SYNTHESIS AND CONFORMATIONAL STUDIES OF INDOLIZINES

THESIS

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ABSTRACT

The present investigation has involved a kinetic and mechanistic study of the thermal cyclization of 3-acetoxy-3-(2-pyridyl)-2-methylenepropanoate esters and related compounds to 2-substituted indolizines. Substrates for the kinetic study were prepared *via* the Baylis-Hillmann reaction of pyridine-2-carboxaldehydes with acrylate esters, acrylonitrile and methyl vinyl ketone. The resulting hydroxy compounds were then acetylated to afford the acetoxy derivatives, thermal cyclization of which gave the corresponding 2-substituted indolizines. The cyclization reactions was followed using ^{1}H NMR spectroscopy and were shown to follow first-order kinetics. The influence of the various substituents on the observed first-order rate constants has been examined and variable temperature studies have permitted evaluation of activation parameters for the formation of methyl indolizine-2-carboxylate and ethyl indolizine-2-carboxylate.

An alternative route to 2-substituted indolizines *via* halogenated derivatives was explored and several halogenated 2-pyridyl derivatives were synthesised and their thermal cyclization to indolizines was attempted.

Novel 5-methylindolizine-2-carboxamides were prepared as part of this investigation and dynamic NMR spectroscopy was used to study internal rotation about the amide N-CO bond in these compounds.

CONTENTS

ACKNOWLEDGEMENTS

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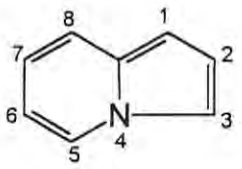
Finally, it would be churlish of me not to appreciate the encouragement and support shown by my parents throughout my studies. To them, this is dedicated with gratitude and love.

1. INTRODUCTION

1.1 HISTORICAL BACKGROUND

The history of indolizine goes back to 1890 when an Italian chemist,Angeli,[1] reported the preparation of the imine-anhydride (**1**) of pyrroylpyruvic acid and suggested the name pyrindole for the completely unsaturated parent base (**2**). Twenty-two years later, in 1912, Scholtz [1] reported the first synthesis of compound (**2**). He treated 2-methylpyridine with acetic anhydride at 200-220°C to give what he called "picolide", acid hydrolysis of which afforded a colourless crystalline solid [subsequently identified as compound (**2**)] which had weakly basic properties. In view of this observation, it was speculated that this compound could not be a true derivative of pyridine. Furthermore,this new compound gave reactions characteristic of pyrroles and indoles and had the same empirical formula (C_8H_7N) as indole and isoindole. In light of these observations, Scholtz ascribed the pyrrolopyridine structure (**2**) to his new compound and named it pyrrocoline, but later adopted the name pyrindole as suggested by Angeli. The validity of Scholtz's formulation was confirmed by Diels and Alder,[1] who established the presence of four double bonds by catalytic reduction of indolizine to a derivative (**3**), which on treatment with cyanogen bromide gave a product shown to be identical in all respects with α-coniceine (**4**) previously prepared by Loffler *et al.* Today, the compound previously known as pyrrocoline or pyrindole,is known as indolizine with the following numbering:-



1.2 SYNTHESIS OF INDOLIZINES

Generally speaking, there are three major approaches to indolizine synthesis,*viz.*, (i) condensation reactions; (ii) 1,3-dipolar cycloadditions; and (iii) 1,5-dipolar cycloadditions.

1.2.1 SYNTHESIS OF INDOLIZINES BY CONDENSATION REACTIONS

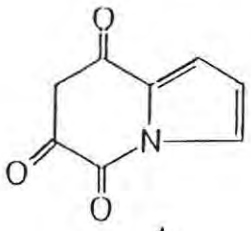
1.2.1.1 SYNTHESIS OF INDOLIZINES BY REACTIONS OF 2-METHYLPYRIDINE AND IT'S DERIVATIVES WITH ACETIC ANHYDRIDE (Scholtz reaction).

Sholtz's synthesis[1] of the first indolizine simply involved treating 2-methylpyridine with acetic anhydride at very high temperature to yield a crystalline compound, which he called "picolide" and which,upon hydrolysis,afforded the indolizine (**2**) (Scheme 1,p 4). The principal difficulty Scholtz faced was in elucidating the structure of "picolide" and in rationalising it's formation. The presence of one carbonyl group in "picolide" was clearly established by the formation of oxime, hydrazone and semicarbazone derivatives. However, it did not give any reactions typical of aldehydes. Furthermore," picolide" was found to possess only feeble basic properties. Taking into account the above observations, Scholtz and Fraude[1] speculated that the nitrogen was acylated and proposed the most suitable structure for "picolide"to be

1-acetyl-2-methyl-4-ketopyrridocoline (**5**). If"picolide" were to have the above-mentioned structure, it would be necessary for it to undergo a complicated initial cleavage, followed by ring closure to a 5-membered pyrrole in order to explain satisfactorily the formation of indolizine (**2**) upon its hydrolysis. Moreover, this structure did not explain the observed formation of " picolide" from the reaction of one mole of propionic anhydride with 2-methylpyridine, and consequently,it was suggested that "picolide" be assigned structure (**6**) (Scheme 2,p 5). However, Tshitschibabin and Stepanow[1] doubted the validity of Scholtz's conclusions and,in 1929, they re-investigated the synthesis and formulated "picolide" as 1,3-diacetylindolizine (**11**) (see Scheme 3,p 5). Since 1929, the Scholtz reaction has gained widespread popularity and has been adopted as a general route to indolizines.

1.2.1.2 SYNTHESIS OF INDOLIZINES BY RING CLOSURE OF THE PYRIDINIUM SALTS (Tschitschibabin reaction).

A novel approach to the synthesis of 2-substituted indolizines was developed, in 1927, by Tschitschibabin.[2] He speculated the existence of tautomerism in α- and ß-alkylated pyridines and suggested that if, for instance,2-methylpyridine (**12**) and an α-halogenoketone were reacted in the presence of an alkali, 2-methylpyridine could react as the aromatic system (**12**) or as it's tautomer (**13**); reaction in the latter form (**13**) would then present good possibilities for ring



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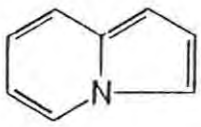

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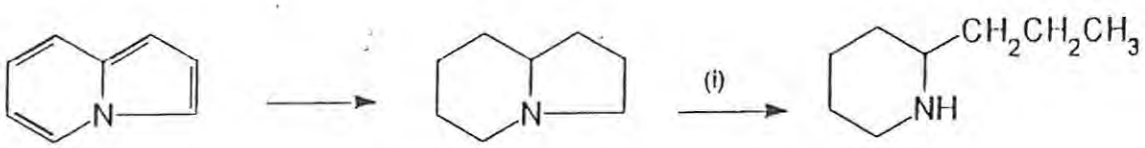
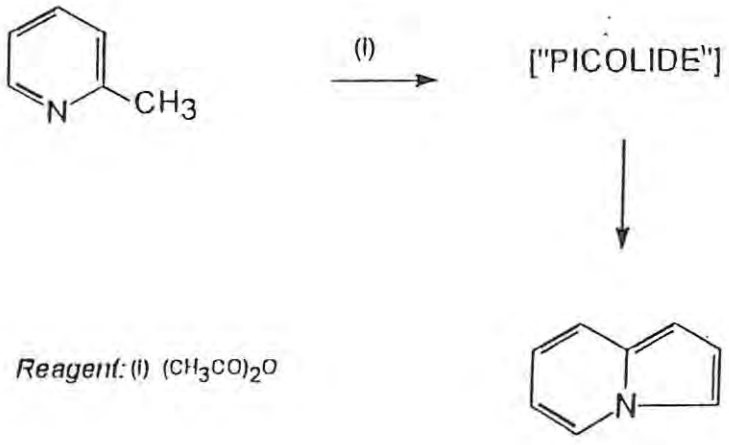


2 3 4

Reagent: (i) CYANOGEN BROMIDE

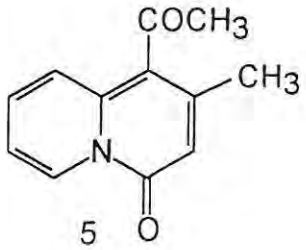
SCHEME 1



Reagent: (i) $(CH_3CO)_2O$

2

4



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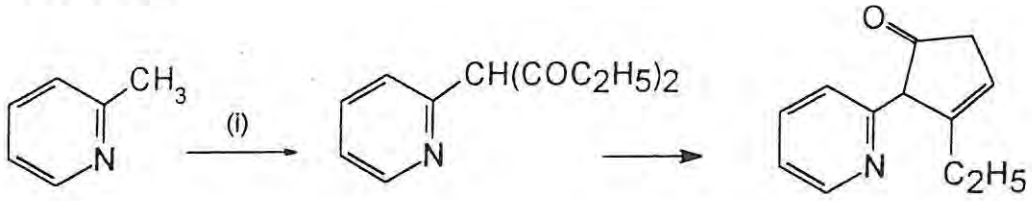
SCHEME 2



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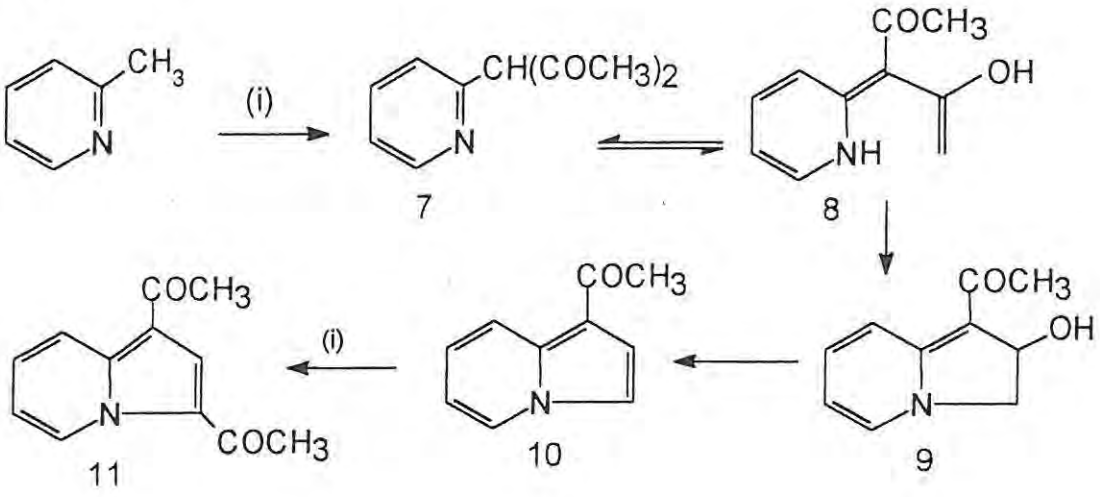
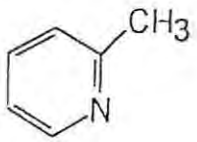
Reagent : (i) $(C_2H_5CO)_2O$

SCHEME 3



Reagent: (i) $(CH_3CO)_2O$

closure, analogous to that observed for compound **(14)** (Scheme 4,p 7). Speculative as this was,it led to the successful synthesis of 2-substituted indolizines **(17)** *via* cyclization of quaternary pyridinium salts **(16)** (Scheme 5,p 7). This approach was fully exploited and several 2-alkyl- and 2-aryl-indolizines were synthesised. Krohnke *et al*,[1] demonstrated that quaternary compounds would react with bases of suitable strength to afford "enol-betaines" which then undergo "acid cleavage" losing an acyl group. In view of this observation, these authors suggested formation of an "enol-betaine" as an intermediate in the Tshitshibabin reaction,ring closure of which would afford an indolizine (Scheme 5,p 7). However, before long, certain drawbacks become apparent. When α-halogenenated aldehydes were used, the quaternary salts were not very easily formed and did not always cyclize to form the required indolizines.[1] In 1965, Wibberly and co-workers [3] observed that the Tshitschibabin reaction of ethyl 2-quinolylacetate with phenacyl bromide afforded 2-ethoxycarbonylmethylene-1-phenacyl-1,2-dihydroquinoline **(18)** which, upon treatment with sodium bicarbonate,did not undergo ring closure as expected. Nevertheless,when treated with boiling acetic anhydride,compound **(18)** underwent an intramolecular aldol type condensation to afford the benzindolizine **(19)**.[4]



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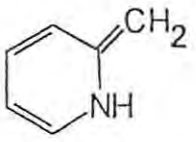
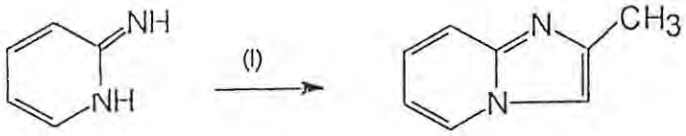


13

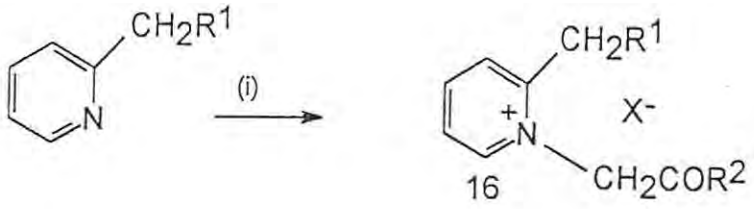
SCHEME 4



14 15

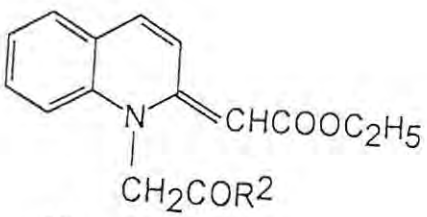
Reagents : (i) $BrCH_2COCH_3$

SCHEME 5



Reagent : (i) R^2COCH_2X.

17



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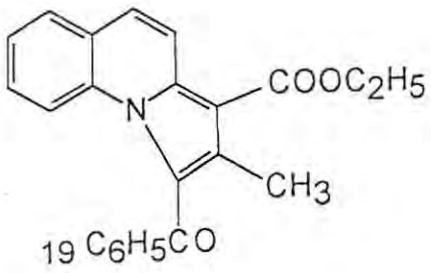


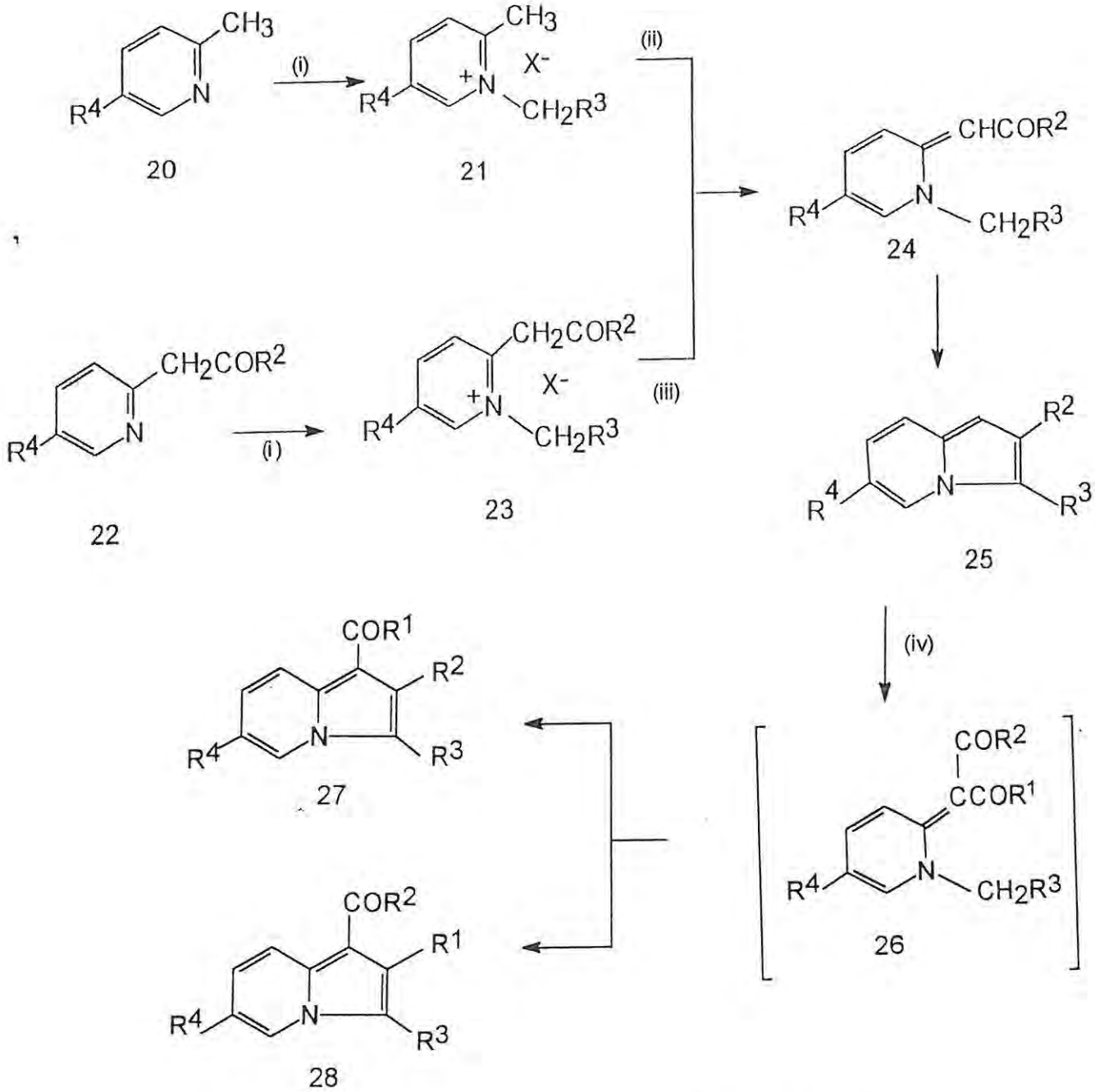
19 C_6H_5CO

This modified Tshitschibabin indolizine synthesis was successfully extended to the synthesis of the indolizines (**25**), (**27**) and (**28**) from the intramolecular aldol type condensation of the corresponding acyl methines (**24**) (Scheme 6,p 9).[5] In 1946, Borrows and co-workers[6,7] attempted the synthesis of acyl- and alkoxycarbonyl indolizines from α-halogeno-ß-diketones and α-halogeno-ß-ketoesters using Tshitschibabin's method. However,they could not form the quaternary salt,and the attempt failed. Almost two decades later, Bragg and Wibberly[8] successfully synthesised ethyl 3-acetyl-2-methylindolizine-1-carboxylate and diethyl 2-methylindolizine-1,3-dicarboxylate from ethyl chloroacetate and 3-chloro-pentane-2,4-dione, using a method which did not require isolation of the quaternary salt. Bragg and Wibberly also synthesised alkyl- and arylindolizine-1-carboxylates from α-halogenoketones and ethyl 2-pyridylacetate.[8] When they treated phenacyl bromide with ethyl 2-pyridylacetate (**29**),ethyl 2-pyridylacetate hydrogen bromide (**30**), instead of the quaternary salt was formed from which the ethyl 2-phenylindolizine (**31**) crystallised (Scheme 7,p 10). From the above results,the authors suggested that a part of the ester was behaving as a base,removing hydrogen bromide and leading to ring closure. This approach opened new doors to indolizine synthesis.

1.2.1.3 SYNTHESIS OF INDOLIZINES BY RING CLOSURE OF 3-(2-PYRIDYL)-1-PROPANOLS AND THEIR ANALOGUES

In 1955,Boekelheide and co-workers[9] treated 3-(2-quinolyl)-1,2-propanediol (**32**) with

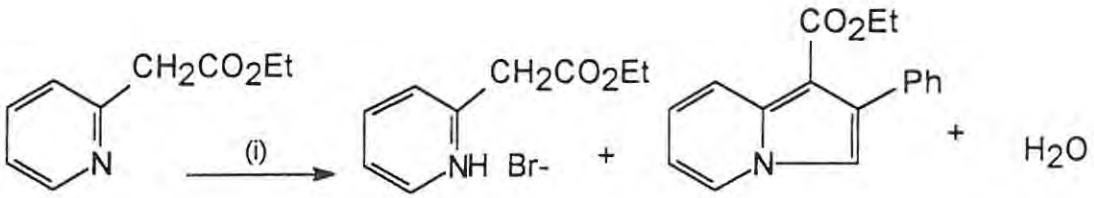
SCHEME 6



Reagents : (i) R^3CH_2X ; (ii) R^2COCl / NaOH ;

(iii) NaOH ; (iv) $(R^1CO_2)O$ / HEAT.

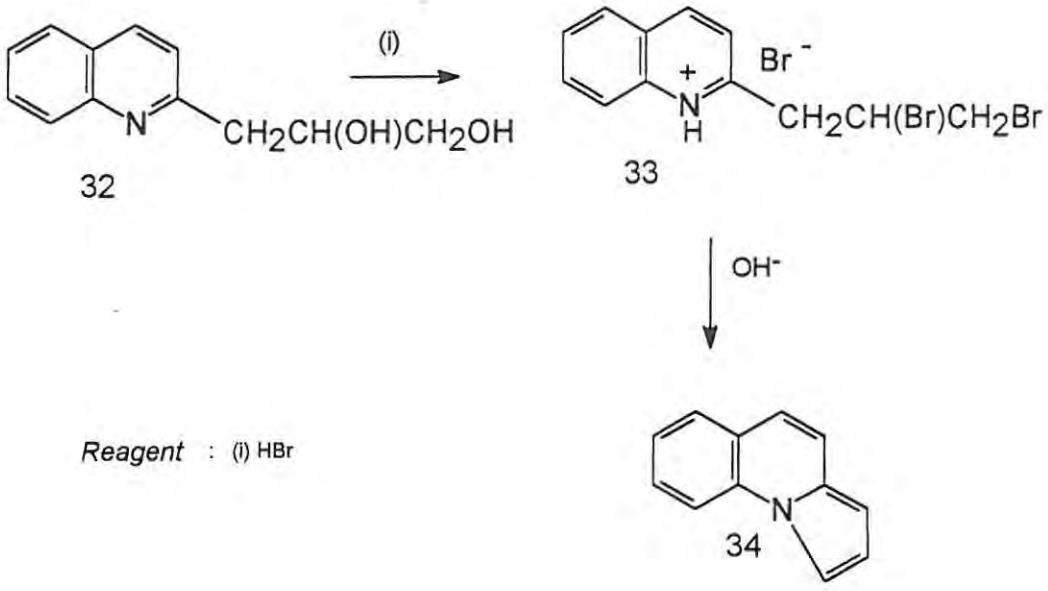
SCHEME 7



29 30 31

Reagent: (i) PHENACYL BROMIDE

SCHEME 8



32 33 34

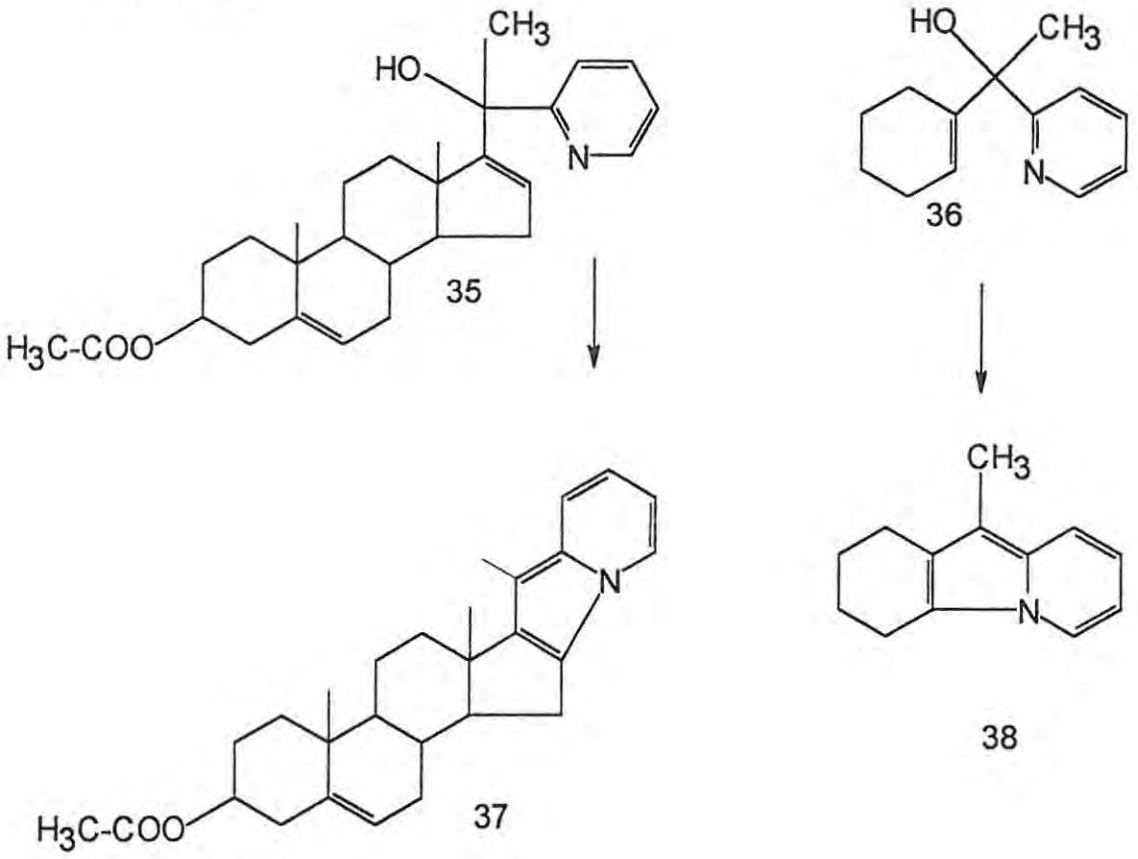
Reagent : (i) HBr

hydrobromic acid and subjected the product (**33**) to steam distillation from alkali to afford 5,6-benzindolizine (**34**) in very high yield (Scheme 8,p 10). This remarkable success caught the interest of chemists all over the world. A year later,two German chemists Hoffmann and Heer,[2] successfully extended this novel approach to the synthesis of the highly substituted indolizines (**37**) and (**38**) from the unsaturated alcohols (**35**) and (**36**) (Scheme 9,p 12).

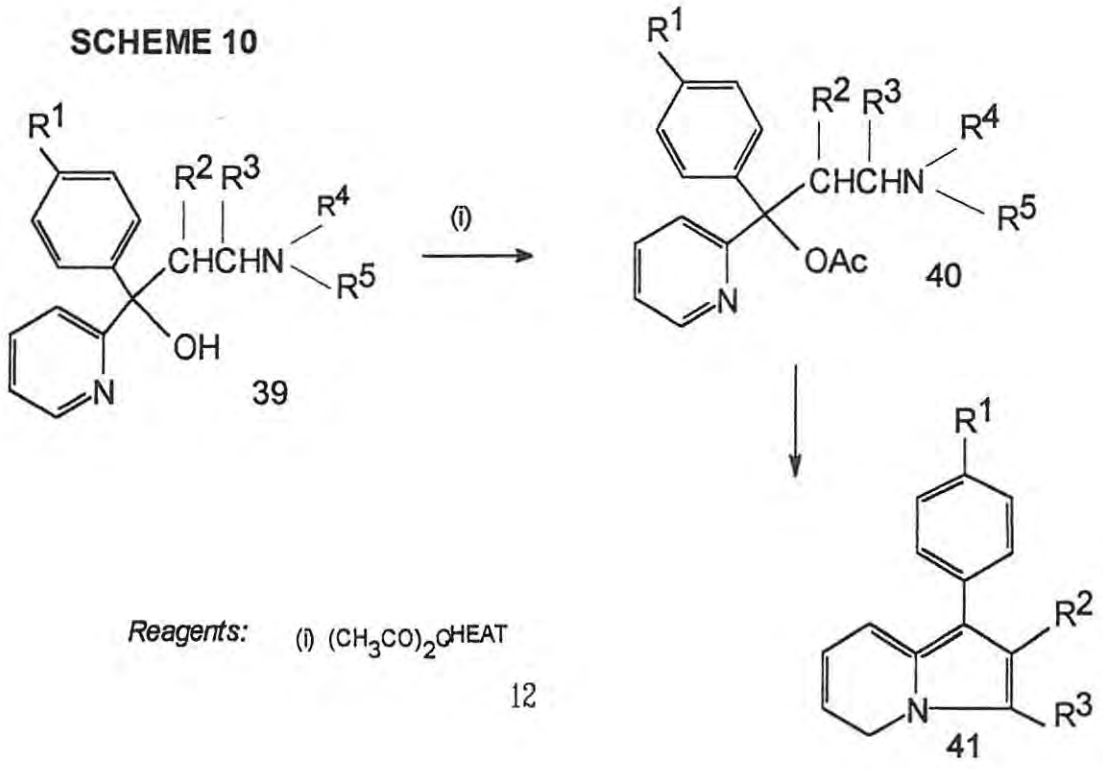
During the next two years, Barret *et al.*,[10] re-investigated Boekelheide's method and conclusively established the ability of amino groups to act as good leaving groups. When they refluxed 3-amino-1-aryl-1-(2-pyridyl)-alkan-1-ols (**39**) with acetic anhydride, compounds (**40**) formed, which cyclised with the elimination of the amino and acetoxy groups to afford the 1-arylindolizines (**41**) (Scheme 10,p 12). This approach was used to synthesise several indolizines including some azaindolizines in high yield.[11,12]

Before 1957, many chemists like Scholtz,[1] Borrows and Holland,[13] Diels and Alder,[2] to mention a few, had reported the synthesis of the parent indolizine (**2**), but never in satisfactory yield. Boekelheide and co-workers[2] subsequently synthesised the parent indolizine with an overall yield of 35% from 2-(3-hydroxypropyl)-pyridine-*N*-oxide (**42**) (Scheme 11,p 13); not long after, Boekelheide and Windgassen Jr, bettered this yield.[14] They found that pyrolysis of

SCHEME 9

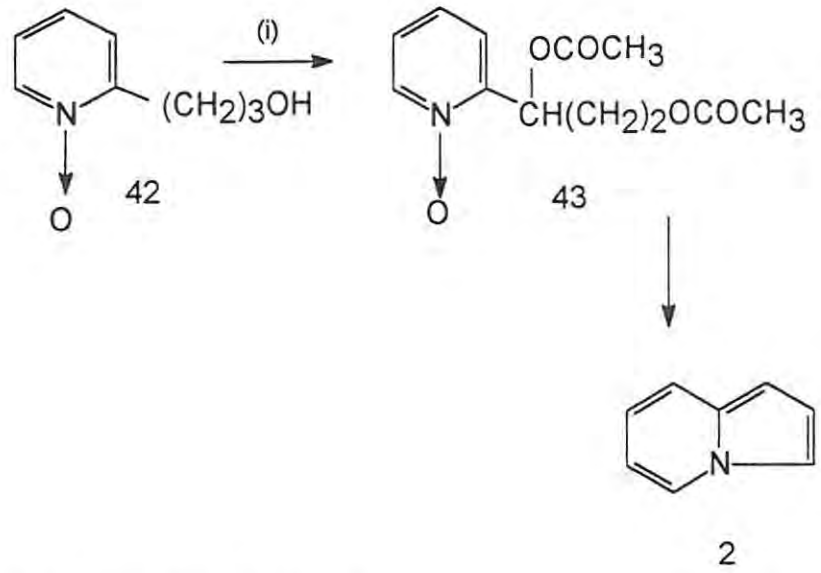


SCHEME 10



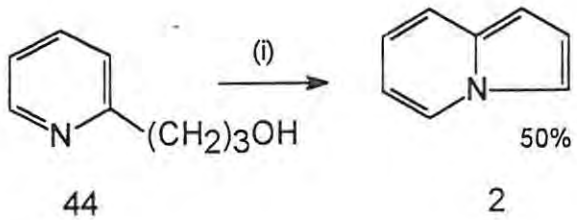
Reagents: (i) $(CH_3CO)_2O$HEAT

SCHEME 11



Reagent: (i) $(CH_3CO)_2O$, HEAT

SCHEME 12



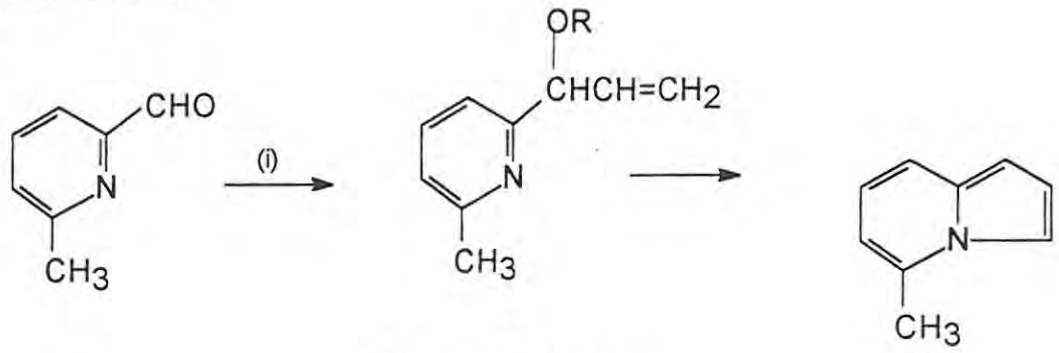
Reagent: (i) Pd/C, 280^0C.

the easily available 3-(2-pyridyl)-1-propanol **(44)** at 280°C in the presence of palladium-carbon afforded indolizine **(2)** in 50% yield (Scheme 12,p 13). Boekelheide and co-workers, [14] also developed methods for synthesising indolizines with no substituents on the 5-membered ring. For example, they treated 6-methylpyridine-2-carboxaldehyde **(45)** with vinylmagnesium bromide to give (in 68% yield) the vinyl alcohol **(46; R=H)**, which was acetylated and the resulting acetate was then subjected to pyrolysis at 450°C to afford the 5-methyl indolizine **(45)** (Scheme 13,p 15).

1.2.1.4 SYNTHESIS OF INDOLIZINES BY CONDENSATION REACTIONS OF HETEROCYCLIC NITROGEN COMPOUNDS WITH ACETYLENIC AND OLEFINIC COMPOUNDS.

