THE SYNTHESIS AND PROPERTIES OF SOME AMINOINDOLIZINES

BY

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SUMMARY

The chemical properties of indolizines, the synthesis of potential precursors of aminoindolizines, and the synthesis and properties of known aminoindolizines, are reviewed.

The work described in this thesis concerned the preparation of further examples of 3-aminoindolizines, and their precursors, and a study of some of their physical and chemical properties. The synthesis of several new 3-azoindolizines and 3-nitrosoindolizines is described, and the successful nitration at the 3- position of indolizine and 2-methylindolizine with acetylnitrate, is reported. The orientation of nitration products of indolizines is discussed and a tentative conclusion has been drawn to rationalise the changes in orientation which occur.

Rapid reduction procedures have given 3-aminoindolizines, and their physical properties and stability is described. The products of acetylation of the 3-aminoindolizines are reported, and the anomolous n.m.r. spectra of the 3-acetamidoindolizines is discussed.

Hydrolytic ring-cleavage of 3-amino and 3-acetamidoindolizines, on treatment with mineral acid, is reported, and a possible mechanism is outlined for this reaction. The products of hydrolysis are shown to be 3-(2-pyridyl)propionic acids.

Ring-cleavage of 3-aminoindolizines under neutral, mild conditions by oxidative reactions, is described, and it is shown that progenitor 3-nitrosoindolizines are capable of oxidising the 3-aminoindolizines. The products of this ring-

cleavage are shown to be cis 3-(2-pyridyl)acrylonitriles. 2-Phenyl-3-(2-pyridyl)acrylonitrile has been prepared by the deoxygenation of 3-nitroso-2-phenylindolizine. The possible nature of an intermediate nitrene is discussed with reference to oxidation of other aromatic amines. The 3-nitrosoindolizines are shown to undergo several autoxidation reactions.

The mass spectra of several 3-nitro, 3-nitroso, 3-amino and 3-acetamidoindolizines, are discussed, together with those of the 3-(2-pyridyl)acrylonitriles derived from these compounds. Possible fragmentation patterns are suggested.

The author would like to thank Professor D. G. Wibberley for his help and encouragement during the course of this work, and Dr. W. J. Irwin for useful discussion.

"These are the Ten Commandments that, as a teacher, I should wish to promulgate,

1. Do not feel absolutely certain of anything.

2. Do not think it worthwhile to proceed by concealing evidence, for the evidence is sure to come to light.

3. Never try to discourage thinking for you are sure to succeed.

4. When you meet with opposition....endeavour to overcome it by argument and not by authority, for a victory dependent upon authority is unreal and illusory.

5. Have no respect for the authority of others, for there are always contrary authorities to be found.

6. Do not use power to suppress opinions you think pernicious, for if you do the opinions will suppress you.

7. Do not fear to be eccentric in opinion, for every opinion now accepted, was once eccentric.

8. Find more pleasure in intelligent dissent than in passive agreement, for, if you value intelligence as you should, the former implies a deeper agreement than the latter.

9. Be scrupulously truthful, even if the truth is inconvenient, for it is more inconvenient when you try to conceal it.

10. Do not feel envious of the happiness of those who live in a fools' paradise, for only a fool will think it is happiness.

BERTRAND RUSSELL

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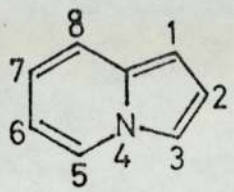
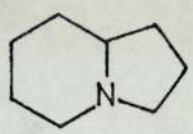
INTRODUCTION

A. The Indolizines

Indolizine (1) was first synthesised by Scholtz [1] in 1912, and its structure was confirmed by catalytic hydrogenation to the known octahydroindolizine (2).[2]



(1)



(2)

The name indolizine, which was first introduced by Tschichibabin [3], is that approved by a 1955 IUPAC conference [4], and the structure is numbered according to the conventions of the American Chemical Society.[5] The numbering order is exceptional, insofar as the bridgehead atom is numbered 4 and not 3a. Other names are found in the literature including the trivial names pyrindole, pyrrodine and pyrrocoline, as well as the systematic name pyrrolo [1,2-a] pyridine.

The syntheses and properties of indolizines have been reviewed by Borrows and Holland in 1948 [6] and by Mosby in 1961.[7]

(i) Physical Properties

Indolizine and simple alkylindolizines are low melting point solids or liquids which are unstable to light and air. The arylindolizines and indolizines bearing electron-withdrawing substituents are generally more stable and have relatively high melting points. Many indolizines are fluorescent

under ultraviolet light, and a number fluoresce under normal illumination. Solutions of indolizines are generally fluorescent under normal illumination.

The ultraviolet absorption spectra of numerous indolizines have been recorded, [7] as have the proton magnetic resonance spectra of indolizine and its methyl derivatives.[8] The mass spectra of indolizines, the seven monomethylindolizines, the six 2,x-dimethylindolizines, and a number of other simple indolizines, have recently been reported.[9]

The pkb's of indolizine, and ten of its methyl homologues, were determined in 60% ethanol,[10] and, although they are relatively weakly basic, indolizines readily form salts with mineral acids.[7] Complexes are formed with picric, picrolinic and chloroplatinic acids, and with auric or mercuric chlorides.[7]

(ii) Chemical Properties

(a) General Survey

Indolizines have a high degree of aromatic character, as would be expected from a fusion of the structures of pyrrole and pyridine. Dewar [11] calculated the resonance energy of indolizine by means of molecular orbital calculations and confirmed its aromatic nature by the result of 52 Kcal/mole. The involvement of the 'Lone-pair' in the molecule, to give an overall 10 π-electron system, allows ten resonance structures to be drawn,[6] and of these, two each involve the delocalisation of the charge on positions 1 and 3 (Fig.1).

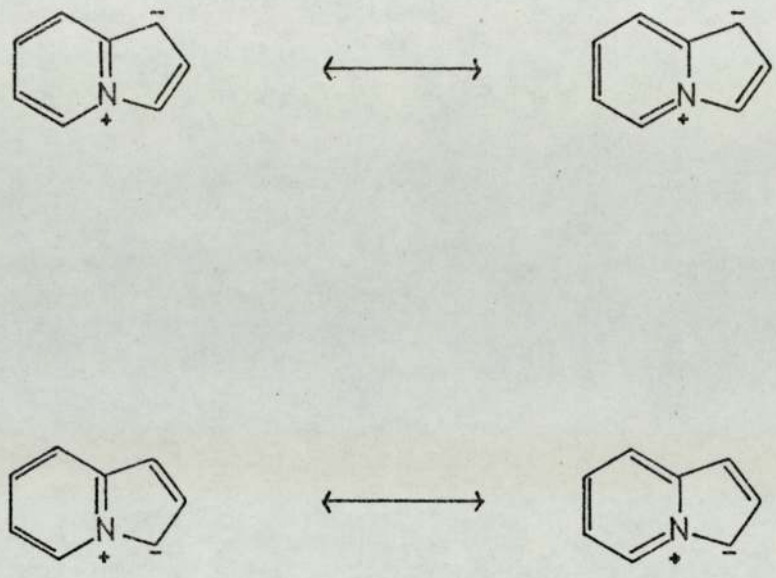


Figure 1

Experimental evidence [7] and the results of theoretical calculations on the electron distribution [12] and atom localisation energies [13,14,15,16] over the molecule, confirm the high degree of reactivity of these two positions. Calculation of atom localisation energies of indolizine by the L.C.A.O. molecular orbital procedure, gives [14] a preference to position 1 as the primary position for attack by an electrophile. The other methods [13,15,16] of calculation, however, each favour position 3 as the primary position for electrophile attack. Both nucleophile and radical reactions have been predicted [14] to take place in the six-membered ring, the atom localisation energies for the 5- and 8- positions being very close in value for both types of reaction. Diels-Alder addition is similarly predicted to take place in the six membered ring at the 5-8 positions, and by the same method of prediction osmium tetroxide oxidation and perhaps ozonolysis, would be expected to occur most readily at the 5-6 bond.

(b) Reactions with Electrophile Reagents

A consideration of the mechanism of attack by an electophile on indolizine at the most reactive positions, 1 or 3, suggests that the primary position for attack is at position 3. Attack at either position (1 or 3) gives rise to an intermediate containing a pyridinium ring. The resonance energy associated with the pyridinium ring is considered to lower the energy of the intermediates relative to the energy of other possible intermediates, and hence favour substitution at positions 1- and 3-. This has been further rationalised by Boekelheide [14] by a consideration and comparison of the two σ-complexes (A) and (B) (Fig.2).

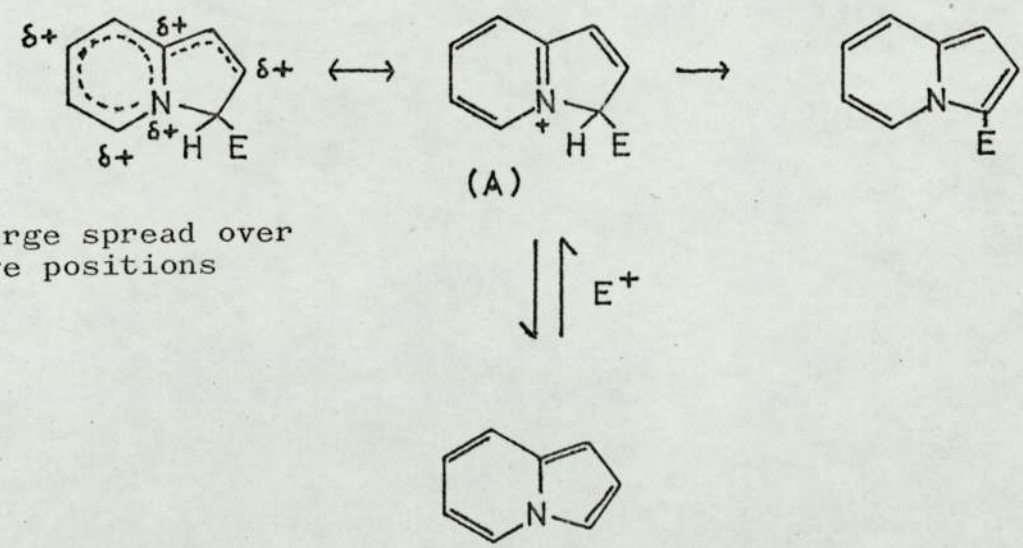


Figure 2

More resonance structures can be drawn for (A) than for (B) and consequently (A) is of lower energy, and as a result of this greater stabilisation is more likely to be favoured than (B).

Studies on the position of protonation of indolizines (essentially an electrophilic attack) by nuclear magnetic resonance spectroscopy have provided further useful evidence for the position of primary electrophilic attack. Fraser [18] studied a number of solutions of indolizinium perchlorates under anhydrous conditions (in T.F.A.), and concluded that in simple alkylindolizines protonation took place solely at the 3- position. Further work by Armarego [19] showed that under aqueous conditions the 3-substituted alkylindolizines, which were unsubstituted in the 1- and 5- positions (the latter position was considered because of steric influences), gave mixtures of both 1- and 3- protonated species.

In all recorded cases of electrophilic attack (alkylation, acetylation, benzoylation, formylation, carboxylation, nitrosation and azo-coupling) on the indolizines, there is only one exception to a preferential attack at the 3- position. Nitration of indolizines by nitric acid or by mixtures of nitric acid and sulphuric or acetic acids is primarily in the 1- position, although small quantities of the 3-isomers are found.[6]

Substitution in an indolizine in which the 3-position is already substituted will take place at a vacant 1-position (and vice-versa for nitration reactions).[7] The third position of preferential electrophilic attack is predicted [12] to be at the 5- or 2- positions, but no experimental evidence exists to verify this prediction. The extreme facility of

electrophilic attack at positions 1 and 3 thwarted an attempt at alkylation by ethyliodide of 1,2,3-trimethylindolizine [20] to determine subsequent positions of attack, the product being a mixture of 1,1,2,3-tetraalkylindolizinium and 1,2,3,3-tetraalkylindolizinium salts.

(c) Reactions with Nucleophilic and Free Radical Reagents.

The sole attempt to subject indolizine to nucleophilic attack by sodamide [7] proved to be unsuccessful, although as stated above, positions 5- and 8- are predicted [14] to be susceptible to such reagents. Similarly, no study has been made of the susceptibility of indolizines to free radicals, except in that predicition by calculation [14] favours the 5- and 8- positions.

(d) Oxidation

Indolizine and indolizines bearing electron donating substituents (e.g. alkyl) are readily and rapidly oxidised by atmospheric oxygen. The presence of electron-withdrawing substituents decreases this susceptibility greatly so that the aryl- and carboxylindolizines are less susceptible to oxidation by the atmosphere and to chemical oxidants such as potassium permanganate and chromic acid. Oxidation of indolizines with peracetic acid has been used extensively [7] to establish substitution position, the product is picolinic acid N-oxide or its homologue if the indolizine was substituted on the six membered ring. A reported oxidation with 3% hydrogen peroxide of 2-methylindolizine to its N-oxide is not proved, no other such compounds are known.[7]

(e) Reduction

The complete reduction of indolizine and alkylindolizines to the corresponding octa-hydroindolizines has been recorded.[7] In general, reduction takes place most easily in the six membered ring to give di- or tetraalkylindolizines,[6,7] the structures of which were proposed after evidence for the presence of a pyrrole-type ring. Reduction of the five membered ring has been claimed for indolizines bearing electron withdrawing substituents on this ring, leaving the six membered ring unsaturated. A reduction by lithium aluminium hydride of the six membered ring has been reported [43] and it is suggested that the presence of a strongly electron-withdrawing group in a position ortho to the electron deficient 5-position activates the ring sufficiently to enable hydride attack.

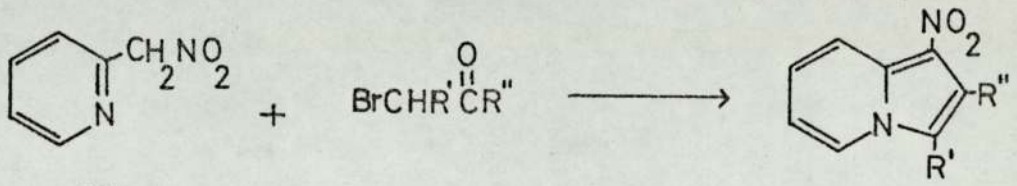
B. The Aminoindolizines

Relatively few aminoindolizines have been prepared and in all recorded cases, the amino group is positioned at either the 1- or 3- position.[22,23,24] The electron donating character of the amino group renders the aminoindolizines highly unstable to both light and the atmosphere, although this instability is decreased by the presence of substituents which withdraw electrons.[23] Two methods exist for the synthesis of aminoindolizines: reduction of the corresponding nitro-, nitroso- or azo-derivatives,[22,23,24] and a direct synthesis.[23] The ready attack by electrophiles on the indolizines, as stated above, provides a number of precursors of indolizine amines:

(i) The Synthesis of Aminoindolizine Precursors

(a) Nitroindolizines

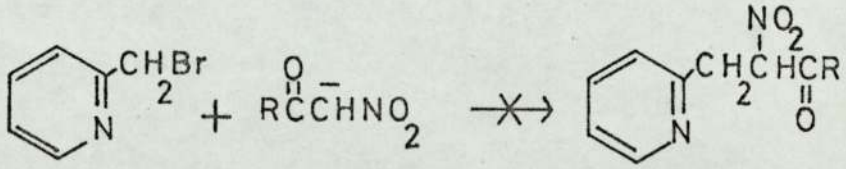
Nitroindolizines have been prepared both by direct synthesis [23] and by nitration procedures.[25] Direct synthesis from 2-nitromethylpyridine (3) by the reaction with an appropriate α-bromoketone gave [23] good yields of a number of 1-nitroindolizines, including 1-nitroindolizine itself (4).



(3)

(4) R'=R"=H

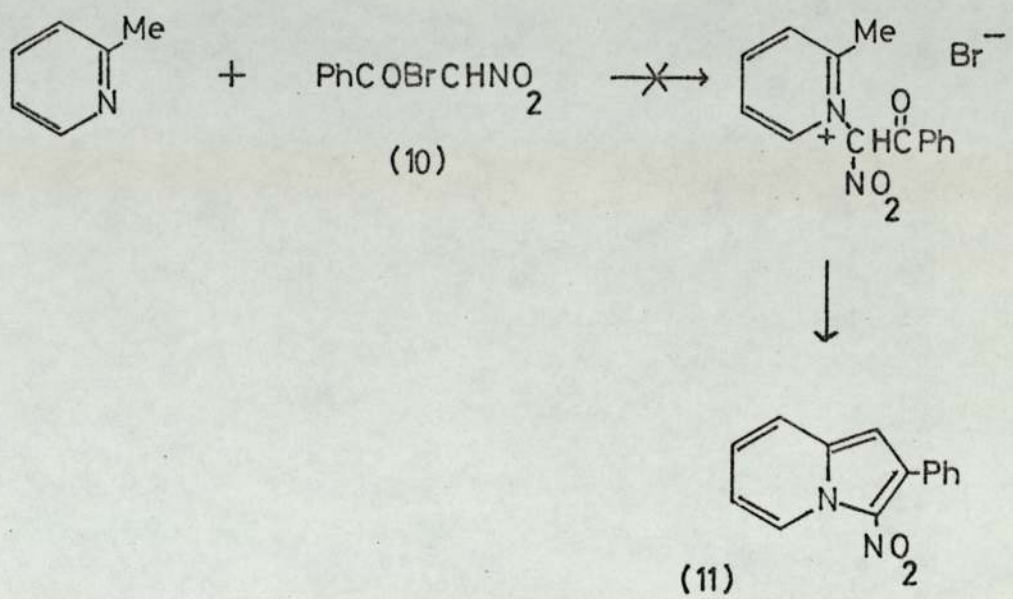
The attempted direct synthesis of two 2-nitroindolizines was unsuccessful [26] due to the failure of the alkylation of the sodium salts of either nitroacetone (6) or ethyl nitroacetate (7) by 2-bromomethylpyridine (5).



(5) (6) R=Me (7) R=Et (8) R=Me (9) R=Et

Cyclisation of the expected products (8) and (9) is similar to a synthesis of indolizine itself carried out by Boekelheide [27] and would have given the first known 2-nitroindolizines.

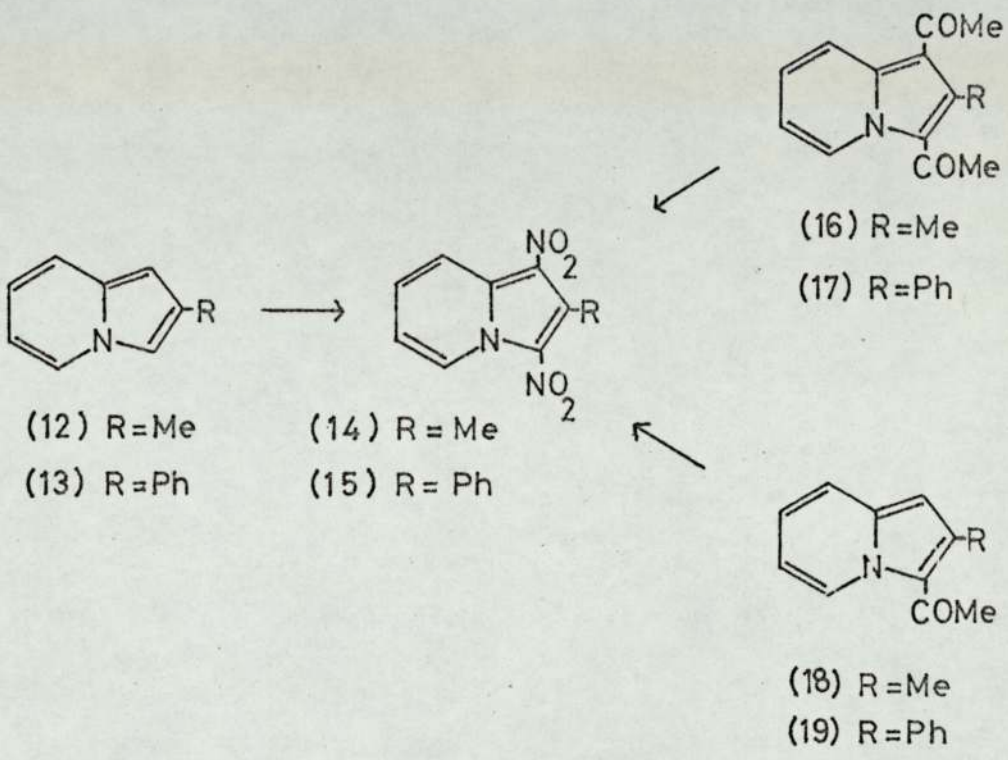
Unsuccessful attempts to prepare 3-nitro-2-phenylindolizine (11) from ω-nitrophenacylbromide (10) by a similar method to that employed successfully in the direct synthesis of 3-nitroso-2-phenylindolizine have been recorded.[25,28]



The nitration of π-excessive systems such as the indolizines, by nitric acid, has proved difficult due to oxidation reactions. Scholtz [29] reported that indolizine could not be nitrated directly because of its sensitivity to oxidising agents, but he showed that 1,3-diacetylindolizine was progressively nitrated to give nitroacetyl- and dinitro-derivatives. A preparation of 1-nitroindolizine-2,3-dicarboxylate showed the importance of the substituents in determining the reactivity of the nucleus and in this respect indolizine behaves similarly to the other π-excessive systems.[30,31]

2-Methylindolizine (12) and 2-phenylindolizine (13) were nitrated by nitric acid at elevated temperatures.[25] The 1,3-dinitroindolizines (14) and (15) were formed and the authors account for the success of the reactions by postulating

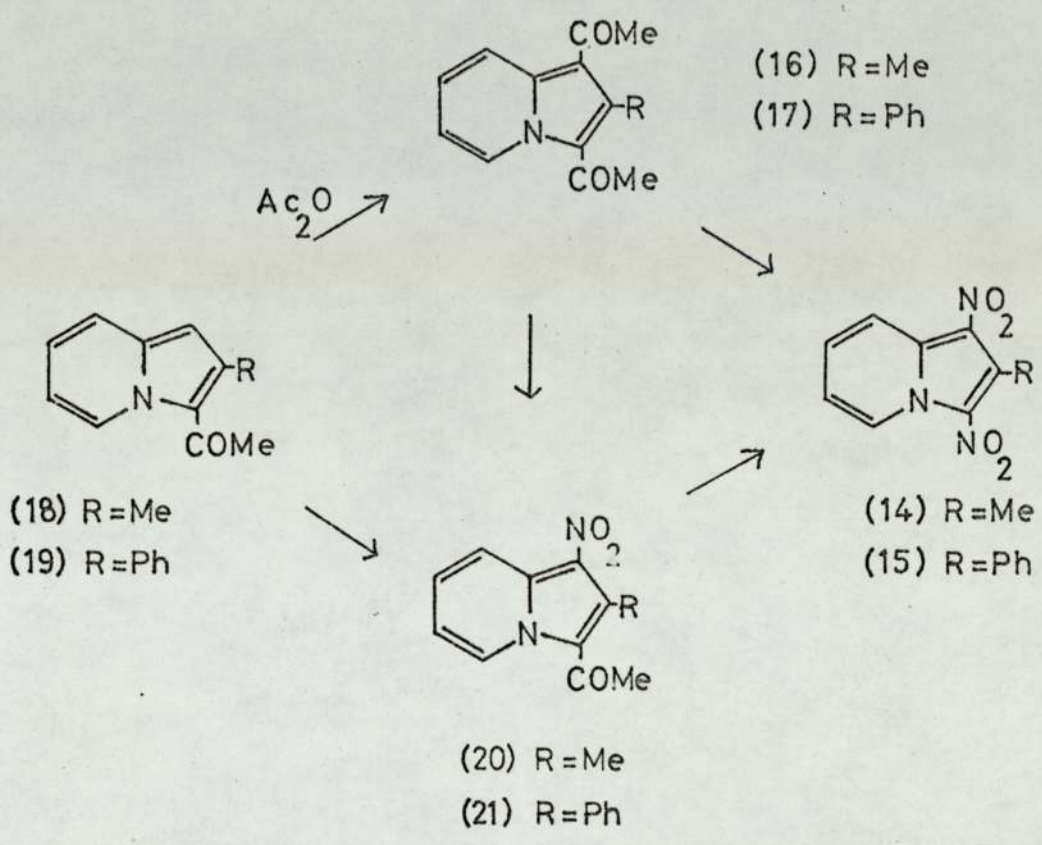
that a rapid reaction minimises oxidative side-reactions. Better yields of the nitro compounds were achieved however by the use of the 1,3-diacetylindolizines (16) and (17) or the 3-acetylindolizines (18) and (19).



The addition of a small quantity of sulphuric acid was made during these nitrations and its absence generally gave a cruder product in lower yield. In the case of 2-methylindolizine (12) the corresponding dinitro compound (14) could be made by the action of hot dilute nitric acid alone.

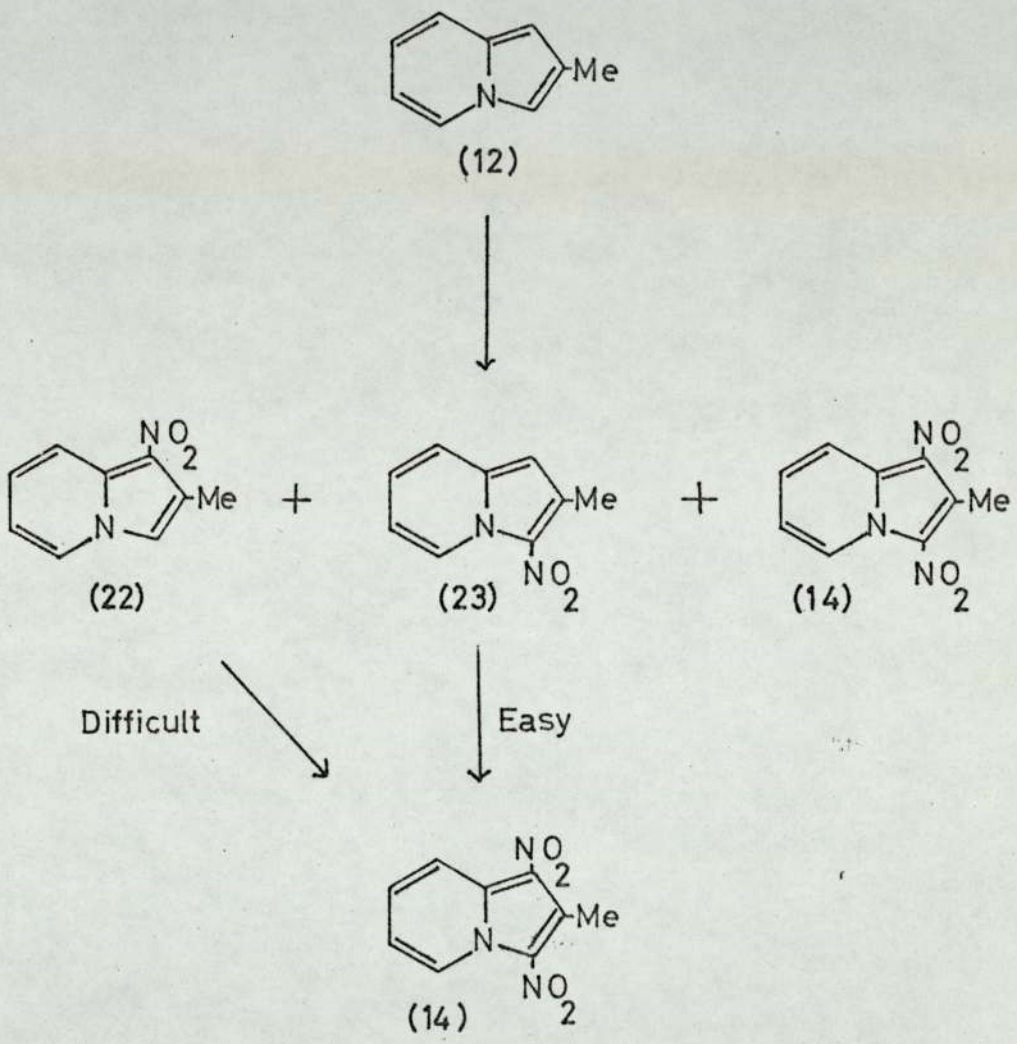
The intermediate nitroacetylindolizines were also prepared and shown to be the 1-nitro-3-acetylindolizines (20) and (21). No product could be obtained, however, on the nitration of 3-acetyl-2-phenylindolizine (19) other than 2-phenylindolizine (13) or the 1,3-dinitrophenylindolizine (15),

demonstrating the ready mobility of the 3-acetyl group.



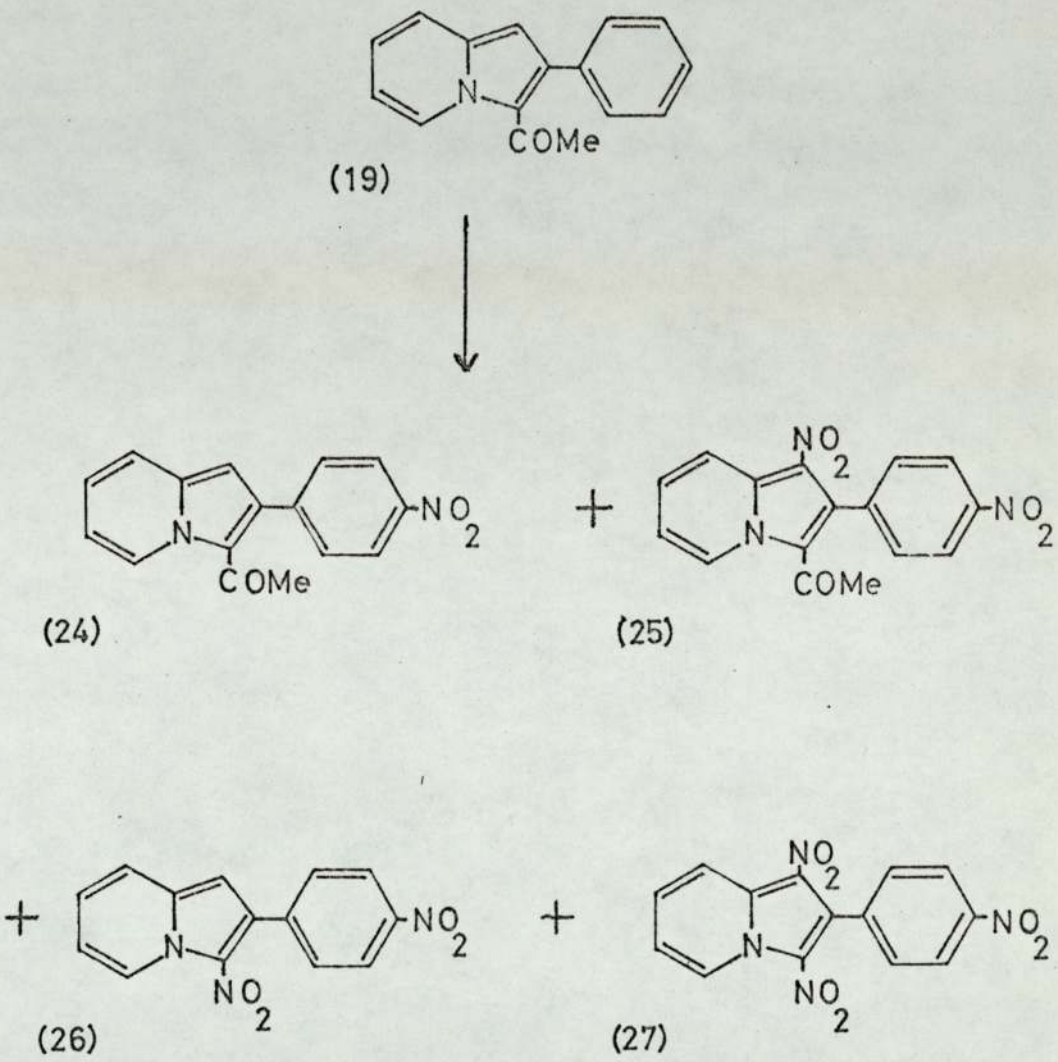
These same authors continued this study of nitration by attempting reactions in sulphuric acid at 0^{o}. Thus 2-methylindolizine (12) gave a mixture of two mononitro-compounds and a dinitro-compound. By acetylation experiments, the major product (63%) was shown to be 1-nitro-2-methylindolizine (22). This compound was most resistant to further nitration, whereas the 3-nitro isomer (23) was nitrated with comparative ease to give the 1,3-dinitro-2-methylindolizine (14). This preferential nitration of the indolizine in position 1 was in marked contrast to the reported easy nitrosation of the indolizine ring.[32]

An attempted nitration of 2-methylindolizine with acetic anhydride and nitric acid gave only an intractable tar, although this method had been successfully employed in the smooth nitration of the pyrroles.[30]



Nitration of 2-phenylindolizine (13) by nitric acid and sulphuric acid at 0° gave primarily 2-p-nitrophenylindolizine together with some 1-nitro 2-p-nitrophenylindolizine (28) and the result is similar to that of a nitration in sulphuric acid of N-phenylpyrrole, the major product being N-p-nitrophenylpyrrole. The protonation of the basic aromatic ring by sulphuric acid is postulated in both cases. Nitration of

3-acetyl-2-phenylindolizine in sulphuric acid at 0° gave a complex mixture:

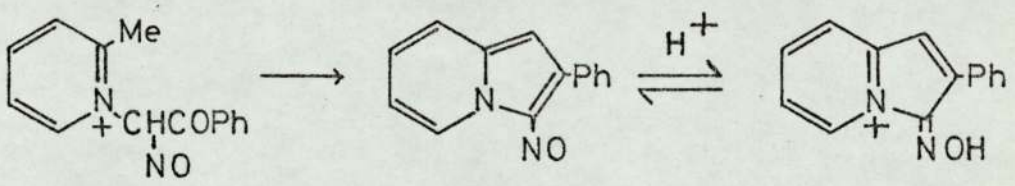


The proportion of products depended upon the quantity of nitric acid employed, and the proportion of polynitro compounds formed increased as this quantity increased. Acetylation of both the 1- and 3-nitro-2-p-nitrophenylindolizines was attempted, but they proved totally resistant to the procedure.

(b) Preparation of Nitrosoindolizines

Unlike the pyrroles[30] and indoles,[31] indolizines having a vacant 3- or 1- position undergo direct nitrosation readily and the majority of known nitrosoindolizines have been made in this way.[7] A direct synthesis of 3 nitroso-2-phenylindolizine (29) was performed by the cyclisation of ω-nitrosophenacyl-2-picolinium bromide (28) in 2N sodium hydroxide.[32]

All the nitrosoindolizines reported are green crystalline solids of good stability. In aqueous solution or in acid solution, they give a red colour suggesting an iso-nitroso compound (29a) is formed.



(28) (29) (29a)

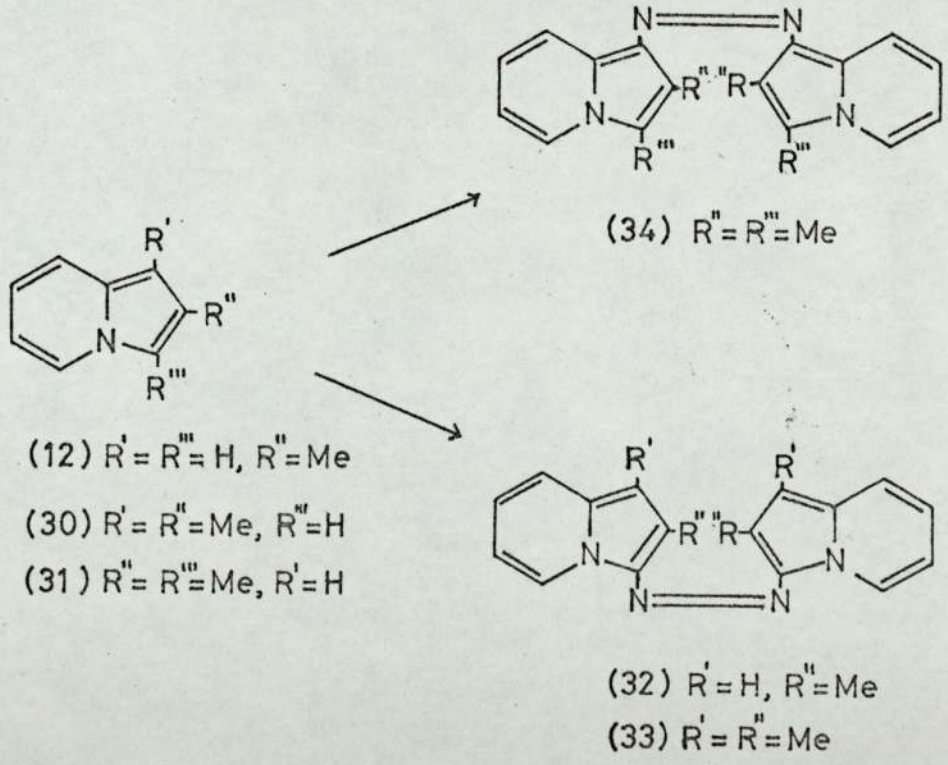
The stability of the nitrosoindolizines, including the alkyl derivatives, was shown chemically by their total resistance to acetylation.[32] 2-Methyl-3-nitrosoindolizine was oxidised, not without difficulty, to 2-methyl-3-nitroindolizine (23) but 3-nitroso-2-phenylindolizine was totally resistant to similar oxidation.[32]

(c) Preparation of Azoindolizines

Neutral diazonium salts, derived from aromatic amines, couple readily with indolizines at the 3-position, or if this is blocked, at the vacant 1- position.[7] The ease of this reaction is similar in the related bridgehead system the

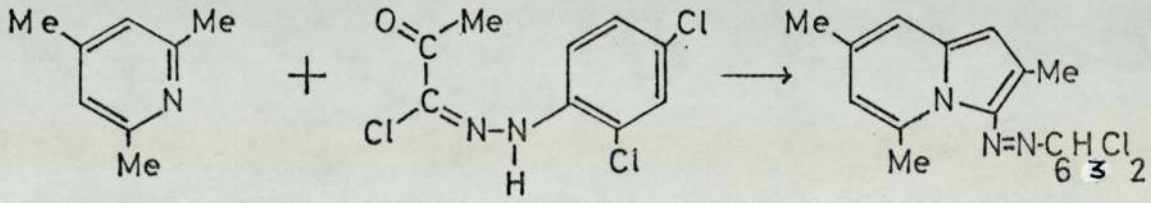
pyrrolo [1,2-c] pyrimidines.[33] Pyrroles and indoles similarly undergo diazo coupling reactions.[30,31]

A synthesis of alkylazobisindolizines by the reaction of alkylindolizines with picryl or tosyl azides has recently been reported.[34] The formation of the 2-methyl-bisazoindolizine (32) and 1,2-dimethylazobisindolizine (33) was reported to be far more rapid than that of 2,3-dimethylazobisindolizine (34) and all of these reactions comparatively more rapid than with the corresponding indoles.[35] This again demonstrates the reactivity of the indolizine ring, and the comparative reactivities of positions 1 and 3.

