STUDIES OF REACTIVE INTERMEDIATES IN ORGANIC CHEMISTRY

by

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Declaration

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application for a Higher Degree.

The thesis describes results of research carried out in the Departments of Chemistry, University of Edinburgh, under the supervision of Professor J. I. G. Cadogan, and University of Amsterdam, under the supervision of Professor Th. J. de Boer, since 1 October 1969, the date of my admission as a research student.

Acknowledgements

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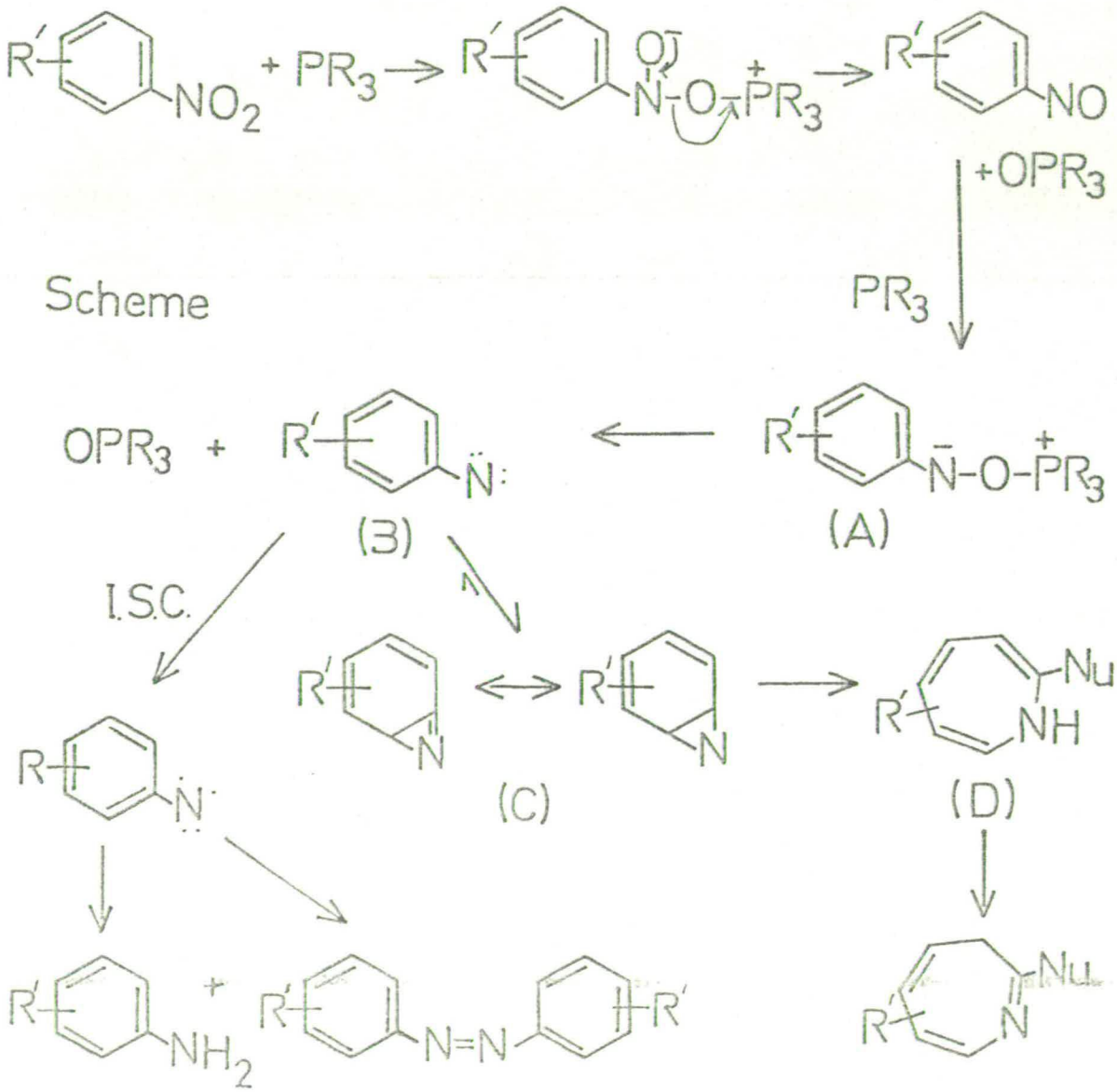
I also wish to express my gratitude and appreciation to Professor Th. J. de Boer for providing laboratory facilities in Amsterdam, and for many helpful discussions, and a warm welcome.

The stimulating and helpful discussions with many members of the academic staff of the Departments of Chemistry of the Universities of Edinburgh and Amsterdam is gratefully acknowledged. Likewise it is with great pleasure that I record my appreciation to the members of the technical staffs for the recording of spectra and microanalysis determinations.

Finally, I wish to thank the Science Research Council for the award of a Research Associateship during the course of this work.

ABSTRACT

This investigation was concerned with the nature of the aryl nitrene intermediate. It was generated both by the photolysis of aryl azides, and by the deoxygenation of nitro- and nitroso-arenes by the phosphorus reagents, triethyl phosphite, trimethyl phosphite, diethyl methylphosphonite, ethyl diphenylphosphinite, tris(diethylamino)phosphine and triphenylphosphine. The intermediate nitrene was trapped by a nucleophile (NuH), of which the most efficient was diethylamine. Others investigated were methanol, ethanol, t-butanol, dimethyl sulphide, aniline, phenylhydrazine, morpholine, 2-hydroxypyridine, ethyl acetoacetate and cyclopentadiene. In the deoxygenation reaction, four intermediates were postulated, as shown in the scheme.



Evidence is presented for the existence of each of these intermediates, and it is also shown that the intermediates (B) and (C) exist in an equilibrium situation, lying heavily on the side of (C). Experiments using chloro- and bromo-nitroarenes have shown that the heavier bromo-substituent promotes intersystem crossing to the triplet nitrenes, resulting in higher yields of amine and lower yields of azepine. Experiments involving the photolysis of phenyl azide in diethylamine in the presence of the singlet sensitiser pyrene confirmed that it is the singlet aryl nitrene which is involved in the formation of azepines.

Nitroarenes containing o-, m-, and p-substituents have been deoxygenated. o-Substituents in diethylamine yield 3-substituted-2-diethylamino-3H-azepines, where the substituent is small, and 7-substituted-2-diethylamino-3H-azepines where the substituent is large. m-Substituents in diethylamine yield 4- and 6-substituted-2-diethylamino-3H-azepines, where electron donating substituents give more of the 4-isomer, and electron-withdrawing substituents more of the 6-isomer. p-Substituents yield 5-substituted-2-diethylamino-3H-azepines in diethylamine. The results for the m-substituents are confirmed by photolysis of m-substituted aryl azides in diethylamine in the presence of pyrene. Explanations are offered for these results.

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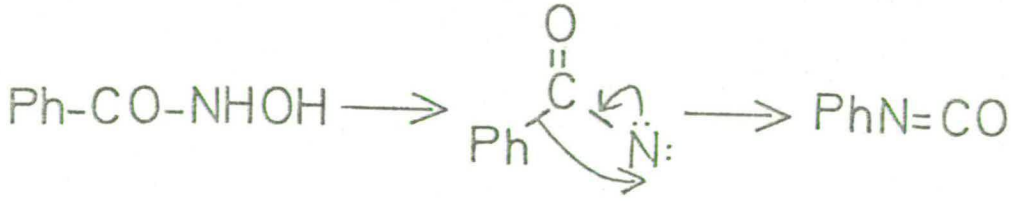
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A. FORMATION OF NITRENES

A.1. HISTORICAL NOTE

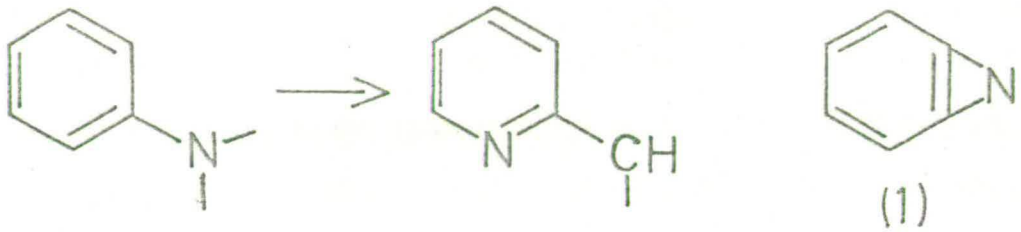
This thesis is concerned with a reactive intermediate known as a nitrene, in particular an arylnitrene: an organic species containing a monovalent, electron deficient nitrogen atom R-N:, having a sextet of electrons in its outer shell, cf. carbene. It is postulated that these nitrenes may be formed in many reactions. Like the carbenes, two electronic states are possible: singlet, having the electrons paired, and an empty orbital which is responsible for its strongly electrophilic character, designated R-$\ddot{N}$:, and triplet, having two orbitals with one electron each, and therefore a diradical character, designated R-$\dot{N}\cdot$. For most nitrenes, it is postulated that the triplet is the ground state, and the singlet an excited state of the nitrene. The triplet ground state has been observed by Smolinsky[1] in an e.s.r. tube at 77°K for phenyl and tolyl nitrenes, and also for benzene- and p-toluenesulphonyl nitrenes, all of which signals disappeared on warming, implying a reactive intermediate. Chemical evidence also indicates that nitrenes may exist and react in either of these states, depending on reaction conditions. The possible existence of a nitrene was first postulated by Tieman,[2] who suggested that a benzoyl nitrene was an intermediate in the rearrangement of N-hydroxybenzamide to phenyl isocyanate, Scheme 1.



Scheme 1

Bertho[25a,b] made an extensive study of the decomposition of many types of azides: acyl, sulphonyl and alkyl as well as substituted aryl, in each case postulating loss of nitrogen and the formation of a nitrene as the first step, followed by the characteristic reactions of nitrenes: addition to double bonds, insertion in C-H bonds, and

abstraction of hydrogen. He also found pyridine in the residues from the reactions, and suggested it was formed by extrusion of carbon from the ring. He also suggested that compounds such as (1) might be formed, Scheme 2. These reactions will all be discussed later.

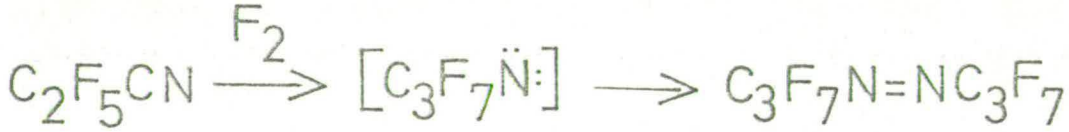


(1)

Scheme 2

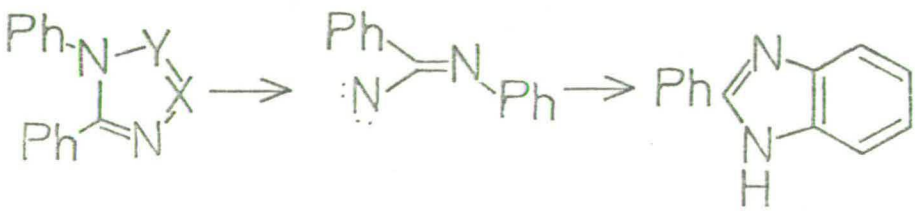
A.2. TYPES OF NITRENE

The nature of the nitrene varies depending on the group attached to the nitrogen, but the principal method of generating it is by the thermolysis or photolysis of the appropriate azide, although individual nitrenes are often produced by specific routes. The parent, HN:, has been extensively studied spectroscopically[3] at low temperatures, because of its great interest to astrophysists. Alkyl nitrenes, RN:, are highly reactive because there is no possibility of delocalisation; no charge separated canonical forms can be written. An alkyl nitrene is reported as the product of fluorination of pentafluoroethyl cyanide,[9] (Scheme 3).



Scheme 3

The more stable allyl nitrene has been generated by elimination of a suitable stable fragment, e.g. CO_2, N_2, SO_2, Ph_3PO from a ring by either thermolysis or photolysis[5, 6, 7, 8, 9], (Scheme 4).



Scheme 4

Because of difficulties in distinguishing between the reactions of excited azides and those of nitrenes, Lwowski[10, 11] sought an

unequivocable method of generating acyl nitrenes, $R\text{-}O\text{-}\overset{\overset{O}{\|}}{C}\text{-}\ddot{N}:$, normally carbethoxy nitrene, R=Et, and he used α elimination from p-nitrobenzenesulphonoxyurethane by treatment with a base, e.g. triethylamine, (equation 1, Scheme 5). Hayashi and Swern[12] generated it by photolysis of N-carbethoxyiminodialkylsulphuranes, (equation 2, Scheme 5). In the photolysis of alkanoyl and aroyl azides, Curtius rearrangement always accompanies nitrene formation. The isocyanate is probably formed not from the nitrene, but directly from the excited azide.

1. $EtOOC\text{-}NH\text{-}OSO_2\text{-}C_6H_4\text{-}NO_2\text{-}p \longrightarrow EtOOC\text{-}\ddot{N}:$

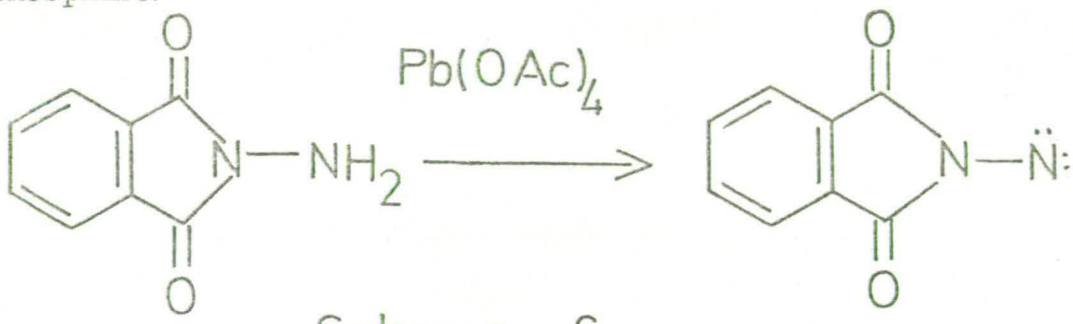
2. $EtOOC\text{-}N{=}SMe_2 \longrightarrow EtOOC\text{-}\ddot{N}:$

Scheme 5

Arylsulphonyl nitrenes, $ArSO_2\ddot{N}:$, have been generated exclusively by azide decomposition, but $Ph_3CS\ddot{N}:$ has been produced in the deoxygenation of the corresponding nitroso compound by trialkyl phosphite.[13]

Amino nitrenes, $R_2N\text{-}\ddot{N}:$, have also been reported, but their properties are different because of the large contribution the resonance form $R_2\overset{+}{N}=\bar{N}:$ plays. They are formed in the long known oxidation of unsymmetrical di-substituted hydrazines with lead tetraacetate or mercuric oxide,[14] which has now been used to generate N-phthalimido nitrene, in which contributions from charge separated resonance structures are minimised by the electron withdrawing nature of the remainder of the molecule, which destabilises the incipient positive charge[15,16], (Scheme 6). Amino nitrenes have also been prepared by the elimination of a suitable leaving group, e.g. alkyl sulphonite in the alkaline hydrolysis of a sulphonyl hydrazine,[17] and by reduction of N-nitrosamines with sodium dithionite,[18] or lithium in liquid

ammonia,[19] or ethyl diphenylphosphinite,[20] but no triphenyl phosphine.[21]



Scheme 6

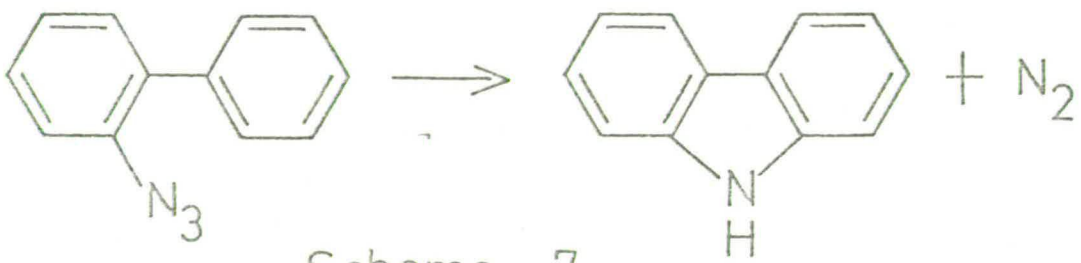
Another nitrene which has been studied only recently is the symmetrical cyano nitrene, $\ddot{N}C\ddot{N}:$, first reported by Herzberg and Travis,[22] who generated it from diazomethane. It is more conveniently prepared from cyanogen azide.[23, 24] It is of interest because experiments involving the labelling of one of the nitrogen atoms have shown that it loses its identity, reacting 50% at each nitrogen atom, which implies the formation of a nitrene.

A.3 FORMATION OF ARYL NITRENES FROM AZIDES

(a) Thermolysis.

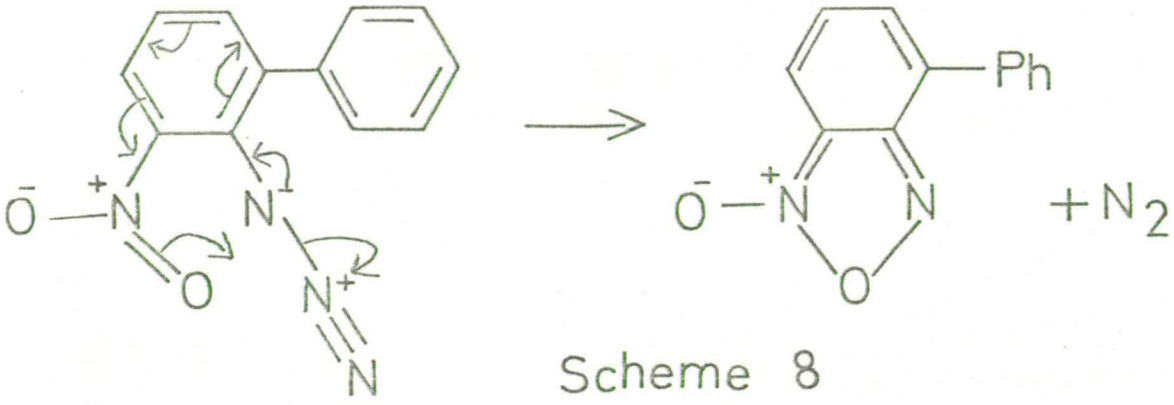
The thermal decomposition of phenyl azide was originally studied by Bertho[25a, b] who found that the part of the azide left after the evolution of nitrogen, he called it "azidreste" but we now know it as nitrene, could dimerise to form azobenzene, abstract hydrogen to form aniline and insert in p-xylol.

Interest in aryl azides was renewed by Smith and co-workers[26a, b, c] who thermolysed o-azidobiphenyls and related compounds in a novel formation of carbazole, and extended the reaction to the synthesis of various heterocyclic compounds, such as phenothiazines[26c], but did not postulate that the mechanism might involve a nitrene, (Scheme 7).



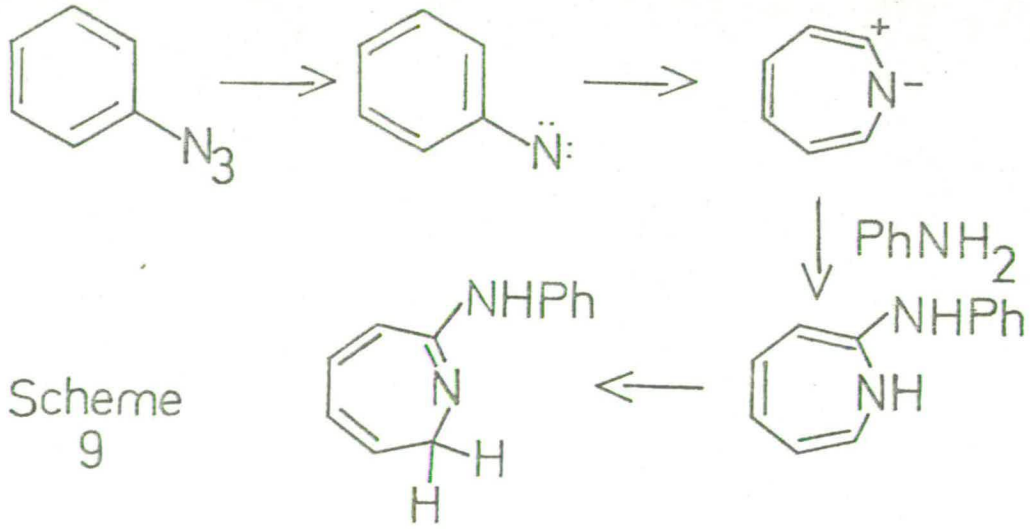
Scheme 7

He did, however, report the preferential formation of 4-phenylfuroxan instead of 2-nitrocarbazole, from 2-azido-3-nitrobiphenyl, at a lower temperature and in high yield, an indication that a different, concerted pathway may be followed, (Scheme 8).



Scheme 8

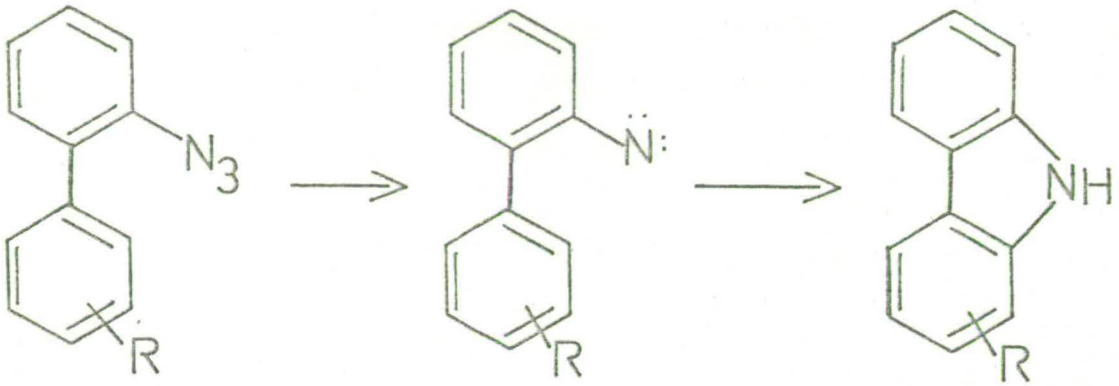
Boyer and Canter[27] rejected the idea of a univalent nitrogen derivative resulting from loss of nitrogen from azides, on the basis that no rearranged products had been found. Huisgen[28a, b, c] first proposed that phenyl azide should decompose to form nitrogen and a phenyl-nitrogen intermediate; he was explaining the observed ring expansion of such a species to form an azepine, in the presence of aniline, (Scheme 9).



Scheme 9

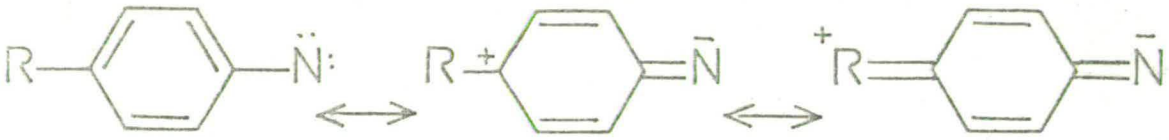
He also carried out kinetic experiments on substituted phenyl azides, and showed that m-substituents did not alter the rate significantly. Further kinetic work has been done by Smith[29] on factors affecting the rate of carbazole formation, where he found that substituents

in the β ring did not affect the rate of loss of nitrogen, implying prior loss of nitrogen to leave a univalent species of nitrogen attached to an aromatic ring, (Scheme 10); this evidence of a nitrene opened the way for extensive mechanistic studies; the information from product studies will be discussed later.