This approach was first introduced by Diels and co-workers [2] in 1932. They isolated indolizines **(50)** and **(51)** from the intermolecular condensation of pyridine with acetylene dicarboxylate **(48)** (Scheme 14,p 15). This approach aroused the interest of Wiley and Knabeshuch [15] and, in 1953,they synthesised the indolizine derivative **(52)** in 29% yield, from 3-methylpyridine and acetylene dicarboxylate (Scheme 15,p 16). Seven years later, Acheson and Taylor,[16] tried the same reaction under different conditions,without much success. They only managed to synthesise the indolizine **(53)** in 6% yield (Scheme 16,p 16). Of particular relevance is a report published in 1968 by Robinson and Acheson,[17] in which they related the

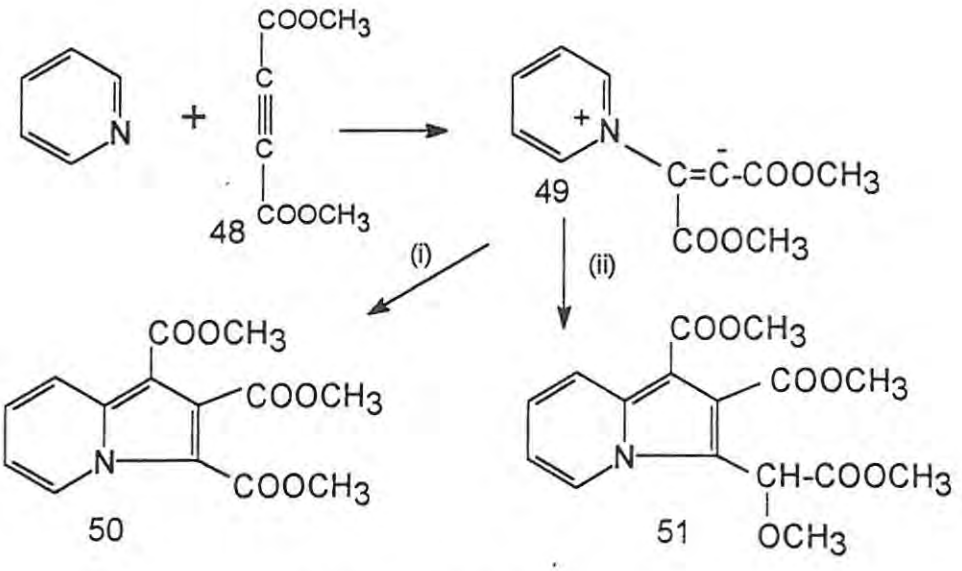
SCHEME 13



45 46 (R=H, $COCH_3$) 47

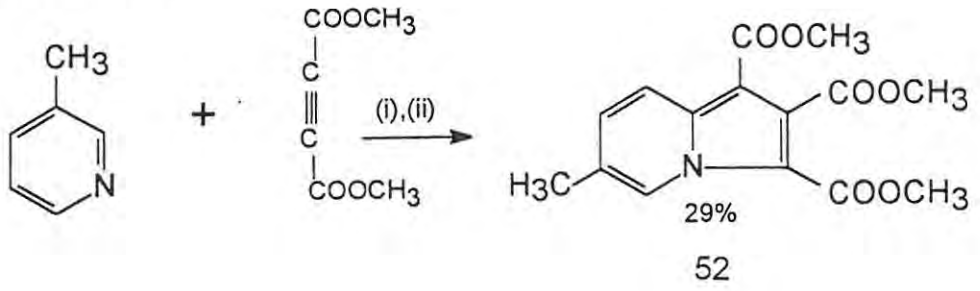
Reagent: (i) $CH_2{=}CH\text{-}MgBr$

SCHEME 14



Reaction conditions : (i) in Et_2O ; (ii) in MeOH

SCHEME 15

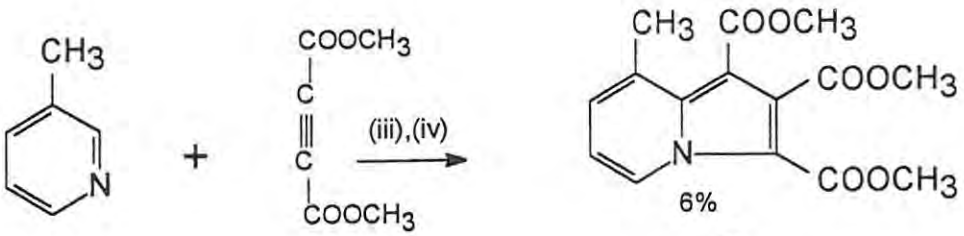


52

Reaction conditions: (i) -78^{0}C/ 1h ;

(ii) -20 ^{0}C / 72 h /Et_2O

SCHEME 16



53

Reaction conditions: (iii) r.t / 15 h/Et_2O;

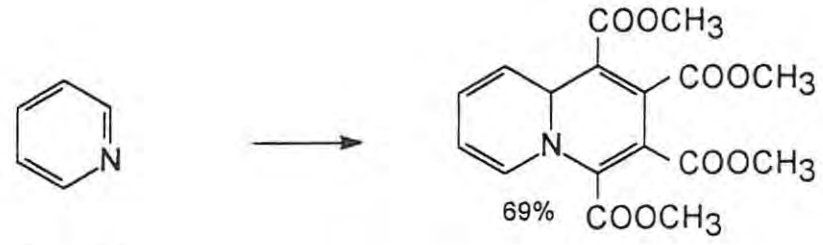
(IV) 100^{0}C / 2M HNO_3

basicities of pyridines to their reactivity towards dimethyl acetylene-dicarboxylate. It was found that when pyridine (pKa value 5.2) was used in the reaction,a quinolizine derivative **(54)** was formed (Scheme 17,p 18). However,when 4-cyano pyridine was used which has a much lower pKa value (1.90), trimethyl 7-cyano-1,2,3-indolizine tricarboxylate **(55)** was synthesised (Scheme 17,p 18). When pyridines with pKa values lower than 1.45 were used,no reaction took place at all. In 1966,Acheson and co-workers,[18] synthesised dimethyl dibenzo indolizine-2,3-dicarboxylates **(58)** from the condensation reaction of phenanthridine 5-oxide **(56)** and dimethyl acetylenedicarboxylate. Compound **(57)** was the intermediate which, on sublimation, cyclised to **(58)** from which the first parent heterocycle **(59)** (R=H) was prepared, although derivatives of this novel heterocycle were known from 1962 (Scheme 18,p 18).

1.2.1.5 SYNTHESIS OF INDOLIZINES USING MISCELLANEOUS CONDENSATION REACTIONS.

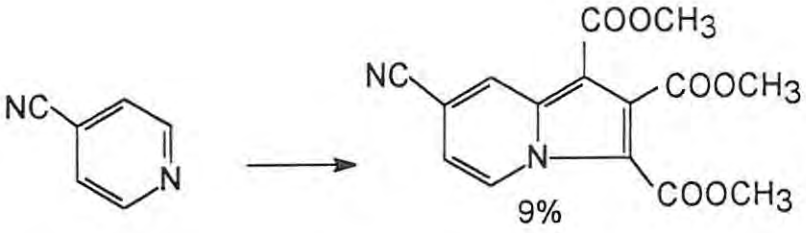
Michael condensation of compounds of the type **(60)** with α,ß-unsaturated compounds provides another general route to indolizine synthesis. This method was introduced as early as 1953 by Boekelheide and co-workers.[19] The authors observed that when acrylonitrile was used,the corresponding 3-substituted 2-amino carbonylbenzindolizine **(61)** were formed (Scheme 19,p 19). On the other hand, when 2-vinylpyridine or ethyl acrylate were used, ketones of the type

SCHEME 17



pKa= 5.2

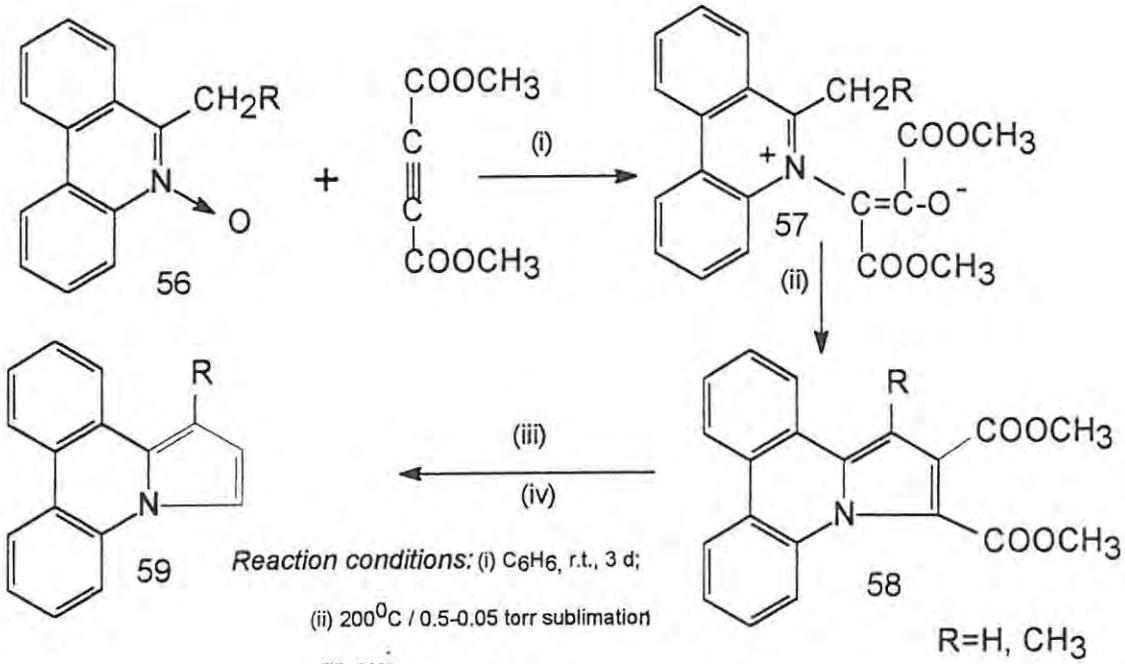
54



pKa = 1.90

55

SCHEME 18



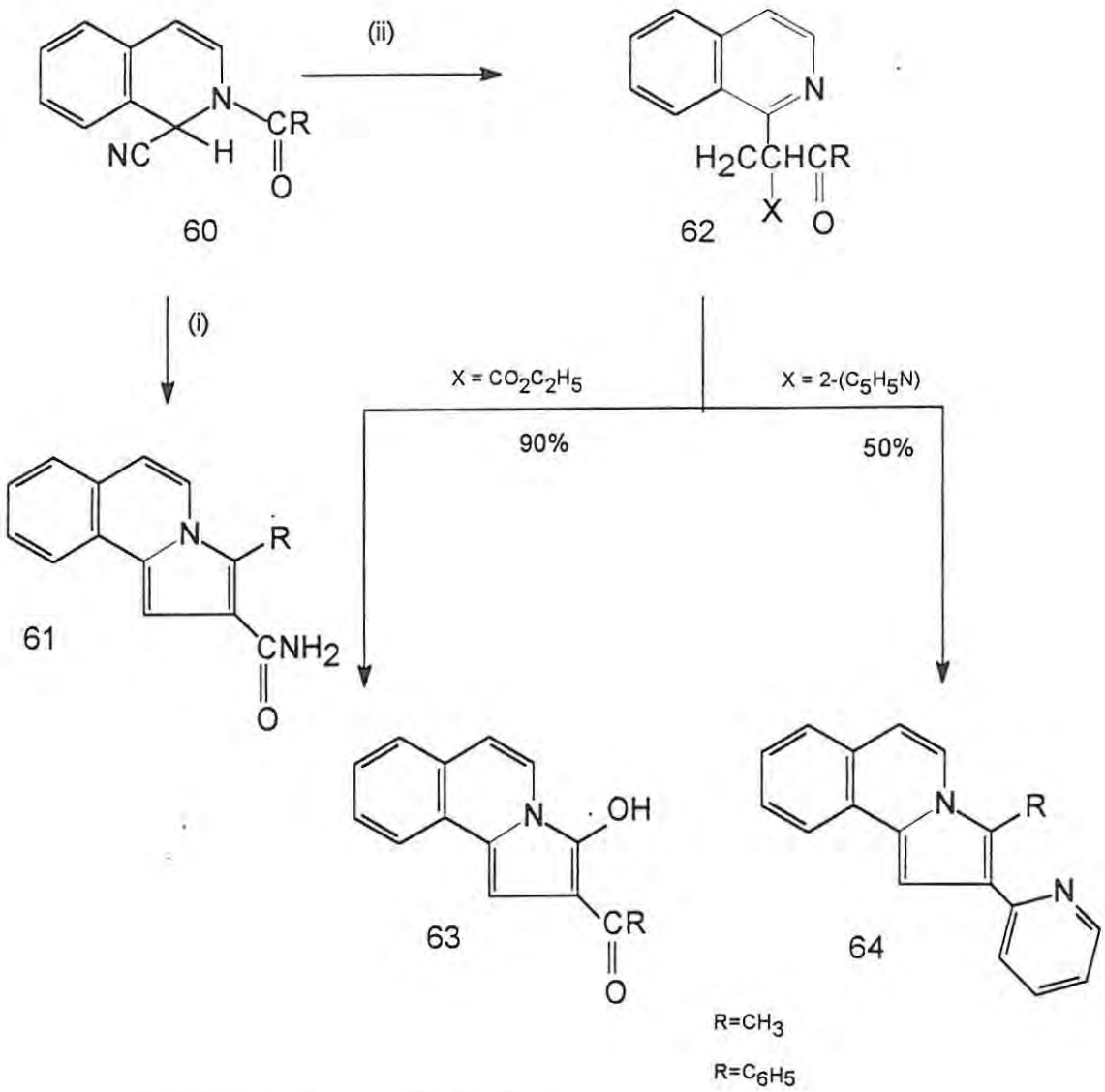
Reaction conditions: (i) C_6H_6, r.t., 3 d;

(ii) 200^0C / 0.5-0.05 torr sublimation

(iii) OH^-

(iv) $NaOH/CaCO_3$

SCHEME 19



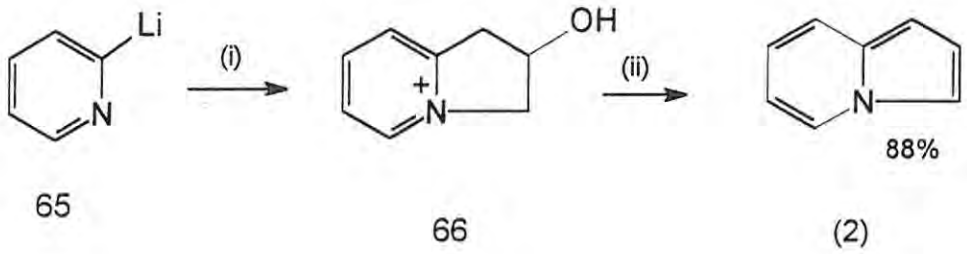
Reagents: (i) $H_2C{=}CH{-}CN$ C_6H_5Li;

(ii) $H_2C{=}CH{-}X$/ C_6H_5Li .

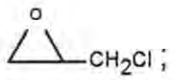
X= $COOC_2H_5$,2-(C_5H_5N)

(62) were formed which, upon heating or treatment with 100% phosphoric acid, underwent ring closure to afford the corresponding benzindolizines **(63)** and **(64)**, respectively (Scheme 19, p 19). Of particular interest was a paper published in 1969 by two German chemists, Flitsh and Gerstmann.[2] They reported one of the most powerful methods for the synthesis of parent indolizine **(2)**. Condensation reaction of 2-pyridyllithium **(65)** with 2-chloromethyloxirane afforded first the 2-hydroxy-2,3-dihydro-1H-indolizinium chloride **(66)** which, upon treatment with 30% sodium hydroxide, gave the parent indolizine **(2)** (Scheme 20).

SCHEME 20



65 66 (2)

Reagents : (i) 

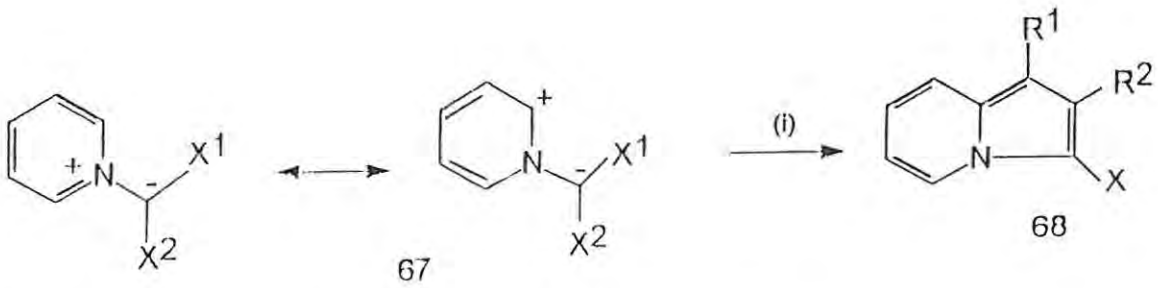
; (ii) NaOH

1.2.2 SYNTHESIS OF INDOLIZINES BY 1,3-DIPOLAR CYCLOADDITION

1,3-Dipolar cycloadditions are among the most widely-used reactions in the synthesis of heterocyclic compounds, particularly 5-membered ring compounds. It has been established that pyridinium ylides (**67**) , even in the absence of a dehydrogenation catalyst, combine with dimethyl acetylenedicarboxylate, diethyl acetylenedicarboxylate methylpropynoate, ethylpropynoate and dicyanoacetylene to mention a few, to form the indolizines (**68**) (Scheme 21,p 22).[20-25] However, when the dipolarophile is an ethenic compound, the reaction often does not yield the indolizine directly but the tetrahydroindolizines (**69**) and the dihydroindolizines (**70**) and (**71**) are isolated; subsequent dehydrogenation in the presence of a catalyst such as palladium on carbon, chloranil or 1,4-benzoquinone affords the respective indolizines. The relative rates of addition of the ylides (**67**) to the dipolarophile were found to be dependent on the substituents x_1 and x_2 (Scheme 21,p 22).

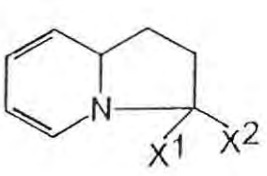
A desirable feature of indolizine synthesis by 1,3-dipolar cycloaddition is that the procedures are generally simple and require only two steps. In 1961, Boekelheide and Fahrenholtz,[20] used this approach for the first time, to synthesis the indolizine (**73**) from 1-phenacylpyridinium methylid (**72**) under dehydrogenating conditions (Scheme 22,p 23). Not long after, Huisgen and co-workers,[26] used this synthetic principle, to develop indolizine derivatives (**75**) from the reaction of the azomethine (**74**) and dimethyl fumarate (Scheme 23,p 23). Of particular interest, was a paper published in 1973, by Nakamura and co-workers. [2] They found that

SCHEME 21

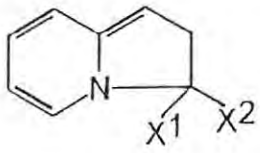


X^1 and X^2 = H, ALKYL, ARYL, ACYL, ALKOXYCARBONYL AND CYANO GROUPS.

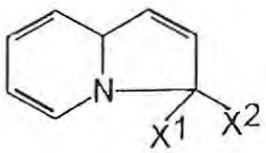
Reagents : (i) $R^1C{\equiv}CR^2$



69

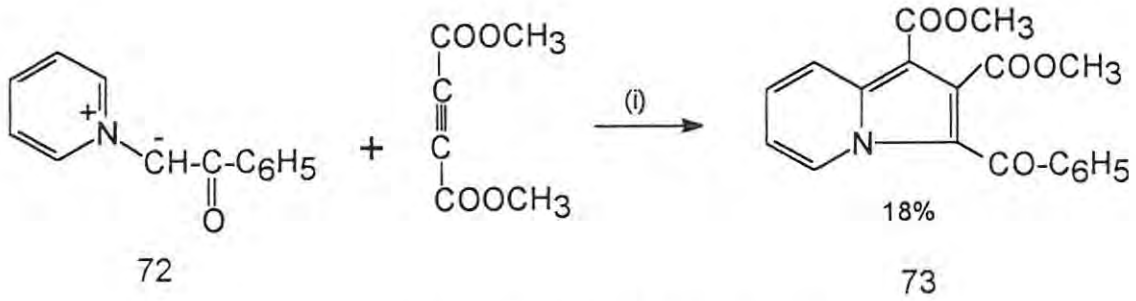


70



71

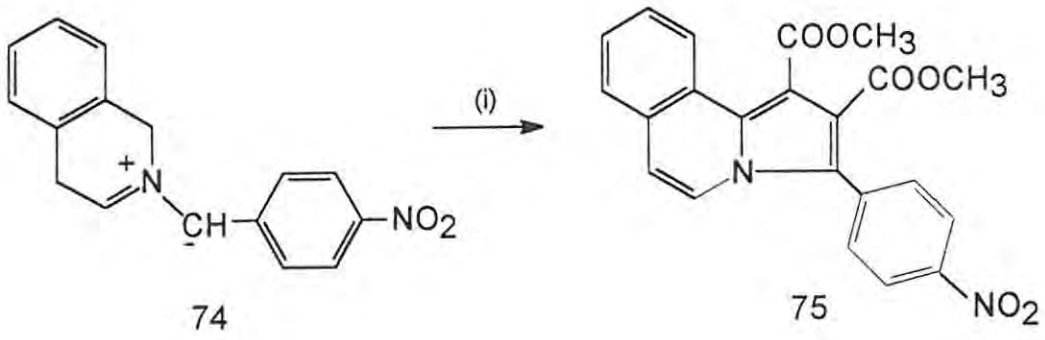
SCHEME 22



72 73

Reaction condition: (i) Pd /C, $C_6H_5CH_3$

SCHEME 23



74 75

Reagents:(i) DIMETHYL FUMARATE and CHLORANIL or XYLENE

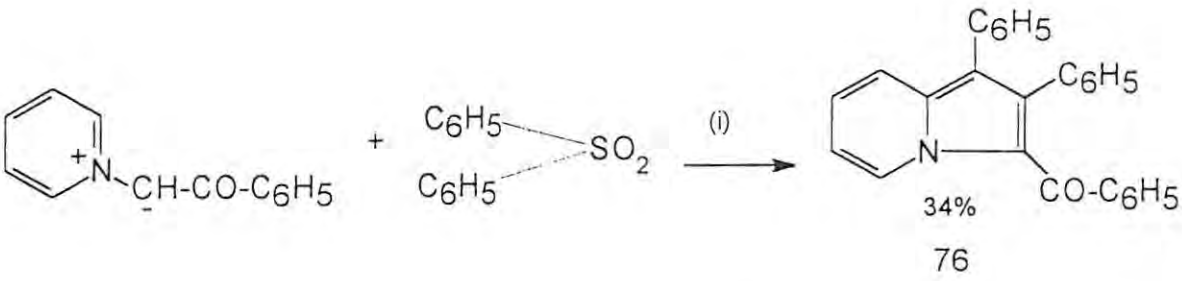
diphenylthiirene-*S,S*-dioxide behaved like acetylenic compounds and reacted with pyridinium methylid to afford, in 34% yield, the indolizine (**76**). In the same year, research done on *N*-allylpyridinium ylides (77) by two Japanese research groups [27-29] established that, in some cases,*N*-allylpyridinium ylides behaves not only as 1,3-dipoles which may cyclo add to another *N*-allylpyridinium ylid to afford the indolizine (**78**) but also as 1,5-dipoles, which undergo ring closure to give the indolizines (**79**) (Scheme 25,p 25).

The preparation of 3-azaindolizines (**81**) can be readily achieved by 1,3-dipolar cycloaddition of the *N*-imminopyridinium ylid (**80**) with acetylenic or ethenic compounds (Scheme 26,p 26).[2]

1.2.3 SYNTHESIS OF INDOLIZINES BY 1,5-DIPOLAR CYCLIZATION

1,5-Dipolar cyclization is one of the most versatile routes to heterocyclic molecules. Because of it's utility and inherently broad scope, this synthetic approach is of considerable importance and Huisgen and co-workers,[2] studied this approach in detail. In 1962, Krohnke and Zecher,[2] successfully extended this approach to the synthesis of the azaindolizine (**85**) from phenacylisoquinolinium bromide (**82**) *via* the 1,5-dipolar intermediate (**84**) (Scheme 27,p 27). The authors also reported the synthesis of several benzindolizines (**87**) by simply treating the *N*-picrylmethylcycloimmonium ylids (**86**) with a base.

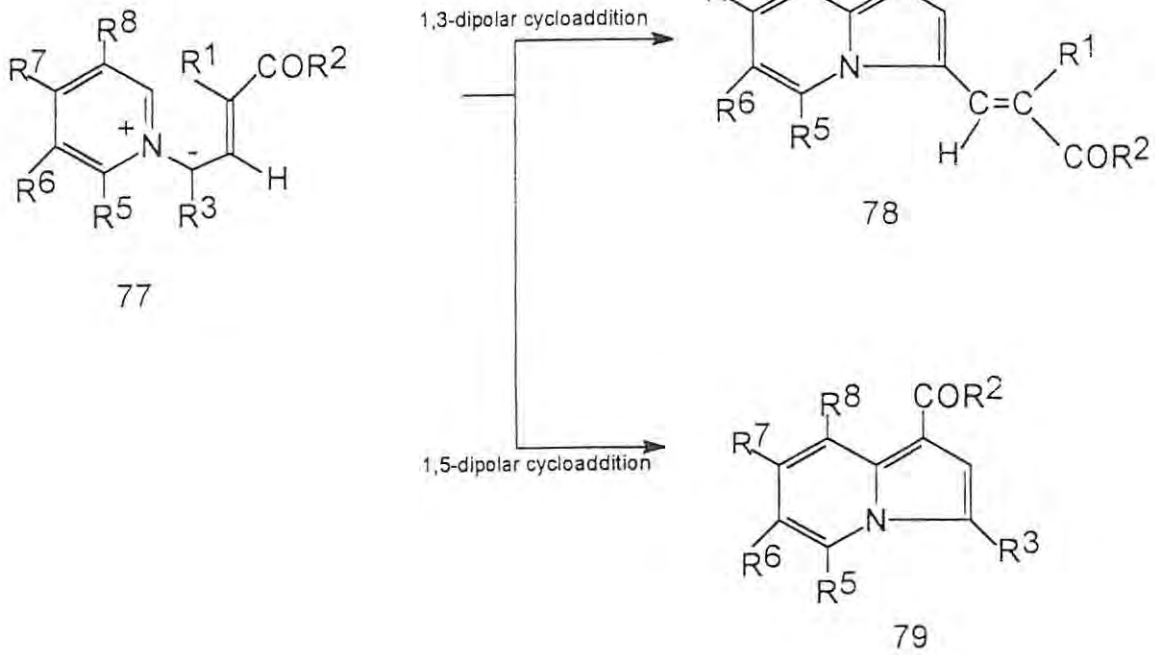
SCHEME 24



76

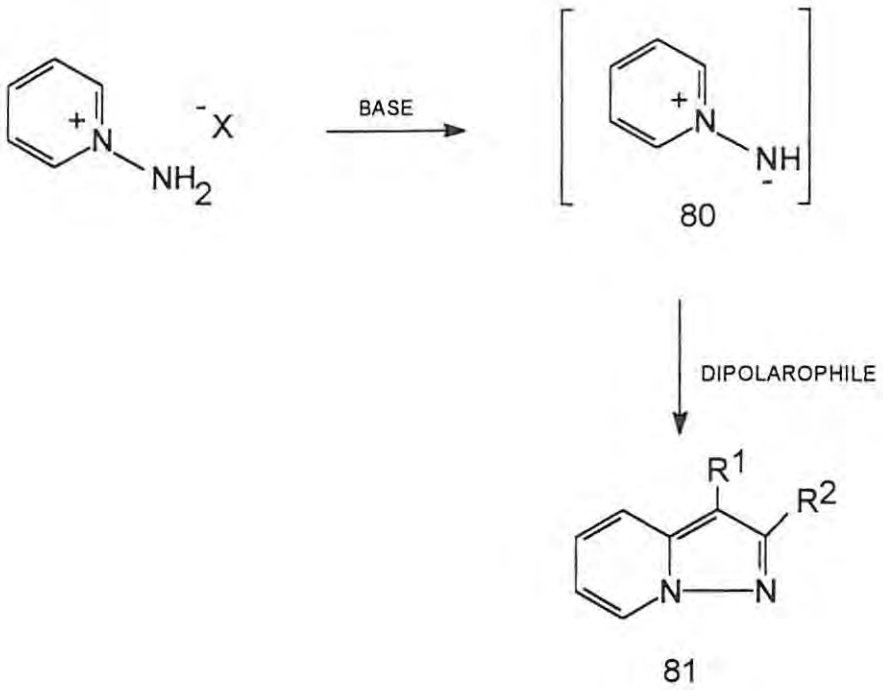
Reagent: (i) C_6H_6, r.t

SCHEME 25

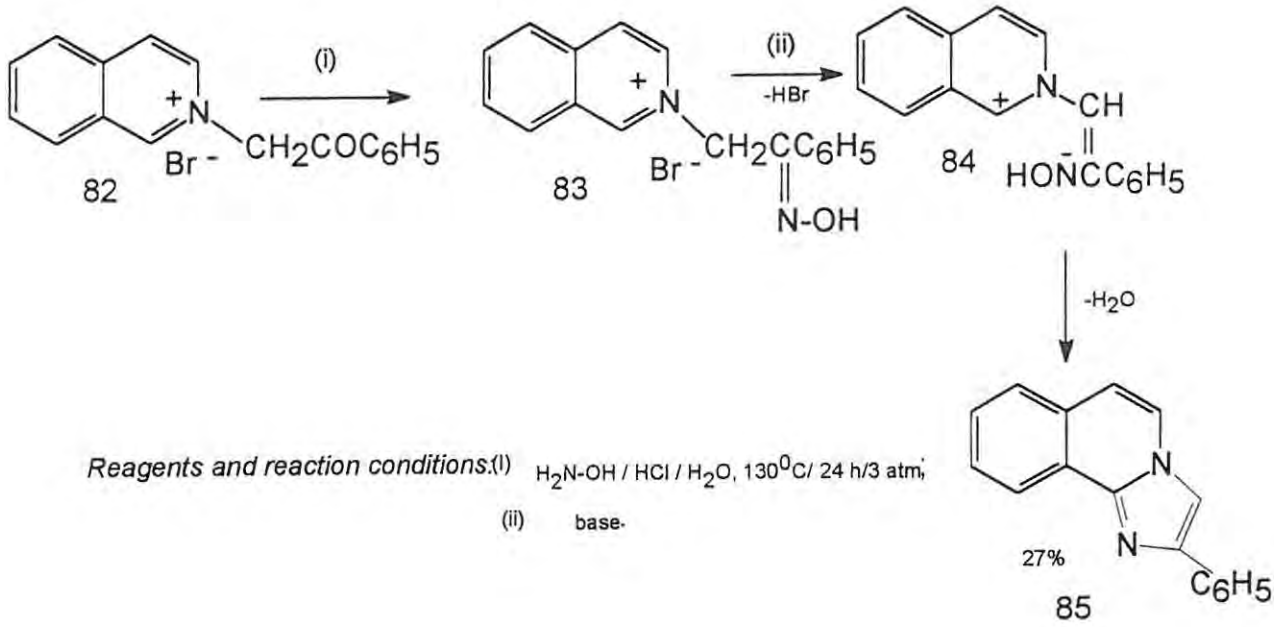


77 78 79

SCHEME 26

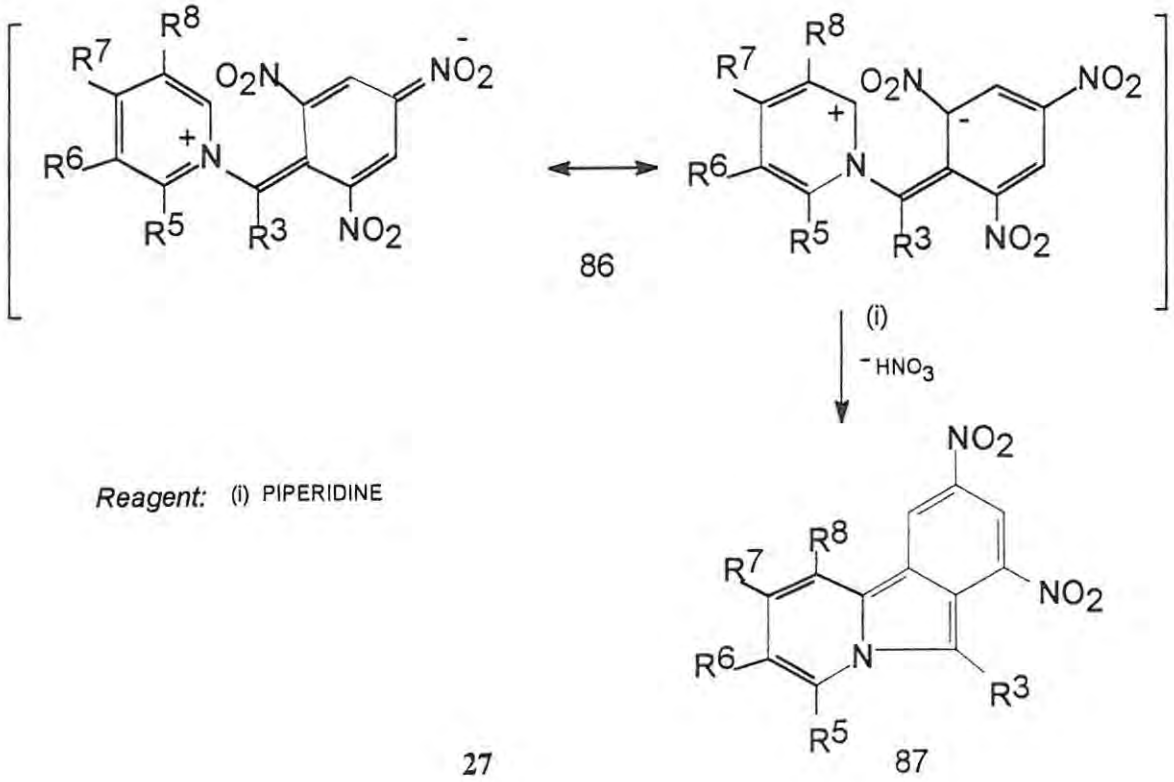


SCHEME 27



Reagents and reaction conditions: (i) H_2N-OH / HCl / H_2O, 130^{0}C/ 24 h/3 atm;
(ii) base.

SCHEME 28

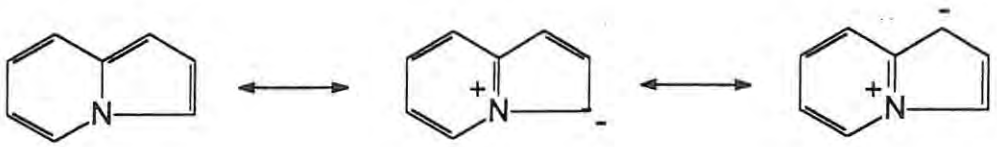


Reagent: (i) PIPERIDINE

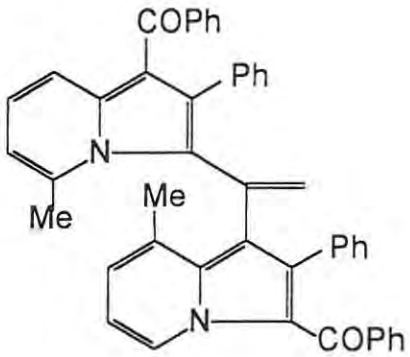
1.3 STRUCTURE, PHYSICAL AND CHEMICAL PROPERTIES OF INDOLIZINES

1.3.1 STRUCTURE OF INDOLIZINES.

Following an early argument that any resonance stabilization in indolizines is simply due to the presence of the pyrrole ring, the parent indolizine was first considered to be best represented by structure **(88)**. However, the resonance energy **(R.E)** calculated for indolizine was found to be 0.29 β,which is larger than the total R.E of pyrrole (0.23β). Furthermore, NMR studies have conclusively established delocalization throughout both rings. Therefore indolizine is now considered to be best represented by a resonance hybrid to which the canonical structures **(88)** **(89)** and **(90)**, contribute. X-ray analysis has shown the crystal structure of the bis-indolizine **(91)** to be nearly planar and the observed bond lengths to correlate well with the Huckels molecular orbital (HMO) bond orders. HMO calculations give the decreasing order of the electron density as: 3> 1 >> 8a >5 > 2 > 7> 6 on the ring carbons.[30]



88 89 90



91

Table 1: Percentage composition of protonated 3-substituted indolizines in trifluroacetic acid.

Compound	3H-cation	1H-cation
3-Methylindolizine	21	79
2,3-Dimethylindolizine	41	59
3-Methyl-2-phenylindolizine	72	28
3-Methyl-2-Methylindolizine	78	22
1,2,3-Trimethylindolizine	100	
1,3-Dimethyl-2-phenylindolizine	100	
3,5-Dimethylindolizine	100	

1.3.2 PHYSICAL PROPERTIES OF INDOLIZINES

The parent indolizine (**2**) and it's alkyl derivatives are either low-melting solids or high-boiling liquids, sensitive to air, light and volatile in steam. However, when a phenyl group is attached at the 2- or the 5- position , the indolizines are found to be stable solids and non-volatile in steam. Most indolizines are highly fluorescent and show feeble basic properties.[1]

1.3.3 CHEMICAL PROPERTIES OF INDOLIZINES

Reference has already been made to the structure of indolizines and , in particular to it's delocalised orbitals. Indolizines readily undergo electrophilic substitution and show resistance to nucleophilic attack. In their chemical reactivity, indolizines resemble pyrroles, indoles and isoindoles.[1] The following section deals with reactions of indolizines with electrophiles, oxidation, reduction and other miscellaneous reactions.

1.3.3.1 Reactions with electrophiles.

Electrophilic substitution in indolizines occurs preferentially at the 3-position and then at the 1-position but sometimes at both 3- and 1-positions simultaneously.[31] The enhanced

susceptibility to electrophilic attack at C-3 and C-1, is consistent with the MO calculations, which indicate C-3 to be the most reactive site for electrophilic attack, followed by C-1.

