INTRAMOLECULAR NITRENE INSERTIONS

INTO AROMATIC SYSTEMS

by

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A B S T R A C T

A study of the intramolecular insertion reactions of aryl nitrenes is described.

In Part I the preparation and photolytic decomposition of a number of aryl azides in diethylamine is described. The usual products were 3H-azepines but in one case ring expansion did not occur and the major product was an aryl amine. Attempts to prepare aza-azulenes and azepinium salts from certain of the decomposition products were unsuccessful.

In Part II an account of the experiments used to determine the effect of annelation upon the nitrene insertion reaction is given. The decomposition of 1- and 2-(azidobenzyl)-naphthalene was shown to give predominantly acridan and acridine products, while the tetrahydro derivatives, 5- and 6-(2-azido-benzyl)tetralin, gave the ring insertion products, benzazepino-indoles. The reasons for the differing reaction pathways are discussed.

In Part III the preparation and thermal decomposition of a number of 2-azidotriphenylmethanes is described. The usual products were acridans and azepinoindoles but in one case, when a 4'-methoxyl group was present in the azide, the major product was an 8,9-methanopyridoindole. Experiments to determine the nature of the [1,3] hydrogen shift observed in the formation of the azepinoindoles are described. A mechanism is proposed which satisfactorily accounts for the observed products and product ratios.

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

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CONTENTS

INTRODUCTION

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

The work described in this thesis concerns the intramolecular insertion reactions of arylnitrenes. The generation and reactions of nitrenes are outlined in the following review.

Thereafter the work is divided into three parts:

Part I describes an investigation into the photolytic decomposition of 4- and 5-azidoindan, 4-azidobenzocyclobutene and 2-azidobiphenylene in diethylamine and attempts to prepare aromatic ten π-electron systems from certain of the decomposition products.

Part II describes an investigation into the thermal decomposition of (2-azidobenzyl)naphthalenes and tetralins and the effect that annelation has upon the reaction pathways.

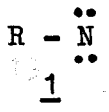
Part III describes an investigation into the thermal decomposition of substituted 2-azidotriphenylmethanes in an attempt to establish the part played by electron availability in the nitrene insertion reaction. Experiments to elucidate the mechanism of the nitrene insertion reaction are also described.

REVIEW

REVIEW

NITRENES

Nitrenes are monovalent nitrogen intermediates in which the nitrogen atom has six electrons in its outer shell. As such they are isoelectronic with carbenes and can exist in either an electrophilic singlet state 1 or a diradical triplet state 2.



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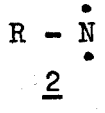


2

Though the formation of nitrenes was postulated[1-4] many years ago to account for the mechanisms of the Hofmann, Curtius, Lossen, Beckmann and Stieglitz rearrangements, extensive interest in and evidence of their intermediacy has only arisen in the last twenty years during which time a considerable number of papers and reviews[5-12] have been published.

Much of the evidence for nitrene intermediacy in a reaction is based on the chemical properties of the species, the nature of the products and the product distribution, though physical data is also available. The ultraviolet spectra of a number of arylnitrenes produced by the photolysis of the corresponding azides in rigid matrices at low temperatures have been described[13] and the transient intermediates produced by the flash photolysis of a variety of aryl azides have been identified as triplet nitrenes from their ultraviolet spectra[14,15].

Data on the electronic spectra of alkylnitrenes are non-existent. Wasserman and co-workers have reported[16] the electron spin resonance spectra of the triplet state of primary, secondary and tertiary alkylnitrenes taken at 4°K. The facility for alkylnitrenes to enter into both intramolecular and intermolecular reactions is revealed in the failure to detect these e.s.r. spectra at 77°K. At this temperature delocalised nitrenes such as aryl- and sulphonyl- are found to be appreciably stable[17,18].

Whilst the triplet nitrene state is well established there is very little direct evidence for the singlet state. Such evidence as there is for singlet nitrene intermediacy is obtained from reaction studies. The formation and reaction of nitrenes will be discussed in the following sections with special emphasis being placed on the formation of nitrenes from azides and on arylnitrenes.

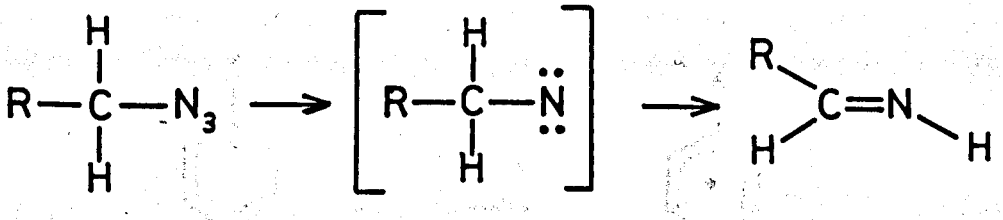
Nitrenes Generated from Azides

The preparation and reactions of organic azides have been reviewed[19,20]. Only the uncatalysed thermal and photolytic decompositions of these azides will be discussed here.

(a) Alkyl Azides

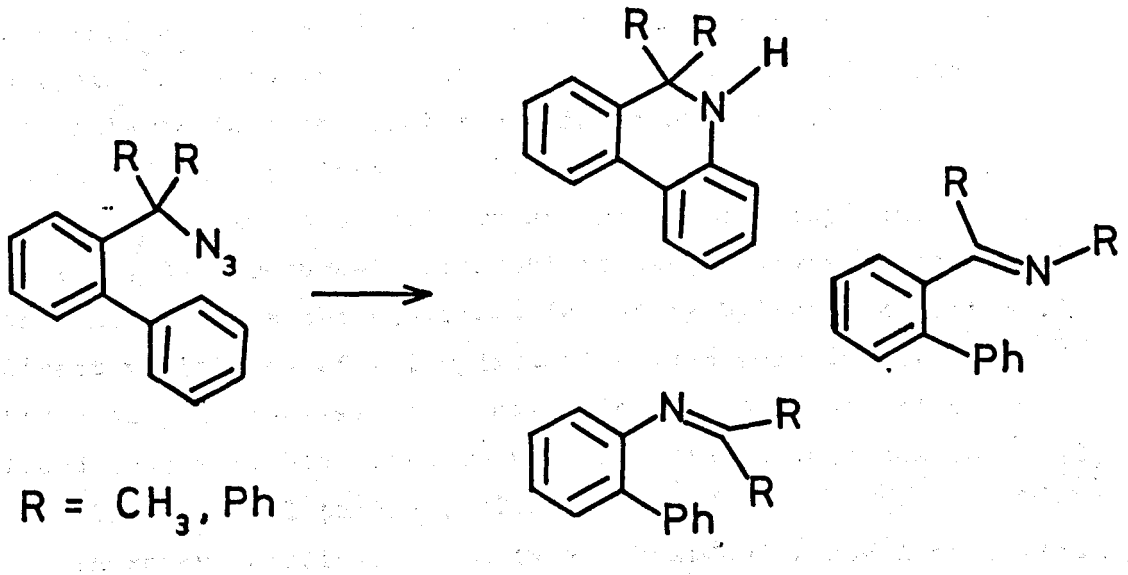
Alkyl azides are thermally stable at room temperature, but at temperatures in excess of 100° nitrogen is evolved in a first-order homogeneous process[21]. If the alkylnitrene so formed has an α-hydrogen atom then imine formation by a 1,2-hydrogen migration is the predominant reaction[7] (Scheme 1). Neither intermolecular hydrogen abstraction to form amines nor intramolecular cyclisation offer serious competition to this rearrangement.

SCHEME 1



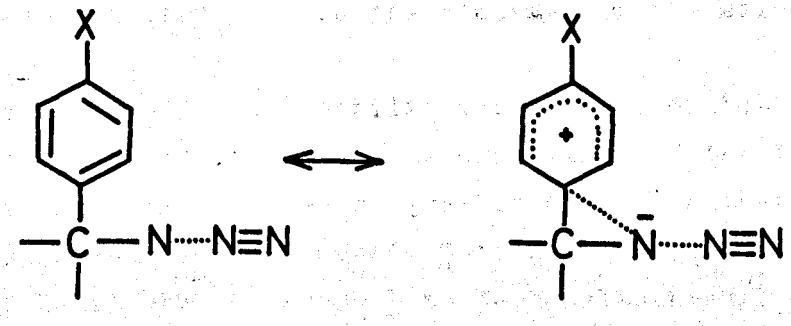
The absence of hydrogen atoms at the α-carbon increases the lifetime of the nitrene sufficiently to make possible non-rearrangement processes, for example, the intramolecular cyclisation shown in Scheme 2[22].

SCHEME 2



The triaryl azides have been extensively studied[23-25]. Saunders and Ware[25] examined the thermolysis of a series of p-substituted triarylmethyl azides and obtained migration aptitudes and activation parameters for each azide. The activation parameters were compatible with the formation of a discrete nitrene intermediate but the kinetic data favoured a small amount of aryl participation in the transition state (Scheme 3).

SCHEME 3



In a recent study of the thermolyses of tertiary alkyl azides Abramovitch and Kyba[22] observed intramolecular aromatic substitution in addition to the expected aryl and alkyl migrations. This observation coupled with a comparison of the migratory aptitudes obtained from these thermolyses (e.g. 2-Ph.C_6H_4 / Me = 2.0)

with those found in the triethyl phosphite deoxygenation of the corresponding tertiary alkyl nitroso derivatives (e.g. 2-Ph.C_6H_4 / Me = 1600) led the authors to conclude that thermolysis leads to the formation of an electrophilic singlet nitrene intermediate and that there is no aryl or alkyl participation in the nitrogen elimination.

The photolyses of primary and secondary alkyl azides are first-order, temperature-independent processes giving as the predominant products the aldimines formed by hydrogen migration. The direct photolyses of triarylmethyl azides were investigated[26] and since no preferential group migration was observed it was concluded that a highly reactive nitrene intermediate was involved, with no alkyl or aryl participation.

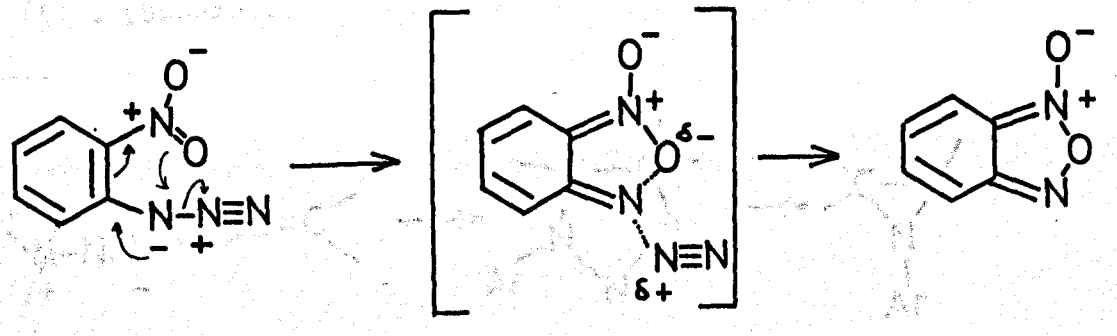
In recent studies, Moriarty and Reardon[27], and Abramovitch and Kyba[28], have detected non-statistical migration, which these authors suggest proves that a discrete nitrene intermediate is not formed and that migration starts before the N-N bond is completely broken. A mechanism has been proposed which involves the preferred ground-state conformations of the azides and the geometry of the orbitals in the photoexcited state of the azido-group.

(b) Aryl Azides

The kinetic studies by Smith and Hall[29] and Walker and Waters[30] on the thermal decomposition of aryl azides in inert media have shown that the decomposition rates are first-order and that the rate-determining step is the cleavage of the azide to form the nitrene.

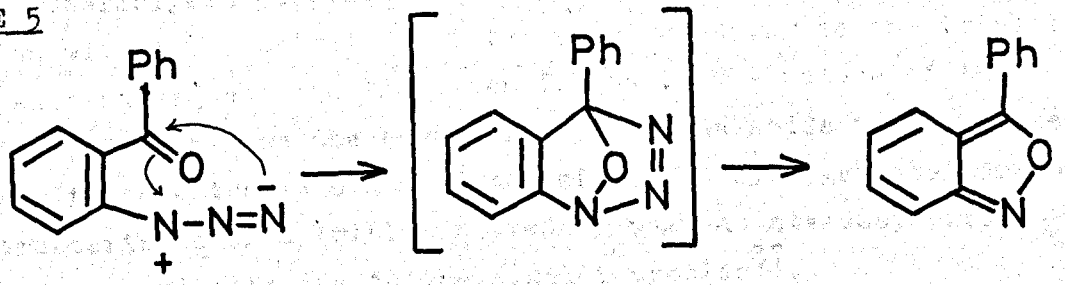
The presence of a nucleophilic substituent ortho- to the azide function can so assist in the decomposition of the latter that a discrete nitrene intermediate is never formed. The thermal decompositions of 2-nitrophenyl azide 3 to give benzofuroxan 4[31,32] (Scheme 4), of 2-azidobenzophenone 5 to 3-phenylanthranil 6[33] (Scheme 5) and the first elimination of nitrogen in the double cyclisation of 2,2'-diazidoazobenzene 7 to 8[34,35] (Scheme 6) probably do not involve nitrene intermediates.

SCHEME 4



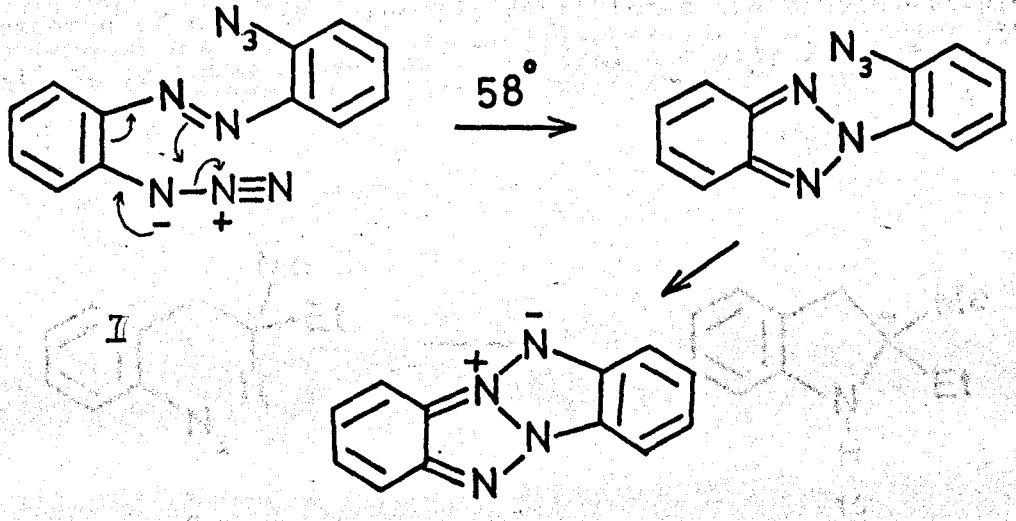
3 4

SCHEME 5



5 6

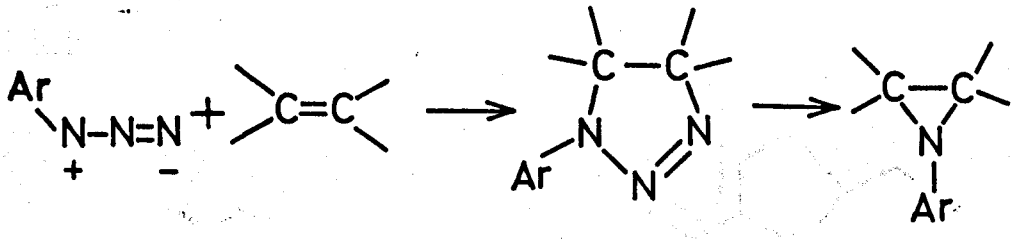
SCHEME 6



7 8

Neither are nitrene intermediates involved in the thermolysis if the azide can undergo 1,3-dipolar addition to the substrate nor if the substrate participates in the rate-determining state[19,30]. (Scheme 7)

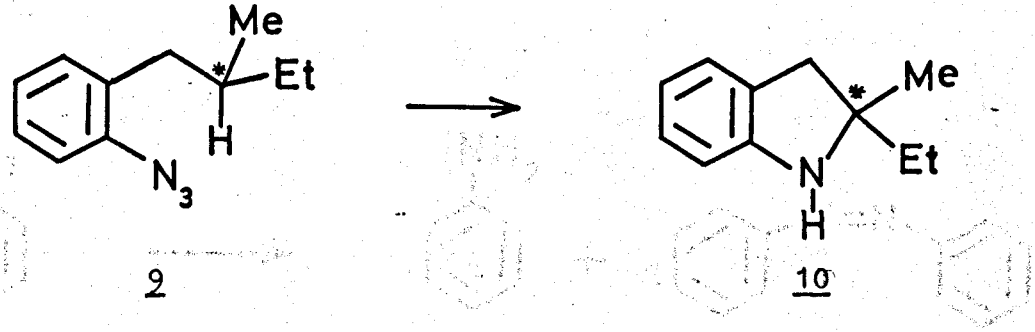
SCHEME 7



Thermolysis generates the nitrene in its singlet state, reaction with the substrate or intersystem crossing to the triplet state with subsequent reaction then follows. The nature of the products obtained upon the decomposition of the azide has been used to infer the electronic state of the nitrene. Hydrogen abstraction is characteristic of a triplet nitrene[36] whereas stereospecific C-H bond insertion is due to the singlet species[37].

The decomposition of the optically active azide 9 gives the indoline 10 (Scheme 8) but the degree of retention of optical activity depends upon the reaction conditions. The vapour-phase pyrolysis of the azide gives almost complete retention, indicating the intermediacy of a singlet nitrene, however, in solution, where the presence of solvent molecules facilitates the singlet-triplet transition, only 60% retention of optical activity is observed[38].

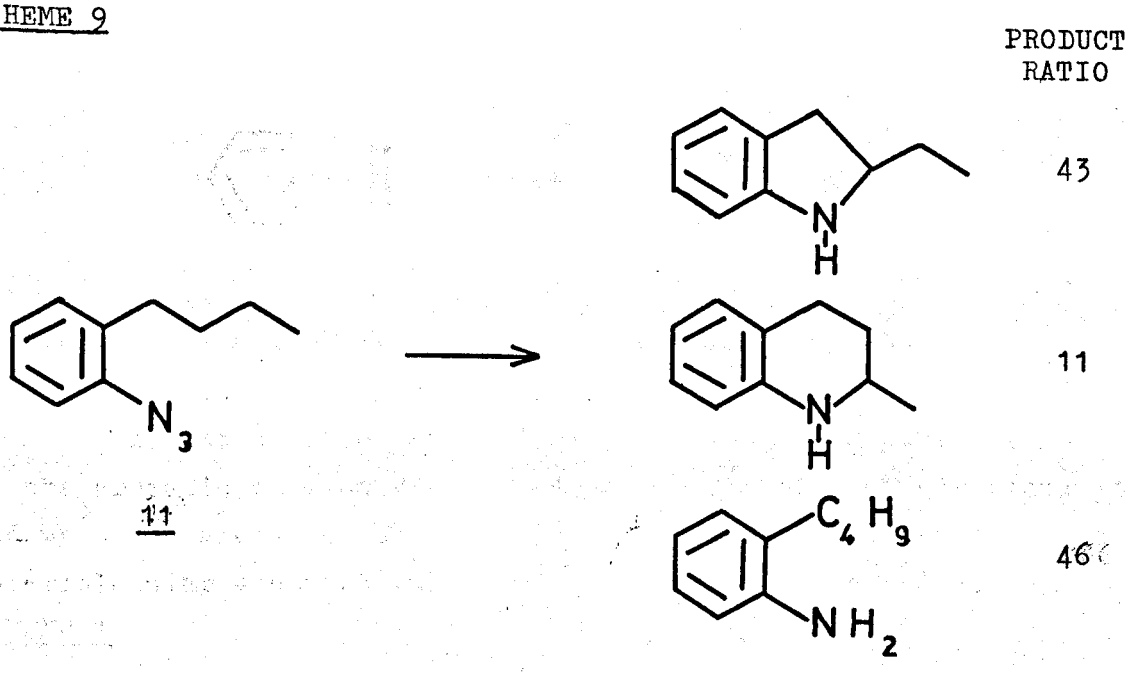
SCHEME 8



9 10

Intramolecular insertion of a nitrene into a saturated C-H bond is favoured over the corresponding bimolecular reaction. This type of cyclisation shows a strong preference for five-membered ring formation and a selectivity for tert. C-H > sec. C-H > prim. C-H. This preference is illustrated in the decomposition of 2-butylphenyl azide 11[39] (Scheme 9).

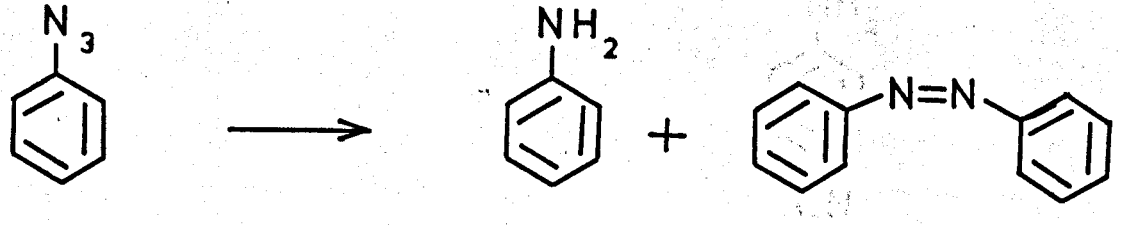
SCHEME 9



11

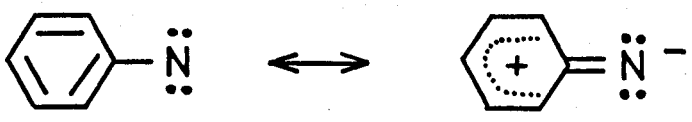
Aromatic azides readily undergo intramolecular, but not intermolecular, aromatic substitution[29,40]. Thus, the thermal decomposition of phenyl azide in benzene[41] does not give diphenylamine but aniline and azobenzene (Scheme 10), the latter caused by dimerisation of the triplet nitrene or reaction of the nitrene with unreacted azide[42].

SCHEME 10



The failure of phenylnitrene to undergo intermolecular attack has been explained[43] by the delocalisation of the electron deficiency resulting in a negative charge i.e. decreased electrophilicity, on the nitrogen atom 12-13 (Scheme 11).

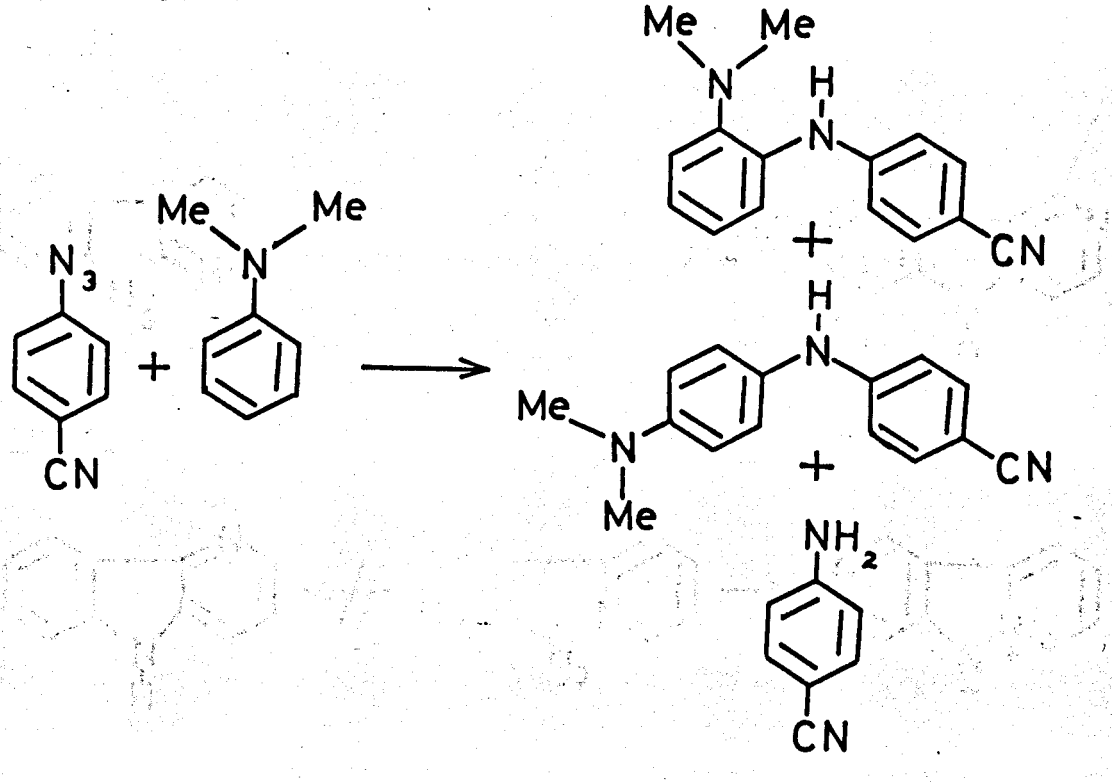
SCHEME 11



12 13

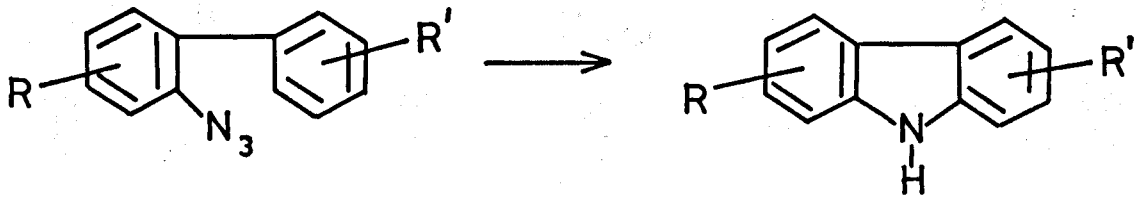
The introduction of an electron-withdrawing substituent in the aromatic nucleus causes the destabilisation of structure 13 and when the aromatic substrate is sufficiently nucleophilic then intermolecular aromatic substitution occurs[44] (Scheme 12).

SCHEME 12



A range of heterocyclic systems has been obtained by aryl azide thermolyses. For example, the intramolecular cyclisation of 2-azidobiphenyl has become the basis of a general synthesis of carbazole and its derivatives[40,45] (Scheme 13).

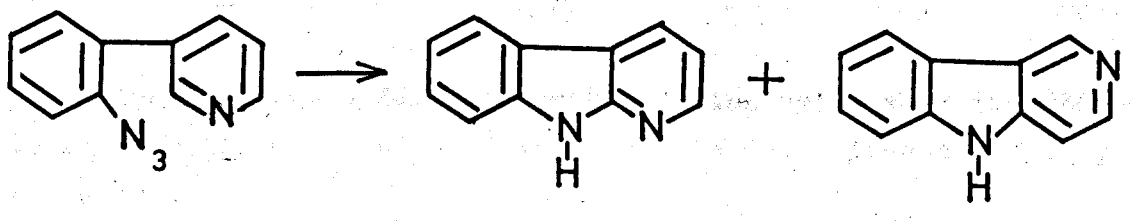
SCHEME 13



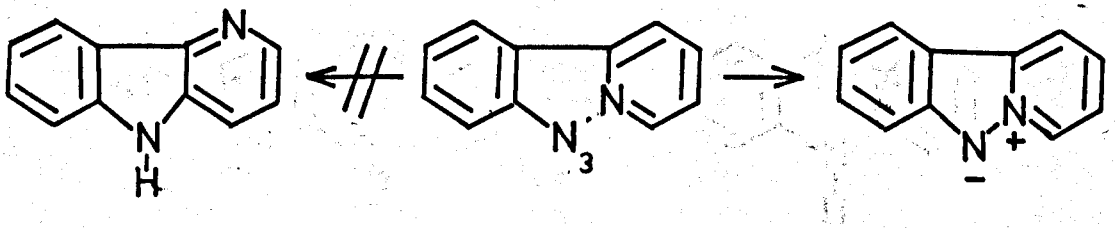
Replacement of the phenyl group by pyridine gives entry into the carboline[46] (Scheme 14) and pyridoindazole[47] series (Scheme 15). In the latter case N-N bond formation competes effectively with N-C bond formation and the isomeric δ-carboline is not found.

In the carbostyril system 14 this preferred bond formation is not observed and the isomeric products 15 and 16 are obtained in equal quantities[48] (Scheme 16).

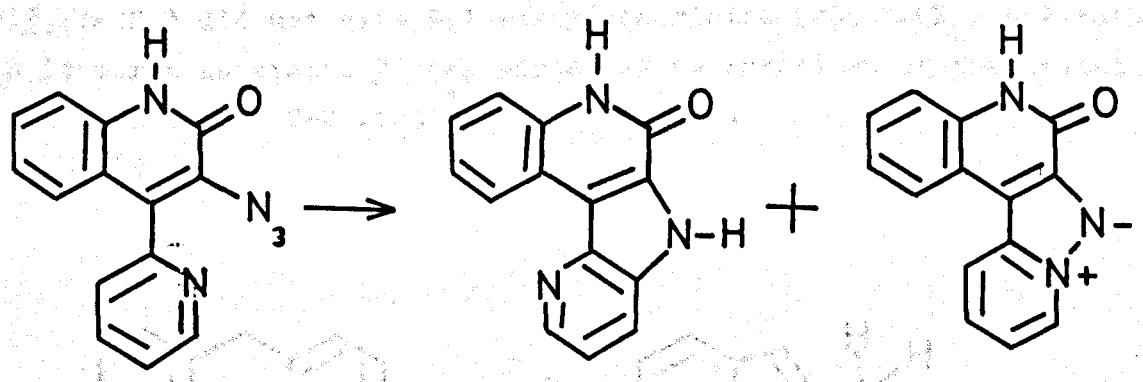
SCHEME 14



SCHEME 15



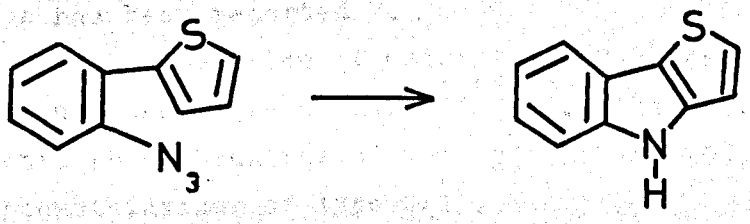
SCHEME 16



14 15 16

Another new heterocyclic system which has been synthesised is thieno[3,2-b]indole 18, obtained by the pyrolysis of 2-(2-azidophenyl)thiophen 17 [46] (Scheme 17).

SCHEME 17

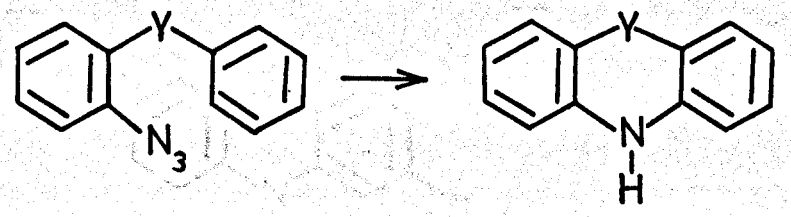


17 18

Cyclisation to form six-membered ring systems by insertion into an aromatic C-H bond has been reported for azides of type 19 (Scheme 18).

SCHEME 18

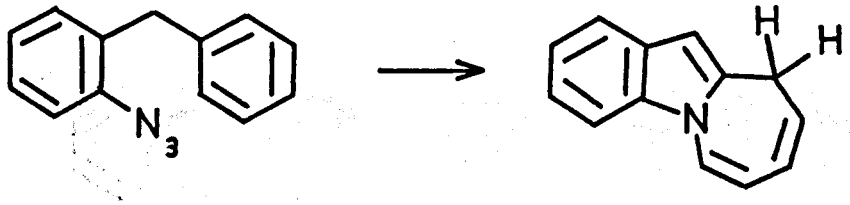
Y	Ref;
S	49,50
SO_2	49
O	49



19 20

However, the decomposition of 2-azidodiphenylmethane (19, $Y=CH_2$) did not give 9,10-dihydroacridine (20, $Y=CH_2$) but rather an isomeric substance 21 corresponding to insertion of the nitrene into an aromatic C-C bond[51,52] (Scheme 19).

SCHEME 19

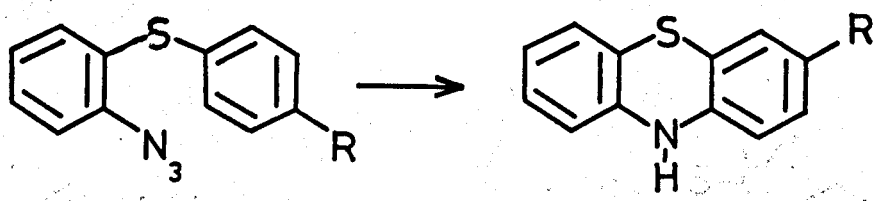


21

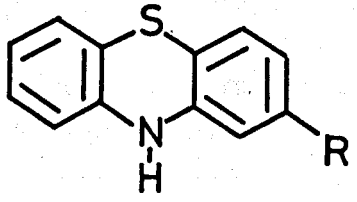
This illustrates again the preference for the formation of a five-membered ring. The decomposition of a number of substituted 2-azidodiphenylmethanes has been studied[53]. Compounds of type 21 are usually obtained but the formation of acridines and dihydroacridines has been reported[54].

The decomposition of substituted 2-azidodiphenyl sulphides 22 has been extensively studied[50,55-57]. These cyclise to give substituted phenothiazines of type 23 (Scheme 20), and in some cases, phenothiazines of type 24[56].

SCHEME 20



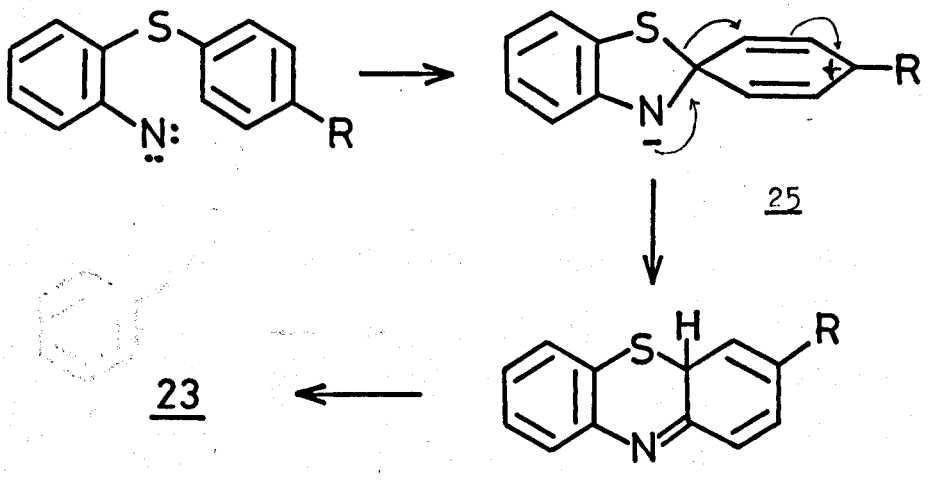
22 23



24

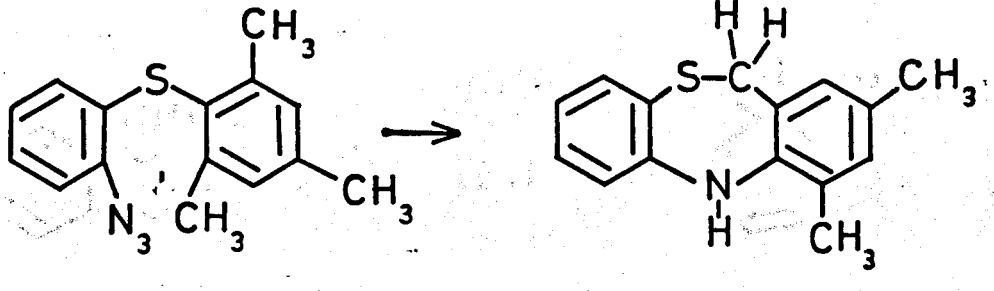
The formation of 24 can be considered to result from direct insertion but the formation of 23 requires a molecular rearrangement. A mechanism has been proposed which involves the spiro-intermediate 25. This undergoes a 1,2-sigmatropic shift of the sulphur atom which, followed by prototropy, leads to the observed product[57] (Scheme 21).

SCHEME 21



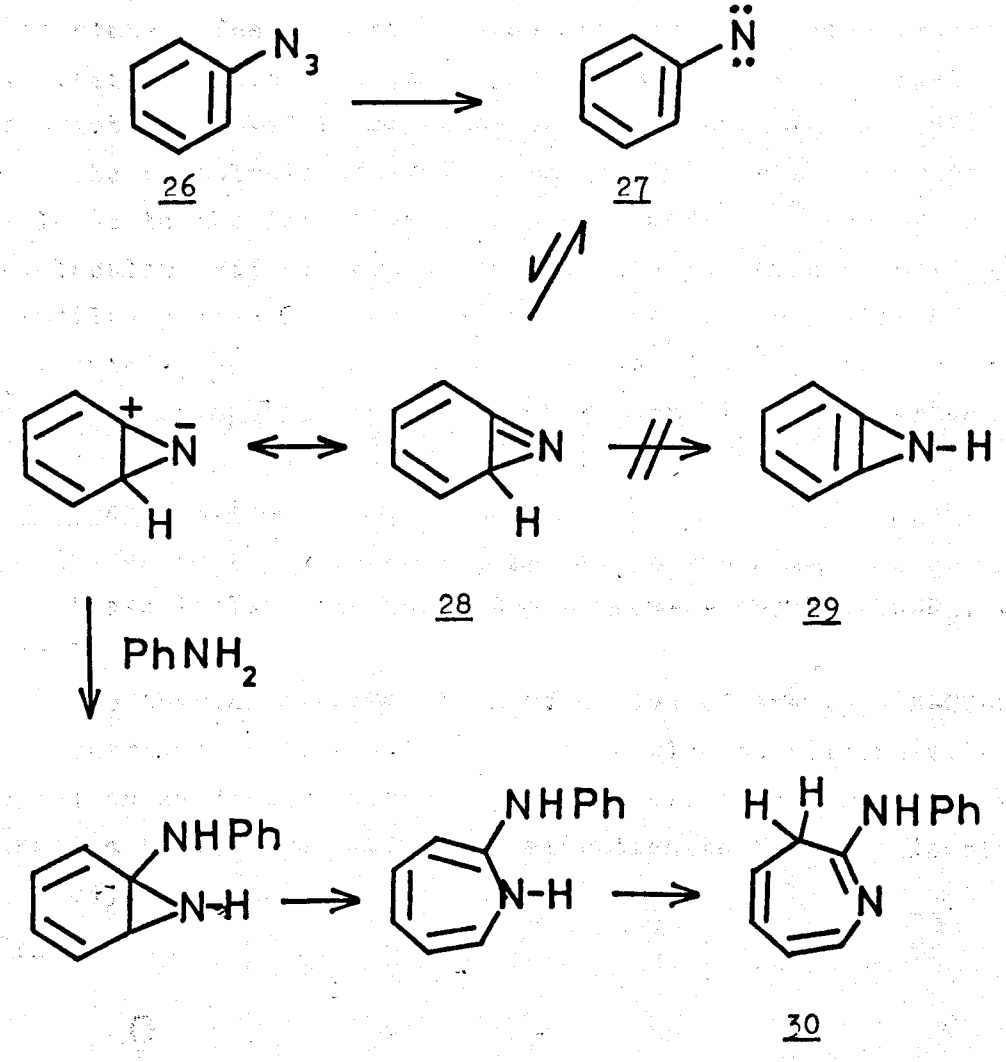
The blocking of both ortho-positions can effect the formation of a seven-membered ring. This has been observed in the decompositions of 2,6-dimethyl- and 2,4,6-trimethylphenyl-2-azidophenyl sulphide[57] (Scheme 22).

SCHEME 22



Ring expansion to form a seven-membered ring system has been observed when arylnitrenes are generated in the presence of strong nucleophiles. It is thought that the singlet nitrene 27 is in equilibrium with the azirine intermediate 28; it has been shown by ^{14}C labelling studies that the 1H-azirine 29 is not an intermediate[61]. The azirine 28 is attacked by the nucleophilic reagent and the three-membered ring opens to form a 1H-azepine which tautomerises to the observed 3H-azepine. Thus 2-anilino-3H-azepine 30 is obtained from the decomposition of phenyl azide 26 in aniline[58] (Scheme 23).

SCHEME 23



The photolysis of aryl azides leads to aryl nitrenes. One of the problems that has received some attention concerns the nature of the electronic state of the nitrene. Studies by Reiser and co-workers[62] on the photolysis of 2-azidobiphenyl showed that the triplet nitrene was an intermediate but that further irradiation was needed to facilitate carbazole formation. This suggested that either an excited triplet or a singlet nitrene was involved in the cyclisation. The use of singlet and triplet sensitisers in this photolysis[63,64] gave evidence which indicated that the singlet species was responsible for cyclisation.

Contradictory evidence was supplied by Lehman and Berry[65] who studied the flash photolysis of 2-azidobiphenyl in cyclohexane. They have suggested a mechanism in which photolysis gives the singlet nitrene which then undergoes rapid intersystem crossing to the triplet state. The triplet nitrene undergoes addition to the phenyl ring. There is then fast intersystem crossing to a singlet intermediate followed by or concurrent with hydrogen migration.

The photolysis of aryl azides in the gas phase or in inert media leads to the formation of azo-compounds[65,66] except where intramolecular cyclisation can occur. The presence of strong nucleophiles causes ring expansion and reasonable yields of 2-substituted-3H-azepines can be obtained[60,67,68]. This ring expansion reaction will be discussed in detail in a later section.

(c) Carbonyl Azides

These include the azide types $R-CO-N_3$ and $R-O-CO-N_3$, where R = alkyl, aryl.

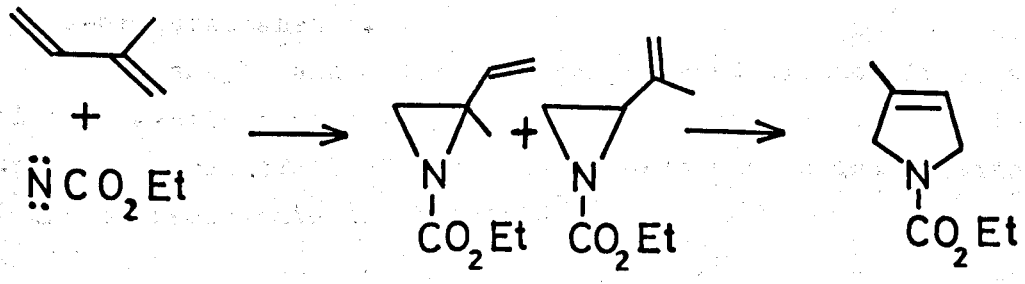
The thermal decomposition of azides of the type $R-CO-N_3$, the Curtius rearrangement, has been shown to give no nitrene products and the reaction evidently proceeds in a concerted manner with the elimination of nitrogen and group migration to form the isocyanate[69] (Scheme 24).

SCHEME 24

Thermolysis of the alkoxycarbonyl azides leads to nitrene intermediates. These nitrenes are more reactive than the aryl-nitrenes and undergo a wider range of reactions[9,20]:

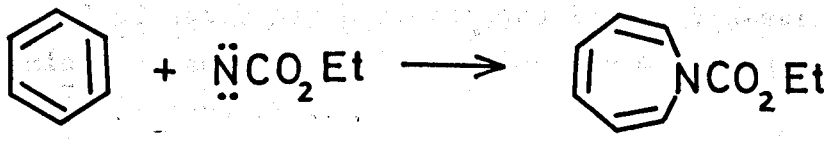
(i) Stereospecific insertion into C-H bonds to give carbamates.
(ii) Insertion into O-H bonds to give alkoxycarbamates.
(iii) Insertion into N-H bonds to give substituted hydrazines.
(iv) Stereospecific addition to C=C double bonds to give aziridines. With 1,3-dienes e.g. isoprene, only 1,2-addition is observed but the primary products can be thermally rearranged to the apparent 1,4-addition products (Scheme 25).

SCHEME 25



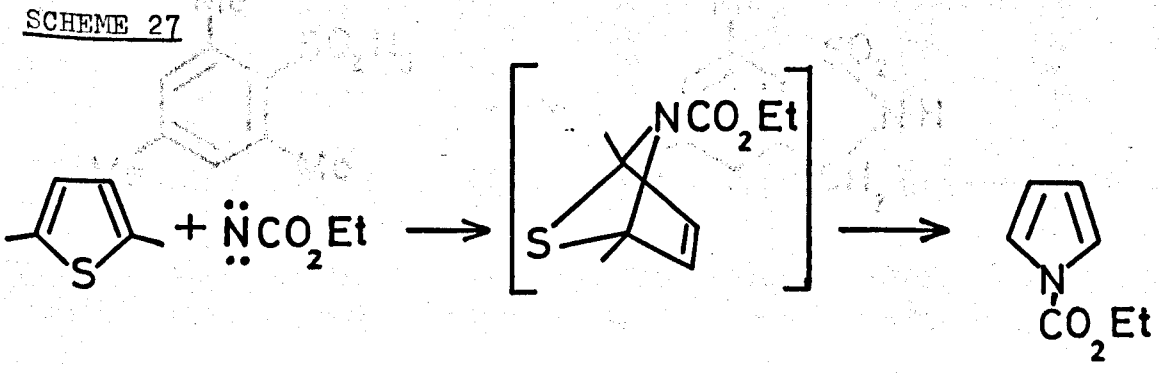
(v) Ring expansion of benzene and its derivatives to form N-alkoxycarbonyl azepines (Scheme 26).

SCHEME 26



(vi) Reaction with heteroaromatics to form substituted pyrroles possibly via a 1,4-bridged intermediate (Scheme 27).

SCHEME 27



Photolysis of the alkoxycarbonyl azides produces both singlet and triplet nitrenes,. Lwowski and co-workers have examined the photolysis of ethoxycarbonyl azides in the presence of cis- and trans-4-methylpentene-2[70,71]. From their observations they concluded that the system $\ddot{\ddot{N}}CO_2Et$ / olefin behaves according to the model introduced by Skell for carbenes[72], i.e. singlet species give stereospecific addition, triplet species give non-stereospecific addition. They further postulated that 30% of the photolytically formed nitrene was in the triplet state.

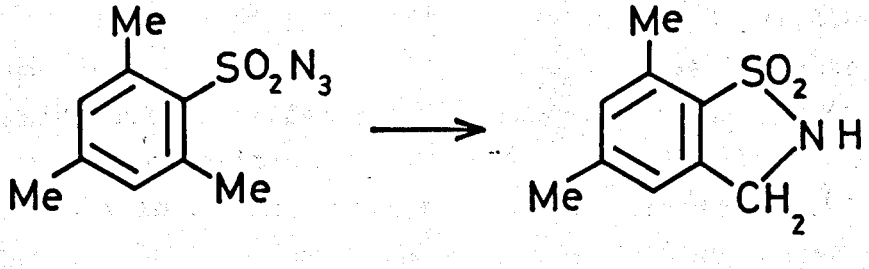
The reactions of the singlet nitrene have already been listed. The triplet nitrene can also undergo intermolecular reactions, e.g. additions to double bonds, hydrogen atom abstraction to form urethanes and reactions with polycyclic aromatic systems to form N-arylurethanes[73].

Alkanoyl- and aroylnitrenes produced by photolysis undergo all the reactions observed for the alkoxycarbonylnitrenes but the Curtius rearrangement of the azide always occurs and substantial yields of isocyanate are obtained[69].

(d) Sulphonyl Azides

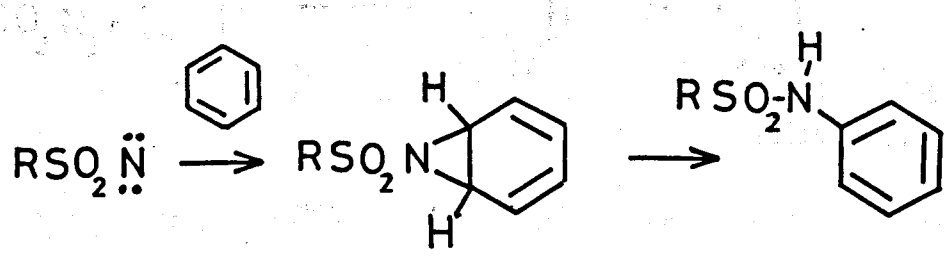
The thermal decomposition of sulphonyl azides to give sulphonylnitrene intermediates and nitrogen is first-order[74] and is independent of solvent[75]. The sulphonylnitrenes undergo most of the reactions observed for the carbonylnitrenes. They will insert into the C-H bond of saturated hydrocarbons to yield N-substituted sulphonamides[76] and undergo intramolecular C-H insertions to give sultams[77,78] (Scheme 28).

SCHEME 28



Thermolysis in the presence of aromatic substrates leads to the formation of N-arylsulphonamides[79-81]. The mechanism is thought to involve the addition of singlet sulphonylnitrene 31 to the aromatic nucleus to give a benzaziridine intermediate 32 with ring-opening of the latter to form the observed sulphonamide 33[82] (Scheme 29).

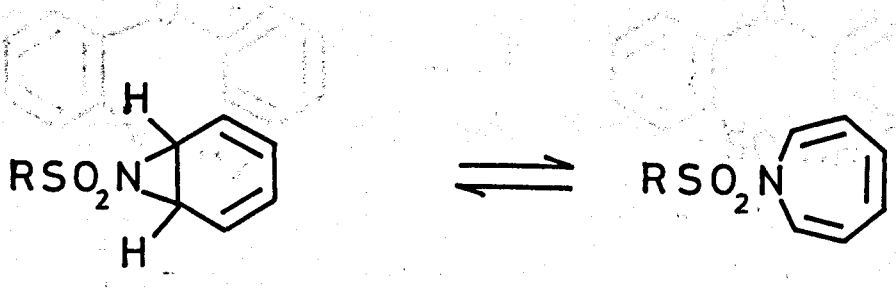
SCHEME 29



31 32 33

The benzaziridine is in equilibrium with the sulphonylazepine 34 (Scheme 30). Azepine 34 (R = CH_3) has been isolated in very low yield from the thermolysis of methanesulphonylazide in benzene at 90°. At higher temperatures it was converted to the sulphonamide 33 (R = CH_3)[82].

SCHEME 30

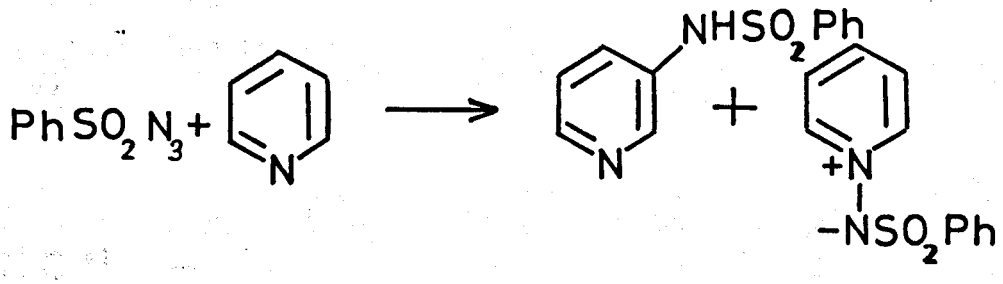


34

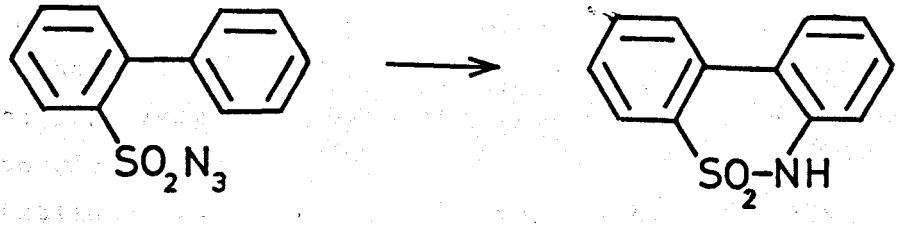
The use of pyridines and substituted pyridines as substrates in the decomposition of the sulphonylazides leads to the formation of N-pyridylsulphonamides and pyridinium ylides[83-85] (Scheme 31).

Decomposition of suitably substituted benzenesulphonylazides can result in intramolecular aromatic substitution[78] (Schemes 32,33).

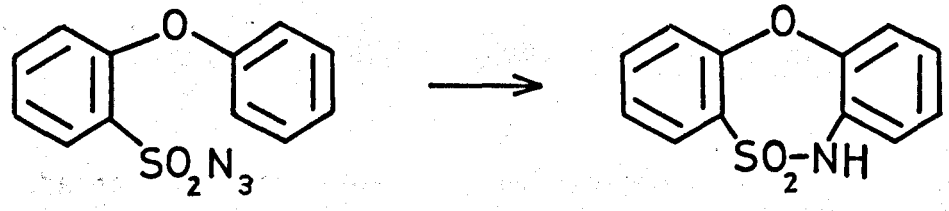
SCHEME 31



SCHEME 32



SCHEME 33

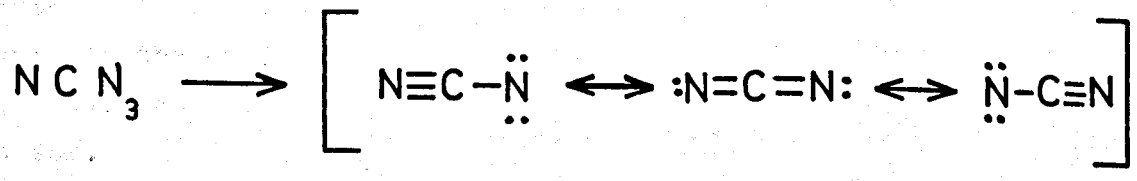


In contrast to the thermolytic decompositions of sulphonyl azides the photolyses of aliphatic- and aromatic sulphonylazides in a variety of solvents produce only insoluble, high-melting materials which have not been characterised. There is no evidence of nitrene formation.

(e) Cyanogen Azide

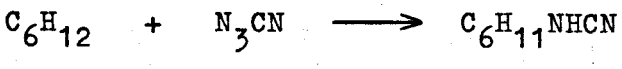
Unlike most azides, which require temperatures in excess of 100° for decomposition to the corresponding nitrene, cyanogen azide smoothly evolves nitrogen when heated to 40-50° [86], to give the symmetrical cyanonitrene (Scheme 34). The equivalence of the nitrogen atoms has been shown by ^{15}N labelling experiments [86,87].

SCHEME 34

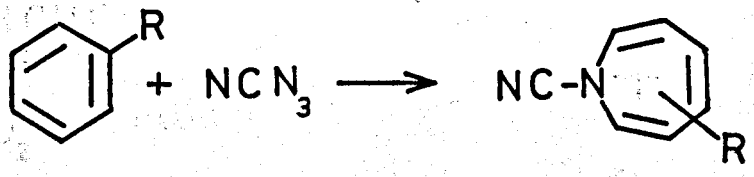


Though the chemistry of cyanonitrene has not been fully explored some reactions are known. Insertions into aliphatic C-H bonds to give cyanamides [86] (Scheme 35) and reactions with benzene and substituted benzenes to give N-cyanoazepines [88] (Scheme 36) have been studied and are believed to involve a discrete nitrene. However the reaction with olefins to form N-cyanoaziridines and 1-alkylalkylidenecyanamides (Scheme 37) probably involves a 1,3-dipolar addition followed by loss of nitrogen [89].

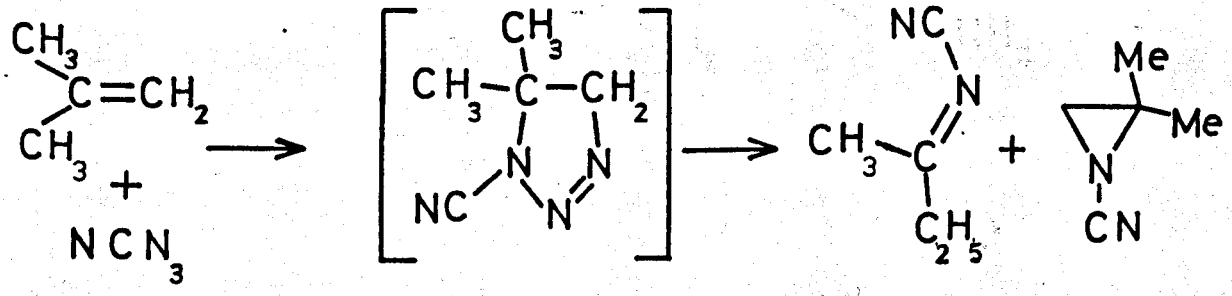
SCHEME 35



SCHEME 36



SCHEME 37



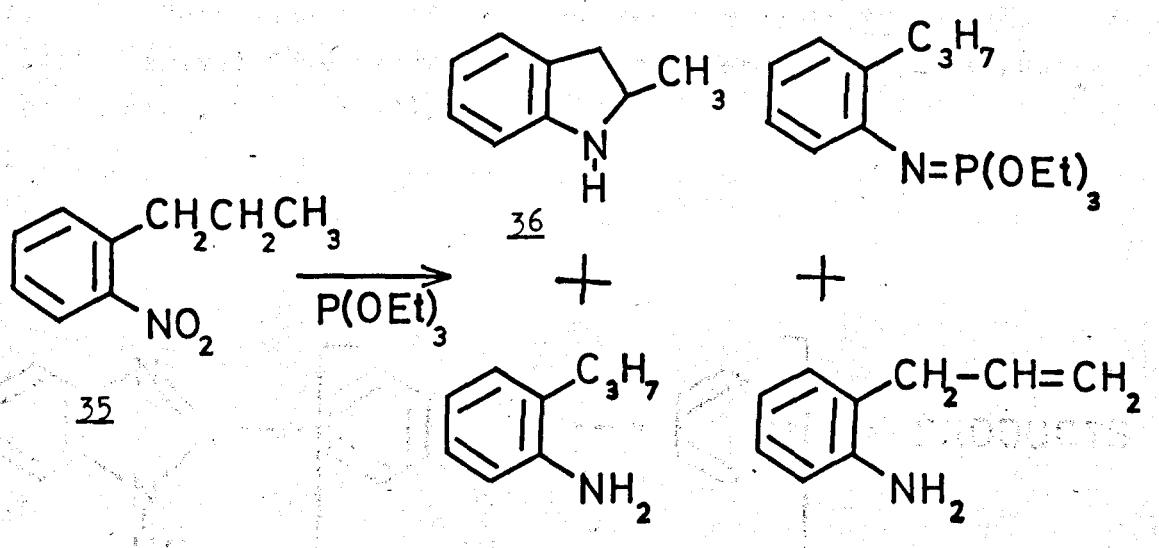
Nitrenes Generated from Nitro- and Nitroso-Compounds

That deoxygenation of a nitro- or nitroso-group may generate a nitrene intermediate is an assumption often supported by similarities with the same intermediate which may be derived from the structurally related azide on elimination of molecular nitrogen. These similarities include inter- and intramolecular insertions and hydrogen abstraction. Deoxygenation can be brought about by the use of metals, metal salts[90], free radicals and tervalent phosphorus reagents[9,91,92]. Of these the deoxygenation using phosphorus reagents is the most useful since the starting materials are more readily available and the reactions are cleaner with less tar formation.

