dipyrrolo[1,2-a:2,1-c]pyrazines discussed in chapter 5.

Reaction between 2,3,8-trimethyl-7-azaindolizine and DMAD

2,3,8-Trimethyl-7-azaindolizine (48) also reacted with excess DMAD to give five compounds whose structures were analogous to the five compounds (157), (158), (163), (167) and (168) just described. The order of elution of these compounds on tlc plates was the same as that for the reaction between 2,8-dimethyl-7-azaindolizine and DMAD (see Figure 15).

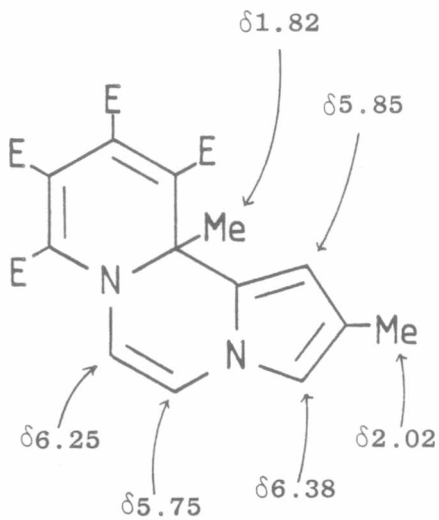
Figure 15. Tlc separation of products in the reaction between 2,3,8-trimethyl-7-azaindolizine and DMAD



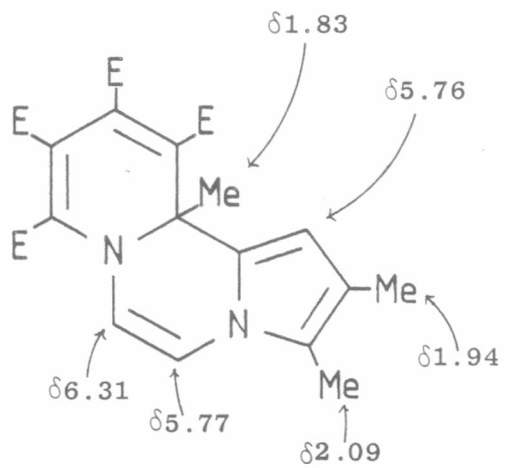
The structure of these compounds are discussed by comparison with the corresponding compounds in the previous reaction and in the same order.

Structure of Compound IIa

The ir and uv spectra (see figure 8) of compound IIa were closely similar to those of compound (157). Its mass spectrum had also a similar fragmentation pattern consisting of a weak molecular ion at m/e 444 (5%) and a base peak at m/e 429 corresponding to the facile loss of a methyl group. On the basis of this evidence, and by analogy with structure (157), compound IIa was assigned structure (171). The close agreement between the pmr proton resonances of (157) and those of (171) is shown below.



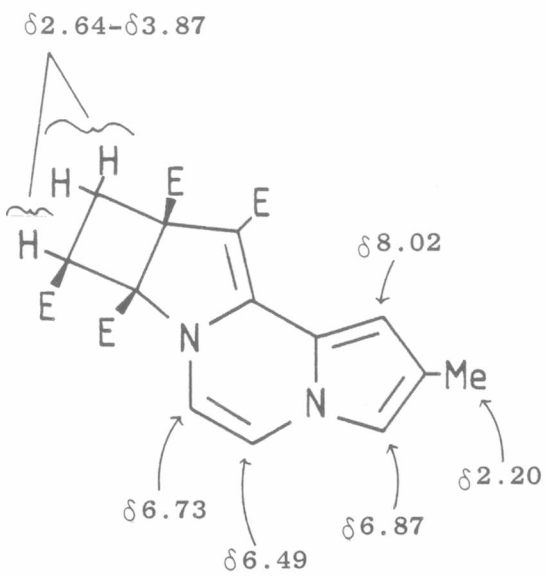
(157)



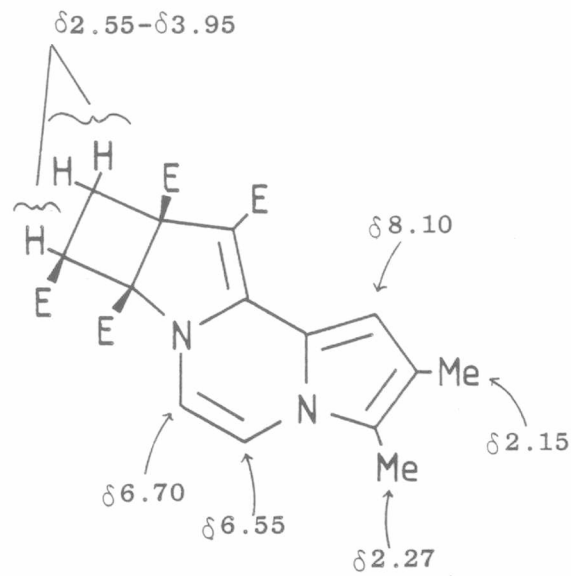
(171)

Structure of Compound IIIa

The elemental analysis and the molecular weight of compound IIIa indicated it to have a molecular formula of $C_{22}H_{24}N_2O_8$. The fragmentation pattern of this compound was similar to that of compound (158). It showed a weak molecular ion peak at m/e 444, and a base peak at m/e 358 corresponding to the loss of CH_2=CHCOOMe. Similarly, as in the pmr spectrum of compound (158), compound IIIa showed four carbomethoxy groups and a complex 3H multiplet between δ2.50 and δ3.90 indicating the presence of a CH_2CH group in the molecule. Also, the ir and uv spectra of IIIa showed close similarities to those of compound (158). Thus from the above observations, structure (172) was attributed to compound IIIa. The agreement between the pmr resonances of (158) and (172) is shown below.



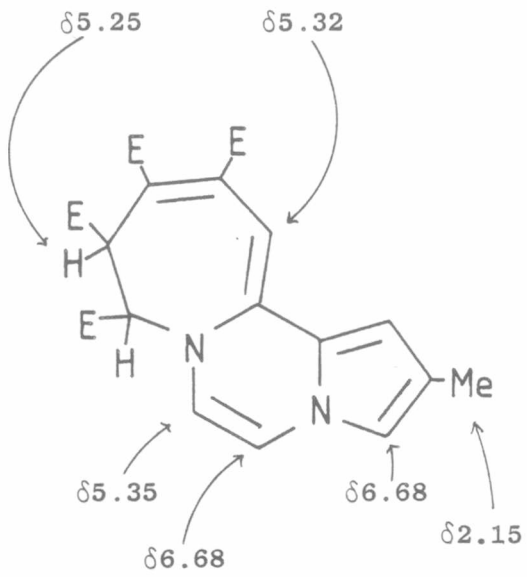
(158)



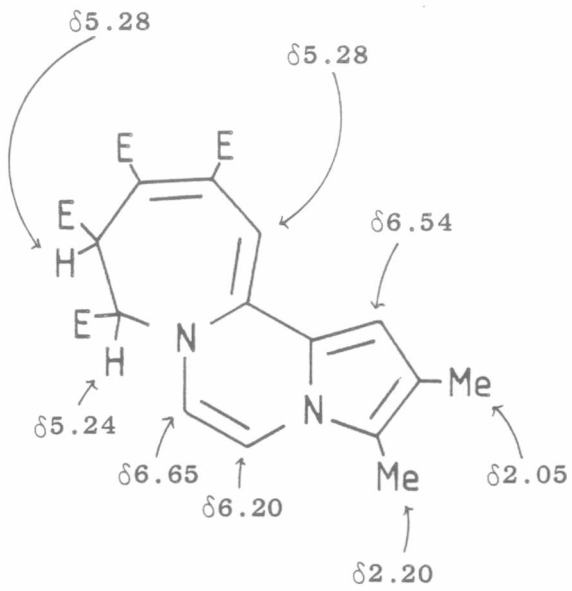
(172)

Stucture of compound Va

Analysis of compound Va indicated it to be isomeric with compounds (171) and (172). Its mass spectrum showed a molecular ion at m/e 444 and a base peak at m/e 385 due to the loss of $COOCH_3$. The fragmentation pattern of this compound was analogous to that of compound (163). The pmr spectrum of compound Va was again closely similar to that of compound (163) as shown by the proton resonances given below. Thus Va is assigned to structure (173):



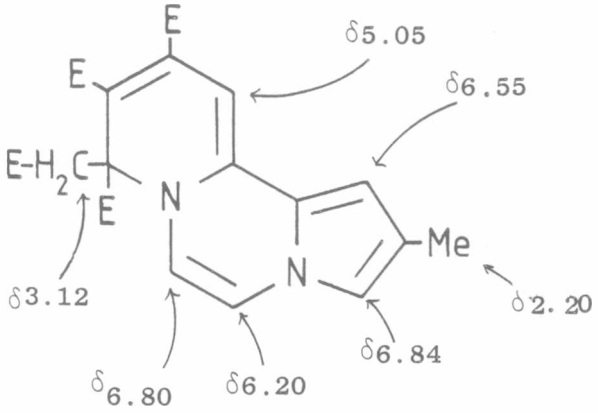
(163)



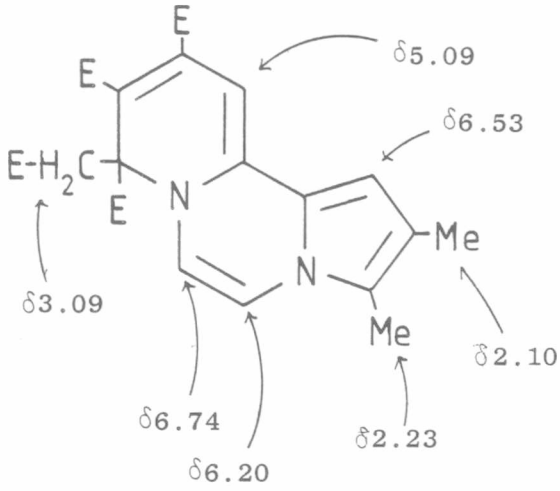
(173)

Structure of Compound IVa

Analysis of this compound showed it to be isomeric with (171), (172) and (173). The mass spectrum consisted of a molecular ion at m/e 444 and a base peak at m/e 385 corresponding to the loss of $COOCH_3$. There was also another significant peak at m/e 371 corresponding to the loss of CH_2COOCH_3. This fragmentation pattern was similar to that observed for compound (167) and the pmr resonances were closely similar to those of compound (167) as shown below. Thus compound IVa is assigned structure (174).



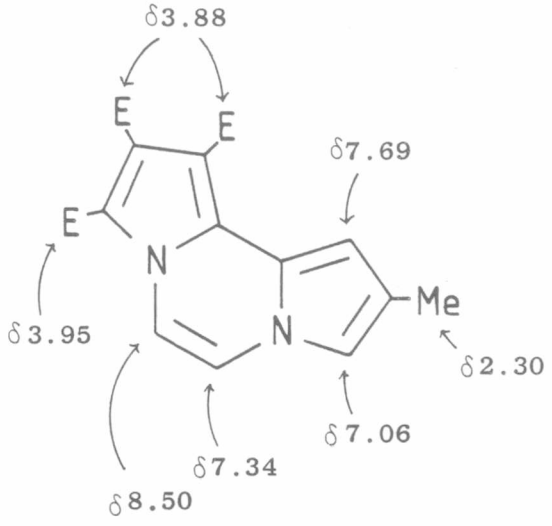
(167)



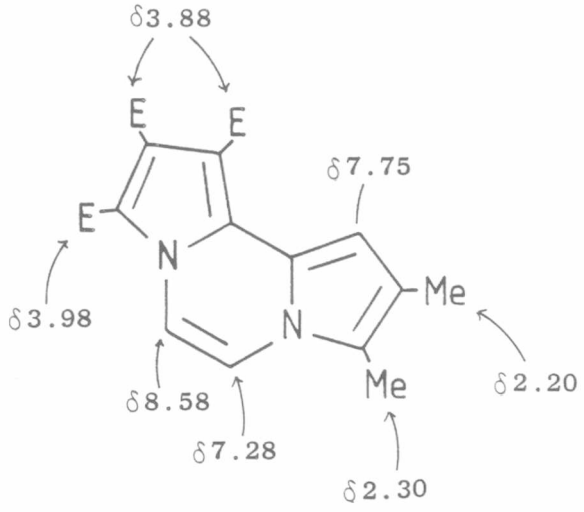
(174)

Structure of compound Ia

The ir and uv spectra of compound Ia were almost identical to those of compound (168). The mass spectrum of compound Ia was very simialr to that of compound (168) and showed only two significant peaks. The first one was the molecular ion at m/e 358, which was also the base peak, while the other peak at m/e 327(20%) corresponds to the loss of OCH_3. The pmr spectrum of compound Ia was closely similar to that of compound (168) as shown below, and thus compound Ia is assigned structure (175):



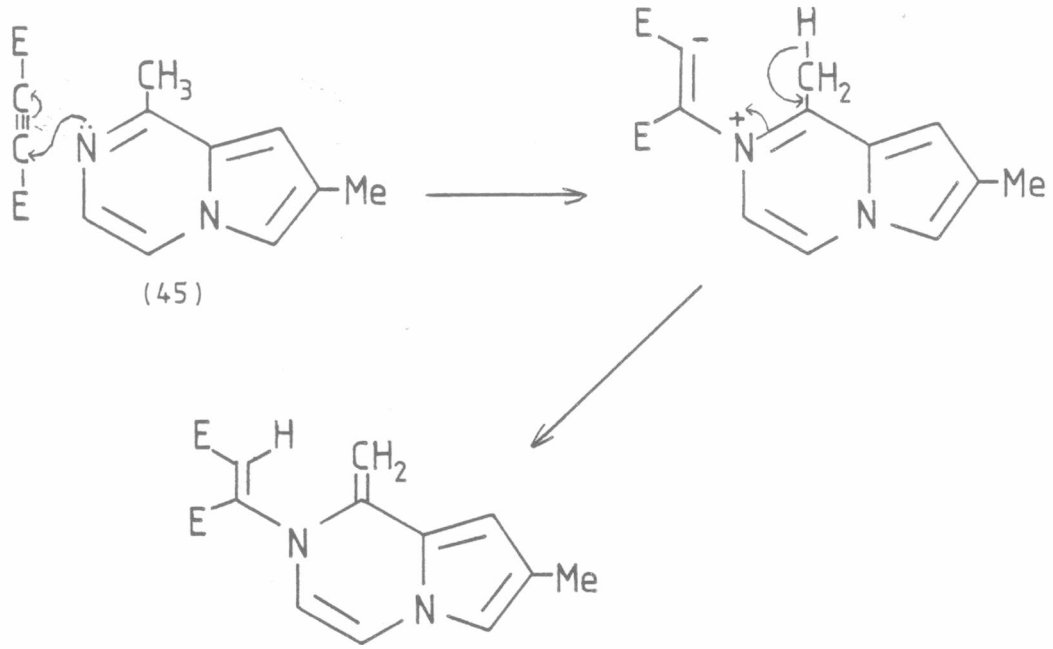
(168)



(175)

Suggested mechanism for the formation of the adducts in the reaction between 8-methyl-7-azaindolizines and DMAD

All the adducts obtained in the reaction between the 8-methyl-7-azaindolizines and DMAD could result from a common intermediate formed by the initial attack of one DMAD unit at the electron rich N-7, followed by proton transfer. For example 2,8-dimethyl-7-azaindolizine (45) could give intermediate (176) as shown below:

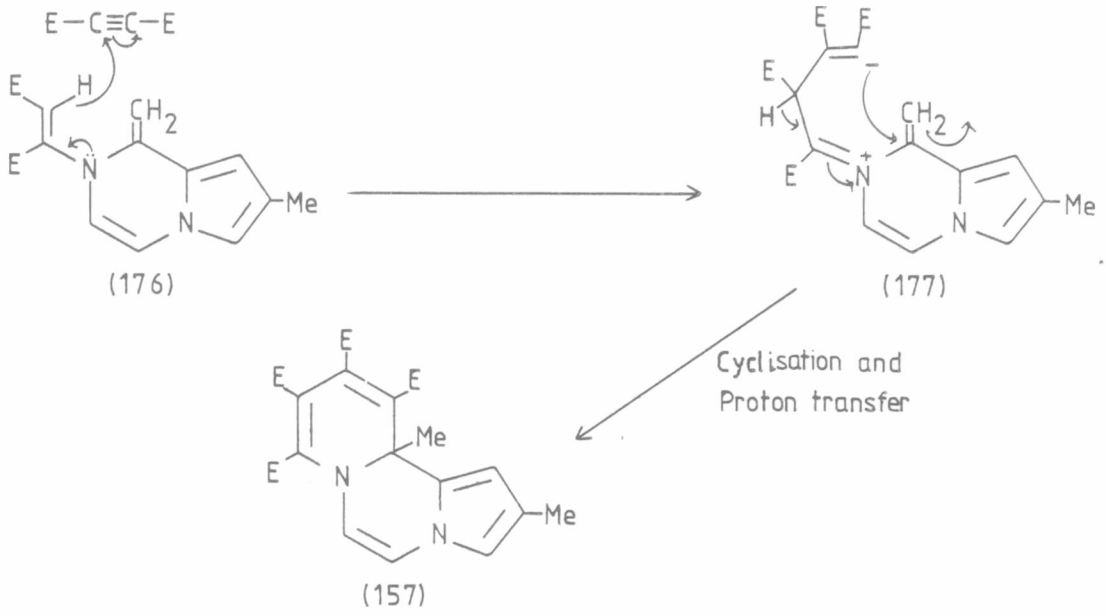


(45)

(176)

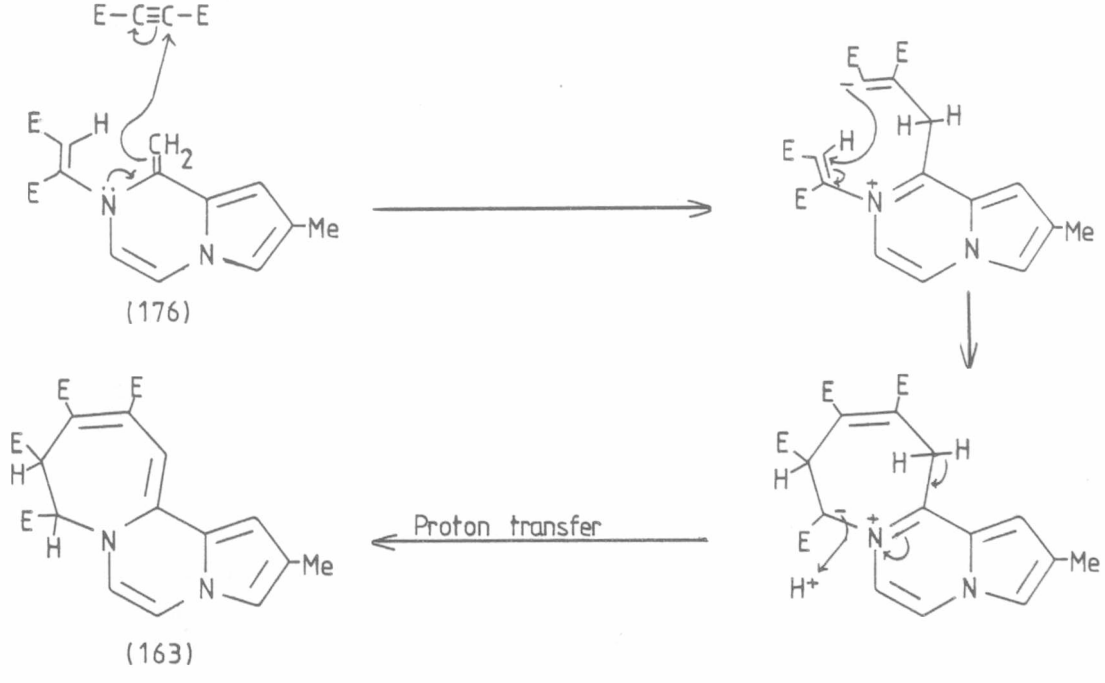
Subsequent reaction with another molecule of DMAD could then give rise to the proposed structures by the pathways illustrated below.

Formation of the pyrido[2,1-c]pyrrolo[1,2-a]pyrazine (157) from (176)

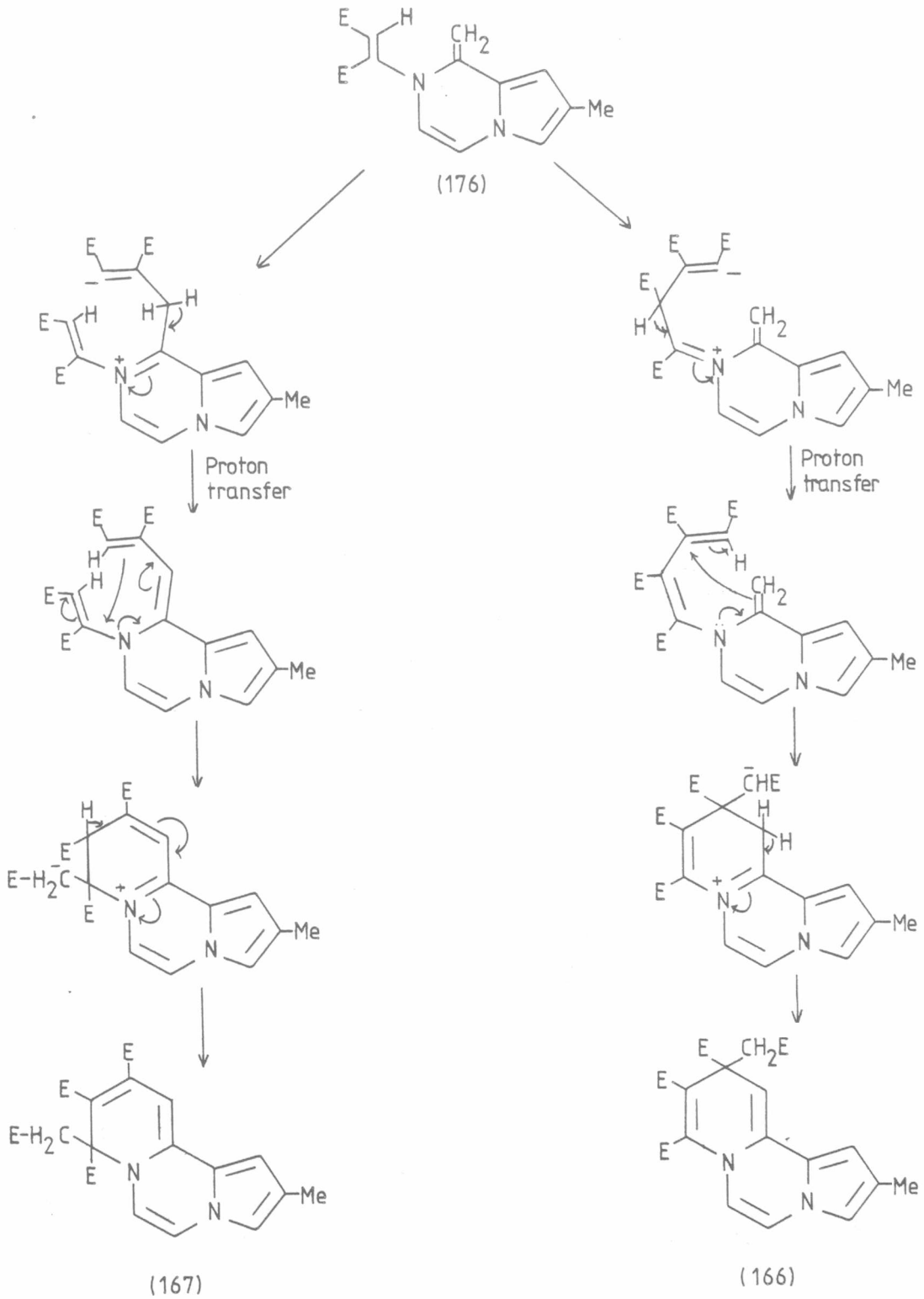


Intermediate (176) adds on another unit of DMAD via the ethylene group at N-7 to give intermediate (177). Subsequent cyclisation via C-8 of the azaindolizine followed by proton transfer gives compound (157).

Formation of the azepine (163) from (176)



Formation of the pyrido[2,1-c]pyrrolo[1,2-a]pyrazine (166) and (167) from (176)



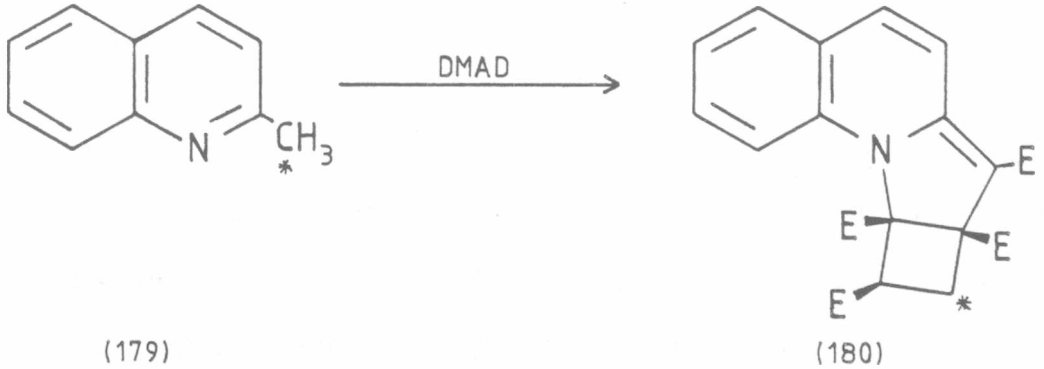
In the reaction pathway shown on page 138, intermediate (176) adds another molecule of DMAD *via* the ethylenic carbon situated at position 8 of the azaindolizine system to give intermediate (178). Cyclisation followed by proton transfer would then give structure (163). A similar mechanism has been proposed by Acheson *et al.* for the formation of azepines from 2-substituted thiazoles[105].

