# SYNTHESIS, REACTIONS, AND MASS SPECTRA OF SOME INDOLIZINES

by

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## SUMMARY

The methods of synthesis and known properties of indolizines are reviewed.

A number of indolizine compounds substituted in both the 5 membered and 6 membered rings have been prepared by known synthetic routes. The use of an ion exchange resin to bring about ring closure of an intermediate quaternary compound is described.

Reduction with lithium aluminium hydride will usually convert indolizine esters to hydroxymethyl derivatives except in the case of the 1 position where reduction proceeds to the alkyl derivative.

Reduction of 2-methyl-7-cyanoindolizine with lithium aluminium hydride gives the expected aminomethyl compound while 2-methyl-6-cyano-indolizine does not. Reduction of the ring system may be occurring.

Reduction of indolizine with sodium and ethanol gives a mixture of a dihydro and tetrahydro product; further treatment yields only the tetrahydro product, 5,6,7,8-tetrahydroindolizine.

The mass spectra of indolizine and some of its derivatives are presented and the cracking patterns discussed. A marked similarity between the spectra of monomethylindolizines and monomethylindoles is noted and a possible explanation is put forward.

# A C K N O W L E D G M E N T S

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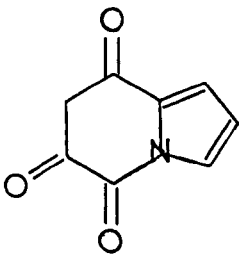
# CONTENTS

# INTRODUCTION

## Nomenclature

In 1890 Angeli[1,2,3] reported the preparation of the imine-anhydride of pyrrcylpyruvic acid (1). He suggested that the parent base should be named pyrindole. The names pyrrodine, 8-pyrrolopyridine, pyrrolo[1,2-a]-pyridine, pyrrocoline and indolizine have also been employed. It is the latter name, first suggested by Tschitschibabin, which is now the accepted one. Three systems of numbering (2, 3 and 4) have been employed.



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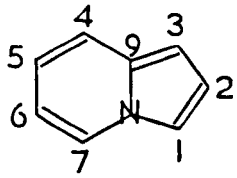

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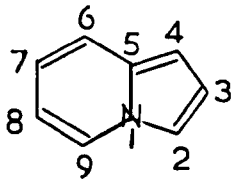

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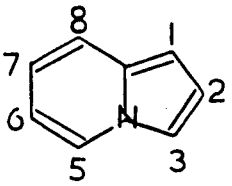


(4)

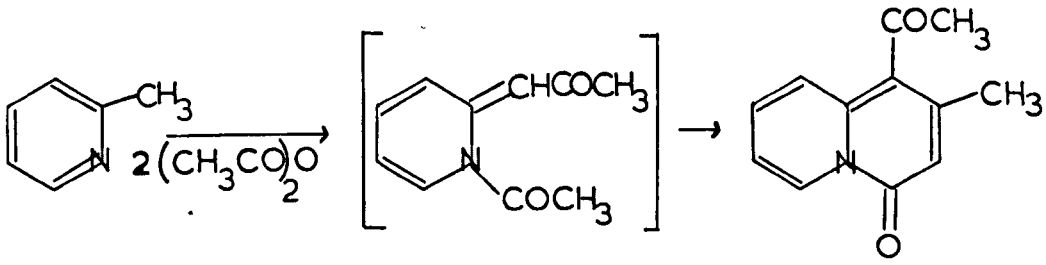
Throughout this thesis the name indolizine and the system of numbering (4) will be employed.

## Survey of Previous Work

### (a) Synthesis of Indolizine Compounds

The parent base, indolizine, was first synthesised by Scholtz.[4] The reaction of 2-picoline with acetic anhydride at 220° afforded a product which he called "picolide" and assigned structure (5). The mechanism of formation which he suggested is shown in Scheme I. Hydrolysis of "picolide" with 25% hydrochloric acid yielded a new base, indolizine (12) with the loss of two acetyl groups.

SCHEME I

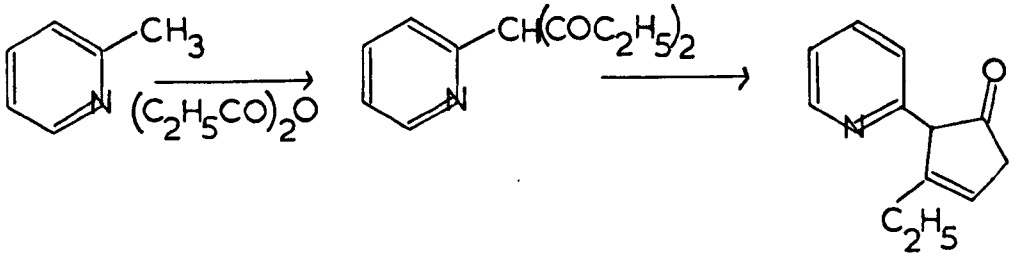



(5)

With this structure for "picolide" it was necessary to propose a mechanism of cleavage followed by ring closure in order to explain the formation of indolizine upon hydrolysis. Further, the mechanism could not explain the reaction[5] of 2-picoline with propionic anhydride for, in this case,

only one mole of anhydride was involved. A different mechanism was proposed and the product formulated as (6) in Scheme II.

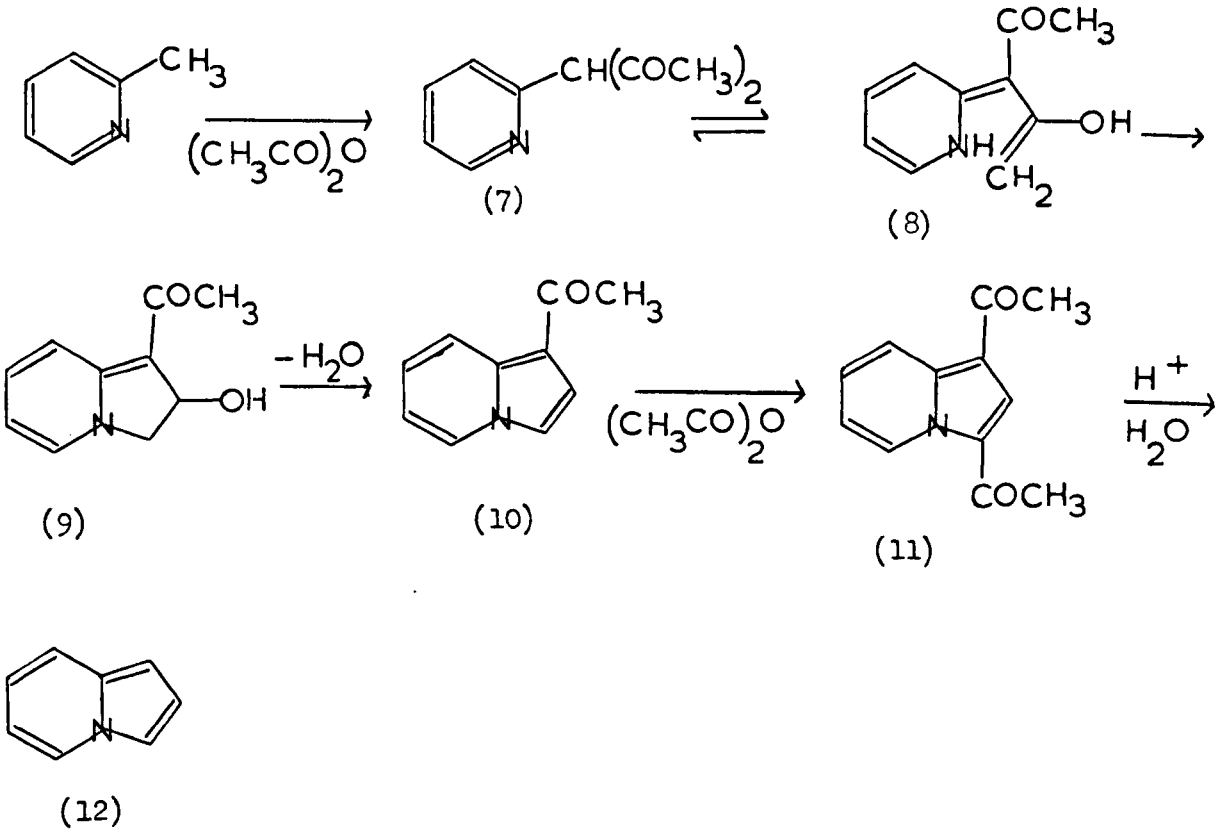
SCHEME II



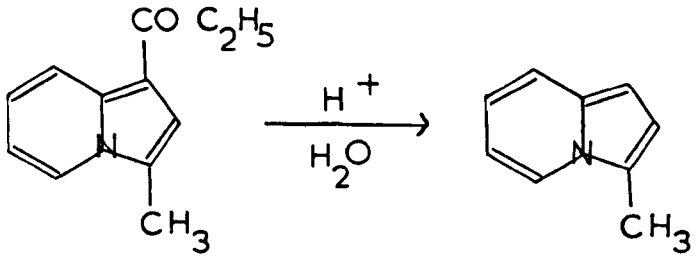
(6)

These mechanisms and structures were unacceptable to Tschitschibabin and Stepanov who said[6] that the indolizine nucleus was present in both "picolide" and the product from the reaction of 2-picoline with propionic anhydride. According to their mechanism, outlined in Scheme III, the first product in the reaction of 2-picoline with acetic anhydride is the $\omega$-diacetylpicoline (7) which reacts in a tautomeric form (8) to undergo ring closure to a dihydroindolizine (9). Dehydration yields 1-acetyl-indolizine (10) which is then further acetylated to produce "picolide" or 1,3-diacetylindolizine (11). Hydrolysis of the diacetyl compound (11) yields indolizine (12).

SCHEME III



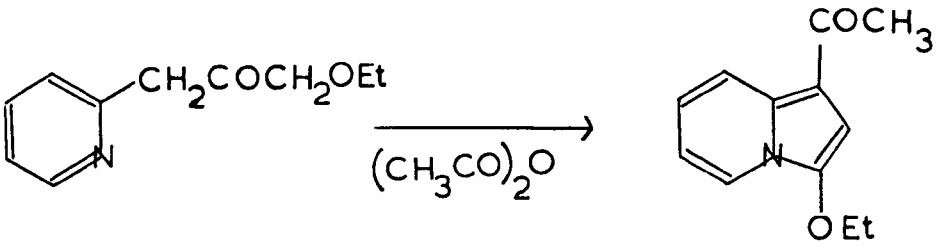

Similarly, the reaction of 2-picoline with propionic anhydride yields[7] 1-propionyl-3-methylindolizine (13) which fails to undergo further acylation under these conditions due to the methyl group in the 3 position.



Acid hydrolysis of the propionyl derivative (13) gave 3-methylindolizine (14) the structure of which was confirmed by Ochiai and Tsuda.[8]

The presence of the indolizine nucleus in "picolide" was finally established by the monoacetylation of indolizine as described by Scholtz,[9] followed by further acetylation[6] at 220° to yield "picolide".

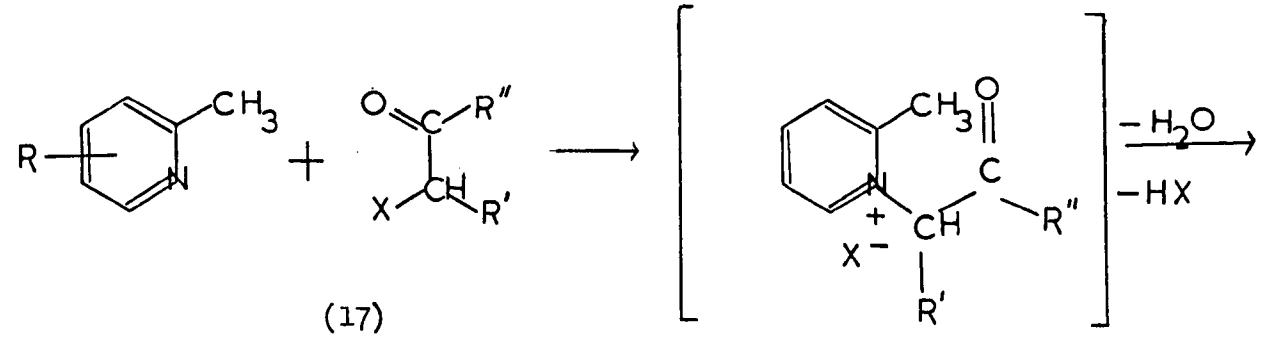
The scope of this synthetic route has been extended to various lutidines and aryl-2-picolines in order to produce indolizines with alkyl[4,10,11] and aryl groups[10] in the six-membered ring. Efforts to use the anhydrides of acids other than acetic and propionic,[5] or to condense quinaldine with acetic anhydride,[12] were not successful. Leonard and Condrow[13] obtained a 3-ethoxyindolizine derivative (16) by treating ethoxymethyl 2-picolyl ketone (15) with acetic anhydride.




(15) (16)

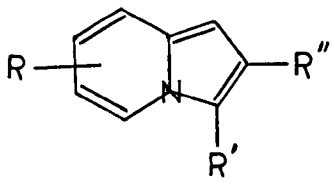
A widely employed synthesis of substituted indolizines was first suggested[14] by Tschitschibabin: the condensation of 2-picolines with α-halogenoketones (17) to form quaternary compounds (18), followed by ring closure to the appropriate indolizine (19). This is shown in Scheme IV.

SCHEME IV



(17)

(18)



(19)

When bromoacetaldehyde was used the synthesis afforded the parent base, indolizine, in only 1% yield.[12] The yields of 2-alkyl- and 2-arylindolizines were very much better and in some cases exceeded 90%. The reaction between the α-halogenoketone and the picoline usually proceeds more smoothly in the presence of a solvent. Absolute ethanol, 95% ethanol and acetone have been used. There is evidence to suggest that α-bromoketones are superior to α-chloroketones in the quaternisation reaction.[16] Steric

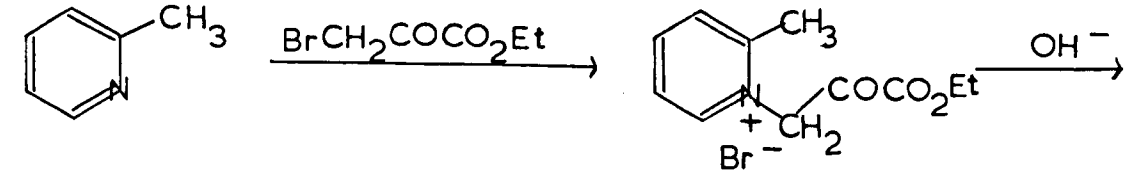
factors are also important. The use of halogenoketones in which either the halogen[12] or the carbonyl group[19] is hindered, or the use of 6-substituted-2-picolines[14,18,20] reduces the yield of the indolizine.

Cyclisation of the quaternary salt is usually accomplished by treatment with a base in aqueous or alcoholic solution. Aqueous sodium bicarbonate[15] is particularly useful.

The method has been applied satisfactorily to prepare 2,3-dimethyl-,[17] 2,5-dimethyl-,[14] 2-methyl-3-ethyl-,[16] 1-phenyl-2-methyl-,[14] 2-methyl-,[14] 2-phenylindolizine[14] and many other compounds of this type.[6,7,14-27] (See Reference 28 for further details).

Borrows, Holland and Kenyon[15,21] attempted to extend the scope of the reaction by use of α-halogeno-β-diketones, α-halogeno-β keto esters and β-halogeno-α-keto esters, namely α-chloroacetylacetone, α-bromobenzoylacetone, ethyl α-chloroacetoacetate, ethyl α-bromobenzoylacetate and bromopyruvic acid or ester. With all but the last it was difficult to form the quaternary salt (18; R' = $COCH_3$, $COC_6H_5$, $CO_2C_2H_5$, etc.) and upon cyclisation the acyl, or ester, function was lost. Ethyl bromopyruvate however, readily gave indolizine-2-carboxylic acid[21] (20) as shown in Scheme V. The acid (20) can be decarboxylated to give[29,30] indolizine.

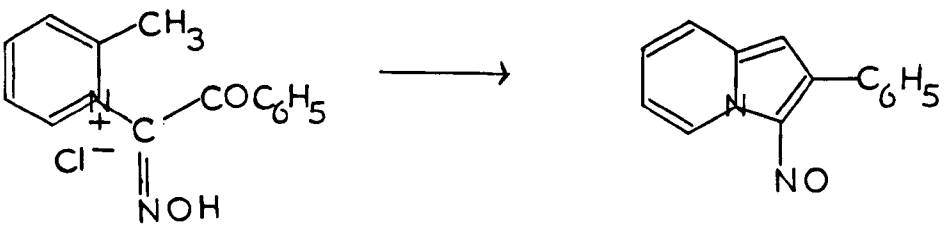
SCHEME V





(20)

1-Ethoxyacetylindolizine-2-carboxylic acid has been produced[13] using bromopyruvic acid. An extension of the synthesis is shown in the preparation[22] of 3-nitroso-2-phenylindolizine (22) from 2-picoline and $\omega$-chloroisonitrosoacetophenone via $\omega$-isonitrosophenacyl-2-picolinium chloride (21).



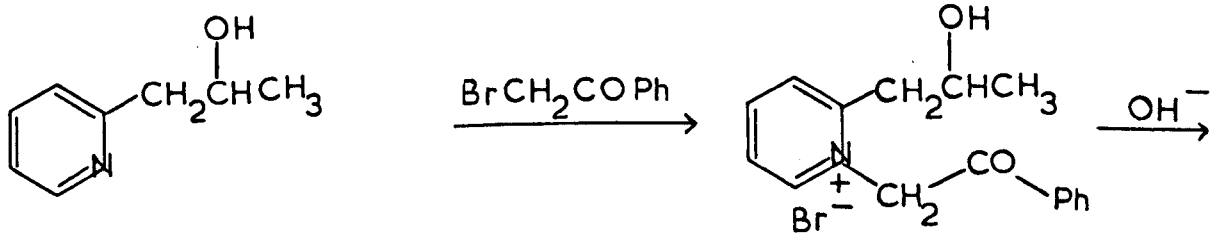

(21) (22)

In contrast, the corresponding quaternary nitro compound from ω-nitro-bromoacetophenone could not be made.[31]

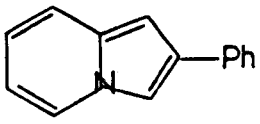
Some pyridines, for reasons other than steric hindrance of the nitrogen atom, will not form quaternary compounds with halogenoketones. Thus 2-pyridylacetone failed[12] to react with ω-bromoacetophenone to produce the desired quaternary product.

Although 1 substituted indolizines may be prepared by the Tschitschibabin synthesis, e.g. using 2-ethylpyridine with halogenoketones,[18] an attempt[32] to prepare 1-hydroxyethyl-2-phenylindolizine from the reaction of 1-(2-pyridyl)-2-propanol with ω-bromoacetophenone failed. The quaternary compound (23) was prepared without difficulty but on attempted ring closure loss of the hydroxyethyl group resulted. The product was 2-phenylindolizine (24).

SCHEME VI

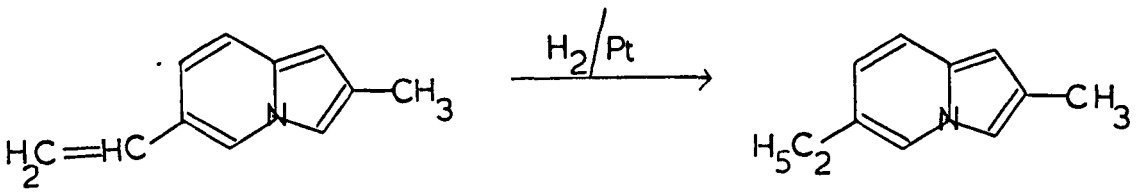



(23)



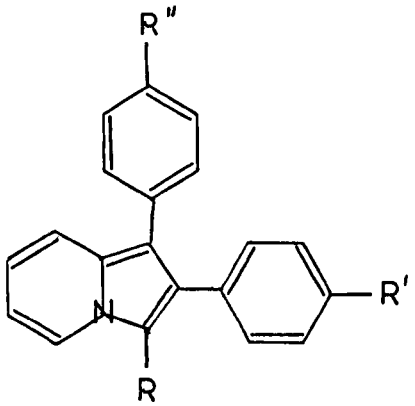

(24)

By this method of synthesis, using bromoacetone, Stepanov and Turchinovich[34] have produced 2-methyl-6-vinylindolizine (25) which can be reduced to the 6-ethyl derivative (26).




(25) (26)

Using 2-benzylpyridines and $\omega$-bromoacetophenones Venturella has prepared[35] a number of 1,2-diphenylindolizines of general formula (27).

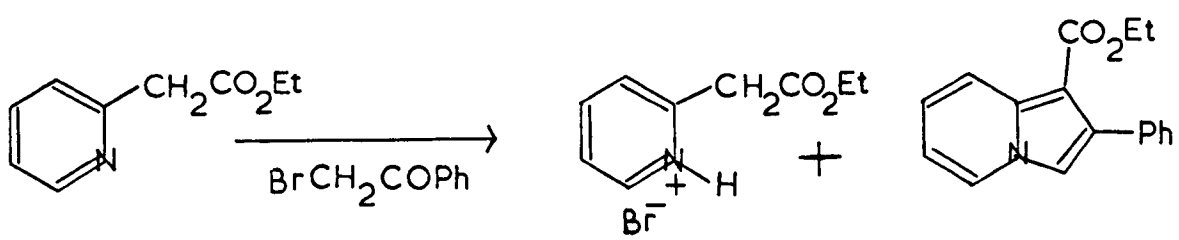



(27)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Where | R | = | H | H | Ph | H | H | Ph |
| | R' | = | Br | $NO_2$ | H | Br | $NO_2$ | H |
| | R" | = | H | H | H | Cl | Cl | Cl |

Bragg and Wibberley[36] found that when ethyl 2-pyridylacetate (28) was boiled under reflux with phenacyl bromide in ether, ethyl 2-pyridylacetate hydrobromide (29) separated instead of the quaternary salt. After filtration and concentration of the filtrate ethyl 2-phenylindolizine-1-carboxylate (30) crystallised. Evidently part of the ester behaves as a base removing hydrogen bromide and causing ring closure as shown in Scheme VII.

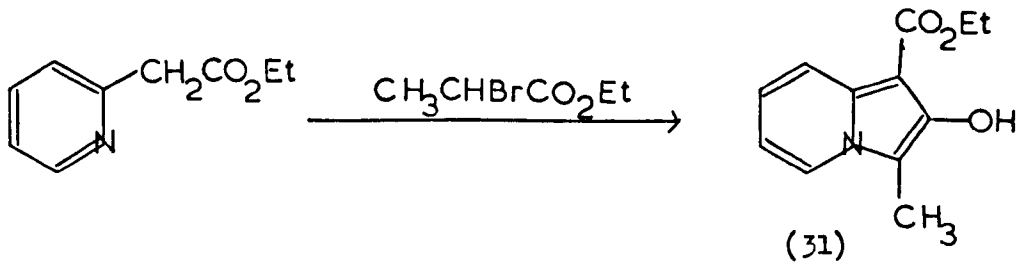
SCHEME VII




(28) (29) (30)

The yield was improved by using two moles of ester and still further by using acetone as solvent. The method is of general application and in this way they have been able to prepare directly indolizines with the nitro group in position 1 and ester, acyl or cyano groups in position 1 or 3.

The reaction of α-bromoesters with ethyl 2-pyridylacetate yielded a series of 2-hydroxyindolizines. Thus ethyl 2-pyridylacetate and ethyl α-bromopropionate afforded ethyl 2-hydroxy-3-methylindolizine-1-carboxylate (31).

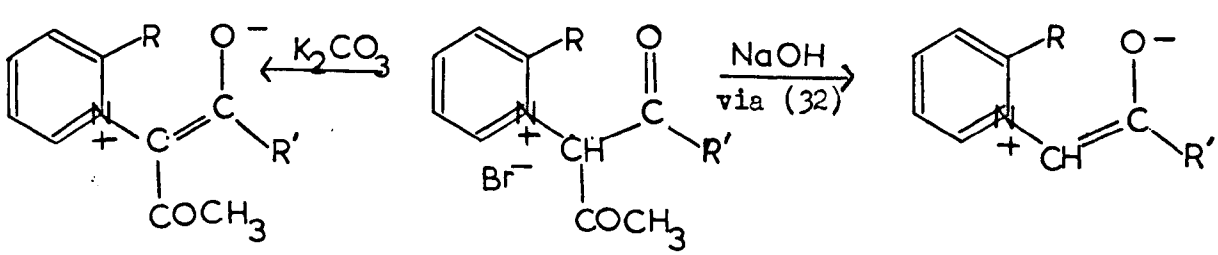



(31)

Kappe has recently shown[66] that the reaction between 2-pyridylacetates and ethyl bromopyruvate yields indolizines and not quinolizines as previously believed.[67]

Previous authors[12,28] imply that the mechanism of the Tschitschibabin synthesis involves an "enol-betaine" (32) as shown in Scheme VIII. Such "enol-betaines" on treatment with strong alkali can undergo so called "acid-cleavage"[39] with loss of an acyl group and this explains the advantage of using weak bases for the ring closure in the indolizine synthesis.

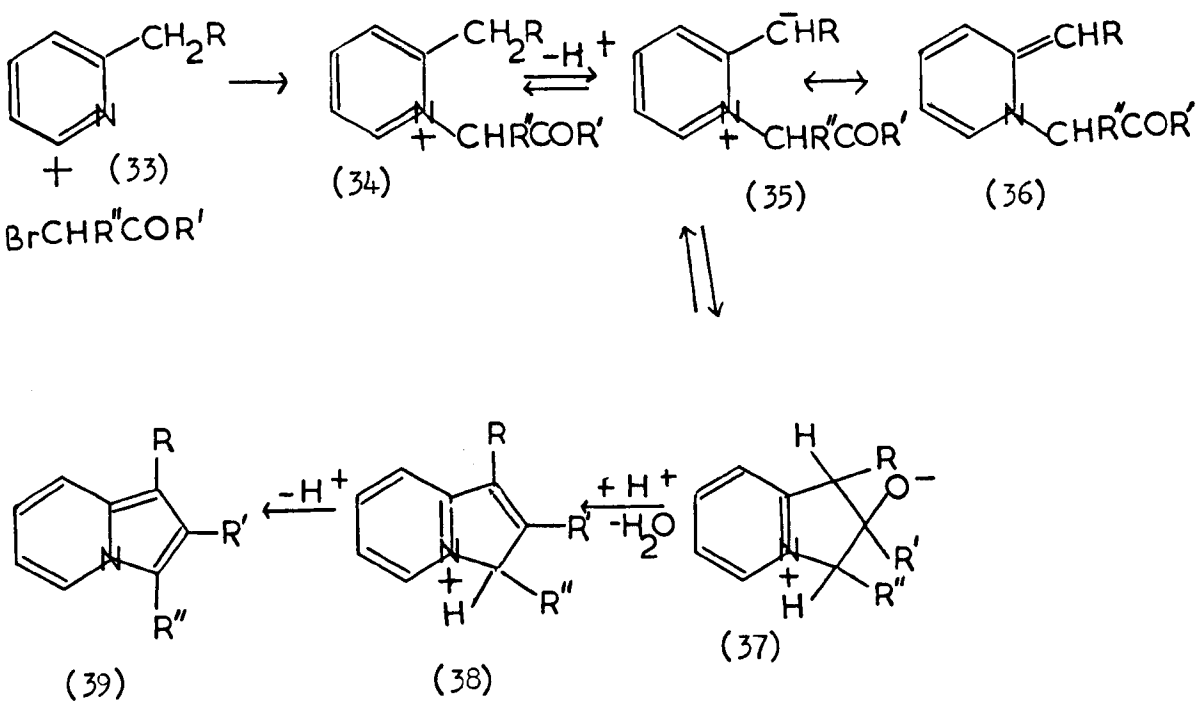
SCHEME VIII




(32)

Bragg and Wibberley[37] suggest that such compounds are not in a form capable of cyclisation and that the formation of indolizines from 2-picoline and its derivatives (33; R = H, $CO_2Et$, CN or COPh) involves an aldol-type condensation as outlined in Scheme IX.

SCHEME IX

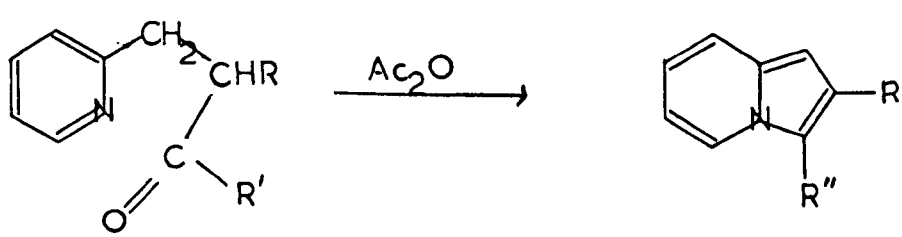



Quaternary salts were not isolated in their synthesis from ethyl 2-pyridylacetate but since the latter is readily quaternised with methyl iodide this points to the fact that the quaternary salt (34) is probably an intermediate in the synthesis. Proton loss from the quaternary salt (34)

to form the carbanion-betaine (35) will be facilitated when the group R is electron withdrawing, and so a second molecule of the picolyl base is adequate to bring about the reaction when R = $CO_2Et$, CN or Bz, but sodium bicarbonate is required when R = H. After cyclisation of the carbanion-betaine (35) by an intramolecular aldol-type reaction, removal of water from the product (37) would yield the indolizinium cation (38). (There is clear evidence[11,40] that in its salts indolizine is protonated in the 3-position). An excess of base would then liberate the indolizine (39).

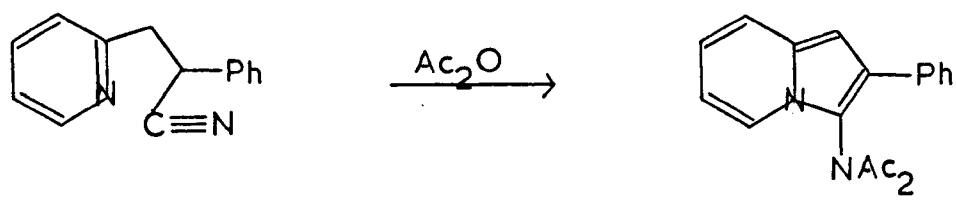
Hurst, Melton and Wibberley[38] investigated an alternative type of indolizine synthesis. 2-Bromomethylpyridine was treated with the sodio-derivatives of methyl and ethyl acetoacetate, diethyl malonate and acetyl acetone. The resulting 2-(2-oxoethyl)pyridines (40) were cyclised by boiling under reflux in acetic anhydride solution to give the indolizines (41; R = $CO_2CH_3$, R" = $CH_3$: R = $CO_2C_2H_5$, R" = $CH_3$: R = $CO_2C_2H_5$, R" = OAc: R = Ac, R" = Me), respectively.

SCHEME X




(40) (41)

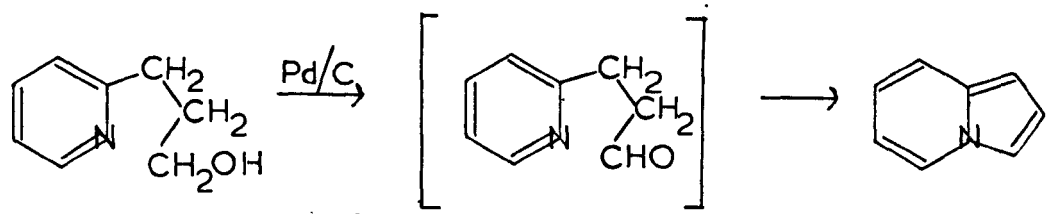
The reaction can be regarded as an intramolecular nucleophilic attack of the ring nitrogen atom on the side-chain carbonyl group together with dehydration. Another example of this type of synthesis is presented by the same authors. 3-Diacetylamino-2-phenylindolizine (43) results from the action of acetic anhydride on 2-β-cyanophenethylpyridine (42).




(42) (43)

The same type of cyclisation has been reported by Boekelheide and Windgassen[41] in their preparation of the parent compound indolizine. The synthesis depends on the known instability of 3-(2'-pyridyl)propionaldehyde[42] (45) coupled with the fact that this compound is able to form indolizine by loss of the elements of water. When 3-(2'-pyridyl)-1-propanol (44) was heated in the presence of a dehydrogenation catalyst, water and hydrogen were eliminated to give indolizine directly in 50% yield. To date, this represents the most convenient synthesis of indolizine.

SCHEME XI

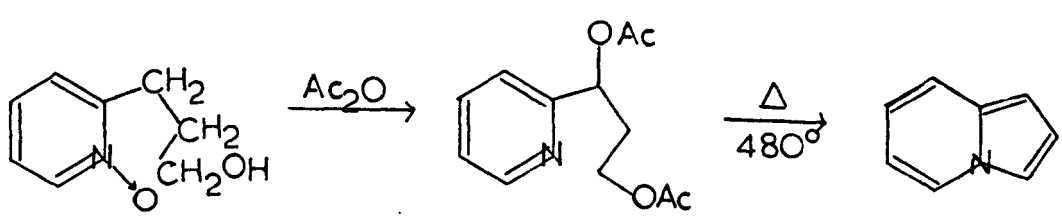



(44) (45)

The intermediate aldehyde was not isolated.

Previously, Boekelheide and Feely[62] had obtained indolizine in 35% yield from 3-(2'-pyridyl)-1-propanol-N-oxide (46) in a two step process. The first step was the formation of the diacetate (47) by treatment with acetic anhydride. Pyrolysis of the diacetate in a nitrogen atmosphere at 480° then gave indolizine directly.

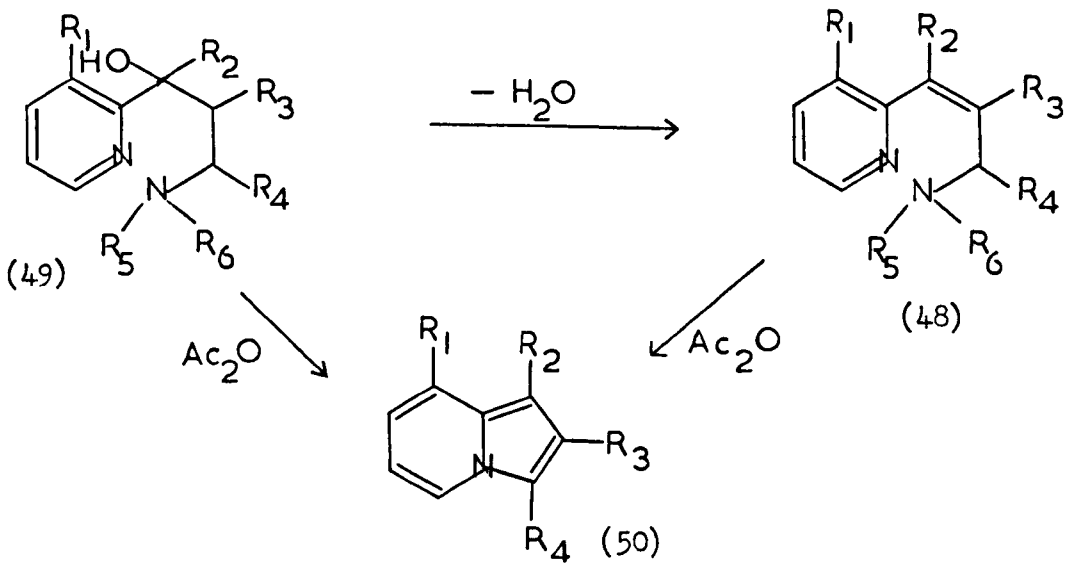
SCHEME XII




(46) (47)

Another synthesis of indolizines is one due to Barrett.[43-46] 1-Alkyl- or 1-arylindolizines can be prepared by the action of acetic anhydride on 3-alkyl (or aryl)-3-(2'-pyridyl)alkenylamines (48) or 3-alkyl(or aryl)-3-hydroxy-3-(2'-pyridyl)propylamines (49).

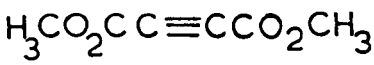
SCHEME XIII



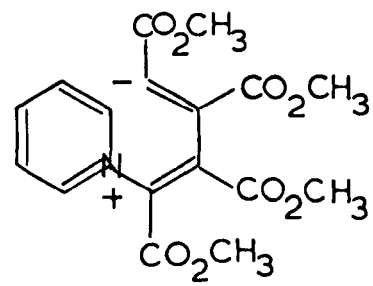

When $R_4$ is hydrogen in the starting material (48 or 49) then $R_4$ in the product is $COCH_3$ due to acetylation. The yield of indolizines from alkenylamines (48) is much higher when the pyridyl and aminoalkyl groups are cis with respect to the double bond.

Diels and his co-workers[47-53] studied the reactions of pyridines with acetylenedicarboxylic ester. In ethereal solution pyridine reacts with dimethyl acetylenedicarboxylate (51) to yield[47,48,49] at least three products; structures were assigned as follows; a red labile adduct (52); a yellow stable adduct (53) and the so-called "Kashimoto compound" (54).

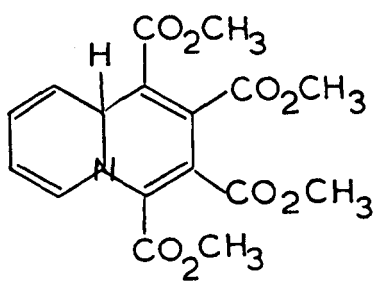
The labile adduct could be readily converted into the stable adduct by recrystallisation from 50% acetic acid or by heating.



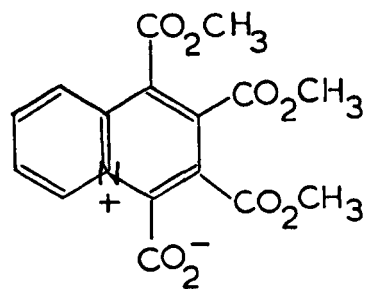
(51)



(52)

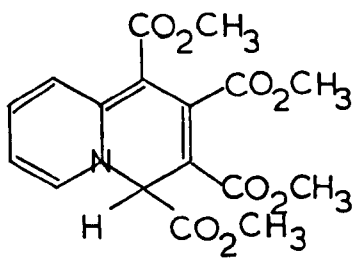


(53)

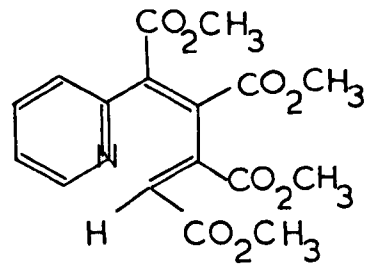


(54)

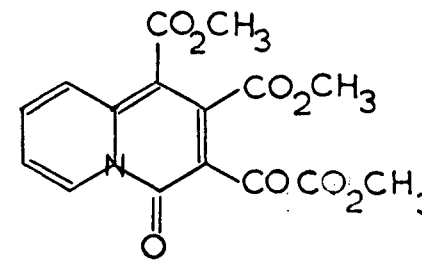
Subsequent workers[54,55] have revised these structures in the light of further evidence. The red labile adduct given the structure (52) by Diels is now thought to be a bicyclic system, tetramethyl 9a-H-quinolizine-1,2,3,4-tetracarboxylate (53). The yellow stable adduct is not the 9a-H compound (53) but thought to be tetramethyl 4H-quinolizine-1,2,3,4-tetracarboxylate (55), however, the 1(2'-pyridyl)-1,3 butadiene (56) cannot be ruled out.[117] "Kashimoto's compound" has been shown[33] to be a triester of structure (57).



(55)

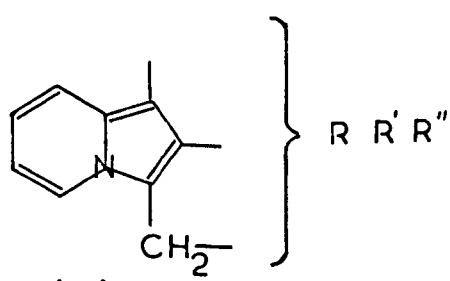


(56)



(57)

Wiley and Knabaschuh[57] using somewhat different conditions obtained trimethyl indolizine-1,2,3-tricarboxylate (59) from the above reaction. The course of the reaction was very susceptible to impurities. Diels and Alder studied the reactions of the stable adduct, thought by them to be the 9a-H compound (53) but now thought to be the 4-H compound (55), with formic acid[58] and phenol.[48] The work was repeated by Acheson and Taylor[56] who showed that the products were indolizines of general structure (58).



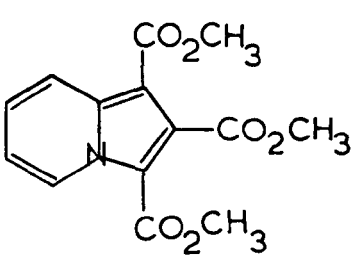
(58)

R R' R"

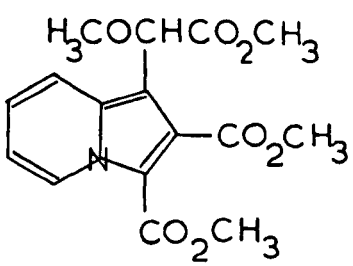
R = R' = R" = $CO_2CH_3$
R = R' = $CO_2Me$; R" = $CO_2H$
R = $CO_2CH_3$; R' = R" = $CO_2H$
etc.

The stable adduct (55) could be converted[48] into trimethyl indolizine-1,2,3-tricarboxylate (59) by oxidation with nitric acid or chromic acid, or treatment with bromine followed by hydrolysis. This work has been confirmed by Acheson and Taylor.[54] Substituted homologues of the foregoing series have also been prepared.[51,53,54,55]

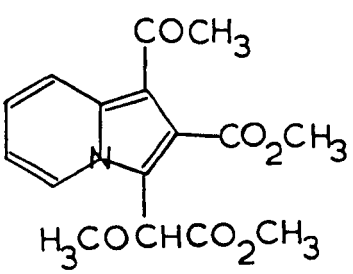
Diels and Meyer[50] studied the reaction of pyridine with acetylenedicarboxylic ester in methanol. They reported the formation of trimethyl indolizine-1,2,3-tricarboxylate (59) when the reaction was allowed to proceed unchecked. When the reaction mixture was kept at 0° then a different product was obtained, a white adduct which was given the structure (60) but now known[59] to be dimethyl 3-methoxycarbomethoxymethyl-indolizine-1,2-dicarboxylate (61). By treatment with bromine in methanol or acetic acid the white adduct could be converted into the trimethyl indolizine-1,2,3-tricarboxylate (59).



(59)



(60)

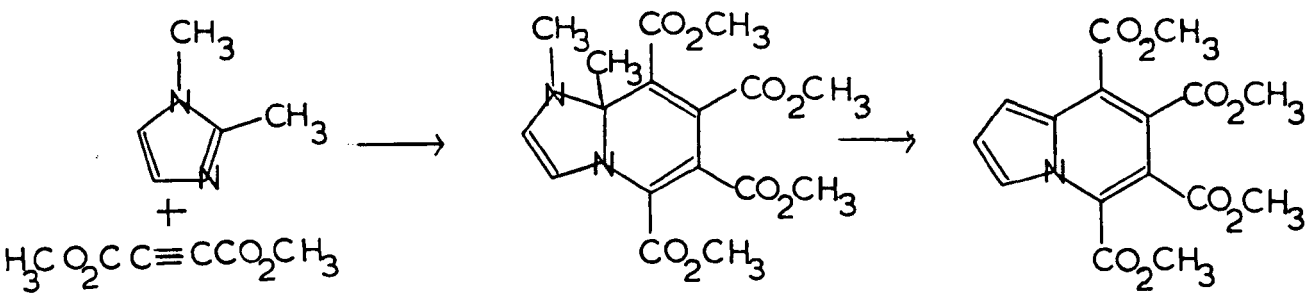


(61)

Borrows and Holland[31] attempted to repeat the direct preparation of the triester (59) by the method outlined above but obtained only a low yield of the white adduct (61).

A further example[61] of this type of condensation is the reaction of 1,2-dimethylimidazole with acetylene dicarboxylic ester to yield an imidazo[1,2-a]pyridine derivative (62) which on treatment with acetic acid loses methylamine to produce tetramethyl indolizine-5,6,7,8-tetra-carboxylate (63).

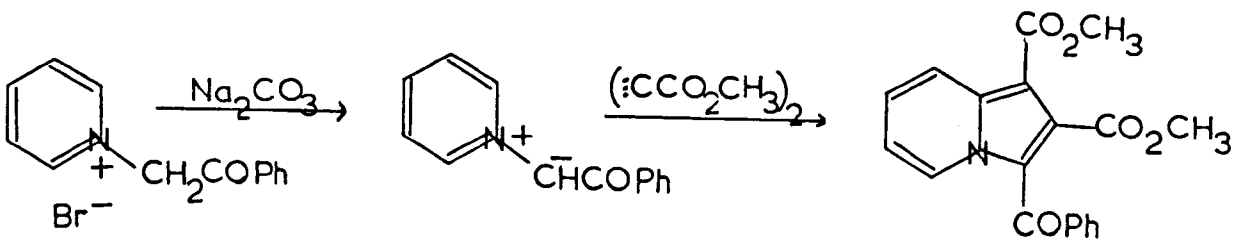
SCHEME XIV



(62) (63)

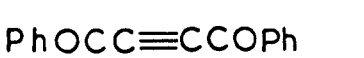
Boekelheide and Fahrenholtz[68] found that treatment of the zwitterion (65) derived from 1-phenacylpyridinium bromide (64) with dimethyl acetylene-dicarboxylate in the presence of a palladium on charcoal catalyst (5%) gave an indolizine (66) in 20% yield.

