THE SYNTHESIS OF AZA-AZULENE DERIVATIVES

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ABSTRACT

Various synthetic routes to the pyrrolo[1,2-a]azepinium system were attempted.

Chapter Two describes the preparation of some 1-azido-3-phenylprop-1-enes. Thermal decomposition of these vinyl azides did not result in any pyrrolo[1,2-a]azepines.

Attempts at [2+2] additions of dichloroketene to 3H-pyrrolizine are described in Chapter Three. Electrophilic attack of dichloroacetyl chloride or trichloroacetyl chloride (precursors to dichloroketene) on 3H-pyrrolizine to give 5-dichloroacetyl-3H-pyrrolizine or 5-trichloroacetyl-3H-pyrrolizine was the predominant reaction. Only in one case was a [2+2] addition product found, 8-trichloroacetyl-3-dichloro -7-azatricyclo[5,3,0,$0^{2,5}$]deca-1(10)3-dien-4-one. Attempted ring expansion of this tricyclic compound under basic conditions failed. Some reactions of 5-trichloroacetyl-3H-pyrrolizine are described, including the novel reaction with potassium carbonate and methanol to give 5-dichloromethyl-3-carbomethoxy-3H-pyrrolizine and a ring opened product, 2-carbomethoxy-5(4-chlorobut-1-en-3-on-1-yl)pyrrole. The synthesis of 5-acetyl-3H-pyrrolizine was achieved via two routes.

The synthesis of 5,6-dihydropyrrolo[1,2-a]azepin-7-one was carried out by an aldol condensation of 1(butan-3-on-1yl)-2-formyl-pyrrole. The syntheses of both pyrrolo[1,2-a]azepin-7-one and 5H-pyrrolo[1,2-a]azepine proceeded from 5,6-dihydropyrrolo[1,2-a]azepin-7-one, the precursor in two separate routes.Protonation and ethylation of pyrrolo[1,2-a]azepin-7-one gave pyrrolo[1,2-a]azepinium

salts but it was not possible to isolate these. Pyrrolo[1,2-a]azepin-7-one underwent a Wittig reaction to give 7-methylene-7H-pyrrolo[1,2-a]azepine, protonation of this failed to yield any isolable salt.

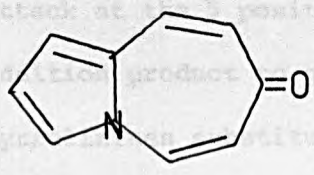
The protonation reaction of pyrrolo[1,2-a]azepin-7-one and of three indolo[1,2-a]azepinones were studied by NMR spectroscopy. The spectral data produced gave some information on the π-bonding of the ketones in neutral solution, in acidic solution and in their ethylated forms.

CONTENTS

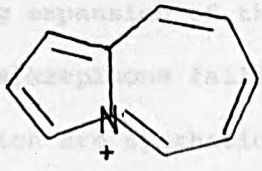
GENERAL INTRODUCTION

The aims of the work described in this thesis are; the synthesis of pyrrolo[1,2-a]azepin-7-one (1), the synthesis of the pyrrolo[1,2-a]azepinium system (2) and the study of the protonation of pyrrolo[1,2-a]azepin-7-one in acid solution by NMR spectroscopy.

Prior to this work pyrrolo[1,2-a]azepin-7-one had not been prepared, although the isomeric ketones, pyrrolo[1,2-a]azepin-5-one and pyrrolo[1,2-a]azepin-9-one have been reported[1,2].



(1)



(2)

Such ketones are interesting as their protonation and alkylation on oxygen could give a ready route to the pyrrolo[1,2-a]azepinium system. There is, as yet, no convenient synthesis of salts such as (2).

Chapter One describes the synthesis of aza-azulenes in general and attempts to prepare pyrrolo[1,2-a]azepinium salts in particular.

In Chapter Two the synthesis of various 1-azido-3-phenylprop-1-enes is described. It was hoped that thermal decomposition of these

azides would provide a route to pyrrolo[1,2-a]azepines, all the decompositions gave a mixture of products but no pyrrolo[1,2-a]azepine.

An attempted route to pyrrolo[1,2-a]azepin-7-ones via a [2+2] addition reaction of dichloroketene to 3H-pyrrolizine is described in Chapter Three. Electrophilic attack of dichloroacetyl chloride or trichloroacetyl chloride (precursors to dichloroketene) at the 5 position of 3H-pyrrolizine competed with dichloroketene formation. Depending on the reactants, either 5-dichloroacetyl-3H-pyrrolizine or 5-trichloroacetyl-3H-pyrrolizine were formed. Only in one reaction was any [2+2] product seen, but this too had undergone electrophilic attack at the 5 position. Attempted ring expansion of the [2+2] addition product to give a pyrrolo[1,2-a]azepinone failed. The 3H-pyrrolizines substituted in the 5 position are synthetically useful compounds as it is difficult to prepare substituted pyrrolizines by the usual methods of ring synthesis for these compounds. There is very little known of the reactions of 3H-pyrrolizines. The chemistry of these 5-substituted 3H-pyrrolizines was investigated.

Chapter Four describes the synthesis of pyrrolo[1,2-a]azepin-7-one and its protonation and alkylation to give pyrrolo[1,2-a]azepinium salts, although it was not possible to isolate pure samples of these salts. The synthesis of 5H-pyrrolo[1,2-a]azepine is also described. This azepine is a potential synthon for pyrrolo[1,2-a]azepinium salts, however reaction of 5H-pyrrolo[1,2-a]azepine with a hydride abstracting agent failed to yield any of the salt (2).

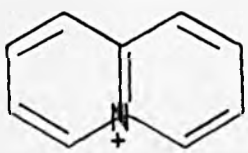
The protonation and ethylation reactions of pyrrolo[1,2-a]azepin-7-one and three indolo[1,2-a]azepinones were studied using ^{1}H NMR

spectroscopy. The NMR data were used to partly describe the π-bonding of these ketones in neutral and acidic solution.

CHAPTER ONE

Historical Review

The quinolizinium cation (3) is a 10π aromatic system bearing a positive charge. The majority of the reactions of quinolizinium salts proceed via nucleophilic attack[3-5], due to the influence of the positive charge.

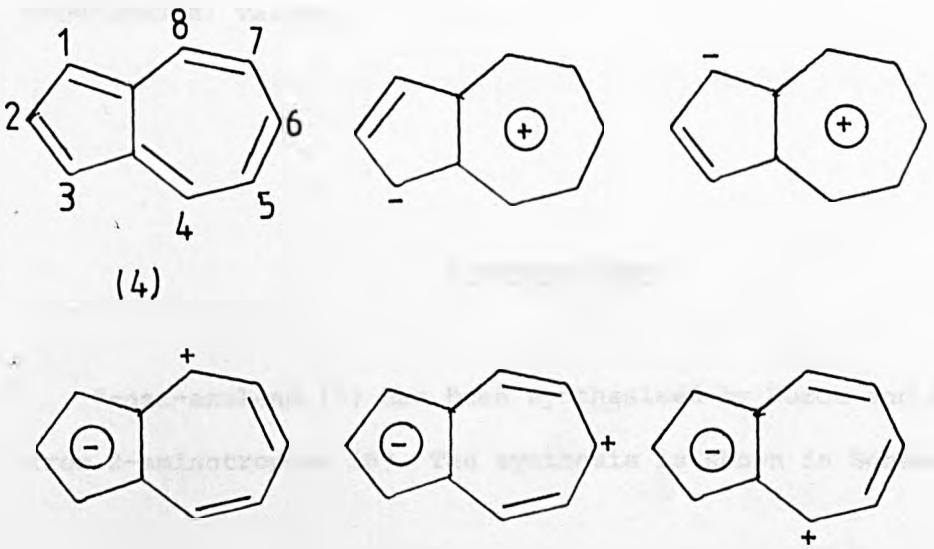


(3)

However, quinolizinium salts do show electrophilic substitution reactions when they carry strongly electron-donating substituents[5-8]. For example, 1-hydroxy-quinolizinium bromide can be easily brominated in the 2-position by treatment with bromine[5-7].

Naphthalene and azulene (4) are isoelectronic with the quinolizinium system. The non-benzenoid azulene shows differing chemical reactivty from naphthalene, this has been explained in terms

of resonance structures in which each ring tends to acquire 6π electrons[9,10]. Thus azulene shows electrophilic substitution at position 1(3) and nucleophilic substitution at positions 4(8) and 6.



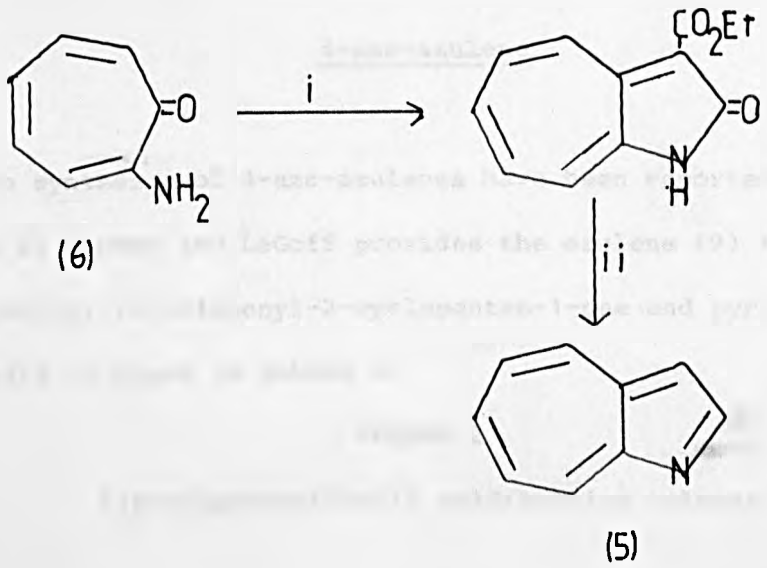
Simplified LCAO calculations[11] show that the effect of substituting a nitrogen atom for a methylene unit in the periphery of azulene should have little effect on the chemical reactivity of the aza-azulene compared with that of the parent hydrocarbon. When the nitrogen is in a bridgehead position and so positively charged as in the pyrrolo[1,2-a]azepinium (alternatively aza-azulenium) salts (2) the chemical reactivity may be very different. One of the objectives of this work is to synthesise pyrrolo[1,2-a]azepinium salts.

The resonance energies of the five isomeric aza-azulenes have been calculated using HMO theory and vary between 0.305β for 1-aza-azulene and 0.127β for 4-aza-azulene[12]. Flitsch and co-workers have calculated the resonance energy of 5-hydroxypyrrolo[1,2-a]azepinium

ion to be 0.50β, although not by the same method as used for the other aza-azulenes. The resonance energy of azulene has been calculated as 3.36β, but this is an over-estimate when compared to experimental values.

1-aza-azulene

1-aza-azulene (5) has been synthesised by Nozoe and co-workers[13] from 2-aminotropone (6). The synthesis is shown in Scheme 1.

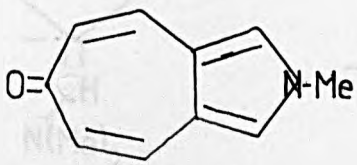


Scheme 1

i)$CH_2(CO_2Et)_2/EtO^-$ ii)a)HBr b)$POCl_3$ c)NH_2NH_2 d)CH_3CO_2H/Cu^{2+}

2-aza-azulene

This compound has been synthesised by Nozoe but no details appear in Chemical Abstracts. The ketone (7) has recently been described by Waig[15]. This compound is similar to that previously described by El'tsov[31] (8).



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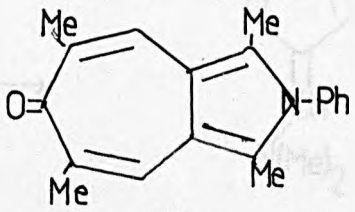


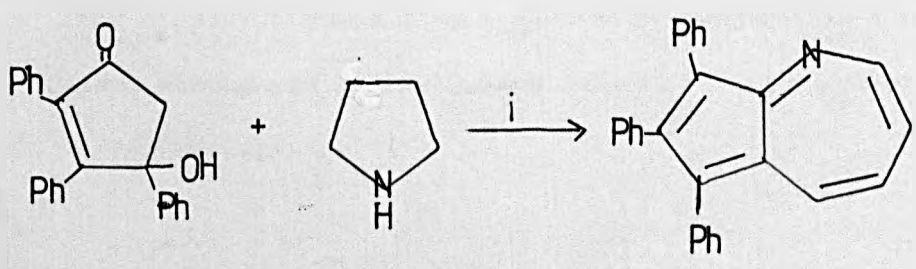
(8)

4-aza-azulene

Two syntheses of 4-aza-azulenes have been reported[16,17], the most recent by Conner and LeGoff provides the azulene (9) in one step from 4-hydroxy-2,3,4-triphenyl-2-cyclopenten-1-one and pyrrolidine. The synthesis is shown in Scheme 2.

Scheme 2

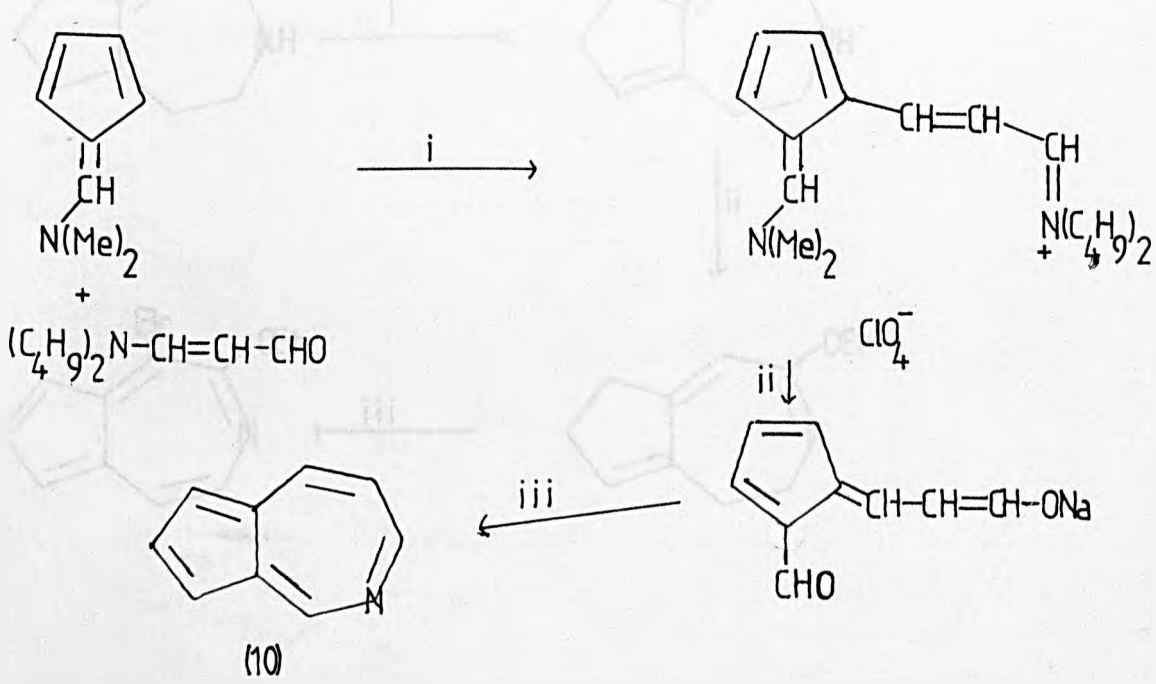
i) p-toluenesulphonic acid/boiling toluene



(9)

5-aza-azulene

A number of 5-aza-azulenes have been reported by Hafner and co-workers[18-20] including a synthesis of the parent compound (10) in three steps from a 6-aminofulvene. This synthesis is shown in Scheme 3.

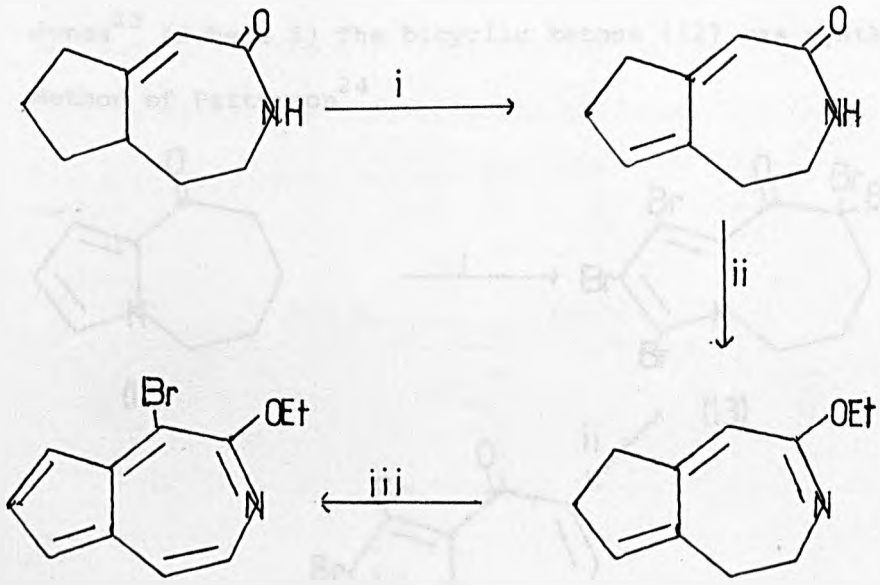


Scheme 3

i) $(COCl)_2$, $NaClO_4$ ii) NaOH iii) NH_3

6-aza-azulene

The only reported synthesis in the literature is that due to Kimura and Tai[21] which proceeds from an azepinone in a number of dehydrogenative steps as shown in Scheme 4.



Scheme 4

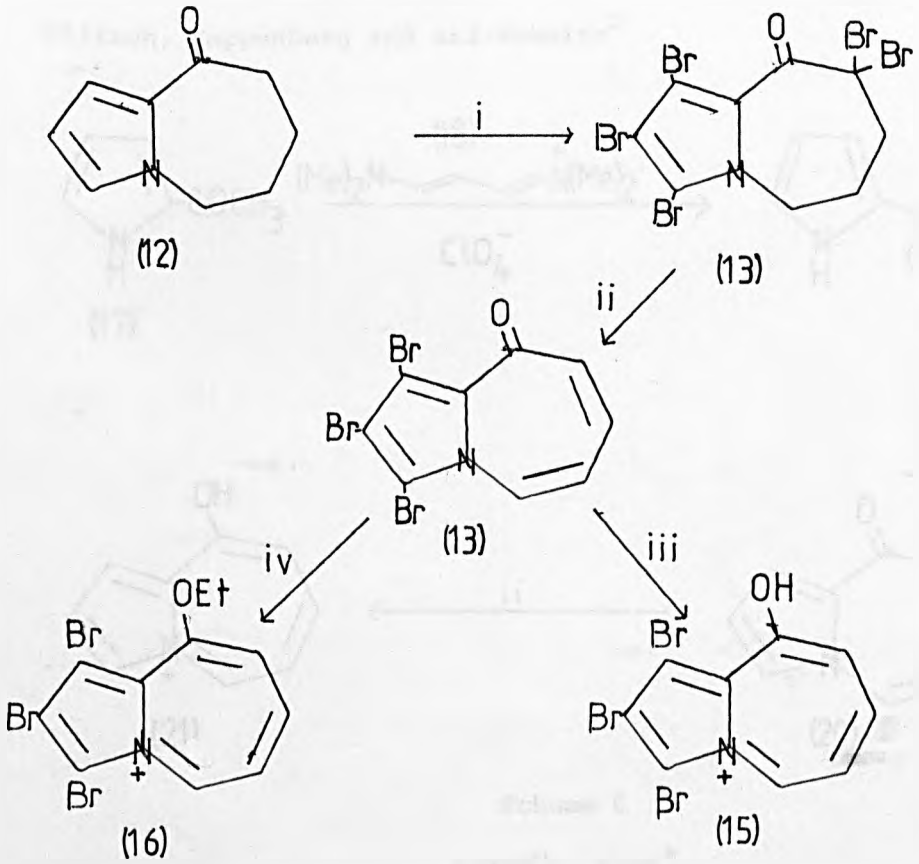
i)$C_5H_5NHBr_3$, LiCl ii)$Et_3O^+BF_4^-$ iii)NBS, Al_2O_3

Pyrrolo[1,2-a]azepines

The first 7,5 fused ring system with nitrogen as a bridgehead atom was discovered by Prelog and Seiwerth[22] as a reduction product of 1-keto-norlupinane (11)

i)Clemmensen reduction

In the suceeding 30 years a variety of syntheses of this and other saturated derivatives were devised. In 1969 the first unsaturated pyrrolo[1,2-a]azepinone was prepared by Collington and Jones[23] (Scheme 5) The bicyclic ketone (12) was synthesised by the method of Patterson[24].

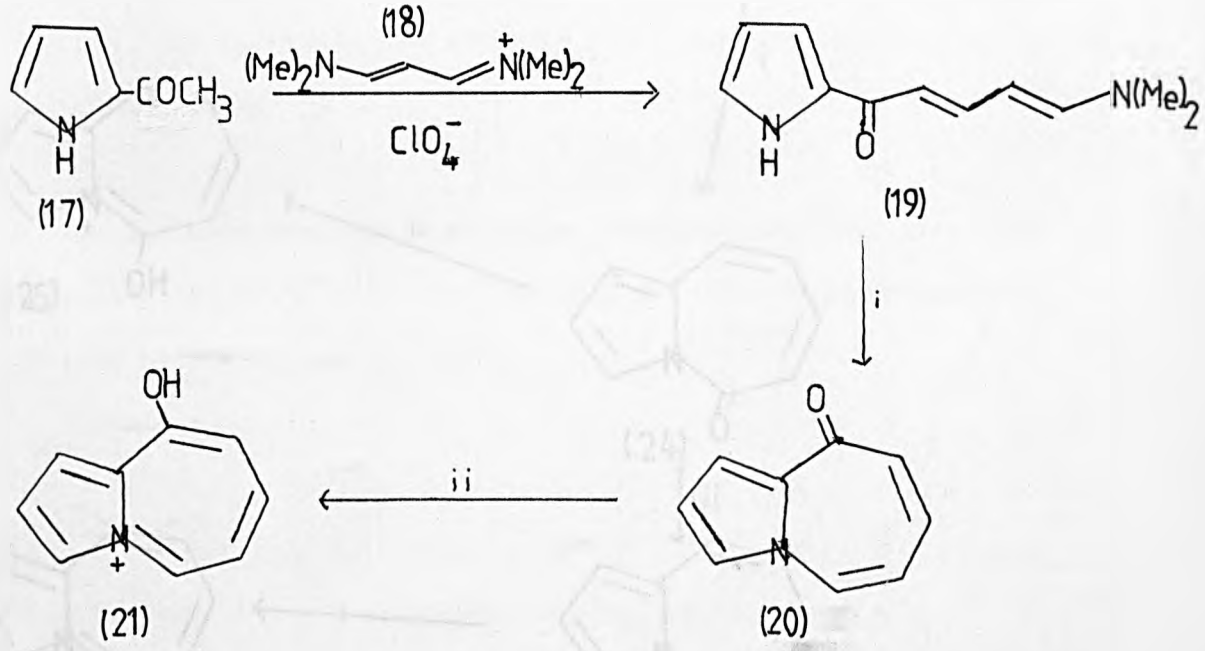


Scheme 5

i)PTAB ii)LiCl iii)HBr iv)$Et_3O^+BF_4^-$

Bromination of the ketone (12) with phenyltrimethylammonium tribromide gave the bromoketone (13) with unavoidable bromination of the pyrrole ring, dehydrobromination of this with lithium chloride gave the tribromo pyrrolo[1,2-a]azepin-9-one (14). From this ketone it was possible to form the corresponding pyrrolo[1,2-a]azepinium salts by protonation (15) or alkylation (16).

The parent pyrrolo[1,2-a]azepin-9-one (21) has been prepared by Flitsch, Kappenberg and and Schmitt[2]



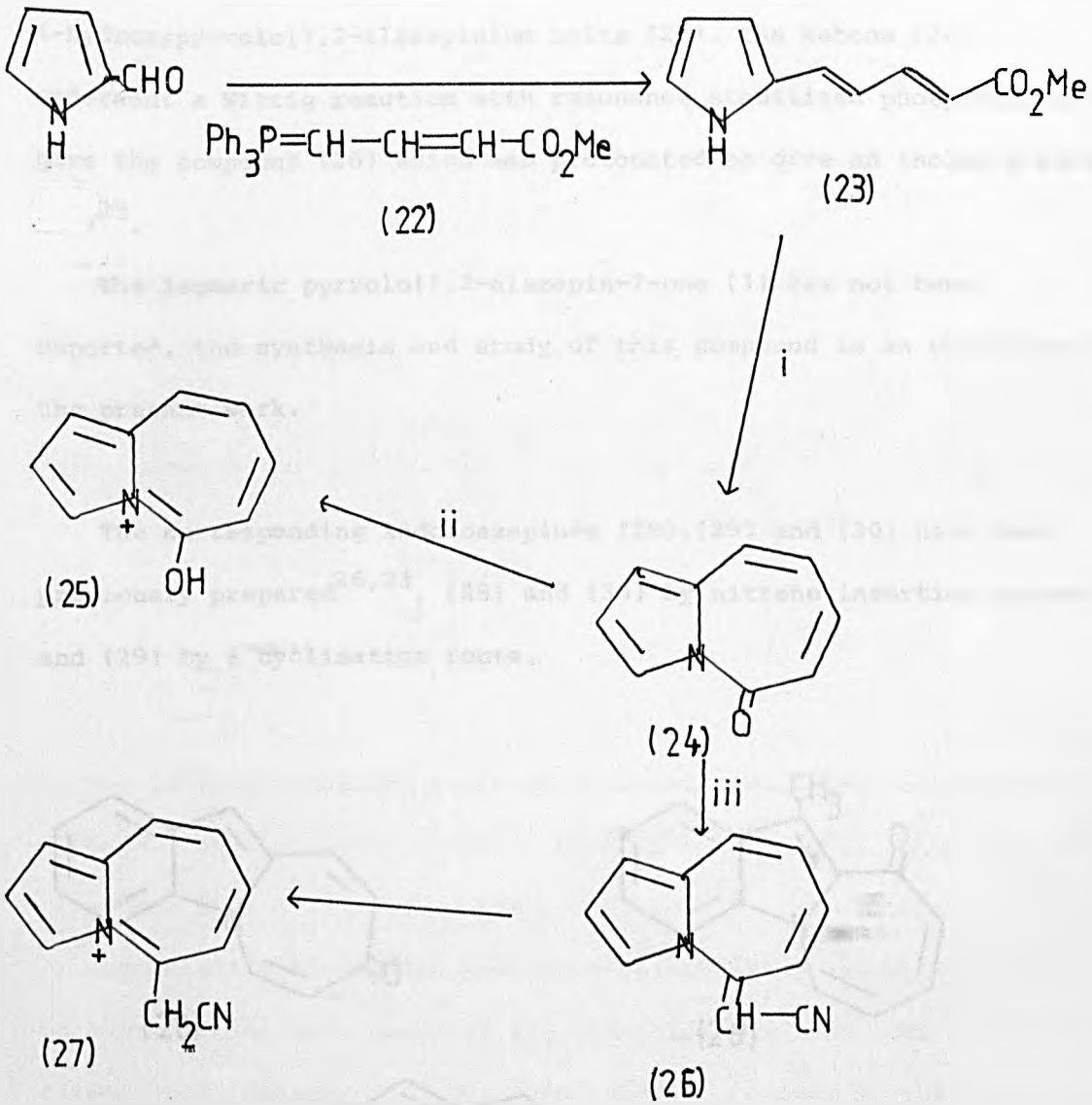
Scheme 6

i)400°C ii)H^+

A condensation reaction of 2-acetylpyrrole with the vinylamidinium salt (18) gave the dienamine (19). Heating this dienamine to 400°C gave pyrrolo[1,2-a]azepin-9-one (20). This ketone can be protonated in acidic media to give a pyrrolo[1,2-a]azepinium salt, this protonation reaction has been studied by NMR in a number

of solvents of differing protonating ability[2].

The isomeric pyrrolo[1,2-a]azepin-5-one (24) has also been prepared, by Flitsch,Muter and Wolf[1] as shown in Scheme 7



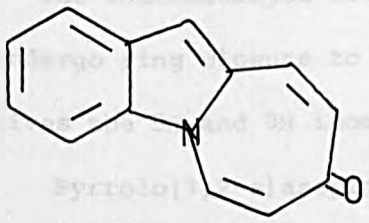
Scheme 7

i)NaH ii)H^+ iii)Ph_3PCHCN

Pyrrole-2-aldehyde was condensed with the stabilized phosphorane (22) to give a diene (23), reaction of this diene with sodium hydride eliminated methoxide to give pyrrolo[1,2-a]azepin-5-one (24), protonation of the azepinone in acidic solvents gave solutions of the 4-hydroxypyrrolo[1,2-a]azepinium salts (25). The ketone (24) underwent a Wittig reaction with resonance stabilized phosphoranes to give the compound (26) which was protonated to give an isolable salt (27)[25].

The isomeric pyrrolo[1,2-a]azepin-7-one (1) has not been reported, the synthesis and study of this compound is an objective of the present work.

The corresponding indoloazepines (28),(29) and (30) have been previously prepared[26,23], (28) and (30) by nitrene insertion routes and (29) by a cyclisation route.



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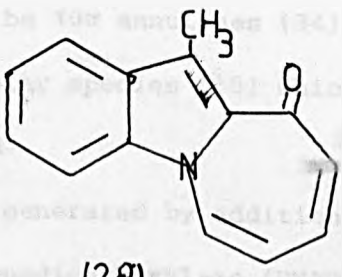

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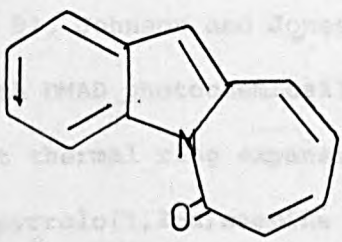
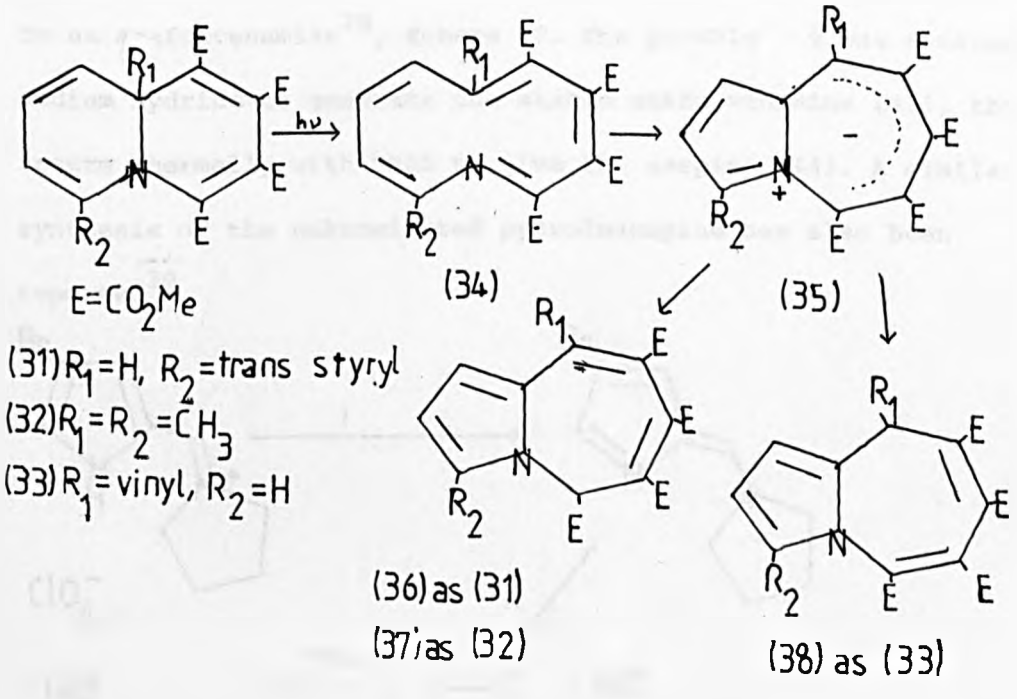


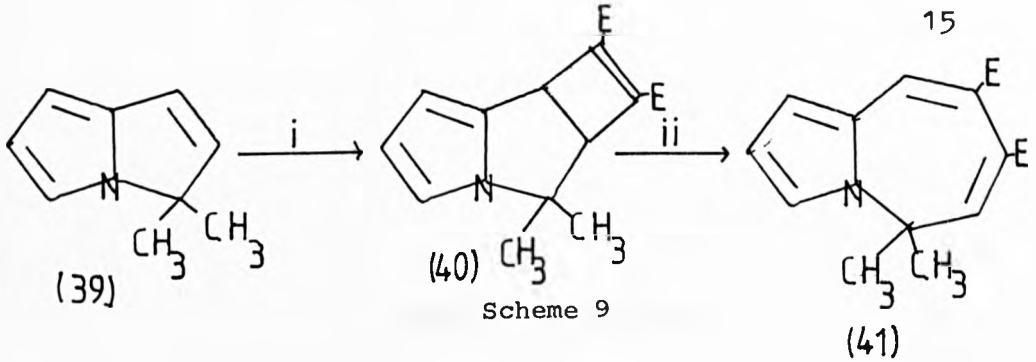
(30)

The first pyrroloazepines reported were those described by Acheson and Stubbs[27] resulting from a photochemical rearrangement of quinolizine esters (Scheme 8), in only one case, (38) was the 9H isomer seen.



The intermediates are believed to be 10π annulenes (34) which undergo ring closure to give the dipolar species (35) which, in turn, gives the 5H and 9H isomers indicated.

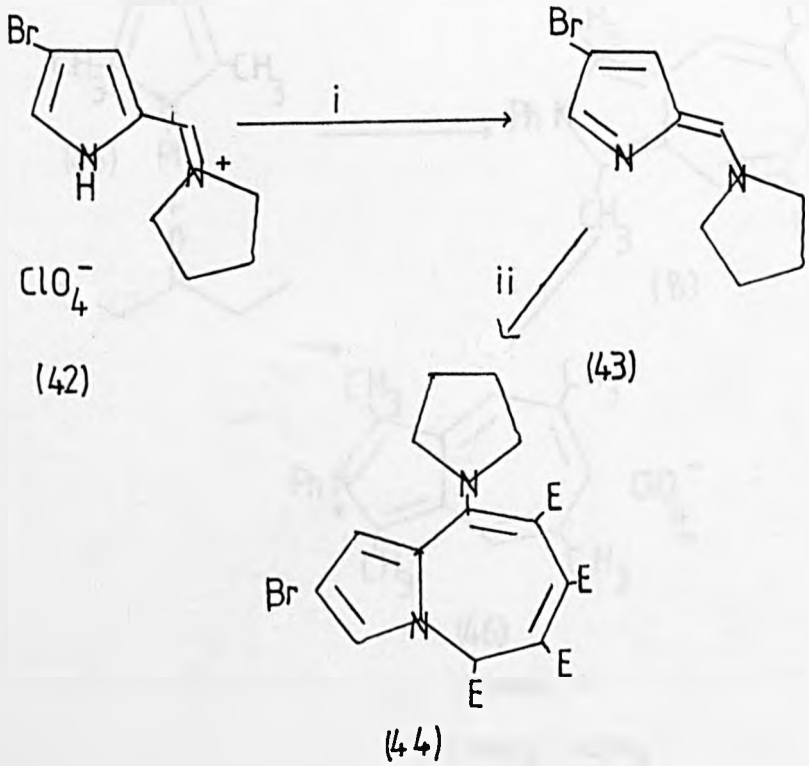
Pyrrolo[1,2-a]azepines have been generated by addition reactions of heterocycles with dimethyl acetylenedicarboxylate (DMAD). In the first route (Scheme 9), Johnson and Jones[28] reacted 3,3-dimethyl-3H-pyrrolizine (39) with DMAD photochemically to give a tricylic adduct (40) which underwent thermal ring expansion to give 5,5-dimethyl-7,8-dimethylcarboxylatepyrrolo[1,2-a]azepine (41)



Scheme 9

i)DMAD ii)Heat

The second approach involves the addition of 2 molecules of DMAD to an azafulvenamine[29], Scheme 10. The perchlorate was treated with sodium hydride to generate the stable azafulvenamine (43), this then reacts thermally with DMAD to give the azepine (44). A similar synthesis of the unbrominated pyrroloazepine has also been reported[30].

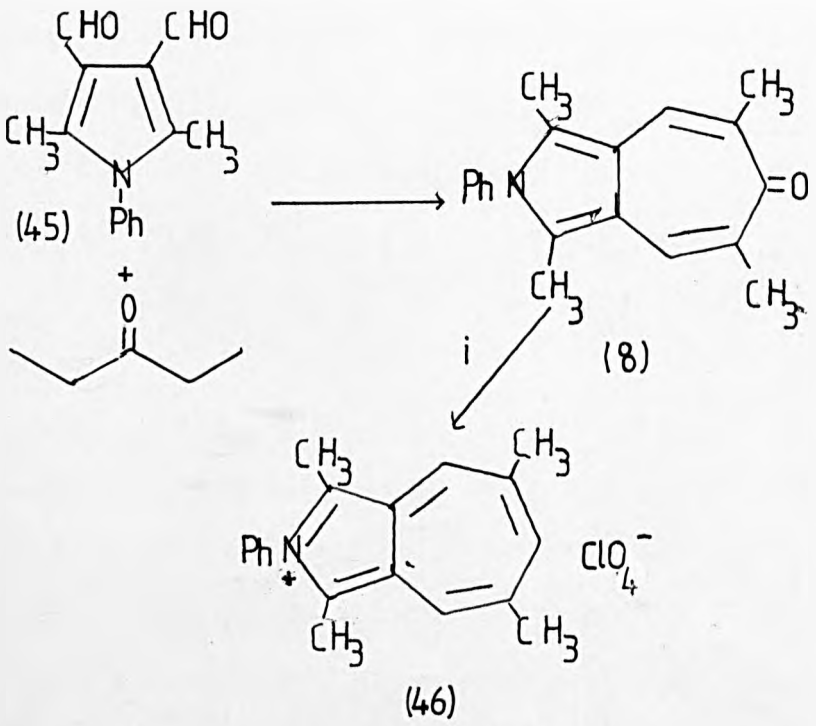


Scheme 10

i)NaH ii)DMAD

Aza-azulenium salts

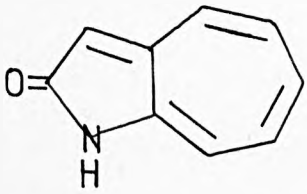
Apart from those already described, (15), (16) and (27), the only other salts reported are those prepared by El'tsov and co-workers[31]. The diformylpyrrole (45) is condensed with diethyl ketone to give the ketone (8), reduction of this to the corresponding alcohol and dehydration with acid gives the azepinium salt (46).



Scheme 11

i)$LiAlH_4$, $HClO_4$

A number of isomeric pyrroloazepinones have also been reported[32-34] for example (47), (48) and (49) but no attempt has been made to generate pyrroloazepinium salts from them.



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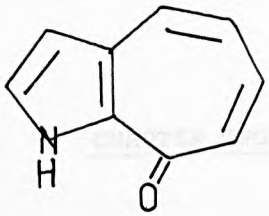

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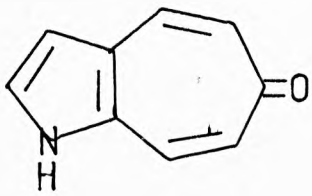

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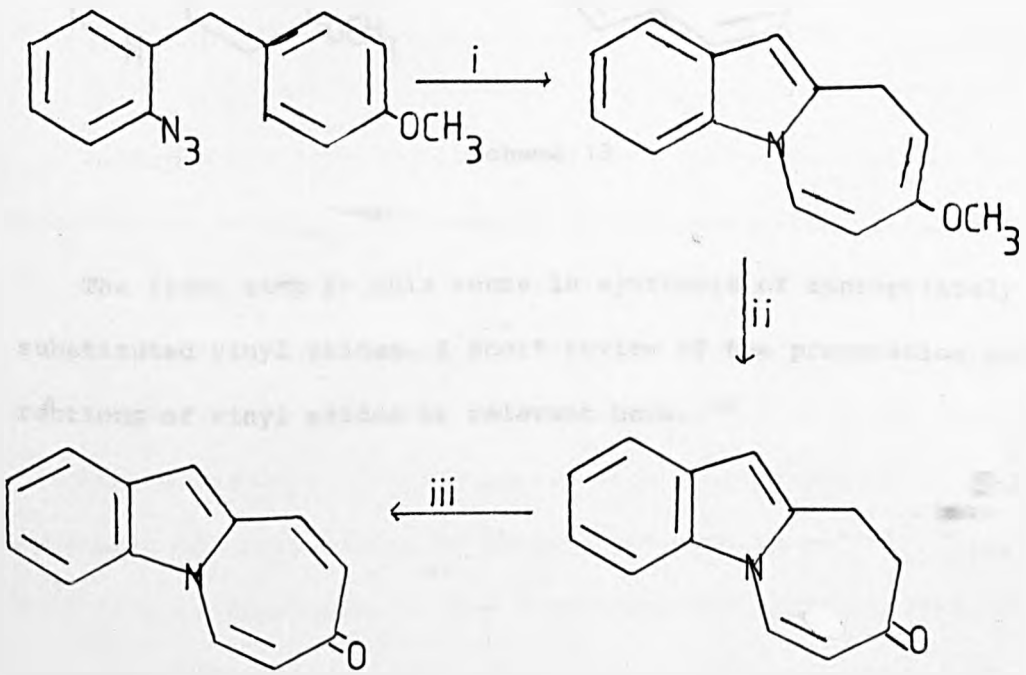
CHAPTER TWO

Vinyl azides as precursors to pyrrolo[1,2-a]azepines

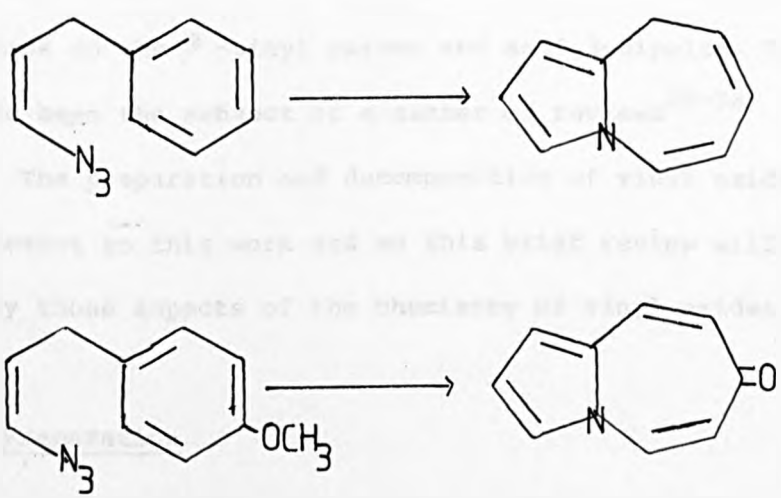
Cliff and Jones[26] have reported the decomposition of obenzylphenylazides to give indolo[1,2-a]azepines and, by choice and manipulation of substituents, indolo[1,2-a]azepinones. Examples are shown in scheme 12.



Scheme 12

i)180-200°C, trichlorobenzene ii)dilute acids iii)DDQ

These results have an obvious implication for the present work. If 1-azido-3-phenylprop-1-enes were to undergo similar reactions then this would provide a route to pyrrolo[1,2-a]azepines, as shown in scheme 13.



Scheme 13

The first step in this route is synthesis of appropriately substituted vinyl azides. A short review of the preparation and rections of vinyl azides is relevant here.

The preparation and decomposition reactions of vinyl azides

Vinyl azides are synthetically versatile compounds, as not only do their decompositions yield a variety of heterocycles and nitriles, they can also react as nucleophiles by undergoing electrophilic attack on the β-vinyl carbon and as 1,3-dipoles. These reactions have been the subject of a number of reviews[35-38]

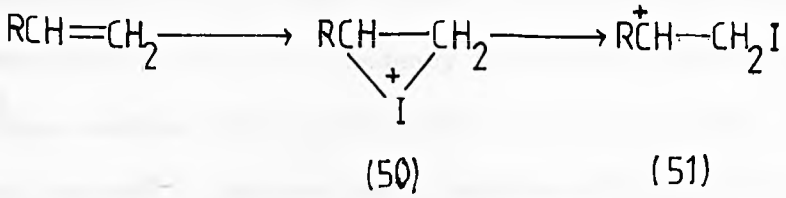
The preparation and decomposition of vinyl azides are most relevant to this work and so this brief review will be confined to only those aspects of the chemistry of vinyl azides.

a) Preparation

Vinyl azides have been prepared by a number of routes. One of the most common is by the elimination of hydrogen halide from suitable halo-azides. Forster and Newman used this method in the first synthesis of a vinyl azide [39], azidoethylene by treatment of 1-azido-2-iodoethane with potassium hydroxide.

Such elimination reactions have been incorporated in a general synthesis of vinyl azides by Hassner and co-workers[40,41]. Hassner's synthesis is regiospecific and stereospecific. Iodine azide adds regiospecifically to olefins in accordance with Markownikov's rule (if iodine is the cation). However the addition may be anti-Markownikov if the olefin is sterically hindered at one carbon, azide preferentially attacking the less hindered site. The regiospecificity of iodine azide addition is explained as due to a cyclic iodonium cation as an intermediate in the reaction (50), as shown in scheme

14.



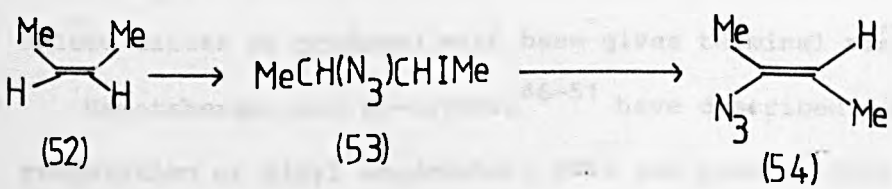
(50) (51)

Scheme 14

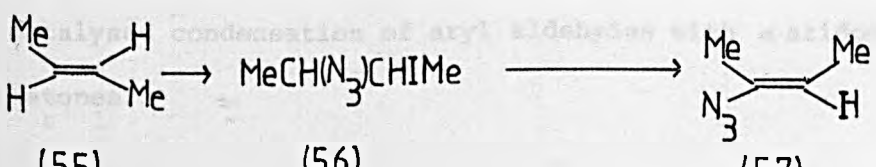
Ring opening of the cation (50) will occur to give the most stable carbonium ion, in the depicted case the secondary carbonium ion (51). Choice of substituents on the olefin will change the relative stabilities of the two possible carbonium ions and so influence the regiospecificity of iodine azide addition.

The elimination of the elements of hydrogen iodide from iodo azides is both regiospecific and stereospecific, scheme 15.

Scheme 15



(52) (53) (54)

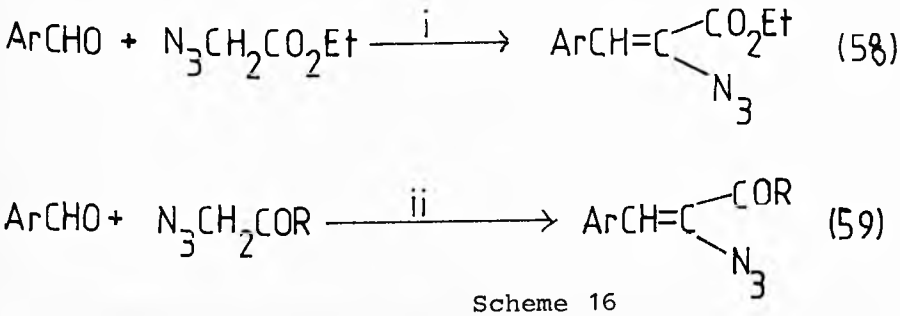


(55) (56) (57)

The Z-olefin (52) gives a **threo** iodoazide which, on reaction with base, gives a Z-vinyl azide (54). Similarly E-olefins (55) give **erythro** iodo azides and E-vinyl azides (57). The regiospecificity is attributed to a directive effect of the azido group and the stereospecificity to a tendency for **trans** elimination. Elimination of hydrogen iodide from cyclic iodo azides gives allyl azides rather than vinyl azides[41]. Despite the directive effect of the azido group **trans** elimination occurs more easily to give an allyl azide, due to the conformation of the cyclic iodo azide.

It is apparent that in general Hassner's method is poor at preparing terminal (α unsubstituted) vinyl azides. Terminal vinyl azides may be more easily prepared by dehydration of an α hydroxy azide which can be prepared by either attack of azide anion on an epoxide[42] or reduction of an α keto azide[43]. A more general method of preparing terminal vinyl azides is by the addition of bromine azide or chlorine azide to terminal olefins to give halo azides[44,45]. Bromine azide shows a greater tendency to react via a free radical mechanism than iodine azide, the proportion of radical products can be enhanced by use of a non-polar solvent. Chlorine azide reacts almost entirely in a radical mechanism. Subsequent treatment of the bromo or chloro azides so produced with base gives terminal vinyl azides.

Hemetsberger and co-workers[46-51] have described a method for the preparation of vinyl azidoesters (58) and ketones (59) by the base catalysed condensation of aryl aldehydes with α-azidoesters and ketones.

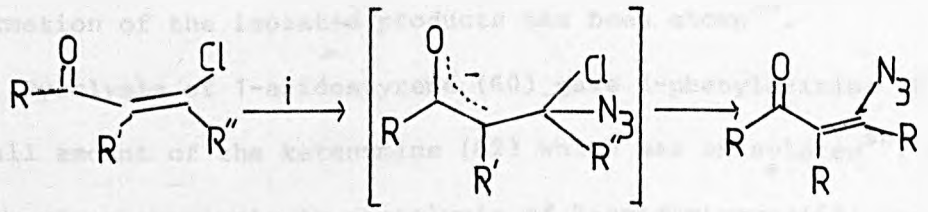


Scheme 16

i)NaOEt ii)Piperidine acetate

A variety of aryl aldehydes have been used successfully in this synthesis, including phenyl, cinnamyl, pyrrolyl, thienyl, furyl and pyridyl aldehydes. The orientation about the newly formed double bond in the products is assumed to be Z on the basis of the ^{1}H NMR spectrum which shows a downfield absorption for the ortho aryl proton.

Vinyl azides may also be prepared by the addition-elimination reaction of azide anion to vinyl halides[52] or vinyl tosylates[53]. This reaction only occurs when the leaving group is β to a group which can stabilise the intermediate carbanion as shown in scheme 17.



Scheme 17

i)N_3^-

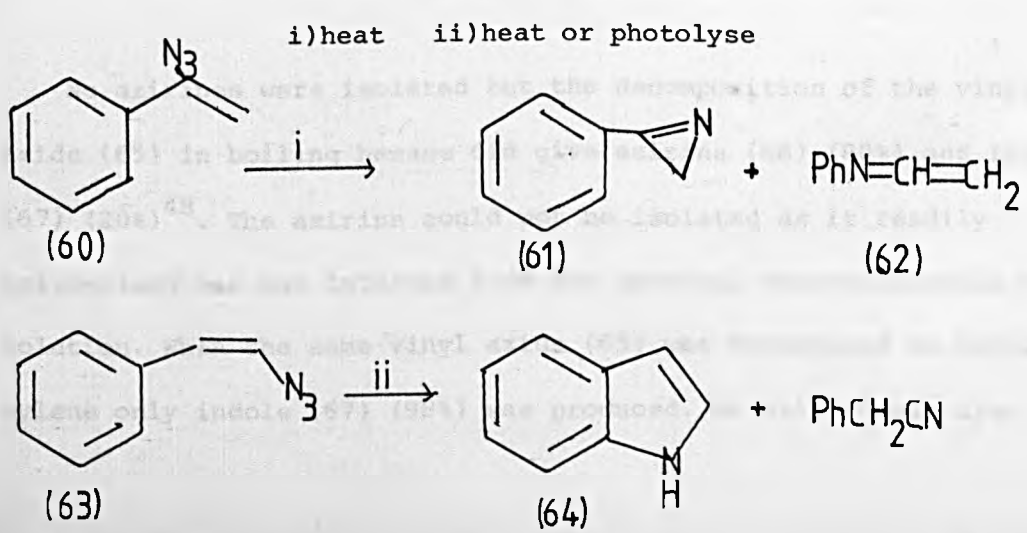
A similar reaction occurs with unsubstituted allenic esters giving β azido vinyl esters[54].

b) Decomposition reactions

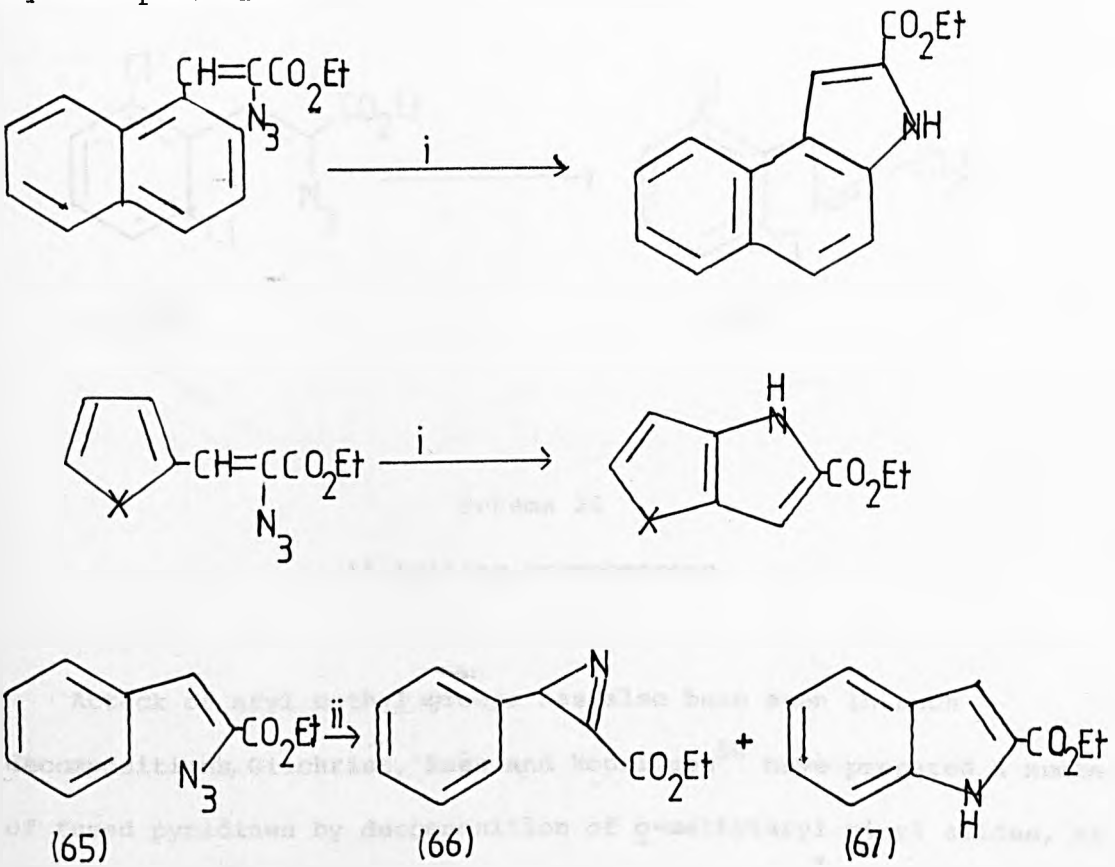
Most reactions of vinyl azides involve the loss of nitrogen and a rearrangement of the remainder of the molecule. In many cases azirines are isolated but so also are other products which are often attributed to reactions of the initially formed azirines. The proportions and types of products isolated is dependent upon the method of decomposition, azirines being preferentially formed in photolysis[35]. Internal azides give stable 2H-azirines, together with ketenimines on thermolysis[36]. Terminal vinyl azides do not generally give stable azirines, but their presence as intermediates in the formation of the isolated products has been shown[55].

Pyrolysis of 1-azidostyrene (60) gave 2-phenylazirine (61) and a small amount of the ketenimine (62) which was unisolated[56]. By comparison pyrolysis or photolysis of 2-azidostyrene(63) gave indole (64) and benzonitrile [57], as shown in scheme (18)

Scheme 18



Ethylα-azidocinnamates, and some hetero cyclic analogues, undergo thermolysis to give a variety of nitrogen containing heterocycles. Hemetsberger and co-workers[48-50] have produced a variety of indoles by this procedure.

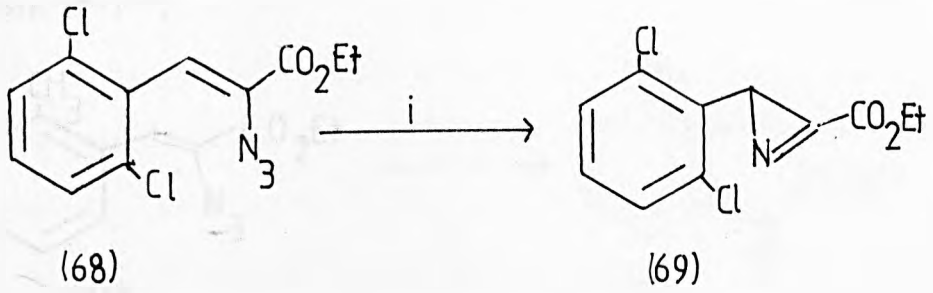


Scheme 19

i)boiling xylene ii)boiling hexane X=O,S,NMe

No azirines were isolated but the decomposition of the vinyl azide (65) in boiling hexane did give azirine (66) (80%) and indole (67) (20%)[48]. The azirine could not be isolated as it readily polymerised but was inferred from the spectral characteristics of the solution. When the same vinyl azide (65) was decomposed in boiling xylene only indole (67) (98%) was produced. An azirine was also

produced when the vinyl azide (68), which has no ortho protons, was decomposed [58] as shown in scheme 20.



(68) (69)

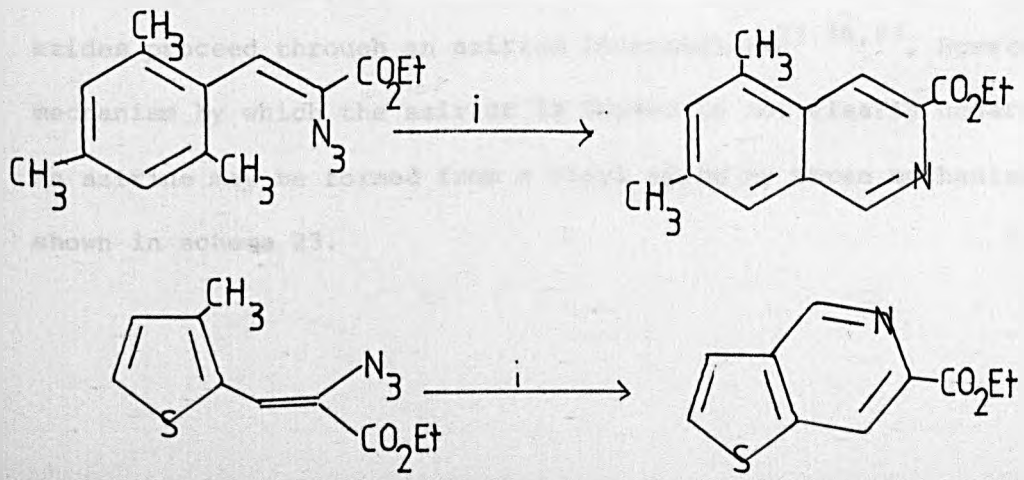
Scheme 20

i) boiling bromobenzene

Attack of aryl methyl groups has also been seen in such decompositions, Gilchrist, Rees and Rodrigues[58] have prepared a number of fused pyridines by decomposition of o-methylaryl vinyl azides, as shown in scheme 21

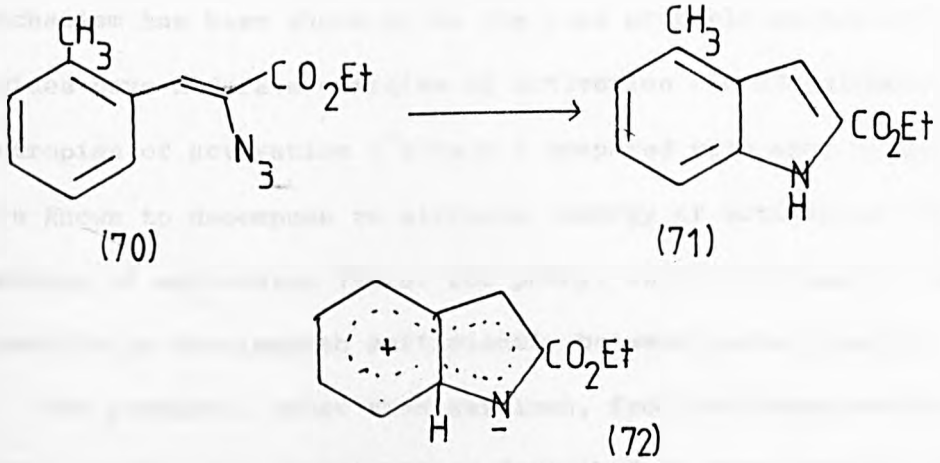
Scheme 21

i)boiling bromobenzene



These reactions proceeded in higher yield when exposed to the atmosphere rather than nitrogen.

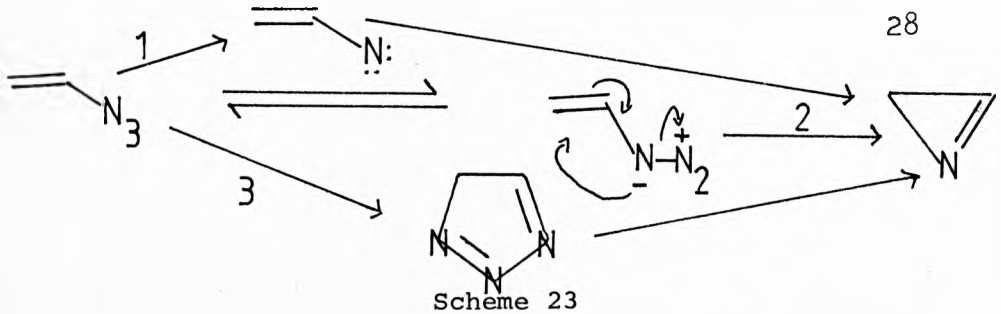
However reaction to give an indole is preferred over that to give a quinoline. The decomposition of the vinyl azide (70) gave only indole (71)[48].



Scheme 22

The formation of solely indole (71) is attributed to the differing reactivity of the methyl C-H bonds and the aryl C-H bonds to the nitrene formed in the reaction, insertion into the aryl C-H bond would permit delocalisation into the aromatic ring, as (72)[48]

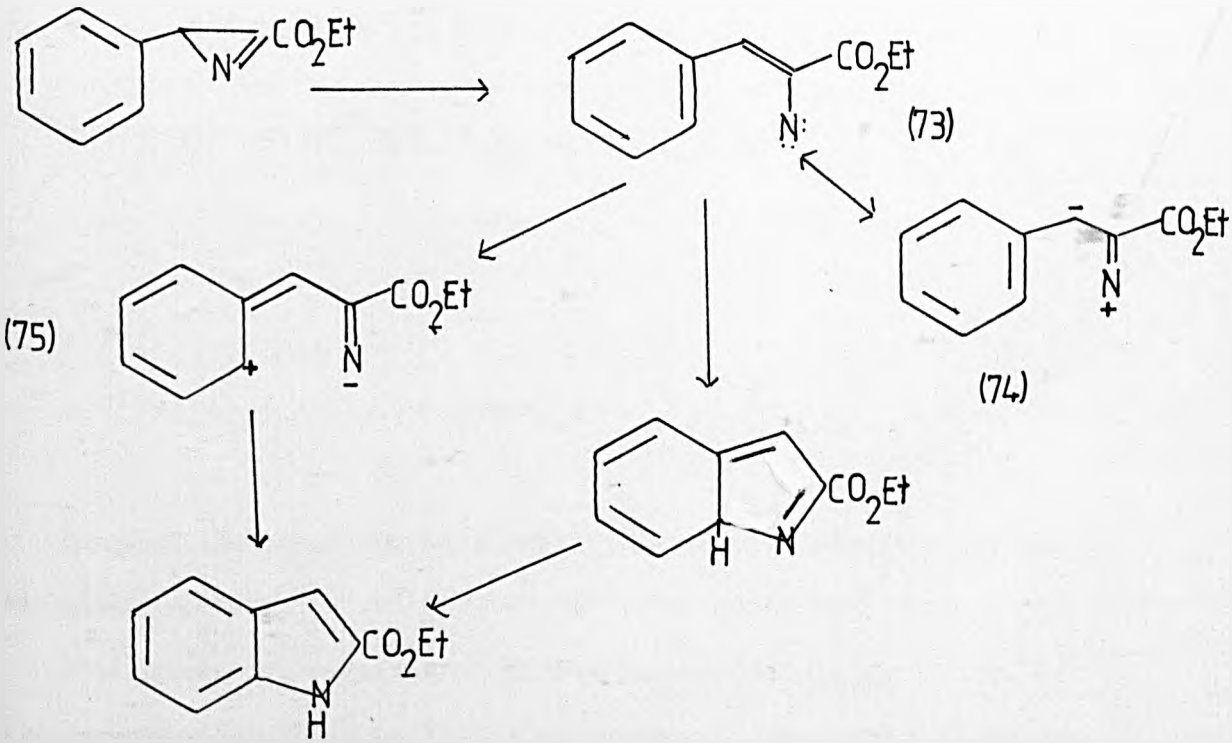
It is generally accepted that these decompositions of vinyl azides proceed through an azirine intermediate[35,36,51]. However the mechanism by which the azirine is formed is not clearly understood. An azirine may be formed from a vinyl azide by three mechanisms[56], as shown in scheme 23.



Scheme 23

A nitrene mechanism (path 1), a concerted process involving ring closure simultaneously with loss of nitrogen (path 2) and the intermediate formation of a 1,2,3-4H-triazole (path 3). The nitrene mechanism has been shown to be the less probable mechanism[36] as vinyl azides have moderate energies of activation (26-30kcal/mole) and low entropies of activation ($^{-}$3-5e.u.) compared with aryl azides which are known to decompose to nitrenes (energy of activation 36kcal/mole, entropy of activation 19e.u. for phenyl azide). It has not been possible to distinguish sufficiently between paths 2 and 3.

The products, other than azirines, from the decomposition of vinyl azides, for example those described by Hemetsberger and co-workers[48-51] are thought to arise by ring opening of the azirine to give a vinyl nitrene.



