STUDIES OF THE REACTIONS OF 3H-PYRROLIZINES WITH ACETYLENES

by

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ABSTRACT

An attempt was made to synthesise azonia-azulenium salts by the 2+2 cycloaddition of acetylenes to 3H-pyrrolizine, and the subsequent ring expansion of the cyclobutene product.

In Part I the attempted syntheses of some new 3H-pyrrolizines are described and a review is included on the syntheses of 3H-pyrrolizines already known.

Part II describes the reactions of 3H-pyrrolizines with dimethyl acetylenedicarboxylate and includes a brief review on the reactions of dimethyl acetylenedicarboxylate with compounds closely related to 3H-pyrrolizine. The thermal reactions of 3H,1-methyl-3H and 1,2-dimethyl-3H-pyrrolizines, with dimethyl acetylenedicarboxylate, gave derivatives of 3-carbomethoxy (carbomethoxymethyl) methylene-3H-pyrrolizine and cycl[4,2,2] azine. Attempts to prepare the cycl[4,2,2] azinium system from a cycl [4,2,2] azine derivative are described, and a review is included on the synthesis and properties of known cyclazines.

The photochemical reaction of dimethyl acetylenedicarboxylate with 3H-pyrrolizine gave a low yield of cyclobutene derivatives and a larger yield of the thermal products. The photochemical reaction with 3,3-dimethyl-3H-pyrrolizine, however, gave a moderate yield of the cyclobutene derivative.

ABSTRACT

,.... contd

The cyclobutene ring of this photolysis product was successfully opened to give a pyrrolo [1,2-a] azepine.

ACKNOWLEDGEMENTS

I am indebted to Dr. G. Jones for his guidance and encouragement throughout this work.

I would like to thank Professor H.D. Springall and the University of Keele for the provision of laboratory facilities and the Science Research Council for financial support.

I would also like to thank Dr. D. Leaver for helpful discussion, and Professor W. Flitsch for the provision of spectral data on 3-ethoxycarbonylmethylene-3H-pyrrolizine.

Finally, I would like to thank my mother, Mrs. C. Johnson, for the typing of this thesis.

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The work reported in this thesis

was carried out by the Author under

the supervision of Dr. G. Jones

CONTENTS

PART II

DISCUSSION (contd) Page

DISCUSSION (contd) Page

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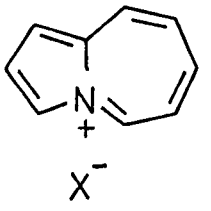
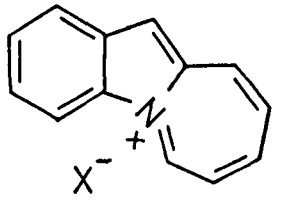
GENERAL INTRODUCTION

Since 1966 various members of this University have, in collaboration with Dr. G. Jones, attempted to synthesise the azonia-azulenium systems (1) and (2) [1-5]



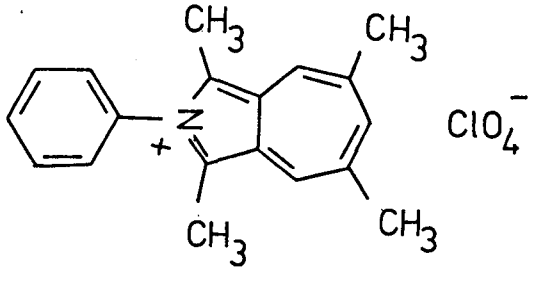
(1)



(2)

These salts are distinct from the only other azonia-azulenium salts reported in the literature, by El'tsov and co-workers, [6-12] in that they have quaternary nitrogen at the bridgehead.

El'tsov and co-workers were, in fact, the first to report an azonia-azulenium salt when they synthesised the highly substituted 2-azonia-azulenium perchlorate (3) in 1967.[6]



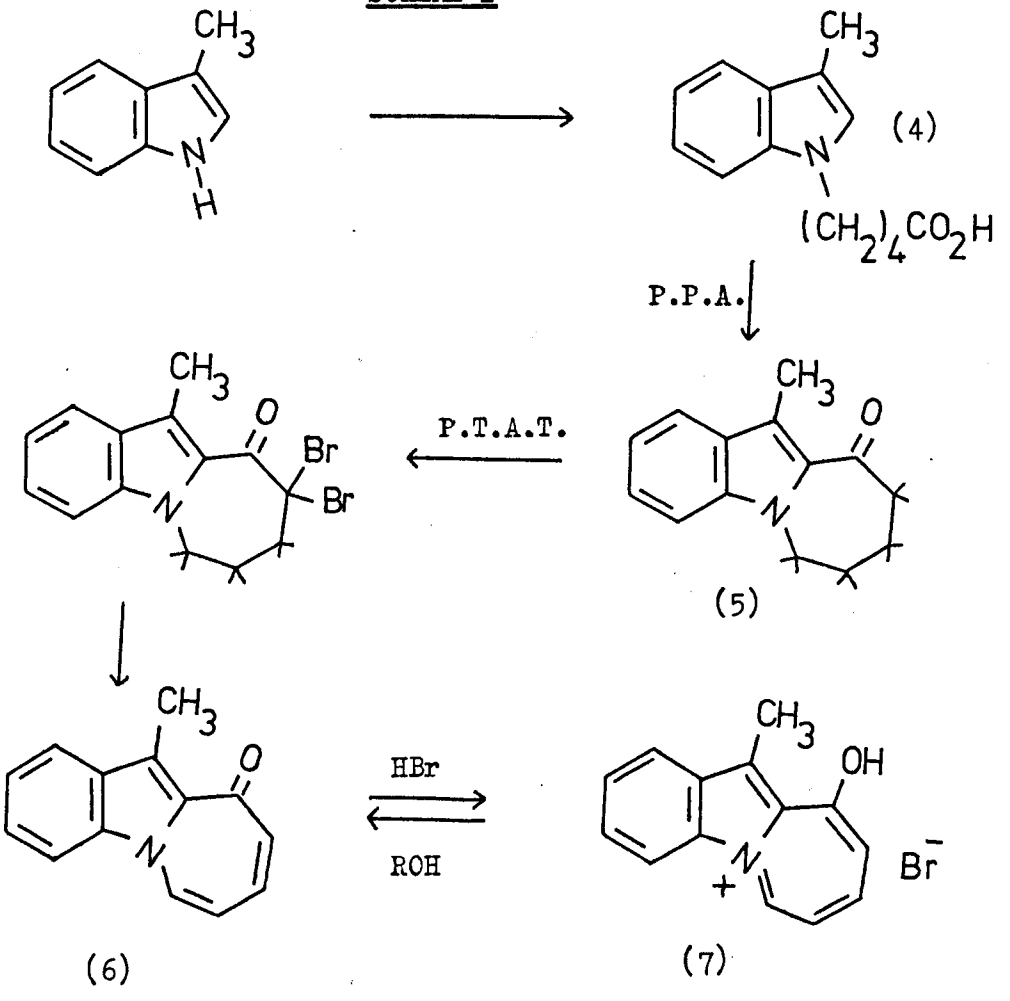
(3)

By means of minor modifications to the synthetic route they have produced a whole series of such 2-azonia-azulenium salts.

In the following brief description of the synthetic approaches to the azonia-azulenium systems (1) and (2), the salts will be given their systematic names. They are pyrrolo [1,2-a] azepinium (1) and azepino [1,2-a]-indolium (2) salts.

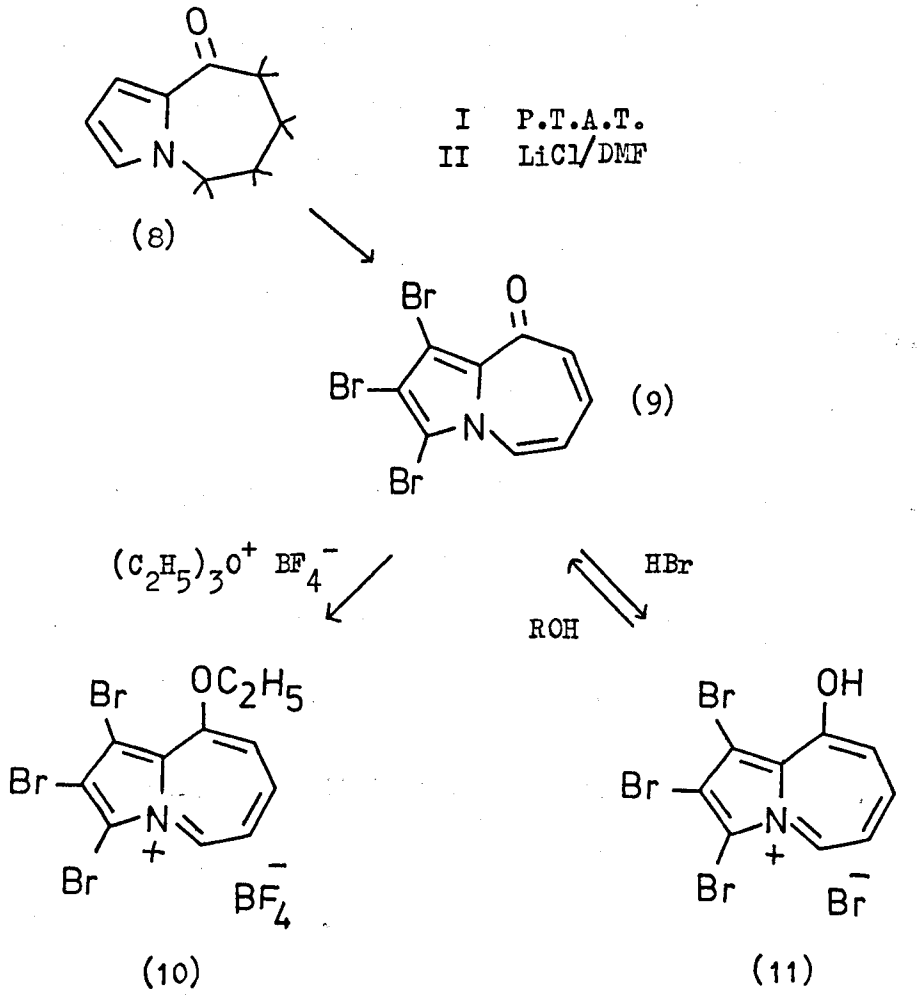
Collington and Jones [1,2] attempted to produce the first nitrogen bridgehead azonia-azulenium salts by synthesising a seven membered ketone ring across the 1 and 2 positions of an existing pyrrole, or indole, ring. Dehydrogenation of the corresponding azepinone, followed by protonation on the carbonyl function, gave the azonia-azulenium salts (7), (10) and (11). The Schemes (1 and 2) for these syntheses are detailed below.

SCHEME I



The 3-methylindolide ion (from 3-methylindole and sodium hydride) reacted with 4-tosyloxybutyl chloride to give the chlorobutylindole, which was converted to the nitrile with sodium cyanide. The nitrile was hydrolysed to the acid (4), which cyclised on treatment with polyphosphoric acid to give the cyclic ketone (5). Bromination alpha to the carbonyl group with phenyltrimethylammonium tribromide (P.T.A.T.), and dehydrobromination with lithium chloride in dimethylformamide, gave 11-methylazepino [1,2-a] indol-10-one (6). Protonation gave the azonia-azulenium system (7).

SCHEME 2



The bicyclic ketone (8) was prepared by reactions similar to those in Scheme 1. On attempted bromination alpha to the carbonyl group, bromine atoms were also unavoidably introduced into the pyrrole ring. Dehydrobromination with lithium chloride in dimethylformamide gave the ketone (9) which on treatment with triethyloxonium fluoborate, or dry hydrogen bromide, gave the azonia-azulenium salts (10) and (11) respectively.

Attempts to reduce the carbonyl group in the azepinoindolone (6), in order to obtain the azonia-azulenium salt by protonation, were unsuccessful [3]. Lithium aluminium hydride and sodium borohydride reduced the seven membered ring as well as the ketone group. An attempted Wolff-Kishner reduction, using hydrazine hydrate, opened the seven membered ring.

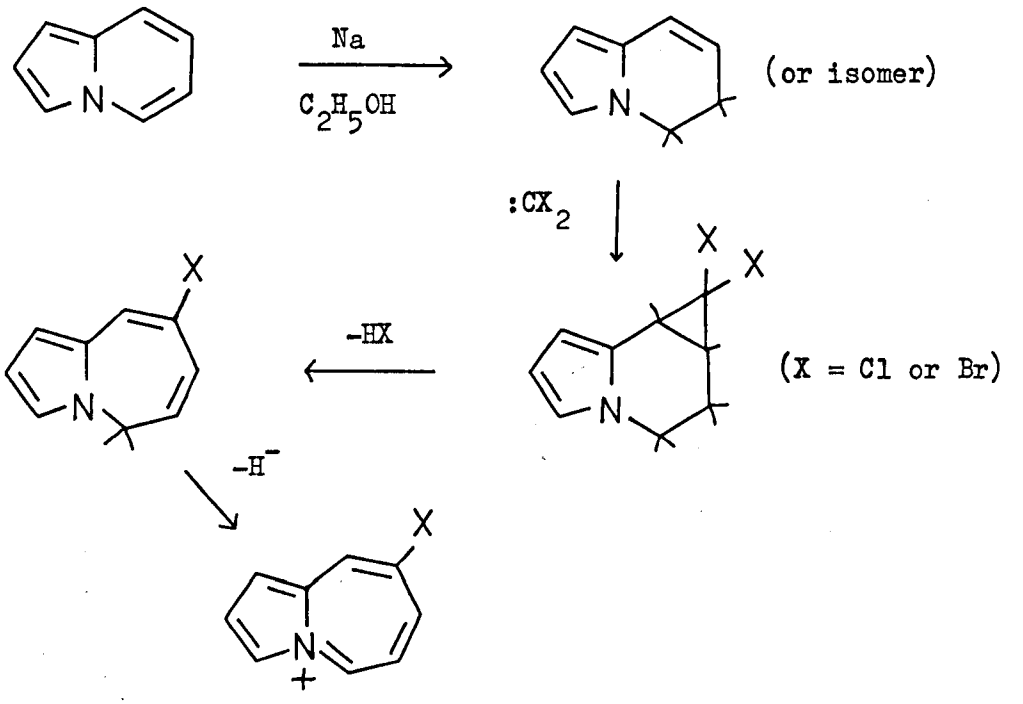
In a new approach to the synthesis of (1) and (2), Cliff and Jones [3-5] attempted two ring expansion routes.

The first route [5] involved the addition of a dihalocarbene to dihydroindolizine. It was hoped that a cyclopropane compound would be produced which would undergo ring expansion to a pyrrolo-[1,2-a] azepine, as envisaged in Scheme 3.

Although indolizines were successfully reduced, the dihydroindolizines obtained failed to undergo carbene addition to the double bond.

Their second approach [4] involved thermal decomposition of

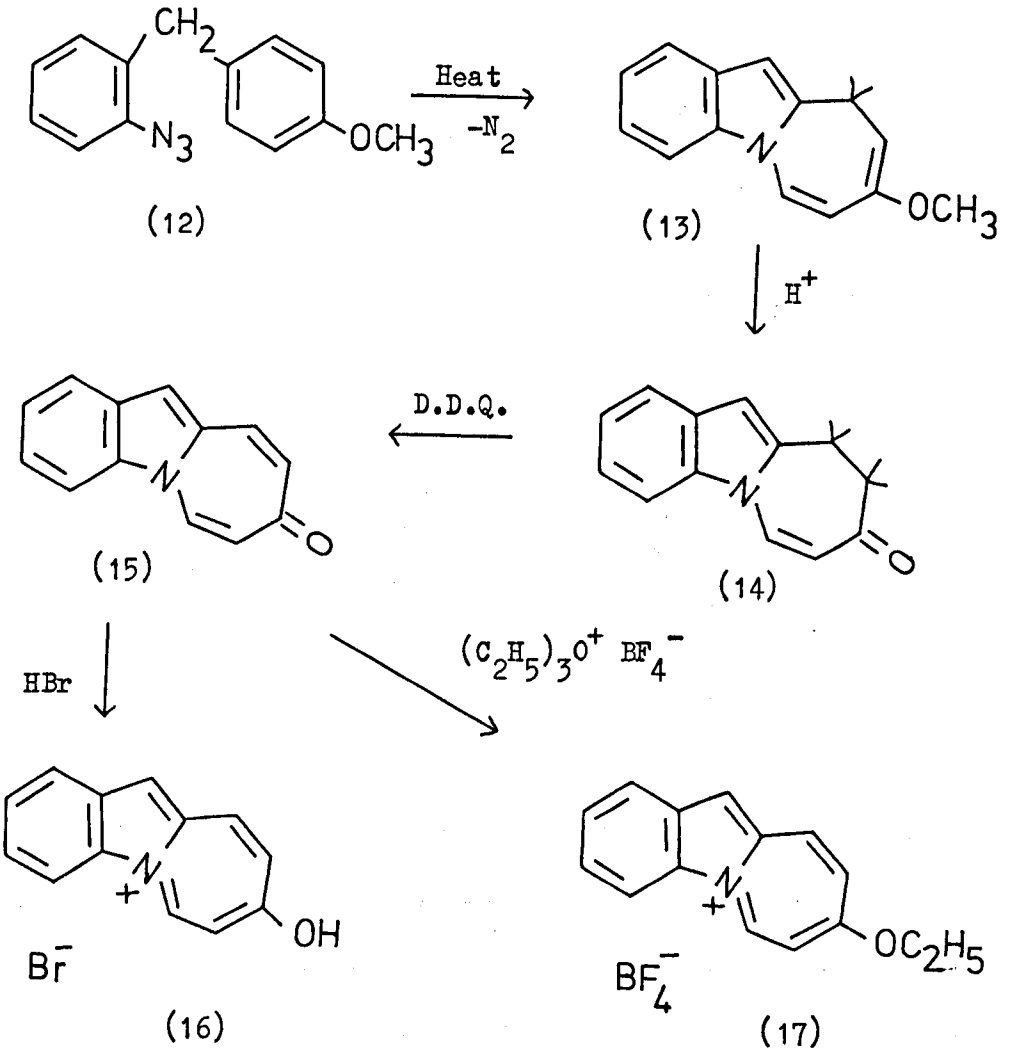
SCHEME 3



o-benzylphenyl azides, to give 10H-azepino [1,2-a] indoles, via a nitrene insertion reaction. Scheme 4 shows the successful route from O-(4-methoxybenzyl) phenyl azide (12) to the azonia-azulenium salts (16) and (17).

Thermal decomposition of the azide (12) gave the 8-methoxy-10H-azepino [1,2-a] indole (13). This was rapidly hydrolysed by dilute acid to the dihydroazepinoindol-8-one (14), and mild dehydrogenation with dichlorodicyanobenzoquinone (D.D.Q.) gave the azepino [1,2-a] indol-8-one (15). Treatment of (15) with dry hydrogen bromide, or triethyloxonium fluoborate, gave the azonia-azulenium salts (16) and (17) respectively.

SCHEME 4

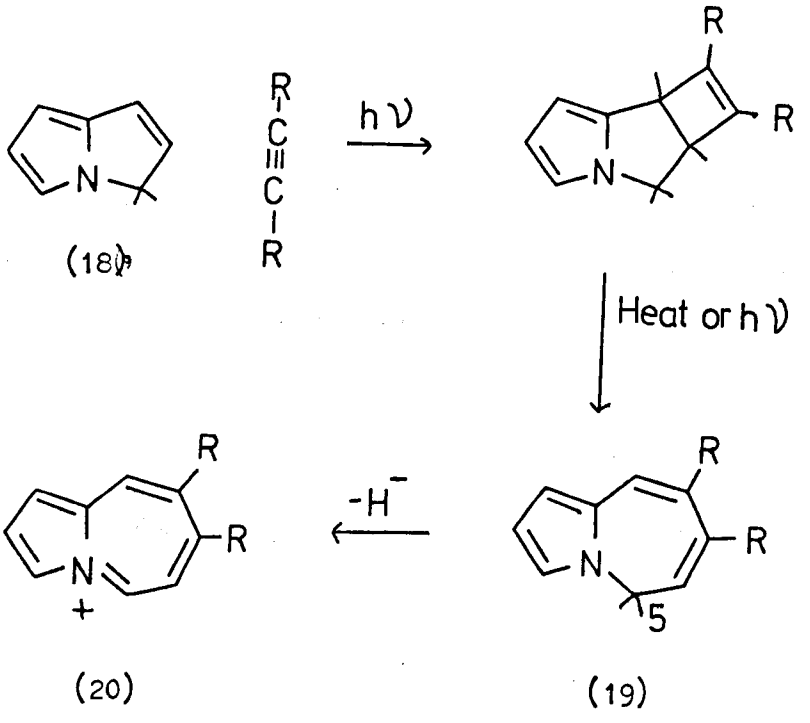


Attempts to reduce the carbonyl group in the ketone (15), to the corresponding carbinol, and hence provide a route to the unsubstituted azonia-azulenium salt (2) were unsuccessful.

The fourth, and final (to date), approach to the synthesis of the azonia-azulenium system (1) forms the basis of the original work described in this thesis, and is shown in Scheme 5.

This route involves the photochemical 2+2 cycloaddition of a substituted acetylene to 3H-pyrrolizine (18). Hopefully, a

SCHEME 5

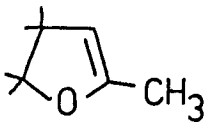


cyclobutene intermediate would be formed, which would be capable of ring expansion, either thermal or photochemical, to give a 5H-pyrrolo [1,2-a] -azepine (19). Abstraction of a hydride ion from the 5 position would then be expected to give the azonia-azulenium system (20).

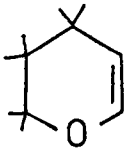
At this point it is relevant to review the thermal and photochemical 2+2 cycloadditions of common acetylenes to alkenes.

THE 2+2 CYCLOADDITION REACTIONS OF ACETYLENES TO ALKENES

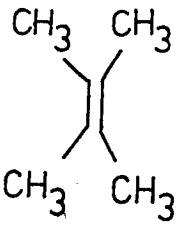
By far the most common acetylene to have been used in photochemical 2+2 cycloadditions, to alkenes, is diphenylacetylene, or tolan. With the compounds listed below (21) to (24), tolan adds in high yield, according to



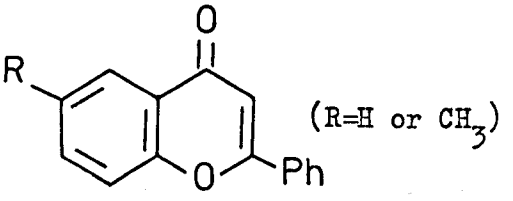
(21)[13]



(22)[14]



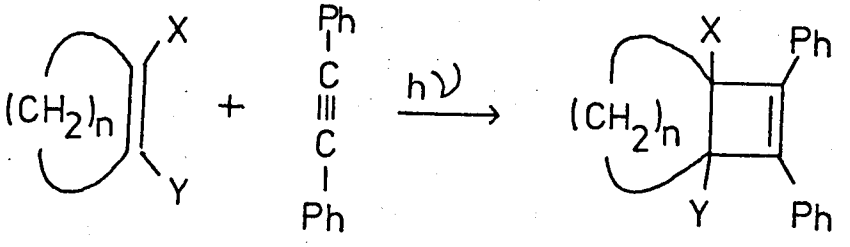
(23)[15]



(24)[16]

the general Scheme 6, to give cyclobutene adducts.

SCHEME 6

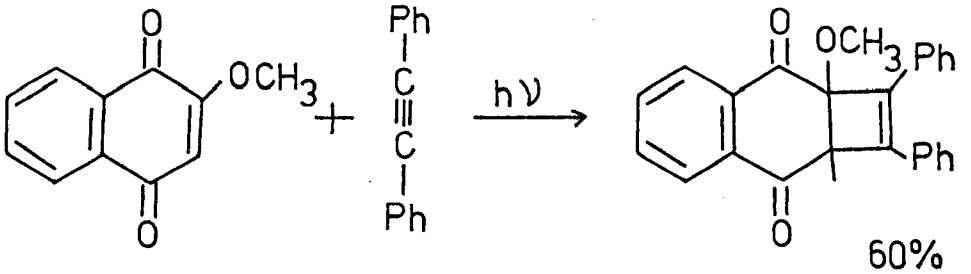


Unfortunately not all cycloadditions of tolan are quite

so simple.

When substituted with a 2-methoxy group, benzoquinone[17], and the correspondingly substituted naphthaquinone[18], add in high yield to tolan. The addition of the naphthaquinone (25) is shown in Scheme 7.

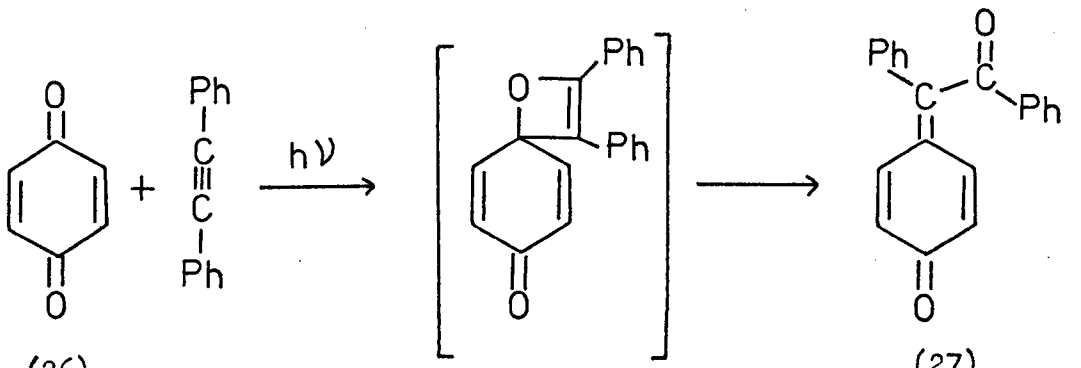
SCHEME 7



(25)

However, in the absence of the methoxy substituent, tolan adds across the carbonyl group of benzoquinone, or naphthaquinone, and the product rearranges to give a quinonoid ketone. Scheme 8 illustrates the reaction of benzoquinone (26) to give the ketone (27).

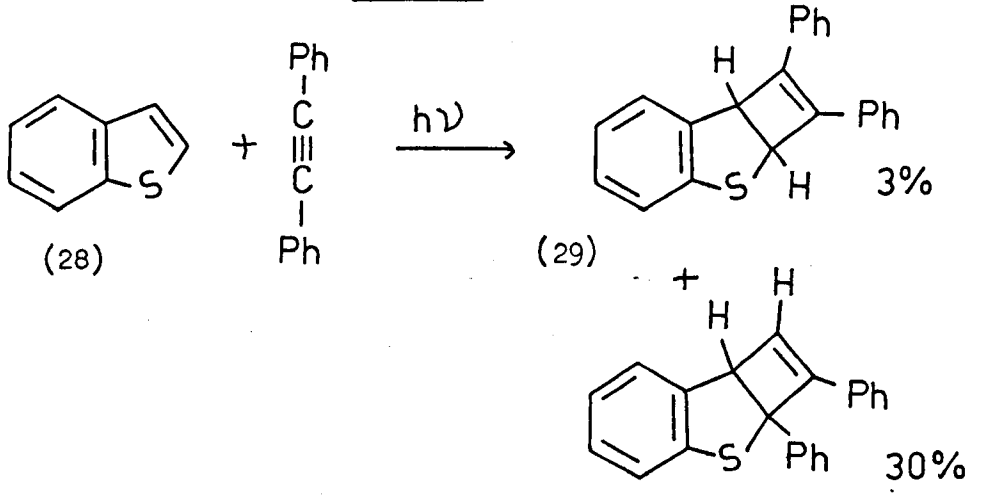
SCHEME 8



(26) (27)

Benzo (b) thiophen (28) also undergoes a photochemical addition with tolan, or dimethyl acetylenedicarboxylate, in which the cyclobutene product rearranges [19,20]. Scheme 9 shows the reaction with tolan.

SCHEME 9



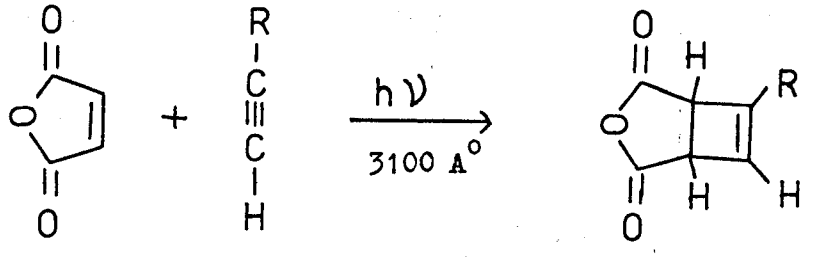
(28) (29) (30)

The expected product (29) was isolated along with the major, rearranged, product (30).

Many other acetylenes have undergone photocycloadditions to alkenes but none as frequently as tolan, e.g.

(a) Hartmann [21] has isolated cyclobutene adducts, in high yield, from maleic anhydride and the series of acetylenes shown in Scheme 10.

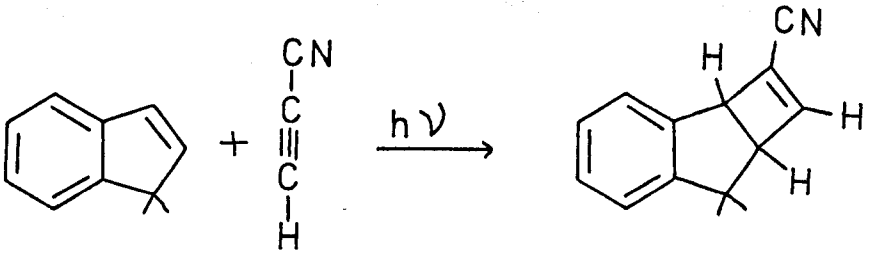
SCHEME 10



R=H, CH_3, C_2H_5, C_3H_7, C_4H_9, and $C(CH_3)_3$

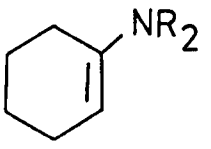
(b) Bowman, McCullough and Swenton [22] have photochemically added cyanoacetylene to indene (31) to give the cyclobutene adduct (32) shown in Scheme 11.

SCHEME 11

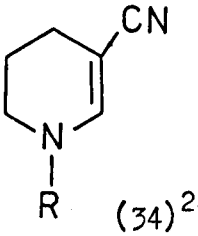


(31) (32)

As well as the photochemically induced 2+2 cycloadditions illustrated above, there have been many examples of thermal 2+2 cycloadditions between electrophilic acetylenes, such as methyl propiolate and dimethyl acetylene-dicarboxylate, D.M.A.D., and electron rich alkenes, e.g. compounds (33) to (37).

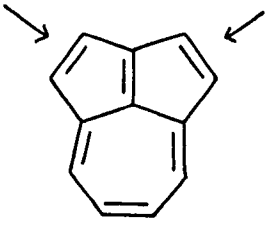


(33)[23]



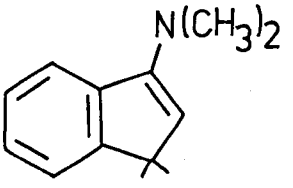
R=CH_3 or CH_2Ph

(34)[24]

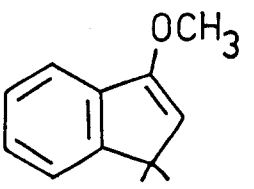


(35)[25]

(↑ addition)



(36)[26]

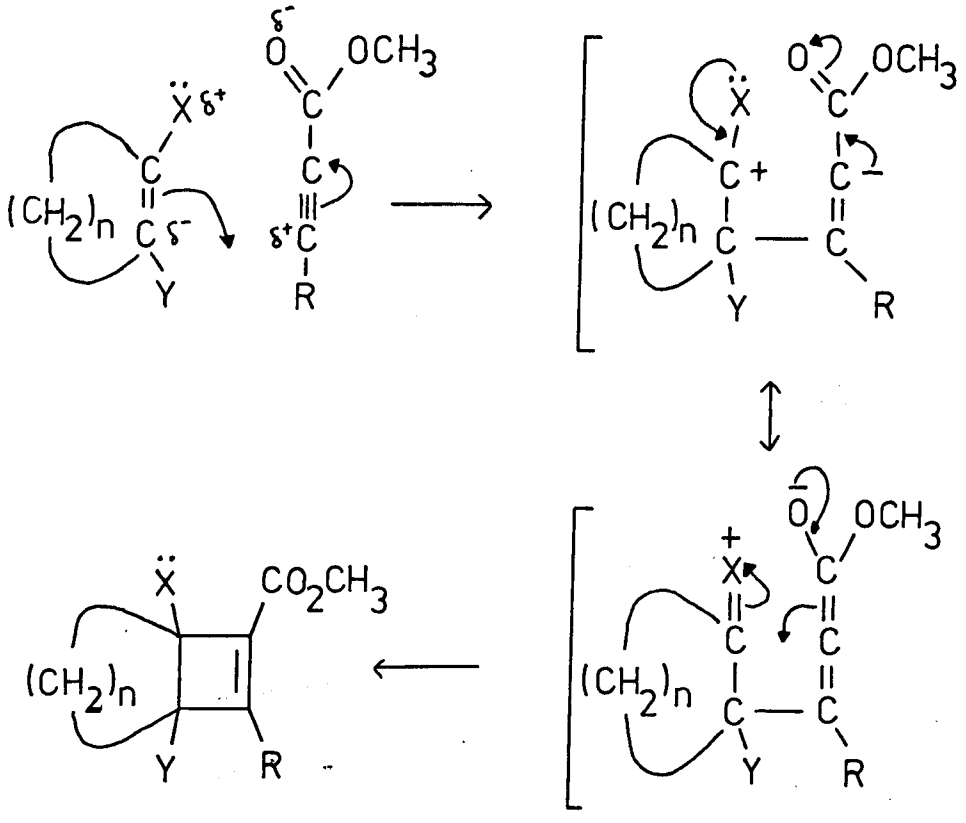


(37)[27]

The reactions probably proceed as envisaged in Scheme 12. The alkene and the acetylene are polarised, as shown, and a bond will quickly result between the negative end of the alkene dipole and the positive end of the acetylene. Both

the positive and negative charges, on the intermediate, can be stabilised, as shown, and eventually the zwitterion will

SCHEME 12

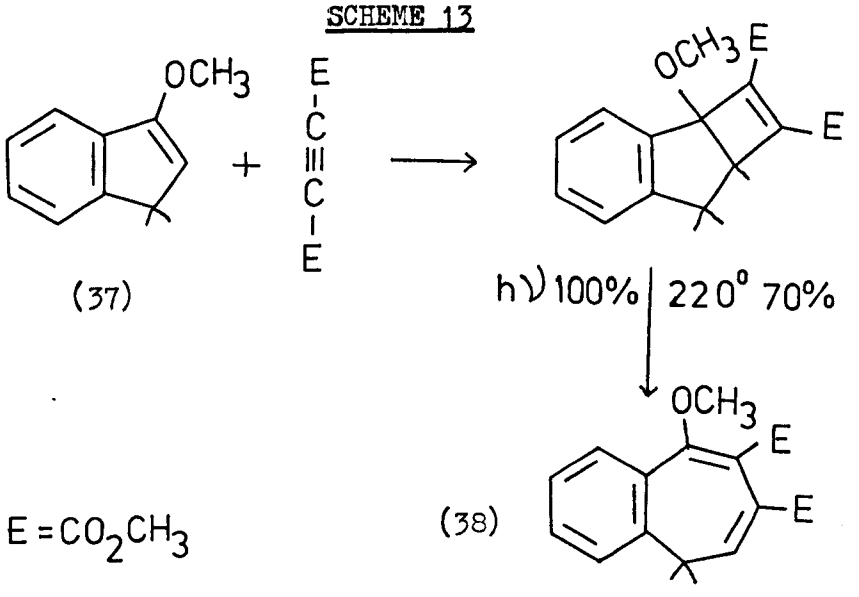


neutralise itself by the formation of the second bond of the cyclobutene ring.