SCHEME XV

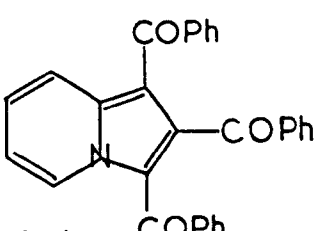



(64) (65) (66)

Henrick, Ritchie and Taylor[70] have examined this type of synthesis in more detail. They found that use of the dehydrogenation catalyst was unnecessary; better yields were obtained without it and under milder conditions. The highest yields (32%) were obtained by generating the ylid from the salt in dimethylformamide by addition of sodium hydride and then adding the ester, when an exothermic reaction ensued. They also found that pyridinium phenacylid (65) reacted with iodine in dimethylacetamide to give 1,2,3—tribenzoylindolizine (68). Dibenzoylacetylene (67) may be an intermediate, formed "in situ", but it could not be detected.



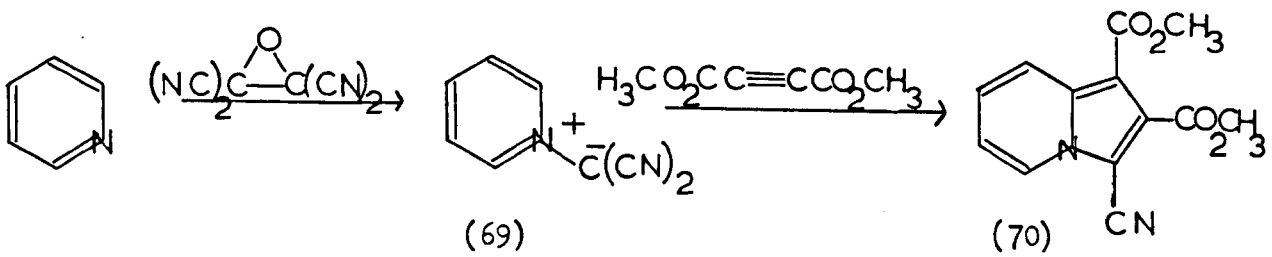

(67)




(68)

Treatment of pyridine with tetracyanoethylene oxide[69] gave a bright yellow compound, pyridinium dicyanomethylid (69), condensation of which with dimethyl acetylenedicarboxylate yielded dimethyl 3-cyano-indolizine-1,2-dicarboxylate (70).

SCHEME XVI




(69) (70)

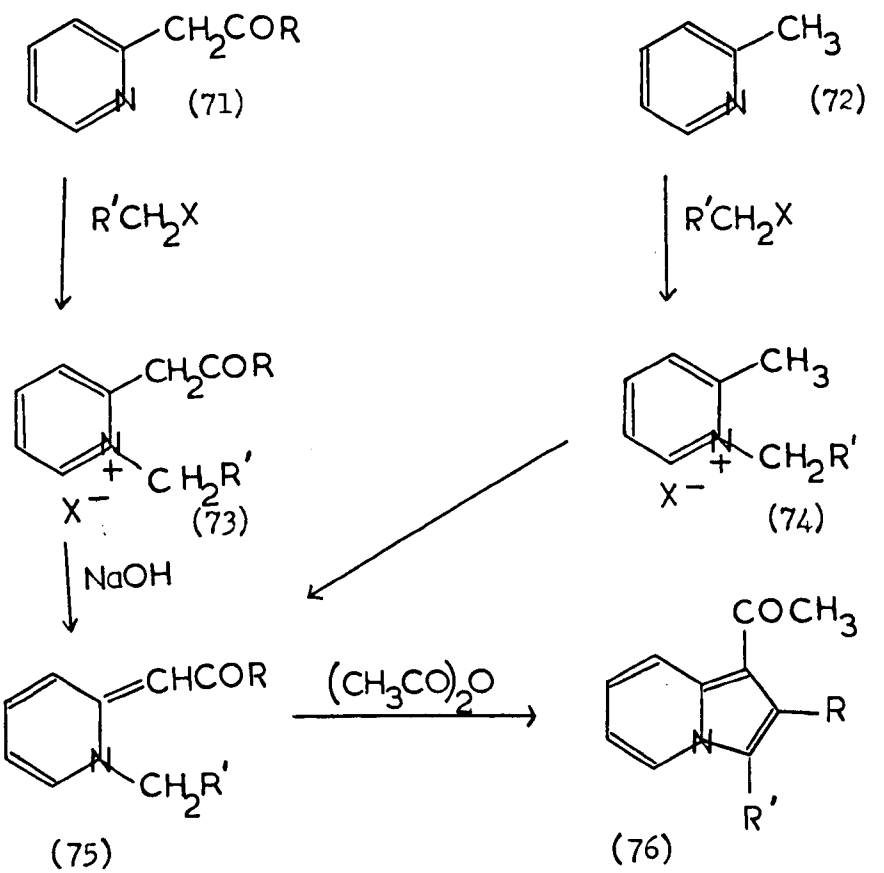
Acetylenedicarboxylic ester reactions have been reviewed by Acheson.[60]

Methyl propiolate reacts with pyridines to give indolizines and cycl[3,2,2]azines.[116]

Indolizines have recently been prepared by a method of ring closure at the 2-3 positions[63] of the 5-membered ring. The cyclisation involves an intramolecular aldol-type condensation of a suitable acyl- or ethoxycarbonylmethine (75) and is accomplished by boiling under reflux with acetic anhydride. The route is useful for the synthesis of 2,3-diaryl-, 2-alkyl-3-aryl-, and 2-acetoxy-3-arylindolizines. In some cases the required methine can be prepared by simultaneous acylation and dehydrohalogenation of a suitable 2-methylpyridinium bromide (74), prepared from the picoline (72).

Usually however, the methine is produced from the quaternary salt (73) of the required substituted picoline (71).

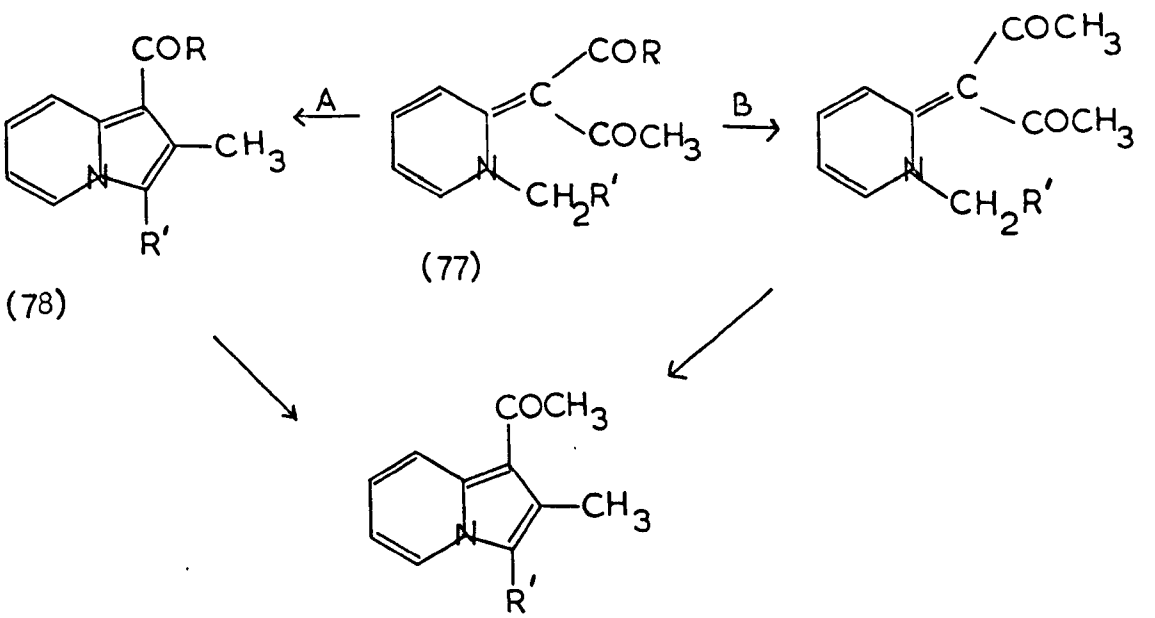
SCHEME XVII




2-Benzoylmethylene-1-benzyl-1,2-dihydropyridine (75; R = R' = Ph) gave 1-acetyl-2,3-diphenylindolizine (76; R = R' = Ph) in 90% yield. With those methines in which either the N-methylene or the side chain carbonyl groups were not appreciably activated, the expected indolizines were not obtained. Thus the 1-ethylmethine (75; R = Ph, R' = Me) yielded

1-acetyl-2,3-dimethylindolizine (76; R = R' = Me). The starting materials are keto-enamines and can undergo C-acetylation. The product of such a C-acetylation, the diacylmethine (77) could form an indolizine by one of two alternative routes A or B.

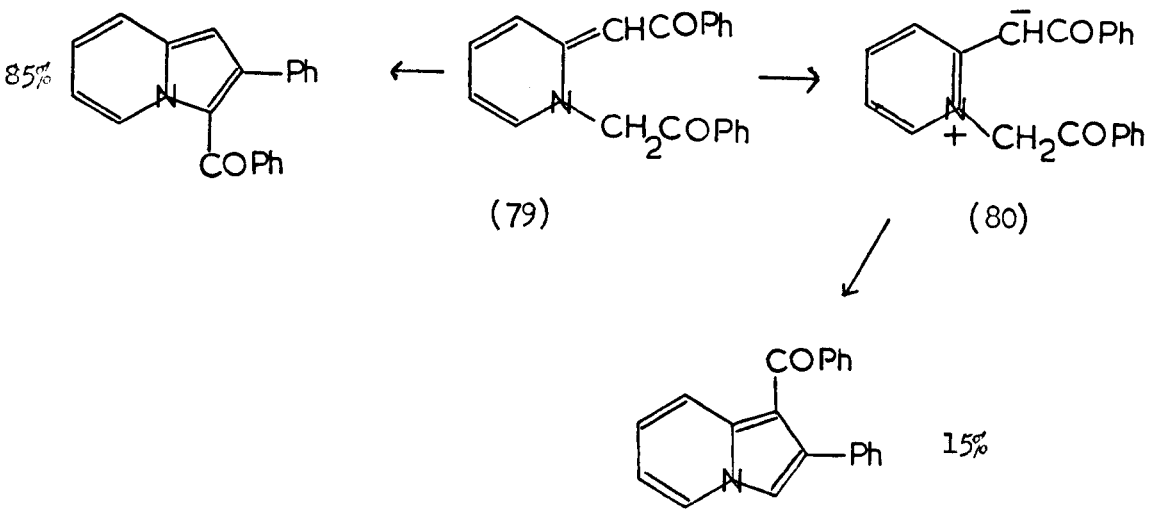
SCHEME XVIII




Cyclisation can occur through the acetyl group (route A) followed by transacylation of the indolizine (78), or the transacylation stage could occur initially (route B) followed by cyclisation.

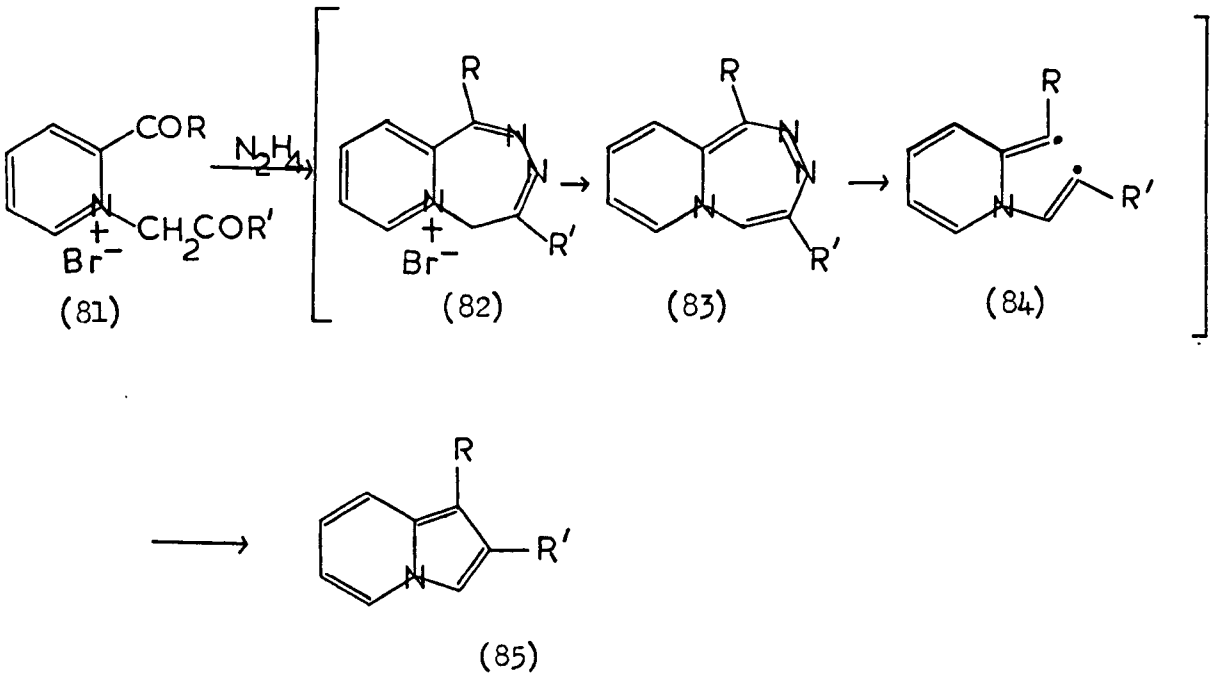
2-Benzoylmethylene-1-phenacyl-1,2-dihydropyridine (79) is theoretically capable of cyclisation by closure at the 2-3 positions under the above conditions or at the 1-2 positions via a carbanion-betaine[37] (80; see (35) page 13 ). Both possible products are obtained.

SCHEME XIX




Kroehnke and Weis[64] have prepared a series of 1,2-disubstituted indolizines from N-acylmethyl-2-acylpyridinium bromides (81) by treatment with hydrazine hydrate (25%). They propose the formation of a ketazine (82) which on elimination of the elements of hydrogen bromide yields a cyclic azocompound (83) which in turn can lose nitrogen to give a diradical (84) which can then yield the 1,2-disubstituted indolizine (85).

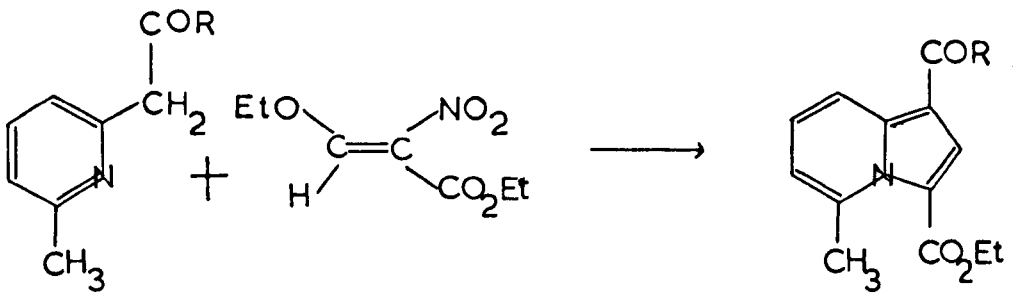
SCHEME XX




Yields in the region of 80-90% were recorded in several cases.

B. S. Thyagarajan and P. V. Gopalakrishnan studied the effect of structural factors influencing indolizine versus quinolizine formation. They found[65] that reaction of 6-methyl-2-pyridylacetone, butanone or 6-methyl-2-phenacylpyridine (86; R = $CH_3$, $C_2H_5$, Ph respectively) with ethyl ethoxymethylenenitroacetate (87) yielded indolizines.

SCHEME XXI

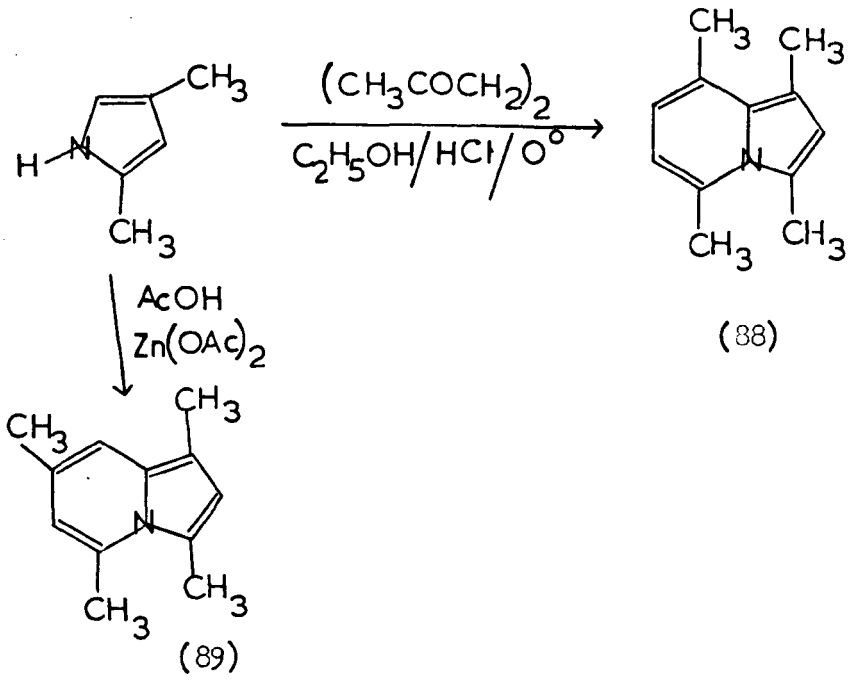



(86) (87)

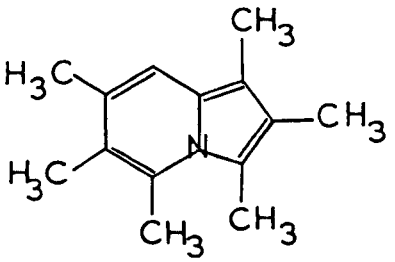
The presence of the 6-methyl group and the displaceable nitrite ion promote the formation of the indolizine system in preference to the quinolizine system.

The condensation of 2,4-dimethylpyrrole with acetonylacetone, and its equivalent self condensation under the influence of zinc acetate in acetic acid were studied by Plancher[71,72] who obtained in each case a base of formula $C_{12}H_{15}N$. Saxton[73] re-examined this work and found that the products were 1,3,5,8- (88) and 1,3,5,7-tetramethylindolizine (89) respectively.

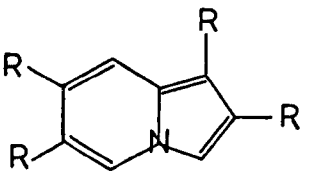
SCHEME XXII




A superior method of producing the 1,3,5,8-compound (88) consisted of treating an ethanolic solution of the reactants at 0° with hydrogen chloride. The self condensation is thought to proceed by a 2,2'-bipyrrolyl adduct. 1,2,3,5,6,7-hexamethylindolizine (90) has been obtained[74] by the action of hydrogen chloride on 2,3,4-trimethylpyrrole. Bonnett, Gale and Stephenson[75] showed that self condensation of 3,4-dimethylpyrrole and 3,4-diethylpyrrole led to 1,2,6,7-tetraalkylindolizines (91; R = $CH_3$, $C_2H_5$ respectively).



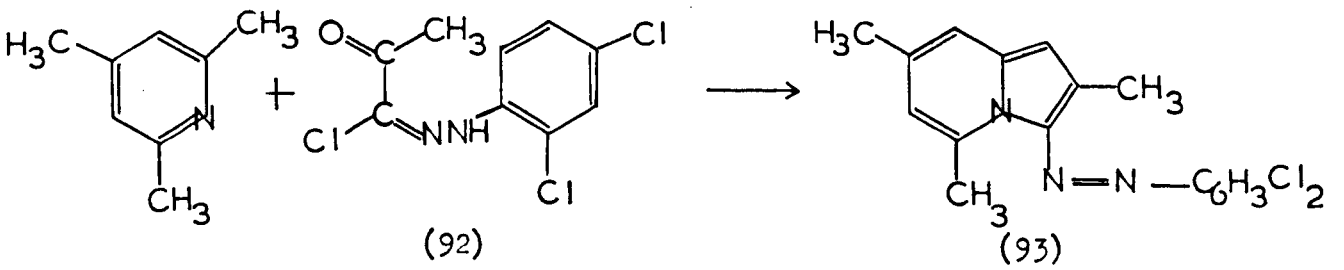
(90)



(91)

Neber and Wörner[76] achieved a synthesis of the indolizine nucleus by heating collidine with the chloro compound (92) and isolated a red-brown substance whose spectra indicated[28] that it was an azoindolizine (93).

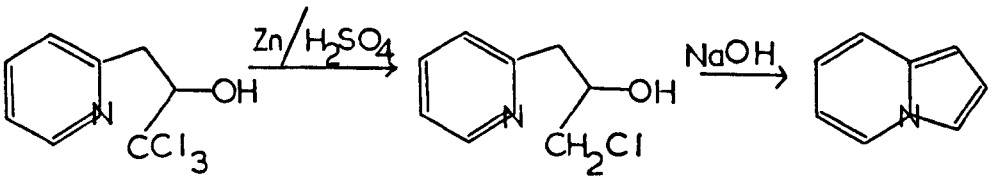
SCHEME XXIII



(92) (93)

Brand and Reuter[77] reduced 2-(γ,γ,γ,-trichloro-β-hydroxypropyl)-pyridine hydrochloride (94), obtained by the action of 2-picoline with chloral, in aqueous sulphuric acid with zinc dust. The product was 2-(γ-chloro-β-hydroxypropyl)pyridine (95) which on treatment with strong alkali afforded indolizine. The overall yield was quite small.

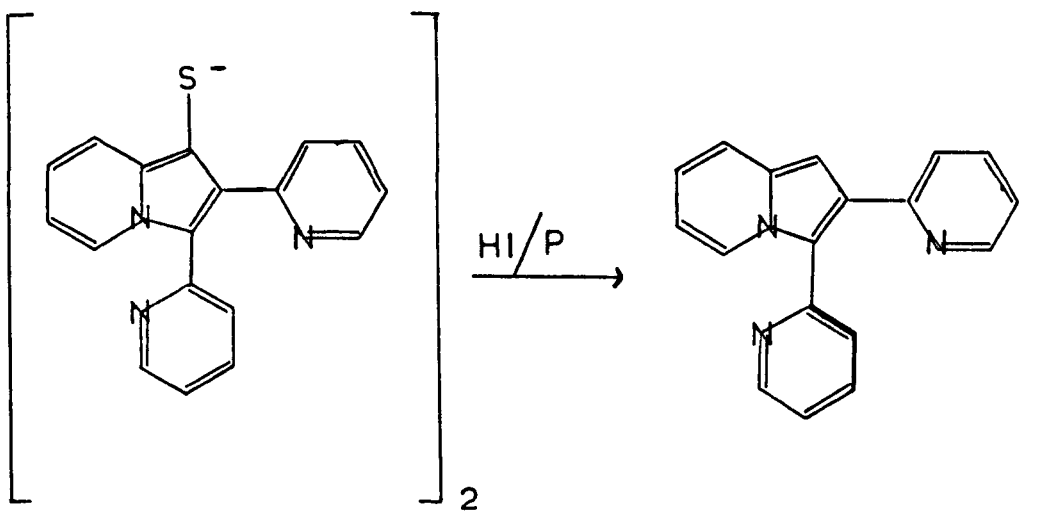
SCHEME XXIV




(94) (95)

When furan and ammonia were passed over alumina at 400° indolizine was one of several products.[78] It was also found among the products of pyrolytic decomposition of pyridines by Krumholtz[79] and by Erner.[80]

When 2-picoline was heated with sulphur a compound of structure (96) was obtained.[122,123] Some of the bipyridyl compound (97) was also obtained and it could be generated by reduction of the sulphur containing compound (96).




(96) (97)

(b) Physical and Chemical Properties

Indolizine is a colourless, crystalline solid of m.p. 74°, distilling without decomposition at 205° and volatile in steam. It yields adducts with chloral,[4] isatin,[9] quinone,[5] maleic anhydride[104] and diethylazodicarboxylate.[109] Other adducts have also been reported.[109,110]

There are ten $\pi$-electrons delocalised over the $\sigma$-bonded framework and indolizines exhibit aromatic properties. Longuet-Higgins and Coulson[81] calculated the $\pi$-electron densities at the various positions of the ring system and concluded that electrophilic substitution would occur first in position 3, or should this be blocked, in the 1 position. The calculations of Fukui and co-workers[82] confirmed this finding qualitatively.

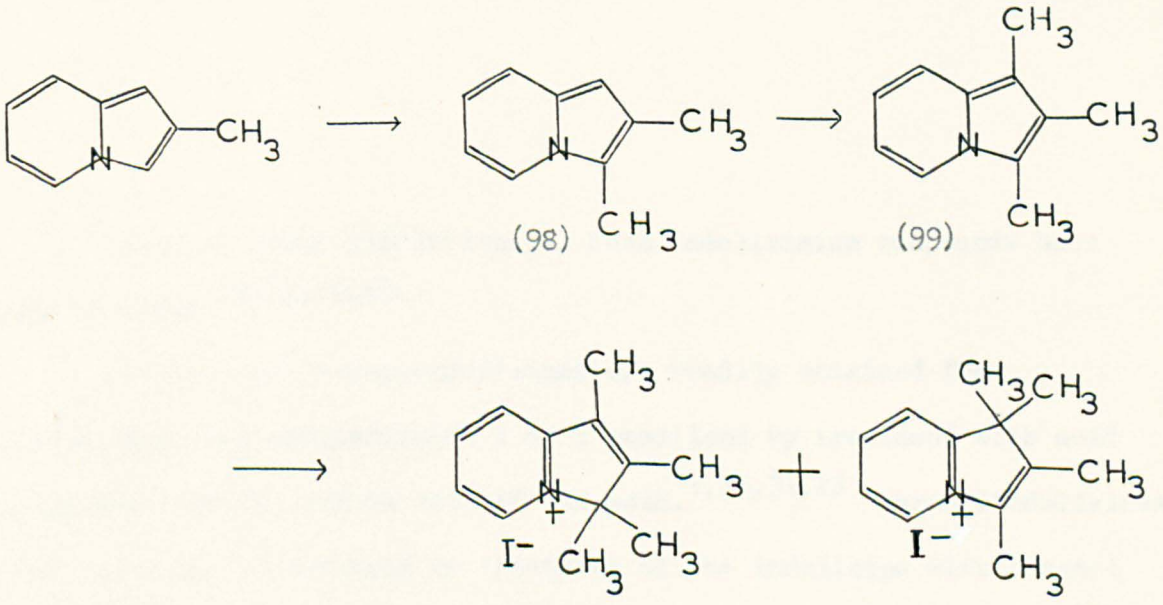
The ultraviolet[11,28,119] and nuclear magnetic resonance[40,118,120] spectra of various indolizines have been reported. They indicate that protonation follows the course predicted above. It occurs preferentially in the 3 position and if this is blocked, then in the 1 position.

Many studies over the years on the substitution reactions in the indolizine series have provided evidence of the greater reactivity of the 3 and 1 positions.[5,12] Except in the case of nitration the 3 position is the first attacked. 2-Methylindolizine has been the compound of choice for much of the work in this field due to its ease of preparation.

Alkylindolizines can be obtained by direct synthesis or by reduction of acylindolizines using lithium aluminium hydride.[24,83] The Wolff-Kishner reduction has also been employed.[16,24] Direct nuclear alkylation was

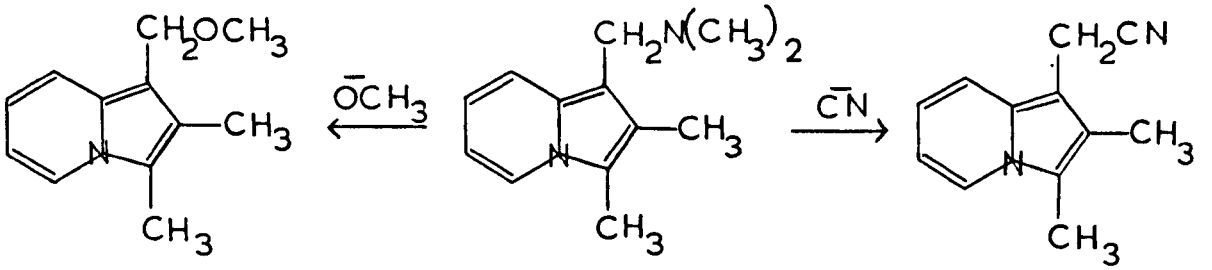
first reported[9,10] by Scholtz. The first product from 2-methylindolizine has been shown to be 2,3-dimethylindolizine[24] (98). On raising the temperature, further methylation occurred to give 1,2,3-trimethylindolizine (99) and eventually a mixture of 1,1,2,3-tetramethyl- (100) and 1,2,3,3-tetramethylindolizinium iodides (101).

SCHEME XXV



Indolizines react with aldehydes and ketones to give[24,44,83] di-indolizinylmethanes. A Mannich reaction has been performed on 2,3-dimethylindolizine[24] to give a dimethylaminomethyl derivative (102) from which can be prepared the cyanomethyl derivative (103) and the methoxymethyl derivative (104). Mannich derivatives of 3-methyl-2-phenyl-,

3-ethyl-2-phenyl- and 1,2-diphenylindolizines have also been prepared.[84,85]

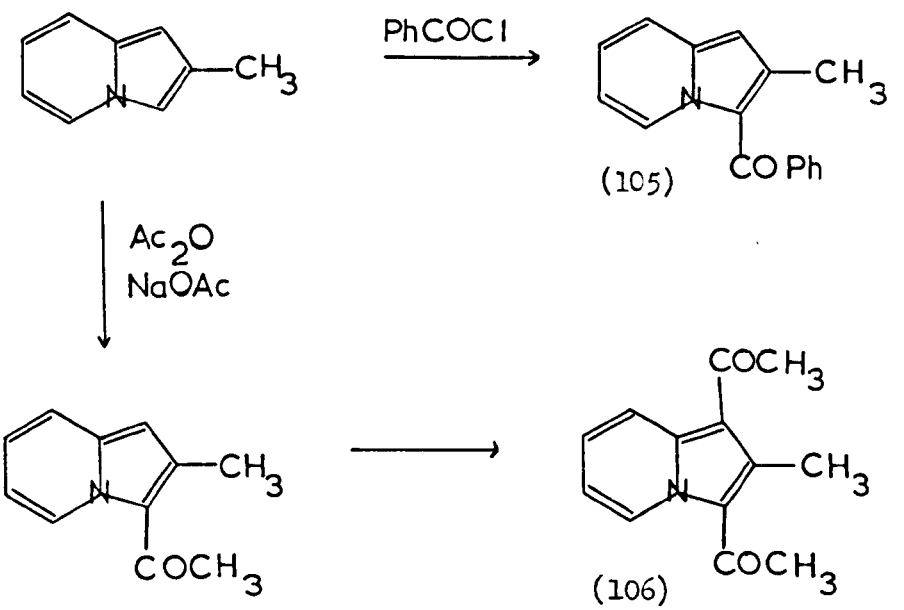



(104) (102) (103)

Various other alkylations to form indolizinium compounds have been reported.[18,24,28,86]

Acetyl- or benzoylindolizines are readily obtained from indolizines with unsubstituted 1 or 3 positions by treatment with acid anhydrides and the sodium salt of the acid.[9,15,31,28] Benzoylindolizines (105) may also be obtained by treatment of the indolizine with benzoyl chloride.[83] More vigorous conditions can lead to a diacyl compound[15] (106). Aluminium chloride has been used[15,87] to promote acylation. Other acyl products have also been prepared.[88] Removal of the acyl group is readily effected by mineral acids.[4,15]

SCHEME XXVI

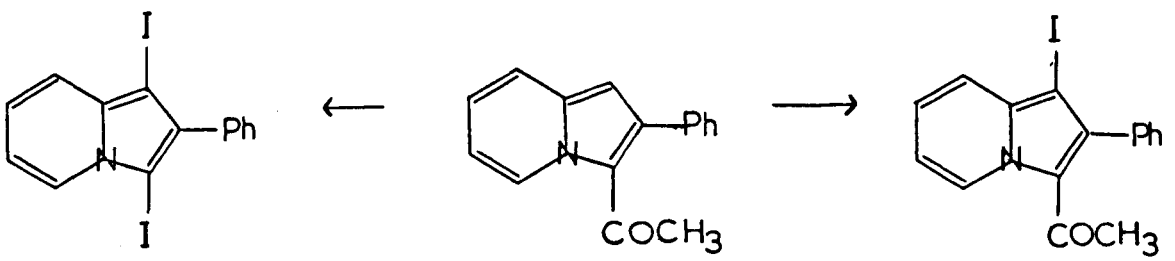



Indolizines with unsubstituted 1 or 3 positions can be formylated by means of the Vilsmaier-Haack technique[24,83,89,90,92] using phosphorus oxychloride and methylformanilide or dimethylformamide. The Reimer-Tiemann reaction[24] on 2-methylindolizine gave some 1,3-diformyl derivative. 3-Formyl-2-methylindolizine has been prepared in high yield[83] by the McFadyen-Stevens reaction on 2-methylindolizine-3-carbonyl chloride. Thioformylindolizines have been prepared.[95]

The carbonyl groups of the 1- and 3-acetyl- and formylindolizines show reduced reactivity towards carbonyl reagents such as hydroxylamine and phenyl hydrazine.[15] This effect is particularly strong in the 3-acetyl- or 3-formylindolizines.

Acyl substituents in the 1 and 3 positions show unusual reactivity towards electrophiles. They are, however, less readily replaced if an electron withdrawing group, such as the nitro group, is also attached to the five-membered ring.[9,31] Acetyl groups can usually be replaced by nitro groups.[9,91] Treatment of 3-acetyl-2-phenylindolizine (107) with iodine in ethanol gave 1,3 di-iodo-2-phenylindolizine (108) but if sodium acetate was present to neutralise the hydrogen iodide formed then 3-acetyl-1-iodo-2-phenylindolizine (109) was formed.[32]

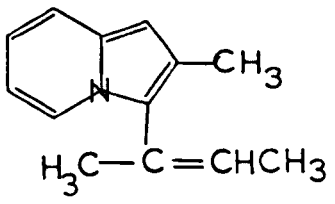
SCHEME XXVII



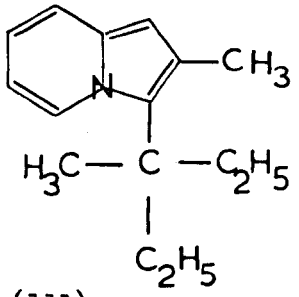

(108) (107) (109)

Reaction of acylindolizines with Grignard reagents usually removes the acyl group from the ring system.[32,93] Thus 3-acetyl-2-phenylindolizine on reaction with a Grignard reagent yielded a complex which on hydrolysis afforded 2-phenylindolizine.[32] Other products, however, have been reported[94] by Kondo and Kokeguchi; using an excess of Grignard reagent on 3-acetyl-2-methylindolizine, some 3(2-but-2-enyl)-2-methylindolizine

(110) and 3-(2-ethyl-2-butyl)-2-methylindolizine (111) were isolated.



(110)



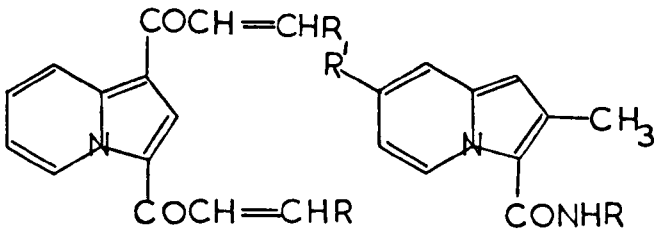
(111)

In contrast, Scholtz and Fraude claimed[5] to have obtained normal tertiary carbinols when "picolide" (11) reacted with one mole of Grignard reagent.

Aromatic aldehydes will react with the methyl group(s) of acetyl- or diacetylindolizines to yield[4,15] mono- or dicinnamoyl derivatives (112).

Certain acids and esters of the indolizine series can be synthesised directly by the Diels-Alder synthesis or the Tschitschibabin synthesis. Scholtz and Fraude[5] obtained a monocarboxylic acid by treating indolizine with phosgene and hydrolysing the acid chloride so formed. Holland and Nayler obtained[83] the 2-methyl-3-carboxylic acid in a similar manner from 2-methylindolizine. Treatment of the acid chloride with dimethyl cadmium gave 3-acetyl-2-methylindolizine. Oxalyl chloride will also condense with indolizines.[121]

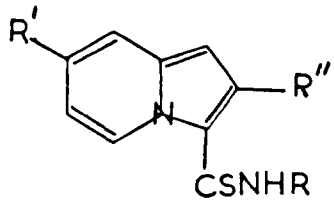
3-Indolizinecarboxanilides (113) have been prepared[97] by treatment of indolizines with acyl azides. The corresponding sulphur analogues (114) have also been prepared[98] using isothiocyanates.




(112)




(113)

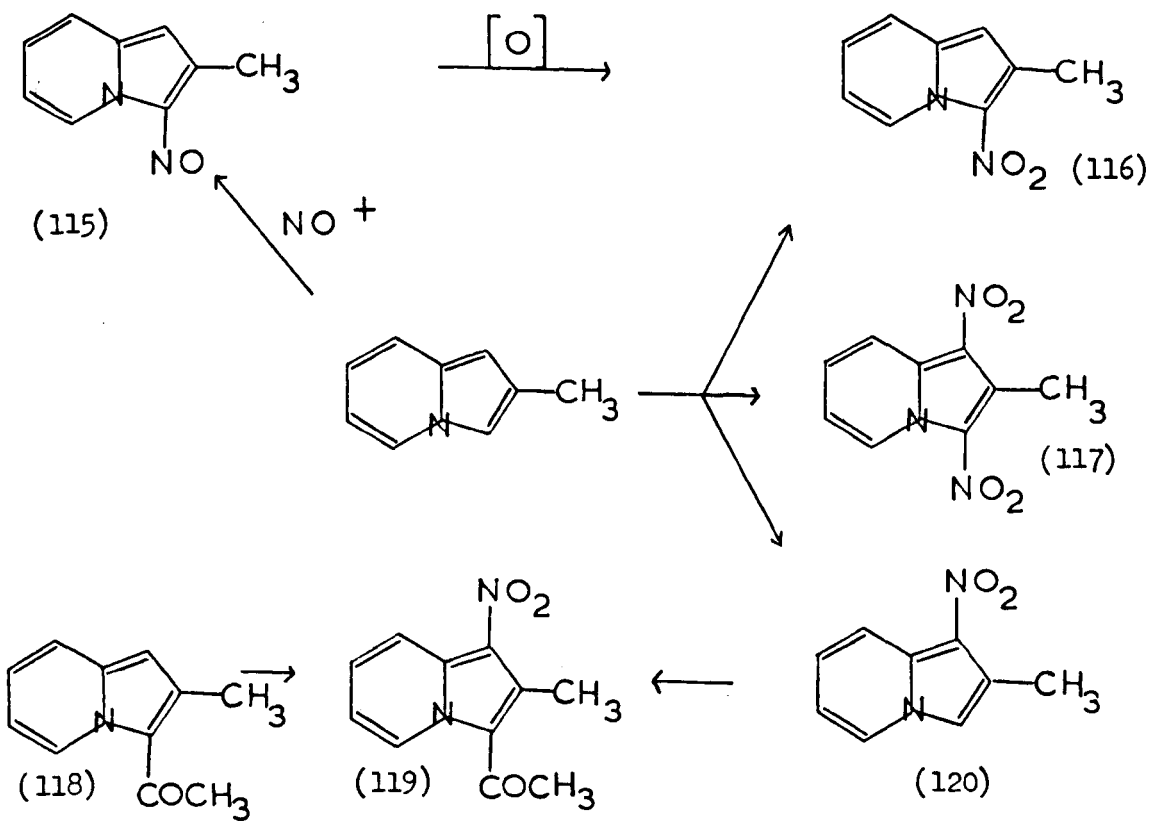



(114)

R', R" = $CH_3$ or H

Direct nitrosation has been performed[19,22,99] to give 1- or 3-nitroso-indolizines (115) using sodium nitrite in dilute acid. N-nitrosodiphenylamine has also been used.[100] Nitrosoindolizines have been converted[22,31] into nitroindolizines by careful oxidation. Nitration of 2-methylindolizine yields a mixture of the 3-and 1-nitro compounds together with some dinitroindolizine;[31] the 3-isomer (116) predominates. Both of the mononitro compounds can be converted into the 1,3-dinitroindolizine (117).

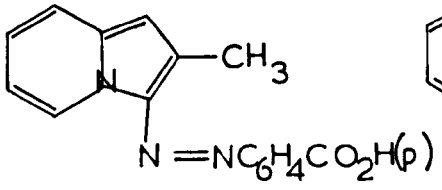
SCHEME XXVIII



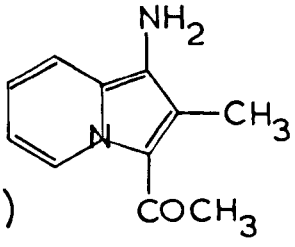

Treatment of "picolide", 1,3-diacetylindolizine (11), with a mixture of nitric and acetic acids yields 1-nitro-3-acetylindolizine or 1,3-dinitroindolizine depending on conditions.[9,101] Nitration of 3-acetyl-2-methylindolizine (118) gave the 1-nitro compound[31] (119). Acetylation of 1-nitro-2-methylindolizine (120) afforded the same compound.

Diazonium coupling occurs without difficulty in the 3-position of indolizines. Benzenediazonium chloride couples with indolizine to give[5] an indolizinyl-azobenzene. 2-Methylindolizine couples with diazotized

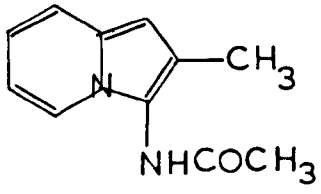
p-aminobenzoic acid to give a 3-substituted derivative (121). Blocking the 3 position directs diazonium coupling to the 1 position;[102] a 3-acetyl-2-methyl-1-phenylazoindolizine has thus been obtained, catalytic reduction of which afforded the 1-amino compound (122). The Schmidt reaction (hydrazoic acid in concentrated sulphuric acid) upon 3-acetyl-2-methylindolizine was shown to yield[83] the 3-acetylamino derivative (123).



(121)



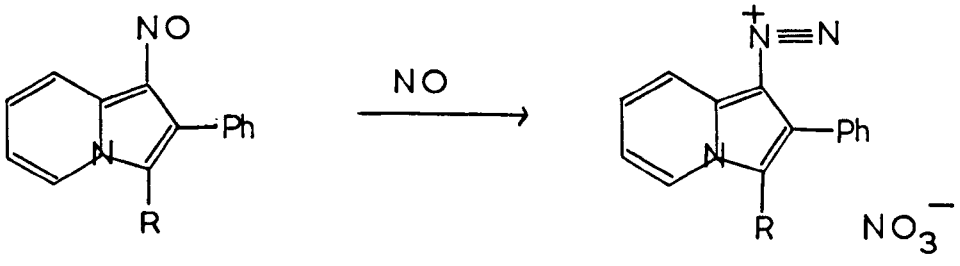
(122)



(123)

Stable diazonium salts (124) have recently been prepared[103] from 1-nitroso-indolizines by treatment with nitric oxide.

SCHEME XXIX

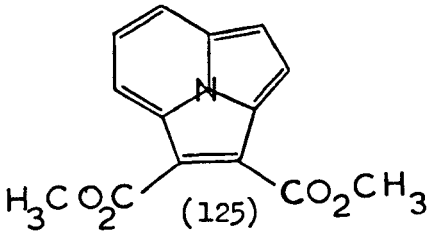


R = Me, Ac

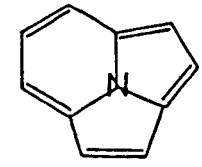
(124)

The reaction of halogens with indolizines has received little attention. Unstable, indefinite products are reported[5] to arise on treatment of indolizine with bromine or iodine.

