INTRAMOLECULAR NITRENE INSERTIONS INTO AROMATIC RINGS

A thesis submitted to the University of Keele in part fulfilment of the requirements for the Degree of Doctor of Philosophy

by

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S T A F F O R D S H I R E

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To my parents

The work in this thesis unless otherwise stated, was carried out by the author under the supervision of Dr. G. Jones.

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ABSTRACT

The synthesis and thermal decomposition of 2'-azidophenyl-(3-pyridyl)methane is described in Chapter One. Pertinent reviews of arylnitrene chemistry and the reactions of nitrenes with pyridine compounds are presented in the introduction.

Decomposition of 2'-azidophenyl-(3-pyridyl)methane and the isomeric 4-pyridyl compound led, in both cases, to polymeric products. A low yield of 9H-pyrrolo[1,2-a]indole was isolated in the thermal decomposition of the 3-pyridyl compound. The synthesis and decomposition of 3-(2-azidobenzyl)pyridine-1-oxide is also discussed and similarly led to extensive polymer formation.

A review of the known chemistry of the 1,3-diazepine ring system and its benzo-fused analogues is given in Chapter Two. Initial attempts to devise synthetic routes to these compounds are also discussed.

Chapter Three describes the synthesis of 2'-nitrophenyl-di-(4-t-butylthien-2-yl)methane and its deoxygenation by triethylphosphite. Two products were characterised from the reaction mixture, 9-(4-t-butylthien-2-yl)-3-t-butylthieno[3,2-b]quinoline and 2-t-butyl-9-(4-t-butylthien-2-yl)-3H-pyrrolo[1,2-a]indol-3-thione. The latter compound is the first example of this type of structure in such nitrene insertion reactions.

The successful synthesis and thermal decomposition of di- and tri-phenylmethane compounds bearing electron-withdrawing groups is described in Chapter Four. Products were isolated where the benzene ring had been expanded to form 10H-azepino[1,2-a]indoles.

These are the first examples of intramolecular nitrene insertion into a π-deficient benzene ring.

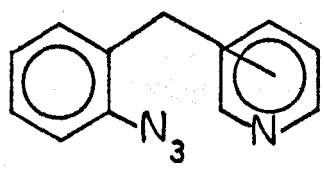
Chapter Five describes the reactivity of the diene system of 10H-azepino[1,2-a]indole towards thermal [4 + 2] cycloaddition and photolysis. The azepinoindole was unreactive towards the majority of dienophiles but formed an unstable [2 + 2] adduct with 4-phenyl-1,2,4-triazoline-3,5-dione. Irradiation of the azepinoindole in methanol solution gave the novel compound 9,10-dihydro-9-methoxy-6H-azepino[1,2-a]indole.

- o O o -

GENERAL INTRODUCTION

This thesis is a continuation of the study of intramolecular nitrene insertions into aromatic rings.[1-11]

At the beginning of this work the chemistry of systems where the "receiving" ring is π -deficient had not been elucidated. Chapter one describes the synthesis and thermal decomposition of compounds bearing a suitably placed pyridine ring (1). A review of relevant nitrene chemistry is also presented, with emphasis on the more recent literature.



(1)

During the course of this work the isolation of 9H-pyrrolo[1,2-a]indole, assumed to have been derived from an intermediate 11H-diazepinoindole, was noted. This result prompted us to investigate synthetic routes to the little known 1,3-diazepine ring system. Chapter two describes our efforts in this direction.

Further investigations of nitrene insertions into thiophene rings and their mechanistic implications are presented in Chapter three.

As an extension of some earlier work,[12] the insertion of nitrenes into benzene rings bearing electron-withdrawing substituents is described in Chapter four.

Finally the photoaddition and cycloaddition reactions of 10H-azepino[1,2-a]indole are reported in Chapter five.

C H A P T E R O N E

INTRAMOLECULAR NITRENE INSERTIONS INTO PYRIDINE RINGS

INTRODUCTION

Part A : NITRENES

Nitrenes are neutral univalent nitrogen intermediates possessing six electrons, two in a bonding orbital, two accommodated as a lone pair and the remaining pair in a non-bonding orbital. These highly reactive species can exist in a singlet (spin paired, electrophilic character) or triplet (unpaired spins, diradical character) configuration.

The existence of nitrenes as short-lived intermediates in chemical reactions was first suggested by Tiemann[13] in 1891 to explain the Lossen rearrangement and by Stieglitz[14] in work connected with the Curtius rearrangement. Since that time the study of the chemical and physical properties of nitrenes has expanded enormously as evidenced by the publication of monographs[15,16] and several recent reviews.[17-23]

This thesis is mainly concerned with aryl nitrenes which are conveniently generated by thermolysis or photolysis of the corresponding azides, or by deoxygenation of nitro or nitroso compounds with tervalent phosphorus reagents.[24] Consequently this part of the review will present the characteristic reactions of aryl nitrenes together with some of the more interesting recent developments in the field.

Aryl nitrenes have triplet ground states or a triplet lying within a few cm^{-1} of the ground state.[25] It has been suggested[26] that aryl nitrenes are able to delocalise one of the unpaired electrons into the ring thus reducing spin density on

nitrogen. However a recent[27] study of <u>para</u>-substituted phenylnitrenes by electron spin resonance and I.N.D.O. calculations concludes that this effect is negligible.

Thermolysis of azides produces a singlet nitrene due to spin conservation.[28] The rate of reaction (k_1) of this species with substrate molecules will be influenced by the nucleophilicity of the substrate and the rate at which it undergoes intersystem crossing (I.S.C.) to the triplet state (k_2). Therefore the ultimate product distribution will reflect this competition between singlet and triplet states and it will be shown here and in subsequent chapters that the reaction can be manipulated to give products derived from a particular spin state.

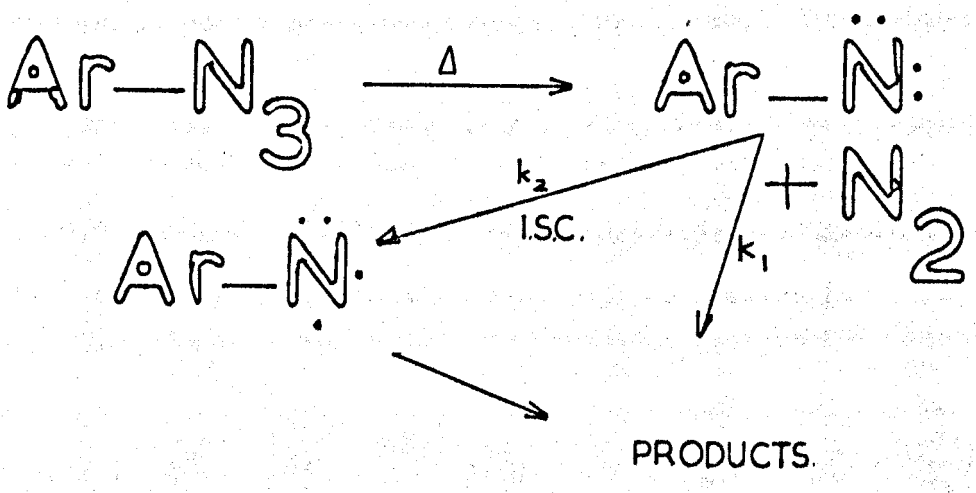
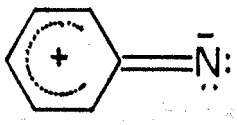


Figure 1.1

Aromatic nitrenes are less reactive as a whole than alkyl or carbonyl nitrenes. Reiser and Leyshon[29] have attributed this to a build up of negative charge on nitrogen to produce resonance structures such as (2).



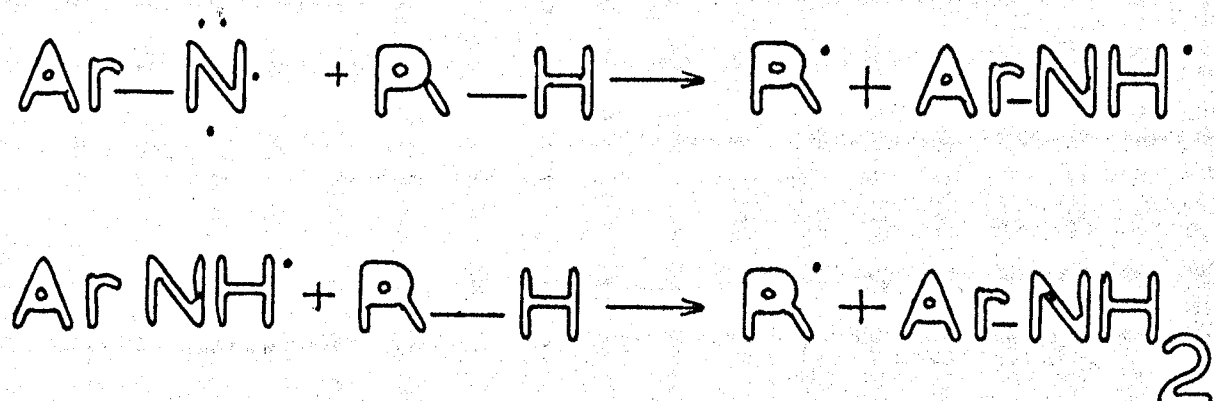
(2)

This type of interaction is absent in carbonyl and other nitrenes.

A number of reactions, typical of aryl nitrenes and relevant to this thesis, are discussed below.

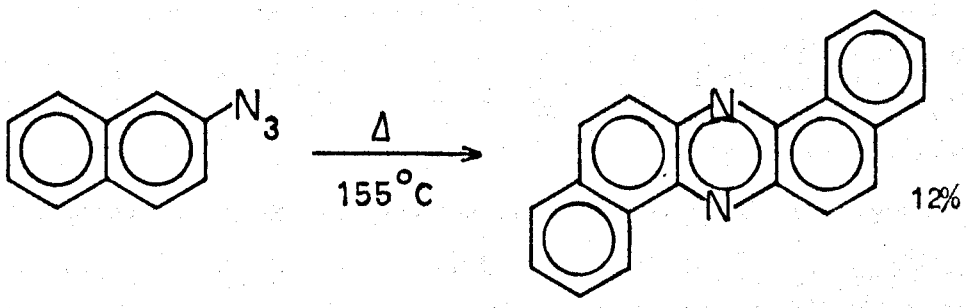
1. Hydrogen abstraction

Abstraction of hydrogen to form primary amines is perhaps the most general reaction when aryl nitrenes are produced in solution. There is evidence[30] to suggest that the hydrogen atoms are abstracted one at a time by the triplet nitrene. Some workers[31] have isolated dehydrogenatively coupled solvent products to support this (although generally not enough to account for all of the amine formed).

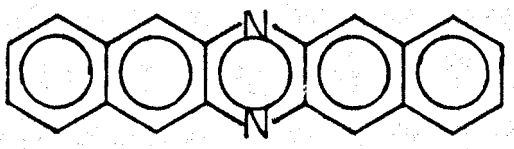


Scheme 1.1

Recently Suschitzky and co-workers have reported the isolation of phenazines[32] from the decomposition of aromatic azides in bromobenzene. Phenazines were formed in low yields together with amines and azo compounds. They interpret the results as proceeding through a triplet nitrene, followed by hydrogen abstraction and subsequent dimerisation of the so formed anilino-radical. It is interesting to note that the formation of phenazines is regiospecific, none of the linear product (3) being isolated.



+ azo-compound (20%) +
amine (10%)



(3)

Scheme 1.2

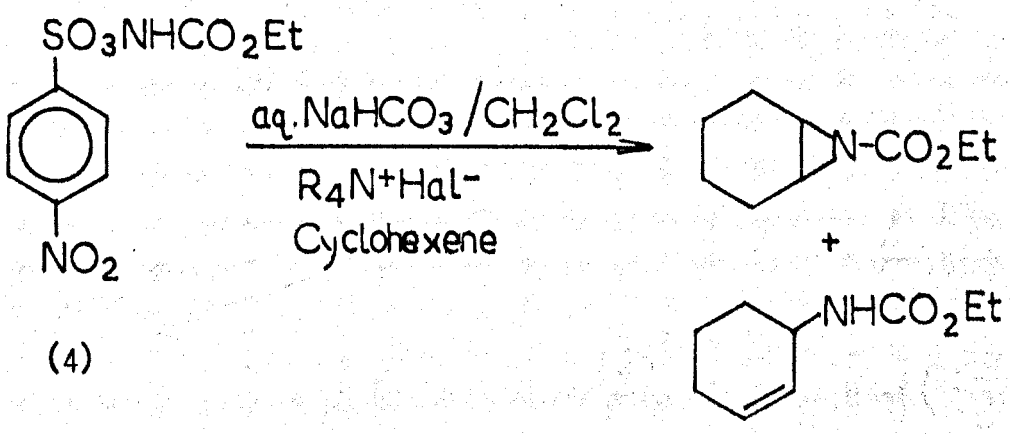
2. Addition to unsaturated C-C bonds

Nitrenes can be trapped with alkenes to give aziridines, however it is doubtful[24] whether a nitrene is actually an intermediate, at least not with polar alkenes. The difficulty arises due to the fact that azides, the most common precursors, can also react with alkenes to

form triazolines and subsequently evolve nitrogen with the formation of an aziridine. The difficulty is usually overcome if the same aziridines, in the same proportions, are obtained from two different nitrene precursors.

The technique of phase-transfer catalysis, successful in the carbene field in recent years,[33] has been applied to the generation of nitrenes.

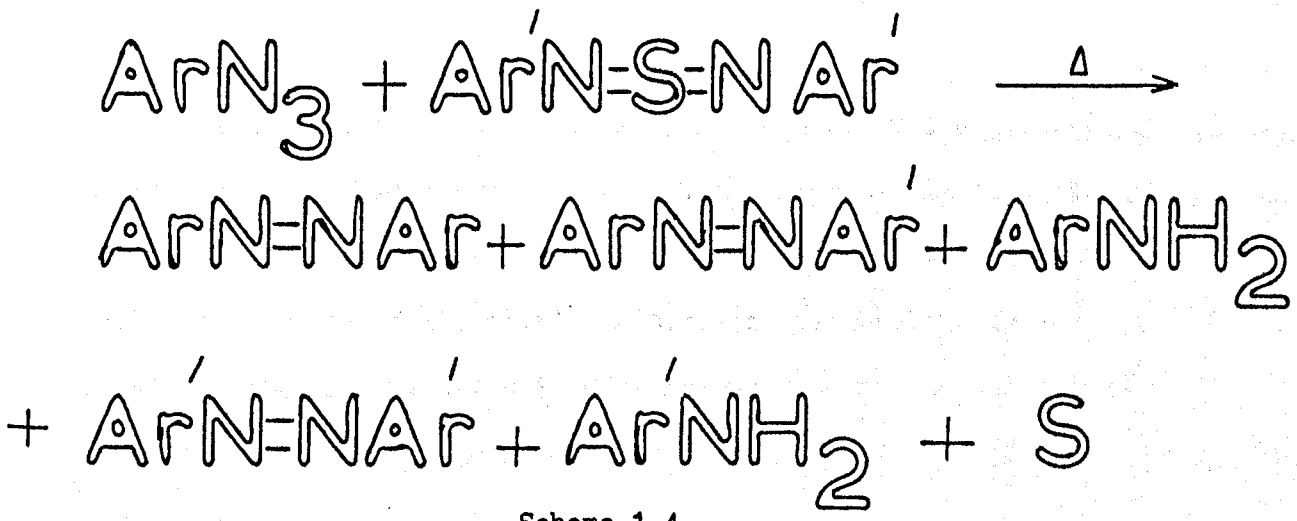
Seno[34] et al. have generated ethoxycarbonylnitrene in an aqueous/dichloromethane medium from ethyl p-nitrobenzenesulphonoxy-carbamate (4) and studied its reactions with cyclohexene and cis and trans 4-methyl-2-pentenes. Product yields and ratios were similar to those obtained under homogeneous conditions.[35] Curiously quarternary iodide salts were found to give higher yields of singlet products than the corresponding chlorides or bromides.



(4)

Scheme 1.3

Cipollini et al.[36] have recently reacted aryl nitrenes with cumulated double bond systems and isolated a mixture of azo compounds. The products were assumed to have arisen from a triplet nitrene with extrusion of sulphur.



Scheme 1.4

New and selective imidoylnitrenes have been reported recently[37] by Lwowski and Subba Rao. The nitrenes (5) and (6) were found to give aziridines stereospecifically in high yields with no trace of C-H insertion products. This is in marked contrast to ethoxycarbonyl nitrene which gives a 56% yield of the aziridine together with 15% of a mixture of three C-H insertion products.[38] Additionally nitrene (5) gave a 60% yield of azepine with benzene, while (6) did not react.

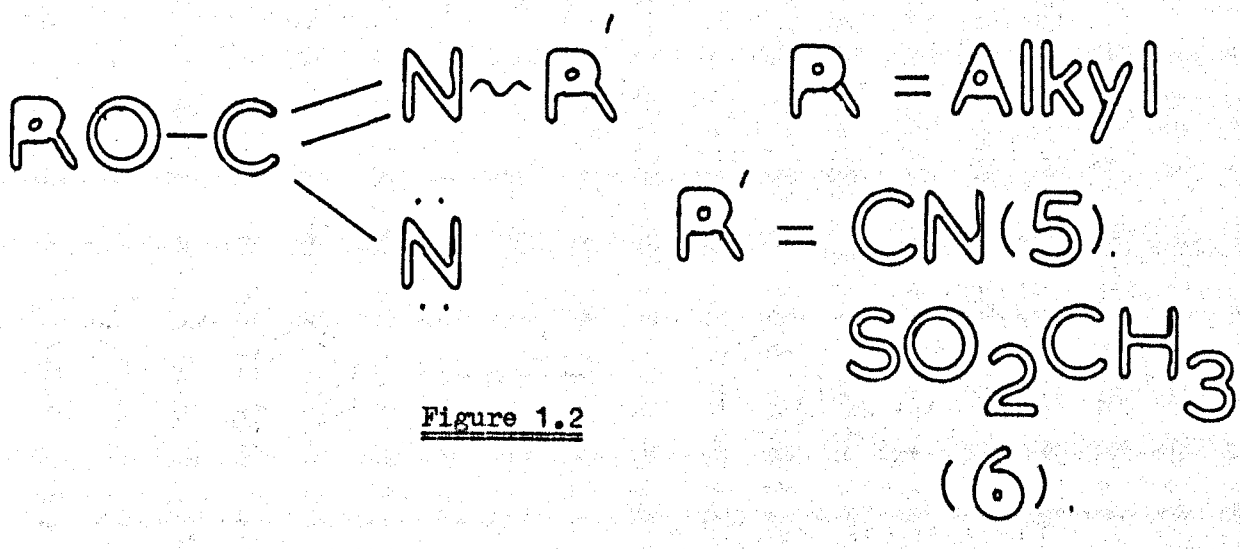
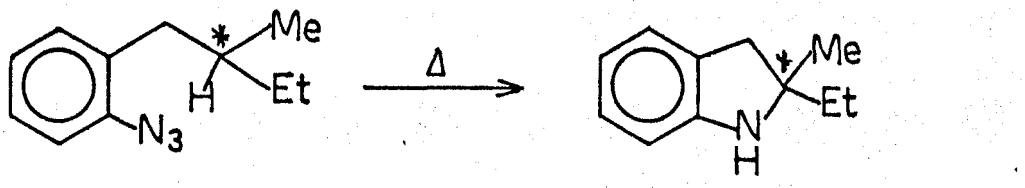


Figure 1.2

3. Insertion into a C-H bond

Intramolecular insertions into C-H bonds are common

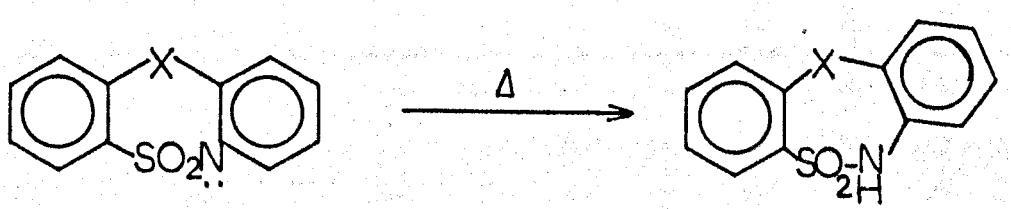
processes in aryl nitrene chemistry and can occur via a singlet or triplet state. Some elegant work[39] with different nitrenes confirms the belief that singlet nitrenes react in a stereospecific manner, while in the case of the triplet nitrene stereospecificity is usually lost. The reaction is most favourable when an unstrained ring is produced.[30]



retention observed

Scheme 1.5

Insertion reactions usually result in the formation of five-or occasionally six-membered rings.[15] Recently Abramovitch[40] has reported the formation of a seven-membered ring by intramolecular C-H insertion, albeit in low yield. Only in cases when the group X is oxygen or carbonyl does the reaction deliver a seven-membered ring.

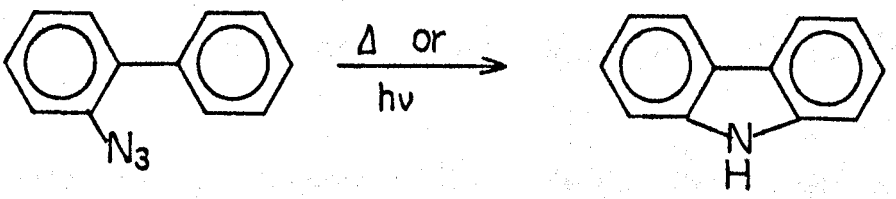


X = O, S, SO_2, CO, $NCOCH_3$, 4,4'-Me_2

+ hydrogen abstraction and solvent insertion products

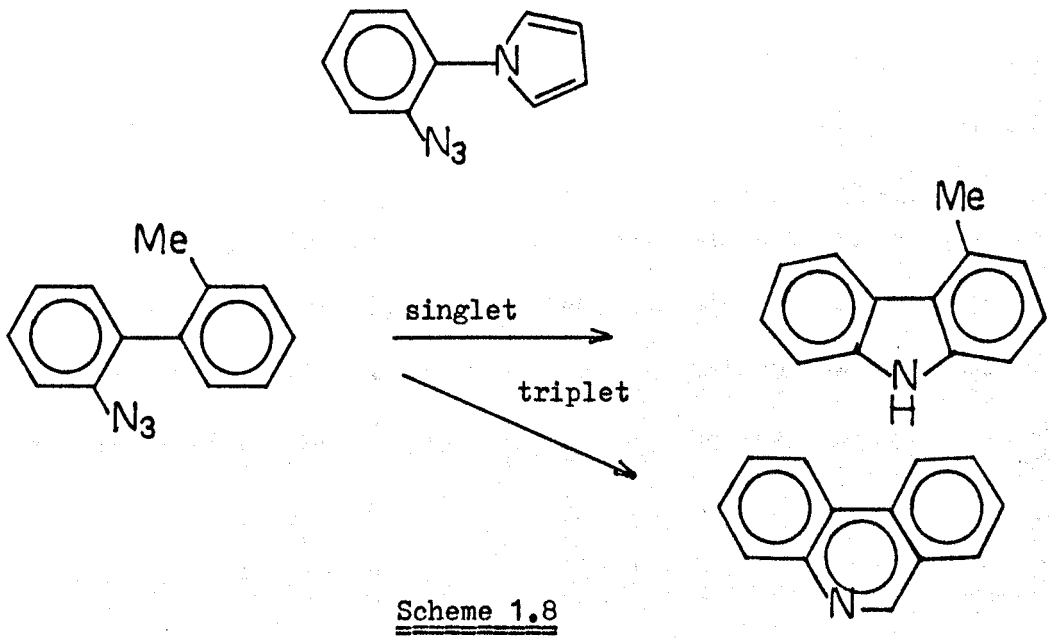
Scheme 1.6

One of the most synthetically useful insertion reactions is the formation of carbazoles from o-azidobiphenyls and numerous examples are known.[15] The reaction is insensitive to substituents (except for nitro and cyano groups which divert the incipient nitrene) and replacement of a phenyl ring by thiophene or pyridine (see part B) does not effect the cyclisation. Yields are often very high.



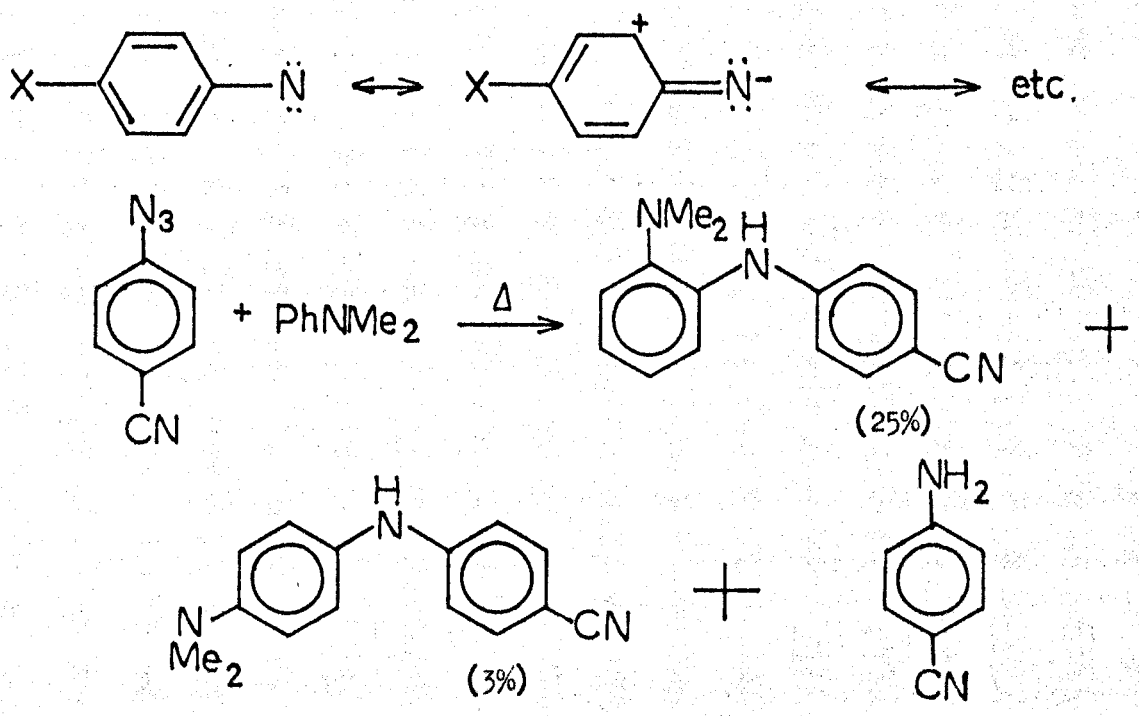
Scheme 1.7

The question of whether a singlet or triplet nitrene was involved in the cyclisation has been a subject of considerable controversy. Recent work by Meth-Cohn and co-workers[41] lends strong support to the view that this is a concerted reaction involving a singlet nitrene. Heterocyclic analogues, e.g. (7) were poor sources of carbazoles and 2-methyl-2'-nitrenobiphenyl gave carbazoles under singlet promoting conditions. Increasing amounts of phenanthridine were produced under triplet conditions by collisional deactivation with bromo compounds and sensitisation with acetophenone.



Scheme 1.8

In contrast to the ready intramolecular substitution by aryl nitrenes, the corresponding intermolecular reactions are relatively unknown. Abramovitch[42,43] has shown that reaction between an electrophilic aryl nitrene and a suitably activated substrate produces diphenylamines in low to moderate yield. This is in accord with the reduced contribution of structures such as (8) when X is a strongly electron withdrawing group.



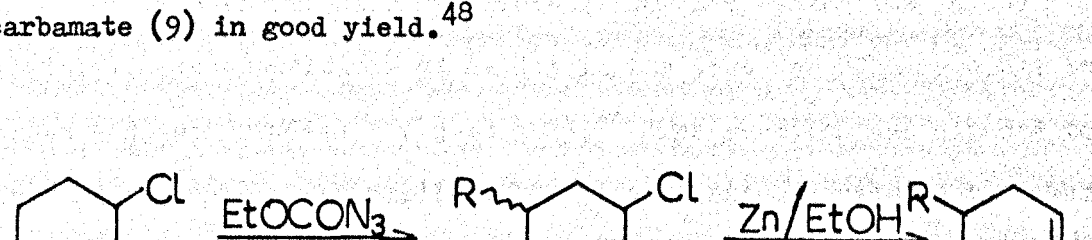
Scheme 1.9

4. Solvent effects

Solvent effects on the electronic state of nitrenes have been much studied recently. The effects of dichloromethane during thermal and photochemical decompositions of azides has received considerable attention.[44-49]

A careful study on the course of the decomposition of pivaloylazide with alkenes, in the presence of dichloromethane, led Lwowski[45] to postulate a stabilised, solvated singlet nitrene/dichloromethane complex. Hydrocarbons do not show this stabilising effect. The interaction is thought to arise via donation of the chlorine lone-pair electrons to the electrophilic singlet nitrene, in a similar manner to that proposed by Hoffmann and Gleiter.[50] The stabilised singlet nitrene yielded aziridines stereospecifically in high yields. Tardella and co-workers[47] have investigated the role of singlet stabilisation in insertion selectivities of bicyclo[4.n.o] alkanes and alkylcyclohexanes towards ethoxycarbonylnitrene. The insertion selectivity was lowered in the presence of dichloromethane and the results rationalised on the basis of a triplet nitrene prominence due to the greater bulk of the singlet complex. Similar conclusions were drawn with studies on adamantane.[49]

These observations have been put to synthetic use, a directed functionalisation by ethoxycarbonylnitrene in dichloromethane gave the carbamate (9) in good yield.[48]



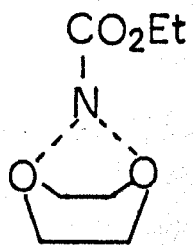
Scheme 1.10

Chlorocyclohexane gave a mixture of isomeric urethanes.

However, in related photolytic studies, Takeuchi et al.[44] conclude that singlet destabilisation by the external heavy atom effect is counterbalanced by singlet interaction with the chlorine lone pairs resulting in stabilisation. In their thermal experiments the outcome is weighted towards the heavy atom effect.

A series of papers[51-54] by Takeuchi's research group has lead to an understanding of the role of 1,4-dioxan in nitrene mediated reactions.

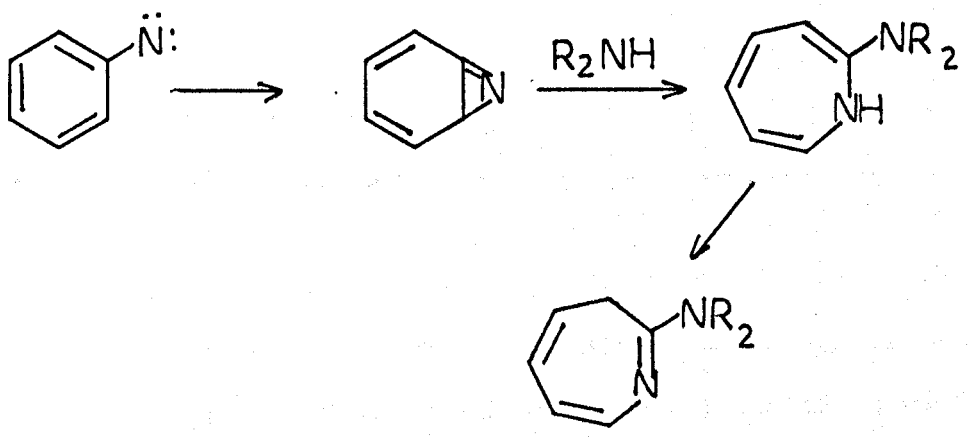
Detailed kinetic analysis of the reactions of ethoxycarbonylnitrene with cyclic ethers,[51] hydrocarbons,[52] alkenes[53] and cyclohexane[54] suggest a stabilised singlet nitrene/dioxan complex such as (10) as an intermediate in these reactions.



(10)

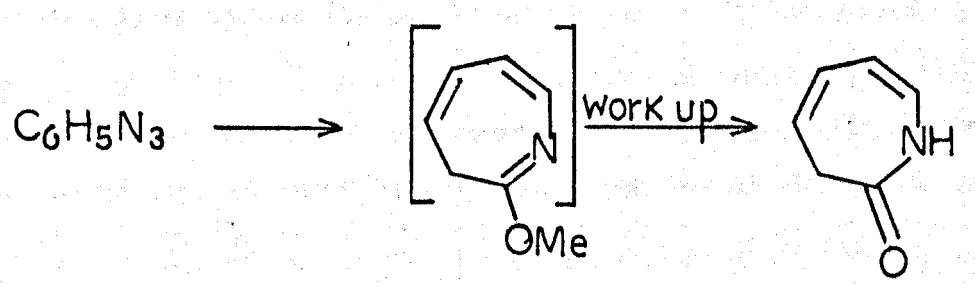
5. Azepine formation

The formation of 2-amino-3H-azepines by the thermal or photolytic decompositions of azides in the presence of amines has been known and well studied for some time.[16] The reaction was assumed to proceed through an intermediate bicyclic azirine, a valence tautomer of the initially formed singlet nitrene. Nucleophilic attack by amine and tautomerisation delivers the 3H-azepine.



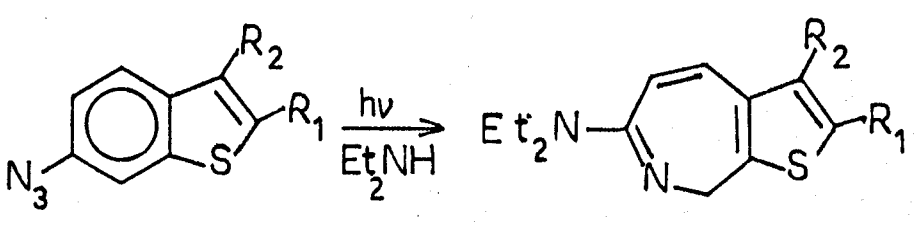
Scheme 1.11

A number of new examples of this reaction have appeared recently. Scriven and Thomas[55] have photolysed phenyl azide in the presence of methoxide ions and dioxan and obtained 3H-azepin-2-one in 35% yield. The success of the reaction was attributed to singlet stabilisation by dioxan and the use of the hard nucleophile methoxide.



Scheme 1.12

Iddon and Suschitzky[56] have reported the first example of expansion of a bicyclic ring during the photolysis of benzo[b]thiophenes (11) and (12).

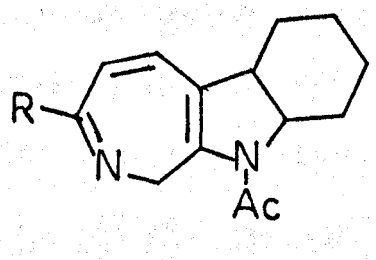


(11) R_1R = Br

(12) R_1 = CO_2Me, R_2 = H

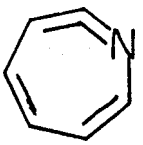
Scheme 1.13

An analogous reaction has also been reported for azidoquinolines.[68] The isolation of the relatively rare 2H-azepines, highlights the fact that formation of the other azirine intermediate would lead to loss of aromaticity in both rings. The first insertion into a tricyclic system has also been reported;[57] 9-acetyl-7-azido-1,2,3,4,4a,9a-hexahydrocarbazole on irradiation in secondary amines gave the azepino[3,4-b]indole (13).



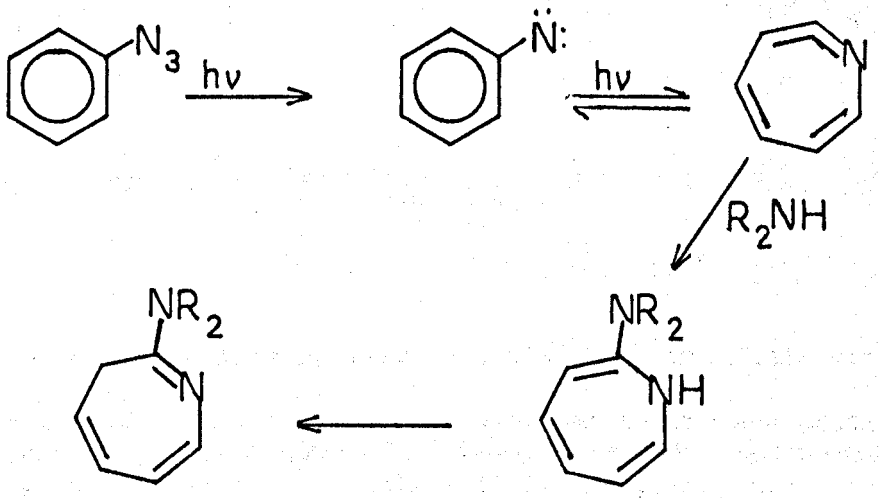
(13)

The intermediacy of a bicyclic azirine intermediate in these ring expansions has been challenged recently by Chapman and co-workers.[58-61] Matrix infra-red studies in argon at low temperature led to the discovery of a new band at 1895 cm^{-1}. Chapman has assigned this to a bent ketimine type structure (14).



(14)

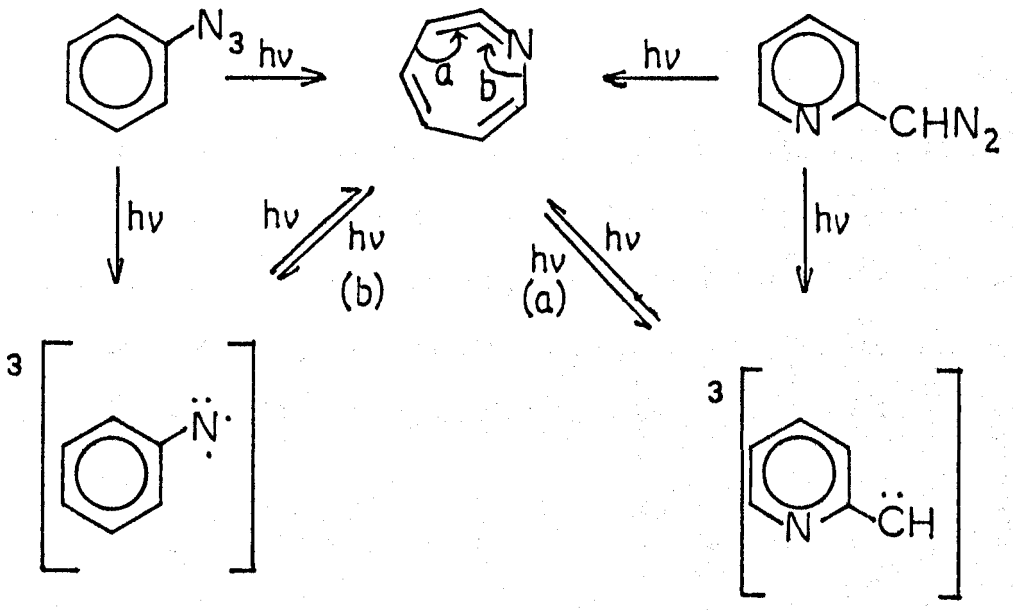
This intermediate is now favoured for phenyl azide photolysis, attack of a nucleophile and tautomerisation gives the observed 3H-azepines. (Scheme 1.14).



Scheme 1.14

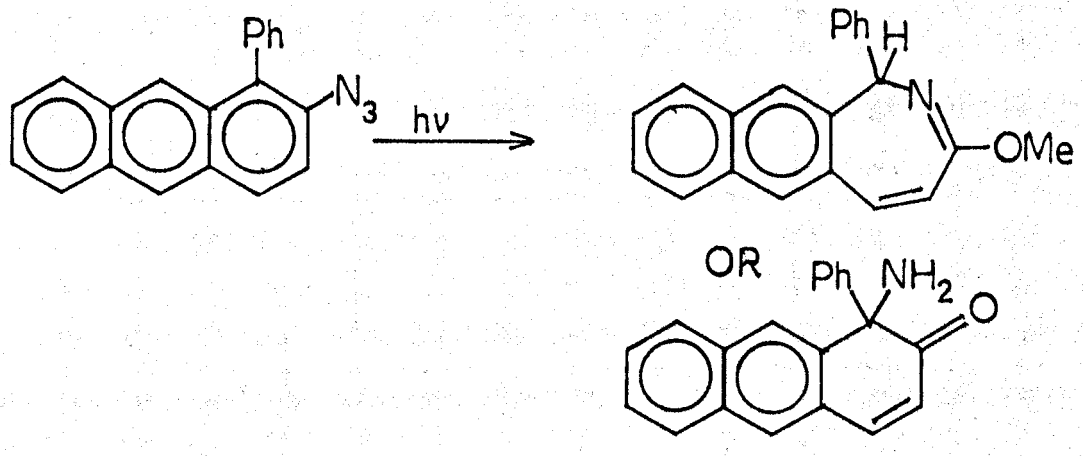
It is an open question whether (14) is formed from singlet phenyl nitrene or excited singlet phenyl azide. Mechanistically the ring expansion of phenyl azide to (14) can be viewed[60] as analogous to the Curtius or Wolff rearrangements.

By a combination of E.S.R. measurements and matrix isolation[61] phenyl azide and 2-diazomethylpyridine were found to be interconvertible on the C_6H_5N energy surface.



Scheme 1.15

Barcelo and co-workers however have disagreed with this view.[63,64] In their work on the ring expansion of napthalene and anthracene azides, photolysed in methanol/MeOK mixtures, they have isolated compounds which they interpret as being derived from an azirine intermediate. Additionally the u.v. spectrum of the solution after irradiation is characteristic of an azirine intermediate.

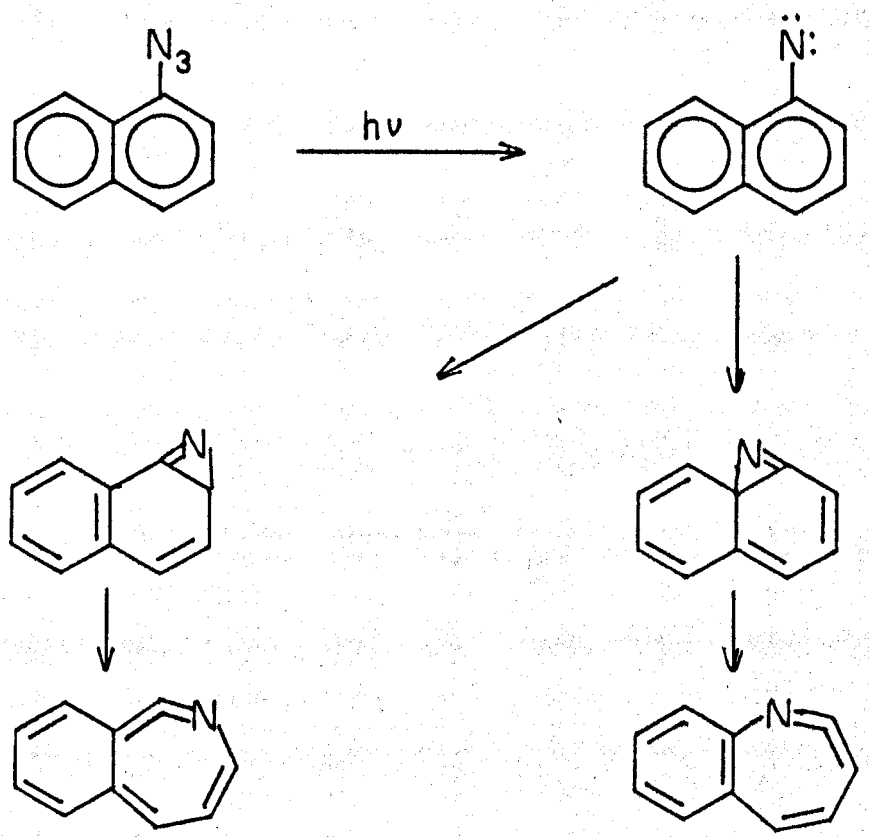


(16)

Scheme 1.16

The outcome of the reaction rests on the conditions after photolysis; (15) being obtained after heating and then neutralisation, whereas (16) is isolated upon immediate neutralisation. The phenyl substituent serves to prevent easy rearomatisation of the intermediate azirine to produce 1,2-disubstituted anthracenes. It would appear from these results that the azirine species is favoured in the anthracene case.

A recent communication by Dunkin[64] has shed some light on this vexing question. Matrix infra-red studies on 1-and 2-azido-napthalenes, photolysed in argon or nitrogen glasses at 12K, revealed that bicyclic azirines are indeed formed; however continued irradiation produces a second intermediate which is assigned a didehydrobenzazepine structure.

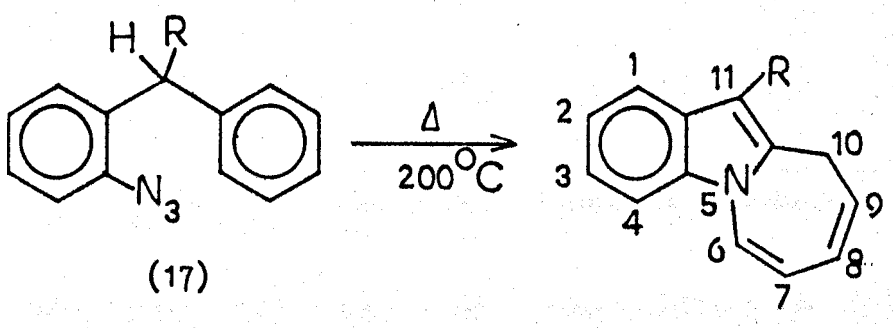


Scheme 1.17

The formation of azepines by an intramolecular insertion has been the subject of considerable research at Keele University for a number of years.[1-12]

This work was initiated by the discovery[2] that 10H-azepino[1,2-a]indole is formed upon thermolysis of the azide (17) in trichlorobenzene and not the 11H-isomer (18) as originally claimed.[65]

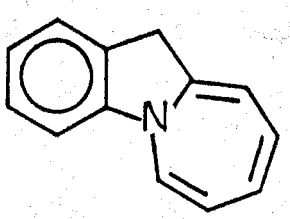
The structural assignment was confirmed by decomposition of the methyl compound (17, R = Me). The alternative 6H-isomer was excluded on N.m.r. chemical shift arguments, however it will be shown later that these isomers are possible under special circumstances.



(17)

R = H, 56%

R = Me, 38%



(18)

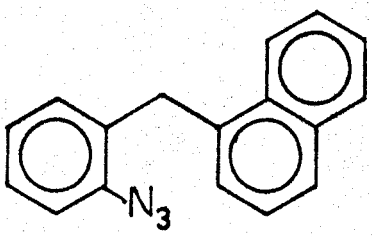
Scheme 1.18

A variety of substituted azidodiphenylmethanes have been synthesised and thermolysed since that time and the results are grouped for convenience in Table 1.1.

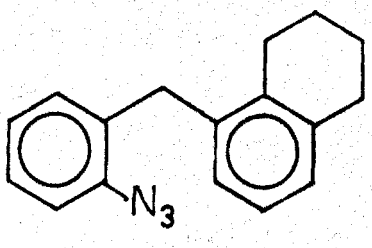
The general trend was formation of azepines in this series by expansion of the adjacent benzene ring; only when an ortho-methoxy

group is present does the insertion produce a six-membered ring. Steric obstruction lead to the isolation of 6 and 8H tautomers in azide (27).

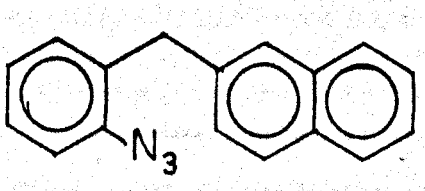
To study the effect of annelation on the insertion process the decomposition of azides (29) - (32) was carried out.[5]



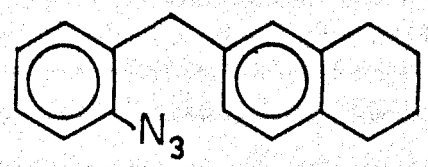
(29)



(30)

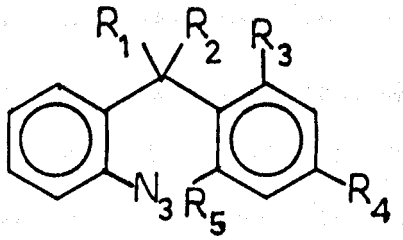


(31)



(32)

TABLE 1.1



Compd	R^1	R^2	R^3	R^4	R^5	% Azepine	% Acridine + Acridan	Others %	Ref.
19	H	H	H	H	H	56	-	-	2
20	D	D	H	H	H	60			11
21	CH_3	H	H	H	H	38	-	-	2
22	CH_3	H	H	CH_3	H	19	0.5	-	66
23	H	H	H	OCH_3	H	48	-	-	3
25	H	H	CH_3	H	H	36.5[a]	-	-	1, 3
26	H	H	OCH_3	H	H	1[b]	46[d]	8[e]	1, 3
27	H	H	CH_3	CH_3	CH_3	74.3[c]	-	-	3
28	H	H	OCH_3	OCH_3	OCH_3	-	46[f]	22.5[g]	3

Notes:

a, 27.5% 10-methyl + 9% 6-methyl

b, 10-methoxy + 6-methoxy

c, 41% 6H + 20.4% 10H + 12.9% 8H isomer

d, 3% acridine + 7% 1-methoxyacridine, 26% 1-methoxyacridan + 10% acridan

e, azepino[1,2-a]indol-6-one

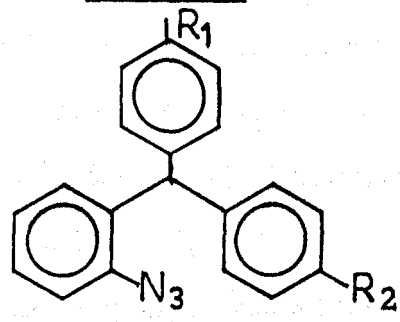
f, 1,3-dimethoxyacridan + 1,3-dimethoxyacridine

g, 8,10-dimethoxyazepino[1,2-a]indol-6-one

As might have been predicted by analogy with the diphenyl methane series the insertions into the tetralins (30) and (32) gave azepines as the major products, very small amounts of six membered ring compounds being produced. Conversely the insertions into a naphthalene system gave virtually acridines and acridans only.

It had been previously shown that the presence of a methyl group on the central methane carbon atom (compounds (21) and (22)) does not divert the reaction and lead to acridine formation. Some more recent work[11] in this area has shown that the presence of a phenyl group has a marked influence on the course of the nitrene insertion process. (Table 1.2).

TABLE 1.2



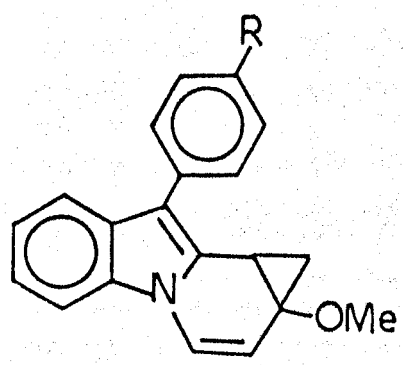
Compd	R^1	R^2	% Azepine	% Acridine + Acridan	% Others	Ref.
33	H	H	31	33	8.5[c]	11
34	H	OCH_3	17[a]	42[b]	34[d]	11
35	OCH_3	OCH_3	1	36.8	13.6[e]	11
36	NMe_2	NMe_2	-	10 + 6[f]	-	11

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

b, 1:1 mixture of insertions into each ring

c, amine + azo compound

d, e, ——



(37) R = H

(38) R = OCH_3

f, 2-dimethylamino-9-(4'-dimethylaminophenyl)acridine

The presence of an unsubstituted phenyl ring results in roughly equal quantities of azepine and acridan/acridine products. The presence of electron donating groups gives a tetracyclic product and little azepine ($R = -OCH_3$), while the strongly electron-donating group ($R = -NMe_2$) gives acridine only.

It was clear at this stage that the reaction was probably proceeding through two intermediates. It is tempting to explain these results as due to the intermediacy of singlet or triplet nitrene intermediates. That this is indeed the case has been indicated by a series of sensitisation and quenching experiments.[11] Photolysis of compounds (33) and (35) in benzene solutions containing acetophenone (a triplet sensitiser) gave mainly azo compounds and acridines, no azepine compounds were detected. A series of experiments with different solvents[11] supports the view that a higher temperature leads to higher yields of singlet insertion products. This has been noted elsewhere[41] in experiments on azidobiphenyl cyclisations. A pronounced 'heavy atom' effect was noted for bromobenzene at 156° (increased yield of acridines) but this is ineffectual at higher temperatures. Naphthalene, which has a low triplet energy, was especially effective in deactivating the singlet state and producing much reduced yields of azepines, concomitant with a corresponding increase in acridine/acridan products.

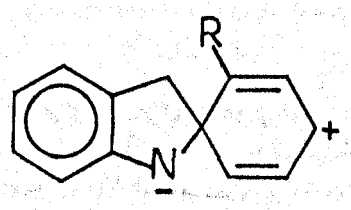
The overall picture which emerges, therefore, is that the azepine (ring expansion) products are derived from the singlet nitrene while the triplet nitrene is responsible for acridine and acridan products (no ring expansion).

The ratio of singlet to triplet derived products will depend on the affinity of the initial singlet nitrene for the substrate and this will be matched against the rate of intersystem crossing to the triplet.

The best illustration of these arguments is provided by the decomposition of the azides (29) and (31). The opportunity for the singlet nitrene to undergo intersystem crossing is at a maximum in these compounds, experimentally only acridan and acridine products are observed. The singlet /triplet interaction may be visualized as:

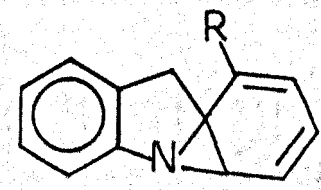
singlet nitrene + ground state naphthalene ⟶ triplet nitrene + triplet naphthalene

Mechanistically the initially generated singlet nitrene can form two possible intermediates upon interaction with the adjacent π - system. Both of these have been proposed as intermediates in intramolecular nitrene insertion reactions.