In the case of compounds (35) to (37) the cyclobutene adducts formed can easily undergo thermal, or sometimes photochemical [27], ring opening to give cycloheptatrienes. This process is illustrated in Scheme 13 by the reaction of DMAD and methoxyindene (37) reported by Doyle [27]. The cycloaddition is carried out in 73% yield by simply refluxing

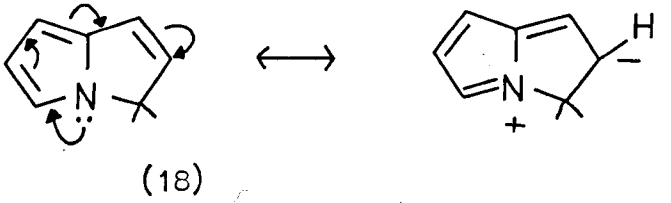
a toluene solution of DMAD and methoxyindene (37). Heating the adduct for 30 minutes at 220°, or irradiation for 3 hours (3100 A°) gives the benzocycloheptatriene (38).

SCHEME 13



From the photochemical reactions outlined in the review above, it would seem reasonable to expect 3H-pyrrolizine (18) to undergo a 2+2 photochemical cycloaddition to tolan, or DMAD, as envisaged in Scheme 5. Also, in the presence of a strong electrophile, we might expect 3H-pyrrolizine to polarise as shown in Scheme 14.

SCHEME 14



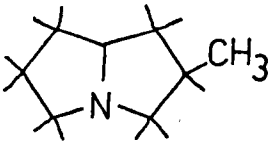
If this polarisation did occur, 3H-pyrrolizine might undergo the type of reaction shown in Scheme 12, and hence we might expect it to undergo a thermal 2+2 cycloaddition with DMAD.

PART I

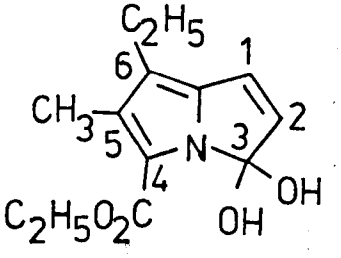
INTRODUCTION

Nomenclature

In 1936 Menshikov [28] isolated compound (39) which he called 2-methylpyrrolizidine. Later in the same year Micheel and Kimple [29] synthesised an unsaturated derivative (40) of pyrrolizidine which they called

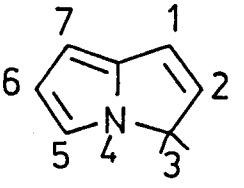


(39)



(40)

a "pyrrolizine" derivative, actually 5-methyl-6-ethyl-4-carbethoxy-pyrrolizin-3-one hydrate. Chemical Abstracts, however, still used the systematic name 3H-pyrrolo [1,2-a]-pyrrole for the pyrrolizine ring system, until they changed to "3H-pyrrolizine" in 1957.

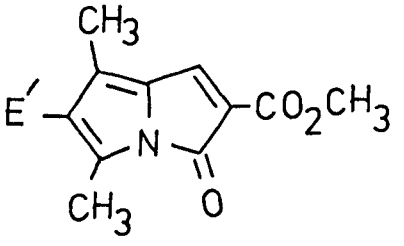


(18)

Their numbering is, however, different from the original numbering, by Micheel and Kimple, demonstrated on compound (40). Throughout this thesis the Chemical Abstracts system, demonstrated on compound (18), will be used.

The Synthesis of 3H-Pyrrolizines

The first pyrrolizine derivative was synthesised by Küster, Brudi and Koppenhöfer [30] in 1925. This was the pyrrolizin-3-one derivative (41) and was produced by boiling 4-carbethoxy-2-[β,β -dicarboxyvinyl] -3,5-dimethylpyrrole (42) in methanol for 60 hours.



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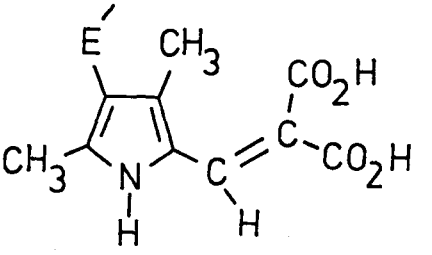


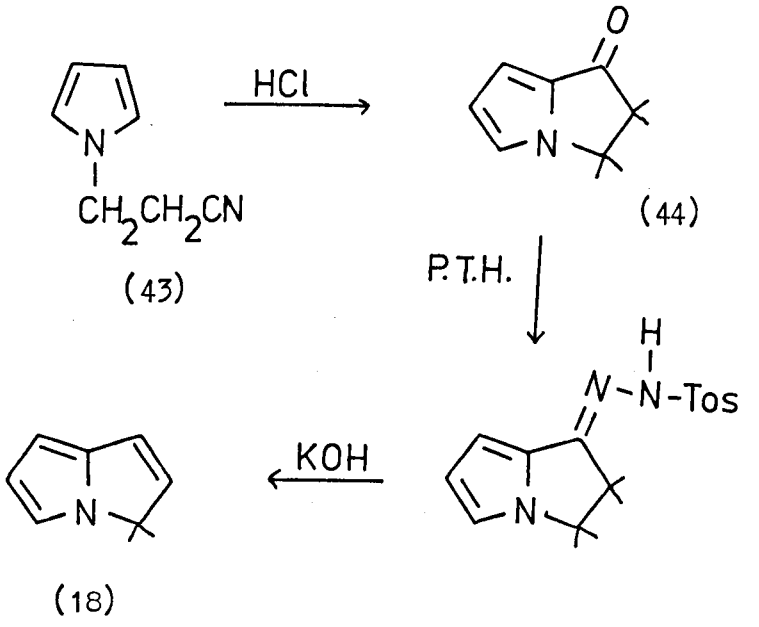
(42)

$E' = CO_2C_2H_5$

Interest was not, however, aroused in the pyrrolizine system until 1936 when Menshikov [28] discovered that 2-methyl-pyrrolizidine (39) was part of the alkaloid Heliotridane. Since that date substituted pyrrolizidine nuclei have been found in many other alkaloids [31], some of the earliest being Retronecine[32] and alpha and beta Longilobines [33].

3H-Pyrrolizine itself was not synthesised until 1963 when Carelli, Cardellini and Morlacchi [34] reported 3 routes. The best route to the parent 3H-pyrrolizine (18) is shown in Scheme 15. N-(β -cyanoethyl) pyrrole (43) was cyclised in ether solution, with dry hydrogen chloride to the dihydropyrrolizin-1-one (44). Condensation of the ketone (44) with p-tolylsulphonylhydrazine (P.T.H.), followed by treatment of the product with potassium hydroxide in triethylene glycol

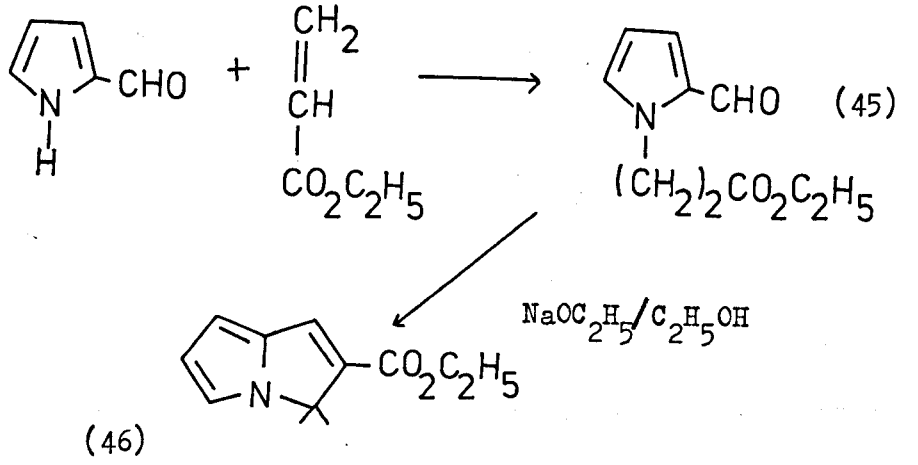
SCHEME 15



gave 3H-pyrrolizine (18) in a 29% overall yield.

A second route to 2-carbethoxy-3H-pyrrolizine (46), in 29% yield from the aldehyde, is shown in Scheme 16.

SCHEME 16

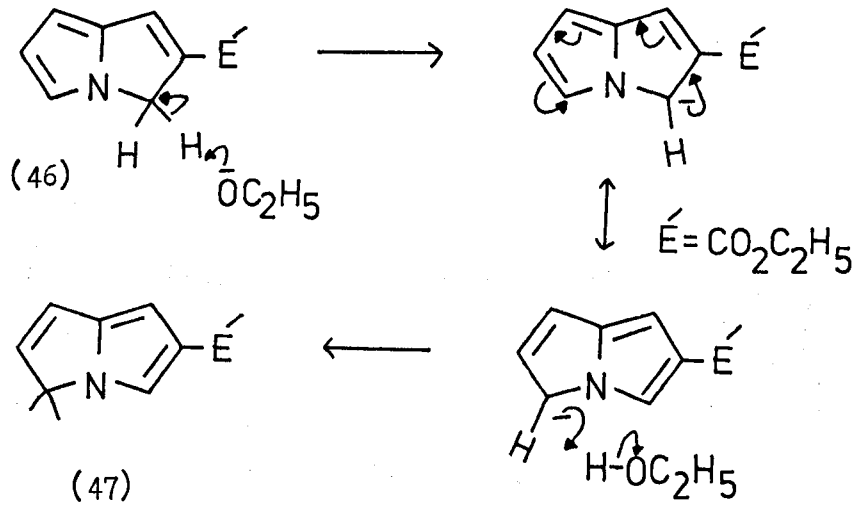


A Michael reaction between pyrrole-2-carboxaldehyde and ethyl acrylate, using finely divided potassium in toluene as base, gave N-(β-carbethoxyethyl)-pyrrole-2-carboxaldehyde (45).

This compound underwent an intramolecular condensation,

catalysed by sodium ethoxide in ethanol, to give what was claimed to be the pyrrolizine (46). However, Flitsch and Heidhues [35] repeated this synthesis in 1968, and proved that the pyrrolizine obtained was, in fact, the isomeric 6-carbethoxy-3H-pyrrolizine (47). It would seem that the pyrrolizine (46) was originally formed but, in the presence of strong base, it isomerised to (47) as shown in Scheme 17.

SCHEME 17

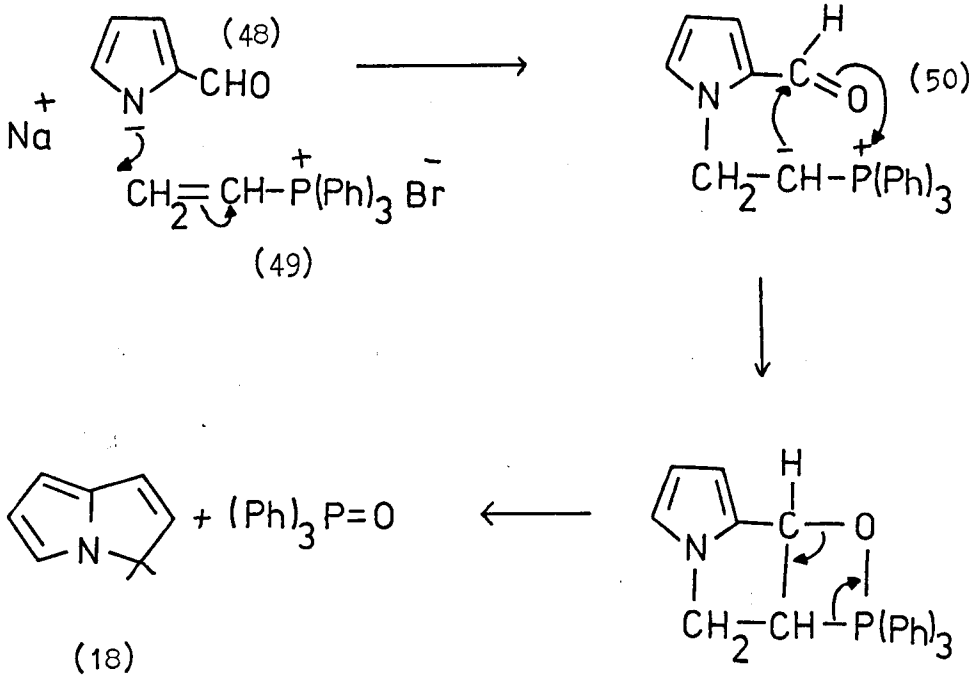


A much cleaner synthesis of 3H-pyrrolizine was reported in 1964 by Schweizer and Light [36]. They discovered a novel reaction between the sodium salt of pyrrole-2-carboxaldehyde, and vinyltriphenylphosphonium bromide, to give 3H-pyrrolizine in 87% yield. They proposed the combined Michael-Wittig mechanism for this reaction, shown in Scheme 18.

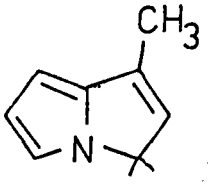
The sodium salt of pyrrole-2-carboxaldehyde (48) is formed by the reaction of sodium hydride on an ethereal solution of pyrrole-2-carboxaldehyde. The pyrrolide anion adds to

vinyltriphenylphosphonium bromide (49) to give the phosphorane-aldehyde (50). This compound undergoes an intramolecular Wittig reaction to give 3H-pyrrolizine (18) and triphenylphosphine oxide.

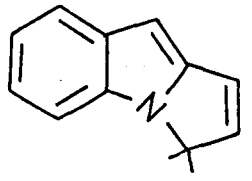
SCHEME 18



Using 2-acetylpyrrole and indole-2-carboxaldehyde in this reaction, Schweizer and Light [37] have also produced 1-methyl-3H-pyrrolizine (51) and 3H-pyrrolo [1,2-a] indole (52).

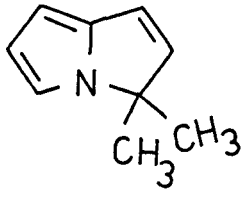


(51)

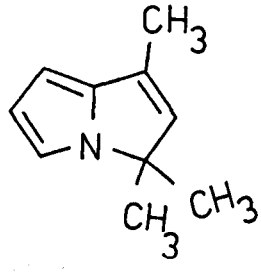


(52)

Schweizer and Light [38] extended this work further by the use of allylphosphonium salts, but a different mechanism is involved. Methallyltriphenylphosphonium chloride (53) reacts with the sodium salts of 2-formylpyrrole (48) and 2-acetylpyrrole to give 3,3-dimethyl-3H-pyrrolizine (55) and 1,3,3,trimethyl-3H-pyrrolizine (56) respectively.



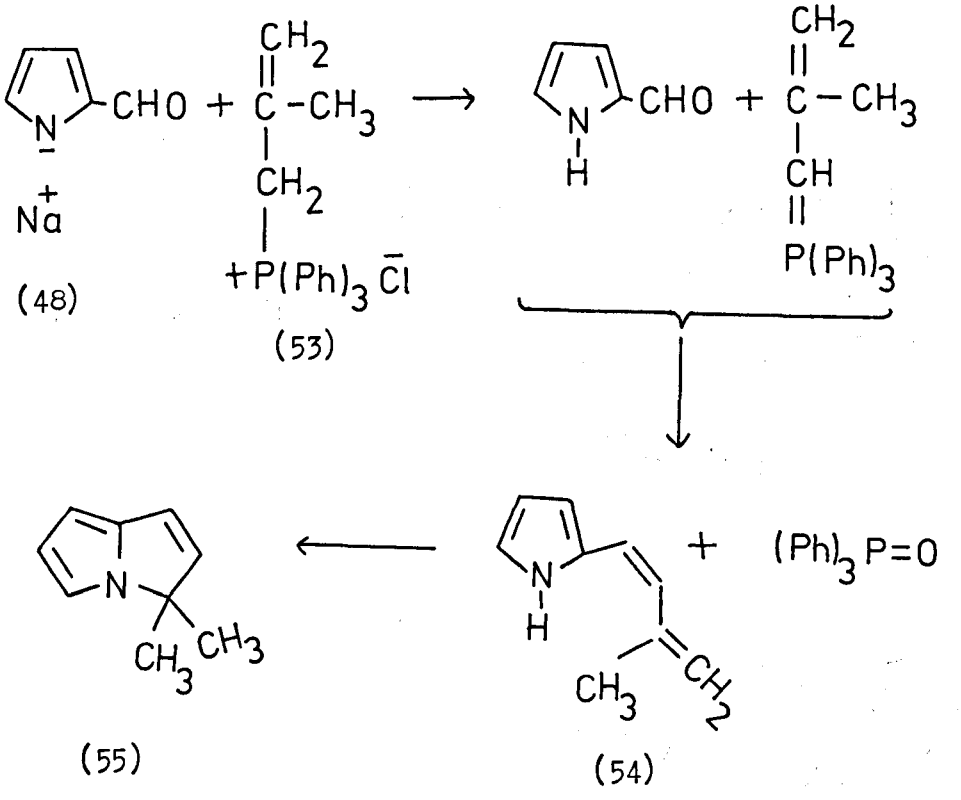
(55)



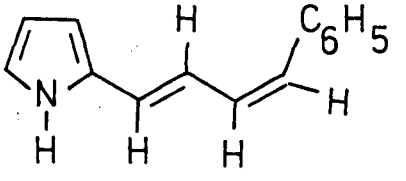
(56)

The mechanism in this case, shown in Scheme 19, proceeds via a butadiene intermediate. The existence of such intermediates was given support by the reaction of compound (48)

SCHEME 19



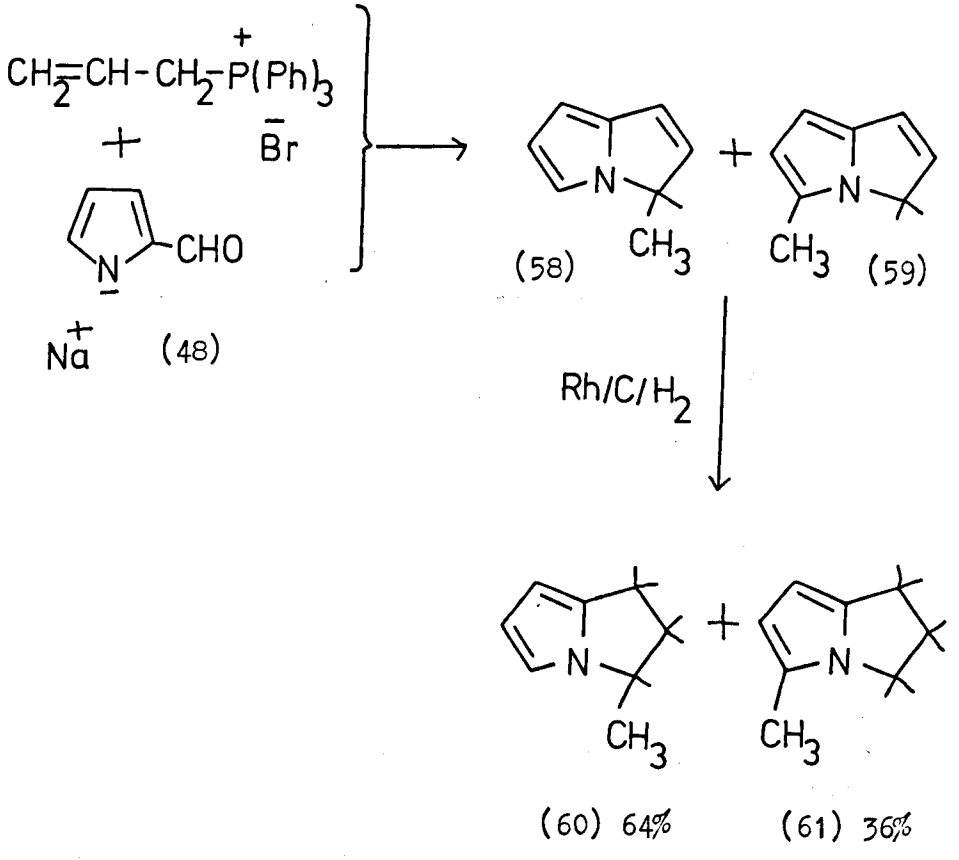
with cinnamyltriphenylphosphonium bromide. The only product obtained from this reaction was the butadiene (57).



(57)

In an attempt to synthesise 3-methyl-3H-pyrrolizine by this route, Schweizer and Light reacted allyltriphenylphosphonium bromide with compound (48). The pyrrolizine they obtained was, in fact, a mixture which they were not able to separate. However, after partial hydrogenation, to the dihydropyrrolizine mixture, they separated both 1,2-dihydro-3-methyl-3H-pyrrolizine (60) and 1,2-dihydro-5-methyl-3H-pyrrolizine (61). Hence the original reaction had given a mixture of 3-methyl-3H-pyrrolizine (58) and 5-methyl-3H-pyrrolizine (59) as shown in Scheme 20.

SCHEME 20



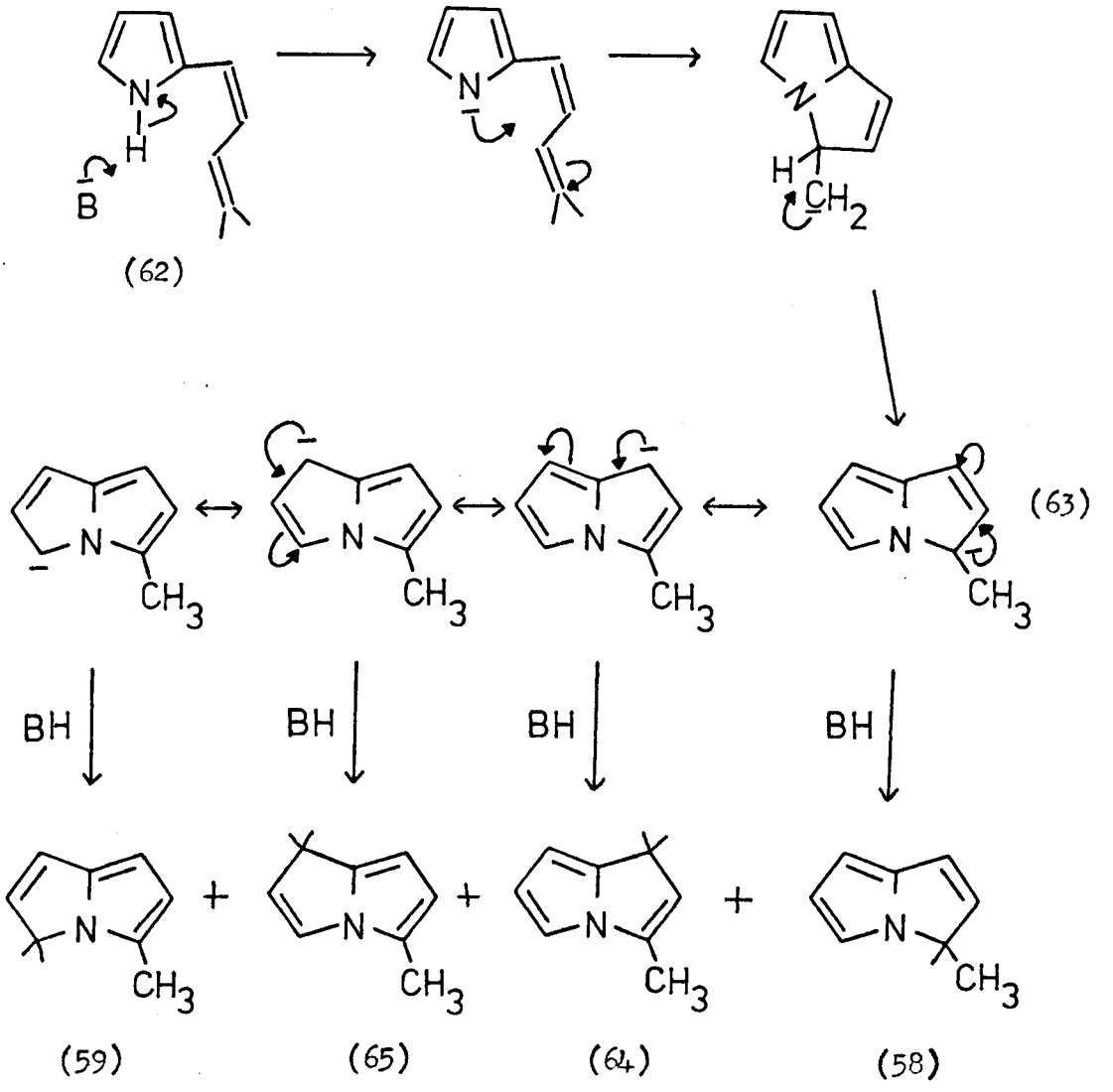
The reaction may have also produced the 1H-isomers of compounds (58) and (59) which would hydrogenate to compounds (60) and (61), but Schweizer and Light did not attempt to prove this.

The explanation for the product mixture, offered by Schweizer, is as follows:-

The butadiene intermediate (62) undergoes an intramolecular Michael reaction to give a methyl substituted 4-azapentalenyl anion (63). Scheme 21 shows the formation of this anion and also the resulting resonance stablisation. When this resonance hybrid is neutralised four products could

theoretically be obtained, the 3H-pyrrolizines (58) and (59) and their 1H-isomers (64) and (65).

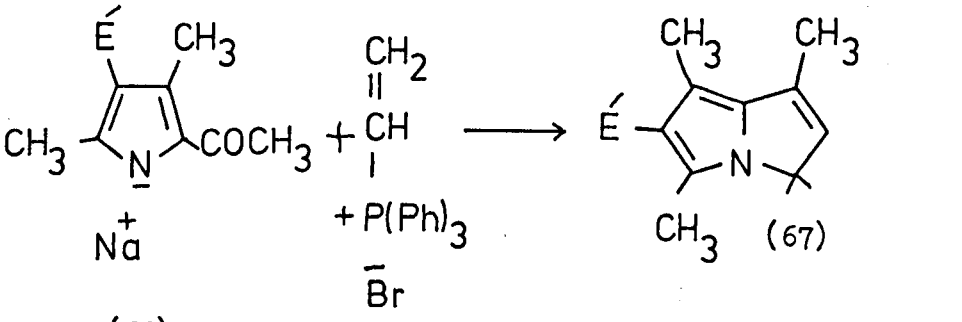
SCHEME 21



Schweizer and Light[38] also obtained another very similar product mixture when they tried to produce 3-ethyl-3H-pyrrolizine from compound (48) and crotyltriphenyl phosphonium chloride.

Flitsch and Heidhues[35], in 1968, reported the production of 1,5,7-trimethyl-6-ethoxycarbonyl-3H-pyrrolizine (67) from

the sodium salt of the appropriate ketone (66) and vinyltriphenylphosphonium bromide.

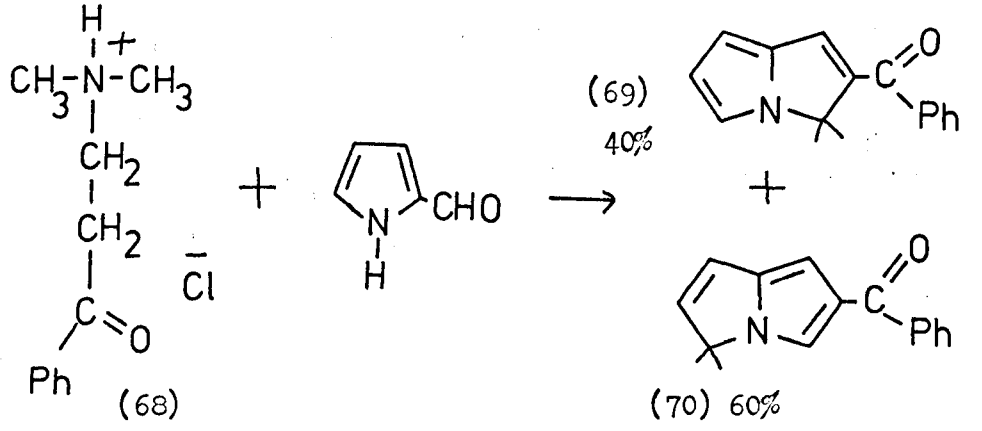


(66)

(67)

$\acute{E}=CO_2C_2H_5$

In this reaction they had no problem with product mixtures. However, when they tried to synthesise 2-benzoyl-3H-pyrrolizine (69) from pyrrole-2-carboxaldehyde and β-diethylaminopropiophenone hydrochloride (68), they obtained the isomers (69) and (70).



(68)

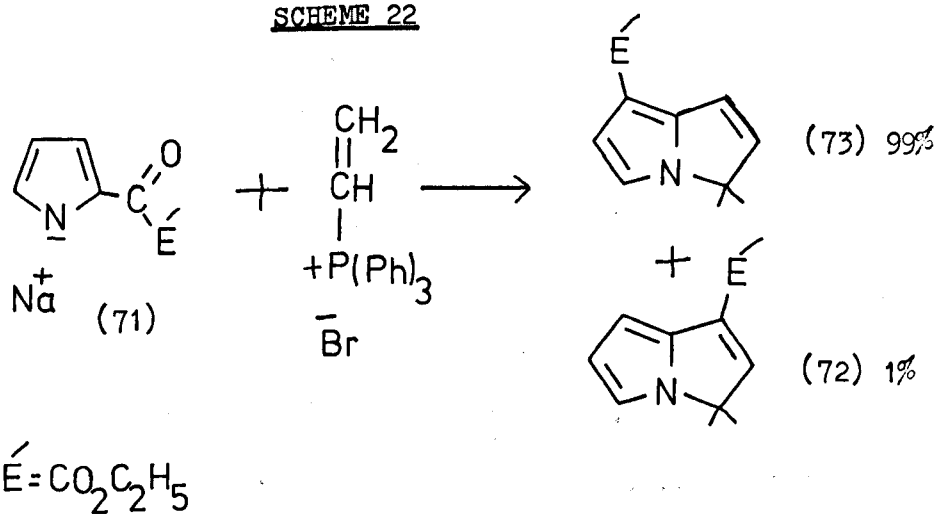
(69) 40%

(70) 60%

Once again the answer seems to be that the 2-benzoyl-3H-pyrrolizine, produced in the condensation, isomerised to a mixture of the 2-and 6-benzoyl isomers, under basic conditions. Even the use of a very weak base, sodium acetate, did not prevent the isomerisation from occurring.

Finally, in a very recent publication, Brandange and Lundin have reported the reaction of the sodium salt of a pyrrolyl keto ester (71) and vinyltriphenylphosphonium bromide. This reaction gave a mixture of pyrrolizines and is illustrated in Scheme 22.

SCHEME 22



The 1-carbethoxy-3H-pyrrolizine (72), formed in the synthesis,[1] had isomerised to give 99% of the 7-carbethoxy isomer (73). The mechanism must once again have been base catalysed isomerisation.

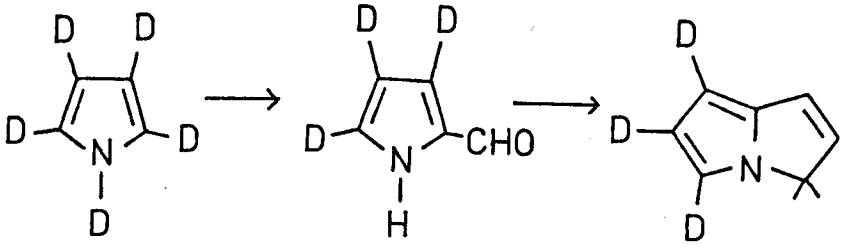
DISCUSSION

During the course of the work described in the discussion of Part II of this thesis, it became necessary to synthesise several new 3H-pyrrolizines. The previous review showed that the routes to 3H-pyrrolizines, reported by Schweizer and Light,[36-38] were the most convenient and gave the highest yields. All the attempts to synthesise new 3H-pyrrolizines, described in the following discussion, were therefore based on these routes.

The attempted synthesis of 5,6,7-trideutero-3H-pyrrolizine (76)

In 1942, F.A. Miller [40] reported the acid catalysed exchange of pyrrole, with deuterium oxide, to give pentadeuteropyrrole. It was hoped that 5,6,7-trideutero-3H-pyrrolizine (76) could be sythesised from pentadeuteropyrrole (74) as shown in Scheme 23.

SCHEME 23

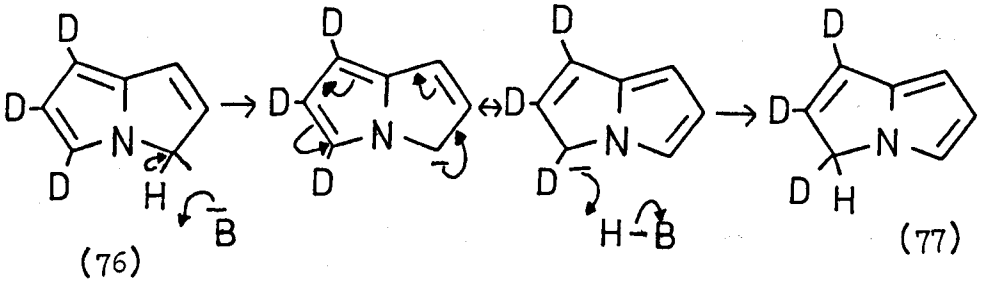


(74) (75) (76)

Pentadeuteropyrrole was obtained, with a 94% D incorporation, after four exchanges with deuterium oxide at pH1. Formylation,

with phosphorus oxychloride and dimethylformamide, gave 3,4,5-trideuteropyrrole-2-carboxaldehyde (75) with a 90% D content on the appropriate positions. The reaction of the aldehyde with sodium hydride and vinyltriphenylphosphonium bromide (V.P.S.) gave a 54% yield of a deuteropyrrolizine. The n.m.r. spectrum of the product showed the deuterium to be spread equally around the pyrrolizine nucleus, and the mass spectrum showed molecular ions of 105 (51%), 106 (77%), 107 (53%) and 108 (23%). The average molecular weight could not easily be calculated because of the complications of P+1, P-1 and P-2 peaks, but it was obvious that the molecular weight lay in the region of 106 to 107, and not 108 as expected.

The scrambling of the deuterium is probably best explained by the base catalysed isomerisation of the trideuteropyrrolizine (76) once it has formed.