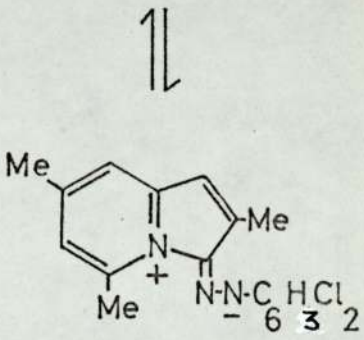


Despite the availability of the nitrosoindolizines there is no record of their reactions with aromatic amines by the Mills Reaction[7] to form azoindolizines.

Neber and Worner [36] performed a direct synthesis of the azoindolizine (35) and its structure (35a) was proved by ultra violet spectroscopy. No attempt to enlarge the scope of this reaction has been made.



(35a)



(35b)

(d) Carbonyl derivatives

The carbonyl derivatives of indolizines are potential precursors of indolizine amines by application of the Hoffmann, Schmidt, Curtius or Lossen rearrangements.

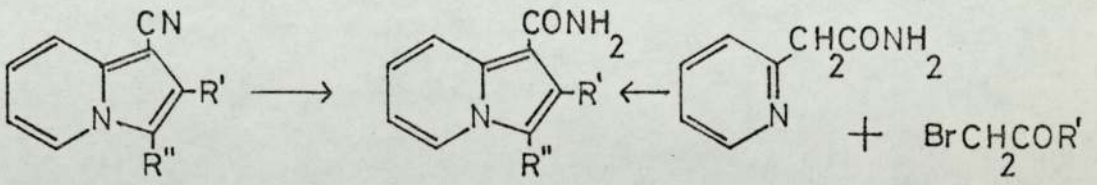
The Barrett,[37] and Scholtz,[38] syntheses of indolizines give acetylindolizines directly, but the majority of the large number of known acetylindolizines have been synthesised by the ready acetylation of the indolizine ring.[7] Similarly, benzoylation and formylation of indolizines readily take place at the 3- position, or if this is substituted, at the 1- position. The ease of these reactions is modified by a strongly electron withdrawing substituent on the five membered

ring, and as has been recorded above (pages 11 and 14) the nitro- and nitrosoindolizines are difficult to acetylate.[25,32]

Cleavage of the acetyl group takes place readily with mineral acid.[7] Resistance to hydrolysis is greater in the diacetylindolizines and with acetylnitro- and acetylnitroso-indolizines, hydrolysis was totally unsuccessful.[25,32]

Common derivatives, such as oximes or phenylhydrazones of 3-acetylindolizines, are difficult to prepared but the 1-acetylindolizines react normally.[7] This reflects the electron density at these two positions.

The Hoffmann, Curtius and Lossen rearrangements involve the synthesis of derivatives of carboxylic acids and acids and their esters may be synthesised in the indolizine series by direct methods: the Diels-Alder synthesis,[39] and the Tschichibabin synthesis using ethyl-2-pyridylacetate.[40] The Tschichibabin synthesis also gives indolizine-2-carboxylic acid. Reaction of phosgene with indolizine and with 2-methyl-indolizine gave the corresponding indolizine-3-carbonyl chlorides.[41,42,43] Carbamoylindolizines have been prepared by a direct synthesis, [24] to give 1-carbamoylindolizines (36) by the reaction of 2-pyridylacetamide (38) with an α-bromoketone,



(37) a R'=Me, R"=H
b R'=R"=H
c R'=H, R"=Ph

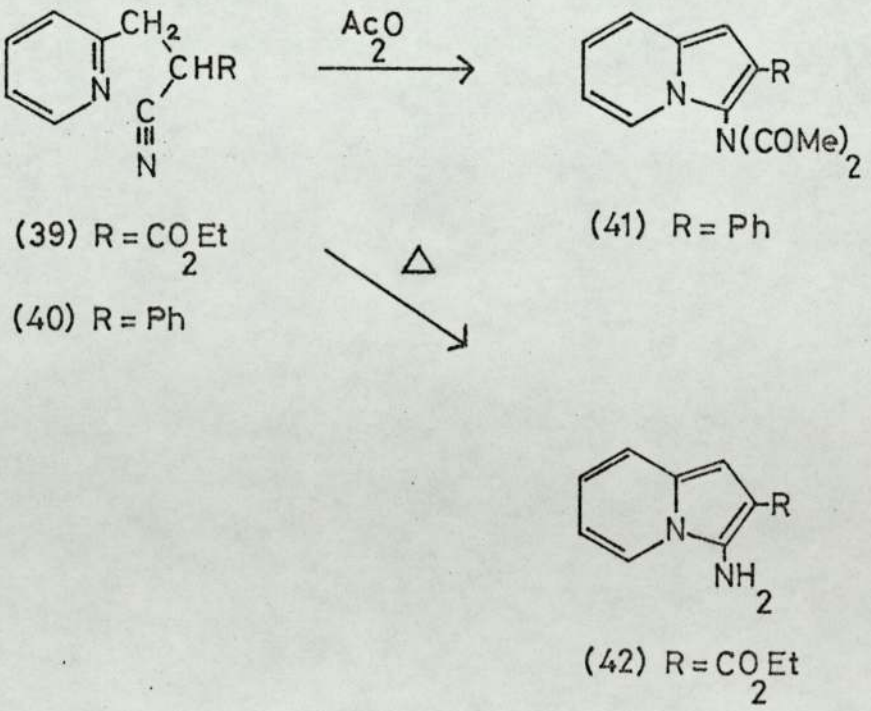
(36)

(38) a R'=Me
b R'=Ph
c R'=CO_2Et

and by the alkaline hydrolysis of the 1-cyanoindolizines (37). 3-Carbamoylindolizines have been prepared from the corresponding acid chlorides, [42,43] and 2-carbamoylindolizine by aminolysis of indolizine-2-carboxylate.[43] Only one example of an amide positioned on the six membered ring is recorded.[43]

(ii) The Synthesis of Aminoindolizines

A cyclisation of the nitrile (39) by heat gave [23] the first known 3-aminoindolizine (42) and was the first direct route for the synthesis of any aminoindolizine. The ease of the cyclisation is dependent upon the nature of the substituent on the alkyl chain of the nitrile, an electron-withdrawing substituent enhancing the electrophilicity of the nitrile carbon atom. The diacetyl derivative (41) of 3-amino-2-phenylindolizine was obtained when cyclisation of the nitrile (40) was effected by acetic anhydride.



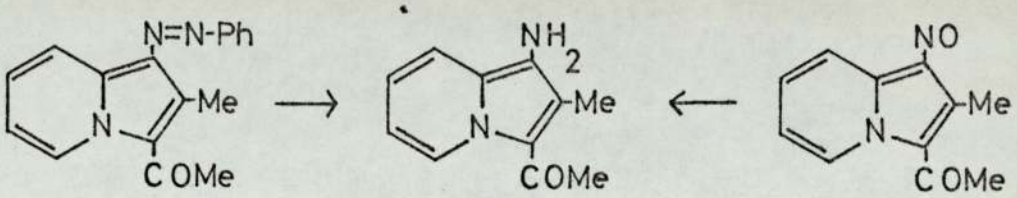
(39) R = CO_2Et

(40) R = Ph

(41) R = Ph

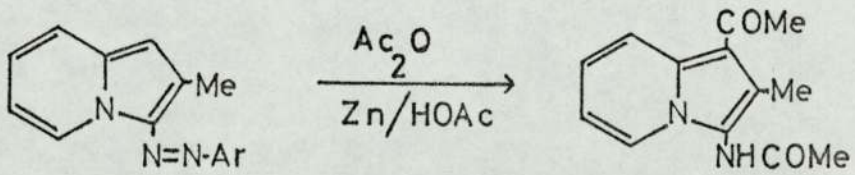
(42) R = CO_2Et

The first recorded 1-aminoindolizine (43) was prepared [22] by reduction of either 3-acetyl-2-methyl-1-phenylazoindolizine (44), or 3-acetyl-2-methyl-3-nitrosoindolizine (45). A number of 1-aminoindolizine hydrochlorides have been prepared by the catalytic hydrogenation of 1-nitroindolizines in hydrochloric acid and the amines liberated by treatment with sodium carbonate solution.[23,24]



(44) (43) (45)

Reductive methods have also been used in the synthesis of 3-aminoindolizines. Rapid catalytic reduction of 3-nitroso-2-phenylindolizine giving the corresponding amine.[44] A reductive acetylation of the azo compound (46) gave the diacetylindolizine (47).[42]



(46) (47)

The Schmidt reaction on 3-acetyl-2-methylindolizine (18) gave the 3-acetamido-2-methylindolizine (50) directly and this was acetylated to the same diacetyl derivative (47) (page 22).

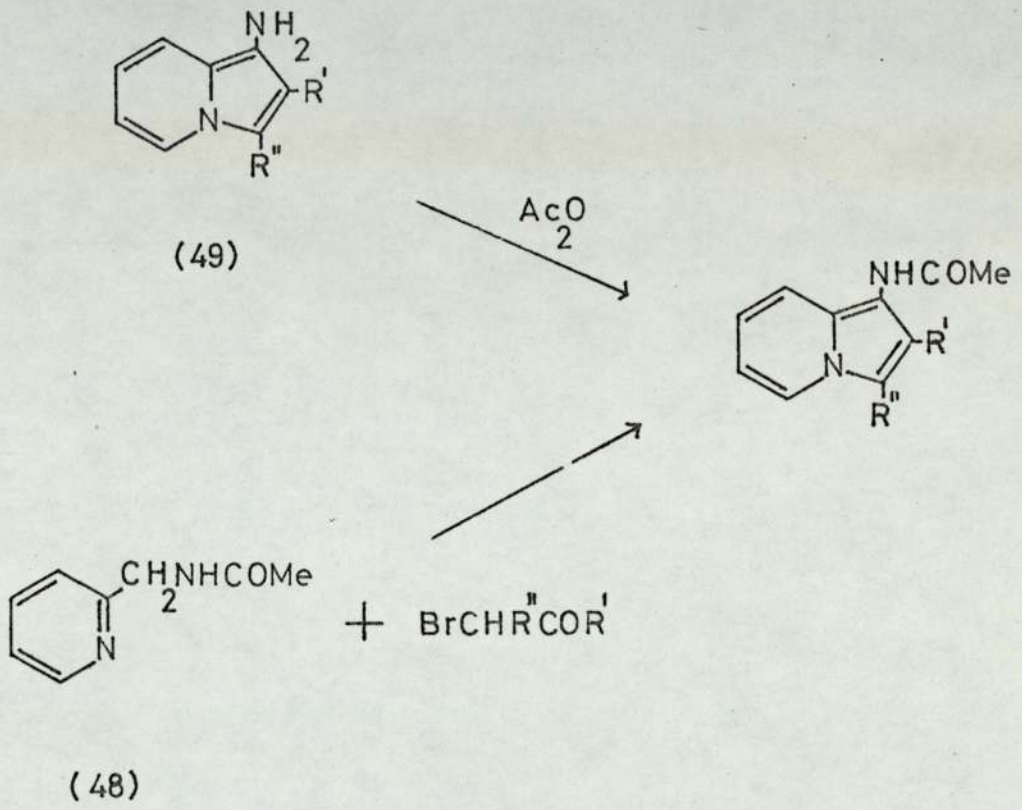
(iii) Properties of Aminoindolizines

The aminoindolizines are yellow crystalline compounds which rapidly decompose on exposure to the atmosphere. This instability is similar to that of other amino-derivatives of π-excessive heterocycles and the ready oxidation of the indolizines bearing electron-donating substituents has been noted above. Thus, 1-aminoindolizine and its hydrochloride were reported [45] to be highly unstable and no stable derivative could be formed. Similarly, 1-amino-2-methylindolizine and its hydrochloride were reported to decompose rapidly, but a stable acetyl derivative was prepared (see below).[23] The presence of electron-withdrawing substituents increases the stability of the aminoindolizines and ethyl 1-aminoindolizine-2-carboxylate and ethyl 3-aminoindolizine-2-carboxylate were both reported to be relatively stable compounds.[23]

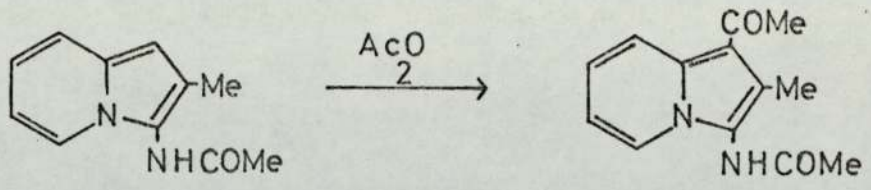
A study of pyrrole and indole amines suggests [30,31] that the least stable isomer is that with the amino substituent at the position of highest electron density, i.e. the 2-position of pyrrole and the 3-position of indole. A suggestion [26] that the 3-aminoindolizines were more stable than their 1-isomers was based upon a comparison of the 1-aminoindolizines with the ethyl 3-aminoindolizine-2-carboxylate which is stabilised by the presence of an ortho electron-withdrawing group.

The synthesis of acetamidoindolizines by reductive acetylation or cyclisation of the nitriles(39) and (40) has been mentioned above. Aminoindolizines undergo smooth acetylation to give monoacetyl compounds, although an attempted preparation of 1-acetamidoindolizine was unsuccessful probably due to the instability of the amine.[45] The

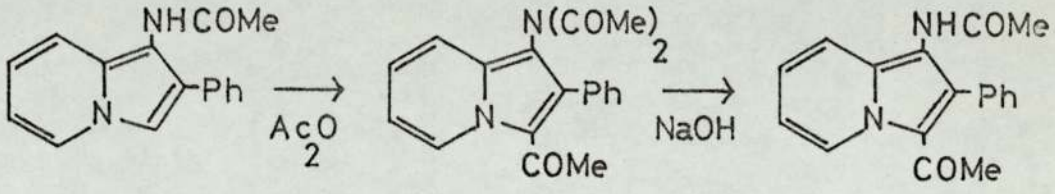
1-acetamidoindolizines have also been synthesised [23,24] directly from 2-acetamidomethylpyridine (48) and the appropriate α-bromketone.



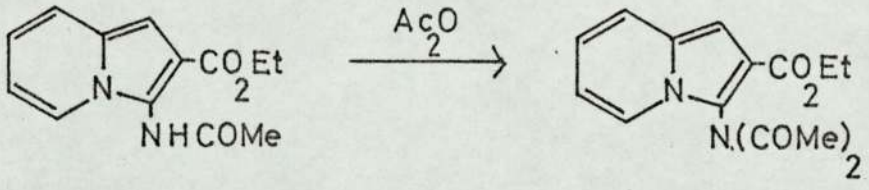
Further acetylation of monoacetylamino compounds gave a variety of products dependent upon the position of the acetamido group and upon the nature of other substituents.[23,42]



(50) (47)



(51) (52) (53)

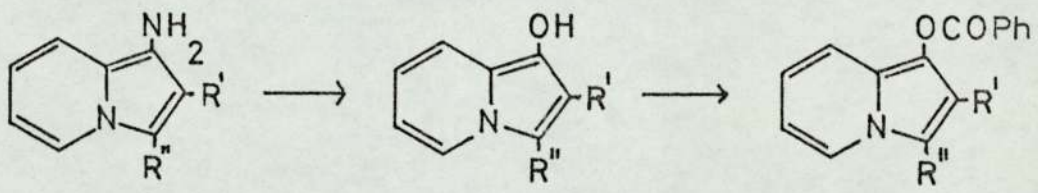


(54) (55)

The attempted hydrolysis of 3-acetamido-2-methylindolizine (50) by hydrochloric acid was unsuccessful [42] and the authors instead reported that extensive disruption of the molecule had taken place, the only identifiable product being ammonium chloride. Basic hydrolysis gave a basic oil, thought to be the corresponding 3-amino compounds, but no positive identification was made. The hydrolysis of the triacetyl compound (52) to give [24] the 3-acetyl-1-acetamido-2-phenylindolizine (53) suggests that the latter compound is the intermediate in the

acetylation of 1-acetamido-2-phenylindolizine (51), and is indicative of the high degree of reactivity of the 3-position on the ring.

Treatment of the 1-aminoindolizines (56) or their acetamido derivatives with concentrated hydrochloric acid gave [24] the first known 1-hydroxyindolizines (57) and their hydrochlorides. Ammonium chloride was isolated from the reaction mixtures. In common with other hydroxy derivatives of π-excessive systems, these compounds were unstable. The hydrolysis of 1-acetamido-2-methylindolizine was carried out but the corresponding hydroxy compound could not be isolated except as its benzoyl derivative (58).



(56) a R'=Ph, R''= H (57) (58) R'=Me, R''=H

b R'= R''= Ph

c R'=Me, R''=H

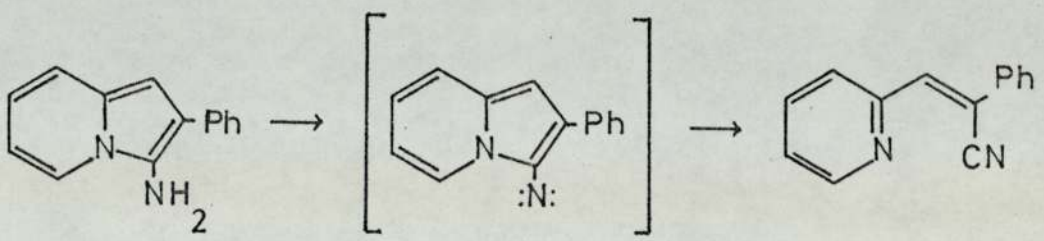
d R'=Me, R''=Ph

Hydrolysis of 3-diacetylamino-2-phenylindolizine (55) gave what was postulated as the corresponding 3-hydroxy compound and ammonium chloride, but no positive proof exists to confirm this.[24]

Diazotisation of 1-amino-2-phenylindolizine (56a) was reported to give an intense red dye after addition to alkaline β-naphthol. A diazonium salt was not isolated.[24]

A neutral ring opening of 3-amino-2-phenylindolizine (59) by an oxidative reaction with palladium charcoal or lead

tetraacetate to the acrylonitrile (61) has been reported,[46] and a possible nitrene intermediate (60) was postulated. This ring opening is similar to that of the 7-amino-pyrrolo [1,2-c] pyrimidines.[47]



(59) (60) (61)

DISCUSSION

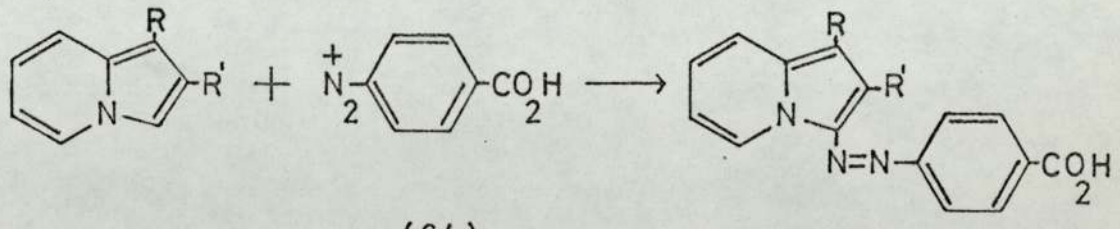
The properties of indolizines and the syntheses of aminoindolizines and some of their precursors, have been reviewed in the introduction. The aim of this work was to synthesise further examples of aminoindolizines and to study some of their physical and chemical properties, especially those involving a ring opening.

THE SYNTHESIS OF SOME AMINOINDOLIZINE PRECURSORS

All the known aminoindolizines were reported to be unstable compounds and therefore amine precursors were chosen which would allow rapid isolation of products in as pure a state as possible.

(i) Azoindolizines

Two azo compounds (62) and (63) were synthesised by the reaction of the corresponding indolizines with a neutral diazonium salt derived from p-aminobenzoic acid (64). The ease of the reaction and the good yield of the products provided a potentially good route to these amine precursors.



(64)

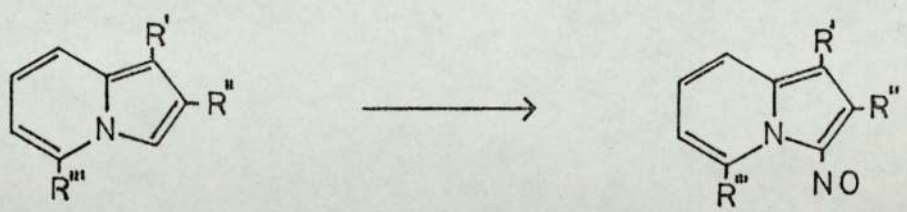
(62) R = H, R' = Ph

(63) R = CO_2Et, R' = Ph

The azo compounds were extremely insoluble in the majority of organic solvents. Their reduction gives a mixture of two amines, and it was considered that the scope of using azo-compounds as aminoindolizine precursors was therefore restricted. Fractional recrystalisation of the mixtures is obviously an unsuitable preparative technique where highly unstable amines are produced, and solubility of the precursor during reduction is a necessary requirement for the rapid production and isolation of an aminoindolizine.

(ii) Nitrosoindolizines

Nitrosation of six indolizines gave the corresponding 3-nitrosoindolizines (65) to (70). The nitrosations were performed in hydrochloric or acetic acid by the addition of an aqueous solution of sodium nitrite. In general, a cleaner product was obtained when the mineral acid was used. The intermediate iso-nitroso compounds were neutralised by aqueous sodium bicarbonate or concentrated ammonia solution to give the nitrosoindolizines, in most cases as green crystalline solids.



(65) $R' = R'' = R''' = H$

(66) $R' = R'' = Ph$, $R''' = H$

(67) $R' = COEt_2$, $R'' = Me$, $R''' = H$

(68) $R' = COEt_2$, $R'' = Ph$ $R''' = H$

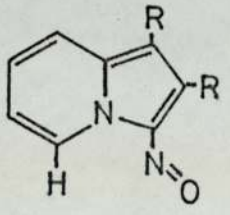
(69) $R' = R'' = COEt_2$, $R''' = H$

(70) $R' = H$, $R'' = Ph$, $R''' = Me$

The nitrosation of indolizine and the alkyl indolizines was more difficult than that of indolizines bearing electron-withdrawing substituents. Large amounts of tarry material accompanied the nitrosation of indolizine and some of this material gave deep blue colours in water. No study of the products from oxidation of indolizine has yet been made, but these blue colours are similar to those produced in the oxidation of indoles [31] and thus it appears that oxidation by a similar mechanism is occurring concurrently with nitrosation. Nitrosoindolizine (65) was isolated by chromatographic separation from the other materials. Unlike the nitroso alkyl-indolizines [32] nitrosoindolizine itself was not stable to hot solvents or prolonged exposure to the atmosphere, and it became dark and tarry in appearance. The absence of a substituent at the 2- position appeared therefore to enhance oxidation of the indolizine ring.

The position of substitution was confirmed by an inspection of the n.m.r. spectra. All the indolizines lacking a substituent at position 5, which were prepared here, showed a low-field doublet at around τ 0.0, with a coupling constant of around 6.5Hz. This is assigned to the 5-proton and its deshielding implies a steric interaction with the nitroso group. A similar *peri* deshielding effect by a 1-ethoxycarbonyl group is seen by the down field signal of the 8- position proton and here the coupling constant $J_{7,8}$ is 9.0 Hz. A recent study of the n.m.r. of *ortho*-substituted nitroso benzenes has shown that where the oxygen atom is on the opposite side (*anti*-) to the substituents, then those substituents will exhibit an unusually low chemical shift and the group on the

same side (syn-) as the nitroso oxygen exhibit unusually high chemical shifts.[48] From this it is assumed that the nitroso oxygen of the nitrosoindolizines lies on the opposite side to the 5-proton (71) and that this proton



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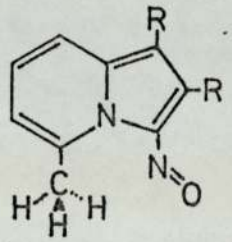
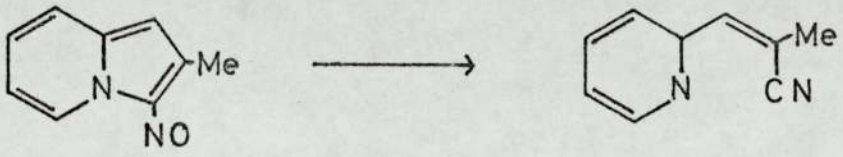


(70)

therefore lies in the deshielding cone. Unlike the benzenes the ortho substituent (at position 2) is not shielded. A consideration of the geometry of the 5-membered ring suggests that such a substituent is further removed sterically from the nitroso group and therefore that it must fall outside the effective range of the shielding cone. 5-Methyl-3-nitroso-2-phenylindolizine (70) does not have a deshielded methyl signal in its n.m.r. spectrum and the very slight downfield shift of τ 0.03 is probably due to an inductive effect alone. This suggests that these methyl protons doe not lie in the effective deshielding cone of the nitroso group and that there does not seem to be a physical contact between the two groupings due to steric crowding. Confirmation that the position of this nitroso compound is at C_3 is given by the lack of a peri deshielded 8-proton and by chemical evidence (page 83).

It was not possible to isolate 3-nitroso-1,2-dimethyl-

indolizine, although the parent base appeared to be nitrosated normally. Attempts to reduce the bulk of the solvent resulted in the production of an intractible tar. On several occasions a similar failure to isolate 2-methyl-3-nitrosoindolizine was encountered. A petrol extract of the brown, tarry material produced in this case, gave a small quanitity of 2-methyl-3-(2-pyridyl)-acrylonitrile (73). No acrylonitrile was isolated from the dimethyl compound however.



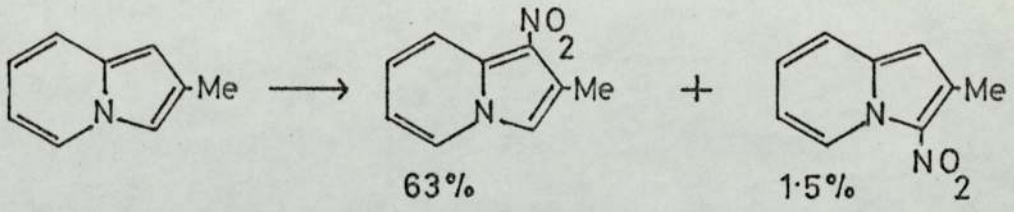
(72) (73)

It is difficult to account for these failures and for the production of the nitrile (73). Work to be described below demonstrated that the nitrosoindolizines are capable of behaving as oxidising agents and it may be that a process of autoxidation is occurring here. The alkyl nitrosopyrroles are reported to be very unstable and have only been isolated as their sodium salts.[30]

(iii) Nitroindolizines

The nitration of 2-methylindolizine and 2-phenylindolizine were described in the introduction (page 8) and, in particular the change of orientation of this electrophilic attack compared to nitrosation, diazo-coupling and other electrophilic attack was noted. Thus, 2-methylindolizine on treatment with a mixture of nitric and sulphuric acids gave 63% of the

1-isomer and 1.5% of the 3-nitro isomer: [25]

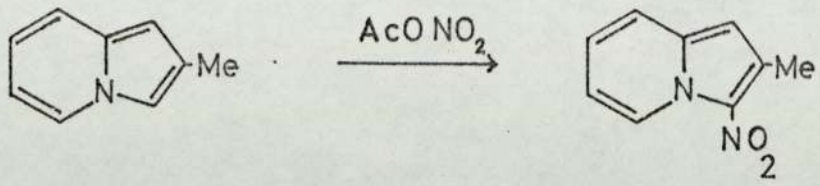


(12) (22) (23)

The nitration of 2-methylindolizine under mild conditions with acetylnitrate was unsuccessful [25] and the nitration of indolizine was reported to be impossible because of concurrent oxidation.[29]

The successful nitration of pyrroles [49] and other π-excessive heterocycles [50] by mild nitrating agents suggested that a re-investigation of the nitration of indolizines under these conditions might prove useful both from a synthetic and mechanistic viewpoint.

2-Methylindolizine was nitrated by a mixture of acetic anhydride and nitric acid. The optimum rate of nitration was achieved by adjustment of the quantity of acetic anhydride used as solvent; excess of this reagent is known to depress the rate of nitration.[51] A solid carbon dioxide-acetone bath was also used to depress the rate of nitration. A chromatographic separation from other material produced in the reaction, which was of a polymeric nature, gave a nitroindolizine in 40% yield with an identical melting point to the product formulated by Borrows, Holland and Kenyon [25] to be 2-methyl-3-nitro-indolizine (23).



(12) (23)

No traces of other isomers, i.e. the 1- or 1,3-dinitro compounds, were found by an inspection of the thin layer chromatograms. Indolizine also underwent nitration under these conditions to give 28% of 3-nitroindolizine, and no other isomers.

The n.m.r. spectra of the products confirmed the position of substitution. 2-Methyl-3-nitroindolizine showed a low-field doublet at τ 0.34 assigned to the 5-H proton, with a coupling constant of 6.5 Hz corresponding to $J_{5,6}$. This is comparable with the spectra of both 2-methyl-3-nitrosoindolizine and 3-acetyl-2-methylindolizine (pages 27 and 49) which have low field doublets at τ-0.25 and τ 0.06 respectively. The n.m.r. spectrum of 2-methyl-1-nitroindolizine has a low-field doublet at τ 1.59 assigned to the 8-H proton with $J_{7,8}$ = 9Hz. The inspection of these peri-deshielded doublets is therefore useful in assigning the position of substitution. 3-Nitroindolizine showed the low field doublet at τ 0.4 with $J_{5,6}$ = 7Hz, and an AB quartet formed by the 1- and 2- protons with $J_{1,2}$ = 5Hz. The coupling constant for the 1- and 2- protons of indolizine is reported to be 3.9 Hz, the coupling constant for the 2- and 3- protons 2.74 Hz .[8] Further confirmation is given by inspection of the mass spectrum (page 96).

The nitration of 2-methylindolizine and 2-phenylindolizine was attempted using tetranitromethane. The reaction with 2-phenylindolizine was abandoned because of the difficulty of finding a suitable solvent. Heterogeneous conditions gave only starting material and quantities of high melting point solids, probably oxidised material. Despite a variety of conditions, including reaction at -70^{o}, 2-methylindolizine rapidly decomposed on contact with tetranitromethane and no nitro compounds were isolated.

The treatment of 2-methyl-3-nitroindolizine with concentrated mineral acids at 100^{o} gave only starting material and polymeric material, and the thin layer chromatograms of the reaction mixtures gave no indication of the formation of other isomers.

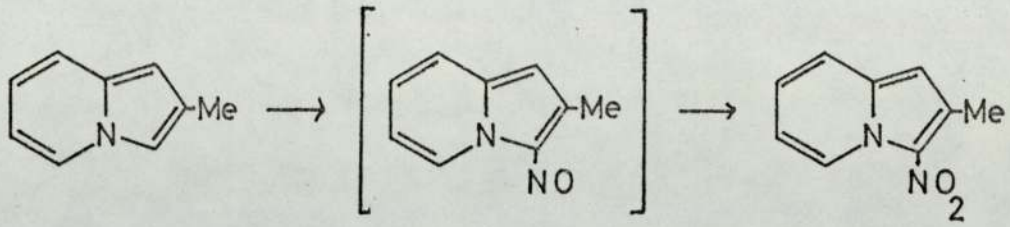
It was felt intuitively that aprotic conditions would give 3-nitroindolizines. A complete explanation for this reversal of orientation is difficult to offer, but a consideration of the nature of both the nitrating species and the substrate under the various conditions employed allows some tentative conclusions to be drawn.

In an inquiry into the nature of the nitrating species involved it must be recalled that theoretical predictions and experimental evidence favour the attack of any electrophile at the 3- position of indolizine (see page 4). Thus, if the nitrating species is considered to be electrophilic then regardless of its strength as an electrophile it is predicted that primary attack will be at position 3, or if this is substituted, at position 1.

The nitration of active aromatic substrates has been the

subject of considerable investigation,[52,53,54] and an increasing amount of evidence suggests [54] that nitration of such compounds by a mixture of acetic anhydride and nitric acid does not take place by a mechanism involving the nitronium ion. The evidence is based upon observations that the nitration of benzene and other reactive aromatic substrates with nitric and sulphuric acids is encounter controlled. Thus a limiting rate is reached when the addition of activating substituents to a substrate does not increase the rate of nitration any further. At reaction rates near the encounter rate, a situation arises where the selectivity between different substrates is lost and the rate of nitration depends upon the acidity of the medium, and hence the concentration of nitronium ions. However, with highly reactive substrates, where the rate of nitration may be up to nearly 10^6 times that of benzene, positional selectivity still remains. This suggests that nitrations of such active substrates in mixtures of acetic anhydride and nitric acid, because positional selectivity is so apparent, must therefore involve a species other than NO_2^+, and which would appear to be a less reactive species than NO_2^+. The readiness of these substrates to undergo nitrosation is known and it is suggested that, unless the possibility of the presence of nitrous acid is eliminated, the nitrosonium ion NO^+, may well be the active species.[55]

The indolizines have been shown, by the present and past work, to be readily nitrosated and thus nitrosation followed by oxidation apparently offers a convenient explanation for the results of the acetic anhydride-nitric acid nitrations.



(12) (72) (23)

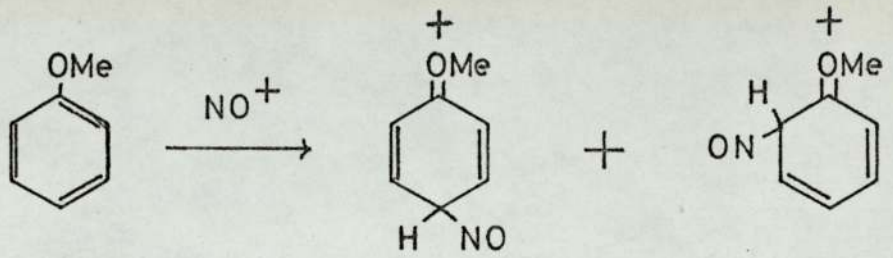
A study of the nitration of thiophens by acetic anhydride-nitric acid has recently been reported [56] and it is concluded that the nitration probably occurs via a nitrosation. It is claimed that the nitrosation is successful in this medium, but not in a mixture of nitric acid and acetic acid where the addition of urea to the mixture (to remove the nitrous acid) increased the yield of nitration product. The authors rationalise this result by a claim that the acetic anhydride supresses the side reactions undergone by the nitroso compound but allows oxidation to take place.

The nitration of indolizines by this reagent is unlikely to have proceeded by a prior nitrosation. The oxidation of 2-methyl-3-nitrosoindolizine (72) is known to be difficult, [25] and the absence of any 2-methyl-3-nitroso indolizine (72) in the reaction mixture is surprising considering its stability. Furthermore, this author feels that the results of the nitration of a number of reactive benzenes suggests that although another species may well be involved, it is unlikely to be the nitrosonium ion.

The most obvious feature of the nitration of certain benzene derivatives by acetic anhydride and nitric acid in aprotic media is the very high $\frac{1}{2}$ o:p ratios. [51,52,57] The common factor between compounds giving the high $\frac{1}{2}$ o:p ratio

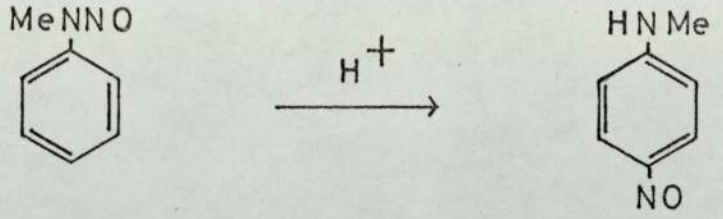
is that a lone pair of electrons is present at a position on, or adjacent to, the ring.

Such substrates generally contain an o,p directing group and a consideration in quantum mechanical terms of the σ-complexes (C) and (D) formed by the attack of an electrophile, suggests that the para-quinoid structure (C) has significantly lower energy than the ortho-quinoid structure (D).[58,59]



(C) (D)

Attack by a weak electrophile, which NO^+ has been shown to be,[60,6] is thus favoured para to the substituent. (Naturally, other effects, steric and inductive, may enter into the overall consideration). The results of nitration by nitrosation of N,N-dimethylaniline,[53] and of the Fischer-Hepp rearrangement support this.[62] The major product of nitration via nitrosation of N,N-dimethylaniline is para-nitro-N,N-dimethylaniline. A small quantity of the ortho nitro isomer is claimed but the details remain unpublished;[53] para-nitroso-N,N-dimethylaniline is also isolated. No ortho-nitroso compound has been isolated. In the Fischer-Hepp rearrangement of N-nitrosamines, such as N-methyl-N-nitrosoaniline (75) by aqueous hydrochloric acid, only para-nitroso-N-methylaniline (76) has been isolated.[62]



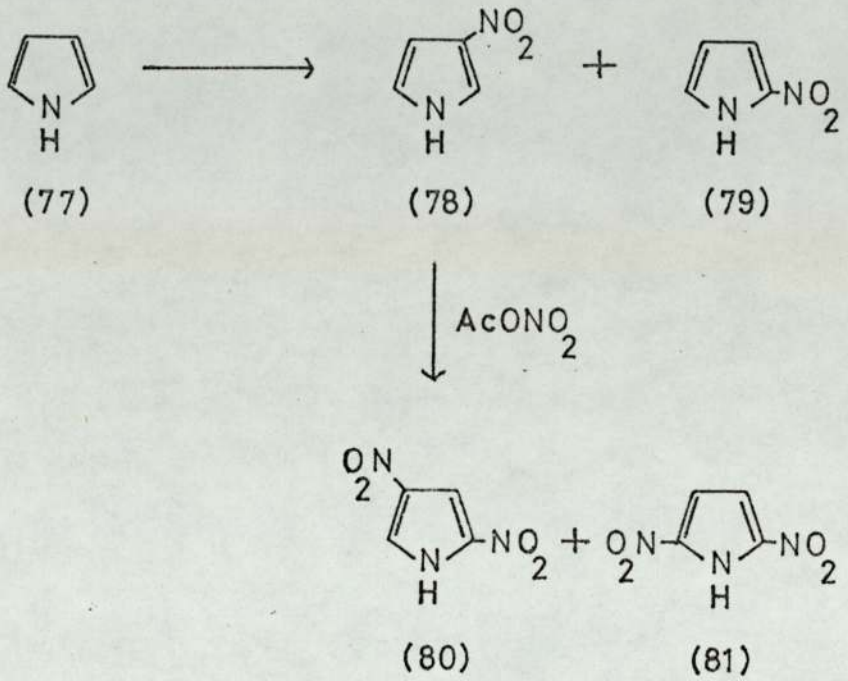
(75) (76)

The high $\frac{1}{2}$ o:p ratios reported for the nitration by acetic anhydride and nitric acid do not therefore appear to be given by a nitration *via* nitrosation, and it is felt that the involvement of the nitrosonium ion in this reagent is limited.