When indolizine is heated with dimethyl acetylenedicarboxylate and palladium on charcoal an addition takes place to yield the dimethyl ester of 1,2-dicarboxylcycl[3,2,2]azine (125). Hydrolysis followed by decarboxylation yields the parent cycl[3,2,2]azine (126).[68,106,108]



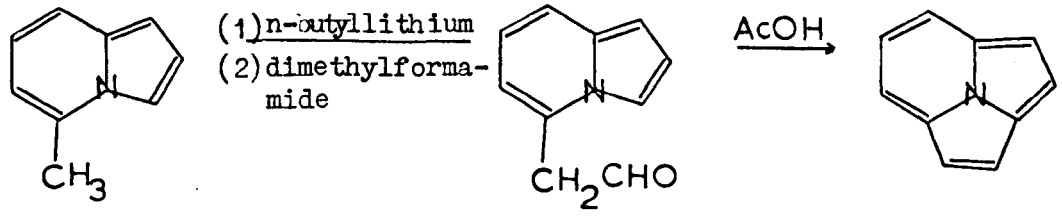
(125)



(126)

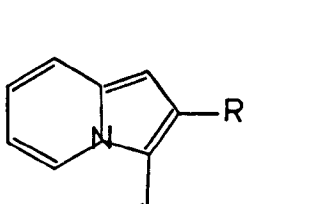
When 5-methylindolizine was treated with n-butyllithium followed by dimethyl formamide an aldehyde (127) was produced. This aldehyde could be cyclised to the cyclazine.[96,107]

SCHEME XXX

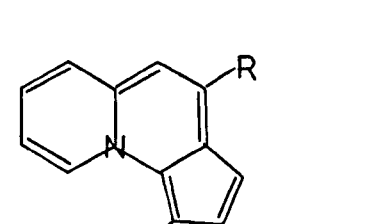



(127)

The reaction between dimethyl acetylenedicarboxylate and the enamine (128; R = Me, Ph, $CO_2CH_3$) was investigated by Gibson and Leaver.[114,115] The product was a cyclopenta[c]quinolizine (129).




(128)




(129)

Simple alkylindolizines are readily degraded by oxidising agents.[4] A useful oxidation procedure which has been used in structure elucidation is the use of perhydrol and acetic acid, when an indolizine unsubstituted in the six-membered ring is degraded to picolinic acid N-oxide.[12,15,16]

Treatment of indolizine with sodium and alcohol gave an oily base which Scholtz[4] considered to be 2-(1-butadienyl)pyrrole (130). Mosby suggested[28] that it may be 5,8-dihydroindolizine (131).



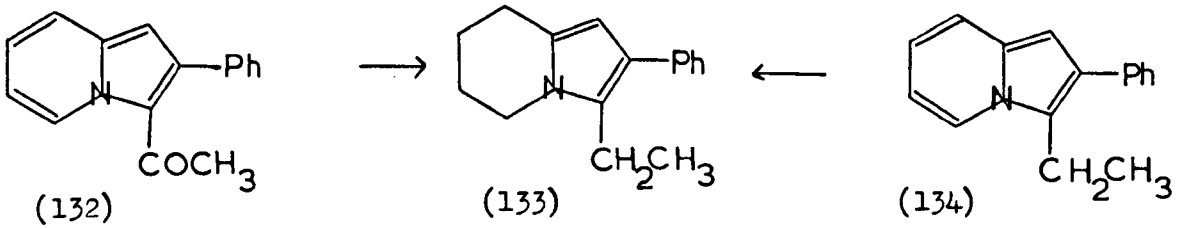

(130)




(131)

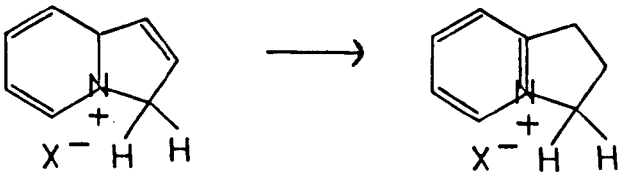
Careful hydrogenation of indolizine, alkyl- or arylindolizines[16,111,112,108] using catalytic methods yielded 5,6,7,8-tetrahydro derivatives. Catalytic reduction of 3-acetyl-2-phenylindolizine (132) or of 3-ethyl-2-phenylindolizine (134) could be made to give[16] 3-ethyl-2-phenyl-5,6,7,8-tetrahydroindolizine (133) in each case.

SCHEME XXXI




(132) (133) (134)

Many cases of the complete reduction of the system to octahydroindolizines (indolizidines) have been reported.[16,17,23,30,28] Hydrogenation of indolizine in the presence of strong mineral acids affords[113] 1,2 dihydro-3H-indolizinium salts (135).

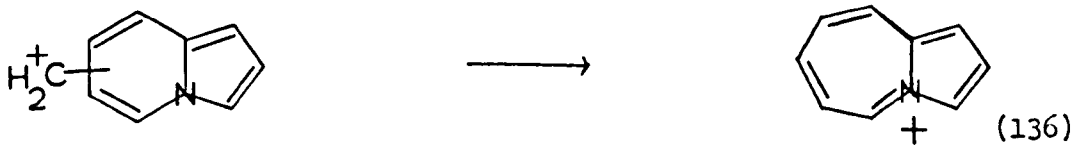



(135)

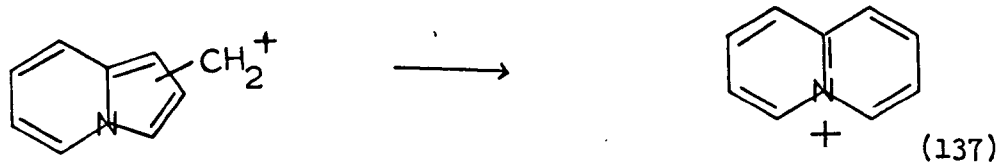
# DISCUSSION

## Introduction

The survey of previous work indicates the general routes by which indolizines can be prepared. It is apparent that many simple compounds, especially those substituted in the six-membered ring, have not been prepared. Certain indolizines might on further reaction proceed via carbonium ion intermediates; given the correct conditions it may be possible for rearrangement to occur into (a) the azonia-azulenium ion (136) or (b) into the quinolizinium cation (137) dependent upon the position of the substituent.



(136)



(137)

It was also thought that partially reduced indolizines such as dihydro derivatives might be suitable compounds on which to attempt ring expansion reactions in order to arrive at a 7,5-bicyclic system with a nitrogen atom at a bridgehead position.

It was decided to prepare simple indolizines with the above aims in mind and to concentrate on hydroxymethyl and aminomethyl derivatives. Further, a study of the mass spectra of indolizine and its derivatives might provide evidence for the above mentioned ions in the breakdown paths of

substituted indolizines.

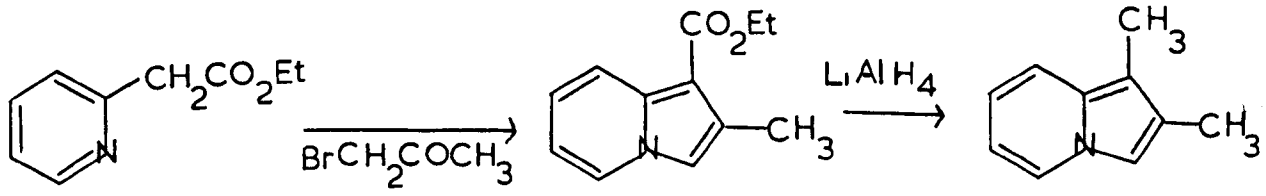
## 1 Substituted Indolizines

Melton and Wibberley[63] have recently reduced 1-cyanoindolizine to the aminomethyl derivative which they characterised as the 3-acetyl-1-diacetylaminomethylindolizine and so this compound was available.

Attempted synthesis of 1-hydroxymethyl-2-methylindolizine (142).

Ethyl 2-methylindolizine-1-carboxylate (138) was prepared from ethyl 2-pyridylacetate and bromoacetone by the method described by Bragg and Wibberley (see page 11).[36] An attempt was made to reduce the ester using lithium aluminium hydride, with tetrahydrofuran as the solvent, but the product of the reaction was clearly shown to be 1,2-dimethylindolizine (139) from its melting point, nuclear magnetic resonance and infrared spectra.

SCHEME XXXII




(138) (139)

The nuclear magnetic resonance spectrum of the ester (138) (Figure 1) showed the expected pattern except for the fact that the proton in the 8 position (1.75 $\tau$ ) was further downfield than the proton in the

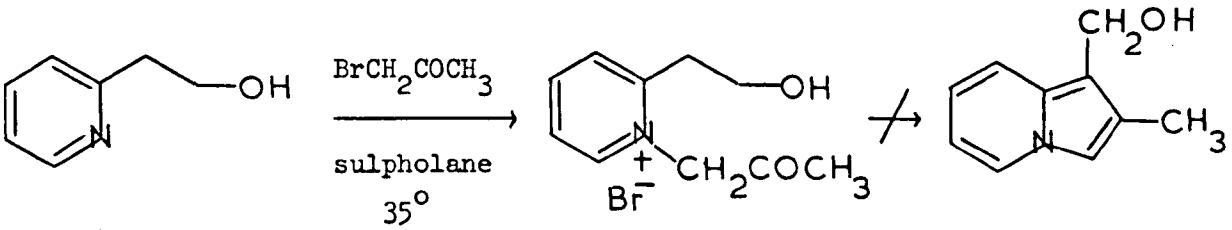
5 position (2.1 $\tau$) which is opposite to that normally found in indolizine or its methyl derivatives. This was no doubt due to the effect of the ester group in the 1 position and a major contribution to the shift must be due to anisotropic deshielding of the 8 position proton by the carbonyl of the ester group. The doublets due to the 5 and 8 position protons could be distinguished by means of the major splitting (J = 6.5 c/s and 9 c/s respectively)[118] due to the effect of their nearest neighbours in the ring (6 and 7 position protons respectively).

In the case of the product of the reduction, 1,2-dimethylindolizine (139) (Figure 2), the order was reversed and the 5 position proton (2.3 $\tau$) was further downfield than the 8 position proton (2.8 $\tau$). The major factor which indicated the nature of the product was loss of the ethoxy peaks from the spectrum and the appearance of a broad singlet at 7.8 $\tau$ which integrated for six protons and was obviously due to two methyl groups.

Attempts were made to reduce the severity of the conditions by employing ether as the solvent but again the product was the dimethyl compound together with unchanged starting material. The use of potassium borohydride or sodium borohydride was not successful and only starting material was recovered in each case.

An alternative approach to the 1-hydroxymethyl compound (142) was attempted. 2-Pyridyl ethanol (140) reacted with bromoacetone in sulpholane when the mixture was kept at 35° for several days, to produce the expected 1-acetonyl-2-hydroxyethylpyridinium bromide (141) in high yield.

SCHEME XXXIII



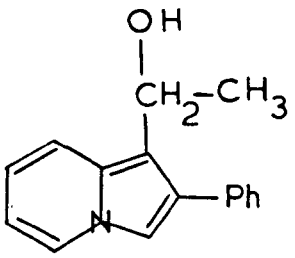

(140) (141) (142)

The nuclear magnetic resonance spectrum of the quaternary compound (141) in trifluoroacetic acid (T.F.A.) was initially very confused but on standing it resolved into the expected pattern, ester formation probably occurring in the acid. In deuterium oxide the methyl group of the acetonyl function showed up as two separate peaks (7.5 $\tau$ and 8.4 $\tau$ ).

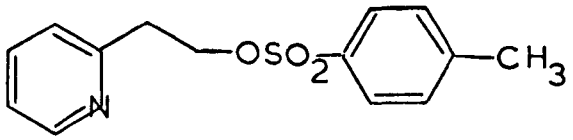
Attempts to cyclise the quaternary compound to the hydroxymethyl-indolizine (142) were not successful. Aqueous sodium bicarbonate and diethylamine in ethanol were both employed and in each case a yellow solid separated from the solution. This was filtered off but could not be characterised. It gave no definite peaks in its spectra and did not have a definite melting point. Previous workers[32] have found that in an attempt to prepare 1(α-hydroxyethyl)-2-phenylindolizine (143) the hydroxy-ethyl group is lost at the cyclisation stage to yield only 2-phenylindolizine (see page 9, Scheme VI). In our case no 2-methylindolizine was obtained.

The effects observed in the nuclear magnetic resonance spectrum of the quaternary compound (141) in deuterium oxide were not observed

in any other compounds of this type prepared in the course of this work. It seems as if the effect must be due in some way to the hydroxyethyl group in the 2 position of the pyridinium system. Since the spectrum in trifluoroacetic acid showed the expected pattern of peaks, once ester formation had occurred, it seemed possible that a derivative of the alcohol might cyclise normally. A tosylate (144) was prepared in 60% yield by adding an acetone solution of p-toluenesulphonyl chloride to the alcohol (140) in sodium hydroxide solution.

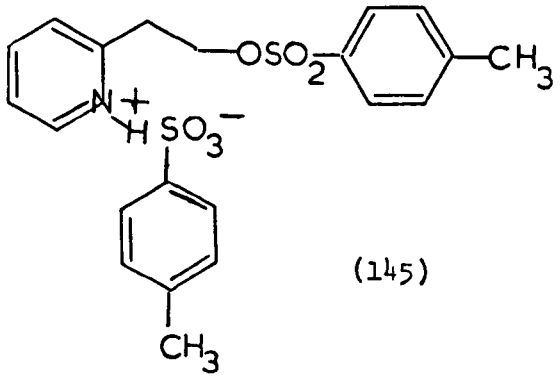


(143)



(144)

When the tosylate (144) was recrystallised from ethanol/petroleum a new compound resulted. The nuclear magnetic resonance spectrum indicated that it was probably of structure (145).



(145)

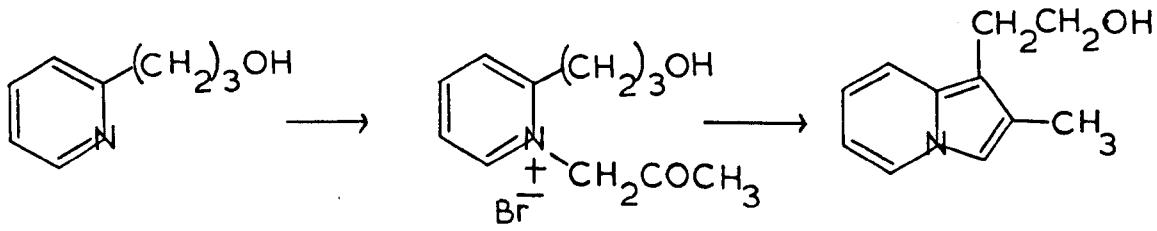
To test this hypothesis an ethereal solution of the tosylate (144) was treated with an ethereal solution of p-toluenesulphonic acid. A white solid precipitated which was identical to that obtained by recrystallisation of the tosylate (144) from ethanol. Treatment of the new compound with sodium hydroxide solution generated the original tosylate (144).

Attempts to quaternise the tosylate (144) using bromoacetone in boiling acetone and in sulpholane failed to give any of the desired product. An attempt was also made to prepare a tosylate of 1-acetonyl-2-hydroxyethylpyridinium bromide (141) but the product was the tosylate of the unquaternised pyridine (144).

1 (β Hydroxyethyl)-2-methylindolizine (147).

Quaternisation of 3(2-pyridyl)-1-propanol (44) with bromoacetone in refluxing acetone proceeded smoothly to yield the quaternary compound (146) as a thick gum; it could not be solidified in spite of intensive efforts; this phenomenon was observed in several of the quaternary compounds prepared. It cyclised without difficulty under the usual conditions to 1(β hydroxyethyl)-2-methylindolizine (147). The compound was unstable and decayed within a short time; its nuclear magnetic resonance spectrum is shown in Figure 3.

SCHEME XXIV




(44) (146) (147)

The proton in the 3 position exchanged with deuterium oxide as well as the expected alcoholic proton. In trifluoroacetic acid solution an ester formed with time, the triplet centred at 5.85 $\tau$ being slowly replaced by one at 5.35 $\tau$ . The trifluoroacetic acid solution was shaken with excess sodium bicarbonate solution and the aqueous solution extracted with ether. The brown liquid which remained after removal of the ether had a strong absorption band at 1780 $cm.^{-1}$ in the infrared. An attempt to form a tosylate of the hydroxyethylindolizine (147) was not successful.

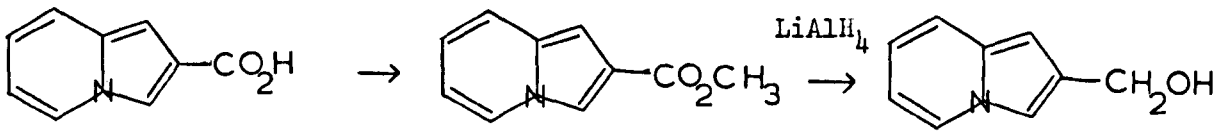
## 2 Substituted Indolizines

2-Hydroxymethylindolizine (149).

Indolizine-2-carboxylic acid (20) was prepared from 2-picoline and ethyl bromopyruvate by the method of Borrows and Holland[21] (see page 8, Scheme V). The methyl ester (148) was prepared by treating a dioxan solution of the acid (20) with an ethereal solution of diazomethane.

Reduction of the ester in ethereal solution with lithium aluminium hydride afforded 2-hydroxymethylindolizine (149) in 79% yield.

SCHEME XXXV

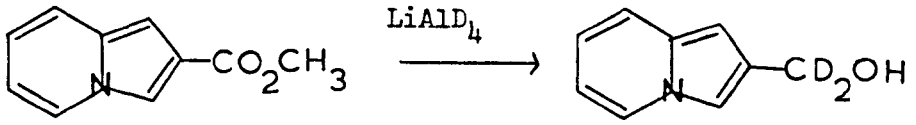



(20) (148) (149)

The 3 position proton again exchanged when a solution was shaken with deuterium oxide. An attempt to prepare 2-chloromethylindolizine by treating an ethereal solution of the hydroxymethylindolizine (149) with thionyl chloride gave an orange precipitate which rapidly decayed and could not be characterised.

The 2-hydroxydideuteromethylindolizine (150) which was required for mass spectrometry work was prepared from the methyl ester (148) in a similar manner to the hydroxymethyl compound (149), lithium aluminium deuteride being used for the reduction.

SCHEME XXXVI

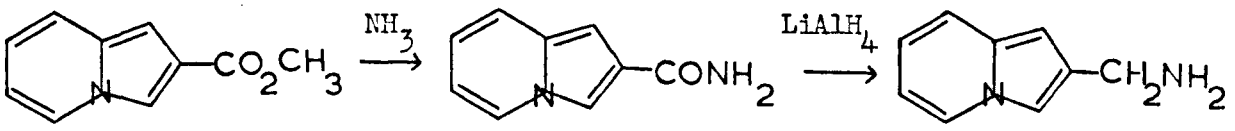



(148) (150)

2-Carbamoylindolizine (151).

Several methods were tried in an attempt to synthesise 2-carbamoylindolizine. These included heating the acid (20) with urea to melting; treating the acid with ammonia, and ammonium carbonate, in an attempt to form an ammonium salt followed by heating of the residue from such reactions to 200°; treating the acid (20) with thionyl chloride in an attempt to prepare the acid chloride followed by treatment with concentrated ammonia solution; action of concentrated ammonia on the ester (148). All these attempts met with little success. Eventually, a solution of methyl indolizine-2-carboxylate (148) in methanol was saturated with ammonia gas at -5° and the resulting solution heated in an autoclave for 65 hr. at 155° where the pressure generated was 22 atmospheres. By this method the amide was obtained in 44% yield.

SCHEME XXXVII




(148) (151) (152)

2-Aminomethylindolizine (152).

Reduction of the amide (151) in tetrahydrofuran solution with lithium aluminium hydride yielded a solid of m.p. 77.5° whose infrared spectrum showed no carbonyl band and weak bands which may be due to the amine function. In the nuclear magnetic resonance spectrum (Figure 4) the singlet at 6.05 $\tau$ is assigned to the methylene group while the broader singlet at 8.05 $\tau$, which varies with concentration, moving to higher field on dilution, and which exchanges with deuterium oxide, is assigned to the amine protons. In trifluoroacetic acid the methylene protons appear as a broad doublet which may in fact be an unresolved quartet at 5.3 $\tau$. There is also a singlet at 4.1 $\tau$ integrating for two protons which indicates protonation of the indolizine ring system.

The aminomethyl compound was unstable and consistent analysis figures could not be obtained.

## 3 Substituted Indolizines

Scholtz and Fraude[5] obtained a monocarboxylic acid by treating a solution of indolizine in toluene with phosgene and hydrolysing the acid chloride so formed. This was undoubtedly the 3-carboxylic acid since Holland and Nayler[83] had obtained the 3-carboxylic acid from a similar treatment of 2-methylindolizine (see page 37). It was decided that this would be a useful entry to the 3 position of the indolizine nucleus.

Synthesis of Indolizine.

The most convenient synthesis of indolizine is that due to Boekelheide and Windgassen[41] (see page 16 Scheme XI). 3-(2'-Pyridyl)-1-propanol (44) when heated with a 10% palladium on charcoal catalyst to 280° for 12 hr. gave indolizine in 33% yield. On one occasion a freshly prepared sample of catalyst was added during the heating period and in this instance the indolizine produced was found to be contaminated with 5,6,7,8-tetrahydroindolizine (212) Presumably the conditions in this case must have been correct for reduction of the indolizine to occur, remembering that hydrogen is released from the 3-(2'-pyridyl)-1-propanol in forming indolizine, or possibly adsorbed hydrogen on the freshly prepared catalyst may have been the cause. The indolizine could be purified by recrystallisation from methanol. Borrows, Holland and Kenyon[16] reported 5,6,7,8-tetrahydro derivatives when Raney nickel or Adams catalyst was used in attempts to reduce indolizine and also reported[12] that "hydrogenation using palladized charcoal as catalyst proceeds slowly." Boekelheide and his co-workers[108] have reported the

reduction of indolizine to 5,6,7,8-tetrahydroindolizine (212) using a palladium on charcoal catalyst. Later in this thesis reference is made to the reduction of indolizine to 5,6,7,8-tetrahydroindolizine (212) using sodium in ethanol.

Indolizine-3-carbonyl chloride (153).

A solution of indolizine in toluene was added to a 12.5% solution of phosgene in toluene and the solution stood overnight. Black indolizine hydrochloride precipitated and was filtered off; indolizine could be recovered by treating the hydrochloride with base. The remaining solution was evaporated to dryness to yield indolizine-3-carbonyl chloride (153) which was recrystallised from light petroleum (b.p. 60-80°).

The nuclear magnetic resonance spectrum of the acid chloride (153) in carbon tetrachloride (Figure 5) showed a doublet from the proton in the 5 position at 0.7 $\tau$ which was quite a way downfield from the next signal, a doublet at 2.28 $\tau$ due to the proton in the 2 position.

Originally the method employed in the synthesis of the acid chloride (153) was that due to Scholtz and Fraude.[5] When the crude acid chloride (153) was treated with dilute sodium hydroxide solution (1%) however, a reaction commenced. The solution was quickly poured into an excess of water and filtered. The filtrate was acidified with hydrochloric acid but no precipitate was observed. On addition of excess 20% sodium hydroxide solution, however, a solid precipitated which was shown to be indolizine. Infrared analysis of the crude residue from the 1% sodium hydroxide treatment showed two carbonyl peaks: one at 1710 $cm.^{-1}$ which was due to

the acid chloride (153) and the other at 1640 cm.$^{-1}$. After crystallisation from light petroleum (b.p. 60-80°) the peak at 1640 cm.$^{-1}$ was no longer present and the nuclear magnetic resonance spectrum showed the sample to be a mixture of the acid chloride (153) and indolizine. The residual oil, recovered from the light petroleum by boiling the solvent away under reduced pressure, reacted in aqueous sodium bicarbonate with evolution of gas to give a precipitate which after drying was shown to be indolizine.

Since Holland and Nayler[83] have prepared 2-methylindolizine-3-carboxylic acid by hydrolysis of the acid chloride and shown that it spontaneously decarboxylates to yield 2-methylindolizine it seems clear that treatment of the acid chloride (153) with dilute sodium hydroxide solution gives the unstable 3-carboxylic acid which decarboxylates to yield indolizine. Scholtz and Fraude[5] managed to separate the acid and characterise it but since the derivatives required could be obtained without recourse to the acid this line of work was not pursued.

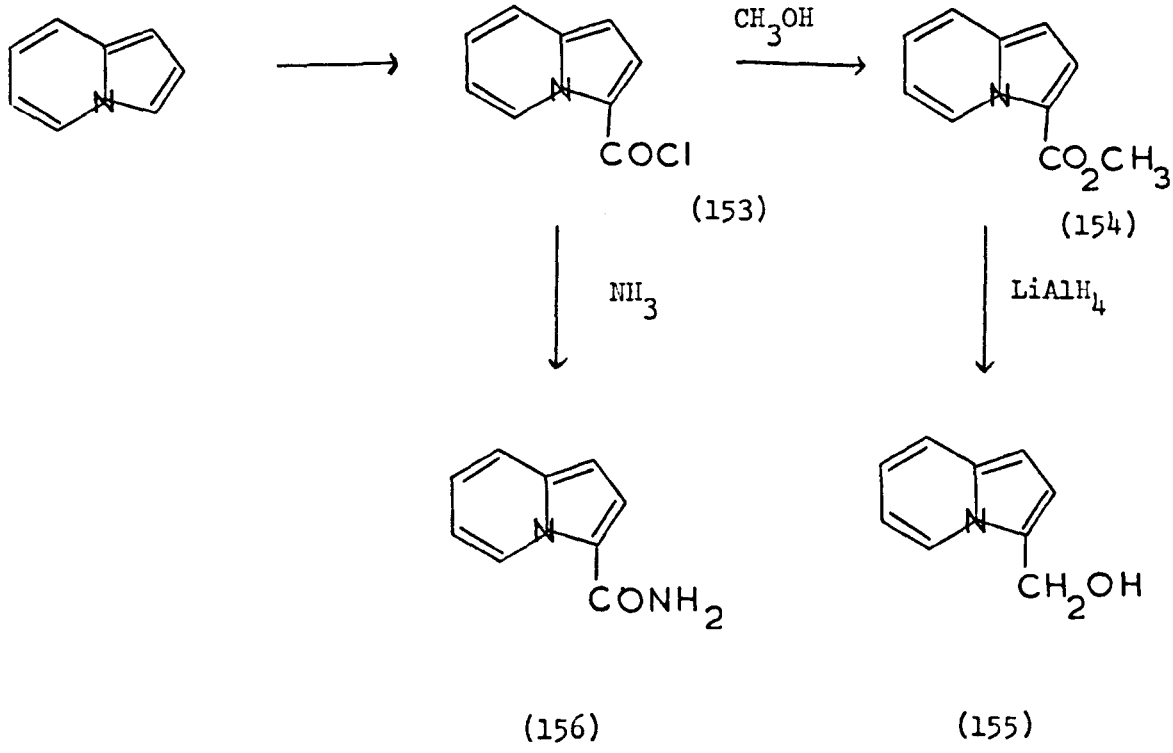
Methyl indolizine-3-carboxylate (154).

When the acid chloride (153) was boiled under reflux in methanol the yellow solid yielded a deep red solution. After removal of excess solvent the residue was treated with aqueous sodium bicarbonate; ether extraction of the solution then afforded methyl indolizine-3-carboxylate (154) in 86% yield. The ester was a brown liquid which boiled at 144-146° (14 mm. of Hg pressure).

The proton in the 5 position was well downfield (0.5 $\tau$ ) from the other aromatic protons in the nuclear magnetic resonance spectrum and

it is clear that the effect of carbonyl groups on the 5 position proton can be useful diagnostically.

SCHEME XXXVIII




3-Hydroxymethylindolizine (155).

3-Hydroxymethylindolizine (155) was obtained in 68% yield by reducing methyl indolizine-3-carboxylate (154) with lithium aluminium hydride in an ether solution, adding ethyl acetate to destroy any excess lithium aluminium hydride and then adding a small quantity of water to precipitate the inorganic material. The required product was recovered from the ether. Attempts to work up the reaction solution in the same way as that for the successful synthesis of 2-hydroxymethylindolizine, that is

adding a large quantity of water followed by 5N hydrochloric acid and adjusting the pH to 5 - 6 with ammonium hydroxide followed by extraction with ether, met with failure, a deep blue colouration being observed.

This successful preparation of 3-hydroxymethylindolizine (155) stands in contrast to the behaviour of the ethyl ester of the 1 position where reduction went through to the 1-methyl derivative.

3-Hydroxymethylindolizine (155) crystallised from light petroleum as white needles but decayed with time giving a blue colouration. A 2% solution in carbon tetrachloride showed a sharp peak at 3610 $cm.^{-1}$ and a broad one centred at 3460 $cm.^{-1}$. The latter peak disappeared on dilution showing the effect of intermolecular hydrogen bonding being broken down on dilution.

3-Carbamoylindolizine (156)

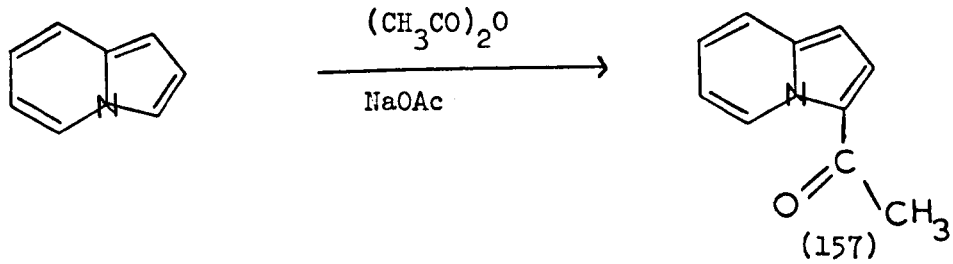
Holland and Nayler[83] have prepared 2-methyl-3-carbamoylindolizine by shaking 2-methylindolizine-3-carbonyl chloride with concentrated ammonium hydroxide. Applying the same reaction to indolizine-3-carbonyl chloride (153) afforded 3-carbamoylindolizine (156) but only in poor yield (28%). The amide proved to be insoluble in most solvents but was recrystallised from ethyl acetate as a faintly yellow solid of m.p. 146°. The effect of the carbonyl group on the 5 position proton is again noticeable in the nuclear magnetic resonance spectrum.

3-Acetylindolizine (157).

Another mode of entry to the 3 position of indolizine is acetylation.[9] It was decided to explore the possible use of 3-acetylindolizine (157) to derive other 3 substituted compounds.

3-Acetylindolizine (157) was prepared by boiling indolizine, together with freshly fused sodium acetate, in acetic anhydride for 6 hr. and distilling the resulting oil.

SCHEME XXXIX




(157)

Holland and Nayler[83] reported that reduction of 3-acetyl-2-methylindolizine with lithium aluminium hydride gave 3-ethyl-2-methylindolizine in 76% yield. Attempts to reduce 3-acetylindolizine with lithium aluminium hydride and potassium borohydride led to products which could not be satisfactorily identified. The lithium aluminium hydride reduction gave an oil whose infrared spectrum indicated that a carbonyl group was present. After repeated column chromatography a sample of the starting material was isolated together with a solid whose infrared spectrum showed no carbonyl absorption. The nuclear magnetic resonance spectrum of this solid had very poor definition and only ill defined peaks could be observed which could not be interpreted. A very similar nuclear magnetic resonance spectrum was obtained for the product of the potassium borohydride reduction.

An attempt was made to perform an iodoform reaction with

3-acetylindolizine by treating a dioxan solution with potassium hydroxide solution followed by a potassium iodide solution saturated with iodine. The product was a green tar which contained some starting material.

3-Acetyl-5-methylindolizine.

A small quantity of 5-methylindolizine (160) was available (see Scheme XL) and an acetyl derivative was prepared in a similar manner to the preparation of 3-acetylindolizine (157) to yield a yellow solid m.p. 55-56°. An attempt to cyclise 3-acetyl-5-methylindolizine to a cycla-[3,2,2]zine by heating it in ethanol to which a few drops of piperidine had been added, in a sealed tube to 140° for 24 hr. was not successful. Only starting material was recovered.

| 3 position | 5 position | carbonyl | 5 proton |
|---|---|---|---|
| | | $cm.^{-1}$ | $\tau$ |
| COCl | H | 1710 (Nujol)<br>1720 ($CCl_4$) | 0.7 ($CCl_4$) |
| $CONH_2$ | H | 1640 (Nujol) | 0.2 ($CH_3COCH_3$) |
| $COOCH_3$ | H | 1690 (Film)<br>1695 ($CCl_4$) | 0.5 ($CCl_4$) |
| $COCH_3$ | H | 1620 (Film) | 0.15 ($CCl_4$) |
| $COCH_3$ | $CH_3$ | 1625 (Nujol)<br>1640 ($CCl_4$) | - |
| H | H | - | 2.2 ($CCl_4$) |

The table draws together some of the features of the spectra of compounds described in this section. The "carbonyl" band for 3-acetylindolizine is at 1620 cm.$^{-1}$ and Hurst, Melton and Wibberley[38] explain that this band is in fact due to C=C-O$^{-}$. The same authors state that 3-acetyl-2-methylindolizine has this band at 1605 cm.$^{-1}$

The effect of carbonyl substituents in the 3 position on the 5 position proton can be clearly seen when compared with the value for indolizine itself.

3-Methylindolizine (14) required for mass spectrometry was prepared from 2-picoline and propionic anhydride by the Scholtz synthesis (see page 4) as described by Armarego.[11]

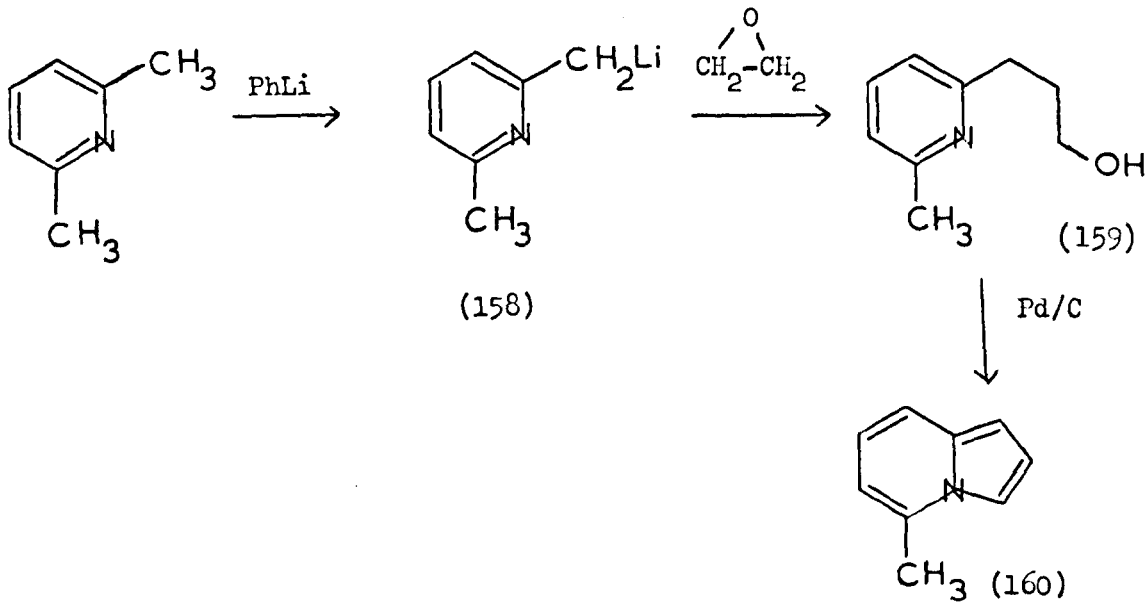
## 5 Substituted Indolizines

Preparation of indolizines with substituents in the 5 position is less easy due to the fact that quaternisation is more difficult when a 2,6-disubstituted pyridine is used in the Tschitschibabin synthesis.

5-Methylindolizine (160).

Boekelheide and Windgassen,[41] Galbraith, Small et al.[108] have shown an improved method for the synthesis of 5-methylindolizine (160) and this method was adopted.

SCHEME XL



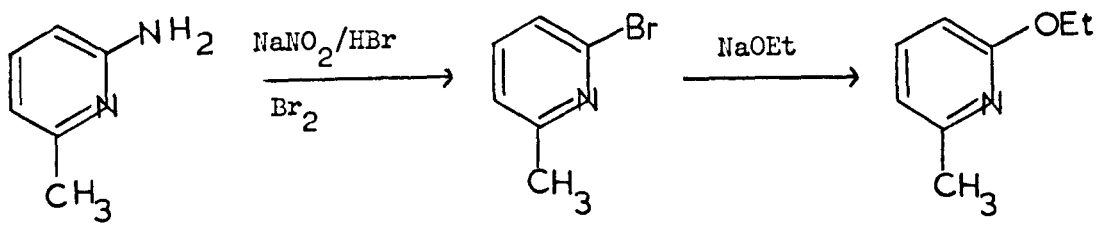

Phenyl lithium exchanges with 2,6 lutidine to give a monolithium derivative (158) if the correct molar quantities are employed; action of ethylene oxide on the latter yields 2-(γ-hydroxypropyl)-6-methylpyridine (159). The alcohol (159) can be converted directly into 5-methylindolizine (160) by heating it for 40 hr. at 240° with a 30% palladium on charcoal catalyst.

It is possible to prepare a lithium derivative of 5-methylindolizine.[107] An attempt was made to prepare 5-indolizinylacetic acid by pouring the reaction mixture of 5-methylindolizine (160) and phenyl lithium on to a slurry of solid carbon dioxide in ether. None of the required acid was isolated. An attempt to brominate 5-methylindolizine by boiling it with N-bromosuccinimide in carbon tetrachloride was not successful either.

Attempted preparation of 2-methyl-5-ethoxyindolizine.

Alkoxyindolizines have received little attention. The only reference to them in the literature is for substituted 3-ethoxyindolizines.[13,124] Since they are potentially interesting compounds attempts were made to prepare 2-methyl-5-ethoxy- and 2-methyl-7-methoxyindolizines. In the case of 2-methyl-5-ethoxyindolizine the starting material 2-methyl-6-ethoxypyridine (163) was prepared[125,126] in a two stage process from 2-methyl-6-aminopyridine (161) via 2-methyl-6-bromopyridine (162).

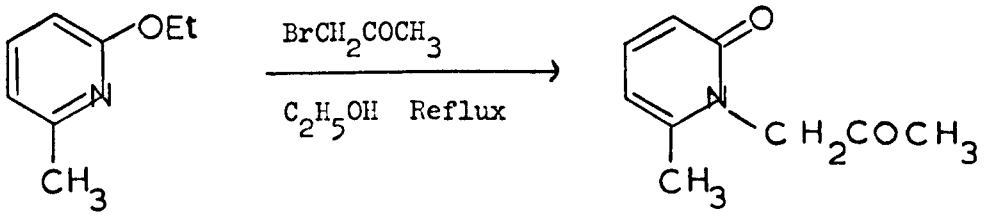
SCHEME XLI




(161) (162) (163)

Treatment of the ethoxypyridine (163) with bromoacetone in refluxing absolute ethanol gave a small yield of a compound which was not the expected quaternary salt but thought to be a pyridone of structure (164).

SCHEME XLII

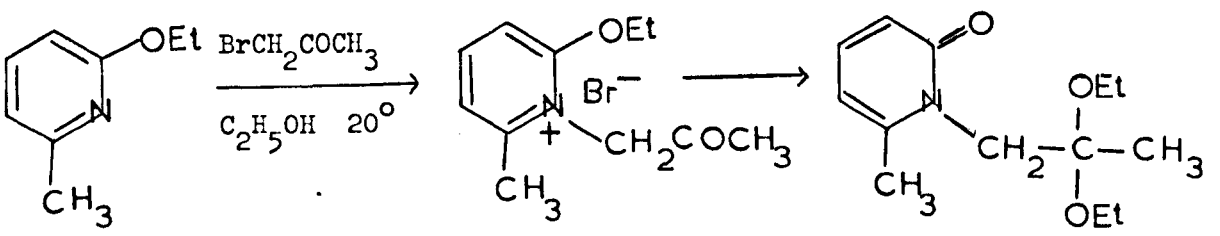



(164)

The nuclear magnetic resonance spectrum showed loss of the ethoxy protons and the infrared spectrum had a strong band at 1652 $cm.^{-1}$ characteristic of the 2-pyridone carbonyl group. The mass spectrum had the molecular ion at 165 m/e and the expected pattern of peaks. This type of reaction has been used to prepare[127] pyridones which are intermediates in the synthesis of oxazalo [3,2-a]pyridinium salts. The same product was obtained from an attempt to quaternise the ethoxypyridine (163) in sulpholane at $40^{\circ}$. The quaternary compound was obtained however in 39% yield by allowing the two reactants to stand together for a month in an ethanol solution at room temperature. No attempt was made to purify the 1-acetonyl-2-methyl-6-ethoxypyridinium bromide (165), which was obtained as deliquescent buff crystals, because of its instability; boiling it in ethanol converted it to the pyridone (164). An attempt to cyclise the quaternary salt (165) to the indolizine using 10% sodium bicarbonate solution again gave the pyridone (164). When the reaction was carried out in ethanol using di-n-butylamine or diethylamine as the base a new compound resulted. There is not sufficient evidence to establish its identity but it seems possible, based on its nuclear

magnetic resonance spectrum, that it is a ketal of structure (166) although base catalysis is not the normal method of preparation of ketals.

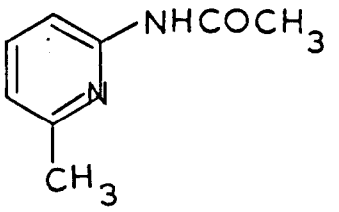
SCHEME XLIII




(163) (165) (166)

When the reaction was conducted in methanol an equivalent dimethoxy compound resulted. The use of a base resin as described in the preparation of 2-methyl-7-cyanoindolizine (193) (see Scheme LIII) was not successful in bringing about cyclisation to an ethoxyindolizine.

Since 2-methyl-6-aminopyridine (161) was on hand from the preparation of the ethoxypyridine (163) its monoacetyl derivative (167) was prepared by boiling it in a 1:1 mixture of acetic acid and acetic anhydride for 30 minutes. Attempts to form a quaternary salt by boiling the acetyl derivative in acetone with bromoacetone or keeping the reactants in sulpholane at 35° for several days were not successful.

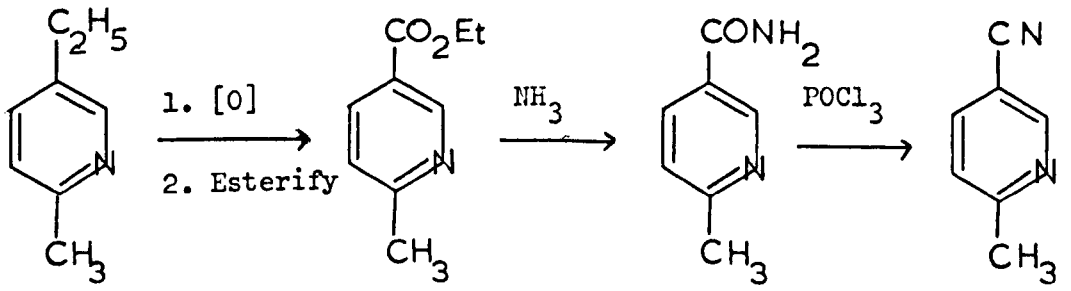


(167)

6 Substituted Indolizines

Plattner, Keller and Boller[128] have prepared ethyl 2-methyl-pyridine-5-carboxylate (169) from 2-methyl-5-ethylpyridine (168) by oxidation with potassium permanganate followed by esterification of the acid. From the ester (169) they also prepared the amide (170) by shaking with ammonia solution. 3-Cyano-6-methylpyridine (171) was prepared from the amide by treatment with phosphorus oxychloride. These compounds were suitable as starting materials and were prepared by this method.

SCHEME XLIV

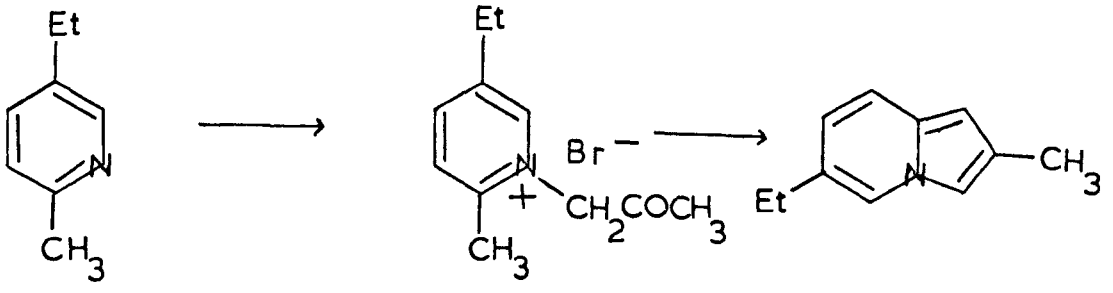


(168) (169) (170) (171)

2-Methyl-6-ethylindolizine (173).

2-Methyl-5-ethylpyridine (168) reacted with bromoacetone in boiling absolute ethanol to yield the quaternary compound (172) as a thick green gum. The quaternary compound was cyclised to the indolizine in 95% ethanol using di-n-butylamine as the base and was obtained in 37% yield.