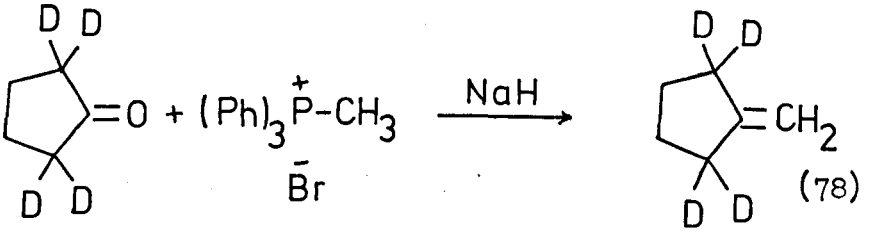
(76) (77)

An equimolar mixture of compounds (76) and (77) would give an equal distribution of deuterium around the pyrrolizine.

This problem of the scrambling, and loss of deuterium during Wittig reactions has also been experienced by Malloy, Hedges and Fisher [41]. Scheme 24 shows their

attempted synthesis of 2,2,5,5,-d_4-methylenecyclopentane (78) by a Wittig reaction. They also used sodium hydride in ether to generate the phosphorane, and the product obtained had deuterium spread on the ring and exocyclic methylene group. Also, some deuterium had been exchanged

SCHEME 24

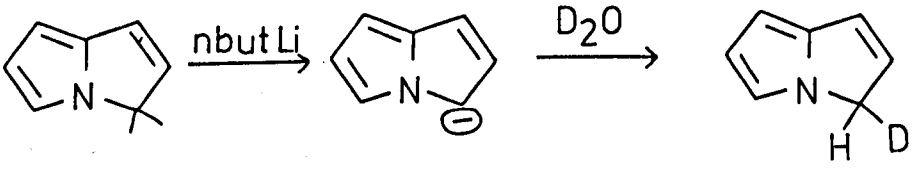


80% D on ring
20% D on methylene

with the solvent. They reported that the use of n-butyl lithium as base, and bis(2-ethoxyethyl) ether as solvent, cut out the deuterium scrambling, and loss, almost completely. However, as Schweizer's reaction is extremely susceptible to changes in reaction conditions, it was thought inadvisable to repeat the attempted synthesis of (77) using a different base or solvent.

The attempted synthesis of 3D-3D-pyrrolizine

Okamura and Katz [42] have conveniently synthesised 3H-3D-pyrrolizine (80) by the reaction of the 4-azapentalenyl anion (79) with deuterium oxide.

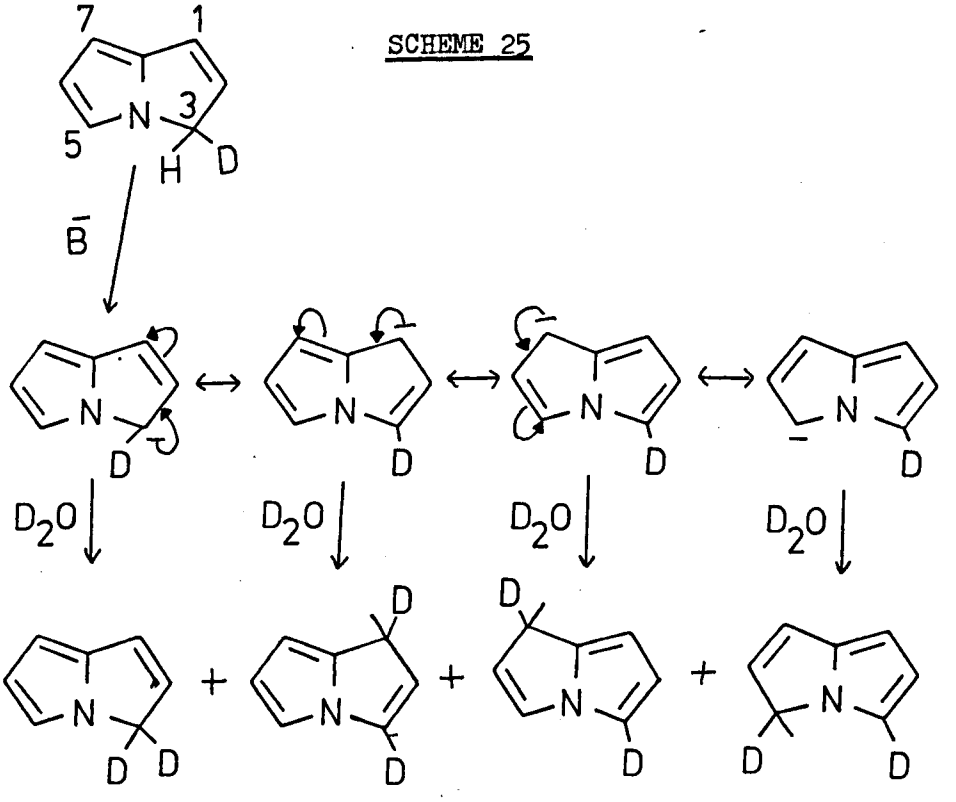


(79) (80)

It was hoped that the deuterium oxide exchange reaction could be repeated on 3H-3D-pyrrolizine to give a pyrrolizine fully deuterated (3D-3D), or even just further enriched with deuterium, on the 3 position.

This was attempted but, after 4 exchange reactions, a deuteropyrrolizine was obtained which had a high deuterium content on positions 1 (40%), 3 (86%), 5 (70%) and 7 (40%). The deuterium contents quoted are only approximate. The explanation for this deuterium scrambling is resonance stabilisation of the anion as shown in Scheme 25.

SCHEME 25

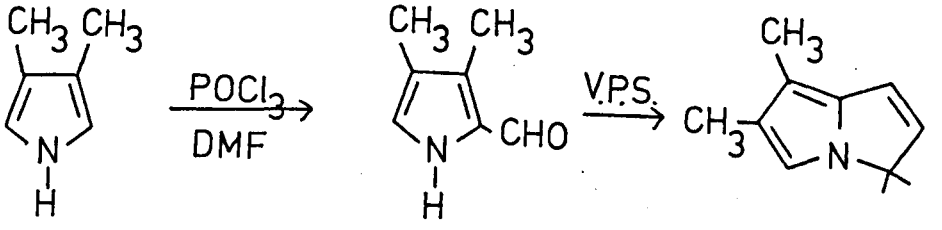


Reaction of such a resonance hybrid with deuterium oxide would give a pyrrolizine mixture having deuterium on the positions 1,3,5 and 7 as was, in fact, found. The relatively low deuterium content found on positions 1 and 7 demonstrated the relative instability of the 1H-pyrrolizines.

The attempted synthesis of 6,7-dimethyl-3H-pyrrolizine (83)

It was hoped that 6,7-dimethyl-3H-pyrrolizine (83) could be synthesised from 3,4-dimethylpyrrole, as shown in Scheme 26.

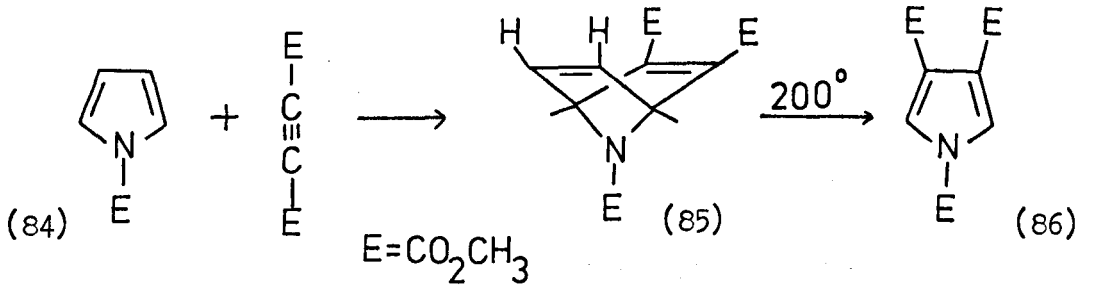
SCHEME 26



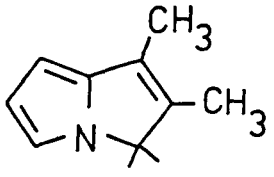
(81) (82) (83)

The synthesis of 3,4-dimethylpyrrole (81) involved two major stages. First of all trimethyl pyrrole-1,3,4-tricarboxylate (86) was synthesised by the Diels-Alder addition, reported by Acheson and Vernon, of dimethyl acetylene dicarboxylate to N-carbomethoxypyrrole (84). The adduct (85), shown in Scheme 27, splits out acetylene at 200°, the reaction temperature, to leave the triester (86).

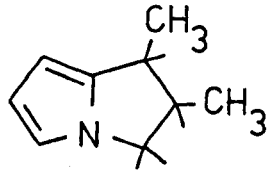
SCHEME 27



The triester (86) was reduced by lithium aluminium hydride according to the method of Hinman and Theodoropulos [44]. The hydride reduced the esters on the 3 and 4 positions, and cleaved the N-C bond, to leave 3,4-dimethylpyrrole (81). Formylation of 3,4-dimethylpyrrole, with phosphorus oxychloride and dimethylformamide, gave 3,4-dimethylpyrrole-2-carboxaldehyde (82) in 50% yield. However, the reaction of the aldehyde with sodium hydride and vinyltriphenylphosphonium bromide gave 1,2-dimethyl-3H-pyrrolizine (87), in 67% yield, and not the expected 6,7-dimethyl isomer (83).



(87)



(88)

The I.R., U.V. and mass spectra of the product were consistent with structures (83) or (87) but the n.m.r. spectrum showed a broad 1 proton singlet at τ 3.40, and a 1 proton triplet (J3Hz) at τ 4.03 and a 1 proton doublet (J3Hz) at τ 4.42. These signals could only be characteristic of the unsubstituted pyrrole ring of compound (87).

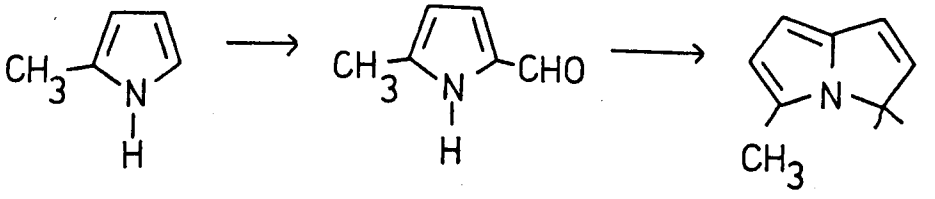
Hydrogenation of the pyrrolizine (87), using 10% Pd/C in ether, gave 1,2-dihydro-1,2-dimethyl-3H-pyrrolizine (88) as expected, thus confirming the identity of compound (87).

Gas-liquid chromatography (g.l.c.) showed only one peak for the pyrrolizine product. It would therefore appear that although 6,7-dimethyl-3H-pyrrolizine (83) had been formed in the reaction, it had undergone a 100% isomerisation, presumably caused by base catalysis once again, to the 1,2-dimethyl isomer (87).

The attempted synthesis of 5-methyl-3H-pyrrolizine (90)

The route envisaged for the synthesis of 5-methyl-3H-pyrrolizine (90) is shown in Scheme 28.

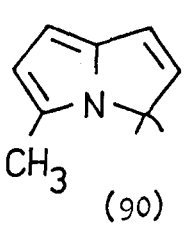
SCHEME 28

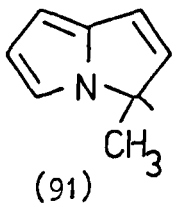


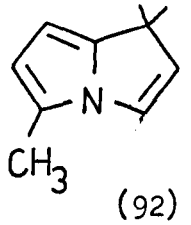
(89) (90)

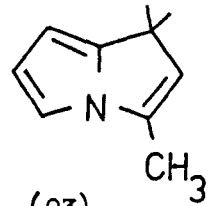
2-Methylpyrrole, readily available from the Wolff-Kishner reduction of pyrrole-2-carboxaldehyde, was formylated by phosphorus oxychloride and dimethylformamide to 5-methylpyrrole-2-carboxaldehyde (89). The aldehyde was reacted with sodium hydride and vinyltriphenylphosphonium bromide and gave a mixture of 3H-pyrrolizines, in 60% yield. G.l.c. analysis of the mixture showed 3 components, one minor (10% approx.) and two

major (each 45% approx). There are four possible products from this reaction, pyrrolizines (90) to (93).


(90)


(91)

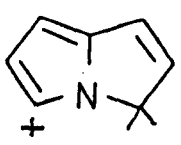

(92)

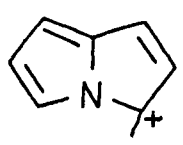

(93)

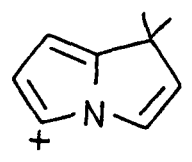
G.l.c/mass spectral analysis of the mixture confirmed that all three components had a molecular weight of 119 and were, therefore, isomers. The mass spectra showed only one large difference between the minor product I and the major products II and III, and this lay in the relative abundance of the M-15 peak, shown below.

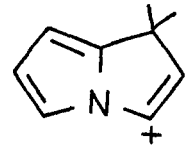
Component		I	II	III
% of mixture (approx)		10	45	45
Relative abundance of ion $^{m}/_{e}$	(119) (M^+)	89%	100%	100%
	(118) (M^+-1)	100%	66%	61%
	(104) (M^+-15)	91%	53%	58%

The high relative abundance of the (M-15) peak in the mass spectrum of product I, suggested the loss of a methyl radical from the molecular ion to leave a stable carbonium ion of mass 104. Loss of a methyl radical from the molecular ions of compounds (90) to (93) would give the carbonium ions (90a) to (93a) respectively.


(90a)

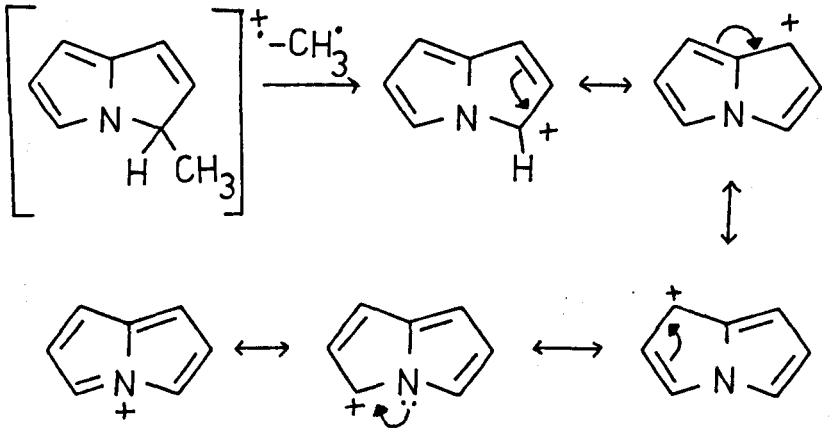

(91a)


(92a)


(93a)

Ion (93a) would have little stabilisation, ions (90a) and (92a) would be stabilised by involvement of the pyrrole ring, but ion (91a) would have much greater resonance stabilisation than the others, as illustrated in Scheme 29.

SCHEME 29

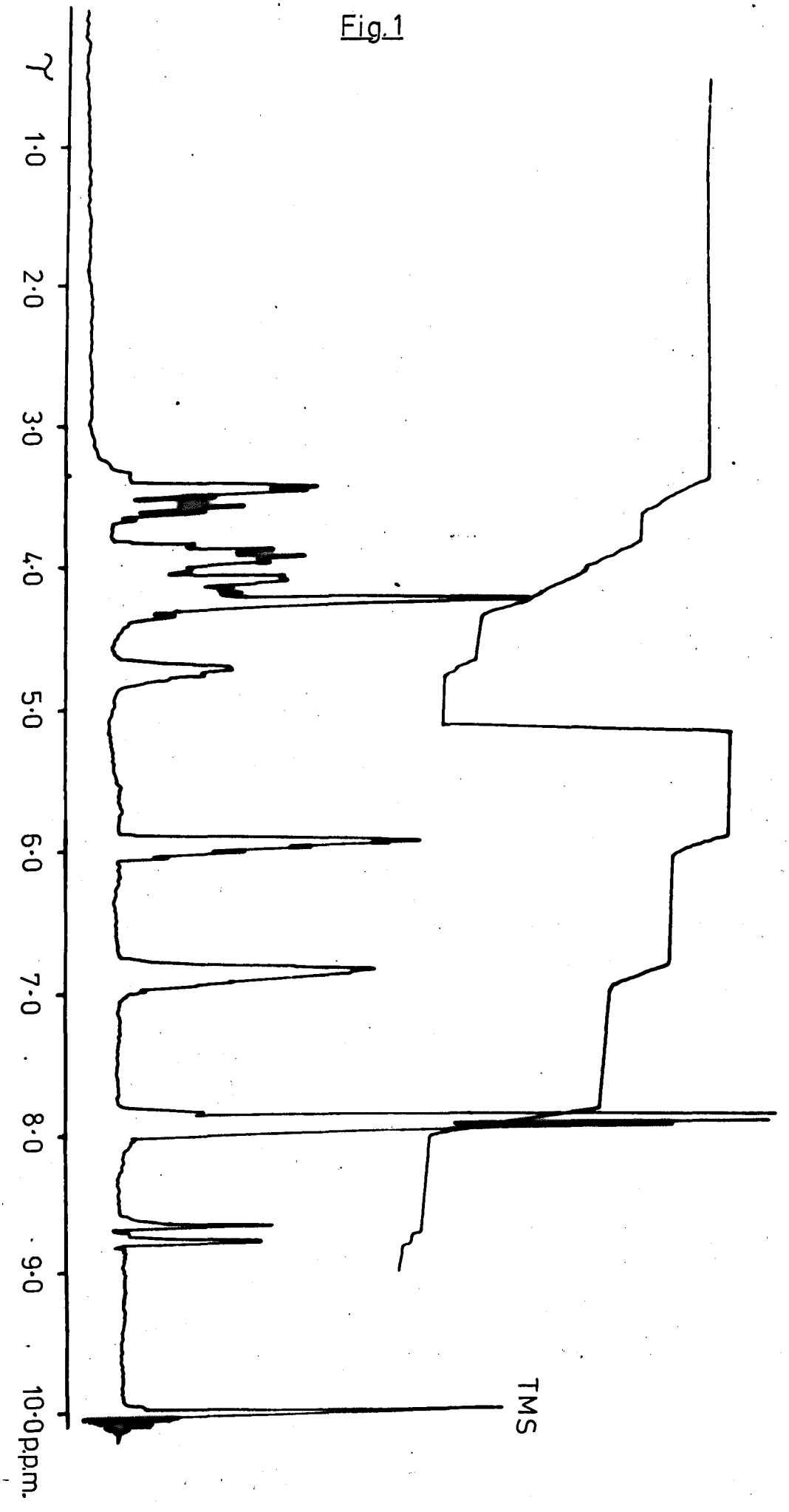


As the (M-15) peak in product I was nearly double the size of those of products II and III it was reasonable to assume that product I, the minor product, was, in fact, 3-methyl-3H-pyrrolizine (91).

The n.m.r. spectrum (fig.1) also agreed with this observation. A very small doublet (J7Hz) at τ 8.71 could also only be attributed to the methyl group, coupling with a geminal proton, of compound (91). From the integral of this n.m.r. signal, compared with the large singlet at τ 7.92 corresponding to the methyl groups of the rest of the mixture, the amount of compound (91) in the mixture was calculated to be 11%.

The n.m.r. spectrum also gave a second vital piece of

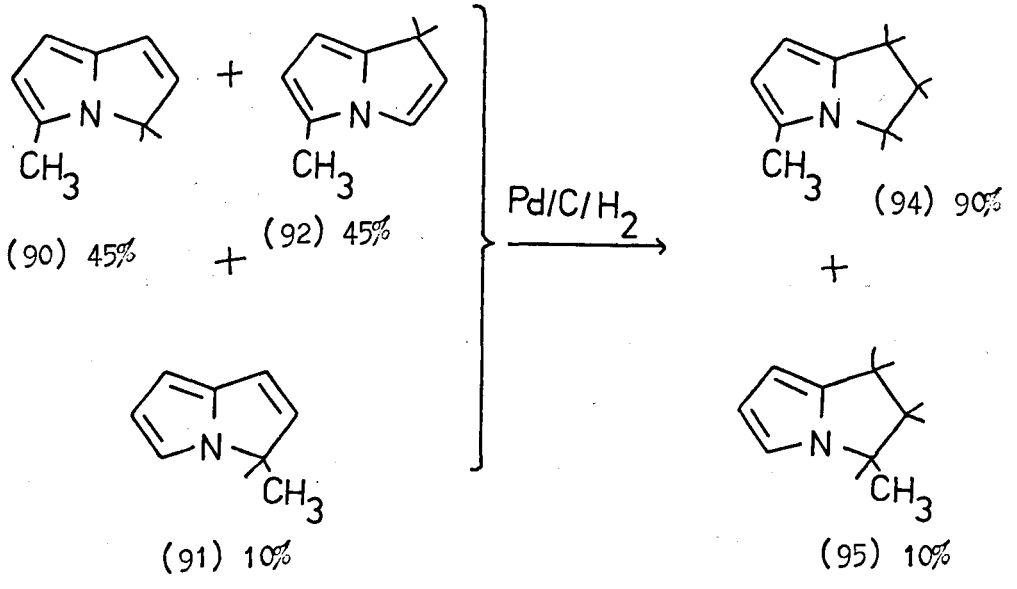
Fig.1



information about the mixture. At τ 5.98 and 6.87 there were broad singlets, each of approximately 1 proton integral. The methylene protons of 3H-pyrrolizine usually resonate as a broad singlet at τ 6.0. The signal at τ 6.87 must therefore be due to the methylene group of a 1H-pyrrolizine. We therefore have both 1H and 3H-pyrrolizines in the mixture which must consist of 11% of compound (91) and an almost equal mixture of compounds (90) and (92), or (90) and (93).

The constitution of the mixture was finally determined by hydrogenation. In the first case Scheme 30 shows that a mixture of 45% compound (90), 45% compound (92) and 10% compound (91) would, on hydrogenation, give a product mixture of 90% compound (94) and 10% compound (95).

SCHEME 30

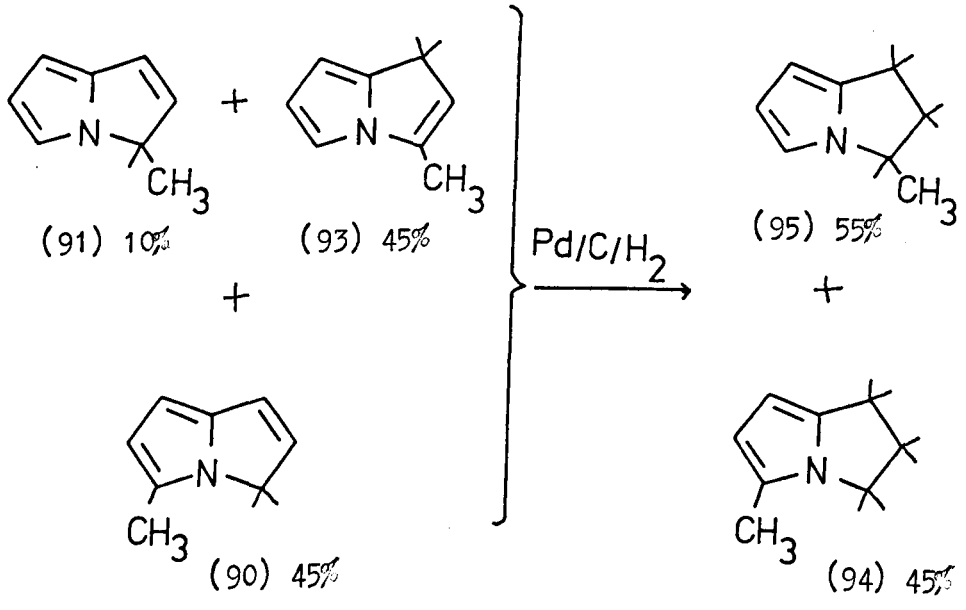


Hydrogenation of the second mixture of 45% compound (90), 45% compound (93) and 10% compound (91) would, as shown in

Scheme 31, give a product mixture of 45% compound (94) and 55% compound (95).

In fact the product mixture shown in Scheme 31 was obtained on hydrogenation of the pyrrolizine mixture with 10% Pd/C in ether. The products were separated by preparative g.l.c. and the n.m.r. and mass spectra confirmed their identity as 1,2-dihydro-5-methyl-3H-pyrrolizine (94),

SCHEME 31



and 1,2-dihydro-3-methyl-3H-pyrrolizine (95). The n.m.r. spectra of compounds (94) and (95) were in very good agreement with those published by Schweizer and Light [38]. They separated compounds (94) and (95) by preparative g.l.c. of a similar hydrogenation product mixture obtained after their attempt to prepare 3-methyl-3H-pyrrolizine.

The pyrrolizine mixture therefore consisted of compounds (90), (91) and (93). From the relative integrals of the methylene signals, in the n.m.r. spectrum, the composition of the mixture was calculated as:-

5-methyl-3H-pyrrolizine	(90)	42%
3-methyl-3H-pyrrolizine	(91)	11%
3-methyl-1H-pyrrolizine	(93)	47%

Once again an attempt to synthesise a substituted pyrrolizine had been frustrated by base catalysed isomerisation of the product. It would appear that in every pyrrolizine synthesis an equilibrium is set up, by base catalysis, which moves towards the most stable pyrrolizine isomer. It seems that the 3H-pyrrolizine system is more stable with mildly electron donating groups (e.g. methyl) on the 1 and 2 positions, rather than the 6 and 7, or with electron withdrawing groups (e.g. esters) on the 6 and 7 positions, rather than the 1 and 2. Hence Schweizer and Light [37] quite easily synthesised 1-methyl-3H-pyrrolizine, but the attempt, described in this thesis, to synthesise 6,7-dimethyl-3H-pyrrolizine resulted in 100% production of the 1,2 isomer. Also, attempts to synthesise 1-carbethoxy [39] and 2-carbethoxy-3H-pyrrolizine [34] have resulted in the production of 99 - 100% of their isomers.

Even the above observations are an oversimplification because Flitsch and Heidhues [35], in an attempt to synthesise 2-benzoyl-3H-pyrrolizine, obtained both the 2-(40%) and

6-(60%) isomers. Finally, whenever an attempt is made to synthesise a 3H-pyrrolizine with substituents on the 3 or 5 positions, a product mixture is obtained. The attempts, described in this thesis, to synthesise 5,6,7-trideutero-3H-pyrrolizine and 3D,3D-pyrrolizine ended up in product mixtures. Also, the attempt by Schweizer and Light [38], to synthesise 3-methyl-3H-pyrrolizine, gave an isomeric mixture of 3 and 5-methyl-pyrrolizines, as did the opposite attempt, described in this thesis, to synthesise 5-methyl-3H-pyrrolizine.

It would appear that a good deal more work needs to be carried out on the synthesis of substituted 3H-pyrrolizines, both to ascertain the cause of the observed isomerisations and, if possible, to find a route to the synthesis of pyrrolizines not involving the use of base in the final stage.

EXPERIMENTAL

Preliminary Notes

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infrared absorption spectra were measured on a Perkin Elmer 257 spectrophotometer. The spectra of solids were determined in solution (usually $CHCl_3$), and those of liquids in solution or as liquid films (Film).

Ultraviolet and visible absorption spectra were recorded on a Unicam SP 800 instrument. Solutions were made up in 95% ethanol unless otherwise stated.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin Elmer R10 60 MHz instrument and are quoted as 'tau' (τ) values in parts per million (p.p.m.). Tetramethylsilane was used as internal standard. The following abbreviations are used: s = singlet, d= doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and br = broadened.

Microanalyses were carried out on an F and M carbon/hydrogen/nitrogen analyser at the University of Keele.

Mass spectra were determined on a Hitachi - Perkin Elmer RMU-6 instrument.

Analytical gas-liquid chromatography (g.l.c.) was performed on a Pye series 104 instrument using a spiral column (1.5m x 4 m.m) packed with OV101 on chromosorb W.

Preparative g.l.c. was performed on a Pye series 105 automatic preparative chromatograph using a spiral column (5.0m x 1.0 cm) packed with SE30 (15%) on chromosorb W.

Column chromatography was carried out on Woelm neutral alumina deactivated by the addition of water (6%).

Thin layer chromatography (t.l.c.) was carried out on 7.5 x 2.5 cm microscope slides coated with silica gel (Merck Kieselgel PF_{254}). The components were visualised under ultraviolet light.

Preparative layer chromatography (p.l.c.) was carried out on 40 x 20 cm glass plates coated with a 1.5 mm layer of silica gel (Merck Kieselgel PF_{254}). The separated components, visualised under ultraviolet light, were isolated by scraping off the silica and extracting 3 times with methanol. The filtered methanolic solution was evaporated to leave a residue containing silica. The residue was dissolved in chloroform and the solution dried (Na_2SO_4) and filtered before evaporation to yield the pure component.

'Light petrol' refers to petroleum-ether bp 40-60°, and 'petrol' refers to petroleum-ether bp 60-80°.

Photochemical reactions were carried out, under an atmosphere of nitrogen, using a Hanovia medium pressure mercury lamp. A quartz filter, fitted to the lamp, gave light of 2537 A°, 3130 A° and 3660 A° wavelength. A pyrex filter, absorbing most radiation of less than 3100 A°, gave light of predominantly 3130 A° and 3660 A° wavelength.

THE PREPARATION OF 3H-PYRROLIZINES

Pyrrole-2-carboxaldehyde

Prepared according to the method of Silverstein, Ryskiewicz and Willard [45]. Starting from 44.7g of pyrrole, 49.2g (78%) of pyrrole-2-carboxaldehyde were obtained as long white needles m.p. 44-45°.

Vinyltriphenylphosphonium bromide

Prepared by an adaptation of the method of Schweizer and Bach [46].

β- Bromophenetole (40g) and triphenylphosphine (52.4g) were added to Analar phenol (250g) and the resulting mixture was heated at 90 ± 3° for 4 days, with the exclusion of moisture. The resulting solution was cooled to 30°, dissolved in anhydrous methylene chloride (200 ml dried over molecular sieve), and added dropwise to vigorously stirred anhydrous ether (2L) whereupon a white precipitate formed. This solid was recrystallised by dissolving in anhydrous methylene chloride (500 ml) and adding the resulting solution dropwise to vigorously stirred anhydrous ether (2L). The product was filtered and washed with 3 portions (250 ml) of anhydrous ether.

The crude phenoxyethyltriphenylphosphonium bromide was stirred under reflux in Analar ethylacetate (8 ml per 1g of the salt) for 24 hrs., with the exclusion of moisture. The resulting

suspension was cooled to 5°, filtered, and washed with anhydrous ether (2 x 250 ml). This elimination reaction was repeated at least 4 times until the melting point of the product (vinyltriphenylphosphonium bromide) exceeded 186°. The crude product was twice recrystallised by dissolving in anhydrous methylene chloride (400 ml) and reprecipitating by the addition of the solution to vigorously stirred anhydrous ether (2L).

Finally, the white crystalline solid was dried at 60°, under vacuum (16 mms), for 8 hrs.

Yield: 54g (73%), m.p. 187° (lit [46] 186 - 190°).

3H-Pyrrolizine (18)

Prepared basically by the method of Schweizer and Light [37].

Freshly crystallised pyrrole-2-carboxaldehyde (10g) was added in small portions to a magnetically stirred suspension of sodium hydride (100 ml NaH dried). The resulting thick white slurry was stirred, with the exclusion of moisture, for 4 hrs., then vinyltriphenylphosphonium bromide (40g) was added. An exothermic reaction occurred with the formation of a yellow solution and a brown precipitate. The mixture was stirred, under reflux and with the exclusion of moisture, for 24 hrs. After cooling, the mixture was filtered through Supercel to remove the sticky precipitate. The Supercel was washed 4 times with hot ether (50 ml) and the combined ether solutions

carefully evaporated to leave a yellow oil. The oil was distilled and the fraction boiling at 67 - 70°/16 mms was collected. This gave pure 3H-pyrrolizine 6.4g (58%) as a pale yellow oil. The pyrrolizine, if stored under nitrogen at -5° could be kept for a few months. However, at room temperature, and especially if open to the atmosphere, it decomposed within hours.

1-Methyl-3H-Pyrrolizine (51)

Prepared by the method of Schweizer and Light [37] from recrystallised 2-acetylpyrrole and vinyltriphenylphosphonium bromide. The suspension of sodium 2-acetylpyrrolide in ether was stirred for 4 hours before the addition of the phosphonium salt.

3,3-Dimethyl-3H-pyrrolizine (55)

Prepared by the method of Schweizer and Light [38] from pyrrole-2-carboxaldehyde and methallyltriphenylphosphonium chloride.

Pentadeuteropyrrole (74)

Prepared as described by Miller [40].

After 4 exchanges with D_2O at pH1 (D_2O acidified with D_2SO_4 using a pH meter), followed by drying (Na_2CO_3) and distillation, 20g of pyrrole yielded 11.7g (58%) of pentadeuteropyrrole. The deuteropyrrole had a deuterium content

of 94% (estimated from n.m.r. spectra).

3,4,5-Trideutero-2-formylpyrrole (75)

Prepared from pentadeuteropyrrole (74) by the method described by Silverstein, Ryskiewicz and Willard [45] for the formylation of pyrrole. The product purification had to be modified to the following:

After distillation of the crude aldehyde, the product was dissolved in benzene and the solution partitioned three times with water. Drying (Na_2SO_4) and evaporation of the benzene solution, left a white solid. Two recrystallisations from light petrol gave 10.0g (63%) of 3,4,5-trideutero-2-formylpyrrole m.p. 44.5° (lit [45] 44 - 45° for 2-formylpyrrole).

The deuterium content on positions 3,4 and 5 was 90% (estimated from the n.m.r. spectrum).

Attempted preparation of 5,6,7-trideutero-3H-pyrrolizine (76)

3,4,5-Trideutero-2-formylpyrrole (9.5g), sodium hydride (4.2g of 50% dispersion), ether (95 ml NaH dried) and vinyltriphenylphosphonium bromide (38g) were reacted as described in the preparation of 3H-pyrrolizine above, (page 42).

A mixture of deuteropyrrolizines was obtained (5.68g, i.e. 54%) as a pale yellow oil b.p. 67 - 69°/16 mms. The n.m.r. spectrum showed the deuterium to be equally distributed around the pyrrolizine, and the mass spectrum showed molecular ions at m/e 105 (51%), 106 (77%), 107 (53%) and 108 (23%).

3H-3D-Pyrrolizine (80)

Prepared as described by Okamura and Katz [42].

Attempted preparation of 3D-3D-pyrrolizine

Three further deuterium exchanges were carried out on 3H-3D-pyrrolizine by the method of Okamura and Katz [42]. However, the pyrrolizine obtained had deuterium on positions 1,3,5 and 7. The approximate deuterium contents of the various positions were estimated from the n.m.r. spectrum. They were (1) 41%, (3) 87%, (5) 68% and (7) 40%.

3,4-Dimethylpyrrole (81)

Prepared as described by Hinman and Theodoropulos [44].

2-Formyl-3,4- dimethylpyrrole (82)

Prepared from 3,4-dimethylpyrrole (81) by the method described by Silverstein, Ryskiewicz and Willard [45] for the formylation of pyrrole.

Instead of distillation the crude product was purified by three recrystallisations, from benzene/light petrol, to give white needles m.p. 133° (lit [47] 133°).

2.5g dimethylpyrrole (81) gave 1.6g (50%) of 2-formyl-3,4-dimethylpyrrole (82).