Examples of reactions in which nitrenes are likely intermediates include;

(i) The formation of 2-methylindoline 36 from 2-nitro-n-propylbenzene 35[93]. The products of hydrogen abstraction and coupling with the phosphorus reagent have also been isolated from this reaction (Scheme 38).

SCHEME 38

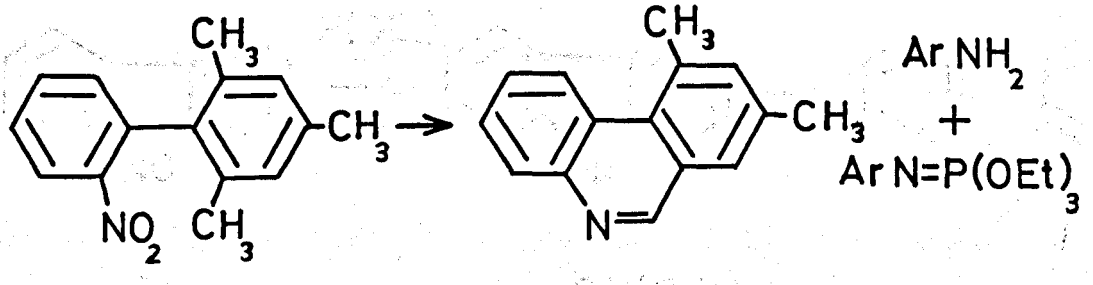


35 36

(ii) The formation of 2-ethylindoline, 2-methyl-1,2,3,4-tetrahydroquinoline and 2-n-butylaniline from 2-nitro-n-butylbenzene[93]. These compounds are obtained in similar yields from the decomposition of the corresponding azide[39] (Scheme 9).

(iii) The deoxygenation of 2'-nitro-2,4,6-trimethylbiphenyl which gives the products of hydrogen abstraction, C-H bond insertion and coupling with the reagent[94] (Scheme 39)

SCHEME 39

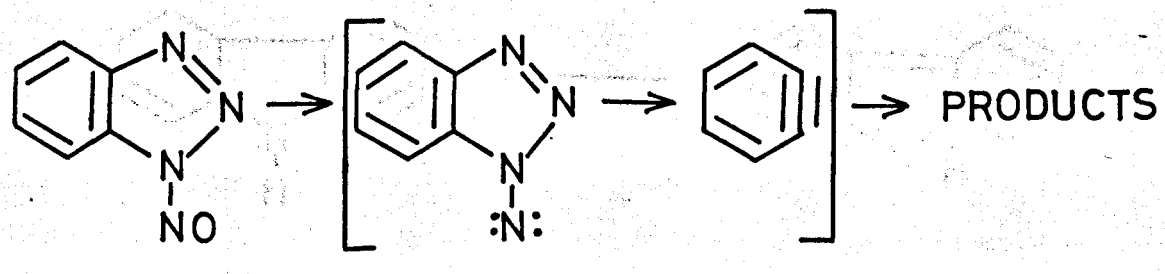


(iv) Azepine formation from the deoxygenation of aryl nitro- and nitroso-compounds in primary or secondary amines[94-97].

(v) The formation of phenothiazines by the deoxygenation of 2-nitrophenyl phenyl sulphides[92].

(vi) The deoxygenation of N-nitrosobenzotriazole 37 to give products derived from benzyne[98] 39. An intermediate N-nitrene 38 is postulated. (Scheme 40).

SCHEME 40

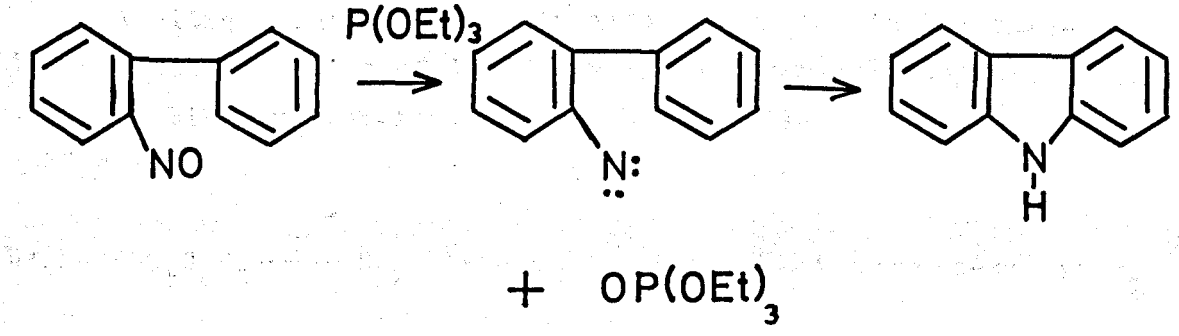


37 38 39

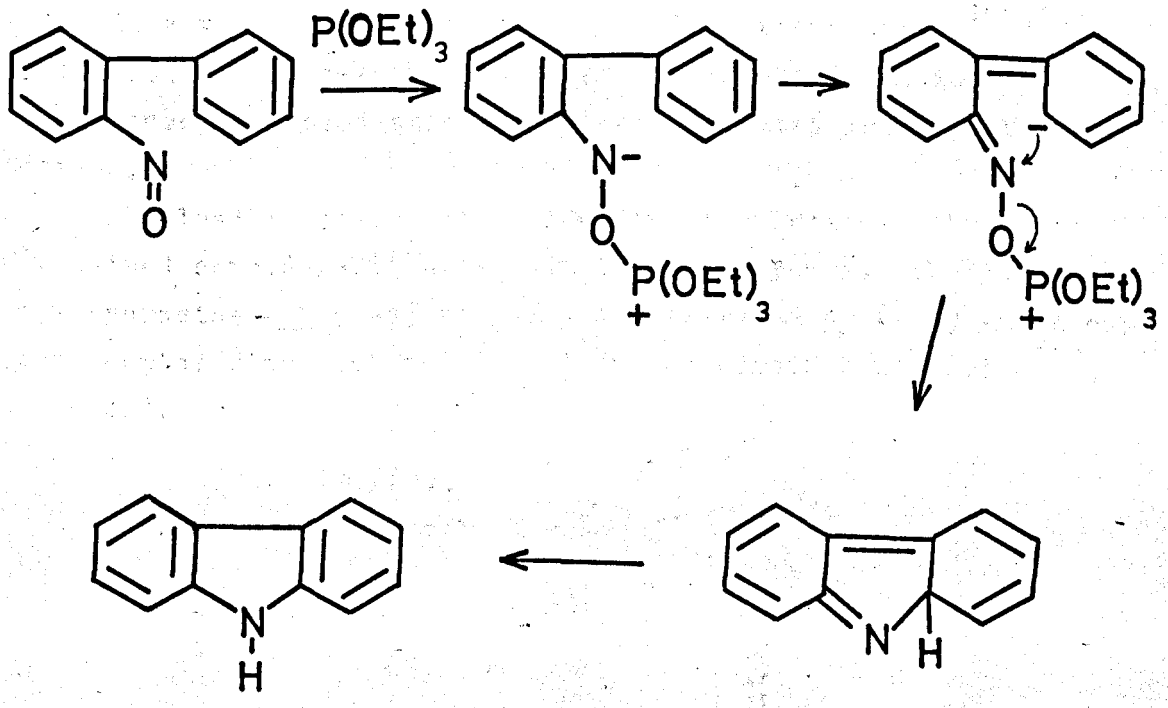
In aromatic nitro- and nitroso-compounds which have an α,β-unsaturated group in the ortho-position there is a strong tendency for cyclisation on deoxygenation[99,100]. Though a nitrene intermediate can be postulated cyclisation by a concerted process cannot be ruled out. For example two mechanisms have been proposed for the formation of carbazole from 2-nitrosobiphenyl[99] (Scheme 41).

SCHEME 41

Nitrene Mechanism:



Non-nitrene Mechanism:



Other Routes to Nitrene Formation

(i) The base-catalysed decomposition of N-arylsulphonoxyurethanes[37]. The reaction involves initial loss of a proton followed by α-elimination of the sulphonoxy group (Scheme 42). The carbonyl-nitrene produced behaves like that generated by thermolysis of the azidoformates.

SCHEME 42

$$ArSO_2\text{-}O\text{-}NHCO_2Et \xrightarrow{OH^-} ArSO_2\text{-}O\text{-}\bar{N}\text{-}CO_2Et \longrightarrow EtCO_2\text{-}N: + ArSO_3^-$$

A nitrene intermediate was also postulated in the base-catalysed decomposition of 1,1-dibenzyl-2-benzenesulphonylhydrazine from which bibenzyl was isolated[101] (Scheme 43).

SCHEME 43

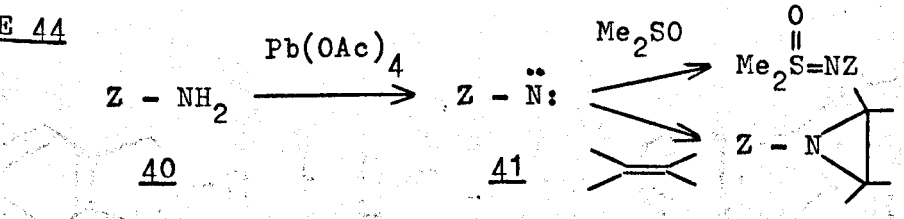
$$Bz_2N\text{-}NHSO_2C_6H_5 \xrightarrow{OH^-} Bz_2N\text{-}\bar{N}\text{-}SO_2C_6H_5 \longrightarrow Bz_2N\text{-}N: \longrightarrow Bz\text{-}Bz + N_2$$

$Bz = C_6H_5CH_2-$

(ii) The oxidation of unsymmetrical disubstituted hydrazines results in a variety of reactions including fragmentation[102,103], ring insertion[104], de-amination[105] and tetrazene formation[106]. Aminonitrenes have been proposed as intermediates in many of these reactions.

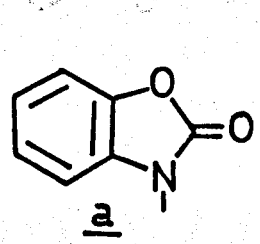
The lead tetra-acetate oxidation of substituted hydrazines has received considerable attention in recent years. The oxidation of the hydrazines 40 (a-d) produces the nitrenes 41 (a-d) which can be intercepted with olefins[107,108,109] and dimethylsulphoxide[110]. (Scheme 44).

SCHEME 44

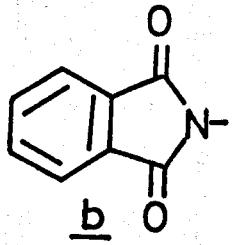


40 41

Z =



a



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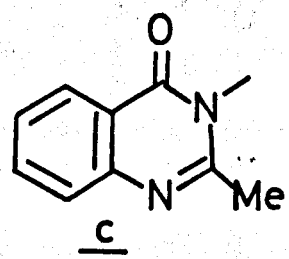

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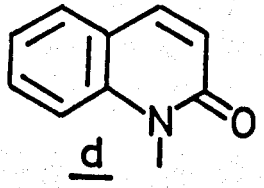
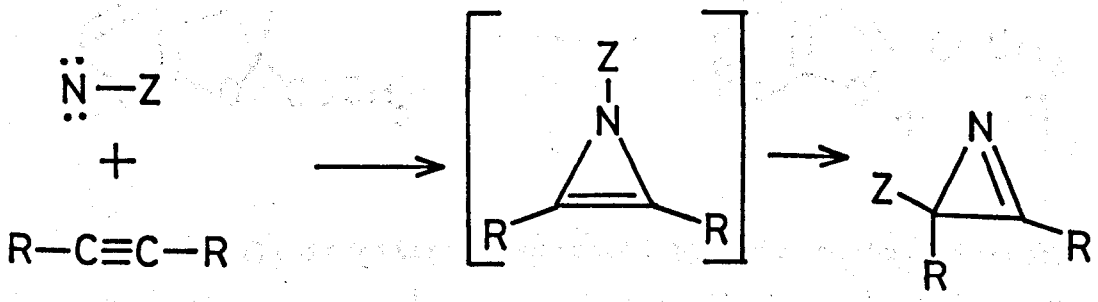


d

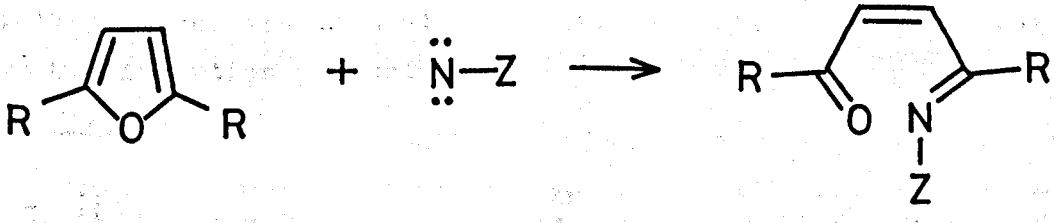
Phthalimidonitrene 41b reacts with alkynes to give 2H-azirines[111] 43 presumably by the rearrangement of an initially formed 1H-azirine 42 (Scheme 45), with simple furans to give ring-opened compounds[112] (Scheme 46) and with benzofurans to give aziridines[113] (Scheme 47)

SCHEME 45

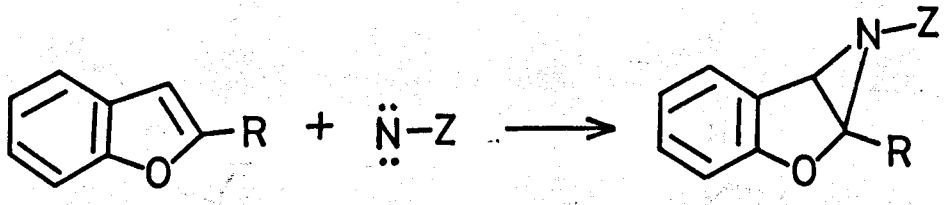


42 43

SCHEME 46

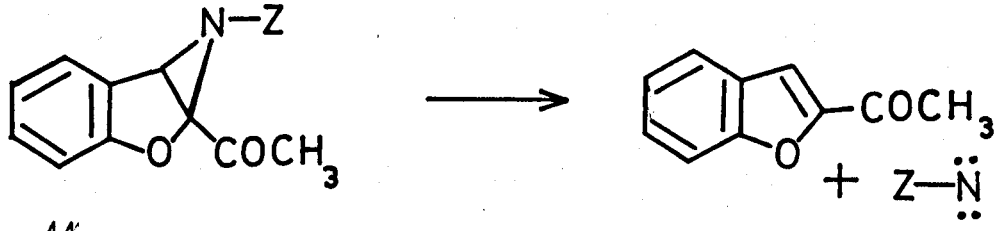


SCHEME 47



(iii) The thermolysis of aziridine 44[114]. The aziridine 44 is simply prepared by the oxidation of N-aminophthalimide in the presence of 2-acetylbenzofuran. In boiling benzene it dissociates to 2-acetylbenzofuran and phthalimidonitrene 41b (Scheme 48)

SCHEME 48

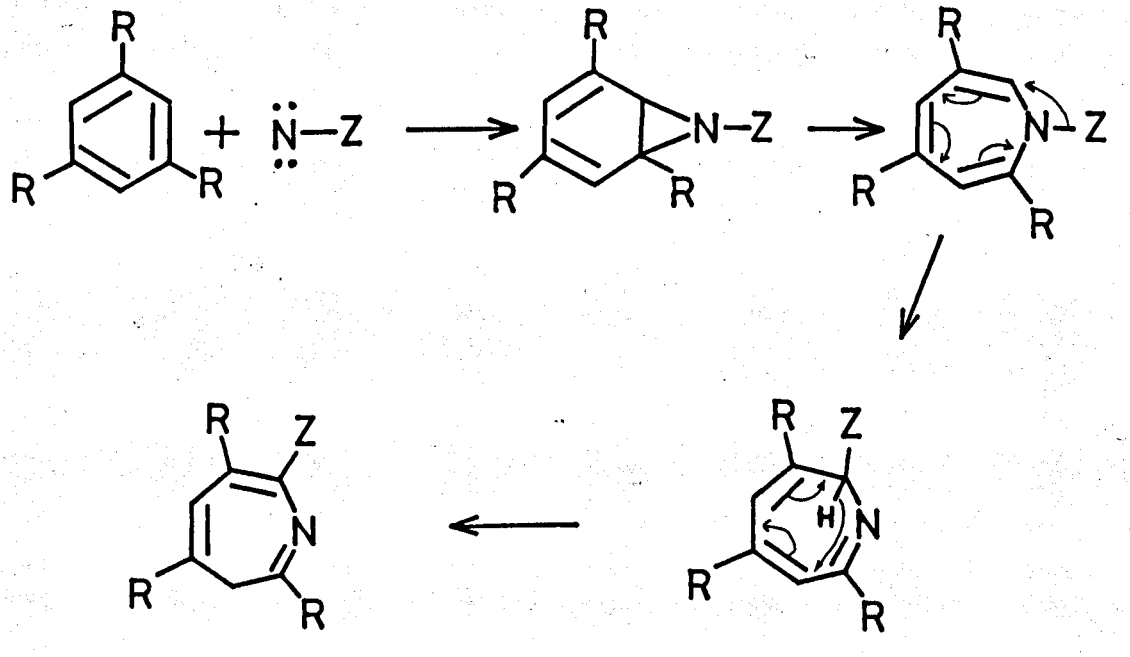


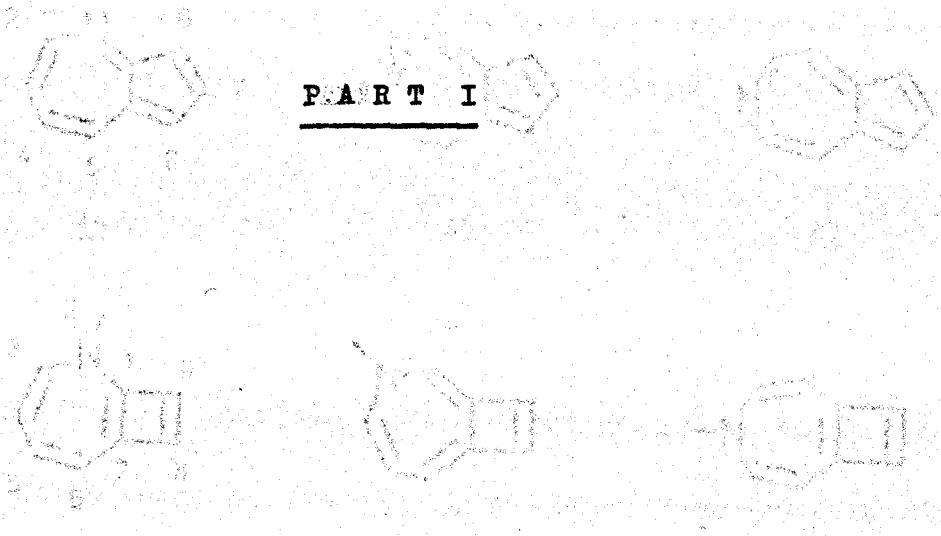
44

The phthalimidonitrene generated by this route undergoes all of the reactions observed for the nitrene generated by oxidation. In addition it reacts with nucleophilic aromatic substrates to give 3H-azepines.[115] Azepine formation is postulated as occurring via a benzaziridine intermediate. There is ring expansion to form a 1-aminoazepine which then undergoes rearrangement to the observed 3H-azepine (Scheme 49).

The nitrene generated by lead tetra-acetate oxidation does not give ring expanded products. The acetic acid produced during the reaction causes the initial benzaziridine intermediate to open to give C-H insertion products.

SCHEME 49



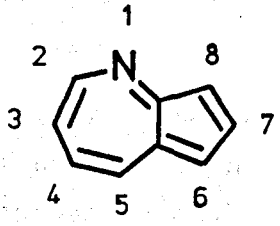


PART I

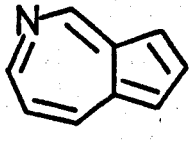
INTRODUCTION

An extensive investigation into the syntheses and reactions of the aza-analogues of the aromatic ten π-electron systems naphthalene and azulene has been conducted at this University by Gurnos Jones and co-workers[52-54, 116-123].

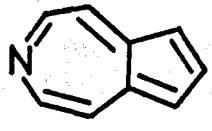
The success of these investigations has encouraged further studies into iso-π-electronic analogues and the aim of the work presented in this section was to prepare derivatives of the aromatic cyclopentazepines 45-47 and the potentially aromatic azabicyclo[5,2,0] nonatetraenes 48-50.



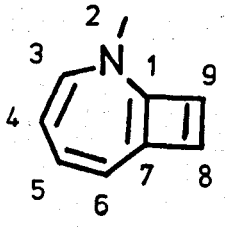
45



46



47



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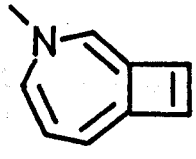

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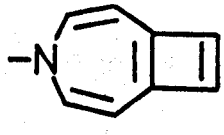


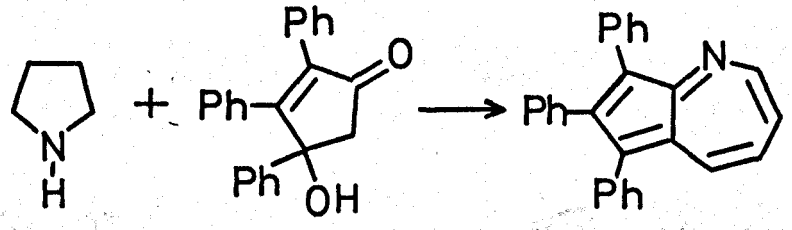
50

There are no reports of cyclopentazepines in the literature prior to 1950 but preparative routes to derivatives of 45 and 46 have since been reported.

Cyclopent[b]azepine

6,7,8-triphenylcyclopent[b]azepine 53 was reported by Conner and LeGoff[124] in 1970. Treatment of pyrrolidine 51 with 4-hydroxy-2,3,4-triphenyl-2-cyclopenten-1-one 52 in toluene containing a catalytic amount of p-toluenesulphonic acid gave, after chromatography, the cyclopent[b]azepine 53 (Scheme 50).

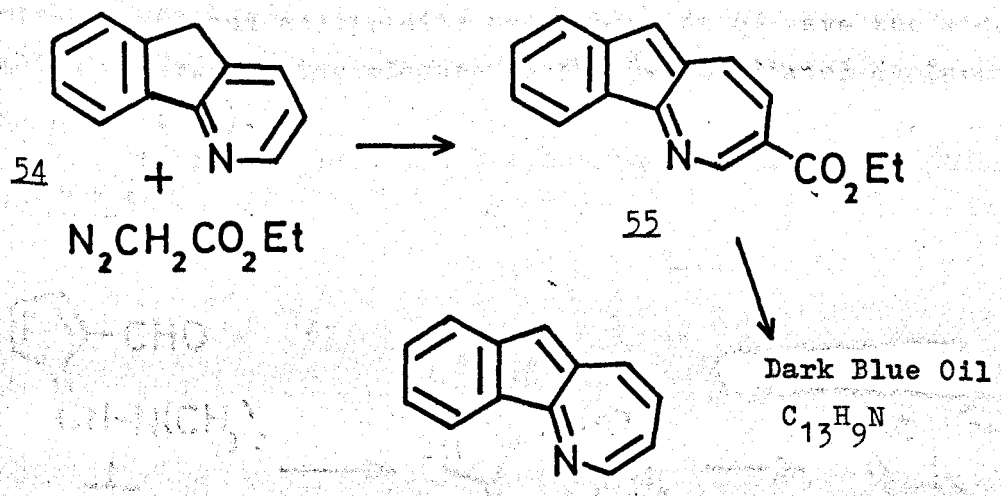
SCHEME 50



51 52 53

Though this synthesis was reported as being the first preparative route to a cyclopent[b]azepine there is an earlier report by Treibs and co-workers[125] of a dark blue oil presumed to be 4-azabenz[c]azulene 56 obtained from 6-ethoxycarbonyl-4-azabenz[c]azulene 55 by treatment with methanolic potassium hydroxide. The ethoxycarbonyl-4-azabenz[c]azulene 55 was obtained by heating 4-azafluorene 54 with ethyl diazoacetate at 130° (Scheme 51).

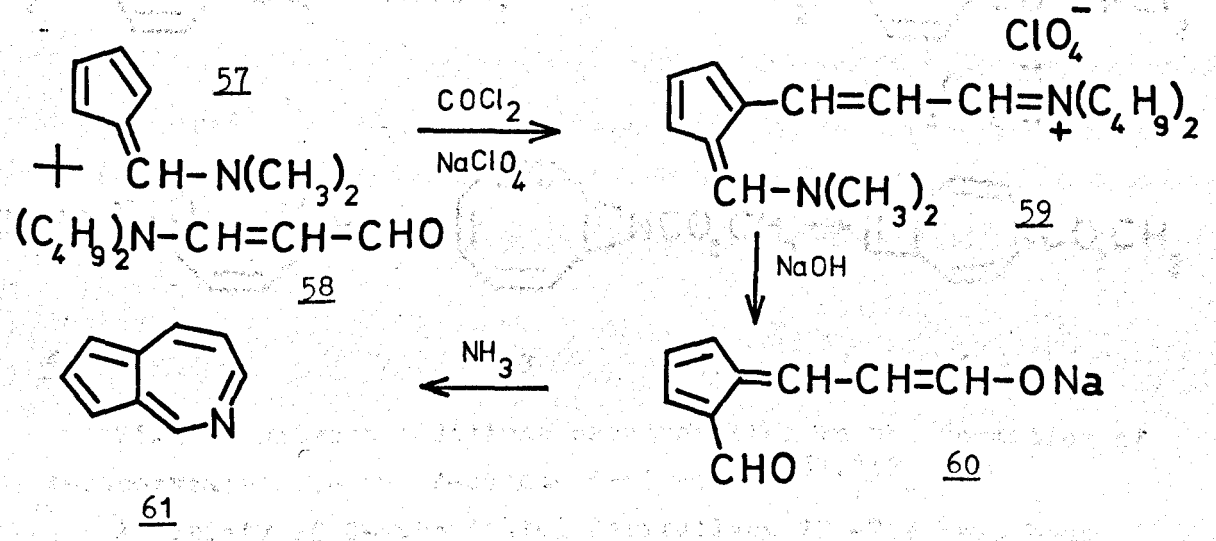
SCHEME 51



Cyclopent[c]azepine

The first synthesis of cyclopent[c]azepine 61 was reported in 1961 by Hafner and Kreuder[126]. The reaction between 6-dimethylaminofulvene 57 and N,N-dibutylaminoacraldehyde 58 in the presence of oxalyl chloride and sodium perchlorate gave the salt 59. Hydrolysis of the salt gave the aldehyde 60 which when treated with ammonia was converted to the cyclopent[c]azepine 61 (Scheme 52).

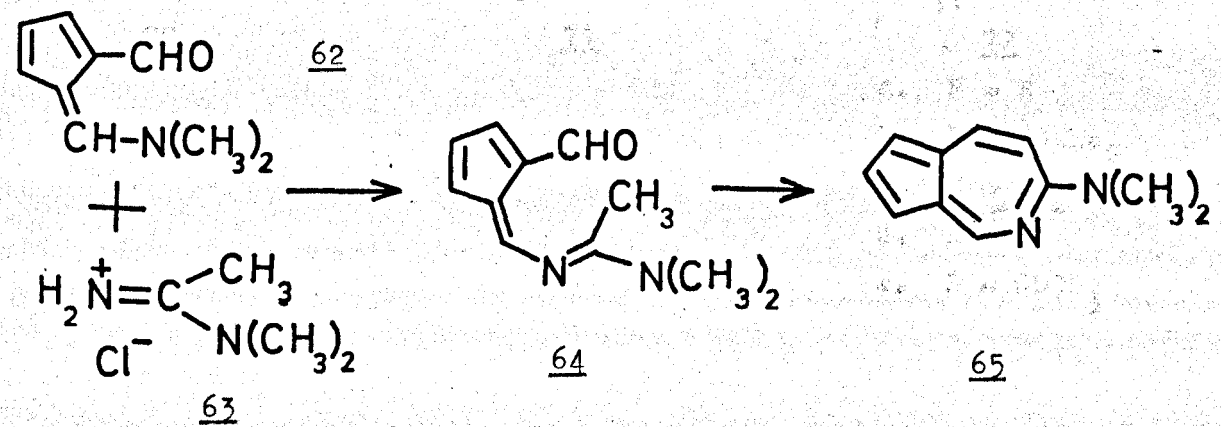
SCHEME 52



The synthesis of a substituted cyclopent[c]azepine has since been reported[127,128]. The reaction between the fulvene aldehyde 62 and acetamidine hydrochloride 63 gave the aldehyde 64 which underwent ring closure to the 3-substituted cyclopent[c]azepine 65 (Scheme 53).

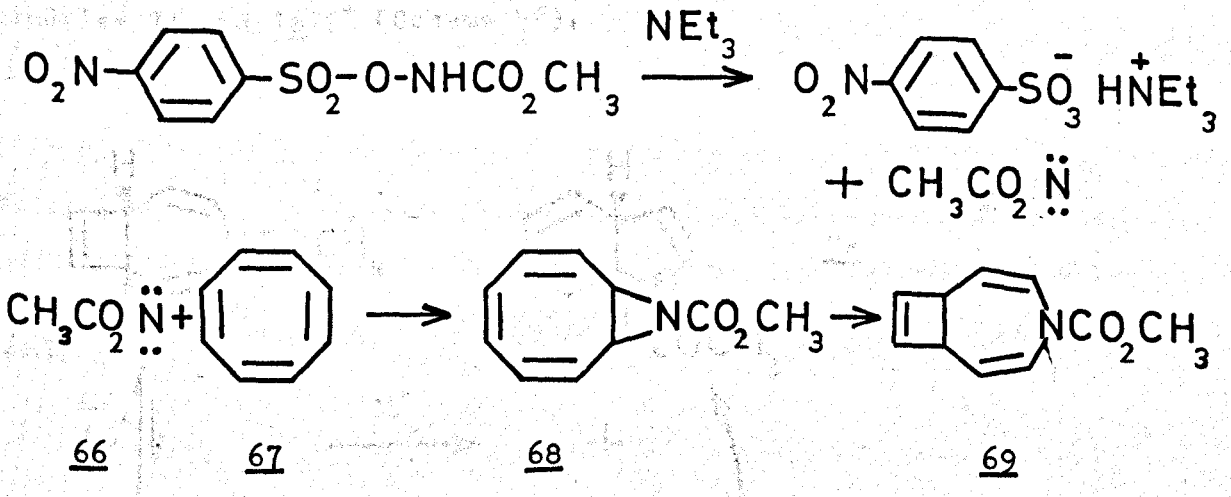
A similar reaction has become the basis of a patent[129].

SCHEME 53



There have been no reports of the synthesis of the azabicyclo[5,2,0]nonatetraenes 48-50 though dihydro- derivatives are known; 4-methoxycarbonyl-4-azabicyclo[5,2,0]nona-2,5,8-triene 69 was first reported by Masamune and Castelucci in 1964[130]. It was prepared by the thermal rearrangement of the 9-azabicyclo[6,1,0]-nonatriene 68 which was itself obtained by the addition of methoxycarbonylnitrene 66 to cyclo-octatetraene 67 (Scheme 54).

SCHEME 54

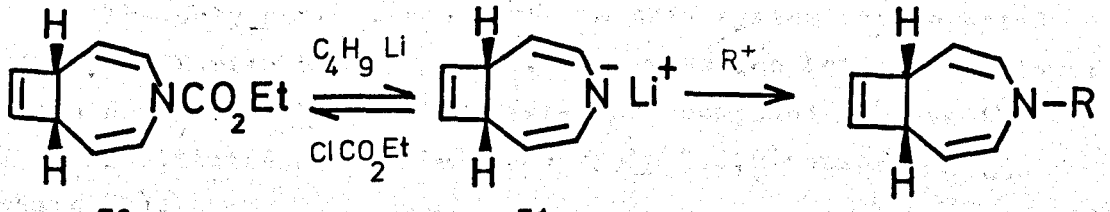


66 67 68 69

Similar nitrene additions have resulted in the formation of the 4-ethoxycarbonyl- and 4-cyano- derivatives[131,132].

A variety of N-substituted derivatives 72a-72e have been prepared[133] from the 4-ethoxycarbonyl compound 70 via the lithium derivative 71 (Scheme 55).

SCHEME 55

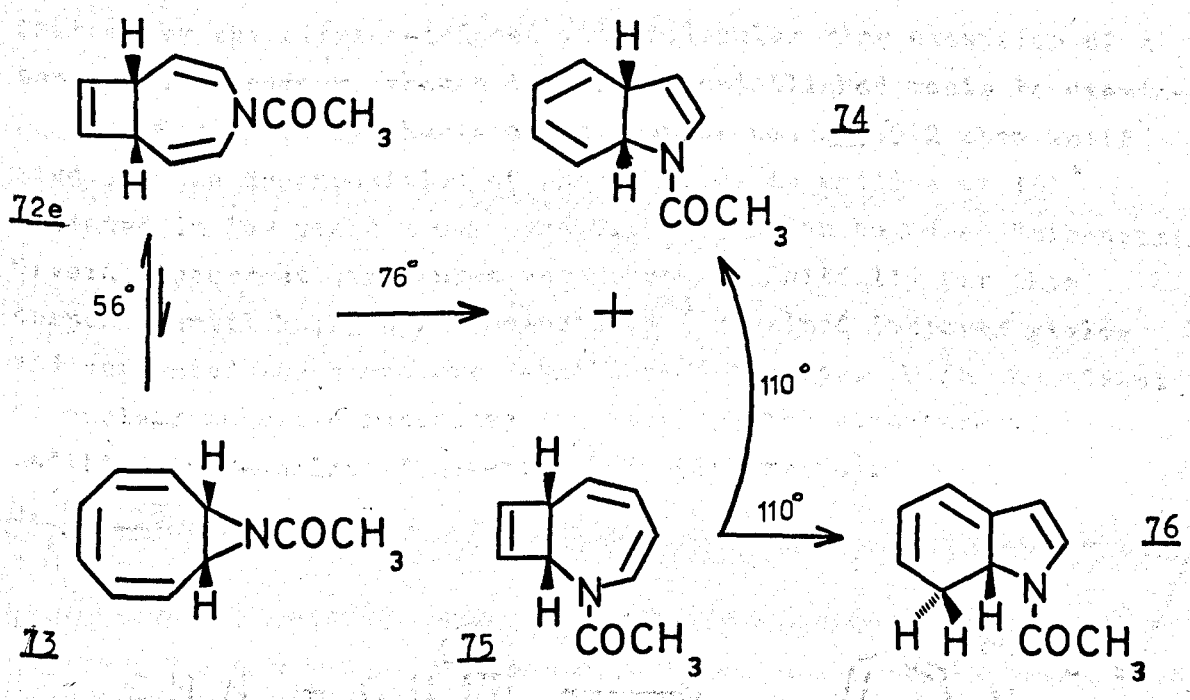


70 71 72

a. R = H
b. R = $CONMe_2$
c. R = CO_2Me
d. R = Me
e. R = $COCH_3$

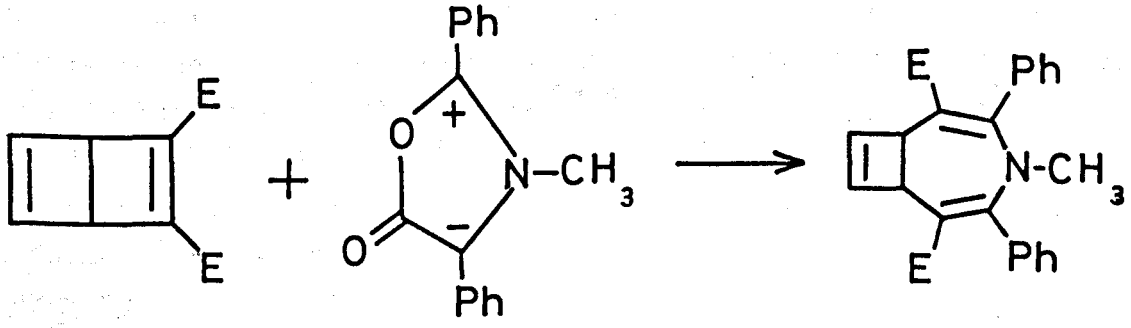
The parent compound 72a is an air-sensitive oil which readily resinifies. There have been no reports of attempts at dehydrogenating this compound or any of its derivatives. This is possibly due to the ease of thermal isomerisation. When warmed to 56° in benzene 4-acetyl-4-azabicyclo[5,2,0]nona-2,5,8-triene 72e produces a two-component equilibrium mixture consisting of 95% 72e and 5% 73. An increase in temperature to 76° results in the formation of the dihydro-indole 74 and the 2-azabicyclo[5,2,0]nona-triene 75 which at higher temperatures isomerises to the dihydro-indoles 74 and 76[134] (Scheme 56).

SCHEME 56



The only non-nitrene route to this system was reported recently by Martin and Hekman[135]. The reaction between the Dewar benzene derivative 77 and the meso-ionic compound 78 gave the highly substituted 4-methyl-4-azabicyclo[5,2,0]nonatriene 79 (Scheme 57).

SCHEME 57



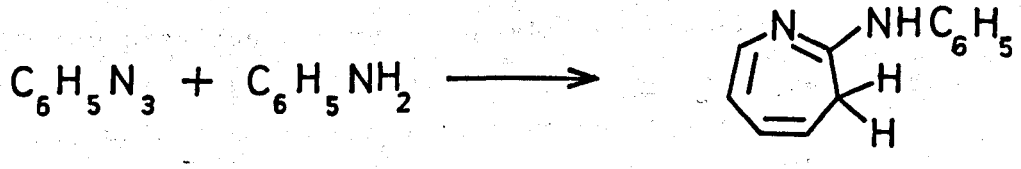
E = $-CO_2CH_3$

77 78 79

There have been no reports of attempts to prepare these systems by the nitrene-induced intramolecular ring expansion of a benzenoid precursor, though this is an established route to azepines.

The first synthesis of an azepine was in 1912 when Wolff[58] studying the decomposition of phenyl azide in aniline at 150° isolated in low yield a compound $C_{12}H_{12}N_2$ which he named "dibenzamil". Several incorrect structures were proposed initially for this compound until Huisgen and co-workers[59] obtained improved yields and suggested the structure 2-anilino-7H-azepine. With the advent of nuclear magnetic resonance spectroscopy the structure was modified to 2-anilino-3H-azepine[60] 80 (Scheme 58).

SCHEME 58

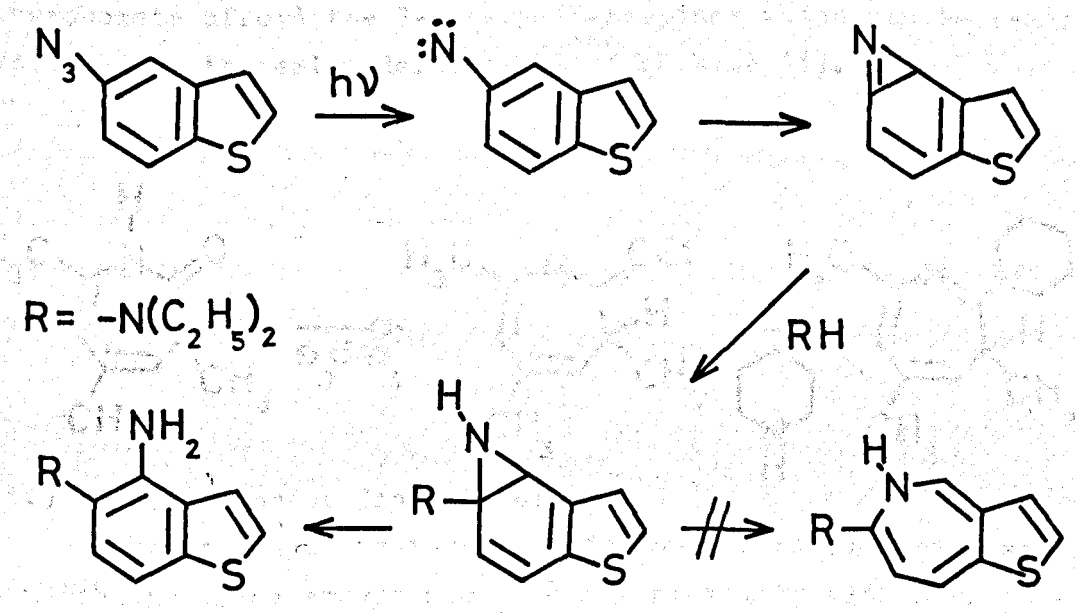


80

The mechanism of the ring expansion has been proposed to involve the formation and subsequent intramolecular cyclisation of phenylnitrene followed by reaction with the amine[59-61] (See Scheme 23). Support for the existence of a 1H-azepine intermediate has come from the studies by Sundberg and co-workers[67] on the photolysis of ortho- substituted aryl azides in diethylamine. The photolyses were shown to lead mainly to oxygen-sensitive meta-stable intermediates rather than directly to the 2-diethylamino-3H-azepines and n.m.r. spectral data indicated that these intermediates were 2-diethylamino-1H-azepines.

Although the thermal and photochemical decomposition of aryl azides in amines appears to provide a facile route to azepines failure to undergo ring expansion has been noted for certain azides. These include the naphthyl azides[59,61], p-nitrophenylazide[136], 4-azidobenzo[b] thiophen[137] and 5-azidobenzo[b]thiophen[137]. The last case is of interest in that a derivative of o-phenylenediamine is formed (Scheme 59).

SCHEME 59



82 81 83

The formation of the diamine 82 has been rationalised as shown in the previous scheme. The ring-opening of the aziridine intermediate 81 to give the thienoazepine 83 would be thermodynamically unfavourable since it involves the loss of aromaticity in both rings.

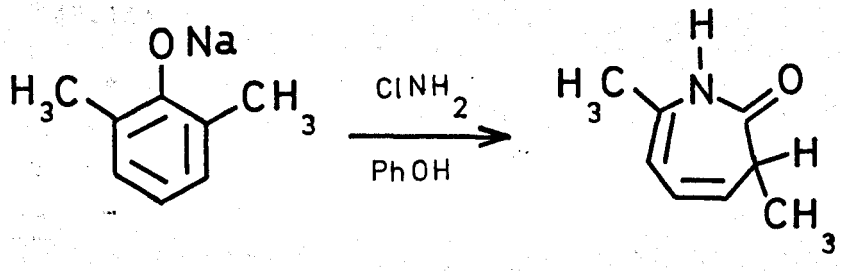
Other routes to 3H-azepines will be summarised briefly;

(i) The deoxygenation of nitro- and nitroso-benzenes in the presence of primary or secondary amines[94-97].

(ii) Reaction of phenoxide ions with chloramine:

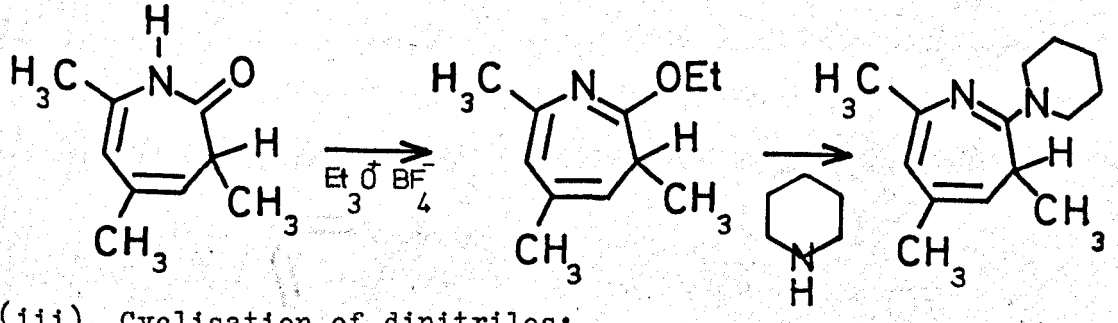
Treatment of a hot solution of sodio-2,6-dialkyl- and 2,4,6-trialkyl phenoxides with chloramine leads to the formation of 1,3-dihydro-2H-azepin-2-ones[138] (Scheme 60).

SCHEME 60



These dihydroazepinones when treated with triethyloxonium fluoroborate afford the 2-ethoxy-3H-azepines which can be readily converted to the amino-derivatives[139] (Scheme 61).

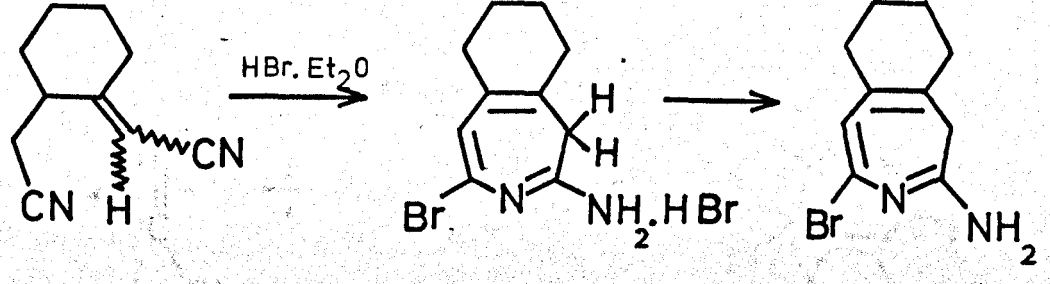
SCHEME 61



(iii) Cyclisation of dinitriles:

The action of hydrogen halides on a dinitrile such as 84 in which the cyano groups are in close proximity with each other leads to cyclisation and formation of the 3H-azepine derivatives 85 and 86[140,141] (Scheme 62).

SCHEME 62

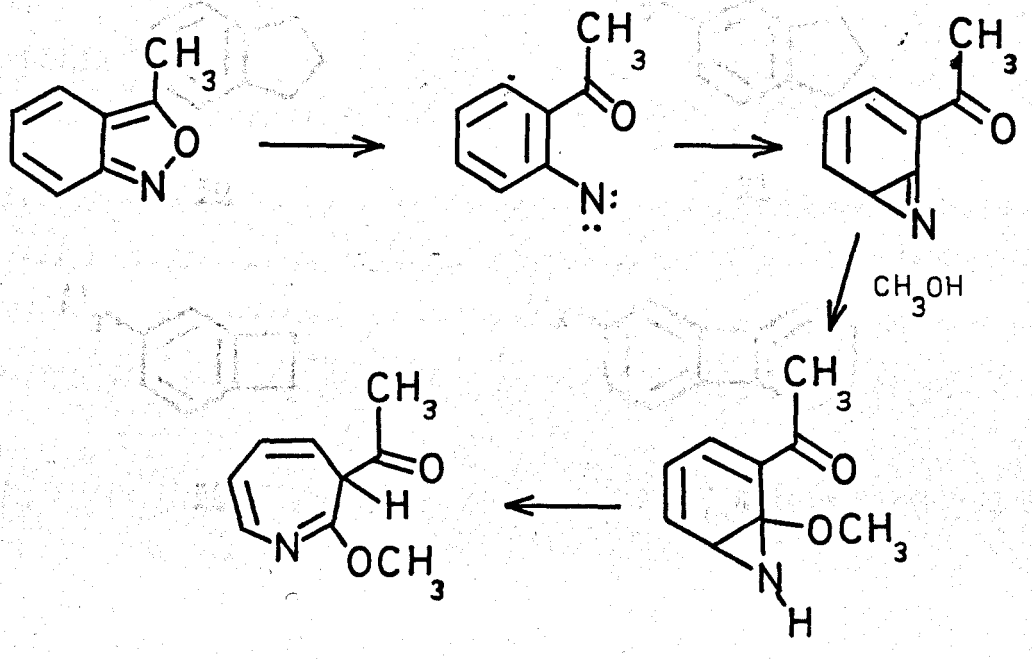


84 85 86

(iv) Photo-rearrangement of anthranils:

Irradiation of anthranils in methanol leads to 3H-azepines[142,143]. A mechanism for this rearrangement involves N-O bond cleavage to give an aryl nitrene which undergoes aziridine formation, addition of methanol and ring expansion to the azepine (Scheme 63).

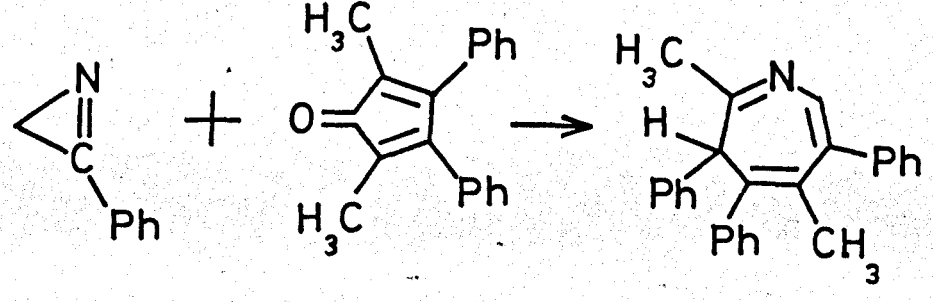
SCHEME 63



(v) Ring expansion of 1-azirines via cyclo-addition:

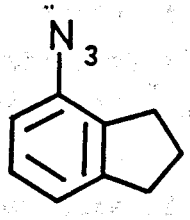
Treatment of 2-phenyl-1-azirine 87 with the cyclopentadienone 88 in refluxing benzene gave the azepine 89[144,145] (Scheme 64).

SCHEME 64

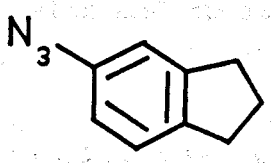


87 88 89

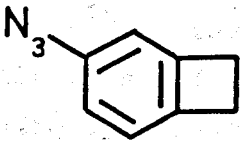
It was decided to prepare azepine derivatives suitable for conversion into compounds of the types 45-50 by the photolysis of substituted phenyl azides in diethylamine. This necessitated the preparation of 4-azidoindan 90, 5-azidoindan 91, 4-azidobenzocyclobutene 92 and 2-azidobiphenylene 93.



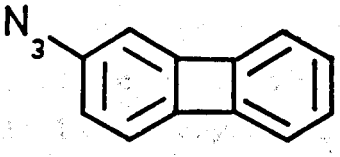
90



91



92



93

DISCUSSION

PREPARATION OF THE AZIDES

Two routes to the desired azides were envisaged. These were from the aryl amines by diazotisation and treatment with sodium azide[146,147] and from the aryl bromide via the Grignard compound[148].

A mixture of 5-amino- and 4-aminoindan was obtained from commercially available indan by nitration[149] and catalytic hydrogenation. Separation was readily achieved by crystallisation of the fumarate salt of 5-aminoindan after the method of Rhomberg and Berger[150]. The aminoindans were converted to the azides by diazotisation and reaction of the diazonium salt with sodium azide. Following a procedure used at this laboratory all diazotisations were carried out in sulphuric acid containing 50% by volume of purified 1,4-dioxan which had the effect of keeping the amine salt in solution even at -5°. 4-azidoindan was also obtained in low yield from 4-bromoindan[151].

Benzocyclobutene was prepared by the methods of Oliver and Ongley[152] and Sanders and Giering[153]. Bromination[154] gave 4-bromobenzocyclobutene in reasonable yield (54%) but attempts to prepare the azide gave poor yields and the product was contaminated with unreacted starting material. Nitration[155] gave a low yield of the 4-nitro derivative but conversion to the amine and thence to the azide was accomplished in a much higher overall yield.

Biphenylene was prepared by the method of Logullo, Seitz and Friedman[156] and converted to the azide via the bromide[157]. In this case reasonable yields of both the bromide and the azide were obtained.

DECOMPOSITION OF THE AZIDES

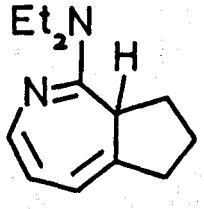
Each azide was decomposed in diethylamine solution at room temperature by irradiation with ultra-violet light from a Rayonet photochemical reactor equipped with 300-nm lamps. The assignment of structures to the decomposition products was based largely on the interpretation of their n.m.r. spectra and these are extensively discussed throughout this section. The mass spectra are discussed collectively at the end of this section.

No attempts were made to characterise all the products of the decompositions. The crude decomposition mixture was examined by gas chromatography (g.l.c.) and linked gas chromatography-mass spectrometry (g.l.c.-m.s.) for azepine products which were then isolated and characterised.

The decomposition of 4-azidoindan 90 gave a black tar which was shown on examination by g.l.c. to comprise at least seven components. Linked g.l.c.-m.s. indicated that three of these components had a molecular ion and fragmentation pattern consistent with a cyclopentazepine structure.

An initial separation of the products was obtained by column chromatography on alumina. Each fraction was then separated by extensive preparative layer chromatography until samples of each cyclopentazepine were isolated.

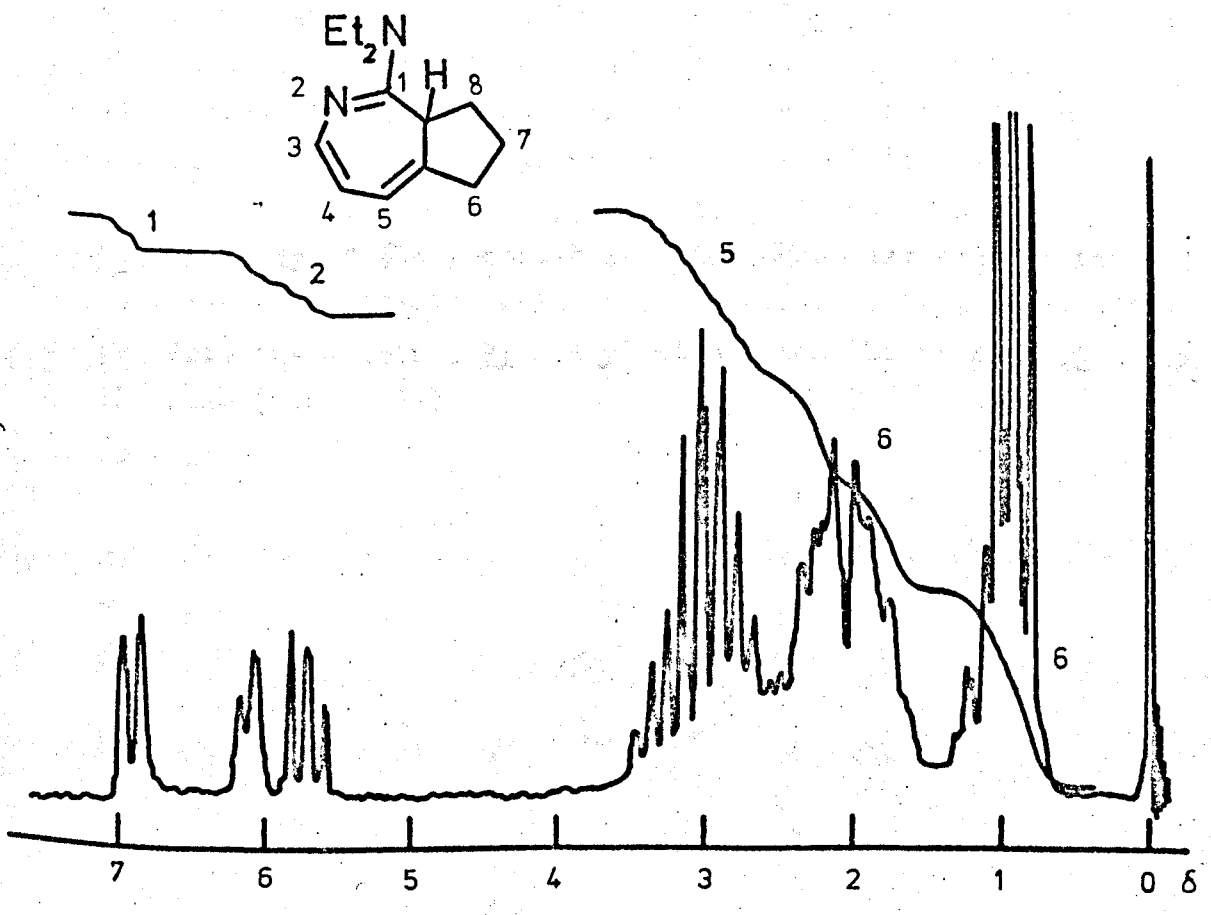
The structure of one of these cyclopentazepines was assigned as 1-diethylamino-6,7,8,8a-tetrahydrocyclopent[c]azepine 94 on the basis of its n.m.r. spectrum (Figure 1).



94

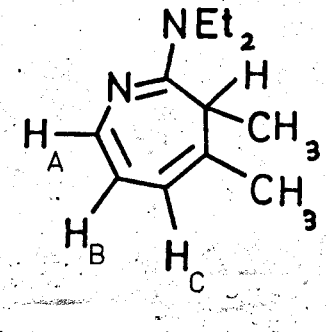
The low-field doublet (J=8Hz) centred at δ6.90p.p.m. is in accord with the partial structure -N=CH-. This doublet is coupled to the signal at δ5.68p.p.m. which has secondary coupling (J=6Hz)

FIGURE 1



to the broadened doublet at δ6.10p.p.m. These chemical shifts and coupling constants are in good agreement with those observed for the structurally related 2-diethylamino-3,4-dimethyl-3H-azepine 95[67].

