SYNTHETIC AND MECHANISTIC STUDIES OF SOME NITRENE INSERTION REACTIONS

by

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To my parents

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ABSTRACT

A short review of aromatic nitrene chemistry is presented in the Introduction, with particular emphasis with recent developments reported in the literature.

Part I of the discussion describes the thermolytic and photolytic decomposition of 2-azidotriphenylmethane in the presence of singlet and triplet sensitizing and quenching reagents. A hypothesis which attempts to relate the observed products to the spin state of the nitrene is discussed.

In Part II of the discussion, the preparation and thermolytic decomposition of 2-azido-4',4"-dimethoxytriphenylmethane is described. Amongst other products, a novel bicyclic pyrido-indole derivative was isolated and a discussion on the mechanism of its formation is included.

In Part III is described the investigation into aromatic nitrene insertions in heterocyclic systems analogous to the di- and triphenylmethanes. Thus the attempted preparation of 2-(2-azidobenzyl)furan, and the successful preparation of α, α-di-(2-furyl)-2-nitrotoluene and its analogues are described. Deoxygenation of the methyl substituted analogue yielded a novel furyl carbazole ring system. The spectral characteristics of this compound and its attempted synthesis are discussed.

Full experimental details for Parts I, II and III are included in the last section of this thesis.

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CONTENTS

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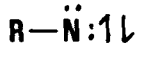
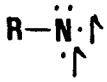
INTRODUCTION

Nitrenes, the nitrogen analogues of carbenes, are monovalent, uncharged nitrogen intermediates; the nitrogen atom has only six electrons in its valence shell and thus the species is iso-electronic with carbenes. The nitrene may exist in two electronic states; the singlet state 1 has two spin-paired electrons and exhibits electrophilic character, whereas the triplet state 2 features two unpaired electrons with parallel spins and is therefore diradical in nature.



singlet 1



triplet 2

The existence of nitrenes, first postulated some years ago to explain the mechanisms of the Hofmann, Curtius, Lossen, Beckman and Stieglitz rearrangements, has now been well established. This is evidenced by the considerable number of reviews which have appeared during the previous ten years.[1-7]

The ultraviolet spectra of several triplet aryl nitrenes have been recorded both from low temperature photolysis[8] and from flash photolytic experiments.[9,10] Low temperature electron spin resonance studies[11,12] have shown that nitrenes have triplet ground states consistent with Hund's rule. Similar direct evidence for the existence of the singlet state has yet to be reported. Most of the evidence for the intermediate singlet species has been obtained from reaction studies.

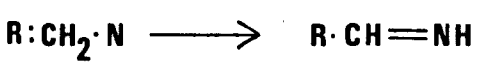
General Features of Nitrenes

Nitrenes can be produced easily from a variety of readily available starting materials, and these have been reviewed.[3] For the

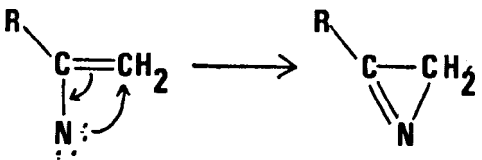
purpose of the discussion in this thesis, only two methods of formation will be considered; the thermal and photolytic decomposition of azides, and the deoxygenation of nitro-compounds. The discussion will be mainly restricted to the formation and reactions of aryl nitrenes. The preparation and reactions of organic azides have been reviewed.[13,14]

Once formed, the highly reactive nitrene can stabilise itself in a number of ways:

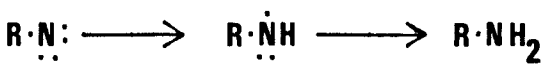
i) by intramolecular rearrangement to the imine



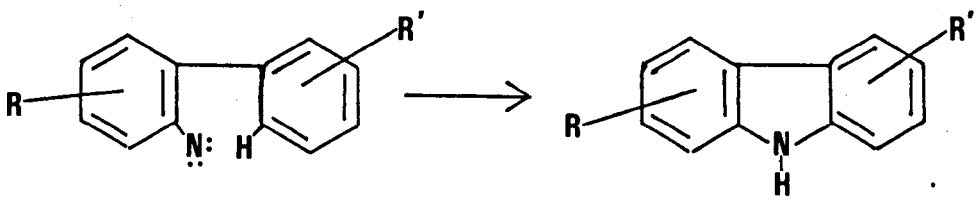
ii) by isomerisation to an azirine



iii) by intermolecular hydrogen abstraction to yield an amine



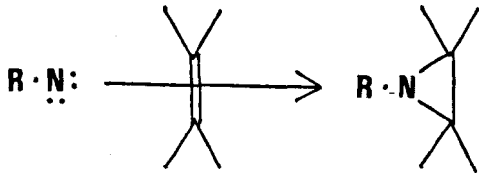
iv) by intramolecular hydrogen abstraction with ring closure



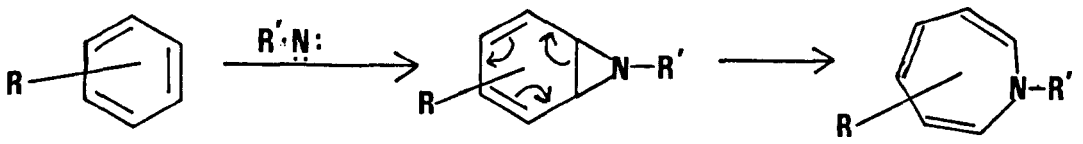
v) by "dimerisation" to an azo compound, R.N=N.R

vi) by intermolecular insertion into a C-H bond[15,16]

vii) by addition to an olefinic bond



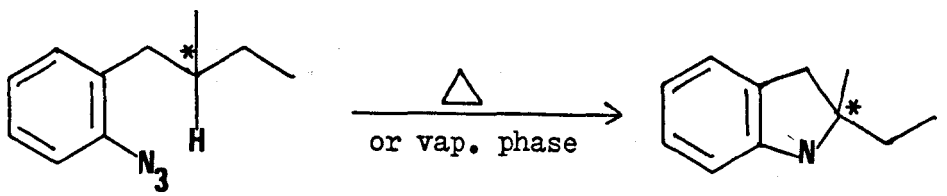
viii) by addition to an aromatic system with subsequent ring expansion.



At room or higher temperature, nitrenes can behave as diradicals (triplet) as well as electrophilic (singlet) species, depending on the nature of the nitrene and on the reaction conditions. In general, nitrenes generated photolytically react as triplets and those generated thermolytically react as singlets; the latter can also undergo intersystem crossing to form the triplet species.

The singlet nitrene undergoes stereospecific C-H bond insertion,[17] whereas hydrogen abstraction is characteristic of the triplet state.[18] Smolinsky and Feuer[19] have studied the decomposition of the optically active azide 1-azido-2-(2-methylbutyl)benzene 3, in both solution and in vapour phase pyrolysis (Scheme 1).

SCHEME 1



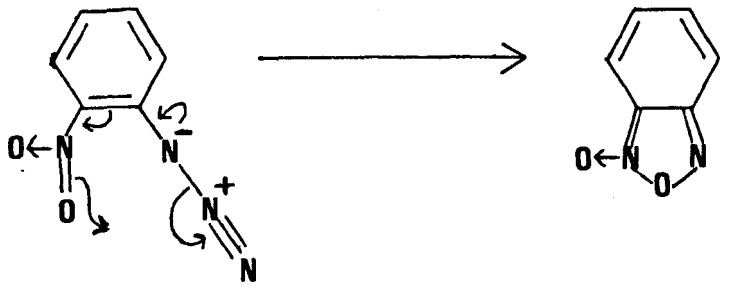
3 4

The nitrene inserts into the C-H bond at the asymmetric carbon atom to yield the indoline 4. In the vapour phase the retention of optical activity was almost complete, indicating the stereospecific singlet insertion, whereas only about 60% retention was observed in solution. This reflects the increased opportunity for a singlet species to be deactivated to a triplet as a result of collisions with the solvent molecules.

It was been shown[20,21] by studies of the thermal decomposition of aryl azides in inert media that the decomposition rates are first-order and that the rate-determining step is the cleavage of the azide to form the nitrene.

The nature of a substituent ortho- to the azide group can have a major influence on the outcome of the decomposition. Ortho-nitroaryl azides, for example, fail to give any products expected from a nitrene precursor, but do give good yields of furoxans 6 (Scheme 2).[13,22,23,24]

SCHEME 2

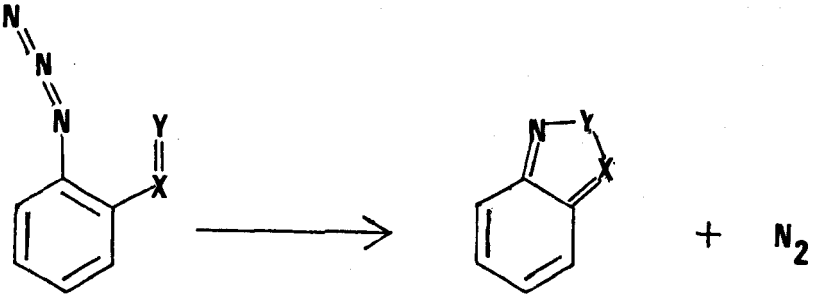


5 6

The nucleophilic nitro group assists the decomposition of the azide 5 to the extent that no discrete nitrene is formed. The decomposition temperature is comparatively low and this is rationalised in terms of the concerted mechanism shown in Scheme 2.

Dyall[25] has undertaken systematic kinetic studies of the decomposition of ortho- and para-substituted phenyl azides in decalin solution. Measurement of the rate constants shows very large rate increases (relative to phenyl azide) when the ortho substituent is phenylazo, nitro, acetyl or benzoyl. A mechanism to account for these results has been suggested which involves a "bridged" nitrene; the driving force is the delocalization energy of the incipient heterocycle (Scheme 3).

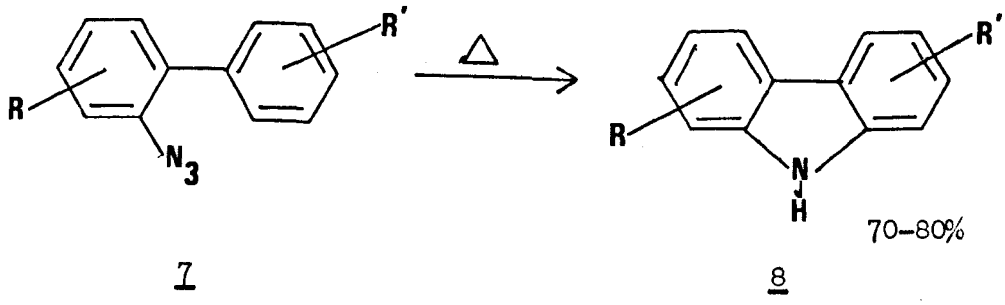
SCHEME 3



As the large increases in the rate constants cannot be explained by steric or normal electronic effects, the rate enhancement is therefore a genuine neighbouring-group effect.

One of the earliest synthetic "successes" of a nitrene intermediate was the formation of carbazoles 8 from ortho-azidodiphenyls 7 (Scheme 4).[22,26,27]

SCHEME 4

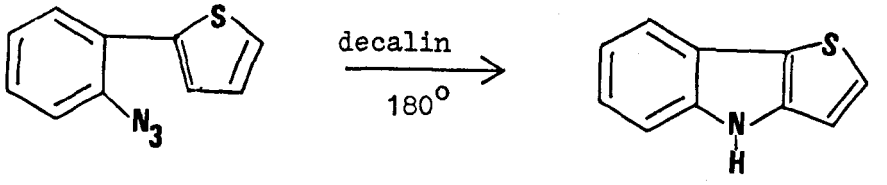


7 8

This reaction was thought to be a straight-forward example of a nitrene inserting intramolecularly into a C-H bond. Recent work by Sundberg and co-workers[28] on the photolytic conversion of azido-biphenyls to carbazoles has demonstrated that the reaction proceeds by at least two routes, one of which involves an intermediate which can be diverted by secondary amines. Three mechanistic schemes that will account for the available data have been proposed; two of these involve two intermediates and the other requires three. The nature of these intermediates has yet to be established. The previous mechanistic view of this reaction was that triplet biphenylnitrene was the precursor to carbazole; this was postulated following the discovery of a transient species with an electronic spectrum similar to that expected for the triplet species. This transient species was apparently converted into carbazole on irradiation. Sundberg has shown that the rate of decay of the transient and the appearance of the carbazole are significantly different.

The decomposition of an ortho-azido group to effect an intramolecular nitrene insertion, as in Scheme 4 above, has been extended to the preparation of many five-membered ring heterocycles. Two examples are given in Schemes 5 and 6.

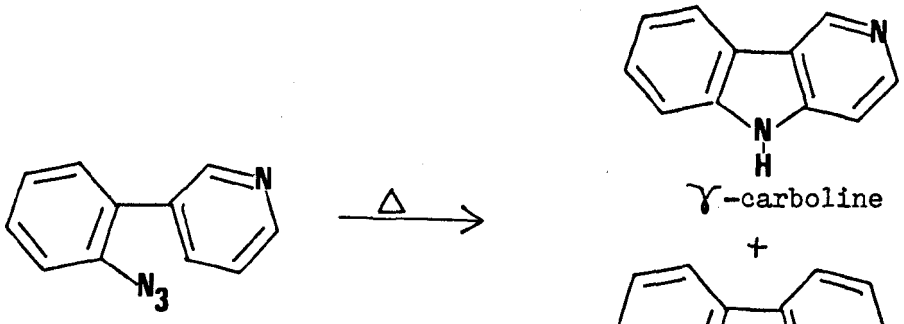
SCHEME 5



Ref. 29

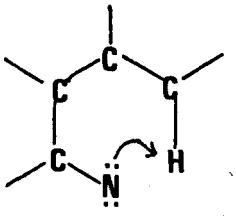
4H-thieno[3,2-b]indole

SCHEME 6



Ref. 30

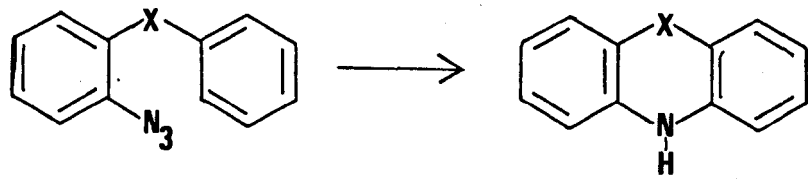
The formation of five-membered rings is favoured in nitrene reactions since hydrogen abstraction or insertion by the nitrene will involve a six-membered transition state 9



9

Cyclization to form six-membered ring systems by insertion into an aromatic C-H bond is less common but examples are known. Smith and co-workers[31] have reported the following products 10 (Scheme 7).

SCHEME 7



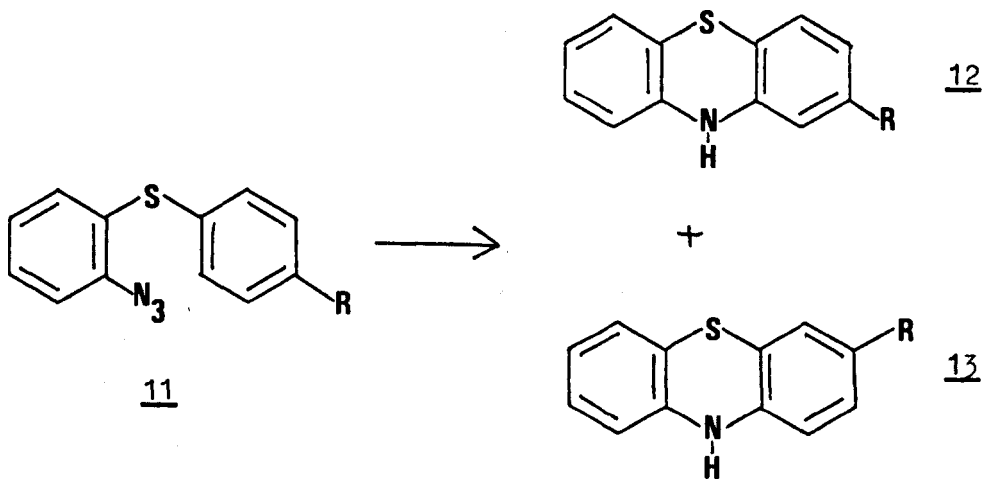
X = S

SO_2

10

Cadogan and co-workers[32,33,34] have studied the decomposition of substituted 2-azidodiphenyl sulphides 11 which were found to cyclise and yield substituted phenothiazines of two types, 12 and 13 (Scheme 8).

SCHEME 8



11

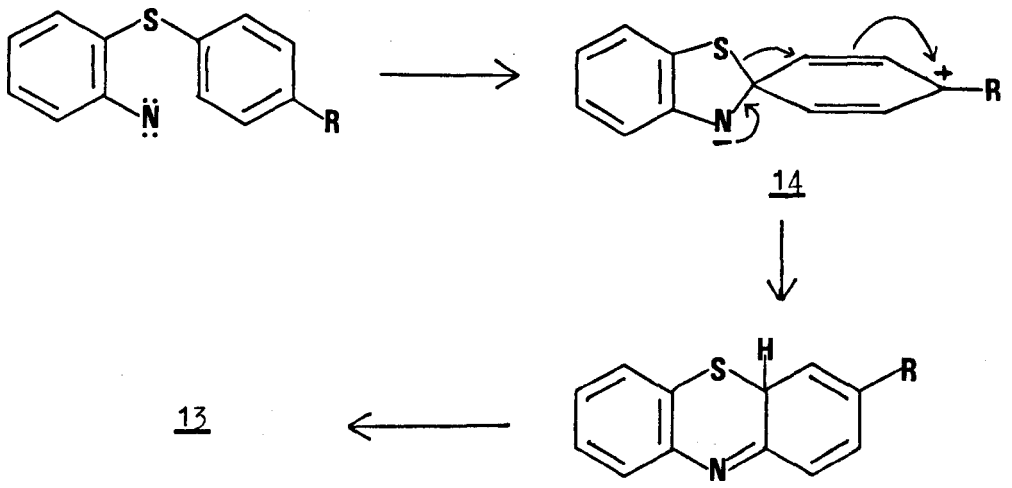
12

13

The formation of the phenothiazines 12 AND 13 raises interesting questions about the mechanism. The product 12 is the expected one from a direct insertion, but 13 requires a molecular rearrangement in its formation. Cadogan has proposed the following mechanism (Scheme 9) which features a spiro-intermediate 14 and a

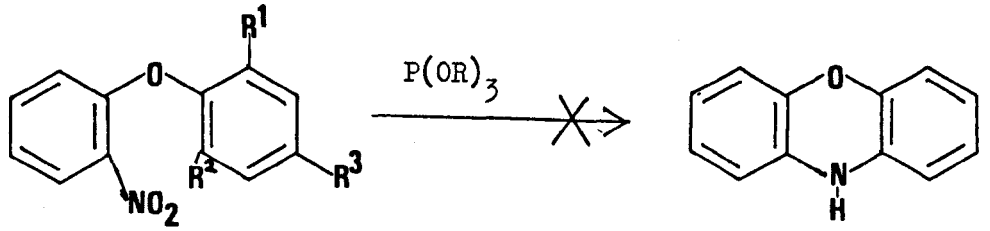
1,2-sigmatropic shift of the sulphur atom followed by prototropy to give 13.

SCHEME 9



The 2-nitroaryl ethers 15 have also been investigated by Cadogan and co-workers,[35(a),(b),(c),(d)] (Scheme 10).

SCHEME 10



15 (a) $R^1 = R^2 = R^3 = H$

(b) $R^1 = R^2 = R^3 = Me$

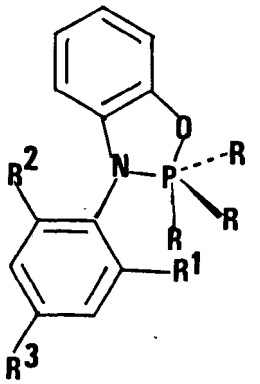
(c) $R^1 = R^2 = OMe$, $R^3 = H$

(d) $R^1 = R^2 = Me$, $R^3 = H$

16

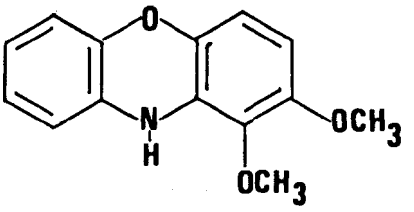
The unsubstituted ether 15a did not give the phenoxazine 16; the trisubstituted ethers, 15b for example, yielded a new series of

heterocycles, the 3-aryl-2,3-dihydro-1,3,2-benzoxazaphosph(v)oles 17.

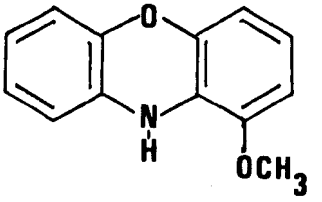


17

The dimethoxy substituted ether, 15c, yielded the disubstituted phenoxazine 18 plus a little monomethoxy compound 19.



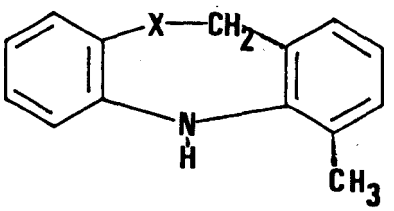
18



19

A mechanism to account for the formation of these compounds is proposed.

Deoxygenation of the dimethyl ether, 15d, gave a poor yield of 5,11-dihydro-4-methyldibenz[b,e][1,4]oxazepine 20.



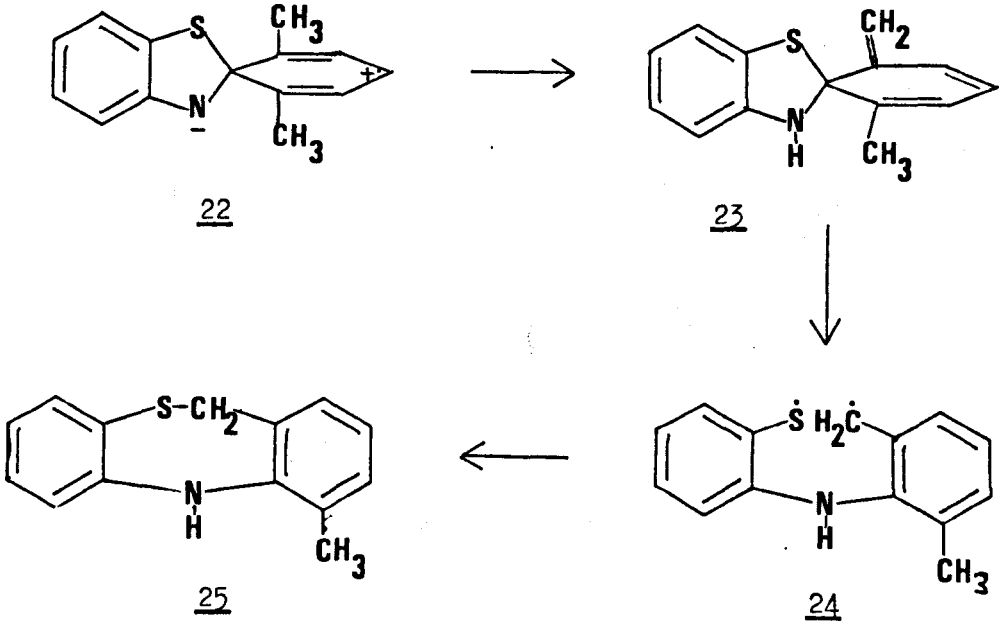
20 X = O

21 X = S

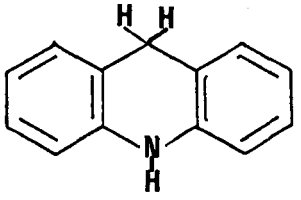
This oxazepine 20 is analogous to the thiazepine 21 formed in the

corresponding reaction with aryl-2-nitrophenyl sulphides.[35(e)] A mechanism has been proposed[35(e)] for the formation of these azepines which proceeds from the spiro-diene intermediate 22, to its isomer 23. The product could be obtained from 23 by a 1,3-suprafacial sigmatropic shift but this is not permitted. Consequently it is suggested that the mechanism proceeds via the diradical species 24 to the observed product 25 (Scheme 11).

SCHEME 11



Six-membered ring heterocycles, derivatives of acridan 26 and acridine 27, are also among the products formed by the decomposition of azides 28 → 31.



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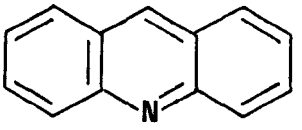
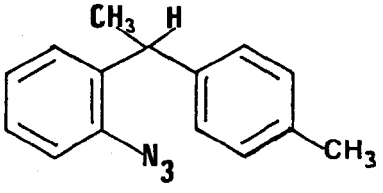
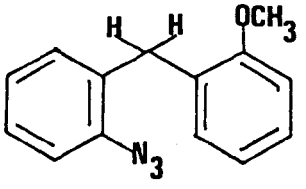


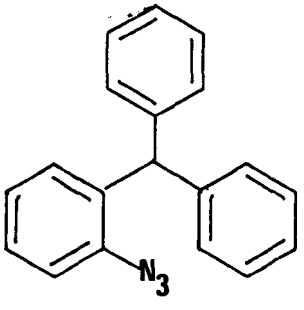
27



Ref. 36 28



Ref. 37,38 29



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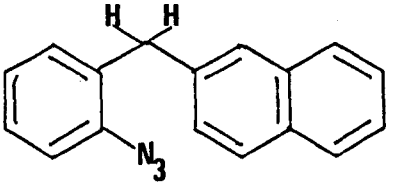
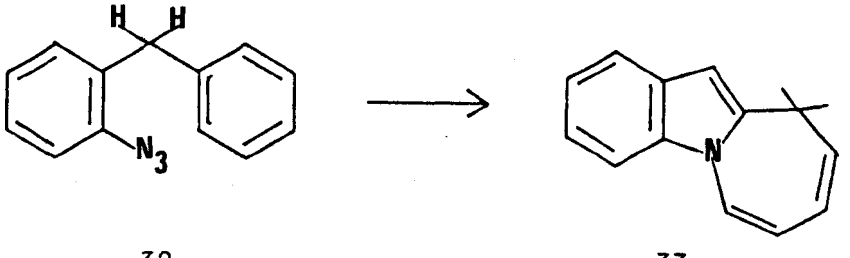


31

Ref. 40

The decomposition of 2-azidodiphenylmethane 32 does not result in acridan formation, but rather in the formation of the indoloazepine 33 as the sole product[41,42] (Scheme 12).