(i) Protonation

Fraser and co-workers [31] studied the protonation of indolizines using NMR spectroscopy. Protonation of indolizines occurs preferentially at position 3. In 3-substituted indolizines, the site of protonation was found to be dependent on the nature of the C-3 substituent as well as the substituents at positions 1, 2 and 5. Indolizines which have the same substituents at position 1 and 3, are exclusively protonated at position 3. Similarly protonation of 3,5-disubstituted indolizines occurs preferentially at position 3. Fraser and co-workers argued that in the 3,5-disubstituted indolizines, intramolecular overcrowding encourages protonation at site 3. In general, protonation of the 3-substituted indolizines affords a mixture of the 3H- and 1H-cations (See Table 1,p 29). It was found that the ratio of the 3H:1H cations could be increased by introducing substituents at position 2. As indicated above, the resulting steric interaction between the C-3 and C-2 substituents is relieved by protonation at C-3. The relief in steric strain may be attributed to the consequent change in the hybridisation state of C-3. Protonation of most of the azaindoliznes is found to occur at the non-bridgehead nitrogen. Surprisingly, protonation of the 5-azaindolizines occurs preferentially at the 3-position followed by the 1-position.[32]

(ii) Nitration

Nitration of the indolizine nucleus often results in oxidation of the substrate with little evidence of nitration. Successful nitration of the indolizine nucleus was achieved for the first time in 1946, by Borrows and co-workers [33] who showed that while the action of nitric acid on 2-methyl and 2-phenylindolizines at moderate temperatures resulted mainly in oxidation, rapid reaction at higher temperatures gave the respective 1,3-dinitro indolizines in low yields. Furthermore, nitration of 2-methylindolizine (**92**) in sulphuric acid has been shown to afford the 1-nitro-2-methylindolizine (**93**) as the main product, accompanied by small quantities of the 3-nitro derivative (**95**) and the 1,3-dinitro derivative (**94**) (Scheme 29,p 34). A similar treatment of the 2-phenylindolizine (**96**) resulted in the phenyl ring being attacked first, giving the 2-*p*-nitrophenylindolizine (**97**) (Scheme 30,p 34). This reaction shows that the indolizine system is closely allied to pyrrole in it's properties, for similar treatment of *N*-phenylpyrrole yields *N*-*p*-nitrophenylpyrrole.[1] Compound (**97**), on further nitration affords 1-nitro-2-*p*-nitrophenylindolizine (**98**) (Scheme 30).

Nitration of 3-acetyl-2-methylindolizine proceeds readily in conc.sulphuric acid to yield the 1-nitro derivative along with a small quantity of the 1,3-dinitro compounds. On the other hand, nitration of the 3-acetyl-2-phenylindolizine under similar conditions affords a mixture of nitrated products.[1]

(iii) Nitrosation

Direct nitrosation of the indolizine nucleus was first achieved by Konde and Nischizawa,[2] in 1937, when they treated 3-acetyl-2-methylindolizine with nitrous acid to give the 1-nitroso derivative. In indolizines, which have their 3-position unsubstituted, nitrosation takes place at the 3-position. The preferential nitrosation at position 3 is in marked contrast to the preferential nitration at position 1, discussed above.

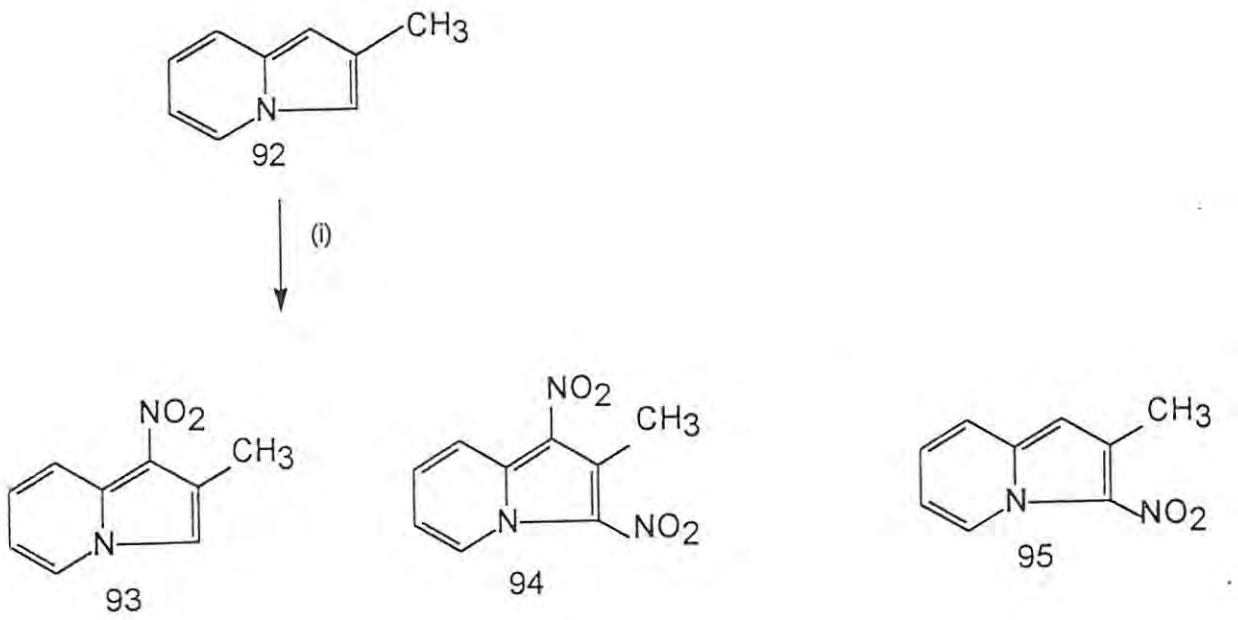
(iv) Halogenation

Not much work has been done on the halogenation of indolizines. Attempts to prepare stable bromo derivatives have not always been successful. However, preparation of stable iodo derivatives has proved possible. For example, iodination of 3-acetylindolizine in alcohol, proceeds readily to give the 1,3-diiodo derivative and, in the presence of sodium acetate, the 1-iodo derivative.[1]

(v) Acylation

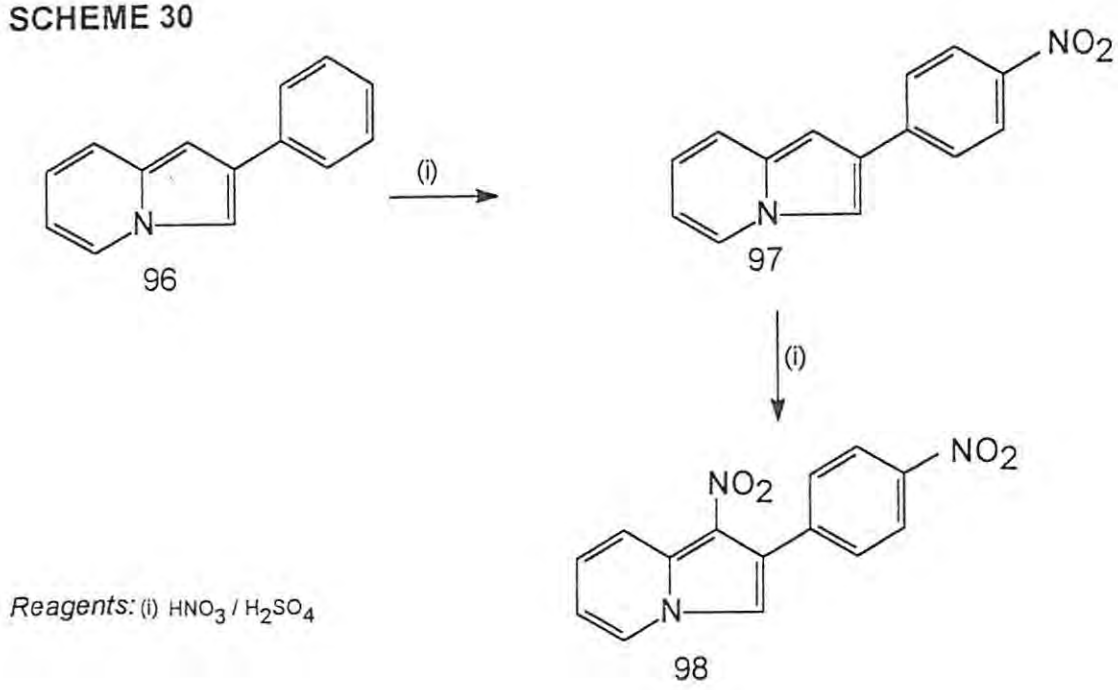
Acylation of indolizines take place preferentially at position 3 and less readily at position 1. Indolizines can be acylated simply by treating with acid chlorides, anhydrides and even esters.

SCHEME 29



Reagents : (i) HNO_3 / H_2SO_4

SCHEME 30

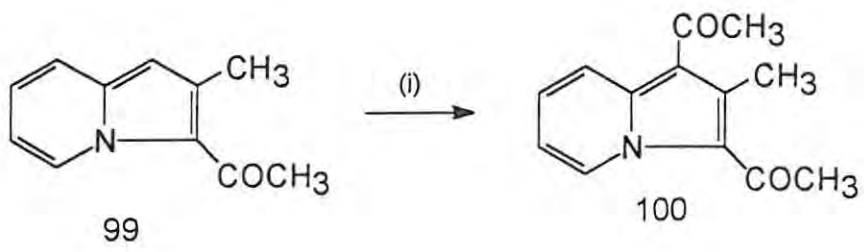


Reagents: (i) HNO_3 / H_2SO_4

One of the most convenient methods for acylating the indolizine nucleus is by heating the indolizine with acid anhydrides in the presence of sodium salt of the corresponding acid.[1] In 1912, Scholtz [1] synthesised, for the first time, the 3-acetyl derivative of the indolizine and the 7-methylindolizine using this approach. Tshitschibabin [1] in 1929, Borrows and Holland in 1946,[6] extended this approach to the preparation of 3-acetyl derivatives of 2-methyl- and 2-phenylindolizine and the 3-benzoyl derivative of 2-phenylindolizine. The monoacetyl indolizines ,on further treatment with acetic anhydride at higher temperatures, were found to yield the respective 1,3-diacetylindolizines.

In 1940, Ochai,[1] a japanese researcher, reported the preparation of 1,3-diacetyl-2-methylindolizine (**100**) from a Friedel-Crafts reaction in CCl_4 on 3-acetyl-2-methylindolizines (**99**) using acetyl chloride and a large excess of aluminium chloride as catalyst (Scheme 31,p 35). Acylation of 2-methylindolizine (**101**) under similar conditions but using carbon disulphide as solvent afforded the diacetyl derivative (**100**) in very low yield (Scheme 32,p 35). With 2-phenylindolizine, however, Friedel-Crafts acylation proceeds readily in carbon-disulphide to give a mixture of 1,3-diacetyl-2-phenylindolizine and 2-p-acetylphenylindolizine. It was found that acetyl chloride and bromide failed to react in the absence of a catalyst. This is in marked contrast to the facile monobenzoylation of indolizine when treated with benzoyl chloride even in the absence of a catalyst.[1]

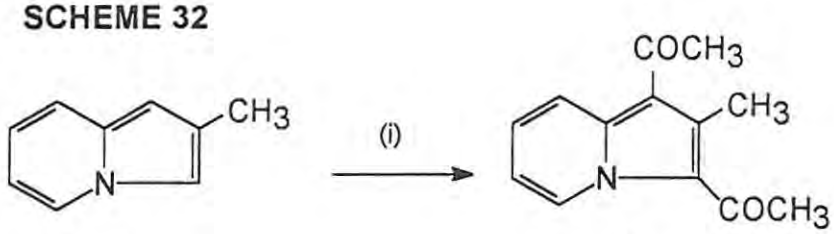
SCHEME 31



99 100

Reagents: (i) CH_3COCl, $AlCl_3$ in CCl_4

SCHEME 32



101 100

Reagents:(i) CH_3COCl, $AlCl_3$ in CS_2.

(vi) Reactions with diazonium electrophiles

The preparation of azo derivatives of indolizines can be easily achieved using arenediazonium ion as an electrophile. Diazo coupling occurs normally at position 3; however, if this position is already occupied, position 1 is attacked resulting in the formation of the 1-azo derivatives. In 1913, Scholtz and Fraude[1] achieved the first synthesis of a 3-azo derivative of indolizine. Similar treatment of 3-acetyl-2-methylindolizine by Kondo and co-workers [1] in 1936, yielded the 1-phenylazo derivative.

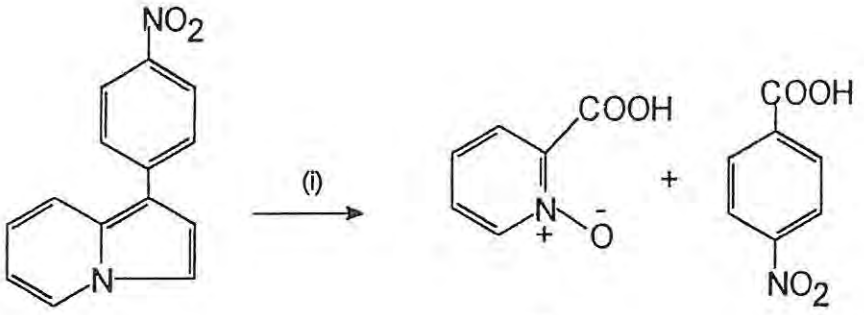
1.3.3.2 Oxidation reactions

Indolizines undergo oxidation very easily. Ring fission is a rather common phenomenon observed in oxidation of indolizines. In the past, this reaction was used for structural elucidation.[34] A typical example is H_2O_2-induced oxidation outlined in Scheme 33. However, some cases of oxidation where ring fission does not occur have been reported. A classic example is the potassium ferricyanide oxidation of the indolizine (**104**), which afforded compound (105) as the oxidation product (Scheme 34,p 37).[35]

1.3.3.3 Reduction reactions

Reduction of the indolizine nucleus was first achieved in 1912 by Scholtz,[1]

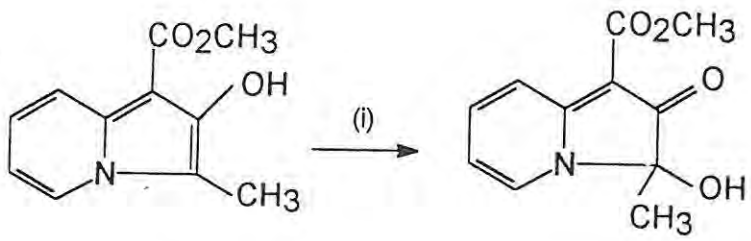
SCHEME 33



102 103 104

Reagents: (i) H_2O_2

SCHEME 34



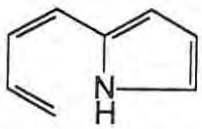
105 106

Reagent: (I) $K_3Fe(CN)_6$

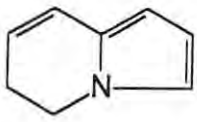
when he treated the parent indolizine **(2)** with sodium and alcohol. Scholtz presumed the structure of the reduction product to be the ring opened system **(107)**. In 1946, Borrows and Holland,[1] proposed the product of the sodium-alcohol reduction as, in fact, the dihydroderivative **(108).** Several reports on the complete hydrogenation of the six-membered ring of the indolizine system have been published.[1] Although the above results indicate that the six membered ring of the indolizine nucleus is more susceptible to hydrogenation than the five membered ring, Diels and Meyer,[1] reported hydrogenation of the five membered ring in the reduction of dimethyl 1-(methoxycarbomethoxymethyl)indolizine-2,3-dicarboxylate **(109)** in the presence of platinium oxide;the isolated product being the tetrahydro compound **(110)** (Scheme 35,p 39). Under more drastic conditions, *e.g.,* in the presence of Raney nickel at high temperature and pressure, complete reduction of the indolizine nucleus has been reported.[1]

1.3.3.4 Reactions with nucleophiles and bases

Indolizines and azaindolizines with electron withdrawing groups undergo nucleophilic attack. Thus, treatment of 8-nitro indolizines with secondary amines and oxygen was found to give 5-amino-8-nitro indolizines. Similarly, 1-azaindolizine **(111),** on treatment with ethyl thioglycolate anion in DMF, afforded the thio derivative **(112) (Scheme 36,p 40)** 6-azaindolizine **(113),** on treatment with phosphoryl chloride, gave the bis-nitrogen bridged [16]annulene **(114)** (Scheme 37).[36]

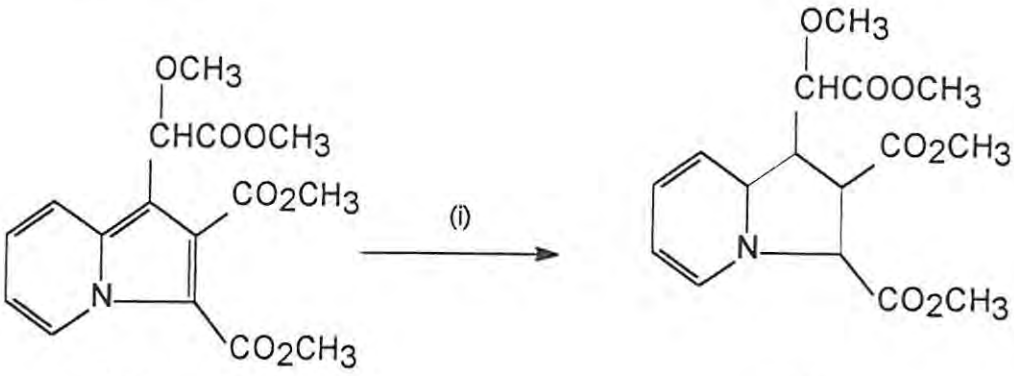


107



108

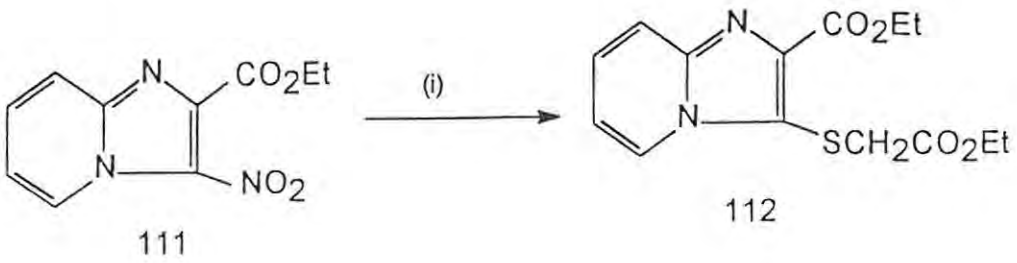
SCHEME 35



109 110

CATALYST:(i) PLATINUM OXIDE

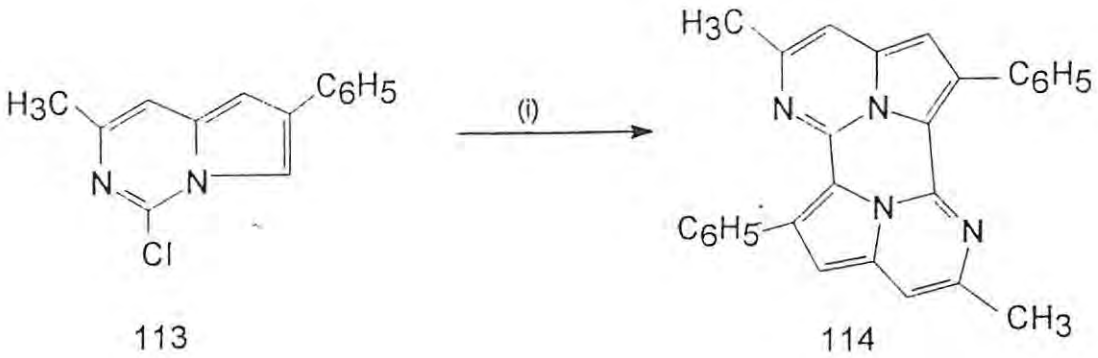
SCHEME 36



111 112

Reagent: (i) ETHYL THIOGLYCOLATE ANION IN DMF.

SCHEME 37

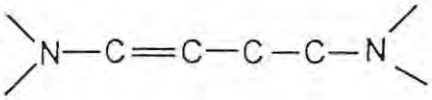


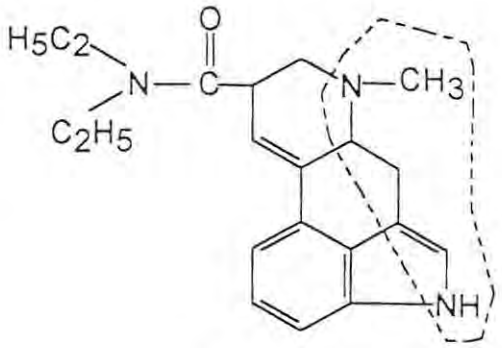
113 114

Reagent: (i) PHOSPHORYL CHLORIDE

1.4 BIOLOGICAL ACTIVITY

In 1960,James M. Price[38] of Wisconsin Medical School suggested the possibility of preparing pharmacologically active indolizine derivatives by replacing the indole ring of biologically active indoles with the indolizine ring system. The striking structural similarity between the indole and indolizine nucleus prompted this speculation. Most of the biologically active indoles such as reserpine,lysergic acid diethylamide and psilocin, have the indole nitrogen and the extraindole nitrogen separated by four carbons.[39]

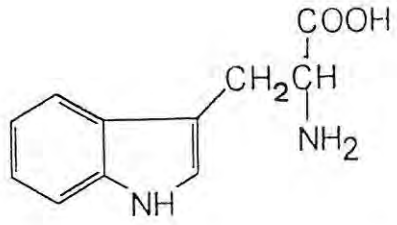




Research on these compounds suggested that their biological activity is partly dependent on the separation between the indole nitrogen and the extraindole nitrogen. This hypothesis provided the lead for developing indolizine analogue of biologically active indoles.

In 1961, Carbon and Brehm[38] prepared ß-(1-indolizyl)alanine (**117**) as an analogue of Tryptophan (**116**), an essential amino acid present in relatively small amounts in proteins. Tryptophan is the precursor of several physiologically important metabolites,but is completely destroyed during acid hydrolysis of proteins. Compound (**117**) is considered to be a potential tryptophan antimetabolite.

By the late sixties, medicinal chemists in several laboratories had recognized the importance of preparing aminoalkyl indolizines for pharmacological studies. 1-(Diethylaminomethyl)-3-methyl-2-phenylindolizine (**118**), prepared in 1966, showed depressant activity on the central nervous system.[40] The LD_{50} was found to be in the range 70-100 mg/kg. A year later, 2-phenylindolizines (**119 a-m**) and their derivatives were synthesised and screened for their effects on the central nervous system in mice and in some cases in cats. (See Table 2,p 43). Many of these compounds (eg:**119b, d,g,h,l**) were stimulants at low doses, depressants at higher doses and lethal at even higher doses. Although compound (**119c**), at doses of 30-100mg/kg, produces slight central nervous system depression, it was found be non-lethal at dosages as high as 1000 mg/kg, while compound (**119e**) led to a loss of aggression in rats. Compound (**119f**), however,showed locomotor depression at low doses which become worse with increased dosage. In 1971, certain indolizine-1-acetic acids (**120**) that exhibited analgesic and anti-inflammatory activity were developed. The resemblance between the structure and pharmacological properties of these indolizines to indomethacin (**121**), a potent anti-inflammatory agent (introduced in 1963),



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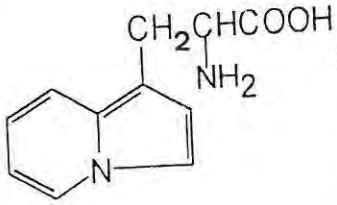
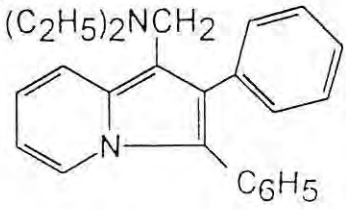


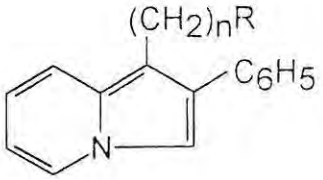
117



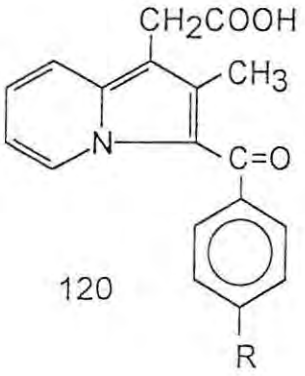
118

TABLE 2:

	n	R
a	1	$NCH_3(COOC_2H_5)$
b	1	$N(CH_3)_2$
c	2	$NHCOOC_2H_5$
d	2	$NHCH_3$
e	2	$NCH_3(COOC_2H_5)$
f	2	$N(CH_3)_2$
g	2	$CON(CH_3)_2$
h	3	$N(CH_3)_2$
i	2	$N(CH_3)_3.Br$
j	2	$N(CH_3)_3.I$
k	2	$NHCOOC_2H_5$
l	2	$NHCH_3.HCl$
m	2	$N(CH_3)_2.HCl$



(119 a-m)



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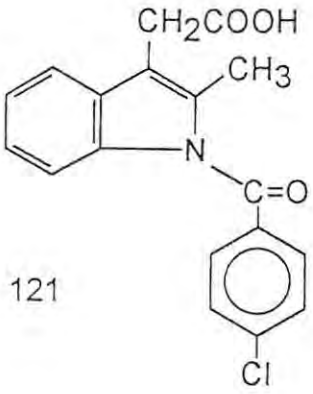

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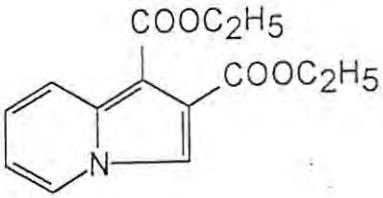


122

suggested that the elementary constitution necessary for anti-inflammatory action was not destroyed by the shift of the "indole nitrogen" (in indomethacin) to the bridgehead position..[41] This encouraged the development of a range of indolizine analogues with anti-inflammatory properties.

The occurrence of the indolizine ring system (**2**) in natural products is not very common. However, alkaloids of the Vinca group,such as vincamine, vindoline, and vindolinine contain several ring systems including the indolizine system.[42] A particularly desirable feature of these alkaloids is that they show hypoglycemic activity,ie. the ability to lower the blood sugar in the body. The presence of the indolizine ring system in the Vinca alkaloids prompted the development of several 2-(*N*-alkylaminomethyl) indolizines which were screened for hypoglycemic activity. Some of the compounds screened showed weak hypoglycamic activity while one of the compounds series showed anti-parkinson activity when taken in high doses. Certain indolizines were also screened for antineoplastic activity, based on an extension of the rationale that some carcinolytic Vinca alkaloids, such as vincristine and vinblastine (used in cancer chemotherapy). However, sporadic attempts in developing carcinolytic indolizines met with little and only one indolizine derivative *viz.*,diethyl indolizine-1,2-dicarboxylate (**122**) showed significant antineoplastic activity.[43] By the late seventies, interest in developing indolizines with pharmacological potential started cooling off and not much research on biologically active indolizines has been reported since then.

1.5 SPECTROSCOPIC STUDIES OF INDOLIZINES

1.5.1 ULTRAVIOLET SPECTRA OF INDOLIZINES

In 1963, an Australian researcher, Armarego,[44] studied the ultraviolet absorption spectra of several indolizines and their cations. He found that the spectra of all indolizines were very similar. They mainly consist of three bands:- a strong band found in the range 225-240 nm; a second band of medium intensity generally found between 270 and 310 nm; and a third broad band of medium intensity found in the range 330 -360 nm. Absorption spectra of indolizine cations were found to be strikingly different from the corresponding indolizines. This is in contrast to what is observed in other heteroaromatic compounds.[44] Armarego states that it is the change in electron distribution between the indolizines and the protonated species that is responsible for the marked difference in their spectra.

1.5.2 MASS SPECTRA OF INDOLIZINES

In 1970, Jones and Stanyer [45] studied the mass spectra of several indolizines. The base peak is the molecular ion (m/e 117) for the indolizine. Loss of HCN and H_2CN gives rise to peaks at 90 and 89 respectively. The authors also studied the spectra of methylindolizines (with the methyl group in different positions). In all cases, the two major peaks were the molecular ion peak at m/e 131 and at m/e 130 corresponding to loss of a hydrogen atom; other

fragmentations include loss of H_2CN giving a peak at m/e 103 and loss of acetylene giving a peak at m/e 77. All methylindolizines gave similar spectra irrespective of the position of the methyl group attached. The mass spectra of dimethylindolizines also showed similar fragmentation patterns .

1.5.3 NMR SPECTRA OF INDOLIZINES AND AZAINDOLIZINES

In 1964, Heffernan and co-workers [46] studied the proton magnetic resonance spectra of indolizines and azaindolizines. In the parent indolizine the authors, observed cross ring coupling between the 1- and 5-protons and between 3- and 8-protons. The chemical shifts obtained showed the 5-proton to be the most deshielded. 1- and 2-azaindolizines also show 1,5 coupling and 3,8 coupling. The spectra of 3-azaindolizine, also showed weak long range coupling involving the 2- and 6-protons in addition to the 1,5 and 3,8 coupling. In 1970,studies on the C-13 magnetic resonance spectra of indolizines, established the high aromaticity of these compounds. Several ^{1}H and ^{13}C NMR studies have been reported [47-50] including a very recent study [51] on 2-substituted indolizines.

1.6 APPLICATIONS OF INDOLIZINES.

Indolizines find use as fabric brightening agents and as photographic sensitisers.[51] Some indolizines have been successfully used as dyes which show great resistance to light and heat.[52] Reference has already been made to the potential applications of indolizines as biologically active compounds. For e.g., β-(1-indolizyl)alanine is considered to be a potential tryptophan antimetabolite. Indolizines that show depressant activity on the central nervous system are known. Certain indolizine-1-acetic acids exhibit analgesic and anti-inflammatory activities.

1.7 AIMS OF THE PRESENT INVESTIGATION

Recent work in our group has led to the discovery of a novel route for the synthesis of indolizines. It was found that thermal cyclization of certain 2-pyridinyl derivatives obtained from Baylis-Hillman reaction of heterocyclic aldehydes and acrylate esters,nitriles or methyl vinyl ketone, provided convenient access to indolizine derivatives (Scheme 38).

The mechanism of cyclization is of obvious interest as is the possibility of developing alternative, but analogous, synthetic approaches to indolizines.

The aims of this research project have thus been:-

1. to investigate the kinetics and the mechanism of the thermal cyclization of Baylis-Hillman products to indolizine derivatives;

2. to explore an alternative route to indolizines *via* halogenated derivatives; and

3. to synthesise novel 6-methylindolizine-2-carboxamides; and undertake dynamic nuclear magnetic resonance studies of rotational isomerism in these compounds.

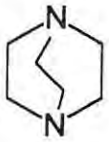
2. DISCUSSION

2.1. SYNTHESIS OF 2-SUBSTITUTED INDOLIZINES

2.1.1 BAYLIS-HILLMAN REACTION

The Baylis-Hillman reaction,[53] first reported in 1972 in the patent literature, involves the coupling of α,β-unsaturated vinyl systems with aldehydes in the presence of a base catalyst to afford intermediates of great synthetic value. In their original work, Baylis and Hillman used cyclic tertiary amines such as 1,4-diazabicyclo [2.2.2] octane (DABCO) (**123**) and quinuclidine (**124**) as catalysts. A decade later, the inherent potential of the DABCO catalysed coupling of aldehydes and acrylate esters was exploited in the synthesis of necic acids such as integerrinecic,retronecic, and senecivernecic acid and other compounds.[54] The reactions typically required 4-7 days for completion and, in some cases, even longer. However, further research in this area showed that using 3-hydroxyquinuclidine (**125**) instead of DABCO, increased the reaction rate considerably.[55] It was also observed that using electrophilic heterocyclic aldehydes or increasing the amount of catalyst resulted in reaction rate enhancement.