(39)

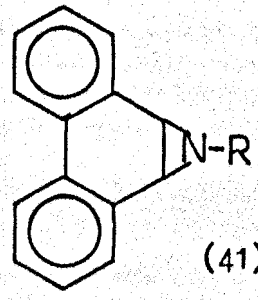
spirodiene



(40)

azanorcaradiene

An azanorcaradiene intermediate is preferred for the majority of reactions discussed in this thesis. Stable aziridines such as (41) have actually been isolated by Blum and co-workers.[67]

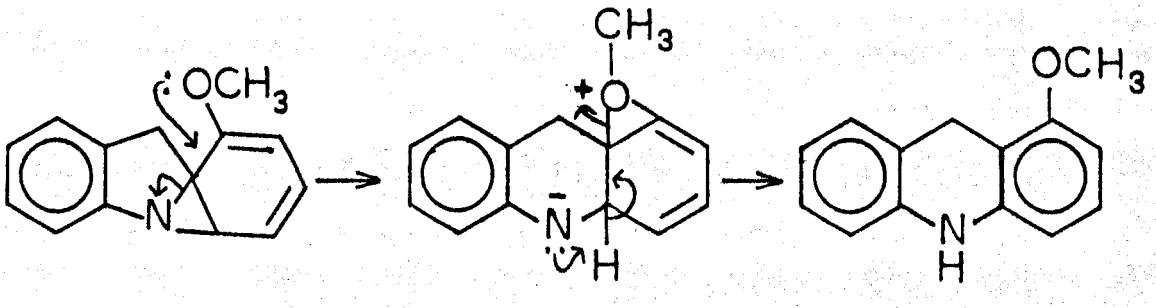


(41)

R = benzyl, n-butyl, cyclohexyl

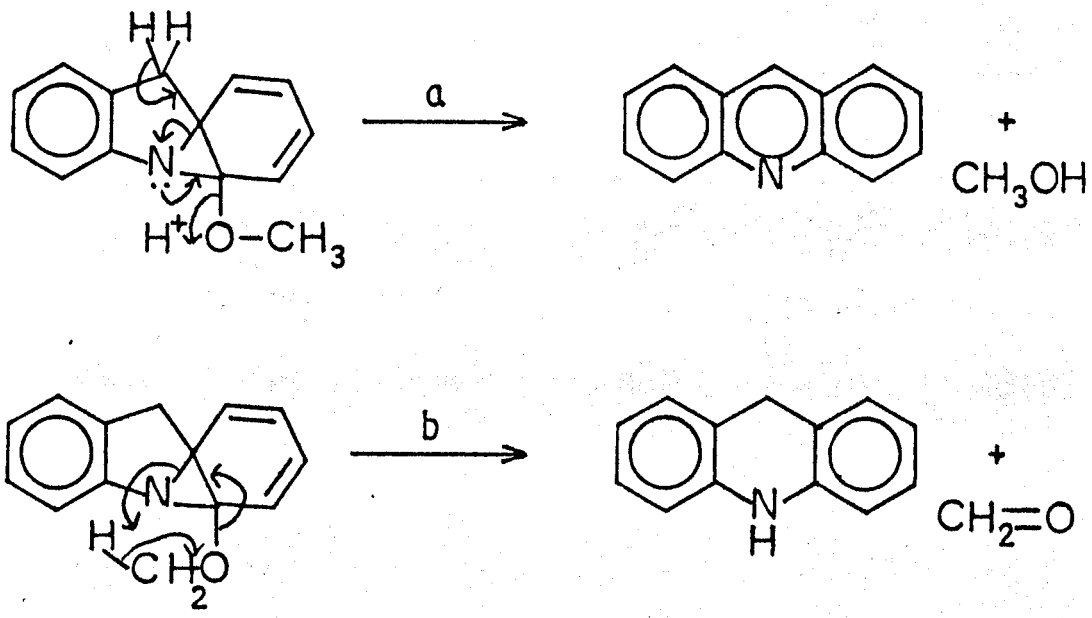
Other workers have also shown that the singlet nitrene reacts to form azepine derivatives,[69-72] probably through an intermediate aziridine.

The formation of acridine compounds when an ortho-methoxy substituent is present in the ring receiving the nitrene is best explained in terms of anchimeric assistance resulting in preferential opening of the intermediate to produce an acridan. Acridine formation is rationalised as occurring via an internal oxidation/reduction system, some acridine was present although the experiment was performed with rigid exclusion of oxygen.[3] The isolation of amines in some decompositions lends some support to this idea.



Scheme 1.19

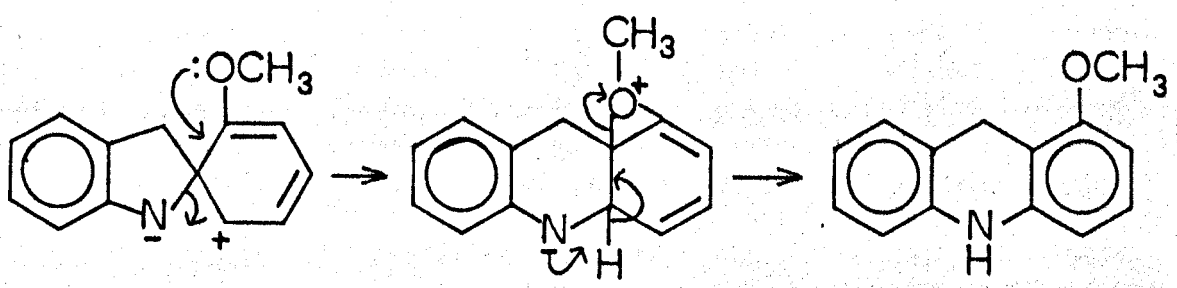
Loss of methanol and formaldehyde to produce acridine or acridan, respectively, can occur as depicted in Scheme 1.20.



Scheme 1.20

It is considered unlikely that route b is plausible as no formaldehyde could be detected in the effluent stream from the reaction.

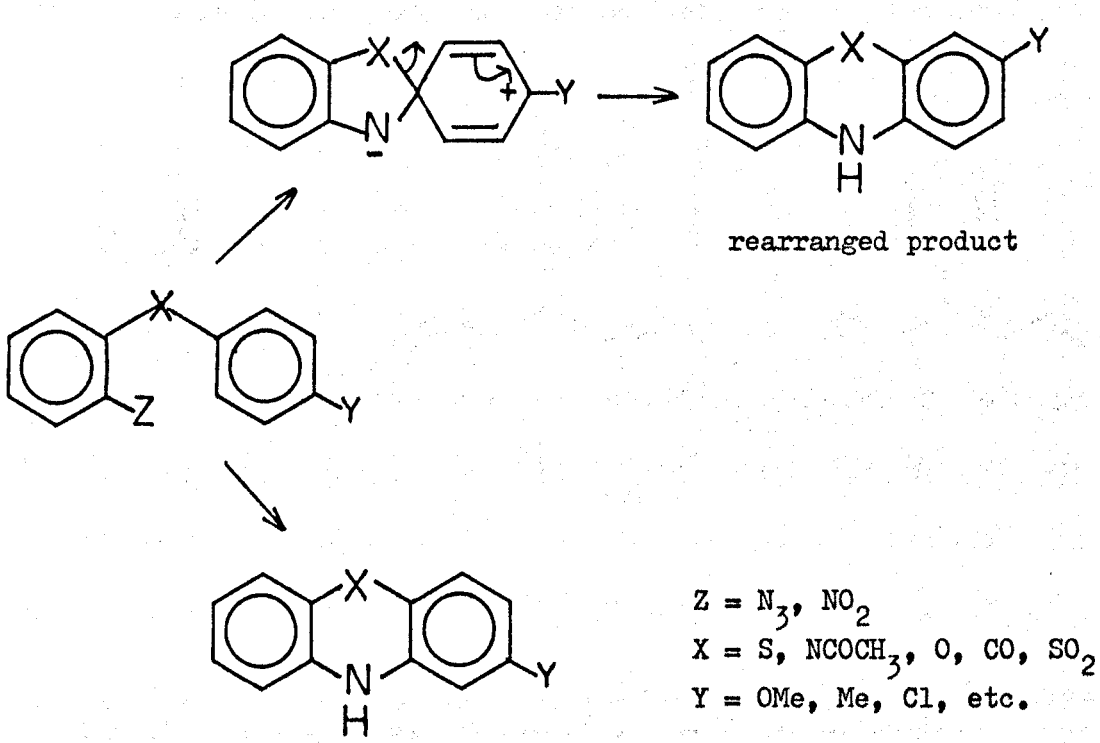
A similar mechanism could be drawn involving spirodiene intermediates, however formation of 1-methoxy acridan necessitates invoking an unusual nitrogen migration.



Scheme 1.21

The intermediacy of spirodienes has been proposed by Cadogan and co-workers[22] to account for rearrangement in the

phenothiazene series.

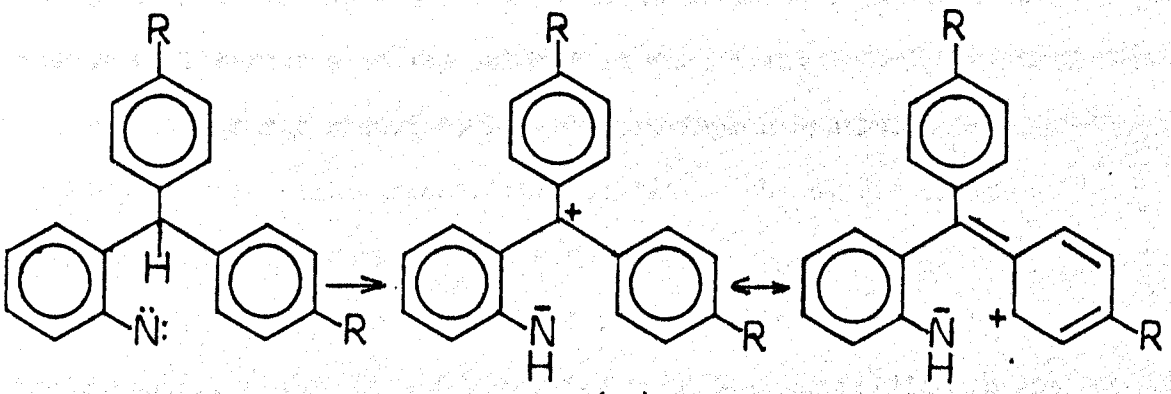


Scheme 1.22

Only in the case of compound (36), a triphenyl methane bearing strongly electron-donating groups,[11,12] is there any evidence of this mechanism being involved in the work discussed so far. There are some important differences in cases where X = CH_2 and for example where X = SO_2 (Scheme 1.22). In earlier work[65] Krbechek and Takimoto found that the amine was the major product on thermolysis of the azide in decalin. In contrast the amine is at best a minor partner in the products where X = SO_2 and is apparently not formed[73, 74] where X = S.

A mechanism which can account for the product distribution in the triphenylmethane series (see Table 1.2) has been proposed.[11] The considerable increase in acridine/acridan products found is best explained by invoking a carbonium ion intermediate. The singlet nitrene

is well set up to abstract hydrogen via a five membered transition state to give a triphenyl carbonium ion which in another mesomeric form is set up for cyclisation to an acridan.



(42)

Figure 1.3

The stability of the carbonium ion (42) results in effective competition with ring opening of the aziridine intermediate to form azepines. Some justification for this mechanism is seen in the increased proportion of acridines in cases where R = OCH_3. Indeed where R = $N(CH_3)_2$ acridines are the only products isolated.[11,12] (Note however the poor total recovery of material in this case).

As yet no study of intramolecular insertion reactions has been carried out where the 'receiving' ring is of the pyridine type. We wished to synthesise and decompose compounds of this type in the hope of isolating novel diazepinoindoles. These reactions would also give valuable insight into our continuing study of the factors influencing singlet and triplet ratios in nitrene reactions.

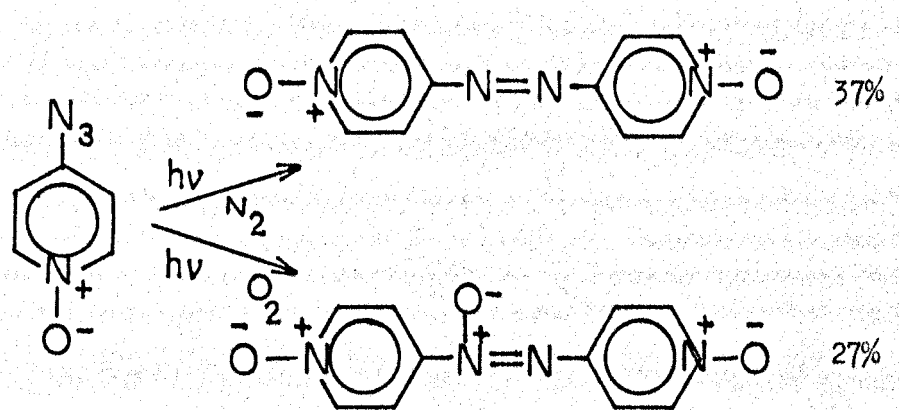
We have therefore synthesised and decomposed several examples of this type of compound. A short review of the known reactions of the pyridine moiety with nitrenes is now presented.

Part B : THE REACTIONS OF NITRENES WITH PYRIDINE COMPOUNDS

A variety of reaction types, analogous to those discussed in Part A, are known for pyridine compounds. However the volume of literature on the subject is much less.

An early report by Boyer[75] provides a synthesis of 1-(α-pyridyl)-2-azidoethane, thermolysis or photolysis of the compound was not investigated however.

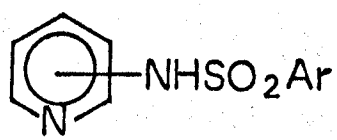
Ring expansions have been attempted in the pyridine field. Scriven and Thomas[55] isolated only 3-aminopyridine in the photolysis of 3-azidopyridine, in the presence of a 1:1 mixture of 3M potassium methoxide/methanol. In contrast azidoquinolines are known to undergo ring expansion.[68] Kamiya et al.[76,77] have photolysed 4-azidopyridine-N-oxide and obtained azo or azoxy compounds.



Scheme 1.23

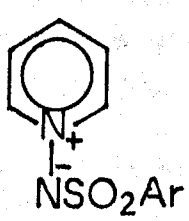
The oxidative cyclisation of ortho-aminoazobenzenes to benzotriazoles has its parallel in the pyridine series[78] in the conversion of 2,6-diamino-3-phenylazopyridine to 5-amino-2-phenyltriazolo-[4,5-b]pyridine, by oxidation with ammoniacal copper sulphate.

Curtius and co-workers[15] have reacted a number of sulphonyl azides with pyridine and isolated, quite often in good yields, compounds which they formulated as (43) by analogy with the reactions of benzene.



(43)

Subsequently the structures of these compounds have been shown to be pyridinium derivatives[79,80] (44).

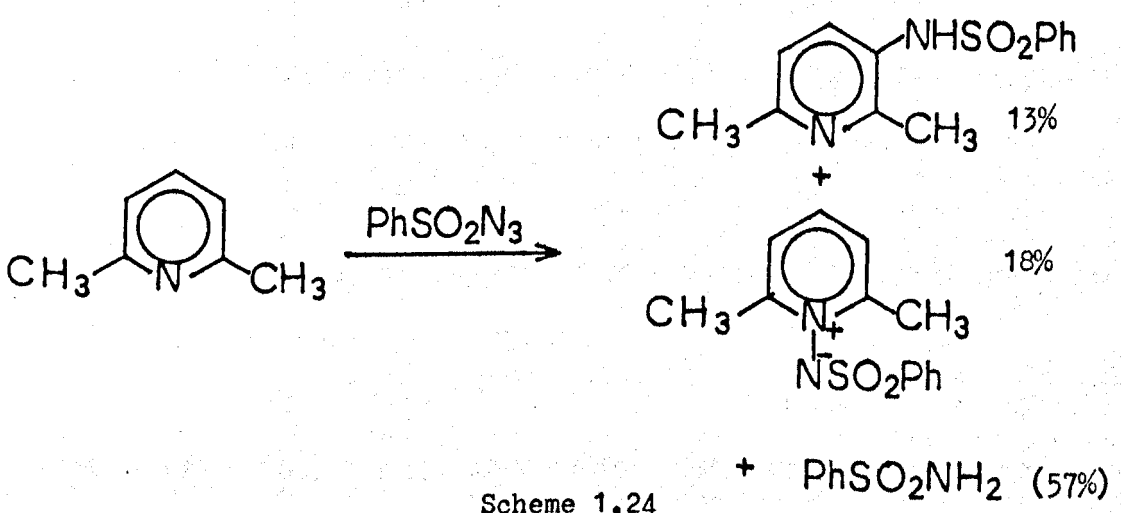


(44)

The compounds have also been synthesised[79] by an unambiguous route. A number of pyridinium derivatives have been prepared where Ar = phenyl, p-ClC_6H_5, p-$CH_3C_6H_5$ etc.[15]

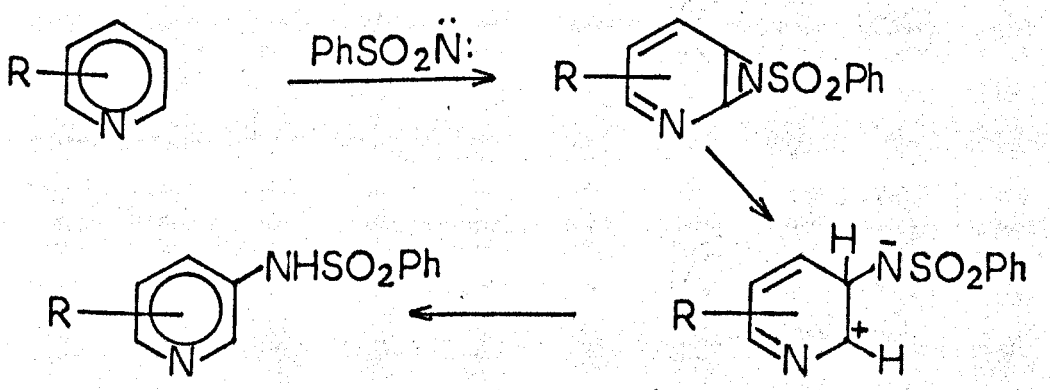
This reaction has been reinvestigated by Abramovitch and

Takaya.[81] They have confirmed that pyridinium ylides are formed in the reaction of pyridine with methane-, benzene-, or p-toluene-sulphonyl azides. The corresponding reactions with 2 and 4-methyl pyridine, 2,6-dimethyl pyridine and 2,4,6-trimethyl pyridine gave the pyridinium ylides and C_3 substitution products.



Scheme 1.24

The formation of a C_3 substitution product is clearly indicative of a singlet sulphonyl nitrene. The observation that only ylide formation was apparent with 4-cyanopyridine is additional evidence for this argument. The proposed mechanism is shown in Scheme 1.25.



Scheme 1.25

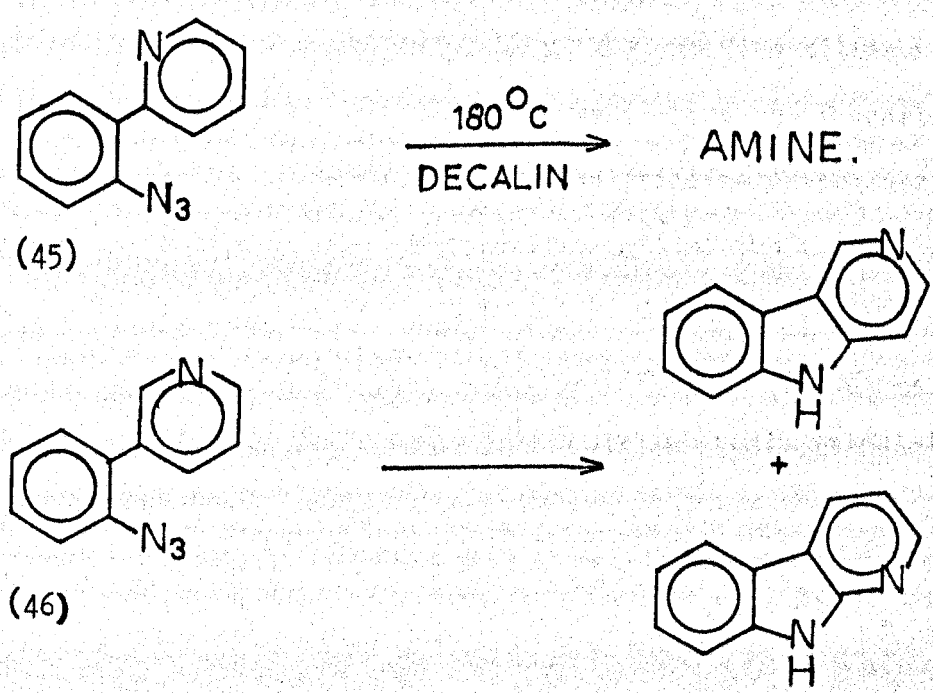
In no cases did ring-opening of the aziridine intermediate occur to produce 1,3-diazepines.

Photolysis of a variety of N-sulphonyliminopyridinium ylides, in the hope of generating singlet sulphonyl nitrenes, has also been investigated by Abramovitch.[82] No evidence was obtained for their formation, however.

The intermediacy of ethoxycarbonylnitrene during the photolysis of 1-ethoxycarbonylimino derivatives of 2,6-dimethylpyridine and 2,4,6-trimethylpyridine has been postulated.[83]

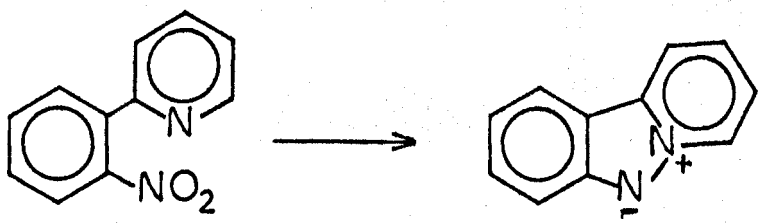
The intramolecular cyclisation of ortho-azidophenylpyridines to yield carbolines has been thoroughly investigated. (Compare the formation of carbazoles in part A).

Smith and Boyer[84] first reported the thermal decomposition of the azides (45) and (46). Only the 3-isomer underwent ring closure to give predominantly the α-carboline. The 2-isomer gave only amine via hydrogen abstraction from the solvent.



Scheme 1.26

The cyclisation of 2-ortho-nitrophenylpyridine with ferrous oxalate at 300°C was reported by Abramovitch[85] in 1957. Ring closure gave pyrid[1,2-b]indazole and no δ -carboline.

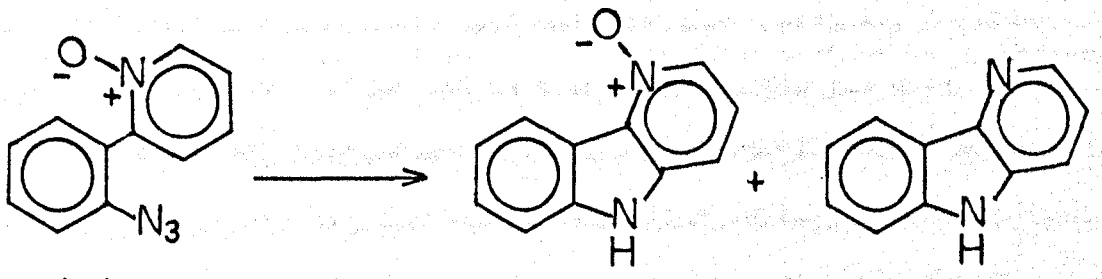


Scheme 1.27

It is doubtful whether this cyclisation involves a discrete nitrene intermediate.[15] The δ -carboline isomer has since been synthesised by thermolysing 3-azido-2-phenylpyridine.[86]

A more detailed[87,90] study of the ferrous oxalate cyclisations has shown that blocking the pyridine nitrogen atom (N-oxide) does not divert the reaction to produce δ -carboline. Deoxygenation and cyclisation onto the pyridine nitrogen gives pyrid[1,2-b]indazole. A reinvestigation[87] of the thermal reaction of the azide (45) revealed that pyrid[1,2-b]indazole is also formed in this reaction and not amine as was previously reported.[84]

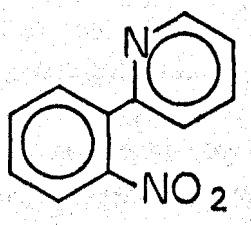
Low yields[87] of the δ -carboline could be obtained by thermolysing the azide (47).



(47)

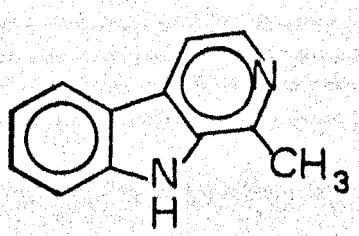
Scheme 1.28

The triethylphosphite deoxygenation of nitroso and nitro compounds analogous to those already discussed gives[88,89] cyclised products in good yields. For example deoxygenation of the nitro compound (48) by boiling triethyl phosphite gives pyrid[1,2-b]-indazole in almost quantitative yield.[88]



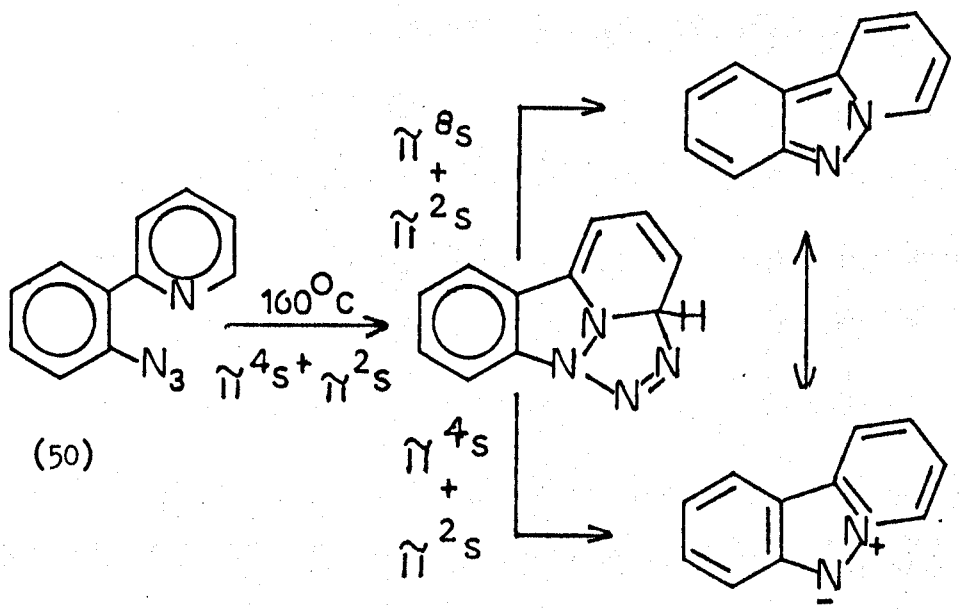
(48)

The general synthesis of carbolines discussed above has been extended by Kametani,[91] to provide a route to the simple β-carboline harman alkaloids, e.g. (49).



(49)

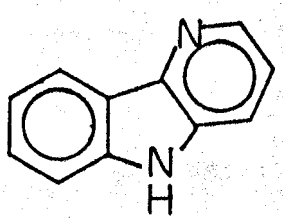
A systematic study of the thermolysis and photolysis of 2-(2-azidophenyl)pyridine has only recently appeared.[92] The thermal conversion to the indazole in quantitative yield is unprecedented for a nitrene reaction. Accordingly Boyer[92] has proposed two thermally allowed pathways (Scheme 1.29).



Scheme 1.29

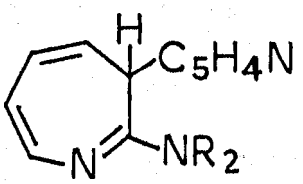
The azide (50) thermolysed in di-n-butylamine was converted nearly quantitatively into a mixture of the indazole and the amine. The lack of azepine was considered as additional evidence for the absence of a nitrene intermediate. Hydrogen abstraction from the solvent can occur without nitrene participation.[93]

Conversely, irradiation gave the indazole and the pyridoindole (51).



(51)

Indole formation was increased under singlet sensitised conditions; indazole formation, however, was subject to triplet sensitisation. Photolysis in the presence of diethyl or di-n-butylamines gave the azepine (52) and minor amounts of the indazole and indole.

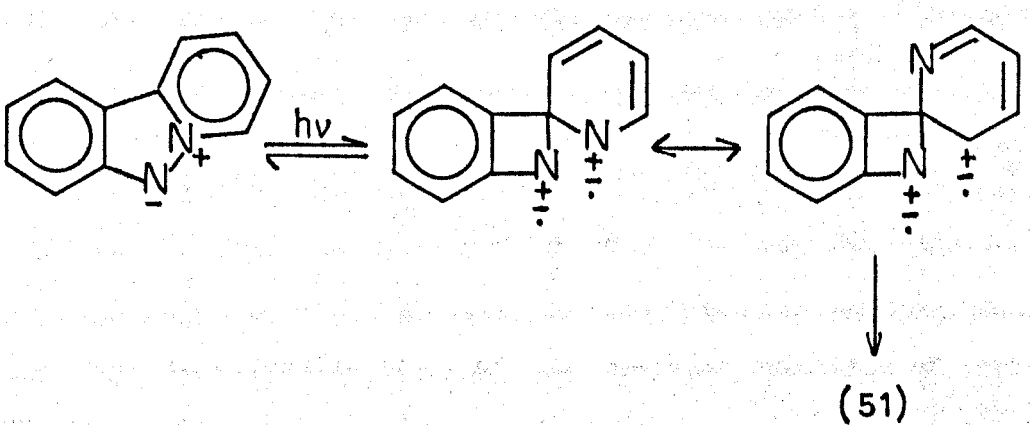


(52)

R = Et, 51%

R = n-Bu, 65%

Prolonged irradiation (136 hrs) of the indazole in tetrahydrofuran gave the indole (51). The isomerisation was less effective in methanol and not detected in cyclohexane. The conversion was rationalised as shown in the scheme.

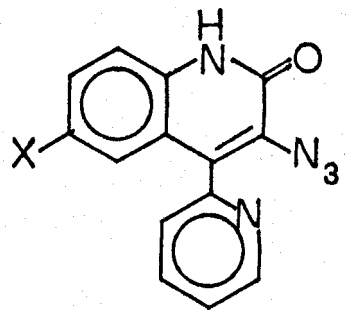


(51)

Scheme 1.30

In contrast to the exclusive indazole formation already described, Ning[94] and co-workers have observed insertion into C-H

bonds in the pyrolysis of azidopyridylcarbostyrils (53).



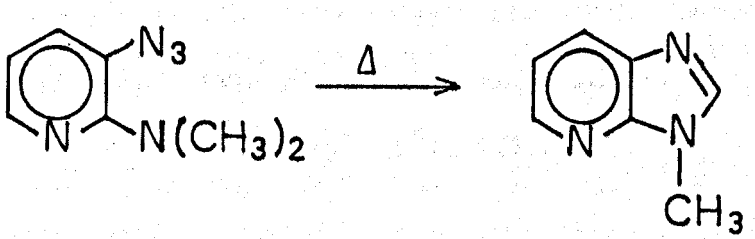
X = H, Br

35%, N-N bond formation

≃ 25%, N-C bond formation

(53)

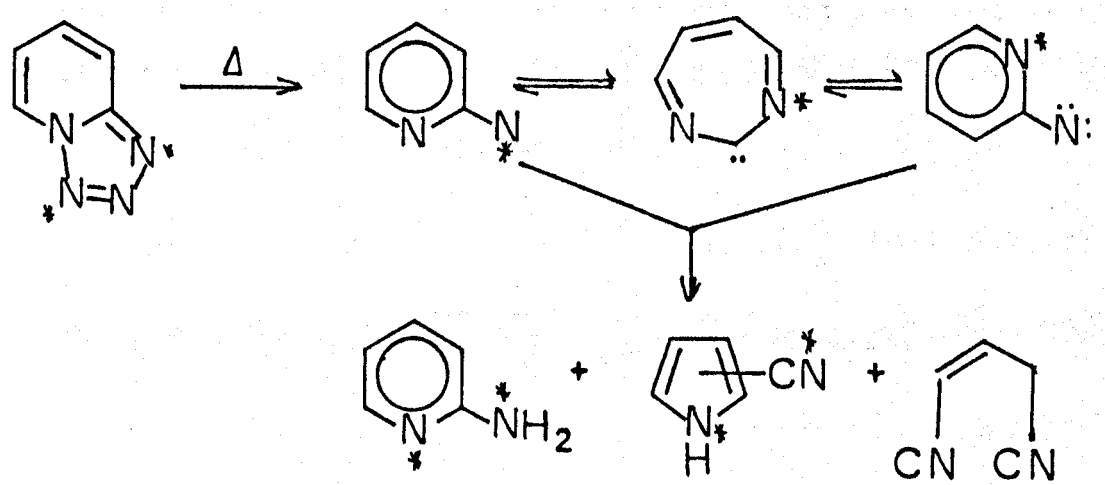
A few insertions of pyridyl azides into suitably placed C-H bonds have been studied.[95,96]



Scheme 1.31

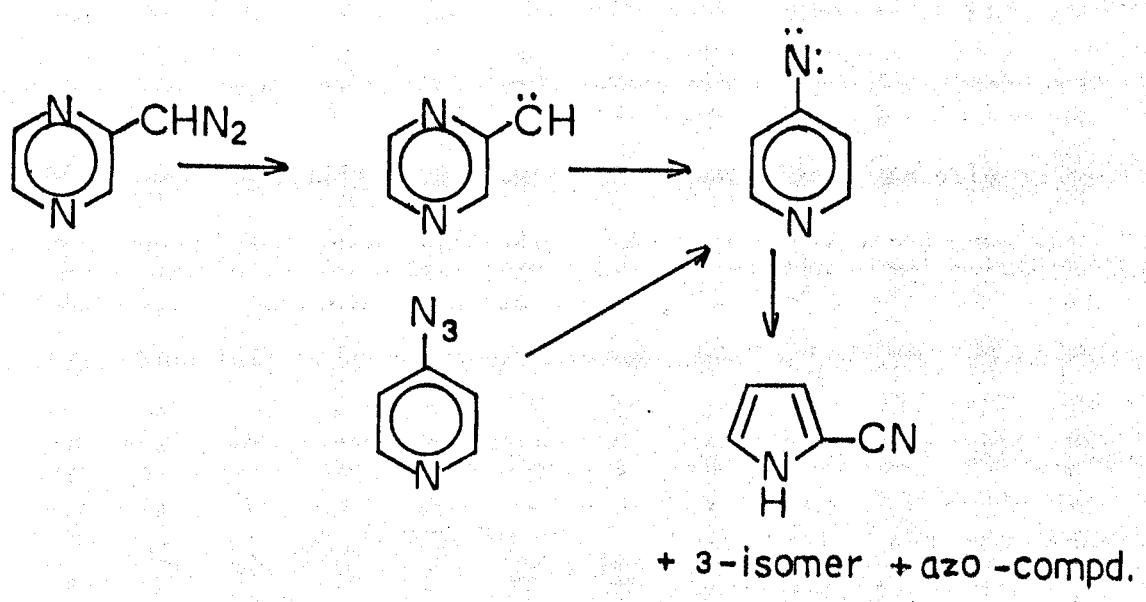
An extensive study of the gas-phase pyrolysis of carbenes and nitrenes has been carried out by Wentrup and co-workers.[97] Pyridyl nitrene, which is conveniently generated from tetrazolo[1,5-a]-pyridine, undergoes three intramolecular reactions. The relative rates are $k_{\text{ring expansion}} > k_{\text{ring contraction}} > k_{\text{ring opening}}$. Hydrogen

abstraction to give 2-aminopyridine is a minor pathway. Labelling studies show that the nitrogen atoms have interconverted before formation of cyanopyrrole and aminopyridine.



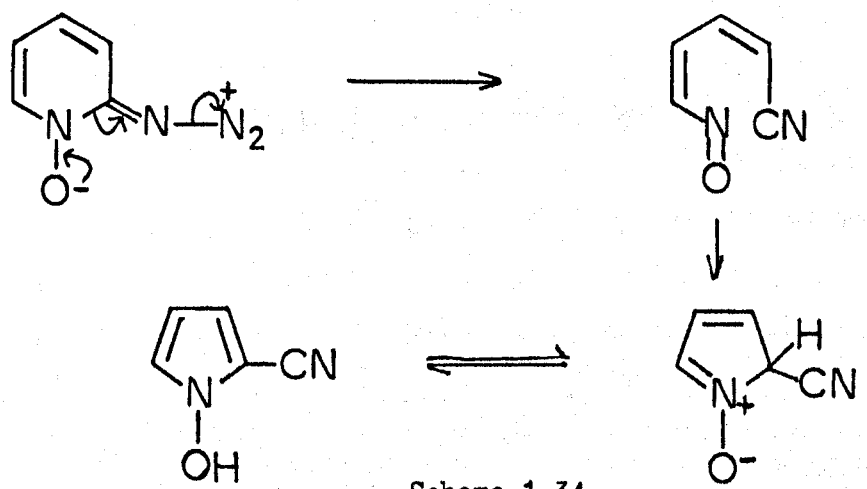
Scheme 1.32

The gas-phase generation of 2-pyridylcarbene results in the same products as obtained from phenylnitrene. This has been shown to be a general observation.[97] e.g. Scheme 1.33.



Scheme 1.33

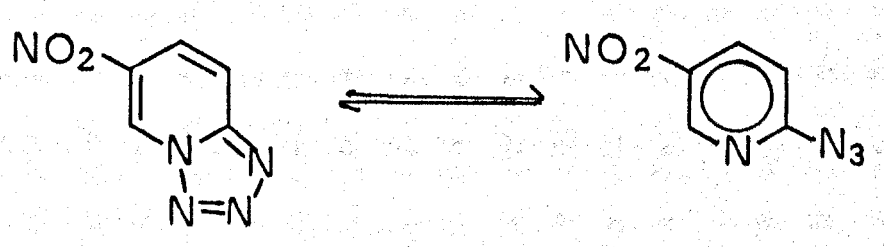
A ring contraction has been reported for the thermolysis of a range of substituted 2-azidopyridine-N-oxides.[98,99] Good yields of 2-cyanopyrroles were obtained. The observation that the azides decomposed at a relatively low temperature, (90°C in benzene) led the authors to postulate a concerted nitrogen elimination with ring opening.



Scheme 1.34

Analogous reactions have been reported in the quinoxaline series.[100]

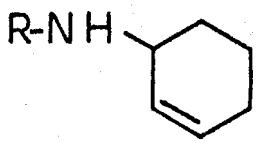
While 3 or 4-azidopyridines exist in the azide form only, 2-azidopyridine generally exists in the tetrazole form. Aspects of this tautomerism have been reviewed.[101] As an exception the 6-nitro derivative exists as an equilibrium mixture.[102]



(54)

Attempts to generate the nitrenes by thermolysis have led only to aminopyridines and no useful nitrene derived products.[103] It was possible to trap the azides as adducts with dimethyl acetylene-dicarboxylate however.

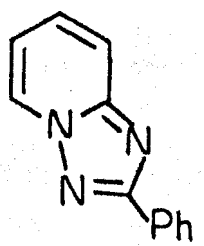
Similarly, Huisgen[104,105] only isolated a 34% yield of 2-aminopyridine in the thermolysis of tetrazolo[1,5-a]pyridine in cyclohexane. A 4% yield of the insertion product (55) was isolated with cyclohexene, together with 46% of the amine.[105]



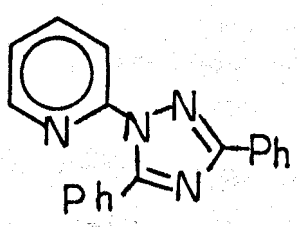
R = 2-pyridyl

(55)

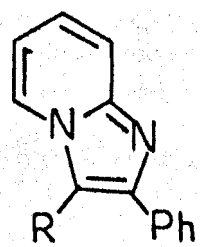
The adducts (56) - (59) were isolated[105] in reactions with benzonitrile, ethyl phenylpropiolate and diphenylacetylene.



(56)



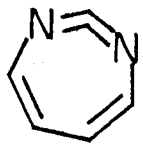
(57)



(58) R = CO_2Et

(59) R = Ph

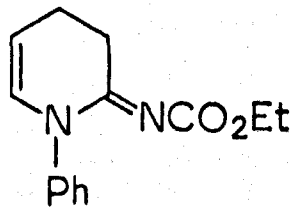
Chapman[61] has obtained evidence to suggest the intermediacy of the cyclic carbodimide (60) in the low temperature photolysis of 2-azidopyridine.



(60)

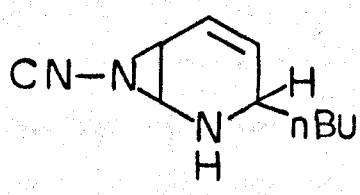
No mention was made of any attempts to isolate a diazepine by trapping with amines.

The reaction of ethyl azidoformate with 1,4-dihydropyridines has been reported.[106] Substitution products were obtained. e.g. (61).



(61)

In contrast 1,2-dihydropyridines[107] do yield products where addition to the double bond has occurred.

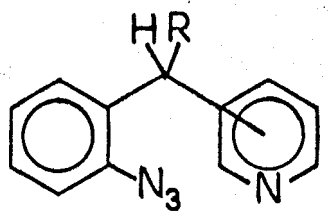


(62)

It was considered unlikely that a free nitrene was involved in these reactions. Addition of azide and elimination of nitrogen was suggested as a plausible mechanism.

DISCUSSION

Our goal in the research described in this chapter was the synthesis and thermal decomposition of compounds of type (63).

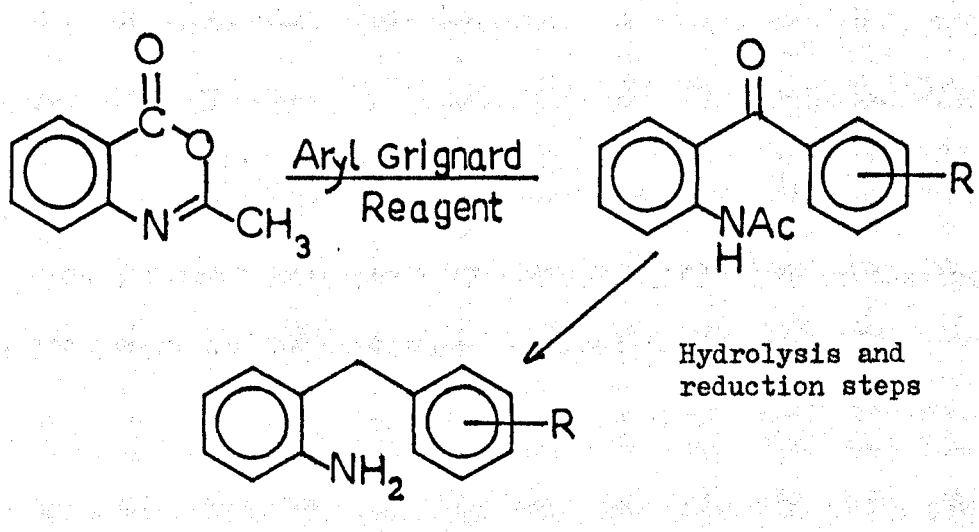


R = H, pyridyl

(63)

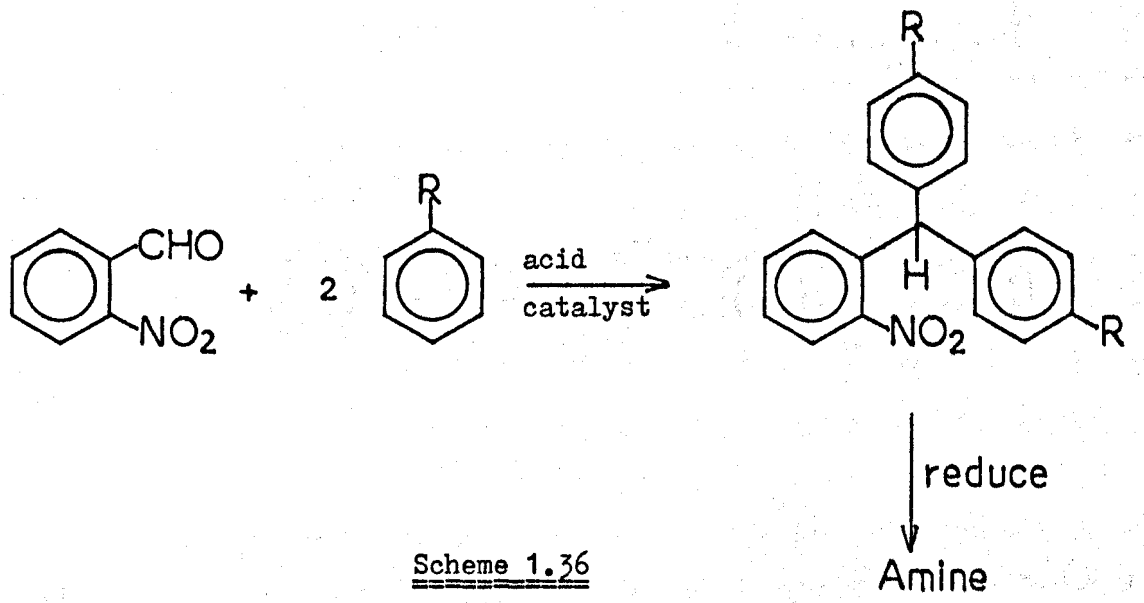
Previous work in this field[1-12] has relied upon two synthetic routes to precursors of the azides (usually the amines).

Route 1



Scheme 1.35

Route 2

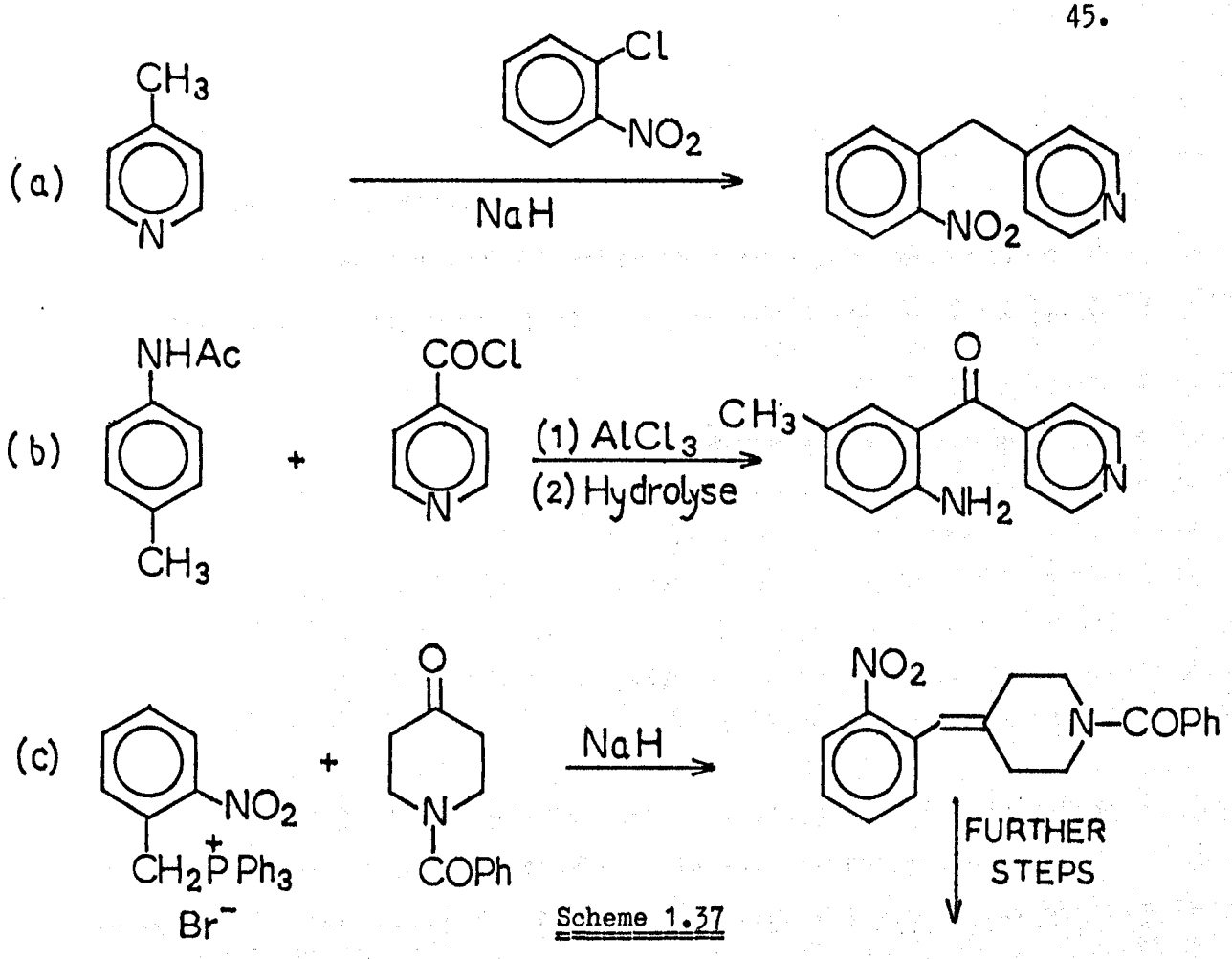


Scheme 1.36

There were two objections to the use of these routes in our synthetic approach to compounds of type (63). Firstly, pyridyl Grignard reagents are usually difficult to form and we did not anticipate good yields by route 1. Secondly, route 2 is only practical when the group R is strongly electron-donating.

At the time of embarking on this work no published routes existed to the 2-azidophenyl-(3-pyridyl)methanes or their 2- or 4-isomers.

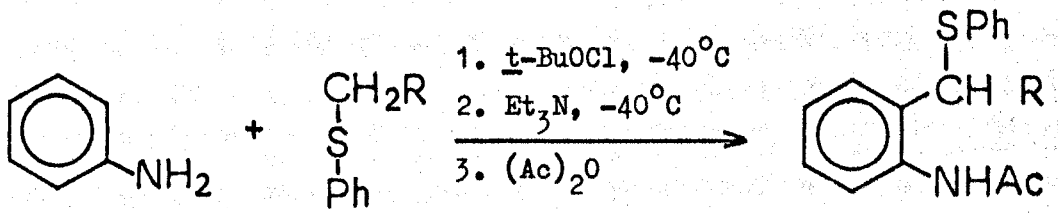
Some initial attempts by Jones and Cliff[108] to synthesise suitable precursors to the azides are outlined in Scheme 1.37.



Scheme 1.37

Route (a) generally gave intractable tars or recovery of starting materials. The Friedel Crafts approach gave the required compound but in unacceptable yields, while the Wittig reagents were too stable to react with ketones.

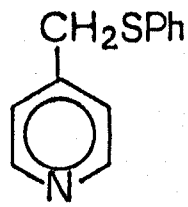
We therefore needed to develop alternative synthetic approaches to our target molecules. At this time Gassman[109,110] had published a useful method for the ortho alkylation of anilines.



Scheme 1.38

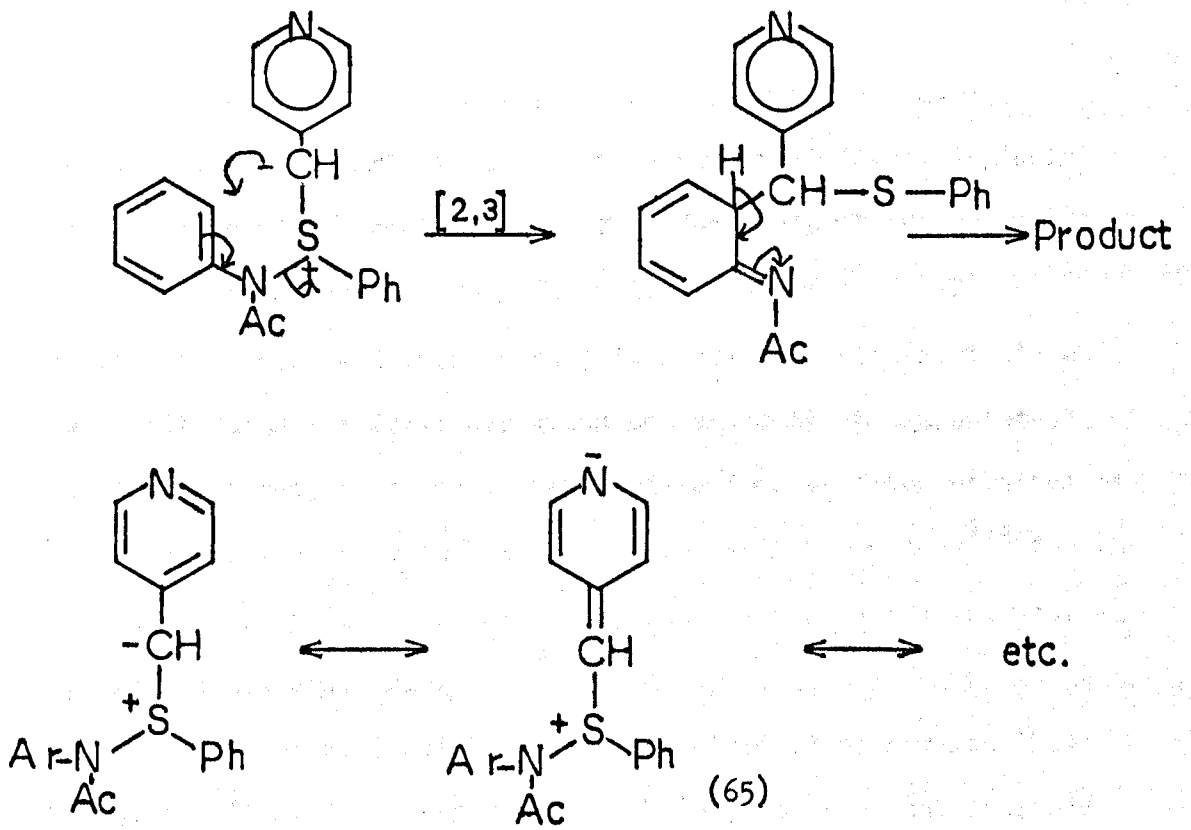
Raney nickel desulphurisation gives the substituted aniline in moderate (40-61%) yields.

We prepared the thioether (64) by a published method[111] from 1-ethoxy-4-picolinium ethyl sulphate and sodium thiophenoxide.



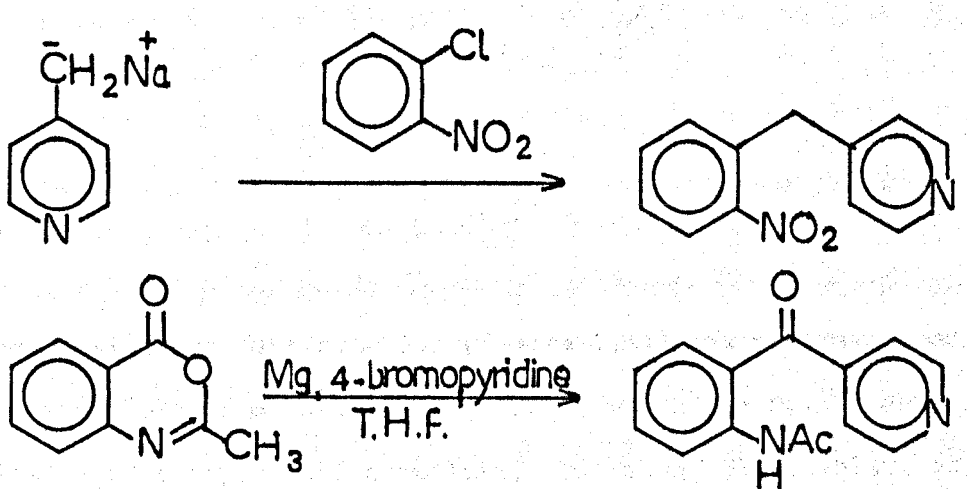
(64)

Reaction with aniline and t-butylhypochlorite under the conditions employed by Gassman did not result in isolation of the required compound. Starting material (64), acetanilide and diphenyldisulphide were the only products obtained after chromatography of the dark reaction mixture. Previous workers[12] have also experienced difficulties with this type of reaction when applied to electron-deficient substrates. The essential step in the mechanism proposed for this reaction[109,110] is a [2,3]-sigmatropic rearrangement in a typical Sommelet-Hauser manner. It is probable that resonance structures such as (65) are responsible for the failure of the reaction.