SCHEME XLV

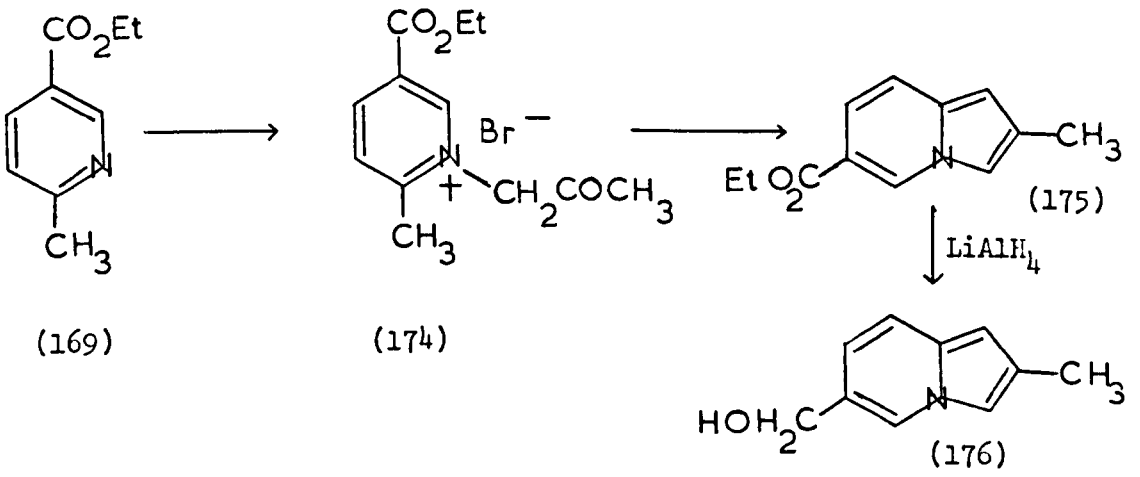



(168) (172) (173)

Ethyl 2-methylindolizine-6-carboxylate (175).

The pyridine ester (169) quaternised with bromoacetone in boiling absolute ethanol; again the quaternary compound (174) was a gum. Cyclisation was effected in two ways, one using aqueous sodium bicarbonate when the overall yield of indolizine from pyridine was 35% and the other using di-n-butylamine in absolute ethanol when the yield overall was 34%.

SCHEME XLVI

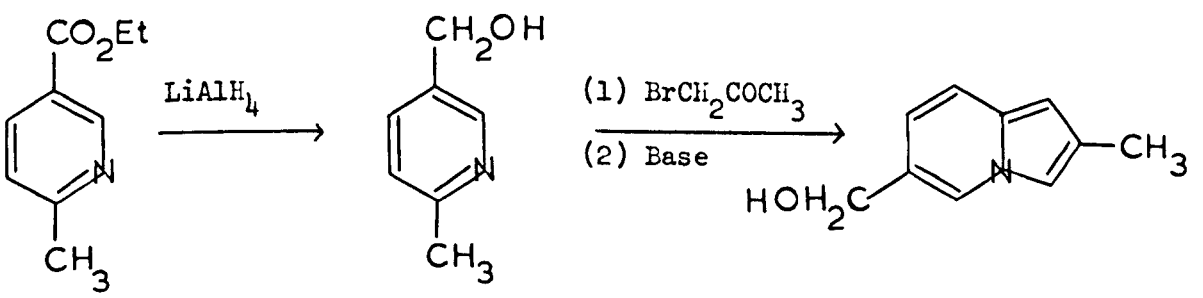



(169) (174) (175) (176)

2-Methyl-6-hydroxymethylindolizine (176).

There were two methods of approaching this compound from the starting materials available. One was to reduce the indolizine ester (175) as indicated in Scheme XLVI. The alternative was to reduce the pyridine ester (169) to the hydroxymethylpyridine (177) and then to quaternise this with the α-halogenoketone followed by cyclisation to the indolizine as shown in Scheme XLVII.

SCHEME XLVII




(169) (177) (176)

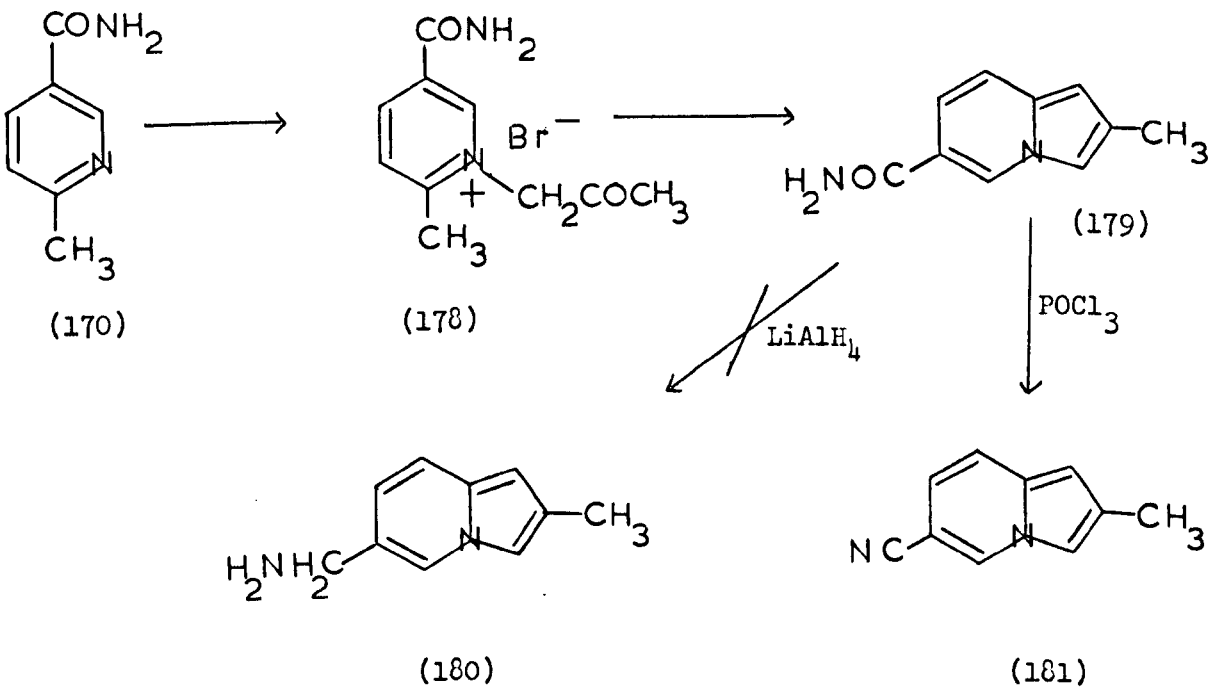
A trial experiment on the reduction of the ethyl 2-methylpyridine-5-carboxylate (169) with lithium aluminium hydride showed that the latter approach was possible since reduction did occur although the conditions used, boiling for 2 hr. in ether, were not sufficient to take the reaction to completion. The former approach, that of reducing ethyl 2-methylindolizine-6-carboxylate (175) in boiling ether solution with lithium aluminium hydride afforded the hydroxymethylindolizine (176) in 88% yield. An attempt to form a tosylate of the hydroxymethylindolizine (176) was not successful.

2-Methyl-6-hydroxydideuteromethylindolizine was prepared in a similar fashion, lithium aluminium deuteride being used for the reduction.

2-Methyl-6-carbamoylindolizine (179).

Boiling 2-methyl-5-carbamoylpyridine (170) with bromoacetone in absolute ethanol yielded the quaternary compound (178) which was insoluble in ethanol and crystallised out of solution in 74% yield. Cyclisation proceeded in 80% yield in 95% ethanol using di-n-butylamine.

SCHEME XLVIII



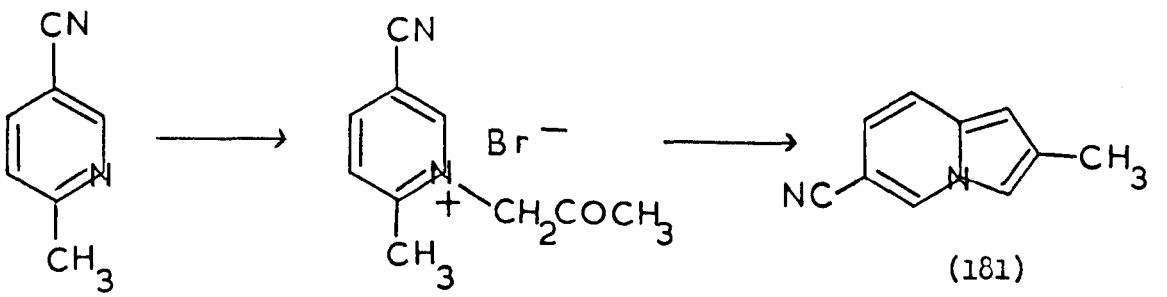

An attempt to reduce the amide (179) to the aminomethylindolizine (180) was not successful. When the amide was treated with lithium aluminium hydride in boiling tetrahydrofuran the nuclear magnetic resonance spectrum of the product indicated (based on evidence discussed later) that ring reduction may have occurred.

2-Methyl-6-cyanoindolizine (181).

Heating 2-methyl-6-carbamoylindolizine (179) with phosphorus oxychloride for 4 hr. at 130° converted the amide to the nitrile (181), but not completely. The product of the reaction was contaminated with starting material. An alternative approach was also pursued, that of

forming the quaternary salt (182) of the pyridine nitrile (171) and then cyclising to the indolizine (181). Quaternisation was achieved in a variety of ways. Boiling 2-methyl-5-cyanopyridine (171) and bromoacetone in acetone for 2½ hr. yielded 1-acetonyl-2-methyl-5-cyano-pyridinium bromide (182) in only 18% yield. Boiling for 7 hr. in absolute ethanol put the yield up to 35%, when this period was extended to 16 hr. the yield was 46%. A superior method consisted of keeping the reactants in sulpholane at 35° for 3 days; at 42° the yield was further increased. However, difficulty was experienced in purifying the quaternary compound from sulpholane. In this case use of the crude product to proceed to the cyclisation stage was found to be satisfactory.

SCHEME XLIX

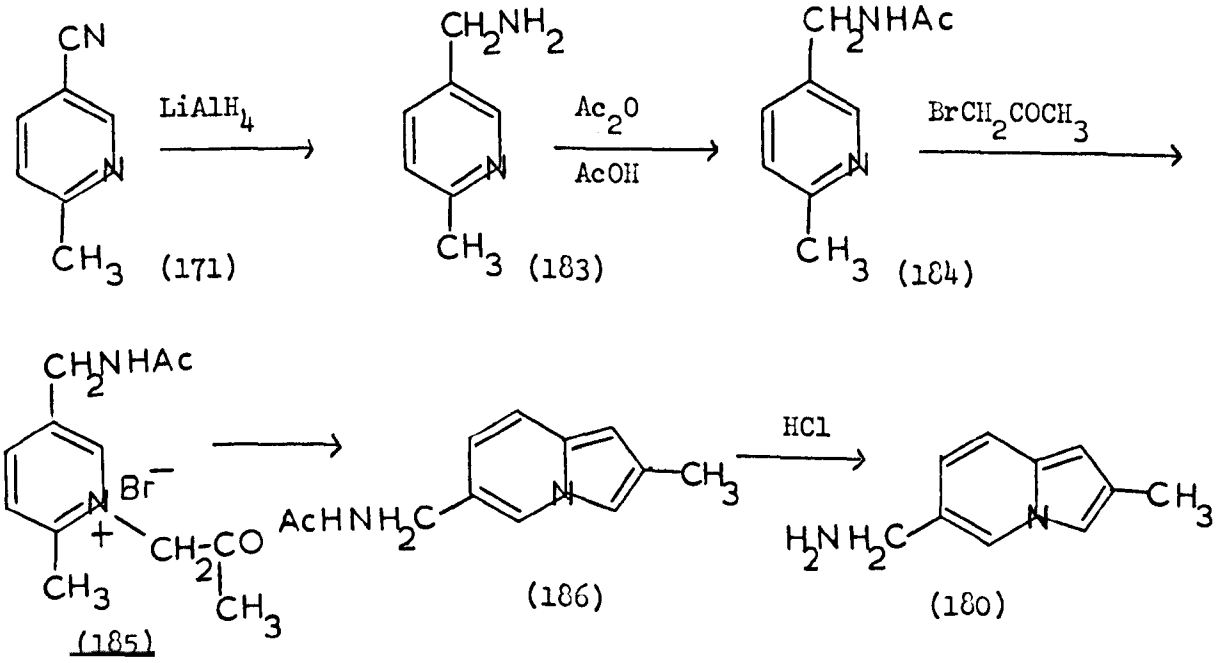



Cyclisation of the quaternary compound (182) was simply achieved in the usual manner using 10% aqueous sodium bicarbonate to give 2-methyl-6-cyanoindolizine (181) in 78% yield. If the treatment with aqueous bicarbonate was prolonged then hydrolysis occurred giving some of the amide (179) as an impurity.

An attempt to reduce the nitrile (181) catalytically with a 10% palladium on charcoal catalyst using 1 atmosphere pressure of hydrogen was not successful. When the nitrile was boiled in ether with lithium aluminium hydride the product gave peaks in the infrared spectrum at 3490 $cm.^{-1}$ and 3400 $cm.^{-1}$ indicating that an amine was present, together with an absence of any band due to the nitrile. The nuclear magnetic resonance spectrum (Figure 6) is rather complex. One can assign peaks for the expected product but the others present indicate that perhaps ring reduction has occurred. An identical spectrum was obtained when the reaction was conducted at room temperature. Subjecting 2,6-dimethylindolizine to the same conditions did not lead to any reduction.

Since a route to the aminomethyl derivative (180) was required a small scale experiment was attempted on the lines of Scheme L.

SCHEME L

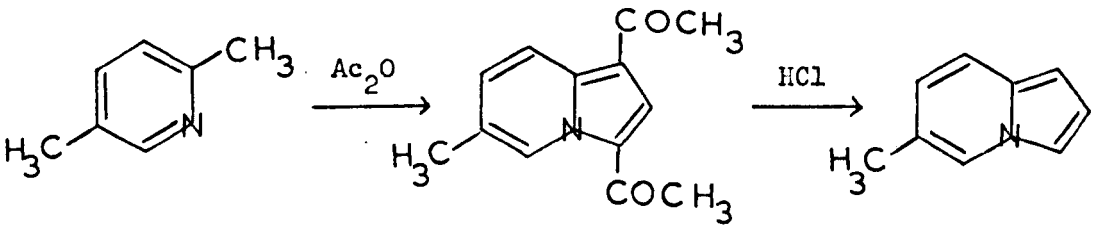


The reduction of the nitrile (171) proceeded smoothly in ether using lithium aluminium hydride to yield a red liquid; however, when this was distilled only a low yield of the aminomethyl compound (183) was obtained (19% yield). An acetyl derivative (184) was prepared which quaternised in refluxing acetone to yield the expected quaternary compound (185). Cyclisation in 10% aqueous sodium bicarbonate then afforded the acetyl derivative (186) of the required aminomethylindolizine. Its nuclear magnetic spectrum is shown in Figure 8. Hydrolysis of the acetyl derivative with concentrated hydrochloric acid yielded a compound whose nuclear magnetic spectrum is that expected for 2-methyl-6-aminomethylindolizine (180).

6-Methylindolizine (188).

6-Methylindolizine (188) required for mass spectrometry was prepared from 2,5 lutidine and acetic anhydride by the Scholtz synthesis. The intermediate diacetyl compound (187) showed the effects of anisotropic deshielding on both the 5 position proton (0.15 $\tau$) and the 8 position proton (1.4 $\tau$). Meta coupling J = $\sim$ 2 c/s between the 5 and 7 position protons enabled the doublets (J = 9 c/s) due to the 7 and 8 position protons to be assigned. In trifluoroacetic acid the compound did not appear to be protonated on the ring. Hydrolysis was brought about using concentrated hydrochloric acid.

SCHEME LI



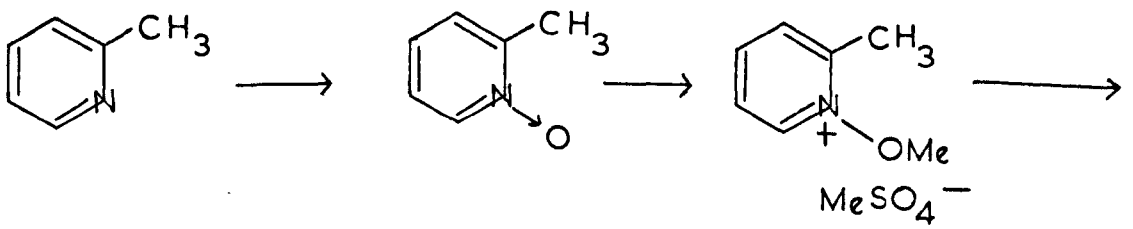

(187) (188)

## 7 Substituted Indolizines

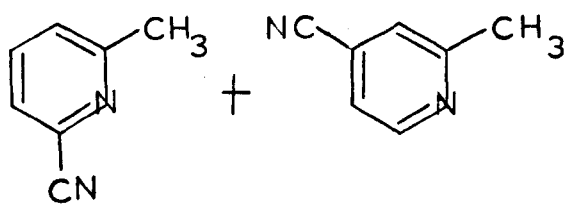
2-Methyl-7-cyanoindolizine (193).

Feely and Beavers[129] have prepared 2-methyl-4-cyanopyridine (191) and their method was followed. The N-oxide of 2-picoline when treated with dimethyl sulphate gave the salt 1-methoxy-2-methylpyridinium methyl sulphate (189) which on treatment with an aqueous solution of sodium cyanide affords a mixture of 2-methyl-6-cyanopyridine (190) and 2-methyl-4-cyanopyridine (191). The mixture can be separated by careful distillation.

SCHEME LII



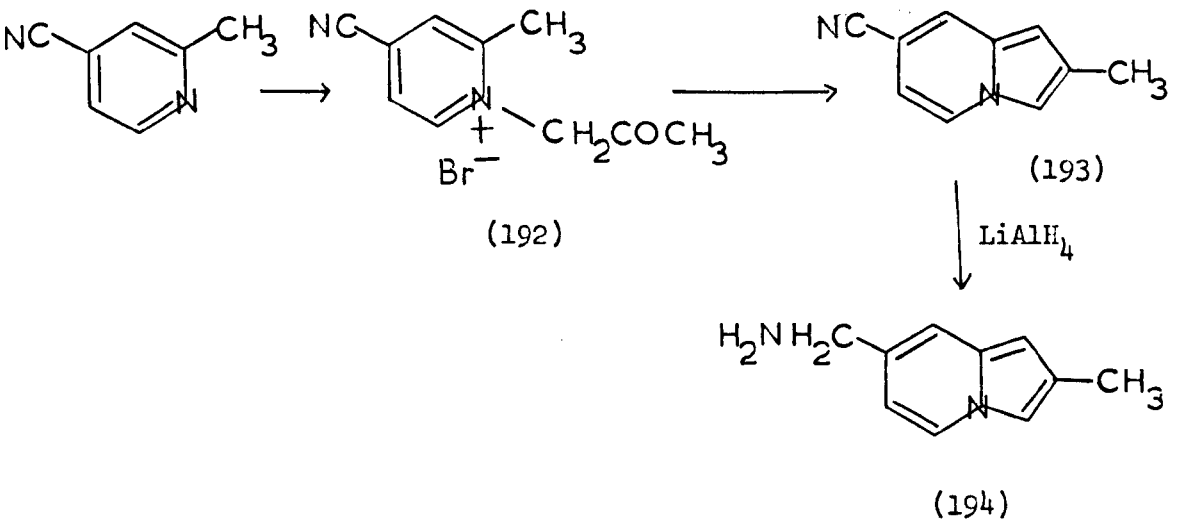
(189)



(190) (191)

It was found that the 4-cyano compound (191) would readily react with bromoacetone in either sulpholane (yield 88%) or acetone (1 hr. reflux yield = 48%) to give the required quaternary compound (192). This was not the case for 2-methyl-6-cyanopyridine (190). An experiment conducted in sulpholane under the same conditions as for the 4-cyano compound (191) yielded no quaternary compound. A sample of the mixed products from aqueous sodium cyanide treatment when treated with bromoacetone in boiling acetone yielded only one quaternary product the 1-acetonyl-2-methyl-4-cyanopyridinium bromide (192). This gave a convenient method of removing traces of the 6-cyano compound (190).

SCHEME LIII

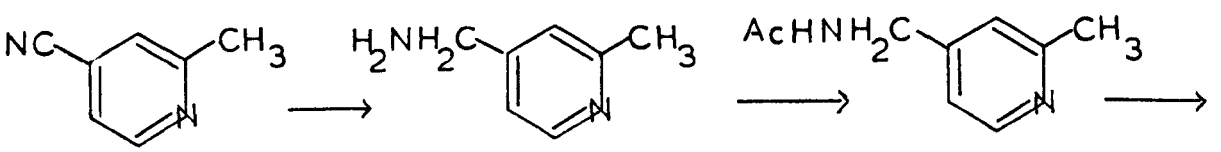



(194)

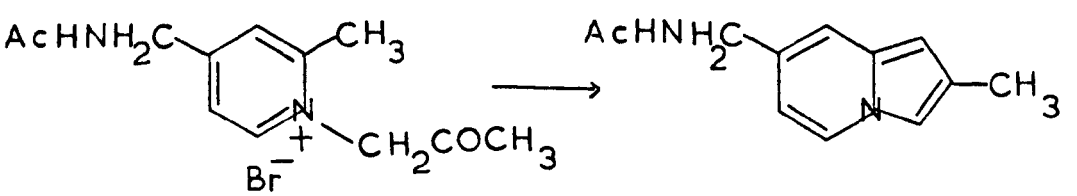
Attempts to cyclise the quaternary compound (192) using 10% sodium bicarbonate solution gave a product contaminated with the amide presumably due to hydrolysis of the cyano group under the conditions of the reaction. When di-n-butylamine was used in 95% ethanol the required indolizine was obtained, but contaminated with di-n-butylamine which was difficult to remove. An alternative approach was adopted. The quaternary compound in 95% ethanol solution was boiled under reflux with a quantity of a basic ion exchange resin. The resin was stable under these conditions and at the end of the period of boiling the resin was filtered off and the solvent removed under reduced pressure to yield a residue which when extracted with light petroleum afforded 2-methyl-7-cyanoindolizine (193) in 24% yield.

Reduction of this nitrile with lithium aluminium hydride, unlike the 6-nitrile (181), proceeded normally. The nuclear magnetic resonance and infrared spectra of the product indicated that it was 2-methyl-7-aminomethylindolizine (194). Figure 7 shows the nuclear magnetic resonance spectrum. In a similar fashion to that described for the 6 position of the ring a small scale experiment was conducted to examine the possibility of arriving at the amine by an alternative route, that is by making the aminomethylpyridine, protecting the group and then quaternising and cyclising in the usual manner. The course of the experiment was followed by spectral examination of the products.

SCHEME LIV




(191) (195) (196)



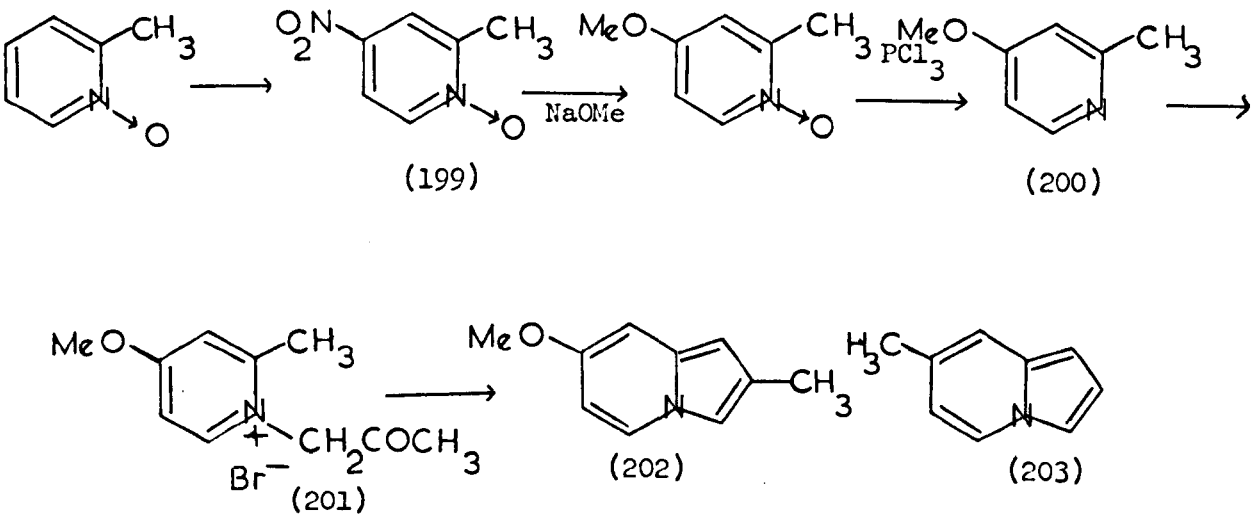

(197) (198)

The reduction of 2-methyl-4-cyanopyridine (191) proceeded without difficulty to the aminomethylpyridine (195) from which an acetyl derivative (196) was prepared. Quaternisation presented no difficulty and the quaternary compound (197) was obtained in high yield by boiling the reactants in acetone. Further experiments indicated that the quaternary compound (197) could be converted into the indolizine (198) by using aqueous sodium bicarbonate or di-n-butylamine in 95% ethanol. This method of preparation was not followed up once it was found that the nitrile (193) was a suitable intermediate in the preparation of the amine.

2-Methyl-7-methoxyindolizine (202).

Attempts to prepare a 5-ethoxyindolizine were not successful but a 7-methoxyindolizine has been prepared. Nitration of 2-picoline-1-oxide[130] gave the 4-nitro derivative (199) which was then converted to the 4-methoxypyridine (200) by nucleophilic replacement of the nitro group by methoxide followed by removal of the N-oxide function using phosphorus trichloride following the method of Endo and Nakashima.[131]

SCHEME LV




Quaternisation to 1-acetonyl-2-methyl-4-methoxypyridinium bromide (201) proceeded quickly and in high yield when the methoxypyridine (200) was warmed with bromoacetone in an acetone solution. Cyclisation proved to be more difficult and boiling for 4 hr. in 10% sodium bicarbonate gave only a 7% yield of 2-methyl-7-methoxyindolizine (202).

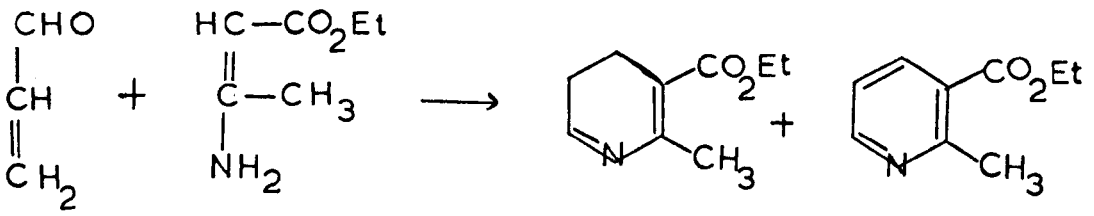
7-Methylindolizine (203).

The Scholtz synthesis as described by Armarego[11] was used to prepare 7-methylindolizine.

## 8 Substituted Indolizines

Sato and Mishima[132] have described a method of obtaining ethyl 2-methylpyridine-3-carboxylate (207) together with the 3,4-dihydro ester (206) by the reaction of ethyl 3-aminocrotonate (204) with acrolein (205) in ethanolic solution in the presence of piperidine.

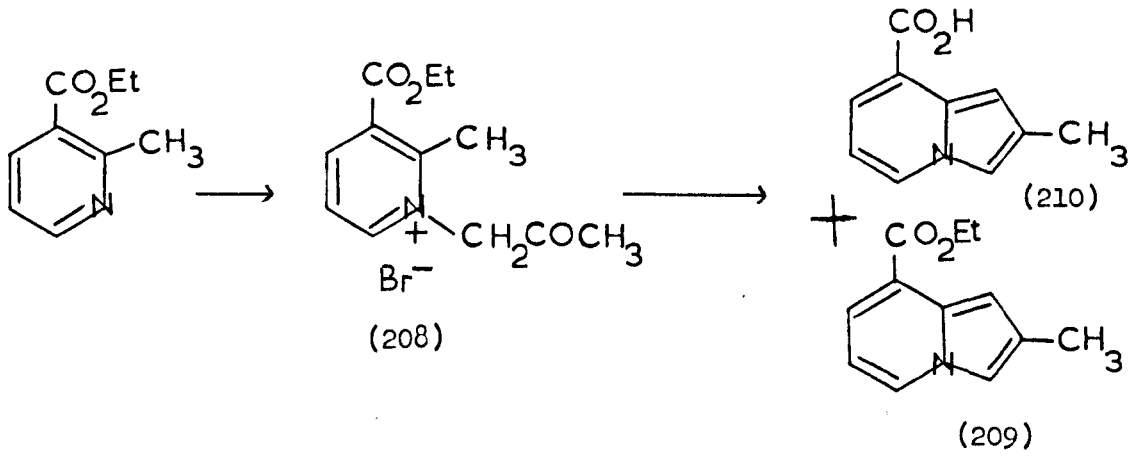
SCHEME LVI



(205) (204) (206) (207)

Oxidation of the dihydroester (206) to the pyridine (207) is possible using sodium nitrate and sulphuric acid. When the reaction was attempted only a very little of the dihydrocompound (206) was produced. The majority of the product was the pyridine ester (207) which was purified by recrystallisation from light petroleum (b.p. 40-60°). The quaternary compound (208) was prepared by boiling with bromoacetone in absolute ethanol and was obtained as a brown gum which could not be solidified.

SCHEME LVII




An attempt to cyclise the quaternary compound (208) in 10% sodium bicarbonate led to a mixture of the indolizine ester (209) and the acid (210) which was obtained by acidification of the aqueous solution after removal of the ester. The compounds were identified by their spectra.

8-Methylindolizine.

8-Methylindolizine-2-carboxylic acid was prepared in the same way as indolizine-2-carboxylic acid, 2,3-lutidine being used instead of 2-picoline (see page 8, Scheme V). The acid was decarboxylated by heating it with calcium oxide and distilling the product out of the reaction flask. 1-Methylindolizine was prepared in a similar fashion from 2-ethylpyridine.

## Dimethylindolizines

A number of dimethylindolizines were prepared for mass spectral investigation. The general procedure was to quaternise the lutidine with bromoacetone and cyclise using aqueous sodium bicarbonate. In this way 2,5-, 2,6-, 2,7-, and 2,8-dimethylindolizine were prepared. A careful study of the nuclear magnetic resonance spectra of these compounds enabled the assignment of each peak to be established. The results are in agreement with published results[118,118,120,40] The usual pattern is for the 5 position proton to be furthest downfield followed by the 8 position proton. When the spectrum was recorded in trifluoroacetic acid then protonation occurred. This has been established to occur at the 3 position. This brings about a change in the nuclear magnetic resonance spectrum and the 7 position proton is usually more affected than the other protons of the 6-membered ring.

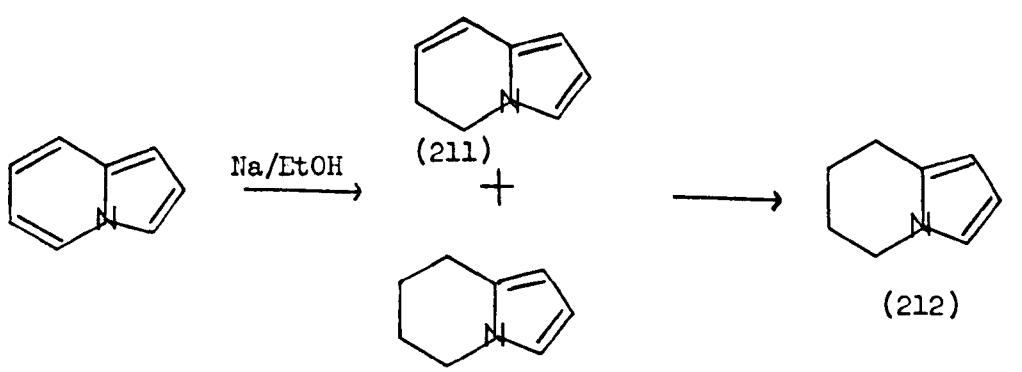
| Position | 2,5-Dimethylindolizine | | | 2,6-Dimethylindolizine | | | 2,8-Dimethylindolizine | | |
|---|---|---|---|---|---|---|---|---|---|
| | $\tau$ $CCl_4$ | $\tau$ T.F.A. | Difference | $\tau$ $CCl_4$ | $\tau$ T.F.A. | Difference | $\tau$ $CCl_4$ | $\tau$ T.F.A. | Difference |
| 1 | 3.72 | 2.95 | 0.77 | 3.90 | 3.12 | 0.78 | 3.82 | 3.00 | 0.82 |
| 3 | 3.05 | 4.70 | 1.65 | 3.06 | 4.60 | 1.54 | 3.05 | 4.52 | 1.47 |
| 5 | - | | | 2.45 | 1.25 | 1.20 | 2.44 | 1.20 | 1.24 |
| 6 | 3.78 | 2.25 | 1.53 | - | - | - | 3.75 | 2.30 | 1.52 |
| 7 | 3.40 | 1.50 | 1.90 | 3.60 | 1.65 | 1.95 | 3.75 | 1.70 | 2.05 |
| 8 | 2.80 | 2.05 | 0.75 | 2.86 | 2.15 | 0.71 | - | - | - |

1,2-Dimethylindolizine was prepared[18] from 2-ethylpyridine and bromoacetone while 2,3-dimethylindolizine was prepared[18] from 2-picoline and 1-bromoethyl methyl ketone. 3,5-Dimethylindolizine was prepared using the Schlotz synthesis of 3-methylindolzine except that 2,6-lutidine was used.[11]

## Reduction Reactions

Scholtz[4] reported that the reduction of indolizine with sodium and ethanol gave a dihydro product and that no further reduction could be effected under these conditions (see page 42). In an attempt to verify this statement it was found that reduction led to a mixture of a dihydroindolizine and 5,6,7,8-tetrahydroindolizine (212). When the experiment was repeated on the mixture a single product was arrived at, the tetrahydroindolizine (212). Reduction of the mixture could also be effected using a palladium on charcoal catalyst and an atmosphere of hydrogen.

SCHEME LVIII



A pure sample of the dihydroindolizine was not isolated but based on nuclear magnetic resonance evidence it would seem to be 5,6-dihydroindolizine (211).

The nuclear magnetic resonance spectrum of 5,6,7,8-tetrahydroindolizine is shown in Figure 10. The peaks centred at 3.65 $\tau$ , 4.05 $\tau$ and 4.3 $\tau$ are assigned to the pyrrole nucleus and, based on the spectra of 2-alkylpyrroles, are positions 3,2,1 respectively of the indolizine ring. The peak centred at 6.15 $\tau$ , which integrates for two protons is considered to be the methylene at the 5 position (1-n-butylpyrrole has $N-CH_2-$ at $\sim$ 6.3 $\tau$ ). The peak centred at 7.25 $\tau$ which again integrates for 2 protons must then be the methylene in the 8 position (2-ethylpyrrole has $-CH_2-$ Pyrrole at 7.37 $\tau$ ). The multiplet centred at 8.15 $\tau$ and which integrates for four protons must then be due to the 6 and 7 positions combined.

When the nuclear magnetic resonance spectrum for the mixture is inspected (Figure 9) the triplet at 6.1 $\tau$ J = 7 c/s must be due mainly to the dihydro product although it lies in the same position as the methylene from the tetrahydro product. Assigning this peak to the 5 position means that the dihydro product must be 5,6-dihydroindolizine. The signal from the methylene in the 6 position is centred at 7.6 $\tau$ . The protons in the 7 and 8 positions must then be found together with the pyrrole protons below 5 $\tau$ . The infrared spectrum of the mixture has bands at 3042 $cm.^{-1}$, 1650 $cm.^{-1}$ and 1625 $cm.^{-1}$ which are not present in the tetrahydroindolizine.

Treating 2,6-dimethylindolizine with sodium and ethanol did not lead to a tetrahydro product. The nuclear magnetic resonance spectrum of the product (Figure 12) indicated a dihydroindolizine and of the possible products a 5,8-dihydro compound seems most likely. The infrared spectrum of the product had bands at 3040 $cm.^{-1}$ and 1682 $cm.^{-1}$.

In the case of 2,7-dimethylindolizine a mixture of dihydro products seems to result (Figure 11). The triplet at 6.2 $\tau$, J = 7 c/s and the one at 7.7 $\tau$, J = 7 c/s by analogy with the reduction of indolizine are considered to be due to the 5 and 6 positions of a 5,6-dihydro compound. Peaks centred at 5.65 $\tau$ and 6.8 $\tau$ by analogy with the reduction of 2,6-dimethylindolizine where they occur at 5.8 $\tau$ and 6.7 $\tau$ are considered to be due to the 5,8-dihydro compound. The infrared spectrum had bands at 3040 $cm.^{-1}$, 1695 $cm.^{-1}$ and 1645 $cm.^{-1}$.

Attempts to reduce both 2-methyl-6-hydroxymethylindolizine (176) and ethyl 2-methylindolizine-6-carboxylate (175) did not yield single products. The nuclear magnetic resonance spectra of the products indicates that ring reduction is proceeding, since the peaks furthest downfield are those due to the pyrrole protons of a partially reduced indolizine. The same effect was found when reduction of 2-methyl-7-methoxyindolizine (202) was attempted.