Formation of pyrido[2,1-c]pyrrolo[1,2-a]pyrazine (167) and (166) from (176)

The suggested pathway as shown on page 139 leading to compound (167) involves the addition of a DMAD unit to intermediate (176) via the ethylenic carbon at C-8 site of the 7-azaindolizine unit. Subsequent cyclisation followed by proton transfer would lead to (167). A similar pathway but involving the initial attack of the DMAD at the ethylenic group on the nitrogen would give ultimately compound (166).

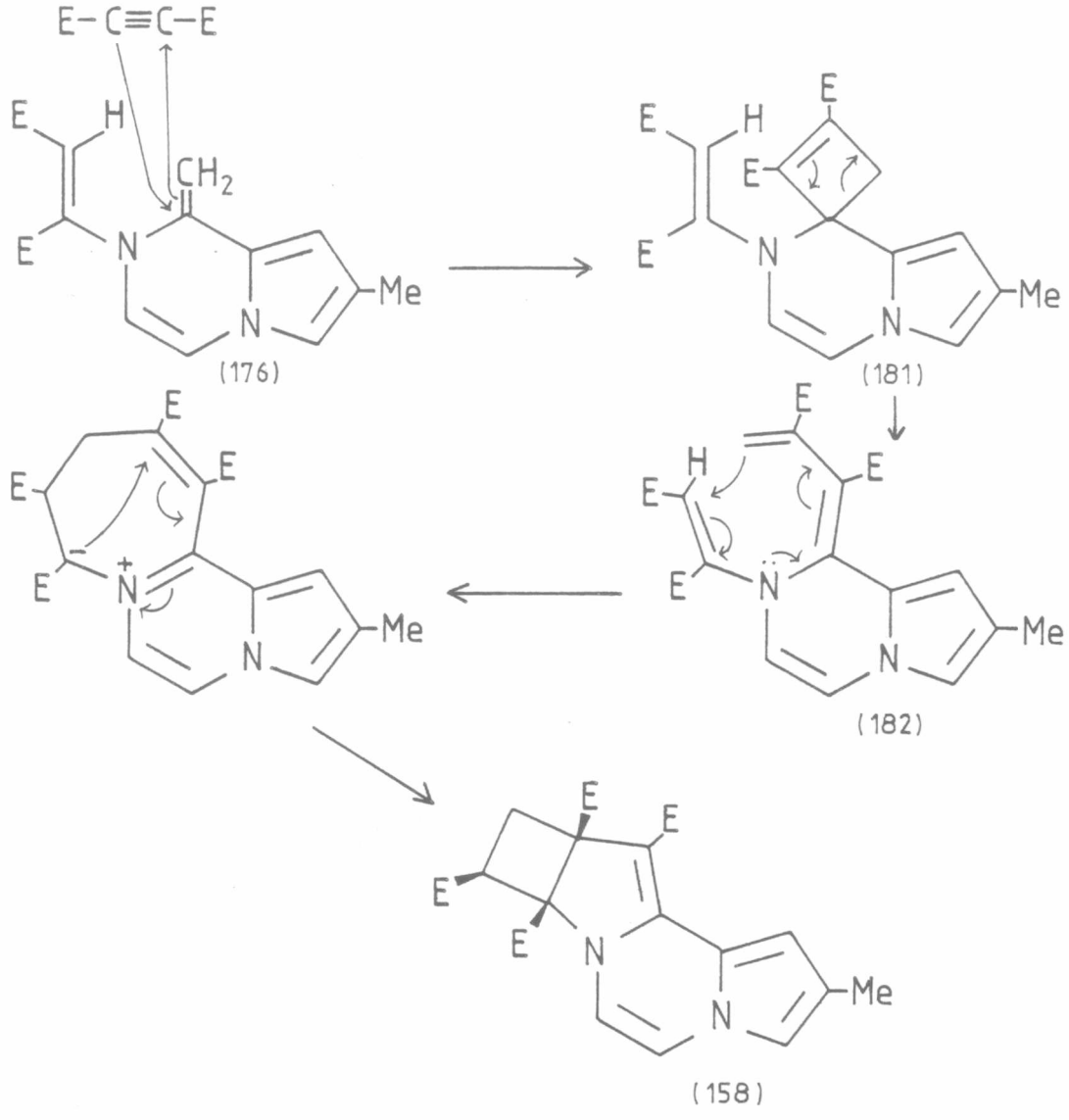
Formation of cyclobutandipyrrolopyrazine (158) from (176)

Acheson *et al.*[96,101] have proposed a mechanism for the formation of the cyclobutapyrroloquinoline (180) from 2-methylquinoline:



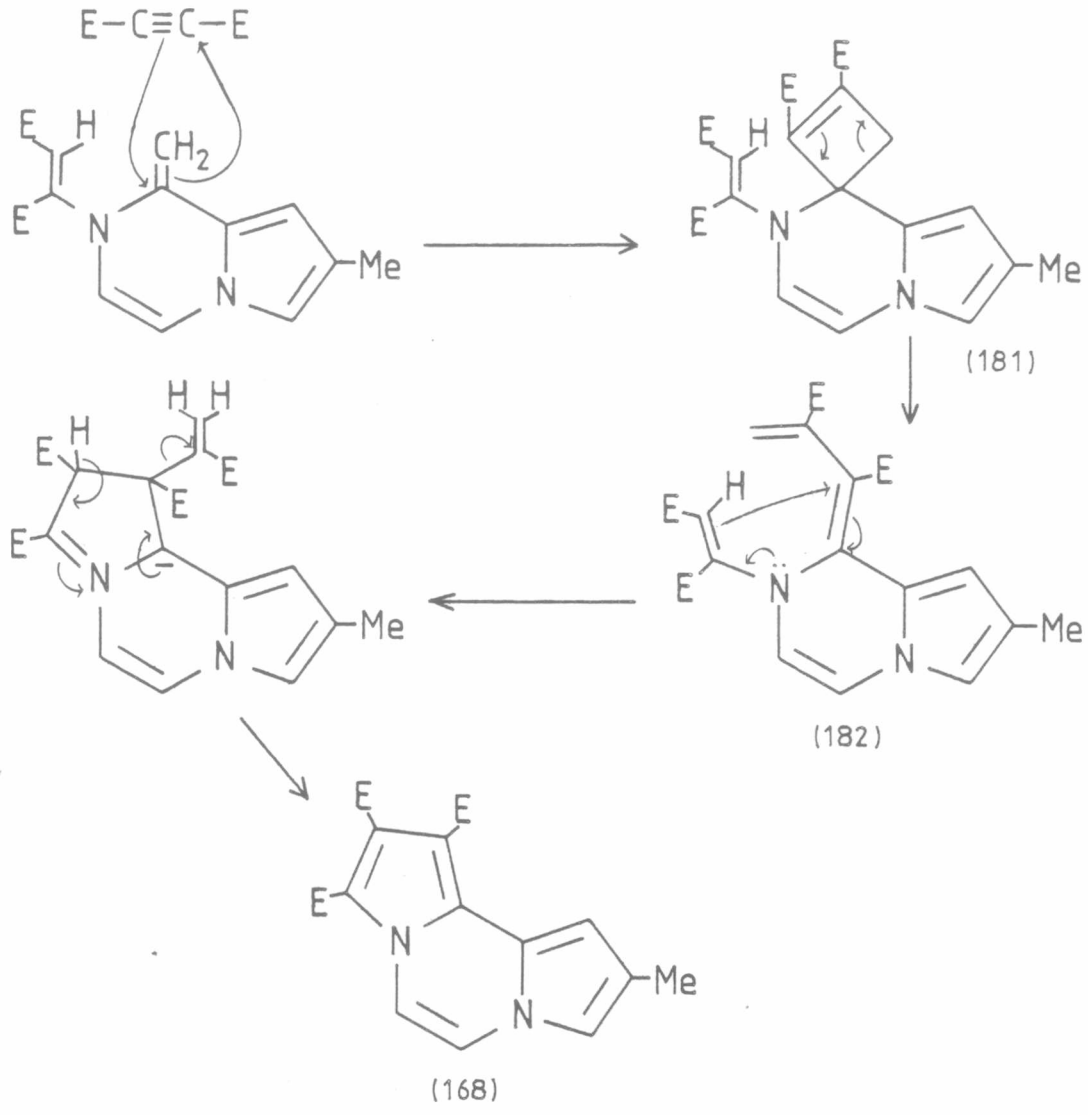
(179) (180)

They demonstrated by ^{14}C labelling that the methyl carbon of methylquinoline (179) becomes the methylene carbon of the cyclobutane ring in (180) as indicated by the astersiks shown[98,103]. Applying Acheson's proposals to the formation of cyclobutandipyrrolopyrazine (158), the mechanism would be as follows:



The suggested pathway leading to compound (158) involves a cyclobutene intermediate (181) which after ring opening and cyclisation eventually gives compound (158).

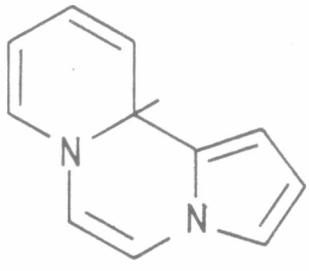
Formation of dipyrrolopyrazine (168) from (176)



This pathway may involve the initial formation of cyclobutene intermediate (181) previously proposed for the formation of (158); on ring opening (182) would be obtained. A second ring closure and subsequent aromatisation with loss of the E-$\bar{C}$=CH_2 unit would give (168).

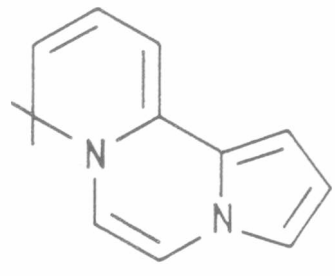
Fragmentation pattern of compounds (155), (156), (157), (167), (171) and (174)

Compounds (155), (156), (167), (171) and (174) all possess the basic ring system (183) or (184) as shown. Each compound showed in its mass spectrum the parent ion resulting from the loss of a group which gives rise to a



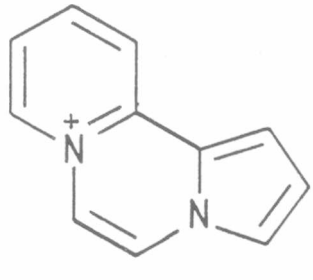
(183)

OR



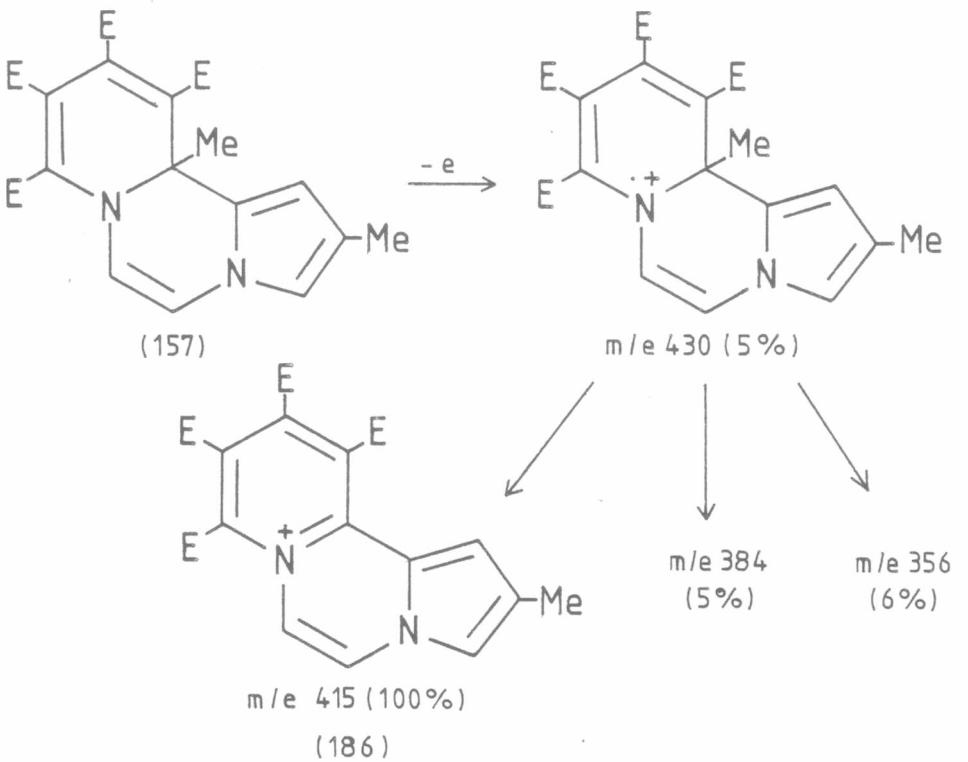
(184)

cation which has the bacic ring system (185). The cation is stabilised by both a 10π 7-azaindolizinium and a 6π pyridinium moiety:



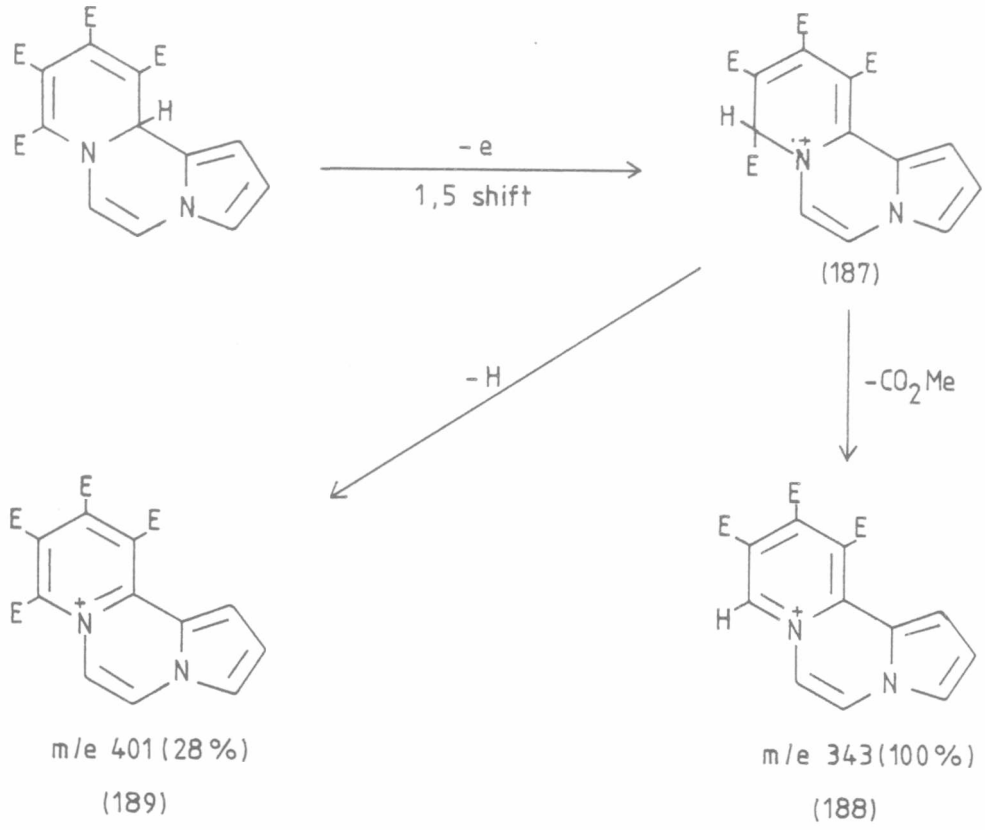
(185)

The mass spectrum of the dimethylpyrido[2,1-c]pyrrolo-[1,2-a]pyrazine (157) showed a relatively weak parent ion at m/e 430(5%) and a base peak at m/e 415. The base peak results from the loss of CH_3 from the parent ion to give (186). All the other fragmentation ions were of low intensity (less than 7%). A similar pattern was observed for the trimethylpyrido[2,1-c]pyrrolo[1,2-a]pyrazine (171).



The other pyrido[2,1-c]pyrrolo[1,2-a]pyrazines (155) and (156) both showed loss of $COOCH_3$ to give the base peak. It is suggested that compound (155) initially undergoes a 1,5 sigmatropic shift in the mass spectrometer to give the radical ion (187) which subsequently loses $COOCH_3$ to give the stable aromatic cation (188) as base peak. A hydrogen atom may also be lost to give a stable aromatic cation (189).

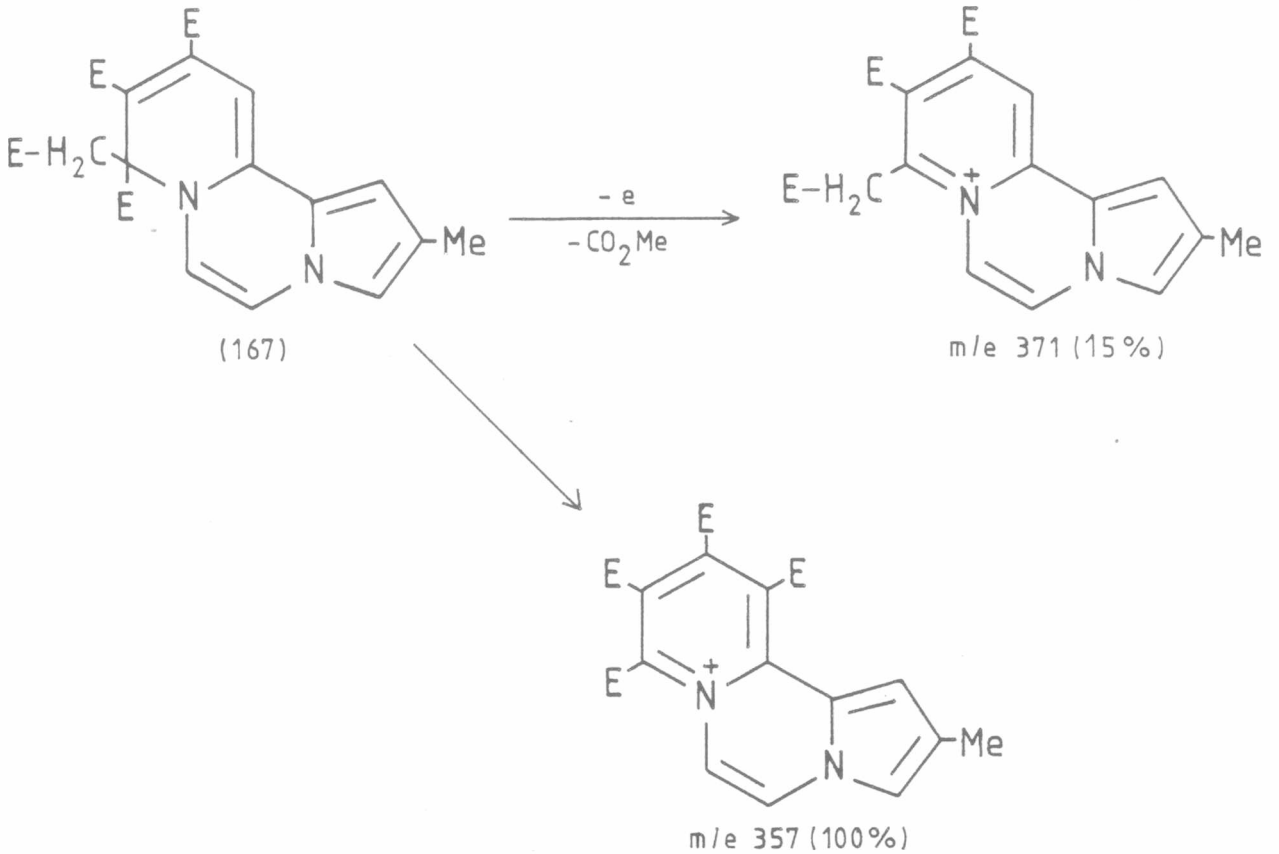
Fragmentation of pyrido[2,1-c]pyrrolo[1,2-a]pyrazine (155)



In a similar fashion the pyrido[2,1-c]pyrrolo[1,2-a]-pyrazine (167)(as shown on page 147) and (174) both lose the fragment $COOCH_3$ or CH_2COOCH_3 to give stable ions. For example, compound (167) loses CH_2COOCH_3 from the molecular ion to give a base peak at m/e 357, whilst another fragment ion at m/e 371(15%) results from the loss of $COOCH_3$ from the molecular ion.

The 2,3-dimethylpyridopyrrolo-pyrazine(174) loses $COOCH_3$ from its molecular ion (m/e 444) to give a base peak at m/e 385, and the loss of CH_2COOCH_3 gives a fragment ion at m/e 371(27%).

Fragmentation of pyrido[2,1-c]pyrrolo[1,2-a]pyrazine (167)



(167)

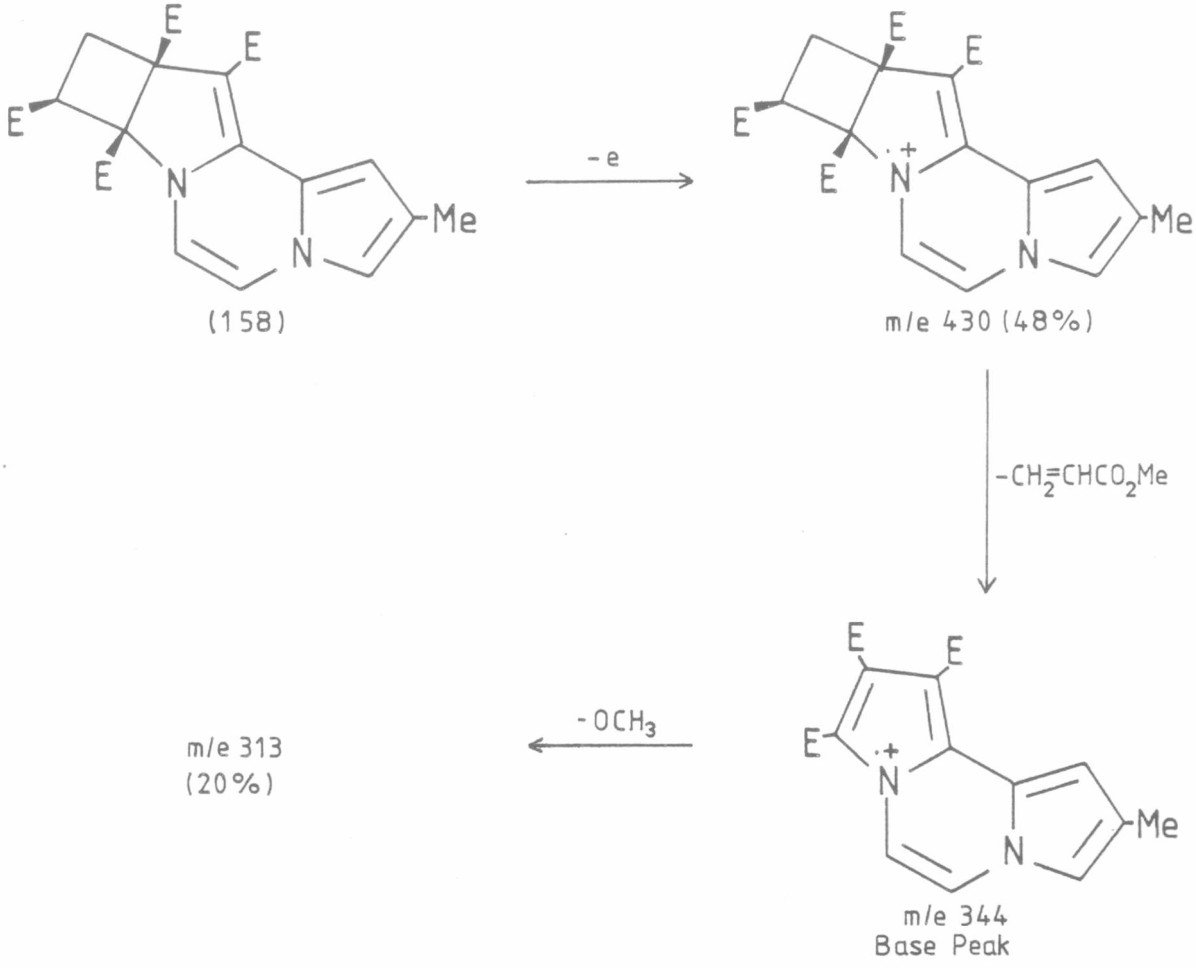
m/e 371 (15%)

m/e 357 (100%)

Fragmentation of the cyclobutandipyrrolopyrazines (158) and (162)

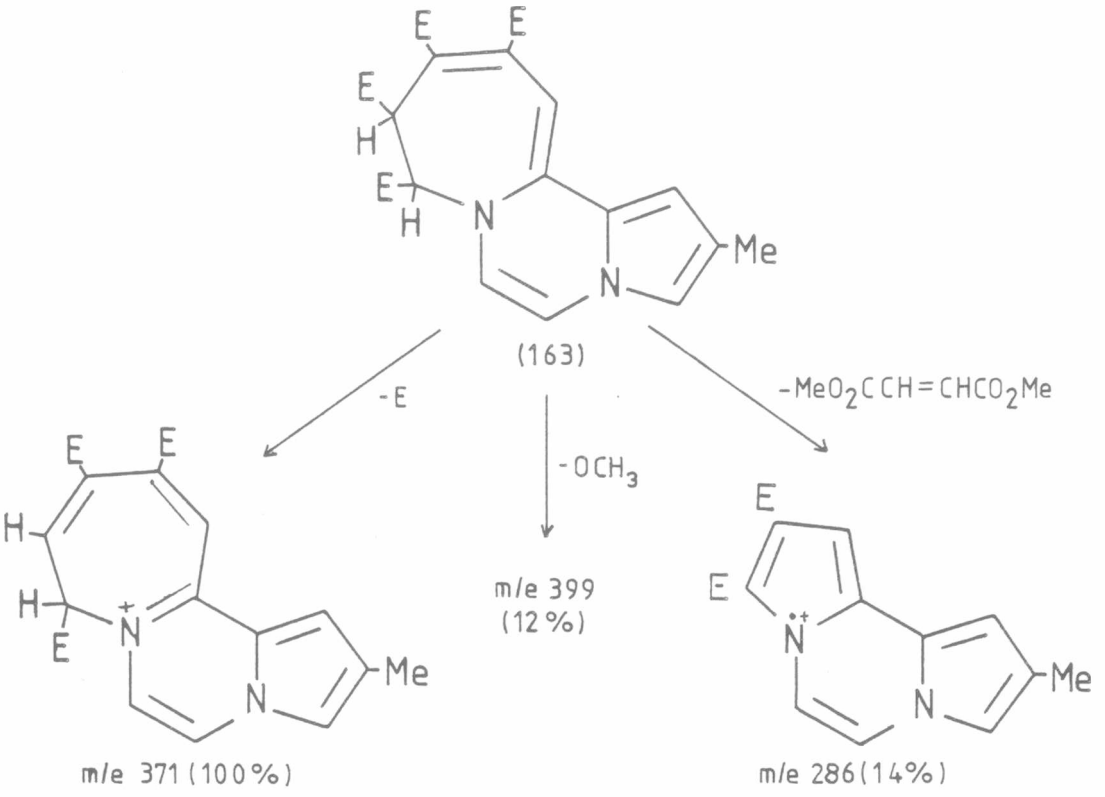
The cyclobutandipyrrolopyrazines (158) and (162) both showed base peaks due to the loss of methyl acrylate, giving resonance stabilised cations. The only other significant fragmentation ion present (m/e 313) is that due to the subsequent loss of a OCH_3 group from the base peak.