Recently, a kinetic and a mechanistic study of the Baylis-Hillman reaction (Scheme 38,p 51) has been completed in our group.[56] The kinetic results show the reaction to be third order



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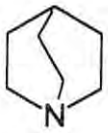
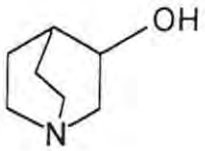
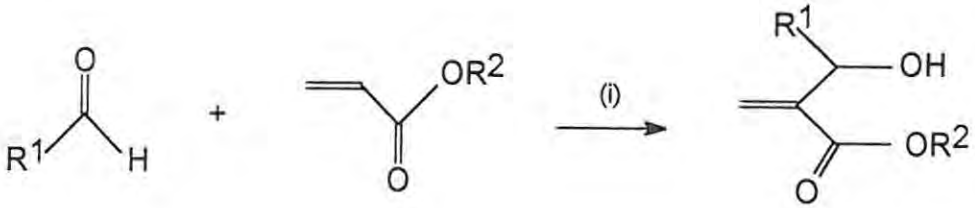


124



125

SCHEME 38



126 127 128

Catalyst: (i) DABCO.

overall, *i.e.*, first order in each of the reactants **[126],[127]** and the catalyst**[3^{0}amine]** (Equation 1). The kinetic data fits a pseudo 2nd order reaction (Equation 2) if the concentration of the tertiary amine is assumed to be constant.

$$\text{Rate} = k_{obs}\,[126]\,[127]\,[3^0\text{amine}] \qquad (1)$$

$$\text{Rate} = k_a\,[126]\,[127] \qquad (2)$$

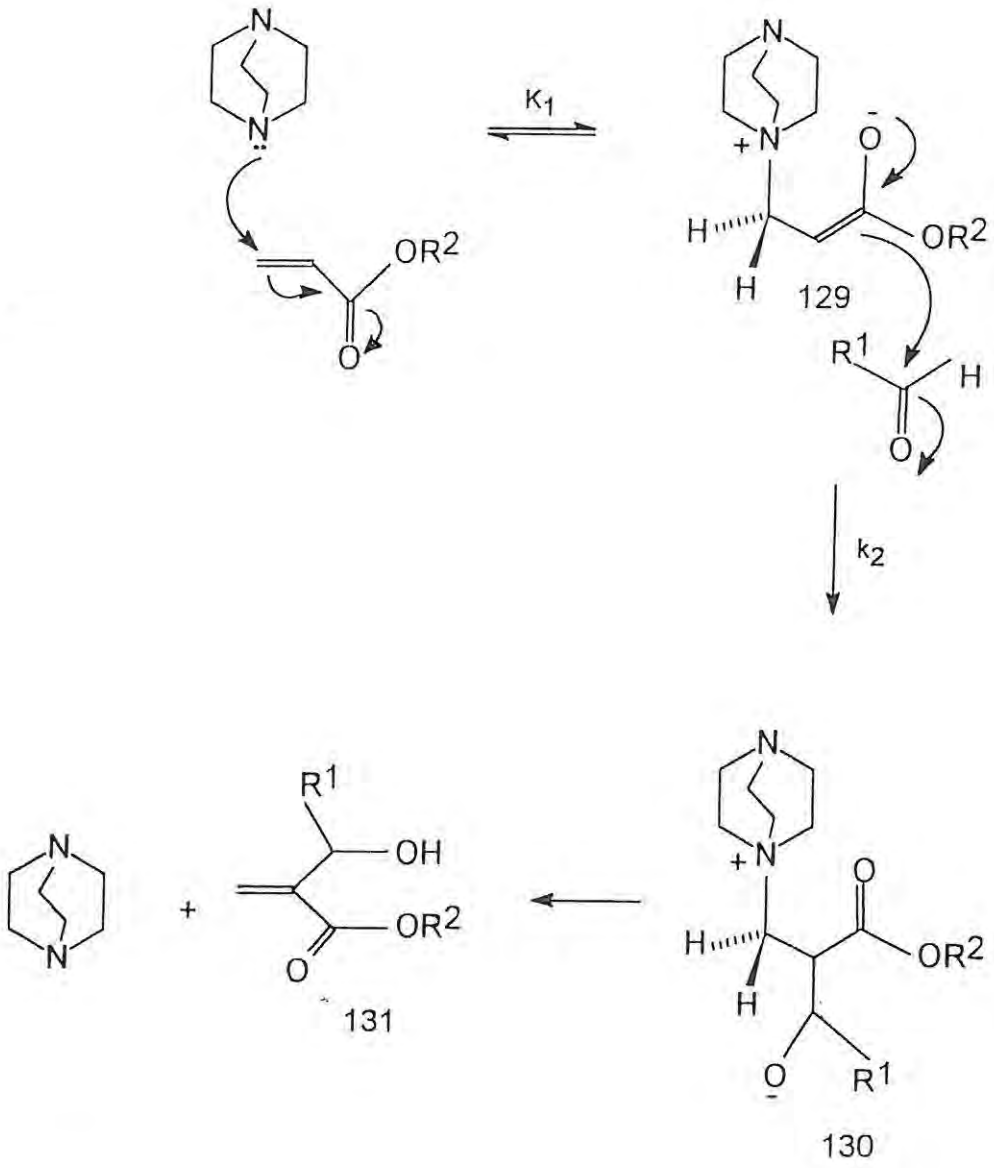
where $k_a = k_{obs}\,[3^0\ \text{amine}]$

$$\text{Rate} = k_2 K_1\,[126]\,[127]\,[3^0\ \text{amine}] \qquad (3)$$

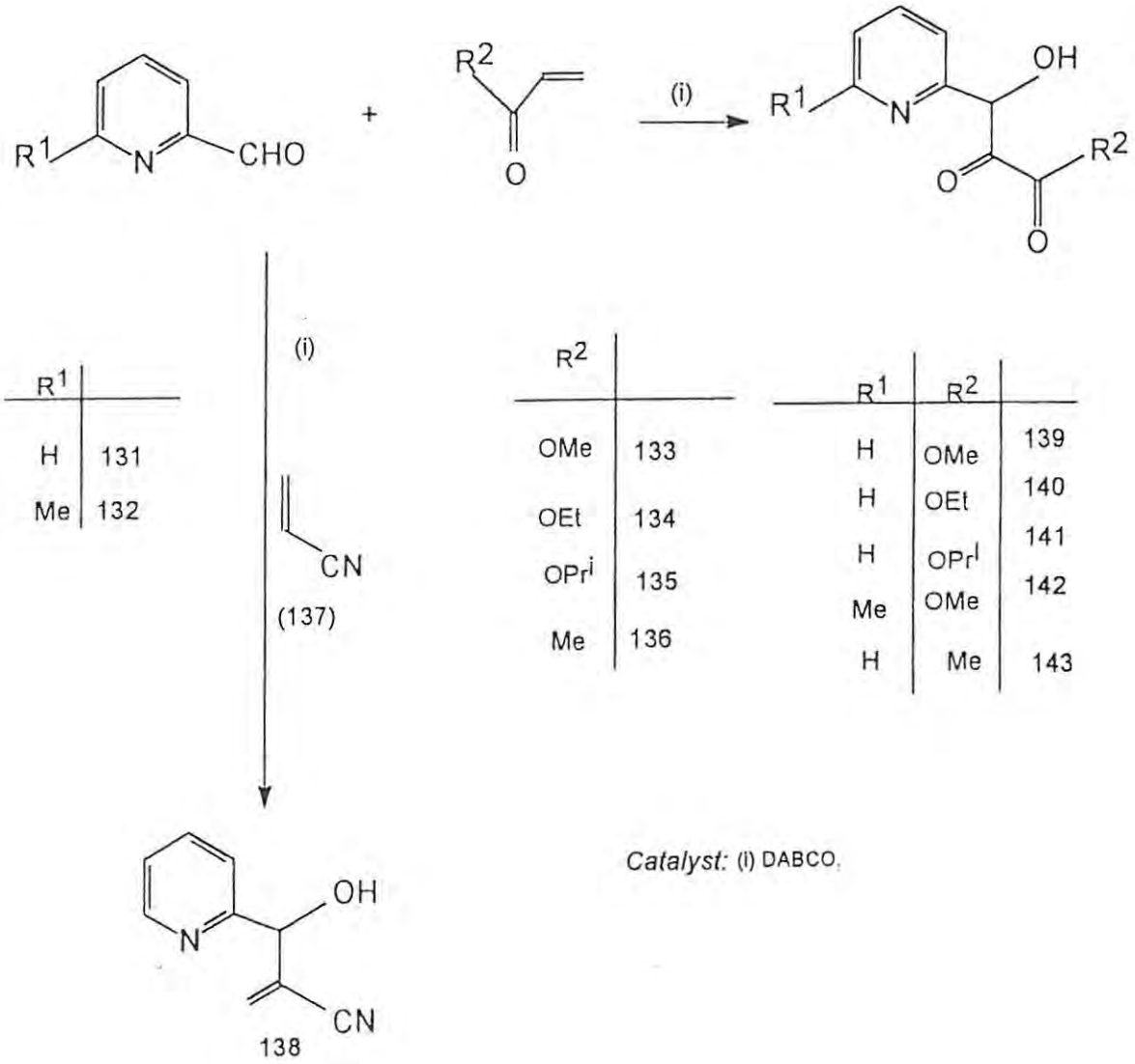
The reaction mechanism is envisaged to be an addition-elimination process. In the first step, a nucleophilic attack on the α,β-unsaturated system by the tertiary amine occurs as shown in Scheme 39,p 54, followed by the nucleophilic attack of the zwitterionic intermediate **(129)** on the aldehyde. Elimination of the tertiary amine, then leads to the Baylis-Hillman product. It was also found that varying the substituent (R^1) on the aldehyde and the substituent (R^2) on the acrylate ester influences the reaction rate. In the case of the acrylate esters, the electron-releasing inductive effect of the alkyl substituent (Me < Et < Pr^i) destabilizes the zwitterion **(129)**, subsequently decreasing the equilibrium constant K_1 and hence k_{obs}, since $k_{obs} = k_2 K_1$ (Equation 3).

For the present kinetic and mechanistic study of the thermal cyclization of selected Baylis-Hillman products to indolizines, it was necessary to prepare a range of appropriate substrates **(138-143)** (Scheme 40,p 55). Reaction of the electrophilic pyridine-2-carboxaldehydes and the acrylate esters in the presence of DABCO as catalyst at room temperature in chloroform, afforded after 2 days 3-hydroxy-2-methylenealkanoate esters **(139-142)** in good yields (Scheme 40,p 55).[57] The heterocyclic aldehydes used were pyridine-2-carboxaldehyde **(131)** and 6-methylpyridine-2-carboxaldehyde **(132)** and the acrylate esters used were methyl acrylate, ethyl acrylate and isopropyl acrylate. Methyl acrylate and ethyl acrylate were commercially available. The isopropyl acrylate, however, was prepared from acryloyl chloride and isopropyl alcohol. Similar treatment of pyridine-2-carboxaldehyde **(131)** with acrylonitrile **(137)** and methyl vinyl ketone (MVK) **(136)** afforded the hydroxy derivatives **(138)** and **(143)** (Scheme 40,p 55) respectively, rapidly and in very high yield (*ca.* 90%). The increased reactivity of acrylonitrile and methyl vinyl ketone over the acrylate esters can be attributed to the greater electrophilic nature of the unsaturated ketone and the nitrile substrates. Reference has already been made to the electron-releasing inductive effect of the alkyl substituent (Me < Et < Pr^i) in acrylate esters, which destabilizes the zwitterion **(144a)**, and decreases the rate of reaction.

SCHEME 39


N
N
OR2
O
K1
N
+N
O
H
H
OR2
129
R1
H
O
k2
N
+N
O
H
H
OR2
O
R1
130
N
N
+
R1
OH
OR2
O
131

SCHEME 40



R^1	
H	131
Me	132

R^2	
OMe	133
OEt	134
OPr^i	135
Me	136

R^1	R^2	
H	OMe	139
H	OEt	140
H	OPr^i	141
Me	OMe	142
H	Me	143

Catalyst: (i) DABCO.

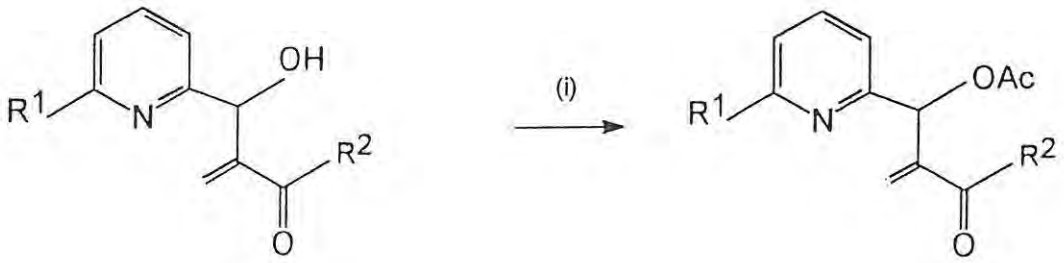
2.1.2 ACETYLATION

The thermal cyclization of the Baylis-Hillman products at *ca* 140°C is characterised by extreme charring and low yields of the indolizine derivatives. It was reported that when the hydroxy group was replaced by a better leaving group, like the acetoxy group, thermal cyclization readily afforded the indolizines in good yields.[57] As mentioned in section 1.7, one of the aims of this research project was the kinetic and mechanistic study of this thermal cyclization, and it was therefore necessary to prepare acetylated derivatives. The hydroxy compounds **(138-142)** were heated with neat acetic anhydride at 100°C for 0.5 h to afford the respective acetoxy derivatives in good yields (Scheme 41,p 57). The hydroxy compound **(143)** from the Baylis-Hillman reaction of pyridine-2-carboxaldehyde and methyl vinyl ketone cyclizes directly to afford the respective indolizine derivative and, consequently, the Baylis-Hillman product **(143)** was not acetylated. The relative ease in cyclization, observed here can be attributed to the enhanced electrophilicity of the vinyl ketone system.

2.1.3 THERMAL CYCLIZATION

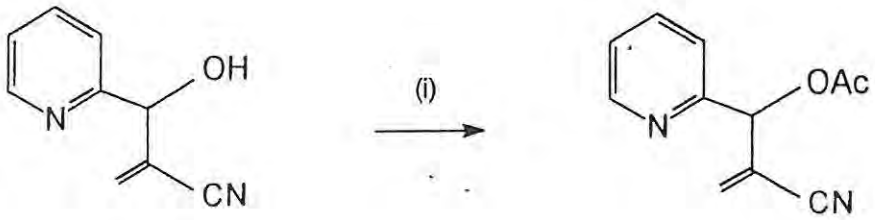
A pre-requisite for the proposed kinetic study of the thermal cyclization of the acetylated compounds was the unambiguous structural analysis of the cyclized, indolizine products. Therefore, the series of acetylated compounds **(144-148)** were heated at 120°C for 1 h to afford

SCHEME 41



R^1	R^2	
H	OMe	139
H	OEt	140
H	OPr^i	141
Me	OMe	142

R^1	R^2	
H	OMe	144
H	OEt	145
H	OPr^i	146
Me	OMe	147



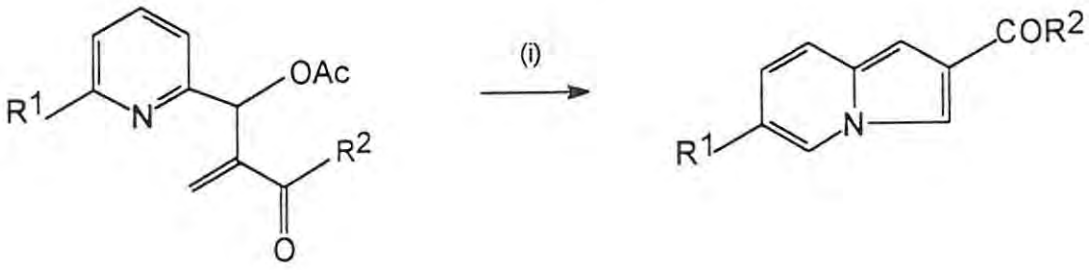
138 148

Reagent: (i) Ac_2O, 100^0C.

the indolizine products **(149-153)** (Scheme 42,p 59). The hydroxy and acetoxy precursors and the indolizine products were identified by infra-red spectroscopy and ^{1}H NMR spectroscopy. The ^{1}H NMR signal assignments were essentially consistent with the data published earlier.[51] The ^{1}H NMR spectra of the hydroxy precursors **(138-143)** are characterised by the broad hydroxy proton peak at 5.21-5.77 ppm (Figure 1,p 60). The ^{1}H NMR spectra of the acetoxy derivatives **(144-148)** are characterised by a singlet at *ca.* 2.1 ppm due to the 3 acetoxy protons (Figure 2,p 61) and by the absence of the broad hydroxy proton peak. In all other chemical shifts, the spectra of the hydroxy precursors and their acetoxy derivatives are very similar.

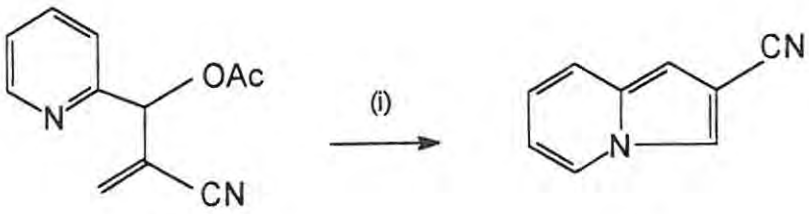
The ^{1}H NMR spectra of the cyclized, indolizine products **(149-153),** however, differ widely from respective acetoxy precursors (Figure 3,p 62). The acetate singlet observed at *ca* 2.1 ppm in the acetoxy compounds is of course, absent in the spectra of the corresponding indolizines. The 6'-H proton doublet (Figure 2,p 61) observed at 8.48-8.77 ppm in the spectra of the acetoxy precursors moves up field in the spectra of the respective indolizines and occurs at *ca.* 7.9 ppm (Figure 3). The acetoxy precursors are also differentiated from the indolizine products by the vinyl proton signals which, in the acetoxy compounds, occur as a pair of, broad uncoupled singlets in the range 6.08-6.75 ppm but, in the cyclised products, the single "vinyl" proton occurs further downfield at *ca.* 7.7 ppm as a multiplet (Figure 3,p 62).

SCHEME 42



R^1	R^2	
H	OMe	144
H	OEt	145
H	OPr^i	146
Me	OMe	147

R^1	R^2	
H	OMe	149
H	OEt	150
H	OPr^i	151
Me	OMe	152



148 153

Reaction condition: (i) 1 h, 120^{0}C.

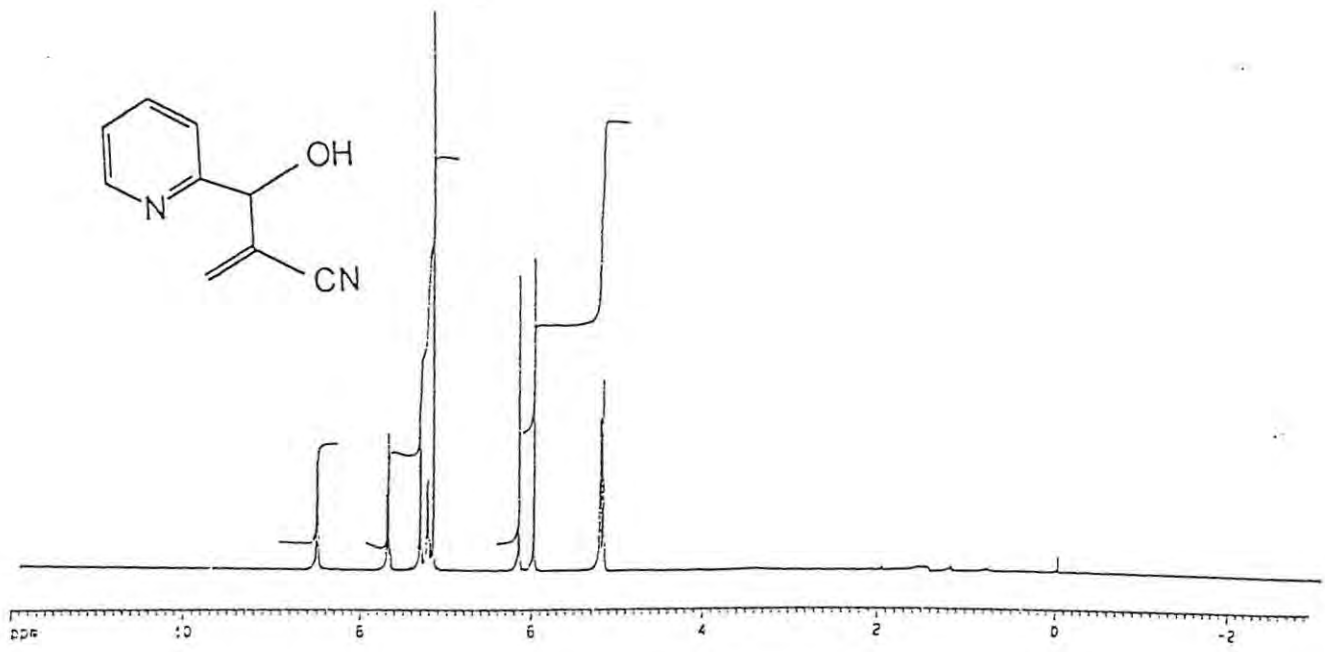


FIGURE 1. ^{1}H NMR spectrum of 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile (138).

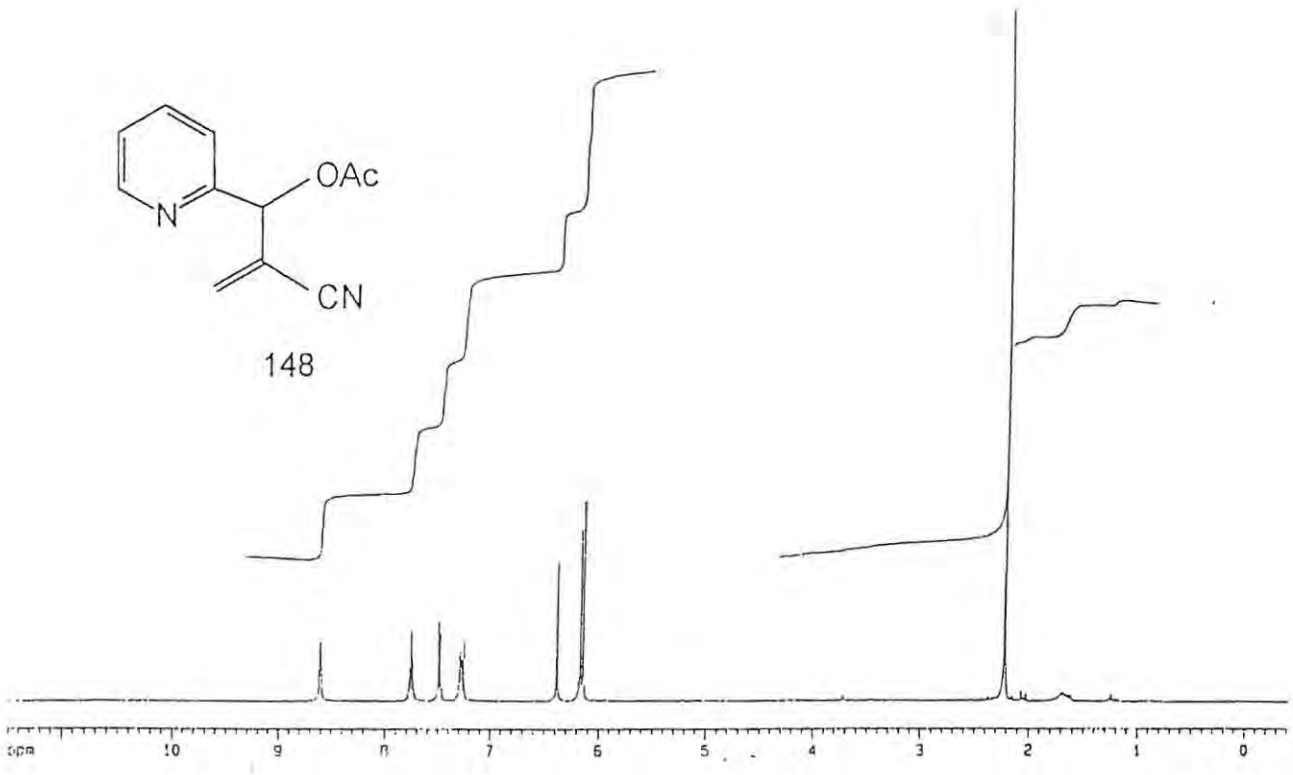


FIGURE 2. ^{1}H NMR spectrum of 3-acetoxy-2-methylene-3-(2-pyridyl)propanenitrile (148).

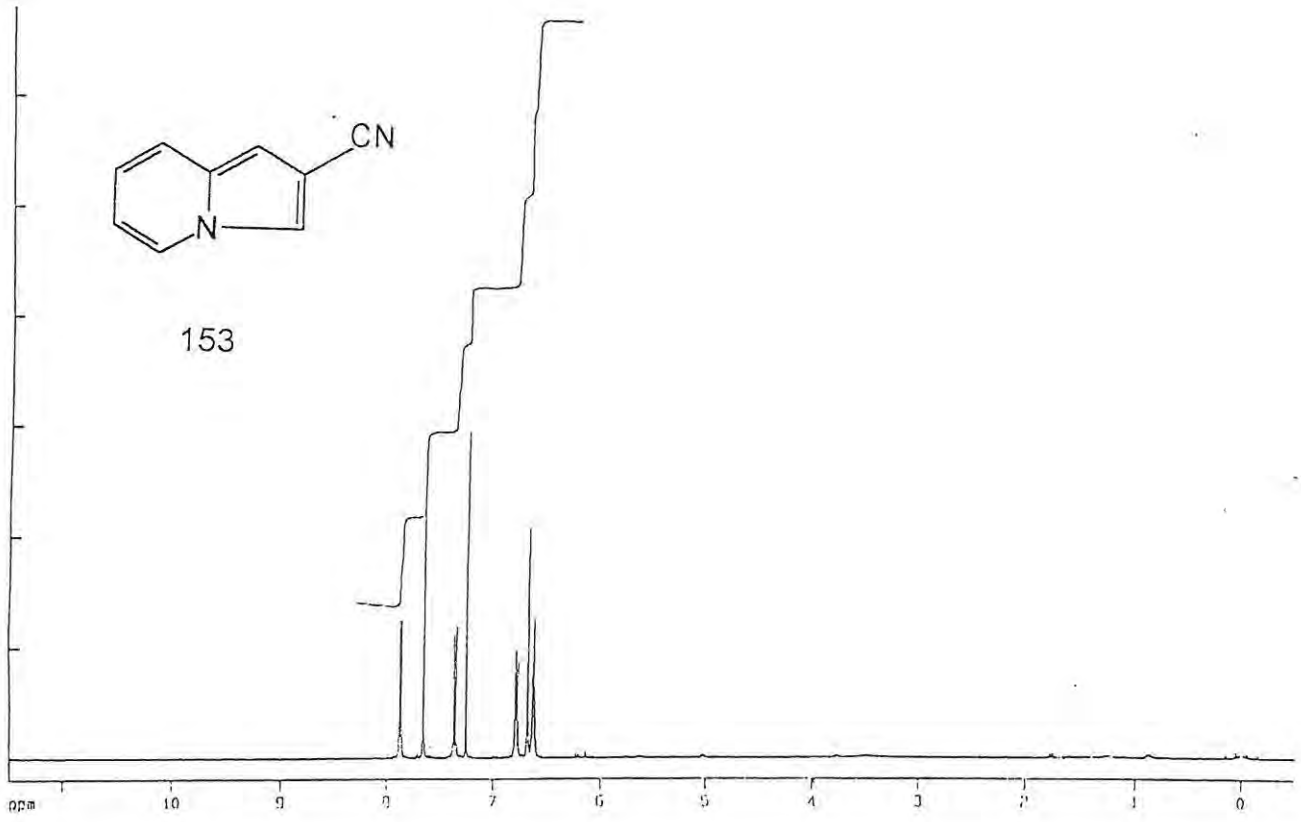


FIGURE 3. ^{1}H NMR spectra of 3-cyanoindolizine (153).

2.2 KINETIC AND MECHANISTIC STUDIES OF THE THERMAL CYCLIZATION OF THE 2-PYRIDYL DERIVATIVES TO INDOLIZINES

The thermal cyclization of the acetoxy compounds (**144-148**) (Scheme 42,p 59) was monitored by ^{1}H NMR spectroscopy. Although, in the original work,[57] the thermal cyclization to indolizines was successfully accomplished by heating the neat pyridyl precursors, in the present kinetic study, the cyclization was performed in an **NMR** tube and followed by **^{1}H NMR** spectroscopy. Consequently a suitable solvent was required and DMSO-d_6 proved to be ideal, allowing efficient cyclization in the temperature range of interest, *viz.*, 363-383 K. The **^{1}H NMR** spectra of the reaction mixture during the first 10 minutes show significant changes which are consistent with the formation of the cyclized product (Figure 4). The ^{1}H NMR spectra detailed in Figure 5 illustrates cyclization of isopropyl acrylate at 378 K.

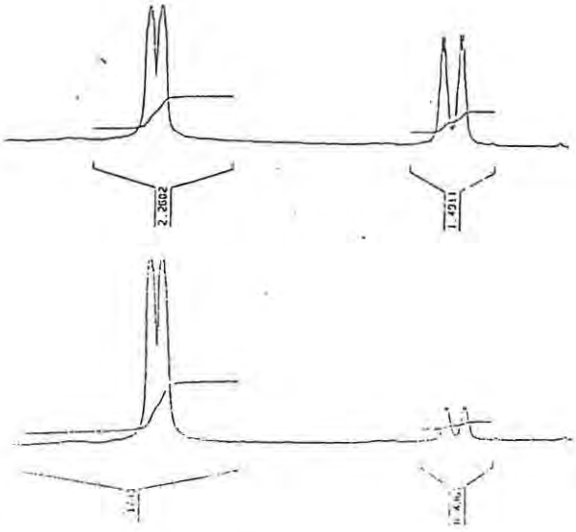


FIGURE 4. ^{1}H NMR spectra at 10 minute intervals of the cyclization of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate at 378 K.

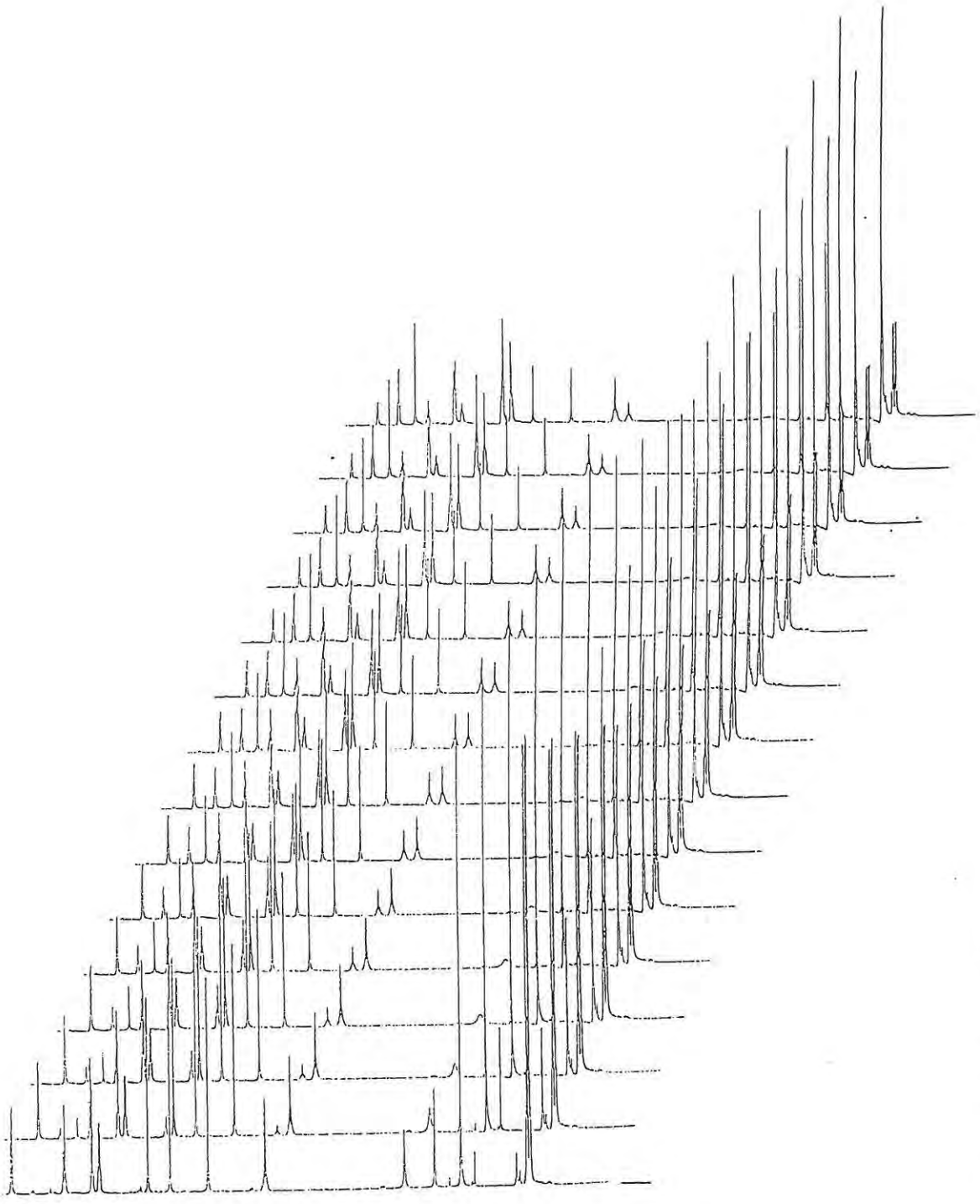


FIGURE 5. ^{1}H NMR spectra of the cyclization of isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate at 378 K, at 10 min. intervals.

In most cases, the thermal cyclization was followed by monitoring the integral ratios of the 6'-H proton which, in the acetoxy compounds, occurs at *ca.* 8.7 ppm, but in the spectra of the cyclized indolizine product, occurs at *ca.* 8 ppm. In the case of the acetoxy precursor (**147**) (which has a methyl group substituted for the 6'-H, the cyclization was followed by monitoring the integral ratios of the vinyl protons. All experiments were duplicated and the experimental data was shown to follow first order kinetics overall (Equation 4). Excellent linear correlations ($R^2 > 0.99$) were observed for the first-order plots of the kinetic data, in all cases examined (Figure 6,p 67). When the concentration of the substrate (**140**) was halved, it was observed that the rate of the reaction was also halved, which conclusively establishes the first-order character of the cyclization. The kinetic data for the thermal cyclization of the acetoxy precursors are summarised in Table 3 (p 68).

$$\text{Rate} = k_{obs}\,[\text{substrate}] \qquad (4)$$

The proposed mechanism for the cyclizaton of the methyl carboxylate substrate (**144**) is illustrated in Scheme 43,p 69. The cyclization is envisaged to be an addition-elimination process, initiated by intramolecular nucleophilic attack of the pyridyl nitrogen to the α,β-unsaturated moiety. The influence of the conjugated electron-withdrawing substituent (COR^2 or CN) cannot be over-emphasised since, in it's absence, the cyclization could occur only by direct displacement (S_N') of the acetoxy group. This requires drastic conditions as illustrated by a report by Boekelheide and Windgassen,[58] who had to heat 3-acetoxy-3-(6-methyl-2-pyridyl)

propene to 450°C to synthesise 5-methylindolizine in 30% yield.

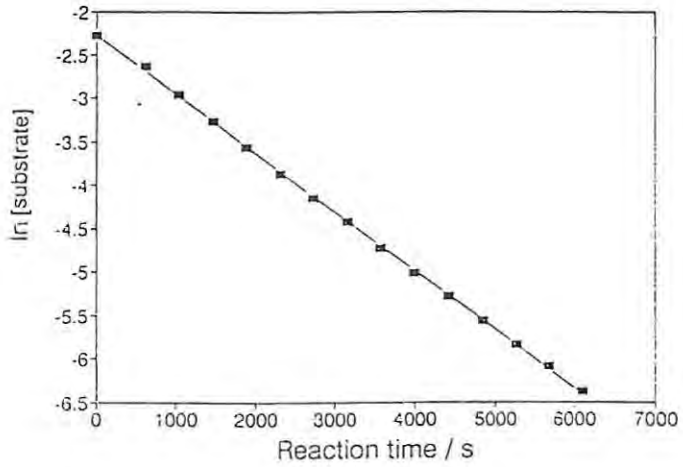
The rate-determining step in the proposed mechanism (Scheme 43,p 69) is presumed to involve elimination of acetate and formation of an intermediate cation (**144b**). The reaction rate can then be expressed in terms of equation 5, which for $k_2K_1 = k_{obs}$ is identical to the experimentally determined rate equation (Equation 4,p 65).

$$\text{Rate} = k_2 K_1 [144] \qquad (5)$$

$$k_2 K_1 = k_{obs} \qquad (6)$$

From the rate constants (k_{obs}, Table 3), it is clearly evident that the reaction rate is sensitive to the nature of the substituent (entries 2,5 and 7). The electron releasing inductive effect of the alkyl substituent (Me < Et < Pr^i) destabilizes the zwitterionic intermediate (**144a**), subsequently decreasing the equilibrium constant K_1 and hence k_{obs}, since $k_{obs} = k_2 K_1$ (Equation 6). It was found that, introducing a 6'-methyl group on the 2-pyridyl precursor more than doubled the rate constant (see entries 2 and 8). This enhancement in rate constant observed, can be attributed to the electron releasing inductive effect of the methyl group which increases the nucleophilicity of the pyridyl nitrogen.

The reduction in the rate constant was observed when the ester functionality is replaced by nitrile group. This trend, however, correlates with the reported order of reactivity of



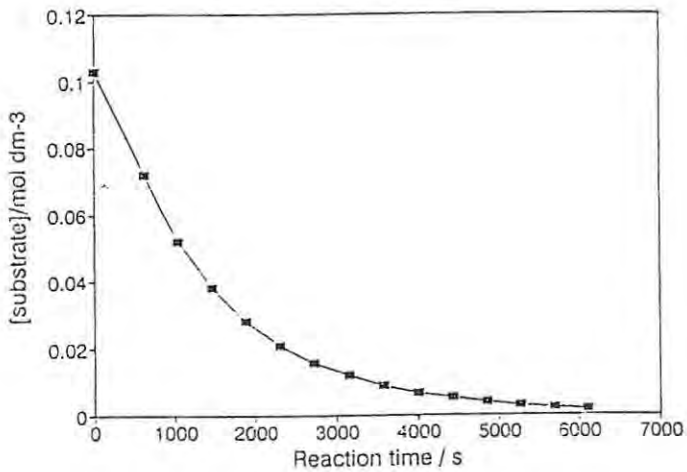


FIGURE 6. Methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (144c) at 388.8 K.

TABLE 3. KINETIC DATA FOR THE THERMAL CYC LIZATION OF 2-PYRIDYL DERIVATIVES.