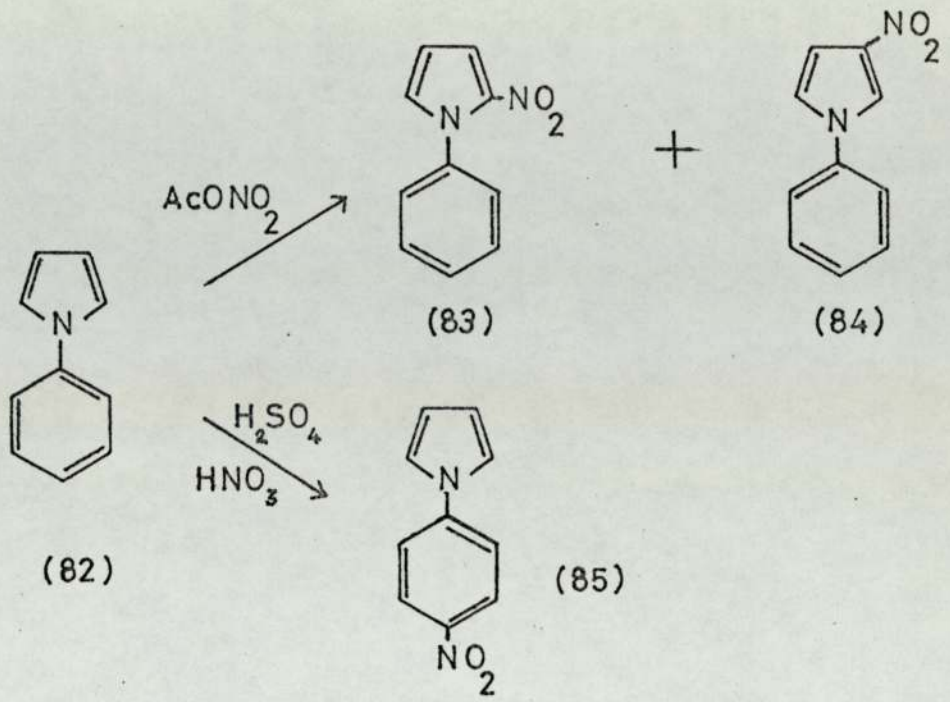
In summary, nitration via nitrosation is considered to be unlikely in the 3-nitration of indolizines. The purity of the reagents was such that the proportions of nitrous acid was minimal. It thus remains to explain why this change of orientation has occurred. The nitration of indolizines by a mixture of acetic anhydride and nitric acid took place at the predicted position of electrophilic attack and therefore, despite the operation of a possibly unknown nitrating species, it is the nitration under protic conditions which is abnormal in giving a 1- nitrated product.

Similar changes in the orientation of the products of nitration occur with a change in nitrating conditions for indoles and pyrroles.[50] In pyrroles, both the π-electron density calculations[63] and a study of the n.m.r. of protonated pyrroles[30,64] indicate that the α-position is favoured for attack. Nitration of pyrrole by acetic anhydride and nitric acid thus gave 2-nitro- and 3-nitropyrrole,(78) and (79), in a 3 to 1 ratio. Further nitration of the deactivated

2-nitropyrrole (78) gave 2,4- and 2,5-dinitropyrroles, (80) and (81), in a 4:1 ratio.[49]



Nitration of N-phenylpyrrole (82) with acetylnitrate gives 2- and 3-nitro N-phenylpyrroles (83) and (84). However nitration with sulphuric acid and nitric acid gave only N-p-nitrophenylpyrrole (85). The protonation of the pyrrole ring is suggested as an explanation of this result.[65] N.m.r. studies confirm that pyrroles are protonated by sulphuric acid. acid.[66]

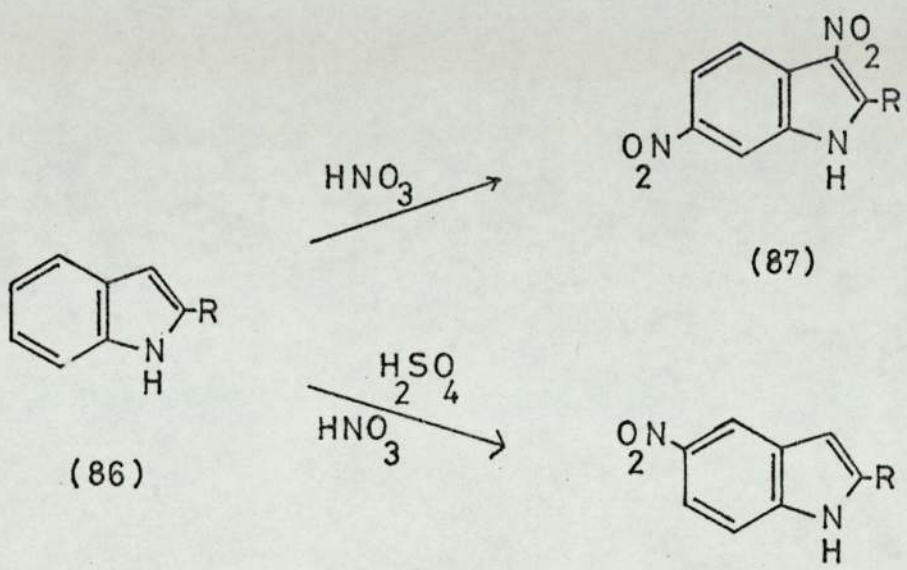


This latter reaction involves the nitration of a phenyl ring bearing a positive pole, and it would be thought that the product would thus be N-m-nitrophenylpyrrole. Arguments have been advanced that in fact a -I substituent, which carries a positive charge, is m,p-directing; the electrostatic effects of such a group determine orientation preferences.[67]

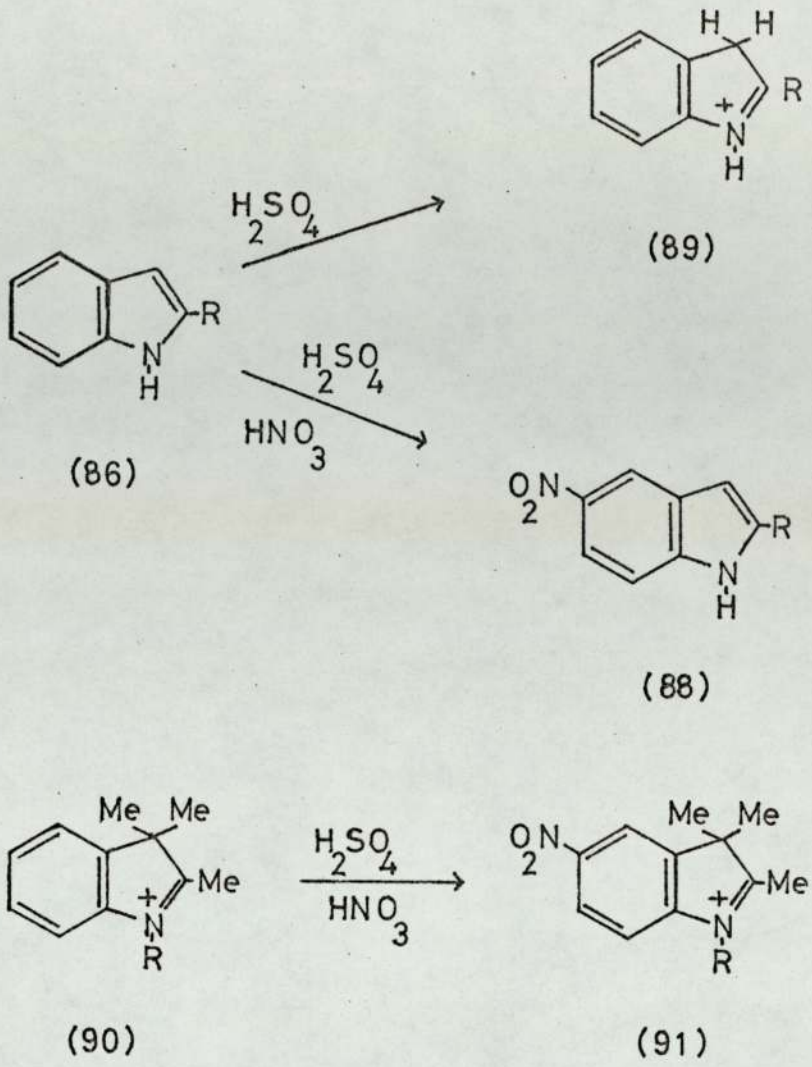
A very similar result is to be found in the orientation of the final products when indoles are nitrated under protic or aprotic conditions. A consideration of the transition states for indoles predicts that position 3 is preferentially attacked by electrophiles.[68] As with pyrrole and the indolizines, nitration of indole under normal conditions is not possible due to concurrent oxidation and thus no observations are available of its mononitration.

The nitration of simple 2-substituted indoles (86) has been studied, and the results have been collected together [31,50]

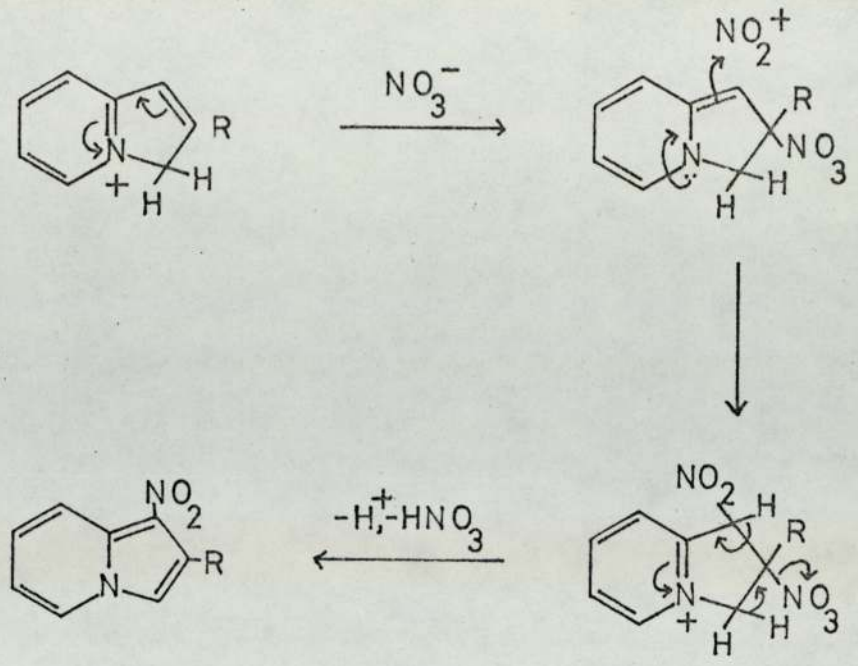
to allow some general conclusions to be drawn. With nitric acid or nitric and acetic acid under mildly protic conditions a predicted 3-nitration takes place, together with dinitration at the six position (87). In strongly protic media, containing sulphuric acid, the 3- position is by-passed and good yields of 5-nitroindoles (88) are given.



Again the result is rationalised by suggesting that in strongly protic media the prime position of electrophilic attack is protonated and under mildly protic conditions that nitration or nitration via nitrosation, takes place as predicted.[69,70] This supposition is supported by the facts that indoles are known to be protonated at the 3- position by sulphuric acid, [71] and that 3,3-dialkyl-3H-indolinium salts (90) are nitrated at the 5-position.[72] The m,p directing effects of the iminium group are explained in the same way as above for positively charged -I substituents.[67]



The possibility that the orientation change in the indolizines is due to protonation must therefore be considered. Protonation of the indolizines was mentioned in the introduction (page 5), and like other electrophilic attacks takes place preferentially at position 3. It would certainly be expected that the indolizines will be protonated under the protic conditions involved for nitrations, but it is difficult to postulate a mechanism which involves electrophilic attack on the protonated five membered ring. An initial nucleophilic attack followed by electrophilic attack and elimination may occur but would seem an unlikely mechanism.

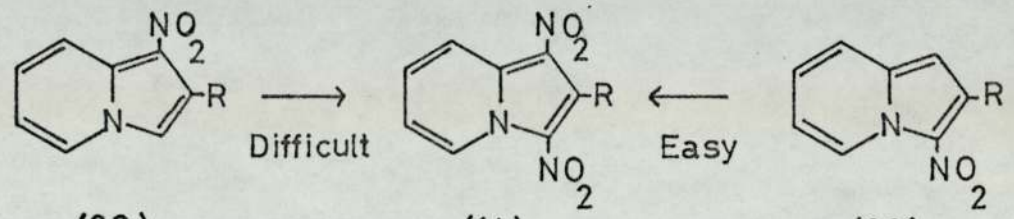


The nitration of a protonated 2-phenylindolizine to give 2-p-nitrophenylindolizine may certainly be involved and the product is similar to that of the protic nitration of N-phenylpyrrole [65] as mentioned above. The subsequent nitration of the 5-membered ring however seems unlikely to be by the mechanism shown, and kinetic data on the role of nucleophiles in the nitration of indolizines would be required before a firm conclusion could be drawn. It is considered that such a mechanism for nitration of pyrrole is unlikely.[30]

The substitution of many pyrroles has been observed to be acid catalysed and it has been suggested [73] that pyrrole, by an association with an anion X^-, becomes activated towards electrophilic attack. However, it is thought that such activation is unlikely to be of the pyrrole, and is more likely to be caused by an activation of the electrophile, for instance the protonation of a carbonyl group.[30]

Protonation may in fact explain the resistance of 2-methyl-1-nitroindolizine (22) to undergo further nitration,

whereas 2-methyl-3-nitroindolizine (23) is readily nitrated.[25] The former, although presenting a deactivated substrate for protonation, will be protonated at the position open for further electrophilic attack, whereas the latter is less likely to be protonated at the 1-position open for attack.

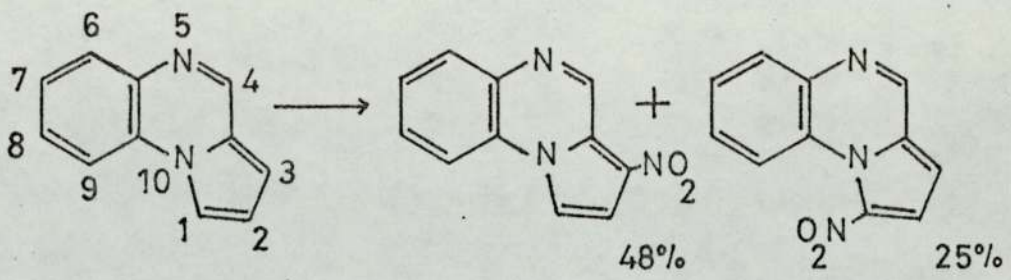


(22) Protonated at free position.

(14)

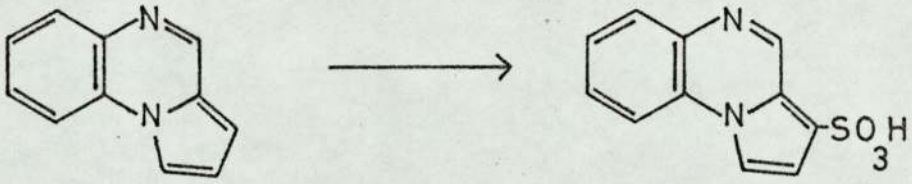
(23) Protonated weakly at free position.

Both changes in orientation of products and difficulty in causing further electrophilic attack according to the position of the primary substituent are observed in a related nitrogen bridgehead system, the pyrrolo[1,2-a]quinoxalines. The results of various electrophilic attacks on this system provide an interesting parallel to the indolizine. The halogenation, nitration and sulphonation of the system has been reported,[74, 75, 76] and from these reactions marked changes in orientation were noted. Nitration was attempted by the use of a variety of reagents, including acetic anhydride and nitric acid, but was only successful when an intimately ground mixture of potassium nitrate and the parent base (92) were added to concentrated sulphuric acid.[74]



(92) (93) (94)

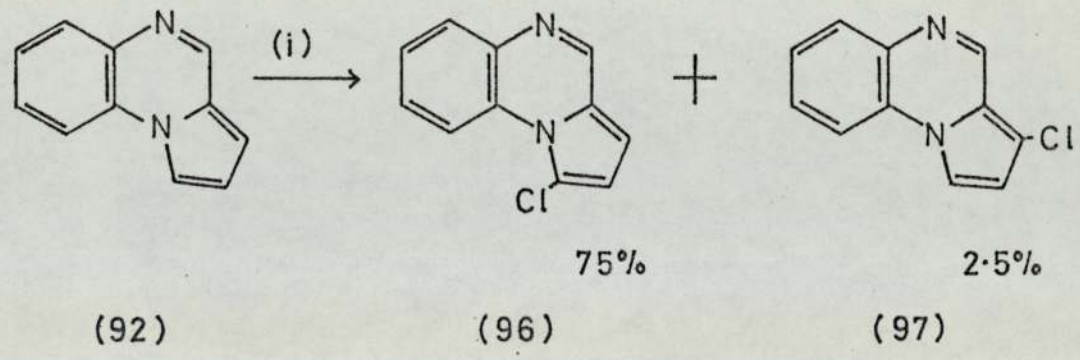
Thus, as with the indolizines, nitration in a protic medium gave preferential substitution at the position removed from the bridgehead nitrogen (93). Similarly, sulphonation in concentrated sulphuric acid at room temperature gave the 3-sulphonic acid (95).[74]



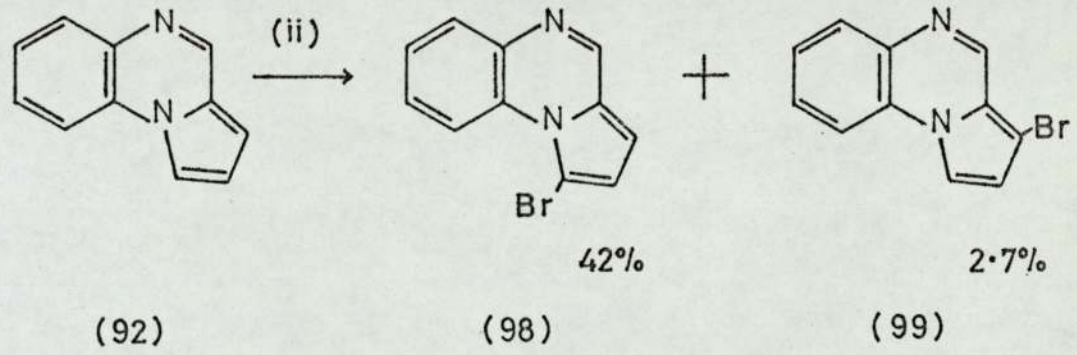
(92) (95)

Protonation of the pyrrolo[1,2-a]quinoxalines is expected to be at position 5 on the pyrazine ring, and thus the orientation would seem unlikely as a consequence of protonation of the 5-membered ring. Cheeseman and his co-workers rationalise the orientation of substituents on the basis of their studies into halogenation of this system.[74,75] The results are shown on page 44.

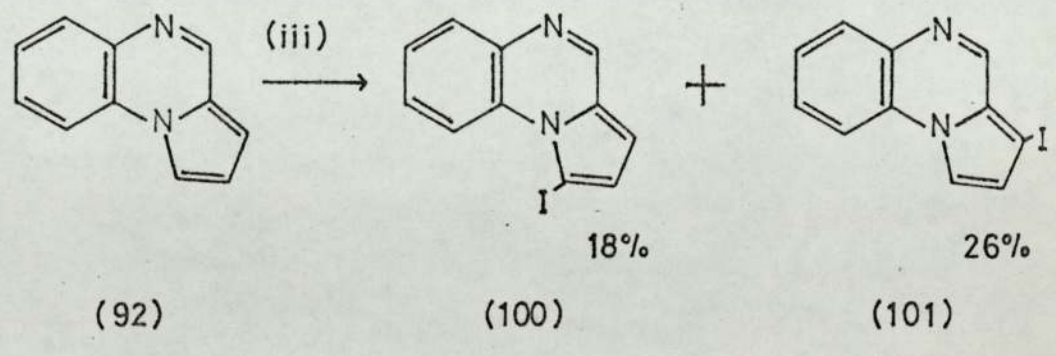
From these results and from the n.m.r. data of the



(92) (96) (97)



(92) (98) (99)



(92) (100) (101)

Reagents: (i) N-Chlorosuccinimide
(ii) N-Bromosuccinimide
(iii) Bispyridine iodinium nitrate

1-nitro compound (94) and 1-chloro compound (96), where a deshielding of the 9-H proton occurs, it was concluded that the orientation of electrophilic substitution was determined by steric considerations.[74] This author considers that whilst the halogenations may certainly be influenced by steric factors, in the progression from chlorine to iodine, the changes in orientation of nitration are also controlled by other factors. It is suggested that the strongly protic nature of the nitrating medium is a determining factor.

Acetylation of the indolizines and pyrrolo [1,2-c] pyrimidines [33] takes place preferentially at the carbon adjacent to the bridgehead nitrogen and thus, despite the size of the acetyl group, steric parameters do not appear to be relevant here. The acetylation of the pyrrolo [1,2-a] quinoxalines has not been reported and so unfortunately such a comparison cannot be made as yet.

Thus in summary, two factors which may determine the reversal of normal orientation when indolizines are nitrated in strongly protic media, seem unlikely to be determinant, that of the nitration of a protonated species and that of a steric effect.

It was felt that perhaps the most important results of the electrophilic substitutions of the pyrrolo[1,2-a]quinoxalines which were relevant to the present problems were those of subsequent rearrangements.[75,76] 1-Bromopyrrolo[1,2-a]quinoxaline (98) was found to rearrange to the 3-isomer (99) on heating with mineral acid and brominations at high temperatures and in acid media, gave large proportions of the thermodynamically favoured products substituted at position 2 and 3, with little of the kinetically favoured 1-isomer. Similarly, strong conditions of sulphonation gave the thermodynamically favoured 2-sulphonic acid.

Attempts to rearrange 3-nitro-2-methylindolizine to the corresponding 1-isomer were unsuccessful. Rearrangements of 1-nitro-pyrrolo[1,2-a]quinoxaline was suggested to involve a mechanism of acid catalysed nucleophilic displacement by chloride ion.[76] Thus, the concept of a predicted 3-nitration of indolizine followed by acid catalysed rearrangements to the thermodynamic 1-isomer, which appears to be such an attractive explanation, does not hold.

A study of the relative leaving abilities and isotope effects in aromatic substitution has produced a tentative guide to the order of increasing leaving abilities of groups.[37] This is based upon the magnitude of the isotope effects operating in substitution, on reactions of model compounds and other kinetic studies.

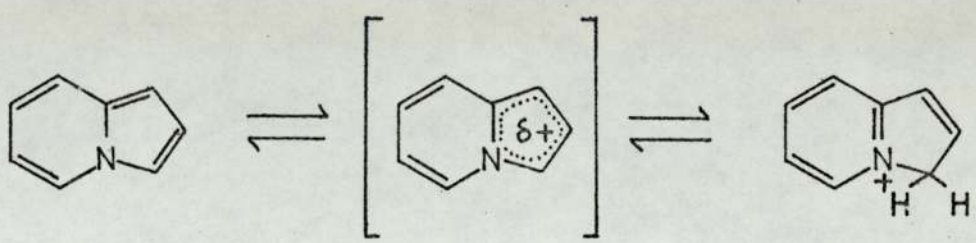
$$Cl^+ \sim NO_2^+ \sim R^+ < Br^+ < D^+ \sim ArN_2^+ \sim SO_3 \sim RCO^+ < NO^+ \sim H \sim I$$

From this it can be assumed that the rearrangement of the nitrogroup would be difficult. It also suggests that if such rearrangements are feasible in the indolizines, that 3-nitroso compounds would be expected to rearrange. The protonation of the 3-nitrosoindolizines to give the iso-nitroso compounds, would be expected to prevent reversal of substitution and subsequent rearrangement. The rearrangements of the pyrrolo [1,2-a] quinoxalines are in keeping with the order of leaving abilities of the groups involved. Thus 1-chloropyrrolo [1,2-a] quinoxaline could not be rearranged, 1-bromo was rearranged to 3-bromo and the 3-sulphonic acids were easily hydrolysed and gave the thermodynamically favoured products under strong conditions.[75]

The overall conclusion which may be drawn in the light of all these considerations would suggest that some barrier to normal 3-substitution is present in strongly protic media, but that it is unlikely to be protonation at this position. (Protonation may be involved in preventing further nitration however. Page 42).

Rearrangement is unlikely due to the weakness of NO_2^+ as a leaving group (since it is a strong electrophile) and thus initial attack must be at position 1. There does not appear to be steric hindrance at position 3 any more than at position 1, and substitution at position 3 occurs even when the 5-position is substituted (page 28). It might be that the nitronium ion is heavily solvated in a protic medium and is thus a bulkier electrophile than for example an acetyl, but it remains difficult to rationalise the marked preference for position 1 on nitration on steric grounds alone.

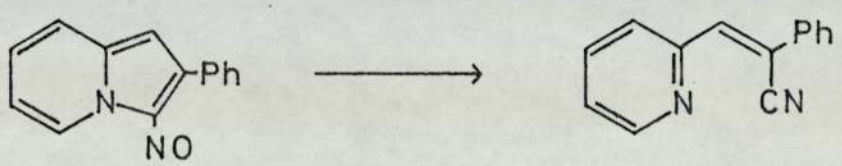
It is tentatively suggested by the author that in a protic medium the indolizine is surrounded by a solvent cage and that the extent of solvation is greater around the positions of highest electron density. Such a solvating effect could effectively deactivate the ring to a certain extent, so that three species of indolizine may be present in the medium: free base, "solvated" base and protonated base, (E), (F) and (G).



(E) (F) (G)

The results of nitration and nitrosation may therefore be rationalised by proposing that the strong electrophile NO_2^+ is deflected from a heavily solvated 3-position to the 1-position which, although deactivated, allows a strong electrophile to undergo substitution. In strongly protic media the equilibrium shown will obviously lie to the right and therefore little free base (E) will be present. Nitrosation although it may be carried out in a medium which will protonate indolizines, is in a less strongly protic medium and the equilibrium will not fall so far to the right as in nitration. Deflection of a nitrosonium ion from the 3-position of the solvated species to the deactivated 1-position may occur but the NO^+ ion is too weak an electrophile to attack here. Nitrosation, therefore, would only occur on the proportion of free base (E) present.

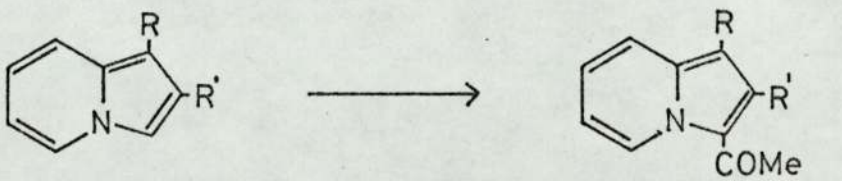
An attempted oxidation of 3-nitroso-2-phenylindolizine (29) by peracetic acid was unsuccessful. A small quantity of the acrylonitrile (61) was isolated from one attempted oxidation by this method. The mechanism of such a ring opening is discussed below (page 68).



(29) (61)

(iv) The Acetylindolizines

Treatment of five indolizines with acetic anhydride and sodium acetate gave the corresponding 3-acetylindolizines. Three of these have been synthesised by this method by earlier workers.[7] 3-Acetyl-1,2-dimethyl- and 3-acetyl-1,2-diphenyl-indolizine have been previously synthesised directly.[37]



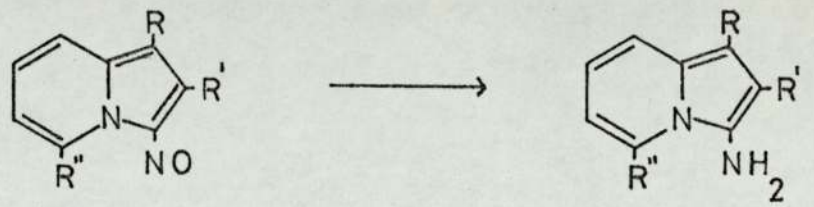
(102) R = R' = H
(18) R = H, R' = Me
(103) R = R' = Me
(19) R = H, R' = Ph
(104) R = R' = Ph

The n.m.r. spectrum of the 3-acetylindolizines showed a low-field doublet at around τ 0.0, $J_{5,6}$ =6.5-7.0Hz. This corresponds to the peri deshielded 5-proton and thus the 3-acetylindolizines

show this property in common with the 3-nitroso- and 3-nitro-indolizines (Pages 27 and 31). The size of the acetyl- and nitro- groups are comparable and suggests that the change of orientation of the nitration of indolizine reported by previous workers is unlikely to be due to steric considerations. The properties of the acetylindolizines were reported in the introduction (page 16).

THE SYNTHESIS OF AMINOINDOLIZINES

Reductive methods have been used to synthesise eight new 3-aminoindolizines (105) to (111). In the choice of a most suitable method of reduction due consideration was given to the unstable nature of the final product. The reduction of the corresponding nitro, nitroso or azo compounds by hydrazine hydrate and palladium on charcoal [78] proved to be the best method.



(105) R = R' = R" = H
(106) R = R" = H, R' = Me
(107) R" = H, R = R' = Ph
(108) R = CO_2Et, R' = Me, R" = H
(109) R = CO_2Et, R' = Ph, R" = H
(110) R = R' = CO_2Et, R" = H
(111) R = H, R' = Ph, R" = Me

The reduction of the precursor took place almost instantaneously in each case and an indication of reduction was given by the rapid discharge of the green colour of 3-nitrosoindolizines. Isolation of the corresponding amines involved simply filtering off the catalyst and the removal of the solvent. In most cases it was possible to isolate amines of a high degree of purity within ten minutes of the commencement of reduction.

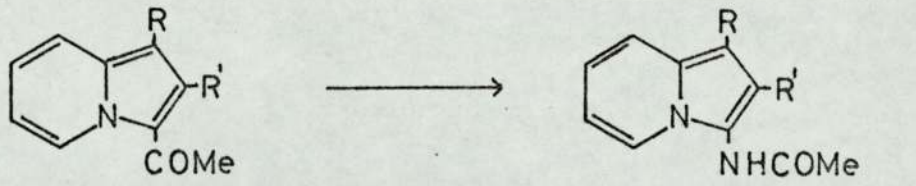
The purity of the final product was dependent upon adequate mixing of the catalyst in a strongly refluxing ethanolic solution of the precursor. The nitrosoindolizines on several occasions gave products of a low degree of initial purity because of reaction of the substrate with undecomposed hydrazine. This was prevented by ensuring an adequate catalyst was present and that it was well stirred.

5-Methyl-3-nitroso-2-phenylindolizine decomposed on contact with the hot solvent (page 83) and special precautions were taken to make the amine in a pure state by adding the precursor to the boiling solvent a few moments before the hydrazine hydrate.

Isolation of the 3-aminoindolizines bearing electron donating substituents, and of 3-aminoindolizine itself, proved to be difficult due to the rapid decomposition of the products on contact with the air (see below). Some difficulty in isolating ethyl 3-aminoindolizine-1,2-dicarboxylate (110) was experienced and on several occasions a red tarry product was given. It is thought that this was due to the reaction of excess hydrazine, either with the nitroso group or with the ester groups. Increasing the quantities of catalyst did not completely prevent side reactions from occurring.

Two slow methods of reduction of 3-nitro and 3-nitroso-indolizines were also attempted. Complex mixtures of products resulted from the use of pressure hydrogenation with palladium on charcoal and from transfer hydrogenation [79] using cyclo-hexene and palladium on charcoal. The nature of these products is discussed below (page 68) and involves the further reaction of the amine under the conditions employed.

The direct synthesis of three new acetamido indolizines was performed by the reaction of the corresponding 3-acetyl-indolizines with hydrazoic acid. The Schmidt reaction of 3-acetyl-2-methylindolizine (18) has been reported [42] to give good yields of the 3-acetamido-2-methylindolizine (50) and the 3-acetylindolizines reacted in the present work to give good yields of the 3-acetamidoindolizines (112) to (114). 3-Acetylindolizine failed to undergo the reaction. Only starting material could be isolated from the reaction mixtures despite various attempts to adjust reaction conditions. In each attempt a quantity of coloured materials was produced but none were in sufficient proportions to permit characterisation. The inability of this compound to undergo the Schmidt reaction is difficult to understand considering the ease of reaction of the alkyl- and aryl- acetylindolizines.



(112) R = H, R' = Ph
(113) R = R' = Me
(114) R = R' = Ph

In common with previous findings the migration of the bulkier group takes place from carbon to nitrogen.

THE PROPERTIES OF AMINOINDOLIZINES

The unstable nature of aminoindolizines prepared by other workers, was noted in the Introduction (page 20). The amines of other related π-excessive systems, for instance pyrrole and indole, are also reported to be highly unstable.[30,31] The properties of such amines have not been studied extensively and it is sometimes difficult to assess whether reactions have been difficult to perform simply because of the inherent instability of the substrate rather than its resistance, or otherwise, to chemical reaction with other agents. Some physical and chemical properties of 3-aminoindolizines are reported below.

(i) Physical Properties

The 3-aminoindolizines were all brightly yellow coloured solids when freshly prepared. On contact with the atmosphere or prolonged contact with hot solvents they decomposed and the rate of this decomposition was dependant upon the nature of the substituents (see below).

The infra-red, nuclear magnetic resonance and mass spectra of the 3-aminoindolizines were determined. The infra-red spectra all contain strong characteristic absorptions at ca. 3200 & 3400, indicative of the amino group. The n.m.r. spectra of the 3-aminoindolizines all contained a characteristic broad, exchangeable signal for the amino group protons. An upfield movement of the aromatic protons is observed, compared with the corresponding indolizines, and thus in the aminoindolizines with a 1-H proton a signal at ca. τ 4.0 was observed (τ 3.72 in indolizine)[8]. These upfield signals provided a useful indication of the proportion of amine present under conditions

of slow reduction; the remaining precursor nitro- or nitroso-indolizine was estimated by the proportion of the 5-H proton appearing downfield. A spectrum of 3-amino-2-phenylindolizine (59) in T.F.A. shows protonation to have occurred at the 1-position. The extent of this protonation was approximately 25%.

The mass spectra of the 3-aminoindolizines are discussed elsewhere (page 98).

(ii) Chemical Properties

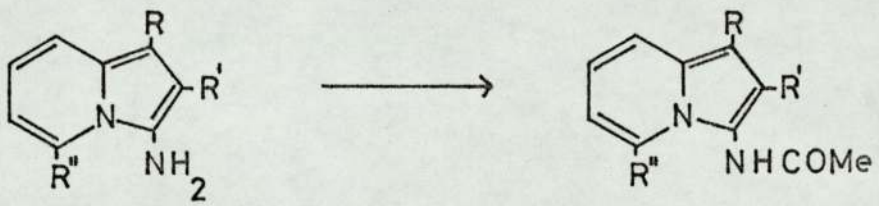
(a) Stability

The aminoindolizines are unstable to the atmosphere and prolonged contact with hot solvents. The bright yellow colour of the freshly prepared amines was lost and a green tinge was observed; finally decomposition to a dark, tarry material may occur. Electron withdrawing substituents stabilise the 3-amino-indolizines and thus ethyl 3-amino-2-phenylindolizine-1-carboxylate (109) was stable for many months without undue precautions being taken for its storage. The unsubstituted amine (105) and 3-amino-2-methylindolizine (106) were both highly unstable and decomposed within one hour of their production. The amines were best stored in a vacuum desiccator protected from light.

Similar observations have been made in the study of the stability of aminopyrroles [30] and aminoindoles.[31] In the latter case the products and mechanism of aerial oxidation have been elucidated.[80] The oxidation by chemical methods of the 3-aminoindolizines is discussed below (page 68).

(b) Acetylation Reactions

The 3-aminoindolizines have been subjected to acetylation by treatment with acetic anhydride or acetyl chloride. All of the amines readily underwent acetylation and good yields of the products were obtained by stirring an ethereal solution of the amine with acetic anhydride at room temperature. The use of acetyl chloride in a basic solvent such as pyridine generally gave poorer yields of the acetylated amine and the reaction mixtures often became green or blue in colour. The use of heat with a two-fold excess of these reagents did not result in further acetylation



(50) R = R" = H, R' = Me
(112) R = R" = H, R' = Ph
(114) R = R' = Ph, R" = H
(115) R = H, R' = Ph, R" = Me
(116) R = CO_2Et, R' = Me, R" = H
(117) R = CO_2Et, R' = Ph, R" = H

Attempts to prepare 3-acetamidoindolizine were unsuccessful. The acetylation of the highly unstable 3-aminoindolizine gave only an intractible tar, and this failure was probably due to the decomposition of the amine rather than its inability to react. The attempted direct synthesis by a Schmidt reaction was recorded above, and also failed.