SCHEME 12

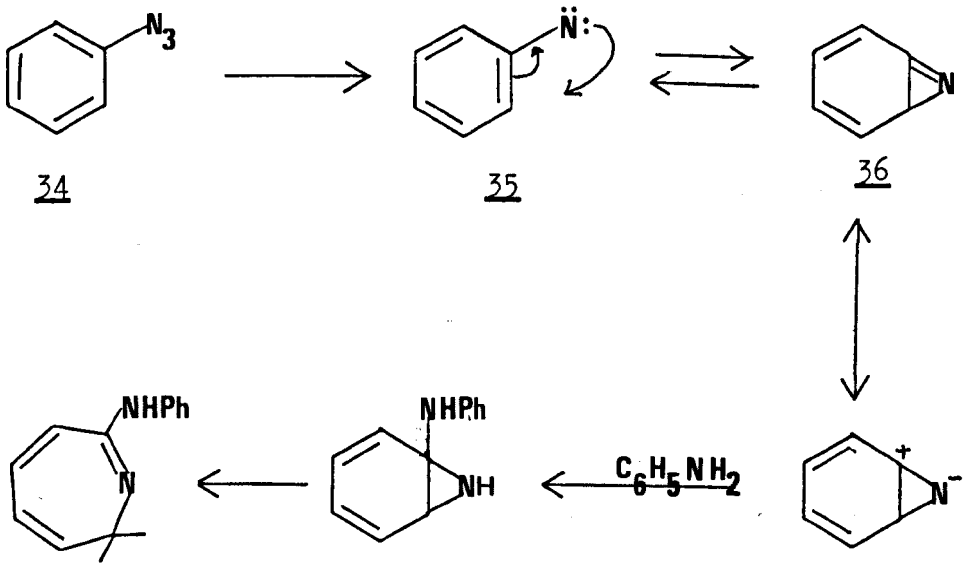


32 33

This is a further example of the preference for five-membered ring formation. Azepinoindole derivatives were also among the products of the decompositions of the azides 28 → 30 above. The formation of these products is discussed extensively in other parts of this thesis.

When an aryl azide is decomposed both thermally and photolytically in an amine solution, the main product is an azepine.[43,44,45] Thus in the decomposition of phenyl azide 34 in aniline the main product is 2-anilino-3H-azepine 37 (Scheme 13).

SCHEME 13



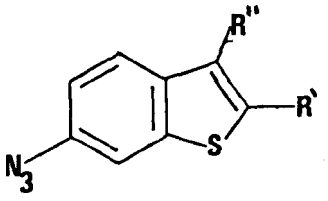
34 35 36 37

Sundberg and others[46] have postulated that the singlet nitrene 35 is in equilibrium with the azirine 36. Attack on the azirine 36 by the nucleophilic amine gives the 1H-azepine which tautomerises to the observed 3H-azepine 37. These two intermediates, the singlet nitrene and the azirine, may well be the intermediates in Sundberg's study[28] (page 6 above) on the mechanism of carbazole formation.

Cadogan and co-workers[47] have compared the ratios of isomeric 3H-azepines formed by deoxygenation of substituted nitrobenzenes with

the corresponding ratios of azepines derived from the decomposition of substituted azidobenzenes. Within experimental error these ratios are identical and it is reasonable to conclude that nitro-arene deoxygenation and azide photolysis have a common intermediate.

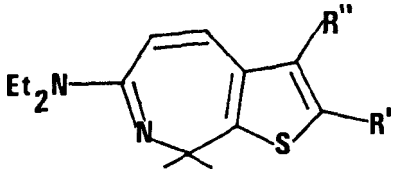
Iddon and co-workers[48] have reported on the photolysis in diethylamine of 6-azidobenzo[b]thiophens 38 and 39.



38 R' = CO_2Me, R'' = H

39 R' = R'' = Br

Low to moderate yields of the thienoazepines 40 and 41 were obtained.



40 R' = CO_2Me, R'' = H

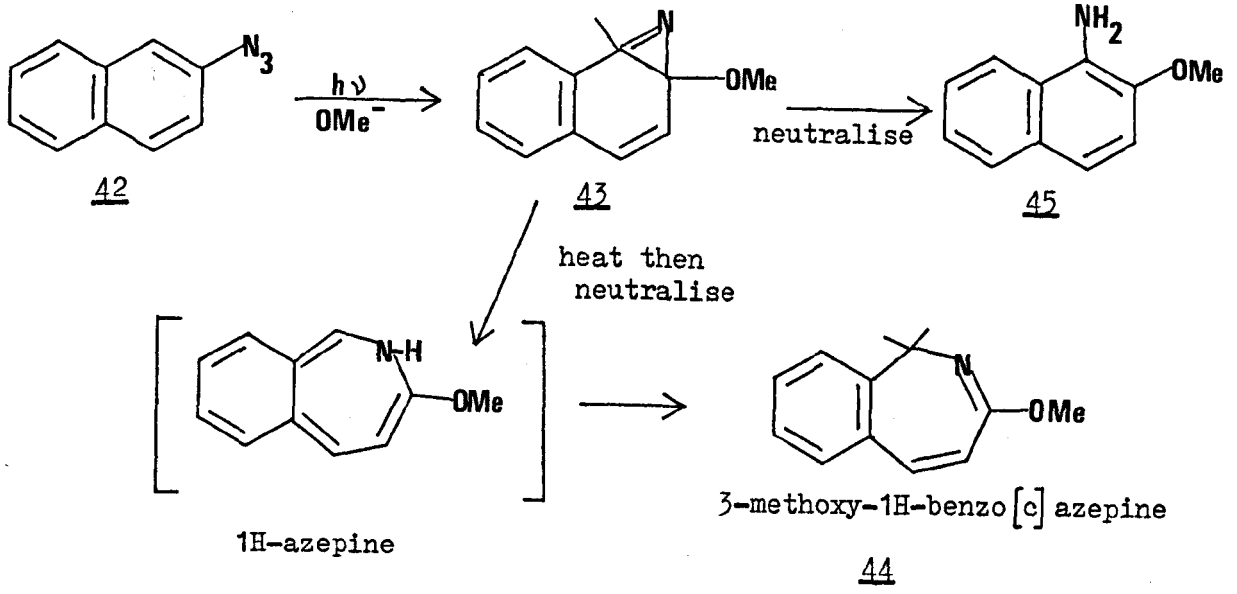
41 R' = R'' = Br

These are the first examples of photolytically initiated ring expansions of condensed bicyclic aromatic azides to azepines, and 40 and 41 are the first examples of 8H-thieno[2,3-c]-azepines; furthermore they are members of the comparatively rare "2H-azepine" series.

A further example of ring expansion in polycyclic systems has been reported by Rigaudy and co-workers.[49] The previous work on azidonaphthalene decompositions in diethylamine[50] indicated that the intermediate azirine was formed in the case of β-naphthyl azide, but only amine was isolated. The present work[49] has shown that photolysis of β-naphthyl azide (and β-azidoanthracene) 42 in the presence of concentrated potassium methoxide in methanol solution leads to a stabilised

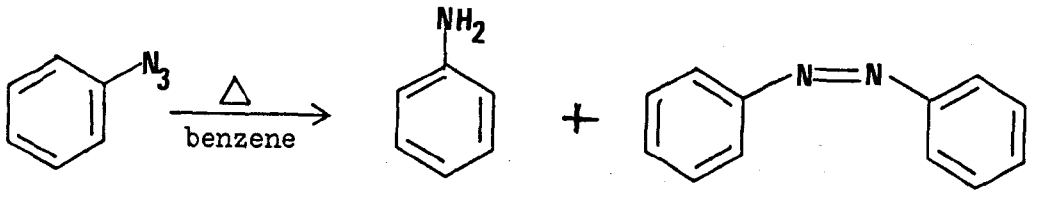
aziridine 43. If the solution is refluxed and then neutralised the aziridine thermally rearranges to give the azepine 44 in excellent yield. If, however, the solution is neutralised immediately after irradiations, the sole product is the normal 1,2-disubstituted bicycle 45. Thus the mode of reaction can be controlled (Scheme 14).

SCHEME 14



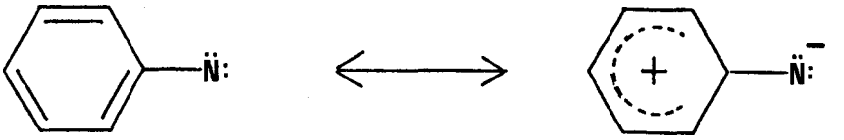
In contrast to the ready intramolecular aromatic substitutions by aryl nitrenes, the corresponding intermolecular reactions are relatively unknown. Thus the decomposition of phenyl azide in benzene[51] does not lead to the formation of diphenylamine; only azobenzene and aniline were formed (Scheme 15). The azobenzene is a result of phenylnitrene attack on unreacted azide.

SCHEME 15



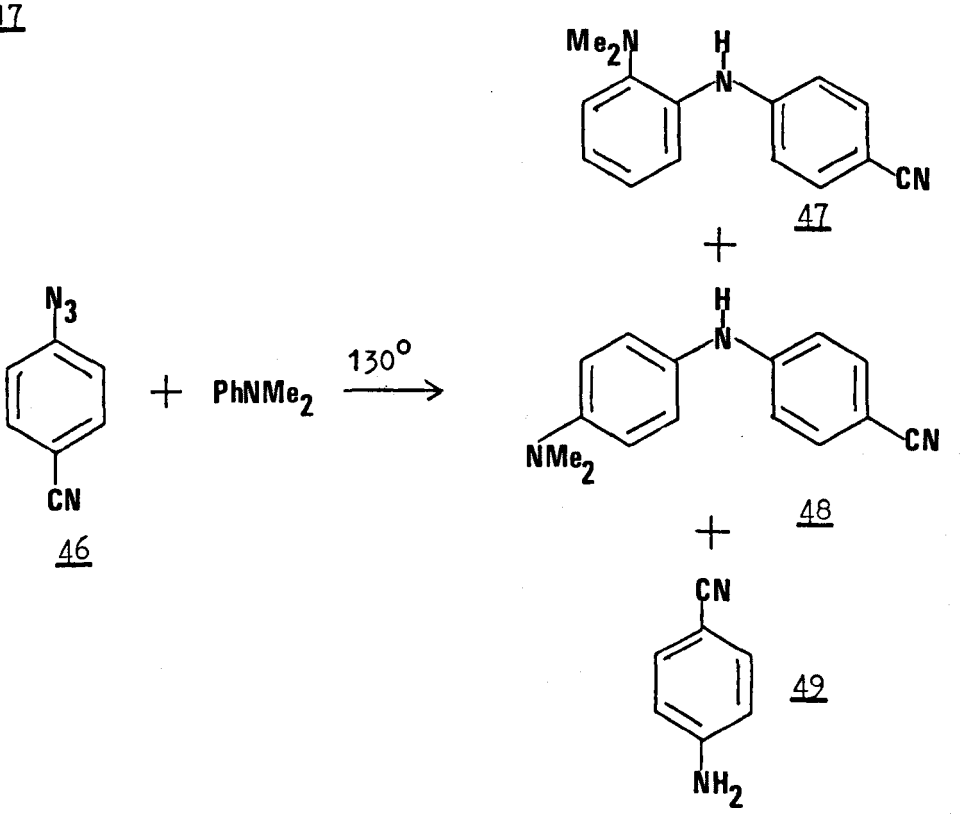
The failure of phenylnitrene to undergo intermolecular reactions has been explained[52] by extensive delocalisation of the electron deficiency resulting in a reduction of the electrophilicity of the nitrogen (Scheme 16).

SCHEME 16



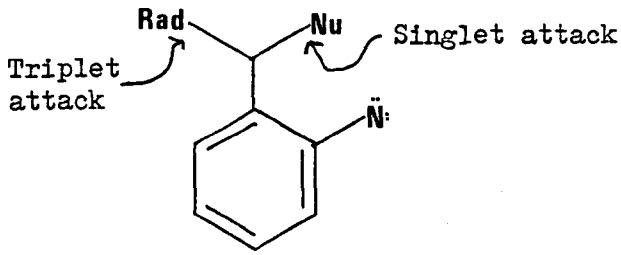
It has therefore been demonstrated[53] that aryl nitrenes will undergo intermolecular reactions provided that the nitrene is made sufficiently electrophilic by the introduction of an electron-withdrawing group in the aromatic nucleus and the aromatic substrate is sufficiently nucleophilic. Thus the decomposition of p-cyanophenyl azide 46 in N,N-dimethylaniline gives the diphenylamines 47 and 48 together with the hydrogen abstraction product 49 (Scheme 17).

SCHEME 17



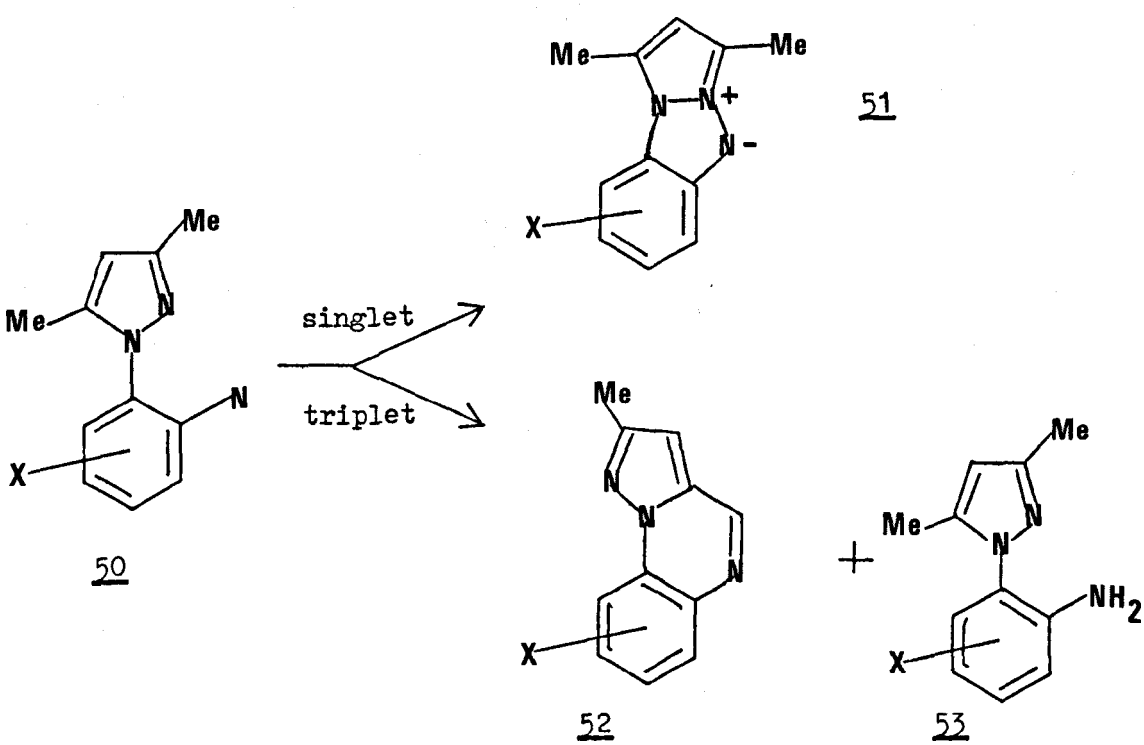
Meth-Cohn and co-workers[54] have recently reported some elegant research aimed at correlating the spin multiplicity of the reacting nitrene with the nature of the reaction site (Scheme 18).

SCHEME 18



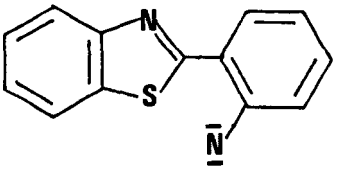
The nitrenes were generated from a series of phenylpyrazoles 50 either by thermal or photolytic decomposition of the corresponding azide or by deoxygenation (TEP) of the appropriate nitro-compound. The general outline of the decompositions is summarised in Scheme 19.

SCHEME 19

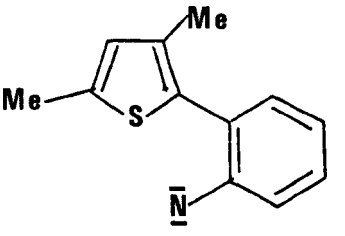


The series of experiments have demonstrated that the singlet product 51 may be optimised by the presence of electron-withdrawing groups para to the nitrene; conversely, the yields of triplet products 52 and 53 are enhanced by electron-releasing groups which decrease the electrophilicity of the nitrene.

Also reported[55] are the decompositions involving the nitrenes 54 and 55.



54



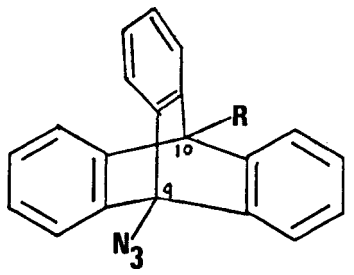
55

Here there is an opportunity for the nitrene to react with the sulphur atom, but no products resulting from attack on sulphur were isolated. Thus the strong preference of the nitrene for the nitrogen nucleophile is clearly demonstrated.

Meth-Cohn also describes[54,55] the effects of various "sensitizers" and "quenchers" in the photolytic decompositions along with demonstrations of the "heavy atom effect" in promoting the triplet nitrene species. These effects will be discussed at length in the next part of this thesis.

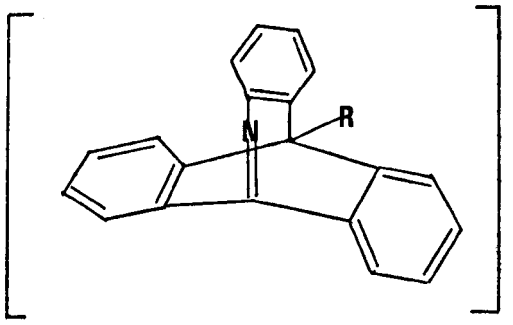
Quast and Eckert have studied[56] the pyrolysis in methanol of the 2-azidotriptycenes 56 (a),(b) (Scheme 20).

SCHEME 20



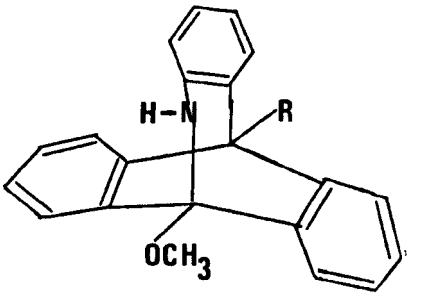
56 (a) R = H
(b) R = Me

hν
$-N_2$



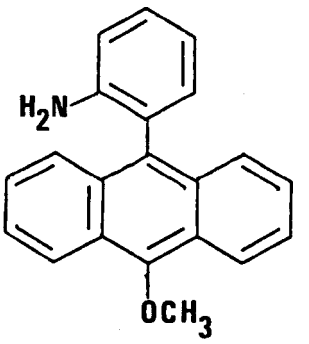
57 (a) R = H
(b) R = Me

CH_3OH

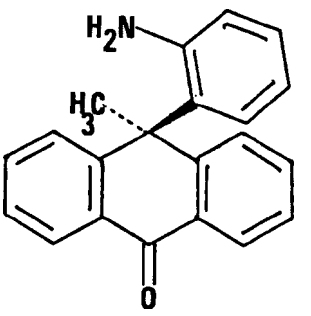


58 (a) R = H
(b) R = Me

H^+
R = H



H^+, H_2O
$R = CH_3$



60

Good yields of the azahomotriptycenes 58 were obtained, which can be regarded as adducts of the solvent to 57, the "bridgehead imine" 58(a) was rapidly converted into the anthracene derivative 59 by trace amounts of acid, but 58(b) required prolonged heating in methanolic acid to form the anthrone 60. Photolysis of 56(a) and (b) in cyclohexane gives compounds which are formally dimers of 57(a) and (b).

D I S C U S S I O N

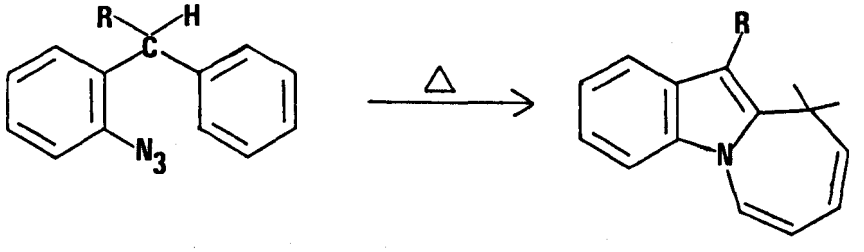
PART I

PART I

DISCUSSION

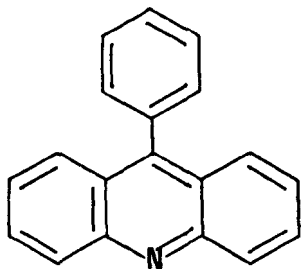
An extensive investigation of the synthesis and decomposition of 2-azidodiphenylmethane and substituted 2-azidotriphenylmethanes has been conducted at this University by Gurnos Jones and co-workers.[37,38,58]

The thermal decomposition of 2-azidodiphenylmethane 32 in 1,2,4-trichlorobenzene yielded the 10H-azepinoindole 33 as the sole isolated product.[58]

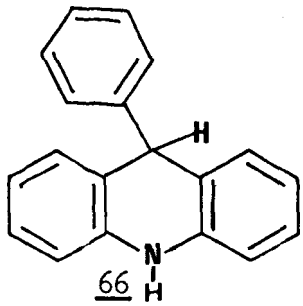


32	R = H	33	R = H
61	R = CH_3	62	R = CH_3
30	R = C_6H_5	64	R = C_6H_5

Cliff and Jones[58] have shown that replacement of one of the methane protons by a methyl group, 61, did not affect the course of the reaction and the product was the 11-methylazepinoindole 62. Carde and Jones[39] have examined the decomposition of 2-azidotriphenylmethane 30 and isolated the expected 11-phenyl-10H-azepinoindole 64; also isolated were 9-phenylacridine 65 and 9,10-dihydro-9-phenylacridine 66.

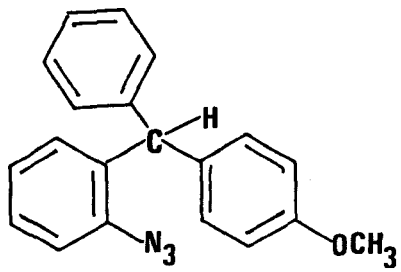


65

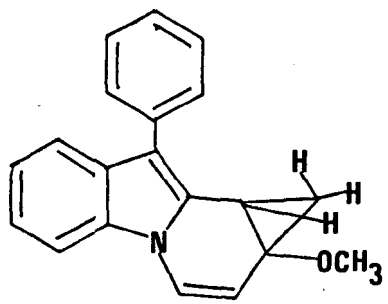


66

This research was extended to the substituted 2-azidotriphenylmethanes,[39] for example 67, and the decomposition products contained azepines and acridines in addition to some products of type 68.



67

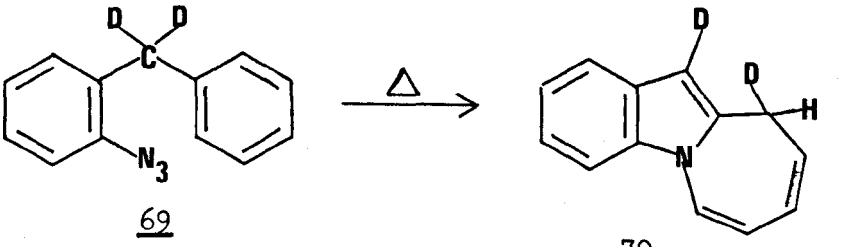


68

The formation of these bicyclic indoloazepines 68 is discussed in Part II of this thesis.

The results of the experiments described above indicated that there was either a different or an additional mechanism operating in the case of the 2-azidotriphenylmethanes. The decomposition of these compounds resulted in acridine as well as azepine formation; the 2-azidodiphenylmethanes produced only azepine. Another feature which must be accounted for is Carde's[39] discovery of an apparently regiospecific hydrogen atom transfer in the formation of azepines. This was demonstrated by the decomposition of the deuterated 2-azidodiphenylmethane 69, which was found to yield the azepine 70 (plus a trace of

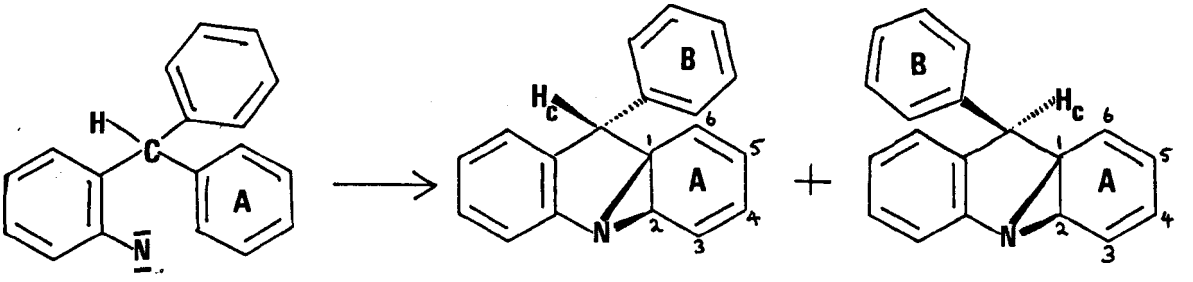
acridine).



69 70

The mechanism proposed by Carde[39] considers the stereochemistry of the reactive intermediate (Scheme 21).

SCHEME 21



71 72 73

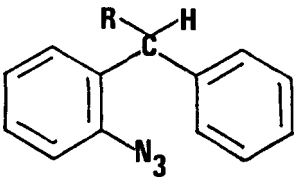
The nitrene 71, formed from the azide, inserts into the π-electron system of the adjacent benzene ring A, resulting in the formation of two stereoisomers 72 and 73 in equal proportions.

Isomer 72 has H_c in a plane parallel to that of ring A; in isomer 73 H_c is in a plane perpendicular to the plane of ring A. In a similar manner, the plane of ring B is isomer 72 is perpendicular to that of ring A, and in isomer 73 it is parallel to the plane of ring A.