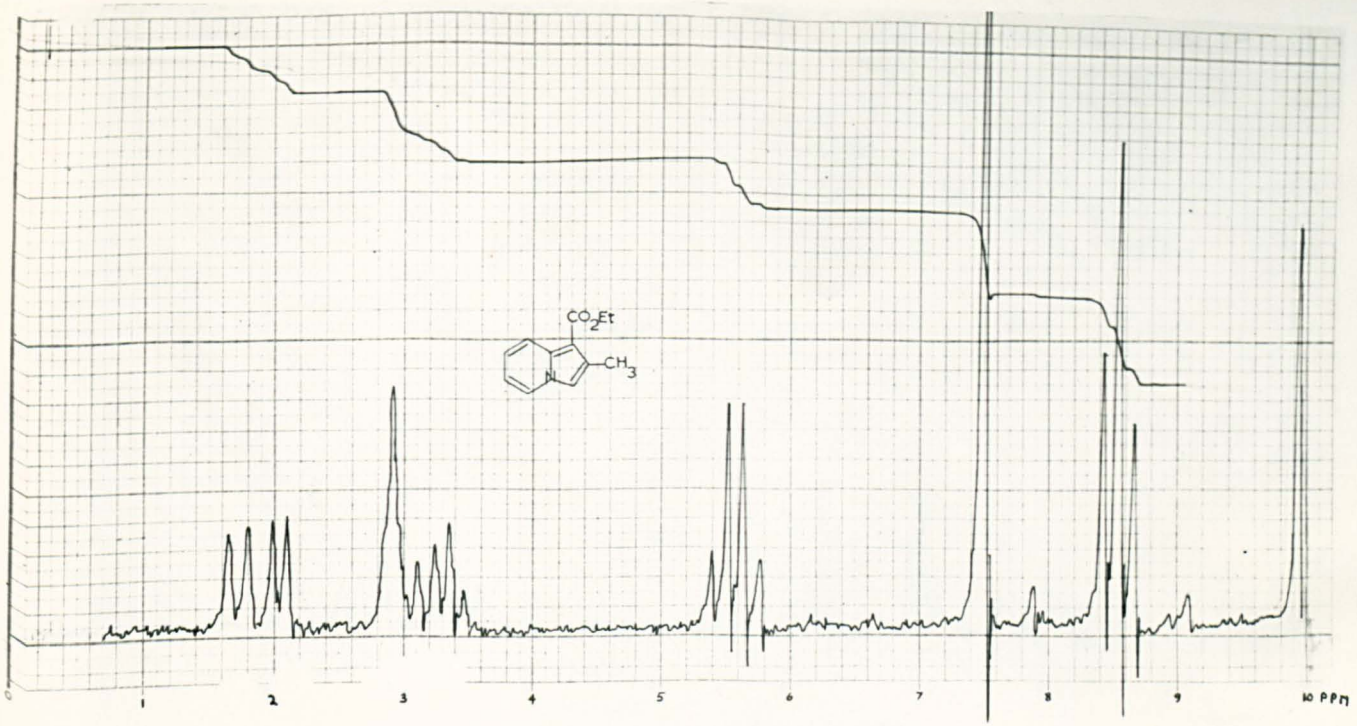



Figure 1 Solvent $CCl_4$

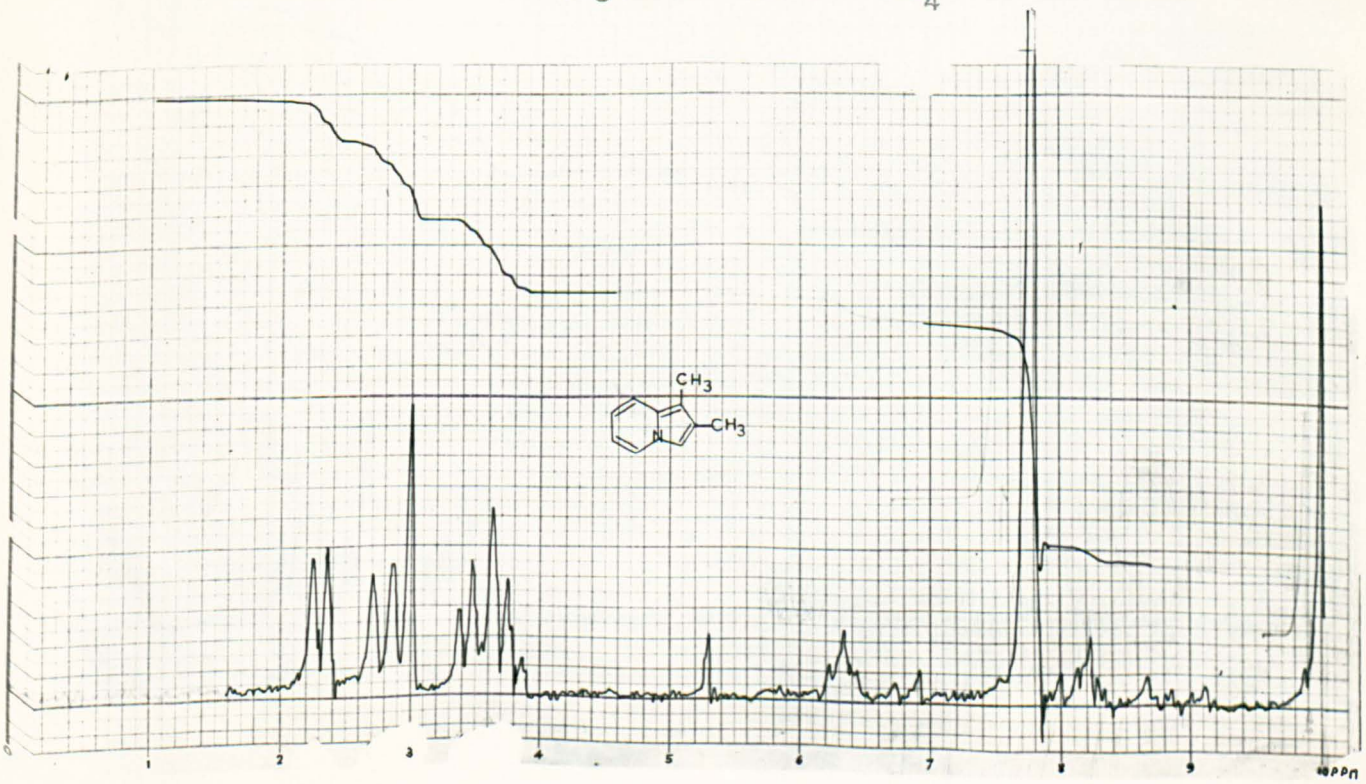



Figure 2 Solvent $CCl_4$

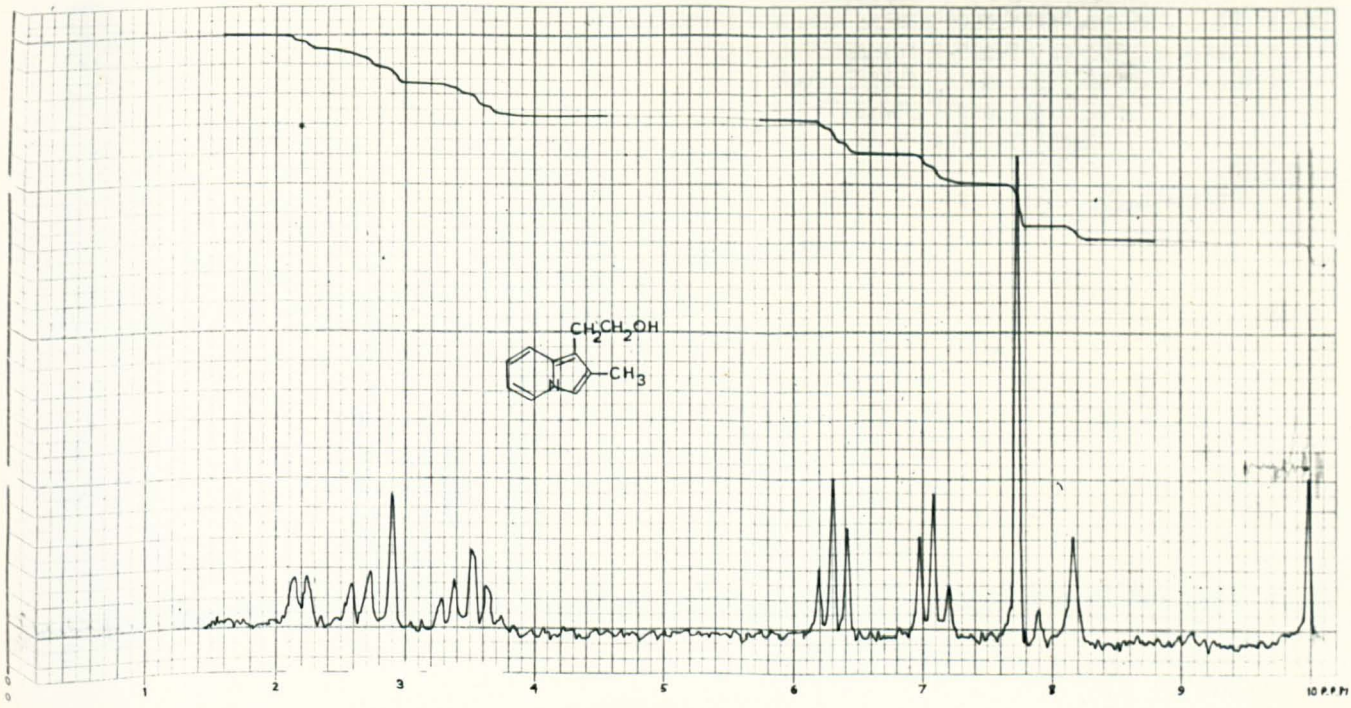



Figure 3 Solvent $CCl_4$

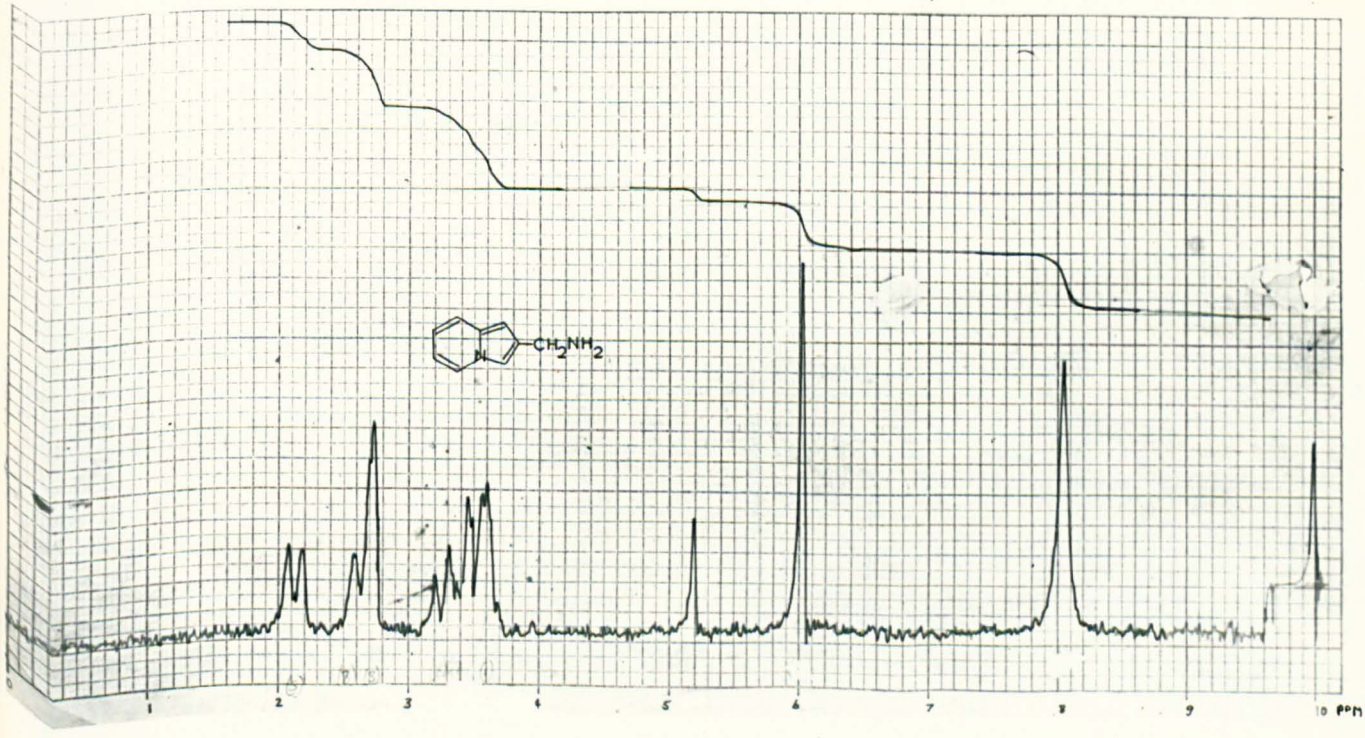



Figure 4 Solvent $CDCl_3$

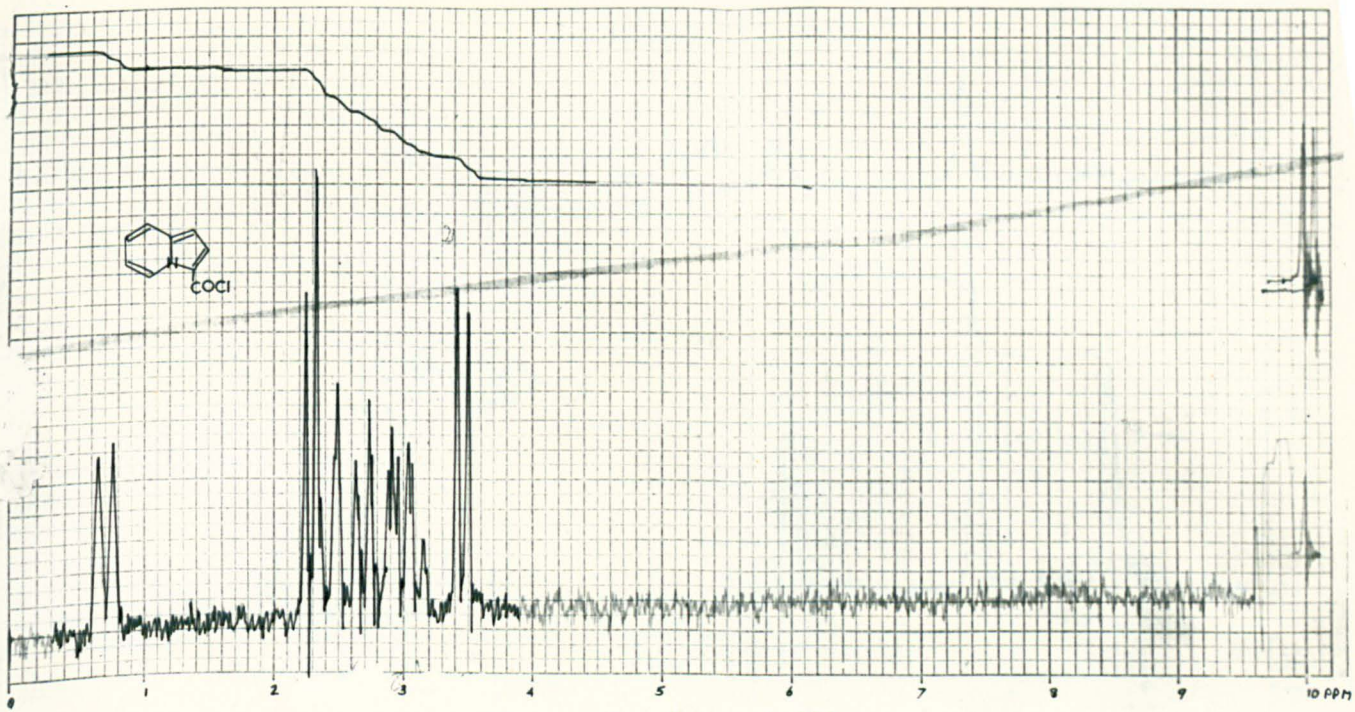



Figure 5 Solvent $CCl_4$

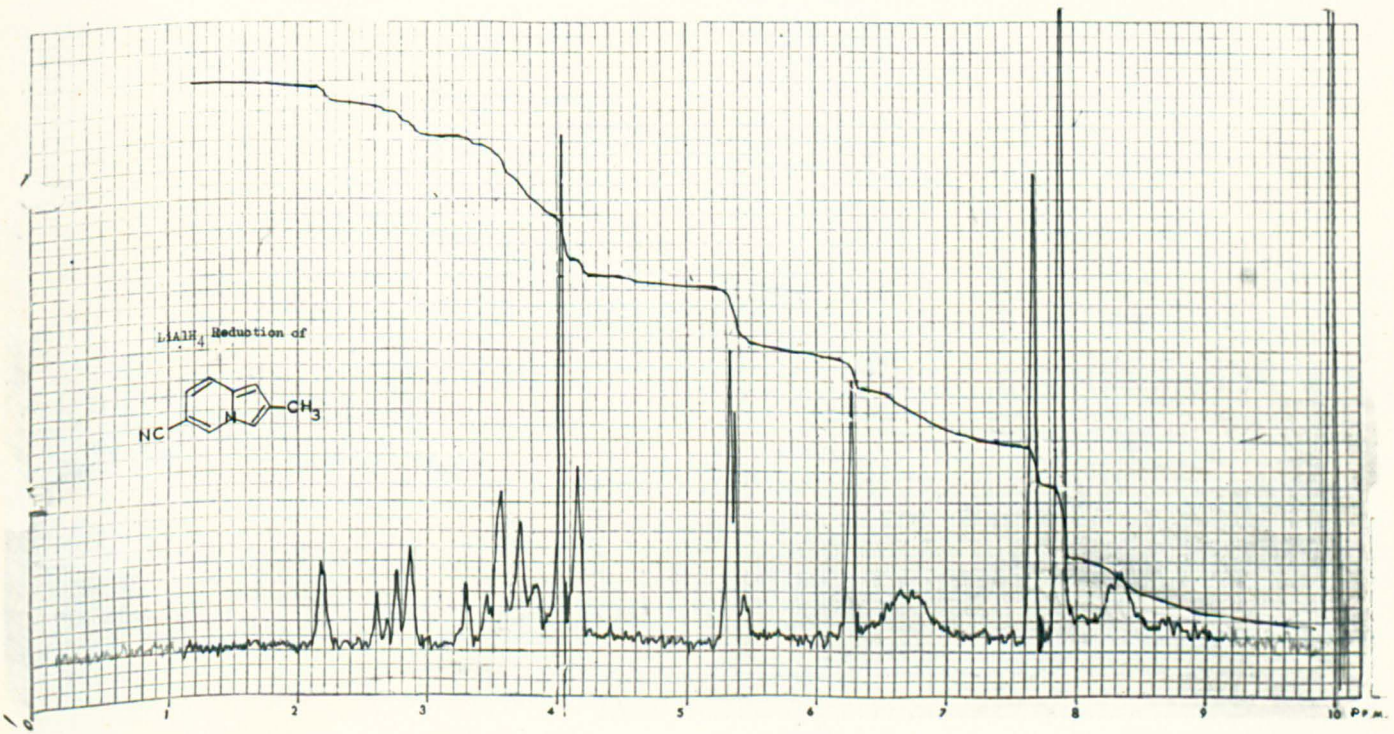



Figure 6 Solvent $CDCl_3$

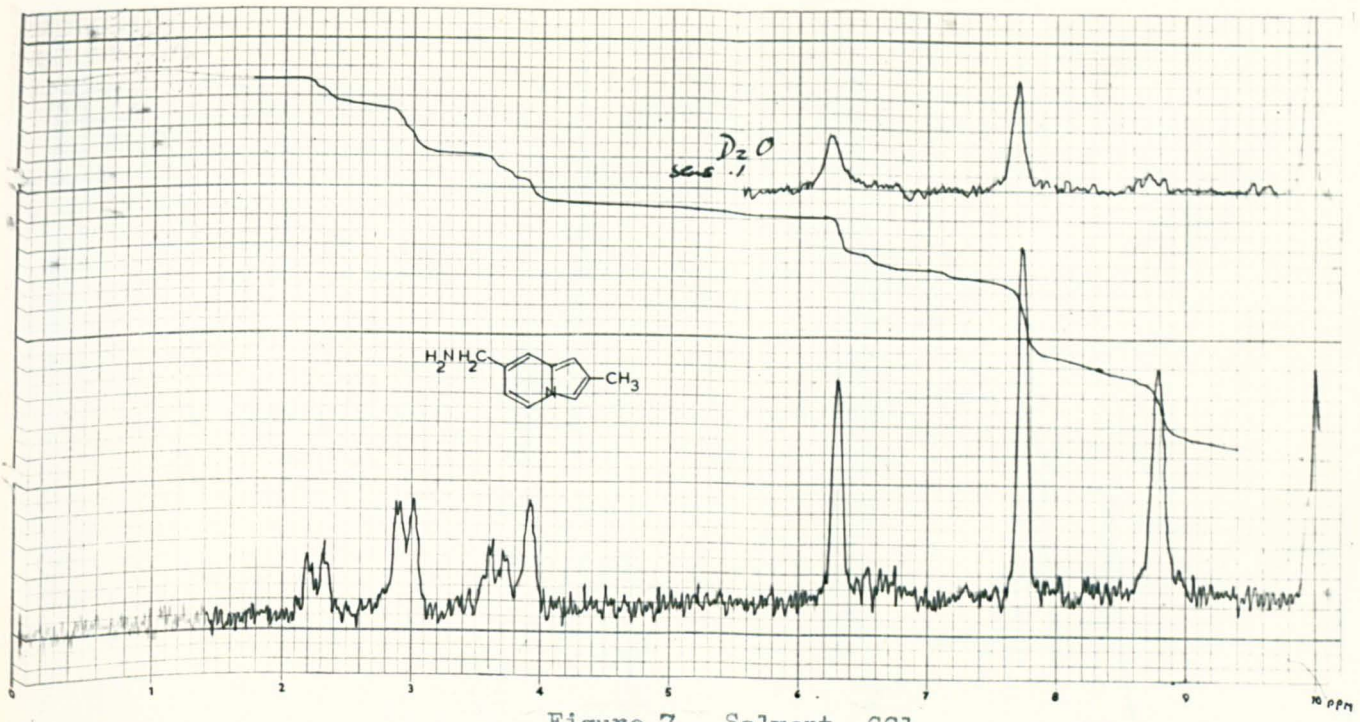



Figure 7 Solvent $CCl_4$

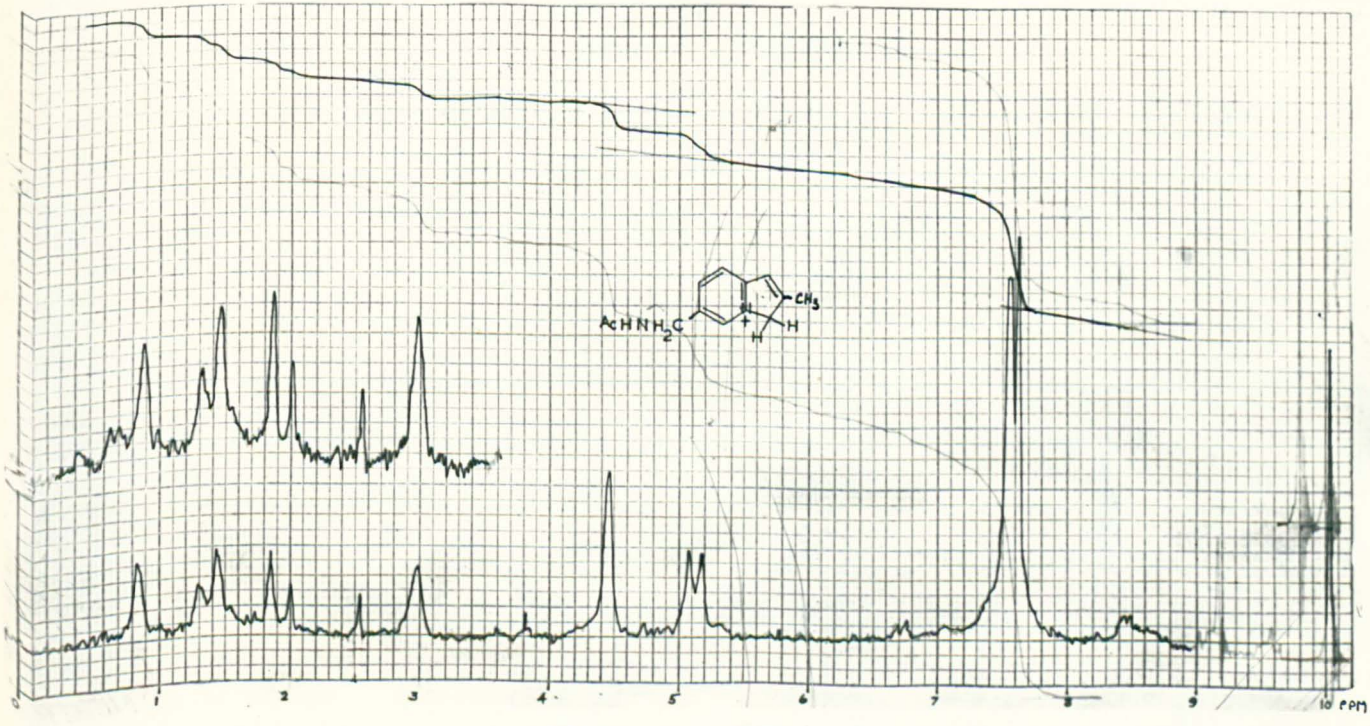



Figure 8 Solvent T.F.A.

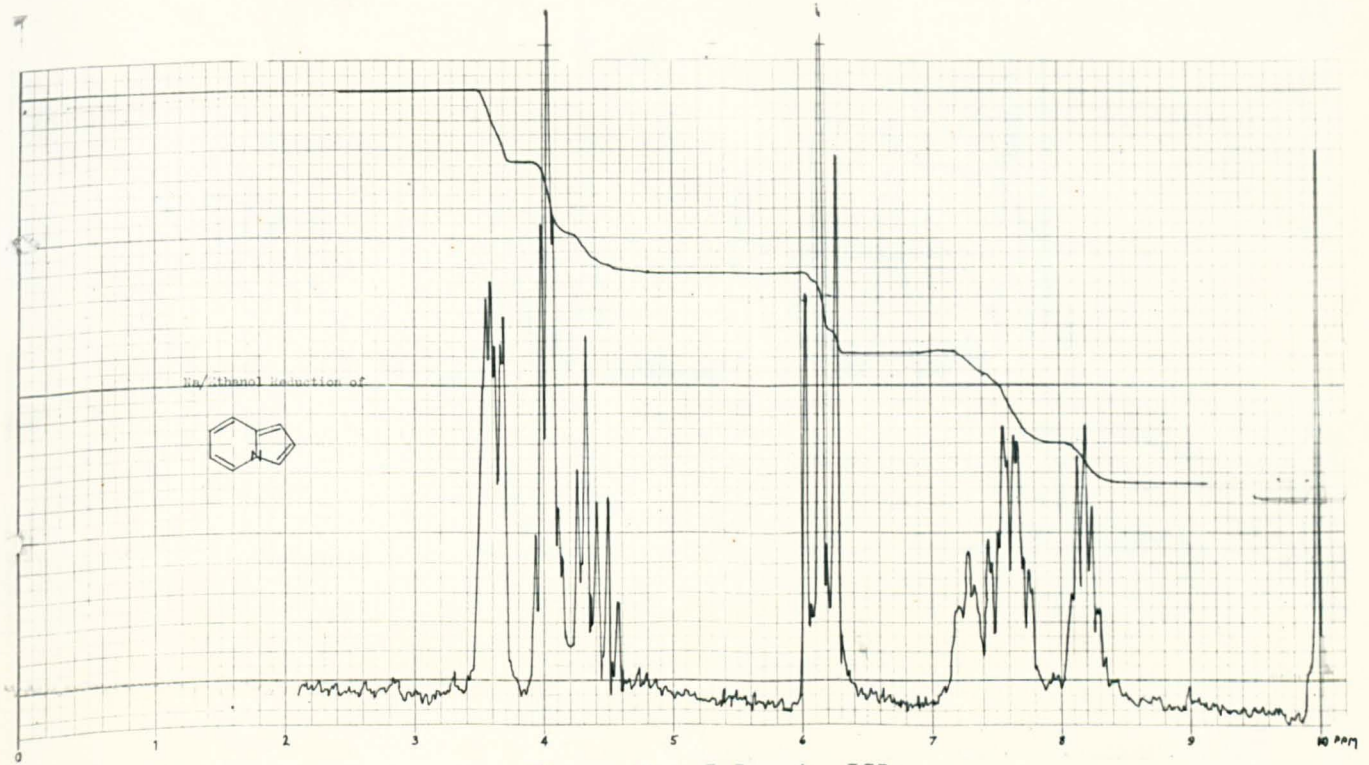



Figure 9 Solvent $CCl_4$

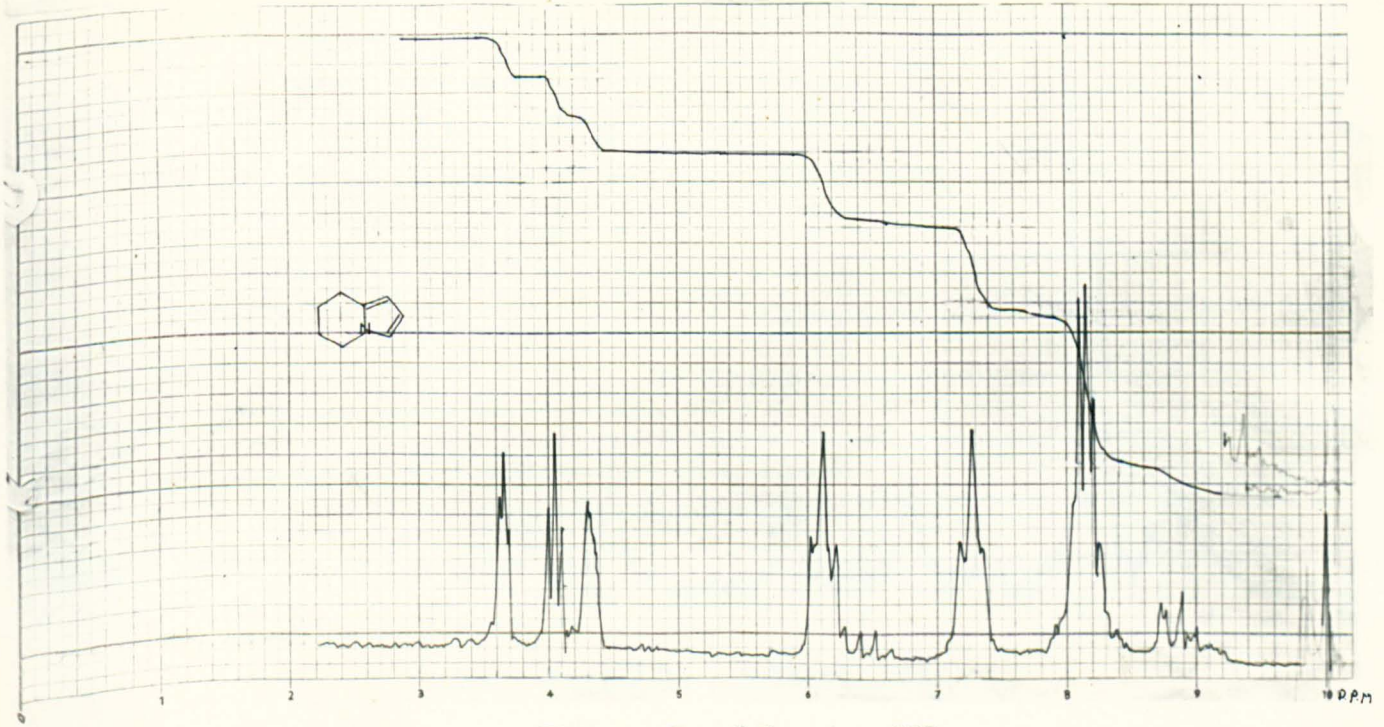



Figure 10 Solvent $CCl_4$

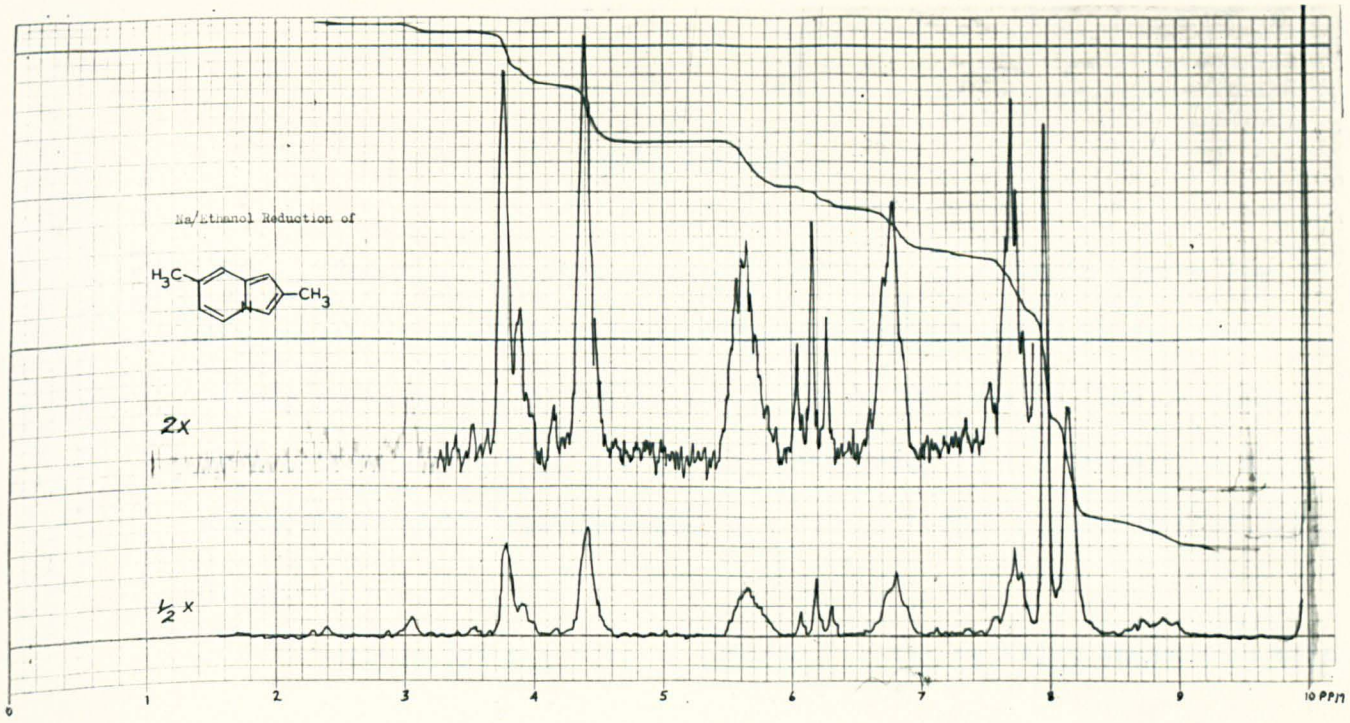



Figure 11 Solvent $CCl_4$

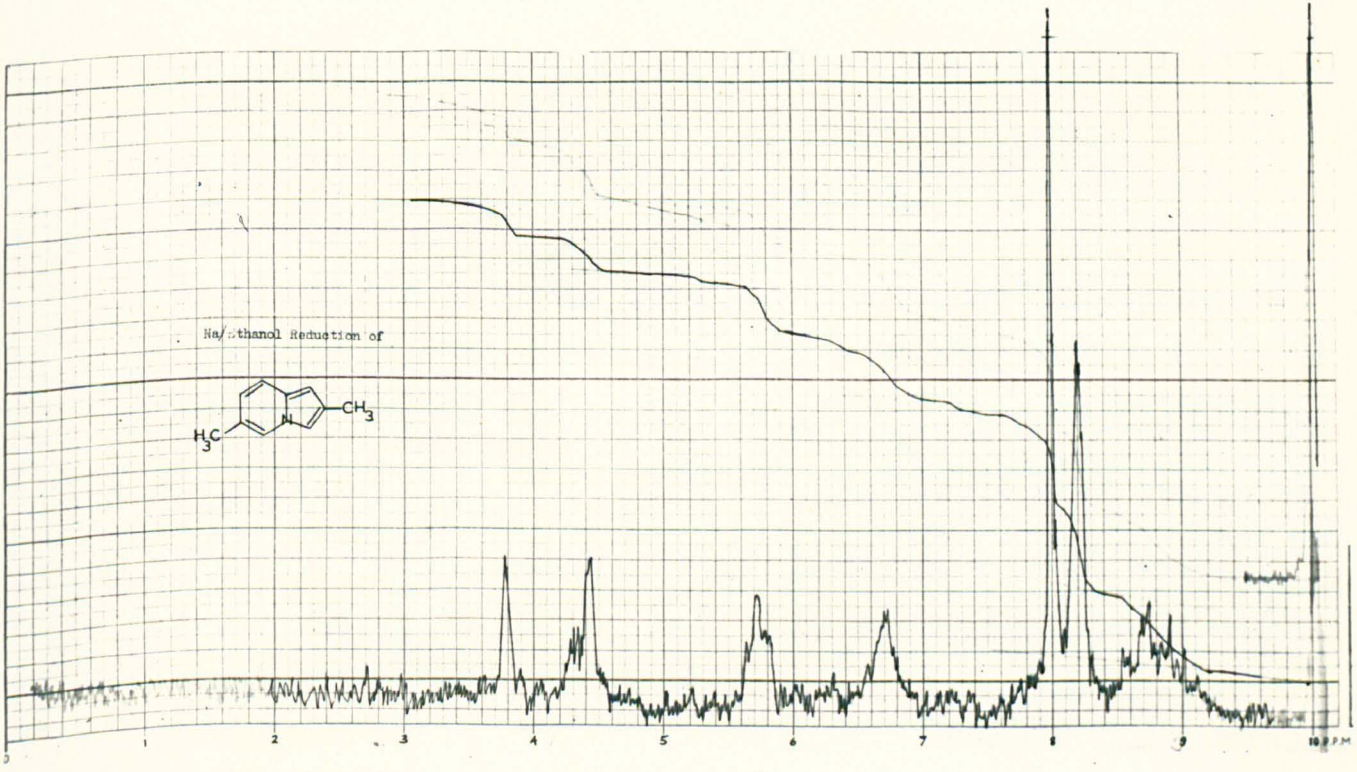



Figure 12 Solvent $CCl_4$

## Mass Spectra

The mass spectrum of indolizine (12) is shown in Figure 13. The molecular ion (m/e 117, base peak) loses HCN and $H_2CN$ to give strong peaks at m/e 90 (relative abundance 38%) and 89 (28%). There is a metastable peak at m/e 69.2 corresponding to the transition M to M-HCN. Presumably rearrangement must occur before elimination of HCN is possible.

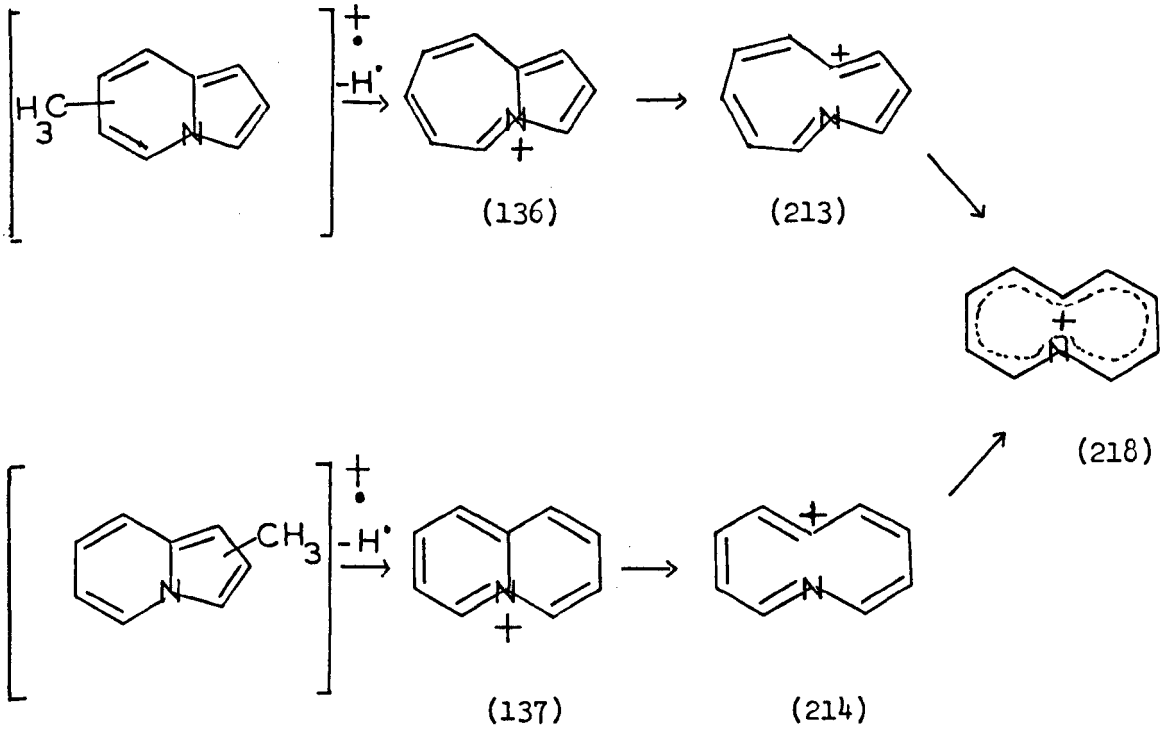
Indole shows a similar pattern,[136] the relative abundances being m/e 90 (40%) and m/e 89 (24%).

The next fragmentation in the indolizine spectrum gives rise to a peak at m/e 64 a loss of 26 from the peak at m/e 90.

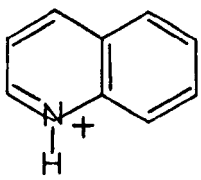
$$C_7H_6^+ \xrightarrow{-C_2H_2} C_5H_4^+$$

In indole the next major peak is at m/e 63[136] suggesting a different breakdown path.

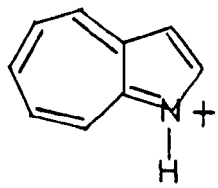
Spectra of the methylindolizines are shown in Figures 14 to 20. The major peaks in every case are the molecular ion M (m/e 131) and an M-1 ion (m/e 130). Based on the analogous case of methylindoles[136,138] one can postulate (a) for 5-, 6-, 7- and 8-methylindolizine an azonia--azulenium ion (136) and (b) for 1-, 2- and 3-methylindolizine a quinolizinium ion (137) for the M-1 peak.



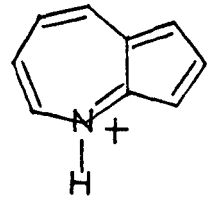

The next step in every case is loss of HCN from the M-1 ion. This is confirmed by metastable peaks at m/e 81.6. Loss of HCN presumably requires some prior rearrangement of the postulated ions at m/e 130 and since the similarity of the spectra is good evidence for the formation of a common intermediate, a transition involving ions of the type (213) and (214) must presumably occur. Rearrangement and reclosure could then give (amongst other possibilities) ions of the type (215), (216) and (217).



(215)



(216)



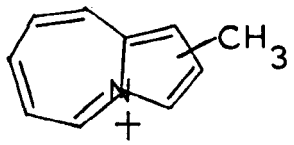
(217)

This would then explain the marked similarity of the spectra of methylindoles and methylindolizines since ions (215) and (216) are postulated for the M-1 peaks of methylindoles.[136] It could well be that structure (218) represents the M-1 ion better than (215), (216) and (217). Powers[136] has stated that there is no evidence bearing on the point of a common intermediate M-1 ion for all methylindoles. He considers it remote due to the extensive molecular rearrangements which would have to be invoked. Since rearrangements need to be invoked to explain (a) loss of HCN from methylindolizines and (b) the similarity of methylindolizine spectra to those of methylindoles, and since all the methylindolizine spectra are essentially similar, a common intermediate may well explain the results.

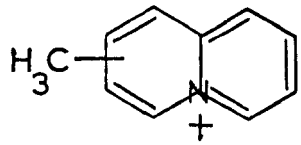
The next transition is m/e 103 to m/e 77 corresponding to the loss of $C_2H_2$. There are metastable peaks in the spectra at m/e 57.5 confirming this transition. A further loss of $C_2H_2$ then occurs. The peaks at m/e 65 are considered to be doubly charged ions of mass 130.

The dimethylindolizines (Figures 21 to 27) again show large M (m/e 145) and M-1 (m/e 144) peaks. For the dimethyl compounds substituted in each ring the M-1 ion can be one of two structures (219) or (220), while in the case of 1,2- and 2,3-dimethylindolizine it must

be of structure (220) (assuming the positive charge is localised at the nitrogen).



(219)



(220)

Loss of HCN from M-1 gives a peak at m/e 117 and so rearrangement must occur.

The peaks at m/e 130 and m/e 115 may indicate successive losses of methyl groups from the parent ion. However, peaks at m/e 115 with a height of about 10% of the base peak have been noted[138] in the spectra of all alkylindoles other than those containing a single methyl substituent. This ion is associated with ions at m/e 116 and m/e 117 having about one third the abundance of the m/e 115 species. The mechanistic origin of this triplet is said to be unclear. The same effect is also found in the alkylindolizines. The transition from m/e 130 to m/e 103 also occurs and is evidenced by metastable peaks at m/e 81.6. This is then followed by loss of $C_2H_2$ and would seem to indicate that at least part of the peak at m/e 130 is due to a ring expanded ion of the type found in monomethylindolizines which arises by loss of 15 ($\cdot CH_3$) from the parent ion or 14 ($:CH_2$) from the M-1 ion.

The large values for the m/e 130 peaks in 1,2- and

2,3-dimethylindolizines may be a reflection of the higher electron densities at positions 1 and 3 in indolizine, leading to a loss of a methyl radical from these positions or it may be due to a vicinal effect.[138]

Loss of acetonitrile does not seem to be particularly favoured from the M-1 ion of 3,5-dimethylindolizine since the peak at m/e 103 (M-42) is approximately the same as in the other dimethylindolizines.

Doubly charged peaks at m/e 65 are again in evidence.

2-Methyl-6-ethylindolizine (Figure 28) has a similar pattern to 2,6-dimethylindolizine once the parent ion has lost 15. Presumably the ion at m/e 144 (M-15) is of structure (219) and arises by β-cleavage.

2-Methyl-6-hydroxymethylindolizine (Figure 30) has a M-17 peak at m/e 144 corresponding to loss of ·OH from the hydroxymethyl group. The pattern then follows as before, loss of HCN occurring. The peak at m/e 132 arises by loss of 29 (·CHO) from the parent ion and that at m/e 130 by loss of 31 ($\cdot CH_2OH$). (Part of the peak at m/e 130 may also be produced by loss of 14 from the m/e 144 ion as mentioned previously). On deuteration (Figure 32) the picture is not immediately clear. Losses of 29, 30 and 31 in the non-deuterated sample become losses of 29, 30, 31, 32 and 33 in the deuterated sample due to the greater number of possibilities of mass losses. Loss of HCN and DCN occur from the ion m/e 146.

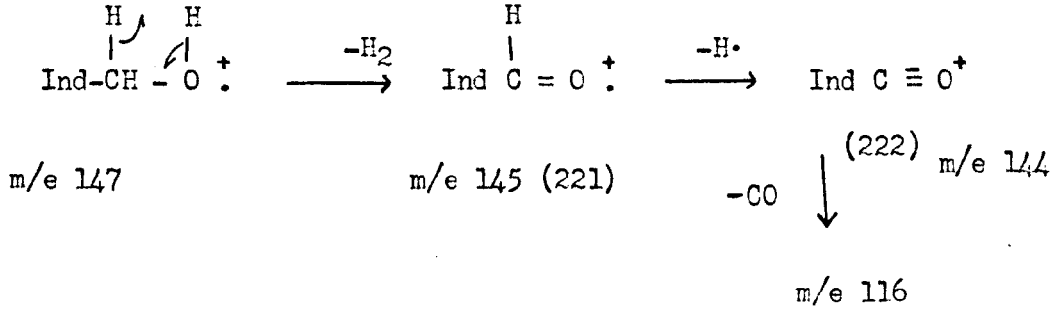
2-Hydroxymethylindolizine and 3-hydroxymethylindolizine are shown in Figures 29 and 33. Loss of 17 from the parent ion gives a peak at m/e 130 which presumably is of structure (137). The usual

pattern then follows.

$$147 \xrightarrow{-\cdot CH} 130 \xrightarrow{-HCN} 103 \xrightarrow{-C_2H_2} 77$$

Losses of 29, 30 and 31 occur from the molecular ion. In the case of the 2-hydroxymethyl compound loss of 32 and 33 also occur when the compound is deuterated (Figure 31). The major peaks in this region are M-29, M-30 and M-31 in both the non-deuterated and the deuterated samples. This may indicate some randomisation of the deuterium in the molecular ion.

The peaks at M-2 and M-3 in 2-hydroxymethylindolizine indicate a type of behaviour found in benzyl alcohol and is explained[138] as loss of a hydrogen molecule to yield an aldehyde (221). Further loss of a hydrogen atom leads to an ion of type (222).




A metastable peak at m/e 93.4 confirms the last transition (m/e 144 to m/e 116).

On deuteration this process seems to be largely suppressed although peaks at m/e 146 and m/e 144 (Figure 31) belonging to the corresponding ions are present to a small extent.

The ethyl esters (Figures 34, 35 and 36) show loss of $C_2H_4$ from the parent ion presumably by a McLafferty rearrangement. Metastable peaks confirm this transition. In the case of the 6 position ester there is then loss of .CH to m/e 158 followed by CO loss; alternatively cleavage of the α bond to give a peak at m/e 130 occurs. The 1 and 8 position esters each show a peak at m/e 131 absent in the 6 position ester. Presumably it arises due to the transfer of ·H from the ester to the peri position with loss of $CO_2C_2H_4$ from the molecular ion. (Metastable ions m/e 84.5 confirm that this occurs). The peak may also arise from decarboxylation of the ionised acid m/e 175).

The peak at m/e 158 can also arise by β cleavage with loss of an ethoxy radical from the parent ion. This is followed by loss of CO to give a peak at m/e 130. (A metastable ion confirms this latter transition).

The methyl esters (Figures 39 and 40) show the expected pattern. β cleavage and loss of $CH_3O\cdot$ gives a peak at m/e 144 which then loses CO to m/e 116.

$$\left[\text{Ind-C(=O)-OCH}_3\right]^{+\cdot} \xrightarrow{-\cdot OCH_3} \left[\text{Ind-C}\equiv\overset{+}{O}\right] \xrightarrow[m^* \ 93.4]{-CO} \left[\text{Ind}\right]^+$$

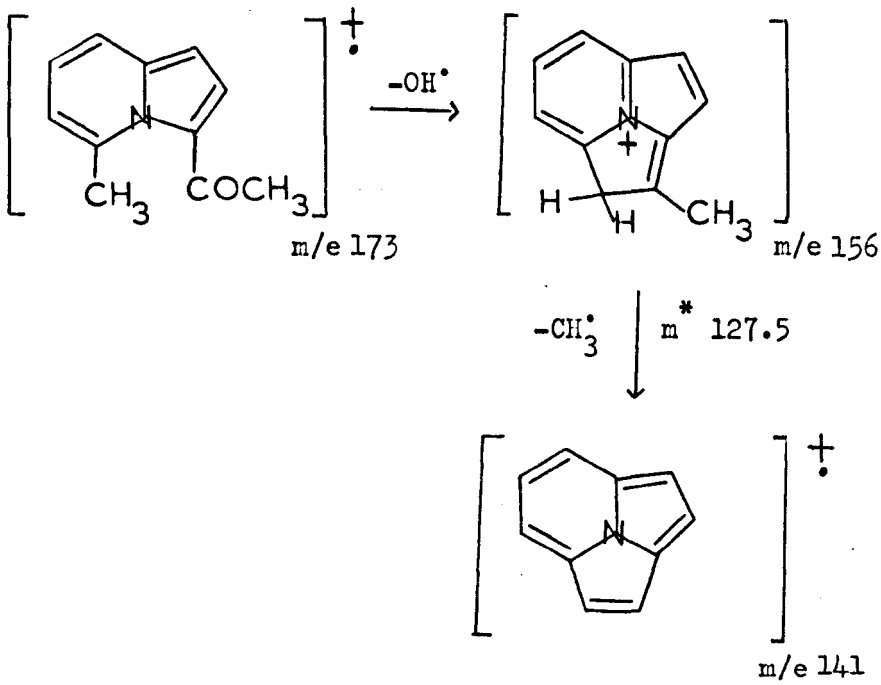
The peak at 117 must arise from loss of $CH_2CO_2$ from the parent ion; in the 2-methylester spectrum a metastable peak at m/e 78.3 verifies this process.

