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APPROACHES TO THE SYNTHESIS OF

AZONIA-AZULENES

by

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in partial fulfilment of the requirements for  
the Degree of Doctor of Philosophy

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## S U M M A R Y

Two approaches to the azonia-azulenium system are described.

In Part I the preparation of a number of azepinoindoles by the thermal decomposition of 2-azido-diphenylmethanes is described. The usual products were 10H-azepino[1,2- $\alpha$ ]indoles and the compound previously reported as 11H-azepino[1,2- $\alpha$ ]indole has been shown to exist in the tautomeric 10H-form. In one case steric obstruction led to the formation of a 6H- and an 8H-azepinoindole, and when a 2'-methoxyl group was present in the azide the major products were acridines and acridans. A mechanism is proposed which satisfactorily accounts for the observed products.

1-(2-Azidophenyl)-1-phenylethanol decomposed to give some 2-acetyldiphenylamine showing another nitrene insertion pathway. Photolytic decomposition of 2-azidodiphenylmethane gave the azo-compound. Azepino[1,2- $\alpha$ ]indol-8-one has been prepared in good yield and converted into hydroxy- and ethoxyazepino[1,2- $\alpha$ ]indolium salts.

In Part II the reduction of indolizine and some substituted indolizines by dissolving metals is shown to



give dihydro- and tetrahydroindolizines. Attempts to add carbenes to dihydroindolizines and thus to produce the 5,7 ring system of the azonia-azulenes by ring expansion were unsuccessful.



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

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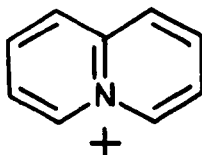
## *INTRODUCTION*

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## I N T R O D U C T I O N

An extensive study of the chemistry of salts of the quinolizinium ion (1) has been conducted at this University by Gurnos Jones and co-workers.<sup>1-8</sup>

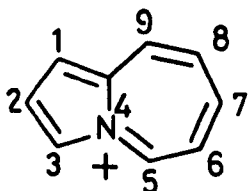


(1)

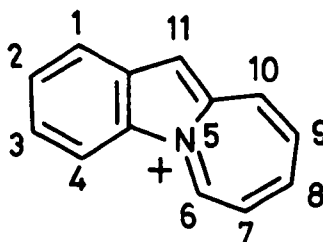
As a ten  $\pi$ -electron aromatic molecule carrying a delocalised positive charge the usual reactions of the quinolizinium system are with nucleophiles<sup>9,10</sup> although when the molecule is substituted with a strongly electron donating group cases where electrophilic substitution occurs have been reported.<sup>4-8</sup>

The success of this work has encouraged investigations into the synthesis and reactions of iso- $\pi$ -electronic analogues of the quinolizinium system and the aim of the work presented in this thesis is to synthesise the unsubstituted azonia-azulenium systems (2) and (3).





(2)

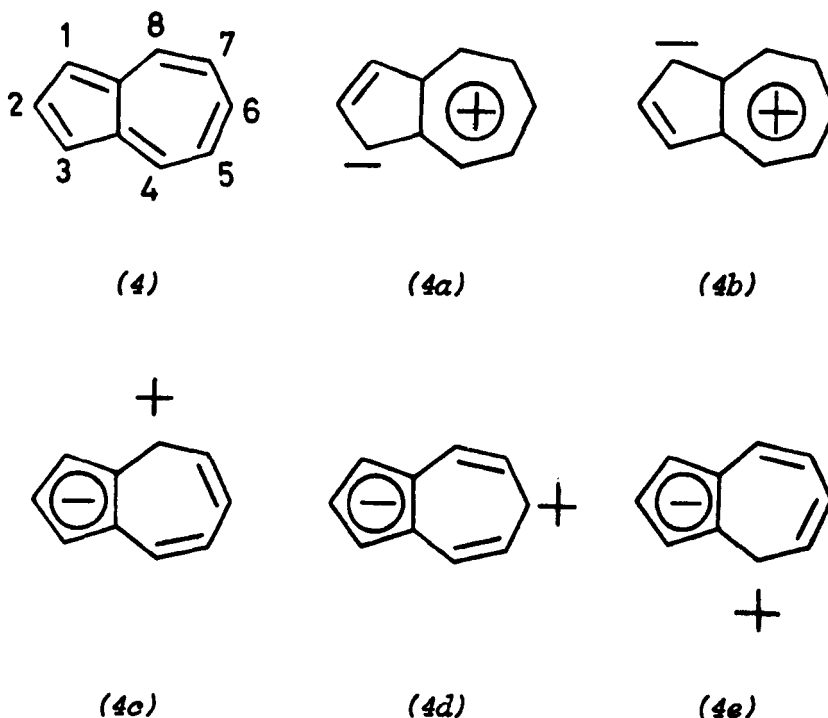


(3)

These systems will be referred to generally as "azonia-azulenium salts" but specific compounds will be given their systematic names which, for salts of the ions (2) and (3), are pyrrolo-[1,2-*a*]azepinium and azepino[1,2-*a*]indolium salts respectively.

Non-benzenoid aromatic hydrocarbons do not show close resemblance to their benzenoid analogues. The differences between azulene (4) and naphthalene, its iso- $\pi$ -electronic benzenoid analogue, have been explained<sup>11,12</sup> in terms of each ring tending to acquire a sextet of  $\pi$ -electrons or, in terms of simple resonance theory, by a contribution to the overall structure of the molecule by the dipolar forms (4a - e).





Thus azulene undergoes electrophilic substitution in the five-membered ring at position 1(3) and nucleophilic substitution in the seven-membered ring at positions 4(8) and 6.

For the five possible aza-analogues of azulene it has been predicted,<sup>13</sup> by a perturbation method based on the Hückel LCAO molecular orbital theory, that the replacement of a carbon atom in azulene by a nitrogen atom will have little or no effect on the orientation of ionic substitution since the large variations in reactivity between the different positions in azulene effectively mask the directive effect of the nitrogen atom.



However, the replacement of an azulene carbon atom by a positively charged nitrogen atom to give the azonia-azulenium system can be expected to have a much greater effect and whereas with azulene electrophilic and nucleophilic substitution take place with equal ease, the main reactions of the azonia-azulenium system can be expected to be with nucleophiles, by analogy with the quinolizinium system.

Considering the dipolar forms (4a - e) of azulene it can be anticipated that the azonia-azulenium system (2) will undergo nucleophilic attack at positions 5, 7 and 9 with greater ease than azulene, and that if electrophilic attack proves possible it will take place at positions 1 or 3.

Previous approaches to aza- and azonia-azulenes are outlined in the following review. Thereafter the work described in this thesis is divided into two parts:

Part I describes an investigation into the thermal decomposition of *o*-azidodiphenylmethanes and attempts to prepare the azonia-azulenium system (3) from certain of these decomposition products.

Part II concerns an approach to the azonia-azulenium system (2) starting from indolizines.



*REVIEW*

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## REVIEW

### AZA-AZULENES

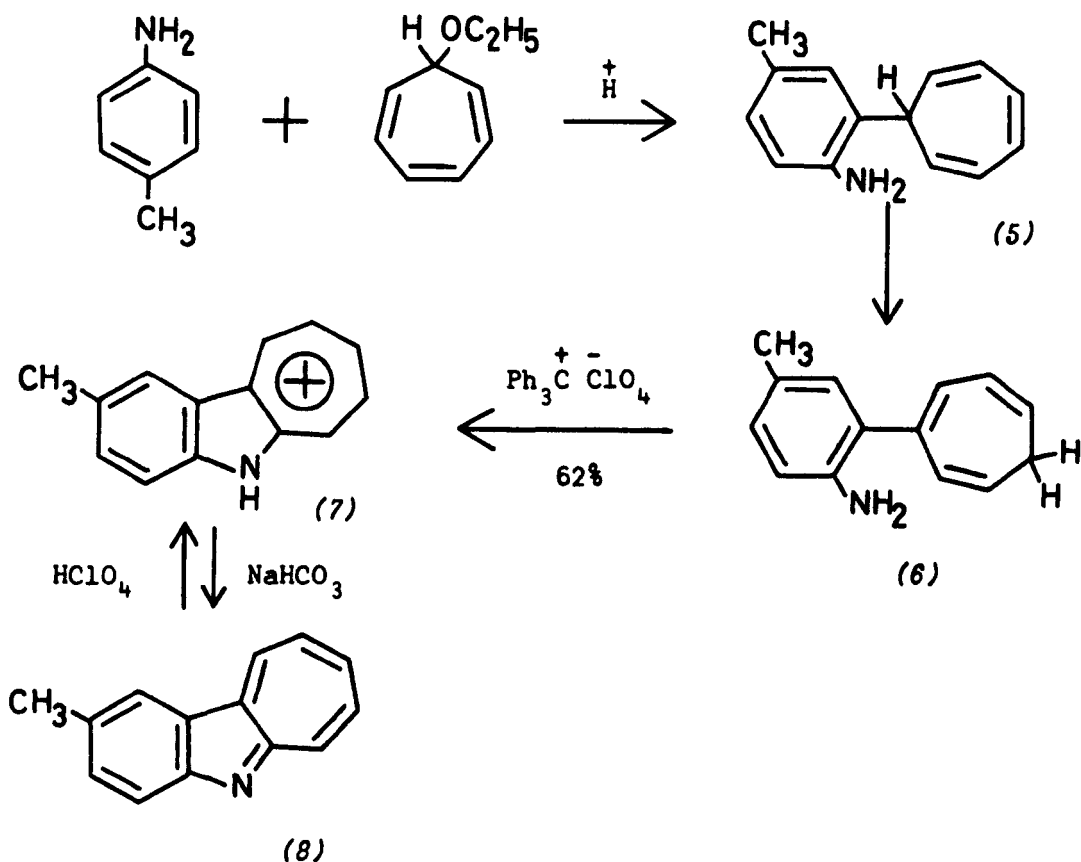
There are no reports of aza-analogues of azulene in the literature prior to 1952; but four of the five possible aza-azulenes where the nitrogen atom is not in a bridgehead position have since been reported.

#### 1-Aza-azulene

Derivatives of 1-aza-azulene, notably 1-azabenz[*b*]-azulene,<sup>14-17</sup> 1-azadibenz[*b,h*]azulene,<sup>16</sup> 1-azadibenz[*b,f*]azulene<sup>18</sup> and 1-azanaphth[*b*]azulene<sup>19</sup> were reported in the early 1950's. These were variously described as purple, deep blue or violet compounds.

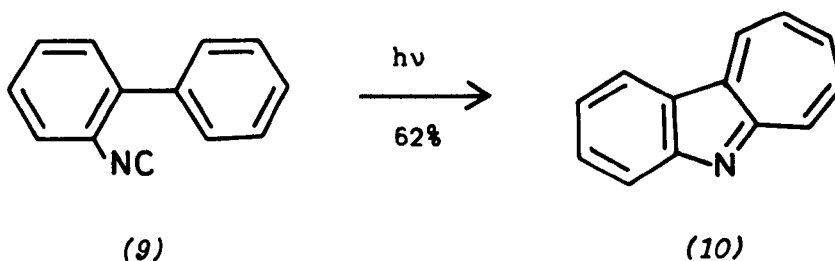
Two recent syntheses which provide simple, high yield routes to 1-azabenz[*b*]azulenes are by the hydride abstraction reactions of *o*-tropylanilines<sup>20</sup> (Scheme 1) and by the photolysis of *o*-biphenylisocyanide<sup>21</sup> (Scheme 2).



SCHEME 1

The tropylation of *p*-toluidine gave 2-(7-tropyl)-*p*-toluidine (5) which isomerised on reduced pressure distillation giving 2-(3-tropyl)-*p*-toluidine (6). Treatment of (6) with 2-3 molar equivalents of triphenylmethyl perchlorate in methylene chloride gave the tropylium perchlorate (7) which on basification gave deep violet crystals of the 1-azabenz[b]azulene (8). The long wavelength absorption in the electronic spectrum was at 490 nm ( $\log_{10} \epsilon$  2.64).

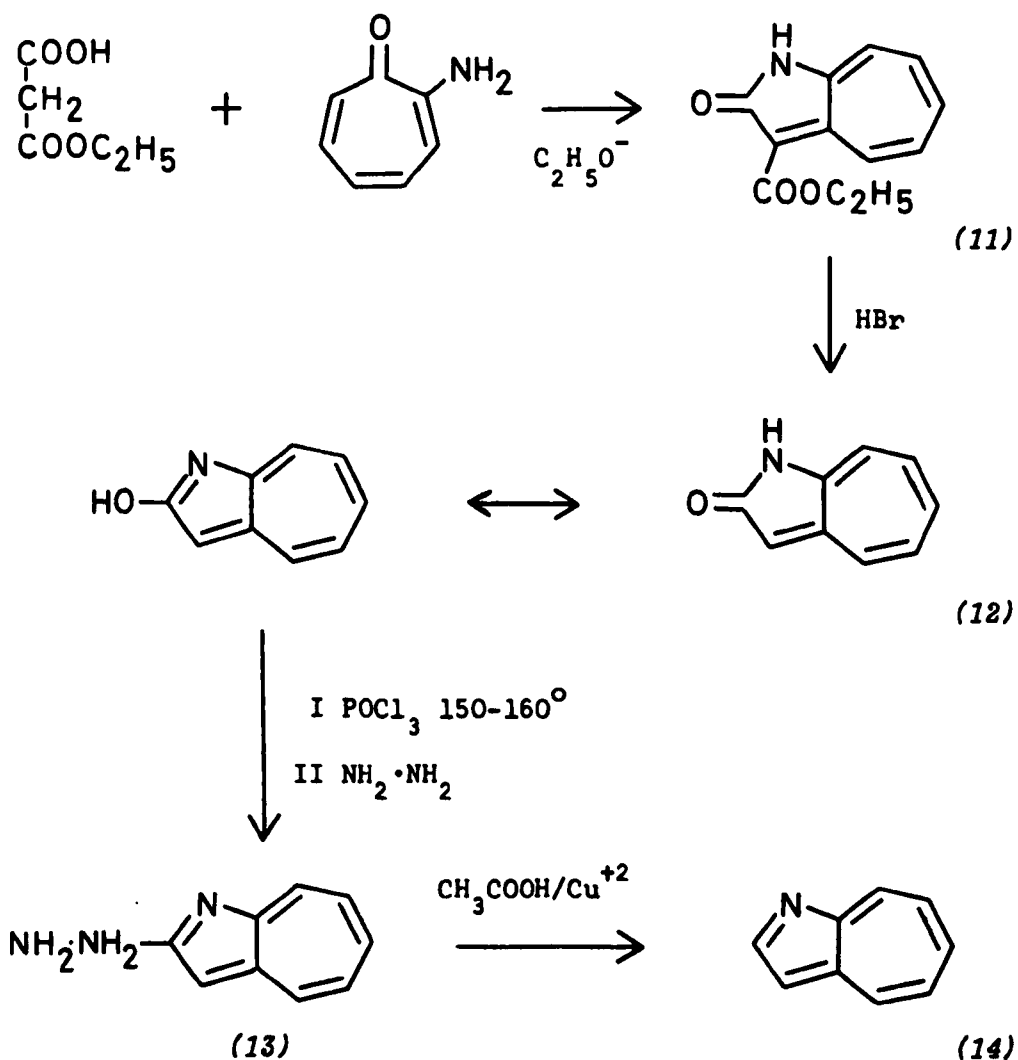


SCHEME 2

Photolysis of *o*-biphenylisocyanide (9) in hexane gave 1-azabenz[*b*]azulene (10). This reaction is interesting in that it was reported as the first example of an aromatic ring expansion brought about by insertion of an isocyanide carbon atom. It was suggested that irradiation developed electrophilic carbenoid properties in the isocyanide function.

Unsubstituted 1-aza-azulene was prepared in 1954 by Nozoe and co-workers<sup>22,23</sup> as detailed in Scheme 3.



SCHEME 3

The condensation of ethyl malonate with 2-aminotroponone in the presence of sodium ethoxide gave, in 83% yield, the carbethoxy-*-aza-azulenone* (11) which on heating with hydrobromic acid at



120 - 130° gave (12). Heating (12) in a sealed tube with phosphorus oxychloride gave 2-chloro-1-aza-azulene in 92% yield and reaction of the chloro-compound with hydrazine hydrate gave the 2-hydrazino-compound (13) which, on heating with dilute acetic acid in the presence of a copper<sup>II</sup> salt, gave in 67% yield 1-aza-azulene (14) as a red oil.

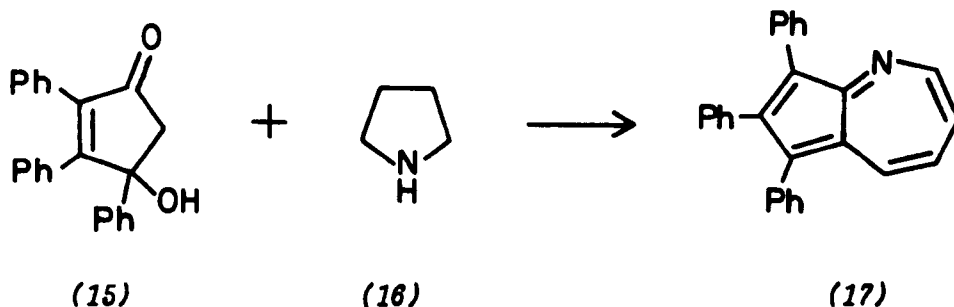
### 2-Aza-azulene

Nozoe<sup>24</sup> has reported a synthesis of 2-aza-azulene but no details are given in Chemical Abstracts.

### 4-Aza-azulene

1,2,3-Triphenyl-4-aza-azulene (17) was reported in 1970 by Conner and LeGoff<sup>25</sup> (Scheme 4).

### SCHEME 4

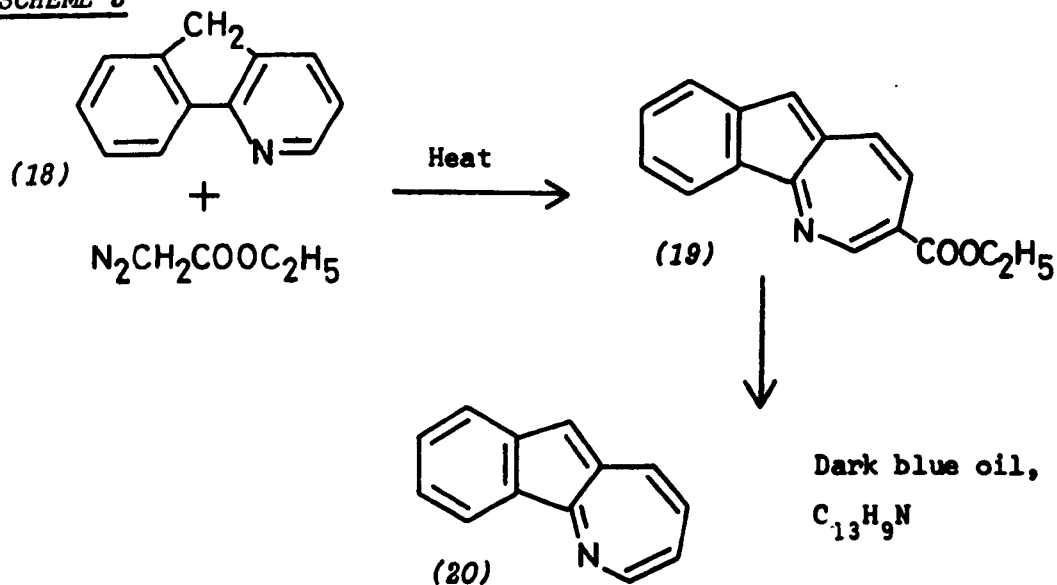




4-Hydroxy-2,3,4-triphenyl-2-cyclopenten-1-one (15) was boiled with pyrrolidine (16) in toluene containing a catalytic amount of *p*-toluenesulphonic acid. The 4-aza-azulene (17) was obtained as green crystals after chromatography. Absorption maxima in the visible spectrum occurred at 610, 656 and 710 nm.

This synthesis was reported as the first example of a 4-aza-azulene but there is an earlier report in the literature by Treibs and co-workers<sup>26</sup> of a dark blue oil, presumed to be 4-azabenz[*c*]azulene (20), obtained from 6-carbethoxy-4-azabenz[*c*]azulene (19) by treatment with methanolic potassium hydroxide followed by three chromatographic separations on alumina (Scheme 5). The carbethoxy-aza-azulene (19) was obtained by heating 4-azafluorene (18) and ethyl diazoacetate for three hours at 130° then for a further hour at 200°. The product was isolated by chromatography on alumina.

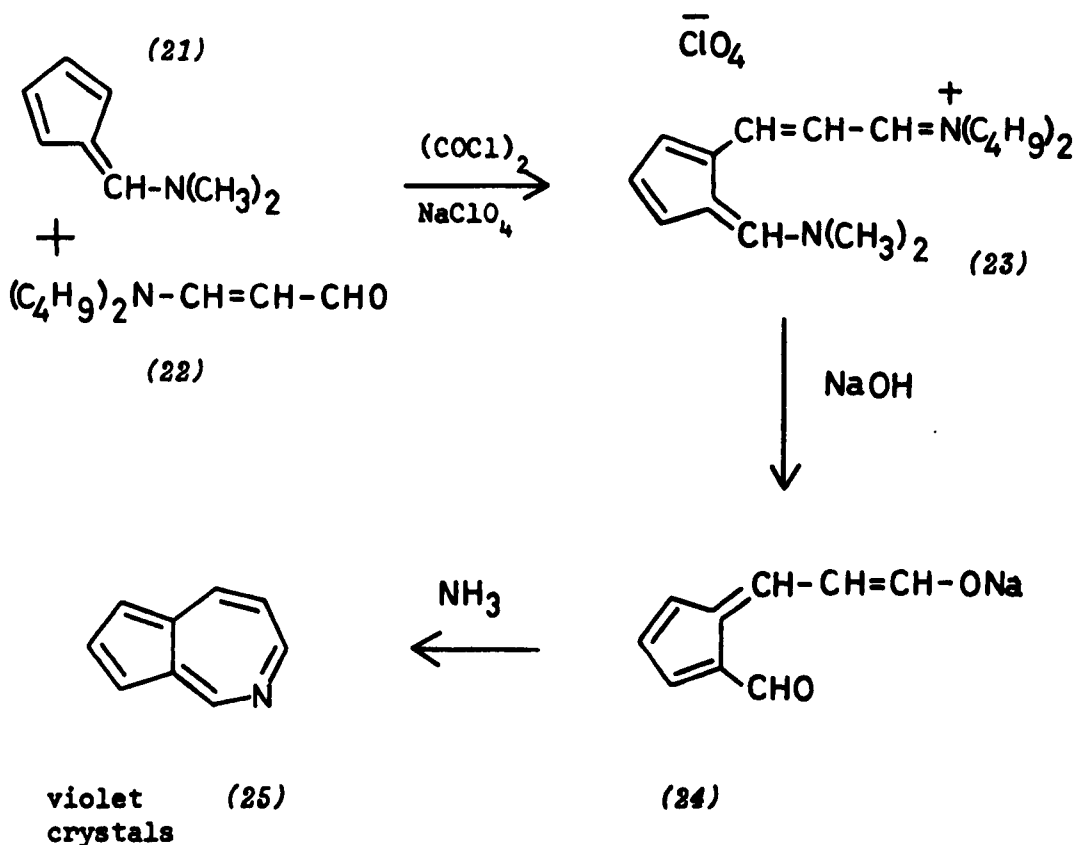
SCHEME 5





5-Aza-azulene

The first synthesis of 5-aza-azulene (25) was reported in 1961 by Hafner and Kreuder<sup>27</sup> (Scheme 6). The reaction between 6-dimethylaminofulvene (21) and *N,N*-dibutylaminoacraldehyde (22) in the presence of oxalyl chloride and sodium perchlorate gave the salt (23). Hydrolysis of the salt (23) gave the aldehyde (24) which was converted to 5-aza-azulene (25) on boiling in aqueous ammonia.

SCHEME 6



The long wavelength absorption in the electronic spectrum occurred at 652 nm.

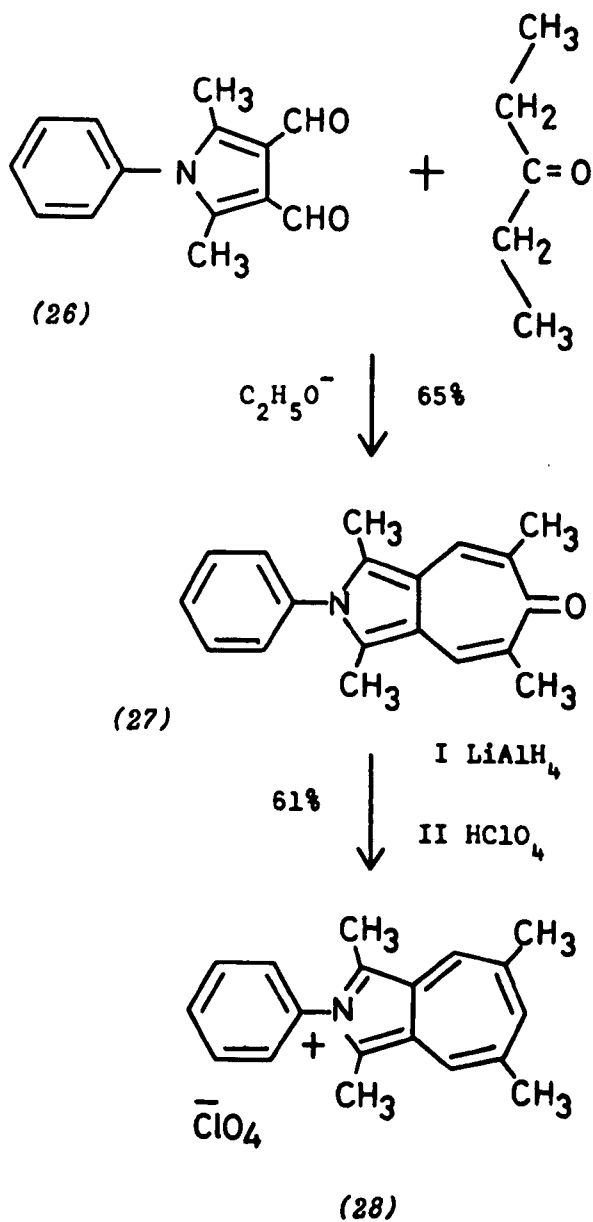
### 6-Aza-azulene

No examples of 6-aza-azulenes have been reported.

### AZONIA-AZULENES

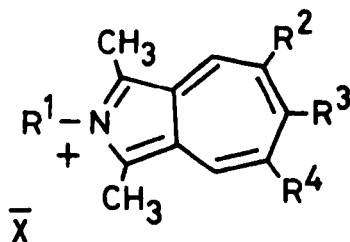
The first synthesis of an azonia-azulenium salt was reported in 1967 by El'tsov and co-workers.<sup>28,29</sup> This was the highly substituted 2-azonia-azulenium salt (28) (Scheme 7). The condensation of 3,4-diformyl-2,5-dimethyl-1-phenylpyrrole (26) with diethyl ketone gave the tropone (27). Reduction of (27) with lithium aluminium hydride gave the carbinol which on treatment with perchloric acid gave 1,3,5,7-tetramethyl-2-phenyl-2-azonia-azulenium perchlorate (28).



SCHEME 7

The same authors have prepared the following 2-azonia-azulenium salts.





	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	X
(29) <sup>30</sup>	Ph	Ph	H	CH <sub>3</sub>	ClO <sub>4</sub>
(30) <sup>30</sup>	Ph	Ph	CH <sub>3</sub>	CH <sub>3</sub>	ClO <sub>4</sub>
(31) <sup>30</sup>	Ph	Ph	Ph	CH <sub>3</sub>	ClO <sub>4</sub>
(32) <sup>31</sup>	Ph	H	H	H	ClO <sub>4</sub>
(33) <sup>32</sup>	H	H	OCH <sub>3</sub>	H	BF <sub>4</sub>
(34) <sup>32</sup>	H	H	OCH <sub>3</sub>	CH <sub>3</sub>	BF <sub>4</sub>
(35) <sup>32</sup>	H	CH <sub>3</sub>	OCH <sub>3</sub>	Ph	BF <sub>4</sub>
(36) <sup>32</sup>	H	CH <sub>3</sub>	OCH <sub>3</sub>	CH <sub>3</sub>	BF <sub>4</sub>

Salts (29) - (32) were prepared from the corresponding tropones by the action of lithium aluminium hydride or Grignard reagents followed by perchloric acid treatment of the carbinol produced. Salts (33) - (36) were prepared by treating the corresponding tropones with methyl iodide and silver fluoborate.

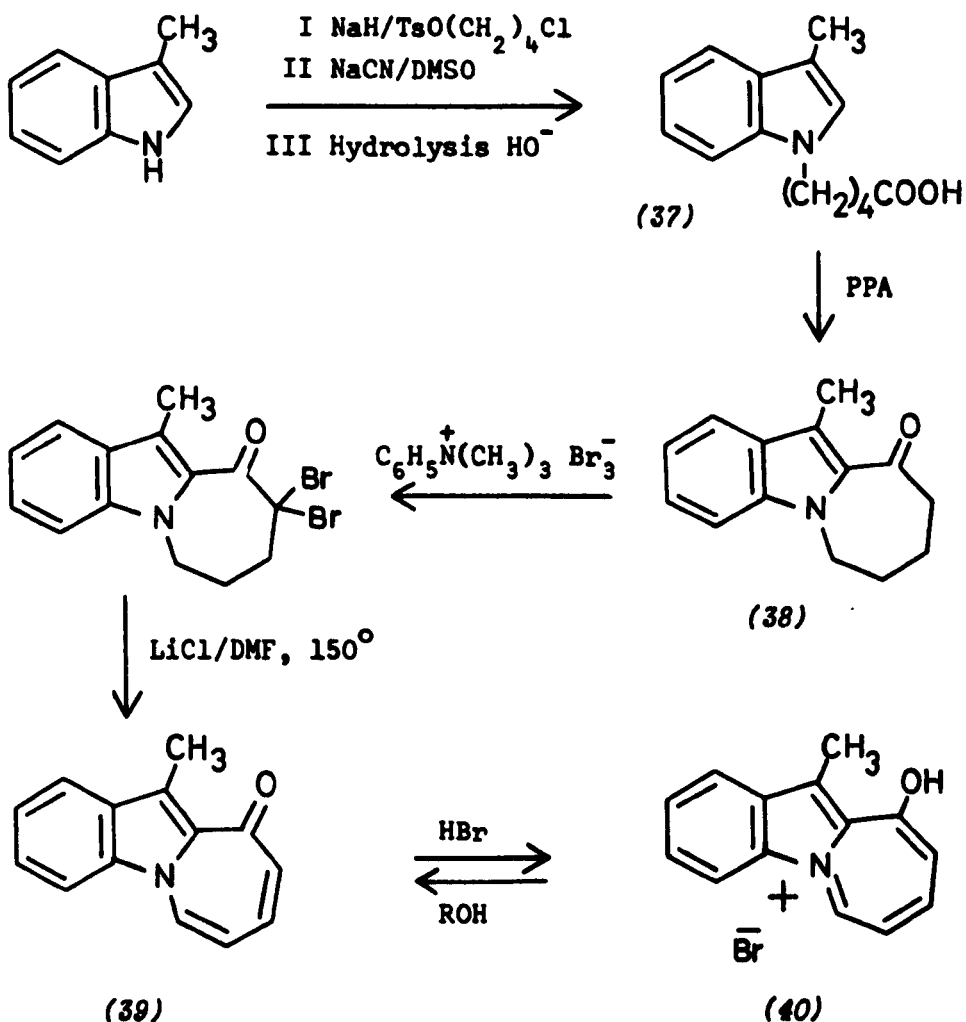
The interaction of the 2-azonia-azulenium salt (28) with the nucleophilic reagents LiAlH<sub>4</sub>, KCN, CH<sub>3</sub>MgI and PhMgI



has shown that positions 4(8) and 6 are the most susceptible to nucleophilic attack.<sup>33,34</sup>

The only examples of azonia-azulenium salts with bridgehead nitrogen atoms are those prepared at this University by Collington and Jones<sup>35,36</sup> (Schemes 8 and 9).

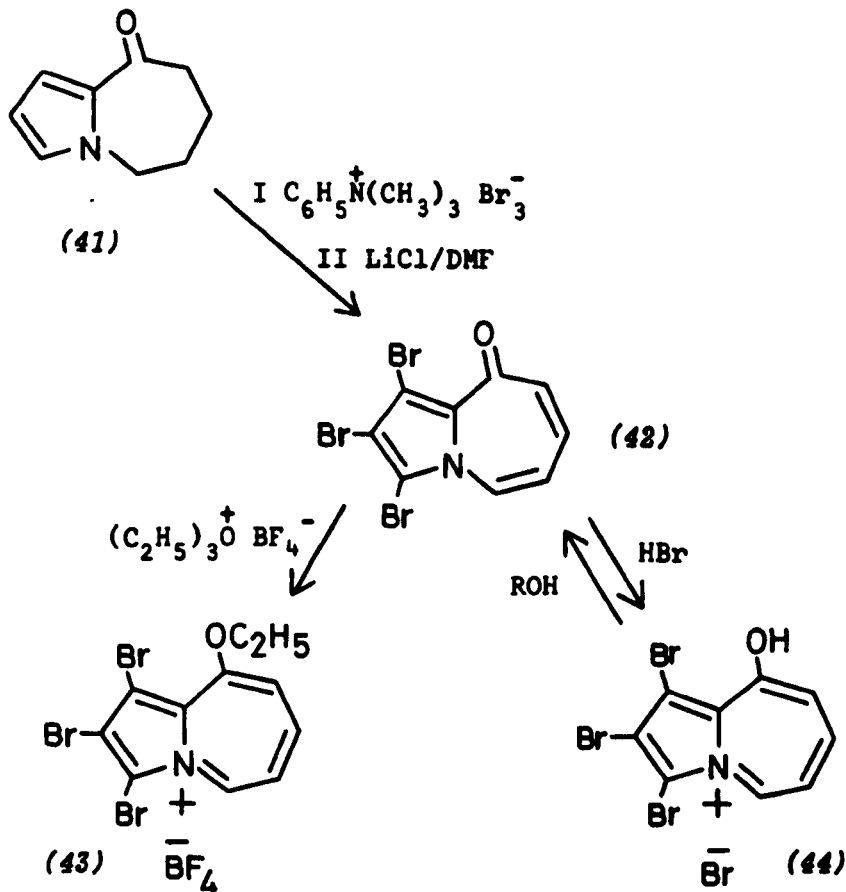
SCHEME 8





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 (37) which cyclised on treatment with polyphosphoric acid to give the cyclic ketone (38). Bromination alpha to the carbonyl group with phenyltrimethylammonium tribromide and dehydrobromination with lithium chloride in dimethylformamide gave 11-methylazepino[1,2-a]indol-10-one (39). Protonation gave the azonia-azulenium system (40).

SCHEME 9





The bicyclic ketone (41) was prepared by reactions similar to those in Scheme 8. On attempted bromination alpha to the carbonyl group bromine atoms were also unavoidably introduced into the five-membered ring. Dehydrobromination with lithium chloride in dimethylformamide gave the ketone (42) which on treatment with triethyloxonium fluoborate or dry hydrogen bromide gave the azonia-azulenium salts (43) and (44) respectively.

Attempts to reduce the carbonyl group in the azepinoindolone (39) in order to obtain the azepinoindolium salt by protonation were unsuccessful.<sup>37</sup> Lithium aluminium hydride and sodium borohydride reduced the seven-membered ring as well as the ketone group and attempted Wolff-Kishner reduction using hydrazine hydrate opened the seven-membered ring.



*P A R T I*

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## I N T R O D U C T I O N

The work described in this part of the thesis concerns the thermal decomposition of 2-azidodiphenylmethanes. It is thought that decompositions of this type proceed via nitrene intermediates and therefore it is useful at this point to review some of the relevant properties of nitrenes, in particular those of aryl-nitrenes.

### NITRENES

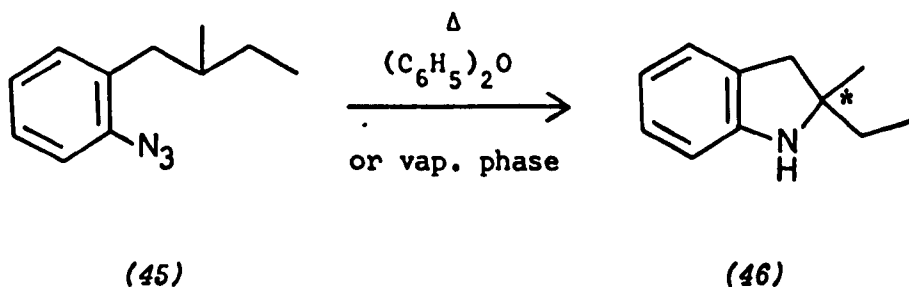
The existence of nitrenes, uncharged monovalent nitrogen intermediates analogous to carbenes, has now been well established and the generation, properties and synthetic utility of nitrenes are the subject of several reviews.<sup>38-43</sup>

It has been shown<sup>44,45</sup> by low temperature electron spin resonance studies that nitrenes have triplet ground states consistent with Hund's rule. At higher temperatures nitrenes can behave as triplet or singlet species depending on the nature of the nitrene and on the reaction conditions, but in general nitrenes are generated photolytically as triplets and thermolytically as singlets. Smolinsky and Feuer<sup>46</sup> have shown that the thermally generated nitrene from optically active



1-azido-2-(2-methylbutyl)benzene (45) inserts into the C-H bond at the asymmetric carbon atom to give the indoline (46) with retention of configuration (Scheme 10). The generation of a triplet nitrene would have resulted in racemisation.

SCHEME 10



Greater retention of optical activity was reported with vapour phase pyrolysis than by heating in solution.

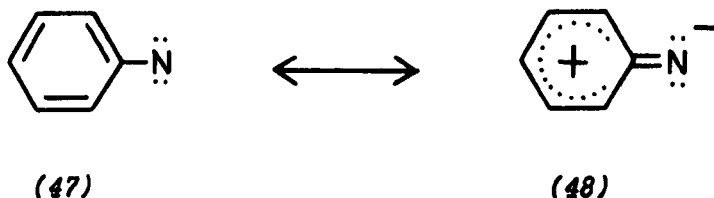
The highly reactive nitrene can stabilise itself by the following reactions: Isomerisation to imines; 'dimerisation' to azo-compounds; intramolecular hydrogen abstraction followed by ring closure to heterocyclic compounds; bimolecular insertion into C-H bonds; addition to an olefinic bond, and by addition to an aromatic system with subsequent ring expansion.

Aryl-nitrenes and arylsulphonylnitrenes exist as stable triplets at 77°K<sup>44</sup> but alkyl- or alicyclic-nitrenes such as n-octyl-, triphenylmethyl- or cyclohexyl- cannot be observed in the e.s.r. spectrum under these conditions.<sup>44,47</sup> The kind



of reactivity shown by aryl-nitrenes also differs from that of the alkyl-nitrenes. Typically the thermal decomposition of *o*-azidobiphenyl gives carbazole in high yield while the decomposition of  $\beta$ -phenylethyl azide does not give indoline.<sup>48</sup> Phenylnitrene also differs in reactivity from ethoxycarbonyl-, sulphonyl- and cyanonitrene since the decomposition of phenyl azide in benzene gives no diphenylamine<sup>49</sup> whereas intermolecular attack of an aromatic nucleus by ethoxycarbonyl-,<sup>50</sup> sulphonyl-,<sup>51</sup> and cyanonitrene<sup>52</sup> has been well documented.

The apparent failure of phenylnitrene to undergo intermolecular attack has been explained<sup>53</sup> by extensive delocalisation of the electron deficiency resulting in an appreciable negative charge on nitrogen (47)  $\leftrightarrow$  (48).



In contrast to ethoxycarbonyl-, sulphonyl- and cyanonitrene, in which the substituent groups are electron withdrawing, singlet phenylnitrene may be less electrophilic at nitrogen than the triplet species.

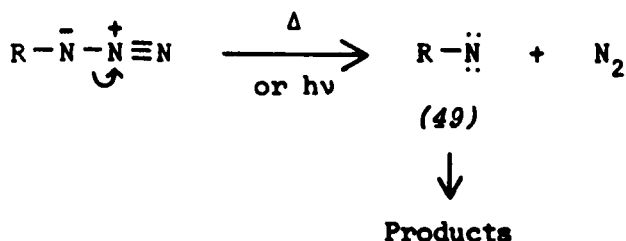
The suggestion<sup>47</sup> that the heightened selectivity



displayed by "delocalised nitrenes" was a result of their longer lifetimes has been confirmed<sup>54</sup> by correlations between the negative charge on nitrogen and the rate of hydrogen abstraction of aromatic nitrenes in polystyrene matrices (a measure of the lifetime of the nitrene).

### Nitrenes from azides

Azides decompose on heating or on irradiation. Nitrogen is lost and the products can usually be rationalised by postulating a nitrene intermediate (49).



Kinetic evidence for the formation of nitrene intermediates in the thermal decomposition of aryl azides is provided by the studies of Smith and Hall<sup>55</sup> and Walker and Waters.<sup>56</sup> In all the cases examined the decomposition rates were first order and the rate determining step was the cleavage of the azide to a nitrene.

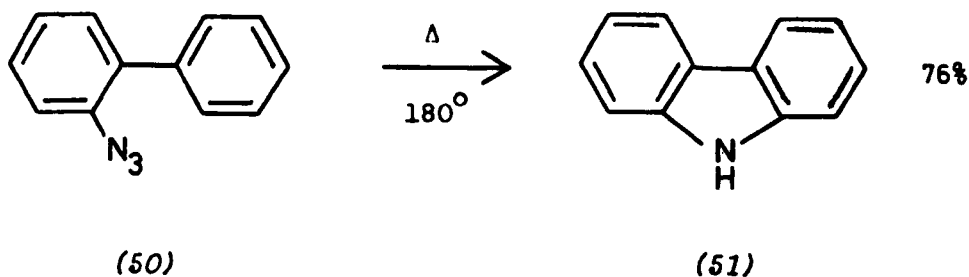
The majority of aryl azide decomposition reactions



lead to the production of five- or seven-membered heterocyclic rings.

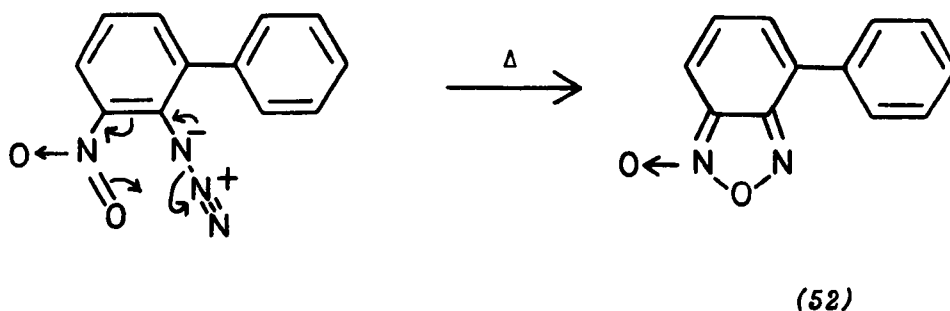
The thermal decomposition of *o*-azidobiphenyl (50)<sup>48,57,58</sup> is one of the best routes to carbazole (51) (Scheme 11) and many substituted carbazoles have been prepared by this method. These reactions involve an intramolecular insertion by the nitrene into a suitably positioned C-H bond.

SCHEME 11



The reaction fails with *o*-nitroaryl azides which give furoxans (52) in good yields<sup>48</sup> (Scheme 12). The lower decomposition temperature compared to other azides is rationalised in terms of a concerted mechanism involving rupture of the  $N-N_2$  bond with concomitant cyclisation.<sup>59</sup>



SCHEME 12

Many other five-membered ring heterocycles have been prepared in high yield by the decomposition of *o*-substituted aryl azides:

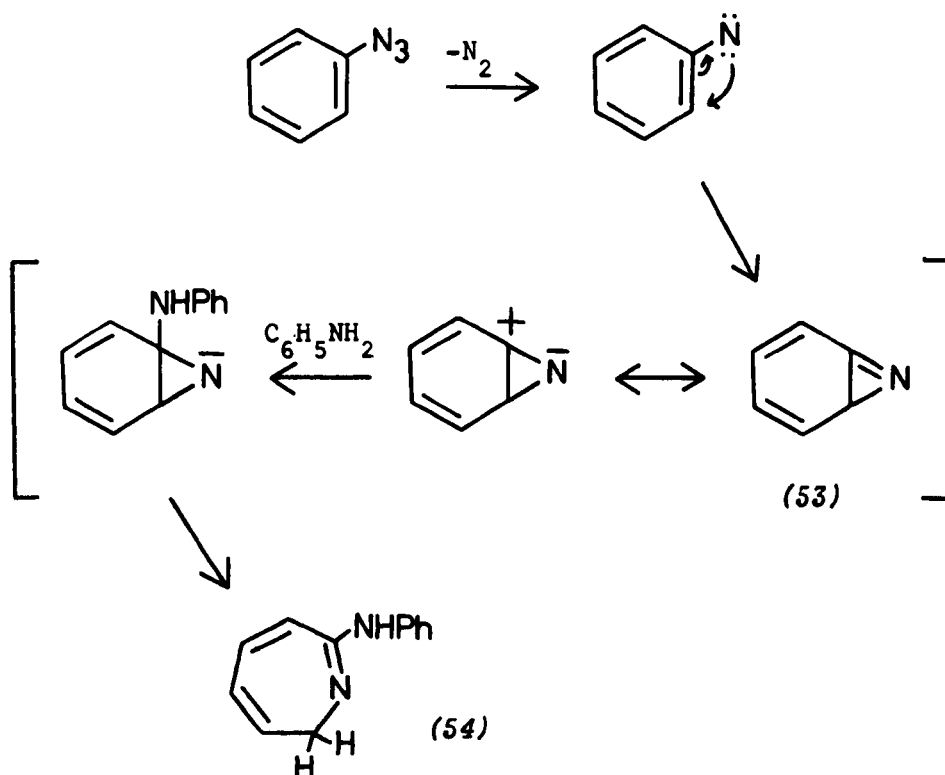
Smith and Boyer<sup>60</sup> have reported the preparation of 4H-thieno[3,2-*b*]indole and  $\alpha$ - and  $\gamma$ -carbolines.

Kametani, Yamanaka and Ogasawara<sup>61,62</sup> have reported the preparation of a highly substituted  $\beta$ -carboline derivative.

Sundberg, Linn and Blackburn<sup>63</sup> have reported the formation of 2-substituted indoles by the pyrolysis of *o*-azidostyrenes.