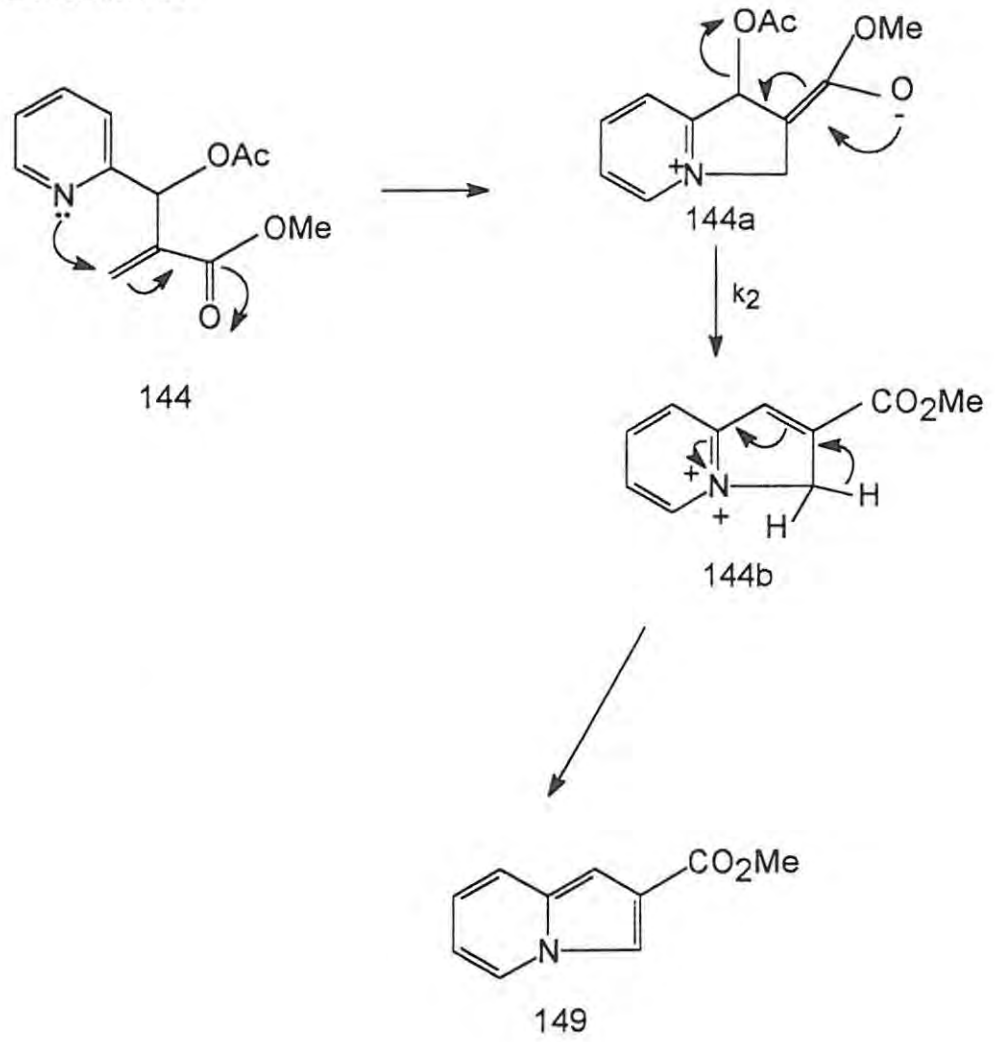
Entry	substrate	R^1	R^2	Substrate Conc.[a]/ mol.dm^{-3}	T[b]/K	$k_{obs.}$[c]/ $10^{-5}s^{-1}$
1	144a	H	CO_2Me	0.1	363(367.3)	10
2	144b			0.1	373(378.0)	24
3	144c			0.1	383(388.8)	61
4	145a	H	CO_2Et	0.1	363(367.3)	7.2
5	145b			0.1	373(378.0)	19
6	145c			0.1	383(388.8)	42
7	146	H	CO_2Pr^i	0.1	373(378.0)	18
8	147a	Me	CO_2Me	0.1	373(378.0)	52
9	147b			0.05	373(378.0)	50
10	148	H	CN	0.1	373(378.0)	9.2
11	139	H	CO_2Me	0.1	383(388.8)	0.39

[a]Nominal initial concentration

[b]Nominal setting followed, in parenthesis, by the corrected temperature.

[c]First order rate constants; mean of duplicate runs.

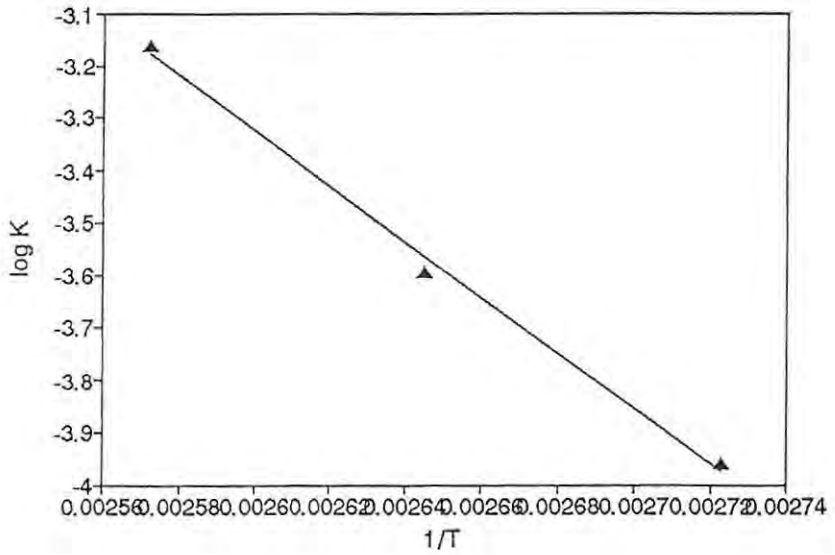
SCHEME 43



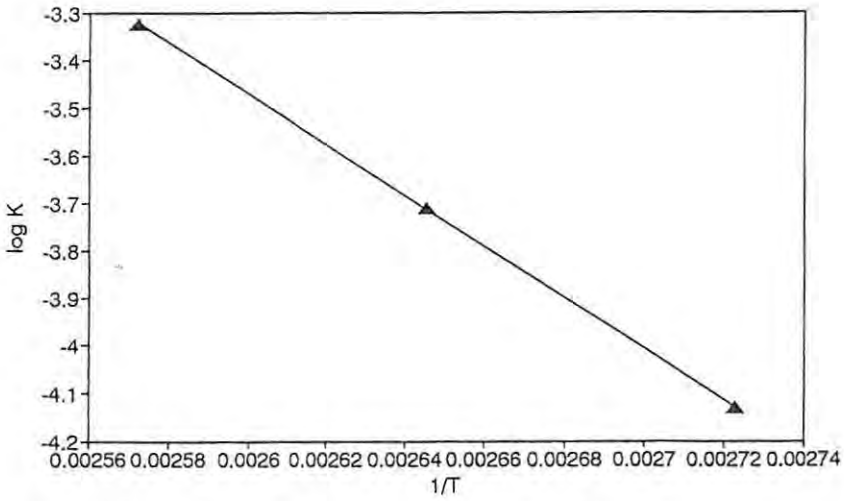
α,β-unsaturated compounds towards nucleophilic attack by amines ,*i.e.*, CH_2=$CHCO_2Me$ > CH_2=CHCN.[58-60] It is apparent that the temperature has a marked effect on the rate of the cyclization; an increase in the cyclization temperature increases the reaction rate dramatically. For example, when the temperature for the cyclization of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**144**) was increased by 20°C, the reaction rate increased six-fold (see entries 1 and 3, Table 3,p 68). A similar increase in the temperature of the ethyl ester analogue (**145**), increased the reaction rate six times (See entries 4 and 6, Table 3).

A significant reduction in the reaction rate was observed for cyclization of the hydroxy precursor (**139**) compared with it's acetoxy derivative (**144**) (see entries 3 and 11, Table 3,p 68). This emphasises the influence of the leaving group; the acetoxy group, being a better leaving group than the hydroxy group facilitates faster cyclization.

The activation energies for the formation of the indolizine-2-carboxylate esters (**149**) and (**150**) were determined from plots of log k_{obs} against 1/T at 367.3, 378.4 and 388.8 K and compared (Figure 7,p 71). The activation energy calculated for the methyl ester (**144**) was found to be 101.6 KJ/mol and that for the ethyl ester (**145**) was found to be 102.6 KJ/mol. These values are consistent with the observation that the rate of formation of the methyl indolizine-2-carboxylate (**149**) is slightly greater than it's ethyl ester analogue (**150**).



(a)



(b)

FIGURE 7. a) Methyl indolizine-2-carboxylate (149) b) Ethyl indolizine-2-carboxylate (150).

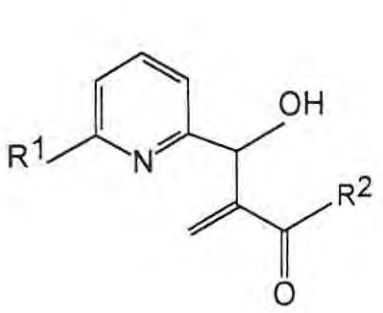
2.3 EXPLORATION OF AN ALTERNATIVE ROUTE TO INDOLIZINES VIA HALOGENATED DERIVATIVES

Reference has already been made to the significance of a good leaving group, such as acetate in the 2-pyridyl precursors, their effect being to accelerate cyclization. Since halogens are good leaving groups, it was speculated that replacing the hydroxy group in the Baylis-Hillman products with a halogen, would facilitate efficient cyclization.

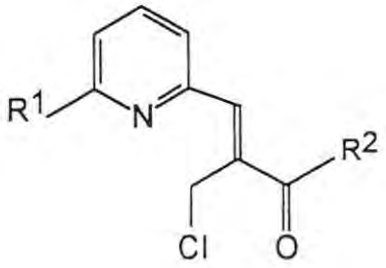
2.3.1 CHLORINATION OF HYDROXY PRECURSORS

Several methods for chlorinating the hydroxy precursors were considered. Of the methods examined, treatment of the hydroxy ester with thionyl chloride in the presence of dimethylformamide (DMF) (using 1,2-dichloroethane as solvent at 60^0C for 45 minutes under nitrogen) was the most efficient method.[61] Consequently, chlorination of the hydroxy derivatives (**138, 139, 140, 142** and **143**)) was attempted. Unfortunately,only the hydroxy derivatives (**139, 140** and **142**) afforded the respective chloro compounds (**154, 155 and 156**) (Scheme 44,p 73); the ^{1}H, ^{13}C and DEPT NMR data, IR and MS data, conclusively established the structure of these compounds as the chloromethyl derivatives (**154-156**) and not the corresponding allyl chlorides (**157, 158 and 159**).

SCHEME 44

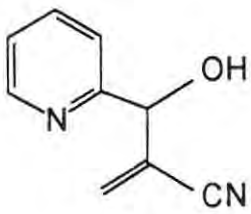


(i)



R^1	R^2	
H	OMe	139
H	OEt	140
Me	OMe	142
H	Me	143

R^1	R^2		% YIELD
H	OMe	154	31
H	OEt	155	79
Me	OMe	156	90
H	Me	–	–



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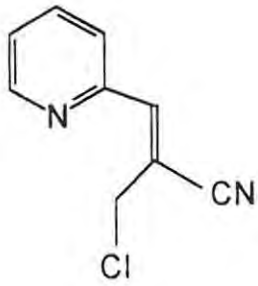
(i)



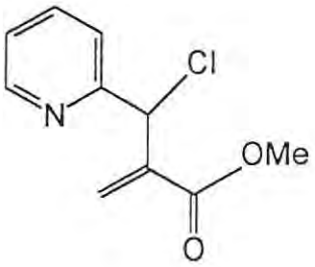
Reagents: (i) $SOCl_2$, DMF and 1,2-DICHLOROETHANE

The ^{1}H NMR spectra of the chloro compounds (**154-156**) are characterised by a singlet observed at *ca.*, 5.1 ppm due to the 2 chloromethyl protons (CH_2Cl) (Figure 8,p 76). The ^{13}C and DEPT NMR spectra of these compounds show a peak at *ca.*, 38 ppm which corresponds to CH_2Cl (Figure 9-10,p 77-78); the IR spectra are characterised by the absence of an OH band. The mass spectra of the chloro compounds showed the corresponding molecular ion peak.

It is interesting to note that the nucleophilic attack by thionyl chloride proceeds *via* allylic displacement ($S_{N'}$) rather than direct displacement (S_N). The reaction is envisaged to occur as shown in Figure 11(p 75), with the allylic carbocation undergoing attack by Cl^- either *via* a tight ion pair (a) or, possibly, a 6-membered transition state (b). On the other hand, acetylation does not involve fission of the C(3)-O bond and, therefore, leads to the observed allylic acetate derivatives (Figure 12,p 75).

2.3.2 ATTEMPTED THERMAL CYCLIZATION OF THE CHLORINATED DERIVATIVES

Thermal cyclization of the chlorinated derivatives (**154-156**) was attempted at temperatures in the range 110-140°C. However, after heating, the **^{1}H NMR** spectra of the mixtures failed to indicate the presence of the expected cyclized products. In fact,it seems that the halogenated derivatives decompose readily, even on standing at room temperature.



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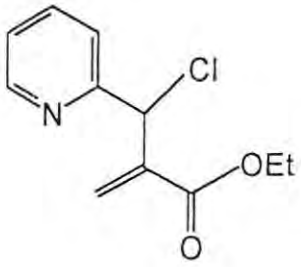

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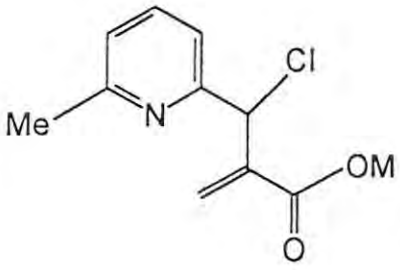

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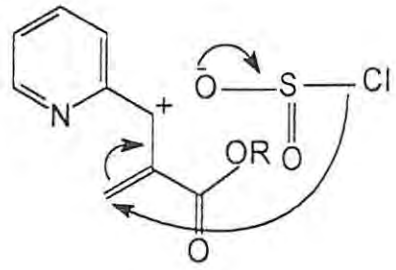
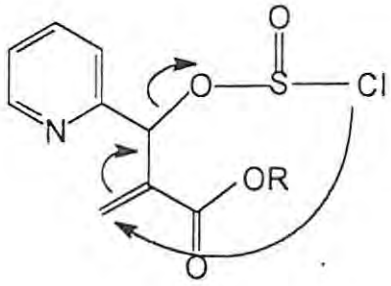
FIGURE 11

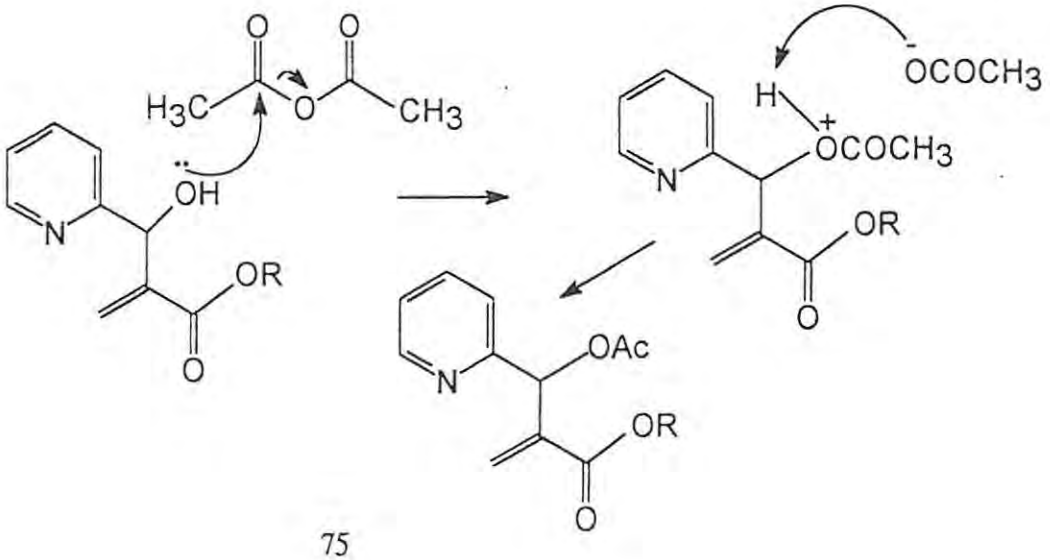


(a)



(b)

FIGURE 12



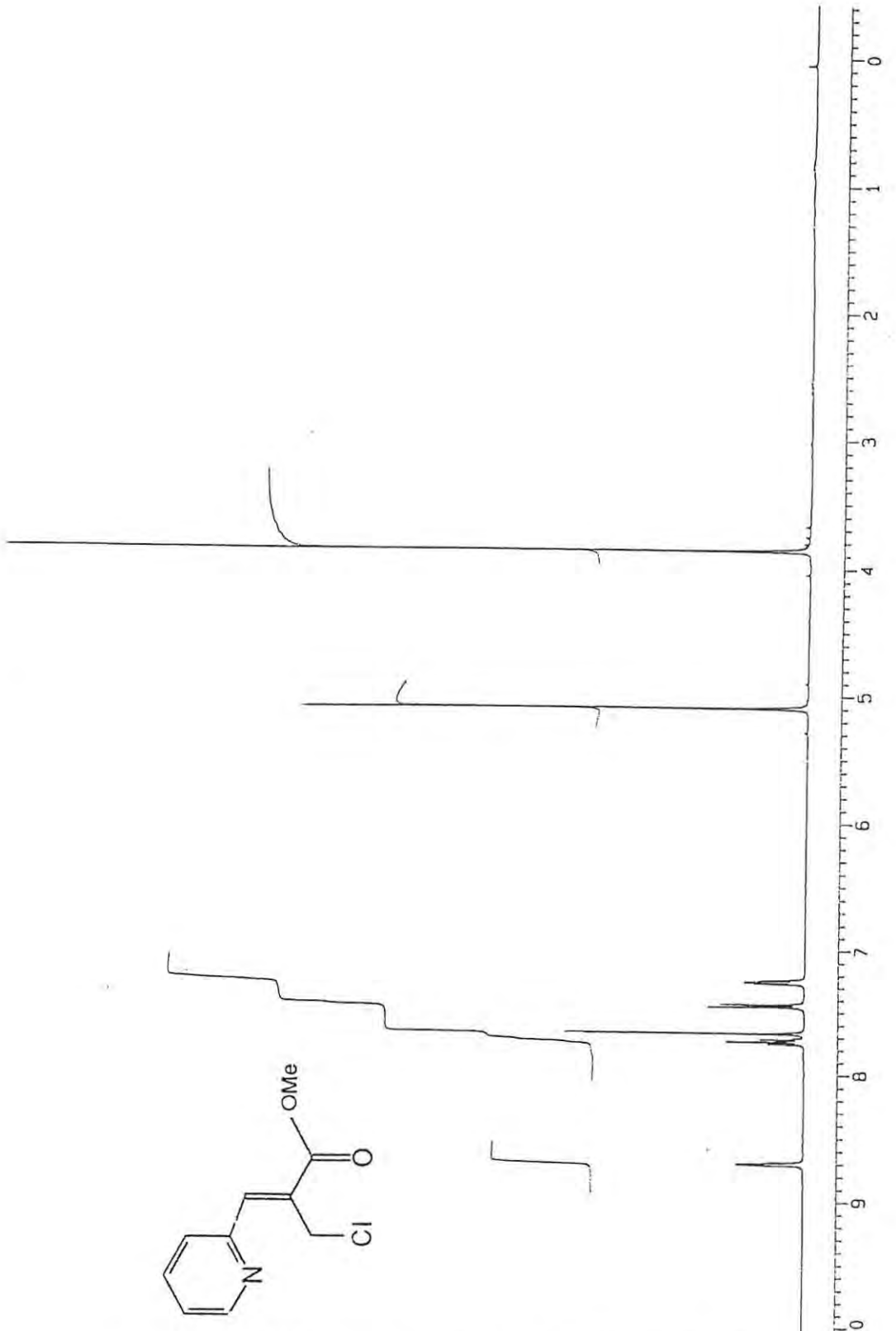


FIGURE 8. ^{1}H NMR spectra of methyl 2-chloromethyl-3-(2-pyridyl)propenoate (154).

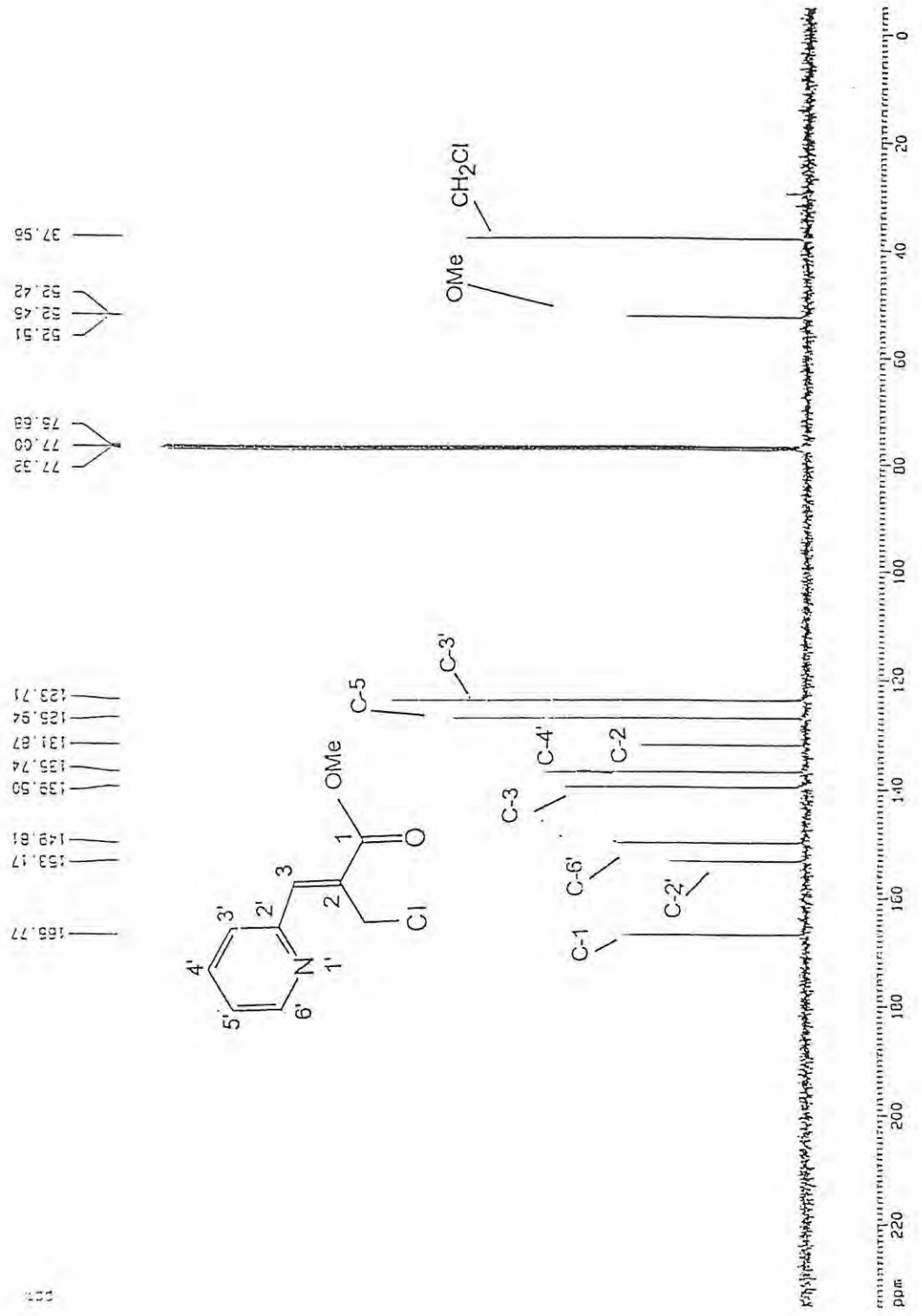


FIGURE 9. ^{13}C NMR Spectra of methyl 2-chloromethyl-3-(2-pyridyl)propenoate (154).

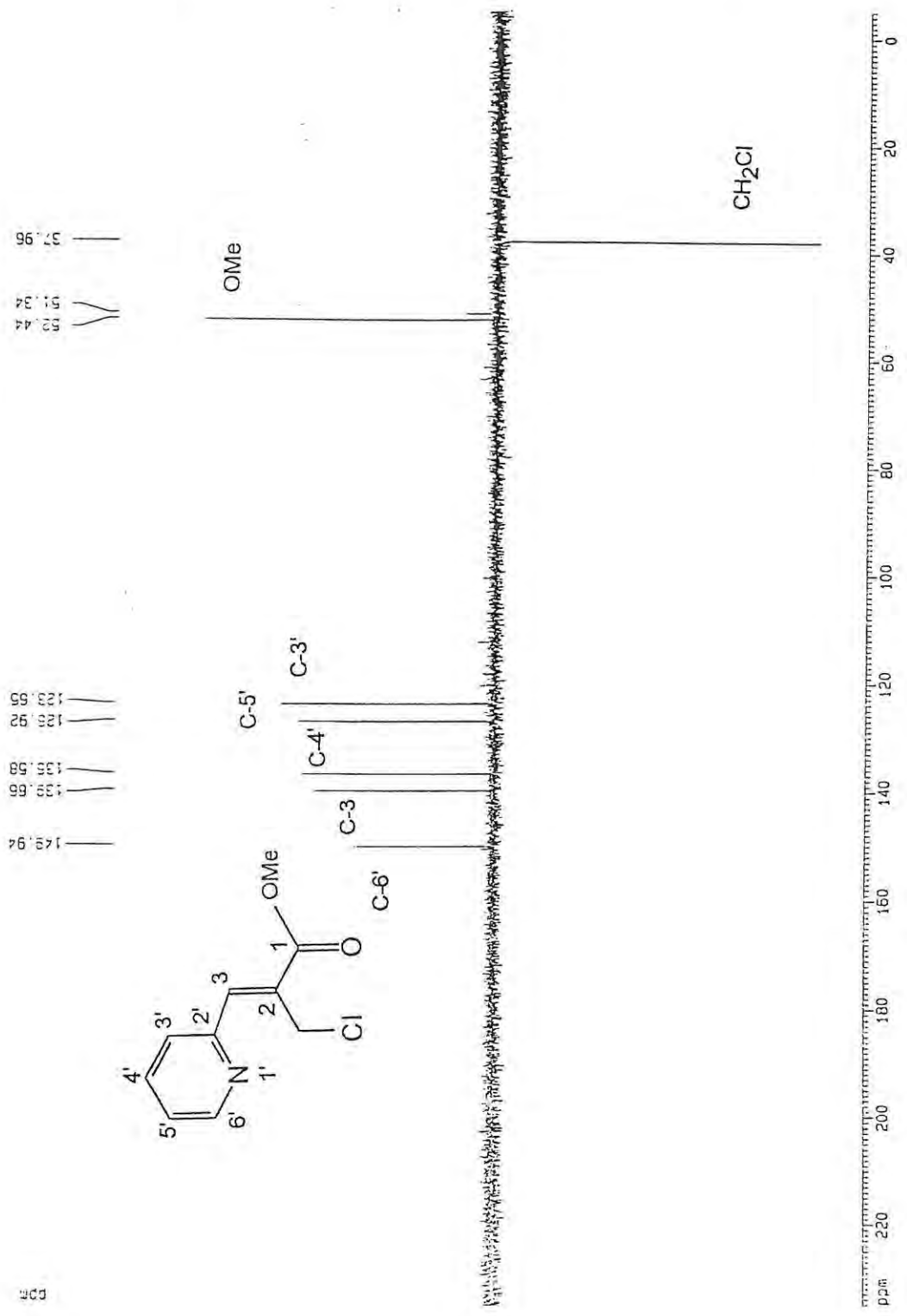


FIGURE 10. DEPT NMR spectra of methyl 2-chloromethyl-3-(2-pyridyl)propenoate(154).

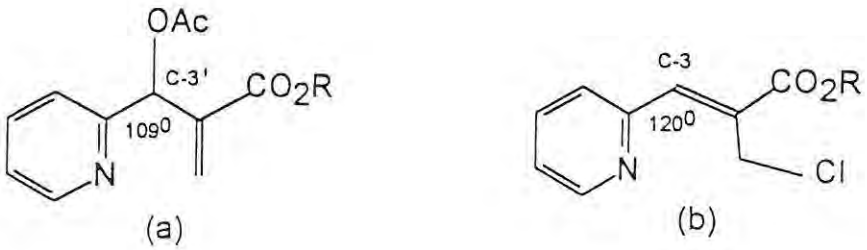
This failure in cyclization may be attributable to the fact that in the halogenated compounds, nucleophilic attack by the nitrogen is more difficult than in the 3-acetoxy compounds (Figure 13b,p 80) because C-3 is sp^2 hybridised in the chloro compounds (Figure 13a,p 80) and therefore, the increased bond angle (from *ca* 109^0 to *ca* 120^0) increases the distance between the nitrogen and the electrophilic centre C-3'.

2.3.3 OTHER ATTEMPTED CHLORINATION REACTIONS

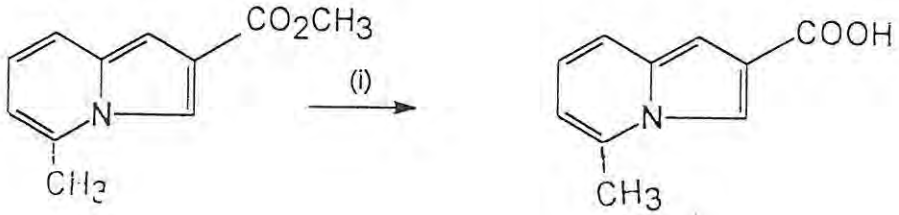
Several other methods for chlorinating the hydroxy compounds were investigated, one of which was the treatment of hydroxy compounds (**139,140 and 142**) with HCl/H_2SO_4.[62] The mixture was left to react at room temperature for 1 day. The spectra of the reaction mixtures after purification however, showed that no reaction had taken place.

Chlorination of the hydroxy compound (139) using PCl_5 was also attempted. The hydroxy compound was refluxed with PCl_5 in cyclohexane for 45 minutes and then kept in the cold room for 20 h.[63] The reaction mixture, after work-up and flash chromatography, afforded two fractions, of which one was the desired chloro compound (**154**) in very low yield 10%; the other fraction was the unreacted starting material. Chlorination of the hydroxy compound (**139**) with oxalyl chloride in benzene, however, afforded the chloro compound (**154**) in 20% yield.[64]

FIGURE 13



SCHEME 45



152 160

Reagents and Reaction conditions:(i) KOH/ EtOH, 16 h, HEAT.

Attempted chlorination of the hydroxy compound (**140**) with thionyl chloride in pyridine and with thionyl chloride in the presence of dimethyl aniline,[65] also failed to give the required chloroderivative (**155**). Similarly, treatment of the hydroxy compound (**140**) with the CCl_4 in the presence of triphenyl phosphine at room temperature for 51 h failed to effect chlorination.

2.3.4 ATTEMPTED BROMINATION AND IODINATION OF THE HYDROXY COMPOUNDS

Bromination of the hydroxy compound (**139**) with HBr/H_2SO_4 by stirring at room temperature was also attempted, but after two days, the unreacted starting material was isolated from the reaction mixture. Treatment of the hydroxy precursor (**139**) by stirring with HI and conc. H_3PO_4 for 5 days, also failed to give the required iodo derivative.[62]

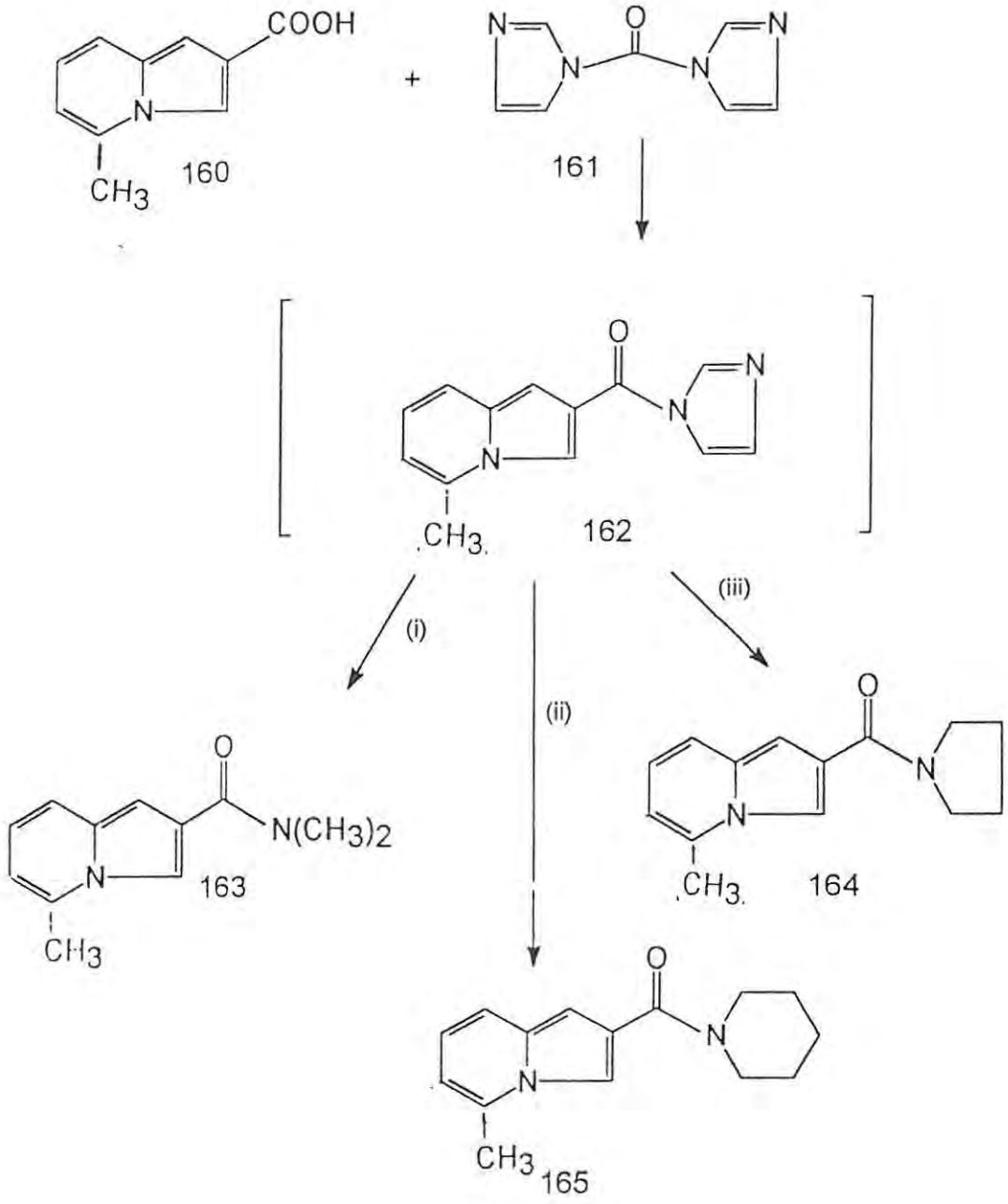
2.4 SYNTHESIS AND DYNAMIC NMR ANALYSIS OF NOVEL 5-METHYLINDOLIZINE-2-CARBOXAMIDES

2.4.1 SYNTHESIS OF NOVEL 5-METHYLINDOLIZINE-2-CARBOXAMIDES

As a pre-requisite for the synthesis of the 5-methyl indolizine-2-carboxamides, it was necessary to first synthesise 5-methylindolizine-2-carboxylic acid (**160**). The carboxylic acid (**160**) was obtained by hydrolysis of the ester, 5-methylindolizine-2-carboxylate (**152**) using a standard literature procedure [66] which involves refluxing with KOH/EtOH for 16 h (Scheme 45,p 80). The 5-methylindolizine-2-carboxamides (**162-164**) were prepared by reacting the carboxylic acid (**160**) with 1,1'-carbonyldiimidazole (CDI) (**161**) in dimethyl formamide (DMF), to form the intermediate (**161**), which was subsequently treated with dimethylamine, pyrrolidine or piperidine to afford the 5-methylindolizine-2-carboxamides (**163-165**) (Scheme 46,p 83).[67] The structure of these carboxamides were conclusively established by means of ^{1}H and ^{13}C **NMR**, **IR** and high resolution **mass** spectroscopy.

As part of the present investigation, the synthesis of indolizine-3- carboxamides was also attempted. As a pre-requisite, it was necessary to prepare the indolizine-3-carboxylic acid precursor. Ethyl indolizine-3-carboxylate (**169**) was prepared following a literature procedure[68-69] which is summarised in Scheme 44,p 84.