	Chemical Shift (δ)	Coupling Constant (J)
H_A	6.93	8 Hz
H_B	5.48	6 & 8 Hz
H_C	6.02	6 Hz

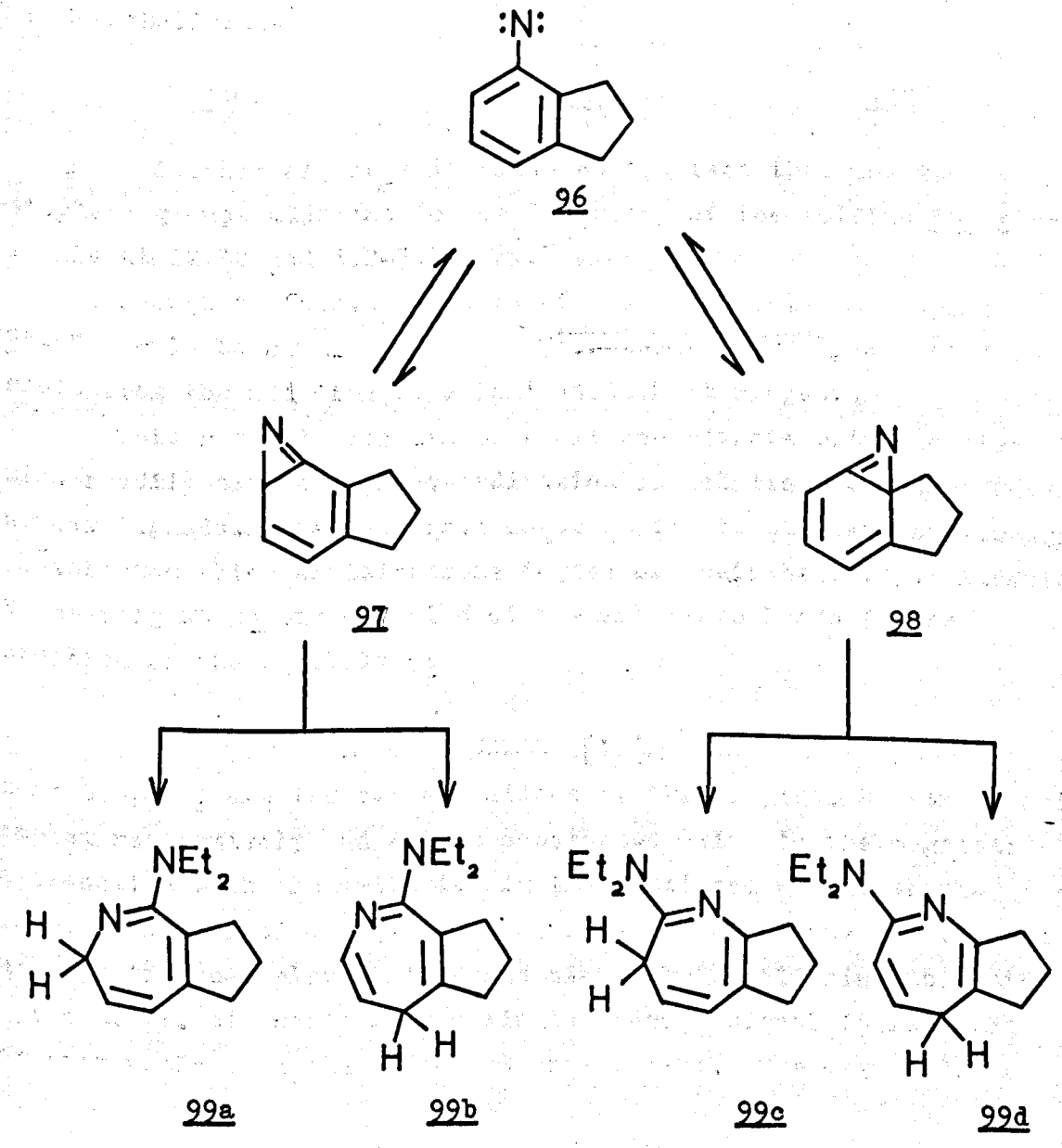


95

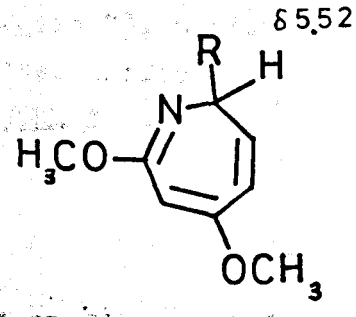
The assignment of structures to the other isomeric cyclopentazepines proved more difficult. The n.m.r. spectrum of each compound shows two signals in the olefinic region: a doublet (J=8Hz) centred between δ6.0 - 6.5 and a 1:3:3:1 quartet centred between δ4.5-5.0p.p.m. These signals are compatible with a carbon framework comprising a methylene group attached to a vinyl structure possessing α and β protons i.e. $-CH_2-CH=CH-$.

A study of the proposed reaction mechanism reveals four cyclopentazepines 99a-99d which have this carbon framework. These derive from the azirines 97 and 98 with which the nitrene 96 is in equilibrium (Scheme 65).

SCHEME 65

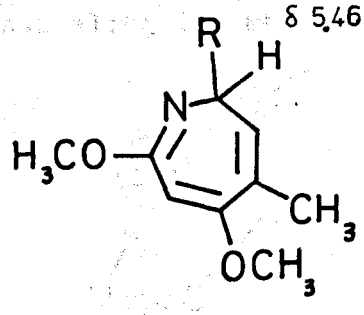


Structure 99a can be excluded on the basis of the chemical shift of the azepine methylene protons which occurs at δ2.5p.p.m. This shift is too small for the methylene situated between a nitrogen atom and a double-bond system as can be shown by reference to the 2H-azepines 100 and 101[158].

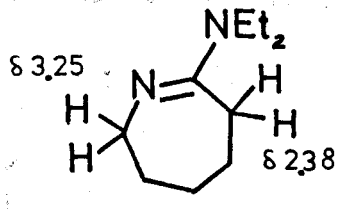


R = N-phthalimido-

100



101



102

A further argument is based on the fact that the two methylene groups adjacent to the C=N group of the amidine 102 give signals at δ2.38 and 3.2-3.3p.p.m.[60].

Though the n.m.r. spectra of the pure cyclopentazepines 99b-99d would be similar, marked differences could be expected to result from the addition of a lanthanide shift reagent.

This reagent consists of a six-co-ordinate metal complex which readily expands its co-ordination in solution to accept further ligands. The substrate co-ordinates to the reagent through a heteroatom which exhibits some degree of Lewis basicity. Addition of the reagent to the solution of the substrate leads to the formation of the equilibrium

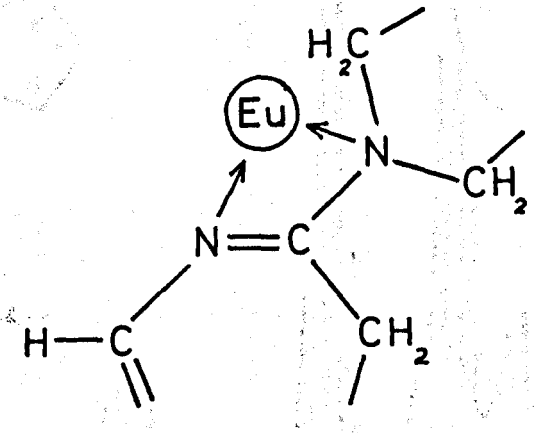
$$L + S \underset{}{\overset{K}{\rightleftharpoons}} [LS]$$

where L,S,[LS] are the concentrations of the reagent, substrate and complex respectively and K is a constant. Owing to the magnetic inter-action with the metal ion in the complexed substrate the n.m.r. positions of associated nuclei in the substrate differ from those in the uncomplexed state and since the equilibrium is rapid in the n.m.r. timescale only a single average signal is recorded for each nucleus in the different environment. The magnitude of

the lanthanide induced shift is proportional to the distance from the metal ion and thus a differential expansion of the spectrum is observed[159].

The 2-diethylaminocyclopentazepines could be expected to co-ordinate to the reagent through the amidine function. The protons most affected by the magnetic inter-action with the metal ion would be those on carbon atoms alpha to the amidine function (Figure 2), protons further along the carbon chain would experience lesser shifts.

FIGURE 2



Figures 3 and 4 show the effect of the shift reagent $Eu(fod)_3$ [tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)-europium(III)] upon the n.m.r. spectra of the cyclopentazepines.

In Figure 3 the largest down-field shifts are observed for the signals attributed to the diethylamino-group and the olefinic proton signal at δ6.40p.p.m. This latter observation enabled the assignment of the 4H-azepine structure 99b to one of the cyclopentazepines.

In Figure 4 resolution of the spectrum has been achieved due to the large down-field shifts of the diethylamino-group signals and the C_8 methylene signal. Both the C_6 and C_8 methylene signals are clearly visible as triplets and the azepine methylene appears as a doublet (J=7Hz). The signal due to the methylene protons has undergone a greater shift than the signals due to the olefinic protons. This would be expected for a structure such as 99c where the methylene group is nearer to the co-ordination site than the olefinic protons.

FIGURE 3

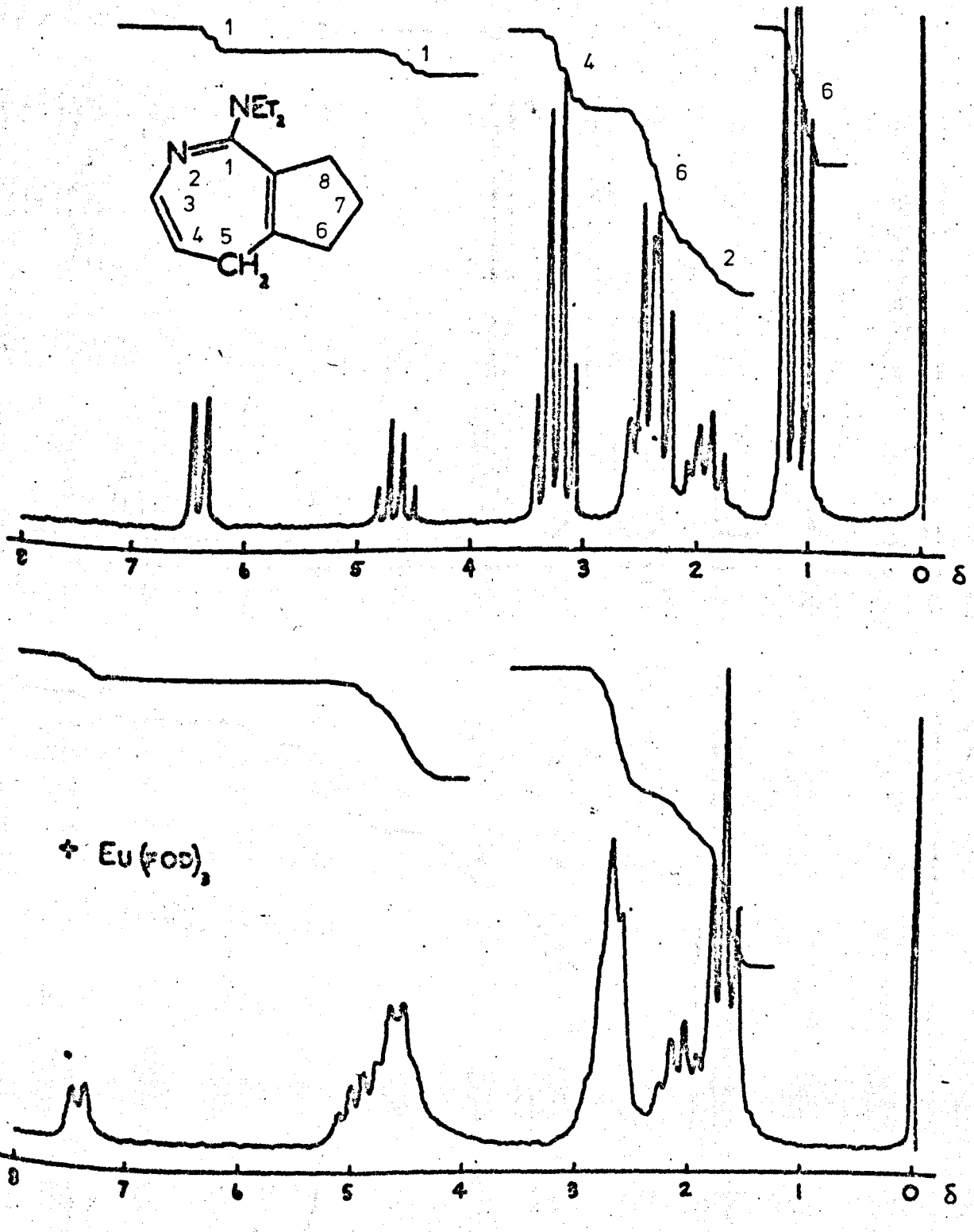
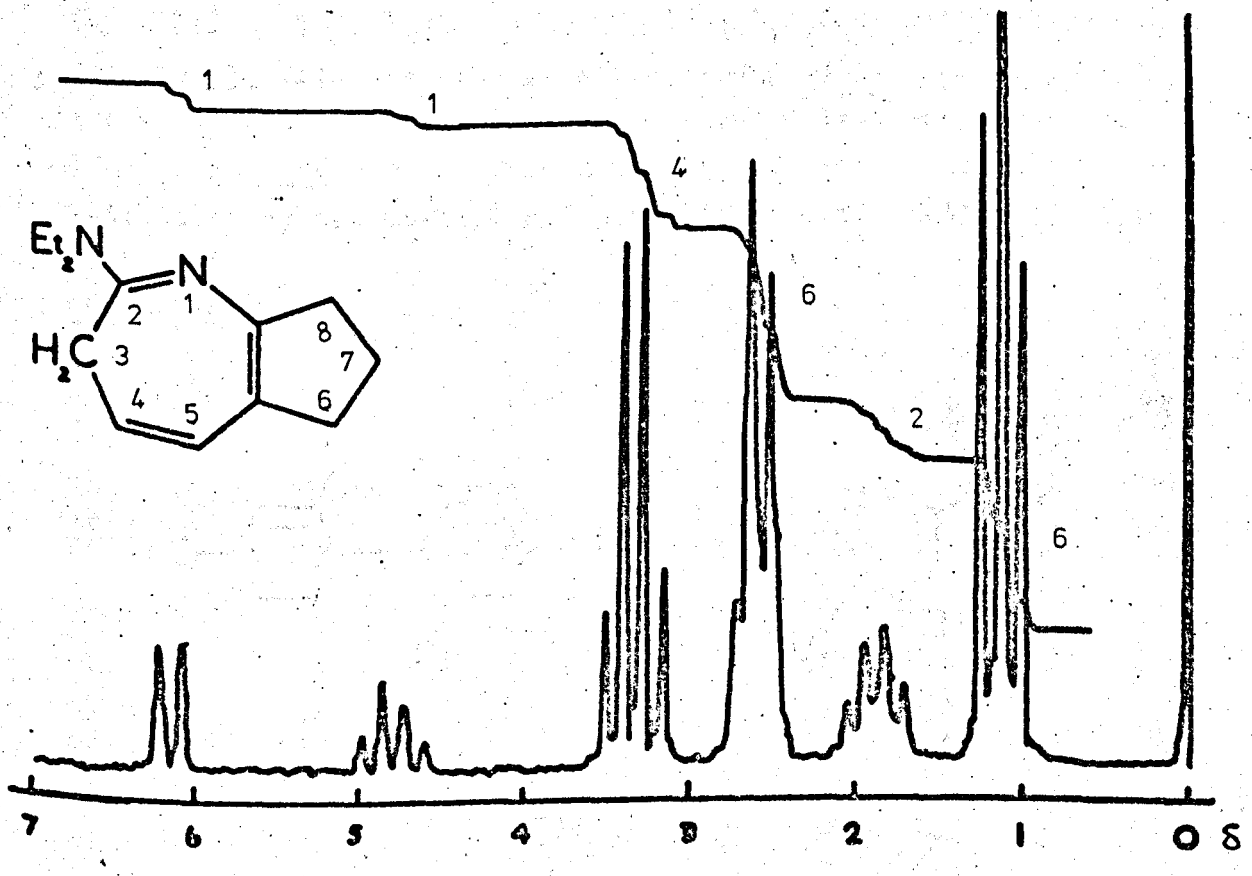
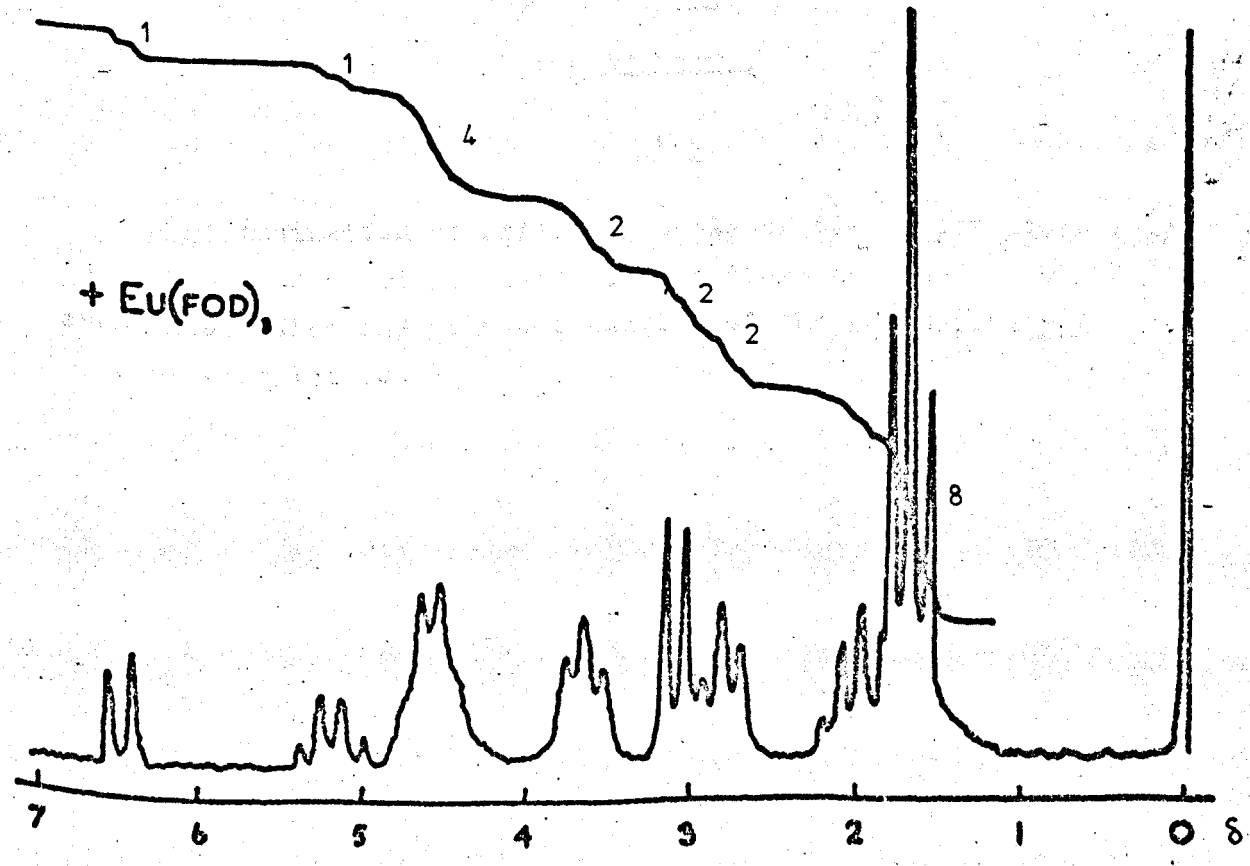


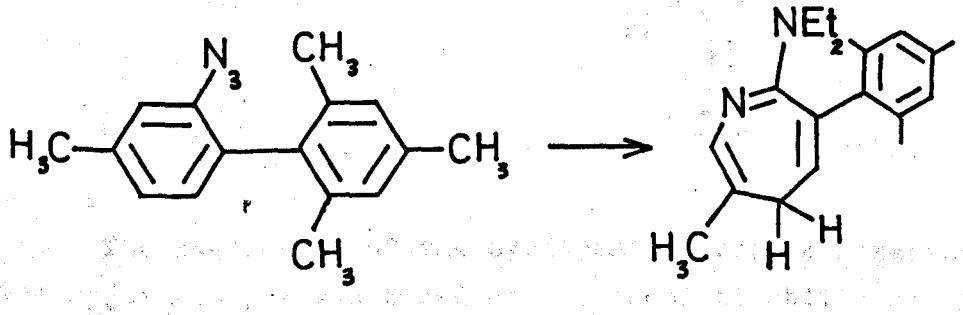
FIGURE 4


1
1
4
6
2
6
Et2N
N
2
1
H2C
3
8
7
4
5
6
7
6
5
4
3
2
1
0
δ

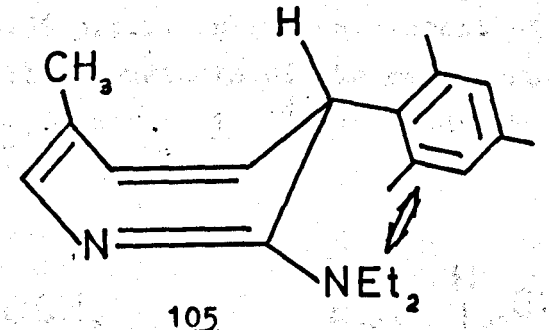

1
1
4
2
2
2
8
+ Eu(FOD)3
7
6
5
4
3
2
1
0
δ

The formation of the 4H-azepine 99b, though unexpected, is not without precedent as Sundberg and co-workers[67] have observed the formation of 7-diethylamino-3methyl-6-(2,4,6-trimethylphenyl)-4H-azepine 104 from the decomposition of 2-mesityl-5-methylphenyl azide 103 (Scheme 66). Sundberg suggested that the predicted 3H-tautomer 105 was not formed because of severe steric interactions introduced by the mesityl group in either conformation of this tautomer.

SCHEME 66



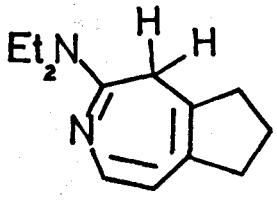
103 104



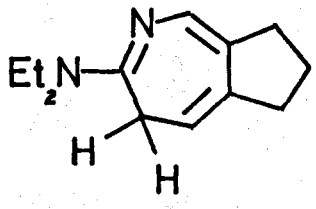
105

Examination of Dreiding models of the cyclopentazepines 94 and 99b and possible precursors to these compounds revealed no such interaction and so the formation of the 4H-azepine 99b remains unexplained.

The decomposition of 5-azidoindan 91 gave a black oil from which was obtained, by bulb-to-bulb distillation, a mixture of 2-diethylamino-1,6,7,8-tetrahydrocyclopent[d]azepine 106 and 3-diethylamino-4,6,7,8-tetrahydrocyclopent[c]azepine 107.



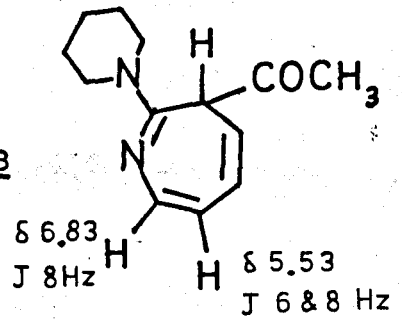
106



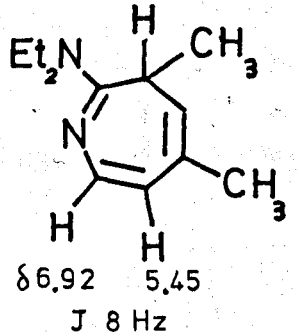
107

The assignment of the cyclopent[d]azepine structure 106 to the major product was based on the chemical shifts of the olefinic protons H-4 and 5 (Figure 5). These occur as a pair of doublets (J = 8Hz) at δ6.77 and 5.56 p.p.m. in good agreement with the chemical shifts and coupling constants of the corresponding protons in 3-acetyl-2-piperidino-3H-azepine 108[143] and 2-diethylamino-3,5-dimethyl-3H-azepine 109[67].

108

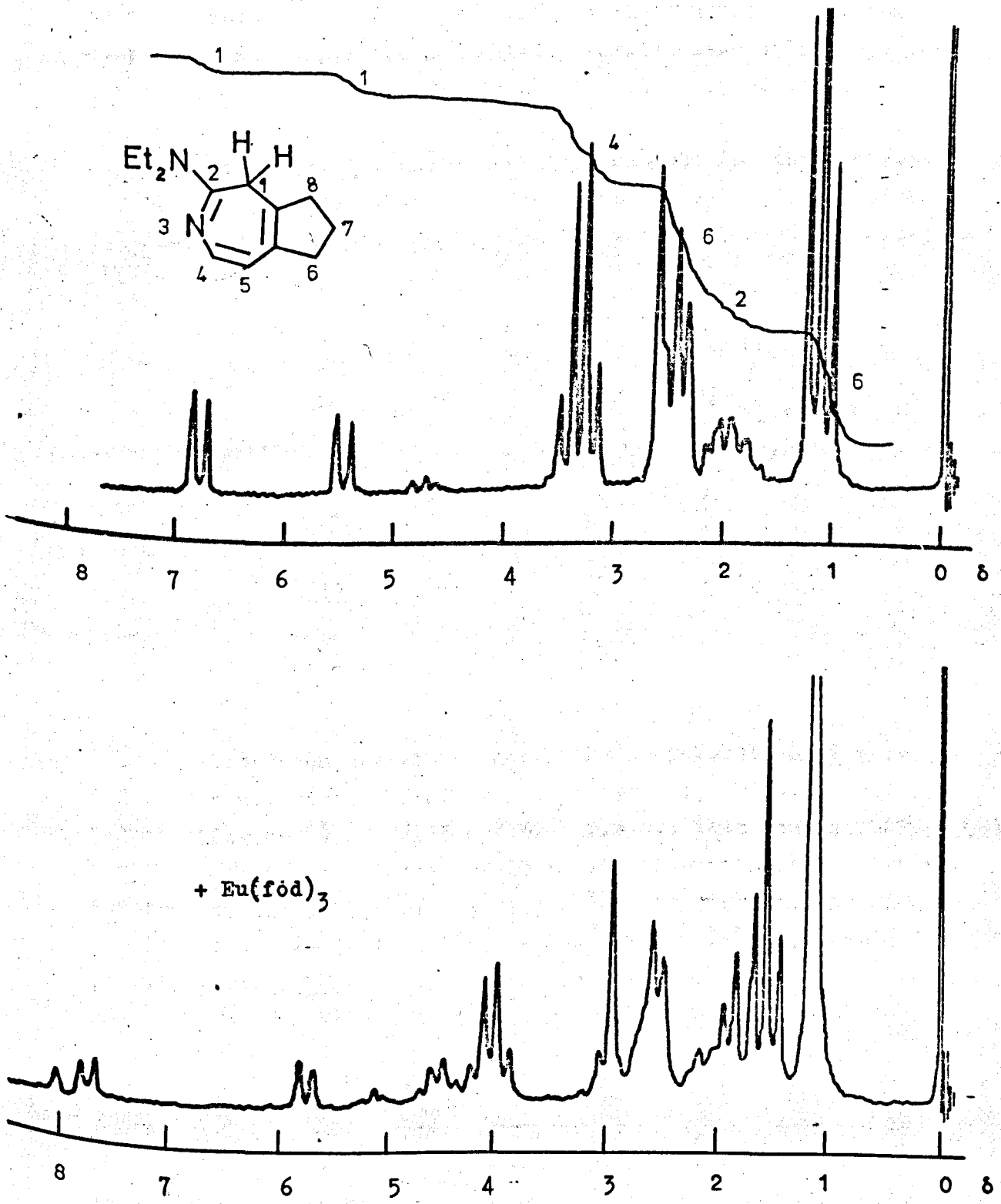


109



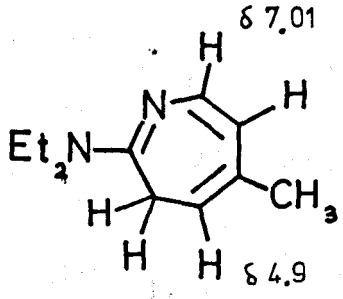
Separation of these isomeric cyclopentazepines was not achieved and the assignment of the cyclopent[c]azepine structure 107 to the minor product was based on the spectral data of the mixture. Linked g.l.c.- m.s. gave, for both compounds, the same molecular ion and similar fragmentation patterns while close examination of the n.m.r. spectrum revealed an ill-defined triplet at δ4.73 p.p.m. and an anomalous enlargement of the down-field peak

FIGURE 5

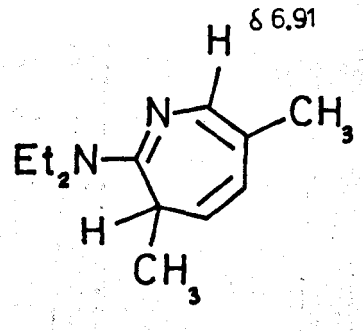


of the doublet at δ6.77 p.p.m. Treatment of the n.m.r. solution with the Europium shift reagent $Eu(fod)_3$ caused a down-field shift of the doublet at δ6.77 p.p.m. with resolution into two signals comprising a singlet and a doublet. Similar resolution into two quartets was observed for the signal at δ3.3 p.p.m. attributed to the methylene protons of the diethylamino residue (Figure 5).

Structure 107 satisfactorily accounts for these observed signals with an adequate comparison provided by 2-diethylamino-3,6-dimethyl-3H-azepine 110 and 2-diethylamino-5-methyl-3H-azepine 111[67].

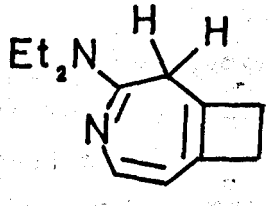


111



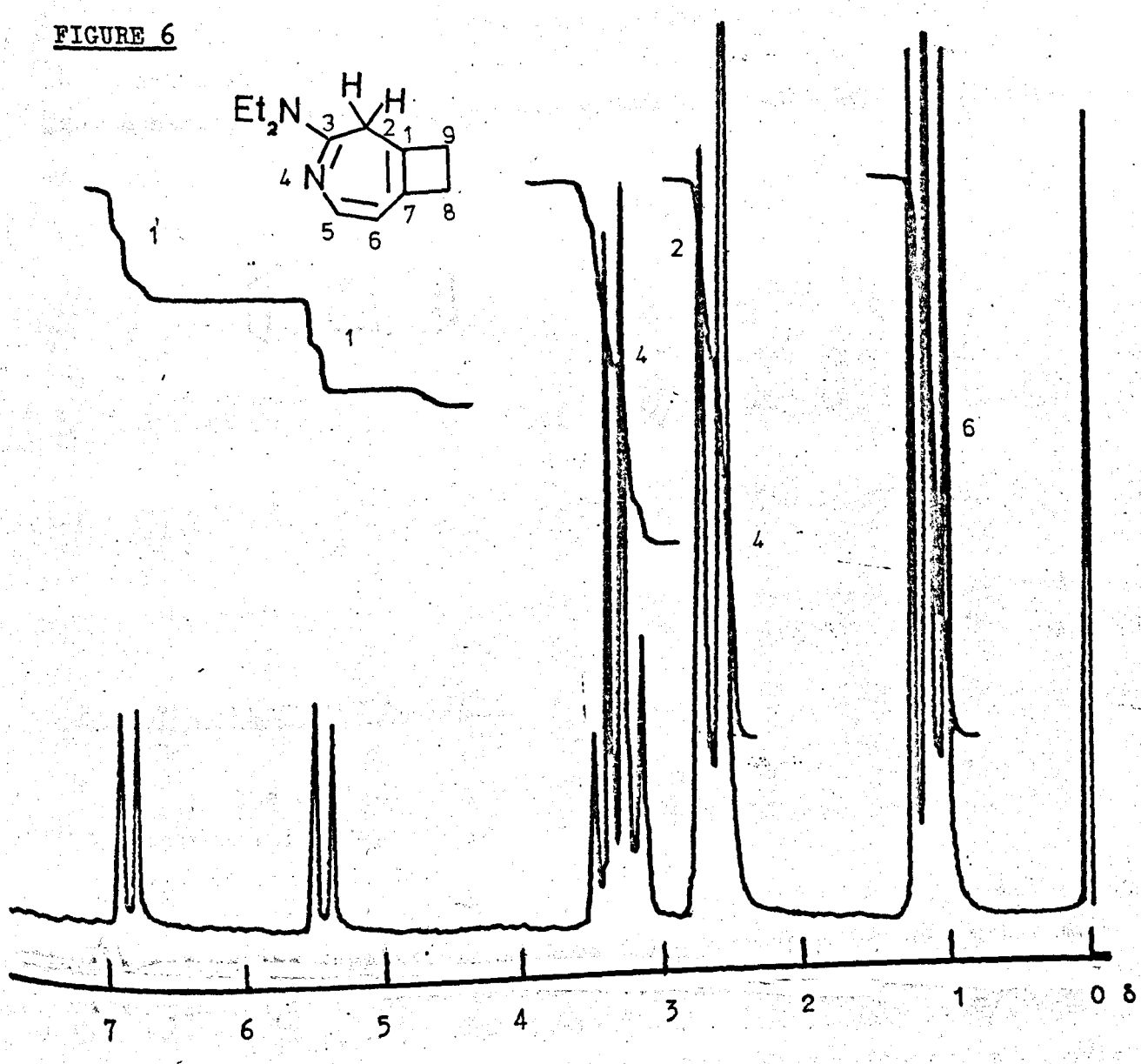
110

The decomposition of 4-azidobenzocyclobutene 92 gave one major product, isolated after chromatography, which had n.m.r. signals (Figure 6) at δ6.75 and 5.36 p.p.m., both doublets (J = 7Hz), and a two-proton singlet at δ2.69 p.p.m. The similarity with the spectrum of the cyclopentazepine 106 was striking and the product was formulated as 3-diethylamino-2H-4-azabicyclo[5,2,0]nona-3,5,7(1)-triene 112.



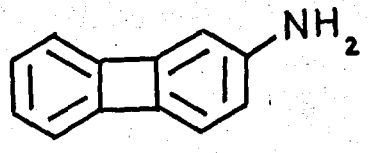
112

FIGURE 6



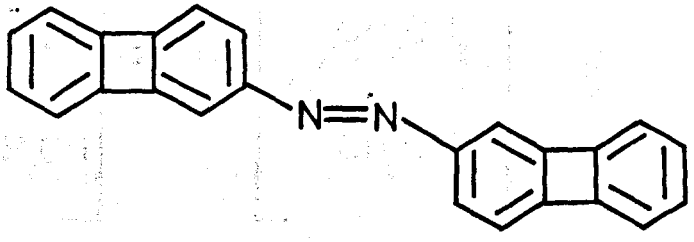
The presence, in trace quantities, of an isomeric azabicyclononatriene was noted in the n.m.r. spectrum of the crude decomposition product. This isomer was not isolated.

The crude product obtained from the decomposition of 2-azidobiphenylene 93 was subjected to preparative layer chromatography. One major and several minor bands were observed. Th major band was removed to yield a compound identified, from literatur data[160], as 2-aminobiphenylene 113.



113

Removal of one of the minor bands yielded a small amount of a coloured material which was identified from its mass spectrum as an azobiphenylene 114. No other products could be identified.



114

MASS SPECTRA OF THE AZEPINES

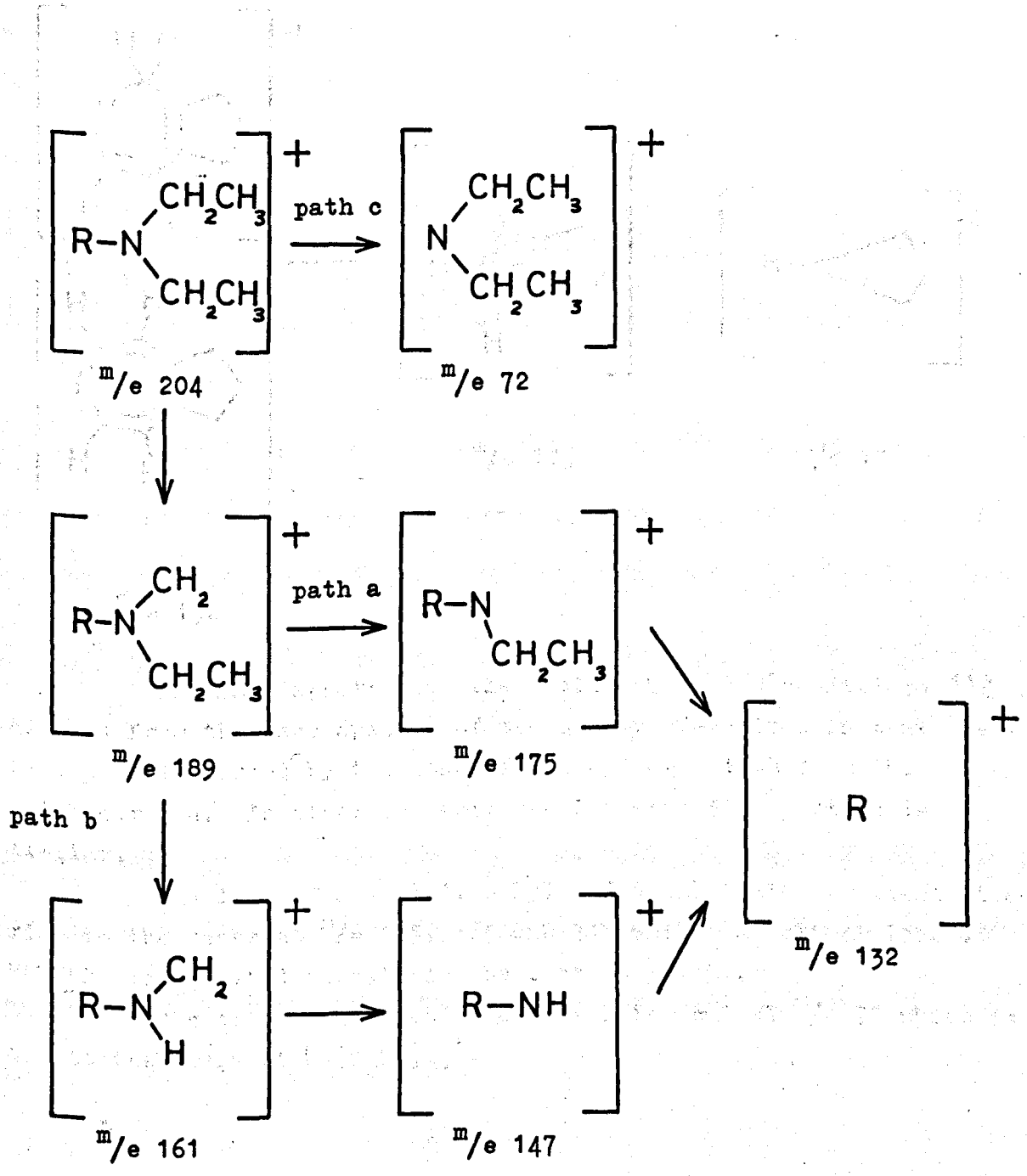
The differences in structure observed for the various cyclopentazepines appear to have little effect upon the mass spectra of the individual compounds. The predominant features are peaks at $^{m}/e$ 204, 189, 175 and 132, which correspond to the molecular ion and to the loss, from the molecular ion, of a methyl, ethyl and diethylamino fragment respectively (Scheme 67, path a).

A minor breakdown pattern, which gives peaks at $^{m}/e$ 161 and 147, could arise by the sequential loss of an ethylene and a methylene fragment from the fragment of $^{m}/e$ 189 (Scheme 67, path b).

The fragmentation of the cyclopentazepine ring system ($^{m}/e$ 132) may proceed by the sequential loss of HCN (27 mass units) and ethylene (28 mass units), since peaks at $^{m}/e$ 105 and 77 are observed (Scheme 68). A similar type of fragmentation of the ion at $^{m}/e$ 147 may have occurred to give peaks at $^{m}/e$ 120 and 91.

The only other significant peak is that at $^{m}/e$ 72 which corresponds to the diethylamino fragment (Scheme 67, path c).

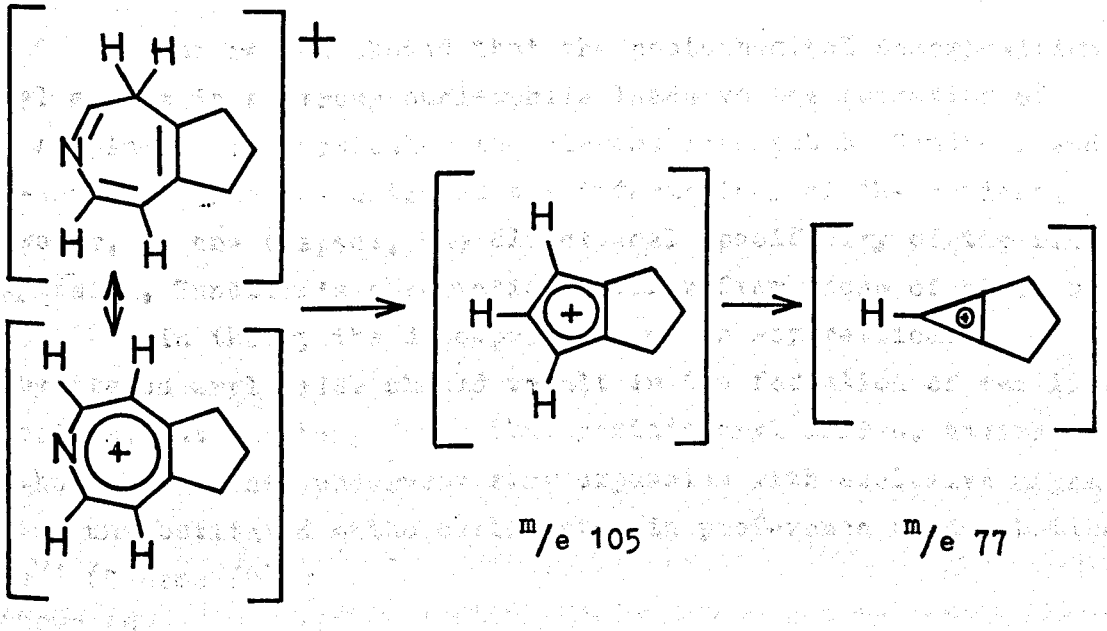
SCHEME 67



Note: Direct loss of C_2H_5 and $N(C_2H_5)_2$, rather than sequential loss will also occur.

R = tetrahydrocyclopentazepine nucleus

SCHEME 68



The mass spectrum of the azabicyclo[5,2,0]nonatriene 112 differs from the mass spectra of the cyclopentazepines in that the base peak is formed by the loss of one hydrogen atom from the molecular ion. In other respects the fragmentation pattern is similar.

The loss of a methyl, ethyl and diethylamino fragment gives rise to the peaks at $^{m}/e$ 175, 161 and 118 whilst a further loss of HCN (27 mass units) results in the peak at $^{m}/e$ 91.

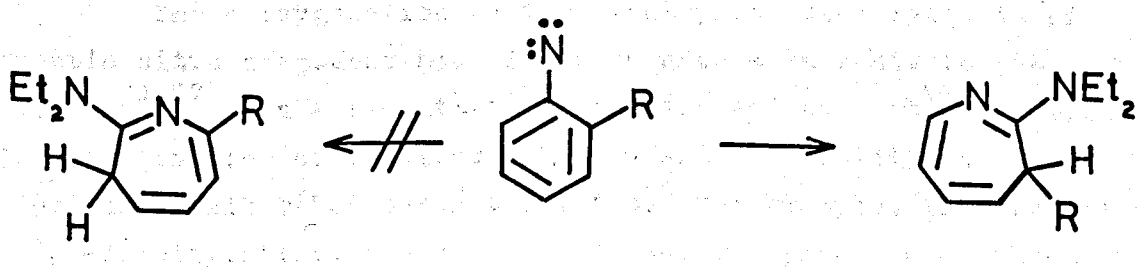
The only other significant peak is that at $^{m}/e$ 72 which is due to the fragment $[N(C_2H_5)_2]^+$.

MECHANISM

The review showed that the photochemical decomposition of aryl azides in a strong nucleophile leads to the formation of 3H-azepines. In particular the elegant research by Sundberg and co-workers[67] has demonstrated the intermediacy of 1H-azepines. However, in one respect, the directional specificity of the ring expansion, Sundberg's observations differ from those of other workers.

In theory the decomposition of an asymmetrically substituted aryl azide should result in the formation of two isomeric azepines, but Sundberg found that certain aryl azides, having only one ortho substituent, underwent ring expansion with exclusive migration of an unsubstituted ortho carbon atom in preference to a substituted one[67] (Scheme 69).

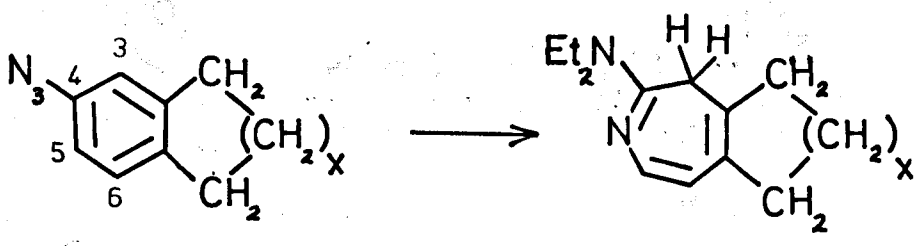
SCHEME 69



Contradictory observations were recorded by Berwick[143] for the decomposition of 2-azidoacetophenone in both methanol and piperidine. Both decompositions gave two isomeric azepine products and in one case, the decomposition in piperidine, the isomeric azepines were obtained in statistical quantities.

Similar results were obtained during the course of this work. The decomposition of 4-azidoindan 90 gave a mixture from which three isomeric tetrahydrocyclopentazepines were obtained. In partial accord with Sundberg's observations insertion had occurred predominantly away from the ortho substituent (80% of azepine formed). Mixtures of isomeric azepines were also obtained from the decomposition of 5-azidoindan 91 and 4-azidobenzocyclobutene 92 and in each case the predominant isomer was the one in which insertion had occurred between C-4 and C-5 (Scheme 70).

SCHEME 70

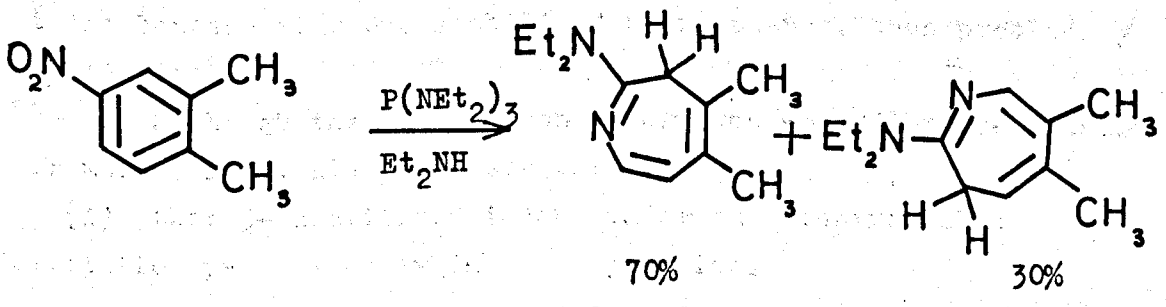


	Yield
x = 1	85%
x = 0	95%

There is a limited knowledge of the factors which govern the directional specificity of the ring insertion. Recent work[27,28] with alkyl azides has indicated that the ground state conformation can be important in determining the migratory aptitudes of groups in the molecule but an attempt to adapt this model to the ring expansion problem met with failure[67].

The deoxygenation by tervalent phosphorus reagents of aromatic nitro compounds has also been used as a route to 3H-azepines[94-97]. In a recent paper Atherton and Lambert[97] described the deoxygenation of a number of mono- and di-substituted nitro-compounds by alkylphosphorus triamides. For example, the reduction of 3,4-dimethylnitrobenzene gave two isomeric products as shown in Scheme 71.

SCHEME 71

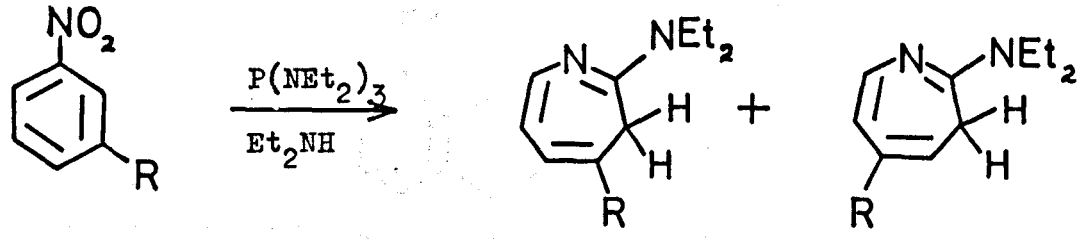


70% 30%

Total yield of azepine = 31%

The reduction of a range of meta-substituted nitro-compounds, which gave the results shown in Scheme 72, led Atherton and Lambert to suggest that electron withdrawing groups in the meta position favoured the production of 6-substituted-3H-azepines and that electron releasing groups, in the same position, favoured the formation of the 4-substituted isomer (Scheme 72).

SCHEME 72

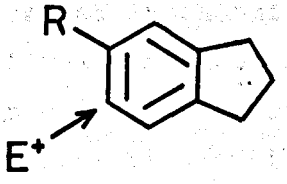


R	4-Isomer	6-Isomer
Cl	5%	28%
Ph	18%	31%
4-pyridyl	19%	30%
CH_3	28%	19%

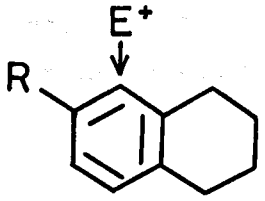
One factor which might have governed the isomer distribution of the azepines derived from 5-azidoindan and 4-azidobenzocyclobutene is the strain effect of the fused ring. An extensive study of the reactivity of aryl positions α and β to a fused strained ring has been made during the last 45 years. Most of the work on tetralin and indan has been directed towards supporting or disproving the possibility of bond fixation in the aromatic part of the molecule. This idea was first postulated in 1930 by Mills and Nixon[161] and disproved soon afterwards by Kistiakowsky[162] whose work on the heats of hydrogenation of alkyl benzene derivatives showed that the benzene ring was stabilised by resonance, thus precluding any bond fixation.

Although the Mills-Nixon theory was soon disproved their observations still stand. These were:

(i) that 5-substituted indans underwent electrophilic substitution predominantly in the 6-position.

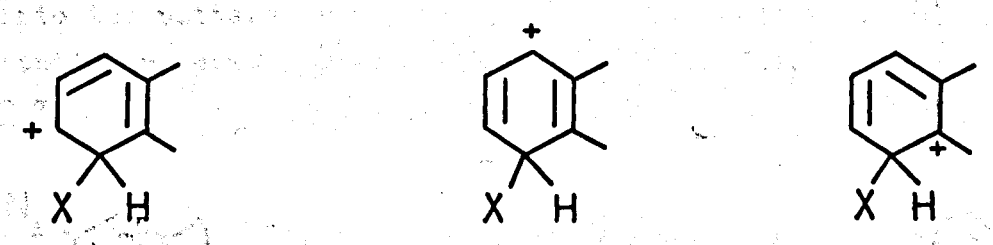


(ii) that 6-substituted tetralins underwent electrophilic substitution predominantly in the 5-position.

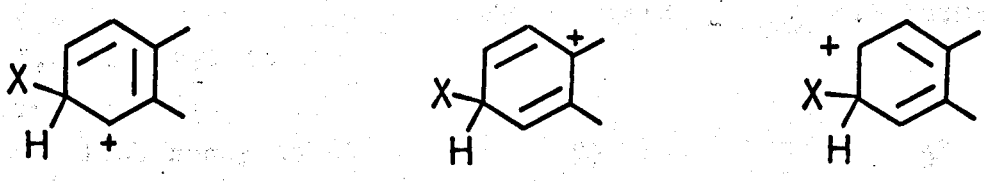


A recent paper[163] concludes that both strain and hybridisation effects co-operate to determine reactivities in aryl groups bearing fused strained rings. Vaughan, Welch and Wright[151] have shown that in electrophilic reactions the ratio of α to β substitution decreases in the order; indan, o-xylene, tetralin. In explanation of this they pointed out that in the Wheland intermediates for α and β substitution, the bond common to both rings has $^2/_3$ and $^1/_3$ double bond character respectively (Scheme 73).

SCHEME 73



α - substitution



β - substitution

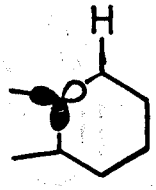
In the case of indan this will lead to increased strain in the fused ring for α- and decreased strain for the β-substitution and thus the latter will be favoured. In tetralin, any strain will be increased in the formation of the transition state for α-substitution and decreased in the case of β-substitution so that the latter will be favoured. The corresponding but much larger

effect would also account for the almost complete β-orientation observed with benzocyclobutene[154,164].

A different explanation of the observed reactivity has been advanced by Streitweiser and co-workers[165]. They postulated that the atomic orbitals of a fused-ring aryl carbon atom used to construct the strained ring have higher p character than usual so that the remaining orbital used in bonding to the adjacent aryl carbon atom has more s character. The α carbon is thus bound to an orbital of higher electronegativity than usual and the consequent electron withdrawal from this carbon atom will lower the reactivity towards electrophiles.

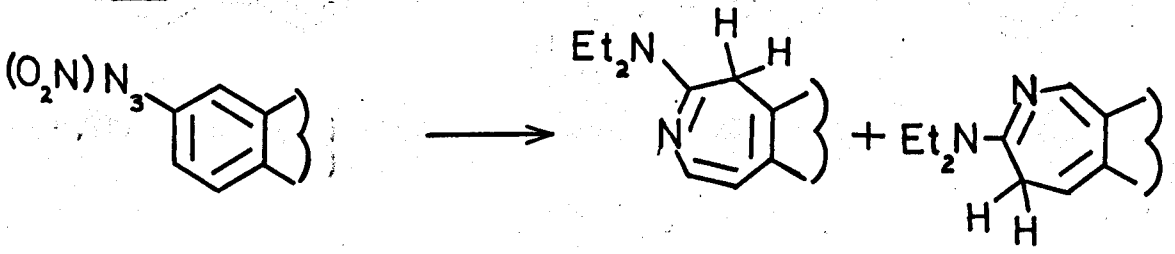
● increased p character

o increased s character



The observed ratios of the isomeric azepines obtained from 3,4-dimethylnitrobenzene, 5-azidoindan and 4-azidobenzocyclobutene fall into the pattern previously set by the electrophilic substitution reactions discussed above (Scheme 74).

SCHEME 74



	4,5-Isomer	5,6-Isomer
3,4-dimethylnitrobenzene	70	30
5-azidoindan	85	15
4-azidobenzocyclobutene	95	5

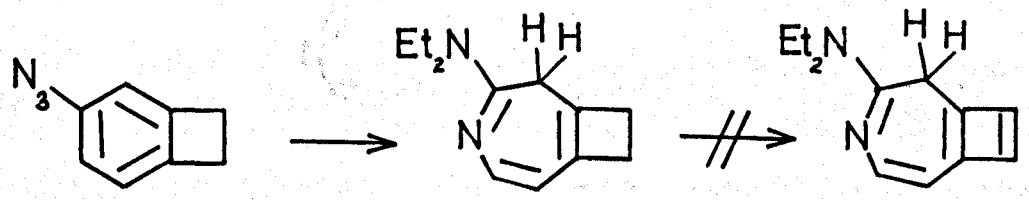
It thus appears that the nitrene is acting as an electrophile and that the strain effects implicit in the fusion of a cycloalkane ring to the aromatic ring are affecting the isomer distribution.

The previous discussion suggests that the decomposition of 6-azidotetralin would give two isomeric azepines with the 5,6-isomer as the major product.

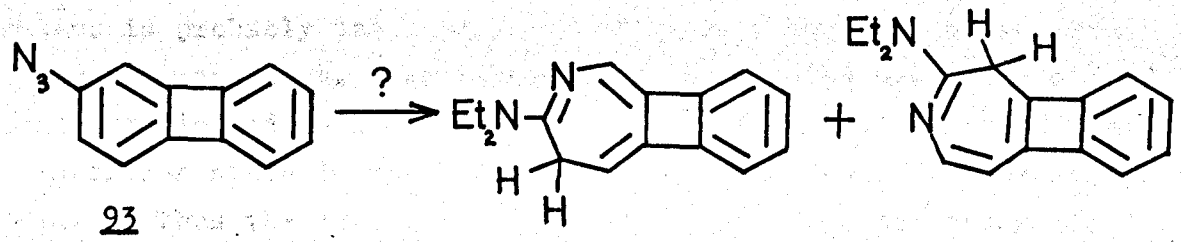
Further work in this field could be directed towards proving this hypothesis and making a thorough study of this area of nitrene chemistry.

It was hoped that the decomposition of 2-azidobiphenylene 93 would give ring expanded products analogous to those obtained from the decomposition of 4-azidobenzocyclobutene. These products would have the extra degree of unsaturation that could not be introduced into the azabicyclo[5,2,0]nonatriene 112 (Scheme 75).

SCHEME 75



112

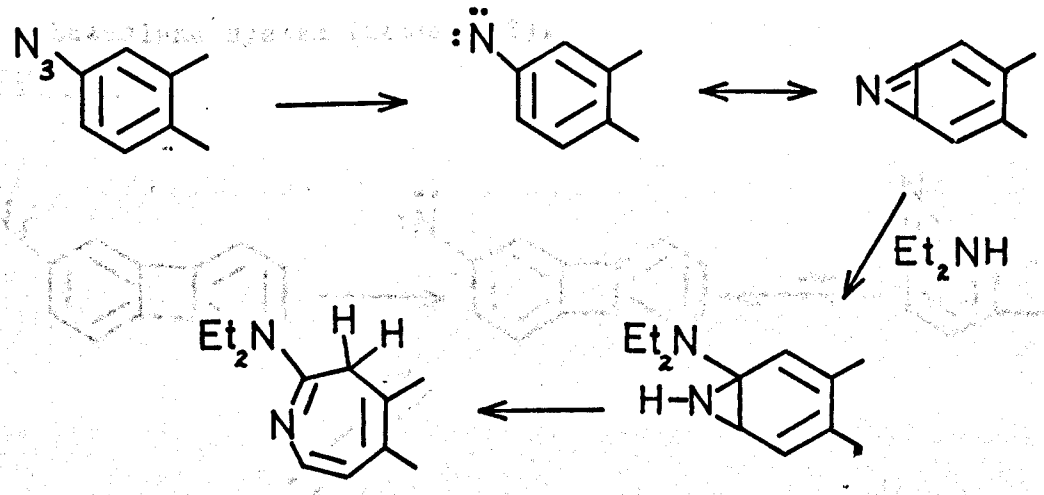


93

The decomposition gave no ring expanded products, only a moderate yield of the hydrogen abstraction product 2-aminobiphenylene. In this, biphenylene is following the pattern set by other polycyclic aromatic systems. The naphthyl azides[59,61] and 4- and 5-azidobenzo-[b]thiophen[137], under the same conditions, do not decompose to give azepine products and no ring expanded products are observed in the reaction between ethoxycarbonylnitrene and naphthalene, anthracene and pyrene[73].