Fragmentation of cyclobutandipyrrolopyrazine (158)



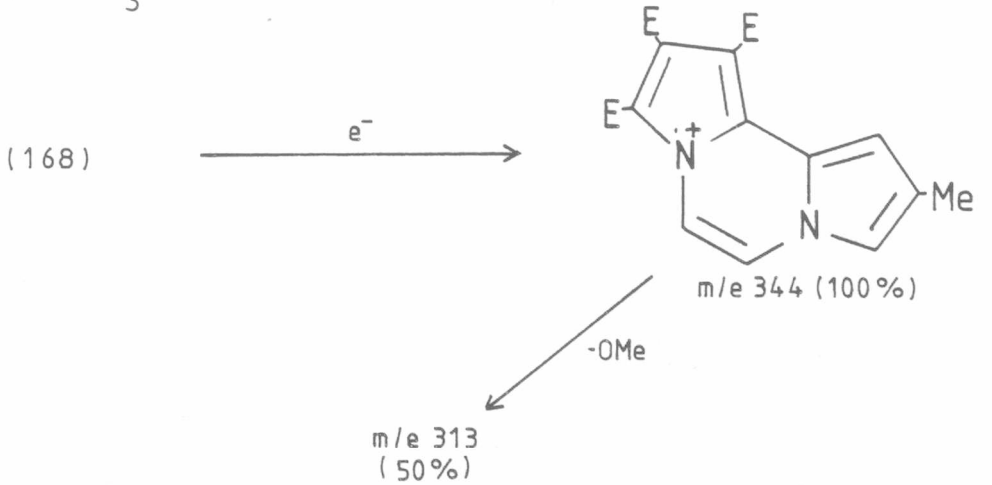
Fragmentation of dihydroazepinopyrrolo[1,2-a]pyrazine (163) and (173)

The dihydroazepinopyrrolo[1,2-a]pyrazine (163) showed a base peak which arises from the loss of an ester group to give a stable ion. The other significant fragments are due to the loss of a methoxyl and dimethyl fumarate unit as shown below. A similar fragmentation pattern was observed for compound (173).



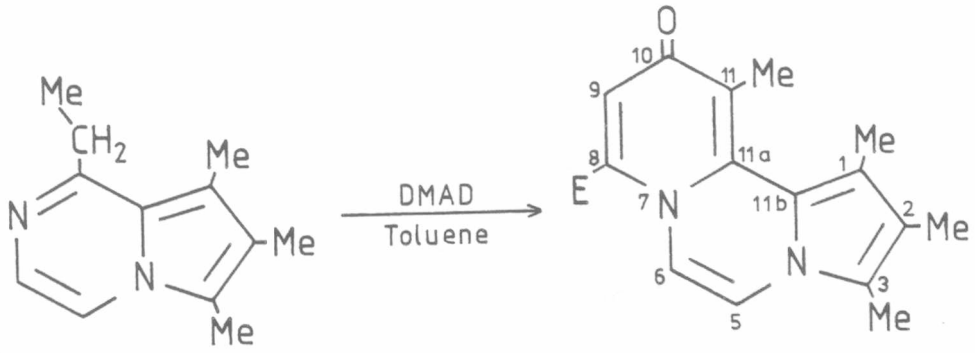
Fragmentation of dipyrrolopyrazines (168) and (175)

These compounds, like indolizines, showed the molecular ion as the base peak, reflecting the stability of the resulting system. The mass spectrum of both compounds (168) and (175) showed only two significant ions viz. the molecular ion as the base peak and the ion resulting from the loss of OCH_3 from the molecular ion:



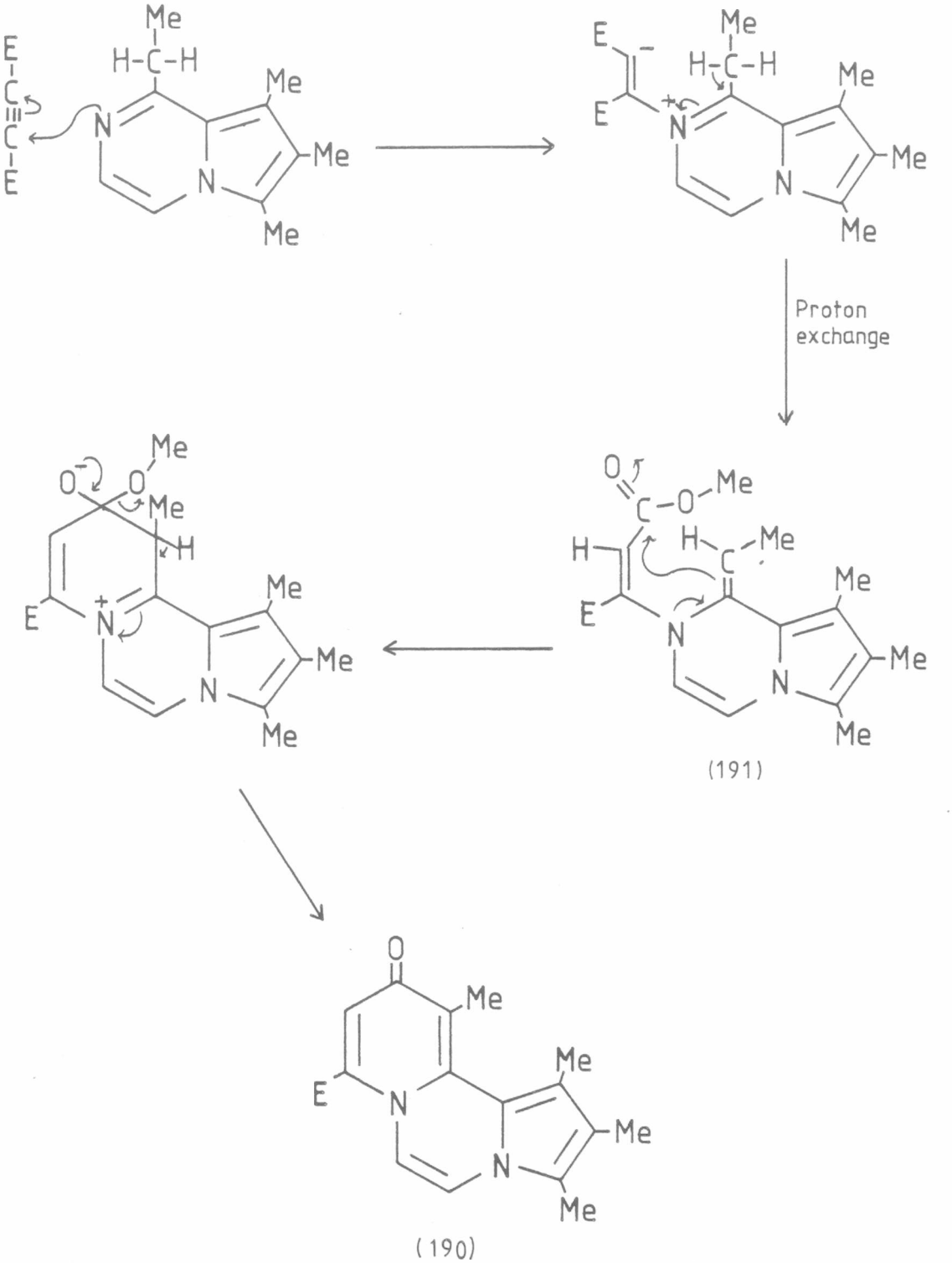
Reaction between 8-ethyl-1,2,3-trimethyl-7-azaindolizine and DMAD

When DMAD was added to a solution of 8-ethyl-1,2,3-trimethyl-7-azaindolizine (55) in toluene, a dark green solid was obtained. The molecular weight of this compound (m/e 298) together with its elemental analysis showed its molecular formula to be $C_{17}H_{18}N_2O_3$. Its ir spectrum showed carbonyl absorption bands at 1700 cm^{-1} and 1636 cm^{-1}. The latter band suggests the presence of a highly conjugated carbonyl group. The pmr spectrum of this compound showed five 3H singlets at δ1.95, δ2.00, δ2.20, δ2.30 and δ3.70, a 1H singlet at δ6.72 and a 2H AB doublet centered at δ6.50 and δ8.10. The absence of a signal for an ethyl group and the presence of only one carbomethoxy methyl signal in the spectrum suggests the interaction of the 8-ethyl group of the 7-azaindolizine and one of the carbomethoxy groups of a DMAD unit in reaction. Thus, these spectral details are consistent with the ketopyrido-pyrrolopyrazine (190). The pmr signals of compound (190) were assigned as follows : the five 3H singlets at δ1.95,



(55) (190)

Scheme 2. Suggested mechanism for the formation of ketopyrido[2,1-c]pyrrolo[1,2-a]pyrazine (190)



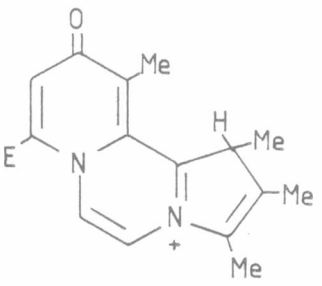
δ2.00, δ2.20, δ2.30 and δ3.70 were assigned to CH_3-1, CH_3-2, CH_3-3, CH_3-11, and the ester CH_3 on carbon 8 respectively, the 1H singlet at δ6.12 to H-9 and the AB doublet at δ6.50 and δ8.10 were attributed to H-5 and H-6 respectively.

suggested mechanism for the formation of the ketopyrido[2,1-c]pyrrolo[1,2-a]pyrazine (190)

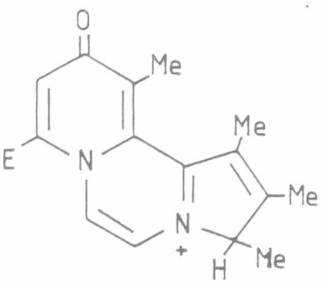
The formation of compound (190) can be accounted for as in the reaction scheme 2. This involves the initial attack of the 7-azaindolizine by a molecule of DMAD via the electron rich N-7 to form intermediate (191). Cyclisation and elimination would then give compound (190).

Protonation of the ketopyrido[2,1-c]pyrrolo[1,2-a]-pyrazine (190)

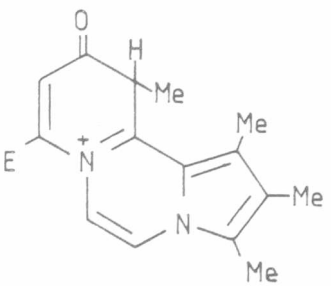
The sites of protonation of compound (190) were shown by the pmr spectrum of this compound in CF_3COOH. This spectrum indicated the presence of two conjugate acid cations in an approximate ratio of 3:2. The least abundant cation showed an AB doublet at δ7.45 and δ8.90. Irradiation of the doublet signal at δ8.90 causes the signal at δ7.45 to sharpen. Furthermore, this spectrum showed the presence of a quartet centered at δ4.45, and a doublet centered at δ1.80, suggesting that protonation in this cation has occurred at a carbon attached to a methyl group. The conjugate acid cations (192), (193) or (194) could have been formed, but protonation at C-11 would be favoured because the corresponding conjugate acid (193) contains the stable 10π 7-azaindolizinium moiety.



(192)

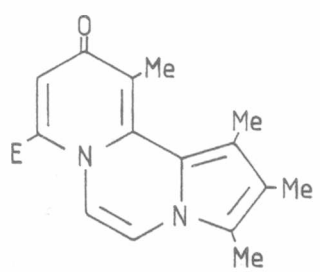


(193)

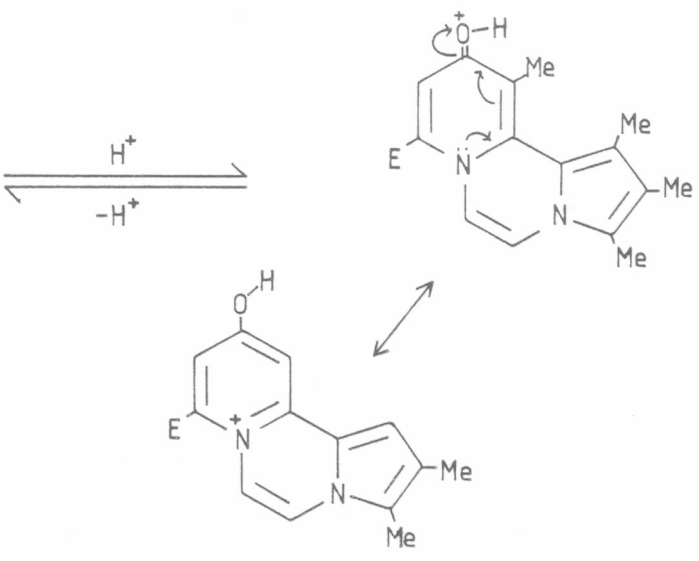


(194)

The spectrum of the most abundant cation showed an AB doublet system centered at δ7.90 and δ9.35 assigned to H-5 and H-6 respectively. The ring methyl protons at sites C-1, C-2, C-3 and C-11 were found between δ2.52 and δ2.90 and the 8-carbomethoxy group at δ4.22. The absence of any quartet-triplet system and methylene signal in the pmr spectrum discounts protonation at either a carbon attached to a methyl group or a carbon attached to a hydrogen. Thus on this basis it can be inferred that protonation has occurred on the carbonyl oxygen at site C-10 to give the conjugate acid cation (195):



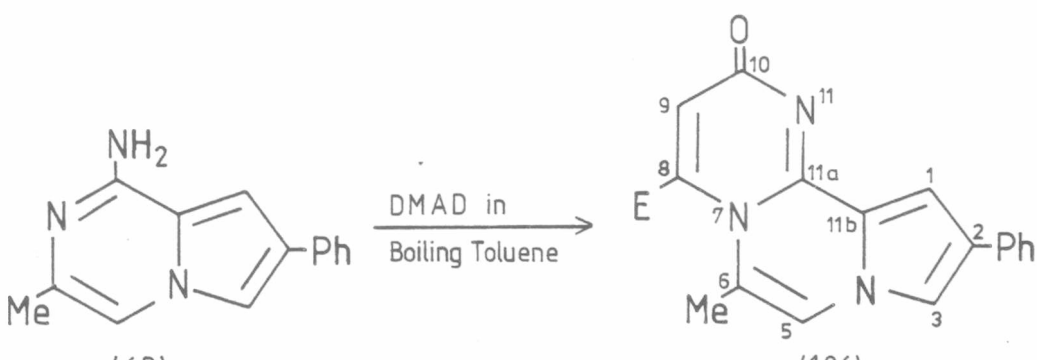
(190)



(195)

Reaction between 8-amino-6-methyl-2-phenyl-7azaindolizine and DMAD

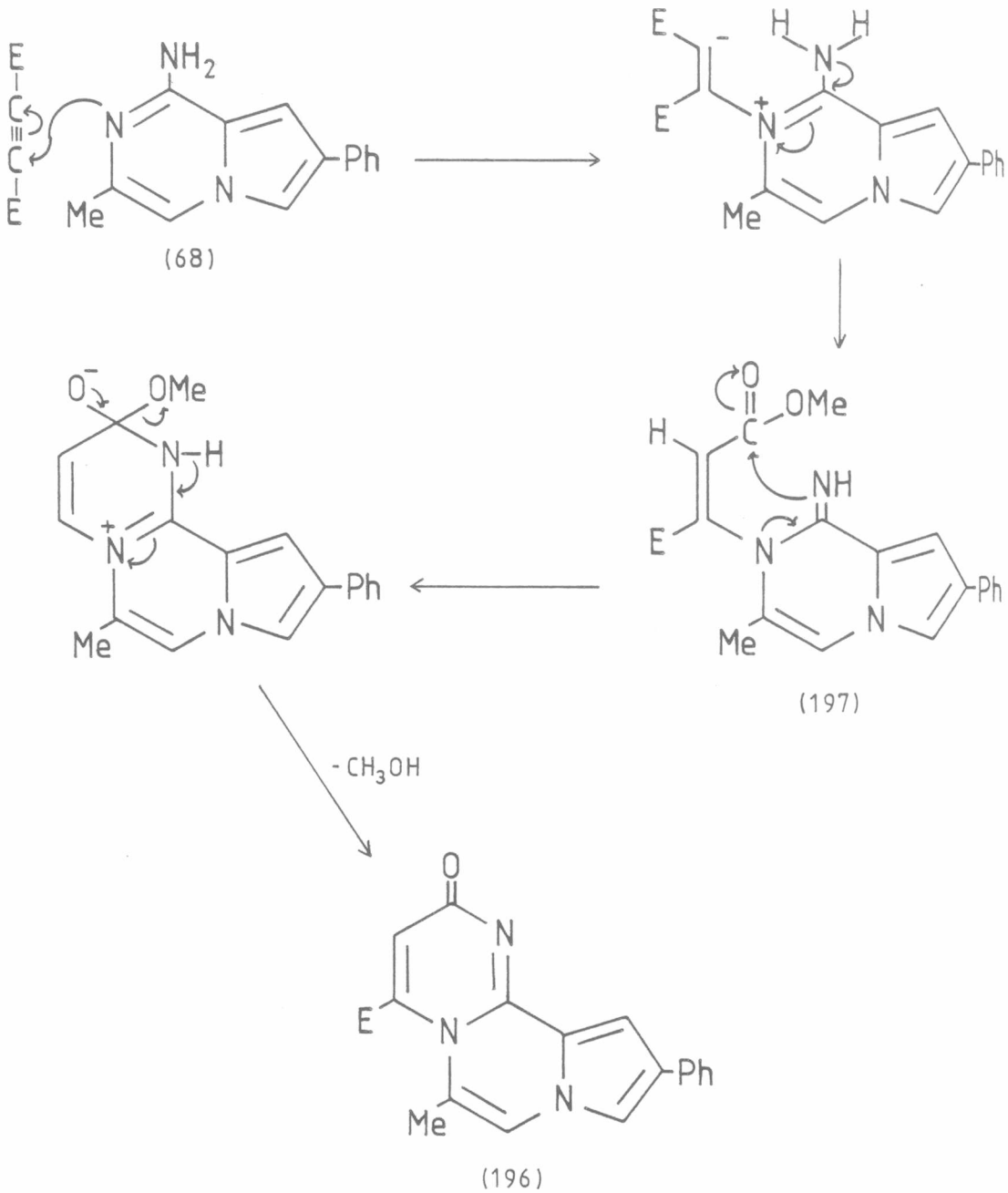
The reaction between 8-amino-6-methyl-2-phenyl-7-azaindolizine (68) and DMAD in boiling toluene afforded a yellow crystalline compound. Its ir spectrum showed strong carbonyl absorptions at 1730 cm^{-1} and 1670 cm^{-1}. Its mass spectrum consisted of the molecular ion at m/e 333(78%), and a base peak at m/e 274 corresponding to the loss of $COOCH_3$ unit from the molecular ion. The pmr spectrum of this compound in DMSO-d_6 showed two 3H singlets at δ2.35 and δ3.68, indicating the presence of a methyl and a carbomethoxy methyl group. Further downfield there was a complex multiplet between δ7.35 and δ8.12 which was ascribed to the phenyl protons and the other four ring protons. On the basis of these observations, and by analogy with compound (190), the proposed structure of this compound is (196). The pmr signals are thus assigned: the two 3H singlets at δ2.45 and δ3.80 were due to methyl group on C-6



(68) (196)

position and the ester methyl group situated at C-8, the complex multiplet between δ7.30 and δ7.75 to the protons on

Scheme 3. Suggested mechanism for the formation of compound (196)



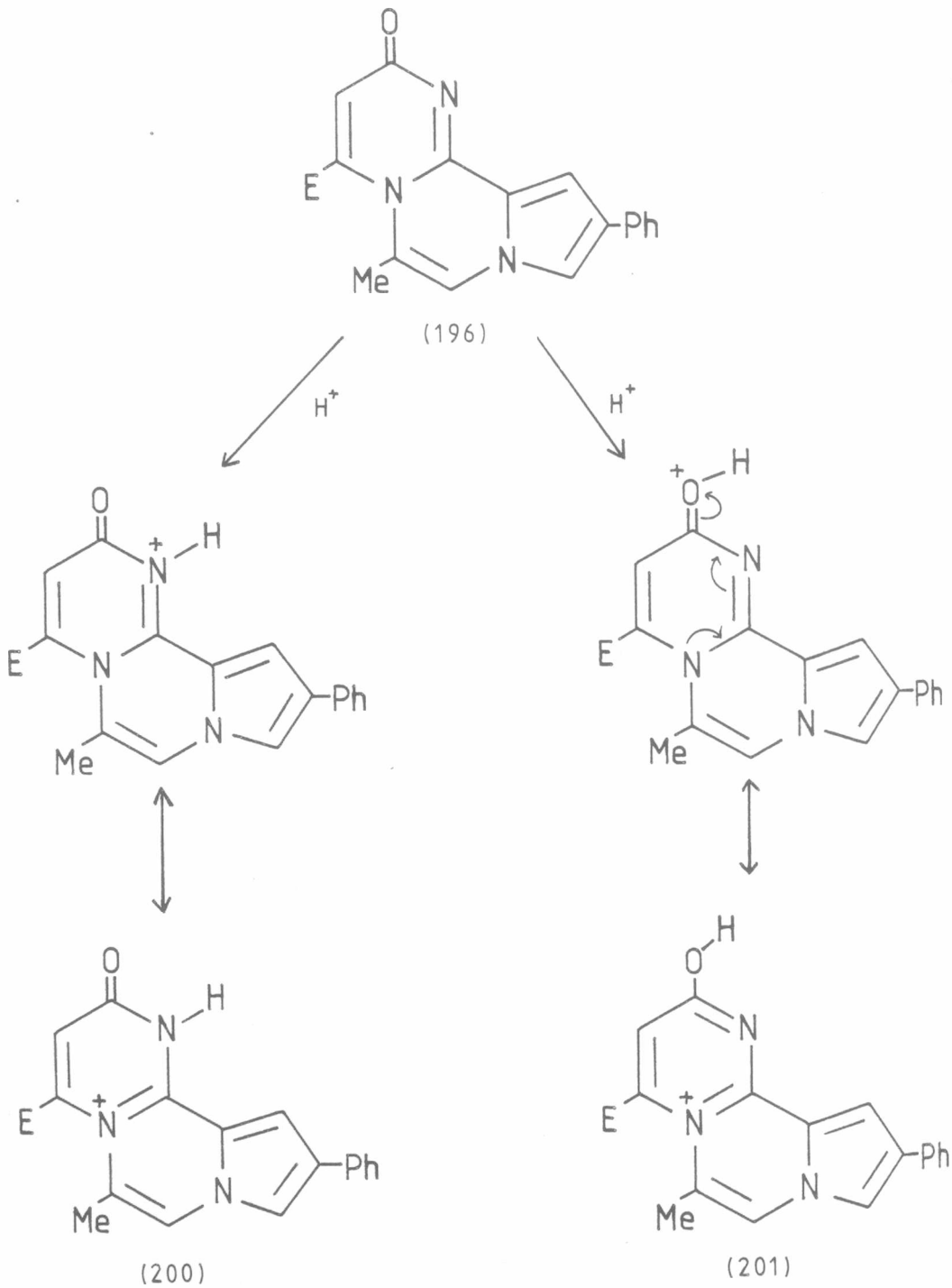
the phenyl group at C-2 and the four 1H singlets at 6.88, 7.25, 7.50 and 8.12 are tentatively assigned to H-9, H-1, H-3 and H-5 respectively.