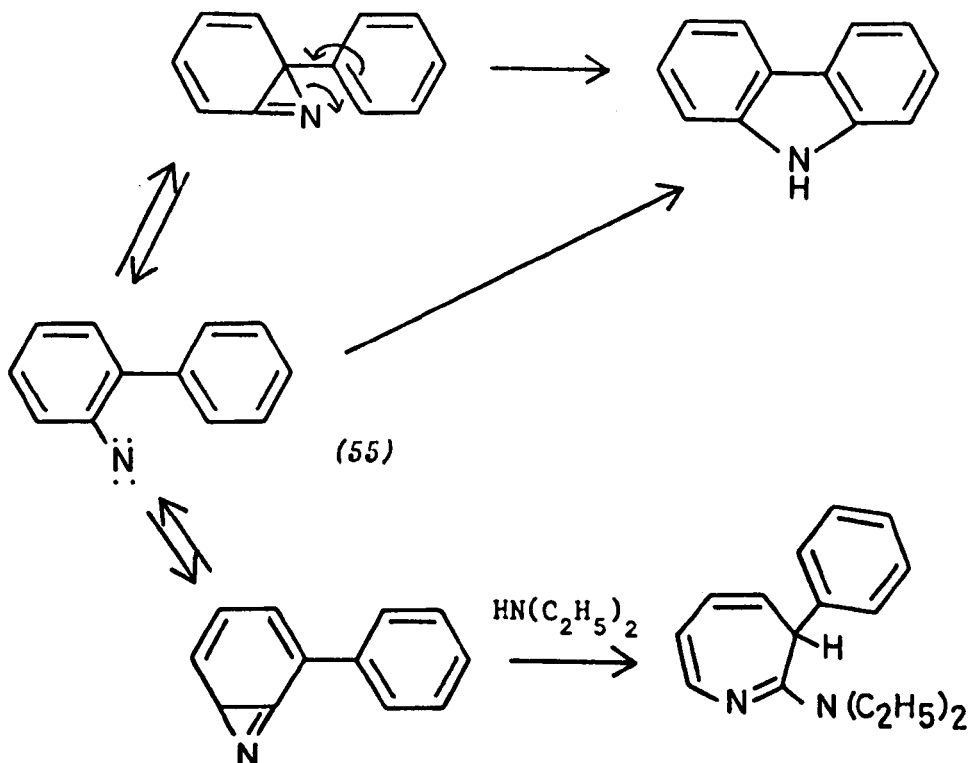
The decomposition of an aryl azide in an amine solution provides a useful route to azepines<sup>49,64,65</sup> (Scheme 13). Phenyl azide decomposed in aniline gave 7-anilino-2H-azepine (54)<sup>64</sup> by ring expansion of the azirine (53).



SCHEME 13

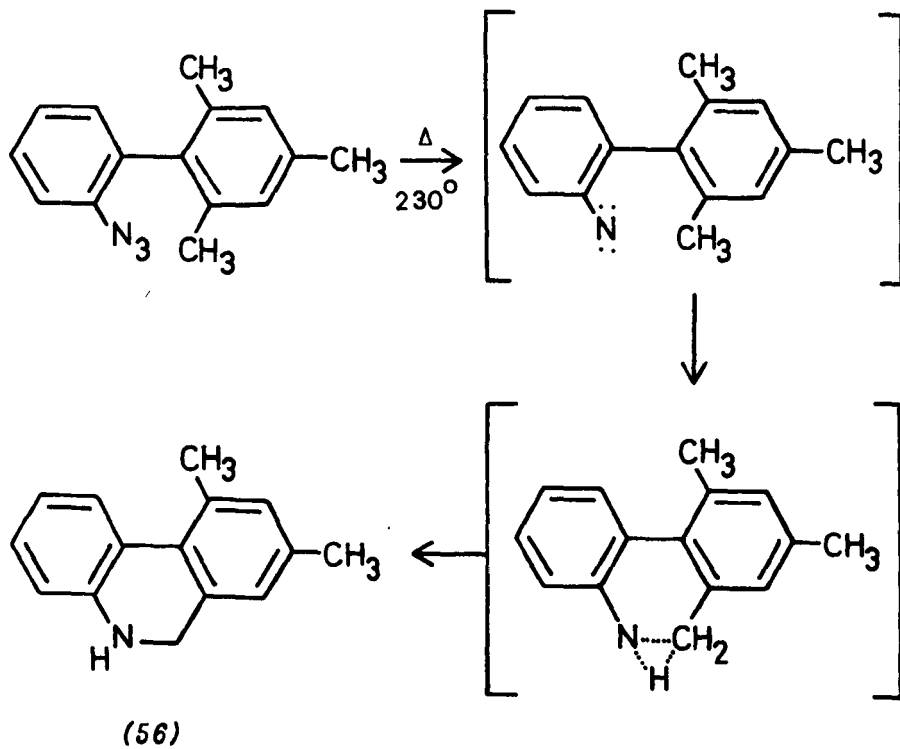
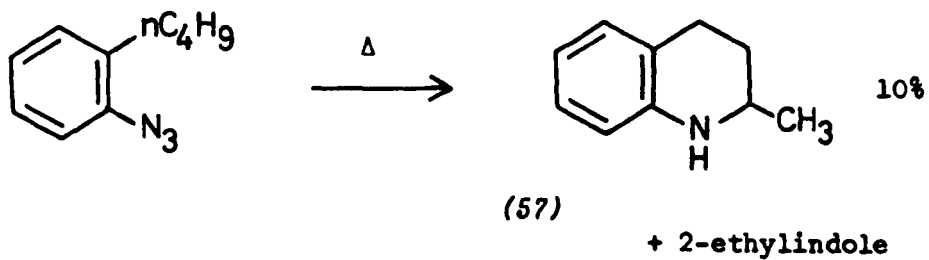
Sundberg and co-workers<sup>66</sup> have demonstrated that *o*-biphenylnitrene (55) can be diverted from carbazole formation by diethylamine (Scheme 14) and follow earlier suggestions<sup>39,67</sup> by proposing that the nitrene undergoes bond reorganisation competitively with intramolecular cyclisation and that the bond reorganisation process is reversible.



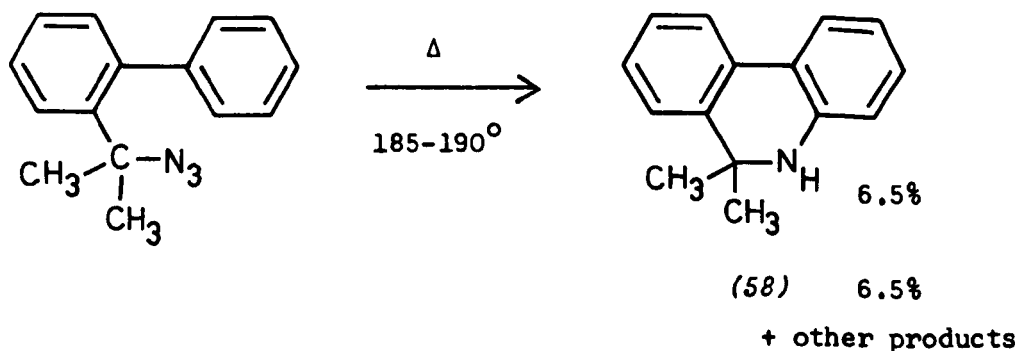
SCHEME 14

Six-membered ring heterocycles are not usually formed via nitrene intermediates. The only examples are: The formation of a dihydrophenanthridine (56) by nitrene insertion into a suitably placed methyl group<sup>68,69</sup> (Scheme 15). The formation of a tetrahydroquinoline (57) by insertion into a methylene group<sup>70</sup> (Scheme 16). The formation of a low yield of a dihydrophenanthridine (58) by the aromatic substitution of an alkyl-nitrene<sup>71</sup> (Scheme 17).



SCHEME 15SCHEME 16



SCHEME 17

Six-membered ring formation is observed in the formation of phenothiazines by the decomposition of *o*-azidodiphenyl sulphide<sup>72</sup> but this reaction has been reinvestigated by two groups of workers<sup>73,74</sup> and found to proceed via initial five-membered ring formation followed by rearrangement. This reaction, which is particularly relevant to the present work, will be discussed more fully later.

Krbecek and Takimoto<sup>75</sup> have reported that the decomposition of *o*-azidodiphenylmethane leads not to the formation of dihydro-acridine by six-membered ring closure but to an indoloazepine by ring expansion. This decomposition has been reinvestigated<sup>37</sup> and a case where the products are based on the acridine ring system has been reported.<sup>76</sup> This work will be discussed in detail later.



### Nitrenes from other sources

The deoxygenation of nitro- and nitroso-compounds by trivalent phosphorus compounds is thought to proceed via nitrene intermediates. It is not certain that all reactions of this type go via nitrene intermediates but the best evidence that some do is provided by a comparison of products and yields obtained from the deoxygenation of nitro-compounds with those obtained from the decomposition of the corresponding azides.<sup>77</sup> For example: The deoxygenation of *o*-nitro- or *o*-nitrosobiphenyls gives carbazoles;<sup>78-80</sup> *o*-nitrostyrenes give indoles;<sup>81,82</sup> *o*-nitrodiphenyl sulphides give phenothiazines;<sup>83</sup> and deoxygenation in the presence of amines gives azepines.<sup>84</sup> The deoxygenation of nitrosobenzene with triethyl phosphite in benzene/trifluoroethanol gives 1-phenylazepine by ring expansion.<sup>85</sup>

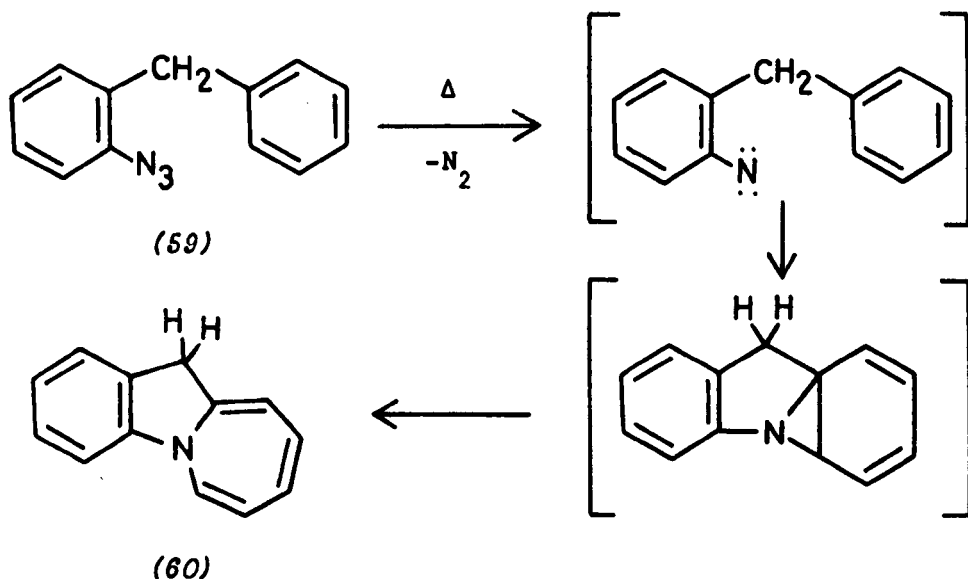
There are many other less general reactions for the generation of nitrenes.<sup>38-43</sup>



# DISCUSSION

The publication in 1968, by Krbecek and Takimoto<sup>75</sup> of a note concerning the thermal decomposition of 2-azido-diphenylmethane (59) was particularly relevant to the present work since the product, formulated as 11H-azepino[1,2-*a*]indole (60), appeared to provide a promising route to the tricyclic azonia-azulenium salt (3) by hydride abstraction. The decomposition (Scheme 18) was thought to proceed by attack of a nitrene intermediate on the adjacent aromatic ring giving an azabicycloheptadiene intermediate which gave compound (60) by ring expansion.

SCHEME 18





At that time the only reports in the literature of 1H-azepines were those where a strongly electron attracting group was attached to nitrogen (Sundberg and Smith<sup>85</sup> have since reported the preparation of 1-phenylazepine) and in view of the tendency of azepines to form 3H-tautomers where possible the proposed structure (60) appeared dubious.

Accordingly it was decided to reinvestigate this decomposition and the decomposition of substituted azides of this type with the following aims in mind:

To prepare azepinoindole derivatives suitable for attempted conversion into azepinoindolium salts.

To investigate the mechanism and scope of the reaction.

The proposed investigation necessitated the preparation of several 2-azidodiphenylmethanes.

#### PREPARATION OF 2-AZIDODIPHENYLMETHANES

Two routes to the desired 2-azidodiphenylmethanes were envisaged. These were from 2-aminobenzophenones by reduction of the carbonyl group followed by conversion of the amine to an azide;<sup>86</sup> and from 2-bromobenzophenones by reduction, followed by the conversion of the bromo-group to an azide via the



Grignard compound.<sup>87</sup>

A simple method for the reduction of 2-aminobenzophenones to 2-aminodiphenylmethanes is by sodium in ethanol. It was thought that the reduction of 2-bromobenzophenones might prove more difficult since Stepanow<sup>88</sup> and Löwerherz<sup>89</sup> quoted by Rodd<sup>90</sup> have reported dehalogenations using sodium or sodium amalgam and alcohol. Consequently the most promising approach to the azides was considered to be via the 2-aminobenzophenones.

Simpson and co-workers<sup>91</sup> have critically reviewed the many routes to 2-aminobenzophenones.

Initial attempts to prepare 2-aminobenzophenone by the Hofmann reaction of 2-benzoylbenzamide with sodium hypochlorite<sup>92,93</sup> gave poor, non-reproducible yields and a much better method of preparation was found to be by the Friedel-Crafts reaction between N-tosylanthraniloyl chloride and benzene using a procedure<sup>94</sup> essentially that of Ullmann and Bleier.<sup>95</sup>

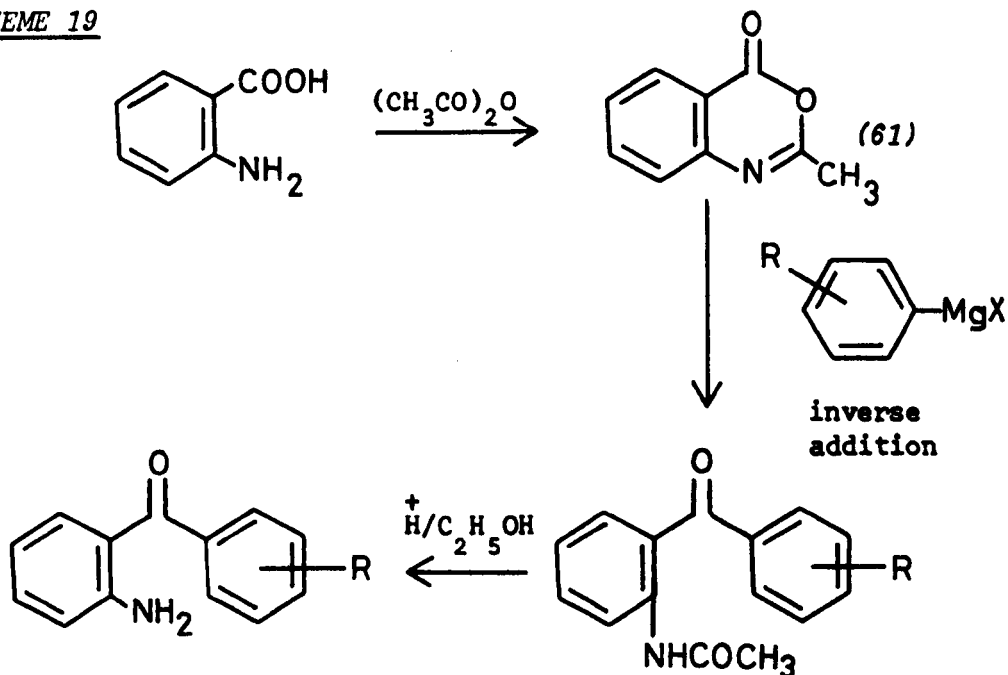
Friedel-Crafts reactions were not used for the preparation of substituted benzophenones because of the possibility in some cases of a difficult separation of isomeric products.

The reaction between acetanthranil (61)<sup>96</sup> and an aryl Grignard reagent was selected as being the most applicable to the synthesis of benzophenones having a wide range of substituents in the non-basic ring (Scheme 19). The method was first proposed by



Lothrop and Goodwin<sup>97</sup> but suffers from the reported disadvantages that acetantranil is unstable and only moderate yields of the benzophenone are obtained. During this work it has been found that acetantranil can be kept for a period of several weeks at  $-10^{\circ}$ .

SCHEME 19

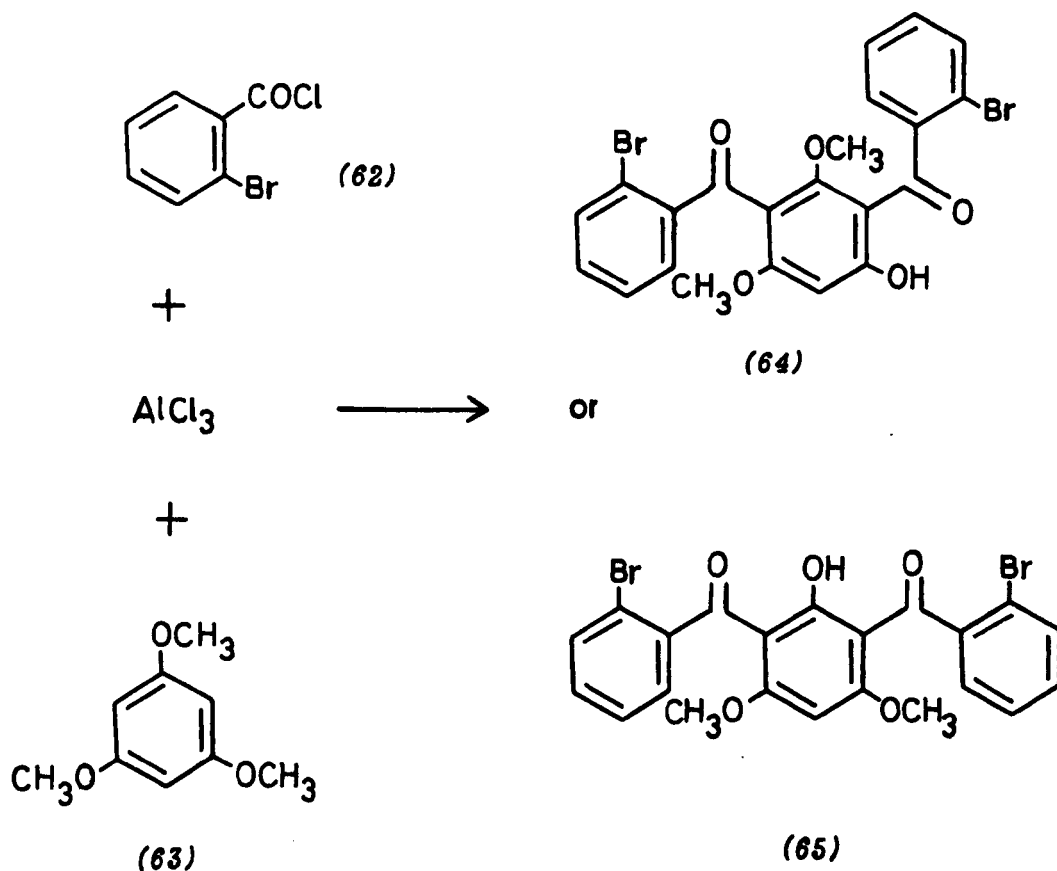


All the 2-aminobenzophenones substituted in the non-basic ring were prepared by this method. The preparation of large quantities of some aryl halides, notably 1-bromo-2,4,6-trimethoxybenzene, for use in this reaction was troublesome and the Friedel-Crafts reaction between 2-bromobenzoyl chloride (62) and trimethoxybenzene (63) was investigated in the hope that this would provide



a simpler route to the benzophenone. The mass spectrum of the product showed the molecular ion at  $m/e$  518 and the ratios of the  $M^+$ ,  $M+2^+$  and  $M+4^+$  peaks showed that the molecule contained two bromine atoms. The product was formulated as either 2,4-di(2-bromobenzoyl)-3,5-dimethoxyphenol (64) or 2,6-di(2-bromobenzoyl)-3,5-dimethoxyphenol (65) from a consideration of the spectral and analytical data but it was not possible to distinguish between these compounds on the available evidence.

SCHEME 20





The nuclear magnetic resonance (n.m.r.) spectrum showed the presence of only two  $-OCH_3$  groups and a signal at  $-3.4$  p.p.m. in  $DMSO-d_6$  which was attributed to an  $-OH$  proton. The reason for the cleavage of one ether group is not clear but this was not entirely unexpected since aluminium chloride has been used to demethylate aromatic ethers.<sup>98</sup> Although this reaction fails to give the simple benzophenone with trimethoxybenzene, where there is considerable activation of the 2, 4 and 6 positions, it could be expected to work in other cases.

The reduction of 2-aminobenzophenones appears to have received little attention in the literature. In 1948 Hewett and co-workers<sup>93</sup> reported on the sodium in ethanol and sodium in amyl alcohol reductions of 2-aminobenzophenone. The best yield was reported with the sodium in ethanol reduction.

Reductions of 2-amino-4'-methoxybenzophenone were reported in 1959 by Engels, Lamchen and Wicken.<sup>99</sup> They found that zinc dust in alkali, Clemmensen reduction, Wolff-Kishner reduction and the Huang-Minlon<sup>100</sup> modification thereof failed to give the desired diphenylmethane. Catalytic hydrogenation with palladium-charcoal failed and with Adams catalyst reduction took place only as far as the alcohol. The best results were obtained by sodium in ethanol reduction. No experimental details



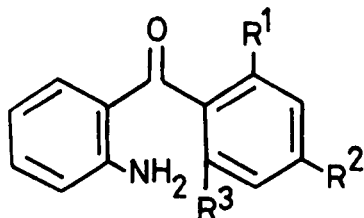
were reported for the Wolff-Kishner reduction and it is surprising that this reaction was reported as a failure because Zahler and Huisgen<sup>101</sup> have reported a 56% yield of 2-amino-4'-methoxydiphenylmethane together with 26% yield of 2-amino-4'-hydroxydiphenylmethane in this reaction.

In the present work all the aminobenzophenones were reduced in good yields using sodium in ethanol.

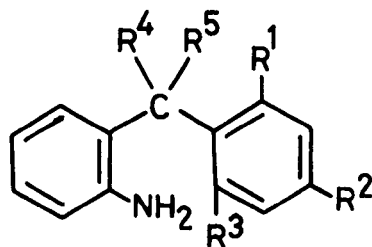
All the amines were converted into the corresponding azides by diazotisation and reaction of the diazonium salt with sodium azide. The hydrochlorides and sulphates of those amines substituted in the non-basic ring were very insoluble in the acidic solutions required for diazotisation with the result that the reaction with nitrous acid was slow and incomplete. In one diazotisation in aqueous hydrochloric acid significant yields of the 2-chloro- and 2-hydroxydiphenylmethanes were obtained. Thereafter the diazotisation of sparingly soluble amine salts was carried out in sulphuric acid containing up to 50% by volume of 1,4-dioxan which had the effect of keeping the amine salt in solution even at  $-5^{\circ}$ . This method resulted in excellent yields of the azides.

The following compounds were prepared:





Benzophenones

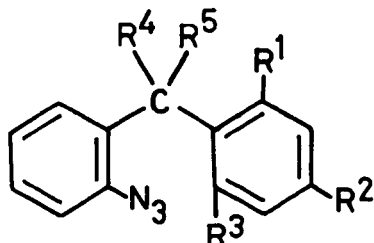


Diphenylmethanes

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	
(66)	H	H	H	H	H	(72)
(67)	H	OCH <sub>3</sub>	H	H	H	(73)
(68)	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H	H	(74)
(69)	CH <sub>3</sub>	H	H	H	H	(75)
(70)	OCH <sub>3</sub>	H	H	H	H	(76)
(71)	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	H	(77)
	H	H	H	CH <sub>3</sub>	OH	(78)
	H	H	H	CH <sub>3</sub>	H	(79)

1-(2-Aminophenyl)-1-phenylethanol (78) was prepared from 2-aminobenzophenone (66) and methylmagnesium iodide by the method of Stoermer and Fincke<sup>102</sup> and 1-(2-aminophenyl)-1-phenylethane (79) was prepared by the dehydration<sup>102</sup> of the alcohol (78) followed by catalytic hydrogenation.





### Azides

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>
(59)	H	H	H	H	H
(80)	H	H	H	CH <sub>3</sub>	H
(81)	H	OCH <sub>3</sub>	H	H	H
(82)	CH <sub>3</sub>	CH <sub>3</sub>	CH <sub>3</sub>	H	H
(83)	CH <sub>3</sub>	H	H	H	H
(84)	OCH <sub>3</sub>	H	H	H	H
(85)	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	H
(86)	H	H	H	CH <sub>3</sub>	OH

### AZIDE DECOMPOSITIONS

Each azide was decomposed under nitrogen in trichlorobenzene solution at 190 - 200°.

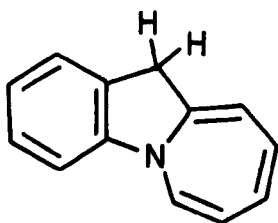
The assignment of structures to the decomposition products was based largely on the interpretation of their n.m.r.



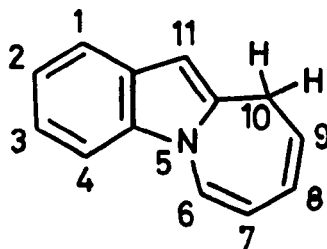
spectra and these are extensively discussed throughout this section. The mass spectra are discussed collectively at the end of the section.

The decomposition of 2-azidodiphenylmethane (59) gave a single product isolated after chromatography, which showed melting point, ultraviolet spectrum and molecular formula identical with those reported by Krbecek and Takimoto<sup>75</sup> for 11H-azepino[1,2-*a*]indole (60). That the product was not azepinoindole (60) was clear from its n.m.r. spectrum reproduced in Figure 1 (page 39).

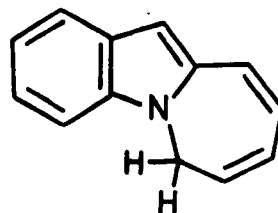
The spectrum shows a two proton doublet at 6.45 $\tau$  which cannot be reconciled with azepinoindole (60) but which can be easily accommodated by the tautomeric 10H-azepinoindole (87).



(60)

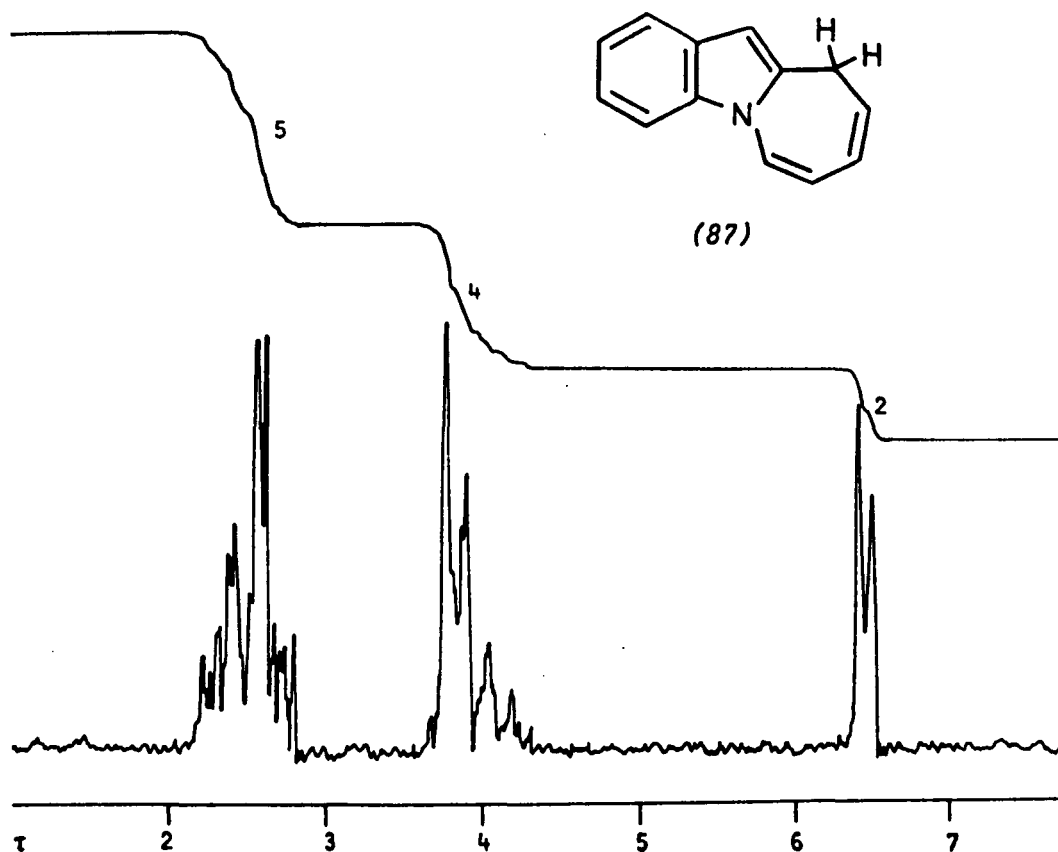


(87)



(88)



FIGURE 1

The other possible structure (88) can be excluded on the basis of the chemical shift of the methylene group. Resonance occurs at too high a value of the applied field for a methylene group attached both to a nitrogen atom and a double bond system. For example, the  $\text{N-CH}_2$  methylene group resonance in 6,7,8,9-tetrahydro-11-methyl-10H-azepino[1,2- $\alpha$ ]indole (91) occurs at 5.6 - 6.0 $\tau$ . The one proton singlet at 3.8 $\tau$  can be assigned to

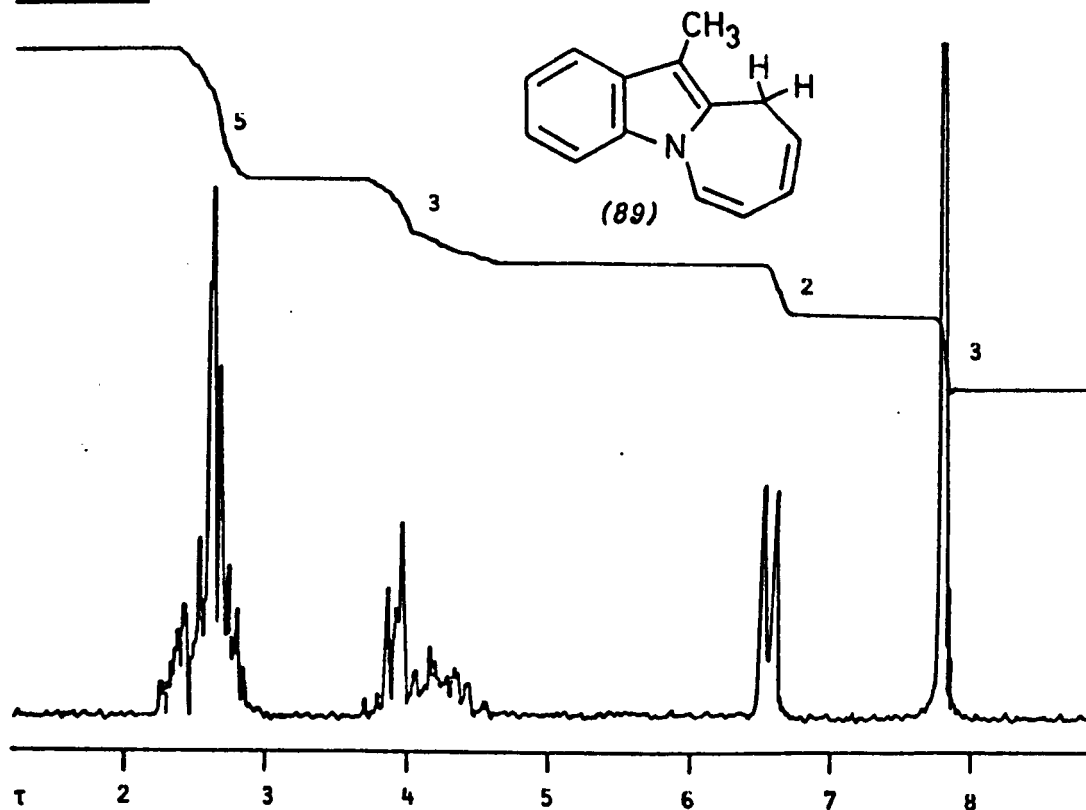


the proton in position 11, the multiplet between 3.8 $\tau$  and 4.3 $\tau$  to the seven-membered ring protons in positions 7,8 and 9 and the five proton multiplet between 2.2 $\tau$  and 2.8 $\tau$  to the four aromatic protons together with the proton in position 6.

Further work on the azepinoindole (87) directed towards its conversion into an azonia-azulenium salt will be described later.

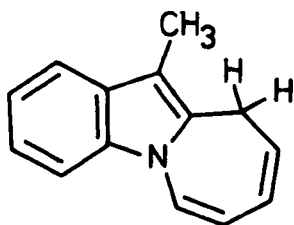
Confirmation of the assignment of structure (87) to the azepinoindole was provided by the synthesis and subsequent decomposition of 1-(2-azidophenyl)-1-phenylethane (80).

FIGURE 2

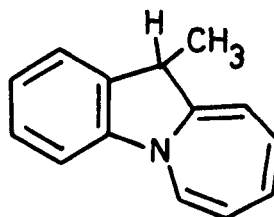




The n.m.r. spectrum of the product (Figure 2) shows a sharp singlet at 7.7 $\tau$  which can be assigned to the methyl group and a two proton doublet at 6.5 $\tau$  as expected for structure (89). If the product had been the 11-methyl-11H-azepinoindole (90), predicted from the formulation of Krbechek and Takimoto,<sup>75</sup> then the methyl group signal would have been expected to appear as a doublet.



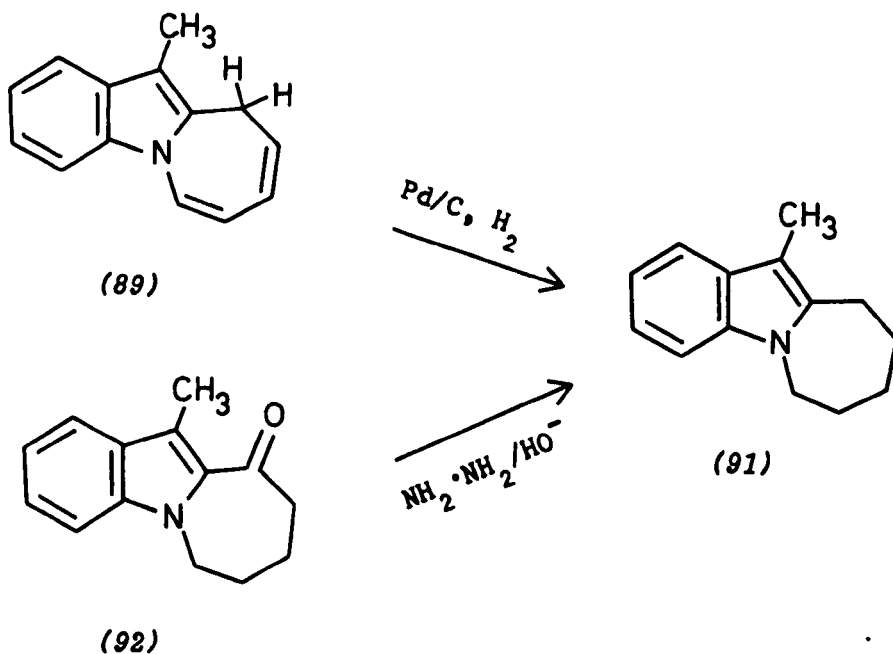
(89)



(90)

Confirmation of the assignment of structure (89) was provided by catalytic reduction which gave a tetrahydro-10H-azepinoindole (91) identical with that produced by Huang-Minlon reduction of the synthetic 6,7,8,9-tetrahydro-11-methylazepino[1,2- $\alpha$ ]indol-10-one (92)<sup>36</sup> (Scheme 21).



SCHEME 21

The decomposition of 2-azido-4'-methoxydiphenylmethane (81) gave one major and two minor products. The major product was isolated by column chromatography and identified from its n.m.r. spectrum (Figure 3) as 8-methoxy-10H-azepino-[1,2-*a*]indole (93) obtained in 48% yield.

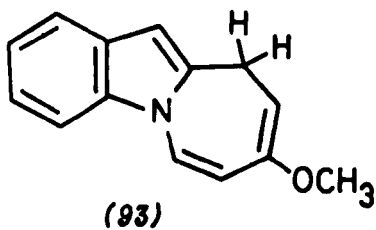
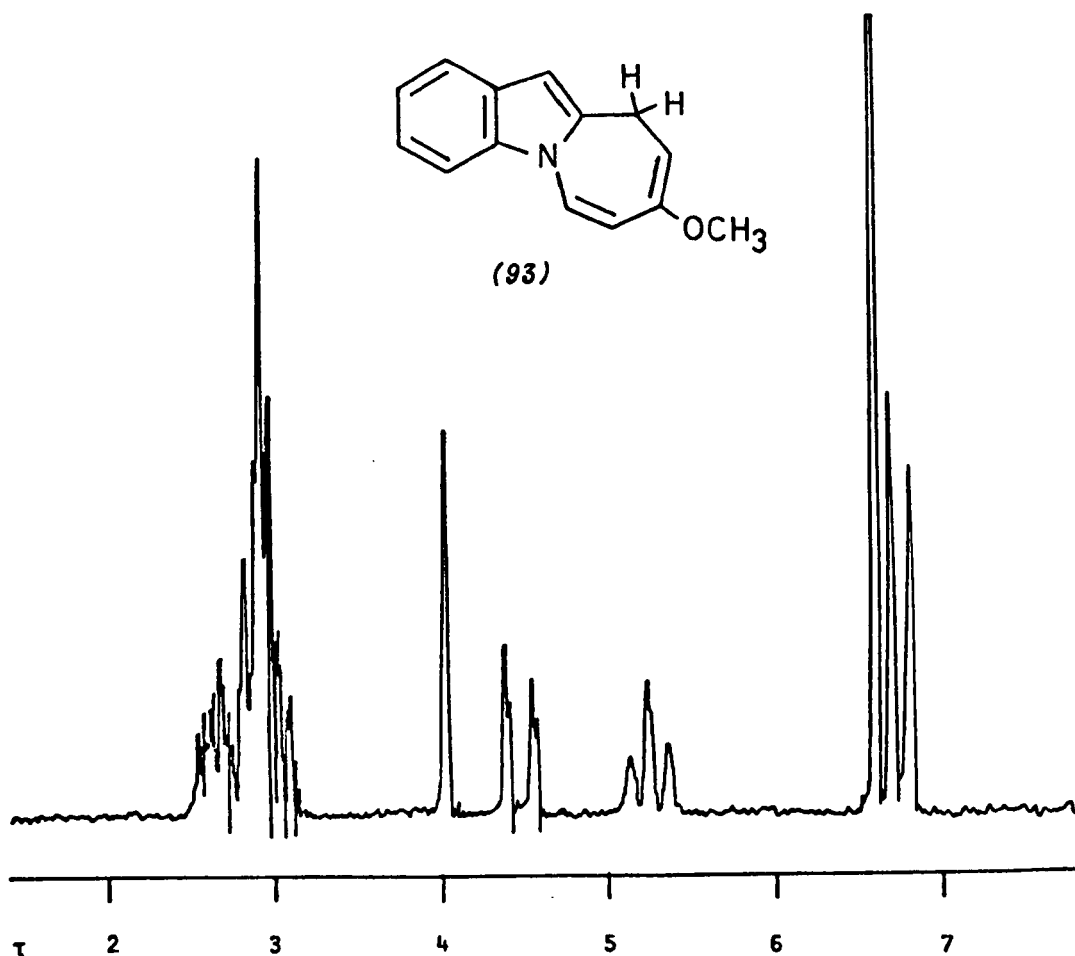




FIGURE 3

The assignment of the 10H-azepinoindole structure to the product is based on the chemical shifts of the methylene group signal and the signal due to the proton on the five-membered ring. These occur at 6.75 $\tau$  and 4.05 $\tau$  respectively, in good agreement with the shifts of the corresponding protons in the 10H-azepinoindole (87). That the methoxyl group is in



position 8 is shown by the splitting pattern of the protons on the seven-membered ring. The signal for proton-9 appears as a triplet at  $5.25\tau$  split by the C-10 methylene protons ( $J_{9,10} = 6\text{Hz}$ ) and broadened by allylic coupling with the proton in position 7. The signal for proton-7 appears as a doublet of doublets centred at  $4.5\tau$ . Major coupling with proton-6 is 10Hz and the minor coupling with proton-9, not discernible in the signal for proton-9, is 2Hz. The signal for proton-6 occurs within the aromatic proton multiplet and that for proton-11 occurs as a sharp singlet at  $4.05\tau$ .

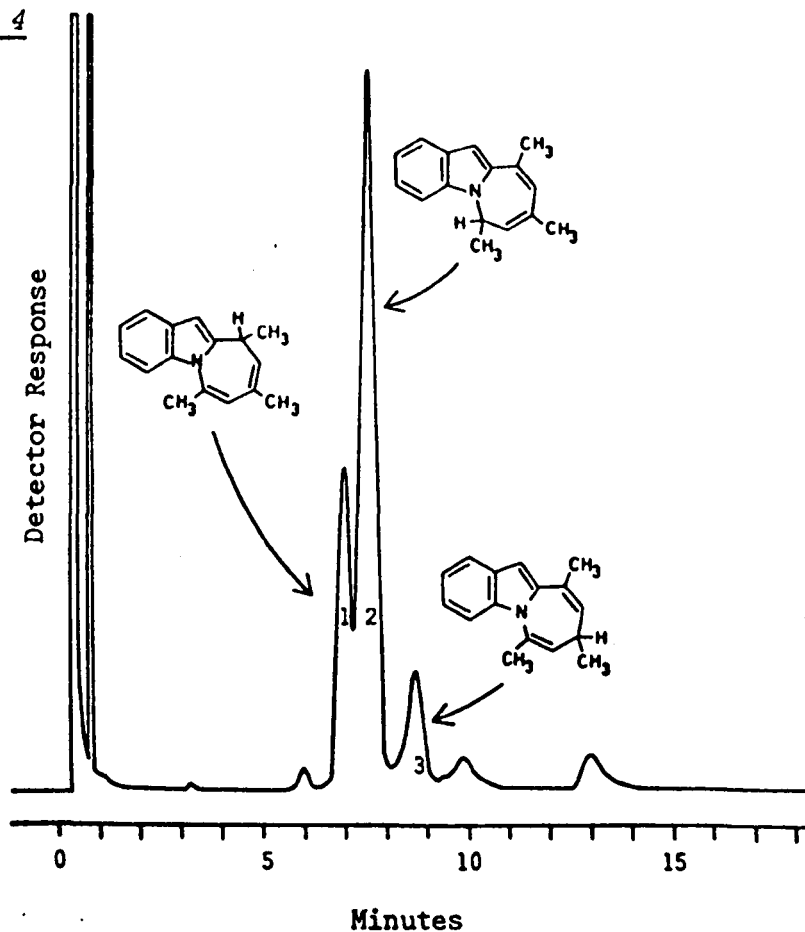
Further work on this decomposition product will be described later.

The decomposition of 2'-azido-2,4,6-trimethyldiphenylmethane (82) gave a mixture which was shown on examination by gas chromatography to comprise mainly three products (Figure 4).

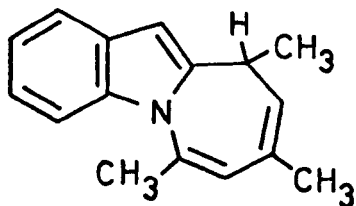
A partial separation of the products was obtained by column chromatography on alumina of high activity. By combining some of the fractions off the column it was possible to isolate small quantities of each of the major products.



FIGURE 4



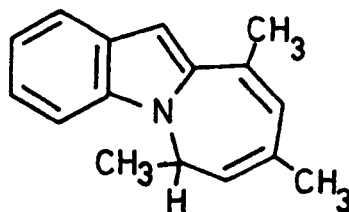
The products were identified from n.m.r., mass and ultraviolet spectra as the isomeric 6,8,10-trimethylazepino-[1,2- $\alpha$ ]indoles (94), (95) and (96).



(94)

20.4% yield

(Product 1)

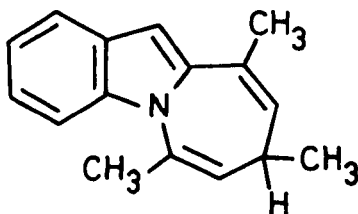


(95)

41% yield

(Product 2)





(96)

12.9% yield

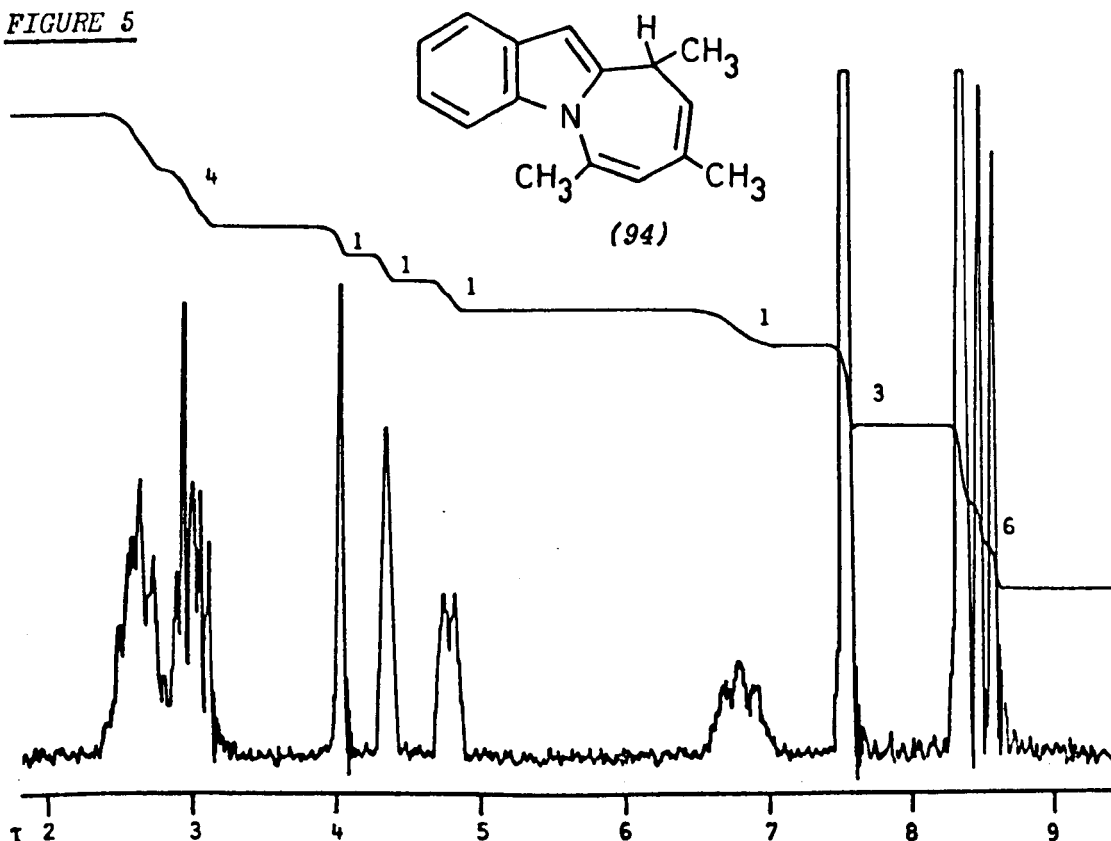
(Product 3)

The yield of each product was estimated by quantitative gas chromatography using an internal standardisation technique.<sup>103</sup> Peak positions and response ratios were established using the isolated samples.