Scheme 1.39

We then briefly turned our attention to two further routes to the required compounds.



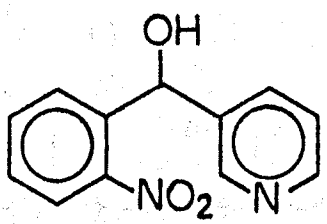
Scheme 1.40

The preparation of 4-picolylsodium was performed readily by a reported procedure,[112] but reaction with ortho-chloronitrobenzene

resulted in recovery of starting materials. This was rather surprising, particularly as it has been reported[113] that 4-picolyl sodium reacts with bromobenzene to form 4-benzylpyridine.

An attempt to form the Grignard reagent of 4-bromo pyridine in T.H.F. and subsequently to react this with acetanthranil was totally unsuccessful. Recovered acetanthranil and a water-soluble substance, presumed to have arisen from self-condensation of the bromopyridine, were isolated. A relatively new method[114] for the preparation of pyridine Grignard reagents was considered impractical for large scale synthesis.

Upon examination of the literature we discovered that Abramovitch[115] had isolated the alcohol (66) as an uncharacterised oil in some studies related to the Pschorr cyclisation.



(66)

We reinvestigated this reaction (Scheme 1.41) and obtained good yields (65-70%) of crystalline material, which had n.m.r. data consistent with the proposed structure. Two downfield doublets at δ 8.35 p.p.m. (J = 7 and 2 Hz) indicate the presence of the pyridine C_2 and C_6 protons. A singlet at δ 6.4 p.p.m. and a broad exchangeable signal at δ 4.9 p.p.m. confirm the presence of the methine proton and the hydroxyl group. The I.R. spectrum has bands at 3300 and 1345 cm^{-1}, indicative of -OH and $-NO_2$ groups. Initially we experienced considerable difficulty in the

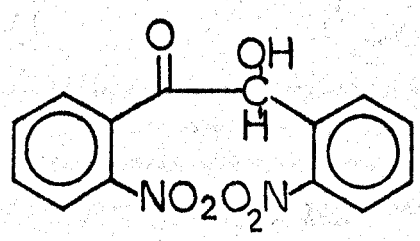
reproducibility of this reaction. After many experiments we determined the conditions necessary to obtain pure products in good yield. To summarise these are:-

(a) Good quality (i.e. Aldrich) n-butyl lithium

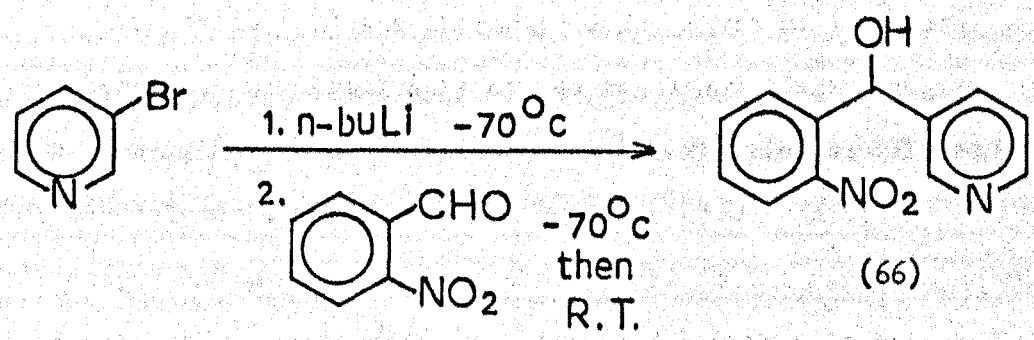
(b) A concentrated solution of n-butyl lithium is preferred (i.e. 15% w/w)

(c) Excessive reaction times should be avoided, two hours at room temperature is sufficient.

By way of example, poor quality n-butyl lithium usually led to a complex mixture of products. The n.m.r. spectrum of the crude products indicated the presence of (66), (67) and products where the n-butyl group appeared to have been incorporated into the pyridine ring.



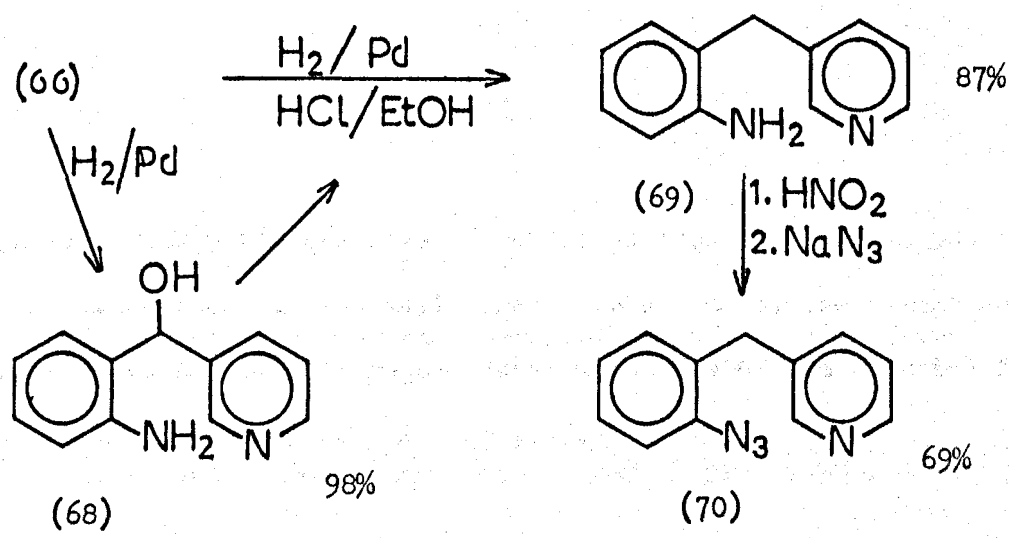
(67)



(66)

Scheme 1.41

The pyridyl alcohol (66) was readily reduced with hydrogen over a palladium catalyst to give the amine (68). Reduction of the alcohol function was less facile however. A method employing boiling hydriodic[116] acid gave only moderate yields of product. Hydrogenolysis[117] in the presence of acid and an excess of catalyst gave the benzylamine (69) in good yield. Subsequent experiments combined the hydrogenations in one step.

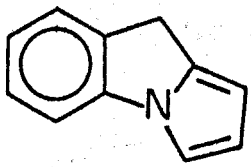


Scheme 1.42

Conversion to the azide was achieved by treatment of a cold buffered[118] solution of the diazonium salt with sodium azide.

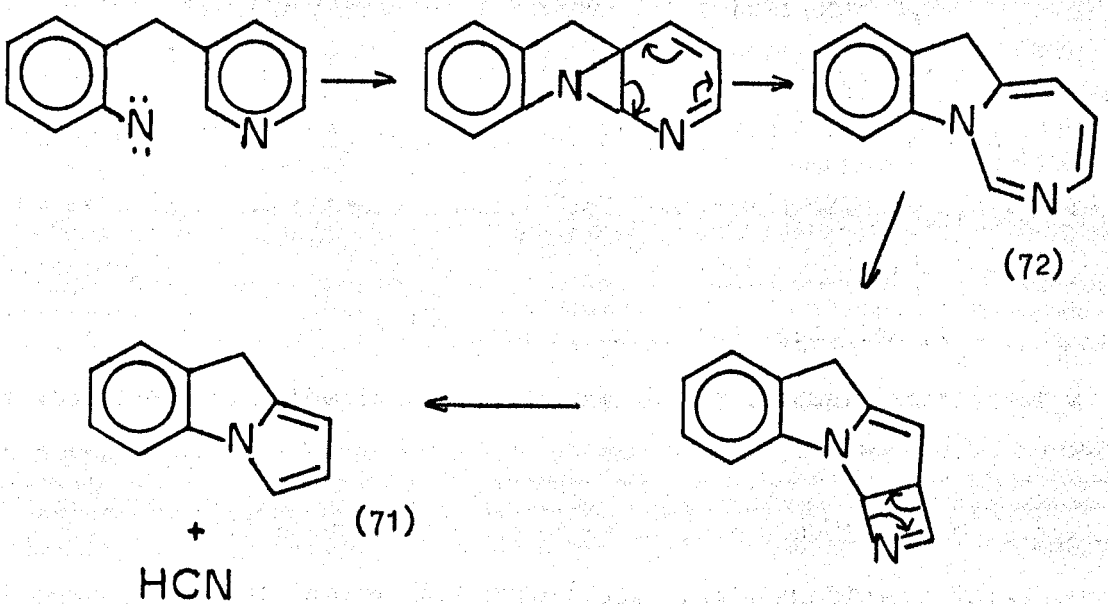
The azide (70) was thermolysed for 4 hrs at 185°C in trichlorobenzene. Chromatography of the resultant black tar gave only two identified products, both in low ($\simeq$ 2%) yields. The major product was polymeric material which was very slow running on chromatography and possessed broad absorptions in the n.m.r. spectrum. Small amounts of the amine (69) were isolated and this is believed to arise from hydrogen abstraction, probably by the triplet nitrene. The

isolation of amines has been noted before in related studies.[1-12] The other compound obtained had analytical and spectral data consistent with the formulation (71).



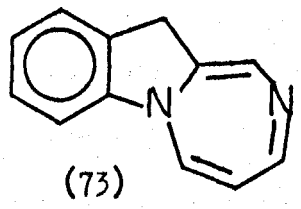
(71)

Comparison with published data[119] confirmed the structure as 9H-pyrrolo[1,2-a]indole. The most likely mechanism for the formation of (71) involves a ring closure and subsequent loss of HCN from the intermediate 11H-diazepino[1,2-a]indole (72).

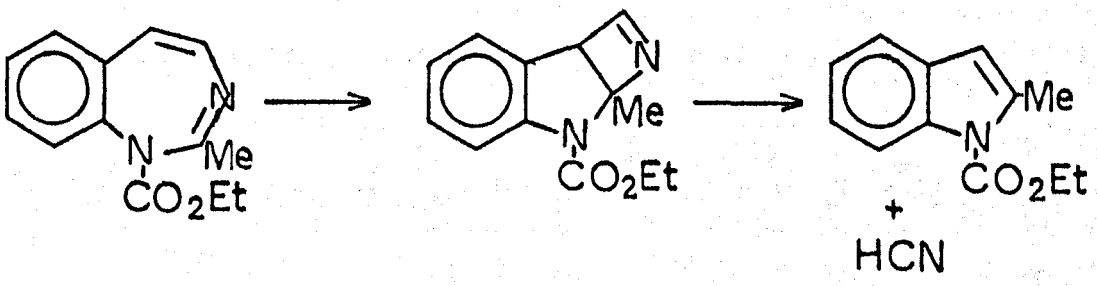


Scheme 1.43

The isomeric intermediate (73) which would also form is unlikely to undergo ring closure and eliminate HCN due to steric effects. There is support for this mechanism in the literature. Tsuchiya et al.[120] have irradiated benzodiazepines and obtained indoles. They have postulated a symmetry allowed electrocyclic reaction followed by extrusion of HCN. (Scheme 1.44)



(73)



Scheme 1.44

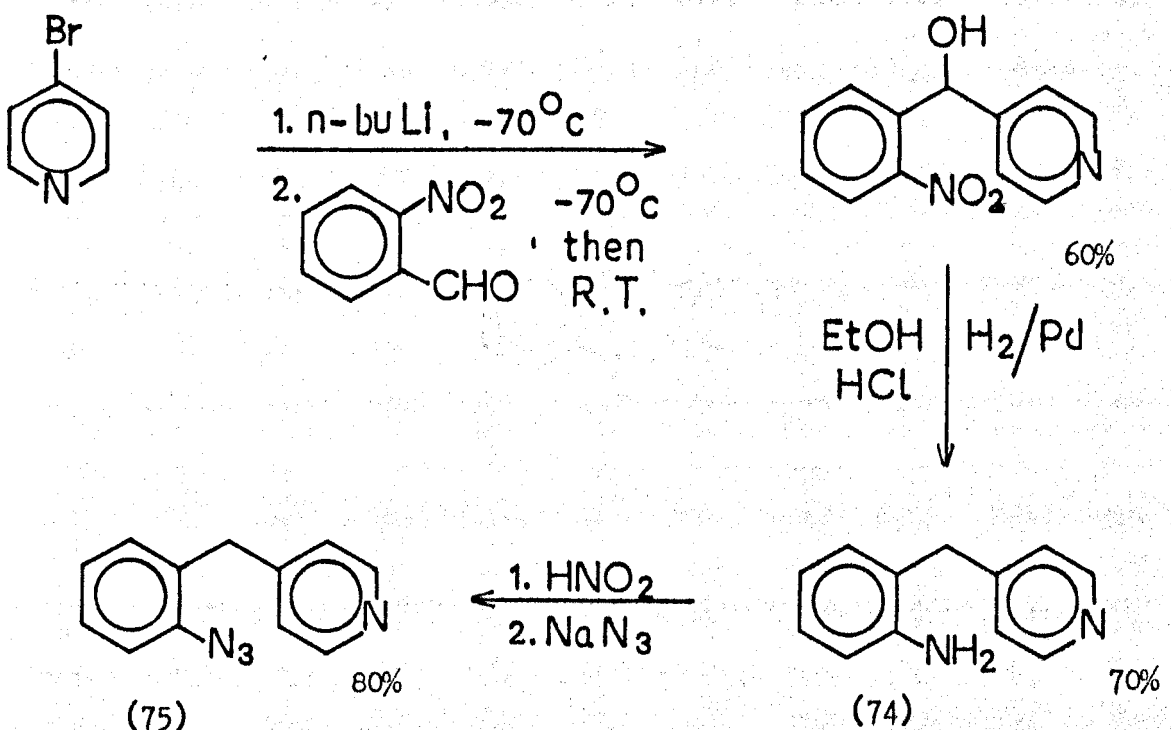
Similar reactions are known for substituted 1,2-diazepines[121] (extrusion of phenylacetylene) and various other diazepines.[122,123] Hydrogen cyanide elimination has also been observed from the nitrene adduct[124] of 5-azido-5H-dibenzo[a,d]cyclo-heptenes.

Barton et al.[123] have reported the isolation of a diazabicyclo[3.2.0]heptadiene compound in the thermal reaction of a 1,2-diazepine.

Small amounts of a brown solid were also isolated from chromatography of the pyridylazide (70). The structure of this compound is unknown at the time of writing. The n.m.r. spectrum had

signals at δ 5.0 p.p.m., δ 6.0, δ 6.15, δ 6.35 and a complex multiplet at δ 6.85 - 7.7 p.p.m. Two poorly resolved signals at δ 8.5 and δ 8.7 were also present. An accurate mass measurement gives the molecular ion at 347.1426 m/e, corresponding to $C_{24}H_{17}N_3$. A loss of pyridine is the only significant feature in the mass spectrum. The u.v. spectrum indicates the presence of extended conjugation in the molecule.

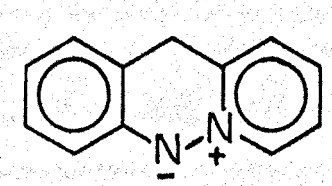
As a further example in this series we then decided to synthesise and thermolyse 2'-azidophenyl-(4-pyridyl)methane. The synthetic route to this compound was essentially the same as for the 3-isomer. The 4-bromopyridine was more difficult to handle than the 3-isomer and was synthesised and reacted with the aldehyde immediately after isolation and drying. Both the 3 and 4-bromopyridines used in this work were conveniently prepared[125,126] from the readily available aminopyridines.



Scheme 1.45

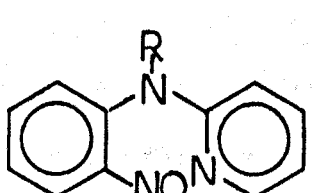
Thermal decomposition of the azide (75) in trichlorobenzene at 180°C under a nitrogen atmosphere led to rapid darkening of the solution. Care was taken to ensure the rigid exclusion of oxygen during the decomposition. Column chromatography gave only one identified product. This was the amine (74) which we again assume to have arisen from the triplet nitrene via a hydrogen abstraction mechanism. The main product was uncharacterised black tar. We did not isolate any of the pyrroloindole (71), this was probably due to the much reduced scale of the decomposition in this case. That the main products in these experiments are polymeric in nature is shown by the broad nature of the resonances in the ^1H n.m.r. spectrum. A ^{13}C n.m.r. spectrum was also extremely complex and these products are only eluted from chromatography columns by solvents of high polarity (e.g. CH_2Cl_2/MeOH).

We decided not to attempt a decomposition of the isomeric 2-azidophenyl-2'-pyridylmethane as this would in all probability lead either to tars or the ylide compound (76) and no products of ring expansion.



(76)

Abramovitch[85,87] has obtained only tarry products from the thermolysis of the pyridine compound (77) with ferrous oxalate.



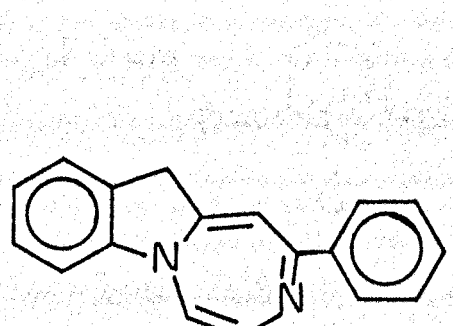
R = H, Me

(77)

We then turned our attention to modifying the structure of the pyridine ring in an attempt to favour ring expansion (or at least the formation of a 6-membered 'acridine-type' product) and reduce the preponderance for tar formation.

It is conceivable that polymer formation is a result of either the azadiene nature of the intermediate (72) or more fundamentally is due to the reluctance of the pyridine moiety to undergo electrophilic attack. Both of these approaches were investigated experimentally.

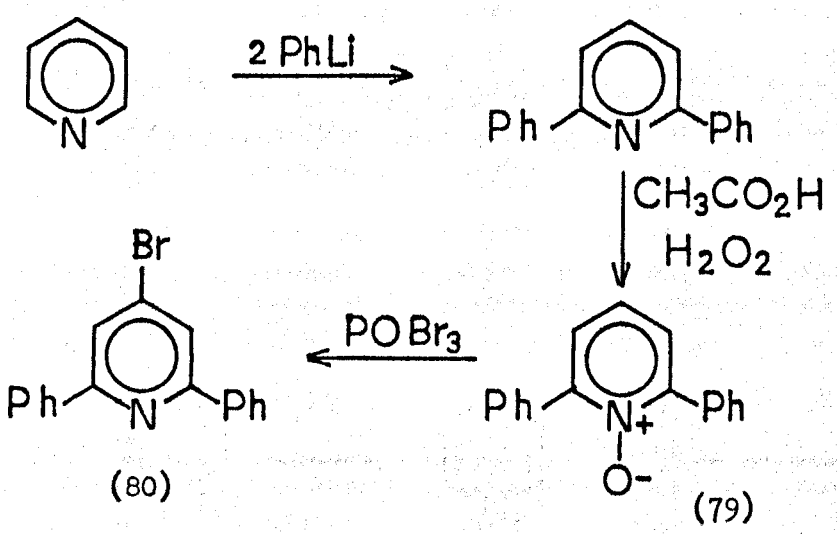
Stilbene compounds are known to be resistant to polymerisation conditions. We therefore adopted this principle in the hope that the intermediate formed (78) would be more stable under the thermolysis conditions.



(78)

The preparation of 2,6-diphenylpyridine was accomplished[127] by sequential addition of phenyl lithium to pyridine in a similar yield to that reported. Prolonged reaction with peracetic acid gave the N-oxide (79) in substantially improved yields over that reported[128] [71% against 14% (based on recovered starting material)]. An attempt to prepare 4-amino-2,6-diphenylpyridine by reaction of 2,6-diphenylpyridine with sodamide in hot xylene gave recovered starting materials. This reaction proceeds in low yield with the 2,6-dimethyl compound.[129]

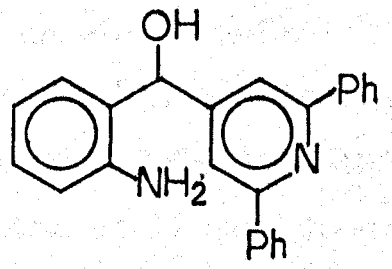
Treatment of the N-oxide (79) with phosphoryl bromide in boiling toluene gave the bromo compound (80) in low yield, together with 2,6-diphenylpyridine. It is known that phosphorus compounds readily deoxygenate N-oxides.[130]



Scheme 1.46

Reaction of the bromopyridine (80) with n-butyllithium and ortho-nitrobenzaldehyde in an analogous manner to that previously described gave a good yield of the required alcohol. Unfortunately

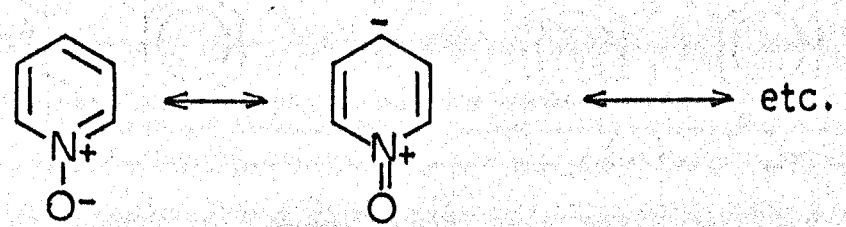
it did not prove possible to reduce the alcohol function. Hydrogenation under forcing conditions gave only the amine (81).



(81)

In view of the difficulty experienced by other workers[12] in reducing the alcohol group and the low yields at the beginning of this synthesis, we decided to abandon this route.

The reactivity of the pyridine ring system towards electrophilic attack is substantially modified by the introduction of the N-oxide function.[131] This is believed to be due to mesomeric electron release by oxygen, resulting in significant contributions by canonical forms such as (82) to the overall structure.



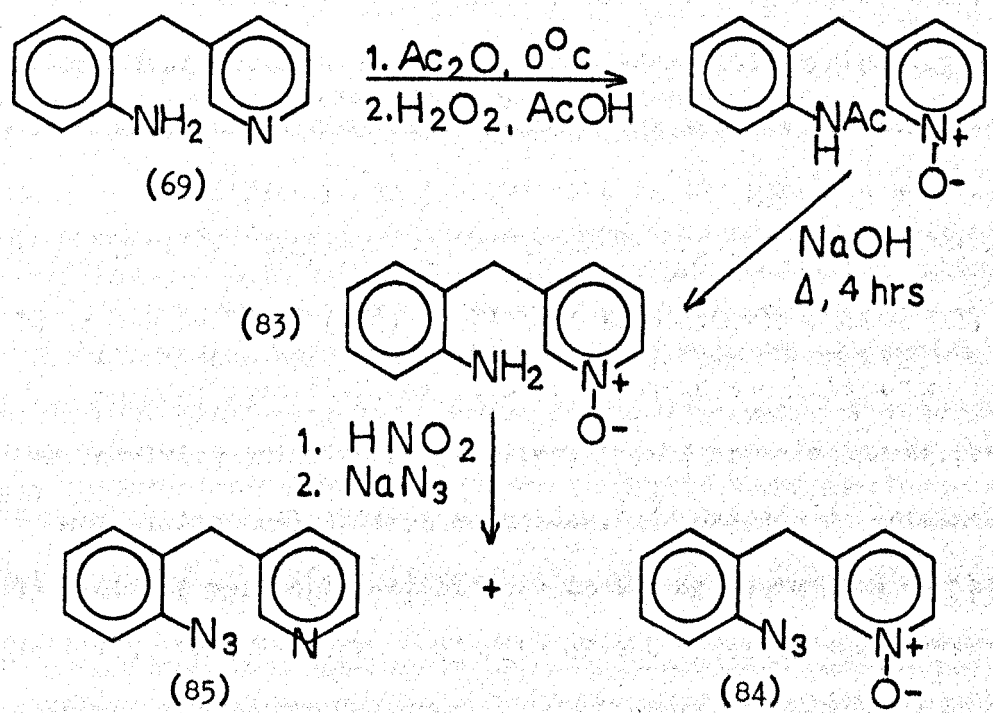
(82)

As an example, nitration of pyridine is very difficult normally and proceeds in low yield under the most vigorous conditions. In

contrast pyridine N-oxide reacts smoothly in good yield under normal nitrating conditions.

We therefore undertook a study of the effect of N-oxidation of pyridine in the nitrene insertion process.

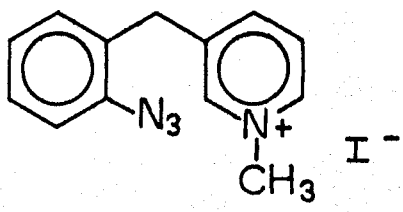
We obtained the amine (69) as previously discussed and it was converted to the acetyl derivative in good yield. Oxidation with peracetic acid and deprotection of the amine function[132] with aqueous base gave the N-oxide (83). Formation of the azide in buffered solution[118] and chromatography gave the two azides (84) and (85). Azide (85) could conceivably arise from in situ deoxygenation with nitrous acid.



Scheme 1.47

Thermal decomposition of the azide (84) in the usual manner gave a dark solution. Chromatography gave no identifiable material, only tars were isolated. We have also synthesised the methiodide (86) but

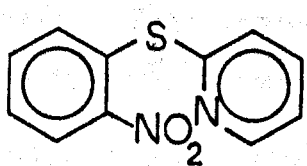
did not carry out a decomposition.



(86)

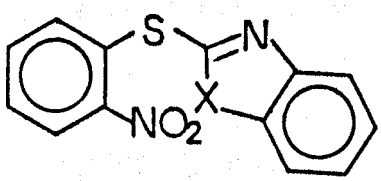
The exclusive tar formation in these reactions probably occurs as a consequence of the reluctance of the pyridine ring to enter into reactions with the singlet (electrophilic) nitrene. Alternatively the nature of the initial ring expansion product (72) may have led to further breakdown products and ultimately tars. Intersystem crossing of the initially formed singlet nitrene to the triplet species might be expected to be efficient in the presence of the pyridine substrate. Triplet nitrenes are diradical in character; chain initiation with suitable compounds, e.g. (72), could lead to polymerised material.

Polymer formation has been reported in the literature for reactions involving triazine derivatives,[133] the irradiation of phenyl azide[134] and azidophenyl thienyl sulphides.[135] Cadogan[136] obtained a low (2%) yield of pyrido[1,2-b]indazole in the deoxygenation of the sulphide (87). Presumably the majority of the material was polymeric



(87)

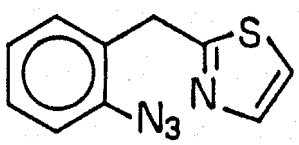
in nature. Meth-Cohn[135] and co-workers obtained only amines in the decomposition of the π-deficient compound (88).



X = S or NH

(88)

Thermolysis of the related thiazole (89) also led to tar formation[12] and amines.



(89)

Thus it would appear that π-deficient heterocyclic systems are in general disappointing substrates for nitrene studies.

EXPERIMENTAL

Preliminary notes

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

Infrared absorption spectra were recorded on a Perkin Elmer 257 instrument or a Perkin Elmer 357/197 combination. Solids were recorded as solutions (e.g. $CHCl_3$) and liquids as thin films.

Ultraviolet and visible absorption spectra were recorded on a Perkin Elmer 402 spectrophotometer.

Nuclear magnetic resonance (N.m.r.) spectra were routinely measured on a Perkin Elmer R.24 instrument at 60 MHz and/or a Varian EM 390 at 90 MHz.

Carbon-13 n.m.r. and proton n.m.r. at 100 MHz were recorded on a Jeol F.X. 100 Fourier Transform instrument. Chemical shift values are quoted in delta (δ) values in p.p.m. with respect to tetramethylsilane as internal standard.

Micro-analyses were carried out on a Perkin Elmer 240 carbon/hydrogen/nitrogen analyser at the University of Keele.

Exact mass measurements were carried out by P.C.M.U. (Harwell).

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

Column chromatography was carried out using deactivated Woelm alumina, neutral grade. The activity values quoted refer to the Brockmann scale "Short-path" column chromatography was performed with Merck 7729 grade silica gel using an automatic fraction collector.

Medium-pressure column chromatography was carried out with Merck grade 9385 silica gel (Kieselgel 60) at a pressure of c.a. 50 p.s.i. Fractions were collected manually. Thin layer chromatography was carried out on 20 x 5 cm glass plates coated with Merck Kieselgel PF_{254} or on polythene sheets coated with silica gel (Camlab. Ltd.). Components were visualised under ultraviolet light or developed in iodine vapour or on aqueous spray of 0.5% $KMNO_4$.

Preparative layer chromatography (P.L.C.) was performed on 40 x 20 cm glass plates coated with a 1.5 mm layer of Kieselgel PF_{254}. The separate components, visualised under ultraviolet light, were scraped off the plates and extracted three times with methanol or dichloromethane. The filtered methanol solution was evaporated, taken up in chloroform, filtered and finally evaporated.

Analytical gas-liquid chromatography was performed on a Pye Series 104 instrument, particular column packings and stationary phases are detailed separately in the relevant experimental sections.

Preparative gas-liquid chromatography was carried out on a Pye Series 105 automatic preparative chromatograph.

Analytical high-pressure liquid chromatography was carried out on a Du Pont 830 L.C. equipped with a Pye LC3 U.V. detector, a 20 x 0.5 cm Partisil 10 silica gel column was employed.

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

Abbreviations used:

s	=	singlet	d of d	=	doublet of doublets
m	=	multiplet	Ex.	=	Exchangeable
tr	=	triplet	br	=	broad
quart.	=	quartet	sh	=	shoulder
quint.	=	quintet	d	=	doublet

Part A

Preparation and thermal decomposition of 2'-azidophenyl-(3-pyridyl)-methane (70)

3-Bromopyridine

Prepared by the method of Talik and Oganowska[125] from 3-aminopyridine and KNO_2/CuBr.

b.pt. 170°C/731 mm

lit.[125] b.pt. 175°C

2'-Nitrophenyl-(3-pyridyl)methanol(66)[115]

A solution of 3-bromopyridine (15 g, 0.095 mol) in anhydrous ether (45 ml) was added over a period of fifteen minutes to a stirred solution of n-butyl lithium (15% w/w in hexane, 50 ml) in anhydrous ether (50 ml) under a dry nitrogen atmosphere at -70°C to -80°C.

The yellow mixture was stirred at that temperature for a further fifteen minutes and then a solution of o-nitrobenzaldehyde (14.5 g, 0.095 mol) in anhydrous ether (100 ml) was added dropwise during thirty minutes.

Stirring was continued for two hours at -70°C and finally at room temperature for two hours.

The light brown reaction mixture was poured into ice/water saturated with salt and sodium metabisulphite. The ether layer was separated and the aqueous phase was extracted with ether (8 x 200 ml). In some cases the product crystallised out as a yellow solid, filtration and washing with 40-60° petroleum ether gave the crude alcohol, 17 g (75%). Usually, the combined ether extracts were evaporated and the residue steam distilled. The residual oil was salted out, extracted

with ether (6 x 50 ml) and dried (Na_2SO_4). Evaporation gave the crude alcohol. (Yields, 64-70%).

M.pt. 105.5 - 106.5°C (CCl_4)

Analysis: Found: C, 62.25%; H, 4.29%; N, 12.18%

$C_{12}H_{10}N_2O_3$ requires: C, 62.60%; H, 4.38%; N, 12.17%

N.m.r. ($CDCl_3$)	δ 8.35 p.p.m.	d of d	2H	pyridine α H's
				J = 7 Hz, 2 Hz
	8.0 - 7.1	m	6H	Aromatic +
				pyridine β/γ H's
	6.4	s	1H	CH
	4.9	br.s	1H	EXD$_2$O, OH

I.R. ($CHCl_3$) ν_{max} 3300, 3000, 2920, 1520, 1345, 735 cm^{-1}

U.V. (95% EtOH) λ_{max} 263 nm $\log_{10} \epsilon$ 3.84

273 nm sh

288 nm sh

Mass spectrum, m/e 213 (16%), 183 (36), 168 (100), 154 (35), 142 (20), 141 (18), 140 (23), 127 (68), 119 (29), 117 (29), 106 (26), 105 (29), 104 (18), 78 (91), 77 (52), 51 (52)

2'-Aminophenyl-(3-pyridyl)methanol (68)

A solution of 2'-nitrophenyl-(3-pyridyl)methanol (2.3 g, 0.01 mol) in 95% ethanol (50 ml) together with 10% palladium on charcoal catalyst (0.5 g) was hydrogenated at room temperature and pressure until three equivalents of hydrogen had been taken up. The solution was filtered and evaporated to give the crude amino-alcohol as a viscous yellow oil (1.96 g, 98%). Trituration with 40-60° petroleum ether gave a yellow solid.

M.pt. 143 - 144°C (Benzene)

Analysis: Found: C, 71.48%; H, 6.06%; N, 13.60%

$C_{12}H_{12}N_2O$ requires: C, 71.98%; H, 6.04%; N, 13.99%

N.m.r. ($CDCl_3$)	δ 8.3 p.p.m.	d of d	2H	Pyridine α H's
				J = 8 Hz, 2 Hz
	7.6	br.d	1H	Pyridine γ H
				J = 7 Hz
	7.3 - 6.5	m	5H	Aromatic +
				pyridine β H
	5.75	s	1H	CH
	4.35	br.s	3H	ExD_2O, OH, NH_2

I.R. ($CHCl_3$) ν_{max} 3450, 3380, 3150, 2915, 2840, 1640, 1590, 1575, 1455, 1295, 1000, 870, 860 cm^{-1}

U.V. (95% EtOH) λ_{max} 242 nm sh
265 nm sh
295 nm $\log_{10}\varepsilon$ 3.47

Mass spectrum, m/e 201 (9%), 200 (33) M^+, 182 (27), 181 (100), 155 (7), 154 (12), 129 (9), 65 (9), 51 (11)

2'-Aminophenyl-(3-pyridyl)methane (69)

A solution of 2'-aminophenyl-(3-pyridyl)methanol (1 g, 0.005 mol) in ethanol (8 cm^3) and 5% conc. hydrochloric acid in ethanol* (26 cm^3) was hydrogenated at room temperature and pressure in the presence of 0.5 g 10% palladium on charcoal catalyst, until one equivalent of hydrogen had been taken up. (Generally about 20 hrs). The solution was filtered, basified (conc. NH_3) and evaporated. The residue was dissolved in dichloromethane and dried (Na_2SO_4). The product (0.8 g, 87%) was a brown oil which crystallised.

N.B. * Use of methanol led to fires on several occasions.

M.pt. 84 - 85°C (Cyclohexane)

Analysis:		Found:	C, 78.40%;	H, 6.60%;	N, 15.40%
	$C_{12}H_{12}N_2$	requires:	C, 78.20%;	H, 6.60%;	N, 15.20%

N.m.r. ($CDCl_3$)	δ 8.5 p.p.m.	d of d	2H	pyridine α-protons
	7.5 - 6.6	m	6H	Aromatic + pyridine β/γ H's
	3.80	s	2H	CH_2
	3.50	br.s	2H	$-NH_2$ Ex. D_2O

I.R. ($CHCl_3$) ν_{max} 3440, 3380, 3190, 3020, 3040 (sh), 2910, 2140, 1700, 1620, 1570, 1580 (sh), 1500, 1475, 1450, 1420, 1270, 1310, 1050, 900 cm^{-1}

U.V. (95% EtOH) λ_{max} 235 nm $\log_{10}\varepsilon$ 3.72
264 nm $\log_{10}\varepsilon$ 3.30
272 nm sh

Mass spectrum, m/e 186 (49%), 185 (96), 184 (100, $M^{+\cdot}$), 183 (96), 182 (62), 181 (44), 170 (18), 169 (60), 168 (91), 167 (91), 166 (87), 157 (45), 156 (91), 140 (33), 139 (36), 130 (31), 129 (25), 128 (25), 117 (22), 107 (67), 106 (91), 104 (27), 78 (45), 77 (62), 65 (45), 63 (27), 51 (36), 39 (36)

2'-Aminophenyl-(3-pyridyl)methanol- Hydriodic acid route

A solution of 2'-aminophenyl-(3-pyridyl)methane (6.1 g, 0.03 mol) in purified* conc. HI (75 ml) was boiled under reflux for 5 hrs. The mixture was poured into water (300 ml) containing sodium metabisulphite (50 g). The residual black tar in the flask was decomposed by boiling with 50% NaOH (100 ml) for 5 minutes; then added to the aqueous sodium metabisulphite. The combined aqueous layers were basified (conc.

* Boiled under reflux with red phosphorus then distilled under a N_2 atmosphere; colourless liquid, b.pt. 126°C.

NH_3), then extracted with CH_2Cl_2 (3 x 150 ml). The organic extracts were dried (Na_2SO_4) and evaporated to yield a dark oil which was distilled, the product had b.pt. 133 - 134°C/0.1 mm.

Column chromatography of the distillation residues (Al_2O_3, IV, 90 g) with benzene as eluant gave further quantities of product. Total yield, 3.3 g (59%). The material had identical N.m.r. spectral properties to previously prepared material.
M.pt. and mixed m.pt. 84°C (cyclohexane)

2'-Azidophenyl-(3-pyridyl)methane (70)

A solution of 2'-aminophenyl-(3-pyridyl)methane (14.8 g, 0.08 mol) in conc. HCl (38 ml), water (38 ml) and purified 1,4-dioxan (100 ml) was treated dropwise with stirring at 0°C with a solution of sodium nitrite (6.25 g, 0.09 mol) in water (140 ml). After stirring for 30 minutes at 0°C the solution was rapidly filtered into a stirred solution of sodium azide (6.25 g, 0.096 mol) and sodium acetate (62.5 g) in water (280 ml) at 0°C. The mixture was stirred for 30 minutes at 0°C then extracted with dichloromethane (2 x 250 ml) which was dried (Na_2SO_4) and evaporated at 30°C. The crude azide, which was obtained as a yellow oil, was chromatographed on a foil-wrapped alumina column (500 g Activity IV). A mixture of 20% benzene in 40 - 60° petroleum ether eluted the azide (11.6 g, 69%) as a pale yellow oil. Column fractions were evaporated at 30°C.

Analysis:	Found:	C, 68.49%;	H, 4.97%;	N, 25.69%	
	$C_{12}H_{10}N_4$ requires:	C, 68.55%;	H, 4.79%;	N, 26.65%	
N.m.r. ($CDCl_3$)	δ 8.3 - 8.4 p.p.m.	d	2H	pyridine α H's	
	7.5 - 6.9	m	6H	Aromatic + pyridine H's	
	3.85	s	2H	CH_2	

I.R. (thin film)	ν_{max} 3240, 3040, 3010, 2910, 2840, 2420, 2210, 2100 (s), 1560, 1470, 1440, 1410, 1290, 1190, 1160, 1140, 1120, 1100, 1040, 1025, 940, 840, 820, 800, 770 cm^{-1}
U.V. (95% EtOH)	λ_{max} 260 nm $\log_{10}\epsilon$ 3.97 263 nm sh 271 nm sh
Mass spectrum, m/e	185 (24%), 184 (52), 183 (96), 182 (100%, $M^{\pm}$ 28), 181 (96), 179 (37), 167 (24), 163 (43), 156 (50), 155 (96), 154 (20), 131 (17), 129 (18), 128 (20), 127 (30), 110 (20), 92 (24), 91 (20), 77 (39), 63 (22), 51 (18), 44 (89), 40 (57).

Thermal decomposition of 2'-azidophenyl-(3-pyridyl)methane (70)

A solution of the azide (11.2 g, 0.053 mol) in 1,2,4-trichlorobenzene (100 ml) was added dropwise over a period of 1 hr to trichlorobenzene (1000 ml) maintained at 185°C in a 2 l flask equipped with mechanical stirrer, condenser and a dry nitrogen inlet. The entire decomposition was carried out under a dry nitrogen atmosphere. After the addition of the azide the dark solution was heated at 185 - 195°C for a further 4 hrs. The decomposition was monitored by the disappearance of the azide stretching frequency in the I.R. spectrum. The solvent was then evaporated (1 mm) to yield a black tar (17.5 g).

G.L.C. (3% OV 101 column, 5 ft, N_2 60 ml/min, 280°C) showed 3 peaks. T.L.C. (10% MeOH/EtOAc) indicated three components with a large amount of baseline material. The black oil was chromatographed on a column of alumina (IV, 530 g); 200 ml fractions were collected. Petroleum ether (40 - 60°) eluted trichlorobenzene (7.6 g) followed by

a yellow crystalline solid whose analytical figures and spectral characteristics suggested the compound to be 9H-pyrrolo-[1,2-a]-indole (71) (0.20 g, 2.4%).

M.pt. 90 - 91°C (Absolute EtOH)

lit m.pt.[119] 90 - 91°C (Absolute EtOH)

Analysis: Found: C, 85.01%; H, 5.83%; N, 9.12%

Calculated for $C_{11}H_9N$: C, 85.13%; H, 5.85%; N, 9.03%

N.m.r. ($CDCl_3$) 100 MHz	δ 7.42 - 6.99 p.p.m.	m	5H	Aromatic + C_3 pyrrole H
	6.38	d of d	1H	C_2 pyrrole H
	6.11	d of d	1H	C_1 pyrrole H
	3.83	br.s	2H	C_9 CH_2
I.R. ($CHCl_3$)	ν_{max} 3060, 3030, 2960, 2905, 1650, 1590, 1550, 1490, 1470, 1310, 1270, 1070, 1040 cm^{-1}			
U.V. (95% EtOH)	λ_{max} 263 nm ($\log_{10}\varepsilon$ 4.16)			
	286 nm sh			
	295 nm sh			

Further elution with mixtures of 40 - 60° petroleum ether and benzene gave mainly unidentified oils. A mixture of 70% benzene and 30% petroleum ether eluted a semi-crystalline brown compound (0.35 g). P.L.C. in a 50% EtOAc/toluene mixture gave two bands. A band at R_F 0.25 contained an unidentified oil (40 mg). The other band, R_F 0.40, gave a brown crystalline solid (0.22 g).

M.pt. 161 - 163°C (yellow needles from 60 - 80° petroleum ether)

Analysis: Found: C, 82.36%; H, 4.77%; N, 12.49%

N.m.r. ($CDCl_3$) 100 MHz	δ 7.9 - 7.05 p.p.m.	m
	6.62	s
	6.36	s
	6.26	s
	5.25	s
I.R. ($CDCl_3$)	ν_{max} 2950, 2850, 1645, 1600, 1565, 1460, 1410, 1360, 1350, 1310, 1150, 1090, 1020, 985, 900 cm^{-1}	
U.V. (95% EtOH)	λ_{max} 265 nm	
	358 nm	
	370 nm sh	
Mass spectrum, m/e	349 (33%), 348 (100), 347 (43), 269 (14), 268 (9.5), 174 (19), 173 (14)	
Accurate mass, m/e	347.1426	

The structure of this compound is not known at the time of writing. Elution with benzene gave crude 2'-aminophenyl-(3-pyridyl)methane (69). P.L.C. (90% EtOAc, 10% MeOH) gave the pure amine, R_F 0.48 (0.25 g, 2.5%). M.pt. and mixed m.pt. 84 - 85°C, identical in every respect with material synthesised previously. Further chromatography with mixtures of benzene and dichloromethane and finally 10% methanol/dichloromethane gave only unidentified oils and tarry compounds. Approximately 5 g of a black solid was eluted with 10% methanol/dichloromethane. This was assumed to be polymeric in nature, owing to its broad proton N.m.r., and the extreme complexity of the ^{13}C N.m.r. spectrum.

Part B

Other synthetic routes to 2-azidophenyl-(3-pyridyl)methane

Attempted preparation of N-acetyl, ∝-thiophenyl, ∝-(3-pyridyl) o-toluidine

4-Methylpyridine-1-oxide

Prepared as for the 2-methyl derivative according to the method of Bockelheide and Linn.[137]

M.pt. 186 - 186.5°C (acetone)

lit.[140] m.pt. 186°C (acetone)

4-Phenylthiomethylpyridine (64)

Prepared by the method of Bauer and Gardella.[111]

B.pt. 110 - 115° / 0.25 mm; m.pt. 49°C (40 - 60° petroleum ether)

lit.[111] b.pt. 126 - 128° / 1 mm; m.pt. 48 - 51°C (40 - 60° petroleum ether)

Reaction of 4-phenylthiomethylpyridine (64) with N-chloroaniline and base. Attempt to prepare N-acetyl, ∝-thiophenyl, ∝-(3-pyridyl) o-toluidine

A stirred solution of distilled aniline (0.93 g, 0.012 mol) in anhydrous dichloromethane (50 ml) was treated with 4-phenylthiomethylpyridine (2.41 g, 0.012 mol) and then freshly prepared t-butylhypochlorite (1.09 g) at -40°C.

The solution was stirred at -40°C for 3 hrs.

Triethylamine (1.01 g, 0.012 mol) was added and the reaction mixture stirred at -40°C for a further ½ hr, then allowed to warm to 0°C. Acetic anhydride (2.05 g, 0.02 mol) was then added and the solution

allowed to warm to room temperature over a 1 hr period. The solution was stirred overnight. The mixture was then dried (Na_2SO_4) and evaporated to yield a semi-crystalline black oil (7 g). The oil was absorbed onto alumina (IV, 35 g) and chromatographed on a column of alumina (IV, 210 g): 40 - 60° petroleum ether eluted an orange oil (0.5 g) whose N.m.r. and mass spectrum indicated the compound to be diphenyldisulphide. A mixture of 35% benzene in petroleum ether (40 - 60°) eluted the starting thio-ether (64), (0.76 g). Further elution with benzene gave acetanilide (0.42 g). Other fractions gave only trace quantities of unidentified oils.

Attempted preparation of N-methoxycarbonyl, α-thiophenyl, α-(3-pyridyl), o-toluidine

According to the method of Gassman,[109] aniline (1.86 g, 0.02mol) t-butyl hypochlorite (2.18 g, 0.02 mol) and the pyridylthio-ether (64) (4.82 g, 0.024 mol) were reacted at -40°C in dry dichloro-methane (50 ml). Triethylamine (2.02 g, 0.02 mol) and methyl chloro-formate (2.3 cm^3, 0.02 mol) were subsequently added. Work-up and extensive chromatography gave only recovered starting materials and unidentified oils.

Reaction of 4-picolylsodium with o-chloronitrobenzene

4-Picolylsodium, prepared from 4-picoline (48.8 ml, 0.5 mol) and sodium (11.5 g, 0.5 mol) in liquid ammonia (400 ml) as reported[112] was treated in anhydrous ether (150 ml) at 0°C with a solution of o-chloronitrobenzene (78.8 g, 0.5 mol) in anhydrous ether (600 ml). The solution was finally refluxed on a boiling water bath for 2 hrs. The mixture was poured into ice/water (500 ml) and the aqueous

phase extracted with ether (3 x 250 ml). Extraction of the ethereal layers with 2M HCl (2 x 250 ml) and basification (conc. NH_3) gave, after re-extraction (2 x 250 ml) to ether and drying, essentially a quantitative recovery of 4-picoline. A high yield ($\simeq$ 90%) of o-chloronitrobenzene was recovered from the original ether layers.

Attempted reaction of the Grignard reagent from 4-bromopyridine with 2-methyl-3,1-benzoxazin-4-one

2-Methyl-3,1-benzoxazin-4-one

Prepared according to the method of Mohr and Kohler[139] in 90% yield.

M.pt. 79 - 80°C (60 - 80° petroleum ether)
lit.[139] m.pt. 80 - 81°C (60 - 80° petroleum ether)

Attempted preparation of the Grignard reagent of 4-bromopyridine

A solution of 4-bromopyridine (6.32 g, 0.053 mol) in dry T.H.F. (80 ml) was reacted with magnesium turnings (1.44 g, 0.06 mol) in dry T.H.F. (20 ml) in the usual manner. Upon addition of a crystal of iodine and slight warming a red-brown precipitate formed. The solution was refluxed for 30 mins. A solution of 2-methyl-3,1-benzoxazin-4-one (6.44 g, 0.04 mol) in dry ether (25 ml) and dry toluene (50 ml) was added dropwise with stirring and the solution boiled under reflux for 3 hrs. The mixture was hydrolysed with saturated ammonium chloride in ammonia (100 ml), the organic layer separated, and the aqueous layers extracted with ether (2 x 100 ml). The combined extracts were dried (Na_2SO_4) and evaporated. N.m.r. revealed only the presence of 2-methyl-3,1-benzoxazin-4-one (6 g).

Part C

Preparation and thermal decomposition of 2'-azidophenyl-(4-pyridyl)methane

4-Bromopyridine

Prepared according to the method of Murray and Langman[126] from 4-aminopyridine by diazotisation of the perbromide salt.

Yield, 82%

M.pt. HCl-salt, 235 - 238°C

lit. m.pt.,[126] 237 - 239°C

2'-Nitrophenyl-(4-pyridyl)methanol

A solution of dry 4-bromopyridine (12.8 g, 0.081 mol) in dry ether (100 ml) was added dropwise with stirring to a solution of n-butyl lithium (15% w/w in hexane, 43 ml) in dry ether (50 ml) at -70°C under an atmosphere of dry nitrogen. The mixture was stirred at -70°C for 30 mins. A solution of o-nitrobenzaldehyde (12.4 g, 0.081 mol) in dry ether (100 ml) was then added dropwise over a period of 30 mins. The mixture was stirred at -70°C for 2 hrs and finally at room temperature for 2 hrs. The light brown reaction mixture was poured into ice/water (1 litre) saturated with salt and sodium meta-bisulphite. The organic layer was separated and the aqueous phase washed with ether (6 x 200 ml). The ethereal layers were dried (Na_2SO_4). A yellow solid, precipitated from the ether layers was filtered and washed with ether (2 x 200 ml), to give virtually pure alcohol, (7.0 g). Column chromatography (IV Al_2O_3, 250 g) of the brown oil isolated from the ether layers gave further alcohol (4.6 g).

Total yield 11.6 g (60%).

M.pt. 169 - 170°C (Ethyl Acetate) colourless needles

Analysis: Found: C, 62.90%; H, 4.42%; N, 12.04%

$C_{12}H_{10}N_2O_3$ requires: C, 62.60%; H, 4.38%; N, 12.17%

N.m.r. (DMSO-d_6) δ 8.4 p.p.m. d 2H J = 6 Hz

8.0 - 7.2 m 6H

6.5 d 1H J = 5 Hz Ex.D_2O

6.2 d 1H J = 5 Hz singlet on addition of D_2O

I.R. (DMSO-d_6) ν_{max} 3200 cm^{-1}, 2850, 1600, 1530, 1410, 1350, 1300, 1170, 850, 780 cm^{-1}

U.V. (95% EtOH) λ_{max} 220 nm $\log_{10}\varepsilon$ 4.19

280 nm $\log_{10}\varepsilon$ 3.89

325 nm $\log_{10}\varepsilon$ 3.71

Mass spectrum, m/e 214 (30%), 213 (58%, M-17), 197 (50), 196 (100), 182 (38), 168 (66), 155 (38), 140 (22), 128 (56), 127 (96), 106 (28), 105 (30), 104 (36), 79 (28), 78 (98), 77 (96), 76 (28), 65 (28), 51 (96)

2'-Aminophenyl-(4-pyridyl)methane (74)

A solution of 2'-nitrophenyl-(4-pyridyl)methanol (6.5 g, 0.028 mol) in 95% ethanol (45 ml) and 5% conc. HCl in 95% ethanol (150 ml) was hydrogenated at normal temperature and pressure in the presence of 10% palladium on charcoal catalyst (3 g). After 4 equivalents of hydrogen had been absorbed (c.a. 43 hrs) the solution was filtered, basified (conc. NH_3) and evaporated. The residue was dissolved in dichloromethane, dried (Na_2SO_4) and evaporated to give a yellow oil which was distilled. The amine distilled at 134 - 140°C/

0.06 mm, yield, 3.70 g (71%).

M.pt. 96 - 98°C (cyclohexane)

Analysis: Found: C, 78.50%; H, 6.84%; N, 15.19%

$C_{12}H_{12}N_2$ requires : C, 78.20%; H, 6.60%; N, 15.20%

N.m.r. ($CDCl_3$) δ 8.3 p.p.m. d of d 2H J = 6 Hz and 1 Hz

7.1 - 6.4 m 6H

3.8 s 2H

3.5 br.s 2H Ex. D_2O

I.R. ($CHCl_3$) ν_{max} 3460 cm^{-1}, 3390, 3190, 3060, 3020, 2940, 2900, 2820, 2205, 2215, 1650, 1600, 1490, 1455, 1415, 1310, 1270, 1245, 1215, 1070, 990, 925, 850, 800 cm^{-1}

U.V. (95% EtOH) λ_{max} 239 nm $\log_{10}\varepsilon$ 3.98

293 nm $\log_{10}\varepsilon$ 3.42

Mass spectrum, m/e 186 (34%), 185 (10), 184 (64, $M^{+\cdot}$), 169 (22), 167 (16), 106 (98), 77 (26), 51 (24)

2'-Azidophenyl-(4-pyridyl)methane (75)

A solution of 2'-aminophenyl-(4-pyridyl)methane (2.2 g, 0.012 mol) in conc. HCl (4 ml) and water (4 ml) was diazotised at 0°C with a solution of sodium nitrite (0.92 g, 0.012 mol) in water (20 ml). The solution was stirred at 0°C for 30 mins. This solution was then added dropwise to a solution of sodium azide (0.92 g, 0.014 mol) and sodium acetate (9.2 g) in water (40 ml) at 0°C. The solution was stirred at 0°C for a further 30 mins. The aqueous phase was then extracted with dichloromethane (2 x 50 ml) and the organic layers dried (Na_2SO_4) and evaporated (30°C) to yield a yellow oil. The oil was then percolated down a foil-wrapped alumina column (100 g IV). A mixture of 50% benzene/40 - 60° petroleum ether eluted the azide (2.0 g, 80%) as a

yellow oil which crystallised. Column fractions were evaporated at 30°C.