Attempted preparation of 6,7-dimethyl-3H-pyrrolizine (83)

2-Formyl-3,4-dimethylpyrrole (1.6g), sodium hydride

(0.6g of 50% dispersion), ether (12.5ml NaH dried) and vinyltriphenylphosphonium bromide (5.0g) were reacted as described in the preparation of 3H-pyrrolizine, on page 42.

The isomeric, 1,2-dimethyl-3H-pyrrolizine (87) was obtained (1.15g, i.e. 67%) as a pale yellow oil b.p. 87 - 90°/ 16 mms.

Owing to rapid decomposition consistent elemental analyses could not be obtained.

λ max (n.m.)	210	285.5
$Log_{10}\varepsilon$	3.77	3.88

Mass spectrum $^{m}/_{e}$ 133 (M^{+}) (80%), 132 (46%), 118 (100%)

N.m.r. (CCl_4): τ 3.39 (1H,brs), 4.01 (1H,t,J3Hz), 4.41 (1H,d,J4Hz), 6.0 (2H,m), 8.18 (6H,brs)

Analytical g.l.c. (115°, N_2 flow rate 40 ml min^{-1}) showed only one peak with a retention time of 153 secs.

1,2-Dihydro-1,2-dimethyl-3H-pyrrolizine (88)

A solution of the dimethyl pyrrolizine (87) (113 mg) in dry ether (35 ml), with Pd/C catalyst (50 mg 10%), was hydrogenated at atmospheric pressure and temperature until the uptake of hydrogen ceased. The catalyst was filtered off and the ether evaporated to give 1,2-dihydro-1,2-dimethyl-3H-pyrrolizine as a brown oil (113 mg, i.e. 100%).

Mass spectrum $^{m}/_{e}$ 135 (M^{+}) (36%), 134 (20%), 120 (100%)

N.m.r. (CCl_4): τ 3.7 (1H,m), 4.05 (1H,t,J3Hz), 4.43 (1H,d,J3Hz), 6.0 - 7.6 (4H,m), 8.7 - 9.2 (6H,m)

2-Methylpyrrole

A Wolff-Kishner reduction was carried out on pyrrole-2-carboxaldehyde using the method reported by Acheson and Vernon [48], for the reduction of 1-methyl-2-formylpyrrole.

21.0g pyrrole-2-carboxaldehyde yielded 12.0g (67%) of 2-methylpyrrole b.p. 146 - 149° (lit [49] 148°).

2-Formyl-5-methylpyrrole (89)

Prepared from 2-methylpyrrole by the method described by Silverstein, Ryskeiwicz and Willard [45] for the formylation of pyrrole.

Distillation of the crude product was not attempted but instead column chromatography was used for the purification. The crude material was put onto a column of alumina, in light petrol, and elution of the column, with a 1:1 mixture of benzene and light petrol gave the product as a yellow solid. Three crystallisations from light petrol/charcoal gave 2-formyl-5-methylpyrrole as a pale yellow solid m.p. 72 - 73° (lit [50] 70°).

N.m.r. (CCl_4) showed τ 0.78 (1H,s), 3.21 (1H,t,J3Hz), 4.06 (1H,t,J3Hz), 7.60 (3H,s)

12g 2-methylpyrrole gave 8.3g (52%) of 2-formyl-5-methylpyrrole.

Attempted preparation of 5-methyl-3H-pyrrolizine (90)

2-Formyl-5-methylpyrrole (8.3g), sodium hydride (3.24g of 50% dispersion), ether (74ml NaH dried) and vinyltriphenylphosphonium bromide (29.4g) were reacted as described in the preparation of 3H-pyrrolizine, on page (42).

A mixture of methylpyrrolizines was obtained (5.4g, i.e. 60%) as a yellow oil b.p. 78 - 80°/16 mms.

Analytical g.l.c. (115°, N_2 flow rate 40 ml min^{-1}) showed 3 peaks with retention times (1) 72 secs: (2) 100 secs: and (3) 111 secs. The approximate composition of the mixture was (1) 10%, (2) 46% and (3) 44% from the peak heights.

G.l.c./mass spectral analysis of the mixture showed:-

Fraction (1) m/e 119 (M^+) (89%), 118 (100%), 104 (91%)

Fraction (2) m/e 119 (M^+) (100%),118 (66%), 104 (53%)

Fraction (3) m/e 119 (M^+) (100%),118 (61%), 104 (58%)

N.m.r. (CCl_4) showed: τ 3.51 (1H approx, m), 3.95 (1H,m),
4.03 - 4.4 (2H approx, m),
4.74 (0.5H,brs), 5.98 (1H,brs),
6.87 (1H,brs), 7.92 (3H,brs)
8.71 (0.3H,d,J7Hz).

Hydrogenation of the methylpyrrolizine mixture

A solution of the pyrrolizine mixture (250 mg) in dry ether (30 ml), with Pd/C catalyst (50 mg 10%), was hydrogenated at atmospheric pressure and temperature until the uptake of

hydrogen ceased. The catalyst was filtered off, and the ether evaporated, to leave a mixture of dihydro-3H-pyrrolizines as a brown oil (250 mg, i.e. 100%).

Analytical g.l.c. on this product (115° and N_2 flow rate 40 ml min^{-1}) showed two peaks with retention times (1) 66 secs: and (2) 96 secs. The approximate composition of the mixture was (1) 53% and (2) 47%.

The components of the mixture, (94) and (95), were separated by preparative g.l.c. using an SE30 column (160° and N_2 flow rate 100 ml min^{-1}). The n.m.r. spectra of these components agreed well with those published by Schweizer and Light [38]. They were:-

1,2-Dihydro-3-methyl-3H-pyrrolizine (95) (Fraction 1)

Mass spectrum m/e 121 (M^+) (52%), 120 (47%), 106 (100%).

N.m.r. (CCl_4) τ 3.66 (1H,m), 4.02 (1H,t,J3Hz), 4.43 (1H,d,J3Hz), 5.93 (1H,q,J6Hz), 7.1 - 8.0 (4H,m), 8.70 (3H,d,J6Hz).

1,2-Dihydro-5-methyl-3H-pyrrolizine (94) (Fraction 2)

Mass spectrum m/e 121 (M^+) (77%), 120 (100%) 106 (33%).

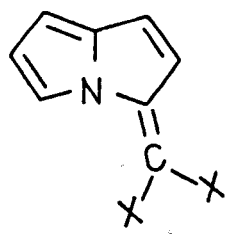
N.m.r. (CCl_4) τ 4.35 (1H,d,J4Hz), 4.55 (1H,d,J4Hz), 6.36 (2H,t,J6Hz), 7.1 - 7.8 (4H,m), 7.89 (3H,s).

PART II

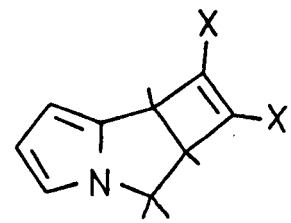
INTRODUCTION

Nomenclature

In the following discussion three types of compounds will be encountered, as products of the reactions between 3H-pyrrolizines and dimethyl acetylenedicarboxylate. It is therefore appropriate to discuss their nomenclature at this stage.



I



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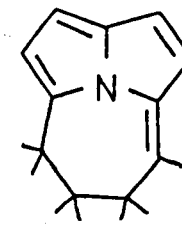
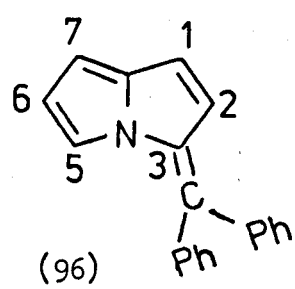
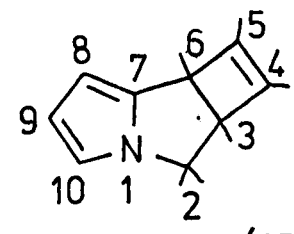


III

Compounds of the type 1 have been reported by Okamura and Katz [42] and Flitsch and co-workers [35,51] and they were referred to, by both sets of authors, as "azafulvenes". Technically these compounds are not azafulvenes, due to the position of the double bonds in the pyrrole ring, but they will be generally referred to as azafulvenes throughout this work. Where compounds are specifically named the nomenclature



(96)

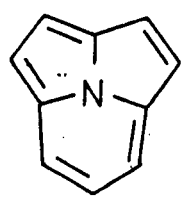


(97)

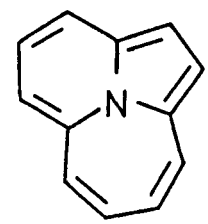
introduced by Flitsch and Heidhues [35] will be used. They are thus named as derivatives of 3H-pyrrolizine and compound (96), for example, is called 3,3-diphenylmethylene-3H-pyrrolizine.

Compounds of the type II will be generally referred to as cyclobutene derivatives but when specifically named the systematic nomenclature will be used, e.g. the hypothetical compound (97) would be named 1-azatricyclo [5,3,$0^{1,7}$,$0^{3,6}$] deca-4,7,9-triene.

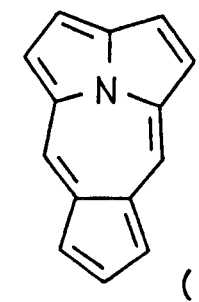
Compounds of the type III are derivatives of the cycl[4,2,2] azine system and will be generally referred to as cyclazine derivatives. Boekelheide and co-workers [52] put forward the name cyclazine, in 1959, to describe "a conjugate unsaturated cycle held planar by 3 covalent bonds to an internal nitrogen". Individual members of the series are named by bracketing the number of carbon atoms, on the peripheral cycle, between points of bonding to the internal nitrogen. Hence compound (98) is



(98)



(99)

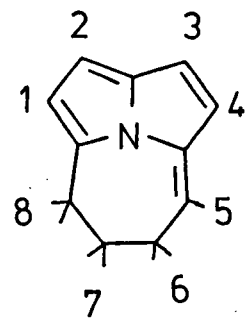


(100)

cycl [3,2,2] azine and compound (99) is cycl [4,3,2] azine. Compound (100) reported by Jessep and Leaver [53], is the only example of the cycl [4,2,2] azine system reported to date

outside this University.

When compounds of the type III are specifically named they will be named as derivatives of 8H-cycl [4,2,2] azine. Thus the hypothetical compound (101) would be called 6,7-dihydro-8H-cycl [4,2,2] azine.



(101)

The thermal reactions of dimethyl acetylenedicarboxylate with 3H-pyrrolizine and related compounds

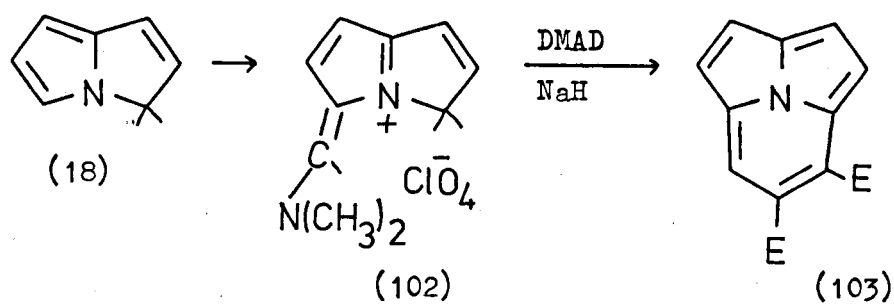
Before discussing the attempted photochemical reaction of 3H-pyrrolizine and dimethyl acetylenedicarboxylate (DMAD) it would be pertinent to review the thermal reactions already known between DMAD and 3H-pyrrolizine, its carbocyclic analogue indene, and pyrrole.

In the following review and discussion the abbreviation 'E' will be used for the methyl ester group ($-CO_2CH_3$) in illustrations.

a) Reaction of DMAD with 3H-pyrrolizine derivatives

The only reactions reported between 3H-pyrrolizine and DMAD are those by Johnson and Jones [54,55] (the contents of the following discussion) and Jessep and Leaver [53].

Jessep and Leaver [53] reacted 3H-pyrrolizine (18) with



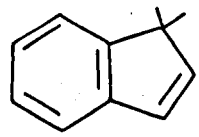
(18) (102) (103)

phosphoryl chloride and dimethylformamide to give a salt, isolated as the perchlorate, which they assumed to be (102). This salt reacted with DMAD, in the presence of sodium hydride, to give the cycl[3,2,2]-azine derivative (103).

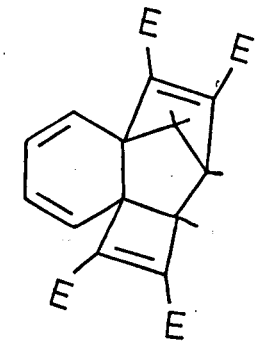
Further reactions of the salt (102) gave various cyclazine derivatives but these will be discussed at a later stage.

b) Reaction of DMAD with indene

In 1942 Alder, Pascher and Vagt [56] reported the reaction of indene (104) and DMAD, in refluxing benzene, to give the diadduct (105.)



(104)



(105)

The structure of this diadduct was not, however, known until 1964 when it was elucidated by Muir, Sim, Strachan and Heubner [57] using X-Ray analysis on a dibromo derivative.

More recently, in 1970, Doyle [26,27] has reported thermal 2+2 cycloaddition reactions between substituted indenes and DMAD. These have, however, been discussed earlier.

c) Reactions of DMAD with pyrroles

Pyrroles have been found to undergo two main types of reaction with acetylenedicarboxylic acid and its dimethyl ester DMAD, Michael type reactions and Diels Alder reactions.

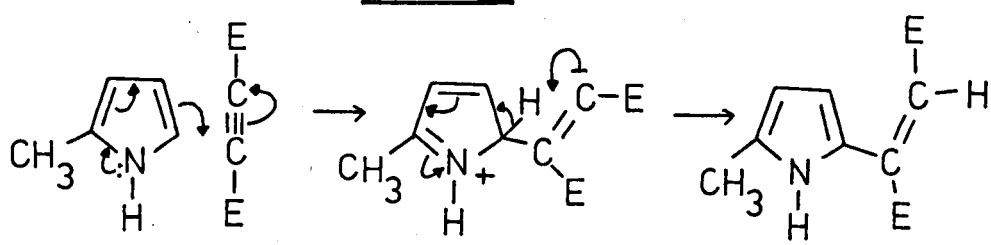
c) contd

Both types of reaction involve the initial attack of a strong electrophile on the 2, or 5, position of the pyrrole ring - the most electron rich positions.

1. Michael type reactions

The reaction between 2-methylpyrrole and DMAD, shown in Scheme 31, was reported by Diels, Alder and Winckler [58] in 1931.

SCHEME 31



(106)

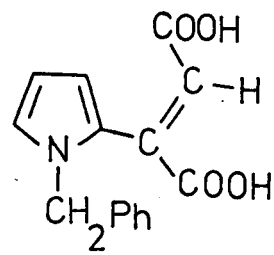
It yielded dimethyl 5-methylpyrrol-2-ylfumarate (106) and maleate. Similar reactions have been reported between 1-benzylpyrrole and acetylenedicarboxylic acid [59] and, also, 1,2-dimethylpyrrole and DMAD.[48] The conditions for all these reactions were refluxing in ether or benzene solution.

2. Diels Alder reactions

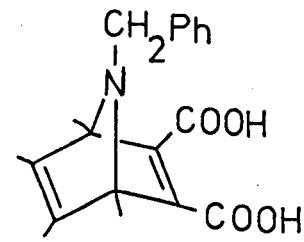
These are less common than the Michael reactions, above, but some examples are known. Mandell and Blanchard [60], in 1957, reported the Diels Alder addition of acetylenedicarboxylic acid to N-benzylpyrrole under very mild conditions (24 hrs. in refluxing ether). As well as

2. contd

the pyrrol-2-ylfumaric acid adduct (107) a Diels Alder adduct (across the 2,5 positions of the pyrrole ring) was isolated (108).



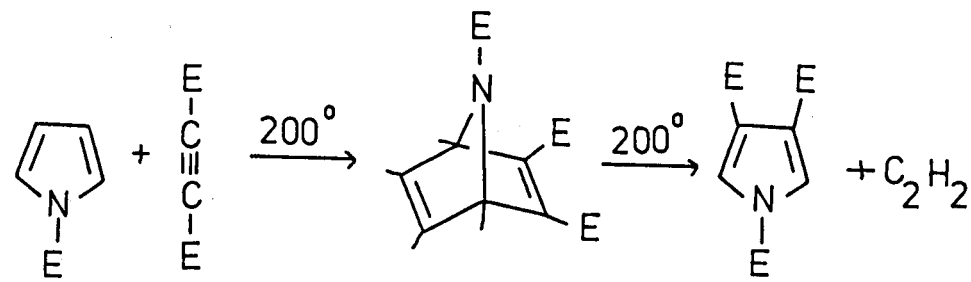
(107)



(108)

Acheson and Vernon [43] have reported the addition-elimination sequence, shown in Scheme 32, involving a Diels Alder intermediate.

SCHEME 32



(85)

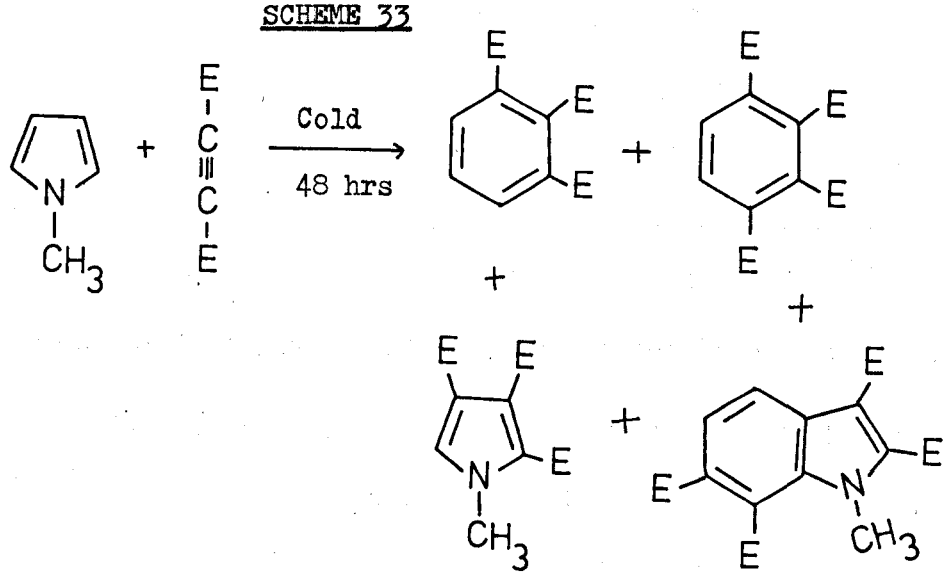
This reaction has been discussed in more detail on page 30 .

Finally, a cold reaction has been reported by Acheson and Vernon [61] between 1-methylpyrrole and DMAD. The products, shown in Scheme 33, are difficult to explain but their formation probably involves Diels Alder addition followed by various elimination, addition and rearrangement

2. contd

reactions.

SCHEME 33



A much more comprehensive review on the reactions between acetylenecarboxylic acids, and their esters, with nitrogen heterocycles, has been written by Acheson [62]. It includes suggested mechanisms for many of the above reactions.

DISCUSSION

1.1 The attempted photochemical reaction of 3H-pyrrolizine with dimethyl acetylenedicarboxylate (DMAD) using light of predominantly 2537 A^{o} wavelength

The first photochemical reaction attempted used light of 2537 A^{o} because, at that time, the equipment available only included a quartz filter. The reaction conditions (apart from the wavelength of light) were modelled on those described by Bowmann, McCullough and Swenton [22] for the sensitized photoaddition of cyanoacetylene to indene.

3H-Pyrrolizine, an equimolar amount of acetophenone, (triplet state sensitizer) and a 10 fold excess of DMAD, were irradiated in benzene solution for 7 hrs. During this time the solution turned deep red and t.l.c. showed the appearance of red and orange products. Evaporation of the resulting solution gave a red oil which was chromatographed on an alumina column. Elution with petrol removed the acetophenone, and excess pyrrolizine, and elution with a 1:1 mixture of petrol and toluene separated an orange band from the remaining red mass. The orange band was collected and further elution with toluene brought off a red band, leaving a great deal of coloured material on the column. Further elution of the column with toluene/chloroform mixtures brought off a brown tar.

The product from the orange band recrystallised from petrol to give orange needles and mass spectral analysis showed it to have

a molecular weight of 247. It was, therefore, a 1:1 adduct of 3H-pyrrolizine and DMAD and will be referred to in future as compound A.

The product from the red band was slightly impure, as obtained from the column, but after purification by p.l.c. (35% benzene, 65% chloroform) a bright red gum was obtained which crystallised on standing. Mass spectral analysis showed a m.wt. of 389 for this compound. It was therefore a diadduct (1 of 3H-pyrrolizine to 2 of DMAD) and will be referred to in future as compound B.

Finally, p.l.c. on the brown tar (80% chloroform, 20% benzene) separated 20 bands. None were of significant yield, compared with compounds A and B, and none had molecular weights corresponding to adducts of 3H-pyrrolizine and DMAD.

In later attempts to produce compounds A and B it was discovered that light was not needed to initiate the reaction. 3H-Pyrrolizine and DMAD reacted in high yield on standing in toluene solution, in the dark, for a few days, or alternatively by refluxing the toluene solution for several hours. Also, if potassium tertiarybutoxide was added to a solution of 3H-pyrrolizine and DMAD, and the mixture stirred for a few hours at room temperature, good yields of A and B were obtained.

Finally, when equivalent quantities of 3H-pyrrolizine and DMAD were reacted, the product yield was 71% A and 6% B, whereas when a 10 fold excess of DMAD was used, the yield was 10% A and 60% B.

Compounds A and B will now be dealt with in separate sections.

1.2: The elucidation of the structure of compound A

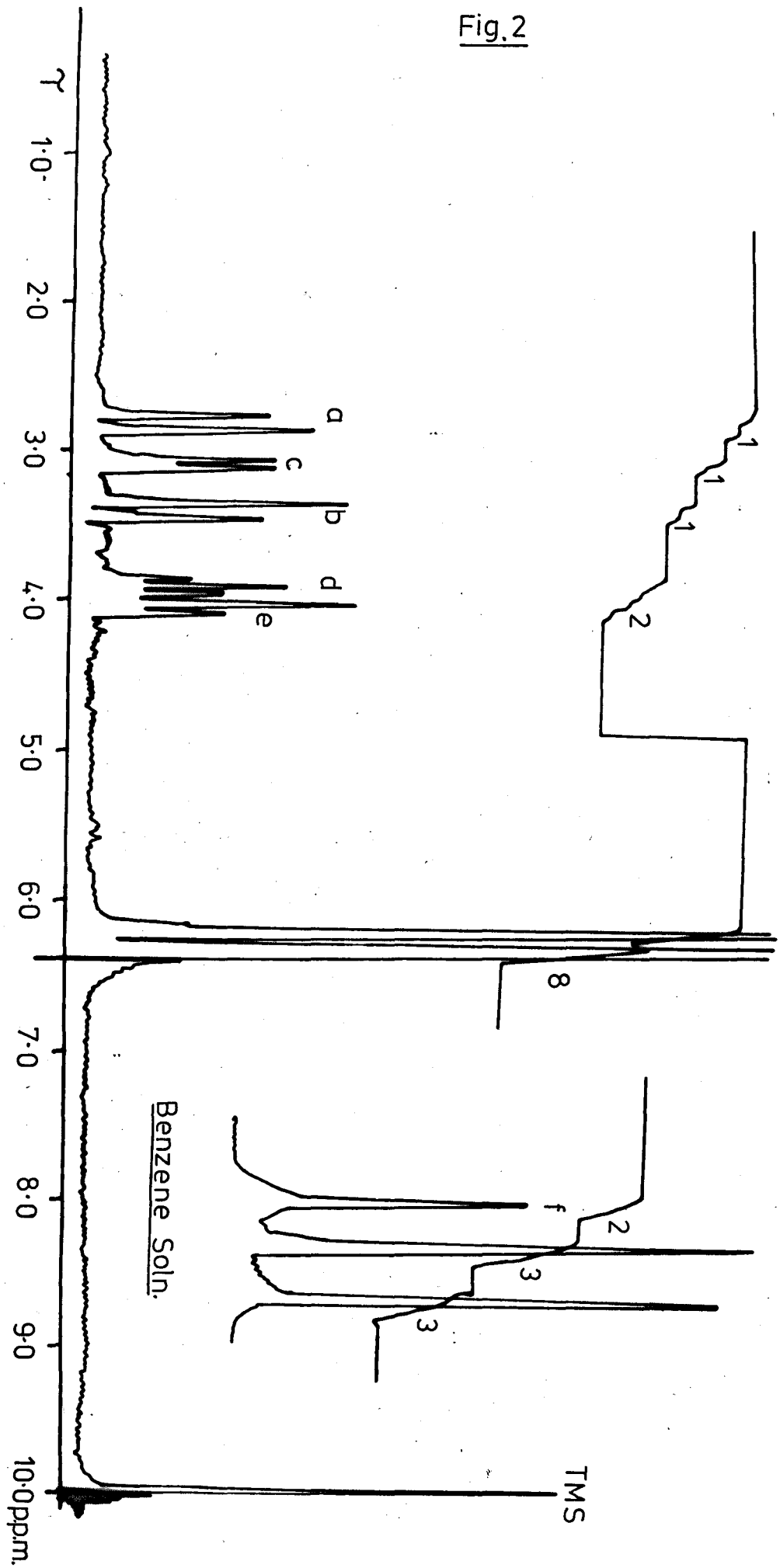
The mass spectrum of compound A showed a molecular weight of 247, and elemental analysis showed the molecular formula to be $C_{13}H_{13}NO_4$, confirming that compound A was a 1:1 adduct.

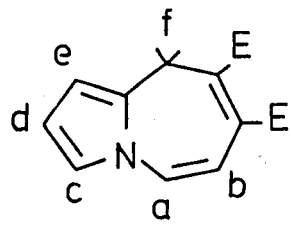
The I.R. spectrum showed ester carbonyl absorptions at 1700 cm^{-1} and 1735 cm^{-1}, showing non-equivalence of the ester groups and suggesting the presence of saturated and α,β-unsaturated esters.

The U.V. spectrum showed absorption maxima at 209.5 n.m. ($\log_{10}\varepsilon$ 4.14), 230 (sh), 322.5 (4.30) and 420 (3.29) indicating extensive conjugation.

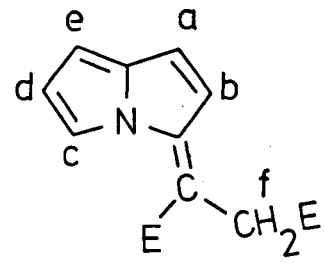
The n.m.r. spectrum, fig. 2, showed 3 pyrrolic proton absorptions (c, d and e) (τ 3.07, 3.90, 4.05) corresponding to a 1,2 disubstituted pyrrole, a pair of AB doublets (a and b) (τ 2.83 and 3.41, J6Hz) corresponding to an isolated cis double bond, and an 8 proton multiplet at τ 6.2 - 6.5. When the spectrum was recorded in benzene solution this multiplet split up to reveal a 2 proton singlet (f) and two 3 proton singlets. The 2 proton singlet corresponded to an isolated methylene group and the two 3 proton singlets were due to the ester methyl groups. Two structures of possible 1:1 adducts would fit this spectrum, the 9H-pyrrolo [1,2-a] azepine (109) and the azafulvene (110).

Fig. 2


τ
1·0
2·0
3·0
4·0
5·0
6·0
7·0
8·0
9·0
10·0 p.p.m.
a
c
b
d
e
1
1
1
2
8
Benzene Soln.
f
2
3
3
TMS



(109)

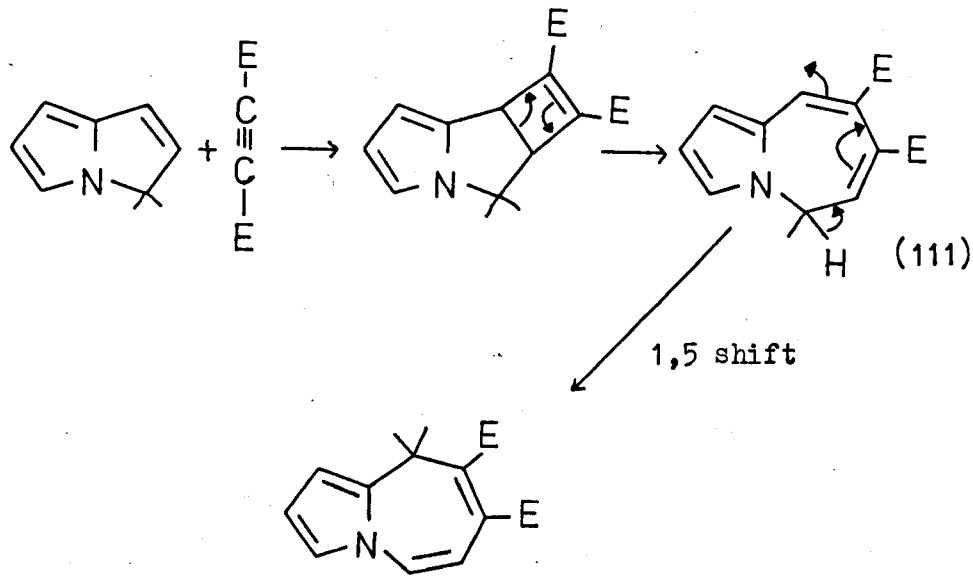


(110)

Both have the required 1,2 disubstituted pyrrole ring, the isolated double bond and the isolated methylene group. Both have extensive conjugation, between the ester carbonyl group, two double bonds and a pyrrole ring, which could account for the U.V. spectrum, but the I.R. spectrum would agree with the azafulvene structure (110), rather better than the azepine structure (109).

Finally, the formation of both compounds (109) and (110) could be accounted for mechanistically using reactions already known. In the first case a thermal 2+2 cycloaddition of DMAD to 3H-pyrrolizine, followed by ring expansion of the cyclobutene intermediate, would give a 5H-pyrrolo [1,2-a] azepine (111) as shown in Scheme 34.

SCHEME 34

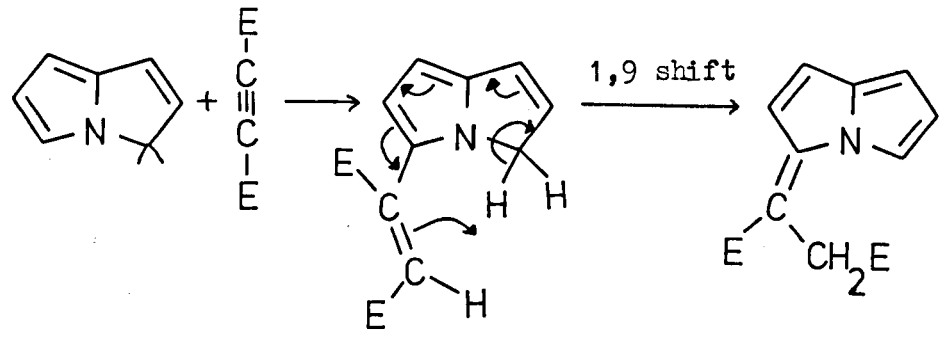


(109)

This, of course, is the reaction initially envisaged between 3H-pyrrolizine and DMAD and was precedented in the reaction, reported by Doyle [27], between methoxyindene and DMAD. A 1,5 sigmatropic shift of the 5 proton would give the required 9H-pyrrolo [1,2-a] azepine (109).

The azafulvene (110) could be formed by the Michael type addition of DMAD to the electron rich 5 position of 3H-pyrrolizine, to give the 3H-pyrrolizin-5-yl maleic ester (112), shown in Scheme 35. Such additions of DMAD to the alpha position of the pyrrole ring are well known, as illustrated in the previous review (page 55). Finally, a 1,9 sigmatropic shift would convert the maleate (112) into the azafulvene (110).

SCHEME 35



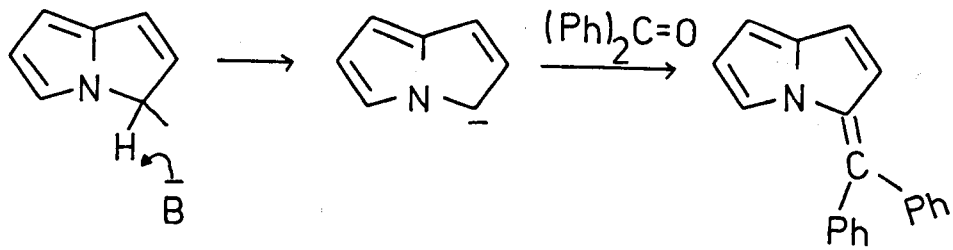
(112) (110)

Both the azafulvene (110) and azepine (109) structures were therefore possible for compound A and the remainder of this section describes the work carried out in order to differentiate between these structures.

1.2.1: The attempted independent synthesis of the possible structures of compound A

If the azepine (109) or the azafulvene (110) could have been synthesised by a different route then the structure of compound A could have been easily elucidated. Pyrrolo-[1,2-a] azepines are not easily synthesised but Flitsch and Heidhues [35] and Okamura and Katz [42] have reported the synthesis of the diphenylazafulvene (96) by the reaction of the 4-azapentalenyl anion (79) with benzophenone. The azapentalenyl anion was generated by the reaction of 3H-pyrrolizine with n-butyl lithium [42] or potassium tertiarybutoxide [35], as shown in Scheme 36.

SCHEME 36



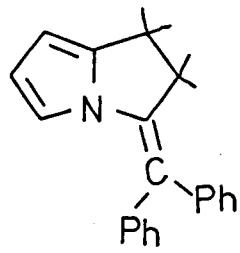
(79) (96)

The azafulvene (96) had a U.V. absorption maxima at 209 nm ($\log_{10}\varepsilon$ 4.34), 242 (4.11), 342 (4.19) and 405 (sh) compared with 209.5 (4.14), 230 (sh), 322.5 (4.30) and 420 (3.29) for compound A. The n.m.r. spectrum showed AB doublets at τ 3.5 and 3.77 (J6Hz), for the fulvene ring double bond, and a 1 proton doublet at τ 4.12 and 2 proton doublet at τ 4.30 for the pyrrole ring protons. This did not correspond as well as had been expected for the n.m.r. spectrum of compound A. (see page 60 and fig.2).

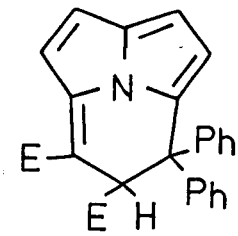
The chemical properties of the azafulvene (96) were also rather different from those of compound A in two reactions.

a) Hydrogenation

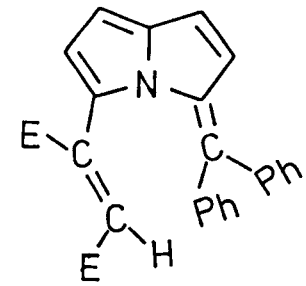
The azafulvene (96) hydrogenated very cleanly (using Pd/C catalyst at room temperature and pressure) to the dihydro compound (113). However, attempts to hydrogenate compound A, either to a dihydro compound or to completion, always produced an inseparable mixture of products.



(113)



(115)



(114)

b) Reaction with DMAD

The azafulvene (96) was reacted with DMAD by refluxing for several hours in toluene solution. The product (69% yield) was a maroon solid and mass spectral and elemental analysis showed it to be a 1:1 adduct of molecular formula $C_{26}H_{21}NO_4$.