The assignment of the 10H-azepinoindole structure (94) to product 1 is based on the similarity of its n.m.r. spectrum (Figure 5) to those of the 10H-azepinoindoles (87) and (93).



FIGURE 5



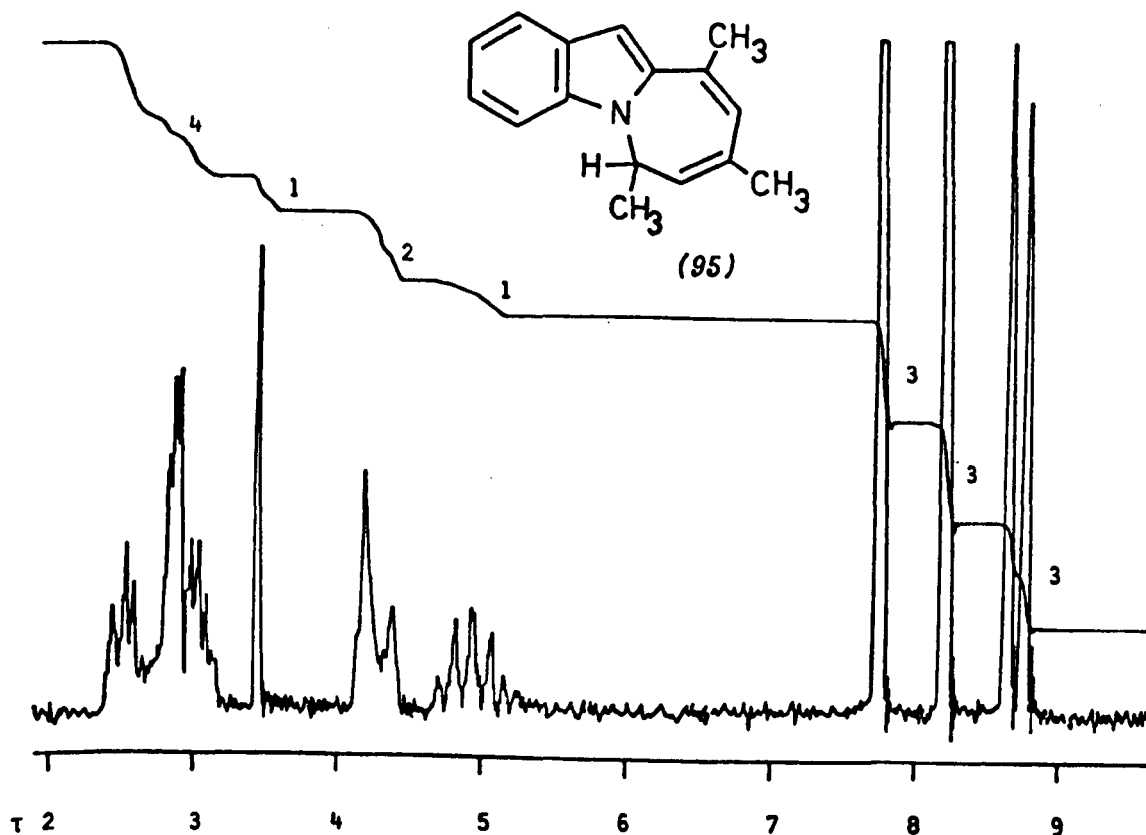
The resonance for proton-11 on the five-membered ring occurs as a sharp singlet at  $4.05\tau$  in the expected position for a 10H-azepinoindole. In place of the C-10 methylene signal of the previously described 10H-azepinoindoles there is a one proton multiplet which can be assigned to the single proton in position 10. The C-10 methyl group signal occurs as a doublet at  $8.5\tau$  ( $J = 7\text{Hz}$ ) and the three proton singlets at  $7.55\tau$  and  $8.35\tau$  are therefore assigned to the other two methyl



groups. The signals for the protons in positions 7 and 9 occur at 4.4 $\tau$  and 4.8 $\tau$  as a one proton singlet and one proton doublet respectively. Both signals are broadened by allylic coupling. The coupling  $J_{9,10}$  can be estimated from the H-9 doublet as 6Hz.

An examination of the n.m.r. spectrum (Figure 6) of product 2, the 6H-isomer, shows several important differences from that of the 10H-isomer.

FIGURE 6





The downfield shift of the proton in position 11 ( $3.5\tau$ ) compared with the chemical shift ( $4.0\tau$ ) of the C-11 proton in the 10H-azepinoindoles (87), (93) and (94) is consistent with the extension of conjugation into the seven-membered ring. Further evidence for the 6H structure (95) is obtained by comparing the positions of the methine  $\text{CHCH}_3$  multiplet. This occurs at  $6.8\tau$  in the 10H-azepinoindole (94) but at  $4.9\tau$  in the 6H-azepinoindole (95) where this proton is on a carbon atom attached directly to nitrogen. The C-6 methyl group signal occurs as a doublet at  $8.75\tau$  ( $J = 7\text{Hz}$ ) and the signals at  $7.55\tau$  and  $8.2\tau$  can be assigned to the two other methyl groups. The signals for the protons in positions 7 and 9 occur as overlapping peaks in the region of  $4.2\tau$ .

A consideration of the structures (94) and (95) of the 10H- and 6H-azepinoindoles shows that the methyl group in position 8 is in the same environment in each structure. Examination of the chemical shifts of the methyl groups then shows that the C-8 methyl group resonance must occur at  $8.35\tau$  in the 10H-azepinoindole (94) and at  $8.2\tau$  in the 6H-azepinoindole (95). Consequently the C-6 methyl group resonance of (94) and the C-10 methyl group resonance of (95) must occur at  $7.55\tau$  and  $7.75\tau$  respectively.

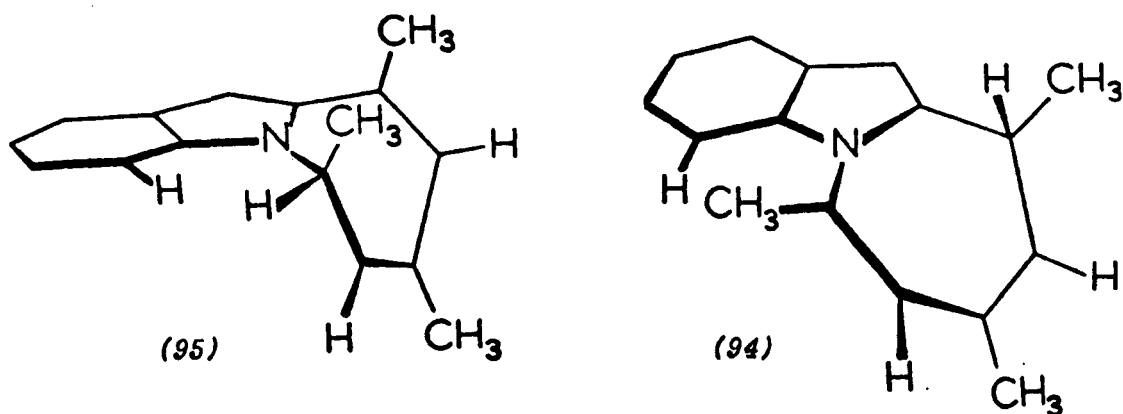
The coupling constant between the methine  $\text{CHCH}_3$



proton and the proton on the adjacent carbon atom is different in the azepinoindoles (94) and (95).

In the 10H-isomer (94)  $J_{9,10}$  is 6Hz and  $J_{6,7}$  in the 6H-isomer (95) is 10Hz. The chemical shifts of the  $\text{CHCH}_3$  methyl groups are also different (8.5 $\tau$  in isomer (94) and 8.75 $\tau$  in isomer (95)). These facts can be explained after considering the projections drawn in Figure 7.

FIGURE 7



In the 6H-azepinoindole the methyl group occupies a quasi-axial position in order to minimise steric interaction which would occur with the proton on C-4 if the methyl group were quasi-equatorial. The protons in positions 6 and 7 are then almost



coplanar leading to the value of 10Hz for  $J_{6,7}$ . In the 10H-azepinoindole the methyl group can be quasi-equatorial and the dihedral angle ( $\sim 120^\circ$ ) between the protons in positions 9 and 10 is in accord with the lower value of 6Hz for  $J_{9,10}$ .

In the decompositions described previously the isolated products were based on the 10H-azepino[1,2-*a*]indole ring system whereas in this decomposition the major product is the 6H-isomer (95). The reason for this becomes apparent on examining the projections drawn in Figure 7. In the 10H-isomer (94), and also to a lesser extent in the 8H-isomer (96), the C-6 methyl group has to occupy a position where it lies in close proximity to the proton in position 4. Thus non-bonded interactions are high and the production of the 6H-isomer as major product together with a significant yield of the 8H-isomer reflects the compromise between obtaining the stable 10H-azepinoindole ring system and minimising the non-bonded interactions.

The assignment of the 8H-azepinoindole structure (96) to product 3 is based on a comparison of its mass and ultraviolet spectra with those of the 10H- and 6H-azepinoindoles (94) and (95), there being insufficient material for an n.m.r. spectrum. The mass spectra of all three isomers are virtually identical, the base peak in each spectrum being at  $M^+ - 15$  and representing the azepinoindolium ion. This is a stable ion as shown by the



doubly charged ion at  $m/e$  104 and little further breakdown takes place.

The ultraviolet absorption spectra (Figure 8) of the 6H- and 8H-azepinoindoles (95) and (96) are very similar.

FIGURE 8

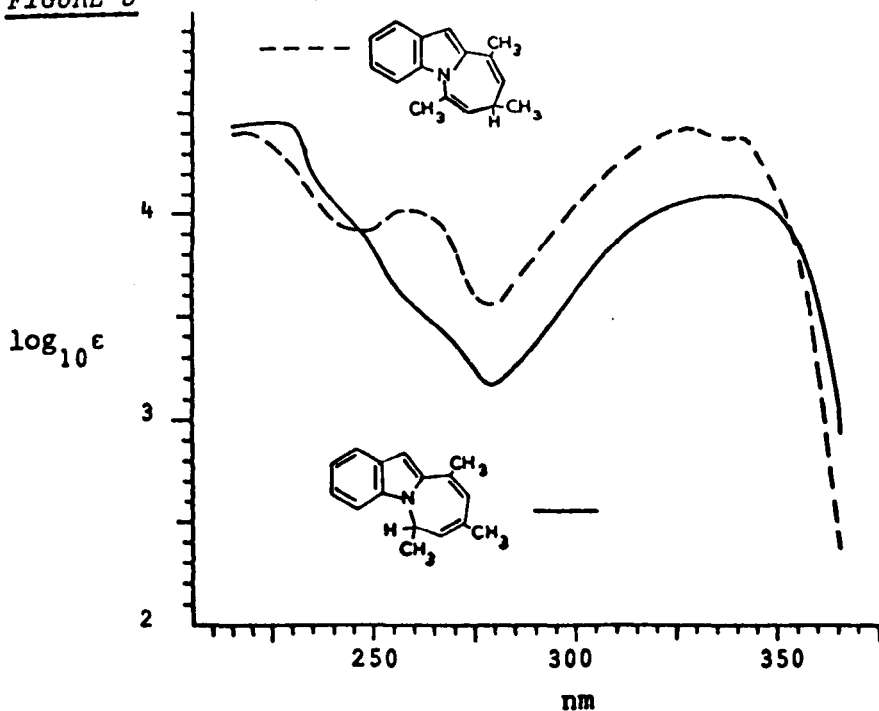
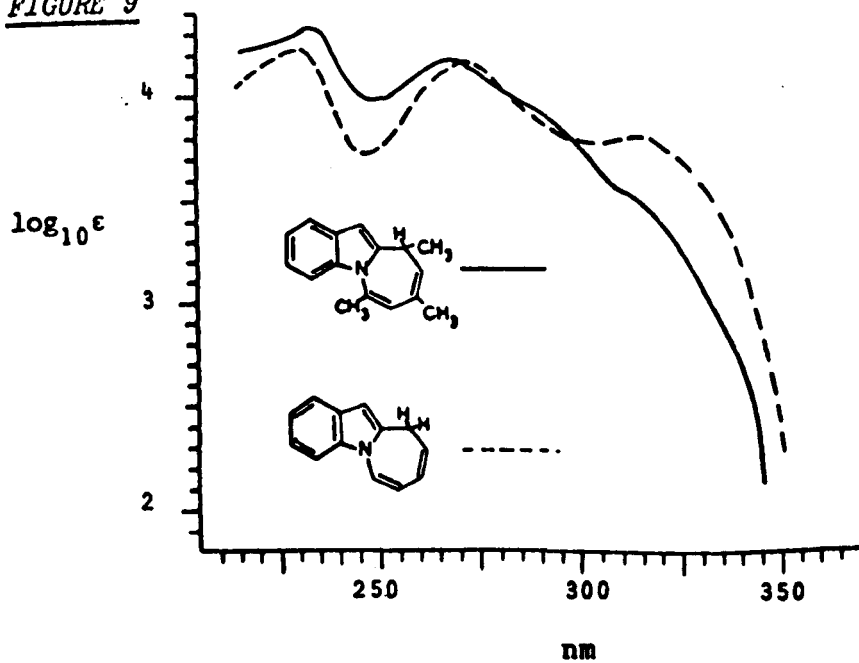


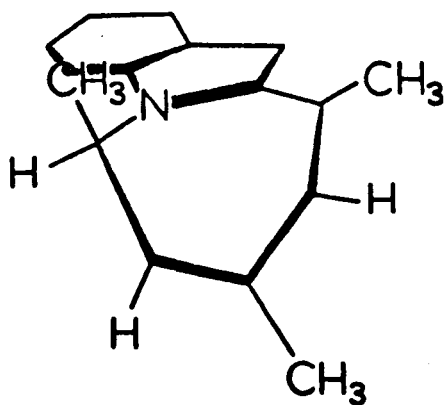
FIGURE 9



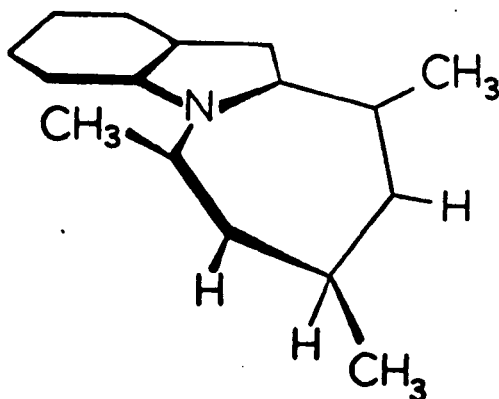


Both spectra show a shift to longer wavelength from those of the 10H-azepinoindoles (87) and (94) (Figure 9) consistent with the extension of conjugation into the seven-membered ring. It might have been expected that the spectrum of the 6H-isomer (95) would show a greater shift to longer wavelength than the 8H-isomer (96) because of the possibility of more extensive conjugation. However, an examination of models and the projections drawn in Figure 10 shows that in the 6H-isomer the 7-8 double bond is in an entirely different plane from that of the 9-10 and 10a-11 double bonds thus preventing significant overlap of the *p*-orbitals. Similarly, in the 8H-isomer (96) conjugation through the nitrogen atom is minimal because the plane of the 6-7 double bond is such that no significant overlap of the nitrogen *p*-orbital with the *p*-orbitals of the double bond can take place.

FIGURE 10



(95)

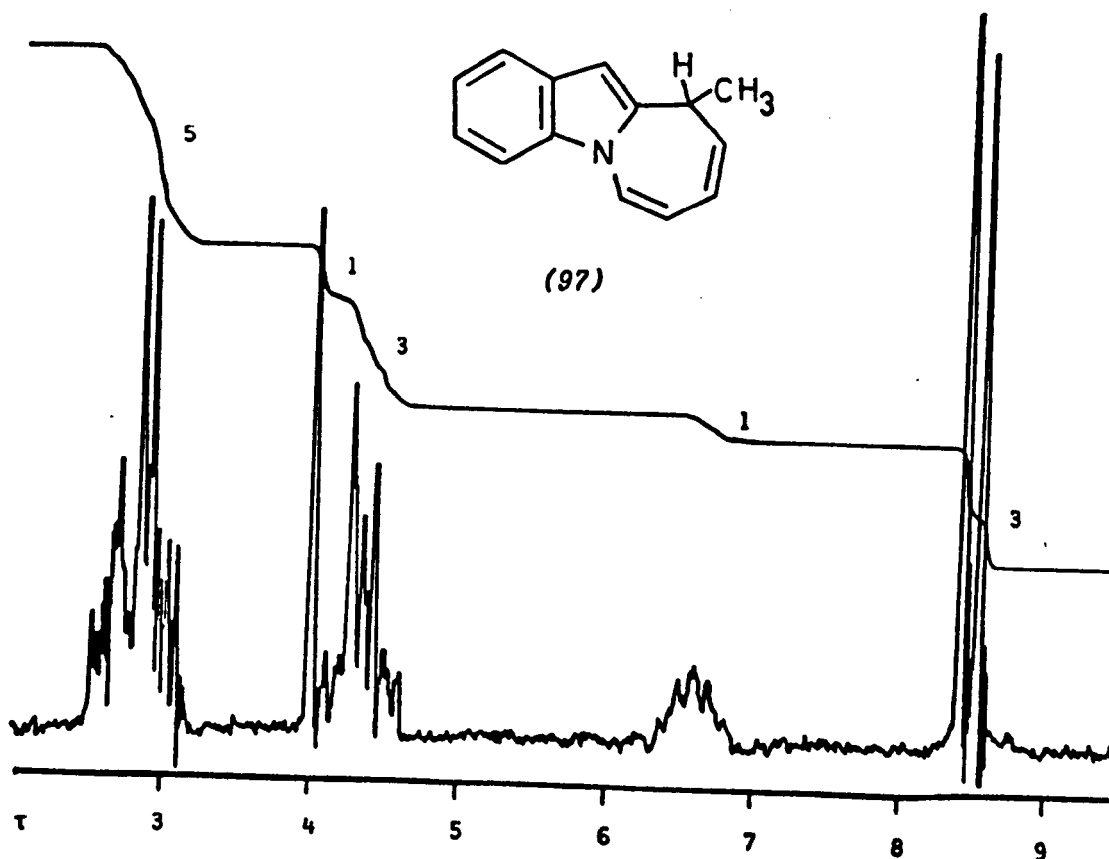


(96)

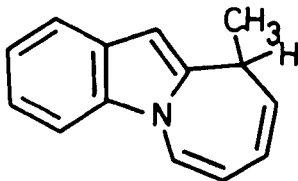


The decomposition of 2-azido-2'-methyldiphenylmethane (83) gave a mixture which was shown by gas chromatography to consist of two major and three minor components. Percolation of the crude mixture through alumina removed dark coloured material and gave the product mixture as a yellow oil from which only one pure component was isolated. This was identified, chiefly from its n.m.r. spectrum (Figure 11) as 10-methyl-10H-azepino[1,2-a]indole (97) obtained in 27.5% yield after chromatography.

FIGURE 11





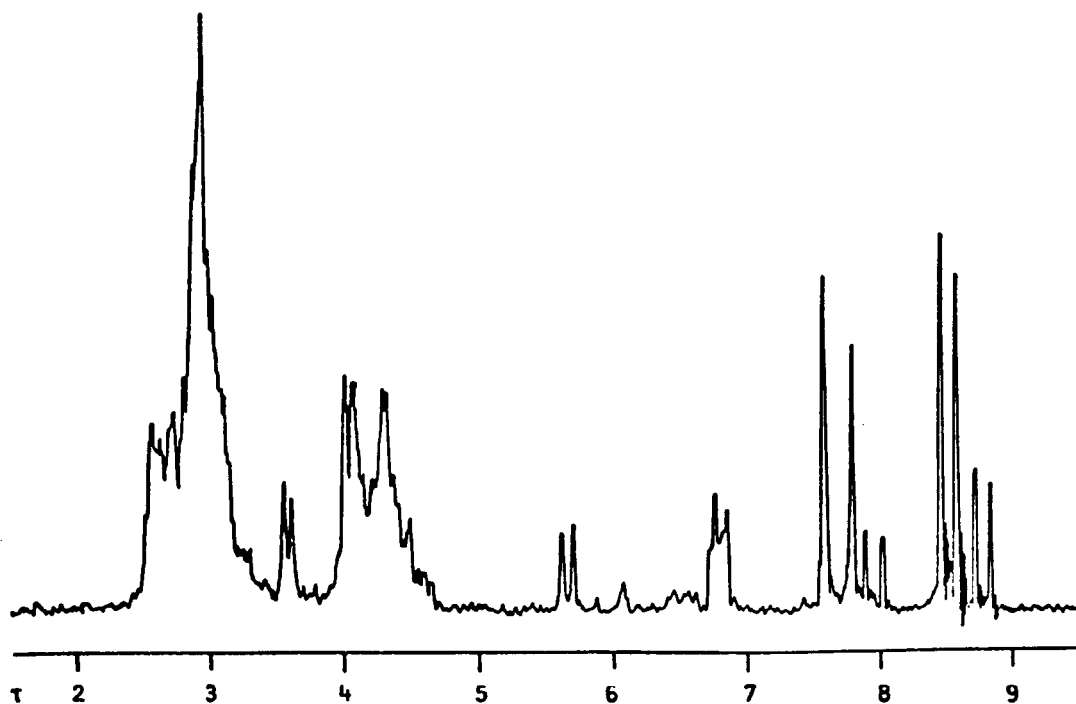


(97)

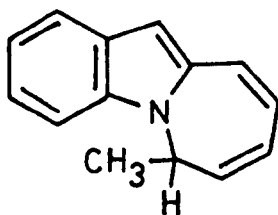
The structure (97) was arrived at by the following reasoning: The n.m.r. spectrum shows the resonance of the proton on the five-membered ring as a sharp singlet at  $4.0\tau$  in the expected position for a 10H-azepinoindole. There is however no methylene doublet in the region of  $6.5\tau$  therefore the methyl group must occupy position 10. This is confirmed by an examination of the spectrum which shows a three proton doublet at  $8.4\tau$  ( $J = 7\text{Hz}$ ) and a one proton multiplet at  $6.3 - 6.8\tau$ . Both signals are in good agreement with the corresponding signals in the spectrum of the trimethyl-10H-azepinoindole (94).

Having established the structure of the isolated product a re-examination of the n.m.r. spectrum of the crude decomposition products (Figure 12) showed that there was evidence for the assignment of structures (98), (99) and (100) to three further products.

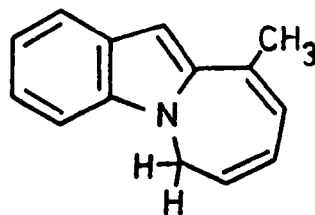


FIGURE 12

There is a second methyl doublet centred at 8.75 $\tau$  which is in good agreement with the position of the C-6 methyl group in the 6H-azepinoindole (95). This suggests the presence of 6-methyl-6H-azepino[1,2-*a*]indole (98).



(98)

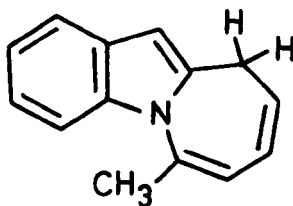


(99)



The doublet at 5.6 $\tau$  ( $J = 6\text{Hz}$ ) is in the expected position for a methylene group situated between a nitrogen atom and a double bond system. This signal and the singlet at 7.7 $\tau$  suggest that 10-methyl-6H-azepino[1,2- $a$ ]indole (99) is a product of the decomposition. Further evidence for structures (98) and (99) is provided by the two signals at 3.5 $\tau$  and 3.6 $\tau$  which can be assigned to the C-11 protons by analogy with the position (3.5 $\tau$ ) of the signal for the C-11 proton in the trimethyl-6H-azepinoindole (95).

The signal at 7.55 $\tau$  together with the poorly resolved doublet at 6.75 $\tau$  indicate the presence of 6-methyl-10H-azepino[1,2- $a$ ]indole (100).



(100)

The decomposition of 2-azido-2'-methoxydiphenylmethane (84) gave, surprisingly in view of the one major product from the isomeric azide (81), a product mixture which on examination by gas



chromatography appeared to contain 10 components, subsequently referred to as products 1 - 10 corresponding to peaks 1 - 10 on this chromatogram (Figure 13, page 60).

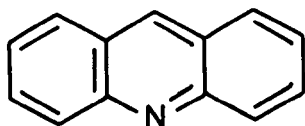
Acid washing of a portion of the crude products extracted three basic compounds, products 3, 6 and 9. A chromatogram of the remaining, neutral compounds showed that products 3 and 9 had been almost completely removed whereas the peak for component 6 had only been reduced in size. Peak 6 was not removed even by prolonged acid washing and this led to the conclusion that peak 6 on the chromatogram represented two products.

An examination of the basic and neutral products using a linked gas chromatograph-mass spectrometer system gave molecular ions for each major peak as shown in Figure 13. A comparison of the mass spectral fragmentation patterns of products 3 and 6 (basic) with authentic specimens showed the presence of acridine (101) ( $m/e$  179) and 2-amino-2'-methoxydiphenylmethane (76) ( $m/e$  213).

An initial separation of the decomposition products was obtained by column chromatography on alumina. Each fraction was then separated further by extensive preparative layer chromatography until pure samples of six products were isolated and characterised. The yield of each product was estimated by



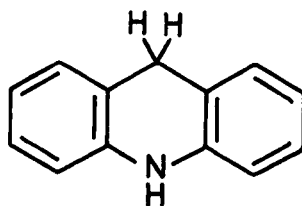
quantitative gas chromatography using an internal standardisation technique.<sup>103</sup> The isolated products and yields are recorded below:



(101)

3% yield

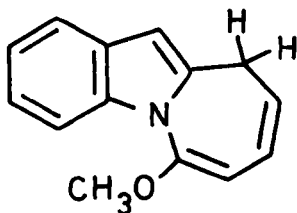
(Product 3)



(102)

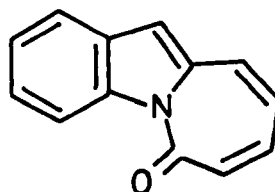
10% yield

(Product 4)



(103)

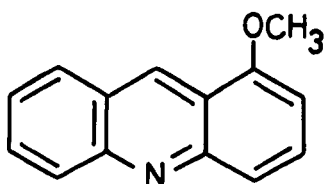
(Product 6 - neutral)



(104)

8% yield

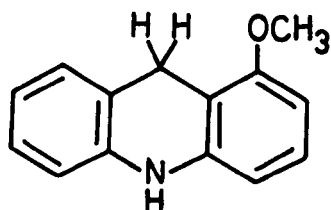
(Product 7)



(105)

7% yield

(Product 9)



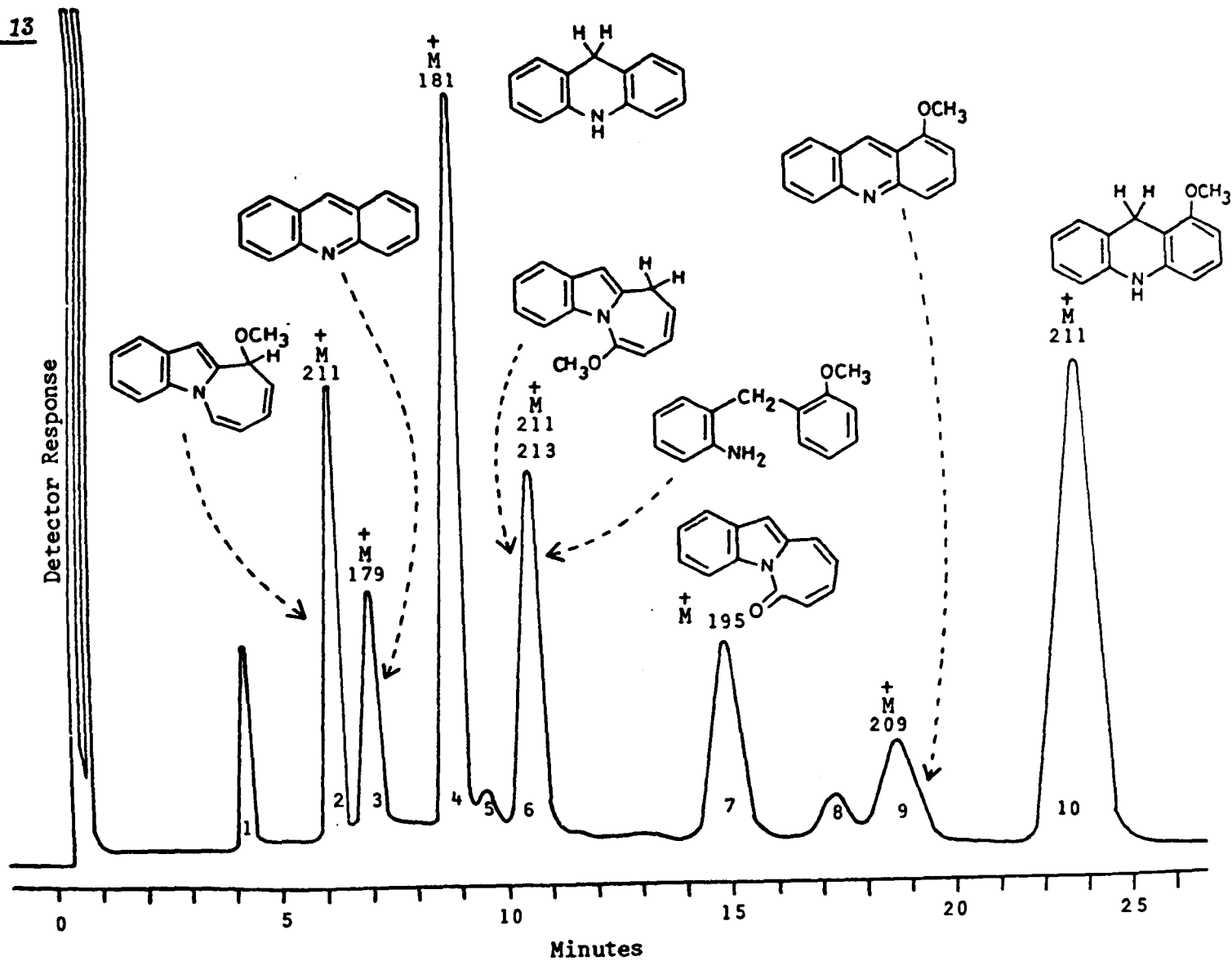
(106)

26% yield

(Product 10)

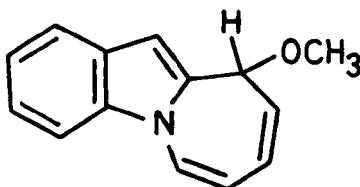


**FIGURE 13**





No product corresponding to peak 2 was isolated. The mass spectrum of product 2 was very similar to the mass spectrum of the isolated methoxy-10H-azepinoindole (103) and also to that of the previously characterised methoxy-10H-azepinoindole (93). All three spectra showed a molecular ion at  $m/e$  211 with initial loss of 15 mass units ( $\text{CH}_3$ ) followed by a loss of 29 ( $\text{CHO}$ ) to give a stable ion at  $m/e$  167 shown by the doubly charged ion at  $m/e$  83.5. It is therefore reasonable to assign the 10-methoxy-10H-azepino-[1,2- $\alpha$ ]indole structure (107) to product 2.

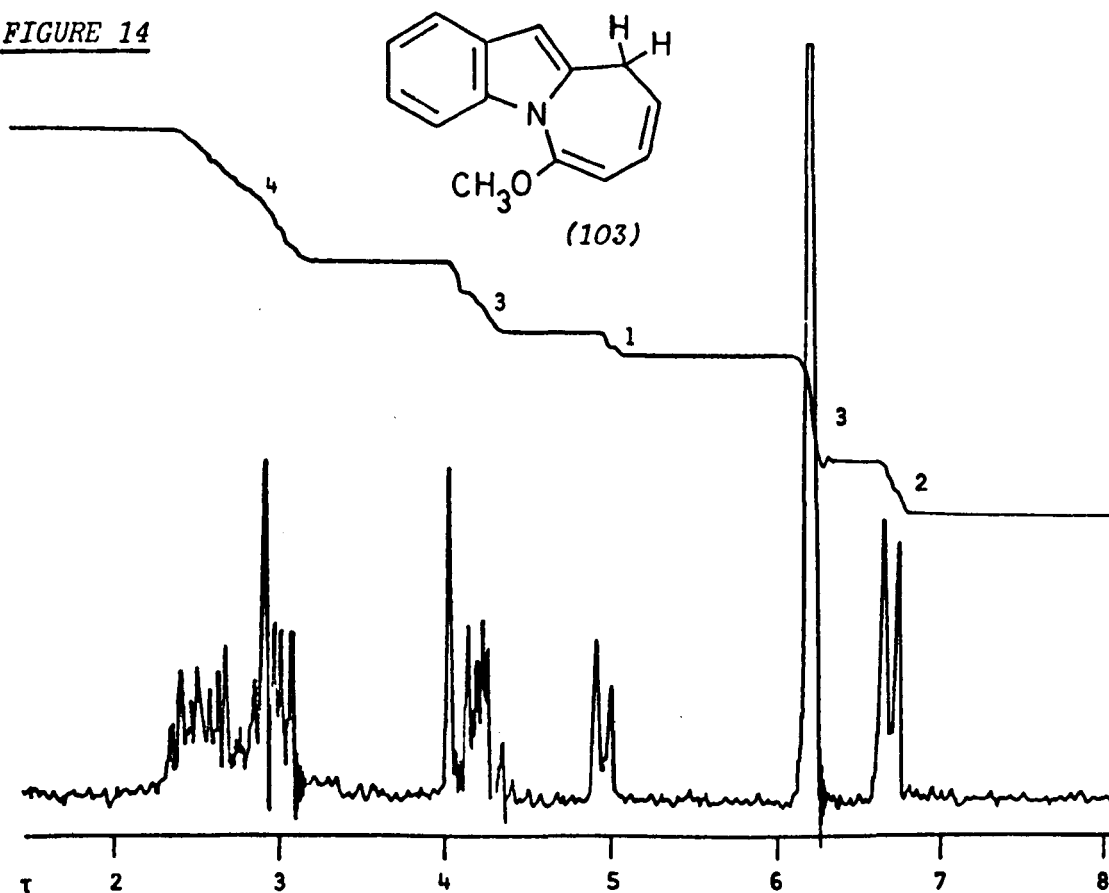


(107)

Thus eight of the decomposition products were identified.

The structure of the 6-methoxy-10H-azepino[1,2- $\alpha$ ]indole (103) was assigned on the basis of its n.m.r. spectrum (Figure 14).



FIGURE 14

The two proton doublet at 6.7 $\tau$  and the sharp singlet at 4.05 $\tau$  are both indicative of the 10H-azepinoindole ring system and the splitting pattern of the seven-membered ring protons shows that the methoxyl group is in position 6. Proton-7 appears as a doublet at 5.0 $\tau$  and protons-8 and -9 as a multiplet at 4.15 - 4.35 $\tau$ .

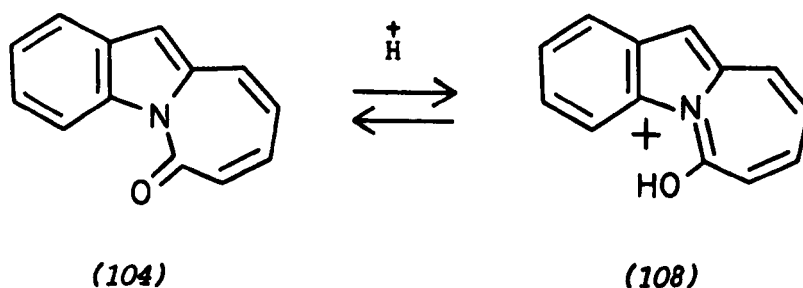
1-Methoxyacridan (106) readily oxidised in air to 1-methoxyacridine (105) and the assignment of structure (105)



as the 1-methoxy-isomer is particularly important when considering the mechanism of the decomposition. The resonance of proton-9 in acridine (101) occurred at 1.3 $\tau$ . That of proton-9 in the methoxyacridine (105) occurred at 0.7 $\tau$  and this downfield shift can only be reconciled with interaction between proton-9 and the methoxyl group which must therefore be in position 1. Confirmation of this assignment was obtained by the comparison of an authentic sample of 1-methoxyacridine with the sample obtained from the decomposition.

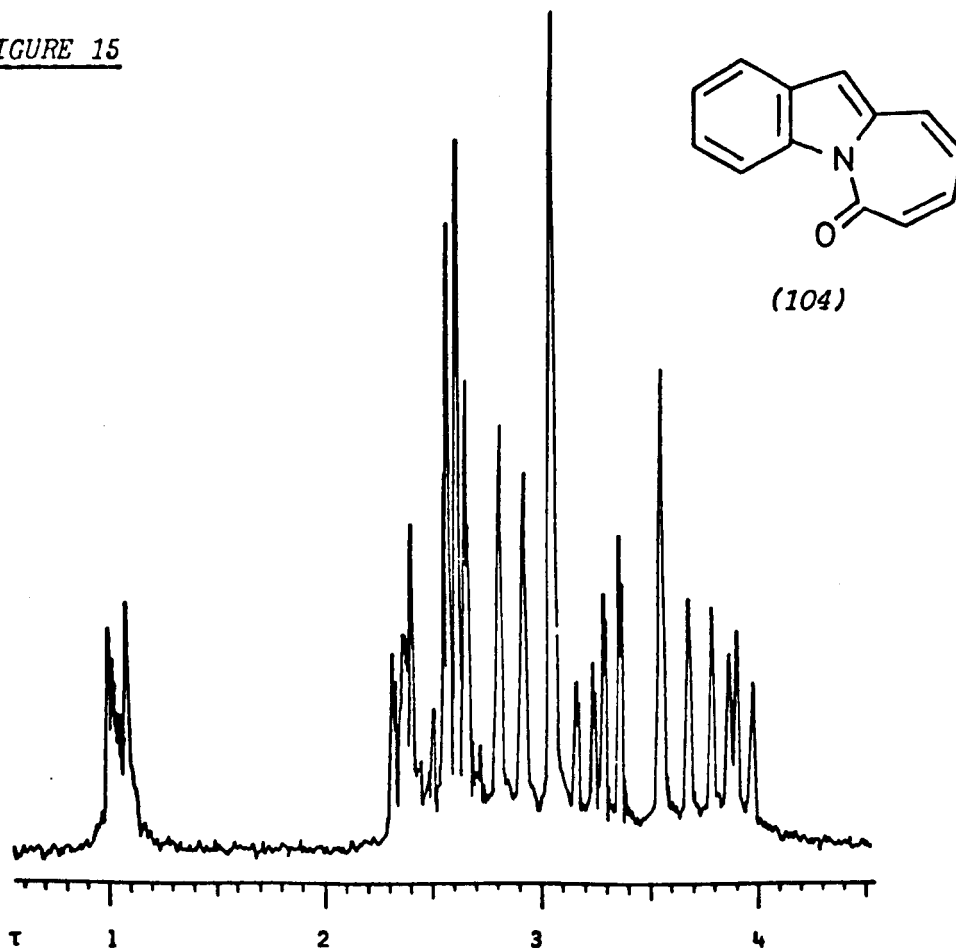
Azepino[1,2- $\alpha$ ]indol-6-one (104) was obtained as deep yellow crystals. A solution in concentrated sulphuric acid was deep blue in colour showing the presence of the protonated form, the azonia-azulenium system (108).

SCHEME 22



The n.m.r. spectrum of the azepinoindolone (104) is shown in Figure 15.



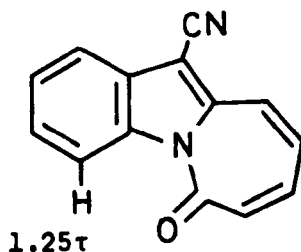
FIGURE 15

The signals for protons-7 and -10 can be expected to occur as primary doublets and two doublets appear in the spectrum centred at 2.8 $\tau$  and 3.6 $\tau$ . The doublet at 3.6 $\tau$  is assigned to proton-7 adjacent to the carbonyl group by analogy with the position (3.6 $\tau$ ) of the proton adjacent to the carbonyl group in the methylazepinoindolone (39).<sup>36</sup> Therefore the doublet at 2.8 $\tau$  can be assigned to proton-10. The couplings  $J_{7,8} = 12.5\text{Hz}$  and  $J_{9,10} = 11\text{Hz}$  allow the assignment of the quartet of



doublets centred at  $3.2\tau$  and the broadened quartet centred at  $3.85\tau$  to protons-8 and -9 respectively. Two values for  $J_{8,9}$  can be estimated from these quartets and these agree well with one another to give a value of 7.5Hz. The minor coupling  $J_{8,10} = 1.5\text{Hz}$  can be measured from the H-8 signal but the minor coupling  $J_{7,9}$  is apparent only by a broadening of the signals for both protons-7 and -9. The signal for proton-11 stands out at  $3.0\tau$  and the downfield complex signal which integrates for one proton must therefore be due to proton-4.

The chemical shift of proton-4 ( $1.0\tau$ ) is in good agreement with that of the corresponding proton in the azepinoindole (109) reported by Kaneko, Yamada and Ishikawa<sup>104</sup> as a product from the photolysis of 9-cyanoacridine 10-oxide.

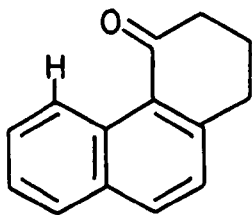


(109)

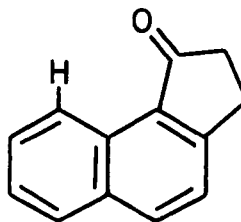
There are many examples of the deshielding of protons which lie close to the oxygen atom and in the same plane as the trigonal carbon atom of a carbonyl group. For instance; Martin,



Defay and Geerts-Evrard<sup>105</sup> have reported that in the compounds (110) and (111) the indicated aromatic protons suffer a downfield shift of 1.67 and 1.26 p.p.m. respectively relative to the corresponding protons in the parent systems.



(110)



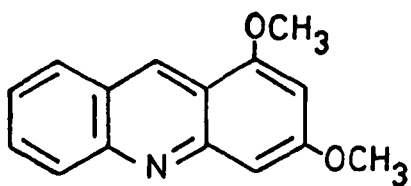
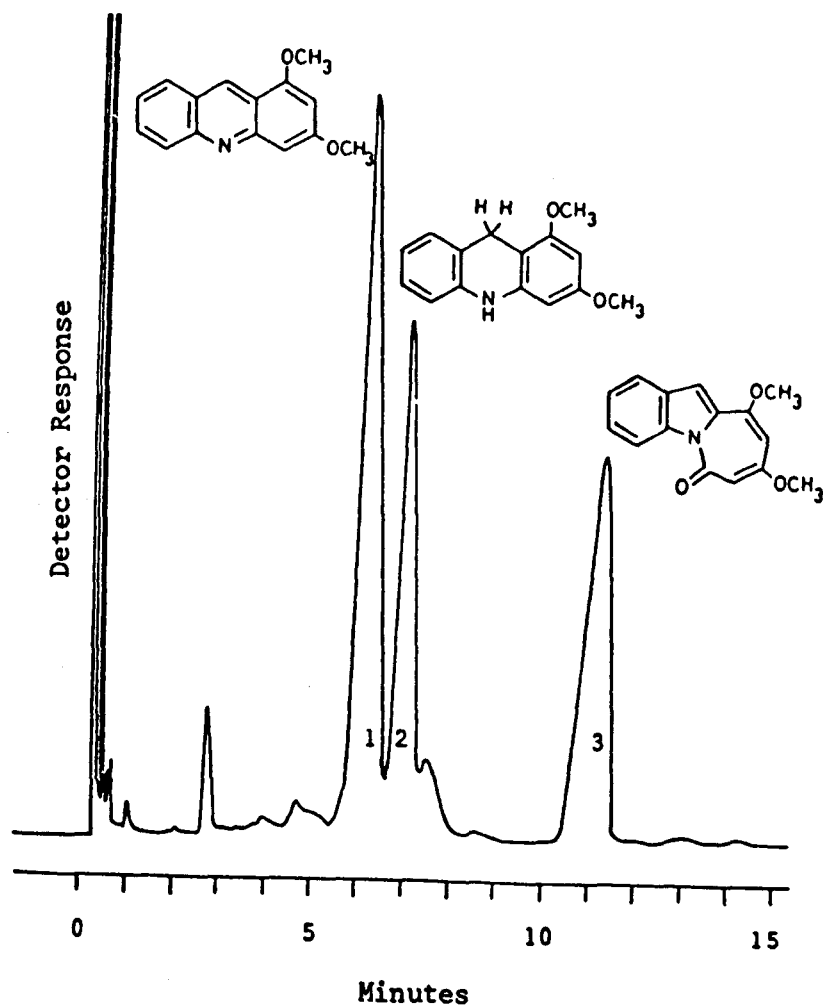
(111)

The decomposition of 2'-azido-2,4,6-trimethoxydiphenylmethane (85) gave a much simpler mixture of products consisting largely of three components as shown by gas chromatography (Figure 16).

The three products were isolated by preparative layer chromatography and identified as 1,3-dimethoxyacridine (112), 1,3-dimethoxyacridan (113) and 8,10-dimethoxyazepino-[1,2-a]indol-6-one (114). The percentage yield of each product was estimated by gas chromatography.