As was shown by the deuteration experiment, the formation of azepine apparently involves regiospecific transfer of H_c to C-6. In

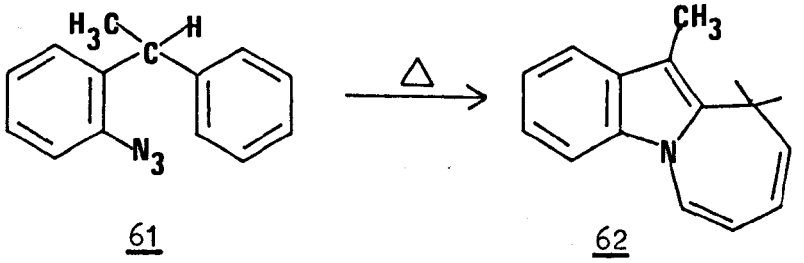
isomer 73, proton H_c is in the plane of the p-orbital of C-6 and this transfer is therefore facilitated. Thus rupture of the C-1 - C-2 bond results in electron-deficiency at C-1; this is relieved by flow of electrons from the C-H_c bond accompanied by the transfer of H_c to C-6. In the case of isomer 72, it is the benzene ring B that is in the plane of the p-orbital; therefore hydrogen atom transfer cannot occur and ring opening to the acridan products is observed.

According to this mechanism, the decomposition of a tri-substituted methane of the type



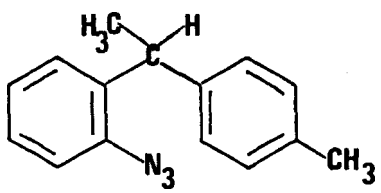
should result in equal yields of acridan and azepine type products. There are, however, two pieces of evidence which cast serious doubt on this theory. Firstly, Cliff and Jones[58] have decomposed the 2-azidodiphenylethane 61 (Scheme 22).

SCHEME 22



61 62

The only product recovered from this reaction was the azepine 62. It has been argued that the acridine and acridan products may have been overlooked as the primary interest at the time of the experiment was the confirmation of the structure of the azepine 62. Secondly, the related compound 28 was decomposed in a similar manner.[36]

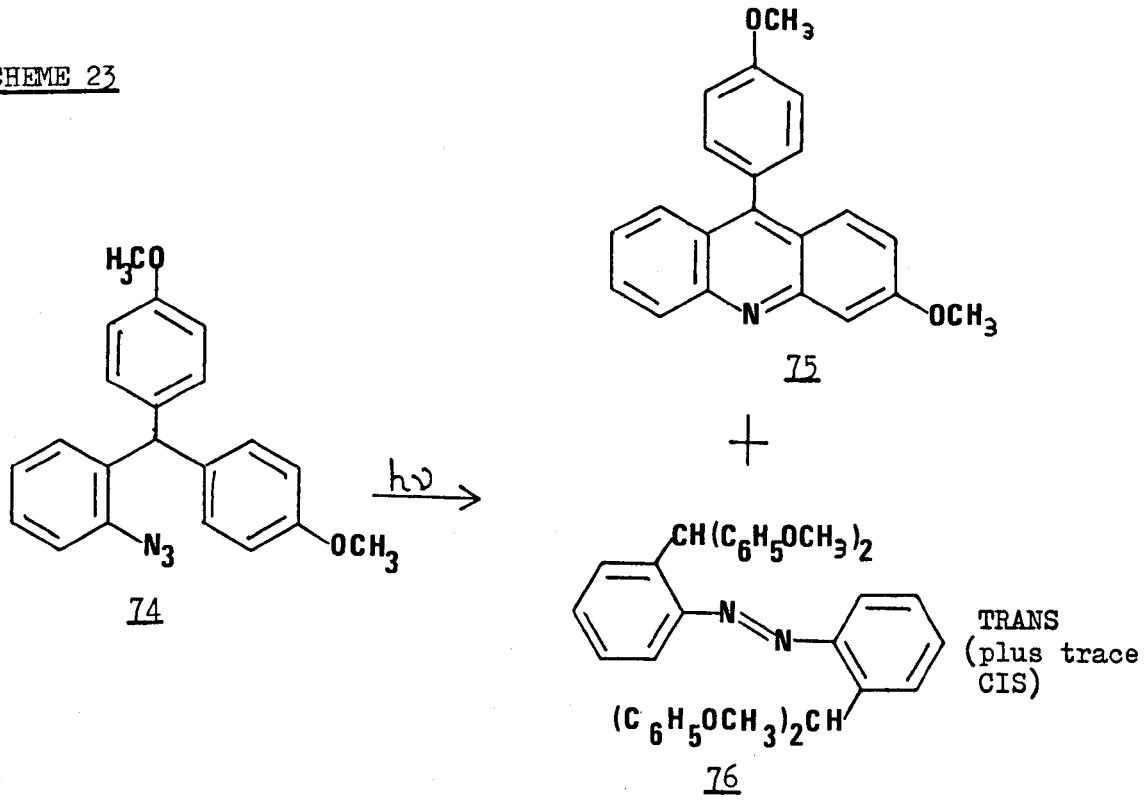


28

Traces of acridine were detected in the product mixture but the main isolable product was, as expected, the azepine. Therefore the stereochemically-based explanation for the different products must be rejected.

The current hypothesis put forward to account for the two types of products considers the two different electronic states in which a nitrene is known to exist under various conditions, namely, singlet and triplet. In its simplest formulation, the hypothesis is that the singlet state of the nitrene gives rise to the azepine type product, whereas the triplet species results in the acridan type products. Scheme 23 outlines the photolytic decomposition in benzene of 2-azido-4',4"-dimethoxytriphenylmethane 74.

SCHEME 23



74 75 76

The only isolable products were the acridine 75 and the azo-compound 76. No azepine products were found to be present. It is reasonable to suggest that the nitrene was in the triplet state, since photolytic conditions are known to promote radical formation.

Another photolysis was performed using the unsubstituted 2-azidotriphenylmethane 30 and, as before, acridine and azo-compound were isolated with no azepine found to be present. In an attempt to extend this work, two further photolytic decompositions of the unsubstituted 2-azidotriphenylmethane were undertaken.

A mole equivalent of the triplet sensitizer acetophenone[60,61] was added to the benzene solution of the azide prior to photolysis in an attempt to boost the yield of acridine, the suspected triplet product. However, no significant difference from the unsensitized run was noted as can be seen from Table 1. The second experiment was aimed at an opposite effect, and the triplet quencher penta-1,3-diene[62] was added as a mole equivalent to the photolysis solution.

TABLE I

Photolyses of 2-azidotriphenylmethane in benzene

	Acridine	Azo-compound (CIS + TRANS)
100% benzene	5 %	59 %
+ acetophenone	3	31
+ penta-1,3-diene	5	8

As can be seen from Table I, the presence of the pentadiene has resulted in a significantly reduced yield of the azo-compound. This is in accordance with the suspected triplet origin of this product. The quantities of the acridine which were isolated in all three cases were quite low - a few hundred milligrams - and any differences between the yields shown in Table I must be considered to be within the limits of experimental error.

Subsequent to these experiments, Meth-Cohn[54,55] has reported the use of acetophenone as a triplet sensitizer in the photolyses of azidophenylpyrazoles. Substantial changes in the product ratio were observed which substantiated the suspected origin of the various products. Meth-Cohn's procedure involved photolysing the azide in acetophenone solution and not merely in the presence of a mole equivalent of the sensitizer. In view of this, it is not altogether surprising that we have observed little, if any, change in product mixtures in the photolyses described above.

It is now generally accepted that a nitrene is generated thermally as the singlet species which can undergo intersystem crossing and thus be converted into the triplet species, which is the preferred ground state of arylnitrenes.[17,63] Under the conditions of

thermolysis, therefore, there exist both singlet and triplet nitrenes which, according to the hypothesis, give rise to the azepine and acridine products respectively.

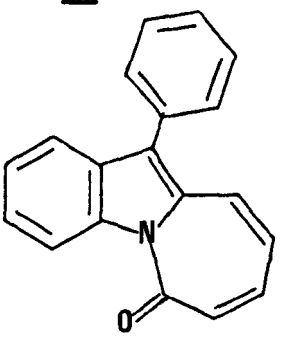
In an attempt to influence the product ratio, 2-azidotriphenylmethane 30 was thermolysed in 1,2,4-trichlorobenzene containing a mole equivalent of N,N-dimethyl-p-nitrosoaniline which is a known triplet quencher.[50,64,65,66] Table II shows the results of this decomposition along with those for the unaided decomposition performed by Carde.[39]

TABLE II

Thermolyses of 2-azidotriphenylmethane 30

Product	Unaided	N,N-dimethyl-p-nitrosoaniline
Acridan -	19 %	9 %
Acridine -	14	17
Azepine -	31	1
* Ketone -		0.5

* provisionally identified from its n.m.r. spectrum as the azepinoindol-6-one 77



77

On first inspection, the results shown in Table II appear to support the opposite effect to the one that was anticipated; the

azepine (singlet product) has decreased in yield, and not the acridines (triplet product). However, the fact that the identified products represent only 28 per cent of the total product in the "quenched" decomposition as opposed to 73 per cent in the "normal" case, and the appearance of the azepinoindol-6-one 77 suggest that additional reactions are occurring when p-nitrosodimethylaniline is present.

Two experiments were performed in order to assess the involvement of the p-nitrosodimethylaniline. Firstly, a sample of azepine was heated in trichlorobenzene at the normal reaction temperature ($\approx 190^{\circ}$) in the presence of a mole equivalent of the quencher. In this experiment it was hoped to establish whether the azepine, once formed, underwent a further reaction with quenching reagent, thus resulting in the much reduced yield of azepine and the large number of products observed. The large number of (unidentified) products obtained from this experiment confirm that the azepine does react with the p-nitrosodimethylaniline, and this reaction must at least partially explain the poor yield of azepine 64.

The second experiment consisted of heating p-nitrosodimethylaniline in trichlorobenzene at the reaction temperature ($\approx 190^{\circ}$) in order to establish if any self-condensation reactions occur at that temperature. This was found to be the case as a very large number of (unidentified) products was visualised by thin and preparative layer chromatography.

In view of the findings from these two test reactions, the results in Table II for the thermolysis in the presence of p-nitrosodimethylaniline cannot be regarded as indicative of any real trend. This approach, of using a triplet quencher, was abandoned in favour of an alternative method.

The ability of molecules which contain a large atom, e.g. bromobenzene, to deactivate a singlet state to a triplet state by absorption of the extra energy as a result of a collision with the species has been well documented.[50,67,68,69,70] This so-called "heavy atom" effect presented a promising method to investigate the nature of the products originating from the triplet nitrene.

Once again, thesystem chosen for investigation was the unsubstituted 2-azidotriphenylmethane 30; one sample of the azide was thermally decomposed in 1,2,4-trichlorobenzene at 156°, and another equal sample in refluxing bromobenzene (b.p. 154-158°) for equal periods of time. After removal of the solvents the products were examined by g.l.c. and found to have identical traces. Each trace contained ten peaks, and in each case peak number 8 was predominant (Figure 1).

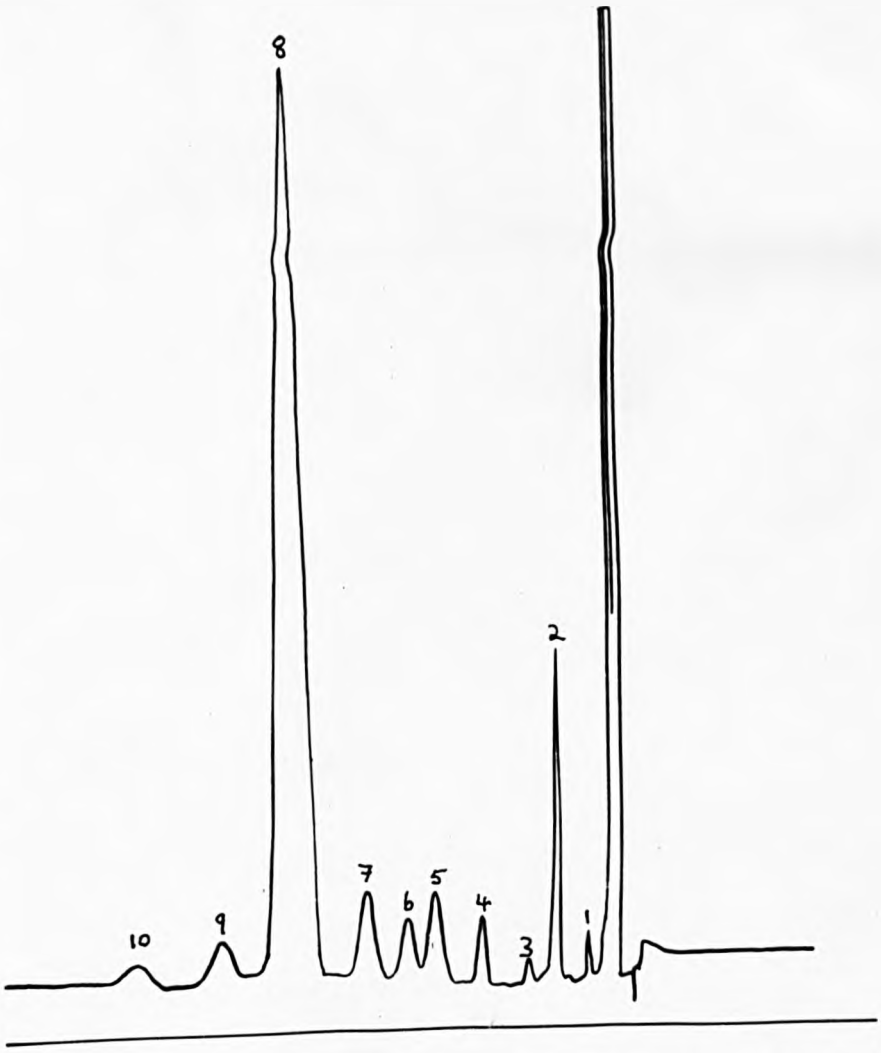


Figure 1 Decomposition of 2-azidotriphenylmethane 30 at 156°

Test performed on pure samples of azepine 64, acridine 65, and acridan 66 confirmed that all three gave rise to g.l.c. peaks with identical retention times, and it was not found possible to achieve adequate separation using g.l.c. However, it was found possible to separate the azepine product from the acridine/acridan products by

using high pressure liquid chromatography (h.p.l.c.). The acridine 65 and acridan 66 had the same retention times on the h.p.l.c. system used, but for the purposes of the main experiment this does not matter.

The results of the two decompositions are shown in Table III.

TABLE III

Thermolyses of 2-azidotriphenylmethane at 156°

	Ratio Acridine + Acridan : Azepine
trichlorobenzene	17 : 10
bromobenzene	95% acridine

There was a trace of azepine in the products from the bromobenzene run, but this could not be estimated with any precision. The overwhelming preference for acridine formation in bromobenzene solution is in accord with the hypothesis.

Although these results appear to substantially prove the singlet/triplet origin of the two types of product, there remained an unsatisfactory aspect of the experiment. The "normal" decomposition temperature in trichlorobenzene was approximately 190°, and the ratio of azepine to acridine/acridan was 1:1 (Table II, page 28). The decompositions described above were performed at the temperature of refluxing bromobenzene (154-158°) and in the case with trichlorobenzene as solvent at 156°, the product ratio is significantly different at almost 1:2. In addition, eight minor products were formed that had not been detected in the "normal" case.

A series of thermolyses of 2-azidotriphenylmethane 30 in different solvents were performed at a temperature of 185-190°C. The decompositions were performed in pairs - heavy atom solvent and hydrocarbon solvent. Table IV shows the solvents used and the results obtained.

TABLE IV

Thermolyses of 2-azidotriphenylmethane at 185-190° in various solvents

	Solvent	Azepine 64	Acridine 65	Azepine:Acridine	Weight of azide
(a)	p-dibromo-benzene	2.5 g	0.1 g	25 : 1	8.5 g
	naphthalene	0.28	2.0	1 : 7	8.5
(b)	p-dibromo-benzene	0.82	1.46	10 : 18	6.0
	diphenyl	0.75	1.5	1 : 2	6.0
(c)	p-dibromo-benzene	1.3	1.1	10 : 9	6.0

p-Dibromobenzene was chosen as a solvent both for its high boiling point, thus enabling the normal decomposition temperature to be obtained, and because it was thought that a solvent containing two bromine atoms would exhibit a strong heavy atom effect. As the results in Table IV show, this is not what was found; the results are variable despite similar reaction times and temperatures. Furthermore, the value obtained in run (a) for the azepine:acridine ratio (25:1)

must be considered suspect as it is so very different from the value obtained in either (b) or (c). A possible explanation for the large proportion of singlet product (azepine) in the heavy atom solvent, is that, at this temperature, the nitrene is formed as a highly excited singlet, most of which reacts in this singlet state to form the product. Only a relatively small proportion of the unreacted singlet nitrene survives for a sufficiently long time to be deactivated to the triplet nitrene.

The azepine:acridine ratio with trichlorobenzene as solvent at 190° is 1:1; with the exception of run (a) in Table IV, the ratios obtained for (b) and (c) in p-dibromobenzene are not vastly different. The fact that the result for diphenyl as solvent ((b) in Table IV) is also of a comparable value, would tend to lend support to the argument that at such an elevated temperature, effects other than the heavy atom effect are more important in determining the spin-multiplicity of the nitrene and the subsequent products.

Naphthalene was substituted for trichlorobenzene in (a) to preclude the possibility of the latter itself exercising a heavy atom effect. As can be seen from Table IV, the azepine:acridine ratio was found to be 1:7, indicating a clear preference for the triplet product. Also recovered from this decomposition was 0.45 g of the azo-compound. As this is almost certainly a triplet derived product, the singlet: triplet ratio is altered even further in favour of the triplet term. There are reports in the literature (for example, ref. 60) of naphthalene being used to influence product mixtures in nitrene reactions, and this has been explained in terms of sensitization by naphthalene. It would appear that naphthalene was taking part in the decomposition as there was a clear preference for the triplet product (acridine). Furthermore, the azo-compound has only been found previously in

photolytic decompositions.[39] For these reasons naphthalene was replaced by diphenyl, and the results as described above, were found to be more consistent with the other data.

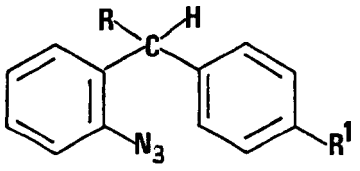
The conclusions that may be drawn from the results presented in this section must, of necessity, be tentative. The results of the decomposition at 156° in bromobenzene would appear to justify the singlet/triplet hypothesis; very little singlet product (azepine) was obtained in the heavy atom solvent. At higher temperatures other factors would appear to be operating. In the several reported cases[50,54,55,67,68] where a heavy atom effect has been successfully demonstrated, it is significant that the temperature of the reaction has been in the range 100-160°. A series of decompositions in different solvents over the range 100-200° would be required to clarify the effect of temperature on the product ratio. The temperature of 190° for the majority of the decompositions described in this thesis was chosen at the start of the research programme several years ago. At this temperature, the 2-azido di- and triphenylmethanes were found to decompose smoothly over a convenient period of time.

P A R T I I

PART II

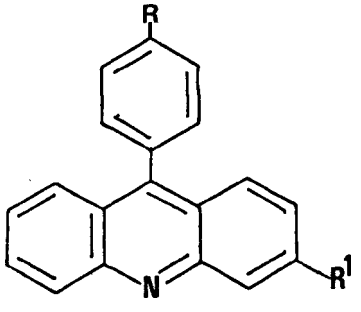
DISCUSSION

In an attempt to study the effect of electron availability on the aromatic nucleus into which the nitrene intermediate inserts, Carde[39] has decomposed 2-azido-4'-methoxytriphenylmethane 67 by thermolysis in trichlorobenzene at 185°C.



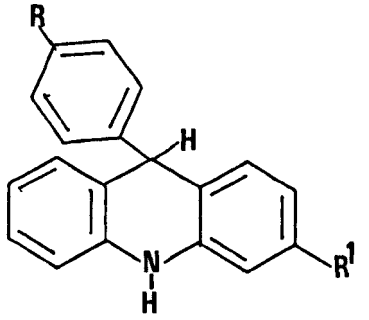
67 R = C_6H_5; R^1 = $-OCH_3$

74 R = p-anisyl; R^1 = $-OCH_3$



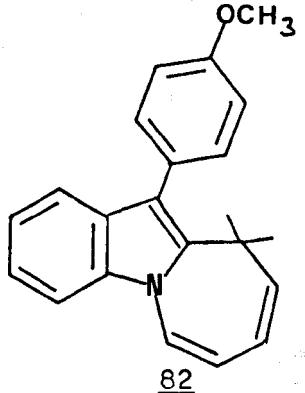
78 R = H; R^1 = $-OCH_3$

79 R = $-OCH_3$; R^1 = H

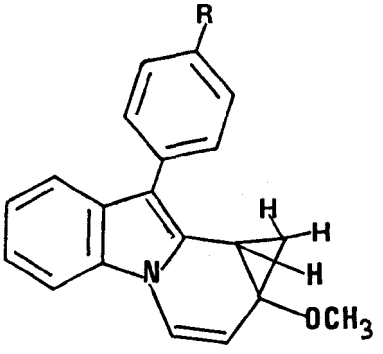


80 R = H; R^1 = $-OCH_3$

81 R = $-OCH_3$; R^1 = H



82



68 R = H

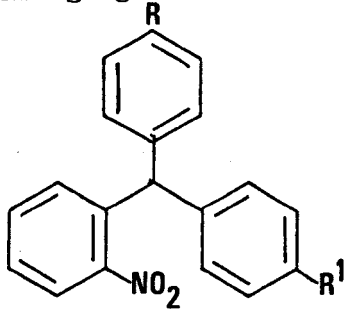
83 R = OCH_3

The products from this decomposition included the expected acridines 78 and 79, acridans 80 and 81, and the azepinoindole derivative 82. Also isolated was a moderate yield of 8,9-dihydro-8,9-methano-8-methoxy-10-phenylpyrido[1,2-a]indole 68.

The author has decomposed 2-azido-4',4"-dimethoxytriphenylmethane 74 in trichlorobenzene at 190°C and the products were found to include 8,9-dihydro-8,9-methano-8-methoxy-10-(4-methoxyphenyl)-pyrido[1,2-a]indole 83 as well as the acridine, acridan and azepinoindole products. Thus pyridoindole formation was found to extend to the disubstituted system. In this part of the thesis are described the isolation and characterisation of the decomposition products, and also included is a discussion of the possible mechanism for formation of the pyridoindole 83.

Preparation of the azide

Condensation reactions between phenol and o-nitrobenzaldehyde have been reported since 1906 when Zincke and Siebert[71] obtained a chlorine-containing substance as a product of the condensation in the presence of hydrochloric-acetic acid. A more thorough investigation by Driver and Mok[72] in 1955 resulted in a fair yield (50%) of 2-nitro-4',4"-dihydroxytriphenylmethane 84 with sulphuric-acetic acid as the condensing agent.



84 R = R^1 = OH

85 R = R^1 = -OCH$_3$

This was the method followed and the red oil obtained could be purified by column chromatography. Several experiments showed, however, that the yield of the dimethoxy derivative 85 was not reduced if the crude dihydroxy compound was used. Methylation was achieved in good yield using methyl iodide and potassium carbonate in refluxing acetone. Purification of the dimethoxy compound 85 was by column chromatography and the resulting oil was easily reduced catalytically using either hydrogen gas or hydrazine hydrate, with 10% palladium on charcoal as catalyst. The resulting amine was converted to the azide by diazotisation in solution in a mixture of 4N sulphuric acid and dioxan, and subsequent reaction of the diazonium salt with sodium azide. The azide was obtained as white crystals after work-up and purification by column chromatography.

Decomposition of the azide 74

The azide was decomposed under nitrogen in 1,2,4-trichlorobenzene solution at 190°C approximately.

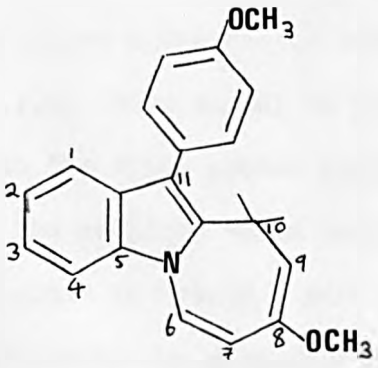
The assignment of structures to the decomposition products was based largely on the interpretation of their n.m.r. spectra and these are discussed throughout this section.

The decomposition of 2-azido-4',4"-dimethoxytriphenylmethane 74 gave a mixture which was shown, on examination by gas chromatography, to comprise five products, one of which was present in relatively small yield (Figure 2).

Figure 2 Decomposition of 2-azido-4',4"-dimethoxytriphenylmethane 74

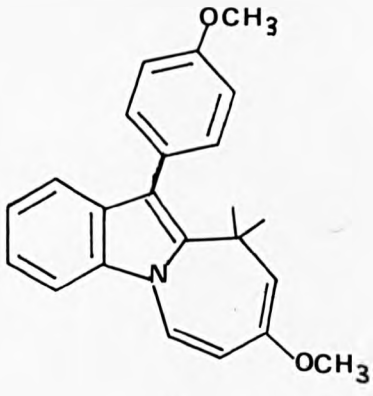
This mixture was separated by column chromatography in benzene when five fractions were obtained. Fractions containing mixtures were separated by preparative layer chromatography. Evaporation of the first fraction from the column gave a colourless oil which was

identified from its n.m.r. spectrum as 1,2,4-trichlorobenzene. The second fraction was evaporated to yield a yellow oil, 8-methoxy-11-(4-methoxyphenyl)-10H-azepino[1,2-a]indole 86.



86

The structure of the azepinoindole 86 was determined on the basis of its n.m.r. spectrum (Figure 3).