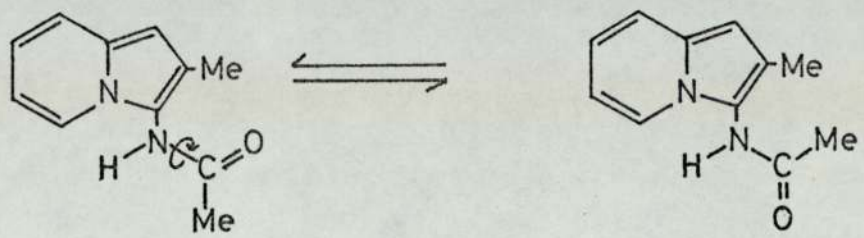
The 3-acetamidoindolizines are stable, crystalline compounds which could be stored for considerable periods of time without decomposition. The ease of their preparation and their stability was useful in keeping derivatives of the amines for further reaction. The products of hydrolysis involved a considerable disruption of the ring and this is discussed below (page 62).

The infra-red, n.m.r. and mass spectra of the 3-acetamidoindolizines have been recorded. The infra-red spectra showed typical absorptions for aromatic amides: N-H stretching at ca. 3400 cm^{-1} and an Amide I band at ca. 1670 cm^{-1}.

The n.m.r. spectra run in deuterochloroform were complicated and initially threw some doubt on the nature of the products. A deuterochloroform solution of 3-acetamido-2-methylindolizine (50) had an n.m.r. spectrum consisting of four singlets at τ 8.32, 8.04, 7.98 and 7.80 and the aromatic signals although integrating correctly, did not show the upfield singlet of the 1-H proton in the region τ3.5-3.8. In the polar solvents pyridine or deuterated D.M.S.O., these singlets in the region τ7.8-8.3 collapsed to one singlet at τ7.76, 7.91 respectively. It was initially considered that the absence of the 1-H proton signal indicated that further acetylation had occurred. The synthesis of this compound by the Schmidt reaction, its mass spectrum and a comparison with the melting point of 3-acetamido-1-acetyl-2-methylindolizine,[42] proved this supposition unfounded. Furthermore, 1,2 disubstituted 3-acetamidoindolizines exhibited the same phenomenon. Thus, the spectrum of 3-acetamido-2-methylindolizine-1-carboxylate (116) had four singlets in the region τ7.8-8.4 and 3-acetamido-1,2-diphenyl-

indolizine (114) two singlets at τ8.02 and 7.89.

The collapse of these multiple signals in polar solvents suggested that an acetamido-acetimido tautomerism was occurring in a non-polar solvent and that two rotamers, having restricted rotation, were present.



(50a) (50b)

The free rotation about a C-N amide bond was postulated by Pauling to be restricted because of a partial double bond character which arose from amide-imide tautomerism.[81] The strength of this π character of such bonds has been determined by n.m.r. studies and the energy of activation calculated from this data.[82]

The two rotamers which may be drawn for 3-acetamido-2-methylindolizine are shown above (50a) and (50b), and an attempt was made to calcuate the energy of activation of this tautomerism. The n.m.r. spectrum was determined at 1° intervals between 40° and 80° as the temperature was increased and as it was decreased. The spectrum before and after raising the temperature was identical but the normal pattern of

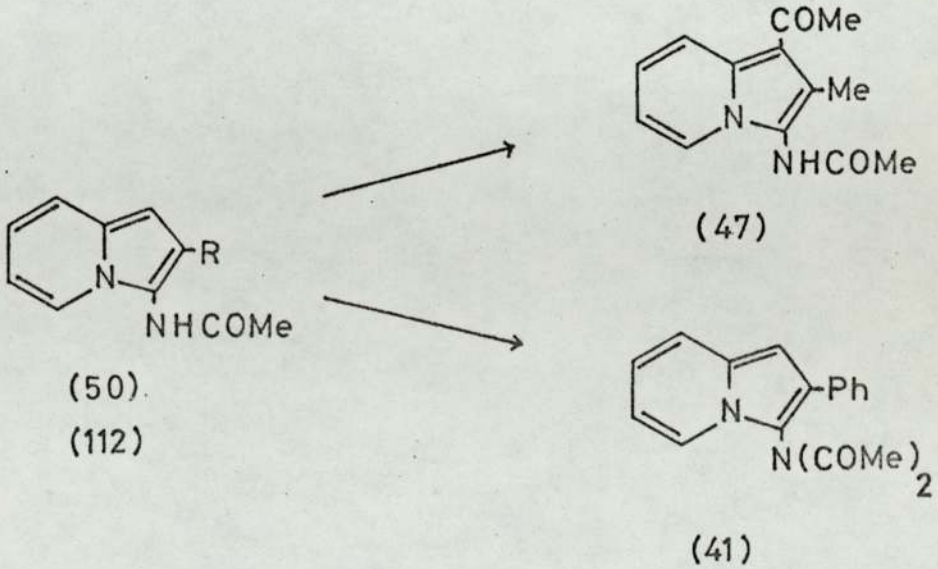
coalescence was not observed. At 59° the three singlets at τ7.8, 7.98 and 8.04 appeared to coalesce, but the upfield signal at τ8.32 remained stationary throughout.

It is not understood why a normal pattern of coalescence was not observed. The signal at τ8.32 in this compound, is also abnormally high (the 2Me protons of 3-amino-2-methyl-indolizine show a signal at τ7.96) and on the basis of the structures drawn (50a) and (50b), it is difficult to postulate a mechanism whereby one of the methyl signals becomes shielded. Restricted rotation of the ring-CHS bond has been reported in the thioformylindolizines and was shown by the multiplicity of the peri-deshielded protons.[83] No peri deshielding of the 5-H proton was observed in the spectra of the 3-acetamido-indolizines.

The further acetylation of both 3-acetamido-2-phenyl-indolizine (112) and 3-acetamido-2-methylindolizine (50) are described below but a consideration of their n.m.r. spectra is useful here. The former gave a 3-diacetylamido compound and its n.m.r. spectrum in deuterochloroform showed a singlet at τ7.9 corresponding to the two acetamido methyl protons which were equivalent, and a normal upfield 1-H signal at τ3.38. It therefore appears that the amide hydrogen is involved in the production of the unusual spectrum of the monoacetamido compound, a fact which is confirmed by the appearance of the spectrum in a polar solvent, like pyridine, which is capable of hydrogen bonding to it. The product of further acetylation of 3-acetamido-2-methylindolizine (50) was 3-acetamido-1-acetyl-2-methylindolizine. This was not soluble in deuterochloroform, and thus a comparison could not be made.

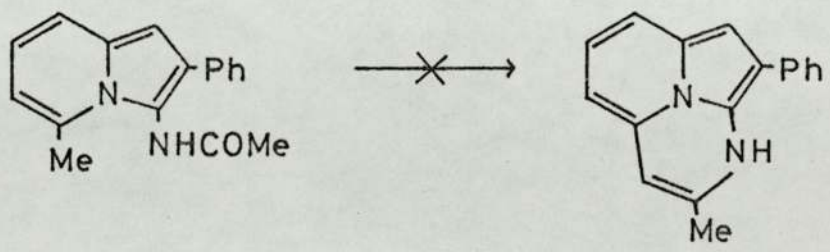
In deuterated D.M.S.O. the spectrum contained three singlets, and it is concluded from this that the collapse to one signal of the four methyl singlets when the n.m.r. spectrum of 3-acetamido-2-methylindolizine (50) was run in pyridine was fortuitous, that is, that the chemical shifts of the 2-Me and 3-acetamido Me signals were the same. The presence of the 1-acetyl group causes a shift of the 2-Me signal and thus all three signals are seen in this further acetylated compound.

Several monoacetamidoindolizines were subjected to further acetylation by refluxing with acetic anhydride and sodium acetate. The further acetylation of 3-acetamido-2-methyl-indolizine (50) had previously been undertaken by Holland and Naylor,[42] and a poor yield of 3-acetamido-1-acetyl-2-methyl-indolizine (47) obtained. Repetition of their experiment and chromatography of the resultant mixture showed that a reflux period of three hours was insufficient with large quantities of starting material remaining. Doubling the reaction time gave the same product in higher yield and less difficulty was experienced in its purification. 3-Acetamido-2-phenylindolizine (112) underwent further acetylation more smoothly than the 2-methyl compound (50) and gave 3-diacetamido-2-phenylindolizine (41).



The position of further substitution of these two acetamidoindolizines (41) and (47) was indicated by inspection of their infra-red, n.m.r. and mass spectra. The i.r. spectrum of (47) showed an N-H absorption, whilst (41) did not. The n.m.r. spectrum of 3-acetamido-1-acetyl-2-methylindolizine in deuterated D.M.S.O. showed a peri deshielded downfield signal at τ1.80 assigned to the 8-H proton, $J_{7,8}$ = 9.0Hz, and three singlets assigned to the three methyl groups. The spectrum of the 3-diacetamido-2-phenylindolizine (41) contained no peri deshielded 8-H proton signal and an upfield singlet at τ3.23 was assigned to the 1-H proton. The mass spectra are discussed below (page 99). The orientation of this second acetyl group reflects the influence of the substituent at position 2.

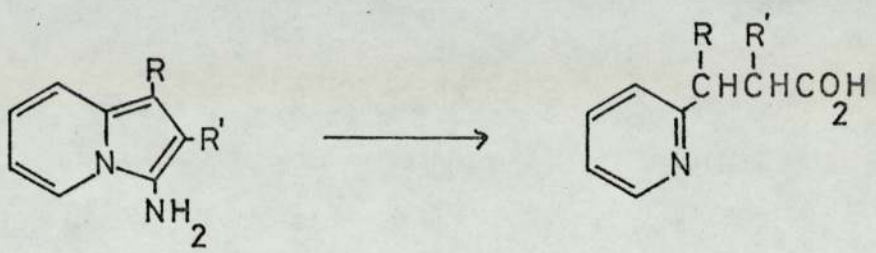
An attempted further acetylation of 3-acetamido-5-methyl-2-phenylindolizine (115) was unsuccessful. It was hoped that the 1 position would be sufficiently deactivated to prevent acetylation here and that the stereochemistry of the 5-methyl and 3-acetamido groupings would allow cyclisation to occur to yield (118). Only starting material was recovered from the reaction mixture.



(115) (118)

(c) Reaction of 3-Aminoindolizines with Acid

The treatment of 3-amino-2-phenylindolizine (59) and 3-amino-1,2-diaphenylindolizine (107) with dilute or concentrated hydrochloric acid caused hydrolysis and ring cleavage. The products were the 3-(2-pyridyl) propionic acids (119) and (120) respectively.

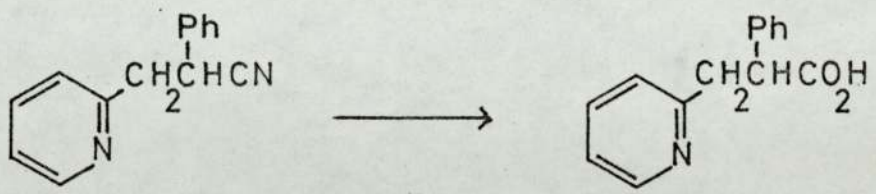


(59) R = H, R' = Ph
(107) R = R' = Ph

(119) R = H, R' = Ph
(120) R = R' = Ph

3-Acetamido-2-methyl- and 3-acetamido-1,2-dimethylindolizine (50) and (113) both appeared to undergo similar hydrolytic cleavage, but the products decomposed during work-up. Ammonium chloride was isolated from all four reactions.

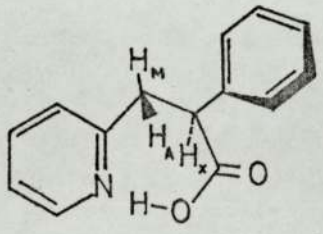
The structure of the products was assigned on the basis of their infra-red and n.m.r. spectra. An unequivocal synthesis of the acid (119) was performed by the acid hydrolysis of 2-phenyl-3-(2-pyridyl) propionitrile (40).



(40)

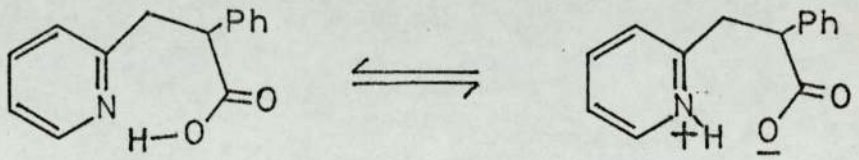
(119)

The infra-red spectra of the acids (119) and (120) contained a typical broad O-H stretch at 2600 cm^{-1}, and this absorption remained at this wavelength when the spectra were run in nujol, pyridine or D.M.S.O. A typical 1700 cm^{-1} C=O absorption was observed in each case. The n.m.r. spectrum of the acids was determined in deuterochloroform, deuterated D.M.S.O. and pyridine. The spectrum of the 2-phenyl-3(2-pyridyl) propionic acid (119) had a broad exchangeable downfield signal at τ-0.75, assigned to the acidic proton, and a doublet at τ1.3 corresponding to the 6-H proton of the pyridine ring. The normal value for this signal is ca. τ1.5 and thus it appears that some inductive or field effect is acting upon this proton. The infra-red spectrum indicates that intra molecular hydrogen bonding is taking place in the molecule, probably between the acidic proton and the pyridine nitrogen. A slightly positive charge on this nitrogen would, by an inductive effect, reduce the chemical shift of the 6-H proton. Further evidence of this intra molecular bonding is indicated by the nature of the spectrum shown by the aliphatic protons in this compound. A typical AMX pattern shows the non-equivalence of the protons on C_3 of the propionic acid. Inspection of a model shows this to be as a consequence of the formation of a cyclic structure (119a).



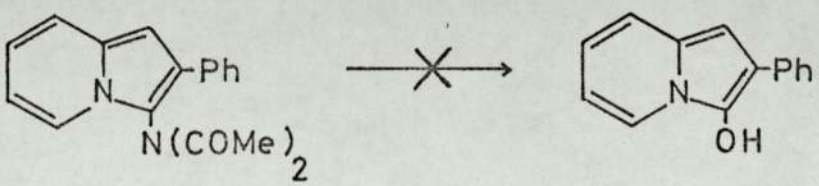
(119a)

The structure shows the H_M proton to be in the plane of the pyridine ring and therefore deshielded more than H_A which is out of plane. The n.m.r. spectrum of 2,3-diphenyl-3-(2-pyridyl) propionic acid does not show this non-equivalence. The possibility of a zwitterionic form (119b) would stabilise such a structure considerably.



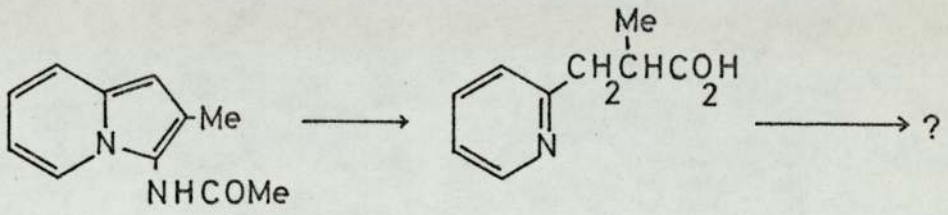
(119a) (119b)

The product of the acid hydrolysis of 3-diacetylamino-indolizine (41), which was thought by Hurst, Melton and Wibberley to be the corresponding 3-hydroxy indolizine (121),[23] was identical with the product (119) above. The stability of the free base indicated that it was unlikely to be a hydroxy derivative of a π-excessive ring; the 1-hydroxy-indolizines are known to be very unstable. The strong carbonyl absorption in the i.r. spectrum may have been thought to be indicative of an oxo-tautomer, since hydroxy pyrroles are known to tautomerise to this form.[84]



(41) (121)

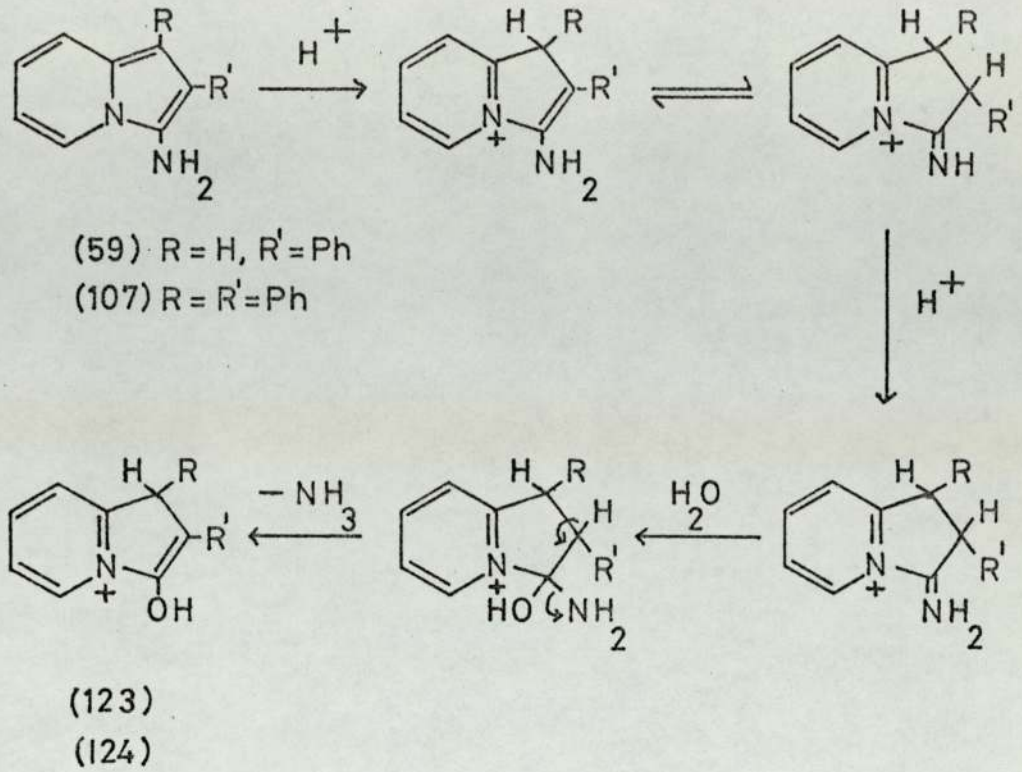
An attempted acid hydrolysis of 3-acetamido-2-methylindolizine (50), by brief heating with dilute hydrochloric acid, has been recorded to have "appeared to disrupt the molecule extensively" and only ammonium chloride was isolated;[42] a similar difficulty in the isolation of the product of this reaction was reported above.



(50) (122)

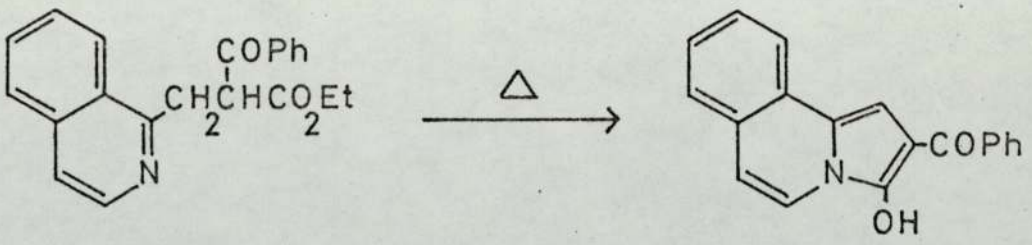
The hydrolysis of 1-aminoindolizines to give 1-hydroxy-indolizines, was discussed above. (page 23). The mechanism for this reaction has been postulated [45] to be similar to that of the hydrolysis of 3-amino-benzo[b]thiophene and involves the protonation of an imino tautomer. The hydrolysis of the 2-aminoindoles to the corresponding oxo-derivatives is similar.[85]

A similar mechanism may be drawn for the hydrolysis of the 3-aminoindolizines. The n.m.r. spectrum of 3-amino-2-phenylindolizine (59) shows that in T.F.A. protonation also occurs at the 1-position. Protonation of a 1-substituted aminoindolizine may be rationalised by consideration of the electron donating character of the 3-amino group. Protonation at position 3 of a 3-aminoindolizine would prevent amino-imino tautomerism.

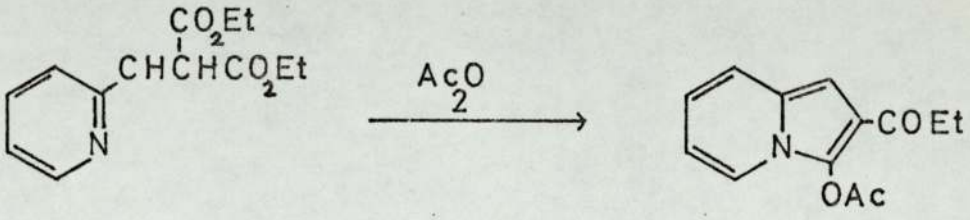


(123)
(124)

The failure to isolate the 3-hydroxyindolizines (123) and (124) from acidic media suggests that further reaction takes place due to the nature of the media. No 3-hydroxyindolizines are known as such, a 3-acetoxyindolizine (126) has been synthesised,[23] but the free hydroxy compound has not been made from this. 3-Hydroxy-pyrrolo[1,2-a] isoquinoline (125) is known and was synthesised under aprotic conditions.[86]

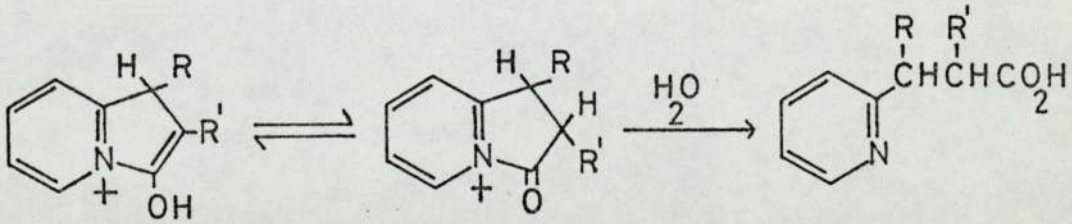


(125)



(126)

If hydroxy-keto tautomerism exists in 3-hydroxyindolizines, then a protonated 3-hydroxyindolizine (123) or (124) would give a structure similar to an N-acyl pyridinium salt (127) and (128):



(123) R = H, R = Ph (127) (119)

(124) R = R = Ph (128) (120)

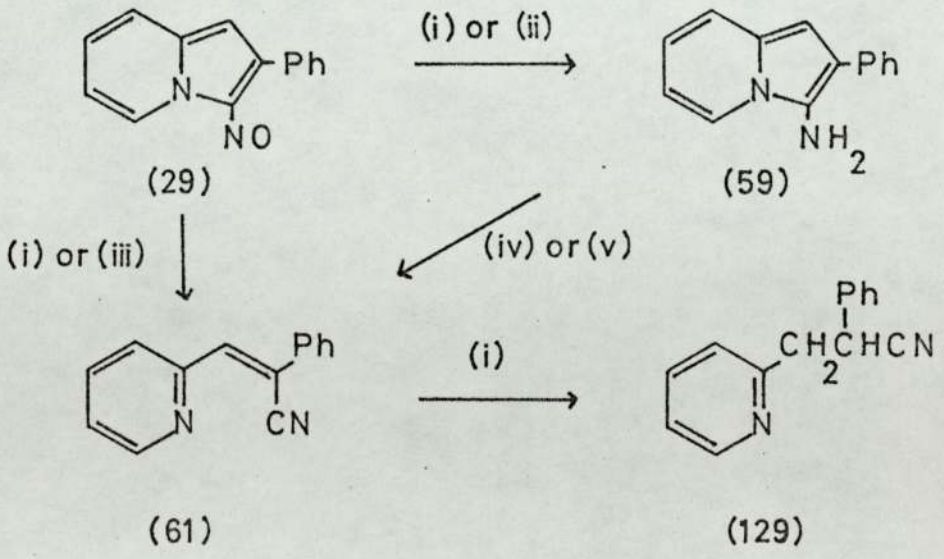
Such salts are known to dissociate and thus nucleophilic attack at C_3 would readily give the acids (119) and (120). The 3-aminoindolizines do not show a contribution of the imino form from their spectroscopic data, nor do 1-hydroxy-

indolizines appear to exist in the oxo-form. The amino- and hydroxypyrroles have been shown to exist mainly in the amino- and oxo- forms respectively,[84] but their reaction suggests both forms may be present.[30]

All attempts to isolate the hydrochloride salts of the 3-aminoindolizines were unsuccessful. When dry hydrogen chloride gas was passed into a solution of the amine in dry diethyl ether, a colourless solid was formed which was presumed to be the amine hydrochloride. On contact with the atmosphere these solids very rapidly decomposed.

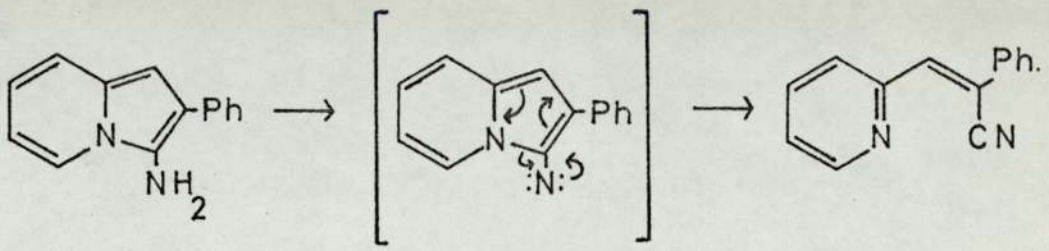
(d) Neutral Ring Opening Reactions

The neutral ring-opening of 3-amino-2-phenylindolizine (59) has been reported by Irwin and Wibberley.[46] Catalytic reduction of 3-nitroso-2-phenylindolizine (29) was reported to give the 3-(2-pyridyl)acrylonitrile (61) and the 3-(2-pyridyl) propionitrile (129) in admixture with the expected amine (59).



Reagents: (i) H_2,Pd-C; (ii) NH_2NH_2,Pd-C; (iii) Cyclohexene,Pd-C; (iv) Pd-C; (v) $Pb(OAc)_4$.

The oxidation of the amine (59) by palladium on charcoal or by lead tetraacetate also gave the acrylonitrile (61). Lead tetraacetate (L.T.A.) oxidises amines *via* what is thought to be a nitrene intermediate,[87] and it was suggested that oxidative ring-cleavage of 3-amino-2-phenylindolizine (59) was taking place *via* such an intermediate (60). Bond isomerisation of (60) yields the unsaturated nitrile (61).

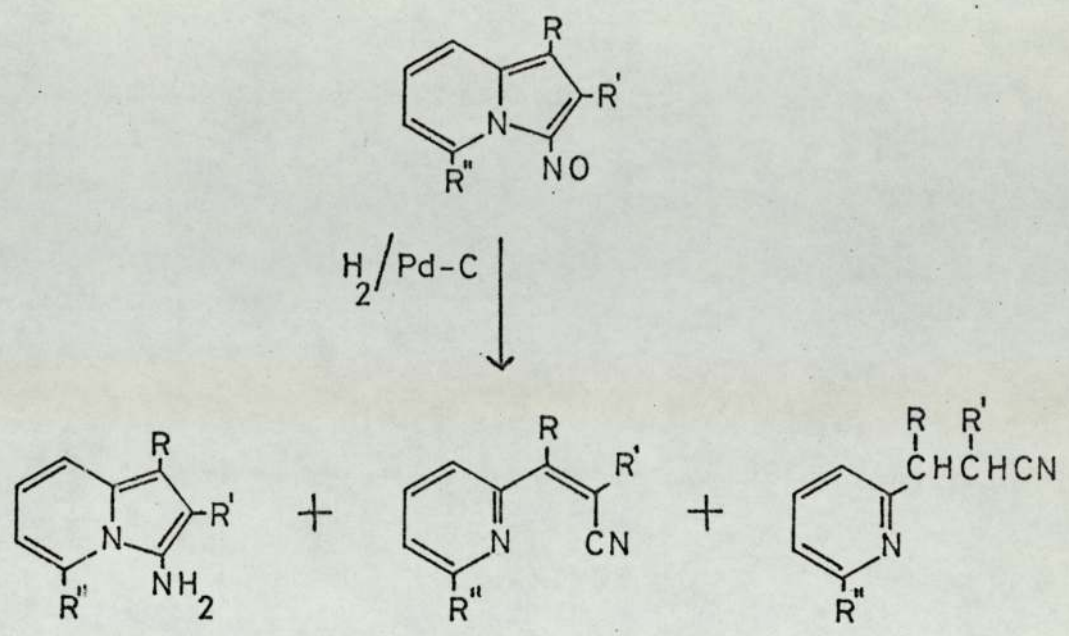


(59) (60) (61)

Slow reduction by cyclohexene and palladium charcoal similarly gave the acrylonitrile, whilst rapid reduction with hydrazine hydrate and palladium on charcoal gave only the amine (59). Corresponding amines and nitriles have been obtained by similar reactions of several 7-nitroso-pyrrolo[1,2-*c*]pyrimidines.[47]

The scope of the ring-cleavage under reductive and oxidative conditions has been further investigated in the present work. Attempts to determine the mechanism of the cleavage have also been made and are described below.

Several 3-nitrosoindolizines have been catalytically reduced and in each case a mixture of the amine and ring-opened products was produced:



(105) R = R' = R" = H (130) (131)

(106) R = H, R' = Me, R" = H (73) (132)

(59) R = H, R' = Ph, R" = H (61) (40)

(107) R" = H, R = R' = Ph (133)

(109) R = CO_2Et, R' = Ph, R" = H

Similar conditions were employed in the catalytic hydrogenation of each of the nitrosoindolizines, although the quantity of solvent was variable in each reduction. From the n.m.r. spectrum of these reduction mixtures an approximate quantitative estimation has been made of each product. The ring-opened products show a downfield aromatic signal at ca. τ1.5 corresponding to the pyridyl 6-H proton and comparison of the integrated signal for this proton with that of the upfield aromatic protons of the amine provides a measure of the proportion of nitriles and amine. The saturated proprionitriles were estimated by integration of the aliphatic signals.

In the case of the reduction products from 5-methyl-3-nitroso-2-phenylindolizine (70), which does not possess a pyridyl 6-H proton when ring-opened the proportion of the signals from the amine and the saturated nitrile aliphatic protons were compared. The infra-red spectrum of the reaction mixtures from the ring-opening reactions described all contained a strong C≡N absorption at ca. 2250 cm^{-1} and the absence of this absorption was taken as an indication that no ring-opened products had been formed.

The approximate proportional yields of the products from these catalytic hydrogenations is shown in Table I.

PRECURSOR	% RING-OPENED	% AMINE
3-nitrosoindolizine	71	29
2-methyl-3-nitrosoindolizine	59	39
3-nitroso-2-phenylindolizine	73	27
5-methyl-3-nitroso-2-phenylindolizine	62	38
3-nitroso-1,2-diphenylindolizine	15	85
ethyl 3-nitroso-2-phenylindolizine-1-carboxylate	7	93

Table I. Approximate % yields of amines and ring-opened products formed after standard hydrogenations of certain 3-nitrosoindolizines.

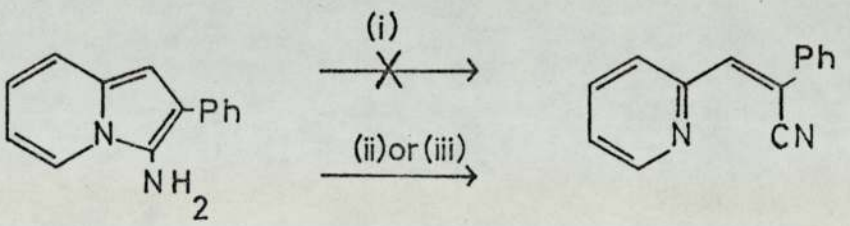
The n.m.r. spectrum of the purified acrylonitrile (130) obtained from the reduction of 3-nitrosoindolizine (65) under these conditions provided evidence for the conformation of the ring-opened products. An AB quartet at τ2.81 and 4.43

was assigned to the 2- and 3- protons of the acrylonitrile, with J=12Hz. After allowing the deuterochloroform solution of this nitrile to stand at room temperature for some hours a second AB quartet began to appear in the n.m.r. spectrum and this was assigned to the trans conformer of the acrylonitrile, with J=16Hz. Thus it is concluded that the first formed acrylonitriles have the pyridyl and nitrile groups in a cis conformation.

The preliminary results [46,47] of the ring-opening reaction suggested that oxidation of the amine formed in the hydrogenator was by the palladium on charcoal. It was expected that the proportion of ring-opened products would decrease when the amine formed bore electron-withdrawing substituents. However, a consistently greater yield of 3-amino-2-methylindolizine (106) as compared with 3-amino-2-phenylindolizine (59) was found and this result could not be rationalised on such terms.

An inspection of the conditions under which 3-amino-2-phenylindolizine (59) underwent ring-cleavage in the presence of palladium charcoal showed that the conditions of the hydrogenation (73% of ring-opened product after one hour) were not comparable with those of refluxing an ethanolic solution of the amine with palladium charcoal (85% of ring-opened product after 18 hours). When an ethanolic solution of 3-amino-2-phenylindolizine (59) was stirred with 20% by weight of palladium on charcoal under an atmosphere of nitrogen, no ring-opened products were formed after one hour and starting material was recovered. When oxygen was passed through a similar reaction for the same period 94% of the acrylonitrile

(61) was isolated. A good yield of the acrylonitrile (61) was also isolated from the reaction of cyclohexene and palladium on charcoal with the amine (59).

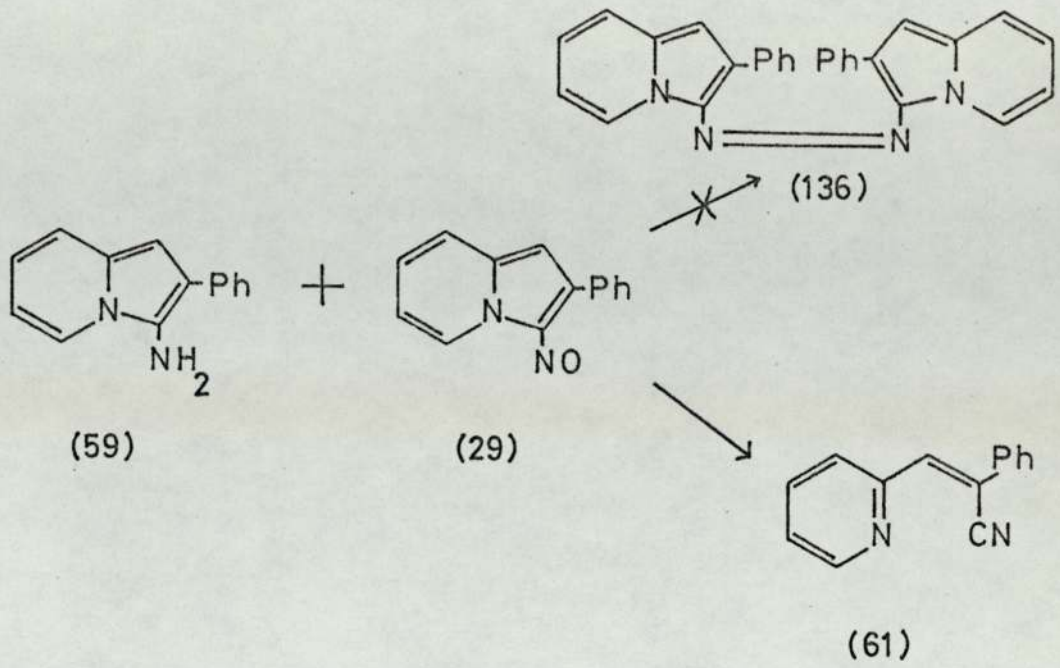


(59) (61)

Reagents: (i) Pd-C; (ii) Pd-C,O_2; (iii) Pd-C,Cyclohexene.

It would appear most unlikely that indolizine amines formed by catalytic reduction become oxidised to any appreciable extent by the palladium on charcoal. Furthermore, if this were the case, very little 3-amino-2-methylindolizine, an amine which is easily oxidised, would be expected in the products from a catalytic reduction.

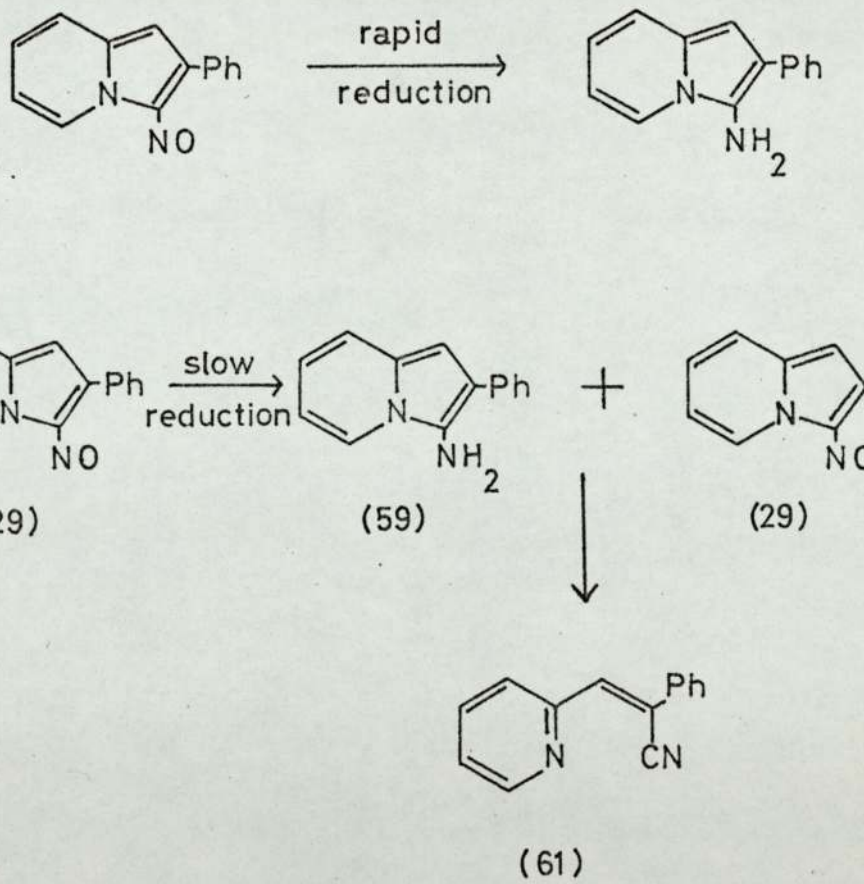
In a separate series of experiments an attempt was made to condense together 3-amino-2-phenylindolizine (59) and 3-nitroso-2-phenylindolizine (29) under neutral conditions in the hope of forming 3,3'-azobis-(2-phenylindolizine)(136). The condensation is normally acid-catalysed but the instability of the amines to acid (see page 62) precluded its use. None of the expected product was isolated but instead a good yield of the acrylonitrile (61) was given.