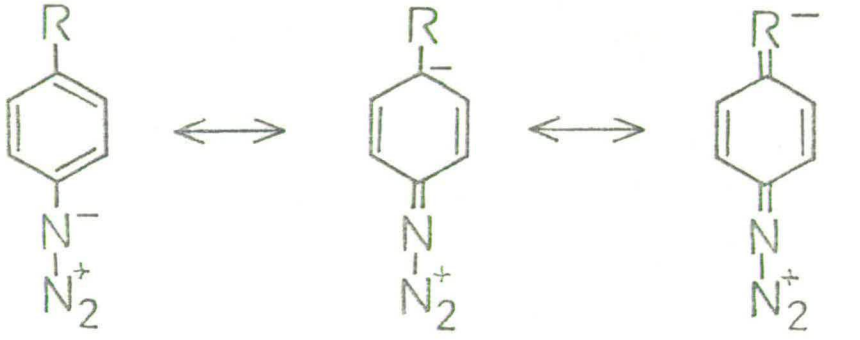
Scheme 10

The problem lies in determining whether loss of nitrogen (a) precedes, (b) is concerted with, or (c) follows other bond formation and whether the nitrenoid species is a transition state or an intermediate with finite lifetime. Kinetic investigations into the effects of varying conditions and substituents have been undertaken by several people. Smith and Hall[30] looked at the rates of nitrogen evolution from m- and p-substituted aryl azides and confirmed that m-substituents had very little effect, while all p-substituents increased the rate, with a maximum effect of X4 for a p-methoxy substituent. The rates were all first order, without any Hammett correlation. A detailed study of the rate of formation of carbazole from substituted 2-azidobiphenyls, revealed that substituents on the β ring did not affect the enthalpy, neither did substituents in the 4-position of the A ring, (m- to the azido group), but substituents in the 5-position showed a small variation in the enthalpy in the order p-NO_2 > H > p-CH_3 > p-Br > p-MeO. This could be accounted for by the stabilisation of an intermediate by electron donating substituents, (Scheme 11), assuming considerable nitrenoid character in the transition state leading to the intermediate.



Scheme 11

The azide itself would be stabilised by electron withdrawing substituents, shown by resonance structures such as equation (12).

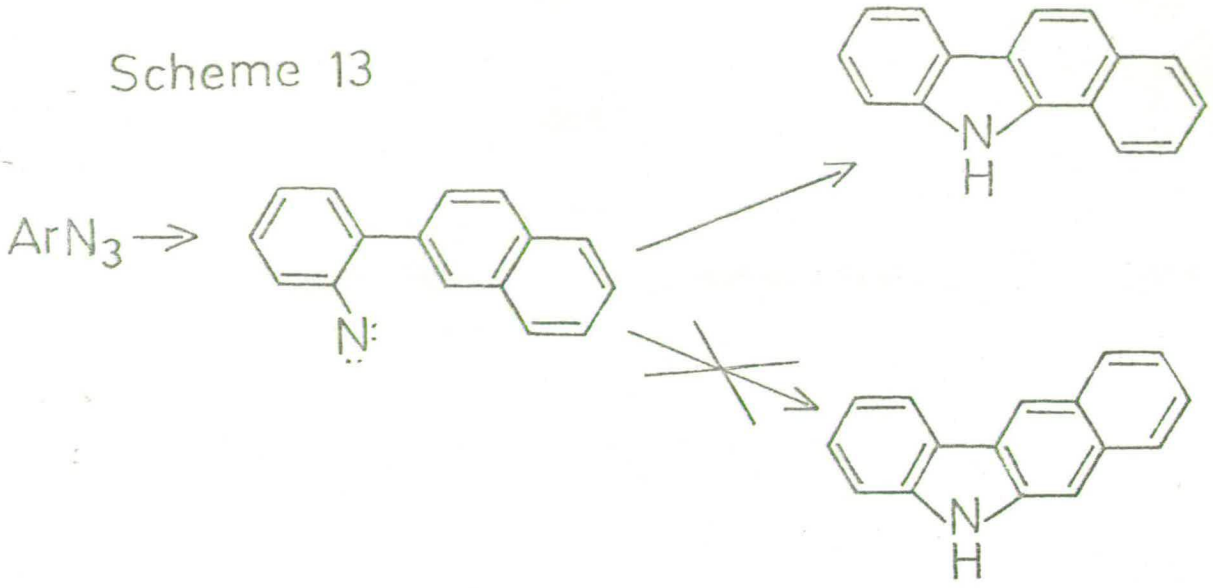


Scheme 12

This is also shown in the o/p directing effect of the azido group towards electrophilic substitution. The rates of decomposition of the substituted phenyl azides correspond closely to those of the substituted biphenyl azides. This evidence all points to the rate determining step being the same in both systems and to the formation of a nitrene intermediate. In the decomposition of β (o-azidophenyl) naphthalene,[29] complete selectivity is shown in the position of cyclisation to the naphthalene ring (Scheme 13), implying that the intermediate must have a half-life considerably longer than the time for rotation about the aryl-aryl bond.

Russell[31] conducted a kinetic study into the decomposition of phenyl azide in various solvents; he found that the rate was first order in tetrahydronaphthalene and in nitrobenzene, explaining the small variation in rates by desolvation effects, and that the rate was considerably enhanced in methyl methacrylate, which was involved in

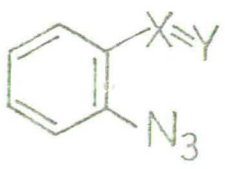
Scheme 13



reaction to form a triazoline initially, which subsequently broke down with loss of nitrogen. He concluded that in inert solvents decomposition was a unimolecular process, forming a diradical and nitrogen.

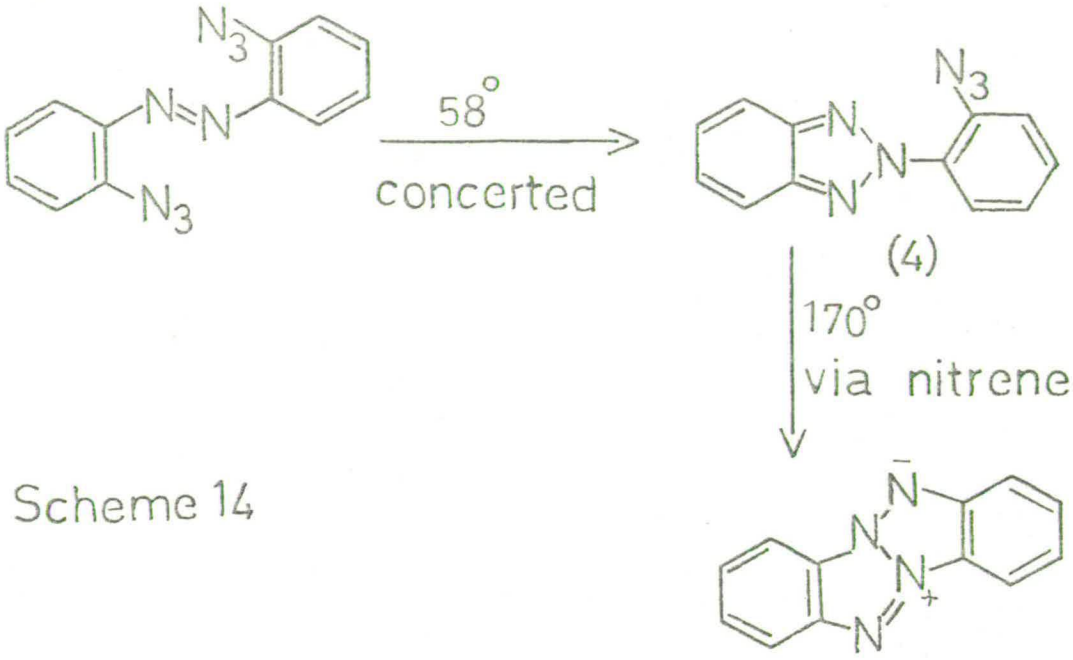
Walker and Waters[32] conducted extensive experiments in many solvents and observed that varying the solvent had little effect on the rate of evolution of nitrogen, either for phenyl azide or for p-methoxyphenyl azide, which was faster by a factor of ten consistently; only when the solvent contained a double bond, e.g. indene, was the rate increased dramatically due to a reaction between the azide and the double bond to form a triazole, where their results also showed that the entropy requirement was small. They concluded that in inert solvents decomposition of the azide formed a nitrene.

The anchimeric assistance of suitable neighbouring groups has also been studied. The ease of formation of furoxan has been observed by Smith[26a] and Huisgen[28a] and many subsequent workers. It has been extended to any system with a double bond o- to the azide, (3).



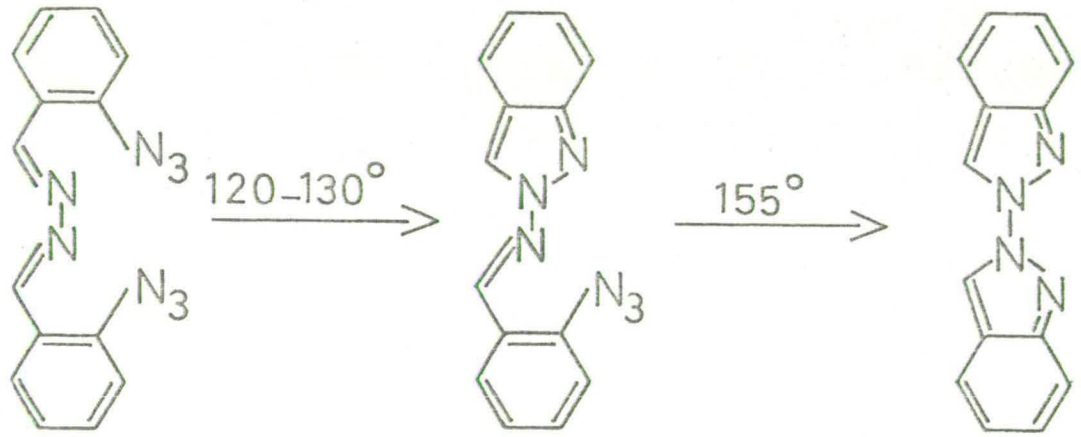
(3)

Carboni and Castle[33] showed how much more easily the concerted reaction occurred than the formation of nitrene, by isolating the intermediate (4) Scheme 14, and Krbechek and Takimoto[34] showed



Scheme 14

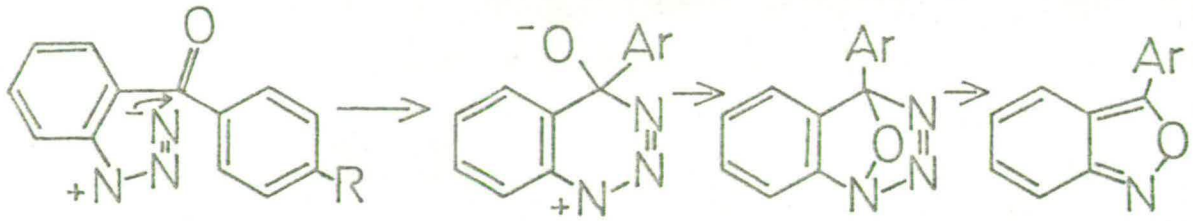
how sensitive the concerted reaction is to the electronic state of the double bond by isolating the intermediate in Scheme 15.



Scheme 15

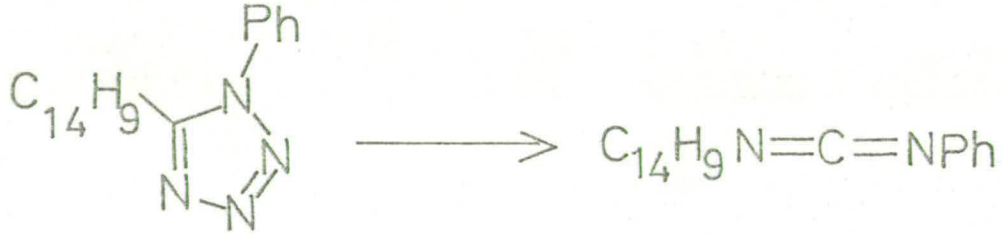
Dyall and Kemp[35] made an extensive kinetic study of neighbouring group participation in the pyrolysis of aryl azides, and found the relative rate for 2-NO_2: 4-NO_2 equal to 1343 : 3.5. Their calculations of the E_{act} also showed that a group in the 3-position, e.g. methyl, could prevent the planarity of the group containing the double bond and hence raise the E_{act} and decrease the rate, but in all examples of cyclisation, the entropy was very low, indicating the

formation of a cyclic transition state. Sundberg and Russel[36] applied this reaction to the synthesis of 2-substituted indoles, and Hall[37], from work on 4'-substituted-2-azidobenzophenones, where they found the rate accelerated by electron withdrawing and retarded by electron donating substituents, postulated a mechanism involving nucleophilic attack by the terminal nitrogen (Scheme 16).



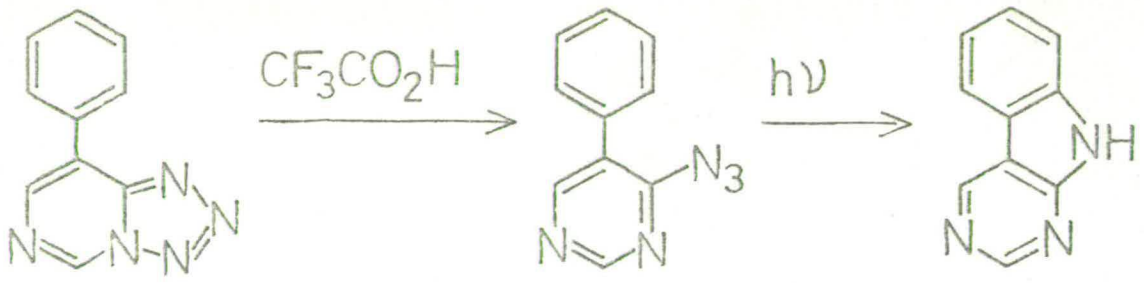
Scheme 16

As an extension of the pyrolysis of azides, it has been observed that the same products were obtained from the pyrolysis of tetrazoles. Smith and Leon[38] obtained carbodiimides from the pyrolysis of a tetrazole (Scheme 17) and postulated that this could be a concerted reaction after ring opening to the azide.



Scheme 17

Susaki[39a, b] studied the azide-tetrazole equilibrium, and found it solvent dependent, ionic solvents, e.g. trifluoroacetic acid, favouring the ionic azide, and dependent on the other substituents attached to the benzene ring; electron withdrawing groups not only destabilised the electron attracting tetrazole ring, but also stabilised the electron donating azido group. They found products which could best be explained by invoking a mechanism involving a nitrene in both thermolysis and photolysis. Swenton and Hyath[40] found from the photolysis of 8-phenyltetrazolo[1, 5-c]pyrimidine in a variety of solvents, that only in trifluoroacetic acid was a good yield of 9H-pyrimido[4, 5-b]indole obtained. Other solvents gave tars, (Scheme 18).



Scheme 18

This shows clearly that the nitrene must come from the azide after ring opening of the tetrazole. Since singlet nitrogen must be formed, it is reasonable to suppose that in those reactions in which a discrete nitrene is formed, it is originally in the singlet state.

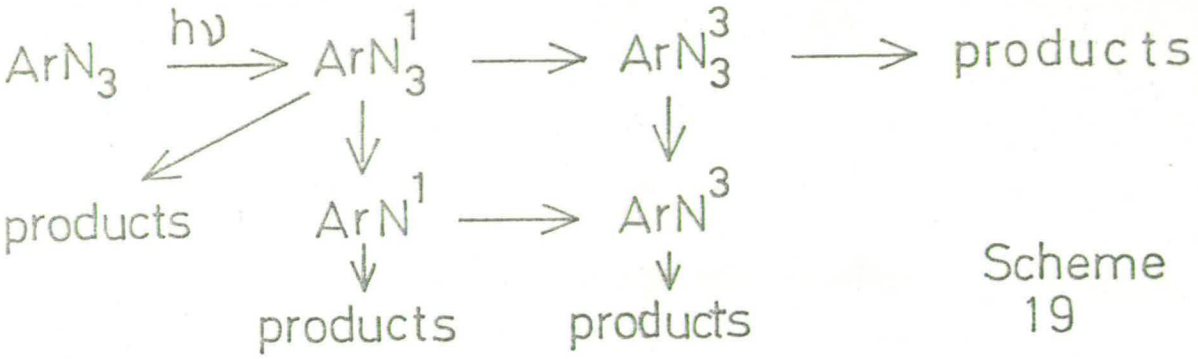
The kinetics of the decomposition of azides other than aryl have also been studied. Breslow[41] found that the decomposition of sulphonyl azides, both aryl, e.g. p-toluenesulphonyl azide, and alkyl, e.g. 1-pentane- and 2-propanesulphonyl azides exhibited first order kinetics, providing the secondary radical reaction of the alkylsulphonyl azides, which gives sulphur dioxide, was inhibited by some radical trap. Various inert solvents were used, confirming the observation made with aryl azides that in the decomposition, the rate determining step does not involve solvent. Huisgen[42] observed that the rate of decomposition of azidoformates, e.g. propyl azidoformate, varied little in a wide selection of solvents, and Breslow[43] found a similar first order thermal decomposition of azidoformates, implying that the general rate determining step is unassisted loss of nitrogen to form a nitrene.

(b) Photolysis

An alternative to the thermolysis is the photolysis of azides. The possible species that are involved in product formation are shown in Scheme 19.

It is reasonable that reactions whose mechanism involves concerted loss of nitrogen on thermolysis may also be concerted on photolysis, especially where the yields of products are high, (tars may be products

of nitrenes).



Scheme 19

Saunders and Caress[44a, b] have compared the migratory aptitudes of methyl, phenyl and substituted phenyl groups in both photochemical and thermal rearrangements of triarylmethyl and related azides. In the decompositions of 1-azido-2,2-diphenylethane, ($Ph_2Me_2CN_3$), and 2-azido-2-phenylpropane, ($PhMe_2CN_3$), the preference for migration of phenyl rather than methyl is very much less than in the carbonium ion rearrangement, but also shows that in photolysis the probability of migration is statistical, while in the thermolysis it is not, (Table 1).

Table 1. Migratory Aptitude of Ph/Me

Ph_2MeCN_3	2.18	2.36
$PhMe_2CN_3$	0.96	4.05

In the photolysis of aryl diphenyl methyl azide, $ArPh_2CN_3$, all p-substituents enhance the migratory aptitude of Ar slightly, while in the thermolysis electron donating groups accelerate and electron withdrawing groups retard the migration of Ar. The implication is that nitrogen loss is probably concerted in the thermal rearrangement, but in the photolysis, rearrangement takes place after the formation of a nitrene, and this nitrene is probably in a triplet state, since all p-substituents would stabilise an odd electron; if the singlet nitrene were involved, the lack of selectivity would be explained by the very high energy content and consequent lack of discrimination of the singlet species.

Marley and Reiser[45] studied the quantum yield of various aromatic azides and its dependence on wavelength, particularly for 1-azidonaphthalene, and concluded that absorption in the main band of an aromatic azide populates a $\pi\pi^*$ excited singlet state, in a vibrational level insufficient to induce bond dissociation. The molecule then undergoes a fast, radiationless conversion to lower excited states, and then to the ground state, which is highly vibrationally excited and allows the transmission of sufficient vibrational energy from the skeleton to the side chain, resulting in the dissociation of the side chain. The internal conversion proceeds through all intervening excited states, such as $n\pi^*$ excited singlet and possibly $n\pi^*$ excited triplet, hence the possibility of generating a triplet nitrene, although the singlet would be more commonly expected.

Reiser[46] has also tried to examine the ground state of the nitrene with physical measurements. He irradiated 2-azidobiphenyl in an EPA matrix at 77°K, and looked at the u. v. spectrum before, during and after irradiation. He observed the formation of a new peak at 342 mμ, simultaneously with the disappearance of the azide peak at 260 mμ. He concluded that a single intermediate was being formed, which was identified as a triplet species because the spectra showed the general characteristics of aromatic structures with an odd electron, e. g. benzyl radical. He then irradiated the solution at the wavelength at which it absorbed, which caused the disappearance of the 2nd peak and the formation of a new 3rd peak at 293 mμ, with a spectrum corresponding exactly to that of carbazole. The same product, carbazole, is formed in the same quantum yield as the intermediate by irradiation at room temperature. The quantum yield of the second step, nitrene ——> carbazole, is very low, implying that it involved activation of the nitrene, but whether to a higher triplet excited state or to a longer lived excited singlet state was not established.

The problem of singlet or triplet states has been explored by several people. Swenton[47a, b] investigated the photolysis of biphenyl azide, and found that singlet sensitisers, e. g. pyrene, naphthalene, piperylene, gave a good yield of carbazole and a trace of 2, 2'-biphenyl-

azobenzene, (4) and triplet sensitisers, e. g. acetone, acetophenone, benzophenone, inhibited the formation of carbazole and gave excellent yields of (4). Similarly Odum and Aaronson[48] altered the product of photolysis of p-cyanophenyl azide in dimethylamine from 1-(p-cyanophenyl)-2, 2-dimethylhydrazine to p-cyanoaniline by using Xanthen-9-one as a triplet sensitiser. This indicates that the azo compounds and the amines formed in all azide decompositions arise from either triplet azide or triplet nitrene, and the insertion and addition products from singlet states.

Lwowski[49] has been trying to determine the singlet or triplet nature of carbethoxy nitrenes by experiments involving stereospecific (from singlet) and non-stereospecific (from triplet) additions to double bonds. He normally found some degree of specificity. When he used triplet sensitisers, the only products isolable were amines, which implied that triplet nitrene arose only from singlet nitrene, not from the azide, in the formation of non-stereospecific products, and the amine came from a reaction of the azide itself.

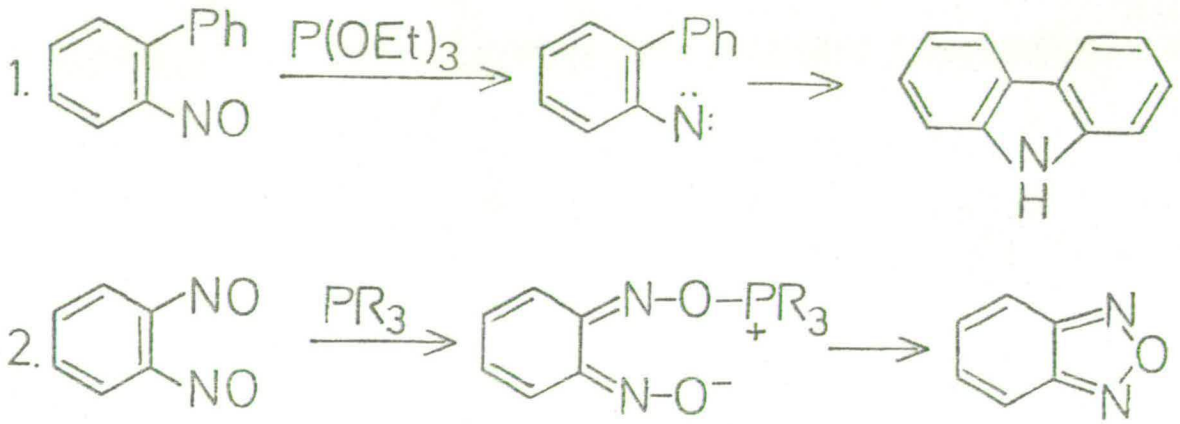
(c) Other reactions of azides to form nitrenes.

There is a report by Knox[66] that iron carbonyls can catalyse the decompositions of aryl and alkyl azides under mild conditions, and they suggested from considerations of the products obtained that a nitrene is thus generated. Such decomposition of an aryl azide is also reported to be catalysed by palladium on charcoal.[67] Kwart and Khan[68] have shown that the decomposition of arylsulphonyl azides may also be catalysed by a metal such as copper, possibly due to a radical-induced decomposition, which is reasonable since the products were amides, known to arise from the triplet species.

A.4 FORMATION OF ARYL NITRENES BY THE DEOXYGENATION OF NITRO AND NITROSO COMPOUNDS.

(a) With Phosphites

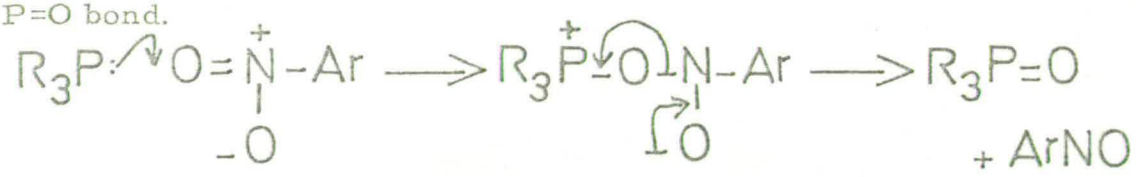
Aryl nitrenes may also be generated by the phosphite deoxygenation of nitro and nitroso compounds. Bunyan and Cadogan[50] first reported the generation of a nitrene in a reaction involving the formation of a high yield of carbazole after the deoxygenation of 2-nitrosobiphenyl by triethyl phosphite, (equation 1, Scheme 20) and successfully extended this reaction[51] to the corresponding 2-nitrobiphenyl. A report by Boyer and Ellzey[52] had noticed the ability of triethyl phosphite to deoxygenate a C-nitroso group in the formation of benzofurazan from o-dinitrosobenzene, for which no nitrene intermediate need be postulated, (equation 2, Scheme 20).