86

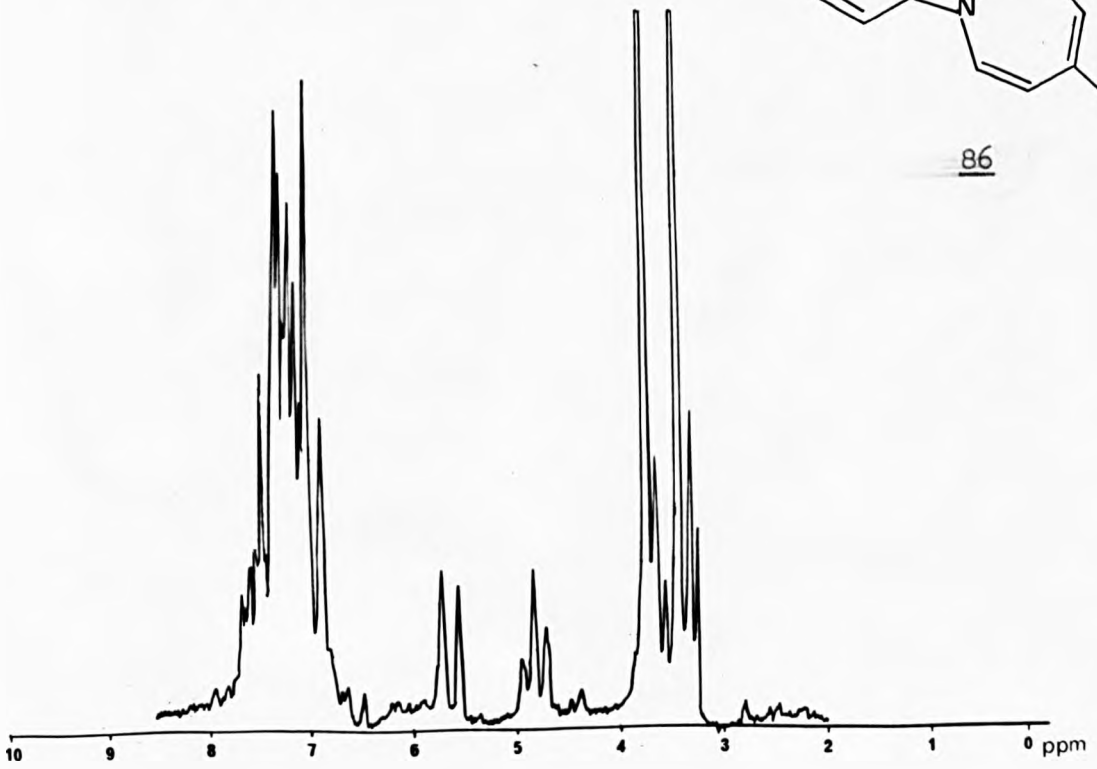
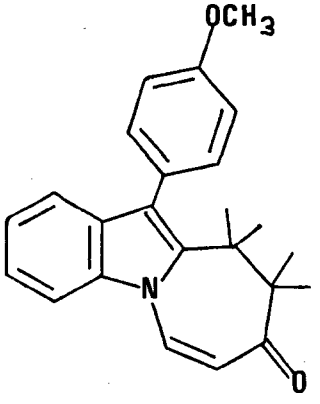


Figure 3

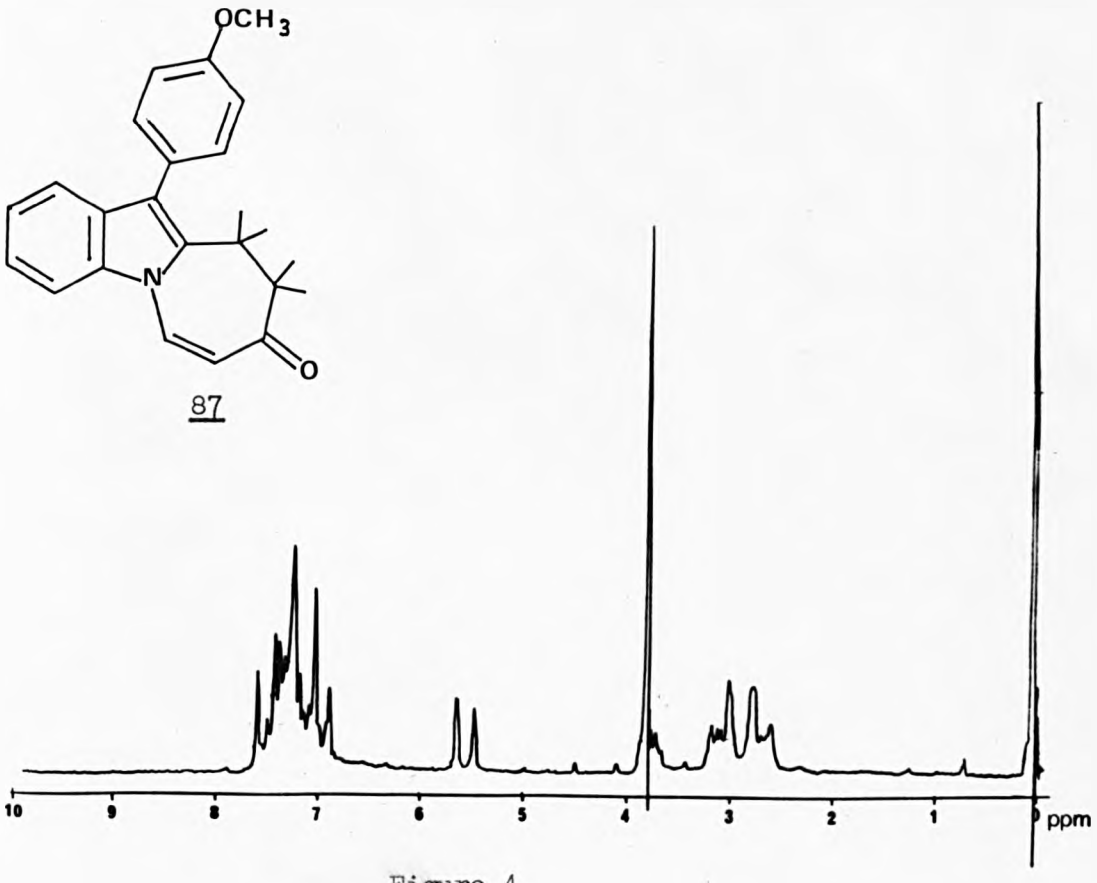
This spectrum has a one proton triplet (H-9) at δ 4.62 p.p.m., and a one proton doublet (H-7) at δ 5.45 p.p.m. By comparison of this spectrum (Figure 3) with that of the 11-phenyl analogue 39, one would expect to see a two proton doublet (H-10) at around δ 3 - 3.5 p.p.m. This signal is present but most of the doublet coincides with the three proton singlet of the phenyl methoxyl protons, and the coupling value cannot be accurately measured.

In order to obtain a pure sample for elemental analysis, the azepinoindole 86 was chromatographed on preparative plates in benzene. No starting material was recovered and the only identifiable product was 9,10-dihydro-11-(4-methoxyphenyl)azepino[1,2-a]indol-8-one 87.



87

The n.m.r. spectrum of the dihydroazepinoindolone 87 is shown in Figure 4.



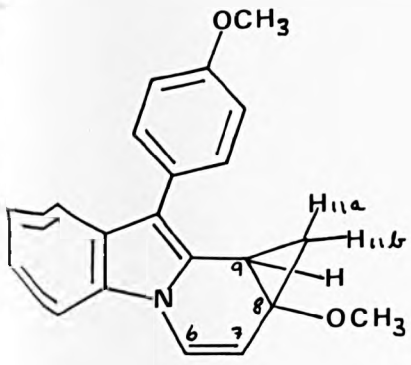
87

Figure 4

The overlapping multiplets centred at δ 2.9 p.p.m. are due to the four protons on C-9 and C-10. The methoxyl protons give a sharp singlet at δ 3.79 p.p.m. The proton on C-7 gives rise to a doublet at δ 5.55 p.p.m. with the coupling value $J_{6,7}$ = 10 Hz. The signal from the proton on C-6 is not discernible among the aromatic signals.

Comparison with the compound reported by Cliff and Jones[59] is possible; in this compound the methylene signals were centred at

δ 2.8 and δ 2.95 p.p.m., and the signal for the proton on C-7 at δ 5.45 p.p.m. ($J_{6,7}$ = 10 Hz). A further comparison is possible with the compound reported by Carde.[39] The corresponding methylene signals are at δ 2.82 and δ 3.22 p.p.m.; and the C-7 proton has its signal at δ 5.71 p.p.m. On evaporation of the solvent, the third fraction from the column was crystallised. Analysis showed a molecular formula $C_{21}H_{19}NO_2$ and the compound was identified as the methano-pyrido-indole 83, principally from its n.m.r. spectrum (Figure 5).



83

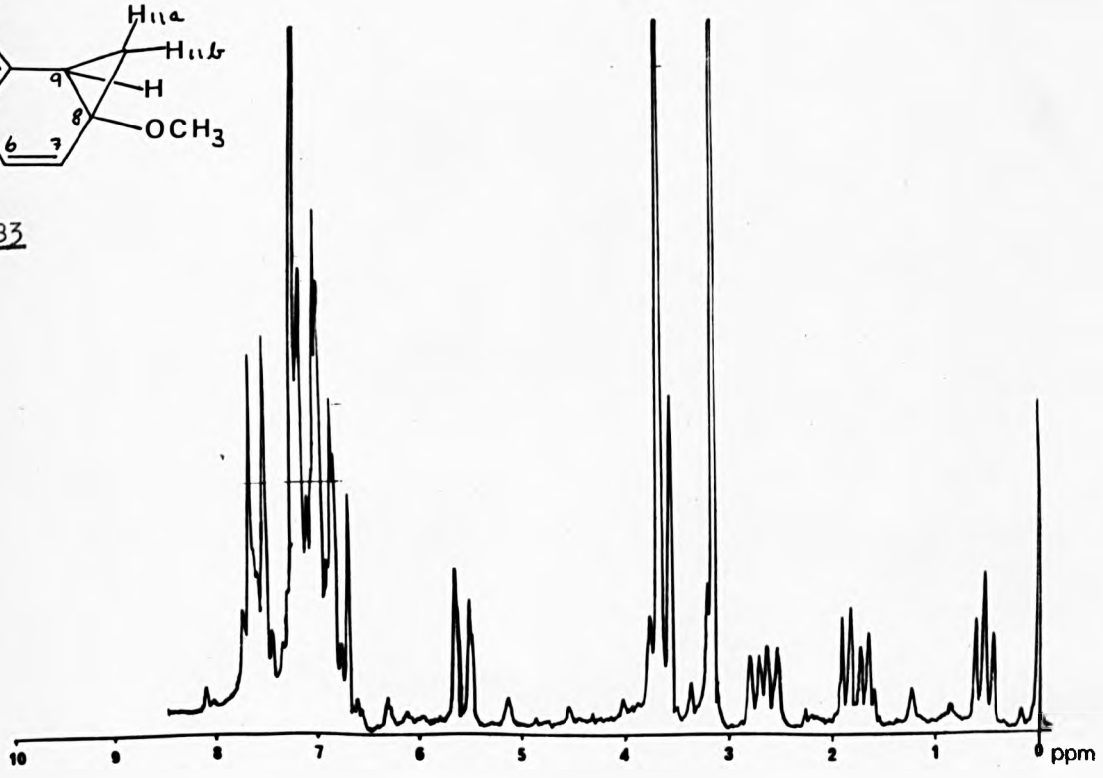
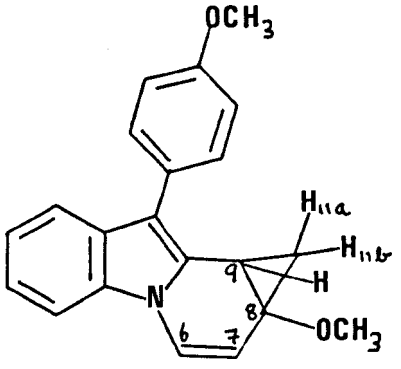


Figure 5



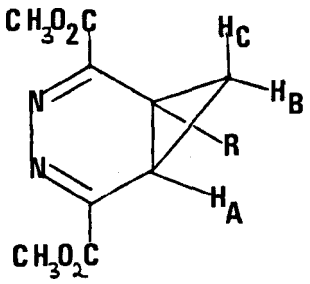
83

The triplet at δ 0.54 p.p.m. was shown, by expanding the spectrum scale, to be a doublet of doublets with coupling constants of 5 and 6 Hz. The high up-field shift of this proton (H-11a in Figure 5) 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 1.81 p.p.m. is due to the proton H-11b. Geminal coupling (5 Hz) with proton H-11a and cis coupling (10.5 Hz) with proton H-9 accounts for the observed splitting pattern.

The complex signal at δ 2.72 p.p.m. is due to the proton on C-9. The observed pattern is formed from the expected cis and trans coupling with proton H-11b and H-11a plus long range or "W" coupling (2 Hz) with proton H-7. The co-planarity of the five atoms which is necessary for this type of coupling to exist can be demonstrated by examination of a Dreiding model of this molecule.

The apparent reversal of the relative magnitudes of the geminal and cis coupling constants for H-11a, H-11b, and H-9 is supported by the values obtained for the diazanorcaradienes 88 and 89.[73] As the table shows the figures are in good agreement with those observed above.



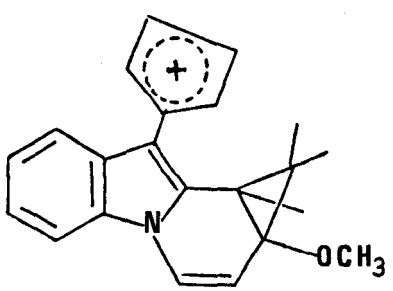
	Chemical Shift δ p.p.m.			Coupling Constant Hz		
	H_A	H_B	H_C	J_{AB}	J_{AC}	J_{BC}
88 R = H_A	3.05	2.28	-0.03	8.92	4.75	3.85
89 R = CH_3	2.70	2.05	0.08	9.51	5.18	4.19

The signal at δ 5.61 p.p.m., due to the olefinic proton H-7, has a coupling of 8 Hz to proton H-6 in addition to the 2 Hz long range coupling to H-9 discussed above.

The signal from the proton on C-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 (0.52 p.p.m.) of the signal due to the methoxyl protons.

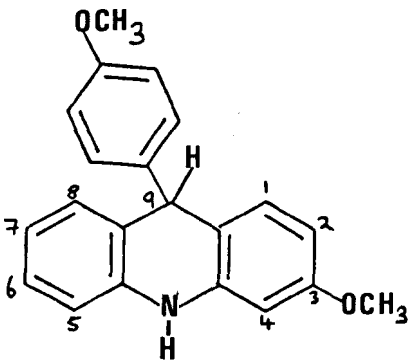
The mass spectrum of the methano-pyridoindole 83 has the molecular ion and base peak at m/e 317. It is known[74] that aromatic methyl ethers lose a methyl radical from the molecular ion, this accounts for the peak at m/e 302. Furthermore this ion is known to lose carbon monoxide to yield the cyclopentadienyl cation 90 at m/e 274.



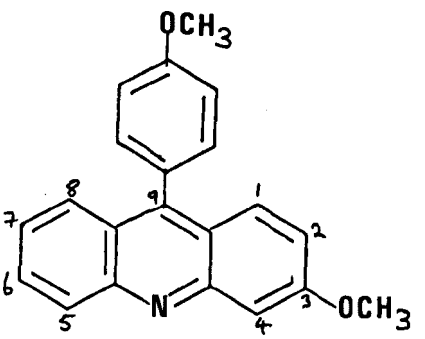
90

An alternative breakdown of such ethers features loss of formaldehyde in the first step. This would account for the peak at m/e 287. This ion now loses a hydrogen atom to give a phenyl cation; m/e 286. Thus it would seem that both breakdown modes are operating. It is possible that the 8-methoxy group is removed by the second mechanism from ion 90 above to leave the ion with m/e 243.

Evaporation of fractions four and five from the column yielded 9,10-dihydro-3-methoxy-9-(4-methoxyphenyl)acridine 91 and 3-methoxy-9-(4-methoxyphenyl)acridine 75 respectively.



91



75

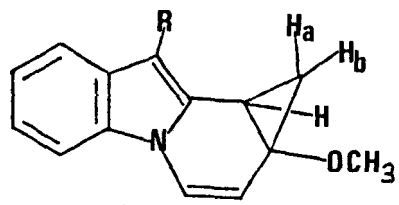
These structures were assigned on the basis of the n.m.r. spectra.

The n.m.r. spectrum of the dihydroacridine 91 had sharp singlets at δ 3.65 p.p.m. and δ 5.1 p.p.m. due to the methoxyl protons and to the single proton on C9 respectively. The amine proton gave rise to a broadened singlet at δ 6.2 p.p.m. which exchanged with deuterium oxide. The signals in the aromatic region (δ 6.4-7.3 p.p.m.) showed the splitting pattern of a para-substituted benzene derivative in the fine structure.

The n.m.r. spectrum of the acridine 75 contains two singlets at δ 3.95 and δ 4.05 p.p.m. due to the methoxyl protons on the phenyl

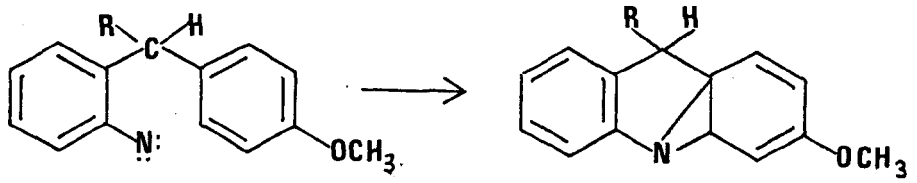
substituent and on C-3 respectively. The position of the methoxy substituent was confirmed by the use of a chemical shift reagent, Eu $(fod)_3$. This results in a down-field shift of the signals due to the protons H-4 and H-5 and shows them to be doublets with coupling constants of 2 Hz and 8 Hz respectively. The meta-coupling of 2 Hz associated with proton H-4 confirms the presence of the methoxyl substituent on C-3. This confirmation of the position of the methoxyl substituent is important in view of the reports by Cadogan and his co-workers[32,33,34] on phenothiazine formation where a spirodiene intermediate is invoked, giving rise to a 2-substituted product.

Mechanism for the formation of the methano-pyridoindole 83



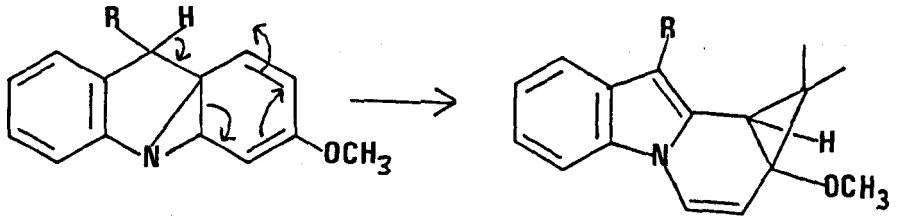
83 R = p-anisyl

The proposed mechanism for the formation of compound 83 features, in the first stage, the insertion of the aryl nitrene 92 into the π-system of the adjacent anisyl ring to give the aziridine intermediate 93.



92 R = p-anisyl 93

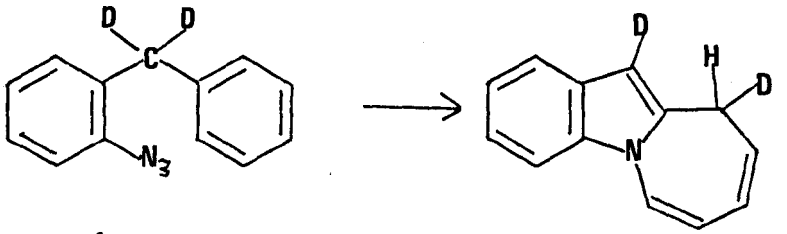
This intermediate 93 was proposed originally by Krbechek and Takimoto[41] and subsequently postulated by Cliff and Jones.[58] The required methano-pyridoindole structure 83 may be obtained from this as shown:



93 R = p-anisyl 83

This involves hydrogen transfer from C-9 in the intermediate 93 to C-11 in the product 83. A supra-facial [1,3] or [1,7] hydrogen shift is forbidden according to the principles of the conservation of orbital symmetry.[75]

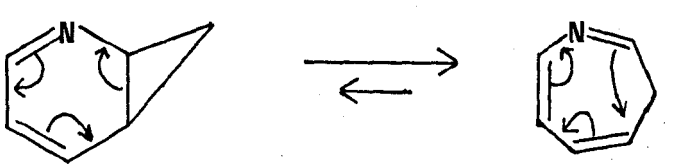
Carde[39] has decomposed the deuterated azide 69 and obtained the azepinoindole 70.



69 70

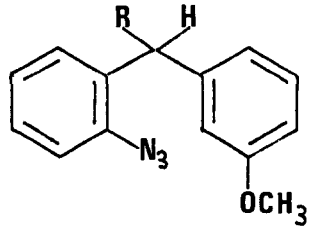
The n.m.r. spectrum of 70 integrated correctly for the structure shown, and as far as could be determined there were no reduced signals from the protons on C-6, 7, 8 or 9 which, if this were the case, would imply that some deuterium was present at these positions. This suggests strongly that a regiospecific [1,3] hydrogen atom transfer is occurring in these systems; if the transfer is not direct, it would be unusual to have several regiospecific shifts with 100% transference of deuterium around the ring.

It was known from the work of Jones and co-workers[39,58,59] that in the absence of both the phenyl and the methoxyl groups, the "normal" azepinoindole products were obtained. This suggests the possibility that the methano-pyridoindole 83 is an abnormally stabilised intermediate in the formation of the azepinoindole 86. In the following situation



the equilibrium would normally lie well to the right, and the bicyclic system would be stabilised by electron-withdrawing groups. This is contrary to the existing conditions in the methano-pyridoindole, where, of

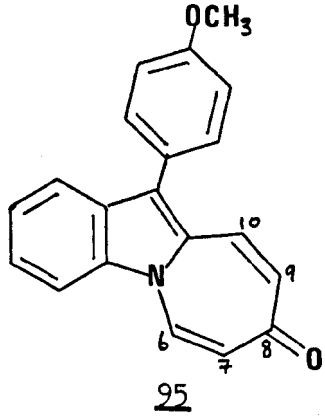
course, the methoxyl group is an electron-donating substituent. In an attempt to assess the role of the methoxyl group in stabilising the bicyclic system in 83 it would be interesting to decompose the azide 94.



94 R = p-anisyl

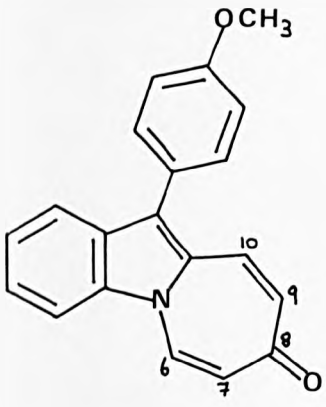
According to the proposed mechanism discussed above, the methoxyl substituent would be on C-7 of the methano-pyridoindole 83. If this product was obtained, other factors must be responsible for the stabilisation of compound 83.

In an attempt to resolve the question as to whether the methano-pyridoindole is an intermediate on the way to the azepino-indole, the compound was heated at 186°C in trichlorobenzene for 22 hours. The n.m.r. spectrum of the residue did not contain any signals associated with the starting material; these had been replaced with a complex pattern. Following a prolonged work-up using preparative layer chromatography 11-(4-methoxyphenyl)azepino[1,2-a]indol-8-one 95 was isolated. No azepinoindole 86 was found to be present in the mixture.



95

This structure was assigned on the basis of the n.m.r. spectrum (Figure 6).



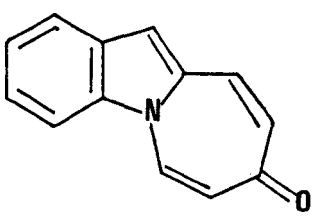
95

Figure 6

The singlet at δ 3.87 p.p.m. arises from the methoxyl protons. Centred at δ 6.5 p.p.m. are two doublets of doublets from the protons on C-7 and C-9. The 1,3 coupling $J_{7,9}$ is 3 Hz; $J_{9,10}$ = 12 Hz; and $J_{6,7}$ = 10 Hz.

As the proton on C-10 is part of an α,β -unsaturated ketone system, its signal is shifted down-field into the aromatic region; the proton on C-6 is likewise not discernible.

This spectrum may be compared with that reported by Cliff[76] for the unsubstituted azepinoindolone 96.



96

This spectrum shows the same splitting pattern at around δ 6.0 p.p.m. with the coupling constant for 1,3 coupling, $J_{7,9}$ = 3 Hz.

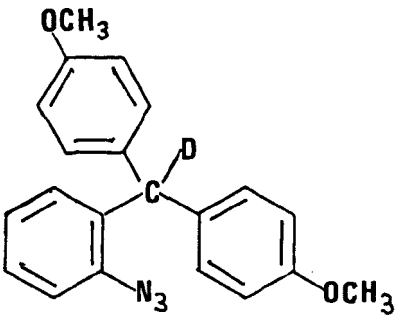
The other products from the decomposition of the pyridoindole 83 were examined by linked gas chromatography - mass spectrometry. Table V shows the values for the molecular ions that were obtained, plus some of the major peaks on breakdown.

TABLE V

	M^+	m/e				
Product I	351	333	316	302	287	280
II	359	333	319	303	287	271
III	351	335	307	291	277	261
IV	367	351	335	319	304	291
V	265	251	236	220	207	
VI	349	316	304	292	287	275
VII	350	320	304	291	278	263
VIII	279	265	250	234		

The molecular weight of the original pyridoindole 83 is 317, and therefore many of the molecular ions were found to be greater than this. None of these products has been positively identified.

An unsuccessful attempt was made to prepare the deuterated azide 97.

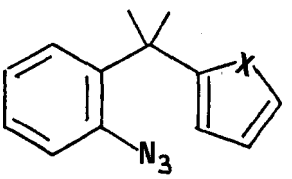


97

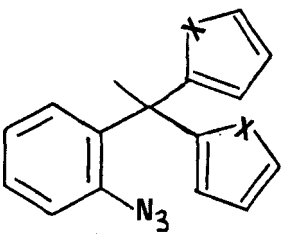
PART III

PART III

The work described in this part of the thesis represents an attempt to extend the application of intramolecular nitrene reactions to systems containing heterocyclic rings. In particular we wished to prepare and decompose the heterocyclic analogues 98 and 99 of 2-azidodi- and triphenylmethane.