An equimolar mixture of 3-nitroso-2-phenylindolizine (29) and 3-amino-2-phenylindolizine (59) was stirred with palladium on charcoal in ethanol at room temperature for one hour and gave 71% of the acrylonitrile (61). Inspection of the n.m.r. spectrum of the crude reaction mixture indicated that no amine remained but that ca. 20% of the unchanged nitroso compound was present.

It is considered that the oxidation of the amine under reductive conditions is therefore likely to be caused by reaction with the progenitor nitroso compound. The reduction potentials of some p-substituted nitrosobenzenes indicate that the oxidative power of the nitroso group is enhanced by electron withdrawing substituents.[88] The apparently anomolous result of the proportions of ring-opening of 3-amino-2-methylindolizine and 3-amino-2-phenylindolizine may therefore be rationalised by proposing that although 3-amino-2-methylindolizine may be

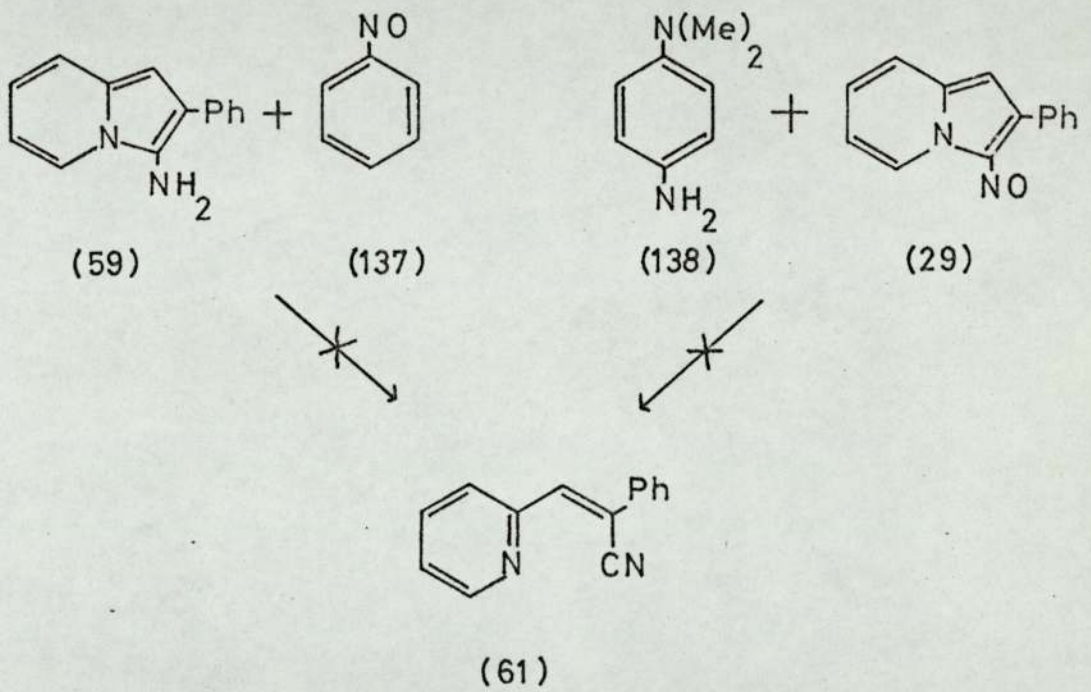
the most easily oxidised of these two amines, its progenitor nitroso-compound is a less powerful oxidising agent. It is therefore expected that the diarylindolizines, although forming stable amines, would possess relatively strongly oxidising nitroso-groups. A balance between these factors therefore explains the results of the hydrogenations. If reduction is rapid (which is more likely with electron-withdrawing substituents) in catalytic hydrogenation, or when a rapid reduction procedure is used, little of the progenitor nitroso-compound will be available for reaction with the amine.



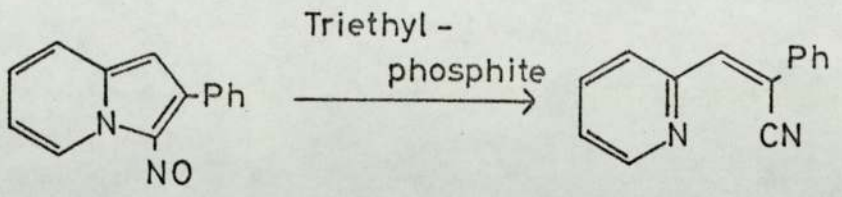
The catalytic reduction of 3-(4-carboxyphenylazo)-2-phenyl-indolizine produced no ring-opened products confirming the

nature of the oxidising species. A similar reduction of 2-methyl-3-nitroindolizine (23) gave the corresponding amine in admixture with the ring-opened products (73) and (132); the intermediate 3-nitroso-compound produced in the reduction[89] presumably being responsible for the oxidation in this case.

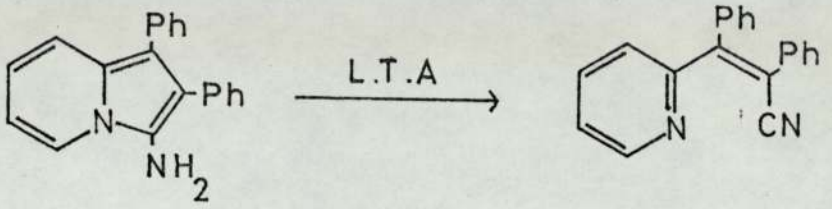
Reactions between 3-amino-2-phenylindolizine (59) and nitrosobenzene (137), and 3-nitroso-2-phenylindolizine (29) and p-amino-N,N-dimethylaniline (138), under neutral conditions were unsuccessful and only starting material was recovered.



The acrylonitrile (61) has been synthesised by the de-oxygenation of 3-nitroso-2-phenylindolizine by triethyl-phosphite and the oxidation of 3-amino-1,2-diphenylindolizine by lead tetraacetate ~~to~~ gives the nitrile (133).



(29) (61)



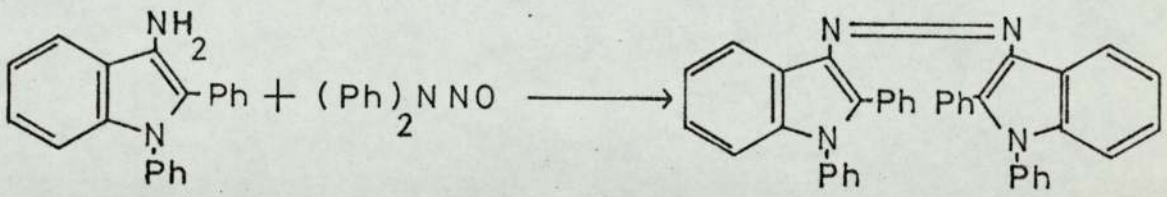
(107) (133)

Both these reagents have been postulated to be capable of generating intermediate nitrenes [87,90,91] and, as recorded above, such an intermediate (60) has been proposed by Irwin and Wibberley [46,47] for the mechanism of this ring-opening.

The mechanism of the ring—cleavage of indolizines which bear a nitrogen substituent at position 3 may be considered best by a comparison of the various conditions under which this cleavage occurs. From such a comparison a common mechanism may be postulated.

The surprising result from the attempted condensation of a 3-nitrosoindolizine with a 3-aminoindolizine has been rationalised in terms of a redox reaction between these two compounds. Normally such a condensation is performed in acetic acid [92] and from a kinetic study [93,94] a rate determining step, in which protonated or acid-activated nitrosobenzene attacks the nitrogen of the aniline, has been postulated. A good correlation between the rate of the reaction and the acidity

has been established, although it is noted that a small positive rate of reaction is predicted at neutrality. The kinetics in unbuffered conditions were found to be complex and the existence of a secondary mechanism of reaction was proposed.[94] The mechanism of condensation of aromatic nitroso compounds and arylhydrazines has been found to be most complicated and many anomolous results are recorded.[89] There appears to be good evidence that the aromatic nitroso compound is acting as an oxidising agent in some of these reactions,[95] and it may therefore be possible that the secondary mechanism occurring in the condensation of aryl amines and nitroso compounds may be due to a similar redox reaction. There are a number of examples recorded of oxidation by aromatic nitroso compounds.[96,97] One which is relevant to the redox system encountered in the reaction between 3-aminoindolizines with 3-nitrosoindolizines is tnat of the oxidation of the 3-aminoindole (139).[98] Reaction of 3-amino-1,2-diphenylindole (139) with N-nitrosodiphenylamine (140) was reported to give the cis azo-compound (141) by an oxidative process.



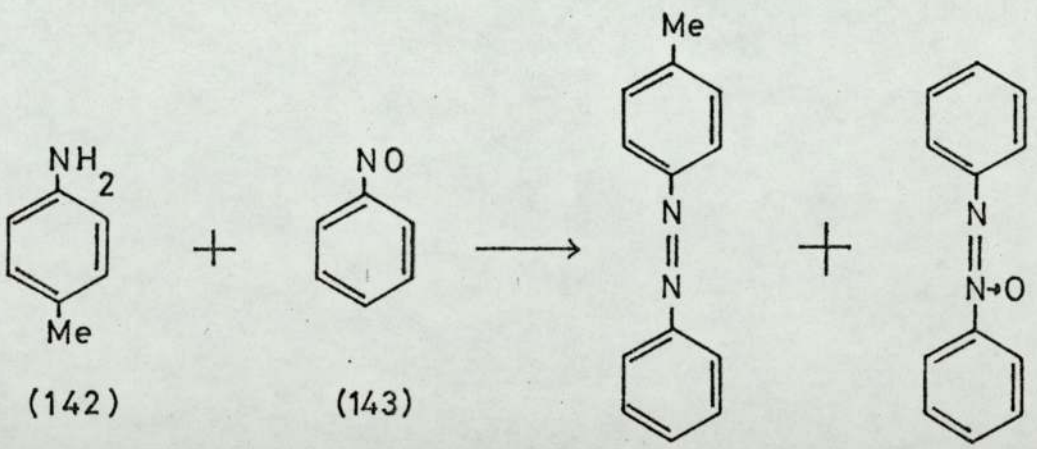
(139) (140) (141)

It is relevant to note that this azo-compound (141) could not be synthesised by the condensation of the amine (139) with its progenitor nitroso compound. The same cis azo-compound (141) was isolated from the mother liquors of a recrystallisation of

3-nitroso-1,2-diphenylindole and from the catalytic reduction of 3-nitroso-1,2-diphenylindole.

Azo-compounds have been formed by the oxidation of substituted anilines by manganese dioxide,[99,100] phenyl iodosoacetate,[101] lead tetraacetate [102] and chloramine.[103] The mechanism of these reactions is obscure, but it has been suggested that nitrenes are possible intermediates.[104]

An investigation of the products of reaction formed by the reaction of an aromatic amine and an aromatic nitroso compound under neutral conditions has been undertaken during the present work, by reacting p-toluidine (142) and nitrosobenzene (143) together at room temperature. p-Toluidine was chosen because of its relative ease of oxidation,[102] and also because the methyl group would act as a 'marker' in the analysis of the source of products. Analysis of the mixture was made by chromatography and n.m.r. and mass spectroscopy.

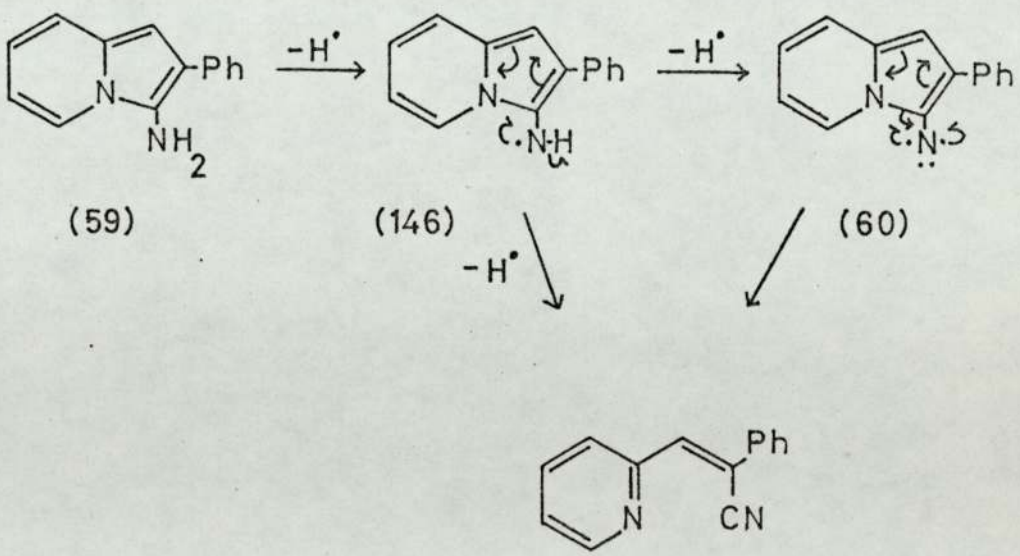


(142) (143) (144) (145)

Both cis and trans 4-methylazobenzene (144) were isolated together with azoxybenzene (145) and a large quantity of starting material. No 4,4'-dimethylazobenzene was isolated

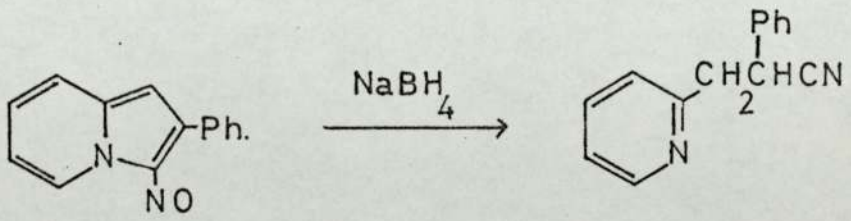
which could have arisen from the dimerisation of an oxidised form of p-toluidine, and the azo-compound (144) formed can be accounted for by a normal condensation. The high yield of azoxybenzene(145)is considered to be indicative of the reaction of nitrosobenzene as an oxidising agent in this reaction. It is known that azoxybenzene (145) is rapidly formed by the reaction of nitrosobenzene and phenylhydroxylamine,[89,105] and thus it appears that reduction of a proportion of nitrosobenzene to phenylhydroxylamine takes place under these conditions. The nitroso group is reported to react with many free radicals [89,105] and hydrogen radical abstraction to form phenylhydroxylamine has been reported.[106]

If the reduction of 3-nitrosoindolizines takes place in a similar manner then both an amino radical (146) or nitrene (60) may be postulated in the oxidation of the 3-aminoindolizines, both of which could give rise to the nitrile (61) by rapid bond isomerisation.



The product of this reaction would also be a 3-hydroxylaminoindolizine. Since none of this product was isolated from any of these reactions, nor the 3,3-azoxyindolizine, which may have been formed from the condensation of the nitroso and hydroxylaminoindolizines, it was considered that either the loss of water to form the acrylonitrile or further reduction to amine may be occurring. Hydroxylamino compounds are known to be intermediates in the reductions of nitroso compounds to amines and the condensation reaction with the nitroso compounds is suggested to account for the azoxy compounds found in reductions.[89] The α-elimination of water from the aromatic hydroxylamines gives rise to an aryl nitrene.[107] Under reductive conditions it is probable that an intermediate 3-hydroxylaminoindolizine will be reduced to an amine. Under weak or non-reductive conditions α-elimination to form the nitrene (60) may occur.

The synthesis of 3-hydroxylamino-2-phenylindolizine was therefore attempted by the use of mild reducing agents. Reduction by zinc and ammonium chloride could not be brought about and sodium borohydride gave solely 2-phenyl-3-(2-pyridyl) propionitrile (40).

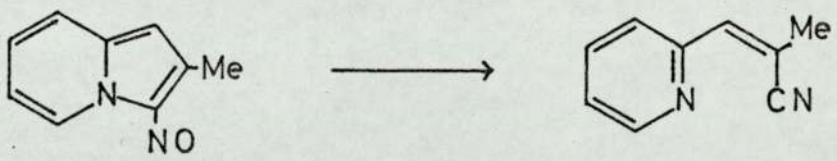


(29) (40)

Failure to isolate the 3-hydroxylaminoindolizine from these mild conditions suggested it to be a labile intermediate.

The reduction of aromatic nitro compounds by sodium borohydride has been shown to give good yields of azoxy compounds through a suggested hydroxylamine-nitroso condensation.[108]

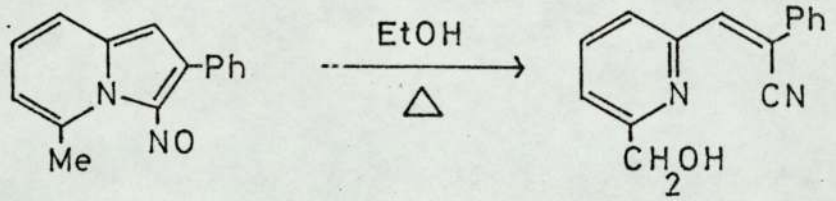
In summary, it has been shown that oxidative cleavage of 3-aminoindolizines under otherwise reductive conditions is by the progenitor 3-nitrosoindolizines. It is suggested that labile 3-hydroxylaminoindolizines are formed which may themselves ring open by α-elimination and bond isomerisation or may become reduced to the corresponding amines, according to the conditions. Before a consideration of the mechanism of this ring-opening, it is pertinent to recall the failure to isolate 1,2-dimethyl-3-nitrosoindolizine and the similar occasional failure with 2-methyl-3-nitrosoindolizine (72). In the latter case (page 28) 2-methyl-3-(2-pyridyl)acrylonitrile (73) was isolated in low yield.



(72) (73)

The alkylindolizines are normally prone to oxidation and it therefore appears that an autoxidation caused by the nitroso group is the reason why 1,2-dimethyl-3-nitrosoindolizine could not be isolated. A similar redox reaction of 3-nitroso-1,2-diphenylindole was reported above (page 78), and in this case it appears that dimerisation of an intermediate takes place, whereas with the indolizines bond isomerisation occurs.

A similar autoxidation has been found to occur with 5-methyl-3-nitroso-2-phenylindolizine (70). Rapid reductions of this compound consistently gave the corresponding amine contaminated by an acrylonitrile (the mixture showed a strong C≡N absorption in the infra-red spectrum). It was initially considered that this ring-opening was occurring due to a steric hindrance by the 5-methyl group of the approach of hydrogen to the reduction intermediates. Difficulties in preparation of a pure sample of this nitroso compound were experienced, and from the ethanolic recrystallisation liquors a small quantity of 2-phenyl-3-(6-hydroxymethylpyrid-2-yl) acrylonitrile (147) was isolated. Prolonged refluxing of the nitroso compound (70) gave 41% of this acrylonitrile:

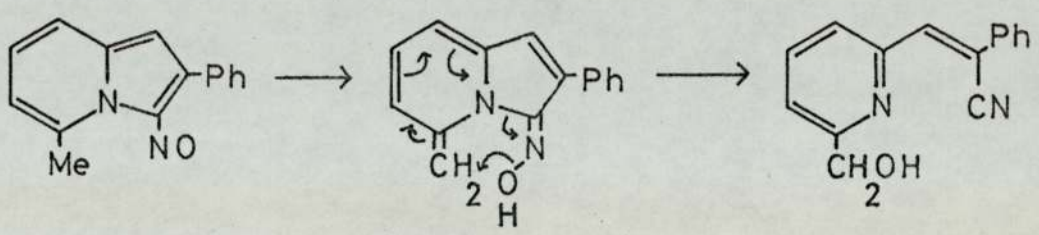


(70) (147)

The infra-red spectrum of the compound showed a strong absorption at 3450 cm^{-1} (O-H) and 2225 cm^{-1} (C≡N). The absence of the 5-methyl signal in the n.m.r. and its replacement by two singlets at τ5.82 and 5.12, the former of which was exchangeable, confirmed the nature of the product, as did the mass spectrum (see page 91).

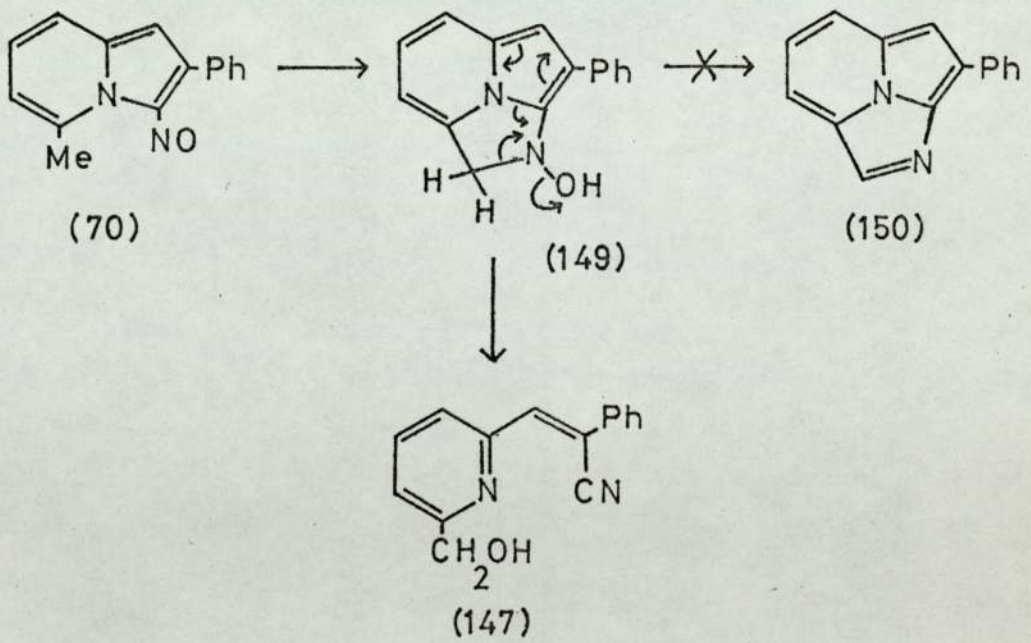
A number of mechanisms may be postulated for this reaction. The reaction of aromatic nitroso-compounds with an active methylene compound, the Erlich-Sachs reaction,[109,110] is base-catalysed, although additional base is not always necessary.

Abstraction of hydrogen by the nitroso-group of (70) may be postulated and this could give the methine (148) which rearranges by a concerted mechanism to give the product (147).



(70) (148) (147)

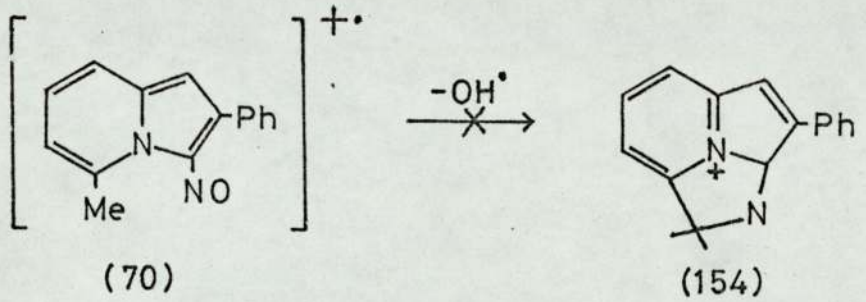
Alternatively, a condensation with the formation of an intermediate tricyclic structure (149) and cleavage of this, since it contains essentially the structure of a 3-hydroxyl-aminoindolizine (see page 81), would by rearrangement give the product (147).



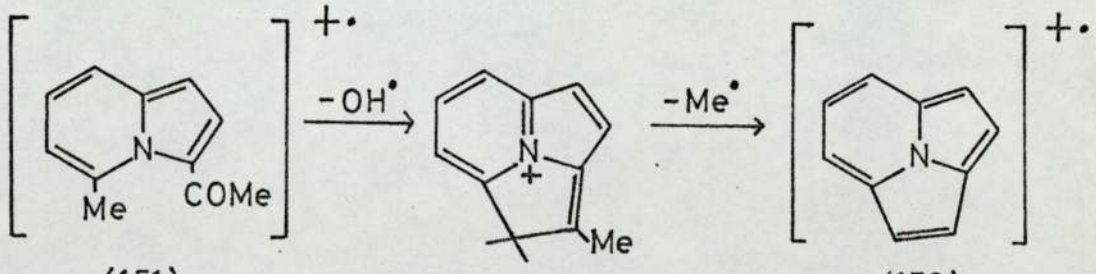
(70) (149) (150) (147)

Attempts to synthesise the 2-azacycl[3,2,2]azine (150) by reaction of the nitroso-compound with piperidine or 5%

sodium hydroxide were unsuccessful. Condensation of several 1- and 3-nitrosoindolizines, including 3-nitroso-2-phenylindolizine, with heterocyclic compounds containing active methylene groups has been reported to take place under these conditions, although low yields are recorded in many cases.[111] It is, therefore, not yet possible to be certain whether a cyclic intermediate is involved in this rearrangement. The mass spectrum of the nitroso compound (70) suggests that a cyclic intermediate (154) is unlikely, whereas good evidence exists for the postulated formation of a cycl[3,2,2]azine structure in the fragmentation of 3-acetyl-5-methylindolizine (151).[9]



(70) (154)

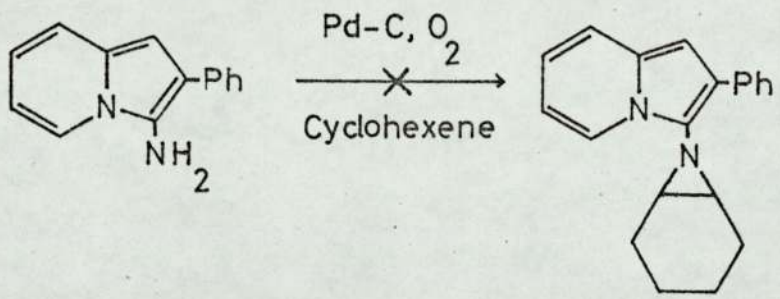


(151) (152) (153)

This suggests that the autoxidation reaction may therefore be intermolecular, although the absence of normal condensation products formed under basic conditions by an intermolecular reaction makes this seem unlikely. The use of a labelled oxygen in the nitroso-group may provide some indication as to the source of oxygen in the product (147).

In all of the neutral ring-openings reported above some assumption of the intermediacy of a nitrene has been made. Evidence for the presence of a nitrene intermediate in any reaction has been most commonly based upon addition to multiple bonds, the abstraction of hydrogen and insertion into a single bond, and dimerisation.[104,112,113] It is usual to attempt an unambiguous proof by the formation of the same products of reaction by a separate route which has been documented to involve a nitrene intermediate.

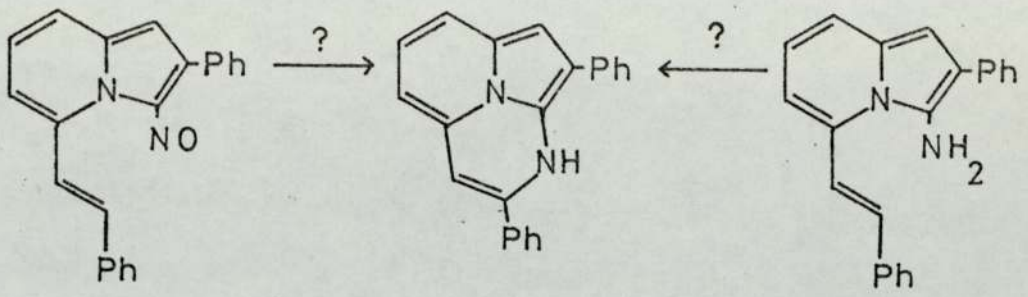
All attempts to trap a possible nitrene from the oxidation reactions of 3-aminoindolizines were unsuccessful. The atmospheric oxidation of 3-amino-2-phenylindolizine over palladium on charcoal in the presence of cyclohexene gave none of the aziridine (155).



(59) (155)

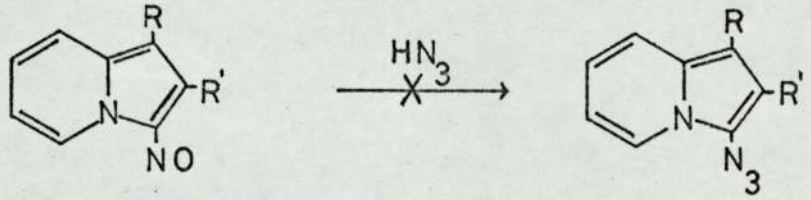
No insertion of a possible nitrene into the 5-methyl group occurred when 3-amino-5-methyl-2-phenylindolizine (111) was oxidised. Attempts to synthesise 5-styryl-2-phenylindolizine were unsuccessful, and it had been hoped to made both the 3-nitroso and 3-amino derivative of this (156) and (157) and to generate a possible nitrene (by deoxygenation of the nitroso-group and oxidation of the amino group) for insertion

into the styryl double bond:



(156) (157)

Generation of a 3-nitrenoindolizine from the photolysis or thermolysis of a corresponding 3-azidoindolizine was envisaged but the synthesis of 3-azido-2-phenyl- (158) and 3-azido-1,2-diphenylindolizine (159) by the reaction of the corresponding 3-nitroso-compounds with hydrazoic acid were unsuccessful.



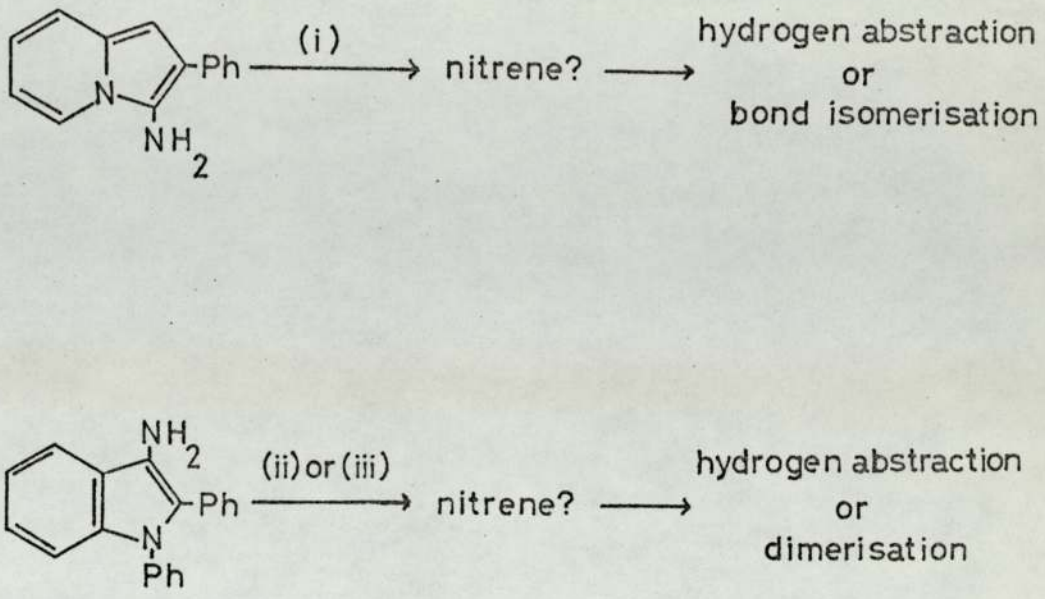
(29) R = H, R' = Ph (158)
(66) R = R' = Ph (159)

The failure of this reaction may be due to the insufficient electrophilicity of the nitroso-nitrogen because of its attachment to a π-excessive ring. Electron-withdrawing groups are reported to enhance the reaction.[114]

The failure to establish the intermediacy of a nitrene by these reactions was not entirely surprising. No positive evidence has yet been provided to prove the existence of C-nitrenes derived from aromatic amines [113] and when such an intermediate is postulated it is often because no other intermediate fits the experimental data so well. The

formation of a common product from different routes, some of which involve procedures known to generate nitrenes, cannot be provided as evidence that the other routes similarly form intermediate nitrenes. Thus the 3-substituted indolizines, which are precursors to the acrylonitriles, although undergoing reactions which elsewhere are postulated to involve a nitrene intermediate, cannot definitely be proposed to have such an intermediate. It is difficult, however, to formulate other mechanisms. The oxidation of aromatic amines to azo-compounds is said to be unlikely to involve a nitrene intermediate,[103,104,112] although thermolysis or photolysis of arylazides and deoxygenation of nitro or nitroso-compounds by triethyl-phosphite, both reactions which are postulated to generate nitrenes, give azo-compounds in good yield.[90,112,115]

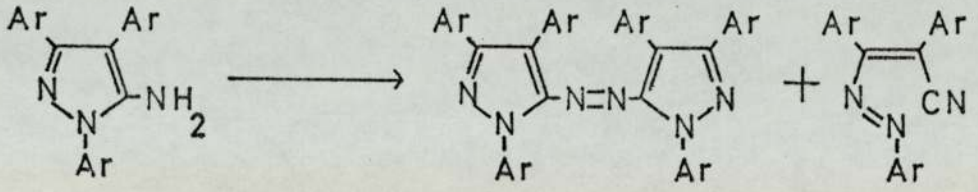
Most of the criteria for defining the presence of a nitrene intermediate is based upon its chemical reaction. Subsequent behaviour of a nitrene intermediate is vitally dependent upon both the inherent stability of the nitrene [104] and upon the nature of the medium in which it is generated.[115] If the oxidation of 3-aminoindolizines give rise to such an intermediate, then bond isomerisation is the most favoured pathway for it to react rather than dimerisation. A similar mechanism may be involved in the oxidation of 3-aminoindoles and here dimerisation would appear to be favoured,[98] although hydrogen abstraction is possible by both:



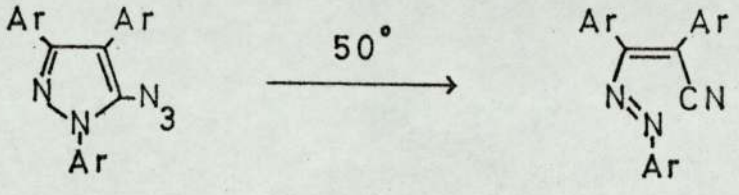
Reagents:
(i) 3-Nitroso-2-phenylindolizine
(ii) N-Nitrosodiphenylamine
(iii) 3-Nitroso-1,2-diphenylindole under reductive conditions

If the involvement of a nitrene in such oxidations is considered unlikely, the mechanism of the reactions therefore become obscure. Some evidence for the involvement of an amino radical has been presented[5], and dimerisation of this radical to form hydrazo-compound, and their subsequent oxidation to azo-compounds, has been suggested. Preliminary accounts [117] of the oxidation of a group of 5-aminopyrazoles (160) with potassium permanganate and the thermolysis of 5-azidopyrazoles,(163) suggests that, because of the difference of products, oxidative ring-cleavage (160 ⟶ 162) is *via* an amino radical and not a nitrene. Generation of the nitrene from the 5-azidopyrazole (163) gives the ring-opened product but no azo-compound (161). However, conditions for

these reactions are not known and again it is difficult to accept any firm conclusions as to the mechanism of the oxidation.



(160) (161) (162)



(163) (162)

Although it is not possible to define the nature of the intermediate in the oxidation of 3-aminoindolizines, it is probable that it has common characteristics with those intermediates formed in the oxidation of many other aromatic amines and like them, its precise nature is as yet obscure.

MASS SPECTRA

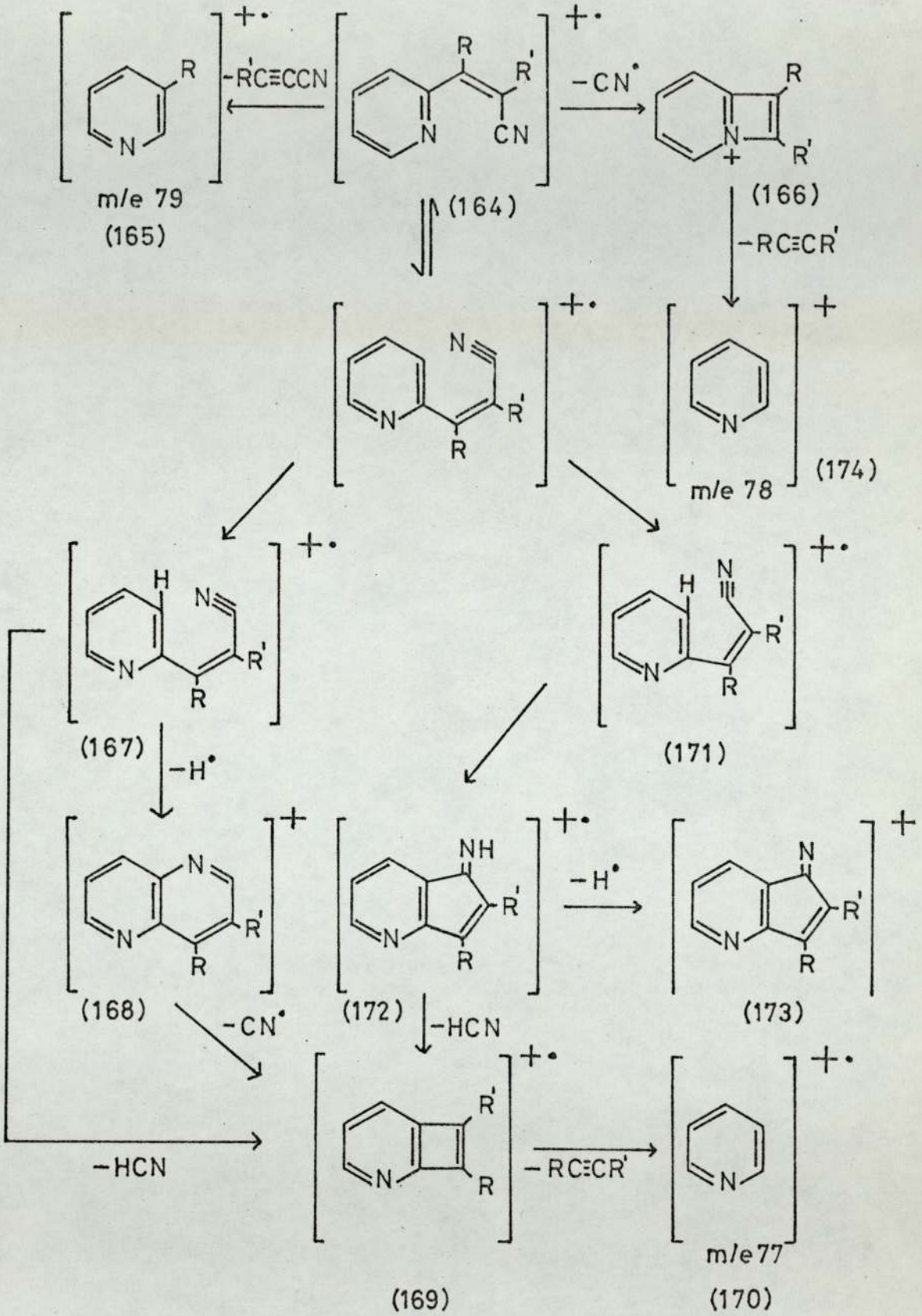
The mass spectra of several 3-nitroso-, 3-nitro-, 3-amino- and 3-acetamidoindolizines are recorded. The mass spectra of several 3-(2-pyridyl)acrylonitriles derived from the 3-amino-indolizines are also recorded and an attempt is made to show possible common pathways of fragmentation for all these classes of compounds. Postulation of fragmentation patterns is in several cases based upon ion source determinations and accurate mass measurements.