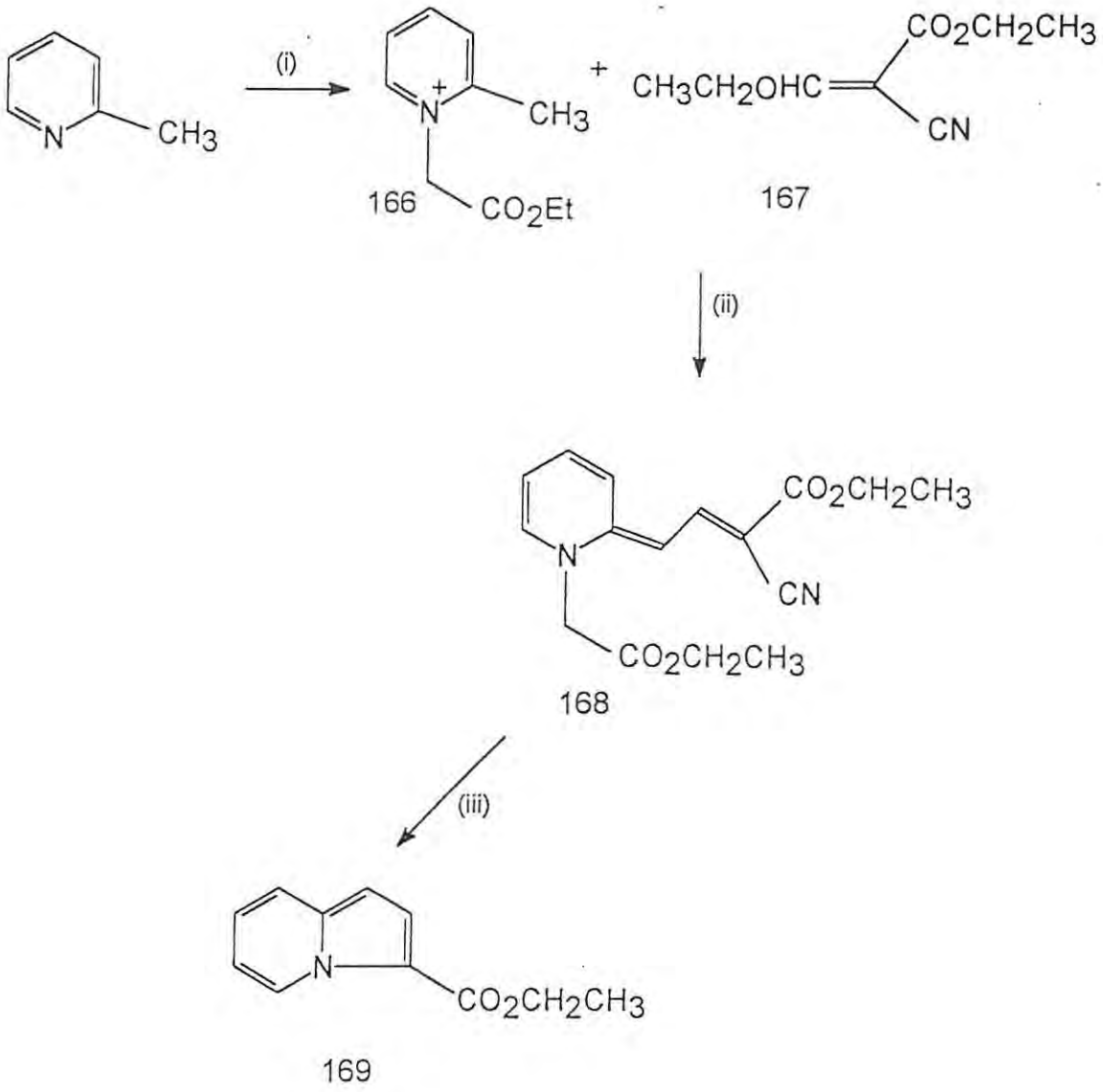
SCHEME 46



Reagents: (i) DIMETHYL AMINE ; (ii) PIPERIDINE;

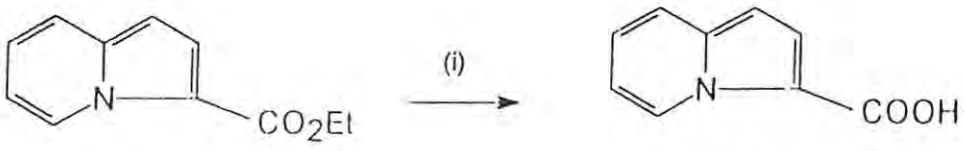
(iii) PYRROLIDINE..

SCHEME 47



Reagents:(i) ETHYL BROMOACETATE; (ii) K_2CO_3 /$CHCl_3$; (iii) XYLENE, HEAT.

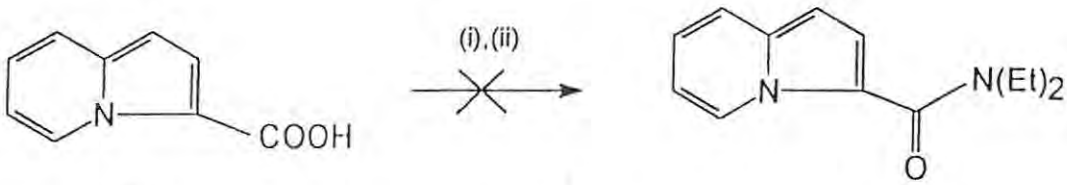
SCHEME 48



169 170

Reagents: (i) KOH /EtOH, HEAT

SCHEME 49



170 171

Reagents: (i) 1,1'-CARBONYLDIIMIDAZOLE; (ii) DIETHYL AMINE.

2-Methylpyridine was treated with ethyl bromoacetate to afford the pyridinium salt (**166**) which, upon treatment with ethyl ethoxymethylene cyanoacetate (**166**) in the presence of potassium carbonate in chloroform for 3-4 days, gave the allylidenedihydropyridine (**168**) in 50 % yield. The allylidenedihydropyridine (**168**) was then refluxed with xylene for 3 days to afford ethyl indolizine-3-carboxylate (**169**) in 90% yield (Scheme 47,p 84). **NMR** and **IR** spectroscopic data for the ethyl indolizine-3-carboxylate (**169**) and all the precursors prepared were found to be consistent with the published data.

The ethyl indolizine-3-carboxylate (**169**) thus prepared, was refluxed with KOH in EtOH for 15 h to afford, after acidification, indolizine-3-carboxylic acid (**170**) (Scheme 48,p 85). Unfortunately an attempt to prepare *N,N*-diethylindolizine-3-carboxamide (**171**) (Scheme 49, p 85) by treating the acid (**170**) with CDI and diethylamine proved unsuccessful.

2.4.2 DYNAMIC NUCLEAR MAGNETIC RESONANCE STUDIES OF ROTATIONAL ISOMERISM IN 5-METHYLINDOLIZINE-2-CARBOXAMIDES

Rotational barriers in amides have been the subject of many dynamic nuclear magnetic resonance (DNMR) investigations.[70] In amides, the nitrogen lone-pair delocalization is responsible for the partial double bond character of the amide N-CO bond (Figure 14),

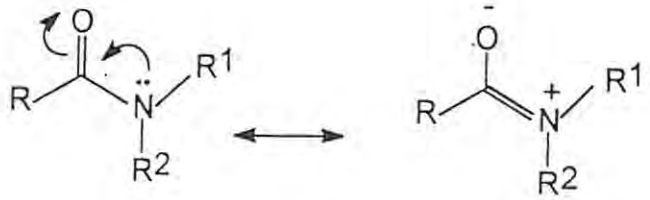


FIGURE 14.

consequently the amide N-CO bond has a large rotational barrier in the range 50-100 kJ/mol. In the NMR spectra of amides, the R^1 and R^2 groups (see Figure 14), even when $R^1 = R^2$ are chemically non-equivalent (*i.e.*, show separate chemical shifts) due to the anisotropy of the diamagnetic susceptibility of the amide carbonyl group. In the present investigation, rotational isomerism in the 5-methylindolizine-2-carboxamides **(163-165)** was studied using DNMR techniques, in which the observed splitting of the *N*-alkyl signals was explained by slow site-exchange of the *N*-alkyl substituents (Figure 15,p 88).

The ^{1}H NMR frequency separation ($\Delta\upsilon$) between the split signals at slow site exchange were in the range 14-57Hz. The coalescence temperatures (T_c) observed for all the amides **(163-165)** lay in the range 299-323 K. Rotational barriers in amides are generally relatively large and the amides **(164 and165)** studied showed splitting of the *N*-alkyl signals at normal probe temperature (303 K). This splitting is illustrated in the ^{1}H NMR spectra of compound **164** (see Figure 15,p 88).

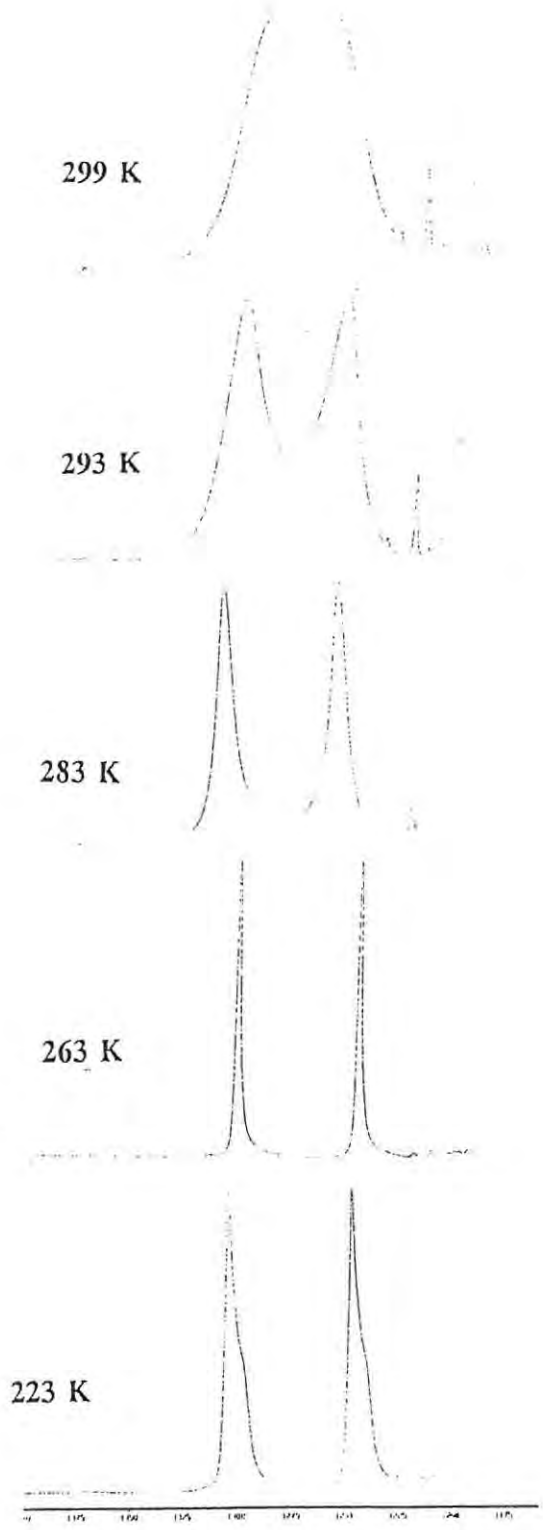


FIGURE 15. VARIABLE TEMPERATURE ^{1}H NMR SPECTRA SHOWING *N*-ALKYL. SIGNALS FOR *N*,*N*,5-TRIMETHYLINDOLIZIN-2-CARBOXAMIDE (163).

The spectra of the dimethyl amide showed splitting when the temperature of the probe was lowered below 299 K. The frequency separation ($\Delta \upsilon_c$) at coalescence temperature (T_c) was determined by a linear extrapolation from the frequency separation of the split signals at lower temperatures (see page 128-ff). Near coalescence errors in the direct measurement in $\Delta \upsilon_c$ become significant and following a procedure reported by Chen and Lai,[71] the linear plots were based on data obtained well below the coalescence temperature. The rotational energy barriers (ΔG^*) were calculated for all three of the amides using the equation (7). The site exchange rate constants (k) at 298 K were then determined from the rotational energy barrier using equation (8).[72]

$$\Delta G^* = RT_c (22.96 + \ln T_c/\Delta) \quad (7)$$

$$\ln k = \ln (k_b T/h) - \Delta G^*/RT \quad (8)$$

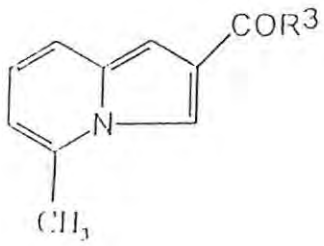
where k_b = Boltzmann constant

h = Planck constant

T = 298 K

The results are summarised in Table 5,p 90. The rotational energy barrier for the piperidine **(165)** was found to be significantly lower (58 KJ/mol) than the rotational barrier of *N,N*-dimethyl and the pyrrolidinyl amides (61 KJ/mol and 67 KJ/mol respectively). The rotational barriers (ΔG^*) obtained for the *N,N*-dimethyl, pyrrolidine and piperidine amides **(163-165)** (Table 5,p 90), correspond very closely to those obtained in a parallel study [73] for indolizine-2-carboxamide analogues which lack the 5-methyl group.

TABLE 5. DATA FROM DYNAMIC NMR ANALYSIS OF 5-METHYLINDOLIZINE-2-CARBOXAMIDES (163-165).



compd.	R^3	T_c/K	Δ υ/Hz	ΔG*/KJ/mol	k_{298}/s
163	$N(Me)_2$	298.42	51.7	61.3	111
164	$N(CH_2)_3CH_2$	323.16	34.3	67.7	9
165	$N(CH_2)_4H_2$	315.63	540.1	58.9	293

The tendency for the pyrrolidine amide to have a higher rotational energy barrier than the piperidine analogue has also been observed in chromone carboxamides and other systems.[74] In pyrrolidine amides, the nitrogen adopts the planar sp^2 arrangement more easily than the piperidine nitrogen due to ring conformational constraints, consequently the pyrrolidine nitrogen has more sp^2 character and hence more effective nitrogen lone-pair delocalization.[74] This effect may rationalise the higher rotational barrier for the pyrrolidine derivative (**164**) than for the piperidine analogue (**165**).

2.6 CONCLUSION

This investigation has been largely concerned with the mechanistic implication of a recently reported cyclization route to indolizines and conformational studies of indolizine-2-carboxamides.

The Baylis-Hillman reaction has been used to prepare various hydroxy precursors, acetylation and thermal cyclization of which has afforded a series of indolizine derivatives. An alternative route to 2-substituted indolizines *via* halogenated derivatives was explored and three novel chloro compounds were synthesised as potential indolizine precursors; attempted cyclization, however, failed to afford the expected indolizines. Methyl 5-methyl indolizine-2-carboxylate was used to prepare 5-methylindolizine-2-carboxylic acid, which was used as a precursor for the synthesis of three novel indolizine-2-carboxamides.

The kinetic study of the thermal cyclization of 2-pyridyl derivatives to 2-substituted indolizines showed that the cyclization reaction follows first-order kinetics. It was found that increasing the cyclization temperature has a marked effect on the rate of the reaction, temperature increases of 20°C resulting in a five- or six- fold increase in the rate constant. Activation energies for cyclization of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate and it's ethyl ester analogue were determined from plots of log k_{obs} versus 1/T and, not surprisingly, the faster reacting methyl ester was found to have the slightly lower activation energy.

The influence of substituents on the rate constant was explored and it has been found that rate constant is lowered by replacing the ester function with nitrile but that introduction of a 6'-methyl substituent on the pyridine nucleus more than doubles the rate constant. These results indicate that the 5-methyl substituent has little effect on the amide N-CO rotational energy barriers, where as the *N*-substituents have a marked effect. The rotational energy barriers for the 5-methylindolizine-2-carboxamides were determined using DNMR analyses and were found to be consistent with those recently obtained for indolizine-2-carboxamides.

Future research in this general area is expected to involve:

i) investigation of halogenated derivatives and their cyclization to indolizine derivatives.

ii) oxidation of Baylis-Hillman products to carbonyl derivatives and their potential cyclization to novel indolizines.

3 EXPERIMENTAL

3.1 GENERAL

NMR spectra of all compounds synthesised were recorded on either a Perkin-Elmer R12 60 MHz NMR spectrometer or a Bruker AMX 400 MHz NMR spectrometer using $CDCl_3$ or DMSO-d_6 solutions. The solvent peaks were used as internal references ($CDCl_3$: δ_H 7.25 and δ_C 77.0 ppm; DMSO-d_6: δ_H 2.50 and δ_C 39.7 ppm). IR spectra were recorded on a Perkin-Elmer 180 spectrophotometer using KBr discs, liquid films or $CHCl_3$ solutions. Low resolution mass spectra were recorded on a Hewlett Packard 5988A mass spectrometer. High resolution mass spectra were obtained by the Cape Technikon mass spectrometry unit using a Kratos high resolution mass spectrometer.

All compounds prepared were purified by chromatography. Flash chromatography[75] was achieved using Merck silica gel 60 [particle size 0.040-0.063 mm (230-400 mesh)]. Preparative layer chromatography was performed on Merck silica gel 60 PF_{254} plates and thin layer chromatography was performed on Merck silica gel 60 F_{254} precoated plates. TLC plates were analysed by inspection under UV light or using iodine vapour.

Solvents were dried using the following procedures:

(i) 1,2-Dichloroethane was distilled over P_2O_5.

(ii) Dimethylformamide was dried over 4A molecular sieves.

(iii) Ether was dried over sodium wire and then distilled under N_2 over sodium wire using benzophenone as indicator.

3.2.1 PREPARATION OF 2-PYRIDYL DERIVATIVES

3-Hydroxy-2-methylene-3-(2-pyridyl)propanenitrile (138).[57] - A solution of acrylonitrile (1.54 g, 29 mmol), DABCO (0.15 g, 1.3 mmol) and pyridine-2-carboxaldehyde (2.95 g, 28 mmol) in $CHCl_3$ (2 ml) was left to react overnight. The resulting reaction mixture was chromatographed [flash chromatography on silica gel; elution with dichloromethane-EtOAc (7:3)] to give 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile (**138**) (4.12 g, 92 %); δ_H (400 MHz; $CDCl_3$) 5.27 (2H, 2 × overlapping s, C*H*OH and OH), 6.02 and 6.22 (2H, 2 × s, C=C*H*) and 7.29-8.57 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 3200 br and 2225.

Methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (139).[57] - Pyridine-2-carboxaldehyde (4.3 g, 39 mmol) was added to a solution of methyl acrylate (3.6 ml, 40 mmol) and DABCO (0.206 g, 1.84 mmol) in $CHCl_3$ (2ml). The resulting reaction mixture was left to stand at room temperature for 3 days. Evaporation of the solvent afforded the crude ester, which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (3:7)] to give methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**139**) as a colourless oil (6.7 g, 90 %); δ_H (400 MHz; $CDCl_3$) 3.7 (3H, s, CH_3OCO) 5.5 (1H, s, OH), 5.9 (1H, s, 3-H), 6.3 (2H, s, $C=CH_2$) and 7.1-8.4 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 3400 br and 1715.

Ethyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (140).[57] - The experimental procedure employed for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**139**) was followed using ethyl acrylate (2.1 g, 21 mmol), DABCO (0.112 g, 1.0 mmol) and pyridine-2-carboxaldehyde (2.14 g, 20 mmol) in $CHCl_3$ (1 ml). The mixture was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (3:7)] to afford ethyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**140**) (2.7 g, 67%); δ_H (400 MHz; $CDCl_3$) 1.2 (3H, t, CH_2CH_3), 4.0 (2H, q, CH_2CH_3), 5.4 (1H, s, OH), 6.1 (1H, s, 3-H), 6.4 (2H, s, $C=CH_2$) and 7.1-8.4 (4H, m, ArH); υ_{max} (liquid film)/cm^{-1} 3400 br and 1715.

Isopropyl 3-hydroxy-2-methylene-3-(2-pyridyl) propanoate (141).[57] - The experimental procedure employed for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**139**) was followed, using isopropyl acrylate (prepared as described below; 2.94 g, 26 mmol), DABCO (0.206 g, 1.84 mmol) and pyridine-2-carboxaldehyde (2.14 g, 20 mmol) in $CHCl_3$ (2 ml). The reaction mixture was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (2:8)] to afford isopropyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**141**) (2.34 g, 51%); δ_H (60 MHz; $CDCl_3$) 1.10 and 1.12 (6H, 2 × CH_3), 4.95 (2H, septet, $CH(CH_3)_2$ and overlapping broad OH), 5.55 (1H, s, CHOH), 5.87 and 6.28 (2H, 2 × s, $C=CH_2$) and 7.1-8.4 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 3390 br and 1715.

Isopropyl acrylate (135). - Acryloyl chloride (10 g, 0.11 mol) was added gradually to a stirred

solution of isopropyl alcohol (9 g, 0.15 mol), hydroquinone (0.5 g) and *N,N*-dimethylaniline (13.4 g, 0.11 mol) in dry ether (190 ml). The resulting reaction mixture was heated under reflux for 2.5 days. The liquid layer was decanted from the pink solid and washed with dil. HCl (**2** × 20 ml) and with 1M NaOH (20 ml), and then dried over $MgSO_4$. The solvent was removed by evaporation under reduced pressure to afford the crude product, vacuum distillation of which afforded isopropyl acrylate **(135)** (6 g, 48%); δ_H (400 MHz; $CDCl_3$) 1.22 (6H, 2 × d, $(CH_3)_2CH$), 5.0 (1H, septet, $(CH_3)_2CH$) 5.75 and 6.35 (2H, 2 × d, CH_2=CH) and 6.07 (1H, t, CH_2=CH); υ_{max} (thin film)/cm^{-1} 1715.

Methyl 3-hydroxy-2-methylene-3-(6-methyl-2-pyridyl)propanoate (142). [57] - A solution of methyl acrylate (2.5 g, 29 mmol), DABCO (0.15 g, 1.34 mmol) and 6-methylpyridine-2-carboxaldehyde (3.4 g, 28 mmol) was left to stand at room temperature for 3 days, after which crystals were observed. The mother liquor was decanted and the crystals were purified by flash chromatography [elution with hexane-EtOAc (5:5)]. The crystals were then recrystallised using EtOAc as solvent to afford pure crystals of methyl 3-hydroxy-2-methylene-3-(6-methyl-2-pyridyl)propanoate **(142)** (5.44 g, 94%), m.p 85°C (lit.,[59] m.p.84-85°C); δ_H (400 MHz; $CDCl_3$) 2.5 (3H, s, CH_3Ar), 3.7 (3H, s, CH_3OCO), 5.2 (1H, d, OH), 5.6 (1H, d, CHOH), 5.9 and 6.3 (2H, 2 × s, C=CH_2) and 7.03-7.52 (3H, m, ArH); υ_{max} (KBr)/cm^{-1} 3130 br and 1715.

α-Hydroxy-3-methylene-4-(2-pyridyl)butan-2-one (143).[57] - The experimental procedure employed for the synthesis of methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propenoate (**139**) was followed, using pyridine-2-carboxaldehyde (4 g, 37 mmol), DABCO (0.12 g, 1.07 mmol) and methyl vinyl ketone (3.27 ml, 4.0 mmol) in $CHCl_3$ (2 ml). The resulting reaction mixture was chromatographed [flash chromatography on silica gel; elution with EtOAc] to give 4-hydroxy-3-methylene-4-(2-pyridyl)butan-2-one (**143**) (5.3 g, 81 %); δ_H (60 MHz; $CDCl_3$) 2.19 (3H, s, CH_3), 4.99 (1H, br s, OH), 5.60 (1H, s, C*H*OH), 6.03 (1H, d, $C=CH_2$), 6.10 (1H, s, $C=CH_2$) and 7.03-8.38 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 3350 br and 1685.

Methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (144).[57] - The hydroxy ester (**139**) (1 g, 5.2 mmol) was heated in Ac_2O (5 ml) at 100°C for 0.5 h after which the reaction mixture was cooled and poured into an aq.$NaHCO_3$-ice mixture. The resulting mixture was then stirred for 0.5 h, basified and then extracted (Et_2O). The organic extract was washed (aq. $NaHCO_3$ and then aq. NaCl), dried (anhyd. $MgSO_4$) and concentrated *in vacuo* to afford the crude acetate which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (4:6)] to afford methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**144**) (0.7 g, 68%); δ_H (60 MHz; $CDCl_3$) 2.16 (3H,s, CH_3CO), 3.7 (3H, s, OCH_3), 6.0 (1H,s, C*H*OAc), 6.4 and 6.6 (2H, 2 × s, $C=CH_2$) and 7.1-8.4 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 1730 and 1750.

Ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (145).[57] - The experimental procedure employed for the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**144**) was followed, using the hydroxy ester (**140**) (2 g, 10 mmol) and Ac_2O (10 ml). Work-up afforded the crude acetate which was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:6)] to give ethyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**145**) (1.74 g, 70%); δ_H (60 MHz; $CDCl_3$) 1.17 (3H, t, CH_3CH_2), 2.11 (3H, s, CH_3CO), 4.11 (2H, q, CH_3CH_2), 5.89 (1H, s, $CHOCOCH_3$), 6.45 and 6.75 (2H, 2 × s, $C=CH_2$) and 7.22-8.58 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 1745 and 1720.

Isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (146).[57] - The experimental procedure employed for the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**144**) was followed, using the hydroxy ester (**141**) (3 g, 13.5 mmol) and Ac_2O (13 ml). The reaction mixture, after work-up was purified by flash chromatography on silica gel [elution with dichloromethane-EtOAc (7:3)] to give isopropyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**146**) (2.13 g, 60%); δ_H (60 MHz; $CDCl_3$) 1.03 and 1.09 (6H, 2 × d, 2 × CH_3), 2.04 (3H, s, CH_3CO), 4.91 [1H, septet, $CH(CH_3)_2$], 5.77 (1H, s, $CHOAc$), 6.35 and 6.63 (2H, 2 × s, $C=CH_2$), and 7.12-8.50 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 1745 and 1715.

Methyl 3-acetoxy-2-methylene-3-(6-methyl-2-pyridyl)propanoate (147).[57] - The experimental procedure employed for the synthesis of methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**144**) was followed, using the hydroxy ester (**142**) (3 g, 14.5 mmol) and Ac_2O (14 ml). The reaction mixture after work up was purified by flash chromatography on silica gel [elution with dichloromethane-EtOAc (7:3)] to give Methyl 3-acetoxy-2-methylene-3-(6-methyl-2-pyridyl)propanoate (**147**) (1.87 g, 52%); δ_H (60 MHz; $CDCl_3$) 2.10 (3H, s, CH_3CO), 2.48 (3H, s, CH_3Ar), 3.67 (3H, s, CH_3O), 5.78 (1H, s, C*H*OAc), 6.41 and 6.67 (2H, 2 × s, $C=CH_2$) and 7.03-7.53 (3H, m, ArH); υ_{max} (thin film)/cm^{-1} 1750 and 1730.

3-Acetoxy-2-methylene-3-(2-pyridyl)propanonitrile (148).[57] - The experimental procedure employed for the synthesis of Methyl 3-acetoxy-2-methylene-3-(2-pyridyl)propanoate (**144**) was followed, using the hydroxy ester (**138**) (3 g, 18.7 mmol) and Ac_2O (18 ml). The reaction mixture after work up was purified by flash chromatography on silica gel [elution with hexane-EtOAc (3:7)] to give 3-Acetoxy-2-methylene-3-(2-pyridyl)propanonitrile (**148**) (2.04 g, 54%); δ_H (400 MHz; $CDCl_3$) 2.14 (3H, s, CH_3CO), 6.08 and 6.11 (2H, 2 × s, $C=CH_2$), 6.33 (1H, s, $CHOCOCH_3$) and 7.03-7.53 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 2225 and 1750.

3.2.2 PREPARATION OF 2-SUBSTITUTED INDOLIZINES

Methyl indolizine-2-carboxylate (149).[57] - Thermal cyclization was effected by heating the acetoxy precursor (**144**) (1 g, 4.4 mmol) in an oil bath at 120°C for 1 h. The resulting mixture was purified by flash chromatography on silica gel [elution with hexane-EtOAc (7:3)] to afford yellowish crystals of methyl indolizine-2-carboxylate (**149**) (0.52 g, 68%), m.p.98-100°C (lit[59].,97-99°C); δ_H (60 MHz; $CDCl_3$) 3.91 (3H, s, CH_3O), 6.52-8.02 (6H, m, ArH); υ_{max}(KBr)/cm^{-1} 2970 and 1710.

Ethyl indolizine-2-carboxylate (150).[57] - The experimental procedure employed for the synthesis of methyl indolizine-2-carboxylate (**149**) was followed, using the acetoxy precursor (**145**) (1 g, 4 mmol). The resulting reaction mixture was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (6:4)] to afford ethyl indolizine-2-carboxylate (**150**) (0.28 g, 38 %); δ_H (60 MHz; $CDCl_3$) 1.38 (3H, t, CH_3CH_2) 4.35 (2H, q, CH_3CH_2) and 6.49-7.83 (6H, m, ArH); υ_{max} (thin film)/cm^{-1} 2975 and 1710.

Isopropyl indolizine-2-carboxylate (151).[57] - The experimental procedure employed for the synthesis of methyl indolizine-2-carboxylate (**149**) was followed, using the acetoxy precursor

(146) (1 g, 4 mmol). The resulting reaction mixture was chromatographed [flash chromatography on silica gel; elution with benzene-EtOAc (5:5)] to afford isopropyl indolizine-2-carboxylate **(151)** (0.186 g, 23 %); δ_H (60 MHz; $CDCl_3$) 1.35 [6H, d, $(CH_3)_2CH$] 5.25 [1H, septet, $CH(CH_3)_2$] and 6.49-7.83 (6H, m, ArH); υ_{max} (thin film)/cm^{-1} 2980 and 1705.

Methyl 5-methylindolizine-2-carboxylate (152).[57] - The experimental procedure employed for the synthesis of methyl indolizine-2-carboxylate **(149)** was followed, using the acetoxy precursor **(147)** (1 g, 4 mmol). The resulting reaction mixture was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (8:2)] to afford methyl 5-methylindolizine-2-carboxylate **(152)** (0.60 g, 80 %); δ_H (60 MHz; $CDCl_3$) 2.42 (3H, s, CH_3Ar), 3.86 (3H, s, CH_3O) and 6.36-7.68 (6H, m, ArH); υ_{max} (thin film)/cm^{-1} 2980 and 1720.

2-Cyanoindolizine (153).[57] - The experimental procedure employed for the synthesis of methyl indolizine-2-carboxylate **(149)** was followed, using the acetoxy precursor **(148)** (1 g, 5 mmol). The resulting reaction mixture was chromatographed [flash chromatography on silica gel; elution with hexane-chloroform (5:5)] to afford 2-cyanoindolizine **(153)** (0.213 g, 30 %); δ_H (400 MHz; $CDCl_3$) 6.62 -7.87 (6H, m, ArH); υ_{max} (KBr)/cm^{-1} 3110 and 2210.

3.3 PREPARATION OF HALOGENATED DERIVATIVES

Methyl 2-chloromethyl-3-(2-pyridyl)propenoate (154). - The hydroxy ester (**139**) (0.5 g, 2.6 mmol), thionyl chloride (0.4 ml) and DMF (0.01 ml) in 1,2-dichloroethane (5.4 ml) was heated at 60°C for 2 h under nitrogen. The resulting mixture was concentrated by evaporation under reduced pressure and chromatographed [preparative layer chromatography; elution with hexane-EtOAc (2:8)] to give *methyl 2-chloromethyl-3-(2-pyridyl)propenoate* ***(154)*** (0.17 g, 31%); δ_H (400 MHz; $CDCl_3$) 3.82 (3H, s, CH_3O), 5.09 (2H, s, CH_2Cl) and 7.22-8.70 (5H, m, ArH); δ_C 37.96 (CH_2Cl), 52.46 (OCH_3), 123.71 (C-3'), 126.94 (C-5'), 131.87 (C-2), 136.74 (C-4'), 139.50 (C-3), 149.81 (C-6'), 153.17 (C-2') and 166.77 (CO); υ_{max} (KBr)/cm^{-1} 1725; *m/z* 211 (m^+ 12 %) and 117 (100 %), (Found M^+: 211.0399 $C_{10}H_{10}NO_2{}^{35}Cl$ requires: *M*, 211.0399).

Ethyl 2-chloromethyl-3-(2-pyridyl)propenoate (155).

Method 1. - Thionyl chloride (0.576 ml) was added to a stirred solution of the hydroxy ester (**140**) (0.90 g, 4.4 mmol) and DMF (0.014 ml) in dry 1,2-dichloroethane (8.3 ml) and the resulting mixture was heated at 60°C for 1 h under nitrogen. The mixture was then concentrated by evaporating off the solvent and purified by flash chromatography on silica gel [elution with hexane-EtOAc (3:7)] to afford *ethyl 2-chloromethyl-3-(2-pyridyl)propenoate* ***(155)*** (0.77 g, 79 %);

δ_H (400 MHz; $CDCl_3$) 1.35 (3H, t, CH_3CH_2), 4.36 (2H, q, CH_3CH_2), 5.09 (2H, s, CH_2Cl) and 7.23-8.70 (5H, m, ArH); δ_C 13.80 (CH_3CH_2), 38.01 (CH_2Cl), 61.43 (CH_3CH_2), 123.62 (C-3'), 126.80 (C-5'), 132.09 (C-2), 136.63 (C-4'), 139.39 (C-3), 149.88 (C-6'), 153.32 (C-2') and 166.27 (CO); υ_{max} (KBr)/cm^{-1} 1725; (Found M^+: 225.0538 $C_{11}H_{12}NO_2Cl$ requires: *M*, 225.0556).

Method 2. A solution of the hydroxy ester **(140)** (1g, 5.2 mmol) and oxalyl chloride (1.6 g, 13 mmol) in dry benzene (10 ml) was stirred at room temperature for 1 h under N_2. The solvent was removed by evaporation under reduced pressure and the residue was purified by flash chromatography to afford the desired product *ethyl 2-chloromethyl-3-(2-pyridyl)propenoate (155)* (0.23 g, 20 %)

Methyl 2-chloromethyl-3-(6-methyl-2-pyridyl)propenoate (156). - Thionyl chloride (0.576 ml) was added to a stirred solution of the hydroxy ester **(142)** (2.0 g, 9.7 mmol) and DMF(0.03 ml) in dry 1,2-dichloroethane (18.5 ml) and the resulting mixture was heated at 60°C for 1 h under nitrogen. The mixture was then concentrated by evaporation under reduced pressure and purified by flash chromatography on silica gel [elution hexane-EtOAc (3:7)] to afford *methyl 2-chloromethyl-3-(6-methyl-2-pyridyl)propenoate (156)* (2 g, 92 %); δ_H (400 MHz; $CDCl_3$) 2.61 (3H, s, CH_3Ar), 3.88 (3H, s, CH_3O), 5.0 (2H, s, CH_2Cl) and 7.23-7.80 (4H,m, ArH);

δ_C 24.40 (CH_3Ar), 38.10 (CH_2Cl), 52.37 (OCH_3), 123.48 (C-3'), 124.00 (C-5'), 131.44 (C-2), 136.93 (C-4'), 139.82 (C-3), 152.38 (C-6'), 158.73 (C-2') and 166.82 (CO); υ_{max} (KBr)/cm^{-1} 1725; (Found: M^+, 225.00559 $C_{11}H_{12}NO_2Cl$ requires: *M*, 225.0556).

3.4 ATTEMPTED HALOGENATION REACTIONS

Several halogenation procedures were used in the unsuccessful attempt to obtain chlorinated, brominated and iodinated derivatives of various hydroxy precursors.

3.4.1 ATTEMPTED CHLORINATION REACTIONS

1. The hydroxy derivative **(138)** was treated under thionyl chloride under various conditions [*viz.*, 60°C for 0.5 h; 40°C for 2 h; 40°C for 1 h and leaving the reaction to react at room temperature for 1 h] but, in all cases, a black crystalline material was obtained which could not be identified and was assumed to be polymeric.

2. The hydroxy ketone **(143)** was treated under thionyl chloride under various conditions [*viz.*, 60°C for 0.5 h; 40°C for 2 h; 40°C for 1 h and leaving the reaction to react at room temperature for 1 h] but, in all cases, a green crystalline material was obtained which could not be identified.

3. Pre-cooled (0^0C) solution of the hydroxy esters **(139, 140 and 142)** in dil.HCl were treated with Conc.H_2SO_4. Work-up, in all three cases, afforded unreacted starting material.

4. The hydroxy ester **(139)** was treated with thionyl chloride in the presence of a) pyridine and b) *N,N*-dimethyl aniline. Work-up in both cases afforded unreacted starting material.

5. A slurry of the hydroxy ester **(138)** in cyclohexane was treated with PCl_5. Work-up afforded the unreacted starting material.

6. Treatment of the hydroxy ester **(139)** with triphenyl phosphine and CCl_4 failed to effect chlorination of the substrate, which was isolated after work-up.

Attempted bromination of the hydroxy ester (139)

The hydroxy ester **(139)** was treated with 50 % HBr and Conc.H_2SO_4. Work-up afforded the starting material.

Attempted iodination of the hydroxy ester (139)

The hydroxy ester **(139)** was treated with HI and Conc.H_3PO_4. Work-up afforded the starting material.