There were two possible structures for this adduct, structure (114) a simple adduct and structure (115) a cycl [3,2,2] azine derivative.

The I.R. spectrum of the product showed two carbonyl absorptions at 1690 cm^{-1} and 1730 cm^{-1} which would fit structure (115) rather than (114).

The n.m.r. spectrum showed very close AB doublets (J6Hz) at τ 3.41 and 3.53 for the fulvene ring double bond, and also close doublets (J3Hz) at τ 3.97 and 4.07 for the pyrrole ring β-protons. These signals, and also the 1 proton singlet at τ 5.34, corresponding to the proton geminal to the ester group, could be characteristic of either structure (115) or (114) but

the differentiating factor lies in the absorptions of the phenyl and ester methyl groups.

The ester methyl groups absorb as two singlets, very far apart at τ 6.20 and 6.89. The esters are therefore in very different electronic environments, as also suggested by the I.R. spectrum, and structure (115) would be more appropriate than structure (114).

The phenyl groups in structure (114) are fixed in the same plane as the pyrrolizine ring system and will therefore be in different environments and should absorb as two singlets in the n.m.r. spectrum. (Exactly as for the azafulvene (96)). However, the n.m.r. spectrum of this product showed only one singlet (10 proton), at τ 2.73, for the phenyl groups as might be expected for compound (115) where the phenyl groups are on either side of the pyrrolizine ring system.

The dramatic shielding of one of the ester methyl groups (shifted from τ 6.2 to 6.89) can also be explained by structure (115), in which one of the ester groups is held very close to one of the phenyl groups. Whereas protons attached to a benzene ring are deshielded by the magnetic field set up by the circulating electrons, anything lying near the centre of the benzene ring, outside the deshielding

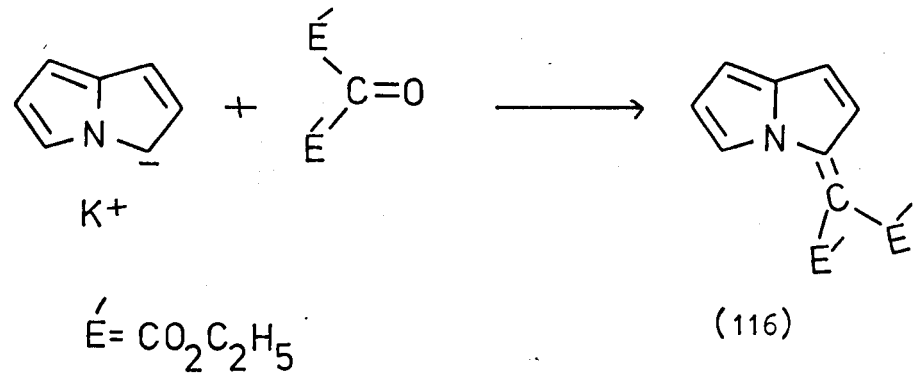
area, will be shielded. Hence, if the ester group of structure (115) is held within the shielding area of one of the phenyl groups, the observed shielding will occur.

The above evidence confirms that the adduct from the azafulvene (96) and DMAD had the reduced cycl [3,2,2]-azine structure (115).

Knowing that the azafulvene (96) reacted with DMAD, and also bearing in mind that 3H-pyrrolizine formed a diadduct with DMAD, it was expected that compound A would react with DMAD to form a diadduct, perhaps even compound B. Attempts were made to react compound A with DMAD by boiling in toluene solution for a few days, by irradiation for 15hr periods (quartz and pyrex filtered U.V. light), and by stirring, in toluene solution, with potassium tertiarybutoxide. However, compound A and DMAD could not be induced to react.

There were, therefore, two major differences in chemical behaviour between compound A and the azafulvene (96). Differences might be anticipated between a fulvene having electron withdrawing (ester) groups on the exocyclic double bond and another with electron donating (phenyl) groups. Attempts were made to synthesise the azafulvene (116), much closer in structure to compound (110), by reacting the azapentalenyl anion with diethyl ketomalonate, as shown in Scheme 37.

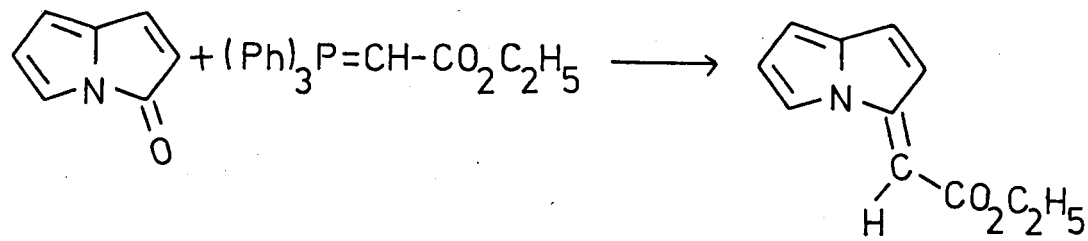
SCHEME 37



$\acute{E}$= $CO_2C_2H_5$

(116)

These attempts failed but very recently Flitsch and Newmann [51] reported the synthesis of the azafulvene (117) by the reaction of pyrrolizin-3-one (118) with ethoxycarbonylmethylenetriphenylphosphorane.



(118)

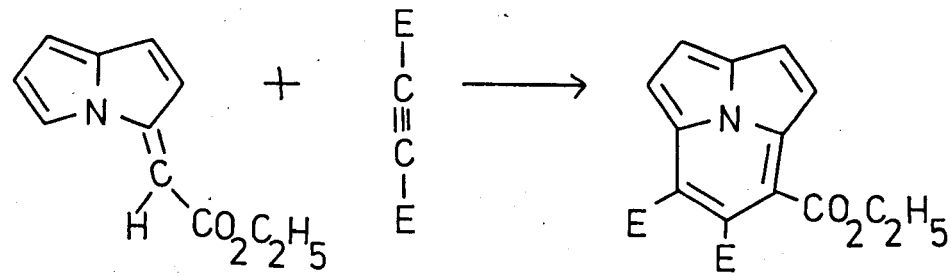
(117)

The azafulvene (117) resembled compound A very closely in its spectra. The U.V. spectrum showed absorption maxima at 210 nm, 230(sh), 333 and 430 compared with 209.5, 230(sh), 322.5 and 420 for compound A.

The n.m.r. spectrum showed AB doublets (J6Hz) for the fulvene ring protons at τ2.97 and 3.43 (c.f. 2.83 and 3.41 for A) and absorptions at 3.05(d), 4.05(t) and 4.20(d) (c.f. 3.07(d), 3.90(t) and 4.05(d) for A) for the pyrrole ring protons.

Hydrogenation of the azafulvene (117) was very sluggish

and gave a tarry mixture, rather like compound A, but the azafulvene did react with DMAD. Boiling a solution of the azafulvene (117) and DMAD in toluene, for 22 hrs., gave a 12% yield of the cycl [3,2,2] azine derivative (119), identified by its spectra.

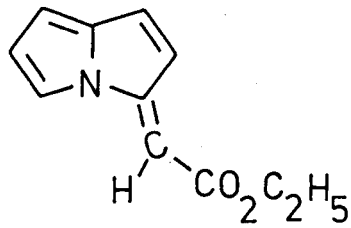


(117) (119)

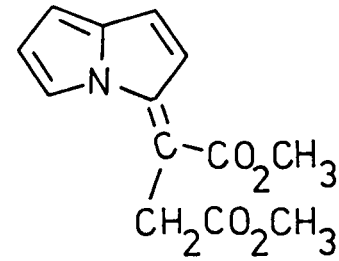
This reaction would have probably gone in higher yield in the presence of a little Pd/C catalyst, or other mild dehydrogenating agent.

It would appear that in having only one ester group on the exocyclic double bond, the character of the azafulvene (117) was somewhere between that of the diphenyl azafulvene (96) and the proposed azafulvene structure for A (110) and it therefore behaved, chemically, somewhere between the two extremes. Thus, on hydrogenation it tended to behave like compound A, and with DMAD it behaved like the diphenyl azafulvene (96), although much slower. (12% product yield after 22 hrs. c.f. 69% after 8 hrs. for compound (96). The production of an aromatic (10 π) system (119) probably forced the reaction to go whilst it would not go in the case of compound A.

In conclusion, the chemical properties of the azafulvene (117) were similar enough to **A**, and the physical properties



(117)



(110) "A"

(U.V. and n.m.r. spectra) so very similar to **A** that it was reasonable to assume that compound A had the azafulvene structure (110), rather than the alternative 9H-pyrrolo [1,2-a] azepine structure (109).

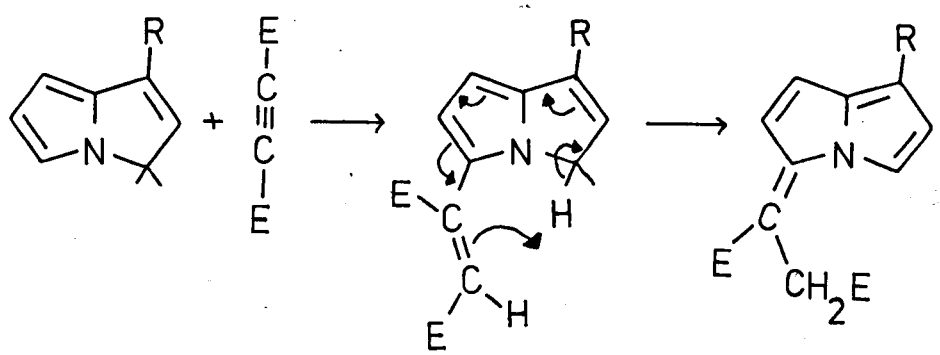
1.3: <u>The establishment of the mechanism for the formation of azafulvenes from 3H-pyrrolizine</u>.

It was mentioned earlier that the most probable route to azafulvenes involved the initial Michael type addition of DMAD to the 5 position of 3H-pyrrolizine, followed by a 1,9 sigmatropic shift of a proton from the 3 position, to give the product. Attempts were made to isolate the intermediate maleate (or fumarate) by carrying out the reaction at -5° (to slow it down), and by working up the product without the use of heat, but these attempts failed.

A second attempt to establish the mechanism involved the labelling of the 3H-pyrrolizine nucleus. Scheme 38 shows that

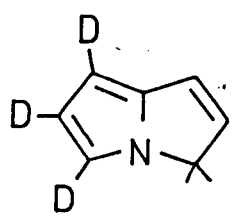
a 3H-pyrrolizine with a group R on the pyrrolenine ring would react with DMAD by the anticipated mechanism to give

SCHEME 38

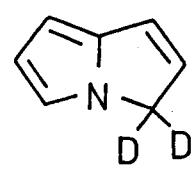


an azafulvene with the group R on the pyrrole ring, and vice versa.

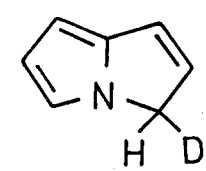
It was initially hoped to use 5,6,7-trideutero-3H-pyrrolizine (76), or 3D-3D-pyrrolizine (120) for this work. However, attempts to synthesise these pyrrolizines, described



(76)



(120)



(80)

in Part I of this thesis, failed.

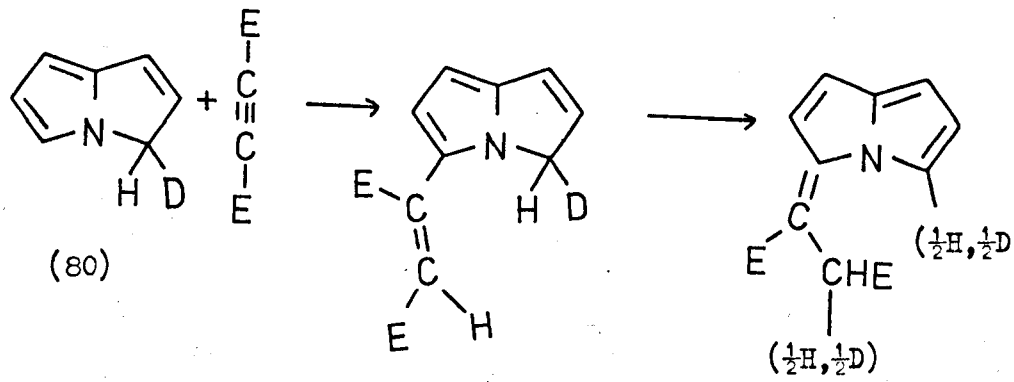
Okamura and Katz [42], have reported the synthesis of 3H-3D-pyrrolizine (80) and this was used as the first

labelled pyrrolizine.

1.3.1: <u>The reaction of 3H-3D-pyrrolizine with dimethyl and diethyl acetylenedicarboxylates</u>

3H-3D-pyrrolizine (80) was reacted in the usual manner with DMAD. The expected reaction is shown in Scheme 39.

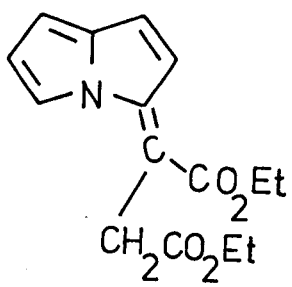
SCHEME 39



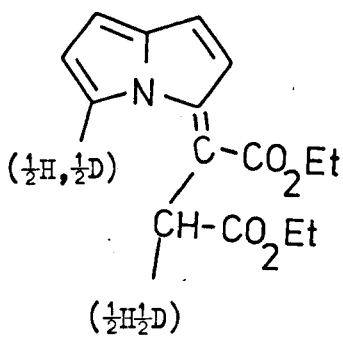
With a 50% deuterium content on the methylene group of the pyrrolizine it was expected that the α-pyrrole position of the azafulvene (121) would be 50% deuterated (i.e. 0.5H, 0.5D) and, also, the methylene group of the azafulvene would be 25% deuterated (i.e. 0.5D, 1.5H). In fact, the azafulvene product from this reaction showed a 50% deuterium content on the α-pyrrole position (from the n.m.r. spectrum) and no deuterium on the methylene group. This was not entirely satisfactory because no deuterium should have been lost during the sigmatropic rearrangement.

The possibility that the deuterium from the methylene group of the azafulvene could have been lost during chromatography could not be excluded, and one way of testing this hypothesis was the use of diethyl acetylenedicarboxylate instead of DMAD. This had two distinct advantages:-

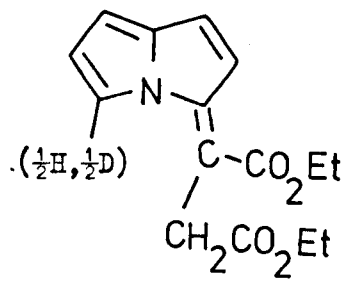
1. Diethyl acetylenedicarboxylate was found to react in high yield with 3H-pyrrolizine to give the azafulvene (122) but no diadduct. The azafulvene could therefore be purified without recourse to chromatography.



(122)



(123)



(124)

2. In the n.m.r. spectrum of the azafulvene (122) the ester methylene groups absorbed as quartets, at τ 5.81, completely clear of the singlet, τ 6.38, for the side chain methylene group. Hence the integral of this methylene group in the diethylazafulvenes (122 - 124) could be accurately measured.

Diethyl acetylenedicarboxylate was reacted with 3H-3D-pyrrolizine (80) and the product, purified by successive recrystallisations, was the deuteroazafulvene (123). The mass spectrum showed a molecular weight of

276 (c.f. 275 for azafulvene (122)) and the n.m.r. spectrum clearly showed a 50% deuterium content (0.5D) on the α-pyrrole position and a 25% deuterium content (0.5D) on the side chain methylene group.

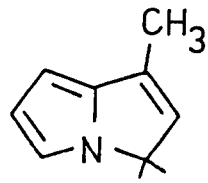
Hence the mechanism, as suggested in Scheme 38, was correct; the attack of DMAD was on the 5 position of the 3H-pyrrolizine and the proton rearrangement was entirely intramolecular.

The assumption that the deuterium of the methylene group of the azafulvene could be exchanged by chromatography was tested by passing the azafulvene (123) down an alumina column. As expected, the product obtained from the column, azafulvene (124) had lost the deuterium from the side chain methylene group. This explains the lack of deuterium in the methylene group of the azafulvene obtained from 3H-3D-pyrrolizine and DMAD.

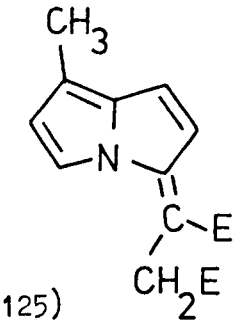
1.3.2: <u>The reaction of 1-methyl-3H-pyrrolizine with DMAD</u>

Schweizer and Light [37] have reported the synthesis of 1-methyl-3H-pyrrolizine (51) by the reaction of the sodium salt of 2-acetylpyrrole with vinyltriphenylphosphonium bromide.

1-methyl-3H-pyrrolizine was another suitably labelled pyrrolizine for testing the mechanism and confirming the results obtained from 3H-3D-pyrrolizine.



(51)



(125)

The pyrrolizine (51) and DMAD were reacted in the usual manner and the product obtained (in 35% yield) was the 7-methyl azafulvene (125). The n.m.r. spectrum showed the absence of one β-pyrrole proton absorption, from the usual azafulvene spectrum (fig. 2 for compound (110)) and a new 3 proton singlet at γ 7.94 for the ring methyl group, confirming the structure of the product as compound (125).

Some diadduct was also obtained from this reaction but will be discussed later.

The product (125) confirmed the earlier findings on the mechanism.

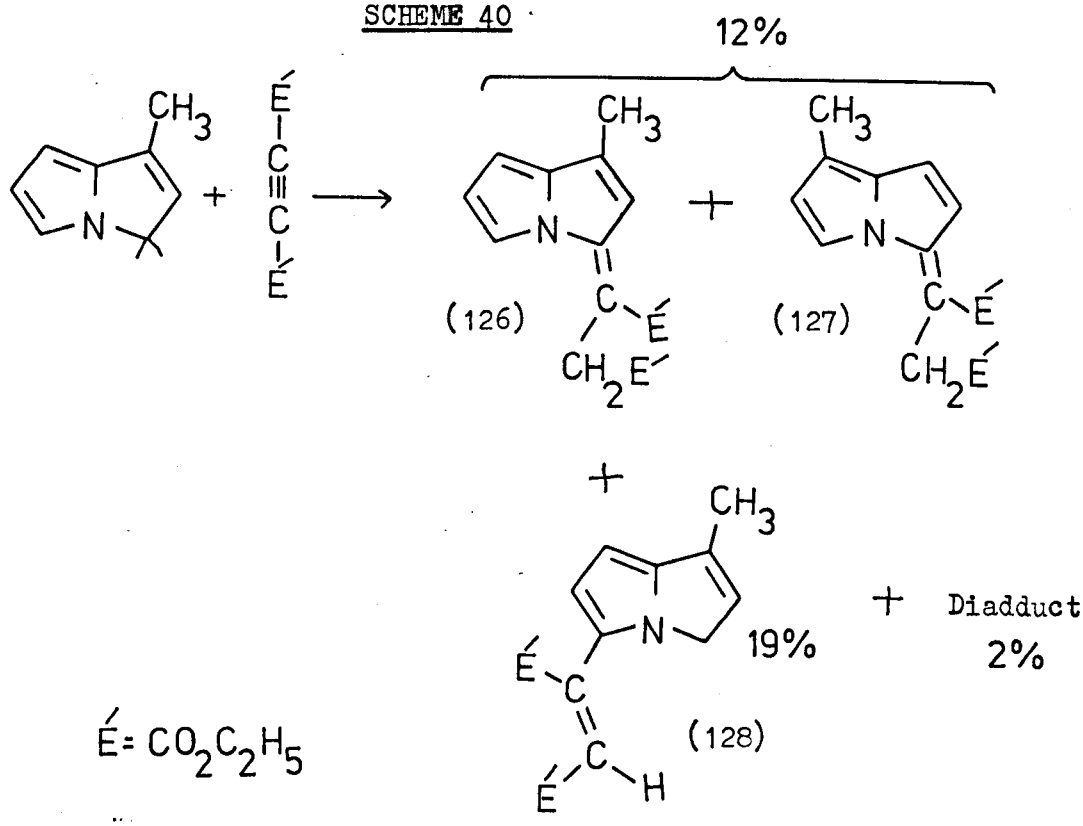
1.3.3: <u>The reaction of 1-methyl-3H-pyrrolizine with diethyl acetylenedicarboxylate</u>

As mentioned earlier, although DMAD reacted with 3H-pyrrolizine to give both mono and diadducts, diethyl acetylenedicarboxylate gave only the azafulvene mono adduct, from 3H-pyrrolizine, even when a 10 fold excess of the acetylene was used. An obvious extension of that work was to react diethyl acetylenedicarboxylate with 1-methyl-3H-pyrrolizine (51) which had

also given both mono and diadducts with DMAD.

The pyrrolizine (51) and diethyl acetylenedicarboxylate were reacted in the usual way and gave a complex product mixture, shown in Scheme 40.

SCHEME 40



The product mixture was chromatographed on an alumina column and two bands were eluted, the first orange (fraction 1) and the second red (fraction 2).

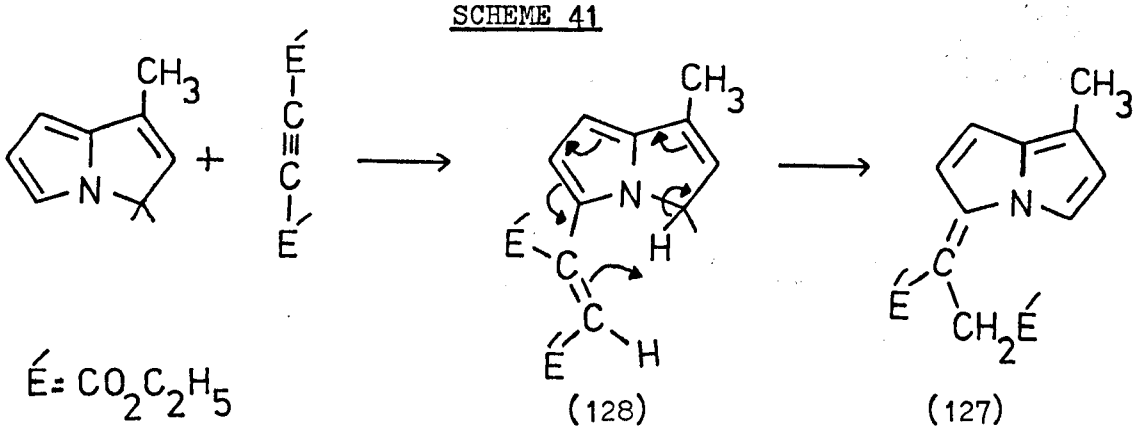
A red gum obtained from fraction 1 was dissolved in boiling petrol and, on cooling, the yellow pyrrolizin-5-yl-maleate (128) crystallised out. Evaporation of the mother liquor gave a red oil and the major product obtained from p.l.c. of that oil was an inseparable mixture of the azafulvenes (126) and (127), in a

combined yield of 12%. Although the production of the azafulvene (126) seemed unlikely from 1-methyl-3H-pyrrolizine, the n.m.r. spectrum of the product could only be attributed to an approximately equal mixture of azafulvenes (126) and (127). P.l.c. of the red gum obtained from fraction 2 yielded a little more of compound (128) and a small amount of diadduct (2%).

Although a mixture of azafulvenes had been obtained from the reaction, the major product (in 19% yield) was the 3H-pyrrolizin-5-ylmaleate (128). Mass spectral and elemental analysis gave a molecular formula of $C_{16}H_{19}NO_4$. The n.m.r. spectrum showed a pair of AB doublets (J3Hz) at τ3.46 and 3.93 for the pyrrole ring, a 1 proton singlet (τ3.93) for the pyrrolenine ring, a sharp 1 proton singlet (τ 4.28) for the maleate proton, a 6 proton multiplet (τ 5.4 - 6.1) for the ester and ring methylene groups, a 6 proton mult. (τ 8.71) for the ester methyl groups and a 3 proton singlet (τ 7.95) for the ring methyl group. This spectrum agrees well with the structure (128) for the product.

The maleate appeared to be the intermediate in the formation of the azafulvene (127), shown in Scheme 41. This was proved by boiling a toluene solution of the maleate for 32 hrs. Chromatography of the product gave the isomeric azafulvene (127) in 21% yield. (This yield was increased to 62% by boiling in ethanol

SCHEME 41

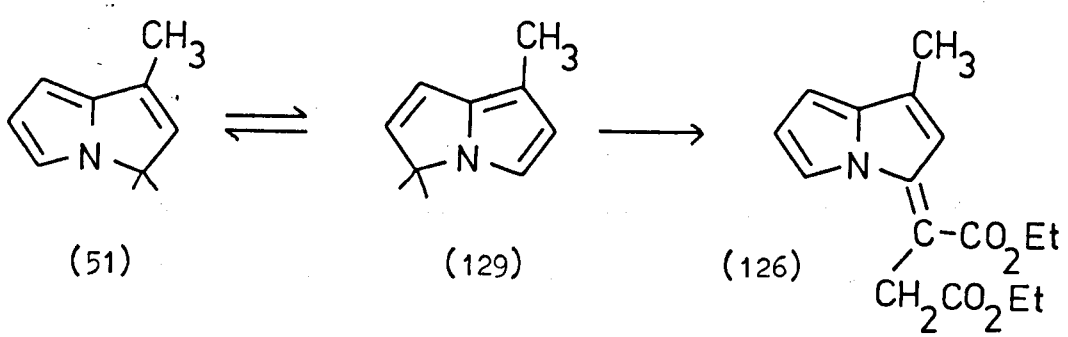


solution for 18 hrs.)

The isolation of a proven intermediate lends even more support to the established mechanism for the formation of azafulvenes from 3H-pyrrolizines. However, the reason for the slightly different reactions of diethyl and dimethyl acetylenedicarboxylates, with 3H-pyrrolizines, remains a mystery. One can only suggest that some steric factor operated to slow down the rearrangement of the intermediate, thus allowing its isolation.

The azafulvene mixture isolated in the reaction between diethyl acetylenedicarboxylate and the methylpyrrolizine (51) was also mysterious. Perhaps, as the reaction was slowed down by steric factors, some of the pyrrolizine (51) isomerised to the 7-methyl isomer (129) and this reacted with the acetylene, as shown in Scheme 42, to give the azafulvene (126). This,

SCHEME 42



(51) (129) (126)

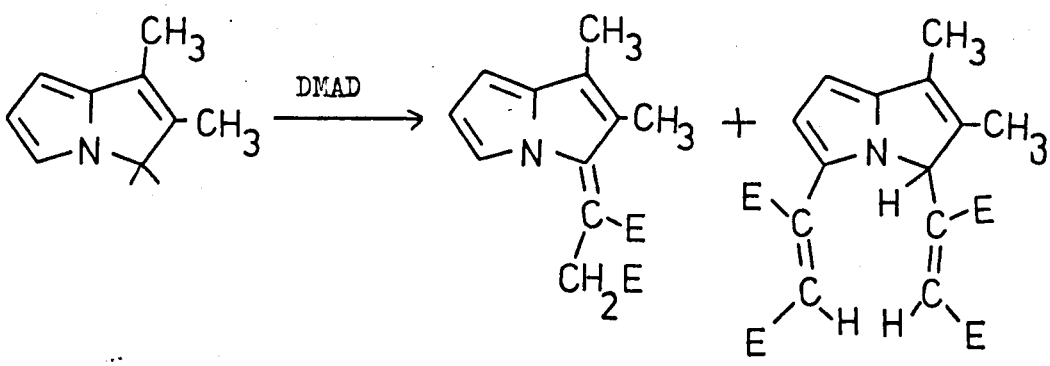
together with the expected azafulvene (127), would give the observed mixture.

The isomerisation theory sounds improbable but the reaction of 1,2-dimethyl-3H-pyrrolizine (87), with DMAD, lends a great deal of support to it.

1.3.4: The reaction of 1,2-dimethyl-3H-pyrrolizine (87) with DMAD

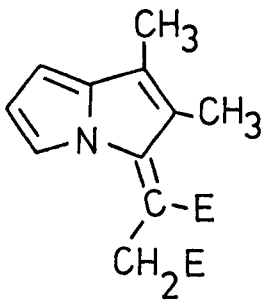
The reaction of the pyrrolizine (87) with an equimolar amount of DMAD gave the product mixture shown in Scheme 43. The pyrrolizin-3,5-yldimaleate (131) was the major product of the reaction, in 40% yield, but this will be dealt with later in the sections on diadducts.

SCHEME 43

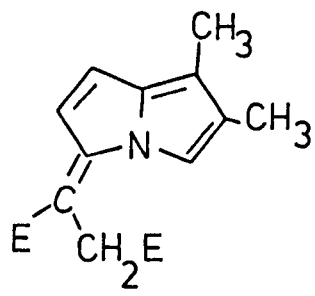


(87) (130) (131)

The azafulvene product, in 34% yield, was not the expected 6,7-dimethylazafulvene (132). The n.m.r. spectrum showed 3 pyrrole proton absorptions at τ 3.08(d), 3.98(t) and 4.24(d), all J3Hz, and no AB doublets for a fulvene ring. The product was therefore the 1,2-dimethyl isomer (130).

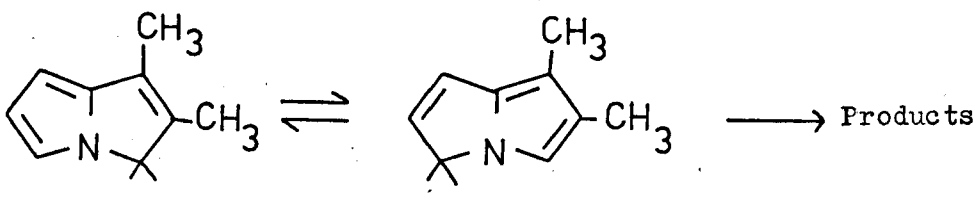


(130)



(132)

In order that the already established mechanism should still apply to this reaction, it is necessary to postulate an initial isomerisation of the 1,2-dimethyl-3H-pyrrolizine (87) to its 6,7-dimethyl isomer (83).

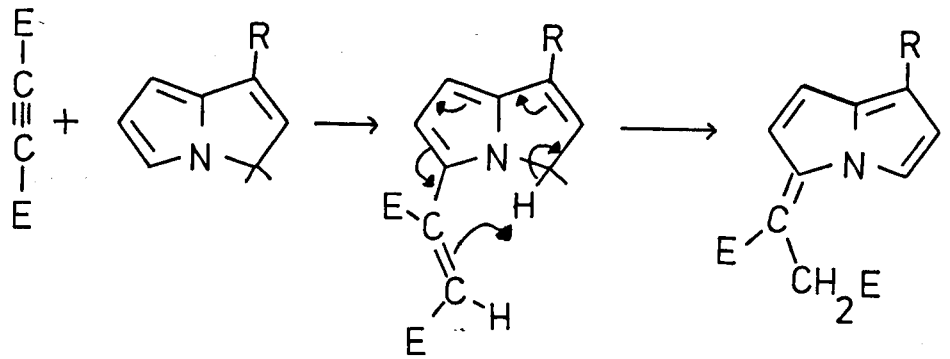


(87) (83)

If the 6,7-dimethyl isomer (83) reacts with DMAD preferentially to the 1,2-dimethyl isomer (87), the pyrrolizine isomerisation equilibrium will be forced to the right, and only the 1,2-dimethylazafulvene (130) will be obtained.

In conclusion, 3H- and substituted 3H-pyrrolizines react with diethyl and dimethyl acetylenedicarboxylates to give azafulvenes, as shown in Scheme 44.

SCHEME 44



The mechanism, as shown, has been proved by the isolation of the intermediate, in one case, and the complete retention of deuterium undergoing the sigmatropic shift. The only real exceptions to the general scheme, found so far, were the isomerisation of 1-methyl-3H-pyrrolizine and 1,2-dimethyl-3H-pyrrolizine before they reacted with diethyl and dimethyl acetylenedicarboxylate, respectively, to give azafulvenes.

1:4 The elucidation of the structure of compound B

In section 1:1. it was mentioned that the reaction of 3H-pyrrolizine with DMAD gave a 1:2 adduct (B) as well as the azafulvene 1:1 adduct (A). When a 10 fold excess of DMAD was used, the diadduct was, in fact, the major product of the reaction (60% B and 10% A). Compound B was usually obtained as a brilliant red gum which solidified upon standing, and could be recrystallised to give a red solid m.p. 105 - 112° (CCl_4). Mass spectral and elemental analysis confirmed the molecular formula to be $C_{19}H_{19}NO_8$ (i.e. 1 mol. of 3H-pyrrolizine + 2 mol. of DMAD).

The I.R. spectrum, like that of the azafulvene A, showed carbonyl absorptions at 1695 and 1725 cm^{-1} (1700 and 1735 cm^{-1} for A) indicating both saturated and α, β - unsaturated ester groups.

The U.V. spectrum showed λ max ($\log_{10} \varepsilon$) at 213 nm (4.12), 235(sh), 334 (4.25) and 440 (3.31). This was very similar to the spectrum of the azafulvene A, i.e. 209.5nm (4.14), 230(sh), 332.5 (4.30) and 420 (3.29) and strongly suggested that the azafulvene chromophore formed a major part of the structure of compound B.

The n.m.r. spectrum (fig. 3) showed a pair of AB doublets (J6Hz) at τ 2.92 and 3.44, typical of a fulvene ring double bond (2.83 and 3.41 in the azafulvene A), a 2 proton singlet at τ 4.15, a 12 proton multiplet at τ 6.1 - 6.5 for the 4 ester methyl groups, and an ABX system shown below.

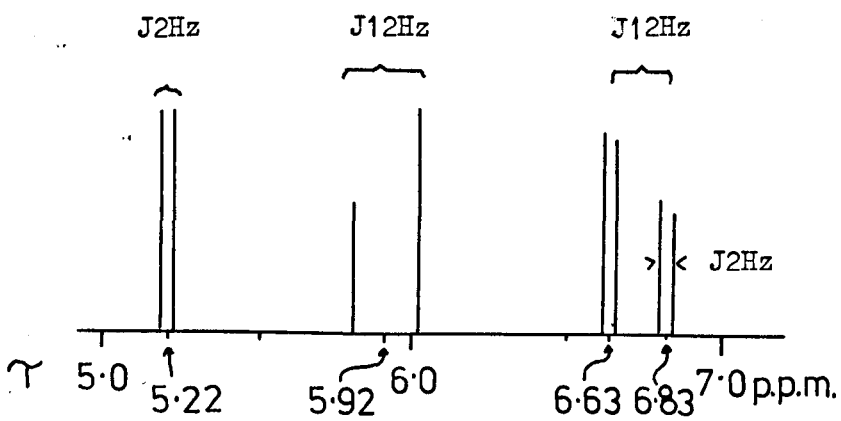
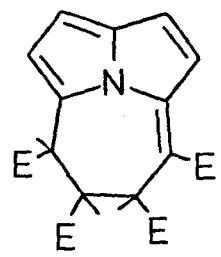
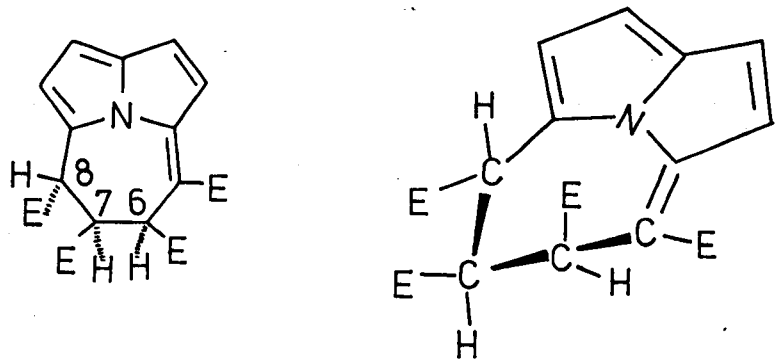


Fig. 3



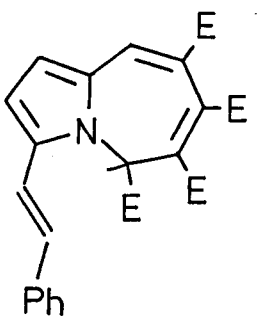
This ABX absorption corresponded to 3 adjacent C-H groups such that the first two had a coupling of 12Hz and the second and third a coupling of 2Hz. The cycl[4,2,2]-azine structure (133) fitted the spectrum well, having a fulvene double bond, 4 ester groups and the ABX system.