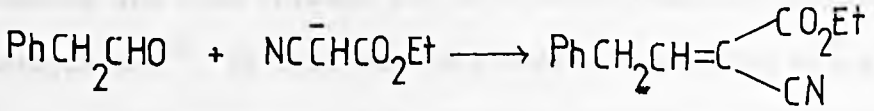
Scheme 24

The vinyl nitrene (73) is in tautomeric equilibrium with the dipolar form (74) which would allow rotation about the vinyl carbon carbon bond. The formation of condensed products may occur by either the insertion of the nitrene into a carbon hydrogen bond or by formation and cyclisation of a 1,5-dipole (75) from the nitrene[49].

Discussion

The simplest route to vinyl azides is that of Hemetsberger and co-workers[46-51], the reaction of aldehydes with ethyl azidoacetate. In such reactions, due to the lability of the azido group in basic solution the temperature must be kept low and the reaction time short. Vinyl azides have a number of spectral features which can be used in their identification, the most useful are the infra-red absorptions at 2130 and 1250cm^{-1}.

The aldehyde required to prepare a suitable vinyl azide such as 1-azido-1-phenyl-prop-1-ene is phenylacetaldehyde. Phenylacetaldehyde, in a similar reaction to that proposed, has been found to react with the sodium salt of ethyl cyanoacetate[59].



Scheme 25

However subsequent workers report that such a reaction gives a different product[60].

The attempted condensation of phenylacetaldehyde with ethyl azidoacetate catalysed by sodium ethoxide was carried out under the

Hemetsberger conditions. Analysis of the products showed that no desired condensation product was present. The reaction conditions were varied; the reaction was carried out at -81°C, with differing proportions of reactants, rates of addition and time of reaction. In no case could any desired vinyl azide be isolated. The only product later identified (from the ^{1}H NMR spectrum) was E-1,3-diphenylpropene. Phenylacetaldehyde has been reported to give E-1,3-diphenylpropene in basic conditions[61] and very readily undergoes aldol type, and other, condensation reactions with itself, both with and without base catalysis[62-66].

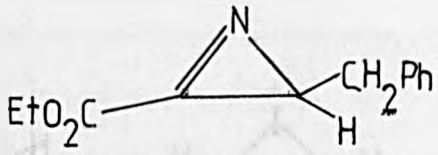
The reaction of an aldehyde with a compound containing an active methylene group to give an olefin with elimination of water can be achieved by the Knoevenagel condensation[67]. In this reaction the catalyst is usually a secondary amine or pyridine. Phenylacetaldehyde has given the expected Knoevenagel condensation products with malonic acid catalysed by pyridine[68] and diethylamine[60] (although rearranged products are also formed) and with diethylmalonate catalysed by diethylamine[69], in this case bis addition products are also formed.

Under the Knoevenagel conditions phenylacetaldehyde and ethyl azidoacetate failed to yield any vinyl azides. Bases used were piperidine, n-butylamine and piperidine acetate; again a small amount of E-1,3-diphenylpropene was identified.

Phenylacetaldehyde has a very active methylene group, between a phenyl group and a carbonyl group. This active methylene group may be reacting under the basic conditions in preference to the methylene group of the ester, so it may be useful to reduce the activity of this methylene group.

α-Phenylpropionaldehyde was prepared[70] and treated with ethylazidoacetate under the same conditions as before, but again no vinyl azide was identified. The ketone 1-phenylpropan-2-one, although it has another group of enolizable hydrogens, should be less reactive than both phenylacetaldehyde and phenylpropionaldehyde. This was borne out by the results which showed that some starting ketone was returned when the same series of reactions was carried out, but no vinyl azide was isolated.

In these reactions under the Knoevenagel conditions the vinyl azide may have been formed and then undergone a nucleophilic substitution by the amine with elimination of azide to give an enamine. This is known to occur with ketovinylazides[71] as does the corresponding reaction with alkoxide to give firstly a vinyl ether which adds alkoxide to give an acetal. Alternatively the vinyl azide may have decomposed to a triazole or, more probably a 2H-azirine such as (76).



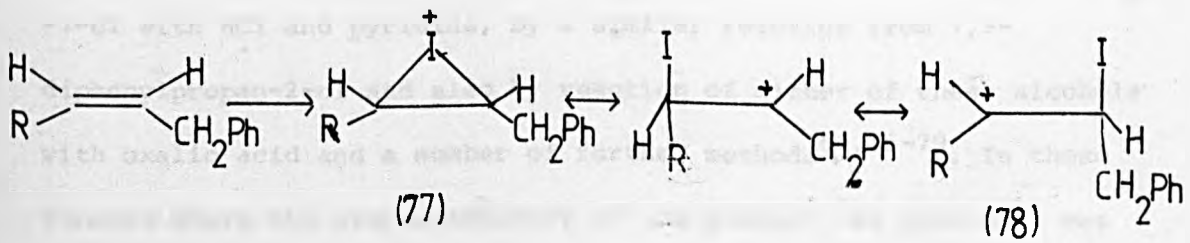
(76)

Such an azirine would be easily recognisable by its AX_2 pattern in a ^1H NMR spectrum and the characteristic infra-red absorption of around $1740cm^{-1}$ [56], although this may be obscured by the ester carbonyl absorption. None of these compounds were identified as products of the reactions described.

An alternative method of preparation of vinyl azides is that of addition of iodine azide to olefins followed by elimination of hydrogen iodide with base as described in the review section of this chapter. Iodine azide is generated in situ by reaction of iodine monochloride with sodium azide in acetonitrile; iodine azide has been shown to exist as a complex with sodium azide in this system[72]. In this synthesis a Z olefin gives a Z-vinyl azide. The implication for this work is that the synthesis must start with a Z-1-azido-3-phenylprop-2-ene.

The regiospecificity of the iodine azide addition must be controlled. The first step is formation of an iodonium cation, as (77) in scheme 26.

Scheme 26

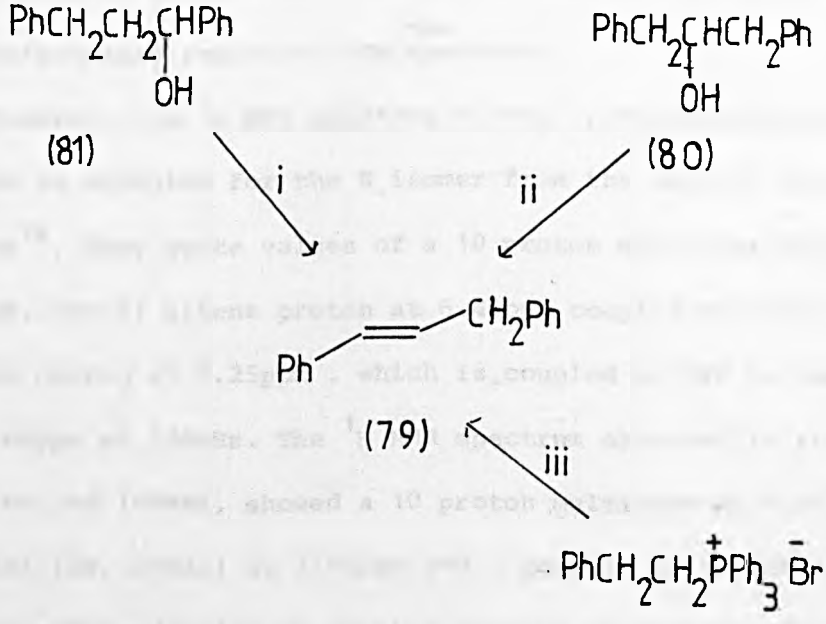


This cation can be opened in two ways, to give the positive charge either α or β to R. This synthesis requires the charge to be α to R, as (78), so R must stabilize an α positive charge. A phenyl group will stabilize an α positive charge, so the first synthetic target was Z-1,3-diphenylpropene. However, if the reaction of the vinyl azide proceeds through decomposition of an azirine intermediate as described earlier then the requirement of Z-stereochemistry is not so important.

Z and E-1,3-diphenylpropene have appeared several times in the literature but there has been some confusion over the identification of the isomers. The first report is that of Francis in 1899[73] who obtained as a by-product from the ethylation of dibenzyl ketone with sodium ethoxide and ethyl iodide a solid (Mp.57^{o}C) which was claimed to be 1,3-diphenylpropene, this has since been shown to be wrong[74]. Dieckmann and Kammerer[75] prepared a compound which they identified as a geometrical isomer of Francis' product. This compound, a liquid (Bp.178-179^{o}C/15mmHg) gave a crystalline dibromide (Mp.110^{o}C). The propene was prepared by a variety of other methods; by debromination of 1,3-diphenyl-1,2-dibromopropane, by reaction of 1,3-diphenylpropan-1-ol with HCl and pyridine, by a similar reaction from 1,3-diphenylpropan-2-ol and also by reaction of either of these alcohols with oxalic acid and a number of further methods[61,75-79]. In those reports where the stereochemistry of the product was stated it was assumed to be E. Tuot and Guyard reported [80] that dehydration of 1,3-diphenylpropan-2-ol with sulphuric acid gave the E isomer (Mp.51^{o}C) and dehydration of 1,3-diphenylpropan-1-ol with sulphuric acid gave the Z isomer (oil). Ten years later Beaven and Johnson[81] reversed

these assignments on the basis of v.p.c. behaviour of these compounds, assigning the solid (Mp.51°C) as the Z isomer and the oil as the E isomer; an investigation of the infra-red spectra of these compounds by Bokadia and co-workers supported these assignments [82]. Confirmation was supplied by Raunio and Bonner[74] who gave full spectral details for each isomer.

E-1,3-diphenylpropene (79) was prepared in a number of ways as shown in scheme 27. Reduction of 1,3-diphenylpropan-2-one with sodium borohydride gave 1,3-diphenylpropan-2-ol (80). A Grignard reaction between benzaldehyde and 2-phenylethylmagnesium bromide gave 1,3-diphenylpropan-1-ol (81). Each of these alcohols was converted into 1,3-diphenylpropene (79), which was also prepared by a Wittig reaction.



Scheme 27

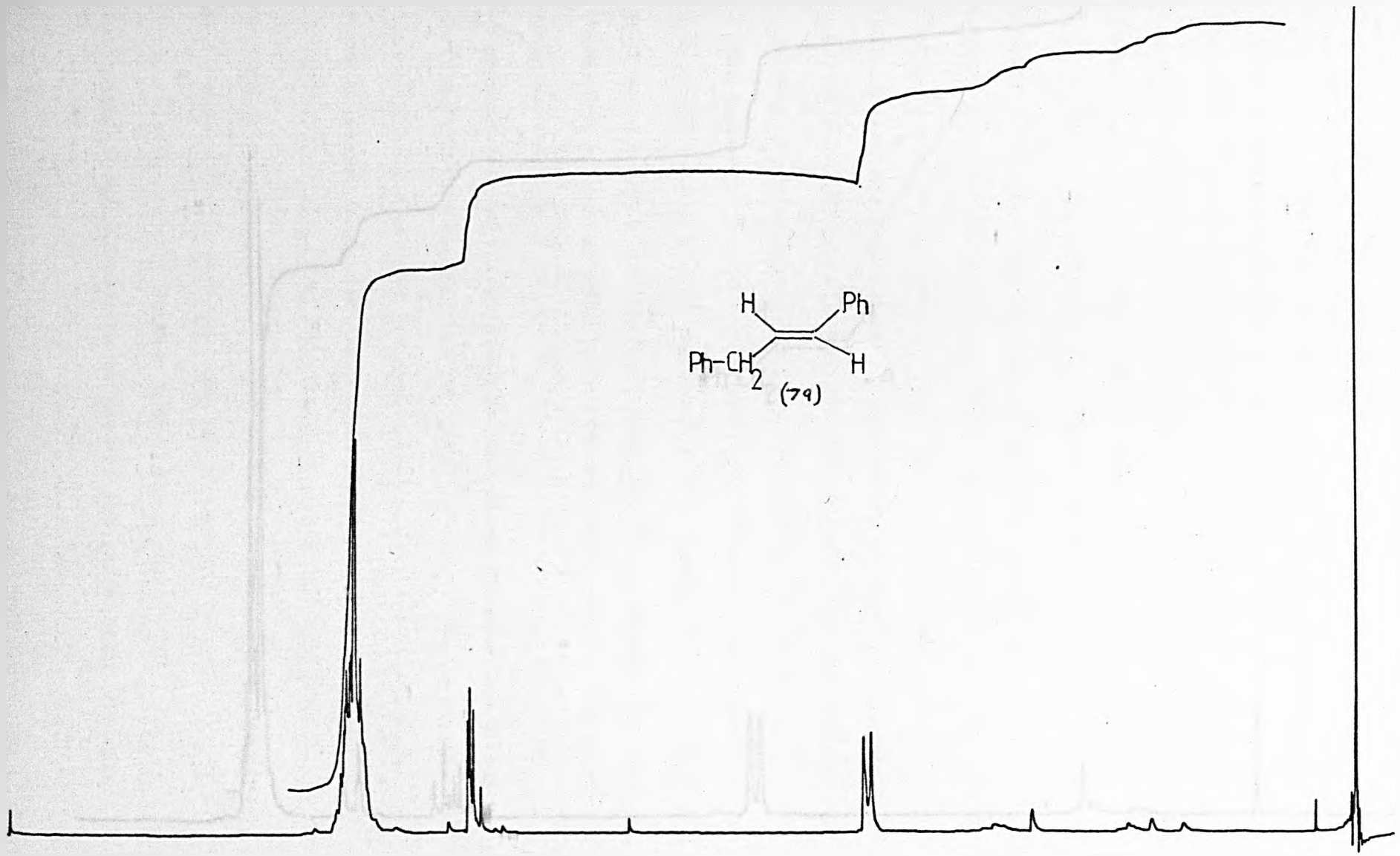
i)oxalic acid or HCl followed by pyridine ii)PCl_5 then pyridine

iii)sodamide then benzaldehyde

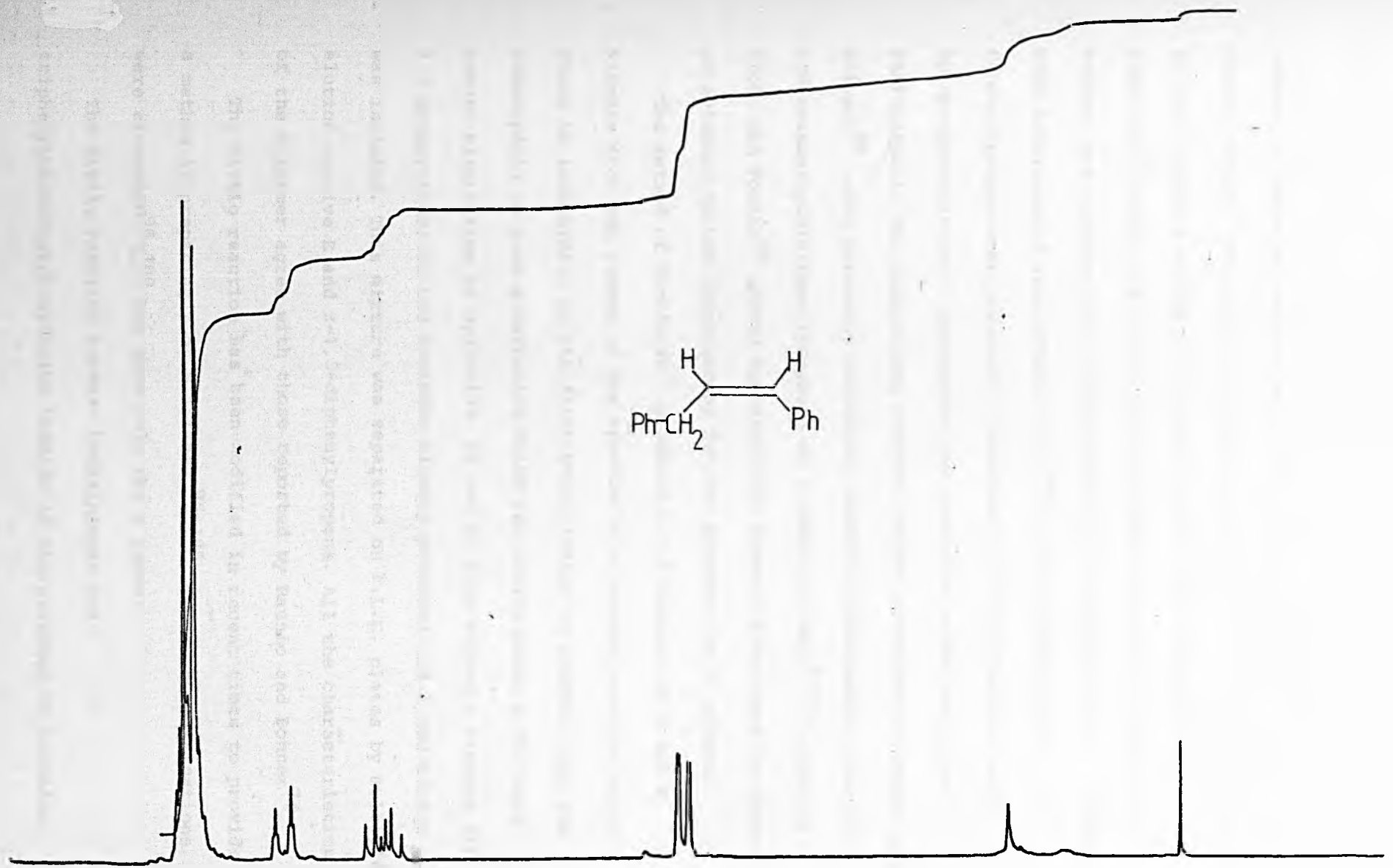
All the samples of olefin show the same physical characteristics, UV and IR spectra as reported for the E isomer[74]. A small amount was converted into the corresponding dibromide (mp.109°C, lit.[75] 110°C) by treatment with bromine in carbon tetrachloride. The ^3J coupling between the protons on the brominated carbons of this dibromide shows, by the Karplus equation[84], that the dihedral angle between the protons is 171° (^3J=9Hz). If the addition of bromine to the double bond was trans then this indicates that the configuration about the double bond must have been E. The ^{13}C NMR spectrum is as expected, although hard to interpret due to the superposition of peaks in the alkene/aromatic region of the spectrum.

However, the ^1H NMR spectrum of the 1,3-diphenylpropene prepared is not as expected for the E isomer from the work of Raunio and Bonner[74]. They quote values of a 10 proton multiplet between 6.9 and 7.5ppm, the C1 alkene proton at 6.40ppm coupled by 16Hz to the C2 alkene proton at 6.25ppm , which is coupled by 5Hz to the C3 protons at 3.48ppm at 100MHz. The ^1H NMR spectrum obtained in this work, at both 60 and 100MHz, showed a 10 proton multiplet at 7.2-7.3ppm, a doublet (2H, J=5Hz) at 3.52ppm and a complex multiplet(2H) at 6.41ppm. The addition of varying amounts of deuterated benzene to the sample failed to resolve the small multiplet, as did irradiation at 3.4ppm.

Attempts were made to transform the E-propene (79) into its Z



(79)


H
H
Ph-CH2
Ph

isomer. A number of methods exist for alkene inversion[85]. Raunio and Bonner report[74] the photolytic isomerization of E-1,3-diphenylpropene to the Z isomer, although no yield is given; a similar reaction is reported[86] to give 5% yield of Z-1,3-diphenylpropene. A number of methods are reported for the stereospecific deoxygenation of epoxides with inversion of stereochemistry [87-90]. The epoxide from E-1,3-diphenylpropene was prepared in moderate yield by treatment with monoperphthalic acid (perbenzoic and peracetic acids had proved ineffectual). The epoxide was reacted, by the procedure of Dervan and Shippey[90], with potassium methoxide, hexamethylphosphoric triamide and hexamethyldisilane (prepared in a number of ways[91-94], that of Brown and Fowles[94] proved superior).The product after work up showed no evidence by NMR spectroscopy for the presence of an alkene.

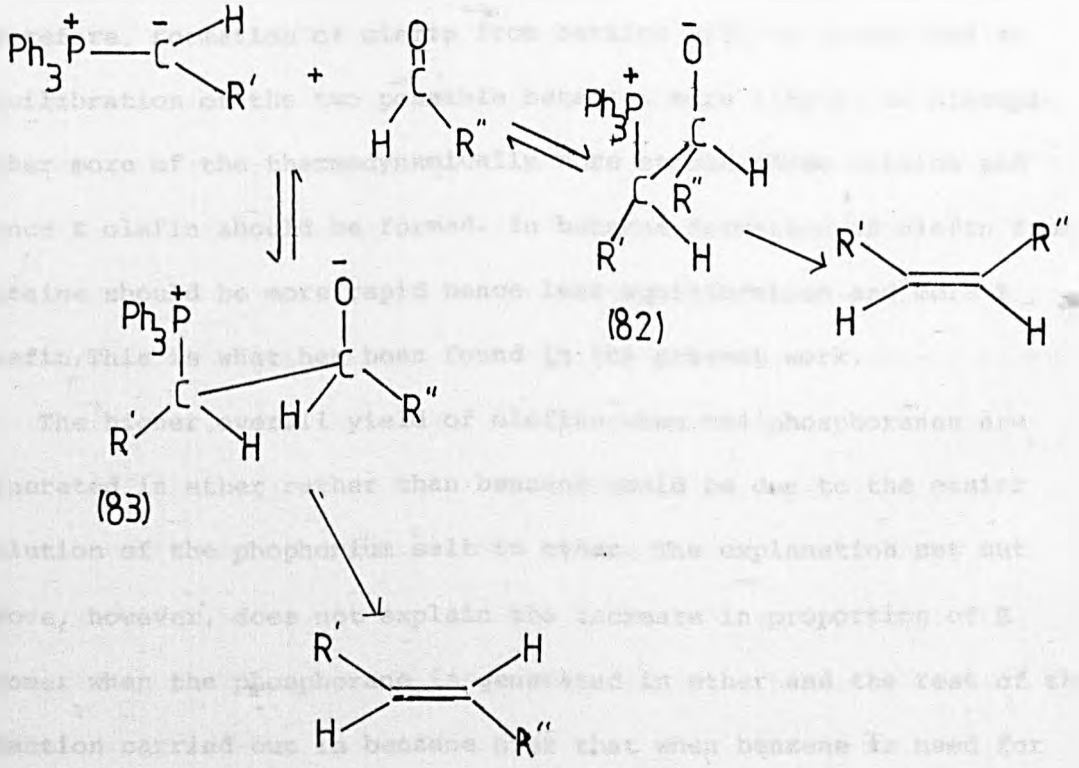
The method of Cornforth[95] produces a 1:1 mixture of Z and E alkenes from one isomer of the epoxide in a one-pot reaction which forms an iodo-hydrin as its first step. Iodine is removed from the iodo-hydrin to give a carbanion which can rotate about a C-C bond before elimination of hydroxide. By use of this method a mixture (in 1:1 proportions) of the E-alkene already produced and a new alkene was isolated. This mixture was separated on P.L.C. plates by multiple elution to give E and Z-1,3-diphenylpropene. All the characteristics of the Z isomer agree with those reported by Raunio and Bonner[74].

The Wittig reaction has been modified in recent times to provide a method of preparing Z or E alkenes [96-105]. Two such modifications were attempted[96,100] but gave only the E isomer.

The Wittig reaction between benzaldehyde and triphenylphenethylphosphonium bromide in the presence of sodamide

gave a variety of yields and proportions of Z and E-1,3-diphenylpropene depending on the solvent for the reaction. In benzene a poor yield (22%) of Z (49%) and E (51%) alkenes was produced, in diethyl ether a better yield of alkene but all E. But if the solvent for the generation of the ylide was ether, the ether was distilled off and replaced by benzene and then benzaldehyde was added a moderate yield (32%) of Z (78%) and E (22%) alkenes was produced.

This isomeric variation with solvent can be explained by a consideration of the mechanism of the Wittig reaction. It has been shown[102] that addition of a phosphorane to a carbonyl compound gives a betaine as an intermediate. There are two possible betaines for each reaction (for non-symmetrical reactants), an **erythro**(82) and a **threo** (83) betaine[103].



Scheme 28

The **erythro** betaine decomposes to a Z olefin and the **threo** betaine decomposes to an E olefin. Betaine formation is reversible and, where formation of olefin from betaine is a slow step, the less sterically hindered **threo** form is the thermodynamically favoured betaine[103]. The sterically hindered **erythro** betaine is thought to be the kinetically favoured intermediate due to steric effects of the three phenyl groups on phosphorus[104], in the **erythro** betaine there is more steric hindrance about the newly formed C-C bond but less about phosphorus.

The solvents used for the Wittig reaction in this work were diethyl ether and benzene. In the more polar diethyl ether polar intermediates will be more stabilized than in benzene. In ether, therefore, formation of olefin from betaine will be slower and so equilibration of the two possible betaines more likely. In diethyl ether more of the thermodynamically more stable **threo** betaine and hence E olefin should be formed. In benzene formation of olefin from betaine should be more rapid hence less equilibration and more Z olefin. This is what has been found in the present work.

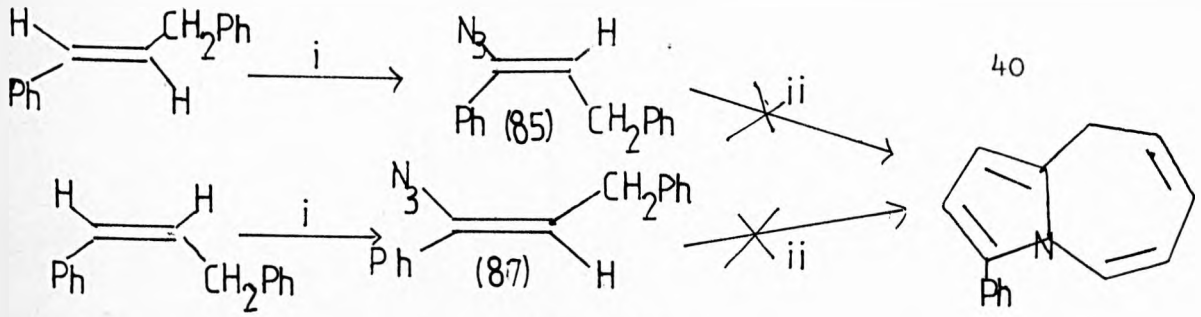
The higher overall yield of olefins when the phosphoranes are generated in ether rather than benzene could be due to the easier solution of the phophonium salt in ether. The explanation set out above, however, does not explain the increase in proportion of Z isomer when the phosphorane is generated in ether and the rest of the reaction carried out in benzene over that when benzene is used for the whole reaction.

of the compound

The chemical behaviour, which has been identified as E-1,3-diphenylpropene in this work, especially its generation together with the Z isomer in the Wittig reactions, shows that despite its ^{1}H NMR spectrum it is indeed E-1,3-diphenylpropene. The values for the coupling constants and chemical shifts given by Raunio and Bonner[74] indicate that the two alkene protons are coupled by 16Hz and the difference in their chemical shifts is 15Hz at 100MHz. Therefore these protons should exhibit second order behaviour, as seen in the spectrum of E-1,3-diphenylpropene shown in this work.

Addition of iodine azide to E-1,3-diphenylpropene proceeded smoothly, though in poor yield. Chromatography of the crude product gave pure iodoazide (84) and also a little vinyl azide (85). Elimination of hydrogen iodide proceeded in better yield (32%) to give the vinyl azide (85). This was identified by its NMR spectrum, $^{3}J_{2,3}$=8Hz, and its IR spectrum which showed a strong band at 2120cm^{-1}. Decomposition of the azide in benzene followed by chromatographic work up gave products which could not be identified.

The similar synthesis from Z-1,3-diphenylpropene gave the iodoazide (86) which was not very stable at room temperature, readily decomposing to a purple gum. Elimination of hydrogen iodide gave the vinyl azide (87), in this case the NMR spectrum shows multiplets instead of the expected doublet and triplet. The structure was however confirmed by the infra-red spectrum. Decomposition of this azide gave a mixture of nine products. The NMR spectrum of these products show that none of them was the expected pyrrolo[1,2-a]azepine or an isomer of it.

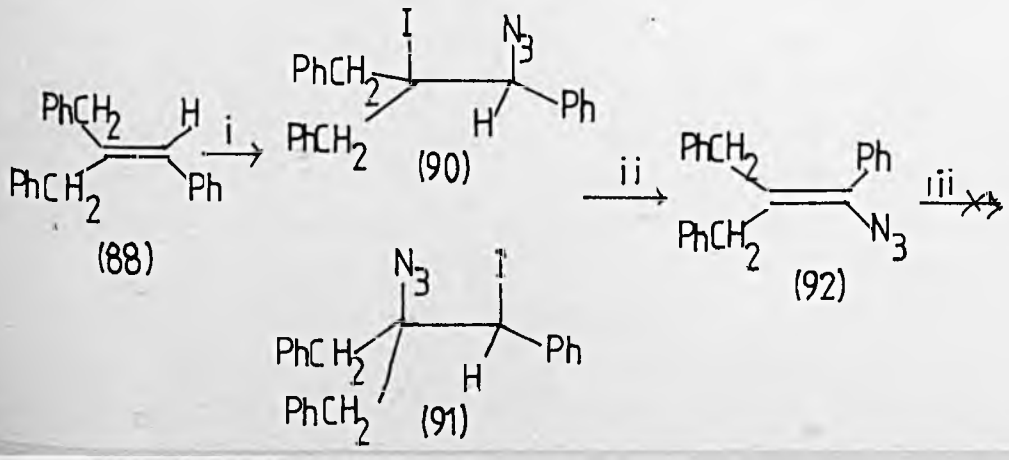


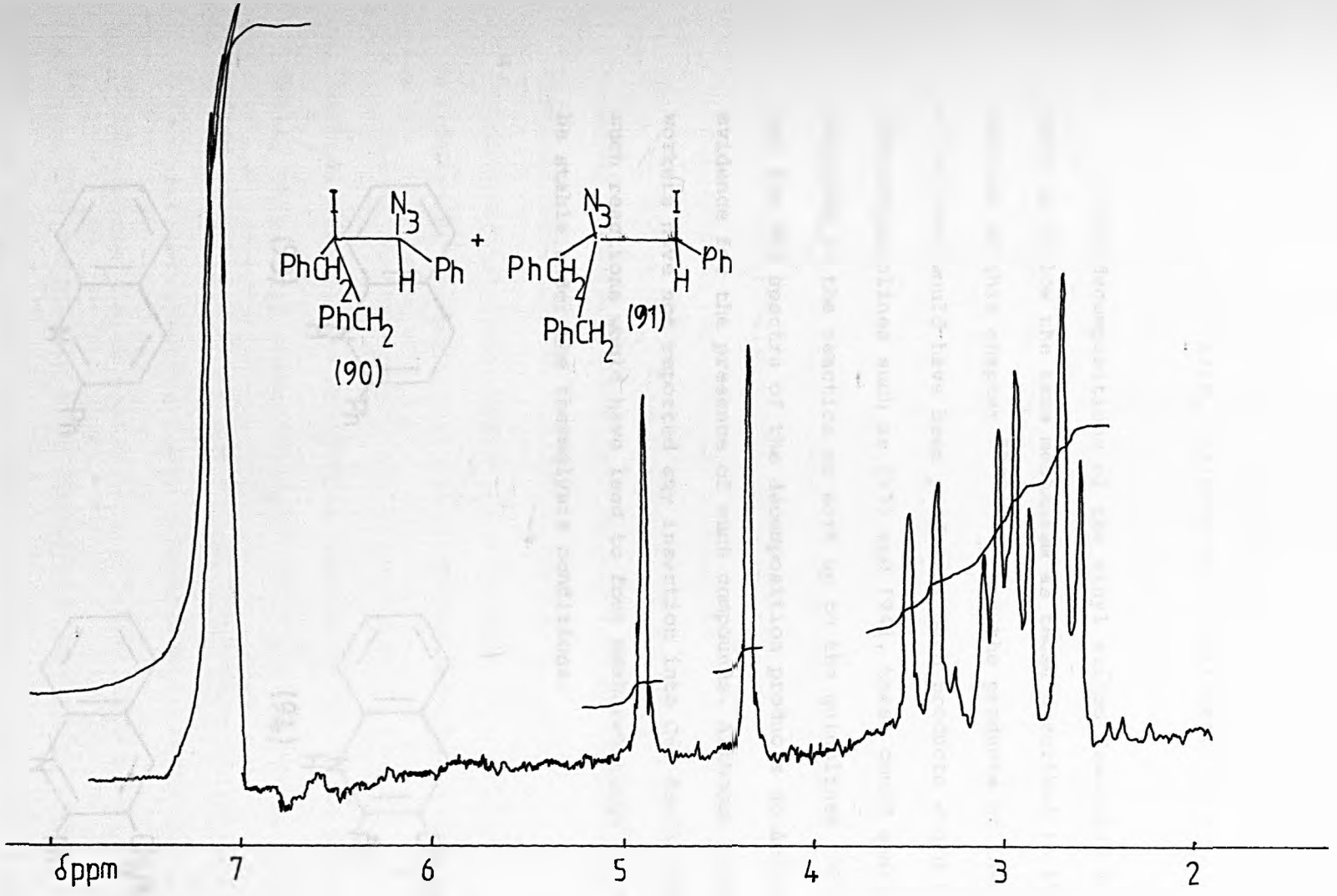
Scheme 29

i)IN_3 then KO<u>t</u>-Bu ii)heat

The lack of success by this route may have been caused by azirine formation and consequent decomposition to unwanted products involving attack at C2 of the propene. Therefore a 1,3-diphenylpropene with a substituent on this postion was prepared.

The propene, 1,3-diphenyl-2-benzylpropene (88) was prepared in good yield by a Wittig reaction between triphenyl-2-phenylethylphosphorane and 1,3-diphenylpropan-2-one. Addition of iodine azide gave a mixture of 1-azido-2-benzyl-1,3-diphenyl-2-iodo-propane (90) and 2-azido-2-benzyl-1,3-diphenyl-1-iodo-propane (91) in the ratio 1.2:1. These assignments are made on the basis of the NMR spectrum which shows each proton. The signals were assigned according to their chemical shift and integral. All attempts at separation of the mixture proved unsuccessful. As only one isomer has a proton α to iodine then treatment of the mixture with base should give only one vinyl azide . This in fact was the case, and 1-azido-2-benzyl-1,3-diphenylpropene (92) was isolated, together with some of the 2-azido-1-iodo compound (91). The vinyl azide (92) was decomposed as before to give a mixture of compounds, none identifiable as a pyrrolo[1.2-a]azepine.

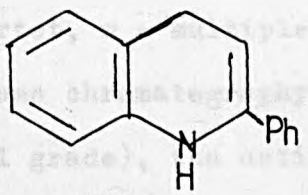



I
N3
PhCH2
H
Ph
PhCH2
(90)
+
N3
I
PhCH2
H
Ph
PhCH2
(91)
δppm
7
6
5
4
3
2

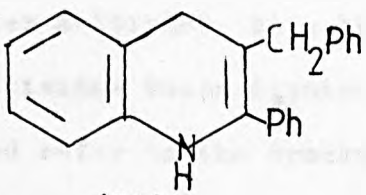
Scheme 30

i)IN_3 ii)KO-t-Bu iii)heat

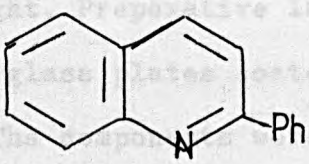
If the decompositions of the vinyl azides described in this work were to follow the same mechanism as those described in the review section of this chapter [46-51,58] then the products of insertion into a C-H bond would have been produced. Such products would be dihydroquinolines such as (93) and (94), these could easily be oxidised in the reaction or work up to the quinolines (95) and (96), but the NMR spectra of the decomposition products do not provide any evidence for the presence of such compounds. Although previous workers have not reported any insertion into C-C double bonds[46-51,58] such reactions would have lead to four membered rings which would not be stable under the thermolysis conditions.



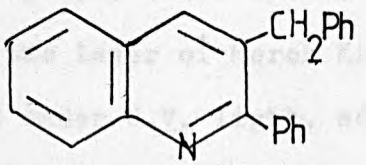
(93)



(94)



(95)



(96)

EXPERIMENTAL

Preliminary Notes

Melting points were determind on a Kofler hot-stage apparatus and are uncorrected. Infra-red absorption spectra were recorded on a Perkin Elmer 257 or a Perkin Elmer 357/197 combination. The spectra of solids were recorded as solutions or KBr discs, liquids as thin films. Micro analyses were determind on a Perkin Elmer 240 C/H/N machine. Mass spectra were run on either a Hitachi Perkin Elmer RMU6 or an AEI MS 12.

NMR spectra were routinely measured at 60MHz on a Perkin Elmer R24, at 100MHz or ^{13}C on a JEOL FX100 F7 or Brucker 300MHz machines. Chemical shifts are quoted as δppm relative to an internal standard(normally TMS, in FSO_3H acetone δ3.9ppm). Multiplicities are denoted as:- s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet, bs = broad singlet.

Column chromatography was on deactivated Woelm Alumina (neutral grade), the activities quoted refer to the Brockmann scale. Thin layer chromatography (TLC) was on 20x5cm glass plates coated with Merck Kieselgel PF_{254}, components visualized under U.V. light. Preperative layer chromatography (PLC) was on 40x20cm glass plates coated with a 1.5mm layer of Merck Kieselgel PF_{254}. The components were visualized under U.V. light, scraped off and extracted in boiling methanol, filtered, solvent removed and the residue extracted with boiling dichloromethane which was then filtered, solvent removed to yield the extracted compound.

Photolytic work was carried out under an atmosphere of nitrogen

using a Hanovia photochemical reactor employing a medium pressure mercury lamp.

Where light petroleum is mentioned this refers to that fraction boiling between 40 and 60°C.

Attempted condensation of ethylazidoacetate and phenylacetaldehyde

To a stirred and cooled (ice bath) solution of sodium ethoxide in anhydrous ethanol (1.84g sodium in 60ml ethanol) was added a mixture of ethylazidoacetate (10.3g, 0.08moles) and phenylacetaldehyde (2.4g, 0.02 moles). The reaction temperature was held below 3°C during addition of the reactants. The mixture was stirred for a further 15 minutes after the addition was complete.

The solvent was removed under reduced pressure . A portion of ammonium chloride solution was added (150mls, 2M), followed by an ice/water mixture (500g). The aqueous solution was extracted with diethyl ether (4 portions of 200mls), the combined organic phases washed with water (200mls), dried and solvents removed to give a yellow gum (0.3g).

Analysis of this gum by NMR and IR did not give the types of spectra expected for an unsaturated azide.

Attempted condensation of ethylazidoacetate and phenylacetaldehyde

To a stirred and cooled (ice bath) solution of sodium ethoxide in anhydrous ethanol (1.84g sodium in 60mls ethanol) was added a mixture of ethylazidoacetate (2.7g, 0.02 moles) and then after stirring for 10 minutes phenylacetaldehyde (2.4g, 0.02 moles). The mixture was stirred for a further 60 minutes .

The solvent was removed under reduced pressure . A portion of ammonium chloride solution (150mls, 2M) was added, followed by an ice/water mixture (500g). The aqueous solution was extracted with diethyl ether (4 portions of 200mls), the combined organic phases were washed with water (200mls), dried and the solvents removed to give a yellow oil (2.4g).

Analysis of this oil by NMR and IR did not give the types of spectra expected for an unsaturated azide.

Attempted condensation of phenylacetaldehyde with ethylazidoacetate. using piperidine as base

To a stirred solution of ethylazidoacetate (5.16g, 0.04 moles) and phenylacetaldehyde (5.20g, 0.044 moles), cooled to -5°C in an ice/salt bath, was added a solution of piperidine (0.05g) in anhydrous ethanol (0.1ml) at such a rate as to keep the reaction temperature below 5°C . The mixture was then kept at 0°C for 4 days.

The mixture was washed with portions of water containing a little acetic acid (4 portions of 100mls containing three drops of acid) and the washings were extracted with diethyl ether (100mls). The combined organic phases were dried and the solvent removed to give a green oil (9.8g).

Analysis of this oil by NMR and IR failed to give the types of spectra expected of an unsaturated azide.

Attempted condensation of ethylazidoacetate and phenylacetaldehyde at low temperature.

A stirred suspension of sodium ethoxide in anhydrous diethyl ether (from sodium hydride/ oil suspension (0.15g) and anhydrous ethanol (0.14g) in diethyl ether (3mls)) was cooled to -81°C in an ethylacetate/liquid nitrogen bath. A solution of ethylazidoacetate (0.37g) in anhydrous ether (3mls) was added and the mixture stirred for 15 minutes. A solution of phenylacetaldehyde (0.14g) in anhydrous ether (50mls) was added dropwise. The yellow mixture was brought to room temperature and stirred overnight.

The mixture was filtered, the residue washed with diethyl ether and the combined organic solutions evaporated at reduced pressure to give a yellow oil. Analysis of this oil by NMR and IR failed to provide evidence of the presence of the desired product.

Attempted condensation of ethylazidoacetate and phenylacetaldehyde with n-butylamine

To a stirred and cooled (ice/salt bath) mixture of ethylazidoacetate (2.58g, 0.02moles) and phenylacetaldehyde (2.40g, 0.02moles) was added n-butylamine (1.46g, 0.02moles)over a period of 5 minutes.

The mixture was kept at 0°C overnight.The yellow mixture was then washed with dilute hydrochloric acid (10mls) and extracted with dichloromethane (100mls). The organic phase was neutralized with sodium carbonate solution (50mls),dried and the solvent removed.

The crude mixture was chromatographed on a column of alumina (Activity IV). Elution with solvents of increasing polarity from light petroleum to chloroform failed to yield any of the desired product.

Attempted preparation of the imine

A solution of aniline (2.33g, 0.03moles), phenylacetaldehyde (3.0g, 0.03moles) and p-toluenesulphonic acid (15mg) in anhydrous benzene (50mls)was refluxed in a Deans and Stark apparatus for 3 hours while the water produced was collected (0.5mls)

The solvent was removed under reduced pressure to give a brown oil (4.22g) this was taken up in dichloromethane (150mls) and washed with dilute hydrochloric acid (150mls). The organic phase was dried and the solvent removed to give a red oil (3.41g). Analysis of this oil by NMR and IR spectroscopy failed to indicate the desired product.

Preparation of α-phenylpropionaldehyde

This aldehyde was prepared as described in Organic Syntheses .

Yield = 35% overall, Bp 87°C/ 9 mmHg (lit. 73°C/ 4 mmHg).

Attempted condensation of α-phenylpropionaldehyde with ethylazidoacetate

To a stirred and cooled (ice/salt bath) solution of ethylazidoacetate (2.02g, 0.02moles) in anhydrous benzene (5mls) was added a portion of a 50% sodium hydride/paraffin suspension (1.0g, 0.022moles of sodium hydride). After stirring for 15 minutes a solution of α-phenylpropionaldehyde (2.68g, 0.02moles) in anhydrous benzene (5mls)was added dropwise, causing effervescence. The mixture was stirred for 4 hours.

The reaction mixture was dissolved in dichloromethane (100mls) and washed with water (3 portions of 20 mls). The organic phase was dried and the solvents removed under reduced pressure to give an orange oil (3.8g). Analysis of this oil by NMR gave a spectrum which was not as expected for the desired product.

Attempted condensation of αphenylpropionaldehyde with ethylazidoacetate

To a stirred suspension of sodium ethoxide (from 0.16g sodium hydride and 3ml of anhydrous ethanol) in 5ml anhydrous ether, cooled to -81° C, was added ethylazidoacetate (0.35g). The mixture was stirred for 15 minutes and αphenylpropionaldehyde (0.17g) was added. The mixture was allowed to reach room temperature and stirred for 8 hours.

The mixture was washed with water (3 portions of 10ml), the organic phase separated, dried and the solvent was removed under reduced pressure to yield a yellow oil (0.42g). Analysis of this oil by NMR and IR spectroscopy showed that it did not contain the desired product.

Attempted condensation of phenylpropionaldehyde with ethylazidoacetate catalysed by piperidine

A solution of ethylazidoacetate (2.02g, 0.020moles), phenylpropionaldehyde (3.47g, 0.027moles), piperidine (1ml) and glacial acetic acid (0.8ml) in anhydrous benzene (35ml) was refluxed in a Deans and Stark apparatus for 8 hours, water (0.3ml) was collected.

The resulting solution was washed with a little water, dried and the solvent was removed under reduced pressure to yield a yellow oil (4.4g). This oil was chromatographed by P.L.C. (70% toluene, 30% light petroleum as eluent) to give seven bands. Analysis of each of these fractions by NMR and IR spectroscopy showed that none of them contained the desired product.

Attempted condensation of 1-phenylpropan-2-one with ethylazidoacetate

To a stirred and cooled (ice/salt bath) solution of sodium ethoxide in anhydrous ethanol (from 1.84g sodium and 60ml ethanol) was added dropwise a solution of ethylazidoacetate (2.7g, 0.02moles) in anhydrous ethanol (10ml) . When the addition was complete a solution of 1-phenylpropan-2-one (2.68g, 0.02moles) in ethanol (10ml) was run in slowly. The mixture was stirred for a further 4 hours then allowed to reach room temperature.

Most of the solvent was removed under reduced pressure and the residue was poured onto crushed ice (50g). The mixture was extracted with dichloromethane (2 portions of 50ml), the combined organic extracts were washed with water, dried and the solvent was removed under reduced pressure to give a brown oil (4.3g). Analysis of this oil by NMR and IR spectroscopy showed that it did not contain any of the desired product.

Attempted reaction of aniline with 1-phenylpropan-2-one

A solution of 1-phenylpropan-2-one (2.68g, 0.02moles), aniline (1.86g, 0.02moles) and p.toluenesulphonic acid (0.1g) in anhydrous benzene (50ml) was refluxed for 3.5 hours.

The resulting yellow solution was washed with aqueous sodium carbonate (30ml of a 5% solution), then with water (30ml), dried and the solvent was removed under reduced pressure to give a yellow oil (2.1g). Analysis of this oil by NMR spectroscopy showed that it did not contain any of the desired product.

Preparation of triphenylbenzylphosphonium bromide

A solution of triphenylphosphine (10g, 0.04moles) and benzyl bromide (5.99g, 0.04moles) in anhydrous benzene (200ml) was refluxed for 4 hours producing copius precipitation.

The white solid was filtered and washed with benzene to give white crystals of triphenylbenzylphosphonium bromide (14.11g, 75% yield).

Attempted Wittig reaction between triphenylbenzylphosphonium bromide and styrene oxide

To a stirred suspension of sodium hydride (0.64g of a 50% suspension in paraffin, 0.0125moles) in anhydrous dimethoxyethane (50ml) under nitrogen was added triphenylbenzylphosphonium bromide (5g, 0.0115moles) producing a strong yellow colour. This was stirred for 20 minutes and styrene oxide was added dropwise (1.1g, 0.0115moles) discharging the colour. The mixture as refluxed for a further 45 minutes and then allowed to cool to room temperature.

The mixture was filtered and the solvent was removed from the filtrate under reduced pressure to give a yellow oil (4.3g). Analysis of this oil by NMR spectroscopy showed that it did not contain any of the desired alkene.

This reaction was repeated with xylene as solvent in place of dimethoxyethane. No difference in the products was observed.

Attempted preparation of 1,3-diphenylpropan-2-ol

A solution of benzyl chloride (23ml, 0.2moles) in anhydrous diethyl ether was added at such a rate as to maintain reflux to a stirred suspension of magnesium turnings (4.86g) in ether (20ml). When the addition was complete the mixture was refluxed for a further 20 minutes then allowed to reach room temperature. A solution of phenylacetaldehyde (11.6ml, 0.2moles) in ether (20mls) was run in to the flask at such a rate as to keep the mixture gently refluxing. The mixture was then refluxed for a further 1.5 hours.

A saturated solution of ammonium chloride/ammonium hydroxide (100ml) was added, the organic phase was separated, dried and the solvent removed under reduced pressure to give a green oil (28.2g).

Analysis of this oil by NMR spectroscopy showed that it did not contain either the expected alcohol or any alkene.

This reaction was repeated with inverse addition of the Grignard reagent to the aldehyde at $-78^{o}C$. No appreciable difference in the product mixture was observed.

Preparation of 2-phenylethylbromide.

To a mixture of water (160ml), sodium bromide (19.25g, 0.175moles) and 2-phenylethylalcohol (18ml, 0.15moles) was added ,with stirring, concentrated sulphuric acid (26.0ml).

The mixture was refluxed for 8 hours. The organic layer was separated, washed with water, then cold concentrated sulphuric acid (2.5ml), and finally was washed with sodium carbonate solution (50ml of a 10% solution). The organic material was dried over calcium chloride to give a yellow oil, (27g).

This oil was distilled to give the desired bromide (20.6g, 73% yield) boiling at 100-102°C/13mmHg. (lit. 92°C/11mmHg. (81)).

Preparation of 1,3-diphenylpropan-1-ol (81)

To a suspension of magnesium turnings (1.21g) in anhydrous diethyl ether (3ml), stirred under a nitrogen atmosphere, was added a solution of 2-phenylethylbromide (9.25g, 0.05moles) in ether (25ml) at such a rate as to maintain reflux. When the addition was complete a portion of benzaldehyde (5.3g, 0.05moles) was slowly added. When this addition was complete the mixture was refluxed for 1 hour.

The complex was destroyed with an excess of saturated ammonium chloride/ ammonium hydroxide solution (100ml). The organic layer was separated, dried and the solvent removed under reduced pressure to give a green oil (6.54g). This oil was distilled under reduced pressure to give the alcohol (81) in 30% yield (3.13g), (138°C/0.3mmHg, lit. 192-4/12mmHg (75)).

Preparation of E-1,3-diphenylpropene

A mixture of 1,3-diphenylpropan-1-ol (1.05g, 0.005moles) and oxalic acid (o.9g,0.01moles) was placed in a vacuum distillation apparatus and heated to 157°C. A vacuum of 38mmHg. was applied and a small amount of an orange oil was distilled over.

Separation of this oil by P.L.C. (10% toluene/90% light petroleum as eluent) gave one major component (0.21g, Rf 0.78) identified by NMR spectroscopy as the E alkene (79)

Analysis: $C_{15}H_{14}$ requires C=92.78% H=7.22%
obtained C=92.73% H=7.22%

Mass spectrum $^{m}/_{e}$= 194 (M^+, 23%), 77 (100%).

IR (ν max, liqiud film) 1490, 1451, 966 cm^{-1}

UV (λ max) 252nm ($\log_{10}\varepsilon$ =4.40)

Preparation of 1,3-diphenylpropene (79) using Hydrogen chloride and Pyridine.

Dry hydrogen chloride gas, prepared by reaction of concentrated hydrochloric and sulphuric acids, was bubbled through a portion of 1,3-diphenylpropan-1-ol (81) (1.5g, 0.0075moles) warmed over a water bath for 1 hour.

The resulting cloudy liquid was taken up in dichloromethane (50ml), the organic phase was washed with water (25ml), saturated sodium carbonate solution (25ml), dried and the solvent was removed under reduced pressure. A green oil was obtained (1.4g).

This oil was dissolved in pyridine (1ml, freshly distilled) and the solution refluxed for 1 hour. The solvent was removed under reduced pressure to give a green oil (1.6g). This oil was distilled under reduced pressure to give the alkene (79) identical to that previously prepared (Bp. 178-182°C/11mmHg, 0.72g, yield 49%).

Preparation of 1,3-diphenylpropan-2-ol(80).

A mixture of 1,3-diphenylpropan-2-one (4.20g, 0.02moles), sodium borohydride (0.2g, 0.005moles) and 95% ethanol (110mls) was allowed to stand at room temperature for 30 minutes, refluxed for 5 minutes and then allowed to cool to room temperature. A portion of water (10mls) was added, the mixture was boiled then allowed to cool and a further portion of water added (110mls).

The mixture was extraced with dichloromethane (100mls), dried and the solvent was removed under reduced pressure to give a green oil (4.18g). This oil was distilled under reduced pressure to give the alcohol (80) (4.08g, 96% yield, Bp. 188-190°C/12mmHg, lit. 198°C/20mmHg(81)).

Preparation of E-1,3-diphenylpropene(79) from 1,3-diphenylpropan-2-ol.

To a solution of phosphorous pentachloride (1.78g, 0.0075moles) in anhydrous light petroleum (150ml) was slowly added a solution of 1,3-diphenylpropan-2-ol in light petroleum (30ml) at such a rate as to maintain reflux. When the addition was complete the the mixture was refluxed for a further 30 minutes.

The solvent was removed under reduced pressure together with any phosphorous oxychloride.

The resulting material was taken up in dichloromethane (100ml), washed with water (50ml), dried and the solvent removed to give a green oil (1.68g). Analysis of this oil by NMR shows that all the starting alcohol had been consumed (the triplet signal at δ=3.8ppm being replaced by a triplet signal at δ=4.2ppm).

This oil was dissolved in pyridine (1.0ml) and refluxed for 1 hour. THe resulting mixture was distilled under reduced pressure to give a clear oil with identical spectral properties with the E-1,3-diphenylpropene already obtained (0.47g, 32% yield, Bp. 178-180°C/11mmHg).

Preparation of **erythro** 1-azido-1,3-diphenyl-2-iodopropane (84) from E-1,3-diphenylpropene.

To a stirred and cooled (methanol/ice bath) slurry of sodium azide (3g, 0.05moles) in acetonitrile (20ml, freshly distilled) was added slowly a portion of iodine monochloride (3.66g, 0.0226moles) over 10 minutes. The mixture was stirred for an additional 10 minutes and a portion of E-1,3-diphenylpropene (79) (3.88g, 0.02moles) was added. The mixture was allowed to reach room temperature and stirred for 20 hours.

The mixture was poured onto water (50ml) and extracted with diethyl ether (3 portions of 50ml). The organic extracts were combined, washed with sodium thiosulphite solution (5%, 120ml), washed with water (18ml), dried and the solvents were removed under reduced pressure to give a brown oil (5.1g).

This brown oil was purified by column chromatography on alumina (150g, activity III). Elution with light petroleum gave the crude **erythro** iodo azide (84) contaminated with a little of the azide (85). This crude sample was further purified by P.L.C. elution with light petroleum gave the pure iodo azide (84) (Rf. 0.24, 0.87g, 12% yield).

^{1}H NMR ($CDCl_3$, TMS as internal standard)

7.1ppm	10H	m	
4.8ppm	1H	d	(J=4Hz.)
4.3ppm	1H	m	
2.1ppm	2H	m	

Analysis

$C_{15}H_{14}N_3I$ requires C=49.58, H=3.86, N=11.57%

obtained C=49.72, H=4.02, N=11.09%

Mass Spectrum

$^m/_e$ 363(21%,M^+), 349(34%).

Preparation of E-1-azido-1,3-diphenylprop-1-ene.

To a suspension of potassium ^{t}-butoxide (from 0.1g potassium and excess ^{t}-butanol) in anhydrous diethyl ether (10ml) stirred under nitrogen was added a portion of the iodo azide (84) (0.7g) in anhydrous diethyl ether (10ml). THe mixture was stirred in an ice bath for 48 hours.

Water (50ml) was added to the mixture, the organic phase was separated, dried and the solvent was removed under reduced pressure to give a yellow oil (0.5g) The mixture was purified by P.L.C., elution with light petroleum giving the unsaturated azide (85) (Rf 0.31, 0.3g, 38%yield).

^{1}H NMR ($CDCl_3$, TMS internal standard)

6.8ppm	10H	m	
5.5ppm	1H	t	(J=8Hz)
2.9ppm	2H	d	(J=8Hz)

IR (ν max) 2120cm^{-1}

Analysis

$C_{15}H_{13}N_3$ requires C=76.59, H=5.53, N=17.87%

obtained C=76.39, H=5.99, N=17.26%.

Decomposition of E-1-azido-1,3-diphenylprop-1-ene(85).

A solution of the azido-alkene (85)(0.1g) in perdeuterobenzene (0.7ml) in an NMR tube (4mm od.) was warmed at 50^{o}C for 9 hours.

The resulting solution gave only streaking on analysis by T.L.C. The NMR spectrum was as follows:-

7.2ppm	2H	m	
6.7ppm	10H	m	
2.5ppm	2H	d of d	(J=5Hz,8Hz)
2.1ppm	1H	m	
1.0ppm	1H	m	

Attempts to purify this mixture by P.L.C. lead only to decomposition.

Attempted preparation of 1,3-diphenylpropene oxide

To a solution of the E-1,3-diphenylpropene (28.1g) in chloroform (100mls) was added a solution of per-benzoic acid in chloroform (400mls containing 0.15moles (1 equiv.) per-acid, determind by liberation of iodine from acidified sodium iodide solution and subsequent titration with sodium thiosulphite solution). The mixture was cooled in an ice bath and stirred for 24 hours.

The mixture was washed with sodium hydroxide solution (100mls, 10%) the organic phase was separated, dried and the solvent removed under reduced pressure to give a green oil (27.3g). NMR analysis of this oil showed it to contain only the E-alkene used as starting material.

Attempted preparation of 1,3-diphenylpropene oxide

To a stirred solution of E-1,3-diphenylpropene (12.8g, 0.07moles) in dichloromethane (100ml) was added a solution of peracetic acid in dichloromethane (1 equivalent in 200ml). The temperature of the reaction was maintained below 35^{o}C during the addition by cooling in a water bath. The mixture was stirred for 23 hours.

The mixture was poured onto water (300ml) and the organic phase separated. The aqueous phase was extracted with dicholoromethane (2 portions of 100ml) and the organic phases combined. The combined organic solution was washed with an acidified ferrous sulphate solution (60g ferrous sulphate, 6ml glacial acetic acid in 110ml water), followed by sodium carbonate solution (2 portions of 100ml of a 10% solution) and water (2 portions of 100ml). The organic phase was separated, dried and the solvent was removed to give a green oil (11.6g).

Analysis of this oil by NMR showed it to contain only the

starting E-alkene.

Preparation of 1,3diphenylpropene oxide

To a stirred and cooled (ice bath) solution of E-1,3-diphenylpropene (79) in diethyl ether (200ml) was added a solution of monoperphthalic acid in diethyl ether (370ml, containing 0.07moles of acid). The mixture was stirred for 48 hours.

The white solid formed was filtered off and found to be phthalic acid The resulting clear filtrate was washed with acidified ferrous sulphate solution (60g ferrous sulphate, 6ml glacial acetic acid in 110ml water), with sodium carbonate solution (200ml of a 10% solution) and with water (100ml). The organic phase was separated, dried and solvent removed under reduced pressure to give a green oil (10.8g).

This oil was purified by column chromatography on alumina (190g, activity IV), elution with light petroleum gave firstly the E-alkene (79)(5.5g, 300ml solvent) and secondly the oxide ( ) (3.9g, 50% yield on recovered starting material, 1200ml solvent). Distillation on an air bath gave analytically pure oxide (174°C/0.4mmHg).

^1H NMR ($CDCl_3$, TMS internal standard)

7.1ppm	10H	m	
3.6ppm	1H	d	(J=2Hz)
3.1ppm	3H	m	

Analysis:

$C_{15}H_{14}O$ requires C=85.71, H=6.67%

obtained C=85.42, H=6.58%.

Mass spectrum: $^m/_e$= 210(19%,M^+) 91(100%).

Attempted reduction of 1,3-diphenylpropene oxide to Z-1,3-diphenylpropene.

To a stirred solution of potassium methoxide (0.028g,0.4m.mole) in hexamethylphosphoric triamide (15ml, freshly distilled from calcium hydride) at 65°C under a nitrogen atmosphere was added a portion of 1,3-diphenylpropene oxide (0.5g,2.4m.mole) and a portion of hexamethyldisilane (0.52g, 3.6m.mole, prepared by the method of Brown and Fowles (94)). The mixture was stirred for 3 hours at 65°C and then allowed to reach room temperature.

A portion of sodium chloride solution (100ml, saturated solution) was added and the mixture extracted twice with hexane (2 portions of 100ml). The organic phases were combined, dried and the solvent removed under reduced pressure to give a brown oil (0.7g). Analysis of this oil by NMR spectroscopy did not show any evidence for the presence of an alkene.

Reduction of 1,3-diphenylpropene oxide to a mixture of E- and Z-1,3-diphenylpropene.

A solution of sodium iodide (8.4g), sodium acetate (2.8g) and water (4g) in acetic acid (18ml) was cooled on an ice bath. A portion of zinc powder (8.4g) was added, followed by a portion of 1,3-diphenylpropene (6g, 0.028moles). The mixture was stirred for 2 hours.

The mixture was filtered, the filtrate was diluted with water (130ml) and extracted with diethyl ether (2 portions of 60ml). The combined organic extracts were washed with sodium carbonate solution (60ml, 10% solution) and water (50ml), dried and solvent removed to give a green oil (5.2g).

This mixture was separated by P.L.C. (10 elutions in light petroleum) to give the E-alkene (1.2g, 22% yield) the Z-alkene (0.5g, 9% yield) and a mixture of the two (0.3g, 5%yield).

Z-1,3-diphenylpropene.

^1H NMR ($CDCl_3$, TMS internal standard)

7.1ppm	10H	m
6.5ppm	1H	d (J=12Hz)
5.7ppm	1H	d of t
3.6ppm	2H	d (J=7Hz)

Analysis:

$C_{15}H_{14}$ requires C=92.78, H=7.22%

obtained C=93.01, H=6.97%

Mass spectrum:

$m/_e$= 194(42%, M^+) 91(100%).

IR (ν max) 1490, 1450, 920, 720cm^{-1}

UV (λ max) 242nm ($\log_{10}\varepsilon$ = 4.23)

Preparation of Triphenylphenethylphosphonium bromide

A solution of phenethyl bromide (3.0g, 0.016moles) and triphenylphosphine (4.2g, 0.016moles) in anhydrous dimethylformamide (30ml) was refluxed for 20 hours.

The solvent was removed under reduced pressure to give a viscous oil (7.2g). Trituration of this oil under anhydrous tetrahydrofuran (200ml) gave crystals of the phosphonium bromide (3.1g, 43% yield, Mp. 89-90°C).

Analysis:

$C_{26}H_{24}PBr$ requires C=69.80 H=5.37%

obtained C=69.66 H=5.57%.

Attempted preparation of Z-1,3diphenylpropene.

A solution of finely divided potassium (1.9g) in hexamethylphosphoric triamide (5ml) was stirred under nitrogen for 75 minutes. A suspension of triphenyl-2-phenylethylphosphonium bromide (1.85g, 5m.moles) in hexamethylphosphoric triamide (5ml) was added producing an orange colour . A vacuum (28mmHg) was applied for 30 minutes then released under nitrogen and the mixture stirred for a further 3.5 hours. A portion of freshly distilled benzaldehyde (0.6ml,5.5m.mole) was added as one and the mixture stirred for 2 hours.

The mixture was diluted with water (20ml) and extracted with benzene (2 portions of 150ml). The combined organic extracts were washed with sulphuric acid (50ml of a 5% solution), sodium bicarbonate solution (50ml of a saturated solution) and water (50ml), dried and the solvents removed under reduced pressure to give a green oil (1.3g).

Analysis of this oil by NMR showed it not to contain any alkene.

Atempted preparation of Z-1,3-diphenylpropene.

A suspension of sodamide in anhydrous benzene (60ml) was prepared from sodium (1.5g) in liquid ammonia (200ml) at -81^{o}C followed by addition of benzene. To this suspension was added a portion of hexamethyldisilazane (8.1g) the mixture was stirred for 5 hours. A portion of triphenyl-2-phenylethylphosphonium bromide (22.3g) was added, producing a red colour, the mixture was stirred for 30 minutes at room temperature then refluxed for 1 hour. The mixture was cooled to room temperature and a portion of benzaldehyde (5.3g) was added, discharging the colour, the mixture was stirred for 19 hours.

The mixture was washed with water (50ml), dried and the solvents removed under reduced pressure to give a green gum (16.5g). Distillation of this gum under reduced pressure gave only E-1,3-diphenylpropene (3.0g, 16% yield) identical to that previously prepared.

Preparation of Z-and E-1,3diphenylpropene.

A suspension of sodium amide in anhydrous benzene (100ml) was prepared from sodium (1.8g) and liquid ammonia (150ml) followed by addition of benzene. To this suspension a portion of triphenylphenethylphosphonium bromide (33g) was added and the mixture refluxed for 2 hours producing a red colour. The mixture was cooled,a portion of benzaldehyde(7.8g) was added and the mixture refluxed for 3 hours.

The solvent was removed under reduced pressure and the resulting oil distilled under reduced pressure to give a mixture of the E- and Z- alkenes (3.0g, 22%). Analysis of the distillate by NMR showed that the isomeric proportions were 49% Z- alkene and 51% E-alkene.

This reaction was repeated with anhydrous diethyl ether as solvent in place of benzene. The distilled product was pure E-1,3-diphenylpropene (50%).

This reaction was repeated with anhydrous diethyl ether as the solvent until just before the addition of benzaldehyde when the ether was distilled off and replaced by benzene, the rest of the reaction following its normal course. The total yield was 32% made up of 78% of the Z- alkene and 22% of the E- alkene (79).

Preparation of **threo** 1-azido-1,3-diphenyl-2-iodoprop-γ-ene.

To a stirred slurry of sodium azide (0.3g, 5m.mole) in freshly distilled acetonitrile (10ml) cooled in a methanol/ice bath was slowly added a portion of iodine monochloride (3.66g, 2.7m.moles) over 5 minutes. The mixture was stirred for 15 minutes then a solution of Z-1,3-diphenylpropene (0.4g,2m.moles) in acetonitrile (10ml) was run in. The mixture was allowed to reach room temperature and stirred for 68 hours.

The mixture was poured onto water (50ml) and extracted with diethyl ether (3 portions of 50ml). The organic extracts were

combined and washed with sodium thiosulphite solution (120ml of a 5% solution), with water (18ml) dried and the solvent removed under reduced pressure to give a yellow oil (1.0g).

This oil was purified by column chromatography on alumina (30g, activity II) with elution with light petroleum. This eluted the desired iodo azide (86) (0.3g, 40% yield)

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.1ppm	10H	m	
4.8ppm	1H	d	(J=5Hz)
3.6ppm	1H	m	
2.7ppm	2H	m	

IR (ν max) 2118cm^{-1}

Analysis:

$C_{15}H_{14}N_3I$ requires C= 49.59 H=3.86 N=11.47%

obtained C= 52.28 H= 4.35 N=10.46% *

Mass spectrum:

A.P.=$^m/_e$=194

* This compound is unstable and quickly develops a purple colouration on standing at 0°C.

Preparation of Z-1-azido-1,3-diphenylprop-1-ene (87).

A suspension of potassium t-butoxide in anhydrous diethyl ether (30ml) was prepared from potassium (0.34g) and excess t-butanol,the alcohol was removed from the alkoxide by distillation under reduced pressure, and ether added. To this mixture was added a portion of the iodo azide (86) (1.6g, 0.0045moles). The mixture was stirred for 65 hours.