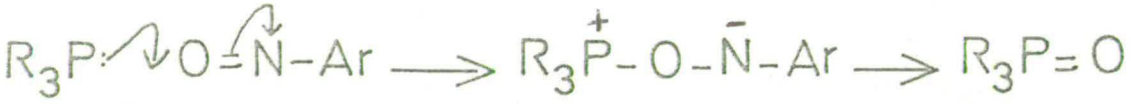


Scheme 20

Since deoxygenation proceeded smoothly with triethyl phosphite and related phosphites, and not at all with phosphorus trichloride,

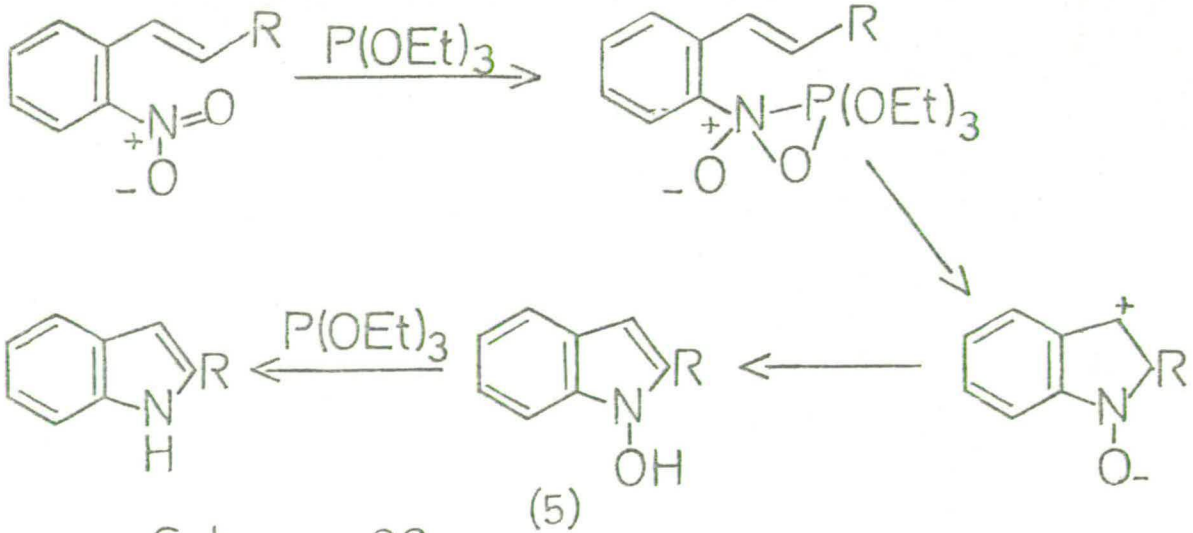
Cadogan[53] proposed that the reaction proceeded by nucleophilic attack by phosphorus on the oxygen atom of the nitro compound, (Scheme 21), with the driving force being the formation of the extremely strong P=O bond.





Scheme 21

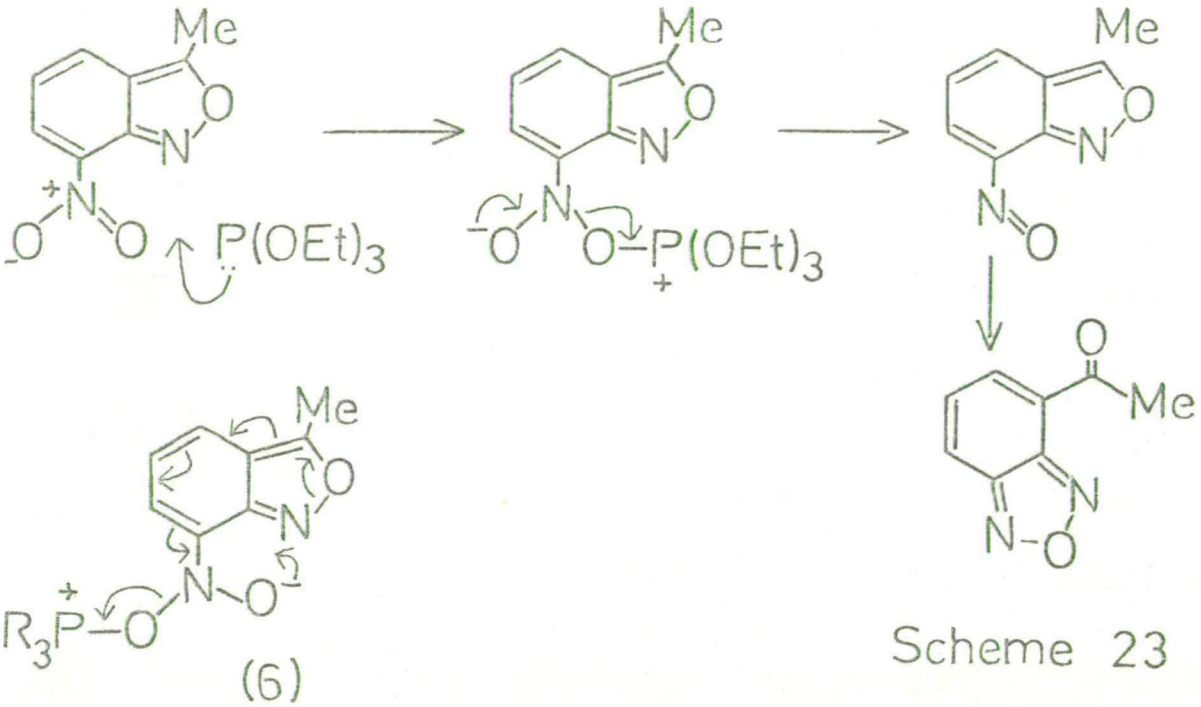
Sundberg[54] proposed a mechanism involving the formation of a three membered NOP ring, as the first step, followed either by nitrene formation or by a concerted reaction as in the formation of 2-phenylindole from β-phenyl-o-nitrostyrene via an intermediate 1-hydroxy-2-phenylindole (5) (Scheme 22). Support for this intermediate, (5), came from the isolation of by-products which were shown to arise in the correct relative amounts when it was subjected to experimental conditions, but (5) itself was also recovered, although it could not be detected in the original reaction mixture.



Scheme 22

Evidence for the formation of an intermediate nitroso compound would apparently come from Katritzky,[55] (Scheme 23), but this could also be described in a concerted fashion, (6). It is normally

impossible to prove the existence of the nitroso compound as an intermediate because of the greater facility with which it reacts with phosphorus reagents. The half-life for deoxygenation with triethyl phosphite of 2-nitrosobiphenyl at 0° is less than two minutes, and for 2-nitrobiphenyl at 160° is five hours.



Scheme 23

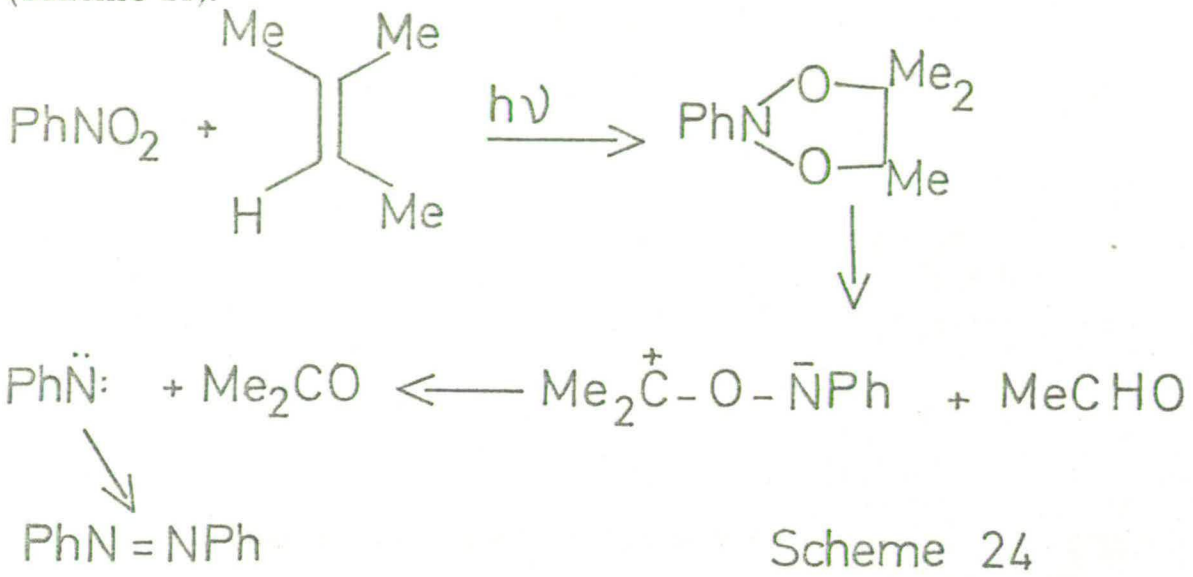
Cadogan[56, 97] reported an order of efficiency for deoxygenation by phosphorus reagents as: $(EtO)_2PMe > (Et_2N)_3P \approx (EtO)P(NEt_2)_2 > (EtO)_3P \approx (Pr^iO)_3P \ggg PCl_3$ from experiments on ease of carbazole formation from 2-nitrobiphenyl. It is reasonable to suppose that the nitrene formed by deoxygenation is in the singlet state, since two electrons are required in the formation of the P=O bond, leaving an empty orbital on the nitrogen, and that any characteristic triplet products, e. g. amines, normally found in these reactions, result from intersystem crossing to the triplet nitrene.

The best evidence for formation of a discrete nitrene in these deoxygenation reactions comes from product studies, especially those where the same products are obtained by a different method of generation of the nitrene. The attraction of this method of acquiring nitrenes

lies in the more readily available starting materials, compared with the unstable azides otherwise needed.

(b) Other Methods

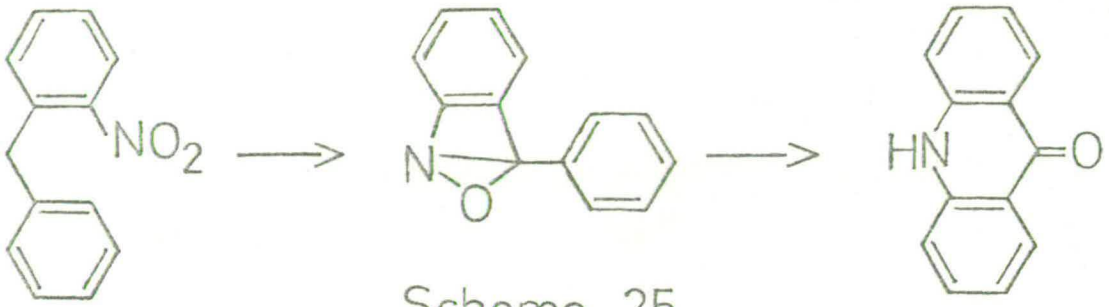
Buchi and Ayer[60] invoked a nitrene to explain the formation of azobenzene in the photochemical addition of nitrobenzene to olefins, (Scheme 24).



Scheme 24

Reduction of nitro compounds with reagents other than phosphites may also proceed through a nitrene. Kmiecik[62] heated nitrobenzene to 210° in the presence of iron pentacarbonyl and excess carbon monoxide to give a high yield of azobenzene, possibly through the nitrene. Vivian[63a, b, c] has experimented extensively with the use of iron, and the better reagent, ferrous oxide as well as lead, phosphorus, carbon (charcoal), and sulphur as deoxygenating reagents for aryl nitro and nitroso compounds and hence has made many substituted phenazines. This can most readily be explained in terms of a nitrene. Abramovitch[83a, b] showed that the reaction must take place on the surface of the ferrous oxalate, because the cis and not the thermodynamically more stable trans azobenzene was obtained from nitrobenzene, although the products from reduction of 2-nitro-2', 4', 6'-trimethylbiphenyl correspond closely to the products obtained from the nitrene generated from other sources. It is possible that the reaction involved attack on an RN—>O species, as postulated by Smith and

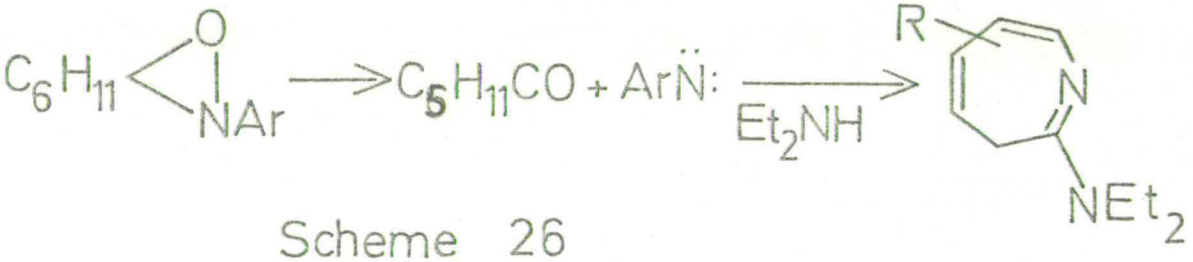
Suschitzky[64] in the formation of hexahydroazepino-(1', 2'-1, 2)-benzimidazole, and by Kliegl[65] (Scheme 25).



Scheme 25

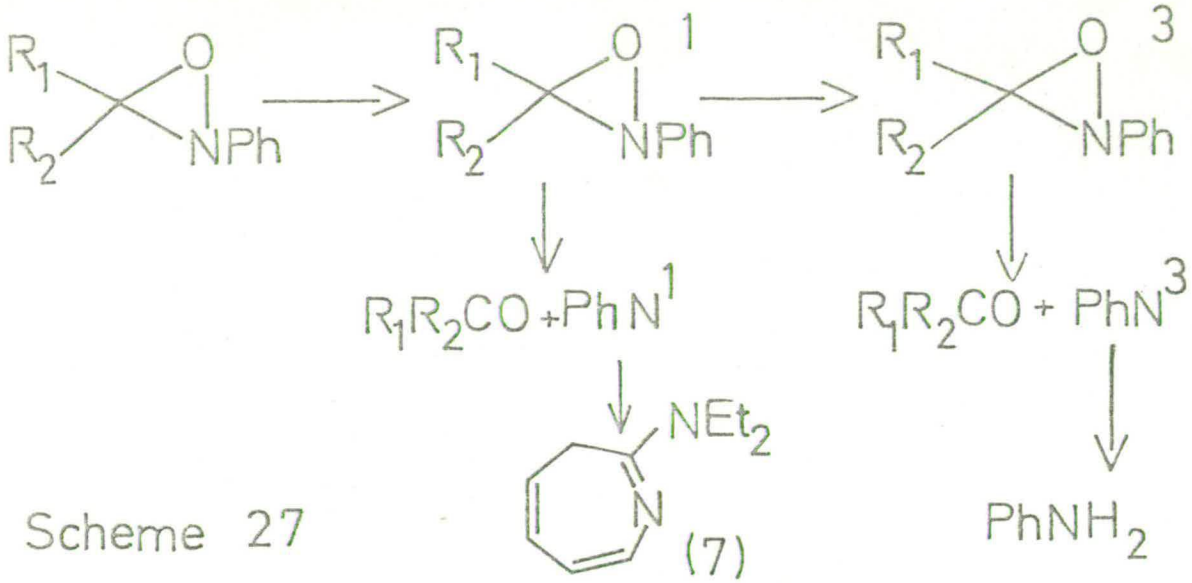
A.5 OTHER SOURCES OF ARYL NITRENES

Aryl nitrenes have also been postulated in various other reactions. Meyer and Griffin[57] photolysed an oxazirane to give an aryl nitrene and cyclohexanone, (Scheme 26), and trapped the nitrene as the azepine after ring expansion in diethylamine.



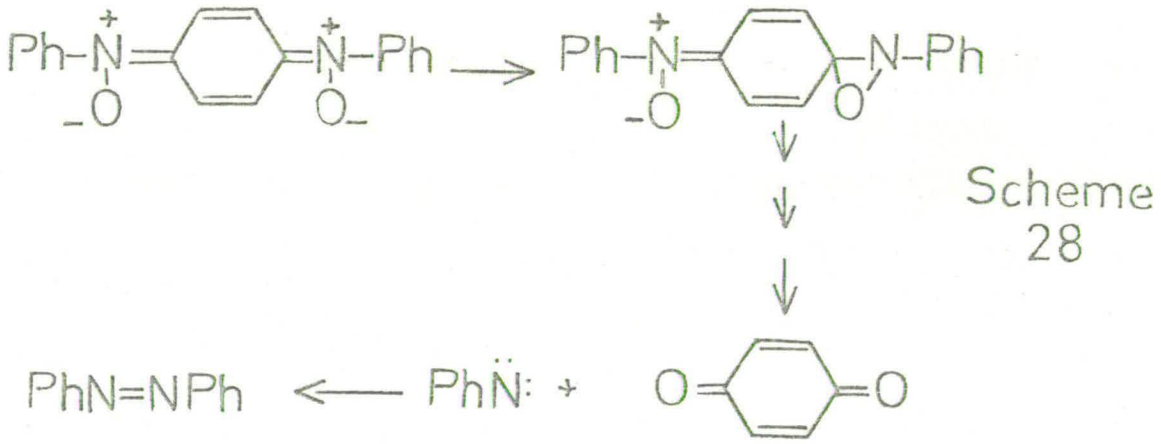
Scheme 26

Splitter and Calvin[58] looked at the e.p.r. spectrum of an aryl nitrene generated from phenyloxaziridine and found it identical to that obtained from phenyl azide by Smolinsky.[1] They conducted experiments which showed that intersystem crossing to the triplet state of oxaziridine was very fast and therefore the products isolated were amines and other triplet products. Even in diethylamine, which reacted rapidly with singlet nitrene to form 2-diethylamino-3H-azepine, (7), little of (7) was formed, and the main product was aniline (55%), (Scheme 27).



Scheme 27

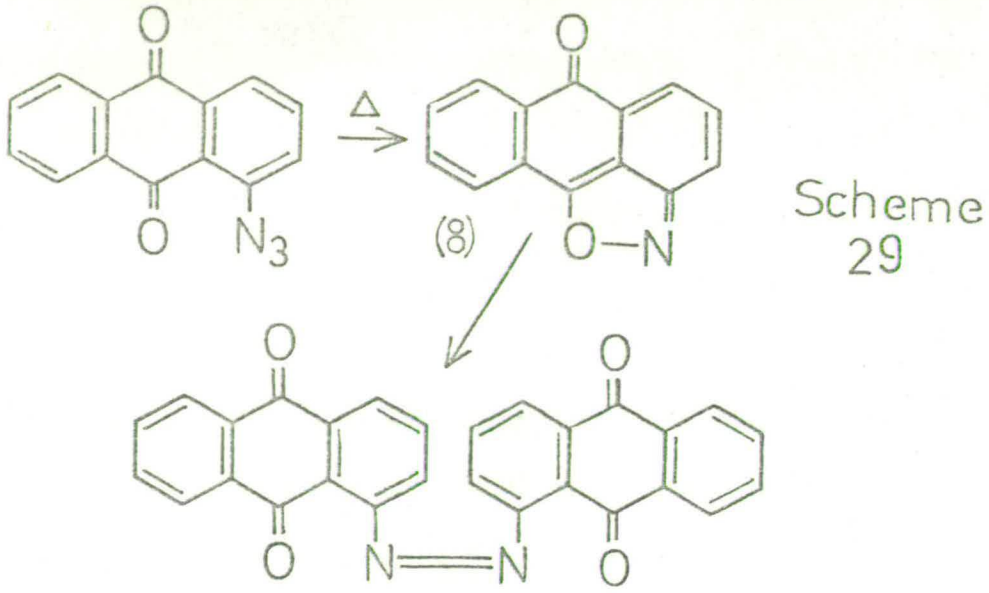
Pederson[59] generated phenyl nitrene by the photolysis of N, N'-diphenyl-p-quinonediimine-N, N'-dioxide, which proceeded through an oxaziridine and yielded azobenzene, (Scheme 28).



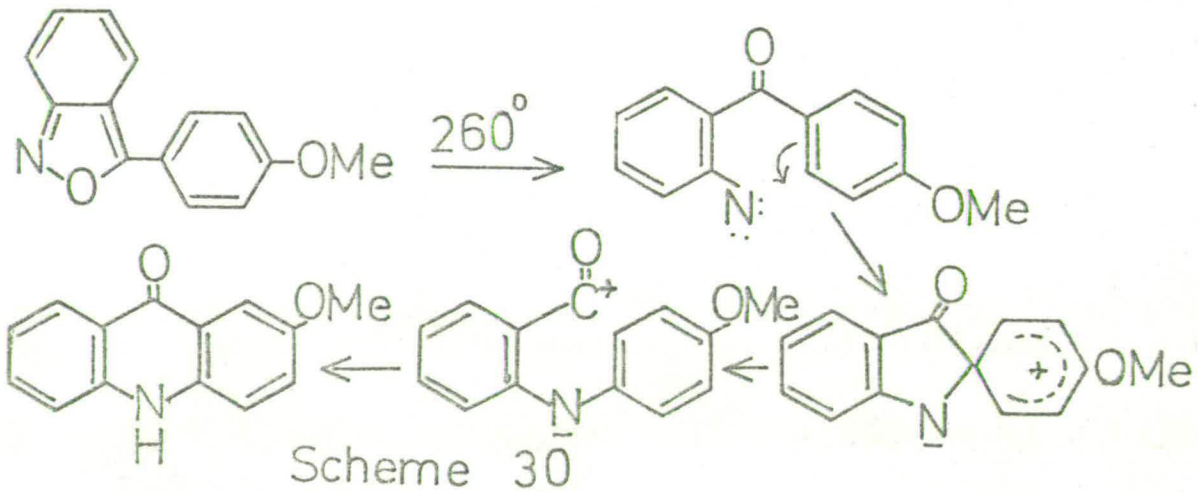
Scheme 28

One of the most recent ways to generate a nitrene is by the thermolysis or photolysis of anthranils, which was originally reported in the literature by Gatterman[69] when he observed the formation of anthranil, (8), from an azide, and the subsequent reaction to form azoanthraquinone, (Scheme 29).

Kwok and Pranc[70] thermolysed 4-substituted phenylanthranils, and found in the case of R=OMe a product which could only be explained by invoking a spiro intermediate, (Scheme 30), after nitrene formation.

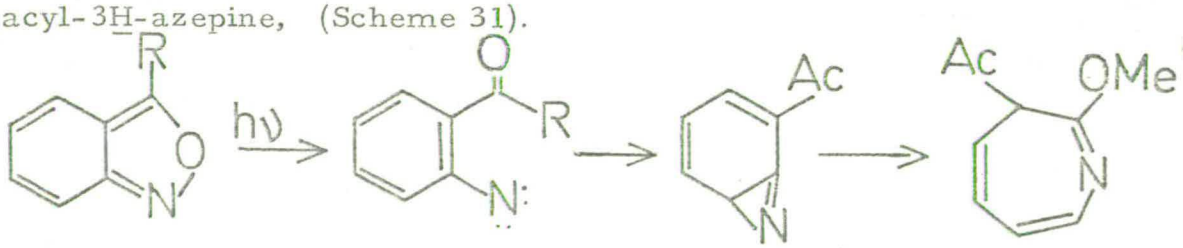


Scheme 29



Scheme 30

Further evidence for the formation of a nitrene in the photolysis of anthranils comes from Matsumoto[72a, b] who succeeded in trapping the nitrene after ring-expansion in methanol to give 2-methoxy-3-acyl-3H-azepine, (Scheme 31).

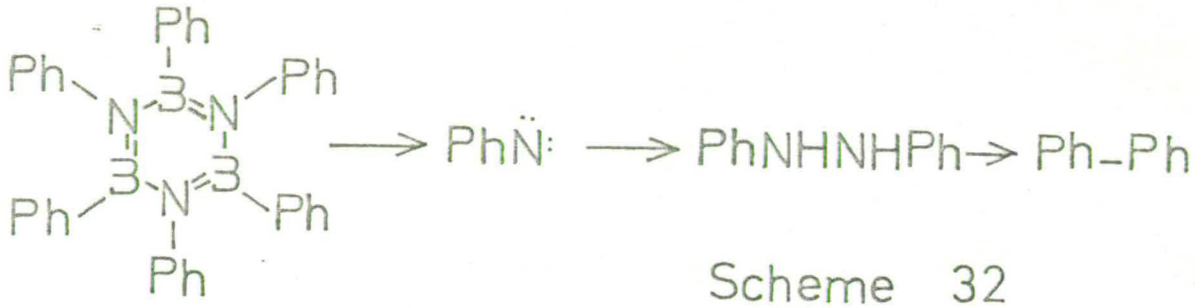


Scheme 31[73]

Crow and Wentrup[73] failed to generate phenyl nitrene from phenyl isocyanate, even at 700°.