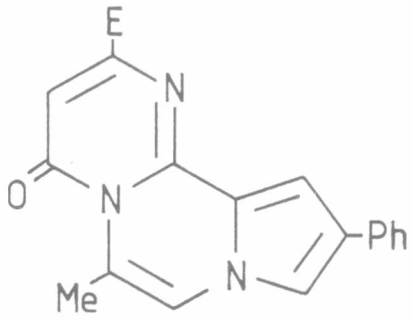
Suggested mechanism for the formation of (196)

The suggested mechanism for the formation of (196) is shown in Scheme 3. It involves nucleophilic attack of the 8-amino-7-azaindolizine (68) to one molecule of DMAD via the N-7 to give intermediate (197). Cyclisation via the imine nitrogen to the carbomethoxy carbonyl would give compound (196) after elimination of methanol.

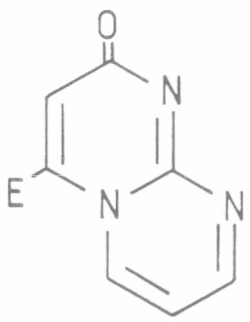
If the nucleophilic atack of the DMAD molecule had occurred at the exocyclic amino group instead of N-7, then this would eventually lead to the formation of compound (198) which could be an alternative to the one suggested, i.e (196). However it has been shown in Chapter 3 (page 52) that protonation of 8-amino-6-methyl-2-phenyl-7-azaindolizine occurs at N-7 and not at the exocyclic amino group; this gives support for the preferential attack at N-7. Furthermore, an analogous reaction between 2-aminopyrimidine[109] and DMAD gives structure (199), which again must have involved the initial attack on the heterocyclic nitrogen. Thus, on the basis of the protonation studies on 8-amino-6-methyl-2-phenyl-7-azaindolizine, and the analogous reaction mentioned, isomer (196) is the preferred structure:

Scheme 4. Protonation of compound (196)





(198)



(199)

Protonation of compound (196)

The pmr spectrum of compound (196) in trifluoroacetic acid showed no methylene signal, which implies that protonation on carbon does not occur. The spectrum consisted of two 3H singlets (δ2.78 and δ4.10) assigned to the methyl group on C-6 and the ester methyl respectively; further downfield, four 1H singlets at δ7.36, δ7.85, δ8.06 and δ8.36 were due to H-9, H-1, H-3 and H-5 respectively, and the complex multiplet between δ7.40 and δ7.70 was due to the protons of the phenyl group on C-2. Thus protonation could have occured either on N-11 or on the oxygen as shown in scheme 4. Attack at either position would give rise to resonance stabilised conjugate acids (200) or (201).

Conclusions

The results described in this chapter indicate that DMAD readily reacts with 7-azaindolizines to give products involving attack at the non-bridgehead nitrogen (N-7) and the adjacent C-8 position or 8-substituent.

Experimental

Explanatory Notes New compounds are underlined when first mentioned. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ultra-violet light absorption data refers to solutions in ethanol unless otherwise stated and were measured using a Perkin Elmer 552 spectrophotometer and 10 mm silica cells. Inflections and shoulders are given in parentheses. Infra-red spectra were recorded with a Perkin Elmer 781 spectrophotometer and are for Nujol mulls unless otherwise stated. Pmr amd cmr spectra refer to solutions in deuterochloroform unless otherwise stated and were recorded with a Varian FT-80A or a Perkin Elmer R12B spectrometer using tetramethylsilane as an internal standard. Values given are on the δ scale (TMS = δ0.00) and refer to singlet absorptions unless otherwise stated. Approximate coupling constants are in hertz. Integration values and signal assignments are in parentheses. For multiplets d=doublet, t=triplet, q=quartet and m=complex multiplet. Signals marked by asterisk are broadened and/or weakly split. Cmr spectra and cmr spin echo experiments were recorded on a JEOL FX90 Q spectrometer; mass spectroscopic data were obtained from a VG 70-250SE spectrometer. These spectroscopic analysis together with the elemental analysis were performed by the analytical laboratories of ICI, Pharmaceutical Division.

The silica gel for column chromatography was Alumina Woelm N,Akt.1 and thin layer chromatography (tlc) was

carried out using Merck Kieselgel GF_{254}. Concentrated hydrochloric, sulphuric, nitric and perchloric acid were 'Analar' grade. Petroleum ether refers the fraction b.p $40-60^{0}C$.

General procedures Organic solutions were dried over anhydrous magnesium sulphate and evaporated at reduced pressure on a rotary film evaporator(r.f.e). Tlc plates were prepared by coating glass plates (20x20 cm) with a slurry of silica gel to a thickness of approximately 0.8 mm. The plates were dried at $100^{0}C$ for three hours and left to cool overnight. Compounds to be chromatographed were applied as solutions in chloroform and the plates developed using toluene/ethyl acetate (3:1) unless otherwise stated. Bands were marked while viewing under ultra-violet light (254 and 350 nm) and extracted with chloroform and are listed in the order of their speed of movement, the fastest being mentioned first.

Vacuum sublimation was performed on a Buchi sublimation apparatus. In cases where the identity of a compound was established by a comparison with an authenticated sample, this was made by nmr and ir spectroscopy unless otherwise stated.

Sources of pyrazines 2-methyl, 2,3-dimethyl-, 2,5-dimethyl-, 2,3,5-trimethyl, 2,3,5,6-tetramethyl-, 2,3-diethyl- and 2-ethyl-3-methyl pyrazines and quinoxalines were obtained commercially. The following pyrazines were synthesised by procedures similar to those given in the literature.

2-Chloro-3-methylpyrazine[69,70] and 3-chloro-2,5-dimethyl pyrazine[69,70] were obtained by bubbling chlorine gas into a solution of the corresponding alkylpyrazine in carbon tetrachloride. An exothermic reaction took place with precipitation of the alkylpyrazine hydrochloride. The latter was filtered off and washed with carbon tetrachloride. The filter cake was slurried with water and the mixture was neutralised with 35% aqueous sodium hydroxide. The crude oil which separated, was distilled to give the chloropyrazines. 2-Chloro-3-methylpyrazine was obtained in 50% yield and 3-chloro-2,5-dimethylpyrazine in 55% yield.

3-Methoxy-2-methylpyrazine was obtained by refluxing a solution of 2-chloro-3-methylpyrazine in methanol with sodium methoxide and 3-chloro-2,5-dimethylpyrazine similarly gave 2,5-dimethyl-3-methoxypyrazine. The product was obtained by filtering off the precipitated sodium chloride and the filtrate was distilled to give the pure methoxypyrazine as a colourless oil.

2-Amino-3,6-dimethylpyrazine was produced by heating a mixture of 3-chloro-2,5-dimethylpyrazine with 30% aqueous ammonia at 180^{0}C in an autoclave for 10 hours. The resulting solution was made basic with potassium hydroxide. The solution was extracted with chloroform. Evaporation of the solvent gave a solid which after recrystallisation from toluene yielded 2-amino-3,6-dimethylpyrazine as colourless crystals(60%).

Experimental procedure for the Chichibabin reaction

The following general procedure was used in the Chichibabin synthesis of 7-azaindolizines and dipyrrolo-[1,2-a:2,1-c]pyrazines unless otherwise stated. The α-bromoketone was added to the methylpyrazine or 8-methyl-7-azaindolizine and left from 3 to 28 days at 35-60^{0}C. Generally the quaternary salt was not isolated unless otherwise stated. Water was added to the salt and the aqueous solution was extracted with ether or chloroform to removed unchanged reactants. The aqueous solution was then warmed to remove dissolved solvent, excess of sodium bicarbonate added and the resulting solution refluxed for 30 minutes and extracted several times with chloroform. The combined chloroform extracts were dried and the chloroform evaporated to leave a residue from which the products were isolated.

CHAPTER II

Reaction between 2-methylpyrazine and bromoacetone

A mixture of 2-methylpyrazine (0.5g, 0.005 mol) and bromoacetone (0.685 g, 0.005 mol) were left together for 5 days at 35^{o}C. The resulting product on washing with ether gave 1-acetonyl-3-methylpyrazinium bromide (41) 1.0g (85%) mp 125-126^{o}C; ir 650, 720, 810, 880, 1250, 1300, 1625, 1720, 3440 cm^{-1}; pmr 2.40 (3H, acetonyl-CH_3), 2.80 (3H, CH_3-3), 6.00 (2H, CH_2), 8.90 (1H, H-5), 9.15 (1H H-2), 9.50 (1H, H-6).

Anal. calcd. for $C_8H_{11}N_2OBr$: C, 41.6; H, 4.7; N, 12.1.

Found: C, 40.8; H, 4.9; N, 12.1.

1-Acetonyl-3-methylpyrazinium bromide (41) (1.0 g, 0.004 mol) was dissolved in water ($25cm^3$) and excess sodium hydrogen carbonate added. The resulting solution was refluxed, cooled and extracted with chloroform, the extracted chloroform after drying and evaporation gave 2-methylpyrazine (0.22g).

Reaction between 2,5-dimethylpyrazine and bromobutan-2-one

2,5-Dimethylpyrazine (1.0 g, 0.009 mol) and bromobutan-2-one (1.3g, 0.009 mol) were left together at $50^{o}C$ for 3 weeks. Basification of the salt gave a dark red oil which on vacuum sublimation ($70^{0}C$, 18 mm) yielded 2,3,6-trimethyl-7-azaindolizine (43) 0.02g (2%) as colourless crystals; mp 99-$102^{o}C$; λ_{max} (210), 225, 243, 252, 294, 306, 346 (broad) nm; log ε 4.39, 4.55, 4.42, 4.40, 3.60, 3.60, 3.63; ir 720, 800, 920, 1060, 1210, 1315, 1510, 1620 cm^{-1}; pmr 2.28 (3H, CH_3-2), 2.36 (3H, CH_3-3), 2.43 (3H, CH_3-6), 6.68 (1H, H-1), 7.38 (1H, H-5), 8.60 (1H, H-8).

Anal. calcd. for $C_{10}H_{12}N_2$: C, 75.0; H,7.5; N, 17.5. Found: C, 74.6; H 7.6, N 17.5.

Reaction between 2,5-dimethylpyrazine and bromopropiophenone

A mixture of 2,5-dimethylpyrazine (1.0g, 0.009mol) and bromopropiophenone (1.8g, 0.009mol) was left at $50^{o}C$ for 4 weeks. The resulting solid on basificiation with sodium bicarbonate produced a crude product which on vacuum

sublimation yielded 3,6-dimethyl-2-phenyl-7-azaindolizine (44) 0.04g (2%) as colourless crystals; mp 114°C; ir 720, 770, 815, 920, 1185, 1325, 1625, 3020 cm^{-1}; pmr 2.45 (3H, CH_3-3), 2.52 (3H, CH_3-6), 6.83 (1H, H-1), 7.35 (1H, H-5), 7.43 (5H, Ph-2), 8.70 (1H, H-8).

Anal. calcd. for $C_{15}H_{14}N_2$: C, 81.1; H, 6.3; N, 12.6. Found: C, 80.6; H, 6.4; N, 12.8.

Reaction between 2,3-dimethylpyrazine and bromoacetone

2,3-Dimethylpyrazine (10.7g, 0.1mol) on reaction with bromoacetone (13.7g, 0.1mol) yielded a glassy dark solid after 7 days at 45°C. Addition of excess sodium bicarbonate gave an oil (8.0g) which was distilled under vacuum (70°C, 18mm) to give 2,8-dimethyl-7-azaindolizine (45) 6.4g (41%) as a pale yellow oil which darkened on standing; λ_{max} 229, 235, 243, 261, 265, 268, 330(broad)nm; log ε 4.42, 4.34, 4.02, 3.60, 3.60, 3.53, 3.34; ir (thin film) 796, 1155, 1310, 1350, 1475, 1560, 1615, 2920, 3040 cm^{-1}; pmr 2.35 (3H, CH_3-2), 2.60 (3H, CH_3-8), 6.55* (1H, H-1), 7.14* (1H, H-3), 7.32d (1H, J=5.5Hz, H-5), 7.55d (1H, J=5.5Hz, H-6); cmr 10.8 (CH_3-2), 19.70 (CH_3-8), 101.92-149.00 (C-1, C-2, C-3, C-5, C-6, C-8 and C-9).

To a solution of 2,8-dimethyl-7-azaindolizine (45) (0.3g, 0.002mol) in ethanol was added excess perchloric acid (0.4 mol 70%) to give a solid which was recrystallised from ethanol to give 2,8-dimethyl-7-azaindolizinium perchlorate (0.2g, 41%) as pale yellow needles; mp 205-208°C; ir 640, 770, 920, 1050, 1110, 1320, 1605, 1655, 3100, 3240 cm^{-1}; pmr DMSO-d_6 2.39 (3H, CH_3-2), 2.84 (3H, CH_3-8), 7.58d (1H, J=

5.3Hz, H-6); 7.6 (1H, H-1), 8.18 (1H, H-3), 8.55d (1H, J= 5.3 Hz, H-5).

Anal. calcd. for $C_9H_{10}N_2O_4Cl$: C, 43.0; H, 4.3; Cl, 14.6; N, 11.4. Found: C, 43.6; H, 4.3; Cl; 14.6; N, 11.4.

Reaction between 2,3-dimethylpyrazine and bromopinacolone

2,3-Dimethylpyrazine (1.4g, 0.13mol) and bromopinacolone (2.32g, 0.013mol) gave a crystalline solid after a week at 45°C. Dissolution of this solid in water and addition of excess of bicarbonate gave a dark oil. Distillation of this crude oil afforded 8-methyl-2-t-butyl-7-azaindolizine (46) 0.8g (33%) as a pale yellow oil; ir 685, 800, 1240, 1320, 1490, 1540, 1620, 3120 cm^{-1}; pmr 1.40 (9H, t-butyl-2), 2.80 (3H, CH_3-8), 6.55* (1H, H-1), 7.14* (1H, H-3), 7.35d (1H, J= 5.5Hz, H-5), 7.55d (1H, J= 5.5Hz, H-6).

Anal. calcd. for $C_{12}H_{16}N_2$: C, 76.6; H, 8.51; N, 14.9. Found : C, 75.5; H, 8.2; N,14.4.

Reaction between 2,3-dimethylpyrazine and phenacyl bromide

2,3-Dimethylpyrazine (5.35g, 0.05mol) and phenacyl bromide (9.99g, 0.05mol) gave a quaternary salt at 50°C after two weeks. Addition of bicarbonate to this salt produced an orange solid which was recrystallised from petroleum ether to yield 8-methyl-2-phenyl-7-azaindolizine (47) 2.2g (21%) as yellow crystals mp 133-135°C; λ_{max} 204, (240), 256, (269), 287 (broad) nm; log ε 4.51, 4.32, 4.55, 4.30, 3.70; ir 745, 770, 800, 882, 1055, 1220, 1550, 3095, 3110 cm^{-1}; pmr 2.66 (3H, CH_3-8), 6.77 (1H, H-1), 7.26-7.70m

(8H, Ph-2, H-3, H-5, H-6).

Anal. calcd. for $C_{14}H_{12}N_2$: C, 80.8; H, 5.8, N, 13.5. Found: C, 81.0; H, 6.3; 12.9.

Reaction between 2,3-dimethylpyrazine and bromobutan-2-one

2,3-Dimethylpyrazine (10.7g, 0.1mol) and bromobutan-2-one (15.1g, 0.1mol) formed a crystalline quaternary salt at 40°C for 14 days. Basification of this salt gave a red oil which crystallised on standing. Vacuum sublimation (80°C, 18mm) yielded 2,3,8-trimethyl-7-azaindolizine (48) 10g (63%) as colourless needles mp 60-61°C; λ_{max} (210), 227, 241, (249), (274), 286, 297, 341(broad) nm, log ε 4.28, 4.62, 4.40, 4.24, 3.50, 3.62, 3.61, 3.33; ir 670, 720, 780, 800, 890, 1220, 1320, 1355, 1490, 1590, 3100cm^{-1}; pmr 2.27 (3H, CH_3-2), 2.32 (3H, CH_3-3), 2.60 (3H, CH_3-8), 6.55 (1H, H-1), 7.55 (2H, H-5, H-6).

Anal. calcd. for $C_{10}H_{12}N_2$: C, 75.0; H, 7.5; N, 17.5. Found: C, 74.9; H, 7.5; N, 17.5.

Reaction between 2,3,5-trimethylpyrazine and bromoacetone

2,3,5-Trimethylpyrazine (12.1g, 0.1mol) and bromoacetone (13.7g, 0.1mol) gave as the quaternary salt a dark red solid at 45°C for 14 days. Dissolution of this salt and addition of excess sodium bicarbonate produced a dark red oil (8.8g). Vacuum distillation (60°C, 18mm) gave 2,6,8-trimethyl-7-azaindolizine (49) 5.0g (31%) as a pale yellow oil; λ_{max} (210), 229, (236), (245), 275, 290, 304, 335 (broad)nm; log ε

4.42, 4.70, 4.62, 4.45, 3.60, 3.75, 3.70, 3.66; ir 805, 935, 1145, 1225, 1475, 1550, 1625, 2920 cm^{-1}; pmr 2.28 (3H, CH_3-2), 2.30 (3H, CH_3-6), 2.54 (3H, CH_3-8), 6.40 (1H, H-1), 6.98 (1H, H-3), 7.28 (1H, H-5).

Anal. calcd. for $C_{10}H_{12}N_2$: C, 75.0, H, 7.5; N,17.5. Found: C, 75.0; H, 7.4; N, 17.2.

Reaction between 2,3,5-trimethylpyrazine and phenacyl bromide

2,3,5-Trimethylpyrazine (6.05g, 0.05mol) and phenacyl bromide (10.0g, 0.05mol) on standing at 55°C for 14 days produced a salt. Addition of bicarbonate gave a black solid (1.4g). Vacuum sublimation of this solid (80°C, 18mm) gave 6,8-dimethyl-2-phenyl-7-azaindolizine (50) 1.0g (9%) as pale yellow crystals; mp 110-111°C; λ_{max} 210, 253, (260), (271), (281), 321 (broad)nm; log ε 4.44, 4.73, 4.68, 4.50, 3.86, 3.86; ir 698, 770, 820, 1160, 1225, 1505, 1620, 3120 cm^{-1}; pmr 2.41 (3H, CH_3-6), 2.69 (3H, CH_3-8), 7.00 (1H, H-1), 7.29-7.77m (7H, Ph-2, H-3, H-5).

Anal. calcd. for $C_{15}H_{14}N_2$: C, 80.0; H, 6.7; N, 13.3. Found: C, 80.2; H, 6.7; N, 13.3.

Reaction between 2,3,6-trimethylpyrazine and bromobutan-2-one

2,3,6-trimethylpyrazine (3.03g, 0.025mol) and bromobutan-2-one (3.78g, 0.025mol) on standing for 14 days at 45°C yielded a salt which upon basification with sodium bicarbonate gave a dark red oil (1.7g). Vacuum sublimation of that oil (90°C, 18mm) gave 2,3,6,8-tetramethyl-7-aza-

indolizine (51) 1.4g (31%) as pale ye ow crystals; mp 83-85°C; λ_{max} 230, 245, 255, 295, 308, 2(broad) nm, log ε 4.41, 4.29, 4.24, 3.44, 3.50, 3.50; ir 6), 770, 790, 1030, 1105, 1215, 1325, 1540, 1625 cm^{-1}; pmr 2.28 (3H, CH_3-2), 2.32 (3H, CH_3-3), 2.60 (6H, CH_3-6, CH_3- , 6.54 (1H, H-1), 7.25 (1H, H-5).

Anal. calcd. for $C_{11}H_{14}N_2$: C, 75.9; H, 8.1; N, 16.1. Found: C, 76.2; H, 8.3; N, 16.0.

Reaction between 2-ethyl-3-methylpy zine and bromo-butan-2-one

2-Ethyl-3-methylpyazine (1.0, 0.008mc and bromobutan-2-one (1.2g, 0.008mol) was boiled under flux in ethanol ($25cm^3$) for 4 hours. Evaporation of the olvent gave a red solid which upon basification yielded dark red oil. Distillation of the oil gave 2-ethyl-3-me ylpyrazine(0.01g) leaving a dark solid which was vacuum sub mated to give 2,3-dimethyl-8-ethyl-7-azaindolizine (53) 0.11g (9%) as colourless crystals; mp 61°C; ir 785, 10, 1275, 1540, 1610, 3100 cm^{-1}; pmr 1.35t (3H, Et-8), 2. (3H,CH_3-2), 2.30 (3H, CH_3-3), 2.90q (2H, Et-8), 6.58 (1 H-1), 7.38 (2H, H-5, H-6).

Anal. calcd. for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1; N, 16.1. Found: C, 75.6; H, 8.2; N, 16.2.

Reaction between 2,3-diethylpyrazine d bromoacetone

2,3-Diethylpyrazine (1.36g, 0.01mol) and bromoacetone (1.36g, 0.01mol) was boiled under reflux for 4 hours in ethanol (25 cm^3). Evaporation of the lvent gave a red

solid which on basification yielded a dark red oil. Distillation of that oil gave 2,3-diethylpyrazine (0.1g) and a solid which was vacuum sublimated to give 1,2-dimethyl-8-ethyl-7-azaindolizine (54) 0.2g (12%) as yellow crystals; mp 30°C, λ_{max} (234), 238, (280), 291, 302, 344 (broad) nm; log ε 4.46, 4.47, 3.13, 3.52, 2.52, 3.50, 3.38; ir 790, 1140, 1280, 1315, 1450, 1610, 3120 cm^{-1}; pmr 1.34t (3H, Et-8), 2.21 (3H, CH_3-1), 2.44 (3H, CH_3-2), 3.06q (2H, Et-8), 7.12 (1H, H-3), 7.40d (1H, J=4.7Hz), H-5), 7.48d (1H, J=4.7Hz, H-6).

Anal. calcd. for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1; N, 16.1. Found: C, 75.6; H, 8.2; N, 16.2.

Reaction between 2,3-diethylpyrazine and bromobutan-2-one

A mixture of 2,3-diethylpyrazine (5.0g, 0.037mol) and bromobutan-2-one (5.6g, 0.037mol) was boiled in ethanol for 4 hours. Removal of the solvent resulted in a red solid which on basification with excess bicarbonate gave a dark red oil (2.0g). Vacuum distillation of that oil (70°C, 18mm) gave 2,3-diethylpyrazine(0.5g) leaving a solid which on vacuum sublimation yielded 1,2,3-trimethyl-8-ethyl-7-azaindolizine (55) 1.4g (23%) as pale yellow crystals; mp 60-61°C; ir 765, 1105, 1280, 1315, 1490, 1615 cm^{-1}; pmr 1.35t (3H, Et-8), 2.19 (3H, CH_3-1), 2.34 (3H, CH_3-2), 2.48 (3H, CH_3-3), 3.08q (2H, Et-8), 7.33 (2H, H-5, H-6).

Anal. calcd. for $C_{12}H_{16}N_2$: N, 14.9. Found: N, 14.6.

Reaction between 2,3-dimethylquinoxaline and bromoacetone

2,3-Dimethylquinoxaline (1.9g, 0.05mol) and bromoacetone (5.5g, 0.05mol) was maintained at 50°C for 4 weeks. The resulting solid was washed with ether before dissolution and basification to yield a dark red oil which on vacuum sublimation (70°C, 10mm) gave 5,6-benzo-2,8-dimethyl-7-azaindolizine (56) 1.0g (10%) as yellow needle crystals; mp 78-79°C; λ_{max} 203, 227, (241), 247, (263), (270) nm; log ε 4.35, 4.47, 4.47, 4.51, 4.08, 4.05; ir 700, 860, 930, 1350, 1555, 1615, 3090 cm^{-1}; pmr 2.35 (3H, CH_3-2), 2.68 (3H, CH_3-8), 6.69* (1H, H-1), 7.45* (1H, H-3), 7.25-7.95m (4H, benzo group at C-5 and C-6).