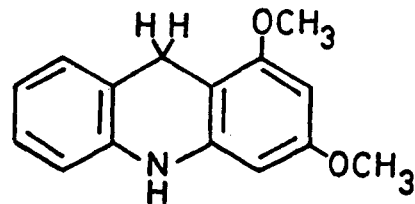


FIGURE 16



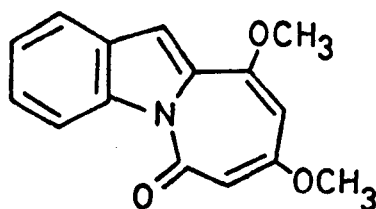
(112)

24.5% yield



(113)

21.4% yield



(114) 22.6% yield



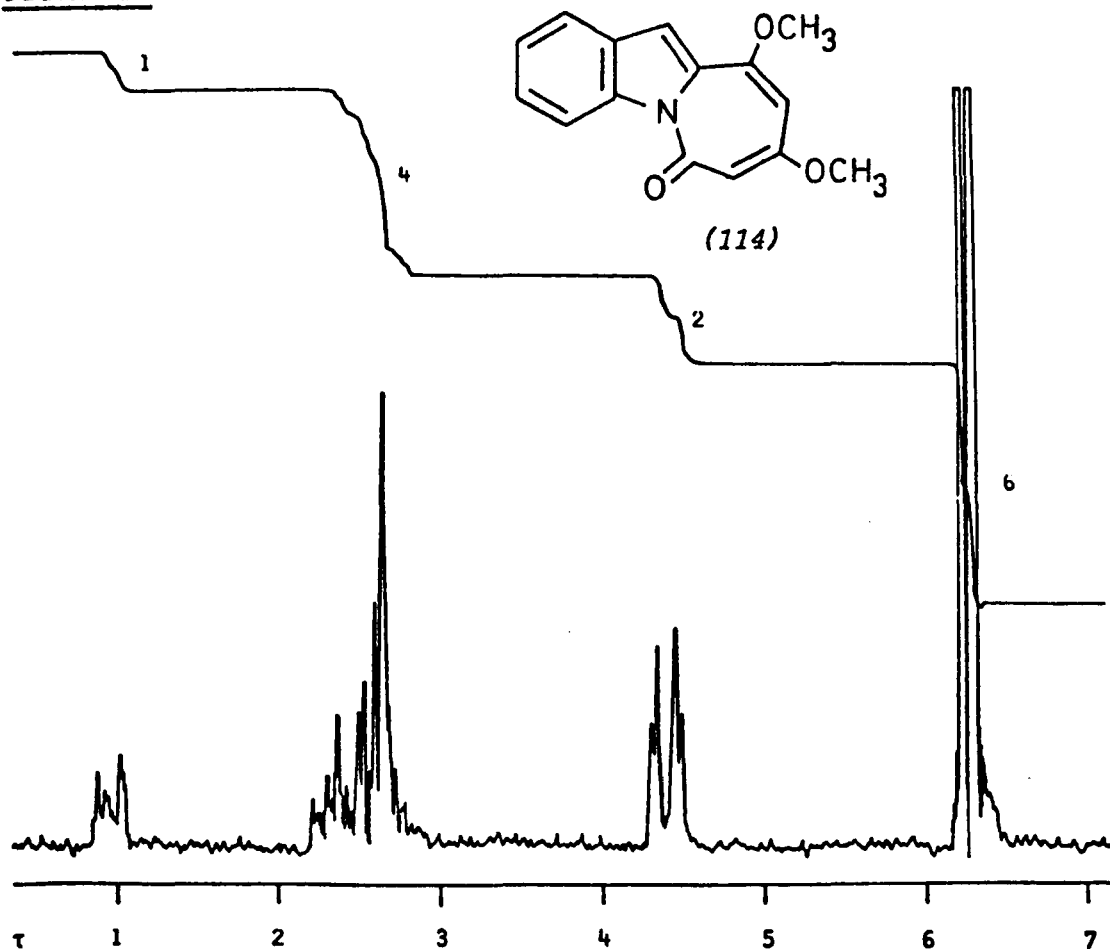
The acridan (113) was contaminated with a small amount of the acridine (112) and could not be completely purified. However, its structure was established beyond doubt by a comparison of the n.m.r. spectrum and g.l.c. retention time of a synthetic sample of 1,3-dimethoxyacridan with those of the acridan (113) isolated from the decomposition. The synthetic sample of 1,3-dimethoxyacridan was prepared by the following unambiguous route:

1,3-Dihydroxyacridine was prepared (from *o*-aminobenzaldehyde<sup>106</sup> and phloroglucinol) by the method of Hughes and Ritchie.<sup>107</sup> This was methylated with diazomethane and catalytically hydrogenated to give the acridan (113).

The assignment of the azepinoindol-6-one ring structure to compound (114) was based on a comparison of its n.m.r. spectrum (Figure 17, page 69) with that of the previously characterised azepino[1,2-*a*]indol-6-one (104).

A similar downfield one proton complex signal occurs at 1.05 $\tau$  and the doublets ( $J = 2\text{Hz}$ ) at 4.3 and 4.45 $\tau$  are assigned to protons-7 and -9 respectively.



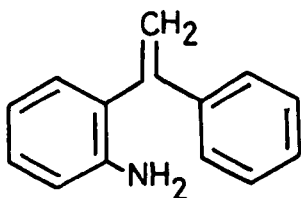
FIGURE 17

The azepinoindoles isolated from the decompositions described above have been based on the 10H-azepinoindole ring system except where steric restrictions made the 6H- and 8H-isomers favourable products. Any reaction schemes which can be advanced give the final product by a 1,3-, a 1,5- or a 1,7-hydrogen shift from an initially formed 11H-azepinoindole.

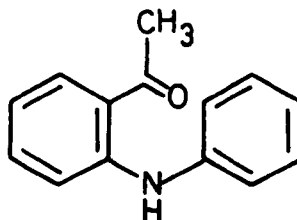
In an attempt to trap the intermediate 11H-species



1-(2-azidophenyl)-1-phenylethanol (86) was decomposed at  $180^{\circ}$ . The major product was 1-(2-aminophenyl)-1-phenylethylene (115) formed by hydrogen abstraction and dehydration.



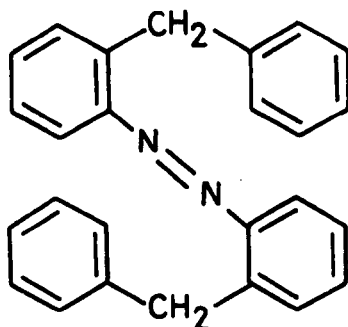
(115)



(116)

Presumably hydrogen abstraction by the nitrene must take place before dehydration because no indole derivatives were isolated, and the decompositions of *o*-azidostyrenes are known to give indoles.<sup>63</sup> The only other isolated product was 2-acetyldiphenylamine (116), identified by its spectral characteristics and comparison with a synthetic sample.<sup>108</sup>

The decomposition of 2-azidodiphenylmethane (59) by photolysis in benzene solution for ten hours gave a good yield of 2,2'-dibenzylazobenzene (117).

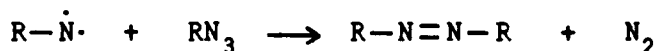


(117)



Azo-compounds have frequently been reported in the photolysis of azides<sup>56,109,110</sup> and their formation has been explained<sup>109</sup> in terms of attack by the nitrene on the azide (Scheme 22) dimerisation of the nitrene being unlikely in dilute solution.

#### SCHEME 22



#### MASS SPECTRA OF THE AZEPINOINDOLES

Three distinct breakdown patterns have been observed:

In the parent 10H-azepinoindole (87) loss of one mass unit from the molecular ion and base peak at  $m/e$  181 gives an ion corresponding to the fully aromatic azepinoindolium system. The only other significant peak in the spectrum, at  $m/e$  90.5, represents the doubly charged azepinoindolium system.

The methyl-azepinoindoles (94), (95), (96) and (97) show a similar pattern. In each case the first loss is of 15 mass units to give the base peak which again



represents the stable fully aromatic system. In the trimethylazepinoindoles (94), (95) and (96) there is a second loss of 15 mass units from the base peak ( $m/e$  208) giving an ion at  $m/e$  193.

In the mass spectra of the methoxyazepinoindoles (93), (103) and (107) the loss of  $\text{CH}_3\text{O}\cdot$  from the molecular ion at  $m/e$  211 appears to be a minor fragmentation since the ion at  $m/e$  180 is only about 30% of the base peak. The major fragmentation is loss of  $\text{CH}_3\cdot$  to give an ion at  $m/e$  196. The peaks at  $m/e$  167 and 168 could then be produced by loss of  $\text{CHO}$  or  $\text{CO}$  respectively.

The expulsion of carbon monoxide from the azepinoindolones (104) and (114) is analogous with the breakdown pattern of tropones.<sup>111,112</sup> The only other significant peak in the spectrum is produced by the loss of 27 mass units ( $\text{HCN}$ ).

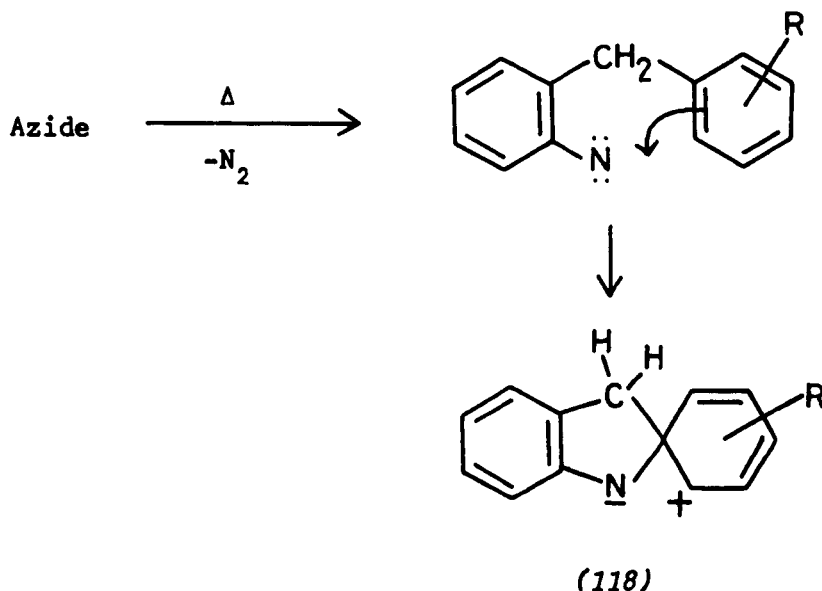
### MECHANISM

The review showed that the thermal decomposition of azides proceeds via nitrene intermediates and that nitrenes generated by the thermolysis of aryl azides are produced in the singlet, electrophilic state. Polarisation of the electrons of



the adjacent aromatic ring to give the five-membered ring spirodiene intermediate (118) is therefore a plausible first step (Scheme 23).

SCHEME 23

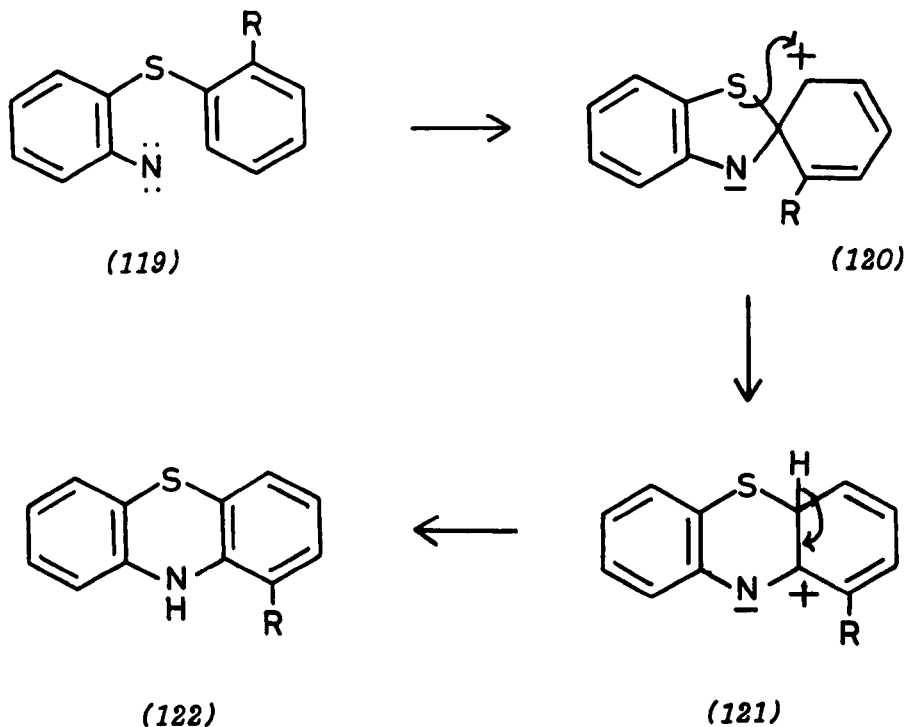


This intermediate (118) is similar to that proposed<sup>73</sup> in the superficially related decomposition of 2-azidodiphenylsulphides. The reaction, originally reported by Smith,<sup>72</sup> was reinvestigated by Cadogan, Kulik and Todd<sup>73</sup> and by Messer and Farge<sup>74</sup> and it was found that a rearrangement took place since a substituent at the 2' position in the azide turned up at position 4 in the phenothiazine (Scheme 24). The mechanism proposed by Cadogan



is shown here.

SCHEME 24



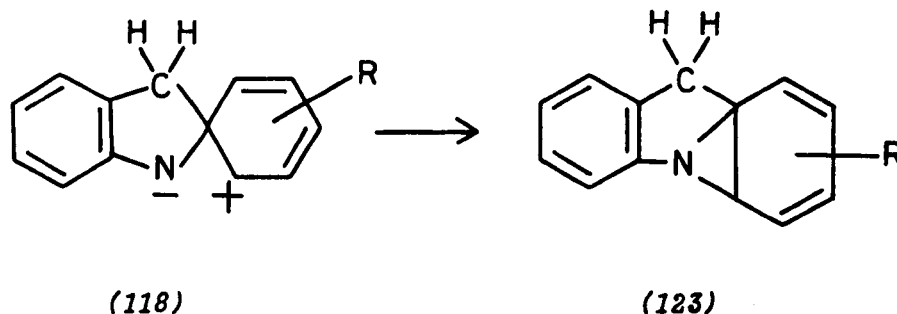
The initially formed nitrene (119) attacks the adjacent ring at the 1' position giving the spirodiene intermediate (120) which rearranges by a sigmatropic shift followed by prototropic shifts to give the phenothiazine (122).

However in the decomposition of the methoxy-  
-azidodiphenylmethanes (84) and (85), the formation of  
1-methoxyacridan (106) and 1,3-dimethoxyacridan (113) has been  
well established. The formation of these products would imply



nitrogen migration in the spirodiene (118) and therefore the most reasonable step from the intermediate (118) is to proceed to the azabicycloheptadiene (123) (Scheme 25).

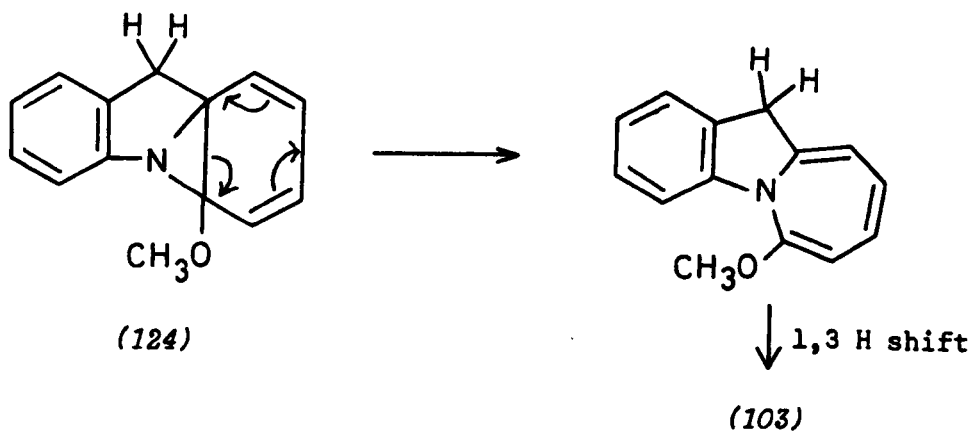
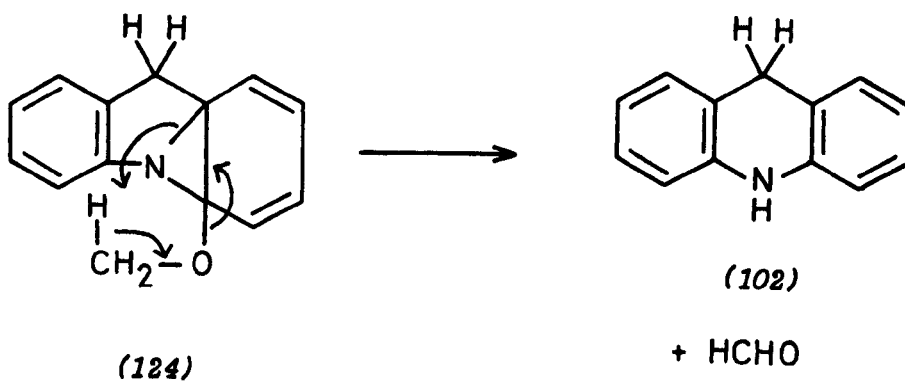
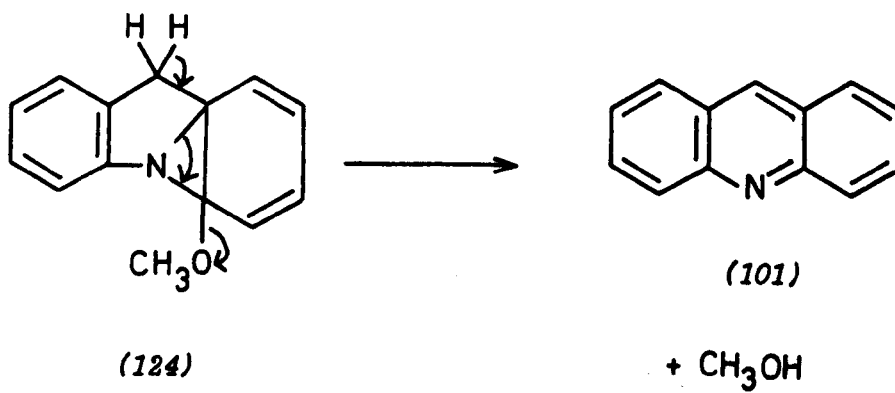
SCHEME 25



This intermediate (123) was also proposed by Krbecek and Takimoto.<sup>75</sup> The intermediacy of the azabicycloheptadiene (123) enables plausible mechanistic pathways to be proposed for both acridan and azepinoindole formation.

Thus in the decomposition of 2-azido-2'-methoxy-diphenylmethane (84) two azabicycloheptadiene intermediates are possible. Intermediate (124) can give rise to 6-methoxy-10H-azepino[1,2-a]indole (103) (Scheme 26), acridan (102) (Scheme 27) by loss of formaldehyde (as has been shown<sup>113</sup> in the phenothiazine case) and acridine (101) (Scheme 28) by loss of methanol.

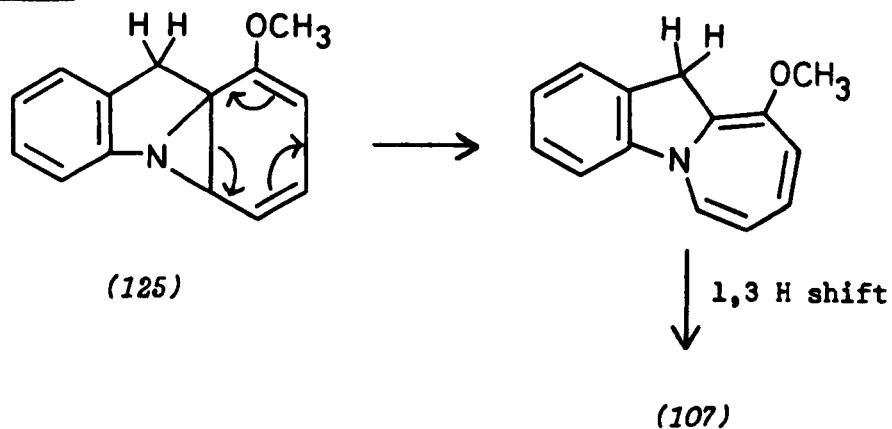


SCHEME 26SCHEME 27SCHEME 28

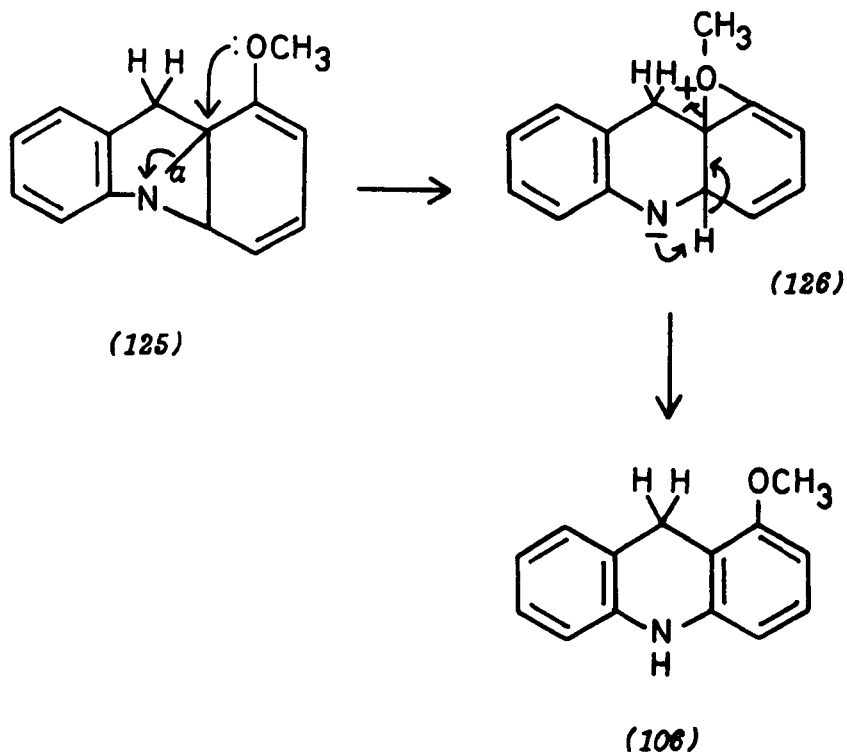


Azabicycloheptadiene intermediate (125) can give rise to 10-methoxy-10H-azepino[1,2-*a*]indole (107) (Scheme 29) or to 1-methoxyacridan (106) (Scheme 30).

SCHEME 29



SCHEME 30





Azepinoindoles are the 'normal' products in the decompositions described and the fact that this decomposition gives the methoxyacridan (106) as major product may be a consequence of assistance in the breaking of bond  $\alpha$  by the lone pair of electrons on the methoxyl group giving the anionic species (126) which readily loses a proton from the bridgehead (Scheme 30).

Schemes 27, 28 and 30 can equally well account for the formation of 1,3-dimethoxyacridan (113) and 1,3-dimethoxyacridine (112) from the decomposition of the azide (85).

However, none of the proposed schemes can account for the formation of 1-methoxyacridine (105) from the decomposition of the azide (84). Although the decomposition was carried out with rigid exclusion of oxygen there was always methoxyacridine in the products and its formation must therefore be due to the operation of an internal oxidation-reduction system. The formation of acridine (101) from (124) by loss of methanol (Scheme 28) then has the advantage of providing a reducible substrate for the methoxyacridan/methoxyacridine system. Scheme 28 is favoured over Scheme 27 since no formaldehyde could be detected in the effluent gas from the decomposition.

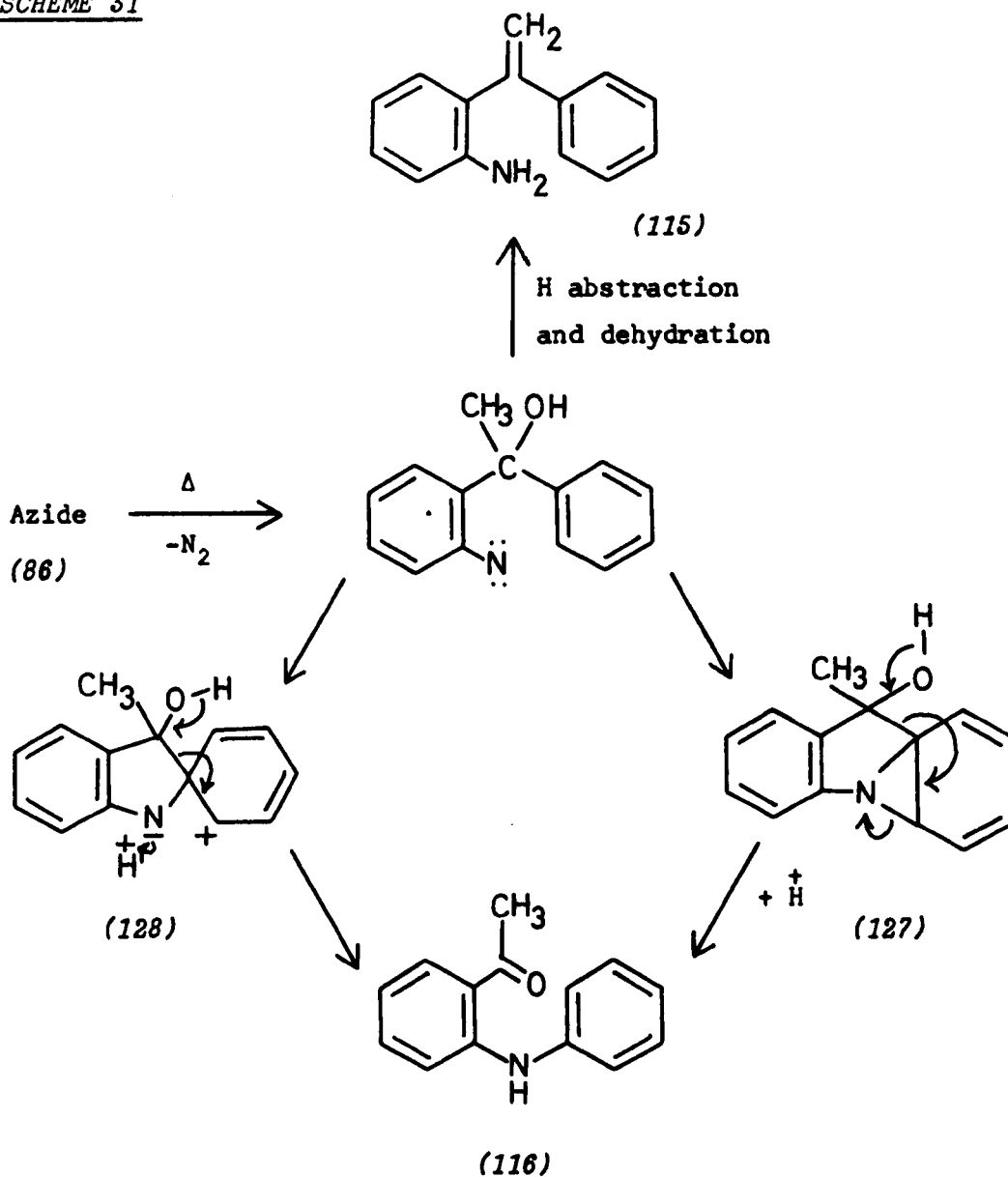
The reason why products based on the acridine ring system are only produced from 2-azidodiphenylmethanes having a



methoxyl substituent in the 2'-position cannot be due to a steric effect because of the 'normal' products from the trimethyl- and methyl-azidodiphenylmethanes (82) and (83). The 4-methoxy-azidodiphenylmethane (81) gives the 'normal' product so an electronic effect can be ruled out. Therefore acridines must be formed because the methoxyl group is a good leaving group enabling the mechanism shown in Scheme 27 to operate; and because a methoxyl group in the 2'-position can assist in the breakage of bond  $\alpha$  (Scheme 30) which results in the formation of acridines.

The decomposition of 1-(2-azidophenyl)-1-phenylethanol (86) to give 2-acetyldiphenylamine represents a third possible fragmentation of an azabicycloheptadiene intermediate (127) as depicted in Scheme 31.



SCHEME 31

2-Acetyldiphenylamine (116) could also arise from the spirodiene intermediate (128).

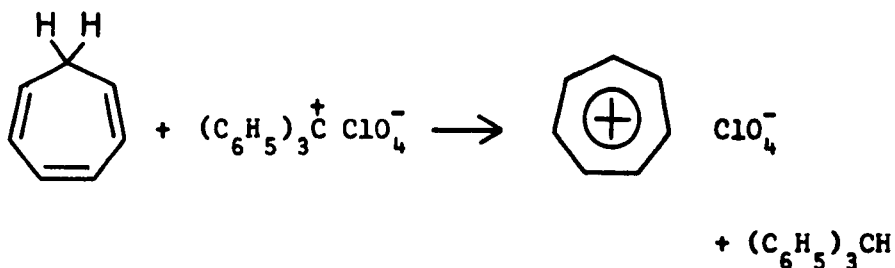


ATTEMPTS TO PREPARE AZONIA-AZULENIUM SALTS FROM THE  
AZEPINOINDOLES

From 10H-azepino[1,2-a]indole (87)

The formation of an azonia-azulenium system from azepinoindole (87) requires the removal of a hydride ion and a reagent which has been used extensively for this purpose is triphenylmethyl perchlorate.<sup>114</sup> For example Dauben and co-workers<sup>115</sup> have prepared tropylium salts by reaction of cycloheptatriene with trityl perchlorate or fluoborate in solution in acetonitrile or liquid sulphur dioxide (Scheme 32).

SCHEME 32



Accordingly azepinoindole (87) was reacted with trityl perchlorate in solution in acetonitrile and the product was obtained as a dark blue residue which did not analyse correctly for the expected azepinoindolium perchlorate. Using excess

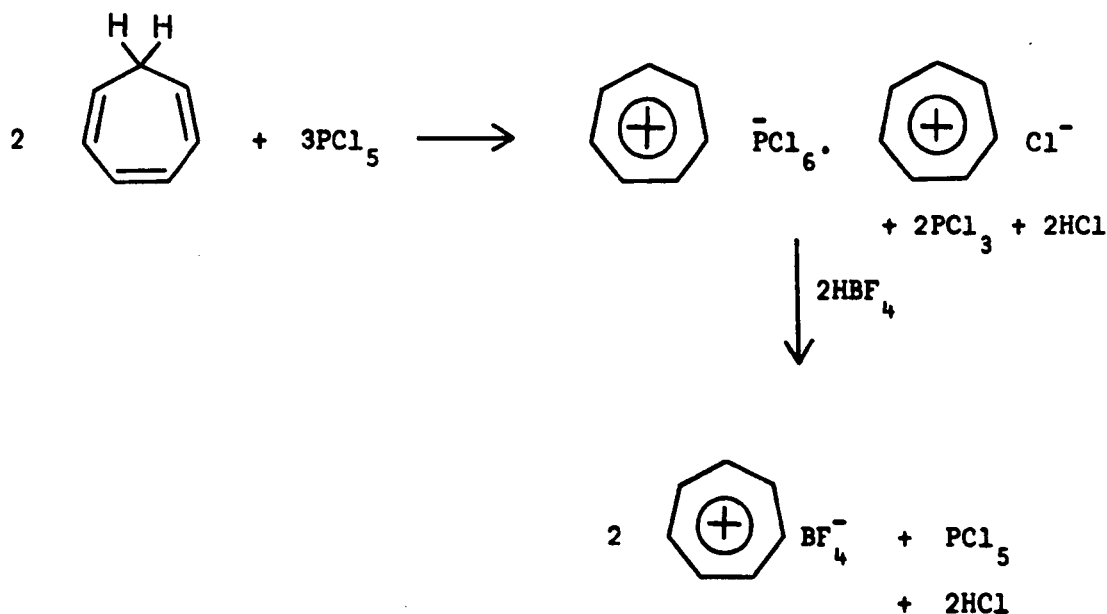


trityl perchlorate or excess azepinoindole made no difference to the reaction and a similar product was obtained in reactions using liquid sulphur dioxide as solvent. An almost quantitative yield of triphenylmethane was obtained in these reactions thus ruling out the possibility of a product incorporating the trityl group.

The nature of the dark blue product could not be established.

Another method which has been used with success for the conversion of cycloheptatriene into tropylium salts is by reaction with phosphorus pentachloride<sup>116</sup> (Scheme 33).

SCHEME 33





The reaction of azepinoindole (87) with phosphorus pentachloride under the conditions described by the above author gave a deep purple solid which gave a deep purple solution in ethanol. The addition of fluoboric acid to a portion of this solution had no effect and the dark blue solid which could be precipitated by addition of the ethanolic solution to a large volume of ether did not analyse correctly for the expected azepinoindolium chloride.

No further attempts were made to convert azepinoindole (87) into an azonia-azulenium salt.

From 8-methoxy-10H-azepino[1,2-a]indole (93)

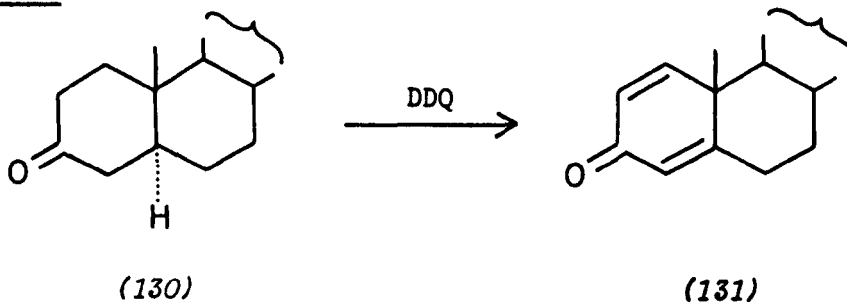
The methoxyazepinoindole (93) was very easily hydrolysed with dilute acid to give a high yield of the expected product, 9,10-dihydro-azepino[1,2-a]indol-8-one (129) (Scheme 35) confirmed by its n.m.r. spectrum (Figure 20, page 88).

A reagent which has been used extensively in steroid syntheses for the introduction of unsaturation  $\alpha,\beta$  to a carbonyl group is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). For example, a saturated 3-keto steroid, partial formula (130), was dehydrogenated by DDQ in boiling benzene or dioxan to the



$\Delta^{1,4}$ -3-ketone (131)<sup>117</sup> (Scheme 34).

SCHEME 34



The reaction of ketone (129) with DDQ in boiling benzene gave azepino[1,2-*a*]indol-8-one (132) in high yield (Scheme 35).

SCHEME 35

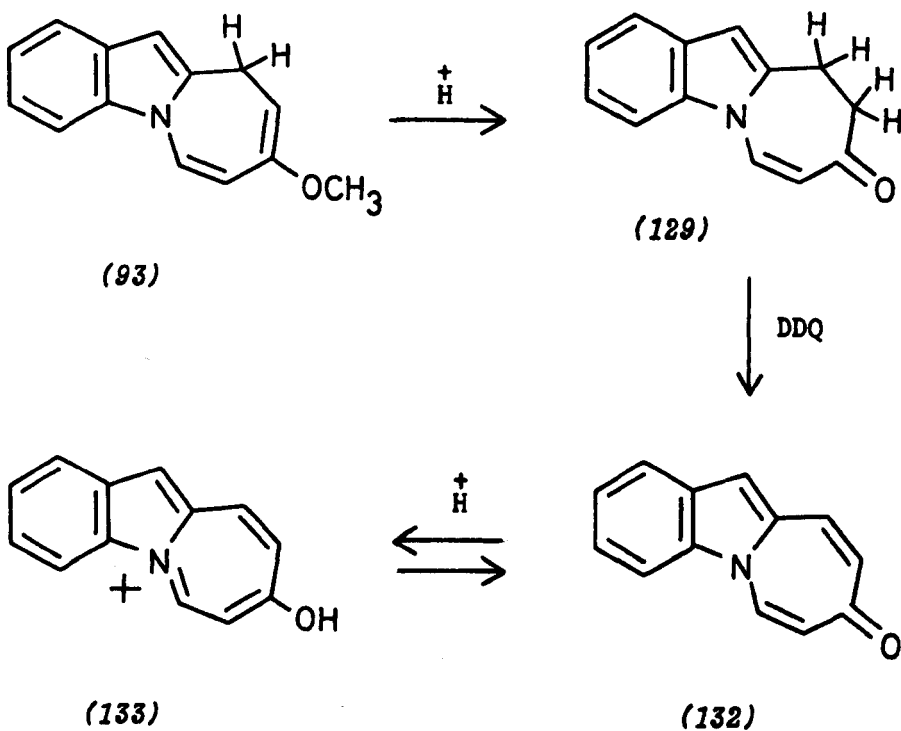
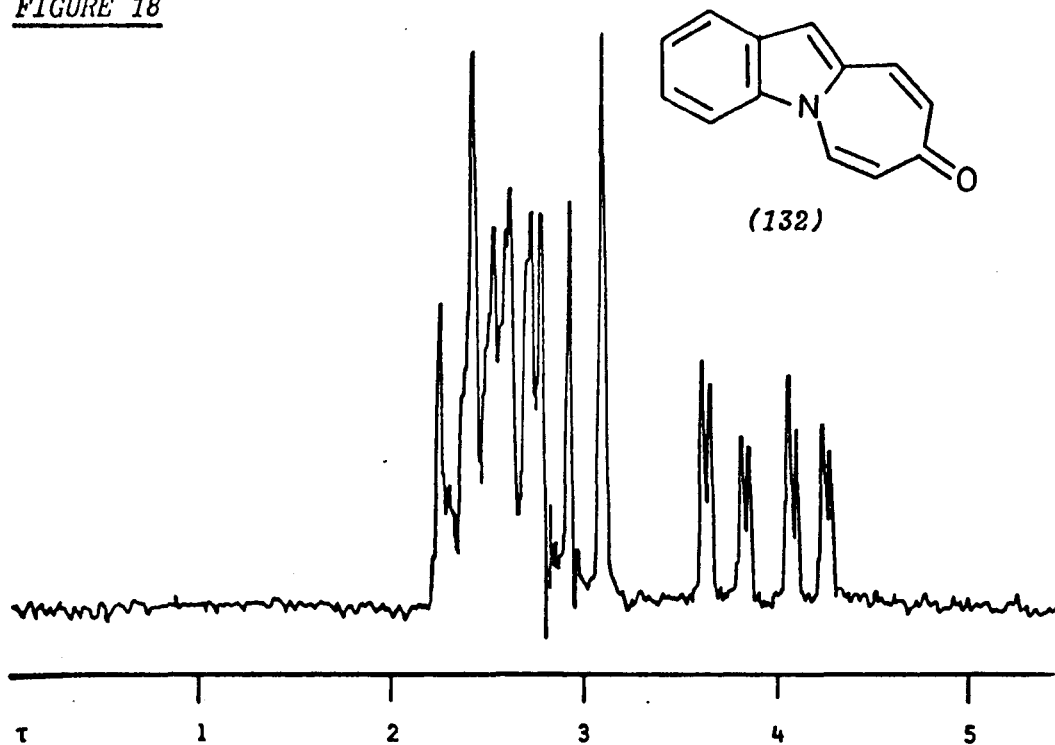
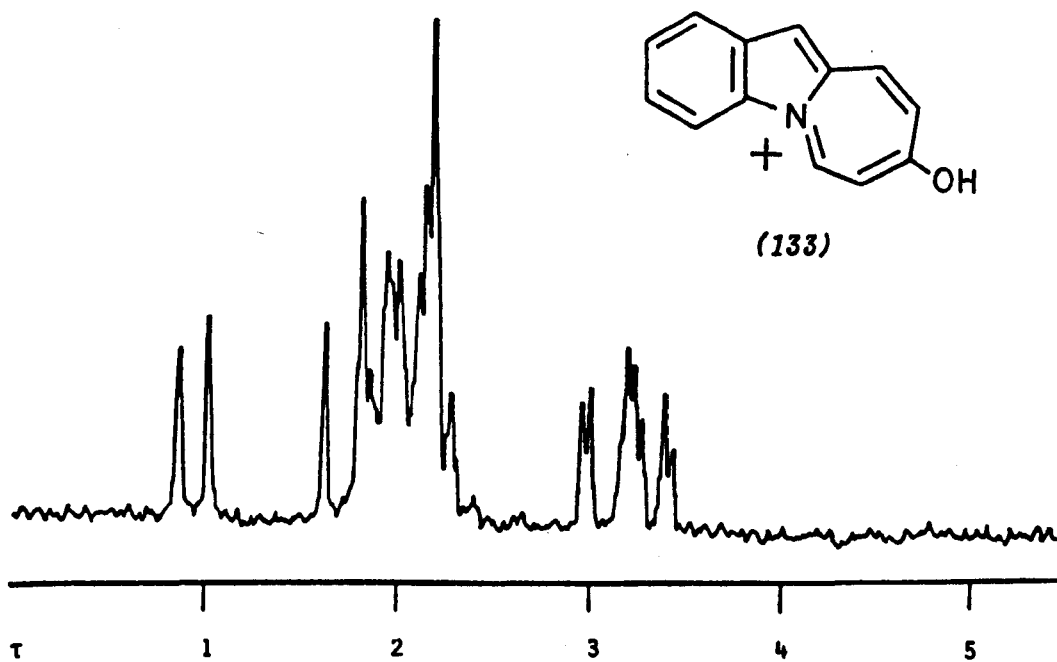




FIGURE 18FIGURE 19



The n.m.r. spectrum of azepinoindolone (132) is shown in Figure 18. The deep blue colour of solutions in strong acids and the associated changes in the n.m.r. spectrum (Figure 19) show the presence of the protonated form (133).

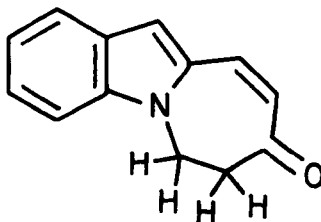
In the spectrum of the hydroxyazepinoindolium salt (133) the one proton downfield doublet,  $J_{6,7} = 10\text{Hz}$ , can be assigned to proton-6, adjacent to the quaternary nitrogen atom. The two upfield doublets of doublets centred at  $3.75\tau$  and  $4.2\tau$  in the ketone (132) and at  $3.1\tau$  and  $3.35\tau$  in the salt (133) can be assigned to protons-7 and -9, adjacent to the carbonyl group, by virtue of their 1,3 coupling (3Hz). Measurement of the major coupling in each doublet then allows an assignment to be made by comparison with the coupling  $J_{6,7}$  obtained from the downfield doublet in Figure 19. In both Figures 18 and 19 the doublet at lowest field is assigned to proton-9.

Attempts to reduce to a secondary alcohol the ketone group in azepinoindolone (132), with a view to obtaining the unsubstituted azepinoindolium salt by protonation and loss of water, were unsuccessful.

In an attempted reduction using sodium bis(2-methoxyethoxy)aluminium hydride only starting material was recovered and lithium aluminium hydride, even at  $-70^{\circ}$  gave 6,7-dihydro-



azepino[1,2-*a*]indol-8-one (134) by attack of the hydride at position 6.



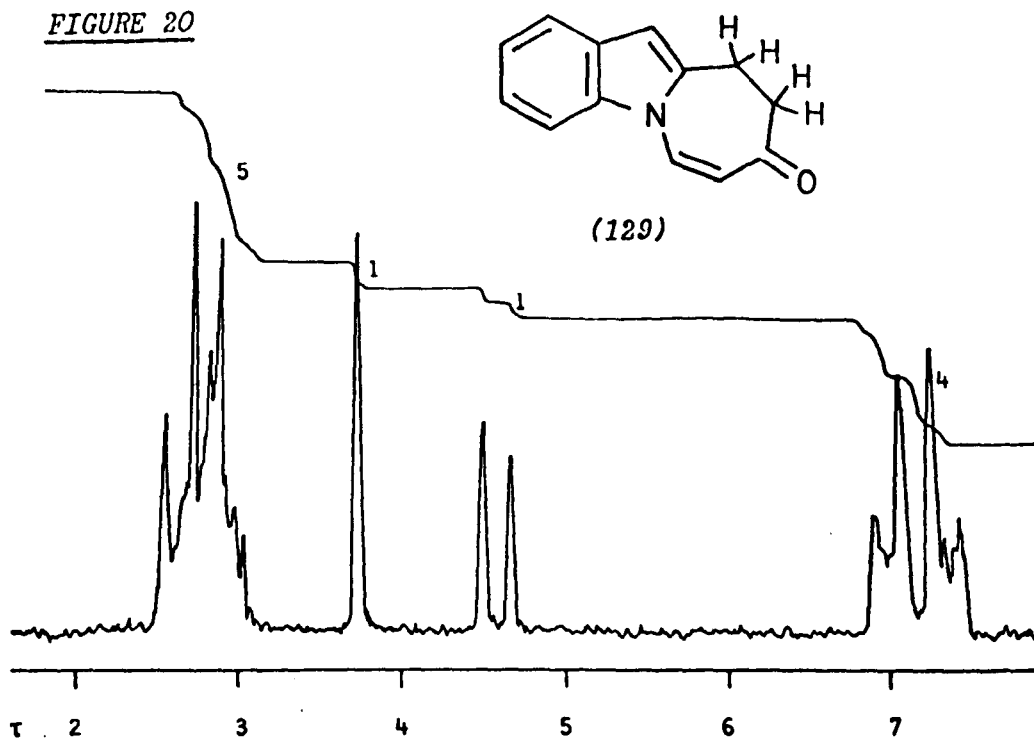
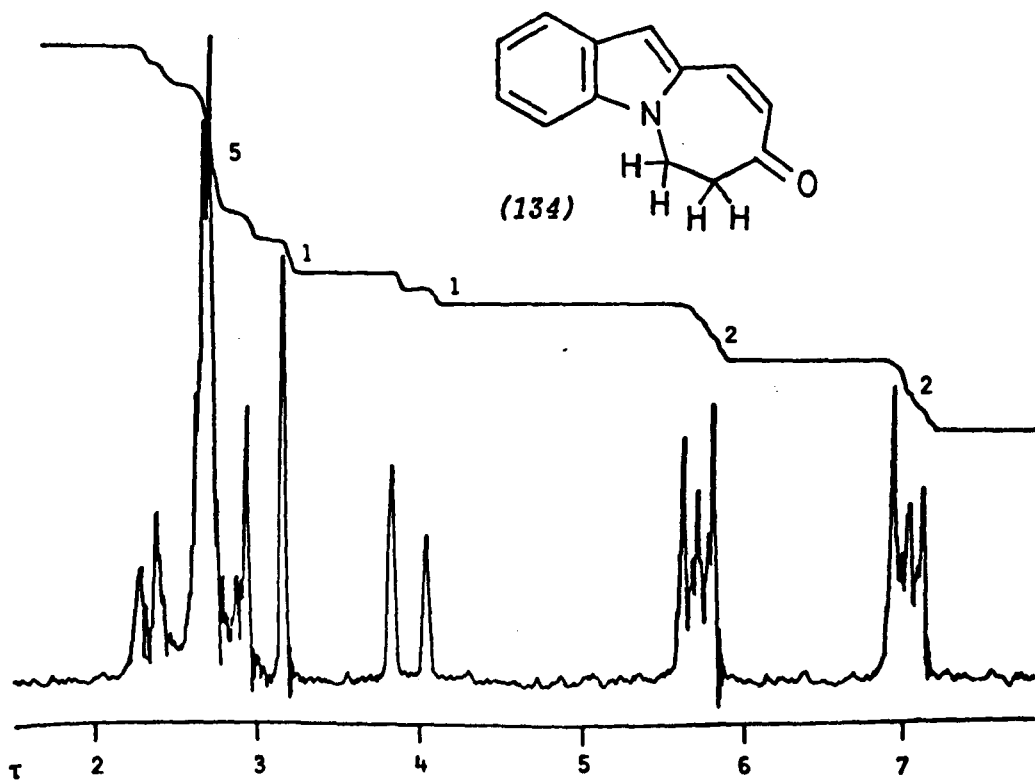
(134)

It was pointed out in the Introduction that azulene undergoes nucleophilic attack in the seven-membered ring at positions 4(8) and 6 and that the substitution of a nitrogen atom for a carbon atom had little effect on the positions of ionic attack. These positions in the azepinoindolone (132) are numbered 6, 8 and 10 and it is interesting that nucleophilic attack appears to proceed only at position 6. Nucleophilic attack has also been observed to occur at position 6 in 11-methylazepino[1,2-*a*]indol-10-one (39).<sup>36</sup>

The n.m.r. spectra of the dihydroazepinoindolones (129) and (134) are reproduced in Figures 20 and 21, page 88.