Newsom[61] postulated that hexaphenylborazole heated to 450° broke down to give a phenyl nitrene which underwent a series of reactions

to give the hydrazobenzene and biphenyl as final products, (Scheme 32).

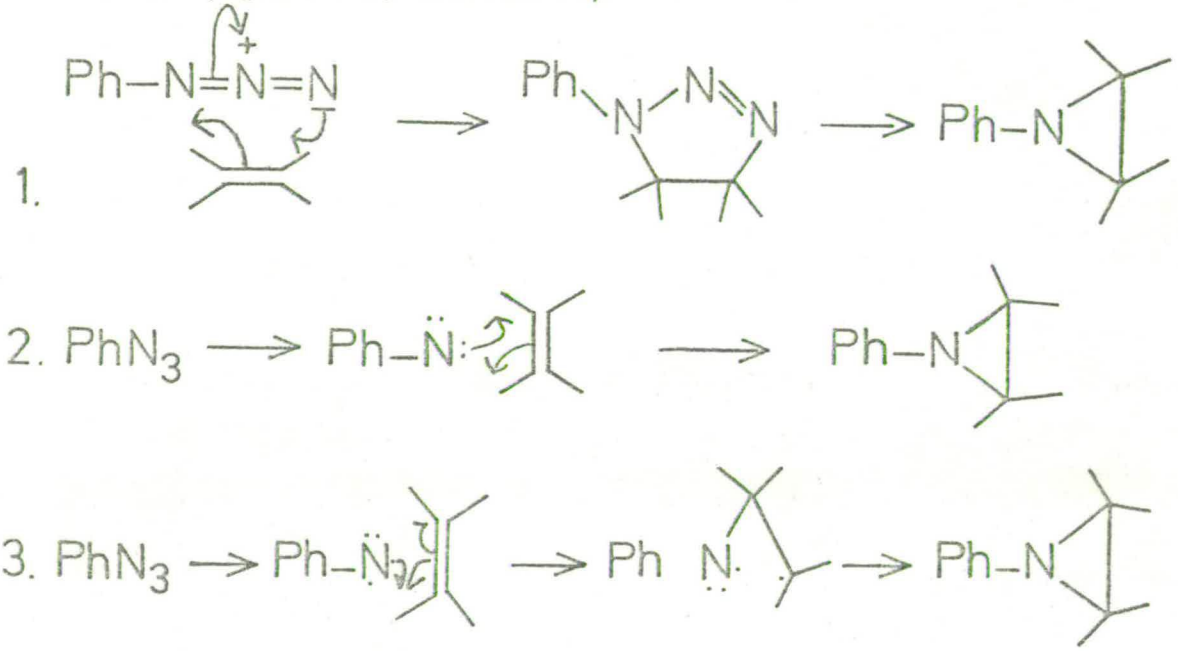


Scheme 32

B. REACTIONS OF NITRENES

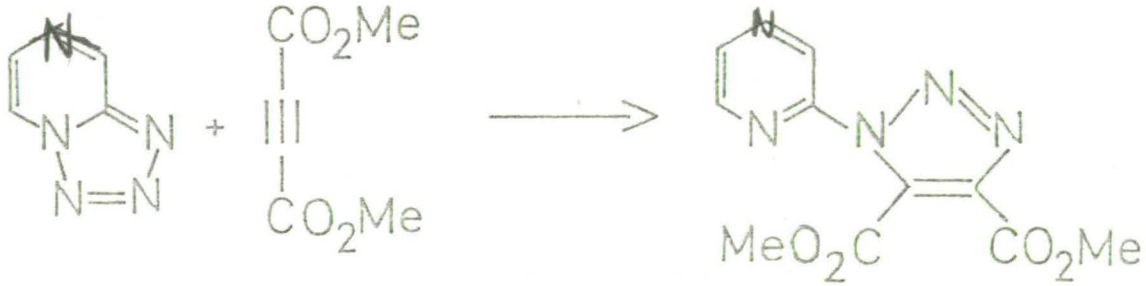
B.1 ADDITION TO A MULTIPLE BOND

Addition to a multiple bond has already been mentioned, where azides add intramolecularly to an o-group containing a double bond in a reaction which is probably concerted. Azides also add intermolecularly to double bonds, probably after concerted addition to form the triazole, followed by subsequent elimination of nitrogen to form the aziridine, (equation 1, Scheme 33).



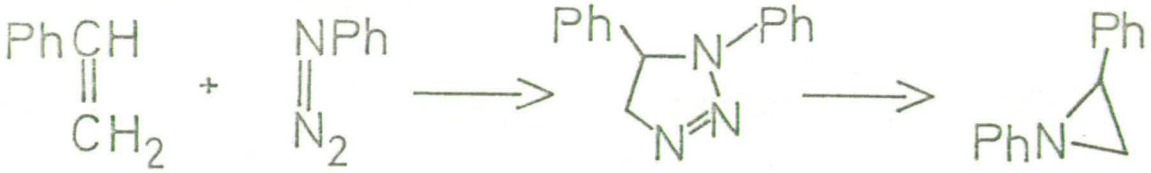
Scheme 33

The possibility of either singlet, (equation 2), or triplet, (equation 3, Scheme 33), aryl nitrene adding to an intermolecular double bond is considered unlikely because the addition products of a nitrene generated from a source other than the azide have never been isolated. The cyclic adduct from 2-pyrimidyl azide and dimethyl acetylenedicarboxylate is stable and isolable,[39a] (Scheme 34).



Scheme 34

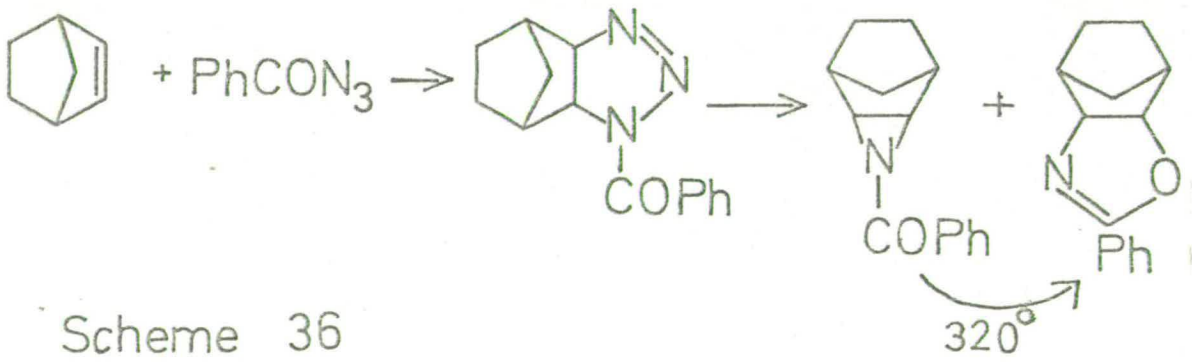
Wolff[74a, b] originally observed that phenyl azide would add to styrene to form 1, 5-diphenyl-4, 5-dihydro-1, 2, 3-triazole, (9), which, on heating to 130° lost nitrogen to form the 1, 2-diphenylaziridine, (10) (Scheme 35).



Scheme 35 (9) (10)

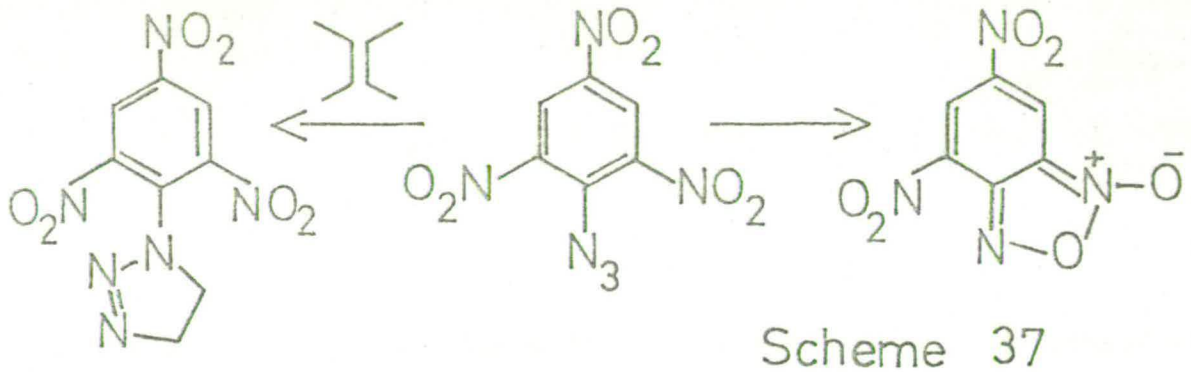
Alder and Stein[75] extended this reaction to a number of olefins, such as cyclopentadiene, dicyclopentadiene and dimethyl fumarate. Fusco[76] extended it to a general preparation of triazoles from aryl azides and enamines as dipolarophiles.

Huisgen[77a, b] has investigated extensively the 1, 3-dipolar concerted addition of aryl azides and others to olefins. He considered the process was concerted because increasing the polarity of the solvent decreased the reaction rate, implying a non-polar intermediate and no charge separation in the transition state. He has also shown[77b, c] that the triazole may lose nitrogen to form an aziridine, (Scheme 36).



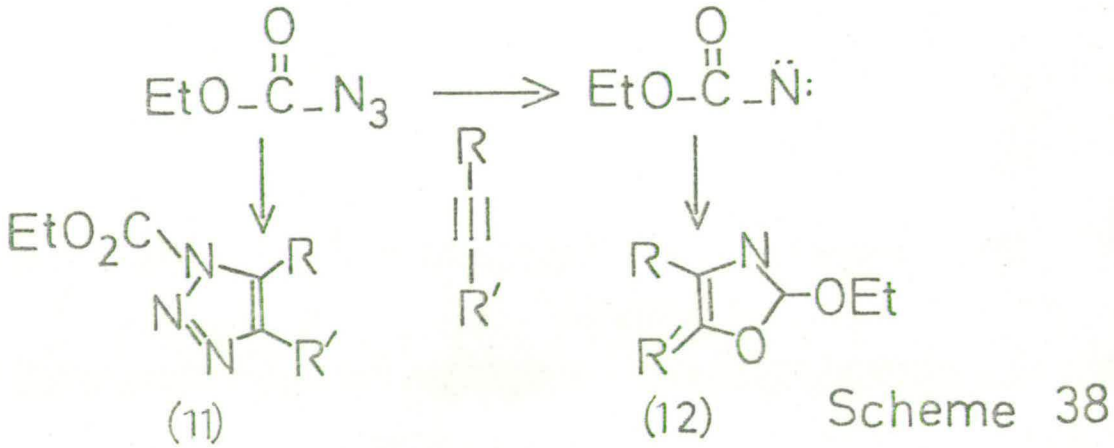
Scheme 36

Bailey and White[78] showed how facile the 1, 3-dipolar addition of an aryl azide to an olefin intermolecularly was by using picryl azide which would normally give a benzofuroxan in another facile concerted reaction, (Scheme 37).



Scheme 37

Huisgen[42] found that the adducts of both carbethoxy nitrene and its precursor ethyl azidoformate with acetylenes were stable and could be isolated from the reaction, implying that those apparently from the nitrene were indeed from the nitrene, (Scheme 38, Table 2).



(11) (12) Scheme 38

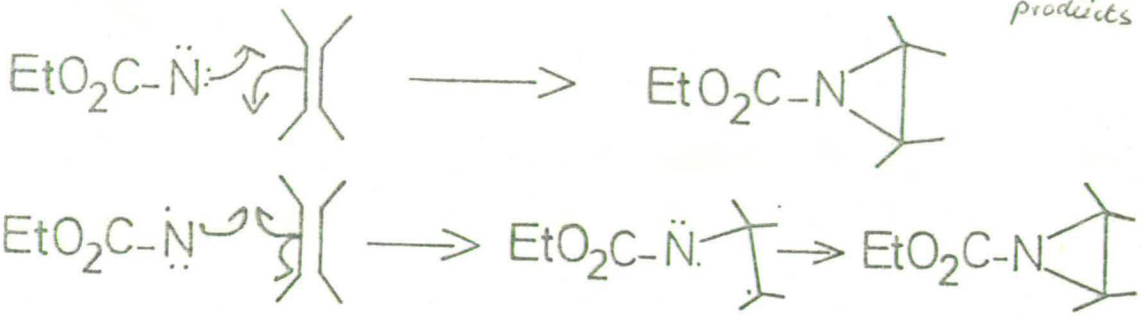
Table 2. Formation of adducts (11) and (12) from carbethoxy azide and nitrene with acetylenes

Acetylene :	R=R'=Ph	R=Ph, R'=CO_2Et	R=Ph, R'=H	R=R'=CO_2Me
Yield (11) :	-	-	16	23
Yield (12) :	33	32	16	3

Acetylene :	R=H, R'=CO_2Me
Yield (11) :	50
Yield (12) :	3

Lwowski encountered problems in distinguishing between the reactions of acyl azides and acyl nitrenes. He wanted to show whether carbethoxy nitrene was in a singlet or a triplet state by looking at its

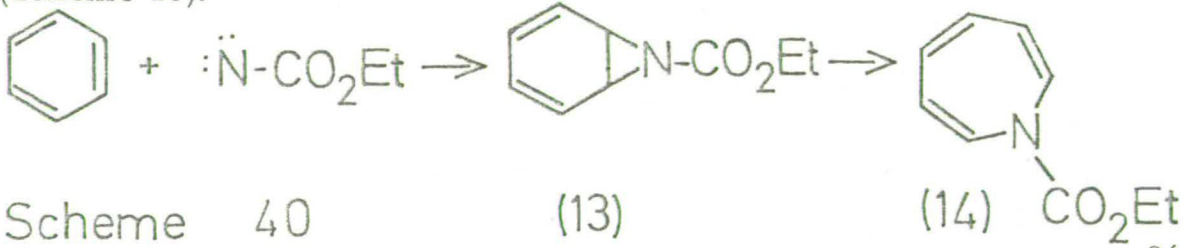
stereospecificity of addition to double bonds, because singlet addition ought to be a one-step process, and triplet, two step, (Scheme 39) which allows time for bond rotation to give non stereospecific products.



Scheme 39

He observed[82] that increasing dilution increased the ratio of non-stereospecific : stereospecific products, because more collisions with solvent molecules enhanced the probability of intersystem crossing; at 100% olefin concentration, complete stereospecificity was obtained, indicating both that the nitrene was originally in the singlet state and that it had a lifetime long enough to survive a number of collisions before meeting the olefin. He measured the rate of evolution of nitrogen[84] and found that it was the same as the rate of disappearance of azide, and concluded that reaction did not take place through a triazoline intermediate.

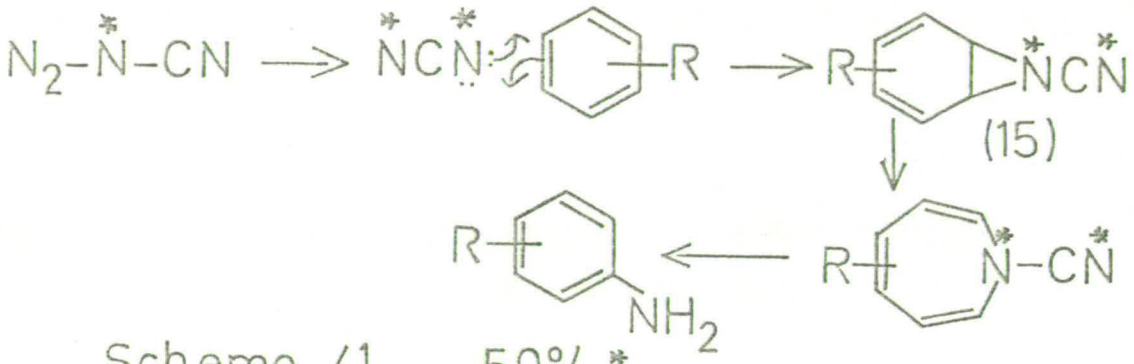
Carbethoxy nitrene also adds to aromatic double bonds intermolecularly,[106a,b] probably via the azabicyclo intermediate, (13), which then ring opens to form 1-carbethoxy-1H-azepine, (14), (Scheme 40).



Scheme 40 (13) (14)

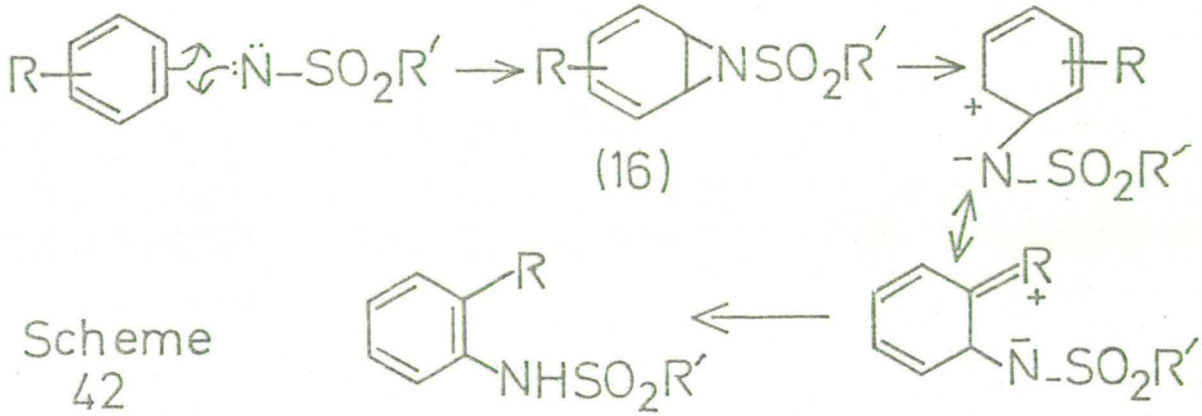
Cyano nitrene also adds to benzene to give an isolable azepine;[86] this has been shown by labelling experiments to involve a discrete nitrene, and probably intermediate (15), since there is a lack of discrimination in the position of substitution, equal amounts of all three azepines being formed, whether the substituent is F (o/p-directing)

or CF_3 (m-directing), which implies a transition state with little charge separation, (Scheme 41).



Scheme 41 50%*

Sulphonyl nitrene reacts readily with the π electron system of the benzene ring, for which a similar first step and intermediate (16), is postulated,[87a, b] but then instead of a ring expansion reaction to form an azepine, the three-membered ring opens to give products of apparent aromatic substitution, (Scheme 42).

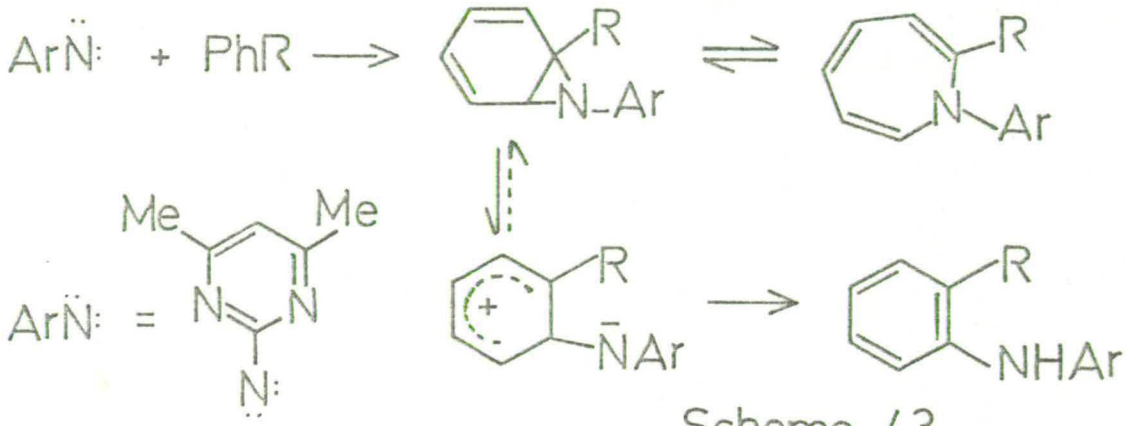


Scheme 42

The highly selective character of the sulphonyl nitrene was shown by Tilney-Bassett,[88] who examined the products of addition to anthracene. A radical reagent would result in substitution at position 9, but aryl sulphonyl nitrene attacked the theoretically strongest double bond, the 1, 2 bond, leading to substitution at position 1. Similarly Beckwith and Redmond[89] have used this reaction to distinguish between singlet and triplet carbethoxy nitrene.

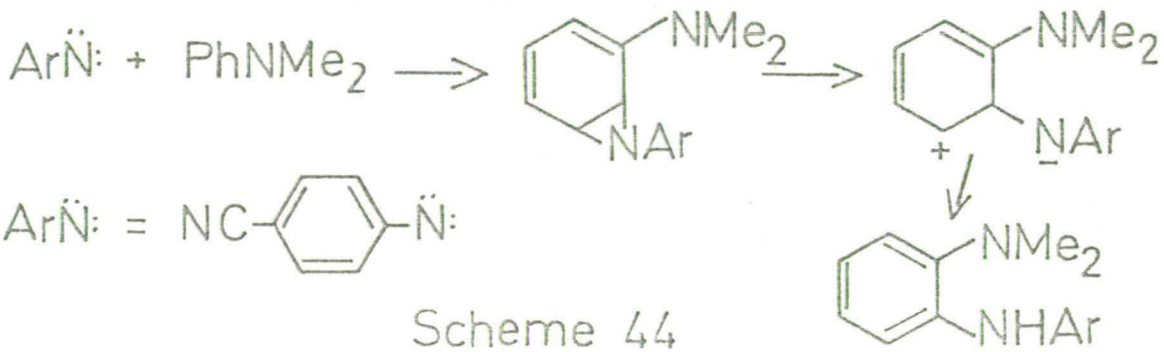
The aryl nitrene will only take part in such intermolecular reactions if suitably activated. Huisgen[90] looked at the reaction between the pyrimidyl nitrene, and substituted benzenes, where the substituents were electron donating, and showed that yields of pyrimid-aminobenzenes increased with increasing activation: with anisole,

a 14% yield, with dimethoxybenzene, a 46%, and trimethoxybenzene, a 50% yield. In reaction with anthracene, although there is much substitution in the 9-position expected of radical behaviour (20%), there is also some substitution in the 1- and 2-positions (19%). This opens the possibility of a reaction mechanism whose first step involved addition to the $\tilde{\pi}$ system, (Scheme 43).



Scheme 43

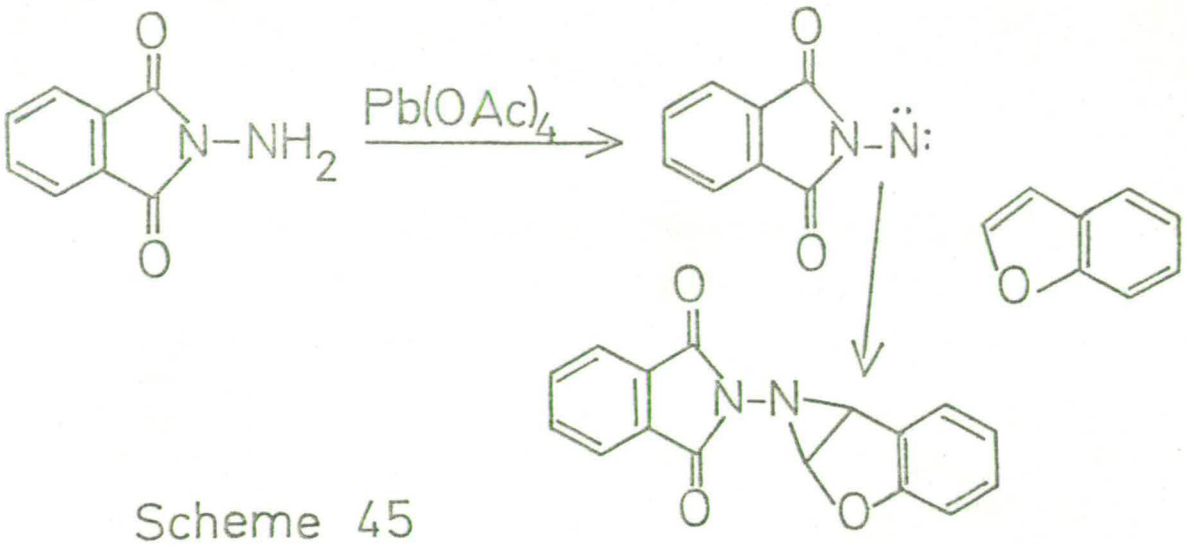
Support for this comes from Abramovitch, Challand, Scriven,[91] who showed that to achieve intermolecular aromatic substitution, the electrophilic character of the nitrene must be increased by the introduction of electron withdrawing groups, e.g. o- and p-cyano, nitro and trifluoromethyl, and the use of activated substrates, e.g. trimethoxybenzene; (they found that anisole was not sufficiently activated). They generated the nitrenes from both nitrosobenzenes and aryl azides, and obtained the highest yield with N,N-dimethylaniline (28.5%), (Scheme 44).