3.5 ATTEMPTED THERMAL CYCLIZATION OF THE CHLORINATED DERIVATIVES

The chlorinated derivative **(154)** (55 mg) was heated in DMSO-d_6 (0.5 ml) at 100°C for 2 h. The reaction was followed by ^{1}H NMR spectroscopy recorded at 15 minute intervals on a Perkin-Elmer R12 60 MHz NMR spectrometer. Even after 2 h, the ^{1}H NMR spectra showed no signs of the expected methyl indolizine-2-carboxylate **(149)**. The reaction was repeated at 110°C, 120°C and at 140°C and, in each case the NMR spectra showed no signs of the expected indolizine. The same experimental procedure was employed in the attempted cyclization of the chloro compounds **155** and **156**.

3.6 PREPARATION OF INDOLIZINE-2-CARBOXAMIDES

5-Methylindolizine-2-carboxylic acid (160). - A solution of methyl 5-methylindolizine-2-carboxylate (**152**) (4.0 g, 21 mmol), KOH (7.4 g, 131.15 mmol) in EtOH (148 ml) was refluxed for 16 h. The resulting mixture was diluted with water, acidified to *ca* pH 2 and the aqueous layer was extracted (EtOAc). The organic extract was dried over anhyd.$MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified [flash chromatography on silica gel; elution with hexane-EtOAc (5:5)] to afford *5-methylindolizine-2-carboxylic acid (160)* (3 g, 79%); δ_H (400 MHz; $CDCl_3$) 2.5 (3H,s, CH_3Ar), 6.4-7.8 (5H, m, ArH) and 9.8 (1H, br s, OH); δ_C 18.49 (CH_3Ar), 101.64 (C-1), 111.65 (C-6), 113.97 (C-3), 118.13 (C-8), 118.74 (C-7), 118.79(C-2), 133.13 (C-9), 133.75 (C-5) and 170.95 (COOH); υ_{max} (thin film)/cm^{-1} 3450 and 1705.

N,N,5-Trimethylindolizin-2-carboxamide (163). - To a solution of 5-methyl indolizine-2-carboxylic acid (**160**) (1 g, 5.7 mmol) in dry DMF (13 ml), carbonyldiimidazole (1.45 g, 9 mmol) was added under nitrogen. Effervescence occurred after which the reaction mixture was heated at 40^{0}C for 5 minutes. This was followed by the addition of *N,N*-dimethylamine (33% in EtOH; 0.72 g, 16 mmol) and the resulting mixture was left to stir for 30 minutes after which 4.7 ml of water. Work up afforded the crude carboxamide (**163**), which was chromatographed [flash chromatography on silica gel; elution with MeOH-$CHCl_3$-hexane (1:7:2)] to afford *N,N,5-trimethylindolizin-2-carboxamide (163)* (0.7 g, 61%);

δ_H (400 MHz; $CDCl_3$) 2.5 (3H, s, CH_3) 3.2 [6H, br s, $N(CH_3)_2$] and 6.34-7.56 (5H, m, ArH); υ_{max} (thin film)/cm^{-1} 1635; *m/z* 202 (m^+ 74%) and 131 (100%), (Found M^+ 202.1099 $C_{12}H_{14}N_2O$ requires: *M*, 202.1106).

1-[(5-methylindolizin-2-yl)carbonyl]pyrrolidine (164). - The experimental procedure employed for the synthesis of *N,N*-5-trimethylindolizin-2-carboxamide (**163**) was followed, using the carboxylic acid (**160**) (1 g, 5.7 mmol), dry DMF (13 ml), carbonyldiimidazole (1.45 g, 9 mmol) and pyrrolidine (1.46 g, 20.5 mmol). Work-up afforded the crude carboxamide (**164**), which was chromatographed [flash chromatography on silica gel; elution with MeOH-$CHCl_3$ (0.5:9.5)] to afford *1-[(5-methylindolizin-2-yl)carbonyl]pyrrolidine (164)* (0.62 g, 48%); δ_H (400 MHz; $CDCl_3$) 1.89 [4H, br s, $CH_2(CH_2)_2CH_2$], 2.5 (3H, s,CH_3), 3.7 [4H, m, $N(CH_2)_2$] and 6.34-7.64 (5H, m, ArH); δ_C 18.40 (CH_3Ar), 24.06 and 26.48 ($NCH_2CH_2CH_2CH_2$), 46.57 (NCH_2), 48.72 (NCH_2), 99.79 (C-1), 110.62 (C-6), 111.92 (C-3), 117.37 (C-7), 118.09 (C-8), 123.98 (C-2), 132.80 (C-9), 132.83 (C-5) and 165.16 (CO); υ_{max} (thin film)/cm^{-1} 1635; *m/z* 228 (m^+ 31 %) and 131 (100 %), (Found M^+: 228.1277 $C_{14}H_{16}N_2O$ requires *M*, 228.1263).

1-[(5-methylindolizin-2-yl)carbonyl]piperidine (165). - To a solution of 5-methyl indolizine-2-carboxylic acid (**160**) (1 g, 5.7 mmol) in dry DMF (13 ml), carbonyldiimidazole (1.45 g, 9 mmol) was added under nitrogen. Effervescence occurred after which the reaction

mixture was heated at 40°C for 5 minutes. This was followed by the addition of piperidine (1.67 ml, 17.2 mmol) and the resulting mixture was left to stir for 30 minutes after which 4.7 ml of water was added. Volatiles were removed on the rotary evaporator and to the residue 2N Na_2CO_3 (53 ml) was added. Extracted the aqueous layer with EtOAc (4×100 ml), the organic layer was washed with water and dried over anhyd.$MgSO_4$. The solvent was removed by evaporation under reduced pressure and the residue was chromatographed [flash chromatography on silica gel; elution with MeOH-$CHCl_3$ (1:9)] to give *1-[(5-methylindolizin-2-yl)carbonyl]piperidine (165)* (0.66 g,48%); δ_H (400 MHz; $CDCl_3$) 1.65 [6H, br d, $(CH_2)_3$)], 2.51 (3H, s, CH_3Ar), 3.7 [4H, br s, $N(CH_2)_2$] and 6.34-7.42 (5H, m, ArH); δ_C 18.54 (CH_3Ar), 24.185, 26.602 and 30.848 ($NCH_2CH_2CH_2CH_2CH_2$), 46.701 (NCH_2), 48.868 (NCH_2), 99.86 (C-1), 110.74 (C-3), 112.10 (C-6), 117.50 (C-3), 118.22 (C-8), 124.05 (C-7), 132.92 (C-2), 132.97 (C-9), 132.97 (C-5) and 165.34 (CO); υ_{max} (thin film)/cm^{-1} 1635; *m/z* 242 (m^+ 0.03 %) and 131 (100 %), (Found M^+: 242.1398 $C_{15}H_{18}N_2O$ requires: *M*,242.1419).

3.7 PREPARATION OF 3-SUBSTITUTED INDOLIZINES

1-(Ethoxycarbonylmethyl)-2-methylpyridinium bromide (166).[68] - Ethyl bromoacetate (2.0 g, 13.3 mmol) was added to 2-methylpyridine (2.0 g, 12 mmol). The precipitated salt was filtered and washed several times (Et_2O) to give 1-(ethoxycarbonylmethyl)-2-methylpyridinium bromide (**166**) [δ_H (60 MHz; $CDCl_3$) 1.41 (3H, t, CH_3CH_2), 3.1 (3H, s, CH_3Ar), 4.32 (2H,

q, CH_3CH_2), 6.29 (2H,s, NCH_2) and 8.21-9.68 (4H, m, ArH); υ_{max} (thin film)/cm^{-1} 1735] which was used without further purification.

1-(Ethoxycarbonylmethyl)-2-(3-cyano-3-ethoxycarbonylallylidene)-1,2-dihydropyridine (168).[69] -To a stirred, slurry of the salt **(166)** (4.0 g, 16 mmol) and potassium carbonate (38.6 g) in $CHCl_3$ (386 ml), ethyl (ethoxymethylene)-cyanoacetate (2.7 g, 16 mmol) was added. The mixture was left to stir for 4 days at room temperature after which the insoluble material was removed by filtration. The filtrate was concentrated by evaporation of the solvent under reduced pressure. The resulting residue was chromatographed [flash chromatography on silica gel;elution with hexane-EtOAc (5:5)] to afford (Ethoxycarbonylmethyl)-2-(3-cyano-3-ethoxycarbonyl allylidene)-1,2-dihydro pyridine **(168)** (2.7 g, 55%); δ_H (60 MHz; $CDCl_3$) 1.30 and 1.37 (6H, 2 × t, 2 × OCH_2CH_3), 4.25 and 4.30 (each 2H, q, OCH_2CH_3), 4.67 (2H, s, NCH_2), 5.37 (1H, d, C_2=C*H*-CH=) and 6.26-8.05 (4H, m, ArH); υ_{max} (KBr)/cm^{-1} 2210, 1740 and 1530.

Ethyl indolizine-3-carboxylate (169).[69]- A solution of the allylidenedihydropyridine **(168)** (2.0 g, 6.6 mmol) in xylene (330 ml) was heated under reflux for 3 days after which the solvent was evaporated under reduced pressure. The residue was purified by chromatography [flash chromatography on silica gel;elution with hexane-EtOAc (3:7)] to afford ethyl indolizine-3-carboxylate

(169) (1.12 g, 90%); δ_H (60 MHz; $CDCl_3$) 1.32 (3H,t, CH_2CH_3), 4.34 (2H, q,OCH_2CH_3), and 6.26-9.4 (6H, m, ArH); υ_{max} (KBr)/cm^{-1} 2210, 1740 and 1530.

Indolizine-3-carboxylic acid (170). - The experimental procedure employed for the preparation of 5-methylindolizine-2-carboxylic acid **(160)** was followed, using the ethyl ester **(169)** (1.0 g, 5.3 mmol) and KOH (1.9 g) in EtOH (37 ml). The residue after work-up was purified by chromatography [flash chromatography on silica gel; elution with hexane-EtOAc (5:5)] to afford indolizine-3-carboxylic acid **(170)** (0.6 g, 69%); δ_H (60 MHz; $CDCl_3$) 6.3-8.5 (6H, m, ArH) and 9.8 (1H, br s, OH); υ_{max} (thin film)/cm^{-1} 1685.

Attempted preparation.- The experimental procedure employed for the synthesis of 1-[(5-methylindolizin-2-yl)carbonyl]piperidine **(165)** was followed, using the carboxylic acid **(170)** (1 g, 6.2 mmol), dry DMF (13 ml), carbonyldiimidazole (1.35 g, 8.4 mmol) and *N,N*-diethylamine (0.72 g, 9.8 mmol). The residue, after work-up, was shown, by ^1H NMR spectroscopy, to be starting material.

3.8 KINETIC STUDIES

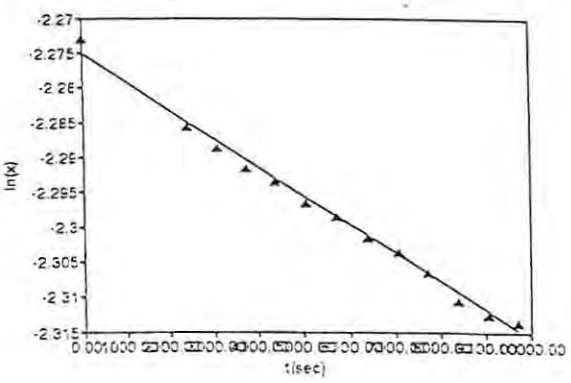
Materials and Instrumentation. - The acetoxy compounds (**144-148**) required for the kinetic study, were purified by flash chromatography or preparative layer chromatography prior to use. The cyclization reaction was monitered by ^{1}H NMR spectroscopy using a Bruker AMX 400 NMR spectrometer, equipped with a variable temperature unit and which has been calibrated using 80% ethylene glycol in DMSO-d_6; temperature stability is estimated at ± 0.1 K.

Kinetic Procedure. - Solutions of the acetoxy precursors (0.103 mols/dm^{-3}) were prepared at room temperature by dissolving the substrates (0.5 mmol) in DMSO-d_6 (0.5 ml). The solution thus prepared was then transferred to an NMR tube which was inserted at $t=t_0$, into the pre-heated NMR probe. The ^{1}H spectra were recorded at intervals of 5 or 10 minutes (depending on the reaction rate) until a substantial transformation had occured. The results are summarised in Table 3, p 68. In all cases examined, exceptional linear correlation ($R^2 \geq 0.99$) for the first-order plots of the kinetic data were observed. The first-order rate constants (k_{obs}) were determined from plots of ln[substrate] against time. The activation energy (E_a) for the esters (**144**) and (**145**) were determined from the plots of logk against 1/T at 388.8 K, 378.4 K and 367.3 K.

139

Run 1

t(sec)	Conc (x)	ln(x)	Y (calc)
0	0.103	-2.273026291	-2.27504358
2419	0.1017	-2.28573	-2.28477
3145	0.1014	-2.28868	-2.28749
3871	0.1011	-2.29165	-2.29021
4597	0.1009	-2.29363	-2.29293
5323	0.1006	-2.2966	-2.29566
6049	0.1004	-2.29859	-2.29838
6775	0.1001	-2.30159	-2.3011
7501	0.0999	-2.30359	-2.30382
8227	0.0996	-2.30659	-2.30654
8953	0.0992	-2.31062	-2.30926
9679	0.099	-2.31264	-2.31198
10405	0.0989	-2.31365	-2.3147
11131	0.0987	-2.31567	-2.31742
11857	0.0984	-2.31871	-2.32014
12583	0.0982	-2.32075	-2.32287
13309	0.098	-2.32279	-2.32559
14035	0.0978	-2.32483	-2.32831
14761	0.0974	-2.32893	-2.33103
15487	0.096	-2.34341	-2.33375

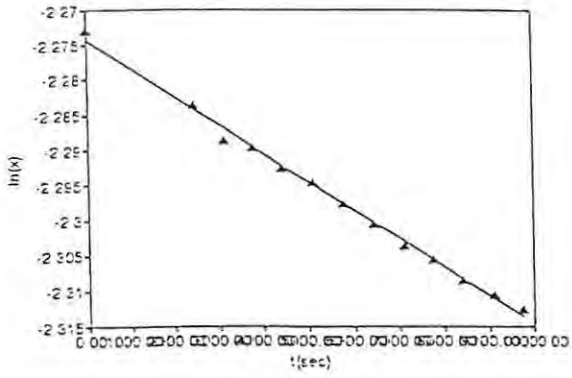


Regression Output:

Constant	-2.2757
Std Err of Y Est	0.002827
R Squared	0.973527
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-3.7E-06
Std Err of Coef.	1.46E-07

Run 2

t(sec)	Conc (x)	ln(x)	Y (calc)
0	0.103	-2.27303	-2.27483
2462	0.1019	-2.28376	-2.28401
3188	0.1014	-2.28868	-2.28672
3914	0.1013	-2.28967	-2.28942
4640	0.101	-2.29263	-2.29213
5366	0.1008	-2.29462	-2.29484
6092	0.1005	-2.2976	-2.29754
6818	0.1002	-2.30059	-2.30025
7544	0.0999	-2.30359	-2.30296
8270	0.0997	-2.30559	-2.30567
8996	0.0994	-2.3086	-2.30837
9722	0.0992	-2.31062	-2.31108
10448	0.099	-2.31264	-2.31379



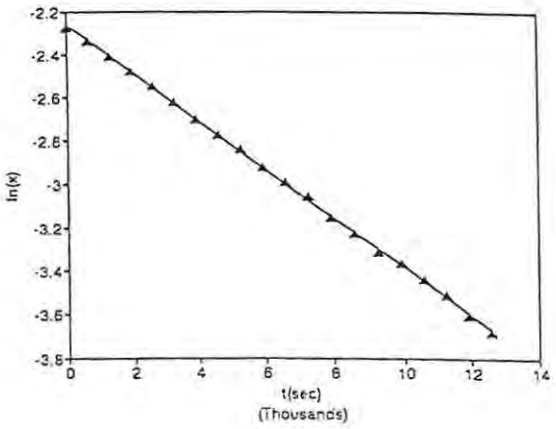
Regression Output:

Constant	-2.27483
Std Err of Y Est	0.000936
R Squared	0.993943
No. of Observations	13
Degrees of Freedom	11
X Coefficient(s)	-3.7E-06
Std Err of Coef.	8.78E-08

144a

RUN 1: RG8KIN5 (363 K)]

t(sec)	Conc.(x)	ln(x)	Y(calc).
0	0.103	-2.273026251	-2.27172624
639	0.0967	-2.33614	-2.33846
1365	0.0901	-2.40684	-2.40926
2091	0.0839	-2.47813	-2.48005
2817	0.078	-2.55105	-2.55085
3543	0.0723	-2.62693	-2.62165
4269	0.0679	-2.68972	-2.69245
4995	0.0629	-2.76621	-2.76325
5721	0.0585	-2.83873	-2.83405
6447	0.0542	-2.91507	-2.90485
7173	0.0508	-2.97986	-2.97565
7899	0.0476	-3.04452	-3.04645
8625	0.0444	-3.11452	-3.1172
9351	0.0417	-3.17725	-3.1880

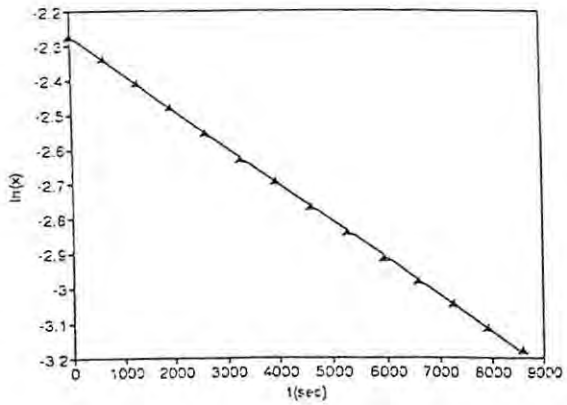


Regression Output:

Constant	-2.27614
Std Err of Y Est	0.005316
R Squared	0.995701
No. of Observations	14
Degrees of Freedom	12
X Coefficient(s)	-9.8E-05
Std Err of Coef.	4.87E-07

RUN 2: RG8KIN5 (363 K)

t(sec)	Conc.(x)	ln(x)	Y(calc)
0	0.103	-2.273026	-2.2584215
628	0.0957	-2.346141	-2.3285235
1354	0.09	-2.407945	-2.4031491
2080	0.084	-2.47025	-2.47694
2806	0.0783	-2.54847	-2.54723
3532	0.0729	-2.62669	-2.61861
4258	0.0671	-2.70491	-2.70151
4984	0.0626	-2.78313	-2.77095
5710	0.0586	-2.86135	-2.83703
6436	0.054	-2.93957	-2.91877
7162	0.0504	-3.01779	-2.98776
7888	0.0471	-3.09601	-3.05548
8614	0.0427	-3.17423	-3.15356
9340	0.0397	-3.25245	-3.2264
10066	0.0364	-3.33067	-3.31319
10792	0.0322	-3.40889	-3.43579
11518	0.0299	-3.48712	-3.5099
12244	0.0272	-3.56534	-3.60454
12970	0.0253	-3.64356	-3.67695
13696			



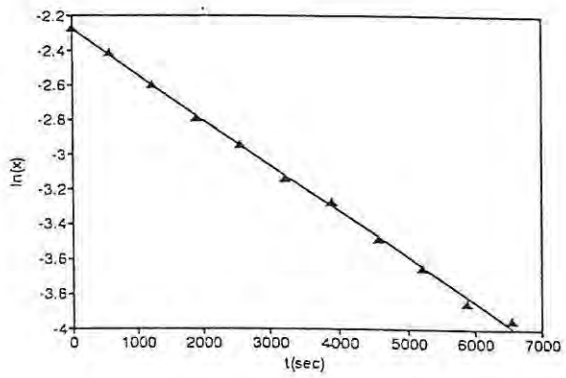
Regression Output:

Constant	-2.0897
Std Err of Y Est	0.02578
R Squared	0.996771
No. of Observations	19
Degrees of Freedom	17
X Coefficient(s)	-0.00011
Std Err of Coef.	1.49E-06

144b

RUN 1.

t(sec)	Conc.(x)	ln(x)	Y(calc).
0	0.103	-2.50048	-2.27303
578	0.08972	-2.6463	-2.41106
1064	0.07449	-2.76892	-2.59709
1550	0.0615	-2.89153	-2.78872
2036	0.05267	-3.01414	-2.94371
2522	0.04324	-3.13675	-3.14099
3008	0.03074	-3.25936	-3.48219
3494	0.02603	-3.38197	-3.64851
3980	0.02134	-3.50458	-3.84717
4466	0.019338	-3.6272	-3.94568
4952	0.01739	-3.74981	-4.05186
5438	0.01616	-3.87242	-4.12522
5924	0.01464	-3.99503	-4.224
6410	0.01066	-4.11764	-4.54126
6896	0.06816	-4.24025	-2.6859

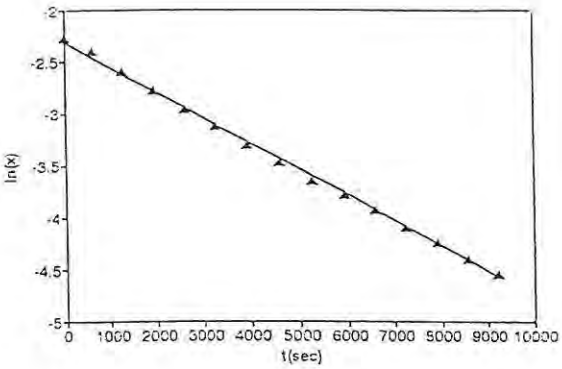


Regression Output:

Constant	-2.50048
Std Err of Y Est	0.503425
R Squared	0.563296
No. of Observations	15
Degrees of Freedom	13
X Coefficient(s)	-0.00025
Std Err of Coef.	6.16E-05

RUN 2

t(sec)	Conc.(x)	ln(x)	Y(calc)
0	0.103	-2.27303	-2.32016
613	0.09057	-2.40163	-2.45735
1339	0.07468	-2.59454	-2.61983
2065	0.06205	-2.77981	-2.78231
2791	0.05152	-2.96579	-2.94479
3517	0.04358	-3.13316	-3.10726
4243	0.0366	-3.30771	-3.26974
4969	0.031036	-3.47261	-3.43222
5695	0.02589	-3.6539	-3.5947
6421	0.02259	-3.79025	-3.75718
7147	0.01967	-3.92866	-3.91966
7873	0.01658	-4.09956	-4.08213
8599	0.014368	-4.24275	-4.24461
9325	0.01225	-4.40223	-4.40709
10051	0.010663	-4.54098	-4.56957
10777	0.009523	-4.65405	-4.73205



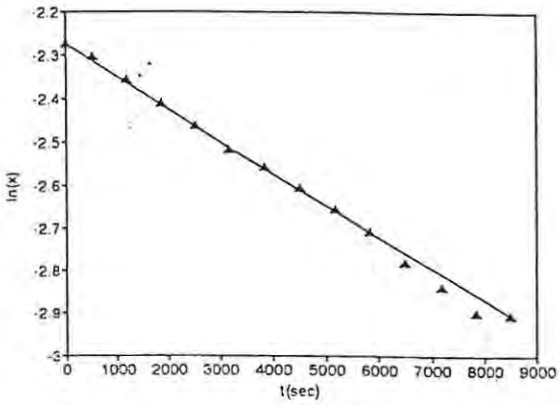
Regression Output:

Constant	-2.32016
Std Err of Y Est	0.039702
R Squared	0.997531
No. of Observations	16
Degrees of Freedom	14
X Coefficient(s)	-0.00022
Std Err of Coef.	2.98E-06

144c

RUN 1:

t(sec)	Conc.(x)	ln(x)	Y(cal)
0	0.103	-2.273026291	-2.1526509
468	0.08241	-2.49605	-2.4738
954	0.06073	-2.80132	-2.77331
1440	0.04485	-3.10443	-3.07282
1926	0.03398	-3.38198	-3.37233
2412	0.02532	-3.67616	-3.67185
2898	0.02021	-3.90158	-3.97136
3384	0.01546	-4.1695	-4.27087
3870	0.01238	-4.39167	-4.57038
4356	0.007347	-4.91346	-4.86989
4842	0.00628	-5.07039	-5.1694
5328	0.00436	-5.43528	-5.46892
5814	0.002906	-5.84098	-5.76843
6300	0.002126	-6.15351	-6.06794
6786	0.001472	-6.52113	-6.36745
7272	0.001346	-6.61062	-6.66696

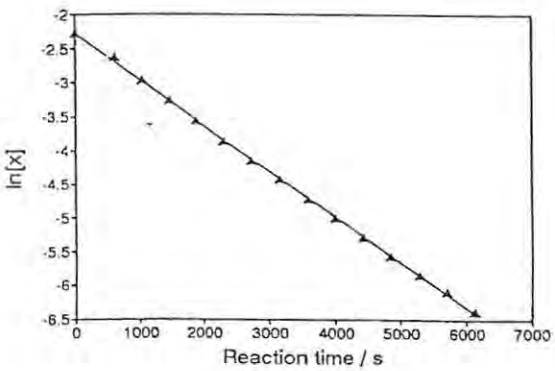


Regression Output:

Constant	-2.18538
Std Err of Y Est	0.088385
R Squared	0.996421
No. of Observations	16
Degrees of Freedom	14
X Coefficient(s)	-0.00062
Std Err of Coef.	9.87E-06

RUN 2:

t(sec)	conc(x)	ln(x)	Y(cal)
0	0.103000	-2.273	-2.272
620	0.0721	-2.6297	-2.68109
1106	0.05184	-2.95959	-2.96915
1592	0.03814	-3.26649	-3.2572
2078	0.02834	-3.56348	-3.54526
2564	0.0208	-3.8728	-3.83332
3050	0.01577	-4.14965	-4.12138
3536	0.01193	-4.4287	-4.40944
4022	0.008868	-4.72531	-4.6975
4508	0.00662	-5.01766	-4.98555
4994	0.00501	-5.29632	-5.27361
5480	0.003847	-5.56046	-5.56167
5966	0.002899	-5.84339	-5.84973
6452	0.002249	-6.09727	-6.13779
6938	0.001698	-6.3783	-6.42585



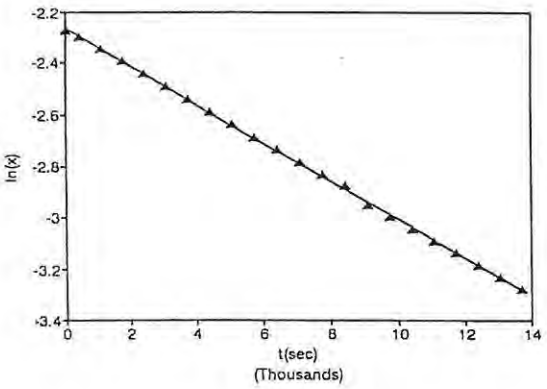
Regression Output:

Constant	-2.31361
Std Err of Y Est	0.032568
R Squared	0.999415
No. of Observations	15
Degrees of Freedom	13
X Coefficient(s)	-0.00059
Std Err of Coef.	3.98E-06

145a

RUN 1.

t(sec)	Conc.(x)	ln(x)	Y(calc)
0	0.103	-2.273026291	-2.260936907
459	0.1004	-2.29859	-2.29927
1185	0.095887	-2.34458	-2.35177
1911	0.091457	-2.39189	-2.40427
2637	0.08693	-2.44265	-2.45677
3363	0.0828	-2.49133	-2.50926
4089	0.07895	-2.53894	-2.56176
4815	0.071729	-2.63486	-2.61426
5541	0.068224	-2.68496	-2.66676
6267	0.064993	-2.73348	-2.71926
6993	0.06182	-2.78353	-2.77175
7719	0.058918	-2.83161	-2.82425
8445	0.056528	-2.87302	-2.87675
9171	0.05239	-2.94904	-2.92925
9897	0.049961	-2.99651	-2.98174
10623	0.047709	-3.04264	-3.03424
11349	0.04548	-3.09048	-3.08674
12075	0.04356	-3.13362	-3.13924
12801	0.041519	-3.1816	-3.19173
13527	0.039502	-3.2314	-3.24423
14253	0.03769	-3.27836	-3.29673

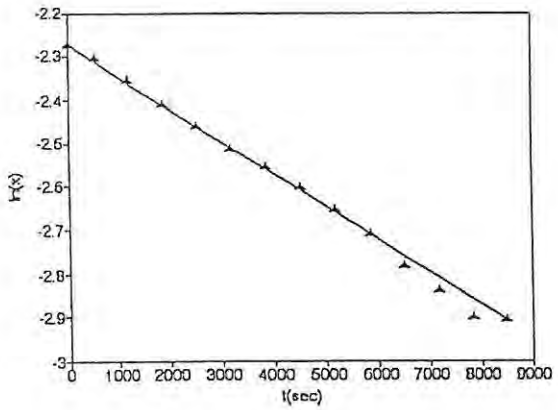


Regression Output:

Constant	-2.26608
Std Err of Y Est	0.014125
R Squared	0.9982
No. of Observations	21
Degrees of Freedom	19
X Coefficient(s)	-7.2E-05
Std Err of Coef.	7.04E-07

RUN 2.

t(sec)	Conc.(x)	ln(x)	Y(calc).
0	0.103	-2.273026291	-2.27335566
537	0.0999	-2.30359	-2.30437
1263	0.09482	-2.35577	-2.35609
1989	0.08986	-2.4095	-2.40781
2715	0.08541	-2.46029	-2.45953
3441	0.080901	-2.51453	-2.51125
4167	0.077596	-2.55624	-2.56297
4893	0.07399	-2.60383	-2.61469
5619	0.07034	-2.65441	-2.66641
6345	0.06675	-2.7068	-2.71813
7071	0.06198	-2.78094	-2.76985
7797	0.058563	-2.83765	-2.82157
8523	0.05501	-2.90024	-2.87329
9249	0.05501	-2.90024	-2.92501



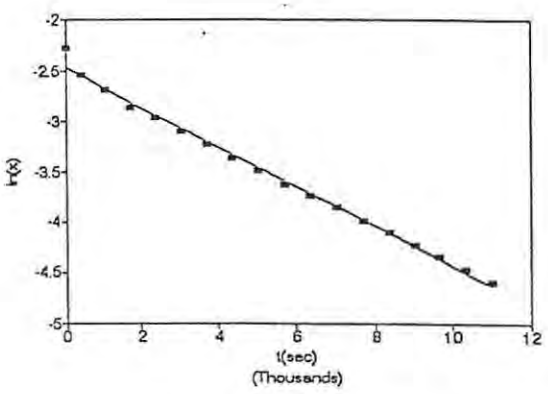
Regression Output:

Constant	-2.26612
Std Err of Y Est	0.013601
R Squared	0.996312
No. of Observations	14
Degrees of Freedom	12
X Coefficient(s)	-7.1E-05
Std Err of Coef.	1.25E-06

145b

RUN 1.

t(sec)	Conc.(x)	ln(x)	Y(cal)
0	0.103	-2.273026291	-2.4632931
403	0.07876	-2.54135	-2.24958
1129	0.06835	-2.68311	-2.40178
1855	0.05727	-2.85998	-2.55398
2581	0.5149	-0.66378	-2.70618
3307	0.04514	-3.09799	-2.85838
4033	0.03957	-3.22968	-3.01058
4759	0.03474	-3.35986	-3.16278
5485	0.030508	-3.48977	-3.31498
6211	0.026819	-3.61864	-3.46718
6937	0.023807	-3.73778	-3.61938
7663	0.02117	-3.85517	-3.77158
8389	0.01857	-3.98621	-3.92378
9115	0.01651	-4.10379	-4.07598
9841	0.01485	-4.20976	-4.22818
10567	0.01305	-4.33897	-4.38038
11293	0.01147	-4.46802	-4.53258
12019	0.01015	-4.59028	-4.68478

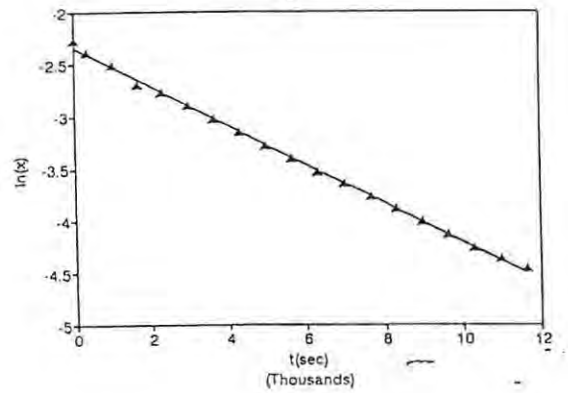


Regression Output:

Constant	-2.16509
Std Err of Y Est	0.540805
R Squared	0.702548
No. of Observations	18
Degrees of Freedom	16
X Coefficient(s)	-0.00021
Std Err of Coef.	3.41E-05

RUN 2.

t(sec)	Conc.(x)	ln(x)	Y(calc).
0	0.103	-2.2730262	-2.338030
392	0.092178	-2.38403	-2.40226
1078	0.080766	-2.5162	-2.52583
1804	0.067097	-2.70162	-2.64939
2530	0.06219	-2.77756	-2.77296
3256	0.05527	-2.89553	-2.89652
3982	0.04824	-3.03157	-3.02009
4708	0.04266	-3.15449	-3.14365
5434	0.0376	-3.28075	-3.26722
6160	0.03317	-3.40611	-3.39078
6886	0.02921	-3.53324	-3.51435
7612	0.02598	-3.65043	-3.63791
8338	0.023	-3.77226	-3.76148
9064	0.02049	-3.88782	-3.88504
9790	0.01818	-4.00743	-4.00861
10516	0.01604	-4.13267	-4.13217
11242	0.014148	-4.25818	-4.25574
11968	0.01264	-4.37089	-4.3793
12694	0.011624	-4.45446	-4.50287



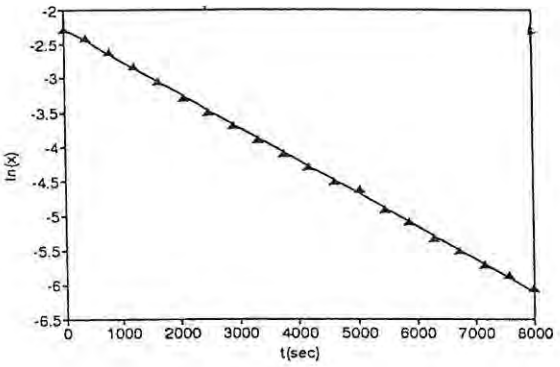
Regression Output:

Constant	-2.34235
Std Err of Y Est	0.026219
R Squared	0.998637
No. of Observations	19
Degrees of Freedom	17
X Coefficient(s)	-0.00017
Std Err of Coef.	1.52E-06

145c

RUN 1

t(sec)	conc.(x)	ln(x)	Y(cal)
0	0.103	-2.273026291	-2.2480386
586	0.081325	-2.5093	-2.61621
1072	0.06369	-2.75373	-2.81384
1558	0.050147	-2.9928	-3.01147
2044	0.03982	-3.22339	-3.20909
2530	0.03119	-3.45175	-3.40672
3016	0.02547	-3.67025	-3.60434
3502	0.02067	-3.86944	-3.80197
3988	0.017024	-4.07313	-3.9996
4474	0.01415	-4.25804	-4.19722
4960	0.011438	-4.47081	-4.39485
5446	0.00944	-4.6628	-4.59247
5932	0.008038	-4.82357	-4.7901
6418	0.006584	-5.02311	-4.98773
6904	0.005635	-5.17876	-5.18535
7390	0.004735	-5.35277	-5.38298
7876	0.003896	-5.5473	-5.58061
8362	0.003171	-5.75371	-5.77823
8848	0.002698	-5.91524	-5.97586
9334	0.002296	-6.07659	-6.17348

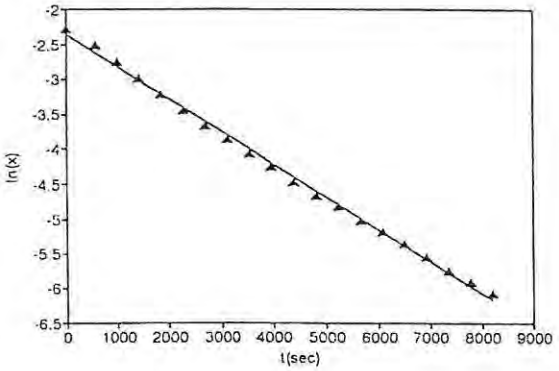


Regression Output:

Constant	-2.37792
Std Err of Y Est	0.064728
R Squared	0.997122
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.00041
Std Err of Coef.	5.15E-06