Anal. calcd. for $C_{13}H_{12}N_2$: C, 79.6; H, 6.1; N, 14.3. Found: C, 79.8; H, 6.3; N, 14.0.

Reaction between 2,3,5,6-tetramethylpyrazine and bromoacetone

A mixture of 2,3,5,6-tetramethylpyrazine (3.4g, 0.025mol) and bromoacetone (2.78g, 0.025mol) was left in the oven at 70°C for 4 weeks. To the dark residue, water ($100cm^3$) was added and shaken vigorously until all the solid was dissolved. On addition of ether ($50cm^3$), the 2,5,6,8-tetramethyl-7-azaindolizinium bromide (58) precipitated out as a yellow solid. The yellow solid was collected, washed with ether and dried to give 2,5,6,8-tetramethyl-7-azaindolizinium bromide (58) 0.2g (3%) as yellow crystals; mp 330°C; λ_{max} (220), 231.5, 245, (252), (304), 315, 349(broad) nm; log ε 4.37, 4.43, 4.28, 4.15, 3.79, 3.88,

3.71; ir 811, 1328, 1610, 1710, 1820, 3040 cm^{-1}; pmr 2.44 (3H, CH_3-2), 2.55 (3H, CH_3-5), 2.79 (3H, CH_3-6), 3.10 (3H, CH_3-8), 7.20 (1H, H-1), 7.50 (1H, H-3).

Anal. calcd. for $C_{11}H_{15}N_2Br$: C, 51.8; H, 5.9; N, 11.0. Found: C, 51.1, H, 6.0; N, 11.1.

The filtrate (aqueous layer) was then extracted with chloroform (2x25 cm^3). Excess sodium bicarbonate was added to the aqueous layer after which it was refluxed for 30 minutes. The resulting solution was extracted with chloroform (3x25 cm^3). Evaporation of the solvent yielded a dark oil which solidified on standing. Vacuum sublimation of that solid (40°C, 18mm) gave pure 2,5,6,8-tetramethyl-7-azaindolizine (57) (1.9g) as pale yellow crystals; mp 49-50°C; λ_{max} (208), 217, (220), 288, 308, 330 nm; log ε 4.42, 4.44, 4.41, 3.57, 3.63, 3.60; ir 610, 740, 790, 1095, 1245, 1480, 1620, 3105 cm^{-1}; pmr 2.32 (3H, CH_3-2), 2.40 (3H, CH_3-5), 2.48 (3H, CH_3-6), 2.55 (3H, CH_3-8), 6.52* (1H, H-1), 7.01* (1H, H-3).

Anal. calcd. for $C_{11}H_{14}N_2$: N, 16.1; Found: N, 15.7. Reaction of compound (57) with perchloric acid in ethanol gave 2,5,6,8-tetramethyl-7-azaindolizinium perchlorate salt as yellow crystals (50%).

Anal. calcd. for $C_{14}H_{15}N_2O_4Cl$: C, 48.1; H, 5.5; N, 10.2. Found: C, 47.8; H, 5.6; N, 10.1.

A solution of 2,5,6,8-tetramethyl-7-azaindolizium bromide (58) (0.2g, 0.007mol) and sodium hydroxide (2M, 25cm^3) was heated for 10 minutes on a water bath. The resulting solution was extracted with chloroform (3x20 cm^3). Evaporation of the solvent gave a residue which was

subjected to vacuum sublimation (60°C, 18mm) to yield pale yellow crystals (0.1g) whose melting point and spectral characteristics were identical to that of 2,5,6,8-tetramethyl-7-azaindolizine (57). For the conversion of 2,3,5,6-tetramethylpyrazine to 2,5,6,8-tetramethyl-7-azaindolizine (57), the yield was calculated to be 52%.

Reaction between 2,3,5,6-tetramethylpyrazine and phenacyl bromide

A mixture of 2,3,5,6-tetramethylpyrazine (3.4g, 0.025mol) and phenacyl bromide (4.9g, 0.025mol) was left at 60°C for 4 weeks. The resultant black solid was washed with ether (2x25 cm^3). Addition of water (100cm^3) to that solid gave a yellow solid and an aqeous solution. The yellow solid was washed with ether and dried to give 2-phenyl-5,6,8-trimethyl-7-azaindolizinium bromide 0.4g; mp 340°C; λ_{max} 207, (254), 261, (286), 345 nm; log ε 4.20, 4.39, 4.42, 3.60, 3.57; ir 760, 1065, 1210, 1240, 1615 cm^{-1}; pmr (CF_3COOH) 2.68 (6H, CH_3-5, CH_3-6), 3.02 (3H, CH_3-8), 7.40-7.80m (5H, Ph-2), 7.85 (1H, H-1), 8.17 (1H, H-3).

Addition of sodium bicarbonate to an aqueous solution of 2-phenyl-5,6,8-trimethyl-7-azaindolizinium bromide gave after purification by vacuum sublimation 2-phenyl-5,6,8-trimethyl-7azaindolizine (59) 0.25g as yellow crystals; mp 99-100°C; λ_{max} 212, 257, 261,(270), (285), 305 nm; log ε 4.40, 4.54, 3.90, 3.84; ir 740, 770, 1220, 1505, 1620 cm^{-1}; pmr 2.48 (3H, CH_3-5), 2.48 (3H, CH_3-6), 2.65 (3H, CH_3-8), 7.00 (1H, H-1), 7.30 (1H, H-3), 7.35-7.80m (5H, Ph-2).

Anal. calcd. for $C_{16}H_{16}N_2$: C, 81.4; H, 6.8; N, 11.9.

Found: C, 81.1; H, 6.7; N, 11.5.

The aqueous solution was extracted with chloroform (3x20 cm^3). Addition of base to the aqueous layer yielded a black solid which was subjected to vacuum sublimation (40°C, 18mm) to yield 2,3,5,6-tetramethylpyrazine (0.7g), and at higher temperature (60°C, 18mm) yellow crystals were obtained whose melting point and spectral characteristics were identical to that of an authentic sample of compound (59). For the conversion of 2,3,5,6-tetramethylpyrazine to 2-phenyl-5,6,8-trimethyl-7-azaindolizine (59), the yield was calculated to be 16%.

Reaction between 2-cholo-3-methylpyrazine and bromo-acetone

2-Chloro-3-methylpyrazine (1.0g, $7.78x10^{-3}$ mol) and bromoacetone (1.06g, $7.78x10^{-3}$ mol) was left in an oven at 45°C for one week. The resulting black solid was dissolved in water ($25cm^3$) and addition of excess bicarbonate gave an oil from which no identifiable compounds could be isolated.

Reaction between 3-chloro-2,5-dimethylpyrazine and bromo-acetone

3-Chloro-2,5-dimethylpyrazine (2.80g, 0.02mol) and bromoacetone (2.22g, 0.02mol) was left to react at 50°C for 10 days. Addition of bicarbonate to the resulting solid gave a dark solid. This dark solid was subjected to preparative tlc to give 8-chloro-2,6-dimethyl-7-aza-indolizine (60) 0.002g (0.07%) as colourless crystals; mp 62-64°C; λ_{max} 208, 229, (238), (244), 294, 308, 324

(broad)nm; log ε 4.26, 4.47, 4.38, 4.26, 3.62, 3.67, 3.54; ir 825, 1020, 1340, 1550, 1625, 3100 cm^{-1}; pmr 2.45 (6H, 2-CH_3. 6-CH_3), 6.55 (1H, H-1), 7.20 (1H, H-3), 7.50 (1H, H-5).

Anal. calcd. for $C_9H_9N_2Cl$: C, 59.8; H, 4.98; N, 15.5; Found: C, 60.1; H, 5.1; N, 15.3. Mass spectrum, mass calcd. for $C_9H_9N_2Cl$: 180. Found: $M^{\cdot+}$(base peak) 180.

Reaction between 3-chloro-2,5-dimethylpyrazine and phencyl bromide

3-Chloro-2,5-dimethylpyrazine (2.8g, 0.02mol) and phenacyl bromide (4.0g, 0.02mol) was left to react for 14 days at 50°C. Addition of excess bicarbonate to the resulting black solid afforded a dark oil. Vacuum sublimation of this solid gave 8-chloro-6-methyl-2-phenyl-7-azaindolizine (61) 0.5g (9%) as brown crystals; mp 141-143°C; ir 950, 975, 1160, 1260, 1425, 1620, 3140 cm^{-1}; pmr 2.45 (3H, CH_3-6), 7.20-7.70m (8H, Ph-2, H-1, H-3 and H-5).

Reaction between 2,5-dimethyl-3-methoxypyrazine and bromoacetone

2,5-dimethyl-3-methoxypyrazine (1.4g, 0.0098mol) and bromoacetone (1.1g, 0.0098mol) was left to react at 45°C for 10 days. The resulting dark red solid was dissolved in water (50cm^3) and extracted with ether (3x15 cm^3). Excess bicarbonate was added to the aqueous layer to yield a dark red oil. Vacuum distillation of the latter gave 2,6-dimethyl-8-methoxy-7-azaindolizine (62) 0.2g (12%) as a

pale yellow oil; λ_{max} (205),(228), 230, 290 (broad), 312 nm; log ε 4.24, 4.57, 4.58, 3.73, 3.60; ir 750, 800, 1180, 1305, 1490, 1540, 1640, 3120 cm^{-1}; pmr 2.25 (6H, CH_3-2, CH_3-6), 4.00 (OCH_3-8), 6.51* (1H, H-1), 6.95* (1H, H-3), 7.14 (1H, H-5).

Anal. calcd. for $C_{10}H_{12}N_2O$: N, 15.9. Found: N, 15.4.

The residual solid was then subjected to vacuum sublimation (18mm, 100°C) to afford 2,6-dimethyl-7-aza-indolizin-8-(7H)-one (63) 0.016g (1.2%) as yellow crystals; mp 209-210°c; ir 630, 810, 880, 1180, 1650, 3140 cm^{-1}; pmr 2.16 (CH_3-2), 2.21 (3H, CH_3-6), 6.61 (1H, H-1), 6.87 (2H, H-3, H-5), 9.90 broad (1H, N-H).

Mass spectrum, mass calcd. for $C_9H_{10}N_2O$: 162. Found: $M^{\cdot+}$ (base peak) 162, 161 (M-1,42), 147 (M-15, 14), 132 (M-30, 8), 93 (M-69, 18).

Reaction between 2,5-dimethyl-3-methoxypyrazine and phenacyl bromide

2,5-dimethyl-3-methoxypyrazine (1.0g, $7.0x10^{-3}$ mol) and phenacyl bromide (1.4g, $7.0x10^{-3}$ mol) was left to react at 55°C for 14 days. To the resulting salt was added excess bicarbonate to yield a crude which after vacuum sublimation gave 8-methoxy-6-methyl-2-phenyl-7-azaindolizine (64) 0.5g (32%) as pale yellow crystals; mp 134°C; pmr 2.28 (3H, CH_3-6), 4.06 (3H, OCH_3-8), 6.96 (1H, H-1), 7.22-790m (7H, Ph-2, H-3, H-5).

Anal. calcd. for $C_{15}H_{14}N_2O$: C, 75.6; H, 5.9, N, 11.8. Found: C, 75.8; H, 6.0; N, 11.8.

Reaction between 3-methoxy-2-methylpyrazine and bromoacetone

3-Methoxy-2-methylpyrazine (4.5g, 0.036mol) and bromoacetone (3.0g, 0.036mol) gave a salt which upon addition of base gave a red oil. The latter was subjected to vacuum distillation (50°C, 18mm) to yield 2-methyl-8-methoxy-7-azaindolizine (65) 0.045g (10.5%)) as a pale yellow oil; ir 760, 1160,1330, 1370, 1520, 1620, 3100 cm^{-1}; pmr 2.26 (3H, CH_3-2), 4.00 (3H, OCH_3-8), 6.65* (1H, H-1), 7.07* (1H, H-3), 7.00d (1H, J=4.6Hz, H-6), 7.35d (1H, J=4.6Hz, H-5).

Anal. calcd. for $C_9H_{10}N_2O$: C,66.7; H, 6.2; N, 17.3. Found: C, 66.3; H, 6.3; N, 16.9.

The residual solid was subjected to vacuum sublimation (95°C, 18mm) to give 2-methyl-7-azaindolizin-8(7H)-one (66) 0.045g (1.5%) as pale yellow needle like crystals; mp 170-171°C; ir 710, 760, 900, 1200, 1650, 3020,3160 cm^{-1}, pmr 2.25 (3H, CH_3-2), 6.50d (1H, J=7.6Hz, H-6), 6.96d (1H, J=7.6Hz, H-5), 6.97 (2H, H-3 and H-1), 10.50 broad (1H, N-H).

Anal. calcd. for $C_8H_8N_2O$: C, 64.8; H, 5.4; N, 18.9. Found C, 65.1; H, 5.5; N, 19.2. Mass spectrum, mass calcd. for $C_8H_8N_2O$: 148. Found: $M^{\cdot+}$(base peak) 148.

Reaction between 2,3-dimethylpyrazine and ethylbromo-pyruvate

2,3-Dimethylpyrazine (2.0g, 0.0185m) and ethylbromo-pyruvate (2.0g, 0.0185m) gave after 2 weeks at 45°C an orange solid. Basification of that solid with bicarbonate gave a brown solid which after vacuum sublimation yielded 2-carboethoxy-8-methyl-7-azaindolizine (67) 0.6g (16%) as pale yellow crystals; mp 102-103°C; ir 780, 1030, 1240, 1330, 1710, 3120 cm^{-1}; λ_{max} 226.5, 238, 274, 285, 323, 337, 305 nm; log ε 4.60, 4.20, 3.43, 3.43, 3.49, 3.43, 3.22; pmr 1.35t (3H, C00Et-2), 2.62 (3H, CH_3-8), 4.35q (2H, C00Et-2), 7.15* (1H, H-1), 7.40d (1H, J=6.7Hz, H-6), 7.60d (1H, J=6.7Hz, H-5), 7.81* (1H, H-3).

Anal. calcd. for $C_{11}H_{12}N_2O_2$: C,64.7; H, 5.9; N, 13.7. Found: C, 64.5; H, 6.0; N, 13.7.

Reaction between 2-amino-3,6-dimethylpyrazine and phenacyl bromide

2-Amino-3,6-dimethlpyrazine (0.5g, $4.06X10^{-3}$ mol) and phenacyl bromide (0.8g, $4.06x10^{-3}$ mol) were left in an oven at 60°C for a week. The resulting solid was basified with sodium bicarbonate to give a solid which was recrystallised from toluene to give 8-amino-6-methyl-2-phenyl-7-aza-indolizine (68) 0.32g (35%) as straw colour crystals ; mp 242°C; λ max (218), 252, 268.5, (278), (311.5), (343); log ε 4.47, 4.71, 4.74, 4.69, 4.11, 3.47; pmr 2.24 (3H, CH_3-6), 4.40 broad (2H, NH_2-8), 7.30-7.67m (8H, H-1, H-3, H-5 and Ph-2).

Anal. calcd. for $C_{14}H_{13}N_3$: C, 75.3; H, 5.8; N, 18.8.

Found: C, 74.6; H, 5.9; N, 18.5. Mass spectrum, mass calcd. for $C_{14}H_{13}N_3$: 223. Found: m/e 223 (base peak).

To 8-amino-6-methyl-2-phenyl-7-azaindolizine (0.01g, $4.5x10^{-5}$ mol) in ethanol ($5cm^3$) was added perchloric acid ($1cm^3$) which resulted in the precipitation of the perchlorate as a white solid. This solid was filtered off, washed with ethanol and dried in a vacuum oven. The resulting solid obtained was 8-amino-6-methyl-2-phenyl-7-azaindolizinium perchlorate (69) 0.01g (69%); mp 277°C; pmr (DMSO-d_6) 2.25 (3H, CH_3-6), 7.30-8.20m (8H, H-1, H-3 and Ph-2), 8.60 broad (2H, NH_2-8), 12.20 broad (1H, H-7).

Anal. calcd. for $C_{14}H_{14}N_3ClO_4$: C, 51.9; H, 4.4; N, 13.0. Found: C, 51.4; H, 4.2; N, 12.5.

Reaction between 2-amino-3,6-dimethylpyrazine and bromoacetone

2-Amino-3,6-dimethylpyrazine (0.1g, $8.1x10^{-4}$ mol) and bromoacetone (0.11g , $8.1x10^{-4}$ mol) were left in an oven at 60°C for a week. The resulting dark red solid was basified with sodium bicarbonate. The resulting solid was purified by preparative tlc to give a solid 0.05g (50%) which showed identical spectral activities to that of 2-amino-3,6-dimethylpyazine.

Quaternisation

To a solution of 7-azaindolizine (5) (0.1g, 8.47×10^{-4} mol) in ethanol ($3cm^3$) was added an excess amount of methyl iodide ($5cm^3$). The formation of a white turbidity was apparent and trituration of this solution with diethyl ether ($2cm^3$) resulted in the precipitation of a pale yellow solid. The latter was thoroughly washed with ether and dried. Recrystallisation of this solid from ethanol gave 7-azaindolizinium methiodide salt (76) 0.09g (41%); mp 108-109°C; ir 784, 1150, 1560, 1660, 3080 cm^{-1}; pmr (CF_3COOH) 4.37 (3H, CH_3-7), 730* (1H, H-1), 7.35m (1H, H-2), 7.65d (1H, J=5.5Hz, H-6), 8.12* (1H, H-3), 8.35d (1H, J=5.5HZ, H-5), 8.88* (1H, H-8).

To a solution of 2,8-dimethyl-7-azaindolizine (45) (0.5g, 3.42×10^{-3} mol) was added an excess of methyl iodide ($10cm^3$), which followed the precipitation of a yellow solid. This solid was recrystallised from ethanol to give 2,8-dimethyl-7-azaindolizinium methiodide (77) 0.6g (61%) as pale yellow crystals; mp 227-228°C; ir 805, 1160, 1305, 1515, 1605 cm^{-1}; pmr (CF_3COOH) 2.48 (3H, CH_3-2), 2.95 (3H, CH_3-8), 4.08 (3H, CH_3-7), 7.25d (1H,J=5.5Hz, H-6), 7.42* (1H, H-1), 7.88* (1H, H-3), 8.15d (1H, J=5.5Hz, H-5).

8-Methyl-2-t-butyl-7-azaindolizine (45) (7.9g, 0.042mol) and bromopinacolone (5.5g, 0.042mol) in ethanol ($3cm^3$) were left at 50°C for a week. The resulting salt was washed with

ether and recrystallised from ethanol to give 8-methyl-2-t-butyl-7-azaindolizinium bromide (78) 10.2g (66%) as colourless crystals; mp 285°C; ir 960, 1650, 1715, 3040 cm^{-1}. pmr (DMSO-d_6) 1.45 (9H, t-butyl), 1.48 (9H, t-butyl), 2.85 (3H, CH_3-8), 5.68 (2H, CH_2-2), 7.20d (1H, J=6.0Hz, H-5), 6.62* (1H, H-1), 8.00* (1H , H-3), 8.20d (1H, J=6.0Hz, H-6).

Anal. calcd. for $C_{18}H_{27}N_2OBr$: C, 58.9; H, 7.4; N, 7.6. Found: C, 60.0; H, 7.8; N, 7.5.

Lithiation

2,8-Dimethyl-7-azaindolizine (45) (1.0g, 6.85×10^{-3} mol) was dissolved in dry diethyl ether (15 cm^3). The solution was cooled down to -15°C in a dry ice/acetone bath. While keeping that temperature constant, a solution of methyl lithium (1.3M) in ether (15cm^3) was added dropwise. This resulted in a sudden change of colour from pale yellow to a deep red solution. Introduction of deuterium oxide (D_2O) (1g) caused the disappearence of the red coloration. The resulting solution was extracted with chloroform (3x10 cm^3) and dried. Evaporation of the solvent afforded the deuterated 2,8-dimethyl-7-azaindolizine (80) 0.8g (79%) as a pale yellow oil; pmr 2.35 (3H, CH_3-2), 2.52 (2H, CH_2D-8), 6.55* (1H, H-1), 7.14* (1H, H-3), 7.35d (1H, J=5.5Hz, H-5), 7.55d (1H, J=5.5Hz, H-6).

2,8-Dimethyl-7-azaindolizine (45) (2.48g, 0.017mol) was dissolved in dry diethyl ether (20cm^3). A solution of methyllithium (1.3M) in ether (25cm^3) was then added while

keeping the temperature constant at -15°C by using a dry ice/acetone bath. This, resulted in the formation of a deep red solution which after addition of methyliodide ($2.4cm^3$) in ether afforded a deep green solution and the reaction mixture was left stirring for 60 minutes at room temperature. Water was then added ($25cm^3$) and the resulting solution was extracted with chloroform ($3x15\ cm^3$). Evaporation of the solvent yielded a black oil (2.68g) which showed two spots on tlc. Separation of this oil by preparative tlc gave two products. The faster moving band gave 8-ethyl-2-methyl-7-azaindolizine (81) 1.6g (63%) as a colourless oil which darkened on standing; λ_{max} (213), 226, 234, (241), 286, 298, 332 nm; log ε 4.26, 4.39, 4.37, 4.18, 3.54, 3.54, 3.42; ir (thin film) 795, 1310, 1475, 1545, 2940, 2980 cm^{-1}; pmr 1.35t (3H, CH_3-2), 2.90d (2H, Et-8), 6.60 (1H, H-3), 7.14 (1H, H-3), 7.35d (1H, J=5.5Hz, H-5), 7.55d (1H, J=5.5Hz, H-6).

The slower moving band gave 8-isopropyl-2-methyl-7-azaindolizine (82) (1.0g, 34%) as a colourless oil which darkened on standing; λ_{max} (214), 225, 240, (244), 285, 296, 334 nm; log ε 4.20, 4.23, 4.21, 4.14, 3.63, 3.63, 3.41; ir 780, 1100, 1300, 1460, 1610, 2940, 2980 cm^{-1}; pmr 1.35d (6H, isopropyl-8), 2.30 (3H, CH_3-2), 3.30m (1H, isopropyl-8), 6.58 (1H, H-1), 7.12 (1H, H-3), 7.35d (1H, J=5.5Hz, H-5), 7.53d (1H, J=5.5Hz, H-6).

Acetylation

A solution of 2,8-dimethyl-7-azaindolizine (45) (0.5g, $3.4x10^{-3}$ mol) in acetic anhydride ($25cm^3$) was left to reflux

for 24 hours. The solution was cooled and the excess acetic anhydride was removed at the r.f.e. The resulting red oil was poured into iced water and basified with sodium hydroxide (2M). The solution was thoroughly extracted with chloroform (4x15 cm^3) to give after evaporation a dark brown residue. Preparative t.l.c on this residue gave back some starting material (45) 0.2g (40%) and 3-acetyl-2,8-dimethyl-7-azaindolizine (84) 0.1g (16%) as pale yellow needle like crystals; mp 138°C; ir 790, 815, 975, 1290, 1410, 1630 cm^{-1}; pmr 2.59 (3H, $COCH_3$-3), 2.65 (3H, CH_3-2), 2.70 (3H, CH_3-8), 6.62 (1H, H-1), 7.72d (1H, J=5.3Hz, H-6), 9.54d (1H, J=5.3Hz, H-5).

Anal. calcd. for $C_{11}H_{12}N_2O$: C, 70.2; H, 6.4; N, 14.9. Found C, 69.9; H, 6.5; N, 14.4.

Nitration

2,6,8-Trimethyl-7-azaindolizine (49) (0.4g, $2.5x10^{-3}$ mol) was carefully mixed to a mixture of conc. HNO_3 (5cm^3) and conc. H_2SO_4 (5cm^3) in an ice bath. After all the 7-azaindolizine had been added, the mixture was left stirring for half an hour. The resulting viscous liquid was poured into iced water and basified with NaOH (4M) which resulted in the formation of a yellow precipitate. The latter was filtered off and washed thoroughly with water. Recrystallisation from ethanol gave 1,3-dintro-2,6,8-trimethyl-7-azaindolizine (85) 0.15g (24%) as yellow crystals; mp 134°C; λ_{max} 213, 271, 283, 292, 377 nm; log ε 4.36, 4.09, 4.08, 4.06, 4.09; ir 820, 830, 1205, 1300, 1380, 1510, 1560, 31050 cm^{-1}; pmr 2.61 (3H, CH_3-2), 2.80 (6H, CH_3-6, CH_3-8),

9.20 (1H, H-5).

Anal. Calcd. for $C_{10}H_{10}N_4O_4$: C, 48.0; H, 4.0; N, 22.4. Found: C, 47.5, H, 3.7; N, 22.5.