Scheme 44

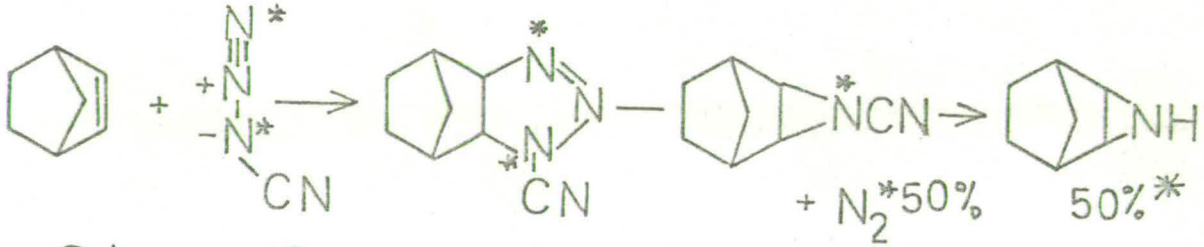
An electron deficient nitrene, such as N-phthalimido nitrene, generated by the oxidation of the amine with lead tetraacetate, is

reported by Jones[92] to add intermolecularly to electron rich double bonds, such as benzofuran, (Scheme 45).



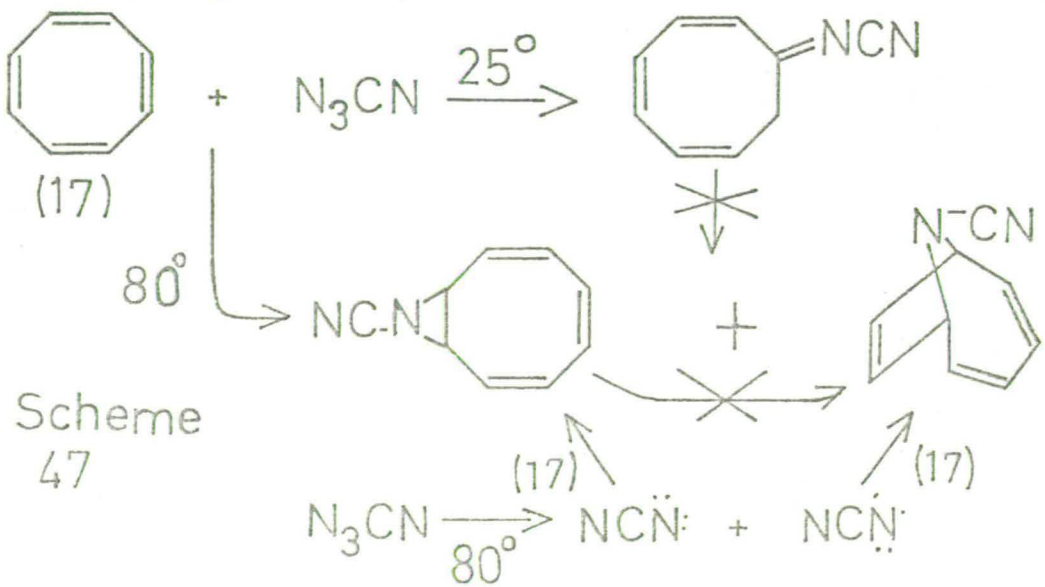
Scheme 45

Anastassiou[93] has shown that cyanogen azide adds in a concerted manner to norbornene before it can decompose to the nitrene, in experiments involving the labelling of the azide, in which the label was incorporated in the final product, (Scheme 46).



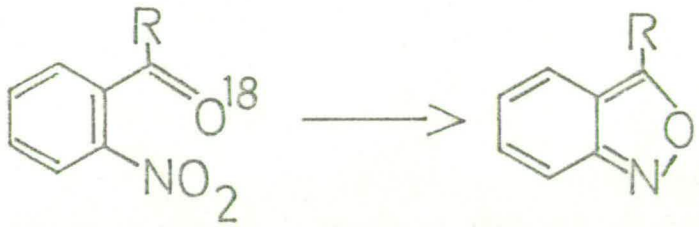
Scheme 46

Addition by the nitrene itself may also occur, as shown by the different and non-interconvertible products obtained under different reaction conditions,[94] (Scheme 47).



Scheme 47

The only reasonable possibility of an intermolecular addition reaction of an aryl nitrene other than to activate aromatic substrates, is reported by Bennett and Hardy[95] who formed an isocyanate by addition of phenyl nitrene to carbon monoxide at 136 atmospheres and 180°. There are, however, many intramolecular reactions which may be attributed to the nitrenes themselves, unlike those such as the formation of benzofurans, indoles, indazoles, benzimidazole and benzoxazoles which have already been mentioned, in connection with the azide. Such reactions from nitro and nitroso compounds as precursors also proceed in high yield, and are probably concerted. It has been shown by a labelling experiment[96] that the reduction of 2-nitrobenzaldehyde with the O^{18} label in the carbonyl group gave the anthranil without excess O^{18}, indicating that the O came from the nitro group (Scheme 48).



Scheme 48



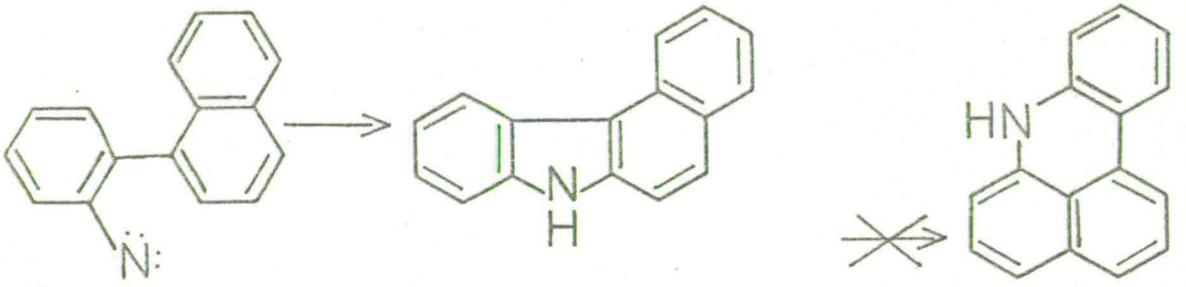
Scheme 49

Reactions such as Scheme 49 can be considered to have been concerted whenever the rate of reaction is enhanced cf. similar substituents in m- and p-positions. Those which may involve a discrete nitrene are those in which X=Y is part of another aromatic ring.

The first addition of this kind which proceeded under reaction conditions (e.g. temperature) similar to those known to produce nitrenes was the formation of carbazole from the thermolysis[26a, 29] and photolysis[47a, b] of o-azidobiphenyl, which has been shown to proceed through the singlet state and the reduction of o-nitrobiphenyl with ferrous oxide[63a] and o-nitro-[51] and o-nitrosobiphenyl[50] with triethyl phosphite. The use of this reaction in establishing that a

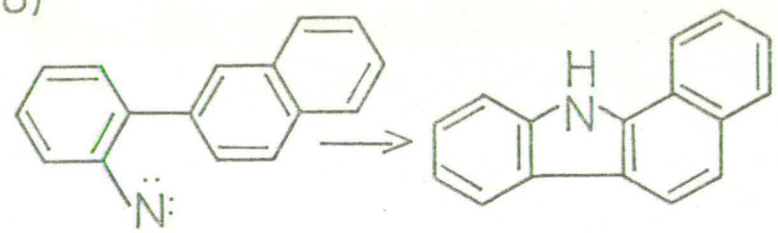
discrete, singlet nitrene exists has already been described. Furthermore, Cadogan and Todd[97] intercepted some of the nitrene as 2-diethylamino-3H-azepine by performing the reaction in diethylamine: this constitutes good evidence that reaction involves a singlet nitrene, and is not concerted.

One of the most interesting features of the reaction involving intramolecular insertion of a nitrene in a C-H bond is its selectivity, of which examples are given in equations 1-9, Scheme 50, with references given in parenthesis.

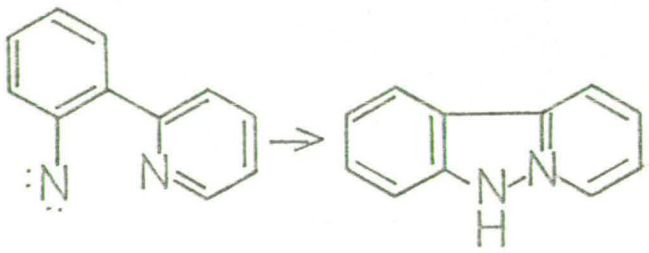


1. $-NO_2$, $(EtO)_3P$ (53)

2. $-N_3$, Δ (38)

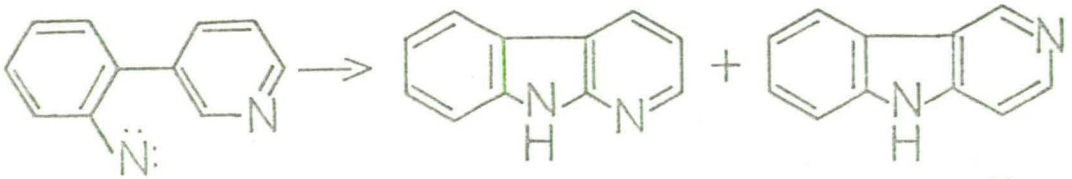


3. $-N_3$, Δ (29)



4. $-NO_2$, $(EtO)_3P$ (53)

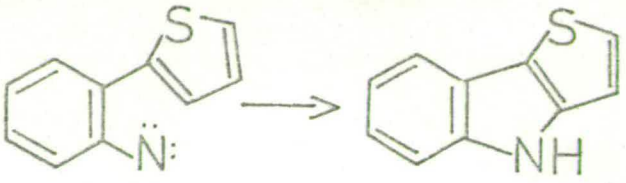
5. $-NO_2$, $(-CO_2)_2Fe$ (63)



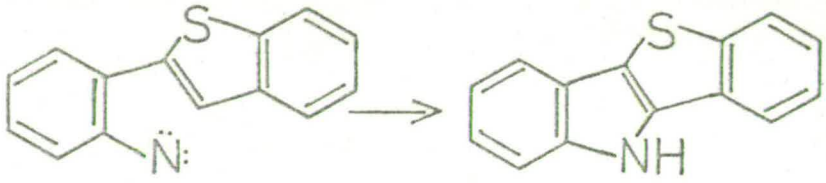
70% 30%

6. $-N_3$, Δ (26b)

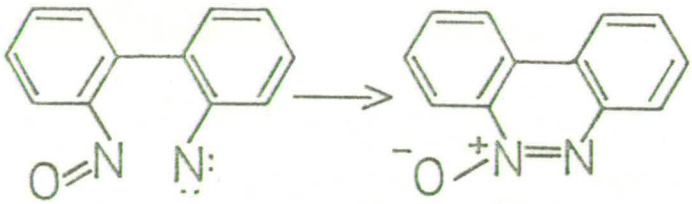
7. - N_3, Δ (26b)



8. - NO_2, $(EtO)_3P$ (98)



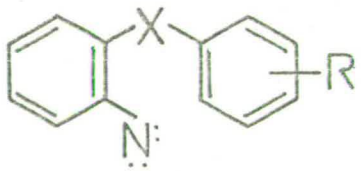
9. - N_3, hν (99)



Scheme 50

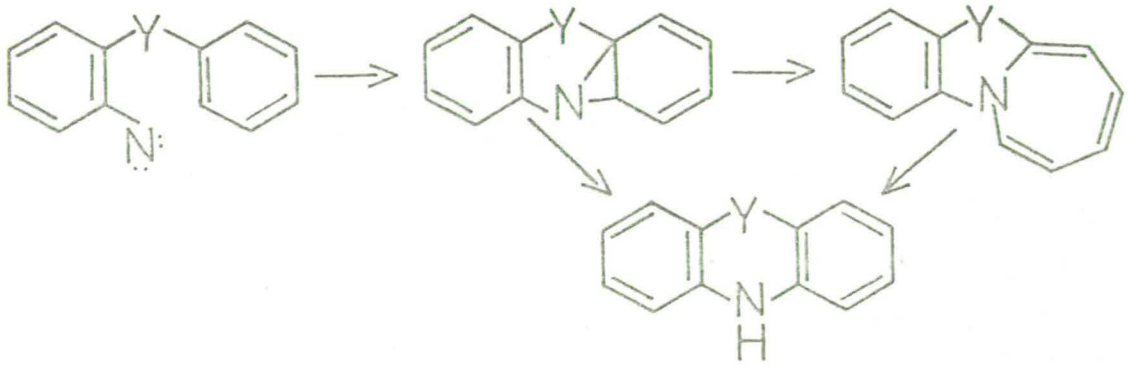
The close similarity of these results, whatever the method of generating the nitrene, and its strong preference for the most electron rich double bond indicate the existence of singlet nitrene.

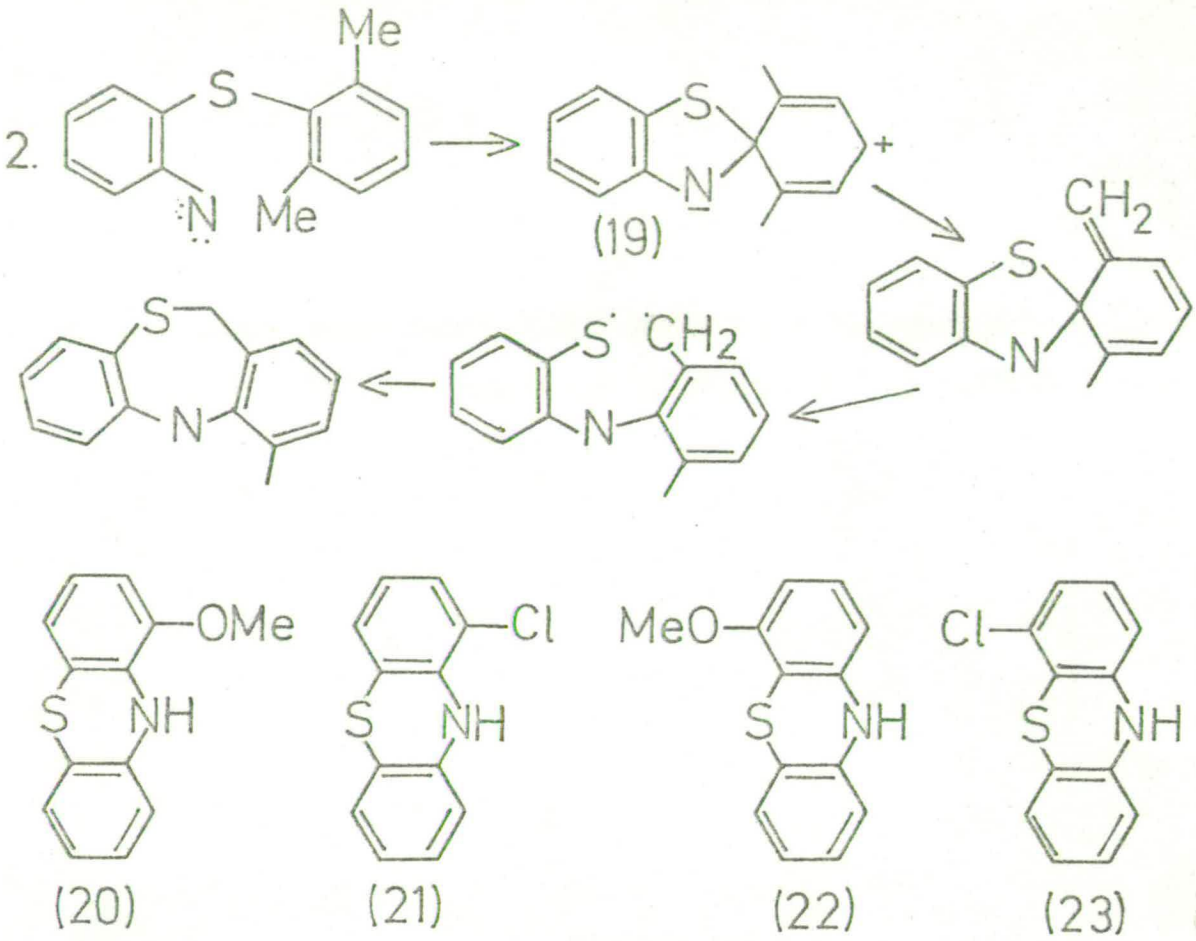
A further group of experiments has been carried out on the bridged structures, (18), in an effort to elucidate the mechanism. The rearrangements where X=S, C=O have already been mentioned. Abromovitch[100] proposed that azepines might be intermediates in attack by the nitrene on other benzene rings, (equation 1, Scheme 51). Cadogan and Kulik[101] showed conclusively that reaction must be through the spiro intermediate, (19), by blocking the ortho positions, and thus forcing the reaction to follow a different path, (equation 2, Scheme 51).



(18)

1.





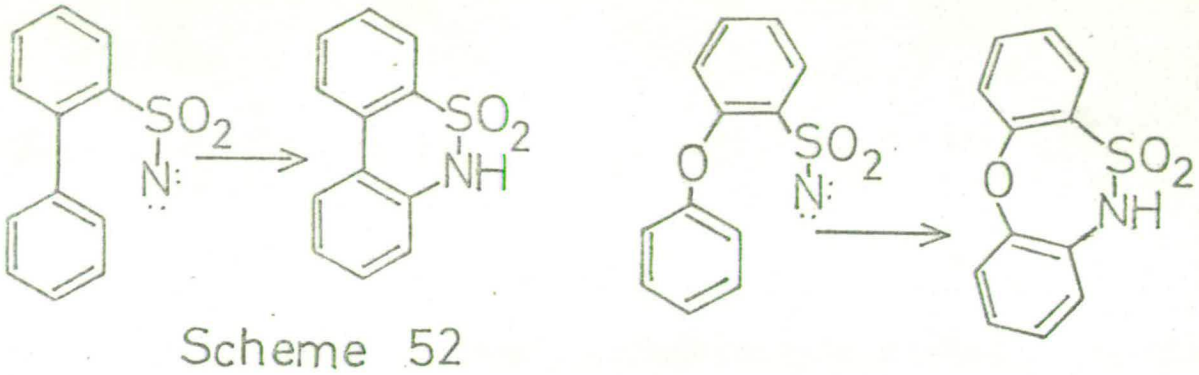
(20) (21) (22) (23)

Scheme 51

Where the blocking groups are methoxy or chloro, which can also act as leaving groups, (20) and (21) are formed, not (22) and (23), which would be expected if the nitrene did not form a spiro intermediate.

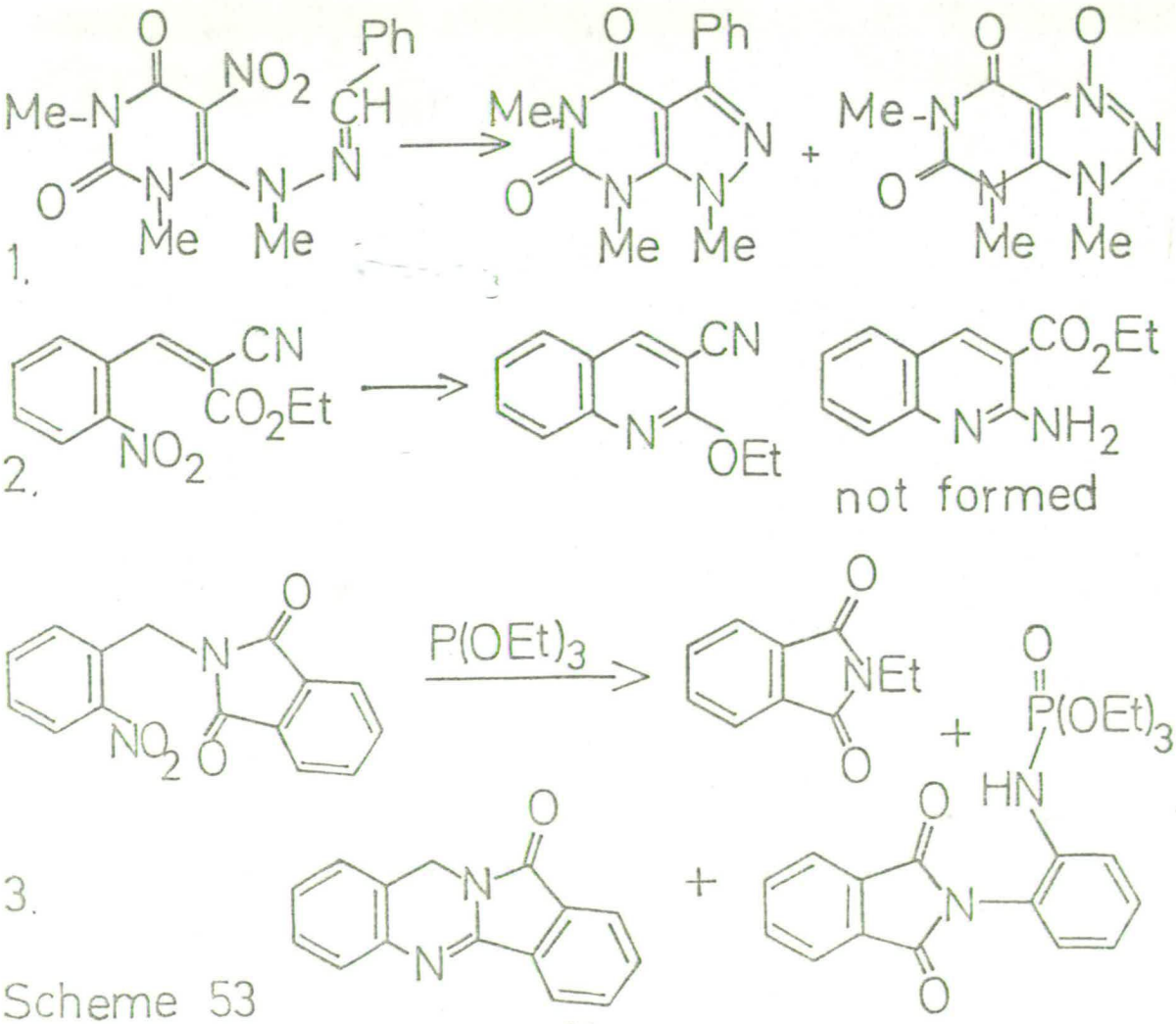
Experiments with (18), X=O, NAc have normally yielded tars; Smith found that the only exception was $X=SO_2$. Cadogan and Lim[102] isolated rearranged products from the "blocked ortho" reaction of 2-azidophenyl 2, 6-dimethoxyphenyl ether, which gave 4-methoxyphenoxazine and 1, 2-dimethoxyphenoxazine. Recently, the phosphite-nitro reaction has been extended[103] to (18), N-Ac, bridged compounds, to form compounds such as 1-methylthio-5-acetyl-5, 10-dihydrophenazine, and to (18), $X=CH_2$, the methylene bridged species[104a, b] to form 10H-azepino[1, 2-a]indoles.

Sulphonyl nitrene is reported to undergo a similar reaction,[105] (Scheme 52).



Scheme 52

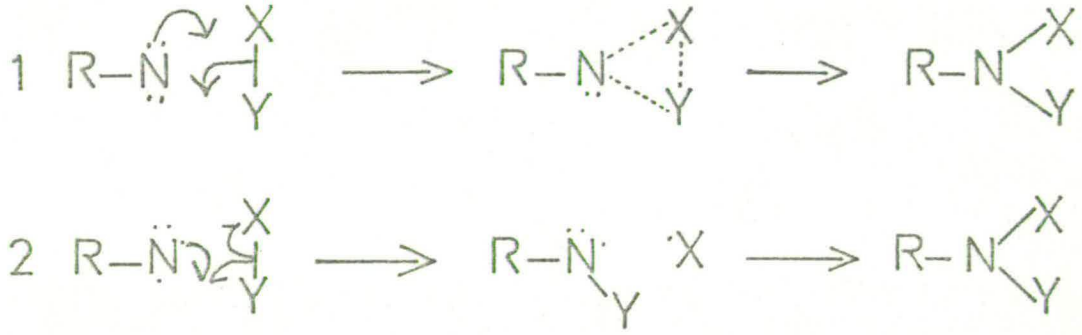
Suzuki[107] postulated that an electron deficient aryl nitrene was involved in an intramolecular addition to a non-aromatic double bond, (equation 1, Scheme 53), but this could be explained better by a concerted mechanism, since the nitrogen in the final product is not completely deoxygenated. Similarly a nitrene may or may not be involved in a reaction reported by Takano,[108] where a C=O bond is attacked in preference to the more nucleophilic C≡N bond; this may also be concerted, (equation 2, Scheme 53). In equation 3, however, the formation of phosphoramidate indicates a route involving a nitrene, and therefore the other products may also arise from a nitrene and not via a concerted mechanism.