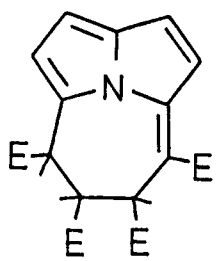
(133)

The Karplus equation [63] forecasts coupling constants of around 0 - 1Hz for dihedral angles of 90°, and > 10Hz for dihedral angles of 180°. For the cyclohexane ring system, in the chair form, axial-axial protons (approx. 180° dihedral) usually have a coupling constant of 10 - 13Hz and axial-equatorial protons (approx. 60°) have a coupling of 2 - 5Hz. With the 7-membered ring of compound (133) having the 6,7 and 8 carbon atoms in a pseudo chair form, as shown, the 6 and 7 protons (a,e) should therefore have a coupling of 2-5Hz and the 7 and 8 protons (a,a) a coupling of 10 - 13Hz. In fact, compound B shows coupling constants of $J_{6,7}$ 2Hz and $J_{7,8}$ 12Hz, agreeing well with structure (133).

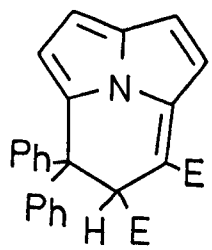
The only problem remaining was the apparent lack of pyrrole β -proton absorptions, in the n.m.r spectrum, and the 2 proton singlet at τ 4.15 where the pyrrole β -proton absorptions would have been expected. The only plausible explanation was that the pyrrole β -protons, for some reason chemically equivalent in compound B, were absorbing together as a 2 proton singlet at τ 4.15. This phenomenon is not unusual. Acheson and Stubbs [64] have reported that the two pyrrole β -protons in the pyrrolo[1,2-a] azepine (134) give a 2 proton singlet in the n.m.r. spectrum at τ 3.1.



(134)



(133)



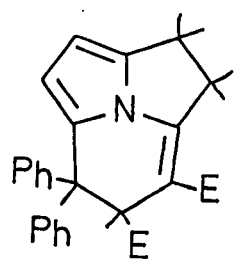
(115)

Also, the n.m.r. spectrum of the cycl [3,2,2] azine derivative (115), prepared as described in section 1.2.1, showed AB doublets for the pyrrole β -protons that were centred only 0.1 p.p.m. apart (τ 3.97 and 4.07), i.e. these protons were only slightly non-equivalent.

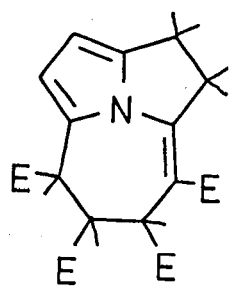
The structure (133), for compound B, was tested by reference to the reactions of the cyclazine derivative (115).

1.4.1 Comparison of compound B with the cycl [3.2.2]-azine (115)

Hydrogenation of the cyclazine (115) with 10% Pd/C in ethanol, gave the dihydrocompound (135). The n.m.r. spectrum of the compound, fig. 4, showed the lack of



(135)

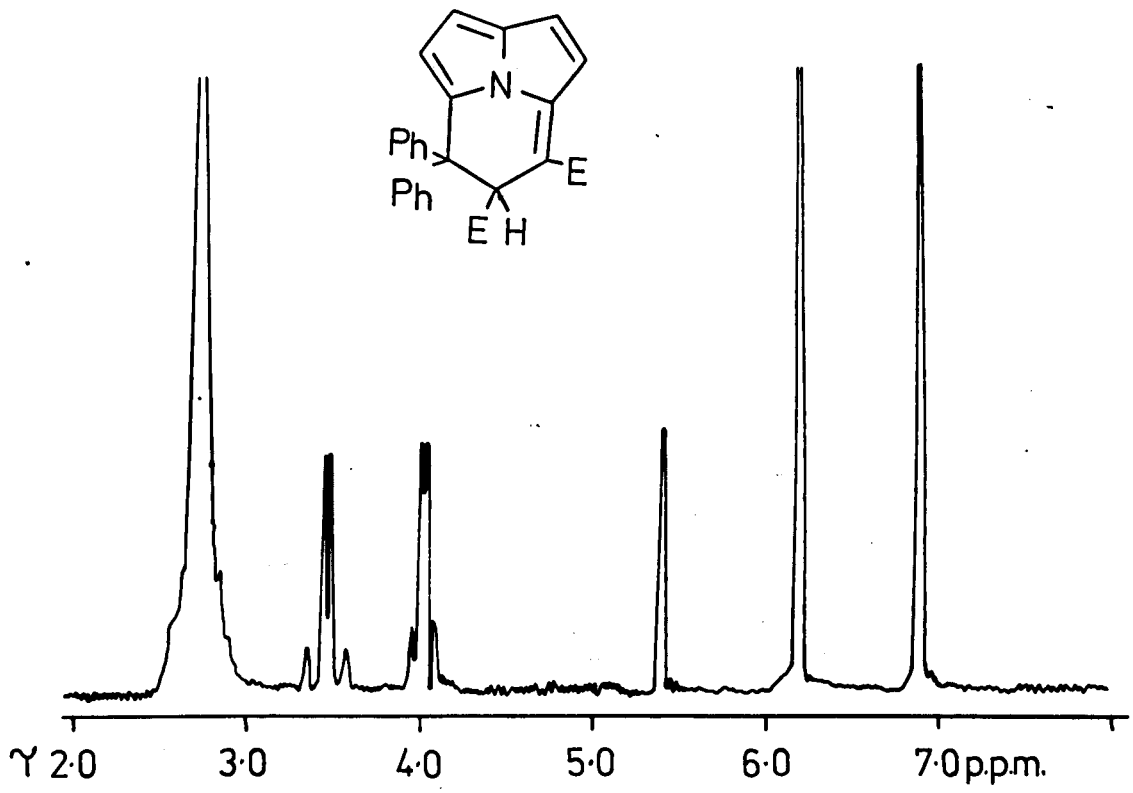


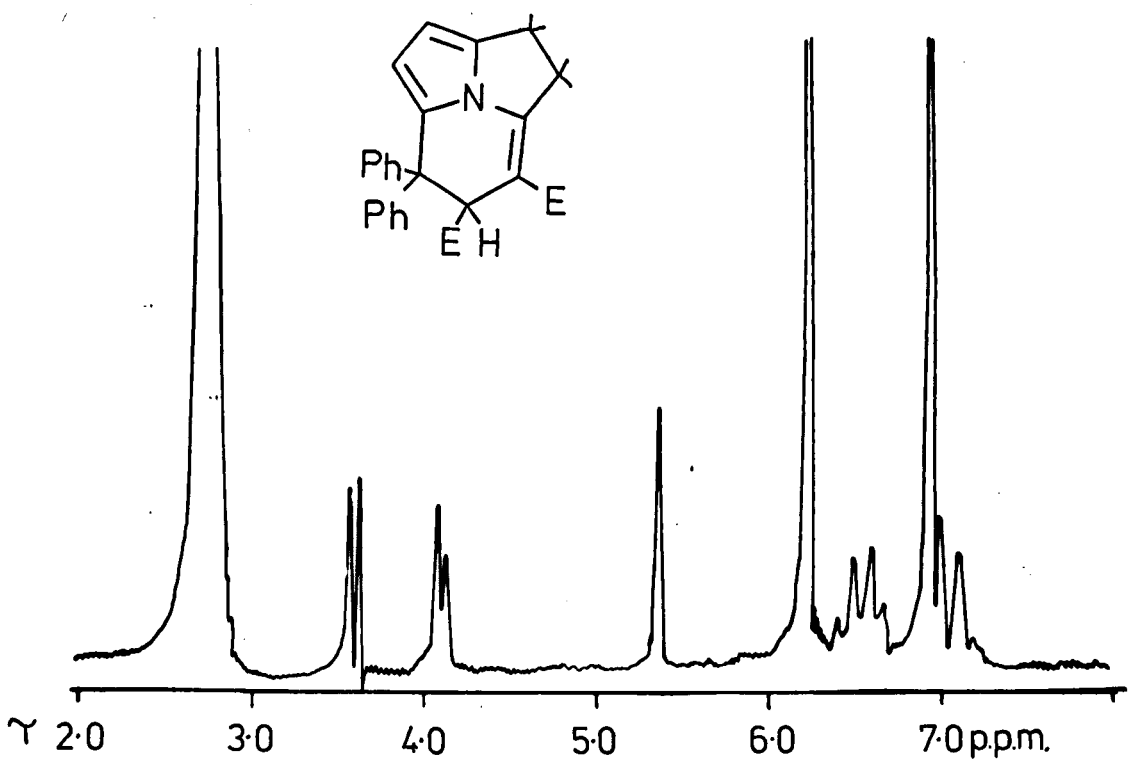
(136)

the AB doublets at τ 3.41 and 3.53 (J6Hz), due to the fulvene ring double bond protons in compound (115), and the appearance of two 2 proton triplets at τ 6.55 and 6.92 for the ring methylene groups of compound (135). More important, however, was the spreading out of the pyrrole β -proton AB doublets (J3Hz) to τ 3.58 and 4.09. The equivalence of the pyrrole β -protons had been lost with the reduction of the fulvene ring double bond.

Compound B was hydrogenated, under the same conditions as compound (115), and gave the dihydrocompound (136). As expected, the n.m.r. spectrum of dihydro B showed no change in the ester or AEX system absorptions but the AB doublets in the spectrum of compound B were replaced by two 2 proton triplets at τ 6.5 (approx) and 7.15. Finally, the 2 proton singlet in the spectrum of

Fig.4





compound B had been replaced by two 1 proton multiplets, at τ 3.7 and 4.1. Hence the 2 proton singlet corresponded to equivalent pyrrole β -protons and reduction of the fulvene ring of compound B, as in the cyclazine (115), had destroyed the equivalence of these protons.

The n.m.r. spectrum of compound B therefore corresponded in every way to the cycl[4,2,2] azine structure (133). That structure also agreed well with the I.R. and U.V. spectra of compound B and it was therefore concluded that compound B was tetramethyl 6,7-dihydro-8H-cycl[4,2,2] azine -5,6,7,8-tetracarboxylate (133).

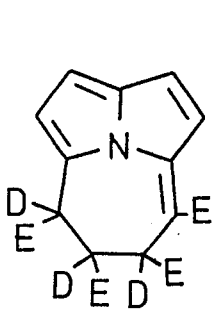
1.5 Establishment of the mechanism of the reaction between 3H-pyrrolizine and DMAD to give cyclazine derivatives

1.5.1 Deuterium labelling experiments

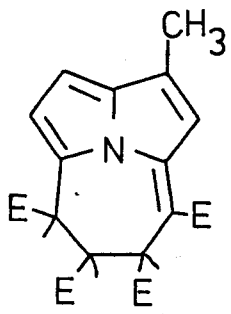
The elucidation of this mechanism presented more problems than the mechanism of the formation of azafulvenes. Deuterium labelling experiments failed due to the need for chromatographic purification of the diadducts. 3H-3D-Pyrrolizine was, in fact, reacted with DMAD but the cyclazine product contained no deuterium. The most plausible explanation was that deuterium on the activated 6,7 and 8 positions (α to ester groups) had exchanged during column chromatography. The explanation was tested by chromatographing compound B on a column of alumina deactivated with deuterium oxide instead of water. The product was the cyclazine (137) and the n.m.r.

1.5.1 contd

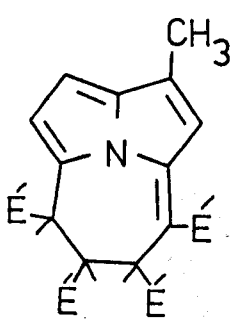
spectrum showed positions 6,7 and 8 to be fully



(137)



(138)



(139)

$\acute{E} = CO_2C_2H_5$

deuterated. Hence any diadduct with deuterium on the 6,7 or 8 positions would exchange during chromatography and deuterium labelling could therefore not be used for mechanistic elucidation.

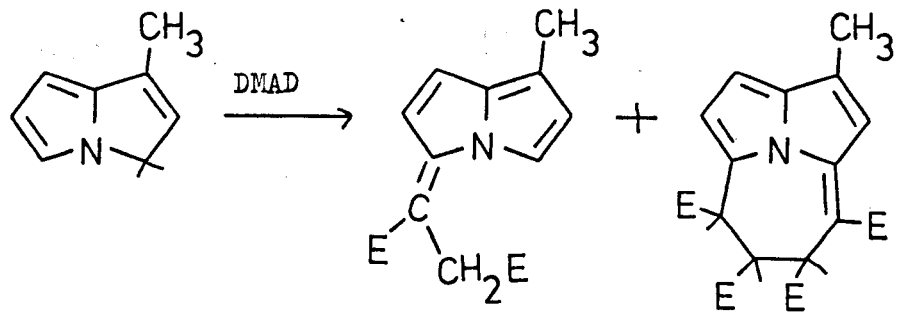
1.5.2 Formation of diadducts from 1-methyl-3H-pyrrolizine

1-methyl-3H-pyrrolizine reacted with DMAD to give the 3-methylcycl [4,2,2] azine derivative (138) in 52% yield. It was also the only pyrrolizine to give a diadduct with diethyl acetylenedicarboxylate, i.e. the cyclazine (139), which was isolated in 7% yield. The significant observation on the reactions of dimethyl and diethyl acetylenedicarboxylates, with 1-methyl-3H-pyrrolizine (51), was the position of the methyl group in the products. Whereas the methyl group on the pyrrolenine ring of 1-methyl-3H-pyrrolizine appeared on the pyrrole ring of the azafulvene product (125),

1.5.2 contd

it appeared on the fulvene ring of the cyclazine product (138), as shown in Scheme 45.

SCHEME 45



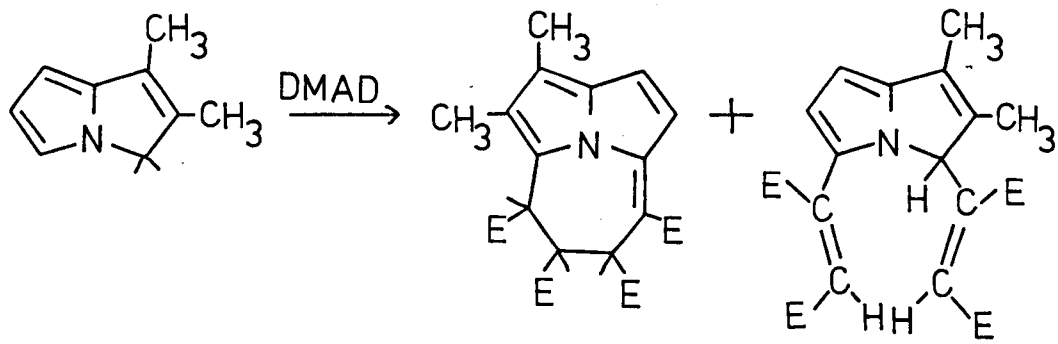
(51) (125) (138)

This indicated either an entirely different mechanism, or a second tautomerism, in the diadduct formation.

1.5.3 The reaction of 1,2-dimethyl-3H-pyrrolizine with excess DMAD

The situation was complicated even further by the reaction of 1,2-dimethyl-3H-pyrrolizine with excess DMAD. Unlike 1-methyl-3H-pyrrolizine, the dimethylpyrrolizine (87) reacted with excess DMAD to give a diadduct (140) with the methyl groups on the pyrrole ring, as shown in Scheme 46.

SCHEME 46



(87) (140) (131)

The major product of the reaction was not, in fact, the cyclazine (140) (19% yield) but the pyrrolizin-3,5-yldimaleate (131) which was isolated in 48% yield.

The n.m.r. spectrum of compound (131) showed two AB doublets (J3Hz) at τ 3.49 and 4.01 for the pyrrole protons, two sharp singlets at τ 4.12 and 4.26 for maleate protons, a 6 proton singlet at τ 8.05 for the ring methyl groups, a 3 proton singlet (τ 6.08) and a 9 proton multiplet (τ 6.3) for the ester methyl groups and, finally, a broad singlet at τ 4.73 for the methine proton. It was suspected that the singlet at τ 4.73 was broad due to coupling of the methine (3) proton with one of the ring methyl groups. This was confirmed by irradiation of the spectrum at τ 8.05 whereupon the singlet sharpened up.

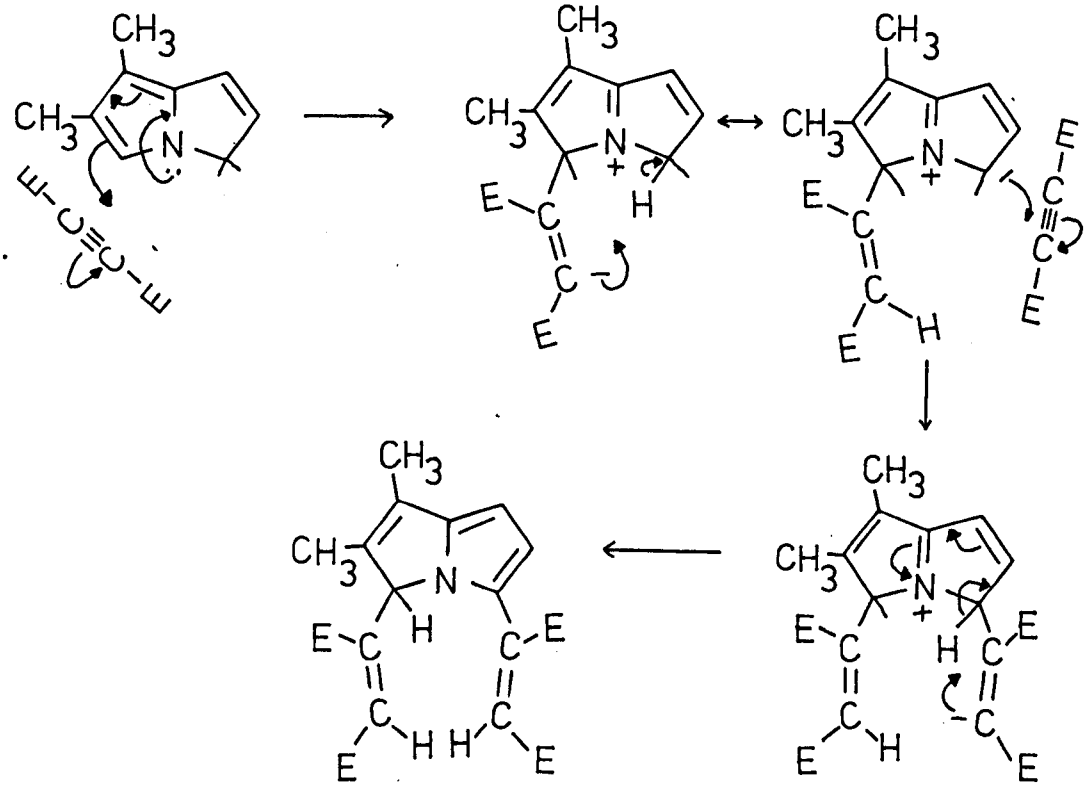
The possibility that the dimaleate (131) was an intermediate in the formation of the diadduct (140) was investigated by refluxing compound (131) in toluene for 3 days, or better still, by standing a methanol solution overnight. P.l.c. on the product (4:1 $CHCl_3$: C_6H_6) gave the isomeric cyclazine derivative (140)

identical in mass spectra and I.R. and undepressed in mixed melting point with a sample of the cyclazine (140) prepared directly.

The only two reactions capable of giving mechanistic evidence on the formation of the cyclazine diadducts were those of 1-methyl and 1,2-dimethyl-3H-pyrrolizine with excess DMAD. Those two reactions, however, gave opposite products so neither could be relied upon for evidence. One can only assume that, as in the case of the reaction to give the mono-adduct, 1,2-dimethyl-3H-pyrrolizine isomerises to its 6,7-dimethyl isomer before reacting with DMAD. It could then react by the same mechanism as 1-methyl-3H-pyrrolizine. Having made that assumption, and considering the pyrrolizin-3,5-yldimaleate to be an intermediate, the mechanism shown in Scheme 47 is a possibility.

The zwitterionic intermediate, formed from the initial attack of DMAD on the pyrrolizine, rearranged by abstraction of a proton from the 3 position. This zwitterion, in the presence of excess DMAD, attacks another molecule of DMAD and, after neutralisation by abstraction of a second proton from the 3 position,

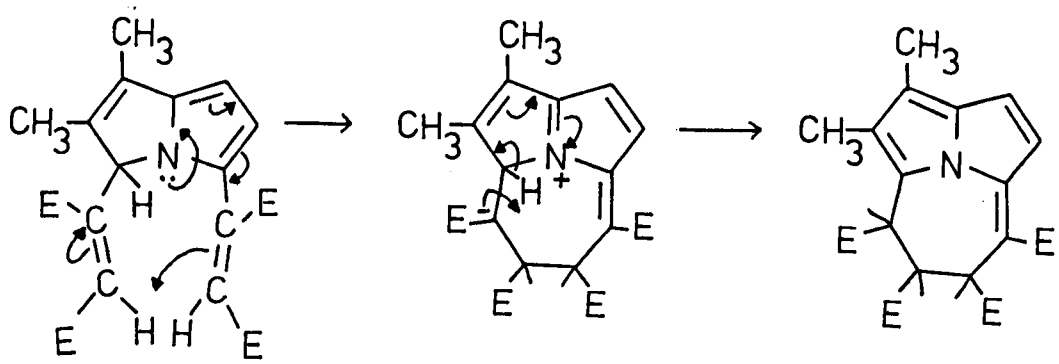
SCHEME 47



(131)

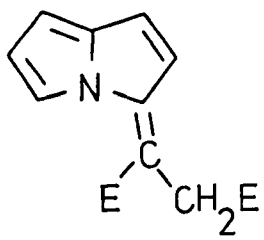
gives the intermediate (131). An intramolecular electrophilic substitution reaction then takes place, as shown in Scheme 48, to give the cyclazine product (140).

SCHEME 48

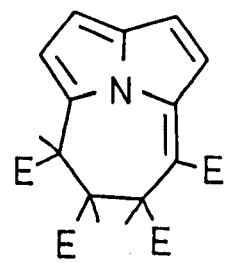


(131) (140)

In conclusion, it has been established that 3H-pyrrolizine and its derivatives react thermally with DMAD to give two types of products, monoadducts, which have the azafulvene structure (e.g. compound (110) i.e. A) and diadducts which have a reduced cycl [4,2,2] azine structure (e.g. compound (133) i.e. B).



(110)

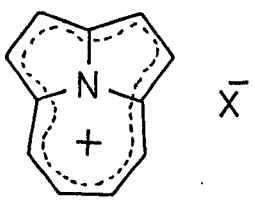


(133)

A mechanism has been established for the production of the azafulvenes and one suggested for the production of the cyclazine derivatives.

2. The attempted synthesis of the cycl[4,2,2]azinium system

When compound B was shown to have a reduced cycl[4,2,2]-azine structure, the interesting possibility arose of converting it into the as yet unknown cycl[4,2,2]azinium system below. This system would have 10π electrons

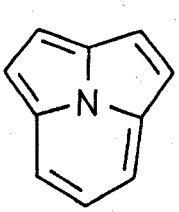


delocalised around the periphery and might therefore be expected, according to the Hückel rule, to be aromatic.

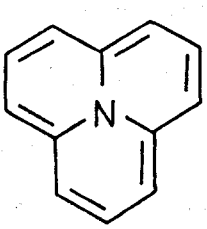
Before attempts to produce this system are discussed, it is pertinent to include a small review on the cyclazine systems already known.

2.1 The synthesis and properties of cyclazines

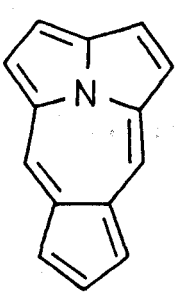
Examples of 3 members of the cyclazine series have been synthesised to date, cycl[3,2,2]azine (98), cycl[3,3,3]azine (141), and a cyclopenta[h]cycl-[4,2,2]azine (100).



(98)



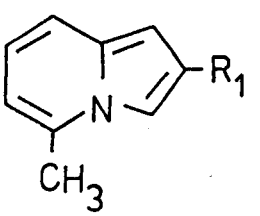
(141)



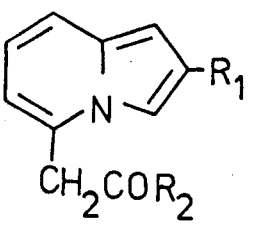
(100)

a) Cycl [3,2,2] azine (98)

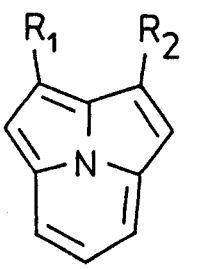
This was the first example of a cyclazine ever reported and was synthesised by Boekelheide and Windgassen [65], in 1958, by the acetic acid catalysed cyclisation of the ketone (143), derived from 2-substituted 5-methylindolizine (142).



(142)



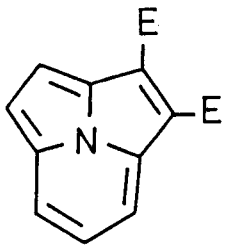
(143)



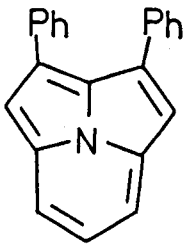
(144)

Cycl [3,2,2] azines (144) with $R_1 = R_2 = H$ (parent), $R_1 = R_2 = C_6H_5$ and $R_1 = H$, $R_2 = C_6H_5$ were prepared by this route.

Boekelheide and co-workers [66,67] also reacted indolizine with DMAD, under dehydrogenating conditions, to give the cycl [3,2,2] azine diester (145) directly. Hydrolysis, followed by decarboxylation, gave the parent cycl [3,2,2] azine (98). Also, the use of methyl phenylpropiolate, instead of DMAD, on 2-phenylindolizine



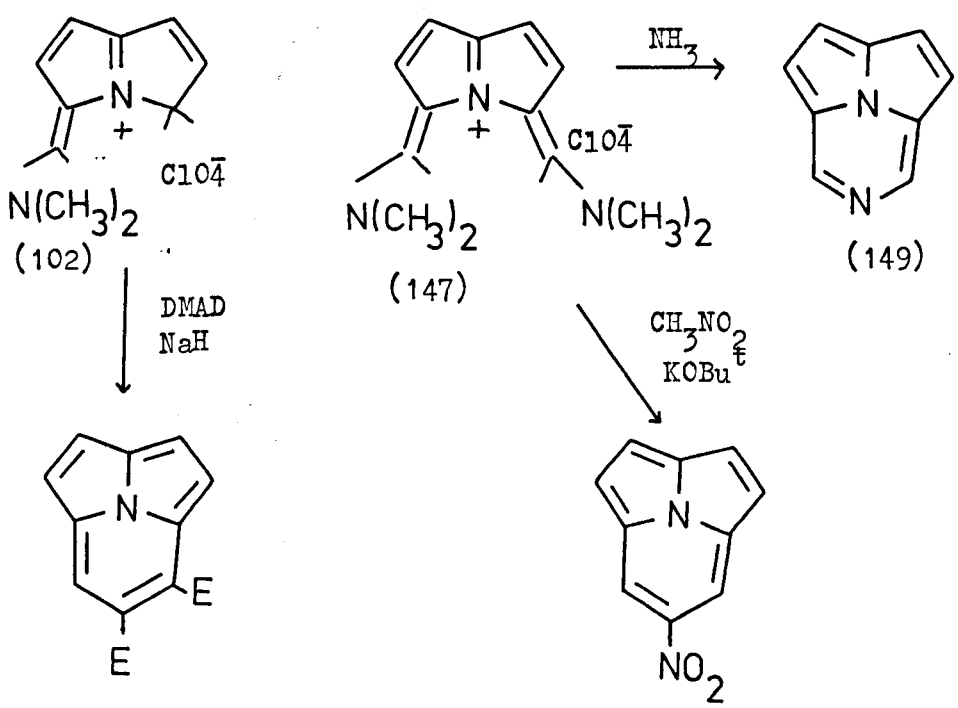
(145)



(146)

gave 2,3-diphenylcycl [3,2,2] azine (146).

More recently Acheson and co-workers [68,69] have produced substituted cycl [3,2,2] azines by the reaction of methyl propiolate with substituted pyridines. Also Jessep and Leaver [53] have synthesised cycl [3,2,2] azine, the 6-nitro derivative (148) and 6-aza derivative (149), from the salts (102) and (147), derived from 3H-pyrrolizine.

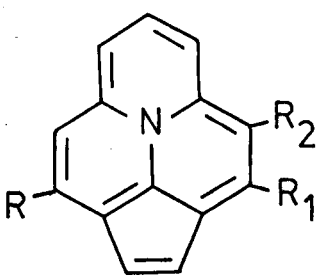


(148)

Boekelheide and Windgassen [65] reported that cycl [3,2,2] - azine showed unusual stability towards air, heat and light, compared with its precursor indolizine, which would agree with it being an aromatic (10π) system. They also reported that it was completely non-basic but these points will be dealt with in detail a little later.

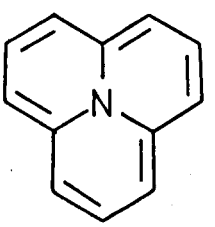
b) Cycl [3,3,3] azine (141)

The cycl [3,3,3] azine system had only been synthesised by Leaver and co-workers [70,71]. In 1965 they reported [70] the substituted cyclazines (150) and (151) and in 1969 they reported [71] the synthesis of the parent cycl [3,3,3] azine (141).



(150) $R=CH_3$, $R_1=R_2$ = E

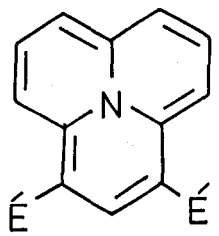
(151) $R=R_1 = C_6H_5$, $R_2=H$



(141)

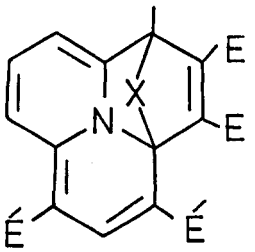
The cycl[3,3,3] azine (141) has 12π electrons around its periphery and one would therefore expect it to be non-aromatic. In fact, Leaver and Farquhar [71] reported that compound (141) decomposed rapidly if exposed to air, or dissolved in CCl_4, chloroform, or hydroxlic solvents.

The diester (152) also underwent a Diels -Alder addition with



(152)

É = $CO_2C_2H_5$



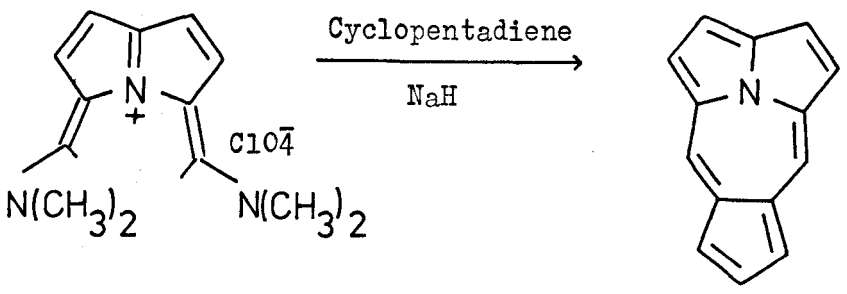
(153)

X = (CH=CH)

DMAD, to give compound (153), confirming that the system as a whole was not aromatic.

c) Cycl [4,2,2] azine

The only cycl [4,2,2] azines reported are the 6,7-dihydro-8H-cycl [4,2,2] azine esters reported by Johnson and Jones [55] and the cyclopenta [h] cycl [4,2,2]-azine (100) reported by Jessep and Leaver [53]. Compound (100) was synthesised from 3H-pyrrolizine via the salt (147).



(147) (100)

The cyclopenta [h] cycl [4,2,2] azine (100) is, in fact, a 14π system and Jessep and Leaver do not report any instability, in contrast to the 12π cycl [3,3,3] azine

c) contd

system.

The criterion of aromaticity in the cyclazine systems seems to be determined by the number of peripheral electrons; 10π and 14π systems show stability, whereas the 12π system is very unstable, in agreement with the Hückel rule. If the peripheral π electrons are forming the aromatic cycle, the internal nitrogen atom would be expected to be sp^3 hybridised with a lone pair of electrons in an sp^3 orbital. It should therefore be basic in character. However, two properties of the aromatic cycl [3,2,2] azine system dispute this.

1) Boekelheide and Windgassen [65] report that cycl [3,2,2] azine has no basicity.

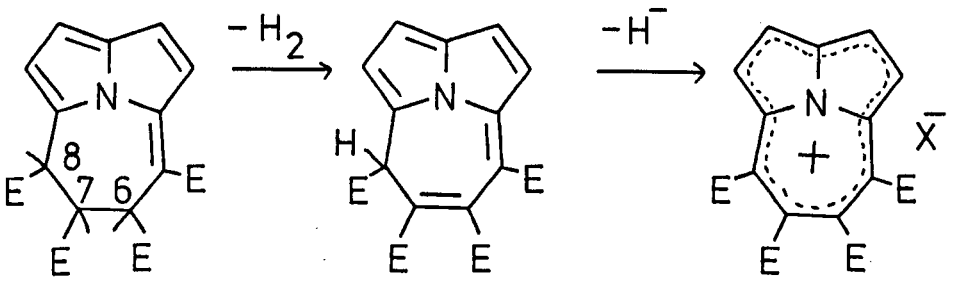
2) An X-ray diffraction study of a dibromo cycl[3,2,2]-azine, carried out by Hanson [72], showed the nitrogen atom to be almost coplanar with the carbon atoms and, therefore, sp^2 hybridised.

In order to be non-basic, and sp^2 hybridised, the nitrogen lone pair of electrons must be somehow delocalised around the ring system. The exact electronic configuration of the cyclazine systems are therefore far from simple, and as yet unexplained, but the use of only the peripheral π electrons to assess the aromaticity (or otherwise) of a cyclazine, although an approximation, has been very effective for the systems reported to date.

2.2 Attempts to synthesise cycl [4,2,2] azinium salts from compound B

The route envisaged for the synthesis of the cycl [4,2,2] azinium salts (155) is shown in Scheme 49.