M.pt. 54.5 - 55°C (40 - 60° petroleum ether)

Analysis: Found: C, 67.92%; H, 4.71%; N, 26.37%

$C_{12}H_{10}N_3$ requires: C, 68.55%; H, 4.79%; N, 26.65%

N.m.r. ($CDCl_3$) δ 8.35 p.p.m. d 2H J = 6 Hz

7.3 - 6.85 m 6H

3.8 s 2H

I.R. ($CHCl_3$) ν_{max} 3060 cm^{-1}, 3010, 2910, 2210, 2120 (s), 1600, 1580, 1485, 1490, 1450, 1415, 1285, 880, 910 cm^{-1}

U.V. (95% EtOH) λ_{max} 255 nm $\log_{10}\varepsilon$ 4.11

265 nm sh

282 nm sh

293 nm sh

Mass spectrum, m/e 210 (10%, $M^{+\cdot}$), 183 (30), 182 (100), 155 (22), 127 (18), 77 (16), 65 (12), 63 (14), 52 (16), 51 (40), 50 (16), 39 (32)

Thermal decomposition of 2'-azidophenyl-(4-pyridyl)methane (75)

A solution of the azide (1.8 g, 0.009 mol) in 1,2,4-trichlorobenzene (20 ml) was added dropwise over a period of 1 hr to trichlorobenzene (200 ml) maintained at 180°C under an atmosphere of dry, oxygen-free nitrogen. The solution was vigorously stirred throughout the decomposition. The solution was heated for 4 hrs at 180°C, until I.R. revealed the absence of azide. Removal of solvent (0.5 mm) gave a black tarry product (2.8 g), which was absorbed on

alumina (20 g, IV) and chromatographed on a column of alumina (100 g, IV). Fractions of 100 ml were collected.

Petroleum ether (40 - 60°) eluted 1,2,4-trichlorobenzene (1.1 g). Elution with 20% benzene/petroleum ether and then benzene gave unidentified oils. Continued elution with benzene and 50% benzene/dichloromethane gave 2'-aminophenyl-(4-pyridyl)methane (74) (0.38 g, 24%) identical in every respect with material previously synthesised.

Elution with 20% methanol/dichloromethane gave a brown solid (1.2 g) whose proton and ^{13}C N.m.r. spectrum indicated the compound to be polymeric in nature.

Part D

Attempted preparation of 2'-azidophenyl-(2,6-diphenyl-pyridin-4-yl)methane

2,6-Diphenylpyridine

Prepared according to the procedure of Overberger et. al.[127] in 58% yield from 2-phenylpyridine. Overall yield 20%.

M.pt. 81°C (EtOH)

lit.[127] m.pt. 80 - 81°C (EtOH)

2,6-Diphenylpyridine-1-oxide (79)

A solution of 2,6-diphenylpyridine (46.2 g, 0.20 mol) in glacial acetic acid (240 ml) and 30% (100 vol.) hydrogen peroxide (20 ml) was boiled under reflux for 2 hrs. An additional 20 ml of 30% hydrogen peroxide was then added and the solution refluxed for a total of 5 days. Further additions of hydrogen peroxide were made at 24 hr intervals. (Total volume added 140 ml). The progress of the reaction was monitored by T.L.C. (1 : 1 Toluene/Ethyl Acetate) and G.L.C. (3% OV101, 5 ft, 258°C). After 5 days reaction had ceased, although starting material was still present. The cooled solution was de-peroxidised by the passage of sulphur dioxide gas through the solution for 15 mins.

Evaporation of the acetic acid, addition of water and re-evaporation gave a brown oil which was dissolved in chloroform (500 ml). The solution was shaken with a stiff aqueous paste of K_2CO_3 until no more CO_2 was evolved, filtered, dried (Na_2SO_4) and evaporated to yield an oil (41 g).

Chromatography on a medium-pressure column, eluting with

toluene gave 2,6-diphenylpyridine (22.6 g). Further elution with 3 : 1 toluene/ethyl acetate gave 2,6-diphenylpyridine-1-oxide (17.7 g, 37%), 71% yield based on recovered starting material.

M.pt. 126 - 127°C ($CHCl_3$/petrol (40 - 60°))

lit.[128] m.pt. 125 - 126°C ($CHCl_3$/petrol (40 - 60°))

Analysis:	Found:	C, 82.60%;	H, 5.08%;	N, 6.03%	
	$C_{17}H_{13}NO$ requires:	C, 82.57%;	H, 5.30%;	N, 5.66%	
N.m.r. ($CDCl_3$)	δ 7.75 p.p.m.	d of d	4H	o-protons on phenyl rings	
	7.50 - 7.35	m	9H		
Mass spectrum, m/e	247 (M^+), 231 (M-16)				

4-Bromo-2,6-diphenylpyridine (80)

To a solution of 2,6-diphenylpyridine-1-oxide (12.3 g, 0.05 mol) in dry toluene (100 ml) was added phosphoryl bromide (43 g, 0.15 mol). The mixture was boiled under reflux for 2½ hrs. The cooled mixture was poured into ice/water (250 ml), basified to pH 10 (conc. NH_3) and the aqueous phase extracted with dichloromethane (2 x 200 ml). Drying (Na_2SO_4) and evaporation gave a red oil (16 g). Chromatography on a medium-pressure column, eluting with 3 : 1 40 - 60° petrol/toluene gave, as a red oil, the bromo compound (5.8 g), further elution gave 2,6-diphenylpyridine (6 g, 52%).

Trituration of the bromo compound with ethanol gave pure 4-bromo-2,6-diphenylpyridine (3.4 g, 22%).

[N.B. The bromo compound is a strong lachrymator in solution.]

M.pt. 90°C (absolute EtOH) colourless needles

Analysis:	Found:	C, 65.64%;	H, 3.71%;	N, 4.64%
	$C_{17}H_{12}BrN$ requires:	C, 65.82%;	H, 3.90%;	N, 4.52%

N.M.r. ($CDCl_3$)	δ 8.0 p.p.m.	m	4H	o-protons on phenyl rings
	7.7	s	2H	
	7.35	m	6H	

I.R. ($CDCl_3$) ν_{max} 3060 cm^{-1}, 1560, 1580, 1490, 1400, 860, 720, 690, 660, 645

U.V. (95% EtOH) λ_{max} 255 nm $\log_{10}\varepsilon$ 4.35; 293 nm sh; 310 nm $\log_{10}$ 3.85

Mass spectrum, m/e 312 (21%), 311 (97), 310 (35), 309 (100), 308 (17), 230 (35), 127 (42), 126 (17), 115 (17), 104 (17), 101 (17), 77 (28), 51 (17)

2'-Nitrophenyl-(2,6-diphenyl-pyridin-4-yl)methanol

A solution of 4-bromo-2,6-diphenylpyridine (1.55 g, 0.005 mol) in dry ether (20 ml) was added dropwise over a period of 10 minutes to a stirred solution of n-butyl lithium (1.6 M in hexane, 3.7 ml) in dry ether (5 ml) at -70°C under a dry nitrogen atmosphere. The yellow mixture was stirred for a further 30 mins at -70°C. A solution of o-nitrobenzaldehyde (0.755 g, 0.005 mol) in dry ether (10 ml) was then added dropwise over a period of 10 mins. The mixture was stirred at -70°C for 2 hrs and finally at room temperature for 2 hrs. The light brown mixture was poured into ice/water (50 ml) saturated with salt and sodium metabisulphite. The aqueous phase was extracted with dichloromethane (3 x 25 ml), dried (Na_2SO_4) and evaporated to give a yellow oil (1.9 g).

The oil was absorbed onto alumina (20 g, IV) and chromatographed on a column of alumina (100 g, IV). A mixture of 40 - 60° petroleum ether and benzene (25%) eluted 4-bromo-2,6-diphenylpyridine (0.2 g, 12%). Further elution with benzene gave 2'-nitrophenyl-(2,6-diphenyl-pyridin-4-yl)methanol (1.4 g, 73%) as a viscous yellow oil. Trituration with 40 - 60° petroleum ether gave a yellow solid.

M.pt. 160°C (benzene) yellow needles

Analysis: Found: C, 75.58%; H, 4.61%; N, 7.45%

$C_{24}H_{18}N_2O_3$ requires: C, 75.38%; H, 4.74%; N, 7.33%

N.m.r. ($CDCl_3/D_6$ acetone)

δ 8.1 - 7.8 p.p.m.	m	4H	
7.7	s	2H	
7.8 - 7.2	m	10H	
6.5	d	1H	J = 5 Hz
			Singlet with D_2O
5.2	br.d	1H	Ex.D_2O J = 5 Hz

I.R. ($CHCl_3$) ν_{max} 3400 cm^{-1}, 2330, 1600, 1580, 1560, 1350, 1120, 880, 850

U.V. (95% EtOH + HCl)

λ 220 nm	$\log_{10} \varepsilon$ 4.59
247 nm	$\log_{10} \varepsilon$ 4.54
320 nm	$\log_{10} \varepsilon$ 4.16

Mass spectrum, m/e 384 (26%), 383 (94), 382 (29, M^+), 381 (100), 352 (26), 351 (83), 350 (34), 349 (58), 348 (58), 336 (20), 335 (26), 322 (23), 274 (20), 247 (66), 202 (54), 128 (26), 127 (94), 126 (29), 120 (46), 105 (46), 104 (40), 103 (23), 102 (32), 101 (32), 93 (26), 77 (89), 65 (20), 51 (43)

Attempted preparation of 2'-aminophenyl-(2,6-diphenyl-pyridin-4-yl) methane

A solution of 2'-nitrophenyl-(2,6-diphenyl-pyridin-4-yl) methanol (0.48 g, 0.00125 mol) in a mixture of ethanol (5 ml) and 5% conc. HCl in ethanol (15 ml) was hydrogenated at normal temperature and pressure in the presence of 10% palladium on charcoal catalyst (0.25 g). After hydrogen uptake had ceased the solution was filtered, basified (conc. NH_3) and evaporated. The residue was dissolved in dichloromethane (100 ml) dried (Na_2SO_4) and evaporated, to give a yellow solid (0.44 g). P.L.C. (90% ethyl acetate/toluene) gave essentially pure 2'-aminophenyl-(2,6-diphenyl-pyridin-4-yl)methanol (81) as a pale yellow solid (0.3 g, 68%).

M.pt. 216 - 217°C (chloroform) colourless plates

Analysis: Found: C, 80.75%; H, 5.62%; N, 7.84%

$C_{24}H_{20}N_2O$ requires: C, 81.79%; H, 5.72%; N, 7.95%

N.m.r. (DMSO d_6)

δ 8.0 p.p.m.	m	4H	
7.6	s	2H	
7.5 - 7.2	m	6H	
7.0 - 6.5	m	4H	
5.85	s	1H	
3.1	br.s	3H	Ex.D_2O

I.R. (DMSO) ν_{max} 3500 cm^{-1}, 1700, 1650, 1600, 1500, 1250, 1150, 950

U.V. (95% EtOH)

λ_{max} 245 nm	$\log_{10}\varepsilon$ 4.54	
265 nm	sh	
292 nm	sh	
305 nm	sh	

Mass spectrum, m/e 353 (37), 352 (100) $M^{+\cdot}$, 337 (33), 336 (28), 335 (52), 334 (61), 333 (35), 332 (20), 257 (63), 233 (39), 232 (30), 230 (48), 129 (20), 127 (20)

Part E

Synthesis and thermal decomposition of 3-(2-azidobenzyl)pyridine-1-oxide (84)

2'-Aminophenyl-(3-pyridyl)methane (69)

Prepared as in Part A, except that hydrogenations were carried out in one step.

Yield 71%

M.pt. 84 - 85°C (cyclohexane)

2'-Acetamidophenyl-(3-pyridyl)methane

A stirred suspension of 2'-aminophenyl-(3-pyridyl)methane (17.4 g, 0.094 mol) in water (112 ml) was treated dropwise at 0°C with acetic anhydride (38 ml, 0.37 mol) and the mixture stirred until all the solid matter had dissolved. The cooled mixture was basified (25% aq. NH_3) to pH 8-9 and the resultant solid filtered, washed with cold water and dried in a vacuum oven at 100°C.

Yield 17.3 g (81%)

M.pt. 140 - 141°C (benzene)

Analysis: Found: C, 74.22%; H, 6.08%; N, 12.50%

$C_{14}H_{14}N_2O$ requires: C, 74.31%; H, 6.24%; N, 12.38%

N.m.r. ($CDCl_3$)	δ 8.35 p.p.m.	br.d	2H	
	7.75	br.s	1H	Ex.D_2O
	7.5 - 7.0	m	6H	
	3.9	s	2H	
	2.0	s	3H	

I.R. ($CHCl_3$) ν_{max} 3430, 3250, 3030, 2400, 1660, 1580, 1550, 1510, 1480, 1450, 1420, 1370, 1300, 1220, 1030, 1040, 930 cm^{-1}

U.V. (95% EtOH) λ_{max} 229 nm $\log_{10} \varepsilon$ 4.51; 272 nm $\log_{10} \varepsilon$ 4.44

Mass spectrum, m/e 227 (19%), 226 (100%, $M^{+\cdot}$), 212 (9), 211 (50), 185 (33), 184 (100), 183 (17), 182 (21), 167 (21), 166 (24), 157 (19), 106 (21), 77 (19), 51 (12)

3-(2-Acetamidobenzyl)pyridine-1-oxide

A solution of 2'-acetamidophenyl-(3-pyridyl)methane (34.4 g, 0.151 mol) in glacial acetic acid (250 ml) and 30% hydrogen peroxide (50 ml) was heated at 55 - 60°C for 2 hrs. An additional 25 ml of hydrogen peroxide was added and the solution heated at 70 - 80°C for 15 hrs.

Evaporation, addition of water and re-evaporation yielded an oil. The oil was dissolved in chloroform and shaken with a stiff aqueous paste of potassium carbonate until CO_2 was no longer evolved. The solution was filtered, dried (Na_2SO_4) and evaporated to give an oil which crystallised (32.6 g).

Chromatography on a medium-pressure column (85% ethyl acetate/methanol) gave unidentified oils followed by 3-(2-acetamidobenzyl)pyridine-1-oxide (24.1 g, 66%) (elution with 70% ethyl

acetate/methanol).

M.pt. 157 - 158°C (acetone)

Analysis: Found: C, 69.07%; H, 5.66%; N, 11.50%

$C_{14}H_{14}N_2O_2$ requires: C, 69.40%; H, 5.83%; N, 11.56%

N.m.r. ($CDCl_3$/DMSO-d_6) δ 9.3 p.p.m. br.s 1H Ex.D_2O

7.9 m 2H

7.4 - 7.0 m 6H

3.9 s 2H

2.0 s 3H

I.R. (DMSO) ν_{max} 3450, 3250, 3180, 3080, 1675, 1600, 1580, 1520, 1480, 1360, 1265, 1155, 755 cm^{-1}

U.V. (95% EtOH) λ_{max} 220 nm $\log_{10} \varepsilon$ 4.44

270 nm $\log_{10} \varepsilon$ 4.30

Mass spectrum, m/e 242 (5%, $M^{+\cdot}$), 228 (10), 227 (51), 226 (93), 211 (20), 185 (22), 184 (100), 183 (20), 182 (32), 168 (15), 167 (24), 166 (46), 157 (10), 155 (12), 106 (10), 77 (15), 51 (15)

3-(2-Aminobenzyl)pyridine-1-oxide (83)

A suspension of 3-(2-acetamidobenzyl)pyridine-1-oxide (24.1 g, 0.106 mol) in 10% aq. sodium hydroxide (550 ml) was boiled under reflux for 4 hrs. The cooled solution was evaporated, the residue dissolved in chloroform (ca. 400 ml), filtered, dried (Na_2SO_4) and evaporated to yield a yellow solid (17 g, 85%).

M.pt. 126 - 127°C (benzene) off-white plates

Analysis: Found: C, 71.99%; H, 5.99%; N, 13.81%

$C_{12}H_{12}N_2O$ requires: C, 71.98%; H, 6.04%; N, 13.99%

N.m.r. (DMSO d_6/Acetone d_6)

δ 8.0 p.p.m.	m	2H	
7.3 - 6.8	m	4H	
6.8 - 6.4	m	2H	
4.8	br.s	2H	Ex.D_2O
3.8	s	2H	

I.R. (DMSO) ν_{max} 3430, 3340 (sh), 3215, 1680, 1590, 1550, 1510, 1485, 1475, 1265, 1150, 750 cm^{-1}

U.V. (95% EtOH) λ_{max} 220 nm $\log_{10} \varepsilon$ 4.41; 240 nm sh; 269 nm $\log_{10}$ 4.13

Mass spectrum, m/e 200 (5%, M^+), 199 (5), 186 (7.0), 185 (61), 184 (100), 183 (23), 182 (30), 168 (17), 167 (28), 166 (70), 157 (12), 155 (12), 149 (7), 144 (6), 140 (7), 139 (6), 131 (7), 129 (7), 128 (7), 127 (6), 117 (7), 115 (9), 106 (20), 91 (17), 77 (18), 51 (11)

3-(2-Azidobenzyl)pyridine-1-oxide (84)

A stirred solution of 3-(2-aminobenzyl)pyridine-1-oxide (16 g, 0.08 mol) in conc. HCl (38 ml) and water (38 ml) was treated with a solution of sodium nitrite (6.25 g, 0.091 mol) in water (140 ml) at 0 - 5°C. The solution was stirred for a further 15 mins at 0 - 5°C. The diazonium salt solution was then added to a solution of sodium azide (6.25 g, 0.096 mol) and sodium acetate (62.5 g) in water (280 ml) at 0°C with stirring. The solution was stirred for a further 30 mins at 0°C. The aqueous phase was extracted with dichloromethane (2 x 250 ml), dried (Na_2SO_4) and evaporated (30°C) to yield a red oil (24.8 g).

The oil was absorbed on alumina (30 g, IV) and chromatographed on a column of alumina (300 g, IV). Aluminium foil was wrapped around

the column to protect it from light. Elution with ethyl acetate produced mixtures (T.L.C. 70% ethyl acetate/methanol). Column fractions were evaporated at 30°C. Further chromatography with mixtures of petroleum ether (40 - 60°) and ether and finally ether gave a yellow oil (1.6 g, 6.7%) identified, from a comparison of N.m.r. spectra, as 2'-azidophenyl-(3-pyridyl)methane (85). Further elution with ether gave mixtures (0.4 g). A mixture of 1 : 1 dichloromethane/ether eluted 3-(2-azidobenzyl)pyridine-1-oxide (4 g, 21%) as a yellow solid.

M.pt. 96°C (cyclohexane)

Analysis: Found: C, 63.77%; H, 4.25%; N, 25.08%

$C_{12}H_{10}N_4O$ requires: C, 63.70%; H, 4.46%; N, 24.77%

N.m.r. ($CDCl_3$) δ 7.95 p.p.m. m 2H

7.4 - 6.9 m 6H

3.8 s 2H

I.R. ($CHCl_3$) ν_{max} 2970, 2120 (s), 1600, 1580, 1480, 1430, 1280, 1260, 1205 (s), 1150, 1015, 965, 920, 770, 720, 665 cm^{-1}

U.V. (95% EtOH) λ_{max} 223 nm $\log_{10}\varepsilon$ 4.41

265 nm $\log_{10}\varepsilon$ 4.28

292 nm sh

Mass spectrum, m/e 226 (39%, M^+), 198 (44), 197 (28), 195 (22), 194 (33), 183 (39), 182 (100), 181 (44), 169 (39), 168 (61), 167 (61), 156 (39), 155 (55), 129 (61), 115 (44), 77 (44), 63 (44), 51 (44)

Thermal decomposition of 3-(2-azidobenzyl)pyridine-1-oxide (84)

A solution of the azide (3.6 g, 0.015 mol) in 1,2,4-trichlorobenzene (100 ml) was added dropwise over a period of 30 mins to trichlorobenzene (500 ml) at 190°C under a dry oxygen-free nitrogen atmosphere. The solution was vigorously stirred throughout the entire decomposition. The progress of the reaction was monitored by I.R. After 4 hrs, an I.R. of the reaction mixture indicated consumption of azide. The cooled solution was evaporated (0.1 mm) to yield a black oil (3.0 g). The oil was absorbed onto alumina (30 g, IV) and chromatographed on a column of alumina (100 g, IV). Elution with 40 - 60° petroleum ether gave 1,2,4-trichlorobenzene (0.3 g). Elution with mixtures of petroleum ether and benzene and then benzene gave unidentified brown oils (0.7 g). Further elution with dichloromethane, ethyl acetate/dichloromethane mixtures and finally methanol gave black oils (0.6 g) and a black solid (0.9 g), whose broad N.m.r. spectra suggested polymeric material. Recovery from the column was 90%.

Preparation of 3-(2-azidobenzyl)pyridine methiodide (86)

A solution of 2'-azidophenyl-(3-pyridyl)methane (1.2 g, 0.0057 mol) in dry distilled acetone (20 ml) was treated with methyl iodide (15 ml , 0.24 mol). The solution was kept at 3°C for 4 days in a stoppered flask protected from the light. The solution was evaporated (30°C) to yield a yellow oil (1.4 g, 70%). The material was characterised as the picrate (for analysis).

M.pt. 135 - 136°C (absolute EtOH)

Analysis: Found: C, 50.21%; H, 3.21%; N, 21.91%

$C_{18}H_{13}N_7O_7$ requires: C, 49.20%; H, 2.98%; N, 22.30%

N.m.r. ($CDCl_3$)	δ 9.0 p.p.m.	d	2H
	8.4 - 7.8	m	2H
	7.5 - 7.0	m	4H
	4.5	s	3H
	4.2	s	2H

I.R. ($CHCl_3$) ν_{max} 2950, 2140 (s), 1630, 1600, 1550, 1360, 1080, 920 cm^{-1}

U.V. (95% EtOH) λ_{max} 250 nm $\log_{10} \varepsilon$ 4.39; 283 sh

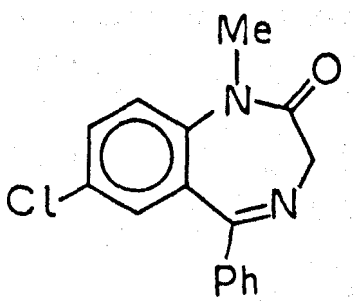
Mass spectrum, m/e 197 (100%, M-28), 182 (50), 77 (40), 51 (30)

CHAPTER TWO

ATTEMPTS TO PREPARE THE 1,3-DIAZEPINE RING SYSTEM

INTRODUCTION

The 1,3-diazepine ring system and its benzo-fused derivatives have not been extensively studied. This is in direct contrast to the 1,2-[141,142] and 1,4-diazepines,[143] whose synthesis and chemistry has been widely explored. A vast number of 1,4-benzodiazepines have been synthesised and they are of particular importance as tranquilising drugs, e.g. valium (90) and librium (91).



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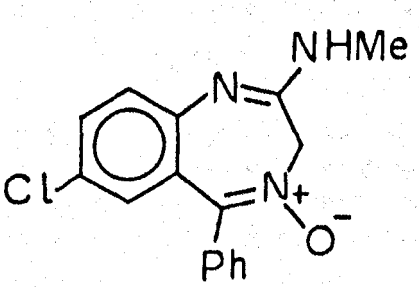
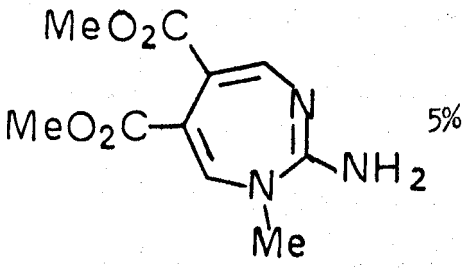


(91)

Reviews of 1,3-diazepines[144,146] and benzodiazepines[145] have appeared in the literature.

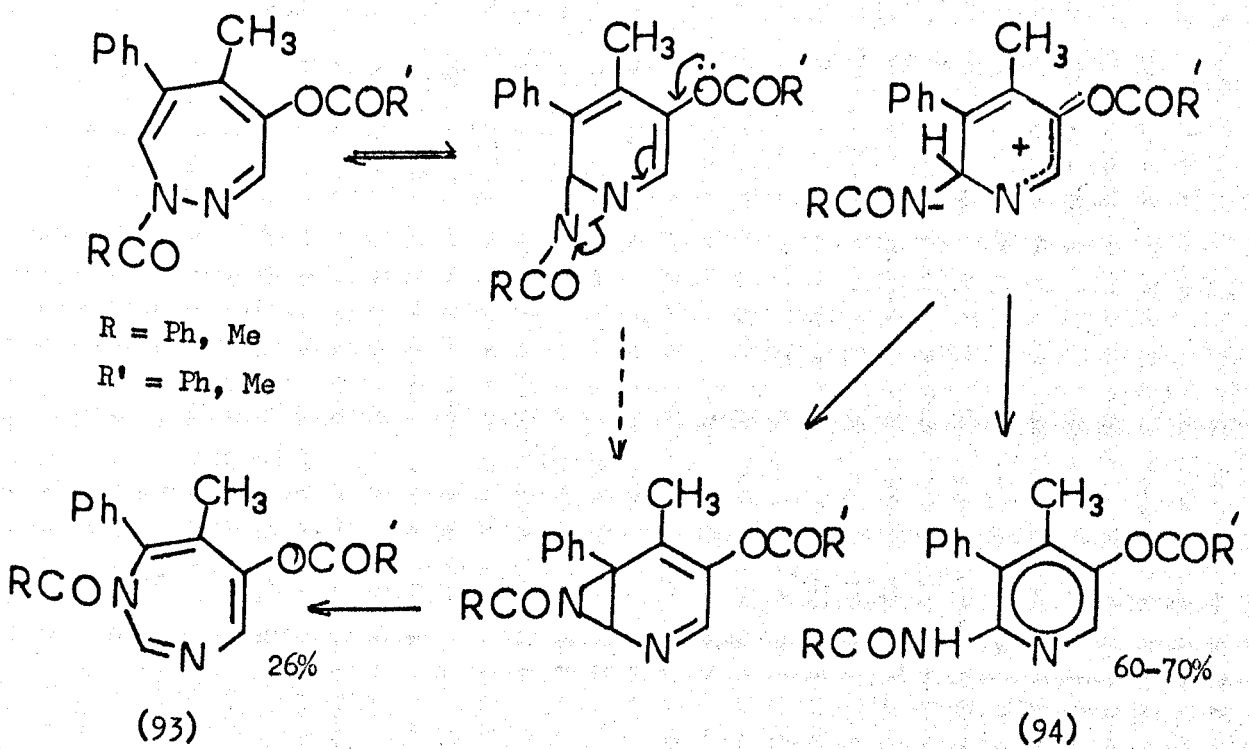
2.1 1,3-Diazepines

Highly unsaturated simple, unsubstituted 1,3-diazepines are not known. There are only three examples of a fully unsaturated 1,3-diazepine. Troxler[147] and co-workers isolated a low yield of the 1,3-diazepine (92) from the cycloaddition of dimethyl acetylene-dicarboxylate with 2-amino-1-methylimidazole.



(92)

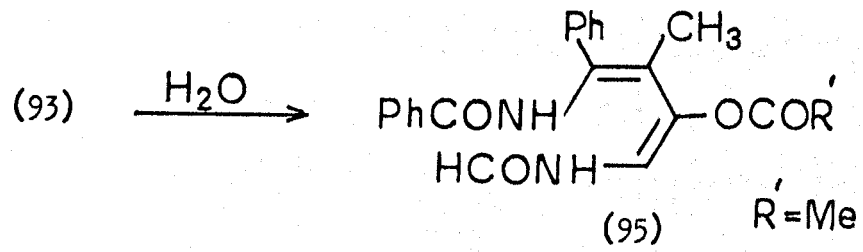
Moore et al. have reported[148,149] the formation of a 1,3-diazepine in the thermal rearrangements of substituted 1,2-diazepines. The structure of the diazepine (93) was solved by X-ray crystallography. Simple 1-benzoyl-1H-1,2-diazepines[151] do not show this reaction, and Moore[149] has attributed the formation of 1,3-diazepines to assistance by the acyloxy group in breaking the N-N bond. (Scheme 2.1)



(93) (94)

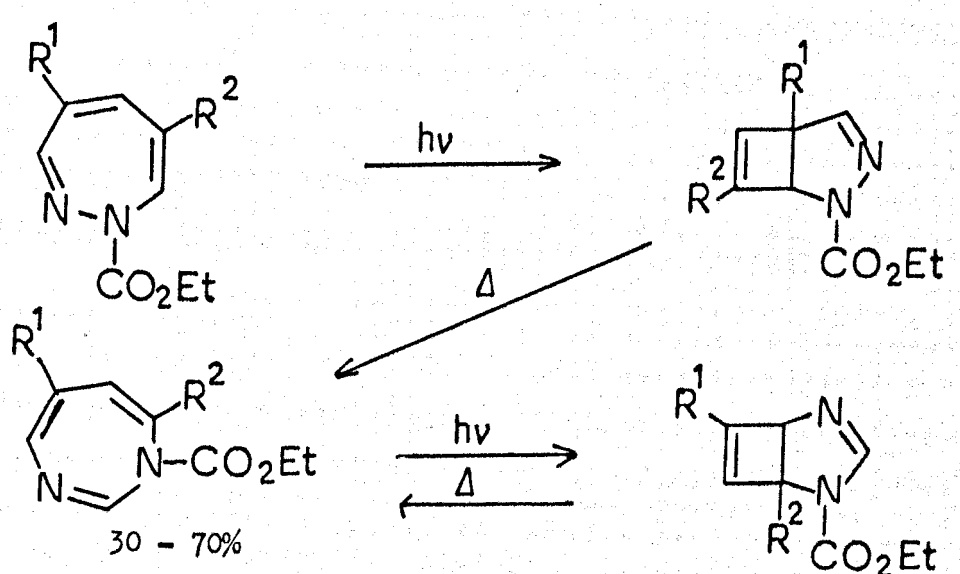
Scheme 2.1

The 1,3-diazepine (93) was thermally stable (6 days at 120°C) but sensitive to moisture and reacted slowly in air to form the acyclic compound (95).



Treatment with base gave the ring contraction product (94) R^1 = H.

A similar approach to 1,3-diazepines has been pursued[150] by Tsuchiya et al. They have thermolysed 1,2-diazepines and obtained 1,3-diazepines. Only in cases where an electron-donating substituent is present at positions 4 and/or 6 in the 1,2-diazepines, does the reaction give 1,3-diazepines. This is in agreement with the arguments put forward by Moore.[149] The requisite 1,2-diazepines are readily available by irradiation of 3-substituted pyridine N-imides.[142] The isolated 1,3-diazepines were rapidly decomposed by water, acids and silica gel.

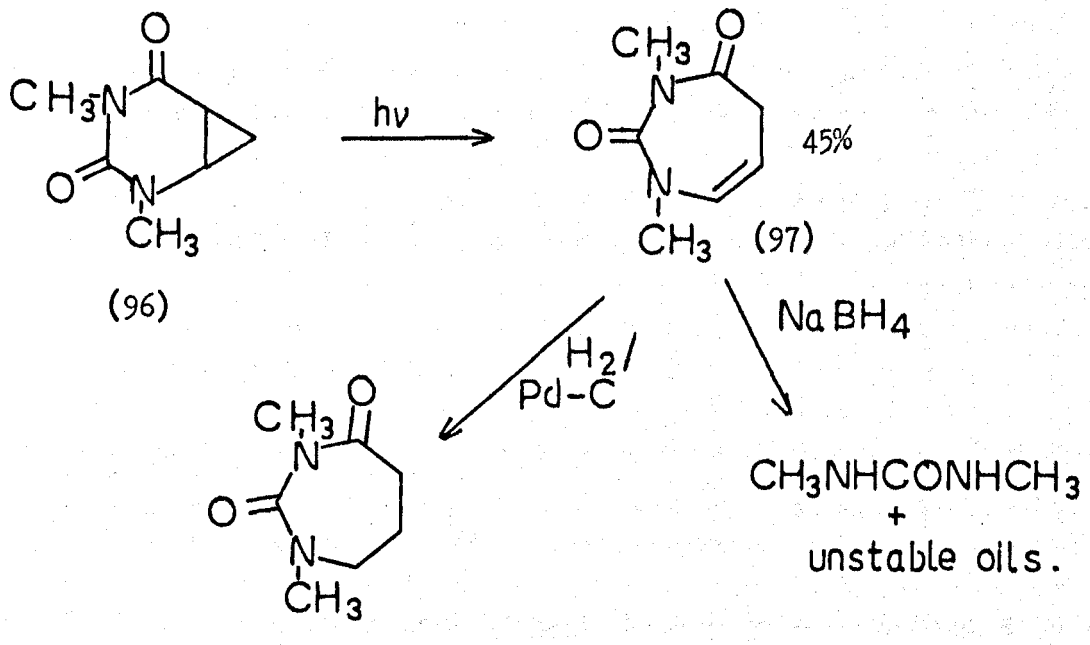


R^1 = Me, H, OMe, NHAc, NEt_2

R^2 = Me, H, OMe, NHAc

Scheme 2.2

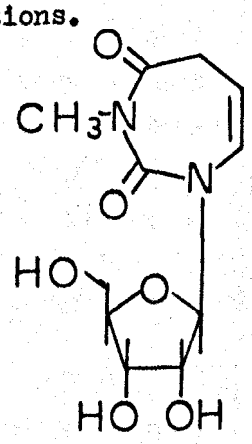
A useful synthesis of 1,3-diazepinediones has been developed by Witkop[152] and by Pandit's[153-156] research groups. Irradiation of the cyclopropane adduct (96) in water gave the ring-expanded compound (97). The diazepine (97) was catalytically reduced and the ring was opened by sodium borohydride.



Scheme 2.3

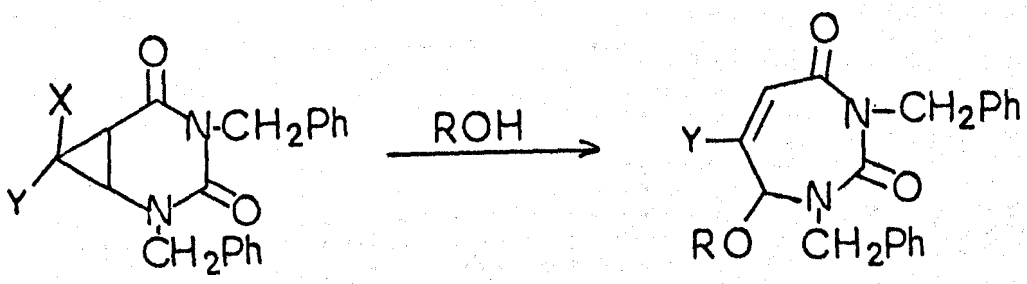
The cyclopropane adducts were readily prepared by the interaction of a dimethyl or dibenzyluracil with dimethyloxosulphonium methylide.

Nucleoside analogues e.g. (98) were also prepared by a similar sequence of reactions.



(98)

Pandit[153,154] has reported similar transformations of the compounds derived from addition of dihalocarbenes to 1,3-dibenzyluracil.

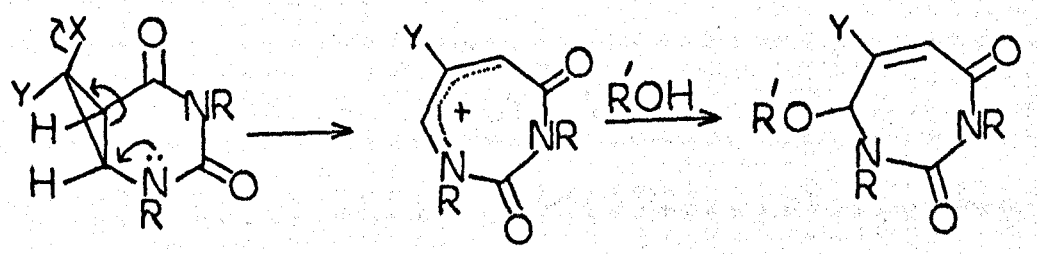


X = Cl, Br

Y = Cl, Br

Scheme 2.4

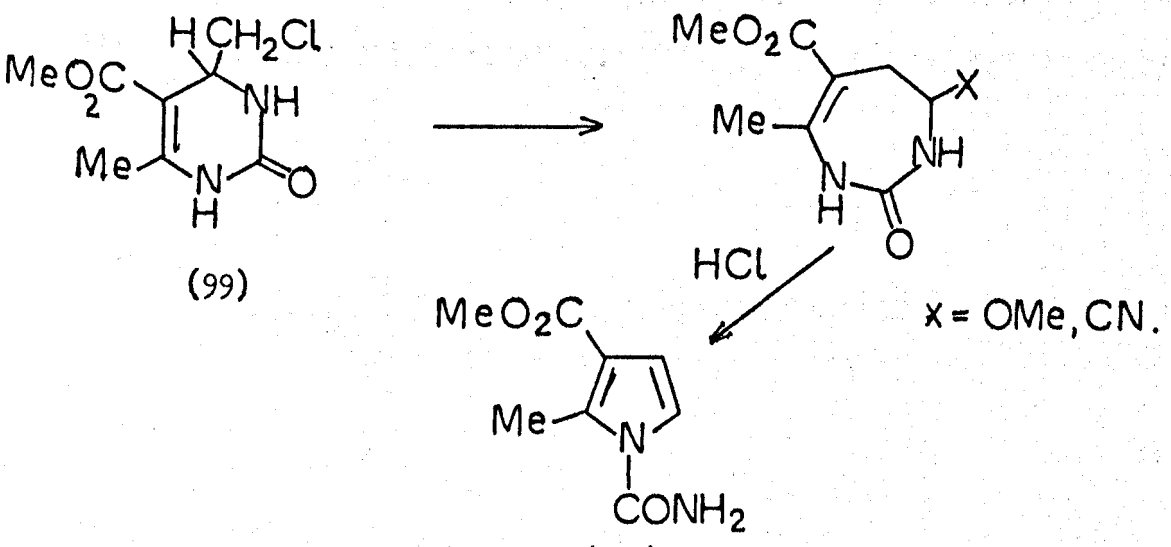
Further reaction with alcohols can occur under more forcing conditions (Y = OR). The reaction was shown to occur via a concerted disrotatory ring-opening and addition of alcohol. The attempted reaction of the exo-chloro isomer (Y = Cl, X = F) led to recovered starting material.



Scheme 2.5

The reaction has also been applied[154] to uridine nucleotides.

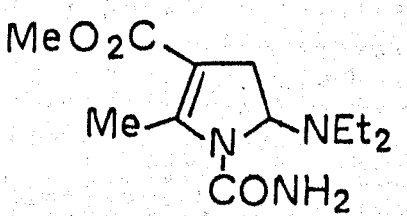
Ring expansion of the pyrimidinone (99) by treatment with sodium methoxide or sodium cyanide has been observed by Gregory and co-workers.[157]



Scheme 2.6

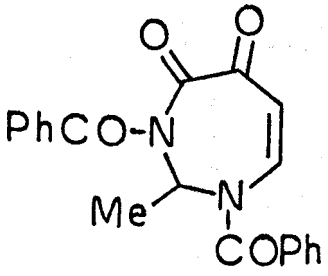
A rapid conversion to the pyrrole (100) took place at room temperature with methanolic or aqueous hydrochloric acid.

Ashby and Griffiths[158] have extended this work and have obtained good yields of 1,3-diazepines by reaction of the pyrimidinone (99) with potassium cyanide in dimethyl sulphoxide. The analogous reaction with amines, however, leads in good yield to pyrrolidine derivatives, e.g. (101).



(101)

Hanafin and Ben-Ishai[159] have recently reported the synthesis of a 1,3-diazepinedione. The usual products from the reaction of methylene bisbenzamides and oxalyl chloride are imidazolidine-4,5-diones. However when ethylidene bisbenzamide is employed the reaction takes a different course and the 1,3-diazepinedione (102) is obtained.



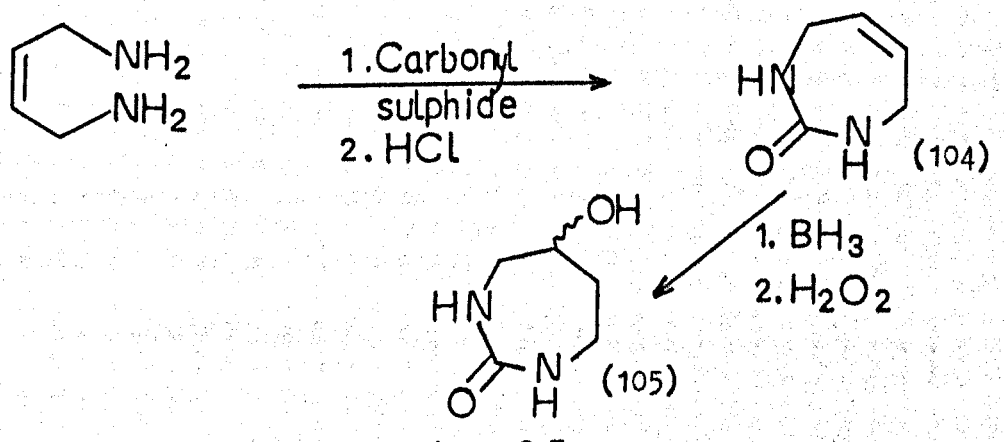
(102)

PhCONHCH=CHCOCOCl

(103)

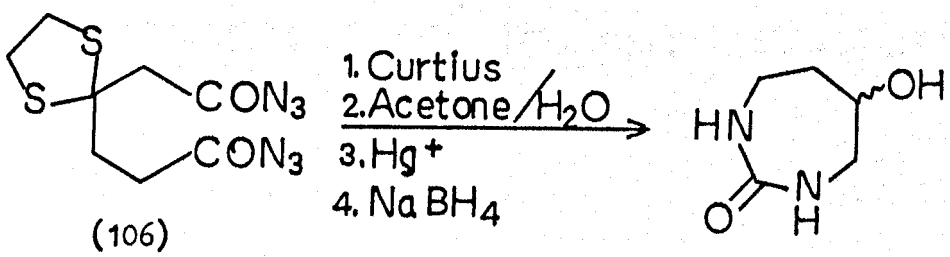
The authors have proposed the formation of N-vinylbenzamide which reacts further to form the acid chloride (103). Condensation of (103) with a second molecule of ethylidene bisbenzamide and elimination of benzamide yields the diazepine (102).

Dihydro and tetrahydrodiazepines (104) and (105) have been synthesised very recently[160] in some studies related to cytidine deaminase inhibitors.



Scheme 2.7

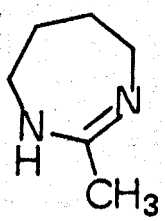
The tetrahydrodiazepinone (105) was also obtained from the protected azide (106), via the Curtius rearrangement. Subsequent condensation and reduction steps gave the alcohol (105).



(106) (105)

Scheme 2.8

A general method for the synthesis of tetrahydro-1,3-diazepines has been developed by Desmarchelier[161] and co-workers. Simply boiling an ethanolic solution of 1,4-diaminobutane and acetamidine hydrochloride gives the 1,3-diazepine (107) in moderate yield.

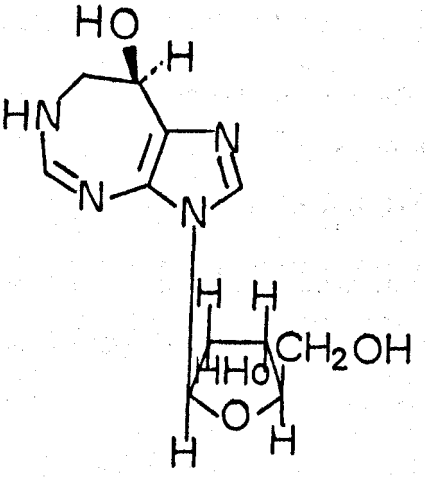


(107)

The diazepine (107) was highly deliquescent and readily formed hydrochloride and trichloromercurate salts.

A potent deaminase inhibitor, containing a 1,3-diazepine ring has been reported.[162] The structure of the imidazo[4,5-d]-diazepinol (108) was solved by single crystal X-ray diffraction

techniques.



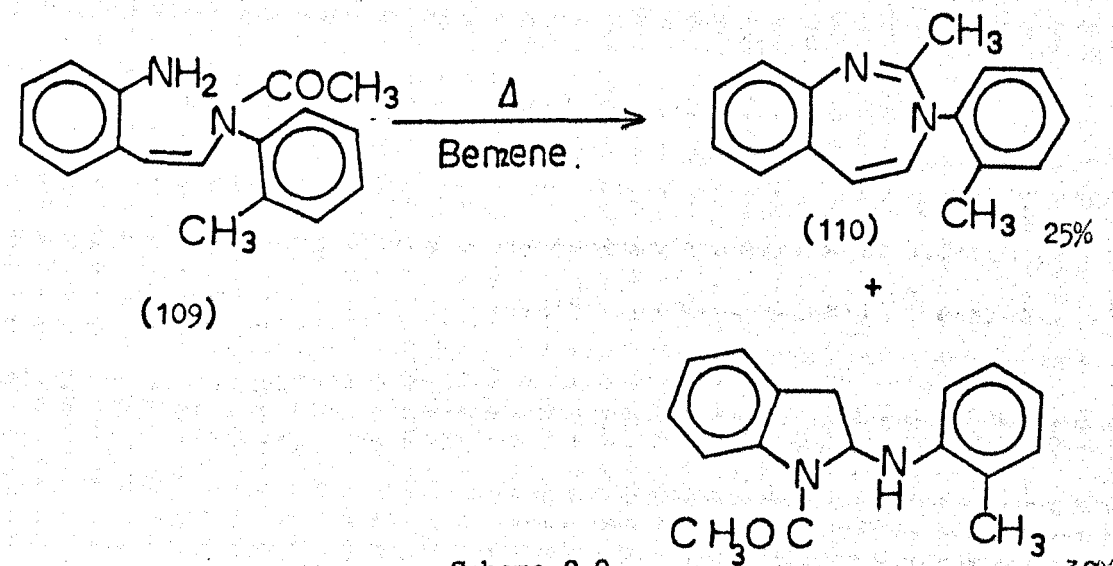
(108)

2.2 Benzodiazepines

2.2 (a) 1,3-Benzodiazepines

Fully unsaturated 1,3-benzodiazepines are rare compounds and only three examples have been reported.

Chen and Forrest[163] successfully cyclised the aminostyrene derivative (109) upon heating in the presence of molecular sieves. The product was rapidly hydrolysed to give the starting material (109).



(109)

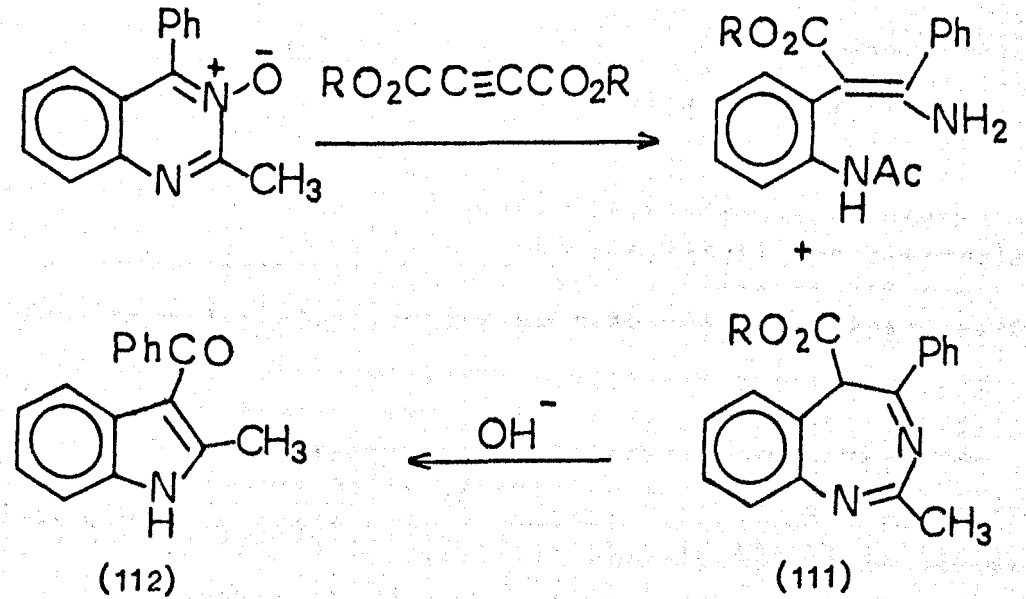
(110) 25%

32%

Scheme 2.9

Cyclisation of the styrene derivative (109) could not be achieved upon reaction with aqueous acid, phosphorus oxychloride or phosphorus trichloride. Reaction with phosphorus reagents gave tars while aqueous acid gave indole. The 4,5-dihydro derivative of the diazepine (110) was prepared by hydrogenating the trans isomer of the aminostyrene (109) and cyclising with phosphorus oxychloride.

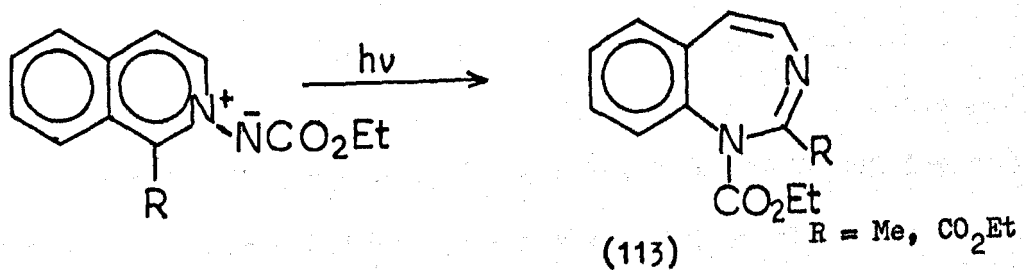
Stauss and co-workers[164] have isolated the diazepine (111) as a by-product in the 1,3-dipolar cycloaddition of 2-methyl-4-phenyl-quinazoline-3-oxide with acetylenedicarboxylic esters. Alkaline hydrolysis of the 1,3-benzodiazepine gave the indole (112).



(112) (111)

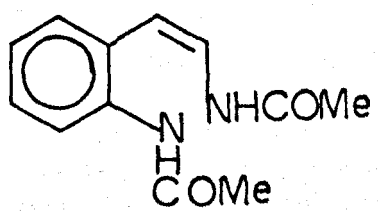
Scheme 2.10

Tsuchiya's group have extended their synthetic approach to 1,3-diazepines to the production of benzo[120] and hetero-fused[165] series. Irradiation of isoquinoline N-imides gave the 1H-1,3-benzodiazepines (113) in about 20% yield.

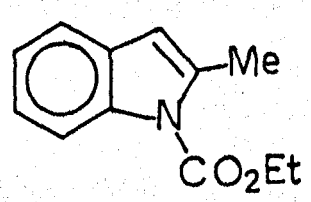


(113)

The benzodiazepines formed unstable adducts with alcohols by addition to the imine double bond, and ring-opened compounds (e.g. 114) were isolated on work up.



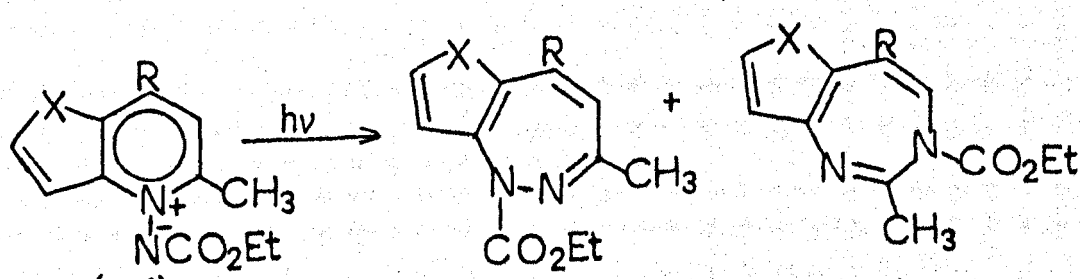
(114)



(115)

Further irradiation of the benzodiazepine (113) gave the indole (115) via a tricyclic valence isomer and sequential extrusion of hydrogen cyanide.

Similar results were obtained with hetero-fused analogues, e.g. (116). In these cases[165] mixtures of 1,2-diazepines and 3H-1,3-diazepines were obtained, e.g. (117).



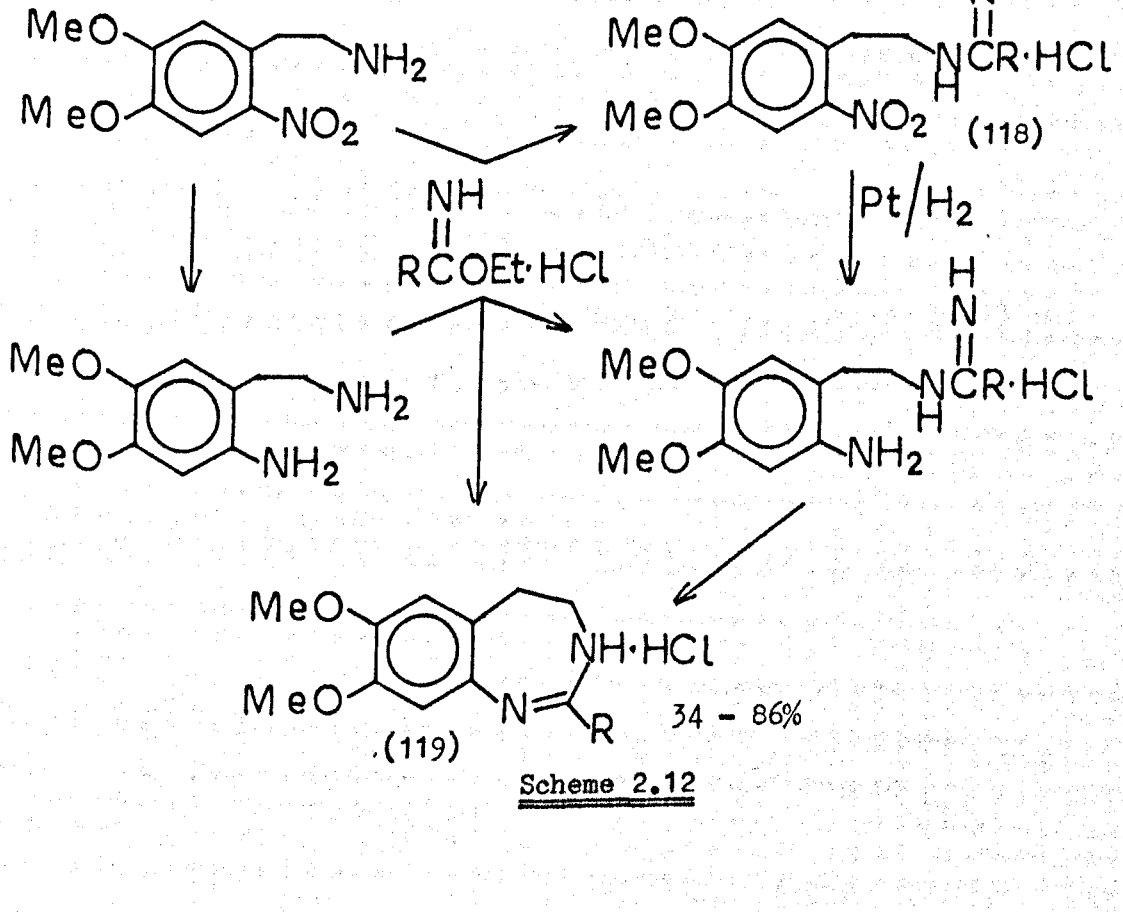
(116) (117)

X = O, S, NMe

R = H, Me

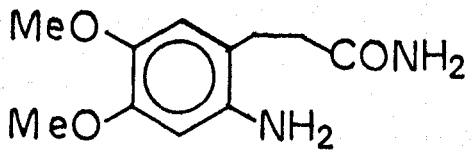
Scheme 2.11

A variety of 4,5-dihydro-3H-1,3-benzodiazepines have been synthesised by DeStevens[166,167] and co-workers. Cyclisation of substituted phenylethylamines and imidate hydrochlorides gave benzodiazepines (119) in moderate to good yields. With aryl imidate hydrochlorides yields are superior when the intermediate amidine compound (118) is catalytically reduced and then cyclised. The reaction was shown to be sensitive to electronic and steric effects, yields are highest when the aryl or alkylimidates contain electron-withdrawing groups. Steric hindrance, in the nature of substitution on the basic amine function, seriously inhibited condensation with the imidate.