Scheme 53

B.2 INSERTION IN A SINGLE BOND

There are many examples of insertion reactions by nitrenes. Two mechanisms may be postulated. The first would involve a singlet nitrene and a one-step insertion process with retention of stereochemical configuration, (equation 1, Scheme 53). The second would involve a triplet nitrene and a two-step, radical process where the recombination of the radicals could be sufficiently slow to allow time for racemisation, if the reagent was optically active. The degree of racemisation in a product molecule could then indicate the extent to which triplet nitrene had been formed, (equation 2, Scheme 53).



Scheme 53

This reaction has been investigated with respect to many types of nitrene, and many different X-Y, e.g. alkyl C-H, aryl C-C alkyl, N-H, O-H, both inter- and intramolecular.

Carbethoxy nitrene is well known to undergo intermolecular insertion reactions into molecules such as cyclohexane; in the reaction involving addition to cyclohexene, some insertion in the C-H bonds occurs as a side-reaction. Many experiments have been conducted to determine the singlet or triplet nature of the reacting species. It has been shown[12] that nitrenes from different sources exist in different proportions of singlet to triplet. The products of photolysis of ethyl azidoformate with and without the presence of triplet sensitisers and of N-carbethoxyiminodimethyl sulphurane, (24), may be identified as products of the singlet or the triplet nitrene, from the sensitised experiments, and investigation of the products from (24) revealed that the nitrene from (24) contained much triplet character. In cyclohexane,

unsensitised azide decomposition yielded 54% insertion products, while (24) yielded only 21% this could imply that the insertion reaction is by singlet nitrene. McConaghy and Lwowski[82] also reported that cyclohexane reacted with singlet but not triplet carbethoxy nitrene, and that by using cyclohexane as solvent, they obtained an increased yield of non-stereospecific addition products. Further evidence of this comes from Breslow and Edwards[43, 109a, b] who found that they could stabilise the singlet nitrene and thus increase the yield of insertion product by the presence of various additives, such as m-dinitrobenzene, sulphur, hydroquinone and hexafluorobenzene, whose action could be explained either by considering them as radical traps or as species which complexed with the singlet nitrene in some way to give a nitrenoid species, still active enough to insert in C-H bonds.

Lwowski[110a, b, c] reported stabilisation by dichloromethane leading to increased yields of insertion in cyclohexane. He has observed that the data for insertion reactions correlate better with hydrogen abstraction by butoxy radicals than with solvolytic reactivity, which implies that in the transition state leading to insertion products, there is little or no positive charge on the carbon atom. This is supported by the fact that insertion in bridgehead C-H bonds takes place readily, e.g. in norbornane. There is only a small isotope effect, $k_H/k_D = 1.3$, which implies direct insertion with retention of configuration, which was also found whatever the concentration and method of generating the nitrene, which implies that only singlet carbethoxy nitrene inserts in unactivated C-H bonds. Anastassiou[111] has noted that triplet carbethoxy nitrenes will insert in activated C-H bonds, e.g. at a tertiary carbon atom, in a non-stereospecific manner. The effect of dilution has been demonstrated by Lwowski[112] who showed that in cyclohexene, where both singlet and triplet nitrene add to substrate, but only singlet inserts, decreasing the concentration of substrate decreased the proportion of insertion reaction. Lwowski[113] concluded that in the absence of a suitable reactant, singlet carbethoxy nitrene crosses to the triplet state, where it may add to double bonds,

abstract hydrogen, or in the gas phase, where these are unavailable, dissociate to give ethoxy and isocyanate radicals.

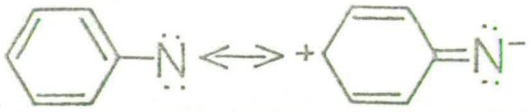
Some estimation of the energy of the triplet state is deduced from the fact that acetone [E_T = 73.6 kcal/mole] but not benzophenone [E_T = 68.5 kcal/mole] sensitises the photolysis of ethyl azidoformate. Beckwith and Redmond[89] have studied the temperature dependence of the singlet-triplet crossing of carbethoxy nitrene, using its reactions with anthracene and the but-2-enes, and found that the intersystem crossing rate increased with increasing temperature: a function of the greater number of collisions.

There is also the possibility that the singlet state may be a diradical with spins parallel, and no empty orbitals, and this would explain the failure to undergo Curtius rearrangement.

Sulphonyl nitrenes, both aryl and alkyl, are reported to undergo insertion in the C-H bonds of saturated hydrocarbons, e.g. cyclohexane, and to exhibit a preference for tertiary C-H. Cyano nitrene inserted in cyclohexane,[93] and it has been shown by labelling experiments that the mechanism involved the discrete nitrene. Insertion by cyanonitrene has been shown to occur with both singlet and triplet species,[114] because insertion in cis and trans 1, 2-dimethylcyclohexanes showed complete stereospecificity, implying a singlet species, until the reaction mixture was diluted with solvents such as ethyl acetate and dichloromethane, when partly stereospecific products were obtained. Photolysis has been shown to give stereospecific products until a triplet sensitiser was used, when stereorandom products were obtained.

Carbethoxy nitrene[110a, b, c] inserted in the C-H bonds of 2-methylbutane in the order 3ry: 2ry : 1ry = 34 : 9 : 1 for a nitrene generated from the azide and 27 : 11 : 1 for the nitrene from p-nitrophenylsulphonoxyurethane. The selectivity for cyano nitrene was reported as 3ry : 2 ry : 1 ry = 67 : 15] 9 : 1.[114] This can be compared with the value for phenyl nitrene found by Hall, Hill and Hu-chic Tsai[115] who found values of 3ry : 2ry : 1 r = 150-300 : 7 : 1, and in n-pentane, 2ry : 1ry = 100 : 1; they explained this much greater selectivity,

implying a longer life-time and lower energy, of phenyl nitrene over carbethoxy and cyano nitrenes by invoking the contribution of structures such as (25) and (26), although the actual yield of insertion products is much smaller, 8% cf. > 50%.

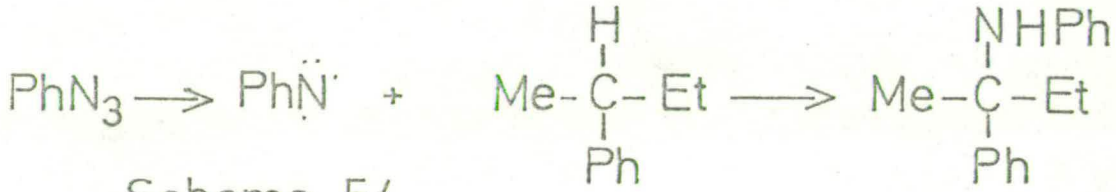


(25)



(26)

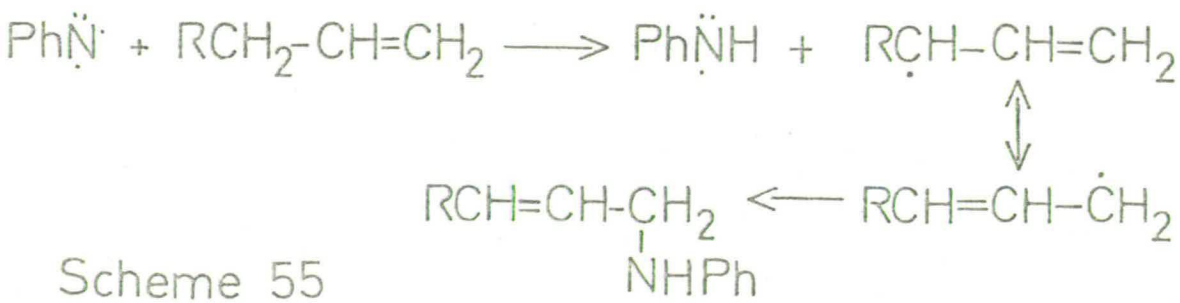
Hall, Hill and Fargher[116] considered that the insertion of phenyl nitrene was by a triplet species, because they found that the ratio of amine, a known triplet product, to insertion product was the same at all dilutions, but found that insertion in optically active species proceeded with only partial racemisation (Scheme 54) and explained the partial activity by saying that coupling with R· must be rapid, and the reaction did not just involve a combination of long-lived radicals, possibly involving a solvent cage.



Scheme 54

There was also a high isotope effect for phenyl nitrene, $k_H/k_D = 4.15$, in the insertion in 2-deutero-2-methylpropane, which implied that the C-H bond broke before the N-C bond formed: a two-step process and a triplet species.

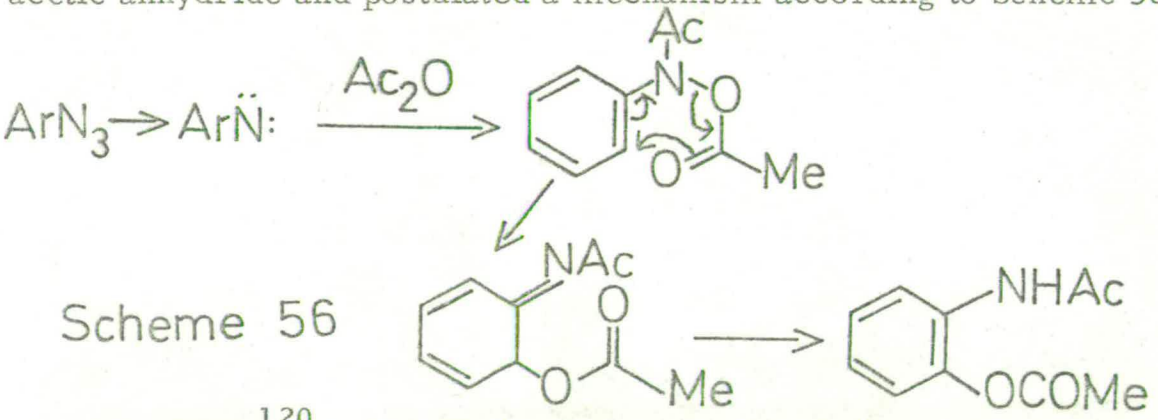
Abramovitch[63a] also considered that insertion in C-H bonds was by a triplet species. He generated phenyl nitrene by the deoxygenation of nitrobenzene with ferrous oxalate, and showed that it inserted in 1-hexadecene to form N-hexadec-2-enylaniline, which he explained by Scheme 55.



Scheme 55

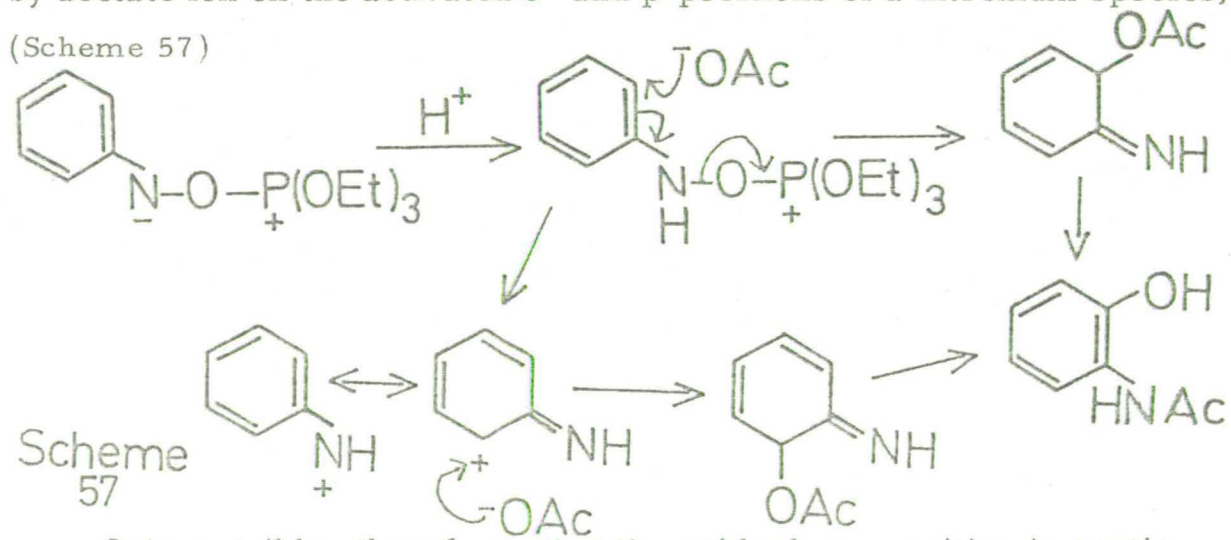
Aryl nitrenes are reported to insert into bonds other than C-H. Suschitzky[117] gave an account of the insertion of p-tolyl nitrene in the C-F bond of perfluoronaphthalene (3.9%), and considered that, since it was quenched by air, it was a reaction of the triplet nitrene, and did not involve addition to the π electron system.

Another type of apparent intermolecular insertion of aryl nitrenes involves reactions with acetic acid and acetic anhydride. Horner[118] found small quantities of 4-acetimidophenyl acetate from the photolysis of phenyl azide in acetic acid, but no insertion product from 4-biphenyl azide in acetic anhydride. Smalley and Suschitzky[119] obtained a low yield of 2-acetimidophenyl acetate from thermolysis of phenyl azide in acetic anhydride and postulated a mechanism according to Scheme 56.



Scheme 56

Sundberg[120] looked at the deoxygenation of nitro- and nitroso-benzenes by triethyl phosphite in the presence of acetic acid and found the normal course of the reaction changed, and obtained products such as 2-acetimidophenol; he postulated a mechanism which involved attack by acetate ion on the activated o- and p-positions of a nitrenium species, (Scheme 57)

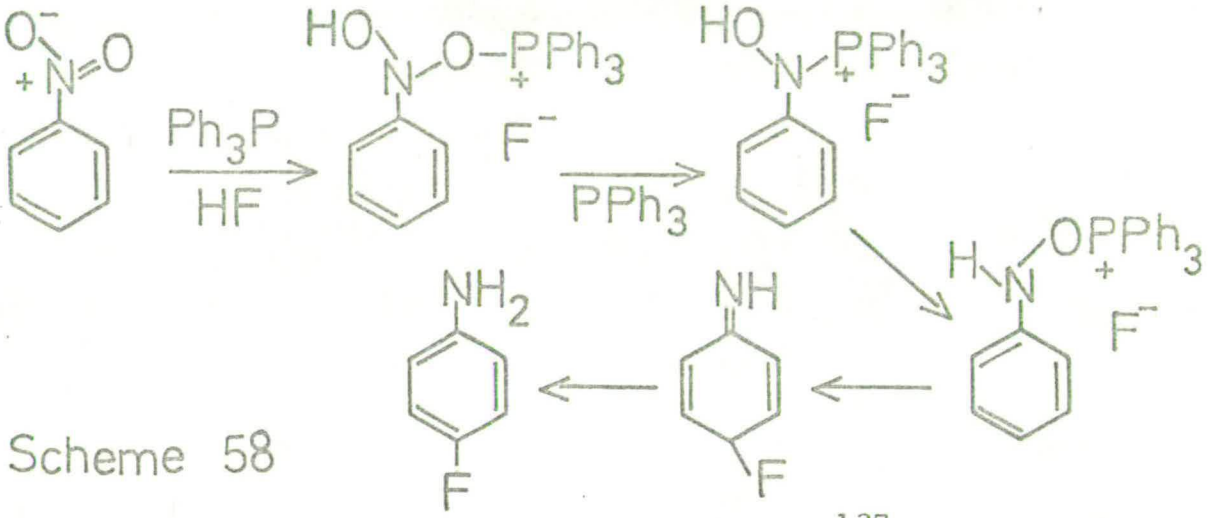


Scheme 57

It is possible, therefore, that the azide decomposition in acetic acid also proceeds through a nitrenium intermediate after protonation

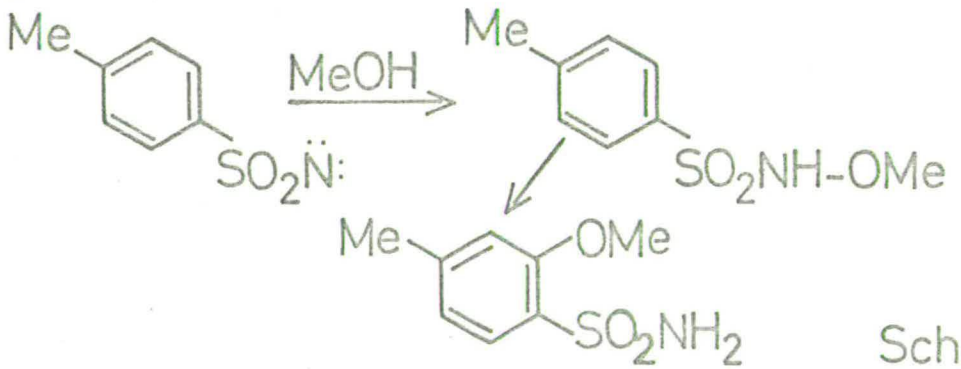
$C \diagdown N^{+} \diagup C$ by Edwards,[122] both of which undergo insertion in C-H bonds.

Scott, Smith, Kober and Churchill[123] also worked in a strongly acidic medium, they used HF, and isolated products resulting from substitution by F^- in the benzene ring, for which they postulated a mechanism according to Scheme 58.



Scheme 58

There is a report by Horner and Christmann[127] that p-tolyl-sulphonyl nitrene, generated from the azide, inserted in the O-H bond of methanol to form as main product N-(p-tolylsulphonyl)-O-methylhydroxylamine, and as a minor product 3-methoxy-4-sulphon-amidotoluene, (Scheme 59). These products may also be explained satisfactorily by invoking the protonation of the nitrene or the nitrene precursor.



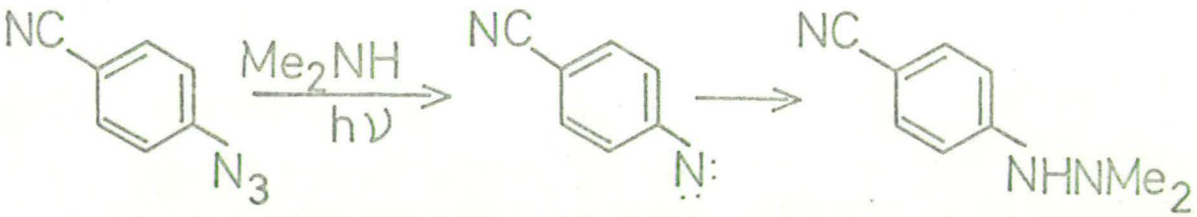
Scheme 59

Further intermolecular reactions involve insertion in N-H bonds. Carbethoxy nitrene from ethyl azidoformate inserts in the N-H bond of an N-alkyl aniline in preference to adding to the benzene ring, normally a facile reaction.[124] This is depicted in Scheme 60.



Scheme 60

The only aryl nitrenes reported to undergo such reactions are highly activated by electron withdrawing groups. Odum and Aaronson[48] reported that p-cyanophenyl nitrene inserted in the N-H bond of dimethylamine, (Scheme 61). Their explanation involved the fact that the highly electronegative cyano group would destabilise contributions from species such as (27), to give a more electrophilic nitrene. The normal product of an aryl nitrene and dimethylamine is a 2-diethylamino-3H-azepine.

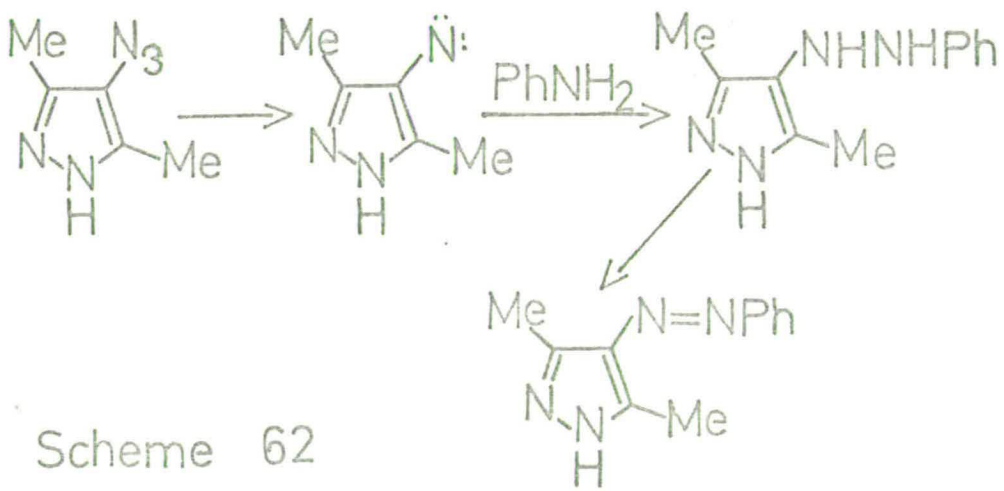


Scheme 61



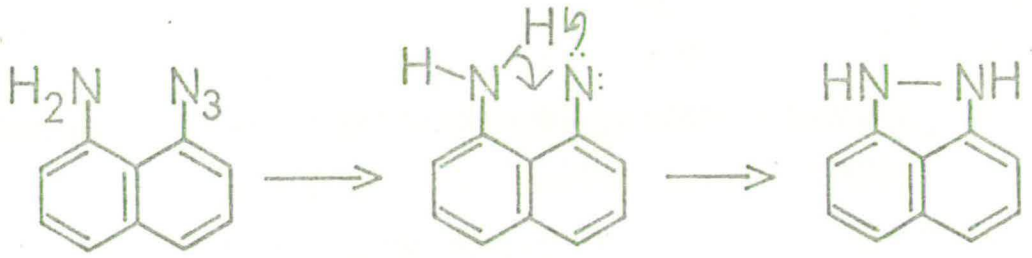
(27)

Smith and Dounchis[125] reported a N-H intermolecular insertion reaction by a highly activated aryl nitrene to form initially a hydrazo compound, which is then oxidised to the corresponding azo compound, (Scheme 62)



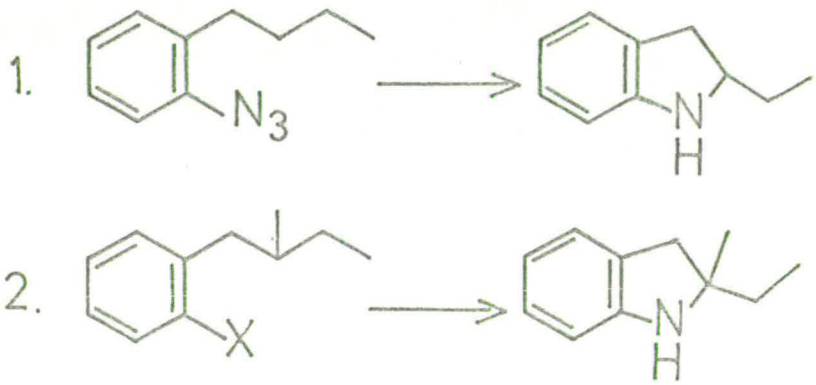
Scheme 62

Rees and co-workers[126] reported an intramolecular insertion reaction of an aryl nitrene and a N-H bond. They found the conditions critical: only vapour phase pyrolysis at 300° was successful. They postulated a nitrene as in Scheme 63.



Scheme 63

There are many reported examples of intramolecular insertion by nitrenes. Smolinsky[128] found that aryl nitrenes inserted preferentially in the C-H bond of the second carbon atom of a side chain ortho to the nitrene, to form a five membered ring, (equation 1, Scheme 64), and showed further[129a, b] that where the centre attacked was optically active, there was some retention of optical purity, and that there was more stereospecificity in the vapour phase, since in solution collisional deactivation and intersystem crossing was enhanced, (equation 2, Scheme 64).



Scheme 64

$X = N_3$ 65% optical purity

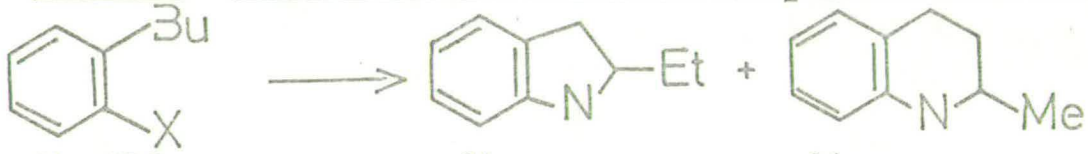
$= NO_2$ 50% " "

Edwards noted that in the intramolecular insertion reactions of alkanoyl azides, δ lactams rather than γ lactams were produced, which implied direct insertion by singlet nitrene, via a six membered transition state. Cyclisation for $R\text{-}CH_2\text{-}CO\text{-}\ddot{N}:$ was favoured as

soon as the chain attached to the carbonyl group had three or four members.