RUN 2

t(sec)	Conc.(x)	ln(x)	Y(cal)
0	0.103	-2.273026291	-2.270145024
380	0.09027	-2.40495	-2.44827
866	0.07276	-2.62059	-2.65129
1352	0.058706	-2.83518	-2.85431
1838	0.047125	-3.05495	-3.05734
2324	0.037228	-3.29075	-3.26036
2810	0.03038	-3.49397	-3.46338
3296	0.02481	-3.69651	-3.6664
3782	0.020237	-3.90024	-3.86942
4268	0.01655	-4.10137	-4.07245
4754	0.01374	-4.28744	-4.27547
5240	0.011054	-4.50496	-4.47849
5726	0.009957	-4.60948	-4.68151
6212	0.007374	-4.90979	-4.88453
6698	0.006125	-5.09538	-5.08756
7184	0.004878	-5.32302	-5.29058
7670	0.004074	-5.50313	-5.4936
8156	0.003331	-5.70448	-5.69662
8642	0.00285	-5.86044	-5.89965
9128	0.002349	-6.05377	-6.10267



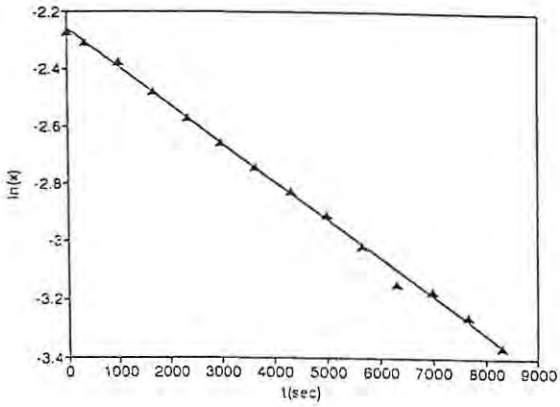
Regression Output:

Constant	-2.28953
Std Err of Y Est	0.033234
R Squared	0.999271
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-0.00042
Std Err of Coef.	2.66E-06

146

RUN 1.

t(sec)	Conc.(x)	ln(x)	Y(calc)
0	0.103	-2.2730262	-2.2554637
360	0.0996	-2.30659	-2.28326
1086	0.0932	-2.37301	-2.41113
1572	0.084	-2.47694	-2.49673
2058	0.0767	-2.56785	-2.58233
2544	0.0703	-2.65498	-2.66792
3030	0.0646	-2.73954	-2.75352
3516	0.0594	-2.82346	-2.83912
4002	0.0546	-2.90772	-2.92472
4488	0.049	-3.01593	-3.01032
4974	0.043	-3.14656	-3.09591
5460	0.042	-3.17009	-3.18151
5946	0.0385	-3.2571	-3.26711
6432	0.0346	-3.3639	-3.35271
6918	0.0318	-3.44829	-3.43831
7404	0.0295	-3.52337	-3.5239

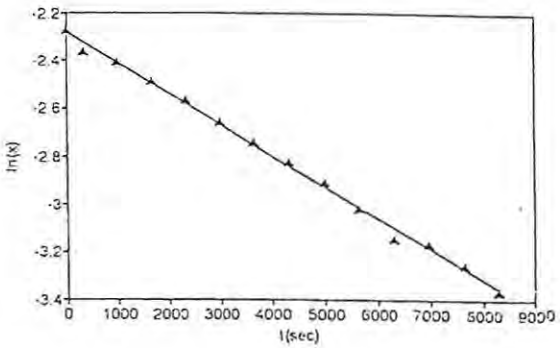


Regression Output:

Constant	-2.21986
Std Err of Y Est	0.025878
R Squared	0.99636
No. of Observations	16
Degrees of Freedom	14
X Coefficient(s)	-0.00018
Std Err of Coef.	2.85E-06

RUN 2.

t(sec)	Conc.(x)	ln(x)	Y(calc)
0	0.103	-2.273026291	-2.276510472
340	0.094	-2.36446	-2.30186
1066	0.09	-2.40795	-2.42709
1552	0.083	-2.48891	-2.51093
2038	0.0767	-2.56785	-2.59476
2524	0.0703	-2.65498	-2.67859
3010	0.0646	-2.73954	-2.76242
3496	0.0594	-2.82346	-2.84626
3982	0.0546	-2.90772	-2.93009
4468	0.049	-3.01593	-3.01392
4954	0.043	-3.14656	-3.09775
5440	0.042	-3.17009	-3.18159
5926	0.0385	-3.2571	-3.26542
6412	0.0346	-3.3639	-3.34925
6898	0.0318	-3.44829	-3.43308
7384	0.0295	-3.52337	-3.51692



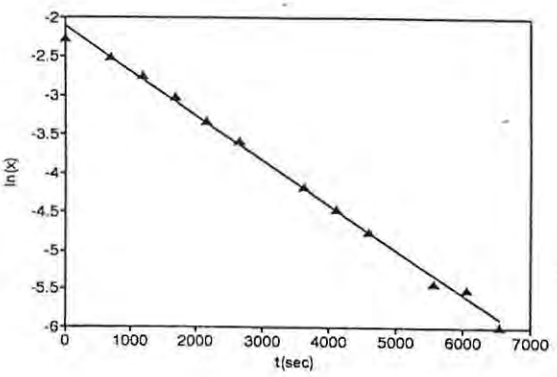
Regression Output:

Constant	-2.24321
Std Err of Y Est	0.028732
R Squared	0.995318
No. of Observations	16
Degrees of Freedom	14
X Coefficient(s)	-0.00017
Std Err of Coef.	3.16E-06

147a

RUN 1.

t(sec)	Conc.(x)	ln(x)	Y(calc).
0	0.103	-2.273026291	-2.108443542
707	0.0815	-2.507152259	-2.516895979
1193	0.064	-2.748872196	-2.797670922
1679	0.049	-3.015934981	-3.078445865
2165	0.0359	-3.327017983	-3.359220807
2651	0.0278	-3.582715258	-3.63999575
3623	0.0154	-4.17336777	-4.201545635
4109	0.0115	-4.465408244	-4.482320578
4595	0.0086	-4.755993076	-4.763095521
5567	0.0044	-5.426150738	-5.324645406
6053	0.0041	-5.496768305	-5.605420349
6539	0.0025	-5.991464547	-5.886195292

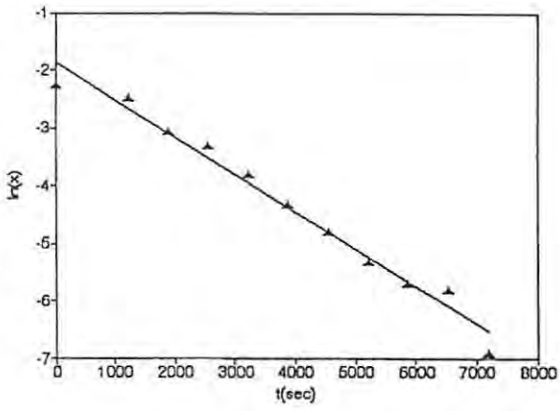


Regression Output:

Constant	-2.108443542
Std Err of Y Est	0.0849167347
R Squared	0.9958618886
No. of Observations	12
Degrees of Freedom	10
X Coefficient(s)	-0.000577726
Std Err of Coef.	1.17767E-05

RUN 2.

t(sec)	Conc.(x)	ln(x)	Y(calc).
0	0.103	-2.2730262	-1.87785...
1294	0.0824	-2.49617	-2.66428
2020	0.046	-3.07911	-3.09429
2746	0.0355	-3.33822	-3.5243
3472	0.022	-3.81671	-3.95432
4198	0.0131	-4.33514	-4.38434
4924	0.0082	-4.80362	-4.81435
5650	0.0049	-5.31852	-5.24436
6376	0.0033	-5.71383	-5.67438
7102	0.003	-5.80914	-6.10439
7828	0.001	-6.90776	-6.5344



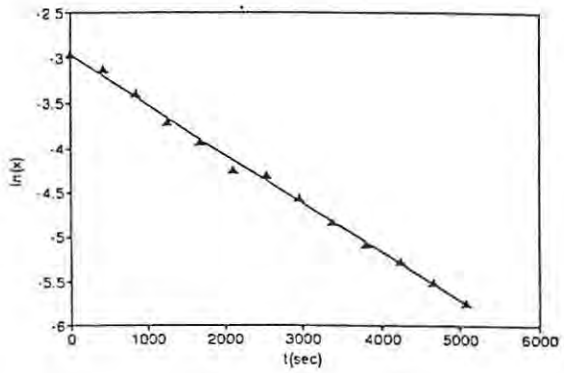
Regression Output:

Constant	-1.89784
Std Err of Y Est	0.225826
R Squared	0.979463
No. of Observations	11
Degrees of Freedom	9
X Coefficient(s)	-0.00059
Std Err of Coef.	2.86E-05

147b

RUN 1.

t(sec)	Conc.(x)	ln(x)	Y(calc).
0	0.0515	-2.966173471	-2.961475655
423	0.04396	-3.12446	-3.18692
909	0.03354	-3.39502	-3.42061
1395	0.02448	-3.7059	-3.6543
1881	0.01987	-3.91854	-3.88799
2367	0.01441	-4.23583	-4.12166
2853	0.01356	-4.30063	-4.35537
3339	0.01045	-4.56115	-4.58906
3825	0.008012	-4.826811	-4.82275
4311	0.006204	-5.08256	-5.05644
4797	0.005124	-5.27382	-5.29013
5283	0.00406	-5.50657	-5.52382
5769	0.0032	-5.7446	-5.75751

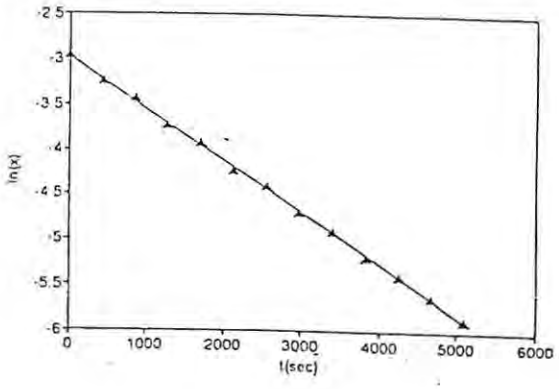


Regression Output:

Constant	-2.98352
Std Err of Y Est	0.050492
R Squared	0.997162
No. of Observations	13
Degrees of Freedom	11
X Coefficient(s)	-0.00048
Std Err of Coef.	7.73E-06

RUN 2

t(sec)	conc.(x)	ln(x)	Y(calc).
0	0.0515	-2.966173471	-2.97732834
439	0.039	-3.24419	-3.04591
925	0.0325	-3.24419	-3.29871
1411	0.0239	-3.42652	-3.55157
1897	0.01956	-3.73388	-3.80437
2383	0.01427	-3.93427	-4.05716
2869	0.012	-4.2496	-4.30996
3355	0.00901	-4.42285	-4.56275
3841	0.0073	-4.70942	-4.81555
4327	0.0055	-5.20301	-5.06835
4813	0.0045	-5.40368	-5.32114
5299	0.00356	-5.63799	-5.57394
5785	0.0028	-5.87814	-5.82674



Regression Output:

Constant	-2.81763
Std Err of Y Est	0.122925
R Squared	0.985822
No. of Observations	13
Degrees of Freedom	11
X Coefficient(s)	-0.00052
Std Err of Coef.	1.88E-05

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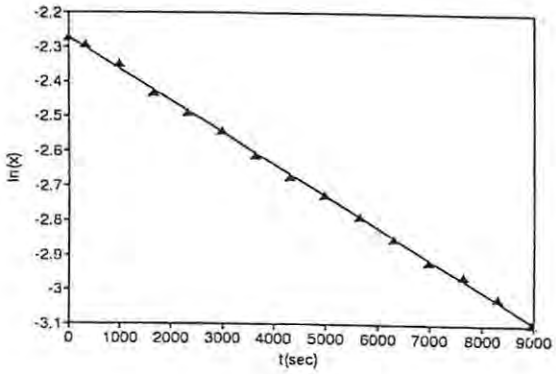
Conc.(x)	t(sec)	ln(X)	Y(calc).
0.103	0	-2.273026291	-2.270203432
0.101	343	-2.29263	-2.25726
0.095581	1069	-2.29263	-2.32728
0.08792	1795	-2.34778	-2.3973
0.07859	2521	-2.43133	-2.46733
0.07335	3247	-2.54351	-2.53735
0.06899	3973	-2.61251	-2.60737
0.06544	4699	-2.67379	-2.67739
0.06163	5425	-2.72662	-2.74741
0.05788	6151	-2.84938	-2.81743
0.0541	6877	-2.91692	-2.88745
0.052	7603	-2.95651	-2.95748
0.0488	8329	-3.02002	-3.0275
0.04534	9055	-3.09357	-3.09752

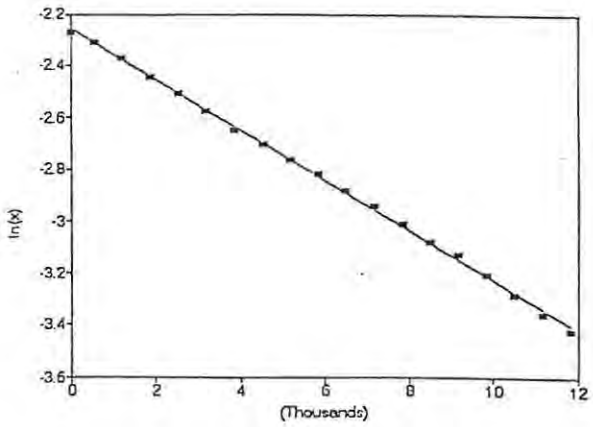


Regression Output:

Constant	-2.22418
Std Err of Y Est	0.030355
R Squared	0.989894
No. of Observations	14
Degrees of Freedom	12
X Coefficient(s)	-9.6E-05
Std Err of Coef.	2.81E-06

RUN 2.

t(sec)	Conc.(x)	ln(x)	Y(calc).
0	0.103	-2.273026291	-2.259244089
543	0.099232	-2.31029	-2.27689
1269	0.09327	-2.31029	-2.33984
1995	0.08676	-2.37226	-2.40279
2721	0.08182	-2.44461	-2.46574
3447	0.076335	-2.50311	-2.52868
4173	0.07098	-2.57265	-2.59163
4899	0.06713	-2.64536	-2.65458
5625	0.06328	-2.70053	-2.71753
6351	0.05985	-2.81591	-2.78048
7077	0.05623	-2.8783	-2.84343
7803	0.053	-2.93746	-2.90638
8529	0.04938	-3.00821	-2.96933
9255	0.04938	-3.00821	-3.03228
9981	0.04606	-3.07781	-3.09522
10707	0.04387	-3.12652	-3.15817
11433	0.04051	-3.20621	-3.22112
12159	0.03741	-3.28582	-3.28407
12885	0.03488	-3.35584	-3.34702
13611	0.03263	-3.42252	-3.40997



Regression Output:

Constant	-2.22981
Std Err of Y Est	0.027808
R Squared	0.994708
No. of Observations	20
Degrees of Freedom	18
X Coefficient(s)	-8.7E-05
Std Err of Coef.	1.49E-06

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3.9 NMR CONFORMATIONAL STUDIES ON INDOLIZINE-2-CARBOXAMIDES

Variable temperature ^{1}H NMR spectra of the indolizine-2- carboxamides (**163-165**) were obtained from $CDCl_3$ solutions using a Bruker AMX 400 MHz NMR spectrometer, equipped with a variable temperature unit which has been calibrated over the appropriate temperature range using 80% ethylene glycol and 40 % methanol in DMSO-d_6.

The coalescence temperatures (T_c) were obtained from the variable temperature spectra (Figure 16, p126). The frequency differences at coalescence ($\Delta \upsilon_c$) were obtained by extrapolation of linear plots of the frequency separation ($\Delta \upsilon$) versus T. The rotational energy barrier ($\Delta G^{\ddagger}$) were calculated from the coalescence temperature and the frequency separation at coalescence.

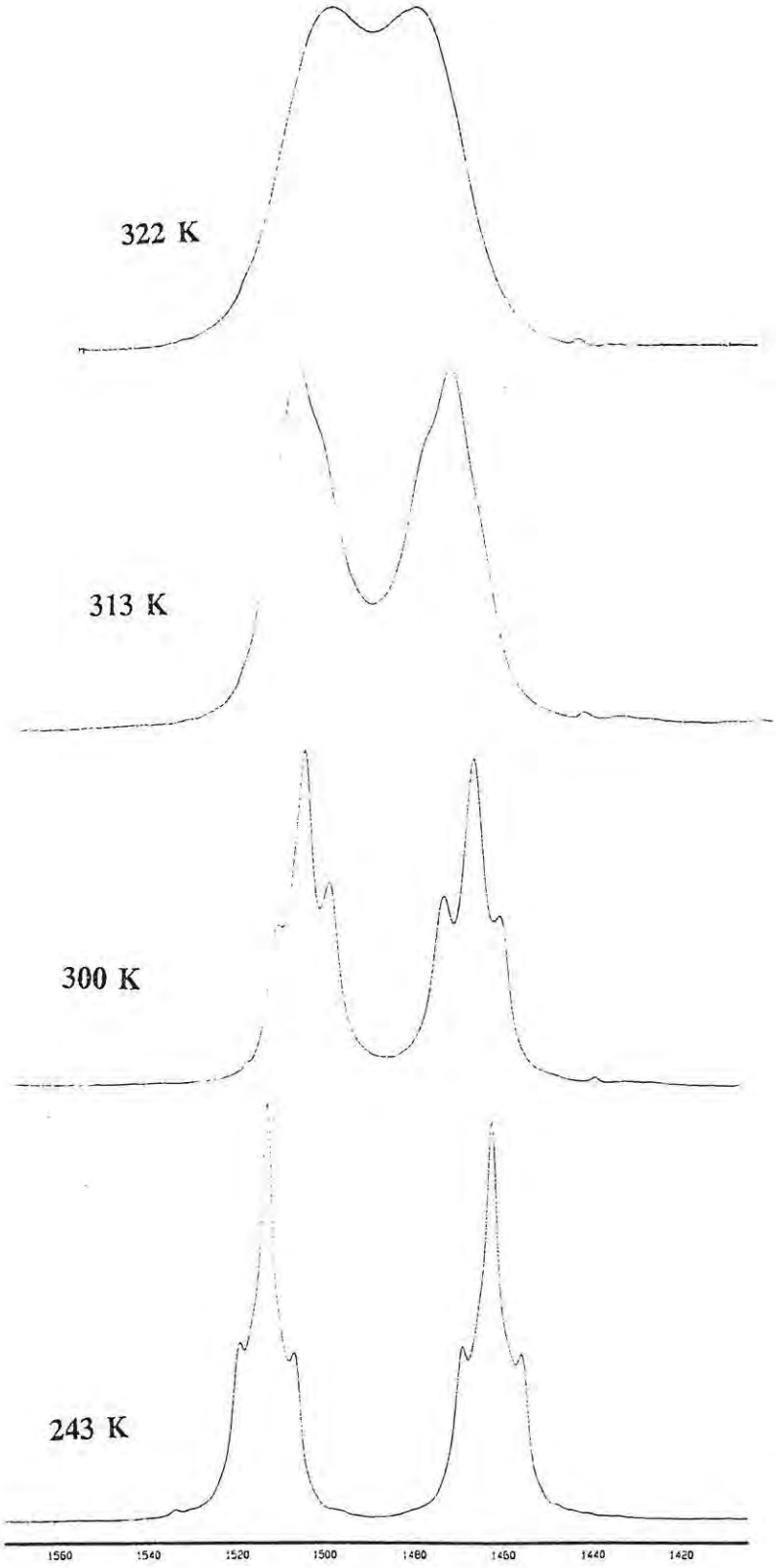


FIGURE 16. VARIABLE TEMPERATURE ^{1}H NMR SPECTRA SHOWING *N*-ALKYL SIGNALS FOR 1-[(5-METHYLINDOLIZIN-2-YL)CARBONYL]PYRROLIDINE (164).

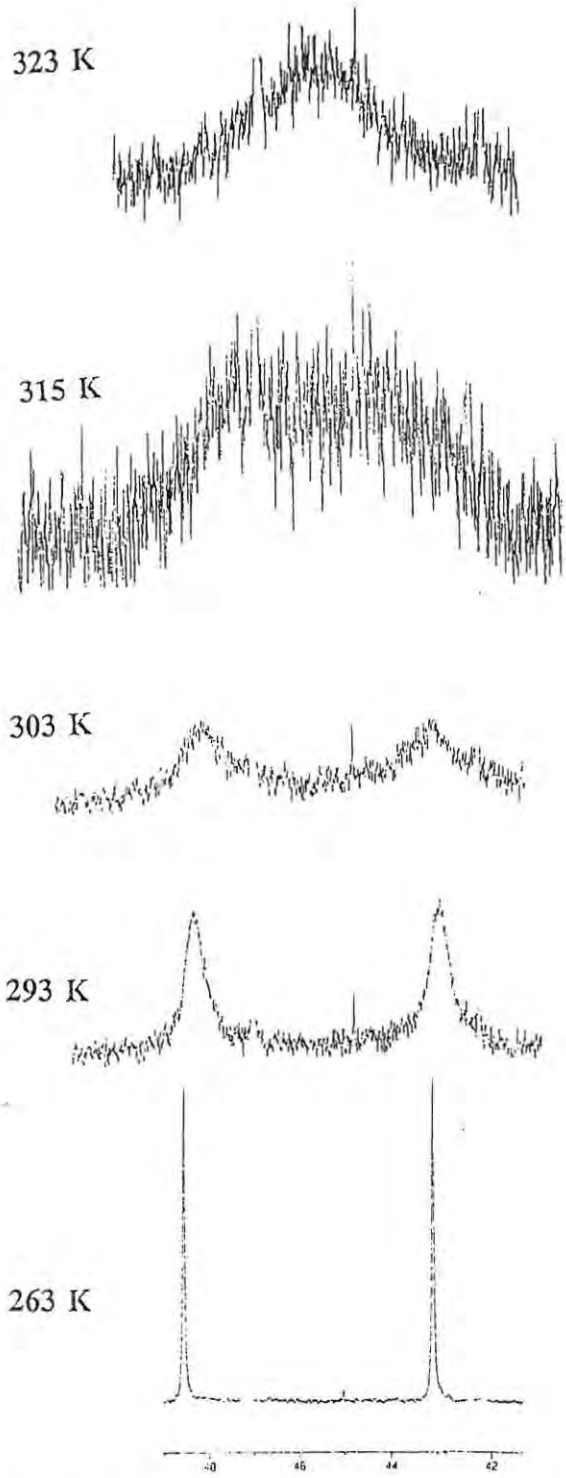
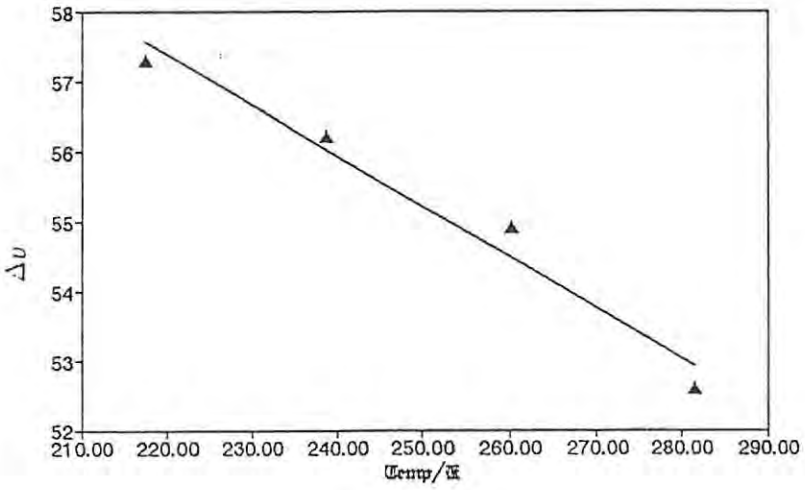


FIGURE 17. VARIABLE TEMPERATURE ^{13}C NMR SPECTRA SHOWING *N*-ALKYL SIGNALS FOR 1-[(5-METHYLINDOLIZIN-2-YL)CARBONYL]PIPERIDINE (165).

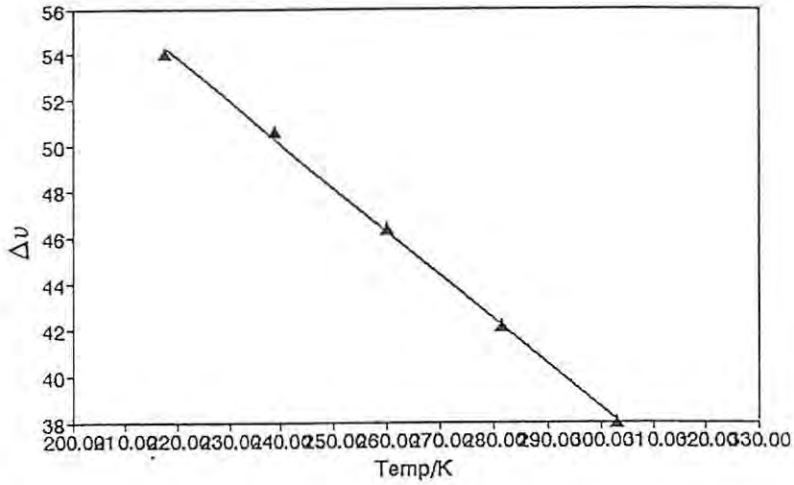
163.



Regression Output:

Constant	73.28463
Std Err of Y Est	0.442719
R Squared	0.968
No. of Observations	4
Degrees of Freedom	2
X Coefficient(s)	-0.0723
Std Err of Coef.	0.009295

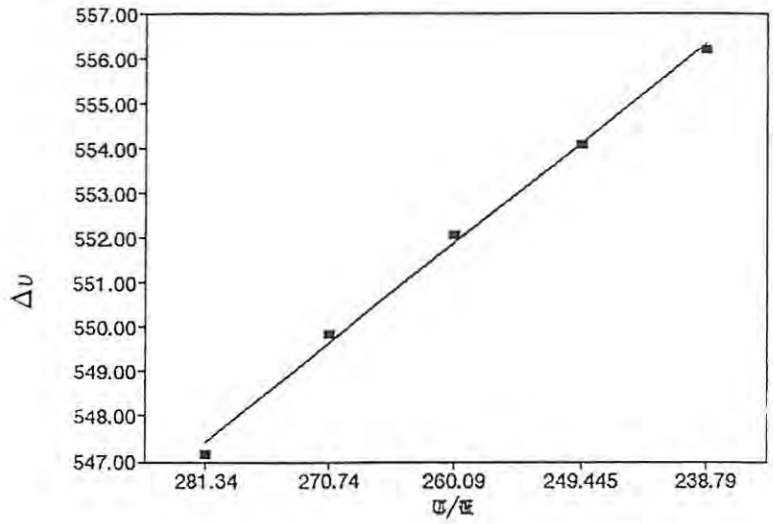
164 .



Regression Output:

Constant	95.52331
Std Err of Y Est	0.273634
R Squared	0.998632
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	-0.18959
Std Err of Coef.	0.004051

165



Regression Output:

Constant	606.5086
Std Err of Y Est	0.245287
R Squared	0.996401
No. of Observations	5
Degrees of Freedom	3
X Coefficient(s)	-0.21009
Std Err of Coef.	0.00729

4. REFERENCES

1. E.T. Borrows and D.O. Holland, *Chem.Rev.*, 1948, **42**, 611.
2. K. Matsumoto and T. Uchida, *Synthesis.*, 1976, 209.
3. T. Melton, J. Taylor and D.G. Wibberly, *J.Chem.Soc.*, 1965, 2948.
4. T. Melton, J. Taylor and D.G. Wibberly, *J.Chem.Soc., Chem.Commun,* 1965, 151.
5. T. Melton and D.G. Wibberly, *J.Chem.Soc.,Chem.Commun*, 1967,983.
6. E.T. Borrows and D.O. Holland, *J.Chem.Soc.*, 1946, 1069.
7. E.T. Borrows, J. Kenyon and D.O. Holland, *J.Chem.Soc.*, 1946, 1075.
8. D.R. Bragg and D.G. Wibberly, *J.Chem.Soc.*, 1962, 2627.
9. E.M. Roberts, M. Gates and V. Boekelheide, *J.Org.Chem.*,1955, **20**, 1443.
10. D.W. Adamson, P.A. Barret, J.W. Billinghurst and T.S.G. Jones, *J.Chem.Soc.*, 1957, 2315.
11. P.A. Barret and K.A. Chambers, *J.Chem.Soc.*, 1958, 338.
12. E.E. Glover, K.D. Vaughan and D.C. Bishop, *J.Chem.Soc., Perkin Trans.1*, 1973, 2595.
13. E.T. Borrows and D.O. Holland, *J.Chem.Soc.*, 1947, 672.
14. V. Boekelheide and R.J. Windgassen, *J.Am.Chem.Soc.*, 1959, **81**, 1456.
15. R.H. Wiley and L.H. Knabeshuh, *J.Org.Chem.*, 1953, **18**, 836.
16. R.M. Acheson and G.A. Taylor, *J.Chem.Soc.*, 1962, 3758.
17. R.M. Acheson and D.A Robinson, *J.Chem.Soc., Chem.Commun*, 1968, 1629.
18. R.M. Acheson, A.S. Bailey and I.A. Selby, *J.Chem.Soc.,Chem.Commun*, 1966, 835;

19. V. Boekelheide and J.C. Godfrey, *J.Am.Chem.Soc.*, 1953, **75**, 3679.

20. V. Boekelheide and K. Fahrenholtz, *J.Am.Chem.Soc.*, 1961, **83**, 458.

21. W.J. Linn, O.W. Webster and R.E. Benson, *J.Am.Chem.Soc.*, 1965, **87**, 3651.

22. T. Sasaki, K.Kanematsu, Y.Yukimoto and S. Ochai, *J.Org.Chem.*, 1971, **36**, 813.

23. C.A. Henrick, E.Ritchie and W.C.Taylor, *Aust.J.Chem.*,1967, **20**, 2467.

24. N. Basketter and A.O. Plunkett, *J.Chem.Soc., Chem.Commun*, 1971, 1578.

25 D.G. Farnum, R.J. Alaimo and J.M. Dunston, *J.Org.Chem.*, 1967, **32**, 1130.

26. R. Huisgen, R. Grashey and E. Steingruber, *Tetrahedron.Lett.*, 1963, 1441.

27. T. Sasaki, K. Kanematsu and A. Kakehi, *J.Chem.Soc.,Perkin Trans 1*, 1973, 2089.

28. T. Sasaki, K.Kanematsu and A. Kakehi, *Tetrahedron.*, 1972, **28**, 4947.

29. Y. Tamura, Y.Sumida and M. Ikda, *J.Chem.Soc., Perkin Trans 1,* 1973, 2091.

30. W. Flitsch,in *Comprehensive Heterocyclic Chemistry,* eds. A.R. Katritzky and C.W. Rees, Pergamon, Oxford, 1984, v ol.4, p445.

31. M. Fraser, S. Mackenzie and D.H. Reid, *J.Chem.Soc.*, 1966, 44.

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

33. E.T. Borrows, D.O.Holland and J. Kenyon, *J.Chem.Soc.*, 1946, 1077.

34. G. Jones, in The Organic Chemistry of Nitrogen, eds. V. Sidgwick, I.T. Millar and H.D. Springall; Clarendon Press, Oxford, 3rd edn., 1966, p 752.

35. R.J. Bowers and A.G. Brown, *J.Chem.Soc., Chem.Commun*,1970, 1434.

36. Reference 30, p458..

37. Reference 30, p459.

38. J. Carbon and S. Brehm, *J.Pharm.Sci.*, 1961, **26**, 3376.

39. W.B. Harrell and R.F. Doerge, *J.Pharm.Sci.*, 1968, **57**, 1989

40. W.B. Harrell and R.F. Doerge, *J.Pharm.Sci.*, 1966, **56**, 225.

41. K.R. Kallay and R.F. Doerge, *J.Pharm Sci.*, 1971, **61**, 949.

42. A.U. DE and B.P. Saha, *J.Pharm.Sci.*, 1973, **62**, 1897.

43. A.U. DE and B.P. Saha, *J.Pharm.Sci.*, 1975, **64**, 249.

44. W.L.F. Armarego, *J.Chem.Soc.*, 1964, 4226.

45. G. Jones and J. Stanyer, *Organic Mass Spectrometry.*, 1970, **3**, 1498.

46. P.J. Black, M.L. Heffernan, L.M. Jackman, Q.N. Porter and G.R. Underwood, *Aust J.Chem.*,1964, **17**, 1128.

47. R.J. Pugmire, J.C. Smith, D.M. Grant, B. Stanovick, M. Tisler and B. Vercik, *J.Heterocyl Chem.*, 1987, **24**, 805.

48. R.J. Pugmire, M.J. Robins, D.M. Grant and R.K. Robins, *J.Am.Chem.Soc.*, 1971, **93**, 1887.

49. A.J. Jones, P.Hanisch, M.L.Heffernan and G.M. Irvine, *Aust.J.Chem.*, 1980, **33,** 499.

50. P. Crews, R.R. Kintner and H.C. Padgett, *J.Org.Chem.*, 1973, **38**, 4391.

51. M.L. Bode and P.T. Kaye, *J.Chem.Soc., Perkin Trans.* 1, 1993, 1809.

52. C.H. Weidner, D.H. Wordsworth, S.L.Bender and D.J. Beltman, *J.Org.Chem.*, 1989,**54**,3660.

53.. S.E. Drewes and G.H.P. Roos, *Tetrahedron.*, 1988, 44, 4653.

54. S.E. Drewes and N.D. Emslie, *J.Chem.Soc.,Perkin Trans.1*, 1982, 2079.

55. F. Ameer,S.E. Drewes,S. Freese and P.T.Kaye, *Synth.Commun.*, 1988, **18**, 495.

56. M.L. Bode and P.T. Kaye, *Tetrahedron Lett.*, 1991, **40**,5611.59.

57. M.L. Bode and P.T. Kaye, *J.Chem.Soc., Perkin Trans. 1*, 1991, 2612.

58. V. Boekelheide and R.J Windgassem Jr, *J.Am.Chem.Soc.*, 1959,**81**, 1456.

59. M. Friedman and J.S. Wall, *J.Org.Chem., 1966, 31, 2888.*

60. H. Shenhav, Z.Rapport and S.Patai, *J.Chem.Soc., [B]*, 1970, 496.

61. G.P Ellis, G.J.P. Becket, D.Shaw, H.k. Wilson, C.J. Vardey and I.F. Skidmore *J.Med.Chem.*, 19778,**21, 1120.**

62. M. Kaeriyama, T. Sato, S. Hashhimoto, M.Mizuno, M.Ando and H. Yoneda, *Chem.Abstr.*, 1976,**85**, 176872e.

63. N. Peet and S.Sunder, *J.Org.Chem.*, 1980, **45,** 536.

64. R. Adams and L.H. Ulich, *J.Am.Chem.Soc.*, 1920, **42**, 599.

65. M. Bennett and C.H. Heathcock, *J.Chem.Soc.*, 1929, 270.

66 D.R Bragg and D.G. Wibberly,*J.Chem.Soc.*, 1962, 2627.

67. W.A. Denny, G.W. Rewcastle and B.C. Baguley, *J.Med.Chem.*, **33,**814.

68. A. Kakehi, S. Ito, T. Funahashi and N. Ogasawara, *Bull.Chem.Soc.Jpn.*, 1976, **49(8)**, 2250.

69. A. Kakehi, S. Ito, T. Maeda, R.Takeda, M.Nishimura, M.Tamashima and T.Yamaguchi, *J.Org.Chem.*, 1978, **43,** 4837.

70. N.S. Issacs, *Physical Organic Chemistry,* Longman, Harlow, 1987, Sections 8.4.1, 8.5 and 8.6.

71. L.H. Lai and P.Chen, *J.Chem.Soc., Perkin Trans.1,* 1989, 1665.

72. R.J. Smith, D.H.Williams and K.James, *J.Chem.Soc., Perkin Trans.1,* 1989, 682.

73. M.L. Bode, Ph.d. Thesis, Rhodes University, 1994.

74. D.N. Davidson, Ph.d. Thesis, Rhodes University, 1992.

75. W.C. Still, M.Kahn and A.Mitra, *J.Org.Chem.*, 1978,43, 2923.