Attempted formylation

A solution of phosphoryl chloride (0.337g, $2.2x10^{-3}$ mol) in dimethylformamide ($2cm^3$) was added to a magnetically stirred solution of 2,8-dimethyl-7-azaindolizine (45) (0.5g, $3.42x10^{-3}$ mol) in dimethylformamide ($4cm^3$) and the resultant solution was left at 40^0C for 12 hours. The product was then poured into 2M aqueous sodium hydroxide ($30cm^3$), diluted with water ($40cm^3$) and the solution extracted with chloroform (3 x15 cm^3). Evaporation of the solvent gave a dark green oil, which on distillation gave back the starting material (45) (0.3g).

Reaction between 2,3,8-trimethyl-7-azaindolizine (48) and ethoxalyl chloride.

2,3,8-Trimethyl-7-azaindolizine (48) (1.01g 0.006mol) was dissolved in dried dichloromethane ($25cm^3$) and ethoxalyl chloride (1.73g, 0.012mol) was then added. The resulting solution was refluxed for 30 minutes. The solvent together with excess ethoxalyl chloride were removed at the r.f.e. The red residue was washed thoroughly with ether and water. The aqueous solution was then extracted with dichloromethane. Evaporation of the solvent gave 2,3-dimethyl-10-ethoxalyl-8,9-diketodipyrrolo[1,2-a:2,1-c]pyrazine (86) 0.47g (25%) as a red solid; mp 250^oC; ir 1630, 1660, 1700, 1730, 1770, 3100 cm^{-1}; pmr (DMSO-d_6) 1.28t (3H, COOEt-10), 2.24 (3H,

CH_3-2), 2.52 (3H, CH_3-3), 4.28q (2H, C00Et-10), 7.40d (1H, J=5.7Hz, H-5), 7.70d (1H, J=5.7HZ, H-6), 8.49 (1H, H-1); cmr 13.20 (CH_3-2), 14.50 (CH_3-3), 17.00 ($COCO_2$Et-10), 64.00 (CH_2-10), 106.00, 122.00, 132.00, 124.50, 151.50 (five quaternary carbons at C-2, C-3, C-10, C-10a, C-10b), 112.00, 114.50, 129.50 (three methine carbon at C-1, C-5, C-6), 177.20, 177.50, 180.18, 180.22 (four carbonyl carbons at C-8, C-9, $COCO_2$Et-10).

Mass spectrum, mass calcd. for $C_{15}H_{12}N_2O_4$: 314. Found: m/e 314 ($M^{\cdot+}$,15), 258 ($M^{\cdot+}$-56, 12), 241 ($M^{\cdot+}$-56, 12), 241 ($M^{\cdot+}$-73, 100), 213 ($M^{\cdot+}$-101, 68).

Reaction between 2,3-dimethyl-8-ethyl-7-azaindolizine and ethoxalyl chloride

2,3-Dimethyl-8-ethyl-7-azaindolizine (53) (1.08g, 0.006mol) in dichloromethane (25cm^3) was refluxed with ethoxalyl chloride (1.69g, 0.012mol) for half an hour. The solvent was removed at the r.f.e to give a solid crude, which was recrystallised from ethanol to give 2,3,10-trimethyl-8,9-diketodipyrrolo[1,2-a:2,1-c]pyrazine (88) 0.2g (15%) as deep green crystals; mp 250°C, ir 1580, 1650, 1750, 2800, 3100 cm^{-1}; pmr 1.91 (3H, CH_3-10), 2.12 (3H, CH_3-2), 2.29 (3H, CH_3-3), 6.47d (1H, J=5.7Hz, H-5), 6.70d (1H, J=5.7Hz, H-6), 6.91 (1H, H-1).

Mass spectrum, mass calcd. for $C_{13}H_{12}N_2O_2$: 228. Found: m/e 228 ($M^{\cdot+}$, 22), 200 ($M^{\cdot+}$-28, 28), 170 ($M^{\cdot+}$-56, 80), 171 ($M^{\cdot+}$-57, 100).

Reaction with nucleophiles

8-Methoxy-2-methyl-7-azaindolizine (65) (0.1g, mol) in conc. hydrochloric acid (20cm^3) was heated on a water bath for half an hour. The mixture was evaporated to dryness and the resulting solid was dissolved in water (25cm^3) and then basified with sodium bicarbonate. After extraction with chloroform (3x15 cm^3) and evaporation of the solvent gave a crude solid, which on sublimation (18mm, 110^{o}C) produced 2-methyl-7-azaindolizin-8(7H)-one (65) 50mg (55%) as colourless needle crystals; mp 170-171^{o}C; λ_{max} (226), 230, 285, (315); log ε 4.59, 4.61, 4.02, 3.49; ir 970, 1160, 1370, 1520,1620, 3100 cm^{-1}; pmr 2.25 (3H, CH_3-2), 6.50* (1H, H-1),6.97 (3H, H-3, H-5 and H-6).

Anal. calcd. for $C_8H_8N_2O$; C, 64.8; H, 5.4; N, 18.9. Found: C, 65.1; H, 5.5; N, 19.2. Mass spectrum, mass calcd. for $C_8H_8N_2O$: 148. Found m/e 148 (base peak).

2-Methyl-7-azaindolizin-8(7H)-one (65) (0.143g, 9.66x 10^{-4} mol) together with phosphoryl chloride (25cm^3) were refluxed for 3 hours. After evaporation of the excess phosphoryl chloride at the r.f.e and basification with bicarbonate, the solution was extracted with chloroform (3x 25 cm^3). Evaporation of the solvent yielded a deep red oil as the crude. Vacuum sublimation on the crude (18mm, 79^{o}C) gave 8-chloro-2-methyl-7-azaindolizine (91) 0.150g (93%) as colourless crystals; mp 28^{o}C; λ_{max} (216.5), 226.5, (238), (244.5), 290, 300, (335) nm, log ε 4.43, 4.47, 4.31, 4.19, 3.57, 3.64, 3.47; pmr 2.31 (3H, CH_3-2), 6.66 (1H, H-1), 7.20d (1H, J=4.5Hz, H-5), 7.63d (1H, J=H.5Hz, H-6).

Mass spectrum, mass calcd. for $C_8H_7N_2Cl$: 166. Found: m/e 166 (base peak).

8-methoxy-2-methyl-7-azaindolizine

8-Chloro-2-methyl-7-azaindolizine (0.03g, $1.8x10^{-4}$ mol) was added to a solution of sodium methoxide in methanol ($50cm^3$) and the mixture was boiled under reflux for 10 hours. Excess methanol was evaporated and water ($20cm^3$) was added to the residue. The resulting solution was extracted with choroform (3x15 cm^3). Evaporation of the solvent gave a yellow oil which on vacuum distillation produced 8-methoxy-2-methyl-7-azaindolizine (65) 0.02g (68%) as a colourless oil; ir 760, 1100, 1160, 1330, 1370, 1620, 3100 cm^{-1}; pmr 2.26 (CH_3-2), 4.00 (OCH_3-8), 6.65 (1H, H-1), 7.00 (1H, H-3), 7.07 (1H, H-5), 7.35 (1H, H-6).

Anal. calcd. for $C_9H_{10}N_2O$: C, 66.6; H, 6.2; N, 17.3. Found: C, 66.3; H, 6.3; N, 16.7.

8-Amino-2-methyl-7-azaindolizine

8-Chloro-2-methyl-7-azaindolizine (0.04g, 2.4×10^{-4}mol) was added to a solution of conc. ammonia ($10cm^3$). The mixture was heated in an autoclave at 180°C for 48 hours. After cooling (-15°C), the solution was made strongly alkaline with potassium hydroxide pellets and extracted with chloroform (3x10 cm^3). Evaporation of the solvent gave 8-amino-2-methyl-7-azaindolizine (71) 0.02g (57%) as white needle like crystals; mp 135°C; λ_{max} 206, (213), 227, 285, (304); log ε 4.31, 4.25, 4.37, 3.78, 3.64; ir 760, 1630, 1650, 3300, 3440 cm^{-1}; pmr 2.29 (3H, CH_3-2), 4.49 (2H,

NH_2-8); 6.27 (1H, H-1), 6.99d (1H, J=4.9Hz, H-5), 7.08 (1H, H-3), 7.28d (1H, J=4.9Hz, H-6).

Mass spectrum, mass calcd. for $C_8H_9N_3$: 147. Found: $M^{\cdot+}$ (base peak) 147, 146 ($M^{\cdot+}$-1, 38), 119 ($M^{\cdot+}$-28, 25).

Chapter 4

Reaction between 8-methyl-2-t-butyl-7-azaindolizine and bromopinacolone

8-Methyl-2-t-butyl-7-azaindolizine (46) (7.9g, 0.042mol) and bromopinacolone (5.5g, 0.042mol) in ethanol ($3cm^3$) were left at 50°C for a week. The resulting quaternary salt (78) (10.2g) was dissolved in water ($40cm^3$) and sodium bicarbonate (10g) was added. Refluxing this solution yielded a solid, which was recrystallised from ethanol to give 2,9-di-t-butyldipyrrolo[1,2-a:2,1-c]pyrazine (92) 5.6g (48%) as colourless crystals; mp 155.7°C; λ_{max} (247), 254, (297), (309) nm; log ε 4.71, 4.75, 4.03, 3.93, 3.92; ir 670, 785, 1550, 1670 cm^{-1}; pmr 1.30 (9H,t-butyl at C-2 and C-9), 6.40* (2H, H-1 and H-10), 6.74* (2H, H-3 and H-8), 6.92 (2H, H-5 and H-6); cmr 30.83 (t-butyl), 31.70 (t-butyl), 97.30 (C-1, C-10), 109.92 (C-3, C-8), 110.84 (C-5, C-6), 124.22 (C-2, C-9), 138.96 (C-10a, C-10b).

Anal. calcd. for $C_{18}H_{24}N_2$: C, 80.1; H, 8.9; N, 10.4. Found: C, 79.9; H, 9.0; N, 10.0. Mass spectrum, mass calcd. for $C_{18}H_{24}N_2$: 268. Found: $M^{\cdot+}$ (base peak) 268.

Reaction between 2,8-dimethyl-7-azaindolizine and bromoacetone

2,8-Dimethyl-7-azaindolizine (45) (2.0g, 0.0137mol) and bromoacetone (1.8g, 0.0137mol) in ethanol ($5cm^3$) was left for two days at 40^oC. The resulting black glassy salt was dissolved in water ($75cm^3$) after which sodium bicarbonate was added (10g). By warming the solution, a solid was obtained which was recrystallised from ethanol to give 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) 1.5g (60%) as colourless crystals; mp $172-174^oC$, λ_{max} (246), 254, (270), 299, 311 nm; log ε 4.65, 4.73, 4.07, 3.95, 3.93; ir 780, 1370, 1490, 3050 cm^{-1}; pmr 2.25 (6H, CH_3-2, and CH_3-9), 6.40* (2H, H-1 and H-10), 6.75* (2H, H-3 and H-8), 6.88 (2H, H-5 and H-6), cmr 12.12 (CH_3-9), 100.49 (C-1, C-10, C-2 and C-9), 110.65 (C-3, C-8); 112.72 (C-5, C-6), 122.29 (C-10a, C-10b).

Anal. calcd. for $C_{12}H_{12}N_2$: C, 78.2; H, 6.5; N, 15.2. Found: C, 78.0; H, 6.5; N, 15.1. Mass spectrum, mass calcd. for $C_{12}H_{12}N_2$: 184. Found: $M^{\cdot+}$(base peak) 184.

Reaction between 2,3,8-trimethyl-7-azaindolizine and bromobutan-2-one

2,3,8-Trimethyl-7-azaindolizine (48) (33.3g, 0.022mol) and bromobutan-2-one (3.3g, 0.0022mol) were left at 45^oC for a week. Addition of base to the resulting salt gave a crude which was recrystallised from ethanol to give 2,3,8,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (94) 1.8g (39%) as pale yellow crystals; mp $199-200^oC$; λ_{max} (249), 252, (264), (290), (303), (318) nm; log ε 4.66, 4.76, 4.63, 3.93, 4.60,

4.05; ir 762, 1445, 1670, 1715, 3100 cm^{-1}, pmr 2.16 (6H, CH_3-2 and CH_3-9), 2.28 (6H, CH_3-3 and CH_3-8), 6.22 (2H, H-1 and H-10), 6.87 (2H, H-5 and H-6).

Anal. calcd. for $C_{14}H_{16}N_2$: C, 79.2; H, 7.5; N, 13.3. Found: C, 78.5; H, 7.5; N, 13.2. Mass spectrum, mass Calcd. for $C_{14}H_{16}N_2$: 212. Found: M^+(base peak) 212.

Reaction between 2,5,6,8-tetramethyl-7-azaindolizine and bromoaectone

2,5,6,8-Tetramethyl-7-azaindolizine (57) (0.4g, $2.3x10^{-3}$ mol) with bromoacetone (0.3g 0.0023mol) gave a salt after a week at 40°C. Basification of this salt afforded a crude which was recrystallised from ethanol to give 2,5,6,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (95) 0.2g (41%) as pale yellow crystals; mp 173-174°C; λ_{max} (248), 256, (271), (296), (311) nm; log ε 4.22, 4.28, 3.67, 3.50, 3.42; ir 750, 1460, 1540, 1560, 1600 cm^{-1}; pmr 2.20 (6H, CH_3-2 and CH_3-9), 2.28 (6H, CH_3-5 and CH_3-6), 6.30 (2H, H-1 and H-10), 6.72 (2H, H-3 and H-8); cmr 12.14 (CH_3-2, CH_3-9), 13.44 (CH_3-5, CH_3-6), 99.85 (C-1, C-10), 109.71 (C-3, C-8), 121.14 (C-2, C-9), 121.68 (C-5, C-6), 124.12 (C-10a, C-10b).

Anal. calcd for $C_{14}H_{16}N_2$: C, 79.2; H, 7.5; N, 13.3. Found: C, 78.9; H, 7.7; N, 12.9. Mass spectrum, mass calcd. for $C_{14}H_{16}N_2$: 212. Found: M^+(base peak) 212.

Reaction between 2,8-dimethyl-7-azaindolizine and bromopinacolone

2,8-Dimethyl-7-azaindolizine (45) (2.55g, 0.0017mol) and bromopinacolone (2.95g, 0.0017mol) were left at 50°C for a

week. Basification of the resulting salt gave 2-methyl-9-t-butyldipyrrolo[1,2-a:2,1-c]pyrazine (96) 0.5g (13%) as colourless crystals; mp 132-6°C, λ_{max} (246), 254, (270), (297), (310.5) nm; log ε 4.69, 4.75, 4.12, 4.03, 4.01; ir 750, 1240, 1530, 1670, 3200 cm^{-1}; pmr 1.30 (9H, t-butyl-9), 2.21 (3H, CH_3-2), 6.35* (1H, H-1), 6.27* (1H, H-10), 6.72* (2H, H-3 and H-8), 6.87 (2H, H-5 and H-6).

Anal. calcd. for $C_{15}H_{18}N_2$: C, 79.6; H, 8.0; N, 12.4. Found: C, 79.1; H, 8.0; N, 12.3.

Reaction between 2,8-dimethyl-7-azaindolizine and phenacyl bromide

2,8-Dimethyl-7-azaindolizine (45) (3.2g, 0.022mol) and phenacyl bromide (4.32g, 0.022mol) were left at 50°C for 14 days. The resulting salt on basification gave a crude which after recrystallisation from ethanol yielded 2-methyl-9-phenyldipyrrolo[1,2-a:2,1-c]pyrazine (97) 0.6g (16%) as pale yellow crystals; mp 188-189°C; λ_{max} (236), (244),270, (303) nm; log ε 4.32, 4.35, 4.72, 4.08; ir 740, 1220, 1540, 1740, 3110 cm^{-1}; pmr 2.25, (3H, CH_3-2), 6.37 (1H, H-1), 6.73 (2H, H-3 and H-10), 6.94 (2H, H-5 and H-6), 7.11-7.63m (6H, H-8 and Ph-9).

Anal. calcd. for $C_{17}H_{14}N_2$: N, 11.4. Found: N, 11.2.

Reaction between 2-carboethoxy-8-methyl-7-azaindolizine and bromoacetone

2-Carboethoxy-8-methyl-7-azaindolizine (67) (0.4g, 0.002 mol) and bromoacetone (0.26g, 0.002mol) were left at 45°C for a week. Basification of the resulting salt gave a solid

which was sublimated (70°C, 18mm) to give 9-carboethoxy-2-methyldipyrrolo[1,2-a:2,1-c]pyrazine (98) 0.20g (42%) mp 64°C; λ_{max} (215), (238), 261.5, 269, 297, (307.5) nm; log ε 4.57, 4.17, 4.65, 4.60, 3.90, 3.82; ir 745, 1220, 1680, 1710, 3140 cm^{-1}; pmr 1.36t (3H, J=7.2Hz, COOEt-9), 2.21 (3H, CH_3-2), 4.21q (2H, COOEt-9), 6.38 (1H, H-1), 6.73 (1H, H-10), 6.93 (1H, H-3), 7.49d (1H, J=1.4Hz, H-6), 6.81 (1H, H-8), 6.94d (1H, J=1.4Hz, H-5).

Mass spectrum, mass calcd. for $C_{14}H_{14}N_2N_2O_2$: 242. Found: $M^{\cdot+}$(base peak) 242.

Chapter 5

Protonation and deuterium exchange

The site of protonation of the prepared dipyrrolo [1,2a: 2,1-c]pyrazines (92-97) has been investigated by dissolving about 0.05g of the compound in CF_3COOH. The pmr spectrum of the resulting solution was then recorded using a R12B Perkin Elmer spectrometer. Deuterium exchange studies were performed by adding a drop of CF_3COOD to a solution of the dipyrrolo[1,2-a;2,1-c]pyrazine in $CDCl_3$.

Acetylation

2,9-Dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) (0.5g, 2.72×10^{-3} mol) was dissolved in acetic anhydride ($20cm^3$) and the solution boiled under reflux for 1 hour. Excess acetic anhydride was removed at the r.f.e and the dark residue was poured into ice water ($15cm^3$) and basified with NaOH (2M). The resulting solution was extracted with chloroform (4x15 cm^3). Evaporation of the solvent afforded a crude which showed two spots on a tlc plate. Preparative tlc on the crude gave from the slow moving band the 3,8-diacetyl-2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (106) 0.07g (10%) as pale blue crystals; mp 245°C; λ_{max} (221), 226.5, 243, (294), 296, (306), 355, 373.5 nm; log ε 4.31, 4.32, 4.23, 4.17, 4.26, 4.23, 4.32, 4.41; ir 778, 955, 1620, 1638, 1660, 31050 cm^{-1}; pmr 2.55 (6H, CH_3-2, CH_3-9), 2.58 (6H, $COCH_3$-3, $COCH_3$-8), 6.55 (2H, H-1, H-10), 9.00 (2H, H-5, H-6).

Mass spectrum, Mass calcd. for $C_{16}H_{16}N_2O_2$: 268. Found:

268 ($M^{\cdot+}$, 100), 253 (M^{+}-15, 66), 225 ($M^{\cdot+}$-43, 26), 182 ($M^{\cdot+}$-86, 10).

The fast moving band gave 3-acetyl-2,9-dimethyldipyrrolo-[1,2-a:2,1-c]pyrazine (107) 0.15g (24%) as pale green crystals; mp 130°C; λ_{max} 236, (253.5), 271, (291), 377 nm; log ε 4.41, 4.25, 4.35, 4.00 4.36; ir 770, 955, 1620, 1624, 1670, 3100, 31040 cm^{-1}; pmr 2.22 (3H, CH_3-9), 2.44 (3H, CH_3-2), 2.46 (3H, $COCH_3$-3), 6.30 (1H, H-10), 6.46 (1H, H-1), 6.88 (1H, H-8), 7.05d (1H, J=5.7Hz, H-6), 8.82d (1H J=5.7Hz, H-5).

Mass spectrum, mass calcd. for $C_{14}H_{14}N_2O$: 226. Found: 226 ($M^{\cdot+}$, 100), 183 ($M^{\cdot+}$-43, 45).

Indirect formylation via Vilsmeier salt

2,9-Dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) (0.5g, $2.7x10^{-3}$ mol) and N,N-dimethylacetamide (0.5g, $5.4x10^{-3}$ mol) were dissolved in boiling anhydrous benzene and phosphoryl chloride (0.83g) was added at such a rate that the reaction did not become too vigorous. The mixture was stirred and boiled for a further 15 minutes and then cooled and diluted with ether. After decantation of the benzene and ether layer, the lower oily layer was dissolved in a minimum quantity of methanol and perchloric acid was added, with cooling, until precipitation was complete. The perchlorate salt was filtered and washed with cold methanol and ether. The crude salt was recrystallised from methanol to give 3,8-dimethylaminoethylidenedipyrrolo[1,2-a:2,1-c]pyrazinium diperchlorate (108) 1.15g (81%) as green crystals; mp 204-205°C; λ_{max} 217, 253, 309, 359 nm; log ε 4.25, 4.54,

3.93, 3.36; pmr 2.4 (6H, CH_3-2, CH_3-9), 3.04 (6H, ethylene methyls at C-3 and 8), 3.80 (6H, amino methyls at C-3 and C-8), 3.92 (6H, ami methyls at C-3, c-8), 7.00 (2H, H-1, H-10), 7.58 (2H, H-5 H-6).

Mass calcd. for $_0H_{28}N_4Cl_2O_8$: C, 45.9; H, 5.4; N, 10.7. Found: C, 45.3; H, 5 ; N, 10.4.

The perchlorate lt (108) (0.5g, $9.5x10^{-4}$ mol) was mixed with an aqueou solution of sodium hydroxide (2M, $15cm^3$) and the sc tion boiled under reflux for 15 minutes. The resulti solution was then extracted with chloroform (4x15 cm . Evaporation of the solvent gave a diacetyl derivative 23g (89%). The spectral character-istics of this con und were identical to that of compound (106).

Formylation

A solution of hosphoryl chloride (0.34g, $2.2x10^{-3}$ mol) in dimethylfor mide ($3cm^3$) was added dropwise to magnetically stirrec olution of 2,9-dipyrrolo[1,2-a:2,1-c]-pyrazine (93) (0.1g, $5.4x10^{-4}$ mol), in dimethylformamide ($4cm^3$) and the resu nt solution poured into 2M aqueous sodium hyroxide (15( ), diluted with water ($10cm^3$) and then extracted with chlo orm (3x15 cm^3). Evaporation of the solvent gave a dar oil. Preparative tlc on this dark oil afforded two prod s. The fast running band gave 3,8-diformyl-2,9-di hyldipyrrolo[1,2-a:2,1-c]pyrazine(110) 0.04g (31%); mp 22(; λ_{max} 221, 257, 312, (319), 371.5, 391.5 nm; log ε 4.3 4.27, 4.38, 4.37, 4.40, 4.50; ir 670, 7.25, 8.30, 930, 13 1350, 1640, 1660, 3105 cm^{-1}; pmr 2.54

(6H, CH_3-2, CH_3-9), 6.58 (2H, H-1, H-10), 8.81 (2H, H-5, H-6), 9.88 (2H, CHO-3, CHO-8).

Mass spectrum, mass calcd. for $C_{14}H_{12}N_2O_6$: 240. Found: 240 ($M^{\cdot+}$, 100), 239 ($M^{\cdot+}$-1, 23), 211 ($M^{\cdot+}$-29, 19).

The slow moving band gave 2,9-dimethyl-1,3-8-triformyldipyrrolo[1,2-a:2,1-c]pyrazine (111) 0.03g (21%) as colourless crystals; mp 245°C; λ_{max} 210, 255, (288), (306), 316, 372.5, (384.5), 392 nm; log ε 4.61, 4.45, 4.43, 4.61, 4.68, 4.53, 4.55, 4.57; ir 690, 760, 840, 930, 1130, 1320, 1640, 1660, 3125 cm^{-1}; pmr 2.61 (3H, CH_3-9), 2.81 (3H, CH_3-2), 7.76 (1H, H-10), 8.50 (1H, J=5.7Hz, H-6), 9.10 (1H, J=5.7Hz, H-5), 10.01 (1H, CHO), 10.04 (1H, CHO), 10.32 (1H, CHO).

Mass spectrum, mass calcd. for $C_{15}H_{12}N_2O_3$: 268. Found: 268 ($M^{\cdot+}$, 100), 267 ($M^{\cdot+}$-1, 12), 240 ($M^{\cdot+}$-28, 30), 212 ($M^{\cdot+}$-56, 23), 211 ($M^{\cdot+}$-57, 16), 183 ($M^{\cdot+}$-85, 12).

Nitrosation

2,9-Dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) (0.5g, $2.7x10^{-3}$ mol) was dissolved in acetone ($20cm^3$) after which a solution of sodium nitrite (0.60g) in water ($10cm^3$) and 2M HCl ($10cm^3$) was added. A sudden change of colour from pale yellow to a deep red coloration was apparent. The mixture was left overnight at 0°C which led to the formation of a dark red solid. The solid was filtered off (0.27g) and the filtrate was treated with water ($50cm^3$) and sulphamic acid (0.2g). The resultant solution was extracted with chloroform ($4x15\ cm^3$). Evaporation of the solvent gave 2,9-dimethyl-3-nitrosodipyrrolo[1,2a:2,1-c]pyrazine (112) 0.2g, (35%) as a dark green crystals; mp 145-146°C; ir 1045, 1060, 1530,

1575, 1650, 3070 cm^{-1}; pmr 2.32 (3H, CH_3-9), 2.80 (3H, CH_3-2), 6.65 (1H, H-10), 6.94 (1H, H-1), 7.30 (1H, H-8), 7.35d (1H, J=5.6Hz, H-6), 8.90 (1H, J=5.6Hz, H-5).