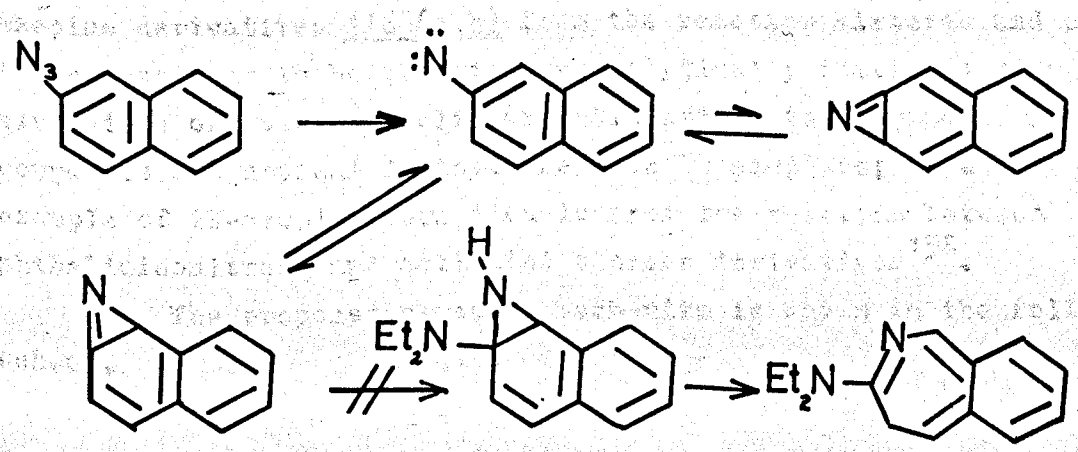
The mechanism of azepine formation was discussed in the Review. Briefly, the aziridine intermediate which arises from the singlet nitrene undergoes addition of diethylamine and ring opening (Scheme 76).

SCHEME 76



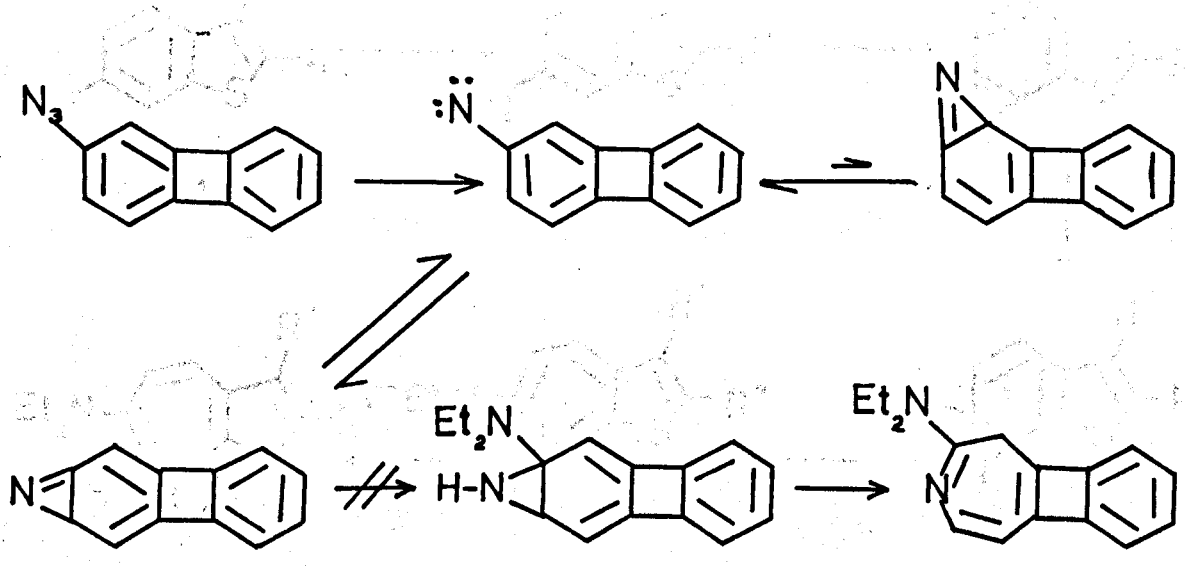
The barrier to ring expansion in the polycyclic aromatic systems is probably the loss of aromaticity which must be incurred during the expansion. For example, the postulated mechanism of the transformation of 2-azidonaphthalene to a benzazepine must include a transition state in which all of the naphthalene resonance energy is lost. Thus the reaction does not proceed and other processes occur which give rise to the observed products (Scheme 77).

SCHEME 77



A similar type of energy barrier is probably operating to divert 2-nitrenobiphenylene from undergoing the insertion reaction. In this case however the strain effects could be due to the formation of a butadiene system (Scheme 78).

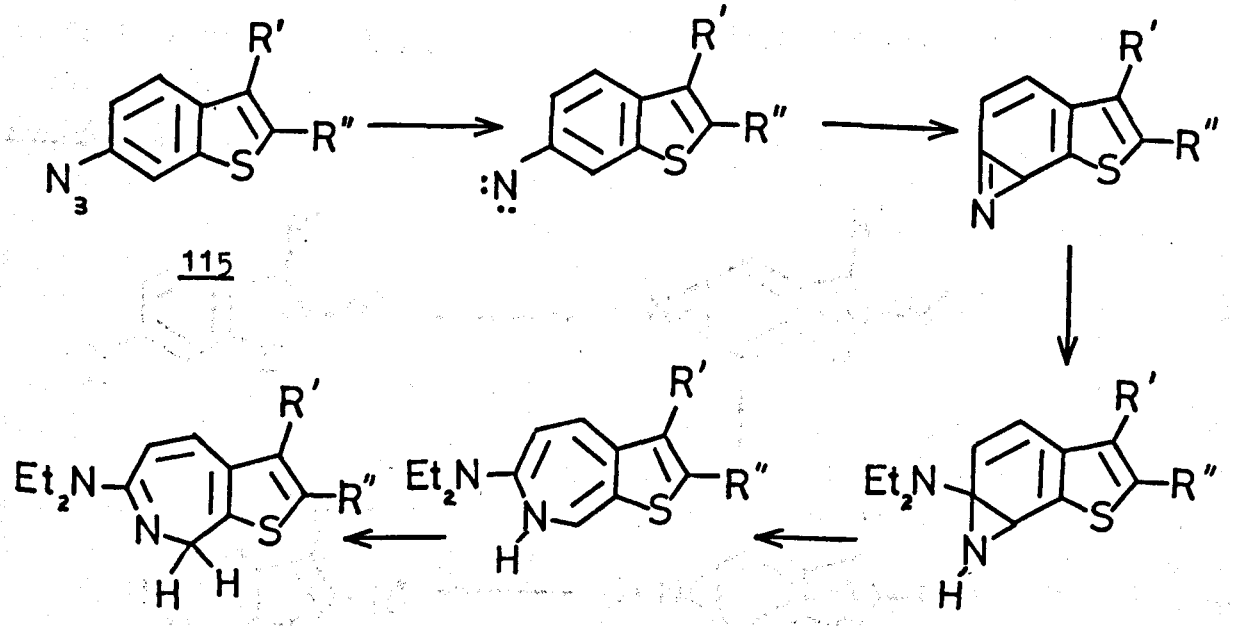
SCHEME 78



A communication by Iddon, Pickering and Suschitzky[166] on the photolytic decomposition of certain 6-azido[b]thiophens 115 (a,b) in diethylamine has recently been published. In this paper the authors report the isolation of 6-diethylamino-8H-thieno[2,3-c]-azepine derivatives 116 (a,b) from the reaction mixtures and claim these reactions to be the first photolytically initiated ring expansions of fused bicyclic aromatic azides to azepines. These compounds are unusual in that they are 2H azepines; the only other example of 2H-azepine formation is from the reaction between phthalimidonitrene and activated benzene derivatives[158].

The proposed reaction mechanism is shown in the following scheme.

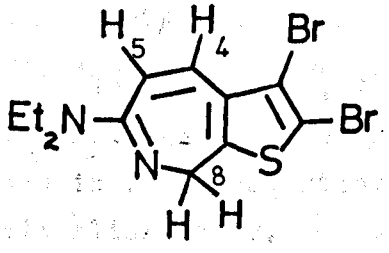
SCHEME 79



115

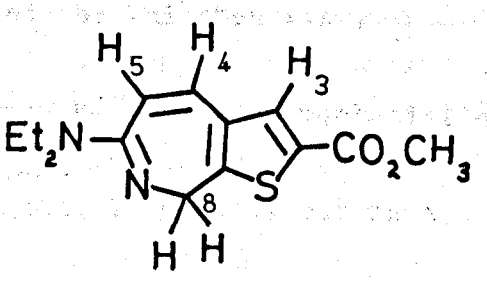
116

The thieno-azepines 116a and 116b have the following n.m.r. data:



116a

H_4 }	δ 6.69 }	J = 12Hz
H_5 }	δ 7.11 }	
H_8	δ 4.20	

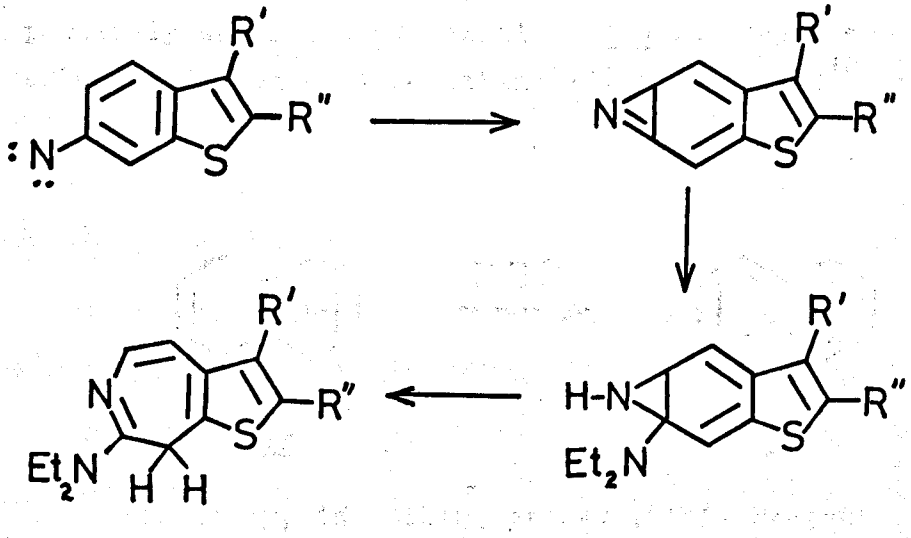


116b

H_3	δ 7.70	
H_4 }	δ 6.60 }	J = 12Hz
H_5 }	δ 7.18 }	
H_8	δ 4.25	

The chemical shifts recorded for the protons H-4 and H-5 seem high for an alkene system isolated from the conjugated nitrogen function and are more in accord with the partial structure = N - CH = CH -. An alternative mechanism to that shown in Scheme 79 leads to a molecule 117 (a,b) containing this partial structure (Scheme 80).

SCHEME 80



117

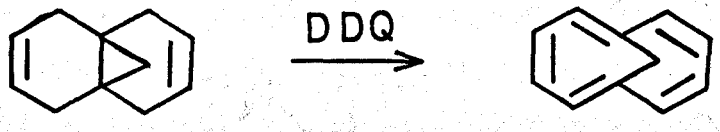
The down-field position of the azepine methylene signal which, it was inferred, was due to the proximity of the methylene group to the ring nitrogen atom, could also be due to the combined effects of the diethylamino group and the thiophen ring.

In conclusion, though it may be argued on mechanistic grounds that the proposed structure 116 is correct, the available evidence is such that structure 117 cannot be ruled out as a possible alternative.

ATTEMPTS TO PREPARE AZEPINIUM SALTS AND AZA-AZULENES FROM THE AZEPINES

The formation of an aza-azulene from the tetrahydrocyclopentazepine system requires the removal of two molecules of hydrogen. A reagent which has been used for the introduction of unsaturation, is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). For example, the partially saturated [10]annulene 118 was dehydrogenated by DDQ in refluxing dioxan to 1,6-methano[10]annulene 119[167] (Scheme 81).

SCHEME 81



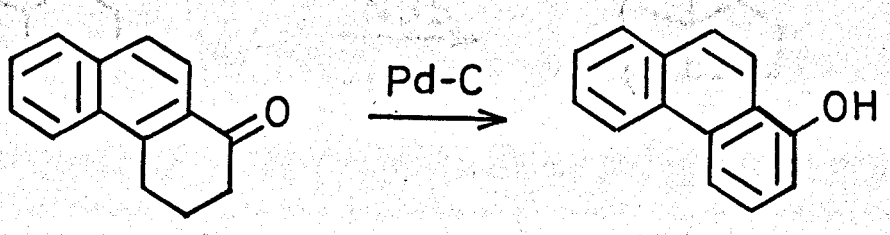
118 119

Similarly, in boiling benzene, this reagent converts tetralin into naphthalene and acenaphthene into acenaphthylene[168].

Accordingly, cyclopent[d]azepine 106 was reacted with DDQ in boiling benzene. Removal of the solvent gave a black tar which resisted attempts at purification and identification. No starting material was recovered.

Dehydrogenation of hydro-aromatic compounds has also been achieved using palladium-on-charcoal. Tetralin and decalin have been dehydrogenated to naphthalene[169] and octahydrophenanthrene and octahydroanthracene gave the aromatic compounds on similar treatment[169]. The hydro-aromatic ketone 120 gave 1-phenanthrol 121 in naphthalene containing the palladium catalyst[170] (Scheme 82).

SCHEME 82



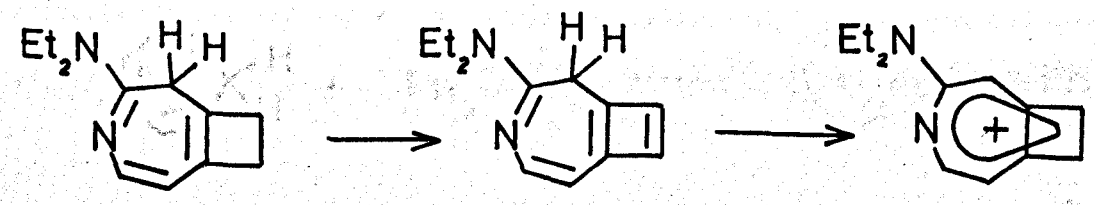
120 121

Treatment of the cyclopent[d]azepine 106 with 10% palladium-on-charcoal in a sealed tube at 250° gave a green oil which did not have analytical figures consistent with 2-diethylaminocyclopent[d]azepine, the expected product. Examination of the n.m.r. spectrum showed the presence of aliphatic protons only.

Because of the limited quantities of the available tetrahydrocyclopentazepine no further experiments were tried.

Attempts were also made to dehydrogenate the azabicyclo-[5,2,0]nonatriene 112. It was hoped that removal of a molecule of hydrogen, to give the tetra-ene 122, could be induced and that the further loss of a hydride ion could also be achieved (Scheme 83).

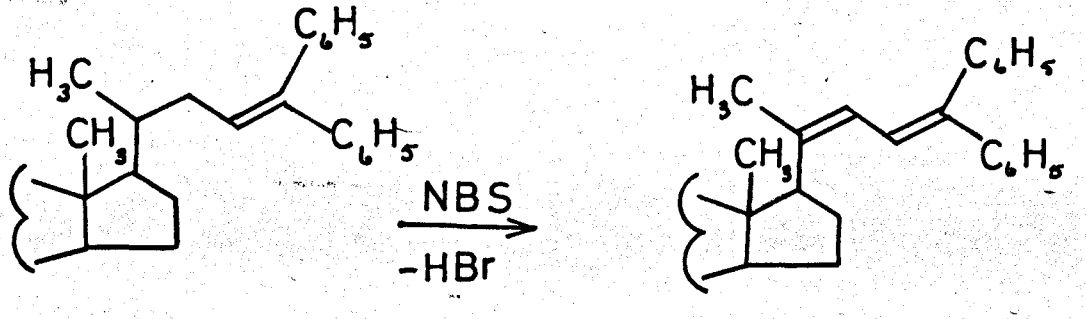
SCHEME 83



112 122

A reagent which has been used to effect double-bond formation is N-bromosuccinimide (NBS). This dehydrogenation is achieved by allylic bromination followed by loss of hydrogen bromide, as for example, in the production of cortisone[171] (Scheme 84).

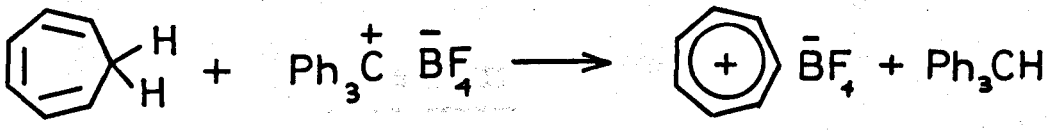
SCHEME 84



The reaction of the azabicyclononatriene with NBS as described by the above author[171,172] gave, instead of a white precipitate of succinimide, a brown, intractable tar which could not be identified. Examination of the liquor revealed the absence of both starting material and the expected product.

The formation of the azepinium system requires the removal of a hydride ion and a reagent which has been used for this purpose is triphenylmethyl fluoroborate. Dauben and co-workers[173] have prepared a tropylium salt by reaction of cycloheptatriene with triphenylmethyl fluoroborate in solution in acetonitrile at -20° (Scheme 85).

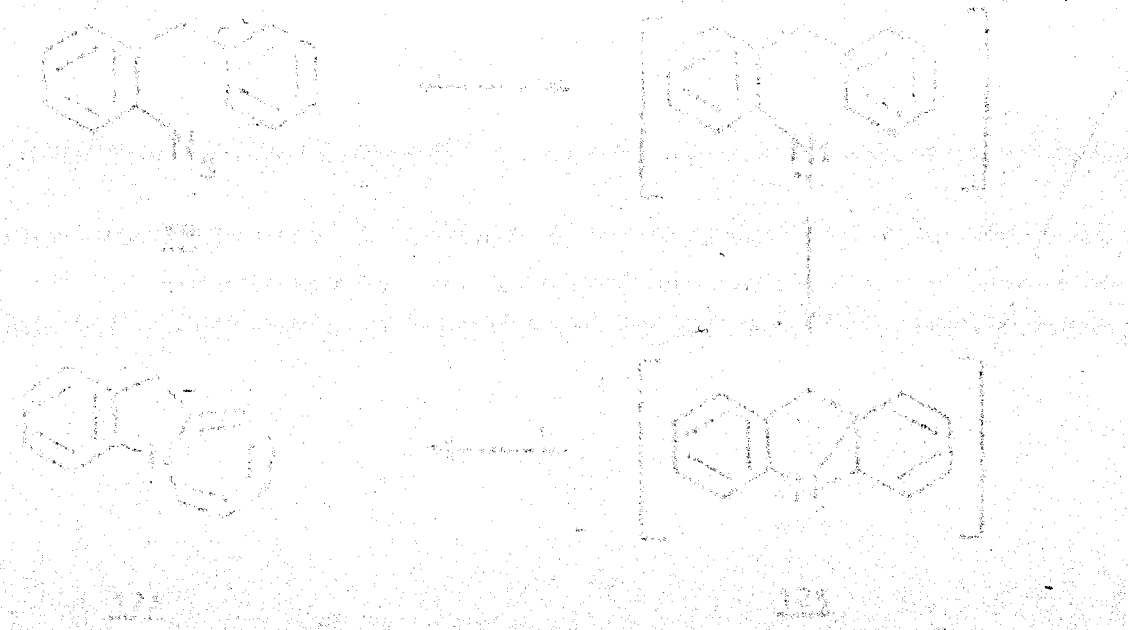
SCHEME 85



The reaction between the azabicyclononatriene 112 and triphenylmethyl fluoroborate under the conditions described by Dauben[174] did not give an azepinium salt. Instead only tarry products were obtained. These could have been formed by the polymerisation of a reactive intermediate which, in view of the instability of related systems[130-134], would not be unexpected.

No further attempts were made to dehydrogenate this compound.

P A R T II

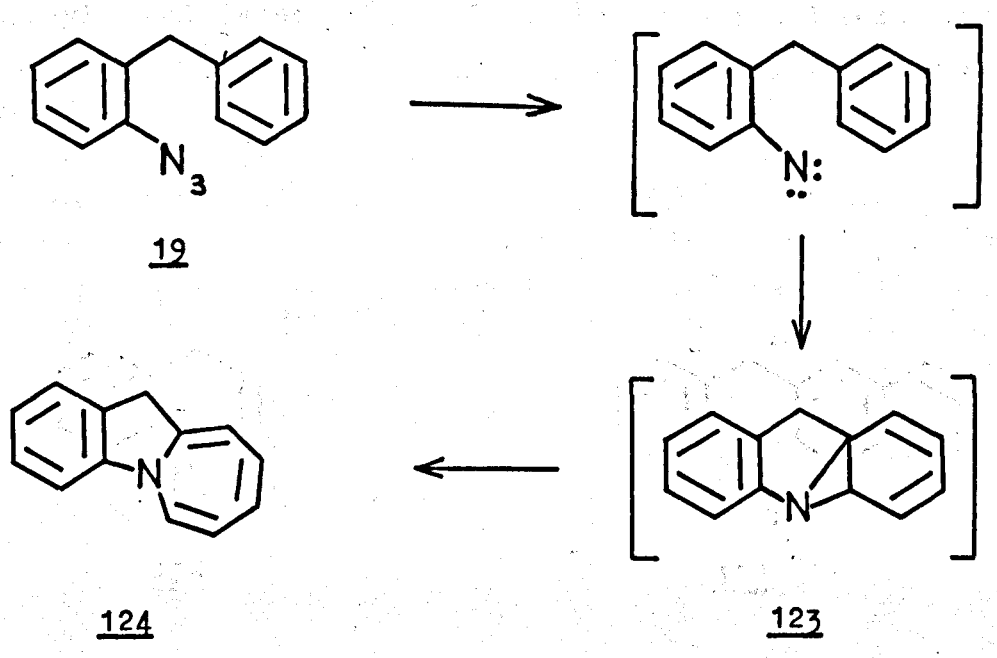


INTRODUCTION

The failure of 2-azidobiphenylene 93 and other polycyclic aromatic azides to undergo ring expansion to azepine derivatives upon decomposition[59,61,137] prompted a study into the effect of annelation* upon the mode of the nitrene insertion reactions.

The system chosen for this study was 2-azidodiphenylmethane 19. The thermal decomposition of this compound was first reported in 1968 by Krbechek and Takimoto[51] who proposed the structure 11H-azepino[1,2-a]indole 124 for the major product. The decomposition was thought to proceed by the attack of a nitrene intermediate on the adjacent aromatic ring giving an azabicycloheptadiene intermediate 123 which underwent ring expansion to the azepine (Scheme 86).

SCHEME 86

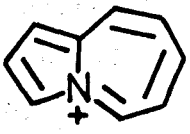


19 124 123

* as used by Clar[175] to indicate the enlargement of an aromatic system by the fusion of a benzene ring.

Jones and co-workers[52-54], in the course of their studies of the azonia-azulenium system 125, re-examined this decomposition and amended the structure of the isolated product to the isomeric 10H-azepino[1,2-a]indole 21 on n.m.r. evidence.

Several substituted 2-azidodiphenylmethanes have since been prepared and decomposed[53]. The usual products were 10H-azepino[1,2-a]indoles and 6H- or 8H-tautomers. In azides having a 2'-methoxyl group, appreciable quantities of 9,10-dihydroacridines and acridines were isolated[54].



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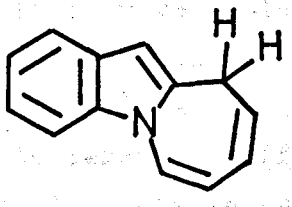
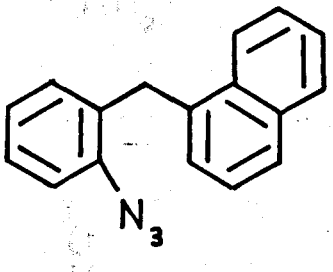
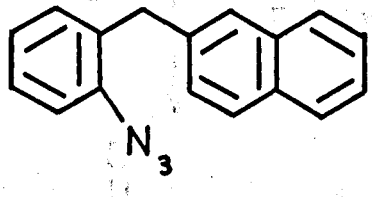


21

In order to study the effect of annelation upon the mode of the nitrene insertion reaction it was decided to investigate the decomposition of the simplest annelated systems derived from 19, the azidobenzylnaphthalenes 126 and 127. To provide a direct comparison the non-annelated systems 128 and 129 were also synthesised and decomposed.



126



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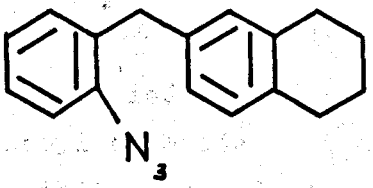
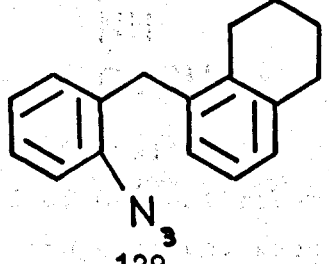


128



129

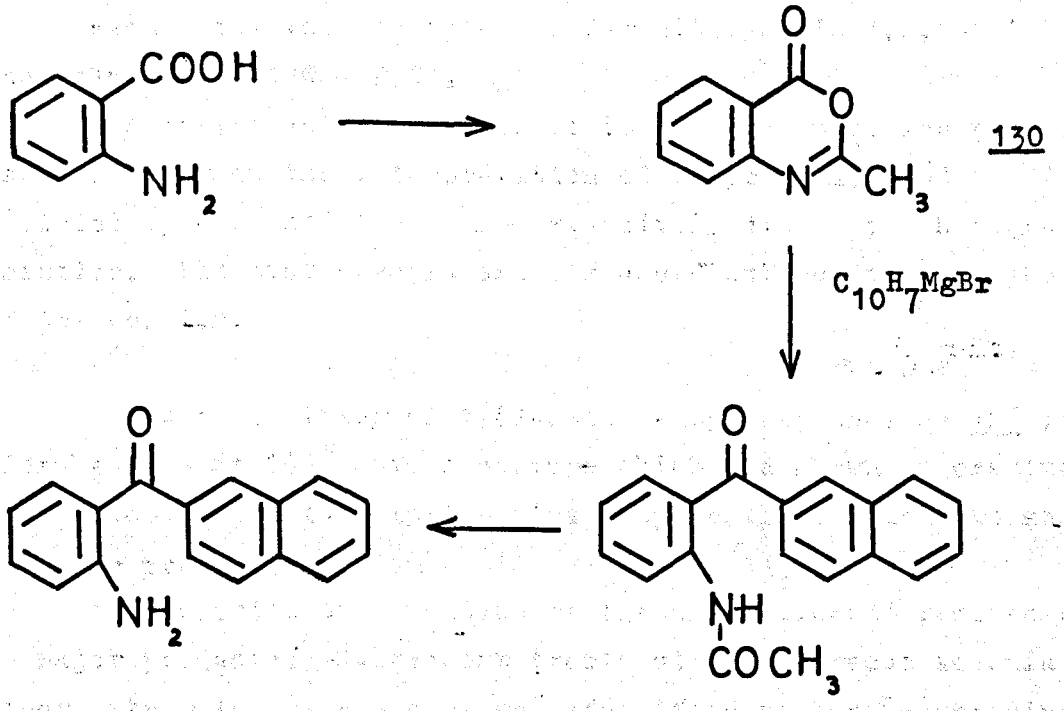
DISCUSSION

PREPARATION OF THE AZIDES

The azidobenzylnaphthalenes and tetralins 126 - 129 were prepared from the aminobenzoyl derivatives by reduction of the carbonyl group followed by conversion of the amine to the azide.

The known aminobenzoylnaphthalenes were isolated from the reaction between 2-methyl-3,1-benzoxazin-4-one (acetanthranil) 130 and the naphthyl Grignard reagents (Scheme 87), a synthesis first employed by Lothrop and Goodwin[176]. This reaction suffers from the reported disadvantage that acetanthranil is unstable and only moderate yields of ketone are obtained but during this work it has been found that distillation of the acetanthranil, prior to use, results in higher yields. The preparation of 5-(2-aminobenzoyl)-tetralin was achieved in a similar manner from 5-bromotetralin[177].

SCHEME 87



The Friedel-Crafts aroylation of tetralin with 2-nitrobenzoyl chloride gave a poor yield of 6-(2-nitrobenzoyl)-tetralin; this compound, on catalytic hydrogenation, gave 6-(2-aminobenzoyl)tetralin.

A simple method of reducing benzophenones to diphenylmethanes is by dissolving sodium in ethanol[178], but this method could not be used because of the ease with which the reagent reduces naphthalene to 1,4-dihydronaphthalene. Of the other methods available for the reduction of ketones to methylene groups[172,179] the Wolff-Kishner/Huang-Minlon reduction[180] seemed the most promising.

Initial attempts at the reduction of 1-(2-aminobenzoyl)-naphthalene gave low yields of 1-(2-aminobenzyl)naphthalene and a high recovery of starting material. Examination of the reaction by gas chromatography revealed that hydrazone formation was extremely slow but when complete high yields (90% +) of the product could be obtained.

All the amines were converted into the corresponding azides by diazotisation in a mixture of 4N-sulphuric acid and 1,4-dioxan and the reaction of the diazonium salt with sodium azide.

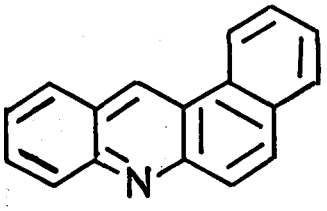
DECOMPOSITION OF THE AZIDES

Each azide was decomposed under nitrogen in 1,2,4-trichlorobenzene solution at 180 - 200°.

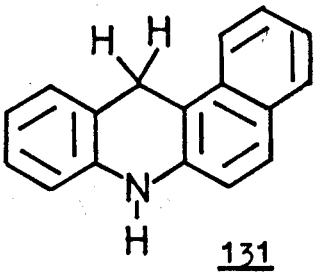
The assignment of structures to the decomposition products was based largely on the interpretation of their n.m.r. and ultra-violet spectra and these are extensively discussed throughout this section. The mass spectra are discussed collectively at the end of the section.

The decomposition of 1-(2-azidobenzyl)naphthalene 126 in trichlorobenzene at 195° gave a mixture which was shown on examination by gas chromatography to comprise five components of which two made up the major proportion.

Acid washing of a portion of the crude product removed one of the major products. Subsequent treatment with aqueous ammonia and ether extraction gave a compound identified as benz[a]acridine 130 from literature data[181]. The other major product was isolated from the residue and identified as 7,12-dihydrobenz[a]acridine 131[182].

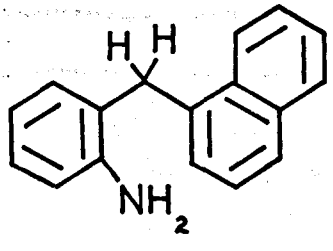


130



131

An initial separation of the decomposition products was obtained by column chromatography. Further separation was achieved by preparative layer chromatography and samples of each of the minor products were isolated. These were identified as 1-(2-aminobenzyl)-naphthalene 132 and two isomers of molecular formula $C_{17}H_{13}N$. On the basis of their n.m.r., mass and ultra-violet spectra these isomers were assigned the structures: 7H-indolo[1,2-a][1]benzazepine 133 and 7H-indolo[2,1-a][2]benzazepine 134.



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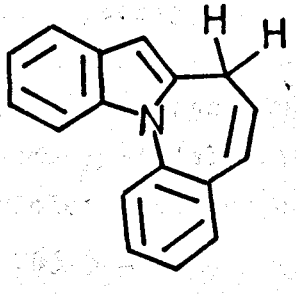
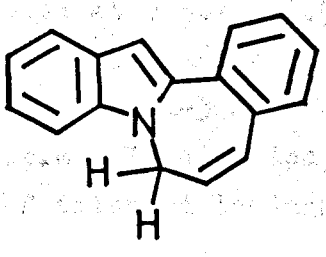
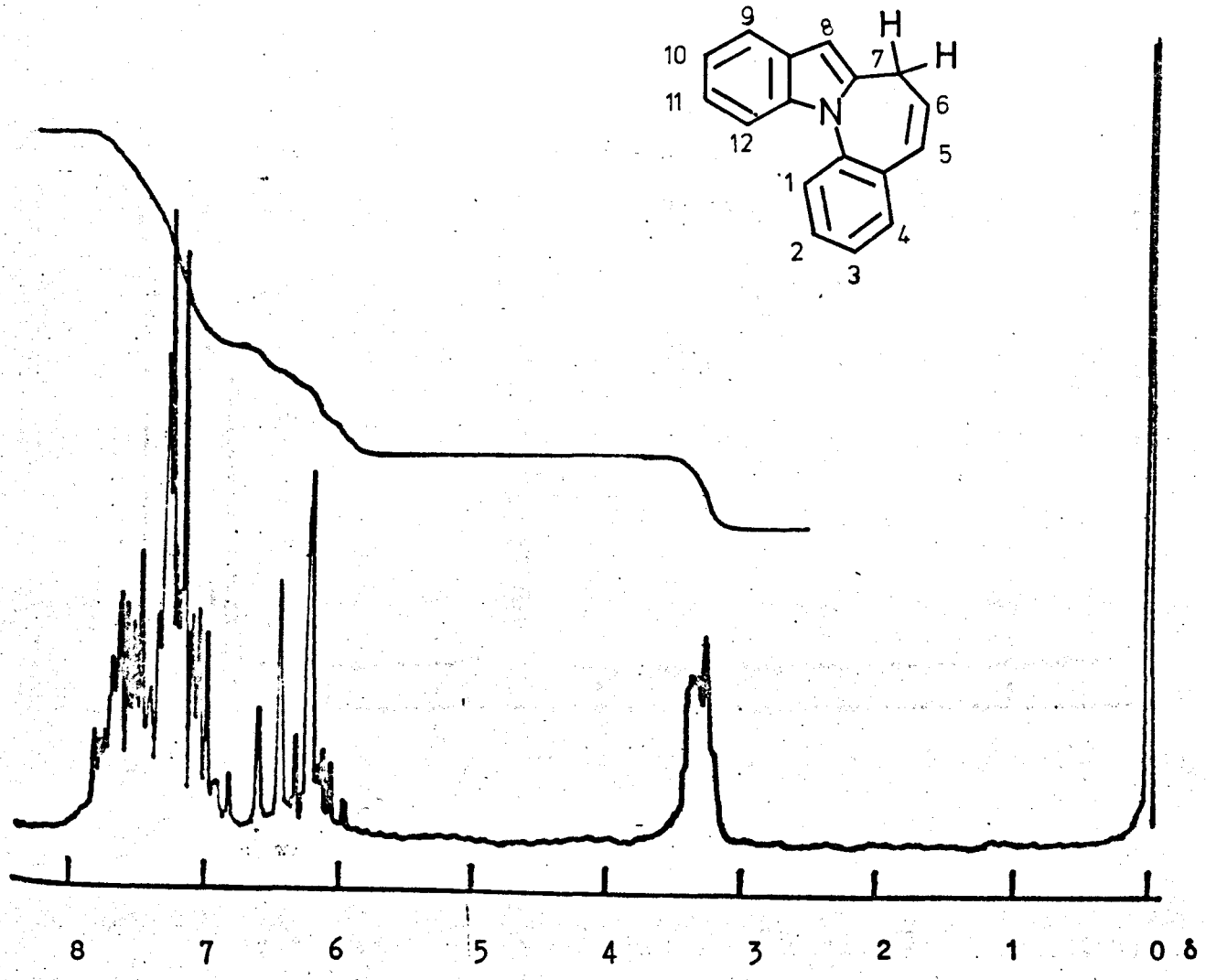


133



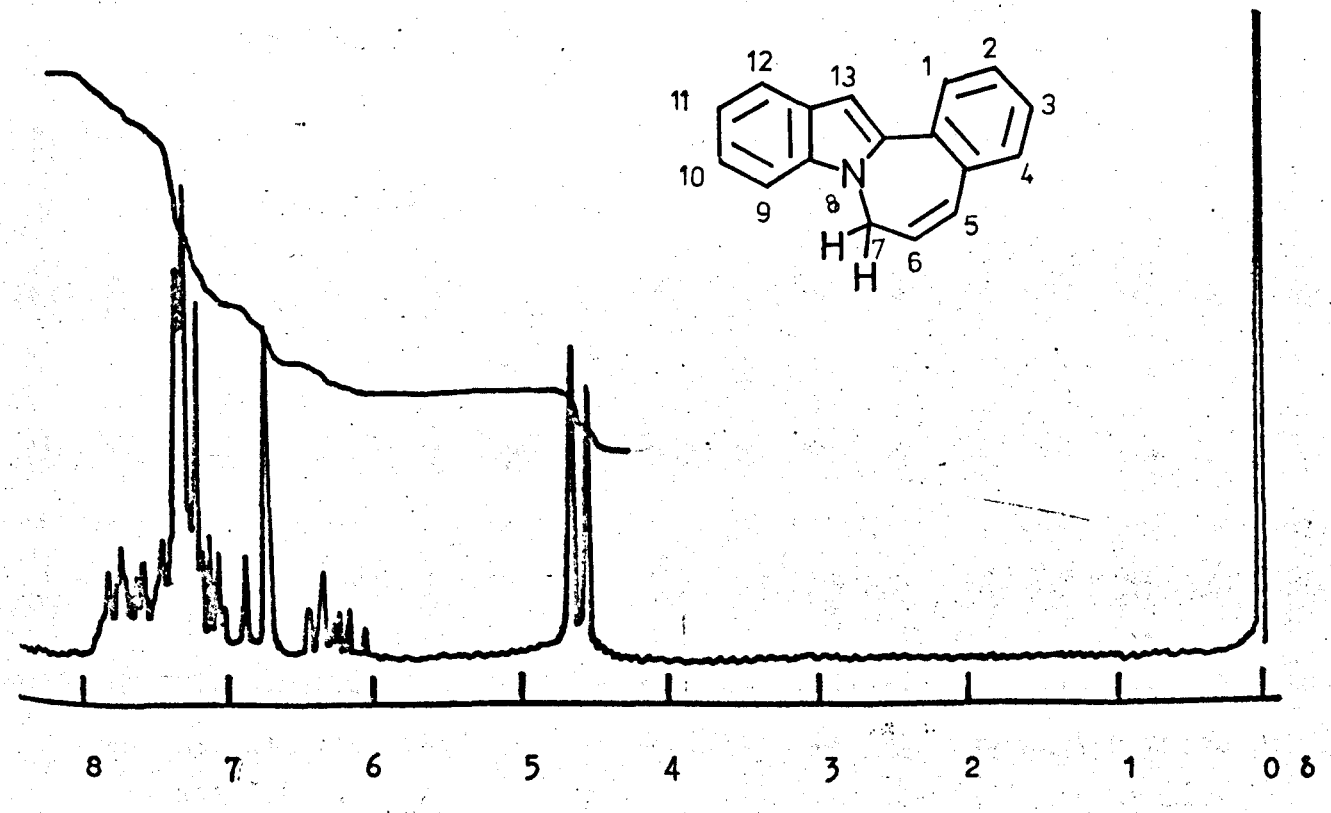
134

FIGURE 7



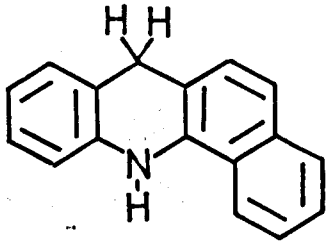
In the former, for which 10H-azepino[1,2-a]indole 21[53] provides an adequate comparison, the n.m.r. spectrum (Figure 7) contains a poorly resolved methylene doublet at δ 3.2 - 3.5, two one-proton signals at δ 6.54 (doublet J = 10.5Hz) and δ 5.9 - 6.4 p.p.m. corresponding to the olefinic protons H-5 and H-6 and a one-proton β-indole singlet at δ 6.21 p.p.m. In addition, the ultra-violet spectrum shows the absence of extended conjugation (λ_{max} 263.5 nm).

FIGURE 8

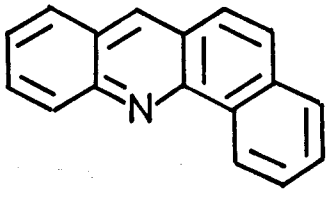


In the latter, the extended conjugation (λ_{max} 275.5, 312nm) and the n.m.r. spectrum (Figure 8) which contains a methylene doublet (J = 6.5Hz) at δ 4.58 p.p.m., two olefinic one-proton signals at δ 6.8 (doublet J = 10.5Hz, H-5) and δ 6.0 - 6.5 (H-6) and a one-proton β-indole singlet at δ 6.71 p.p.m., can be compared with the spectra of 6,8,10-trimethyl-6H-azepino[1,2-a]indole[53].

Decomposition of the isomeric 2-(2-azidobenzyl)naphthalene 127 at 180° gave a red oil which consisted of one major and two minor components. Trituration of the crude product with ethanol precipitated 7,12-dihydrobenz[c]acridine 135 identified from literature data[181]. The residue was separated by column chromatography and the remaining components identified as benz[c]acridine 136[181] and 2-(2-aminobenzyl)naphthalene 137.



135



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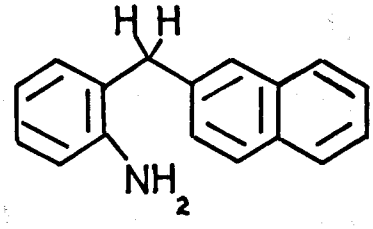
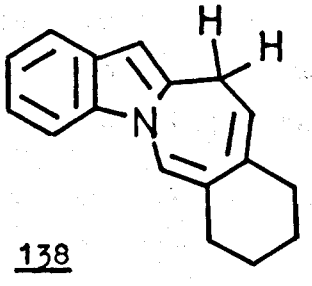


137

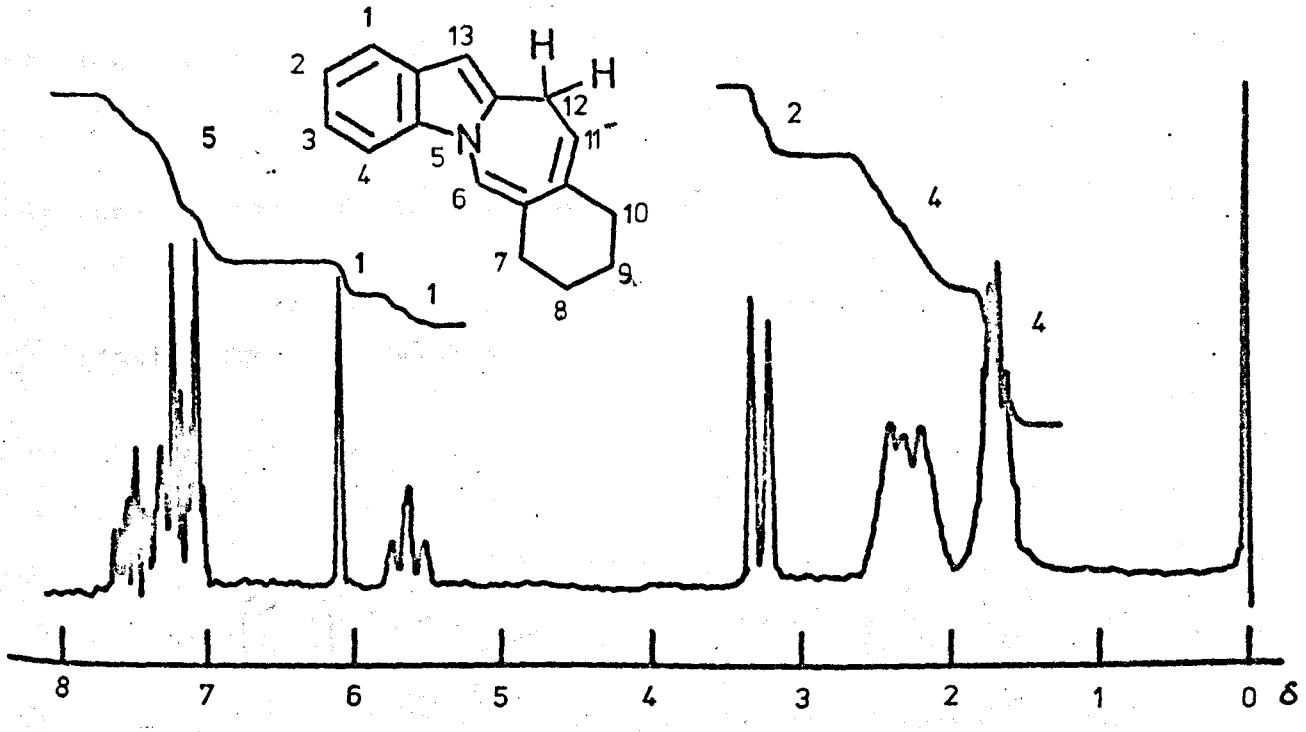
Whereas the thermolysis of the azidobenzylnaphthalenes gave predominantly acridine and dihydroacridine products the decomposition of 6-(2-azidobenzyl)tetralin 128 gave as the major product 7,8,9,10-tetrahydro-12H-indolo[1,2-b][2]benzazepine 138.



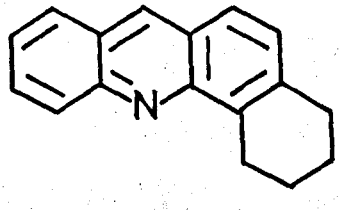
138

The ultra-violet spectrum of the compound showed the absence of extended conjugation (λ_{max} 270 nm) and the n.m.r. spectrum (Figure 9) showed a β-indole singlet at δ 6.07, a broadened methylene doublet at δ 3.26 (J = 7Hz) and a one-proton triplet at δ 5.63 p.p.m. (H-11); all spectral data agree well with those of the 10H-azepinoindoles[53].

FIGURE 9



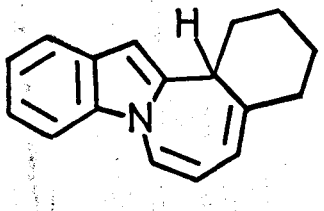
A number of minor products were also formed during the decomposition but only one was isolated and identified. From the characteristic ultra-violet absorption and the n.m.r. spectrum this product was identified as 1,2,3,4-tetrahydrobenz[c]acridine 139.



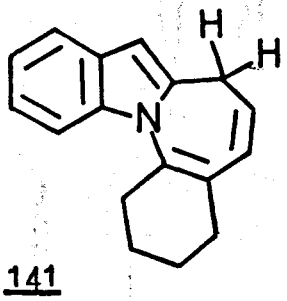
139

The decomposition of 5-(2-azidobenzyl)tetralin 129 in 1,2,4-trichlorobenzene at 183° gave a product mixture which, on examination by gas chromatography and thin-layer chromatography, appeared to contain at least eight components. Partial separation of the mixture was achieved by column chromatography on alumina. Each fraction was then separated by preparative layer chromatography until pure samples of five products were isolated and characterised.

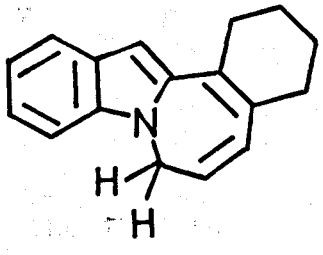
The isolated products are recorded below in order of elution from the column.



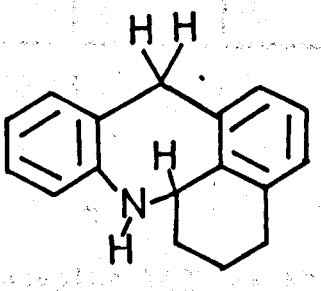
140



141



142



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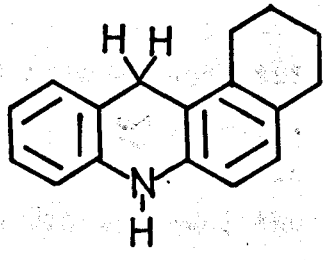
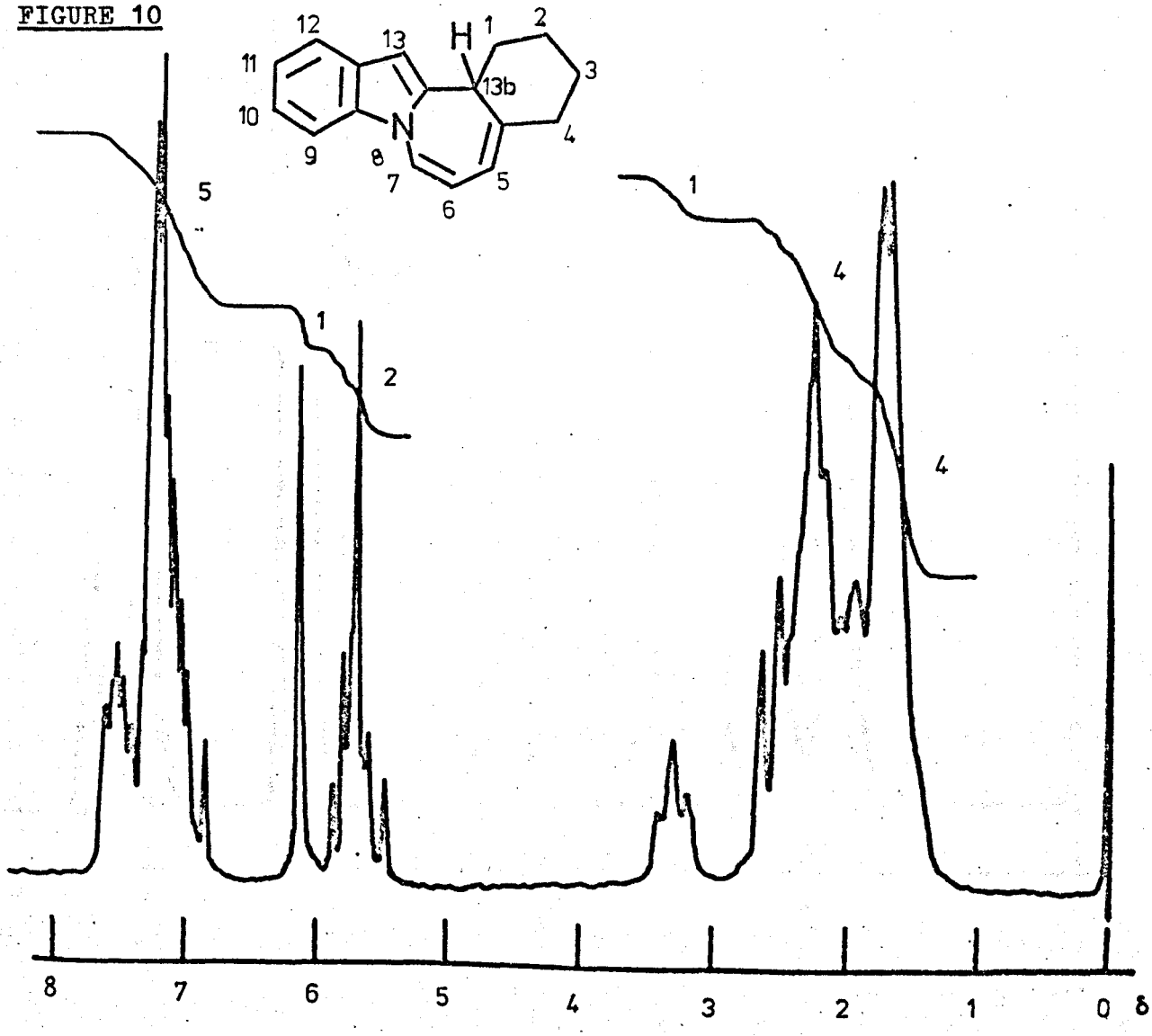


144

FIGURE 10

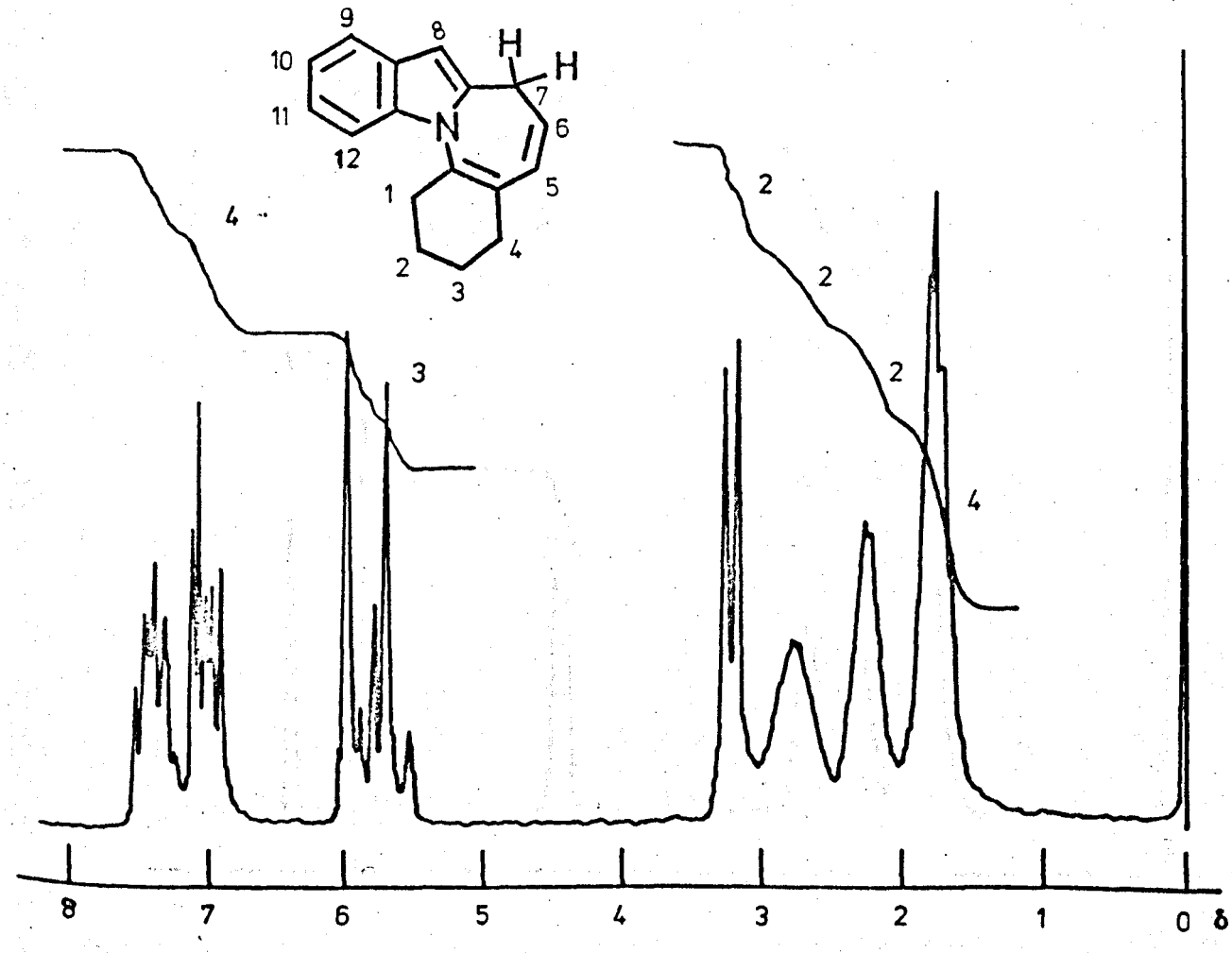


The 13bH-indolo[2,1-a][2]benzazepine 140 was an unstable oil and its structure was assigned on limited spectral data.

The n.m.r. spectrum (Figure 10) showed a multiplet at δ 5.4 - 5.9 due to the olefinic protons H-5 and H-6, a β-indole singlet at δ 6.12 and a one-proton triplet (J = 7Hz) at δ 3.33 p.p.m. ascribed to the methine proton, H-13b.

Additional evidence for this structure was provided by the ultra-violet spectrum which showed the absence of extended conjugation (λ_{max} 271.5 nm).

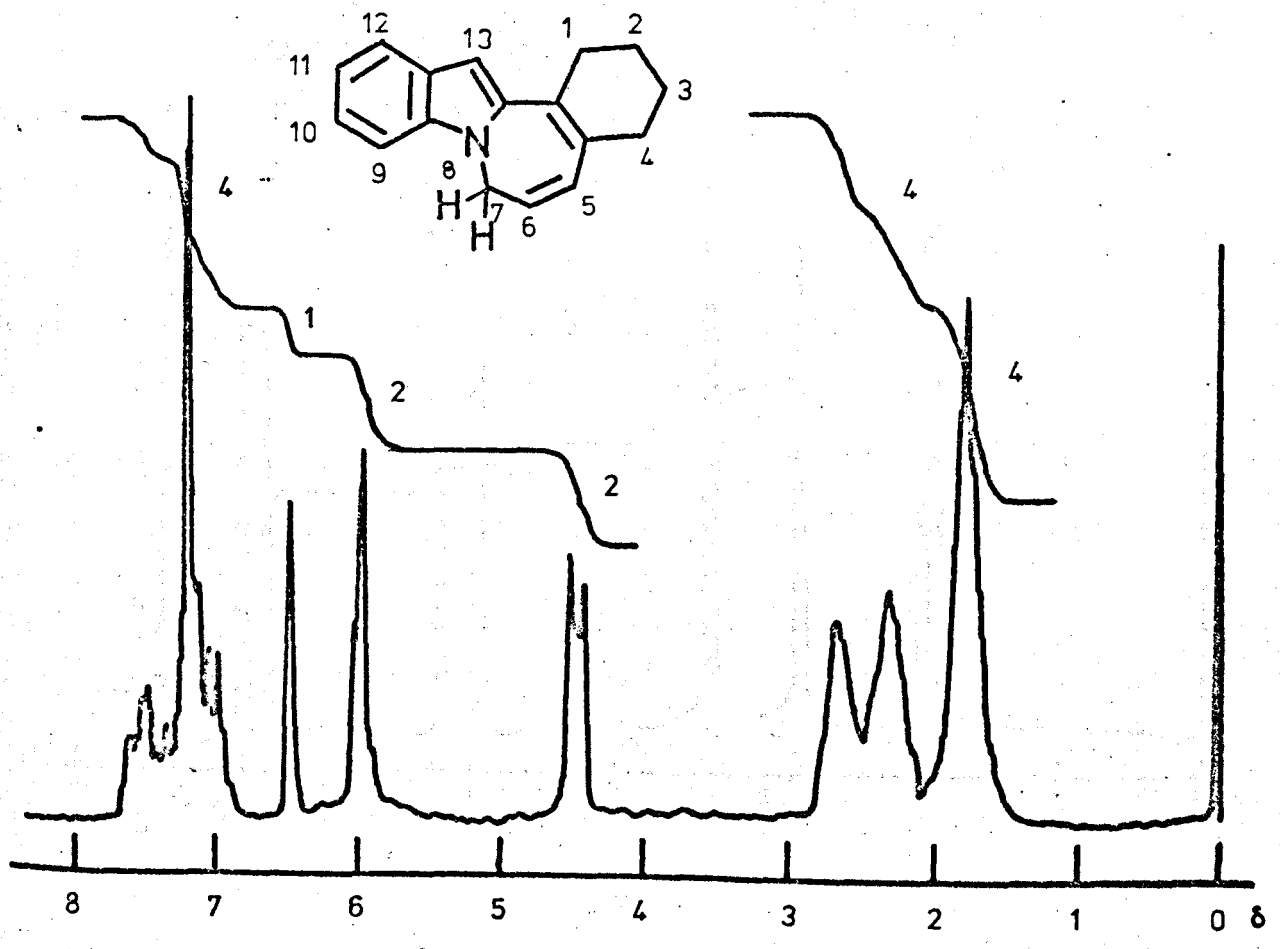
FIGURE 11



The structure of the 7H-indolo[1,2-a][1]benzazepine 141 was readily assigned on the basis of its n.m.r. spectrum (Figure 11).