A portion of water (100ml) was added, the organic phase was

separated, dried and the solvent was removed under reduced pressure to give a red gum (0,9g). This gum was purified by column chromatography on alumina (30g, activity IV), elution with light petroleum gave a yellow oil (0.4g). This oil was further purified by P.L.C., elution with toluene gave the Z-1-azido-1,3-diphenylprop-1-ene (87) (0.35g, 33% yield, Rf 0.86).

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.1ppm	10H	m
5.2ppm	1H	m
3.6ppm	2H	m

IR (νmax) 2120, 1605, 1270cm^{-1}

Analysis:

$C_{15}H_{13}N_3$ requires C=76.60, H=5.53, N=17.87%
obtained C=77.07, H=5.76, N=17.22%.

Mass spectrum:

$^m/_e$= 235(34%, M+) 207(53%) 91(100%).

Decomposition of Z-1-azido-1,3diphenylprop-1-ene.

A solution of Z-1-azido-1,3-diphenylprop-1-ene (103mg) in trichlorobenzene (8ml) was heated at 180-183°C for 4 hours under a nitrogen atmosphere.

The solvent was removed under reduced pressure to give a brown gum (0.1g). This gum was purified by P.L.C., elution in toluene gave 9 bands. Extraction of these bands and analysis by NMR showed that none of them were the desired product.

Preparation of 2-benzyl-1,3-diphenylpropene(88).

To a stirred suspension of sodium hydride (4.8g of a 50% sodium hydride/paraffin suspension, 0.1moles) in anhydrous benzene (1000ml) was added a portion of triphenylphenethylphosphonium bromide (43.2g, 0.1mole) and the mixture was refluxed for 2 hours. A solution of 1,3-diphenylpropan-2-one (21g, 0.1moles) in benzene (100ml) was added and the mixture was refluxed for a further 120 hours.

The mixture was filtered and the solvent removed from the filtrate under reduced pressure. The residue was triturated in light petroleum (120ml) to give a solid which was discarded. The solvent was removed from the resulting solution to give a green oil (29.9g) of nearly pure alkene.

This oil was further purified by column chromatography on alumina (100g, activity IV), elution with light petroleum gives the pure 2-benzyl-1,3-diphenylpropene (88) (26.2g, 96% yield).

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.2ppm	10H	m
6.5ppm	1H	s
3.5ppm	2H	s
3.3ppm	2H	s

Analysis:

$C_{22}H_{20}$ requires C=92.91, H=7.09%

obtained C=92.56, H=7.31%

Mass spectrum:

$^m/_e$= 284(13%,M^+), 91(100%).

Addition of Iodine azide to 2-benzyl-1,3-diphenylpropene.

To a stirred and cooled (methanol/ice bath) slurry of sodium azide (3.0g) in acetonitrile (100ml) was added a portion of iodine monochloride (3.6g) over 5 minutes, The mixture was stirred for a further 15 minutes. A solution of 2-benzyl-1,3-diphenylpropene (5.6g, 0.019moles) in acetonitrile (20ml) was added. The mixture was stirred for 66 hours.

Work up was as for the previous iodine azide addition reactions. A yellow oil (7.1g) was isolated. This oil was purified by column chromatography on alumina (140g, activity III), elution with light petroleum gave, after a forerun of starting alkene (0.4g) a mixture of the two isomeric iodo azides, 1-azido-2-benzyl-1,3-diphenyl-2-iodopropane (90) and 2-azido-2-benzyl-1,3-diphenyl-1-iodopropane (91) in a ratio of 1.2:1 respectivly, as a yellow oil (2.9g, 37%).

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.1ppm	30H	m
4.9ppm	1H	s*
4.4ppm	1H	s
3.5ppm	1H	*
3.2ppm	1H	*
3.1ppm	1H	*
3.0ppm	1H	
2.9ppm	1H	
2.8ppm	1H	*
2.7ppm	1H	
2.6ppm	1H	

* these peaks are identified as due to the 1-azido-2-iodo alkane (90).

Attempted separation of this mixture by P.L.C. proved unsuccessful.

Preparation of 1-azido-2-benzyl-1,3-diphenylprop-1-ene(92).

To a stirred suspension of potassium t-butoxide (from 0.16g potassium) in anhydrous diethylether (20ml) was added a portion of the mixture of iodo-azides (90) and (91) (1.6g 0.004moles) in ether (10ml) The mixture was stirred for 4.5 days.

Work up as described before for the preparation of vinyl azides by this method gave a red oil (1.4g). This oil was purified by P.L.C., elution with light petroleum gave the desired vinyl azide (92) as a yellow gum (0.25g, 19% yield).

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.2ppm	15H	m
3.5ppm	4H	bs

IR (ν max) 2120cm^{-1}

Analysis:

$C_{22}H_{19}N_3$ requires C=81.23, H=5.85, N=12.92%

obtained C=81.05, H=6.32, N=12.69%.

Decomposition of 1-azido-2-benzyl-1,3-diphenylprop-1-ene (92).

A solution of the azide (92) (0.3g) in trichlorobenzene (10ml) was heated at 100^{o}C for 3 hours. The solvent was removed under reduced pressure to give a brown gum (0.3g).

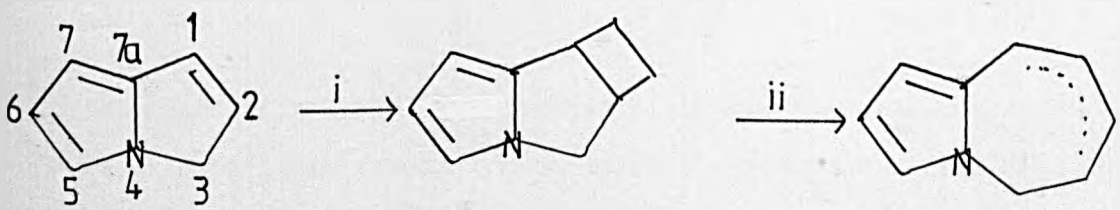
This gum was purified by P.L.C., elution with toluene gave 6 bands. None of the compounds eluted showed NMR spectra similar to that expected for the pyrroloazepine.

CHAPTER THREE

An investigation of the preparation of pyrrolo[1,2-a]azepines from 3H-pyrrolizine

Introduction

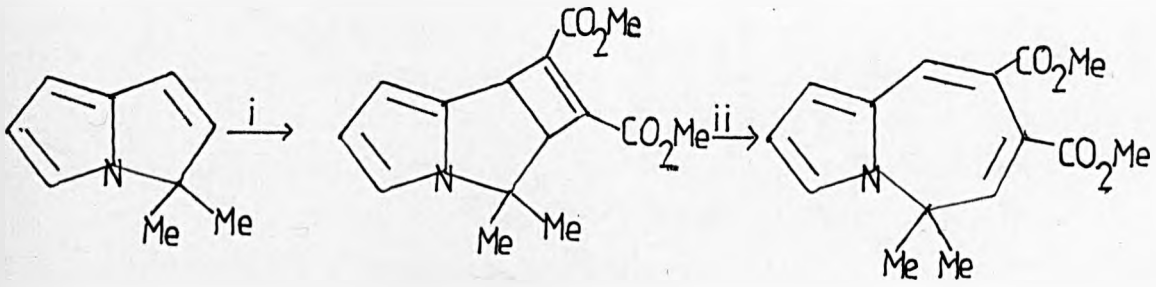
The structure of 3H-pyrrolizine with two fused five membered rings, a bridgehead nitrogen and an isolated double bond would seem to lend itself to ring expansion of one of the five membered rings by a two carbon unit to form the pyrrolo[1,2-a]azepine skeleton. This could most easily be achieved by a $[2\pi+2\pi]$ addition to 3H-pyrrolizine followed by ring expansion of the resulting tricyclic compound (Scheme 31).



(97)

Scheme 31 i) Alkene or alkyne ii) ring expansion conditions would depend on the nature of i).

This has been attempted with some success by Johnson and Jones[28]. A [2π+2π] addition of dimethyl acetylenedicarboxylate (DMAD) to 3,3-dimethyl-3H-pyrrolizine gave a tricyclic compound in 26% yield. Thermal ring opening of this tricyclic compound gave the pyrrolo[1,2-a]azepine



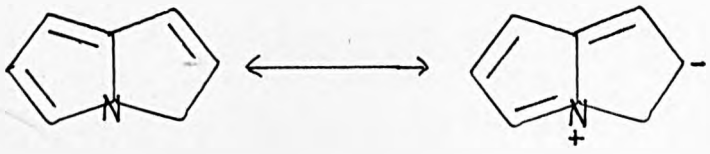
Scheme 32

i)DMAD, acetophenone, irradiate ii)200°C

The disadvantage of this synthesis lies in the use of the dimethyl pyrrolizine leading to a dimethyl pyrrolo[1,2-a]azepine derivative from which it is difficult to generate the corresponding pyrrolo[1,2-a]azepinium salt. Use of the parent 3H-pyrrolizine however, gives a prohibitively low yield of the tricyclic compound and much unwanted side products.

The work of Johnson and Jones does show however that 3H-

pyrrolizine is susceptible to [2π+2π] addition with an electron deficient "enophile" This bears out the postulated polarization of 3H -pyrrolizine (scheme 33) which would make position 2 of the isolated double bond nucleophilic.

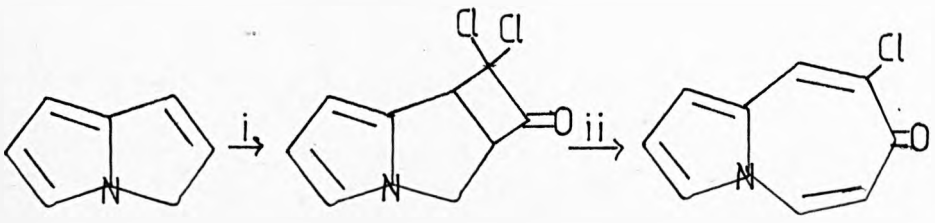


Scheme 33

A compound which is known to react with electron rich and inactivated double bonds to give exclusively [2π+2π] addition products is dichloroketene. A survey of the reactions of this compound is presented later. It is possible that a synthesis of pyrrolo[1,2-a]azepines may be achieved by the [2+ 2] addition of dichloroketene to 3H-pyrrolizine to give a tricyclic adduct. This adduct would have two acidic protons, one of which may be abstracted by base together with elimination of chloride to give the ring expanded product, a pyrrolo[1,2-a]azepinone (Scheme 34).

Scheme 34

i)dichloroketene ii)base

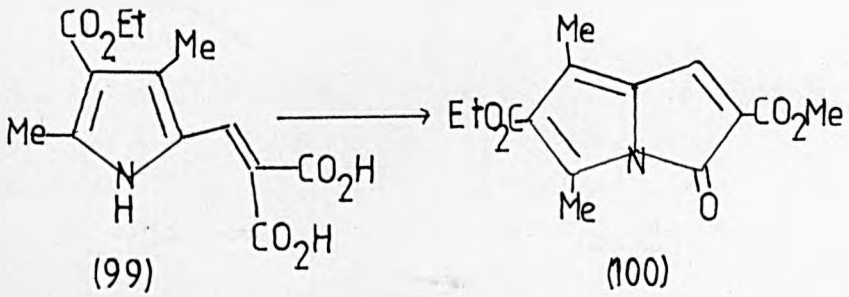


It is pertinent to review the synthesis and reactions of 3H-pyrrolizine.

The synthesis and reactions of 3H-pyrrolizine

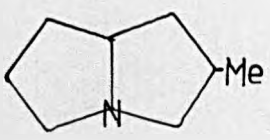
a) Synthesis

The first pyrrolizine derivative was synthesised in 1925 by Kuster, Brudi and Kopenhofer [105]. This was the pyrrolizin-3-one derivative (100), produced from 4-carbethoxy-2-[β, β dicarboxyvinyl]-3,5-dimethylpyrrole (99) in boiling methanol.



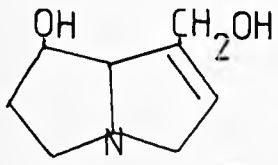
(99) (100)

There was little subsequent work done on this class of compounds until Men'shikov[106] discovered in 1936 that 2-methylpyrrolizidine (101) (a saturated pyrrolizine) was part of the alkaloid heliotridane.

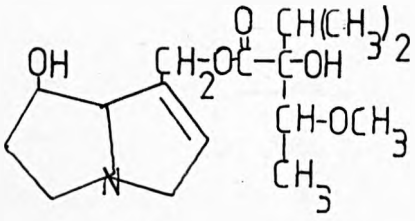


(101)

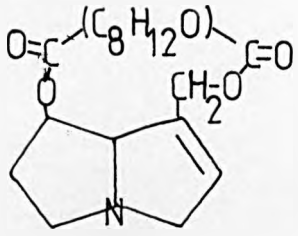
Since then this structure has been found in a number of alkaloids[107], notably retronicine[108] (102),heliotrine[109] (103) and longiboline[110] (104).



(102)

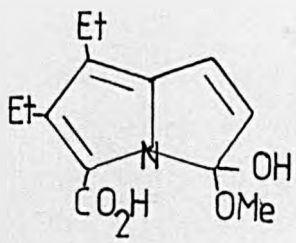


(103)



(104)

Although much work was done on the saturated pyrrolizidines[111,112] the only synthesis of a pyrrolizine for some time was that of Micheel and Kimpel[113] in which they prepared the highly substitued pyrrolizine (105).

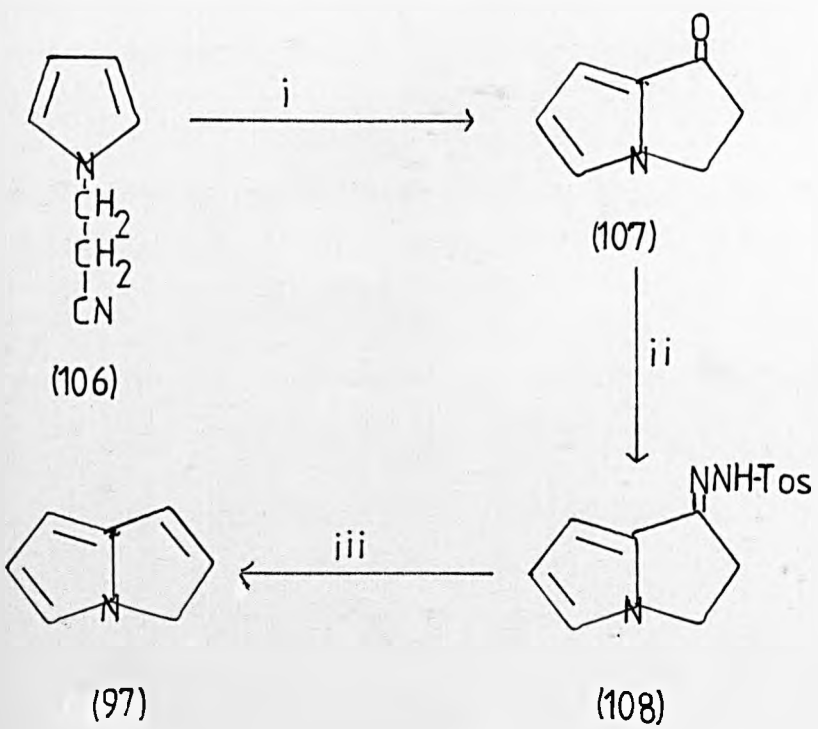


(105)

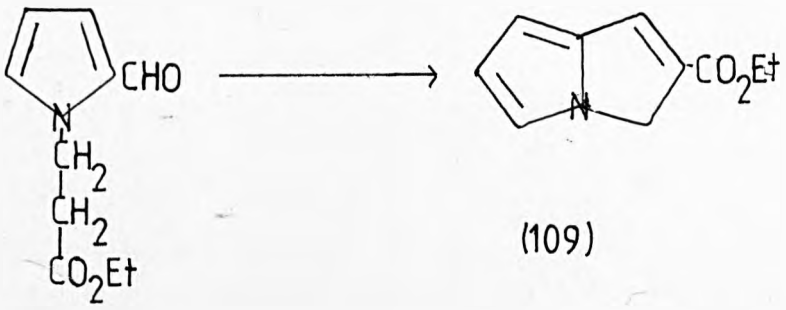
The first synthesis of the parent compound was reported by Carelli, Cardellini and Morlacchi in 1963[114]. Three syntheses were reported in the one paper by these workers, the best route being that shown in scheme 35. N-(β-cyanoethyl)pyrrole (106) was cyclised to 2,3-dihydropyrrolizin-1-one (107) in ether by treatment with dry hydrogen chloride. The corresponding tosyl hydrazone was prepared from the ketone (107) . Nitrogen and toslyate were eliminated from the hydrazone (108) by treatment with potassium hydroxide in triethylene glycol at 140°C to give 3H-pyrrolizine in an overall yield of 29%.

Scheme 35

i)Dry HCl/Et_2O ii)p-tolylsulphonyl hydrazine iii)KOH/triethylene glycol

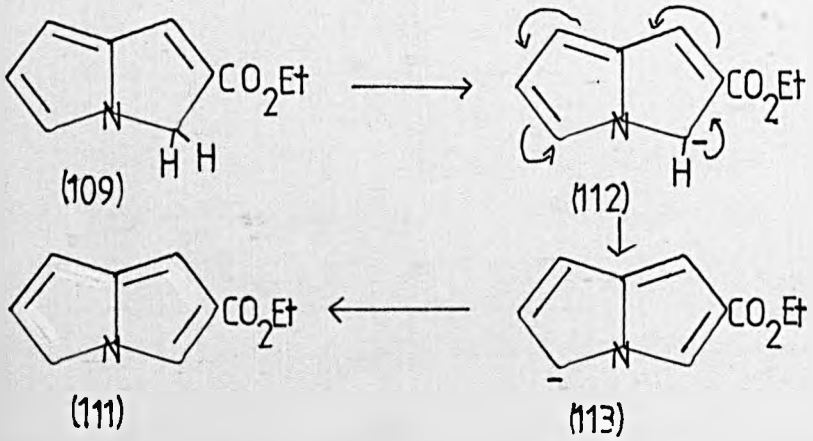


Carelli, Cardellini and Morlacchi[114] also reported the preparation of 2-carbethoxy-3H-pyrrolizine (109) by the intramolecular condensation of N-(β-carbethoxyethyl)-2-formylpyrrole (110) catalysed by sodium ethoxide in ethanol.



(110) (109)

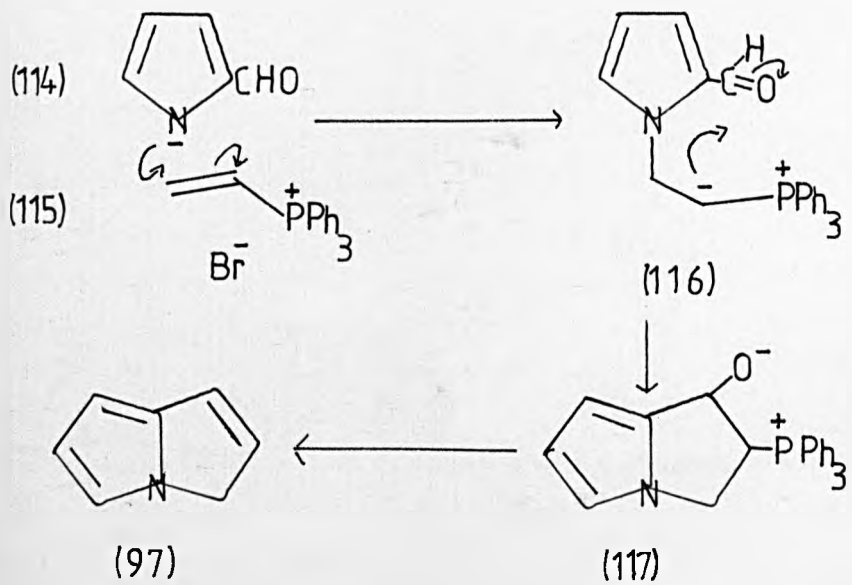
Flitsch and Heidues[113] have reinvestigated this reaction and have shown that the product is the isomeric 6-carbethoxy-3H-pyrrolizine (111). This is believed to be formed from the 2-carbethoxy isomer (109) which is the first product. Under strongly basic conditions a proton is abstracted to give the 4-azapentalenyl anion (112), a 10π system. This can then isomerise to give the isomeric anion (113) which seems to be more stable under the reaction conditions and is protonated to give the observed product (111).



(109) (112) (111) (113)

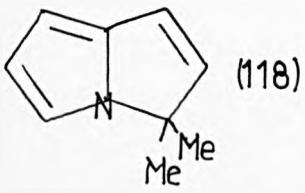
A simple synthesis of 3H-pyrrolizine from the sodium salt of 2-formylpyrrole and triphenylvinylphosphonium bromide was reported by Schweizer and Light[114a]. A combined Michael-Wittig mechanism was proposed (scheme 36). The sodium salt of 2-formylpyrrole (114) is formed by attack of sodium hydride on 2-formylpyrrole. The pyrrolide anion adds to the phosphonium salt to give a phosphorane (116) which then undergoes an intramolecular Wittig reaction to give 3H-pyrrolizine (in 87% yield) together with triphenylphoshine oxide.The 1-methyl derivative has been prepared from 2-acetylpyrrole by the same method.

Scheme 36

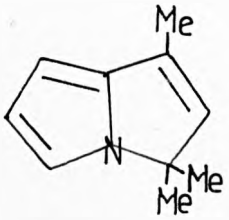


Schweizer and Light have further investigated this reaction using allyltriphenylphosphonium salts[116]. The reactions of 2-formylpyrrole and 2-acetylpyrrole with methallyltriphenylphosphonium chloride (117) give 3,3-dimethyl-3H-pyrrolizine and 1,3,3-trimethyl-3H-pyrrolizine

respectively.



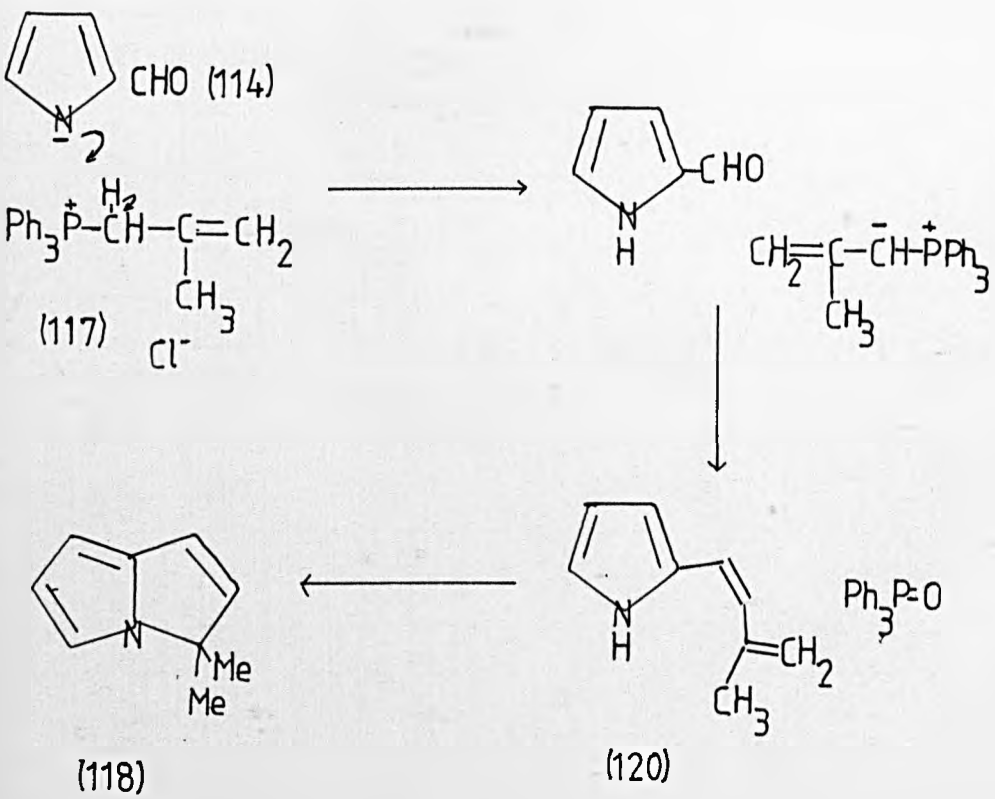
(118)



(119)

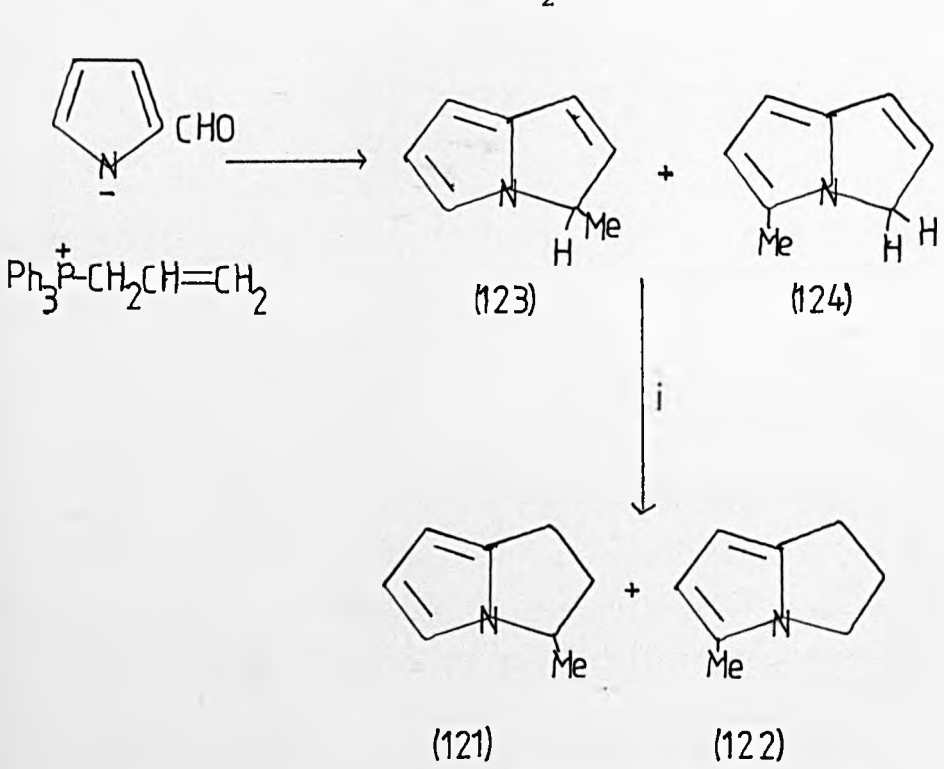
In this case the reaction proceeds as shown in scheme 37. The 2-formylpyrrole anion (114) acts as a base and forms the phosphorane from the phosphonium salt (117). This phosphorane then undergoes a normal Wittig reaction to give a butadienylpyrrole derivative (120) which cyclises to the pyrrolizine (118).

Scheme 37



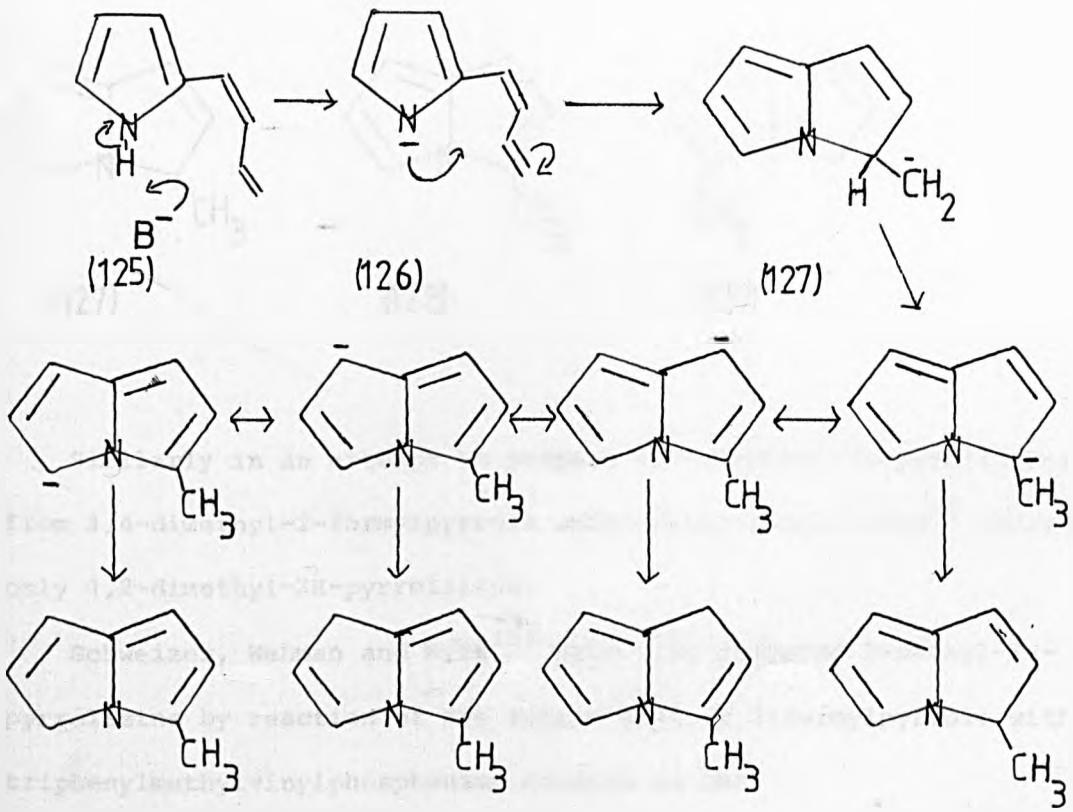
In a attempt to prepare 3-methyl-3H-pyrrolizine Schweizer and Light reacted allyltriphenylphosphonium bromide with the anion of 2-formylpyrole. Instead of the expected pyrrolizine they obtained a mixture of methylpyrrolizines, which could not be separated. However hydrogenation gave a mixture of 1,2-dihydropyrrolizines comprising 64% 1,2-dihydro-3-methyl-pyrrolizine (121) and 36% 1,2-dihydro-5-methylpyrrolizine (122). From this they deduced that the original product mixture contained 3-methyl-3H-pyrrolizine (123) and 5-methyl-3H-pyrrolizine (124), there may also have been the corresponding 1H isomers but this was not investigated.

Scheme 38



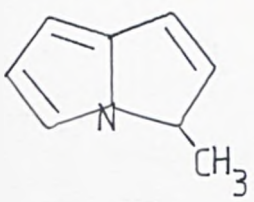
To explain this Schweizer proposed the mechanism shown in scheme 39

Scheme 39

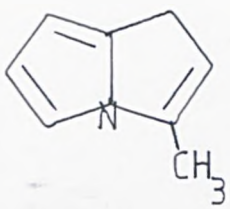


The butadienylpyrrole intermediate (125) can lose a proton to base, forming an anion (126) which undergoes an intramolecular Michael addition and transfer of charge to give a 3-methyl-4-azapentalenyl anion (127). The anion (127) can isomerise to 3 other 4-azapentalenyl anions, each of which can be protonated to give corresponding methyl pyrrolizines. Johnson and Jones found a similar effect when they attempted to prepare 5-methyl-3H-pyrrolizine by the reaction of 2-formyl-5-methylpyrrole anion with

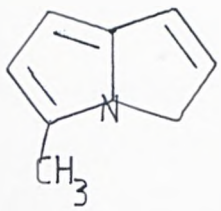
triphenylvinylphosphonium bromide. They obtained a product mixture which was shown to be a mixture of 3-methyl-3H-pyrrolizine (127) (10%), 3-methyl-1H-pyrrolizine (128) (45%) and 5-methyl-3H-pyrrolizine (129) (45%).



(127)



(128)



(129)

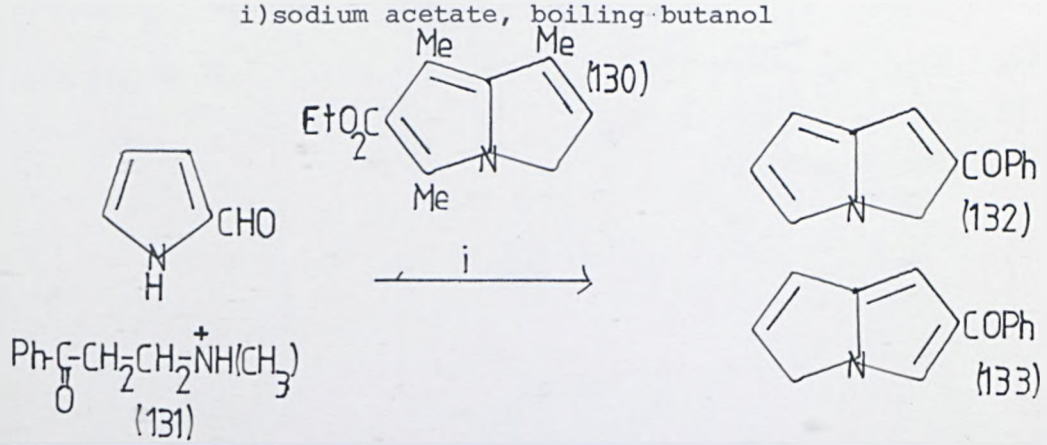
Similarly in an attempt to prepare 6,7-dimethyl-3H-pyrrolizine from 3,4-dimethyl-2-formylpyrrole anion Johnson and Jones[28] isolated only 1,2-dimethyl-3H-pyrrolizine.

Schweizer, Wehman and Nyez[167] have also prepared 2-methyl-3H-pyrrolizine by reaction of the sodium salt of 2-formylpyrrole with triphenylmethylvinylphosphonium bromide in DMF.

In 1968 Flitsch and Heidues[113a] prepared 1,5,7-trimethyl-6-ethoxycarbonyl 3H-pyrrolizine (130) from 2-acetyl-3,5-dimethyl-4-ethoxycarbonylpyrrole anion and triphenylvinylphosphonium bromide, they reported no isomerisation to give product mixtures.

Scheme 40

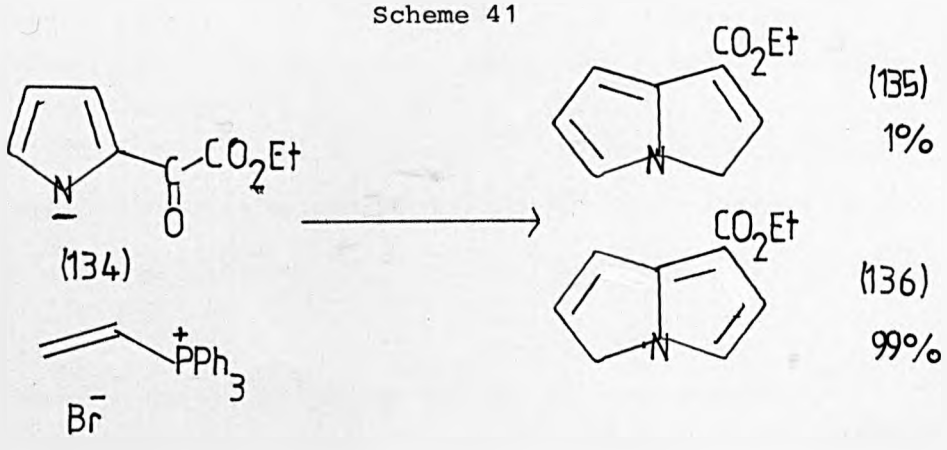
i) sodium acetate, boiling butanol



However in their reaction of 2-formyl-pyrrole with β-diethylaminopropiophenone (131) using sodium acetate in butanol Flitsch and Heidues[113a] found a mixture of 2-benzoyl-3H-pyrrolizine (132) and 6-benzoyl-3H-pyrrolizine (133). This was thought to have come about by isomerisation, even in these weakly basic conditions.

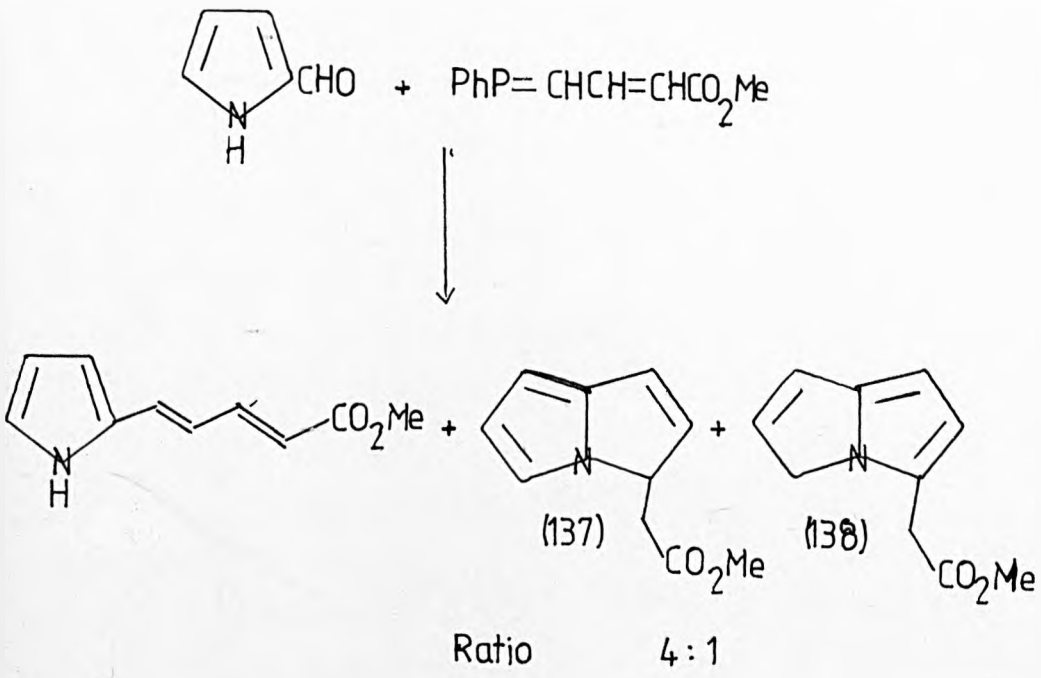
Similarly when Brandänge and Lundlin[118] reacted the sodium salt of a pyrrolyl ketoester (134) with vinyltriphenylphosphonium bromide they obtained a mixture of the two pyrrolizine esters (135) and (136). The initially formed 1-carbethoxy-3H-pyrrolizine (135) isomerised to give a preponderance of 7-carbethoxy-3H-pyrrolizine (136).

Scheme 41



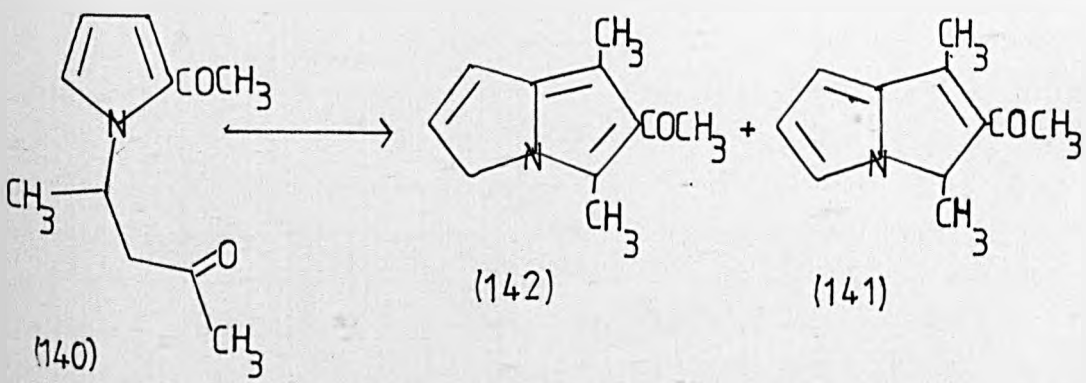
By using a Wittig reaction Flitsch, Mueter and Wolf[1] have synthesised a mixture of the pyrrolizine esters (137) and (138) from 2-formylpyrrole.

Scheme 42



An intramolecular aldol condensation of the pyrrolodiketone (140) provided Flitsch, Kappenberg and Schmitt[2] with a synthesis of the isomeric pyrrolizine ketones (141) in 23% yield and (142) in 11% yield.

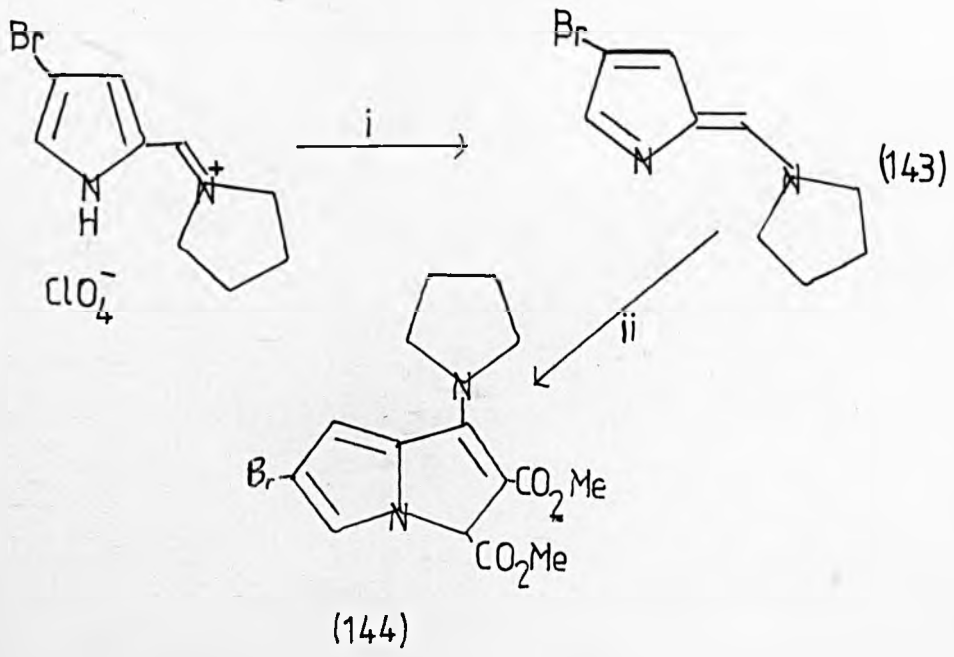
Scheme 43



Sonnet, Flippen and Gilgardi[29] have reported the use of an azafulvenamine in the preparation of a pyrrolizine derivative, scheme 44. The reaction of sodium hydride with (4-bromo-1-pyrrol -2-yl methylene)pyrrolidium perchlorate gave the stable azafulvenamine (143), this was reacted with DMAD to give the pyrrolizine derivative (144) as well as a 1:2 adduct.

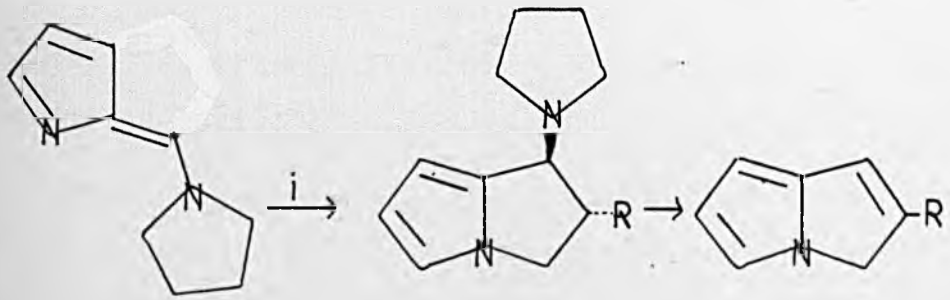
Scheme 44

i)NaH ii)DMAD



(144)

A similar synthesis has been described by Mori, Watanabe, Kajigaeshi and Kanemasa[119].



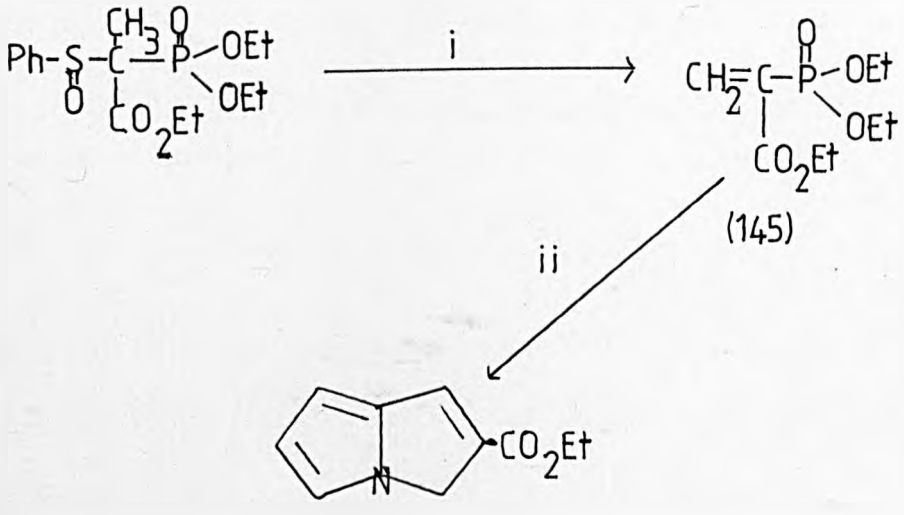
Scheme 45

i)$RCHCH_2$, R=CN, CO_2Et, CO_2Me and Ac.

In both of these syntheses, as no base is used the product is a pyrrolizine with the electron withdrawing group on the partially saturated ring only. The most recent synthesis of a 3H-pyrrolizine is that due to Minami, Suganuma and Agawa[120], shown in scheme 46.

Scheme 46

i)Thermolysis ii)2-formylpyrrole anion/ THF or DMF/2-3 hours/60-80°C



The unsaturated phosphonate (145) is prepared by thermolysis. Reaction of this, presumably by a combined Michael-Wittig Horner reaction, with the anion of 2-formylpyrrole gives 2-carbethoxy-3H-pyrrolizine. Despite the basic conditions used no isomerisation is reported.

b)Reactions

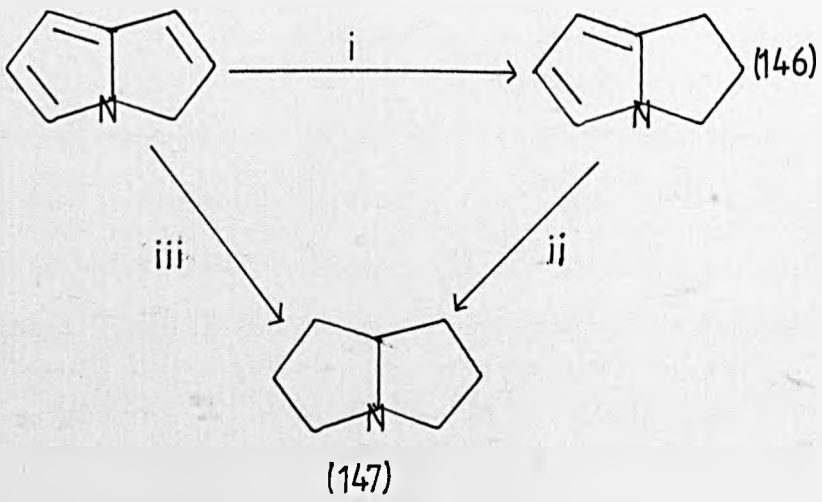
There have been few reactions carried out on 3H-pyrrolizine and the majority of these have been with the aim of preparing a larger ring system. There have been very few simple reactions of 3H-pyrrolizine reported.

The first reaction in the literature was hydrogenation reported by Carelli, Cardellini and Morlacchi[114]. 3H-pyrrolizine is hydrogenated in ethanol to 1,2-dihydro-3H-pyrrolizine (146), however in acetic acid the hydrogenation proceeds to hexahydropyrrolizine (147). Schweizer and Light found similarly that a catalyst of 5%Rh/C in ether will reduce the isolated double bond, but the same catalyst in ethanol produces complete reduction[115]

Scheme 47

i)H_2/PtO_2 or H_2/5%Rh/C/Et_2O ii)H_2/AcOH or $H_2$5%Rh/C/EtOH

iii)H_2/5%Rh/C/EtOH

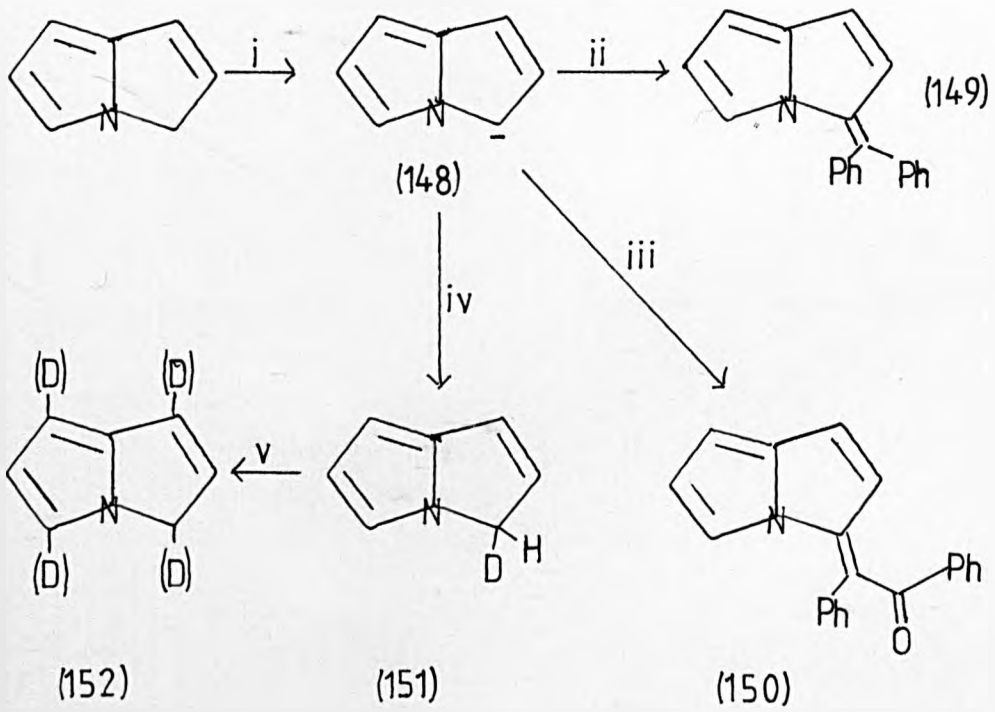


Reaction of 3H-pyrrolizine with strong base generates the 4-azapentalenyl anion[121](148). This can then react with electrophiles as shown in scheme 48.

Scheme 48

i)nBuLi,or K, or Na, or KO-t-Bu in THF ii)benzophenone

iii)benzil iv)D_2O v)a)n-BuLi b)D_2O

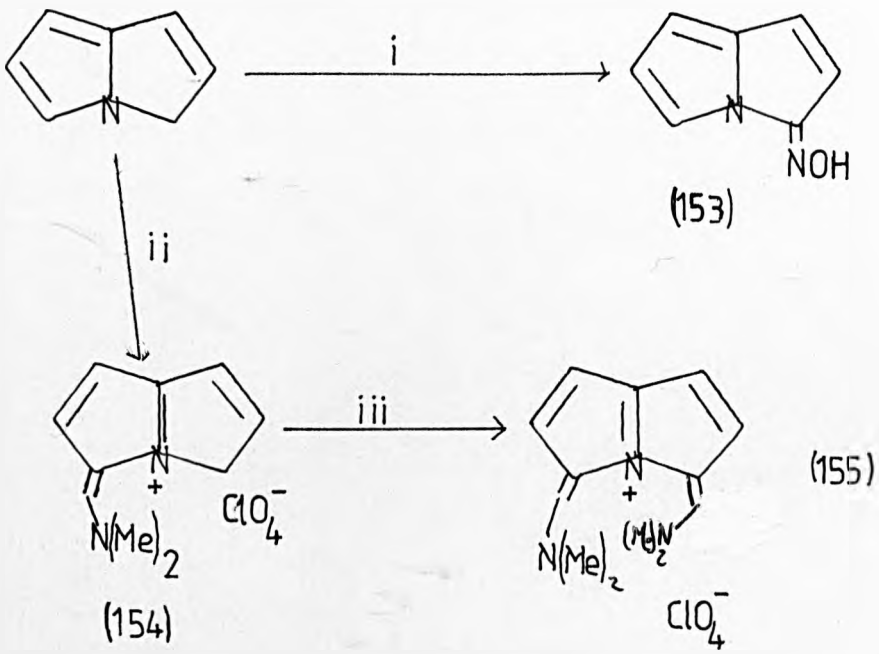


Reaction of the anion with ketones such as benzophenone or benzil gives the corresponding methylene compounds (149) or(150). Reaction of the anion with D_2O gives 3D-3H-pyrrolizine (151), however Johnson and Jones[122] have found that regeneration of the anion from this and treatment with more D_2O gives scrambling of deuterium around the ring (152), the product mixture having 86% deuterium on position 3, 40% on 1, 40% on 7 and 70% on 5.

Reaction of 3H-pyrrolizine with 3-methylbutyl nitrite gives 3-oximino-3H-pyrrolizine (153)[113].

Scheme 49

i) 3-methylbutyl nitrite ii)$POCl_3$/DMF, $HClO_4$ iii)DMF

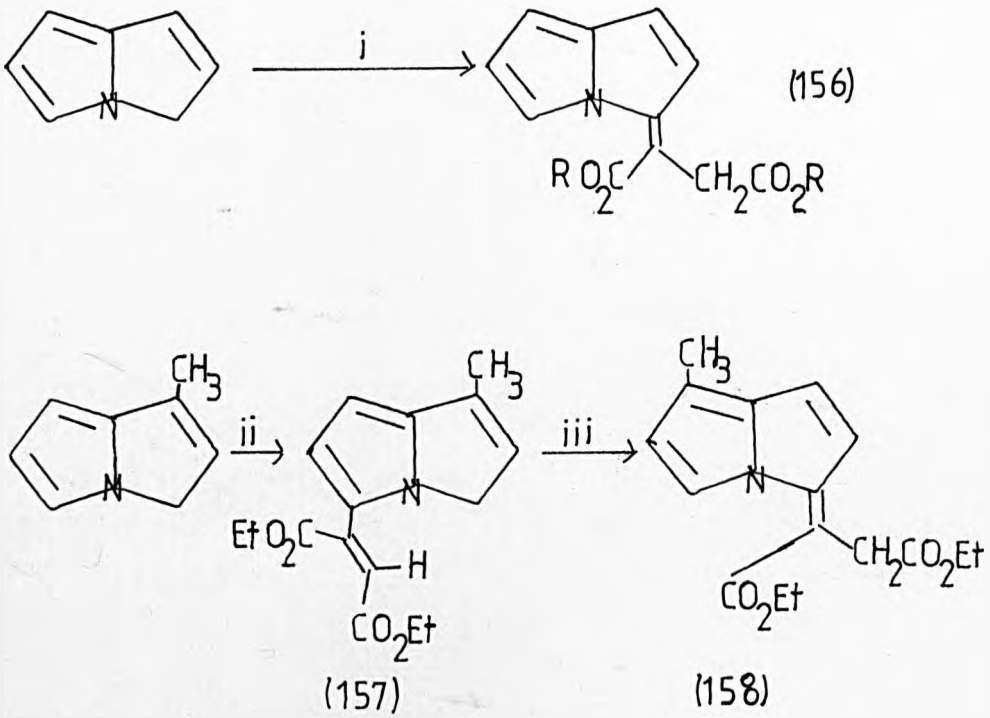


Under the Vilsmeier conditions and wih careful isolation of the intermediate the adduct (154) can be isolated [123], this can be reacted with more DMF to give (155).

Like pyrrole, 3H-pyrrolizine seems to undergo electrophilic attack at the position next to nitrogen (5) by acetylene dicarboxylate esters. In their attempts to form pyrrolo[1,2-a]azepines Johnson and Jones[122] prepared some 1:1 adducts of 3H-pyrrolizines and dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate

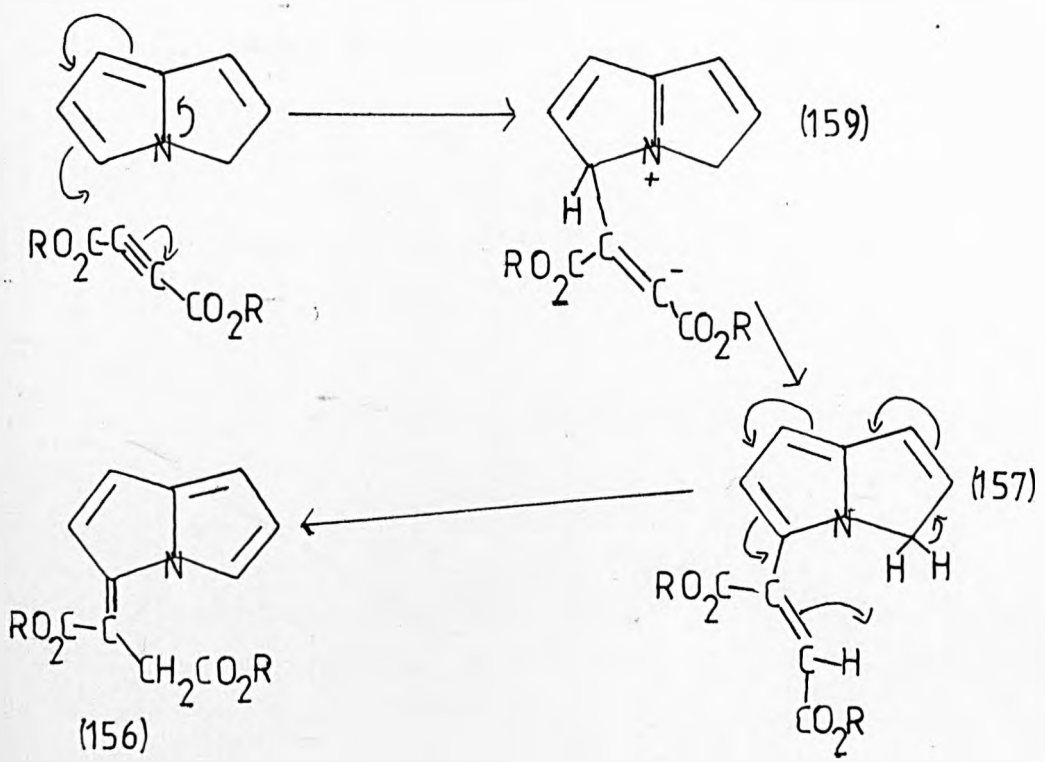
Scheme 50

i)RO_2CCCCO_2R, R=Me or Et ii)EtO_2CCCCO_2Et iii)boiling toluene



Reaction of 3H-pyrrolizine with both DMAD and DEAD gives azafulvenes (156). With DEAD 1-methyl-3H-pyrrolizine was found to give a different adduct, this was the maleate ester (157). This maleate was demonstrated to be an intermediate in the formation of azafulvenes by thermal conversion of the maleate into the azafulvene (158) in boiling toluene. The mechanism invoked to explain this is shown in scheme 51.

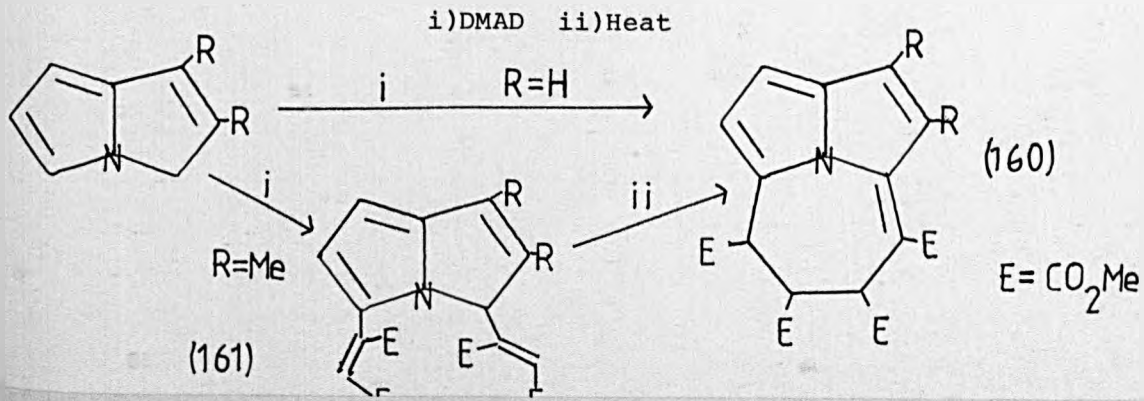
Scheme 51



The initial attack of the acetylene on position 5 gives a dipolar species (159), a 1,3 hydrogen shift and neutralization of the charge gives the maleate (157), this can then easily rearrange to give the azafulvene (156).

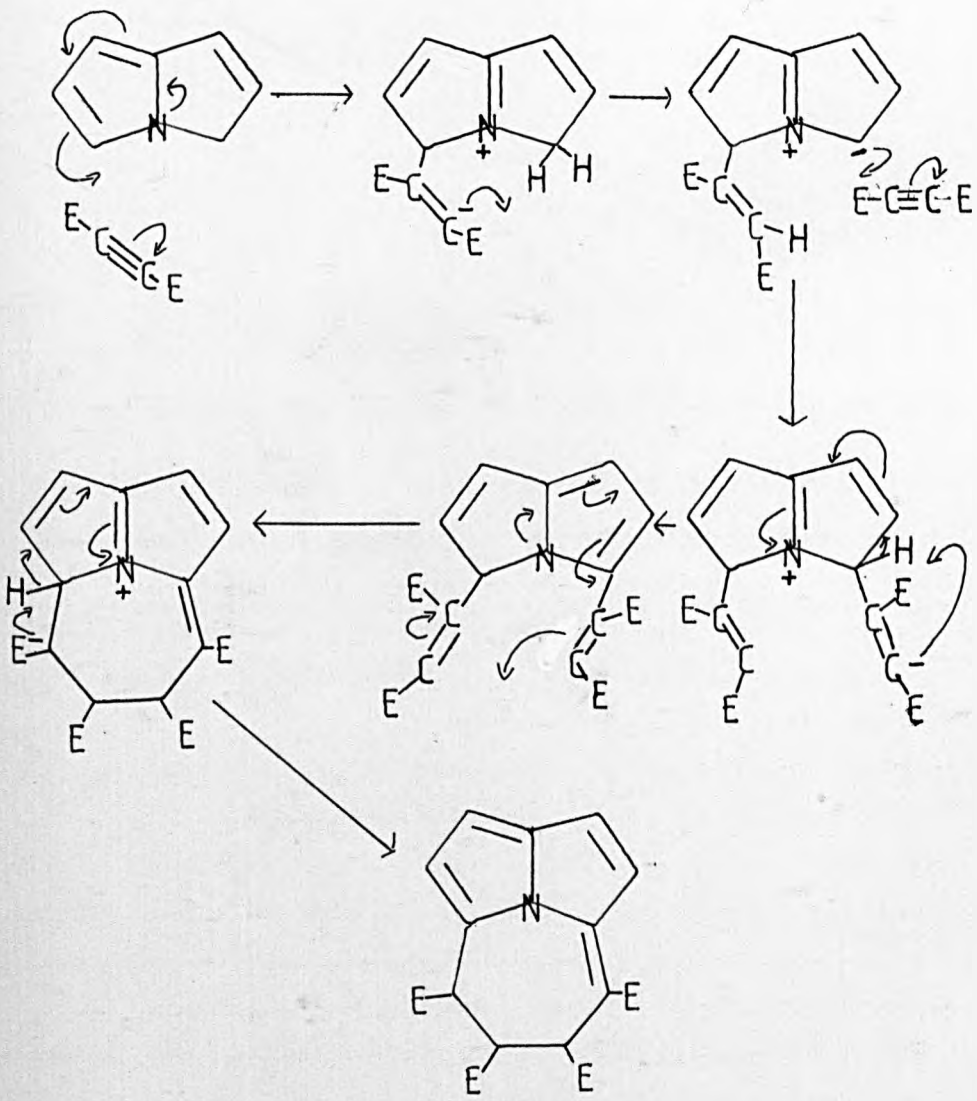
Johnson and Jones also found 2:1 adducts of acetylenic esters and 3H-pyrrolizines[124].

Scheme 52



Reaction of DMAD with 3H-pyrrolizine gave the dihydrocycla[4.2.2]azine derivative (160) as well as the azafulvene (156). 1,2-dimethyl-3H-pyrrolizine (described as the 6,7 dimethyl isomer in the paper but later corrected[28]) gave a dimaleate ester (161), this was found to be an intermediate in the formation of cyclazine derivatives as heating (161) in benzene gave (160). The mechanism put forward to explain this is shown in scheme 53.

Scheme 53

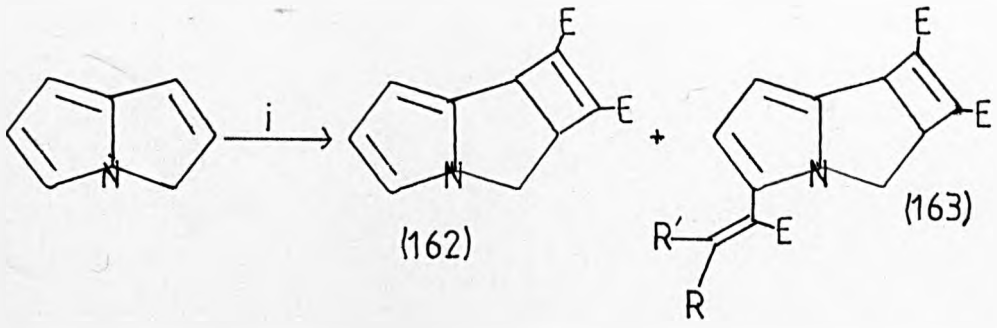


Under certain conditions 3H-pyrrolizine derivatives react with DMAD photochemically to give [2π+2π] cycloadducts, as in scheme 54.

Scheme 54

i)DMAD, acetophenone/ benzene/ irradiate

E =CO_2Me. R=E ,R^1=H. R=H,R^1=E

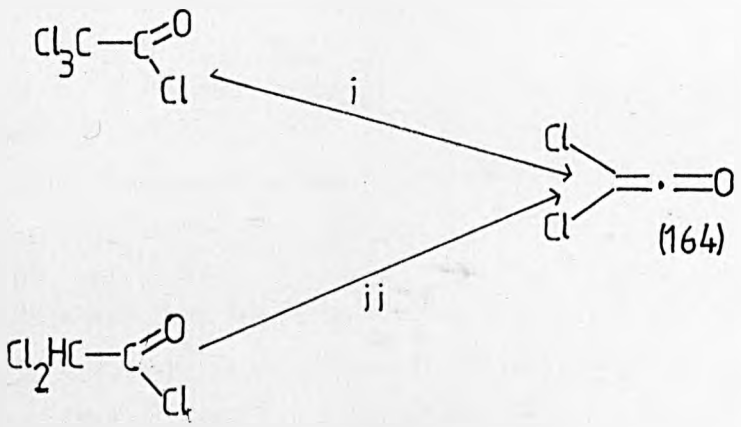


As well as the previously described azafulvene and cyclazine derivatives the photochemical reaction of DMAD with 3H-pyrrolizine also yields small amounts of the [2π+2π] cycloaddition product (162) and also the two 2:1 adducts which were identified as the fumarate and maleate esters (163).