Sundberg[130a, b] on the other hand found both five membered and six membered rings from vapour phase pyrolysis and solution pyrolysis of aryl azides and from the deoxygenation of nitrobenzenes by triethyl phosphite, (table III), although from o-propylphenyl nitrenes, which offer the alternatives of secondary or primary C-H bonds to form five or six membered rings respectively, he found only the five membered ring, 2-methyl-2, 3-dihydroindole, 43% from deoxygenation reaction and 39% from azide solution pyrolysis.

Table III Products of cyclisation from an o-alkyl aryl nitrene



X =		
NO_2	31	14
N_3 vapour phase	47	15
N_3 solution	37	10

Smalley and Suschitzky[131] have extended this reaction in the formation of more elaborate heterocyclic systems, (Scheme 65).

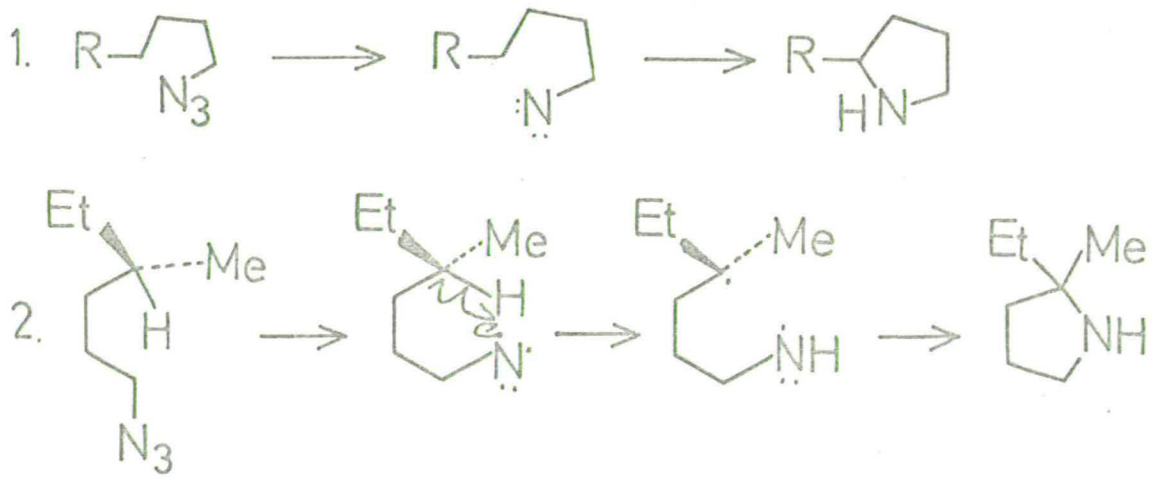


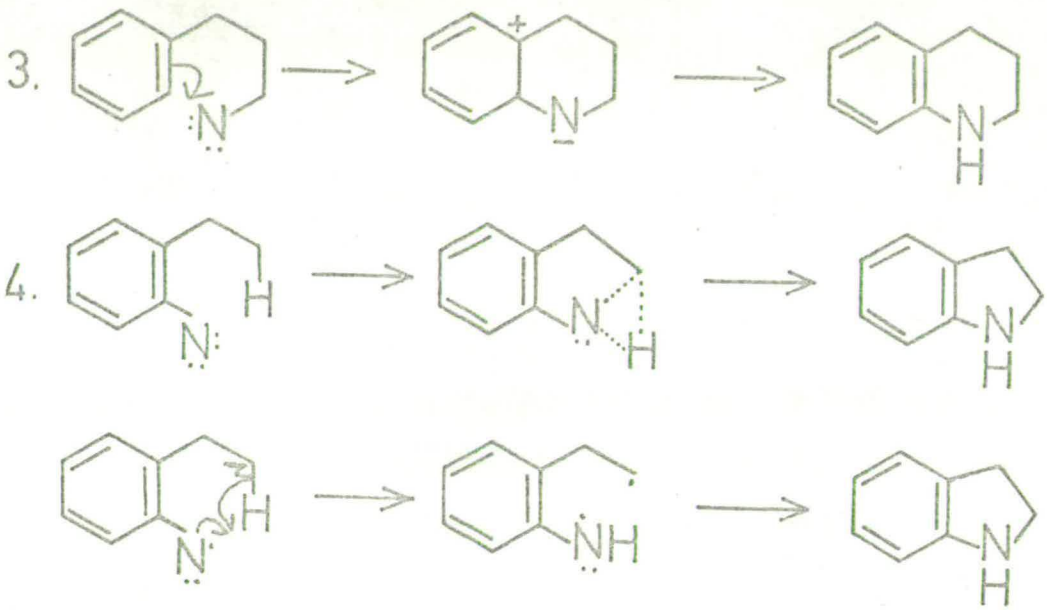
Scheme 65

Smolinsky attempted to use this reaction as a criterion for determining whether the mechanism proceeded through an intermediate nitrene or not. He found that o-nitroalkylbenzene when heated with ferrous oxalate, did not produce an indoline although both deoxygenation with triethyl phosphite and thermolysis of the corresponding o-azido-alkylbenzene did. He concluded that while the latter two may involve a nitrene, deoxygenation with ferrous oxalate does not.

Viewed the other way round, Barton[130a], in the synthesis of the natural product conessine, used an alkyl azide in an intramolecular

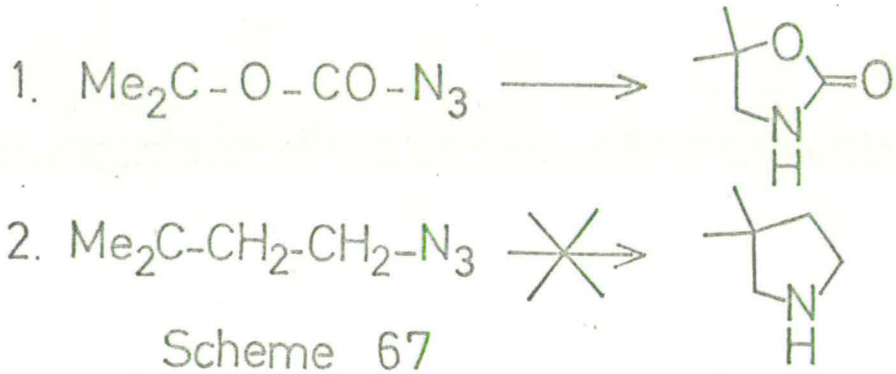
cyclisation to a benzene ring, although later papers[132b] reported that they were unable to repeat these experiments satisfactorily. He found that 1-azido-2-phenylethane would not ring close, but 1-azido-3-phenylpropane did; Smolinsky also reported that 1-nitro-2-phenylethane would not cyclise. With respect to insertion by alkyl nitrenes in alkyl C-H bonds, Barton found that five membered rings were formed, (equation 1, Scheme 66), and postulated that a six membered ring must be formed in the transition state, and that the reaction did not involve direct bond insertion, because complete racemisation occurred, (equation 2). In cyclisation to the benzene ring, the necessary six membered ring in the transition state can be postulated if cyclisation is to the ring itself initially, and not to the aryl C-H bond, (equation 3). In the case of the aryl nitrene cyclising to the alkyl side chain, a six membered ring is once more the transition state if the nitrene attacks the C-H bond on the second carbon atom, (equation 4). Attack on the C-H bond of the third carbon atom would mean a seven membered transition state, which is apparently less favourable, but not impossible, and to some extent depends on the nature of the C-H bond; where the 2-C-H bond is tertiary, entirely to the 2-C-H, and where the 3-C-H bond is primary, there is never any cyclisation to the 3-C-H. The cyclisation by alkyl nitrenes would apparently involve the triplet state to give a long-lived diradical exhibiting complete racemisation, but the aryl nitrene is at least 50% in the singlet state, and may depend on the mode of formation: there is more racemisation from a nitrene from the phosphite deoxygenation reaction than from azide decomposition.





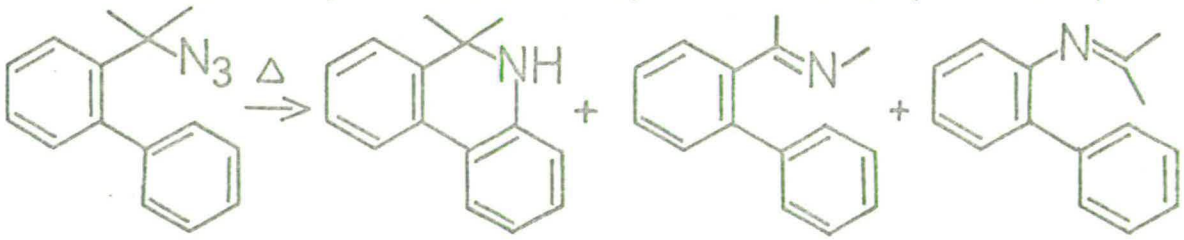
Scheme 66

The striking difference in reactivity between acyl and alkyl nitrenes is illustrated by Pritzkow[133] and Krehner.[134] Pritzkow, unlike Barton, found only imines from a facile 1, 2-H migration and no products of cyclisation for alkyl nitrenes, (equation 2, Scheme 67) compared with the ready cyclisation of the acyl nitrene (equation 1).



Scheme 67

Abramovitch[135] reported that he isolated the product from insertion of an alkyl nitrene in an aryl C-H bond, (Scheme 68).



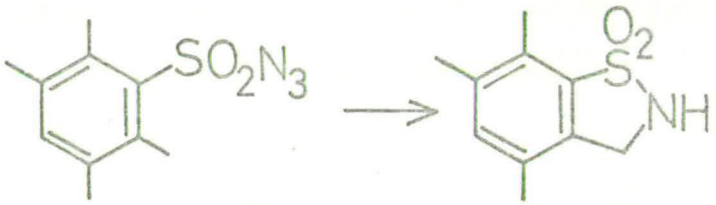
Scheme 68

With perfluorinated alkyl nitrenes, the C-F bond is sufficiently strong to promote preferential alkyl migration,[136] (Scheme 69)



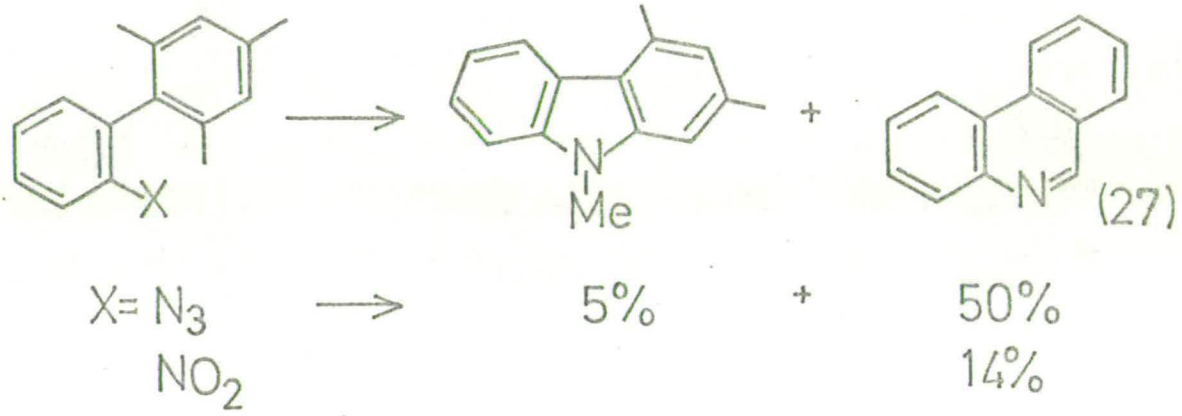
Scheme 69

Sulphonyl nitrenes also undergo intramolecular insertion reactions in C-H bonds (Scheme 70).



Scheme 70

Insertion in a C-C bond has also been observed by aryl nitrenes from various sources. Smolinsky[137] thermally decomposed 2-azido-2', 4', 6'-trimethylbiphenyl, where the methyl groups block the possibility of the normal carbazole reaction, and found products resulting from both C-C and C-H bond insertion (Scheme 71).



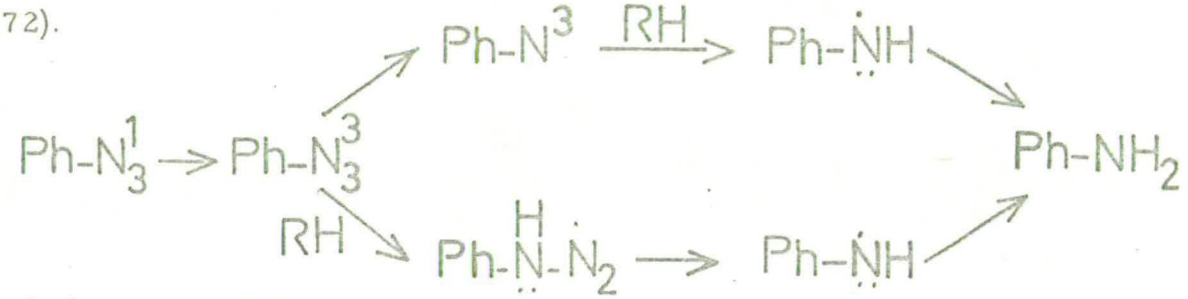
Scheme 71

Cadogan and Todd[138] confirmed the probability that a nitrene was involved by isolating (27) (14%) from the phosphite deoxygenation of the corresponding nitro compound, in which reaction triethyl phosphite competes with insertion for the nitrene, to give a good yield of the phosphorimidate. Treatment of the nitro compound with ferrous oxalate at 200° also gives (27) (23%),[63a] but the possibility of reaction on the surface of the oxalate is not ruled out.

In all these insertion reactions, the similarity of behaviour by species generated from an azide and from the phosphite-nitro deoxygenation reaction implies that a common intermediate, a nitrene, must be involved.

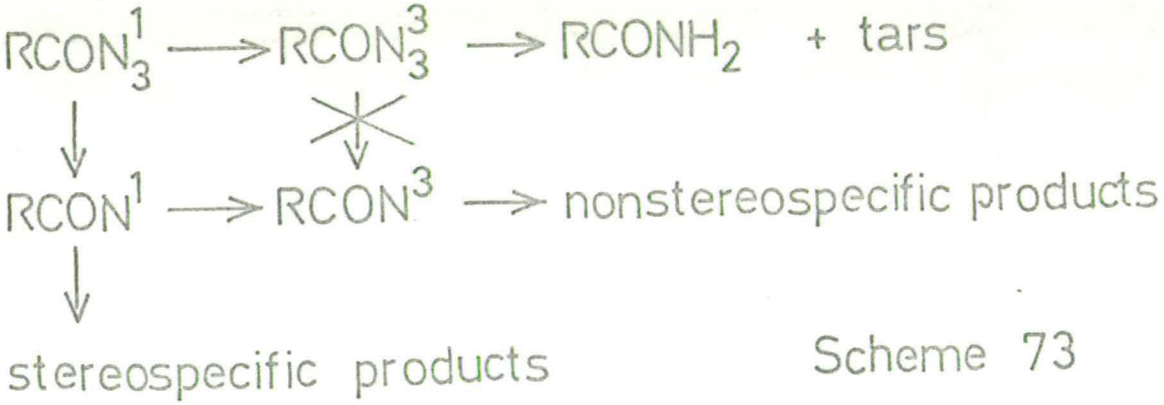
B.3 ABSTRACTION OF HYDROGEN

In almost every reaction involving a nitrene, hydrogen abstraction to form amine is found simultaneously. It has been shown that amine arises from the triplet species. Odum and von Doering[172] used xanthen-9-one as a triplet sensitiser and obtained p-cyanoaniline (70%) compared with (5%) without the sensitiser. This does not prove whether the amine arises from triplet azide or triplet nitrene (Scheme 72).



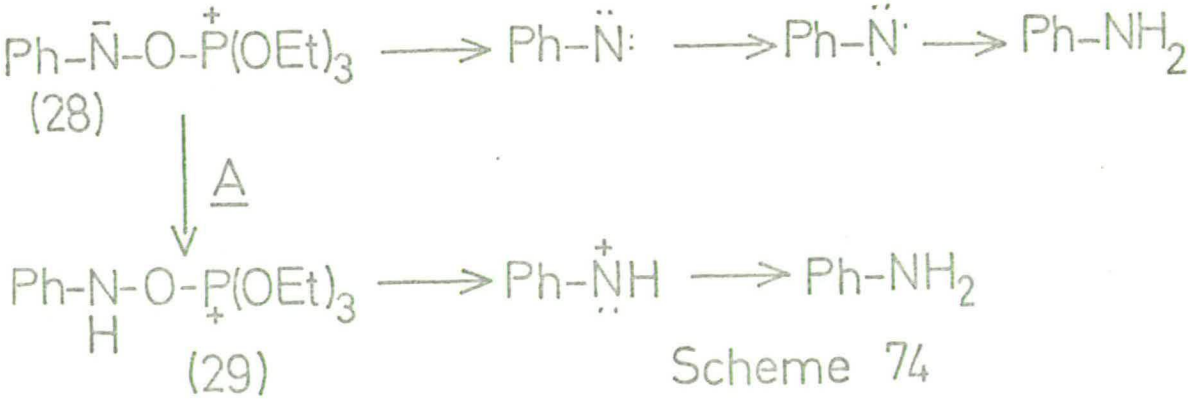
Scheme 72

Indeed Lwowski has shown that when he photolysed ethyl azidoformate in the presence of a triplet sensitiser, he didn't find any of the expected non-stereospecific addition products, but only amines and tars, (Scheme 73).



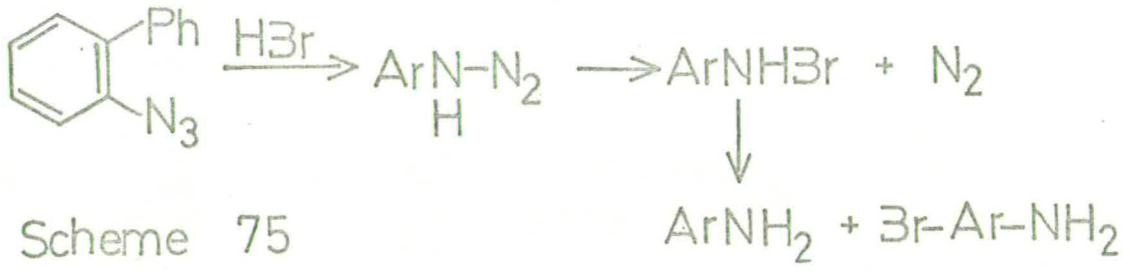
Scheme 73

Similarly it may be postulated that intermediate (28) in the phosphite nitro deoxygenation reaction may be protonated before it breaks down, (Scheme 74).



Scheme 74

Pathway A is supported by evidence from experiments with acetic acid[120] and hydrogen fluoride,[123] which involve the protonated intermediate (29) in attack by a sufficiently strong nucleophile on the benzene ring itself. Smith and Brown[139] treated o-azidobiphenyls with hydrogen halides, and found halogenated amines in every case, via a species involving protonation, and no carbazoles, the normal product of this facile reaction, (Scheme 75). He found the ease of reaction



Scheme 75

in order HI>HBr>HCl>HF. This route to amines may only be preferred if the concentration of H^+ is high enough.

Shingaki[140] has shown that the rate of decomposition of phenyl azide and phenylsulphonyl azide may be enhanced in some solvents, e.g. disulphides, thiols and free radical sources, e.g. tetraphenylhydrazine and triphenyl methyl hydroperoxide, and the products are aniline and phenyl sulphonamide, with by products in thiophenol of o-aminodiphenyl sulphide and diphenyl sulphide, which indicated a mechanism involving attack by radicals such as R-S on the azide group. Leffler and Gibson[141] showed that trichloromethyl radicals could induce decomposition of phenyl azide to give aniline, and Horner and Bauer[142] showed that radicals could also induce the decomposition of other azides, e.g. benzoyl azide and ethyl azidoformate, always to form amines. The question is thus raised of whether apparent abstraction of hydrogen by a nitrene is in fact induced decomposition of the azides caused by traces of peroxides in inert solvents.

An indication that the amine may arise from the nitrene at least sometimes comes from Splitter and Calvin[58] who isolated amines from the photochemical decomposition of 3-substituted-2-phenyloxaziridines, after looking at the e.p.r. spectrum of the nitrene, which they found

identical to that generated from phenyl azide.

It has been shown that amines arise from triplet species of nitrenes other than aryl also. Carbethoxy nitrene from the photolysis of ethyl azidoformate has the yield of ethyl formamide increased from 3% to 73% by the presence of a triplet sensitiser.[12] Vice versa, when the singlet state is stabilised by additives e.g. m-dinitrobenzene,[109b] the yield of amine is reduced from 25%to 17%, since the amount of intersystem crossing is reduced.

Bertho[25] originally identified aniline in the products of thermolysis of phenyl azide. Wherever there is no other possibility for reaction, amine is formed in increased yield; e.g. from o-azidobenzyl alcohol a 65% yield of o-aminobenzyl alcohol is obtained.[128] Where there are other possible modes of reaction, they will normally be preferred, and the yield of amine correspondingly reduced, particularly where the other reactions are very favourable; e.g. in the formation of carbazole, the yield of amine is reduced to 5%. For any given nitrene, the yield of amine may be similar under similar conditions, whatever its mode of production; in the thermolysis of o-azidobutylbenzene, the yield is 29%, and in the deoxygenation of o-nitrobutylbenzene, the yield is 24%,[130a] cf in the vapour phase the yield of amine is less than 1%, because intersystem crossing is enhanced by collision in solution.

Cadogan[138] showed that the hydrogen abstracted by the nitrene could come from the solvent, by isolating bicumyl after reactions in cumene. Sundberg[130] found evidence that hydrogen abstraction could occur intramolecularly; from o-butylphenyl nitrene he obtained 1-(o-anilino)but-1-ene, with some of the other two isomers, in yields of 25%, from both methods of generating the nitrene in solution. In the vapour phase, this was the only source of hydrogen for the nitrene, to give a 36% yield of the amine. In solution, 29% o-butylaniline was also obtained. Similarly he found 1-(o-anilino)prop-2-ene (40%) from o-propylphenyl nitrene, in each of three methods of generating the nitrene.

Hall, Hill and Farquhar[116] also showed that a substantial proportion of the hydrogen was abstracted from the substrate itself. Deuterated phenyl azide was thermolysed in pentane and the aniline so

produced contained 40% N-D. When phenyl azide was thermolysed in 2-deutero-2-methylpropane, the aniline contained only 7% N-D.

Amino nitrenes have quite different properties from other nitrenes, particularly with respect to protonation, which takes place readily to give a stable, conjugate acid, (Scheme 76).



Scheme 76

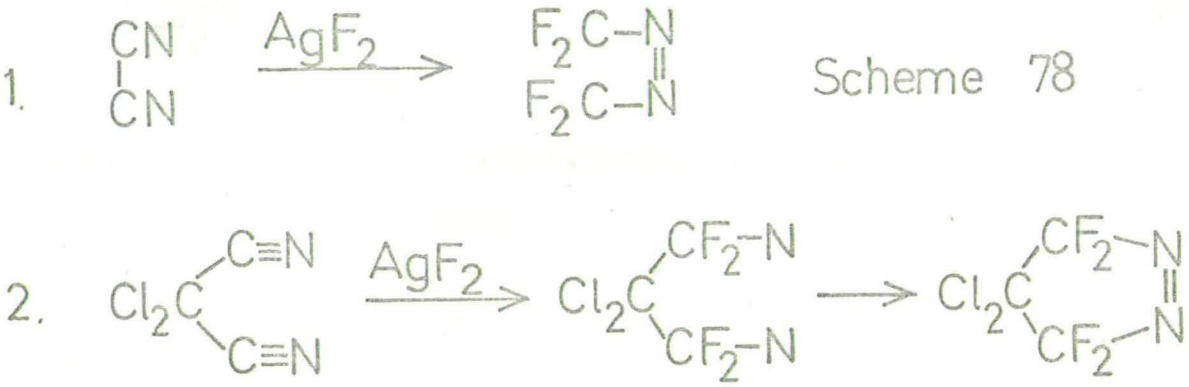
B.4 DIMERISATION

Azo compounds are frequently isolated as evidence of apparent dimerisation of nitrenes, the earliest report of azobenzene from phenyl azide being by Bertho.[25] Literature reports that they are formed in high yield, both in the decomposition of azides and in the deoxygenation of nitroso compounds, wherever, like the formation of amines, there are no alternative pathways. Smolinsky[128] found azobenzene (72%) and 2, 2'-bis(trifluoromethyl)azobenzene (80%) in the vapour phase pyrolyses of phenyl azide and o-trifluoromethylphenyl azide respectively. Cadogan[143] found both azobenzenes and azoxybenzenes in the deoxygenation of nitroso compounds with triethyl phosphite: the mechanism of this latter reaction will be discussed later. Buckler[144] in one of the earliest deoxygenations of nitrobenzene by phosphine in the presence of potassium hydroxide obtained azoxybenzene (80%). Intramolecular azo formation occurs in the deoxygenation of 2, 2'-dinitrobiphenyl with ferrous oxide[63a] or iron pentacarbonyl and carbon monoxide,[62] (Scheme 77).