The two-proton doublet at δ 3.20 and the sharp singlet at δ 5.99 p.p.m. were both indicative of the 10H-azepinoindole ring system and the chemical shifts of the remaining seven-membered ring protons (δ 5.5 - 5.9 p.p.m.) showed them to be isolated from the nitrogen atom thus indicating the presence of the [1]benzazepine structure. Confirmation was provided by the ultra-violet spectrum which showed no extended conjugation (λ_{max} 268 nm).

FIGURE 12

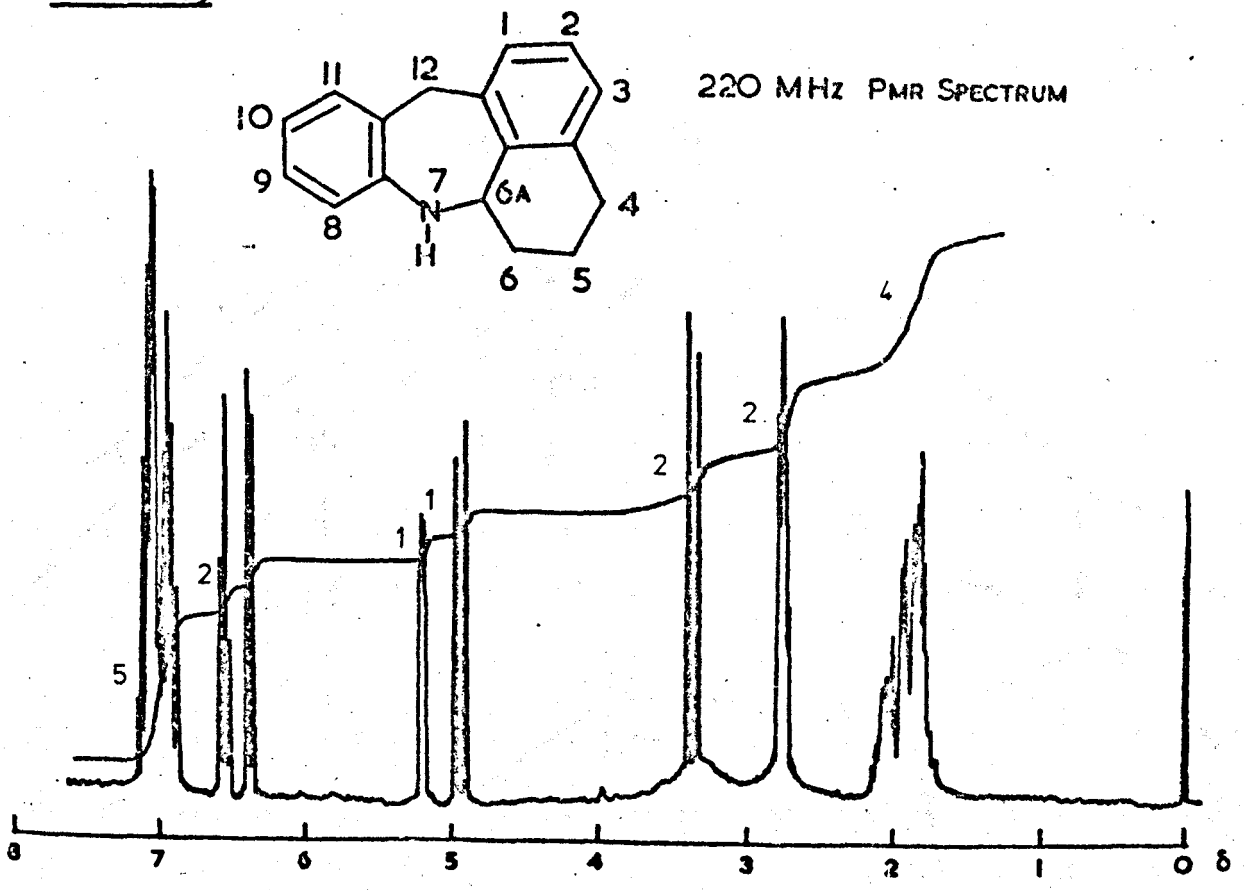


The presence of extended conjugation (λ_{max} 325, 348 nm) in the ultra-violet spectrum of the third compound eluted from the column indicated the 7H-indolo[2,1-a][2]benzazepine structure 142. This was confirmed by the n.m.r. spectrum (Figure 12) which showed a broadened methylene doublet at δ 4.5, a two-proton multiplet at δ 5.8 - 6.2 (H-5, H-6) and a β-indole singlet at δ 6.48 p.p.m.

The fourth product eluted from the column was a secondary amine with a molecular formula $C_{17}H_{17}N$ and was assigned the structure 4,5,6,6a,7,12-hexahydronaphtho[1,8-bc][1]benzazepine 143 after an analysis of its 220 MHz n.m.r. spectrum (Figure 13).

Nitrene attack at the peri-methylene group must have occurred to give this compound.

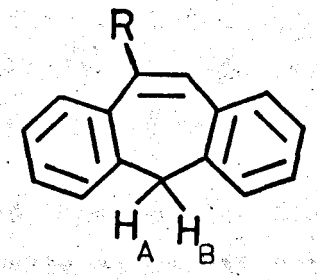
FIGURE 13



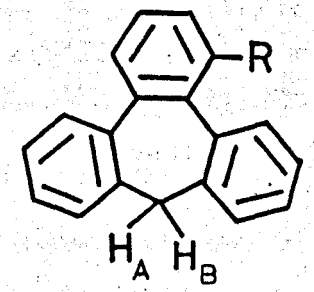
The most striking feature of this spectrum was the pair of one-proton doublets (J = 15.2 Hz) at δ 3.36 and δ 4.92 p.p.m. These signals were attributed to the methylene group protons of the seven-membered ring. The constraints applied by the tetralin ring system hold the molecule in one conformation, thus restricting ring inversion and making the methylene group protons non-equivalent.

Similar conformational effects are seen in the n.m.r. spectra of the dibenzo- and tribenzocycloheptatrienes 145 and 146[183].

145



R = $C(CH_3)_2OH$, J_{AB} = 12.2 Hz

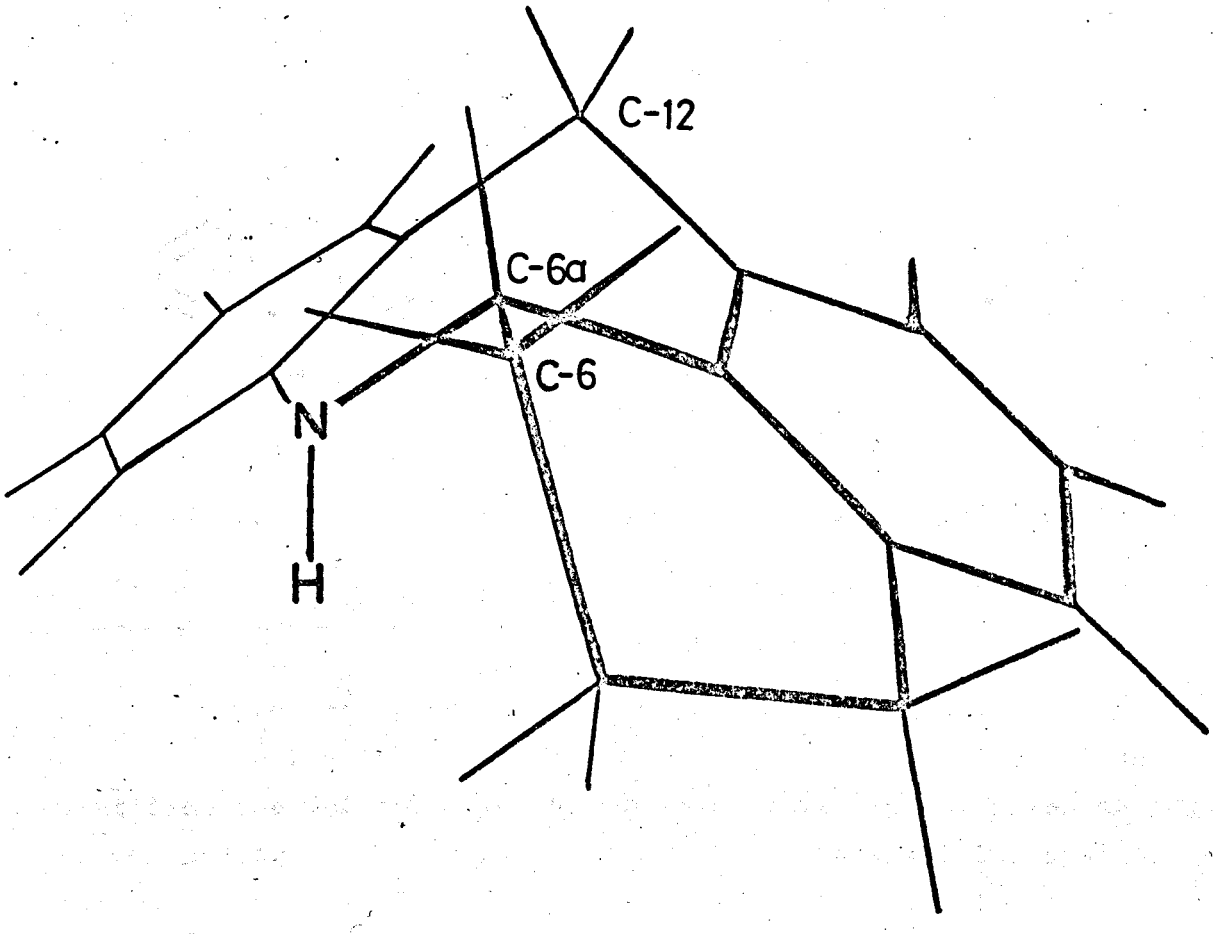


146

R = H, J_{AB} = 12.5 Hz

R = C_2H_5, J_{AB} = 12.5 Hz

FIGURE 14



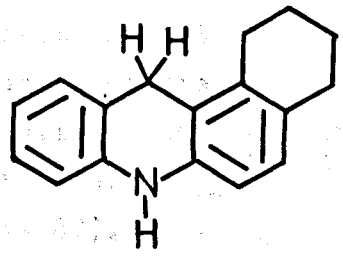
Other signals include a broadened one-proton singlet at δ 3.3 which undergoes deuterium exchange and is due to the amine proton and a one-proton signal at δ 5.1 - 5.2 p.p.m. which is assigned to the methine proton H-6a.

The latter signal is split, superficially, into a quartet by vicinal coupling with the methylene group at C-6 (Figure 14). The quartet results from equatorial-axial and equatorial-equatorial interactions with the non-equivalent protons of the methylene group; the non-equivalence is caused by the inflexibility of the molecule.

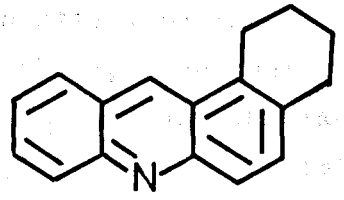
The n.m.r. spectrum of the hexahydrobenzacridine 144 contained a two-proton singlet at δ 3.94 and a one-proton, D_2O-exchangeable signal at δ 5.72 p.p.m.

Rapid oxidation of this compound made it necessary to characterise it as the tetrahydro- derivative 147. This compound

showed the typical spectral properties of the acridine system.



144

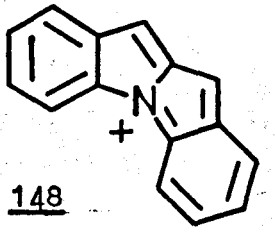


147

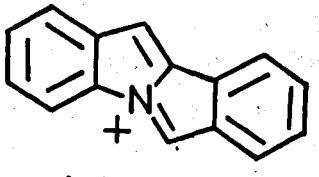
MASS SPECTRA OF THE INDOLOBENZAZEPINES

Two breakdown patterns have been observed:

In the indolobenzazepines 133 and 134 the loss of one mass unit from the molecular ion and base peak at $^{m}/e$ 231 gives an ion corresponding to the fully aromatic indolobenzazepinium system. A Further loss of 26 mass units (HC≡CH) gives the only other significant peak in the spectrum, at $^{m}/e$ 204 which could correspond to the azapentalene systems 148 (from 133) and 149 (from 134).



148



149

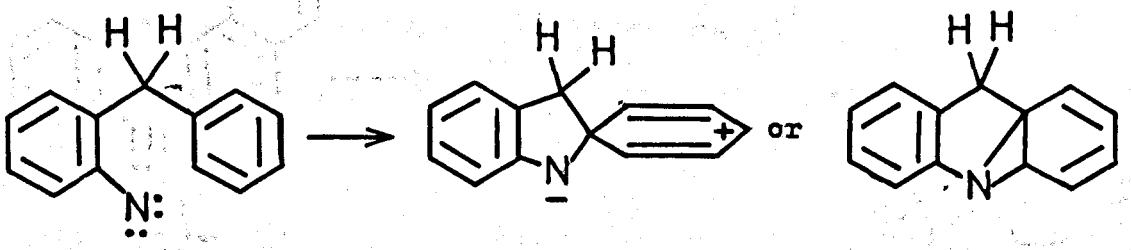
A peak at $^{m}/e$ 115.5 is due to the doubly charged indolobenzazepine system.

The tetrahydroindolobenzazepines 138, 140, 141 and 142 show a similar pattern. In each case the first loss is of one mass unit from the molecular ion and base peak which again represents the aromatic system. A second loss of 28 mass units ($CH_2 = CH_2$) gives the other major peak at $^{m}/e$ 206.

MECHANISM

The Review showed that the thermal decomposition of aryl azides proceeds via an electrophilic singlet nitrene intermediate. The reaction must then continue with an attack by the nitrene on the adjacent aromatic ring. The nature of the species thus produced is in question; both a spirodienyl system 150[184] and the isomeric azanorcaradiene 151[51,53] have been proposed as intermediates (Scheme 88).

SCHEME 88



150 151

The spirodiene intermediate was proposed to explain the rearrangements observed in the decomposition of substituted 2-azidodiphenyl sulphides (Schemes 20 and 21) and related compounds and an azanorcaradiene intermediate was postulated by Krbechek and Takimoto in their paper[51] on the decomposition of 2-azidodiphenylmethane.

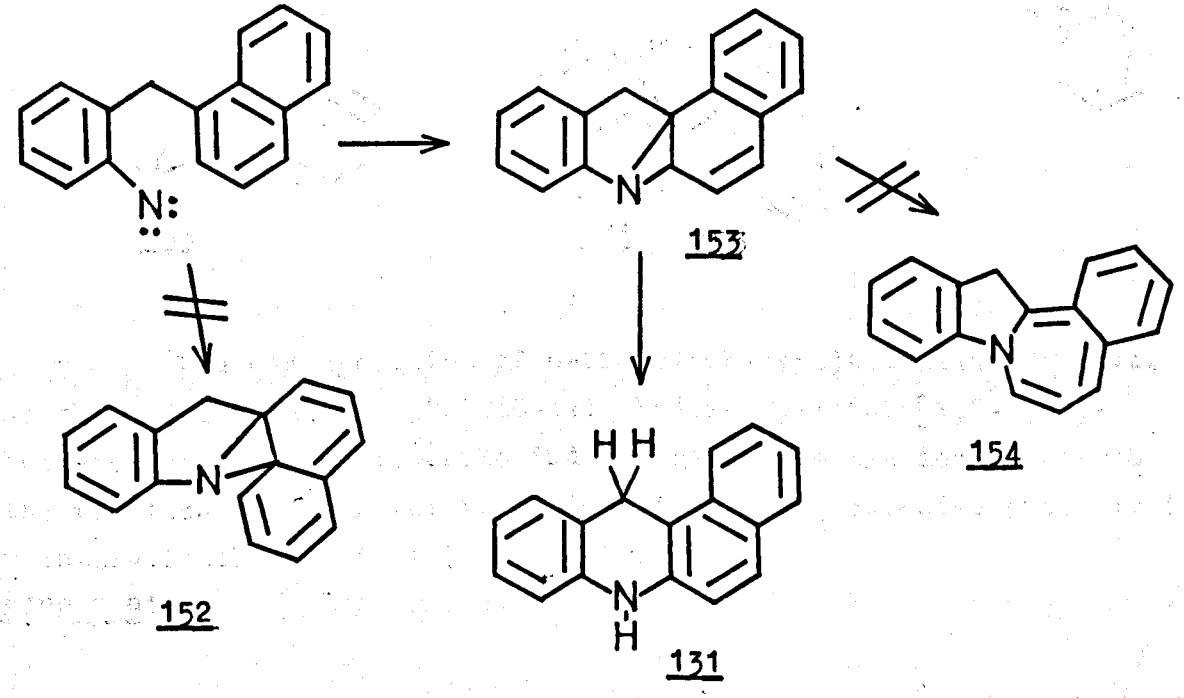
Although there is no direct evidence for either form, for simplicity of discussion, the azanorcaradiene intermediate will be used throughout this section.

The experiments described earlier in this section suggest explanations for the failure of annelated systems such as naphthalene to undergo ring expansion following nitrene insertion. The decomposition of the tetralins 128 and 129 shows that the geometry of the naphthalene systems 126 and 127 is suitable for π-bond insertion and that the preferred reaction is ring expansion to azepinoindole derivatives.

The loss of aromaticity inherent in the ring expansion of the naphthalene derivatives must be the factor that influences the reaction pathway. In the decomposition of the 1-naphthyl derivative

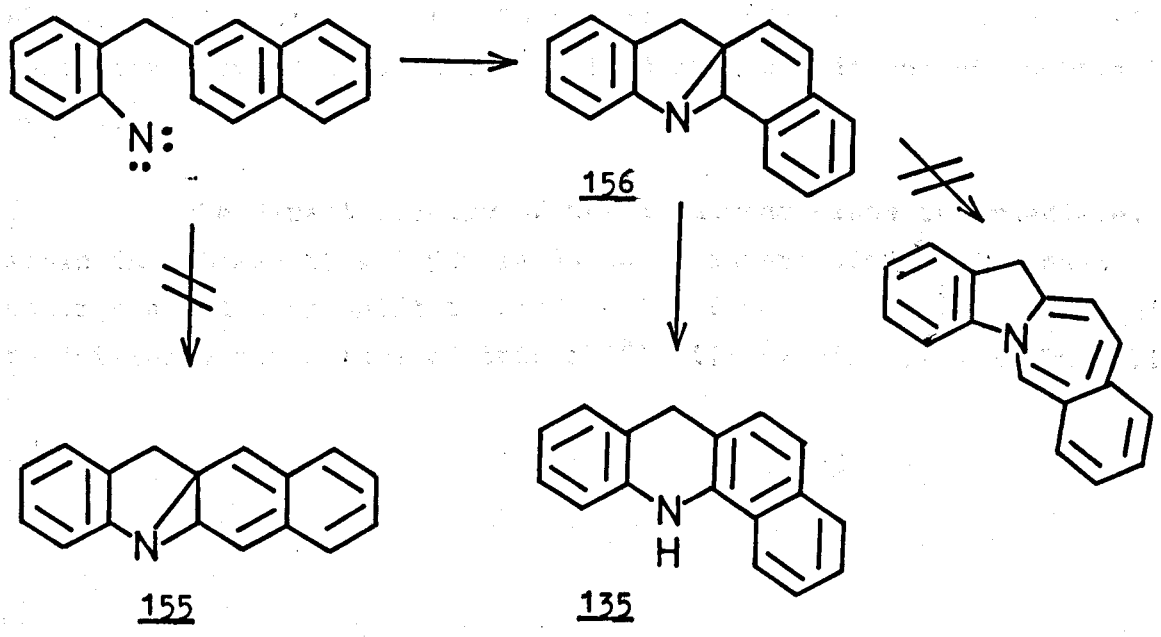
126, two intermediate azanorcaradienes 152 and 153 are possible (Scheme 89). The formation of 152 requires the complete loss of resonance energy of the naphthalene system and so is disfavoured relative to intermediate 153 in which the resonance energy of only one ring is lost. However, if this intermediate proceeds to the necessary precursor for indolobenzazepine formation 154, the remaining resonance energy is lost; hence ring opening to give benzacridan 131 is favoured.

SCHEME 89



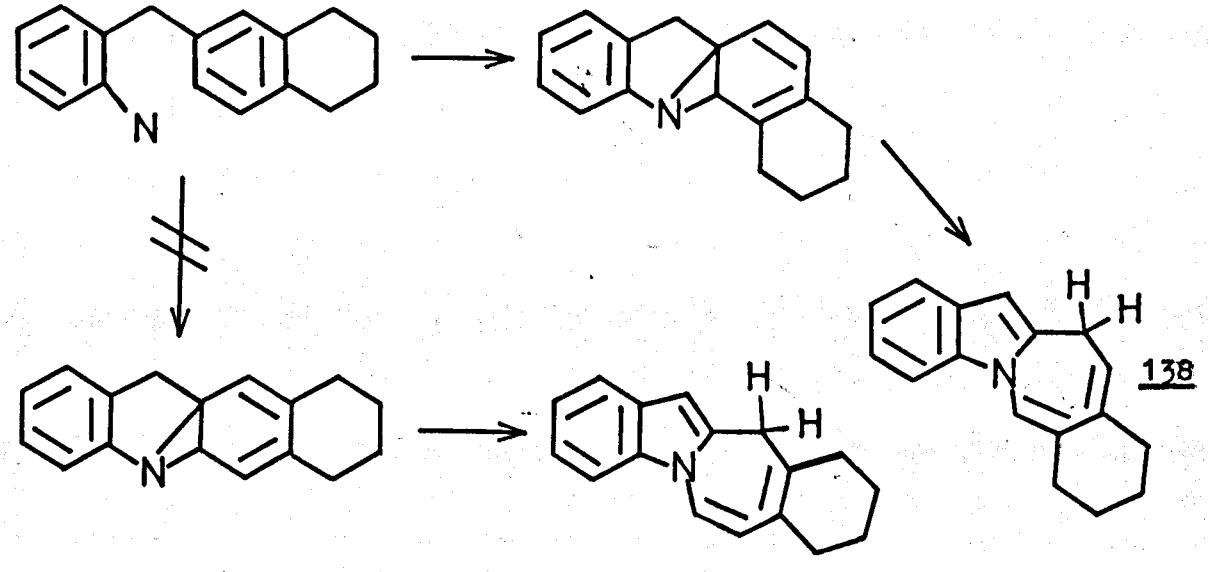
Similarly the decomposition of 2-(2-azidobenzyl)-naphthalene 127 gives two azanorcaradienes (155 and 156) and the more energetically favoured path is through intermediate 156 to the benzacridan 135 (Scheme 90).

SCHEME 90



The decomposition of 6-(2-azidobenzyl)tetralin 128 gave, as the major product, 7,8,9,10-tetrahydro-12H-indolo[1,2-b][2]-benzazepine 138. No isomeric indolobenzazepine was isolated from the reaction although the formation of two ring expanded products is mechanistically feasible (Scheme 91).

SCHEME 91



In this behaviour the system is acting normally, as reactivity studies have shown that tetralin is activated towards electrophilic attack in the 5- position. (The reactivity of aryl positions α and β to a fused strained ring was discussed in Part I, page 53).

The direct opening of the azanorcaradiene intermediate, as shown in Schemes 89 and 90, leads to an intermediate which must undergo a hydrogen shift to produce the final product. Experiments to determine the nature of this shift will be discussed in Part III.

PART III

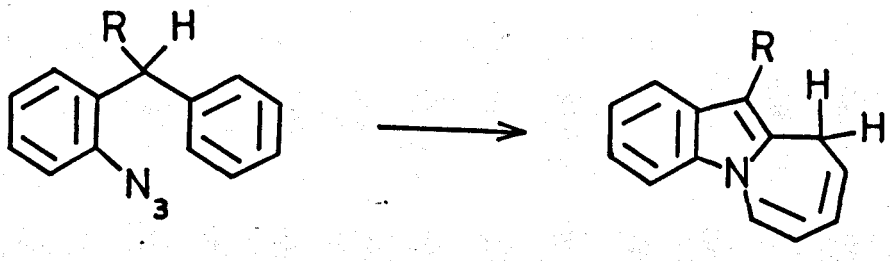
I N T R O D U C T I O N

The decomposition of the naphthalene systems described in Part II gave an insight into the reactivity of nitrenes towards polycyclic aromatic species. The work described in this part of the thesis attempts to correlate the reactivity of the nitrene intermediate with the electron availability of the aromatic nucleus into which it inserts and to elucidate the mechanism of the insertion.

During the course of their studies into the synthesis of the azonia-azulene system Cliff and Jones[52,53] examined the decomposition of 2-azidodiphenylmethane 19. This compound decomposed at 180° in an inert solvent to give a single product, identified as 10H-azepino[1,2-a]indole 21 (Scheme 92). These authors also showed that replacement of one of the methane protons by a methyl group 156 did not affect the course of the reaction; in this case a moderate yield of 11-methyl-10H-azepino[1,2-a]indole 157 was obtained.

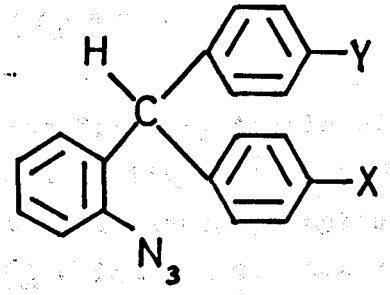
The replacement by a phenyl group of one of the methane protons in 2-azidodiphenylmethane might also be envisaged as having no effect upon the reaction mechanism; however, both phenyl groups would be vulnerable to attack from the nitrene intermediate. In the simplest case, with two unsubstituted phenyl rings 158, the expected product would be 11-phenyl-10H-azepino[1,2-a]indole 159 but the presence of a substituted ring with a differing electron availability might cause preferential attack of the nitrene intermediate and the predominance of one expected product over the other.

SCHEME 92



19	R = H	21	R = H
156	R = CH_3	157	R = CH_3
158	R = C_6H_5	159	R = C_6H_5

Accordingly it was decided to investigate the decomposition of substituted 2-azidotriphenylmethanes. The compounds chosen for investigation were:



158	X = H,	Y = H
160	X = OCH_3,	Y = H
161	X = CO_2CH_3,	Y = H
162	X = CO_2CH_3,	Y = OCH_3

(i) 2-azidotriphenylmethane 158

(ii) 2-azido-4'-methoxytriphenylmethane 160

(iii) the methyl ester of 2-azido-4'-carboxytriphenylmethane 161

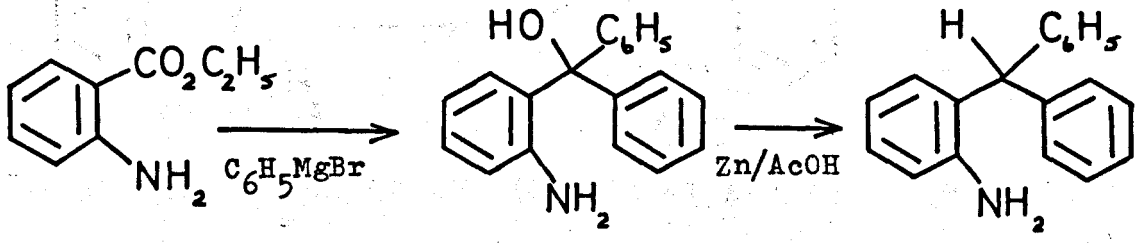
(iv) the methyl ester of 2-azido-4'-carboxy-4"-methoxytriphenylmethane 162.

D I S C U S S I O N

PREPARATION OF THE AZIDES

The first synthesis of 2-aminotriphenylmethane was achieved by Baeyer and Villiger[185] in 1904. The reaction between ethyl anthranilate and excess phenylmagnesium bromide gave 2-aminotriphenylcarbinol 163 which, on treatment with zinc dust and acetic acid, gave 2-aminotriphenylmethane 164 (Scheme 93).

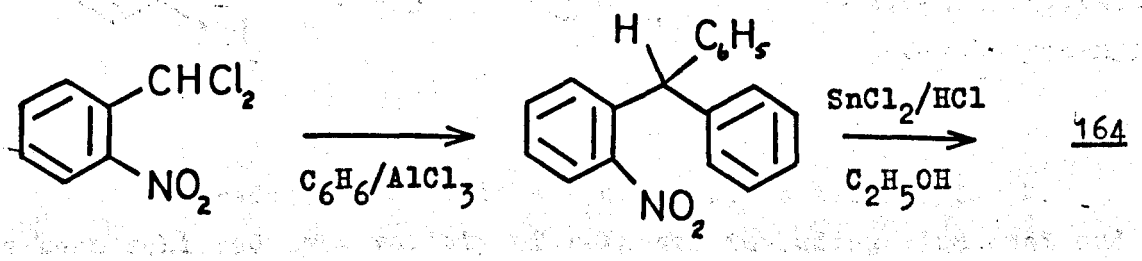
SCHEME 93



163 164

A second synthesis was reported by Kliegl[186] a few years later. This worker reacted 2-nitrobenzal chloride 165 with benzene in the presence of aluminium chloride and obtained 2-nitrotriphenylmethane 166 which he reduced to the amine using alcoholic stannous chloride (Scheme 94).

SCHEME 94



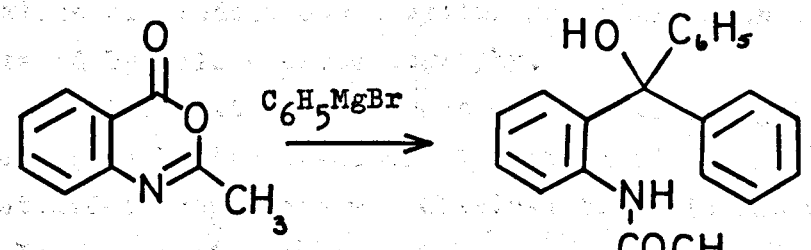
165 166

A third reaction, which has been used with some success, is the Lewis acid catalysed condensation of 2-nitrobenzaldehyde with activated benzene derivatives. Tanasescu and co-workers[187,188] prepared the 2-nitro-4',4"-diamino derivative from aniline in the

presence of anhydrous zinc chloride and the 2-nitro-4',4"-dihydroxy compound from phenol and phosphoric acid. The latter compound underwent a number of reactions including benzoylation, acetylation and methylation. Reaction with benzene in the presence of aluminium chloride to give 2-nitrotriphenylmethane has also been achieved[189].

The preparation of 2-acetamidotriphenylcarbinol 167 from 2-methyl-3,1-benzoxazin-4-one 130 and excess phenylmagnesium bromide was first reported by Lothrop and Goodwin[176] (Scheme 95). This reaction has been used by Sisti and Cohen[190] to prepare a number of substituted 2-aminotriphenylcarbinols.

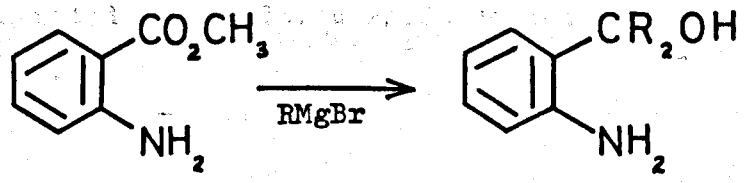
SCHEME 95



130 167

Stiles and Sisti[191] have also used the reaction between methyl anthranilate and an excess of a Grignard reagent to prepare various substituted 2-aminotriphenylcarbinols (Scheme 96).

SCHEME 96



R
p-anisyl
o-anisyl
o-tolyl
2,4-dimethylphenyl
2,6-dimethylphenyl
2-ethoxyphenyl

The reduction of triphenylcarbinol to triphenylmethane has been achieved by a variety of reagents including zinc dust and acetic acid[185], a solution of sodium borohydride/boron trifluoride in diglyme/tetrahydrofuran[192], 98% formic acid[193] and isopropanol and aqueous sulphuric acid[194]. In this work most of the triphenylcarbinols were reduced, in good yields, using formic acid.

The preparative procedures listed above have one common feature in that they introduce two identical aromatic groups into the molecule. No procedure for the introduction of two different groups into the molecule could be found in the available literature.

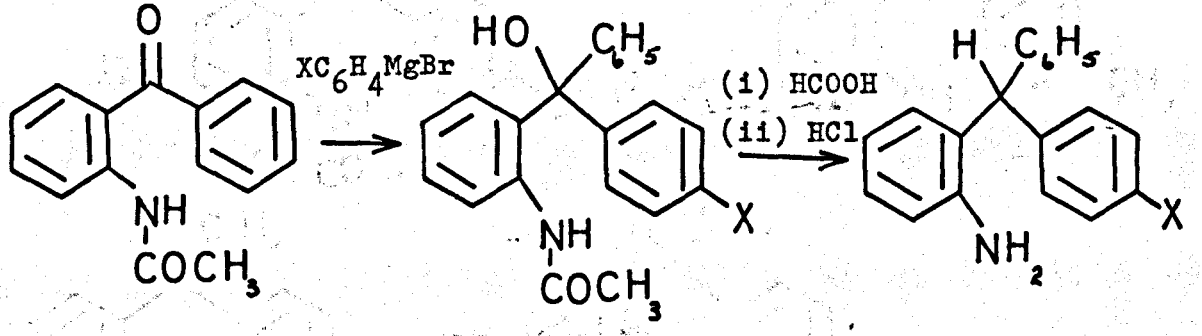
The preparation of 2-acetamidotriphenylcarbinol 167 was achieved in good yield (60%) from 2-methyl-3,1-benzoxazin-4-one 130 by the method of Lothrop and Goodwin[176]. The 4'-methoxy derivative was obtained using commercially available 2-aminobenzophenone. Several experiments were tried to achieve optimum results.

The reaction between excess p-anisylmagnesium bromide and 2-aminobenzophenone in tetrahydrofuran at 0° gave, after hydrolysis, a mixture of product and starting material which could not be separated by column chromatography.

A repeat of the above experiment using 2-acetamidobenzophenone gave better results. A mixture of the acetamidocarbinol and 2-acetamidobenzophenone was obtained but this was readily separated by column chromatography.

A third experiment involved the addition of a solution of 2-acetamidobenzophenone 168 in tetrahydrofuran to a refluxing solution of the Grignard reagent in ether. Work-up gave an oil which on trituration with methanol gave 2-acetamido-4'-methoxytriphenylcarbinol 169 in good yield. Both 2-acetamidotriphenylcarbinol 167 and 2-acetamido-4'-methoxytriphenylcarbinol 169 were reduced in high yields by treatment with formic acid and were hydrolysed to the amines 164 and 170 by a refluxing mixture of concentrated hydrochloric acid and methanol (Scheme 97).

SCHEME 97



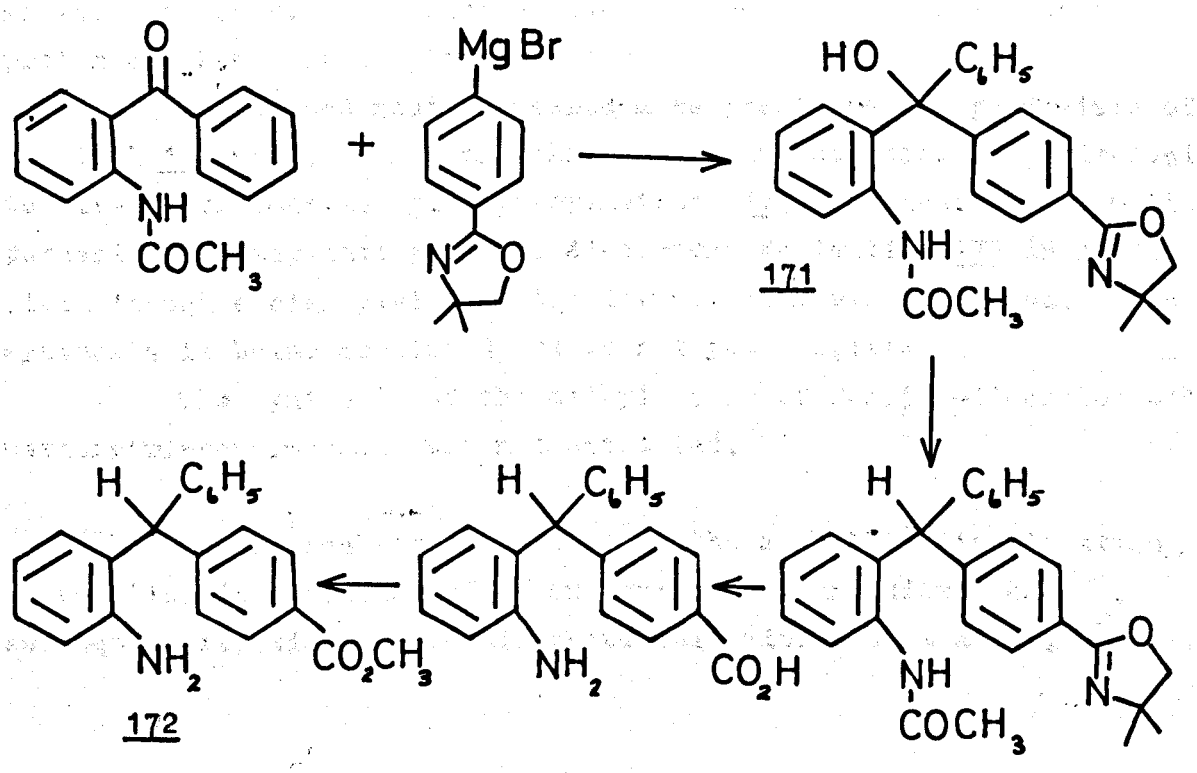
168

X = OCH_3, 169
X = H, 167

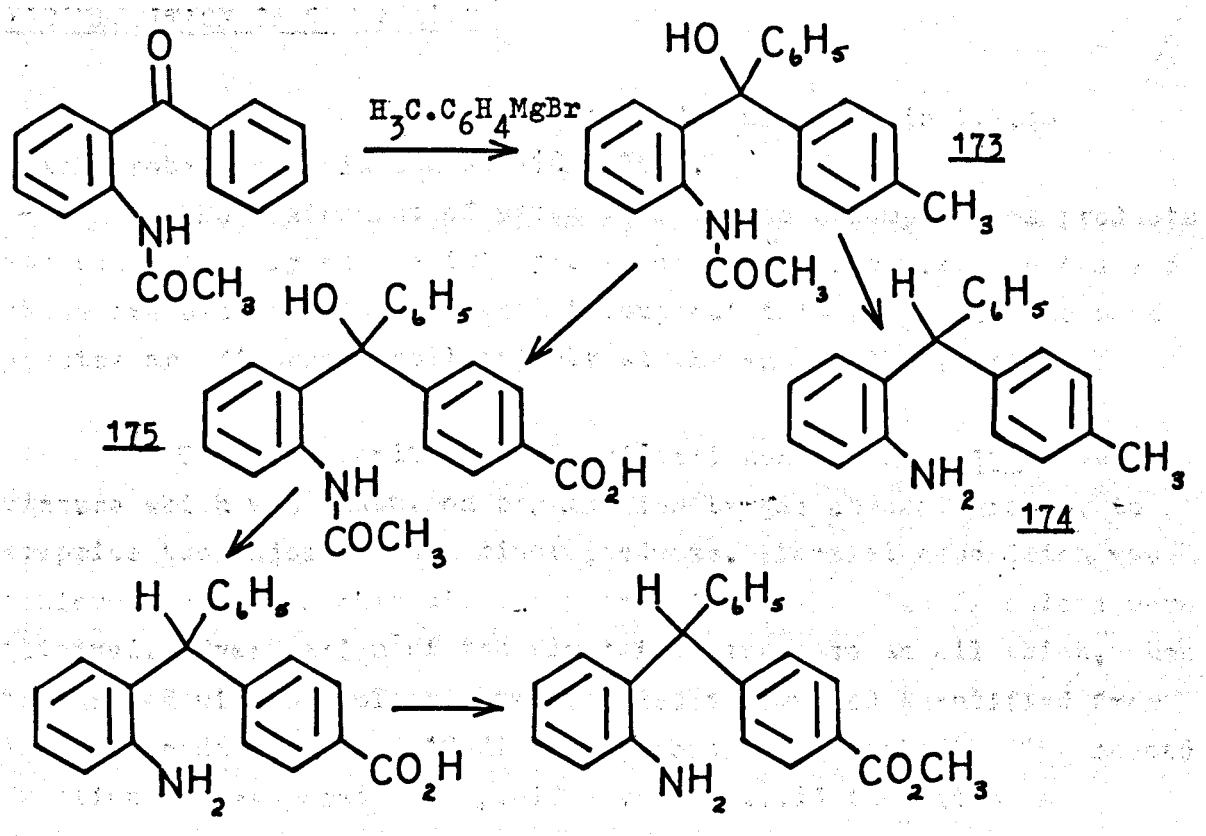
X = OCH_3, 170
X = H, 164

The preparation of the methyl ester of 2-amino-4'-carboxytriphenylmethane 172 proved difficult and the synthesis remains incomplete. Two synthetic routes were tried (Schemes 98,99).

SCHEME 98



SCHEME 99



The first scheme makes use of the resistance of the 2-oxazoline ring system to attack by Grignard reagents. The synthesis of the carbinol 171 was achieved but treatment with formic acid gave a large number of products and the examination of the crude mixture by n.m.r. spectroscopy revealed the absence of a methine proton and hence of triphenylmethane.

The second route appeared more promising. A good yield of carbinol 173 was obtained and this underwent reduction and hydrolysis to give 2-amino-4'-methyltriphenylmethane 174. Oxidation with neutral potassium permanganate gave the 4'-carboxy derivative 175 in good yield though a high yield of starting material was recovered. This synthesis is being continued but is not yet complete.

The synthesis of the methyl ester of 2-amino-4'-carboxy-4"-methoxytriphenylmethane was not attempted.

The amines were converted to the azides by diazotisation in solution in a mixture of 4N sulphuric acid and dioxan and subsequent reaction of the diazonium salt with sodium azide.

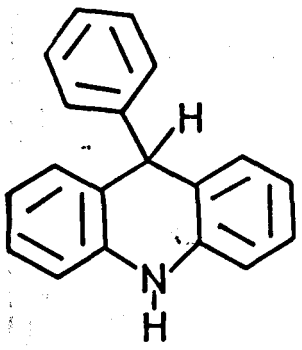
DECOMPOSITION OF THE AZIDES

Each azide was decomposed under nitrogen in 1,2,4-trichlorobenzene solution at 180 - 200°.

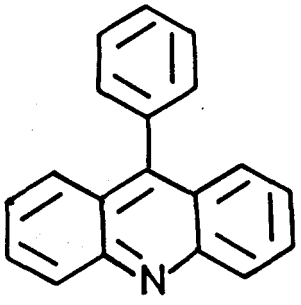
The assignment of structures to the decomposition products was based largely on the interpretation of their n.m.r. spectra and these are extensively discussed throughout this section. The mass spectra are discussed collectively at the end of the section.

The decomposition of 2-azidotriphenylmethane 158 gave a mixture which was shown, on examination by gas chromatography, to comprise two major and two minor products. Partial separation was achieved by column chromatography in benzene when two fractions were obtained. Evaporation of the first fraction gave an oil which, when triturated with petroleum, precipitated a compound identified from literature data[195] as 9,10-dihydro-9-phenylacridine 176. The second fraction was evaporated to yield a yellow solid identified as

9-phenylacridine 177[195].

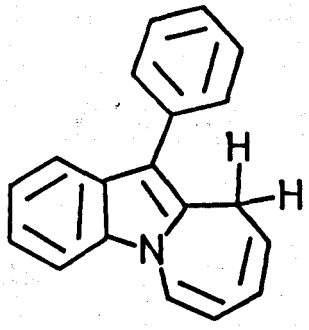


176



177

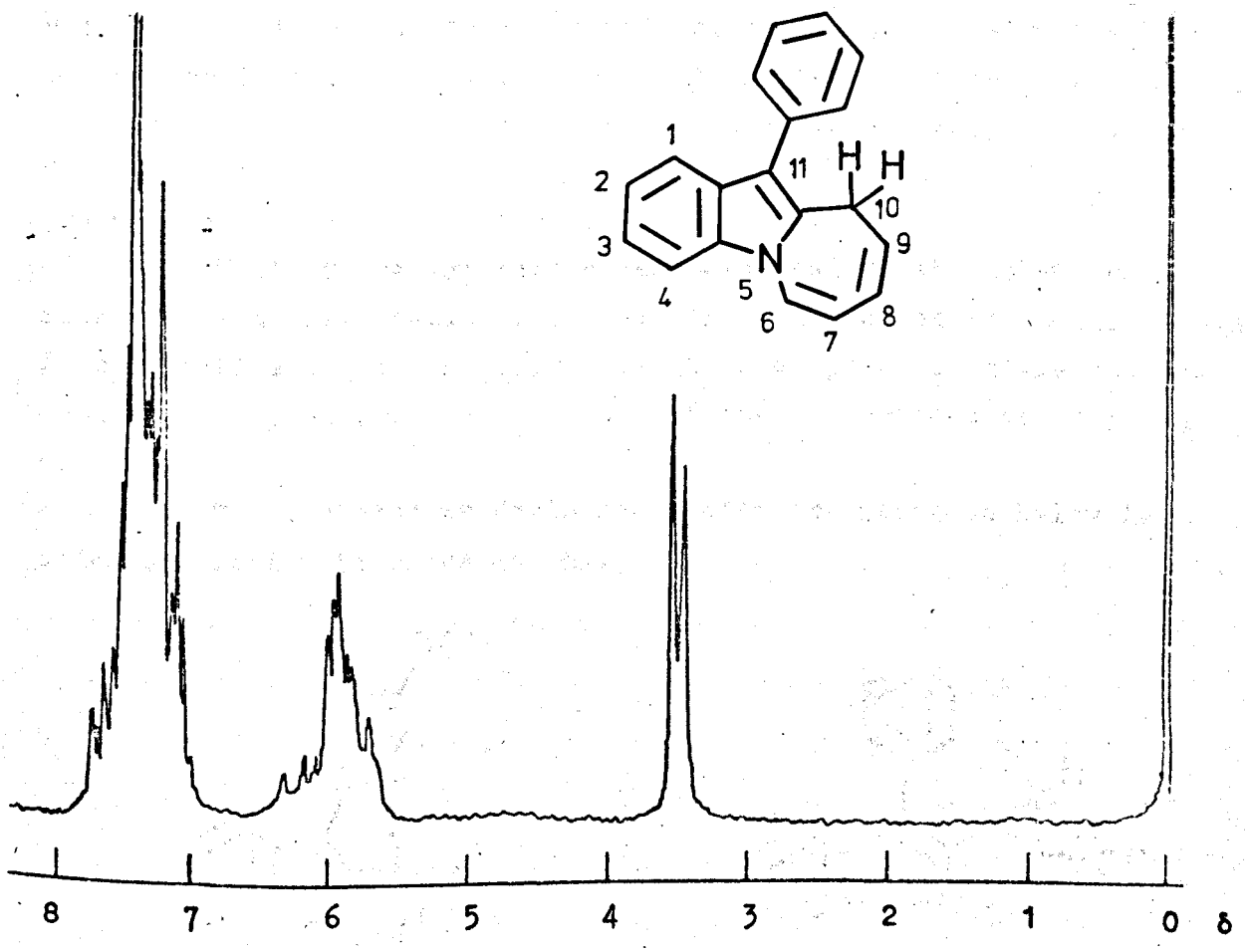
The residues from the crystallisations were chromatographed on alumina in petroleum to give, in the first fraction, 11-phenyl-10H-azepino[1,2-a]indole 178. The structure of this compound was assigned on the basis of its n.m.r. spectrum (Figure 15). The two-proton doublet at δ 3.5 and three-proton multiplet at δ 5.6 - 6.3 p.p.m. (H-7,8 and 9) were both indicative of the 10H-azepino-indole system and the absence of a sharp singlet at δ 6.0 revealed the presence of a substituent at C-11.

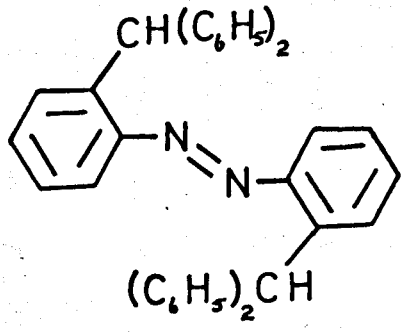


178

The residue from the column was separated by preparative layer chromatography. Two previously unidentified compounds were isolated from bands on the plates. One was identified as 2-amino-triphenylmethane 164. The other product had peaks in its mass spectrum at 514, 512, 257 and 256 mass numbers and was identified as 2,2'-bis(diphenylmethyl)azobenzene 179.

FIGURE 15





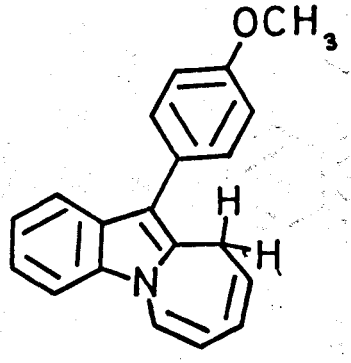
179

Azo-compounds have frequently been reported in the decomposition of azides and their formation has been explained in terms of attack by the nitrene on the azide, dimerisation of the nitrene being unlikely in dilute solution[15,42].

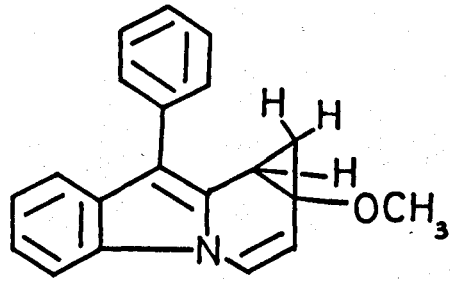
The decomposition of 2-azido-4'-methoxytriphenylmethane 160 gave a product which, on examination by gas chromatography, appeared to contain five components. Separation of the decomposition products was achieved by column chromatography on alumina. Pure samples of five products were isolated and characterised but another two products could not be isolated in a pure state.

Most of the material chromatographed on the column was recovered and this enabled the yield of each product to be calculated from a combination of the direct weighing of pure materials and the estimation, by n.m.r. spectroscopy, of the proportions of components of mixtures.

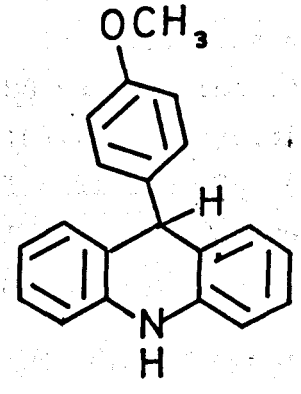
The isolated products and yields are recorded below in order of elution from the column.



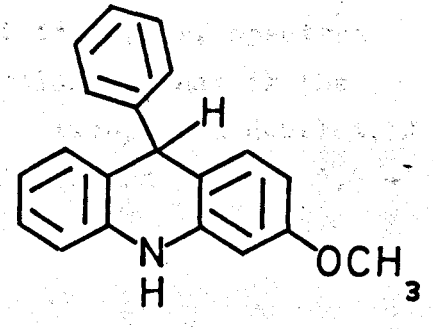
180
17% yield



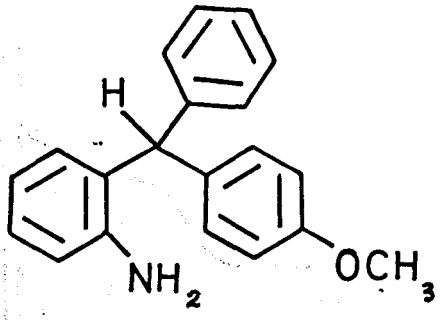
181
34% yield



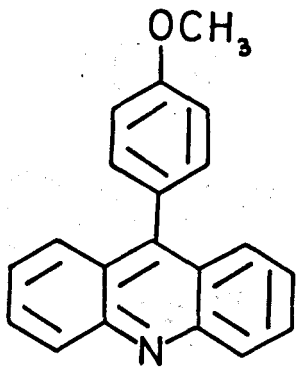
182
12% yield



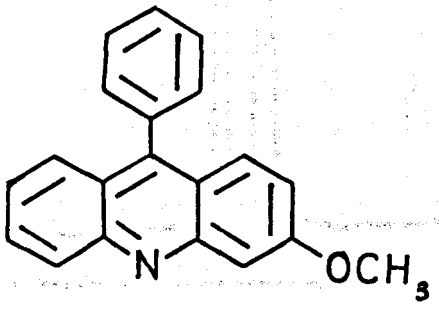
183
14% yield



170
7% yield



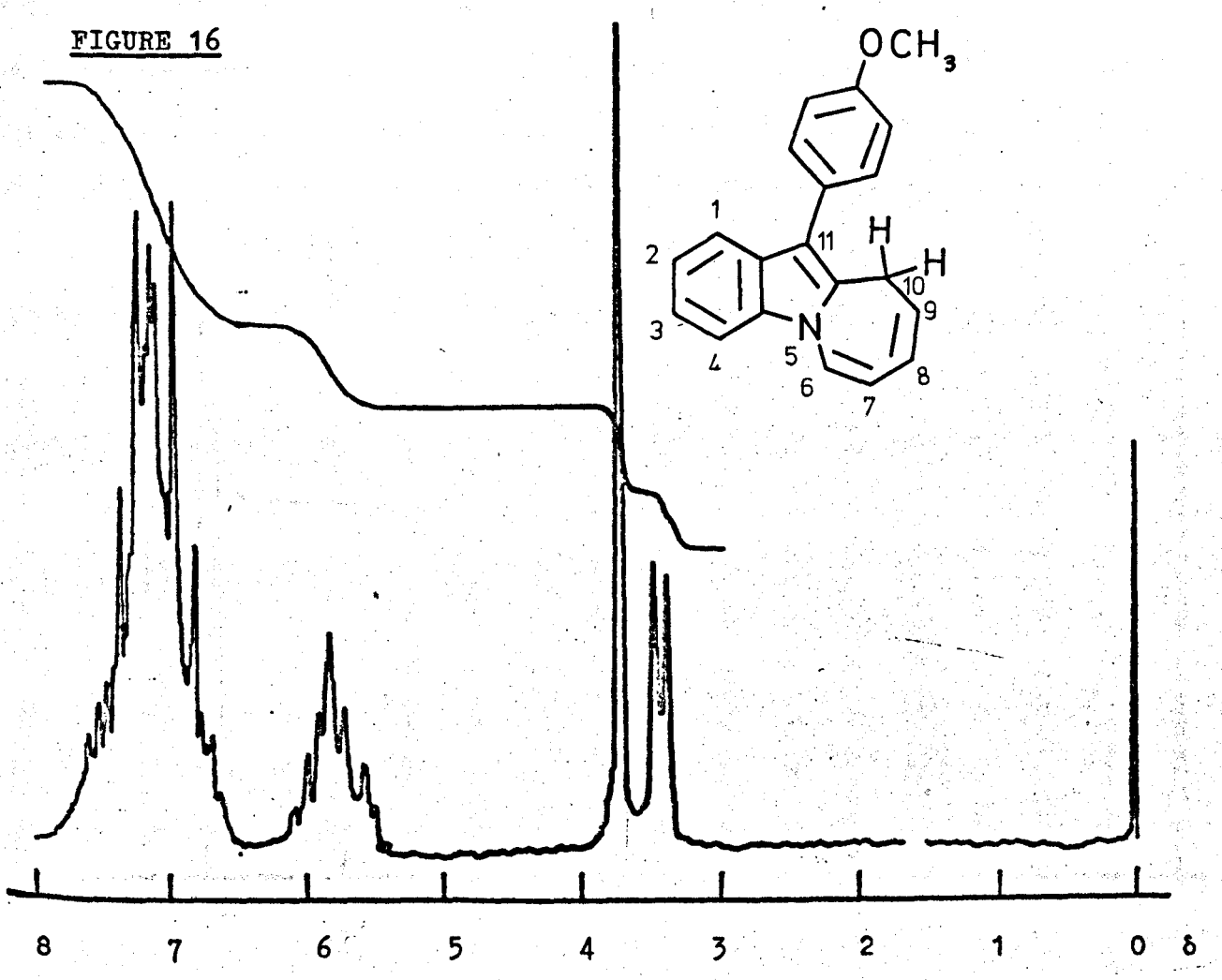
184
6% yield



185
10% yield

The structure of 11-(4-methoxyphenyl)-10H-azepino[1,2-a]-indole 180 was determined on the basis of its n.m.r. spectrum (Figure 16). This spectrum, which is similar to that of the 11-phenyl analogue 178 (Figure 15), has a two-proton doublet, J = 5Hz, at δ 3.44 and a three-proton multiplet (H-7,8 and 9) at δ 5.5 - 6.1 p.p.m.