In keeping with previous observations the signal due to proton-11 on the five-membered ring occurs at lower field in the 6,7-dihydro compound (134) than in the 9,10-dihydro compound



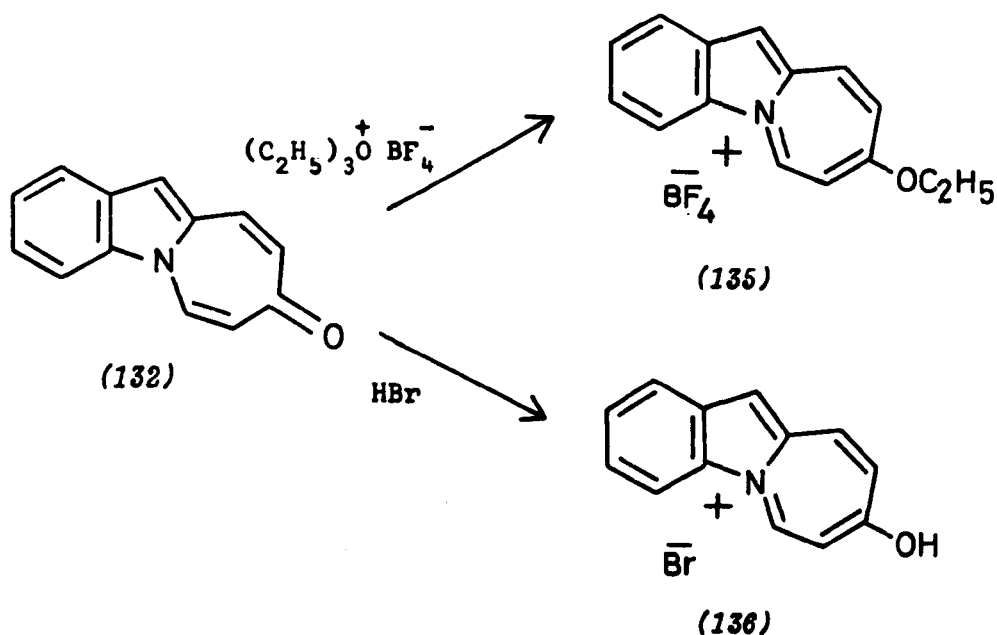
FIGURE 20FIGURE 21



(129) consistent with conjugation extending into the seven-membered ring. In Figure 21 the resonance at 5.7 $\tau$  must be that of the methylene group adjacent to the nitrogen atom. The doublets at 4.55 $\tau$  in Figure 20 and at 3.95 $\tau$  in Figure 21 can be assigned to protons-7 and -9 respectively. The couplings  $J_{6,7} = 10\text{Hz}$  and  $J_{9,10} = 12\text{Hz}$  are in good agreement with the corresponding couplings in the azepinoindolone (132).

The treatment of a methylene chloride solution of azepino[1,2- $\alpha$ ]indol-8-one (132) with triethyloxonium fluoborate<sup>118</sup> gave 8-ethoxyazepino[1,2- $\alpha$ ]indolium fluoborate (135) (Scheme 36). By passing dry hydrogen bromide through a methylene chloride solution of ketone (132) 8-hydroxyazepino[1,2- $\alpha$ ]indolium bromide (136) was obtained.

SCHEME 36





Thus, the hope that the decompositions of 2-azidodiphenylmethanes would lead to the production of azepinoindoles which could be converted into azepinoindolium salts has been realised, although the parent azepinoindolium system has not been prepared.

The investigation has revealed a novel formation of acridines from the decomposition of azides having a methoxyl substituent in the 2' position and although this decomposition bears a superficial resemblance to that of 2-azidodiphenylsulphides it has been shown to proceed by a different mechanism. The mechanism proposed can adequately account for the production of both azepinoindoles and acridines.



## EXPERIMENTAL

### PRELIMINARY NOTES

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

Infrared absorption spectra were recorded on a Perkin Elmer 257 spectrophotometer. The spectra of solids were determined in solution (e.g.  $\text{CCl}_4$ ) or as potassium bromide discs (KBr). The spectra of liquids were determined as liquid films (film) or in solution.

Ultraviolet and visible absorption spectra were recorded on a Unicam SP800 instrument.

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

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

Mass spectra were recorded on a Hitachi-Perkin Elmer



RMU-6 instrument. For the determination of the mass spectra of the components of mixtures the inlet system of this instrument was connected via a Biemann separator and an all glass line to a Pye Series 104 gas chromatograph equipped with a 1.5 m x 2 mm glass column. Helium was used as carrier gas. Mass spectra were scanned as the leading edge of each peak appeared on the total ion monitor recording from the mass spectrometer.

Analytical gas liquid chromatography was performed on a Pye Series 104 instrument equipped with a 1.5 m x 4 mm glass column packed with a support material coated with 3% loading of stationary phase. The stationary phases used were: OV101 (dimethyl silicone fluid), PEG 20M (polyethylene glycol, av. mol. wt. 20000) and Apiezon L (hydrocarbon grease). Detection of the eluted components of a mixture was by a hydrogen flame ionisation detector. The recorder chart speed, normally 1 cm/min, was increased to 3 cm/min during quantitative work in order to give larger peaks for area measurements. Peak areas were measured using a planimeter and the values, in arbitrary units, represent the average of several measurements.

Thin layer chromatography (t.l.c.) was carried out on microscope slides (7.5 x 2.5 cm) coated with silica gel (Merck Kieselgel PF<sub>254</sub>). The components were visualised under ultraviolet light or developed in iodine vapour.



Preparative layer chromatography was carried out on glass plates (40 x 20 cm) coated with a 1.5 mm layer of silica gel (Merck Kieselgel PF<sub>254</sub>). The separated components, visualised under ultraviolet light, were isolated by scraping off the silica and extracting with methanol. The filtered methanol solution was evaporated to leave a residue which contained silica. The residue was dissolved in chloroform, filtered, and evaporated.

Chromatography plates coated with silver nitrate impregnated silica gel were prepared from a slurry of Kieselgel PF<sub>254</sub> (500 g) and a solution of silver nitrate (50 g) in water. The plates, which were spread in artificial light, were dried overnight in the dark at room temperature and activated at 100° for two hours before use. The material to be chromatographed was spread on the plates in artificial light and elution was carried out in the dark.

Alumina for column chromatography was Woelm neutral grade and was deactivated by the addition of water. The activity values quoted refer to the Brockmann scale.

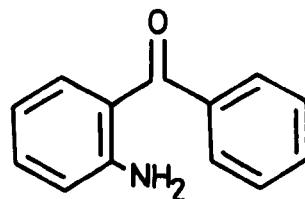
All solvents used in chromatography were distilled before use.

Photolytic work was performed under an atmosphere of nitrogen using a Hanovia photochemical reactor (medium pressure mercury lamp).



Where reactions were carried out under nitrogen the nitrogen used conformed to B.S. 4366, Industrial Nitrogen, Type 2, which permits a maximum oxygen content of 10 p.p.m. by volume.



SECTION 1PREPARATION OF 2-AMINO AND 2-BROMOBENZOPHENONES2-Aminobenzophenone (66)

Prepared by the method of Scheifele and DeTar<sup>94</sup> from N-tosylanthraniloyl chloride and benzene.

M.p. 105 - 106° (ethanol)

Lit.<sup>94</sup> 105 - 106° (ethanol)

All other 2-aminobenzophenones were prepared from acetanthranil<sup>96</sup> and an appropriately substituted phenylmagnesium bromide or iodide by a modification of the method used by Lamchen and Wicken<sup>119</sup> for the preparation of 2-amino-2'-methoxybenzophenone.

The following procedure, for 2-amino-2'-methoxybenzophenone, is illustrative and results in an increased yield over that obtained by the above authors.

The Grignard reagent from 2-iodoanisole (97 g) [Note 1] and magnesium turnings (11 g, excess) in dry ether (500 ml) [Note 2]



was added slowly during 1 hour to a rapidly stirred solution of acetanthranil<sup>96</sup> (67 g) in a mixture of dry benzene (500 ml) and dry ether (250 ml) at  $-5^{\circ}$ . Stirring was continued at  $0^{\circ}$  for 1 hour and at  $30^{\circ}$  for 1 hour. The yellow complex was hydrolysed by the addition of 10% hydrochloric acid (750 ml) and the upper, organic layer was separated. The aqueous layer was extracted with ether (200 ml) and the extract was combined with the benzene-ether solution.

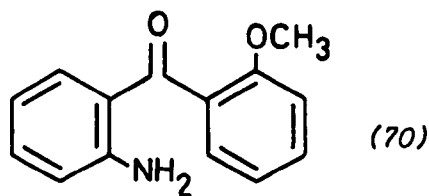
Evaporation of this solution produced a yellow oil which was hydrolysed by boiling for  $2\frac{1}{2}$  hours in a solution of concentrated hydrochloric acid (200 ml) and 95% ethanol (500 ml). This solution was then treated with charcoal, filtered, made alkaline with 10% sodium hydroxide solution and ether extracted (3 x 200 ml). The combined ethereal extracts were dried ( $\text{MgSO}_4$ ) and evaporated leaving a dark brown oil which, on dilution with an equal volume of 95% ethanol and cooling, deposited dark coloured crystals. Filtration and recrystallisation from ethanol gave yellow crystals of 2-amino-2'-methoxybenzophenone (20 g). The mother liquor from this recrystallisation was combined with that from the original crystallisation and evaporated to dryness. The resulting brown oil was passed down a column of alumina (500 g, activity IV) with methylene chloride. Evaporation of the eluate left a yellow oil which crystallised from ethanol giving a further quantity of product (25 g). Total yield of 2-amino-2'-methoxybenzophenone was 45 g (47%).



M.p. 113.5° (ethanol)

Lit.<sup>120</sup> 110 - 111°

119 109 - 111° (dil. alcohol)



*NOTE 1*

Aryl halides for use in the above reaction were prepared as follows:

2 and 4-iodoanisoles and 2-iodotoluene were prepared from the corresponding anisidine or toluidine via the diazonium-compound.

The procedure as described by Vogel<sup>121</sup> for iodobenzene was used.

Mesitylene was brominated by the method of L.I. Smith.<sup>122</sup>

1-Bromo-2,4,6-trimethoxybenzene was prepared by methylation of phloroglucinol<sup>123</sup> and subsequent bromination according to the method of Mayer et al.<sup>124</sup>

*NOTE 2*

The Grignard reagent from bromotrimethoxybenzene was prepared using dry tetrahydrofuran as solvent because this halide was insufficiently soluble in diethyl ether.

2-Amino-4'-methoxybenzophenone (67)

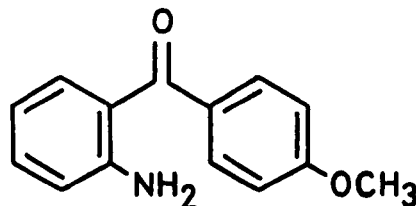
33% yield

M.p. 77 - 78° (ethanol)

Lit.<sup>120</sup> 77 - 77.5°

91 78 - 80° (benzene/petrol)

125 76.2 - 76.8°

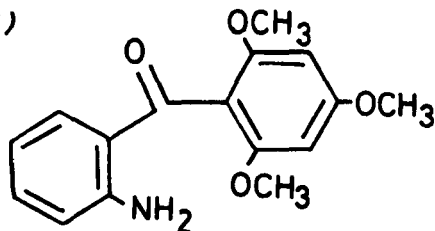




2'-Amino-2,4,6-trimethoxybenzophenone (71)

69% yield

M.p. 180 - 182° (ethanol)



## Analysis

Found: C, 66.6; H, 6.15; N, 4.4%

C<sub>16</sub>H<sub>17</sub>NO<sub>4</sub> requires: C, 66.9; H, 5.95; N, 4.85%N.m.r. (CDCl<sub>3</sub>)τ2.6 - 3.8 p.p.m. m 8H arom. + NH<sub>2</sub> (2H ex. with D<sub>2</sub>O)6.2 s 3H p-OCH<sub>3</sub>6.35 s 6H o-OCH<sub>3</sub>I.r. (CCl<sub>4</sub>)ν<sub>max</sub> 3500, 3340, 1625 cm<sup>-1</sup>

U.v. (95% ethanol)

λ<sub>max</sub> 230 nm log<sub>10</sub> ε 4.44

261 3.92

372 3.84

2-Amino-2'-methylbenzophenone (69)

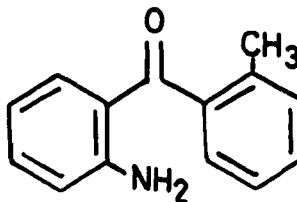
31% yield

M.p. 81 - 82° (ethanol)

Lit.<sup>126</sup> 79 - 80°

97 84°

120 81 - 82°

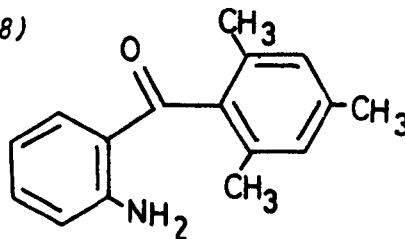




2'-Amino-2,4,6-trimethylbenzophenone (68)

30% yield

M.p. 130 - 131° (ethanol)



## Analysis

Found: C, 80.6; H, 7.45; N, 6.0%

C<sub>16</sub>H<sub>17</sub>NO requires: C, 80.3; H, 7.15; N, 5.85%N.m.r. (CDCl<sub>3</sub>)τ2.65 - 3.5 p.p.m. m 8H arom. + NH<sub>2</sub> (2H ex. with D<sub>2</sub>O)7.7 s 3H *p*-CH<sub>3</sub>7.9 s 6H *o*-CH<sub>3</sub>I.r. (CCl<sub>4</sub>)ν<sub>max</sub> 3500, 3340, 1635 cm<sup>-1</sup>

## U.v. (95% ethanol)

λ<sub>max</sub> 222 nm log<sub>10</sub> ε 4.36

232 4.37

262 3.97

373 3.89

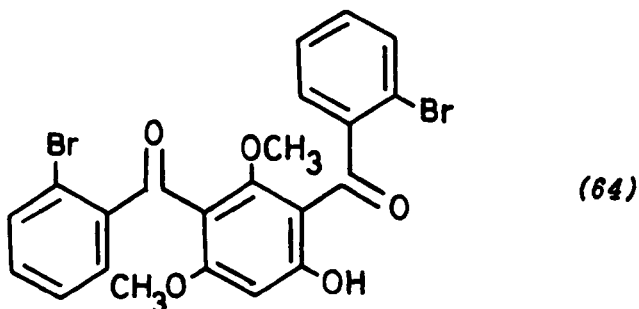
Attempted preparation of 2'-bromo-2,4,6-trimethoxybenzophenone

2-Bromobenzoyl chloride was prepared from 2-bromobenzoic acid (25 g) by boiling in a solution of chloroform (50 ml) and excess purified thionyl chloride (50 ml) for 2 hours. The chloroform and

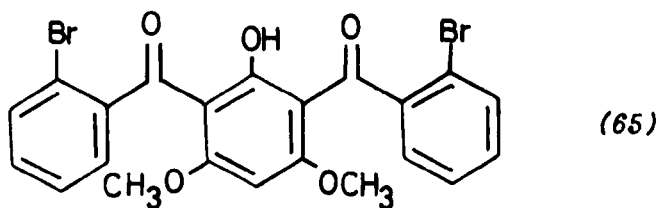


excess thionyl chloride were removed by distillation and the acid chloride, dissolved in carbon disulphide (100 ml) was added dropwise, with stirring to a mixture of 1,3,5-trimethoxybenzene<sup>123</sup> (21 g), carbon disulphide (150 ml) and anhydrous aluminium trichloride (17 g). After boiling for 2 hours the reaction mixture was decomposed by the addition of 10% hydrochloric acid (200 ml). Carbon disulphide was removed by distillation under reduced pressure and the product was obtained by ether extraction (3 x 150 ml). Evaporation of the ether gave a thick dark coloured oil (35 g) which crystallised from benzene. Three crystallisations from benzene gave pale yellow crystals which did not have the expected spectral properties of 2'-bromo-2,4,6-trimethoxybenzophenone.

The product was identified from the properties described below as either 2,4-di(2-bromobenzoyl)-3,5-dimethoxyphenol (64) or 2,6-di(2-bromobenzoyl)-3,5-dimethoxyphenol (65). On the available spectral evidence it was not possible to distinguish between these two compounds.







M.p. 182 - 183° (benzene)

#### Analysis

Found: C, 50.8; H, 3.04%

$C_{22}H_{16}Br_2O_5$  requires: C, 50.8; H, 3.10%

#### N.m.r.

( $CDCl_3$ )  $\tau$ 2.3 - 2.8 p.p.m. m 8H  
 4.1 s 1H H on C-2 of (64)  
 or C-4 of (65)  
 6.4 s 6H  $-OCH_3$

#### ( $DMSO-d_6$ )

$\tau$ -3.4 p.p.m. s 1H  $-OH$   
 2.1 - 2.6 m 8H  
 3.7 s 1H  
 6.3 s 6H

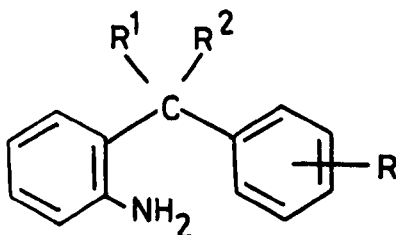
#### Mass spectrum

$m/e$  522 ( $\overset{+}{M}+4$ )(8%), 520 ( $\overset{+}{M}+2$ )(16%), 518 ( $\overset{+}{M}$ )(8%), 441 (24%),  
 440 (99%), 439 (21%), 438 (100%), 283 (37%), 269 (23%),  
 207 (25%), 185 (40%), 183 (53%), 157 (25%), 155 (25%).



## SECTION 2

### PREPARATION OF 2-AMINODIPHENYLMETHANES



Where  $R^1$  and  $R^2$  are not hydrogen the amines were prepared from 2-aminobenzophenone by methods to be described individually later in this section.

Where  $R^1$  and  $R^2$  are both hydrogen the amines were prepared from the corresponding 2-aminobenzophenones by reduction according to the following general procedure which is basically that of Engels, Lamchen and Wicken.<sup>99</sup>

The 2-aminobenzophenone (15 g) [Note 1] dissolved in 95% ethanol (150 ml) was added all at once to metallic sodium (30 g) cut into small pieces and contained in a 2 l three-necked flask fitted with a stirrer and two double surface water cooled condensers. Rapid stirring was commenced and the vigorous reaction was allowed to proceed unchecked. When the initial



reaction had subsided the flask was heated gently to maintain boiling and 95% ethanol (150 ml) was added in three portions over a period of  $\frac{1}{2}$  hour. At this stage the yellow colour of the 2-aminobenzophenone had completely disappeared [Note 2] and the sodium had dissolved. Water (800 ml) was added and the solution was ether extracted (3 x 200 ml). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated leaving a pale yellow oil which was dissolved in benzene (25 ml). Concentrated hydrochloric acid (25 ml) was added and on cooling and scratching the amine hydrochloride separated [Note 3]. The mixture was filtered and the white crystals were washed well with dry ether, then dissolved in hot water (200 ml), made alkaline with dilute sodium hydroxide solution, cooled, and ether extracted (3 x 100 ml). The combined ether extracts were dried ( $\text{MgSO}_4$ ) and evaporated. The resulting 2-amino-diphenylmethane was crystallised from petrol or petrol/benzene.

#### NOTE 1

Quantities up to 20 g of aminobenzophenone could be reduced with ease. Larger amounts were best reduced in several portions to obtain optimum yield.

#### NOTE 2

If the yellow colour of the aminobenzophenone persisted (usually due to insufficient stirring, allowing the sodium to agglomerate, or to overheating, causing ethoxide to be deposited on the heated



surface trapping sodium) more sodium was added down the condenser followed by more alcohol.

*NOTE 3*

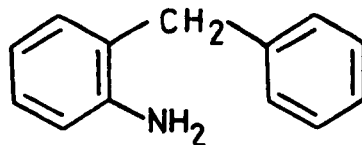
2'-Amino-2,4,6-trimethyl and -2,4,6-trimethoxydiphenylmethanes formed hydrochlorides less readily than the other aminodiphenylmethanes and were purified by passing the free bases through an alumina column (product to adsorbent ratio 1:15) with 60 - 80° petrol. The solvent was evaporated and the product crystallised as already described.

2-Aminodiphenylmethane (72)

84% yield

B.p. 121 - 124°, 0.25 mm

Lit.<sup>101</sup> 184 - 185°, 20 mm



2-Amino-2'-methoxydiphenylmethane (76)

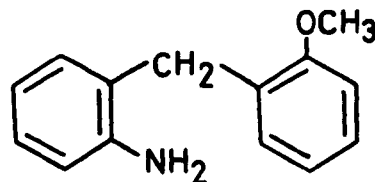
85% yield

M.p. 66° (60 - 80° petrol)

Analysis

Found: C, 78.8; H, 7.15; N, 6.8%

C<sub>14</sub>H<sub>15</sub>NO requires: C, 78.85; H, 7.1; N, 6.55%





N.m.r. ( $\text{CCl}_4$ )

$\tau$ 2.8 - 3.8 p.p.m.	m	8H	arom.
6.3	s	2H	$-\text{CH}_2-$
6.4	s	3H	$-\text{OCH}_3$
6.6	br s	2H	$-\text{NH}_2$ (ex. with $\text{D}_2\text{O}$ )

I.r. ( $\text{CCl}_4$ )

$\nu_{\text{max}}$  3480, 3395  $\text{cm}^{-1}$

U.v. (95% ethanol)

$\lambda_{\text{max}}$	224 nm	$\log_{10} \epsilon$	4.07
	240	sh	
	273	sh	
	279		3.58

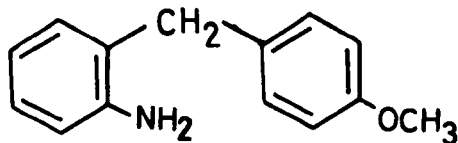
2-Amino-4'-methoxydiphenylmethane (73)

82% yield

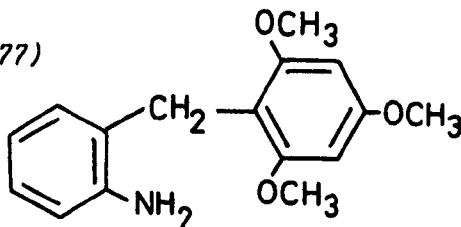
M.p. 54 - 55° (60 - 80° petrol)

Lit.<sup>101</sup> 55 - 56° (methanol)

99 52 - 55° (petrol)





2'-Amino-2,4,6-trimethoxydiphenylmethane (77)

55% yield

M.p. 134 - 136° (benzene/60 - 80° petrol)

## Analysis

Found: C, 70.20; H, 6.73; N, 5.00%

 $C_{16}H_{19}NO_3$  requires: C, 70.31; H, 7.01; N, 5.13%N.m.r. ( $CCl_4$ ) $\tau$ 2.7 - 3.8 p.p.m. m 6H arom.5.9 br s 2H  $-NH_2$  (ex. with  $D_2O$ )6.2 s 11H  $-CH_2-$  and  $-OCH_3$ I.r. ( $CCl_4$ ) $\nu_{max}$  3470, 3380  $cm^{-1}$ 

U.v. (95% ethanol)

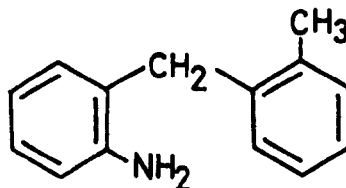
 $\lambda_{max}$  228 nm  $\log_{10} \epsilon$  4.21

280 3.46

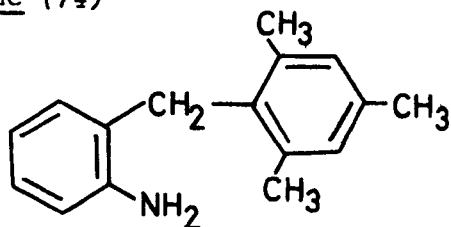
2-Amino-2'-methyldiphenylmethane (75)

70% yield

M.p. 70 - 71° (60 - 80° petrol)

Lit.<sup>127</sup> 67 - 69° (ether/60 - 80° petrol)

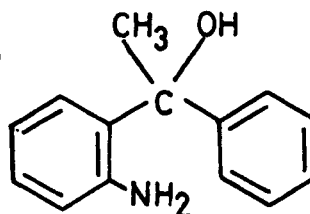


2'-Amino-2,4,6-trimethyldiphenylmethane (74)

56% yield

M.p. 90 - 91° (60 - 80° petrol)

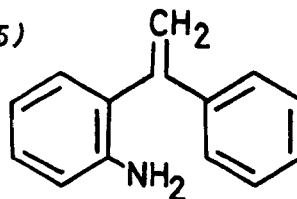
Lit.<sup>128</sup> 89 - 89.5° (ethanol)

1-(2-Aminophenyl)-1-phenylethanol (78)

Prepared in 95% yield from 2-aminobenzophenone (66)<sup>94</sup>  
and methyllmagnesium iodide by the method of Stoermer and Fincke.<sup>102</sup>

M.p. 84 - 86° (benzene/60 - 80° petrol)

Lit.<sup>102</sup> 84 - 85° (benzene/petrol)

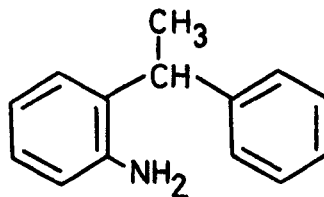
1-(2-Aminophenyl)-1-phenylethylene (115)

Prepared in 85% yield by the dehydration of  
1-(2-aminophenyl)-1-phenylethanol as described by Stoermer  
and Fincke.<sup>102</sup>

M.p. 75 - 77° (60 - 80° petrol)

Lit.<sup>102</sup> 76 - 77.5°



1-(2-Aminophenyl)-1-phenylethane (79)

A solution of 1-(2-aminophenyl)-1-phenylethylene (115)<sup>102</sup> (10.5 g) in 95% ethanol (150 ml) was hydrogenated at atmospheric temperature and pressure using 10% palladium-carbon catalyst (1 g). Hydrogen uptake (1 mol) was complete after 4 hours. The solution was filtered, evaporated at reduced pressure and the solid residue, on crystallisation from 60 - 80° petrol, gave 1-(2-aminophenyl)-1-phenylethane (10.1 g, 95%) as colourless crystals, m.p. 58°.

## Analysis

Found: C, 85.6; H, 7.5; N, 7.2%

C<sub>14</sub>H<sub>15</sub>N requires: C, 85.2; H, 7.65; N, 7.1%

N.m.r. (CCl<sub>4</sub>)

τ2.35 - 3.3 p.p.m.	m	9H	arom.
5.8	q	1H	-CH-CH <sub>3</sub> , <i>J</i> = 8Hz
6.6	br s	2H	NH <sub>2</sub> (ex. with D <sub>2</sub> O)
8.35	d	3H	-CH-CH <sub>3</sub> , <i>J</i> = 8Hz

I.r. (CCl<sub>4</sub>)

$\nu_{\max}$  3460, 3380 cm<sup>-1</sup>

## U.v. (95% ethanol)

$\lambda_{\max}$  235 nm  $\log_{10} \epsilon$  3.81  
285 3.38



### SECTION 3

#### PREPARATION OF 2-AZIDODIPHENYLMETHANES

The following general procedures were used. Procedure II was used when extreme insolubility of the amine salt made diazotisation difficult, resulting in a lower yield of the azide.

##### Procedure I

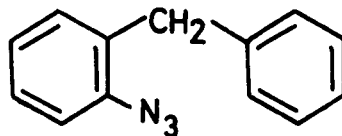
A solution of 0.05 mol of the appropriate 2-amino-diphenylmethane in 2*N* sulphuric acid (250 ml) was cooled to  $-5^{\circ}$  and diazotised by the addition with stirring, of a solution of sodium nitrite (3.5 g, 0.05 mol) in water (20 ml). A solution of sodium azide (3.9 g, 0.06 mol) in water (20 ml) was added to the stirred diazonium salt solution which was then warmed gently to  $30^{\circ}$  and extracted with ether (3 x 150 ml). The combined ethereal extract was washed with 5% sodium hydroxide solution and dried ( $\text{MgSO}_4$ ). The solvent was removed under reduced pressure at  $30^{\circ}$  and the residual yellow oil was passed through a column of alumina (200 g, activity IV) with 60 -  $80^{\circ}$  petrol. Evaporation of the solvent left the azide as a colourless oil, or on evaporation of the petrol to small volume colourless crystals of azide were deposited.



Procedure II

A solution of 0.05 mol of the appropriate 2-amino-diphenylmethane in 4*N* sulphuric acid (250 ml) and purified 1,4-dioxan (250 ml) was cooled to  $-5^{\circ}$  and a solution of sodium nitrite (3.5 g, 0.05 mol) in water (20 ml) was added with stirring. After 15 minutes a solution of sodium azide (3.9 g, 0.06 mol) in water (20 ml) was added and the solution was warmed gently to  $30^{\circ}$ . The azide was extracted and purified as in procedure I.

All azides were pure by thin layer chromatography.

2-Azidodiphenylmethane (59)

93% yield by procedure I

Pale yellow liquid at room temperature

N.m.r. ( $\text{CCl}_4$ )

$\tau$ 2.85 - 3.05    m    9H    arom.

6.15            s    2H     $-\text{CH}_2-$

I.r. ( $\text{CCl}_4$ )

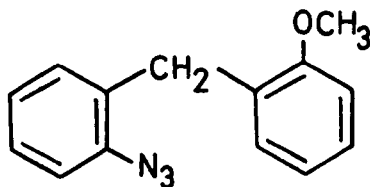
$\nu_{\text{max}}$  2130  $\text{cm}^{-1}$



2-Azido-2'-methoxydiphenylmethane (84)

89% yield by procedure II

M.p. 31.5 - 32.5° (60 - 80° petrol)



## Analysis

Found: C, 70.2; H, 5.4; N, 16.9%

C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O requires: C, 70.25; H, 5.5; N, 17.5%N.m.r. (CCl<sub>4</sub>)

τ2.8 - 3.5 p.p.m. m 8H arom.

6.15 s 2H -CH<sub>2</sub>-6.25 s 3H -OCH<sub>3</sub>

## I.r. (film)

ν<sub>max</sub> 2130, 1290, 1250 cm<sup>-1</sup>

## U.v. (95% ethanol)

λ<sub>max</sub> 221 nm log<sub>10</sub> ε 3.92

253 3.95

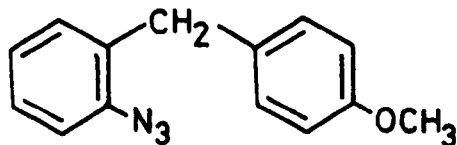
278 sh

290 sh

2-Azido-4'-methoxydiphenylmethane (81)

92% yield by procedure II

M.p. 41.5° (60 - 80° petrol)





## Analysis

Found: C, 70.6; H, 5.55; N, 17.3%

$C_{14}H_{13}N_3O$  requires: C, 70.3; H, 5.5; N, 17.6%

N.m.r. ( $CCl_4$ )

$\tau$ 2.8 - 3.5 p.p.m. m 8H arom.

6.25 s 2H  $-CH_2-$

6.35 s 3H  $-OCH_3$

I.r. (film)

$\nu_{\max}$  2130, 1290, 1250  $cm^{-1}$

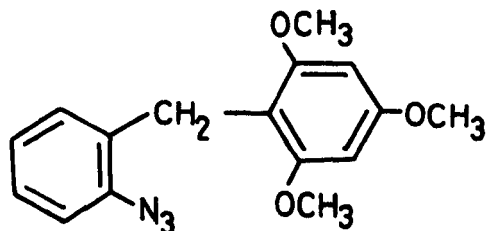
U.v. (95% ethanol)

$\lambda_{\max}$  234 nm  $\log_{10}\epsilon$  4.03

250 4.00

278 sh

2'-Azido-2,4,6-trimethoxydiphenylmethane (85)



80% yield by procedure II

M.p. 95 - 98° (60 - 80° petrol)

## Analysis

Found: C, 64.5; H, 5.75; N, 13.7%

$C_{16}H_{17}N_3O_3$  requires: C, 64.2; H, 5.70; N, 14.05%



N.m.r. ( $\text{CCl}_4$ ) $\tau$ 2.9 - 4.0 p.p.m. m 6H arom.

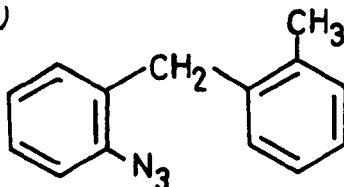
6.2	s	} 11H	-CH <sub>2</sub> - and -OCH <sub>3</sub>
6.25	s		

I.r. ( $\text{CCl}_4$ ) $\nu_{\text{max}}$  2120, 1290  $\text{cm}^{-1}$ 

U.v. (95% ethanol)

 $\lambda_{\text{max}}$  215 nm  $\log_{10} \epsilon$  4.52

256 sh

2-Azido-2'-methyldiphenylmethane (83)

73% yield by procedure II

Pale yellow liquid at room temperature

## Analysis

Found: C, 75.25; H, 5.75; N, 18.95%

 $\text{C}_{14}\text{H}_{13}\text{N}_3$  requires: C, 75.4; H, 5.85; N, 19.1%N.m.r. ( $\text{CCl}_4$ ) $\tau$ 2.9 - 3.3 p.p.m. m 8H arom.6.2 s 2H -CH<sub>2</sub>-7.85 s 3H -CH<sub>3</sub>

I.r. (film)

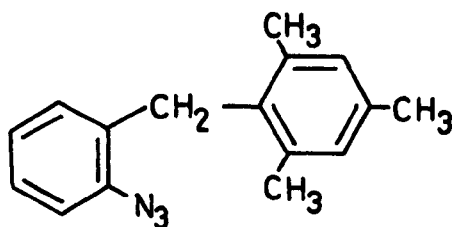
 $\nu_{\text{max}}$  2130, 1290  $\text{cm}^{-1}$



U.v. (95% ethanol)

$\lambda_{\max}$	219 nm	$\log_{10} \epsilon$	4.18
	251		4.00
	280	sh	
	287	sh	

2'-Azido-2,4,6-trimethyldiphenylmethane (82)



75% yield by procedure II

M.p. 111.5° (60 - 80° petrol)

Analysis

Found: C, 76.75; H, 6.55; N, 16.40%

$C_{16}H_{17}N_3$  requires: C, 76.45; H, 6.80; N, 16.70%

N.m.r. ( $CCl_4$ )

$\tau$ 2.8 - 3.6 p.p.m.	m	6H	arom.
6.15	s	2H	$-CH_2-$
7.75	s	3H	<i>p</i> - $CH_3$
7.9	s	6H	<i>o</i> - $CH_3$

I.r. ( $CCl_4$ )

$\nu_{\max}$  2120, 1280  $cm^{-1}$



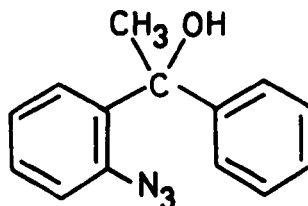
U.v. (95% ethanol)

$\lambda_{\max}$  212 nm  $\log_{10} \epsilon \sim 4.4$   
 253 3.91

1-(2-Azidophenyl)-1-phenylethanol (86)

89% yield by procedure I

M.p. 67° (60 - 80° petrol)



Analysis

Found: C, 70.8; H, 5.6; N, 17.6%

$C_{14}H_{13}NO$  requires: C, 70.25; H, 5.45; N, 17.55%

N.m.r. ( $CCl_4$ )

$\tau$ 2.4 - 3.2 p.p.m. m 9H arom.

6.35 s 1H -OH (ex. with  $D_2O$ )

8.25 s 3H - $CH_3$

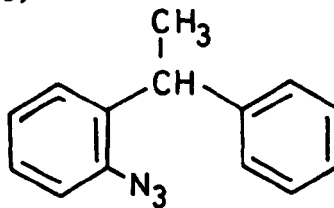
I.r. ( $CCl_4$ )

$\nu_{\max}$  3550, 2130, 1290  $cm^{-1}$

U.v. (95% ethanol)

$\lambda_{\max}$  253 nm  $\log_{10} \epsilon$  4.00  
 287 sh



1-(2-Azidophenyl)-1-phenylethane (80)

92% yield by procedure I

Pale yellow liquid at room temperature

### Analysis

Found: C, 75.3; H, 5.85; N, 18.8%

$C_{14}H_{13}N_3$  requires: C, 75.4; H, 5.85; N, 19.1%

### N.m.r. ( $CCl_4$ )

$\tau$ 2.5 - 2.75 p.p.m.	m	9H	arom.	
5.45	q	1H	-CH-CH <sub>3</sub>	} $J = 8\text{Hz}$
8.4	d	3H	-CH-CH <sub>3</sub>	

### I.r. ( $CCl_4$ )

$\nu_{\text{max}}$  2130, 1290  $\text{cm}^{-1}$

### U.v. (95% ethanol)

$\lambda_{\text{max}}$	221 nm	$\log_{10} \epsilon$	3.92
	253		3.95
	278	sh	
	290	sh	



## SECTION 4

### DECOMPOSITION OF 2-AZIDODIPHENYLMETHANES

All azides were decomposed thermally in 1,2,4-trichlorobenzene. 2-Azidodiphenylmethane was also decomposed by photolysis.

The general procedure for thermal decompositions was as follows:

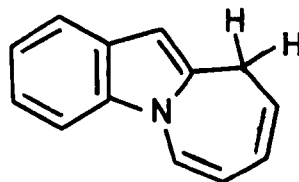
A solution of the azide (10 g) in 1,2,4-trichlorobenzene (100 ml) was added dropwise during 15 minutes to trichlorobenzene (1 l) maintained at a specified temperature in the range 180 - 200°. The trichlorobenzene was stirred vigorously during the addition of the azide and a slow stream of dry nitrogen was passed through the solution during the entire decomposition, which was followed by thin layer chromatography. When t.l.c. no longer showed a spot for the azide (usually about 4 hours) the solution was cooled and the solvent removed (1 mm pressure). The black, tarry residue was treated as described for the individual azides.



DECOMPOSITION OF 2-AZIDODIPHENYLMETHANE (59)

The azide (10 g) was decomposed at 200° for 4 hours. The black, tarry residue left after removal of the trichlorobenzene was chromatographed on a column of alumina (300 g, activity IV). Elution with 60 - 80° petrol and evaporation of the eluate to small volume deposited colourless crystals of 10H-azepino[1,2-*a*]indole (87) (4.85 g, 56%).

M.p. 91° (60 - 80° petrol)



Analysis

Found: C, 86.5; H, 5.95; N, 7.7%

C<sub>13</sub>H<sub>11</sub>N requires: C, 86.15; H, 6.1; N, 7.75%

N.m.r. (CCl<sub>4</sub>) [Figure 1, page 39]

τ 2.2 - 2.8 p.p.m. m 5H H on C-1,2,3,4 and 6

3.7 - 4.3 m 4H H on C-7,8,9 and 11

6.45 d 2H -CH<sub>2</sub>-, J<sub>9,10</sub> = 6Hz

U.v. (95% ethanol)

λ<sub>max</sub> 230 nm log<sub>10</sub> ε 4.24

272 4.18

313 3.79

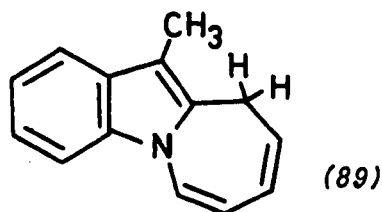
Mass spectrum

m/e 181 (<sup>+</sup>M)(100%), 180 (87%), 90.5 (12%), 90 (12%)



DECOMPOSITION OF 1-(2-AZIDOPHENYL)-1-PHENYLETHANE (80)

The azide (10 g) was decomposed for five hours at  $200^{\circ}$ . The black, tarry residue left after removal of the trichlorobenzene was chromatographed on a column of alumina (300 g, activity IV). Elution with  $60 - 80^{\circ}$  petrol, evaporation of the eluate, and crystallisation of the resulting orange coloured oil from  $40 - 60^{\circ}$  petrol (charcoal) gave 11-methyl-10H-azepino[1,2-a]indole (3.35 g, 38.5%). Recrystallisation gave pale yellow crystals m.p.  $47^{\circ}$ .



Analysis

Found: C, 85.6; H, 6.7; N, 7.1%

$C_{14}H_{13}N$  requires: C, 86.1; H, 6.7; N, 7.15%

N.m.r. ( $CCl_4$ ) [Figure 2, page 40]

$\tau 2.2 - 2.8$ p.p.m.	m	5H	H on C-1,2,3,4 and 6
$3.75 - 4.35$	m	3H	H on C-7,8 and 9
6.5	d	2H	$-CH_2-$ , $J_{9,10} = 6\text{Hz}$
7.7	s	3H	$-CH_3$



## U.v. (95% ethanol)

$\lambda_{\text{max}}$	234 nm	$\log_{10} \epsilon$	4.30
	275		4.14
	300	sh	
	324	sh	

## Mass spectrum

$m/e$  195 ( $\overset{+}{M}$ )(72%), 194 (100%), 180 (40%), 167 (12%),  
152 (12%), 83.5 (20%)



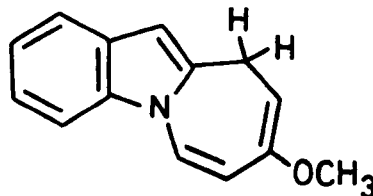
DECOMPOSITION OF 2-AZIDO-4'-METHOXYDIPHENYLMETHANE (81)

The azide (10 g) was decomposed at  $180^{\circ}$  for 4 hours and the trichlorobenzene was removed under reduced pressure.

Gas chromatography (3% OV101 on Chromosorb W, 40 ml/min nitrogen,  $172^{\circ}$ ) of the residue showed that there were three products with, under the above conditions, retention times of 16.5, 19 and 21 minutes and having peak areas in the ratio 9:1:1.

The brown, tarry residue was chromatographed on a column of alumina (300 g, activity IV). The fraction eluted with  $60 - 80^{\circ}$  petrol gave 8-methoxy-10H-azepino[1,2-a]indole (93) as colourless plates from petrol (4.25 g, 48%).

M.p.  $95.5^{\circ}$  ( $60 - 80^{\circ}$  petrol)



Analysis

Found: C, 80.1; H, 6.4; N, 6.8%

$C_{14}H_{13}NO$  requires: C, 79.6; H, 6.2; N, 6.65%

N.m.r. ( $CCl_4$ ) [Figure 3, page 43]

$\tau 2.5 - 3.2$  p.p.m. m 5H H on C-1,2,3,4 and 6

4.05 s 1H H on C-11



τ4.5	d of d	1H	H on C-7, $J_{6,7} = 10\text{Hz}, J_{7,9} = 2\text{Hz}$
5.25	t of d	1H	H on C-9, $J_{9,10} = 6\text{Hz}, J_{7,9} = 2\text{Hz}$
6.6	s	3H	-OCH <sub>3</sub>
6.75	d	2H	-CH <sub>2</sub> -, $J_{9,10} = 6\text{Hz}$

## U.v. (95% ethanol)

$\lambda_{\text{max}}$	226 nm	$\log_{10} \epsilon$	4.38
	263	sh	
	270		4.25
	312		3.89

## Mass spectrum

$m/e$	211 ( $\overset{+}{M}$ )(100%), 196 (39%), 180 (33%), 168 (55%), 167 (47%)
-------	---

This material was shown by gas chromatography to be the major decomposition product. The two minor products were not isolated.



DECOMPOSITION OF 2'-AZIDO-2,4,6-TRIMETHYLDIPHENYLMETHANE (82)

The azide (10 g) was decomposed at 190° for four hours. The trichlorobenzene was evaporated under reduced pressure and a sample of the dark coloured, tarry residue was injected into a gas chromatograph (3% OV101 on Chromosorb W, 40 ml/min nitrogen, 200°).

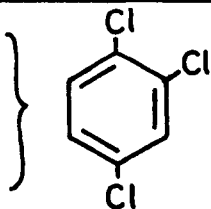
The chromatogram (reproduced on page 45) showed that the crude product comprised three major components subsequently referred to as products 1 - 3 corresponding, in order of increasing retention time to peaks 1 - 3 on this chromatogram.

An attempt was made to separate the products by column chromatography: In a trial run the crude decomposition product (1.5 g) was chromatographed on a column of alumina (50 g, activity IV). The column was eluted with 40 - 60° petrol, 25 ml fractions were collected, and the composition of each fraction was checked by gas chromatography. All the major products were eluted in the second and third fractions with no separation.

In a second trial run using activity grade II alumina it was found necessary to lag the column in order to prevent polymerisation, apparently initiated by light. This column gave a better separation and, although this was by no means complete, it was considered sufficiently good to obtain an initial separation of the bulk of the crude product.



Accordingly, the remainder of the crude decomposition product (9.1 g) was chromatographed on alumina (450 g, activity II) using a lagged column. The eluting solvent was 40 - 60° petrol, 200 ml fractions were collected and the composition of each fraction was checked by gas chromatography. After fraction 14 2% benzene was added to the 40 - 60° petrol and after fraction 18, 5% benzene was added.

Fraction	Weight(g)	Composition*	Fraction	Weight(g)	Composition*
1	0.002		13	0.129	2, 3
2	1.681		14	0.104	2, 3
3	0.610		15	0.110	2, 3
4	0.360	1, 2	16	0.061	2, 3
5	0.880	1, 2	17	0.086	2, 3
6	0.782	1, 2, 3	18	0.115	2, 3
7	0.485	1, 2, 3	19	0.063	2, 3
8	0.432	2, 3	20	0.027	2, 3
9	0.325	2, 3	21	0.043	2, 3
10	0.279	2, 3	22	0.072	3
11	0.187	2, 3	23	0.029	3
12	0.141	2, 3	24	0.022	

\* Composition is presented in terms of the peaks present on gas chromatography.