Scheme 2.12

The amide (120) resisted attempts at condensation with even the reactive ethyl chloroacetimidate hydrochloride.

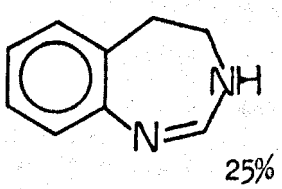


(120)

Methylation of the 1,3-benzodiazepines occurred at N-3 upon treatment with n-butyl lithium and methyl p-toluenesulphonate. Reaction with methyl iodide at elevated temperatures lead to fully methylated derivatives.

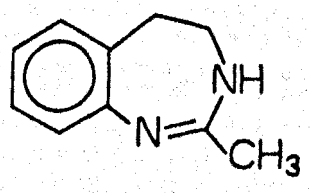
Similar routes to tetrahydro-1,3-benzodiazepines have been reported by Suh and Schnettler.[168-170] They have treated phenylethylamines, similar to those in Scheme 2.12, with carbon disulphide to give 1,3-benzodiazepine-2-thiones. Methylation of these compounds and nucleophilic displacement with a variety of primary and secondary amines led to 2-substituted 4,5-dihydro-1,3-benzodiazepines which possessed activity in the central nervous system.

The parent 4,5-dihydro-3H-1,3-benzodiazepine (121) and the 2-methyl compound (122) have been synthesised from 2-(o-aminophenyl)ethylamine by reaction with formamide acetate[171] and acetamidine hydrochloride[161] respectively.



25%

(121)

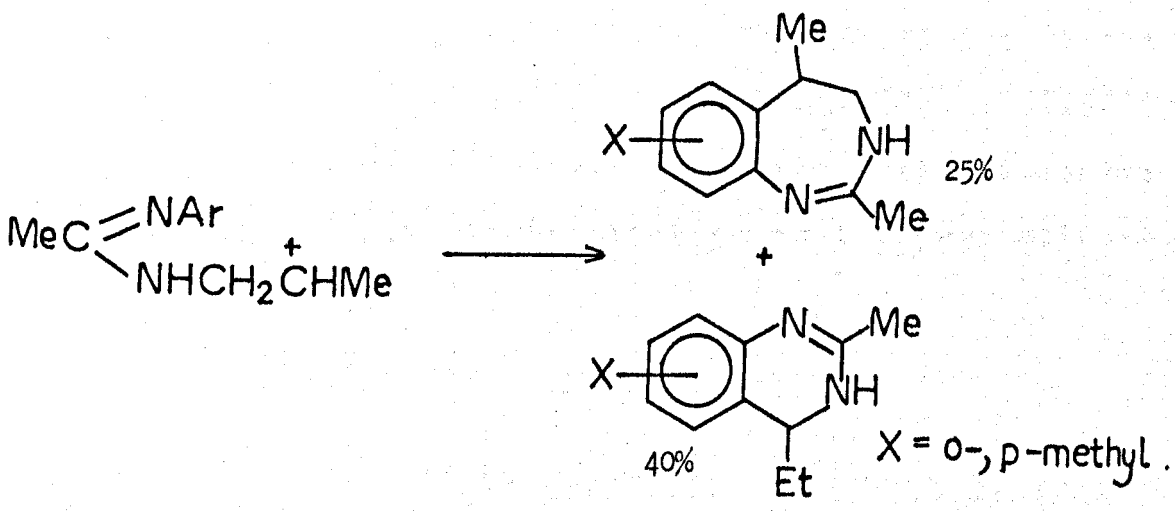


71%

(122)

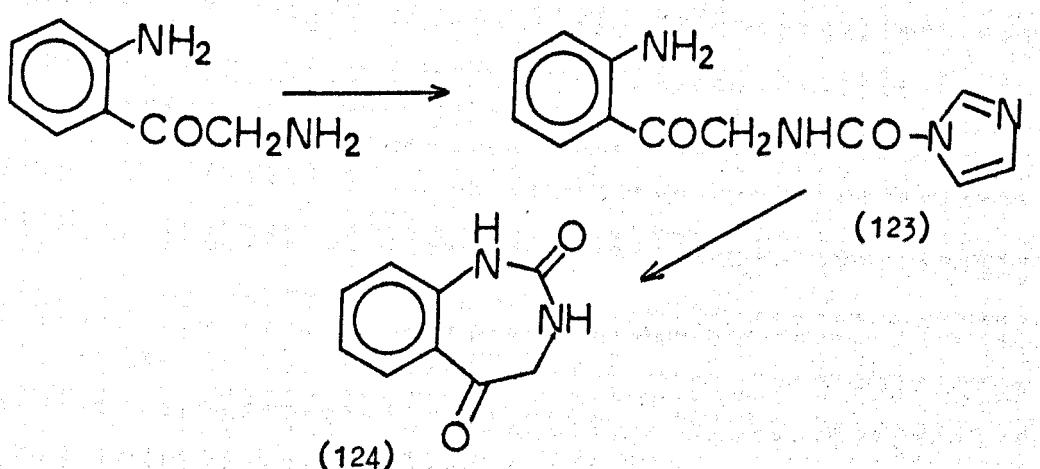
Substituted 4,5-dihydro-1,3-benzodiazepines are isolated

in certain cases[172] in the polyphosphoric acid cyclisation of N-allyl-N'-arylacetamidines.



Scheme 2.13

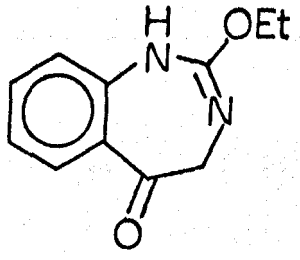
Taylor and Tully[173] have synthesised the 1,3-diazepine-2,5-dione (124) from 2,2'-diaminoacetophenone and 1,1'-carbonyldiimidazole. The intermediate (123) cyclised in good yield to the diazepinedione.



Scheme 2.14

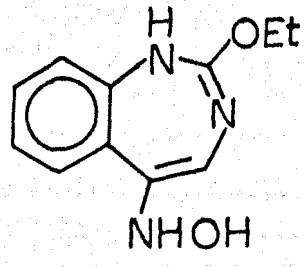
The 5-keto group was found to possess typical ketonic reactivity and formed oximes readily. Reduction with sodium borohydride and reaction

with Grignard reagents led to alcohols which could not be dehydrated to introduce a double bond at the 4,5 position. Ring contraction products were isolated from these reactions. The benzodiazepine (124) could not be alkylated under normal conditions, however treatment with triethyloxonium tetrafluoroborate gave the dihydrodiazepinone (125) which was converted into the fully unsaturated compound (126)



(125)

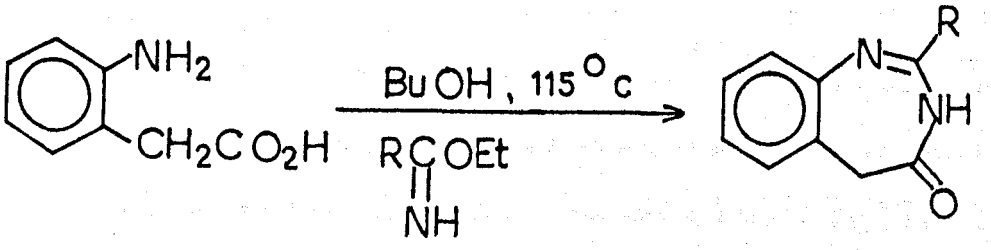
with hydroxylamine.



(126)

The alcohols derived from the benzodiazepinone (125) were also resistant to dehydration and gave instead ring-opened or ring contraction products.

Taub and Loeffler[174] have disclosed a route to 3H-1,3-benzodiazepin-4-one via an imidate cyclisation method.

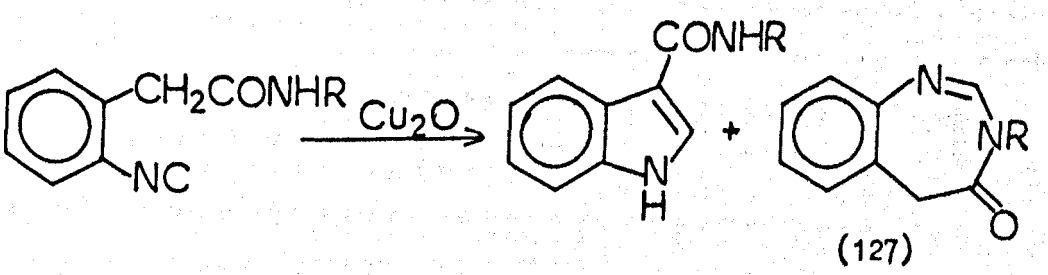


R = alkyl, aryl

Scheme 2.15

The compounds are useful as psychosedatives, hypnotics and muscle relaxants.

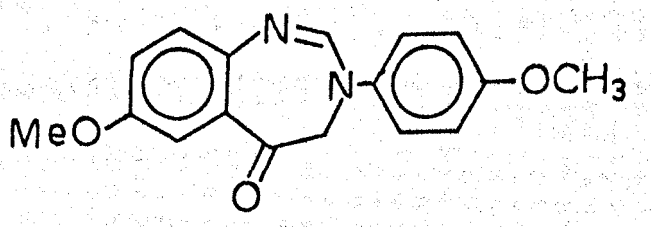
The related diazepinone (127) has been isolated in some instances in the copper mediated cyclisation of N-substituted o-isocyanophenylacetamides.[175] Indoles are the sole products when R is a bulky group.



(127)

Scheme 2.16

The 3-(p-methoxyphenyl)-4,5-dihydro-7-methoxy-1,3-benzodiazepin-5-one structure (128) has been suggested[176] for the yellow base isolated in very low yield from the reaction of p-anisidine with formaldehyde.

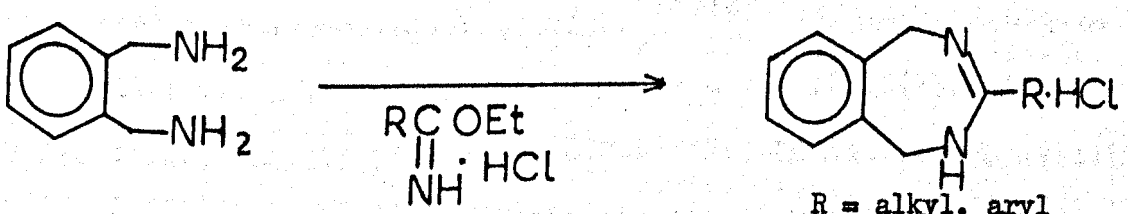


(128)

Various tricyclic and tetracyclic derivatives have been prepared from 1,3,4,5-tetrahydro-5-methyl-2H-1,3-benzodiazepin-2-thione by Elslager et al.[177] The synthesis of the thione was accomplished in a similar manner to that employed by Suh and Schnettler.[168-170]

2.2 (b) 2,4-Benzodiazepines

In contrast to the 1,3-benzodiazepines the 2,4-isomers are little-known compounds. Two useful routes to these compounds have been published however. DeStevens,[166,178] in a parallel approach to that employed for the 1,3-benzodiazepine series, has synthesised 4,5-dihydro-1H-2,4-benzodiazepines by condensation of appropriate diamines with imidate hydrochlorides.

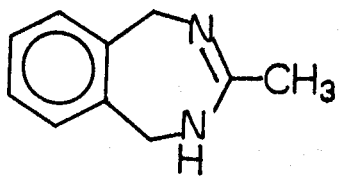


R = alkyl, aryl
28 - 84%

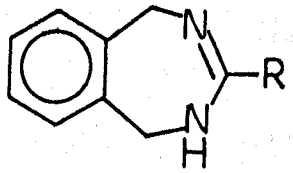
Scheme 2.17

The order of reactivity of the imidates, i.e. chloromethyl > alkyl > aryl resembled that in the isomeric 1,3-series. The rate of reaction was always faster than that of the corresponding 2-(o-aminophenyl) ethylamine condensations, this was explained by the greater nucleophilicity of the alkylamine in the final step of the reaction.

An equivalent synthetic methodology has been adopted by Desmarchelier[161] and Suh et al.[179,180] Desmarchelier obtained the 2,4-benzodiazepine (129) in 58% yield from the condensation of o-xylenediamine with acetamidine hydrochloride.



(129)



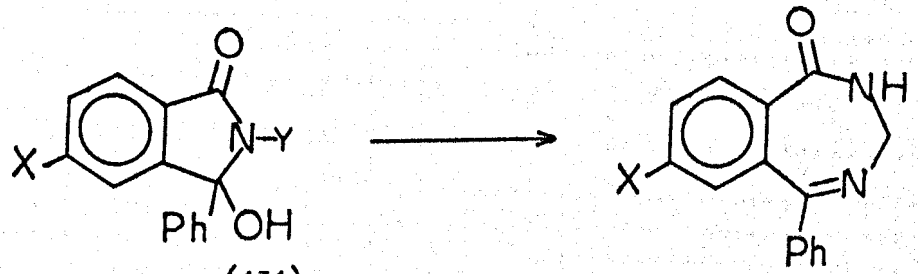
R = SMe, pyrazinyl etc.

(130)

Suh and co-workers obtained the benzodiazepines (130) by reaction of the diamine with carbon disulphide and then methyl iodide. A variety of 3-substituents were introduced by a displacement reaction.

Elslager[181] and co-workers originally prepared 1,2,4,5-tetrahydro-3H-2,4-benzodiazepine-3-thione and the methyl compound (130) by the same route as used by Suh et al.

The elusive 2,3-dihydro-1H-2,4-benzodiazepin-1-one molecule has recently been synthesised by Golik.[182-184] Formaldehyde addition to o-benzoylbenzamide in basic media gave the isoindole (131, Y = CH_2OH) in high yield. Conversion to the chloro derivative and the azide, followed by catalytic hydrogenolysis gave the amine (131, Y = CH_2NH_2). Acid catalysed condensation gave the benzodiazepin-1-one (132) in 60% yield. Preparation of the 7-chloro derivative was also accomplished (132, X = Cl). The activity of these compounds in the central nervous system was similar to those of the Valium type.



(131)

X = H, Cl

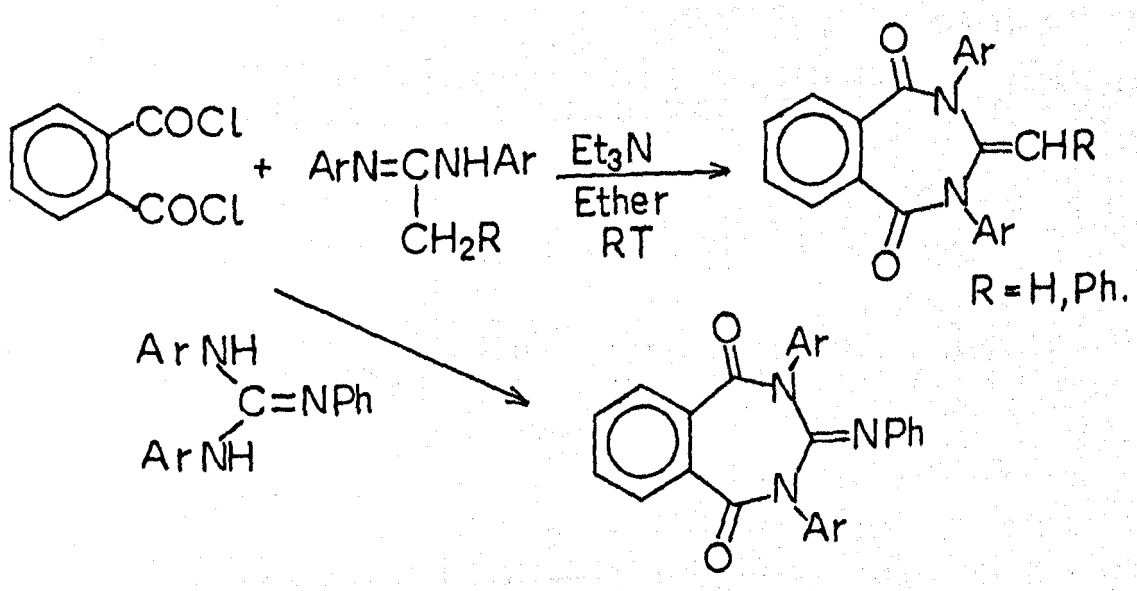
Y = CH_2OH, CH_2Cl

CH_2N_3, CH_2NH_2

(132)

Scheme 2.18

The reaction of various diacyl chlorides with substituted amidines and guanidines has been investigated and represents a general synthesis of 1H-2,4-benzodiazepine-1,5(2H)-diones[185,186] in excellent yield.

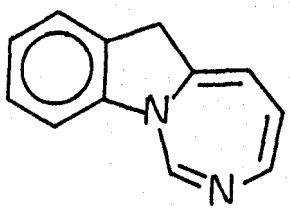


Scheme 2.19

The diazepinediones underwent a variety of ring contraction and rearrangement reactions.

DISCUSSION

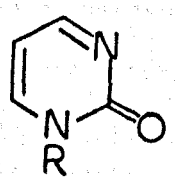
During our work on the nitrene insertion reactions into pyridine rings we had observed the formation of 9H-pyrrolo-[1,2-a]indole in low yield. This must have arisen from the intermediate (133) by ring closure and elimination of hydrogen cyanide.



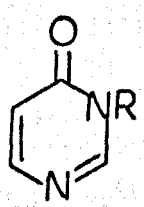
(133)

This result, together with the fact that there are no general routes to simple 1,3-diazepines, prompted us to carry out some exploratory work towards the synthesis of these elusive compounds.

The majority of the research discussed involved attempts to expand the pyrimidinones (134) and (135).



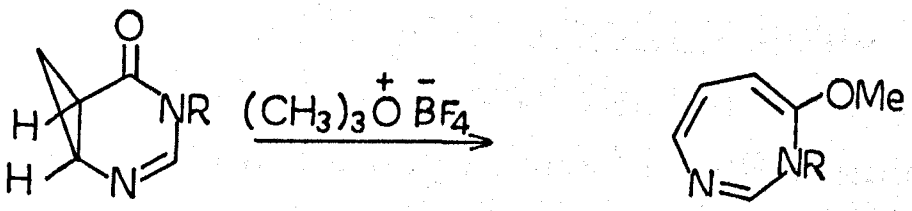
(134)



(135)

R = Me, CH_2Ph

The basis of our synthetic approach to the 1,3-diazepines was a carbene type of addition to form cyclopropane adducts of (134) and/or (135) and then ring expansion to form the diazepines, e.g. (136).

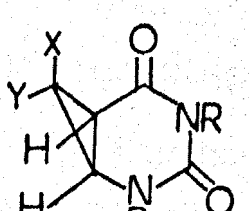


(136)

Scheme 2.20

Synthesis of 1-benzyl-2(1H)-pyrimidinone was achieved in moderate yield by treatment of the parent compound with benzyl chloride.[187] Attempts to achieve cyclopropanation in a classical Simmons-Smith reaction[188] led to orange solids which could not be characterised. A modified procedure[189] employing a zinc/silver couple also gave unidentified products. A photolytic addition of methylene[190] which had been applied successfully to various olefinic compounds gave only recovered starting materials.

Seyferth[191] and co-workers have described a convenient method for the generation of dihalocarbenes from phenyl(trihalomethyl)-mercury compounds. Generation of dibromocarbene in the presence of 1-benzyl-2(1H)-pyrimidinone resulted in the isolation of starting material despite extended reaction periods. Dihalocarbenes generated from this type of precursor have been successfully reacted with uracil compounds[192] to form adducts, e.g. (137) in moderate to good yields.



X = F, Cl, Br

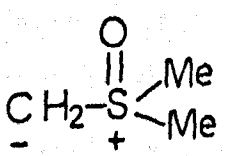
Y = F, Cl, Br

(137)

Other carbene precursors e.g. sodium trichloroacetate or chloroform/base combinations gave no adducts. Similarily Simmons-Smith reagent failed to react.

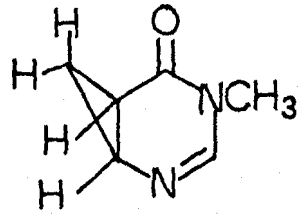
In view of these disappointing results we turned our attention to the isomeric 4-pyrimidinone (135). Attempts to prepare the 3-benzyl derivative by a published route[193] were not successful. However the 3-methyl compound[194] was successfully prepared in moderate yield. Reaction with dibromocarbene again gave only recovered starting materials. Ethoxycarbonylcarbene is known to possess enhanced reactivity towards unreactive substrates,[24] for example it reacts with benzene to produce cycloheptatriene esters. Reaction of this carbene in the presence of a copper catalyst[192] and the pyrimidinone (135, R = Me) led to oils which could not be characterised.

As an alternative approach to the synthesis of cyclopropane adducts, the generation and reaction of the sulphur ylide (138) was investigated.



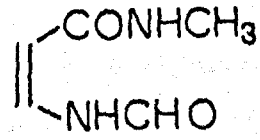
(138)

This could be readily prepared[195] in-situ from trimethyl oxosulphonium iodide and sodium hydride in anhydrous dimethyl sulphoxide. Sequential addition of 3-methyl-4(3H)-pyrimidinone and heating at 60°C gave, after work up, a yellow solid. The N.m.r. spectrum indicated a 1:1 mixture of starting material (135, R = Me) and the expected adduct (139).



(139)

Signals were present at δ 1.3, 1.8 and 2.8, clearly indicating the presence of alicyclic protons. An upfield singlet at δ 7.1 and an N-methyl at δ 3.1 further supported the structure (139). Unfortunately all attempts to separate the components of the mixture gave the starting material (135) and a few milligrammes of the ring-opened compound (140).



(140)

This material arises from ring-opening of the starting material, presumably in the work up stage.

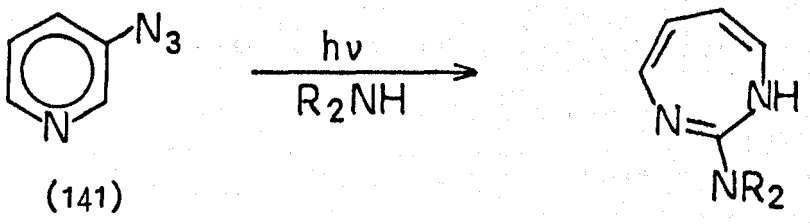
The cyclopropane adduct (139) was clearly unstable to chromatographic conditions. All attempts to achieve a separation by selective extraction into a variety of solvents failed.

Reaction of the pyrimidinone (135) with two equivalents of the sulphur ylide led to unidentified solids which possessed broad absorptions in the N.m.r. spectrum.

An attempt to synthesise a cyclopropane adduct of the pyrimidinone (134, R = CH_2Ph) by this method led to unidentified products.

Two further synthetic approaches to the 1,3-diazepines have been examined.

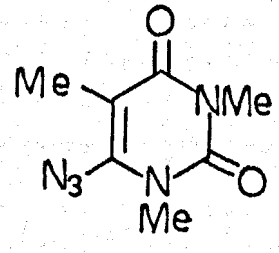
The photolysis of 3-azidopyridine (141) was investigated in amine solvents. Only tars were isolated from these reactions. Scriven and Thomas[55] have reported similar results. Sasaki et al.[103] did not isolate diazepines in the thermolysis or photolysis of tetrazolo[1,5-a]pyridine in amine solvents.



(141)

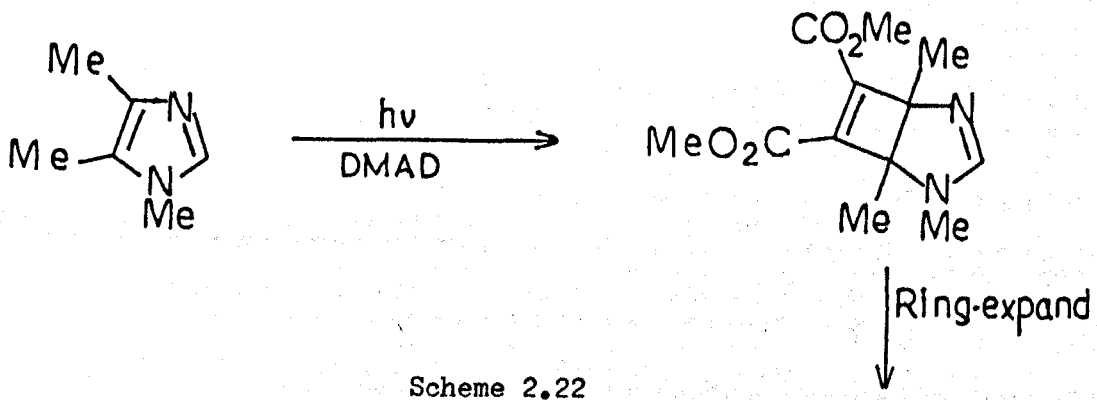
Scheme 2.21

An intramolecular insertion of this type has been recently observed in the uracil compound (142).



(142)

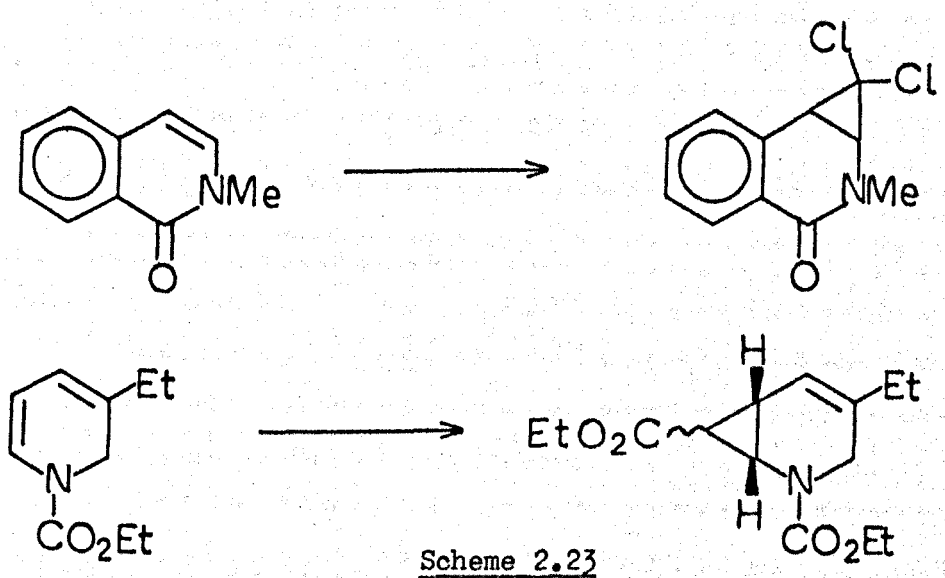
The cycloaddition of dimethyl acetylenedicarboxylate and 1,4,5-trimethylimidazole was also investigated.



Scheme 2.22

Starting material (41%) and unidentified viscous red oils were isolated.

Our efforts to ring-expand the pyrimidinones with reactive carbene intermediates were probably unsuccessful as a result of the greater aromatic character of these compounds. In the case of the uracil compounds (137) this is not a problem. Simmons-Smith reactions have also been known to fail in certain circumstances, for example no adduct was reported in a reaction with 2-vinylpyridine.[196] However dichlorocarbene and ethoxycarbonylcarbene have recently been reacted with an isoquinolone[197] and a dihydropyridine[198] to form adducts.



Scheme 2.23

Further work with 2-substituted-4(3H)-pyrimidinones may lead to adducts with the sulphur ylide (138) which are stable to chromatography.

EXPERIMENTAL

1-Benzyl-1H-pyrimidin-2-one (134)

Prepared according to the procedure of Brown and Harper[187] with the modifications described below.

The 2(1H)-pyrimidone (4.8 g, 0.05 mol) was freed from its hydrochloride salt by shaking with saturated aqueous sodium bicarbonate. The water was removed under reduced pressure and the material dried in a vacuum dessicator. The dried pyrimidone was added to a stirred solution of 2M ethanolic (absolute) potassium hydroxide (100 ml) and anhydrous, distilled benzyl chloride (25.3 g, 0.20 mol). The mixture was stirred for 27 hrs and finally boiled under reflux for 4 hrs. The cooled mixture was acidified with conc. HCl to pH 5-6, heated to boiling and filtered. Evaporation of the solvent ($< 80^{\circ}C$) gave crude 1-benzyl-1H-pyrimidin-2-one, recrystallised from ethyl acetate (c.a. 100 ml). Yield 5.0 g (54%), lit.[187] yield 25%.

M.pt. 138 - 139°C colourless plates

lit.[187] m.pt. 138 - 139°C (ethyl acetate)

N.m.r. (Acetone-d_6)

δ	8.5 p.p.m.	br	1H
	8.2	d of d	1H
	7.3	s	5H
	6.6	d of d	1H
	5.1	s	2H

Reaction of 1-benzyl-1H-pyrimidin-2-one with 'Simmons-Smith' reagent

A mixture of zinc dust (1.70 g, 0.026 mol) and Cu(I) chloride (0.26 g, 0.026 mol) in dry T.H.F. (50 ml) was stirred under a nitrogen atmosphere and boiled under reflux for 30 mins. Anhydrous, distilled methylene iodide (1.05 ml, 0.013 mol) and 1-benzyl-1H-pyrimidin-2-one (1.86 g, 0.01 mol) were added and the mixture boiled under reflux for 24 hrs. The cooled mixture was filtered (Hyflo-supercel) and evaporated to yield a red oil. The oil was extracted with dichloromethane (50 ml) filtered, washed with saturated ammonium chloride solution (50 ml), 5% sodium bicarbonate (2 x 50 ml) and finally water (2 x 50 ml). The dichloromethane layer was dried (Na_2SO_4) and evaporated to give an orange powder (1.2 g).

M.pt. 157 - 159°C (dec.) (ethyl acetate)

Analysis: Found: C, 66.25%; H, 5.63%; N, 13.03%

$C_{12}H_{12}N_2O$ requires: C, 71.98%; H, 6.04%; N, 13.99%

N.m.r. (acetone-d_6)

δ	7.1 p.p.m.	br.s
	6.1	br
	4 - 4.5	br

I.R. (DMSO) ν_{max} 3400, 1720, 1695, 1650, 1450, 1250 cm^{-1}

Mass spectrum, m/e 221 (Base peak), 206, 187, 188, 149, 113, 115, 91, 65, 51

Irradiation of 1-benzyl-1H-pyrimidin-2-one with methylene iodide

A solution of 1-benzyl-1H-pyrimidin-2-one (0.93 g, 0.005 mol) and distilled methylene iodide (1.8 ml, 0.015 mol) in dichloromethane (200 ml) was irradiated for 5 days with a Hanovia medium pressure lamp under an atmosphere of nitrogen. The solution was washed with saturated sodium thiosulphate (2 x 50 ml) and saturated potassium carbonate (50 ml), and the organic layers dried (Na_2SO_4) and evaporated to yield an orange product. The N.m.r. spectrum showed only the presence of starting materials.

Phenyl(tribromomethyl)mercury

Prepared by the method of Gillespie et al.[199]

M.pt. c.a. 110°C (dec.)
lit.[199] m.pt. c.a. 120°C (dec.)

Reaction of 1-benzyl-1H-pyrimidin-2-one with phenyl(tribromomethyl)-mercury

To a stirred solution of dry potassium iodide (0.29 g, 0.00175 mol) and dry phenyl(tribromomethyl)mercury (0.93 g, 0.00175 mol) in dry benzene (50 ml) under a dry nitrogen atmosphere, was added the benzyl pyrimidinone (0.98 g, 0.00525 mol) in one portion. The resultant mixture was boiled under reflux for seven hours. The cooled mixture was filtered and evaporated to yield an orange solid, the N.m.r. spectrum indicated that starting material only was present.

Reaction of 1-benzyl-1H-pyrimidin-2-one with a modified 'Simmons-Smith' reagent

A zinc-silver couple[189] was prepared by adding glacial

acetic acid (2.1 ml) to silver acetate (4.2 mg) and boiling under reflux, zinc dust (361 mg) was added in one portion whilst stirring under nitrogen. After 30 secs the acetic acid was pipetted off and the couple washed with fresh glacial acetic acid (2.1 ml), followed by washing with five portions of dry T.H.F. (5 x 2.1 ml). Finally dry T.H.F. (3.2 ml) was added as the reaction solvent. Dry, distilled methylene iodide (0.44 g, 0.0023 mol) and the benzyl pyrimidinone (0.30 g, 0.0016 mol) were added in dry T.H.F. (3.2 ml) to the suspension of the zinc-silver couple and the mixture boiled under reflux for 24 hrs. The cooled mixture was filtered and evaporated (0.3 mm) to give a yellow solid (0.9 g). The N.m.r. spectrum showed only broad absorptions.

3-Methyl-3H-pyrimidin-4-one (135)

Prepared according to the method of Jonak et al.[194] except that the material was isolated by sublimation at 170°C/ 2×10^{-4} mm. Yield 49%

M.pt. 127 - 128°C ($CHCl_3$)

lit.[194] m.pt. 121 - 122°C ($CHCl_3$)

N.m.r. ($CDCl_3$)	δ	8.05 p.p.m.	s	1H	
		7.75	d	1H	J = 6 Hz
		6.35	d	1H	J = 6 Hz
		3.5	s	3H	
U.V. (H_2O)	λ_{max}	223 nm	$\log_{10}\varepsilon$	3.86	
		277 nm	$\log_{10}\varepsilon$	3.60	

Reaction of 3-methyl-3H-pyrimidin-4-one with phenyl(tribromomethyl)-mercury

A stirred solution of 3-methyl-3H-pyrimidin-4-one (1.16 g, 0.0105 mol) and phenyl(tribromomethyl)mercury (1.36 g, 0.0035 mol) in dry 1,2-dimethoxyethane (50 ml) under a dry nitrogen atmosphere was treated with dry potassium iodide (0.23 g, 0.0035 mol) and the mixture boiled under reflux for 3½ hrs. The cooled solution was filtered and evaporated to yield a fawn solid. The N.m.r. spectrum of the material indicated that only starting material was present.

Trimethyloxosulphonium iodide

Prepared according to the method of Kuhn and Trischimann[200] in 56% yield.

Reaction of dimethyloxosulphonium ylide with 3-methyl-3H-pyrimidin-4-one

A suspension of sodium hydride (0.53 g, 50% in oil, 0.011 mol) in dry dimethylsulphoxide was prepared by washing the sodium hydride with dry 40 - 60° petroleum ether (10 ml) and decanting the petroleum layer under a dry nitrogen atmosphere, dry DMSO (25 ml) was then added rapidly. Dry trimethyloxosulphonium iodide (2.53 g, 0.0115 mol) was added in two portions over a period of 10 minutes. A brisk evolution of hydrogen was noted. The mixture was stirred for a further 30 mins at room temperature, 3-methyl-3H-pyrimidin-4-one (1.10 g, 0.010 mol) in dry DMSO (10 ml) was then added dropwise over a period of 5 mins. The solution was stirred for one hour and finally heated at 60°C for 30 mins. Water (5 ml) was then added and the solvents removed under reduced pressure (eventually at 0.3 mm). The

product (1.2 g) was spread on preparative T.L.C. plates (Eluant 70 : 30 EtOAc : MeOH). Two bands were observed. Band 1. (R_F 0.4) was the starting pyrimidinone (0.53 g). Band 2. (R_F 0.6) was a yellow oil (0.21 g), trituration with chloroform gave a small amount of a fawn solid, identified as 3-formylamino-N-methyl-2-propenamide (140).

M.pt. 190 - 192°C

N.m.r. ($CDCl_3$)	δ 11.30 p.p.m.	br.d	1H	Ex.D_2O J = c.a. 9 Hz
	8.30	br.s	1H	
	7.25	d of d	1H	J = 9 Hz, 8 Hz
	6.8	br	1H	Ex.D_2O
	5.15	d of d	1H	J = 9 Hz, 3 Hz
	2.8	d	3H	J = 5 Hz

I.R. ($CHCl_3$) ν_{max} 3450, 3260, 2900, 1700, 1660, 1640, 1550, 1450, 1360, 1230, 840 cm^{-1}

Mass spectrum, m/e 128 (M^+, 44%), 110 (28), 100 (100), 98 (50), 96 (28), 71 (28), 70 (74), 58 (22), 42 (61)

Ethyl diazoacetate

Freshly prepared according to the method of Searle.[201] Yield 76%.

Reaction of 3-methyl-3H-pyrimidin-4-one with ethyl diazoacetate

Copper (Organic synthesis grade, Hopkin and Williams Ltd.) was activated by washing with 2M HCl (2 x 25 ml), water (2 x 25 ml), ethanol (3 x 25 ml) and finally ether (6 x 25 ml). The activated material was dried in a vacuum dessicator.

To a stirred solution of 3-methyl-3H-pyrimidin-4-one (1.10 g, 0.01 mol) in dry 1,2-dimethoxyethane (15 ml) was added activated copper (0.61 g). The mixture was boiled under reflux under a dry nitrogen atmosphere. A solution of ethyl diazoacetate (3.03 g, 0.027 mol) in dry 1,2-dimethoxyethane (30 ml) was then added dropwise over a period of 1 hr. The mixture was boiled under reflux for a further 2 hrs. The cooled mixture was filtered and evaporated to yield a red-black oil (3.6 g). The N.m.r. spectrum revealed only very broad signals.

Reaction of dimethyloxosulphonium ylide with 1-benzyl-1H-pyrimidin-2-one

A suspension of sodium hydride (0.53 g, 50% in oil, 0.011 mol) in dry dimethylsulphoxide (25 ml) was prepared in a similar manner to that employed for the reaction with 3-methyl-3H-pyrimidin-4-one (135). Dry trimethyloxosulphonium iodide (2.53 g, 0.0115 mol) was added in 2 portions over a period of 10 minutes. The reaction was carried out under an atmosphere of dry nitrogen. The mixture was then stirred for a further 30 mins at room temperature. A solution of 1-benzyl-1H-pyrimidin-2-one (1.86g,0.01 mol) in dry DMSO (10 ml) was added dropwise over a period of 5 mins. The solution was stirred for 1 hr at room temperature and then heated for 30 mins at 60°C. Water (5 ml) was added and the solution evaporated under reduced pressure (eventually at 0.1 mm). An N.m.r. spectrum gave only broad signals.

3-Azidopyridine (141)

Prepared according to a known procedure[202] via the amine. Yield 76%, (Yellow oil)

N.m.r. ($CDCl_3$)	δ 8.25 p.p.m.	s and d	2H
	7.22 - 7.15	m	2H
I.R. ($CHCl_3$)	ν_{max} 2120 (s), 1575, 1475, 1420, 1310, 1020, 800 cm^{-1}		

Irradiation of 3-azidopyridine (141) in aniline

A solution of 3-azidopyridine (2.1 g, 0.0178 mol) in dry distilled aniline (600 ml) was irradiated with a medium pressure mercury lamp through a pyrex sleeve under an atmosphere of dry nitrogen. After 18 hrs had elapsed the consumption of starting material was complete (I.R. monitoring). The aniline was evaporated to yield a black oil (0.9 g). P.L.C. gave only tars and traces of aniline.

4,5-Dimethylimidazole

Prepared according to the method of Bredereck and Theilig.[203] Yield 39%.

M.pt. 115°C

lit.[203] m.pt. 117°C

1,4,5-Trimethylimidazole

Prepared according to the method of Pyman[204] except that dimethylsulphate was used. Yield 13%.

M.pt. 47°C

lit.[204] m.pt. 46°C

Irradiation of 1,4,5-trimethylimidazole and dimethyl acetylene-dicarboxylate in benzene

A solution of 1,4,5-trimethylimidazole (1.10 g, 0.01 mol)

in dry benzene (200 ml) was treated with dimethyl acetylene-dicarboxylate (1.42 g, 0.01 mol). An immediate red colour was produced. The resultant solution was irradiated with a medium pressure mercury lamp through a pyrex sleeve under an atmosphere of nitrogen, for 16 hrs. Evaporation of the solvent gave a red viscous oil (2.5 g). The oil was absorbed on alumina (IV, 10 g) and chromatographed on a column of alumina (IV, 80 g). Benzene and a mixture of dichloromethane/benzene (3 : 7) eluted 1,4,5-trimethyl-imidazole (0.45 g, 41%). Further elution with dichloromethane and dichloromethane/methanol (7:3) gave unidentified red oils (0.5 g).

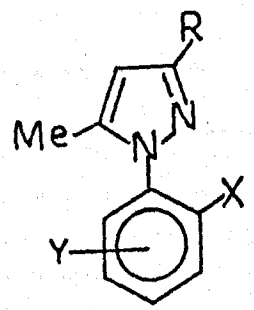
C H A P T E R T H R E E

INTRAMOLECULAR NITRENE INSERTIONS INTO THIOPHENE RINGS

INTRODUCTION

The intramolecular nitrene insertion reactions of thiophene and a variety of other heterocyclic systems have been studied and in general the products parallel those obtained in the carbocyclic series. There are a number of important differences however. Products of ring-expansion are usually absent while ring opening reactions can become a dominant feature in the chemistry of these systems.

Meth-Cohn[205,206] and co-workers have studied the reactions of the pyrazoles (143) in considerable depth.



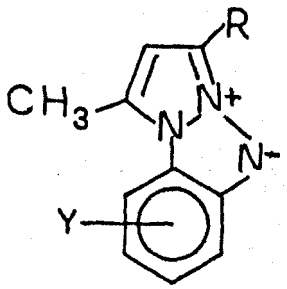
R = H, Me

X = NO_2, N_3

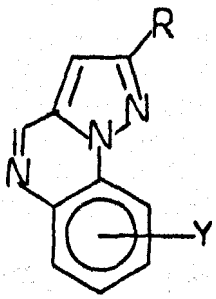
Y = H, Cl

(143)

Thermolysis or photolysis of the azide (143, X = N_3) or alternatively deoxygenation of the nitro compound (143, X = NO_2) with triethyl phosphite gave two types of products. The pyrazolobenzotriazole (144) was shown to be a singlet derived product while the pyrazoloquinoxaline (145) is the triplet insertion product. Varying amounts of amine (143, X = NH_2) assumed to have arisen from the triplet nitrene were also isolated.



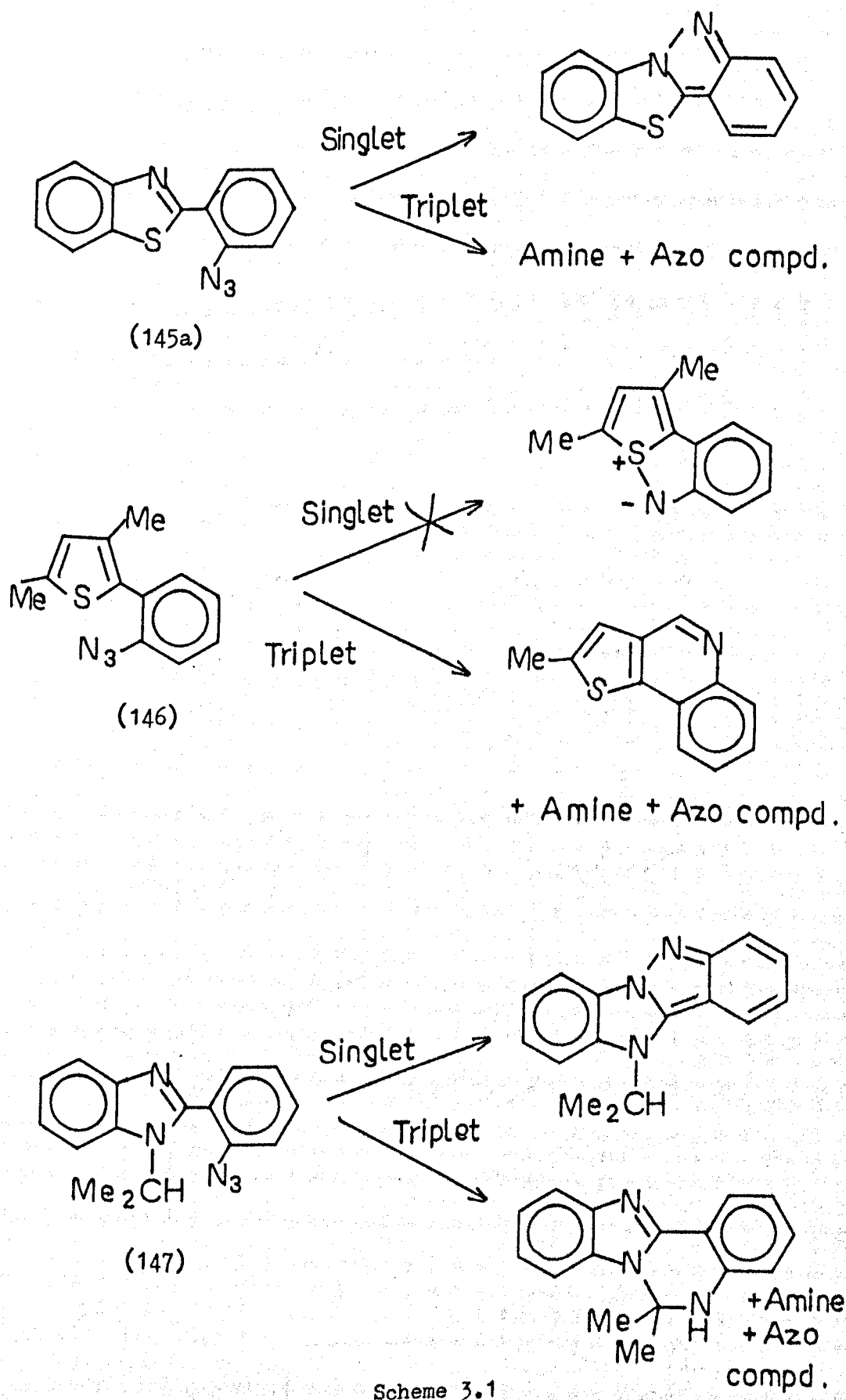
(144)



(145)

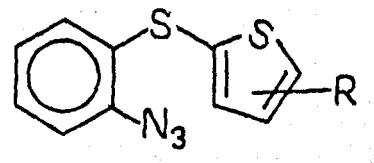
A variety of triplet and singlet sensitisation experiments together with substituent effects provided convincing evidence for the origin of the products. A combination of increased electrophilicity in the nitrene function (Y = p-Cl) and increased nucleophilicity of the pyrazole nitrogen (R = Me) led to increased yields of the pyrazolobenzotriazole (144).

Similar studies of the heterocyclic systems (145a - 147) gave analogous results.[207] Products where nucleophilic attack on sulphur could occur were not isolated. A dimethylamino group para to the azide in the benzimidazole (147) totally eliminated the singlet reactivity and only triplet products were isolated.

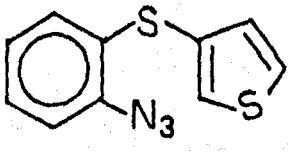

Singlet
Triplet
Amine + Azo compd.
(145a)
Me
Me
Singlet
Triplet
(146)
+ Amine + Azo compd.
Me2CH
Singlet
Triplet
(147)
+Amine
+Azo
compd.

Scheme 3.1

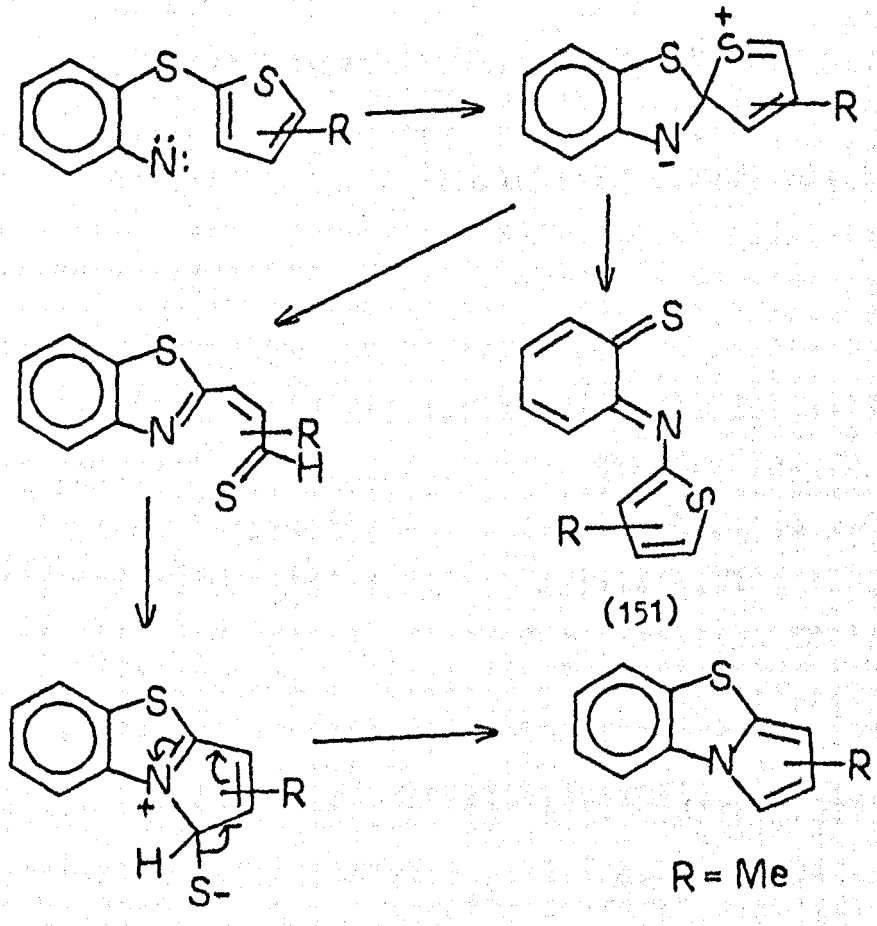
Meth-Cohn and co-workers[135] have also studied the decomposition of the thienyl sulphides (148) and (149). The predominant reaction is cleavage of the thiophene ring as depicted in Scheme 3.2 to form pyrrolo[2,1-b]benzothiazoles. The unsubstituted compounds (R = H) gave large quantities of purple polymers. An alternative pathway (Scheme 3.3) is available for the dimethyl thiophene (148, 3,5-dimethyl) to give the benzothiazole (150) which is formed in admixture with pyrrolobenzothiazoles.



(148)



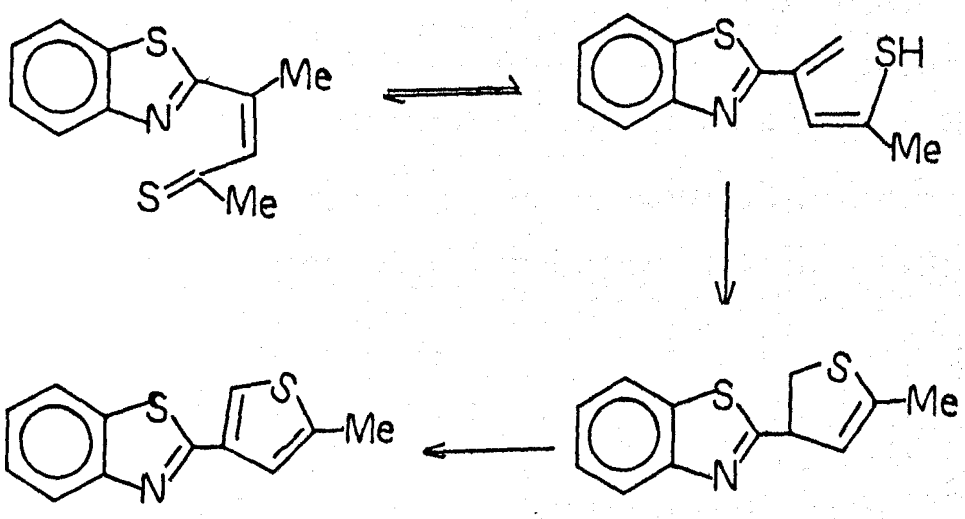
(149)



(151)

R = Me

Scheme 3.2

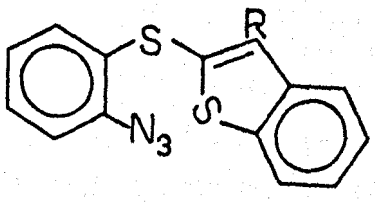


(150)

Scheme 3.3

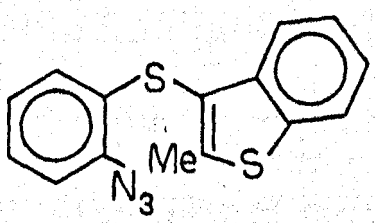
Polymer formation in the unsubstituted compounds was attributed to the ortho-quinonoid intermediate (151) which demonstrates another mode of cleavage of the spiro-diene compound.

The benzo-fused analogues (152) and (153) have been investigated by Meth-Cohn et al.[208]



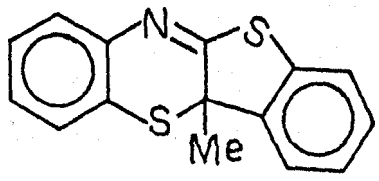
R = H, Me

(152)



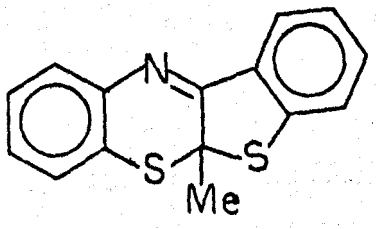
(153)

It was anticipated that the spiro intermediates postulated would show different pathways as a consequence of the fusion of a benzene ring. The unsubstituted compound (152, R = H) gave a green polymer. Both of the methyl compounds reacted cleanly and gave the benzothienobenzothiazines (154) and (155) from the azides (152) and (153) respectively.



41%

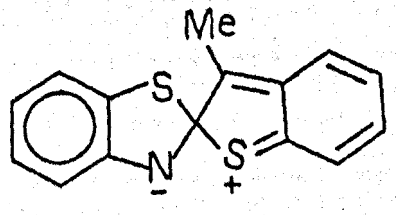
(154)



100%

(155)

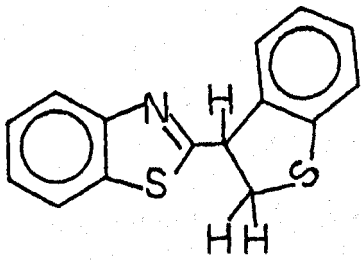
These are similar types of products to those obtained in related phenothiazine work (see Chapter 1, Introduction). The ring-opening of the intermediate e.g. (154a) is disfavoured in these compounds due to a loss of resonance energy in the final products (compare Scheme 3.2).