Reaction with ethoxalyl chloride

2,9-Dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) (0.27g, $1.86x10^{-3}$ mol) was dissolved in dichloromethane ($50cm^3$). Ethoxalyl chloride (1.51g) was then added dropwise. The solution was refluxed for two hours after which the solvent was evaporated leaving a green solid. This solid was washed thoroughly with diethyl ether to remove any starting materials. The crude product (0.36g) was recrystallised from ethanol to give 3,8-diethoxalyl-2,9-dimethyldipyrrolo-[1,2-a:2,1-c]pyrazine (113) 0.25g (35%) as green crystals; mp 154.1°C; λ_{max} 221.5, 262.0, (320), 328.0, 379.0 nm; log ε 4.35, 4.13, 4.31, 4.34, 4.34, 4.42; ir 775, 980, 1020, 1060, 1620, 1730, 1745, 3160 cm^{-1}; pmr 1.45t (6H, $COCO_2Et$-3, $COCO_2Et$-8), 2.40 (6H, CH_3-2, CH_3-9), 4.45 (4H, $COCO_2Et$-3, $COCO_2Et$-8), 6.65 (2H, H-1, H-10), 9.00 (2H, H-5, H-6).

Anal. calcd. for $C_{20}H_{20}N_2O_6$: C, 62.5, H, 5.2; N, 7.3. Found: C, 62.1; H, 5.2; N, 7.1.

3,8-Diethoxalyl-2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (113) was added to polyphosphoric acid. The solution was heated up to 80°C and was left stirring for 1 hour. The resulting red viscous liquid was poured into ice, with the formation of a white turbidity. This solution was then basified and left on a steam bath for another 30 minutes to give a greyish precipitate. Tlc examination of this precipitate showed the presence of two products. The

fast running band showed identical spectral characteristics to that of compound (93) while the slow running band showed identical spectral characteristics to that of compound (113).

2,5,6,9-Tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (95) (0.01g, 4.7×10^{-5} mol) was dissolved in dichloromethane ($15 cm^3$) after which ethoxalyl chloride (1.0g) was added dropwise. The resulting solution was boiled under reflux for 1 hour. Evaporation of the solvent gave a green residue which was washed with water and then ether. Recrystallisation of the crude from ethanol afforded 3,8-diethoxalyl-2,5,6,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (115) 0.008g (41%) as pale green crystals; mp 141-142°C; λ_{max} 230, (245.5), (271.5), 294, 234, 358 nm; log ε 4.20, 4.10, 3.89, 3.69, 3.97, 3.87; ir 960, 1030, 1200, 1620, 1645, 1735, 1750 cm^{-1}; pmr 1.42t (6H, $COCO_2Et$-3, $COCO_2Et$-8), 2.39 (12H, CH_3-2, CH_3-5, CH_3-6, CH_3-9), 4.43 (4H, $COCO_2Et$-3, $COCO_2Et$-8), 6.63 (2H, H-1, H-10).

Anal. calcd. for $C_{22}H_{24}N_2O_6$: C, 64.1; H, 5.8; N, 6.8. Found: C, 63.7; H, 5.8; N, 6.4.

3,8-Diethoxalyl derivative (115) (0.01g, 2.4×10^{-5} mol) was dissolved in ethanol ($2 cm^3$) and then refluxed in a solution of sodium ethoxide (0.2g Na in $15 cm^3$ of dry ethanol) for 15 hours. The ethanol was evaporated and water was added to the residue. The resulting solution was extracted with chloroform. Evaporation of the solvent yielded a compound whose spectral characteristics were identical to that compound (95).

2,3,8,9-Tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (94) (0.5g, $2.35x10^{-3}$ mol) reacted with ethoxalyl chloride (0.64g) in dichloromethane to give a red solid after evaporation of the solvent. Trituration of the resulting solid with methanol liberated a yellow precipitate which was filtered off. The yellow solid was recrystallised from methanol/petroleum ether to give 1-ethoxalyl-2,3,8,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (120) 0.4g (55%) as yellow crystals; mp 129-130°C; λ_{max} 235, (278), 314, 353 nm; log ε 4.70, 4.02, 4.02, 4.03; ir 720, 1120, 1230, 1320, 1620, 1720 cm^{-1}; pmr 1.40t (3H, $COCO_2Et$-1), 2.17 (3H, CH_3-9), 2.23 (3H, CH_3-8), 2.25 (3H, CH_3-2), 2.33 (3H, CH_3-3) 4.40q (2H, $COCO_2Et$-1), 6.94d (1H, J=4.4Hz, H-6), 7.16d (1H, J=4.4Hz, H-5), 7.94 (1H, H-10).

Anal. calcd. for $C_{18}H_{20}N_2O_3$: C, 69.2; H, 6.5; N, 8.7. Found: C, 68.8, H, 6.5; N, 8.7.

Preparative tlc on the filtrate gave 1,10-diethoxalyl-2,3,8,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (119) 0.1g (10%) as orange crystals; mp 207-208°C; λ_{max} (214), 228, 280, 298, 355 nm; log ε 4.70, 4.75, 4.18, 4.14, 4.20; ir 740, 1160, 1245, 1520, 1620, 1675, 1730, 3140 cm^{-1}; 1.34t (6H, $COCO_2Et$-1, $COCO_2Et$-10), 2.19 (6H, CH_3-2, CH_3-10), 2.24 (6H, CH_3-2, CH_3-9), 4.28q (4H, $COCO_2Et$-1, $COCO_2Et$-10), 7.10 (2H, H-5, H-6).

Anal. calcd. for $C_{22}H_{24}N_2O_6$: C, 64.1; H, 5.9; N, 6.8. Found: C, 63.6; H, 5.7; N, 6.4.

The monoethoxalyl derivative (120) (0.20g, $6.4x10^{-4}$ mol) with polyhosphoric acid ($10cm^3$) at 80°C gave back the menoethoxalyl derivative (120) (0.1g) and another compound

whose spectral characteristics was identical to that of compound (94) (0.08g, 59%).

Reaction with DMAD

2,9-Dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) (0.2g, $1.1x10^{-3}$ mol) was dissolved in toluene ($15cm^3$). DMAD (0.156g, $1.1x10^{-3}$ mol) in toluene ($5cm^3$) was then added dropwise which resulted in an exothermic reaction. The reaction mixture was left to stand overnight. Evaporation of the solvent gave a dark oil. Preparative tlc using toluene/ethyl acetate in a ratio of 2:1 as mobile phase on this oil gave a mixture of two compounds. The faster moving band gave the trans-3-dicarbomethoxyethene-2,9-dimethyl-dipyrrolo[1,2-a:2,1-c]pyrazine (122) 0.05g (14%) as yellow crystals. Compound (122) was characterised from its pmr spectrum; pmr 2.06 (3H, CH_3-9), 2.23 (3H, CH_3-2), 3.62 (3H, $COOCH_3$-3), 3.79 (3H, $COOCH_3$-3), 6.36 (2H, H-1, H-10), 6.76 (1H, H-8), 6.61d (1H, J=6.0Hz, H-6), 6.92d (1H, J=6.0Hz, H-5), 7.07 (1H, vinyl proton at C-3).

The slow moving band gave the cis-3-dicarbomethoxy-ethene-2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine(121) 0.09g (25%) as orange crystals; compound (121) was characterised by its pmr spectrum; pmr 2.24 (6H, CH_3-2, CH_3-9), 3.78 (3H, $COOCH_3$-3), 3.88 (3H, $COOCH_3$-3), 5.99 (1H, vinyl proton at C-3), 6.37 (2H, H-1, H-10), 6.80 (1H, H-8), 6.97 (1H, J=6.1Hz, H-6), 7.25 (1H, J=6.1Hz, H-5).

2,9-Dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) (0.2g, $1.08x10^{-3}$ mol) was dissolved in warm toluene ($15cm^3$) and

DMAD (0.31g, 2.17×10^{-3} mol) was then added dropwise. The resulting solution was left to stand for two days. Evaporation of the solvent gave a dark red oil. Preparative tlc of the oil gave cis-cis-didicarbomethoxyethene-2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (125) 0.15g (30%) as yellow crystals; mp 152-154°C; λ_{max} (216), 246, (257), 287, 334 nm; log ε 4.15, 4.39, 4.35, 4.04, 3.82; ir 760, 1160, 1250, 1590, 1730, 1750 cm^{-1}; pmr 2.25 (6H, CH_3-2, CH_3-9), 3.79 (6H, $COOCH_3$ x 2), 3.89 (6H, $COOCH_3$x2), 6.04 (2H, vinyl proton x 2), 6.48(2H, H-1, H-10), 7.31 (2H, H-5, H-6).

Mass spectrum, mass calcd. for $C_{24}H_{24}N_2O_8$: 468. Found: 468 ($M^{\cdot+}$,100), 409 ($M^{\cdot+}$-59, 30), 350 ($M^{\cdot+}$-118, 10), 232 ($M^{\cdot+}$-236, 10).

To 2,3,8,9-tetramethyldipyrrolo[1,2-a:2,1-c]pyrazine (94) (1.0g, 4.7×10^{-3} mol) in toluene ($75cm^3$) was added DMAD (1.33g, 9.4×10^{-3} mol) and the mixture was left to stand at room temperature for 2 days. Evaporation of the solvent gave an oil which after preparative tlc afforded cis-1-dicarbomethoxyethene-2,3,8,9-tetramethyldipyrrolo[1,2a:2,1-c]-pyrazine (126) 0.1g (6%) Compound (126) was characterised by its pmr spectrum; pmr 2.12 (3H, CH_3-9), 2.18 (3H, CH_3-2), 2.28 (6H, CH_3-8), 3.84 (6H, $COOCH_3$x2), 6.20 (1H, vinyl proton), 6.55 (1H, H-10), 6.85d (1H, J=5.7Hz, H-5), 6.95d (1H, J=5.7Hz, H-6).

Cis-derivative (126) (0.1g, 2.8×10^{-4} mol) was dissolved in a mixture of ethanol ($10cm^3$) and concentrated hydrochloric acid ($5cm^3$). The resulting solution was refluxed for half an hour. Evaporation of the ethanol on a

steam bath gave a solid after which was added water ($10cm^3$) and sodium hydroxide (2M). Extraction of the aqueous solution with chloroform ($3x10\ cm^3$) yielded a crude which after preparative tlc afforded compound (126) viz. the starting material (0.05g).

Reaction with diethyl azodicarboxylate (DAD)

To 2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (93) (0.31g, $1.68x10^{-3}$ mol) in toluene ($25cm^3$) was added DAD (0.61g). The mixture was refluxed for ten minutes which resulted in the formation of a precipiate which was washed with toluene and ether to yield 3,8-diethylazodicarboxylate-2,9-dimethyldipyrrolo[1,2-a:2,1-c]pyrazine (129) 0.80g (89%) as yellow crystals; mp 226-227°C; ir 780, 1065, 1245, 1525, 1720, 1755, 3190 cm^{-1}; pmr (CF_3COOH) 1.27t (6H, azo ethyl at C-3 and C-8), 2.15 (6H, CH_3-2, CH_3-9), 4.21q (4H, azo ethyl at C-3 and C-8), 6.29 (2H, H-1, H-10), 7.12 (2H, H-5, H-6), 7.55 (2H, N-H x 2).

Anal. calcd. for $C_{24}H_{32}N_6O_8$: C, 54.1; H, 6.1; N, 15.8. Found: C, 54.7; H, 6.2; N, 15.6.

To 2,9-di-t-butyldipyrrolo[1,2-a:2,1-c]pyrazine (92) (0.4g, $1.5x10^{-3}$ mol) in toluene ($25cm^3$) was added DAD (0.52g, $3.0x10^{-3}$ mol). The mixture was refluxed for 30 minutes which after evaporation of the solvent yielded a dark residue. Preparative tlc on this residue gave 3,8-dietylazodicarboxylate-2,9-di-t-butyldipyrrolo[1,2-a:2,-1-c]pyrazine (130) 0.4g (43%) as brown crystals; mp 139-141°C; λ_{max} (254), 261, 399, 410 nm; log ε 4.73, 4.82,

4.02, 4.00; ir 780, 1060, 1230, 1470, 1710, 1730, 1740, 3300 cm^{-1}; pmr 1.31 (30H, t-butyl-2, t-butyl-9, azo ethyl at C-3 and C-8), 4.24q (2H, azo ethyl at C-3 and C-8), 6.41 (2H, H-1, H-10), 6.93 (2H, H-5, H-6), 7.89 (1H, N-H), 7.94 (1H, N-H).

Anal. calcd. for $C_{30}H_{44}N_6O_8$: C, 58.4; H, 7.1; N, 13.6. Found: C, 58.3; H, 7.5; N, 13.2.

CHAPTER 6

Synthesis of 7-azaindolizine[7]

A mixture of 2-pyrrolealdehyde (8.0g), aminoacetaldehyde diethylacetal (13.0g) and toluene ($35cm^3$) was refluxed in a flask fitted with a Dean-Stark trap of $20cm^3$ capacity until no apparent increase in volume of water phase (approximately 20 minutes). The solvent and excess aminoacetaldehyde were removed at the r.f.e and the residue distilled (119-125°C, 2mm) to give 2-pyrrolealdehyde aminoacetal 10.3g (58%) as a viscous oil.

To polyphosphoric acid (15g) heated at 100°C was added phosphoryl chloride ($20cm^3$) with stirring. The heating was discontinued and the aminoacetal derivative (2.1g) was added dropwise immediately to this mixture with vigorous stirring over a 10 minute period. Temperature was raised to 120°C as soon as addition was completed and held at this level until no additional hydrogen chloride evolved. The mixture was allowed to cool and it was dissolved in water ($150cm^3$). The aqueous solution was extracted with toluene, basified and again extracted with sufficient toluene. Evaporation of the solvent gave a dark oil which upon vacuum distillation (71°C, 2mm) yielded 7-azaindolizine (5) 0.25g (21%) as a colourless oil.

Reaction between 7-azaindolizine and DMAD

7-Azaindolizine (5) (0.5g, 4.23×10^{-3} mol) was dissolved in toluene ($25cm^3$). DMAD (1.26g, 8.8×10^{-3} mol) was added dropwise which resulted in an exothermic reaction together

with a sudden change of colour from colourless to an intense dark red solution. The reaction was allowed to stand for 3 hours at room temperature. Tlc examination of the reaction mixture showed only one spot with a different R_f value to that of the starting material. Evaporation of the solvent afforded a dark red oil which was triturated with methanol to liberate a yellow precipitate (0.5g). Recrystallisation of the precipitate from acetone yielded tetramethyl 11aH-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10,11-tetracarboxylate (155) 0.4g (11%) as yellow crystals; mp 176°C; ir 730, 1165, 1535, 1620, 1700, 1730, 3095, 3150 cm^{-1}; pmr 3.62 (3H, $COOCH_3$), 3.68 (3H, $COOCH_3$), 3.85 (6H, $COOCH_3$x2), 5.80-6.80m (6H, complex multiplet, H-1, H-2, H-3, H-5, H-6, H-11a); cmr 55.88 ($COOCH_3$-11), 55.99 ($COOCH_3$-10), 56.34 ($COOCH_3$-9), 57.15 ($COOCH_3$-8), 58.80 (C-11a), 99.42, 114.96, 129.56, 142.47, 151.91 (five quaternary carbons at C-8, C-9, C-11, C-11b), 112.12, 113.64, 116.29, 121.13, 123.66 (five methine carbons at C-1, C-2, C-3, C-5, C-6, 171.13, 168.28, 167.51, 166.69 (four carbonyl carbons at C-8, C-9, C-10, C-11).

Anal. calcd. for $C_{19}H_{18}N_2O_8$: C, 56.7; H, 4.5; N,7.0. Found: C, 56.0; H, 4.5; N,6.6. Mass spectrum, mass calcd. for $C_{19}H_{18}N_2O_8$: 402. Found: 402 ($M^{\cdot+}$, 2), 401 ($M^{\cdot+}$-1, 28), 343 ($M^{\cdot+}$-59,100).

Reaction between 2,3,6-trimethyl-7-azaindolizine and DMAD

2,3,6-Trimethyl-7-azaindolizine (43) (0.1g, $6.25x10^{-4}$ mol) in toluene ($15cm^3$) was added DMAD (0.18g, $1.25x10^{-3}$

mol) which resulted in an exothermic reaction followed by a sudden change of colour to a dark orange coloration. Evaporation of the solvent afforded a dark residue which after separation by preparative tlc yielded mainly tetramethyl 2,3,6-trimethyl-11aH-pyrido[2,1-c]pyrrolo[1,2-a]-pyrazine-8,9,10,11-tetracarboxylate (156) 0.01g (4%) as yellow crystals; mp 130-131°C; ir 705, 1020, 1240, 1510, 1620, 1715, 1750 cm^{-1}; pmr 1.95 (6H, CH_3-2, CH_3-3), 2.12 (3H, CH_3-6), 3.60 (3H, $COOCH_3$-11), 3.72 (3H, $COOCH_3$-10), 3.80 (3H, $COOCH_3$-9), 3.90 (3H, $COOCH_3$-8).

Mass spectrum, mass cacld. for $C_{22}H_{24}N_2O_8$: 444. Found: 444 ($M^{\cdot+}$, 47), 429 ($M^{\cdot+}$-15, 65), 413 ($M^{\cdot+}$-31, 14), 397 ($M^{\cdot+}$-47, 14), 385 ($M^{\cdot+}$-59, 100).

Reaction between 2,8-dimethyl-7-azaindolizine and DMAD

2,8-Dimethyl-7-azaindolizine (45) (0.9g, 6.16×10^{-3} mol) was dissolved in toluene (15cm^3). DMAD (1.7g, 0.012mol) was then added dropwise which resulted in an exothermic reaction together with the change in colour to a deep orange solution. The reactionn mixture was left to stand for 1 day at room temperature. Evaporation of the solvent gave a deep red oil. Tlc examination of this oil showed five different bands when viewed under uv light. The compounds in this reaction were isolated by preparative tlc on the oil by using toluene/ethyl acetate as molbile phase in a ratio of 3:1.

The fastest moving band (I) gave 2-methyl-8,9,10-tri-carbomethoxydipyrrolo[1,2-a:2,1-c]pyrazine (168) 0.07g (3.3%) as straw colour crystals; mp 142°C ; ir 795, 1050,

1120, 1215, 1690, 1710, 1745, 3160 cm^{-1}; pmr 2.30 (3H, CH_3-2), 3.88 (6H, $COOCH_3$-9, $COOCH_3$-10), 3.95 (3H, $COOCH_3$-8), 7.06 (1H, H-3), 7.34d (1H, J=6.0Hz, H-5), 7.69 (1H, H-1), 8.50d (1H, J=6.0Hz, H-6).

Mass spectrum, mass calcd. for $C_{17}H_{16}N_2O_6$: 344. Found: 344 ($M^{\cdot+}$, 100), 313 ($M^{\cdot+}$-31, 48).

The second fastest moving band (II) gave an orange solid which was recrystallised from methanol to give tetramethyl 2,11a-dimethyl-11aH-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8,9-,10,11-tetracarboxylate (157) 0.4g (15%) as orange crystals; mp. 86.2°C; λ_{max} (226.6), (260), 284, (340) nm; log ε 4.10, 4.00, 4.18, 3.08; ir 1140, 1230, 1550, 1620, 1705, 1740, 3120 cm^{-1}; pmr 1.82 (3H, CH_3-11a), 2.02 (3H, CH_3-2), 3.69 (3H, $COOCH_3$-11), 3.74 (3H, $COOCH_3$-10), 3.76 (3H, $COOCH_3$-9), 3.93 (3H, $COOCH_3$-8), 5.85d (1H, J=6.0Hz, H-5), 5.86* (1H, H-1), 6.38d (1H, J=6.0Hz, H-6), 6.38* (1H, H-3); cmr 11.44 (CH_3-11a), 25.14 (CH_3-2), 51.63 (ester methyl at C-11), 52.12 (ester methyls at C-9 and C-10), 53.10 (ester methyl at C-8), 61.33 (C-11a), 100.98 (C-2), 109.43, 110.03, 110.63, 115.56 (C-1, C-3, C-5 and C-6), 120.16, 124.71, 125.69, 128.83 (four quaternary carbons viz. C-8, C-9, C-10, C-11), 143.40 (C-11b), 163.55, 163.72, 165.45, 166.48 (four corbonyl carbons at C-8, C-9, C-10 and C-11).

Anal. calcd. for $C_{21}H_{22}N_2O_8$: C, 58.6; H, 5.2; N, 6.5. Found: C, 58.2; H, 5.1; N, 6.2. Mass spectrum, mass calcd. for $C_{21}H_{22}N_2O_8$: 430. Found: 430 ($M^{\cdot+}$, 5), 415 ($M^{\cdot+}$-15, 100).

The third fastest moving band (III) gave a pale yellow solid which upon recrystallisation from methanol/petroleum ether gave tetramethyl 7a,8,9,9a-tetrahydro-2-methylcyclo-

buta[4,5]dipyrrolo[1,2-a:2,1-c]pyrazine-7a,8,9a,10-tetracarboxylate (158) 0.15g (6%) as colourless crystals; mp 191.9°C; λ_{max} (239.5), 244.4, (285), 293.6, (308), 331.8, (367), 383.4 nm; log ε 4.07, 4.09, 4.18, 4.27, 3.91, 4.06, 4.22; ir cm^{-1}; pmr 2.20 (3H, CH_3-2), 3.63 (3H, $COOCH_3$-8), 3.66 (3H, $COOCH_3$-9a), 3.70 (3H, $COOCH_3$-7a), 3.76 (3H, $COOCH_3$-10), 2.64-3.87m (3H, CH_2CH), 6.87* (1H, H-3), 6.49d (1H, J=6.0Hz, H-5), 6.73d (1H, J=6.0Hz, H-6), 8.02* (1H, H-1).

Anal. calcd. for $C_{21}H_{22}N_2O_8$: C, 58.6; H, 5.1; N,6.5. Found: C, 58.2; H, 5.2; N, 6.3. Mass spectrum, mass calcd. for $C_{21}H_{22}N_2O_8$: 430. Found: 430 ($M^{\cdot+}$, 45); 344 ($M^{\cdot+}$-86, 100).

The fourth fastest moving band (IV) gave a solid which after recrystallisation from methanol yielded trimethyl 8-methoxycarboxylmethyl-2-methyl-8H-pyrido[2,1-c]pyrrolo-[1,2-a]pyrazine-8,9,10-tricarboxylate (167) 0.07g (3.3%) as red crystals; mp 191°C; λ_{max} (215), 240, (245), 272.5, (282), 300, 325 nm; log ε 4.04, 4.26, 4.25, 3.79, 3.59, 3.58; ir 1160, 1250, 1670, 1730, 1740, 3120 cm^{-1}; pmr 2.20 (3H, CH_3-2), 3.12 (2H, CH_2-8), 3.60 (3H, $COOCH_3$), 3.70 (3H, $COOCH_3$), 3.82 (3H, $COOCH_3$), 3.85 ($COOCH_3$), 5.05 (1H, H-11), 6.20d (1H, J=6.0Hz, H-5), 6.55 (1H, H-1), 6.80 (1H, J=6.0Hz, H-6), 6.84 (1H, H-3); cmr 11.81 (CH_3-2), 40.96 (CH_2-8), 51.41, 51.99, 52.17, 53.41 (four ester methyls at C-8, C-9 and C-10), 69.54 (C-8), 84.79 (C-11), 100.00 (C-2), 109.49, 110.41, 113.01, 117.40 (C-1, C-3, C-5, C-6), 121.89, 124.98 (C-9, C-10), 138.15, 142.81 (C-11a, C-11b), 164.21, 164.35, 170.00, 170.38 (four carbonyl carbons).

Anal. calcd. for $C_{21}H_{22}N_2O_8$: C, 58.6; H, 5.1; N, 6.5. Found: C, 58.2; H, 5.0; N, 6.3. Mass spectrum, mass calcd. for $C_{21}H_{22}N_2O_8$: 430. Found: 430 ($M^{\cdot+}$, 10), 398 ($M^{\cdot+}$-32, 10), 371 ($M^{\cdot+}$-32, 10), 371 ($M^{\cdot+}$-59, 15), 357 ($M^{\cdot+}$-73, 100).