3-Acetylindolizine (Figure 37) shows loss of a methyl radical followed by elimination of CO.

$$159 \xrightarrow[m^{*}\ 130.4]{-\cdot CH_3} 144 \xrightarrow[m^{*}\ 93.4]{-CO} 116$$

The breakdown then follows the usual course.

3-Acetyl-5-methylindolizine (Figure 38) shows loss of a methyl radical followed by loss of CO in a similar fashion to 3-acetylindolizine. There is also a peak at m/e 156 corresponding to a M-17 ion. This is followed by loss of 15 to give a peak at m/e 141 which could be interpreted as a cyclisation to the [3,2,2]cyclazine as shown.



The amides (Figure 41 and 42) show loss of $\cdot NH_2$ followed by loss of CO. The usual pattern then follows of loss of HCN followed by loss of $C_2H_2$. Another pathway is loss of $H_2O$ from the parent ion, from then onwards the spectra are similar to those of nitriles. This is clearly shown in the case of 2-methyl-6-carbamoyl indolizine (Figure 42) where the loss of $H_2O$ gives a peak at m/e 156 whose subsequent breakdown can be compared with the nitrile (Figure 44).

The nitriles (Figure 43 and 44) show two successive losses of HCN from the M-1 ion.

Finally Figures 45 and 46 show two carboxylic acids. Indolizine-2-carboxylic acid (Figure 45) shows loss of CH$^{\cdot}$ followed by loss of CO. The peak at m/e 117 must indicate decarboxylation of the parent ion. The lower mass end of the spectrum must be treated with caution since it appears that the sample was contaminated (2-picoline).

2-Methylindolizine-8-carboxylic acid (Figure 46) has an unusual feature. Loss of 14 from the parent ion occurs to give an ion m/e 161. The breakdown after this point is then similar to the 2-carboxylic acid (Figure 45).

$$175 \xrightarrow{-:CH_2} 161 \xrightarrow{-OH^{\cdot}} 144 \xrightarrow[m^{*}\ 93.4]{-CO} 116 \xrightarrow[m^{*}\ 68.2]{-HCN} 89$$

$$117 \xrightarrow[m^{*}\ 69.2]{-HCN} 90$$

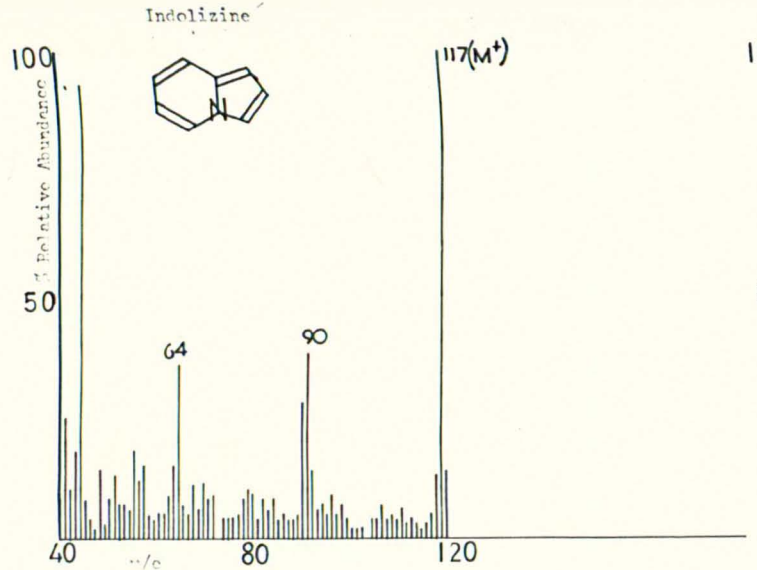



Figure 13

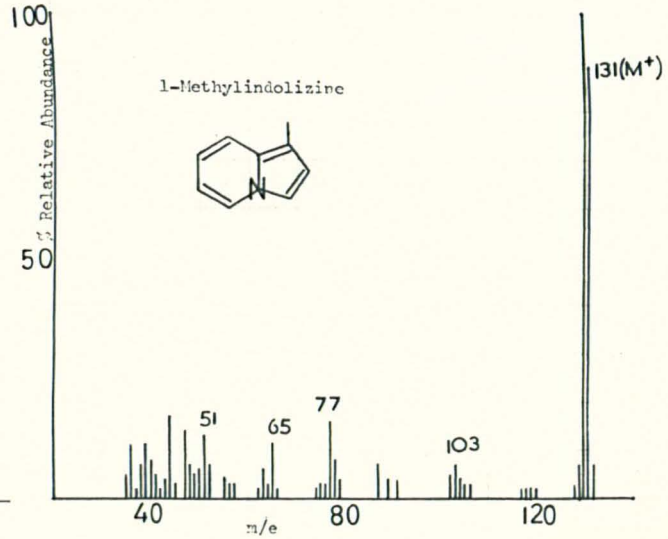



Figure 14

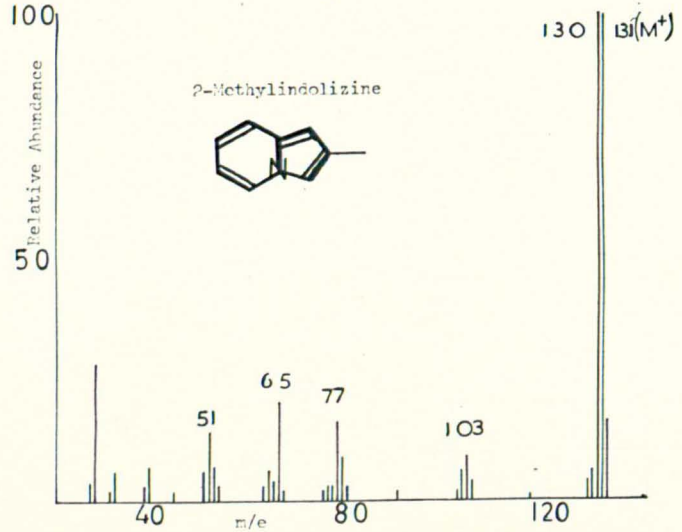



Figure 15

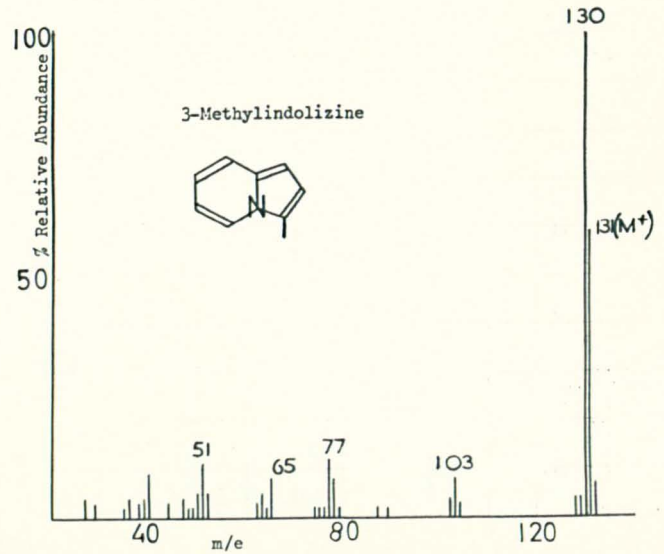



Figure 16

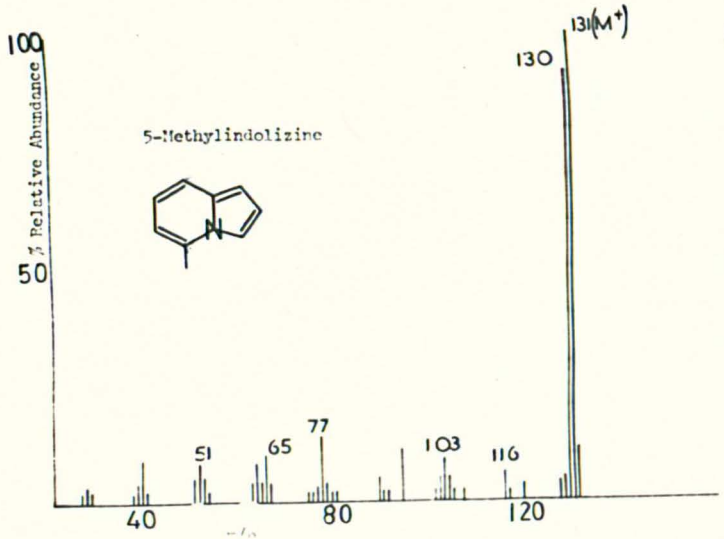



Figure 17

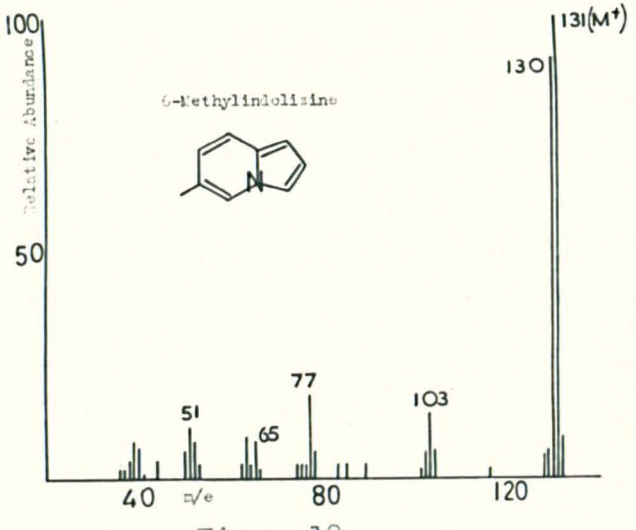



Figure 18

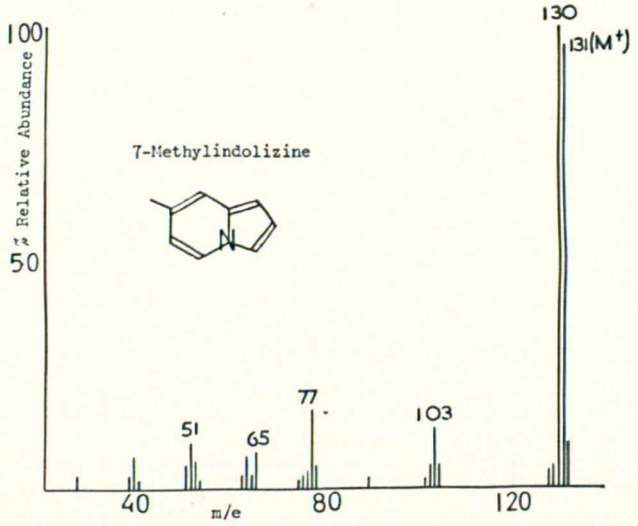



Figure 19

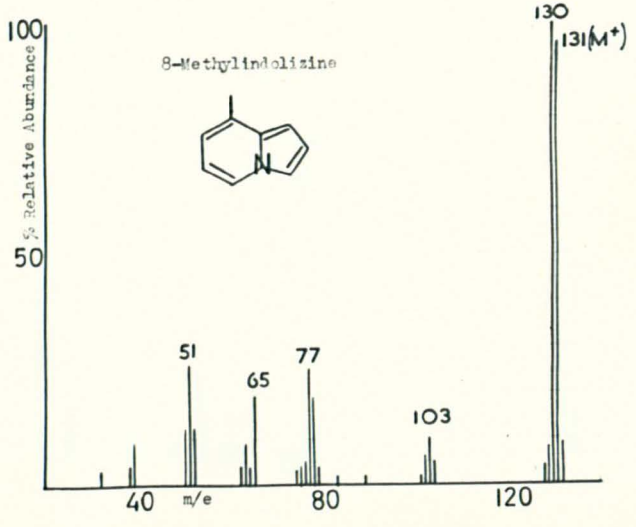



Figure 20

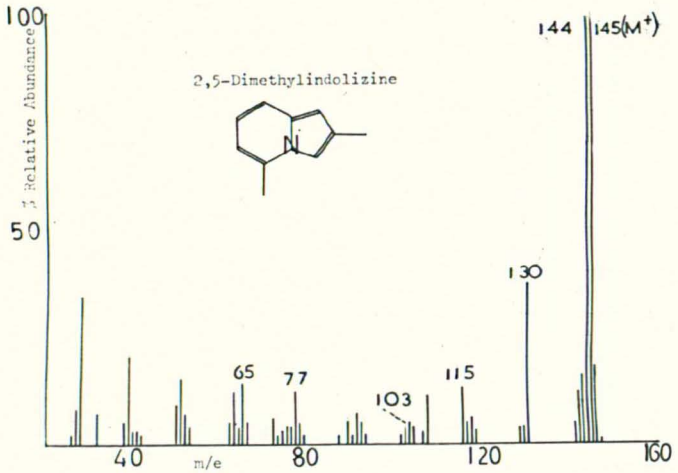



Figure 21

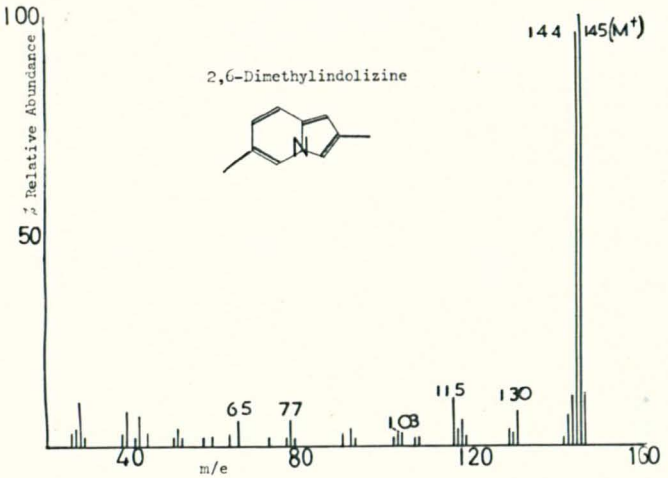



Figure 22

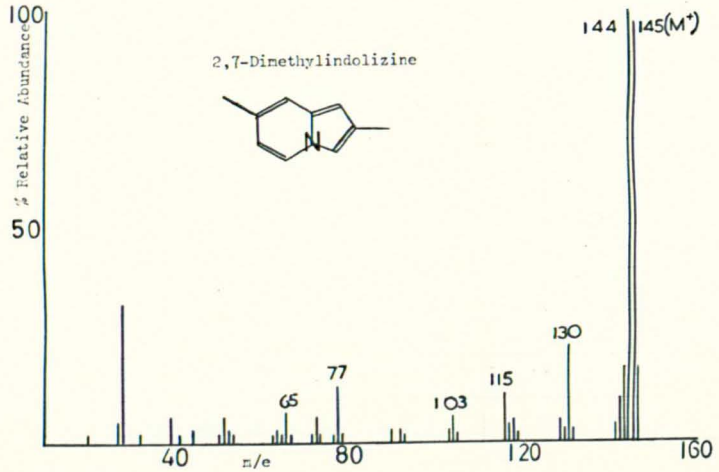



Figure 23

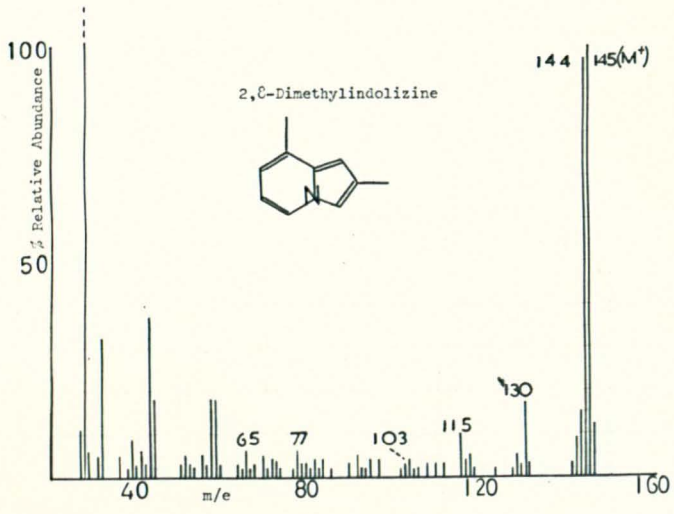



Figure 24

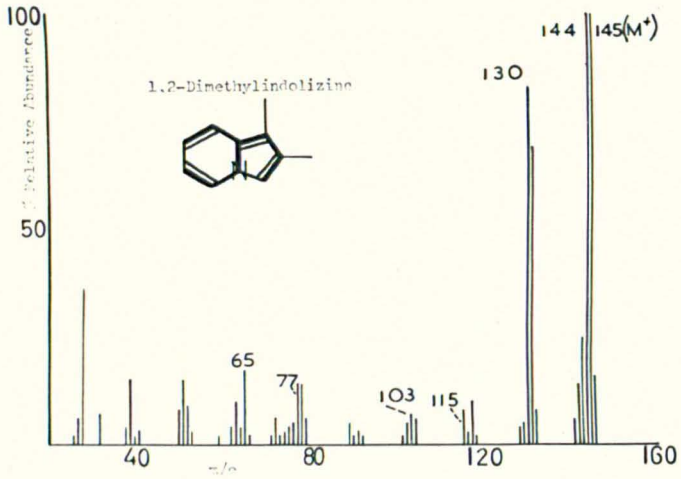



Figure 25

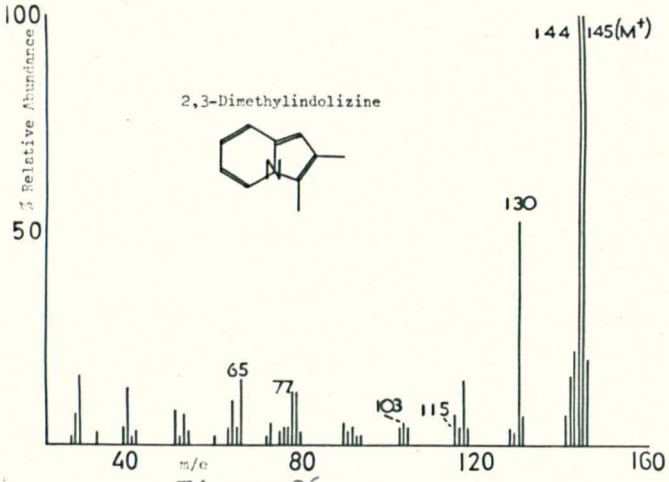



Figure 26

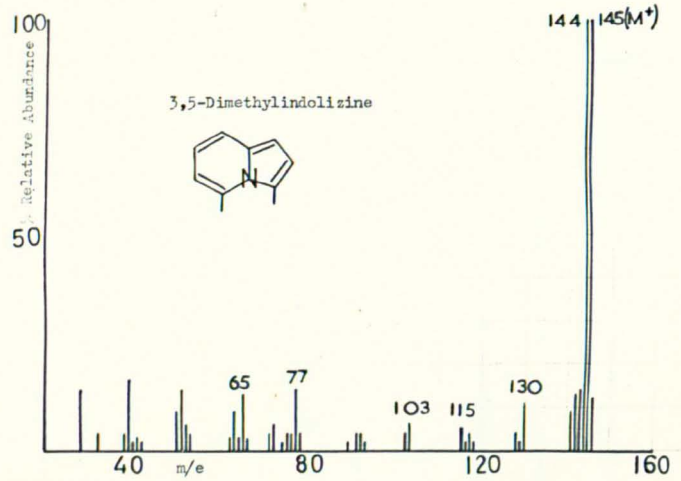



Figure 27

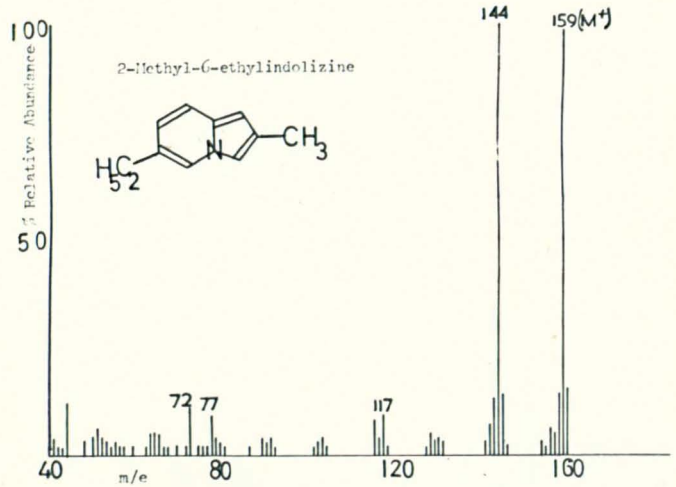



Figure 28

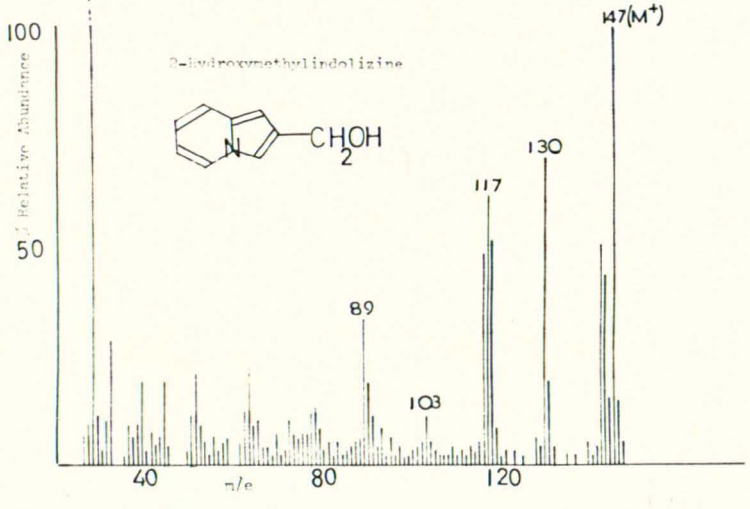



Figure 29

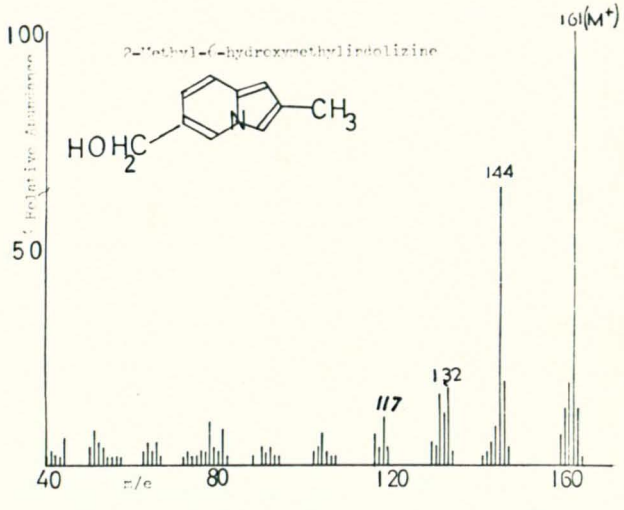



Figure 30

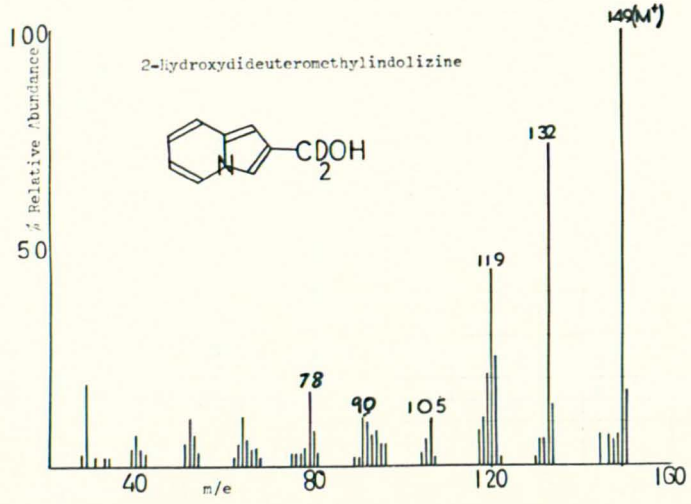



Figure 31

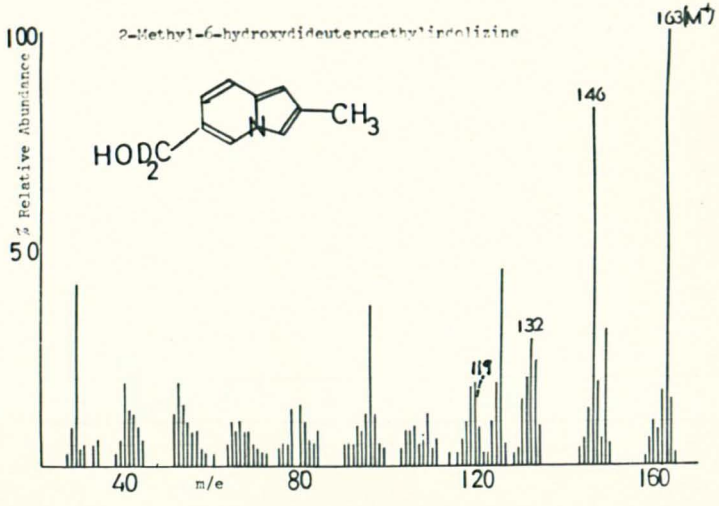



Figure 32

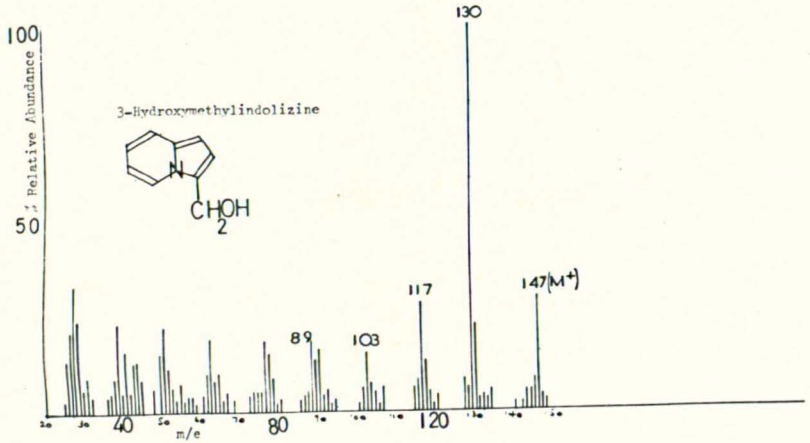



Figure 33

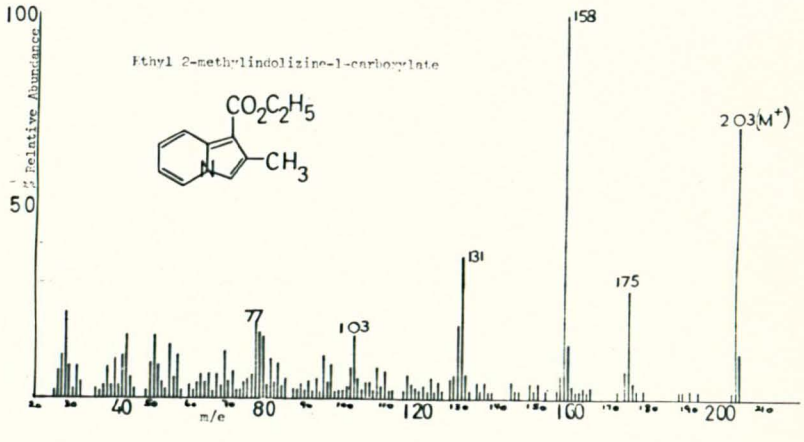



Figure 34

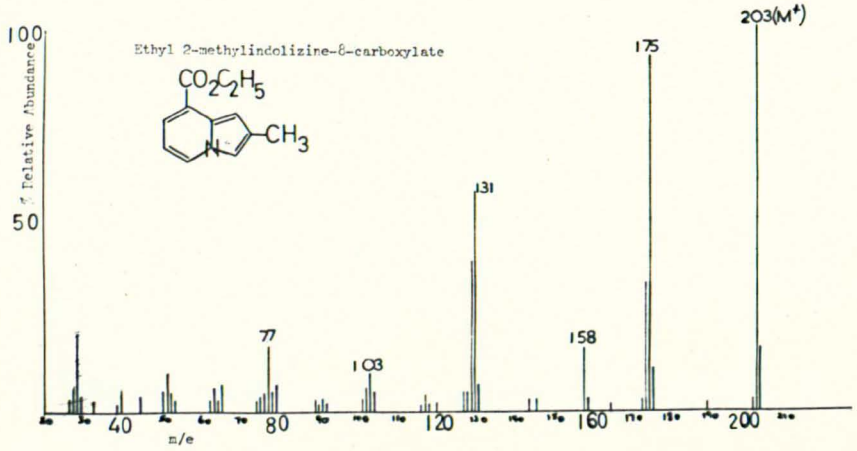



Figure 35

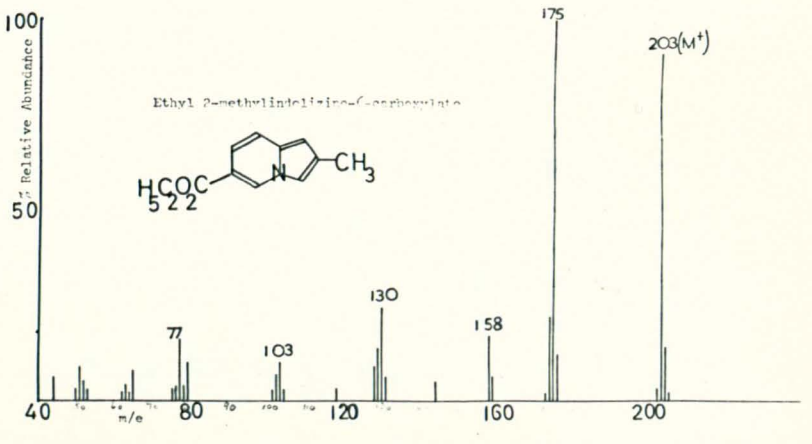



Figure 36

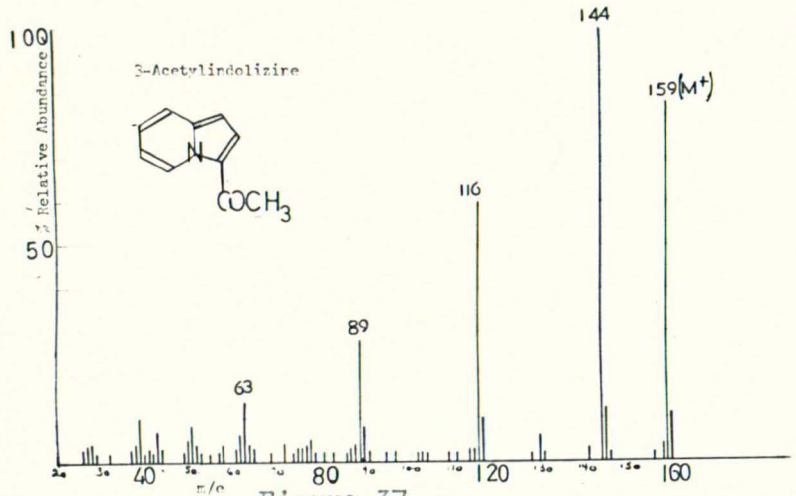



Figure 37

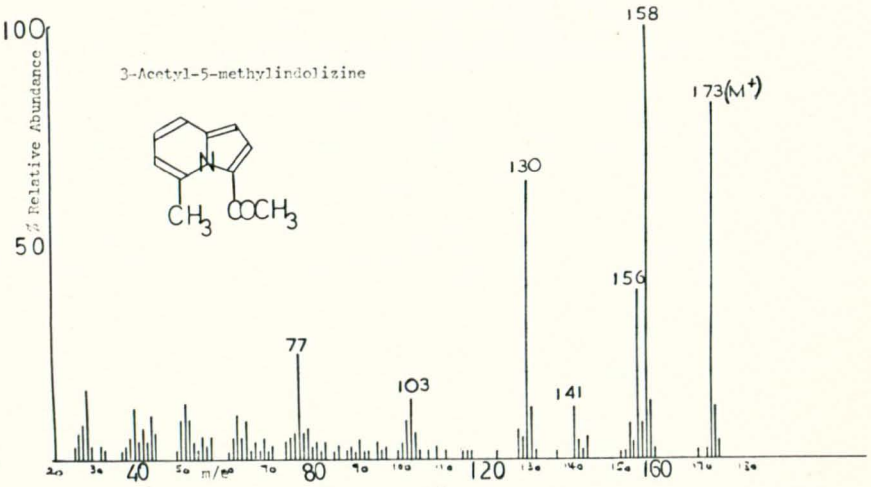
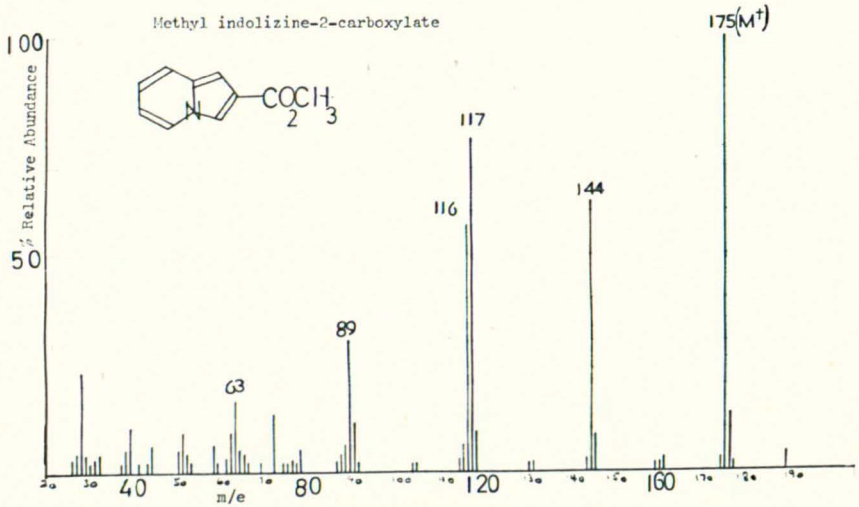



Figure 38

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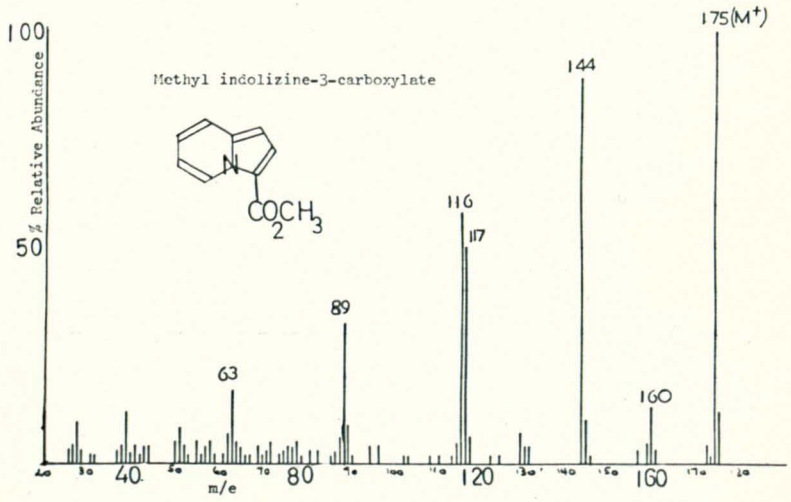


Figure 40

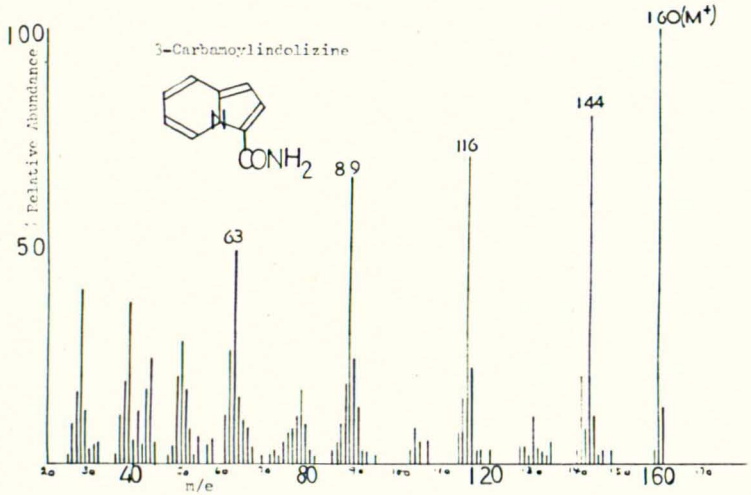


Figure 41

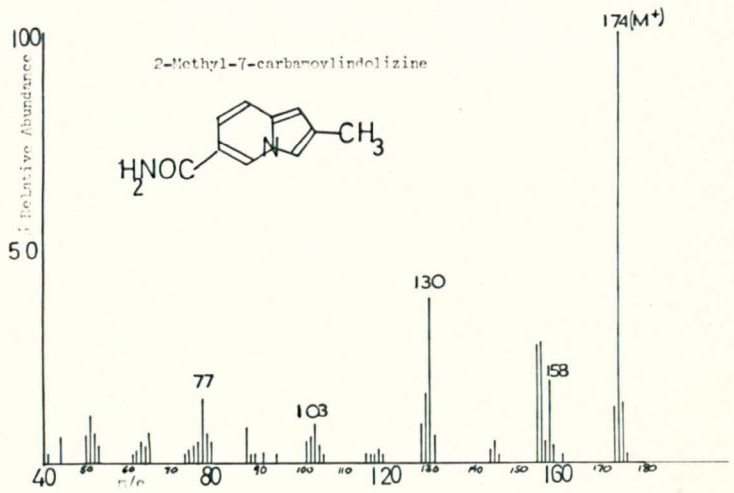


Figure 42

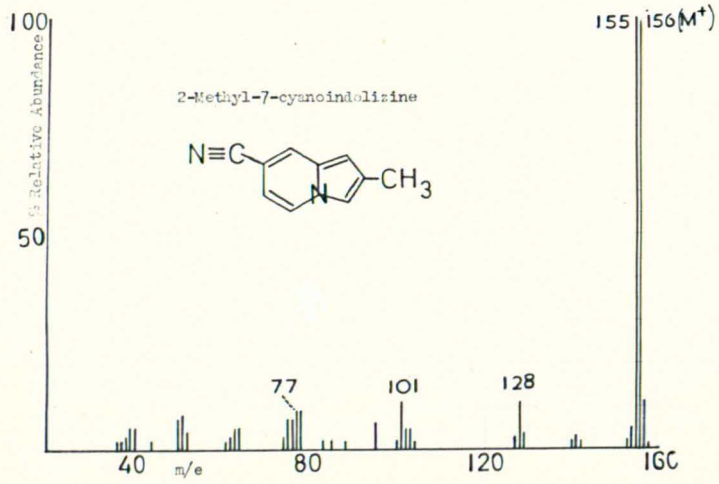


Figure 43

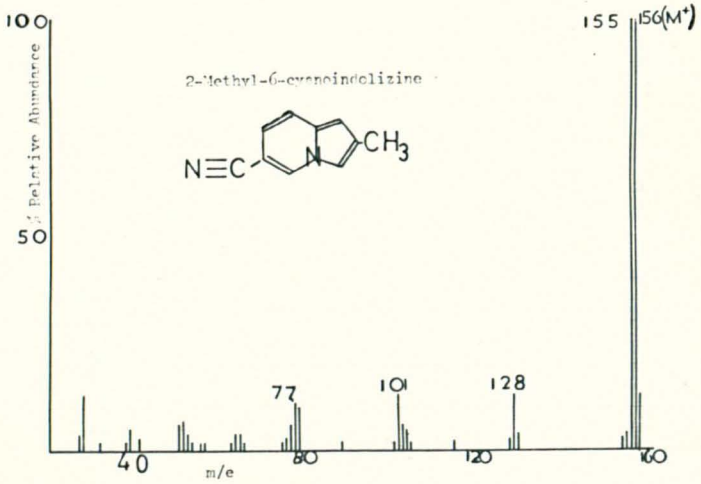


Figure 44

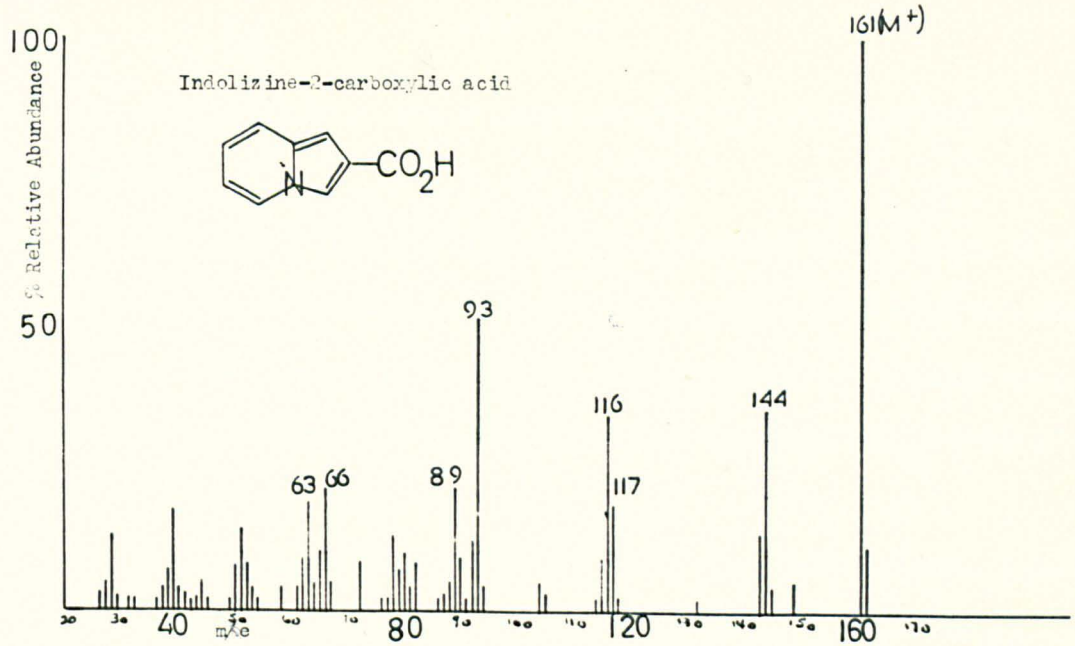


Figure 45

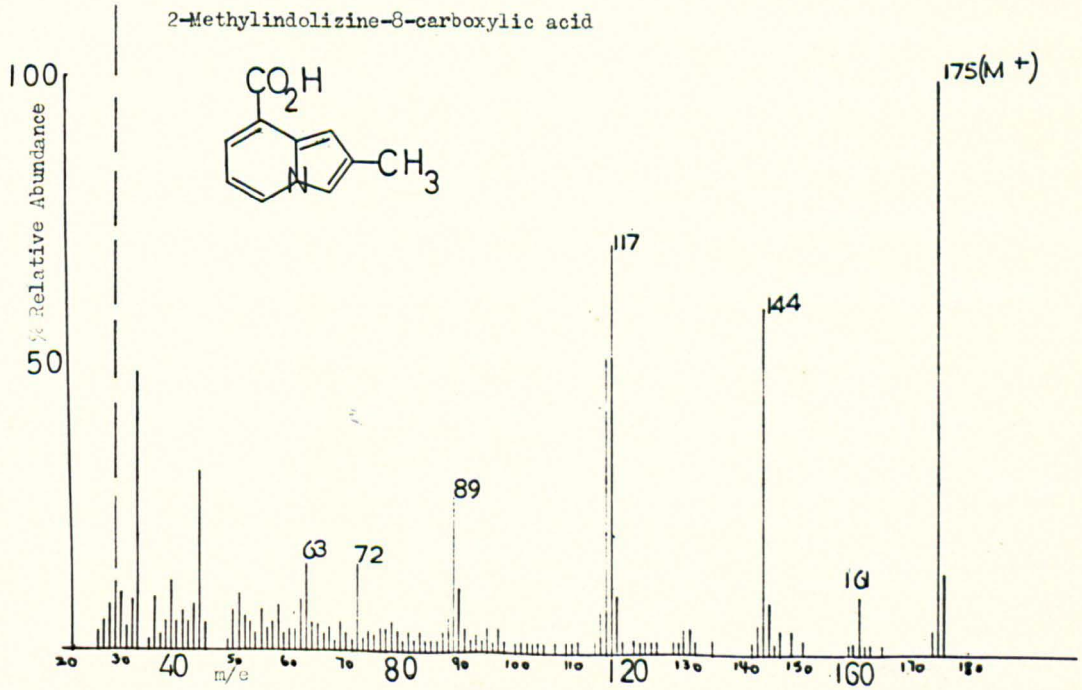


Figure 46

## EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected.

Infrared absorption spectra were measured with Perkin Elmer 257 and 221 spectrophotometers. The spectra of solids were determined as Nujol mulls, indicated as (Nujol). The spectra of liquids were determined as films (Film). Solutions denoted e.g. ($CCl_4$) were also used.