(154a)

An additional product in the decomposition of (152) was the

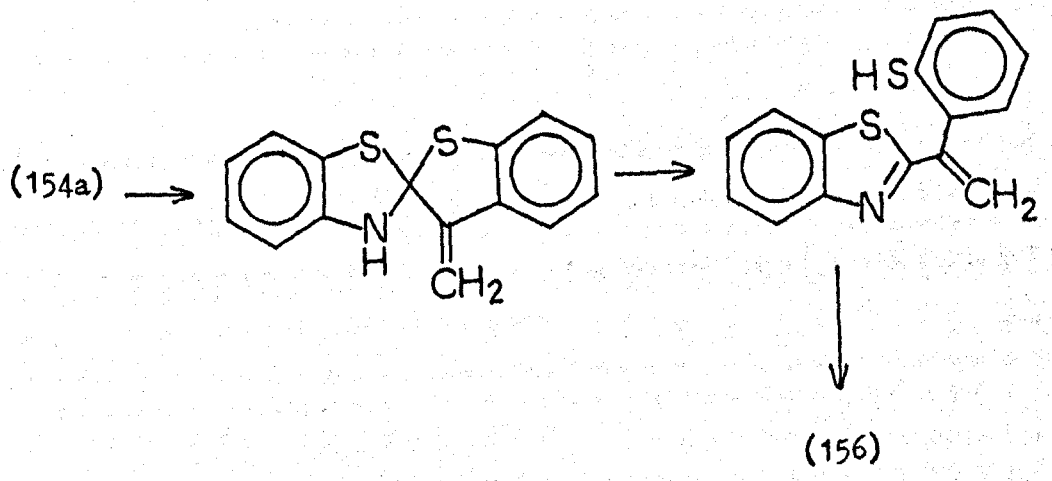
benzothiazole (156).



+ dehydrogenated compound

(156)

This was explained on the basis of a re-aromatised intermediate which underwent ring-chain tautomerism and cyclisation to the benzothiazole (156).



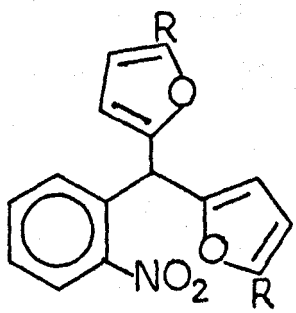
Scheme 3.4

This mechanism also accounted for the absence of an indolobenzothiazole (the 1,2-benzologue of pyrrolo[2,1-b]benzothiazole) in this series.

Intramolecular nitrene insertion reactions with suitably placed heterocyclic rings have been the subject of study of Jones

and co-workers[4,6,8-10] for some years.

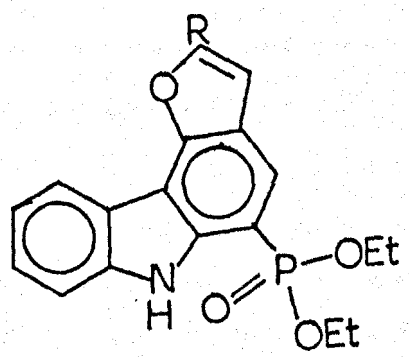
The furans (157) have been prepared and deoxygenated with triethyl phosphite.[10] It was not possible to prepare an o-azidobenzylfuran due to the instability of the furan ring towards diazotisation conditions.



R = H, Me, Et, Bu^t

(157)

The parent compound (157, R = H) gave many products none of which could be characterised. The substituted compounds gave the phosphonate derivative of the new ring system furo[3,2-c]carbazole (158).

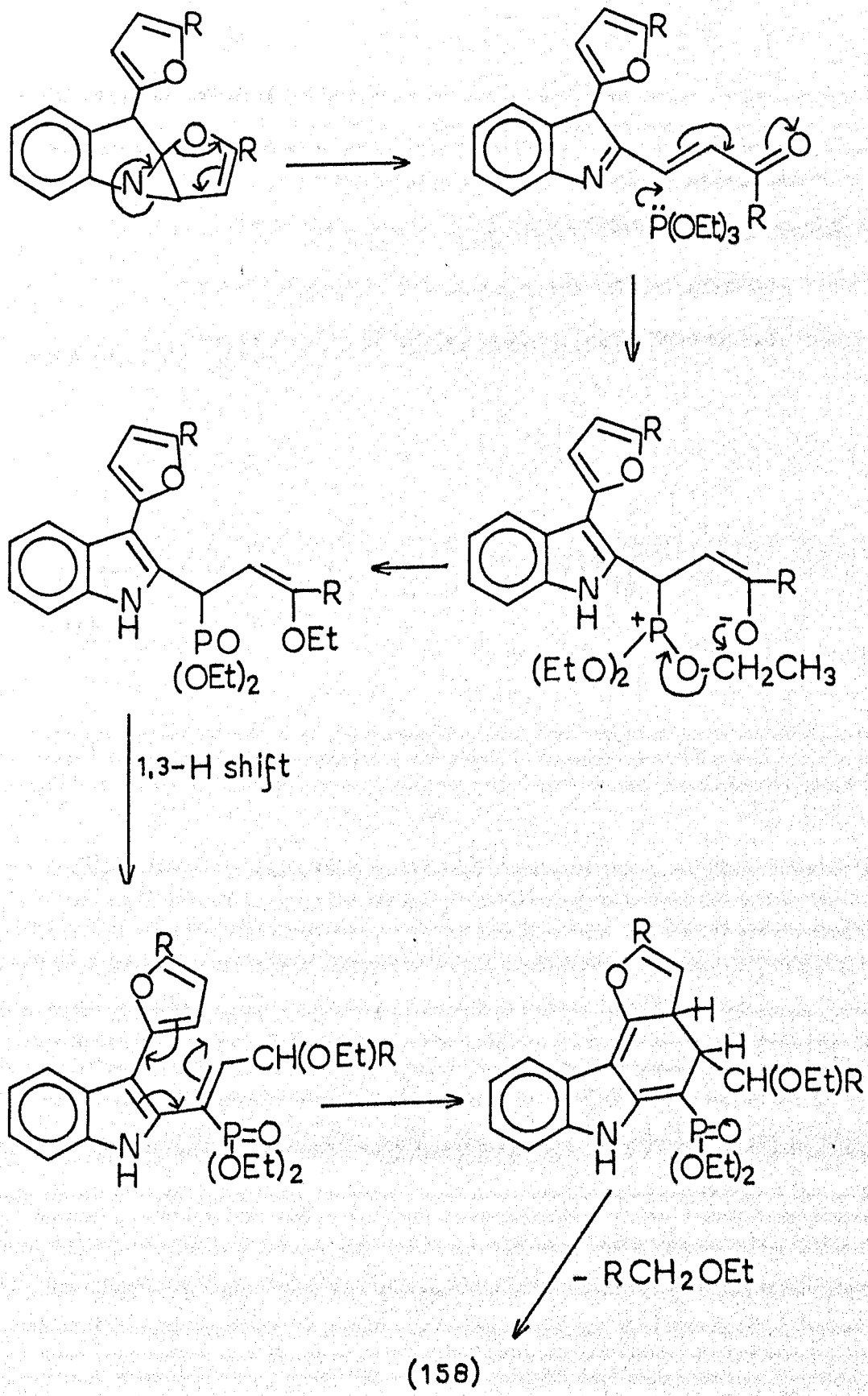


12 - 28%

(158)

The mechanism of formation of the furocarbazole is obscure. The

proposed mechanism[10] involves ring opening of the aziridine intermediate to give an α, β -unsaturated indolenyl ketone, which undergoes attack by phosphite and ring closure to the furocarbazole. The exact mechanism of ring closure and elimination of the acyl group is uncertain. Only acetaldehyde was detected in the effluent from the reaction; however this is obtained from compounds (157) R = Et and Bu^t and probably arose from triethyl phosphite decomposition. (Scheme 3.5)

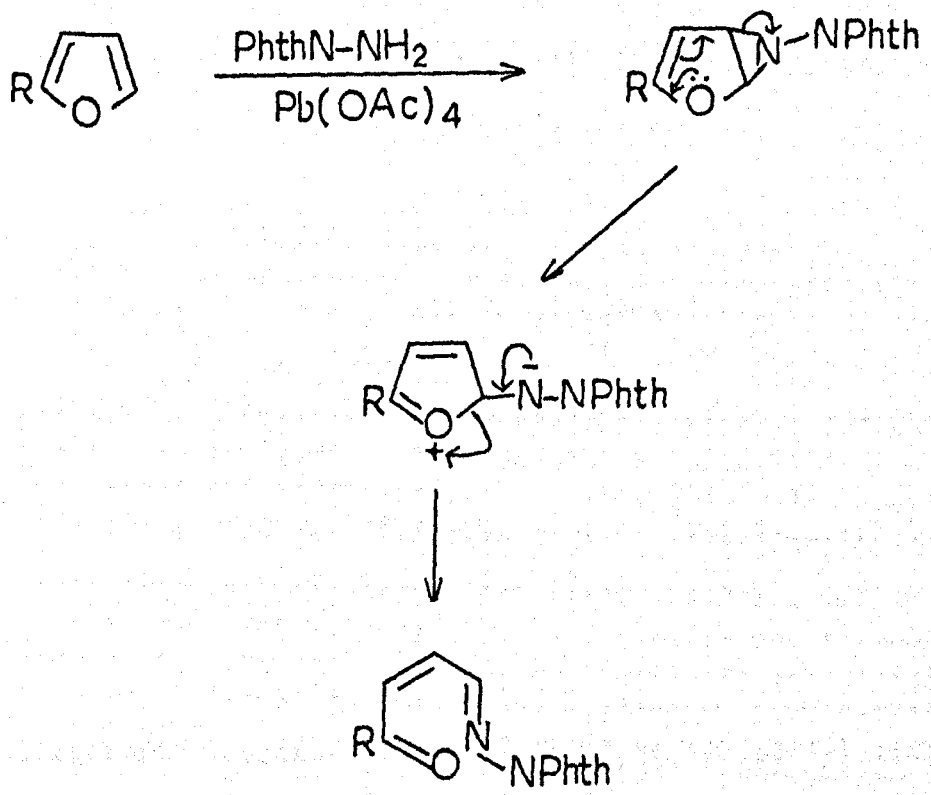


(158)

Scheme 3.5

The failure to isolate compound (158), R = H was attributed to the tendency of furylacroleins towards polymerisation.

Cleavage of a furan ring has been reported elsewhere during nitrene-mediated reactions. D.W. Jones[209,210] has isolated products of ring cleavage during the reactions of phthalimido-nitrene with benzo[b]furan and simple furans, e.g. Scheme 3.6.

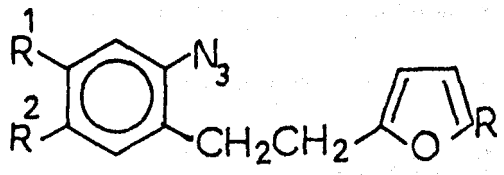


Scheme 3.6

A ring cleavage has been suggested[211] to account for the formation of pyrrolones in the reaction of ethoxycarbonyl-nitrene with furan.

A recent paper by Furukawa[212] describes the thermolysis

and photolysis of the furans (159).



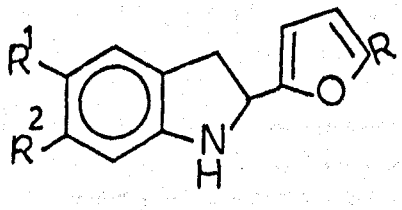
(159)

R = CO_2Me

R^1 = H, OCH_2OH, OMe

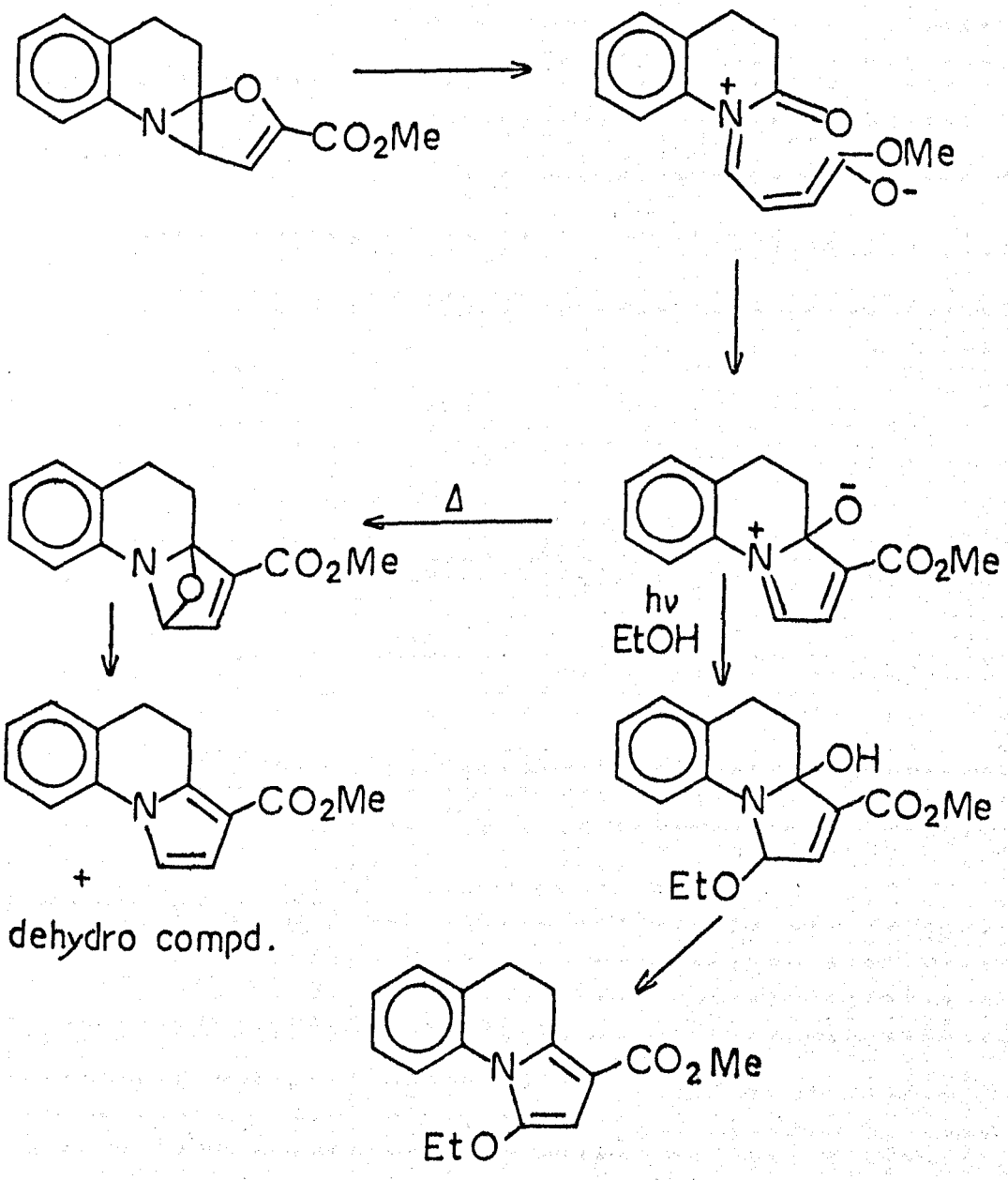
R^2 = H, OCH_2OH, OMe

Together with the products of 'normal' nitrene reactions i.e. (160) and its dehydro derivative, pyrrolo[1,2-a]quinolines were obtained.



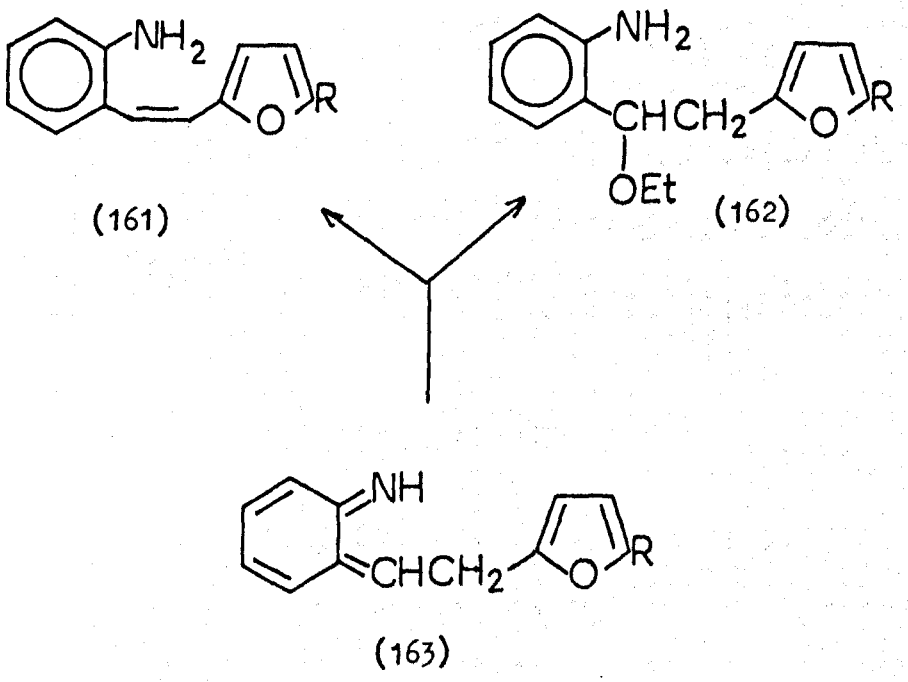
(160)

Photolysis of the azides in ethanol solution gave pyrroloquinolines and primary amines. The products formed were rationalised on the basis of ring opening of an aziridine intermediate (Scheme 3.7).



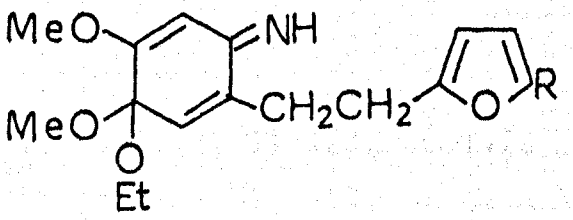
Scheme 3.7

The amines (161) and (162) were assumed to have arisen from the intermediate (163).



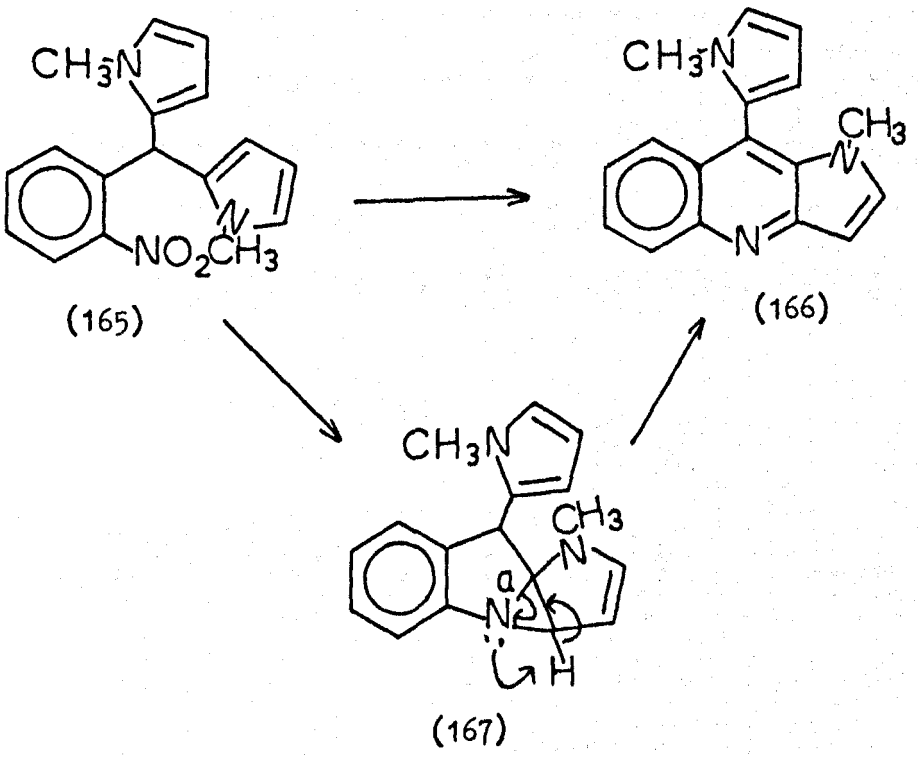
Scheme 3.8

The unusual imine (164) was isolated in one reaction.



(164)

Jones et al. have also investigated the decomposition of the pyrrole (165).[10] The only identified compound was the pyrrolo[3,2-b]quinoline (166).

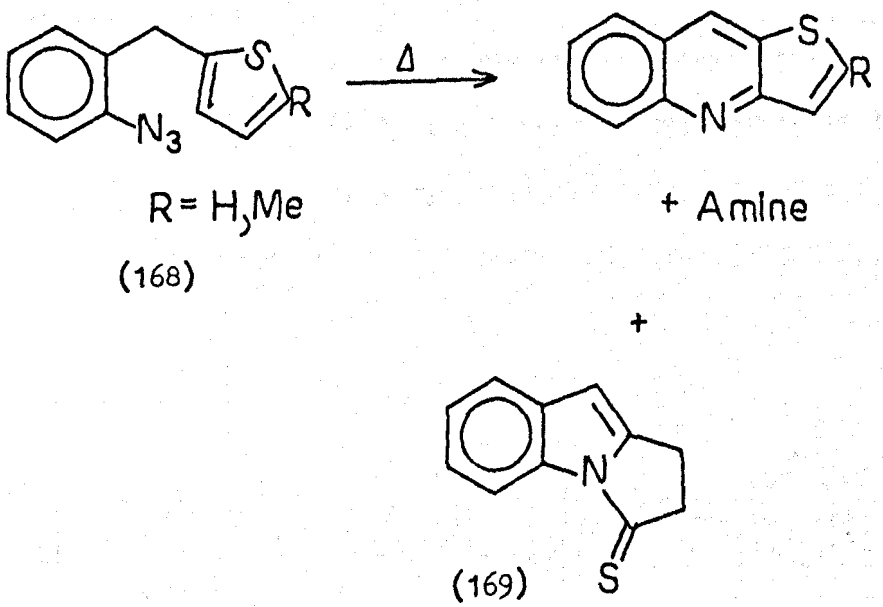


Scheme 3.9

This can arise by cleavage of bond 'a' in the aziridine (167) and subsequent dehydrogenation (probably by the triplet nitrene) to yield the pyrroloquinoline. No evidence for opening of the pyrrole ring was obtained in this case.

Studies of the thiophene analogues[6,9] have provided mechanistic insight into the reactions of nitrenes with heterocyclic rings.

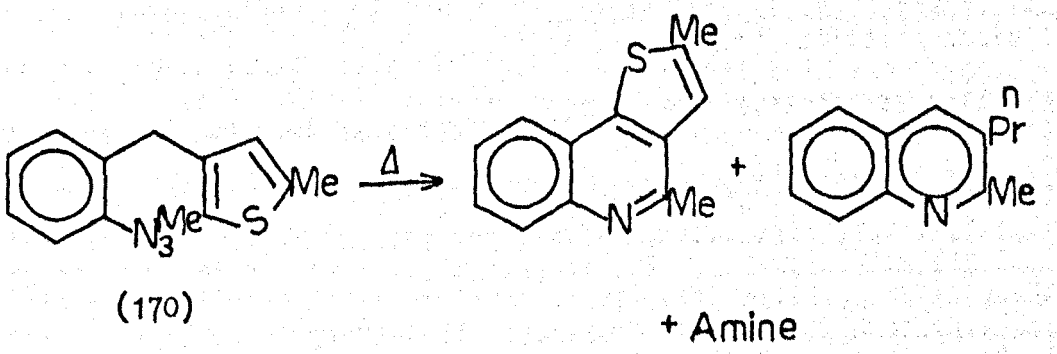
Decomposition of the thiophenes (168) gave thieno[3,2-b]-quinolines and amines (168, NH_2 instead of N_3) as major products.



Scheme 3.10

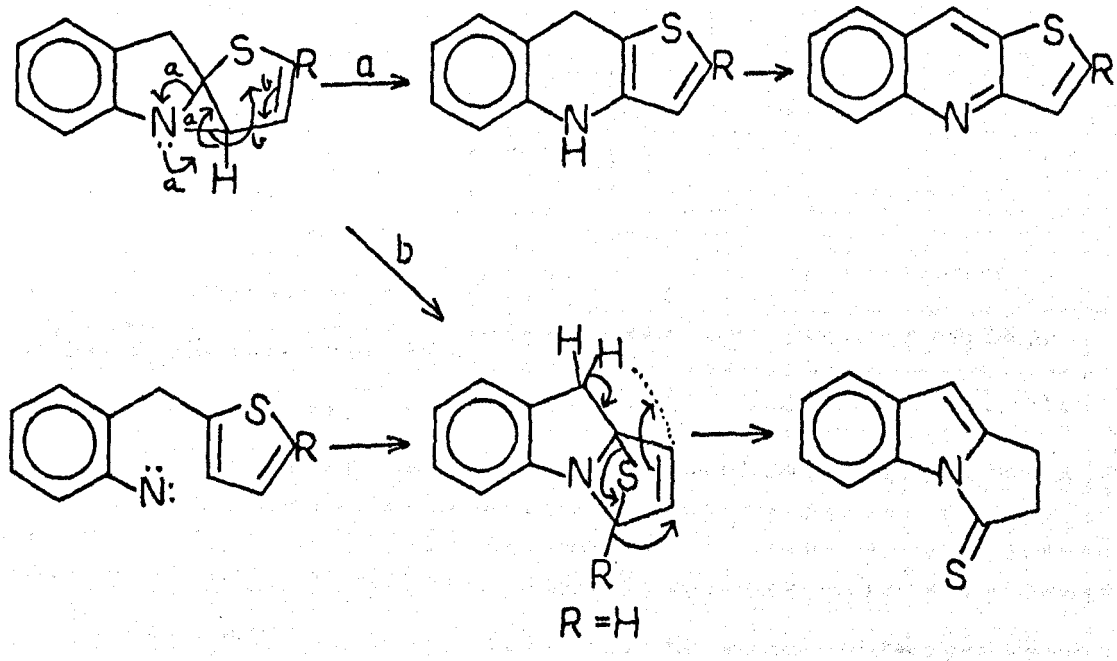
The thione (169) was also obtained from the unsubstituted thiophene (168, R = H).

Decomposition of the β-substituted thiophene (170) gave a mixture of five products of which three were characterised (Scheme 3.11).



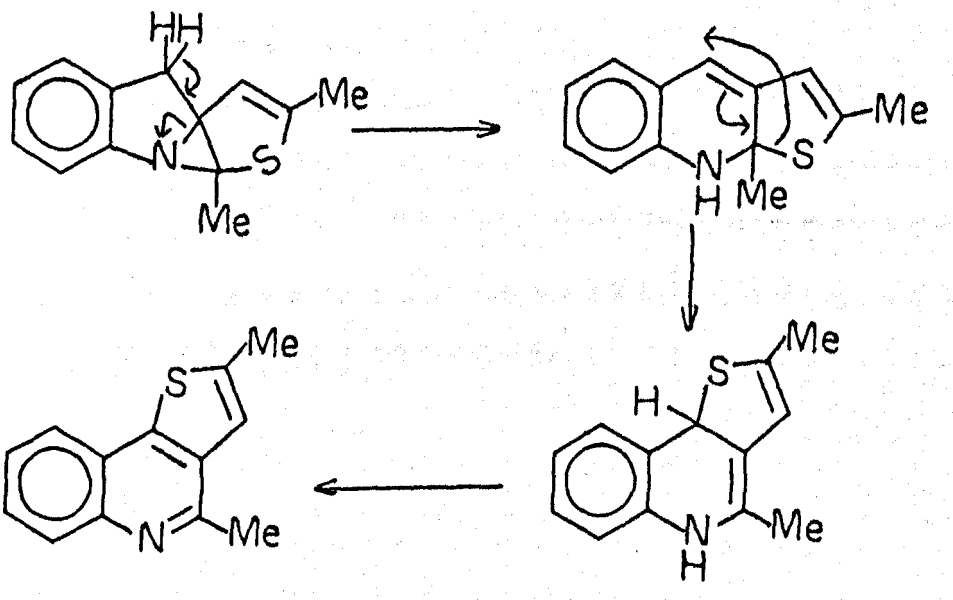
Scheme 3.11

The thienoquinolines arise via an aziridine intermediate in a similar manner to that postulated for the pyrrole (165). The thione (169) could conceivably be formed from ring-opening of this intermediate,[4] or possibly from a 1,4-addition product in a similar manner to that proposed by Hafner.[211]



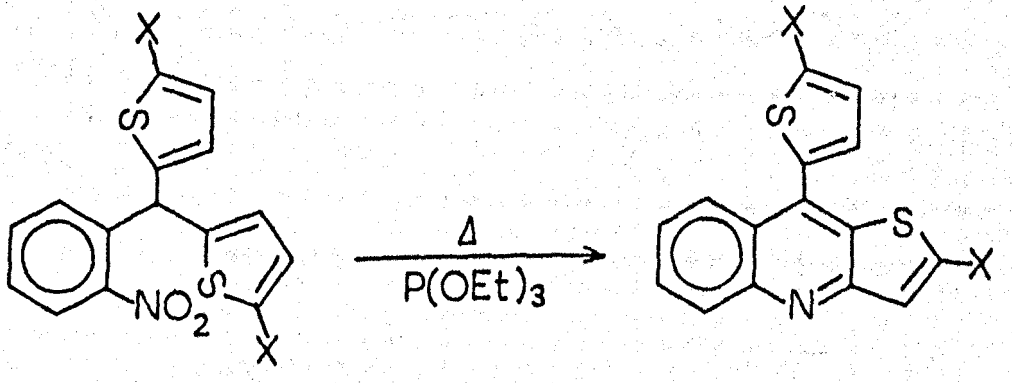
Scheme 3.12

In the β-substituted thiophene (170) a similar aziridine intermediate was postulated, proton transfer and a 1,3-sulphur shift delivers the observed product.



Scheme 3.13

Recent work[9] on the decomposition of the o-nitrophenyl-di-(5-alkylthienyl)methanes (171) has produced convincing evidence that an aziridine intermediate is involved in these reactions. The principal product in each case was the thienoquinoline (172).

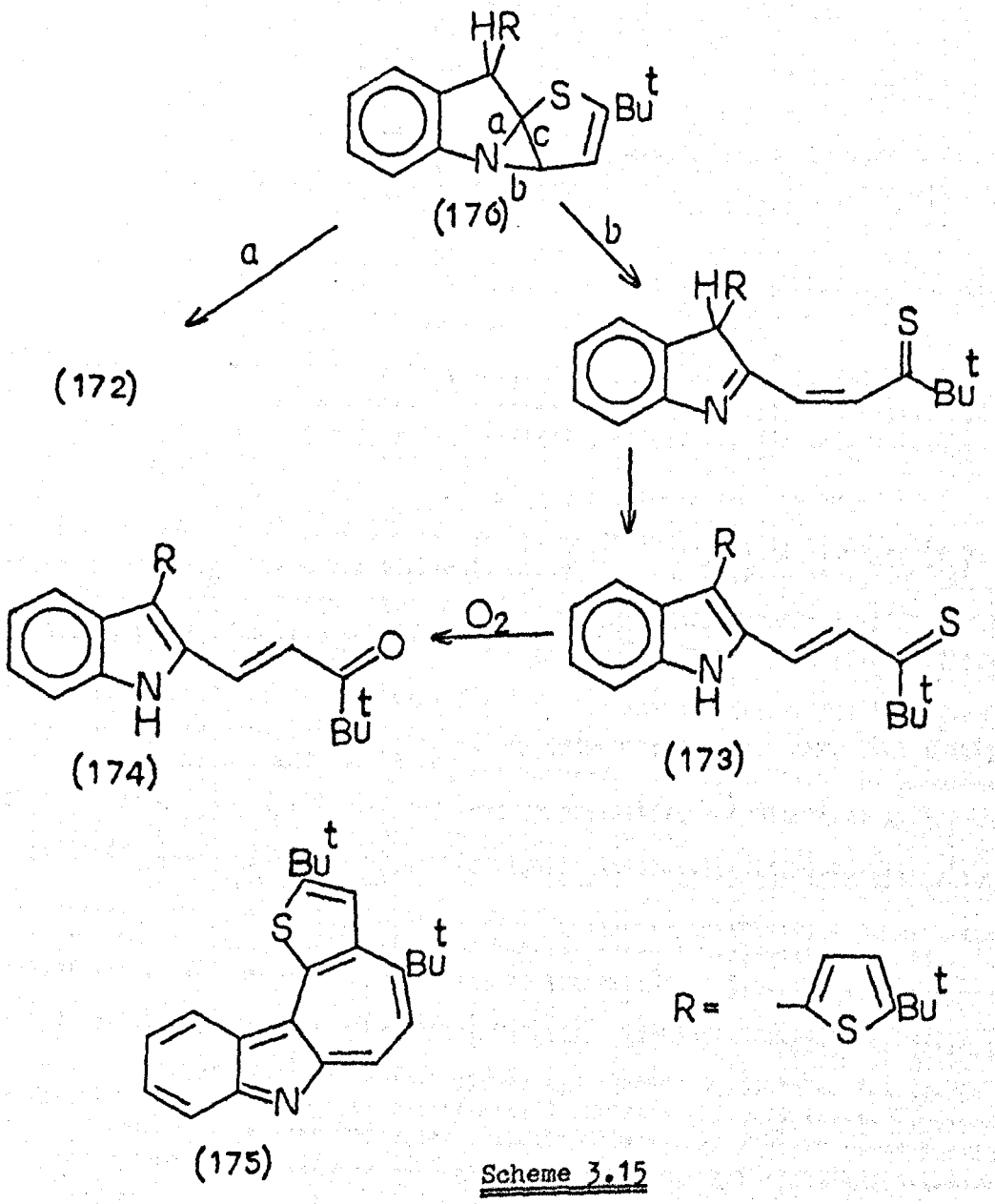


(171) (172)

X = H, Me, Et, Bu^t

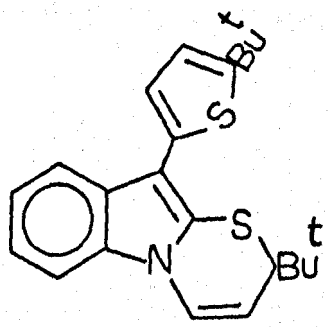
Scheme 3.14

From the deoxygenation of (171), R = Bu^t three additional products were obtained. The unstable thione (173) and the ketone (174) were isolated in low yield together with a blue material thought to be the polycycle (175). Individual products can be satisfactorily explained as being derived from the common intermediate (176), Scheme 3.15.



Scheme 3.15

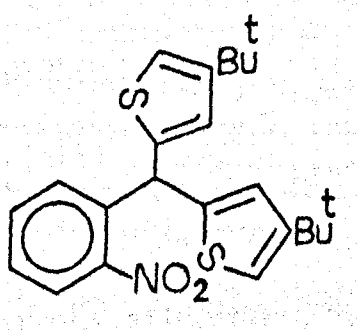
More recent work[213] has resulted in the characterisation of the product of ring expansion (177); obtained by cleavage of bond c in the intermediate (176).



(177)

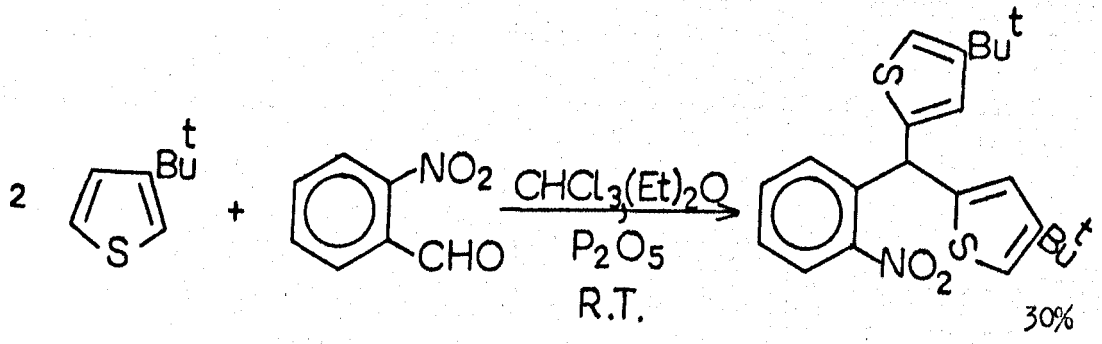
That all these compounds are true nitrene derived products was shown by decomposing the azide (171, R = Bu^t, N_3 instead of NO_2) when all products were obtained in approximately the same proportions.[9]

As a further example in this series we wished to study the decomposition of the 3-t-butyl compound (178) and this work is presented in the discussion.



DISCUSSION

The synthesis of the required nitro compound (178) was performed in a similar manner to that employed for the 2-alkyl series,[9] e.g. compound (171). The details are given in Scheme 3.16.



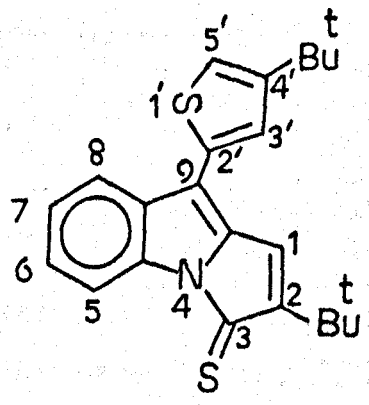
(178)

Scheme 3.16

Careful distillation through a 'spinning-band' fractionating column gave an efficient separation of 2 and 3-t-butylthiophene (prepared from thiophene and t-butylchloride with $SnCl_4$ as catalyst). However a minor proportion of 2-isomer was always present as shown by N.m.r.

The nitro compound (178) was obtained as a yellow oil. The N.m.r. spectrum showed signals in the aromatic region and an upfield sharp singlet at δ 1.2 p.p.m. A downfield multiplet at δ 7.7 p.p.m. in the aromatic region integrated for one proton and corresponds to the hydrogen ortho to the nitro group. A doublet (J = 1.5 Hz) at δ 6.5 p.p.m. (thiophene β-proton) is in agreement with that found for similarly substituted compounds.[214] The methine C-H and thiophene α-proton were coincidental at δ 6.7 p.p.m.

Strong absorptions at 1360 and 870 cm^{-1} in the infra-red spectrum indicated the presence of an aromatic nitro group. The presence of a minor amount of the isomeric 2-t-butyl compound was shown by an additional singlet in the N.m.r. spectrum at δ 1.28 p.p.m. Deoxygenation of the nitro compound (178) with triethyl phosphite in boiling cumene for three days gave a red oil which was chromatographed on an alumina column. The initial fractions were all an intense red colour. Further chromatography was performed on a medium pressure silica column. Evaporation of the initial fractions gave a red oil which crystallised. This compound was the substituted 3H-pyrrolo[1,2-a]indol-3-thione (179).



c.a. 32%

(179)

The ^1H n.m.r. spectrum was particularly informative. Two singlets were present at δ 1.38 and δ 1.65 p.p.m., these can be assigned to the 4' and 2-t-butyl groups respectively. A multiplet at δ 8.22 (C_5, C_8) and two further doublets at δ 7.20 and δ 7.39 p.p.m. (C_3' and C_5') J = 1.5 Hz, together with a singlet at δ 7.48 p.p.m. (C_1) support the proposed structure. The ^1H N.m.r. spectrum of the

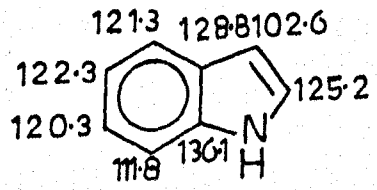
thione (179) is shown in Figure 3.1. The ^{13}C N.m.r. values and those of the thione (169) are given in Table 3.1.

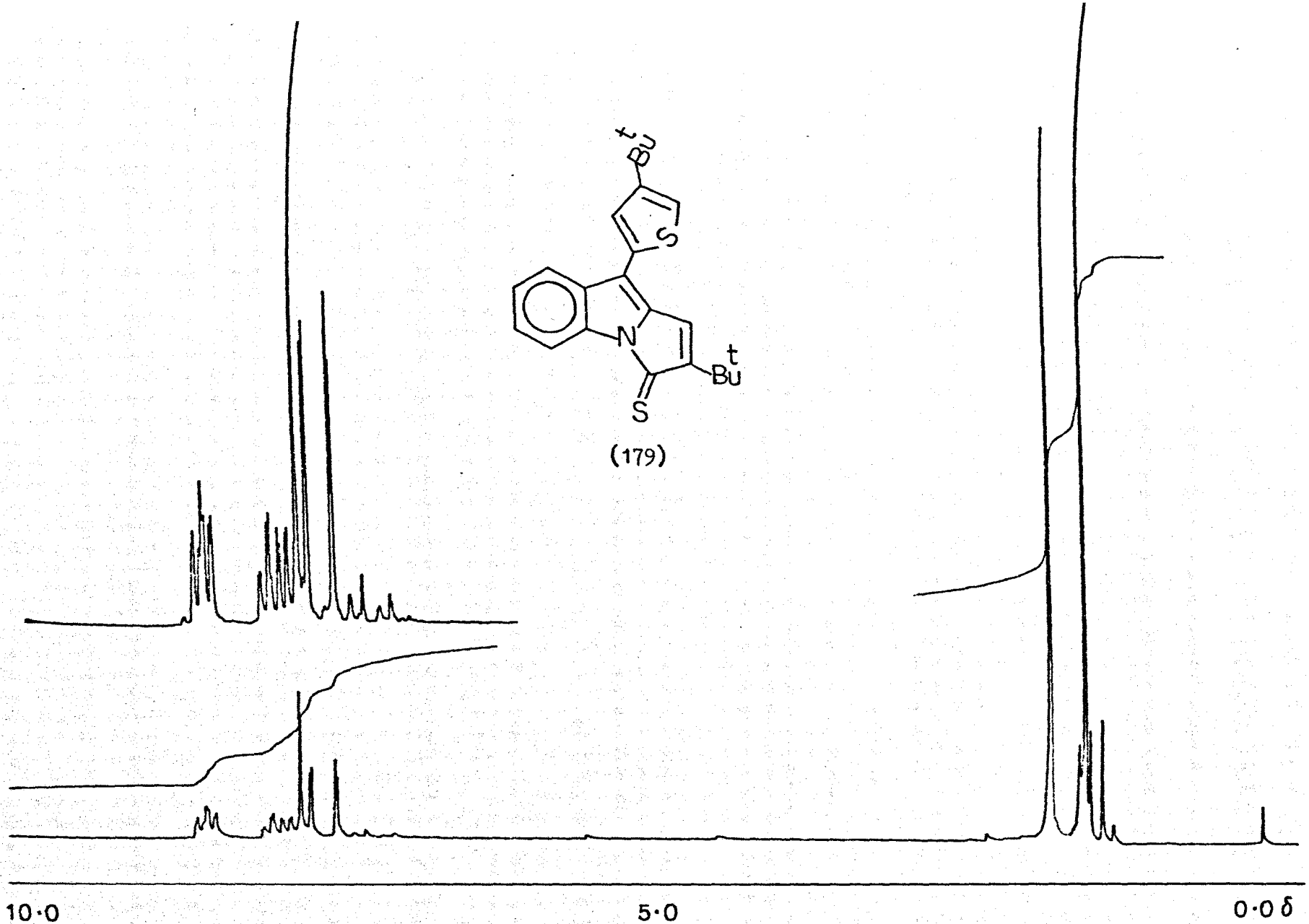
TABLE 3.1

	Compound (179)		Compound (169)
δ p.p.m.	29.6, 31.4 quartets 33.9, 35.2 singlet 119.9, 123.1, 125.7, 128.4, 129.1, 129.8, 133.9, all doublets 124.7, 127.3, 135.5, 136.1, 145.8, 146.4, 153.6, 155.1, all singlets	δ p.p.m.	21.3, 48.9, triplets 100.9, 114.3, 120.3, 123.7, 125.0, all doublets 131.8, 135.8, 147.0, 201.7, all singlets

These values are reasonable for the structure proposed. Compounds of this type are not known in the chemical literature, therefore lack of an adequate model precludes an unambiguous structure for compound (179).

The ^{13}C shifts for indole[215] are given below for comparison.

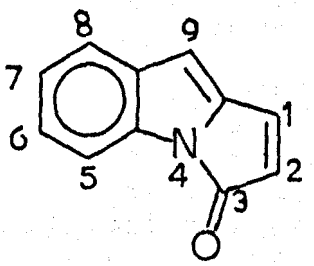




(179)

Figure 3.1 ^{1}H N.m.r. of the thione (179)

The deshielding of C_8 in the ^1H N.m.r. has been noted[9] before for thienoquinolines (172). Franck and Auerback[216] have reported spectral details of 3H-pyrrolo[1,2-a]indol-3-one (180), which serve as useful comparisons for the chemical shifts of C_1 and C_5 in the thione (179). This compound may also be synthesised and treated with P_2S_5 at a later date to provide a model system for N.m.r. studies.



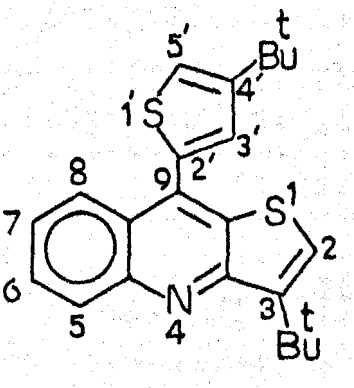
(180)

<u>^1H N.m.r.</u>

δ 5.93 C_2,
6.31 C_9, 6.9-7.45,
C_1 C_{6-8} 7.69 C_5

Attempts to reduce the 1,2-double bond of the thione (179) with sodium borohydride or by catalytic hydrogenation gave only starting material. The attempted reductions however served to discharge the red colour and gave the thione (179) as a yellow oil.

The only other identified compound isolated was the thieno[3,2-b]quinoline (181).

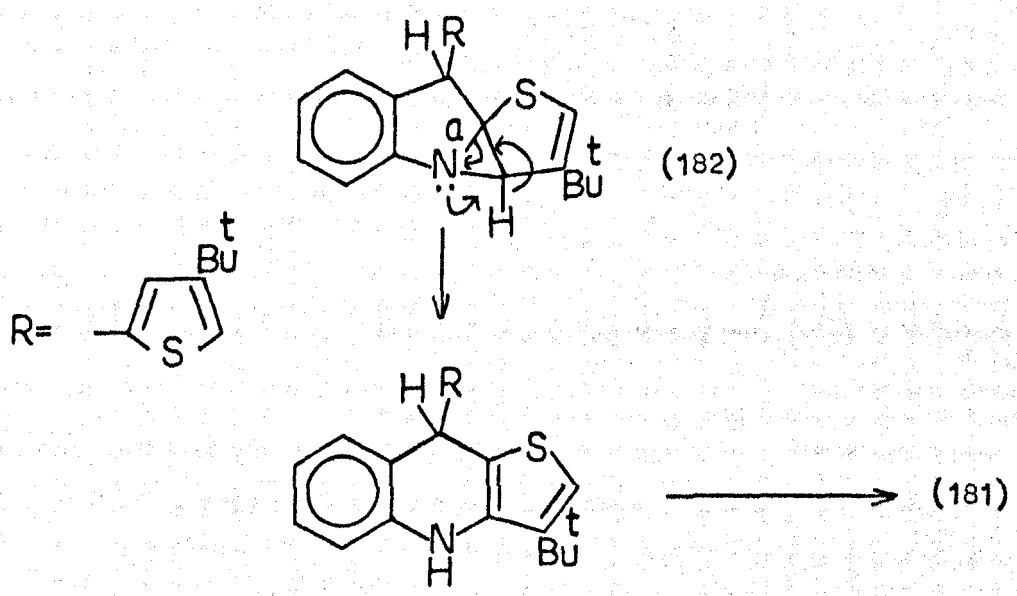


1.1%

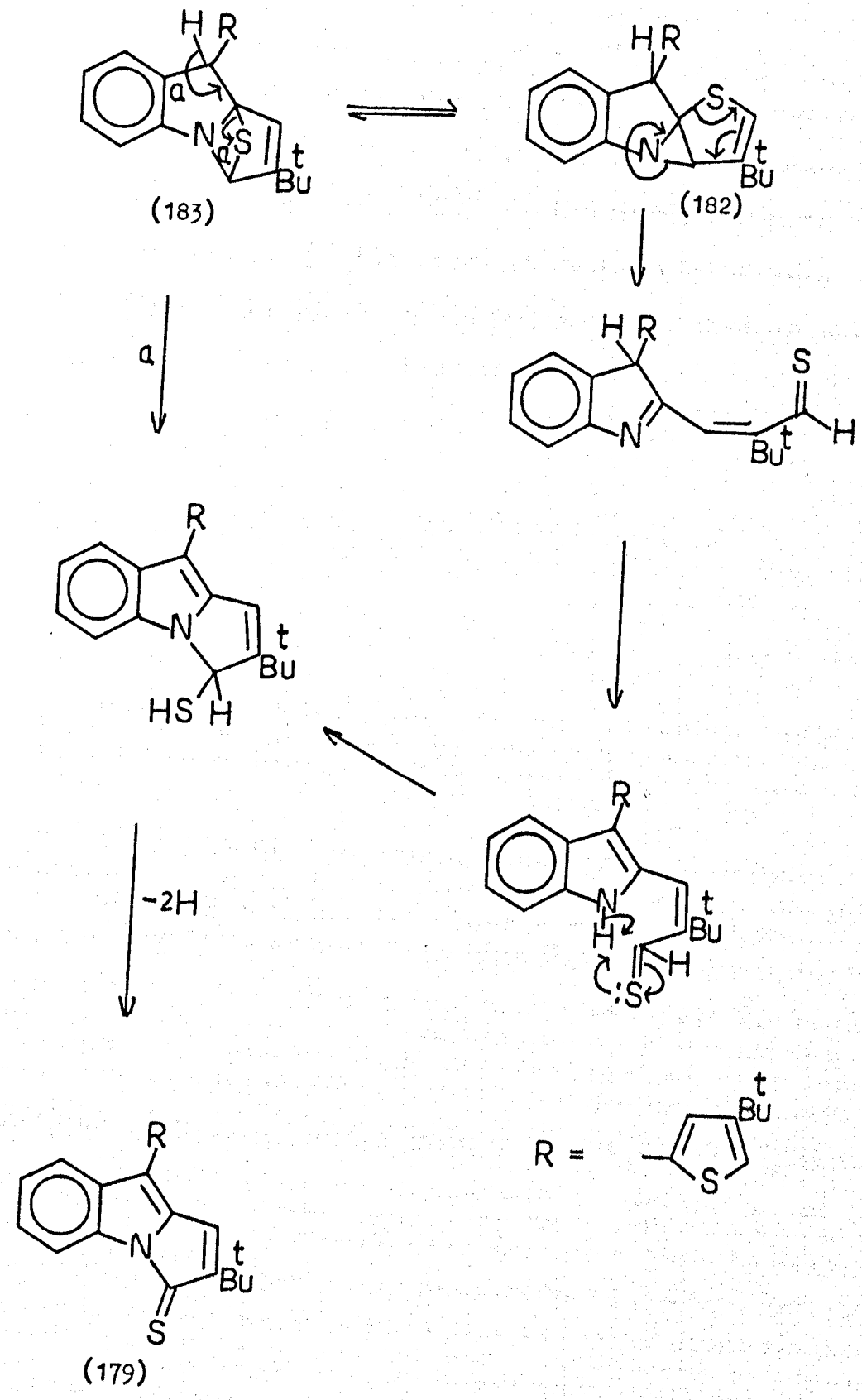
(181)

The ^{1}H spectrum revealed two singlets at δ 1.40 and δ 1.48 p.p.m. ascribable to the 4' and 3-t-butyl groups. The most notable feature of the spectrum was a downfield multiplet at δ 8.19 p.p.m.; addition of a europium shift reagent to the N.m.r. solution revealed two broad doublets. This multiplet is due to C_5 and C_8, the C_5 proton moving downfield in the presence of the shift reagent. Two doublets (J = 1.6 Hz) at δ 7.42 (C_5') and δ 7.23 (C_3') confirm the presence of the 2-thienyl substituent. A singlet at δ 7.38 p.p.m. must be due to C_2 of the fused thiophene ring. An overlapping triplet of doublets at δ 7.3-7.8 p.p.m. (C_6, C_7) was also present. The spectral details are very similar to those of the isomeric thienoquinoline (172, X = t-butyl).

Both of these products can be accounted for on the basis of an aziridine intermediate (182). The thione (179) must arise via a dehydrogenation (possibly by a triplet nitrene).



Scheme 3.17



Scheme 3.18

The adduct of a formal 1,4-addition to the thiophene ring (183) is also possible either as a discrete intermediate or in equilibrium with the aziridine (182). The failure to isolate the ring-opened intermediates in this case is probably due to the instability of the α, β -unsaturated thioaldehyde function. The thione (179) is a novel product in the thiophene series and underlines the varied and interesting results that have been obtained in this work.

EXPERIMENTAL

3-t-Butylthiophene

Prepared according to the method of Sy et al.[217] The 3-isomer was separated from the 2-compound by distillation through a spinning band column. The N.m.r. spectrum revealed the presence of a minor proportion of 2-isomer.

2'-Nitrophenyl-di-(4-t-butylthien-2-yl)methane (178)

To a solution of o-nitrobenzaldehyde (11.3 g, 0.075 mol) in chloroform (55 ml, dried over $CaCl_2$ to remove EtOH) and anhydrous ether (20 ml) was added rapidly 3-t-butylthiophene (19.5 g, 0.139 mol) and phosphorus pentoxide (26 g). The mixture was heated to boiling briefly and then left at room temperature for 6 days, with a drying tube attached to prevent ingress of moisture. The lumps of solid which formed were broken up each day with a spatula and the mixture well shaken.

The mixture was then added to ice/water (100 ml) and the mixture stirred until all the solid material had dissolved. The organic layer was separated and the aqueous phase extracted thoroughly with chloroform. The organic layer was washed with saturated sodium metabisulphite (50 ml), the organic layer separated, dried (Na_2SO_4) and evaporated. The resultant red/black oil was chromatographed on a column of alumina (800 g, IV). Petroleum ether (40 - 60°) eluted 2'-nitrophenyl-di-(4-t-butylthien-2-yl)methane contaminated with unreacted 3-t-butylthiophene. This was removed by distillation at 80°C/0.1 mm on a rotary evaporator. The yield was 8.9 g (30%). A sample was purified by P.L.C. (multiple elution with petroleum ether 40 - 60°), b.pt. 190°C/0.15 mm (bulb to bulb distillation) yellow oil.