Preparations and reactions of dichloroketene

Dichloroketene (164) has, for some years, been used in synthesis to form molecules containing a cyclobutanone fragment[125]. Dichloroketene is most easily prepared by one of two methods, scheme 55.

Scheme 55



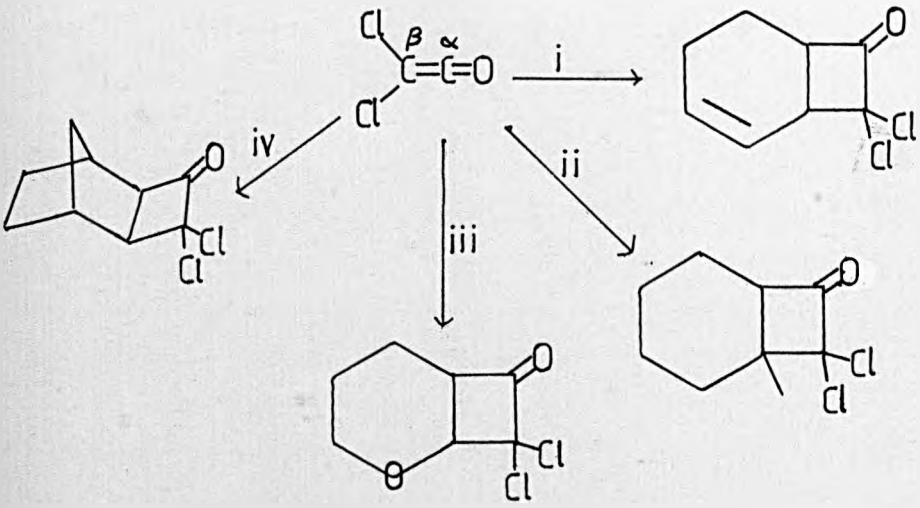
i)Zn-Cu/Et_2O ii)Et_3N/hexane

The dechlorination of trichloroacetyl chloride by activated zinc in diethyl ether and the dehydrochlorination of dichloroacetyl chloride by triethylamine in hexane both give dichloroketene in good yield. Dichloroketene easily polymerizes and dimerizes, therefore it is generated "in situ" with the substrate alkene with which it will react. There have recently appeared a number of improvements in the methodology of preparation of dichloroketene. Hassner and Krepski[125-

[126] have prepared dichloroketene by the zinc dehalogenation procedure in the presence of alkenes with an equimolar amount of $POCl_3$, they report that this leads to increased and cleaner yields of cycloadducts, less polymerization in the presence of zinc salts and increased reactivity so that adducts are formed from previously unreactive trisubstituted alkenes. They attribute this improvement to the complexation of zinc salts by $POCl_3$. Brady and Bak[127] have found that a very slow addition of trichloroacetyl chloride to the mixture of alkene and activated zinc increases the yield of cycloaddition to even unreactive alkenes. Brady and Bak explain this as a consequence of the lower concentration of dichloroketene in the solution at any one time, and so a lesser degree of polymerization of the ketene.

Dichloroketene gives α,α-dichlorocyclobutanone adducts with alkenes. It reacts well with unactivated and electron-rich alkenes, it does not react with electron-deficient alkenes such as methyl methacrylate.

Scheme 56



i)cylcohexadiene ii)1-methylcyclohexene iii)dihydropyran

iv)norbornene, low yield.

The reaction is stereospecific, the substituents on the 4 membered ring are in the same configuration as in the alkene. The reaction is also regiospecific, in the adducts the most nucleophilic carbon of the alkene is attached to the ∝ carbon of the ketene.

Discussion

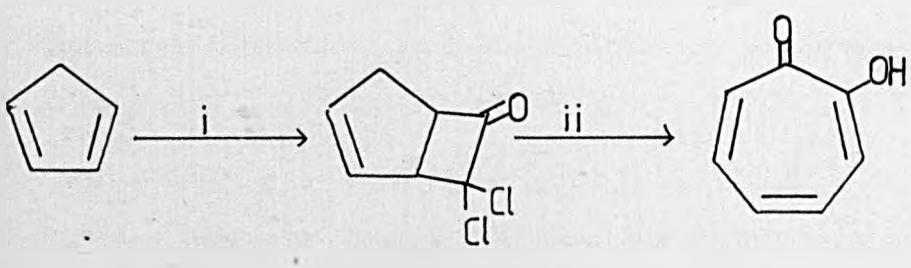
Attempted [2π+2π] addition reactions of 3H-pyrrolizine

a) With dichloroketene

In the previous section the possible preparation of pyrrolo[1,2-a]azepines from pyrrolizines was indicated (scheme 34). 3H-pyrrolizine would be expected to react with dichloroketene in a [2π +2π] manner[128] to give a cyclobutanone derivative. Although dichloroketene is electrophilic it shows a greater tendency to react in cycloaddition reactions than in electrophilic addition/elimination reactions. The 2-position of 3H-pyrrolizine is the most nucleophilic and so it would be reasonable to expect 3H-pyrrolizine to react with dichloroketene to give the adduct shown in scheme 34. Elimination of HCl with base should prove easy. In a similar synthesis Stevens, Reich, Brandt, Fountain and Gaughan[129] report the preparation of tropolone from cyclopentadiene (scheme 58)

Scheme 58

i)dichloroketene ii)a)acetate b)copper sulphate c)sodium carbonate



A number of experiments were carried out to prepare the cyclobutanone adduct .

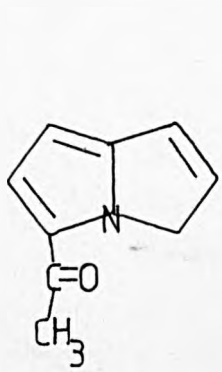
The method of Schweizer and Light[114] was employed for the preparation of 3H-pyrrolizine.

The improved method for preparing dichloroketene described by Brady and Bak [127] was followed. After slow addition (4 hours) of trichloroacetyl chloride solution to the mixture of activated zinc and 3H-pyrrolizine solution the mixture was boiled under reflux, worked-up and chromatographed on alumina. Light petroleum eluted a fraction containing yellow solid. The solid was recrystallized from light petroleum. The infra-red spectrum of the crystals shows a strong carbonyl absorption, but at 1640cm^{-1} (indicative of an α,β-unsaturated ketone) not the expected absorption due to an α,α dichlorocyclobutanone (around 1800cm^{-1}).

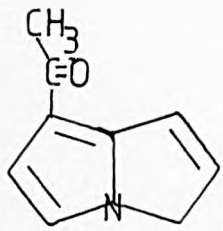
The ^{1}H NMR spectrum at 100MHz shows a sharp singlet at 2.30ppm integrating for three protons, this would indicate a methyl ketone. There is a broad singlet at 4.70ppm integrating for two protons, which would indicate a 3H-pyrrolizine (the methylene group of 3H-pyrrolizine appears as a broad singlet at 4.27ppm). The downfield shift of this resonance over that of the parent compound indicates the presence of an electron withdrawing substituent. There is a one proton doublet at 5.85ppm with a coupling of 4.03Hz to another one proton doublet at 6.88ppm. The only other peak is a broad signal at 6.60ppm which integrates for two protons, when the peak at 4.70ppm is irradiated this peak simplifies to a pair of doublets coupled together 4.00Hz.

The mass spectrum shows a molecular ion at 147 mass units and

easy loss from this of fragments of 15(75%) and 43(28%) mass units, indicating that the product is an acetyl pyrrolizine. The molecular analysis confirms the formula as C_9H_9NO. The two possible structures are therefore (165) and (166).



(165)

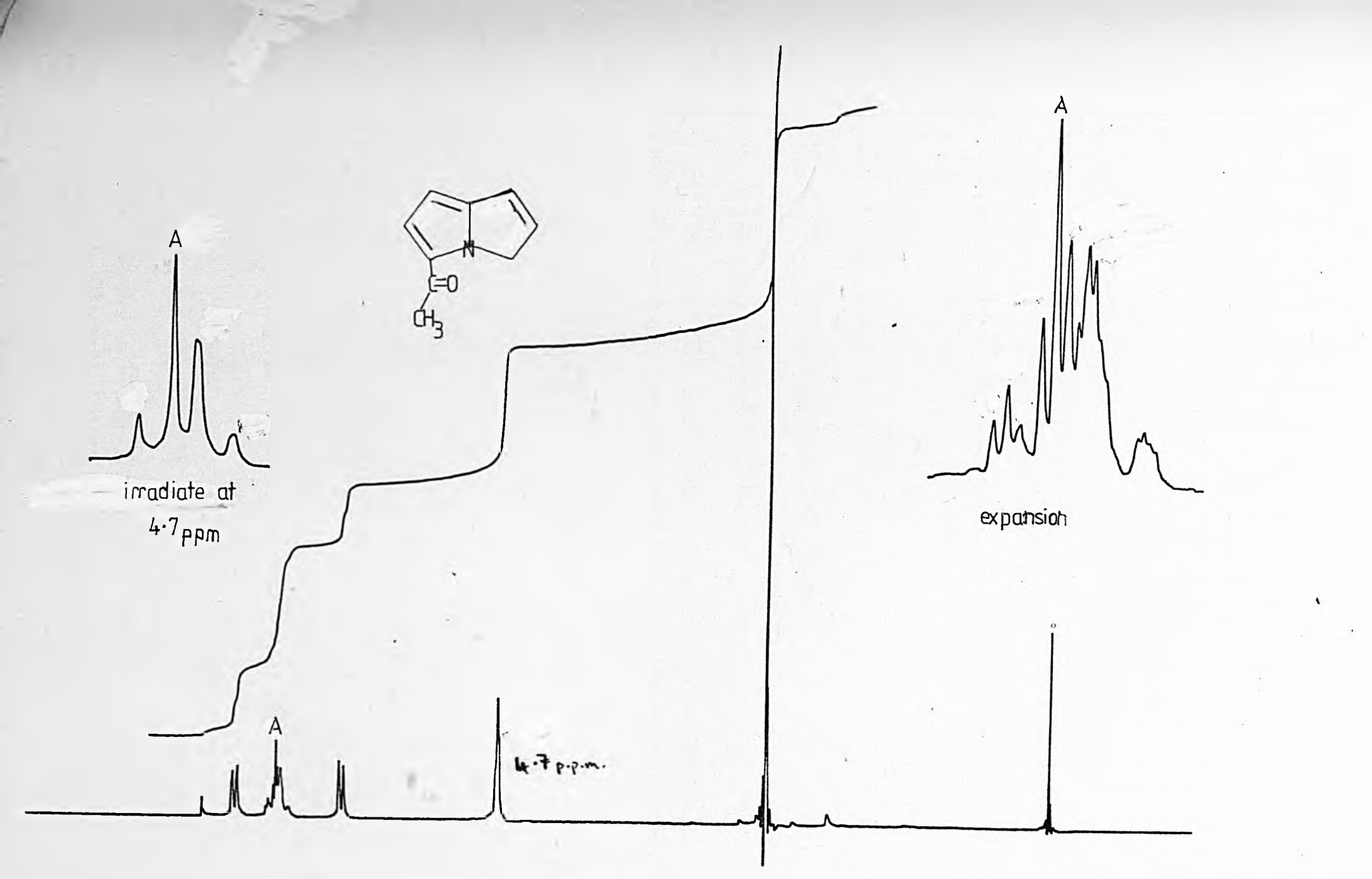


(166)

The pair of doublets that appear in the ^1H NMR spectrum at 6.88 and 5.85ppm with a coupling of 4.03Hz are either protons 6 and 7 in (165) or 5 and 6 in (166) .

Flitsch, Heidues and Paulsen[130] have reported ^1H NMR data for 3H-pyrrolizine. However reinterpretation of the spectra show that some of their assignments are incorrect. The coupling constants between the 5 and 6 protons on 3H-pyrrolizine is 2.57Hz and that between 6 and 7 3.17Hz. So on the basis of the observed coupling constants the structure (165) is more probable. If this compound came about by electrophilic attack on 3H-pyrrolizine then the more probable site is position 5 as in pyrrole itself the α-position is more susceptible to electrophilic attack than the β-position (corresponding to 7 in 3H -pyrrolizine).

Later experiments will indicate how this compound could have been

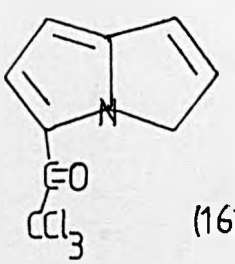

A
irradiate at
4·7 ppm
N
C=O
CH3
A
expansion
A
4·7 p.p.m.

formed. Further elution of the chromatography column gave some material which could not be identified.

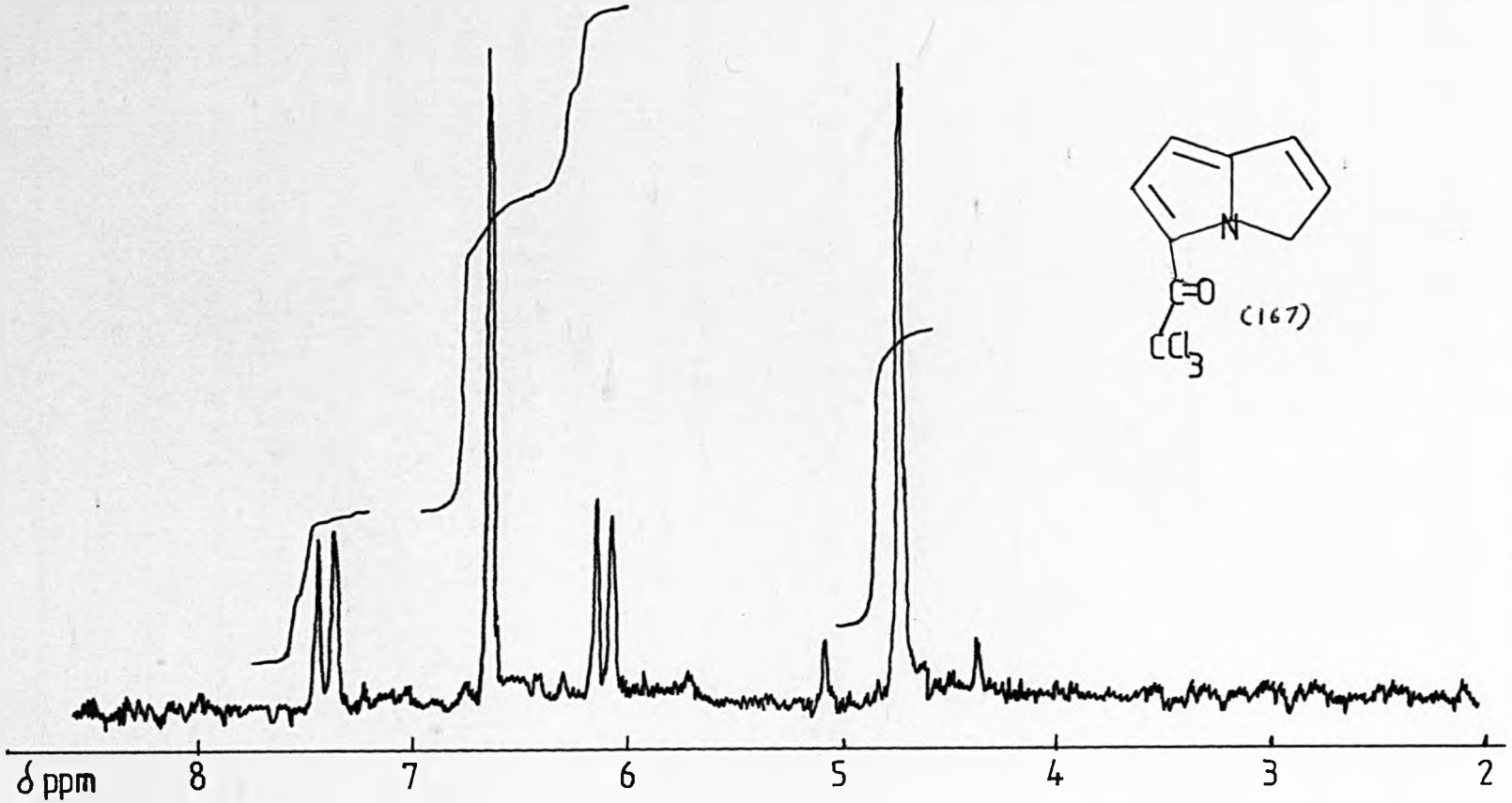
Hassner and Krepski[125,126] have reported a method of preparing dichloroketene in the presence of $POCl_3$. This method was applied to the reaction with 3H-pyrrolizine. Work up of the reaction mixture gave a yellow solid which was recrystallized from light petroleum as yellow needles.

The infra-red spectrum of these needles shows a strong band at $1650cm^{-1}$ and also many bands between 840 and $680cm^{-1}$, indicative of carbon halogen bonds.

The ^1H NMR spectrum is very similar to that of the methyl ketone (167). The differences from the spectrum of the previous compound are that there is no methyl singlet and the two doublets are at slightly lower field (0.4ppm lower). The NMR and IR data points to the trichloroacetyl pyrrolizine (167).



(167)


δ ppm
8
7
6
5
4
3
2
N
C=O
CCl3
(167)

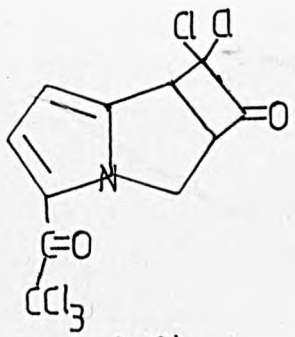
The more electron withdrawing trichloroacetyl group would cause the protons at positions 6 and 7 to appear more downfield than in the methyl ketone (165). This structure is substantiated by the infra-red spectrum where the peaks between 840 and 680cm^{-1} are typical of halogenated compounds. The mass spectrum and analysis confirm this structure.

This ketone (167) may have been the precursor in the previous reaction for the ketone (165). Zinc in the presence of a protic solvent will reductively dechlorinate chlorinated compounds[131-133] and this may have occurred in this case. It seems reasonable to suppose therefore, that both of these ketones arose by electrophilic attack of trichloroacetyl chloride on 3H-pyrrolizine. It is known that pyrroles will react easily with trichloroacetyl chloride in the presence of weak bases in this way[134,135] to produce 2-trichloroacetylpyrroles. This reaction competes successfully with the generation of dichloroketene.

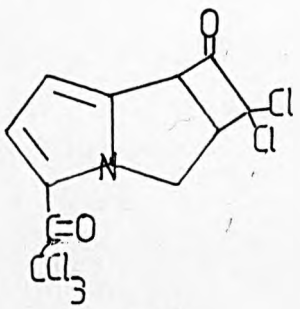
Both of the previous methods for the generation of dichloroketene have emphasised the mildness of the conditions used, Jeffs[136] has developed a method for generating dichloroketene which uses more vigorous conditions. In this method the trichloroacetyl chloride solution is added to the reaction mixture fast enough to cause boiling of the solvent (ether).

This method was followed to give, after work up a brown oil which separated by P.L.C. into two compounds. One of the products was 5-trichloroacetyl-3H-pyrrolizine (167), the other was new. The new compound was recrystallized from benzene/light petroleum to give yellow needles. The infra-red spectrum shows strong peaks at 1680,

1815 and between 800 and 600cm^{-1} indicating both an α,β-unsaturated ketone and an α,α-dichloro-cyclobutanone structure. The ^{1}H NMR spectrum shows a pair of doublets at 7.4 and 6.5ppm coupled by 4Hz, there is a multiplet at 4.8ppm of 2 protons and one at 4.3ppm of 2 protons. The mass spectrum supports a diadduct structure and the analysis agrees with $C_{11}H_6NO_2Cl_5$. The two possible structures are therefore (168) and (169).

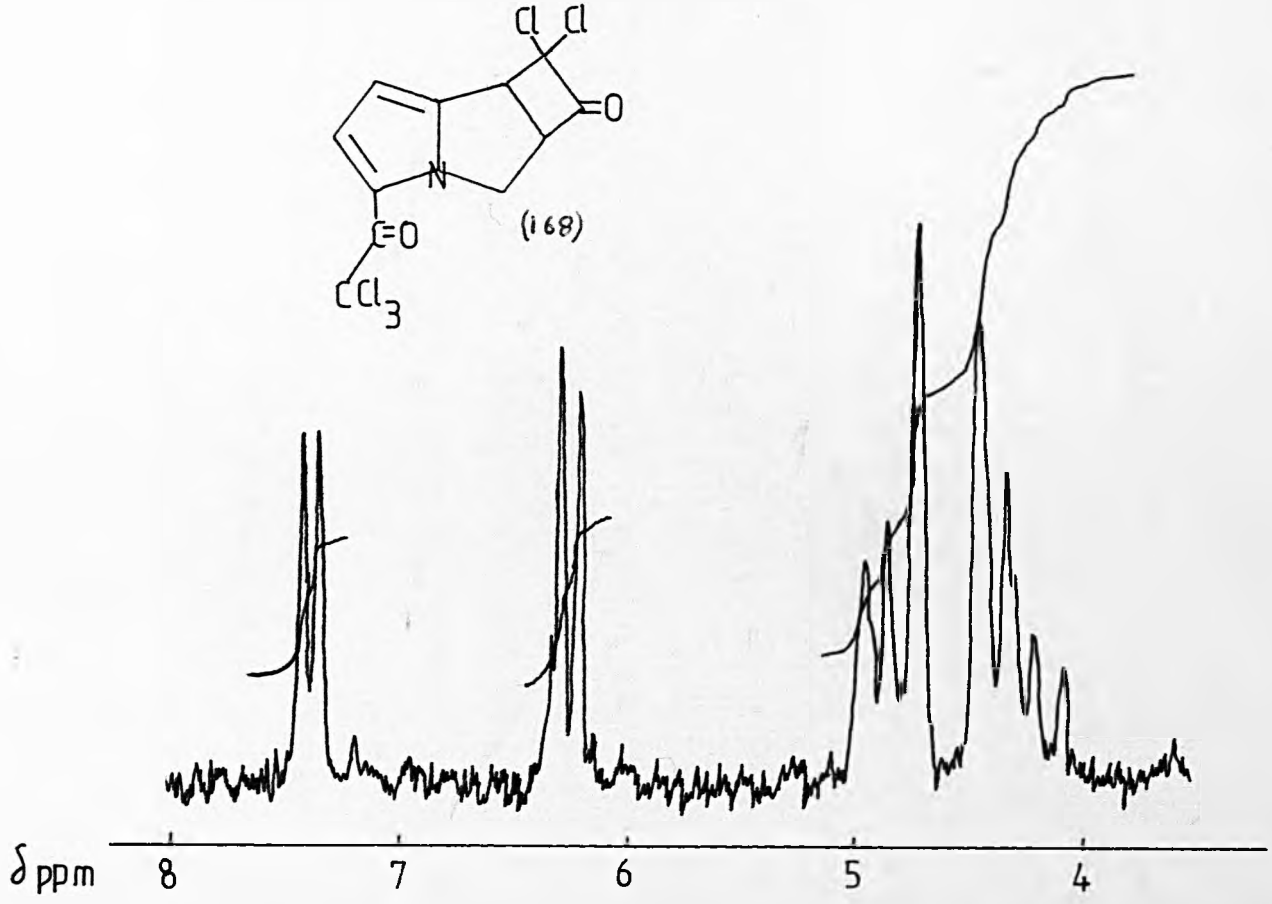


(168)



(169)

The structure (168) is the one that would be expected. In the ^{1}H NMR spectrum the multiplet at 4.8ppm may be seen as a one proton doublet (J=4Hz) and a one proton broad singlet, whereas it is not so easy to resolve the multiplet at 4.3ppm. If this is the case then the doublet would correspond to proton 1 (on the original 3H-pyrrolizine skeleton)and the broad singlet for proton 2, the methylene group would be expected to exhibit complex couplings. As the most simple signal, the doublet, is the furthest downfield then this must be adjacent the most deshielding group, the dichloromethylene, rather than the carbonyl. Therefore structure (168), 8-trichloroacetyl-3,3-dichloro-7-azatricyclo[5.3.0.0^{2,5}]deca-1(10),3-dien-4-one is


Cl Cl
O
N
C=O
CCl3
(168)
δ ppm
8
7
6
5
4

indicated.

The diadduct (168) may have originated from either the trichloroacetyl ketone (167) with subsequent cycloaddition, or alternatively the cyclo adduct may have been formed first and undergone electrophilic substitution. To decide which of these was the case the trichloroacetyl ketone (167) was reacted with dichloroketene under the conditions of Hassner and Krepski and also under the conditions which resulted in the formation of the diadduct (168). In both reactions only starting ketone was recovered. This shows that the cycloaddition occurred prior to electrophilic attack. Also it appears the presence of the trichloroacetyl group reduces the electron density in the 1,2 double bond such that it is no longer attacked by the electrophilic dichloroketene.

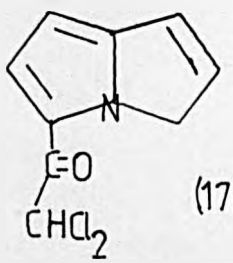
The reactions of 5-trichloroacetyl-3H-pyrrolizine with DMAD were also investigated. The photochemical reactions (irradiation through a pyrex sleeve, with and without acetophenone) gave only polymeric deposition and starting materials. The thermal reaction (boiling benzene for 40 hours) also gave only starting materials. Therefore, as with dichloroketene, the presence of the 5-trichloroacetyl substituent has deactivated the 1,2 bond of the pyrrolizine to attack by the electrophilic acetylene.

The tricyclic compound (168) was treated with base (lithium tetramethylpiperidide) in an attempt to produce a pyrrolo[1,2-a]azepinone derivative as in scheme 34. The products of the reaction were separated by P.L.C. to give a number of compounds, none of which were identifiable. Therefore the ring opening reaction has not occurred, or if it has the product is unstable. It may be that the

base has attacked the trichloroacetyl group which would be susceptible to nucleophilic attack, also adducts of dichloroketene and alkenes are known to undergo ring opening of the cyclobutanone ring with amines to give amides. However lithium tetramethylpiperidide is a hindered base and should have low nucleophilicity.

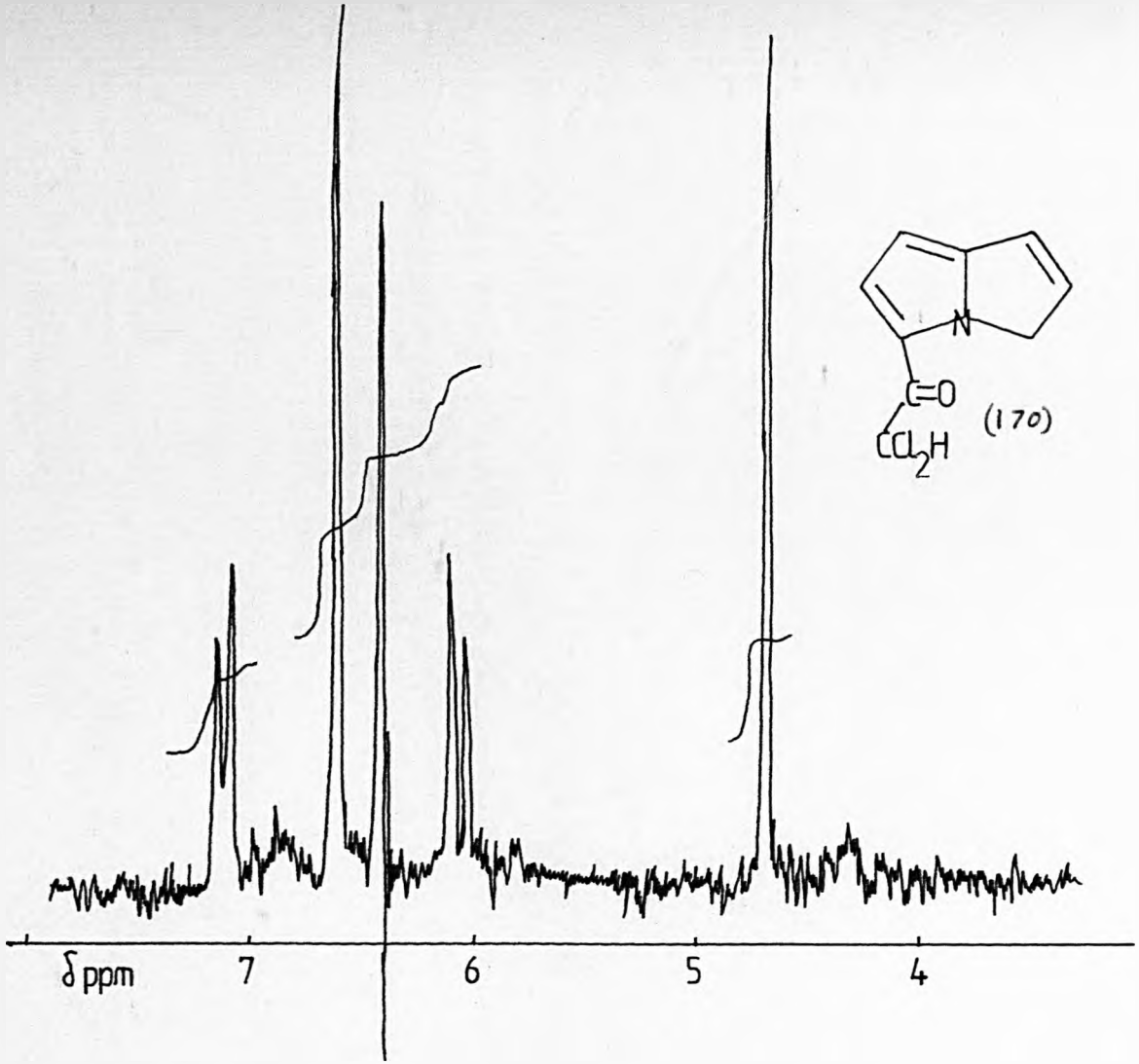
The other route by which dichloroketene may be prepared is by dehydrochlorination of dichloroacetyl chloride with triethylamine. This method has not been used much in recent years but the method of Ghosez[128] gives good yields.

When this method was applied to the reaction with 3H-pyrrolizine a yellow solid was isolated which was recrystallized from light petroleum. The ^{1}H NMR spectrum of the solid leaves no doubt that this is the dichloroacetylpyrrolizine (170).



(170)

There is a pair of doublets at 7.1 and 6.1ppm coupled by 3Hz and a broad singlet at 6.6ppm integrating for two protons. The dichloromethyl proton appears as a sharp singlet at 6.4ppm and the methylene protons appear at 4.7ppm. The infra-red spectrum supports this structure (1650cm^{-1}) as do the analysis figures and mass



(170)

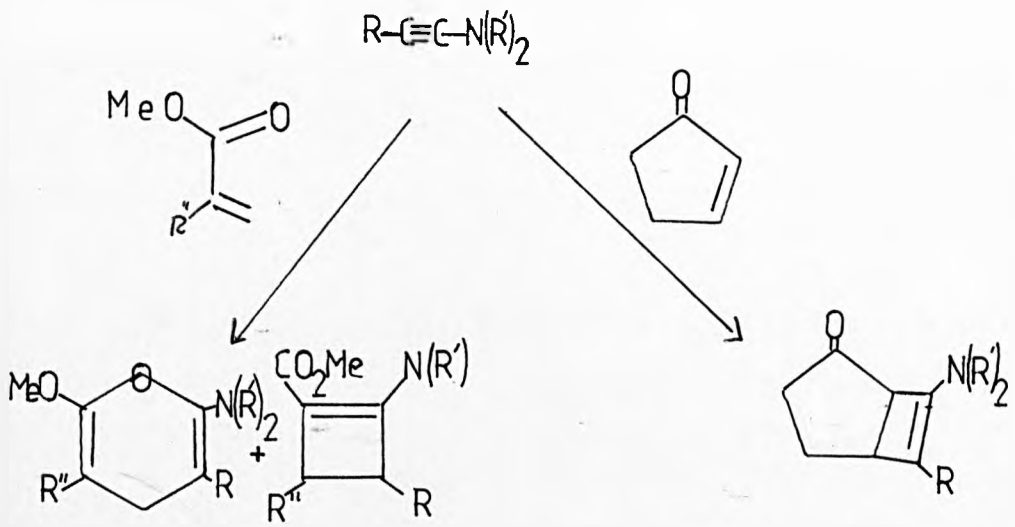
spectrum.

It appears that again electrophilic attack by the acetyl chloride has occurred faster than generation and reaction of dichloroketene. In this case the conditions favour electrophilic substitution as the pyrrolizine and acetyl chloride were mixed prior to addition of base. The experiment was repeated but with addition of dichloroacetyl chloride to base and pyrrolizine, but dichloroacetylpyrrolizine (170) was still formed, although in slightly lower yield (83 against 92%). This experiment was repeated a number of times with modifications aimed at maximising the production of dichloroketene and minimising the amount of substitution product formed. The most extreme experiment consisted of adding the chloride to diethylamine solution and after two minutes adding the pyrrolizine solution. In this extreme case there was considerable tar formation (presumably due to dichloroketene polymerization) but also a low yield of dichloroacetylpyrrolizine (170).

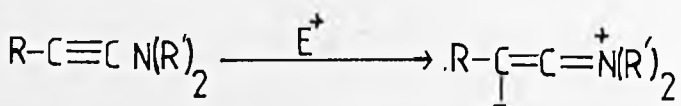
b)With an ynamine

Ynamines are nucleophilic acetylenes which have found much use in synthesis[137]. They undergo a wide variety of reactions with electrophiles, for example acylation with acid chlorides to give chloro-enaminoketones or alkylation by alkyl halides in complex reactions giving a variety of products. They also easily undergo cycloaddition reactions with electron deficient alkenes, some examples are shown in scheme 59[138,139].

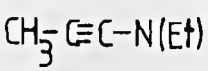
Scheme 59



Both [2+2] and [2+4] products are formed in certain cases. In all reactions of electrophiles with ynamines the intermediate (171) is thought to be formed.



(171)



(172)

An ynamine which is readily available is N,N-diethylprop-1-yne (172). Both the thermal (boiling in acetonitrile) and photochemical reactions of this ynamine with 3H-pyrrolizine were attempted. No identifiable products were given by either reaction. Both reactions

were characterized by long reaction times, monitoring by T.L.C., 55 hours irradiation and 39 hours reflux. This shows the extreme reluctance of the nucleophilic ynamine to react with the electron rich heterocycle. The reaction products may have been due to decompositions of the reactants.

Work towards 5-subsituted pyrrolizines

The attempt to react 3H-pyrrolizine with dichloroketene failed due to the nucleophilicity of the 5 position of 3H-pyrrolizine, and the consequent tendency of 3H-pyrrolizine to undergo electrophilic substitution at this position, so producing products which are inert to electrophilic cycloaddition or are unsuitable substrates for further reactions. The same problem dogged the attempts of Johnson and Jones[28,122,124] to produce a [2+2] adduct of DMAD and 3H-pyrrolizine as a precursor to pyrrolo[1,2-a]azepines. Their adducts of DMAD, with only the exception of certain cases (162), were the product of electrophilic attack of DMAD on position 5 of the pyrrolizine. Their attempts to solve this problem by synthesising 5-methyl-3H-pyrrolizine were only partially successful[28] due to the thermodynamic instability of 3H-pyrrolizines with mildly electron donating groups on positions 5,6 and 7 compared with their isomers with alkyl groups on 3,2 and 1 under the basic conditions used in their synthesis. So a synthesis of a 5-substituted-3H-pyrrolizine would be valuable.

The 5-acetylpyrrolizines already prepared in this work (165),(170) and (167) could provide a route to 5-alkylpyrrolizines. The best candidate of these would seem to be 5-acetyl-3H-pyrrolizine itself. This was prepared in low yield in a reaction of 3H-pyrrolizine with trichloroacetyl chloride in the presence of activated zinc. A reaction designed to prepare this ketone may give better yields.

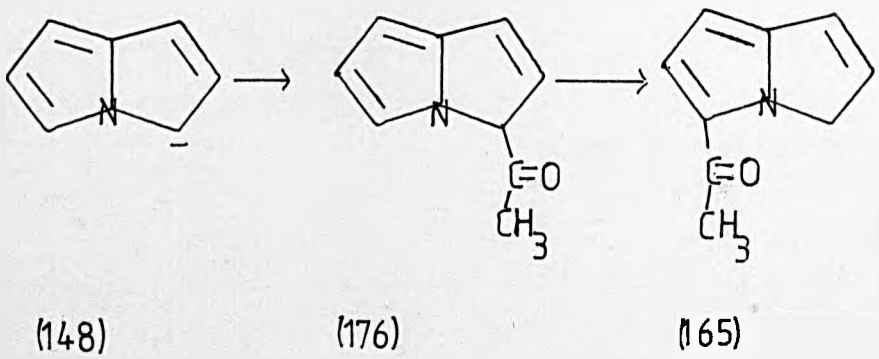
Pyrrole can be acylated in the two position by a variety of

methods; the Vilsmeier reaction with phosphorus oxychloride and N,N-dimethylacetamide [140,141]; acylation occurs with a variety of acyl chlorides, with or without Lewis acid catalysts[142-146]; acylation also occurs with acetic anhydride, however both 1 and 2 acylation occurs in varying proportions. [148]

The acylation of 3H-pyrrolizine with acetyl chloride was attempted. Reaction without a Lewis acid gave only starting materials, both with and without a base. Reaction in the presence of $ZnCl_2$ gave a tar-like gum in which no acetylpyrrolizine could be detected. These results seem to indicate that the reactivity of 3H-pyrrolizine to electrophiles is somewhat less than that of pyrrole.

The 4-azapentalenyl anion (148) should be reactive to electrophiles and so would be attacked by acetyl chloride (scheme 60).

Scheme 60



(148) (176) (165)

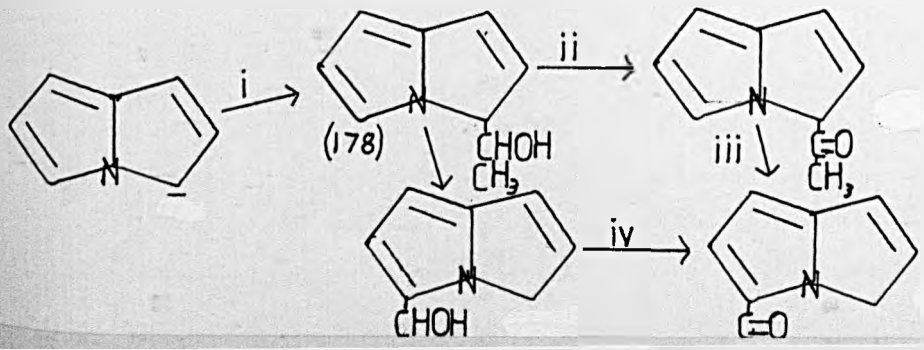
The kinetic product (176) should, under the basic conditions, isomerise to 5-acetylpyrrolizine (165) as pyrrolizines substituted in the 5,6, or 7 positions by electron withdrawing substituents seem more thermodynamically stable under basic conditions than their isomers substituted at 3,2 or 1.

The azapentalenyl anion was generated by the method of Okamura and Katz[121], treatment of this with acetyl chloride gave a gum from which only a small amount (7%) of the acetylpyrrolizine was isolated. The product was the 5 substituted isomer (165) which must have arisen by the mechanism discussed above. This reaction did not give reproducible yields. Attempts to increase the yield by use of a non-nucleophilic base failed.

The poor yields of product in this reaction may be due to the reactivity of the product under the basic conditions in which it can undergo enolisation and subsequent reaction or attack at the carbonyl group. This problem may be overcome if a compound at a lower oxidation level were to be prepared and then oxidised. Attempts were made to prepare the alcohol (178) which could then be oxidised to the ketone (176) and then equilibrated to (165) or isomerisation may occur during the condensation or oxidation reactions.

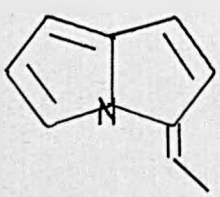
Scheme 61 .

i)CH_3CHO ii)[O] iii)base iv)[O]

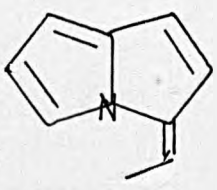


The reaction of acetaldehyde with the 4-azapentalenyl anion gave an unstable yellow oil which could not be isolated by the usual methods of purification (column or preparative layer chromatography, distillation). The oil was however identified by its ^1H NMR spectrum as 1-(3H-pyrrolizin-3-yl)-ethanol (178). The multiplet at 6.7ppm was attributed to proton 5 and the two proton multiplet at 5.9ppm to protons 6 and 7. The 1 proton appears at 6.4ppm as a doublet (J=3Hz) coupled to proton 2 at 5.8ppm which too appears as a doublet when the peak at 4.3ppm (proton 3) is irradiated. The methine proton appears as a multiplet at 3.5ppm, the hydroxyl proton at 2.8ppm (exchanges with D_2O) and the methyl protons at 1.1ppm.

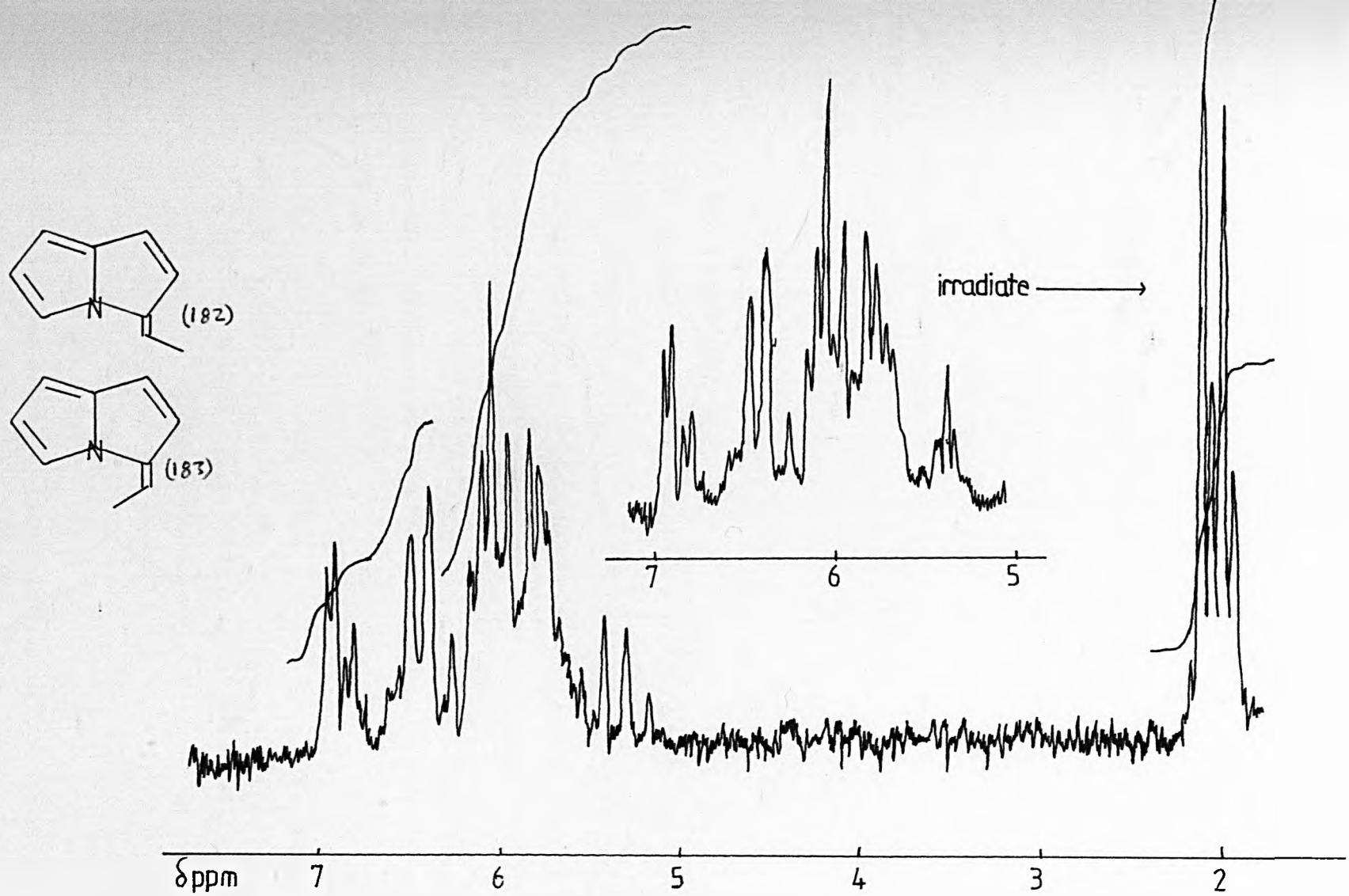
When this material was chromatographed on Florasil a new product was eluted with light petroleum, before the alcohol. The molecular ion of the new material in the mass spectrum shows it to be derived from the alcohol with loss of water. The infra-red spectrum confirmed the loss of the hydroxyl group. The ^1H NMR spectrum showed that the material was a mixture of the isomeric E-3-ethylidene-3H-pyrrolizine (182) and Z-3-ethylidene-3H-pyrrolizine (183) in the Z/E ratio 9/4.



(182)



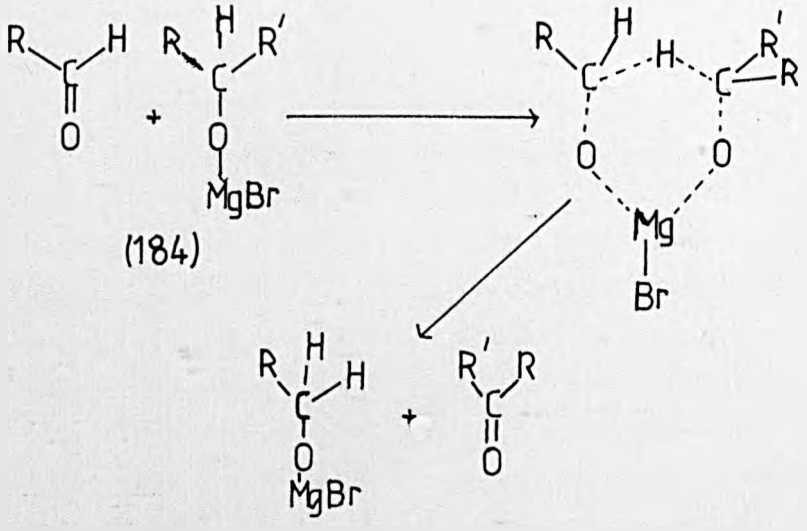
(183)


(182)
(183)
irradiate
7
6
5
δppm
7
6
5
4
3
2

The pair of doublets at 6.9 and 6.8ppm (J=3Hz) (ratio 9/4) are the 5 protons on the Z and E isomers respectively. The 1,2,6 and 7 protons all occur in a complex multiplet between 6.4 and 5.8ppm. There is a quartet at 5.8ppm and a pair of doublets at 2.0 and 1.9ppm coupled 7Hz which are the ethylidene protons, the methyl groups resonating with different chemical shifts, the quartet is broadened as it is due to both isomers. The U.V. of the mixture is as expected for such an azafulvene stucture (cf. Okamura and Katz[121], Johnson and Jones[122]) It proved impossible to separate the mixture of isomers by the usual chromatagraphic methods without decomposition and the mixture could not be crystallized.

It has been noted [149,150] that in Grignard reactions an excess of carbonyl compound can cause production of a ketone rather than a alcohol by a mechanism similar to the Oppen auer oxidation. The mechanism is thought[149] to proceed via a 6 membered transition state. The initially formed product, the halo-magnesium alkoxide (184) is oxidised by excess carbonyl compound to give a ketone and the alkoxide of the now reduced carbonyl compound.

Scheme 62



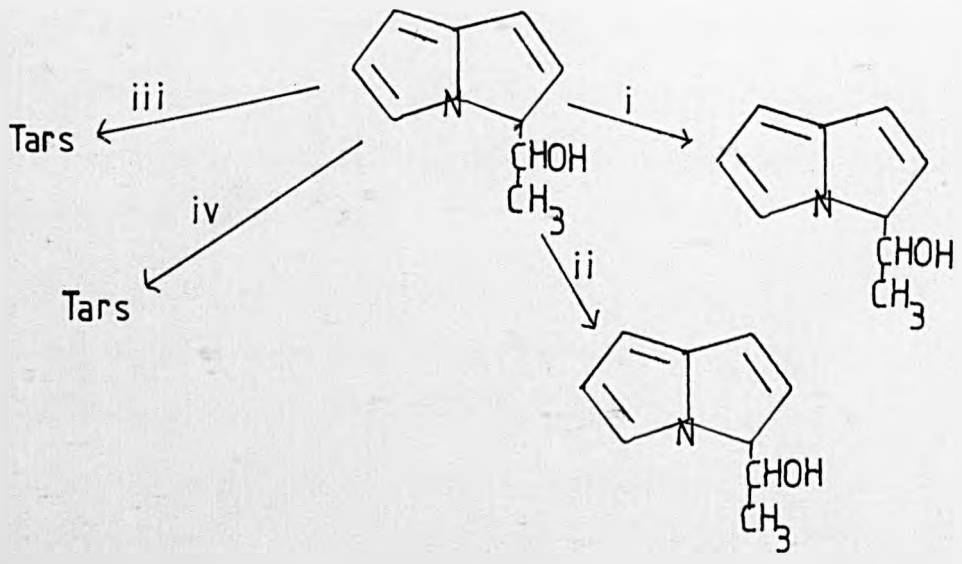
Gilman and Swiss[151] report, with few details, the reaction of a solution of an alkyl lithium compound with magnesium iodide to give what they assume is the alkylmagnesium halide and lithium iodide. Such a reaction was attempted with the 4-azapentalenyl anion and acetaldehyde in two ways. The anion was treated with magnesium iodide.diethyl ether complex followed by excess acetaldehyde and in the second attempt the 4-azapentalenyl anion was treated with acetaldehyde followed by magnesium bromide and more acetaldehyde. In both cases the only isolated product was the alcohol (178) in yields comparable with those first obtained.

Attention was then turned to oxidation of the crude alcohol (178). A number of reagents and reagent systems have recently been developed which achieve oxidation of secondary alcohols to ketones in good yields under mild conditions. Four of these methods were tried as shown in scheme 63.

Scheme 63

i)$Al_2O_3/KMnO_4$ ii)$KMnO_4/CuSO_4$ iii)$(CH_3)_2SO/(COCl)_2$ complex

iv)$C_5H_6N^+ CrO_3Cl^-$



The reactions using heterogenous oxidants $Al_2O_3/KMnO_4$[154] and $KMnO_4/CuSO_4$[155] gave only starting materials after extended reaction times.The reaction with buffered pyridinium chlorochromate[156] and with the DMSO/oxalyl chloride system[157,158] (at $^{-}60^{o}C$ to suppress the Pummerer oxidation) gave only tars from which no identifiable compound could be isolated.

The direct preparation of 5-acetyl-3H-pyrrolizine (165) does not seem to be easily accomplished but the trichloroacetyl and dichloroacetyl pyrrolizines can provide another route to acetyl pyrrolizine.

These chloroketones were prepared as unwanted products when trying to react 3H-pyrrolizine with dichloroketene. A simpler preparation of these ketones by reaction of the appropriate acid chloride with 3H-pyrrolizine in the presence of potassium carbonate to scavenge for acid produced was developed. Stirring at $0^{o}C$ for 5 minutes was sufficient to prepare the ketones in good yield.

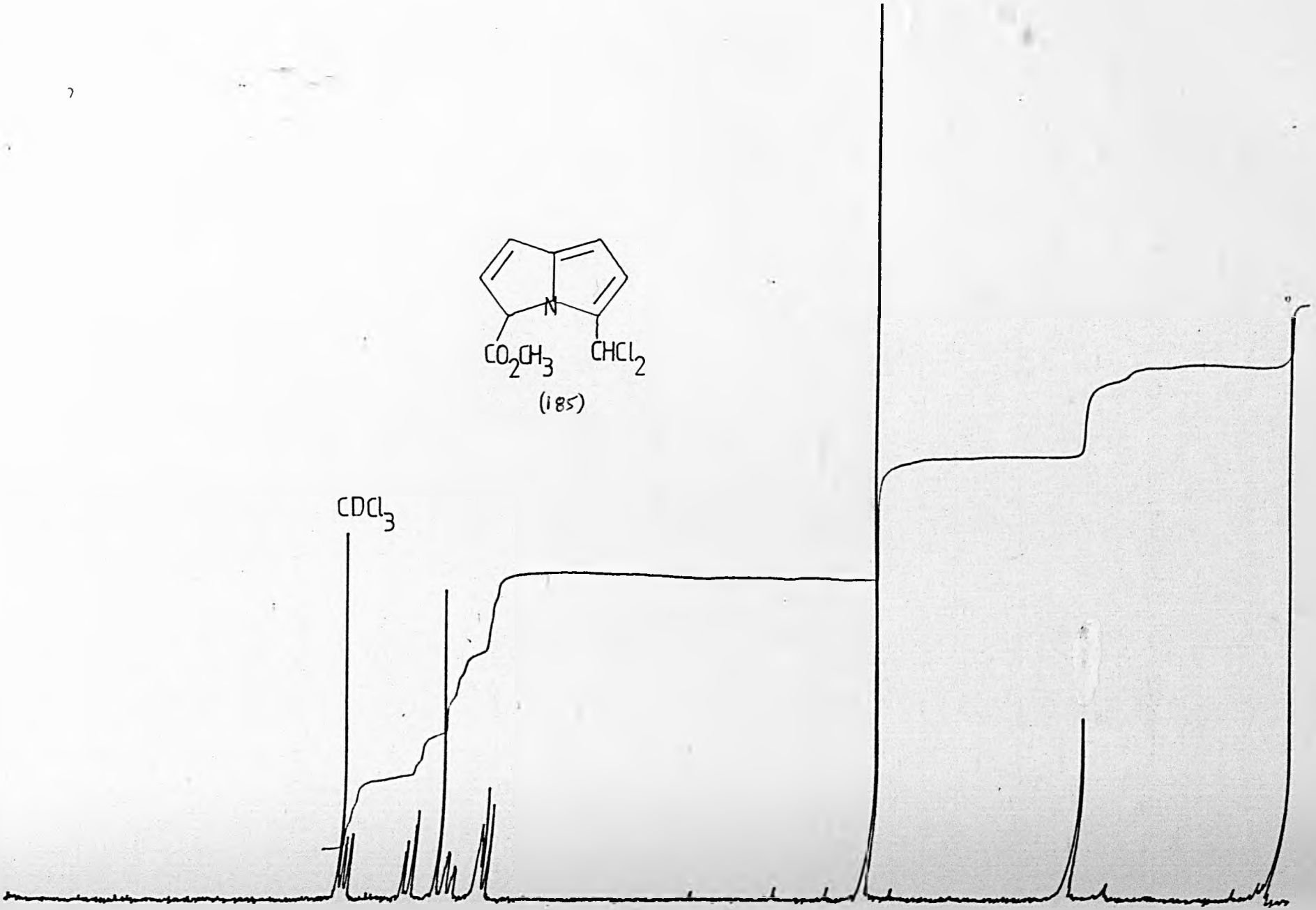
Reaction of 5-trichloroacetyl-3H-pyrrolizine with zinc dust[132] in acetic acid gave 5-acetyl-3H-pyrrolizine in 27% yield. Further reduction using zinc/mercury amalgam and conc. hydrochloric acid with the trichloro ketone gave only tars. The hydride reduction of 5-acetyl-3H-pyrrolizine with lithium aluminiumhydride gave unfortunatly only a small amount of material which was not the expected ethyl pyrrolizine or an alcohol.

Therefore, although the three 5-keto pyrrolizines have been prepared attempts to prepare alkyl pyrrolizines from these have failed. However 5-trichloroacetyl-3H-pyrrolizine bears a synthetically useful group in the trichloroacetyl moiety.

Trichloroacetylpyrroles have been converted to the corresponding acids[134] and esters[135].

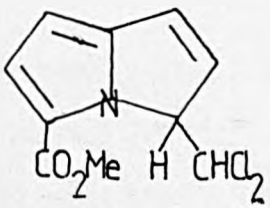
Reaction of 5-trichloromethyl-3H-pyrrolizine with 2N NaOH[134] gave only tarrish products and nothing which could be identified as a 3H-pyrrolizinyl carboxylic acid. The same result was seen when the trichloroacetyl pyrrolizine was treated with potassium carbonate in a 1:1 mixture of THF and water.

The published procedures for converting trichloroacetyl pyrroles into the corresponding methyl esters involves reaction with base in methanol[135]. When 5-trichloroacetyl-3H-pyrrolizine was treated with sodium methoxide in methanol only tars resulted. However on warming in methanol with potassium carbonate a yellow/red oil was isolated. This oil was separated into two components by P.L.C. The faster running component was recrystallized from hexane to give yellow crystals. The infra-red spectrum shows strong bands at 1765, 1220 and 1100cm^{-1} indicating the ester function, and also bands at 805, 785,710 and 690cm^{-1} indicating carbon-halogen bonds. The mass spectrum shows the presence of two chlorine atoms in the molecule and the analysis figures agree with a formula of $C_{10}H_9NO_2Cl_2$ Therefore the ester group has been formed but there has been further reaction . The ^1H NMR spectrum (100MHz) shows a singlet (3H) at 3.17ppm, as expectd for a methyl ester. All the other proton resonances are between 6.0 and 7.5ppm. There are two pairs of doublets, one with coupling of 4.01Hz at 7.20ppm (subsplitting 0.70Hz)and at 6.13ppm (no subsplitting), the other pair of doublets have a coupling of 5.98Hz and occur at 6.72ppm (subsplitting 0.98Hz) and at 6.38ppm (subsplitting 0.70 and 1.59Hz). The other peaks are a sharp singlet

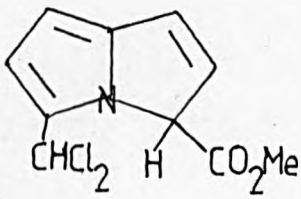


(185)

at 6.49ppm and a multiplet at 6.18ppm. By comparison with the spectrum of 3H-pyrrolizine it seems that this is a 3 and 5 disubstituted pyrrolizine. The pair of doublets with coupling of 4.01Hz are those at positions 6 and 7 (J=3.5Hz in pyrrolizine) and the pair with coupling of 5.98Hz are those at 1 and 2 (J=6.2Hz in pyrrolizine). One of the substituents is the carbomethoxy group, this leaves $-CHCl_2$ from the molecular formula and the peak at 6.49ppm has the correct chemical shift for a dichloromethyl proton attached to a mildly deshielding nucleus. There are, therefore two possible structures (185) and (186).



(185)



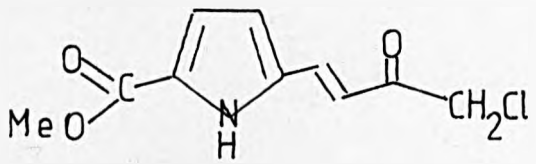
(186)

That structure (186) is correct is shown by the absolute lack of coupling of the dichloromethyl proton, which is as expected for structure (186) but not (185). The ^{13}C NMR spectrum agrees with this stucture, the carbonyl quaternary carbon appearing at 174.9ppm which is typical for aliphatic esters[159] (cf. aromatic esters at around 165ppm). The complete ^{1}H NMR couplings are presented in the experimental section.

The second compound isolated from this reaction was slower running on P.L.C. and recrystallized to give a white solid. The infra-red spectrum of this compound showed strong peaks at 1705, 1665, 1655, 1290 and 1210cm^{-1} indicating an ester group, probably bonded to some unsaturation, and an α,β-unsaturated ketone. The analysis and mass spectrum indicate a molecular formula of $C_{10}H_{10}NO_3Cl$.

The ^1H NMR spectrum shows a three proton singlet at 3.74ppm which would correspond to the methyl ester group, a two proton sharp singlet at 4.71ppm, a pair of doublets at 6.62 and 7.63ppm, each one proton coupled by 16.1Hz, a pair of one proton multiplets at 6.76 and 7.17ppm and a broad one proton peak at 11.39ppm. The broad peak is exchangable with D_2O, simplifying the the multiplets at 6.76 and 7.17ppm to sharp doublets (J=3.9Hz). The doublets coupled by 16.1Hz show too large a coupling constant to be part of a pyrrolizine and are more suitable as an E alkene[160] The exchangable proton is not an hydroxyl (IR) but has the correct chemical shift for a pyrrole NH proton where the pyrrole is substituted with electron withdrawing groups.

The multiplet/doublet protons are therefore on the pyrrole ring and their coupling constant (3.9Hz) indicates them to be on positions 3 and 4. The compound must therefore be a pyrrole substituted on positions 2 and 5 with a carbomethoxy group and an α,β-unsaturated ketone with the alkene protons isolated. All the molecular formula but CH_2Cl is now accounted for. This must be responsible for the sharp singlet at 4.71ppm, and so this group must be isolated. The chemical shift of these protons indicate they must be adjacent at least one electron withdrawing group. The only structure with all these features is the pyrrole (187)

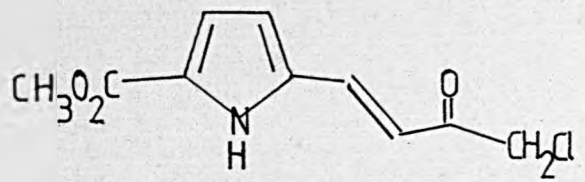


(187)

The ^{13}C NMR spectrum supports this (carbonyl carbons at 181.7ppm, an α,β-unsaturated ketone and at 167.0ppm, aryl methyl ester).

These two compounds are rather surprising products from a reaction which, for pyrrole, gives good yields of esters with no reported rearrangement.

In an attempt to gain more information on the mechanism of the reaction some of the pyrrolizine (186) was submitted again to the reaction condidtions The work up gave material whose ^1H NMR spectrum showed it to be mainly the pyrrole (187). This seems to indicate that

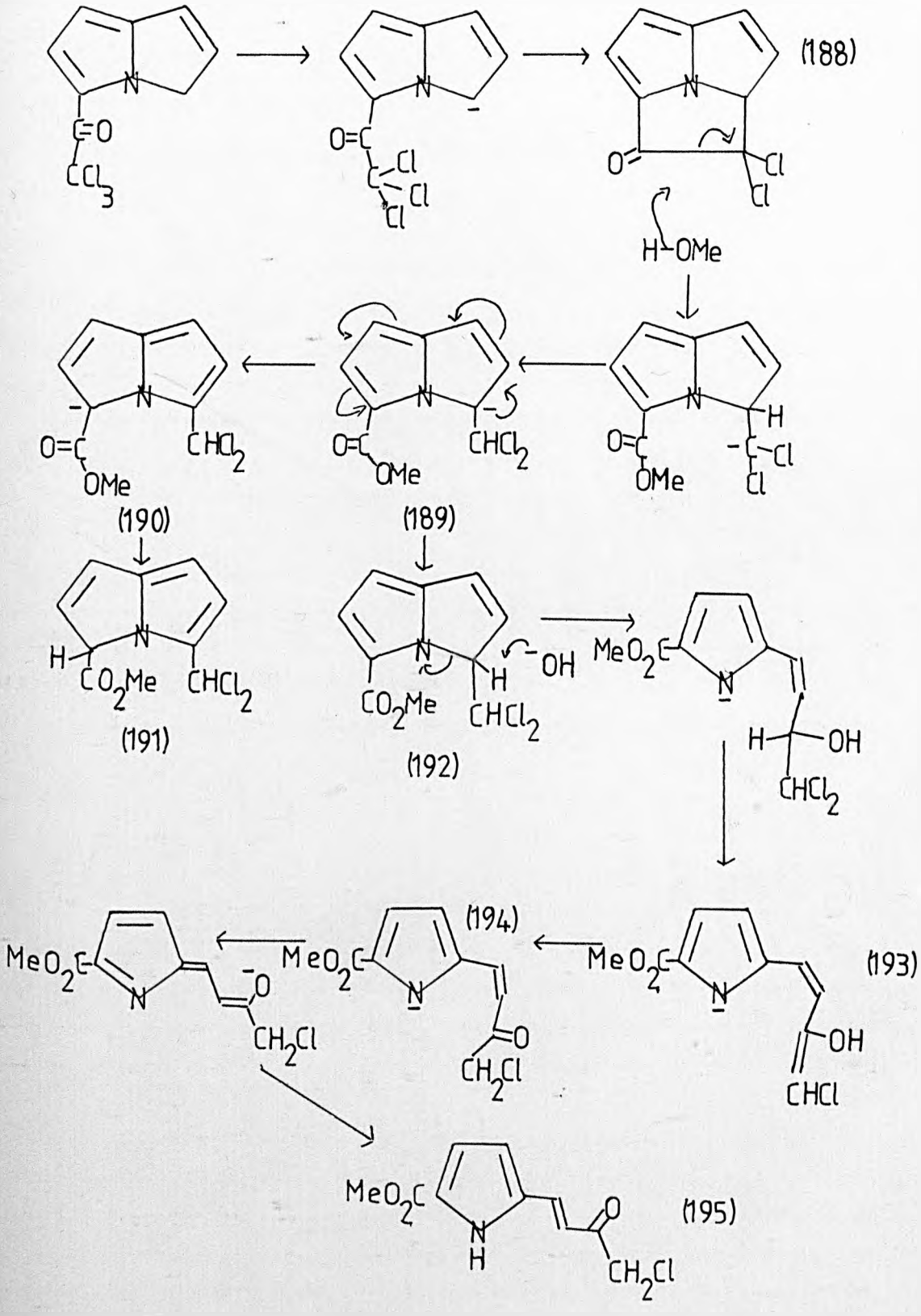


(187)

the pyrrolizine (186) is a precursor of the pyrrole (187) in the reaction mechanism.

One mechanism which may explain the course of the reaction is shown in scheme 64.