(i) 3-(2-pyridyl)acrylonitriles

The base peak of the 3-(2-pyridyl)acrylonitriles is not the molecular ion. The spectra of 2-methyl-, 2-phenyl-, 2,3-diphenyl and 2-phenyl-3-(6-methylpyrid-2-yl)acrylonitrile show a base peak at (M-1); the parent acrylonitrile at m/e 79 (M-51) and 2-phenyl-3-(6-hydroxymethylpyrid-2-yl)acrylonitrile at m/e 219 (M-17). The former four compounds show a trend in the abundance of the molecular ion according to the nature of the substituents. Thus 2-methyl-3-(2-pyridyl)acrylonitrile shows a M^+ of 85% abundance, the 2-phenyl a 60% and 2,3-diphenyl a 47% abundance of the molecular ion.

The fragmentation of the compounds initiated by an initial M-H loss is postulated to proceed via either pathways (1) or (2) as shown in scheme 1. Pathway 1 is favoured because of the formation of an aromatic structure (168). The fragmentation to an ion at(M-27) (169) initiated by the loss of HCN from the parent is observed only in the spectrum of the parent acrylonitrile and 2-methyl-3-(2-pyridyl)

SCHEME 1

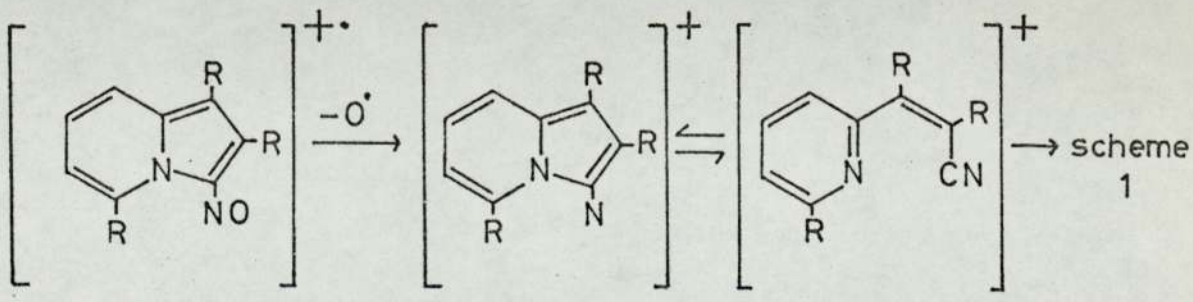

-R'C≡CCN
-CN•
m/e 79
(165)
(164)
(166)
-RC≡CR'
m/e 78
(174)
(167)
-H•
(171)
(168)
-CN•
(172)
-HCN
-H•
(173)
-HCN
-RC≡CR'
m/e77
(169)
(170)

acrylonitrile. It is probable that the structure (168) will be stabilised in the case of the aryl compounds, and that an HCN loss from (167) or possibly (171) is more likely when R=H or alkyl. Fragmentation to the ion (166) by CN loss appears to be favoured when R=H or alkyl. The base peak of the parent acrylonitrile is at m/e 79 (M-51) and is postulated to arise from a loss of a molecule of cyanoacetylene from the molecular ion.

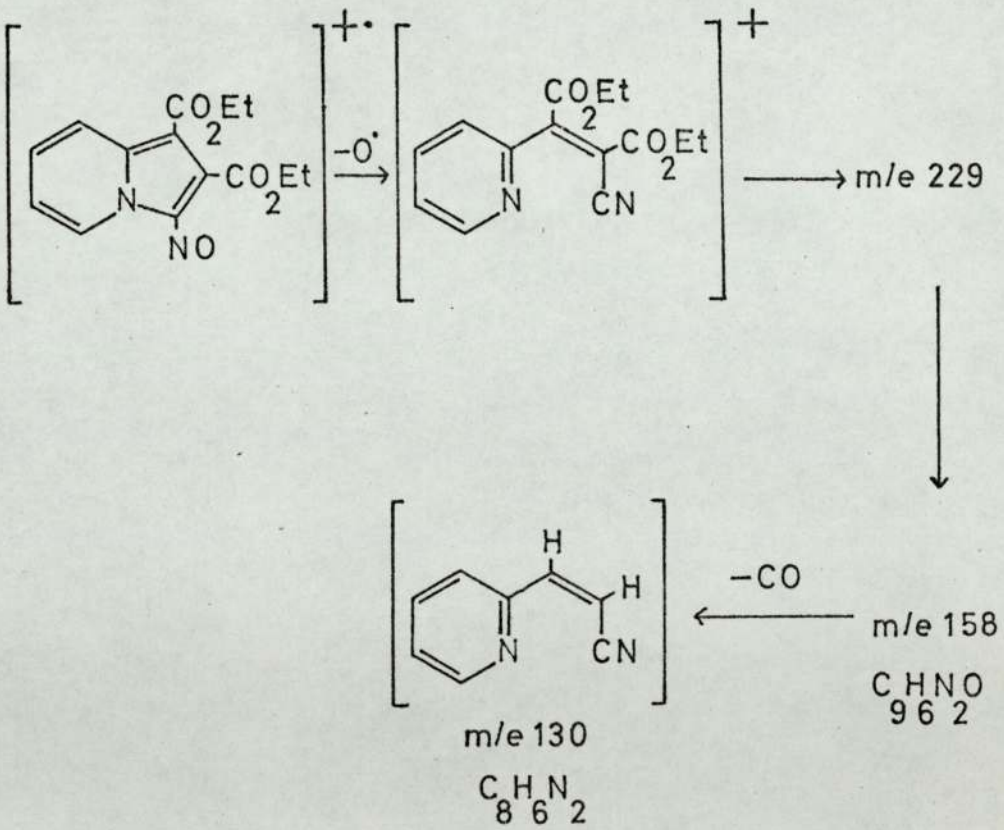
(ii) 3-Nitrosoindolizines

The mass spectra of the 3-nitrosoindolizines showed three common major losses from the parent ion: loss of nitric oxide (M-30), of oxygen (M-16) and an (M-17) which appears to be a hydrogen loss from the (M-16) ions. The loss of the functional group (M-NO) is most apparent in the case of the parent 3-nitrosoindolizine and the base peak at m/e 116 corresponds to this. The abundance of the (M-30) ions decreases with electron-withdrawing substituents.

The loss of oxygen from the parent ions appears to be favoured by electron withdrawing substituents. The aryl-3-nitrosoindolizines (with the exception of 5-methyl-3-nitroso-2-phenylindolizine) have as their base peak the (M-17) ion, and each of the 3-nitrosoindolizines which show the (M-16) ion also have an (M-17) ion. The subsequent losses from the (M-16) ions suggest these ions to be isomeric with the 3-(2-pyridyl)acrylonitrile:

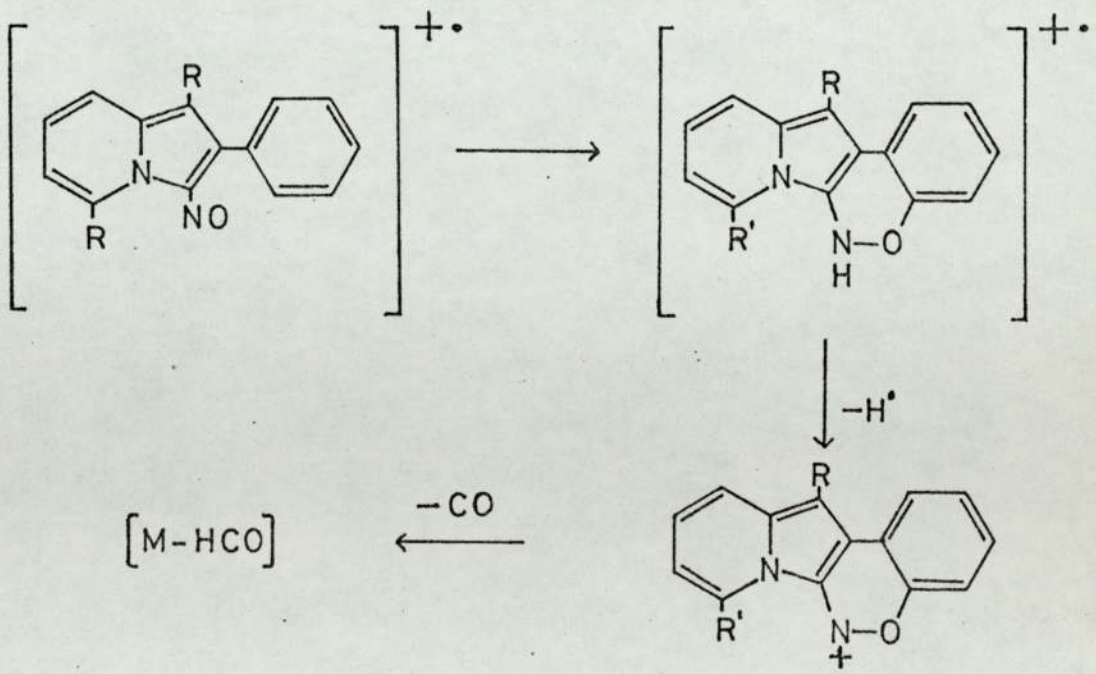


The initial fragmentations of the ethyl 3-nitrosoindolizine-1-carboxylates appear to arise from the ester function. Ethyl 3-nitroso-2-methylindolizine-1-carboxylate shows an (M-72) loss, whereas the corresponding 2-phenyl-compound shows an initial (M-73) loss. Jones and Stanyer [9] reported an (M-72) loss from the molecular ion of ethyl 2-methylindolizine-1-carboxylate, and suggested an initial transfer of H to the peri position. The spectrum of diethyl 3-nitrosoindolizine-1,2-dicarboxylate (69) is complex and shows a base peak at m/e 130 (M-160). Ion source determinations and accurate mass measurements indicate this ion to have arisen by a complicated process from an ion at m/e 158.

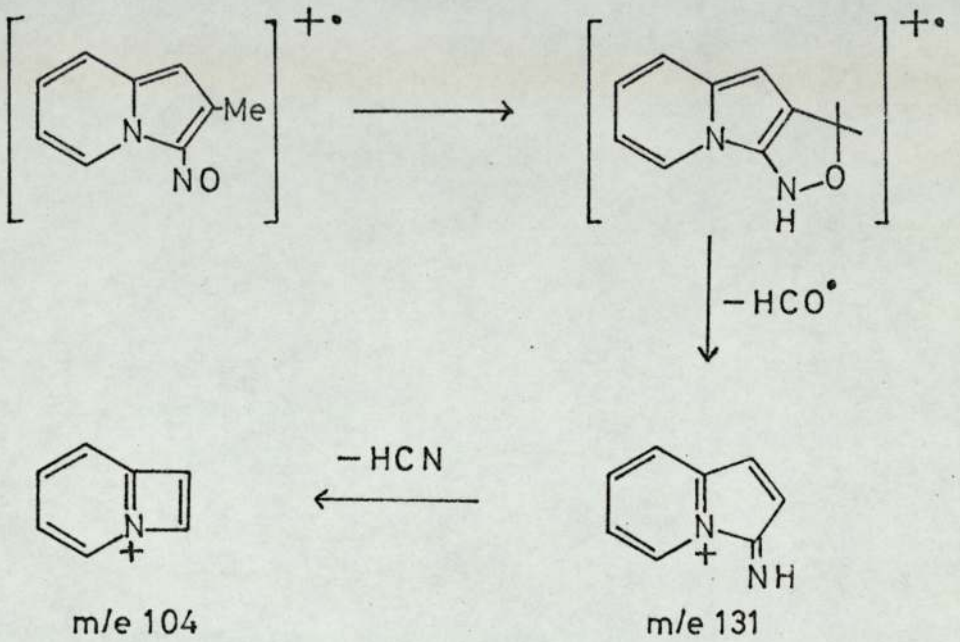


Although isomeric with 3-(2-pyridyl)acrylonitrile, this ion at m/e 130 does not follow a similar fragmentation pattern to the acrylonitrile (see page 91), and thus the expected cyonoacetylene loss to give an ion at m/e 79 is not apparent. The ion source determinations indicate that a loss of oxygen from the parent ion to give an ion at m/e 274 is substantial and initiates subsequent fragmentation. An M-16 ion at m/e 274 is not visible in the spectrum however. Intermediate structures are difficult to suggest, especially that of the ion at m/e 158.

There appears to be some evidence for a rearrangement of the type found in the spectrum of o-nitrotoluene [118] in the spectra of 3-nitroso-2-methyl, 3-nitroso-2-phenyl, 3-nitroso-1,2-diphenyl- and 5-methyl-3-nitroso-2-phenylindolizine. An (M-1) ion and the subsequent loss of carbon monoxide to an (M-29) ion is present in the spectra of the 2-aryl-3-nitroso-indolizines and these losses suggest a fragmentation pattern arising from a cyclic structure of the type shown:



The spectrum of 3-nitroso-2-methylindolizine shows a 29% abundance of an ion m/e 131 (M-29) and this loss of HCO from the parent is confirmed by a metastable ion at m/e 107.5, and by ion source determinations. This loss is postulated to involve the formation of a cyclic structure, similar to those above.



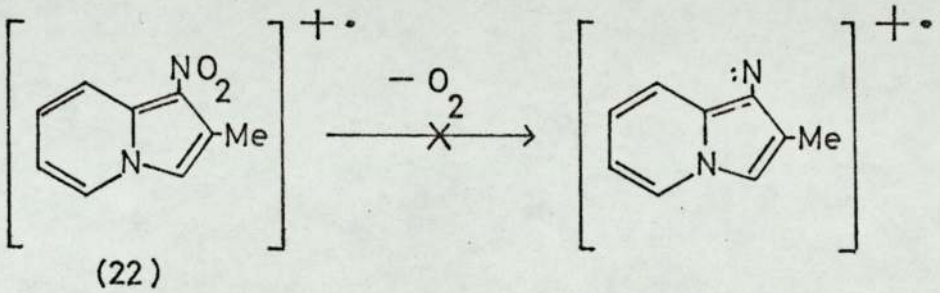
m/e 104 m/e 131

The loss of HCN from the ion at m/e 131 to give an ion at m/e 104 is confirmed by an ion source determination. Similar losses occur in the spectra of 2-methyl-3-nitroindolizine and 2-methyl-1-nitroindolizine.

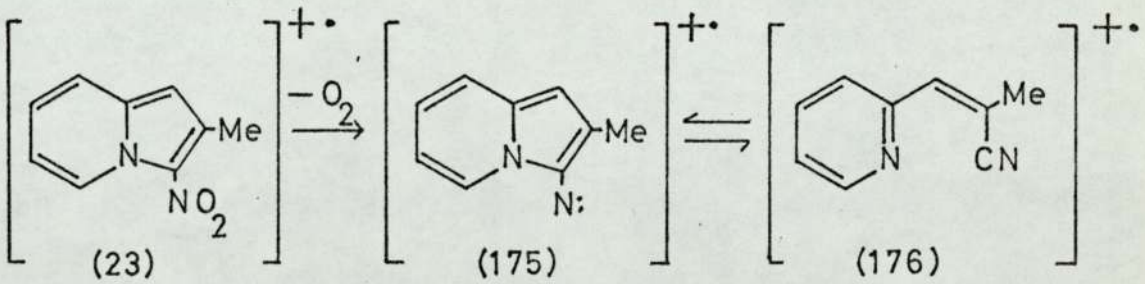
(iii) Nitroindolizines

The major breakdown pathways of the 1- and 3-nitro-indolizines are very similar to those observed in other aromatic nitro-compounds. Thus, the initial loss of oxygen, nitric oxide and the total loss of the nitro group from the molecular ion initiate the major fragmentation patterns.

Loss of oxygen to give the corresponding nitroso-compound initiates a fragmentation pattern similar to that of the corresponding nitroso-compounds (see above). An important difference is observed between the subsequent fragmentations of the ($M-O_2$) ions arising from 2-methyl-3-nitroindolizine (23) and 2-methyl-1-nitroindolizine (22). The former compound (23) loses oxygen in a pattern similar to 2-methyl-3-nitroso-indolizine, to give the structure (175) which is isomeric with the acrylonitrile (176). No such oxygen loss is observed in the spectrum of 2-methyl-1-nitroindolizine.



(22)

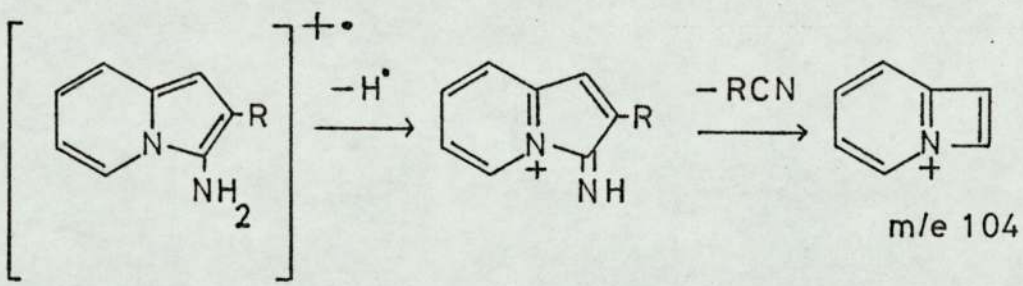


(23) (175) (176)

The loss of OH from the methyl nitroindolizines (22) and (23) is similar to that seen in the spectrum of o-nitrotoluene,[118] and the subsequent fragmentation is also similar to that postulated for the nitrosoindolizines (see above).

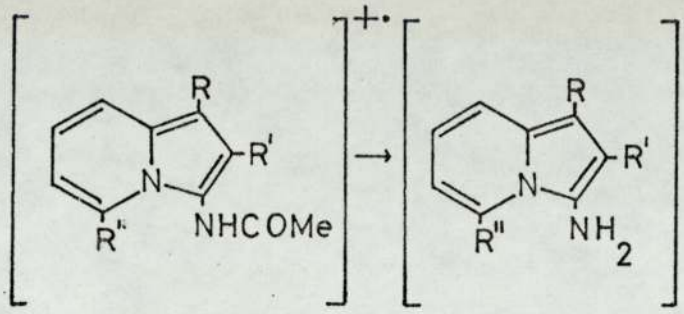
(iv) 3-Aminoindolizines

The mass spectra of the 3-aminoindolizines are similar to the spectra of other aromatic amines, and the major losses are of HCN and H_2CN from the molecular ion. The loss of H_2CN is favoured by electron-donating substituents. Loss of one and two hydrogens is also observed, and again is generally favoured in the 3-aminoindolizines with electron-donating substituents. An exception is ethyl 3-amino-2-phenylindolizine -1-carboxylate which has a base peak corresponding to M-1. The m/e 104 ion is common to the spectra of 3-aminoindolizine, 3-amino-2-methylindolizine and 3-amino-2-phenylindolizine and is postulated to arise from the fragmentation of the (M-1) ion by loss of R-CN.



The base peak in the spectrum of the parent amine is at m/e 79 (M-53) and it is postulated that this may arise from the fragmentation of an (M-2) ion caused by loss of hydrogen and then of cyanoacetylene. The m/e 79 ion is also prominent in the spectra of 3-nitrosoindolizine, 3-nitroindolizine and 3-(2-pyridyl)acrylonitrile, all of which may give ions isomeric with that derived from the acrylonitrile:

The base peak is at (M-43) for all the 3-acetamidoindolizines except ethyl 3-acetamido-2-phenylindolizine-1-carboxylate, which has a base peak at (M-42). Direct loss of ketene (M-42) is apparent in all the spectra under consideration here and appears to be favoured by electron-withdrawing groups, which will stabilise the amine formed.



R	R'	R''	I% (M-42)
Me	Me	H	13
H	Me	H	17
H	Ph	H	26
H	Ph	Me	26
Ph	Ph	H	30
CO_2Et	Ph	H	100

A loss of $(R\text{-}C{=}C{=}NH)^{\bullet}$ occurs from the 3-acetamidoindolizines after acetyl or ketene-1 loss, i.e. (M-43) losses.

The mass spectrum of 3-diacetamido-2-phenylindolizine indicates an initial loss of ketene from the molecular ion to give the 3-acetamido-2-phenylindolizine which then loses an acetyl radical. 1-Acetyl-3-acetamido-2-methylindolizine first loses an acetyl radical and then ketene, which indicates, by a comparison with the spectrum of 3-acetamido-2-methyl-indolizine (50), that the acetyl is most probably lost from the ring and ketene from the acetamido group in the usual way.

EXPERIMENTAL

Infra-red spectra were determined as chloroform solutions, unless otherwise stated, with a Unicam S.P. 200 spectrophotometer.

Nuclear magnetic resonance spectra were determined, unless otherwise stated, with tetramethyl-silane as internal standard, on a Varian A60-A spectrometer. All the peaks are assigned in terms of τ values. Abbreviations used in the interpretation of n.m.r. spectra are:
s = singlet; d = doublet; t = triplet; q = quartet;
m = multiplet; J = coupling constant; a = removed on deuteration.

Mass spectra were determined on an A.E.I. MS9 spectrometer, operating at 100 μa and 70 eV. $\underline{M}^+$ signifies the molecular ion peak. Abbreviations used in the results of ion source determinations are v = very; s = small; m = medium; l = large to describe the size of the deflection of the collector meter. The figures refer to the value of the scan kV.

Melting points are uncorrected. Reaction temperatures are those of an external oil bath.

Indolizine (1) was prepared by the method of Boekelheide and Windgassen,[27] m.p. 73-74°, colourless plates (from the minimum of methanol).

The n.m.r. and mass spectra of indolizine have been recorded elsewhere.[8,9]

3-Acetylindolizine (102).— Indolizine (3.5 g) was refluxed with acetic anhydride (3.0 cm^3) and fused sodium acetate (2.4 g) in toluene (10 cm^3) for 4 h. After the removal of solvent and excess acetic anhydride, the mixture was extracted with light petroleum (b.p. 40-60°) to give the acetylindolizine (3.2 g, 81%) as a yellow oil, b.p. 286° (decomp.) (lit., 288°).[119]

ν_{max} 1725 (C=O) cm^{-1}

$\tau(CDCl_3)$ 7.61(3H,s,3-COMe), 3.67(1H,d,J=5Hz,1-H),
3.3(1H,m,6-H), 2.9(1H,m,7-H),
2.6(1H,m,8-H), 2.67(1H,d,J=5Hz,2-H),
0.22(1H,d,J=6.5Hz,5-H).

3-Nitroindolizine (74).— A mixture of fuming nitric acid (d 1.5) (2.0 g, 1.5 equivalents) and acetic anhydride (5.0 cm^3) was added dropwise to a stirred solution of indolizine (2.4 g) in acetic anhydride (20 cm^3) cooled in an acetone - solid carbon dioxide bath. After the final addition the mixture was stirred for a further 0.5 h, then poured onto crushed ice and neutralised with 40% aqueous potassium hydroxide solution. The neutral solution was extracted with ether and the combined extracts dried ($MgSO_4$). Removal of the solvent gave a dark tar which was chromatographed on a

column of basic alumina, with benzene as eluent. The broad, yellow band which developed was collected, and, after removal of solvent, gave the nitroindolizine (0.92 g, 28%), yellow needles, m.p. 93-94° (from light petroleum b.p. 60-80°).

(Found: C,59.5; H,3.9; N,17.1; M^+,162. $C_8H_6N_2O_2$
requires: C,59.3; H,3.7; N,17.3; M^+,162).

ν_{max} 1510,1350 (NO_2) cm^{-1}.

$\tau(CDCl_3)$ 3.39(1H,d,J=5Hz,1-H), 2.6(3H,m,6-,7-, and 8-H)
2.19(1H,d,J=5Hz,2-H), 0.4(1H,d,J=7Hz,5-H).

3-Nitrosoindolizine (65).— A solution of sodium nitrite (2.8 g) in water (15 cm^3) was added dropwise to a solution of indolizine (4.7 g) in concentrated hydrochloric acid (20 cm^3) and water (10 cm^3) over 0.25 h at 0°C. The mixture was stirred at this temperature for 0.5 h and neutralised by the addition of a saturated aqueous solution of sodium bicarbonate. The mixture was extracted with chloroform (5x50 cm^3); the extracts combined and dried ($MgSO_4$). Removal of the solvent gave a dark tar which was chromatographed on a column of neutral alumina, with a mixture of benzene and ethyl acetate (1:2) as eluent. The green fraction was collected and the solvent removed to give the nitrosoindolizine (0.83 g, 14.5%), green needles, m.p. 39.5-41° (from petroleum ether).

The product became tarry on prolonged heating in hot solvents and a sample suitable for analysis could not be prepared.

(Found: $\underline{M}^+$, 146.04801; $C_8H_6N_2O$
requires: $\underline{M}^+$, 146.04813).
ν_{max} 1620 (N=O) cm^{-1}.
$\tau(CDCl_3)$ 3.21(1H,d,J=5Hz,1-H), 2.9(1H,m,6-H), 2.4(2H,m,7-, and 8-H), 1.94(1H,d,J=5Hz,2-H), -0.21(1H,d,J=6.5Hz,5-H).

3-Aminoindolizine (105).— Hydrazine hydrate (1.0 cm^3) was added dropwise to a vigorously stirred solution of 3-nitrosoindolizine (1.0 g) under reflux in ethanol (20 cm^3) and containing 10% palladium charcoal (0.2 g). After the evolution of gas had ceased, the mixture was filtered rapidly through celite and the solvent removed under reduced pressure (at a temperature not exceeding 50°) to give the aminoindolizine (0.79 g, 87.5%) as a yellow gum. On exposure to the atmosphere, the product rapidly decomposed, giving a dark tar.
(Found: $\underline{M}^+$, 132.06874. $C_8H_8N_2$
requires: $\underline{M}^+$, 132.06850).
ν_{max} 3350, 3300 (NH_2) cm^{-1}.
A sufficiently resolved n.m.r. spectrum was unobtainable.

Attempted Acetylation of 3-Aminoindolizine.— Freshly prepared 3-aminoindolizine (0.5 g) in dry ether (30 cm^3) was stirred at room temperature with acetic anhydride (1.0 cm^3). Removal of the solvent after 6 h gave an intractable tar.

Attempted Schmidt Reaction on 3-Acetylindolizine.— A solution of 3-acetylindolizine (1.59 g) in a solution of hydrazoic acid in chloroform (6.0 cm^3, 1.2 equivalents) was added dropwise over 0.25 h to a stirred mixture of chloroform (20 cm^3) and

concentrated sulphuric acid (10 cm^3) at -5°. After a further 0.5 h, the mixture was poured onto ice, neutralised with 40% aqueous potassium hydroxide solution, and the chloroform solution separated off and dried ($MgSO_4$). Removal of the solvent and chromatography on a column of neutral alumina, with benzene as eluent, gave the unchanged acetyl compound (1.43 g, 90%). Although many coloured bands developed during chromatography, none afforded sufficient material for analysis.

2-Methylindolizine (12) was prepared by the method of Holland and Naylor,[20] m.p. 59°.
The n.m.r. and mass spectra of 2-methylindolizine have been recorded elsewhere.[8,9]

3 Acetyl-2-methylindolizine (18) was prepared by the method of Borrows, Holland and Keynon,[42] m.p. 83°.

ν_{max} 1600 (C=O) cm^{-1}.

$\tau(CDCl_3)$ 7.52(3H,s,2-Me), 7.49(3H,s,3-COMe),
3.77(1H,s,1-H), 2.5-3.4(3H,m,6-,7-,and 8-H),
0.06(1H,d,J=7Hz,5-H).

2-Methyl-3-nitroindolizine (23).— A mixture of fuming nitric acid (d 1.5) (0.63 g, 1.5 equivalents) and acetic anhydride (3 cm^3) was added dropwise to a stirred solution of 2-methyl-indolizine (1.43 g) in acetic anhydride (30 cm^3) over 0.25 h, cooling in an acetone - solid carbon dioxide bath. After a further 0.5 h the mixture was poured onto ice and made neutral by the addition of 40% aqueous

potassium hydroxide solution. The neutralised mixture was extracted with chloroform, the extracts combined and dried ($MgSO_4$). Removal of the solvent gave a tarry material which was chromatographed on a column of neutral alumina, with benzene as eluent. Collection of the broad, yellow band which developed, and removal of the solvent, gave the nitroindolizine (0.77 g, 40%) yellow needles, m.p. 103-104° (from aqueous ethanol). The melting point was undepressed on admixture with a sample prepared by the method of Borrows, Holland and Keynon.[25]

ν_{max} 1520, 1345 (NO_2) cm^{-1}.

$\tau(CDCl_3)$ 7.35(3H,s,2-Me), 3.56(1H,s,1-H),
2.3-3.2(3H,m,6-,7-and 8-H),
0.34(1H,d,J=6.5Hz,5-H).

Attempted Nitration of 2-Methylindolizine with Tetranitromethane.— A solution of tetranitromethane (0.98 g) in ethanol (5 cm^3) was added dropwise to a stirred solution of 2-methylindolizine (0.65 g) in pyridine (15 cm^3) at -50°. After stirring for a further 5 min the mixture was washed with 10% HCl (100 cm^3) and extracted into chloroform. Only brown polymeric material could be isolated from these extracts. No evidence for the presence of nitro compounds was available from a thin layer chromatogram.

2-Methyl-3-nitrosoindolizine (72) was prepared by the method of Borrows, Holland and Keynon, [32] m.p. 105° (lit., 106-107°).

ν_{max} 1620 (N=O) cm^{-1}.

$\tau(CDCl_3)$ 7.14(3H,s,2-Me), 3.51(1H,s,1-H),
2.9(1H,m,6-H), 2.6(2H,m,7-and 8-H)
-0.25(1H,d,J=7Hz,5-H).

3-Amino-2-methylindolizine (106).— Hydrazine hydrate (1 cm^3) was added dropwise to a vigorously stirred solution of 2-methyl-3-nitrosoindolizine (1.0 g) under reflux in ethanol (20 cm^3) and containing 10% palladium on charcoal (0.2 g). When the evolution of gas had ceased, the mixture was filtered rapidly through celite. Removal of the solvent and trituration with dry ether, gave the amino-indolizine (0.86 g, 94%), yellow plates, m.p. 38-41°. The product decomposed rapidly on exposure to the atmosphere, or upon prolonged contact with hot solvents.

(Found: $\underline{M}^+$, 146.08512. $C_9H_{10}N_2$
requires: $\underline{M}^+$, 146.08439).

ν_{max} 3350, 3290 (NH_2) cm^{-1}.

$\tau(CDCl_3)$ 7.96(3H,s,2-Me), 7.16(2H,broad s,3-NH_2)[a]
3.92(1H,s,1-H), 3.5(2H,m,6-and 7-H),
2.8(1H,m,7-H), 2.4(1H,m,5-H).

The amine was synthesised in 87% yield, by a similar procedure, from 2-methyl-3-nitroindolizine.

3-Acetamido-2-methylindolizine (50).— A freshly prepared sample of 3-amino-2-methylindolizine (0.5 g) in solution in dry ether (20 cm^3) was stirred at room temperature with acetic anhydride (1 cm^3) (6 h). The removal of solvent

and excess acetic anhydride gave a dark oil, which, on trituration with petroleum ether, yielded the acetamidolizine (0.32 g, 51%), colourless needles (from benzene), m.p. 147-148°, which was undepressed on admixture with a sample prepared by the method of Holland and Naylor.[42]

ν_{max} 3250 (NH), 1680 (C=O) cm^{-1}.

$\tau(CDCl_3)$ 8.32,8.04,7.98,7.80(6H,singlets,2-Me and 3-NHCOMe).
3.1-3.8(3H,m,1-6-and 7-H),
2.1-2.8(3H,m,3-NHCOMe[a],5-and 8-H).

τ(pyridine) 7.76(6H,s,2-Me,3NHCOMe).

τ(d.D.M.S.O.) 7.91(6H,s,2-Me,3NHCOMe).

Attempts to coalesce the methyl singlets (in the spectrum run in $CDCl_3$) were unsuccessful.

3-Acetamido-1-acetyl-2-methylindolizine (47).— 3-Acetamido-2-methylindolizine (0.94 g), acetic anhydride (7.5 cm^3) and sodium acetate (1.5 g) were refluxed together for 6 h. The excess acetic anhydride was removed and the mixture boiled several times with ethylacetate and charcoal. Removal of the solvent and trituration with ether gave the acetamido-acetylindolizine (0.72 g, 63%), colourless needles, m.p. 187-188° (from ethyl acetate) (lit., 190°).[42] Shorter periods of reflux gave the same compound in admixture with starting material.

ν_{max} 3300 (NH), 1660 and 1610 (C=O) cm^{-1}.

τ(d.D.M.S.O.) 7.86,7.73,7.57(9H,singlets,1-COMe,2-Me and 3-NHCOMe).
2.5-3.1(2H,m,6-and7-H), 2.09(1H,d,J=6.5Hz,5-H),
1.80(1H,d,J=9Hz,8-H).

2-Phenylindolizine (13) was prepared by the method of Borrows, Holland and Kenyon,[120] m.p. 215-216°.
No suitable solvent for the determination of an n.m.r. spectrum was available.

3-Acetyl-2-phenylindolizine (19) was prepared by the method of Borrows, Holland and Keynon,[120] m.p. 64-65° (lit., 64.5°).

ν_{max} 1600 (C=O) cm^{-1}.

$\tau(CDCl_3)$ 8.07(3H,s,3-COMe), 3.68(1H,s,1-H),
2.6-3.4(8H,m,2-C_6H_5,6-,7-and 8-H),
-0.03(1H,d,J=6.5Hz,5-H).

Attempted Nitration of 2-Phenylindolizine with Tetranitromethane. — A solution of 2-phenylindolizine (0.2 g) in 2-ethoxyethanol (30 cm^3) was treated with tetranitromethane (0.2 g) at 0°. After 1 h, removal of the solvent gave a dark intractable solid.

Attempted Oxidation of 3-Nitroso-2-phenylindolizine with Peracetic Acid. — Attempts to synthesise 3-nitro-2-phenylindolizine from the nitroso compound using peracetic acid, peracetic acid/hydrogen peroxide or aqueous hydrogen peroxide (90%) were unsuccessful. A solution of 3-nitroso-2-phenylindolizine when treated with peracetic acid (0.4 g) at the reflux for 0.5 h, gave a tar which was chromatographed on a column of neutral alumina, with benzene as eluent. Collection of the first fraction gave the acrylonitrile (61) (0.021 g, 2.3%), and further elution gave the starting material (0.783 g, 78%).

3-(4-Carboxyphenylazo)-2-phenylindolizine (62).— A neutral diazonium salt derived from p-aminobenzoic acid (2.8 g) was added to 2-phenylindolizine (3.8 g) in D.M.F. (200 cm^3) and the mixture stirred at 20° for 4 h. 10% Acetic acid was added to yield the azo-dye (5.1 g, 76%), dark red prisms, m.p. 246° (decomp.) (from 2-ethoxyethanol). (Found: C,74.0; H,4.5; N,12.3; M^+341. $C_{21}H_{15}N_3O_2$ requires: C,74.0; H,4.4; N,12.0; M^+341).

ν_{max} (Nujol) 1690 (C=O).

No suitable solvent was available for the determination of a n.m.r. spectrum.

Attempted Preparation of 3-Azido-2-phenylindolizine (158).— A solution of 3-nitroso-2-phenylindolizine (1.11 g) in absolute ethanol (35 cm^3) was treated with an 8% chloroform solution of hydrazoic acid (5 cm^3, 2 equivalents) at room temperature and left to stir for 24 h. There was no visible evolution of gas during this period and the starting material was recovered on removal of the solvent (100%).

3-Nitroso-2-phenylindolizine (29) was prepared by the method of Borrows, Holland and Keynon,[32] m.p. 98 (lit., 97.5-98°).

ν_{max} 1620 (N=O) cm^{-1}.

$\tau(CDCl_3)$ 3.07(1H,s,1-H), 2.85(1H,m,6-H), 2.45(5H,m,2-C_6H_5), 1.85(2H,m,7-and 8-H), -0.50(1H,d,J=7Hz,5-H).

3-Amino-2-phenylindolizine (59).— Hydrazine hydrate (1.0 cm^3) was added dropwise to a vigorously stirred solution of 3-nitroso-2-phenylindolizine (1.0 g) under reflux in ethanol,(20 cm^3) containing 10% palladium on charcoal. After the evolution of gases had ceased, the mixture was filtered rapidly through celite. Concentration and cooling of the bright yellow solution yielded the aminoindolizine (0.92 g, 98%), yellow plates, m.p. 107-108° (from the minimum of ethanol). The product darkened after exposure to the atmosphere or upon prolonged exposure to hot solvents.

(Found: $\underline{M}^+$,208.10002. $C_{14}H_{12}N_2$
requires: $\underline{M}^+$,208.10004).

ν_{max} 3400,3350 (NH_2) cm^{-1}.

$\tau(CDCl_3)$ 6.60(2H,broad s,3-NH_2)[a],
3.60(1H,m,6-H),3.54(1H,s,1-H),
2.3-2.8(8H,m,2-C_6H_5,5-,7-and 8-H).