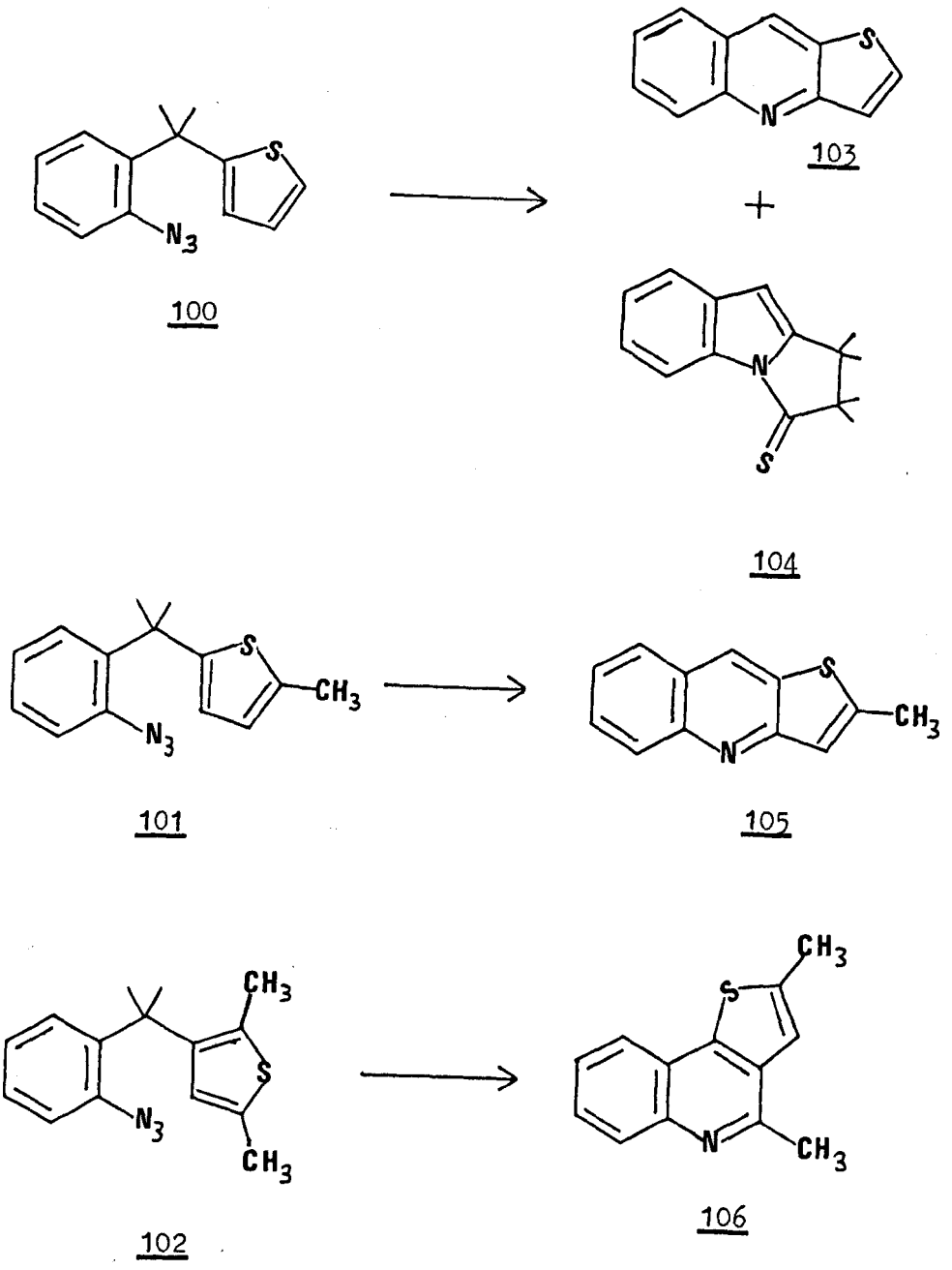
98 X = O, S



99

Jones and co-workers[57] have examined the decompositions of the three 2-azidobenzylthiophenes 100, 101, and 102. The main products of these decompositions are shown in Scheme 24.

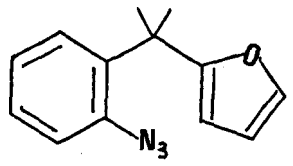
SCHEME 24



The thienoquinolines 103 and 105 are the result of six-membered ring formation and as such are reminiscent of acridine formation in the analogous di- or triphenylmethane systems discussed above. However, both compound 104 and compound 106 can only be formed by a ring-opening or rearrangement reaction and represent

departures from the normal pattern.

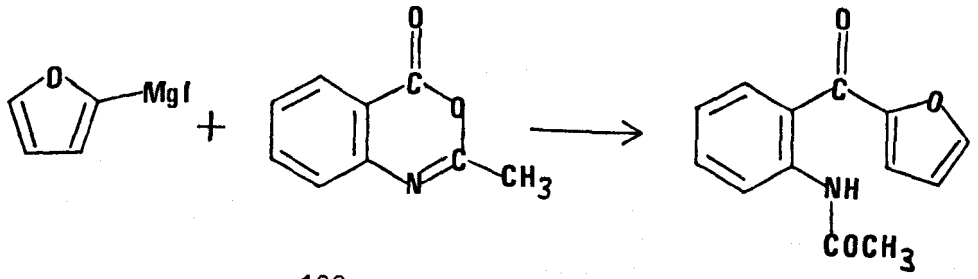
The first compound selected for synthesis was 2-(2-azidobenzyl)furan 107.



107

The first approach to this synthesis proceeded via the addition of 2-furylmagnesium iodide to acetanthranil 108 to give the ketone 109 as the precursor to 107 (Scheme 25).

SCHEME 25



108 109

This procedure is similar to that used for the preparation of the diphenylmethanes.[38] Acid hydrolysis of the ketone 109 should yield the amine and the ketone might be reduced by Wolff-Kisher procedures and by modified Clemmensen reactions.

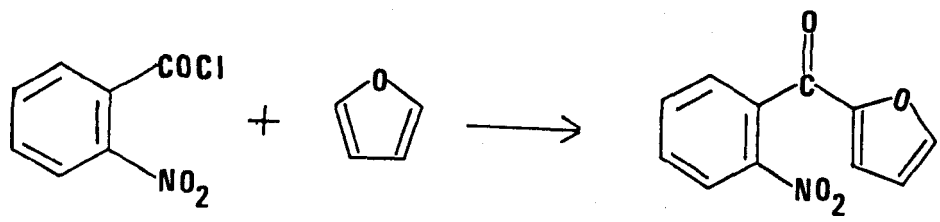
The 2-iodofuran was prepared from 2-chloromercurifuran and iodine after the method of Gilman and Wright.[77] The Grignard reaction

proceeded smoothly and basic hydrolysis followed by extraction and evaporation yielded a brown oil whose n.m.r. spectrum was compatible with the ketone structure 109. All attempts to purify this product failed and the oil was found to resinify on standing. Furthermore, contact with even dilute mineral acid resulted in tar formation and ammonium hydrolysis of the Grignard product was necessary to prevent polymerisation. Presumably the acid causes rupture of the furan ring.

It was decided to try and proceed with the synthesis without isolating the ketone 109 due to its unstable nature. The hydrolysis to form the amine was attempted by using a 10% sodium hydroxide solution under reflux. This reaction gave many products, none of which was identified.

Another proposed synthetic route was to prepare the nitro-ketone 110 by a Friedel-Crafts reaction between furan and a suitable aromatic substrate as shown in Scheme 26, for example.

SCHEME 26



110

Table VI lists the substrates, catalysts and products of several experiments.

TABLE VI

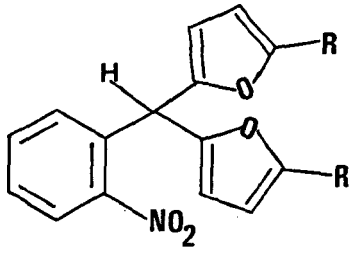
SUBSTRATES		CATALYST	PRODUCTS
Furan	o-nitrobenzoyl chloride	$TiCl_4$[78]	o-nitrobenzoic acid
"	" "	$SnCl_4$	" "
"	" "	I_2	starting material
2-Methyl-furan	o-nitrobenzoicanhydride	H_3PO_4	" "
Furan	"	$BF_3:Et_2O$	" "

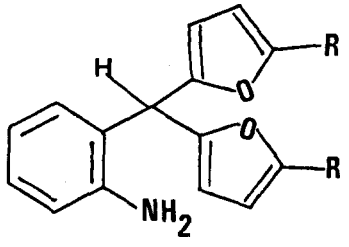
As can be seen from Table VI, none of the desired ketone 110 was isolated. On several runs milligram quantities of material were found where n.m.r. spectra indicated that they might be the products, but this was not confirmed. A feature common to all of these experiments was the formation of black tar. As a result the first stage in the work-ups was continuous extraction with methanol. Typically, many products were formed in very small yield; the aromatic substrate was usually the only material to be identified.

The third synthetic pathway to be investigated was the possible reaction between the 2-furyllithium reagent and either o-bromobenzaldehyde, or o-bromobenzylbromide, or o-nitrobenzylbromide. The reactions were also tried with the lithium reagent from 2-methylfuran. In all cases only starting material was recovered. No further attempts were made to prepare the α-(2-furyl)toluene derivatives.

Attention was now focussed on the synthesis of the heterocyclic triphenylmethane analogue 99. The first attempt at preparing the α, α'-(2-difuryl)-2-nitrotoluene 111 paralleled the

synthesis of the dimethoxytriphenylmethane 85 above, and consisted of the condensation of o-nitrobenzaldehyde and furan in the presence of concentrated sulphuric acid and glacial acetic acid at 0° C.





111 R = H

113 R = CH_3

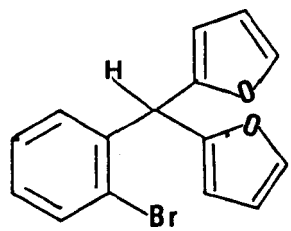
112 R = H

114 R = CH_3

This reaction was accompanied by much tar formation, but product 111 was obtained as a brown oil, in 33% yield, by eluting the crude product mixture on an alumina column with a mixture of 5% benzene in petrol (b.p. 40-60°). The oil would not crystallise but a sample was distilled and gave a correct elemental analysis. The n.m.r. spectrum of compound 111 proved to be interesting. The furan signals at δ 6.3 p.p.m. obscured the signal from the methine proton; this was confirmed by the successive additions of Eu $(fod)_3$ shift reagent which caused the singlet due to the methine proton to move downfield clear of the furan signals. This singlet integrated correctly for one proton. Furthermore, the signals at δ 6.3 p.p.m. did not integrate correctly for the required seven protons (six furan plus one methine) but for five protons only. Further examination of the integral of signals in the aromatic region revealed that an extra two protons, one from each furan ring (H on C-5), were among the aromatic signals.

The nitro compound 111 was reduced to the corresponding amine 112 in 70% yield using hydrogen gas at atmospheric pressure and 10% palladium-on-charcoal as the catalyst. The amine was purified by column chromatography with benzene/petrol (1:1) as the eluent. The n.m.r. spectrum of the amine shows the methine proton signal to be clear of the furan signals at δ 5.5 p.p.m..

The amine 112 was found to resinify slowly on standing. An attempt was made to diazotise the amine by the usual method, but the reaction mixture went tarry on addition of the 4N sulphuric acid. This was to be expected from our previous observations of reaction between furan and mineral acid, and it indicated that an alternative to the acid diazotisation for the preparation of the azide would have to be adopted. Accordingly, the ortho-bromo compound 115 was prepared in 25% yield by a method similar to that used for the nitro derivative 111.



115

Repeated attempts to prepare the Grignard reagent from compound 115 proved largely unsuccessful. Approximately 90% of the magnesium was recovered unused from the reaction mixture. Had the Grignard reagent been formed, it was intended to add to it a solution of tosyl azide,[79,80] yielding the azide without contact with acid.

Another possible route which proceeds under milder conditions involves formation of the diazonium fluoborate of the amine 112. The mixture darkened on addition of the amine 112 to the fluoboric acid

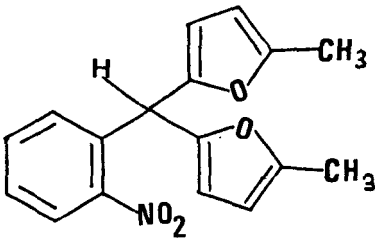
solution, and the flask was filled with black, tarry material after the addition of the sodium nitrite solution. This reaction was attempted several times, but the result was always as described above. No diazonium fluoborate derivative was isolated.

As it was thought that a substituted furan would be less susceptible to ring opening, o-nitrobenzaldehyde was condensed with 2-methylfuran as described above. This reaction was slightly cleaner than in the case of the unsubstituted furan and the yield of the nitro compound 113 was improved to 50%. The amine 114 was obtained by catalytic reduction, but a tarry residue was once again all that resulted from an attempted diazotisation. A further attempt at preparation of the azide was made in which the sodium azide solution was buffered using sodium acetate. This did indeed lead to a cleaner reaction, but the brown solid that was isolated was not the required azide and could not be identified.

As the prospects for a successful diazotisation of the amine were becoming increasingly worse, it was decided to attempt a deoxygenation of the unsubstituted nitro compound 111 using triethylphosphite (T.E.P.). The nitro compound and T.E.P. were refluxed together in cumene solution for 46 hours, after which time gas liquid chromatography showed the absence of any starting material. Removal of the solvent was followed by column chromatography on alumina. Only mixtures of compounds were recovered from the column and an attempt was made to separate these by preparative layer chromatography. The developed plates showed many bands, mainly brown in colour; in addition several minor bands exhibited strong fluorescence on exposure to ultraviolet radiation. After extracting these bands with methanol and evaporation of the solvent, the n.m.r. spectra of the resulting oils showed only badly resolved signals in the aromatic region. In

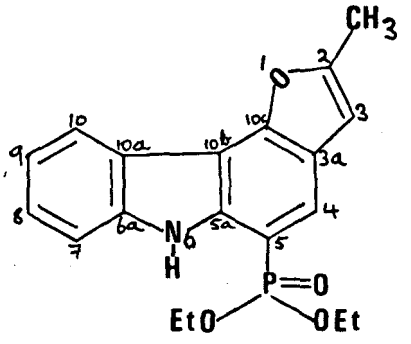
addition, the oils were not very soluble in any of the common solvents and darkened on standing. The general darkening of the liquor coming off the column and the brown colour of the bands on the plates would suggest that decomposition was taking place. No compounds were identified.

The deoxygenation using T.E.P. was repeated on the methyl substituted furan derivative 113.



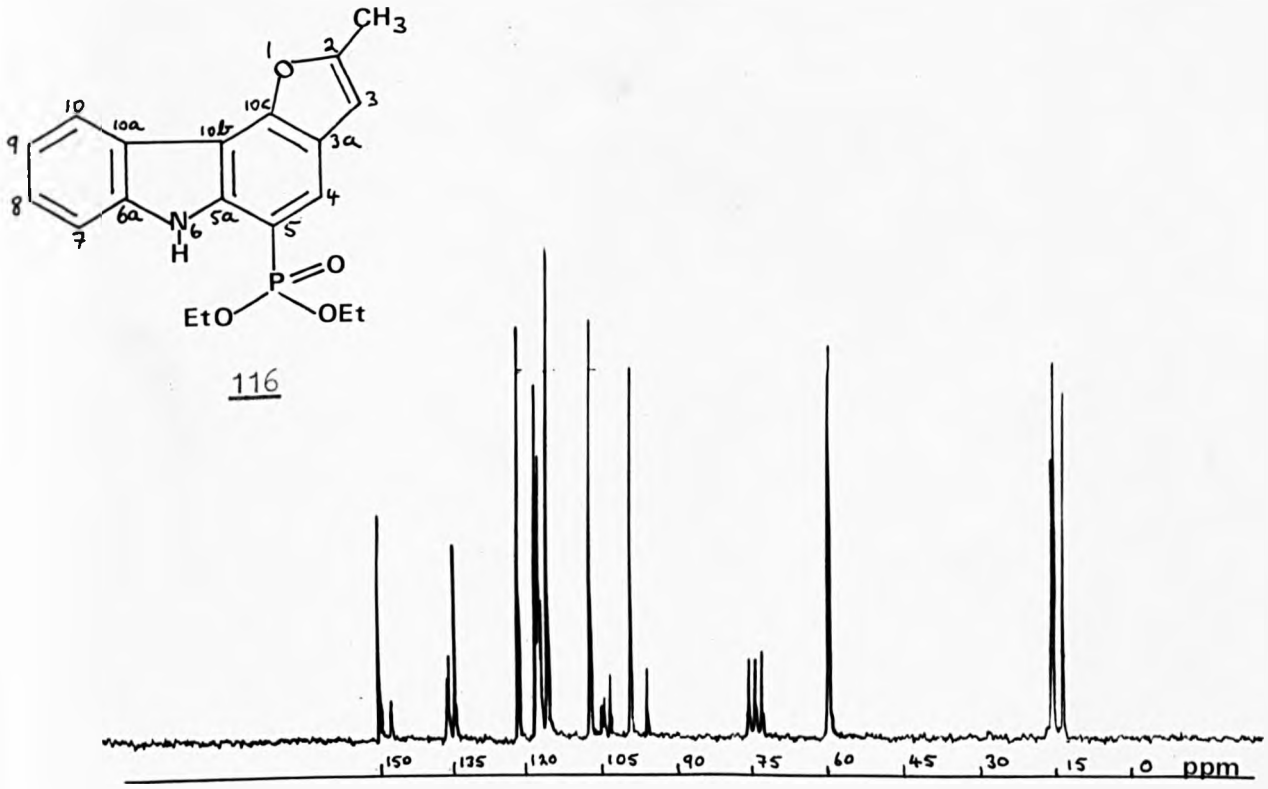
113

After removal of the solvent, t.l.c. and g.l.c. analysis showed the presence of at least twelve products. The only material to be identified after column chromatography was a brown solid (5.0 g, 28%) subsequently identified as described below from the ^{1}H n.m.r., ^{13}C n.m.r., and ^{31}P n.m.r. spectra as diethyl (2-methyl-furo[3,2-c]carbazol-5-yl) phosphonate 116.



116

The $^{13}C\{^{1}H\}$ n.m.r. spectrum[81] is shown in Figure 7.



116

Figure 7

The chemical shifts are expressed in p.p.m. from tetramethylsilane. It was not possible to fully interpret either the decoupled or undecoupled spectra; the following discussion attempts to assign the signals by comparison with those of known compounds.

The signal at δ 13.9 p.p.m. arises from the methyl group on C-2. This compares well with the value of δ 14.0 p.p.m. obtained

by Page and co-workers[82] for the methyl carbon in 2-methylfuran. The doublets at δ 16.3 p.p.m. ($J \approx 2$ Hz) and δ 62.3 p.p.m. ($J \approx 2$ Hz) are due to the methyl and methylene carbon atoms respectively of the phosphonate group. The comparable values for diethyl ethylphosphonate[83] are δ 16.5 p.p.m. ($J = 6.9$ Hz) and δ 61.4 p.p.m. ($J = 6.2$ Hz). The three signals centred at δ 77.2 p.p.m. are due to chloroform.

Table VII below gives the values for some of the carbon atoms in the ^{13}C n.m.r. spectrum of carbazole[84] with the values for the comparable carbon atoms in the system under discussion.

TABLE VII

C-no. in 116	carbazole	furylcarbazole 116
		p.p.m.
6a	139.5	139.2
7	110.5	111.1
8	119.4	120.0
9	120.3	121.0
10	125.7	126.0
10a	123.4	122.5

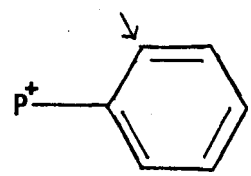
As would be expected, there is good agreement in the values.

Comparison with the ^{13}C n.m.r. spectrum of 2-methylbenzofuran[85] enables the following signals to be assigned (Table VIII).

TABLE VIII

C-no. in 116	2-methylbenzofuran	furylcarbazole 116
		p.p.m.
2	155.2	154.7
3	102.6	102.9
10c	154.9	154.3

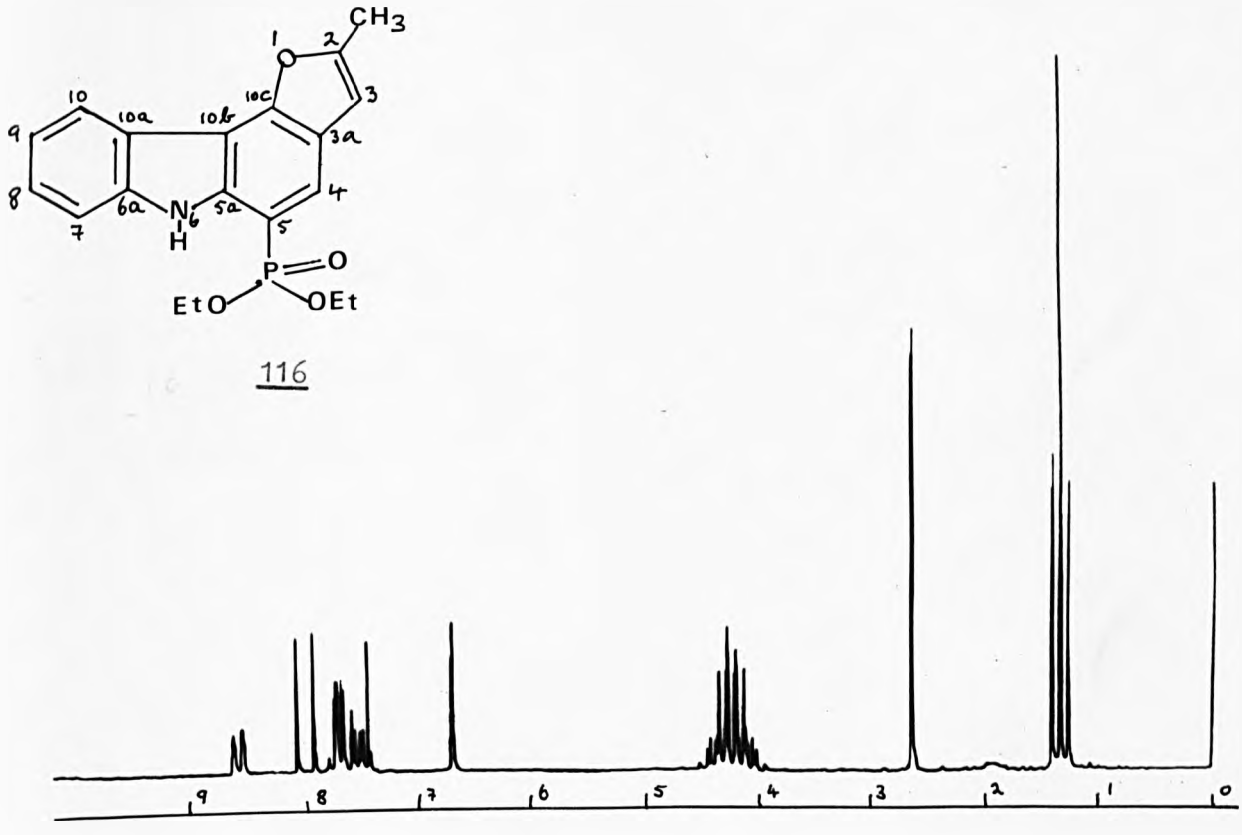
The doublet at δ 108.4 p.p.m. ($J \approx 4$ Hz) is due to C-4; the $^{13}C\left[^{31}P\right]$ spectrum confirms the coupling of C-4 to the phosphorus atom and the coupling constant compares with the value of J = 9-10 Hz for the system.[86]



J (P-C-C) = 9-10 Hz

It was not possible to assign positively values for C-5, -5a, or -10b.

The ^{1}H n.m.r. spectrum is shown in Figure 8.



116

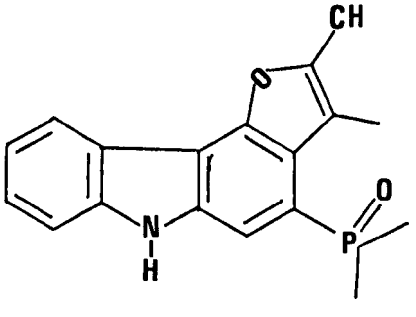
Figure 8

[Note: the spectrum reproduced in Figure 8 does not show the signal arising from the amine proton. This signal appears at δ 10.1 p.p.m.] The triplet and quartet at δ 1.3 and δ 4.1 p.p.m. respectively are due to the ethyl groups of the phosphonate substituent. The spectrum recorded at 100 MHz shows the complex fine structures due to the coupling with the phosphorus atom. The signal from the methyl protons

of the furyl substituent is at δ 2.55 p.p.m., and the furyl β-proton gives rise to a complex singlet at δ 6.42 p.p.m. The remaining five aromatic protons give rise to a multiplet at δ 6.3 - 7.1 p.p.m. The signal from the amine proton appears as a broad singlet at δ 10.1 p.p.m.

Examination of the $^{1}H[^{31}P]$ n.m.r. spectrum reveals that the complex methyl triplet (δ 1.3 p.p.m.) has collapsed to a simple triplet, and most of the fine splitting of the methylene quartet (δ 4.1 p.p.m.) has also disappeared. This decoupling confirms the position of the ethoxy groups attached to the phosphorus atom. The ^{1}H n.m.r. spectrum (Figure 8) also features a doublet in the aromatic region at δ 7.65 p.p.m. (J = 15 Hz); the ^{31}P decoupled spectrum shows the doublet to have collapsed to a singlet. Furthermore, the addition of $Eu(fod)_3$ shift reagent to the ^{1}H n.m.r. solution results in a downfield shift of this doublet with successive additions of shift reagent. The signal from the amine proton also experiences a downfield shift.

These shifts may be rationalised by assuming that the $Eu(fod)_3$ complexes to the oxygen of the phosphonate group and this "contact shift"[87] causes the signals from the C-4 and amine protons to move downfield. The signal from the β-furyl proton is not affected as this proton is too remote from the point of complex. If the phosphonate was on C-4 as in structure 117, a movement of the β-furyl



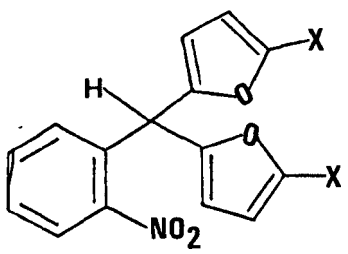
117

signal would have been observed. Furthermore, the C-5 proton signal should be seen to shift and not the carbazole NH signal. Therefore

the results of these studies are in accord with the proposed structure 116.

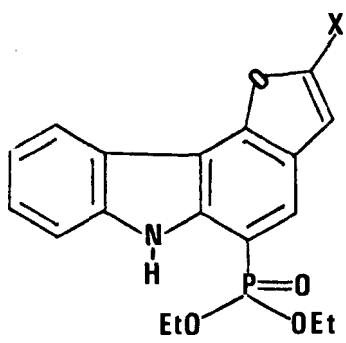
The ^{31}P n.m.r. spectrum featured a broad singlet at a position -21 p.p.m. from H_3PO_4. This is compatible with the proposed structure 116.

Additional examples of compounds containing the parent ring system of structure 116 are provided by some recent work by Jones.[67] Deoxygenation (T.E.P.) of the t-butyl and ethyl analogues 118 and 119, 113 yielded the corresponding furylcarbazoles 120 and 121.



118 X = t-butyl

119 X = ethyl



120 X = t-butyl

121 X = ethyl

The proton n.m.r. spectra of compounds 120 and 121 were identical to that obtained for the furylcarbazole 116 except for the replacement of the methyl protons' signal by those from the t-butyl and ethyl groups. It is hoped therefore that it will be possible to prepare a series of compounds containing this novel ring system. At the time of writing, no method has been found of removing the phosphonate group.

There is not a complete and satisfactory mechanism to account for the formation of the furylcarbazole 116. It is possible, however, to note several features which are relevant to any proposed

mechanism. These are discussed below.