Nuclear magnetic resonance spectra were recorded on a Perkin Elmer R10 60 megacycle instrument and are quoted in units of "tau" ($\tau$) using a tetramethyl silane (T.M.S.) standard. When spectra were recorded in deuterium oxide the T.M.S. standard was recorded externally in a solution of carbon tetrachloride. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet, p = proton.

Ultraviolet spectra were recorded on a Unicam S.P. 800 instrument.

Microanalyses were carried out by Drs. Weiler and Strauss of Oxford and by Mr. J. Boulton of Keele University.

Mass spectra were determined by Drs. H. M. Fales and J. D. Baty, National Instutute of Health, Washington, U.S.A. and I.C.I. Pharmaceutical Division, Alderley Park, Cheshire.

Ethyl 2-methylindolizine-1-carboxylate (138).

Prepared from ethyl 2-pyridylacetate by the method of Bragg and Wibberley.[36]

$\nu_{max}$(Nujol) cm.$^{-1}$ 1700 (ester CO).

The nuclear magnetic resonance spectrum is shown in Figure 1.

Attempted synthesis of 1-hydroxymethyl-2-methylindolizine (142).

(i) From ethyl 2-methylindolizine-1-carboxylate (138).

(a) A solution of ethyl 2-methylindolizine-1-carboxylate (138) (1.02 g.) in tetrahydrofuran (15 ml.) was added to a stirred suspension of lithium aluminium hydride (1.0 g.) in tetrahydrofuran (20 ml.). The resulting solution was boiled under reflux for 1 hr. Water (2 ml.) was added dropwise with stirring and the solution filtered, dried over sodium sulphate and the tetrahydrofuran removed under reduced pressure. The pale yellow residue was recrystallised from light petroleum (b.p. 40-60°) and sublimed under vacuum. The nuclear magnetic resonance spectrum of the product (Figure 2) was identical to that of an authentic sample of 1,2-dimethylindolizine (139). Yield 0.45 g. (62%) m.p. 61° (lit.[18] 63°).

(b) A solution of ethyl 2-methylindolizine-1-carboxylate (138) (1.70 g.) in ether (150 ml.) was added dropwise to a suspension of lithium aluminium hydride (0.32 g.) in ether (25 ml.) with constant stirring. The solution was stirred for ½ hr. at room temperature and then boiled under reflux for 1 hr. The mixture was cooled in an ice bath and excess lithium aluminium hydride was decomposed using ethyl acetate.

Cold water (40 ml.) was cautiously added followed by 5N hydrochloric acid (20 ml.). The pH of the solution was adjusted to between 5 - 6 with dilute ammonia solution. The ether layer was removed and the aqueous layer was further extracted with ether. The combined ether layers were dried over sodium sulphate and the solvent removed on a steam bath. The tar-like residue could not be solidified; its nuclear magnetic resonance spectrum indicated it to be a mixture of starting material and 1,2-dimethylindolizine (139).

(c) Potassium borohydride (1.0 g.) was added to a solution of ethyl 2-methylindolizine-1-carboxylate (138) (1.0 g.) in absolute ethanol (15 ml.). The solution was boiled under reflux overnight. A sample was removed and treated with water. The aqueous solution was extracted several times with benzene and the benzene extracts dried over sodium sulphate. Vapour phase chromatographic analysis indicated starting material only.

(d) A solution of sodium borohydride (1.08 g.) and ethyl 2-methylindolizine-1-carboxylate (138) (1.14 g.) in methanol (30 ml.) was boiled under reflux for 6 hr. Water (50 ml.) was added to the solution which was then extracted with ether. The ether extracts were dried over sodium sulphate and the ether removed on a steam bath. Only starting material was recovered.

(ii) From 2-pyridylethanol (140).

(a) 2-Pyridylethanol (140) (6.2 g.) and bromoacetone (6.8 g.) were dissolved in sulpholane (30 ml.) and kept at 35° for 3 days. The resulting solution was added dropwise to a large excess of acetone with trituration. The acetone was poured off from the dense oil which deposited. The oil was dissolved in water and the aqueous solution extracted with ether and chloroform. The water was removed from the aqueous layer under reduced pressure and a solid remained. On reduction of the acetone to a small volume a further amount of solid crystallised out. The combined solids were recrystallised from acetone to yield 1-acetonyl-2-hydroxyethylpyridinium bromide (141) 11.9 g (92%) m.p. 144°.

Found: C, 46.1; H, 5.4 ; N, 5.4%

$C_{10}H_{14}BrNO_2$ requires: C, 46.2; H, 5.45; N, 5.3%

$\nu_{max}$(Nujol) 1725 cm.$^{-1}$ (acetonyl CO).

$\tau(D_2O)$ 1.2 - 2.2, 4p; 4.1s, 2p (exchanges); 5.95 m, 2p; 6.75 m, 2p; 7.5 s; 8.4 s.

$\tau$(T.F.A.) after standing overnight. 0.9 - 1.4 m, 2p; 1.5 - 1.9 m 2p; 3.8 s, 2p; 5.0 t J = 6 c/s, 2p; 6.3 t J = 6 c/s 2p; 7.3 s, 3p.

1-Acetonyl-2-hydroxyethylpyridinium bromide (141) (4.0 g.) was added to a near saturated solution of sodium bicarbonate (200 ml.). The resulting solution was heated on a steam bath for 2 hr. A yellow solid precipitated after 15 - 20 min. The solid was filtered off and dried in desiccator. 2.0 g. were collected. It could not be characterised and

spectra could not be obtained. When heated it turned black above 300° but did not melt. Ether extraction of the aqueous solution did not yield any material.

1-Acetonyl-2-hydroxyethylpyridinium bromide (141) (0.3 g.) was dissolved in absolute ethanol (20 ml.). Diethylamine (1 ml.) was added and the solution was boiled under reflux for ½ hr. A yellow solid came out of solution. The product was similar to that obtained previously and could not be characterised.

(b) 2-Pyridylethanol (140) (10.0 g.) was dissolved in sodium hydroxide solution (100 ml., 10%). A solution of p-toluenesulphonyl chloride (20.0 g.) in acetone (150 ml.) was slowly added with shaking. The solution was shaken for 20 min. and then poured into water (500 ml.). The resulting solution was extracted several times with ether. The ether extracts were dried over sodium sulphate, filtered, and the ether evaporated on a steam bath. The remainder was a brown liquid which on standing solidified to a yellow solid. It was recrystallised from light petroleum (b.p. 60-80°) to give the tosylate of 2-pyridylethanol (144) 14.3 g. (60%). White solid m.p. 44°.

Found: C, 57.1; H, 5.3; N, 4.8%

$C_{14}H_{15}NO_3SH_2O$ requires: C, 56.9; H, 5.7; N, 4.7%

$\nu_{max}$(Nujol) cm.$^{-1}$ 1590, 1350, 1170, 910, 765.

$\tau(CCl_4)$ 1.5 m, 1p; 2.0 - 3.0 m, 7p; 5.55 t J = 7 c/s, 2p; 6.9 t J = 7 c/s, 2p; 7.6 s, 3p.

When the tosylate (144) (2.0 g.) was recrystallised from a mixture of light petroleum (b.p. 60-80°) and ethanol a white solid (145) resulted which was recrystallised from acetone, m.p. 134°.

Found: C, 50.3; H, 5.1; N, 2.9%

$\nu_{max}$(Nujol) cm.$^{-1}$ 1640, 1590, 1360, 1230, 1170, 990, 780.

$\tau$($CDCl_3$) 1.0 m, 1p; 1.5 m, 1p; 1.9 - 2.8 m, 10p; 5.5 t J = 6 c/s, 2p; 6.4 t J = 6 c/s, 2p (or 3p); 7.6 d, 6p.

Shaking this latter compound (1.0 g.) with aqueous sodium hydroxide (50 ml., 10%) gave an insoluble liquid which solidified. The solution was extracted with ether and the ether extracts dried over sodium sulphate. The ether was removed to yield a white solid which had identical infrared and nuclear magnetic resonance spectra to those of the original tosylate (144).

Treatment of the tosylate of 2 pyridylethanol (144) in ethereal solution (1 g., 50 cc) with an ethereal solution of p-toluenesulphonic acid ( 1 g., 50 cc) yielded a white precipitate (145). The solid was identical to that obtained when the tosylate (144) was recrystallised from a petroleum/ethanol solution.

Attempted quaternisation of the tosylate (144) using bromoacetone.

(a) The tosylate (144) (1.14 g.) was dissolved in sulpholane (10 ml.) and bromoacetone (0.80 g.) was added. The solution was kept at 40° for 3 days. The solution was added dropwise to ethyl acetate (100 ml.). A brown gum precipitated which could not be characterised.

(b) The tosylate (144) (1.14 g.) was boiled under reflux in acetone (20 ml.) with bromoacetone (1.0 g.) for 3 hr. The acetone was removed under reduced pressure on a steam bath to yield a gum whose nuclear magnetic resonance spectrum was too complex to analyse.

Attempted preparation of a tosylate of 1-acetonyl-2-hydroxyethylpyridinium bromide.

1-Acetonyl-2-hydroxyethylpyridinium bromide (141) (1.0 g.) was dissolved in sodium hydroxide solution (100 ml., 10%). A solution of p-toluenesulphonyl chloride (2.0 g.) in acetone (15 ml.) was slowly added with shaking. The shaking was continued for 20 min. The solution was then poured into water (50 ml.). The resulting solution was extracted with ether and the ether extracts dried over sodium sulphate, filtered, and the ether removed on a steam bath. The product was the tosylate of 2-pyridylethanol (144).

1(β-Hydroxyethyl)-2-methylindolizine (147).

3-(2'-pyridyl)-1-propanol (44) (7.0 g.) and bromoacetone (7.0 g.) were boiled under reflux for 1 hr. in acetone (20 ml.). The quaternary compound (146) came out of solution as a gum. The solution was cooled and the acetone decanted off. Any further solvent was removed under reduced pressure.

Yield 12.1 g. of crude 1-acetonyl-2-(3-propan-1-ol) pyridinium bromide (146).

$\nu_{max}$(Film) 1730 cm.$^{-1}$ (acetonyl CO)

Chloroplatinate m.p. 168°.

The gum (146) was dissolved in aqueous sodium bicarbonate solution (50 ml., 10%) and heated on a steam bath for 40 min. The resulting solution was cooled and a solid formed which was extracted with ether. The ether extracts were dried over sodium sulphate, filtered, and the ether removed on a steam bath to yield an oil (6.63 g.) which was extracted with light petroleum (b.p. 60-80°) to yield a white solid 1(β-hydroxyethyl)-2-methylindolizine (147) 4.8 g. (54%) m.p. 53-55°.

Found: C, 75.7; H, 7.3; N, 8.0%

$C_{11}H_{13}NO$ requires: C, 75.4; H, 7.5; N, 8.0%

$\nu_{max}$(Nujol) cm.$^{-1}$ 3330 broad (OH), 1630, 1300, 1040, 735.

$\tau(CDCl_3)$ 2.3 m, 1p; 2.75 m, 1p; 2,95 s, 1p; 3.55 m, 2p; 6.25 t J = 6 c/s, 2p; 7.05 t, J = 5c/s 2p; 7.75 s, 3p; 8.2 s, 1p,

on shaking with $D_2O$ the singlets at 2.95 and 8.2 exchange.

Attempted preparation of a tosylate of 1(β-hydroxyethyl)-2-methylindolizine.

The indolizine (147) (1.0 g.) was dissolved in aqueous sodium hydroxide (10 ml., 10%) together with enough acetone to give a solution. p-Toluenesulphonyl chloride (2.0 g.) in acetone (150 ml.) was added with shaking and the shaking continued for 25 min. The solution was extracted with ether to give an orange solution. After drying over sodium sulphate the ether was evaporated to leave a brown oil. Nuclear magnetic resonance showed that none of the expected product was present.

1-Methylindolizine-2-carboxylic acid.

Prepared by the method of Borrows and Holland[21] using 2-ethylpyridine.

Green rods, m.p. 231° (decomp.).

Found: C, 68.7; H, 5.1; N, 7.9%

$C_{10}H_9NO_2$ requires: C, 68.6; H, 5.2; N, 8.0%

$\nu_{max}$(Nujol) cm.$^{-1}$ 1680 (acid CO)

$\tau$(T.F.A.) 0.8 m, 1p; 1.3 - 2.0 m, 3p; 4.0 s, 2p; 7.15 s, 3p.

The acid was decarboxylated by heating with calcium oxide according to the method of Diels and Alder.[29,30]

Ethyl pyruvate.

Ethyl pyruvate was prepared from pyruvic acid by the method of Goldberg and Kelley.[134]

$\nu_{max}$(Film) cm.$^{-1}$ 1730 (ester CO).

Ethyl bromopyruvate.

Prepared from ethyl pyruvate.[134]

$\nu_{max}$(Film) cm.$^{-1}$ 1735 (ester CO).

Indolizine-2-carboxylic acid (20).

Prepared by the method of Borrows and Holland.[21]

$\nu_{max}$(Nujol) cm.$^{-1}$ 1675 (acid CO).

Methyl indolizine-2-carboxylate (148).

The method of Borrows and Holland[21] was employed. Indolizine-2-carboxylic acid (20) (6.0 g.) was dissolved in dry dioxan (240 ml.) and then mixed with an ethereal solution of diazomethane until excess diazomethane was present. An aliquot of the solution was tested for excess diazomethane by adding acetic acid when nitrogen was evolved. The solution was stood overnight and then the solvent removed under reduced pressure. The buff residue crystallised from aqueous alcohol 5.4 g. (83%).

m.p. 101° (lit.[21] 97-99°).

$\nu_{max}$(Nujol) cm.$^{-1}$ 1720 (ester CO).

$\tau$(T.F.A.) 0.85 m, 1p; 1.1 - 2.1, 4p; 4.1 s, 2p; 5.87 s, 3p.

2—Hydroxymethylindolizine (149).

A solution of methyl indolizine-2-carboxylate (148) (5.0 g.) in dry ether (400 ml.) was added dropwise with constant stirring to a suspension of lithium aluminium hydride (1.1 g.) in dry ether (75 ml.) After stirring for ½ hr. the solution was boiled under reflux for ¼ hr. Ethyl acetate was added to decompose any excess lithium aluminium hydride. Water (100 ml.) was added, followed by hydrochloric acid (5N, 50 ml.). The pH was adjusted to 5 - 6 using ammonium hydroxide and the ether layer was separated. The aqueous solution was extracted several times with ether. The combined ether extracts were dried over sodium sulphate and the ether evaporated. The buff residue was crystallised from light petroleum (b.p. 40-60°) to yield white plates of 2-hydroxymethylindolizine

(149) 3.3 g. (79%) m.p. 105°.

Found: C, 73.7; H, 6.2; N, 9.3%

$C_9H_9NO$ requires: C, 73.5; H, 6.2; N, 9.5%

$\nu_{max}$(Nujol) cm.$^{-1}$ 3310 (OH)

($CCl_4$) cm.$^{-1}$ 3590 (OH)

$\tau$($CDCl_3$) 2.15 d J = 6 c/s, 1p; 2.7 m, 2p; 3.2 - 3.7 m, 3p; 5.22 s, 2p; 8.15 s, 1p.

On shaking with deuterium oxide the singlet at 8.15 $\tau$ exchanges as does part of the multiplet at 2.7 $\tau$.

2-Hydroxydideuteromethylindolizine (150).

Methyl indolizine-2-carboxylate (148) (0.7 g.) was dissolved in dry ether (85 ml.) and added to a suspension of lithium aluminium deuteride (0.3 g.) in ether (15 ml.). The resulting solution was stirred for 1 hr. and then boiled under reflux for 40 min. After cooling, water (0.6 ml.) was added dropwise with constant stirring and the ether solution was filtered. The residue was extracted several times with boiling ether and the collected extracts were dried over sodium sulphate. After removal of the ether, 0.5 g. of compound remained. Nuclear magnetic resonance showed that the singlet at 5.22 $\tau$ was no longer present, indicating that the methylene group was deuterated.

2-Carbamoylindolizine (151).

(a) Indolizine-2-carboxylic acid (20) (1.0 g.) was heated to melting with urea (1.0 g.). The molten mixture was held at 160° for ½ hr. After cooling, the residue was extracted with benzene; after the benzene had been removed the infrared spectrum of the remainder indicated that it was unchanged acid (20). The residue from benzene extraction was dissolved in ethanol and re-precipitated by the addition of water. After drying, this solid also was found to contain none of the desired amide.

(b) The acid (20) (1.0 g.) was treated with ammonia solution (0.88) and evaporated to dryness on a steam bath. The residue was then heated to 200° and maintained at this temperature for ½ hr. Infrared analysis of the residue indicated that it was unchanged acid.

(c) The acid (20) (0.8 g.) was dissolved in carbon tetrachloride (20 ml.) and thionyl chloride (0.6 g.) was added. The solution was boiled under reflux for 2½ hr. The solvent was then removed under reduced pressure and ammonia solution (0.88) (20 ml.) was added to the solid. The solution was evaporated to dryness. The infrared spectrum of the product did not compare with that of an authentic sample of the amide as prepared in (e).

(d) Shaking the ester (148) (1.0 g.) with concentrated ammonia solution for 2 hr. and then standing overnight did not yield the amide.

(e) The ester (148) (15.0 g.) was dissolved in absolute methanol (500 ml.). The solution was saturated with ammonia at $-5^{\circ}$ and then heated in an autoclave with constant stirring at $155^{\circ}$ for 65 hr. The pressure generated was 22 atmospheres. The methanol and any excess ammonia were removed under reduced pressure on a steam bath and the remainder was crystallised from water.

Yield 6.0 g. 44% of 2-carbamoylindolizine, a brown solid m.p. $133^{\circ}$ which then solidified and remelted at $158^{\circ}$.

Found: C, 67.1; H, 4.8; N, 17.2%

$C_9H_8N_2O$ requires: C, 67.5; H, 5.0; N, 17.5%

$\nu_{max}$(Nujol) cm.$^{-1}$ 3340, 3170 (NH) 1665 (amide CO)

($CHCl_3$) cm.$^{-1}$ 3660, 3520, 3415, 1665.

$\tau$ (T.F.A.) 0.8 d (broadened) J = 6 c/s 1p; 1.1 - 2.6, 6p; 4.0 s, 2p.

2-Aminomethylindolizine (152).

The amide (151) (0.5 g.) was dissolved in dry tetrahydrofuran (25 ml.) and added to a suspension of lithium aluminium hydride (0.3 g.) in tetrahydrofuran (20 ml.). The solution was stirred for 30 min. at room temperature and then boiled under reflux for 70 min. Water (0.6 g.) was added dropwise with constant stirring and the solution was filtered. The solid residue was extracted several times with boiling solvent. All the extracts were collected and dried over sodium sulphate, filtered and the solution evaporated to dryness under reduced pressure.

0.28 g. of a buff solid was collected, this was crystallised from light petroleum (b.p. 60-80°) m.p. 77.5°. It was not stable and inconsistent analysis figures were obtained.

$\nu_{max}$($CHCl_3$) $cm.^{-1}$ 3470, 3380 (amine NH)

$\lambda_{max}$ (95% EtOH) mμ 238, 277, 285, 296, 340.

The nuclear magnetic resonance spectrum is shown in Figure 4.

2-Methylindolizine

2-Picoline (9.4 g.) and bromoacetone (13.7 g.) were boiled under reflux in absolute ethanol (50 ml.) for 4 hr. The solvent was removed under reduced pressure to yield a crude product (20.1 g.) which was recrystallised from acetone to yield 1-acetonyl-2-methylpyridinium bromide 16.1 g. (70%) m.p. 194-6° (lit.[18] 196°).

Found: C, 46.9; H, 4.95; H, 6.0%

Calculated for $C_9H_{12}BrNO$: C, 47.0; H, 5.2; N, 6.1%

$\nu_{max}$(Nujol) 1725 (acetonyl CO)

$\tau$(T.F.A.) 0.9 - 2.0, 4p; 3.9 s, 2p; 7.1s, 3p; 7.3 s, 3p.

To a solution of the quaternary compound (7.7 g.) in water (300 ml.) was added sodium bicarbonate (20.0 g.). The solution was heated on a steam-bath for 4 hr. and the product was steam distilled from the flask.

The white solid was recrystallised from light petroleum (b.p. 40-60°) to yield 3.3 g. (55%) of 2-methylindolizine.

$\tau(CCl_4)$ 2.15 m, 1p; 2.65 m, 1p; 2.9 s, 1p; 3.45 m, 2p; 3.72 s, 1p.

Attempted preparation of 2-chloromethylindolizine.

A solution of 2-hydroxymethylindolizine (149) (0.2 g.) in ether (15 ml.) was treated with a solution of an equimolar amount of thionyl chloride in ether (10 ml.). An orange solid formed immediately and on stirring it darkened in colour. On attempting to filter off the solid it went black immediately and decayed.

Palladium on charcoal catalyst.

The catalyst was prepared by the hydrogen reduction procedure as described in Organic Syntheses Collected Volume III, Horning P. 687, section D.

Indolizine

A modified version of the synthesis due to Boekelheide and Windgassen[41] was employed. The indolizine collected in a vertical air condenser attached to the reaction flask and was periodically removed.

3-(2-Pyridyl)-1-propanol (44) (70.0 g.) gave indolizine 19.5 g. (33%) m.p. 73° (lit.[41] 73-4°).

During one preparation freshly prepared catalyst was added during the course of the reaction. In this case it was found that the indolizine was contaminated with 5,6,7,8-tetrahydroindolizine which was removed by successive recrystallisations from methanol.

Indolizine-3-carbonyl chloride (153).

A solution of indolizine (12) (8.0 g.) in dry toluene was added dropwise to a stirred solution of phosgene in toluene (50 ml., 12.5% W/V) with cooling. The solution was allowed to stand overnight and the black indolizine hydrochloride was filtered off. The solution was evaporated to dryness under reduced pressure and the green solid which remained was crystallised from light petroleum (b.p. 60-80°) to yield 7.5 g. (61%) of indolizine-3-carbonyl chloride m.p. 82° (lit.[5] 81°).

Found: C, 60.7; H, 3.3; N, 8.0%

Calculated for $C_9H_6NOCl$: C, 60.3; H, 3.3; N, 7.8%

$\nu_{max}$ (Nujol) cm.$^{-1}$ 1710 (carbonyl)

($CCl_4$) cm.$^{-1}$ 1720 (carbonyl).

The nuclear magnetic resonance spectrum is shown in Figure 5.

Treatment of indolizine-3-carbonyl chloride with 1% aqueous sodium hydroxide.

Treatment of the crude product from the reaction of indolizine (15.0 g.) and phosgene in benzene with 1% sodium hydroxide caused an immediate reaction. The solution was diluted with water and filtered

as quickly as possible. Treatment of the filtrate with excess hydrochloric acid caused no precipitation but treatment with 20% sodium hydroxide solution gave a cream precipitate which, after drying under vacuum, was shown to be indolizine (3.7 g.).

The remaining solid from the treatment with aqueous base (7.3 g.) was recrystallised from light petroleum (b.p. 60-80°) and was found to be a mixture of indolizine (12) and indolizine-3-carbonyl chloride (153) (by infrared and nuclear magnetic resonance spectra). The light petroleum was evaporated and the residue treated with sodium bicarbonate solution. A gas was evolved and a precipitate formed which was filtered off and dried under vacuum. Its spectra showed that it was indolizine (12).

Methyl indolizine-3-carboxylate (154).

Indolizine-3-carbonyl chloride (153) (3.0 g.) was boiled under reflux in methanol (30 ml.) for 20 min. The yellow solid yielded a deep red solution. The excess solvent was removed by evaporation under reduced pressure and the residue was treated with an excess of a saturated solution of sodium bicarbonate. The alkaline solution was extracted several times with ether. The ether extracts were dried over sodium sulphate and the ether evaporated to yield a brown liquid which distilled at 144-146° at 14 mm of Hg. pressure to yield 2.5 g. (86%) of methylindolizine-3-carboxylate (154).

Found: C, 68.3; H, 5.0; N, 7.9%

Calculated for $C_{10}H_9NO_2$: C, 68.6; H, 5.2; N, 8.0%

$\nu_{max}$(Film) cm.$^{-1}$ 1690 (ester CO)

($CCl_4$) cm.$^{-1}$ 1695 (ester CO)

$\tau$ ($CCl_4$) 0.52 d (broad) J = 6 c/s 1p; 2.55 m, 2p; 3.1 m,2p; 3.6 d J = 5 c/s, 1p; 6.15 s, 3p.

3-Carbamoylindolizine (156).

Indolizine-3-carbonyl chloride (153) (2.0 g.) was shaken for 24 hr. with concentrated ammonia solution (30 ml. 0.88) and then stood for a further 24 hr. The yellow solid which formed was filtered off and recrystallised from ethyl acetate to yield 0.5 g. (28%) of 3-carbamoylindolizine (156), m.p. 146-7°.

Found: C, 67.2; H, 5.0; N, 17.1%

$C_9H_8N_2O$ requires: C, 67.5; H, 5.0; N, 17.5%

$\nu_{max}$(Nujol) cm.$^{-1}$ 3370, 3190 (NH), 1640.

$\tau$(Acetone) 0.2 m, 1p; 2.4 m, 2p; 2.8 - 3.6 m, 5p.

3-Hydroxymethylindolizine (155).

A solution of methyl indolizine-3-carboxylate (154) (3.0 g.) in dry ether (100 ml.) was added dropwise with stirring to a suspension of lithium aluminium hydride (0.7 g.) in dry ether (100 ml.). The solution was stirred for 1 hr. at room temperature and then boiled

under reflux for 15 min. The light brown solution turned pale green. Ethyl acetate (3.0 g.) was added dropwise followed by water (0.7 g.) and the solution was filtered. The solid residue was extracted several times with ether and the combined extracts were dried over sodium sulphate. The solvent was evaporated to yield a brown solid which was crystallised from light petroleum (b.p. 40-60°) to yield 1.7 g. (68%) of white needles of 3-hydroxymethylindolizine (155) m.p. 101°C.

Found: C, 73.8; H, 6.2; N, 9.5%

$C_9H_9NO$ requires: C, 73.45; H, 6.2; N, 9.5%

$\nu_{max}$($CCl_4$ 1%) cm.$^{-1}$ 3610 (OH), 1455, 1360, 1310, 1030, 935.

$\tau$($CCl_4$) 0.95 m, 1p; 2.6 m, 1p; 3.1 - 3.7, 4p; 5.15 s, 2p; 8.20 s, 1p (exchanges with deuterium oxide).

3-Acetylindolizine (157).

Prepared by the method of Scholtz[9] 12.5 g. of indolizine (12) gave 9.3 g. (55%) of 3-acetylindolizine (157). Yellow liquid b.p. 104-6° at 2 mm of Hg pressure. (lit.[9] b.p. 195° at 18 mm of Hg pressure).

$\nu_{max}$(Film) cm.$^{-1}$ 1620, 1510, 1470, 1385, 1340, 1230.

$\tau$ ($CCl_4$) 0.15 m, 1p; 2.4 - 3.4 4p; 3.6 d J = 5 c/s, 1p; 7.53 s, 3p.

In T.F.A. the compound was not protonated.

Attempted reduction of 3-acetylindolizine (157).

(a) With lithium aluminium hydride.

3-Acetylindolizine (157) (3.0 g.) was dissolved in dry ether (100 ml.) and the solution added dropwise with constant stirring to a suspension of lithium aluminium hydride (0.4 g.) in dry ether (50 ml.). The solution was stirred for ½ hr. and then boiled under reflux for ½ hr. Ethyl acetate (2.0 g.) was added to destroy excess lithium aluminium hydride and then water (0.4 ml.) was added. The solution was filtered and the residue was extracted with ether. The ether extracts were combined and dried over sodium sulphate. The solvent was removed under reduced pressure on a steam bath to yield a green tar. It was dissolved in benzene and chromatographed on 100 g. of Grade III alumina. The first fraction was a light green solid (1.0 g.) and the second a green liquid which had an identical infrared spectrum to that of the starting material.

The solid was rechromatographed using a 5:1 mixture of benzene and light petroleum (b.p. 40-60°) on grade II alumina. The process was again repeated on grade I alumina.

The infrared spectrum of the product indicated that there was no carbonyl absorption but the nuclear magnetic resonance spectrum was ill defined and little could be gained from it.

(b) With potassium borohydride.

3-Acetylindolizine (157) (2.0 g.) and potassium borohydride (1.4 g.) were added to isopropyl alcohol (50 ml.) and boiled under

reflux for 6 hr. Water (1 ml.) was added and the solution boiled for a further 2 hr. After cooling, the solution was filtered and the solvent removed under reduced pressure on a steam bath to leave a dark brown liquid which solidified. It was extracted with light petroleum (b.p. 60-80°) from which it crystallised as a buff solid m.p. 78-82°. Its infrared and nuclear magnetic resonance spectra were identical to the product obtained using lithium aluminium hydride but again were ill defined.

Found: C, 82.3; H, 6.8; N, 9.1%

$\nu_{max}$(Nujol)cm.$^{-1}$ 1310, 1230, 1155, 1020, 750, 720.

Attempted iodoform reaction with 3-acetylindolizine.

3-Acetylindolizine (157) (3.6 g.) was dissolved in dioxan (100 ml.), A solution of potassium hydroxide (20 ml., 10%) was added and the resulting solution warmed to 70° on a steam bath. An aqueous solution of potassium iodide saturated with iodine was added dropwise until the iodine colour persisted. The solution was diluted with water and gave a yellow turbid solution; it was extracted with ether and the aqueous phase was then acidified with hydrochloric acid (5%). The colour changed from orange-brown to dark green. It was extracted with ether and the ether extracts dried over sodium sulphate and the ether evaporated to leave a small amount of green tar which was mainly insoluble in deuterochloroform, the part that was soluble was starting material, the remainder proved to be intractable.

3-Methylindolizine (14).

Prepared from 2-picoline and propionic anhydride as described by Armarego.[11]

$\tau(CCl_4)$ 2.1 - 2.7 m, 2p; 3.2 - 3.7 m 4p; 7.52 s, 3p.

3-Acetyl-5-methylindolizine.

Prepared by the method of Scholtz.[9]

1.6 g. of 5-methylindolizine (160) gave 0.76 g. (35%) of 3-acetyl-5-methylindolizine, m.p. 55-56° (lit.[41] 56.5 - 57°).

Found: C, 76.6; H, 6.4; N, 8.0%

Calculated for $C_{11}H_{11}NO$: C, 76.3; H, 6.4; N, 8.1%

$\nu_{max}$ (Nujol) cm.$^{-1}$ 1625

($CCl_4$) cm.$^{-1}$ 1640

$\tau(CCl_4)$ 2.5 — 3.6, 5p; 7.45 m, 6p.

Attempted cyclisation of 3-acetyl-5-methylindolizine.

3-Acetyl-5-methylindolizine (0.1 g.) was dissolved in absolute ethanol (15 ml.) and a few drops of piperidine were added. The solution was sealed in a glass tube and heated at 140° for 12 hr. Spectral analysis of the product after removal of the solvent indicated that no reaction had occurred.

5-Methylindolizine (160).[41,108]

Phenyl lithium.

Into a three necked flask fitted with a condenser, stirrer and dropping funnel was placed 200 ml. of dry ether. Freshly cut lithium ribbon (7.9 g., 1.14 moles) was added. The experiment was conducted under an atmosphere of nitrogen. Bromobenzene (89.0 g., 0.57 moles) was added dropwise with constant stirring over a period of an hour and the mixture was then stirred for a further hour.

3-(2-(6'-Picolyl) )-1-propanol (159).

To the phenyl lithium solution was added 2,6 lutidine (60.9 g., 0.57 moles). The mixture was stirred during the addition and for a further 1 hr. After cooling the solution in an ice bath, ethylene oxide (25.0 g., 0.57 moles) was added dropwise with stirring and the solution stood overnight. Methyl alcohol was added to remove any excess lithium; the solution was then acidified with dilute hydrochloric acid. The aqueous layer was removed, basified and extracted with ether. The ether extracts were dried over calcium sulphate and the ether evaporated. The residue was distilled. b.p. 100°. 0.1 mm of Hg pressure, 23.8 g. of product (28%).

$\nu_{max}$(Film) 3300 (broad).

30% Palladium on charcoal catalyst.

Prepared by the formaldehyde reductive procedure. Organic Syntheses Collected Volume III, p. 686. C.

Cyclisation.

3-(2-(6'-Picolyl) )-1-propanol (159) (21.64 g.) together with the catalyst (0.5 g.) was heated under reflux with stirring for 40 hr. at 240°. A constant stream of nitrogen was passed through the reaction vessel for the removal of water as it formed. The contents of the flask were steam distilled and the distillate extracted with ether. The ether extracts were dried over calcium sulphate and the ether evaporated. The liquid was distilled. 10.5 g. (56%) b.p. 88-95° 10 mm. of Hg pressure. A yellow oil which darkened on standing.

$\lambda_{max}$ (95% EtOH) mμ ($\log_{10}\varepsilon$) 334 (3.42), 295 (3.75), 288 (3.62), 283 (3.64), 232 (4.56).

$\tau(CCl_4)$ 2.6 - 3.8, 6p; 7.46 s, 3p.

Attempted bromination of 5-methylindolizine.

5-Methylindolizine (160) (1.97 g.) and N-bromosuccinimide (2.67 g.) were boiled under reflux for 2½ hr. in carbon tetrachloride (50 ml.). The solution was filtered and an infrared spectrum taken. It showed mainly starting material. On removal of the solvent a black tar resulted; it was extracted with ether and the ether removed to yield starting material.

Attempted preparation of 5-indolizinylacetic acid.

Phenyl lithium was prepared as described above. It was added dropwise to a solution of 5-methylindolizine (160) (6.3 g., 0.05 moles) in ether (10 ml.). An equimolar amount being used. The solution was stirred for 2 hr. at room temperature under an atmosphere of nitrogen. The solution was then transferred to a Dewar flask which contained a mixture of solid carbon dioxide and ether. The flask was allowed to stand overnight.

The product was treated with water (60 ml.) and then ether (50 ml.) added. An emulsion resulted. Dilute sulphuric acid was added until the two layers separated and the ether layer was removed and shaken with a saturated sodium carbonate solution. The aqueous layer was treated with dilute sulphuric acid to the change point of congo red and a lime-green froth developed. The solution was extracted with ether and the ether layer dried over sodium sulphate. The ether was evaporated leaving a faintly yellow solid (0.82 g.) the infrared spectrum of which was identical with that of benzoic acid.

The ether solution from which acid constituents had been extracted with sodium carbonate solution was dried over sodium sulphate and the ether removed to leave a liquid (7.3 g.).

$\nu_{max}$ cm.$^{-1}$ (Film) 1660, 1640, 1600.

The sample was distilled and yielded two fractions (a) b.p. 89-92° 10 mm Hg pressure, 1.85 g. shown to be 5-methylindolizine.

(b) 98-99° 0.3 mm Hg pressure brown liquid (0.38 g.). The nuclear magnetic resonance spectrum indicated that it was a mixture of starting material and benzophenone.

A dinitrophenylhydrazine was prepared and its infrared spectrum was identical to that of an authentic dinitrophenylhydrazine derivative of benzophenone.

2-Methyl-6-ethoxypyridine (163).

Prepared from 2-methyl-6-aminoindolizine (161) in a two stage process.[125,126]

Quaternisation of 2-methyl-6-ethoxypyridine (163) with bromoacetone.

(a) 2-Methyl-6-ethoxypyridine (163) (5.0 g.) was boiled under reflux in absolute ethanol with bromoacetone (5.0 g.) for 3½ hr. The initially colourless solution went brown. The solvent was removed under reduced pressure and the remainder treated with ethyl acetate to yield a grey solid (164) 0.6 g., m.p. ~ 205°.

$\nu_{max}$ (Nujol) cm.$^{-1}$ 1650

$\tau$ (T.F.A.) 1.6 m, 1p; 2.55 m, 2p; 5.05, 2p; 7.2 s, 3p; 7.85 s, 3p.

$\tau$ ($D_2O$) 2.1 m, 1p; 3.1 m, 2p; 4.95 s, 2p; 7.6 s, 3p; 7.8 s, 3p.

Mass spectrum m/e 165 ($M^+$), 150, 123, 122, 109, 94.

(b) 2-Methyl-6-ethoxypyridine (5.0 g.) and bromoacetone (5.0 g.) were added to sulpholane (12 ml.) and kept for 7 days at 40° . The solution

went brown with time. On adding it to ethyl acetate no precipitate was observed but after warming gently a white solid precipitated 0.18 g. The compound was identical to that found in (a).

(c) 2-Methyl-6-ethoxypyridine (5.0 g.) and bromoacetone (5.0 g.) were kept in absolute ethanol (20 ml.) at room temperature for 7 days. After this time it was poured into excess ether (100 ml.) and a white deliquescent solid precipitated 0.9 g. (9%) of 1-acetonyl-2-methyl-6-ethoxypyridinium bromide (165).

$\nu_{max}$(Nujol) cm.$^{-1}$ 1725

$\tau$($D_2O$) 1.45 m, 1p; 2.4 m, 2p; 4.3 s, 2p; 5.3 q (under HDO peak); 7.3 s, 3p; 7.5 s, 3p; 8.5 t, 3p J = 7.5 c/s.

When the ethanolic solution was kept for 1 month then 3.93 g. (39%) of quaternary compound (165) were obtained.

No attempt was made to purify the quaternary compound due to its instability.

Attempted cyclisation of 1-acetonyl-2-methyl-6-ethoxypyridinium bromide (165).

(a) 1-Acetonyl-2-methyl-6-ethoxypyridinium bromide (165) (0.2 g.) was heated on a steam bath for 1 hr. in 10% sodium bicarbonate solution (10 ml.). The cooled solution was extracted with ether and the ether extracts dried over sodium sulphate. The ether was evaporated. Nuclear magnetic resonance showed that the product was the pyridone (164).

(b) 1-Acetonyl-2-methyl-6-ethoxypyridinium bromide (165) (0.5 g.) was boiled under reflux for 15 min. in absolute ethanol (20 ml.), with di-n-butylamine (2 ml.). The solution went yellow immediately. The solution was poured into water and the aqueous solution extracted with ether. The ether extracts were dried over sodium sulphate and the ether evaporated. The solid residue (166) was examined by nuclear magnetic resonance.

$\tau(CCl_4)$ 2.8 m, 1p; 3.7 d, 1p; 4.1 d, 1p; 5.7 s (broad) 1½p?; 6.45 q, 4p; 7.5 s, 3p; 8.8 m, 9p.

(c) 1-Acetonyl-2-methyl-5-ethoxypyridinium bromide (165) (0.5 g.) was boiled under reflux for 15 min. in absolute ethanol (20 ml.) with di-n-butylamine (2 ml.). The solvent and excess base were removed under reduced pressure by heating on a steam bath. The solid product was extracted with light petroleum (b.p. 60-80°) from which a yellow solid crystallised m.p. 72°.

$\nu_{max}$(Nujol) cm.$^{-1}$ 1730, 1660, 1580, 1550, 1125, 1040.

The nuclear magnetic resonance spectrum was the same as the product of (b). A small amount of compound (164) was also present.

(d) The experiment was repeated using methanol as solvent and the boiling continued for ½ hr. The product was examined by nuclear magnetic resonance.

$\tau$ ($CCl_4$) 2.8 m, 1p; 3.6 d, 1p; 4.1 d, 1p; 5.7 s (broad, 1½p?;
6.7 s, 6p; 7.5 s, 3p; 8.8 s, 3p.

Again, a small amount of the pyridone (164) was present.

(e) 1-Acetonyl-2-methyl-6-ethoxypyridinium bromide (165) (0.5 g.) was dissolved in 95% ethanol (30 ml.) and 10 g. of IR-4B (OH) ion exchange resin added. The solution was boiled under reflux for 10 min. and then filtered. The solvent was removed under reduced pressure on a steam bath and the residue examined by nuclear magnetic resonance. A mixture of products was observed, the main constituent being the pyridone (164).

Boiling the compound (165) in ethanol converted it to the pyridone (164).

Acetylation of 2-methyl-6-aminopyridine.

2-Methyl-6-aminopyridine (161) (5.0 g.) was boiled under reflux in a 1:1 mixture of acetic anhydride and acetic acid (50 ml.) for ½ hr. The solution was poured into water (100 ml.) and excess sodium carbonate solution was added. The aqueous solution was extracted with ether and the ether extracts dried over sodium sulphate. The ether was evaporated to yield the acetyl derivative (167) 5.37 g. (77%) m.p. 88°.

$\nu_{max}$ (Nujol) 3240, 1660 (Acetyl CO).

$\tau$ ($CCl_4$) 0.6 s (broad), 1p; 1.8 m, 1p; 2.45 m, 1p; 3.1 m, 1p;
7.6 s, 3p; 7.85 s, 3p.

Attempted quaternisation of the acetyl derivative (167).

(a) The acetyl derivative (167) (2.52 g.) was dissolved in acetone (20 ml.) and an equimolar amount of bromoacetone added (2.3 g.). The solution was boiled under reflux for 7 hr. The solvent was removed under reduced pressure and the residue treated with water; it did not dissolve. Chloroform was added and the layers were separated. Only starting material was recovered.

(b) The acetyl derivative (167) (2.85 g.) was added to sulpholane (15 ml.) together with an equimolar amount of bromoacetone (2.5 g.). The solution was kept at 35° for 3 days and then poured into ether. No quaternary compound could be isolated.

Ethyl 2-methylpyridine-5-carboxylate (169).

The ester (169) was prepared from 2-methyl-5-ethylpyridine (168) by the method of Plattner, Keller and Boller.[128]

$\nu_{max}$(Film) 1715 (C=O ester).

2-Methyl-5-carbamoylpyridine (170).

The amide (170) was prepared[128] from the ester (169) by treatment with concentrated ammonia solution.

$\nu_{max}$(Nujol) cm.$^{-1}$ 3300, 3140, (NH), 1675 (amide CO).

2-Methyl-5-cyanopyridine (171).

The cyanopyridine (171) was prepared from the amide (170) by treatment with phosphorus oxychloride.[128]

$\nu_{max}$(Nujol) 2220 cm.$^{-1}$ (CN).

Attempted reduction of ethyl 2-methylpyridine-5-carboxylate (169) with lithium aluminium hydride.

The ester (169) (4.12 g.) in dry ether (50 ml.) was reduced with lithium aluminium hydride (1.0 g.) in ether (40 ml.) in the usual way. The solution was boiled under reflux for 2 hr. After working up in the usual way[135] 1.74 g. of product were collected, m.p. 38°. The spectra of the product indicated that it was a mixture of starting material and 2-methyl-5-hydroxymethylpyridine (177). A partial separation could be achieved by extracting the hydroxymethyl compound (177) with water.

Attempted reduction of 2-methyl-5-carbamoylpyridine (170) with lithium aluminium hydride.

The amide (34 g.) was added directly to the stirred suspension of lithium aluminium hydride (1.7 g.) in ether (80 ml.) and the solution boiled under reflux for several hours. After working up in the usual way[135] only starting material was recovered.

Reduction of 2-methyl-5-cyanopyridine (171) with lithium aluminium hydride.

2-Methyl-5-cyanopyridine (171) (11.8 g.) was reduced in the usual way[135] with lithium aluminium hydride by boiling under reflux for ½ hr. The product was a red liquid 7.9 g. and was distilled b.p. 100° 20 mm of Hg pressure to yield 2.32 g. (19%) of 2-methyl-5-aminomethylpyridine (183). A pale yellow solid m.p. 62° (lit[137] 61-62°).

$\nu_{max}(CCl_4)$ cm.$^{-1}$ 3390, 3190 (faint) (NH ).

Acetyl derivative of 2-methyl-5-aminomethylpyridine.

2-Methyl-5-aminomethylpyridine (183) (2.4 g.) was boiled under reflux for ½ hr. with a mixture of acetic acid and acetic anhydride (5 ml. 1:1). The resulting solution was poured into water (10 ml.) and 10% sodium hydroxide solution added until the solution was basic. The solution was then extracted with ether and the ether extracts dried over sodium sulphate. The ether was evaporated to leave 2.1 g. of product. Spectra showed that it was the acetyl derivative (184).

$\tau(CDCl_3)$ 1.3 - 2.8 4p; 5.5 d, 2p; 7.4 s, 3p; 7.9 s, 3p.

On shaking with $D_2O$ one of the protons at 1.3 - 2.8 $\tau$ disappeared and the doublet at 5.5 $\tau$ collapsed to a singlet.

Quaternisation of the acetyl derivative (184).

The acetyl derivative (184) (2.1 g.) was boiled under reflux in acetone (100 ml.) with bromoacetone (2.0 g.) for 4 hr. The solvent was removed under reduced pressure, the residue taken up in water and the aqueous solution extracted with chloroform. The aqueous layer was boiled to dryness under reduced pressure to yield the quaternary salt (185) (2.6 g.), a brown solid.

$\nu_{max}$(Nujol) 1725 (acetonyl CO), 1665 (acetyl CO), cm.$^{-1}$
Picrate m.p. 116-120°.