FIGURE 16



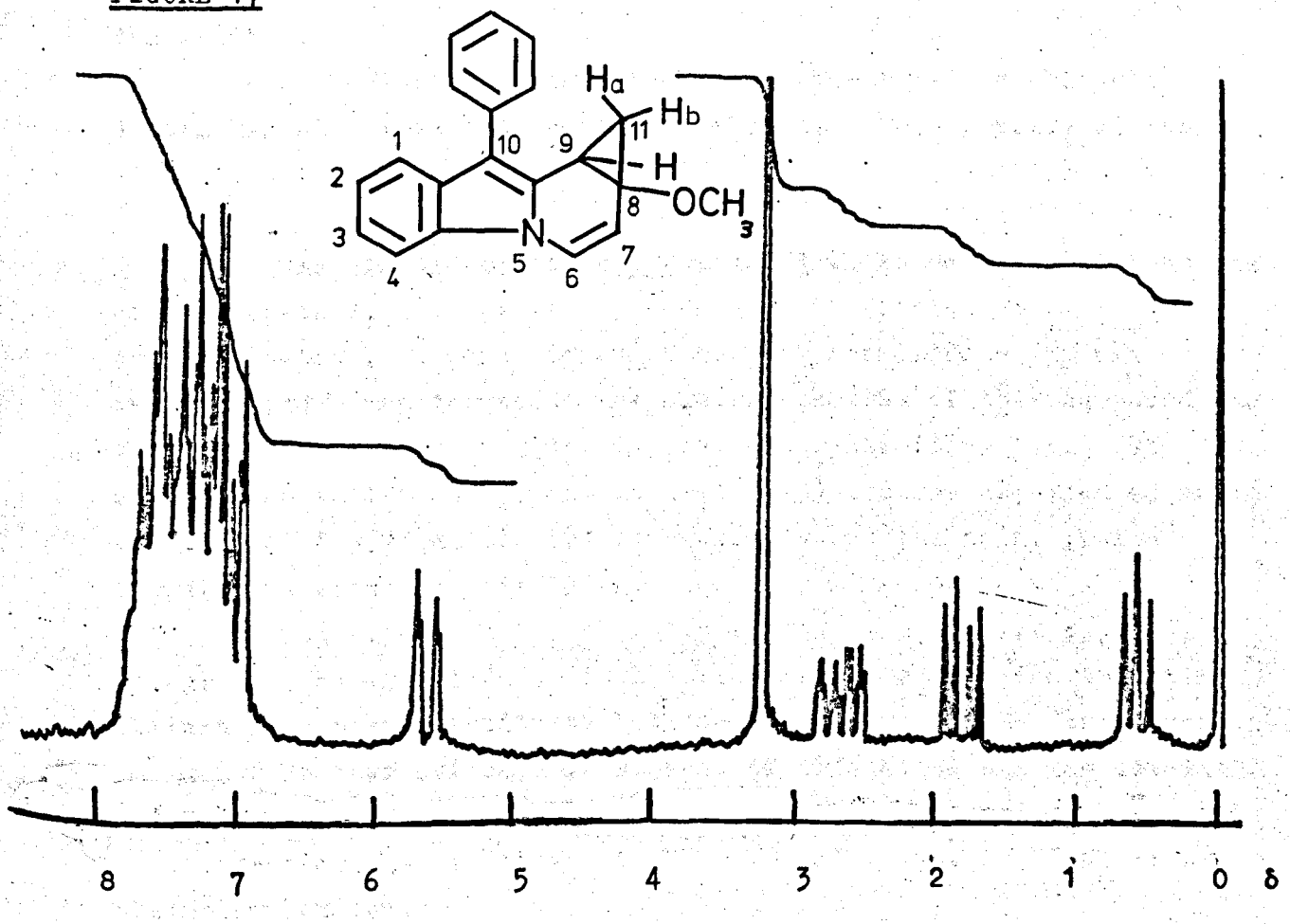
The pyrido-indole 181 was obtained as an air-stable white solid and identified from its n.m.r. spectrum (Figure 17).

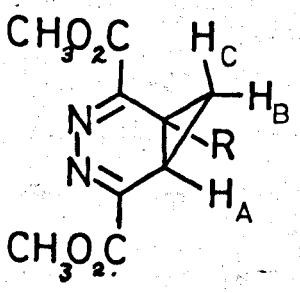
The triplet at δ 0.59 was shown on close examination to be a pair of doublets with coupling constants of 4.8 and 5.8Hz. The high up-field shift of this proton (H-11a in Figure 17) is due to the geometrical restraint of the three-membered ring forcing it into the strong diamagnetic shielding region of the π-electron system.

The signal at δ 1.83 corresponds to the proton H-11b. Geminal coupling (4.8Hz) with H-11a and cis coupling (10.2Hz) with H-9 accounts for the observed splitting pattern.

These figures are in good agreement with those observed for the diazanorcaradienes 186 and 187.[196]

FIGURE 17





		Chemical Shift			Coupling Constant		
		H_A	H_B	H_C	J_{AB}	J_{AC}	J_{BC}
186	R = H_A	3.05	2.28	-0.03	8.92	4.75	3.85
187	R = CH_3	2.70	2.05	0.08	9.51	5.18	4.19

In addition to the expected cis and trans coupling with the protons H-11b and H-11a the signal at δ 2.7 (H-9) has a minor coupling of 2Hz which is due to long range coupling with proton H-7. This long range coupling or "W" coupling between hydrogen atoms[197], separated by three carbon atoms, occurs when the five atoms are co-planar. Examination of a Dreiding model of this compound showed the co-planarity of the atoms involved.

The signal at δ 5.65, due to the olefinic proton H-7, has the long range coupling to H-9 discussed above and is also coupled to

proton H-6. The signal from H-6 is in the aromatic region and is not discernible.

The change from the aromatic to the tertiary aliphatic system has also resulted in an up-field shift (0.5 p.p.m.) of the signal due to the methyl group.

The dihydroacridines 182 and 183 which were eluted from the column together, were partially separated by fractional crystallisation. A pure sample of the dihydroacridine 182 was isolated and characterised. The n.m.r. spectrum of this compound was very similar to that of 9,10-dihydro-9-phenylacridine 176. The signals due to the methyl and methine (H-9) protons appeared as sharp singlets at δ 3.73 and δ 5.24 respectively and the amine proton signal as a broadened singlet at δ 6.1 p.p.m.

The signal in the aromatic region (δ 6.6 - 7.2 p.p.m.), integrated, as expected for twelve protons and showed the splitting pattern of a para-substituted benzene derivative in the fine structure.

Further evidence in support of this structure was obtained from the mass spectrum which gave as the base peak an ion at $^{m}/e$ 180. This corresponds to the loss of 107 mass units i.e. $CH_3OC_6H_4$ from the molecular ion.

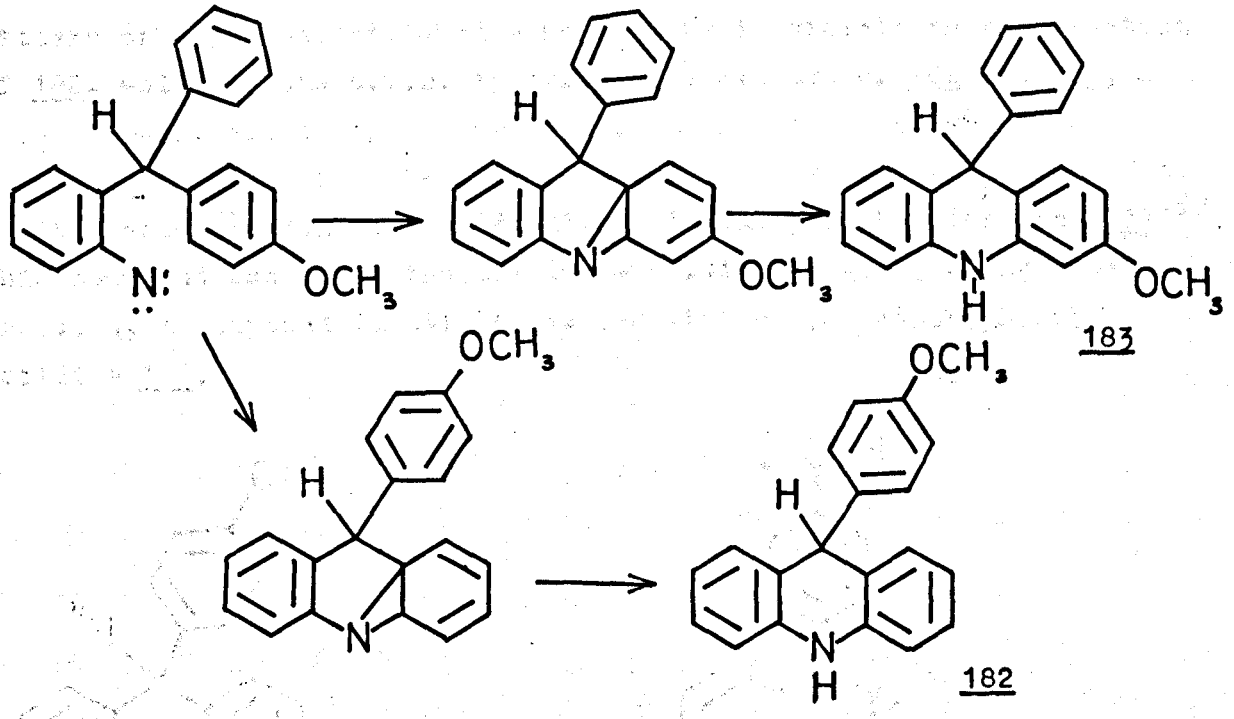
Continued elution of the column gave, in quick succession, 2-amino-4'-methoxytriphenylmethane 170 which was identified by comparison with an authentic specimen and a mixture of the acridines 184 and 185.

Complete separation of these isomers proved impossible but a pure sample of 9-(4-methoxyphenyl)acridine 184 identified from literature data[198] was obtained by fractional crystallisation of the mixture of isomers.

The assignment of the structures 183 and 185 to the uncharacterised products must be examined in view of the discussions over the mechanism of the reaction.

The mechanism postulated by Krbechek and Takimoto[51] and used by Jones and co-workers[52,53], predicts the formation of the dihydroacridines 182 and 183 (Scheme 100).

SCHEME 100

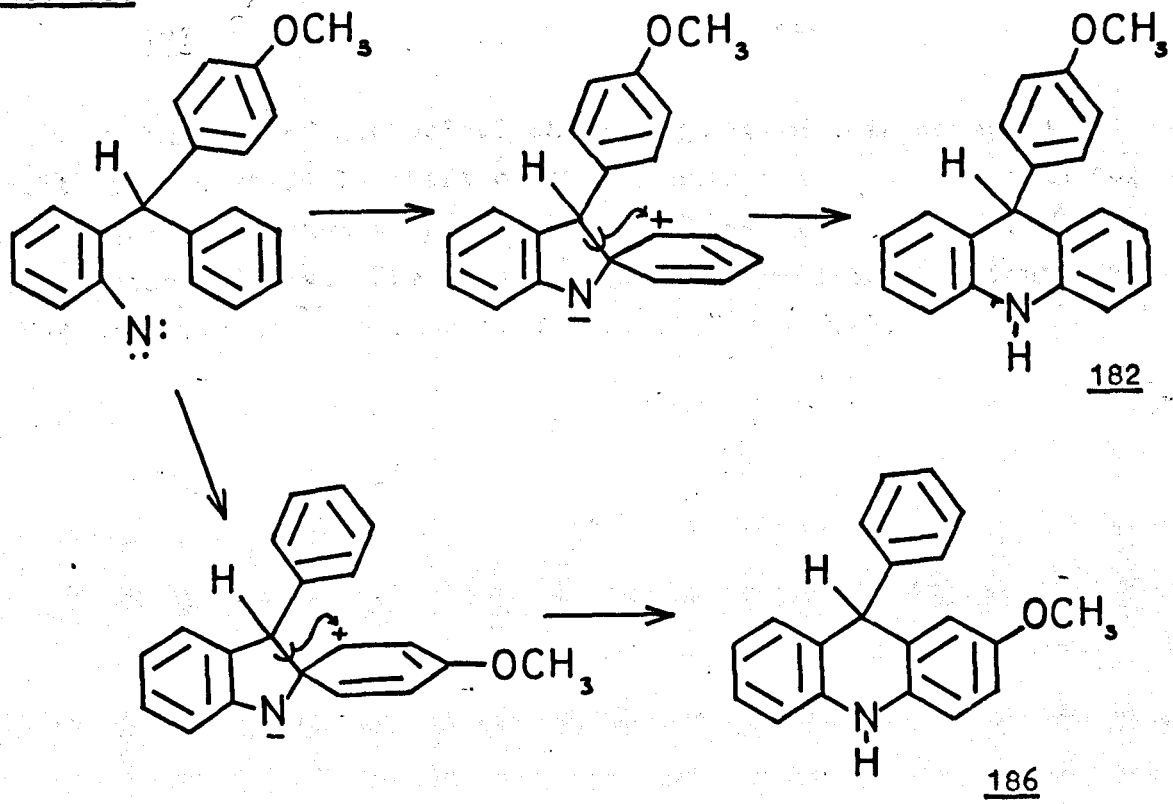


183

182

The spirodienyl mechanism used by Cadogan and co-workers[184] predicts the formation of the dihydroacridines 182 and 186 (Scheme 101).

SCHEME 101

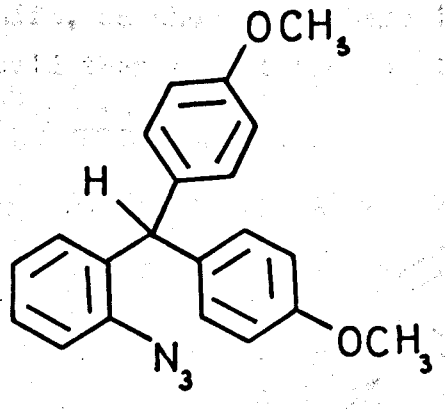


182

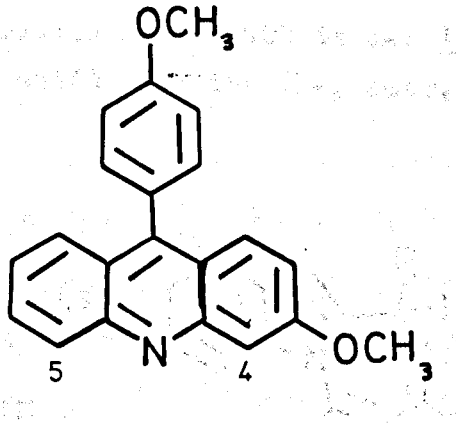
186

The n.m.r. spectra of compounds 182 and 183 differ only in the fine structure of the aromatic proton absorption. The splitting pattern of a para-substituted benzene ring is visible in the spectrum of 182, while in the n.m.r. spectrum of a mixture of 182 and 183, a large singlet due to the absorption of a phenyl group is evident.

Evidence for the 3-methoxy structure was obtained from data on the decomposition of 2-azido-4',4"-dimethoxytriphenylmethane 187[199]. This compound undergoes thermal decomposition to give, amongst other products, a compound identified as 3-methoxy-9-(4-methoxyphenyl)-acridine 188.



187



188

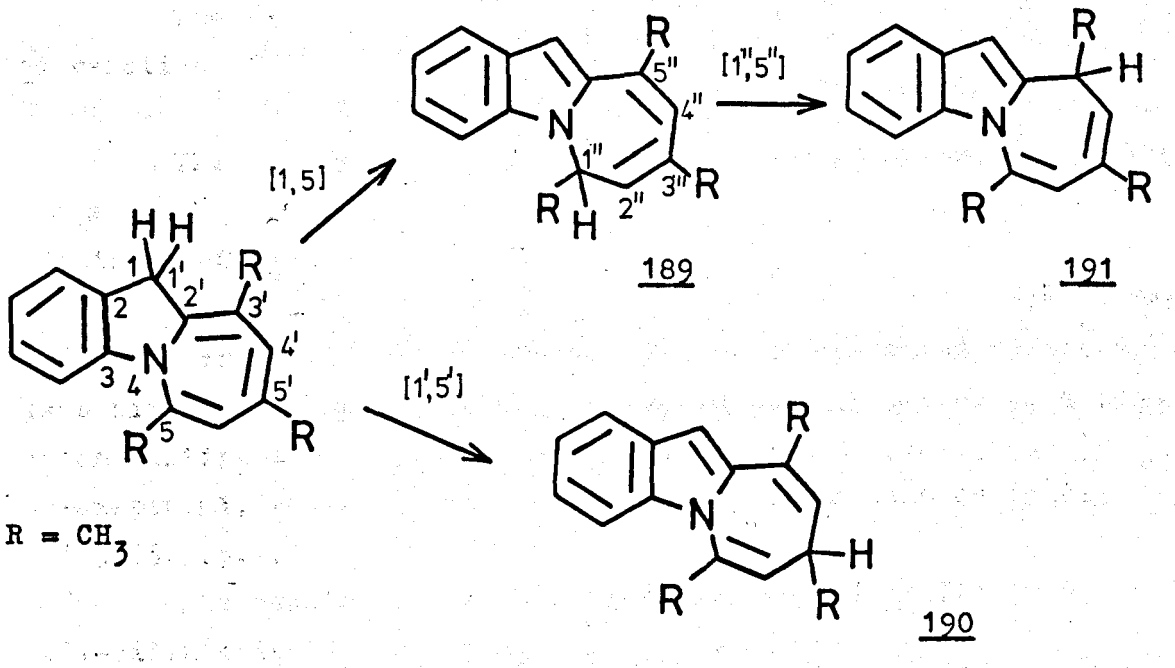
The use of a chemical shift reagent on this compound results in a down-field shift of the signals due to the protons H-4 and H-5 and shows them to be doublets with coupling constants of 2 and 8Hz respectively. The meta-coupling observed in the signal due to H-4 confirms the presence of a substituent at C-3.

MECHANISM

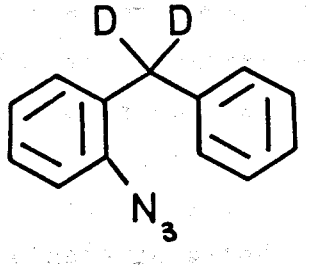
The formation of the 10H-azepino[1,2-a]indoles, according to either of the proposed mechanisms[51,53,184], requires the shift of a hydrogen atom from C-11 to C-10. A suprafacial [1,3] hydrogen shift is forbidden according to the principles of the conservation of orbital symmetry[200] and so other factors must be operating.

The formation of the 6H and 8H isomers 189 and 190[53] could be explained in terms of the symmetry-allowed suprafacial [1,5] hydrogen shift, as shown in Scheme 102; the formation of the 10H isomer 191 could then result from a [1,5] hydrogen shift from the 6H-isomer.

SCHEME 102



To test the validity of this hypothesis it was decided to synthesise and decompose α-(2-azidophenyl)-α',α''-dideuteriotoluene 192. The decomposition of this compound should result, if the above argument is correct, in a distribution of deuterium around the seven-membered ring.



192

Preparation and Decomposition of α-(2-azidophenyl)-α',α"-dideuteriotoluene

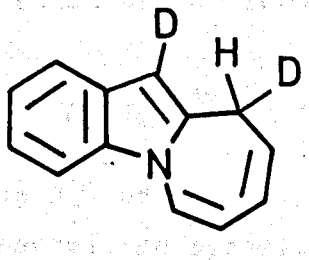
The synthesis of α-(2-aminophenyl)-α',α"-dideuteriotoluene was achieved in high yield (93%) by the reduction of 2-aminobenzophenone by lithium aluminium deuteride and aluminium chloride in a manner analogous to that of the hydride reduction[201-203].

The azide 192 was prepared from the amine by diazotisation and reaction of the diazonium salt with sodium azide.

The decomposition of azide 192 in trichlorobenzene at 187° gave a black solid which recrystallised from petroleum to give the dideuterio derivative of 10H-azepino[1,2-a]indole.

The 220 MHz n.m.r. spectrum of this compound revealed the absence of the H-11 proton which, in the non-deuterated compound, gives rise to a sharp singlet at δ 6.20 and the presence of a one-proton multiplet at δ 3.37 p.p.m.; the C-10 methylene group in 10H-azepino[1,2-a]indole 21 gives a two-proton broadened doublet at δ 3.55 p.p.m.[53].

The remaining signals integrated correctly for 10,11-dideuterio-10H-azepino[1,2-a]indole 193.



193

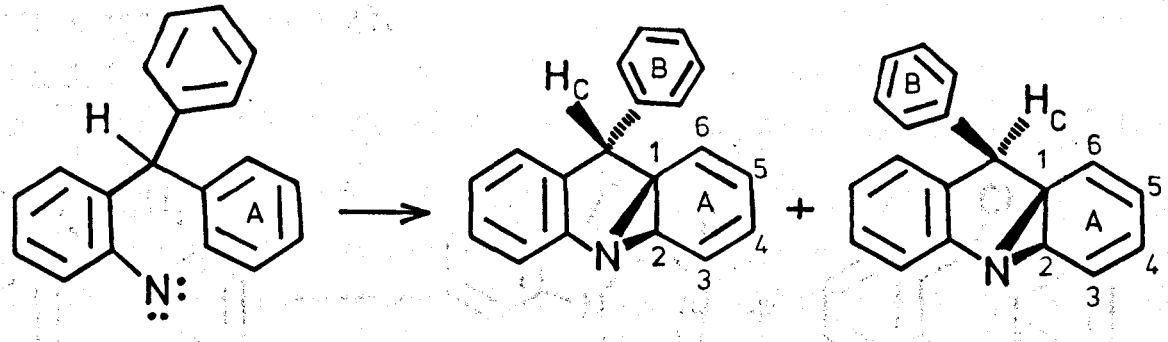
It thus appears that a regiospecific hydrogen atom transfer is occurring in these systems. Whether the transfer is concerted or non-concerted with ring expansion or whether intermolecular hydrogen shifts are occurring is not known. The latter process seems unlikely at the dilutions used in the decomposition.

The transition from a disubstituted methane to a trisubstituted methane resulted, in both the cases studied, in a large increase in the yield of acridan/acridine products (a trace of acridine was noted in the decomposition described above).

The simplest explanation of this is to assume that singlet-triplet transitions had occurred and that the triplet nitrene, in the absence of a proton-donor solvent, underwent intramolecular hydrogen abstraction followed by radical coupling to give the acridan products. The acridine products can be explained in terms of nitrene attack on an acridan or by atmospheric oxidation of the acridan.

A second mechanism considers the stereochemistry of the reactive intermediate (Scheme 103).

SCHEME 103



194 195 196

The insertion of the aryl nitrene 194 into the π-system of the adjacent benzene ring A results in the formation of two stereo-isomers 195 and 196 in equal proportions:

Isomer 195 has H_C and ring B in planes parallel and perpendicular to the plane containing ring A.

Isomer 196 has H_C and ring B in planes perpendicular and parallel to the plane containing ring A.

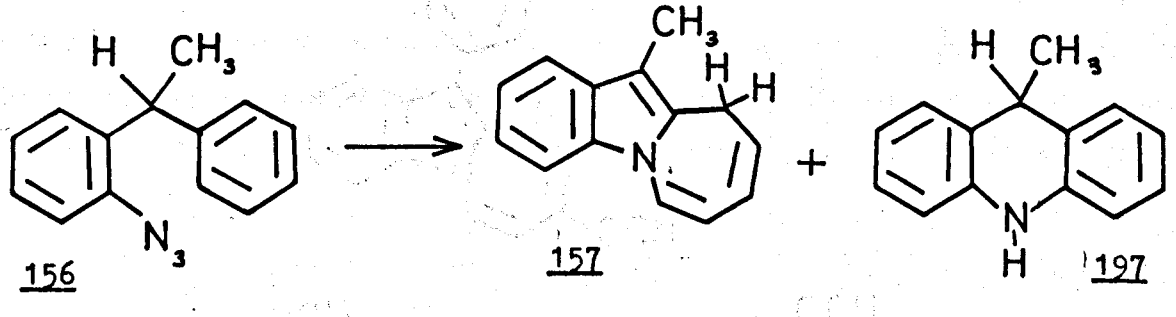
In the ring expansion to an azepinoindole derivative there is a transfer of the methine hydrogen H_C to C-6 of ring A. In isomer 196 this transfer will be facilitated because H_C is in the same plane as the p-orbital of C-6. Thus the fission of the bond between C-1 and C-2 (ring A) results in an electron deficiency at C-1 which is filled by an electron flow from the C-H_C bond and the transfer of the hydrogen atom H_C to C-6.

In isomer 195 the benzene ring B is in the same plane as the p-orbital; hydrogen transfer cannot occur and ring opening to an acridan is observed.

This mechanism could account for the equality in yields observed for the acridan/acridine and azepinoindole products obtained from the decomposition of 2-azidotriphenylmethane and for the regiospecific deuterium transfer observed in the decomposition of the azide 192.

The decomposition of 1-(2-azidophenyl)-1-phenylethane 156 would give, according to the above mechanism, equal yields of 11-methyl-10H-azepino[1,2-a]indole 157 and 9,10-dihydro-9-methyl-acridine 197 (Scheme 104).

SCHEME 104



156 157 197

Jones and Cliff[53] examined the decomposition of this compound and obtained the azepinoindole 157 in 38% yield from the crude product by column chromatography. No other products were isolated from the mixture, probably because, at the time the experiment was performed, the main interest lay in confirming the structure of 10H-azepino[1,2-a]indole. The acridan and acridine products would have a much longer retention time on the column than the azepinoindole 157, particularly with petroleum as the eluant and would not be observed.

The product distribution obtained from the decomposition of 2-azido-4'-methoxytriphenylmethane 160 tends to agree with the theoretical distribution of products discussed above.

The reaction pathway favoured the anisyl ring to an extent of approximately 65% and the ratio of ring-inserted to acridan products was again approximately 50:50.

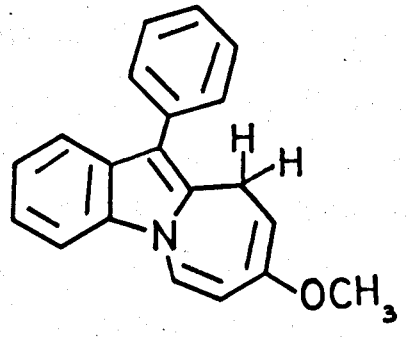
The mechanism of the formation of the pyrido-indole 181 derivative is unknown.

The features which are known about the formation of the pyrido-indole 181 are as follows:

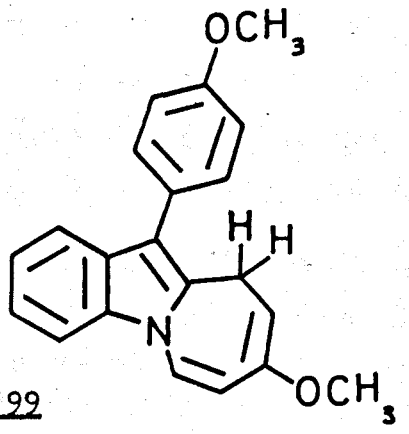
The formation must be due to the presence of both the phenyl group and the methoxyl group since the absence of either results in 'normal', azepinoindole, products being obtained.

Although the methoxyazepino[1,2-a]indole 198 was not detected amongst the decomposition products, the pyrido-indole cannot be an abnormally stabilised intermediate in its formation because:

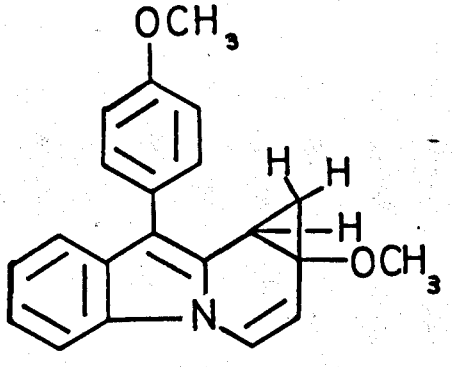
(a) Jones and McKinley[199] have observed the presence of both the azepinoindole 199 and the pyrido-indole 200 in the decomposition of 2-azido-4,4'-dimethoxytriphenylmethane 187.



198



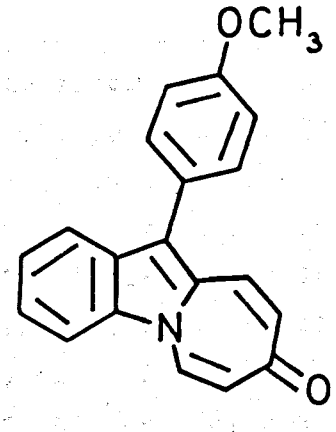
199



200

and (b) the pyrido-indole 181 on prolonged heating at 195° in trichlorobenzene does not give the azepinoindole but a complex mixture of products. Some of these products had g.l.c. retention times which were similar to those observed for the acridan and acridine products obtained from the decomposition of the azide 160.

The decomposition of the dimethoxy pyridoindole 200 also gave a mixture of products, one of which was isolated and characterised as the azepino[1,2-a]indol-8-one 201[199].



201

MASS SPECTRA

In the mass spectrum of 11-phenyl-10H-azepinoindole 178 the loss of one mass unit from the molecular ion and base peak at $^{m}/e$ 257 gives an ion corresponding to the aromatic azepinoindolium system. Other significant peaks in the spectrum are at $^{m}/e$ 180 which represents the loss of a phenyl group and at $^{m}/e$ 128.5 which is due to the doubly charged 11-phenyl-10H-azepinoindole system.

The mass spectrum of the 11-(4-methoxyphenyl)-10H-azepinoindole 180 is dominated by the breakdown pattern of the anisyl group. The major fragmentation is loss of CH_3 to give an ion at $^{m}/e$ 272. The peak at $^{m}/e$ 242 could then be produced by loss of CO and H. Other minor peaks occur at $^{m}/e$ 180, which represents the loss of the anisyl group and at $^{m}/e$ 143.5 which is due to the doubly charged 11-anisyl-10H-azepinoindole system.

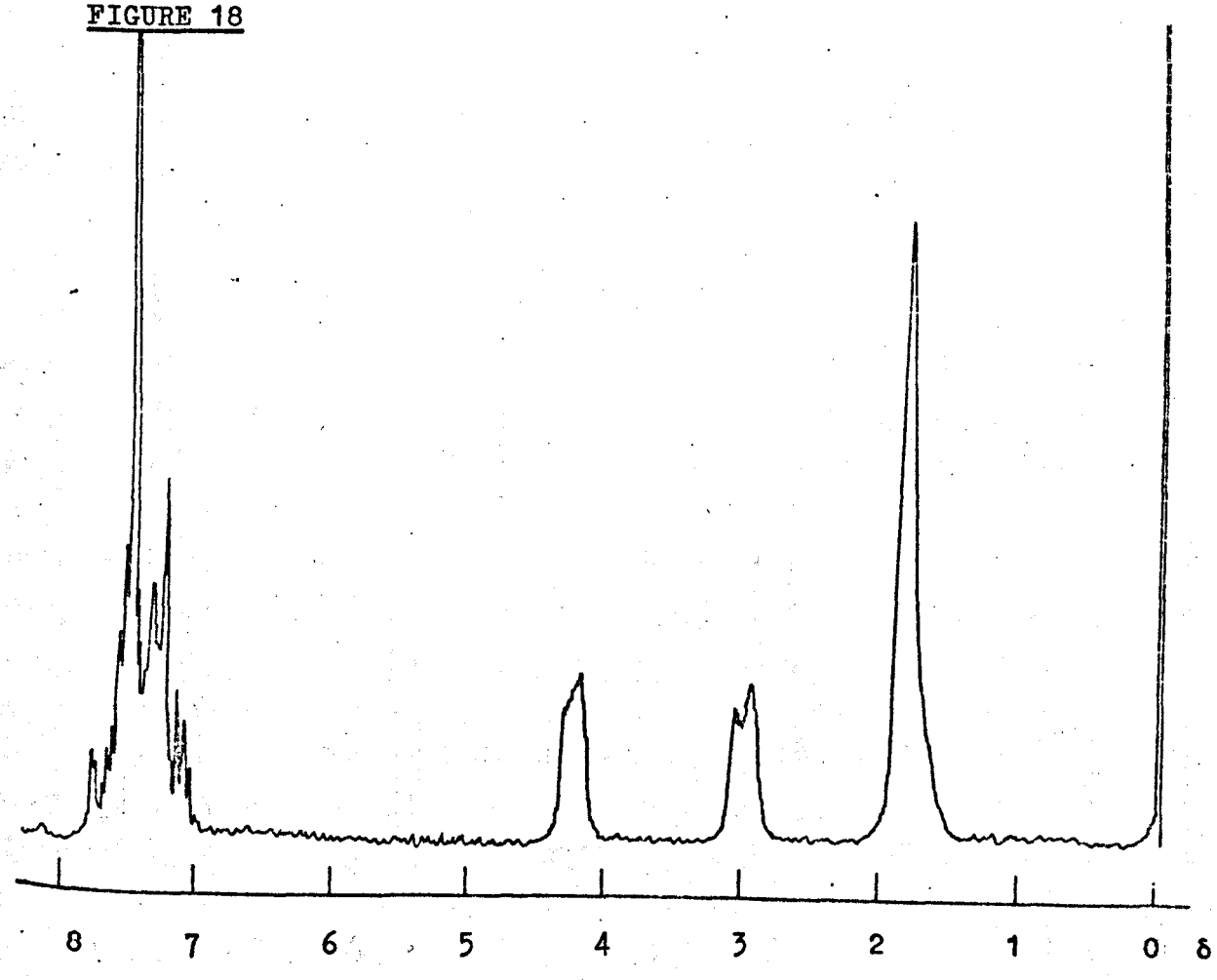
The principle features of the mass spectrum of the pyridoindole 181, excluding the molecular ion and base peak at $^{m}/e$ 287, are peaks at $^{m}/e$ 274, 256 and 242. The first two peaks are due to the loss of CH_3 and CH_3O respectively from the molecular ion. The third peak corresponds to the loss of 14 mass units (CH_2) from the peak at $^{m}/e$ 256 and could be due to the cleavage of the cyclopropane ring methylene group.

FURTHER WORK ON THE AZIDE DECOMPOSITION PRODUCTS

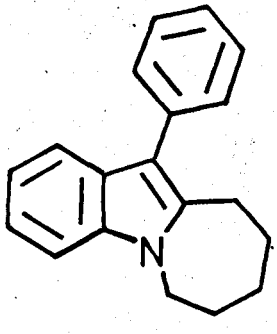
Reduction of 11-phenyl-10H-azepino[1,2-a]indole

The catalytic reduction of the azepinoindole 178 gave a high yield of a compound identified as 6,7,8,9-tetrahydro-11-phenyl-10H-azepino[1,2-a]indole 202 from its n.m.r. spectrum (Figure 18). This spectrum is very similar to that of the corresponding 11-methyl derivative[52,53].

FIGURE 18



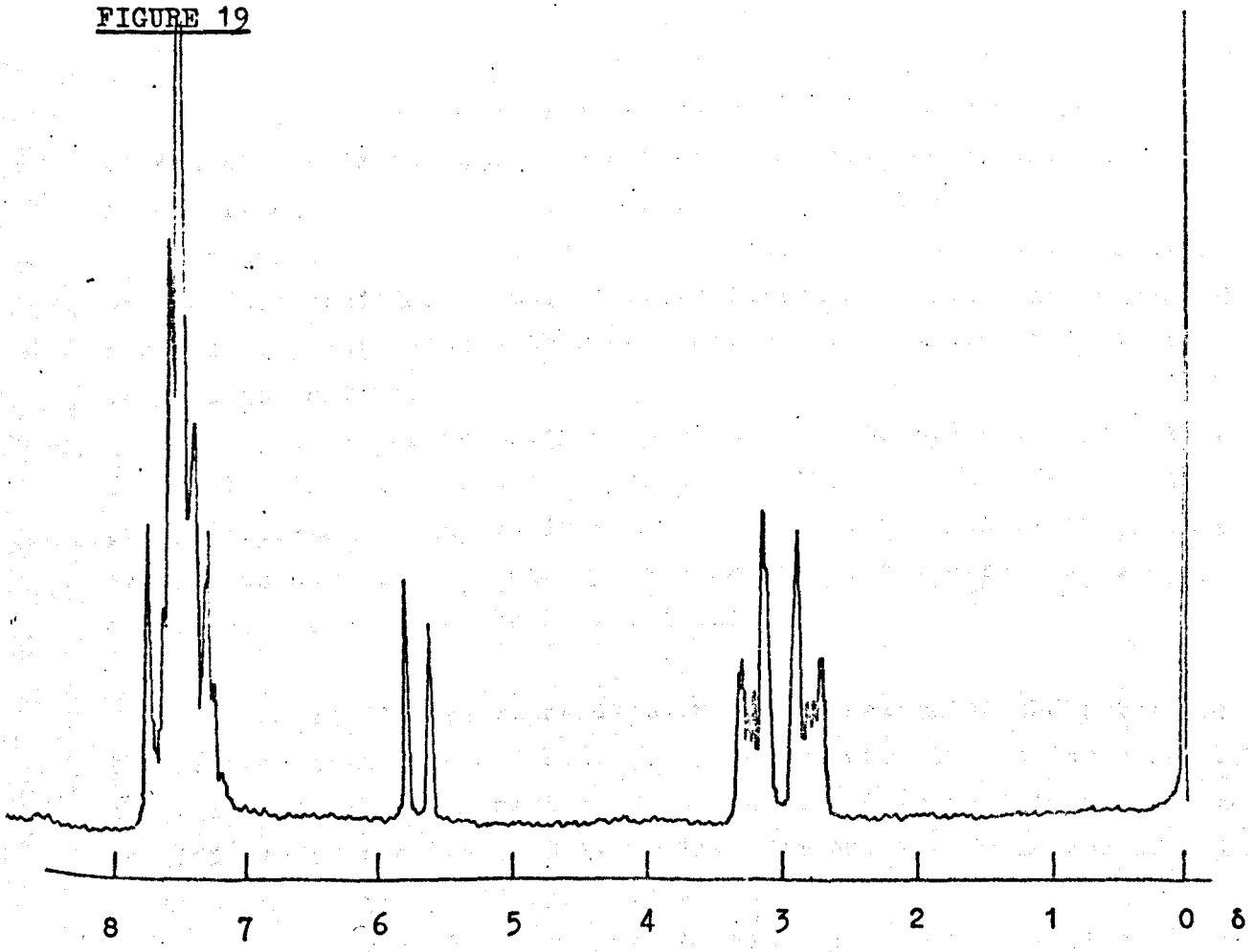
202



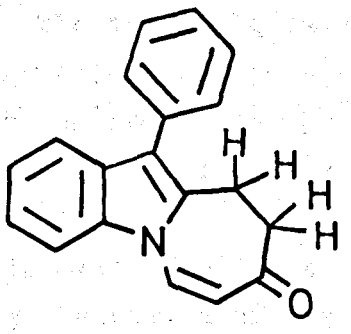
Hydrolysis of the pyridoindole 181

The pyridoindole 181 dissolved readily in concentrated hydrochloric acid with hydrolysis of the methyl ether. A high yield of the expected product, 9,10-dihydro-11-phenylazepino[1,2-a]-indol-8-one 203 was obtained. Its structure was confirmed by the examination of its n.m.r. spectrum (Figure 19).

FIGURE 19



203



The mass spectrum of this compound shows, in addition to the molecular ion and base peak at $^{m}/e$ 273, two major peaks at $^{m}/e$ 245 and 244. These are due to the loss of CO and CHO from the molecular ion.

CONCLUSION

The experiments discussed in Part II clearly show the effect of annelation upon the nitrene insertion reaction. The normal reaction towards a benzene ring is insertion and subsequent ring expansion and the formation of an azepinoindole as illustrated by the decomposition of the tetralin derivatives. In the annelated systems ring expansion either does not occur or occurs only to a very slight extent.

Since the geometry of the naphthalene and tetralin systems is similar the different stabilisation pathway of the (2-nitrenophenyl)naphthalene derivatives must be due to the inability of these systems to overcome the energy barrier associated with the loss of aromaticity of the naphthalene molecule.

Part III describes experiments to determine the nature of the nitrene insertion and hydrogen atom transfer in the formation of the azepinoindoles. A mechanism is postulated to explain the regiospecificity of the hydrogen atom transfer and the formation of both acridan and azepinoindole products.

A series of experiments to determine the reactivity of the nitrene towards phenyl groups bearing different substituents was planned but not completed. The available data indicates the tendency of the nitrene to favour the anisyl group in preference to the phenyl group but no general conclusion about the correlation of nitrene reactivity and electron availability can be drawn from this evidence.

Other work in this area of nitrene chemistry could be directed towards completing the series of experiments and widening its scope to include other electron donating groups in order to determine whether the formation of the pyridoindole derivative is primarily a function of the methoxyl group.

EXPERIMENTAL

EXPERIMENTAL

PRELIMINARY NOTES

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

Infra red absorption spectra were recorded on a Perkin Elmer 257 spectrophotometer. The spectra of solids were determined in nujol mulls (mull) or in solution (e.g. CCl_4). The spectra of liquids were determined as liquid films (film) or in solution.

Ultra violet and visible absorption spectra were recorded on a Unicam SP 800 instrument.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Perkin Elmer R10 60 MHz instrument, Hitachi-Perkin Elmer R24 60 MHz instrument and HR - 220 MHz instrument (P.C.M.U., Harwell). The chemical shifts are quoted as 'delta' (δ) values in parts per million (p.p.m.) using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet; d = doublet; t = triplet; q = quadruplet; m = multiplet; br = broadened; and ex = exchanged.

Micro-analyses were carried out on an F and M carbon/hydrogen/nitrogen analyser and Perkin Elmer Elemental Analyser 240 at the University of Keele.

Mass spectra were recorded on a Hitachi-Perkin Elmer RMU-6 instrument using a heated inlet. 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.

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 were: OV101 (dimethyl silicone fluid) and OV17

(phenyl methyl silicone fluid). Detection of the eluted components of a mixture was by a hydrogen flame ionisation detector. The chart speed was normally 1 cm/min.

Thin layer chromatography was carried out on microscope slides (7.5 x 2.5 cm) coated with silica gel (Merck Kieselgel PF_{254}). The components were visualised under ultra violet 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_{254}). The separated components, visualised under ultra violet 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.

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

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.

The photolytic work was performed using a Rayonet Preparative Reactor with 16 RUL-3000 A lamps of maximum intensity at 300 nm. The solutions were contained in a quartz vessel (capacity 650 ml) and kept at room temperature by means of a 'cold finger' apparatus.

PART I

SECTION 1

PREPARATION OF 4- AND 5-AZIDOINDAN

4- and 5-nitroindan

A mixture consisting of ∿40% 4-nitroindan and ∿60% 5-nitroindan was obtained from indan by the following procedure which is a modification of the reaction originally described by Lindner and Bruhin[149].

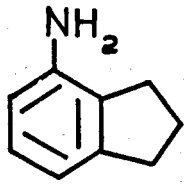
A solution of fuming nitric acid (50 g) in sulphuric acid (150 g) was added dropwise to vigorously stirred indan (100 g) maintained at -5°. When the addition was complete (5 h) the mixture was poured on to crushed ice. The red oily product was separated, washed with saturated aqueous sodium carbonate (3 x 100 ml) and water (3 x 100 ml), dissolved in ether and dried ($MgSO_4$). The solvent was removed and the oil eluted down a column of alumina (300 g, activity IV) in petroleum (b.p. 60-80°). From the eluate was obtained 45 g of the mixed 4- and 5-nitroindans.

4- and 5-aminoindan

A solution of the mixed nitroindans (16.3 g) in methanol (150 ml) containing 10% palladium-on-charcoal (1.0 g) in suspension was hydrogenated at atmospheric temperature and pressure until absorption had ceased (3 molar-equivalents H_2). The filtered solution was warmed to 60° and treated with fumaric acid (6.1 g) as described by Rhomberg and Berger[150]. When the acid had dissolved the solution was cooled to 0° and kept at this temperature for four hours to facilitate crystallisation of the 5-aminoindan fumarate. The salt was filtered off and washed with cold methanol until it was colourless.

The filtrate and washings were evaporated to dryness and the residue stirred with ether (50 ml) and petroleum (b.p. 60-80°) (50 ml). The mixture was kept at 0° for one hour and then filtered. The residue was washed with ether/petroleum (100 ml 1:1) and then

discarded. The combined ether/petroleum solutions were evaporated to small volume and cooled. The mixture was filtered, the residue washed with ether/petroleum (100 ml 1:1) and discarded. The combined washings and filtrate were evaporated to dryness to give 4-aminoindan (4.5 g, 33%).



4-aminoindan

B.p. 65°, 0.1 mm Hg

N.m.r. (CCl_4)

δ 1.7 - 2.25 p.p.m.		m	2H	H on C-2
2.35 - 3.0		m	4H	H on C-1 and 3
3.55	br	s	2H	$-NH_2$ (ex. with D_2O)
6.23		d	1H	H on C-5 $J_{5,6}$ = 7.5Hz
6.52		d	1H	H on C-7 $J_{6,7}$ = 7.5Hz
6.84		t	1H	H on C-6

I.r. (film)

ν_{max} 3450, 3362, 1620 cm^{-1}

U.v. (95% ethanol)

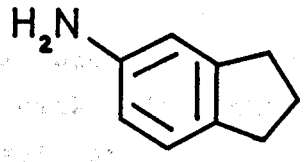
λ_{max}	237 nm	$\log_{10} \varepsilon$	3.83
	283		3.19

Mass spectrum

m/e 134 (23%), 133 (M^+)(100%), 132 (84%), 131 (12%), 130 (14%), 120 (7%), 119 (5%), 118 (9%), 117 (23%), 116 (10%), 115 (21%), 106 (7%), 105 (6%), 104 (5%), 103 (7%), 91 (6%), 79 (6%)

The fumarate salt was shaken with a mixture of saturated aqueous sodium carbonate (75 ml) and chloroform (30 ml) for one hour. The chloroform was separated and the aqueous layer washed with chloroform (2 x 30 ml). The combined chloroform solutions were dried (Na_2SO_4) and evaporated to give 5-aminoindan (5.3 g, 40%).

5-aminoindan



M.p. 34° (petroleum b.p. 60-80°)

Lit.[150] 33 - 34°

N.m.r. (CCl_4)

δ 1.8 - 2.2 p.p.m.	m	2H	H on C-2	
2.73	br t	4H	H on C-1 and 3	
3.25	s	2H	$-NH_2$ (ex. with D_2O)	
6.28	d of d	1H	H on C-6	$J_{6,7}$ = 8Hz, $J_{4,6}$ = 2Hz
6.37	br s	1H	H on C-4	
6.84	d	1H	H on C-7	$J_{6,7}$ = 8Hz

I.r. (film)

ν_{max} 3420, 3345, 1616 cm^{-1}

U.v. (95% ethanol)

λ_{max}	236.5 nm	$\log_{10} \varepsilon$ 3.88
	293	3.39

Mass spectrum

m/e 134 (13%), 133 (M^+)(89%), 132 (100%), 131 (15%), 130 (19%), 117 (22%), 115 (19%), 106 (9%), 105 (8%), 104 (6%), 103 (8%), 102 (6%), 92 (6%), 77 (16%)

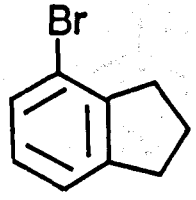
4-bromoindan

A solution of 2-bromotoluene (243 g) in carbon tetrachloride (1 l) was refluxed for five hours with N-bromosuccinimide (252 g) to give 2-bromobenzyl bromide (292 g 82%). This was added dropwise over two hours to a refluxing solution of diethyl malonate (264 g) and sodium (34.5 g) in dry ethanol (750 ml). The solution was refluxed for a further five hours and then ethanol (600 ml) was distilled out and water (1 l) added. The 2-bromobenzyl malonic ester was separated and dissolved in a refluxing solution of potassium hydroxide (300 g) in water (1 l). Addition of hydrobromic acid (500 ml) to the cooled solution precipitated the 2-bromobenzyl malonic acid which was filtered off

and heated to 170° to effect decarboxylation to give 2-bromobenzyl acetic acid (194 g, 73%).

Treatment of the acid with thionyl chloride (165 g) followed by aluminium chloride (248 g) in carbon disulphide (250 ml) gave after hydrolysis and removal of the solvent 4-bromoindan-1-one. Clemmensen reduction using ethanol as co-solvent gave 4-bromoindan (63 g, 38%).

4-bromoindan



B.p. 109°, 13 mm Hg

Lit.[151] 90°, 0.1 mm Hg

N.m.r. (CCl_4)

δ 1.9 - 2.4 p.p.m.	m	2H	H on C-2
2.7 - 3.2	m	4H	H on C-1 and 3
6.7 - 7.4	m	3H	arom.

I.r. (film)

ν_{max} 3055, 1597, 1566 cm^{-1}

U.v. (95% ethanol)

λ_{max}	219 nm	sh
	228	sh
	251	$\log_{10} \varepsilon$ 3.34

Mass spectrum

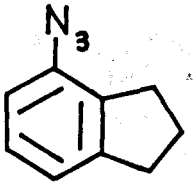
m/e 198 ($M^+ + 2$) (30%), 197 (6%), 196 (M^+) (35%), 195 (3%), 118 (25%), 117 (100%), 116 (40%), 115 (96%), 114 (7%), 91 (14%), 89 (12%).

4-azidoindan 90

Method A: A solution of 4-aminoindan (5.85 g, 0.05 M) in a mixture of 4N sulphuric acid (250 ml) and purified 1,4-dioxan (250 ml) was cooled to -5° and a solution of sodium nitrite (3.8 g, 0.055 M) in water (50 ml) was added with stirring. After 15 minutes a solution of sodium azide (3.6 g, 0.055 M) in water (50 ml) was added and the solution was warmed gently to 30°.

The azide was extracted with ether (3 x 200 ml) and the combined ethereal extracts dried ($MgSO_4$). The solvent was removed under reduced pressure at 30° and the residual oil was percolated through a column of alumina (200 g, activity IV, column length 0.2m) in petroleum (b.p. 40-60°). Evaporation of the solvent, under reduced pressure at 30°, left the azide as a pale yellow oil (4.8 g, 60%).

4-azidoindan 90



Analysis

Found:	C, 67.5;	H, 6.1%
$C_9H_9N_3$ requires:	C, 67.9;	H, 5.7%

N.m.r. ($CDCl_3$)

δ 1.8 - 2.4 p.p.m.	m 2H	H on C-2
2.6 - 3.1	m 4H	H on C-1 and 3
6.7 - 7.2	m 3H	arom

I.r. (film)

ν_{max} 2105, 1295 cm^{-1}

U.v. (95% ethanol)

λ_{max}	252.5 nm	$\log_{10} \varepsilon$ 4.0
	278.5	3.47
	288	3.38

Mass spectrum

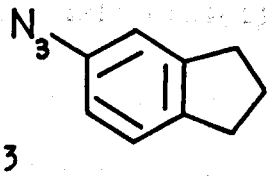
$^m/_e$ 159 (M^+) (20%), 132 (15%), 131 (100%), 130 (20%), 102 (20%)

Method B : The Grignard reagent from 4-bromoindan (29.3 g) and magnesium (7.41 g) in dry ether (200 ml) was added at -5° to a stirred solution of p-toluenesulphonylazide (32.3 g) in dry ether (500 ml). The precipitated triazene salt was filtered off, washed with ether and vacuum-dried. A saturated aqueous solution of sodium pyrophosphate (500 ml) was added dropwise to a cold (-5°), stirred, suspension of the dried triazene salt in dry ether. The mixture was stirred (24 h), the ether layer removed and the aqueous layer extracted with ether (2 x 200 ml). The combined ethereal

extracts were dried ($MgSO_4$) and evaporated at 30° under reduced pressure. Purification as in Method A gave 4-azidoindan 90 (6.5 g, 27%) identical with that prepared as in A.

5-azidoindan 91

Prepared by Method A, as above, from 5-aminoindan in 22% yield, 5-azidoindan 91 was a yellow oil.



N.m.r. (CCl_4)

δ 1.8 - 2.2 p.p.m.	m	2H	H on C-2
2.5 - 2.9	m	4H	H on C-1 and 3
6.8 - 7.2	m	3H	arom

I.r. (film)

ν_{max} 2105, 1298 cm^{-1}

U.v. (95% ethanol)

λ_{max}	250 nm	$\log_{10} \varepsilon$	4.0
	280		3.45
	290		3.3

Mass spectrum

$^m/_e$ 159 (M^+) (10%), 132 (20%), 131 (100%), 130 (10%), 102 (15%).

PREPARATION OF 4-AZIDOBENZOCYCLOBUTENE

Benzocyclobutene

Benzocyclobutene was prepared by the following methods:

i. The vapour phase pyrolysis of 1,3-dihydroisothianaphthen-2,2-dioxide as described by Oliver and Ongley[152].

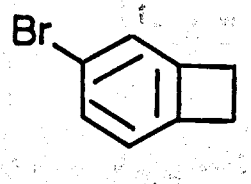
ii. The reduction of 1,2-dibromobenzocyclobutene with tri(n-butyl)tin hydride as described by Sanders and Giering[153].

4-bromobenzocyclobutene

A solution of benzocyclobutene (8.6 g) and iodine (0.2 g) in acetic acid (100 ml) was cooled to 0° and a solution of bromine (14.6 g) in acetic acid (10 ml) added dropwise. The mixture was left for 48 hours and then water (1 l) was added. The oily product was extracted with petroleum (b.p. 40-60°, 4 x 100 ml); the extracts were washed with saturated aqueous sodium sulphite (2 x 50 ml), saturated aqueous sodium carbonate (2 x 50 ml) and water (2 x 50 ml) and then dried ($MgSO_4$).

Evaporation of the solvent gave a yellow oil which was shown by thin layer chromatography to comprise two components. Chromatography on alumina (260 g, activity IV) in petroleum (b.p. 40-60°) gave in the first fraction 4-bromobenzocyclobutene (11.2 g, 74%)

4-bromobenzocyclobutene



B.p. 110 - 120°, 16 mm Hg

Lit.[154] 118 - 119°, 20 mm Hg

N.m.r. (CCl_4)

δ 3.08 p.p.m.	s	4H	H on C-1 and 2
6.6 - 7.4	m	3H	arom

I.r. (film)

ν_{max} 1570 cm^{-1}

U.v. (95% ethanol)

λ_{max} 273 nm $\quad \log_{10} \varepsilon$ 3.34

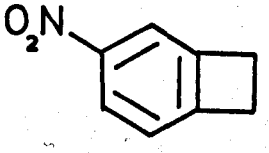
Mass spectrum

$^{m}/_{e}$ 185 (22%), 184 (M^{+}+ 2) (84%), 183 (24%), 182 (M^{+}) (84%), 104 (51%), 103 (100%), 102 (27%), 77 (54%)

4-nitrobenzocyclobutene

Benzocyclobutene (25.8 g) was added dropwise to a stirred mixture of fuming nitric acid (103 ml) and acetic acid (52 ml) maintained at 10°. When the addition was complete the solution was allowed to warm to room temperature and then diluted with water (1 l). The organic material was extracted with ether (3 x 200 ml), the ethereal extracts were washed with water (2 x 100 ml), 1N-sodium hydroxide solution (100 ml) and water (2 x 100 ml) and dried ($MgSO_4$). Column chromatography on alumina (200 g, activity IV) in petroleum (b.p. 40-60°)/dichloromethane (4:1) gave a mixture from which 4-nitrobenzocyclobutene was obtained by distillation, (10 g, 26%).

4-nitrobenzocyclobutene



B.p. 70 - 85°, 0.1 mm Hg

Lit.[155] 60 - 85°, 0.05 mm Hg

N.m.r. (CCl_4)

δ 3.22 p.p.m.	s	4H	H on C-1 and 2	
7.08	d	1H	H on C-6	$J_{5,6}$ = 8Hz
7.72	s	1H	H on C-3	
7.96	d of d	1H	H on C-5	

$J_{5,6}$ = 8Hz, $J_{3,5}$ = 2Hz

I.r. (film)

ν_{max} 1515, 1345 cm^{-1}

U.v. (95% ethanol)

λ_{max}	221 nm	$\log_{10} \varepsilon$	3.92
	275		3.82

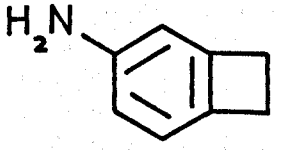
Mass spectrum

$^{m}/e$ 150 (10%), 149 (M^+) (100%), 103 (40%), 102 (20%), 91 (32%), 78 (8%), 77 (76%), 76 (10%), 75 (10%), 74 (10%)

4-aminobenzocyclobutene

A solution of the nitro- compound (9 g) in methanol (250 ml) containing 10% palladium-on-charcoal (1 g) in suspension was hydrogenated at atmospheric temperature and pressure until absorption ceased. Evaporation of the filtered solution gave 4-aminobenzocyclobutene (6.9 g, 98%) as a brown oil.

4-aminobenzocyclobutene



B.p. 85 - 90°, 0.15 mm Hg

N.m.r. (CCl_4)

δ 3.1 p.p.m.	s	4H	H on C-1 and 2
3.32	s	2H	$-NH_2$ (ex. with D_2O)
6.2 - 6.8	m	3H	arom

I.r. (film)

ν_{max} 3420, 3340, 3200, 1605, 1590 cm^{-1}

U.v. (95% ethanol)

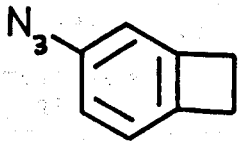
λ_{max}	$\log_{10} \varepsilon$
236 nm	3.76
293	3.35

Mass spectrum

$^{m}/e$ 120 (9%), 119 (M^+) (100%), 118 (51%), 117 (13%), 104 (7%), 93 (8%), 92 (8%), 91 (35%), 65 (10%), 59 (10%)

4-azidobenzocyclobutene 92

Method A : Prepared as described for 4-azidoindan 90 in 74% yield, the azide 92 was a yellow oil.



N.m.r. (CCl_4)

δ 3.1 p.p.m.	s	4H	H on C-1 and 2
6.6 - 7.0	m	3H	arom

I.r. (film)

ν_{max} 2109, 1292 cm^{-1}

U.v. (95% ethanol)

λ_{max} 251.5 nm	$\log_{10} \varepsilon$ 4.01
282.5	3.56

Mass spectrum

m/e 145 (M^+) (18%), 120 (26%), 119 (100%), 118 (89%), 117 (44%), 116 (27%), 104 (13%), 103 (15%), 93 (13%), 92 (21%), 91 (49%), 90 (37%), 89 (37%), 77 (27%), 65 (27%), 51 (29%)

Method B : Prepared from 4-bromobenzocyclobutene via the Grignard reagent and tosyl azide in 11% yield, the 4-azidobenzocyclobutene 92 was identical with the material derived from the amine.

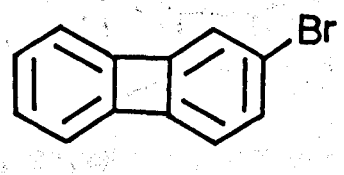
PREPARATION OF 2-AZIDOBIPHENYLENE

Biphenylene

Biphenylene was prepared by the thermal decomposition of benzenediazonium-2-carboxylate in boiling 1,2-dichloroethane according to the method of Logullo, Seitz and Friedman[156]. Eight decompositions yielded 23 g (13%) of dried biphenylene.

2-bromobiphenylene

A solution of bromine (5.5 ml) in carbon tetrachloride (25 ml) was added dropwise to a stirred solution of biphenylene (10 g) in carbon tetrachloride (100 ml) and pyridine (0.1 ml). After refluxing for 0.5 hours the solution was cooled, washed with saturated aqueous sodium bicarbonate (2 x 50 ml) and water (2 x 50 ml), dried ($MgSO_4$) and distilled. The fraction boiling between 120 - 150°, 2 mm Hg gave 2-bromobiphenylene[157] (7.6 g, 50%).