1) The phosphonate must add to an intermediate and not to the end product.

2) Acetaldehyde has been detected during the formation of the unsubstituted, the ethyl, and the t-butyl analogues of the compound 116.

3) Rupture of one furan ring must occur.

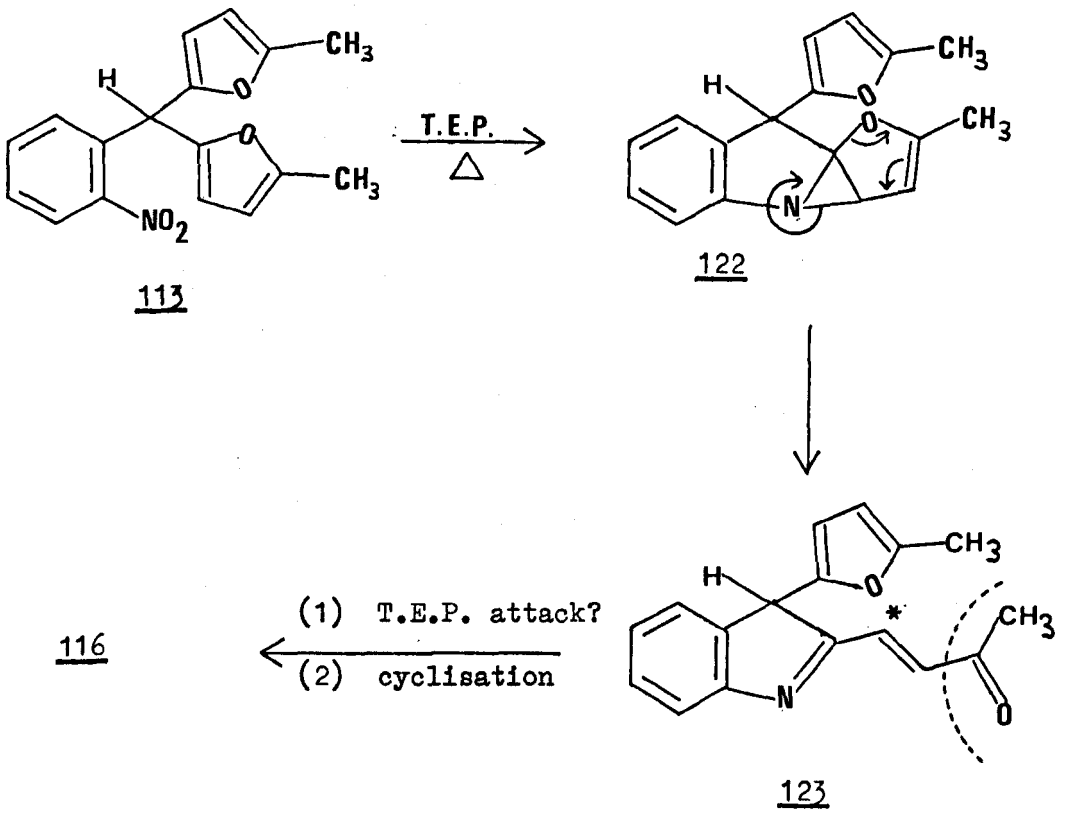
4) There are many brightly coloured compounds which were not identified.

The first point follows from the work of Cadogan and co-workers[88] who have prepared carbazoles by a route involving phosphorus reagents, including T.E.P. There is no account in this work of a carbazole having been isolated which bears a phosphonate substituent. Therefore the addition must occur before the formation of the final ring system.

The detection of acetaldehyde in the formation of the methyl substituted analogue 116 would not have been unexpected since the components of acetaldehyde are lost in the transformation. Accordingly, it might have been expected to detect formaldehyde, propionaldehyde, and t-butylaldehyde in the reactions involving these analogues of compound 116. Instead acetaldehyde was detected in the emission gases in all three cases (even though no unsubstituted analogue was isolated (page 61). As the methyl compound 116 was the first to be prepared, the experiment did not include the identification of emitted gases, but it would seem to be a reasonable assumption that acetaldehyde was formed in that case as well. This fact, along with the observation of multiple products, suggests that the mechanism is not simple.

In light of these considerations, it is possible to write a partial mechanism as shown in Scheme 27.

SCHEME 27



113

122

123

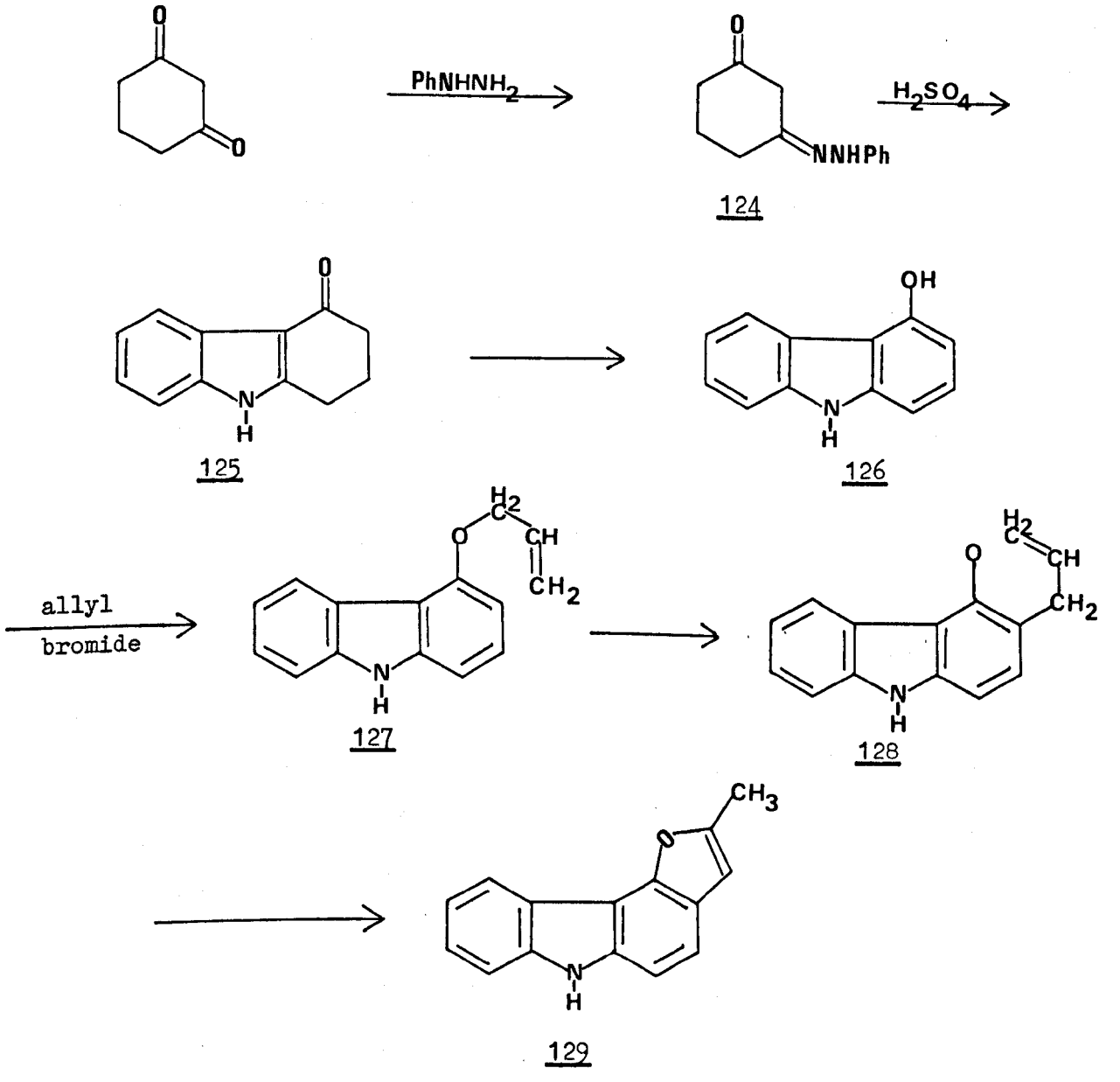
116

The nitro compound 113 undergoes deoxygenation by T.E.P. to give the nitrene which inserts intramolecularly into the 2,3-bond of one of the furan rings to give the aziridine 122 as previously postulated.[89] This aziridine may or may not develop into a spirodiene intermediate (not shown) as discussed in the Introduction and by Jones and co-workers.[92] From either the aziridine or the spirodiene the next most likely step is rupture of one of the furan rings to give, possibly, the structure 123. The formation of a furoaziridine and the subsequent rupture of one of the furan rings has been postulated by D.W. Jones to account for the products formed by phthalimidonitrene attack on benzofurans and simple substituted furans.[89,90,91] The proposed partial mechanism is also analogous to that proposed by Jones to account for the decomposition products from 2-(2-azidobenzyl)-thiophene.[92]

The phosphonate could attack at this stage as structure 123 contains an α,β-unsaturated carbonyl fragment. Attack by phosphorus at the C-atom marked (*) would result in the phosphorus atom being in the correct position in the final product. Also from structure 123, loss of acetaldehyde could be envisaged as shown. However, this view must be considered as too simplistic as acetaldehyde is formed regardless of the nature of the substituent on the original furan ring. As discussed above, attack by phosphonate must be followed eventually by cyclisation to the observed product 116, but there is no evidence at the time of writing which might help to elucidate the mechanism of the cyclisation.

An attempt was made at an unambiguous synthesis of the methyl-furylcarbazole 116. The synthetic route envisaged is shown in Scheme 28.

SCHEME 28


PhNHNH2
H2SO4
NNHPh
124
OH
125
126
allyl
bromide
127
128
CH3
129

The preparation of the phenylhydrazone 124 was first reported by Merling in 1894[93] and subsequently by Hester[94] in 1970. This condensation between 1,3-cyclohexadione and phenylhydrazine in the presence of acetic acid proceeded in 45% yield. On standing, the product 124 becomes progressively more red, presumably due to the formation of an azo derivative. The Fischer synthesis for the indole 125 was effected by heating the hydrazone in 40% sulphuric acid,[95] and the indole was obtained in 31% yield.

The dehydrogenation to form the hydroxy carbazole 126 was not at first successful. The method of Cummins and Tomlinson,[96] which involves heating the tetrahydro compound 125 with 10% palladium-on-charcoal in an atmosphere of nitrogen followed by alkaline extraction, yielded only starting material. Subsequent attempts[97] yielded up to 25% of the hydroxycarbazole 126, but the major product was carbazole by elimination of the elements of water. Treatment of the hydroxycarbazole 126 with sodium methoxide in methanol, followed by allyl bromide, gave a mixture. Column chromatography of the mixture gave a poor yield (25 - 30%) of a compound having the correct n.m.r. spectrum for the allyloxycarbazole 127.

An alternative route was via bromination of the ketone 125 using phenyltrimethyl ammonium tribromide (P.T.A.B.) in methanol followed by dehydrobromination by stirring a methanolic solution of the intermediate with Spence alumina, which is particularly basic. This is a procedure used previously by Gurnos Jones in this laboratory. T.l.c. of the crude product revealed three spots and work-up was by column chromatography using petrol/benzene (1:1). The only identified material to be recovered was the starting material. This procedure was repeated using other solvents, lest the insolubility of reactants and products was the source of the problem, but none of the desired

hydroxycarbazole 126 was obtained from this method.

The next stage in the synthesis, involves the arrangement of the allyl ether 127 to yield the allyl-substituted hydroxy-carbazole 128. This has not been attempted at the time of writing. If this reaction proves to be successful, the final stage of the synthesis would be cyclisation of this compound 128 to form the desired furylcarbazole 129.[98]

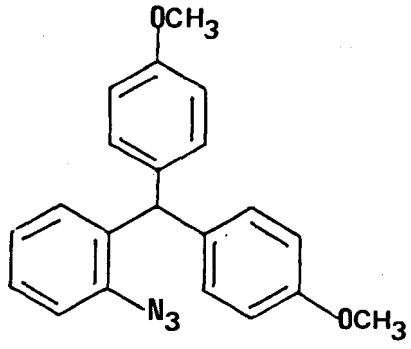
EXPERIMENTAL

PART I

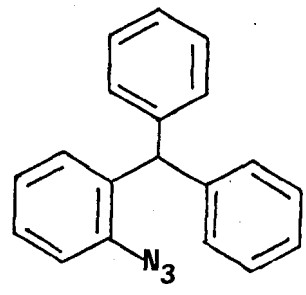
PART I

EXPERIMENTAL

Preparation and decomposition of 2-Azido-4',4"-dimethoxytriphenylmethane 74 and 2-Azidotriphenylmethane 30



74



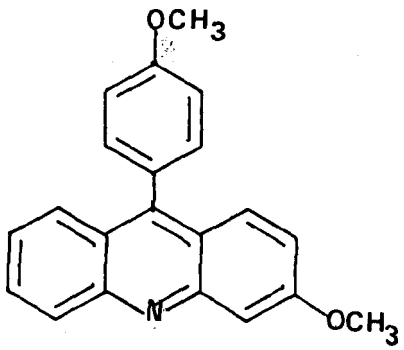
30

The dimethoxy azide 74 was prepared as described in Part II of this thesis, and the unsubstituted azide 30 was prepared by the method of Carde.[39] Photolyses were performed on a solution of the azide in dry benzene contained in a quartz vessel and this was irradiated in a Rayonet Preparative Photochemical reactor using 16 RUL-3000A lamps of maximum intensity at 300 nm.

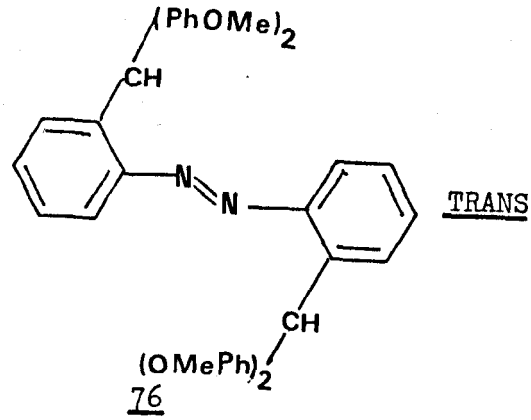
Photolysis of 2-Azido-4',4"-dimethoxytriphenylmethane 74

The azide 74 (4.0 g) was irradiated in dry benzene (750 ml) for 120 hours after which time t.l.c. in benzene showed that all of the azide had been consumed. Evaporation of the deep red solution left an oil (3.5 g) which was absorbed onto alumina (10 g, Activity IV) and was then chromatographed on alumina (100 g, Activity IV, 20 x 2.5 cm) with petrol (b.p. 40-60) as eluant. The

first material off the column was a brown oil (0.43 g) which was chromatographed on preparative plates in benzene. The developed plates contained three major bands; only one was identified and it contained the starting azide 74 (156 mg). The eluant was changed to 15% benzene/petrol and a mixture (1.2 g) was obtained. Preparative layer chromatography of this mixture in benzene yielded 6-methoxy-9-(4-methoxyphenyl)acridine 75 (0.35 g). The next compound to come off the column was the azo-compound 76 (0.23 g). This was identified from its ultra-violet spectrum, mass spectrum, and by comparison with the data for the unsubstituted azo-compound found by Carde.[39]



75

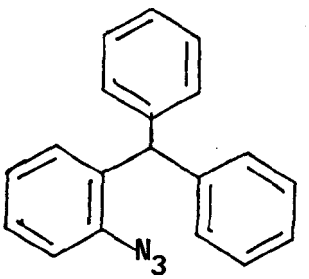


76

The proportions of CIS and TRANS isomer of the azo-compound 76 were not established.

The eluting solvent was changed to 100% benzene and then to 100% chloroform. Mixtures were obtained from the column which were subjected to preparative layer chromatography. Typically, the mixture was found to comprise 12-20 compounds, all in very small yield, and none was identified.

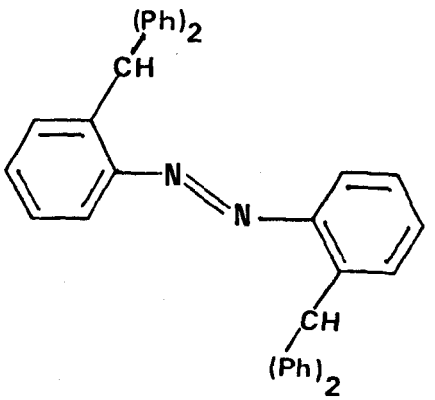
Photolysis of 2-Azidotriphenylmethane 30



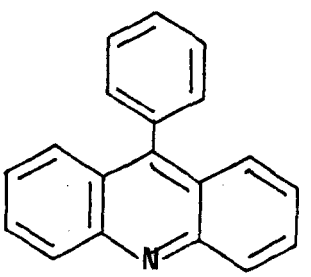
30

(a) *in neat benzene*

The azide (3.1 g) was irradiated in dry benzene (600 ml) for a total of 138 hours. Evaporation of the solvent yielded a red oil which was absorbed onto alumina and chromatographed on a column of alumina with petrol (b.p. 40-60°) as eluant. The first material to be recovered from the column was the azide 30 (100 mg); this was followed by the azo-compound 130 (1.2 g, 39 %).



130



65

The eluting solvent was changed to 15% benzene/petrol and 9-phenylacridine 65 (0.15 g, 5%) was recovered. As in the previous case, a series of mixtures were collected from the column which were shown on examination by t.l.c. to comprise many products. None of these was

identified, and the yield of identified material was 50%.

(b) with acetophenone

The azide (4.7 g) was irradiated for 128 hours in dry benzene (500 ml) containing freshly distilled acetophenone (2 ml, mole equivalent). The solvent was evaporated and the residue was chromatographed on alumina as described in (a) above. Table IX summarises the result of the column chromatography.

TABLE IX

Product	Weight	Yield
azide 30	0.14 g	3%
azo-compound 130	1.4	31
acridine 65	0.14	3

total identified = 37%

(c) with penta-1,3-diene

The azide 30 (4.0 g) was irradiated for 124 hours in dry benzene (500 ml) containing penta-1,3-diene (1.0 g, mole equivalent). The solvent was evaporated and the crude mixture (4.0 g) was chromatographed on a column of alumina. Table X below shows the products that were identified in the order of elution.

TABLE X

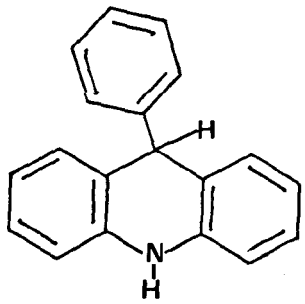
Product	Weight	Yield
azide 30	0.2 g	7%
*amine	0.07	2
azo-compound 130	0.3	8
acridine 65	0.2	5

total identified = 22%

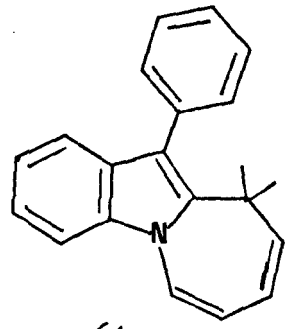
* "amine" is the amine precursor to 2-azido-triphenylmethane 30

Thermolysis of 2-Azidotriphenylmethane 30 with N,N-dimethyl-p-nitrosoaniline

The azide 30 (7.2 g) was decomposed at 185-190° for 4 hours in 1,2,4-trichlorobenzene containing a molar equivalent of the triplet quencher N,N-dimethyl-p-nitrosoaniline. The general procedure for the thermolysis is described in Part II (page 94) of this thesis. The solvent was evaporated and the residue chromatographed on a column of alumina with petrol (b.p. 40-60) as eluant. After traces of trichlorobenzene, the first product off the column was 9,10-dihydro-9-phenylacridine 66 (0.54 g, 9%). On changing the solvent to 5% benzene/petrol mixture 9-phenylacridine 65 (1.06 g, 17%) was obtained. The azepinoindole 64 (0.04 g, 0.7%) was isolated from a mixture which came off the column when the solvent was changed to 20% benzene/petrol.

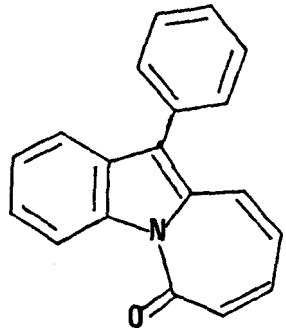


66



64

The only other compound to be identified from the column was 19 mg of a compound which was provisionally identified from its n.m.r. spectrum as the indol-6-one 77.



77

There was not sufficient material to permit a complete characterisation of compound 77.

Several grams of dark products were obtained off the alumina column as the solvent was gradually changed to 100% benzene and then to methanol. It was shown by t.l.c. that all of these "products" were very complex mixtures. Some separation was achieved using preparative layer chromatography in toluene; the developed plates all exhibited closely spaced bands ranging in colour from purple to green to orange. Each band, however, was found to contain only a few milligrams of product and none was

identified.

Additional work concerning the thermolysis of 2-Azidotriphenylmethane 30 in the presence of N,N-dimethyl-p-nitrosoaniline

(a) Azepinoindole 64 (0.1 g) was heated in 1,2,4-trichlorobenzene (10 ml) at 190° for 4 hours in the presence of a molar equivalent of N,N-dimethyl-p-nitrosoaniline. The solvent was evaporated and the products were subjected to preparative layer chromatography with toluene as solvent. The developed plates showed that the mixture comprised at least 10 components; each was present in only a few milligrams and none was identified.

(b) N,N-dimethyl-p-nitrosoaniline (0.2 g) was heated in 1,2,4-trichlorobenzene (10 ml) at 190° for 4 hours. After removal of the solvent, the residual oil was put onto preparative plates and eluted with toluene. Examination of the developed plates revealed that there were at least six components; none of these compounds was identified.

Thermolysis of 2-Azidotriphenylmethane 30 - investigation of the "heavy-atom" effect

(a) Decomposition in bromobenzene at 156°C

The azide 30 (9.5 g) was heated in refluxing bromobenzene (1 l, 154-8°) for 7.5 hours, after which time no azide could be detected by t.l.c. A parallel decomposition was performed in 1,2,4-trichlorobenzene maintained at the same temperature (156°), for the same length of time. Evaporation of the solvent was followed, in

each case, by investigation of the residue by g.l.c. (3% OV 101 on Supasorb A.W., 60 ml/min N_2, 222°C). The g.l.c. traces are shown in Figure 1 (page 30) and the yields for each product are shown in Table XI. The yields were calculated from the g.l.c. traces by taking an average of three "cut and weigh" runs for each peak. The yield is expressed as this weight as a percentage of the combined weights of the peaks.

TABLE XI

	Solvent		
Peak no.	trichlorobenzene	bromobenzene	
1	0.6 %	0.8 %	
2	5.8	5.4	
3	0.3	0.6	
4	1.4	1.9	
5	2.7	4.3	
6	3.1	3.3	
7	5.3	5.4	
8	77.4	73.7	Azepine + acridine
9	2.3	2.5	
10	1.2	2.2	

The ratio of azepine to acridine was measured by using high pressure liquid chromatography (h.p.l.c.). The following equipment and conditions were used:

Chromatromix 3100 liquid chromatograph (constant pressure

type) fitted with a Waters Differential Refractometer (Model R 401). The column (500 mm x 2.1 mm I.O.) was of stainless steel coated with Spherisorb silica (10 micron). The optimum solvent system was a mixture of iso-octane (84%), chloroform (15%), and methanol (1%). The flow-rate was 0.8 ml/min and the temperature was ambient.

As stated in the discussion, the acridine 65 and acridan 66 had the same retention time on h.p.l.c.. The azepine : acridine + acridan ratio was determined by the "cut and weigh" technique. The decomposition in bromobenzene resulted in the production of a very small amount of azepine product, and the amount could not be estimated with any certainty. The parallel decomposition in trichlorobenzene gave an azepine : acridine ratio of 10 : 17. Attempts were made to separate, by preparative layer chromatography, the remaining products from the decompositions, but these were unsuccesssful and none was identified.

(b) Decompositions in p-dibromobenzene and naphthalene at 190°.

The azide 30 (8.5 g) was dissolved in dry benzene (100 ml) and added dropwise to p-dibromobenzene (1 kg, ≈ 500 ml) maintained at 185-190°. The benzene was allowed to boil off, and the temperature was maintained for 4 hours. In a similar manner, another sample of azide 30 (8.5 g) was added to naphthalene (500 ml) maintained at 185 - 190°. After 4 hours at this temperature, the solvents were distilled off under reduced pressure, an adapted air condenser being used to collect the solids. The minimum pot volume that could be achieved in the distillation was approximately 50 ml in each case. Examination of these residues by g.l.c. under the conditions described

above revealed, in each case, the presence of 6 compounds. The retention times of these compounds corresponded to those peaks numbered 1, 2, 4, 7, 8, and 9 in Figure 1 (page 30) above. The work-up was by column chromatography as it was not known what effect the substantial amount of decomposition solvent would have on the h.p.l.c. determination of the azepine/acridine ratio. The crude mixture from each run was absorbed onto alumina (100 g) and put onto a column of alumina (activity IV) which had a ground glass joint half-way along its length. A volume of petrol (b.p. 40-60°), equal to the "dead volume" of the upper half of the column, was run through the column. Then the column was split and the lower half was eluted with petrol to yield, in each case, the decomposition solvent followed by azepine 64. The upper portion of the original column was connected to another column of alumina (activity IV, 200 g, 20 cm) and eluted with petrol. A further small amount of the decomposition solvent was followed off the column by azepine 64, and, after further elution, by the acridine 65. Table XII summarises the results for the two decompositions.

TABLE XII

	Solvent	
Compound	p-dibromobenzene	naphthalene
Azepine 64	2.5 g	0.28 g
Acridine 65	0.1	2.0
Azo-compound 130		0.45

No other material was identified from these decompositions.

(c) Decompositions in diphenyl and p-dibromobenzene

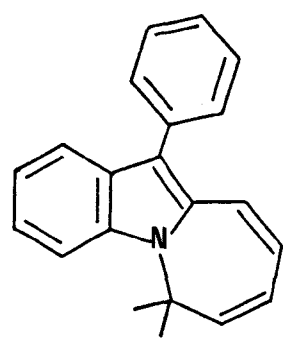
Following the same procedure as in (b), the azide 30 (6.0 g) was added to diphenyl (500 ml) and to p-dibromobenzene (500 ml) at 185-190° and maintained at that temperature for 4 hours. The bulk of the solvent was distilled off, the residue absorbed onto alumina (50 g), and chromatographed on a single column of alumina (activity IV, 300 g, 60 cm) and eluted with petrol (b.p. 40-60°).

Table XIII summarises the results of the decompositions.