Analysis: Found: C, 66.68%; H, 6.44%; N, 3.07%

$C_{23}H_{27}NO_2S_2$ requires: C, 66.78%; H, 6.58%; N, 3.34%

N.m.r. ($CDCl_3$) δ 7.7 p.p.m. m 1H

7.3 - 6.9 m 3H

6.7 m 3H

6.5 d 2H J = 1.5 Hz

1.2 s 18H

I.R. ($CHCl_3$) ν_{max} 2970, 2910, 2890, 1610, 1570, 1460, 1390, 1360, 1300, 1070, 870 cm^{-1}

U.V. (95% EtOH) λ_{max} 205 nm $\log_{10}\varepsilon$ 4.29

236 nm $\log_{10}\varepsilon$ 4.29

Mass spectrum, m/e 414 (5%), 413 (25, M^+), 397 (30), 342 (10), 341 (10), 340 (60), 309 (30), 214 (25), 202 (45), 167 (30), 131 (45), 130 (30), 91 (45), 64 (45), 57 (100)

Deoxygenation of 2'-nitrophenyl-di-(4-t-butylthien-2-yl)methane (178) with triethylphosphite

A solution of 2'-nitrophenyl-di-(4-t-butylthien-2-yl)methane (10.3 g, 0.025 mol) in anhydrous, distilled cumene (160 ml) was treated dropwise with distilled triethyl phosphite (14 ml) and the solution boiled under reflux in a dry nitrogen atmosphere for 3 days. The cooled solution was evaporated (eventually at 0.1 mm) to yield a red oil (18.7 g). The red oil was absorbed onto alumina (60 g, IV) and chromatographed on a column of alumina (500 g, IV). Petroleum ether (40 - 60°) eluted a red oil (Fractions 1-6, 3.0 g) which was further purified by medium pressure liquid chromatography (eluant, petroleum ether 60 - 80°) to give fairly pure 2-t-butyl-9-(4 -t-butylthien-2 -yl)-3H-pyrrolo[1,2-a]indol-3-thione (179) ($\simeq$ 32%). A sample triturated with petroleum ether

(40 - 60°) gave red crystals.

M.pt. 127 - 129°C (40 - 60° petroleum ether)

Analysis:	Found:	C, 72.90%;	H, 6.77%;	N, 3.65%
	$C_{23}H_{25}NS_2$ requires:	C, 72.80%;	H, 6.64%;	N, 3.69%

N.m.r. ($CDCl_3$)	δ 8.22 p.p.m.	m	2H	
100 M.Hz	7.79-7.48	tr. of d.	2H	
	7.48	s	1H	
	7.39	d	1H	J = 1.5 Hz
	7.20	d	1H	J = 1.5 Hz
	1.65	s	9H	
	1.38	s	9H	

^{13}C N.m.r. ($CDCl_3$) - Multiplicities in off-resonance spectrum shown in brackets

δ 29.6 p.p.m. (quart.), 31.4 (quart.), 33.9 (s), 35.2 (s), 119.9 (d), 123.1 (d), 124.7 (s), 125.7 (d), 127.3 (s), 128.4 (d), 129.1 (d), 129.8 (d), 133.9 (d), 135.5 (s), 136.1 (s), 145.8 (s), 146.4 (s), 153.6 (s), 155.1 (s)

I.R. ($CHCl_3$) ν_{max} 3100, 2950, 2905, 2870, 1610, 1600, 1560, 1450, 1380, 1360, 1320, 1145, 1135, 1125, 1090, 1075 (s), 965, 910, 850 cm^{-1}

U.V. (95% EtOH) λ_{max} 268 nm $\log_{10} \varepsilon$ 4.73; 353 nm $\log_{10} \varepsilon$ 3.77; 490 nm $\log_{10} \varepsilon$ 3.13

Mass spectrum, m/e 380 (22%), 379 (10, M^+), 365 (14), 349 (14), 339 (8), 337 (52), 323 (8), 292 (32), 277 (64), 235 (40), 153 (20), 96 (100), 94 (100), 57 (16), 51 (62), 49 (100)

Further elution with petroleum ether and mixtures of benzene/petroleum ether (1:4, Fractions 7-32) gave unidentified oils (0.5 g) and triethyl phosphite (0.9 g). P.L.C. of these oils gave no characterisable materials. Continued elution with 50% benzene/petroleum ether (Fractions 33-58), gave a brown oil (0.8 g). Preparative layer chromatography (15% ethylacetate/toluene) gave 3 bands. Band 1 (R_F 0.75) was a brown oil (0.2 g) which could not be characterised. Band 2 (R_F 0.65) also yielded uncharacterisable material (0.2 g). Band 3 (R_F 0.50) gave 9-(4 -t-butylthien-2 -yl)-3-t-butylthieno[3,2-b]quinoline (181) as a yellow oil (0.1 g, 1.1%). B.pt. 240°C/0.04 mm (bulb to bulb distillation)

Analysis: Found: C, 73.05%; H, 6.40%; N, 3.92%

$C_{23}H_{25}NS_2$ requires: C, 72.75%; H, 6.65%; N, 3.65%

N.m.r. ($CDCl_3$)	δ 8.19 p.p.m.	d	2H	H5 and H8
100 M.Hz	7.8-7.3	tr. of d.	2H	
	7.42	d	1H	J = 1.6 Hz
	7.38	s	1H	
	7.23	d	1H	J = 1.6 Hz
	1.48	s	9H	
	1.40	s	9H	

Other signals present, due to the compound derived from the isomeric 2-t-butyl material, at 6.99δ , d, J = 3.7 Hz, 7.27 d, J = 3.7 Hz, 1.49 s.

Addition of Eu.$(fod)_3$ gave 2 broad doublets for the signal previously at 8.19 p.p.m.

I.R. ($CHCl_3$) ν_{max} 3050, 2970, 2930, 2900, 2860, 1555, 1480, 1470, 1460, 1380, 1365, 1345, 1220, 930, 750, 670 cm^{-1}

U.V. (95% EtOH) λ_{max} 227 nm $\log_{10} \varepsilon$ 4.21

230 nm sh

262 nm $\log_{10} \varepsilon$ 4.82

349 nm $\log_{10} \varepsilon$ 4.06

370 nm sh

Mass spectrum, m/e 381 (10%), 380 (21), 379 (80, M^+), 366 (6), 365 (12), 364 (60), 349 (6), 348 (6), 334 (8), 308 (10), 231 (4), 219 (4), 181 (8), 174 (20), 169 (10), 160 (16), 149 (12), 146 (16), 130 (12), 119 (16), 69 (59), 57 (21), 51 (8), 44 (100), 41 (12), 40 (33)

G.L.C. (270°C, 3% OV 101, N_2 60 ml/min): revealed 2 peaks: retention times, 5.5 mins (7% relative area) and 7.5 mins (83% relative area)

Further elution of the column with benzene and 30% dichloromethane/benzene (Fractions 59-86) gave uncharacterised oils which T.L.C. showed to be complex mixtures.

Attempts to reduce 2-t-butyl-9-(4 -t-butylthien-2-yl)-3H-pyrrolo[1,2-a]indol-3-thione (179) with sodium borohydride and by catalytic reduction

1. Sodium borohydride

A solution of the thione (0.2 g, 0.000528 mol) in anhydrous methanol (10 ml) was treated with sodium borohydride (1 pellet) at room temperature. The solution was stood at room temperature for 2½ hrs during which time the red colour of the solution discharged. The reaction was quenched with water (10 ml) and evaporated. The residue

was extracted into dichloromethane (50 ml), dried (Na_2SO_4) and evaporated to yield a yellow oil (0.2 g) whose N.m.r. spectrum was identical to that of starting material.

2. Catalytic reduction

A solution of the thione (0.2 g, 0.000528 mol) in 95% ethanol (25 ml) was hydrogenated at normal temperature and pressure in the presence of 10% palladium on charcoal catalyst (0.2 g). After 2 days hydrogen uptake had ceased. The solution was filtered and evaporated to yield a green oil (0.2 g) whose N.m.r. spectrum was identical to that of the thione (179).

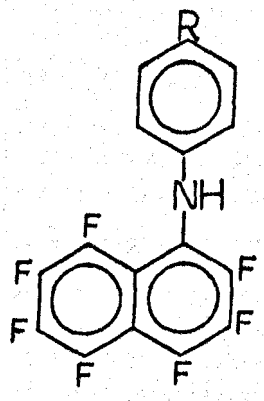
CHAPTER FOUR

INTRAMOLECULAR NITRENE INSERTIONS INTO π-DEFICIENT BENZENE RINGS

INTRODUCTION

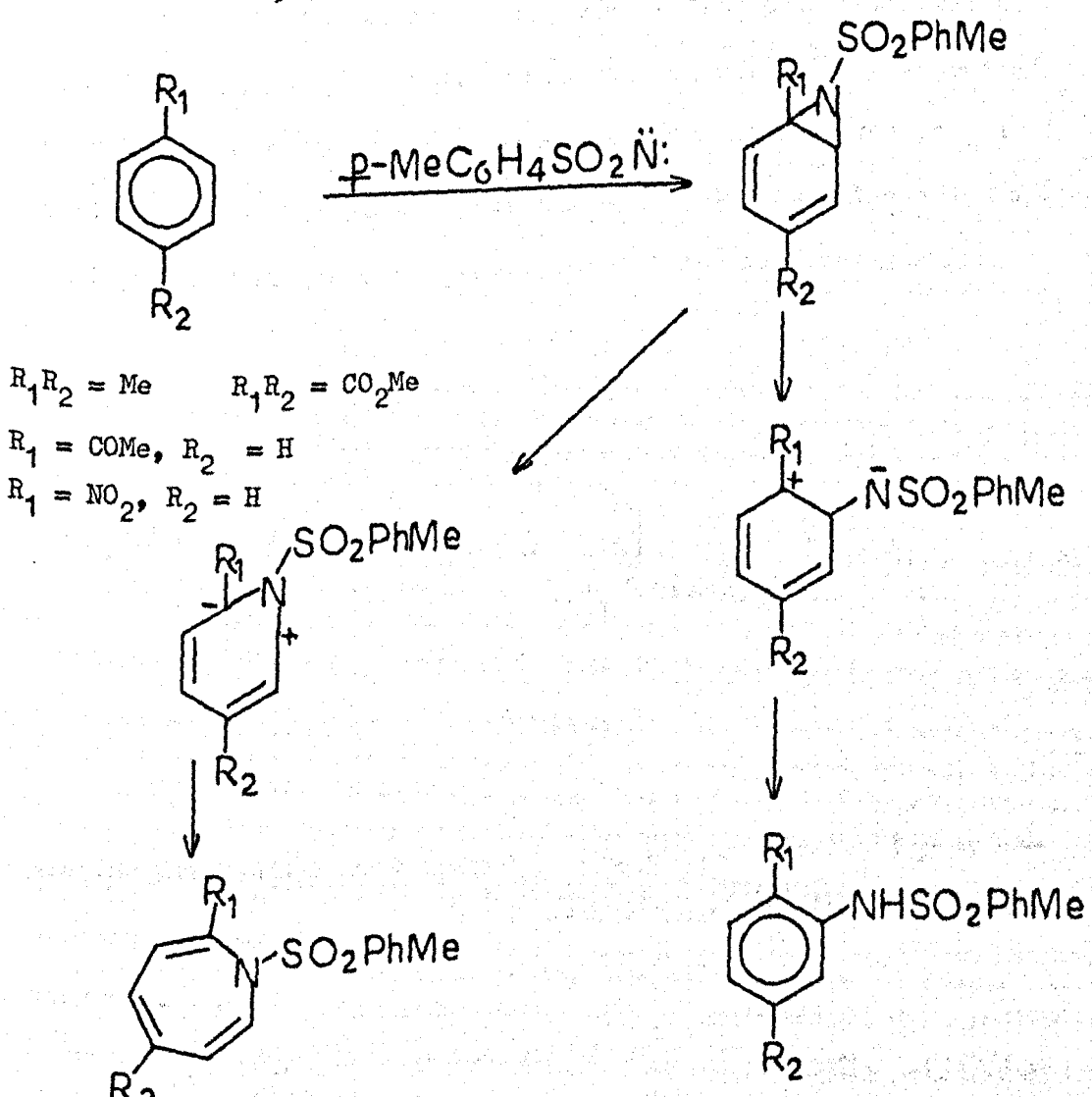
The intramolecular insertion of nitrenes into electron-poor aromatic and heteroaromatic rings is a rare occurrence as might be expected on electronic arguments. A number of examples are known where electron-withdrawing groups are present on the same ring as the nitrene function. This approach has led to intermolecular processes which had not previously been observed, e.g. the intermolecular insertion into N-H bonds[42,43] discussed in Chapter 1 (p.11). A combination of electron-withdrawing substituents in the nitrene ring and an activated substrate has been employed by several workers, mainly on work involving pentafluorophenylnitrene.[218-223]

A number of intermolecular insertions into electron-deficient substrates have been reported. Suschitzky and co-workers[224] have isolated a low yield of the substituted perfluoronaphthalene (184) during the thermolysis of p-tolyl and p-anisylazides in perfluoronaphthalene. The reaction was attributed to the triplet nitrene (no substitution products were obtained when the reaction was performed in an atmosphere of air).



(184)

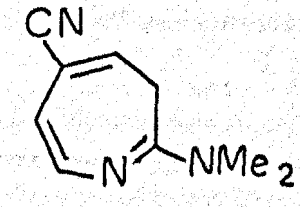
Recently Tilak et al.[225,226] have reported insertions of sulphonylnitrenes into dimethyl terephthalate and related systems. The formation of an azepine derivative in some cases (these are rare for sulphonylnitrenes) was explained on the basis of stabilisation of a zwitterionic intermediate rather than the more familiar aziridine structure. No azepines were isolated when R_1R_2 = Me or OCH_3.



Scheme 4.1

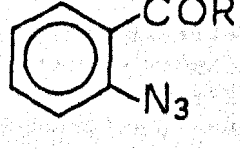
Abramovitch[227] has conducted related studies with methanesulphonyl azide, substituted N-sulphonanilides were the sole products. A careful study of isomer ratios in the presence of triplet sensitisers provided evidence for the participation of singlet and triplet nitrenes during the thermolysis. The meta isomers are the preferred products of the singlet nitrene, while ortho isomers are produced by the diradical triplet nitrene.

The formation of 3H-azepines from the photolysis of phenyl azides in amine solvents is well known.[15,24] A number of examples have been reported where insertion is observed into a π-deficient aromatic ring. Odum and Wolf[228] obtained the azepine (185) during the photolysis of p-cyanophenyl azide in dimethylamine.

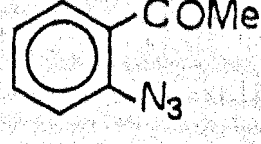


(185)

Azepine derivatives were formed during the photolysis of o-azidobenzoic acid derivatives[229,230] and the ketone[231] (186) in alcoholic solvents.

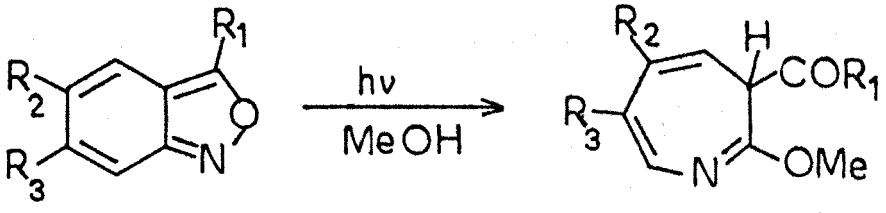


R = PhNH, NH_2, OPh, OMe



(186)

Similar results were achieved by photolysis[232] of the anthranils (187).



(187)

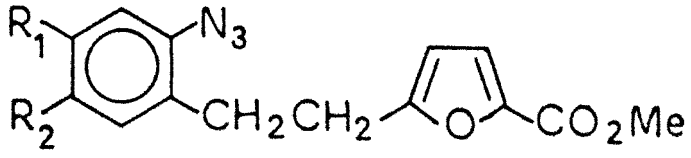
R_1 = H, CH_3, Ph

R_2R_3 = H, Cl

Scheme 4.2

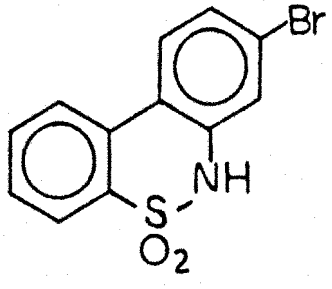
Smalley and co-workers[230] have studied these reactions most thoroughly. Good yields (50 - 80%) were obtained in a methanol/tetrahydrofuran mixture. The presence of an electron-withdrawing group was found to be essential for azepine formation since phenyl azide, o-tolyl azide, o-azidobenzyl alcohol and o-azidobenzyl methyl ether all failed to undergo expansion when photolysed in methanol/T.H.F. mixtures. The reaction was interpreted as proceeding through a singlet species with electron-withdrawing groups enhancing the electrophilicity of the incipient nitrene and leading to ring-expansion.

Intramolecular insertion of a nitrene into electron-poor aromatic rings is very rare. The reactions of the furans (188) have already been discussed[212] (see Chapter 3 - Introduction). In this case insertions into the C-H bonds of the ethane bridging group and opening of the furan ring were the observed reactions.



(188)

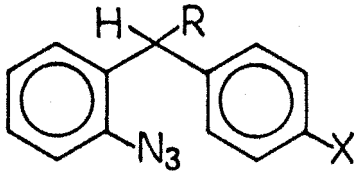
Abramovitch[233] has obtained a low yield of the dibenzothiazine 5,5-dioxide (189) from the thermolysis of 4'-bromobiphenyl-2-sulphonyl azides in various solvents.



(189)

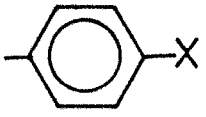
The other products isolated were derived from insertion into solvent molecules.

As a continuation of our research into intramolecular nitrene insertion reactions we wished to study the effect of electron-withdrawing groups in the di and triphenylmethane compounds (190).

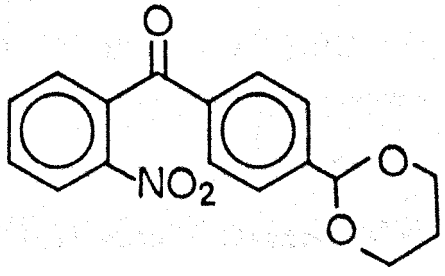


(190)

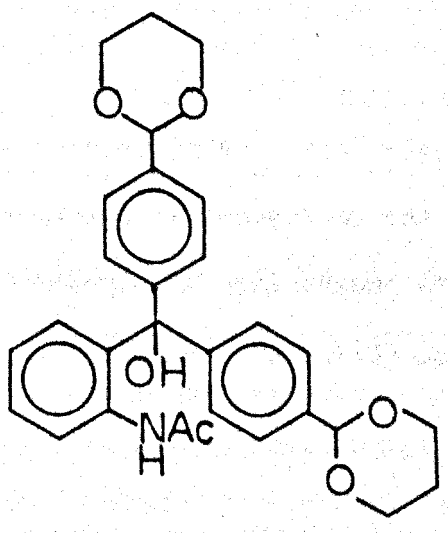
X = electron-withdrawing group

R = H, 

Previous workers[12] have investigated synthetic routes to precursors of the azides (190). The 1,3-dioxan group was found to be a versatile protecting group and survived the conditions of Grignard reactions. The ketone (191) and the alcohol (192) could be readily prepared by reaction of the Grignard reagent from 4-(1,3-dioxan-2-yl)-bromobenzene with o-nitrobenzaldehyde and 2-methyl-3,1-benzoxazin-4-one respectively.

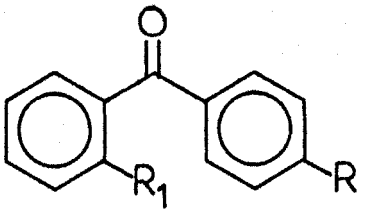


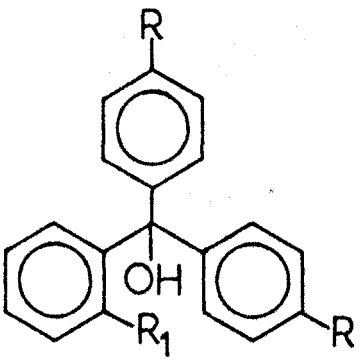
(191)



(192)

The ketone (191) is produced as a mixture with the expected alcohol in the presence of excess o-nitrobenzaldehyde at room temperature, presumably by a mechanism similar to that of the Oppenauer oxidation. Both compounds (191) and (192) could be converted into the ester derivatives (193) and (194) by treatment with N-bromosuccinimide.



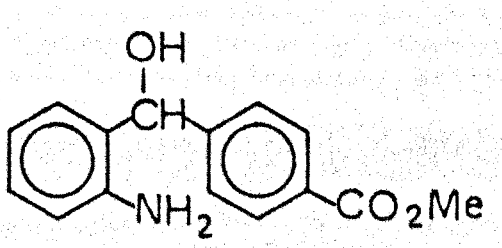


(193) R = $CO_2(CH_2)_3Br$
$R_1 = NO_2$

(194) R = $CO_2(CH_2)_3Br$
R_1 = NHAc

(195) R = CO_2Me, $R_1 = NO_2$

Attempts to carry out further synthetic transformations on compound (194) gave complex mixtures of products or intractable tars. Similar difficulties were experienced with the ketone (193). Recently,[234] however the alcohol (196) has been obtained. Treatment of the ketone (195) with palladium catalyst in the presence of cyclohexene followed by reduction of the isolated product with sodium borohydride gave the alcohol (196) in good yield.

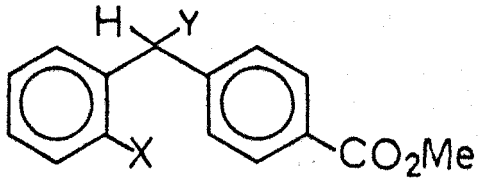


(196)

Further synthetic transformations of the compounds (194) and (196) and the thermal decomposition of the azides (190, X = CO_2Me) are presented in the discussion.

DISCUSSION

Preparation of the benzophenone (191) and conversion to the ester (193) was performed as discussed in the Introduction in yields of 43% and 100% respectively. Treatment of the bromopropylester (193) with acidic boiling methanol gave in good yield the ester (195). Transfer hydrogenation of the nitro group of compound (195) and sodium borohydride reduction of the carbonyl function gave the alcohol (196).



(196) X = NH_2, Y = OH

(197) X = NH_2, Y = H

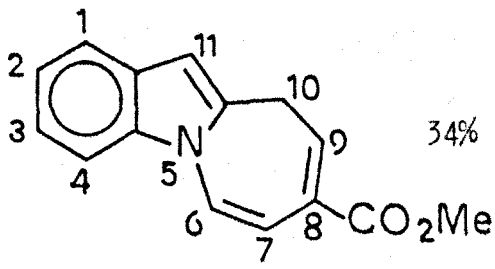
(198) X = N_3, Y = H

Catalytic hydrogenation of the alcohol (196) in the presence of excess catalyst gave a clean conversion to the diphenylmethane (197) in 80% yield. Diazotisation of the amine in a mixture of 1,4-dioxan and sulphuric acid and sequential addition of sodium azide yielded the required azide (198) in 77% yield.

Thermal decomposition of the azide (198) in trichlorobenzene at 200°C gave a red oil after evaporation of the solvent. Thin-layer chromatography and G.L.C. indicated a mixture of five compounds

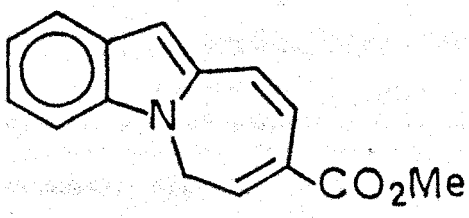
with one major component.

Column chromatography and preparative layer chromatography (P.L.C.) gave three characterised compounds in addition to unidentified oils. The major component of the mixture was 8-methoxycarbonyl-10H-azepino[1,2-a]indole (199).

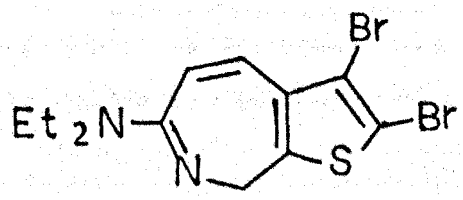


(199)

The ^{1}H N.m.r. spectrum also indicated the presence of traces (c.a. 8%) of the 6H-tautomer (200). (A doublet at δ 4.69 p.p.m. was present in the N.m.r.)



(200)



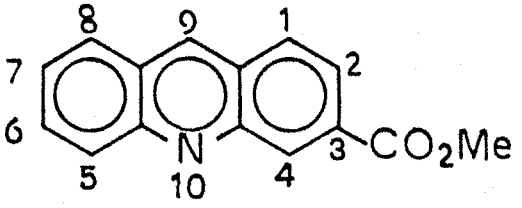
(201)

A value of δ 4.2 p.p.m. was reported[56] for the thienoazepine (201). The isolation of a 6H-isomer is unusual, though previous work[3] has shown that 6H and 8H tautomers are possible where steric hindrance is present (Compound (27) p.21).

The structure of azepinoindole (199) was assigned from spectral data, principally the ^{1}H N.m.r. spectrum. A methylene doublet at δ 3.54 p.p.m. (C_{10}) was coupled to a broadened triplet centred at δ 7.03 p.p.m. (J = 6.8 Hz). This places C_9 at δ 7.03 p.p.m., which is downfield with respect to the unsubstituted compound[2] due to the presence of the methoxycarbonyl moiety. Two further doublets could be discerned, an upfield doublet (δ 6.24 p.p.m.) was coupled (J = 9.2 Hz) to a doublet in the aromatic region at δ 7.35 p.p.m. These two signals can be assigned to C_7 and C_6 respectively. The proton at C_7 is deshielded only by the inductive effect of the adjacent methoxycarbonyl group. The cis coupling constant is in the range accepted for a seven-membered ring.[235] A singlet at δ 6.15 p.p.m. (C_{11}) and an aromatic multiplet (C_1 - C_4) have chemical shifts expected for the proposed structures. A sharp singlet at δ 3.75 p.p.m. confirmed the presence of the methoxycarbonyl group. Addition of an europium shift reagent to the N.m.r. solution caused downfield shifts in the doublet at δ 6.24 p.p.m. and the triplet at δ 7.03 p.p.m. confirming the position of the methoxycarbonyl substituent at C_8.

The mass spectrum of the azepinoindole (199) showed peaks at m/e 239 (M^+) with major losses of 1 and 59 (CH_3CO_2) to give the stable aromatic system.

Two minor components of the mixture were also characterised. The amine (197), 4.2%, was identified by comparison with an authentic specimen. The other compound was 3-methoxycarbonylacridine (202) obtained in 4% yield.



(202)

The structure was supported by the ^{1}H N.m.r. spectrum. With the exception of a singlet at δ 4.02 p.p.m. ($CO_2\underline{Me}$) all signals were below δ 7.4 p.p.m., this is in accord with the aromatic structure (202). Two signals were downfield from the aromatic region. The farthest downfield signal was a doublet (J = 1.2 Hz) at δ 8.99 p.p.m. This is C_4, deshielded by both the methoxycarbonyl group and the lone pair of the acridine nitrogen atom and <u>meta</u>-coupled to C_2. A broadened singlet at δ 8.78 p.p.m. is assigned to C_9. The broadening of the signal is attributed to cross ring coupling to C_5 and C_4. A further subsplit doublet at δ 8.27 p.p.m. (J = 9 Hz) could be discerned (C_5). Overlapping signals integrating for three protons were present at δ 8.06 p.p.m. Characteristic triplet of doublets (C_6/C_7) were present upfield of the main resonances at δ 7.57 at δ 7.83 p.p.m. Irradiation of the signals at δ 8.06 p.p.m. caused the doublet at δ 8.99 p.p.m. to collapse to a singlet. Irradiation of the triplet of doublets at δ 7.83 p.p.m. removed the major coupling of the doublet at δ 8.27 p.p.m.; hence the signal at δ 7.83 p.p.m. must be C_6 and at δ 7.57 C_7. Addition of europium shift reagent to the N.m.r. solution simplified the spectra considerably. The signal at δ 8.99 p.p.m. experienced a large downfield shift and the group of signals at δ 8.06 p.p.m. also moved downfield to varying degrees, allowing the individual signals to be clearly seen. Three doublets were visible

and all had ortho-coupling ($J \simeq 8$ Hz), thus the original overlapping signals at δ 8.06 p.p.m. can be assigned to C_1, C_2 and C_8.

The ^1H N.m.r. spectra of the azepino-indole (199) and the acridine (202) are given in Figure 4.1 and Figure 4.2 respectively.

Having successfully synthesised the azide (198) and determined that decomposition leads to the ring-expansion product (199) we then turned our attention to synthesising and decomposing a triphenylmethane derivative bearing electron-withdrawing groups.

The alcohol (192) (see Introduction) was prepared and converted into the ester (194) by established procedures,[12] again making use of the 1,3-dioxan group as a masked ester function. The hydrolysis of the acetamido-function in the ester (194) is normally carried out in similar compounds with a mixture of hydrochloric acid and ethanol.[3] This reagent would probably lead to side-reactions arising from the production of a stable carbonium ion from compound (194). Consequently a hydrogenolysis of the alcohol group in a manner previously described was attempted. The product was a mixture containing (N.m.r.) compounds (203) and (204) and none of the desired product.

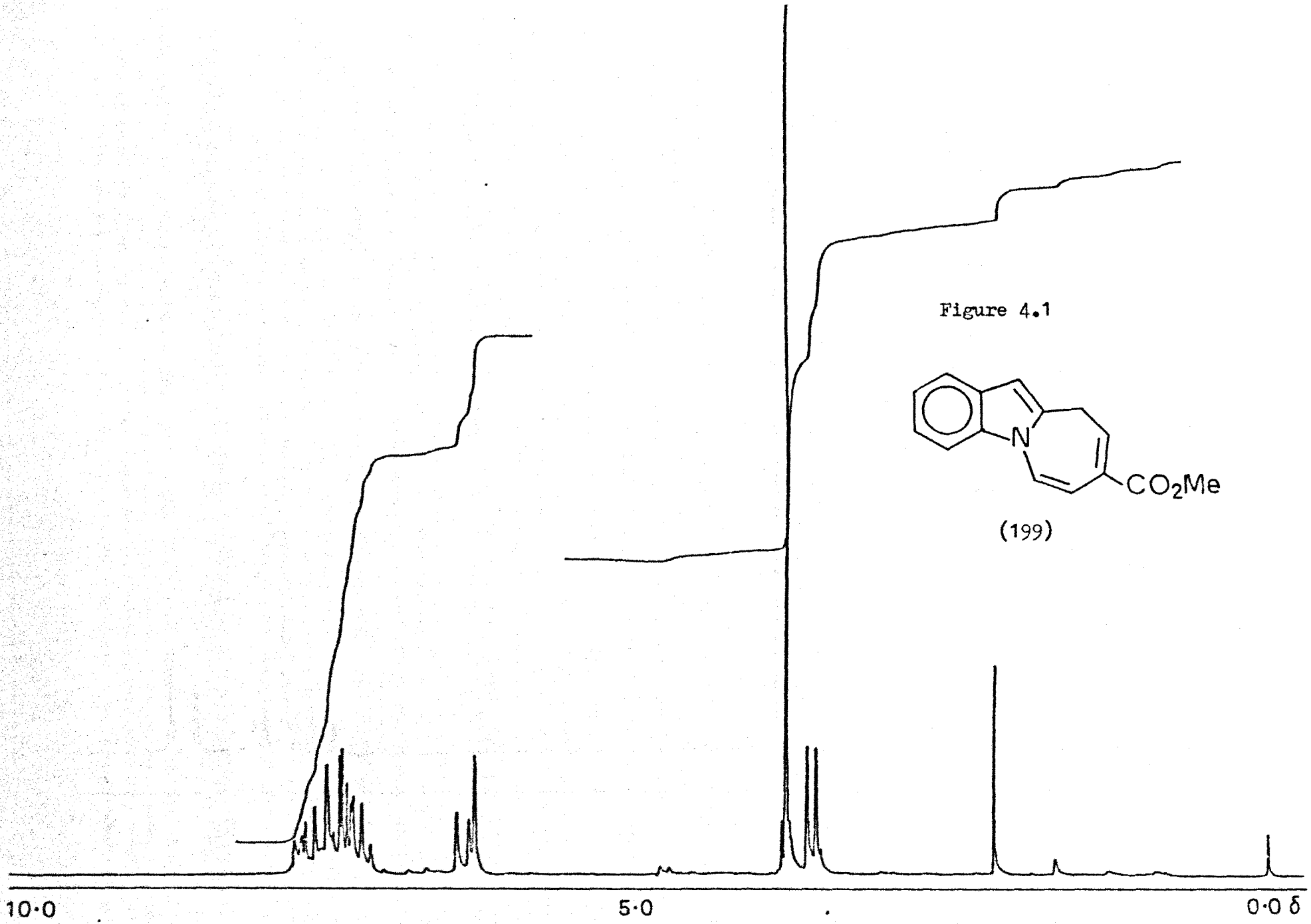
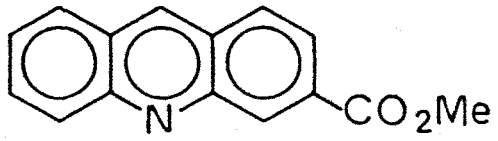


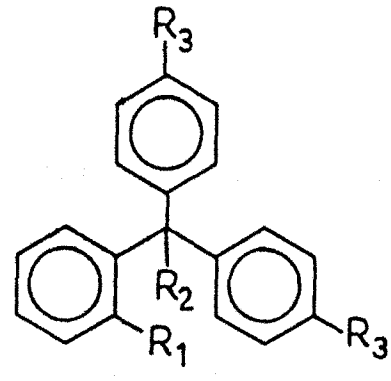
Figure 4.1

(199)

Figure 4.2



(202)



(203) $R_1 = NHCH_2CH_3$, $R_2 = OH$, $R_3 = CO_2(CH_2)_3Br$

(204) $R_1 = NHAc$, $R_2 = OH$, $R_3 = CO_2(CH_2)_2CH_3$

(205) $R_1 = NH_2$, $R_2 = OH$, $R_3 = CO_2CH_3$

(206) $R_1 = NH_2$, $R_2 = H$, $R_3 = CO_2CH_3$

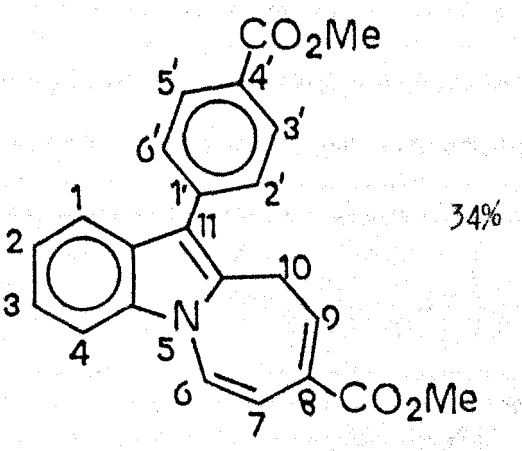
(207) $R_1 = N_3$, $R_2 = H$, $R_3 = CO_2CH_3$

Hydrolysis of the ester (194) was therefore performed as normal in boiling ethanolic hydrochloric acid. The crude green oil from this reaction was not isolated as such but converted directly into the methyl ester (205) by boiling in acidic methanol (94%). The methyl ester (205), which could not be obtained analytically pure, had an N.m.r. spectra consistent with the proposed structure. A sharp singlet (6H) at δ 3.8 p.p.m. and an exchangeable broad signal at δ 4.3 p.p.m. (3H) account for the methyl ester and hydroxyl + amino functional groups respectively. A prominent A,A', B,B' pattern is obvious in the aromatic region together with an upfield multiplet at δ 6.5 p.p.m. (2H) due to protons ortho and para to the amino group.

Reduction of the alcohol function in the methyl ester (205) proved to be difficult. Hydrogenolysis with an excess of catalyst failed with this compound, possibly due to steric hindrance on the catalyst surface. Starting compound (205) was recovered unchanged. Reductions with formic acid,[11] trifluoroacetic acid/sodium borohydride[236] and concentrated sulphuric acid/isopropyl alcohol[237] all gave recovered

starting materials. This is no doubt a consequence of the lack of formation of the intermediate carbonium ions in the reaction. Reduction with red phosphorus and iodine in boiling acetic acid[238] was successful and gave the crude triphenylmethane (206) as a fawn solid (92%). Conversion to the required azide (207) was performed in an analogous manner to that described for the diphenyl compound (198).

Thermal decomposition of the azide (207) in trichlorobenzene at 190°C gave, after evaporation of the solvent, a yellow oil. Thin-layer chromatography showed four spots. Separation of the mixture was achieved by a combination of medium-pressure and preparative layer chromatography. The less polar component of the mixture was 8-methoxycarbonyl-11-(p-methoxycarbonylphenyl)-10H-azepino[1,2-a]indole (208).



34%

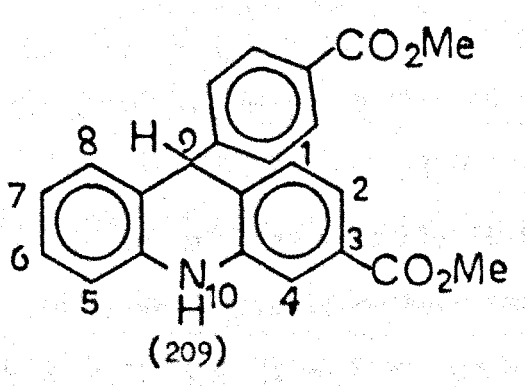
(208)

The structure of azepinoindole (208) followed from its N.m.r. spectrum and comparison with azepinoindole (199). Two methyl signals at δ 3.79 p.p.m. (C_8 - CO_2Me) and δ 3.96 p.p.m. (4'-CO_2Me) were

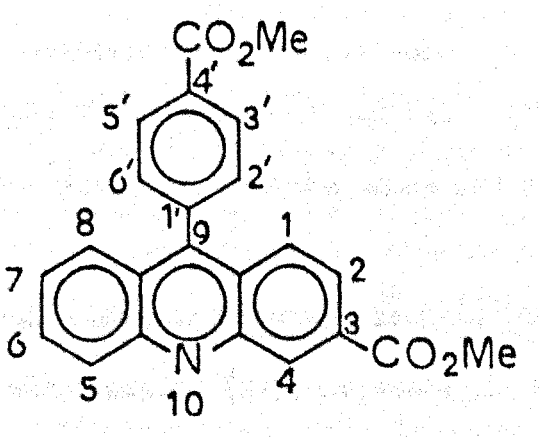
present as expected together with a doublet (J = 6.8 Hz) at δ 3.65 p.p.m. (C_{10}). Double resonance experiments confirmed that this was coupled to a triplet (J = 6.8 Hz) at δ 7.09 p.p.m. (C_9). An upfield doublet (J = 9.4 Hz) at δ 6.39 p.p.m. (C_7) was also coupled to the signal at δ 7.49 p.p.m. (C_6). The A,A', B,B' pattern of the methoxycarbonylphenyl substituent was clearly visible as two widely spaced doublets (J = 8.6 Hz) at δ 8.15 p.p.m. and δ 7.54 p.p.m. Addition of europium shift reagent to the N.m.r. solution caused a large downfield shift in the singlet at δ 3.96 p.p.m. (4'-CO_2Me) with a smaller shift for the signal at δ 3.79 p.p.m. (C_8-CO_2Me). Both the doublet at δ 6.39 p.p.m. and the triplet at δ 7.09 p.p.m. experienced downfield shifts.

The mass spectrum of azepinoindole (208) showed a strong molecular ion at m/e 373 with major losses of hydrogen and methoxycarbonyl fragments to give the fully aromatic system.

Two further compounds were isolated, one of these could not be obtained analytically pure, this was the acridan (209). Attempts to purify this material led to rapid oxidation to the acridine (210). Isolated yields of these compounds were 9.8% and 4.9% respectively.



(209)



(210)

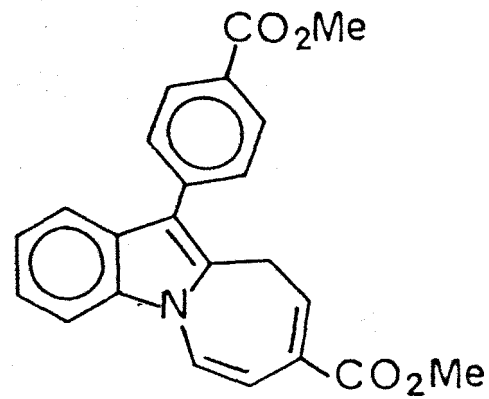
The acridan (209) had signals in the N.m.r. spectrum at δ 8.8 p.p.m. (singlet, C_4), a complex multiplet at δ 6.6 - 8.0 p.p.m. (15H, 1H Ex.D_2O) and a singlet at δ 5.3 p.p.m. assigned to the C_9 C-H proton.

The acridine (210) was characterised by a consideration of the detailed ^{1}H N.m.r. spectrum and comparison with acridine (202).

The ^{1}H N.m.r. had two methyl singlets at δ 4.02 and δ 4.03 p.p.m. All other signals were below δ 7.5 p.p.m. The most notable features of the spectrum was a doublet of doublets at δ 9.04 p.p.m. (J = 1.6, 0.8 Hz) which was assigned to C_4 and two doublets at δ 8.3 (3H) and δ 7.95 p.p.m. (1H). The doublet at δ 7.95 p.p.m. was assigned to C_5, all three couplings could be seen in the fine structure of this signal. Irradiation of the doublet at δ 8.3 p.p.m. caused the doublet in the aromatic region at δ 7.53 p.p.m. (J = 8 Hz) to collapse to a singlet. This places the A,A',B,B' system of the phenyl substituent at δ 8.3 and δ 7.53 p.p.m. Addition of europium shift reagent to the solution simplified the doublet at δ 8.3 p.p.m. to reveal an additional doublet underneath this signal which is assigned to C_2. The europium shift reagent complexes preferentially with the basic nitrogen and the 4'-methoxycarbonyl group at low metal concentrations giving a larger downfield shift for the 3', 5' protons. Two methyl signals could now be clearly distinguished for the same reasons. The ^{1}H N.m.r. spectra of the azepinoindole (208) and the acridine (210) are given in Figures 4.3 - 4.5. None of the amine (206) was isolated in this decomposition.

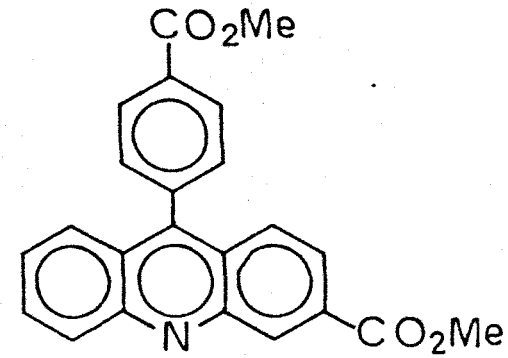
The azepine products in these decompositions can be explained on the basis of an aziridine intermediate (211) as depicted in Scheme 4.3. The amine (197) probably arises via a hydrogen

Figure 4.3



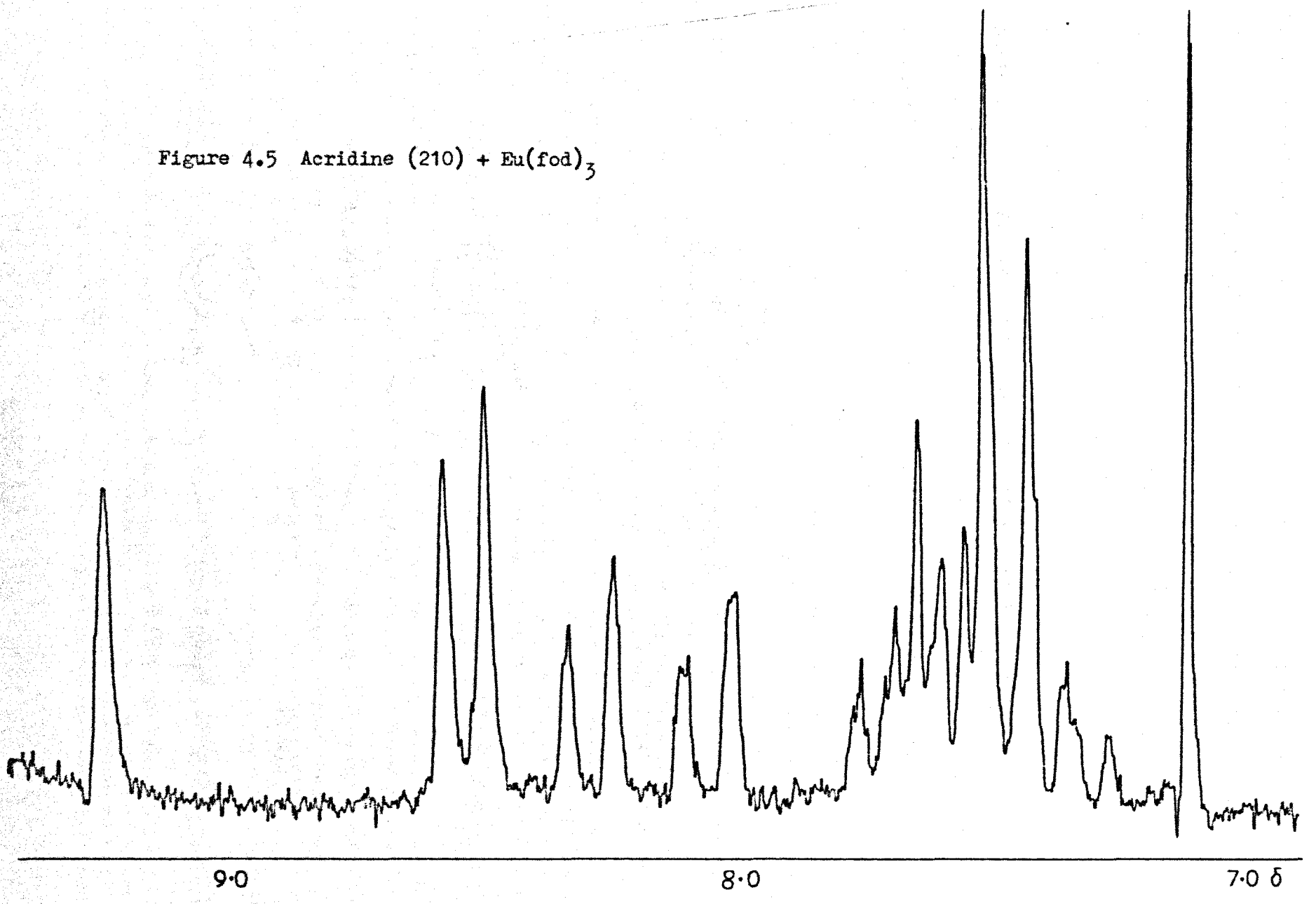
(208)

Figure 4.4

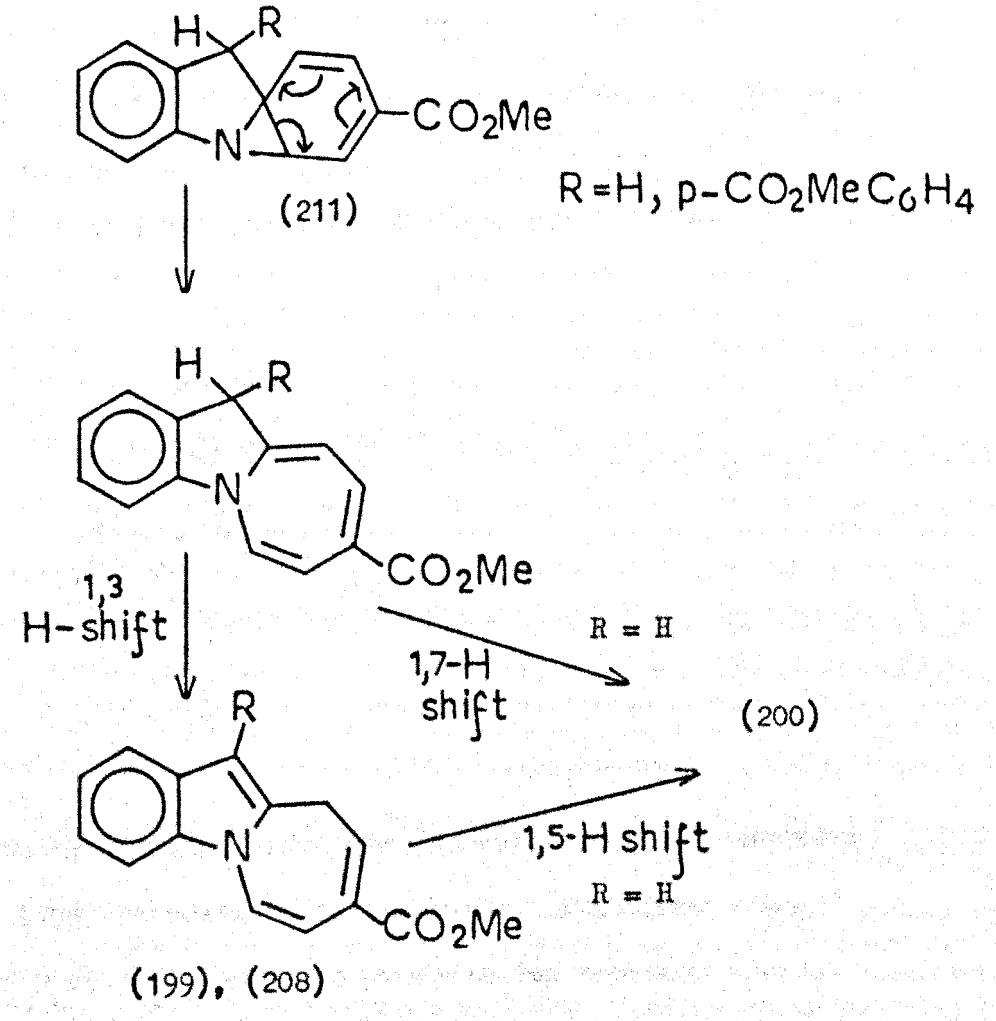


(210)

Figure 4.5 Acridine (210) + $Eu(fod)_3$



abstraction process. The azepinoindoles (199) and (208) are the first examples of ring-expansion products where the 'receiving' ring is electron deficient. Clearly the systems described in this chapter are not as deactivated towards nitrene attack as the pyridine compounds discussed in chapter 1. The methoxycarbonyl group does however deactivate the aromatic ring to some extent. A comparison of the yields obtained in this work with those of the unsubstituted di and triphenylmethanes is given in Table 4.1. The presence of a small percentage of a 6H-isomer has also been noted in a reinvestigation of the thermolysis of o-azidodiphenylmethane (see Chapter 5). The acridan and acridine products can be postulated to arise from the triplet nitrene by analogy with previous work.[11]



Scheme 4.3

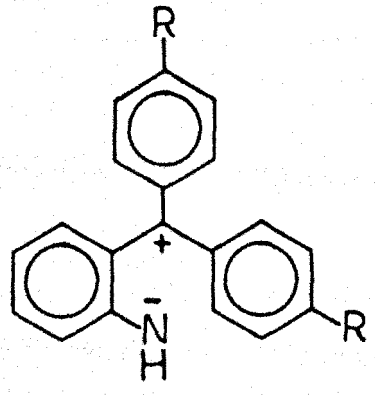
TABLE 4.1

Compound No.	Azepinoindole %	Acridan + Acridine %	Amine %
198	34	4	4.2
207	34	14.7	-
19	56	1.6 [a]	0.9[a]
33	31	33	8.5[b]

Notes: a See Chapter 5

b Amine + azo compound

The increase in the acridine + acridan products in the triphenylmethane compounds relative to the corresponding diphenylmethanes has been explained[11] on the basis of a carbonium ion intermediate (212), (see also Introduction to Chapter 1) which can compete effectively with ring opening to give increased acridine/acridan yields.



(212)

R = H, CO_2Me

The increase in the acridine products for compound (207) compared with compound (198) supports this hypothesis. Furthermore the reduction in the yield of acridine products for compound (207), compared with that of the unsubstituted compound (33) reflects the

decreased stability of the proposed carbonium ion (212) when electron-withdrawing groups are present in the phenyl rings.

EXPERIMENTAL

Part A : Preparation and thermal decomposition of methyl 2-azidodiphenylmethane-4'-carboxylate (198)

4-(1,3-Dioxan-2-yl)-2'-nitrobenzophenone (191)

Prepared from 4-(1,3-dioxan-2-yl)phenyl magnesium bromide and o-nitrobenzaldehyde by a reported procedure[12] in 38% yield.

M.pt. 126 - 127°C (methanol)

lit.[12] m.pt. 126 - 127°C (methanol)

3-Bromopropyl 2-nitrobenzophenone-4'-carboxylate (193)

A solution of 4-(1,3-dioxan-2-yl)-2'-nitrobenzophenone (28.6 g, 0.086 mol) in hot carbon tetrachloride (270 ml) was treated with N-bromosuccinimide (15.28 g, 0.086 mol) in one portion. The mixture was boiled under reflux for 3 hrs, cooled and filtered. The filtrate was washed with saturated sodium thiosulphate solution (2 x 100 ml) water (2 x 100 ml), dried (Na_2SO_4) and evaporated to yield a pale yellow oil (34.6 g, 103%) which had identical spectral properties to previously prepared material.[12]

Methyl 2-nitrobenzophenone-4'-carboxylate (195)

A solution of 3-bromopropyl 2-nitrobenzophenone-4'-carboxylate (34.6 g, 0.089 mol) dissolved in anhydrous methanol saturated with dry HCl gas (360 ml) was boiled under reflux for 18 hrs. The solution was cooled and the hydrogen chloride gas removed on the rotary evaporator (no heat). The product which then crystallised was filtered and dried. Yield: 18.6 g (74.5%).

M.pt. 130 - 132°C (methanol)

lit.[12] m.pt. 130 - 132°C (methanol)

Methyl 2-aminobenzophenone-4'-carboxylate

A solution of methyl 2-nitrobenzophenone-4'-carboxylate (18.6 g, 0.065 mol) in 95% ethanol (930 ml) and cyclohexene (112 ml) was treated with 10% palladium on charcoal (10 g) and boiled under reflux for 2 hrs. The mixture was then cooled, filtered and evaporated to yield a fawn solid (15.3 g, 92%).