$\tau$($D_2O$) 1.0 - 2.0 3p; 4.1s, 2p; (slowly exchanges with $D_2O$);
5.4 singlet (under HDO); 7.3 s, 3p; 7.5 s, 3p; 7.9 s, 3p.

Cyclisation of the Quaternary Compound (185)

The quaternary compound (185) (0.5 g.) was heated on a steam bath in 10% aqueous sodium bicarbonate (50 ml.) for 3 hr. The cooled solution was extracted with chloroform and the chloroform extracts dried over sodium sulphate. The solvent was removed under reduced pressure to yield a solid whose nuclear magnetic resonance spectrum confirmed that it was an indolizine, 2-methyl-6-acetylaminomethyl-indolizine (186).

$\nu_{max}$($CCl_4$) cm.$^{-1}$ 3430 (NH), 1670 (acetyl CO).

$\tau$ (T.F.A.) 1.0 - 3.0, 4p; 3.4 s, 1p; 4.9 s, 2p; 5.6 d, 2p;
7.9 s, 3p; 8.0 s, 3p.

Hydrolysis of 2-methyl-6-acetylaminomethylindolizine (186).

The acetyl derivative (186) (0.1 g.) was boiled in concentrated hydrochloric acid (10 ml.) for 1 hr. The acid was removed under reduced pressure and sodium hydroxide solution (10%) was added dropwise to an aqueous solution of the residue. When basic, the aqueous solution was extracted with chloroform. The chloroform extracts were dried over sodium sulphate and the chloroform evaporated under reduced pressure to leave a solid (0.025 g.) which was taken up in deuterochloroform and a nuclear magnetic resonance spectrum obtained.

$\tau$ ($CDCl_3$) 2.0 - 4.0, 5p; 6.2 s, 2p; 7.6 s (broad) 3p; 7.3 - 8.0 broad bulge 2p. exchanges with $D_2O$.

2-Methyl-6-ethylindolizine (173).

2-Methyl-5-ethylpyridine (168) (12.1 g.) was boiled under reflux in absolute ethanol (100 ml.) with bromoacetone (13.7 g.) for 7 hr. The solvent was removed under reduced pressure to yield a thick gum which was taken up in water and the solution extracted with ether. The water was removed under reduced pressure to yield 20.8 g. of 1-acetonyl-2-methyl-5-ethylpyridinium bromide (172).

$\nu_{max}$ (Film) $cm.^{-1}$ 1725 (acetonyl CO).

Picrate (ethanol) m.p. 149°.

The gum (20.0 g.) was taken up in absolute ethanol (100 ml.) and di-n-butylamine (25 ml.) was added. The solution was boiled under

reflux for 2 hr. and the solvent was then removed under reduced pressure. Water (200 ml.) was added and the resulting solution was extracted with ether. The ether extracts were dried over sodium sulphate and the ether evaporated to leave a black liquid which was distilled under reduced pressure. There were two main fractions.

(1) b.p. 54 - 60° at 19 mm of Hg pressure, di-n-butylamine.

(2) b.p. 80° at 0.3 mm of Hg pressure. It solidified in the receiver flask, faintly yellow solid 5.9 g. (37%) which was crystallised from light petroleum (b.p. 40-60°) to yield white flakes of 2-methyl-6-ethylindolizine (173) m.p. 28°.

Found: C, 82.6; H, 8.0; N, 8.5%

Calculated for $C_{11}H_{13}N$: C, 83.0; H, 8.2; N, 8.8%

Picrate m.p. 106°

$\nu_{max}$(Nujol) cm.$^{-1}$ 1640, 1555, 1520, 1295, 1250, 1205, 1135.

$\tau(CCl_4)$ 2.4 s (broad) 1p; 2.8 d J = 9 c/s, 1p; 3.0 s, 1p;
3.52 d (also J = 2 c/s split) J = 9 c/s 1p; 3.82 s, 1p;
7.5 q, J = 7.5 c/s, 2p; 7.7 s, 3p; 8.8 t, J = 7.5 c/s, 3p.

Ethyl 2-methylindolizine-6-carboxylate (175).

Ethyl 2-methylpyridine-5-carboxylate (169) (8.25 g.) and bromoacetone (8,0 g.) were boiled under reflux in absolute ethanol (30 ml.) for 6 hr. The solvent was removed under reduced pressure to yield a green gum. An aqueous solution of the gum was extracted with chloroform to remove any non quaternary material. After removal of the water by

boiling under reduced pressure 13.7 g. of ethyl 1-acetonyl-2-methyl-pyridinium bromide-5-carboxylate (174) remained.

Cyclisation could be effected in one of two ways:

(1) The quaternary compound (174) (13.7 g.) was heated on a steam bath for 2 hr. in 10% sodium bicarbonate solution (180 ml.). The green solution went brown. The cooled solution was extracted with ether and the ether extracts dried over sodium sulphate. The ether was evaporated to leave a yellow solid (4.2 g.) which was crystallised from light petroleum (b.p. 40-60°) to yield 3.5 g. (35%) of a yellow solid ethyl-2-methylindolizine-6-carboxylate (175) m.p. 73.5°.

Found: C, 71.1; H, 6.1; N, 6.7%

$C_{12}H_{13}NO_2$ requires: C, 70.9; H, 6.5; N, 6.9%

$\nu_{max}$(Nujol) 1705 (ester CO).

$\tau$ ($CCl_4$) 1.4 s (broad), 1p; 2.8 s (broad), 3p; 3.8 s (broad), 1p; 5.7 q J = 7.5 c/s, 2p; 7.7 s, 3p; 8.6 t J = 7.5 c/s, 3p.

$\tau$(T.F.A.) 0.3 s, 1p; 0.9d, 1p; 1.8 d, 1p; 2.9 s, 1p; 4.4 s, 2p; 5.3 q J = 7.5 c/s, 2p; 7.5 s, 3p; 8.4 t J = 7 c/s, 3p.

(2) The quaternary compound (174) (7.6 g.) was boiled under reflux in absolute ethanol (100 ml.) with di-n-butylamine (2.5 ml.) for 2½ hr. The solvent was removed under reduced pressure and the residue treated with water. The aqueous mixture was extracted with ether and the ether extracts dried over sodium sulphate. The ether was

evaporated and the residue was crystallised from light petroleum (b.p. 40-60°) to yield 1.9 g. (34%) of ethyl 2-methylindolizine-6-carboxylate (175).

Treatment of ethyl 2-methylindolizine-6-carboxylate (175) with sodium and ethanol.

Ethyl 2-methylindolizine-6-carboxylate (175) (1.0 g.) was boiled under reflux in absolute ethanol (25 ml.). Sodium (0.7 g.) was added in small pellets down the condenser over a period of ½ hr. The solution was boiled for a further 10 min. and then the excess ethanol removed under reduced pressure. Water (50 ml.) was added and the solution was extracted with ether. After drying the ethereal solution over sodium sulphate the ether was evaporated. The residue was examined by nuclear magnetic resonance. A confused spectrum resulted but the peaks furthest downfield were at 3.75 $\tau$ and 4.4 $\tau$ indicating reduction had occurred. There was no longer any signal due to the ethoxy group protons.

1-Acetonyl-2-methyl-5-carbamoylpyridinium bromide (178).

2-Methyl-5-carbamoylpyridine (170) (5.0 g.) and bromoacetone (6.0 g.) were boiled under reflux in absolute ethanol (50 ml.) for 7 hr. The quaternary product crystallised from the alcohol solution. The solid was filtered off and the solution reduced in volume by removal of solvent under reduced pressure. Further solid crystallised and was collected. The total yield was 7.4 g. (74%) of quaternary compound (178);

it was recrystallised from aqueous alcohol to give white flakes m.p. 253°.

Found: C, 44.4; H, 4.6; N, 10.1%

$C_{10}H_{13}BrN_2O_2$ requires: C, 44.0; H, 4.8; N, 10.3%

$\nu_{max}$(Nujol) cm.$^{-1}$ 3270, 3120 (NH) 1735 (acetonyl CO) 1690 (amide CO).

Chloroplatinate m.p. 212°.

$\tau$(T.F.A.) 0.3 s, 1p; 0.7 d, 1p; 1.6 d + bulge, 3p; 3.8 s, 2p; 7.0 s, 3p; 7.3 s, 3p.

2-Methyl-6-carbamoylindolizine (179).

The quaternary salt (178) (3.3 g.) was boiled in 95% ethanol with di-n-butylamine (5 ml.) for 2½ hr. On cooling a yellow solid crystallised and was filtered off. Further solid was obtained by reducing the volume of the solution. The faintly yellow solid was recrystallised from 95% ethanol to yield 1.7 g. (81%) of 2-methyl-6-carbamoylindolizine (179) m.p. 205° (decomp.).

Found: C, 68.8; H, 5.7; N, 15.9.

$C_{10}H_{10}N_2O$ requires: C, 69.0; H, 5.8; N, 16.1%

$\nu_{max}$(Nujol) 3370, 3190 (NH) 1655 (amide CO), 1630, 1600, 1427, 1120, 740.

$\tau$(T.F.A.) 0.4 s (broad), 1p; 1.0 d, 1p; 1.9 d + bulge, 3p; 2.9 s (broad), 1p; 4.4 s, 2p; 7.5 s, 3p.

Attempted dehydration of 2-methyl-6-carbamoylindolizine (179) to 2-methyl-6-cyanoindolizine (181).

The amide (179) and phosphorus oxychloride (5 ml.) were heated at 130° for 4 hr. The excess phosphorus oxychloride was removed by distillation under reduced pressure. The residue was covered with chloroform (30 ml.) and a concentrated solution of sodium carbonate added until reaction ceased. The aqueous solution was extracted with chloroform and the chloroform extracts washed with water. After drying over sodium sulphate the chloroform was removed under reduced pressure to leave a brown solid (0.59 g.). The infrared spectrum indicated both the required product and starting material were present.

$\nu_{max}(CHCl_3)$ cm.$^{-1}$ 2230 (CN) 1670 (amide CO).

Attempted reduction of 2-methyl-6-carbamoylindolizine (179) with lithium aluminium hydride.

(a) The amide (179) (0.3 g.) was subjected to reducing conditions in the usual way[135] using lithium aluminium hydride (0.5 g.) in tetrahydrofuran (70 mls. total). The solution was stirred for ½ hr. and then boiled under reflux for 5 min. After working up in the usual way only starting material was recovered.

(b) The experiment was repeated and the solution was boiled under reflux for 4½ hr. The solution went green. After working up in the usual way material was obtained which could not be characterised but nuclear magnetic resonance indicated that ring reduction may have

occurred. The product was soluble in carbon tetrachloride and there were no peaks below 3.75 $\tau$ .

$\nu_{max}$(Film) cm.$^{-1}$ 3460, 3370, 1645, 1430, 1280, 1130, 1060, 785.

1-Acetonyl-2-methyl-5-cyanopyridinium bromide (182).

(a) 2-Methyl-5-cyanopyridine (171) (7.1 g.) and bromoacetone (9.0 g.) were boiled under reflux in absolute ethanol for 7 hr. The solvent was removed under reduced pressure and the residue taken up in water and extracted with chloroform. Starting material (1.2 g.) was subsequently recovered from the chloroform layer. The aqueous layer was boiled to dryness under reduced pressure to yield a buff solid which crystallised from acetone 5.4 g. (35%) m.p. 156°.

Found: C, 47.1; H, 4.1; N, 10.6%

$C_{10}H_{11}BrN_2O$ requires: C, 47.1; H, 4.3; N, 11.0%

$\nu_{max}$(Nujol) cm.$^{-1}$ 2250 (CN) 1735 (acetonyl CO).

$\tau(D_2O)$ 0.5 s, 1p; 0.9 d, 1p; 1.6 d, 1p; 3.9 s, 2p (exchanges slowly); 7.1 s, 3p; 7.4 s, 3p.

(b) 2-Methyl-5-cyanopyridine (171) (2.0 g.) and bromoacetone (4.7 g.) were boiled under reflux in acetone (25 ml.) for 2½ hr. and worked up in the usual way. The product crystallised from acetone 0.46 g. (17.5%).

(c) The experiment was repeated in absolute ethanol and the solution boiled under reflux for 16 hr. 1.0 g. of 2-methyl-5-cyanopyridine (171) afforded 1.0 g. (46%) of the quaternary compound (182).

(d) The nitrile (171) (2.0 g.) and bromoacetone (4.7 g.) were kept in sulpholane (10 ml.) for 3 days at 35°. The solution was poured into excess ethyl acetate and the quaternary compound (182) filtered off. 2.3 g. (53%) were collected.

(e) The nitrile (171) (10.1 g.) and bromoacetone (20.0 g.) were kept in sulpholane (50 ml.) at 42° for 3 days. The solution was poured into excess ethyl acetate and the solid was filtered off; it appeared to be still contaminated with sulpholane. The compound was dissolved in water and the aqueous solution was extracted with chloroform and ether. The aqueous solution was boiled to dryness under reduced pressure to yield a dark green solid (23.3 g.). This crude quaternary compound was used for cyclisation without further purification.

2-Methyl-6-cyanoindolizine (181).

1-Acetonyl-2-methyl-5-cyanopyridinium bromide (182) (5.46 g.) was heated on a steam bath in 10% sodium bicarbonate (100 ml.) for 1½ hr. The cooled solution was extracted with chloroform and the chloroform extracts dried over sodium sulphate.

The solvent was removed under reduced pressure and the dark residue was extracted with light petroleum (b.p. 60-80°). A yellow

solid crystallised from the solvent. 2.44 g. (78%) m.p. 99°.

Found: C, 76.6; H, 4.8; N, 17.6%

$C_{10}H_8N_2$ requires: C, 76.9; H, 5.2; N, 17.9%

$\nu_{max}$(Nujol) 2225 cm.$^{-1}$ (CN)

$\lambda_{max}$ (95% Ethanol) mμ (log $\varepsilon$) 207 (4.24), 253 (4.71), 259 (4.71), 291 (3.57), 310 (3.50).

$\tau$($CDCl_3$) 1.7 s, 1p; 2,7 m, 2p; 3.3 m J = 9 c/s also further split J = 2 c/s, 1p; 3.6 s, 1p; 7.9 s, 3p.

If the treatment with aqueous sodium bicarbonate solution was prolonged amide formation occurred.

Attempted reduction of 2-methyl-6-cyanoindolizine (181).

(a) The cyanoindolizine (181) (1.0 g.) was dissolved in absolute ethanol (80 ml.) and a 10% Pd/C catalyst added. Subjecting the solution to one atmosphere pressure of hydrogen for 2 days had no effect and only starting material was recovered.

(b) The cyanoindolizile (181) was subjected to lithium aluminium hydride reduction in ether at room temperature. After working up in the usual way the product was examined and found to be identical to that found in (c).

(c) The cyanoindolizine (181) (0.5 g.) in dry ether (70 ml.) was added to a suspension of lithium aluminium hydride (0.5 g.) in ether (50 ml.) under an atmosphere of dry nitrogen. The solution was boiled under reflux for $2\frac{1}{2}$ hr. and then worked up in the usual way.[135] The product was a pale brown liquid (0.4 g.).

$\nu_{max}$(Film) cm.$^{-1}$ 3460, 3370, 3200, 1645

$\nu_{max}$(benzene) cm.$^{-1}$ 3490, 3400, 1645

$\lambda_{max}$ (95% ethanol) mμ 210, 242, 303, 339.

The nuclear magnetic spectrum is shown in Figure 6.

Treatment of 2,6-dimethylindolizine with lithium aluminium hydride.

When 2,6-dimethylindolizine was boiled in ether with an excess of lithium aluminium hydride for $4\frac{1}{2}$ hr. only starting material was recovered and no reaction occurred.

2-Methyl-6-hydroxymethylindolizine (176).

Ethyl 2-methylindolizine-6-carboxylate (175) (1.83 g.) was reduced with lithium aluminium hydride (1.0 g.) in ether (45 ml.). The solution was stirred for 15 min. and then boiled under reflux for 1 hr. The reaction was worked up in the usual way to yield a cream solid 1.28 g. (88%) which crystallised from light petroleum (b.p. 60-80°) m.p. 96°.

Found: C, 74.2; H, 6.6; N, 8.3%

$C_{10}H_{11}NO$ requires: C, 74.5; H, 6.9; N, 8.7%

$\nu_{max}$(Nujol) cm.$^{-1}$ 3240 (broad) (OH) 1300, 1020, 810, 735.

$\tau$($CDCl_3$, 15%) 2.35 s, 1p; 2.75 d, 1p; 3.0 s, 1p; 3.45 d, 1p; 3.7 s, 1p; 5.6 s, 2p; 7.15 s, 1p; 7.7 s, 3p.

The proton in the 3 position exchanges when the solution is shaken with $D_2O$ as well as the singlet at 7.15 $\tau$ . After standing overnight both the 3 and 1 position protons exchange.

Attempted preparation of a tosylate of 2-methyl-6-hydroxymethylindolizine (176).

The hydroxymethylindolizine (176) (0.1 g.) was dissolved in pyridine (0.3 ml.) and p-toluenesulphonyl chloride (0.2 g.) was added. The solution was heated on a steam bath for 1 hr., cooled and added to 5% hydrochloric acid (3 ml.). A dark green solid precipitated which could not be characterised.

Treatment of 2-methyl-6-hydroxymethylindolizine (176) with sodium and ethanol.

To a boiling solution of the hydroxymethylindolizine (176) (0.5 g.) in absolute ethanol was added sodium (7.0 g.) in small pellets down the condenser over a period of $\frac{1}{2}$ hr. The resulting solution

was boiled under reflux for a further 1 hr. The excess ethanol was removed under reduced pressure and water (100 ml.) was added to the residue. The aqueous solution was extracted several times with ether and the ether extracts dried over sodium sulphate. The ether was evaporated leaving a dark brown oil. An attempt to purify the product using thick layer chromatography was not successful. Several constituents were observed but the material decayed on the plates. Nuclear magnetic resonance indicated that reduction had taken place. The peaks furthest downfield were at 3.6 $\tau$ and 4.2 $\tau$.

2-Methyl-6-hydroxydideuteromethylindolizine.

Ethyl 2-methylindolizine-6-carboxylate (175) (0.38 g.) was treated in ether (50 ml.) with lithium aluminium deuteride in the usual way. The solution was stirred for 1 hr. and then boiled under reflux for 1½ hr. After working up 0.33 g. of product was collected. The nuclear magnetic resonance spectrum had no signal at 5.6 $\tau$ which is the position of the methylene group protons in the non deuterated compound.

6-Methylindolizine (188).

6-Methylindolizine (188) was prepared by the method of Scholtz as described by Armarego.[11]

1,3-Diacetyl-6-methylindolizine (187).

$\tau$ ($CDCl_3$) 0.15 s (broad), 1p; 1.4 d, J = 9 c/s, 1p; 2.05 s, 1p; 2.6 m, J = 9 c/s, J = 2 c/s, 1p; 7.4 d, 6p; 7.6 s, 3p.

6-Methylindolizine (188).

$\tau$ ($CCl_4$) 2.25 s (broad), 1p; 2.5 - 2.8 m, 2p; 3.2 - 3.7 m, 3p; 7.8 s, 3p.

2-Picoline-1-oxide.

Prepared from 2-picoline by the method of Feely and Beavers.[129,133]

1-Methoxy-2-methylpyridinium methyl sulphate (189).

Prepared from 2-picoline-N-oxide and dimethyl sulphate.[129,133]

2-Methyl-4-cyanopyridine (191).

Prepared from 1-methoxy-2-methylpyridinium methyl sulphate (189) by treatment with aqueous sodium cyanide.[129,133]

406 g. of 1-methoxy-2-methylpyridinium methyl sulphate gave 138 g. of a dark red liquid as the crude product. It was distilled, b.p. 200-230°. Yield 82.5 g. On standing, part of it crystallised. It was filtered. The solid was mainly 2-methyl-6-cyanopyridine (190) (5.0 g.). Distillation of the liquid at reduced pressure gave a fraction b.p. 90-104° 15 mm of Hg pressure which was predominately the required compound (191) (47.8 g.).

A total of 29.0 g. of 2-methyl-6-cyanopyridine (190) was also collected, b.p. 104-120° at 15 mm of Hg pressure, and was recrystallised from light petroleum (b.p. 40-60°).

2-Methyl-6-cyanopyridine (190).

$\nu_{max}$(Nujol) 2240 (CN)

$\tau$($CCl_4$) 2.0 - 2.7 3p; 7.4 s, 3p.

2-Methyl-4-cyanopyridine (191).

$\nu_{max}$ (Film) 2245 (CN)

$\tau$($CCl_4$) 1.25 d, 1p; 2.6 m, 2p; 7.37 s, 3p.

1-Acetonyl-2-methyl-4-cyanopyridinium bromide (192).

(a) 2-Methyl-4-cyanopyridine (191) (7.0 g.) and bromoacetone (14.0 g.) were kept in sulpholane (30 ml.) for 3 days at 35°. The solution was added dropwise with trituration to ethyl acetate (150 ml.). A thick oil separated which eventually solidified. The solid was filtered off, taken up in water and the solution washed with ether. The aqueous solution was then boiled to dryness under reduced pressure to yield a pink solid (192) 13.3 g. (88%). It crystallised from acetone m.p. 152-5°. Chloroplatinate (water) 186° (decomp.).

(b) 2-Methyl-4-cyanopyridine (191) (14.2 g.) was boiled under reflux in acetone (80 ml.) with bromoacetone (20.0 g.) for 1 hr.

The quaternary compound (192) came out of solution as a thick gum and with trituration it solidified and was filtered off. 14.8 g. (48%).

$\nu_{max}$(Nujol) (CN absent) 1735 (acetonyl CO).

$\tau(D_2O)$ 0.95 d, 1p; 1.4 s, 1p; 1.55 d, 1p; 4.0 s, 2p; 7.15 s, 3p; 7.45 s, 3p.

2-Methyl-7-cyanoindolizine (193).

(a) When the quaternary compound (192) was heated on a steam bath in 10% sodium bicarbonate the product of the reaction was a mixture of the required product (193) and the corresponding amide.

$\nu_{max}$(Nujol) cm.$^{-1}$ 3380, 3200 (NH), 2225 (CN), 1655 (amide CO).

The process was repeated using only 5 min. warming. In this case a negligible amount of product was collected.

(b) The quaternary compound (192) (7.0 g.) was boiled under reflux in 95% ethanol for 2 hr. with di-n-butylamine (10 ml.). The initially yellow solution went deep red. The solution was stood overnight and then the solvent removed under reduced pressure. The residue was treated with water and chloroform and the chloroform layer removed and dried over sodium sulphate. When the chloroform was evaporated a black tar remained. The tar was treated with hydrochloric acid (50 ml, 10%) and the solution extracted with chloroform. After removal of the solvent

under reduced pressure it was found that the product was still contaminated with di-n-butylamine. Nuclear magnetic resonance indicated the correct product was also present.

(c) The quaternary compound (192) (4.8 g.) was boiled under reflux in 95% ethanol for $\frac{1}{2}$ hr. with IR-4B (OH) ion exchange resin (30 g.). The resin was filtered off and the ethanol evaporated under reduced pressure. The residue was extracted with light petroleum (b.p. 60-80°) and a yellow solid crystallised from it. 0.75 g. (24%) 2-methyl-7-cyanindolizine (193) m.p. 75.5°.

Found: C, 76.5; H, 5.1; N, 18.0%

$C_{10}H_8N_2$ requires : C, 76.9; H, 5.2; N, 17.9%

$\nu_{max}$(Nujol) 2235 (CN)

$\tau(CCl_4)$ 2.1 m, 2p; 2.6 s, 1p; 3.4 m, 2p; 7.65 s, 3p.

Reduction of 2-methyl-7-cyanoindolizine (193) with lithium aluminium hydride.

2-Methyl-7-cyanoindolizine (193) (0.14 g.) was reduced with lithium aluminium hydride by boiling an ether solution (40 ml.) for 15 min. The reaction was worked up in the usual way[135] to yield a cream solid (194) 0.1 g. (72%). It crystallised from light petroleum (b.p. 60-80°) 2-methyl-7-aminomethylindolizine, m.p. 94°.

Found: N, 17.3%

$C_{10}H_{12}N_2$ requires: N, 17.3%

$\nu_{max}$(Nujol) cm.$^{-1}$ 3360, 3280 (NH)

The nuclear magnetic resonance is shown in Figure 7.

Attempted quaternisation of 2-methyl-6-cyanopyridine (190).

2-Methyl-6-cyanopyridine (190) (7.0 g.) was kept in sulpholane (30 ml.) for 3 days at 35° with bromoacetone (14.0 g.). On adding the solution to ethyl acetate no precipitate was observed. The same procedure was employed using ether but again no precipitate was obtained. It was concluded that 2-methyl-6-cyanopyridine would not react with bromoacetone under these conditions.

Reduction of 2-methyl-4-cyanopyridine (191) with lithium aluminium hydride.

2-Methyl-4-cyanopyridine (191) (5.0 g.) in dry ether was added dropwise with stirring to a suspension of lithium aluminium hydride (3.2 g.) in dry ether (40 ml.). The solution was boiled under reflux for 3½ hr. Water (6 ml.) was added dropwise with stirring and the solution filtered. The residue was extracted with boiling ether. The ether extracts were dried over sodium sulphate and the ether evaporated to leave 4.12 g. of a red liquid. The product was distilled and the fraction boiling at 112-116° at 15 mm Hg pressure collected. 2-Methyl-4-aminomethylpyridine (195).

$\nu_{max}$(Film) cm.$^{-1}$ 3370, 3290 (NH)

$\tau(CDCl_3)$ 1.4 d, 1p; 2.8 m, 2p; 6.1 s, 2p; 7.4 s, 3p;
8.35 s, 2p. (exchanges with $D_2O$).

Acetyl derivative (196).

The amine (195) (1.0 g.) was added to a mixture of acetic acid (6 ml.) and acetic anhydride (2 ml.) and the solution heated at 100° for ½ hr. A deep blue solution resulted. The majority of the solvent was removed at reduced pressure and to the residue was added a saturated solution of sodium carbonate until the solution remained basic. The aqueous solution was then extracted with chloroform. The chloroform layer was dried over sodium sulphate and the chloroform evaporated under reduced pressure. 1.12 g. of a magenta coloured liquid were obtained.

$\nu_{max}$(Film) cm.$^{-1}$ 3280 (broad) (NH) 1660 (acetyl CO).

$\tau(CDCl_3)$ 1.5 d, 1p; 2.5 wide bulge, 1p; 2.9 m, 2p; 5.6 d, 2p;
7.5 s, 3p; 7.95 s, 3p.

Quaternisation of 2-methyl-4-acetylaminomethylpyridine (196).

The acetyl derivative (196) (1.1 g.) was boiled under reflux in acetone (25 ml.) for 3½ hr. with bromoacetone (2.0 g.). The solution was stood overnight and a buff solid crystallised from the solution. It was filtered off and recrystallised from an acetone/ethanol mixture to yield a white solid, 1-acetonyl-2-methyl-4-acetylaminomethylpyridinium bromide (197) 1.76 g. (87%) m.p. 197°.

Found: C, 47.4; H, 5.6; N, 8.9%

$C_{17}H_{17}BrN_2O_2$ requires: C, 47.8; H, 5.7; N, 9.3%

$\nu_{max}$(Nujol) cm.$^{-1}$ 3280 (NH), 1730 (acetonyl CO), 1665 (acetyl CO).

$\tau(D_2O)$ 1.35 d, 1p; 2.1 m, 2p; 4.15 s, 2p (exchanges slowly);
7.3 s, 3p; 7.5 s, 3p; 7.85 s, 3p.

$\tau$(T.F.A.) 1.2 m, 2p; 1.9 m, 2p; 4.1 s, 2p; 4.95 d J = 6 c/s, 2p;
7.2 s, 3p; 7.35 s, 3p; 7.45 s, 3p.

Cyclisation of 1-acetonyl-2-methyl-4-acetylaminomethylpyridinium bromide (197).

The quaternary compound (197) (0.5 g.) was heated on a steam bath with an aqueous sodium bicarbonate solution (40 ml., 10%) for $\frac{1}{2}$ hr. The initially yellow solution turned orange. The solution was extracted with ether and the ether layer dried over sodium sulphate, filtered, and the ether evaporated to leave 0.17 g. (51%) of 2-methyl-7-acetylaminomethyl-indolizine which crystallised from light petroleum (b.p. 60-80°) m.p. 158°.

$\nu_{max}$(Nujol) cm.$^{-1}$ 3300 (NH), 1650 (acetyl CO).

4-Nitro-2-methylpyridine-1-oxide (199).

2-Methylpyridine-1-oxide[129] was nitrated according to the method of Ochiai.[130]

4-Methoxy-2-methylpyridine (200).

4-Methoxy-2-methylpyridine (200) was prepared from 4-nitro-2-methylpyridine-1-oxide (199) by treatment with sodium methoxide to give

4-methoxy-2-methylpyridine-1-oxide which was converted to 4-methoxy-2-methylpyridine (200) by treatment with phosphorus trichloride.[131]

2-Methyl-7-methoxyindolizine (202).

4-Methoxy-2-methylpyridine (200) (6.81 g.) was added to acetone (20 ml.) together with bromoacetone (9.0 g.). After warming slightly a reaction commenced and it was allowed to go to completion. The solution was then warmed for a further 15 min. on a steam bath, cooled and filtered. The buff solid was washed with acetone. Yield 11.9 g. (83%) of 1-acetonyl-2-methyl-4-methoxypyridinium bromide (201) a deliquescent solid m.p. 146°.

$\nu_{max}$(Nujol) cm.$^{-1}$ 1725 (acetonyl CO)

$\tau$(T.F.A.) 1.4 d, 1p; 2.5 m, 2p; 4.2 s, 2p; 5.75 s, 3p; 7.3 s, 3p; 7.4 s, 3p.

The quaternary compound (201) (5.0 g.) was heated on a steam bath for 4 hr. with 10% sodium bicarbonate solution (50 ml.). After cooling, the solution was extracted with ether and the ether layer dried over sodium sulphate. The ether was evaporated on a steam bath and the residue crystallised from light petroleum (b.p. 40-60°) to yield 0.20 g. (7%) of 2-methyl-7-methoxyindolizine (202) m.p. 88-91°.

Found: C, 74.2; H, 6.65; N, 8.7%

$C_{10}H_{11}NO$ requires: C, 74.5; H, 6.9; N, 8.7%

$\nu_{max}$(Nujol) cm.$^{-1}$ 1650, 1525, 1250, 1220, 1025, 820, 780, 760, 710.

$\tau$($CCl_4$) 2.25 d J = 7 c/s, 1p; 3.05 s, 1p; 3.45 d J = 3 c/s, 1p; 3.8 m, 1p; 4.0 s, 1p; 6.2 s, 3p; 7.7 s, 3p.

Treatment of 2-methyl-7-methoxyindolizine (202) with sodium in ethanol.

2-Methyl-7-methoxyindolizine (0.1 g.) was boiled under reflux in absolute ethanol (20 ml.) and sodium (1.0 g.) was added pellet-wise down the condenser over a period of $\frac{1}{2}$ hr. After boiling for a further 1 hr. the solution was poured into water (250 ml.) and the aqueous solution extracted with ether. After drying over sodium sulphate the ether was evaporated and the residue taken up in deuterochloroform. A nuclear magnetic resonance spectrum was obtained.

$\tau$($CDCl_3$) 3.6 s; 4.15 s; 4.4 s; 6.3 m; 7.4 m; 7.9 s; 8.7 s (v broad); 9.05 s.

The spectrum indicates that reduction has occurred.

7-Methylindolizine (203).

7-Methylindolizine was prepared by the method of Armarego.[11]

$\tau$($CCl_4$, 2%) 2.1 d J = 7 c/s, 1p; 2.8 m, 2p; 3.3 m, 1p; 3.7 m, 2p; 7.7 s, 3p.

Ethyl 2-methylpyridine-3-carboxylate (207).

The ester was prepared by the method of Sato and Mishma.[132]

Ethyl aminocrotonate (204) 64.5 g. was dissolved in absolute ethanol (250 ml.) and piperidine (1.5 g.) was added. Acrolein (205) (33.5 g.) was added dropwise over 3 hr. with stirring, the temperature being maintained at 40-50° on a water bath. The mixture was then boiled under reflux for 3 hr. and then the ethanol and piperidine distilled off under reduced pressure to give a product which was distilled under reduced pressure b.p. 132° 0.6 mm of Hg pressure, 33.5 g. collected. The nuclear magnetic resonance spectrum of the product indicated that it was essentially the required product and that only a small amount of dihydro compound was present. It was crystallised from light petroleum (b.p. 40-60°).

$\nu_{max}(CCl_4)$ cm.$^{-1}$ 1725 (ester CO)

$\tau(CCl_4)$ 1.5 m, 1p; 1.9 m, 1p; 2.9 m, 1p; 5.7 q J = 7 c/s, 2p; 7.34 s, 3p; 8.65 t, J = 7 c/s, 3p.

Quaternisation

The ester (207) (6.0 g.) was boiled under reflux in absolute ethanol (50 ml.) with bromoacetone (5.0 g.) for 5 hr. The solvent was removed under reduced pressure and ethyl acetate was added. A thick gum resulted which would not solidify. The ethyl acetate was decanted from the product and the last traces removed under reduced pressure. The product was taken up in water and the solution washed with ether.

After removal of the water under reduced pressure the quaternary compound (208) was still a gum.

$\nu_{max}$(Film) cm.$^{-1}$ 1720 (broad peak)

Cyclisation

The quaternary compound (208) was heated for 4 hr. on a steam bath in a saturated solution of sodium bicarbonate. The aqueous solution was extracted with chloroform and the chloroform extracts dried over sodium sulphate. After the solvent had been evaporated under reduced pressure 0.64 g. of a brown liquid remained. Nuclear magnetic resonance, infrared and mass spectra indicated that it was ethyl-2-methylindolizine-8-carboxylate (209).

$\nu_{max}$(Film) cm.$^{-1}$ 1705 (ester CO)

$\tau$($CCl_4$) 2.15 d, 1p; 2.6 m, 1p; 2.95 s (broad) 1p; 3.2 s (broad), 1p; 3.7 m, 1p; 5.65 q J = 7 c/s 2p; 7.7 s, 3p; 8.6 t J = 7 c/s, 3p.

The aqueous solution after chloroform extraction was acidified with hydrochloric acid (20%) and again extracted with chloroform. After the solvent had been evaporated under reduced pressure there remained a yellow solid 0.9 g. m.p. > 300° (decomp.). Nuclear magnetic resonance, infrared and mass spectra indicated that it was 2-methylindolizine-8-carboxylic acid (210).

$\nu_{max}$(Nujol) cm.$^{-1}$ 1665 (broad) (acid CO).

$\tau$ (T.F.A.) 0.9 m, 2p; 2.1 m, 2p; 4.45 s, 2p; 7.45 s, 3p.

8-Methylindolizine.

The method employed was as described for the preparation of indolizine-2-carboxylic acid by Borrows and Holland[32] but 2,3 lutidine was used. The acid was decarboxylated as described by Diels and Alder.[29,30]

Dimethylindolizines.

The method employed to prepare 2,5-, 2,6-, 2,7- and 2,8-dimethylindolizine is described fully for 2,5-dimethylindolizine. The others were prepared in a similar fashion.

2,5-Dimethylindolizine.

2,6 Lutidine (10.7 g.) and bromoacetone (14.0 g.) were boiled under reflux in absolute ethanol (100 ml.) for 6 hr. The ethanol was evaporated under reduced pressure to leave a crude product which was crystallised from acetone to which 5% ethanol had been added. Yield 6.7 g. of 1-acetonyl-2,6-dimethylpyridinium bromide a white crystalline solid, m.p. 194°.

Found: C, 49.4; H, 5.8; N, 5.8%

Calculated for $C_{10}H_{14}BrNO$: C, 49.2; H, 5.7; N, 5.7%

$\nu_{max}$(Nujol) cm.$^{-1}$ 1720 (acetonyl CO)

$\tau$(T.F.A.) 1.55 m, 1p; 2.05 m, 2p; 4.05 s, 2p; 7.2 s, 6p; 7.3 s, 3p.

1-Acetonyl-2,6-dimethylpyridinium bromide (2.0 g.) was heated on a steam bath for $\frac{1}{2}$ hr with 10% sodium bicarbonate solution (50 ml.). The solution was extracted with ether and the ether solution dried over sodium sulphate. The ether was evaporated to leave a dark liquid (0.32 g.). The product was distilled and two fractions were collected.

(1) b.p. 40° at 15 mm Hg pressure shown to be 2,6 lutidine.

(2) b.p. 116° at 15 mm pale yellow liquid 2,5-dimethylindolizine.

$\tau$ ($CCl_4$) 2.8 d J = 9 c/s, 1p; 3.05 s (broad), 1p; 3.1 - 3.9, 3p; 7.6 s, 3p; 7.65 s, 3p.

$\tau$ (T.F.A.) 1.5 m, 1p; 2.0 - 2.4 m, 2p; 2.96 s (broad) 1p; 4.7 s, 2p; 7.1 s, 3p; 7.5 s, 3p.

$\lambda_{max}$ (95% EtOH) m$\mu$ (log $\varepsilon$) 215 (4.08), 238 (4.34), 267 (3.60), 274 (3.56), 287 (3.47), 299 (3.56), 335 (3.28).

2,6-Dimethylindolizine.

1-Acetonyl 2,5 dimethylpyridinium bromide

$\nu_{max}$ (Nujol) cm.$^{-1}$ 1722 (acetonyl CO)

$\tau$ (T.F.A.) 1.4 - 2.2, 3p; 4.1 s, 2p; 7.25 s, 3p; 7.37 s, 6p.

2,6-Dimethylindolizine

$\tau$ ($CCl_4$) 2.45 s (broad), 1p; 2.86 d J = 9 c/s, 1p; 3.05 s, 1p; 3.6 m, 1p; 3.9 s, 1p; 7.74 s, 3p; 7.83 s, 3p.

$\tau$(T.F.A.) 1.25 s (broad), 1p; 1.65 d J = 8 c/s, 1p; 2.15 d J = 8 c/s, 1p; 3.12 s (broad), 1p; 4.6 s, 2p; 7.4 s, 3p; 7.6 s, 3p.

$\lambda_{max}$(95% EtOH) m$\mu$ (log $\varepsilon$) 218 (4.06), 243 (4.40), 285 (3.22), 292 (3.32), 303 (3.29), 345 (3.29).

2,7-Dimethylindolizine.

1-Acetonyl-2,4-dimethylpyridinium bromide

$\nu_{max}$(Nujol) cm.$^{-1}$ 1725 (acetonyl CO)

$\tau$(T.F.A.) 1.3 d, 1p; 2.05 m, 2p; 4.07 s, 2p; 7.3 m, 9p.

2,7-Dimethylindolizine

$\tau$($CCl_4$) 2.38 d J = 7 c/s, 1p; 3.05 s (broad), 2p; 3.9 m, 2p; 7.72 s, 3p; 7.78 s, 3p.

$\lambda_{max}$(95% EtOH) m$\mu$ (log $\varepsilon$) 217 (4.14), 242 (4.52), 280 (3.46), 287 (3.54), 300 (3.59), 345 (3.31).

2,8-Dimethylindolizine.

1-Acetonyl-2,3-dimethylpyridinium bromide

$\nu_{max}$(Nujol) cm.$^{-1}$ 1735 (acetonyl CO).

$\tau$(T.F.A.) 1.4 m, 2p; 2.0 m, 1p; 3.95 s, 2p; 7.3 m, 9p.

2,8-Dimethylindolizine distilled at 120° at 20 mm Hg pressure.

$\tau$($CCl_4$) 2.45 d J = 6 c/s, 1p; 3.05 s (broad), 1p; 3.75 m, 3p; 7.7 s, 6p.

$\tau$(T.F.A.) 1.2 d J = 6 c/s, 1p; 1.7 d J = 8 c/s, 1p; 2.3 m, 1p;
3.0 s (broad), 1p; 4.5 s, 2p; 7.35 s, 3p; 7.56 s, 3p.

$\lambda_{max}$(95% EtOH) m$\mu$ (log $\varepsilon$) 239 (4.56), 278 (3.38), 286 (3.50),
298 (3.58), 337 (3.42).

1,2-Dimethylindolizine.

Prepared by the method of Holland and Nayler[18].

1-Acetonyl-2-ethylpyridinium bromide

$\nu_{max}$(Nujol) cm.$^{-1}$ 1725 (acetonyl CO)

$\tau$(T.F.A.) 1.0 - 2.0, 4p; 3.95 s, 2p; 6.9 q J = 7 c/s, 2p;
7.32 s, 3p; 8.5 t J = 7 c/s, 3p.

1,2-Dimethylindolizine

$\tau$($CCl_4$) 2.3 d, J = 7 c/s, 1p; 2.75 d J = 9 c/s, 1p; 2.97 s, 1p;
3.6 - 3.9 m, 2p; 7.75 s, 6p.

$\tau$ (T.F.A.) 1.0 d J = 7 c/s, 1p; 1.36 m, 1p; 2.0 m, 2p; 4.6 s, 2p; 7.65 m, 6p.

2,3-Dimethylindolizine.

Prepared by the method of Holland and Nayler.[18]

2-Methyl-1-(1-methyl-2-oxopropyl)pyridinium bromide.

$\tau$(T.F.A.) 1.0 - 2.0, 4p; 3.75 q J = 8 c/s, 1p; 7.05 s, 3p; 7.33 s, 3p;
7.75 d J = 8 c/s, 3p.

2,3-Dimethylindolizine.

$\tau(CCl_4)$ 2.1 - 3.8, 5p; 7.7 s (broad), 6p.

3,5-Dimethylindolizine.

Prepared by the Scholtz synthesis as described by Armarego.[11]

## Reductions using sodium and ethanol

Indolizine (12).

Indolizine (12) (3.0 g.) was boiled under reflux in absolute ethanol and sodium (5.0 g.) was added pellet-wise down the condenser over a period of $\frac{1}{2}$ hr. The solution was boiled under reflux for a further 1 hr. and then poured into an excess of water. The aqueous solution was extracted with ether and the ether layer dried over sodium sulphate. The solvent was evaporated leaving a liquid (1.61 g.). It was distilled under an atmosphere of nitrogen b.p. $94^{\circ}$ at 15 mm of Hg pressure. The nuclear magnetic resonance spectrum was not altered by distilling the liquid. Vapour phase chromatography indicated that it was a mixture. The nuclear magnetic resonance spectrum is shown in Figure 9.

$\nu_{max}$(Film) cm.$^{-1}$ 3100, 3045, 1650, 1625

$\lambda_{max}$ (95% EtOH) m$\mu$ 206, 236, 282.

(a) The mixture was dissolved in 95% ethanol (50 ml.) and hydrogenated under 1 atmosphere of hydrogen using a 10% palladium on charcoal catalyst until no more hydrogen was taken up. The product was 5,6,7,8-tetrahydroindolizine (212).

(b) The reduction in ethanol using sodium was repeated on 6 g. of indolizine to yield, after distillation, 1.7 g. of a mixture. The mixture was again subjected to reducing conditions in ethanol (50 ml.) and 7.8 g. of sodium were added. The product was 1.0 g. (16%) of 5,6,7,8-tetrahydroindolizine (212) b.p. $84^{o}$ at 15 mm Hg pressure.

Found: C, 79.3; H, 9.2; N, 11.4%

Calculated for $C_8H_{11}N$: C, 79.3; H, 9.2; N, 11.6%

The nuclear magnetic resonance spectrum is shown in Figure 10.

$\nu_{max}$(Film) $cm.^{-1}$ 3100, 1330, 1250, 1160, 1130.

$\lambda_{max}$ $m\mu$ (log $\varepsilon$) 207 (3.71), 221 (3.76). (95% EtOH)

2,6-Dimethylindolizine.

Reduction of 2,6-dimethylindolizine (0.79 g.) in ethanol (25 ml.) with sodium (1.3 g.) by the method outlined above gave 0.51 g. of a yellow liquid. Vapour phase chromatography showed it was a mixture. The mixture was again treated with sodium and ethanol until the nuclear magnetic resonance spectrum indicated that no starting material remained.

$\tau(CCl_4)$ 3.6 s, 1p; 4.35 m, 2p; 5.7 s (broad), 2p; 6.7 s (broad), 2p; 8.0 s, 3p; 8.2 s (broad), 3p.

$\nu_{max}$(Film) cm.$^{-1}$ 3090, 3040, 1685.

$\lambda_{max}$ (95% Ethanol) m$\mu$ (log $\varepsilon$) 208 (3.81), ~ 230 (3.69).

2,7-Dimethylindolizine.

2,7-Dimethylindolizine (0.7 g.) was reduced in ethanol (25 ml.) using sodium (1.5 g.). The product was an olive green liquid which contained starting material. The process of reduction was repeated until no starting material remained.

$\tau(CCl_4)$ 3.8 d; 4.4 s; 5.6 s (broad); 6.2 t J = 7 c/s; 6.8 m; 7.7 m; 8.0 s; 8.15 s (broad).

$\nu_{max}$(Film) 3090, 3040, 1695, 1645.

$\lambda_{max}$ (95% Ethanol) m$\mu$ 207, 237, 289, 300.

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