TABLE XIII

	Solvent	
Compound	diphenyl	p-dibromobenzene
Azepine 64	0.75 g	0.8 g
Acridine 65	1.5	1.46

In the case of the azepine recovered from the run with dibromobenzene as solvent, the n.m.r. spectrum of the later azepine fractions contained an extra doublet at δ 4.35 p.p.m. This was interpreted as arising from the isomeric 6H-azepine 131.



131

Repeated attempts by preparative layer chromatography failed to separate the 6H and 10H azepines.

No other material from the column was identified.

(d) Decomposition in p-dibromobenzene

As the results described in (b) and (c) above from the decompositions in p-dibromobenzene are at variance, a further sample of the azide 30 (6.0 g) was decomposed in p-dibromobenzene. Work-up was by column chromatography as in (c). Azepine 64 (1.3 g) and acridine 65 (1.1 g) were recovered from the column. There was no evidence for the presence of the 6H-azepine 131 in this experiment.

P A R T I I

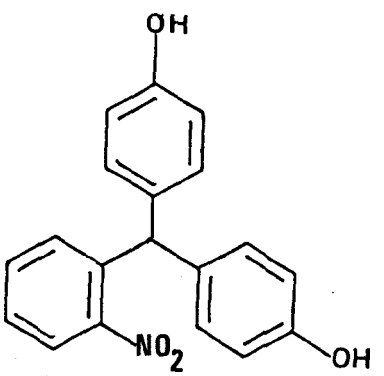
PART II

EXPERIMENTAL

2-Nitro-4',4"-dihydroxytriphenylmethane 84

A mixture of concentrated sulphuric acid (8 ml) and glacial acetic acid (40 ml) was added dropwise to a stirred solution of o-nitrobenzaldehyde (20 g, 0.132 m) and phenol (25 g, 0.264 m) in glacial acetic acid (75 ml) maintained at 0-5°C. The mixture was left in the refrigerator at 0-5°C for 48 hours and was then poured onto crushed ice with stirring. After allowing the mixture to warm to room temperature, the organic material was extracted with hot benzene (3 x 200 ml). Evaporation of the solvent yielded crude 2-nitro-4',4"-dihydroxytriphenylmethane 84 (28 g, 63%). Purification was by column chromatography on alumina (300 g, activity IV) with benzene as eluant.

2-Nitro-4',4"-dihydroxytriphenylmethane 84



84

M.p. 161° ($CHCl_3$)

Analysis

Found	C, 71.30;	H, 4.54;	N, 4.32 %
$C_{19}H_{15}NO_4$ requires	C, 71.02;	H, 4.67;	N, 4.36 %

N.m.r. (acetone d_6)

δ 6.04	p.p.m.	s	1H	methine H
6.65-7.85		m	12H	aromatic H
8.14		s	2H	$(OH)_2$ exchange with D_2O

I.r. (mull)

ν_{max} 3360 br, 1610, 1590 cm^{-1}

U.v. (95 EtOH)

λ_{max}	228 n.m.	$\log_{10}\varepsilon$	4.33
	283		3.64

Mass spectrum

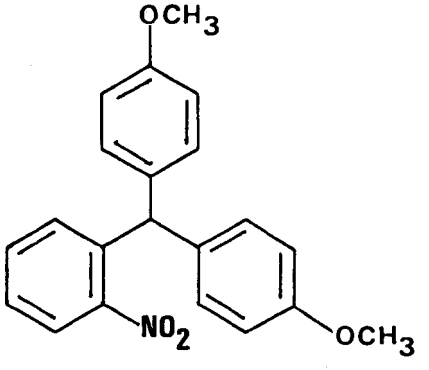
m/e 321 (M^+) (41%), 304 (76%), 303 (27%), 287 (27%), 263 (23%), 247 (11%), 212 (19%), 185 (20%), 152 (13%), 121 (33%), 78 (100%)

2-Nitro-4',4"-dimethoxytriphenylmethane 85

Methyl iodide (42 g) was added to a solution of crude 2-nitro-4',4"-dihydroxytriphenylmethane 84 (28 g) in dry acetone (500 ml) containing anhydrous potassium carbonate (42 g). The mixture was refluxed with stirring for 2 hours, then additional methyl iodide (20 g) was added and reflux continued for a further 3 hours. The mixture was allowed to cool and then filtered. The liquor was evaporated

to give a red oil which was taken up in chloroform (200 ml), washed with dilute NaOH (2 x 150 ml), and water (3 x 150 ml), dried ($MgSO_4$) and evaporated. The residue was 2-nitro-4',4"-dimethoxytriphenylmethane 85 (23.4 g, 76.5%), a red oil. Purification was by column chromatography on alumina (300 g, activity IV) with benzene as eluant.

2-Nitro-4',4"-dimethoxytriphenylmethane 85



85

Analysis

Found C, 72.45; H, 5.40; N, 4.30 %

$C_{21}H_{19}NO_4$ requires C, 72.2; H, 5.45; N, 4.01 %

N.m.r. ($CDCl_3$)

δ 3.75	p.p.m.	s	6H	$(OCH_3)_2$
6.18		s	1H	methine H
6.7-7.9		m	12H	aromatic H

I.r. (film)

ν_{max} 2860-3100 m, 2840, 1758 br, 1610 cm^{-1}

U.v. (95 EtOH)

λ_{max}	230 n.m.	$\log_{10}\varepsilon$	4.39
	268		4.04

Mass spectrum

m/e 349 (34%) (M^+), 333 (24%), 332 (100%), 316 (15%), 315 (51%), 301 (15%), 289 (15%), 272 (19%), 227 (17%), 226 (53%), 225 (85%), 210 (25%), 182 (81%), 154 (29%), 135 (54%), 108 (68%), 94 (31%), 85 (53%), 83 (73%)

2-Amino-4',4"-dimethoxytriphenylmethane 132

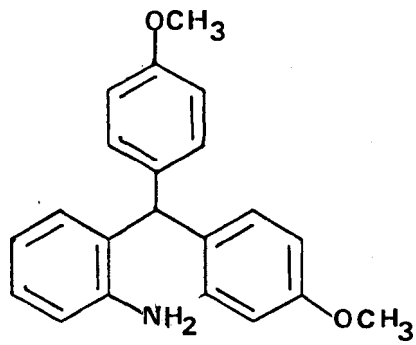
Method A

A solution of the nitro-compound 85 (12.5 g) in ethanol (95%, 1 l) containing 10% palladium-on-charcoal (2 g) in suspension was hydrogenated at atmospheric temperature and pressure until approximately 3 litres of hydrogen had been absorbed. Evaporation of the filtered solution gave 2-amino-4',4"-dimethoxytriphenylmethane 132 (11.4 g, 98%) as a red oil. A sample was distilled for analysis.

Method B

Hydrazine hydrate (98%, 5 ml) was added dropwise to a stirred solution of the nitro-compound 85 (4 g) in ethanol (95%, 200 ml) maintained at 50°C. To this was added 10% palladium-on-charcoal (0.1 g) and the mixture was heated to reflux. After 2 hours a further 0.1 g of catalyst was added and reflux continued for another 2 hours. The cooled solution was filtered and the filtrate evaporated to leave 2-amino-4',4"-dimethoxytriphenylmethane 132 (3 g, 70%) as a brown oil.

2-Amino-4',4"-dimethoxytriphenylmethane 132



132

B.p. 270-280°/35 mm Hg

Analysis

Found C, 79.2; H, 6.32; N, 4.38 %

$C_{21}H_{21}NO_2$ requires C, 79.1; H, 6.6; N, 4.21 %

N.m.r. ($CDCl_3$)

δ 3.6	p.p.m.	s	8H	2H (NH_2) (exchange with D_2O) 6H $(OCH_3)_2$
5.29		s	1H	methine H
6.4-7.0		m	12H	aromatic H

I.r. (film)

ν_{max} 3370 br, 3000, 2950, 2835, 1610 cm^{-1}

U.v. (95 EtOH)

λ_{max}	230 n.m.	$\log_{10}\varepsilon$	4.39
	278		3.79

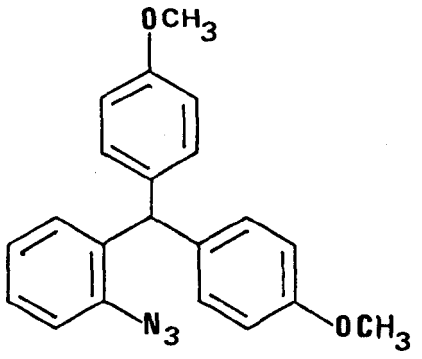
Mass spectrum

m/e 320 (10%), 319 (M^+) (45%), 318 (8%), 288 (8%), 229 (15%), 228 (24%), 227 (24%), 226 (15%), 214 (16%), 213 (17%), 211 (15%), 197 (18%), 196 (13%), 149 (10%), 135 (16%), 121 (15%), 107 (15%), 106 (24%), 94 (28%), 93 (100%), 86 (66%), 84 (76%), 77 (19%)

2-Azido-4',4"-dimethoxytriphenylmethane 74

A solution of 2-amino-4',4"-dimethoxytriphenylmethane 132 (15 g) in a mixture of 4N sulphuric acid (250 ml) and purified 1,4-dioxan (250 ml) was cooled to -5°C and a solution of sodium nitrite (3.7 g) in water (50 ml) was added with stirring. After 15 minutes a solution of sodium azide (4.0 g) in water (50 ml) was added and the solution warmed gently to 30°C. The solution was extracted with ether (3 x 200 ml) and the combined etheral extracts dried ($MgSO_4$). The solvent was removed under reduced pressure at 30°C and aluminium foil was used to protect solutions and residues from exposure to direct sunlight. The residual oil was percolated through a column of alumina (200 g, activity IV, 20 x 3.5 cm) with petrol (b.p. 40-60°)/benzene (15%) as the eluant. Evaporation of the solvent under reduced pressure at 30°C gave 2-azido-4',4"-dimethoxytriphenylmethane 74 (14.7 g, 93%) as a white crystalline solid.

2-Azido-4',4"-dimethoxytriphenylmethane 74



74

Analysis

Found C, 72.81; H, 5.52; N, 11.98 %

$C_{21}H_{19}N_3O_2$ requires C, 73.1; H, 5.5; N, 12.2 %

N.m.r. ($CDCl_3$)

δ 3.76	p.p.m.	s	6H	$(OCH_3)_2$
5.74		s	1H	methine H
6.2-7.2		m	12H	aromatic H

I.r. (mull)

ν_{max} 2125 cm^{-1}

U.v. (95 EtOH)

λ_{max} 230 n.m. $\log_{10}\varepsilon$ = 4.44

Mass spectrum

m/e 345 (M^+) (13%), 318 (39%), 317 (100%), 316 (37%), 303 (56%), 287 (17%), 273 (9%), 258 (9%), 242 (6%), 230 (7%), 228 (6%), 211 (30%), 167 (17%), 149 (17%)

Decomposition of 2-azido-4',4"-dimethoxytriphenylmethane 74

A solution of the azide 74 (4.7 g) in 1,2,4-trichlorobenzene (150 ml) was added dropwise during 20 minutes to 1,2,4-trichlorobenzene maintained at 190°C. 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. The solution was tested after 4 hours by t.l.c. (benzene) and the spot due to the azide was not present. After cooling, the solvent was removed under reduced pressure to leave a dark oil (5 g) which gave five peaks on a g.l.c. trace (3% OV 101 on Supasorb A.W., 60 ml/min nitrogen, 283°).

The mixture was separated by column chromatography; the crude decomposition product (5 g) was chromatographed on a column of alumina (350 g, activity IV, column length 1 m). Elution was started with benzene/petrol (b.p. 40-60°) (1 : 1), and 25 ml fractions were collected. The following table (Table XIV) shows the products eluted from the column and the weight of each fraction.

TABLE XIV

Product	Weight
1	146 m.g.
2	275
3	680
4	440
5	1423

Recovery = 60%

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

Product 2 was identified from its n.m.r. spectrum as 8-methoxy-11-(4-methoxyphenyl)-10H-azepino[1,2-a]indole 86.

Product 3 was crystallised from petrol (b.p. 40-60°) and identified as 8,9-dihydro-8,9-methano-8-methoxy-10-[4-methoxyphenyl]pyrido[1,2-a]indole 83.

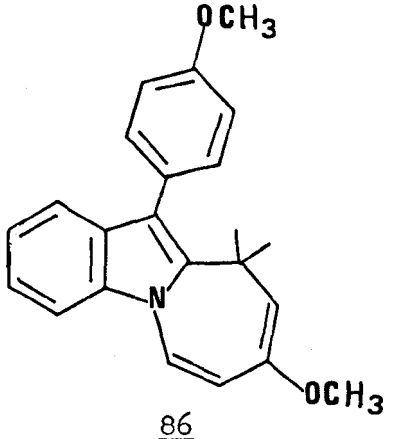
Products 4 and 5 crystallised in a similar manner and were identified as 9,10-dihydro-3-methoxy-9-(4-methoxyphenyl)acridine 91 and 3-methoxy-9-(4-methoxyphenyl)acridine 75 respectively.

The yields of the isolated products quoted below are calculated as the percentage:

$$\frac{\text{weight of isolated product X100}}{\text{total weight of crude products}}$$

Properties of the isolated products

8-Methoxy-11-(4-methoxyphenyl)-10H-azepino[1,2-a]indole 86



86

Product 2, yield 5.5%

N.m.r. ($CDCl_3$)

δ 3.2	p.p.m.	s	3H $-OCH_3$ on C-8
3.3-3.6		m	5H 2H on C-10, $-OCH_3$ on phenyl
4.62		t	1H H on C-9
5.45		d	1H H on C-7
6.6-7.5		m	9H aromatic H, H on C-6

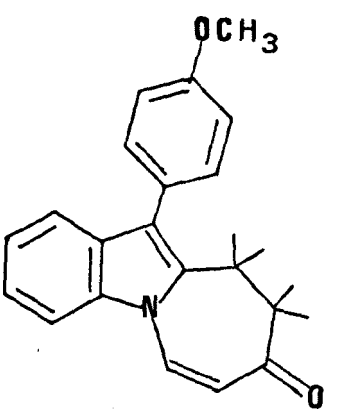
I.r. (film)

ν_{max} 3055, 3010, 1655, 1635 cm^{-1}

U.v. (95% ethanol)

λ_{max}	227 n.m.	$\log_{10}\varepsilon$	4.38
	257		4.21
	351.5		4.02

After these spectra had been recorded, the azepinoindole 86 was chromatographed on preparative plates in benzene in order to obtain a pure sample for elemental analysis. No starting material was recovered, and the only identifiable product was 9,10-dihydro-11-(4-methoxyphenyl)azepino[1,2-a]indol-8-one 87.



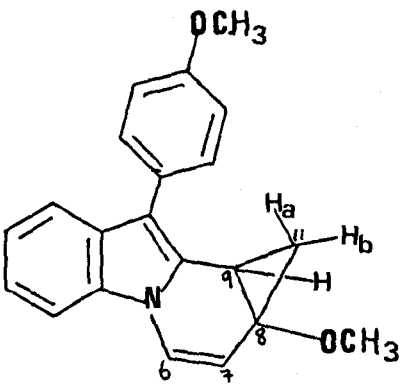
87

N.m.r. ($CDCl_3$)

δ 2.7	p.p.m.	overlapping triplets	4H on C-9, C-10 $J_{9,10}$ = 14 Hz
3.79		s	3H $-OCH_3$
5.55		d	1H H on C-7, $J_{6,7}$ = 10 Hz
6.88-7.58		m	9H aromatic H, H on C-6

There was insufficient pure material for a complete characterisation, and the assignment is based on the n.m.r. spectrum and by comparison of this data with that of the known 9,10-dihydro-11-phenylazepino[1,2-a]indol-8-one.[39]

8,9-Dihydro-8,9-methano-8-methoxy-10-(4-methoxyphenyl)pyrido[1,2-a]-indole 83



83

Product 3, yield = 13.6%

M.p. 159-160° (Petrol, 40-60°)

Analysis

Found C, 79.4; H, 5.93; N, 4.41 %

$C_{21}H_{19}NO_2$ requires C, 79.6; H, 6.0; N, 4.42 %

N.m.r. ($CDCl_3$)

δ 0.54 p.p.m.	d of d	1H	H_a on C-11
	$J_{11a,11b}$ = 5 Hz,		
	$J_{11a,9}$ = 6 Hz		
1.81	d of d	1H	H_b on C-11
	$J_{11a,11b}$ = 5 Hz,		
	$J_{11b,9}$ = 10.5 Hz		
2.72	m	1H	H on C-9
	$J_{11a,9}$ = 6 Hz		
	$J_{11b,9}$ = 10.5 Hz		
	$J_{7,9}$ = 2 Hz		
3.18	s	3H	$-OCH_3$ on C-8
3.70	s	3H	$-OCH_3$ on phenyl
5.61	d of d	1H	H on C-7
	$J_{7,9}$ = 2 Hz		
	$J_{6,7}$ = 8 Hz		
6.7-7.8	m	9H	aromatic H, H on C-6

I.r. (mull)

ν_{max} 3035, 1650, 1610 cm^{-1}

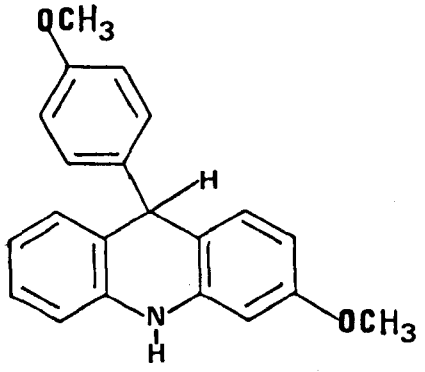
U.v. (95% ethanol)

λ_{max}	229 n.m.	$\log_{10}\varepsilon$	4.35
	257.5		4.47
	313		4.16

Mass spectrum

m/e 318 (35%), 317 (M^+) (100%), 316 (18%), 303 (12%), 302 (48%), 287 (18%), 286 (52%), 274 (18%), 271 (21%), 270 (15%), 258 (20%), 243 (9%), 242 (16%), 241 (10%), 230 (12%), 210 (9%), 204 (9%), 159 (14%), 151 (7%), 120 (12%)

9,10-Dihydro-3-methoxy-9-(4-methoxyphenyl)acridine 91



91

Product 4, yield = 8.8%

Analysis

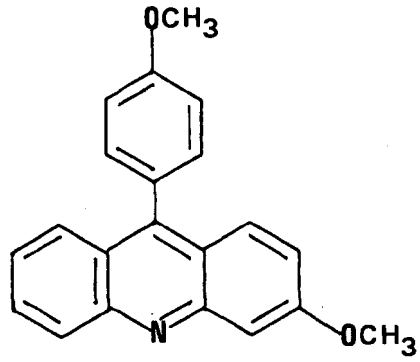
Found C, 79.12; H, 5.90; N, 4.37 %

$C_{21}H_{19}NO_2$ requires C, 79.49; H, 5.99; N, 4.41 %

N.m.r. ($CDCl_3$)

δ 3.65	p.p.m.	s	6H	$(OCH_3)_2$
5.1		s	1H	H on C-9
6.2		s	1H	-NH (exchange with D_2O)
6.4-7.3		m	11H	aromatic H

4-Methoxy-9-(4-methoxyphenyl)acridine 75



75

Product 5, yield 28.4%

M.p. 168-170° (petrol/CCl_4).

Analysis

Found	C, 79.8;	H, 5.32;	N, 4.35 %
$C_{21}H_{17}NO_2$ requires	C, 80.0;	H, 5.39;	N, 4.44 %

N.m.r. ($CDCl_3$)

δ 3.95	p.p.m.	s	3H	phenyl $-OCH_3$
4.05		s	3H	C-3 $-OCH_3$
7.0-8.3		m	11H	aromatic H

I.r. (mull)

ν_{max} 1630, 1610 cm^{-1}

U.v. (95% ethanol)

λ_{max}	226 n.m.	$\log_{10}\varepsilon$	4.08
	260		4.50
	355		3.56

Mass spectrum

m/e 316 (M^+) (96%), 315 (100%), 300 (8%), 272 (7%), 257 (7%), 228 (9%)

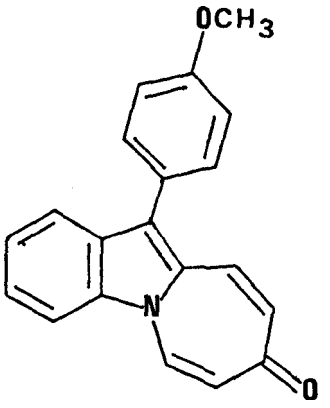
Attempted isomerisation of the pyridoindole 83

A solution of the pyridoindole 83 (0.65 g) in 1,2,4-trichlorobenzene (5 ml) contained in a pyrex test-tube was maintained at a temperature of 186°C by refluxing decalin. After 22 hours the trichlorobenzene was evaporated and the residual oil was examined by g.l.c. and n.m.r. spectroscopy. In the n.m.r. spectrum, the upfield signals due to the pyridoindole had disappeared and a complex pattern had emerged in the region δ 3.0-4.0 p.p.m. The g.l.c. trace revealed the presence of seven components (including four major products) and some with similar retention times to the decomposition products of the azide.

The mixture was chromatographed on preparative plates in chloroform. Three bands each containing less than 10 milligrams of material were removed and extracted but not identified. The remaining material on the plates was not satisfactorily separated and was removed, extracted, replated, and run twice in chloroform. The major

band on these plates, with an orange/yellow colour, was removed and extracted, and subsequently identified as 11-(4-methoxyphenyl)-azepino[1,2-a]indol-8-one 95. Several other bands were removed and with the minor bands from the first plates they were examined by linked gas chromatography - mass spectrometry. No further compounds were identified and the reaction was not repeated.

11-(4-Methoxyphenyl)azepino[1,2-a]indol-8-one 95

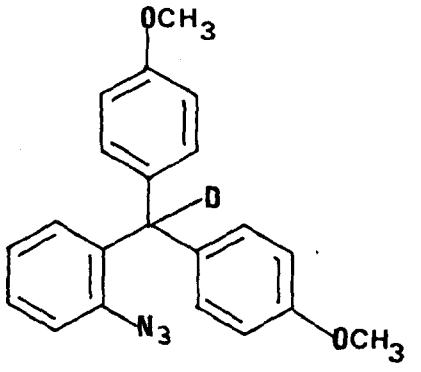


95

N.m.r. ($CDCl_3$)

δ 3.87	p.p.m.	s	3H	$-OCH_3$
6.68		d of d	2H	H on C-7, C-9
				$J_{9,10}$ = 12 Hz,
				$J_{7,9}$ = 3Hz
6.9-7.9		m	10H	aromatic H,
				H on C-6, C-10

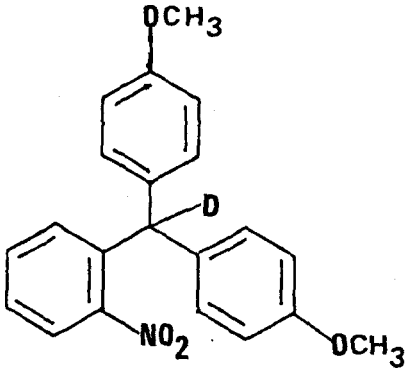
Attempted preparation and decomposition of α-(2-Azidophenyl)-α'-(4-methoxyphenyl)-α"-deuterio-4-methoxytoluene 97



97

The experiments described in this section were performed on samples of the amino 132 or nitro 85 precursor to azide 74. The preparation of these compounds is described above.

Preparation of α-(2-Nitrophenyl)-α-(4-methoxyphenyl)-α-deuterio-4-methoxytoluene 133

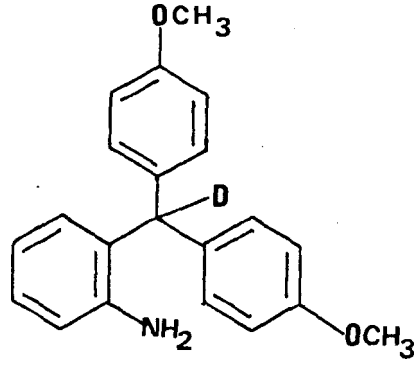


133

Sodium hydride (50% in oil, 10 g) was dissolved in a mixture of purified dimethylsulphoxide (60 ml) and freshly distilled tetrahydrofuran (300 ml). The solution was maintained at 55° for 1 hour

with stirring, after which time a solution of the nitro-compound 85 (11.0 g) in tetrahydrofuran (75 ml) was added dropwise and stirring was continued for 15 minutes. To this mixture D_2O (3 ml, excess) was added via a syringe and septum and stirring was continued for a further 20 minutes. Evaporation of the solvent yielded an oil (contaminated with DMSO) which was taken up in dichloromethane (200 ml) and dried ($MgSO_4$). Filtration followed by removal of the solvent yielded an oil which was chromatographed on alumina (100 g, activity IV) and eluted with benzene. The early fractions contained DMSO; 4.8 g (44%) of the deuterated nitro-compound 133 were collected. The n.mr. spectrum confirmed that the exchange had taken place as the methine proton signal at δ 6.18 p.p.m. was absent.

Attempted reduction of the deuterio-nitro-compound 133 to the deuterio-amine 134



134

The reduction was attempted via the alcoholic hydrazine hydrate method (Method B above, page 90). Examination of the n.m.r. spectrum of the product revealed that back exchange to hydrogen had occurred.

Attempted formation of the deuterio-amine 134 from the proton-amine 132

A solution of freshly distilled di-isopropylamine (1.9 ml) in ether (4 ml) and tetrahydrofuran (6 ml) was maintained at 0°C in an atmosphere of nitrogen. To this stirred mixture was added a solution of n-butyllithium (8.8 ml, 15% in hexane) in ether (5 ml) and tetrahydrofuran (10 ml) via a syringe and septum. After stirring at 0°C for 2 hours the mixture was transferred under nitrogen to a dropping funnel and was added dropwise with stirring to a solution of the amine 132 (3 g) in ether (20 ml) and tetrahydrofuran (30 ml). Stirring was continued at 0° for 30 minutes and then for 10 minutes at room temperature. D_2O (1 ml, excess) was added dropwise via a syringe and septum and stirring continued for a further 40 minutes at room temperature. Filtration, followed by evaporation, of the solvent yielded a brown oil. Examination of the n.m.r. spectrum of this compound revealed that 80-90% of deuterium exchange had taken place.

The amine was also successfully deuterated (80-90%) using the sodium hydride / dimethylsulphoxide method described above for the nitro-compound 85. A further complication in this case was a trace of dimethylsulphoxide which could not be removed by pumping. This was eventually overcome by stirring a solution of the compound in dry benzene overnight in the presence of silica gel in an atmosphere of dry nitrogen.