τ(T.F.A.) 5.95(Ca.05H,s,indolizinium 1-$\underline{CH_2}$),
2.1-2.8(9H,m,2-C_6H_5,5-,6-,7-and 8-H).

3-Acetamido-2-phenylindolizine (112).— A solution of 3-acetyl-2-phenylindolizine (2.35 g) in chloroform (10 cm^3) and a solution of hydrazoic acid in chloroform (6 cm^3, 1.2 equivalents) were mixed and added dropwise to a vigorously stirred mixture of chloroform (30 cm^3) and concentrated sulphuric acid (10 cm^3) at -5° over 0.25 h. The reaction mixture was stirred for a further 0.5 h and then poured onto crushed ice and neutralised with 40% aqueous potassium hydroxide solution. The chloroform solution was separated and dried

($MgSO_4$). Removal of the solvent gave the acetamidoindolizine (2.2 g, 78%), pale yellow prisms, m.p. 196-197°(from aqueous ethanol).

(Found: C,76.7; H,5.6; N,10.9; M^+,250. $C_{16}H_{14}N_2O$
requires: C,76.8; H,5.6; N,11.2; M^+,250.)

ν_{max} (Nujol) 3250(N-H), 1670(C=O)cm^{-1}.

τ($CDCl_3$) 8.42,7.86(3H,singlets,3-NHCOMe),
3.25-3.50(3H,m,1-,6- and 7-H),
2.26-2.82(8H,m,2-C_6H_5,5- and 8-H,3-NHCOMe[a]).

τ(pyridine) 7.72(3H,s,3-NHCOMe).

The amide was also prepared from the amine (59).— Acetic anhydride (1 cm^3) was stirred with a solution of 3-amino-2-phenylindolizine (1.0 g) in ether (100 cm^3) for 12 h. The mixture was filtered and the solid collected to yield the indolizine amide (0.76 g, 64%), having properties identical to the sample as prepared above.

3-Diacetylamino-2-phenylindolizine (41).— 3-Acetamido-2-phenylindolizine (0.5 g), acetic anhydride (5 cm^3) and fused sodium acetate (1.0 g) were refluxed for 4 h. The excess acetic anhydride was removed and the sticky solid boiled with charcoal and ethyl acetate. After filtration through celite, and removal of the solvent, the resultant oil was triturated with ethanol to yield the diacetylaminoindolizine (0.43 g, 74%), pale yellow prisms, m.p. 113-114°(from ethanol). (Hurst, Melton and Wibberley [23] quote a m.p. of 113-114° in a preparation from 2-phenyl-3-(2-pyridyl)propionitrile (40)).

(Found: C,73.7; H,5.6; N,9.4; $\underline{M}^+$,292. $C_{18}H_{16}N_2O_2$ requires: C,73.9; H,5,5; N,9.6; $\underline{M}^+$,292).

ν_{max} (Nujol) 1720(C=O)cm^{-1}.

$\tau(CDCl_3)$ 7.91(6H,s,3-N(CO$\underline{Me}$)$_2$),
3.23(1H,s,1-H),
3.28-3.5(2H,m,6- and 7-H),
2.5-2.8(7H,m,2-C_6H_5,5- and 8-H).

1,2-Dimethylindolizine (177) was prepared by the method of Holland and Naylor, [20] m.p. 58-60 (lit., 63°).

$\tau(CDCl_3)$ 7.80(6H,s,1- and 2-Me),
3.45-3.95(2H,m,6- and 7-H), 3.06(1H,s,3-H)
2.85(1H,d,J=8Hz,7-H), 2.42(1H,d,J=7Hz,5-H).

3-Acetyl-1,2-dimethylindolizine (103).— Acetic anhydride (20 cm^3), fused sodium acetate (4.0 g) and 1,2-dimethylindolizine were refluxed together for 4 h. The excess acetic anhydride was removed and the tarry material boiled several times with ethylacetate and charcoal. After filtration through celite, and concentration,cooling gave the acetylindolizine (4.3 g, 72%), straw coloured needles m.p. 97-98° (lit., 99-100°) [37] (from ethylacetate).

ν_{max} 1600(C=O)cm^{-1}.

$\tau(CDCl_3)$ 7.75(3H,s,1-Me), 7.60(3H,s,2-Me)
7.51(3H,s,3-CO$\underline{Me}$),
2.65-3.45(3H,m,6-,7- and 8-H),
0.13(1H,d,J=7Hz,5-H).

Attempted Nitrosation of 1,2-Dimethylindolizine.— An aqueous solution of sodium nitrite (2.0 g, 10 cm^3 water) was added dropwise to a stirred solution of 1,2-dimethylindolizine (4.5 g) in concentrated hydrochloric acid and water (30 cm^3: 10 cm^3) at 0° over 0.25 h. The reaction was stirred for a further 0.5 h and then neutralised with a saturated solution of sodium bicarbonate. The resultant red solution was extracted with chloroform and the combined extracts dried ($MgSO_4$). On concentration of this deep green solution no nitroso compound was isolated, but instead an intractable tar was formed.

1,2-Dimethyl-3-nitroindolizine (178).—A mixture of fuming nitric acid (d. 1.5) (2.0 g, 1.5 equivalents) and acetic anhydride (2.0 cm^3) was added dropwise to a solution of 1,2-dimethylindolizine (2.9 g) in acetic anhydride (20 cm^3) cooling in an acetone-carbice bath (0.25 h). The reaction was stirred for a further 0.5 h,then poured onto ice and neutralised with 40% aqueous potassium hydroxide solution. The mixture was extracted with chloroform, the extracts combined and dried ($MgSO_4$). Removal of the solvent, gave a tar which was chromatographed on a column of neutral alumina with diethyl ether as eluent. The broad yellow band which developed was collected and the solvent removed to give the nitroindolizine (1.91g, 50%), yellow prisms, m.p. 148-149° (from petroleum ether, b.p. 60-80°).

(Found: C,62.9; H,5.3; N,14.7; M^+,190. $C_{10}H_{10}N_2O_2$
requires: C,63.2; H,5.3; N,14.5; M^+,190.).

ν_{max} 1520,1350(NO_2)cm^{-1}.

$\tau(CDCl_3)$ 7.83(3H,s,1-Me), 7.51(3H,s,2-Me),
2.4-3.2(3H,m,6-,7- and 8-H).
0.44(1H,d,J=7Hz,5-H).

3-Acetamido-1,2-dimethylindolizine (113).— A solution of 3-acetyl-1,2-dimethylindolizine (1.87 g) in a chloroform solution of 8% hydrazoic acid (6 cm^3, 1.2 equivalents) was added dropwise to a stirred mixture of chloroform (20 cm^3) and concentrated sulphuric acid (10 cm^3) at 0° (0.25 h). The mixture was stirred for a further 0.5 h, then poured onto ice and neutralised with 40% aqueous potassium hydroxide solution. The chloroform solution was separated off, dried ($MgSO_4$) and the solvent removed to give the acetamidoindolizine (1.74 g, 86%), buff needles, m.p. 188-190° (from ethyl acetate).

(Found: C,71.2; H,6.8; N,14.0; M^+,202. $C_{12}H_{14}N_2O$
requires: C,71.3; H,7.0; N,13.9; M^+,202).

ν_{max} 3450(N-H), 1700(C=O)cm^{-1}.

$\tau(CDCl_3)$ 8.3,7.96,7.87,7.80,7.78(9H, singlets,
1- and 2-Me, 3-NHCOMe),
3.2-3.65(2H,m,6- and 7-H),
2.3-3.1(3H,m,5- and 8-H, 3-NHCOMe[a])

1,2-Diphenylindolizine (179).— Phenacyl bromide (9.9 g) and 2-benzylpyridine (8.45 g) were refluxed together in acetone (50 cm^3) for 24 h. The quaternary salt was filtered off, washed with a little acetone, and then dissolved in water (100 cm^3) containing sodium bicarbonate (10 g) and heated at 100° for 1 h. The solid which formed on cooling was filtered off, washed with a little hot water and dried, giving the

diphenylindolizine (7.5 g, 56%), straw needles, m.p. 111-112° (lit., 112°) [37] (from ethanol).

ν_{max} ($CHCl_3$) 1600(Ar)cm^{-1}.

τ ($CDCl_3$) 3.7(2H,m,6- and 7-H), 3.0(11H,m,1- and 2-C_6H_5, 3-H), 2.6(2H,m,5- and 8-H).

3-Acetyl-1,2-diphenylindolizine (104).— A mixture of acetic anhydride (50 cm^3) and fused sodium acetate (3 g) was refluxed with 1,2-diphenylindolizine (3 g) for 6 h. The excess acetic anhydride was removed and the remaining mixture boiled several times with ethylacetate and charcoal. Filtration through celite and concentration gave, on cooling, the acetylindolizine (3.3 g, 95%), straw coloured needles, m.p. 176-178° (lit., 175-176°) [37] (from ethyl acetate).

ν_{max} 1610(C=O)cm^{-1}.

τ($CDCl_3$) 8.05(3H,s,3-COMe), 2.86(5H,s,1-C_6H_5), 2.75(5H,s,2-C_6H_5), 2.4-3.3(3H,m,6-,7- and 8-H), -0.05(1H,d,J=7Hz,5-H).

3-Nitroso-1,2-diphenylindolizine(66).— A solution of sodium nitrite (0.35 g) in water (10 cm^3) was added dropwise to a solution of 1,2-diphenylindolizine (1.35 g) in glacial acetic acid (30 cm^3) at 15° over 0.25 h. After a further 0.5 h. the solution was neutralised with concentrated ammonia solution and then extracted with chloroform. The combined extracts were dried ($MgSO_4$) and the solvent removed to give the nitroso-indolizine (1.44 g, 96%), dark green needles, m.p. 176.5-178°, (from aqueous ethanol).

(Found: C,80,4; H,4.8; N,9.2; $\underline{M}^+$,298. $C_{20}H_{10}N_2O$
requires: C,80,6; H,4.7; N,9.4; $\underline{M}^+$,298.).

ν_{max} 1620(N=O)cm^{-1}.

$\tau(CDCl_3)$ 2.4-3.2(13H,m,1- and 2-C_6H_5,6-,7- and 8-H),
-0.18(1H,J=7Hz,5-H).

Attempted preparation of 3-Azido-1,2-diphenylindolizine (159).— A solution of 3-nitroso-1,2-diphenylindolizine (2.7 g) in ethanol (40 cm^3) was treated with an 8% chloroform solution of hydrazoic acid (2 equivalents, 10 cm^3) at room temperature and left to stir for 12 h. No evolution of gas was observed during this time and upon removal of the solvent only starting material was found (97%).

3-Amino-1,2-diphenylindolizine (107).— Hydrazine hydrate (1.0 cm^3) was added dropwise to a vigorously stirred solution of 3-nitroso-1,2-diphenylindolizine (1.0 g) under reflux in ethanol (25 cm^3) containing 10% palladium on charcoal (0.2 g). After the evolution of gas had ceased the mixture was filtered rapidly through celite. Removal of the solvent gave the aminoindolizine (0.87 g, 91%), yellow prisms, m.p. 94-96° (from methanol).

(Found: $\underline{M}^+$,284.13134. $C_{20}H_{16}N_2$
requires: $\underline{M}^+$,284.12958).

ν_{max} 3400,3300(NH_2)cm^{-1}.

$\tau(CDCl_3)$ 6.7(2H, broad s,3-NH_2)[a], 3.36(1H,m,6-H),
2.1-3.2(13H,m,1- and 2-C_6H_5,5-,7- and 8-H).

3-Acetamido-1,2-diphenylindolizine (114).— A solution of 3-acetyl-1,2-diphenylindolizine (3.0 g) in a solution of hydrazoic acid in chloroform (6.0 cm^3, 1.2 equivalents) was added dropwise to a stirred mixture of chloroform (15 cm^3) and concentrated sulphuric acid (7.5 cm^3) at -5°C over 0.5 h. The mixture was stirred for a further 0.5 h, poured onto crushed ice and neutralised with 40% aqueous potassium hydroxide solution. The chloroform layer was separated off and dried ($MgSO_4$). Removal of the solvent gave an oily material which, when triturated with benzene, yielded the acetamidoindolizine (2.67 g, 86%), colourless prisms, m.p. 271-273°(from benzene).

(Found: C,80.7; H,5.5; N,8.8; $\underline{M}^+$,326. $C_{22}H_{18}N_2O$
requires: C,80.9; H,5.6; N,8.6; $\underline{M}^+$,326).

ν_{max} (Nujol) 3300(NH), 1670(C=O)cm^{-1}.

$\tau(CDCl_3)$ 8.02,7.89(3H, singlets, 3-NHCO<u>Me</u>),
2.35-3.2(14H,m,1- and 2 C_6H_5,5-,6-,7- and 8-H).

The acetamido compound was also obtained by the treatment of the amine (107) with acetic anhydride in ether for 12 h. (82%).

Ethyl 2-Methylindolizine-1-carboxylate (180) was prepared by the method of Bragg and Wibberley [40] m.p. 43-44°.

ν_{max} 1690(C=O)cm^{-1}.

$\tau(CDCl_3)$ 8.6(3H,t,J=7Hz,1-COOCH$_2$<u>Me</u>),
7.51(3H,s,2-Me), 5.62(2H,q,J=7Hz,1-COO<u>CH$_2$</u>Me),
3.2(2H,m,6- and 7-H), 3.0(1H,s,3-H),
2.15(1H,d,J=7Hz,5-H), 1.94(1H,d,J=9Hz,8-H).

Ethyl 2-Methyl-3-nitrosoindolizine-1-carboxylate (67).— A solution of sodium nitrite (0.5 g) in water (10 cm^3) was added dropwise to a stirred solution of ethyl 2-methylindolizine-1-carboxylate (1.0 g) in a mixture of concentrated hydrochloric acid (20 cm^3) and water (10 cm^3) over 0.5 h, at 0°C. The mixture was stirred for a further 0.5 h at this temperature, then neutralised by the addition of a saturated aqueous solution of sodium bicarbonate. The crude solid was collected to give the nitrosoindolizine (0.92 g, 80%), green prisms, m.p. 129-130° (decomp.) (from petroleum ether b.p. 40-60°).

(Found: C,61.8; H,5.3; N,12.2; M^+,232. $C_{12}H_{12}N_2O_3$ requires: C,62.0; H,5.2; N,12.0, M^+,232).

ν_{max} 1690(C=O), 1610(N=O)cm^{-1}.

$\tau(CDCl_3)$ 8.55(3H,t,J=7Hz,1-$COOCH_2$Me), 6.96(3H,s,2-Me), 5.54(2H,q,J=7Hz, 1-$COOCH_2$Me), 2.8(1H,m,6-H), 2.26(1H,m,7-H), 1.54(1H,d,J=9Hz,8-H), -0.22(1H,d,J=7Hz,5-H).

Ethyl 3-Amino-2-methylindolizine-1-carboxylate (108).— Hydrazine hydrate (1.0 cm^3) was added dropwise to a vigorously stirred solution of ethyl 2-methyl-3-nitrosoindolizine-1-carboxylate (1.0 g) under reflux in ethanol (30 cm^3) containing 10% palladium on charcoal (0.2 g). After the evolution of gases had ceased the mixture was filtered rapidly through Keiselguhr and the solvent removed to give a yellow gum which, when triturated with petroleum ether gave the aminoindolizine (0.64 g, 68%), yellow plates, m.p. 83-86°. The product

darkened on exposure to the atmosphere and upon contact with hot solvents.

(Found: $\underline{M}^+$, 218.10552. $C_{11}H_{14}N_2O_2$
requires: $\underline{M}^+$, 218.10556).

ν_{max} 3400, 3350(NH_2), 1685(C=O)cm^{-1}.

$\tau(CDCl_3)$ 8.6(3H, q, J=7Hz, 1-$COOCH_2\underline{Me}$)
6.8(2H, broad s, 3-NH_2)[a],
7.6(3H, s, 2-Me), 5.62(2H, q, J=7Hz, 1-$COO\underline{CH_2}Me$),
3.15(2H, m, 6- and 7-H), 1.9(2H, m, 5- and 8-H).

Ethyl 3-Acetamido-2-methylindolizine-1-carboxylate (116).— A solution of ethyl 3-amino-2-methylindolizine-1-carboxylate (0.5 g) in ether (25 cm^3) and pyridine (8 cm^3) was stirred at room temperature with acetic anhydride (0.5 cm^3) for 17 h. After the removal of excess acetic anhydride and solvents, the resultant brown oil was triturated with ether to give the acetamidoindolizine (0.41 g, 69%), buff prisms, m.p. 153-154° (from ethyl acetate).

(Found: C, 64.4; H, 6.1; N, 10.8; M^+, 260. $C_{14}H_{16}N_2O_3$
requires: C, 64.6; H, 6.2; N, 10.8; M^+, 260).

ν_{max} (Nujol) 3400 (NH), 1665 (C=O) cm^{-1}.

$\tau(CDCl_3)$ 8.71(3H, t, J=7Hz, 1-$COOCH_2\underline{Me}$),
8.38, 8.14, 7.95, 7.84(6H, singlets, 2-Me and
3-$NHCO\underline{Me}$), 5.77(2H, q, J=7Hz, 1-$COO\underline{CH_2}Me$),
3.0-3.45(2H, m, 6- and 7-H),
2.50(1H, d, J=6.5Hz, 5-H), 2.02(1H, d, J=9Hz, 8-H).

Ethyl 2-Phenylindolizine-1-carboxylate (181) was produced by the method of Bragg and Wibberley,[40] m.p. 106-107°.

ν_{max} 1680(C=O)cm^{-1}.

$\tau(CDCl_3)$ 8.8(3H,t,J=7Hz,1-COOCH$_2$Me), 5.75(2H,q,J=7Hz,1-COOCH$_2$Me), 3.34(1H,m,6-H), 2.97(1H,m,7-H), 2.4-2.9(6H,m,2-C_6H_5 and 3-H), 2.06(1H,d,J=7Hz,5-H), 1.75(1H,d,J=9Hz,8-H).

Ethyl 3-(4-Carboxyphenylazo-2-phenylindolizine-1-carboxylate (63).— A neutral diazonium salt derived from p-aminobenzoic acid (1.4 g) was added to ethyl 2-phenylindolizine-1-carboxylate (1.0 g) in ethanol (120 cm^3) and the mixture stirred at 20° for 1 h. 10% acetic acid was added to yield the azo-dye (1.53 g, 98%), orange prisms, m.p. 278-279° (decomp.), (from 2-ethoxyethanol).

(Found: C,69.5; H,4.7; N,10.4; M^+,413, $C_{24}H_{19}N_3O_4$
requires: C,69.7; H,4.6; N,10.2; M^+,413).

ν_{max} (Nujol) 1690(C=O)cm^{-1}.

A suitable solvent for the determination of an n.m.r. spectrum was not available.

Ethyl 3-Nitroso-2-phenylindolizine-1-carboxylate (68).— A solution of sodium nitrite (0.7 g) in water (10 cm^3) was added dropwise to a solution of ethyl-2-phenylindolizine-1-carboxylate (2.6 g) in glacial acetic acid (75 cm^3) at 15°. After 1 h, the solution was neutralised by the addition of strong ammonia solution and the green solid filtered off to give the nitrosoindolizine (2.7 g, 92%), green needles, m.p. 158-159°. (from ethanol).

Ethyl 3-Amino-2-phenylindolizine-1-carboxylate (109).— Hydrazine hydrate (1.0 cm^3) was added dropwise to a vigorously stirred solution of ethyl 3-nitroso-2-phenylindolizine-1-carboxylate (1.0 g) under reflux in ethanol, containing 10% palladium on charcoal (0.2 g). After the evolution of gas had ceased, the product was filtered rapidly through celite. Concentration and cooling in the refrigerator gave the amino-indolizine (0.62 g, 58%), yellow prisms, m.p. 90-92°, (from ethanol).

(Found: $\underline{M}^+$, 280.12132. $C_{17}H_{16}N_2O_2$
requires: M^+, 280,12120).

ν_{max} 3400, 3300(NH_2), 1690(C=O)cm^{-1}.

$\tau_{(CDCl_3)}$ 8.89(3H, t, J=7Hz, 1-COOCH$_2$Me),
7.73(2H, broad s, 3-NH_2)[a]
5.85(2H, q, J=7Hz, 1-COO$\underline{CH_2}$Me)
3.2(2H, m, 6- and 7-H),
2.7(5H, m, 2-C_6H_5), 2.15(1H, d, J=7Hz, 5-H),
1.80(1H, d, J=8Hz, 8-H).

The product was synthesised from ethyl 3-(4-carboxyphenylazo)-2-phenylindolizine-1-carboxylate (63) by a similar procedure, fractional recrystallisation from ethanol giving the amine (109) (52%).

Ethyl 3-Acetamido-2-phenylindolizine-1-carboxylate (117).— A solution of ethyl 3-amino-2-phenylindolizine-1-carboxylate (0.5 g) in pyridine (10 cm^3) was stirred with acetic anhydride (2 cm^3) at room temperature for 17 h. The excess acetic anhydride and solvent was removed and the oily material triturated with ether to give the acetamidoindolizine (0.45 g,

78%), pale yellow prisms, m.p. 167.5-169°, (from ethanol).

(Found: C,70.7; H,5.7; N,8.5; $\underline{M}^+$,322. $C_{19}H_{18}N_2O_3$
requires: C,70.8; H,5.6; N,8.7; $\underline{M}^+$,322).

ν_{max} 3350(N-H), 1680(C=O)cm^{-1}.

$\tau(CDCl_3)$ 8.90(3H,t,J=7Hz,1-$COOCH_2\underline{Me}$),
8.44,8.06(3H,singlets,3-NHCOMe),
2.85-3.04(2H,m,6- and 7-H), 2.70(5H,s,2-C_6H_5),
2.32(1H,d,J=6.5Hz,5-H), 2.76(1H,d,J=9Hz,8-H).

Diethyl Indolizine-1,2-dicarboxylate (182) was prepared by the method of Bragg and Wibberley,[40] m.p. 83-84°.

ν_{max} 1810,1780(C=O)cm^{-1}.

A suitable solvent for determination of an n.m.r. spectrum was not available.

Diethyl 3-Nitrosoindolizine-1,2-dicarboxylate (69).— A solution of sodium nitrite (0.7 g) in water (10 cm^3) was added dropwise to a solution of diethyl indolizine-1,2-dicarboxylate (2.6 g) in a mixture of concentrated hydrochloric acid (30 cm^3) and water (10 cm^3) over 0.25 h, at 0°C. The mixture was neutralised by treatment with a saturated, aqueous solution of sodium bicarbonate and the solid filtered off to give the nitrosoindolizine (2.9 g, 83%), bright green needles, m.p. 109-111° (from aqueous ethanol).

(Found: C,57.9; H,5.0; N,9.9; $\underline{M}^+$,290. $C_{14}H_{14}N_2O_4$
requires: C,57.9; H,4.9; N,9.7; $\underline{M}^+$,290).

ν_{max} 1820,1700(C=O), 1620(N=O)cm^{-1}.

$\tau(CDCl_3)$ 8.6(6H,t,J=7Hz,1- and 2-$COOCH_2\underline{Me}$),
5.5(4H,q,J=7Hz,1- and 2-$COO\underline{CH_2}Me$),

2.68(1H,m,6-H), 2.23(1H,m,7-H),
1.56(1H,d,J=9Hz,8-H), 0.11(1H,d,J=6Hz,5-H).

Diethyl 3-Aminoindolizine-1,2-dicarboxylate (110).— Hydrazine hydrate (1.0 cm^3) was added dropwise to a vigorously stirred solution of diethyl 3-nitrosoindolizine-1,2-dicarboxylate (1.0 g) under reflux in ethanol (40 cm^3), containing 10% palladium on charcoal (0.2 g). After the evolution of gas had ceased, the mixture was filtered through celite and the solvent removed to give a yellow gum, which, on trituration with ether, gave the aminoindolizine (0.78 g, 82%), yellow plates, m.p. 94-96° (from the minimum of methanol).

On several occasions the gum was difficult to solidify and the product became tarry on prolonged heating with solvents.

(Found: M^+, 276.11100. $C_{14}H_{16}N_2O_4$
requires: M^+, 276.11018).

ν_{max} 3400,3300(NH_2), 1680(C=O)cm^{-1}.

τ($CDCl_3$) 8.75(6H,t,J=7Hz,1- and 2-$COOCH_2$Me),
5.62(4H,q,J=7Hz,1- and 2-$COO\underline{CH_2}$Me),
4.8(2H,broad s,3-NH_2)[a]
3.3(2H,m,6- and 7-H), 2.2(2H,m,5- and 8-H).

5-Methyl-2-phenylindolizine (183) was prepared by the method of Boekelheide and Windgassen,[121] m.p. 83-85° (lit. 83°).

τ($CDCl_3$) 7.52(3H,s,5-CH_3), 3.35-3.70(2H,m,6- and 7-H),
3.23(1H,d,J=1.5Hz,1-H), 2.72(1H,d,J=1.5Hz,3-H),
2.15-2.75(6H,m,2-C_6H_5 and 8-H).

5-Methyl-3-nitroso-2-phenylindolizine (70). — A solution of sodium nitrite (0.35 g) in water (5 cm^3) was added dropwise to a stirred solution of 5-Methyl-2-phenylindolizine (1.0 g) in a mixture of concentrated hydrochloric acid (15 cm^3) and water (7 cm^3) over 0.25 h, at 0°. After a further 0.5 h, the mixture was neutralised by the addition of a saturated aqueous solution of sodium bicarbonate. Filtration gave the nitroso-indolizine (1.08 g, 75%), green needles, m.p. 144-145°, (from light petroleum b.p. 60-80°). The product decomposed on contact with hot, polar solvents (see below).

(Found: C,76.4; H,5.3; N,11.7; $\underline{M}^+$, 236. $C_{15}H_{12}N_2O$
requires: C,76.3; H,5.1; N,11.9; $\underline{M}^+$, 236).

ν_{max} 1630 (N=O) cm^{-1}.

$\tau(CDCl_3)$ 7.49(3H,s,5-CH_3), 3.10(1H,m,6-H),
2.3-2.6(7H,m,2-C_6H_5,7- and 8-H).

2-Phenyl-3-(6-hydroxymethylpyrid-2-yl)acrylonitrile (147). — A solution of 5-methyl-3-nitroso-2-phenylindolizine (1.18 g) in absolute ethanol (50 cm^3) was refluxed for 17 h. The solvent was removed and the black solid extracted with petroleum ether (b.p. 60-80°). The ether solution on concentration, gave the nitrile (0.48 g, 41%), colourless needles, m.p. 103-104°, (from light petroleum, b.p. 60-80°).

(Found: C,76.0; H,5.2; N,11.7; $\underline{M}^+$,236. $C_{15}H_{12}N_2O$
requires: C,76.3; H,5.1; N,11.9; $\underline{M}^+$,236).

ν_{max} 3450(O-H), 2225(C≡N)cm^{-1}.

$\tau(CDCl_3)$ 5.82(1H,s,pyridyl-6-$CH_2\underline{OH}$)[a],
5.12(2H,s,pyridyl-6-$\underline{CH_2}OH$),
2.05-2.80(9H,m,pyridyl 3-,4- and 5-H,
-ene-3-H,-ene-1-C_6H_5).

Reaction of 5-Methyl-3-nitroso-2-phenylindolizine (70) with Piperidine.— A solution of 5-methyl-3-nitrosoindolizine (1.18 g) in ethanol (20 cm^3) was refluxed with piperidine (0.45 g) for 10 h. The solvent was removed and the reddish tar was chromatographed on a column of neutral alumina, eluting with ethylacetate. The starting material (0.96 g, 81%) was recovered, the remaining material being of a polymeric nature. Under similar conditions with 5% sodium hydroxide, only starting material was recovered along with polymeric material.

3-Amino-5-methyl-2-phenylindolizine (111).— Hydrazine hydrate (1.0 cm^3) was added to a vigorously stirred solution of 5-methyl-3-nitroso-2-phenylindolizine (1.0 g) under reflux in ethanol (30 cm^3) and containing 10% palladium on charcoal (0.2 g). When the evolution of gases had ceased, the mixture was filtered rapidly through celite and the solvent removed to give the aminoindolizine (0.83 g, 88%), yellow plates, m.p. 99-101°, (from ethanol).

Several similar preparations contained variable quantities of the nitrile (147). This was eliminated by adding the nitroso-compound (70) to the ethanol under reflux, containing palladium on charcoal, at a time immediately preceding the addition of the hydrazine hydrate. The amine darkened on exposure to the atmosphere and upon prolonged contact with hot solvents.

(Found: M^+, 222.11569. $C_{15}H_{14}N_2$
requires: M^+, 222.11536).

ν_{max} 3400, 3300(NH_2)cm^{-1}.

τ($CDCl_3$) 7.61(3H,s,5-CH_3), 6.8(2H,broad s,3-NH_2)[a], 3.25-3.80(2H,m,6- and 7-H), 2.2-2.85(7H,m,1-H,2-C_6H_5 and 8-H).

3-Acetamido-5-methyl-2-phenylindolizine (115).— A solution of 3-amino-5-methyl-2-phenylindolizine (1.0 g) in ether (50 cm^3) was stirred at room temperature with acetic anhydride (1.0 cm^3) for 17 h. The cream solid was collected to yield the acetamidoindolizine (0.51 g, 83%), pale cream prisms, m.p. 150-152°, (from aqueous ethanol).

(Found: M^+,264.12626. $C_{17}H_{16}N_2O$
requires: M^+,264.12675).

ν_{max} (Nujol) 3250(NH), 1650(C=O)cm^{-1}

τ($CDCl_3$) 8.37,7.91,7.60,7.54(6H,singlets,5-Me and 3-NHCOMe). 3.10-3.74(2H,m,6- and 7-H), 2.35-2.90(8H,2-C_6H_5,1- and 8-H,3-NHCOMe[a]).

Reaction of 3-Acetamido-5-methyl-2-phenylindolizine with Acetic Anhydride and Sodium Acetate.—3-Acetamido-5-methyl-2-phenylindolizine (0.3 g) was refluxed with acetic anhydride (5 cm^3) and sodium acetate (0.5 g) for 12 h. The excess acetic anhydride was removed and the dark mixture which remained, was chromatographed on a column of basic alumina, eluting with a mixture of benzene and ethylacetate (1:1). The only identifiable material recovered was the starting material (37%).

Attempted preparations of 2-phenyl-5-styrylindolizine

(i) From 5-methyl-2-phenylindolizine (170).— Benzaldehyde (0.58 g) was refluxed with 5-methyl-2-phenylindolizine (1.04 g) and acetic anhydride (0.55 g) in dioxan (5 cm^3) for 17 h. The solvent and excess reagents were removed and the dark tarry material was chromatographed on a column of neutral alumina, eluting with benzene. The cream band was collected to give bis-(5-methyl-2-phenylindolizine-3-yl)-phenylmethane (1.05 g, 42%), pale cream needles, m.p. 213° (decomp.) (from ethanol).

(Found: M^+, 502.24089. $C_{37}H_{30}N_2$
requires: M^+, 502.23967).

ν_{max} 1610, 1540(Ar.), 1430(Al.)cm^{-1}.

$\tau(CDCl_3)$ 7.67(6H, s, 5- and 5'-CH_3),
3.50-3.75(7H, m, 1-, 6- and 7-H, 1'-, 6'-, 7'-H and -CHPh-),
2.70-2.90(11H, m, 2- and 2'-C_6H_5, 8- and 8'-H).

(ii) From 2-methyl-6-styrylpyridine.— All attempts to form a quaternary salt from 2-methyl-6-styrylpyridine and phenacyl bromide were unsuccessful.

Reactions of 3 Aminoindolizines with Hydrochloric Acid.

3-Amino-2-phenylindolizine (59).— (0.5 g) was refluxed with concentrated hydrochloric acid (5 cm^3) for 0.5 h. The mixture was cooled, the white solid collected, and washed with a little ether to give 2-phenyl-3-(2-pyridyl) propionicacid hydrochloride (0.53 g, 90%), colourless needles, m.p. 200-202° (from ethanol and ether).

(Found: C,63.4; H,5.5; N,5.4; $\underline{M}^+$,227. $C_{14}H_{14}NO_2Cl$
requires: C,63.8; H,5.5; N,5.3; $\underline{M}^+$,227).

ν_{max} (Nujol) 2600(OH), 1700(C=O)cm^{-1}

A sample of 2-phenyl-3-(2-pyridyl) propionic acid (119) was obtained by treatment of the above hydrochloride with aqueous sodium bicarbonate solution. Colourless needles, m.p. 150-151° (from ethanol).

(Found: C,74.2; H,5.8; N,6.0. $C_{14}H_{13}NO_2$
requires: C,74.0; H,5.8; N,6.2).

ν_{max} (Nujol) 2400(OH), 1700(C=O)cm^{-1}.
(D.M.S.O.) 2400(OH), 1700(C=O)cm^{-1}.
(Pyridine) 2400(OH), 1700(C=O)cm^{-1}.

$\tau(CDCl_3)$ (220MHz spectrum)
6.73(1H,q,J=14.5Hz,J=7.5Hz,-C$\underline{H}$H-CHPh-),
6.32(1H,q,J=14.5Hz,J=7.5Hz,-CH$\underline{H}$-CHPh-),
5.73(1H,t,J=7.5,J=7.5,-CHH-C$\underline{H}$Ph-),
2.25-2.84(8H,m,2-C_6H_5,pyridyl 3-,4- and 5-H),
1.32(1H,d,J=6Hz,pyridyl 6-H),
-0.75(1H,s,-COO$\underline{H}$)[a].

τ (Pyridine) -0.73(1H,s,-COO$\underline{H}$)[a].

The same product (119) was obtained by the action of concentrated hydrochloric acid upon 3-acetamido-2-phenylindolizine (112) (76%), and by the action of dilute hydrochloric acid upon 3-amino-2-phenylindolizine (59) (73%), both under identical conditions to those above.

2-Phenyl-3-(2-pyridyl) propionitrile (40) was prepared by the method of Hurst, Melton and Wibberley,[23] m.p. 53-54°.

ν_{max} 2250(C≡N)cm^{-1}.

$\tau(CDCl_3)$ 6.8(2H,d,J=8Hz,-$\underline{CH_2}$CHCN),

5.5(1H,t,J=8Hz,-$CH_2\underline{CH}$CN),

2.6(8H,m,-C_6H_5,pyridyl 3-,4- and 5-H),

1.4(1H,d,J=5Hz,pyridyl 6-H).

2-phenyl-3(2-pyridyl)propionic acid (119).— A solution of 2-phenyl-3(2-pyridyl) propionitrile (3.0 g) was refluxed with concentrated hydrochloric acid (5.0 cm^3) for 3 h. The solid was collected after cooling, dissolved in water and neutralised with sodium bicarbonate. Collection of the solid gave the propionic acid (3.4 g, 96%), identical with a sample as prepared above from 3-amino-2-phenylindolizine (59).

3-Amino-1,2-diphenylindolizine (107) (1.0 g) was refluxed with concentrated hydrochloric acid (10 cm^3) for 0.5 h, cooled and the solid collected to give 2,3-diphenyl-3-(2-pyridyl) propionic acid hydrochloride (0.93 g, 87%), pale cream prisms, m.p. 214° (decomp.), (from ethanol).

(Found: C,70.4; H,5.4; N,4.3; $\underline{M}^+$,303. $C_{20}H_{18}NO_2Cl$

requires: C,70.7; H,5.3; N,4.1; $\underline{M}^+$,303).

ν_{max} (Nujol) 2300(OH), 1700(C=O)cm^{-1}.

A sample of 2,3-diphenyl-3-(2-pyridyl) propionic acid (120) was obtained by treatment of the above hydrochloride with sodium bicarbonate. Pale cream prisms, m.p. 181° (decomp.) (from ethanol).

ν_{max} (Nujol) 2300(OH), 1700(C=O)cm^{-1}.

$\tau(CDCl_3)$ 5.32(2H,d,J=10Hz,-$\underline{CH}C_6H_5\underline{CH}C_6H_5$-), 2.5-2.9(13H,m,2- and 3-C_6H_5,pyridyl 3-, 4- and 5-H), 1.4(1H,d,J=5Hz,pyridyl 6-H), -1.5(1H,broad s,-COO$\underline{H}$)[a].

The same product (120) was obtained by the action of concentrated hydrochloric acid upon 3-acetamido-1,2-diphenylindolizine (114) (72%),and by the action of dilute hydrochloric acid upon 3-amino-1,2-diphenylindolizine (107) (79%), both under conditions identical to those above.

3-Amino-2-methylindolizine (106).— A solution of 3-amino-2-methylindolizine (0.5 g) in concentrated hydrochloric acid (5 cm^3) was refluxed for 0.5 h. The excess acid was removed under reduced pressure and gave a brownish oil. This was triturated with ether but proved intractible. Attempts to characterise the crude products by a n.m.r. spectrum in D_2O, also proved unsuccessful.

3-Acetamido-1,2-dimethylindolizine (113).— A solution of 3-acetamido-1-2-dimethylindolizine (1.0 g) in concentrated hydrochloric acid (5 ml) was refluxed for 0.5 h. After removal of the excess hydrochloric acid, the greenish oil was triturated with ether. Ammonium chloride was precipitated out (0.23 g, 78%), leaving an unstable green oil which did not permit characterisation.

A n.m.r. spectrum of the crude products, although poorly resolved, indicated hydrolytic ring cleavage:

τ (D_2O) 8.5-9.1(6H,m,1- and 2-CH_3),
6.3-7.3(2H,m,-CHMe-CHMe-COOH),
1.4-2.2(4H,m,pyridyl-H).

Reaction of 3-nitro-2-methylindolizine with mineral acids.— A solution of the 3-nitro-2-methylindolizine (0.5 g) in the mineral acid (10 cm^3) was refluxed for 1 h. (A determination of the presence of other isomers was made on the reaction mixture by T.L.C. 1,3-dinitro-2-methylindolizine, 1-nitro-2-methylindolizine and 3-nitro-2-methylindolizine [25] were run alongside. Silica plates with diethyl ether/petroleum-ether (40-60°) (3:1) eluent were used). The mixture was poured into water (15 cm^3) and made neutral with sodium bicarbonate. The products were extracted into chloroform, the extracts dried ($MgSo_4$), and the solvent removed. Chromatography on a column of neutral alumina with benzene eluent was used when necessary.