Gas chromatography showed that fraction 4 (360 mg) was predominantly product 1. Two crystallisations from 40 - 60° petrol (charcoal) gave pure product 1, identified from spectral properties as 6,8,10-trimethyl-10H-azepino[1,2-*a*]indole (94).

Fractions 8 to 20 were mixtures, in varying proportions, of products 2 and 3. These fractions were bulked together (2.24 g).

Using silica gel coated thin layer plates no solvent system could be found which would separate this material into two spots.

Using thin layer plates coated with silver nitrate impregnated silica gel (10% AgNO<sub>3</sub>) two spots could be discerned after elution with ether/benzene (9:1). Each spot was removed from the plate and the sample washed off the silica with methanol. Gas chromatography of each of the methanolic solutions showed that a fairly good separation had been obtained.

The bulk sample of products 2 and 3 (0.746 g) was spread on four preparative layer plates coated with silver nitrate impregnated silica gel (10% AgNO<sub>3</sub>) and the plates were eluted with ether/benzene (9:1). After elution it was noticed that in several places large areas of the coating had lifted from the glass surface and crumbled. No separation of the products was obtained and material removed from the plates turned black on removal of the solvent. No



material was recovered.

A further attempt to separate products 2 and 3 was made by column chromatography. The bulk sample of products 2 and 3 (1.34 g) was chromatographed on alumina (50 g, activity II) using a lagged column. The eluting solvent was 40 - 60° petrol and 10 ml fractions were collected automatically (using the syphon balance principle). Twenty-six fractions (A - Z) were collected and the composition of each fraction was checked by gas chromatography.

Fractions F to H (223 mg) were predominantly product 2. Two crystallisations from 40 - 60° petrol gave colourless crystals of pure product 2, identified from spectral properties as 6,8,10-trimethyl-6H-azepino[1,2-*a*]indole (95).

Fractions I to Z were mixtures.

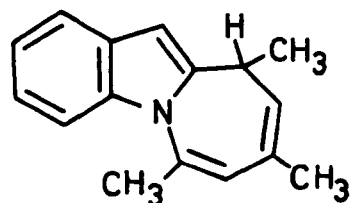
Fractions 21 to 23 combined together (144 mg) gave a mixture of products 2 and 3, largely product 3. Two crystallisations from 40 - 60° petrol gave pure product 3 identified as 6,8,10-trimethyl-8H-azepino[1,2-*a*]indole (96).

Properties of the isomeric trimethylazepinoindoles:



6,8,10-Trimethyl-10H-azepino[1,2-a]indole

(94)



M.p. 52 - 54° (40 - 60° petrol)

## Analysis

Found: C, 86.05; H, 7.60; N, 6.35%

C<sub>16</sub>H<sub>17</sub>N requires: C, 86.05; H, 7.65; N, 6.25%N.m.r. (CCl<sub>4</sub>) [Figure 5, page 47]

τ2.45 - 3.2 p.p.m.	m	4H	arom.
4.05	s	1H	H on C-11
4.4	s	1H	H on C-7
4.8	d	1H	H on C-9, $J_{9,10} = 6\text{Hz}$
6.8	m	1H	-CH-CH <sub>3</sub>
7.55	s	3H	-CH <sub>3</sub>
8.35	s	3H	-CH <sub>3</sub>
8.5	d	3H	-CH-CH <sub>3</sub> , $J = 7\text{Hz}$

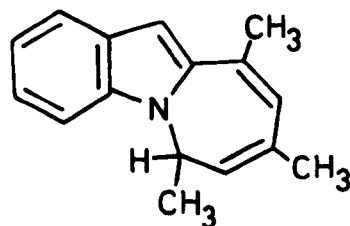
U.v. (95% ethanol)

$\lambda_{\text{max}}$	233 nm	$\log_{10} \epsilon$	4.34
	267		4.18
	290	sh	

## Mass spectrum

 $m/e$  223 ( $M^+$ )(45%), 208 (100%), 193 (12%), 104 (9%)



6,8,10-Trimethyl-6H-azepino[1,2-*a*]indole (95)

M.p. 77 - 79° (40 - 60° petrol)

## Analysis

Found: C, 86.3; H, 7.80; N, 6.4%

C<sub>16</sub>H<sub>17</sub>N requires: C, 86.05; H, 7.65; N, 6.25%

N.m.r. (CCl<sub>4</sub>) [Figure 6, page 48]

τ 2.45 - 3.2 p.p.m.	m	4H	arom.
3.5	s	1H	H on C-11
4.2	s	1H	H on C-9
4.3	d	1H	H on C-7, $J_{6,7} = 10\text{Hz}$
4.9	m	1H	-CH-CH <sub>3</sub>
7.75	s	3H	-CH <sub>3</sub>
8.2	s	3H	-CH <sub>3</sub>
8.75	d	3H	-CH-CH <sub>3</sub> , $J = 7\text{Hz}$

U.v. (95% ethanol)

$\lambda_{\text{max}}$	222 nm	$\log_{10} \epsilon$	4.55
	240	sh	
	338		4.12

## Mass spectrum

$m/e$  223 ( $M^+$ )(54%), 208 (100%), 193 (17%), 104 (10%)



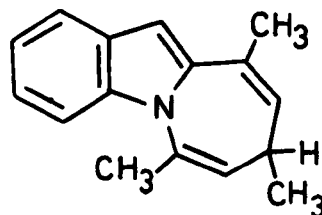
6,8,10-Trimethyl-8H-azepino[1,2-a]indole (96)

Pale yellow crystals

M.p. 60 - 62.5° (40 - 60° petrol)

U.v. (95% ethanol)

$\lambda_{\max}$	218 nm	$\log_{10} \epsilon$	4.42
	258		4.04
	327		4.45
	340	sh	



Mass spectrum

$m/e$  223 ( $M^+$ )(51%), 208 (100%), 193 (15%), 104 (14%)

$C_{16}H_{17}N$  requires  $m/e$  223

Quantitative gas chromatography

The yield of each of the isomeric trimethylazepinoindoles was estimated by gas chromatography using the internal standardisation technique described in detail on page 150. Page 150 should also be referred to for an explanation of the equations used in the following calculations.

Products 1 and 2 could not be completely resolved but it was possible to measure their areas by extending the sides of the peaks to the baseline in the region of the overlap.



The standard substance chosen was 10H-azepino-[1,2- $\alpha$ ]indole which had a retention time of 2.75 minutes under the conditions used (3% OV101 on Chromosorb W, 40 ml/min nitrogen, 200°).

$$w_i = K_{i(s)} w_s \frac{A_i}{A_s} \quad . \quad . \quad . \quad . \quad . \quad \text{Eqtn. II}$$

$$K_{i(s)} = \frac{w'_i A'_s}{w'_s A'_i} \quad . \quad . \quad . \quad . \quad . \quad \text{Eqtn. III}$$

where  $K$ ,  $w$ ,  $A$ ,  $w'$  and  $A'$  are defined on page 151.

In order to determine the response coefficient of each product relative to the standard it was decided to run separately a pure sample of each product containing a known weight of standard (Table 1). This eliminated the errors associated with area measurements of the overlapping peaks which would have resulted from the preparation of a reference mixture containing the three products and the standard.



TABLE 1

Product	$w'$ mg in MeOH (2 ml)	Peak, Area $A$	$K_{i(s)}$
S	10.0	65	1.004
1	8.78	56.9	
S	10.9	78	0.829
2	8.6	74.3	
S	8.4	56.3	1.195
3	8.56	48	

A solution was prepared containing the standard substance (9.4 mg) and the crude decomposition product (37.8 mg) in methanol (2 ml). From peak area measurements and a knowledge of the response coefficient for each product the exact weight  $\underline{W}_i$  mg of each isomer present in the crude decomposition product was calculated (Table 2) using equation II.



TABLE 2      Sample solution

Product	Peak Area $A_i$	$W_i$ mg
S	83	
1	40.5	4.61
2	99.3	9.32
3	21.7	2.94

The weight of crude product used for the sample solution was 0.0378 g out of the 14.80 g of residue obtained from 10.0 g of azide. The total weight, and hence yield of each product was calculated and the results are recorded in Table 3.

TABLE 3

Product		wt. produced in decomp.(g)	% yield
1	6,8,10-trimethyl-10H-azepino[1,2- $\alpha$ ]indole	1.81	20.4
2	-6H-	3.65	41.0
3	-8H-	1.15	12.9



DECOMPOSITION OF 2-AZIDO-2'-METHYLDIPHENYLMETHANE (83)

The azide (10 g) was decomposed at 190° for four hours and the trichlorobenzene evaporated under reduced pressure.

Gas chromatography of a sample of the residue using 3% OV101 as the stationary phase indicated possibly two major products with three minor products but separation of the peaks was poor. No better separation was obtained using either Apiezon L or PEG 20M as the stationary phase.

The black, tarry residue was chromatographed on a column of alumina (400 g, activity IV). Elution with 40 - 60° petrol removed trichlorobenzene and moved a yellow band from the origin. Continued elution removed the yellow band from the column. Evaporation of the petrol left a yellow oil (8.64 g) which was shown by gas chromatography to contain all the decomposition products.

Thin layer chromatography of this oil, eluting with petrol/ether (1:1), showed one spot which could not be separated using any of the common solvent systems. Elution of the thin layer plate four times with 40 - 60° petrol separated the spot into two very close spots. On a preparative scale the yellow oil (1.208 g) was spread onto six thick layer plates and the plates were eluted repeatedly with 40 - 60° petrol until sufficient separation of the overlapping bands was obtained (4 runs). Examination of the plates



under u.v. light showed six bands with poor separation. (Bands 1 - 6 in order of decreasing  $R_f$ ).

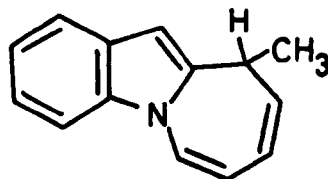
Bands 1 and 2:

These were faint and were not removed from the plates.

Band 3 (0.335 g):

Shown by gas chromatography to be a single compound and one of the major products. Crystallisation from 40 - 60° petrol gave colourless crystals of 10-methyl-10H-azepino[1,2-*a*]indole (97) in 27.5% yield as calculated from the weight of material isolated after chromatography.

M.p. 59° (40 - 60° petrol)



#### Analysis

Found: C, 85.8; H, 6.95; N, 7.3%

$C_{14}H_{13}N$  requires: C, 86.1; H, 6.7; N, 7.2%

N.m.r. ( $CCl_4$ ) [Figure 11, page 54]

$\tau$ 2.45 - 3.1 p.p.m.	m	5H	Protons on C-1,2,3,4 and 6
4.0	s	1H	Proton on C-11
4.05 - 4.5	m	3H	Protons on C-7,8 and 9
6.3 - 6.8	m	1H	-CH-CH <sub>3</sub>
8.4	d	3H	-CH-CH <sub>3</sub> , $J = 7\text{Hz}$



U.v. (95% ethanol)

$\lambda_{\text{max}}$	229 nm	$\log_{10} \epsilon$	4.31
	273		4.22
	315	sh	

Mass spectrum

$m/e$  195 ( $M^+$ )(87%), 180 (100%), 90 (15%)

Band 4 (0.382 g):

Shown by gas chromatography to be a mixture of two products, one major and one minor. The mixture was spread onto two preparative layer plates and eluted, as previously, four times with 40 - 60° petrol. The material corresponding to band 4 was removed from the plates (0.130 g) but this was found to be still a mixture (by g.c.). This material also bulb distilled (140 - 150°,  $1.5 \times 10^{-2}$  mm) unchanged. The n.m.r. of the distillate suggested that the mixture was predominantly 6-methyl-10H-azepino-[1,2-*a*]indole (100). The significant signals in the n.m.r. spectrum were as follows: 2.5 - 3.2 $\tau$  (m), 4.0 - 4.5 $\tau$  (m) with a singlet at 4.0 $\tau$  (H on C-11), 6.6 - 6.9 $\tau$  poorly resolved doublet  $J = 6\text{Hz}$  ( $-\text{CH}_2-$ ) and 7.55 $\tau$  (s) ( $-\text{CH}_3$ ). These signals integrated in approximately correct ratios. This material could not be purified.



Bands 5 and 6 (0.16 g and 0.078 g respectively):

The material extracted from these bands was very tarry and n.m.r. spectra were uninterpretable.

No further work on these bands was attempted.

Also thought to be present from an examination of the n.m.r. spectrum of the crude decomposition product was 6-methyl-6H-azepino[1,2-*a*]indole (98) the relevant signals in the spectrum being a singlet at 3.5 $\tau$  (H on C-11) and a doublet at 8.75 $\tau$ ,  $J = 7\text{Hz}$  ( $-\text{CH}-\text{CH}_3$ ) which integrated approximately in the ratio 1:3. No compound having this structure was isolated but the integration indicated that the 6-methyl-6H isomer was present in approximately one third the quantity of the 10-methyl-10H isomer.



DECOMPOSITION OF 2-AZIDO-2'-METHOXYDIPHENYLMETHANE (84)

The azide (10 g) was decomposed at  $190^{\circ}$  for  $4\frac{1}{2}$  hours. The trichlorobenzene was removed under reduced pressure and a sample of the dark coloured residue was injected into a gas chromatograph operating at a column oven temperature of  $180^{\circ}$  and a carrier gas flowrate of 40 ml/min. The stationary phase was 3% OV101 on Chromosorb W. The resulting chromatogram (reproduced on page 60) showed that the crude product comprised ten components, subsequently referred to as products 1 - 10 corresponding in order of increasing retention time to peaks 1 - 10 on this chromatogram.

The crude decomposition product was investigated further by the following procedures:-

- (a) Separation into acidic, basic and neutral compounds.
- (b) Gas chromatography monitored by mass spectrometry.
- (c) Separation by column and preparative layer chromatography.
- (d) Quantitative gas chromatography.

(a) Separation into acidic, basic and neutral compounds

In a 50 ml separatory funnel, equipped with a micro-stirrer and an inlet tube for nitrogen, a solution of the crude decomposition product (0.1 g) in diethyl ether (20 ml) was stirred



rapidly for 1 minute with 2*N* sulphuric acid (20 ml) under a nitrogen atmosphere. The acid layer was run into a second separatory funnel and the sulphuric acid extraction was repeated. The combined acid extracts were basified with 2*N* sodium hydroxide solution and ether extracted (2 x 25 ml). The ether extracts were dried ( $\text{MgSO}_4$ ) and evaporation of the ether left a yellow oil which solidified on standing and which contained the basic products of the azide decomposition. The basic compounds were shown to be products 3, 6 and 9 by gas chromatography.

The ether solution of the crude products was stirred with two 20 ml portions of 2*N* sodium hydroxide solution. This basic extract was acidified with 2*N* sulphuric acid, ether extracted (2 x 25 ml) and dried ( $\text{MgSO}_4$ ). Evaporation of the ether left no residue showing that no acidic products were produced in the decomposition.

The ether solution of the crude decomposition products was washed with water (20 ml), dried ( $\text{MgSO}_4$ ) and evaporated. The brown, oily residue which solidified on standing contained the neutral products of the azide decomposition. Gas chromatography showed that products 3 and 9 had been almost completely removed by acid extraction. The area of peak 6 on the chromatogram had been reduced by about 50%.



(b) Gas chromatography monitored by mass spectrometry

For this work a gas chromatograph was connected to the inlet system of the mass spectrometer via a Biemann separator and an all glass line which were maintained at a temperature of 230°. The chromatograph was equipped with a 1.5 m x 2 mm column packed with 3% OV101 on Chromosorb W and was operated at a column oven temperature of 180° and carrier gas (helium) flowrate of approximately 12 ml/min.

Samples of both the basic and neutral fractions obtained in (a) were injected into this system.

## Basic fraction:

Mass spectra were obtained corresponding to peaks 3, 6 and 9 on the chromatogram of the crude mixture.

Peak 3  $m/e$  179 ( $M^+$ )(100%), 178 (21%), 89.5 (10%).

Spectrum identical with the mass spectrum of acridine.(101)

Peak 6  $m/e$  213 ( $M^+$ )(100%), 182 (60%), 180 (50%), 152 (15%), 106 (33%).

Spectrum identical with the mass spectrum of  
2-amino-2'-methoxydiphenylmethane. (76)

Peak 9  $m/e$  209 ( $M^+$ )(100%), 194 (20%), 166 (85%).

## Neutral fraction:

Mass spectra were obtained corresponding to peaks 2, 4, 6 and 10



on the chromatogram of the crude mixture.

Peak 2  $m/e$  211 ( $M^+$ )(49%), 196 (87%), 180 (25%), 167 (100%),  
83.5 (22%).

Peak 6  $m/e$  211 ( $M^+$ )(78%), 196 (100%), 180 (30%), 168 (54%),  
167 (60%), 83.5 (18%).

Mass spectra of peaks 2 and 6 were similar to the  
mass spectrum of 8-methoxy-10H-azepino[1,2- $\alpha$ ]indole (93).

Peak 4  $m/e$  181 ( $M^+$ )(100%), 180 (12%), 153 (15%),  
91 (17%).

Peak 10  $m/e$  211 ( $M^+$ )(72%), 210 (100%), 196 (19%), 195 (42%),  
180 (17%), 167 (30%).

(c) Separation of each component by column and preparative  
layer chromatography

The crude decomposition product (8.5 g) was  
chromatographed on a column of alumina (400 g, activity IV).  
Elution with 60 - 80° petrol moved first a pale yellow band, then  
a deep yellow band down the column. As the pale yellow band moved  
down the column, the eluate was found to contain trichlorobenzene  
(0.75 g).

Continued elution with 60 - 80° petrol removed the pale  
yellow band from the column. On evaporation of this fraction to  
small volume (~75 ml) white crystals were deposited which were



subsequently identified from their spectral properties as acridan (102) (product 4). The crystals were removed by filtration, washed with cold petrol and dried in vacuum (0.67 g). Evaporation of the filtrate and washings left a yellow oil (1.72 g), shown by gas chromatography to consist predominantly of products 2, 3, 4 and 6 with traces of products 5, 7 and 8. The total weight of material eluted in this fraction was 2.398 g.

Elution with 60 - 80° petrol/chloroform (9:1) removed the deep yellow band from the column. Evaporation of the eluate left a brown oil (3.533 g) which solidified on standing and which was shown by gas chromatography to consist predominantly of products 7, 9 and 10.

Further separation of each fraction was obtained by preparative layer chromatography.

Part of the petrol fraction (1.438 g) was spread on eight preparative layer plates. Elution with 60 - 80° petrol/ether/benzene (6:2:2) produced four fairly clearly defined bands (bands I - IV in order of decreasing  $R_f$ ) and several overlapping bands close to the baseline.

Band I	0.239 g
II	0.456 g
III	0.047 g
IV	0.109 g



The material from each of these bands proved to be a mixture by t.l.c. Accordingly, material from bands I, II and IV was re-run on a series of preparative layer plates.

Band I re-run:

Elution with 60 - 80° petrol/ether (45:55) and removal of the main band gave 0.115 g of material which was not identified.

Band II re-run:

Elution with 60 - 80° petrol/ether (45:55) and removal of the main band gave a pale yellow oil (0.216 g) which was bulb distilled (150 - 200°,  $\sim 10^{-4}$  mm) and identified from mass and n.m.r. spectra as 6-methoxy-10H-azepino[1,2-a]indole (103) (product 6).

Band IV re-run:

Elution with 60 - 80° petrol/ether (70:30) and removal of the main band, which showed a bright blue fluorescence in ultraviolet light, gave a dark coloured solid (0.08 g) which was extracted with hot petrol. On cooling the petrol solution deposited pale yellow crystals of acridine (101) (product 3) identified by comparing its spectral properties with those of an authentic sample.

Part of the petrol/chloroform (9:1) fraction (1.540 g) was spread on six preparative layer plates. Elution with petrol/chloroform (45:55) gave five clearly defined bands (bands A - E in order of decreasing  $R_f$ ).



Bands A and B:

These were visible only as faint bands under ultraviolet light and were not removed from the plates.

Band C (0.788 g):

This material was shown by gas chromatography to be a mixture of products 9 and 10 in approximately equal amounts. Extraction with hot 60 - 80° petrol gave a yellow solution from which, on cooling, two crystalline materials separated; colourless needles and yellow crystals. The n.m.r. spectrum of this mixture suggested the presence of a methoxyacridine and a methoxyacridan.

The mixture (0.191 g) was spread on two preparative layer plates and eluted with 60 - 80° petrol/ether (45:55). The upper, colourless band gave colourless crystals from 60 - 80° petrol, identified as 1-methoxyacridan (106) (product 10). The lower, yellow band yielded yellow crystals from 60 - 80° petrol identified by spectral properties and mixed melting point with an authentic sample as 1-methoxyacridine (105) (product 9).

Band D (0.259 g):

Extracted material from this band crystallised from methanol giving bright yellow crystals (0.199 g) identified as azepino[1,2- $\alpha$ ]indol-6-one (104) (product 7).

Band E:

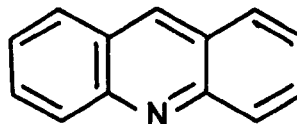
Removal from the plates gave a brown oil (0.04 g) which



was not identified.

Properties of the compounds isolated:-

Acridine (Product 3) (101)



M.p.  $111^{\circ}$  (60 -  $80^{\circ}$  petrol)

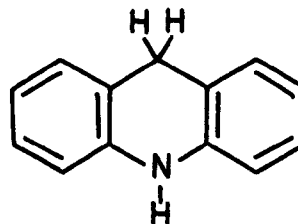
Lit.<sup>129</sup>  $111^{\circ}$

N.m.r. ( $\text{CDCl}_3$ )

$\tau 1.3$  p.p.m. s 1H H on C-9

1.6 - 2.8 m 8H

Acridan (Product 4) (102)



M.p.  $175^{\circ}$  (60 -  $80^{\circ}$  petrol)

Lit.<sup>129</sup>  $169^{\circ}$

Analysis

Found: C, 85.7; H, 6.35; N, 7.8%

Calculated for  $\text{C}_{13}\text{H}_{11}\text{N}$ : C, 86.15; H, 6.1; N, 7.75%

N.m.r. ( $\text{CCl}_4$ )

$\tau 2.8 - 3.5$  p.p.m. m 8H arom.

4.1 br s 1H NH (ex. with  $\text{D}_2\text{O}$ )

6.0 s 2H  $-\text{CH}_2-$



I.r. ( $\text{CCl}_4$ )

$\nu_{\text{max}}$  3430  $\text{cm}^{-1}$

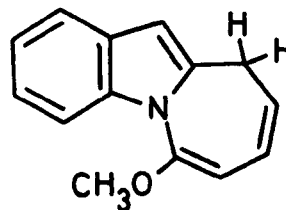
U.v. (95% ethanol)

$\lambda_{\text{max}}$  288 nm  $\log_{10} \epsilon$  4.13

6-methoxy-10H-azepino[1,2-a]indole (103)

(Product 6 - neutral)

B.p. 150 - 200°,  $\sim 10^{-4}$  mm



N.m.r. ( $\text{CCl}_4$ ) [Figure 14, page 62]

$\tau$ 2.35 - 3.15 p.p.m.	m	4H	H on C-1,2,3 and 4
4.05	s	1H	H on C-11
4.15 - 4.35	m	2H	H on C-8 and 9
5.0	d	1H	H on C-7, $J_{7,8} = 5\text{Hz}$
6.25	s	3H	$-\text{OCH}_3$
6.7	d	2H	$-\text{CH}_2-$ , $J_{9,10} = 6\text{Hz}$

Mass spectrum

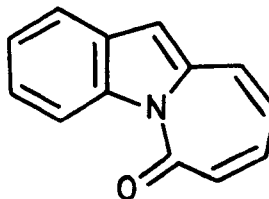
$m/e$  211 ( $M^+$ )(78%), 196 (100%), 168 (49%), 167 (65%),  
83.5 (18%).

$\text{C}_{14}\text{H}_{13}\text{NO}$  requires  $m/e$  211



Azepino[1,2-*a*]indol-6-one (104)

(Product 7)



M.p. 93 - 96° (methanol)

## Analysis

Found: C, 80.0; H, 4.85; N, 7.2%

C<sub>13</sub>H<sub>9</sub>NO requires: C, 79.95; H, 4.65; N, 7.15%100 MHz n.m.r. (CDCl<sub>3</sub>)

[Figure 15, page 64]

τ1.0 p.p.m.	complex signal	1H	H on C-4
2.25 - 2.7	m	3H	H on C-1,2 and 3
2.8	br d	1H	H on C-10, $J_{9,10} = 11\text{Hz}$
3.0	s	1H	H on C-11
3.2	q of d	1H	H on C-8, $J_{7,8} = 12.5\text{Hz},$ $J_{8,9} = 7.5\text{Hz},$ $J_{8,10} = 1.5\text{Hz}$
3.6	br d	1H	H on C-7
3.85	br q	1H	H on C-9

I.r. (CCl<sub>4</sub>) $\nu_{\text{max}}$  1690, 1670, 1640 cm<sup>-1</sup>



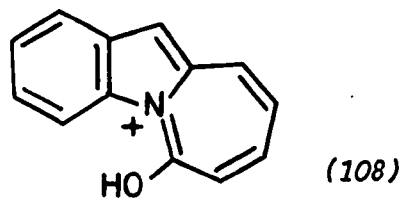
U.v. (95% ethanol)

$\lambda_{\max}$	225 nm	sh	
	252	sh	
	270		$\log_{10} \epsilon$ 4.39
	282		4.45
	304	sh	
	321	sh	
	420		3.46

Mass spectrum

$m/e$  195 ( $M^+$ )(78%), 167 (100%), 140 (14%), 139 (16%), 83.5 (20%)

A solution of azepino[1,2-*a*]indole-6-one in concentrated sulphuric acid had the following electronic absorption spectrum:

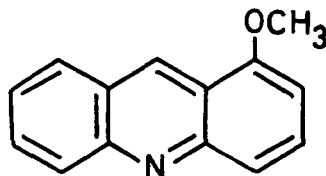


$\lambda_{\max}$	223 nm	$\log_{10} \epsilon$	4.16
	270		4.20
	300		4.46
	320	sh	
	516		3.06
	630	sh	



1-Methoxyacridine (105)

(Product 9)

M.p. and mixed m.p.  $122^{\circ}$  (60 -  $80^{\circ}$  petrol)Lit.<sup>130</sup>  $122^{\circ}$  (petrol) $155 - 156^{\circ}$ 

## Analysis

Found: C, 80.2; H, 5.25; N, 6.7%

Calculated for  $C_{14}H_{11}NO$ : C, 80.35; H, 5.3; N, 6.7%N.m.r. ( $CDCl_3$ ) $\tau 0.7$  p.p.m. s 1H H on C-9

1.5 - 2.6 m 6H

3.25 d of d 1H H on C-4,

 $J_{3,4} = 7\text{Hz}, J_{2,4} = 1\text{Hz}$ 6.0 s 3H  $-OCH_3$ 

## U.v. (95% ethanol)

 $\lambda_{\text{max}}$  234 nm sh

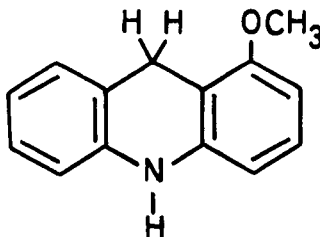
248 sh

256  $\log_{10} \epsilon$  4.77



1-Methoxyacridan (106)

(Product 10)

M.p.  $82^{\circ}$  ( $60 - 80^{\circ}$  petrol)

## Analysis

Found: C, 79.5; H, 6.2; N, 6.7%

 $C_{14}H_{13}NO$  requires: C, 79.6; H, 6.2; N, 6.65%N.m.r. ( $CDCl_3$ )

$\tau$ 2.85 - 4.0 p.p.m.	m	7H	arom.
4.25	br s	1H	-NH (ex. with $D_2O$ )
6.0	s	2H	$-CH_2-$
6.25	s	3H	$-OCH_3$

I.r. ( $CCl_4$ ) $\nu_{max}$   $3430\text{ cm}^{-1}$ 

## U.v. (95% ethanol)

$\lambda_{max}$	234 nm	$\log_{10}\epsilon$	4.16
	287		4.06
	307	sh	

(d) Quantitative gas chromatography

The yield of each of the decomposition products isolated was determined by gas chromatography using an internal standardisation



technique (see for example reference 103 for details). The standard substance chosen was 11-methylazepino[1,2- $\alpha$ ]indol-10-one which had a retention time of 28.5 minutes under the conditions used. (Gas chromatography data was the same for this work as described previously on page 137).

A further quantity of azide (8.75 g) was decomposed, taking care to exclude all traces of oxygen both during the decomposition and during the removal of the solvent, as described later in this section (page 153) Evaporation of most of the trichlorobenzene left a solution which weighed 24.41 g.

The standard substance, S (29.2 mg) was dissolved in a solution of the decomposition product (209.6 mg) in methanol ( $\sim 3$  ml) and the solution was diluted with methanol to 4 ml in a volumetric flask. A sample of this solution was injected into a gas chromatograph and, in order to determine approximately the weights required to make up a reference solution from the isolated products, the weights  $w_1, w_2 \dots w_{10}$  of each component, in relation to the weight ( $w_s$ ) of the standard, were calculated according to equation II assuming that  $K_1 = K_2 = K_3 = \dots = K_s = 1$  (see Table 1)

$$w_i = K_i A_i \text{ for component } i$$

$$w_s = K_s A_s \text{ for standard}$$



where  $w$  = wt. in mg

$A$  = area

$K$  = response coefficient

$$\therefore \frac{w_i}{w_s} = \frac{K_i A_i}{K_s A_s} \quad . . . . \text{Eqtn. I}$$

And, taking  $K_s$  arbitrarily as 1

$$w_i = K_{i(s)} w_s \frac{A_i}{A_s} \quad . . . . \text{Eqtn. II}$$

where  $K_{i(s)}$  is  $K_i$  relative to  $K_s$

TABLE 1 Sample solution

Product	Peak Area $A_i$	$w_i$ mg	$\frac{w_i}{w_s}$ mg
S	1536		
10	1170	22.2	17.2
9	337	6.4	4.54
7	320	6.1	4.70
4	913	17.4	5.61
3	140	2.6	1.58



Using each of the isolated products of the decomposition a reference mixture was prepared containing approximately these weights ( $w_i$ ) dissolved in methanol (4 ml). Using the peak area measurements ( $A_i'$ ) obtained from the chromatogram of this reference mixture it was possible, by equation III, to calculate  $K_i$  values, relative to  $K_s$ , taking  $K_s$  arbitrarily as 1 (see Table 2).

$$K_{i(s)} = \frac{w_i' A_s'}{w_s' A_i'} \quad . . . . \text{Eqtn. III}$$

where  $w'$  and  $A'$  refer to the  
reference mixture

TABLE 2      Reference solution

Product	$w_i'$ mg	Peak Area $A_i'$	$K_{i(s)}$
S	24.2	480	1.0
10	21.8	559	0.774
9	6.7	188	0.708
7	6.2	160	0.773
4	17.2	1056	0.323
3	3.6	120	0.595



Returning to the first chromatogram (of the sample solution) the exact weights,  $W_i$ , of each component present in the solution were calculated by substitution of the  $K_{i(s)}$  values into equation II (see Table 1).

The weight of product used for the sample solution was 0.2096 g out of the 24.41 g of product solution obtained from 8.75 g of azide. The total weight, and hence the yield, of each product was calculated. The results are shown in Table 3.

TABLE 3

Product		wt. produced in decomp.(g)	% yield
10	1-methoxyacridan (106)	2.00	25.9
9	1-methoxyacridine (105)	0.529	6.9
7	azepino[1,2-a]indol-6-one (104)	0.548	7.7
4	acridan (102)	0.654	9.9
3	acridine (101)	0.184	2.8

#### Decomposition with rigid exclusion of air

A further quantity of azide (8.75 g) was decomposed. The decomposition apparatus was connected directly to a nitrogen flushed rotary evaporator and after the decomposition the



trichlorobenzene was removed without admitting air.

A sample of the residue, on injection into a gas chromatograph, gave the same peaks in exactly the same proportions as previously. The residue was used immediately for the quantitative gas chromatography work.

Effluent gas from the decomposition apparatus was passed through a solution of 2,4-dinitrophenylhydrazine (11.15 g) in methanol (160 ml) and concentrated sulphuric acid (16 ml) in an attempt to detect formaldehyde. No formaldehyde-2,4-DNP was isolated.



DECOMPOSITION OF 2'-AZIDO-2,4,6-TRIMETHOXYDIPHENYLMETHANE (85)

The azide (10 g) was decomposed at 190° for four hours. The trichlorobenzene solvent was removed under reduced pressure leaving a brown, tarry residue (11.250 g).

Gas chromatography (3% OV101 on Chromosorb W, 40 ml/min nitrogen, 220°) showed that the residue contained three major products, designated products 1 - 3 corresponding, in order of increasing retention time, to the peaks 1 - 3 obtained by gas chromatography. (The chromatogram is reproduced on page 67).

Trial column chromatography of the residue (1 g) on alumina (45 g, activity IV) gave poor separation and consequently no further attempt was made to separate the products by this method.

Thin layer chromatography, eluting with benzene/ether (7:3) gave three well separated spots, therefore an attempt to separate the crude material was made using preparative layer chromatography.

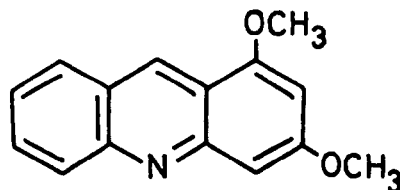
The crude product (2.5 g) was spread on eight preparative layer plates. Elution with benzene/ether (7:3) gave three clearly defined bands (bands A - C in order of decreasing  $R_f$ ).

Band C (450 mg):

Crystallisation from petrol/acetone (charcoal) gave



pure product 1 as bright yellow crystals. This product was identified from spectral properties as 1,3-dimethoxyacridine (112). This assignment of structure was confirmed by comparing n.m.r. spectra and melting points with a synthetic sample of 1,3-dimethoxyacridine.<sup>107</sup>



M.p. and mixed m.p.  $114^{\circ}$  (60 -  $80^{\circ}$  petrol/acetone)

Lit.<sup>107</sup>  $114^{\circ}$

N.m.r. ( $\text{CDCl}_3$ )

$\tau 1.0$ p.p.m.	s	1H	H on C-9
1.8 - 2.6	m	4H	H on C-5,6,7 and 8
2.95	d	1H	} H on C-2 and 4, $J_{2,4} = 3\text{Hz}$
3.6	d	1H	
6.05	s	6H	-OCH <sub>3</sub>

Mass spectrum

$m/e$  239 ( $M^+$ )(100%), 224 (16%), 196 (32%), 181 (16%),  
153 (24%).

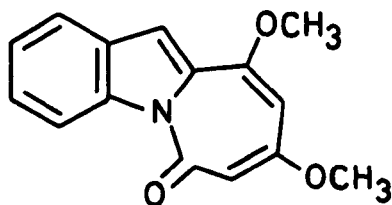
Band B (533 mg):

This material was a mixture of products 1 and 3, the



major constituent being product 3.

After re-running up three further preparative layer plates and removing the middle bands nearly pure product 3 was obtained. Two crystallisations from absolute ethanol (charcoal) gave pure product 3 as pale yellow crystals which were identified as 8,10-dimethoxyazepino[1,2-*a*]indol-6-one (114).



M.p. 159 - 159.5° (ethanol)

#### Analysis

Found: C, 70.9; H, 5.12; N, 5.4%

C<sub>15</sub>H<sub>13</sub>NO<sub>3</sub> requires: C, 70.60; H, 5.15; N, 5.50%

N.m.r. (CDCl<sub>3</sub>) [Figure 17, page 69]

τ1.05 p.p.m.	complex signal	1H	H on C-4, $J_{3,4} = 9\text{Hz}$
2.2 - 2.9	m	4H	H on C-1,2,3 and 11
4.3	d	1H	H on C-7
4.45	d	1H	H on C-9
			} $J_{7,9} = 2\text{Hz}$
6.25	s	3H	-OCH <sub>3</sub>
6.3	s	3H	-OCH <sub>3</sub>

I.r. (CCl<sub>4</sub>)

$\nu_{\text{max}}$  1665, 1635, 1595 cm<sup>-1</sup>



U.v. (95% ethanol)

$\lambda_{\max}$	242 nm	$\log_{10} \epsilon$	4.28
	270	sh	
	278		4.70
	311	sh	
	363		3.49

Band A (433 mg):

Gas chromatography showed that this material was a mixture of 1,3-dimethoxyacridine (product 1) and product 2. After re-running on three further preparative layer plates and removing the upper band it was found that product 2 was still contaminated with about 25% (considering only g.c. peak areas) of 1,3-dimethoxyacridine. The n.m.r. spectrum of this mixture indicated that product 2 was 1,3-dimethoxyacridan. (In the acridan the chemical shifts of the protons on C-2 and C-4 were different to the shift of the corresponding protons in the acridine. A two proton singlet at 6.05 $\tau$  was also indicative of an acridan.)

A sample of 1,3-dimethoxyacridan was synthesised (page 159) and by comparing the n.m.r. spectrum of the mixture of products 1 and 2 with the n.m.r. spectra of synthetic 1,3-dimethoxyacridan and 1,3-dimethoxyacridine respectively it was confirmed that product 2 was indeed 1,3-dimethoxyacridan (113). The synthetic acridan also had the same g.c. retention time as product 2.



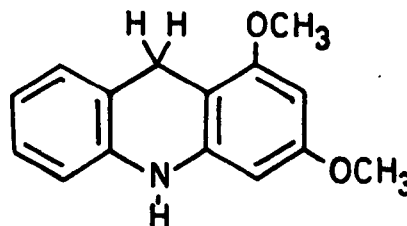
Preparation of 1,3-dimethoxyacridine (112)

1,3-Dihydroxyacridine was prepared from 2-amino-benzaldehyde<sup>131</sup> and phloroglucinol according to the method of Hughes and Ritchie<sup>107</sup> and methylated with diazomethane as described in the same paper.

Preparation of 1,3-dimethoxyacridan (113)

A solution of 1,3-dimethoxyacridine (500 mg) in 95% ethanol (100 ml) was hydrogenated at atmospheric temperature and pressure, using 10% palladium-carbon catalyst (50 mg), until one equivalent of hydrogen had been absorbed. Filtration, evaporation of the filtrate and crystallisation of the residue from methanol gave 1,3-dimethoxyacridan as colourless plates.

M.p. 125° (methanol)



Analysis

Found: C, 75.1; H, 6.7; N, 6.0%

C<sub>15</sub>H<sub>15</sub>NO<sub>2</sub> requires: C, 74.65; H, 6.25; N, 5.80%

N.m.r. (CCl<sub>4</sub>)

τ2.8 - 3.6 p.p.m. m 4H H on C-5,6,7 and 8

4.0 d 1H H on C-2 or C-4, J<sub>2,4</sub> = 3Hz



$\tau$ 4.15	br s	1H	-NH (ex. with D <sub>2</sub> O)
4.25	d	1H	H on C-2 or C-4
6.05	s	2H	-CH <sub>2</sub> -
6.25	s	3H	-OCH <sub>3</sub>
6.3	s	3H	-OCH <sub>3</sub>

I.r. (CCl<sub>4</sub>)

$\nu_{\text{max}}$  3440 cm<sup>-1</sup>

Crystallisations of the acridan had to be carried out quickly because solutions were rapidly oxidised in air. Crystalline 1,3-dimethoxyacridan oxidised less rapidly but had to be used immediately if appreciable oxidation was to be avoided.

#### Quantitative gas chromatography

The yield of each product was determined by gas chromatography using the internal standardisation technique described in detail on page 150. Page 150 should also be referred to for an explanation of the equations used in the following calculations.

The standard substance chosen was 1-methoxyacridine. This had a retention time of 4 minutes under the conditions used. (3% OV101 on Chromosorb W, 40 ml/min nitrogen, 220°)



$$w_i = K_{i(s)} w_s \frac{A_i}{A_s} \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{Eqtn. II}$$

where  $i$  refers to component  $i$

$s$  refers to standard

$w$  = wt. in mg

$A$  = area

$K_{i(s)}$  is the response coefficient of  
component  $i$  relative to that of  
the standard

$$K_{i(s)} = \frac{w'_i A'_s}{w'_s A'_i} \quad . \quad . \quad . \quad . \quad . \quad . \quad \text{Eqtn. III}$$

where  $w'$  and  $A'$  refer to the reference mixture

A solution was prepared containing the standard substance (4.9 mg) and the crude decomposition product (47.8 mg) in methanol (2 ml). In order to determine approximately the weights required to make up a reference solution from the isolated products the weights  $w_1$ ,  $w_2$  and  $w_3$  of each component in relation to the weight ( $w_s$ ) of the standard were calculated according to equation II assuming that  $K_1 = K_2 = K_3 = K_s = 1$  (See Table 1).



TABLE 1 Sample solution

Product	Peak Area $A_i$	$w_i$ mg	$\underline{w}_i$ mg
S	120		
1	246	10.15	8.29
2	134.8	5.50	7.29
3	167.7	6.85	8.13

Using each of the three isolated products a reference mixture was prepared containing approximately these weights ( $w_i$ ) dissolved in methanol (total volume 2 ml). Using the peak area measurement ( $A'_3$ ) obtained from the chromatogram of this reference mixture it was possible, by equation III, to calculate  $K_3$ , relative to  $K_8$ , taking  $K_8$  arbitrarily as 1 (Table 2).  $K_1$  and  $K_2$  could not be calculated at this stage because the sample of 1,3-dimethoxyacridan used to prepare the reference mixture contained a small amount of 1,3-dimethoxyacridine.

A chromatogram of the acridan used for this work showed the following areas:

1,3-dimethoxyacridan	342.7
1,3-dimethoxyacridine	73.7



The area of the acridine impurity peak which corresponded to the area ( $A_2'$ ) of the acridan peak in the reference mixture was calculated and subtracted from the area ( $A_1'$ ) of the acridine peak in the reference mixture giving an area  $A_{1(corr)}'$  which was used to calculate the response coefficient ( $K_1$ ) of 1,3-dimethoxyacridine.

The difference between areas  $A_1'$  and  $A_{1(corr)}'$  corresponded to the weight of acridine impurity in the acridan and, knowing the response coefficient of the acridine this weight was calculated and subtracted from the actual weight of the acridan used to prepare the reference mixture. This gave a corrected weight ( $w_{2(corr)}'$ ) which was used to calculate the response coefficient ( $K_2$ ) of 1,3-dimethoxyacridan (Table 2).

TABLE 2 Reference mixture

Product	$w_i'$ mg	$w_{i(corr)}'$	Peak Area $A_i$	$A_{i(corr)}'$	$K_{i(s)}$
S	5.1	-	99.8	-	1.0
1	10.2	-	266.7	242	0.825
2	8.8	7.76	114.7	-	1.324
3	6.8	-	112.3	-	1.186



Returning to the first chromatogram (of the sample solution) the exact weights,  $W_i$ , of each product were calculated by substitution of the calculated  $K_{i(s)}$  values into equation II (See Table 1).

The weight of crude product used for the sample solution was 0.0478 g out of the 11.250 g of residue obtained from 10.00 g azide. The total weight, and hence the yield, of each product was calculated. The results are shown in Table 3.

TABLE 3

Product		wt. produced in decomp.(g)	% yield
1	1,3-dimethoxyacridine (112)	1.961	24.5
2	1,3-dimethoxyacridan (113)	1.725	21.4
3	8,10-dimethoxyazepino[1,2- $\alpha$ ] indol-6-one (114)	1.923	22.6



DECOMPOSITION OF 1-(2-AZIDOPHENYL)-1-PHENYLETHANOL (86)

The azide (10 g) was decomposed at 200° for four hours. The removal of trichlorobenzene under reduced pressure left a black, tarry residue which was chromatographed on alumina (300 g, activity IV). Elution with 60 - 80° petrol moved a bright yellow band down the column. This was closely followed by an orange band and, since pronounced "funnelling" occurred these bands were collected together (3.41 g).

Preparative layer chromatography:

The material eluted from the column (2.69 g) was spread onto eight preparative layer plates and the plates were eluted with 60 - 80° petrol/toluene (15:85). Examination of the plates under ultraviolet light showed three clearly defined bands near the top of the plates. (Bands I to III in order of decreasing  $R_f$ ).

Band I (317 mg):

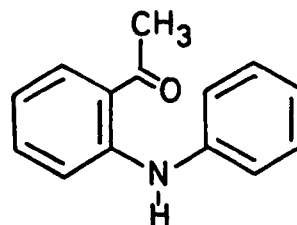
This material was very impure, being close to the solvent front and was not identified.

Band II (331 mg):

This material crystallised from 60 - 80° petrol (charcoal)



giving bright yellow crystals of 2-acetyldiphenylamine (116).



M.p.  $63.5^{\circ}$

Lit.<sup>108</sup>  $62 - 64^{\circ}$  (dil. alcohol)

Mixed m.p. with authentic sample  $62 - 64^{\circ}$

#### Analysis

Found: C, 79.8; H, 6.15; N, 6.6%

Calculated for  $C_{14}H_{13}NO$ : C, 79.6; H, 6.2; N, 6.65%

N.m.r. ( $CCl_4$ )

$\tau 2.45$ p.p.m.	d	1H	$J_{5,6} = 8\text{Hz}$
2.75 - 3.0	m	8H	(1H ex. with $D_2O$ )
3.3 - 3.6	m	1H	
7.45	s	3H	-CO-CH <sub>3</sub>

I.r. ( $CCl_4$ )

$\nu_{\text{max}}$  3230, 1640  $\text{cm}^{-1}$

U.v. (95% ethanol)

$\lambda_{\text{max}}$	229 nm	$\log_{10} \epsilon$	4.30
	251		4.15
	287		4.08
	383		3.87

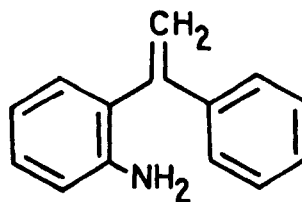


## Mass spectrum

$m/e$  211 ( $M^+$ )(100%), 196 (86%), 168 (24%), 167 (32%),  
166 (9%), 120 (37%)

Band III (451 mg):

Crystallisation from 60 - 80° petrol (charcoal) gave colourless crystals of 1-(2-aminophenyl)-1-phenylethylene (115) m.p. 76 - 77°, identical with material prepared previously (page 107).