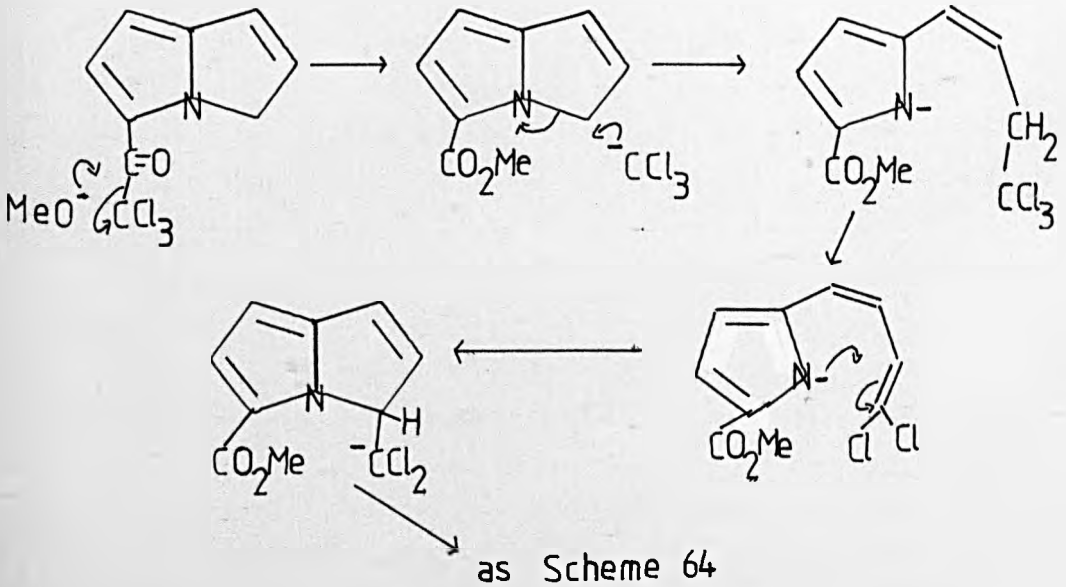
Scheme 64



The first step is ionisation of the pyrrolizine in the basic conditions (3H-pyrrolizine has a pKa value reported of 29[121] and it is reasonable to expect the trichloroacetyl substituent to reduce this). The anion cyclises with elimination of chloride to give the tricyclic intermediate (188). This could then be ring opened by methoxide or methanol followed by a hydrogen shift to give the anion (189). This is in equilibrium with the anion (190) which can protonate to give the first product . The anion (189) can also protonate to give the pyrrolizine (192). This may be attacked by hydroxide which could lead to ring opening and loss of HCl to give an enol (193) which can rearrange to the ketone (194). The enolate can be formed from this, which on protonation gives the pyrrole with the E double bond.

Harbuck and Rapoport[135] propose that the mechanism of the conversion of trichloroacetyl pyrroles to esters occurs by displacement of trichloromethyl anion by methoxide. It is possible to write a mechanism involving such a step as in scheme 65.

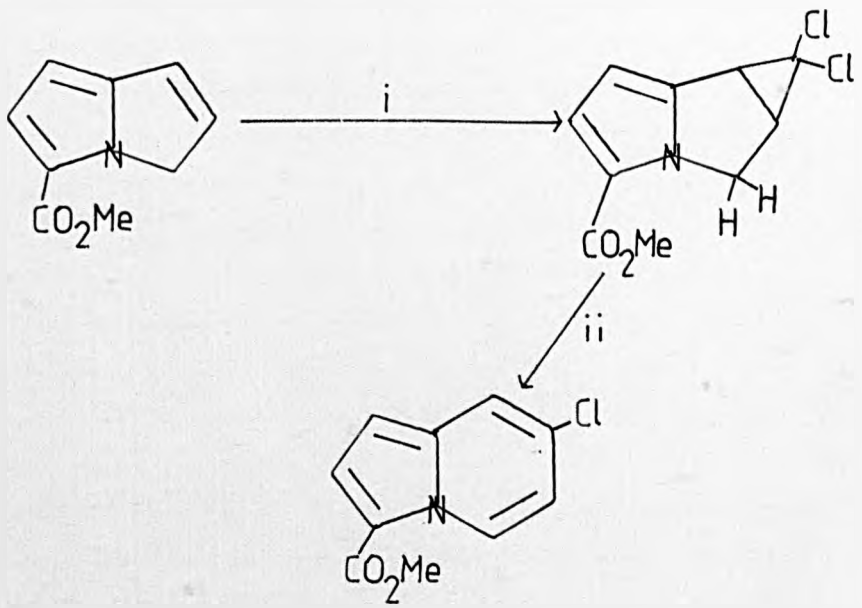
Scheme 65



The disadvantages with this mechanism are that there is a ring opening followed by a ring closure step (although the exocylic double bond will probably stay Z and thus the geometry for ring closure will be favourable), and that the trichloromethyl anion is involved. The trichloromethyl anion may lose a chloride anion to form dichlorocarbene (this is the rate determining step in dichlorocarbene formation[161]). If dichlorocarbene were to be formed then it would be likely to undergo reactions typical of dichlorocarbene. Although a Reimer-Tieman mechanism may be inhibited as the pyrrole is disubstituted, the carbene may be expected to attack the 1,2 double bond as in scheme 66 to produce, under basic conditions, an indolizine.

Scheme 66

i):CCl_2 ii)base



However Harbuck and Rapoport [135] do not report any products which could be derived from a carbene reaction, even though they have used a variety of dipyrrylmethanes and unsaturated alcohols.

The evidence at present available does not permit any mechanism to be postulated with confidence.

Simple reactions of 3H-pyrrolizine

There have been very few simple reactions of 3H-pyrrolizine. In order to try to extend knowledge of 3H-pyrrolizine chemistry a bromination and a nitration reaction were attempted.

Pyrrole can be brominated with bromine in neutral or slightly acidic conditions [162], those pyrroles having electron withdrawing substituents giving the best results. Accordingly a solution of 3H-pyrrolizine was treated with a bromine solution in the presence of potassium carbonate. Work up gave a yellow solution, however when the solvent was removed only black tars resulted.

Nitration was attempted with a mixture of fuming nitric acid in acetic anhydride, a mixture which has proved successful with pyrroles[163]. The crude product contained a number of components, none of which could be identified.

Preparation of 3H-pyrrolizine.

3H-pyrrolizine was prepared by the method of Schweizer and Light in 56% yield.

Attempted reaction of 3H-pyrrolizine with dichloroketene by the method of Brady and Bak[127].

A mixture of 3H-pyrrolizine (1.2g, 0.011moles) and activated zinc (2.13g) in anhydrous diethylether (100ml) was stirred under reflux whilst trichloroacetyl chloride (1.92g, 0.011moles) was added over a period of 4 hours. THe mixture was stirred under reflux for a further 18 hours.

The mixture was allowed to cool and was filtered. The solvent was removed from the filtrate under reduced pressure at room temperature to give a red oil (4.5g). This oil was purified by chromatography on alumina (120g, activity IV), elution with a benzene/light petroleum mixture (20/80) gave yellow crystals identified as the ketone (165)(0.15g, 9% yield). Elution with solvents of increasing polarity to ethylacetate gave some material (0.48g) which was unidentified.

5-acetyl-3H-pyrrolizine (165).

Mp. 48-49°C (light petroleum)

IR (ν max. KBr disc) 1640cm^{-1}

^{1}H NMR ($CDCl_3$, TMS internal standard, 100MHz)

6.88ppm	1H	d	(J=4.03Hz)
6.60ppm	2H	m*	
5.85ppm	1H	d	(J=4.03Hz)
4.70ppm	2H	bs	
2.30ppm	3H	s	

* Irradiation at 4.70ppm simplifies this peak to a pair of doublets (J=4.00Hz).

Analysis:

C_9H_9NO requires C=73.45, H=6.16, N=9.51%.

obtained C=73.00, H=6.13, N=9.30%.

Mass spectrum:

m/e= 147(70%,M^+), 132(75%), 105(28%), 104(100%), 77(51%), 51(28%), 43(36%).

Attempted reaction of 3H-pyrrolizine with dichloroketene by the method of Hassner[125].

To a stirred mixture of 3H-pyrrolizine (1.05g, 0.01moles) and activated zinc (1.95g, 0.03moles) in anhydrous diethyl ether (50ml) was added a solution of trichloroacetyl chloride (3.64g, 0.02moles) and phosphorus oxychloride (3.10g, 0.02moles) in ether (50ml) over 1 hour. When the addition was complete the mixture was refluxed for 20 hours.

The mixture was allowed to cool to room temperature and was filtered through a pad of Celite. The filtrate was washed successively with water (50ml), sodium carbonate solution (50ml of a 5% solution) and sodium chloride solution (50ml of a saturated solution). The organic solution was dried and the solvent removed under reduced pressure at room temperature to give a yellow solid.

This solid was recrystallized from light petroleum to give yellow needles (1.6g, 64% yield) of 5-trichloroacetyl-3H-pyrrolizine (167).

5-trichloroacetyl-3H-pyrrolizine (167)

Mp. 111-112°C yellow needles (light petroleum)

IR (ν max. KBr disc) 1650, 840, 810, 790, 770, 705, 680cm^{-1}.

^1H NMR ($CDCl_3$, TMS internal standard)

7.3ppm	1H	d	(J=4.0Hz)
6.6ppm	2H	m	
6.1ppm	1H	d	(J=4.0Hz)
4.7ppm	2H	m	

Analysis:

$C_9H_6NOCl_3$ requires C=43.15, H=2.41, N=5.59%

obtained C=43.24, H=2.42, N=5.82%.

Mass spectrum:

m/e= 253(4%), 251(13%), 249(13%), 188(10%) 186(17%) 151(12%), 133(20%), 132(100%), 104(40%), 78(25%), 77(24%), 51(34%), 39(15%).

UV (95% ethanol, λmax) 358nm ($\log_{10}\varepsilon$=3.57)

Attempted reaction of 3H-pyrrolizine with dichloroketene.

To a stirred mixture of 3H-pyrrolizine (1.05g, 0.01moles) and activated zinc (5g) in anhydrous diethyl ether (80ml) was added a solution of trichloroacetyl chloride (6.8ml, 0.06moles) in ether (60ml) at such a rate as to initially cause boiling and then to maintain a gentle reflux. The mixture was stirred overnight at room temperature.

The dark brown solution was filtered through Celite. The filtrate was washed with water (3 portions of (50ml) and sodium bicarbonate solution (50ml of a saturated solution). The organic solution was filtered through a short plug of alumina and the solvent removed under reduced pressure at room temperature to give a brown oil (2.4g).

This oil was purified by P.L.C., elution with an ethylacetate/toluene mixture (1/1) gave two bands. The faster running band (Rf. 0.97) was the trichloroacetylpyrrolizine (167)(1.4g, 56%yield). The slower running band (Rf. 0.77) was recrystallized from a benzene/light petroleum mixture (1/10) to give the diketone (168) as yellow needles (1.0g, 28% yield).

8-trichloroacetyl-3,3-dichloro-7-azatricyclo[5.3.0.$0^{2,5}$]deca-1(10),3-dien-4-one

Mp. 144-146°C

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.4ppm	1H	d (J=4Hz)
6.3ppm	1H	d (J=4Hz)
4.8ppm	2H	m
4.3ppm	2H	m

^{13}C NMR ($CDCl_3$, TMS internal standard)

Values in ppm, quarternary carbon indicated by (q)

194.1(q), 173.6(q), 141.8(q), 123.3, 120.6(q), 107.9, 95.5(q),86.8(q), 63.1, 51.2, 50.0.

IR (νmax, KBr disc) 1815, 1680cm^{-1}

Analysis:

$C_{11}H_6NO_2Cl_5$ requires C=36.51, H=1.66, N=3.87%

obtained C=36.93, H=1.79, N=4.11%.

Mass spectrum:

$^m/_e$= 365(1.4%), 363(2.1%), 361(1.3%), 359(1.4%), 251(8.3%), 249(8.3%), 242(7.0%), 188(6.9%), 186(6.9%), 132(100%), 104(9.7%), 55(30.5%).

UV (λmax, 95% ethanol) 321nm ($\log_{10}\varepsilon$ =3.08)

Attempted ring expansion of the diketone (168).

To a stirred and cooled (ice/salt bath) solution of the diketone (168) (0.12g, 0.3m.moles) was added under an atmosphere of nitrogen a freshly prepared solution of lithium tetramethylpiperidide (from 0.046g freshly distilled 2,2,6,6-tetramethylpiperidine and 0.25ml of a 1.5M solution of methyl lithium in ether) over 10 minutes. The mixture was stirred for a further hour.

A portion of water (5ml) was added to the mixture and the organic phase separated. The aqueous phase was treated with sodium bicarbonate solution (10ml of a 5% solution) and extracted with ether. The combined organic phases were dried and the solvent removed under reduced presssure at room temperature to give a brown oil (0.15g). The oil was purified by P.L.C., elution with toluene gave 8 bands, the only indentifiable component being tetramethylpiperidine.

Attempted reaction of 3H-pyrrolizine with dichloroketene by the method of Ghosez[128].

To a stirred, refluxing solution of 3H-pyrrolizine (1.05g, 0.01moles) and dichloroacetyl chloride (0.75g, 0.005moles) in anhydrous hexane (100ml) was added a solution of triethylamine (0,5g, 0.005moles, freshly distilled) in anhydrous hexane over 1 hour. The mixture was refluxed for a further 2 hours and stirred overnight.

Water (50ml) was added to the mixture, the organic phase was separated and washed successively with hydrochloric acid (100ml of a 5% solution), sodium bicarbonate solution (3 portions of 100ml of a 5% solution) and water (50ml). The organic solution was dried and the solvent removed under reduced pressure at 30°C or lower to give a yellow solid. This solid was recrystallized from light petroleum to give the dichloroketone (170) (1.0g, 92% on chloride)

5-dichloroacetyl-3H-pyrrolizine (170).

Mp. 87-88°C yellow needles (light petroleum)

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.1ppm	1H	d (J=3Hz)
6.6ppm	2H	bs
6.4ppm	1H	s
6.1ppm	1H	d (J=3Hz)
4.7ppm	2H	bs

IR (ν max) 1650, 1470 cm^{-1}

Analysis:

$C_9H_7NOCl_2$ requires C=50.00, H=3.24, N=6.48%

obtained C=49.86, H=3.17, N=6.45%.

Mass spectrum:

$m/_e$= 219(3.8%), 217(23.8%), 215(40.0%)
154(7.7%), 152(21.5%), 133(20.0%), 132(100%)
117(29.2%), 116(10.0%), 105(7.7%), 104(76.9%)
103(8.4%).

Attempted reactions between 3H-pyrrolizine and dichloroketene.

To a stirred solution of 3H-pyrrolizine (1.05g, 0.01moles) and triethylamine (0.5g, 0.005moles) in anhydrous hexane (100ml) was added a solution of dichloroacetylchloride (0.75g, 0.005moles) in hexane (100ml) over 1.75 hours with refluxing. The mixture was stirred at room temperature overnight.

The reaction mixture was poured onto water (50ml) and the organic phase was washed successively with dilute hydrochloric acid (100ml of a 5% solution) sodium bicarbonate solution (3 portions of 100ml of a 5% solution) and water (50ml). The organic solution was dried and solvent removed under reduced pressure at or below 30°C to give a yellow solid (0.9g) analysis of this solid shows it to be the dichloroketone (170) (83% yield on chloride)

This reaction was repeated with the following experimental modifications.

1) Without heating during addition. Only the ketone was isolated (40%)

2) Without heating and with one equivalent of pyrrolizine. The ketone in 52% yield was recovered.

3) Addition of acid chloride solution to triethylamine solution over 5 minutes, stirred for 2 minutes, pyrrolizine solution added and stirred a further 1 hour. The ketone in low yield (4%) and much tar formation resulted

4) As 3 with the modification that the acid chloride addition was over 2 minutes. The products were the ketone (5%) and much tar.

Photochemical reaction of 3H-pyrrolizine and N,N-diethylprop-1-yne.

A solution of 3H-pyrrolizine (0.26g, 2.5m.moles), N,N-diethylprop-1-yne (2.77g, 25m.moles) and acetophenone (0.5g) in anhydrous benzene was purged with a stream of dry nitrogen for 30 minutes. The solution was then irradiated by a UV lamp through a pyrex sleeve for 55 hours.

The solvent was removed to give a brown solid (2.2g). Analysis of this crude material by NMR showed that the methyl group of the acetylene is no longer present. Purification by P.L.C. of the solid gave 5 components, one unreacted 3H-pyrrolizine (Rf 0.76, 0.3g), one acetophenone (Rf 0.37, 0.4g) and the others unidentified.

Thermal reaction between 3H-pyrrolizine and N,N-diethylprop-1-yne.

A solution of 3H-pyrrolizine (0.53g, 5m.moles) and N,N-diethylprop-1-yne (0.55g, 5m.moles) in freshly distilled acetonitrile (50ml) was refluxed under a nitrogen atmosphere for 39 hours. The

The solvent was removed under reduced pressure to give a brown oil (1.1g). This oil was purified by column chromatography on alumina (30g, activity IV). Elution with light petroleum gave 3H-pyrrolizine (0.21g). Elution with a benzene/light petroleum mixture (1:1) gave a yellow oil (0.19g). Purification of this oil by P.L.C. (toluene) showed it to contain 4 components, the NMR spectrum of only one of these (Rf 0.50, 0.05g) showed absorptions due to unsaturated protons, however the spectrum lacked absorptions due to ethyl groups. Further elution from the column (benzene) gave an oil (0.39g). Purification of this oil showed it to contain 3 components, analysis of each of these by NMR spectroscopy showed that none of them was the desired adduct.

Attempted acetylation of 3H-pyrrolizine.

To a stirred and cooled (ice bath) mixture of 3H-pyrrolizine (1.05g, 0.01moles) and zinc chloride (1.4g) in anhydrous carbondisulphide (25ml) was added over one hour a solution of acetyl chloride (0.8g, 0.01moles) in carbondisulphide (25ml). quickly producing a red colouration. The mixture was stirred for 1 hour then refluxed for a further 1.5 hours

The mixture was poured onto crushed ice (50g), extracted with diethyl ether (2 portions of 50ml). The combined ethereal extracts were washed with sodium bicarbonate solution (50ml of a saturated solution) and with water (50ml), dried to give a yellow solution, the solvent was removed under reduced pressure at room temperature to give a black tar-like gum (1.8g). Analysis of that part of the gum which would dissolve in $CDCl_3$ by NMR showed that there was no acetyl group present.

Attempted preparation of 5-acetyl-3H-pyrrolizine.

To a stirred solution of 3H-pyrrolizine (0.25g,2.5m.moles) and triethylamine (0.25g, 2.5m.moles) in anhydrous hexane (100ml) was added a solution of acetyl chloride (0.2g,2.5m.moles) in hexane (100ml) over 1 hour. The mixture was stirred for a further 18 hours then refluxed for 8 hours.

The mixture was shaken with water (50ml), the organic solution was separated, dried and the solvent removed under reduced pressure to give an oil (0.22g) This oil was found to be 3H-pyrrolizine.

Attempted preparation of 5-acetyl-3H-pyrrolizine.

To a stirred solution of 3H-pyrrolizine (1.05g, 0.01moles) in anhydrous diethyl ether (100mls) was added a solution of acetyl chloride (0.78g, 0.01moles) in diethyl ether (100ml) over 1.25 hours. The mixture was stirred overnight and refluxed a further 5 hours

The solvent was removed under reduced pressure to give a brown tar which was insoluble in ether. Extraction of this tar with boiling light petroleum (250ml) gave a faint yellow solution, removal of solvent gave 3H-pyrrololizine (0.04g).

Preparation of 5-trichloroacetyl-3H-pyrrolizine (167).

A mixture of 3H-pyrrolizine (0.9g, 9m.moles) and potassium carbonate (9g) in anhydrous diethyl ether (40ml) was stirred in an ice/water bath. A solution of trichloroacetylchloride (3.3g, 18m.moles) in diethyl ether (40ml)was added over a period of 5 minutes and the mixture stirred for a further 5 minutes A portion of water (15ml) was slowly added.

The ethereal layer was separated and washed successively with sodium biucarbonate solution (20ml of a saturated solution), sodium chloride solution (20 ml of a saturated solution) and water (20ml). The organic layer was separated, dried and the solvent removed under reduced pressure to give a yellow/brown solid (2.1g).

The solid was recystallized from hexane to give the trichloroacetyl pyrrolizine (167) (1.8g, 84%yield).

Preparation of 5-dichloroacetyl-3H-pyrrolizine (170).

To a stirred mixture of 3H-pyrrolizine (0.25g, 2.5m.moles) and potassium carbonate (2.5g) in diethyl ether (20ml) cooled in an ice/water bath was added a solution of dichloroacetyl chloride (1.0g, 5m.moles) in diethyl ether (10ml) over a period of 5 minutes. The mixture was stirred for a further 5 minutes and a portion of water slowly added (5ml).

The ethereal layer was separated and washed successively with sodium bicarbonate solution (10ml of a saturated solution), sodium chloride solution (10 ml of a saturated solution) and water (10ml). The organic layer was separated, dried and solvent removed under reduced pressure to give a black tar. The tar was extracted with

boiling petrol (40ml) to give a yellow solution from which the solvent was removed to give a solid (0.4g). The solid was recrystallized from hexane to give yellow crystals of the ketone (170) (0.3g, 58% yield).

Attempted reaction of 5-trichloroacetyl-3H-pyrrolizine with dichloroketene.

A mixture of the pyrrolizine (0.2g) and activated zinc (0.15g) in anhydrous diethyl ether (30ml) was stirred under a nitrogen atmosphere. A solution of trichloroacetyl chloride (0.3g) and phosphorus oxychloride (0.15ml) in diethyl ether (10 ml) was added dropwise over 1hour. The mixture was refluxed for 2 hours and stirred overnight.

The reaction mixture was filtered through a pad of Celite. The filtrate was washed successively with water (50ml), sodium bicarbonate solution (50ml of a 5% solution) and sodium chloride solution (50ml of a saturated solution). THe organic phase was dried and solvent removed under reduced pressure to give a yellow solid (0.2g). The NMR spectrum of the solid identified it as the starting ketone.

Attempted reaction of 3H-5-trichloroacetylpyrrolizine with with dichloroketene.

A mixture of the pyrrolizine (0.25g), activated zinc (0.5g) and anhydrous diethyl ether (40ml) was stirred under nitrogen. A solution of trichloroacetyl chloride (0,7ml) in diethyl ether (20ml) was run in, at first rapidly to cause boiling then at such a rate as to maintain reflux. The mixture was stirred at room temperature overnight.

The mixture was filtered to give a yellow solution which was washed with water (3 portions of 25ml), sodium bicarbonate soution (3 portions of 25ml of a saturated solution), sodium chloride solution

(3 portions of 25ml of a saturated solution) and water (25ml). The organic phase was dried and the solvent removed under reduced pressure to give a yellow solid (0.2g). The NMR spectrum of the solid identified it as the starting ketone.

Photochemical reaction between dimethyl acetylenedicarboxylate and 5-trichloroacetyl-3H-pyrrolizine.

A solution of trichloroacetylpyrrolizine (0.25g, 1m.mole), dimethyl acetylenedicarboxylate (DMAD) (1.5g, 10m.moles) and acetophenone (0.5g) in anhydrous benzene (600ml) was purged with a stream of nitrogen for 30 minutes. The solution was irradiated by a UV lamp through a pyrex sleeve (light predominatly 313 and 336nm) for 7 hours.

The solvent was removed to give a brown oil. This oil was purified by column chromatography on alumina (150g, activity IV). Elution with light petroleum gave acetophenone but further elution with solvents of increasing polarity (to methanol) failed to elute any more material.

This reaction was repeated with the ommission of acetophenone. Irradiation for 44 hours gave only starting materials together with some deposition of polymeric material on the flask walls.

Attempted thermal reaction between 5-trichloroacetyl-3H-pyrrolizine and DMAD.

A solution of 5-trichloroacetyl-3H-pyrrolizine (0.9g, 3.6m.moles) and DMAD (4.5g, 33m.moles) in anhydrous benzene (100ml) was refluxed under nitrogen for 40 hours.

The solvent was removed to give a brown oil. T.L.C. and NMR analysis of this oil showed it to contain only starting materials.

Preparation of 5-acetyl-3H-pyrrolizine (165).

To a stirred solution of 3H-pyrrolizine (0.2g, 2m.moles) in anhydrous tetrahydrofuran (10ml) cooled to -81°C in a liquid nitrogen/ethylacetate bath was added dropwise a soluton of n-butyl lithium (1.4ml of a 1.6M solution in hexane, 2.2m.moles) to give an orange solution. The mixture was stirred for 10 minutes and a solution of acetyl chloride (0.16ml, 2.0m.moles) in tetrahydrofuran (10ml) was added over 10 minutes. The mixture was stirred at low temperature for 40 minutes and allowed to reach room temperature where it was stirred overnight.

A portion of water (10ml) was added, the organic phase separated and the aqueous phase extracted with diethyl ether (50ml). The combined organic phases were dried and the solvent removed under reduced pressure to give a black tar (0.4g). The tar was treated with 250ml of boiling diethyl ether to give a yellow solution from which the solvent was removed to give a small amount of solid, identified by its NMR spectrum as the acetylpyrrolizine (165) (0.02g, 7% yield).*

*This yield was not consistently reproducible and was often lower.

This experiment was repeated with lithiumdiisopropylamide in place of n-butyllithium and with inverse addition of base. In neither case was any indentifiable product isolated.

Preparation of 1-(3H-pyrrolizin-3-yl)ethanol (178) and Z and E-3-ethylidine-3H-pyrrolizine (181) and (182).

To a stirred and cooled (ethylacetate/liquid nitrogen bath) solution of 3H-pyrrolizine (0.5g, 5m.moles) in anhydrous tetrahydrofuran (50ml) under nitrogen was added a solution of n-butyllithium (4.2ml of a 1.4M solution, 1.1equiv. in hexane). The mixture was stirred 10 minutes. A solution of freshly distilled acetaldehyde (0.3g, 5m.moles) in tetrahydrofuran (10ml) was added as 1 portion to give a clear yellow solution. The mixture was stirred

for 1 hour and then allowed to reach room temperature.

A solution of ammonium chloride/ammonium hydroxide (30ml of a saturated solution) was added, followed by ether (100ml). The organic phase was washed with water (30ml), dried and solvent removed under reduced pressure to give a yellow oil (0.7g, pure by T.L.C.). The NMR spectrum of this oil showed it to be the alcohol (178).

^{1}H NMR ($CDCl_3$, TMS internal standard)

6.7ppm	1H	m	
6.4ppm	1H	d	(J=3Hz)
5.9ppm	2H	m	
5.8ppm	1H	m	*
4.3ppm	1H	m	
3.5ppm	1H	m	
2.8ppm	1H	bs	!
1.1ppm	3H	cm	

* becomes a doublet (J=3Hz) when the peak at 4.3ppm is irradiated

! exchanges with D_2O

Attempts to purify this compound were unsuccessful, column chromatography on alumina, P.L.C., and distillation produced extensive decomposition. Column chromatography on Florasil (0.6g product on 18g Florasil) gave a yellow oil (0.08g) on elution with light petroleum . This oil was identified as a mixture of the isomeric azafulvenes Z-3-ethylidine-3H-pyrrolizine (183) and E-3-ethylidine-3H-pyrrolizine (182) in the ratio 9:4 respectively.

^{1}H NMR ($CDCl_3$, TMS internal standard)

6.9ppm		d	(J=3Hz)
6,8ppm		d	(J=3Hz)
6.4ppm	1H	cm	
6.0ppm	1H	cm	
5.8ppm	1H	cm	
5.35ppm	1H	q	(J=7Hz)
2.0ppm		d	(J=7Hz) Z isomer
1.9ppm		d	(J=7Hz) E isomer

IR (ν max) 1420, 1270cm^{-1}

UV (λ max, 95% ethanol) 297nm ($\log_{10}\varepsilon$ =5.07)
305nm ($\log_{10}\varepsilon$ =5.06)
360nm ($\log_{10}\varepsilon$ =4.54)

Analysis:

C_9H_9N	requires	C=82.40,	H=6.92,	N=10.68%
	obtained	C=82.85,	H=6.81,	N=10.19%

Attempted oxidation of the alcohol (178) by potassium permanganate/ copper sulphate mixture.

A suspension of the crude alcohol (178) (0.4g) and an intimate mixture of potassium permanganate and copper sulphate (2:1 w:w, 3.78g) in anhydrous benzene (10ml) was stirred at room temperature for 24 hours. The mixture was filtered and the solvent removed to give a brown oil (0.4g), which was shown by its NMR spectrum to be identical to the starting material.

Attempted oxidation of the alcohol (178) by potassium permanganate/ alumina mixture.

A suspension of neutral alumina (1.25g, activity I), potassium permanganate (2g) and the crude alcohol (178) (0.4g) in anhydrous benzene (10ml) was stirred for 24 hours at room temperature. The mixture was filtered and solvents removed from the filtrate to yield a brown oil (0.2g) which was shown by its NMR spectrum to be the starting alcohol.

Attempted oxidation of the alcohol (178) by dimethylsulphoxide/ oxalylchloride complex.

To a stirred and cooled (below -50°C) solution of freshly distilled oxalylchloride (0.25ml, 1.1equivalents) in anhydrous dichloromethane (10ml) under nitrogen was added a solution of freshly distilled dimethylsulphoxide (0.43ml, 2.2 equivalents) in dichloromethane (2ml). The mixture was stirred for 2 minutes and a solution of the crude alcohol (0.4g, 1 equivalent) in dichloromethane (10ml) was added over 5 minutes. The mixture was stirred for 15 minutes and triethylamine (1.75ml, 5 equivalents) was added. The mixture was stirred a further 5 minutes then allowed to reach room temperature.

Water (20ml) was added and the mixture was extracted with

dichloromethane (2 portions of 20 ml), the combined organic extracts were washed with sodium chloride solution (30ml of a saturated solution), water (30ml), hydrochloric acid (30ml of a 0.5% solution), water (30ml), sodium carbonate solution (30ml of a saturated solution) and water (30ml). The organic phase was dried and the solvent removed under reduced pressure to give a tarry gum (0.2g). The NMR spectrum of this gum shows no recognisable peaks, T.L.C. (25%ethylacetate/75%toluene) gives only a streak.

Attempted oxidation of alcohol (178) by pyridinium chlorochromate

To a stirred suspension of pyridinium chlorochromate (1.15g,0.005moles) and anhydrous sodium acetate (0.1g) in anhydrous dichloromethane (15ml) was added a solution of the crude alcohol (0.4g, 0.0025moles) in dichloromethane (5ml). The mixture was stirred for 2.5 hours.

The mixture was diluted with 5 volumes of anhydrous diethyl ether, the solution decanted off and the black solid filtered and washed with more ether. The combined organic extracts were concentrated to give a brown oil,the ^{1}H NMR spectrum of which shows only broad peaks. This oil was purified by P.L.C. (25% ethyl acetate/75% toluene) to give two bands, neither of which was identifiable.

Preparation of anhydrous magnesium bromide/tetrahydrofuran complex.

This was prepared by the method of Ashby and Arnott[153].

Preparation of anhydrous magnesium iodide/diethyl ether complex

This was prepared by the method of Hammond and Wu[152].

Attempted preparation of 5-acetyl-3H-pyrrolizine

To a stirred and cooled (ethyl acetate/liquid nitrogen bath) solution of 3H-pyrrolizine (0.5g, 0.005moles) in anhydrous tetrahydrofuran was added under nitrogen a solution of n-butyllithium in hexane (4.2ml of a 1.4M solution). The mixture was stirred for 10 minutes and a portion of freshly distilled acetaldehyde (0.3g, 0.005moles) was added. After stirring for 5 minutes a solution of magnesium bromide/tetrahydrofuran complex (2.0g, 0.006moles) in tetrahydrofuran (20ml) was added as one portion producing effervescence. The mixture was stirred for 15 minutes and a further portion of acetaldehyde was added (0.3g, 0.005moles). The reaction mixture was stirred at low temperature for 90 minutes and then allowed to reach room temperature.

An ammonium chloride/ammonium hydroxide solution (20 ml of a saturated solution) was added and the mixture extracted with diethyl ether. The organic extract was dried and the solvent removed to give a yellow oil (0.5g). Analysis of this oil by NMR spectroscopy showed it to be a mixture of the previously prepared alcohol (178) and 3H-pyrrolizine.

This reaction was repeated with the modifications that magnesium iodide/ diethyl ether complex (1 equivalent) was added to the 4-azapentaenyl lithium solution followed by acetalehyde (3 equivalents). Work up of this reaction gave also the alcohol and no acetyl pyrrolizine.

Preparation of 5-acetyl-3H-pyrrolizine

A mixture of 5-trichloroacetyl-3H-pyrrolizine (0.16g, 0.0006moles) zinc dust (1g) and acetic acid (5ml) were stirred in an ice bath for 90 minutes, refluxed for 30 minutes and allowed to reach room temperature.

The mixture was poured onto crushed ice (50g) and diethyl ether (30ml) and neutralized with sodium bicarbonate solution (saturated). The ethereal layer was separated, washed with saturated sodium bicarbonate solution (10ml), then with water, dried and the solvent removed under reduced pressure to give a yellow gum. Recrystallization from hexane gave yellow crystals of 5-acetyl-3H-pyrrolizine (25mg, 27%).

Attempted preparation of methyl-3H-pyrrolizine-3-carboxylate

To a stirred solution of sodium methoxide in methanol (from 0.05g sodium in 15ml absolute methanol) under nitrogen and cooled in an ice bath was added a solution of 5-trichloroacetyl-3H-pyrrolizine (0.25g, 1mmole) in methanol (20ml). The mixture turned black in 30 seconds. Removal of solvent gave a black tar (0.3g). The NMR spectrum of this tar showed no identifiable peaks.

Reaction of 5-trichloroacetyl-3H-pyrrolizine with potassium carbonate and methanol

A mixture of 5-trichloroacetyl-3H-pyrrolizine (0.1g, 4mmole), potassium carbonate (0.1g) and methanol (0.5ml) were stirred at 60^{o}C for 15 minutes to give a black/red mixture.

The reaction mixture was diluted with diethyl ether (20ml), filtered and the filtrate was washed with sodium chloride solution (25 ml of a saturated solution), with water (25 ml) and dried. The solvent was removed under reduced pressure to give a yellow/red oil(0.1g). This oil was purified on P.L.C. (10% ethyl acetate/90%

toluene) which gave two bands.

5-dichloromethyl-3-carbomethoxy-3H-pyrrolizine (186)

Rf. 0.42 30mg 30% yield
Yellow crystals 80-81°C (hexane)

^{1}H NMR ($CDCl_3$, TMS internal standard, 100MHz)

7.20ppm	$1H_6$
6.72ppm	$1H_1$
6.49ppm	$1H_{5a}$
6.38ppm	$1H_2$
6.18ppm	$1H_3$
6.13ppm	$1H_7$
3.17ppm	3H (CH_3

Coupling constants (Hz)

$J_{1,2}$=5.98 $J_{1,3}$=0.98
$J_{2,3}$=1.59 $J_{2,7}$=0.73
$J_{6,7}$=4.01
subscripts refer to positions on the pyrrolizine nucleus

^{13}C NMR ($CDCl_3$, TMS internal standard)
completely decoupled (multiplicity at off resonance), ppm
174.93(s), 147.01(s), 135.10(d), 125.42(s), 124.50(d), 124.21(d), 90.11(d), 67.45(d), 52.62(q).

IR (KBr disc, ν max) 1765, 1220, 1100, 805, 785, 710, 690 cm^{-1}

UV (95% EtOH, λ max) 258 nm ($\log_{10}\varepsilon$ 3.09)
352 nm ($\log_{10}\varepsilon$ 3.59)

Analysis:

$C_{10}H_9NO_2Cl_2$ requires C=48.78% H=3.66% N=5.69%
obtained C=48.87% H=3.73% N=5.70%

Mass spectrum

249(6%) 248(2) 247(38) 246(6) 245(37) 162(100)

2-carbomethoxy-5(4-chlorobut-1-en-3-on-1-yl)pyrrole

Rf. 0.29 40mg. 45% yield

White crystals 179-180°C (dichloromethane/hexane)

^{1}H NMR (CD_3COCD_3, TMS internal standard, 100MHz)

11.39ppm	$1H_1$	bs	(exchanges with D_2O)
7.63ppm	1H	d	(J=16.1Hz)
7.71ppm	$1H_3$	m	(d, J=3.9Hz with D_2O)
6.76ppm	$1H_4$	m	(d, J=3.9Hz with D_2O)
6.62ppm	1H	d	(J=16.1Hz)
4.71ppm	2H	s	
3.74ppm	3H	s	

^{13}C NMR (CD_3COCD_3, TMS internal standard)

181.70(s), 167.04(s), 135.47(s), 133.48(d)
132.19(s), 118.71(d), 118.36(d), 114.14(d)
51.62(q), 45.53(t)

IR (KBr disc, νmax) 1705, 1665, 1655, 1290, 1210cm^{-1}

UV (95% EtOH, λmax)		
	213nm	($\log_{10}$ =3.13)
	226	sh
	342nm	($\log_{10}$ =3.20)
	353	sh

Analysis:

$C_{10}H_{10}NO_3Cl$	requires	C=51.66% H=4.20% N=5.92%
	obtained	C=51.46% H=4.29% N=6.07%

Mass spectrum

229(13.9%), 228(5.3%), 227(23.2%),
198(4.9%), 196(13.5%), 179(19.5%),
178(79.5%), 146(100%)

This reaction was repeated using 5-dichloromethyl-3-carbomethoxy-3H-pyrrolizine as starting material. The major product, as shown by NMR was 2-carbomethoxy-5-(4-chlorobut-1-en-3-on-1-yl) pyrrole.

Attempted reduction of 5-trichloroacetyl-3H-pyrrolizine

A solution of the trichloro ketone (0.1g) in methanol (2ml) was added to a mixture of zinc/mercury amalgam (1.0g), concentrated hydrochloric acid (2ml) and water (1ml). The mixture was refluxed for 30 minutes and allowed to cool.

The reaction mixture was diluted with water (30ml) and extracted with diethyl ether (2 portions of 100ml). The combined organic extracts were washed with sodium bicarbonate solution (40ml of a saturated solution), dried and the solvent was removed under reduced pressure to give a black tar (0.7g). This tar proved insoluble in all the common solvents.

Attempted reduction of 5-acetyl-3H-pyrrolizine

To a stirred solution of lithium aluminium hydride (50mg, 6mmoles) in anhydrous tetrahydrofuran (20ml) was added a solution of the acetyl pyrrolizine (0.1g, 0.6mmoles) in tetrahydrofuran (10ml). The mixture was stirred for 2 hours then water (15ml) was slowly added.

The reaction mixture was extracted with diethyl ether until the aqueous phase was colourless (5 portions of 20 ml). The combined organic extracts were dried and the solvent removed under reduced pressure to give a yellow oil (0.08g). The NMR spectrum of this oil does not show any identifiable peaks.

Reaction between 5-trichloroacetyl-3H-pyrrolizine and sodium hydroxide

A mixture of the trichloro ketone (0.1g) in sodium hydroxide solution (15ml of a 2M solution) was stirred at 55^{o}C for 45 minutes.

The mixture was cooled and filtered, leaving a reddish gum and a brown filtrate. The filtrate was poured onto an excess of cold dilute sulphuric acid (40ml) and the mixture extracted with dichloromethane (2 portions of 50ml). The combined organic extracts were dried and

the solvent removed under reduced pressure to give a very small amount of a cream gum. The NMR spectrum of this gum has only one broad peak between 6.1 and 7.0ppm. The NMR spectrum of the reddish gum shows only alkyl absorptions between 2 and 1 ppm.

Attempted bromination of 3H-pyrrolizine

A stirred mixture of 3H-pyrrolizine (0.15g 0.015moles), potassium carbonate (1g) and diethyl ether (20ml) was cooled in an ice bath A solution of bromine (0.24g, 0.015moles) in diethyl ether (10ml) was added dropwise over 2 minutes to give a black solution which was stirred for a further 3 minutes. The mixture was filtered and the filtrate washed successively with water (50ml), sodium chloride solution (50ml of a saturated solution), and water (50ml). The organic phase was dried and the solvent removed from the yellow solution at 20^{o}C under nitrogen to give a black gum (0.2g) which could not be induced to dissolve in organic solvents.

Attempted nitration of 3H-pyrrolizine

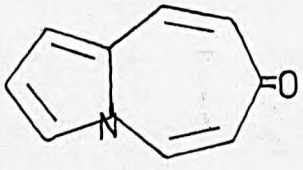
To a stirred mixture of fuming nitric acid (5ml) and acetic anhydride (50ml) cooled in an ice bath was added 3H-pyrrolizine (0.6g) over 10 minutes, the temperature being kept below 10^{o}C. The mixture immediatly turned black and was stirred for a further hour.

The reaction mixture was poured onto crushed ice and extracted with dichloromethane (200ml). The organic extract was neutralized by washing with sodium carbonate solution (40ml of a 5% solution) and with water. The organic phase was dried and the solvent removed to give black tar (0.4g). A small amount of the tar was soluble in diethyl ether and was purified on P.L.C. (10%ethyl acetate/90% toluene) to give 3 faint bands none of which showed any NMR absorption.

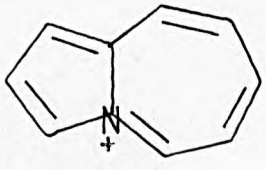
CHAPTER FOUR

Synthetic routes to pyrrolo[1,2-a]azepin-7-ones and pyrrolo[1,2-a]azepinium salts

The synthetic targets of this work, the ketone (1) and the salt (2), both have an unsaturated bond in the 7-membered ring which is α,β to postion 9a (the ring junction).



(1)

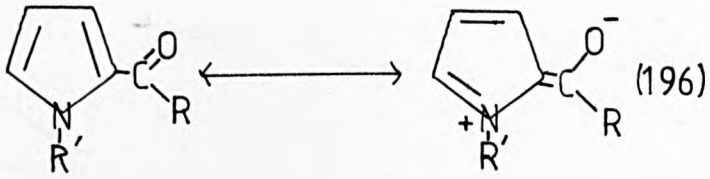


(2)

If the syntheses of such compounds are to start from a substituted pyrrole then a suitable synthon for this bond would be the carbonyl group of a 2(5)acyl pyrrole. The use of acyl pyrroles in heterocyclic synthesis is indicated in the following summary.

The use of acyl pyrroles in heterocyclic synthesis

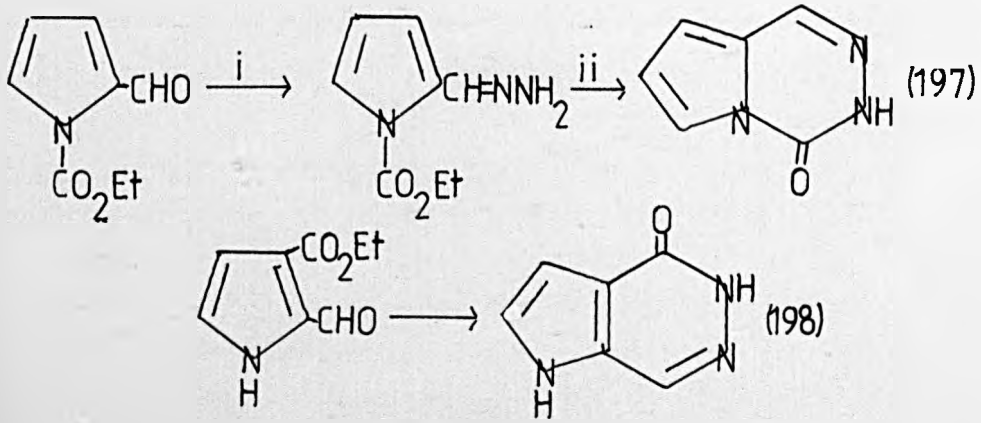
Acyl pyrroles undergo reactions typical of aromatic carbonyl compounds, although the reactivity of the carbonyl group is modified by tautomerisation to the zwitterionic canonical form (196)

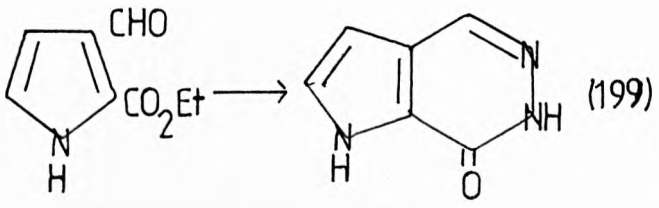


Thus, for example, 2 or 3 formylpyrroles in general fail to give positive tests with Fehlings or Tollens reagent. The reactions of acylpyrroles are also much modified by the type of substituents on the carbonyl group of the pyrrole nucleus.

a) Reactions with amines

Acylpyrroles react with amines or hydrazines to give the corresponding imino compounds, for example in the synthesis of the dihydrooxopyrrolotriazines (197-199)[164]





Scheme 67

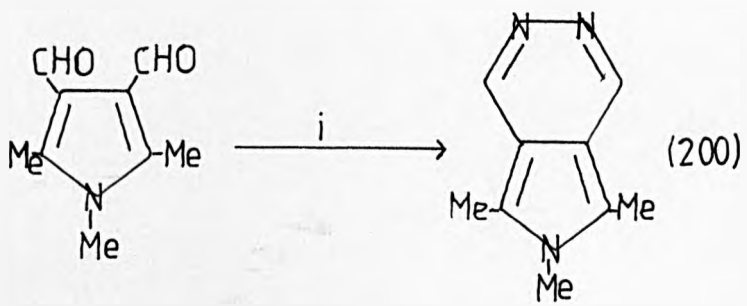
i) hydrazine ii) acid catalysis

Variations of the position of the formyl and carbethoxy substituents permits the synthesis of various isomers.

Diformylpyrroles can undergo two condensations as in the synthesis of pyrrolo[3,4-d]pyridazine (200)[167] in scheme 68.

Scheme 68

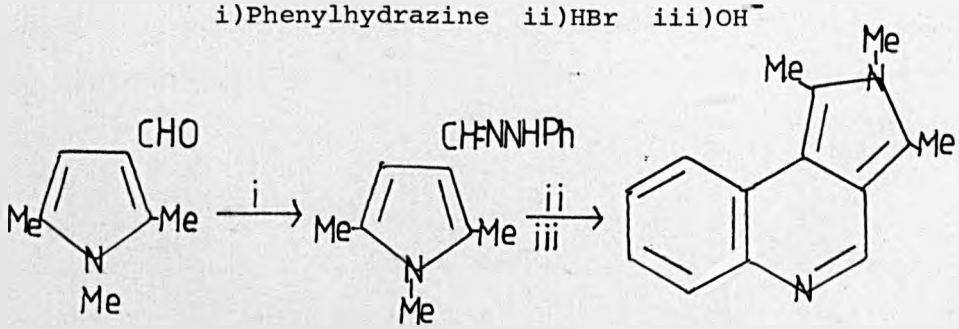
i) hydrazine



When phenyl hydrazines are used the hydrazone formed with 3-formylpyrroles can rearrange under acidic conditions to give a pyrrolo[3,4-c]quinoline as shown in scheme 69.[168]

Scheme 69

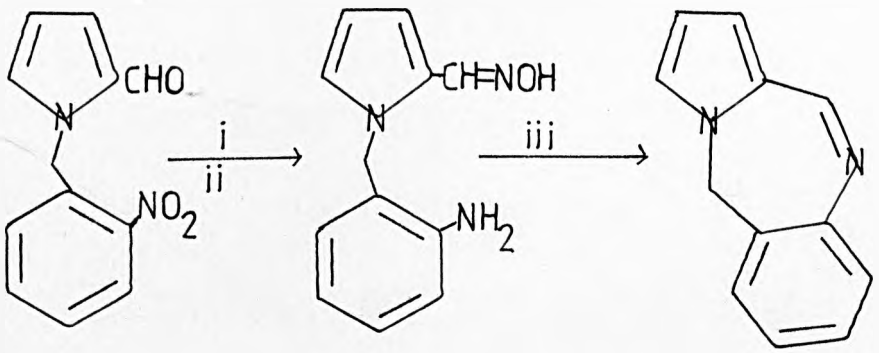
i)Phenylhydrazine ii)HBr iii)OH^-



Acyl pyrroles can be converted into their oximes and this reaction has been used in the synthesis of heterocycles, for example in the synthesis of 5H-pyrrolo[2,1-c][1,4]benzodiazepine (201)[169,170]

Scheme 70

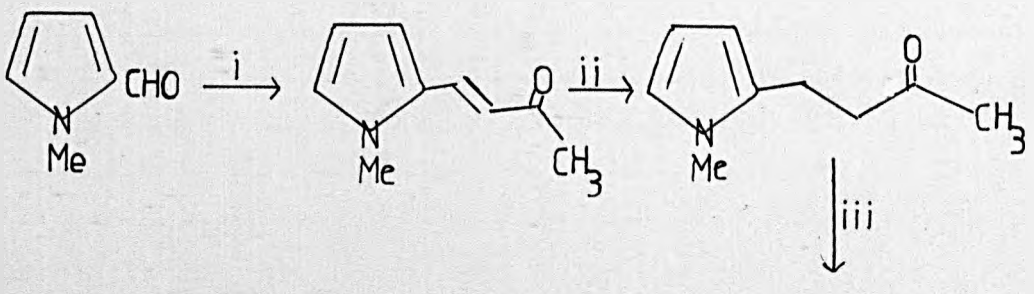
i) NH_2OH ii) H_2/PtO_2 iii) H^+

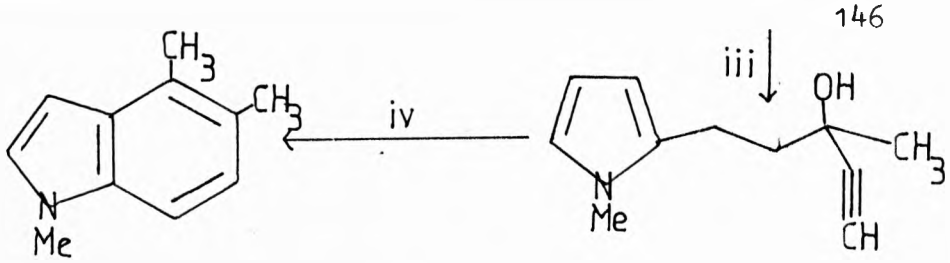


b) Formation of C-C bonds

Acylpyrroles undergo the common C-C bond formation reactions at the carbonyl carbon, although sometimes with more difficulty than other aromatic carbonyl compounds.

Formylpyrroles react in aldol-type condensations under basic conditions to give, normally, α,βunsaturated ketones as in the synthesis of indoles shown in scheme 71.





Scheme 71

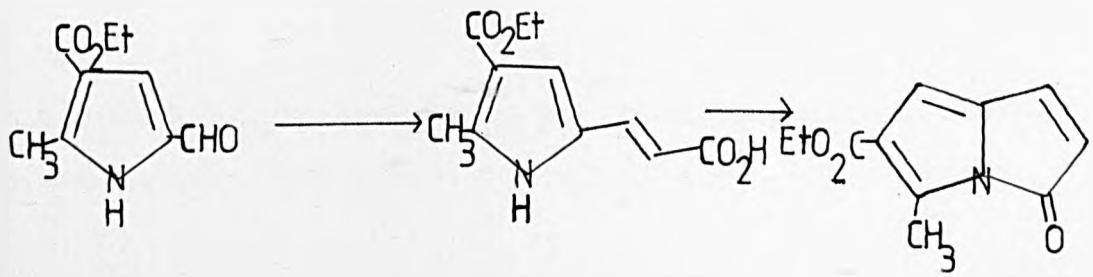
i)base, acetone ii)H_2/Pd/C iii)sodium acetylide iv)Lewis acid

Diformylpyrroles can undergo double condensations with ketones to give cyclic dienones as exemplified by the synthesis of pyrrolo[4,5-b] cycloheptatrien-6-ones[172,173]

Formylpyrroles react successfully in the Knoevenagel condensation as in Flitsch and Neuman's [174] synthesis of 3H-pyrrolizin-3-ones

Scheme 73

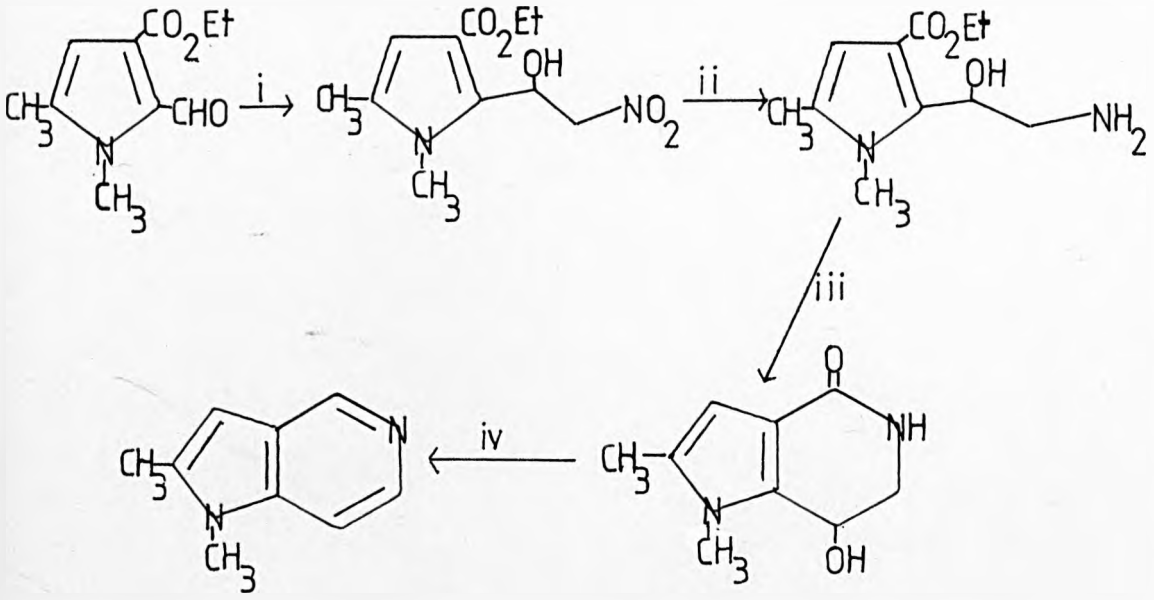
i)malonic acid, piperidine ii)acetic anhydride



Similarly formylpyrroles react in a base catalysed reaction with nitromethane to give pyrryl-2-nitroethanols. These can be used in the synthesis of azaindoles[174].

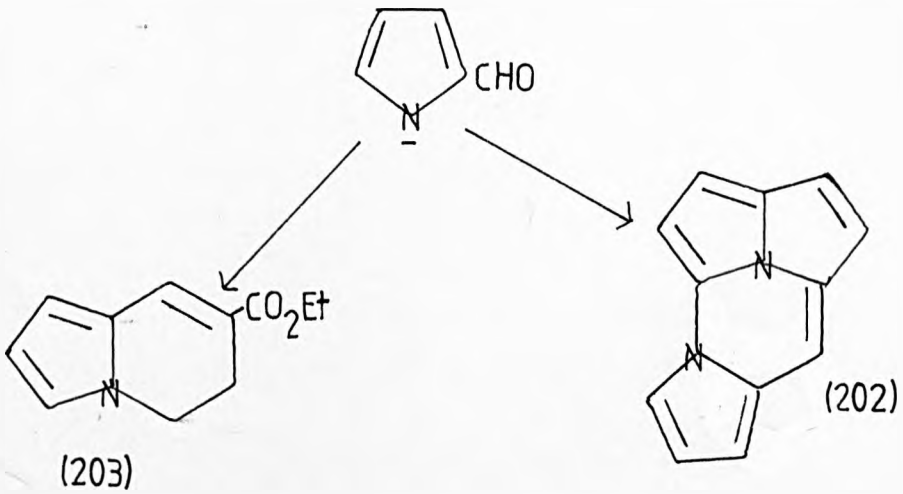
Scheme 74

i)CH_3NO_2/NaOEt ii)H_2/Raney Ni iii)Et_3N iv)Δ,$POCl_3$,C/Pd



Formylpyrroles react readily with reactive phosphoranes and with resonance stabilized phosphoranes in the Wittig reaction, however the reaction proceeds poorly, if at all, with pyrrolyl ketones. This reaction has been much used in the synthesis of heterocycles, the synthesis of 3H-pyrrolizine by Schweizer and Light and of pyrrolo[1,2-a]azepin-5-one by Flitsch, Muter and Wolf have already been mentioned. The 2-formylpyrrole anion undergoes the Wittig reaction, to give a cyclazine (202)[176] with a bis vinylphosphonium salt and a dihydroindolizine (203)[177] with 1-ethoxycarbonylcyclopropyltriphenylphosphonium salts.

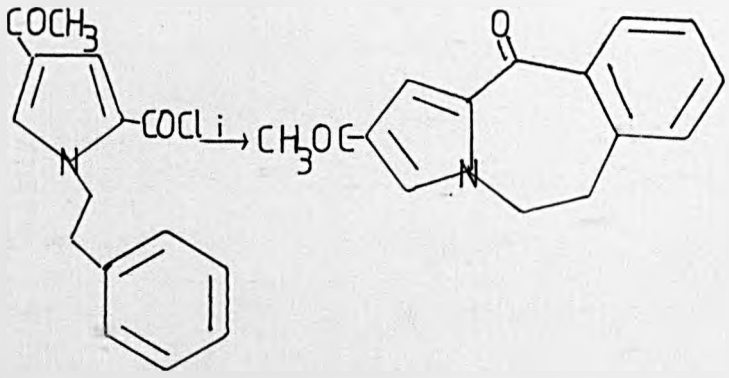
Scheme 75



Pyrrolyl acylchlorides can undergo Friedel-Crafts acylations; if the acylation is intramolecular then heterocycles will result. An example is the synthesis of the benzopyrrolo[1,2-a]azepinone (204), shown in scheme 78[178]

Scheme 78

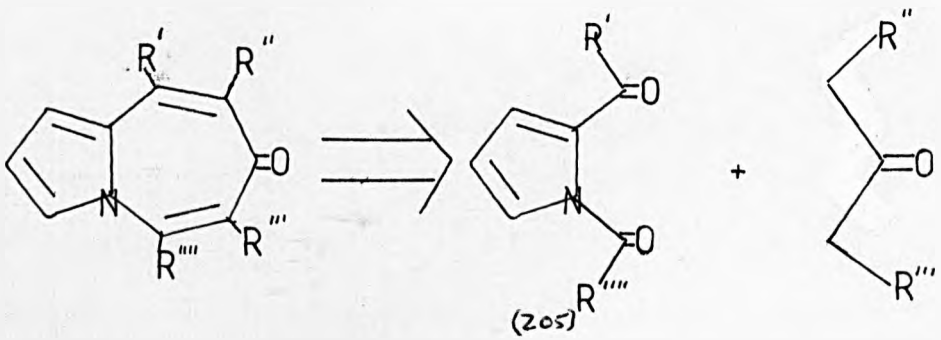
i)$AlCl_3$



Discussion

Synthesis of pyrrolo[1,2-a]azepin-7-one

The review of the reactions of acylpyrroles has shown that the reactions in which α,β-unsaturated pyrroles are easily made are the Wittig reaction, aldol condensations, and the Knoevenagel condensation. As the aldol condensation gives enones this route was chosen for the synthesis of pyrrolo[1,2-a]azepinones.



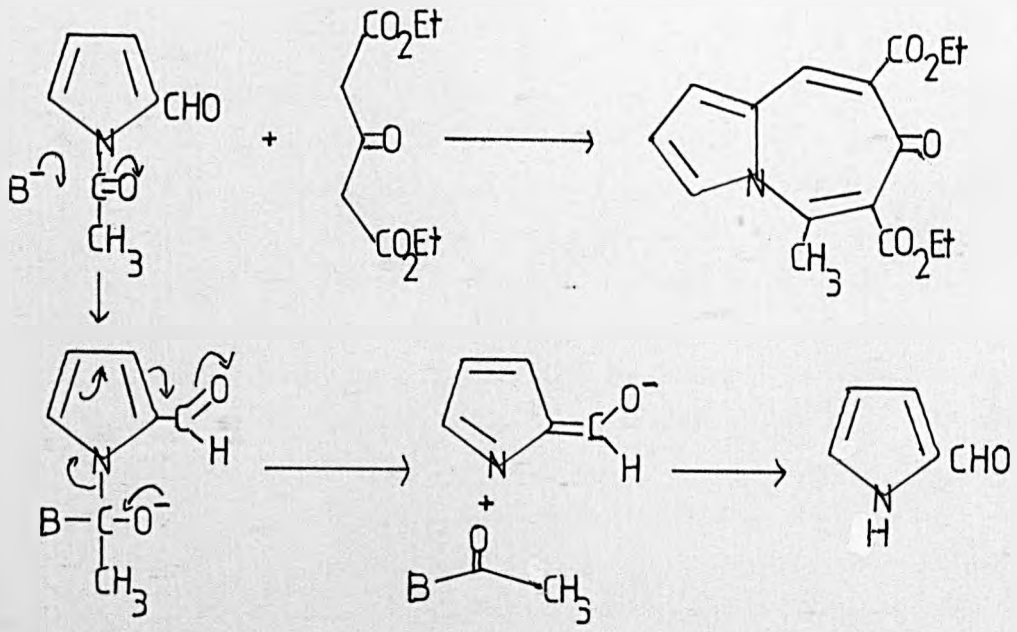
Scheme 78

If the molecule is disconnected at the two double bonds as in scheme 78 the result is a diacylpyrrole (205) and a ketone. The simplest such pyrrole, 1,2-diformylpyrrole, is unknown in the literature. However 1-acetyl-2-formylpyrrole is readily available. The published syntheses of 1-acetyl-2-formylpyrrole were not suited for use at the time (one uses thallium ethoxide, the other unavailable compounds[179,180]). 1-acetyl-2-formylpyrrole was prepared

by treating pyrrole with N-acetylimidazole[181] to give 1-acetylpyrrole[182], this was then formylated by the Vilsmeier procedure to give 1-acetyl-2-formylpyrrole. Formylation of pyrrole and reaction of 2-formylpyrrole with N-acetylimidazole failed to give any 1-acetyl-2-formylpyrrole, presumably because the formyl group deactivates the pyrrole nucleus to electrophilic attack.

This keto-aldehyde was reacted with diethyl acetone-1,3-dicarboxylate under basic conditions (lithium diisopropylamide or sodium ethoxide). After work up the only identifiable products were 2-formylpyrrole and a yellow oil whose ^{1}H NMR showed only peaks due to ethoxy groups. It seems reasonable to suppose that under basic conditions the N-acetyl bond is cleaved and that the diethyl acetone-1,3-dicarboxylate undergoes self-condensation reactions. The cleavage of N-acylpyrroles in basic conditions is a known reaction[183] and the presence of the electron withdrawing formyl group would facilitate this reaction.

Scheme 79

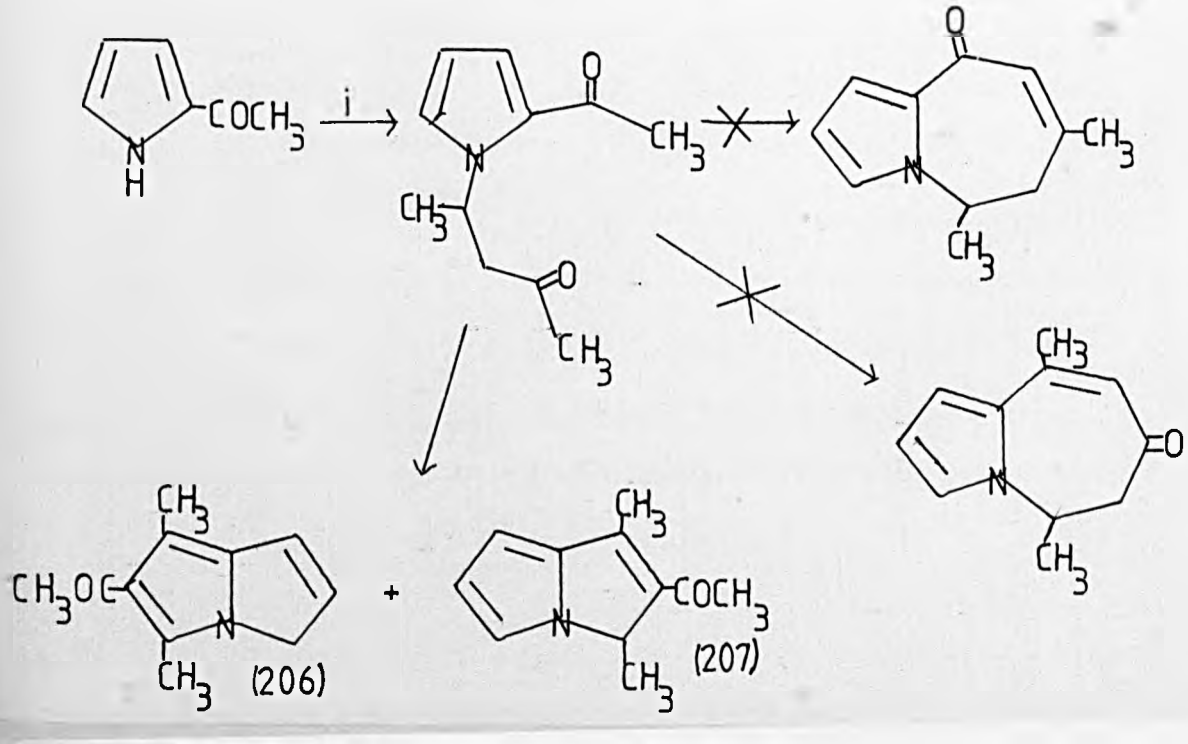


This is shown in scheme 79 where B^- is base or the anion of diethyl acetone-1,3-dicarboxylate. In this mechanism B is unlikely to be the non-nucleophilic diisopropylamide. 1-acetyl-2-formylpyrrole is also an enolisable ketone and so may undergo condensations, however diethyl acetone-1,3-dicarboxylate possesses considerably more acidic protons.

As the attempt to generate the 5,6 and 8,9 bonds in pyrrolo[1,2-a]azepin-7-one in one reaction had failed, attention then turned to synthetic routes which would generate these bonds sequentially. Pyrrole anions undergo Michael additions to a number of vinyl compounds to give 1-(2-substituted ethyl)pyrroles [184]. If the substituent were to contain a methyl ketone then this could condense in an aldol condensation to form a dihydropyrroloazepine. Flitsch, Kappenberg and Schmitt[185] have attempted such a route in their synthesis of pyrrolo[1,2-a]azepin-9-one (scheme 80).