An attempt was made to diazotise this amine 134 in the normal manner as described above (page 92). The n.m.r. spectrum of the azide was examined after purification by column chromatography and a complete reversion to the proton species had taken place. The two most likely causes were thought to be the mineral acid (H_2SO_4) used in

the diazotisation and the alumina of the column which had been deactivated with H_2O.

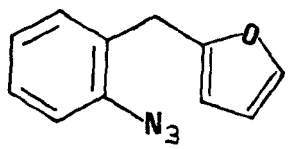
A second sample of the deuterio-amine 134 was diazotised by the same method except that D_2SO_4 and D_2O were used in place of H_2SO_4 and H_2O, including deactivation of the alumina by D_2O. Only the proton species of the azide was recovered; the sample must have been contaminated either by exposure to the air or by an unknown impurity in one of the solvents.

PART III

PART III

EXPERIMENTAL

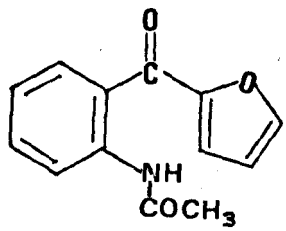
Attempted preparation of 2-(2-Azidobenzyl)furan 107



107

(a) Grignard route

2-Iodofuran was prepared from furan via the 2-mercurichloro derivative by the method of Gilman and Wright.[77] The Grignard reagent was prepared from the iodofuran in the normal way and added to a cooled solution of 2-methyl-3,1-benzoxazin-4-one ("acetanthranil") in equal proportions of toluene and ether. On completion of the addition, stirring was continued for 2 hours at 0°C and then for 4 hours at room temperature. The mixture was hydrolysed with a saturated solution of ammonium chloride in ammonia (5 g,0.88) and the organic material was extracted with ether. Evaporation of the ether yielded a dark oil which became resinous on standing. The oil gave a poorly resolved n.m.r. spectrum which suggested that some of the desired ketone 109 may be present.



109

The oil was refluxed with an aqueous 10% solution of sodium hydroxide for 6 hours in an attempt to prepare the amine. Extraction with ether followed by column chromatography failed to yield any of the desired product. Many products were found to be present and it was suspected that decomposition was occurring on the alumina.

(b) Friedel-Crafts route

Table XV shows the substrates, catalysts, and products for the various experiments.

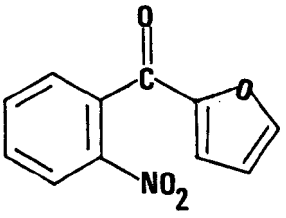
TABLE XV

Substrates		Catalyst	Product
furan	o-nitrobenzoyl chloride	$TiCl_4$ [78]	o-nitrobenzoic acid
"	"	$SnCl_4$	"
"	"	I_2 [99]	starting material
2-methylfuran	o-nitrobenzoic-anhydride	H_3PO_4 [160]	"
furan	"	$BF_3:Et_2O$	"

A typical procedure is shown by the attempted reaction between o-nitrobenzoyl chloride and furan with $TiCl_4$ as the catalyst.

A solution of furan (22.6 g) in carbon disulphide (140 ml) was vigorously stirred with a Hershberg stirrer and maintained at 0°C. To this was added dropwise over 2 hours a mixture containing o-nitrobenzoyl chloride (61.8 g) and $TiCl_4$ (80 g) in carbon disulphide (200 ml). On commencement of the addition, the liquor in the flask

became dark, and by the completion of the addition, the contents of the flask were black and tarry. The ice-bath was removed and the mixture refluxed for 1 hour, allowed to cool, and then poured into ice water. The tarry material was filtered off and continuously extracted with carbon tetrachloride. Evaporation of the carbon tetrachloride yielded an oil which was chromatographed on alumina to give a small quantity of material with an n.m.r. spectrum similar to that expected for the ketone 110.



110

The oil could not be purified any further and was not characterised due to the extremely low yield. Ether extraction of the liquor from the filtration gave a brown oil which was not identified.

(c) Via 2-furyllithium

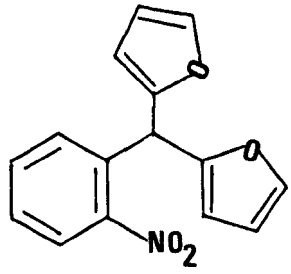
The attempted reaction between o-bromobenzaldehyde and 2-furyllithium[101] illustrates the typical procedure.

A solution of furan (3.4 g) in dry ether (20 ml) was added to a solution of n-butyllithium (34 ml, 15% w/w in hexane) in dry ether (50 ml) maintained at -20°C. The mixture was allowed to warm to room temperature and then refluxed for 4 hours. After cooling to -20°, o-bromobenzaldehyde (9.25 g) in dry ether (30 ml) was added dropwise with stirring. When the addition was complete, the mixture was refluxed for 6 hours, during which time the solution became darker in colour. The contents of the flask were then poured onto crushed

ice, the organic layer was separated, dried ($MgSO_4$), and evaporated to leave a brown oil (9 g). T.l.c. of this oil in benzene revealed the presence of at least three components. A sample was chromatographed on a column of alumina (activity IV) and a yellow band was eluted with carbon tetrachloride. This was shown by t.l.c. to be a mixture and was put onto preparative plates and eluted with benzene; five bands were found to have separated but none was in sufficient quantity to permit identification. Other bands eluted from the alumina column with benzene were found to contain mixtures of products. Further attempts at separation were made using alumina (activity III), and silica columns, and both yielded complex mixtures. This indicates the decomposition of the original products on both alumina and silica. No products or starting material were identified in this experiment.

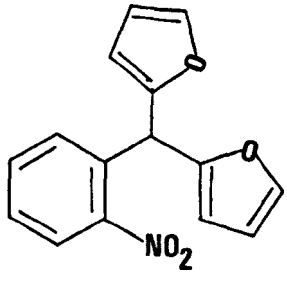
Similar procedures were tried using o-nitrobenzylbromide and o-bromobenzylbromide leading only to the recovery of starting material. Variations on this procedure included preparation of furyllithium from phenyllithium[102] and inverse addition of the furyllithium reagent to the aromatic substrate, but the outcome of the reaction was not changed.

Preparation of α, α-Di-(2-furyl)-2-nitrotoluene 111



111

A solution of o-nitrobenzaldehyde (10 g) and furan (15.5 g) in glacial acetic acid (40 ml) was cooled to 0°C. To this was added dropwise with stirring a solution of concentrated sulphuric acid (4 ml) in glacial acetic acid (20 ml). The contents of the flask became very dark and immobile at the end of this addition. The flask was stoppered and left in the refrigerator for 2-3 days at 0-5°C. This was followed by pouring onto crushed ice followed by extraction using chloroform (3 x 200 ml). After drying ($MgSO_4$), the chloroform was removed and the resulting oil was absorbed onto alumina (30 g) and chromatographed on a column of alumina (200 g, Grade IV) with 5% benzene in petrol (b.p. 40-60) as eluant. The first band off the column was identified as the required α,α-di-(2-furyl)-2-nitrotoluene 110. The best yield of 111 obtained was 33%.



111

B.p. 120°/0.7 mm Hg

Analysis

Found	C, 67.18;	H, 4.35;	N, 4.90 %
$C_{15}H_{11}NO_4$ requires	C, 66.91;	H, 4.09;	N, 5.20 %

N.m.r. ($CDCl_3$)

δ 6.2	p.p.m.	m	5H	4H on C-3, C-4 furan methine H
7.2-8.1		m	6H	4H aromatic 2H on C-5 furan

I.r. (mull)

ν_{max} 3110, 1607 cm^{-1}

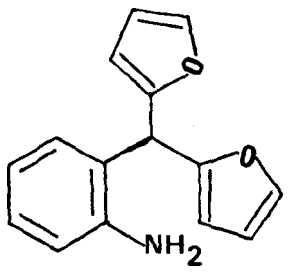
U.v. (95% ethanol)

λ_{max} 260 (sh) n.m. $\log_{10}\varepsilon$ 2.69

Mass spectrum

m/e 269 (M^+) (22%), 253 (74%), 236 (36%), 208 (21%), 196 (27%), 194 (30%), 167 (29%), 166 (34%), 165 (100%), 130 (36%)

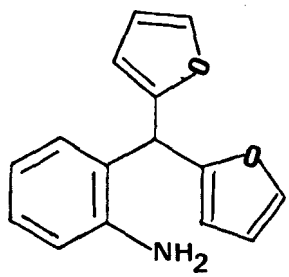
<u>α,α-Di-(2-furyl)-2-aminotoluene 112</u>



<u>112</u>

A solution of the nitro-compound <u>111</u> (2.0 g) in ethanol (95%, 100 ml) containing 10% palladium-on-charcoal (0.25 g) in suspension was hydrogenated at atmospheric temperature and pressure for one hour during which approximately 500 ml of hydrogen had been absorbed. Evaporation of the filtered solution gave an oil which was absorbed onto alumina (10 g, Grade IV) and chromatographed on a

column of alumina (100 g, Grade IV) with petrol (b.p. 40-60°) as the eluent. The first band to come off was identified as α,α-di-(2-furyl)-2-aminotoluene 112 1.3 g (70%). The oil would not crystallise and was found to resinify on standing.



112

B.p. 140°/0.3 mm Hg

Analysis

	Found	C, 75.41;	H, 5.56; N, 5.58 %
$C_{15}H_{13}NO_2$	requires	C, 75.31;	H, 5.43; N, 5.85 %

N.m.r. ($CDCl_3$)

δ 3.47	p.p.m.	s	2H	$-NH_2$ (exchange D_2O)
5.50		s	1H	methine H
6.17		m	4H	H on C-3, C-4 furan
6.47-7.4		m	4H	aromatic
			2H	H on C-5 furan

I.r. (film)

ν_{max} 3400 (d), 1625, 1495 cm^{-1}

U.v. (95% ethanol)

λ_{max} 290 n.m. $\log_{10}\varepsilon$ 3.53
226(sh) 4.36

Mass spectrum

m/e 241 (48%), 240 (78%), 239 (M^+) (100%), 197 (30%), 196 (29%), 168 (18%), 147 (28%), 144 (18%)

Attempted diazotisation of the amine 112

An attempt was made to diazotise the amine 112 by the same procedure as used for the aminotriphenylmethanes (Part II). This method requires 4N sulphuric acid, and upon the addition of the diazotisation mixture the contents of the flask became increasingly black and tarry, and no material was recovered from the reaction.

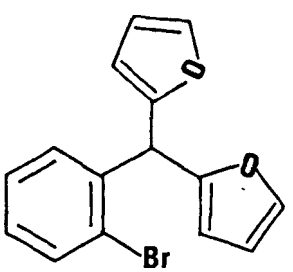
Attempted preparation of the diazonium fluoborate of the amine 112

The amine 112 (2 g) was dissolved in fluoboric acid (12 ml); the mixture turned green and some tar formed. The liquor was filtered off and cooled; to this solution was added dropwise with stirring a cold solution of sodium nitrite (0.56 g) in water (1.5 ml). This was followed by the addition of a little dry ice, which has been found empirically to improve the yield of the reaction. By this stage the diazonium fluoborate should have been precipitated if it had been

formed, but filtration did not yield any product. It is felt that the original contact between fluoboric acid and the amine caused ring-opening of the furan rings in the latter as evidenced by black tar formation. This reaction was repeated with dioxan (12 ml) as a solvent. The final reaction mixture was considerably more mobile than in the former case but it was still very black and nothing was recovered from the mixture.

Preparation of α, α -Di-(2-furyl)-2-bromotoluene 115

o-Bromobenzaldehyde and furan were condensed together using concentrated sulphuric acid in glacial acetic acid in exactly the same way as described for o-nitrobenzaldehyde and furan above. The product 115 was obtained in 25% yield as an oil by percolating the crude reaction mixture through a column of alumina (activity IV, 200 g, 20 cm) using 5% benzene in petrol (b.p. 40-60°) as solvent.



115

Analysis

Found C, 59.42; H, 3.63 %

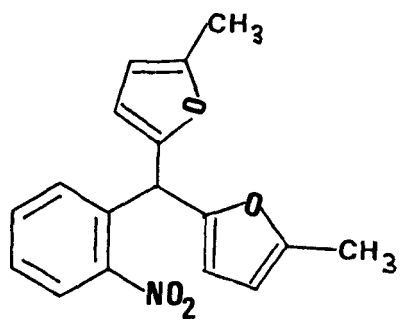
$C_{15}H_{11}O_2Br$ requires C, 59.41; H, 3.63 %

N.m.r. ($CDCl_3$)

δ 6.1	p.p.m.	m	1H	methine H
			4H	furan C-3, C-4
6.8-7.6		m	4H	aromatic H
			2H	furan C-5

Several attempts were made to prepare the Grignard reagent from 115 using both tetrahydrofuran and ether as solvents, but all were unsuccessful. Approximately 90% of the magnesium was recovered unused from the reaction mixtures.

Preparation of α , α -Di-(5-methyl-2-furyl)-2-nitrotoluene 113



113

This compound was obtained in 50% yield by the reaction between o-nitrobenzaldehyde and 2-methylfuran in the presence of concentrated sulphuric/glacial acetic acids as described above.

M.p. 80°C (petrol, b.p. 40-60°)

Analysis

Found	C, 68.91;	H, 5.11;	N, 4.78 %
$C_{17}H_{15}NO_4$ requires	C, 68.68;	H, 5.05;	N, 4.71 %

N.m.r. ($CDCl_3$)

δ 2.16	p.p.m.	s	6H	methyl H
5.86		s	4H	furan H
6.2		s	1H	methine H
7.1-7.9		m	4H	aromatic H

I.r. (mull)

ν_{max} 1602, 1560 cm^{-1}

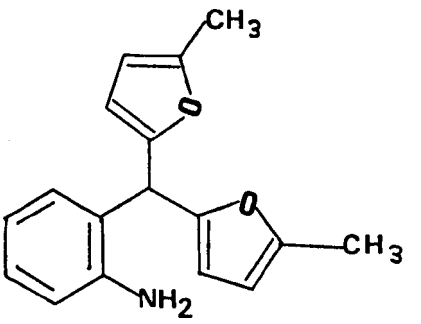
U.v. (95% ethanol)

λ_{max} 220 n.m. $\log_{10}\varepsilon$ = 4.39

Mass spectrum

m/e 297 (M^+) (50%), 280 (100%), 263 (8%), 250 (10%), 238 (23%), 237 (15%), 236 (15%), 235 (56%), 222 (15%), 210 (11%), 209 (11%), 200 (15%), 196 (8%), 194 (8%), 178 (12.9%)

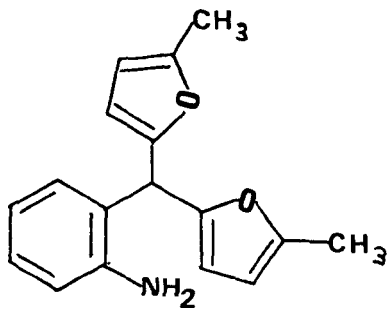
<u>α , α -Di-(5-methyl-2-furyl)-2-aminotoluene 114</u>



<u>114</u>

The nitro-compound <u>113</u> was reduced in 95% ethanol solution with hydrogen gas at atmospheric temperature and pressure with 10%

palladium-on-charcoal as catalyst according to the procedure described above. Following purification by column chromatography on alumina with 10% benzene in petrol (b.p. 40-60°) as eluant, the amine 114 was obtained in 53% yield. The alternative method of using hydrazine hydrate was also found to be successful and gave a higher yield (80%). In both cases, the amine 114 was obtained as an oil which would not crystallise. A sufficiently pure sample for elemental analysis was obtained by purification by column chromatography on alumina.



114

Analysis

	Found	C, 76.48;	H, 6.58; N, 5.10 %
$C_{17}H_{17}NO_2$	requires	C, 76.40;	H, 6.37; N, 5.24 %

N.m.r. ($CDCl_3$)

δ 2.17	p.p.m.	s	6H	methyl H
3.52		s	2H	amine H
5.35		s	1H	methine H
5.85		s	4H	furan H
6.5-7.25		m	4H	aromatic H

I.r. (liquid film)

ν_{max} 3440, 3380, and 1625 cm^{-1}

U.v. (95% EtOH)

λ_{max} 225 n.m. $\log_{10}\varepsilon$ = 4.57

287 n.m. 3.28

Mass spectrum

m/e 267 (M^+) (100%), 266 (60%), 224 (26%), 210 (52%), 185 (17%), 182 (12%), 180 (16%), 170 (12%), 160 (10%), 145 (18%), 131 (12%), 117 (20%), 102 (21%), 91 (26%)

Attempted diazotisation of α,α-Di-(5-methyl-2-furyl)-2-amino-toluene 114

The normal diazotisation procedure was followed but the reaction mixture became dark and tarry as in the case of the unsubstituted furan derivative described above. No material was recovered or identified from this reaction.

A further attempt at diazotisation was made using a buffered azide solution. A stirred solution of the amine 114 (10 g) in a mixture of concentrated hydrochloric acid (10 ml), water (10 ml), and purified dioxan (20 ml) at 0-5°C was treated dropwise with a solution of sodium nitrite (2.8 g) in water (40 ml). The reaction flask was found to contain several grams of an orange-coloured precipitate. The mixture was filtered through a glass wool filter into a dropping funnel and the liquor was added dropwise to a stirred solution of sodium azide (2.8 g) and sodium acetate (28 g) in water (200 ml) at 0-5°C. After stirring at 0-5° for a further 30

minutes the mixture was allowed to warm to room temperature and extracted with ether (3 x 100 ml); the ether extracts were dried ($MgSO_4$), and the solvents evaporated to leave 3 grams of a brown solid. Examination of the n.m.r. and infrared spectra of this solid revealed that it was not the azide and it could not be identified.

Deoxygenation of the nitro-compounds 111 and 113

The procedure is described for α, α -di-(5-methyl-2-furyl)-2-nitrotoluene 113.

A solution of triethylphosphite (T.E.P.) (35 ml) in cumene (50 ml) was added dropwise to a stirred solution of the nitro-compound 113 (15 g) in cumene (350 ml). The cumene and T.E.P. were suitably purified, the apparatus was dried, and the reaction was performed under an atmosphere of nitrogen. The mixture was refluxed and the progress of the starting material was followed by g.l.c. and t.l.c. After 46 hours there was no trace of the nitro-compound and the reflux was stopped and the solvent evaporated. The residual brown oil (21 g) was still contaminated by solvent and was absorbed onto alumina (Grade IV, 60 g) and put onto an alumina column (Grade IV, 400 g, 3.5 cm diameter). Elution with petrol (b.p. 40-60°) gave initially some cumene followed by 2.2 grams of material from yellow/brown bands. T.l.c. (benzene) revealed that they contained many compounds; an attempt was made at separation by preparative layer chromatography but with no success as decomposition seemed to be taking place.

These mixtures were followed off the column by triethyl-phosphate and some T.E.P. The eluting solvent was gradually changed

to 50% benzene/petrol and 5 grams of a brown solid were obtained. The identification of this product is discussed immediately below.

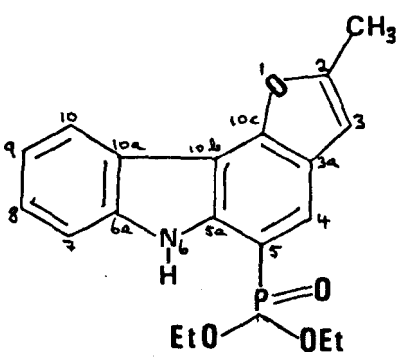
Elution of the column was continued with 100% benzene followed by 50% ethyl acetate/benzene. The liquors coming off became progressively darker in colour and were shown by t.l.c. to be comprised of a large number of compounds. Approximately 10 grams of dark oil were obtained; satisfactory separation could not be achieved by preparative layer chromatography or by using a silica column (100-200 mesh, 2.5 cm diameter). The mixture was analysed by linked gas chromatography - mass spectrometry and the following values for the molecular ion were obtained:

300 293 252 291 385 259 432

(Starting material M^+ 297)

None of these products was identified.

The brown solid was found to have a value for the molecular ion of 357 and examination of its H^1, C^{13}, and P^{31} n.m.r. spectra showed it to be diethyl (2-methylfuro[3,2-c]-carbazol-5-yl) phosphonate 116.



116

M.p. 154.5° (CCl_4)

Analysis

Found	C, 63.76;	H, 5.61;	N, 3.97 %
$C_{19}H_{20}NO_4P$ requires	C, 63.86;	H, 5.60;	N, 3.92 %

^1H n.m.r. spectrum ($CDCl_3$)

δ 1.3	p.p.m.	t	6H	phosphonate methyl H
2.55		s	3H	furyl methyl H
4.1		q	4H	phosphonate ethyl H
6.42		s	1H	-furyl H
7.1-8.8		m	5H	aromatic H
10.1		s	1H	amine H

^{13}C $[^1H]$ n.m.r. ($CHCl_3$)

(For assignation of signals, see Discussion page 63)

Assigned signals:

δ 13.9	p.p.m.	methyl carbon on C-2
16.3		d (J $\approx$ 2 Hz) methyl carbons on P
62.3		d (J $\approx$ 2 Hz) methylene carbons on P
77.2		t chloroform impurity
102.9		C-3
108.4		d (J $\approx$ 4 Hz) C-4
111.1		C-7
120.0		C-8
121.0		C-9
122.5		C-10a
126.0		C-10

139.2	C-6a
154.3	C-2
154.7	C-10c

Unassigned signals

δ 99.4 p.p.m.
107.0
121.2
121.6
121.9
140.3
140.7
152.2
152.3

^{31}P n.m.r. ($CDCl_3$)

-21 p.p.m. from H_3PO_4 broad singlet

I.r.

ν_{max} 3261, 1225, 1145, 1155 cm^{-1}

U.v. (95% EtOH)

λ_{max}	250 n.m.	$\log_{10}\varepsilon$	4.86
	275		4.40
	292		4.19
	301		4.42
	353		3.88

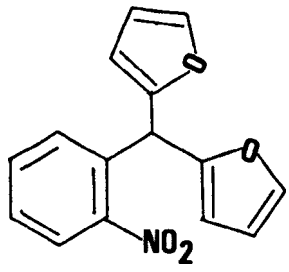
Mass spectrum

m/e 358 (23%), 357 (M^+) (100%), 330 (40%), 329 (14%), 302 (4%), 301 (16%), 284 (16%), 283 (61%), 282 (14%), 236 (10%), 221 (13%), 220 (16%), 219 (6%), 192 (4%), 191 (10%), 190 (10%), 165 (6%), 164 (6%), 163 (6%), 151 (10%), 149 (17%), 141 (8%), 68 (59%), 67 (9%)

Report of a biological assay performed by Allen and Hanburys Ltd.

"(The compound) was found to have minimum inhibitory concentration of > 50 μg/ml when tested against Staph. aureus CN 491, E. coli AH, Candida albicans 1549 and Mycoplasma galliseptum X95 in the presence of serum."

Deoxygenation of α,α-Di-(2-furyl)-2-nitrotoluene 111



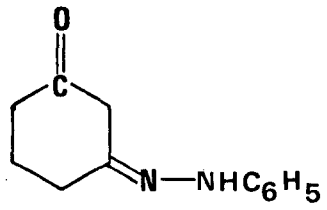
111

This compound 111 was deoxygenated using T.E.P. under conditions identical to those described above for the deoxygenation

of the methyl-substituted compound 113. After evaporation of the solvent, the crude reaction mixture was chromatographed on alumina (grade IV) with petrol (b.p. 40-60°) as the eluant. The early fractions contained traces of cumene and triethyl-phosphate. When the eluting solvent was gradually changed to 100% benzene, 2 g of a dark material were recovered from the column which were found by t.l.c. to be a mixture of four compounds. After work-up preparative layer chromatography in ethyl acetate, the developed plates showed seven orange/brown bands in the visible spectrum. These compounds were found to be relatively insoluble and their n.m.r. spectra contained only poorly resolved signals in the aromatic region. None of these compounds was identified.

Elution of the column was continued using increasing proportions of chloroform as the solvent. This failed to yield any further material, and the column was stripped using methanol to give 4 g of dark material, which, by t.l.c. was found to be a complex mixture. Attempts were made at purification by preparative layer chromatography, but they were unsuccessful. Furthermore, the mixture became progressively darker on standing and no compounds could be identified.

Preparation of 1,3-Cyclohexadione phenylhydrazone 124

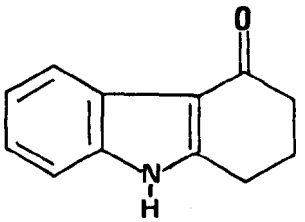


124

This was prepared after the method of Merling.[93] A solution

of phenylhydrazine (3 g) in aqueous ethanol (1:1, 10 ml) was added dropwise to a solution of 1,3-cyclohexadione (3 g) in water (15 ml) with stirring. Both solutions had been previously cooled to approximately 5°C prior to the addition. The resulting dark precipitate (2.7 g, 45%) was filtered off and stored in the refrigerator under nitrogen until required. Due to its unstable nature, this compound was not characterised, but was assumed to be the required hydrazone 124 and was used in this crude state.

Preparation of 1,2,3,4 - Tetrahydrocarbazol-4-one 125



125

The hydrazone 124 (2.7 g) was dissolved in 40% sulphuric acid(35 ml) and heated on a steam bath for 1.5 hours. The liquor was decanted from the tar which had formed, and was then slowly diluted with water (110 ml). The resultant grey precipitate was filtered off and recrystallised from ethanol to give the product 125 (1.2 g, 31%).

M.p. 223°C

Analysis

Found	C, 77.59;	H, 6.12;	N, 7.68 %
$C_{12}H_{11}NO$ requires	C, 77.84;	H, 5.96;	N, 7.57 %

N.m.r. spectrum (D.M.S.O. D_6)

δ	2.3 p.p.m.	m	4H	H on C-1, C-2
	2.95	m	2H	H on C-3
	7.0-8.0	m	4H	aromatic H
	11.83	s	1H	amine H

I.r. (mull)

ν_{max} 1610 cm^{-1}

U.v. (95% EtOH)

λ_{max}	213 n.m.	$\log_{10} \varepsilon$	4.44
	242		4.21
	266		4.12
	297		4.02

Mass spectrum

m/e 186 (16%), 185 (M^+) (100%), 158 (16%) 157 (97%), 156 (9%), 130 (9%), 129 (17%), 128 (16%), 103 (5%), 102 (14%), 101 (6%), 78 (14%), 77 (9%)

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