Concentrated sulphuric acid.— The starting material was recovered (82%) with no indication of the formation of other isomers.

Concentrated hydrochloric acid.— The starting material was recovered (74%) with no indication of the formation of other isomers.

Tetrafluoroboric acid.— The evolution of nitrogen dioxide was noted but the starting material was recovered (68%) from a large quantity of polymeric material, with no indication of other isomers.

Reactions Involving a Neutral Ring-Opening of 3-Substituted Indolizines

Catalytic hydrogenations

General method.— A solution of the 3-nitrosoindolizine (1.0 g) in sufficient ethanol to effect solution (about 30 cm^3), containing 10% palladium on charcoal (0.2 g), was shaken together with hydrogen at 3 atm for 1 h. The mixture was filtered through celite and the solvent removed. An approximate estimation of the proportions of products was made at this stage to avoid further possible atmospheric oxidation during work up. This involved n.m.r. and i.r. spectroscopy of the mixture, from which it was possible to estimate the nature and proportion of starting material and products. Isolation of the products was achieved by the chromatographic technique indicated.

3-Nitrosoindolizine (65).— Hydrogenation gave 3-aminoindolizine (29%), 3-(2-pyridyl)acrylonitrile (12%) and 3-(2-pyridyl) propionitrile (59%). The mixture was chromatographed on a column of neutral alumina with benzene as eluent, and gave:

3-(2-pyridyl)acrylonitrile (130) as an oil.

(Found: $\underline{M}^+$, 130.05310. $C_8H_6N_2$ requires: 130.05316).

ν_{max} 2250(C≡N)cm^{-1}.

$\tau(CDCl_3)$ 4.43(1H,d,J=12Hz,cis-CH=CH-CN),
2.81(1H,d,J=12Hz,cis-CH=CH-CN),
2.1-2.9(3H,m,pyridyl 3-,4- and 5-H),

1.35(1H,d,J=5Hz,pyridyl 6-H).

A small quantity of the trans isomer was formed on standing at room temperature:

τ($CDCl_3$) 3.45(1H,d,J=16Hz,trans-CH=CH-CN).

3(2-pyridyl)propionitrile (131) as an oil which formed a picrate, m.p. 140-141° decomp., (lit., 140-142° decomp.).[122]

ν_{max} 2250(C≡N)cm^{-1}.

τ($CDCl_3$) 7.15(4H,m,-CH_2-CH_2CN),

2.3-2.9(3H,m,pyridyl 3-,4- and 5-H),

1.53(1H,d,J=5Hz,pyridyl 6-H).

The amine was not collected.

2-Methyl-3-nitrosoindolizine (72).— Hydrogenation gave 3-amino-2-methylindolizine (39%), 2-methyl-3-(2-pyridyl) acrylonitrile (37%) and 2-methyl-3-(2-pyridyl)propionitrile (24%). The mixture was separated by chromatography on a column of basic alumina, with benzene as eluent and gave

2-Methyl-3-(2-pyridyl)acrylonitrile (73) as an oil, which formed a picrate, m.p. 128-129°, decomp.

(Found: M^+,144.06917. $C_9H_8N_2$

requires: M^+,144.06875).

(Picrate.Found:

C,48.0; H,3.0; N,18.6. $C_{15}H_{11}N_5O_7$

requires: C,48.3; H,2.9; N,18.6).

ν_{max} 2250(C≡N), 1640(C=C)cm^{-1}.

τ($CDCl_3$) 7.84(3H,d,J=2Hz,-CH=CMeCN),

2.87(1H,d,J=2Hz,-CH=CMeCN),

2.3-3.0(3H,m,pyridyl 3-,4- and 5-H),

1.31(1H,d,J=5Hz,pyridyl 6-H).

2-Methyl-3-(2-pyridyl)propionitrile (132) as an oil.

(Found: M^+, 146.08531. $C_9H_{10}N_2$

requires: M^+, 146.08441).

ν_{max} 2250(C≡N)

$\tau(CDCl_3)$ 8.65(3H,d,J=6Hz,$-CH_2$-CHMeCN),

6.9(3H,m,$-CH_2$-CHMeCN),

2.3-3.0(3H,m,pyridyl 3-,4- and 5-H),

1.40(1H,d,J=5Hz,pyridyl 6-H).

2-Methyl-3-nitroindolizine (23).— Hydrogenation under similar conditions gave the amine (42%), the acrylonitrile (34%), and the propionitrile (24%).

3-Nitroso-2-phenylindolizine (29).— Hydrogenation gave 3-amino-2-phenylindolizine (27%), 2-phenyl-3-(2-pyridyl) acrylonitrile (52%) and 2-phenyl-2-(2-pyridyl)propionitrile (21%). The mixture was separated by chromatography on a column of basic alumina, eluting with benzene and gave

2-phenyl-3-(2-pyridyl)acrylonitrile (61), colourless needles, m.p. 61-63° (from petroleum ether, b.p. 60-80°).

(Found: C,81.5; H,5.0; N,13.4; M^+,206. $C_{14}H_{10}N_2$

requires: C,81.5; H,4.9; N,13.6; M^+,206).

ν_{max} ($CHCl_3$) 2250(C≡N), 1630(C=C)cm^{-1}.

τ($CDCl_3$) 2.0-2.8(9H,m,2-C_6H_5,pyridyl 3-,4- and 5-H and -CH=CPhCN). 1.40(1H,d,J=5Hz,pyridyl 6-H).

2-Phenyl-3-(2-pyridyl)propionitrile (40), identical with a sample prepared as above (page 129).

3-(4-Carboxyphenylazo)-2-phenylindolizine.— Hydrogenation under similar conditions with D.M.F. as solvent (100 cm^3) gave 3-amino-2-phenylindolizine in admixture with p-amino benzoic acid. The absence of ring-opened products was presumed by the absence of a peak at 2250 cm^{-1} (C≡N) in the i.r. spectrum, and the absence of a τ 1.4-1.5 signal (pyridyl 6-H) in the n.m.r. spectrum of the crude products.

3-Nitroso-1,2-diphenylindolizine (66).— Hydrogenation gave 3-amino-1,2-diphenylindolizine (85%), and 2,3-diphenyl-3-(2-pyridyl)acrylonitrile (15%). The mixture was chromatographed on a column of basic alumina with benzene as eluent, and gave

2,3-Diphenyl-3-(2-pyridyl)acrylonitrile (133) as colourless needles, m.p. 145-146° (from petroleum ether, b.p. 60-80°).
(Found: C,85.3; H,5.0; N,9.8; M^+,282. $C_{20}H_{14}N_2$ requires: C,85.1; H,5.0; N,9.8; M^+,282).
ν_{max} ($CHCl_3$) 2220(C≡N)cm^{-1}.
τ($CDCl_3$) 2.3-3.0(13H,2- and 3-C_6H_5,pyridyl 3-,4- and 5-H), 1.35(1H,d,J=5Hz,pyridyl 6-H).

5-Methyl-3-nitroso-2-phenylindolizine (70).— Hydrogenation gave 3-amino-5-methyl-2-phenylindolizine (38%), 2-phenyl-

3-(6-methylpyrid-2-yl)acrylonitrile (17%) and 2-phenyl-3-(6-methylpyrid-2-yl)propionitrile (45%). The mixture was separated by chromatography on a column of basic alumina, with benzene as eluent, and gave:

2-Phenyl-3-(6-methylpyrid-2-yl)acrylonitrile (134) as colourless prisms, m.p. 69-70° (from petroleum ether, 60-80°).

(Found: C,81.9; H,5.5; N,12.7; $\underline{M}^+$,220. $C_{15}H_{12}N_2$ requires: C,81.7; H,5.5; N,12.5; $\underline{M}^+$,220).

ν_{max} ($CHCl_3$) 2250(C≡N), 1640(C=C)cm^{-1}.

τ($CDCl_3$) 7.45(3H,s,pyridyl 6-Me), 2.1-2.9(9H,m,2-C_6H_5,pyridyl 3-,4- and 5-H and -$\underline{CH}$=CPhCN).

2-Phenyl-3-(6-methylpyrid-2-yl)propionitrile (135) as an oil which formed a picrate, m.p. 166-167°.

(Found: C,55.7; H,3.9; N,15.4; $\underline{M}^+$,222. $C_{21}H_{17}N_5O_7$ requires: C,55.6; H,3.8; N,15.5; $\underline{M}^+$,222).

ν_{max} ($CHCl_3$) 2250(C≡N)cm^{-1}.

τ($CDCl_3$) 7.50(3H,s,pyridyl 6-Me), 6.83(2H,d,J=8Hz, -$\underline{CH_2}$-CHPhCN), 5.57(1H,t,J=8Hz,-CH_2-$\underline{CH}$PhCN), 2.4-3.1(8H,m,2-C_6H_5,pyridyl 3-,4- and 5-H).

Ethyl 3-Nitroso-2-phenylindolizine-1-carboxylate (68).— Hydrogenation gave ethyl 3-amino-2-phenylindolizine-1-carboxylate (109) (93%). The presence of a peak at 2250 cm^{-1} (C≡N) in the i.r. spectrum and of a τ 1.4 signal in the n.m.r. spectrum (pyridyl 6-H) of the crude products, suggested that a quantity (7%) of the ring-opened product(s) was

present. Attempts to isolate such a product(s) was unsuccessful.

Transfer Hydrogenation with Cyclohexene

3-Nitroso-2-phenylindolizine (29).— A solution of the nitroso-compound (1.0 g) in ethanol (20 cm^3) containing 10% palladium on charcoal (0.2 g) was refluxed with freshly distilled cyclohexene (3 cm^3) for 48 h. The mixture was filtered through celite and the solvent removed. Extraction of the tarry material with light petroleum (b.p. 60-80°) gave 2-phenyl-3-(2-pyridyl)acrylonitrile (61) (0.63 g, 68%), identical with a sample prepared as above (page 135).

2-Methyl-3-nitrosoindolizine (72).— A solution of the nitroso-compound (1.0 g) in ethanol (20 cm^3) containing 10% palladium on charcoal (0.2 g) was refluxed with freshly distilled cyclohexene (3 cm^3) for 48 h. The mixture was filtered through celite and the solvent removed. Chromatography on a column of basic alumina, with benzene as eluent, gave 2-methyl-3-(2-pyridyl)acrylonitrile (73) (0.54 g, 55%), identical with a sample prepared as above (page 134). No other products were isolated from the reaction; what appeared to be polymeric material remained on the column.

Reactions of 3-Aminoindolizines Involving Neutral Ring-Opening

Reaction with 10% Palladium on Charcoal.— A solution of 3-amino-2-phenylindolizine (59) (1.0 g) in ethanol (25 cm^3) was refluxed with 10% palladium on charcoal (0.2 g) for 1 h. The mixture was filtered through celite and the solvent removed to give the unchanged amine (98%). Under the same conditions with a reflux time of 18 h, the reaction gave 2-phenyl-3-(2-pyridyl)acrylonitrile (61) (0.88g, 89%), identical with a sample prepared as above (page 135).

Reaction with 10% Palladium on Charcoal and Oxygen.— A solution of 3-amino-2-phenylindolizine (59) (1.0 g) in ethanol (25 cm^3) was stirred at room temperature with 10% palladium on charcoal and oxygen bubbled through the reaction mixture for 1 h. The mixture was filtered through celite and the solvent removed to give 2-phenyl-3-(2-pyridyl)acrylonitrile (61) (0.92 g, 94%), identical with a sample prepared as above (page 135).

Reaction with 10% Palladium on Charcoal and Nitrogen.— A solution of 3-amino-2-phenylindolizine (59) (1.0 g) in ethanol (25 cm^3) was stirred at room temperature with 10% palladium on charcoal and nitrogen bubbled through the reaction mixture for 1 h. The mixture was filtered through celite and the solvent removed to give the unchanged amine (100%).

Reaction with 10% Palladium on Charcoal and Cyclohexene.— A solution of 3-amino-2-phenylindolizine (1.0 g) in ethanol (25 cm^3) containing 10% palladium on charcoal (0.2 g) was refluxed with freshly distilled cyclohexene (3.0 cm^3) for 4 h. Nitrogen gas was bubbled through the mixture during the course of the reaction. The mixture was filtered through celite and the solvent removed to give 2-phenyl-3-(2-pyridyl) acrylonitrile (61) (0.81g, 80%), identical with a sample prepared as above (page 135).

Reaction of 3 Amino-2-phenylindolizine (59) with 3-Nitroso-2-phenylindolizine (29).— A solution of the amine (1.0 g) and the nitroso-compound (1.1 g) in ethanol (50 cm^3) was refluxed for 4 h. The solvent was removed to give a tar which, when extracted with petroleum ether, gave 2-phenyl-3-(2-pyridyl)acrylonitrile (61) (1.42 g, 73%), identical with a sample prepared as above (page 135).

A similar reaction prepared at room temperature for 1 h., containing,in addition, 10% palladium on charcoal, gave the nitrile (61) (71%) together with the nitroso-compound (29) (19%). No amine was detected in the reaction mixture after this time (as estimated by t.l.c., i.r., n.m.r.).

Reaction of 3-Amino-2-phenylindolizine (59) with Lead Tetraacetate.— The amine (59) (1.0 g), lead tetraacetate (2.0 g) and benzene (50 cm^3) were refluxed together for 1 h. Ethanol was added to precipitate lead dioxide, the mixture

was filtered, and the solvent removed to give 2-phenyl-3-(2-pyridyl)acrylonitrile (61) (0.78 g, 77%), identical with a sample prepared as above (page 135).

3-Amino-1,2-diphenylindolizine (107), when similarly treated, gave 2,3-diphenyl-3-(2-pyridyl)acrylonitrile (133) (82%), identical with a sample as prepared above (page136).

Ethyl 3-Amino-2-phenylindolizine-1-carboxylate (109) when similarly treated, gave an intractible tar, a crude i.r. spectrum, of which indicated the presence of a nitrile.

Reaction of 3-Amino-2-phenylindolizine (59) with 1-Nitroso-N,N-dimethylaniline and 10% Palladium on Charcoal.— A solution of the amine (59) (1.0 g) and p-nitroso-N,N-dimethylaniline (1.5 g) in ethanol (50 cm^3) containing 10% palladium on charcoal, was stirred at room temperature for 12 h. The mixture was filtered through celite, the solvent removed and a spectroscopic examination made of the reaction mixture. It was estimated that no products other than starting materials were present (i.r. and n.m.r.).
A similar reaction with nitrosobenzene also indicated no reaction between the nitroso-compound and the amine.

Reaction between 3-Nitroso-2-phenylindolizine (29) and Triethylphosphite.— The nitroso-compound (29) (1.0 g) was heated at 100°C under an atmosphere of nitrogen with

triethylphosphite (2.0 g) for 6 h. The excess reagent was removed by gentle heat under reduced pressure, and the remaining dark tarry material chromatographed on a column of basic alumina, with benzene as eluent, to give 2-phenyl-3-(2-pyridyl)acrylonitrile (61) (0.8g,80%), identical with a sample prepared as above (page135).

Reaction between 3-Nitroso-2-phenylindolizine (59) and Sodium Borohydride.— A solution of the nitroso-compound (29) (0.55 g) in isopropanol (25 cm^3) was added over 5 minutes to a suspension of 10% palladium on charcoal (0.1 g) with sodium borohydride (0.1 g) in isopropanol (30 cm^3) and the mixture stirred for 12 h. Nitrogen gas was bubbled through the mixture during the course of the reaction. The mixture was then filtered through celite and the solvent removed to give 2-phenyl-3-(2-pyridyl)propionitrile (40) (0.45 g, 87%), identical with a sample as prepared above (page129).
An attempted mild reduction of the nitroso-compound with zinc and ammonium chloride was unsuccessful, only starting material being recovered.

Reaction between 3-Nitroso-2-phenylindolizine (29), p-Amino-N,N-dimethylaniline and 10% Palladium on Charcoal.— A solution of the nitroso-compound (29) (0.55 g) in ethanol (20 cm^3) containing 10% palladium on charcoal (0.1 g) and p-amino-N,N-dimethylaniline (0.34 g) was stirred at room temperature for 6 h. The mixture was filtered through celite and the solvent removed. No products, except the starting materials, were identified by inspection of the n.m.r. and i.r. spectra of the mixture.

Reaction between p-Toluidine (142) and Nitrosobenzene (143) under neutral conditions.— A solution of p-toluidine (4.0 g) and nitrosobenzene (4.0 g) in ethanol (60 cm^3) was purged with nitrogen gas, stoppered and stirred at room temperature for 3 weeks. The solvent was removed and the mixture chromatographed on a column of neutral alumina, with light petroleum as eluent (b.p. 80-100°) to give:

trans-4-Methylazobenzene (144a) (1.106 g, 15.2%), orange plates, m.p. 70-72° (lit., 71°).[123]

(Found: M^+, 196.09958. $C_{13}H_{12}N_2$
requires: M^+, 196.10004).

τ($CDCl_3$) 7.62(3H,s,4-Me),
2.15 and 2.55(9H,m,aromatic-H).

Azoxybenzene (145) (5.62 g, 76%), dull orange plates, m.p. 33-35° (lit., 36°).[124]

(Found: M^+, 198.07931. $C_{12}H_{10}N_2O$
requires: M^+, 198.07931).

τ($CDCl_3$) 2.6 and 1.7(10H,m,aromatic-H).

cis-4-Methylazobenzene (144b) (0.566 g, 7.7%), dull red oil.

(Found: M^+, 196.10103. $C_{13}H_{12}N_2$
requires: M^+, 196.10004).

The only other material isolated was p-toluidine (3.44 g, 86%). (The yields of azo- and azoxy-compounds are based on nitroso benzene).

Ethyl bromopyruvate.— Bromine (16.0 g) was added dropwise over a period of 1.5 h to a gently refluxing solution of ethyl pyruvate (11.6 g) in carbon tetrachloride (100 cm^3). The hydrogen bromide formed was expelled from the reaction by a steady stream of nitrogen gas. When the final addition had been made, the mixture was stirred and refluxed for a further 4 h, washed with water (2 x 100 cm^3) and finally with a saturated solution of potassium carbonate (100 cm^3). The carbon tetrachloride solution was separated off, dried ($MgSo_4$) and the solvent removed to yield a yellow oil (18.5 g, 95% ethylbromopyruvate). Distillation, and collection of the fraction at 55-56°, 0.7 mm, gave ethylbromopyruvate (10.2 g, 52%). (A preparation by the method of Borrows and Holland,[125] gave a crude mixture of ethyl mono-, di- and tribromopyruvate).

MASS SPECTRAL TABLES

(i) 3-Nitrosoindolizines

3-nitrosoindolizine (65).

m/e	147	146(M^+)	131	130	129	117	116	115	104
I%	10	93	7	52	15	9	100	4	10
m/e	103	91	90	89	88	79	78	77	76
I%	5	4	15	74	47	54	10	6	9
m/e	75	65	64	63	62	61	58	53	52
I%	7	5	7	28	9	3	15	7	45
m/e	51	50	49	41	40	39	38	37	
I%	59	49	6	9	5	5	20	14	

m^* 114(146→130), 92.1(146→116).

2 Methyl-3-nitrosoindolizine (72).

m/e	161	160	159	145	144	143	142	132	131
I%	11	100(M^+)	11	4	25	39	16	4	29
m/e	130	129	128	119	118	117	116	105	104
I%	43	6	10	5	5	18	10	5	15
m/e	103	102	101	91	90	89	80	79	78
I%	25	10	4	4	6	7	4	17	24
m/e	77	76	75	74	65	64	63	62	53
I%	39	8	6	4	5	6	11	5	4
m/e	52	51	50	39	38	37			
I%	11	30	15	18	6	4			

m^* 126(160→142), 107.5(160→131), 94(143→116).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
131	131.06092	$C_8H_7N_2$	131.06104
104	104.05002	C_7H_6N	104.04945
103	103.05477	C_8H_7	103.05431

Ion source determinations. Meta-stable scan at 4-8 kv.

m/e 131	m/e 104	m/e 103
146→131(s 0.117)	131→104(vl 0.285)	130→103(vl 0.263)
160→131(vl 0.220)	144→104(l 0.384)	158→103(s 0.533)
	159.54→104(l 0.534)	

3-Nitroso-2-phenylindolizine (59).

m/e	223	222	221	207	206	205	194	193	192
I%	12	72($\underline{M}^+$)	27	8	53	100	8	28	27
m/e	191	190	177	168	167	166	165	164	163
I%	53	14	5	4	4	4	7	4	5
m/e	151	139	103	101	89	83	78	77	76
I%	4	4	5	5	7	4	8	8	5
m/e	75	74	62	61	51	50			
I%	5	4	7	3	12	6			

m^* 191.1(222→206).

5-Methyl-3-nitroso-2-phenylindolizine (70).

m/e	237	236	235	223	222	221	220	219	207
I%	16	100($\underline{M}^+$)	14	4	25	10	5	16	13
m/e	206	205	204	203	202	191	190	180	179
I%	66	66	20	43	4	10	5	6	20

m/e	178	176	163	152	151	139	128	119	118
I%	6	6	4	6	4	4	5	6	7
m/e	115	104	103	102	93	92	91	90	89
I%	5	7	8	18	5	6	7	14	12
m/e	88	87	78	77	76	75	74	65	64
I%	5	4	4	14	10	7	5	8	4
m/e	63	62	52	51	50	39			
I%	12	4	5	13	6	14			

m^* 183(232→206).

Ethyl-2-Methyl-3-nitrosoindolizine-1-carboxylate (67).

m/e	233	232	216	215	205	204	203	188	187
I%	14	96($\underline{M}^+$)	7	51	7	4	14	12	71
m/e	174	172	171	169	160	159	158	157	156
I%	6	12	35	5	27	7	6	12	4
m/e	146	145	144	143	142	131	130	129	128
I%	4	4	29	52	100	9	21	60	21
m/e	118	117	116	115	114	104	103	102	101
I%	10	23	17	10	6	14	10	12	6
m/e	91	89	88	87	79	78	77	76	75
I%	6	10	15	6	19	58	14	12	12
m/e	74	65	64	63	62	52	51	50	44
I%	4	6	10	17	6	15	33	15	14
m/e	43	39							
I%	69	25							

Ethyl 3-Nitroso-2-phenylindolizine-1-carboxylate (68).

m/e	295	294	293	278	277	266	265	250	249
I%	20	100($\underline{M}^+$)	12	4	5	7	30	4	19
m/e	238	237	236	235	222	221	220	219	206
I%	4	8	4	7	8	44	7	10	7
m/e	205	194	193	192	191	190	181	180	179
I%	14	5	14	20	19	18	3	7	8
m/e	178	165	164	163	152	89	79	78	77
I%	5	4	7	7	4	4	4	20	7
m/e	63	51	39						
I%	5	10	5						

m^* 239(294→265).

3-Nitroso-1,2-diphenylindolizine (66).

m/e	299	298	297	283	282	281	280	279	269
I%	4	17($\underline{M}^+$)	11	9	50	100	5	15	4
m/e	268	266	256	254	206	204	167	151	141
I%	12	4	4	6	4	21	4	4	4
m/e	140	127	126	125	124	79	78	77	52
I%	9	6	12	4	7	5	14	7	4
m/e	51	44	39						
I%	15	5	6						

Ethyl 3-Nitrosoindolizine-1,2-dicarboxylate (69).

m/e	291	290	245	231	230	229	217	202	201
I%	10	68($\underline{M}^+$)	18	7	42	12	5	10	58
m/e	188	174	160	158	157	145	143	142	131
I%	7	7	4	15	5	11	10	13	13

m/e	130	129	128	117	116	104	103	102	101
I%	100	84	17	12	13	5	7	5	9
m/e	89	88	79	78	76	75	52	51	50
I%	10	7	10	41	7	10	7	12	7
m/e	43	42	39						
I%	23	8	7						

m^* 176(230→201).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
245	245.05623	$C_{12}H_9N_2O_4$	245.05639
230	230.06914	$C_{12}H_{10}N_2O_3$	230.06926
201	201.03001	$C_{10}H_5N_2O_3$	201.03112
188	188.03476	$C_{10}H_6NO_3$	188.03417
174	174.04292	$C_9H_6N_2O_2$	174.04282
158	158.04801	$C_9H_6N_2O$	158.04804
142	142.02929	C_9H_4NO	142.02891
130	130.05309	$C_8H_6N_2$	130.05303

Ion source determinations. Meta-stable scan at 4-8 kv.

m/e 245	m/e 230	m/e 201
263→245(s 0.075)	248→230(vs 0.080)	217→201(s 0.081)
274→245(m 0.120)	274→230(vl 0.192)	229→201(vl 0.140)
290→245(m 0.182)	268→230(s 0.268)	246→201(m 0.225)
		261.5→201(m 0.301)
		274→201(m 0.365)
		290→201(m 0.441)

m/e 188	m/e 174	m/e 158
217→188(l 0.155)	202→174(l 0.161)	186→158(vs 0.059)
227→188(vs 0.210)	218→174(m 0.254)	202.5→158(vs 0.094)
231→188(vs 0.230)	230→174(s 0.322)	229→158(l 0.150)
262→188(m 0.393)	246→174(m 0.412)	248→158(vs 0.189)
290→188(s 0.540)	262→174(m 0.505)	290→158(vs 0.279)
	289→174(m 0.660)	

m/e 142	m/e 130
157→142(vs 0.036)	158→130(l 0.071)
170→142(vs 0.066)	185→130(vs0.142)
	201→130(vs0.183)
	245→130(m 0.296)
	288→130(l 0.406)

(ii) Nitroindolizines

3-Nitroindolizine (74).

m/e	163	162	146	133	132	130	129	117	116
I%	8	83($\underline{M}^+$)	9	8	77	25	6	8	72
m/e	115	114	105	104	103	90	89	88	87
I%	6	5	6	43	6	19	100	11	7
m/e	86	79	78	77	76	75	74	65	64
I%	4	54	54	14	16	11	7	9	15
m/e	63	62	61	53	52	51	50	49	44
I%	59	26	84	5	28	49	36	5	10
m/e	43	40							
I%	8	5							

m^* 83(162→116), 68.3(116→89).

2-Methyl-3-nitroindolizine (23).

m/e	177	176	160	159	158	147	146	145	144
I%	11	100($\underline{M}^+$)	9	21	4	4	28	6	45
m/e	143	142	131	130	129	127	119	118	117
I%	56	10	16	29	8	13	5	23	51
m/e	116	105	104	103	102	101	93	92	91
I%	13	5	19	27	13	5	7	5	10
m/e	90	89	88	79	78	77	76	75	74
I%	13	11	4	18	42	45	11	9	5
m/e	65	64	63	62	53	52	51	50	44
I%	9	10	18	8	6	19	46	20	5
m/e	39	38	37						
I%	39	10	4						

m^* 143.6(176→159) 117.9(176→144).

2-Methyl-1-nitroindolizine (22).

m/e	177	176	175	160	146	145	143	131	130
I%	12	100($\underline{M}^+$)	5	9	25	5	5	10	23
m/e	129	128	117	106	105	104	103	102	89
I%	6	7	6	13	24	11	26	14	5
m/e	79	78	77	76	75	74	64	63	62
I%	18	80	39	11	9	7	5	12	6
m/e	55	52	51	50	39	38			
I%	5	14	32	15	24	7			

m^* 143.6(176→159), 131(160→114), 57.5(105→78).

1,2-Dimethyl-3-nitroindolizine (178).

m/e	191	190	176	174	173	159	158	157	156
I%	12	100($\underline{M}^+$)	13	9	24	9	41	45	4
m/e	155	146	145	144	143	142	141	132	131
I%	8	5	11	38	36	38	7	9	8
m/e	130	129	128	118	117	116	115	106	105
I%	28	6	5	17	52	9	13	8	9
m/e	104	103	102	93	91	90	89	79	78
I%	15	8	6	8	9	5	8	18	35
m/e	77	76	75	65	64	63	62	53	52
I%	16	6	6	9	6	14	5	8	18
m/e	51	50	44	43	41	39			
I%	35	13	5	7	5	24			

(iii) 3-Aminoindolizines

3-Aminoindolizine (105)

m/e	133	132	131	130	129	126	124	117	116
I%	13	99($\underline{M}^+$)	78	72	18	8	4	4	8
m/e	109	107	106	105	104	103	100	94	92
I%	4	6	6	27	28	7	11	6	6
m/e	90	89	83	80	79	78	77	76	75
I%	5	7	5	10	100	37	13	10	6
m/e	66	65	64	63	62	58	57	56	55
I%	9	6	4	7	4	20	7	9	5
m/e	54	53	52	51	50	44	41	40	39
I%	4	7	25	28	18	8	13	5	14

m/e	38	37
I%	6	5

m^* 130(132→131), 82.5(131→104).

3-Amino-2-methylindolizine (106).

m/e	147	146	145	144	143	131	119	118	117
I%	10	100($\underline{M}^+$)	54	15	18	21	10	52	32
m/e	116	104	93	92	91	90	89	79	78
I%	6	10	12	4	8	9	8	17	19
m/e	76	75	74	72	71	66	65	64	63
I%	5	5	4	14	19	4	10	6	12
m/e	62	57	55	54	53	52	51	50	45
I%	5	20	9	7	5	15	24	12	4
m/e	43	42	41	40	39	38	37		
I%	6	6	10	6	29	10	5		

m^* 96(145→118), 70.5(118→91).

3-Amino-2-phenylindolizine (59).

m/e	209	208	207	206	205	182	181	153	104
I%	15	100($\underline{M}^+$)	31	5	8	7	44	4	10
m/e	103	91	80	79	78	52	51		
I%	8	6	7	9	5	4	5		

m^* 157(208→181).

3-Amino-1,2-diphenylindolizine (107).

m/e	285	284	283	282	281	256	254	207	206
I%	23	100($\underline{M}^+$)	22	14	23	15	7	7	6

m/e	205	180	178	167	142	141	140	134	128
I%	7	6	4	12	6	10	6	5	6
m/e	127	126	79	78	77	63	52	51	39
I%	11	55	8	17	8	3	5	12	5

3-Amino-5-methyl-2-phenylindolizine (111).

m/e	223	222	221	220	219	208	207	206	205
I%	17	100($\underline{M}^+$)	37	7	5	4	23	13	4
m/e	204	145	119	111	110	103	102	93	92
I%	5	3	4	14	6	5	6	10	10
m/e	77	76	65	51	43	39			
I%	7	3	7	4	4	5			

Ethyl 3-Amino-2-methylindolizine-1-carboxylate (108).

m/e	219	218	217	191	190	189	187	174	173
I%	15	100($\underline{M}^+$)	6	8	59	15	4	5	31
m/e	172	171	165	146	145	144	143	142	129
I%	5	16	6	16	24	12	18	13	7
m/e	120	119	118	117	116	104	103	95	93
I%	8	16	50	32	12	9	17	5	17
m/e	92	91	90	89	80	79	78	77	76
I%	12	8	9	12	5	11	28	9	5
m/e	75	74	69	66	65	64	63	59	57
I%	4	8	4	5	12	6	10	10	7
m/e	55	52	51	50	45	44	43	42	41
I%	5	10	16	7	18	6	11	4	8
m/e	39								
I%	15								

m* 155.8(218→190), 70.3(118→91).

Ethyl-3-Amino-2-phenylindolizine-1-carboxylate (109).

m/e	281	280	279	253	233	208	207	206	205
I%	2	20	100	14	7	10	9	8	31
m/e	181	180	179	178	165	152	151	103	102
I%	7	48	10	6	5	8	4	12	4
m/e	90	89	79	78	77	76	75	63	51
I%	13	40	8	48	11	67	36	44	13
m/e	39								
I%	7								

m* 227.6(279→252).

(iv) 3-Acetamidindolizines

3-Acetamido-2-methylindolizine (50).

m/e	189	188	146	145	144	143	118	117	91
I%	4	27($\underline{M}^+$)	17	100	3	4	9	12	4
m/e	78	65	51	43					
I%	7	3	5	5					

m* 111.3(188→146), 96.0(145→118), 70.3(118→91).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Calculated
145	145.07657	$C_9H_9N_2$	145.07535
144	144.06875	$C_9H_8N_2$	145.06763
118	118.06567	C_8H_8N	118.06520

117	117.05785	C_8H_7N	117.057862
91	91.05477	C_7H_7	91.05474

Ion source determinations. Meta-stable scan at 4-8 kv.

m/e 145	m/e 144	m/e 118
187→145(vl 0.292)	158→144(s 0.100)	144→118(vl 0.218)
	171→144(l 0.186)	158→118(vs 0.339)
	185→144(l 0.286)	186→118(vs 0.575)

m/e 117	m/e 91
144→117(vl 0.227)	118→91(vl 0.294)
131→117(vs 0.118)	144→91(l 0.588)

3-Acetamido-1-acetyl-2-methylindolizine (47)

m/e	231	230	189	188	187	173	161	160	146
I%	5	36($\underline{M}^+$)	5	39	100	7	5	9	13
m/e	145	144	143	142	129	119	118	117	93
I%	83	9	9	5	4	19	29	5	4
m/e	92	91	90	89	79	78	77	63	52
I%	19	5	5	6	6	25	5	5	6
m/e	51	50	43	39					
I%	9	4	52	8					

m^* 3 152(230→187), (145→118). 96.1

3-Acetamido-2-phenylindolizine (112)

m/e	251	250	208	207	206	205	180	152	78
I%	6	34($\underline{M}^+$)	26	100	5	8	14	4	8

m^* 171.3(250→207), 156.3(207→180).

3-Diacetamido-2-phenylindolizine (41).

m/e	293	292	251	250	232	208	207	206	205
I%	3	16($\underline{M}^+$)	6	33	5	22	100	45	11
m/e	180	78	51	43					
I%	13	13	6	30					

m^* 214.0(292→250), 171.4(250→207), 156.3(207→180).

3-Acetamido-1,2-dimethylindolizine (113).

m/e	203	202	188	187	186	173	172	160	159
I%	4	22($\underline{M}^+$)	7	5	12	7	6	13	100
m/e	158	157	145	144	143	142	141	117	115
I%	5	4	4	30	10	8	3	18	4
m/e	105	79	78	77	63	52	51	43	39
I%	4	5	9	5	4	5	8	15	8

m^* 125.0(202→159).

3-Acetamido-1,2-diphenylindolizine (114).

m/e	327	326	285	284	283	282	281	272	256
I%	10	36($\underline{M}^+$)	4	30	100	7	7	5	8
m/e	254	182	178	168	167	155	78	77	51
I%	9	4	4	5	30	7	22	6	6
m/e	43	39							
I%	7	2							

m^* 246(326→283), 98.6(283→167).

3-Acetamido-5-methyl-2-phenylindolizine (115).

m/e	265	264	263	222	221	220	219	206	119
I%	16	61	5	26	100	7	8	5	5
m/e	109	103	102	97	95	93	92	83	81
I%	4	4	13	5	5	4	19	5	5
m/e	77	72	71	69	58	57	55	45	44
I%	5	4	4	7	7	7	8	4	4
m/e	43	39							
I%	26	4							

m^* 185(264→221), 192(206→221).

Ethyl 3-Acetamido-2-methylindolizine-1-carboxylate (116).

m/e	261	260	218	217	215	190	189	187	173
I%	8	11($\underline{M}^+$)	20	100	10	4	9	6	6
m/e	172	144	143	142	129	118	117	116	89
I%	50	7	16	9	4	8	11	10	8
m/e	78								
I%	14								

Ethyl 3-Acetamido-2-phenylindolizine-1-carboxylate (117).

m/e	323	322	281	280	252	250	234	227	226
I%	16	68($\underline{M}^+$)	5	100	5	4	6	6	7
m/e	225	180	179	178	78	43			
I%	35	8	6	5	37	25			

m^* 227.5(280→252).

(v) 3-(2-Pyridyl)acrylonitriles

3-(2-Pyridyl)acrylonitrile (130).

m/e	131	130	129	105	104	103	93	92	89
I%	3	96($\underline{M}^+$)	22	22	21	8	5	5	5
m/e	80	79	78	77	76	75	69	65	63
I%	7	100	15	15	14	7	5	11	6
m/e	57	56	55	52	51	50	41	39	38
I%	19	8	7	19	24	17	15	12	5

2-Methyl-3-(2-pyridyl)acrylonitrile (73).

m/e	145	144	143	142	119	118	117	104	93
I%	10	82($\underline{M}^+$)	100	12	10	51	13	13	9
m/e	90	89	79	78	77	76	75	65	64
I%	13	12	10	13	4	6	4	4	7
m/e	63	62	58	52	51	50	39		
I%	12	6	6	12	20	10	13		

m^* 142.8(144→143).

Accurate mass measurements on selected ions:

m/e	Found	Empirical Formula	Required
104	104.05002	C_7H_6N	104.04895
90	90.04695	C_7H_6	90.04803

Ion source determinations. Meta-stable scan 2-8 kv.

m/e 104	m/e 90
144→104(m 0.127)	117→90(vl 0.099)
	142→90(s 0.193)

2-Phenyl-3-(2-pyridyl)acrylonitrile (61).

m/e	207	206	205	180	177	151	103	89	78
I%	9	60($\underline{M}^+$)	100	3	4	4	4	4	4
m/e	77	51							
I%	3	6							
m^*	204(206→205).								

2,3-Diphenyl-3-(2-pyridyl)acrylonitrile (133).

m/e	283	282	281	280	279	254	206	140	128
I%	9	47($\underline{M}^+$)	100	4	12	6	20	8	5
m/e	127	126	125	79	78	77	51		
I%	11	4	6	3	10	4	9		

2-Phenyl-3(6-methylpyrid-2-yl)acrylonitrile (134).

m/e	221	220	219	218	205	109	51	39
I%	9	61($\underline{M}^+$)	100	7	5	4	4	5

2-Phenyl-3(6-hydroxymethylpyrid-2-yl)acrylonitrile (147)

m/e	237	236	235	234	221	220	219	218	217
I%	7	35($\underline{M}^+$)	7	4	4	33	100	18	11
m/e	216	208	207	206	205	190	180	178	177
I%	5	10	7	6	19	5	9	6	7
m/e	154	153	152	151	124	110	98	84	78
I%	14	7	8	7	9	6	19	7	8
m/e	77	76	51						
I%	9	5	10						
m^*	203.2(232→219).								

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