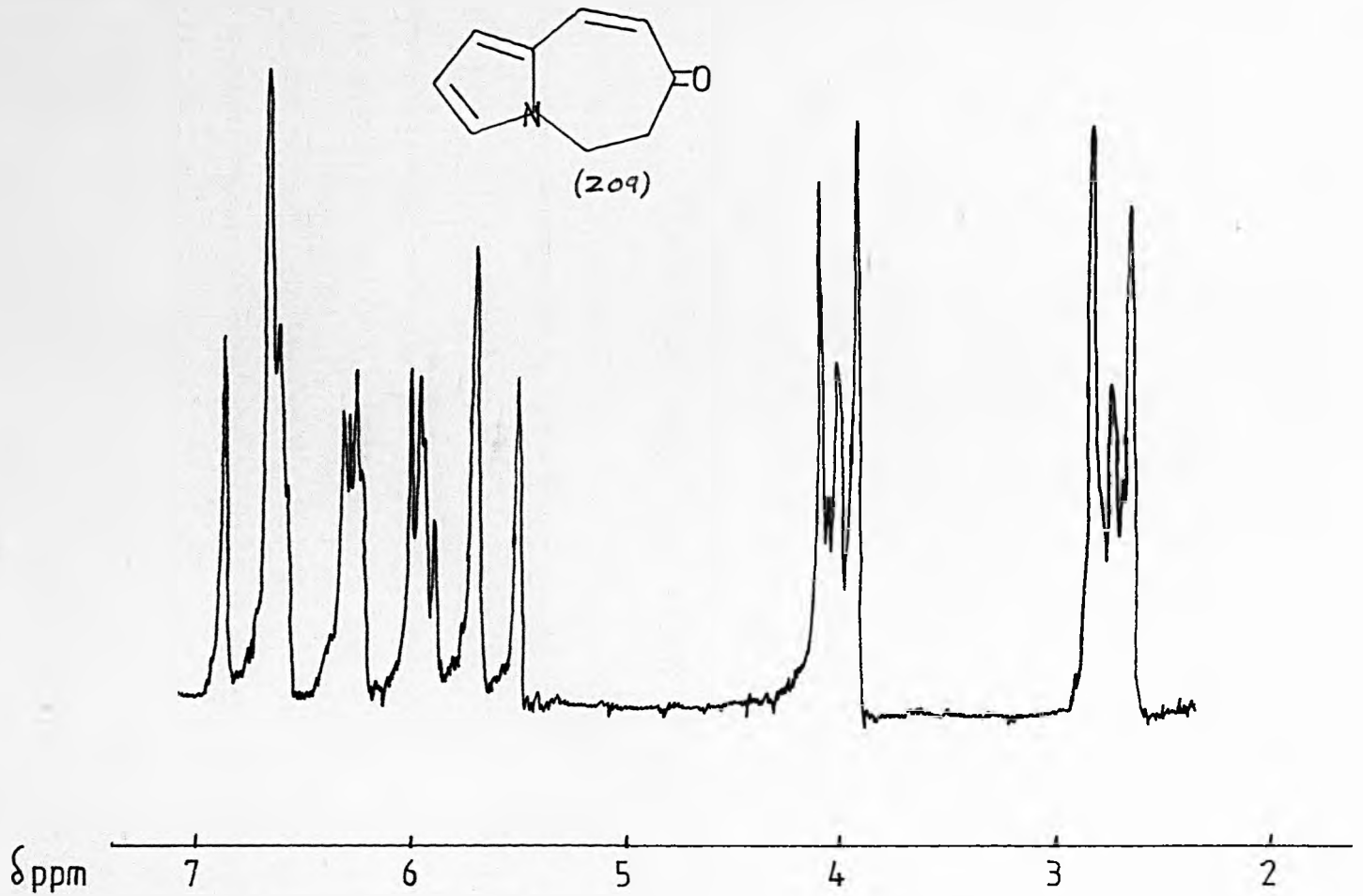
Scheme 80

i) Penten-2-one/NaOMe in MeOH



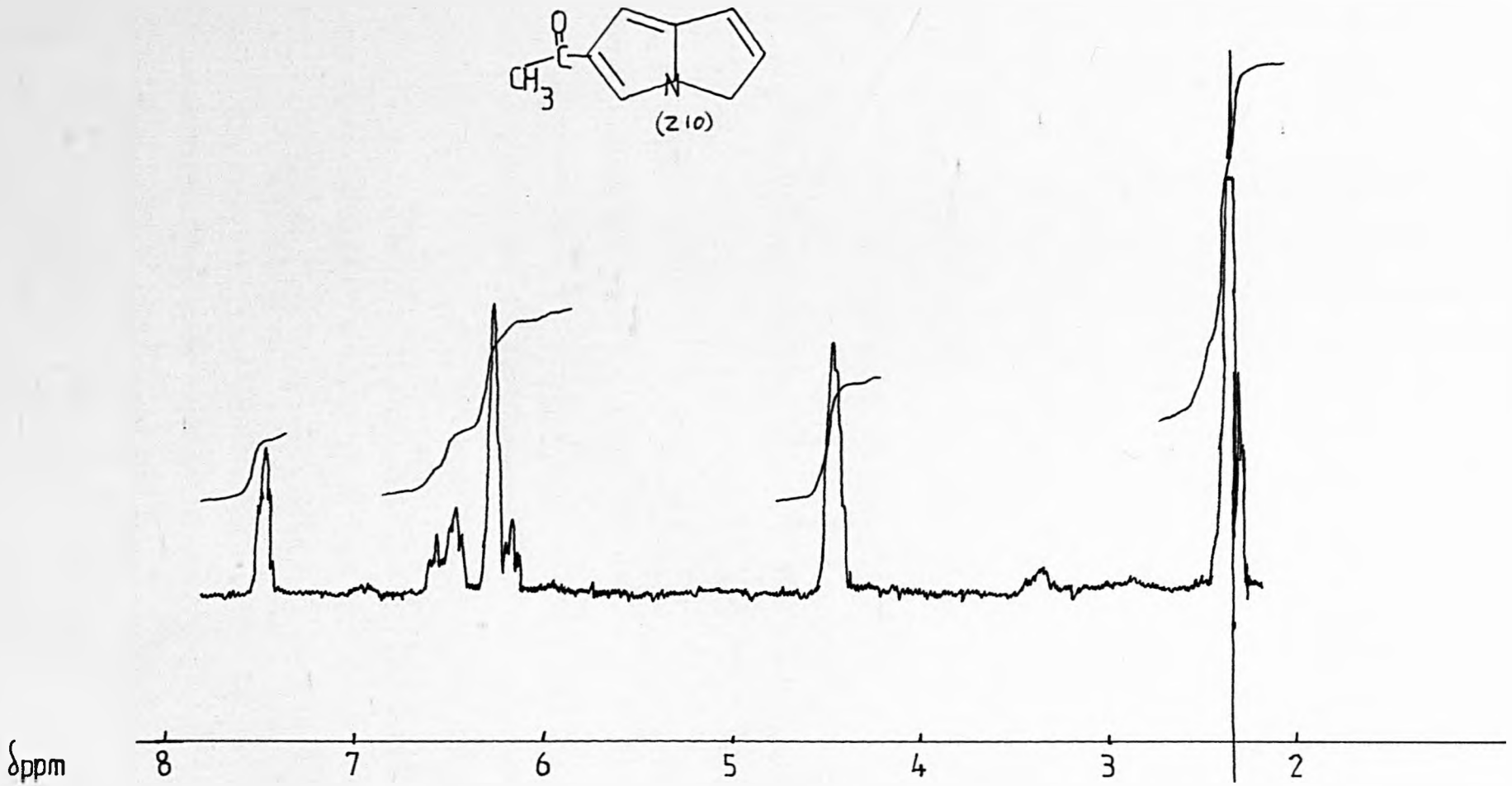
The action of sodium methoxide on 2-acetylpyrrole and penten-2-one gave only the isomeric pyrrolizines (206) and (208). These must have arisen via the diketone (208), the methylene group α to the pentanone carbonyl proving most acidic under the reaction conditions. None of the desired dihydropyrrolo[1,2-a]azepin-9-one, or more importantly for this work, the isomeric dihydropyrrolo[1,2-a]azepin-7-one was formed. However with less methyl groups the reaction can take a different course. D.Leaver has reported the condensation of 1-(butan-3-on-1-yl)-2-formylpyrrole to give only 5,6-dihydropyrrolo[1,2-a]azepin-7-one[186].

The reaction of 2-formylpyrrole and methylvinylketone in the presence of phenyltrimethylammonium hydroxide (Triton B hydroxide) in dioxan gave 1-(butan-3-on-1-yl)-2-formylpyrrole in good yield after distillation. Reaction of this keto-aldehyde with sodium ethoxide in boiling ethanol, followed by work up and chromatography on alumina gave two compounds. The first eluted compound (benzene/light petroleum 30/70) was a yellow oil which was recrystallized from hexane as yellow crystals. The infra-red spectrum of this compound shows strong bands at 1610 and 1665cm^{-1} indicative of an α,β unsaturated ketone. The ^{1}H NMR spectrum shows a pair of one proton doublets (J=11Hz) at 7.05ppm and 5.90ppm. There are three one proton multiplets at 6.86, 6.40 and 6.10ppm with peak shapes typical of pyrrolic protons. The other peaks are a pair of two proton multiplets at 4.05 and 2.85ppm, their shapes are typical coupled methylene groups in a 7-membered ring[181a]. This data indicates that this compound is 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209), the mass spectrum and analysis confirm this assignment.


O
N
(209)
δ ppm
7
6
5
4
3
2

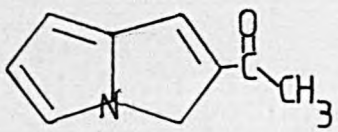
The second compound from the column (benzene/light petroleum 40/60) was recrystallized as yellow needles from hexane. The infra-red spectrum of this compound shows strong bands at 1650 and 1710cm^{-1} indicating an unsaturated ketone similar to that in the previous compound; however for this compound there is less conjugation between the carbonyl group and the unsaturation. The ^{1}H NMR spectrum shows the following details; a one proton broadend singlet at 7.5ppm, two single proton multiplets at 6.5 and 6.2ppm, a one proton singlet at 6.28ppm, a two proton multiplet at 4.45ppm and a sharp three proton singlet at 2.35ppm. When the multiplet at 4.45ppm was irradiated the peaks at 6.2 and 6.5ppm become doublets (J=5Hz) This broad peak coupled to a pair of multiplets coupled by 5Hz indicate the 1,2 and 3 protons of a 3H-pyrrolizine. The three proton singlet at 2.35ppm indicates a methyl ketone , this must be on positions 5,6, or 7 of the pyrrolizine. As the protons at 7.5 and 6.28ppm are not appreciably coupled together then the acetyl group is on position 6, proton 5 resonates at 7.5ppm and proton 7 at 6.28ppm. The compound is 6-acetyl-3H-pyrrolizine (210). This structure is supported by the mass spectrum which shows loss of 15 and of 43 mass units from the molecular ion.

This reaction was also carried out under different conditions, in tetrahydrofuran at $^{-}$78^{o}C with lithium diisopropylamide as base. Work up and purification by chromatography (column and P.L.C.) gave three products. Two were immediately identified as the starting keto-aldehyde (31%) and 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209) (16%). The third compound was new. It was eluted from chromatography as a yellow oil which recrystallized as yellow crystals from hexane. The


O
C
CH3
N
(210)
δppm
8
7
6
5
4
3
2

infra-red spectrum shows a strong bands at 1650 and 1565cm^{-1} indicating a conjugated α,β-unsaturated ketone. The ^{1}H NMR spectrum shows one proton multiplets at 7.2ppm and 6.9ppm, a two proton multiplet at 6.2ppm a broad singlet at 4.6ppm integrating for 2 protons and a three proton singlet at 2.35ppm. The three proton singlet in the NMR spectrum and the infra-red data indicate a methyl ketone. The NMR peak at 4.2ppm indicates a 3H-pyrrolizine structure. Two acetyl pyrrolizines, 5-acetyl-3H-pyrrolizine and 6-acetyl-3H-pyrrolizine have been prepared in the course of this work and the spectral details of those compounds differ from those of the new compound. The other isomeric acetylpyrrolizines are 1 or 2 or 3 or 7-acetyl -3H-pyrrolizine. The 3-acetyl compound can be ruled out as there is a two proton methylene in the NMR spectrum. This compound is not the 7-acetylpyrrolizine as there would be a clearly visible coupling of about 3Hz between protons 5 and 6 in the NMR spectrum. The 1-acetyl isomer would be expected to show a coupling of about 2.5Hz between protons 2 and 3, which is not visible in the NMR spectrum. The spectral evidence therefore, indicates that the new compound is 2-acetyl-3H-pyrrolizine (211). This assignment is confirmed by the mass spectrum which shows loss of 15 and 43 mass units from the molecular ion to give a stable fragment (100%) at 104 mass units. The assignment of this structure also has the virtue of being readily obtained from the starting material.

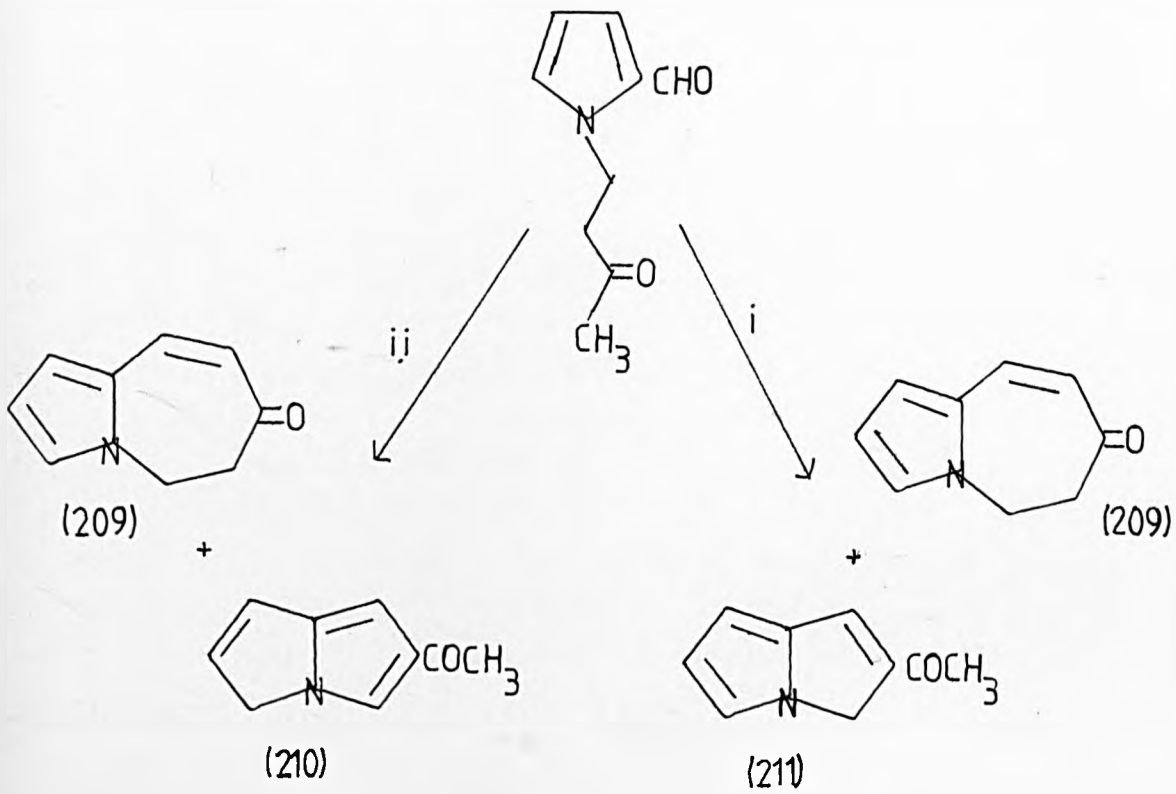
The products obtained from the base catalysed condensation of 1-(butan-3-on-1-yl)-2-formylpyrrole under the two sets of conditions used are shown in scheme 81.



(211)

Scheme 81

i)LDA/THF/$^{-}$78^{o}C ii)NaOEt/EtOH, boiling

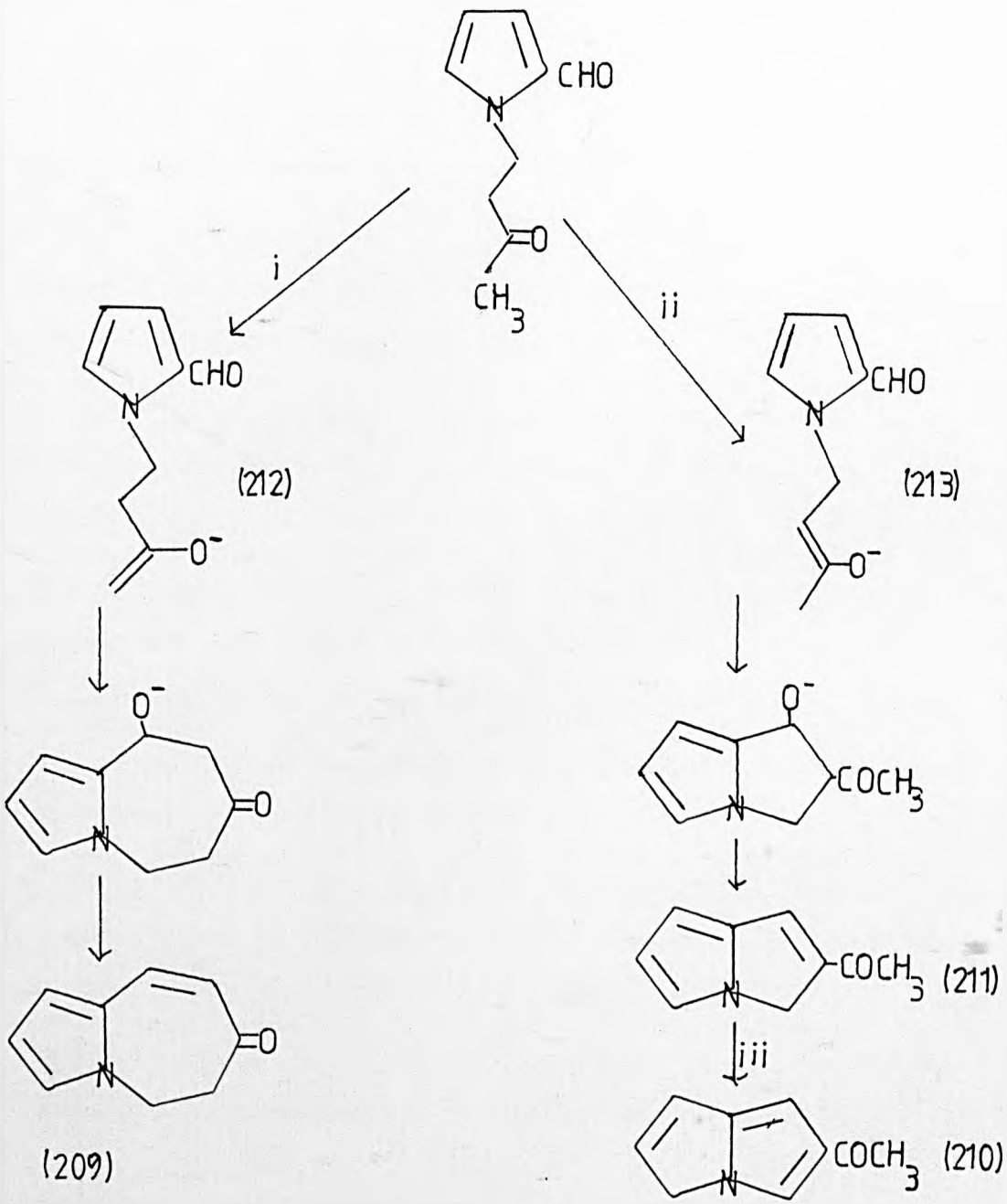


Under the conditions which favour thermodynamically stable products (sodium ethoxide in boiling ethanol) the azepinone (209) is formed in greater yield than the pyrrolizine (210) (40% against 31%). The pyrrolizine formed under these conditions is the more thermodynamically stable isomer as it has the electron withdrawing group on the saturated ring, in common with past experience of 3H-pyrrolizines (see review in chapter three). Under conditions wich

favour generation of kinetically stable products (lithium diisopropylamide in a nonhydroxylic solvent at low temperature) the distribution of isomers is different. In this case there is more pyrrolizine than pyrroloazepinone (39% against 23% if unreacted starting material is accounted for, 23% against 16% if not). Also the pyrrolizine formed is the less thermodynamically stable isomer, there is no trace of the other isomer. This isomer distribution may be explained by a consideration of the enolates formed during the reaction, these are shown in scheme 82.

Scheme 82

i)Equilibrating conditions ii)Kinetic conditions iii)NaOEt/EtOH



Two enolates may be formed from the keto-aldehyde; one of these enolates will be the "kinetic" enolate and hence regiounstable the other will be the "thermodynamic" enolate. There has been considerable work on the regiospecific preparation of enolates[182a]. In general the kinetic enolate will be the less conjugated enolate, prepared by abstraction of the less hindered proton in aprotic solvents in the presence of a strong, hindered base at low temperatures. The thermodynamic enolate is generated under equilibrating conditions, in protic media at room temperature or above, and is usually the more substituted or conjugated enolate. In most cases choice of these two differing reaction conditions will result in the production of a great excess of one enolate over the other (not less than 90:10 ratio).

In this case the two different reaction conditions lead only to a slight excess of one enolate over the other. Therefore it seems reasonable to conclude that neither of the enolates has much greater thermodynamic stability than the other and that the steric crowding of the protons are not greatly different. However there is a preference for one enolate over another. In equilibrating conditions the enolate (212) is preferentially formed and so must be the more thermodynamically stable enolate. In kinetic conditions enolate (213) is the more favoured enolate and so must be the less thermodynamically stable enolate.

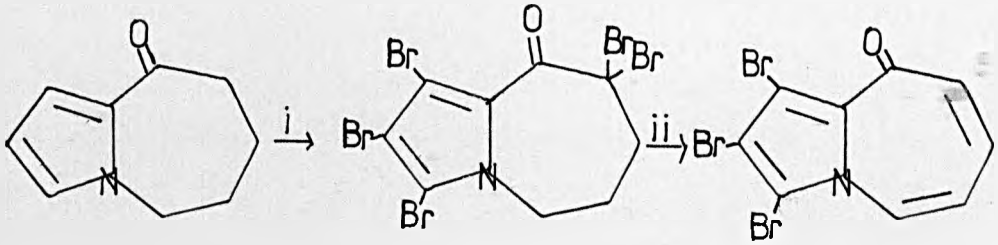
The preparation of the two different acetylpyrrolizines under the different conditions is a reflection of the differing thermodynamic stabilities of these two isomers under basic conditions. The 2-acetyl -3H-pyrrolizine (211) is the kinetic product but under equilibrating

conditions this is isomerised to the more thermodynamically stable isomer(210). Treatment of 2-acetyl-3H-pyrrolizine with sodium ethoxide in boiling ethanol gave 6-acetyl-3H-pyrrolizine.

With having prepared 5,6-dihydropyrrolo[1,2-a]azepin-7-one attention was turned to oxidation of this compound to give the fully unsaturated pyrrolo[1,2-a]azepin-7-one (1). A number of procedures exist for the generation of unsaturation; one of these which has been applied to the preparation of cycloheptatrienones[183a] is bromination followed by dehydrobromination. Collington and Jones[23] have successfully used this method in the preparation of the pyrrolo[1,2-a]azepin-9-one (214) although there was also unavoidable bromination on the pyrrole ring.

Scheme 83

i)Br_2 ii)LiCl/DMF



(214)

In the present case only one bromine atom need be introduced. A reagent which has been successfully used for the bromination of a ketone in the presence of a double bond is phenyltrimethylammonium tribromide (PTAB) [184-186]. Treatment of 5,6-pyrrolo[1,2-a]azepin-7-one with one equivalent of PTAB gave only starting materials, repetition of the reaction in the presence of calcium carbonate gave a small amount of a yellow oil in addition to starting material after chromatography.

The infra-red spectrum of this compound shows strong bands at 1660 and 1585cm^{-1}, indicative of an α,β-unsaturated ketone. The mass spectrum shows two peaks for the molecular ion separated by two mass units and of equal intensities (227,225 34%) indicating a monobromocompound and the analysis agrees with a formula of C_9H_8NOBr.

The ^1H NMR spectrum however shows that the compound has bromine at the 8 position and not the 6 position as intended. There is a sharp singlet corresponding to either the 8 or 9 proton (substitution at 5 or 6 can be ruled out by the intregals and shapes of the peaks at 4.15 and 3.0ppm). The additive substituent coefficient of the chemical shift due to bromine when it replaces hydrogen in a Z alkene is +0.4ppm[187]. Therefore in the nonbrominated compound (209) this proton resonated at approximatly 7.2ppm and so is proton 9 (actual chemical shift in (209) 7.05ppm). The monobromo compound is therefore 5,6-dihydro-8-bromo-pyrrolo[1,2-a]azepin-7-one (215).

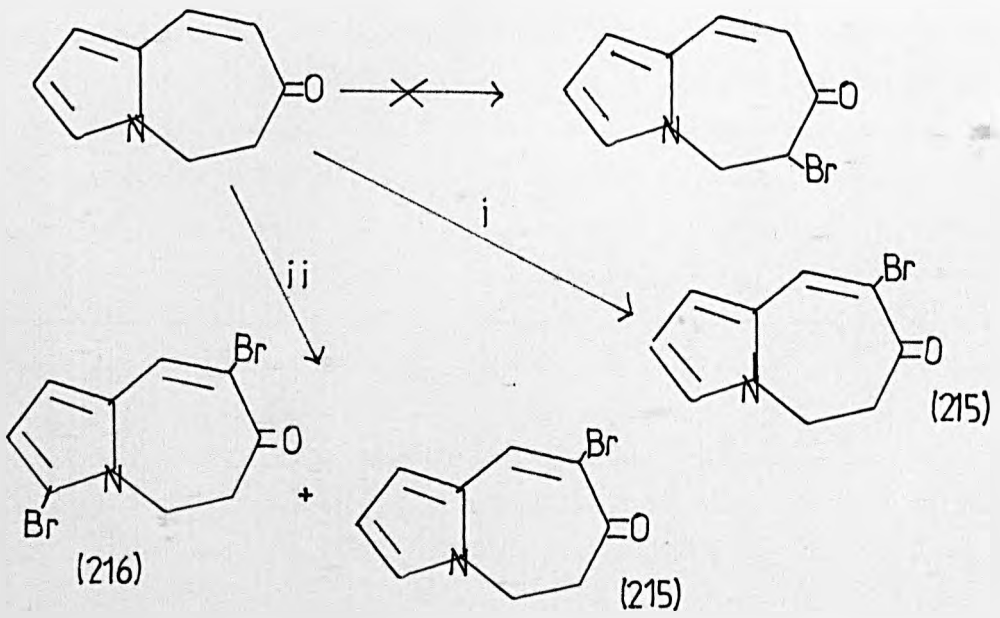
Reaction of 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209) with one equivalent of bromine in the presence of calcium carbonate gave the previously identified monobromo compound (215) (27% yield) and also a dibromo compound, identified as such by the three peaks for

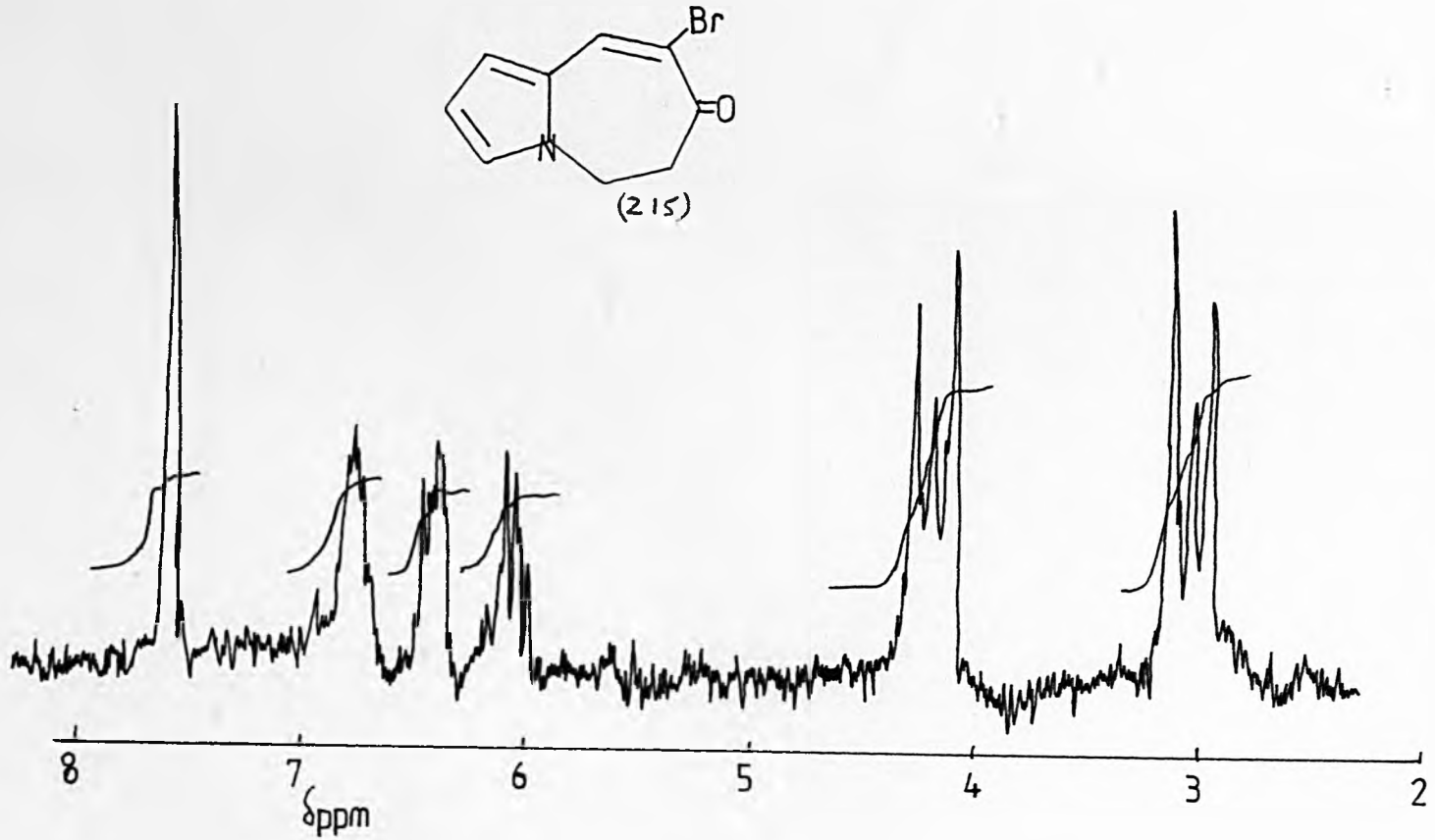
the molecular ion in the mass spectrum two mass units apart in the ratios 19:37:20%. The infra-red spectrum of this compound showed the same peaks as the monobromo compound, indicating that the carbonyl groups are in the same environment in each compound. The ^{1}H NMR spectrum showed a similar spectrum as that of the monobromo compound. The pair of multiplets at 4.2 and 3.0ppm indicating no substitution in the 5 or 6 positions, the singlet at 7.5ppm indicating an 8 bromocompound. The remaining peaks are a pair of doublets at 6.4 and 6.1ppm (J=4Hz) their chemical shifts and coupling constants indicate them to be the 1 and 2 protons. The new compound is therefore 3,8-dibromo-5,6-dihydropyrrolo[1,2-a]azepin-7-one (216).

Reaction of the dihydro ketone (209) with N-bromosuccinimide gave the same two compounds.

Scheme 84

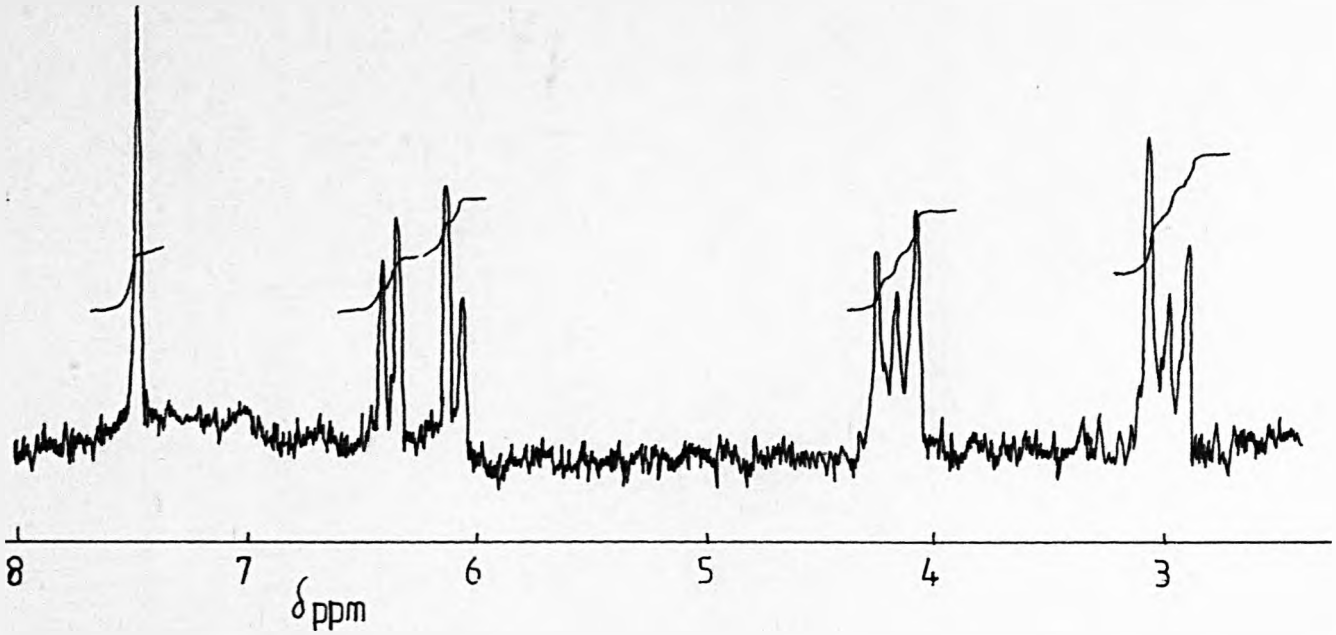
i)PTAB ii)$Br_2/CaCO_3$ or NBS/$CaCO_3$





(215)

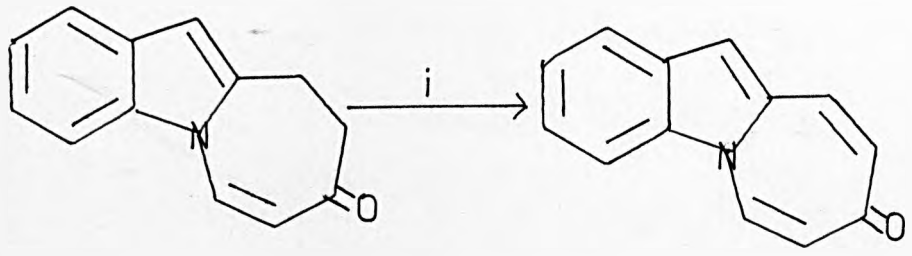
(216)



Another method which has been used with success in the generation of unsaturated carbon-carbon bonds is oxidation with dichlorodicyanoquinone (DDQ). The most relevant example of this is the preparation by Cliff and Jones[26] of azepino[1,2-a]indol-8-one.

Scheme 85

i)DDQ in boiling benzene



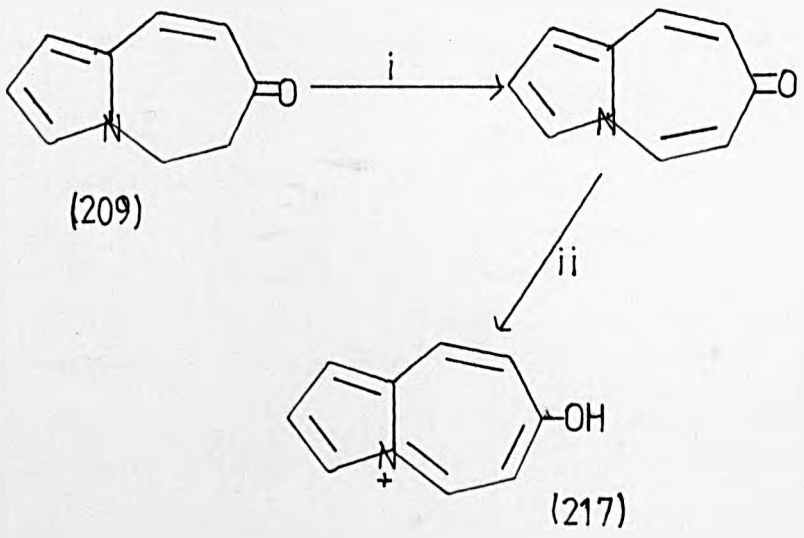
The dihydropyrroloazepinone (209) was treated with DDQ in boiling benzene, work up and chromatography gave a small amount of a yellow gum which was crystallized from hexane. The infra-red spectrum of this compound showed strong bands 1620 and 1650cm^{-1}, indicative of an α,β-unsaturated ketone.

The ^{1}H NMR spectrum of this compound in acetone left no doubt that this was the pyrrolo[1,2-a]azepin-7-one (1). There is a one proton doublet at 7.79ppm (J=10.37Hz) for proton 5 coupled to a doublet of doublets at 5.85ppm (J=10.37 and 2.44Hz) for proton 6. This is coupled in a W coupling to proton 8 at 6.10ppm which is

coupled by 12.33Hz to proton 9 at 7.34ppm. The pyrrolic protons appear at 7.55, 6.85 and 6.55ppm. The NMR spectra of this compound and the information to be gained from it is discussed more fully in the next chapter. In strong acids this ketone produces an intensely red solution which is believed due to the presence of the protonated form, a 10π7-hydroxypyrrolo[1,2-a]azepinium salt. This can be observed by NMR spectroscopy or by following the UV absorption which shifts to longer wavelengths in the protonated form.

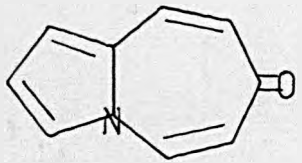
Scheme 86

i)DDQ, boiling benzene ii)H^+

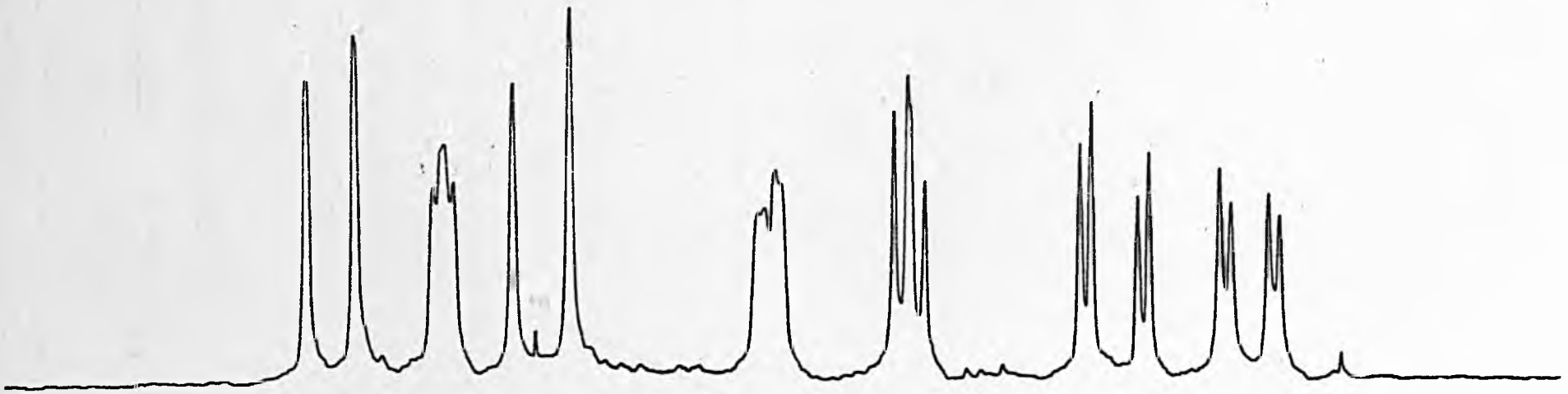


The yield of pyrrolo[1,2-a]azepin-7-one by DDQ oxidation is very low (1%), variation of the experimental conditions failed to increase the yield.

The generation of unsaturated carbon-carbon bonds has been achieved by use of palladium on charcoal, as in Ainsworth's[188] preparation of indazole from a partially saturated precursor. A



(in CD_3COCD_3)

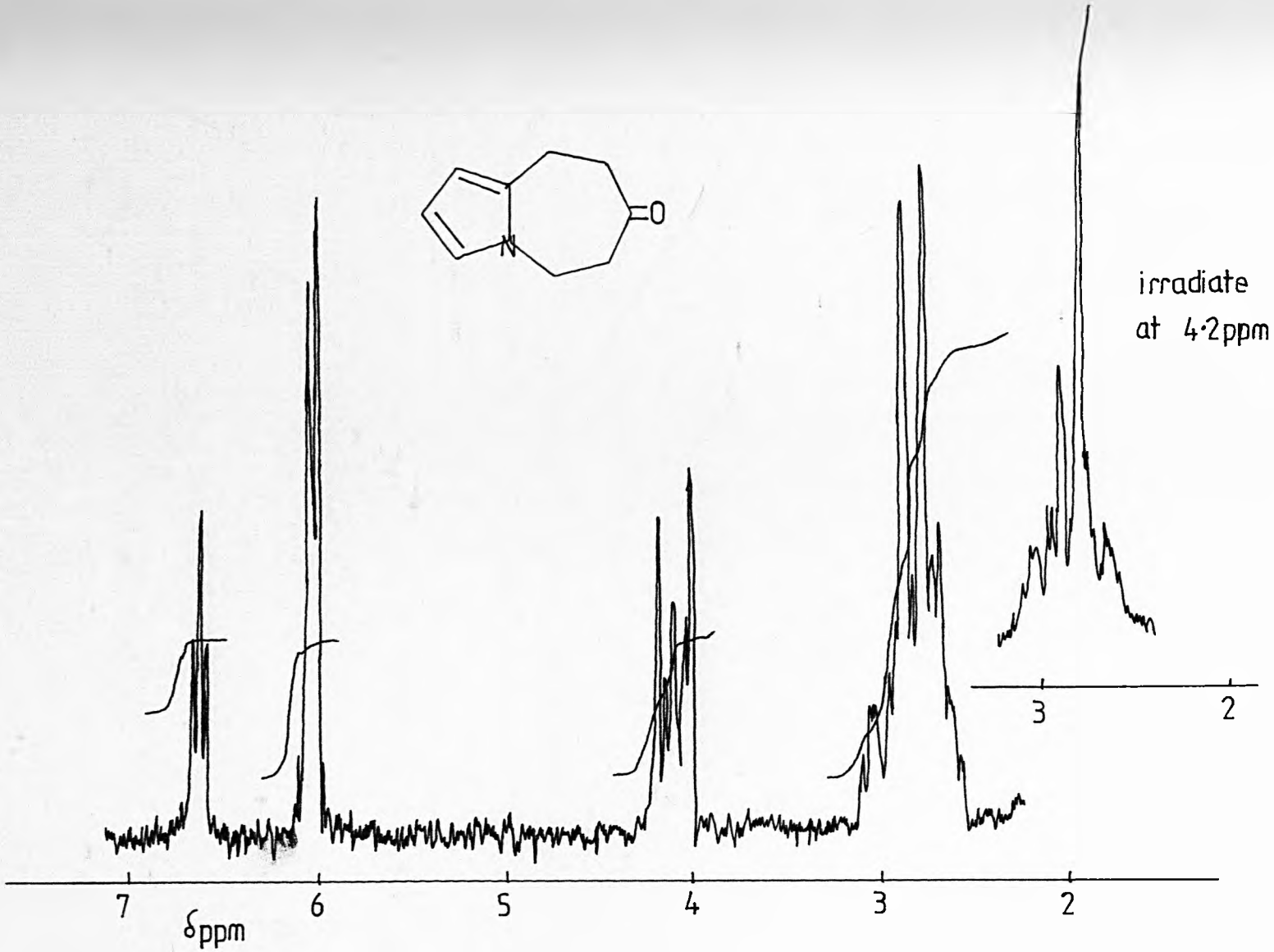


solution of 5,6-dihydropyrrolo[1,2-a]azepin-7-one was boiled in decalin in the presence of 10%Pd/C. Work up and chromatographic separation gave two compounds, one was identified as naphthalene, the other was recrystallized as cream needles from hexane. The infra-red spectrum of the new compound showed a strong peak at $1700cm^{-1}$, indicating that the ketone was no longer conjugated to the same extent as in the starting material. The ^{1}H NMR spectrum shows three pyrrolic protons; at 6.60ppm (a doublet of doublets J=2Hz) and as two superimposed doublets at 6.05ppm. There is a two proton multiplet at 4.10ppm and a six proton multiplet at 2.80ppm. This would indicate that the new compound is 5,6,8,9-tetrahydropyrrolo[1,2-a]azepin-7-one (218). This assignment is in agreement with the mass spectrum and analysis.

It would appear that this compound has arisen by hydrogenation on the palladium on carbon with hydrogen abstracted from the solvent, the formation of the aromatic naphthalene could provide the driving force for the reaction.

Palladium catalysed transfer hydrogenation [189-191] has been successful in reducing nitro groups to amines in the presence of cyclohexene which becomes oxidised to benzene. This reaction was attempted using nitrobenzene, 10%Pd/C and the dihydropyrroloazepinone (209) with the hope that the pyrroloazepinone would provide hydrogen for the reduction of nitrobenzene. Only starting materials were isolated.

Solid phase reactions were carried out between palladium on charcoal and 5,6-dihydropyrrolo[1,2-a]azepin-7-one under various conditions, those in sealed tubes gave slightly better yields ($250^{o}C$,


O
N
irradiate
at 4·2ppm
3
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δppm
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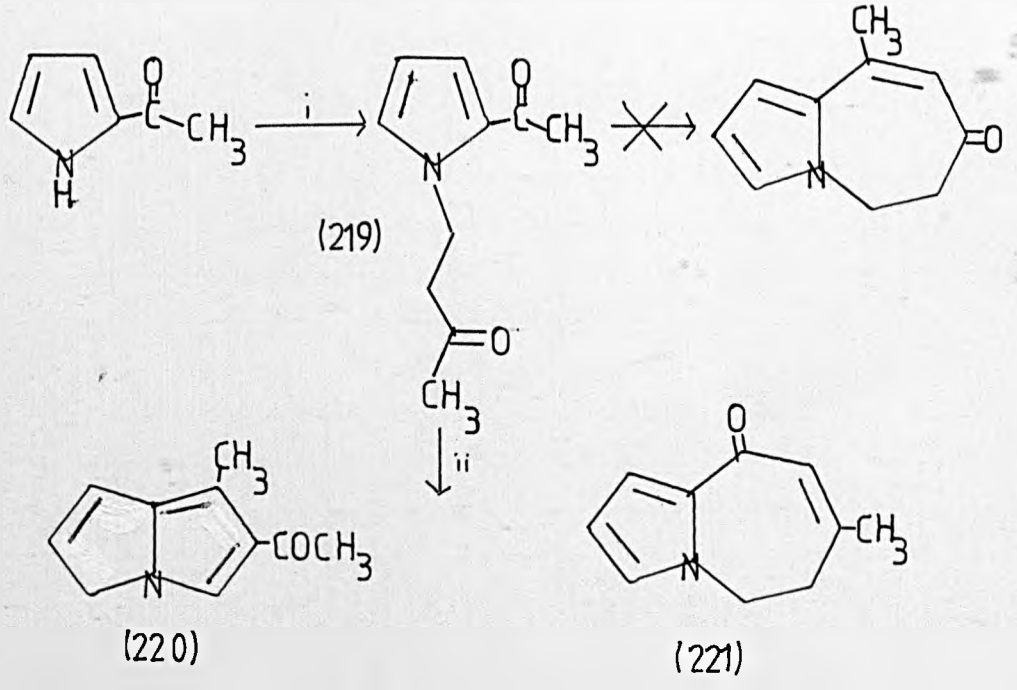
2

7%; 180°C, 8%). The best yields were gained by reaction at atmospheric pressure between palladium on charcoal and the dihydro ketone (209) at 170°C (up to 43%). The yields of this reaction were variable, sometimes being much lower. This was attributed to the heterogeneous nature of the reaction, resulting in inhomogeneous mixing and heating. This method was the method of choice for all subsequent preparations of the compound.

Attempts were made to prepare 9-methyl-5,6-dihydropyrrolo[1,2-a]azepin-7-one and dehydrogenate this. A Vilsmeier-Haack procedure produced 2-acetylpyrrole[192], which was N-alkylated as before to give the diketo pyrrole (219). Reaction of this in boiling ethanol with sodium ethoxide failed to give any of the desired ketone and gave instead small amounts of two isomeric ketones (220) and (221) as shown in scheme 87.

Scheme 87

i)Triton B, methyl vinyl ketone ii)NaOEt,HOEt

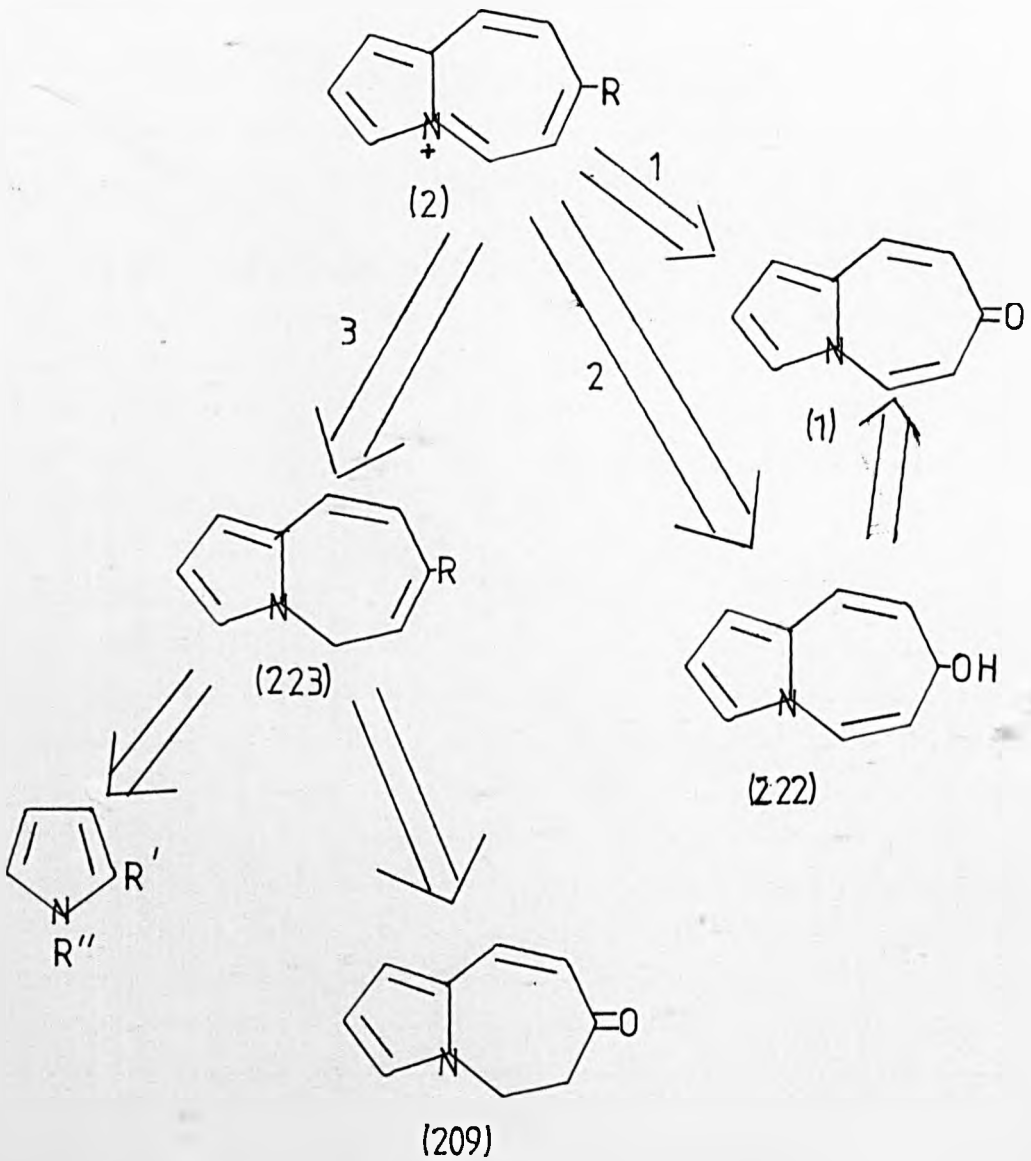


Thus the synthesis of pyrrolo[1,2-a]azepin-7-one has been established and sufficient material is available for further work.

The synthesis of pyrrolo[1,2-a]azepinium salts

The synthesis of the pyrrolo[1,2-a]azepinium system could now be approached via three routes, as shown in scheme 88.

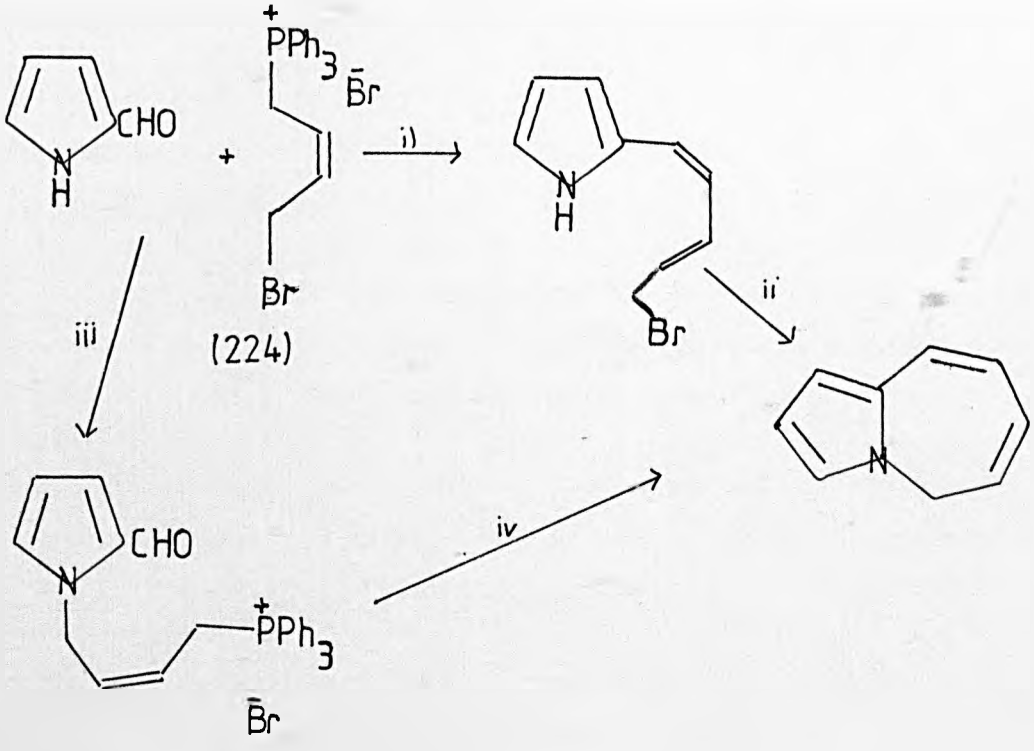
Scheme 88



These routes are; 1) from the previously prepared pyrrolo[1,2-a]azepin-7-one (1) by reaction with electrophiles which would be expected to attack the carbonyl group as do acids; 2) by removal of hydroxide from the alcohol (222), which could itself be prepared from the ketone (1); and 3) by hydride abstraction from a pyrrolo[1,2-a]azepine such as (223) which could be formed from the previously prepared 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209) or by a different cyclisation method from a suitably functionalized pyrrole.

The third route, from a pyrrole, was attempted using a Wittig reaction with 2-formylpyrrole to form the 8,9 double bond and an alkylation on nitrogen to form the 4,5 bond. The suggested synthesis is shown in scheme 89.

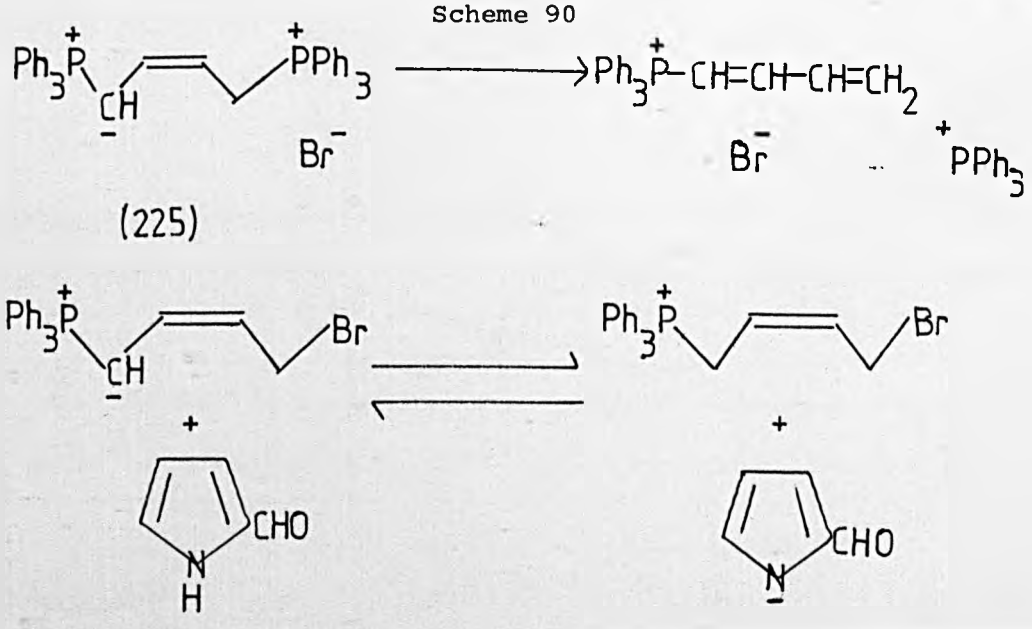
Scheme 89



The Wittig reaction and alkylation might occur in the same step under the influence of an appropriate base.

The phosphonium salt (224) has been reported before, although not isolated[193]. Z-but-2-ene-1,4-diol was dibrominated with phosphorus tribromide[194] and the phosphonium salt prepared in good yield by treatment of this dibromide with triphenylphosphine in benzene. However, further reactions of this compound were not so successful. During the attempted Wittig reaction it was probable that an ylide was generated, as evidenced by the appearance of a red colour. This colour was discharged on addition of 2-formylpyrrole to give a yellow solution. Work up gave only 2-formyl pyrrole. The ylide (225) undergoes an elimination reaction to form a salt[195], so it is possible that such a rearrangement reaction may occur in this reaction , with bromide as the leaving group; but the maintenence of the characteristic red colour would indicate not. It seems more probable that the ylide is acting as a base, forming the stable anion of 2-formylpyrrole and the starting phosphonium salt, thus discharging the red colour.

Scheme 90

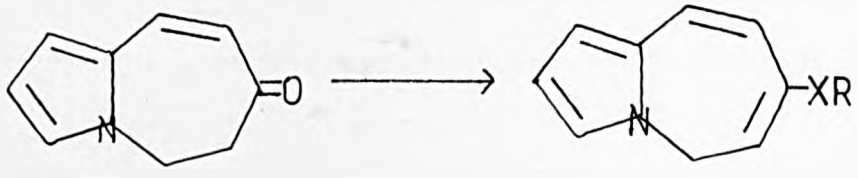


Attempts to effect the synthesis by first alkylating 2-formylpyrrole on nitrogen with the phosphonium salt using sodium hydride in DMSO were unsuccessful, producing two unidentified white solids whose NMR spectra showed only the presence of phenyl groups.

Attention was then turned to route 3 using 5,6-dihydropyrrolo[1,2-a]azepin-7-one as starting material in preparing the azepine system. The problem here is to convert a keto group into an endocyclic carbon-carbon double bond. One of simplest ways of doing this would be to generate the enol ether or enamine from the ketone.

Scheme 91

X=O or N*R*



(209)

There are a number of methods of forming enol ethers from ketones which fall into two classes, those which involve O-alkylation of an enolate prepared by action of base on the ketone and those which are acid catalysed.

To deal with the acid catalysed methods first, the method of House[196] of preparing enol acetates by reaction of ketones with

acetic anhydride in the presence of a catalytic amount of perchloric acid was attempted. After extended reaction times only starting materials were recovered. The same result occurred when Wohl's[197] method of generating methyl enol ethers was attempted under a variety of conditions. The attempted preparation of an enamine using standard methods[198] with morpholine or di-n-butylamine also gave only starting materials.

The preparation of enolates by reaction of base upon methylene ketones has been referred to previously in this thesis . Suitable choice of solvents can direct alkylation of the enolate onto oxygen, rather than carbon. Dimethoxyethane (DME) has been found to be a good solvent for this purpose[199].

The dihydro ketone (209) was treated with lithium diisopropylamide in DME at low temperature; quenching with D_2O and work up gave a yellow oil. The ^1H NMR spectrum of this oil shows that there has been deuteration at the 6 position. The mass spectrum of this oil shows peaks at 147, 148 and 149 mass units indicating that the oil is a mixture of dideuterated, monodeuterated and nondeuterated ketones; the height of the two peaks at lower mass are greater than would be expected from loss of proton or deuterium from the dideuterated compound. This reaction was repeated with the use of lithium hydroxide as base at room temperature. The ^1H NMR spectrum of the product leaves no doubt that the dideuterated compound has been prepared. This is confirmed by the mass spectrum. These results show that in both cases the enolate is formed from the ketone.

The low temperature reaction with the ketone was repeated a number of times, using as quenching agents; methyl iodide, acetyl

δ ppm
7
6
5
4
3
2
D
D
O

chloride[199] and trimethylchlorosilane[200], in various molar proportions and at longer reaction times. In no case was any product other than starting ketone isolated. The reaction with lithium hydroxide was repeated using methyl iodide as the alkylating agent, again only starting ketone was produced. A reaction between the dihydro ketone (209) and acetaldehyde in the presence of sodium hydroxide was attempted but, apart from self-condensation products of acetaldehyde, only the starting ketone was isolated. No condensation products between the ketone and acetaldehyde were produced.

These results are surprising as it is hard to envisage a mechanism where deuteration could occur α to the carbonyl group without enolisation and if such enolisation occurred it is hard to explain why no alkylation occurred. The ketone and alkylating agents are not sterically hindered to any great extent. The work up procedures excluded acid conditions.

The reaction with base of tosylhydrazones of ketones which have α hydrogen has been extensively used for the preparation of olefins in recent years[201-205]. Treatment of such hydrazones with strong base such as methyl lithium gives a vinyl anion (which can be protonated to an alkene), nitrogen and lithium tosylate. For such a route to be feasible the hydrazone must first be prepared from the ketone. Treatment of 5,6-dihydropyrrolo[1,2-a]azepin-7-one with tosylhydrazide under standard conditions of acid catalysis (p-toluenesulphonic acid, hydrochloric acid or acetic acid) or base catalysis (sodium acetate)[205] gave only the starting ketone as isolated product.

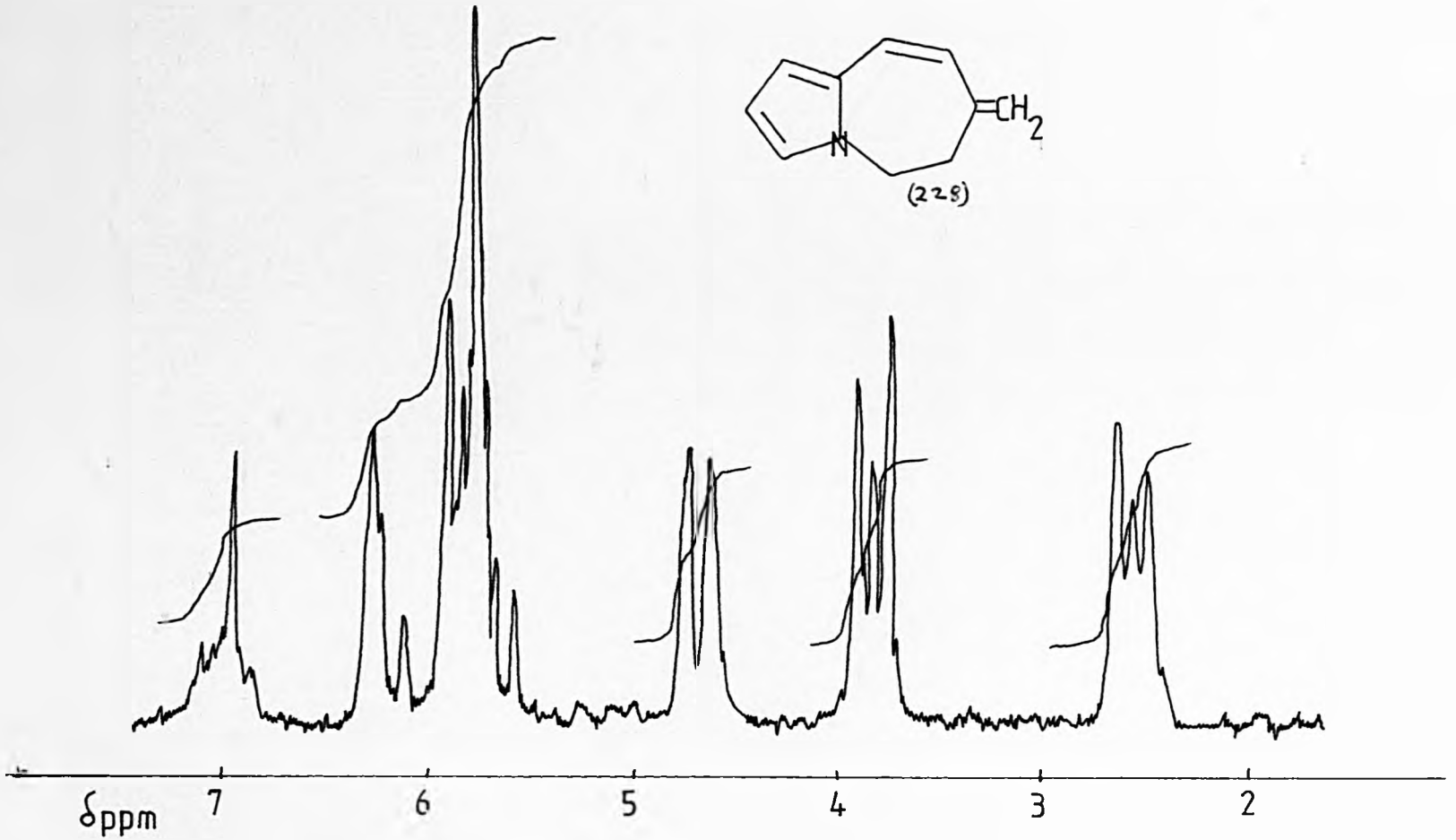
Alicyclic compounds with exocyclic methylene groups can undergo

equilibration in the presence of acid or base to give an equilibrium mixture of endo and exo alkenes[206,207]. In this equilibrium mixture the endo isomer usually predominates, in a 7-membered ring the proportions are 97% endo to 3% exo[207]. The Wittig reaction is a good method of preparing such exocyclic methylene compounds from cyclic ketones.