N.m.r. ( $CCl_4$ )

τ 2.3 - 3.2 p.p.m.	m	9H	arom.
4.0	d	1H	} =CH <sub>2</sub> , $J = 2\text{Hz}$
4.45	d	1H	
6.45	br s	2H	-NH <sub>2</sub> (ex. with D <sub>2</sub> O)

I.r. ( $CCl_4$ )

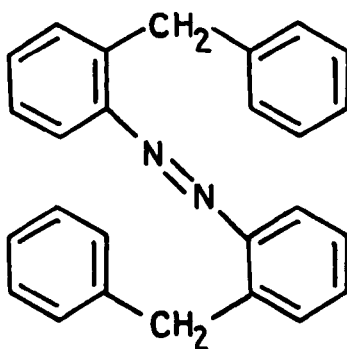
$\nu_{\text{max}}$  3490, 3400, 1620  $\text{cm}^{-1}$

No other products from the decomposition were identified.



PHOTOLYTIC DECOMPOSITION OF 2-AZIDODIPHENYLMETHANE (59)

The azide (1 g) dissolved in dry benzene (25 ml) was photolysed for ten hours using a pyrex filter over the light source. Thin layer chromatography indicated that there was still a trace of azide present but the solvent was evaporated and the residue chromatographed on a column of alumina (35 g, activity IV) with 60 - 80° petrol. Evaporation of the petrol fraction gave bright red crystals of 2,2'-dibenzylazobenzene (117) (0.388 g, 47%). M.p. 115° (60 - 80° petrol).



## Analysis

Found: C, 86.6; H, 6.15; N, 7.7%

C<sub>26</sub>H<sub>22</sub>N<sub>2</sub> requires: C, 86.15; H, 6.1; N, 7.7%

N.m.r. (CCl<sub>4</sub>)

τ2.75 - 2.9 m 18H arom.

5.5 s 4H -CH<sub>2</sub>-



I.r. ( $\text{CHCl}_3$ )

$\nu_{\text{max}}$  1600  $\text{cm}^{-1}$

U.v. (95% ethanol)

$\lambda_{\text{max}}$  234 nm  $\log_{10} \epsilon$  4.10

331 4.21

Mass spectrum

$m/e$  362 ( $\text{M}^+$ )(30%), 285 (58%), 180 (100%), 165 (100%),

152 (57%)

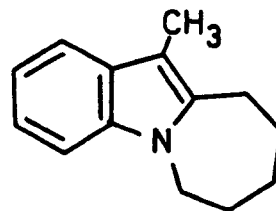


# SECTION 5

## FURTHER WORK ON THE AZIDE DECOMPOSITION PRODUCTS

### Reduction of 11-methyl-10H-azepino[1,2-*a*]indole (89)

A solution of the methylazepinoindole (89) (171 mg) in 95% ethanol (50 ml) was hydrogenated at atmospheric temperature and pressure using 10% palladium-carbon catalyst (60 mg). Uptake of hydrogen (2 mol) was complete after four hours. Filtration, evaporation of the filtrate, and crystallisation of the residue from 40 - 60° petrol gave 6,7,8,9-tetrahydro-11-methyl-10H-azepino[1,2-*a*]indole (91) as colourless crystals, m.p. 94.5 - 95°.



### Analysis

Found: C, 84.3; H, 8.85; N, 7.1%

C<sub>14</sub>H<sub>17</sub>N requires: C, 84.35; H, 8.6; N, 7.05%

### N.m.r. (CCl<sub>4</sub>)

τ2.3 - 3.0 p.p.m. m 4H arom.

5.6 - 6.0 m 2H N-CH<sub>2</sub>

6.9 - 7.3 m 2H H on C-10



$\tau$ 7.7	s	3H	-CH <sub>3</sub>
8.0 - 8.4	m	6H	H on C-7,8 and 9

U.v. (95% ethanol)

$\lambda_{\text{max}}$	232 nm	$\log_{10} \epsilon$	4.42
	288		3.78

Reaction of 10H-azepino[1,2-a]indole (87) with triphenylmethyl perchlorate

To a solution of triphenylmethyl perchlorate<sup>114</sup> from triphenylcarbinol (2.58 g, 10 mmol) and 60 - 62% perchloric acid (2.25 ml) in dry acetonitrile (25 ml) under nitrogen was added a solution of the azepinoindole (87) (0.79 g, 4.4 mmol) in dry acetonitrile (25 ml). The solution was stirred for 1 hour. Evaporation of the solvent left a dark blue residue which was ground in a mortar with ether. The ether suspension was filtered and the solid washed well with acetone and ether and air dried. This material (m.p. >300°) did not have analytical figures consistent with azepino[1,2-a]indolium perchlorate, the expected product.

**Analysis**

Found: C, 79.1; H, 5.50; N, 4.0%

C<sub>13</sub>H<sub>10</sub>NC10<sub>4</sub> requires: C, 55.85; H, 3.60; N, 5.0%



The reaction between trityl perchlorate (5 mmol) and azepinoindole (87) (5.5 mmol) under the above conditions produced a similar dark blue solid which had similar analytical figures.

The reaction between trityl perchlorate (3.1 mmol) and azepinoindole (87) (3.6 mmol) in liquid sulphur dioxide cooled in acetone/solid CO<sub>2</sub> gave a dark blue solid which again failed to analyse correctly for the expected product.

Found: C, 72.15; H, 5.05; N, 4.2%

Evaporation of the ether after removal of the blue solid by filtration gave a residue (0.88 g) the n.m.r. spectrum of which showed the expected signals for triphenylmethane i.e.  $\tau$ 2.8 - 3.0, m, 15H (arom.) and  $\tau$ 4.5, s, 1H (-CH).

The nature of these dark blue solids has not been established.

Reaction between 10H-azepino[1,2- $\alpha$ ]indole (87) and phosphorus pentachloride

To a suspension of phosphorus pentachloride (1.67 g, 8 mmol) in dry carbon tetrachloride (15 ml) was added a solution of azepinoindole (87) (0.72 g, 4 mmol) in carbon tetrachloride (5 ml).



The mixture was stirred for  $2\frac{1}{2}$  hours at room temperature and filtered. On addition to ethanol (25 ml) the solid material removed by filtration gave a deep purple solution. The ethanol solution was evaporated to small volume, added to a large volume of dry ether and the precipitated dark blue solid was removed by filtration, washed well with ether and air dried. Analytical figures did not agree with those expected for azepino[1,2- $\alpha$ ]indolium chloride but were closer to those required by the formula:  $C_{15}H_{14}NOCl$ .

#### Analysis

Found: C, 67.05; H, 5.15; N, 5.45%

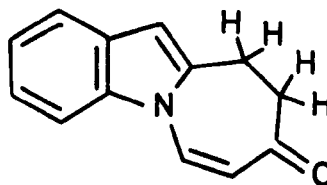
$C_{13}H_{10}NOCl$  requires: C, 72.3; H, 4.65; N, 6.5%

$C_{15}H_{14}NOCl$  requires: C, 69.3; H, 5.4; N, 5.4%

#### Hydrolysis of 8-methoxy-10H-azepino[1,2- $\alpha$ ]indole (93)

A solution of the methoxyazepinoindole (93) (2 g) in ether (50 ml) was shaken with N hydrochloric acid (25 ml) for two minutes. The ether layer was separated, washed with 5% sodium bicarbonate solution, dried ( $Na_2SO_4$ ) and evaporated. The residue was crystallised from methanol giving 9,10-dihydro-azepino[1,2- $\alpha$ ]indol-8-one (129) (1.75 g, 94%) as cream coloured crystals, m.p.  $106.5 - 107.5^{\circ}$ .





(129)

## Analysis

Found: C, 79.1; H, 5.95; N, 7.1%

 $C_{13}H_{11}NO$  requires: C, 79.15; H, 5.6; N, 7.1%N.m.r. ( $CCl_4$ ) [Figure 20, page 88]

τ2.45 - 3.0 p.p.m.	m	5H	H on C-1,2,3,4 and 6
3.7	s	1H	H on C-11
4.55	d	1H	H on C-7, $J_{6,7} = 10\text{Hz}$
7.05 } 7.2 }	overlapping triplets		4H H on C-9 and 10, $J_{9,10} = 10\text{Hz}$

I.r. ( $CCl_4$ ) $\nu_{\text{max}}$  1660, 1630  $\text{cm}^{-1}$ 

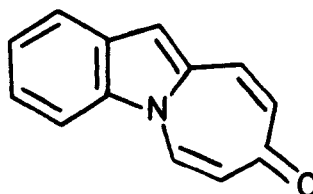
U.v. (95% ethanol)

$\lambda_{\text{max}}$	221 nm	$\log_{10} \epsilon$	4.31
	274		4.20
	279		4.21
	338		4.22



Reaction of 9,10-dihydro-azepino[1,2-*a*]indol-8-one (129) with  
2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

A solution of the dihydroketone (129) (2 g) and DDQ (4.5 g) in dry benzene (60 ml) was boiled for 15 hours under an atmosphere of nitrogen. The solvent was removed by distillation and the residue was chromatographed on alumina (60 g, activity IV). Elution with chloroform, evaporation of the eluate, and two crystallisations of the residue from methanol gave deep yellow crystals of azepino[1,2-*a*]indol-8-one (132) (1.58 g, 80%), m.p. 128.5°.



Analysis

Found: C, 79.7; H, 4.95; N, 7.2%

C<sub>13</sub>H<sub>9</sub>NO requires: C, 79.95; H, 4.65; N, 7.15%

N.m.r. (CDCl<sub>3</sub>) [Figure 18, page 85]

τ2.2 - 2.95 p.p.m.	m	6H	H on C-1,2,3,4,6 and 10
3.1	s	1H	H on C-11
3.75	d of d	1H	H on C-9, $J_{9,10} = 12\text{Hz}$ , $J_{7,9} = 3\text{Hz}$
4.2	d of d	1H	H on C-7, $J_{6,7} = 10\text{Hz}$ , $J_{7,9} = 3\text{Hz}$



I.r. (mull)

$\nu_{\max}$  1635, 1600  $\text{cm}^{-1}$

U.v. (95% ethanol)

$\lambda_{\max}$  221 nm  $\log_{10} \epsilon$  4.10

235 sh

288 sh

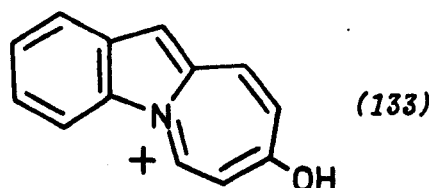
297 4.76

354 3.74

Mass spectrum

$m/e$  195 ( $M^+$ )(57%), 167 (100%), 140 (16%), 139 (16%),  
83.5 (21%)

Solutions of azepinoindolone (132) in acids were deep blue and had the following spectral properties:



N.m.r. (TFA)

10.95 p.p.m.	d	1H	H on C-6, $J_{6,7} = 10\text{Hz}$
1.75	d	1H	H on C-10, $J_{9,10} = 12\text{Hz}$
1.8 - 2.3	m	5H	H on C-1,2,3,4 and 11
3.1	d of d	1H	H on C-9, $J_{9,10} = 12\text{Hz}$ , $J_{7,9} = 3\text{Hz}$
3.35	d of d	1H	H on C-7, $J_{6,7} = 10\text{Hz}$ , $J_{7,9} = 3\text{Hz}$



U.v. ( $\text{H}_2\text{SO}_4$ )

$\lambda_{\text{max}}$	223 nm	$\log_{10} \epsilon$	4.12
	241		4.16
	256		4.19
	320		4.56
	331	sh	
	404		3.81
	520		3.07

Reaction of azepino[1,2-a]indol-8-one (132) with sodium bis(2-methoxyethoxy)aluminium hydride

To a solution of azepinoindolone (132) (0.30 g) in dry tetrahydrofuran under nitrogen was added a 70% benzene solution of the reducing agent (0.22 ml, 1 equiv.). The solution was boiled for 3 hours then water (20 ml) was added and the inorganic compounds were removed by filtration. The THF was evaporated and the residue extracted with chloroform. Evaporation of the dried extracts gave a yellow solid identical with the starting material.



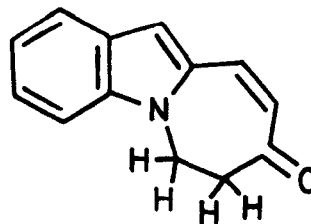
Reaction of azepino[1,2-*a*]indol-8-one (132) with lithium aluminium hydride

To a stirred suspension of lithium aluminium hydride (0.19 g, 5 mmol) in dry tetrahydrofuran (5 ml) and dry ether (5 ml) cooled in acetone/solid CO<sub>2</sub> was added a solution of azepinoindolone (132) in THF (10 ml). After stirring for 1 hour water (10 ml) was added and inorganic material was removed by filtration. The organic solvents were evaporated from the filtrate which was then extracted with ether. Evaporation of the dried extracts left a yellow oil (0.9 g) which, on preparative layer chromatography (3 plates, eluted with chloroform) gave two bands.

The upper, orange band gave material (17 mg) which was not identified.

The lower, pale yellow band gave material (500 mg) which was crystallised from methanol and identified as 6,7-dihydro-azepino[1,2-*a*]indol-8-one (134).

M.p. 109.5° (methanol)



**Analysis**

Found: C, 79.7; H, 5.95; N, 7.2%

C<sub>13</sub>H<sub>11</sub>NO requires: C, 79.2; H, 5.65; N, 7.1%



N.m.r. ( $\text{CDCl}_3$ ) [Figure 21, page 88]

2.3 - 2.95 p.p.m.	m	5H	H on C-1,2,3,4 and 10
3.2	s	1H	H on C-11
3.95	d	1H	H on C-9, $J_{9,10} = 12\text{Hz}$
5.7	m	2H	N-CH <sub>2</sub> -
7.0	m	2H	-CH <sub>2</sub> -

I.r. ( $\text{CCl}_4$ )

$\nu_{\text{max}}$  1660, 1605  $\text{cm}^{-1}$

U.v. (95% ethanol)

$\lambda_{\text{max}}$	210	$\log_{10} \epsilon$	4.48
	259		3.74
	263		4.30

8-Ethoxyazepino[1,2-a]indolium fluoborate (135)

To a stirred solution of triethyloxonium fluoborate<sup>118</sup> from boron trifluoride etherate (2.75 ml) and epichlorohydrin (1.3 ml) in methylene chloride (15 ml) under nitrogen was added a solution of azepino[1,2-a]indol-8-one (132) in methylene chloride (15 ml). After stirring for 1 hour most of the solvent was evaporated and dry ether (200 ml) was added to the residue which, on cooling and scratching, gave a dark red solid which was filtered



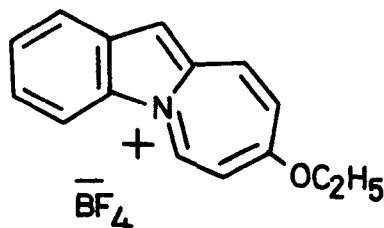
under nitrogen, washed well with dry ether and dried in vacuum.

I.r. ( $\text{CH}_2\text{Cl}_2$ )

$\nu_{\text{max}}$  1070, 1025  $\text{cm}^{-1}$

U.v. ( $\text{CH}_2\text{Cl}_2$ )

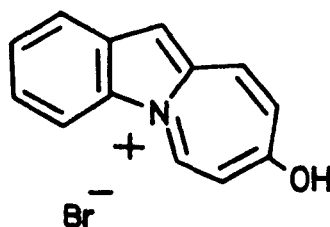
$\lambda_{\text{max}}$  235, 300, 313, 400, 530 nm



8-Hydroxyazepino[1,2-a]indolium bromide (136)

Dry hydrogen bromide was bubbled through a stirred solution of azepino[1,2-a]indol-8-one (132) in dry methylene chloride for 5 minutes. Dry ether (200 ml) was added and the precipitated dark blue solid was filtered under nitrogen, washed well with ether and dried under vacuum.

M.p. 140 - 145°



Analysis

Found: N, 5.1%

$\text{C}_{13}\text{H}_{10}\text{NOBr}$  requires: N, 5.4%



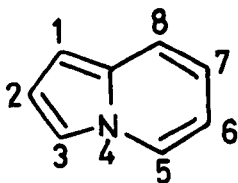
*P A R T    I I*

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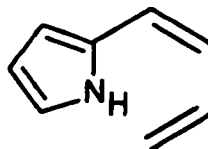


# I N T R O D U C T I O N

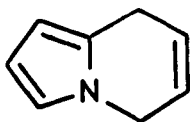
The reduction of indolizine (137) was first attempted by Scholtz<sup>132</sup> who obtained an oily base which, he reported, could not be further reduced. Scholtz made the suggestion that the product was 2-(1-butadienyl)pyrrole (138) but Borrowes and Holland<sup>133</sup> have proposed a dihydroindolizine structure for the product.



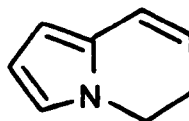
(137)



(138)



(139)



(140)

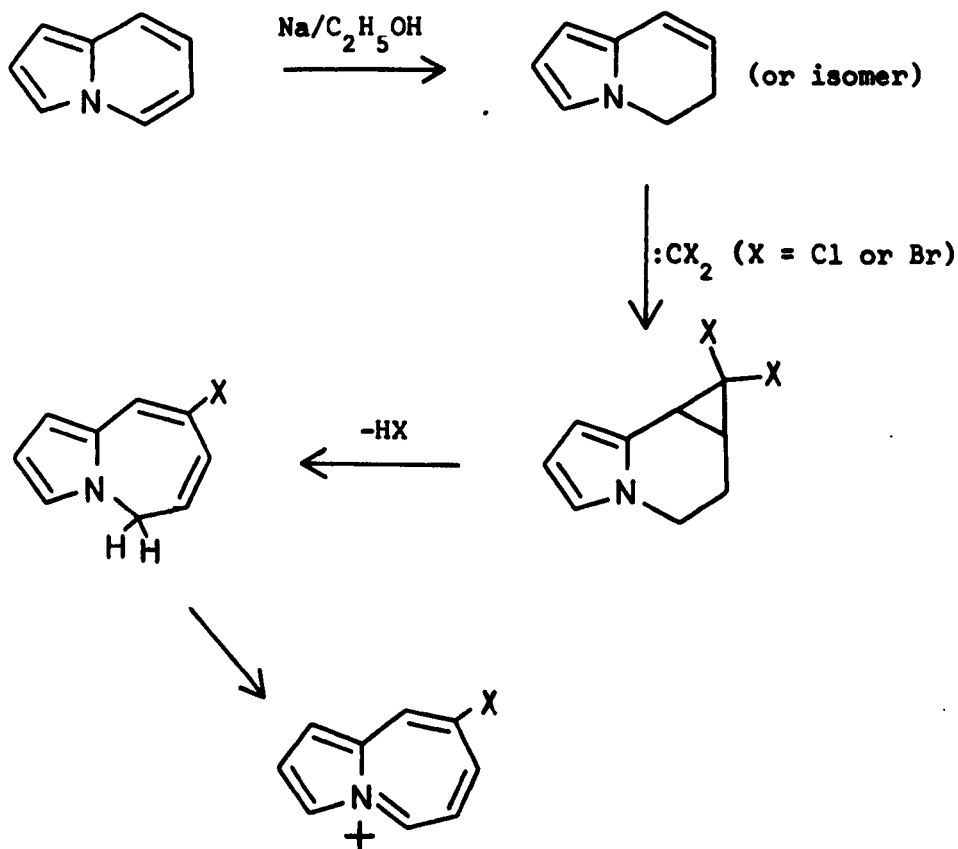
The fact that no further reduction took place led Mosby<sup>134</sup> to suggest that the product was 5,8-dihydroindolizine (139). In a recent investigation<sup>135</sup> the reduction gave a mixture which was thought to contain 5,6-dihydroindolizine (140).

The aim of the work presented in this part of the



thesis is to reinvestigate the reductions of several indolizines in the hope of isolating a single dihydro product suitable for attempted conversion into the 5,7 ring system of the azonia-azulenes. It was hoped that the addition of a halocarbene to a dihydroindolizine would provide a cyclopropane compound which would undergo ring expansion as envisaged in Scheme 37.

SCHEME 37



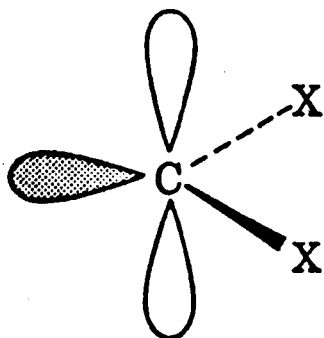


Carbenes have been the subject of several reviews<sup>42,136,137</sup> but nevertheless it is useful at this point to mention some of the relevant properties and reactions of dihalocarbenes bearing in mind the proposed reaction scheme.

### DIHALOCARBENES

Carbenes are electron deficient divalent carbon intermediates bearing no formal charge. The carbon atom of carbenes has only a sextet of electrons and accordingly its reactions are with nucleophiles.

The postulated structure of the dichlorocarbene intermediate (141) is that shown.<sup>138,139</sup>



(141)

The trigonal carbon is considered to have two covalent bonds joining it to the halogen atoms, a pair of electrons having antiparallel spins (singlet state) and an unoccupied *p*-orbital.

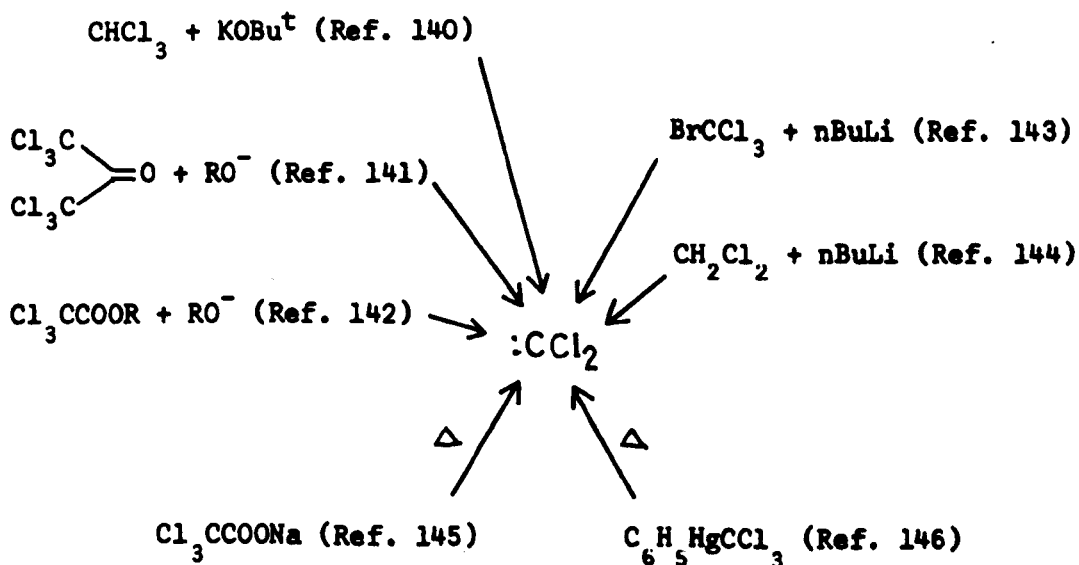


It is probable that considerable stabilisation of this structure is the consequence of overlap of the unshared  $p$ -electrons of the halogen atoms with the vacant  $p$ -orbital.<sup>138</sup> However the resulting energy gain by this delocalisation is insufficient to provide dichlorocarbene with complete stability such as in the other divalent carbon species, carbon monoxide or the iso-nitriles.

### Generation

The main routes to dihalocarbenes and their variations are summarised in Scheme 38.

### SCHEME 38





## Reactions

Insertion at a C-H bond, commonly observed for methylene ( $\text{:CH}_2$ ) has not been observed in the reactions of halocarbenes.

The main reactions of dihalocarbenes are with olefinic and aromatic carbon-carbon double bonds:

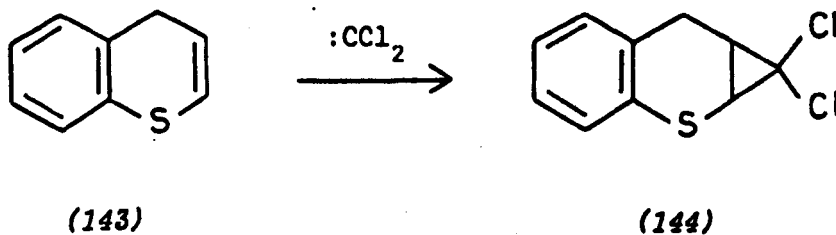
Cyclohexene and dichlorocarbene gave dichloronorcarane (142).<sup>140</sup>



(142)

4H-1-Benzothiapyran (143) and dichlorocarbene gave 1,1-dichlorocycloprop[*b*][1]benzothiapyran (144)<sup>147</sup> as shown in Scheme 39.

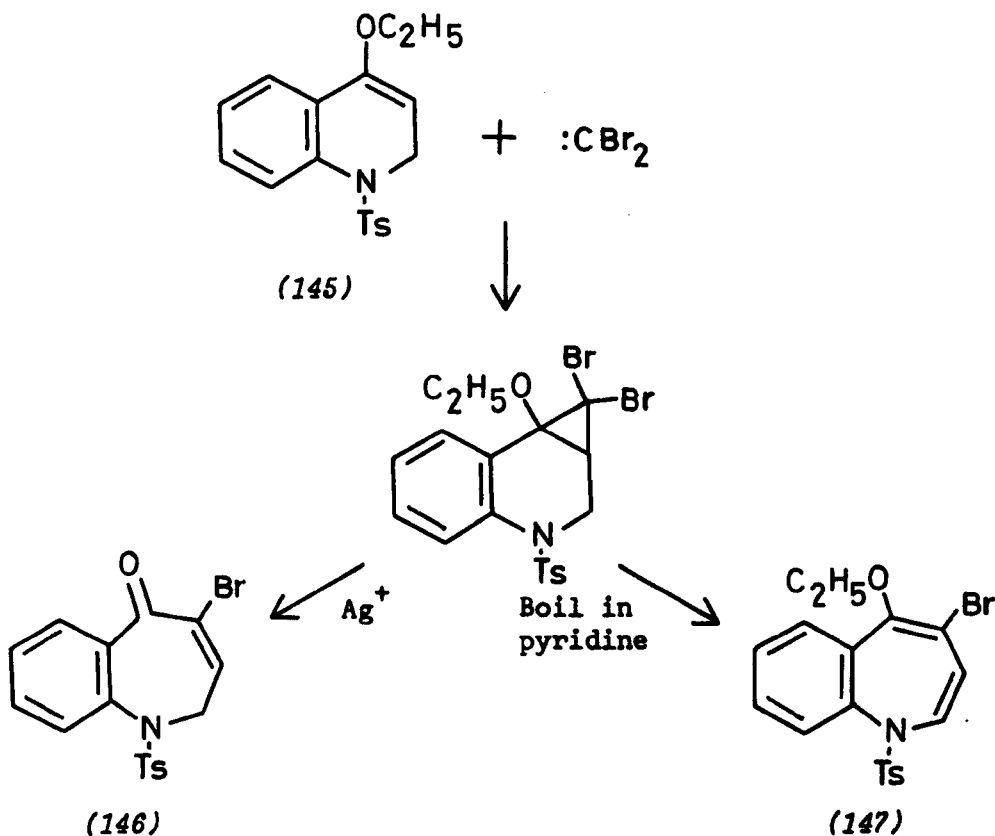
### SCHEME 39





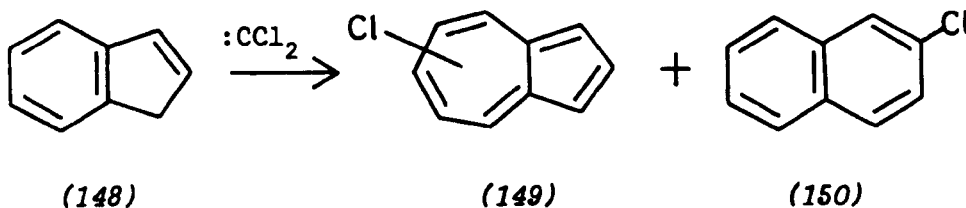
The synthesis of azepinone (146) and azepine (147) was accomplished<sup>148</sup> by a procedure involving reaction of the dihydroquinoline (145) with dibromocarbene (Scheme 40).

SCHEME 40

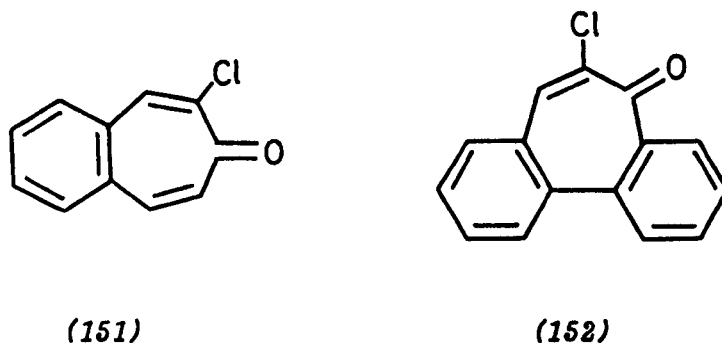


The formation of a small amount of a chloro-azulene (149), together with 2-chloronaphthalene (150), from indene (148) and dichlorocarbene resulted from attack of the carbene on an aromatic double bond<sup>149</sup> (Scheme 41).



SCHEME 41

Chlorotropones (151) and (152) were produced when 2-methoxynaphthalene and 9-methoxyphenanthrene were reacted with dichlorocarbene.<sup>150</sup>



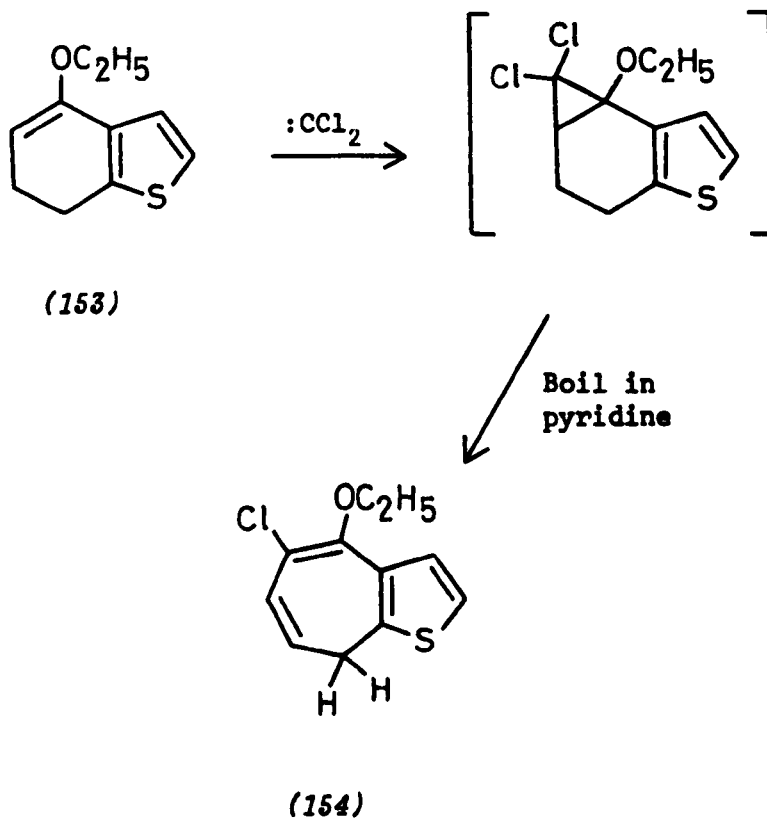
With the dihydroindolizine (140) which is essentially a vinyl pyrrole the question arises as to whether attack of the dihalocarbene will take place at the isolated double bond, enabling expansion of the six-membered ring to take place, or at the pyrrole ring with expansion giving a six-membered ring.

Both indoles and pyrroles have been reported to



undergo attack by dichlorocarbene in the five-membered ring giving 3-chloroquinoline and 3-chloropyridine respectively,<sup>149</sup> but the dihydrobenzo[*b*]thiophen (153) which is a comparable compound to dihydroindolizine (140) has been reported<sup>151</sup> to be attacked by dichlorocarbene at the isolated double bond giving the thia-azulene (154) (Scheme 42). No product where expansion of the five-membered ring had taken place was isolated.

SCHEME 42



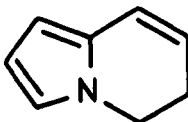


## DISCUSSION

### INDOLIZINE REDUCTIONS

The reduction products of indolizine and 2-methylindolizine were very unstable and structural assignments were based entirely on the interpretation of mass and n.m.r. spectra.

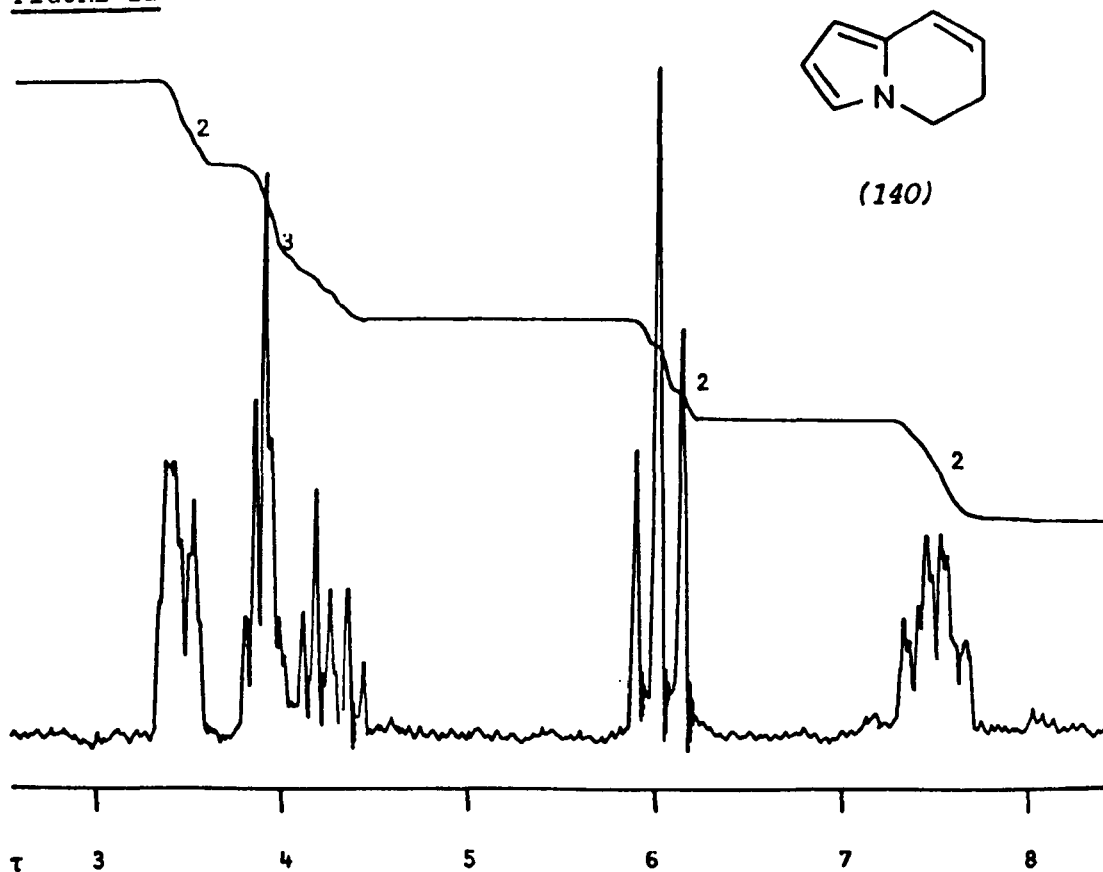
The reduction of indolizine (137) with sodium and ethanol gave non-reproducible results and on one occasion only was the product shown to be substantially pure on examination by gas chromatography. The mass spectrum of the product (Figure 24, page 193) showed the molecular ion at  $m/e$  119, consistent with a dihydroindolizine, and the n.m.r. spectrum (Figure 22) showed that it was 5,6-dihydroindolizine (140).



(140)



FIGURE 22

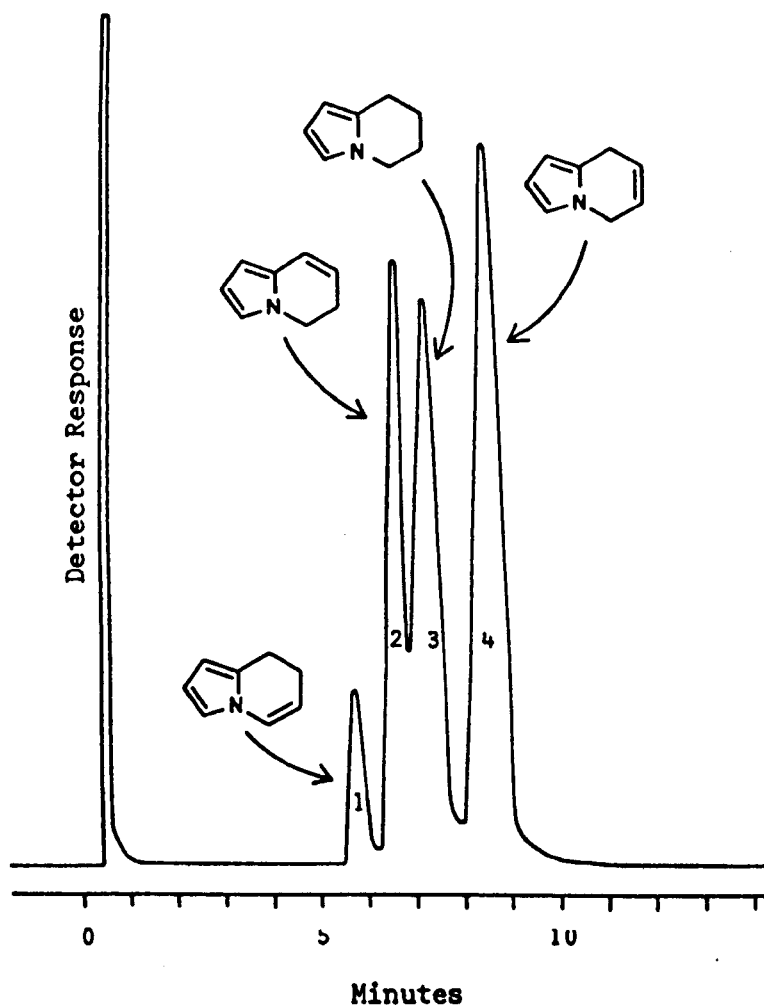


The 5,6-dihydro structure (140) can be assigned on the basis of the position of the methylene group triplet (6.15 $\tau$ ) which occurs at too low a value of the applied field to be at any position in the molecule other than adjacent to the nitrogen atom. (For comparison 1-*n*-butylpyrrole has N-CH<sub>2</sub> at 6.3 $\tau$ <sup>152</sup>). The multiplet at 7.6 $\tau$  can be assigned to the C-6 methylene protons and the multiplet 4.1 - 4.45 $\tau$  to proton-7.



This reduction was apparently fortuitous and more usual was the production of a mixture. A gas chromatogram of the products of a typical reduction is shown in Figure 23.

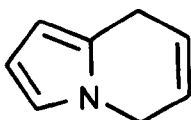
FIGURE 23



The products could not be separated by distillation but it proved possible to achieve some separation by chromatography on alumina of high activity. By combining some of the

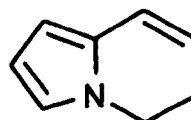


fractions off the column small quantities of products 1 and 4 were isolated and products 2 and 3 were obtained as a mixture which could not be separated. The four products were assigned structures (139), (140), (155) and (156) on the basis of the evidence presented below:



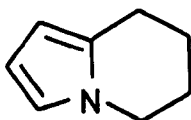
(139)

(Product 4)



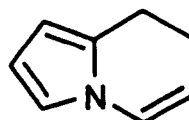
(140)

(Product 2)



(155)

(Product 3)



(156)

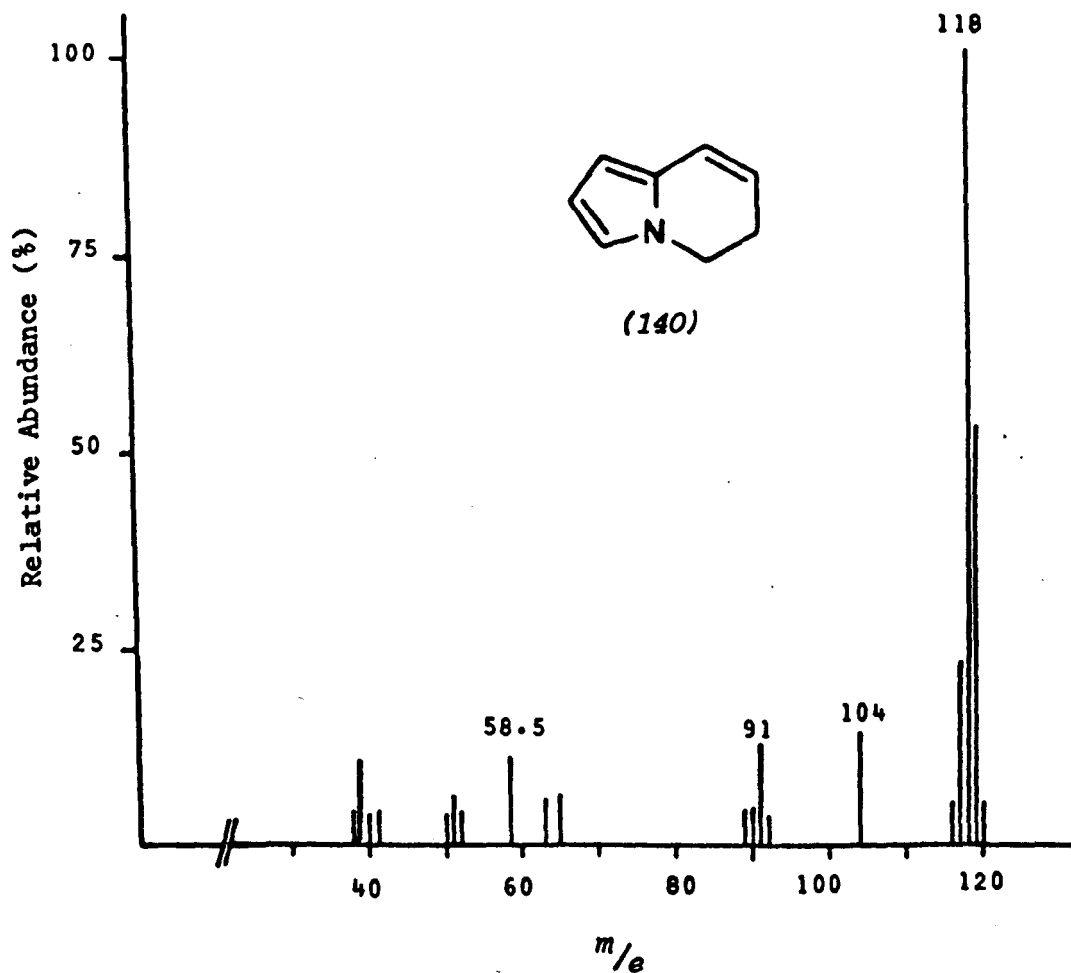
(Product 1)

From the mixture of products 2 and 3, using a linked gas chromatograph-mass spectrometer system, mass spectra were obtained which showed the presence of a dihydroindolizine and tetrahydroindolizine. The mass spectra of products 1 and 4



were practically identical and indistinguishable from that of product 2. All three spectra showed molecular ions at  $m/e$  119 thus identifying these products as isomeric dihydroindolizines. The mass spectrum of 5,6-dihydroindolizine (140) is shown in Figure 24.