M.pt. 95 - 97°C (40 - 60° petroleum ether)

lit.[12] m.pt. 95 - 97°C (40 - 60° petroleum ether)

Methyl 2-aminodiphenylmethanol-4'-carboxylate (196)

A solution of methyl 2-aminobenzophenone-4'-carboxylate (15.0 g, 0.059 mol) in anhydrous methanol (150 ml) was treated with sodium borohydride (15 pellets). The mixture was stood at room temperature for 2½ hrs with occasional shaking. The mixture was diluted with water (100 ml) and then extracted with dichloromethane (2 x 100 ml). The organic extracts were dried (Na_2SO_4) and then evaporated to yield a fawn solid (14.5 g, 96%).

M.pt. 133 - 135°C (benzene)

lit.[234] m.pt. 134°C (benzene)

Methyl 2-aminodiphenylmethane-4'-carboxylate (197)

A solution of methyl 2-aminodiphenylmethanol-4'-carboxylate (13.9 g, 0.054 mol) in 95% ethanol (500 ml) was treated with 10% palladium on charcoal catalyst (7 g) and the stirred mixture was hydrogenated at normal temperature and pressure for 37 hrs: (T.L.C.)

The mixture was filtered and evaporated to yield a fawn solid, (10.4 g, 80%).

M.pt. 101 - 103°C (60 - 80° petroleum ether)

Analysis:	Found:	C, 74.74%;	H, 6.16%;	N, 5.64%
	$C_{15}H_{15}NO_2$ requires:	C, 74.66%;	H, 6.27%;	N, 5.81%

N.m.r. ($CDCl_3$)	δ 7.80 p.p.m.	d	2H	J = 8 Hz
	7.20 - 6.45	m	6H	
	3.85	s	2H	
	3.80	s	3H	
	3.25	br.s	2H	Ex. D_2O

I.R. ($CHCl_3$) ν_{max} 3380, 3460, 2950, 2900, 2830, 1715 (s), 1620, 1610, 1550, 1450, 1430, 1310, 1280, 1110, 1020, 965 cm^{-1}

U.V. (95% EtOH) λ_{max} 237 nm $\log_{10} \varepsilon$ 4.37
285 nm $\log_{10} \varepsilon$ 3.55

Mass spectrum, m/e 242 (17%), 241 (M^+, 100%), 240 (11.5), 226 (9), 219 (17), 183 (9), 182 (56), 181 (17), 180 (28), 167 (9), 165 (17), 106 (32), 105 (28), 77 (14), 51 (9)

Methyl 2-azidodiphenylmethane-4'-carboxylate (198)

A stirred solution of methyl 2-aminodiphenylmethane-4'-carboxylate (10.4 g, 0.043 mol) in 2N sulphuric acid (215 ml) and purified 1,4-dioxan (215 ml) was diazotised at -5°C with a solution of sodium nitrite (3.02 g, 0.043 mol) in water (17 ml). The solution was stirred at -5°C for 30 minutes. A solution of sodium azide (3.36 g, 0.052 mol) in water (17 ml) was then added at -5°C and the solution

slowly warmed to 30°C. The aqueous phase was extracted with dichloromethane (2 x 100 ml), and the organic layers washed with 5% NaOH (50 ml). The combined organic layers were dried (Na_2SO_4) and evaporated (30°C) to yield the crude azide as a yellow oil. The oil was chromatographed on a column of alumina (IV, 200 g) which was protected from the light by wrapping in aluminium foil. Petroleum ether (40 - 60°)/dichloromethane (5%) eluted the azide as a yellow solid (8.5 g, 77%).

M.pt. 69 - 70°C (40 - 60° petroleum ether) pale yellow needles

Analysis:	Found:	C, 67.15%;	H, 4.83%;	N, 15.77%	
	$C_{15}H_{13}N_3O_2$ requires:	C, 67.40%;	H, 4.90%;	N, 15.72%	
N.m.r. ($CDCl_3$)	δ 7.85 p.p.m.	d	2H	J = 8 Hz	
	7.35 - 6.95	m	6H		
	3.95	s	2H		
	3.85	s	3H		
I.R. ($CHCl_3$)	ν_{max} 2940, 2130 (s), 1730, 1610, 1580, 1450, 1280, 1110, 1040, 965 cm^{-1}				
U.V. (95% ETOH)	λ_{max} 245 nm	$\log_{10} \varepsilon$ 4.41			
	282 nm	sh			
	292 nm	sh			
Mass spectrum, m/e	267 (4% M^+), 240 (12), 239 (24), 224 (8), 195 (20), 180 (100), 152 (16), 77 (8), 51 (12)				

Thermal decomposition of methyl 2-azidodiphenylmethane-4'-carboxylate (198)

A solution of the azide (8.1 g, 0.030 mol) in dry 1,2,4-trichlorobenzene (100 ml) was added dropwise over a period of ½ hr to vigorously stirred 1,2,4-trichlorobenzene (1 litre) maintained at 200°C

under a dry nitrogen atmosphere. The solution was heated for a further 4 hrs under a dry nitrogen atmosphere. Infra-red spectroscopy indicated consumption of starting material. The cooled solution was evaporated (0.3 mm) to yield a red oil (8.9 g). This red oil was chromatographed on a column of alumina (IV, 300 g). Petroleum ether (40 - 60°) eluted residual trichlorobenzene (1.5 g). A mixture of petroleum ether (40 - 60°) and benzene, 3:1 eluted 8-methoxycarbonyl-10H-azepino[1,2-a]indole (199), (2.4 g, 34%) as a yellow solid.

M.pt. 106 - 108°C (petroleum ether 60 - 80°) yellow prisms

Analysis:	Found:	C, 75.63%;	H, 5.45%;	N, 5.84%
	$C_{15}H_{13}NO_2$ requires:	C, 75.30%;	H, 5.48%;	N, 5.85%

N.m.r. ($CDCl_3$)	δ 7.6-7.1 p.p.m.	m	4H	
100 MHz	7.35	d	1H	J = 9.2 Hz
	7.03	br. tr.	1H	J = 6.8 Hz
	6.24	d	1H	J = 9.2 Hz
	6.15	s	1H	Indole C-H
	3.75	s	3H	$-CO_2\underline{Me}$
	3.54	d	2H	J = 6.8 Hz

A doublet centred at δ 4.69 p.p.m. indicated the presence of trace amounts of the 6H-tautomer (200). A mass spectrum of each component of the mixture had m/e 239 (G.L.C./M.S.)

I.R. ($CHCl_3$) ν_{max} 3130, 2950, 2860, 2840, 2805, 1720, 1640, 1610, 1560, 1455, 1400, 1340, 1310, 1080, 1040, 950 cm^{-1}

U.V. (95% EtOH) λ_{max} 222 nm sh

249 nm $\log_{10} \varepsilon$ 4.18

277 nm $\log_{10} \varepsilon$ 4.02

292 nm sh

330 nm $\log_{10} \varepsilon$ 3.43

Mass spectrum, m/e 239 (91%, M^+), 238 (72), 224 (22), 180 (100), 168 (7), 152 (14), 77 (18), 51 (7)

Further elution of the column with benzene/petroleum ether(40 - 60°) (1:1) gave trace amounts of unidentified oils (0.2 g). Elution with benzene gave a mixture containing methyl 2-aminodiphenylmethane-4'-carboxylate (197) and 3-methoxycarbonylacridine (202), [total: 1.55 g] Preparative layer chromatography (10% ethyl acetate/toluene) gave four bands.

Band 1 (R_F 0.2) was the acridine (200 mg, 4%), obtained as yellow needles.

M.pt. 153.5 - 155.5°C (petroleum ether 60 - 80°)

Analysis: Found: C, 75.26%; H, 4.44%; N, 6.17%

$C_{15}H_{11}NO_2$ requires: C, 75.93%; H, 4.67%; N, 5.90%

N.m.r. ($CDCl_3$)	δ 8.99 p.p.m.	d	1H	J = 1.2 Hz
100 MHz	8.78	br.s	1H	
	8.27	subsplit d	1H	J = 9 Hz
	8.06	d. of d	2H	
	8.00	subsplit d	1H	
	7.83	tr. of d	1H	
	7.57	tr. of d	1H	
	4.02	s	3H	

I.R. ($CHCl_3$) ν_{max} 2940, 2920, 2840, 1730, 1615, 1605, 1440, 1310, 1270, 1090, 990, 970 cm^{-1}

U.V. (95% EtOH) λ_{max} 238 nm sh
255 nm sh
264 nm $\log_{10} \varepsilon$ 4.76
337 nm sh
344 nm sh
356 nm $\log_{10} \varepsilon$ 3.69

Mass spectrum, m/e 238 (26%), 237 (96, M^+), 207 (19), 206 (100), 178 (67), 151 (22), 104 (5)

Band 2 (R_F 0.35) gave methyl 2-aminodiphenylmethane-4'-carboxylate (197), yield 300 mg (4.2%), identical with previously synthesised material.

M.pt. and mixed m.pt. 101 - 104°C

Band 3 (R_F 0.50) and Band 4 (R_F 0.56) gave unidentified oils (0.9 g)

Continued elution of the column with dichloromethane and finally methanol gave dark oils (1 g) which could not be characterised.

Part B : Preparation and thermal decomposition of dimethyl 2-azidotriphenylmethane-4',4"-dicarboxylate (207)

2-Acetamido-4',4"-di(1,3-dioxan-2-yl)triphenylmethanol (192)

Prepared by a reported procedure[12] from acetanthranil and 4-(1,3-dioxan-2-yl)phenyl magnesium bromide in 45% yield (lit.[12] 30%).

M.pt. 175 - 177°C (CH_2Cl_2)

lit.[12] m.pt. 176 - 177°C (CH_2Cl_2)

Di(3-bromopropyl) 2-acetamidotriphenylmethanol-4',4"-dicarboxylate (194)

Prepared according to a reported procedure[12] in quantitative yield. A sample was purified by P.L.C. (3:1 toluene/ethyl acetate) for analysis.

M.pt. 69 - 72°C (40 - 60° petroleum ether) fawn needles

Analysis:		Found:	C, 53.53%;	H, 4.59%;	N, 2.11%
	$C_{29}H_{29}Br_2NO_6$	requires:	C, 53.80%;	H, 4.51%;	N, 2.16%
N.m.r. ($CDCl_3$)	δ	9.0 p.p.m.	br.s	1H	Ex.D_2O
		8.0-6.5	m	12H	
		6.05	br.s	1H	Ex.D_2O
		4.45	tr.	4H	J = 6 Hz
		3.55	tr.	4H	J = 6 Hz
		2.35	quint.	4H	J = 6 Hz
		1.5	s	3H	

I.R. ($CHCl_3$) ν_{max} 3570, 3390, 2950, 2920, 2850, 1720 (s), 1605, 1580, 1440, 1370, 1330, 1280, 1110, 1000 cm^{-1}

U.V. (95% EtOH) λ_{max} 244 nm $\log_{10}\varepsilon$ 4.60

Dimethyl 2-aminotriphenylmethanol-4',4"-dicarboxylate (205)

A solution of the di(bromopropyl) ester (10.3 g, 0.0159 mol) in concentrated HCl (1 part) and 95% ethanol (2.5 parts) (40 ml) was boiled under reflux for 3 hrs. The green solution was evaporated (eventually at 0.05 mm) to yield a green solid which was dissolved in anhydrous methanol saturated with dry HCl gas (400 ml) and boiled under reflux for 18 hrs. The solution was evaporated and the residual green tar treated with saturated sodium bicarbonate (100 ml). The aqueous phase was extracted with dichloromethane (2 x 150 ml) dried (Na_2SO_4) and evaporated to yield a green solid, yield 6.6 g (94%). A sample was purified by P.L.C. (9:1 toluene/ethyl acetate).

M.pt. 93 - 95°C (60 - 80° petroleum ether) yellow needles

N.m.r. ($CDCl_3$)	δ	7.9 p.p.m.	d	4H	J = 8 Hz
		7.4-6.9	m	6H	
		6.8-6.3	m	2H	
		4.3	br.s	3H	Ex.D_2O
		3.8	s	6H	

I.R. ($CHCl_3$) ν_{max} 3420, 2950, 2850, 1725, 1610, 1440, 1450, 1280, 1100, 1010, 970, 860 cm^{-1}

U.V. (95% EtOH) λ_{max} 245 nm $\log_{10} \varepsilon$ 4.42; 250 nm sh

Mass spectrum, m/e 374 (M^+-OH, 35%), 367 (50), 354 (100), 312 (75), 256 (20), 237 (45), 170 (25), 142 (20), 128 (30), 100 (15), 79 (15)

Dimethyl 2-aminotriphenylmethane-4',4"-dicarboxylate (206)

A mixture of red phosphorus (10.1 g) and iodine (4.7 g) in glacial acetic acid (337 ml) was allowed to stand at room temperature for 20 minutes. Water (34 ml) and dimethyl 2-aminotriphenylmethanol-4',4"-dicarboxylate (13.5 g, 0.035 mol) were added in one portion and the mixture was boiled under reflux for 4 hrs. The warm mixture was filtered and poured slowly into a solution of sodium metabisulphite (70 g) in water (200 ml). The cooled solution was basified (NH_3 solution) with external cooling. The aqueous phase was extracted with dichloromethane (2 x 250 ml), dried (Na_2SO_4) and evaporated to yield a fawn solid (11.9 g, 92%). A sample was purified by P.L.C. (9:1 toluene/ethyl acetate). A derivative was prepared for analysis.

Benzoyl derivative (Schotten-Baumann method) m.pt. 130 - 132°C (cyclohexane)

Analysis:	Found:	C, 75.40%;	H, 5.40%;	N, 2.34%	
	$C_{30}H_{25}NO_5$ requires:	C, 75.14%;	H, 5.26%;	N, 2.92%	
N.m.r. ($CDCl_3$)	δ 7.9 p.p.m.	d	4H	J = 8 Hz	
	7.1	d	4H	J = 8 Hz	
	7.1-6.5	m	4H		
	5.5	br.s	1H		
	3.85	s	6H		
	3.3	br.s	2H	Ex.D_2O	
I.R. ($CHCl_3$)	ν_{max} 3430, 3390, 2920, 2850, 1720 (s), 1625, 1610, 1570, 1440, 1310 (sh), 1280, 1110, 1040, 970 cm^{-1}				
U.V. (95% EtOH)	λ_{max} 244 nm	$\log_{10}\varepsilon$ 4.43			
	295 nm	sh			

Mass spectrum, m/e 376 (30%), 375 (M^+, 100%), 360 (16), 344 (16), 316 (24), 240 (20), 193 (10), 179 (26), 148 (16), 105 (36), 77 (14)

Dimethyl 2-azidotriphenylmethane-4',4"-dicarboxylate (207)

A solution of dimethyl 2-aminotriphenylmethane-4',4"-dicarboxylate (11.6 g, 0.031 mol) in 2N H_2SO_4 (150 ml) and purified 1,4-dioxan (150 ml) was diazotised at -5°C with a solution of sodium nitrite (2.21 g, 0.032 mol) in water (15 ml). The solution was stirred at -5°C for a further 30 mins, then a solution of sodium azide (2.41 g, 0.037 mol) in water (15 ml) was added in one portion at -5°C. The solution was then slowly warmed to 30°C. The aqueous phase was extracted with dichloromethane (2 x 100 ml), the organic phase separated and washed with 5% NaOH (100 ml). The organic phase was dried (Na_2SO_4) and evaporated (30°C) to yield the crude azide as a red oil (14 g). The oil was chromatographed on a column of alumina (IV, 250 g) protected from the light with aluminium foil. Elution with 40 - 60° petroleum ether/dichloromethane (5%) gave the azide as a yellow oil, 2.6 g (21%).

Analysis:		Found:	C, 67.71%;	H, 4.89%;	N, 10.04%
	$C_{23}H_{19}N_3O_4$	requires:	C, 68.81%;	H, 4.77%;	N, 10.47%
N.m.r. ($CDCl_3$)	δ	7.85 p.p.m.	d	4H	J = 8 Hz
		7.3 - 6.7	m	8H	
		5.8	br.s	1H	
		3.8	s	6H	
I.R. ($CHCl_3$)	ν_{max}	2960, 2900, 2850, 2130 (s), 1720 (s), 1610, 1580, 1490, 1410, 1300, 1110, 1040, 970 cm^{-1}			
U.V. (95% EtOH)	λ_{max}	247 nm	$\log_{10}\varepsilon$ 4.42		
		282 nm	sh		
		292 nm	sh		

Mass spectrum, m/e 401 (M^+, 2%), 473 (40), 443 (50), 297 (1), 295 (1), 283 (1), 281 (1), 209 (4), 207 (6), 192 (8), 167 (18), 154 (8), 142 (10), 139 (8), 127 (8), 126 (16), 100 (100), 77 (8), 73 (58), 61 (54), 55 (20).

Thermal decomposition of dimethyl 2-azidotriphenylmethane-4',4"-dicarboxylate (207)

A solution of the azide (2.2 g, 0.0055 mol) in anhydrous 1,2,4-trichlorobenzene (50 ml) was added dropwise over a period of 30 mins to trichlorobenzene (250 ml) at 190°C under a dry nitrogen atmosphere. The solution was vigorously stirred throughout the addition, the solution was then heated for a further 4 hrs at 190°C. I.R. spectroscopy indicated that all the azide had reacted. The solvent was then removed (0.1 mm) to yield a yellow oil (2.0 g). The oil was chromatographed on a medium pressure column (3:1 petroleum ether/ethyl acetate) and 50 ml fractions collected. Fractions 1-3 were residual trichlorobenzene (0.5 g). Fractions 4-12 gave 8-methoxycarbonyl-11-(p-methoxycarbonylphenyl)-10H-azepino[1,2-a]indole (208) (0.7 g, 34%) as a yellow solid.

M.pt. 157 - 160°C (cyclohexane) bright yellow prisms

Analysis:		Found:	C, 73.81%;	H, 5.20%;	N, 3.52%
	$C_{23}H_{19}NO_4$	requires:	C, 73.98%;	H, 5.13%;	N, 3.75%
N.m.r. ($CDCl_3$)	δ	8.15 p.p.m.	d	2H	J = 8.6 Hz
100 MHz		7.9-7.2	m	4H	
		7.54	d	2H	J = 8.6 Hz
		7.49	d	1H	J = 9.4 Hz
		7.09	tr	1H	J = 6.8 Hz

	6.39	d	1H	J = 9.4 Hz
	3.96	s	3H	
	3.79	s	3H	
	3.65	d	2H	J = 6.8 Hz

I.R. ($CHCl_3$) ν_{max} 3150, 2950, 2900 (sh), 1790, 1720, 1640, 1610, 1570, 1450, 1370, 1270, 1100, 950, 900 cm^{-1}

U.V. (95% EtOH) λ_{max} 225 nm sh; 243 nm $\log_{10} \varepsilon$ 4.58; 256 nm sh; 325 nm $\log_{10} \varepsilon$ 4.30; 350 nm sh

Mass spectrum, m/e 374 (30%), 373 (M^+, 100%), 372 (30), 358 (18), 342 (12), 314 (60), 298 (30), 267 (25), 254 (30), 239 (6), 238 (6), 163 (78), 77 (12)

Fractions 13-18 off the column gave an oily compound (0.1 g) which was not identified. Fractions 19-33 were a mixture of 3-methoxycarbonyl-9-(p-methoxycarbonylphenyl)acridine (210) and 3-methoxycarbonyl-9-(p-methoxycarbonylphenyl)acridan (209). P.L.C. of this mixture (3:1 60 - 80° petroleum ether/ethyl acetate) gave three bands, after several elutions.

Band 1 was the acridan (0.2 g, 9.8%) which could not be obtained pure for analysis.

N.m.r. ($CDCl_3$) δ	8.8 p.p.m.	s	1H	
	8.2	d	2H	J = 8 Hz
	8.0-6.6	m	15H	
	5.3	br.s	1H	

Band 2 (strong fluorescence) was the acridine (0.1 g, 4.9%) obtained as a yellow solid.

M.pt. 189 - 192°C (cyclohexane)

Analysis:		Found:	C, 74.11%;	H, 4.49%;	N, 4.24%
	$C_{23}H_{17}NO_4$	requires:	C, 74.38%;	H, 4.61%;	N, 3.77%
N.m.r. ($CDCl_3$)	δ	9.04	d of d	1H	J = 1.6, 0.8 Hz
100 MHz		8.3	br.d	3H	
		7.95	d of d (subsplit)	1H	J = 9.1, 1.6, 0.7 Hz
		7.85-7.5	m	4H	
		7.53	d	2H	J = 8 Hz
		4.02	s	3H	
		4.03	s	3H	

Addition of $Eu(fod)_3$ simplified the doublet at δ 8.3 to reveal an additional doublet at δ 8.41, (1H) (J = 8.5 Hz).

I.R. ($CHCl_3$) ν_{max} 2950, 1720 (s), 1610, 1570, 1480, 1440, 1355, 1345, 1280, 1245, 1110, 1090, 1030 cm^{-1}

U.V. (95% EtOH) λ_{max} 232 nm $\log_{10} \varepsilon$ 4.64

263 nm $\log_{10} \varepsilon$ 4.88

347 nm sh

363 nm $\log_{10} \varepsilon$ 3.90

383 nm sh

Mass spectrum, m/e 372 (78%), 371 (100, M^+), 356 (2), 340 (63), 312 (50), 296 (6), 279 (6), 267 (20), 253 (43), 169 (72), 154 (38), 139 (16), 125 (27), 112 (23)

Band 3 was an unidentified oil (50 mg).

Further elution of the column with 1:1 petroleum ether/ethyl acetate gave unidentified red oils (0.2 g) which were slow running on T.L.C. Recovery from the column was 100%.

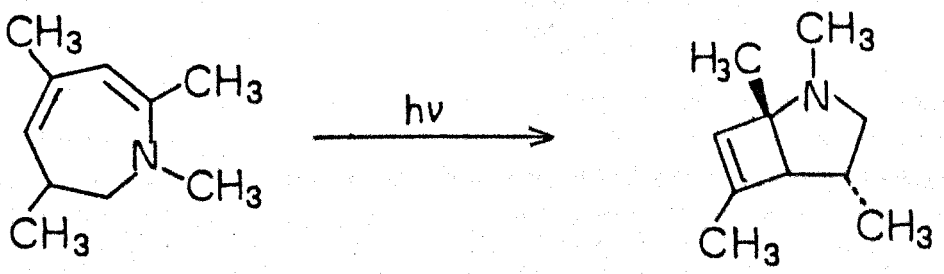
CHAPTER FIVE

CYCLOADDITIONS AND PHOTOADDITIONS OF 10H-AZEPINO[1,2-a]INDOLE

INTRODUCTION

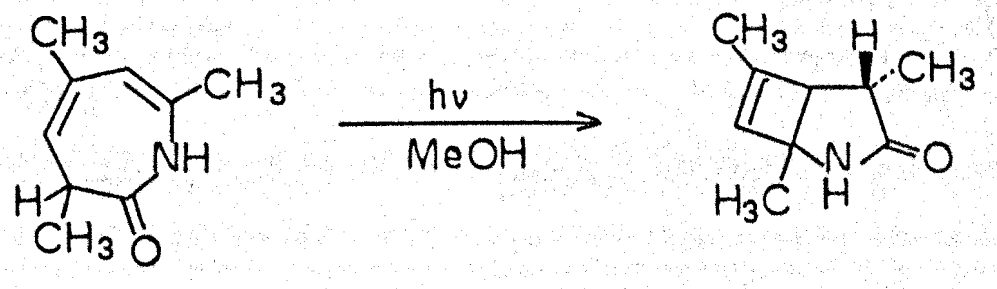
The most common photoreaction of conjugated dienes is the formation of cyclobutenes, and this has been reported both in cyclic and acyclic dienes.[239] Tropones[240-242] and cycloheptadienes[243] have been reported to form bicyclic valence tautomers when irradiated and this type of reaction is often a good route to these compounds.

This reaction is frequently observed in heterocyclic systems. A number of aza-cycloheptadienes are photochemically isomerised, in a similar manner to cycloheptadiene itself, to bicyclic derivatives,[244] e.g. Scheme 5.1.



Scheme 5.1

The process has been extended to include the dihydroazepinone (213) and related systems.[245-247]

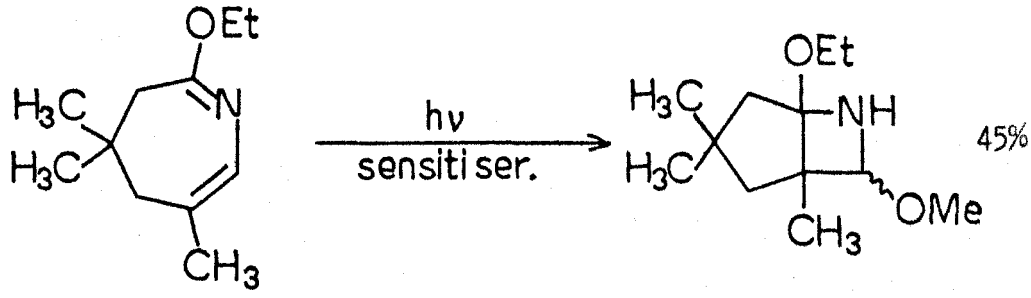


(213)

Scheme 5.2

Similar reactions are known for pyrimidinones,[248,249] 1,2-diazepines[121,123] and benzodiazepines.[122,250]

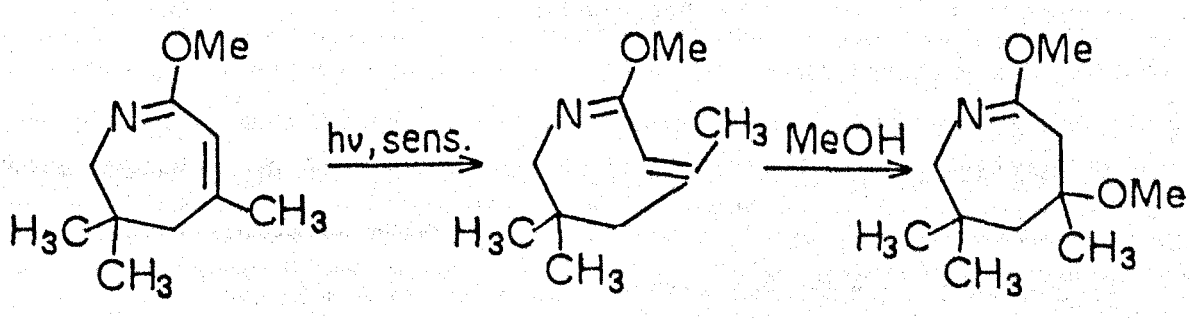
Irradiation of the conjugated imino ether (214) in methanol containing 1% sodium methoxide resulted in addition of methanol to the intermediate azetidine.[251]



(214)

Scheme 5.3

Koch and co-workers[252] have also isolated solvent addition products from the azepine (215). An intermediate transoid structure (216) was suggested as the reactive species.

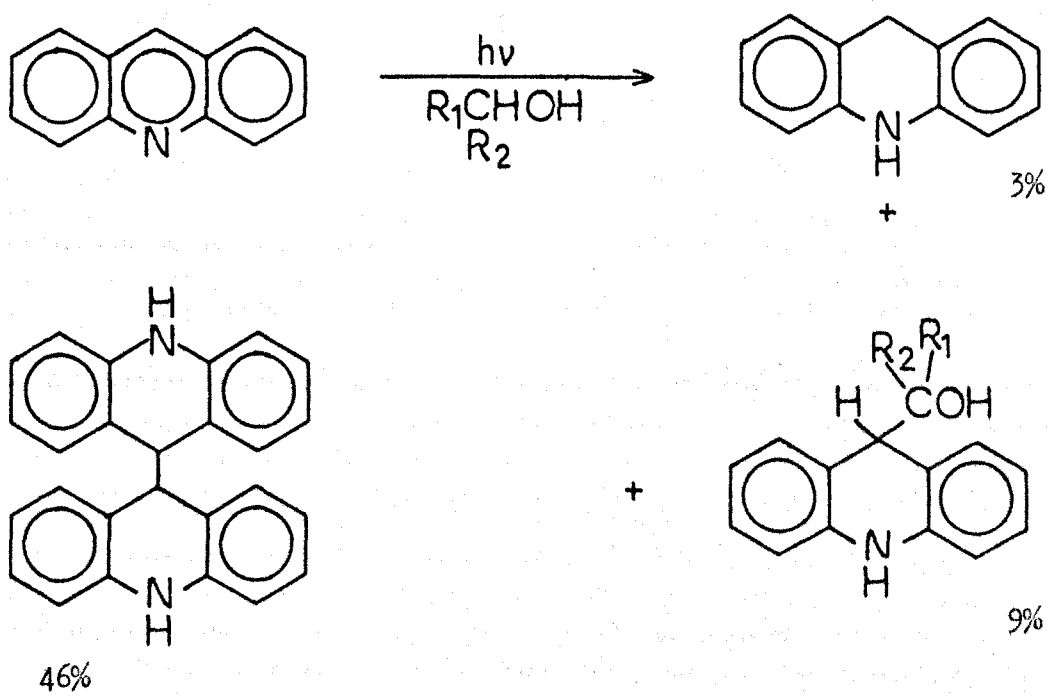


(215) (216)

Scheme 5.4

Attempts to observe or trap the intermediate were unsuccessful.

The photoaddition of water and primary alcohols to unsaturated bonds has been reported for uracil[253,254] and cytosine derivatives.[255] These additions are believed to be implicated in the photochemistry of deoxyribonucleic acid. The photochemistry of acridine and phenazine has been widely studied.[256] A radical addition occurs in alcoholic solvents to give as major product 9,9'-diacridan.[257-259]



Scheme 5.5

There appear to be no examples of this type of addition for cyclic and heterocyclic dienes or trienes.

Cyclohexenes and cycloheptenes commonly add methanol in an ionic fashion in a 1,2-addition process. Twisted or trans isomers are often postulated as intermediates in these reactions. With cyclic alkenes with fewer than six carbons in the ring, for which trans isomers

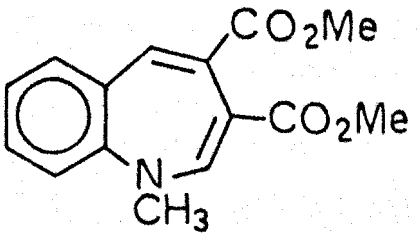
are highly improbable, free-radical addition of alcohols is observed.[260]

Cycloadditions

Diels-Alder cycloaddition reactions of azepines and diazepines are known, however no rigorous study of the reactivity of these compounds has been carried out.

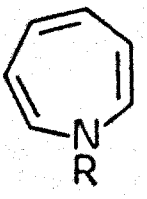
The non-planar ring in simple azepines restricts conjugation and these compounds behave predominantly as dienes. The reaction of N-ethoxycarbonylazepine with tetracyanoethylene, 4-phenyl-1,2,4-triazoline-3,5-dione, 1,4-phthalazinedione and N-phenylmaleimide results in Diels-Alder addition to the 2,5 positions to give adducts.[143] Diethyl azodicarboxylate and nitrosobenzene however both add across the 2,7 positions in a step-wise $(2 + 6)\pi$ cycloaddition.[261,262]

The benzazepine (217) undergoes a ready addition of dimethyl acetylenedicarboxylate to give an adduct in high yield.[263]



(217)

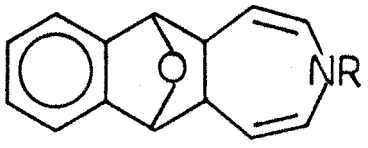
The azepines (218) also behave as dienophiles[264,265] in reactions with



R = CO_2Et, SO_2Me

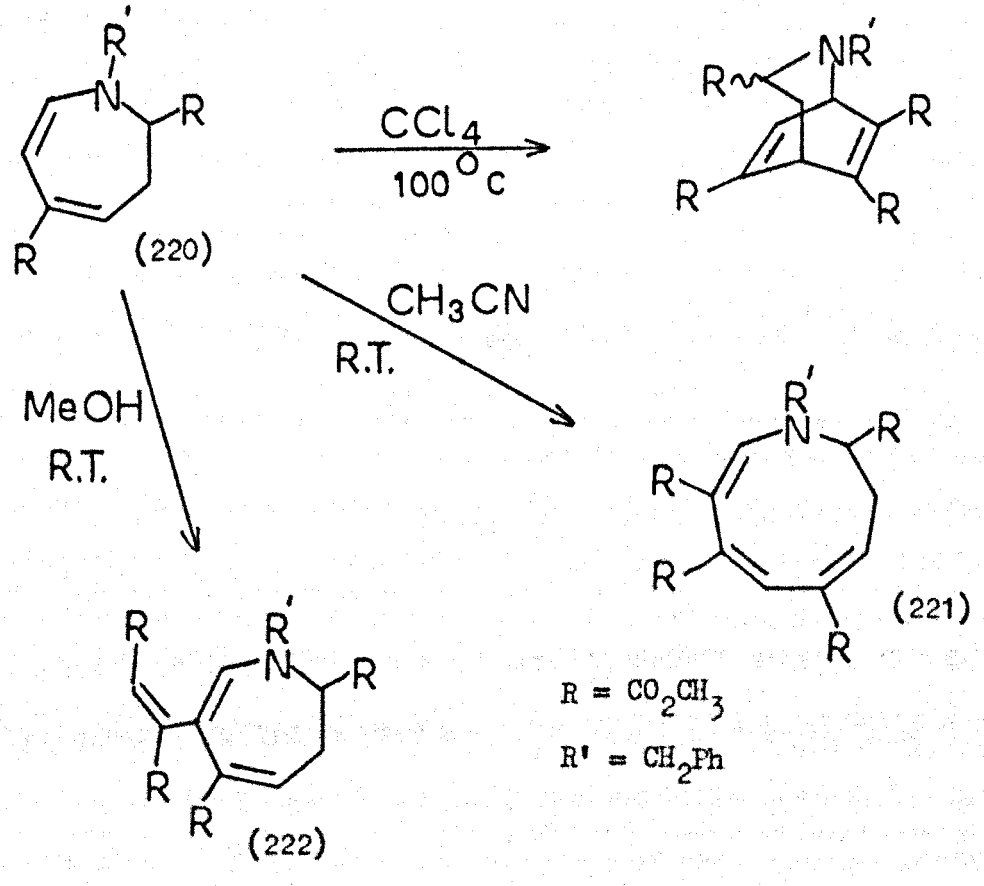
(218)

substituted cyclopentadienes or 1,3-diphenylisobenzofuran to give adducts across positions 4 and 5, e.g. (219).



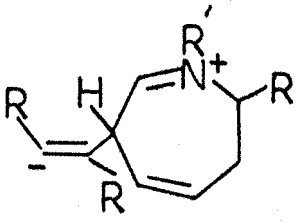
(219)

A recent communication by Eberbach et al.[266] reveals a strong solvent effect in the reaction of the azepine (220) with dimethyl acetylenedicarboxylate.



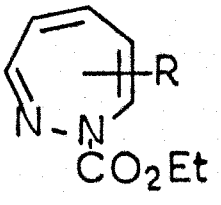
Scheme 5.6

Yields for all three products were high (90%). The azacyclononatriene (221) and the vinylazepine (222) are products of the intermediate dipolar species (223), which competes effectively with 1,4-addition in polar solvents.



(223)

The diazepines (224) form Diels-Alder adducts in moderate yield with tetracyanoethylene but are inert to maleic anhydride, dimethyl acetylenedicarboxylate and diethyl azodicarboxylate.[83] Substituents at C_4 and C_6 hindered the reaction and low yields of adducts were obtained.



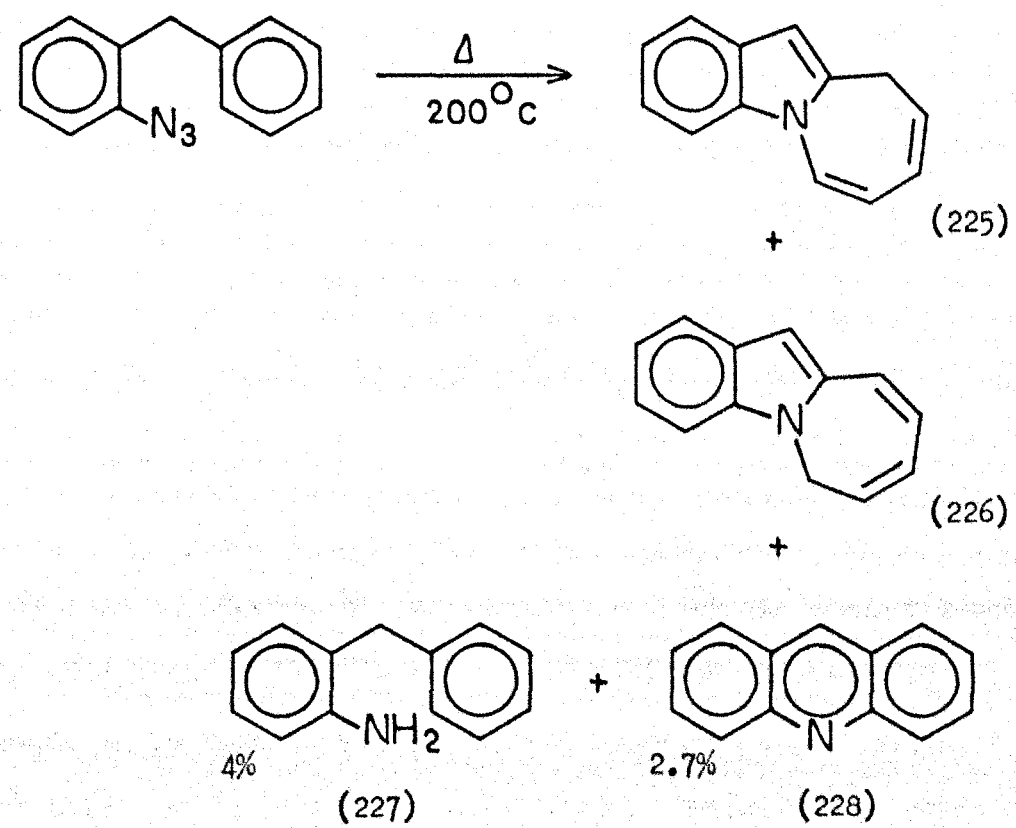
R = H, Me

(224)

Di and trisubstituted diazepines (C_3 and C_7 methyl groups, C_3, C_7 and C_5 methyl groups) failed to react.

DISCUSSION

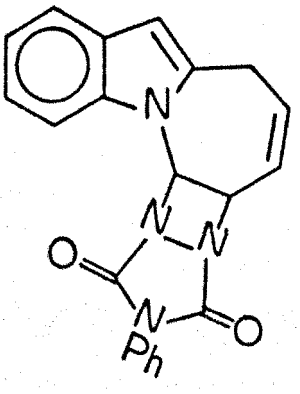
As an extension of our research into intramolecular nitrene insertion reactions it was of interest to study the reactivity of the diene system of the azepinoindole products obtained. The 10H-azepino[1,2-a]indole (225) could be obtained conveniently in large quantities[3] therefore this was synthesised and studied in some detail. Thermal decomposition of (2-azidophenyl)phenylmethane gave the required azepinoindole (225) which was contaminated with trace amounts (approx. 8%) of the 6H-isomer (226). Further chromatography of the decomposition mixture gave low yields of the amine (227) and acridine (228). These products are derived from reactions of the triplet nitrene.



Scheme 5.7

Attempts to separate and characterise the 6H-azepinoindole (226) failed.

Reaction of the mixture of azepinoindoles (225 + 226) in boiling toluene with maleic anhydride, 2,3-dimethylbut-2-ene and diethyl azodicarboxylate gave recovered starting material and varying amounts of tars, even after several days. The reaction of the potent dienophile,[268] 4-phenyl-1,2,4-triazoline-3,5-dione was then investigated. This compound reacted readily at room temperature (as judged by the discharge of the colour of the dienophile solution) to yield an unstable green oil. Chromatography gave recovered starting material (40%) and a fawn solid which could not be obtained in a pure state. The N.m.r. spectrum suggests the structure (229).



c.a. 22%

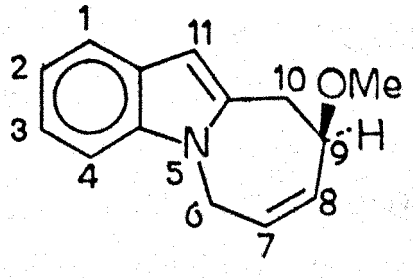
(229)

A methylene doublet at δ 3.6 p.p.m. (J = 6 Hz) was present together with multiplets at δ 5.7 - 6.2 p.p.m. (4H) and δ 7.1 - 7.7 p.p.m. Attempts to increase the yield of this compound (with 2 moles of dienophile) led to uncharacterised solids. Subsequent attempts to obtain further quantities of the adduct (229) for purification purposes led to decomposition of the reaction mixture before chromatography could be

carried out. Evidently the adduct (229) is unstable to normal purification procedures.

Examination of Dreiding models of the azepinoindole (225) shows the diene system to be virtually non-conjugated. This presents an inherent high energy barrier to cycloaddition and may explain the lack of reactivity towards simple dienophiles. It is known however that 2,3-benzotropone reacts normally with maleic anhydride.[269] A recent report by Olah[270] describes the catalysis of Diels-Alder reactions by perfluorinated sulphonic acid copolymers. Use of this technique did not lead to the isolation of cycloadducts of azepinoindole (225).

The photochemistry of 10H-azepino[1,2-a]indole (225) was also investigated. Irradiation of the azepinoindole in methanol (pyrex apparatus) led to the substituted azepine (230) and not to a tetracyclic product as was expected. The ^{1}H N.m.r. spectrum is reproduced in Figure 5.1.

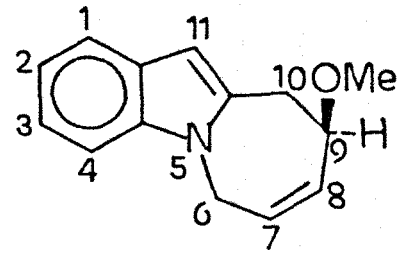


57%

(230)

Microanalysis and mass spectrometry confirmed the constitution (230). The structure was elucidated from a consideration of the ^{1}H and ^{13}C N.m.r. spectra. Signals were present in the aromatic region at δ 7.65 p.p.m.

Figure 5.1



(230)

(C_1) and δ 6.92 - 7.26 p.p.m. (C_2 - C_4), a singlet at δ 6.32 p.p.m. was assigned to the C_{11} proton by analogy with compounds of similar structure. The alkene protons were present as a subsplit doublet at δ 5.74 p.p.m. (C_8) and a 16 line multiplet at δ 5.47 p.p.m. (C_7). A sharp singlet at δ 3.08 p.p.m. confirmed the presence of the methoxyl substituent, other multiplets were seen at δ 3.95 p.p.m. (C_6), δ 3.69 p.p.m. (C_9) and δ 3.05 p.p.m. (C_{10}). Double resonance experiments confirmed the assignments and approximate coupling constants were extracted in some cases. Irradiation at the frequency of the C_9 signal removed the fine structure of the C_8 proton and collapsed the other alkene signal at δ 5.47 p.p.m. to 8 lines ($J_{7,9}$ = 1.7 Hz, $J_{7,6}$ = 2.8 Hz, $J_{7,6'}$ = 6.3 Hz). The major coupling constant ($J_{7,8}$ = 12.1 Hz) is acceptable for seven-membered ring compounds.[235] Irradiation at the frequency of the C_6 methylene group removed all minor couplings from both of the alkene protons. Irradiation at a lower power gave a doublet of doublets for C_7 (J = 12.1, 1.7 Hz) and a subsplit doublet for C_8 (J = 12.1 Hz). Irradiation of the C_8 alkene proton simplified the signals of the methine CH proton and the C_6 methylene group but coupling constants could not be extracted in this case. Irradiation of the C_7 alkene proton proved to be more fruitful. The C_8 proton collapsed to a singlet and fine structure was removed from the C_9 proton signal. The C_6 methylene signal had simplified to reveal a simple doublet (J = 2.8 Hz) and a multiplet. This confirmed that the methylene protons of C_6 were nonequivalent. From a consideration of the small coupling constant between C_8 and C_9 and inspection of models the stereochemistry at C_9 is as depicted in diagram (230).

Addition of a europium shift reagent to the N.m.r. solution produced downfield shifts in the C_8, C_9 and C_{10} signals and to a lesser

extent the C_7 alkene multiplet. This accords well with the structure (230).

The ^{13}C spectrum of the azepinoindole (230) and that of azepinoindole (225) are recorded in Table 5.1. The values are reasonable for the proposed structure (230).

From a comparison of the values for the azepinoindole (225) and indole[215], tentative assignments have been made as shown below.

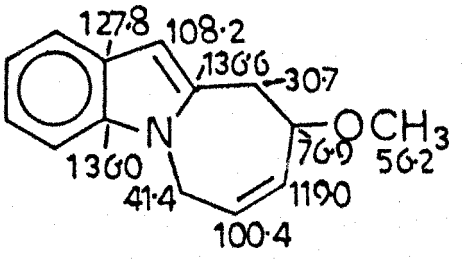
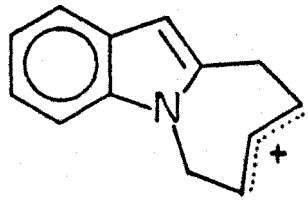


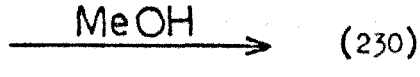
TABLE 5.1

Azepinoindole (230)	Azepinoindole (225)
δ 30.7 (tr), 41.4 (tr), 56.2 (quart), 76.9 (d), 100.4 (d), 108.2 (d), 119.0 (d), 119.9 (d), 120.6 (d), 124.7 (d), 127.8 (s), 132.6 (d), 136.0 (s), 136.6 (s)	δ 27.62 (tr), 98.29 (d), 108.86 (d), 112.1 (d), 119.88 (d), 120.37 (d), 121.0 (d), 124.79 (d), 126.32 (d), 127.78 (d), 129.50 (s), 135.0 (s), 141.88 (s)

The isolation of the product of 1,4-addition (230) is quite novel. (It has been shown in the Introduction that cyclobutane formation is common in cyclic dienes). A mechanism for the formation of the azepinoindole (230) could involve a strained trans intermediate as has been suggested for cyclic alkenes.[273] Protonation and formation of the stabilised carbocation intermediate (231) followed by methanol addition would give the isolated product (230). However this mechanism does not account for the regioselectivity observed in our reaction.



(231)



(230)

Similar arguments have been proposed by Baldry[271,272] on work concerning the photochemistry of arylbutadienes.

Attempts to obtain further examples of this interesting reaction have so far failed. Irradiation of the azepinoindole (225) in ethanol, t-butanol and diethylamine gave in all cases uncharacterised solids. Irradiation of the azepinoindole (199) in methanol also led to unidentified material.

EXPERIMENTAL

10H-Azepino[1,2-a]indole (225)

Prepared according to the method of Jones and Cliff[3] via the thermal decomposition of (2-azidophenyl) phenylmethane.

Yield 55%

M.pt. 90 - 91.5°C colourless plates

lit.[3] m.pt. 91.5°C

N.m.r. indicated the presence of the 6H-isomer (226).

G.L.C./Mass spectrometry gave m/e 181 for both compounds.

Reaction of 10H-azepino[1,2-a]indole (225) with maleic anhydride

A solution of the azepinoindole (0.25 g, 0.00138 mol) and maleic anhydride (0.135 g, 0.00138 mol) in dry xylene (10 ml) was boiled under reflux for 4 days. The dark brown solution was cooled and evaporated to give a residue which was extracted with boiling 40 - 60° petroleum ether (2 x 25 ml) to yield the starting azepinoindole (0.17 g, 68%). The petroleum ether insoluble tar was not soluble in common polar organic solvents.

Reaction of 10H-azepino[1,2-a]indole with 2,3-dimethylbut-2-ene

A solution of the azepinoindole (0.25 g, 0.00138 mol) and 2,3-dimethylbut-2-ene (0.128 g, 0.00152 mol) in dry toluene (10 ml) was boiled under reflux for 3 days. The cooled solution was evaporated to yield an oil, petroleum ether (40 - 60°) extraction (2 x 25 ml) gave the starting azepinoindole (0.22 g, 88%). A small quantity of tar was also present, which was not further examined.

Reaction of 10H-azepino[1,2-a]indole with diethyl azodicarboxylate

A solution of the azepinoindole (0.25 g, 0.00138 mol) and diethyl azodicarboxylate (0.24 g, 0.00138 mol) in dry toluene (10 ml) was boiled under reflux for 3 days. Evaporation of the dark solution and extraction of the residual oil with petroleum ether (40 - 60°) gave the starting azepinoindole (0.21 g, 84%). A dark tarry substance was also present, which could not be extracted into common organic solvents.

Reaction of 10H-azepino[1,2-a]indole with 4-phenyl-1,2,4-triazoline-3,5-dione[267]

A stirred solution of N-phenyl urazole (0.244 g, 0.00138 mol) in dry 1,4-dioxan (25 ml) was treated with t-butyl hypochlorite[138] (0.164 g, 0.00151 mol) at room temperature. The red solution was stirred at room temperature for 1 hr. A solution of 10H-azepino[1,2-a]-indole (0.25 g, 0.00138 mol) in dry dioxan (20 ml) was added dropwise over a period of 5 mins. The resultant green solution was stirred at room temperature for 2 hrs, and finally boiled under reflux for 1½ hrs. The solvent was evaporated under reduced pressure (eventually 0.1 mm) and the residual oil chromatographed on a "short-path" silica column, (solvent, 3 : 1 ether/40 - 60° petroleum ether, 50 g SiO_2). The first fractions were starting azepinoindole (0.1 g, 40%), identical in every respect with synthesised material. Further fractions gave a fawn solid (0.16 g, 22%) believed to be the [2 + 2] adduct (229).

M.pt. 187°C (dec.) (Benzene/petroleum ether 40 - 60°)

Analysis: Found: C, 69.60%; H, 4.53%; N, 14.70%

$C_{21}H_{16}N_4O_2$ requires: C, 70.77%; H, 4.53%; N, 15.72%

N.m.r. ($CDCl_3$) δ 7.1 - 7.7 p.p.m. m 10H

6.2 - 5.7 m 4H

3.6 d 2H J = 6 Hz

I.R. ($CHCl_3$) ν_{max} 3345, 2950, 2920, 2860, 1775, 1710, 1640, 1605, 1610, 1575, 1500, 1480, 1460, 1410, 1260, 765, 740 cm^{-1}

Spectra in nujol mull does not show band at 3345 cm^{-1}.

Further column fractions gave unidentified material.

Reaction of 10H-azepino[1,2-a]indole (225) with maleic anhydride in the presence of 'Nafion-H'

'Nafion-H' - prepared by a reported procedure.[270]

A solution of maleic anhydride (0.135 g, 0.00138 mol) and 10H-azepinoindole (0.25 g, 0.00138 mol) in anhydrous toluene (20 ml) was treated with 'Nafion-H' (0.12 g) and the solution boiled under reflux for 4 days. The dark solution was evaporated to yield an oil (0.3 g). N.m.r. revealed the presence of starting materials.

Irradiation of 10H-azepino[1,2-a] indole (225) in methanol

A solution of the azepinoindole (0.5 g, 0.00276 mol) in A.R. methanol (250 ml) was flushed with nitrogen for 30 mins. The solution was then irradiated with a Hanovia medium pressure mercury lamp through a pyrex filter. After 3½ hrs the solution was evaporated to yield an oil which was chromatographed on a "short-path" silica column, (9 : 1 petroleum ether 40 - 60°/ether, 50 g SiO_2). Early fractions gave the starting azepinoindole (0.035 g, 7%), identical with previous

material. Further elution gave small amounts of oils (c.a. 50 mg). Continued elution gave the major component, identified as 9,10-dihydro-9-methoxy-6H-azepino[1,2-a]indole (230) (0.339 g, 57%). M.pt. 96 - 97°C (40 - 60° petroleum ether) pale yellow plates

Analysis: Found: C, 78.75%; H, 7.03%; N, 6.45%

$C_{14}H_{15}NO$ requires: C, 78.84%; H, 7.09%; N, 6.57%

N.m.r. (Benzene-d_6)	δ 7.65 p.p.m.	m	1H
100 MHz	7.26 - 6.92	m	3H
	6.32	s	1H
	5.74	subsplit d	1H
	5.47	16 line m	1H
	3.95	m	2H
	3.69	m	1H
	3.08	s	3H
	3.05	subsplit d	2H

^{13}C N.m.r. ($CDCl_3$) Multiplicities in off-resonance spectrum in brackets

δ 30.7 p.p.m. (tr), 41.4 (tr), 56.2 (quart), 76.9 (d), 100.4 (d), 108.2 (d), 119.0 (d), 119.9 (d), 120.6 (d), 124.7 (d), 127.8 (s), 132.6 (d), 136.0 (s), 136.6 (s)

^{13}C N.m.r. of 10H-azepino[1,2-a]indole for reference ($CDCl_3$)

δ 27.62 p.p.m. (tr), 98.29 (d), 108.86 (d), 112.10 (d), 119.88 (d), 120.37 (d), 121.0 (d), 124.79 (d), 126.32 (d), 127.78 (d), 129.50 (s), 135.0 (s), 141.88 (s)

I.R. ($CHCl_3$) ν_{max} 2950, 2920, 2870, 2820, 1550, 1450, 1460, 1370, 1250, 1080, 780, 748 cm^{-1}

U.V. (95% EtOH) λ_{max} 222 nm $\log_{10}\varepsilon$ 4.55
276 nm $\log_{10}\varepsilon$ 3.89
282 nm $\log_{10}\varepsilon$ 3.89
292 nm sh

Mass spectrum, m/e 214 (31%), 213 (M^+, 100%), 198 (16), 182 (47), 181 (83), 180 (47), 168 (34), 167 (38), 155 (18), 154 (18), 130 (29), 129 (95), 128 (18), 115 (15), 102 (22), 84 (83), 69 (29), 51 (15)

Irradiation of 10H-azepino[1,2-a]indole in ethanol, t-butanol, benzene and diethylamine

Performed as for the experiment with anhydrous methanol. All solvents were anhydrous and the solutions purged with nitrogen for 30 minutes before irradiation commenced. In the case of t-butanol the experiment was performed at approx. 40°C. In all cases P.L.C. of the crude products gave unidentified compounds which had broad absorptions in the N.m.r. spectra.

Similarly irradiation in a mixture of T.H.F. and distilled water (1 : 1) led to no identifiable material.

Irradiation of 8-methoxycarbonyl-10H-azepino[1,2-a]indole (199)

A solution of the azepinoindole (0.5 g, 0.00209 mol) in anhydrous methanol (200 ml) was flushed with nitrogen for 30 minutes. The solution was then irradiated with a Hanovia medium pressure mercury lamp through a pyrex sleeve for 15 hrs. The solution was evaporated to yield a brown solid (0.5 g). Preparative layer chromatography (3 : 1 toluene/ethyl acetate) yielded unidentified oils and products with broad absorptions in the N.m.r. spectrum.

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