Reaction of 5,6-dihydropyrrolo[1,2-a]azepin-7-one with triphenylmethylenephosphorane gave after work up a pale yellow oil. The infra-red spectrum of this oil shows no carbonyl absorption. The ^{1}H NMR spectrum shows that the compound is the expected exo methylene compound (228). The peak centred at 4.7ppm is that due to the exocyclic methylene group. The unsaturated protons show considerably different chemical shifts from those in the ketones (1) and (209) as the anisotropy of the carbonyl group has been lost, so the chemical shifts are similar and it is not easy to identify coupling constants. This structure is supported by analysis and mass spectral data.

Reaction of this methylene compound with DDQ gave 5,6-dihydropyrrolo[1,2-a]azepin-7-one. This is surprising as although DDQ will oxidise alkanes to aldehydes and ketones[208-210] by an unknown mechanism, the cleavage a double bond to give a ketone has not been reported.

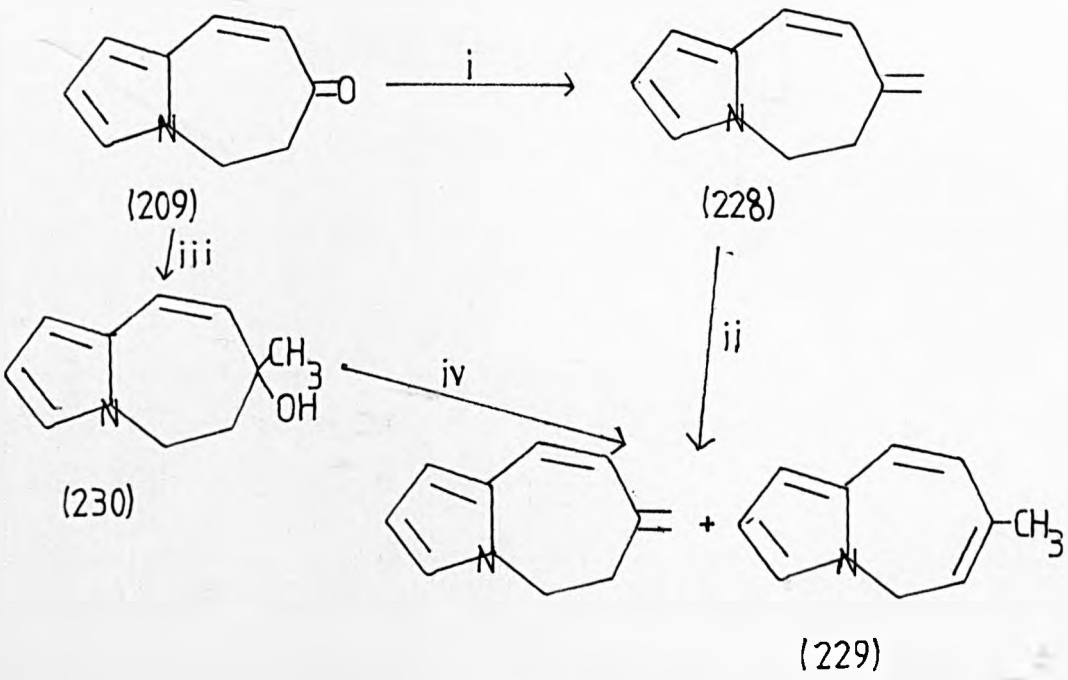
Equilibration of this methylene compound (228) using potassium t-butoxide in DMSO for 19 hours gave a yellow oil. The ^{1}H NMR showed the presence of the majority of starting material, but a singlet and a doublet at 4.3ppm(J=5Hz) (corresponding to the 6 proton on 7-methylpyrroloazepine (229)) show the presence of some endo isomer. The proportions are 37.5% endo 62.5% exo by integration of the NMR


CH2
N
(228)
δppm
7
6
5
4
3
2

spectrum. Reaction of this mixture for a further 70 hours increased the endo fraction only slightly (40% and 60%). Attempts at separation of these compounds proved unsuccessful, the compounds showed decomposition on silica P.L.C. plates.

Scheme 92

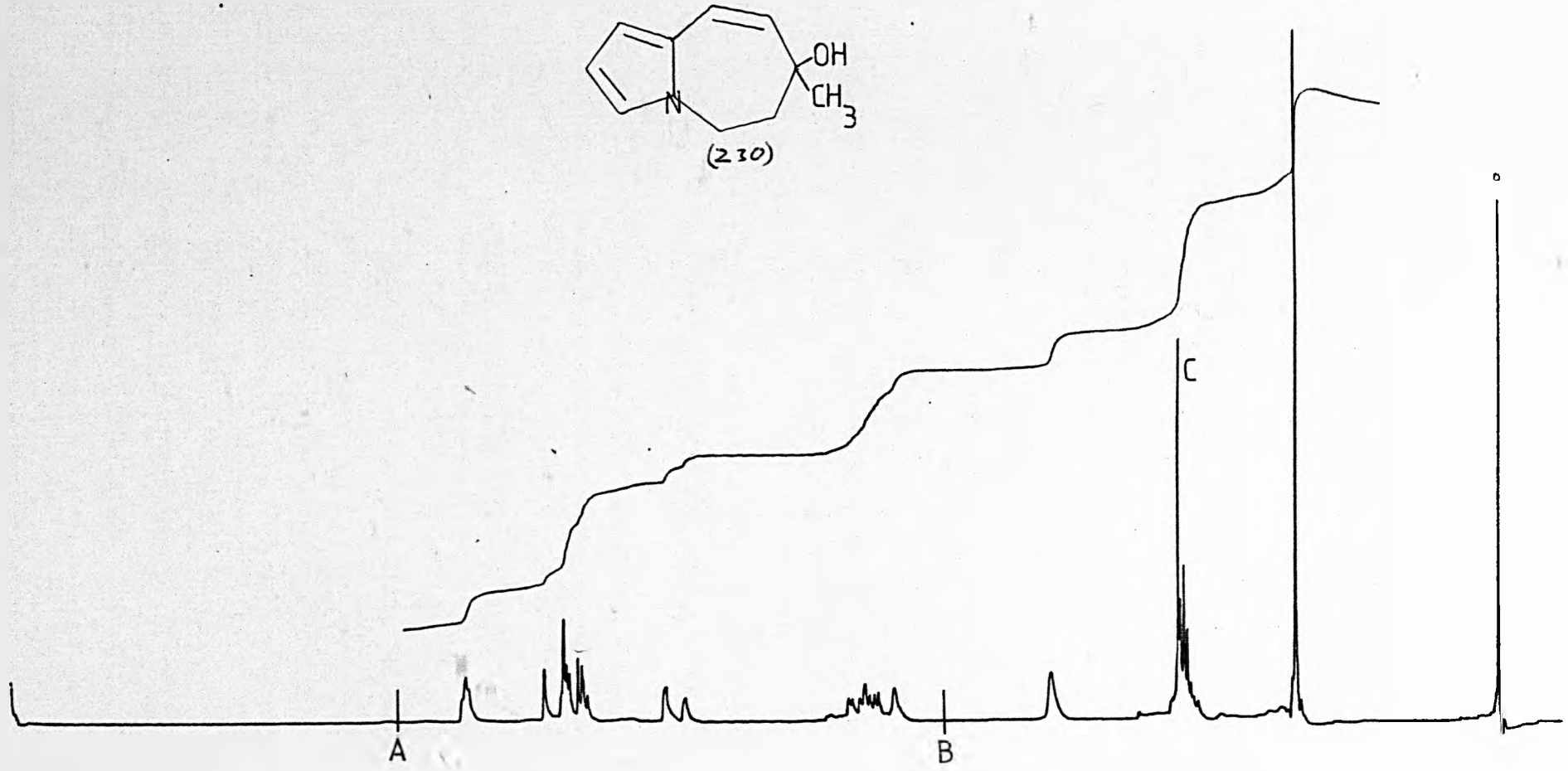
i)Ph_3PCH_2 ii)KO-t-Bu/DMSO

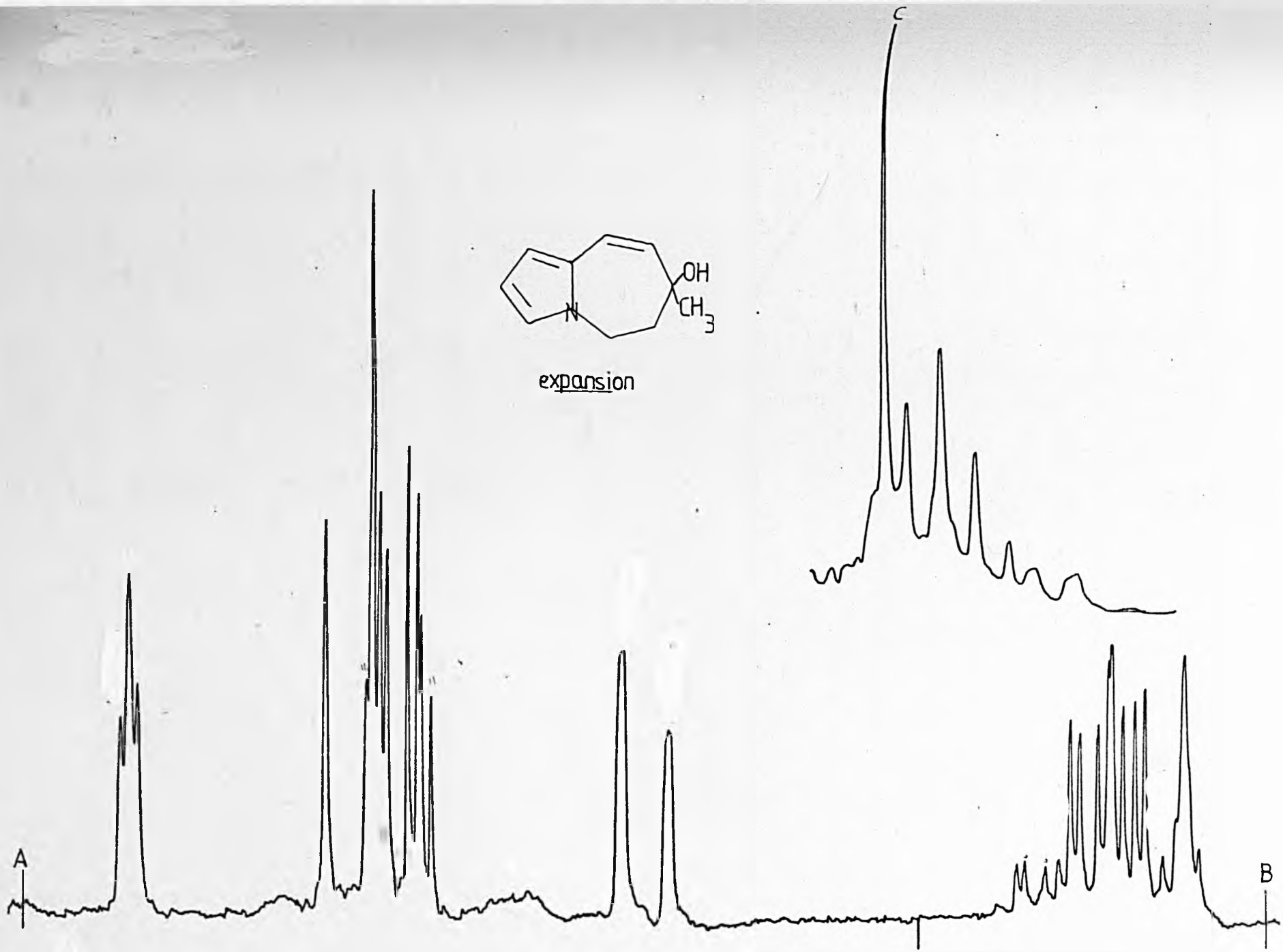


iii)MeLi/LiBr iv)p-TSA

An alternative preparation of the pyrroloazepine system would be by alkylation or reduction of the carbonyl group in the dihydro ketone (209) with subsequent elimination of water from the alcohol to give a pyrrolo[1,2-a]azepine.

The dihydro ketone (209) was treated with one equivalent of


OH
CH3
N
(230)
A
B
C
D


OH
CH3
N
expansion
C
A
B

methyl lithium; work up and purification by P.L.C. gave a yellow oil (56%) identified as 7-methyl-5,6-dihydropyrrolo[1,2-a]azepin-7-ol (230). The infra-red spectrum shows strong peaks at 1630 and 3410cm^{-1}. The ^{1}H NMR spectrum shows the expected spectrum. The notable features are the methyl singlet at 1.32ppm, the hydroxyl peak at 3.91ppm (exchangeable with D_2O) and the pair of doublets at 5.32 and 6.17ppm coupled by 12.45Hz due to protons 8 and 9 respectively. The mass spectrum shows loss of water from the molecular ion, also loss of 17 to give a peak at 146, the mass of the 7-methylpyrrolo[1,2-a]azepinium cation.

This alcohol (230) was dehydrated (in benzene) with a catalytic amount of p-toluenesulphonic acid. The products were the same mixture of endo and exo isomers (228) and (229), this time in the proportions of 50% exo 50% endo.

To eliminate the possibility of exo dehydration direct reduction of ketone (209) by hydride reducing agents was attempted. Previous workers had mixed success with such an approach. Cliff and Jones[26] found that reduction of indoloazepinone gave preferential attack of a conjugated double bond rather than the carbonyl. Collington and Jones[214] found that the action of sodium borohydride or lithium aluminiumhydride on some indoloazepinones gave only the desired product in one, irreproducible, instance.

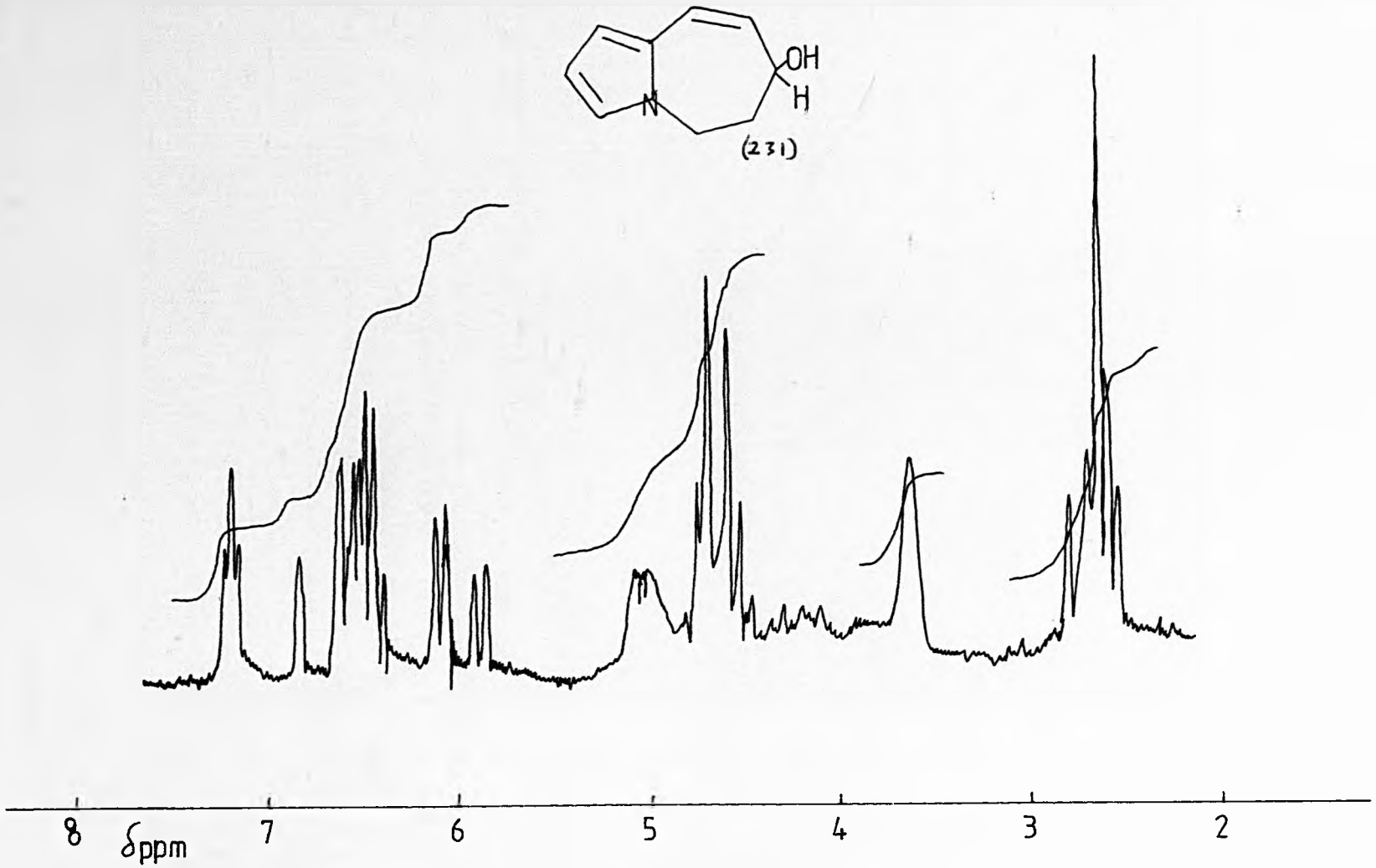
The best hydride reduction agent for this purpose would appear to be 9-borabicyclo[3.3.1]nonane (9-BBN). This reagent selectively reduces enones to allylic alcohols in good yields[211,212]. The dihydro ketone (209) was treated with 9-BBN, but work up gave only a small amount of recovered starting material.

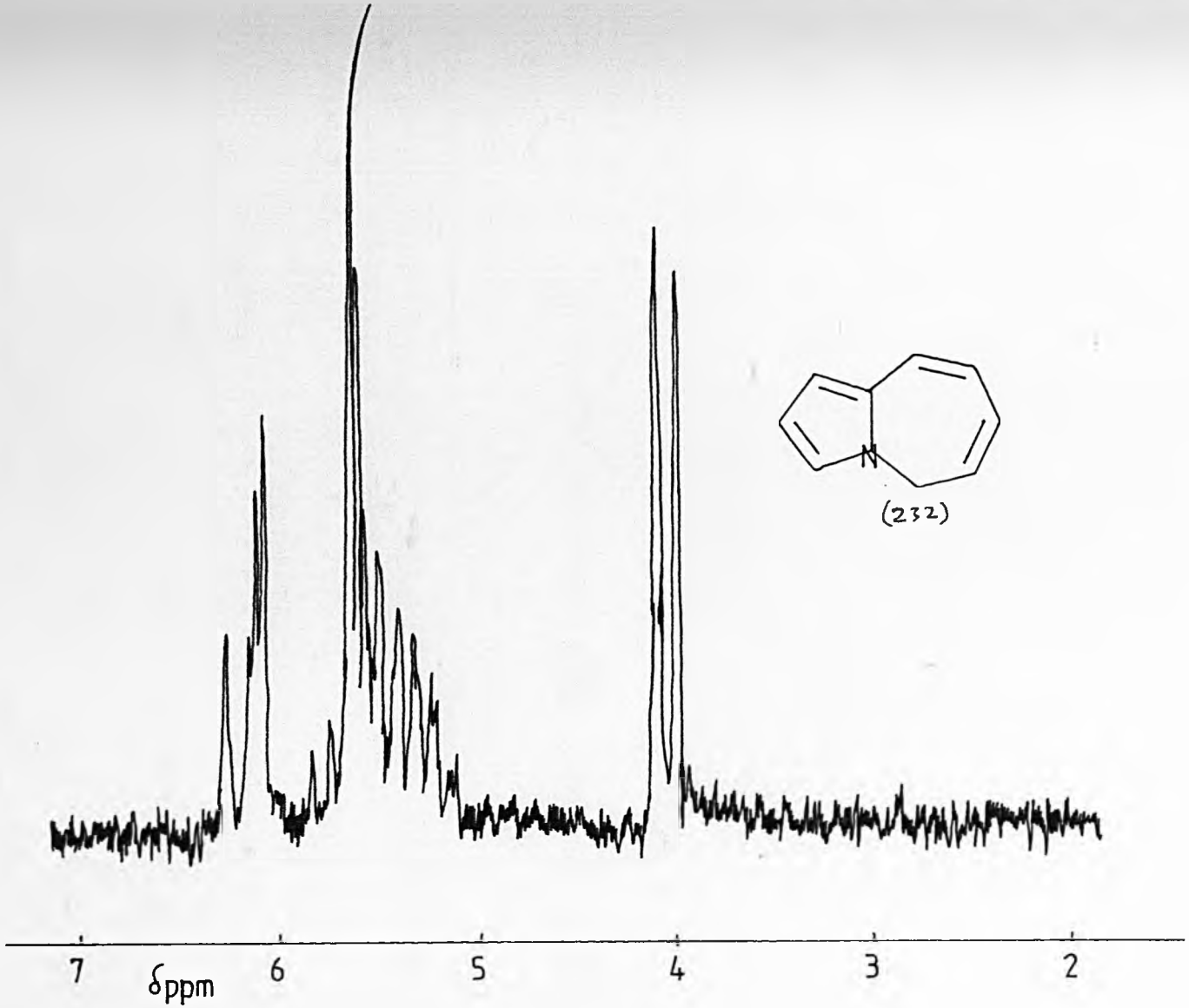
There has recently been a report[213] of the reduction of an enone to an allylic alcohol in good yield by use of an excess of sodium borohydride. The dihydro ketone (209) was treated with two equivalents (0.5 molar proportions) of sodium borohydride in ethanol at 0°C. After work up and chromatography a yellow oil was isolated. The similarity in the spectral details of this compound and the 7-methyl-7hydroxy compound (230) leaves no doubt that the 7-hydroxypyrroloazepine (231) has been prepared. The infra-red spectrum shows similar bands. The ^{1}H NMR spectrum is similar also, with the exceptions that the doublet at 5.4ppm now also shows coupling of 3Hz to the 7 proton which appears as a multiplet at 4.42pm. The two proton peak for the 6 protons appears at 2.1ppm as a multiplet.

This alcohol (231) was dehydrated by the same method as used for the 7-methyl alcohol (230) but with a longer reaction time. Chromatography on alumina gave the first unsubstituted 5H-pyrrolo[1,2-a]azepine (232). The ^{1}H NMR spectrum shows a complex pattern, however the two proton doublet (J=5Hz) for the 5 protons, the doublet of the 9 proton (J=9Hz) and the multiplet for the 3 proton are visible. The infra-red spectrum and mass spectrum support this structure.

To transform this alkene into the parent pyrrolo[1,2-a]azepinium salt now requires the removal of a hydride ion. A commonly used reagent for this purpose is triphenylmethyl perchlorate or tetrafluoroborate, which has been used by Dauben and co-workers[215] to prepare the tropylium system from cycloheptatriene.

The pyrroloazepine (231) was treated with 1 equivalent of trityl tetrafluoroborate in dichloromethane, when a blue solution was

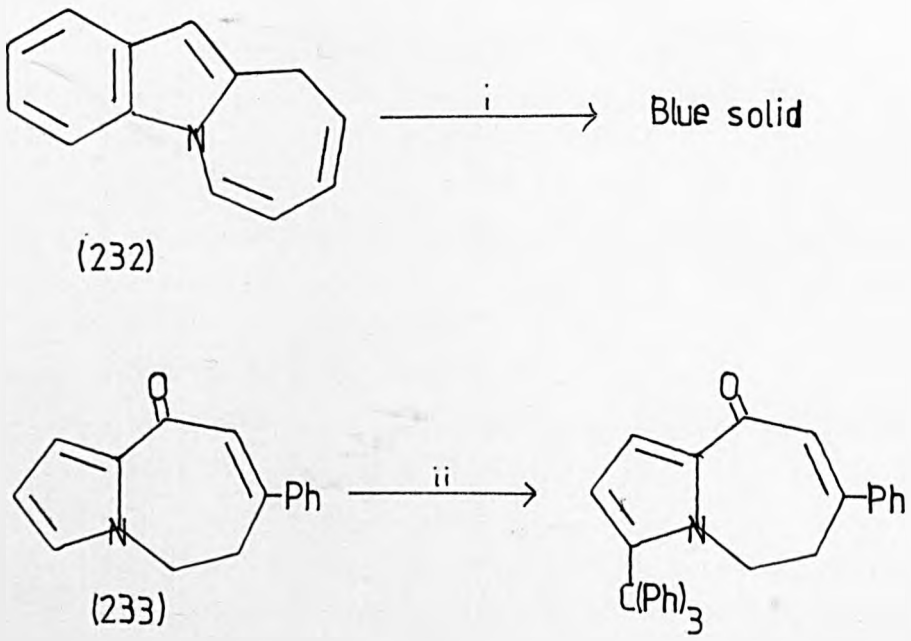

OH
H
N
(231)
8
δppm
7
6
5
4
3
2



(232)

quickly formed. Removal of dichloromethane and precipitation from diethyl ether gave a blue solid which could not be characterized. Such blue solids have been produced by similar attempted hydride abstractions from the azepinoindole (232).

i)Trityl perchlorate ii)Trityl perchlorate/Et_3N



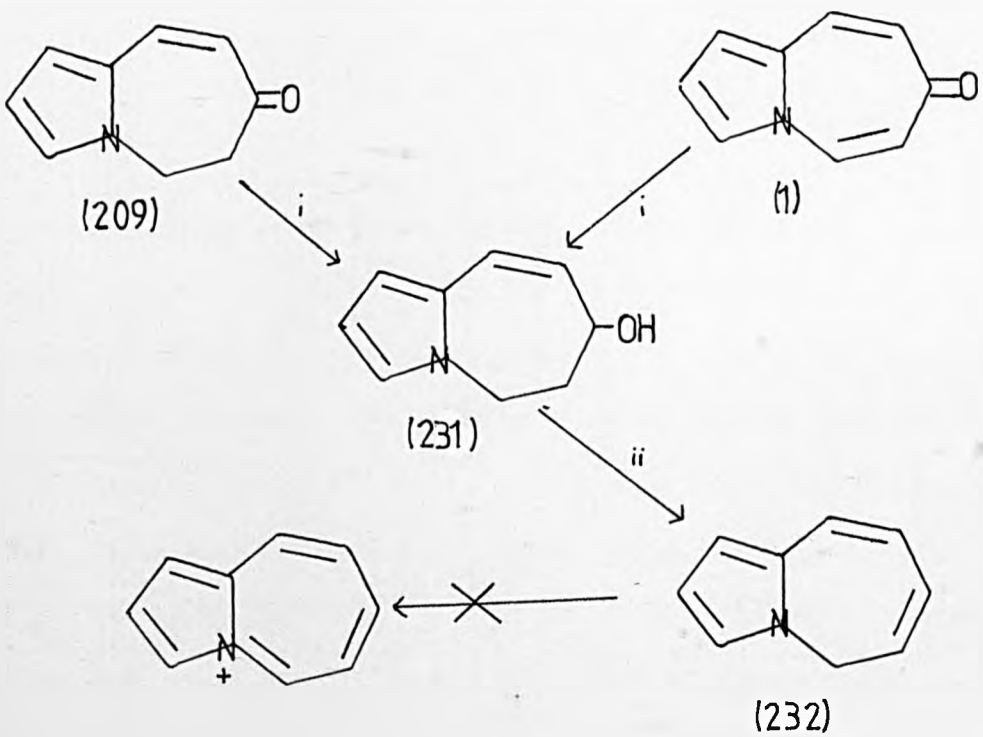
In a similar reaction the ketone (233) was found to be s substituted by the trityl group, although the authors[185] did not mention the colour or UV absorption of the product.

Therefore, although a pyrrolo[1,2-a]azepine has been made the final step of hydride abstraction to the salt has not been achieved.

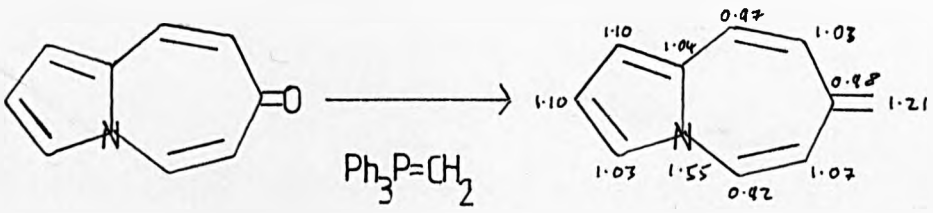
The third approach to the pyrrolo[1,2-a]azepinium system discussed earlier was from pyrrolo[1,2-a]azepin-7-one (1), either via

the corresponding alcohol or by reaction of the carbonyl group with certain electrophiles. Pyrrolo[1,2-a]azepin-7-one (1) was treated with methyl lithium under conditions successful for the preparation of the methyl alcohol (230), but unsuccessfully. Treatment of ketone (1) with sodium borohydride gave the dihydro alcohol (231). In this case reduction of the double bond has occurred as well as that of the carbonyl group. This bears out the observation of Jones and Cliff[26] that this double bond is the more reactive bond in such compounds.

i)$NaBH_4$ ii)p-toluenesulphonic acid



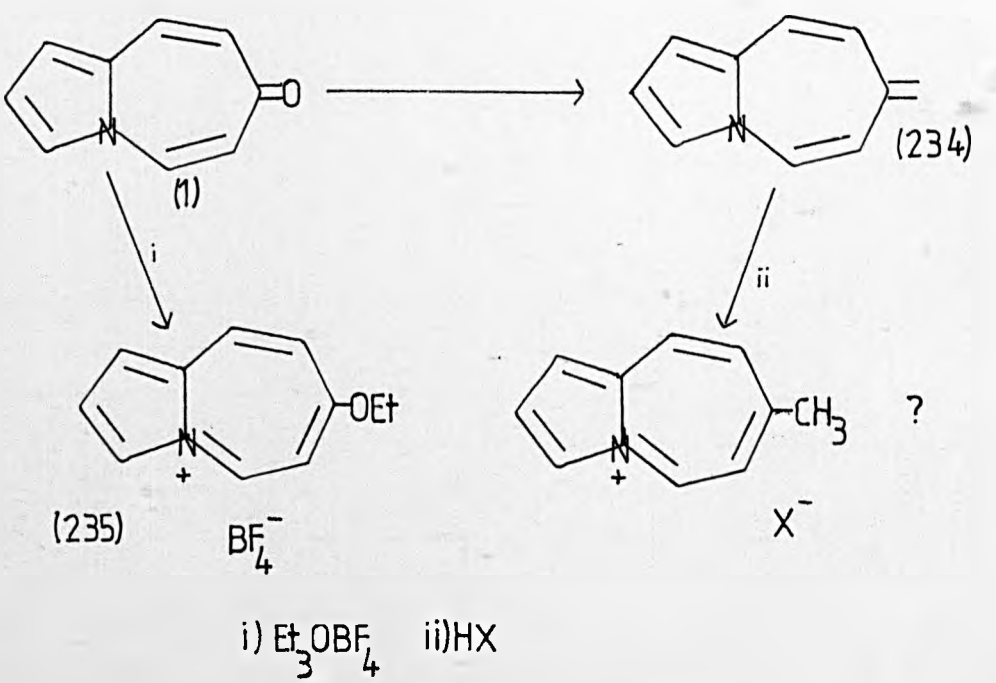
The unsaturated ketone (1) undergoes a Wittig reaction with triphenylmethylenephosphorane to give the methylene compound (234) in the same manner as the dihydro ketone (209). Simple Huckel MO calculations [216] on the methylene compound (234) (h_N=1.5 k_{CN}=1.0) give the charge densities as shown below.

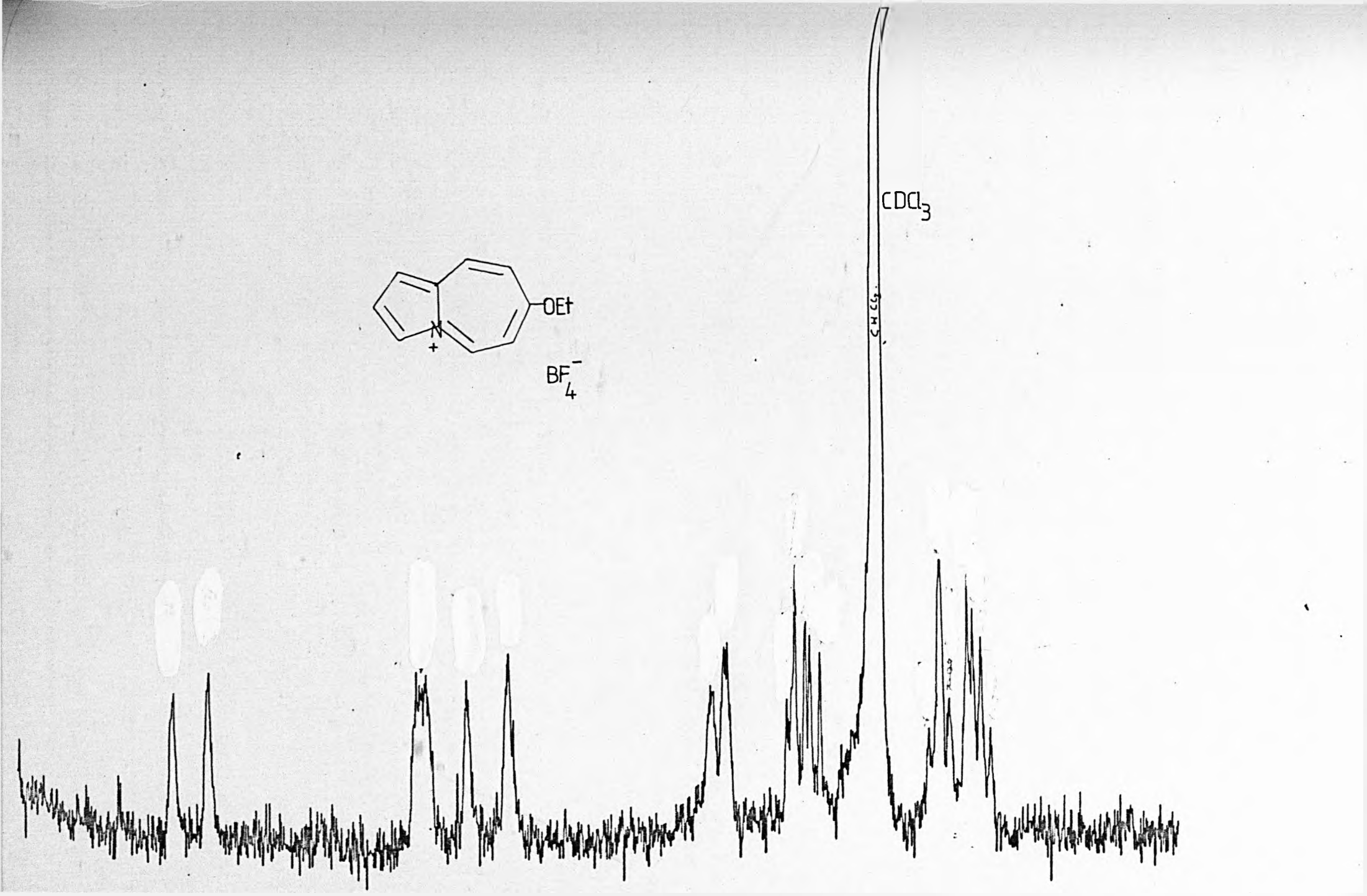


(234)

These charge densities imply that protonation of this compound should occur on the exocyclic double bond and so give a pyrrolo[1,2-a]azepinium salt. Protonation was achieved by a variety of protonating acids (HBr, TFA, HBF_4); all gave a deep red solution (λ max 475nm) indicating the presence of the pyrrolo[1,2-a]azepinium system. However all attempts to obtain NMR spectra or isolate these salts failed and only reddish gums resulted. This may have been due to cationic polymerization, one protonated molecule attacking an unprotonated molecule in an electrophilic condensation to give another cation. In order to minimize this possibility the methylene compound was dissolved in fluorosulphonic acid, although a red solution was produced the NMR spectrum was again unsatisfactory.

The parent ketone (1) will protonate to varying extents in different acidic media to give good NMR spectra showing the presence of the protonated form. However application of this technique with the object of isolating the salts failed to give any crystalline products, despite the rigid exclusion of moisture (such salts depronate easily to the parent ketone[26]). One other method which has been successful[26] is ethylation with triethyloxonium tetrafluoborate[217]. Treatment of a dichloromethane solution of the ketone (1) with this reagent produced a red solution. Removal of solvent and trituration in diethyl ether under nitrogen gave a red solid. The UV spectrum of the solid was as expected. The NMR spectrum in $CDCl_3$ is almost identical with those of the fully protonated ketone (1). (See next chapter). However the integration of the NMR spectrum shows that the ethyl peaks are too intense, indicating that the solid still contains some triethyloxonium tetrafluoborate which is borne out by the analysis figures and it proved impossible to remove this contaminant.




OEt
BF4−
CDCl3

Therefore although some of the pyrrolo[1,2-a]azepinium salt (235) has been produced it has not been possible to prepare a pure sample.

Preparation of 1-(butan-3-on-1-yl)-2-formylpyrrole

To a stirred solution of 2-formylpyrrole (17g, 0.18moles) and but-1-en-3-one (20.4g, 0.28moles) in 1,4-dioxan (500ml) cooled in an ice bath was added a portion of benzyltrimethylammonium hydroxide in methanol (3ml of a 40% solution) over a period of 10 minutes. The mixture was stirred for a further 45 minutes.

The solution was added to water (1500ml) and neutralized with dilute hydrochloric acid. The solution was extracted with dichloromethane (3 portions of 500ml), the combined organic extracts dried and the solvents removed under reduced pressure. The yellow oil was distilled under reduced pressure to give the keto-aldehyde at 81°C/0.05mmHg (20.2g, 68%).

^{1}H NMR ($CDCl_3$, TMS internal standard)

9.35ppm	1H	s	
6.90ppm	2H	m	
6.15ppm	1H	m	
4.40ppm	2H	t	(J=7Hz)
2.90ppm	2H	t	(J=7Hz)
2.05ppm	3H	s	

IR ($CHCl_3$ ν max) 1660, 1720cm^{-1}

UV (95% EtOH λ max) 221nm ($\log_{10}\varepsilon$ =3.41)
280 sh
300 ($\log_{10}\varepsilon$ =3.54)

Analysis:

$C_9H_{11}NO_2$ requires C=65.45% H=6.67% N=8.49%
obtained C=65.27% H=6.23% N=9.02%

Mass spectrum

165(40.9%), 122(49.9), 94(68.2)
66(31.8), 44(27.3), 43(100), 39(45.5)

Aldol condensation of 1-(butan-3-on-1-yl)-2-formylpyrrole using sodium ethoxide.

A solution of 1-(butan-3-on-1-yl)-2-formylpyrrole (10g, 0.06mole) in absolute ethanol (10ml) was added over 5 minutes to a stirred boiling solution of sodium ethoxide in ethanol (from 1.4g sodium in 500ml absolute ethanol). The mixture was refluxed for 40 minutes then allowed to cool.

Most of the solvent was removed under reduced pressure and the brown residue partitioned between water (300ml) and dichloromethane (500ml). The aqueous phase was extracted with dichloromethane (5 portions of 500ml), the combined organic phase dried and solvent removed under reduced pressure. The resulting brown gum was purified by column chromatography on alumina (120g of activity IV). Elution with benzene/light petroleum (30/70) gave 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209) (3.5g, 40%) as a yellow oil, further elution with benzene/light petroleum (40/60) gave 6-acetyl-3H-pyrrolizine (210) (2.7g, 31%) as a yellow gum.

5,6-dihydropyrrolo[1,2-a]azepin-7-one (209)

^1H NMR ($CDCl_3$, TMS internal standard)

7.05ppm	1H	d (J=11Hz)
6.80ppm	1H	m
6.40ppm	1H	m
6.15ppm	1H	m
5.90ppm	1H	d (J=11Hz)
4.05ppm	2H	m
2.85ppm	2H	m

Yellow crystals Mp. 55-56°C (hexane)

IR ($CHCL_3$, νmax) 1610, 1665cm^{-1}

Analysis:

C_9H_9NO requires C=73.47%, H=6.12%, N=9.52%

obtained C=73.33%. H=6.39%, N=9.71%

Mass spectrum

$^{m}/_{e}$ 147(M^+, 13.5%), 146(100%)
118(56.8%), 117(72.9%), 90(40.5%)
64(18.9%), 39(16.2%).

6-acetyl-3H-pyrrolizine (210)

yellow needles Mp. 60-61°C (hexane)

^1H NMR ($CDCl_3$, TMS internal standard)

7.50ppm	1H	bs
6.50ppm	1H	m (d J=5Hz when 4.45ppm irradiated)
6.28ppm	1H	s
6.20ppm	1H	m (d J=5Hz when 4.45ppm irradiated)
4.45ppm	2H	bs
2.35ppm	3H	s

IR (mull ν max) 1650, 1710cm^{-1}

UV (95% EtOH, λ max) 250nm ($\log_{10} \varepsilon$ 3.31)
292nm ($\log_{10} \varepsilon$ 2.95)

Analysis:

C_9H_9NO requires C=73.47% H=6.12% N=9.52%
obtained C=73.12% H=5.87 N=9.64%

Mass spectrum

$^{m}/_{e}$ 147(M^+ 48%) 146(100%), 132(37%),
131(92%), 118(48%), 104(47%), 103(100%)
39(26%).

Preparation of pyrrolo[1,2-a]azepin-7-one (I) by DDQ oxidation

A solution of the dihydro ketone (209) (1g) and dichlorodicyanobenzoquinone (DDQ) (3.1g) in anhydrous benzene (100ml) was refluxed for 7 hours under nitrogen.

The mixture was filtered to give a red filtrate from which the

solvent was removed under reduced pressure. The residue was purified by column chromatography on alumina (30g activity IV), elution with chloroform/benzene (20/80) gave yellow crystals of the ketone (ı) which were recrystallized from hexane to give yellow needles Mp 119-120°C (10mg, 1%).

^{1}H NMR (CD_3COCD_3, TMS internal standard)

7.79ppm	1H	d (J=10.37Hz)
7.55ppm	1H	m
7.34ppm	1H	d (J=12.33Hz)
6.85ppm	1H	m
6.55ppm	1H	dd (J=3.76,2.85Hz)
6.10ppm	1H	dd (J=12.33,2.44Hz)
5.82ppm	1H	dd (J=10.37,2.44Hz)

IR ($CHCl_3$ ν max) 1620, 1650cm^{-1}

UV (95%EtOH) 260nm ($\log_{10}\varepsilon$ 4.66)
290 3.77
307 3.67
360 3.47

(96%H_2SO_4) 262nm ($\log_{10}\varepsilon$ 3.81)
297 4.04
356 3.86
455 2.87

Mass spectrum

$^m/_e$ 145(M^+ 91%), 144(38%), 142(43%), 117(100%), 90(49%), 89(28%), 39(26%).

Analysis C_9H_7NO requires C=74.47, H=4.86, N=9.65%
obtained C=74.70, H=4.58, N=9.45%

Attempted transfer dehydrogenation of 5,6-dihydropyrrolo[1,2-a]azepin-7-one

A mixture of the dihydro ketone (209) (1g, 6.8mmoles), nitrobenzene(0.5g 4.5mmoles) and 10% palladium on charcoal (1g) in ethanol (50ml of 95%) was refluxed for 6 hours.

The mixture was filtered and solvent removed from the filtrate to a give residue which contained only starting materials.

Preparation of 5,6,8,9-tetrahydropyrrolo[1,2-a]azepin-7-one

A mixture of the dihydro ketone (209) (0.2g), 10% palladium on charcoal (0.2g) and decalin (30ml) was refluxed under nitrogen for 90 minutes.

The mixture was cooled and filtered and the filtrate extracted with portions of methanol (4 portions of 10ml). The solvent was removed from the combined methanolic extracts to give a pale yellow oil still containing decalin. This oil was purified by P.L.C. (20%ethyl acetate/toluene). Two main fractions were produced. The faster running fraction was found to be naphthalene.

The slower running fraction was recrystallized from hexane as cream needles, the tetrahydro ketone (218) (Mp.93-94°C, 18mg, 9%).

5,6,8,9-tetrahydropyrrolo[1,2-a]azepin-7-one (218)

^{1}H NMR ($CDCl_3$, TMS internal standard)

6.60ppm	1H	dd (J=2Hz)
6.05ppm	2H	superimposed d (J=2Hz)
4.10ppm	2H	m
2.80ppm	6H	m

IR ($CHCl_3$, ν max) 1700cm^{-1}

Analysis:

$C_9H_{11}NO$ requires C=72.45%, H=7.43, N=9.39

obtained C=72.04%, H=7.38, N=9.22

Mass spectrum

$^m/_e$ 149(M^+, 15%), 148(100%), 147(89%), 105(92%), 78(29%)

Preparation of pyrrolo[1,2-a]azepin-7-one without solvent

A mixture of the dihydro ketone (209) (0.1g) and 10% palladium on charcoal (0.1g) in a sealed Carius tube was heated at 250°C for 6 hours.

The tube was allowed to cool, was opened and the mixture extracted with dichloromethane (150ml) and filtered. The solvent was removed from the filtrate to give a yellow oil. Purification of this oil by P.L.C. (25% ethyl acetate/toluene) gave the starting ketone (13.2mg) and pyrrolo[1,2-a]azepin-7-one (1) (7.7mg, 7%yield).

This reaction was repeated at 180°C for 15 hours to give a slightly improved yield of pyrrolo[1,2-a]azepin-7-one (8%).

The best yield of pyrrolo[1,2-a]azepin-7-one was achieved by heating the same proportions of reactants at 180°C under nitrogen at atmospheric pressure for 20 hours, (40% yield). This yield was, however very variable and was often lower with a considerable proportion of starting material being returned.

Bromination of 5,6-dihydropyrrolo[1,2-a]azepin-7-one

To a stirred mixture of dihydro ketone (209) (0.1g, 0.7mmoles), calcium carbonate (0.5g) and carbon tetrachloride (30ml) was added dropwise a solution of bromine in carbon tetrachloride (2ml of a 5% solution, 0.7mmoles). The mixture was stirred for a further 4 hours.

The reaction mixture was filtered and the solvent removed from the filtrate under reduced pressure at room temperature to give a brown oil (0.13g). This brown oil was purified by P.L.C. (35% ethyl acetate/toluene) to give two bands.

3,8-dibromo-5,6-dihydropyrrolo[1,2-a]azepin-7-one (216)

Rf 0.83 (31%) Mp 125°C (diethyl ether) yellow crystals

^{1}H NMR (CCl_4, TMS internal standard)

7.5ppm	1H	s
6.4ppm	1H	d (J=4Hz)
6.1ppm	1H	d (J=4Hz)
4.2ppm	2H	m
3.0ppm	2H	m

IR (CCl_4 ν max) 1660, 1585cm^{-1}

Analysis:

$C_9H_7NOBr_2$ requires C=35.4%, H=2.6, N=4.6

obtained C=35.28%, H=2.78, N=4.46

Mass spectrum

$^m/_e$ 307(18.9%), 305(36.7%), 303(20.2%),
227(13.4%), 226(40.5%), 224(41.7%),
150(100%), 118(20.2%), 117(37.95), 93(40.5%),
91(43.1%), 39(18.9%)

8-bromo-5,6-dihydropyrrolo[1,2-a]azepin-7-one (215)

Rf 0.66 (27%) Yellow oil

^{1}H NMR (CCl_3 TMS internal standard)

7.6ppm	1H	s
6.7ppm	1H	m
6.4ppm	1H	m
6.05ppm	1H	m
4.15ppm	2H	m
3.0ppm	2H	m

IR (CCl_4 ν max) 1660, 1585cm^{-1}

Analysis:

C_9H_8NOBr requires C=47.8%, H=3.5% N=6.2%

obtained C=47.21%, H=3.52 N=6.28%

Mass spectrum

$m/_e$ 227(34.4%), 225(34.4%), 147(35.8%),
145(49.9%), 118(68.7%), 117(34.4%), 109(21.8%)
93(100%), 91(93.7%), 81(53.1%)

Bromination of 5,6-dihydropyrrolo[1,2-a]azepin-7one with PTAB

To a stirred solution of the dihydro ketone (209) (0.1g, 0.7mmoles) in anhydrous tetrahydrofuran (30ml) was added under nitrogen a portion of phenyltrimethylammonium tribromide (PTAB) (0.25g, 0.7mmoles). The mixture was stirred for 4.5 hours then filtered. The filtrate was mixed with sodium bicarbonate solution (50ml, 5%) and extracted with dichloromethane (50ml). The organic phase was dried and the solvent removed under reduced pressure to give a brown oil which was shown by NMR analysis to contain only the starting materials.

This reaction was repeated in the presence of calcium carbonate (0.5g) to give again starting material and a little (5%) of the monobromo ketone (215).

Bromination of 5,6-dihydropyrrolo[1,2-a]azepin-7-one with N-bromosuccinimide

A mixture of the dihydro ketone (209) (0.1g, 0.7mmoles), N-bromosuccinimide (NBS) (0.12g, 0.7mmoles) and carbon tetrachloride (25ml) was refluxed over a tungsten lamp (150W) for 3.5 hours.

The mixture was filtered and the solvent removed to give a green oil. NMR analysis of this oil shows the presence of a large proportion of the starting ketone and a little of the previously identified bromo compounds (215) and (216).

The oil was treated with more NBS (0.24g, 1.4mmoles) under the same conditions. Work up as before gave an oil (0.24g). Analysis of

this oil by NMR showed it to contain the mono bromo ketone (215) and the di bromo ketone (216) in the ratio 5:2.

Preparation of 2-acetylpyrrole

2-acetylpyrrole was prepared by a Vilsmeier procedure using N,N-dimethylacetamide to give cream crystals of 2-acetylpyrrole (from water). Mp 89-90°C (lit 90°C) in 70% yield.

Preparation of 1-(butan-3-on-1-yl)-2-acetylpyrrole (219)

This was prepared by the same procedure as was used to prepare 1-(butan-3-on-1-yl)-2-formylpyrrole (219) in 97% yield without distillation.

^{1}H NMR (CCl_4, TMS internal standard)

6.80ppm	2H	m	
5.90ppm	1H	m	
4.35ppm	2H	d	(J=6Hz)
2.80ppm	2H	d	(J=6Hz)
2.30ppm	3H	s	(acetyl)
2.00ppm	3H	s	

Aldol condensation of 1-(butan-3-on-1-yl)-2-acetylpyrrole

The procedure followed was the same as that used for the condensation the corresponding formyl derivative using sodium ethoxide in ethanol.

The addition of a solution of the acetyl pyrrole (219) (1.8g 0.01moles) to boiling sodium ethoxide solution (0.23g sodium in

150ml ethanol) gave after work up a brown oil (1.4g).

This oil was purified by P.L.C. (25%ethyl acetate/toluene) to give two major products.

7-methyl-6-acetyl-3H-pyrrolizine (220)

Rf 0.71 30mg (2%)

^1H NMR ($CDCl_3$ TMS internal standard)

6.9ppm	1H	m
6.7ppm	1H	m
6.1ppm	1H	m
4.5ppm	2H	bs
2.4ppm	3H	s
2.3ppm	3H	s

IR ($CHCl_3$ ν max) 1640, 1665cm^{-1}

Analysis:

$C_{10}H_{11}NO$ requires C=74.51% H=6.88% N=8.69%

obtained C=74.18% H=6.62% N=8.83%

Mass spectrum

$^m/_e$ 161(M^+, 40.3%), 160(29.0%), 146(16.1%), 145(29.0%), 144(19.4%), 135(11.3%), 130(17.7%), 120(16.1%), 118(83.9%), 117(22.6%), 109(100%), 94(96.7%), 44(93.2%), 39(35.6%).

7-methyl-5,6-dihydropyrrolo[1,2-a]azepin-9-one (221)

Rf 0.49 14mg 1% Yellow oil

^1H NMR ($CDCl_3$, TMS internal standard)

6.85ppm	1H	m
6.50ppm	1H	m
5.95ppm	2H	m
4.10ppm	2H	m
2.60ppm	2H	m
2.00ppm	3H	s (fine coupling to 5.95ppm)

IR ($CHCl_3$, ν max) 1670, 1590cm^{-1}

Analysis:

$C_{10}H_{11}NO$ requires C=74.51, H=6.88, N=8.69%

obtained C=73.87, H=6.28, N=8.84%

Mass spectrum

$m/_e$ 161(28.1%), 160(89.5%), 148(10.8%), 146(10.8%), 145(21.1%), 132(56.1%), 131(94.7%), 130(17.5%), 118(21.2%), 117(100%), 116(56.2%), 108(35.1%), 93(43.8%), 78(28.1%), 69(45.6%), 39(35.6%).

Aldol condensation of 1-(butan-3-on-1-yl)-2-formylpyrrole under kinetic conditions

To a stirred and cooled (liquid nitrogen/ethyl acetate bath) solution of freshly distilled diisopropylamine (0.6ml, 0.007moles) in anhydrous tetrahydrofuran (50ml) was added under nitrogen a solution of n-butyllithium (4.2ml of a 1.6M solution in hexane, 0.007moles). A solution of the keto aldehyde (1.0g, 0.006moles) in tetrahydrofuran (10ml) was run in and the mixture stirred for 4 hours.

The mixture was allowed to reach room temperature and a solution of ammonium chloride/ammonium hydroxide (50ml of a saturated solution)
was added. The organic material was extracted with diethyl ether (100ml), dried and the solvent removed to give a yellow oil (0.98g).

The oil was purified by column chromatography on alumina (30g, activity IV) Elution with benzene/light petroleum (10/90) and subsequent purification by P.L.C. (10% ethyl acetate/toluene) gave 2-acetyl-3H-pyrrolizine (211) (Rf 0.68, 0.24g, 27%). Elution with benzene/light petroleum (40/60) and subsequent purification by P.L.C. (10% ethyl acetate/toluene) gave 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209) (Rf 0.31, 0.14g, 16%). A major contaminant was unreacted starting material (0.31g, 31%).

2-acetyl-3H-pyrrolizine (211)

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.20ppm	1H	m
6.90ppm	1H	m
6.20ppm	2H	m
4.60ppm	2H	bs
2.35ppm	3H	s

IR($CHCl_3$ ν max) 1650, 1565cm^{-1}

UV(95%EtOH λ max) 242nm ($\log_{10}$ ε 3.31)
373nm ($\log_{10}$ ε 4.07)

Analysis:

C_9H_9NO requires C=73.45 H=6.16 N=9.52%
obtained C=73.25 H=6.19 N=9.64%

Mass spectrum

$^m/_e$ 147(90%), 146(98%), 131(91%),
117(28%), 105(21%), 104(100%),
103(100%), 102(44%), 76(94%), 75(97%),
39(51%).

Attempted acid catalysed reaction of acetic anhydride with 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209)

A mixture of the dihydro ketone (209) (0.7g, 5mmoles), acetic anhydride (2.25ml, 22.5mmoles), perchloric acid (1 drop of a 70% solution) and carbon tetrachloride (15ml) was stirred for 22 hours. Removal of solvent and analysis of the resulting oil by NMR showed that no reaction had occurred.

Attempted acid catalysed reaction of trimethyl orthoformate with 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209)

A mixture of the dihydro ketone (209) (0.5g, 3.4mmoles), trimethyl orthoformate (0.4g, 4mmoles), p-toluenesulphonic acid (1 crystal) and methanol (20ml) was stirred at room temperature for 24 hours.

The methanol was removed under reduced pressure and the residue taken up in dichloromethane (30ml). The dichloromethane solution was washed with sodium bicarbonate solution (50ml of a 5% solution), dried and the solvent removed . The residue was shown by NMR analysis to be the starting ketone (209).

This experiment was repeated in refluxing benzene in place of methanol. Only starting material was isolated after 24 hours reflux. The same result was seen when the acid was omitted.

Attempted reaction of acetic anhydride with 5,6-dihydropyrrolo[1,2-a]azepin-7-one

A solution of the dihydro ketone (209) (0.1g, 0.7mmoles) in acetic anhydride (50ml) was refluxed for 3 hours. No reaction had occurred as shown by T.L.C. Sulphuric acid (1 drop of conc. acid) was added. The solution was refluxed for a further 2 hours.

The mixture was shaken with sodium bicarbonate solution (60ml of a saturated solution) and extracted with dichloromethane (40ml) The organic extract was dried and the solvent was removed to give a black gum. This gum proved insoluble in all common solvents. The ^{1}H NMR spectrum of the gum in trifluoroacetic acid showed only broad peaks between 6 and 5ppm.

Preparation of N-acetylimidazole and N-acetylpyrrole

The method of Reddy was followed to give N-acetylpyrrole (83%, Bp 72°C/11mmHg).

Preparation of 1-acetyl-2-formylpyrrole

This was prepared by a normal Vilsmeier-Haack formylation of N-acetylpyrrole to give 1-acetyl-2-formylpyrrole (52%, Mp. 76-77°C, lit 76-78°C).

Attempted condensation of 1-acetyl-2-formylpyrrole with diethyl acetone-1,3-dicarboxylate

A solution of diethyl acetone-1,3-dicarboxylate (1.47g, 7.5mmoles) in anhydrous diethyl ether (100ml) was stirred under nitrogen and cooled in an ethyl acetate/liquid nitrogen bath. A solution of lithium diisopropylamide in diethyl ether (from 0.8g diisopropylamine, 8mmoles and 4.8ml of a 1.6M solution of n-butyllithium) was added over a period of 2 minutes. The mixture was stirred for 1 hour. A solution of 1-acetyl-2-formylpyrrole (1.0g, 7.3mmoles) in diethyl ether (10ml) was added and the mixture stirred for 2 hours. A second portion of base (the same amount as before) was added. The mixture was allowed to reach room temperature and then stood overnight.

A portion of water (20ml) was added, the organic phase separated, dried and solvent removed to give a yellow oil (1.2g). This oil was purified by chromatography on alumina (60g, activity IV). Elution with light petroleum gave a little 1-acetylpyrrole (0.02g) and a yellow oil, the NMR spectrum of which showed only ethyl peaks. Elution with benzene/light petroleum (30/70) gave 2-formylpyrrole (0.5g). Further elution with solvents of increasing polarity (to ethyl acetate) failed to elute any more material.

Attempted condensation of 1-acetyl-2-formylpyrrole with diethyl acetone-1,3-dicarboxylate

To a refluxing solution of sodium ethoxide in ethanol (0.34g, 15mmoles sodium in 120ml ethanol) was added a solution of diethyl acetone-1,3-dicarboxylate (1.5g, 7.5moles) in ethanol (10ml). After 5 minutes a solution of 1-acetyl-2-formylpyrrole (1.0g, 7.5mmole) in ethanol (20ml) was added. The mixture was boiled under reflux for 1 hour then cooled.

The solvent was removed under reduced pressure and the residue partitioned between dichloromethane (100ml) and water (100ml). The organic phase was dried and solvent removed to leave a yellow oil (0.35g). Chromatography of this oil on alumina (activity IV) yielded no identifiable products beyond those produced in the previous reaction.

Preparation of Z-1,4-dibromobut-2-ene

To a stirred and cooled (ice bath) solution of but-2-ene-1,4-diol (8.8g 0.1mole) in anhydrous benzene (30ml) was added phosphorus tribromide (6.4ml 0.1mole) dropwise over 2.5 hours. The mixture was stirred for a further 3 hours.

The reaction mixture was poured onto crushed ice (100g) and extracted with benzene. The organic phase was dried and the solvent removed to give a clear oil (11.6g, 53.7%), the NMR spectrum of which shows it to be the pure dibromide

^{1}H NMR ($CDCl_3$,TMS internal standard)

5.75ppm	2H	t	(J=5Hz)
3.90ppm	4H	d	(J=5Hz)

Titration of a small sample of the dibromide ( ) (0.22g, 1mmole) in carbon tetrachloride (10ml) with a solution of bromine in carbon tetrachloride (0.1M) required 9.6ml of bromine solution to produce a permanent colour.

Preparation of triphenylphosphonium-4-bromobut-2-en-1-yl bromide

A solution of the dibromobutene (11.0g) and triphenylphosphine (13.0g) in anhydrous benzene was stood at room temperature overnight producing copius white crystals.

The solid was filtered and washed with anhydrous benzene to give white crystals of the phosphonium salt (224) (23.2g, 98%).

Mp 179-180°C

Analysis:

$C_{22}H_{21}PBr_2$ requires C=55.46, H=4.41%

obtained C=55.63, H=4.45%

Reaction between 2-formylpyrrole and the phosphorane derived from salt (224).

To a stirred solution of phosphonium salt (224) (1.25g, 2.6mmoles) in anhydrous tetrahydrofuran (30ml) under nitrogen was added a solution of n-butyllithium in hexane (1.7ml of a 1.43M solution, 2.5mmoles) producing a deep red colour. The mixture was stirred at room temperature for 1 hour then heated at 60°C for a further 2 hours. A solution of 2-formylpyrrole (0.25g, 2.6mmoles) in tetrahydrofuran (10ml) was added, immediatly discharging the colour,The mixture was stirred for 2 hours.

The reaction mixture was filtered and solvent removed under reduced pressure to give a yellow oil (1.5g). Chromatography of this oil on alumina (40g, activity IV) gave as the only eluted product 2-formylpyrrole (0.2g, 80%).

Reaction between 2-formylpyrrole and the phosphonium salt (224)

To a stirred suspension of sodium hydride (0.15g of a 50% suspension in paraffin) in dimethyl sulphoxide (15ml) under nitrogen was added 2-formylpyrrole (0.25g, 2.6mmole) in one portion producing effervescence. The mixture was stirred for 15 minutes and the phosphonium salt (224) (1.25g, 2.6mmole) was added as one portion. The mixture was stirred overnight.

The reaction mixture was poured into stirred 1,2-dimethoxyethane (DME) (200ml) producing precipitation, the first solid.

This first solid was filtered off and dissolved in the minimum dichloromethane. The dichloromethane solution was filtered through a glass wool plug onto rapidly stirred diethyl ether (300ml) giving white crystals which were collected and dried.

The white solid (0.48g, Mp>260°C,decomposistion) had analysis figures as;

C=30.00%, H=2.36%, N=0.24%

The DME solution was added to stirred diethyl ether (300ml) to produce a greenish precipitate, this was collected, dissolved in dichloromethane and reprecipitated from ether to give white crystals which yellow on exposure to air (0.57g, Mp 99-101°C). The ^{1}H NMR spectrum shows only phenyl peaks. Analysis gives;

C=60.58&, H=4.67%, N=0.35%

Deuteration of 5,6-dihydropyrrolo[1,2-a]azepin-7-one

To a stirred and cooled (ethylacetate/liquid nitrogen bath) solution of diisopropylamine (0.1g, 1mmole) in anhydrous DME (50ml) was added under nitrogen a solution of n-butyllithium (0.6ml, 1mmole, of a 1.6M solution). A solution of the dihydroketone (209) (0.12g, 0.9mmole) in DME (10ml) was run in and the mixture stirred for 2.25 hours. A portion of deuterium oxide (2g) was added, the mixture allowed to reach room temperature and stirred for 4.5 hours.

The yellow mixture was diluted with water (20ml) and extracted with dichloromethane (2 portions of 60ml). The combined organic phases were dried and solvents removed to give a yellow oil (0.1g).

T.L.C. showed only one component, the NMR spectrum showed that deuteration had occurred in the 6 position.

Mass spectrum:

$^{m}/_{e}$ 149(31%), 148(29%),147(18%)

Attempted trapping of the enolate generated from 5,6-dihydropyrrolo[1,2-a]azepin-7-one

To a stirred and cooled (ethyl acetate/liquid nitrogen bath) solution of diisopropylamine (0.1g, 1mmole) in anhydrous DME (50ml) was added under nitrogen a solution of n-butyllithium (0.6ml of a 1.6M solution in hexane). A solution of the dihydro ketone (209) was added and the mixture was stirred for 2 hours. A portion of methyl

iodide (0.2g, 0.9mmoles) was added, the mixture allowed to reach room temperature and stirred overnight.

The mixture was diluted with water (50ml) and extracted with dichloromethane (3 portions of 50 ml). The combined organic phases were dried and the solvents removed to give a yellow oil (0.1g). Analysis of this oil by NMR and T.L.C. showed only the presence of the starting ketone (209).

This reaction was repeated using the electrophiles shown below. All attempts gave the starting ketone as product.

Methyl iodide	14g	(70 equivalents)
Bromine	0.14g	(1 equivalent)*
Trimethylchlorosilane	0.16g	(1.5 equivalents)

* The reaction with bromine gave a little (9%) of the mono brominated compound (215).

Deuteration of 5,6-dihydropyrrolo[1,2-a]azepin-7-one

To a stirred mixture of the dihydro ketone (209) (0.15g, 1mmole), lithium hydroxide (0.05g, 1.5mmole) and DME (20ml) was added deuterium oxide (5ml). The mixture was stirred for 1 hour.

The mixture was diluted with water (30ml) and extracted with dichloromethane (2 portions of 20ml). The combined organic phases were dried and solvents removed to give a brown oil (0.1g).

The ^{1}H NMR spectrum of this oil showed it to be the starting ketone doubly deuterated in the 6 position, there was no signal at 2.85ppm.

Mass spectrum

m/e 149(46%), 148(12%).

This reaction was repeated with the substitution of methyl iodide (2ml) for D_2O. Only starting ketone was produced.

Reaction between 5,6-dihydropyrrolo[1,2-a]azepin-7-one and acetaldehyde

To a stirred mixture of sodium hydroxide (0.07g), dihydro ketone (209) (0.15g, 1mmole), water (1ml) and DME (50ml) was added acetaldehyde (10ml) as one portion. The reaction was stirred for 1 hour.

The mixture was diluted with water (30ml) and extracted with dichloromethane (2 portions of 30ml). The combined organic phases were dried and solvent removed to give a brown oil (0.15g).

Analysis of this oil by NMR showed that the starting ketone was unchanged.

Preparation of 7-methylene-5,6-dihydropyrrolo[1,2-a]azepine (228).

To a stirred suspension of triphenylmethylphosphonium bromide (2.0g, 5.5mmoles) in anhydrous tetrahydrofuran (100ml) was added under nitrogen a solution of n-butyllithium (4ml of a 1.6M solution in hexane) giving a red solution.