The fifth band (V) gave a deep yellow solid which was recrystallised from methanol to give tetramethyl 8,9-dihydro-2-methylazepino[2,1-c]pyrrolo[1,2-a]pyrazine-8,9,10,-11-tetracarboxylate (163) 0.15g (6%) as deep yellow crystals; mp 197-198°C; λ_{max} (212), 240, (268), 314 nm; logε 3.99, 4.28, 3.72, 3.67; ir 1125,1250, 1530, 1680, 1735, 1750, 3120 cm^{-1}; pmr 2.15 (3H, CH_3-2), 3.59 (3H, $COOCH_3$-9), 3.65 (3H, $COOCH_3$-8), 3.74 (3H, $COOCH_3$-10), 3.83 (3H, $COOCH_3$-11), 5.25d (1H, J=6.0Hz, CH-9), 5.35d (1H, J=6.0Hz, CH-8), 6.18* (1H, H-1), 6.18d (1H, J=6.0Hz, H-5), 6.68d (1H, J=6.0Hz, H-6), 6.75* (1H, H-3); cmr 11.87 (CH_3-2), 48.99 (C-9), 52.00 ($COOCH_3$), 52.41 ($COOCH_3$), 52.63 ($COOCH_3$), 52.96 ($COOCH_3$), 67.49 (C-8), 88.38 (C-12), 108.45, 108.59 (C-5, C-6), 109.89 (C-2), 117.01, 120.94 (C-1, C-3), 124.82 (C-10, C-11), 139.04 (C-12a), 143.25 (C-12b), 166.12, 167.20, 170.45, 171.10 (four carbonyl carbons at C-8, C-9, C-10 and C-11).

Anal. calcd. for $C_{21}H_{22}N_2O_8$: C, 58.6; H, 5.2; N, 6.5. Found: C, 58.1; H, 5.2; N, 6.2. Mass spectrum, mass calcd. for $C_{21}H_{22}N_2O_8$: 430. Found: 430 ($M^{\cdot+}$, 45), 399 ($M^{\cdot+}$-31, 12), 371 ($M^{\cdot+}$-59, 100), 286 ($M^{\cdot+}$-144, 14).

Reaction between 2,3,8-trimethyl-7-azaindolizine and DMAD

To 2,3,8-trimethyl-7-azaindolizine (48) (1.7g, 0.01mol) in toluene (25 cm^3) was added DMAD (3.1g, 0.02mol) in a dropwise manner. This resulted in an exothermic reaction together with a change of colour to a deep orange coloration. The reaction mixture was left at room temperature for 24 hours. Evaporation of the solvent afforded an oil. Preparative tlc on that oil yielded five compounds. The first fastest running band (Ia) gave 2,3-dimethyl-8,9,10-tricarbomethoxydipyrrolo[1,2-a:2,1-c]pyrazine (176) 0.2g (6%) as cream crystals; mp182 ^oC; ir 782, 1095, 1210, 1530, 1690, 1700, 1745, 3160 cm^{-1}; pmr 2.20 (3H, CH_3-2), 2.30 (3H, CH_3-3), 3.88 (6H, $COOCH_3$-9, $COOCH_3$-10), 3.98 (3H, $COOCH_3$-8), 7.28d (1H, J=6.0Hz, H-5), 7.75 (1H, H-1), 8.58d (1H, J=6.0Hz, H-6).

Mass spectrum, mass calcd. for $C_{18}H_{18}N_2O_6$: 358.3539. Found: 358.1158 ($M^{\cdot+}$, 100), 357 ($M^{\cdot+}$-1, 11), 327 ($M^{\cdot+}$-31, 21).

The second fastest running band (IIa) afforded a yellow solid which was recrystallised from methanol to give tetramethyl 2,3,11a-trimethyl-11aH-pyrido[2,1-c]pyrrolo-[1,2-a]pyrazine-8,9,10,11-tetracarboxylate (171) 0.58g (13%) as yellow crystals; mp 152-153^oC; λ_{max} (220), (244), 281, (340) nm; log ε 4.13, 4.01, 4.22, 3.07; ir 1000, 1210, 1245, 1540, 1605, 1700, 1740 cm^{-1}; pmr 1.83 (3H, CH_3-11a), 1.94 (3H, CH_3-2), 2.09 (3H, CH_3-3), 3.68 (3H, $COOCH_3$-11), 3.75 (3H, $COOCH_3$-10), 3.92 (3H, $COOCH_3$-8), 5.76 (1H, H-1), 5.77d (1H, J=6.0Hz, H-5), 6.31d (1H, J=6.0Hz, H-5).

Mass spectrum, mass calcd. for $C_{22}H_{24}N_2O_8$: 444. Found:

444 ($M^{\cdot+}$, 5), 429 ($M^{\cdot+}$-15, 100).

The third fastest running band (IIIa) yielded tetramethyl 7a,8,9,9a-tetrahydro-2,3-dimethylcyclobuta-[4,5]dipyrrolo[1,2-a:2,1-c]pyrazine-7a,8,9a,10-tetracarboxyl-ate (172) 0.08g (2%) as colourless crystals; mp 249-250°C; ir 1045, 1060, 1095, 1210, 1530, 1680, 1745, 3040 cm^{-1}; pmr 2.15 (3H, CH_3-2), 2.27 (3H, CH_3-3), 2.55-3.95m (3H, $CHCH_2$), 3.65 (3H, $COOCH_3$), 3.70 (3H, $COOCH_3$), 3.75 (3H, $COOCH_3$), 6.55d (1H, J=6.0Hz, H-5), 6.70d (1H, J=6.0Hz, H-6), 8.10 (1H, H-1).

Mass spectrum, mass calcd. for $C_{22}H_{24}N_2O_8$: 444. Found: 444 ($M^{\cdot+}$, 8), 385 ($M^{\cdot+}$-59, 5), 358 ($M^{\cdot+}$-86, 100), 327 ($M^{\cdot+}$-117, 25).

The fourth fastest running band (IVa) yielded trimethyl 8-methoxycarboxylmethyl-2,3-dimethyl-8H-pyrido[2,1-c]pyrrol-o[1,2-a]pyrazine-8,9,10-tricarboxylate (174) 0.08g (2%) as red crystals; mp 176-177°C; ir 1120, 1170, 1250, 1500, 1660, 1730, 1740, 3120 cm^{-1}; pmr 2.10 (3H, CH_3-2), 2.23 (3H, CH_3-3), 3.09 (2H, CH_2-8), 3.57 (3H, $COOCH_3$), 3.65 (3H, $COOCH_3$), 3.79 (3H, $COOCH_3$), 3.83 (3H, $COOCH_3$), 5.09 (1H, H-11), 6.24d (1H, J=6.2Hz, H-5), 6.53 (1H, H-1), 6.74 (1H, J=6.2Hz, H-6).

Mass spectrum, mass calcd. for $C_{22}H_{24}N_2O_8$: 444. Found: 444 ($M^{\cdot+}$, 65), 412 ($M^{\cdot+}$-15, 45), 385 ($M^{\cdot+}$-59, 100), 371 ($M^{\cdot+}$-73, 25), 353 ($M^{\cdot+}$-91, 40).

The fifth fastest running band (Va) gave an orange solid which was recrystallised from methanol to yield tetramethyl 8,9-dihydro-2,3-dimethylazepino[2,1-c]pyrrolo[1,2-a]pyrazin-e-8,9,10,11-tetracarboxylate (173) 0.3g (7%) as orange

crystals; mp 214-215°C; ir cm^{-1}; pmr 2.05 (3H, CH_3-2), 2.20 (3H, CH_3-3), 3.56 (3H, $COOCH_3$), 3.64 (3H,$COOCH_3$), 3.72 (3H, $COOCH_3$), 3.82 (3H, $COOCH_3$), 5.24d (1H, J=6.0Hz, H-9), 5.28d (3H, J=6.0Hz, H-8), 5.28 (1H, H-12), 6.20d (1H, J=6.0Hz, H-5), 6.54 (1H, H-1), 6.65d (1H, J=6.0Hz, H-5), 6.54(1H, H-1), 6.65d (1H, J=6.0Hz, H-6).

Mass spectrum, mass calcd. for $C_{22}H_{24}N_2O_8$: 444.4452. Found: 444.1515 ($M^{\bullet+}$, 37), 413 ($M^{\bullet+}$-31, 10), 385 ($M^{\bullet+}$-59, 100), 353 ($M^{\bullet+}$-91, 22).

Reaction between 8-ethyl-1,2,3-trimethyl-7-azaindolizine and DMAD

8-Ethyl-1,2,3-trimethyl-7-azaindolizine (55) (0.61g, $3.24x10^{-3}$ mol) was dissolved in toluene (25 cm^3). DMAD (0.52g, $3.24x10^{-3}$ mol) was then added dropwise. The sudden change in colour to a deep green solution was apparent. The solution was left to stand for half an hour which resulted in the formation of a green precipitate at the bottom of the flask. This precipitate was collected and recrystallised from ethanol to give methyl 1,2,3,11-tetramethyl-10-keto-10H-pyrido[2,1-c]pyrrolo[1,2-a]pyrazine-8-carboxylate (189) 0.41g (38%) as green needlelike crystals; mp 208-209°C; ir 1020, 1190, 1555, 1640, 1670, 1710, 3130 cm^{-1}; pmr 1.95 (3H, CH_3-1), 2.00 (3H, CH_3-2), 2.20 (3H, CH_3-3), 2.30 (3H, CH_3-11), 3.70 (3H, $COOCH_3$-8), 6.12 (1H, H-9), 6.50d (1H, J=5.9Hz, H-5), 8.10d (1H, J=5.9Hz, H-6).

Anal. calcd. for $C_{17}H_{18}N_2O_3$: C, 68.5, H, 6.0; N, 9.4. Found: C, 68.4; H, 6.1; N, 9.3. Mass spectrum, mass calcd. for $C_{17}H_{18}N_2O_3$: 298 ($M^{\bullet+}$, 100), 283 ($M^{\bullet+}$-15, 8), 267

($M^{\cdot+}$-31, 12), 255 ($M^{\cdot+}$-43, 25), 210 (M^{+}-88, 25).

Reaction between 8-amino-6-methyl-2-phenyl-7-azaindolizine and DMAD

8-Amino-6-methyl-2-phenyl-7-azaindolizine (68) (0.1g, 4.48×10^{-4} mol) was dissolved in hot toluene ($25 cm^3$). DMAD (0.127g, 8.96×10^{-4} mol) was then added and the solution refluxed for half an hour. A deep yellow precipitate was formed which was filtered off and washed with toluene. The resulting solid was dried in a vacuum oven to give methyl 6-methyl-2-phenyl-10-keto-10H-pyrimido[2,1-c]pyrrolo[1,2-a]-pyrazine-8-carboxylate (195) 0.1g (67%) as yellow crystals; mp 241°C; ir 1220, 1170, 1570, 1675, 1710, 1730 cm^{-1}; pmr (DMSO-d_6) 2.35 (3H, CH_3-6), 3.68 (3H, $COOCH_3$-8), 6.88 (1H, H-9), 7.25 (1H, H-1), 7.50 (1H, H-3), 7.30-7.75m (5H, Ph-2), 8.12 (1H, H-5); pmr (CF_3COOH) 2.80 (3H, CH_3-6), 4.10 (3H, $COOCH_3$-8), 7.35-7.75m (5H, Ph-2), 7.85 (1H, H-1), 8.05 (1H, H-3), 8.38 (1H, H-6).

Anal. calcd. for $C_{19}H_{15}N_3O_3$: N, 12.6. Found: N, 12.1. Mass spectrum, mass calcd. for $C_{19}H_{15}N_3O_3$: 333. Found: 333 ($M^{\cdot+}$, 80), 302 ($M^{\cdot+}$-31, 10), 274 ($M^{\cdot+}$-59, 100).

REFERENCES

1 Borrows, E.T; Holland, D.O; Chem. Rev. 1948, **42**, 611.

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

3 Prostakov, N.S; Baktibaev, O.B. Russ. Chem. Rev. 1975, **4**, 748.

4 Maury, G. Chem. Heterocycl. Comp. 1977, **30**, 179.

5 Kuhla, D.E; Lambardino, I.G. "Advances in Heterocyclic Chemistry" 177, **21**, 31.

6 Tisler, M. Pure & Appl. Chem. 1980, **52**, 1611.

7 Herz, W.; Tocker, S. J.Am. Chem. Soc. 1955, **77**, 6355.

8 Putochin, N. Ber. deutsch. Chem. Ges. 1926, **59**, 1996.

9 Smith, D.R; Maienthal, M.; Tipton, J. J. Org. Chem. 1952, **17**, 294.

10 Schroter, R. Methoden der Organischen Chemie (Honben-Weyl). 1957, **11(1)**, 499.

11 Flament, I.; Sounay, P.; Ohloff, G. Helv. Chim. Acta. 1977, **60**, 1872.

12 Herz, W.; Raden, D.S; Morty, D.R.K. J. Org. Chem. 1956, **21**, 896.

13 Shedov, V.I; Altukhova, L.B; Grinev, A.N. Khim.Geterotsikl. Soedin, 1970, 1048.

14 Boekelheide, V.; Fahrenholtz, K. J. Am. Chem. Soc. 1961, **83**, 458.

15 Sasaki, T.; Kanematsu, K.; Yukimoto, Y.; Ochiai, S. J. Org. Chem. 1971, **36**, 813.

16 Acheson, R.M. "Advances in Heterocyclic Chemistry" 1963, **1**, 132.

17 Kobayashi, Y.; Katsuma, K.; Morinaga, K. Chem. Pharm. Bull. 1971, **19**, 2106.

18 Lown, J.W.; Matsumoto, K. Can. J. Chem. 1971, **49**, 1165.

19 Lown, J.W.; Matsumoto, K. Can. J. Chem. 1971, **49**, 3119.

20 Houminer, Y.; J. Heterocycl. Chem. 1981, **18**, 445.

21 Corbet, J.P; Paris, J.M; Cotrel, C. Tetrahedron lett. 1982, **23**, 3565.

22 Galasso, V.; De Alti, G.; Bigotto, A. Theor. Chim. Acta, 1968, **9**, 222.

23 Fraser, M. J. Org. Chem. 1971, **36**, 3087.

24 Armarego, W.L.F. J. Chem. Soc., 1964, 4226.

25 Fraser, M. J. Org. Chem. 1972, **37**, 3027.

26 Shand, C. PhD Thesis, RGIT, Aberdeen, 1977.

27 Dunham, D.E. PhD Thesis, University of Ohio, Athens, 1967.

28 Dvoryantsera, G.G; Ul'yanova,T.N; Alekseeva, L.M; Sheinker, Yu.N; Altukhova, L.B; Mazentseva, M.V; Shvedov, V.I; Grinev, A.N. Khim. Geterosikl. Soedin. 1979, **8**, 1109.

29 Bower, J.D., Ramage, G.R. J. Chem. Soc., 1955, 2834.

30 Grandberg, I.I; Nikitina, S.B.; Moskalenko, V.A; Minkin, V.I. Khim. Geterotsikl. Soedin., 1967, 1076; See Chem. Abstr., 1968, **69**, 52067w.

31 Taylor, J.; Wibberly, D.G. J. Chem. Soc. C, 1968, 2693.

32 Zupan, M.; Stanovnik, B.; Tisler, M. J. Heterocycl. Chem. 1971, **8**, 1.

33 Pentimalli, L.; Bozzini, S.; Boll. Sci. Fac. Chim. Ind. Bologna, 1965, **23**, 181; See Chem. Abstr. 1965, **63**, 14848e.

34 Almirante, L.; Mugnaini, A.; Fritz, L.P.; Provinciali, E. Boll. Chim. Farm. 1966, **32**, 105; See Chem. Abstr. 1966, **65**, 699h.

35 Fuentes, O.; Paudler, W.W. J. Heterocycl. Chem. 1975, **12**, 379.

36 Buchan, R.; Fraser, M.; Shand, c. J. Org. Chem. 1977,**42**, 2448.

37 Buchan, R.; Fraser, M.: Shand, C. J. Org. Chem. 1979, **41**,351.

38 Paudler, W.W.; Kuder, J.E. J. Org. Chem., 1967, **32**, 2430.

39 Paolini, J.P., Robins, R.K. J. Org. Chem., 1965, **30**, 4085.

40 Lynch, B.M.; Lem, B.P. J. Heterocycl. Chem. 1974, **11**, 223.

41 Paudler, W.W.; Blewitt, H.L. J. Org. Chem., 1965, **30**,4081.

42 Glover, E.E.; Vaughan, K.D.; Bishop, D.C. J. Chem. Soc. Perkin Trans. 1, 1973, 2595.

43 Paudler, W.W, Dunham, D.E. J. Heterocycl. Chem. 1965, **2**, 410.

44 Flitsch, W.; Kramer, U. Tetrahedron Lett., 1968, 1479.

45 Flitsch, W.; Kramer, U. Justus Liebigs Ann. Chem. 1970, **35**, 735.

46 Paolini,J.P.; Robins, R.K. J. Heterocycl. Chem. 1965, **2**, 53.

47 Paudler, W.W.; Pokorny, D.J.; Good, J.J. J. Heterocycl. Chem. 1971, **8**, 37.

48 Buchan, R.; Fraser, M.; Shand, C. J. Org. Chem., 1978, **43**, 3544.

49 Paudler, W.W.; Chao, C.I.P.; Helmick, L.S. J. Heterocycl. Chem., 1972, **9**, 1157.

50 Godfrey, J.C. J. Org. Chem., 1959, **24**, 581.

51 Galbraith, A.; Small, T.; Barnes, R.A.; Boekelheide, V. J. Am. Chem. Soc. 1961, **83**, 453.

52 Boekelheide, V.; Miller, A. J. Org. Chem. 1961, **26**, 431.

53 Boekelheide, V.; Kertelj, S.S. J. Org. Chem. 1963, **28**, 3212.

54 Taurins, A. Chem. Heterocycl. Compd. 1977, **30**, 245.

55 Flitsch, W.; Kramer, U. Adv. Heterocycl. Chem., 1978, **22**, 321.

56 Lee, S.J., Cook, J.M. Heterocycles, 1983, **20**, 87.

57 Burger, U.; Drier, F. Tetrahedron, 1983, **39**, 2065.

58 Pfizer, INC.; U.S Patent No. 609914.

59 Casagrande, C.; Galli, A.; Ferrini, R.; Miragoli, G. Arzneim-Forsch, 1971, **21**, 808.

60 Likhosherstov, A.M.; Nazarova, L.S.; Skoldinov, A.P. Fr. Pat. 1,510,781.; See Chem. Abstr. 1969, **70**, 68427.

61 Freed, M.E. (to American Home Products Corp.) U.S Pat. 3,164,598.; See Chem. Abstr. 1965, **62**, 9154.

62 Freed, M.E. (to American Home Products Corp.) U.S Pat. 3,531,485.; See Chem. Abstr. 1970, **73**, 120672.

63 Freed, M.E. (to American Home Products Corp.) U.S Pat. 3,176,017.; See Chem. Abstr. 1965, **62**, 16272.

64 Lovell, C.H. Ger. Offen. 2,226,063.; See Chem Chem. Abstr. 1973, **78**, 56458.

65 Tschitschibabin, A.E. Chem. Ber. 1927, **60**, 1607.

66 Borrows, E.T.; Holland, D.O.; Kenyon, J. J. Chem. Soc. 1946, 1069.

67 Buchan, R.; Fraser, M.; Shand, C. J. Org. Chem. 1976, **41**, 351.

68 Buchan, R.; Fraser, M.; Shand, C. J. Org. Chem. 1977, **42**, 2448.

69 Gainer, H.; Kokorudz, M.; Langdon Keith, W. J. Am. Chem. Soc. 1961, **26**,2360.

70 Hirschberg, A.; Spoerri Paul, E. J. Am. Chem. Soc. 1961, **26**, 2356.

71 Batterham, T.J. " NMR Spectra Of Simple Heterocycles". John Wiley and sons, N.Y. 1973, **10**, 514.

72 Smith, I.C.; Schneider, W.G. Can. J. Chem. 1961, **39**, 1158.

73 Gibson, W.K.; Leaver, D.; Roff, J.E.; Cummings, C.W. Chem. Commun. 1967, 214.

74 Armarego, W.L.F. J. Chem. Soc. 1965, 2775.

75 Leaver, D.; Skinner, D. J. Chem. Soc. Chem. Commun. 1984, 821.

76 Courtesy of Kirby, E.C. The Resource Use Institute Ltd. 14 Lower Oakfield, Pitlochry, Perthshire, PH16 5DS, SCOTLAND.

77 Gibson, W.K.; Leaver, D. J. Chem. Soc. C, 1966, 324.

78 Boekelheide, V.; Galbraith, A.; Small, T. J. Org. Chem. 1959, **24**, 582.

79 Boekelheide, V.; Miller, A. J. Org. Chem. 1961, **26**, 431.

80 Boekelheide, V.; Kertelj, S.S. J. Org. Chem. 1963, **28**, 3212.

81 Acheson, R.M.; Woollard, J. J. Chem. Soc. Perkin Trans 1. 1975, 438.

82 Acheson, R.M.; Taylor, G.A. Proc. Chem. Soc. 1959, 186.

83 Acheson, R.M.; Taylor, G.A. J. Chem. Soc. 1960, 1691.

84 Acheson, R.M.; Gagan, J.M.F.; Taylor, G.A. J. Chem. Soc. 1963, 1903.

85 Acheson, R.M.; Jones, B.J. J. Chem. Soc. C, 1970, 1301.

86 Acheson, R.M.; Gagan, J.M.F.; Feinberg, R.S. J. Chem. Soc. 1965, 948.

87 Acheson, R.M.; Foxton, M.W.; Hands, A.R. J. Chem. Soc. C, 1968, 387.

88 Acheson, R.M.; Wallis, J.D.; Woollard, J. J. Chem. Soc. Perkin Trans 1. 1979, 585.

89 Acheson, R.M.; Hole, F. J. Chem. Soc. 1962, 748.

90 Acheson, R.M.; Gagan, J.M.F.; Harrison, D.R. J. Chem. Soc. 1968, **C**, 362.

91 Diels, O.; Alder, K.; Kashimoto, T.; Friedrichsen, W.; Eckhardt, W.; Klare, H. Annalen. 1934, **498**, 16.

92 Diels, O.; Alder, K.; Friedrichsen, W.; Peterson, E.; Brondersen; Kech, H. Annalen. 1934, **510**, 87.

93 Diels, O.; Kech, H. Annalen. 1935, **519**, 140.

94 Van Tamelen, E.E.; Aldrich, P.E.; Bender, P.; Miller, G.R. Proc. Chem. Soc. 1959, 309.

95 Crabtree, A.; Jacckman, L.M.; Johnson, A.W. J. Chem. Soc. 1962, 4417.

96 Jackman, L.M.; Johnson, A.W.; Tebby, J.C. J. Chem. Soc. 1960, 1579.

97 Acheson, R.M.; Nisbet, D.F. J. Chem. Soc. C, 1971, 3291.

98 Acheson, R.M.; Flowerday, R.F. J. Chem. Soc. Perkin Trans 1. 1975, 394.

99 Abbott, P.J.; Acheson, R.M.; Forder, R.A.; Watkin, D.J.; Carruthers, J.R. Acta Crystallogr. 1977, **B33**, 898.

100 Acheson, R.M.; Procter, G. J. Chem. Soc. Perkin Trans 1. 1977, 1924.

101 Acheson, R.M.; Nisbet, D.F. J. Chem. Soc. Perkin Trans 1. 1973, 1338.

102 Acheson, R.M.; Abbott, P.J.; Forder, R.A.; Watkin, D.J.; Carruthers, J.R. Acta. Crystallogr. 1976, **B32**, 1927.

103 Acheson, R.M.; Procter, G. J. Chem. Soc. Perkin Trans 1. 1979, 2171.

104 Acheson, R.M.; Alpin, R.T.; Harrison, D.R. J. Chem. Soc. C, 1968, 383.

105 Acheson, R.M.; Foxton, M.W.; Miller, G.R. J. Chem. Soc. 1965, 3200.

106 Acheson, R.M. Acc. Chem. Res. 1971, **4**, 177.

107 Acheson, R.M.; Stubbs, J.K. J. Chem. Soc. C, 1971, 3285.

108 Sharma, M.N. Curr. Sci. 1974, **43**, 179. [CA, 1974, **81**, 3891].

PUBLICATIONS

The results of part of the work detailed in this thesis have been published in a paper entitled " Azaindolizines. 6. The synthesis of 7-azaindolizines from methylpyrazines ": see Robert Buchan, Martin Fraser and Paul V.S Kong Thoo Lin, Journal Of Organic Chemistry, 1985, **50**, 324.

POST-GRADUATES STUDIES

During my three years of research work, I have attended and participated in a number of lectures and seminars at the University of Aberdeen and at Robert Gordon's Institute Of Technology. In addition I have attended a number of symposia as follows:

Medicinal chemistry , Dundee University, Nov.84.

Progress in Heterocyclic chemistry, London, Jan. 85.

7^{th} Lakeland Heterocyclic, symposium, Grasmere, May 85.

5^{th} International symposium of Novel Aromatic compounds, St. Andrews University, July 85, at which I presented a poster.

Modern Aspect Of Heterocyclic Chemistry, March 86, University of Nottingham.

Fifteenth Scottish Regional Meeting for the reading of original papers, December 1986, University of Aberdeen.