SCHEME 49



(133) (154) (155)

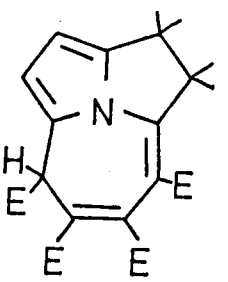
The first attempt at the dehydrogenation of compound (133) involved the use of N-bromosuccinimide to brominate the 6,7 or 8 positions. It was envisaged that the brominated hydrocyclazine would undergo dehydrobromination to give the 8H-cycl [4,2,2] azine (154). The reaction of N-bromosuccinimide with compound (133) gave a mixture of products, some with bromine on the pyrrole ring, and the major product isolated (14% yield) was, in fact, compound (154). The deeper colour and bathochromic shift in the U.V. spectrum showed compound (154) to have more extensive conjugation than its precursor, compound (133) as expected.

The n.m.r. spectrum showed AB doublets (J6Hz) at τ 2.5 and

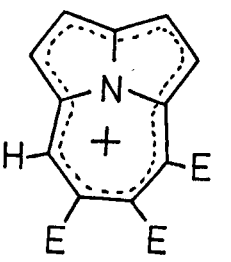
2.2 contd

3.05 for the fulvene ring protons and, also, at τ 3.38 and 3.51 (J3Hz) for the pyrrole ring protons. The AEX system in compound (133) was replaced by a 1 proton singlet (τ 4.07) for the 8 proton of compound (154). The spectrum fitted structure (154) well and the structure was further confirmed by hydrogenation to give the dihydrocompound (156).

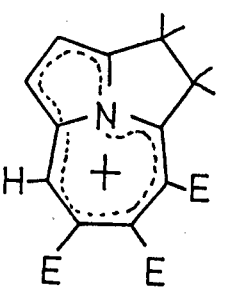
The mass spectra of compounds (154) and (156) were very interesting. Compound (154) showed a molecular ion at 387 (9%).



(156)



(157)



(158)

and loss of a methyl ester group ($^{m}/e$ 59) gave the cyclazinium cation (157) as the base peak. Also, compound (156) had a molecular ion at 389 (11%) and once again loss of a methyl ester group gave the azonia-azulenium cation (158) as the base peak. In both cases only very small peaks were recorded at lower masses than the base peaks, demonstrating the stability of the azonia-azulenium and cycl [4,2,2] azinium cations.

The yield of compound (154) from compound B (133) was increased to 64% by the use of dichlorodicyanobenzoquinone (D.D.Q.) as the dehydrogenating agent. However, attempts to remove a hydride ion from the 8H-cycl [4,2,2] azine (154), to give the cyclazinium salt (155), were not successful.

Treatment of compound (154) with the usual hydride abstracting agents, e.g. triphenylmethyl fluoborate [73], phosphorus pentachloride [74], and D.D.Q. in perchloric acid [75], failed to give indentifiable products. The most probable explanation was that the 8 carbon of compound (154), attached to an ester group, was positive in nature and the abstraction of a hydride ion from such a carbon atom would be difficult.

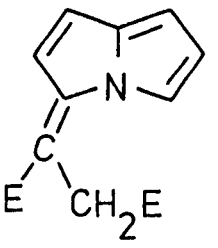
Attempts were made to hydrolyse the ester, on the 8 position, with a view to subsequent decarboxylation, but acid hydrolysis gave a great deal of polymeric material and basic hydrolysis gave highly coloured compounds which were not identifiable.

Williams and Sgoutas [76] have reported the use of chlorosulphonic acid to hydrolyse and decarboxylate a cyclopropenyl ester leaving the cyclopropenium salt. However, treatment of compound (154) with chlorosulphonic acid, in methylenechloride, gave only polymeric material.

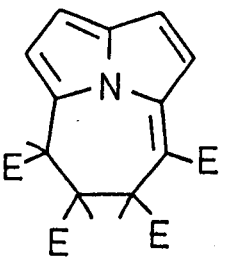
Finally, Prof. H. Lund (Aarhus University, Denmark) is at present attempting the electrochemical oxidation of compound (154), in acetonitrile, and in the presence of sodium perchlorate. He has reported [77] the isolation of a green perchlorate salt, formed from compound (154), but as yet has not been able to identify it.

3. <u>The photochemical reaction of 3H-pyrrolizine and DMAD using radiation of predominantly 3130 A° and 3360 A° wavelength</u>

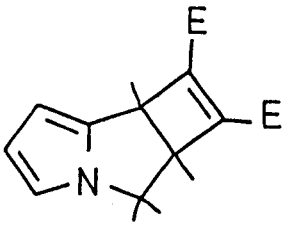
Irradiation of a solution of 3H-pyrrolizine, DMAD and acetophenone (triplet state sensitizer) with light of predominantly 2537 A° wavelength, was shown in section 1 of this discussion to give a mixture of the azafulvene (110) and the cyclazine derivative (133). The same



(110)



(133)



(159)

products were also obtained by a thermal reaction.

In a second attempt to obtain the cyclobutene adduct (159), by the photochemical 2+2 cycloaddition of 3H-pyrrolizine to DMAD, a solution of 3H-pyrrolizine, acetophenone and a 10 fold excess of DMAD, in benzene, was irradiated for 7 hrs. through a pyrex sleeve. During this time the solution turned brown in colour and t.l.c. showed the formation of many products. Evaporation of the solution gave a brown oil which was chromatographed

3. contd

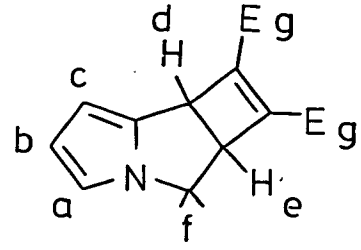
on an alumina column. (Full details in the experimental section). Compounds A and B were obtained in high yield from the column. P.l.c. on the fraction between compounds A and B yielded a new compound, C, as a yellow oil, and p.l.c. on the fraction following compound B gave two new isomeric diadducts, compounds D and E.

The structures of the new adducts were determined from their spectra.

Compound C, a yellow oil, was shown by mass spectral and elemental analyses to have the molecular formula $C_{13}H_{13}NO_4$, i.e. it was a monoadduct. The I.R. spectrum showed only one carbonyl absorption (1710 cm^{-1}) indicating that the ester groups were equivalent. The U.V. spectrum showed λ max ($\log_{10}\varepsilon$) at 206 nm(sh) and 219 (4.11) which indicated a loss of conjugation from 3H-pyrrolizine - 218nm (3.40) and 290 (3.79). The n.m.r. spectrum, fig. 5, showed 3 pyrrole proton absorptions at τ 3.65 (1H,m), 3.99 (1H,t,J3Hz) and 4.20 (1H,d,J3Hz), a six proton singlet at τ 6.27 for the ester methyl groups and a 4 proton broadened doublet at τ 5.9.

Doyle [27] reported that the cyclobutene ring proton of compound (160) gave a multiplet, in the n.m.r. spectrum, at τ 6.1 - 6.25. Also, pyrrolyl N-methylene groups commonly absorb at τ 6.0 and below. Hence the doublet at τ 5.9, in

Fig 5


d
H
E g
c
E g
b
N
H
e
a
f

1
1
1
4
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6
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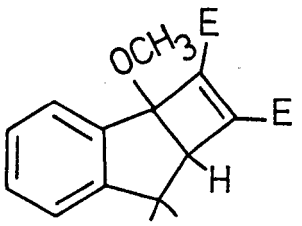
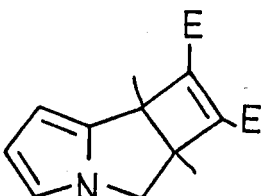


(160)

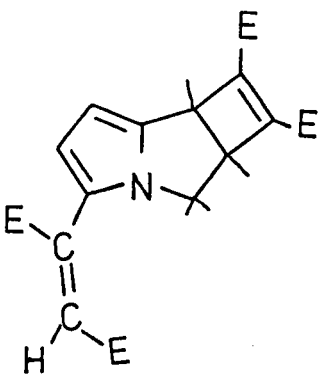
3. contd

the n.m.r. spectrum of compound C, could easily be due to the methylene group and cyclobutene ring protons of compound (159).

The spectral data of compound C fitted the structure (159) very well and that structure was therefore assigned to compound C.



(159)



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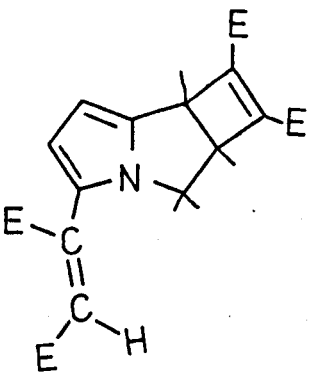


(162)

The n.m.r. spectra of the diadducts D and E, like that of compound (159), showed a 4 proton broadened singlet at τ 5.8 for the methylene group and cyclobutene ring protons. (Clearer in compound E). The pyrrole β -protons gave AB doublets (J4Hz) in both cases and 1 proton singlets at τ 3.39,

3. contd

in compound D, and τ4.12 in compound E, were attributed to fumarate (D) and maleate (E) protons.

The n.m.r. spectra, together with the I.R., U.V. and mass spectra, left no doubt that the diadducts D and E had the structures (161) and (162) respectively.

The reaction was repeated several times and the yields, especially of the diadducts, were variable. Typical yields were:-

A (110) 42%, B (133) 8%, compound (159) 5%, compound (161) 3% and compound (162) 3%.

An attempt was made to cut down the diadduct formation by the irradiation of a solution of equimolar quantities of 3H-pyrrolizine, acetophenone and DMAD, for 7 hrs. The result was the production of the azafulvene A, in 10% yield, but no diadducts or cyclobutene derivatives could be isolated.

It became obvious that even under the very favourable conditions for a photochemical 2+2 cycloaddition reaction, used above, the thermal reaction between 3H-pyrrolizine and DMAD was taking place much faster than the photochemical reaction. The product mixture, therefore, contained much higher yields of the thermal than the photochemical products.

A new approach was needed to slow down the thermal reaction and thereby allow the photochemical reaction to go in higher yield. Two possibilities were apparent:-

3. contd

a) The use of an acetylene other than DMAD, e.g.

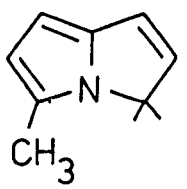
I) Diphenylacetylene (tolan) which undergoes many photochemical 2+2 cycloaddition reactions, but is in no way electrophilic.

II) Methyl propiolate which, although electrophilic in nature, is not as strong an electrophile as DMAD.

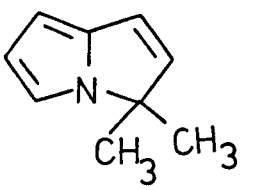
Either tolan or methyl propiolate might have been expected to add photochemically to 3H-pyrrolizine, but neither would be expected to react thermally.

b) The use of a 3H-pyrrolizine substituted in such a way that the reaction with DMAD would be impeded or even prevented, e.g.

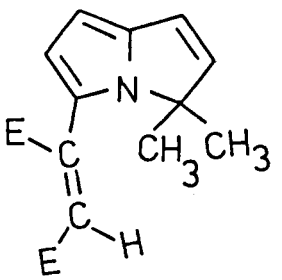
I) 5-methyl-3H-pyrrolizine (90) would not allow the attack of DMAD on the usual 5 position.



(90)



(55)



(163)

II) 3,3-dimethyl-3H-pyrrolizine (55) would theoretically allow the initial attack of DMAD on the 5-position but would not allow the usual rearrangement to give

3. contd

II) the azafulvene. The maleate intermediate (163), if formed, would still be capable of undergoing the desired photochemical 2+2 cycloaddition.

4. The attempted reactions of 3H-pyrrolizine with methyl propiolate and diphenylacetylene

The attempted reactions are summarised in the table below. Thermal reactions were carried out by refluxing reactants in toluene solution and photochemical reactions by irradiation of the reactants (and acetophenone) in benzene solution. In every case the resulting solution was evaporated and the residue chromatographed on an alumina column. 5-fold excesses of diphenylacetylene and 10-fold excesses of methyl propiolate were used.

Reaction	Acetylene	Conditions	Time	Product
4.1)	Methyl propiolate	Heat	20hr	None
4.2)	" "	hν/Quartz	12hr	Polymer
4.3)	" "	hν/Pyrex	13hr	Polymer
4.4)	Diphenyl-acetylene	Heat	14hr	None
4.5)	" "	hν/Quartz	15hr	Polymer
4.6)	" "	hν/Pyrex	15hr	Polymer

The two acetylenes, methyl propiolate and diphenylacetylene, reacted neither thermally nor photochemically with 3H-pyrrolizine, under the conditions tried. DMAD had already been shown (Section 3) to be capable of undergoing photochemical 2+2 cycloadditions to 3H-pyrrolizine, but the competing thermal reaction needed to be slowed down. The search for more suitable acetylenes was therefore abandoned in favour of using substituted 3H-pyrrolizines that would undergo photochemical, but not thermal, reactions with DMAD.

5. The reactions of 3,3-dimethyl-3H-pyrrolizine with DMAD

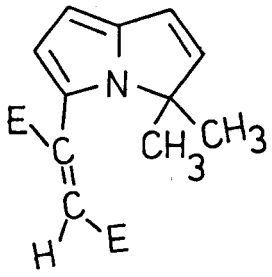
5.1) The thermal reaction

3,3-Dimethyl-3H-pyrrolizine and an equimolar amount of DMAD were refluxed in methanol solution for 22 hrs. Evaporation of the resulting solution gave a red gum and chromatography on the gum (column and p.l.c.) yielded two isomeric adducts, F & G.

Adduct F, a red oil, was shown by mass spectral and elemental analyses to have the molecular formula $C_{15}H_{17}NO_4$, i.e. it was a monoadduct. The U.V. spectrum showed λ max ($\log_{10}\varepsilon$) at 209 nm (4.19), 287.5 (3.88) and 391 (3.24) showing that the conjugation of the pyrrolizine system had been extended. The n.m.r. spectrum showed AB doublets at τ 3.62 (1H,J6Hz), 4.26 (1H,J4Hz) and 4.00 (2H,J5Hz approx.), for the pyrrole and pyrrolenine rings, 3 proton singlets at τ 6.35 and 6.50 for the ester methyl groups, a 6 proton singlet at τ 8.69 for the ring methyl groups and a 1 proton singlet at τ 3.13 which was attributed to a fumarate proton.

On the basis of the spectral data, the fumarate structure (164) was assigned to the adduct F.

5.1 contd



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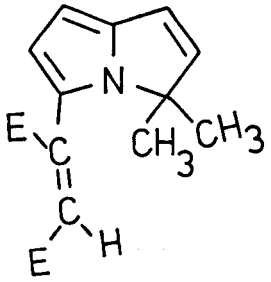


(163)

The adduct G was a orange/yellow oil but it could not be obtained in a pure form as it rapidly decomposed and isomerised. Mass spectral analysis indicated a molecular weight of 275 confirming that the adduct G was isomeric with the fumarate adduct F. The n.m.r. spectrum showed AB doublets at τ 3.65 and 3.86 (J6Hz) and 3.65 and 4.15 (J4Hz), for the pyrrolenine and pyrrole rings, 3 proton singlets at τ 6.20 and 6.32 for the ester methyl groups, a 6 proton singlet at τ 8.35 for the ring methyl groups and a 1 proton singlet at τ 3.87 which was attributed to a maleate proton.

From the n.m.r. and mass spectra the adduct G was assigned the maleate structure (163).

In the above reaction the yields of the adducts were 26% of the fumarate (164) and 5% of the maleate (163). The reaction was repeated using toluene, instead of methanol, and after 56 hrs. refluxing the only product was the fumarate (164) in 5% yield.

5.1 contd

Clearly, if 3,3-dimethyl-3H-pyrrolizine and DMAD only reacted to give 5% of an adduct after 56 hrs. refluxing in toluene, the yield of thermal product produced during 7 hrs. of irradiation would be negligible.

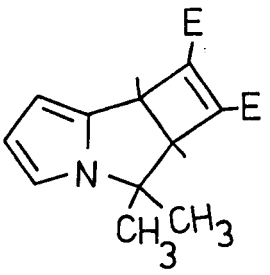
5.2 <u>The photochemical reaction of 3,3-dimethyl-3H-pyrrolizine with DMAD</u>

A solution of 3,3-dimethyl-3H-pyrrolizine, acetophenone and a 10-fold excess of DMAD, in dry benzene, was irradiated for 7 hrs. through a pyrex sleeve. Evaporation of the irradiated solution, and column chromatography on the residue, gave a crude adduct K as a yellow oil. Two separate p.l.c's were necessary to purify the product and the pure adduct K was finally obtained, in 26% yield, as a yellow gum.

Mass spectral and elemental analyses gave a molecular formula of $C_{15}H_{17}NO_4$ confirming that the compound K was a monoadduct. The U.V. spectrum was almost identical to that of the cyclobutene derivative (159), showing λmax at 206 nm(sh) and 218 ($\log_{10}\varepsilon$ 4.12). The n.m.r. spectrum, again like that of compound (159), showed 3 pyrrole proton absorptions at τ3.67 (1H,m), 4.00 (1H,t,J3Hz) and 4.23 (1H,d,J3Hz), two 3 proton singlets at τ8.52 and 8.60 for the ring methyl groups, a 7 proton multiplet at τ6.1 to 6.3 for the ester methyl groups and one cyclobutene ring proton and a doublet at τ5.85 (1H,J5Hz) for the other cyclobutene ring proton.

5.2 contd

From the spectral data, and its similarity with the data for compound (159), the adduct K was assigned the structure (165).



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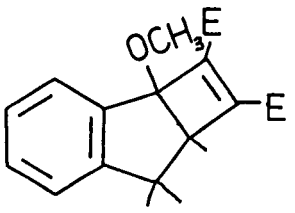

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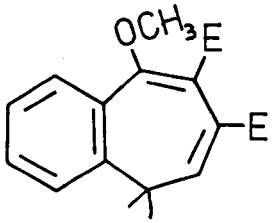


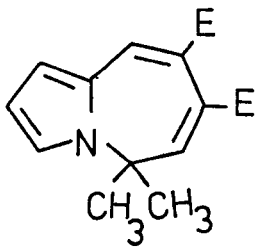
(38)

The problem of producing a cyclobutene adduct from a 3H-pyrrolizine and DMAD had been solved with the production of compound (165) in 26% yield. The next stage was the ring opening of compound (165) and the attempts were modelled on the work of Doyle[27]. He reported the ring opening of the methoxyindene adduct (160) to give the benzocycloheptatriene (38) by both thermal and photochemical reactions.

5.3 <u>The thermal ring opening of the cyclobutene derivative</u> (165)

The adduct (165) was heated, under a nitrogen blanket, in an oil bath at 180 - 200°C. The reaction was monitored by t.l.c. and after 90 mins. the adduct (165) appeared to have been completely converted to a new product. P.l.c. on the product gave the pyrrolo[1,2-a] azepine (166) as a

5.3 contd



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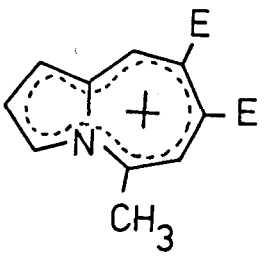


(167)

pale yellow oil, in 61% yield.

Mass spectral and elemental analyses on the product confirmed that it had the molecular formula $C_{15}H_{17}NO_4$ and the U.V. spectrum showed greatly increased conjugation, compared with the precursor (165), with λmax ($\log_{10}\varepsilon$) at 205 nm (4.09), 227(sh), 247.5 (3.76), 283 (3.71) and 366 (4.07). The n.m.r. spectrum showed 3 pyrrole proton absorptions at τ 3.12 (1H,m), 3.46 (1H,m) and 3.78 (1H,t,J3Hz), two 3 proton singlets for the ester methyl groups at τ 6.28 and 6.36, a 6 proton singlet (τ 8.39) for the ring methyl groups and two singlets at τ 2.29 and 3.66 for the protons of the azepine ring.

The spectral data left no doubt that the product was, as expected, the pyrrolo [1,2-a] azepine (166).

The mass spectrum of compound (166) was very interesting. It showed a molecular ion at 275 (45%) and loss of a methyl

5.3 contd

radical to leave the azonia-azulenium cation (167) as the base peak ($^{m}/e$ 260).

5.4 The attempted photochemical ring opening of the cyclobutene derivative (165)

A solution of the cyclobutene derivative (165), in redistilled cyclohexane, was irradiated for 13 hrs. through a pyrex sleeve. The solution turned very cloudy due to polymer deposition. Evaporation of the solution, followed by p.l.c. on the residue, gave unchanged compound (165) (6%), and a dimer (15%) as the only identifiable product.

Mass spectral analysis of the dimer showed a molecular weight of 550, as expected, but elemental analyses were consistently wrong, for the required formula of $C_{30}H_{34}N_2O_8$, and a sensible molecular formula could not be derived from the results obtained. The U.V. spectrum was very similar to the monomer (165), as expected, and the n.m.r. spectrum was similar apart from two exceptions:-

a) The ring methyl groups which gave close singlets at τ8.52 and 8.60 in the n.m.r. spectrum of the monomer gave singlets at τ8.54 and 8.78 in the spectrum of the dimer.

b) The ester methyl groups also gave close singlets at τ6.1 - 6.3 in the spectrum of the monomer but the singlets were further apart at τ6.2 and 6.6 in the

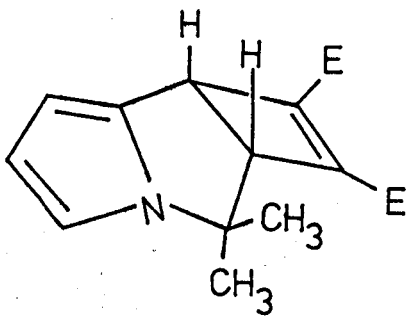
5.4 contd

b) spectrum of the dimer.

Clearly, the methyl groups and ester groups had become even more non-equivalent in the dimer. This could be explained if one ester, from each end of the dimer, was very close to one methyl group.

The close proximity of 2 ester and 2 methyl groups, deduced from the n.m.r. spectrum of the dimer, gave some indication as to the possible structure of the dimer.

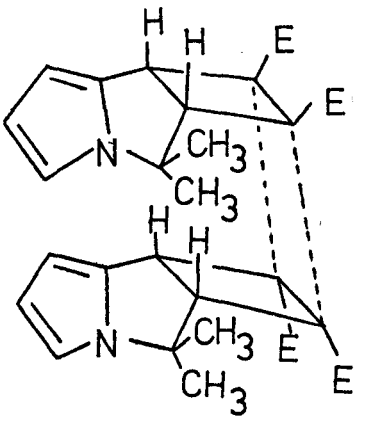
There are two possible modes of dimerisation, cis and trans, and for each mode the cyclobutene rings can couple either head to head or head to tail. In the cyclobutene derivative (165) the ester groups, attached to sp^2 carbon atoms, are held



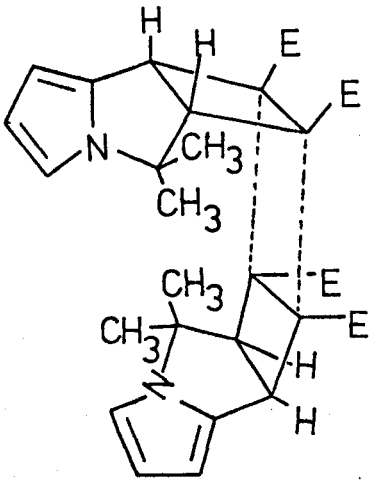
(165)

in the plane of the cyclobutene ring, and are therefore clear of the pyrrolenine ring methyl groups. The head to head cis isomer (A) would have only one methyl group close to an ester group, and the head to tail cis isomer (B) would have no methyl and ester groups close together.

5.4 contd

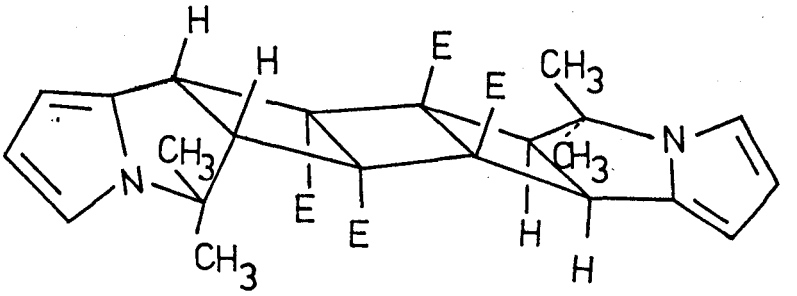


(A)



(B)

Hence neither of these cis isomers would fit the n.m.r. spectrum of the dimer (168). Other possible cis isomers and all of the trans isomers, on the other hand, have two methyl groups close to ester groups, as demonstrated below on the head to tail trans isomer (C). These would fit the



(C)

n.m.r. spectrum of the dimer (168),

5.4 contd

but an X-ray analysis on the dimer would be needed to differentiate between all the possible isomers.

In conclusion, a photochemical 2+2 cycloaddition reaction was carried out between 3,3-dimethyl-3H-pyrrolizine and DMAD to give a moderate yield (26%) of cyclobutene product. The cyclobutene product was successfully ring opened to give the pyrrolo [1,2-a]-azepine (167) but it was not possible to remove a methyl group from the 5 position of the azepine (167), and thereby obtain an azonia-azulenium salt.

If azonia-azulenium salts are to be synthesised by this route a new 3H-pyrrolizine will have to be synthesised which will:-

a) react photochemically with DMAD
b) take part in no thermal reaction with DMAD
c) have a hydrogen on the 3 position available for eventual abstraction to give the azonia-azulenium salt.

The only simple 3H-pyrrolizine expected to have all three of the above properties is 5-methyl-3H-pyrrolizine. However, as yet it has only been synthesised as part of a mixture of isomeric pyrrolizines, and the attempted synthesis was described in Part I of this thesis.

EXPERIMENTAL

3-Carbomethoxy (carbomethoxymethyl) methylene-3H-pyrrolizine (110)

The first two methods outlined below (a) and (b), can be regarded as general procedures for the synthesis of azafulvenes.

a) 3H-pyrrolizine (525mg, i.e. 5m mole) and DMAD (710mg, i.e. 5m mole) were dissolved in dry toluene (100ml) in a 250ml flask. The flask was flushed with nitrogen, stoppered, and stood at room temperature for 9 days. Evaporation of the toluene gave the crude product as red oil.

b) The solution described in (a) above was refluxed for 5 hrs. then allowed to stand overnight. Once again evaporation of the toluene gave a red oil as the crude product.

The red oil from either of the above reactions was chromatographed on an alumina column (75g in petrol). The oil was put onto the column in a small quantity of toluene and the column eluted with a 1:1 mixture of petrol/toluene. An orange band separated from a deep red band and was eluted. Evaporation gave a red oil which crystallised on standing, and recrystallisation from petrol gave the azafulvene (110) as orange needles m.p. 76°. The yield from either reaction (a) or (b) was 880mg, i.e. 71%.

c) Using base catalysis, and an excess of DMAD, the reaction produced a mixture containing a large amount of diadduct.

c) contd

3H-Pyrrolizine (525mg, i.e. 5m mole) and DMAD (3.55g, i.e. 25m mole) were added to a magnetically stirred suspension of potassium tertiarybutoxide (560mg, i.e. 5m mole) in toluene (100ml NaH dried). The resulting suspension was stirred for 3.5 hrs. during which time it had turned deep red in colour. The suspended salts were filtered off and dissolved in water (10ml) and the resulting aqueous solution extracted with ether (4 x 50ml). The ether and toluene solutions were combined, dried (Na_2SO_4), and evaporated to leave a dark red oil.

The red oil was chromatographed on an alumina column (180g in petrol). Elution with a 1:1 mixture of petrol/ toluene separated the azafulvene (110) as an orange band. Further elution with toluene removed the trailing red band. Evaporation of this fraction gave a deep red gum which solidified on standing. Recrystallisation from CCl_4 gave the cyclazine derivative (133) as a red solid m.p. 105 - 112°. The yields from this reaction were 714mg (i.e. 58%) of the azafulvene (110) and 532mg (i.e. 27%) of the cyclazine (133).

For the azafulvene (110) Found: C,63.20; H,5.42; N,5.60%

$C_{13}H_{13}NO_4$ requires C,63.15; H,5.30; N,5.65%

I.R. ν(C=O) 1735 and 1700cm^{-1}

U.V. λ_{max} ($\log_{10}\varepsilon$) 209.5nm (4.14), 230(sh), 332.5(4.30) and 420 (3.29)

N.m.r. (CCl_4): τ 2.83 (1H,d,J6Hz), 3.07 (1H,d,J3Hz), 3.41 (1H,d,J6Hz), 3.90 (1H,t,J3Hz), 4.05 (1H,d,J3Hz), 6.23 (3H,s,OCH_3), 6.35 (3H,s,OCH_3) and 6.35 p.p.m. (2H,s,CH_2)

M.S. m/e 247 (M^+) (72%), 215 (11%), 188 (100%), 160 (33%), 128 (33%).

3-Carboethoxy (carboethoxymethyl) methylene-3H-pyrrolizine (122)

Prepared as described in the general method (b) above. 3H-pyrrolizine (820mg) and diethyl acetylenedicarboxylate (1.34g) gave the azafulvene (122) (1.84g, i.e. 86%) as orange needles m.p. 84 - 85° (from petrol).

Found: C,65.50; H,6,34; N,5.00%

$C_{15}H_{17}NO_4$ requires C,65.40; H,6.23; N,5.09%

I.R. ν (C=O) 1730 and 1693 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 209.5nm (4.15), 230(sh), 333 (4.30) and 419 (3.29)

N.m.r. (CCl_4): τ 2.81 (1H,d,J6Hz), 3.05 (1H,d,J3Hz), 3.41 (1H,d,J6Hz), 3.92 (1H,t,J3Hz) 4.07 (1H,d,J3Hz), 5.81 (4H, m ,2 x OCH_2), 6.38 (2H,s,CH_2) and 8.75 p.p.m. (6H,q,2 x CH_3)

M.S. m/e 275 (M^+) (68%), 229 (14%), 202 (100%), 174 (41%) 129 (73%)

3-Carbomethoxy (carbomethoxymethyl) methylene-7-methyl-3H-pyrrolizine (125)

Prepared as described in the general method (b) above.

1-methyl-3H-pyrrolizine (357mg) and DMAD (426mg) gave the azafulvene (125) (274mg, i.e. 35%) as orange needles m.p. 105 - 108° from light petrol.

Found: C,64.70; H,5.63; N,5.30%

$C_{14}H_{15}NO_4$ requires C,64.70; H,5.79; N,5.36%

I.R. ν (C=O) 1730 and 1690 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 211.5(4.18), 235(sh), 346 (4.31) and 423 (3.44).

N.m.r. (CCl_4): τ 2.87 (1H,d,J6Hz), 3.18 (1H,d,J3Hz), 3.39 (1H,d,J6Hz), 4.10 (1H,d,J3Hz), 6.23 (3H,s,OCH_3), 6.35 (3H,s,OCH_3), 6.42 (2H,s,CH_2) and 7.94 p.p.m. (3H,s,CH_3)

M.S. m/e 261 (M^+) (43%), 229 (5%), 202 (100%), 174 (25%), 142 (41%).

3-Carbomethoxy (carbomethoxymethyl) methylene-1,2-dimethyl-3H-pyrrolizine (130)

Prepared as described in the general method (b) above.

1,2-Dimethyl-3H-pyrrolizine (400mg) and DMAD (426mg) gave the azafulvene (130) as a red oil. (283mg, i.e. 34%).

Found: C,65.60; H,6.25; N,5.10%

$C_{15}H_{17}NO_4$ requires C,65.40; H,6.23; N,5.09%

I.R. ν (C=O) 1725 and 1690 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 210nm (4.10), 235(sh), 320 (4.09) and 400(sh)

N.m.r. (CCl_4): τ 3.08 (1H,d,J3Hz), 3.98 (1H,t,J3Hz)

4.24 (1H,d,J3Hz), 6.25 (3H,s,OCH_3),
6.35 (3H,s,OCH_3), 6.41 (2H,s,CH_2),
8.05 (3H,s,CH_3) and 8.18 p.p.m. (3H,s,CH_3)

3,3-Diphenylmethylene-3H-pyrrolizine (96)

Prepared as described by Flitsch and Heidhues [35].

Dimethyl 6,7-dihydro-7,7-diphenylcycl[3,2,2]azine-5,6-dicarboxylate (115)

A solution of the azafulvene (96) (240mg) and DMAD (400mg), in dry toluene (100ml), was refluxed for 8 hrs. then stood overnight. Evaporation of the toluene gave a dark red oil which was chromatographed on an alumina column (75g in petrol). Elution with petrol removed a yellow band (starting material) and elution with toluene removed a maroon band which, on evaporation, gave a maroon solid. Recrystallisation from aqueous ethanol gave the cyclazine derivative (115) as a maroon solid m.p. 158° (254 mg, i.e. 69%).

Found: C,75.53; H,5.38; N,3.34%
$C_{26}H_{21}NO_4$ requires C,75.85; H,5.15; N,3.40%

I.R. ν (C=O) 1725 and 1690 cm^{-1}

U.V. λ_{max} ($\log_{10}\varepsilon$) 212nm (4.36), 240(sh), 370 (4.04) and 480 (3.22).

N.m.r. ($CDCl_3$): τ 2.73 (10H,br.s.), 3.41 (1H,d,J6Hz), 3.53 (1H,d,J6Hz), 3.97 (1H,d,J3Hz), 4.07 (1H,d,J3Hz), 5.40 (1H,s), 6.20 (3H,s,OCH_3) and 6.89 p.p.m. (3H,s,OCH_3).

M.S. $^{m}/e$ 411 (M^+) (100%), 396 (10%), 352 (50%), 334 (10%), 350 (52%)

Pyrrolizin-3-one (118)

Prepared as described by Flitsch and Newmann[51].

3-Ethoxycarbonylmethylene-3H-pyrrolizine (117)

Prepared by the Wittig reaction of pyrrolizin-3-one (118) and ethoxycarbonylmethylenetriphenyl phosphorane[78].

The pyrrolizin-3-one (1.82g) and an equimolar amount of the phosphorane (5.32g) were refluxed in dry benzene (200ml) for 5 days. Evaporation of the solution gave a red oil which was chromatographed on an alumina column (100g in petrol). Elution with a 9:1 mixture of light petrol/ether removed a single orange band which gave the azafulvene (117) as an orange oil (290 mg, i.e. 10%).

N.m.r. (CCl_4): τ 2.97 (1H,d,J6Hz), 3.05 (1H,d,J3Hz), 3,38 (0.5H,d,J2Hz), 3.48 (0.5H,d,J2Hz), 4.05 (1H,t,J3Hz), 4.20 (1H,s), 4.24 (1H,m), 5.83 (2H,q,OCH_2) and 8.72 p.p.m. (3H,t,CH_3)

The spectrum agreed well with the spectral data of compound (117), provided by W. Flitsch[79].