After 30 minutes a solution of the dihydroketone (209) (0.8g, 5.5mmoles) in tetrahydrofuran (10ml)was added. The mixture was stirred for a further 3 hours.

The mixture was filtered and the solvents removed. The resulting gum was purified by column chromatography. on alumina (25g, activity IV). Elution with light petroleum gave a pale yellow oil, the methylene compound (228).

7-methylene-5,6-dihydropyrrolo[1,2-a]azepine (228)

(0.37g, 47%, Bp.155°C/0.05mmHg, air bath)

^{1}H NMR ($CDCl_3$, TMS internal standard)

6.9ppm	1H	m
6.3ppm	1H	m
5.8ppm	3H	m
4.7ppm	2H	m

3.8ppm	2H	m
2,5ppm	2H	m

Analysis:

$C_{10}H_{11}N$ requires C=82.72, H=7.64, N=9.65%

obtained C=82.28, H=7.38, N=9.29%

Mass spectrum

m/e 145(M^+ 52%), 144(100%), 143(74·9%), 142(67%), 141(36%), 129(53%), 117(53%), 116(82%), 114(76%), 104(58%), 103(67%), 90(79%), 77(63%), 65(52%), 39(67%).

Reaction of DDQ with 7-methylene-5,6-dihydropyrrolo[1,2-a]azepine (228)

A solution of the methylene compound (228) (0.15g, 1mmole) and DDQ (0.23g, 1mmole) in anhydrous benzene (50ml) was stirred for 17 hours at room temperature and then refluxed for a further 3 hours.

After cooling the mixture was filtered. The yellow filtrate was washed with sodium bicarbonate solution (20ml of a 5% solution). The organic phase was dried and the solvent removed under reduced pressure to give a brown oil (0.1g).Analysis of this oil by NMR and T.L.C. showed it to be 5,6-dihydropyrrolo[1,2-a]azepin-7-one (209) almost exclusively.

Reaction of base with 7-methylene-5,6-dihydropyrrolo[1,2-a]azepine

A mixture of potassium t-butoxide (freshly prepared from 0.05g potassium, 1.2mmole), the methylene compound (228) (0.15g, 1mmole) and anhydrous dimethylsulphoxide (30ml) was stirred at 50°C for 19 hours.

The mixture was poured onto an ice/water mixture (150g) and extracted with pentane (4 portions of 100ml) and then benzene (100ml). The combined organic extracts were dried and the solvents removed under reduced pressure to give a yellow oil.

Analysis of this oil by NMR showed the presence of starting material and also a doublet at 4.3ppm (J=5Hz).

The oil was re-reacted under the same conditions for 70 hours. Work up showed only a small increase in the proportion of the new compound as estimated by NMR.

Attempted separation by P.L.C. (light petroleum, multiple elution) failed to yield any separated material.

Preparation of 7-ethoxypyrrolo[1,2-a]azepinium tetrafluoroborate (235)

A solution of pyrrolo[1,2-a]azepin-7-one (0.05g, 0.4mmole) in dichloromethane (10ml) was added under nitrogen to a stirred solution of triethyloxonium tetrafluoroborate (from 0.04ml epichlorohydrin and 0.07ml boron trifluoride etherate, 0.4mmole) to give a red solution which was stirred for 2.5 hours.

The solvent was removed under nitrogen and replaced by anhydrous diethyl ether (20ml). Repeated trituration and cooling under nitrogen of the deposited red gum eventually formed a red solid.

^{1}H NMR ($CDCl_3$, TMS internal standard, 100MHz)

9.20ppm	1H	d (J=10.01Hz)
8.53ppm	1H	m
8.35ppm	1H	d (J=11.84Hz)
7.68ppm	1H	dd(J=4.55,3.17Hz)
7.43ppm	1H	m
6.97ppm	2H	m

The ethyl peaks are obscured by the large ethyl peaks of the triethyloxonium salt.

Analysis:

$C_{11}H_{12}NOBF_4$ requires C=50.57, H=4.59, N=5.36%

obtained C=43.47, H=5.13, N=3.54%

UV ($CHCl_3$, λ max) 356nm

455nm

Attempted preparation of 7-hydroxypyrrolo[1,2-a]azepinium bromide

Dry hydrogen bromide gas was bubbled through a solution of pyrrolo[1,2-a]azepin-7-one (0.05g) in anhydrous dichloromethane (20ml) for 20 minutes producing a red colour. The solvent was removed under nitrogen and replaced with anhydrous diethyl ether (20ml). Repeated trituration and cooling produced only a black gum. The NMR spectrum of this gum (D_6 DMSO) showed only a broad peak between 5 and 6ppm. The UV spectrum showed absorptions 355 and 450nm.

Attempted reaction of p-toluenesulphonyl hydrazide with 5,6-dihydropyrrolo[1,2-a]azepin-7-one

A solution of the dihydro ketone (209) (0.1g, 0.7mmole), p-toluenesulphonyl hydrazide (0.1g, 0.7mmoles) and p-toluenesulphonic acid (1 small crystal) in absolute ethanol was boiled under reflux in an atmosphere of nitrogen for 30 minutes then cooled in an ice bath. No sign of crystallization was seen. The mixture was refluxed for a further 2.5 hours.

The solvent was removed under reduced pressure and the residue purified by P.L.C. (10% ethyl acetate/toluene) to give starting materials as the only identifiable products.

This experiment was repeated under the following conditions;

Tetrahydrofuran as solvent , 3 drops of conc HCl as catalyst and 5 hours reflux.

Acetic acid as solvent, no catalyst, stirring overnight.

Methanol as solvent, sodium acetate (0.1g) as catalyst and stirring overnight.

In all cases only starting materials were detected.

Attempted reaction of morpholine with 5,6-dihydropyrrolo[1,2-a]azepin-7-one

A solution of the dihydro ketone (209) (0.1g, 0.7mmole), morpholine (0.1g, 1.4mmole) and p-toluenesulphonic acid (1 small crystal) in anhydrous benzene (30ml) were boiled under reflux in a Deans and Stark apparatus for 5 hours.

The solvent was removed under reduced pressure to give a brown oil (0.2g) which was shown by analysis by T.L.C. and its NMR and IR spectra to be a mixture of the starting materials.

This experiment was repeated with di-n-butylamine in place of morpholine, again only starting materials were recovered.

Preparation of 7-methylenepyrrolo[1,2-a]azepine (234)

To a stirred mixture of triphenylmethylphosphonium bromide (0.25g, 0.7mmole) in anhydrous tetrahydrofuran (50ml) under nitrogen was added a solution of n-butyllithium (0.9ml of a 0.7M solution in hexane). The mixture was stirred for 20 minutes and a solution of the ketone (*1*) (0.1g, 0.7mmole) in tetrahydrofuran (10ml) was added.

The majority of the solvent was removed under reduced pressure and diethyl ether (150ml) was added producing precipitation. The solid was filtered and the solvent removed from the filtrate to give a pale yellow oil (0.1g). This oil was purified by P.L.C. (10%ethyl acetate/toluene) to give one major product, the desired methylene compound (234) (Rf. 0.91 0.02g, 20%yield)

^{1}H NMR ($CDCl_3$, TMS internal standard)

7.5-7.1ppm	7H	cm
5.8ppm	2H	bs

UV ($CHCl_3$ λ max) 258nm ($\log_{10}\varepsilon$ 3.02)
319nm ($\log_{10}\varepsilon$ 2.08)

Analysis:

$C_{10}H_9N$ requires C=83.88, H=6.34, N=9.78%
obtained C=83.21, H=6.58, N=9.42%

Mass spectrum

$^m/_e$ 143(M^+ 42%), 129(92%), 117(43%),
39(100%).

Attempted preparation of 7-methylpyrrolo[1,2-a]azepinium bromide

Hydrogen bromide gas (dried by passage through conc. H_2SO_4 and a solution of phenol in dichloromethane) was bubbled through a solution of the alkene (234) in anhydrous dichloromethane for 20 minutes to give a red solution. This solution was taken up in anhydrous diethyl

ether (20ml) without any crystallization. The solvent was removed under reduced pressure to give a red gum. This was triturated under nitrogen in diethyl ether to give dark red crystals (0.12g).

Mp. 122-124°C

^1H NMR spectrum showed only a broad unresolved peak between 8 and 7ppm.

UV λ 270nm
350nm
475nm

Mass spectrum- highest $^m/_e$ values at 263, 262 (both 40%), none at 144.

Attempted preparation of 7-methylpyrrolo[1,2-a]azepinium trifluoroacetate

The alkene (234) (0.03g) was dissolved in trifluoroacetic acid (2ml) under nitrogen to give a red/black solution. The ^1H NMR spectrum of this solution shows only one broad peak between 7.5 and 7.2ppm. The UV spectrum of the solution shows absorptions at 356, 370 and 430nm. Removal of trifluoroacetic acid in a stream of nitrogen gave a black gum which would not dissolve in triflouroacetic acid.

Attempted preparation of 7-methylpyrrolo[1,2-a]azepinium fluorosulphonate

Fluorosulphonic acid was distilled under a vacuum (oil pump) into an NMR tube containing a mixture of acetone/D_6acetone (0.05ml) and the alkene (234) (0.04g) cooled in liquid nitrogen. The NMR tube was sealed and removed from the vacuum line. The ^1H NMR spectrum shows no absorptions which may be attributed to the desired salt although a

deep red solution is produced.

Attempted preparation of 7-methylpyrrolo[1,2-a]azepinium tetrafluoroborate

To a stirred solution of the alkene (234) (0.05g) in acetic anhydride (2ml) was added dropwise a solution of fluoroboric acid (0.1ml of a 42% solution), producing a red colouration. The mixture was added to anhydrous diethyl ether (40ml) producing a yellow solution but no solid precpitation.

Attempted photochemical dehydrogenation of 5,6-dihydropyrrolo[1,2-a]azepin-7-one

A solution of the dihydro ketone (209) (0.15g, 1mmole) and benzophenone (1.5g 10mmole) in anhydrous benzene (400ml) was purged with a stream of nitrogen for 30 minutes and then irradiated through a quartz filter (light of predominantly 254nm) for 5 hours.

Much brown solid was deposited on the glassware during the irradiation. The solvent was removed under reduced pressure to give a brown oil (1.6g). Analysis of this oil by NMR and T.L.C. showed that it contained neither the starting ketone (209) nor the desired unsaturated ketone (1).

Attempted reaction of methylmagnesium iodide with 5,6-dihydropyrrolo[1,2-a]azepin-7-one

A solution of the dihydro ketone (209)in diethyl ether (50ml) was added to a solution of methylmagnesium iodide (from 140mg methyl iodide and 24mg magnesium in 10ml ether). The mixture was stirred for 4 hours.

Water (50ml) was added and the ethereal layer separated and dried. The solvent was removed under reduced pressure to give a yellow oil (0.15g). Chromatography of this oil on Florasil (20g) gave only the starting ketone (0.12g).

The same result was obtained when the experiment was repeated with tetrahydrofuran as solvent.

Preparation of 7-methyl-7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-a]azepine (210)

To a stirred and cooled (ethyl acetate/liquid nitrogen bath) solution of the dihydro ketone (209) (0.15g, 1mmole) in anhydrous tetrahydrofuran (40ml) was added a solution of methyllithium/lithium bromide complex (0.7ml of a 1.4M solution in diethyl ether, 1mmole). The mixture was stirred for 4 hours then brought to room temperature and stirred for a further 2 hours.

Water was added (20ml) and the mixture extracted with diethyl ether (2 portions of 50ml). The combined ethereal extracts were dried and the solvent removed to give a brown oil (0.15g). This oil was purified by P.L.C. (25%ethyl acetate/toluene) to give two products, 2-formylpyrrole (20%) and the alcohol (210) (0.8g, 56% yield)

7-methyl-7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-a]azepine (210)

^{1}H NMR (CD_3COCD_3, TMS internal standard, 100MHz)

6.69ppm	1H	m
6.17ppm	1H	d (J=12.45Hz)
6.05ppm	1H	m
5.93ppm	1H	dd (J=3.14,2.56Hz)
5.32ppm	1H	d (J=12.45Hz)
4.11ppm	2H	m
3.91ppm	1H	bs (exchanges with D_2O)
2.04ppm	2H	m
1.32ppm	3H	s

IR (liquid film ν max) 1630, 3410cm^{-1}

Analysis:

$C_{10}H_{13}NO$ requires C=74.51 H=6.88 N=8.69%

obtained C=74.39 H=6.42 N=9.11%

Mass spectrum

$m/_e$ 163(14%), 148(20%), 147(20%), 146(21%) 145(100%), 144(70%), 130(58%), 119(23%), 118(18%), 104(12%), 103(10%), 91(14%), 77(14%), 65(12%), 63(8%), 51(13%), 39(16%).

This reaction failed to give any identifiable product when pyrrolo[1,2-a]azepin-7-one was the substrate.

Attempted reduction of 5,6-dihydropyrrolo[1,2-a]azepin-7-one with 9-borabicyclo[3.3.1]nonane

To a stirred and cooled (ice bath) solution of the dihydro ketone (209) (0.15g, 1mmole) in anhydrous tetrahydrofuran (20ml) was added dropwise a solution of 9-borabicyclo[3.3.1]nonane (9-BBN) in tetrahydrofuran (2ml of a 0.5M solution, 1mmole). The mixture was stirred for 2 hour then at room temperature for 1 hour. Methanol (1ml) was added.

The solvent was removed from the mixture and light petroleum added (10ml) causing a browning of the mixture. The solvents were removed under reduced pressure and the residue separated by P.L.C. Elution with ethyl acetate/toluene (25/75) gave only the starting ketone as an identifiable product together with 7 unidentified fractions.

Reduction of 5,6-dihydropyrrolo[1,2-a]azepin-7-one by sodium borohydride

A solution of the dihydro ketone (209) (0.15g, 1mmole) in ethanol (10ml) was dropped onto a stirred and cooled (ice bath) mixture of sodium borohydride (0.02g, 0.5mmole) in ethanol (15ml). The mixture was stirred under nitrogen at 0°C for 2 hours and then at room temperature overnight.

All but a small amount (5ml) of the solvent was removed under reduced pressure and the residue partitioned between water (50ml) and dichloromethane (50ml). The organic phase was washed with brine (30ml of a saturated solution) and water (30ml), was dried and solvent removed under reduced pressure to give a yellow oil(0.1g). This oil was purified by P.L.C. Elution with ethyl acetate/toluene (25/75) gave a yellow oil, the alcohol (231) (0.05g, 31%).

7-hydroxy-6,7-dihydro-5H-pyrrolo[1,2-a]azepine (231)

^{1}H NMR (CD_3COCD_3)

6.6ppm	1H	m
6.2pm	1H	d (J=11Hz)
5.9ppm	2H	m
5.4ppm	1H	dd (J=11,4Hz)
4.5ppm	1H	m
4.0ppm	2H	m
3.1ppm	1H	bs (exchanges with D_2O)
2.1ppm	2H	m

IR (liq. film ν max) 1265, 1430, 1655, 3380 cm^{-1}

UV (95%EtOH λ max) 278nm ($\log_{10} \varepsilon$ 3.02)

Analysis:

$C_9H_{11}NO$ requires C=72.45 H=7.43 N=9.39%

obtained C=72.18 H=7.34 N=9.62%

Mass spectrum

m/e 149(2%), 132(100%), 118(36%), 104(15%), 51(13%), 39(47%).

Treatment of pyrrolo[1,2-a]azepin-7-one under the same conditions for 27 hours gave the same alcohol (231) in 14% yield.

Dehydration of alcohol (231)

A solution of the alcohol (231) (0.06g, 0.5mmole) in anhydrous benzene (30ml) with p-toluenesulphonic acid (3 crystals) was stirred at room temperature for 24 hours then boiled under reflux for 2 hours.

The mixture was washed with sodium bicarbonate solution (50ml of a saturated solution) and water (50ml), was dried and the solvent removed under reduced pressure to give a brown oil (0.02g). This oil was purified by column chromatography on alumina (10g), elution with light petroleum gave a pale brown oil, the azepine (232) (15mg, 31%).

5H-pyrrolo[1,2-a]azepine (232)

^{1}H NMR (CD_3COCD_3)

6.7ppm	1H	d (J=7Hz)
6.6ppm	1H	m
6.0ppm	5H	m
4.5ppm	2H	d (J=5Hz)

UV (95%EtOH λ max) 272nm ($\log_{10}\varepsilon$ 2.74)

Analysis:

C_9H_9N requires C=82.40, H=6.92, N=10.68%

obtained C=81.63, H=6.65, N=11.26%

Mass spectrum

$^m/_e$ 147(16%), 130(3%), 111(42%),
97(67%), 95(74%), 69(100%), 39(16%)

Attempted hydride abstraction from azepine (213)

To a stirred solution of the azepine (213) (10mg, 0.075mmole) in anhydrous dichloromethane (2ml) cooled in an ice bath was added a solution of trityl tetrafluoroborate (0.1mmole) in dichloromethane (5ml) over 5 minutes. The mixture was stirred for 2 hours.

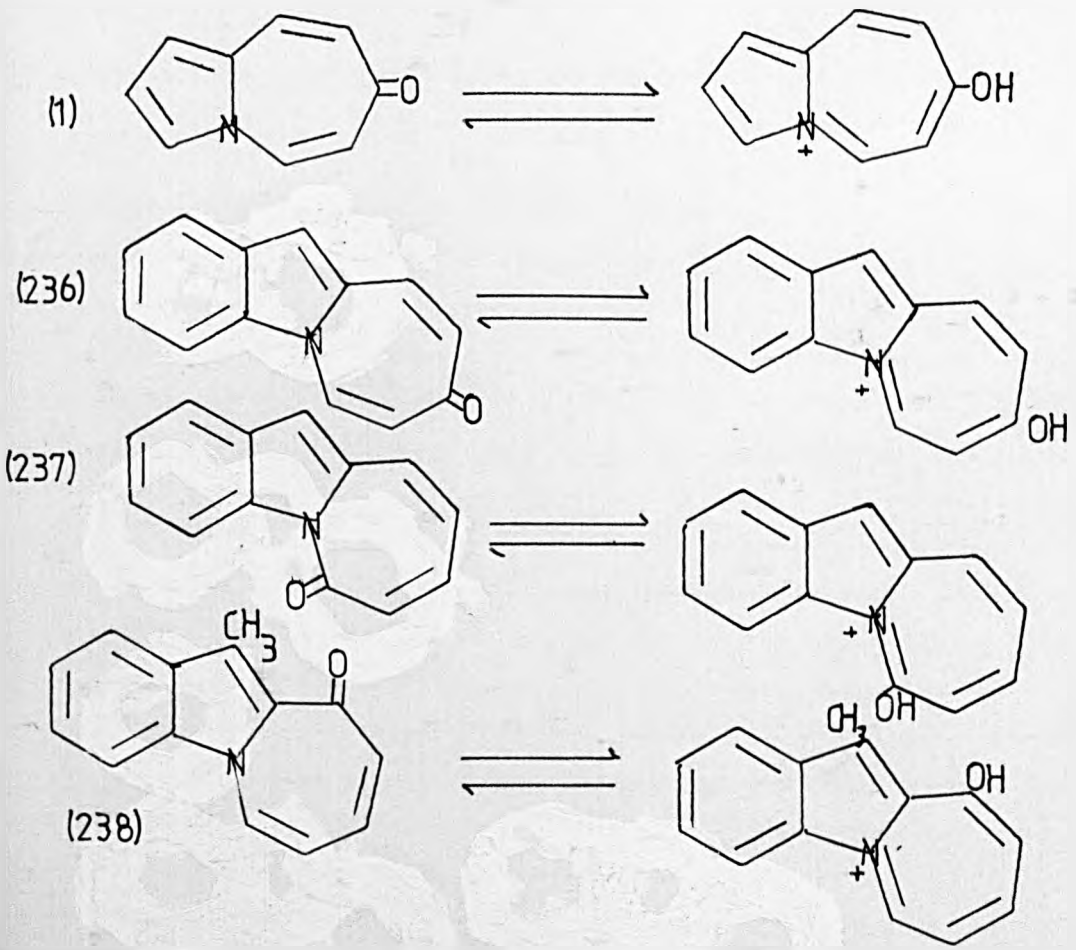
The solvent was evaporated in the nitrogen stream and anhydrous diethyl ether (10ml) added to give a blue solution. The solvent was removed and the mixture taken up in toluene (2ml) and added to light petroleum (20ml) producing some blue solids (5mg).

The ^{1}H NMR spectrum of the solid showed only absorptions due to phenyl groups, the UV spectrum showed strong absorptions at 342 and 742nm. The solid does not melt below 300°C.

CHAPTER FIVE

NMR studies

The ketone (1), pyrrolo[1,2-a]azepin-7-one, gives a red solution when dissolved in protonating solvents. The ^{1}H NMR spectra of such solutions show a downfield shift of the observed peaks. Such behaviour is also characteristic of the two isomeric pyrrolo[1,2-a]azepinones (20) and (24) and the indolo[1,2-a]azepinones (236-238). This behaviour has been attributed [1,2,23,26] to protonation on the carbonyl oxygen with formation of a fully conjugated system.



The reaction of ketones (20) and (24) with acids have been studied in solvents of varying protonating ability by NMR methods[2]. Similarly NMR parameters have also been used to estimate the degree of aromaticity in 2-pyridones[218], in various 4-pyrones[219-220] and in fused heterocyclic systems[221,222].

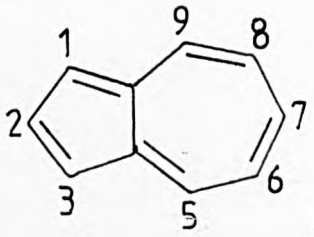
NMR spectra provide two sorts of data, chemical shifts and coupling constants. The values, or changes in values, of these have been applied to the indentification of aromaticity in a compound. The chemical shifts of protons in a cyclic aromatic compound will be at lower field than those of a corresponding cyclic polyene. This is attributed to a ring current of π electrons around the conjugated periphery of the compound which creates a diamagnetic anisotropy. This anisotropy is such that a proton in an aromatic system is deshielded and shifted downfield (and "inner protons" in (4 +2) annulenes upfield). This obvious effect of ring current on NMR spectra was put forward by Elvidge and Jackman in 1961[218] as an aid to identifying aromatic systems. It has since become clear however, that the possession of downfield chemical shifts may not be a sufficient indication of aromaticity in small rings[223]. For example, the chemical shifts of tropone protons are further downfield from those of cycloheptatriene than would be expected from a consideration of the effect of the tropone carbonyl group[224], this has been attributed to an induced ring current and hence aromaticity. However both cycloheptatriene and tropone show the same degree of bond alternation.

The ^{3}J coupling constants of aromatic cyclic compounds will differ from those of corresponding polyenes. This is because in a

polyene the π electrons are assumed to be fixed and there is bond alternation. As an example of this the ^{3}J values and chemical shifts of the protons on the 7-membered rings of azulene (4) and 1,2-benzazulene (239) are presented in Table 1 (numbering as in pyrrolo[1,2-a]azepines and indolo[1,2-a]azepines for ease of comparison). The ^{3}J values of azulene are similar, indicating bond delocalisation, whereas those of the annelated compound (239) show alternation of bonds. The chemical shifts of the protons in the 7-membered rings are very similar.

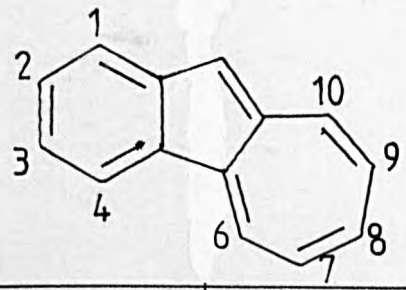
Vicinal coupling constants in cyclic systems are also dependent on stereochemical factors such as the non-planarity of the ring which has an influence on the dihedral angle between protons and the H-C-C angles and also on electronic factors such as the electronegativity of substituents; due account should be taken of these In general it has been found that for planar bond alternant 7-membered rings the ^{3}J coupling across single bonds is around 8Hz and deviation from planarity will cause this to decrease to around 5.5Hz for full boat conformations, for delocalised compounds ^{3}J will average to around 10Hz.[235].

Table 1



(4)

Proton	Chemical Shift
5	8.10
6	6.82
7	7.29
	^3J
5,6	9.50
6,7	10.00

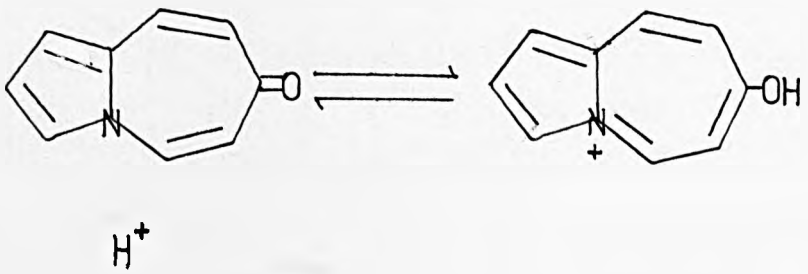


(239)

6	8.32
7	6.88
8	7.04
9	6.71
10	7.33
	^3J
6,7	8.20
7,8	10.40
8,9	8.50
9,10	10.90

Studies on pyrrolo[1,2-a]azepin-7-one

In acids this ketone gives a red solution. The NMR spectra of these red solutions show a downfield shift compared with those in a neutral solution. This is assumed to be due to a protonation on oxygen forming the conjugated pyrrolo[1,2-a]azepinium system.



The ketone and hydroxy compound are assumed to be in equilibrium. Protonation and deprotonation reactions are fast on the NMR time scale, so the spectra are a series of weighted averages of the chemical shifts and coupling constants of the two forms.

The spectra were taken in $CDCl_3$, trifluoroacetic acid (TFA) and fluorosulphonic acid (the last at $-40^{\circ}C$). The NMR spectrum of 7-ethoxypyrrolo[1,2-a]azepinium tetrafluoroborate in $CDCl_3$ was also taken. All the spectra are similar, the chemical shifts and coupling constants varying with the solvent. The chemical shifts of the protons and their coupling constants are shown in Table 2 and also

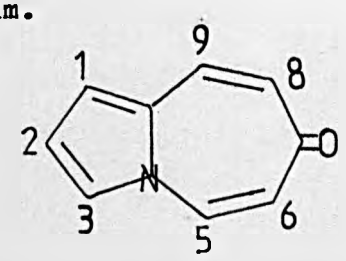
Table 2

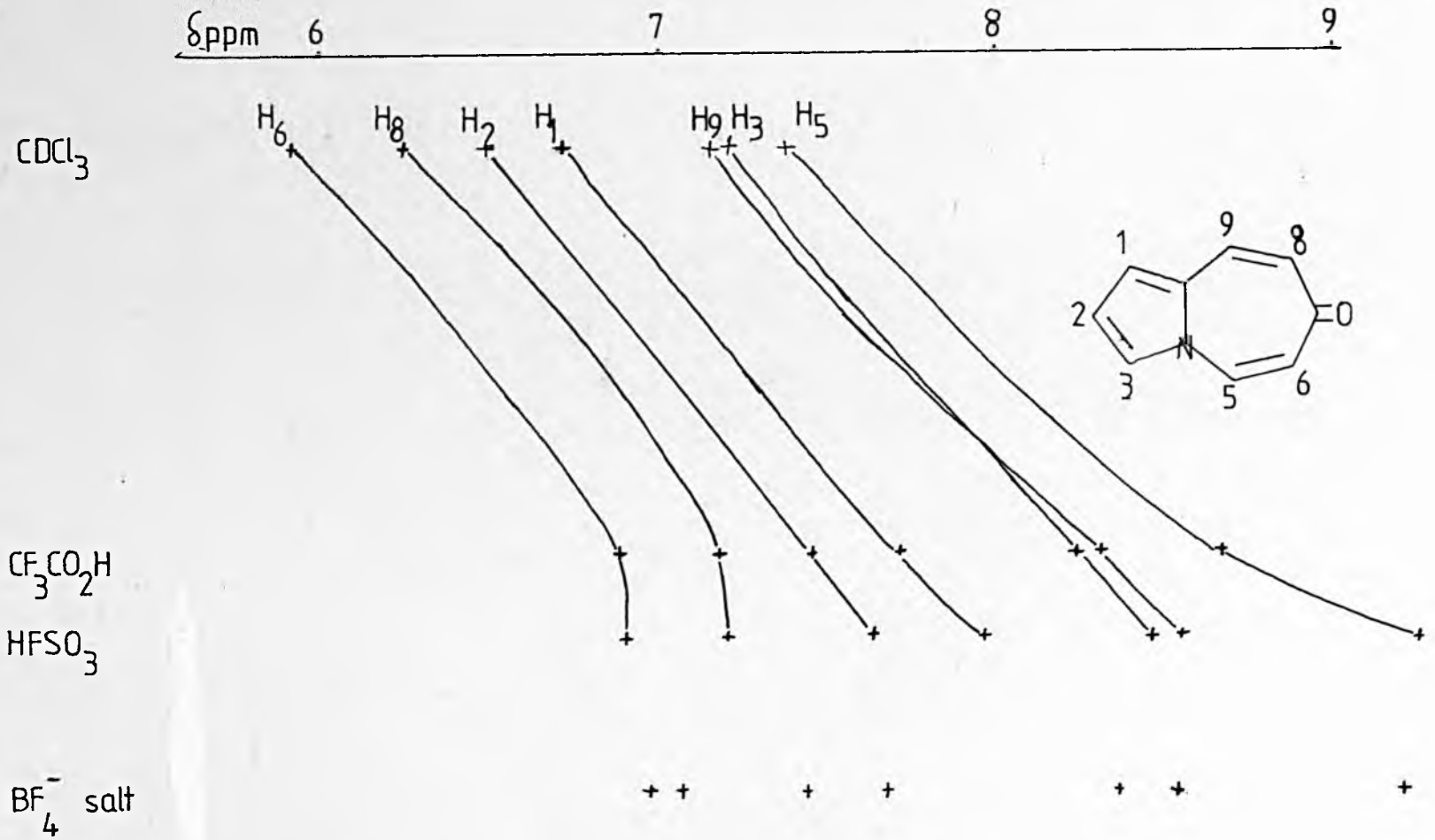
Solvent / Proton	Chemical Shift					
	$CDCl_3$	TFA	FSO_3H_a	Salt/$CDCl_3$	$\Delta/CDCl_3/FSO_3H$	Acetone
1	6.72	7.22	7.93	7.66	1.21	6.85
2	6.52	7.44	7.62	7.43	1.10	6.55
3	7.20	8.22	8.45	8.53	1.25	7.55
5	7.39	8.65	9.21	7.20	1.82	7.79
6	5.93	6.87	6.89	6.96	0.96	5.81
8	6.25	7.09	7.08	7.05	0.83	6.10
9	7.15	8.30	8.52	8.35	1.20	7.34
			^3J			
1,2	3.76	4.47	4.55	4.55	0.79	3.82
2,3	2.85	2.93	3.05	3.17	0.20	2.89
5,6	10.39	9.51	9.26	9.56	-1.13	10.37
8,9	12.38	11.23	11.04	11.84	-1.34	12.33

$$\Delta/CDCl_3/FSO_3H = \delta_{FSO_3H} - \delta_{CDCl_3}$$

$$= {}^3J_{FSO_3H} - {}^3J_{CDCl_3}$$

a = 300 MHz spectrum.




δ ppm 6
7
8
9
CDCl3
CF3CO2H
HFSO3
BF4− salt
H6
H8
H2
H1
H9
H3
H5
1
2
3
N
5
6
9
8
O

shown graphically.

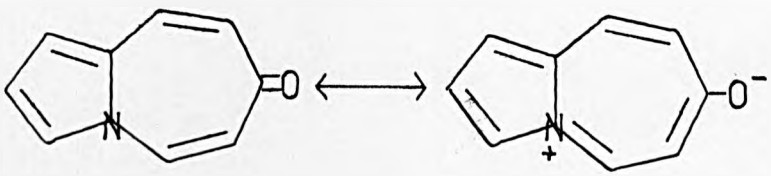
A number of observations are apparent from this data. The chemical shifts increase on increasing protonating power of the solvent. This may be due to the presence of a ring current, however the positive charge on the molecule will also cause a downfield shift. More persuasive evidence of delocalization in the protonated form is provided by the change in charge coupling constants in the 7-membered ring, these decrease from those typical of a double bond in a 7-membered ring [226] to those values more typical of azulene. That $^3J_{5,6}$ and $^3J_{8,9}$ are not the same can be attributed to the differing bond angles at each double bond imposed by the N bridgehead for the 5-6 bond and the C bridgehead for the 8-9 bond. The ketone in fluorosulphonic acid is wholly in the protonated form, this is shown by the similarity of the spectrum in this solvent and that of the salt (235) in $CDCl_3$ (the only difference which may be significant is in the $^3J_{8,9}$ values, which differ by 0.8Hz).

All the chemical shifts are affected by a similar amount with the exception of protons 5,6 and 8 with change of solvent from TFA to FSO_3H. Protons 6 and 8 are adjacent to the carbonyl group in the ketone and are strongly influenced by its anisotropic effect. In fluorosulphonic acid all the compound is in the hydroxy form and so this anisotropic effect no longer applies. Flitsch and co-workers have found a similar effect with the ketone (20)[2].

Proton 5 is adjacent to the nitrogen which will, under these conditions, carry a positive charge. The large downfield shift of this proton could be due to some delocalisation of the charge on to carbon 5, although it is hard to explain why there is not then equal

delocalisation on to carbon 3. In their work on the protonation of ketone (20) Flitsch and co-workers[2] found that whereas the majority of the proton resonances moved downfield by around 1.0-0.9ppm, those of protons 3 and 5 adjacent to nitrogen moved 1.25ppm down field.

In a non acidic medium the ketone (1) ground state may have contributions from both the form (1) and the dipolar form (238). If this is so then polar solvents, by being more stabilizing to dipoles, should increase the contribution due to form (238).



(238)

There are differences in the spectra of this compound in $CDCl_3$ and in D_6acetone (the more polar solvent). These differences are in the expected direction if the contribution to the ground state of (238) increases in polar solvents, most of the chemical shifts are downfield in acetone and the coupling constants change in the expected way. However the changes in the spectra are small and may not be significant.

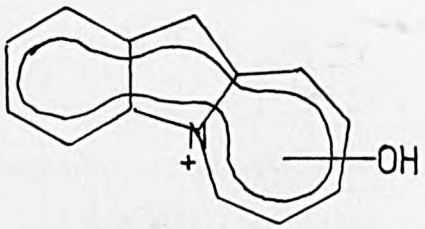
These results agree well with those of Flitsch, Kappenberg and Schmitt[2] concerning the two isomeric ketones (20) and (24). The

changes in chemical shift on going from a non-polar solvent to fluorosulphonic acid are similar showing that, despite the different distances between nitrogen and oxygen in the three compounds, there is approximately the same degree of conjugation from nitrogen to carbonyl in $CDCl_3$.

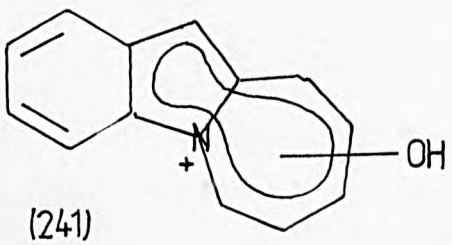
That the protonation reaction has caused electron release from nitrogen rather than from oxygen can be indicated by the greater change in chemical shift of protons α to nitrogen as compared with those α to carbonyl.

Studies on indolo[1,2-a]azepinones

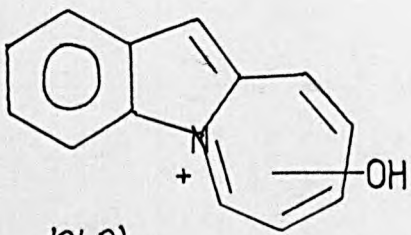
Previous work on the three indolo[1,-a]azepinones (236),(237) and (238)[23,26] has indicated that they undergo the same protonation reactions as do the pyrroloazepinones. The resulting hydroxy compounds are thought to possess 14 π electrons. There are a number of resonance forms which could describe the bonding in the tricyclic system; as a 14π conjugated system (240) as a 10π aromatic system fused to a diene fragment, as a 6π benzenoid aromatic system fused to an olefinic bicyclic fragment (242), as an indole system bonded to a diene system carrying a positive charge (243) or simply as a positively charged polyene.



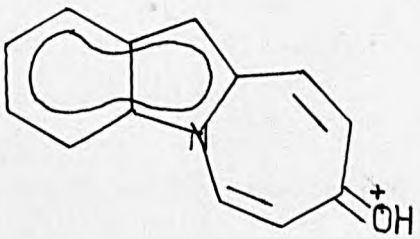
(240)



(241)



(242)



(243)

Gunther and co-workers [227,228] have carried out theoretical calculations and some NMR studies on carbocyclic systems where a benzene ring is fused to an annulene ring. On the basis of previous work, for example [229], they neglect situations where the benzene ring is part of a larger conjugated system and base their treatment upon molecules where the benzene ring is aromatic and fused to a cyclic polyene and where the benzene ring is a diene fragment and the remaining two "benzene" electrons are part of an aromatic or antiaromatic system. A series of equations have been derived relating the ^3J value in the six membered ring to the π bond order of the relevant carbon carbon bond ($P_{\mu\nu}$ calculated by HMO and SCF methods). These equations are of the form.

$$^3J = xP_{\mu\nu} + y$$

Where x and y are constants depending on the type of system. Bond order s in a fused benzene ring will vary according to the bonding in the annelated ring. The ratios of bond orders for adjacent carbon carbon bonds, the "Alternanzparameter" Q, is indicative of the bonding in the annelated ring;

$$P_{1,2}/P_{2,3} = Q_1 \qquad P_{3,4}/P_{2,3} = Q_2$$

where the subscripts 1,2,3 and 4 refer to the positions on the benzene ring. As ^3J is proportional to P the similar equation relating ^3J to Q can be written.

$$^{3}J_{1,2}/J_{2,3} = Q_1 \qquad ^{3}J_{3,4}/J_{2,3} = Q_2$$

The values of Q are such that for an aromatic annelated system Q=1.14-1.20, for an olefinic system Q=1.04-1.10 and for an antiaromatic system Q=0.75-1.03. Thus measurements of the ^{3}J values of the benzene ring give information on the bonding in the annelated ring.

A similar technique has been developed by Crews, Kintner and Padgett[230] for deciding if an annelated or other benzenoid ring is aromatic or olefinic. This method uses the correspondence between ^{3}J ratios and bond alternation. A quantity J_{ratio} is defined such that;

$$J_{ratio} = J_{2,3}/J_{1,2}$$

Values of J_{ratio} of around 0.5 were assigned to a diene system (for example 1,2-dihydropyridine, J_{ratio} = 0.55) and values near to 1.0 to an aromatic system (pyridine J_{ratio} = 1.00). This technique was applied to isoindole to give a J_{ratio} of 0.74, the authors therefore concluded that there was only slight aromaticity in the 6-membered ring of isoindole. This technique was applied to isoindole again by Chacko, Bornstein and Sandella[231], who argued that a more approximate model for a diene system would be the two Z double bonds of Z-Z-octatetraene as these are not on the termini of a conjugated system. This model gives J_{ratio} = 0.71, implying that isoindole has no aromaticity in the 6-membered ring. However calculation of the resonance energies[232] shows that isoindole has a greater resonance energy than pyrrole (by 3.2kcal/mole) thus indicating some

delocalization in the 6-membered ring.

These techniques should therefore allow identification by NMR spectroscopy of the types of bonding which are the major forms of the protonated indolo[1,2-a]azepinones. Those such as (240) should show a J_{ratio} indicative of delocalisation in the 6-membered ring and no bond alternation in the 7-membered ring. Those such as (241) should show Q values indicative of an aromatic annelated ring, a J_{ratio} value of a diene and no bond alternation in the 7-membered ring. Those such as (242) should show Q values indicative of an annelated olefin, a J_{ratio} close to 1.0 and bond alternation in the 7-membered ring. Those such as (243) should show ^3J values in the 6-membered ring similar to indole and bond alternation in the 7-membered ring. This case would be hard to distinguish from (242). However the differing location of the positive charge in (242) and (243) would be expected to influence the chemical shifts in the 7-membered ring in different ways. The polyene would show bond alternation in both the 6 and 7-membered rings.

The NMR spectra of these three ketones were taken at 300MHz in $CDCl_3$ and deuterated TFA. It was necessary to use deuterated solvents as the quantities of material were limited. For this reason too, the ethoxy tetrafluoroborate salts of the three ketones were prepared in CD_2Cl_2 instead of taking the spectra in FSO_3H. The assumption that the salts have the same electronic structure as the fully protonated forms was shown to be true for pyrrolo[1,2-a]azepin-7-one and is assumed to be true here. A spectrum of each compound is reproduced. The data are shown on tables 3-5.

The assignment of peaks to protons 1 and 4 was made by assuming

that as for indoles and N-acylcarbazoles[233], proton 1 is more downfield than proton 4, and that $^3J_{4,3}$ is larger than $^3J_{1,2}$. There is no visible meta or para coupling in these systems.

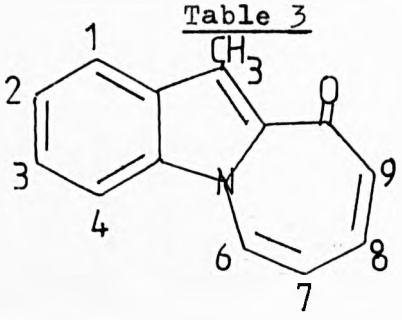
The data for compound (238) is presented in Table 3. The change in chemical shift of the protons is downfield, that of proton 6 the greatest as would be expected from developing positive charge on the nitrogen. However there is no downfield shift on going from the spectrum in TFA to that of the salt, this would indicate that the molecule is fully protonated in TFA.

The coupling constants of the 7-membered ring show bond delocalization on going from $CDCl_3$ to TFA but this is not maintained in the salt. The $^3J_{6,7}$ value is unusually low for a π bond in a 7-membered ring. However the corresponding values in the pyrrolo[1,2-a]azepinone (20) is also low (9.57Hz)[2]. The Q values show the presence of an annelated aromatic ring in $CDCl_3$ as would be expected for an indole (the average Q value for indole is 1.12). In TFA the Q values increase showing an increase of aromatic character in the 7-membered ring at the expense of that in the the 6-membered ring, as does the averaged J_{ratio} (0.82). This is borne out by the coupling constants in the 7-membered ring, although the coupling constants indicate a considerable contribution by the localized form.

In the salt the trends previously mentioned are not continued. Although the chemical shifts are similar to those in TFA the coupling constants in the 7-membered ring show a higher degree of bond localisation, although less than in the unprotonated spectra. The Q values show an olefinic character in the 5 and 7 membered rings.

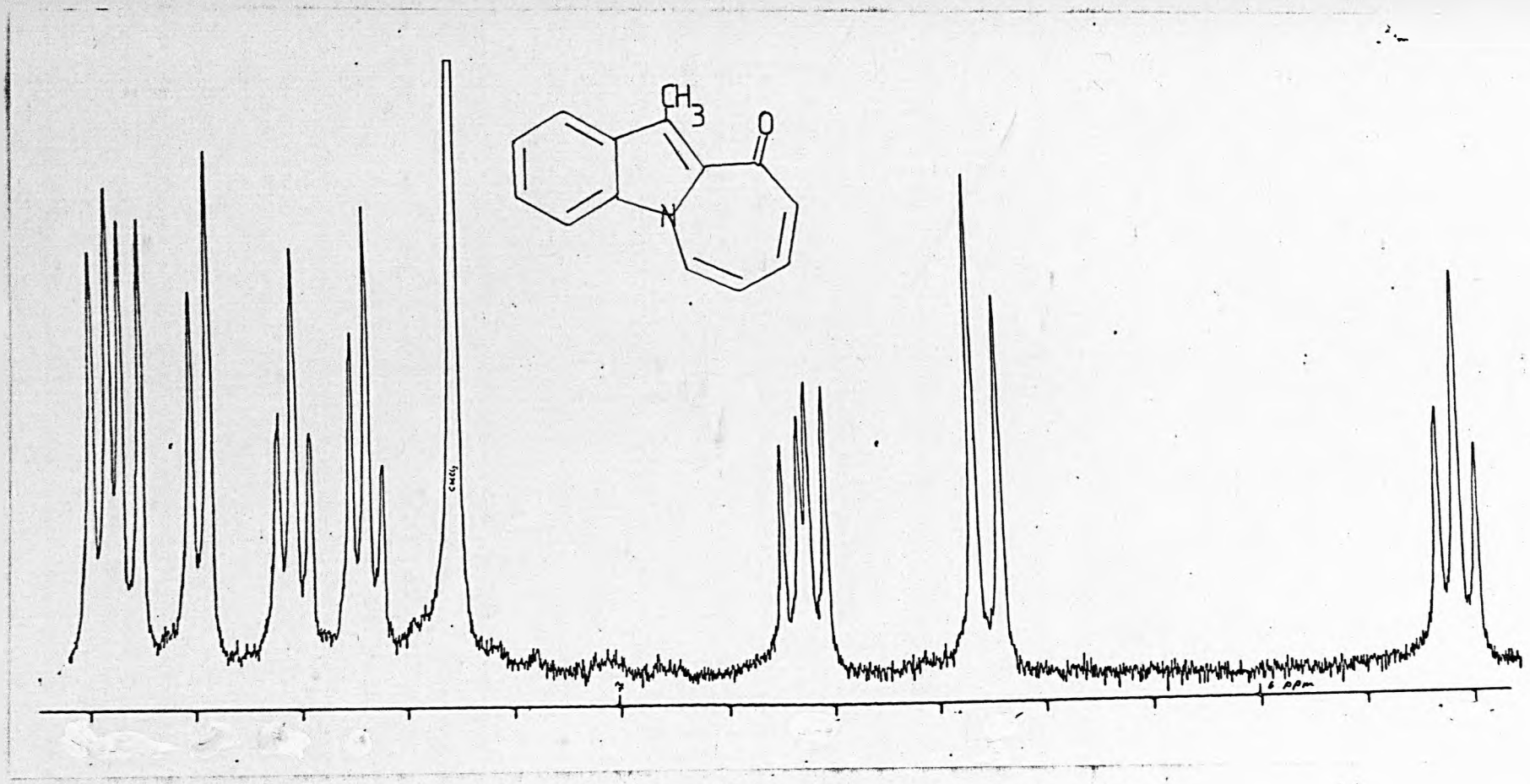
The data shows then that in the unprotonated form the 5 and 6

Table 3



(238)

Solvent / Proton	Chemical Shift $CDCl_3$	TFA	Salt
1	7.84	8.26	8.23
2	7.51	8.03	7.92
3	7.36	7.90	7.82
4	7.67	8.20	8.13
6	7.76	9.01	8.96
7	6.70	6.62	6.62
8	5.68	7.85	7.79
9	6.40	7.12	7.14
		^3J	
1,2	7.96	8.65	8.85
2,3	7.08	7.14	8.18
3,4	8.18	8.79	8.40
6,7	9.95	9.07	9.95
7,8	8.65	9.35	9.06
8,9	11.94	11.27	11.72
Q_1	1.12	1.21	1.08
Q_2	1.15	1.23	1.03
$\frac{Q_1 + Q_2}{2}$	1.14	1.22	1.05

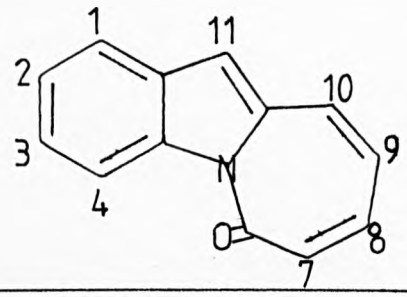

CH3
O
N
CHCl3
δ ppm

rings show an indole-like aromaticity. With increasing protonation a degree of delocalisation is developed in the 5 and 7-membered rings at the expense of that in the 6 membered ring. But on complete alkylation (assumed equivalent to increased protonation) the 6-membered ring shows a return to the delocalisation of the unprotonated form and the 5 and 7-membered rings an olefinic character, with a small amount of delocalisation, that is similar to the electronic distribution of benz[c,d]azulene[223].

The spectral data of the ketone (237) is shown in Table 4. The spectra of this compound show second order behaviour in the 6-membered ring protons. Attempts to reproduce the spectra using the simulation program (JEOL HA100) and so identify the coupling constants have not been successful but have indicated that this system has strong virtual coupling. Therefore no measurements of Q or J_{ratio} values were possible.

The chemical shifts do not change significantly on protonation or in the salt from those of the compound in neutral solvent. This could indicate that either the compound exists in a dipolar form as a major contribution to the ground state or that it is not protonated in acids. However a red colour (the other indolo[1,2-a]azepinones show a blue colour) is seen in acids. The coupling constants in the 7-membered ring show bond fixation. Therefore the available NMR data indicate that the electron distribution is unchanged in acid solution or in the salt form. This indicates that either no reaction is occurring in acid solution or that the molecule exists as the dipolar form (244). The results of Flitsch and co-workers[2] on the pyrroloazepinone (20) show that this molecule is protonated in acid

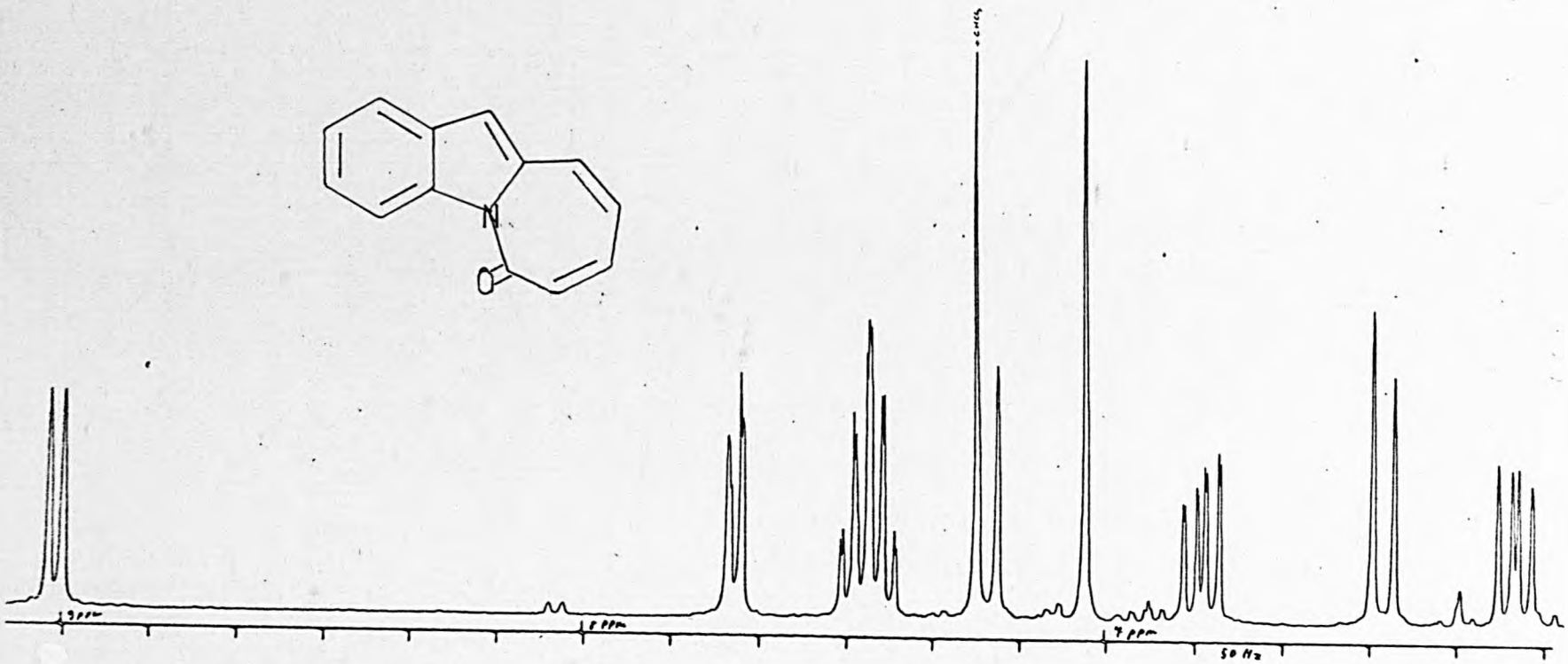
Table 4



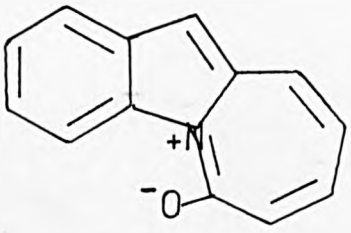
(237)

Solvent / Proton	Chemical Shift $CDCl_3$	TFA	Salt
1	7.72	7.79	7.30
2	7.45	7.46	7.46
3			
4	8.95	8.94	8.83
7	6.47	6.62	6.43
8	6.82	7.14	6.97
9	6.22	6.42	6.31
10	7.22	7.46	7.33
11	7.04	7.23	7.12
		^3J	
1,2	7.08		
2,3			
3,4	8.96		
7,8	12.61	12.61	12.49
8,9	7.74	7.96	7.74
9,10	11.50	11.50	11.28

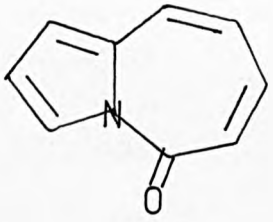
WH 300



solution. The dipolar form of (20) would imply a loss of resonance energy of the pyrrole ring, whereas the form (244) has the resonance energy of the benzene ring but has lost that of the indole portion of the molecule.



(244)



(20)

However there is a change in the bonding of the molecule in acid solution as shown by its UV spectrum in acid which shows a marked shift to longer wavelength compared to that in neutral solvents[26]. In the absence of further data it is not possible to put forward a convincing explanation for this seeming discrepancy between the NMR spectra and the UV spectra.

The spectral data for the ketone (236) is shown in Table 5.

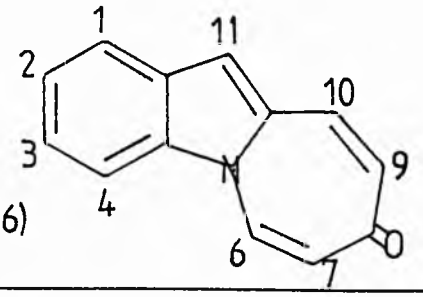
In this compound the assignments of protons 1 and 4 is uncertain. The most downfield proton on the 6-membered ring , which had been assigned to proton 1 for ketone (238) by analogy with indoles, had the larger ^{3}J coupling which is not the case for indoles. The assignment of proton 4 as the most downfield on the basis of its coupling, is presented in Table 5, however it should be borne in mind that the assignment may be misleading.

The data for the salt show that there are two compounds shown in the spectra (I and II). The assignments of peaks to each compound is on the basis of their intregal (the ratio is 1.1:1) with the more upfield peaks representing the major form. There is some ambiguity to this due to the nearly equal proportions and the low accuracy of the integration. These two forms of the ethoxy form will be discussed later

The chemical shifts show increasing downfield shift with protonation and alkylation. The chemical shifts of the compound in TFA are very similar to those in the two salts indicating that protonation is nearly complete, if the salts do represent complete protonation.

The coupling constants on the 7-membered ring show decreased values on protonation and in the salts which may indicate a lesser degree of bond alternation. The Q values in $CDCl_3$ indicate participation of the benzene ring inthe aromaticity of the indole fragment. In TFA there is a degree of delocalization in the 7-membered ring at the expense of the benzene ring, indicated by the lower Q value, higher J_{ratio} and confirmed by the ^{3}J coupling

Table 5

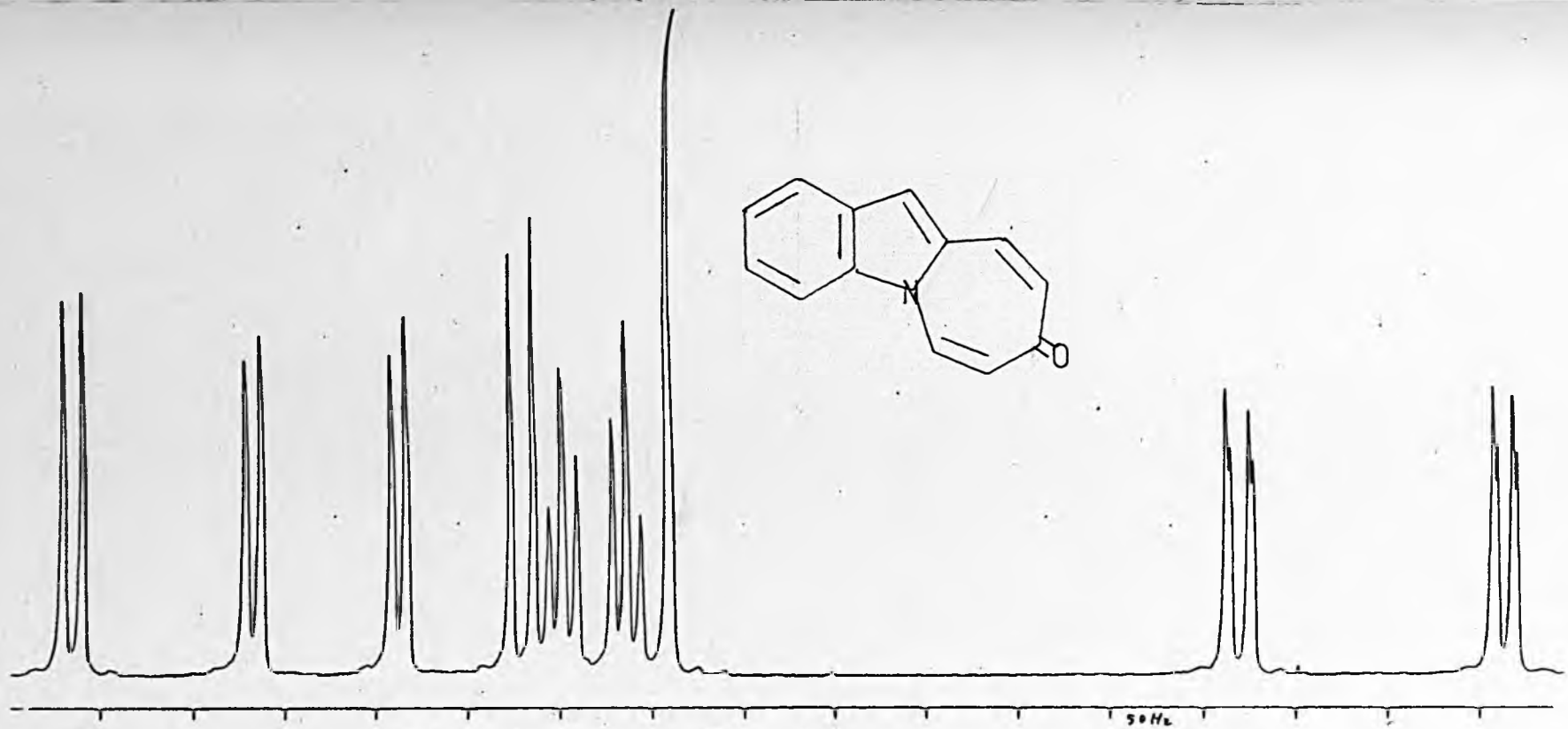


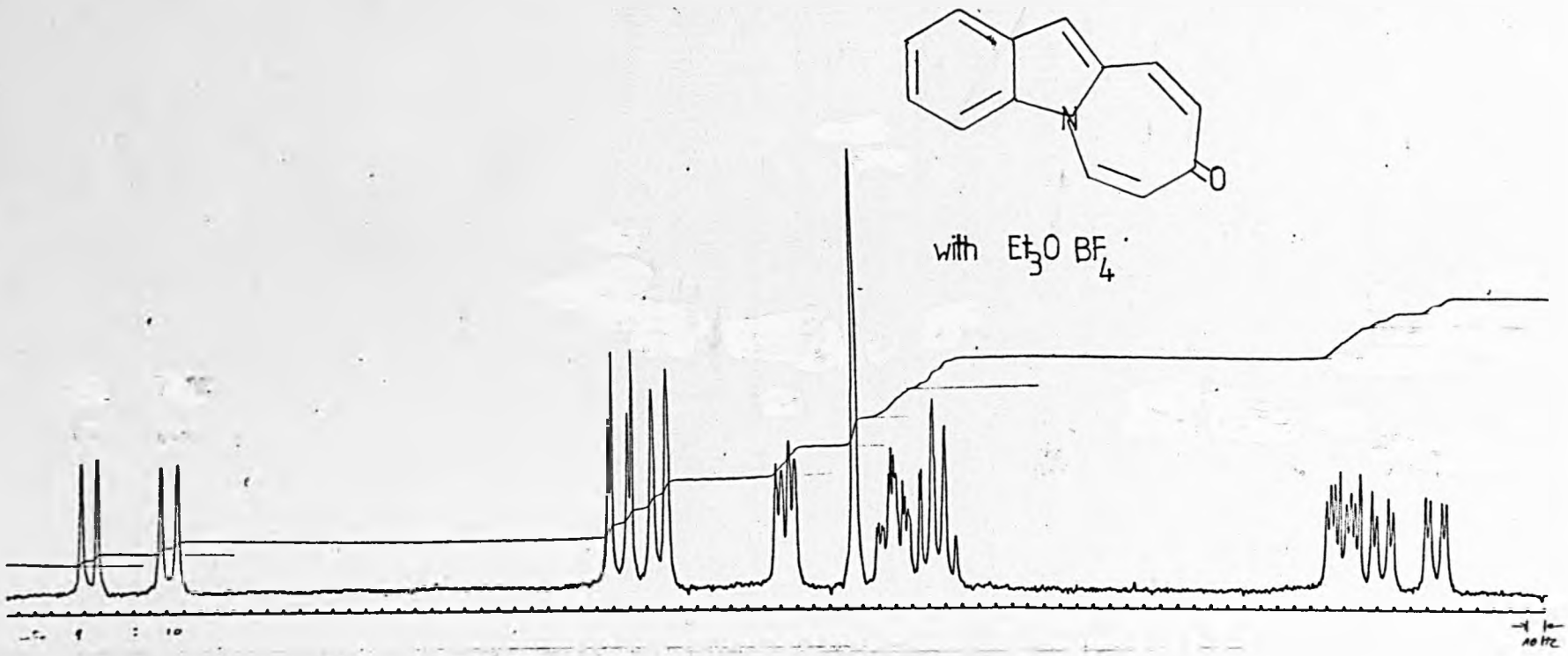
(236)

Solvent / Proton	Chemical Shift			
	$CDCl_3$	TFA	Salt I	Salt II
1	7.74	8.13	8.06	8.05
2	7.49	7.94	7.75	7.75
3	7.37	7.84	7.84	7.84
4	7.82	8.20	8.31	8.31
6	8.07	9.18	9.45	9.29
7	5.78	6.76	6.85	6.74
9	6.25	7.02	6.94	6.93
10	7.56	8.37	8.40	8.38
11	7.26	7.91	7.91	7.91
	^3J			
1,2	7.58	8.18	7.96	8.18
2,3	7.00	7.52	7.07	7.07
3,4	8.27	8.62	8.62	8.62
6,7	10.34	9.51	9.97	9.73
9,10	12.41	11.94	11.72	11.94
Q_1	1.08	1.09	1.13	1.16
Q_2	1.18	1.14	1.22	1.22
Q_1+Q_2	1.13	1.15	1.17	1.19
J^2_{ratio}	0.88	0.87	0.85	0.84

Ratio of integrals of Salt I and II

1.1 : 1.0

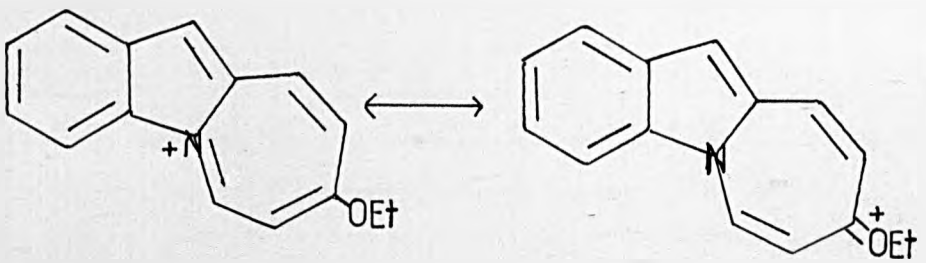

N
O
50 Hz


N
O
with $Et_3O\ BF_4$

constants. The degree of delocalization is much smaller than that of the ketone (238) described before, this may be due to the greater number of bonds which now separate the nitrogen and the carbonyl group. In both forms of the salt the trend noticed for TFA is continued, although with a smaller change in ^{3}J values in the 7-membered ring, this trend is more marked in form II than I.

The existence of two forms of the salt is puzzling. As their chemical shifts and coupling constants are very similar, and the same for some protons, it is reasonable to assume that they are a pair of stereo isomers or valence isomers, rather than resulting from different chemical reactions.

It is possible that there is a tautomerism in this alkylated compound between the form with the positive charge on nitrogen and that with the charge on oxygen (the chemical shifts rule out a whole charge on carbon).



(245) (246)

This would explain the chemical shifts and coupling constants (although only poorly for those in the 7-membered ring). But such a tautomerism in which bonds are not made or broken are fast on an NMR time scale and do not show discrete spectra.

If the major contribution to the structure was a form such as (240) with positive charge on oxygen then there would be restricted rotation about the C_8-O bond and two forms would exist with the ethyl group syn or anti, C_6-C_7 bond, the ethyl group can be folded back along the molecule (Dreiding models). The orientation of the ethyl group would be expected to give small changes in chemical shift of the ring protons, as there would be a different environment for these protons is each structure. The protons most affected would be expected to be those on the 7-membered ring and proton 4 (which may be assigned as 1 in the Table), models show that proton 11 is further from the ethyl group than proton 4.

Some of the NMR data disagrees with the formulation of a positive charge on oxygen. Proton 6 shows the greatest change in chemical shift from the neutral form (1.20ppm) indicating the greatest degree of positive charge adjacent to this, however this may not be a true comparison as protons 7 and 9 are two bonds from the assumed positive charge on oxygen. A more serious criticism of this structure is that the Q values for the two forms of the salt show that the benzene ring is annelated to an aromatic ring system and this appears more than is due to the indole ring (Q_1 = 1.10, Q_2 = 1.14) The 5 and 7-membered rings in the form (246) with the positive charge localised on oxygen could not be aromatic. The available evidence seems to be conflicting and no definite conclusion can be drawn.

The use of the spectra of ethoxy salts to substitute for the spectra of the ketones in FSO_3H has lead to a number of problems in interpretation of the spectra and trends on increasing protonation. These salts may not provide a sufficiently good model for the fully protonated form.

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