M.p. 64 - 65° (petroleum b.p. 40 - 60°)

Lit.[157] 64 - 65°

Analysis

Found:	C,	61.9;	H, 3.2%
$C_{12}H_7Br$ requires:	C,	62.3;	H, 3.0%

N.m.r. (CCl_4)

δ 6.3 - 7.0 p.p.m. m

I.r. (mull)

ν_{max} 3065, 3040, 1570 cm^{-1}

U.v. (95% ethanol)

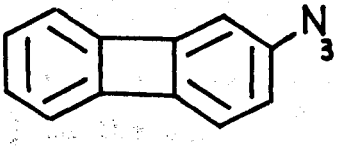
λ_{max}		$\log_{10} \varepsilon$
245.5 nm		4.75
253		4.85
326	sh	
345		3.71
359		3.69

Mass spectrum

$^{m}/e$ 233 (16%), 232 ($M^+ + 2$) (100%), 231 (16%), 230 (M^+) (100%), 152 (18%), 151 (68%), 150 (43%)

2-azidobiphenylene 93

The Grignard reagent from 2-bromobiphenylene (7 g) and magnesium (0.88 g) in dry tetrahydrofuran (200 ml) was filtered and added dropwise to a stirred solution of tosyl azide (13 g) in dry ether (250 ml) maintained at 0°. When the addition was complete, petroleum (b.p. 40-60°, 250 ml) was added and the mixture stirred (0.5 h) until precipitation was complete. The triazene salt was filtered off, washed with dry ether, and vacuum-dried. Decomposition of the triazene with aqueous sodium pyrophosphate as described for the preparation of 4-azidoindan (Method B) gave, after percolation through alumina, 2-azidobiphenylene 93 (2.6 g, 44%).



M.p. 80 - 81° (petroleum b.p. 60 - 80°)

Analysis

Found:	C, 74.5;	H, 4.05;	N, 21.4%
$C_{12}H_7N_3$ requires:	C, 74.6;	H, 3.65;	N, 21.75%

N.m.r. (CCl_4)

δ 6.2 - 6.8 p.p.m. m

I.r. (CCl_4)

ν_{max} 2100, 1288 cm^{-1}

U.v. (95% ethanol)

λ_{max}	$\log_{10} \varepsilon$
239 nm	4.34
261.5	4.66
353	3.88
363	3.88

Mass spectrum

$^{m}/e$ 193 (M^+) (30%), 167 (14%), 166 (18%), 165 (100%), 164 (84%), 139 (21%), 137 (12%)

SECTION 2

DECOMPOSITION OF THE AZIDES

Standard Procedure : A solution of the azide in dried (NaOH), distilled diethylamine (concentration range 2.5 - 7 g/600 ml), contained in a quartz vessel, was irradiated in a Rayonet Preparative Photochemical Reactor using 16 RUL - 3000A lamps of maximum intensity at 300 nm. Evaporation of the solvent gave an oil or tar which was examined by linked gas chromatography-mass spectrometry for azepine products. The products were isolated as described for the individual azides.

DECOMPOSITION OF 4-AZIDOINDAN 90

Irradiation of the azide 90 (6.5 g) (40 h) gave, after removal of the solvent, a black tar which was dissolved in benzene and chromatographed on alumina (300 g, activity IV) in the same solvent.

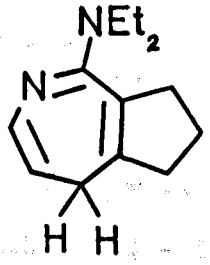
Seven fractions (100 ml) were obtained:

Fraction 1 (0.1 g) was not identified.

Fraction 2 (1.0 g) was chromatographed on five preparative layer plates using benzene/acetone (4 : 1) as the solvent. Two major bands were observed. The one of lower R_F was removed and extracted to yield 20 mg of cyclopentazepine 99c (see below). The one of higher R_F gave cyclopentazepine 94 (110 mg) (see below).

Fraction 3 (1.4 g) was chromatographed on seven plates in benzene/acetone (4 : 1). Four major bands were observed, three of which were identified. In order of increasing R_F value these were:

(a) 1-diethylamino-5,6,7,8-tetrahydrocyclopent[c]azepine 99b



Yield 170 mg

B.p. 90°, 0.02 mm Hg

Analysis

Found: N, 13.7%

$C_{13}H_{20}N_2$ requires: N, 13.7%

N.m.r. (CCl_4)

δ 1.11 p.p.m.	t	6H	$-CH_2-\underline{CH_3}$	J = 7Hz
1.6 - 2.2	m	2H	H on C-7	
2.2 - 2.7	m	6H	H on C-5, 6 and 8	
3.26	q	4H	$-\underline{CH_2}-CH_3$	J = 7Hz
4.6	br q	1H	H on C-4	
6.41	d	1H	H on C-3	$J_{3,4}$ = 7Hz

I.r. (film)

ν_{max} 1638, 1587 cm^{-1}

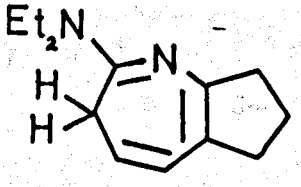
U.v. (95% ethanol)

λ_{max}	225 nm	$\log_{10} \varepsilon$ 4.02
	284	3.80

Mass spectrum

m/e 205 (20%), 204 (M^+) (100%), 203 (20%), 202 (10%), 189 (69%), 176 (20%), 175 (98%), 161 (25%), 160 (6%), 159 (6%), 147 (18%), 134 (12%), 133 (38%), 132 (41%), 131 (12%), 130 (16%), 120 (24%), 105 (16%), 104 (8%), 102 (8%), 91 (16%), 79 (16%), 78 (8%), 77 (20%), 72 (35%)

(b) 2-diethylamino-3,6,7,8-tetrahydrocyclopent[b]azepine 99c



Yield 200 mg

B.p. 110°, 0.1 mm Hg

Analysis

Found: C, 77.1; H, 9.85; N, 13.7%

$C_{13}H_{20}N_2$ requires: C, 76.45; H, 9.85; N, 13.7%

N.m.r. ($CDCl_3$)

δ 1.1 p.p.m.	t	6H	$-CH_2-\underline{CH_3}$	J = 7Hz
1.6 - 2.1	m	2H	H on C-7	
2.4 - 2.8	m	6H	H on C-3, 6 and 8	
3.34	q	4H	$-\underline{CH_2}-CH_3$	J = 7Hz
4.80	br q	1H	H on C-4	
6.15	d	1H	H on C-5	$J_{4,5}$ = 8.5Hz

Addition of $Eu(fod)_3$ resolved the signal at δ 2.4 - 2.8 p.p.m. into

d	2H	H on C-3	$J_{3,4}$ = 7Hz
br t	2H	H on C-6	$J_{6,7}$ = 7Hz
br t	2H	H on C-8	$J_{7,8}$ = 7Hz

I.r. (film)

ν_{max} 1602, 1555 cm^{-1}

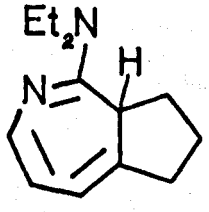
U.v. (95% ethanol)

λ_{max}	219 nm	$\log_{10} \varepsilon$	4.08
	278		3.85
	290 sh		3.84

Mass spectrum

m/e 205 (25%), 204 (M^+) (100%), 203 (13%), 189 (66%), 176 (13%), 175 (97%), 161 (25%), 160 (9%), 159 (25%), 147 (19%), 134 (13%), 133 (50%), 132 (53%), 131(3%), 130 (25%), 120 (25%), 118 (13%), 117 (19%), 105 (19%), 104 (9%), 102 (9%), 91 (28%), 79 (26%), 78 (13%), 77 (28%), 72 (38%)

(c) 1-diethylamino-6,7,8,8a-tetrahydrocyclopent[c]azepine 94



Yield 420 mg

B.p. 100°, 0.1 mm Hg

N.m.r. ($CDCl_3$)

δ 0.7 - 1.3 p.p.m.	m	6H	$-CH_2-\underline{CH_3}$	
1.7 - 2.5	m	6H	H on C-6, 7 and 8	
2.6 - 3.4	m	5H	$-\underline{CH_2}-CH_3$ and H on C-8a	
5.68	d of d	1H	H on C-4	$J_{3,4}$ = 8Hz, $J_{4,5}$ = 6Hz
6.1	br d	1H	H on C-5	$J_{4,5}$ = 6Hz
6.9	d	1H	H on C-3	$J_{3,4}$ = 8Hz

I.r. (film)

ν_{max} 1575, 1570 cm^{-1}

U.v. (95% ethanol)

λ_{max}		$\log_{10} \varepsilon$
228 nm		3.94
250	sh	
285		3.75

Mass spectrum

$^{m}/_{e}$ 205 (8%), 204 (M^{+}) (41%), 203 (8%), 189 (27%), 176 (16%), 175 (100%), 161 (20%), 160 (8%), 159 (8%), 147 (8%), 134 (16%), 133 (37%), 132 (33%), 131 (12%), 130 (12%), 120 (12%), 118 (10%), 117 (18%), 105 (24%), 104 (16%), 91 (16%), 79 (16%), 78 (14%), 77 (18%), 72 (43%)

Fractions 4 - 7 (0.5 g) were chromatographed on one plate in benzene/acetone (4 : 1). The main band was removed to give the cyclopentazepine 99b (170 mg).

The total yields of the cyclopentazepines isolated were: 94; 530 mg, 99b; 340 mg, 99c; 220 mg. Total recovery, 1.09 g = 13% yield.

DECOMPOSITION OF 5-AZIDOINDAN 91

The azide 91 (2.4 g) was irradiated for 17 hours. Removal of the solvent and distillation of the residual black oil gave a pale yellow oil (0.92 g, 31%) which was shown by gas chromatography and linked g.l.c.- m.s. to consist of two cyclopentazepines (estimated ratio 85 : 15).

The major product was identified as 2-diethylamino-1,6,7,8-tetrahydrocyclopent[d]azepine 106. Separation of the isomeric cyclopentazepines could not be achieved by any chromatographic technique. The following data is characteristic of the mixed azepines.

B.p. 87 - 90°, 0.3 mm Hg

Analysis

Found: C, 76.4; H, 9.5; N, 13.7%

$C_{13}H_{20}N_2$ requires: C, 76.45; H, 9.85; N, 13.7%

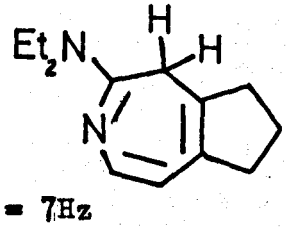
I.r. (film)

ν_{max} 1620, 1565 cm^{-1}

U.v. (95% ethanol)

λ_{max}		$\log_{10} \varepsilon$
219 nm		4.20
294		3.86

Data characteristic of the major product 2-diethylamino-1,6,7,8-tetrahydrocyclopent[d]azepine 106.



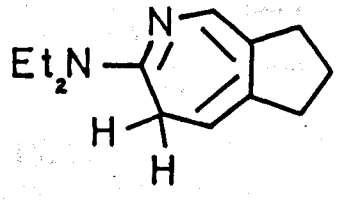
N.m.r. (CCl_4)

δ					
1.13 p.p.m.	t	6H	$-CH_2-\underline{CH_3}$	J = 7Hz	
1.6 - 2.25	m	2H	H on C-7		
2.44	br t	4H	H on C-6 and 8		
2.61	s	2H	H on C-1		
3.35	q	4H	$-\underline{CH_2}-CH_3$	J = 7Hz	
5.49	d	1H	H on C-5	$J_{4,5}$ = 8Hz	
6.79	d	1H	H on C-4	$J_{4,5}$ = 8Hz	

Mass spectrum

$^{m}/_{e}$ 205 (16%), 204 (M^{+}) (94%), 203 (13%), 189 (15%), 176 (19%), 175 (100%), 161 (13%), 160 (11%), 159 (13%), 147 (19%), 134 (11%), 133(32%), 131 (13%), 120 (16%), 118 (13%), 117 (13%), 105 (11%), 104 (19%), 102 (13%), 91 (19%), 79 (13%), 78 (11%), 77 (19%), 72 (40%)

Data characteristic of the minor product, 3-diethylamino-4,6,7,8-tetrahydrocyclopent[c]azepine 107.



N.m.r. (CCl_4)

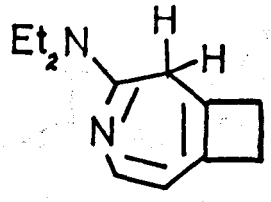
δ 3.33 p.p.m.	q	4H	$-\underline{CH_2}-CH_3$
4.73	t	1H	H on C-5
6.85	s	1H	H on C-1

Mass spectrum

$^{m}/_{e}$ 205 (16%), 204 (M^{+}) (100%), 203 (16%), 190 (6%), 189 (46%), 176 (20%), 175 (92%), 161 (23%), 160 (7%), 159 (10%), 148 (13%), 147 (19%), 134 (17%), 133 (76%), 132 (60%), 131 (14%), 130 (13%), 120 (30%), 118 (17%), 117 (10%), 106 (19%), 105 (39%), 104 (15%), 103 (16%), 102 (7%), 91 (20%), 79 (24%), 78 (17%), 77 (28%), 72 (47%).

DECOMPOSITION OF 4-AZIDOBENZOCYCLOBUTENE 92

Irradiation of the azide 92 (5.6 g) for 20 hours followed by evaporation of the solvent gave a red oil. This was chromatographed on alumina (200 g, activity IV) using petroleum, b.p. 40 - 60° (300 ml), then petroleum/benzene (4 : 1) (600 ml) to give 3-diethylamino-2H-4-azabicyclo[5,2,0]nona-3,5,7(1)-triene 112 (4.0 g, 55%).



M.p. 52 - 53° (petroleum b.p. 60 - 80°)

Analysis

Found: C, 75.45; H, 9.85; N, 15.0%

$C_{12}H_{18}N_2$ requires: C, 75.8; H, 9.5; N, 14.7%

N.m.r. ($CDCl_3$)

δ 1.11 p.p.m.	t	6H	$-CH_2-\underline{CH_3}$	J = 7Hz
2.54	s	4H	H on C-8 and 9	
2.69	s	2H	H on C-2	
3.32	q	4H	$-\underline{CH_2}-CH_3$	J = 7Hz
5.40	d	1H	H on C-6	$J_{5,6}$ = 7.5Hz
6.81	d	1H	H on C-5	$J_{5,6}$ = 7.5Hz

I.r. (mull)

ν_{max} 1628 cm^{-1}

U.v. (95% ethanol)

λ_{max}	220.5 nm	$\log_{10} \varepsilon$ 4.16
	293.5	3.96

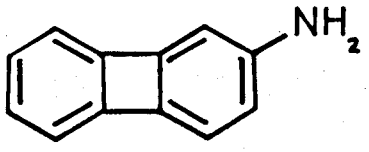
Mass spectrum

m/e 190 (M^+) (50%), 189 (100%), 175 (11%), 161 (22%), 120 (16%), 119 (14%), 118 (32%), 117 (11%), 106 (11%), 99 (14%), 92 (17%), 91 (43%), 78 (11%), 77 (16%), 72 (30%)

The presence of trace quantities of the isomeric compound 4-diethylamino-5H-3-azabicyclo[5,2,0]nona-1,3,6-triene was noted in the crude product. This compound was not isolated.

DECOMPOSITION OF 2-AZIDOBIPHENYLENE 93

The azide 93 (2.6 g) was irradiated for 40 hours. Evaporation of the solvent gave a black tar which was chromatographed on eight preparative layer plates in benzene/acetone (1 : 1). One major and several minor bands were observed. The major band was shown to be 2-aminobiphenylene 113 (1.0 g, 44%).



M.p. 126° (petroleum b.p. 40 - 60°)

Lit.[160] 123 - 124°

Analysis

Found:	C, 86.4;	H, 5.55;	N, 8.2%
$C_{12}H_9N$ requires:	C, 86.2;	H, 5.4;	N, 8.4%

N.m.r. (CCl_4)

δ 3.2 p.p.m.	br s	2H	$-NH_2$	(ex. with D_2O)
5.7 - 6.6	m	7H	arom.	

I.r. (mull)

ν_{max} 3400, 3320, 1660, 1603 cm^{-1}

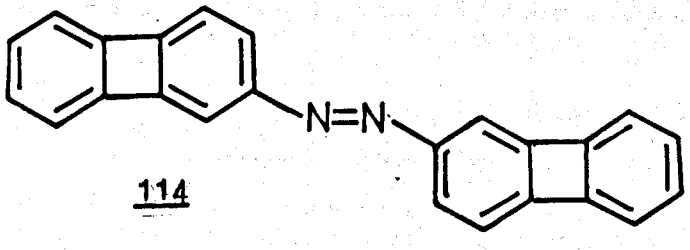
U.v. (95% ethanol)

λ_{max}	258.5 nm	$\log_{10} \varepsilon$	4.57
	357 sh		
	366		3.91

Mass spectrum

m/e 168 (20%), 167 (M^+) (100%), 166 (15%), 151 (10%), 83.5 (8%)

A minor band (orange) was shown by its mass spectrum to be an azobiphenylene; m/e 331 (4%), 330 (M^+) (16%), 303 (26%), 302 (100%), 151 (37%)



114

PART II

SECTION 1

PREPARATION OF THE (2-AMINOBENZOYL)NAPHTHALENES AND TETRALINS

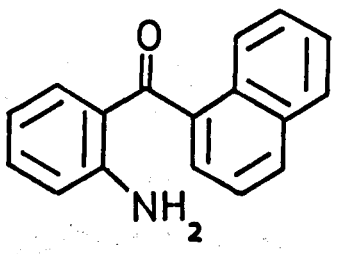
1-(2-aminobenzoyl)naphthalene

Prepared from 1-naphthylmagnesium bromide and 2-methyl-3,1-benzoxazin-4-one, by the following procedure, which is essentially that of Lothrop and Goodwin[176].

The Grignard reagent from 1-bromonaphthalene (41.6 g) and magnesium (5.24 g excess) in dry tetrahydrofuran (200 ml) was added slowly during 0.5 hours to a vigorously stirred solution of freshly distilled 2-methyl-3,1-benzoxazin-4-one (32.2 g) in a mixture of dry toluene (500 ml) and dry ether (250 ml) at -5°. Stirring was continued at 0° for two hours and at room temperature for four hours. The yellow complex was hydrolysed by the addition of 10% hydrochloric acid and the upper, organic layer was separated. The aqueous layer was extracted with ether (200 ml) and the extract was combined with the toluene-ether solution.

Evaporation of this solution produced a yellow solid which was hydrolysed by boiling for four hours in a solution of 10N hydrochloric acid (200 ml) and 95% ethanol (500 ml). The cooled solution was made alkaline with 10% aqueous sodium hydroxide solution and ether extracted (3 x 300 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated leaving a red solid. This residue was passed down a column of alumina (250 g activity IV) with toluene. Evaporation of the eluate gave 1-(2-aminobenzoyl)naphthalene (26.2 g 53%).

1-(2-aminobenzoyl)naphthalene



M.p. 138 - 140° (95% ethanol)

Lit.[176] 138°
[204] 140.5°

Analysis

Found:	C, 82.7; H, 5.65; N, 5.6%
$C_{17}H_{13}NO$ requires:	C, 82.55; H, 5.30; N, 5.65%

N.m.r. ($CDCl_3$)

δ 6.2 - 6.8 p.p.m.	m	4H	arom. + NH_2 (2H ex. with D_2O)
7.0 - 7.6	m	6H	arom.
7.7 - 8.0	m	3H	arom.

I.r. (CCl_4)

ν_{max} 3490, 3335, 1632, 1612 cm^{-1}

U.v. (95% ethanol)

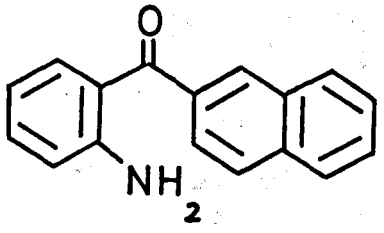
λ_{max} 222 nm		$\log_{10} \varepsilon$ 4.85
238	sh	
260		4.01
283	sh	
292	sh	
378		3.82

Mass spectrum

m/e 248 (24%), 247 (M^+)(73%), 246 (100%), 230 (20%), 218 (12%), 217 (8%), 155 (11%), 127 (30%), 120 (27%), 101(10%), 92 (16%)

2-(2-aminobenzoyl)naphthalene

Prepared as described above from 2-bromonaphthalene in 30% yield (Lit[176] yield 8.3%).



M.p. 109 - 110° (95% ethanol)

Lit.[176] 106°

[205] 110 - 111°

Analysis

Found: C, 82.6; H, 5.50; N, 5.5%

$C_{17}H_{13}NO$ requires: C, 82.55; H, 5.30; N, 5.65%

N.m.r. (CCl_4)

δ 5.88 p.p.m.	br	s	2H	$-NH_2$ (ex. with D_2O)
6.3 - 6.7		m	2H	arom.
6.9 - 8.1		m	9H	arom.

I.r. (mull)

ν_{max} 3475, 3370, 1635, 1610 cm^{-1}

U.v. (95% ethanol)

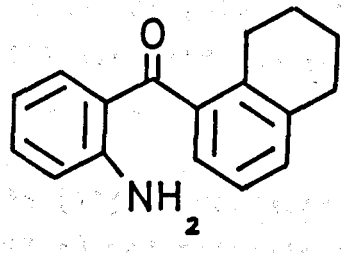
λ_{max}	218 nm		$\log_{10} \varepsilon$ 4.72
	236	sh	
	255	sh	
	281	sh	
	379		3.81

Mass spectrum

m/e 248 (11%), 247 (M^+)(62%), 246 (10%), 230 (9%), 155 (10%), 127 (30%), 120 (21%), 109 (12%), 92 (22%)

5-(2-aminobenzoyl)-1,2,3,4-tetrahydronaphthalene

Prepared as described above from 5-bromo-1,2,3,4-tetrahydronaphthalene[177] in 31% yield.



M.p. 121 - 122° (95% ethanol)

Analysis

Found:	C, 81.0; H, 6.6; N, 5.5%
$C_{17}H_{17}NO$ requires:	C, 81.25; H, 6.8; N, 5.55%

N.m.r. ($CDCl_3$)

δ 1.5 - 1.9 p.p.m.	m 4H	H on naphthalene C-2 and 3
2.4 - 2.9	m 4H	H on naphthalene C-1 and 4
6.1 - 6.7	m 4H	arom. + NH_2 (2H ex. with D_2O)
6.8 - 7.4	m 5H	arom.

I.r. (mull)

ν_{max} 3430, 3320, 1625, 1610 cm^{-1}

U.v. (95% ethanol)

λ_{max}	220 nm	$\log_{10} \varepsilon$	4.29
	233.5		4.32
	261.5		3.90
	374		3.80

Mass spectrum

m/e 252 (31%), 251 (M^+)(100%), 250 (47%), 236 (50%), 235 (39%), 234 (55%), 233 (36%), 224 (16%), 223 (58%), 222 (28%), 208 (13%), 207 (19%), 206 (36%), 158 (34%), 130 (36%), 110 (28%), 105 (27%)

Preparation of 1,2,3,4-tetrahydro-6-(2-nitrobenzoyl)naphthalene

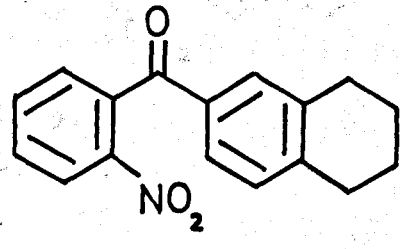
A mixture of 2-nitrobenzoic acid (83.6 g) and thionyl chloride (200 ml) was refluxed until the acid had dissolved. The excess thionyl chloride was removed by distillation and the residue distilled to give 2-nitrobenzoyl chloride as a yellow oil (b.p. 85°/0.1 mm Hg, lit[206] 105°/0.5 mm Hg).

Powdered anhydrous aluminium chloride (133 g) was added slowly to a solution of the acid chloride (93 g) and tetralin (66 g) in dry carbon disulphide (33 ml) at -5°. When evolution of hydrogen chloride had ceased the mixture was boiled for two hours.

The cooled mixture was hydrolysed by ice-cold dilute hydrochloric acid and the organic layer separated. The aqueous layer was extracted with chloroform (3 x 250 ml) and the extracts combined with carbon disulphide solution.

Evaporation of the organic solvent left a black tar which was chromatographed on a column of alumina (400 g, activity IV). Elution with chloroform gave 20 g of a mixture of product and tetralin. Further chromatography (alumina 150 g, activity IV) in petroleum (b.p. 60-80°) gave the nitrobenzoyltetralin (13.6 g 10%).

1,2,3,4-tetrahydro-6-(2-nitrobenzoyl)naphthalene



M.p. 140.5 - 141° (methanol)

Analysis

Found: C, 72.8; H, 5.4; N, 4.9%

$C_{17}H_{15}NO_3$ requires: C, 72.6; H, 5.35; N, 4.9%

N.m.r. ($CDCl_3$)

δ 1.7 - 2.0 p.p.m.	m 4H	H on naphthalene C-2 and 3
2.7 - 3.0	m 4H	H on naphthalene C-1 and 4
7.0 - 8.4	m 7H	arom.

I.r. (mull)

ν_{max} 1660, 1528, 1355 cm^{-1}

U.v. (95% ethanol)

λ_{max} 266 nm $\log_{10} \varepsilon$ 4.34

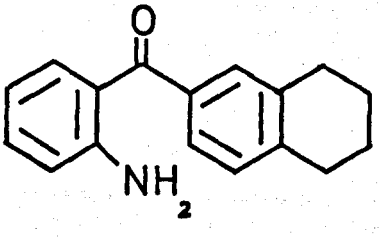
Mass spectrum

$^{m}/e$ 282 (11%), 281 (M^+)(51%), 264 (9%), 236 (11%), 165 (11%), 160 (13%), 159 (74%), 148 (14%), 147 (100%), 134 (26%), 131 (35%), 130 (13%), 129 (17%), 128 (11%), 119 (13%), 116 (17%), 115 (17%), 104 (20%), 91 (46%)

Preparation of 6-(2-aminobenzoyl)-1,2,3,4-tetrahydronaphthalene

A solution of the nitro-compound (9.3 g) in 95% ethanol (250 ml) containing 10% palladium-on-charcoal (0.5 g) in suspension was hydrogenated (60 lb. $in.^{-2}$) until absorption ceased. Evaporation of the filtered solution gave a red oil which when purified by column chromatography (alumina 100 g, activity IV) in petroleum (b.p. 60-80°) gave the aminobenzoyltetralin (7.5 g 86%) as a yellow oil.

6-(2-aminobenzoyl)-1,2,3,4-tetrahydronaphthalene



B.p. 155 - 160°, 0.3 mm Hg

Analysis

Found:	C, 81.7;	H, 7.05;	N, 5.2%
$C_{17}H_{17}NO$ requires:	C, 81.25;	H, 6.8;	N, 5.55%

N.m.r. ($CDCl_3$)

δ 1.5 - 2.1 p.p.m.		m	4H	H on naphthalene C-2 and 3
2.4 - 3.0		m	4H	H on naphthalene C-1 and 4
5.95	br	s	2H	$-NH_2$ (ex. with D_2O)
6.4 - 7.6		m	7H	arom.

I.r. (CCl_4)

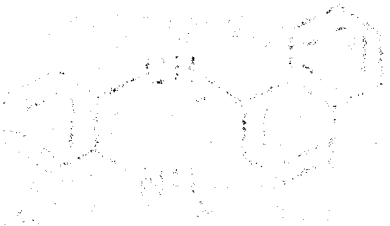
ν_{max} 3490, 3350, 1635, 1617 cm^{-1}

U.v. (95% ethanol)

λ_{max}	230.5 nm	$\log_{10} \varepsilon$	4.21
	268		4.10
	376		3.62

Mass spectrum

m/e 252 (19%), 251 (M^+)(75%), 250 (100%), 222 (50%), 159 (33%), 120 (28%), 106 (28%), 92 (30%)



SECTION 2

PREPARATION OF THE (2-AMINOBENZYL)NAPHTHALENES AND TETRALINS

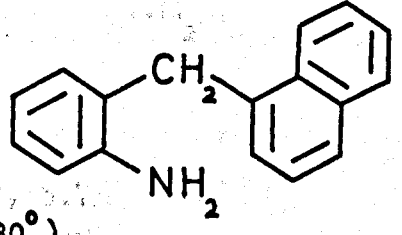
These were prepared by the Wolff-Kishner/Huang Minlon reduction of the corresponding ketones.

1-(2-aminobenzyl)naphthalene

A solution of 1-(2-aminobenzoyl)naphthalene (15 g) and hydrazine hydrate (12 ml) in dry ethylene glycol (250 ml) was maintained at 150° until hydrazone formation was complete (24h. - reaction followed by gas chromatography). Potassium hydroxide (20 g) was added slowly and the temperature was raised until distillation of water and hydrazine had ceased. The solution was maintained at 180° for four hours and then allowed to cool to room temperature.

Water (1 l) was added and the solution was ether extracted (3 x 200 ml). The dried ($MgSO_4$) ether extracts were evaporated and the residue crystallised from petroleum (b.p. 60-80°) to give 1-(2-aminobenzyl)naphthalene 132 (12.8 g, 91%).

1-(2-aminobenzyl)naphthalene



M.p. 101.5 - 102.5° (petroleum b.p. 60-80°)

Analysis

Found:	C, 87.6;	H, 6.6;	N, 6.2%
$C_{17}H_{15}N$ requires:	C, 87.5;	H, 6.5;	N, 6.0%

N.m.r. ($CDCl_3$)

δ 3.3 p.p.m.	br s	2H	$-NH_2$ (ex. with D_2O)
4.13	s	2H	$-CH_2-$
6.4 - 8.0	m	11H	arom.

I.r. (film)

ν_{max} 3450, 3370, 1620 cm^{-1}

U.v. (95% ethanol)

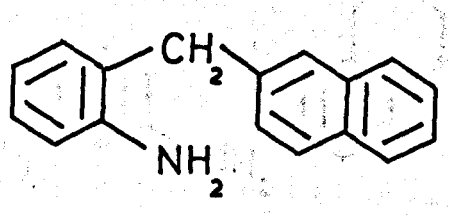
λ_{max} 225 nm		$\log_{10} \varepsilon$ 4.88
263	sh	
274	sh	
283		3.97
292	sh	

Mass spectrum

m/e 234 (19%), 233 (M^+)(100%), 232 (45%), 218 (25%), 217 (13%), 215 (23%), 128 (19%), 116 (13%), 106 (15%)

2-(2-aminobenzyl)naphthalene

Prepared as described above from 2-(2-aminobenzoyl)-naphthalene in 90% yield.



B.p. 160 - 170°, 0.05 mm Hg.

Lit.[205] 150 - 160°, 0.001 mm Hg.

Analysis

Found:	C, 87.5; H, 6.45; N, 5.7%
$C_{17}H_{15}N$ requires:	C, 87.5; H, 6.5; N, 6.0%

N.m.r. ($CDCl_3$)

δ 3.39 p.p.m.	br s	2H	$-NH_2$	(ex. with D_2O)
3.95	s	2H	$-CH_2-$	
6.5 - 7.9	m	11H	arom.	

I.r. (film)

ν_{max} 3430, 3365, 1620 cm^{-1}

U.v. (95% ethanol)

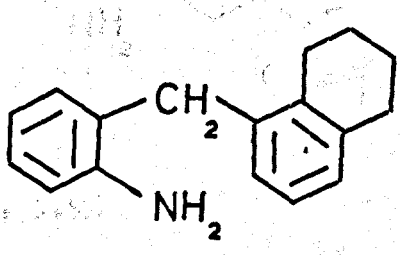
λ_{max}	226.5 nm	$\log_{10} \varepsilon$	5.00
	269 sh		
	276		3.85
	279 sh		

Mass spectrum

m/e 234 (20%), 233 (M^+)(100%), 232 (54%), 231 (9%), 230 (19%), 218 (20%), 217 (17%), 216 (9%), 215 (29%), 141 (9%), 128 (22%), 115 (21%), 106 (26%)

5-(2-aminobenzyl)-1,2,3,4-tetrahydronaphthalene

Prepared as described above from 5-(2-aminobenzoyl)tetralin in 83% yield.



M.p. 68.5 - 69° (petroleum b.p. 40-60°)

Analysis

Found:	C, 86.4; H, 8.25; N, 5.8%
$C_{17}H_{19}N$ requires:	C, 86.05; H, 8.05; N, 5.9%

N.m.r. ($CDCl_3$)

δ 1.6 - 2.0 p.p.m.	m	4H	H on naphthalene C-2 and 3	
2.5 - 3.0	m	4H	H on naphthalene C-1 and 4	
3.4	br s	2H	$-NH_2$	(ex. with D_2O)
3.73	s	2H	$-CH_2-$	
6.5 - 7.1	m	7H	arom.	

I.r. ($CHCl_3$)

ν_{max} 3450, 3375, 1619 cm^{-1}

U.v. (95% ethanol)

λ_{max} 219 sh

234 sh

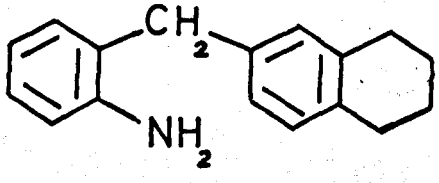
285 $\log_{10} \varepsilon$ 3.37

Mass spectrum

m/e 238 (19%), 237 (M^+)(74%), 158 (28%), 146 (17%), 145 (30%), 144 (85%), 143 (32%), 142 (50%), 141 (65%), 132 (20%), 131 (69%), 130 (24%), 129 (100%), 128 (58%), 127 (17%), 118 (19%), 117 (17%), 116 (17%), 115 (46%), 107 (35%), 106 (76%), 93 (50%), 91 (43%)

6-(2-aminobenzyl)-1,2,3,4-tetrahydronaphthalene

Prepared as described above from 6-(2-aminobenzoyl)tetralin in 94% yield.



B.p. 165 - 170°, 0.45 mm Hg.

Analysis

Found: C, 85.9; H, 7.75; N, 5.8%

$C_{17}H_{19}N$ requires: C, 86.05; H, 8.05; N, 5.9%

N.m.r. ($CDCl_3$)

δ 1.6 - 1.9 p.p.m.	m	4H	H on naphthalene C-2 and 3
2.5 - 2.9	m	4H	H on naphthalene C-1 and 4
3.39	br s	2H	$-NH_2$ (ex. with D_2O)
3.78	s	2H	$-CH_2-$
6.4 - 7.2	m	7H	arom.

I.r. (film)

ν_{max} 3440, 3360, 1620 cm^{-1}

U.v. (95% ethanol)

λ_{max} 224 nm sh
237 sh
280.5 $\log_{10} \varepsilon$ 3.8
289 sh

Mass spectrum

m/e 238 (25%), 237 (M^+)(100%), 236 (33%), 208 (13%), 194 (13%), 180 (11%), 144 (28%), 131 (21%), 129 (14%), 106 (52%), 91 (14%)

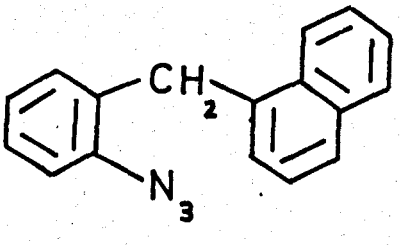
SECTION 3

PREPARATION OF THE (2-AZIDOBENZYL)NAPHTHALENES AND TETRALINS

1-(2-azidobenzyl)naphthalene

A solution of 1-(2-aminobenzyl)naphthalene 132 (11.7 g, 0.05 M) in a mixture of 4N sulphuric acid (250 ml) and purified 1,4-dioxan (250 ml) was cooled to -5° and a solution of sodium nitrite (3.8 g, 0.055 M) in water (50 ml) was added with stirring. After 15 minutes a solution of sodium azide (3.6 g, 0.055 M) in water (50 ml) was added and the solution was warmed gently to 30°. The azide was extracted with ether (3 x 200 ml) and the combined ethereal extracts dried ($MgSO_4$). The solvent was removed under reduced pressure at 30° and the residual oil was percolated through a column of alumina (200 g, activity IV, column length 0.2m) in petroleum (b.p. 40-60°). Evaporation of the solvent, under reduced pressure at 30°, left the azide as a pale yellow oil (10.8 g, 84%).

1-(2-azidobenzyl)naphthalene 126



Analysis

Found:	C, 78.5;	H, 5.1; N, 15.6%
$C_{17}H_{13}N_3$ requires:	C, 78.75;	H, 5.05; N, 16.2%

N.m.r. (CCl_4)

δ 4.23 p.p.m.	s 2H	$-CH_2-$
6.9 - 7.8	m 11H	arom.

I.r. (film)

ν_{max} 2125, 1285 cm^{-1}

U.v. (95% ethanol)

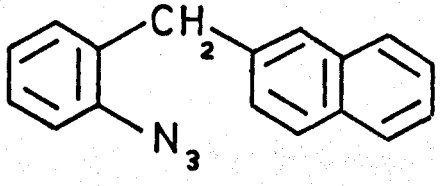
λ_{max}		$\log_{10} \varepsilon$
221.5 nm		4.92
253		4.08
260	sh	
271	sh	
281		4.01

Mass spectrum

m/e 260 (4%), 259 (M^+)(13%), 232 (29%), 231 (100%), 230 (12%), 229 (7%), 202 (6%), 115 (11%)

2-(2-azidobenzyl)naphthalene 127

Prepared as above from 2-(2-aminobenzyl)naphthalene 137 in 56% yield as a yellow oil.



N.m.r. ($CDCl_3$)

δ 3.98 p.p.m.	s	2H	$-CH_2-$
6.9 - 7.8	m	11H	arom.

I.r. (film)

ν_{max} 2125, 1290 cm^{-1}

U.v. (95% ethanol)

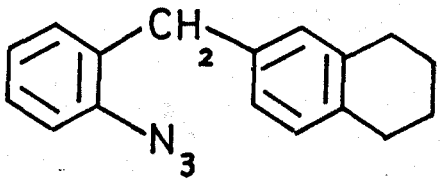
λ_{max}		$\log_{10} \varepsilon$
228 nm		4.93
253		4.15
275	sh	
285	sh	

Mass spectrum

m/e 259 (M^+)(8%), 232 (30%), 231 (100%), 230 (60%), 229 (20%), 202 (20%), 115.5 (18%), 115 (20%), 114.5 (10%), 101 (13%)

6-(2-azidobenzyl)-1,2,3,4-tetrahydronaphthalene 128

Prepared as above from 6-(2-aminobenzyl)tetralin in 62% yield.



M.p. 44 - 45° (95% ethanol)

Analysis

Found:	C, 78.1;	H, 6.75; N, 15.9%
$C_{17}H_{17}N_3$ requires:	C, 77.55;	H, 6.5; N, 15.95%

N.m.r. ($CDCl_3$)

δ 1.6 - 1.9 p.p.m.	m	4H	H on naphthalene C-2 and 3
2.5 - 2.9	m	4H	H on naphthalene C-1 and 4
3.83	s	2H	$-CH_2-$
6.8 - 7.2	m	7H	arom.

I.r. (mull)

ν_{max} 2118, 1288 cm^{-1}

U.v. (95% ethanol)

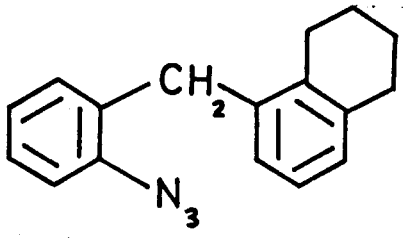
λ_{max} 251.5 nm		$\log_{10} \varepsilon$ 3.99
279	sh	
289	sh	

Mass spectrum

m/e 263 (M^+)(9%), 235 (40%), 234 (100%), 207 (21%), 206 (48%), 194 (13%), 192 (25%), 191 (23%), 180 (10%), 115 (11%)

5-(2-azidobenzyl)-1,2,3,4-tetrahydronaphthalene 129

Prepared as above from 5-(2-aminobenzyl)tetralin in 90% yield.



M.p. 48 - 50° (petroleum b.p. 40-60°)

Analysis

Found:	C, 78.1;	H, 6.85;	N, 15.6%
$C_{17}H_{17}N_3$ requires:	C, 77.55;	H, 6.5;	N, 15.95%

N.m.r. ($CDCl_3$)

δ 1.5 - 1.9 p.p.m.	m	4H	H on naphthalene C-2 and 3
2.3 - 2.9	m	4H	H on naphthalene C-1 and 4
3.81	s	2H	$-CH_2-$
6.6 - 7.2	m	7H	arom.

I.r. (film)

ν_{max} 2130, 1290 cm^{-1}

U.v. (95% ethanol)

λ_{max}	251.5 nm	$\log_{10} \varepsilon$	3.99
	278	sh	
	288	sh	

Mass spectrum

m/e 263 (M^+)(2%), 236 (50%), 235 (100%), 234 (25%), 207 (54%), 206 (76%), 205 (15%), 204 (32%), 193 (32%), 192 (37%), 105 (22%)

SECTION 4

DECOMPOSITION OF THE (2-AZIDOBENZYL)NAPHTHALENES AND TETRALINS

All azides were decomposed thermally in 1,2,4-trichlorobenzene by the following procedure:

A solution of the azide (9.5 g) in 1,2,4-trichlorobenzene (100 ml), was added dropwise during 45 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.

After four hours the solution was cooled and the solvent removed by distillation under reduced pressure (1 mm Hg). The residue was treated as described for the individual azides.

DECOMPOSITION OF 1-(2-AZIDOBENZYL)NAPHTHALENE 126

The azide (9.5 g) was decomposed at 195° for four hours and the trichlorobenzene removed under reduced pressure.

Gas chromatography (3% OV17 on Supasorb AW, 50 ml/min nitrogen, 244°) of the residual yellow solid showed the presence of five components of which products 4 and 5 (in increasing retention time) made up the bulk of the material.

A solution of the crude decomposition product (100 mg) in ether (25 ml) in a 50 ml separatory flask was shaken for one minute with 4N sulphuric acid (10 ml). Examination of the ethereal solution revealed that product 4 had been removed completely. Similar treatment of 2 g of the crude product gave after basification of the acid extracts a solid crystallising from petroleum (b.p. 60-80°) which was identified as benz[a]acridine 130 (0.5 g, 25%).

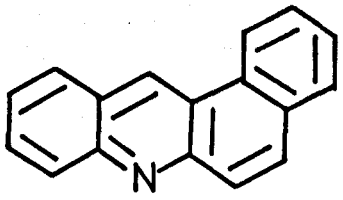
Evaporation of the ethereal solution after removal of product 4 gave a solid residue; product 5 crystallised from petroleum (b.p. 60-80°) and was identified as 7,12-dihydrobenz[a]acridine 131 (1.0 g, 50%).

The crude decomposition product (4 g) was chromatographed on a column of alumina (300 g). The column was eluted with toluene and four fractions were collected. The third fraction gave pure product 2 identified as 1-(2-aminobenzyl)naphthalene 132 by comparison with material previously prepared.

The first fraction which contained products 1,3 and 4 was evaporated and the residue spread on to two preparative layer plates. Elution with toluene produced two clearly defined bands.

The upper band gave a yellow oil which was shown by gas chromatography to be a mixture of products 1 and 3. Separation of this mixture was achieved by column chromatography (alumina, 100 g; petroleum b.p. 60-80°) and products 1 and 3 were obtained as pale yellow oils which were identified from spectral data as 7H-indolo[1,2-a][1]benzazepine 133 and 7H-indolo[2,1-a][2]benzazepine 134 respectively.

Properties of the compounds isolated:



Benz[a]acridine (Product 4) 130

M.p. 130.5 - 131° (petroleum b.p. 60-80°)

Lit.[181] 131°

Analysis

Found:	C, 89.5;	H, 5.10; N, 6.2%
$C_{17}H_{11}N$ requires:	C, 89.05;	H, 4.85; N, 6.1%

N.m.r. ($CDCl_3$)

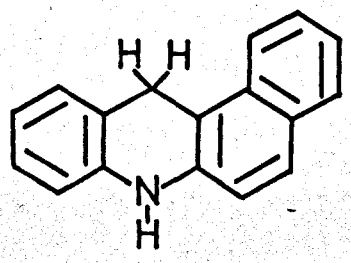
δ 7.3 - 8.0 p.p.m.	m	8H	arom.
8.0 - 8.6	m	2H	arom.
8.96	s	1H	H on C-12

U.v. (95% ethanol)

λ_{max}		$\log_{10}\varepsilon$
222.5 nm		4.59
234		4.52
276.5		4.73
285	sh	
345		3.81
362		3.86

Mass spectrum

m/e 230 (28%), 229 (M^+)(100%), 228 (20%), 227 (13%), 202 (5%), 201 (7%), 200 (7%), 114 (13%), 101 (9%), 100 (9%)



7,12-dihydrobenz[a]acridine (Product 5) 131

M.p. 166 - 168° (petroleum b.p. 60-80°)

Lit.[182] 166 - 168°

Analysis

Found:	C, 87.9;	H, 5.65; N, 6.0%
$C_{17}H_{13}N$ requires:	C, 88.3;	H, 5.65; N, 6.05%

N.m.r. ($CDCl_3$)

δ 4.4 p.p.m.	s	2H	$-CH_2-$
5.9	br s	1H	NH (ex. with D_2O)
6.5 - 7.9	m	10H	arom.

I.r. (mull)

ν_{max} 3400 cm^{-1}

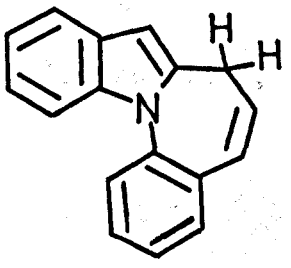
U.v. (95% ethanol)

λ_{max}	223 nm	$\log_{10} \varepsilon$	4.57
	267		4.33
	276.5		4.35
	315		4.06
	367.5		3.53

Mass spectrum

m/e 232 (56%), 231 (M^+)(100%), 230 (30%), 229 (9%), 202 (7%), 115 (6%), 114 (4%), 102 (8%), 101 (9%), 100 (5%)

<u>7H-indolo[1,2-a][1]benzazepine</u> (Product 1) <u>133</u>



N.m.r. ($CDCl_3$)

δ 3.2 - 3.5 p.p.m.	br d	2H	$-CH_2-$	
5.9 - 6.4	m	1H	H on C-6	
6.21	s	1H	H on C-8	
6.54	d	1H	H on C-5	$J_{5,6}$ = 10.5Hz
6.9 - 7.9	m	8H	arom.	

I.r. (film)

ν_{max} 1580, 1558 cm^{-1}

U.v. (95% ethanol)

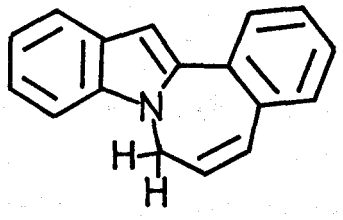
λ_{max} 220, 263.5sh, 291sh, 297sh, nm

λ_{min} 244 nm

Mass spectrum

m/e 232 (21%), 231 (M^+)(100%), 230 (89%), 229 (14%), 228 (20%), 204 (11%), 203 (7%), 202 (12%), 115.5 (11%), 115 (11%), 114.5 (11%), 114 (15%), 102 (14%), 101 (9%).

7H-indolo[2,1-a][2]benzazepine (Product 3) 134



N.m.r. ($CDCl_3$)

δ 4.58 p.p.m.	d	2H	$-CH_2-$	$J_{6,7}$ = 6.5Hz
6.23	d of t	1H	H on C-6	$J_{6,7}$ = 6.5Hz, $J_{5,6}$ = 10.5Hz
6.71	s	1H	H on C-13	
6.79	d	1H	H on C-5	$J_{5,6}$ = 10.5Hz
7.0 - 7.9	m	8H	arom.	

I.r. (film)

ν_{max} 1630, 1590 cm^{-1}

U.v. (95% ethanol)

λ_{max} 230.5, 253sh, 262sh, 275.5, 312 nm

λ_{min} 272, 284 nm

Mass spectrum

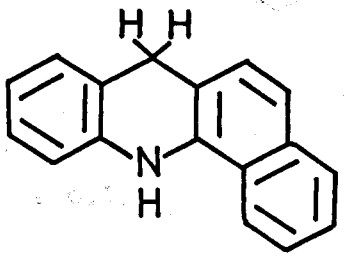
m/e 232 (19%), 231 (M^+)(100%), 230 (63%), 229 (8%), 228 (14%), 204 (21%), 203 (6%), 202 (8%), 201 (4%)

DECOMPOSITION OF 2-(2-AZIDOBENZYL)NAPHTHALENE 127

The azide (3.2 g) was decomposed at 180° for four hours. Evaporation of the trichlorobenzene gave a red oil which crystallised on cooling. Gas chromatography (3% OV17 on Supasorb AW, 50ml/min nitrogen, 243°) showed the product to consist of one major and two minor components.

Trituration of the crude products with ethanol (95%) gave 7,12-dihydrobenz[c]acridine (1.0 g 35%).

7,12-dihydrobenz[c]acridine 135



M.p. 140 - 141° (aqueous ethanol)

Lit.[181] 140°

Analysis

Found: C, 87.9; H, 5.60; N, 5.8%

$C_{17}H_{13}N$ requires: C, 88.3; H, 5.65; N, 6.05%

N.m.r. ($CDCl_3$)

δ 4.12 p.p.m.	s	2H	$-CH_2-$
6.41	br s	1H	NH (ex. with D_2O)
6.5 - 7.8	m	10H	arom.

I.r. (mull)

ν_{max} 3420 cm^{-1}

U.v. (95% ethanol)

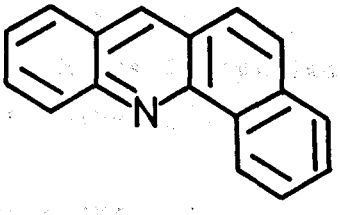
λ_{max}	223 nm	$\log_{10} \varepsilon$	4.70
	259		4.26
	278 sh		
	346		3.94

Mass spectrum

m/e 232 (9%), 231 (M^+)(47%), 230 (100%), 229 (97%), 228 (32%), 227 (14%), 226 (9%), 216 (7%), 215 (5%), 203 (9%), 202 (12%), 201 (9%), 200 (7%), 115.5 (10%), 115 (18%), 114.5 (19%), 114 (24%), 113.5 (10%), 113 (9%).

The filtrate after trituration was evaporated and the residue absorbed onto alumina. Elution with petroleum (b.p. 60-80°) gave two fractions. The first fraction contained a small amount of material which was not identified. The second fraction gave benz[c]acridine 136 (1.0 g 35%).

Benz[c]acridine 136



M.p. 108 - 109° (petroleum b.p. 60-80°)

Lit.[181] 107 - 108°

Analysis

Found:	C, 88.9; H, 4.80; N, 6.1%
$C_{17}H_{11}N$ requires:	C, 89.05; H, 4.85; N, 6.1%

N.m.r. ($CDCl_3$)

δ 7.4 - 8.1 p.p.m.	m	8H	arom.
8.34	d	1H	H on C-11 J = 9Hz
8.5	s	1H	H on C-7
9.3 - 9.7	m	1H	H on C-1

U.v. (95% ethanol)

λ_{max}		$\log_{10} \varepsilon$
220 nm	sh	
223.5		4.56
235	sh	
256	sh	
266	sh	
274.5		4.78
289.5		4.67
363.5		3.75
378.5		3.68

Mass spectrum

m/e 130 (21%), 129 (100%), 128 (29%), 114.5 (13%)

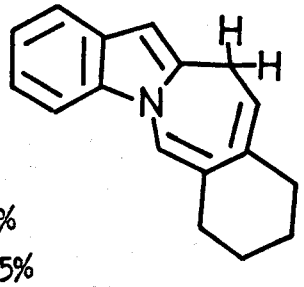
Elution with toluene gave two fractions; the first was identified as 2-(2-aminobenzyl)naphthalene 137 (0.3 g 10%) and the second as 7,12-dihydrobenz[c]acridine 135 (0.1 g).

DECOMPOSITION OF 6-(2-AZIDOBENZYL)TETRALIN 128

The azide (5 g) was decomposed at 185° for four hours and the trichlorobenzene was removed under reduced pressure.

Gas chromatography of the residual oil (3% OV17 on Supasorb AW, 50ml/min nitrogen, 221°) showed the presence of one major and four minor components. Trituration with ethanol (95%) precipitated the major product (3.1 g 70%) which was identified as 7,8,9,10-tetrahydro-12H-indolo[1,2-b][2]benzazepine 138.

7,8,9,10-tetrahydro-12H-indolo[1,2-b][2]benzazepine 138



M.p. 125.5 - 126.5° (95% ethanol)

Analysis

Found:	C, 87.1;	H, 7.40; N, 6.0%
$C_{17}H_{17}N$ requires:	C, 86.75;	H, 7.3; N, 5.95%

N.m.r. ($CDCl_3$)

δ 1.5 - 1.9 p.p.m.	m	4H	H on C-8 and 9	
2.0 - 2.6	m	4H	H on C-7 and 10	
3.26	d	2H	H on C-12	$J_{11,12}$ = 7Hz
5.63	t	1H	H on C-11	
6.07	s	1H	H on C-13	
7.0 - 7.6	m	5H	H on C-1,2,3,4 and 6	

I.r. (mull)

ν_{max} 1649, 1620 cm^{-1}

U.v. (95% ethanol)

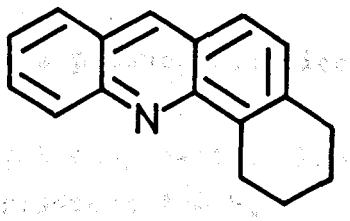
λ_{max}	231.5 nm	$\log_{10} \varepsilon$	4.39
	270		4.29
	288 sh		

Mass spectrum

m/e 236 (17%), 235 (M^+)(100%), 234 (33%), 220 (8%), 218 (8%), 207 (10%), 206 (15%), 205 (7%), 194 (6%), 193 (6%), 192 (6%), 180 (5%), 167 (5%)

The residue from the trituration was washed with acid, the acid extracts neutralised and extracted with ether. Evaporation of the ethereal extracts gave brown needle-like crystals of 1,2,3,4-tetrahydrobenz[c]acridine 139 (60 mg, 1-2%).

1,2,3,4-tetrahydrobenz[c]acridine 139



M.p. 79 - 80° (aqueous ethanol)

Analysis

Found:	C, 87.5;	H, 6.5;	N, 6.0%
$C_{17}H_{15}N$ requires:	C, 87.5;	H, 6.5;	N, 6.0%

N.m.r. ($CDCl_3$)

δ 1.8 - 2.1 p.p.m.	m	4H	H on C-2 and 3	
2.6 - 3.1	m	2H	H on C-4	
3.2 - 3.6	m	2H	H on C-1	
7.0 - 8.0	m	5H	H on C-5,6,8,9	and 10
8.26	d	1H	H on C-11	J = 8Hz
8.53	s	1H	H on C-7	

I.r. (mull)

ν_{max} 1630, 1615 cm^{-1}

U.v. (95% ethanol)

λ_{max}	250 nm	sh	
	257	$\log_{10}\varepsilon$	5.23
	343	sh	
	357		3.90

Mass spectrum

m/e 233 (M^+)(100%), 232 (72%), 218 (56%), 217 (33%), 204 (19%),

Addition of the lanthanide shift reagent $Eu(fod)_3$ to the n.m.r. solution causes large down-field shifts in the signals at δ 3.2 - 3.6 p.p.m. and at δ 8.26 p.p.m.

DECOMPOSITION OF 5-(2-AZIDOBENZYL)TETRALIN 129

The azide (5.3 g) was decomposed at 183° for six hours. The trichlorobenzene was evaporated under reduced pressure and a sample of the residual red oil was injected into a gas chromatograph (3% OV17 on Supasorb AW, 50ml/min nitrogen, 223°).

The chromatogram showed that the crude product comprised two major and three minor components though thin layer chromatography indicated the presence of eight components. These components are subsequently referred to as products 1 - 5, corresponding in order of increasing retention time to the peaks on the chromatogram.

An attempt was made to separate the products by column chromatography; the crude decomposition product (2.5 g) was chromatographed on a column of alumina (300 g activity IV column length 1m).

The column was eluted with petroleum (b.p. 40-60°), 15ml fractions were collected and the components of each fraction were checked by gas chromatography.

The following table (Table 1) lists the products eluted from the column, the fractions in which they appeared and the isolated yield of pure material:

TABLE 1

Product	Fractions	Isolated Yield		
—	1 - 32			
2	33 - 39	33 - 38	200 mg	8%
1	40 - 60	42 - 53	450 mg	18%
4	52 - 82	62 - 70	300 mg	12%
—	83 - 157			

After Fraction 157 the column was eluted with methanol, the methanol evaporated and the residue re-chromatographed on an alumina column (100 gm activity IV).

This column was eluted with toluene and again 15ml fractions were collected and analysed by gas chromatography. Table 2 lists the products eluted from the column.

TABLE 2

Product	Fractions	Isolated Yield
-	1 - 4	
3	5 - 14	5 - 14 450 mg 18%
-	15 - 35	
5	36 - 50	36 - 50 250 mg 10%

Product 2 was characterised only by spectral data since it rapidly decomposed on standing. The spectral data were sufficient to be able to characterise it as 1,2,3,4-tetrahydro-13bH-indolo[2,1-a][2]benzazepine 140.

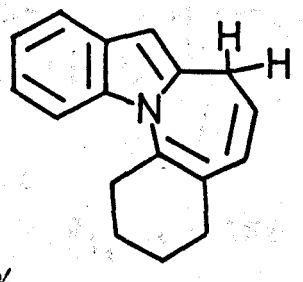
Products 1 and 4 crystallised from petroleum to give pure samples of 1,2,3,4-tetrahydro-7H-indolo[1,2-a][1]benzazepine 141 and 1,2,3,4-tetrahydro-7H-indolo[2,1-a][2]benzazepine 142 respectively.

Product 3, a viscous oil, was identified from spectral data as 4,5,6,6a,7,12-hexahydronaphtho[1,8-b c][1]benzazepine 143

Product 5 was identified from its n.m.r. spectrum as 1,2,3,4,7,12-hexahydrobenz[a]acridine 144 , however, it underwent rapid oxidation and was characterised as its oxidation product 1,2,3,4-tetrahydrobenz[a]acridine 147.