Dimethyl 5-ethoxycarbonylcycl [3,2,2] azine-6,7-dicarboxylate (119)

The azafulvene (117) (203mg) and a 5-fold excess of DMAD (710mg) were refluxed in toluene solution (50ml) until t.l.c. showed the absence of the azafulvene. Evaporation of the toluene solution gave a red oil which was chromatographed on an alumina column (50g in petrol). The oil was put on

with, and the column eluted with, a 1:1 mixture of benzene/petrol. That separated a small orange band from deep red bands. The orange band was eluted and yielded unchanged azafulvene (117) (16mg). Elution of the column with a 1:1 mixture of benzene/chloroform removed the red bands which yielded a red gum (281mg). The gum was separated into 12 bands by p.l.c. (50% light petrol, 50% ether). The major components were an orange band (azafulvene (117) - 36mg) and a deep red band which gave the cycl[3,2,2]azine (119) (44mg, i.e. 12%) as a red solid. Recrystallisation from petrol gave orange needles m.p. 129 - 130°.

Found: C,61.60; H,4.86; N,4.30%

Required for $C_{17}H_{15}NO_6$ C,61,98; H,4.60; N,4.25%

I.R. ν (C=O) 1717 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 218nm (4.44), 263.5 (4.46), 283 (4.51), 322.5 (3.77) and 470 (3.20).

N.m.r. ($CDCl_3$): τ 2.20 (2H,d,J5Hz), 2.33 (1H,d,J2Hz), 2.42 (1H,d,J2Hz), 5.41 (2H,q,OCH_2), 5.90 (6H,s, 2xOCH_3) and 8.48 p.p.m. (3H,t,CH_3).

M.S. m/e 329 (M^+) (93%), 298 (16%), 285 (22%), 270 (9%), 238 (100%).

The reaction of 3H-3D-pyrrolizine with DMAD

In an attempt to produce both the mono and diadducts containing deuterium two reactions were carried out

simultaneously.

a) 3H-3D-pyrrolizine (80) (350mg) and an equimolar amount of DMAD (426mg) were refluxed in dry toluene (100ml) for 5 hrs. then the solution stood overnight.

b) 3H-3D-pyrrolizine (80) (350mg) and a large excess of DMAD (2.13g) were refluxed in dry toluene (100ml) for 5 hrs. then the solution stood overnight.

The two solutions from (a) and (b) above were evaporated and the products combined and chromatographed on an alumina column (200g in petrol). Elution with a 1:1 mixture of petrol/toluene removed the orange band (the azafulvene) and further elution with toluene removed the red band (diadduct).

The orange band yielded an orange solid and recrystallisation from petrol gave orange needles m.p. 74°. The n.m.r. spectrum was identical to that of compound (110) except that the doublet at τ 3.07 p.p.m. was reduced to 0.5H (5 proton) and the triplet at τ 3.90 p.p.m. was partially collapsed. The spectrum thus indicated a 50% deuterium content of the 5 position of the azafulvene.

The red band yielded the diadduct as a red gum which solidified on standing. The solid was purified by p.l.c. ($CHCl_3$) which yielded the pure diadduct (200mg) as a red solid m.p. 105 - 112°. However, the n.m.r. spectrum of the solid, identical to that of compound (133), showed that the compound contained no deuterium.

The reaction of 3H-3D-pyrrolizine with diethyl acetylenedicarboxylate

3H-3D-pyrrolizine (80)(500mg) and an equimolar quantity of diethyl acetylenedicarboxylate (850mg) were refluxed in dry toluene (100ml) for 5 hrs. then the solution stood overnight. Evaporation of the toluene left a red oil which crystallised on standing. The crystals were filtered off and recrystallised three times from petrol to give orange needles m.p. 84 - 85°. The n.m.r. spectrum of the deutero-azafulvene (123), below, showed 50% D on the 5 position and 25% D on the methylene group. The I.R. and U.V. spectra were identical to those of compound (122).

N.m.r. (CCl_4): τ 2.81 (1H,J6Hz), 3.05 ($^{0.5H}_{0.5D}$,d,J3Hz), 3.41 (1H,d,J6Hz), 3.92 (1H,collapsing t,J3Hz), 4.07 (1H,d,J3Hz), 5.81 (4H, m,2xOCH_2), 6.38 ($^{1.5H}_{0.5D}$,s,methylene) and 8.75 p.p.m. (6H,q,2xCH_3).

M.S. m/e 276 (M^+) (80%) and 203 (100%) compared with 275 (M^+) 68%) and 202 (100%) for the non-deuterated azafulvene (122).

The reaction of 1-methyl-3H-pyrrolizine (51) with diethyl acetylenedicarboxylate

Reactions to prepare the mono and diadducts were carried out simultaneously.

a) 1-methyl-3H-pyrrolizine (51) (595mg) and an equimolar amount of diethyl acetylenedicarboxylate (850mg) were

a) contd

refluxed in dry toluene (100ml) for 5 hrs. then the solution stood overnight.

b) 1-methyl-3H-pyrrolizine (51) (357mg) and an excess of diethyl acetylenedicarboxylate (2.55g) were refluxed in dry toluene (100ml) for 5 hrs. then the solution stood overnight.

Combination and evaporation of the solutions from (a) and (b) above gave a dark red oil which was chromatographed on an alumina column (250g in petrol). Elution with a 1:1 mixture of petrol/toluene brought an orange mass down the column but no clear separation occurred. When the majority of the orange band had eluted (fraction 1), the column was eluted with toluene which removed a deep red band (fraction 2).

Fraction (1) (1.68g) was taken up in boiling petrol and, on cooling, diethyl 1-methyl-3H-pyrrolizin-5-ylmaleate (128) crystallised out as yellow plates (500mg 19%). P.l.c. ($CHCl_3$) on a red gum, obtained by evaporation of the mother liquor, yielded more of the maleate (128) and an inseparable mixture of the azafulvenes (126) and (127) (270mg total, i.e. 12%).

Fraction (2), on p.l.c. (60% $CHCl_3$ 40% C_6H_6), yielded more of the maleate (128) and the cycl[4,2,2]azine derivative (139) (102mg).

The major product of the reaction was the yellow maleate (128) which was crystallised from petrol to give yellow

plates m.p. 110°.

Found: C,66.50; H.6.69; N,4.80%

Required for $C_{16}H_{19}NO_4$ C,66.42; H,6.63; N,4.84%

I..R. ν (C=O) 1700 cm^{-1}

U.V. λ max ($log_{10}\varepsilon$) 215nm(sh), 240 (4.19), 247(sh) and 377 (4.32)

N.m.r. (CCl_4): τ 3.46 (1H,d,J3Hz), 3.93 (1H,d,J3Hz), 3.93 (1H, br.s.), 4.28 (1H,s,maleate), 5.4 - 6.1 (6H,m,CH_2+2xOCH_2), 7.95 (3H,m,CH_3) and 8.71 p.p.m. (6H,q,2xCH_3).

M.S. m/e 289 (M^+) (95%), 244 (50%), 243 (100%), 216 (55%), 215 (96%), 187 (46%), 171 (26%), 142 (72%).

Isomerisation of the maleate (128) to 3-carboethoxy-(carboethoxymethyl) - methylene-7-methyl-3H-pyrrolizine (127)

A solution of the maleate (128) (100mg) in dry toluene (30ml) was refluxed for 30 hrs. Evaporation of the toluene gave a red oil and p.l.c. (80% $CHCl_3$ 20% C_6H_6) on the oil yielded the unchanged maleate (128) (51mg) and the isomeric azafulvene (127) (21mg, i.e. 21%).

The yield of isomeric azafulvene (127) was increased to 62% by refluxing compound (128) in ethanol solution for 18 hrs. Recrystallisation of the azafulvene from light petrol gave orange needles m.p. 57 - 59°.

Found: C,66.50; H,6.47; N,4.90%

Required for $C_{16}H_{19}NO_4$ C,66.42; H6.63; N,4.84%

I.R. ν (C=O) 1727 and 1692 cm^{-1}.

U.V. λ max ($\log_{10}\varepsilon$) 210.5nm (4.22), 235(sh), 346 (4.32) and 432 (3.46)

N.m.r. (CCl_4): τ 2.86 (1H,d,J6Hz), 3.14 (1H,d,J3Hz), 3.41 (1H,d,J6Hz), 4.10 (1H,d,J3Hz), 5.82 (4H, m,2xOCH_2), 6.42 (2H,s,CH_2), 7.90 (3H,s,CH_3) and 8.75 p.p.m. (6H,q,2xCH_3)

M.S. m/e 289 (M^+) (67%), 244 (9%), 216 (100%), 142 (25%)

Tetramethyl 6,7-dihydro-8H-cycl [4.2.2] azine - 5.6.7.8-tetracarboxylate (133)

A solution of 3H-pyrrolizine (525mg, i.e. 5m mole) and DMAD (7.10g, i.e. 50m mole), in dry toluene (100ml), was refluxed for 7 hrs. then stood overnight. Evaporation of the toluene left a dark red oil which was chromatographed on an alumina column (200g in petrol). The oil was put onto the column in a small amount of toluene and the column eluted with a 1:1 mixture of petrol/toluene. An orange band separated from the red mass and was eluted. Evaporation yielded the azafulvene (110) (100mg, i.e. 8%). Further elution with toluene removed a red band from the column, leaving pink and brown bands. Evaporation of the red solution gave the cyclazine derivative (133) as a deep red gum which solidified on standing (1.144g, i.e. 59%). The cyclazine was virtually pure but could be further purified by p.l.c. (35% C_6H_6 65% $CHCl_3$), or recrystallisation from CCl_4/petrol, to give a bright red solid m.p. 105 - 112°.

Found: C,58.60; H,5.19; N,3.70%

Required for $C_{19}H_{19}NO_8$ C,58.60; H,4.90; N,3.60%

I.R. ν (C=O) 1725 and 1695 cm^{-1}.

U.V. λ max ($\log_{10}\varepsilon$) 213nm (4.12), 235(sh), 334 (4.25) and 440 (3.31)

N.m.r. (CCl_4): τ 2.95 (1H,d,J6Hz), 3.45 (1H,d,J6Hz), 4.15 (2H,s), 5.22 (1H,d,J2Hz), 5.93 (1H,d,J12Hz), 6.1 - 6.5 (12H,m,4xOCH_3), 6.63 (0.5H,d,J2Hz) and 6.83 p.p.m. (0.5H,d,J2Hz)

M.S. m/e 389 (M^+) (10%), 357 (27%), 330 (9%), 298 (13%) 270 (100%)

Tetramethyl 6,7-dihydro-3-methyl-8H-cycl [4.2.2] azine - 5,6,7,8-tetracarboxylate (138)

Prepared and chromatographed as described for compound (133) above. 1-methyl-3H-pyrrolizine (51) (357mg) and DMAD (4.26g) gave 633mg (52%) of the cyclazine (138) as a red oil which crystallised on standing. Recrystallisation gave red needles m.p. 153 - 162° (from CCl_4/petrol).

Found: C,59.90; H,5.22; N,3.40%

Required for $C_{20}H_{21}NO_8$ C,59.55; H,5.21; N,3.47%

I.R. ν (C=O) 1730 and 1690 cm^{-1}.

U.V. λ max ($\log_{10}\varepsilon$) 214.5nm (4.12), 235 (4.06) 332 (4.24) and 437 (3.33)

N.m.r. ($CDCl_3$): τ 3.15 (1H,s), 4.04 (2H,s), 5.06 (1H,d,J2Hz), 5.75 (1H,d,J12Hz), 6.1 - 6.5 (12H,m,4xOCH_3), 6.52 (0.5H,d,J2Hz), 6.72 (0.5H,d,J2Hz) and

N.m.r. (contd)

7.94 p.p.m. (3H,s).

M.S. $^{m}/e$ 403 (M^{+}) (4%), 371 (13%), 344 (4%), 284 (100%)

Tetraethyl 6,7-dihydro-3-methyl-8H-cycl[4,2,2] azine - 5,6,7,8-tetracarboxylate (139)

Prepared in the reaction of 1-methyl-3H-pyrrolizine with diethyl acetylenedicarboxylate (page 126).

1-methyl-3H-pyrrolizine (357mg) and excess diethyl acetylenedicarboxylate (2.550g) gave 102mg (7%) of the cyclazine (139) as a red oil which would not crystallise after 3 purifications by p.l.c.

N.m.r. (CCl_4): τ 3.25 (1H,s), 4.13 (2H,s), 5.26 (1H,d,J2Hz), 5.4 - 6.2 (9H,m,H+4xOCH_2), 6.63 (0.5H,d,J2Hz), 6.83 (0.5H,d,J2Hz), 7.95 (3H,s,CH_3) and 8.7 p.p.m. (12H,m,4xCH_3).

Dimethyl 3,4,6,7-tetrahydro-7,7-diphenylcycl[3,2,2] azine - 5,6-dicarboxylate (135)

A solution of the cycl [3,2,2] azine derivative (115) (80mg) in methanol, with Pd/C catalyst (30mg of 10%), was hydrogenated at atmospheric pressure and temperature until the uptake of hydrogen had ceased. The catalyst was filtered off and the methanol evaporated to give the almost pure tetrahydrocyclazine (135). Recrystallisation from aqueous ethanol gave cream needles (80mg, i.e. 97%) m.p. 189 - 190°.

Found: C,75.40; H,5.65; N,3.20%

Required for $C_{26}H_{23}NO_4$ C,75.50; H,5.60; N,3.40%

I.R. ν (C=O) 1725 and 1690 cm^{-1}.

U.V. λ_{max} ($log_{10}\varepsilon$) 211 (4.31) and 301.5 (4.19)

N.m.r. ($CDCl_3$): τ 2.75(10H, br.s.), 3.58 (1H,d,J3Hz), 4.09 (1H,d,J3Hz), 5.34 (1H,s), 6.21 (3H,s,OCH_3), 6.55 (2H,m,CH_2) and 6.92 p.p.m. (5H,m,CH_2+OCH_3)

M.S. m/e 413 (M^+) (100%), 398 (38%), 354 (76%) 336 (69%), 322 (26%)

Tetramethyl 3,4,6,7-tetrahydro-8H-cycl[4,2,2]azine - 5,6,7,8-tetracarboxylate (136)

A solution of the cycl[4,2,2]azine (133) (396mg) in methanol (40ml), with Pd/C catalyst (100mg of 10%), was hydrogenated at atmospheric pressure and temperature until the uptake of hydrogen had ceased. The catalyst was filtered off and the methanol evaporated to leave a light brown oil. P.l.c. (75% $CHCl_3$ 25% C_6H_6) separated the oil into 5 components, the major component being the tetrahydro-8H-cycl[4,2,2] azine (136) (200mg, i.e. 50%). Recrystallisation from petrol gave compound (136) as pale yellow plates m.p. 115 - 116°.

Found: C,58.40; H,5.60; N,3.60%

$C_{19}H_{21}NO_8$ requires C58.30; H,5.41; N,3.58%

I.R. ν (C=O) 1730 and 1690 cm^{-1} .

U.V. λ max ($\log_{10}\varepsilon$) 207nm(sh), 213 (3.95) and 283 (4.33)

N.m.r. ($CDCl_3$): τ 3.7 (1H,m), 4.1 (1H,m), 5.12 (1H,d,J2Hz), 5.72 (1H,d,J12Hz), 6.0 - 6.6 (15H,m,CH_2+H+4xOCH_3), and 7.15 p.p.m. (2H,t,CH_2)

M.S. m/e 391 (M^+) (12%), 359 (38%), 332 (15%), 300 (13%), 272 (100%)

Tetramethyl 6,7-dihydro-1,2-dimethyl-8H-cycl[4.2.2]azine-5,6,7,8-tetracarboxylate (140)

A solution of 1,2-dimethyl-3H-pyrrolizine (87) (400mg) and a 10-fold excess of DMAD (4.26g), in dry toluene (100ml) was refluxed for 5 hrs. then stood overnight. Evaporation of the toluene gave a red oil and when the oil was dissolved in toluene, for chromatography, a yellow solid (compound (131)) precipitated out. The solid was filtered off and the remaining red solution chromatographed, as described in the preparation of compound(133) above. The cyclazine (140) was obtained as a red oil which crystallised on standing. Recrystallisation, from ether, gave a red solid m.p. 151 - 152° (191mg, i.e. 15%).

Found: C,60.30; H,5.97; N,3.40%

Required for $C_{21}H_{23}NO_8$ C,60.40; H,5.60; N,3.36%

I.R. ν (C=O) 1730 and 1690 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 214.5nm (4.23), 240(sh), 356 (4.29) and 447 (3.25)

N.m.r. ($CDCl_3$): τ 2.97 (1H,d,J6Hz), 3.38 (1H,d,J6Hz), 5.05 (1H,d,J4Hz), 5.41 (1H,d,J4Hz), 5.67 (1H,t,J4Hz)

N.m.r. contd

6.28 (3H,s,OCH_3), 6.44 (9H,s,3xOCH_3),
8.08 (3H,s,CH_3) and 8.22 p.p.m. (3H,s,CH_3)

M.S. m/e 417 (M^+) (16%), 385 (25%), 358 (5%), 326 (12%),
298 (100%)

The yellow solid, obtained in 48% yield from the above reaction, was tetramethyl 1,2-dimethyl-3H-pyrrolizin-3,5-yldimaleate (131). Recrystallisation from benzene gave yellow plates m.p. 166° (Dec).

Found: C,60.40; H,5.51; N,3.40%

Required for $C_{21}H_{23}NO_8$ C60.40; H,5.60; N,3,36%

I.R. ν(C=O) 1720 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 209.5nm (4.24), 240.5 (4.27),
247(sh) and 382 (4.21)

N.m.r. ($CDCl_3$): τ 3.49 (1H,d,J3Hz), 4.01 (1H,d,J3Hz),
4.12 (1H,s) and 4.26 (1H,s) for maleate
protons, 4.73 (1H,br.s.), 6.08 (3H,s,OCH_3),
6.30 (9H,m,3xOCH_3) and 8.05 p.p.m. (6H,s,2xCH_3)

Irradiation of the spectrum at τ 8.05 p.p.m. caused the singlet at τ 4.73 p.p.m. to sharpen up. Hence the proton on the 3 position was coupled to one of the ring methyl groups.

M.S. m/e 417 (M^+) (37%), 385 (22%), 358 (10%), 326 (22%),
298 (100%)

Isomerisation of the dimaleate (131) into the cyclazine (140)

A solution of the dimaleate (131) (100mg) in toluene (25ml)

was refluxed for 3 days. Evaporation of the toluene gave a red oil which was separated by p.l.c. (80% $CHCl_3$ 20% C_6H_6). One of the components separated was shown by t.l.c. to be the cyclazine (140) but the major component was the unchanged dimaleate (131).

In a second isomerisation attempt the dimaleate (131) (62mg) was stood in methanol solution overnight. Evaporation of the methanol gave a red oil and p.l.c. gave a red solid m.p. 144 - 151° (from ether). The solid was identical in I.R. and mass spectra and undepressed in mixed melting point with the cyclazine (140) prepared directly.

Yield: 40mg (i.e. 60%) of the cyclazine (140).

Tetramethyl 8H-cycl [4.2.2] azine - 5.6.7.8-tetracarboxylate (154)

a) Equimolar quantities of the hydrocyclazine (133) (264mg) and N-bromosuccinimide (121mg), in chloroform solution, were stirred at room temperature for 3 hrs. The solution was washed 3 times with water, dried (Na_2SO_4), and evaporated to leave a dark red oil. P.l.c. on the oil (80% ether, 20% petrol) separated at least 6 compounds. Some were shown by their n.m.r. spectra to be brominated products but the major product, a brilliant red oil, was shown by n.m.r. and mass spectra to be the 8H-cycl[4,2,2] azine (154).

Yield: 37mg, i.e. 14%.

b) The cyclazine derivative (133) (800mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (D.D.Q) (940mg) were refluxed

b) contd

in dry benzene solution (100ml) for 7 hrs. and then the mixture stood overnight. After filtering off the solids the solution was evaporated to leave a black tar. The tar was chromatographed on an alumina column (25g in petrol) and elution with a 9:1 mixture of toluene/chloroform separated, and removed, a deep red band. The band yielded the 8H-cycl[4,2,2] azine (154) as a deep red oil which solidified on standing (515mg, i.e. 64%). Recrystallisation from CCl_4 gave a bright red solid m.p. 150°.

Found: C,59.0; H,4.80; N,3.70%

Required for $C_{19}H_{17}NO_8$ C,58.90; H,4.43; N,3.62%

I.R. ν (C=O) 1735 and 1705 cm^{-1}.

U.V. λ max ($\log_{10}\varepsilon$) 206.5nm (4.01), 220(sh), 287 (4.35), 381 (3.54) and 480 (3.47)

N.m.r. (CCl_4): τ 2.5 (1H,d,J6Hz),3.05 (1H,d,J6Hz), 3.38 (1H,d,J3Hz), 3.51 (1H,d,J3Hz), 4.07 (1H,s), 6.15 (9H,m,3xOCH_3) and 6.53 p.p.m. (3H,s,OCH_3)

M.S. $^m/_e$ 387 (M^+) (9%) and 328 (100%)

<u>Tetramethyl 3,4-dihydro-8H-cycl [4.2.2] azine-5.6.7.8-tetracarboxylate</u> (156)

A solution of the 8H-cyclazine (154) (315mg) in 95% ethanol (50ml), with Pd/C catalyst (100mg of 10%), was hydrogenated at atmospheric pressure and temperature. When the solution had

discharged its bright red colour, and the uptake of hydrogen had slowed down considerably, the catalyst was filtered off, and the ethanol evaporated, to leave a light brown oil. P.l.c. (50% $CHCl_3$ 50% C_6H_6) separated the oil into 3 bands, the major (yellow) band being the hydrogenated product (156) (180mg, i.e. 57%). The product was crystallised from petrol to give white needles m.p. 112 - 113°.

Found: C,58.90; H,4.62; N,3.80%

Required for $C_{19}H_{19}NO_8$ C,58,60; H,4.90; N,3.60%

I.R. ν (C=O) 1725 and 1697 cm^{-1}.

U.V. λ max ($\log_{10}\varepsilon$) 204.5 (4.05), 258.5 (4.36), 317.5 (3.98), and 355 (4.05)

N.m.r. (CCl_4): τ 3.55 (1H,d,J4Hz), 3.96 (1H,d,J4Hz), 4.45 (1H,s), 6.1 - 6.6 (14H,m,CH_2+4xOCH_3) and 7.04 p.p.m. (2H,t,CH_2)

M.S. m/e 389 (M^+) (11%), 357 (3%), 330 (100%), 298 (11%), 270 (12%)

The photochemical reaction of 3H-pyrrolizine with DMAD

3H-pyrrolizine (550mg, i.e. 5m mole), acetophenone (1.0g) and DMAD (7.1g, i.e. 50m mole) were dissolved in dry benzene (1L). The solution was purged with nitrogen for 30 mins. before irradiation (pyrex sleeve) for 7 hrs. Evaporation of the resulting solution gave a brown oil which was chromatographed on an alumina column (300g in

petrol). The oil was put onto the column in petrol/toluene solution and the column eluted as shown in the table below.

Eluant	Fraction	Colour	Yield mg	Compound
9:1 Petrol/Tol.	1	Pale yellow	1,050	Acetophenone
	2		347	
1:1 Petrol/Tol.	3	Orange	153	(110)
	4		38	
	5	Pale yellow	86	(159)
	6		188	
Toluene	7	Red	89	(133)
	8		64	
	9	Yellow	295	(161) & (162)
1:1 Tol./$CHCl_3$	10	Black	350	Polymer

Fraction (1) contained acetophenone and excess 3H-pyrrolizine.

Fractions (2), (3) and (4) gave virtually pure azafulvene (110) which, on recrystallisation from petrol, gave orange needles m.p. 76° (538mg, i.e. 42%).

Fractions (5) and (6) were combined and p.l.c. (35% ether, 65% petrol) gave the cyclobutene derivative (159) as a yellow gum (60mg, i.e. 5%) which would not crystallise (Data below).

Fractions (7) and (8) gave the cyclazine (133) (153mg, i.e. 8%).

P.l.c. on fraction (9) (40% petrol 60% ether) yielded the

fumarate diadduct (161) (63mg, i.e. 3%), as a red oil, and the maleate diadduct (162) as a yellow solid m.p. 155-160° (from CCl_4/petrol). The yields of the diadducts were variable and compound (162) was obtained in yields of 0 - 14%.

Dimethyl 1-azatricyclo[5.3.$0^{1,7}$.$0^{3,6}$]deca-4.7.9-triene-4.5-dicarboxylate (159)

Obtained from the above reaction as a yellow gum (60mg, i.e. 5%).

Found: C,63.15; H,5.30; N,5.65%

$C_{13}H_{13}NO_4$ requires C,63.20; H,5.70; N,5.20%

I.R. ν(C=O) 1710 cm^{-1}.

U.V. λ max ($\log_{10}\varepsilon$) 206nm(sh) and 219 (4.11)

N.m.r. (CCl_4): τ 3.65 (1H,m), 3.99 (1H,t,J3Hz), 4.20 (1H,d,J3Hz), 5.9 (4H,br.d) and 6.27 p.p.m. (6H,s,2xOCH_3)

M.S. m/e 247 (M^+) (39%), 216 (16%), 188 (53%), 143 (50%), 129 (30%), 115 (66%), 105 (100%)

Dimethyl 1-aza-4.5-dicarbomethoxytricyclo[5.3.$0^{1,7}$.$0^{3,6}$]deca-4.7.9-triene-10-ylfumarate (161)

Obtained from the above reaction as a red oil (3%).

I.R. ν(C=O) 1710 cm^{-1}

N.m.r. (CCl_4): τ 3.39 (1H,s,fumarate), 3.70 (1H,d,J4Hz), 4.07 (1H,d,J4Hz) and 5.6 - 6.5 p.p.m. (16H,m)

M.S. m/e 389 (M^+) (70%), 357 (52%), 342 (57%), 330 (61%), 298 (37%), 270 (61%), 247 (52%), 215 (100%)

Dimethyl 1-aza-4,5-dicarbomethoxytricyclo[5.3.0^{1,7},0^{3,6}]deca-4,7,9-triene-10-ylmaleate (162)

Obtained from the above reaction (0-14%) yield as a yellow solid m.p. 155 - 160° (CCl_4/petrol).

Found: C58,60; H,4.70; N,3.70%

$C_{19}H_{19}NO_8$ requires C58.60; H,4.90; N,3.60%

I.R. ν (C=O) 1725, 1710 and 1700 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 221nm (4.15) and 341 (4.30)

N.m.r. ($CDCl_3$): τ 3.57 (1H,d,J4Hz), 3.88 (1H,d,J4Hz), 4.12 (1H,s,maleate), 5.8 (4H,br.s), and 5.9 - 6.6 p.p.m. (12H,m,4xOCH_3).

M.S. m/e 389 (M^+) (100%), 357 (67%), 342 (79%), 330 (55%), 298 (30%), 270 (68%), 247 (17%), 215 (68%)

The thermal reaction of 3,3-dimethyl-3H-pyrrolizine with DMAD

a) 3,3-dimethyl-3H-pyrrolizine (800mg, i.e. 6m mole) and DMAD (850mg, i.e. 6m mole) were refluxed in methanol (100ml) solution for 22 hrs. Evaporation of the solution gave a dark red oil which was chromatographed on an alumina column (75g in petrol). The oil was put onto the column in toluene/petrol and the column eluted as shown in the table below.

Eluant	Fraction	Colour	Yield (mg)	Compound
9:1 Petrol/Tol.	1	Yellow	20	Pyrrolizine
4:1 Petrol/Tol.	2	Orange	364	(164)
	3		97	
Toluene		Yellow		
	4		235	(163)
$CHCl_3$	5	Red	117	Polymer

Dimethyl 3,3-dimethyl-3H-pyrrolizin-5-ylfumarate (164)

P.l.c. on fractions (2) and (3) from the column (50% petrol 50% ether) gave the fumarate (164) as a red oil (423mg, i.e. 26%).

Found: C,65.60; H,6.58; N,5.10%

$C_{15}H_{17}NO_4$ requires C,65.42; H,6.23; N,5.09%

I.R. ν(C=O) 1710 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 209nm (4.19), 287 (3.88) and 391 (3.25)

N.m.r. (CCl_4): τ 3.13 (1H,s,fumarate), 3.62 (1H,d,J6Hz), 4.00 (2H,br.d.J5Hz), 4.26 (1H,d,J4Hz), 6.35 (3H,s,OCH_3), 6.50 (3H,s,OCH_3) and 8.69 p.p.m. (6H,s,CH_3)

M.S. $^m/_e$ 275 (M^+) (48%), 260 (10%), 243 (16%), 215 (64%) 200 (55%), 184 (26%), 156 (100%)

Dimethyl 3,3-dimethyl-3H-pyrrolizin-5-ylmaleate (163)

P.l.c. on fraction (4), from the column (60% petrol 40% ether) gave the pyrrolizin-5-ylmaleate (163) as a yellow oil (78mg, i.e. 5%). Repeated p.l.c. did not purify the oil because it rapidly decomposed and isomerised to the fumarate isomer (164).

I.R. ν (C=O) 1725 and 1705 cm^{-1}

N.m.r. (CCl_4): τ 3.65 (1H,d,J6Hz), 3.65 (1H,d,J4Hz), 3.86 (1H,d,J6Hz), 3.87(1H,s,maleate), 4.15 (1H,d,J4Hz), 6.20 (3H,s,OCH_3), 6.32 (3H,s,OCH_3), and 8.35 p.p.m. (6H,s,2xCH_3)

M.S. m/e 275 (M^+) (49%), 260 (12%), 243 (16%), 215 (65%), 200 (64%), 184 (26%), 156 (100%)

b) 3,3-dimethyl-3H-pyrrolizine (530mg) and DMAD (570mg) were refluxed in dry toluene (100ml) for 56 hrs. and stood at room temperature for 108 hrs. Evaporation of the solution, and chromatography as described in reaction (a) above, gave the pyrrolizin-5-ylfumarate (164) (51mg, i.e. 5%).

The photochemical reaction of 3,3-dimethyl-3H-pyrrolizine with DMAD

3,3-dimethyl-3H-pyrrolizine (665mg, i.e. 5m mole), DMAD (7.10g, i.e. 50m mole) and acetophenone (1.0g) were dissolved in dry benzene (1L). After 30 mins. purging with nitrogen, the solution was irradiated for 7 hrs. through a pyrex sleeve. Evaporation of the resulting solution gave a brown oil which was chromatographed on an alumina column (240g in petrol). The oil was put onto the column in a small amount of toluene/petrol and the column eluted with petrol until acetophenone (and excess pyrrolizine) had ceased to be eluted. Elution with a 1:1 mixture of petrol/toluene, followed by toluene, removed a yellow solution, and evaporation of that solution gave the cyclobutene derivative (165). Two p.l.c's were necessary to purify the crude product (a) 60% $CHCl_3$, 40% C_6H_6 and, (b) 70% ether, 30% petrol. The pure product (363mg, i.e. 26%) was obtained

as a yellow gum which could not be induced to crystallise.

Dimethyl 1-aza-2,2-dimethyltricyclo [5,3,$0^{1,7}$,$0^{3,6}$] deca-4,7,9-triene-4,5-dicarboxylate (165)

Obtained in 26% yield from the photochemical reaction of DMAD with 3,3-dimethyl-3H-pyrrolizine, above.

Found: C,65.60; H,6.00; N,4.90%

$C_{15}H_{17}NO_4$ requires C65.42; H,6.23; N,5.09%

I.R. ν (C=O) 1695 cm^{-1}

U.V. λ max ($log_{10}\varepsilon$) 206nm(sh) and 218 (4.12)

N.m.r. (CCl_4): τ 3.67 (1H,m), 4.00 (1H,t,J3Hz), 4.23 (1H,d,J3Hz), 5.85 (1H,d,J5Hz-cyclobutene H), 6.1 - 6.3 (7H,m,H+2xOCH_3), 8.52 (3H,s,CH_3) and 8.60 p.p.m. (3H,s,CH_3).

M.S. m/e 275 (M^+) (48%), 260 (95%), 243 (24%), 216 (44%) 184 (88%), 156 (56%), 142 (36%), 133 (100%)

Attempted ring expansion of the cyclobutene derivative (165)

a) Thermal expansion

The cyclobutene derivative (165) (127mg) was transferred by ether to a small bore (5mm) glass tube and maintained under a nitrogen blanket by means of a capillary nitrogen inlet. The tube was heated to 180 - 200° in an oil bath (90 mins) then, after cooling, it was crushed and the product mixture extracted with chloroform. Evaporation of the chloroform solution gave a black tar which was separated by p.l.c. (50% petrol 50% ether). Two components

a) contd

were obtained from the p.l.c., the unchanged cyclobutene (165) (27mg, i.e. 21%) and the pyrrolo [1,2-a] azepine (166) (77mg, i.e. 61%).

Dimethyl 5,5-dimethyl-5H-pyrrolo [1,2-a] azepine-7,8-dicarboxylate (166)

Obtained in 61% yield, from the above reaction, as a pale yellow gum which could not be induced to crystallise.

Found: C65,40; H,6.36; N,4.80%

$C_{15}H_{17}NO_4$ requires C65.42; H,6.23; N,5.09%

I.R. ν (C=O) 1705 cm^{-1}

U.V. λ max ($log_{10}\varepsilon$) 205nm (4.09), 227(sh), 247.5 (3.76) 283 (3.71) and 366 (4.07)

N.m.r. (CCl_4): τ 3.12 (1H,m), 3.46 (1H,m), 3.78 (1H,t,J3Hz), 2.29 (1H,s), 3.66 (1H,s), 6.28 (3H,s,OCH_3), 6.36 (3H,s,OCH_3) and 8.39 p.p.m. (6H,s,2xCH_3)

M.S. m/e 275 (M^+) (45%), 260 (100%), 243 (37%), 216 (29%) 184 (69%), 156 (37%)

b) Attempted photochemical ring opening

A solution of the cyclobutene derivative (165) (363mg) in redistilled cyclohexane (1L) was purged with nitrogen for 30 mins. then irradiated, through a pyrex sleeve, for 13 hrs. T.l.c. showed nothing but polymer build-up and, after 13 hrs., the solution was cloudy due to polymer deposition. Evaporation of the solution gave a brown gum and p.l.c.

b) contd

on this gum (50% ether 50% petrol) gave only two identifiable compounds, the unchanged cyclobutene derivative (165) (21mg, i.e. 6%) and its dimer (168) (55mg, i.e. 15%). Recrystallisation of the dimer from light petrol gave a white solid m.p. 64 - 67°.

Found: C,66,80; H,7.10; N,4.70%

$C_{30}H_{34}N_2O_8$ requires C,65.42; H,6.23; N,5.09%

I.R. ν (C=O) 1720 cm^{-1}

U.V. λ max ($\log_{10}\varepsilon$) 206nm(sh) and 221 (4.16)

N.m.r. (CCl_4): τ 3.60 (2H,m), 3.97 (2H,t,J3Hz), 4.40 (2H,d,J3Hz), 6.20 (6H,s,OCH_3), 6.45 (2H,d,J6Hz), 6.70 (2H,d,J6Hz), 6.60 (6H,s,OCH_3), 8.54 (6H,s,CH_3) and 8.78 p.p.m. (6H,s,CH_3)

M.S. m/e 550 (M^+) (46%), 519 (5%), 491 (9%), 459 (5%), 431 (6%), 326 (52%), 204 (60%), 133 (100%)

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