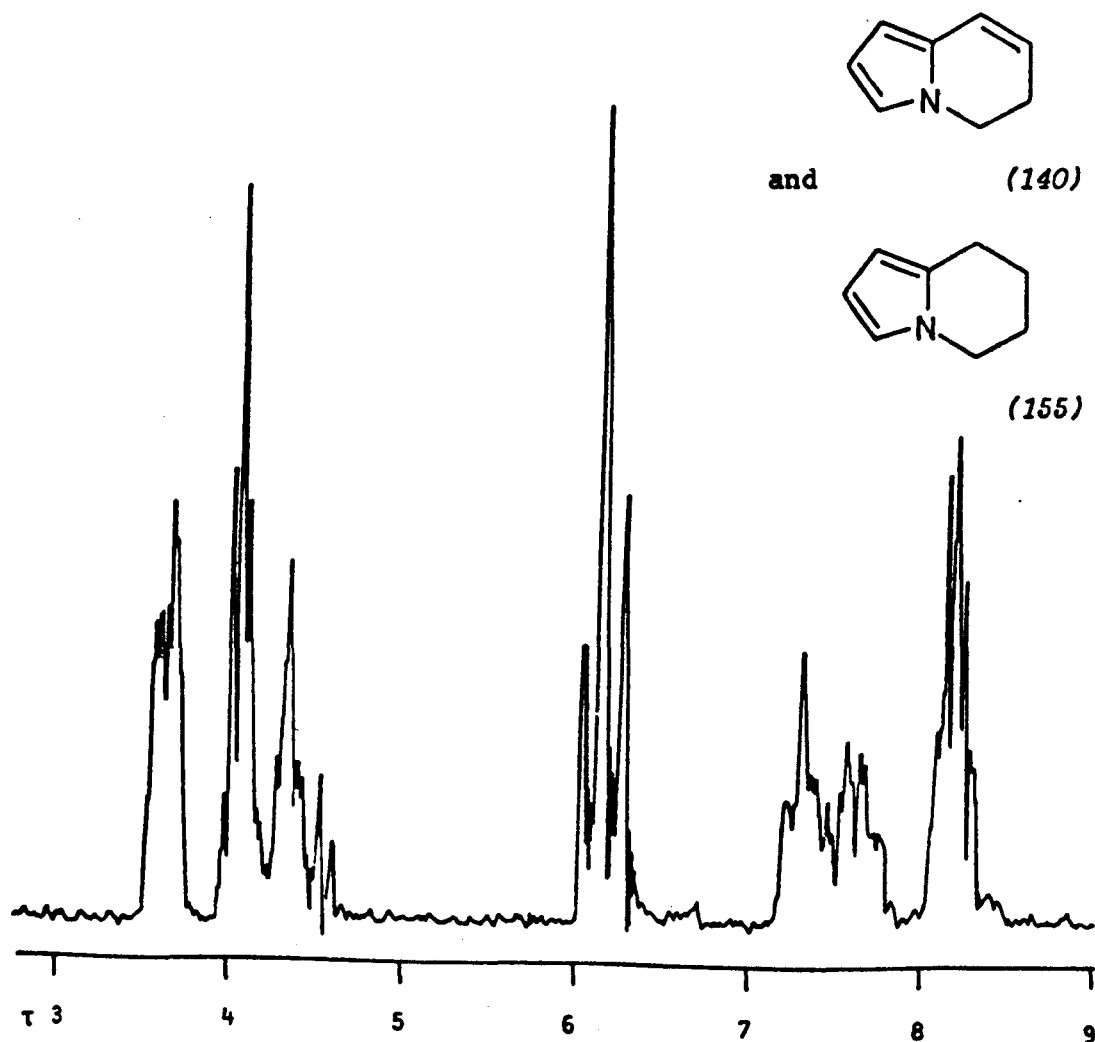
FIGURE 24





Loss of one mass unit from the molecular ion gives the base peak at  $m/e$  118 and the peak at  $m/e$  91 can then be formed either by loss of 27 mass units (HCN) from the base peak, or by loss of  $H_2CN$  from the molecular ion. Losses of HCN and  $H_2CN$  have been reported previously in the electron impact fragmentations of indolizines.<sup>153</sup>

FIGURE 25

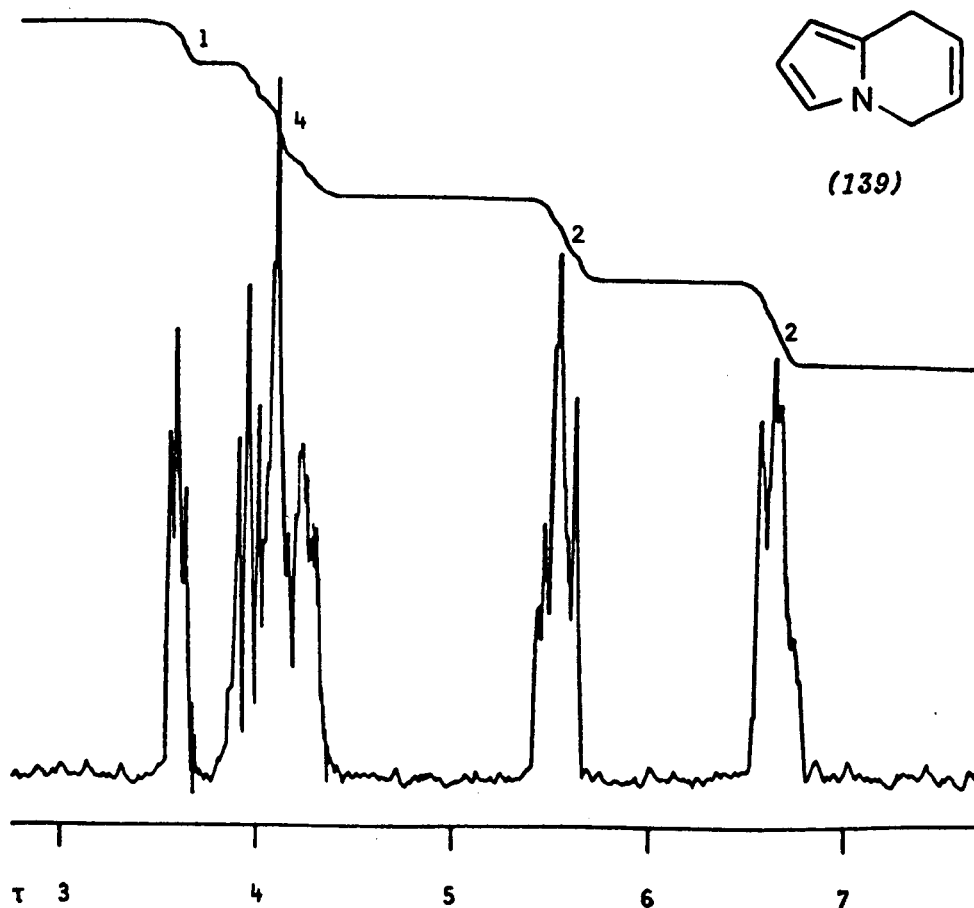




A comparison of the n.m.r. spectrum of the mixture of products 2 and 3 (Figure 25, page 194) with that of the previously characterised 5,6-dihydroindolizine (140) (Figure 22, page 190) and also with that of 5,6,7,8-tetrahydroindolizine (155) (Figure 27, page 197), the preparation of which will be described later, then allowed the assignment of structures (140) and (155) to products 2 and 3 respectively.

The assignment of the 5,8-dihydroindolizine structure (139) to product 4 was based on the interpretation of its n.m.r. spectrum (Figure 26).

FIGURE 26





The two multiplets at 5.4 - 5.65 $\tau$  and 6.6 - 6.8 $\tau$  are in good accord with the expected chemical shifts for the C-5 and C-8 methylene groups of structure (139). The signal for the N-CH<sub>2</sub> group of 5,6-dihydroindolizine (140) occurs at 6.15 $\tau$  (Figure 22) and that of the C-8 methylene group of 5,6,7,8-tetrahydroindolizine (155) occurs at 7.3 $\tau$  (Figure 27). The downfield shift of approximately 0.6 p.p.m. observed for the corresponding signals in Figure 26 is consistent with the attachment of each group to a double bond and this must therefore be in the 6,7 position. The signals for protons-6 and -7 occur together with those for protons-1 and -2 in the multiplet at 3.9 - 4.3 $\tau$ . The signal for proton-3 occurs at 3.6 $\tau$ .

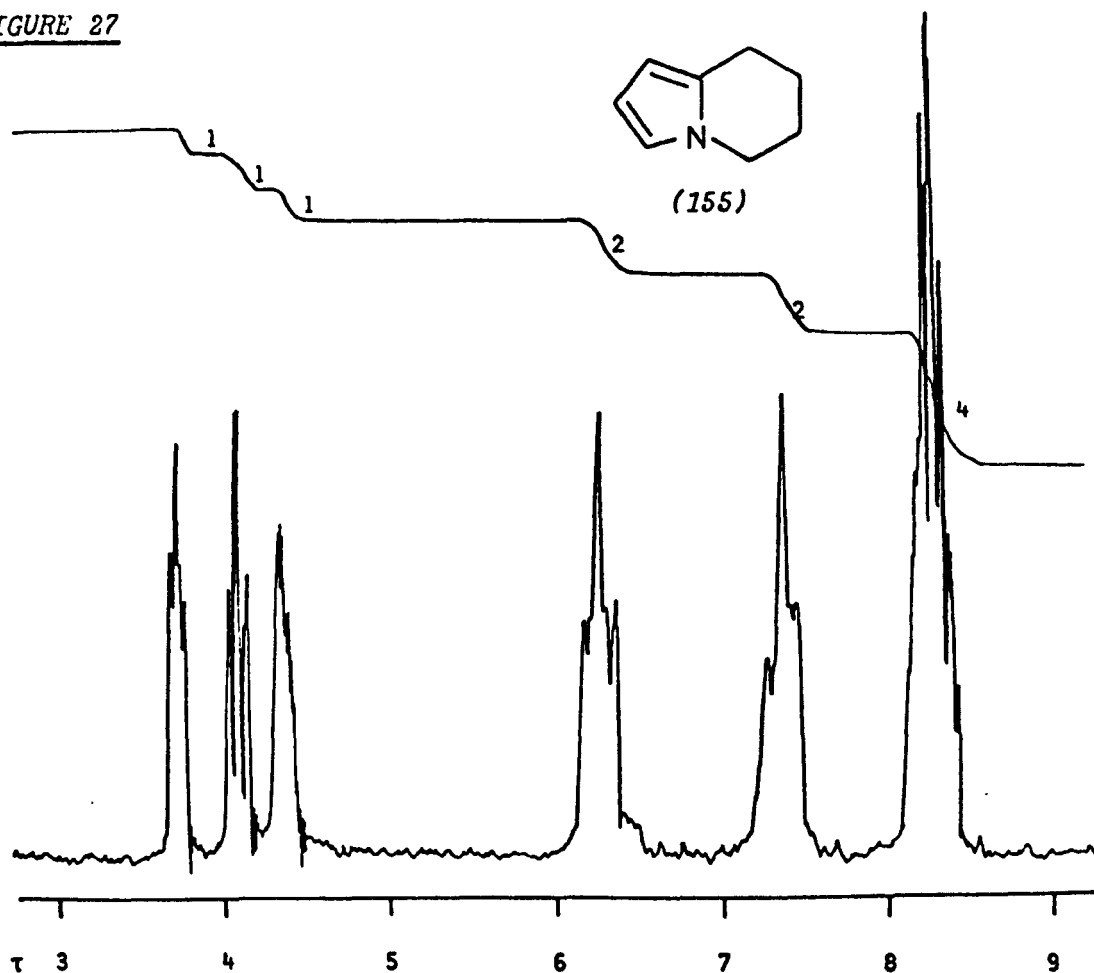
The assignment of the 7,8-dihydroindolizine structure (156) to product 1 was based entirely on the similarity of its mass spectrum to those of the characterised indolizines (139) and (140) since insufficient material for an n.m.r. spectrum was isolated.

Further treatment with sodium in ethanol of the products from this reduction of indolizine, until examination by gas chromatography showed the presence of mainly one



compound, gave 5,6,7,8-tetrahydroindolizine (155) identified by the interpretation of its n.m.r. spectrum (Figure 27) and mass spectrum.

FIGURE 27



The signals at 3.75 $\tau$ , 4.1 $\tau$  and 4.3 - 4.5 $\tau$  are assigned to the protons on the five-membered ring in positions 3, 2 and 1 by analogy with the n.m.r. spectrum of 2-ethylpyrrole.<sup>152</sup> The methylene triplet centred at 6.15 $\tau$  can be assigned to the



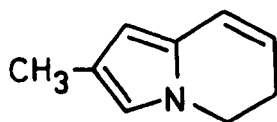
N-CH<sub>2</sub> group and the methylene triplet at 7.3 $\tau$  must then be due to the C-8 methylene protons (2-ethylpyrrole has -CH<sub>2</sub>-resonance at 7.37 $\tau$ <sup>152</sup>). The multiplet at 8.15 - 8.45 $\tau$  can then be assigned to the C-6 and C-7 methylene protons.

The mass spectrum of tetrahydroindolizine (155) showed the molecular ion at  $m/e$  121 and base peak at  $m/e$  120. The peak at  $m/e$  93 was considered to arise by either loss of HCN from the base peak or by loss of H<sub>2</sub>CN from the molecular ion.

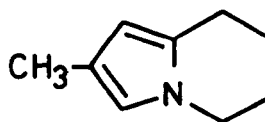
The reduction of indolizine (137) using lithium in *iso*-propylamine gave a mixture of indolizine (140) and tetrahydroindolizine (155). The structures of the products were assigned by comparing mass and n.m.r. spectra with the previously prepared samples.

The sodium in ethanol reduction of 2-methylindolizine gave a mixture of 5,6-dihydro-2-methylindolizine (157) and 5,6,7,8-tetrahydro-2-methylindolizine (158).





(157)

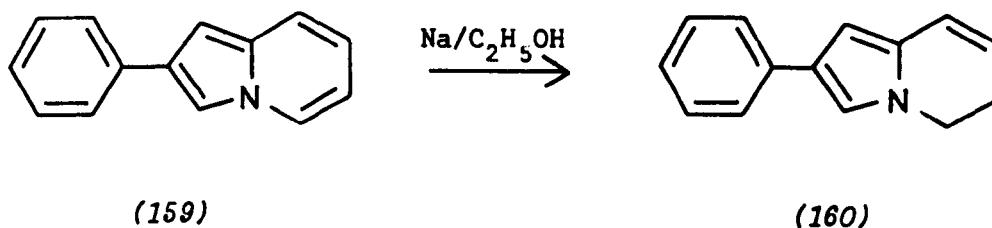


(158)

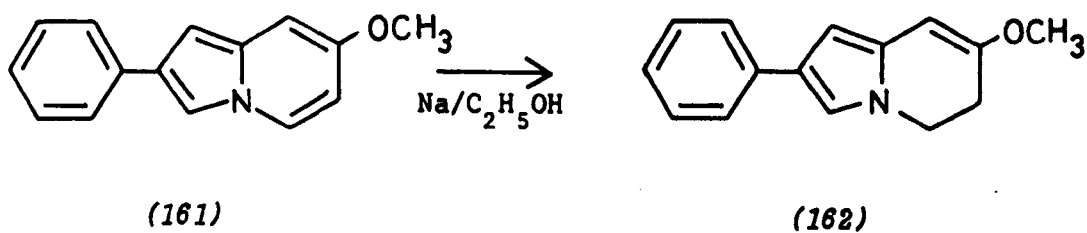
These structures were assigned by comparing the n.m.r. spectrum of the reduction mixture with the spectra of the previously characterised products from the sodium in ethanol reduction of indolizine. Thus the n.m.r. spectrum of the mixture showed a multiplet at  $8.2\tau$  due to the methylene protons in positions 6 and 7 of the tetrahydroindolizine (158) and a multiplet at  $7.6\tau$  which corresponded well with the C-6 methylene group signal in the dihydroindolizine (140) and which could therefore be assigned to the C-6 methylene protons in the dihydro-2-methylindolizine (157).

Reduction of 2-phenylindolizine (159) by sodium in ethanol gave a crystalline dihydro derivative (Scheme 43) which was shown to be 5,6-dihydro-2-phenylindolizine (160).



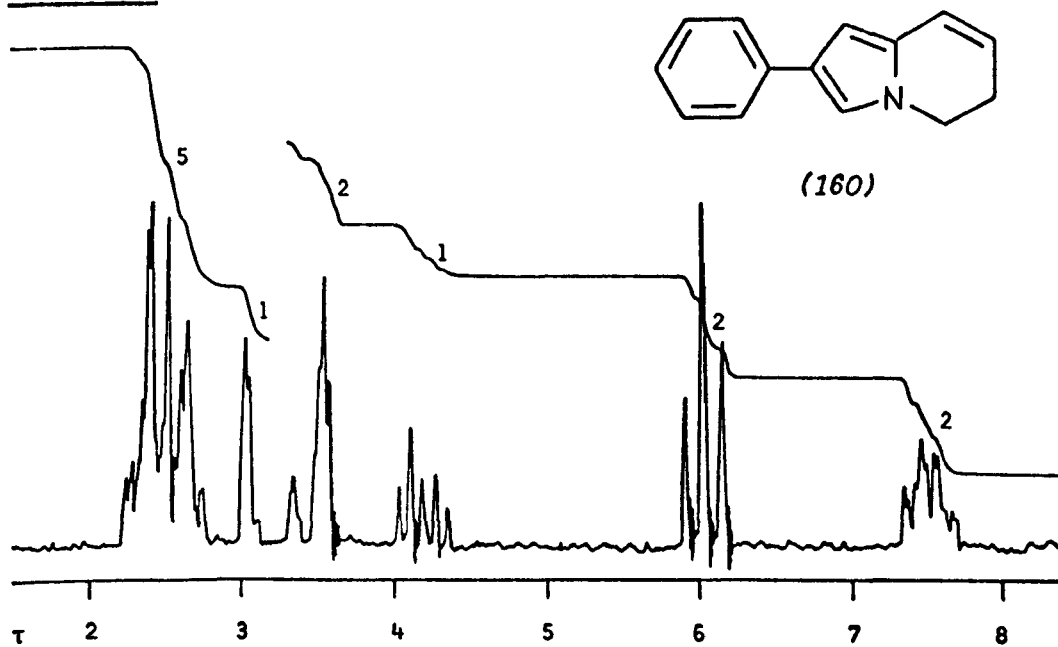
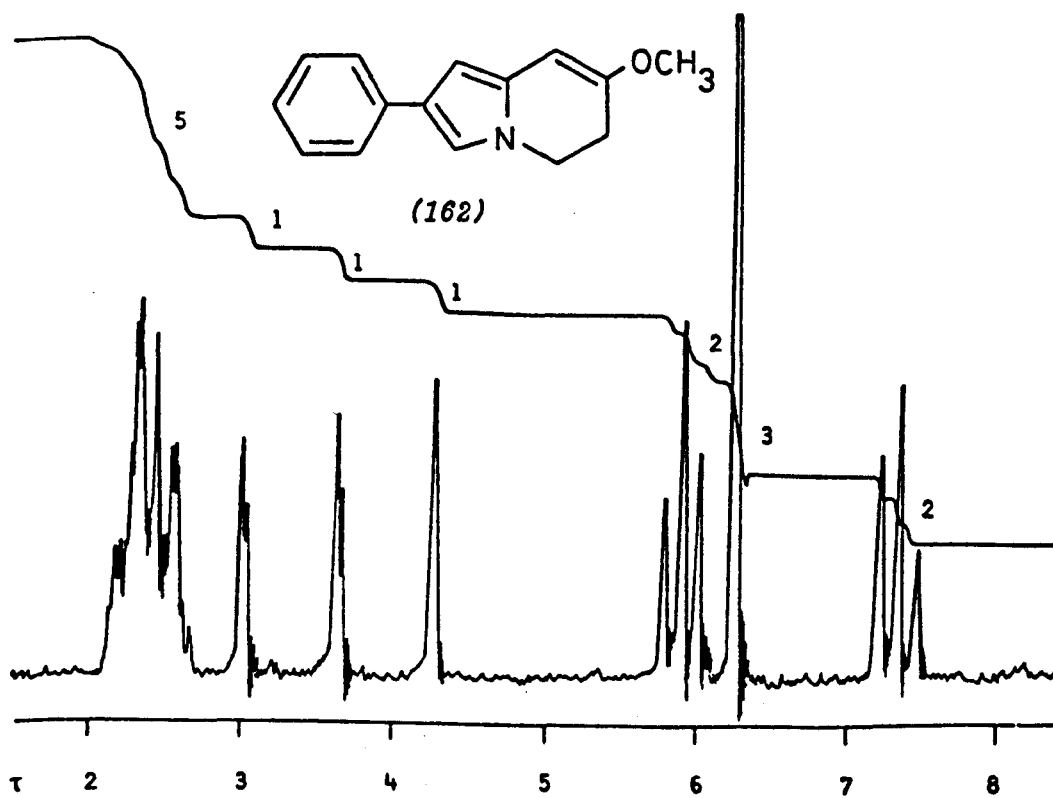
SCHEME 43

A similar reduction on 7-methoxy-2-phenylindolizine (161) gave 5,6-dihydro-7-methoxy-2-phenylindolizine (162) (Scheme 44).

SCHEME 44

The n.m.r. spectra of the dihydroindolizines (160) and (162) are reproduced in Figures 28 and 29.



FIGURE 28FIGURE 29



In both Figures 28 and 29 the two proton triplets at  $6.05\tau$  and  $5.9\tau$  respectively can be assigned to the  $N-CH_2$  methylene protons by analogy with the position of the corresponding signal in the dihydroindolizine (140).

In Figure 29 the two proton triplet at  $7.35\tau$  can be assigned to the C-6 methylene protons. This signal appears as a simple triplet, since there is no proton-7, in contrast to the multiplet for C-6, at  $7.5\tau$ , in Figure 28. The absence of proton-7 also means that the signal for proton-8 appears as a singlet at  $4.25\tau$  in Figure 29. The doublets at  $3.05\tau$  and  $3.65\tau$  can be assigned to protons-3 and -1 respectively.

In Figure 28 the one proton multiplet at  $4.0 - 4.4\tau$  is assigned to proton-7, being split by both proton-8 and the C-6 methylene protons. The signal for proton-8 occurs together with that for proton-1 as a multiplet at  $3.35 - 3.6\tau$ .

### MECHANISM

Dissolving metal reductions of organic compounds have been widely reported. The most common reductions of this type are those employing liquid ammonia or low molecular weight amine

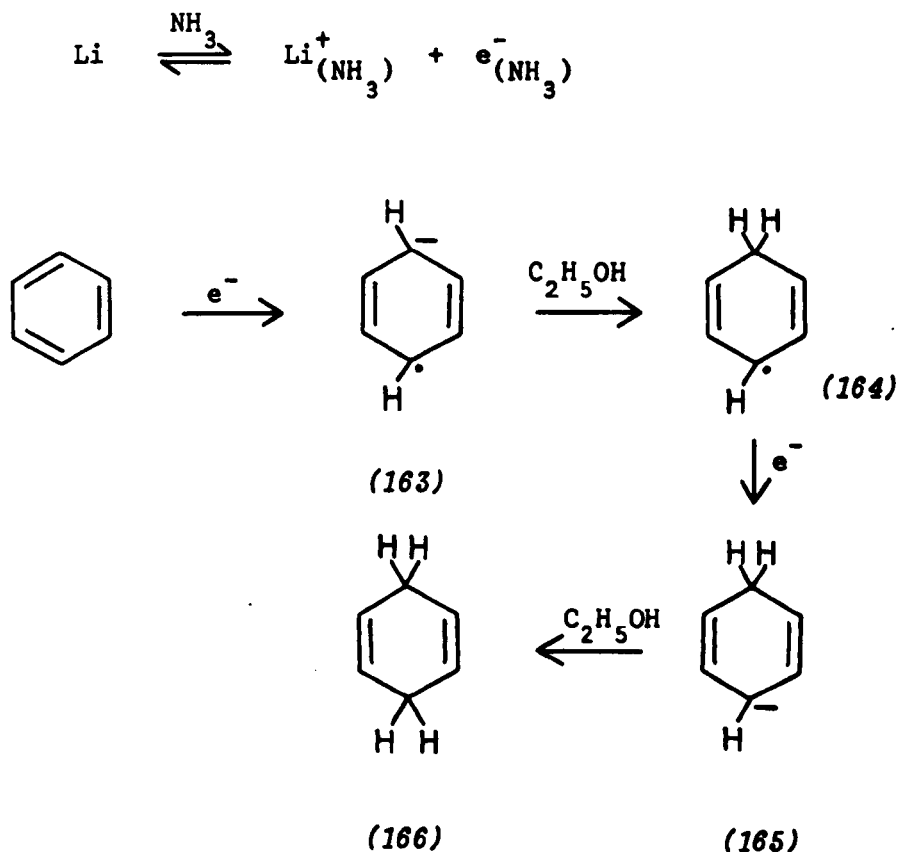


solutions of alkali metals when a proton donor, commonly alcohol, is present in the reaction medium or is added during the isolation; and those where the metal is added directly to a solution of the compound being reduced in a hydroxylic solvent. An example of the first type is the Birch reduction (sodium in liquid ammonia) and of the second type is the Clemmensen reduction (zinc amalgam and hydrochloric acid) both of which have been reviewed.<sup>154,155</sup>

Dissolving metal reductions, originally considered<sup>156</sup> to be effected by the production of 'nascent' hydrogen atoms which added to organic compounds before they combined to molecular hydrogen, are now regarded as taking place by the transfer of an electron from the metal surface (or from the metal in solution) to the organic molecule being reduced.

The mechanism of dissolving metal reductions of aromatic compounds has been well established, largely due to the work of Birch.<sup>154</sup> For example, the lithium in liquid ammonia and ethanol reduction of benzene<sup>157</sup> proceeds as in Scheme 45 to give 1,4-dihydrobenzene (166).



SCHEME 45

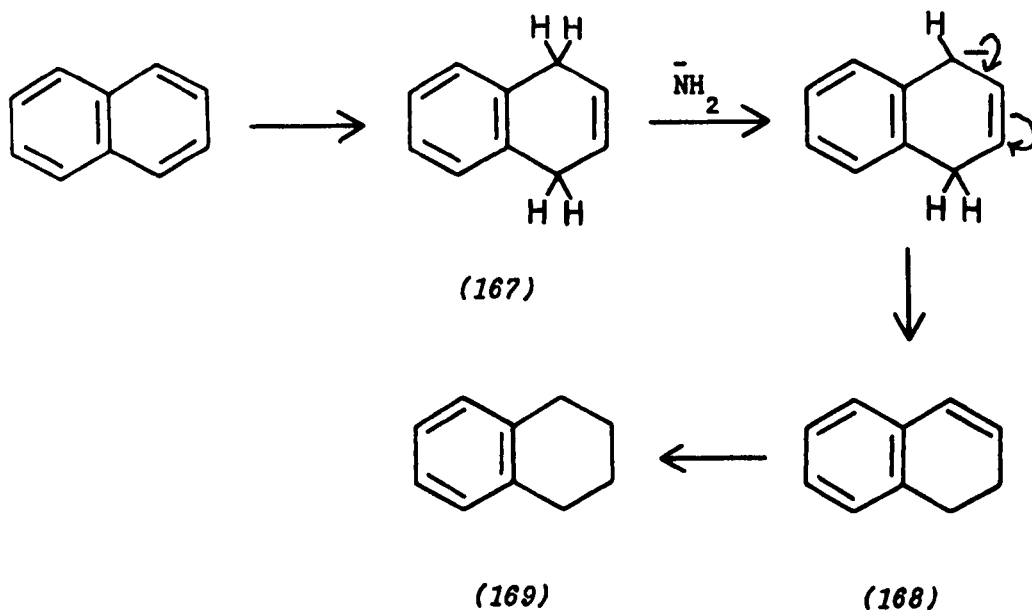
The anion radical (163) is formed reversibly in low concentration and then reacts further with the protonic solvent to form the radical (164), and subsequently the anion (165) and the dihydro derivative (166).

Under conditions of irreversible proton addition the product of aromatic ring reduction is the unconjugated 1,4-dihydro compound which is not reduced further. When proton addition is



reversible secondary products can be formed. For example the reduction of naphthalene<sup>158</sup> by sodium in liquid ammonia at the boiling point has been interpreted<sup>159</sup> as follows:

SCHEME 46



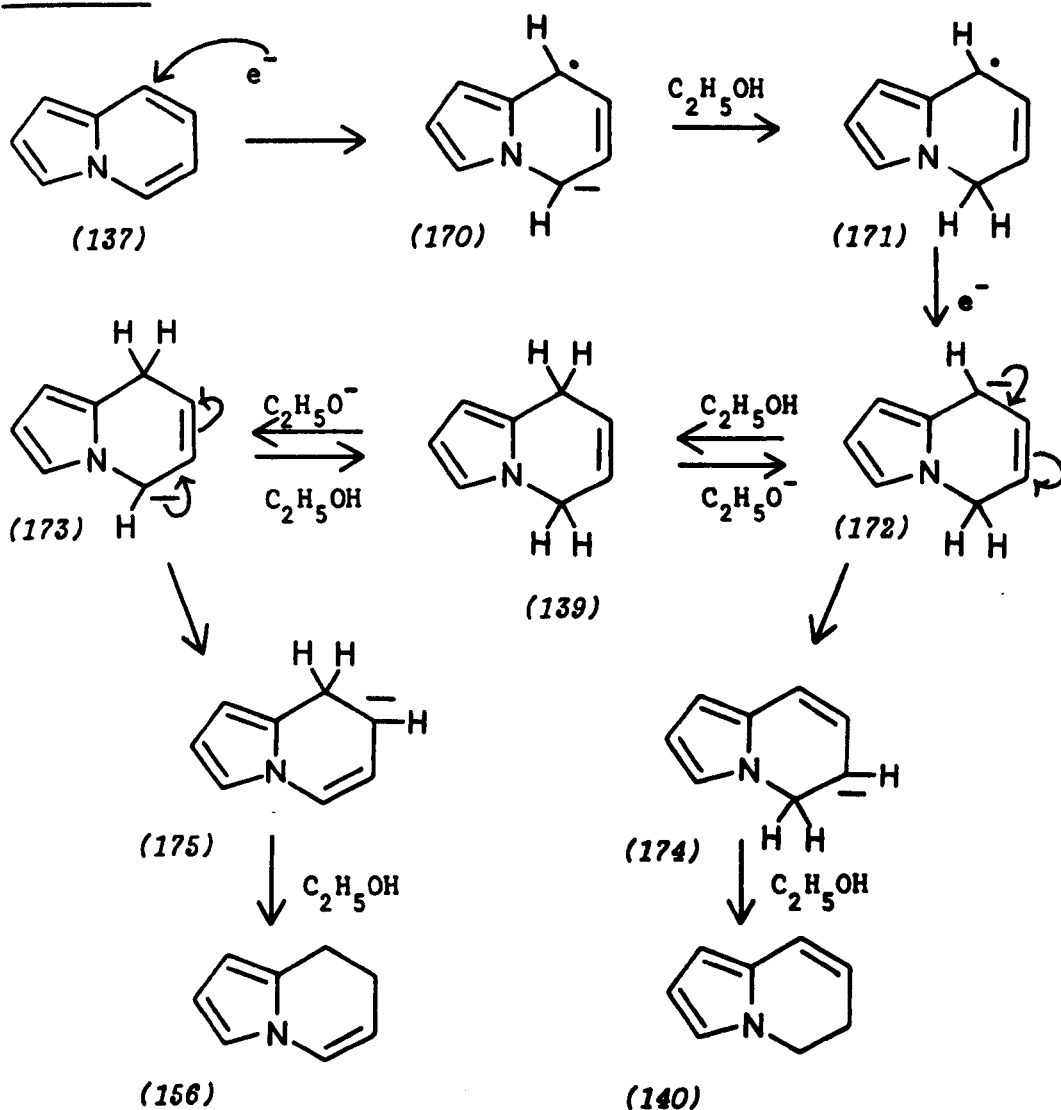
1,4-Dihydronaphthalene (167) is formed by the sequence shown in Scheme 45 and this is isomerised by the sodium amide formed in the process to the conjugated 1,2-dihydronaphthalene (168) which can then be reduced further to tetrahydronaphthalene (169).

The dissolving metal reductions of indolizine can therefore be interpreted as follows:



The initial addition of a solvated electron to indolizine can be expected to take place at the position of lowest electron density. Coulson and Longuet-Higgins<sup>160</sup> have calculated the  $\pi$ -electron densities of indolizine by the molecular orbital method and have found that position 8 has least charge density.

SCHEME 47



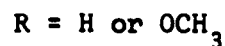
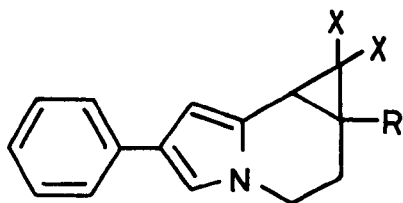


Thus the anion radical (170) is first formed (Scheme 47) and this reacts further with the protonic solvent to form the radical (171). 5,8-Dihydroindolizine (139) can then be formed via the anion (172). The unconjugated dihydroindolizine (139) is the primary product of the reduction but under the conditions of the reaction and in the presence of the sodium ethoxide produced in the process anions (172) or (173) can be formed which lead to the formation, via the conjugated anions (174) and (175), of 5,6-dihydroindolizine (140) and 7,8-dihydroindolizine (156) respectively. The removal of a proton from dihydroindolizine (139) must take place preferentially from position 8 since only traces of 7,8-dihydroindolizine (156) were observed.

#### ATTEMPTS TO REACT DIHYDROINDOLIZINES WITH DIHALOCARBENES

As the 2-phenyl-dihydroindolizines (160) and (162) were the only compounds showing appreciable stability these were used in attempted carbene additions in the hope of preparing the cyclopropyl adduct (176).





(176)

Reaction between 5,6-dihydro-2-phenylindolizine (160) and chloroform/potassium *tert*-butoxide gave a black intractable tar from which no product could be identified. The use of sodium trichloroacetate<sup>145</sup> on dihydroindolizine (160) or of phenyl(tribromomethyl)mercury<sup>146</sup> on compounds (160) or (162) gave no products, unchanged dihydroindolizines being recovered.

The failure of the reactions with dihalocarbenes was disappointing. However a useful contribution to the chemistry of indolizine has been made by the investigation of dissolving metal reductions; reactions which for a long time have required elucidation. It appears that, in common with the dissolving metal reductions of other aromatic systems, the 1,4-dihydro compound is the primary product of the



reduction of indolizine. Further work on this reaction could usefully be directed towards establishing the conditions required to prevent isomerisation to the conjugated dihydro compound.



## EXPERIMENTAL

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### SECTION I

#### PREPARATION OF INDOLIZINES

Indolizine was prepared from 3-(2'-pyridyl)-1-propanol by the method of Boekelheide and Windgassen.<sup>161</sup>

2-Methylindolizine was prepared from 2-methylpyridine and bromoacetone by the method of Holland and Nayler.<sup>162</sup>

2-Phenylindolizine was prepared from 2-methylpyridine and  $\alpha$ -bromoacetophenone by the method of Borrows, Holland and Kenyon.<sup>163</sup>

#### 7-Methoxy-2-phenylindolizine

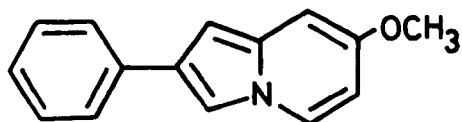
4-Methoxy-2-methylpyridine was prepared from 2-methylpyridine by nitration of the N-oxide and reaction of the nitro compound with sodium methoxide as described by Den Hertog and co-workers for the preparation of 4-methoxypyridine.<sup>164,165</sup>

To a solution of 4-methoxy-2-methylpyridine (11.8 g) in dry acetone (25 ml) was added  $\alpha$ -bromoacetophenone<sup>166</sup> (19.1 g).



The solution was boiled for  $1\frac{1}{2}$  hours, cooled, and the deposited 4-methoxy-2-methyl-1-phenacylpyridinium bromide was removed by filtration, washed with acetone and air dried (23.5 g, 76%).

This salt (15 g) was dissolved in water (150 ml), sodium bicarbonate (15 g) was added and the solution was boiled gently until no more 7-methoxy-2-phenylindolizine was precipitated. The precipitated crystals were filtered, washed with water and air dried. A portion recrystallised from ethanol gave colourless plates m.p.  $172^{\circ}$ .



(161)

#### Analysis

Found: C, 80.4; H, 5.55; N, 6.1%

$C_{15}H_{13}NO$  requires: C, 80.7; H, 5.9; N, 6.3%



## SECTION II

### REDUCTION OF INDOLIZINES

#### Sodium/ethanol reduction of indolizine

A solution of indolizine (5 g) in 95% ethanol (50 ml) was boiled gently under nitrogen whilst small pieces of metallic sodium were added down the condenser. The addition of sodium was continued until no more indolizine was present as shown by gas chromatography (3% OV101, 40 ml/min  $N_2$ ,  $85^\circ$ ). The reaction mixture was poured into water (150 ml) and ether extracted (3 x 50 ml). Evaporation of the dried extracts gave a pale yellow oil (3.2 g) which was shown, by gas chromatography, to be a mixture of four compounds, although t.l.c. showed only one spot. The g.c. retention times of products 1 - 4 were 5.4, 6.2, 6.8 and 8.0 minutes respectively.

The oil was distilled in a micro-distillation apparatus (b.p.  $144 - 146^\circ$ , 518 mm) and a gas chromatogram of the distillate was identical with that before distillation.

An attempt was made to separate the products by column chromatography.

The oil (0.66 g) was chromatographed with 40 -  $60^\circ$  petrol



on alumina (45 g, activity II) using a wrapped column. The composition of each 5 ml fraction collected was checked by gas chromatography and the fractions were bulked into four samples according to their composition.

#### SAMPLE 1

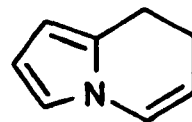
(Fractions 9 - 12, 2 mg, mainly component 1)

The mass spectrum of this material indicated a dihydroindolizine.

$m/e$  119 ( $M^+$ )(54%), 118 (100%), 117 (30%), 91 (15%), 58.5 (15%)

$C_8H_9N$  requires  $m/e$  119

This component may be 7,8-dihydroindolizine



(156)

#### SAMPLE 2

(Fractions 14 - 18, 148 mg, components 2 and 3)

The n.m.r. spectrum of this sample showed a mixture of 5,6-dihydroindolizine (140) and 5,6,7,8-tetrahydroindolizine (155). This was confirmed by the injection of a sample into a linked gas chromatograph - mass spectrometer system.

Peak 2  $m/e$  119 ( $M^+$ )(53%), 118 (100%), 117 (23%), 104 (13%),  
91 (12%), 58.5 (10%)

$C_8H_9N$  requires  $m/e$  119

Peak 3  $m/e$  121 ( $M^+$ )(82%), 120 (100%), 93 (43%), 80 (14%)

$C_8H_{11}N$  requires  $m/e$  121



Spectrum identical with that of

5,6,7,8-tetrahydroindolizine

N.m.r. spectrum: See Figure 25, page 194.

Integration indicated a ratio (140):(155) of 1:0.8.

### SAMPLE 3

(Fractions 19 - 39, 210 mg, mixture of components 2,3 and 4)

### SAMPLE 4

(Fractions 40 - 66, 42 mg, component 4)

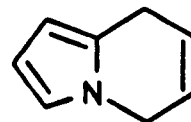
Identified from mass and n.m.r. spectra as 5,8-dihydroindolizine (139).

$m/e$  119 ( $M^+$ )(60%), 118 (100%), 117 (44%), 104 (12%), 91 (20%),  
58.5 (13%)

$C_8H_9N$  requires  $m/e$  119

N.m.r. ( $CCl_4$ ) [Figure 26, page 195]

$\tau$ 3.6 p.p.m.	d of d	1H	H on C-3
3.9 - 4.3	m	4H	H on C-1,2,6 and 7
5.4 - 5.65	m	2H	N-CH <sub>2</sub>
6.6 - 6.8	m	2H	H on C-8



(139)

Further sodium/ethanol reduction of the distilled product from the previous reduction until there was only one product on gas chromatography and work up as previously described gave 5,6,7,8-tetrahydroindolizine (155).

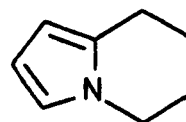


$m/e$  121 ( $M^+$ )(82%), 120 (100%), 93 (43%), 80 (14%)

$C_8H_{11}N$  requires  $m/e$  121

N.m.r. ( $CCl_4$ ) [Figure 27, page 197]

τ3.75 p.p.m.	d of d	1H	H on C-3
4.1	t	1H	H on C-2
4.3 - 4.5	m	1H	H on C-1
6.15	br t	2H	$N-CH_2$
7.3	br t	2H	H on C-8
8.15 - 8.45	m	4H	H on C-6 and 7

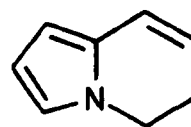


(155)

The sodium/ethanol reduction of indolizine was not reproducible and on one occasion from indolizine (4.9 g) and sodium (11.7 g) an almost pure product was obtained. This was distilled (b.p. 83 - 84°, 18 mm) and identified from its n.m.r. spectrum as 5,6-dihydroindolizine (140).

N.m.r. ( $CCl_4$ ) [Figure 22, page 190]

τ3.35 - 3.6 p.p.m.	m	2H	H on C-3 and 8
3.8 - 4.05	m	2H	H on C-1 and 2
4.1 - 4.45	m	1H	H on C-7
6.15	t	2H	$N-CH_2$
7.6	m	2H	H on C-6



(140)



Sodium/ethanol reduction of 2-methylindolizine

Using an identical procedure to that used for the reduction of indolizine the product was obtained as a pale yellow oil which was shown by its n.m.r. spectrum to be a mixture of 5,6-dihydro-2-methylindolizine (157) and 5,6,7,8-tetrahydro-2-methylindolizine (158).

N.m.r. ( $\text{CCl}_4$ )

$\tau$ 3.5 - 4.5 p.p.m.	m	H on C-1 and 3 of (157) and (158) and C-7 and 8 of (157)
6.15	t	N-CH <sub>2</sub> of (157) and (158), $J_{5,6} = 7\text{Hz}$
7.3	br t	H on C-8 of (158)
7.6	m	H on C-6 of (157)
7.95	s	-CH <sub>3</sub> of (157) and (158)
8.2	m	H on C-6 and 7 of (158)

Integration indicated approximately equal amounts of (157) and (158).

Lithium/*iso*-propylamine reduction of indolizine

Lithium ribbon (0.24 g, 34 mmol) was added to a solution of indolizine (2 g, 17 mmol) in distilled *iso*-propylamine (50 ml) and the solution was stirred under nitrogen at room temperature for



1½ hours. Water (10 ml) was added with cooling, most of the *iso*-propylamine was evaporated and the product was obtained as a yellow oil by ether extraction. The n.m.r. spectrum of the product was consistent with a mixture of equal amounts of indolizine and 5,6,7,8-tetrahydroindolizine.

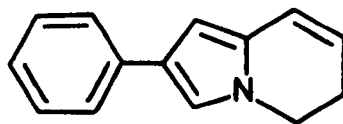
#### Sodium/liquid ammonia reduction of indolizine

A 500 ml three-necked flask containing indolizine (4 g, 34 mmol) and dry ether (50 ml) was equipped with a stirrer and inlet for ammonia. A stream of nitrogen was passed through the flask to exclude atmospheric moisture. Dry ammonia gas was passed into the flask through a coil condenser cooled in acetone/solid CO<sub>2</sub> until about 300 ml of liquid ammonia had collected. The solution was stirred continuously without external cooling whilst metallic sodium (1.57 g, 68 mmol) was added in small pieces during 15 minutes. After stirring for 1 hour ethanol (25 ml) was added dropwise and the ammonia was allowed to evaporate overnight. Water (50 ml) was added and the product was obtained by ether extraction. The n.m.r. spectrum of the product was consistent with a mixture of 5,6-dihydroindolizine and 5,6,7,8-tetrahydroindolizine.



Sodium/ethanol reduction of 2-phenylindolizine

A solution of 2-phenylindolizine (5 g) in a mixture of absolute alcohol (100 ml) and 1,2-dimethoxyethane (350 ml) was boiled gently whilst metallic sodium was added in small pieces. The addition of sodium was stopped when gas chromatography showed that no 2-phenylindolizine remained. Water (250 ml) was added and organic solvents were removed by distillation. The product was obtained by ether extraction. Evaporation of the dried extracts and crystallisation of the residue from ethanol (charcoal) gave 5,6-dihydro-2-phenylindolizine (160) (3.5 g, 69%) as colourless crystals, m.p. 124 - 125°.



Analysis

(160)

Found: C, 86.0; H, 6.5; N, 7.1%

C<sub>14</sub>H<sub>13</sub>N requires: C, 86.1; H, 6.7; N, 7.2%

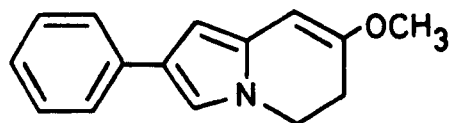
N.m.r. (CDCl<sub>3</sub>) [Figure 28, page 201]

τ2.2 - 2.75 p.p.m.	m	5H	phenyl
3.05	d	1H	H on C-3
3.35 - 3.6	m	2H	H on C-1 and 8
4.0 - 4.4	m	1H	H on C-7
6.05	t	2H	N-CH <sub>2</sub> , $J_{5,6} = 7\text{Hz}$
7.5	m	2H	H on C-6



Sodium/ethanol reduction of 7-methoxy-2-phenylindolizine

The same procedure was used as for the reduction of 2-phenylindolizine. The product, 5,6-dihydro-7-methoxy-2-phenylindolizine (162) (60% yield), was obtained as colourless crystals from ethanol, m.p. 164°



(162)

Analysis

Found: C, 80.4; H, 6.55; N, 6.3%

C<sub>15</sub>H<sub>15</sub>NO requires: C, 79.95; H, 6.7; N, 6.2%

N.m.r. (CDCl<sub>3</sub>) [Figure 29, page 201]

τ2.15 - 2.6 p.p.m.	m	5H	phenyl	
3.05	d	1H	H on C-3	} $J_{1,3} = 1.5\text{Hz}$
3.65	d	1H	H on C-1	
4.25	s	1H	H on C-8	
5.9	t	2H	N-CH <sub>2</sub> , $J_{5,6} = 7\text{Hz}$	
6.25	s	3H	-OCH <sub>3</sub>	
7.35	t	2H	H on C-6	



### SECTION III

#### REACTIONS BETWEEN DIHYDROINDOLIZINES AND DIHALOCARBENE PRECURSORS

##### Reaction between 5,6-dihydro-2-phenylindolizine (160) and chloroform/potassium *tert*-butoxide

A solution of the dihydroindolizine (160) (1 g, 5.2 mmol) in alcohol free chloroform (15 ml) and dry pentane (15 ml) was cooled to  $-10^{\circ}$ . Potassium *t*-butoxide<sup>167</sup> (1.12 g, 10 mmol) was added slowly during  $\frac{1}{2}$  hour whilst stirring. The mixture was kept at  $-10^{\circ}$  for 1 hour, allowed to warm to room temperature and poured into water (50 ml). No product could be identified from the black intractable tar obtained by chloroform extraction.

##### Reaction between 5,6-dihydro-2-phenylindolizine (160) and sodium trichloroacetate

Anhydrous sodium trichloroacetate (2.78 g, 15 mmol) and the dihydroindolizine (160) (2.92 g, 15 mmol) were boiled in 1,2-dimethoxyethane (50 ml) under nitrogen for 33 hours. The mixture was filtered and the filtrate evaporated to dryness. The n.m.r. spectrum of the residue was identical with that of the starting material.



Reaction between 5,6-dihydro-2-phenylindolizine (160) and  
phenyl(tribromomethyl)mercury

Phenyl(tribromomethyl)mercury<sup>146</sup> (0.37 g, 0.7 mmol) and the dihydroindolizine (160) (0.41 g, 2.1 mmol) were boiled in dry benzene (10 ml) until t.l.c. no longer showed a spot for  $C_6H_5HgCBr_3$  (3 hours). The mixture was filtered and the filtrate, on evaporation to dryness, gave a residue which had identical n.m.r. spectrum to that of the starting material.

Reaction between 5,6-dihydro-7-methoxy-2-phenylindolizine (162)  
and phenyl(tribromomethyl)mercury

Phenyl(tribromomethyl)mercury<sup>146</sup> (2.64 g, 0.5 mmol) and the dihydroindolizine (162) (1.13 g, 0.5 mmol) were boiled in dry benzene until t.l.c. no longer showed a spot for  $C_6H_5HgCBr_3$  (3 hours). The residue, obtained after filtration of the reaction mixture and evaporation of the filtrate, was identical with the starting material.

\* \* \* \* \*



Reaction between 5,6-dihydro-2-phenylindolizine (160) and phenyl(tribromomethyl)mercury

Phenyl(tribromomethyl)mercury<sup>146</sup> (0.37 g, 0.7 mmol) and the dihydroindolizine (160) (0.41 g, 2.1 mmol) were boiled in dry benzene (10 ml) until t.l.c. no longer showed a spot for  $C_6H_5HgBr_3$  (3 hours). The mixture was filtered and the filtrate, on evaporation to dryness, gave a residue which had identical n.m.r. spectrum to that of the starting material.

Reaction between 5,6-dihydro-7-methoxy-2-phenylindolizine (162) and phenyl(tribromomethyl)mercury

Phenyl(tribromomethyl)mercury<sup>146</sup> (2.64 g, 5 mmol) and the dihydroindolizine (162) (1.13 g, 5 mmol) were boiled in dry benzene until t.l.c. no longer showed a spot for  $C_6H_5HgCBr_3$  (3 hours). The residue, obtained after filtration of the reaction mixture and evaporation of the filtrate, was identical with the starting material.

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*C O M P O U N D   I N D E X*

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# C O M P O U N D   I N D E X

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