Properties of the compounds isolated:

1,2,3,4-tetrahydro-7H-indolo[1,2-a][1]benzazepine 141 Product 1



M.p. 100 - 101° (petroleum b.p. 60-80°)

Analysis

Found:	C, 86.6; H, 7.15; N, 6.0%
$C_{17}H_{17}N$ requires:	C, 86.75; H, 7.3; N, 5.95%

N.m.r. ($CDCl_3$)

δ 1.5 - 2.0 p.p.m.	m	4H	H on C-2 and 3
2.0 - 2.4	m	2H	H on C-4
2.5 - 3.0	m	2H	H on C-1
3.2	d	2H	H on C-7 $J_{6,7}$ = 6Hz
5.5 - 6.1	m	2H	H on C-5 and 6
5.99	s	1H	H on C-8
6.8 - 7.6	m	4H	H on C-9,10,11 and 12

I.r. (mull)

ν_{max} 1640, 1618 cm^{-1}

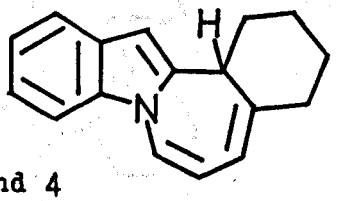
U.v. (95% ethanol)

λ_{max}	232 nm	$\log_{10} \varepsilon$ 4.38
	268	4.13
	285 sh	

Mass spectrum

m/e 236 (17%), 235 (M^+)(100%), 234 (32%), 220 (6%), 219 (4%), 218 (4%), 217 (4%), 208 (3%), 207 (17%), 206 (21%), 205 (7%), 204 (9%), 194 (8%), 193 (4%), 192 (7%), 191 (6%), 180 (6%), 167 (4%)

1,2,3,4-tetrahydro-13bH-indolo[2,1-a][2]benzazepine 140 Product 2



N.m.r. ($CDCl_3$)

δ 1.5 - 2.7 p.p.m.	m	8H	H on C-1,2,3 and 4	
3.33	t	1H	H on C-13b	$J_{1,13b}$ = 7Hz
5.4 - 5.9	m	2H	H on C-5 and 6	
6.12	s	1H	H on C-13	
6.9 - 7.6	m	5H	H on C-7,9,10,11 and 12	

I.r. (film)

ν_{max} 1660, 1642, 1618 cm^{-1}

U.v. (95% ethanol)

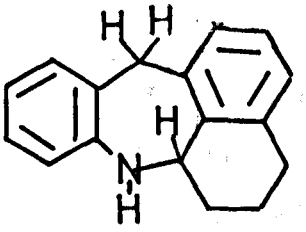
λ_{max}	228 nm	$\log_{10} \varepsilon$	4.12
	248 sh		
	271.5		3.95
	310 sh		

Mass spectrum

$^m/_e$ 236 (16%), 235 (M^+)(100%), 234 (26%), 220 (12%), 219 (4%), 218 (11%), 217 (7%), 207 (30%), 206 (51%), 205 (13%), 204 (18%), 194 (19%), 193 (12%), 192 (11%), 191 (11%), 181 (6%), 180 (15%), 179 (6%), 178 (11%), 167 (13%)

4,5,6,6a,7,12-hexahydronaphtho[1,8-b c][1]benzazepine 143

Product 3



Analysis

Found: C, 86.60; H, 7.05; N, 5.62%

$C_{17}H_{17}N$ requires: C, 86.75; H, 7.30; N, 5.95%

N.m.r. ($CDCl_3$ HR-220 MHz spectrum)

δ 1.7 - 2.2 p.p.m.	m	4H	H on C-5 and 6	
2.68 - 2.85	m	2H	H on C-4	
3.3	br s	1H	NH (ex. with D_2O)	
3.36	d	1H	H on C-12	J = 15.2Hz
4.92	d	1H	H on C-12	J = 15.2Hz
5.1 - 5.2	m	1H	H on C-6a	
6.36	d	1H	H on C-8	J = 8Hz
6.54	t	1H	H on C-10	J = 8Hz
6.8 - 7.2	m	5H	H on C-1,2,3,9 and 11	

I.r. (film)

ν_{max} 3490, 1604 cm^{-1}

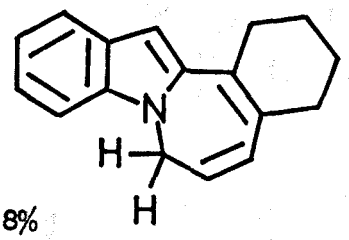
U.v. (95% ethanol)

λ_{max}	$\log_{10} \varepsilon$
235 nm	3.44
260	3.91

Mass spectrum

m/e 236 (13%), 235 (M^+)(85%), 234 (65%), 233 (13%), 218 (13%), 208 (18%), 207 (100%), 206 (30%), 204 (13%)

1,2,3,4-tetrahydro-7H-indolo[2,1-a][2]benzazepine 142 Product 4



M.p. 103 - 104° (petroleum b.p. 40-60°)

Analysis

Found: C, 86.5; H, 7.25; N, 5.8%

$C_{17}H_{17}N$ requires: C, 86.75; H, 7.3; N, 5.95%

N.m.r. ($CDCl_3$)

δ 1.6 - 2.0 p.p.m.	m	4H	H on C-2 and 3
2.1 - 2.8	m	4H	H on C-1 and 4
4.4 - 4.6	br d	2H	H on C-7
5.8 - 6.2	m	2H	H on C-5 and 6
6.48	s	1H	H on C-13
7.0 - 7.8	m	4H	H on C-9,10,11 and 12

I.r. (mull)

ν_{max} 1635, 1580 cm^{-1}

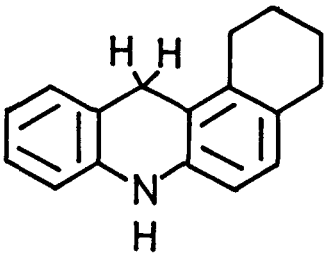
U.v. (95% ethanol)

λ_{max}	224 nm	$\log_{10} \varepsilon$	4.48
	248 sh		
	290 sh		
	325		4.02
	348 sh		

Mass spectrum

m/e 236 (25%), 235 (M^+)(100%), 234 (30%), 220 (11%), 219 (4%), 218 (6%), 217 (4%), 208 (6%), 207 (25%), 206 (32%), 205 (7%), 204 (9%), 196 (8%), 195 (7%), 194 (7%), 193 (7%), 192 (6%), 180 (13%), 167 (8%)

1,2,3,4,7,12-hexahydrobenz[a]acridine 144 Product 5

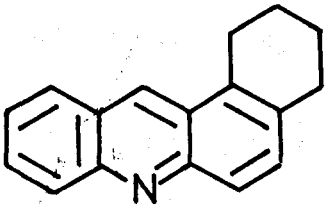


M.p. 168 - 170° (petroleum b.p. 60-80°)

N.m.r. ($CDCl_3$)

δ 1.6 - 2.0 p.p.m.		m	4H	H on C-2 and 3
2.5 - 2.9		m	4H	H on C-1 and 4
3.94		s	2H	H on C-12
5.72	br	s	1H	NH (ex. with D_2O)
6.3 - 7.2		m	6H	H on C-5,6,8,9,10 and 11

1,2,3,4-tetrahydrobenz[a]acridine 147



M.p. 119.5-120.5° (petroleum b.p. 60-80°)

Analysis

Found:	C, 87.3; H, 6.25; N, 6.0%
$C_{17}H_{15}N$ requires:	C, 87.5; H, 6.5; N, 6.0%

N.m.r. ($CDCl_3$)

δ 1.6 - 2.0 p.p.m.	m	4H	H on C-2 and 3
2.6 - 3.0	m	4H	H on C-1 and 4
6.9 - 8.3	m	6H	H on C-5,6,8,9,10 and 11
8.42	s	1H	H on C-12

I.r. (mull)

ν_{max} 1625 cm^{-1}

U.v. (95% ethanol)

λ_{max}	250 nm sh	
	256	$\log_{10} \varepsilon$ 5.15
	355	3.97

Mass spectrum

m/e 234 (18%), 233 (M^+)(100%), 232 (19%), 218 (14%), 217 (12%), 205 (49%), 204 (23%), 192 (14%)

P A R T III

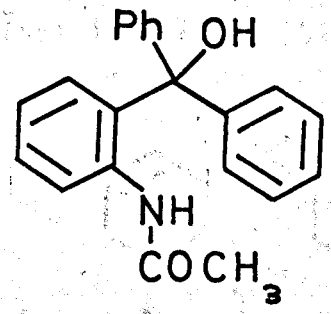
SECTION 1

PREPARATION OF THE 2-ACETAMIDOTRIPHENYLCARBINOLS

2-acetamidotriphenylcarbinol 167

Prepared from phenylmagnesium bromide and 2-methyl-3,1-benzoxazin-4-one by the following procedure which is a modification of the reaction first described by Lothrop and Goodwin[176].

A solution of 2-methyl-3,1-benzoxazin-4-one (30 g) in dry benzene (100 ml) was added dropwise with vigorous stirring to a refluxing solution of the Grignard reagent formed from bromobenzene (65 g) and magnesium (10 g) in dry ether (250 ml). The mixture was refluxed for 4 hours, allowed to cool and then hydrolysed with a saturated solution of ammonium chloride in ammonia (s.g. 0.880) (500 ml). The upper organic layer was separated and the aqueous layer extracted with ether (3 x 150 ml). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give a red oil which, when triturated with methanol, gave 2-acetamidotriphenylcarbinol 167 (35 g, 60%).



M.p. 200 - 201° (methanol)

Lit.[185] 192°

[176] 197 - 198°

Analysis

Found: C, 79.4; H, 6.15; N, 4.4%

$C_{21}H_{19}NO_2$ requires: C, 79.45; H, 6.05; N, 4.4%

N.m.r. ($CDCl_3$)

δ 1.54 p.p.m.	s	3H	$-CH_3$	
3.96	s	1H	$-OH$	(ex. with D_2O)
6.5 - 7.5	m	13H	arom.	
7.97	d	1H	arom.	J = 8Hz
8.78	br s	1H	-NH-	(ex. with D_2O)

I.r. (mull)

ν_{max} 3450 - 3000 br, 3300, 3220, 1670, 1610, 1585 cm^{-1}

U.v. (95% ethanol)

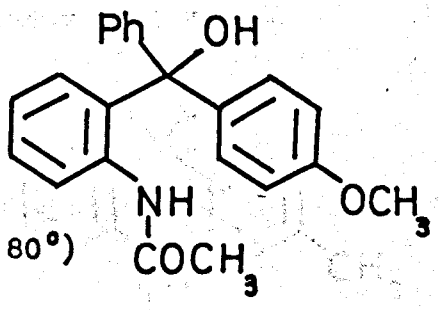
λ_{max} 246 nm $\log_{10} \varepsilon$ 4.06

Mass spectrum

m/e 317 (M^+) (2%), 299 (20%), 283 (12%), 258 (16%), 257 (58%), 256 (100%), 255 (16%), 254 (24%), 180 (22%), 165 (12%), 152 (14%), 105 (12%), 77 (14)

2-acetamido-4'-methoxytriphenylcarbinol 169

A solution of 2-acetamidobenzophenone (44 g) in dry tetrahydrofuran (100 ml) was added dropwise with vigorous stirring to a refluxing solution of the Grignard reagent from p-bromoanisole (105 g) and magnesium (14 g) in dry ether (500 ml). The mixture was refluxed for 4 hours. Work-up as described above gave a yellow solid which was crystallised from petroleum (b.p. 60-80°)/carbon tetrachloride to yield 2-acetamido-4'-methoxytriphenylcarbinol 169 (22 g, 35%).



M.p. 158 - 160° (CCl_4/petroleum b.p. 60 - 80°)

Analysis

Found:	C, 73.7; H, 5.9; N, 3.7%
$C_{22}H_{21}NO_3$ requires:	C, 76.05; H, 6.1; N, 4.05%
$C_{22}H_{21}NO_3 \cdot \frac{1}{2} H_2O$ requires:	C, 74.1; H, 6.2; N, 3.9%

N.m.r. ($CDCl_3$)

δ 1.52 p.p.m.	s	3H	$-COCH_3$	
3.72	s	3H	$-OCH_3$	
4.78	s	1H	$-OH$	
6.5 - 7.5	m	12H	arom.	
8.0	d	1H	arom.	J = 7Hz
9.1	br s	1H	$-NH-$	

I.r. (mull)

ν_{max} 3450 - 3100 br, 1665, 1608, 1585 cm^{-1}

U.v. (95% ethanol)

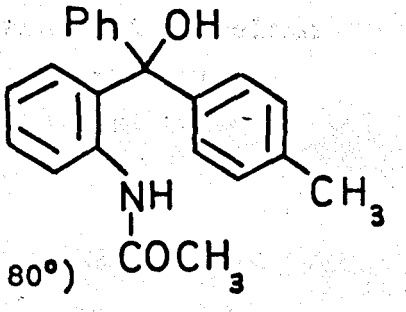
λ_{max}	212 nm	$\log_{10} \varepsilon$	4.48
	230.5		4.26
	245	sh	
	271	sh	
	282	sh	

Mass spectrum

m/e 347 (M^+) (9%), 330 (12%), 329 (47%), 315 (7%), 288 (13%), 287 (61%), 286 (100%), 285 (8%), 273 (7%), 272 (33%), 271 (6%), 270 (8%), 256 (11%), 254 (6%), 242 (12%), 210 (17%), 180 (17%), 135 (14%), 120 (28%), 105 (20%), 77 (24%)

2-acetamido-4'-methyltriphenylcarbinol 173

Prepared as described above from 2-acetamidobenzophenone (48 g) and the Grignard reagent from p-bromotoluene (103 g) and magnesium (16 g) in 52% yield.



M.p. 183 - 185° (CH_2Cl_2/petroleum b.p. 60 - 80°)

Analysis

Found:	C, 79.95;	H, 6.30;	N, 4.00%
$C_{22}H_{21}NO_2$ requires:	C, 79.75;	H, 6.40;	N, 4.20%

N.m.r. ($CDCl_3$)

δ 1.51 p.p.m.		s	3H	$-COCH_3$
2.32		s	3H	$-CH_3$
4.45		s	1H	$-OH$ (ex. with D_2O)
6.5 - 7.4		m	12H	arom.
8.01		d	1H	arom.
9.0	br	s	1H	$-NH-$ (ex. with D_2O)

I.r. (mull)

ν_{max} 3500 - 3000 br, 1665, 1583 cm^{-1}

U.v. (95% ethanol)

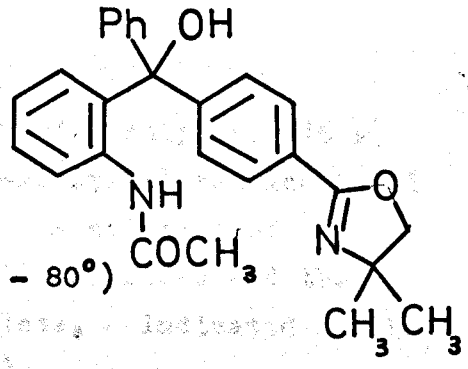
λ_{max}	214.5 nm	$\log_{10} \varepsilon$ 4.41
	248	4.05

Mass spectrum

m/e 331 (M^+) (6%), 314 (8%), 313 (29%), 298 (4%), 272 (9%), 271 (44%), 270 (100%), 269 (6%), 257 (6%), 256 (23%), 254 (10%), 194 (11%), 180 (14%), 120 (10%), 119 (6%), 105 (10%), 93 (6%), 92 (5%), 91 (7%), 86 (7%), 84 (11%), 77 (11%)

2-acetamido-4'-(4,4-dimethyl-2-oxazolin-2-yl)triphenylcarbinol 171

A solution of 2-acetamidobenzophenone (12 g) in tetrahydrofuran (50 ml) was added dropwise to a refluxing solution of the Grignard reagent from 2-(4-bromophenyl)-4,4-dimethyl-2-oxazoline[207] (25.4 g) and magnesium (2.65 g) in tetrahydrofuran (300 ml). Work-up as described above gave a red oil (25.7 g) which consisted of starting material and product. Separation was achieved by column chromatography on alumina (300 g, activity IV). Elution with benzene (1 l) followed by methylene chloride (1 l) gave the carbinol (5.5 g, 27%).



M.p. 103 - 105° (CCl_4/petroleum b.p. 60 - 80°)

Analysis

Found:	C, 70.5; H, 6.15; N, 6.2%
$C_{26}H_{26}N_2O_3$ requires:	C, 75.35; H, 6.30; N, 6.75%
$C_{26}H_{26}N_2O_3 \cdot 1\frac{1}{2} H_2O$ requires:	C, 70.75; H, 6.55; N, 6.3%

N.m.r. ($CDCl_3$)

δ 1.32 p.p.m.	s	6H	$-CH_3$	
1.56	s	3H	$-COCH_3$	
4.05	s	2H	$-CH_2-$	
5.1	br s	1H	-OH	(ex. with D_2O)
6.5 - 8.0	m	13H	arom.	
8.9	br s	1H	-NH-	(ex. with D_2O)

I.r. (mull)

ν_{max} 3500 - 2800 br, 1670, 1630 cm^{-1}

U.v. (95% ethanol)

λ_{max} 246.5 nm $\log_{10} \varepsilon$ 4.37

Mass spectrum

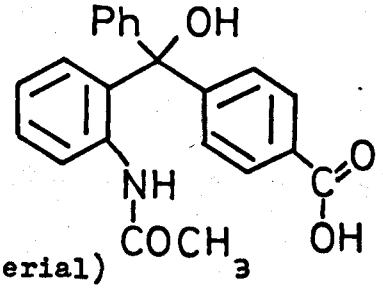
m/e 414 (M^+) (4%), 396 (11%), 354 (42%), 353 (100%), 281 (12%), 274 (24%), 273 (100%), 272 (15%), 269 (13%), 258 (20%), 255 (15%), 254 (15%), 197 (44%), 196 (79%), 194 (15%), 182 (29%), 181 (26%), 180 (68%), 179 (13%), 167 (12%), 165 (25%), 120 (26%), 105 (21%), 92 (17%), 77 (24%)

2-acetamido-4'-carboxytriphenylcarbinol 175

A vigorously stirred solution of magnesium sulphate (16 g) in water (450 ml), containing 2-acetamido-4'-methyltriphenylcarbinol (10 g) in suspension, was heated to reflux. A solution of potassium permanganate (16 g) in water (50 ml) was added and the mixture was left until the reaction was complete, as indicated by the disappearance of the purple colouration (4 h).

The precipitated manganese dioxide was filtered off and washed with hot water (500 ml). The combined filtrate and washings were cooled and acidified with 2N sulphuric acid. The product was filtered off and dried under vacuum.

The manganese dioxide was washed with chloroform (3 x 200 ml) to yield 6 g of starting material.



Yield 2 g (55% based on recovered starting material)

M.p. 191 - 194° (ethyl acetate)

Analysis

Found:	C, 73.15;	H, 5.10;	N, 3.55%	
$C_{22}H_{19}NO_4$ requires:	C, 73.15;	H, 5.25;	N, 3.90%	

N.m.r. (DMSO - d_6)

δ 1.56 p.p.m.	s	3H	- CH_3	
3.4	br s	1H	carbinol - OH	(ex. with D_2O)
6.3 - 8.0	m	13H	arom.	
9.2	s	1H	- NH -	(ex. with D_2O)
11.0 - 13.5	br	1H	- COOH	(ex. with D_2O)

I.r. (mull)

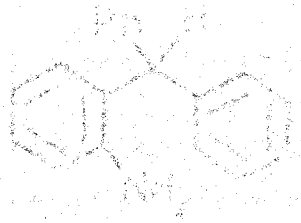
ν_{max} 3600 - 2500 br, 3490 br, 3375, 1690, 1655 cm^{-1}

U.v. (95% ethanol)

λ_{max} 240.5 nm $\log_{10} \varepsilon$ 4.34

Mass spectrum

$^{m}/e$ 361 (M^+) (5%), 344 (7%), 343 (19%), 302 (14%), 301 (62%), 300 (100%), 299 (14%), 283 (7%), 257 (10%), 256 (38%), 255 (10%), 254 (21%), 224 (17%), 180 (17%), 105 (7%), 77 (7%)

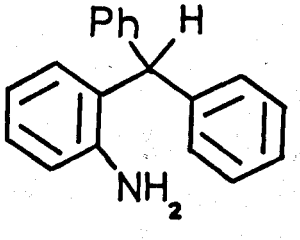


SECTION 2

PREPARATION OF THE 2-AMINOTRIPHENYLMETHANES

2-aminotriphenylmethane 164

A solution of 2-acetamidotriphenylcarbinol 167 (30 g) in 98% formic acid (250 ml) was refluxed for 24 hours. The acid was distilled off under reduced pressure and the residue dissolved in a mixture of methanol (250 ml) and concentrated hydrochloric acid (250 ml). This solution was refluxed for 5 hours, cooled and made basic with aqueous ammonium hydroxide. The organic material was extracted with chloroform (3 x 200 ml); the chloroform solution was dried ($MgSO_4$) and evaporated to leave a yellow oil which when triturated with petroleum (b.p. 60-80°) gave 2-aminotriphenylmethane 164 (18 g, 74%).



M.p. 126.5 - 127.5° (benzene/petroleum b.p. 60 - 80°)

Lit.[185] 129° (ether)

Analysis

Found:	C, 87.8;	H, 6.55;	N, 5.2%
$C_{19}H_{17}N$ requires:	C, 88.0;	H, 6.60;	N, 5.4%

N.m.r. ($CDCl_3$)

δ 3.22 p.p.m.	br s	2H	$-NH_2$	(ex. with D_2O)
5.26	s	1H	methine	C - H
6.4 - 7.3	m	14H	arom.	

I.r. (mull)

ν_{max} 3440, 3360, 1620, 1598 cm^{-1}

U.v. (95% ethanol)

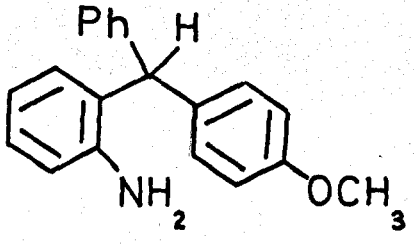
λ_{max}			$\log_{10} \varepsilon$
213 nm			4.40
235	sh		3.86
286			3.38

Mass spectrum

m/e 260 (25%), 259 (M^+) (100%), 258 (18%), 241 (7%), 183 (10%), 182 (62%), 181 (10%), 180 (37%), 168 (5%), 167 (15%), 166 (10%), 165 (34%), 77 (10%)

2-amino-4'-methoxytriphenylmethane 170

Prepared as described above from 2-acetamido-4'-methoxytriphenylcarbinol in 85% yield.



B.p. 170 - 180°, 0.1 mm Hg

N.m.r. ($CDCl_3$)

δ				
3.39 p.p.m.	br s	2H	$-NH_2$	(ex. with D_2O)
3.69	s	3H	$-OCH_3$	
5.42	s	1H	methine	C - H
6.5 - 7.4	m	13H	arom.	

I.r. (film)

ν_{max} 3465, 3355, 1618, 1250 cm^{-1}

U.v. (95% ethanol)

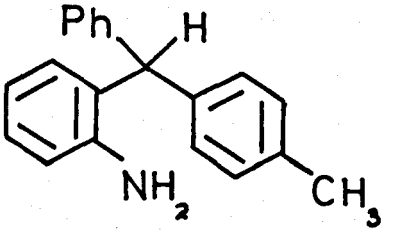
λ_{max}		$\log_{10} \varepsilon$
229.5 nm		4.34
252	sh	
275	sh	
286	sh	
374		3.40

Mass spectrum

m/e 289 (M^+) (5%), 288 (17%), 211 (5%), 197 (11%), 196 (72%), 195 (100%), 179 (17%), 167 (11%), 166 (11%), 120 (57%), 105 (23%), 92 (37%), 77 (48%)

2-amino-4'-methyltriphenylmethane 174

Prepared as described above from 2-acetamido-4'-methyltriphenylcarbinol in 92% yield.



B.p. 180 - 190°, 0.04 mm Hg

Analysis

Found: C, 88.35; H, 6.75%

$C_{20}H_{19}N$ requires: C, 87.9; H, 7.0%

N.m.r. ($CDCl_3$)

δ 2.27 p.p.m.		s	3H	- CH_3
3.16	br	s	2H	- NH_2 (ex. with D_2O)
5.4		s	1H	methine C - H
6.5 - 7.4		m	13H	arom.

I.r. (film)

ν_{max} 3440, 3360, 3205, 1630, 1600 cm^{-1}

U.v. (95% ethanol)

λ_{max}		$\log_{10} \varepsilon$
224 nm	sh	
249	sh	
255		4.16
285.5		3.40
356		3.02

Mass spectrum

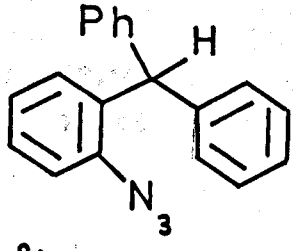
$^{m}/e$ 274 (25%), 273 (M^{+}) (100%), 272 (13%), 258 (19%), 196 (30%), 194 (13%), 182 (22%), 181 (20%), 180 (50%), 179 (12%), 165 (27%), 77 (10%)

SECTION 3

PREPARATION OF THE 2-AZIDOTRIPHENYLMETHANES

2-azidotriphenylmethane 158

A solution of 2-aminotriphenylmethane 164 (5 g) in a mixture of 4N sulphuric acid (250 ml) and purified 1,4-dioxan (250 ml) was cooled to -5 and a solution of sodium nitrite (1.45 g) in water (50 ml) was added with stirring. After 15 minutes a solution of sodium azide (1.4 g) in water (50 ml) was added and the solution was warmed gently to 30°. The azide was extracted with ether (3 x 200 ml) and the combined ethereal extracts dried ($MgSO_4$). The solvent was removed under reduced pressure at 30° and the residual oil was percolated through a column of alumina (200 g, activity IV, column length 0.2 m) in petroleum (b.p. 40-60°). Evaporation of the solvent under reduced pressure at 30° gave 2-azidotriphenylmethane (4 g, 73%) as a white crystalline solid.



M.p. 94.5 - 95.5° (petroleum b.p. 40 - 60°)

Analysis

Found:	C, 80.4;	H, 4.9;	N, 14.6%
$C_{19}H_{15}N_3$ requires:	C, 80.0;	H, 5.3;	N, 14.7%

N.m.r. ($CDCl_3$)

δ 5.8 p.p.m.	s	1H methine C - H
6.7 - 7.4	m	14H arom.

I.r. (mull)

ν_{max} 2125, 1285 cm^{-1}

U.v. (95% ethanol)

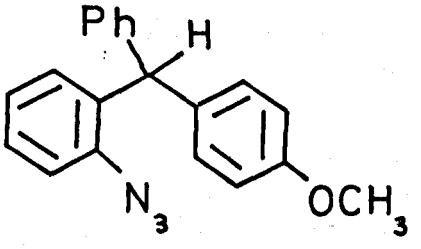
λ_{max}	222 nm	sh	
	253.5		$\log_{10} \varepsilon$ 4.03
	263	sh	
	280	sh	
	289	sh	
λ_{min}	235 nm		$\log_{10} \varepsilon$ 3.69

Mass spectrum

$^{m}/e$ 285 (M^+) (1%), 258 (37%), 257 (100%), 256 (22%), 255 (31%), 180 (50%), 179 (22%)

2-azido-4'-methoxytriphenylmethane 160

Prepared as described above from 2-amino-4'-methoxytriphenylmethane 170 in 87% yield.



Analysis

Found:	C, 76.4;	H, 5.85;	N, 12.9%
$C_{20}H_{17}N_3O$ requires:	C, 76.2;	H, 5.45;	N, 13.3%

N.m.r. ($CDCl_3$)

δ	3.75 p.p.m.	s	3H $-OCH_3$
	5.75	s	1H methine C – H
	6.8 – 7.4	m	13H arom.

I.r. (film)

ν_{max} 2130, 1298, 1282, 1250 cm^{-1}

U.v. (95% ethanol)

λ_{max}	230 nm	sh	
	252		$\log_{10} \varepsilon$ 4.01
	264	sh	
	280	sh	
	290	sh	

Mass spectrum

m/e 315 (M^+) (10%), 288 (7%), 287 (43%), 286 (100%), 285 (17%), 273 (7%), 272 (34%), 271 (8%), 256 (10%), 254 (7%), 244 (9%), 243 (15%), 242 (25%), 241 (10%), 226 (21%), 210 (21%), 198 (15%), 197 (9%), 180 (16%), 167 (14%), 134 (28%), 133 (28%), 120 (20%), 119 (40%), 105 (40%).

S E C T I O N 4

DECOMPOSITION OF THE 2-AZIDOTRIPHENYLMETHANES

The azides were decomposed thermally in 1,2,4-trichlorobenzene. The general procedure for the decompositions was as follows:

A solution of the azide in 1,2,4-trichlorobenzene (100 ml) was added dropwise during 45 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.

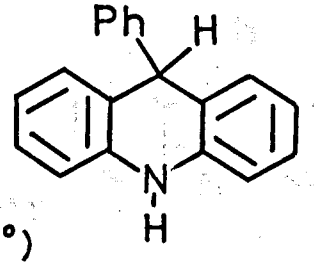
After 4 hours the solution was cooled and the solvent removed by distillation under reduced pressure (1 mm Hg). The residue was treated as described for the individual azides.

DECOMPOSITION OF 2-AZIDOTRIPHENYLMETHANE 158

Decomposition of the azide (3.8 g) gave, after removal of the solvent, a black oil which was shown by gas chromatography to comprise two major and two minor products. The oil was chromatographed on a column of alumina (200 g, activity IV). The column was eluted with benzene and two fractions were obtained.

The first fraction (1 l) was evaporated to leave a red oil (2.25 g) which on trituration with petroleum (b.p. 60-80°) gave 9,10-dihydro-9-phenylacridine 176 (0.41 g).

9,10-dihydro-9-phenylacridine 176



M.p. 170 - 171° (petroleum b.p. 60 - 80°)

Lit.[195] 170° (benzene)

Analysis

Found:	C, 88.65;	H, 5.7;	N, 5.5%	
$C_{19}H_{15}N$ requires:	C, 88.65;	H, 5.9;	N, 5.45%	

N.m.r. ($CDCl_3$)

δ 5.28 p.p.m.	s	1H	H on C-9	
6.1	br s	1H	- NH -	(ex. with D_2O)
6.6 - 7.3	m	13H	arom.	

I.r. (mull)

ν_{max} 3375, 1608, 1604, 1582 cm^{-1}

U.v. (95% ethanol)

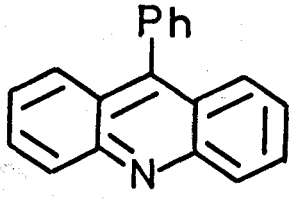
λ_{max}	224 nm	sh	
	254	sh	
	289		$\log_{10} \varepsilon$ 4.13
	312	sh	
λ_{min}	246		$\log_{10} \varepsilon$ 3.70

Mass spectrum

m/e 258 (7%), 257 (M^+) (35%), 256 (13%), 255 (18%), 254 (18%), 181 (17%), 180 (100%), 179 (7%), 155 (9%), 77 (9%)

The second fraction (500 ml) was evaporated to give 0.65 g of a yellow solid which recrystallised from petroleum (b.p. 60-80°) and was identified as 9-phenylacridine 177 (0.38 g).

9-phenylacridine 177



M.p. 183 - 184° (petroleum b.p. 60 - 80°)

Lit.[195] 184° (ethanol)

Analysis

Found: C, 89.35; H, 5.10; N, 5.40%

$C_{19}H_{13}N$ requires: C, 89.4; H, 5.10; N, 5.50%

N.m.r. ($CDCl_3$)

δ 7.2 - 8.4 p.p.m. m arom.

I.r. (mull)

ν_{max} 1630, 1608 cm^{-1}

U.v. (95% ethanol)

λ_{max} 219 nm sh

253.5 $\log_{10}\varepsilon$ 5.10

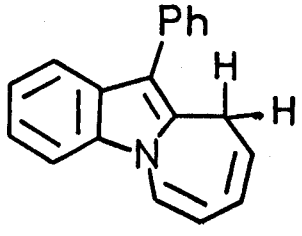
359 4.00

Mass spectrum

m/e 256 (18%), 255 (M^+) (100%), 254 (66%), 253 (13%), 226 (6%), 127.5 (11%), 127 (18%), 126.5 (6%), 126 (15%)

The combined residues from the crystallisations were chromatographed on a column of alumina (200 g, activity IV) in petroleum (b.p. 60-80°). The first fraction (500 ml) eluted from this column gave, on evaporation of the solvent, 11-phenyl-10H-azepino[1,2-a]indole 178 (1.05 g)

11-phenyl-10H-azepino[1,2-a]indole 178



M.p. 74 - 75° (petroleum b.p. 60 - 80°)

Analysis

Found:	C, 88.9;	H, 5.85;	N, 5.40%
$C_{19}H_{15}N$ requires:	C, 88.65;	H, 5.9;	N, 5.45%

N.m.r. ($CDCl_3$)

δ 3.49 p.p.m.	d	2H	H on C-10 $J_{9,10}$ = 5Hz
5.6 - 6.3	m	3H	H on C-7, 8 and 9
7.0 - 7.7	m	10H	H on C-6 and arom.

I.r. (mull)

ν_{max} 3050, 3025, 1636, 1602, 1567 cm^{-1}

U.v. (95% ethanol)

λ_{max}		$\log_{10} \varepsilon$
234 nm		4.41
270.5		4.24
305	sh	
325	sh	

Mass spectrum

m/e 258 (21%), 257 (M^+) (100%), 256 (41%), 255 (10%), 254 (16%), 241 (5%), 180 (15%), 128.5 (7%), 127.5 (11%), 127 (11%), 120.5 (7%)

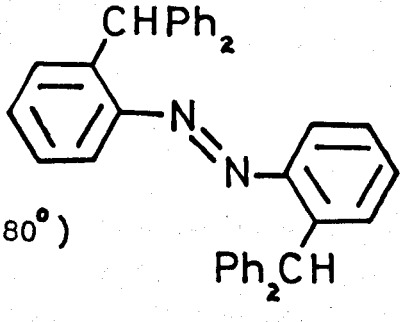
The second and third fractions (1 l) contained a small amount of material which was not identified. The column was then washed with chloroform to remove some coloured bands. This yielded 850 mg of a mixture of products which was spread on to three preparative plates and eluted with toluene. Five fairly clearly defined bands (Bands I - V in order of decreasing R_F) were produced.

Band	I	19 mg
Band	II	18 mg
Band	III	130 mg
Band	IV	260 mg
Band	V	100 mg

Band I was not identified.

Band II gave a red solid which was identified from its mass spectrum as 2,2'-bis(diphenylmethyl)azobenzene 179.

2,2'-bis(diphenylmethyl)azobenzene 179



M.p. 119 - 122° (petroleum b.p. 60 - 80°)

U.v. (cyclohexane)

λ_{max}		$\log_{10} \varepsilon$
257 nm		4.66
268	sh	4.64
287		4.54
310		4.49
342		4.28
390		3.76

Mass spectrum

m/e 514 (M^+) (12%), 513 (15%), 512 (35%), 511 (8%), 510 (12%), 259 (15%), 258 (25%), 257 (54%), 256 (100%), 255 (13%), 254 (19%), 243 (30%), 180 (15%)

Band III was identified as 9,10-dihydro-9-phenylacridine 176.

Band IV was identified as 2-aminotriphenylmethane 164 by comparison with an authentic sample.

Band V was identified as 9-phenylacridine 177

The remaining crystallisation liquors were evaporated and the residue similarly chromatographed on preparative plates with toluene to yield the azepinoindole 178 (270 mg), 9-phenylacridan (20 mg) and 9-phenyl acridine (8 mg).

The total yields of isolated products were:

11-phenyl-10H-azepino[1,2-a]indole	178	1.05 g	31%
9-phenylacridan	176	0.56 g	19%
9-phenylacridine	177	0.49 g	14%
2-aminotriphenylmethane	164	0.26 g	7.5%
Azo compound	179	0.018 g	1%

DECOMPOSITION OF 2-AZIDO-4'-METHOXYTRIPHENYLMETHANE 160

The decomposition of the azide (9 g) at 185° for four hours gave, after removal of the solvent, a red tar which gave five peaks on a g.l.c. trace (3% OV 101 on Supasorb A.W., 50 ml/min nitrogen 209°), although t.l.c. showed the presence of seven components.

An attempt was made to separate the mixture by column chromatography; the crude decomposition product (2.75 g) was chromatographed on a column of alumina (300 g, activity IV, column length 1 m).

The column was eluted with petroleum (b.p. 40 - 60°)/benzene (50/50), 25 ml fractions were collected and the fractions checked by gas chromatography and n.m.r. spectroscopy.

The following table (Table 3) lists the products eluted from the column, the fractions in which they appeared and the weight of each fraction.

TABLE 3

Product	Fractions	Weight (mg)
1	1 - 3	410
2	4,5	350
2,3	6,7	460
3	8 - 15	597
4,5	16 - 30	403
6	31 - 50	165
7,8	51 - 123	330
		2,715
Recovery	99%	

Product 1 was a colourless oil and was identified from its n.m.r. spectrum as 1,2,4-trichlorobenzene.

Products 2 and 3 crystallised from petroleum (b.p. 60 - 80°) to give pure samples of 11-(4-methoxyphenyl)-10H-azepino[1,2-a]-indole 180 and 8,9-dihydro-8,9-methano-8-methoxy-10-phenylpyrido-[1,2-a]indole 181 respectively.

The mixture of products 4 and 5 was dissolved in boiling petroleum (b.p. 60 - 80°) and the solution allowed to cool to room

temperature. Pure product 4 crystallised slowly. It was identified from its spectral data as 9,10-dihydro-9-(4-methoxyphenyl)acridine 182. Cooling in an ice-salt mixture promoted co-crystallisation of products 4 and 5.

A pure sample of product 7 was obtained in a similar manner. This compound was identified as 9-(4-methoxyphenyl)acridine 184 by comparison of its melting point and Ultra violet spectrum with literature data.

Pure samples of products 8 and 5 were not isolated but spectral data was obtained from mixtures. These compounds were identified as 3-methoxy-9-phenylacridine 185 and its 9,10-dihydro derivative 183 respectively.

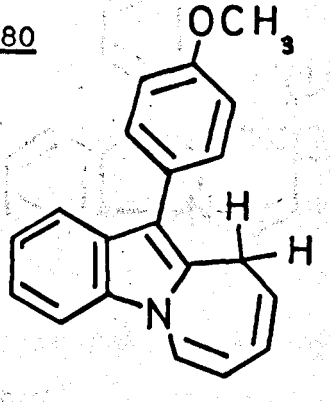
Product 6 was an oil and was identified from its n.m.r. spectrum as 2-amino-4'-methoxytriphenylmethane 170.

The high recovery from the column enabled the yield of each compound to be calculated. The proportions of compounds in mixtures could easily be calculated from the n.m.r. spectrum of the mixture. The methoxyl group in each component had a different chemical shift so the proportions were calculated using the area of the methoxyl peak as measured by its integral.

$$\text{Percentage of product X} = \frac{\text{peak area of methoxyl group in X}}{\text{sum of peak areas of methoxyl groups in X,Y....}} \times 100$$

Properties of the isolated products:

11-(4-methoxyphenyl)-10H-azepino[1,2-a]indole 180



Product 2

Yield: 17%

M.p. 97 - 99° (petroleum b.p. 60 - 80°)

Analysis

Found:	C, 83.85;	H, 6.20;	N, 4.70%
$C_{20}H_{17}NO$ requires:	C, 83.60;	H, 6.00;	N, 4.85%

N.m.r. ($CDCl_3$)

δ 3.44 p.p.m.	d	2H	H on C-10 J = 5Hz
3.62	s	3H	$-OCH_3$
5.5 - 6.1	m	3H	H on C-7,8 and 9
6.8 - 7.6	m	9H	H on C-6 and arom.

I.r. (mull)

ν_{max} 3058, 3030, 3018, 1632, 1600 cm^{-1}

U.v. (95% ethanol)

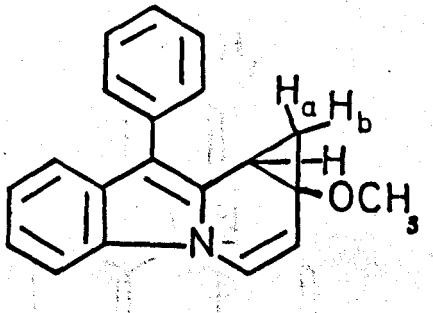
λ_{max}	234.5 nm	$\log_{10} \varepsilon$	4.45
	267.5		4.29
	296	sh	
	325	sh	
	335	sh	

Mass spectrum

m/e 288 (23%), 287 (M^+) (100%), 286 (34%), 273 (17%), 272 (83%), 271 (8%), 244 (13%), 243 (11%), 242 (19%), 241 (13%), 180 (21%), 143 (12%)

8,9-dihydro-8,9-methano-8-methoxy-10-phenylpyrido[1,2-a]indole 181

Product 3



Yield: 34%

M.p. 155 - 157° (petroleum b.p. 60 - 80°)

Analysis

Found:	C, 83.4;	H, 5.80;	N, 4.95%
$C_{20}H_{17}NO$ requires:	C, 83.6;	H, 6.00;	N, 4.85%

N.m.r. ($CDCl_3$)

δ 0.59 p.p.m.	d of d	1H	Ha on C-11
			$J_{11a,11b}$ = 4.8Hz, $J_{11a,9}$ = 5.8Hz
1.83	d of d	1H	Hb on C-11
			$J_{11a,11b}$ = 4.8Hz, $J_{11b,9}$ = 10.2Hz
2.68	m	1H	H on C-9
			$J_{11a,9}$ = 5.8Hz,
			$J_{11b,9}$ = 10.2Hz,
			$J_{7,9}$ = 2.0Hz
3.22	s	3H	$-OCH_3$
5.65	d of d	1H	H on C-7
			$J_{7,9}$ = 2.0Hz, $J_{6,7}$ = 8.0Hz
6.9 - 7.9	m	10H	H on C-6 and arom.

I.r. (mull)

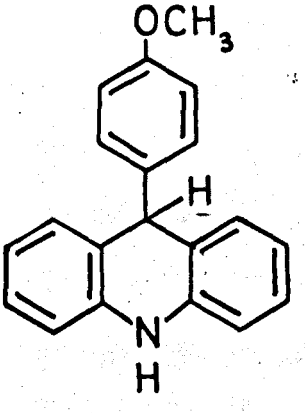
ν_{max} 3062, 1650, 1600 cm^{-1}

U.v. (95% ethanol)

λ_{max} 227.5 nm	$\log_{10}\varepsilon$	4.41
256		4.49
285 sh		
314		4.18

Mass spectrum

m/e 288 (31%), 287 (M^+) (100%), 286 (22%), 273 (9%), 272 (28%), 271 (10%), 270 (20%), 257 (16%), 256 (41%), 255 (9%), 254 (20%) 244 (7%), 243 (27%), 242 (30%), 241 (14%), 240 (18%)



9,10-dihydro-9(4-methoxyphenyl)acridine 182

Product 4

Yield: 12%

M.p. 181 - 182° (petroleum b.p. 60 - 80°)

Analysis

Found: H, 5.70; N, 4.75%

$C_{20}H_{17}NO$ requires: H, 5.95; N, 4.9%

N.m.r. ($CDCl_3$)

δ 3.71 p.p.m.	s	3H	$-OCH_3$
5.24	s	1H	methine C-H
6.1	br s	1H	-NH- (ex. with D_2O)
6.6 - 7.2	m	12H	arom.

I.r. (mull)

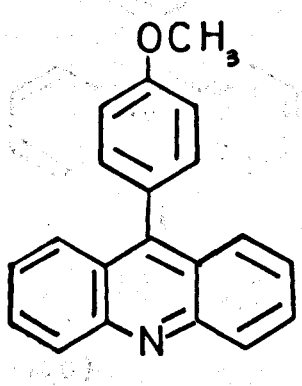
ν_{max} 3380, 1610, 1581 cm^{-1}

U.v. (95% ethanol)

λ_{max} 228 nm	$\log_{10} \varepsilon$	4.30
285.5		4.15
315 sh		

Mass spectrum

m/e 288 (8%), 287 (M^+) (37%), 286 (14%), 285 (5%), 242 (6%), 241 (5%), 210 (18%), 181 (17%), 180 (100%), 179 (7%)



9-(4-methoxyphenyl)acridine 184

Product 7

Yield: 6%

M.p. 213 - 214° (petroleum b.p. 40 - 50°/ether)

Lit.[198] 213°

Analysis

Found:	H, 5.25; N, 5.65%
$C_{20}H_{15}NO$ requires:	H, 5.3; N, 4.90%

N.m.r. ($CDCl_3$)

δ 3.87 p.p.m.	s	3H	$-OCH_3$
6.9 - 8.3	m	12H	arom.

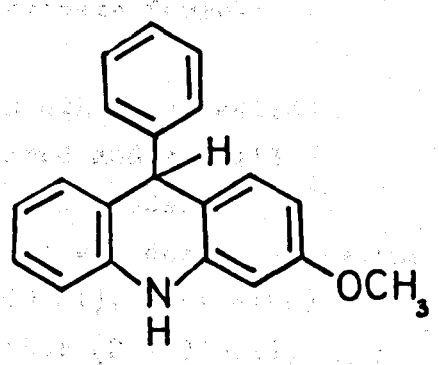
U.v. (95% ethanol)

λ_{max}		$\log_{10} \varepsilon$
220 nm		4.41
227	sh	4.37
253		5.01
343	sh	
356		3.97

Mass spectrum

m/e 286 (48%), 285 (M^+) (100%), 284 (17%), 271 (6%), 270 (27%), 255 (7%), 254 (23%), 243 (5%), 242 (28%), 241 (47%), 240 (27%), 142.5 (5%), 135 (12%), 120.5 (16%)

9,10-dihydro-3-methoxy-9-phenylacridine 183



Product 5

Yield: 14%

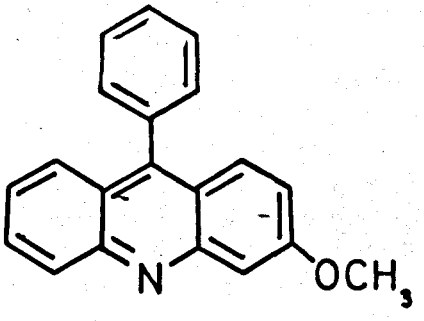
I.r. (mull)

ν_{max} 3360 cm^{-1}

N.m.r. ($CDCl_3$)

δ 3.77 p.p.m.	s	3H	$-OCH_3$	
5.24	s	1H	methine	C-H
5.95	br s	1H	-NH	(ex. with D_2O)

3-methoxy-9-phenylacridine 185



Product 8

Yield: 10%

N.m.r. ($CDCl_3$)

δ 3.95 p.p.m.	s	3H	$-OCH_3$
6.9 - 8.3	m	12H	arom.

SECTION 5

PREPARATION AND DECOMPOSITION OF α-(2-AZIDOPHENYL)-α',α''-DIDEUTERIOTOLUENE 192

Preparation of α-(2-aminophenyl)-α',α''-dideuteriotoluene

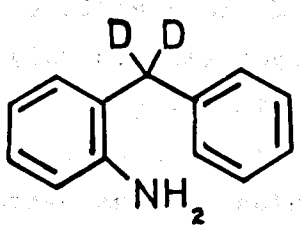
A complex of lithium aluminium deuteride and aluminium chloride was prepared by dissolving anhydrous aluminium chloride (20 g, added in portions) in dry ether (100 ml) and adding the deuteride (4 g). This gave a complex of approximate formula $LiAlD_4 \cdot 1\frac{1}{2}AlCl_3$.

A solution of 2-aminobenzophenone in ether was added dropwise with stirring until coagulation occurred and a solid precipitated. Approximately 7 g of the ketone was added.

The excess lithium aluminium deuteride was destroyed by the addition of wet ether and eventually water (500 ml). The ether was separated and the aqueous layer washed with ether (2 x 200ml). The combined washings were dried ($MgSO_4$) and evaporated to leave a brown oil (6.1 g, 93%).

The n.m.r. spectrum of the oil showed only aromatic signals and a signal due to the amine protons and the infra red spectrum revealed the absence of the carbonyl absorption. The oil was not purified further but used directly.

α-(2-aminophenyl)-α',α''-dideuteriotoluene



B.p. 114 - 116°, 0.35 mm Hg

Analysis

Found:	C, 84.2;	H(D), 7.20;	N, 7.5%
$C_{13}H_{11}D_2N$ requires:	C, 84.25		N, 7.55%
H_{13} for a compound of molecular weight 185.3		H, 7.0;	

N.m.r. ($CDCl_3$)

δ 3.58 p.p.m.	s 2H	$-NH_2$ (ex. with D_2O)
6.5 - 7.3	m 9H	arom.

I.r. (film)

ν_{max} 3445, 3362, 1622, 2190, 2130, 2095 cm^{-1}

U.v. (95% ethanol)

λ_{max} 233.5 nm	$\log_{10} \varepsilon$	3.87
285		3.36

Mass spectrum

m/e 186 (16%), 185 (M^+) (100%), 184 (47%), 183 (11%), 182 (9%), 181 (9%), 169 (9%), 168 (9%), 167 (16%), 166 (22%), 165 (7%), 108 (36%), 107 (24%), 106 (9%), 105 (7%)

Preparation of α-(2-azidophenyl)-α',α"-dideuteriotoluene 192

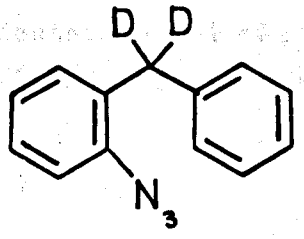
A solution of the amine (6.1 g) in a mixture of 4N sulphuric acid (200 ml) and purified dioxan (200 ml) was cooled to 0° and a solution of sodium nitrite (2.53 g, excess) in water (25 ml) was added dropwise with stirring. After 15 minutes a solution of sodium azide (2.55 g) in water (25 ml) was added and the solution was allowed to warm to room temperature.

The azide was extracted with ether (3 x 300 ml), the ether extracts dried ($MgSO_4$) and evaporated under reduced pressure at 30°.

The residual oil was percolated through a column of alumina (200 g, activity IV, column length 0.2 m) in petroleum (b.p. 40 - 60°).

Evaporation of the solvent at 30° under reduced pressure gave the azide 192 (5.1 g, 73%) as a colourless oil.

α-(2-azidophenyl)-α',α"-dideuteriotoluene 192



N.m.r. ($CDCl_3$)
δ 6.9 - 7.3 p.p.m. m

I.r. (film)
ν_{max} 2130, 1290 cm^{-1}

Mass spectrum
m/e 211 (M^+) (0%), 183 (29%), 182 (90%), 181 (100%), 180 (50%), 179 (12%), 155 (6%), 154 (7%), 153 (10%), 152 (10%), 91 (8%), 91.5 (9%), 90 (10%)

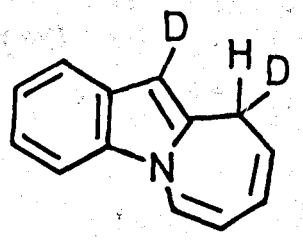
Decomposition of α-(2-azidophenyl)-α',α"-dideuteriotoluene 192

The azide 192 (5.0 g) was decomposed at 187° for four hours. The solvent was removed under reduced pressure to leave a black solid which was shown by g.l.c. examination to consist of one major and several minor components. Recrystallisation from petroleum (charcoal) gave the azepinoindole as a pale yellow solid (3.5 g, 60%).

Comparative gas chromatographic analysis of the minor products indicated that they were acridan, acridine and the amine precursor to the azide 192. An attempt to isolate these products by chromatographic separation of the residue from the crystallisation failed. However, the azepinoindole isolated from the column was found to have undergone deuterium exchange on the column and a singlet due to the H-11 proton was observed in the n.m.r. spectrum. An attempt to reverse the exchange by elution of the azepinoindole down a column of alumina, deactivated by D_2O, met with only partial success.

The azepinoindole was shown to be deuterated at the C-10 and 11 positions by careful analysis of its 220 MHz n.m.r. spectrum.

10,11-dideuterio-10H-azepino[1,2-a]indole 193



M.p. 91.5 - 92.5° (petroleum b.p. 60 - 80°)

Analysis

Found:	C, 85.3;	H, 6.10;	N, 7.65%
$C_{13}H_9D_2N$ requires:	C, 85.2		N, 7.65%

H_{11} for a compound of molecular weight 183.3 H, 6.0

N.m.r. (220 MHz Spectrum, CCl_4)

δ 3.32 - 3.43 p.p.m.	m	1H	H on C-10
5.59	d of d	1H	H on C-9
			$J_{9,10}$ = 5.5Hz, $J_{8,9}$ = 9.0Hz
5.72 - 5.86	m	1H	H on C-8
5.90	d of d	1H	H on C-7
			$J_{6,7}$ = 10.2Hz, $J_{7,8}$ = 5.5Hz
6.98 - 7.09	m	2H	arom. or H on C-6 and arom.
7.14 - 7.25	m	2H	arom. or H on C-6 and arom.
7.34 - 7.46	m	1H	arom.

I.r. (mull)

ν_{max} 1640, 1605 cm^{-1}

U.v. (95% ethanol)

λ_{max} 226 nm	$\log_{10} \varepsilon$	4.37
271		4.20
278 sh		
314		3.84

Mass spectrum

m/e 184 (12%), 183 (M^+) (80%), 182 (100%), 181 (65%), 180 (18%), 179 (7%), 156 (5%), 155 (7%), 154 (11%), 153 (11%), 152 (7%), 129 (5%), 128 (6%), 91.5(9%), 91 (8%), 90.5 (6%), 90 (6%), 78 (8%), 77.5 (6%), 77 (7%), 76 (5%), 75 (5%)

Appearance potential = 15 eV 184(13%), 183 (M^+) (100%)

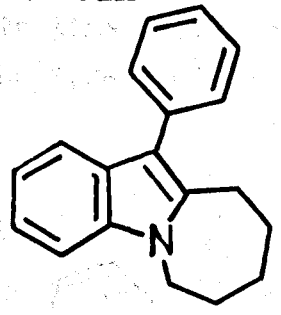
SECTION 6

FURTHER WORK ON THE DECOMPOSITION PRODUCTS

Reduction of 11-phenyl-10H-azepino[1,2-a]indole

A solution of the azepinoindole 178 (0.25 g) in methanol containing 10% palladium-on-charcoal (0.1 g) was hydrogenated at atmospheric pressure and temperature until absorption had ceased. (2 moles H_2 absorbed). The filtered solution was evaporated and the residue recrystallised from petroleum (b.p. 60 - 80°) to give the tetrahydro derivative 202 (0.22 g, 87%).

6,7,8,9-tetrahydro-11-phenyl-10H-azepino[1,2-a]indole 202



M.p. 107.5 - 108.5° (petroleum b.p. 60 - 80°)

Analysis

Found:	C, 87.15;	H, 7.25;	N, 5.30%
$C_{19}H_{19}N$ requires:	C, 87.30;	H, 7.35;	N, 5.35%

N.m.r. ($CDCl_3$)

δ 1.7 - 2.0 p.p.m.	m	6H	H on C-7,8 and 9
2.9 - 3.2	m	2H	H on C-10
4.1 - 4.5	m	2H	H on C-6
7.1 - 7.9	m	9H	arom.

U.v. (95% ethanol)

λ_{max} 230 nm		$\log_{10} \varepsilon$	4.47
277	sh		
282.5			4.12

Mass spectrum

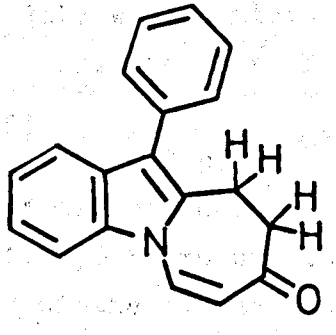
$^{m}/e$ 262 (27%), 261 (M^{+}) (100%), 260 (20%), 246 (5%), 233 (9%), 232 (13%), 220 (9%), 218 (7%), 217 (7%), 206 (10%), 205 (8%), 204 (11%), 184 (55%), 130.5 (4%), 77 (5%)

Hydrolysis of the pyridoindole 181

A solution of the pyridoindole (0.2 g) in ether (25 ml) was shaken with 2N hydrochloric acid (25 ml) for two minutes. The ether was separated, dried ($MgSO_4$) and evaporated to give a residue identified as the starting material.

The residue was treated with concentrated hydrochloric acid (25 ml). It readily dissolved to give a red solution. Shaking the solution with ether (25 ml) did not remove the colouration so the acid was neutralised with aqueous ammonia and the neutral solution extracted with ether (3 x 25 ml). The combined ether extracts were dried ($MgSO_4$) and evaporated to give a yellow crystalline solid (0.15 g) identified as 9,10-dihydro-11-phenylazepino[1,2-a]indol-8-one 203.

9,10-dihydro-11-phenylazepino[1,2-a]indol-8-one 203



M.p. 144 - 144.5° (methanol)

Analysis

Found:	C, 83.25;	H, 5.85;	N, 5.0%
$C_{19}H_{15}NO$ requires:	C, 83.50;	H, 5.55;	N, 5.15%

N.m.r. ($CDCl_3$)

δ 2.82 p.p.m.	m	2H	H on C-10
3.22	m	2H	H on C-9
5.71	d	1H	H on C-7 $J_{6,7}$ = 10Hz
7.2 - 7.8	m	10H	arom. and H on C-6

I.r. (mull)

ν_{max} 1650, 1626, 1605 cm^{-1}

U.v. (95% ethanol)

λ_{max} 227 nm		$\log_{10} \varepsilon$ 4.45
251	sh	
275.5		4.19
279	sh	
347		4.20

Mass spectrum

m/e 274 (23%), 273 (M^+) (100%), 246 (18%), 245 (75%), 244 (93%), 243 (18%), 230 (18%), 217 (15%)

Attempted isomerisation of the pyridoindole 181

A solution of the pyridoindole 181 (0.2 g) in 1,2,4-trichlorobenzene (1 ml) contained in an n.m.r. tube was maintained at a temperature of 195° by refluxing decalin. The progress of the thermolysis was followed by n.m.r. spectroscopy.

As time progressed the emergence of a peak 0.2 p.p.m. down-field of the pyridoindole methoxyl group signal was observed. This peak gradually increased in height and after 30 hours was the predominant peak. The corresponding diminution of the pyridoindole signals was also observed. Several other peaks in the region δ 3.0 - 4.0 p.p.m. also appeared.

After 55 hours the reaction was stopped. The signals due to the pyridoindole had almost disappeared and a complex pattern had emerged in the region of δ 3.0 - 4.0 p.p.m. Examination of the solution by g.l.c. revealed the presence of six components, some of which had retention times similar to the acridan/acridine products.

The solvent was removed and the residue spread onto a preparative plate. Elution with benzene gave five ill-defined bands.

1.	R_F	0.72	red
2.		0.63	orange
3.		0.40	colourless/black U.V. reaction
4.		0.09	yellow/black U.V. reaction
5.		0.03	colourless/blue U.V. reaction

These bands were removed and examined by linked gas chromatography - mass spectrometry but because of the very high background no useful data was obtained.

The reaction was not repeated.

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