Scheme 77

Emeléus and Hurst,[145] (equation 1), and Hynes, Bishop and Bigelow[146] (equation 2, Scheme 78) report a further intramolecular coupling of nitrenes.



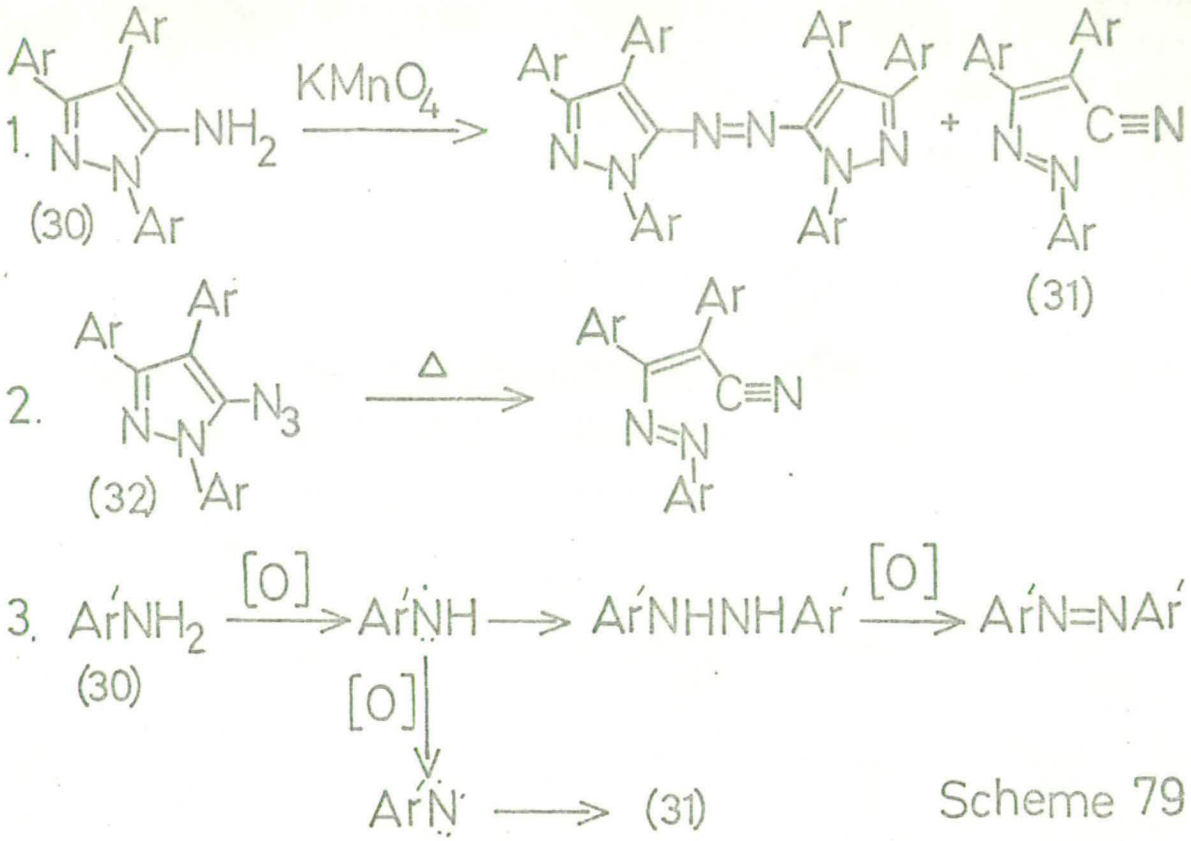
Scheme 78

Newsom[61] postulated that when hexaphenyl borazole broke down (under extreme conditions), azobenzene was one of the products, but that it subsequently lost nitrogen to form the final isolated product, biphenyl.

The yields of azo compounds are also influenced by the medium, implying competition by the aryl nitrene in the formation of azo compound or abstraction of hydrogen. A high yield of azobenzene was obtained by thermolysis of phenyl azide in difluorotetrachloroethane (50%),[147] compared with none at all in n-pentane at the same temperature,[116] when there was a good yield of aniline. The highest yield (72%) was obtained by Smolinsky[128] in the vapour phase. The yield is also strongly influenced by substituents on the benzene ring: Horner, Christmann and Gross[118] obtained from p-chlorophenyl azide, 0%, from p-anisyl azide, 18%, and from p-biphenyl azide 81% of the corresponding azo compounds.

There has been discussion as to whether azo compounds arise from the nitrene or from an amino radical. Smith[148] has shown that oxidation by potassium permanganate of amines such as (30) can give both azo compound and the product of ring fission (31) (equation 1), while thermolysis of the corresponding azide, (32), gives only ring fission, (equation 2), which suggests that the azo compounds do not arise from the nitrene, (equation 3, Scheme 79).

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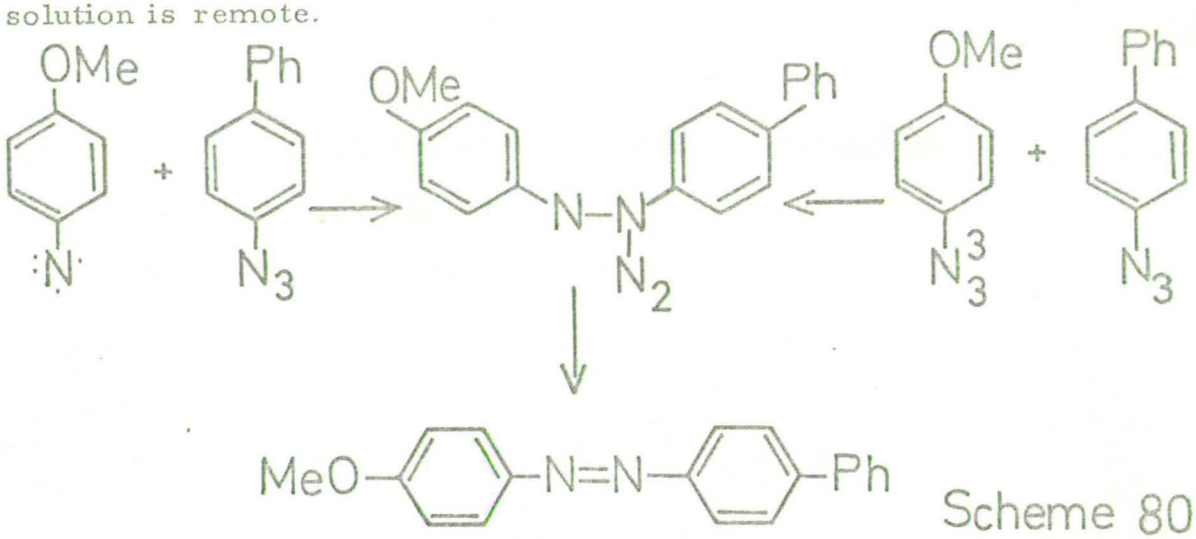


Scheme 79

Azobenzene has been shown to arise from a triplet species. It is normally found as a minor product in the photolytic formation of carbazole from o-azidobiphenyl, but Swenton[47] conducted the photolysis in the presence of a triplet sensitiser, and obtained azobenzene as the major product (80%). Splitter and Calvin[58] also isolated it as a product after looking at the e.s.r. spectrum of triplet nitrene, which implies that it can be a product from the nitrene itself, not just from a reaction of the nitrene precursor, here activated azide. The fact that formation of azobenzenes is prevented by the presence of air,[117] a triplet quencher, also indicates that the participating species are in the triplet state.

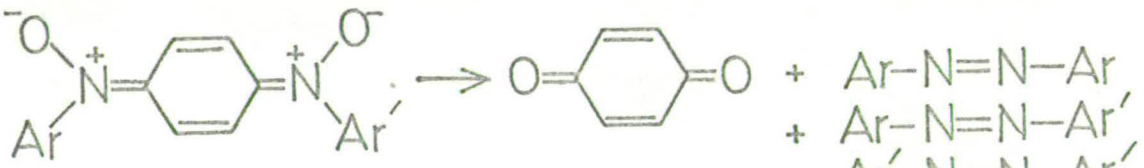
There have been experiments to determine whether the nitrene or its precursor is the reacting species. Horner, Christmann and Gross[118] attempted to prove the involvement of nitrene by isolating the mixed azo compound, 4-methoxy-4'-phenylazobenzene as well as the non-mixed azo compounds, 4,4'-dimethoxyazobenzene and 4,4'-biphenylazobenzene from photolysis of a mixture of 4-azidoanisole and 4-azidobiphenyl, but, as they pointed out, this can also be explained by

reactions other than between two nitrenes, in induced decompositions of the azides (Scheme 80). The probability of two highly reactive species such as nitrenes living long enough to meet each other in dilute solution is remote.



Scheme 80

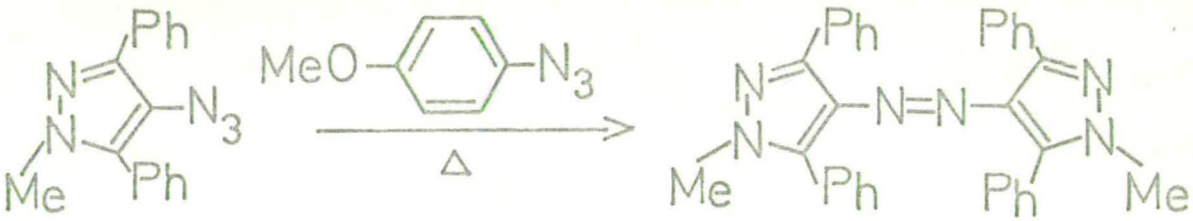
Pedersen[59] found mixed azo compounds from the nitrenes generated from N, N'-disubstituted-p-quinonediimine-N, N'-dioxides, (Scheme 81). The three possible azo compounds were found in a statistical distribution, where the aryl groups were of the same kind, e. g. p-methoxyphenyl and phenyl or naphthyl and phenyl. It is hard to explain this reaction other than through a nitrene intermediate.



Scheme 81

Dounchis[125] hoped to distinguish between the dimerisation of two nitrenes and attack by a nitrene on another azide molecule, by decomposing one azide thermally, in the presence of another, but below the decomposition temperature of the second azide. He found no mixed azide: the nitrene formed in the decomposition of the first azide did not attack the second (Scheme 82).

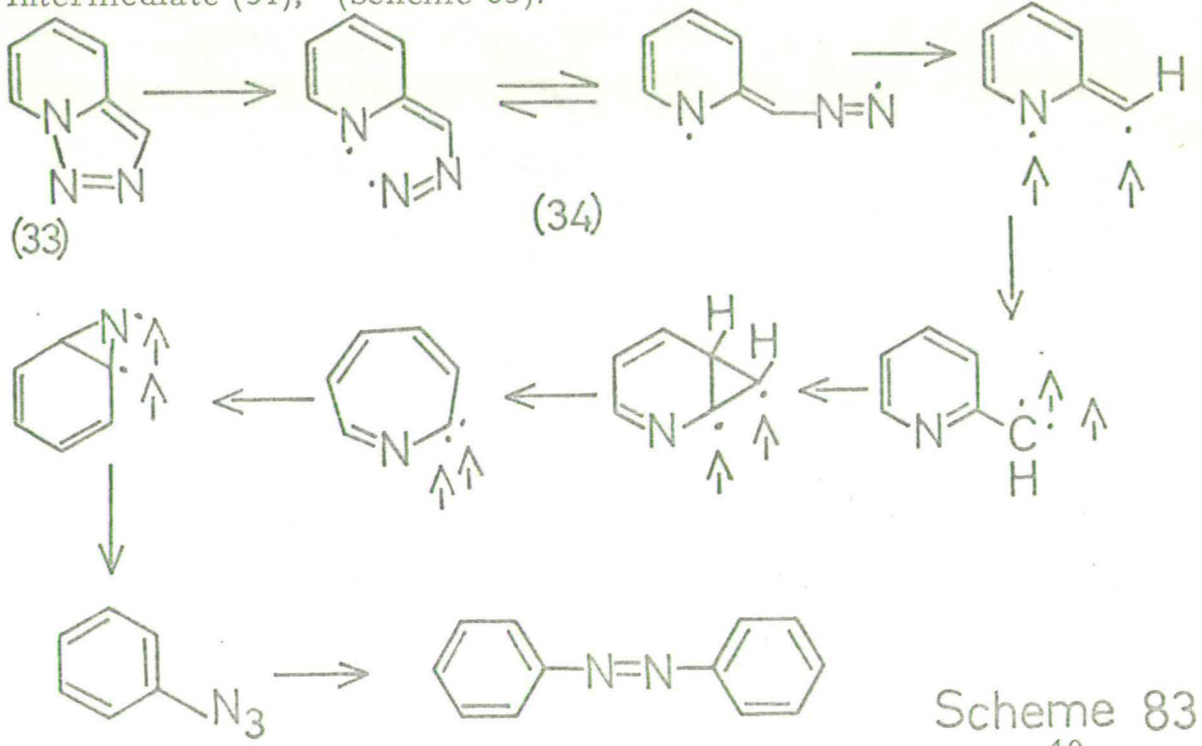
Lwowski[150] considered that azo compounds could not arise from the nitrene, even a reaction between the nitrene and the azide, because



Scheme 82

when he generated carbethoxy nitrene by *α*-elimination from p-nitrobenzenesulphonoxyurethane in the presence of ethyl azidoformate, no diethyl azodiformate was obtained, although it is normally formed in both photolysis and thermolysis of ethyl azidoformate.

C row[151] reported that phenyl nitrene obtained from vapour phase pyrolysis of $\underline{\nabla}$-triazolo[1, 5-a]pyridine, (33) gave none of the products attributed to reactions of the singlet state, such as cyanocyclopentadiene, and Susaki[39a] reported also no ring expansion products from 2-pyridyl nitrene in aniline, but only the triplet products, 2-aminopyridine and 2, 2'-azopyridine. The explanation by C row is that (33) generates the nitrene directly in the triplet state, due to the spin state of the intermediate (34), (Scheme 83).



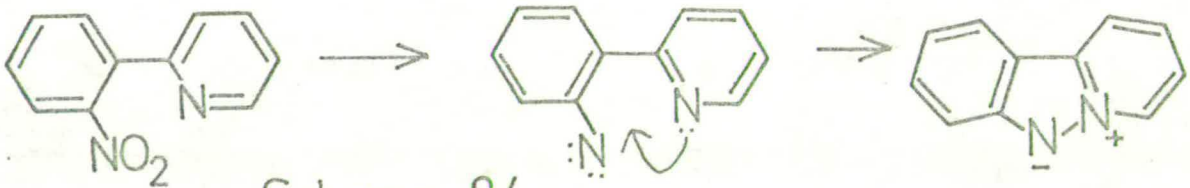
Scheme 83

This is supported by the evidence of Swenton and Hyath[40] who subjected 8-phenyltetrazolo[1, 5-c]pyrimidine to ionic conditions (CF_3CO_2H) which favour the azide side of the equilibrium, which

resulted in a good yield of the singlet product carbazole, while all other solvents left the equilibrium on the side of the tetrazole, which would give a triplet nitrene leading to tars and no carbazole, as found.

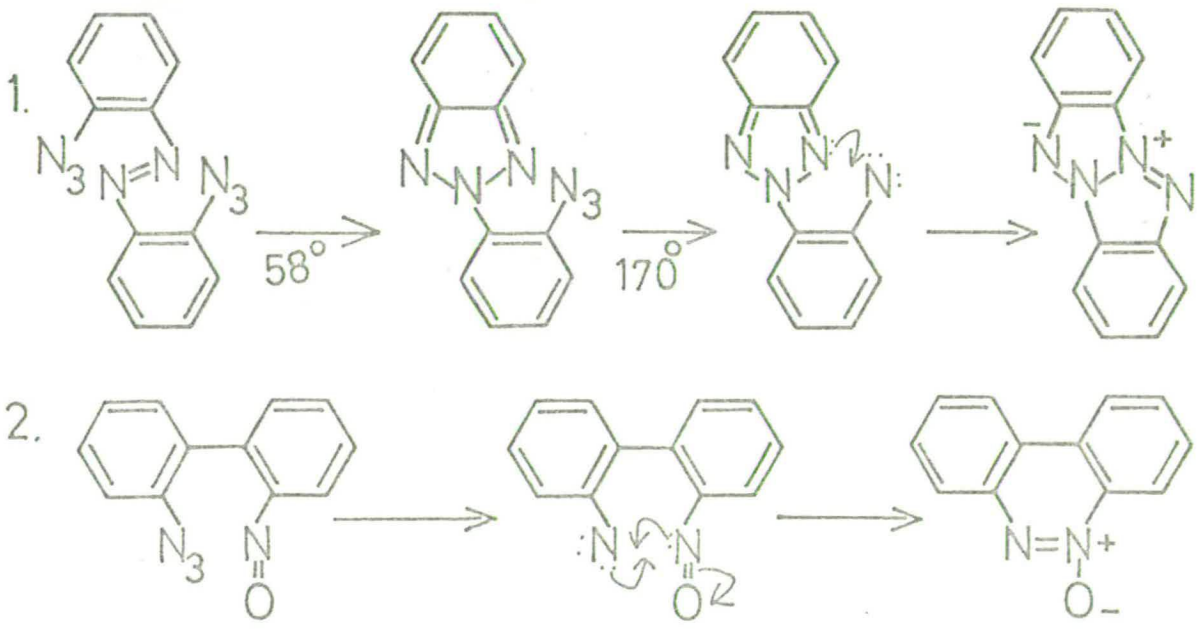
B.5 BOND FORMATION WITH AN UNSHARED PAIR

Another mode of reaction for nitrenes is bond formation at an unshared pair, which is normally considered to be a reaction of the singlet state.[85] Examples have been reported of reaction with the lone pairs of N, P and S, where the d orbitals of P and S are normally involved in π bonding, while with N the products are dipoles, normally stabilised by delocalisation of the charge over an aromatic system. Such a reaction is exhibited in the deoxygenation of 2-o-nitrophenyl pyridine by either ferrous oxalate[63a] or triethyl phosphite,[53] (Scheme 84). From 2, 2'-diazidoazobenzene, Carboni



Scheme 84

and Castle[33] reported the formation of dibenzo-1, 3a, 4, 6a-tetraaza-pentalene, where the first step of the reaction was concerted and the second involved a nitrene, (equation 1, Scheme 85).



Scheme 85

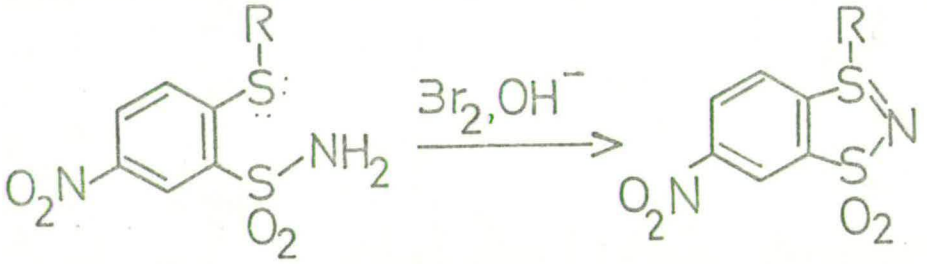
The involvement of a lone pair of the nitrogen of a nitroso group was shown by Neiman, Maimind and Shemyakin,[99] (equation 2, Scheme 85).

Carbethoxy nitrene has also been shown to undergo such reactions easily,[124] (Scheme 86).



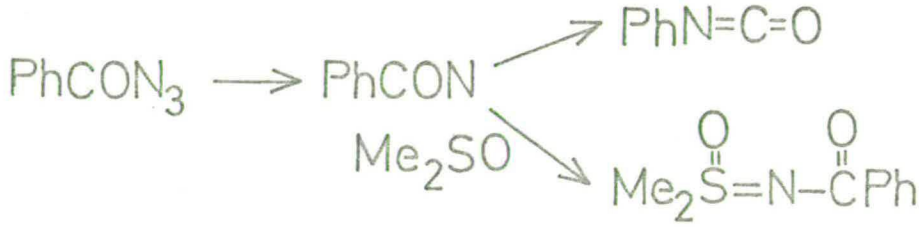
Scheme 86

With P and S, the use of the empty d orbitals as acceptors for the negative charge and hence the formation of double bonds gives very stable substances. An example of such a reaction occurring intramolecularly with a sulphonyl nitrene was reported by Wagner and Banholzer,[153] (Scheme 87).



Scheme 87

There are a number of reports that both dimethyl sulphide and dimethyl sulphoxide will readily trap acyl nitrenes and heterocyclic nitrenes e.g. amino, sulphonyl and cyano nitrenes. Horner and Christmann[127] used several sulphoxides, (tetramethylene, dibenzyl and dimethyl), and also dimethyl sulphide to trap arylsulphonyl nitrenes and acyl nitrenes, the dimethyl sulphide being a sufficiently good trap to intercept benzoyl nitrene before it rearranged to the isocyanate, and N-benzoyldimethylsulphoximine (28%) was isolated, (Scheme 88).

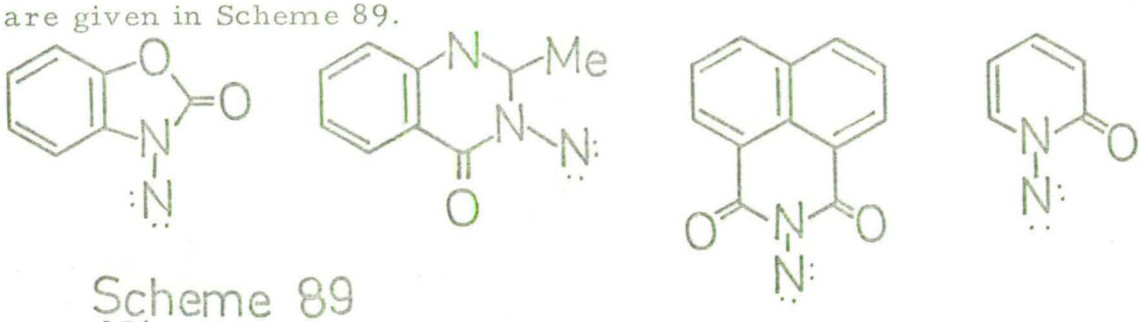


Scheme 88

Yields for nitrenes trapped with dimethyl sulphide were 50% for electron rich nitrenes, but with the electron withdrawing group, nitro, as a substituent, (which also enhances intersystem crossing to the triplet

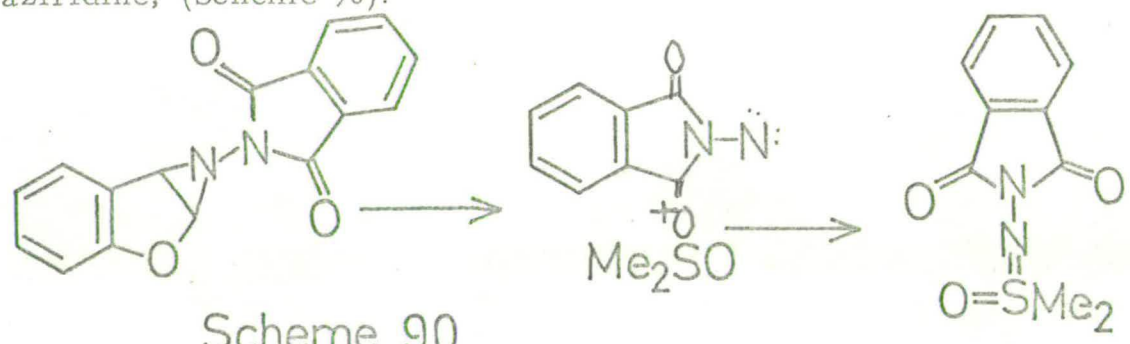
state[48]), no trapped nitrene was obtained.

There has recently been renewed interest in DMSO as a trap; Rees[126] has generated several electron deficient amino nitrenes by treatment of the corresponding N-amino compound with lead tetra-acetate, and has trapped all these nitrenes with various sulphoxides, (e.g. dimethyl, diphenyl, dibenzyl). Examples of the nitrenes used are given in Scheme 89.



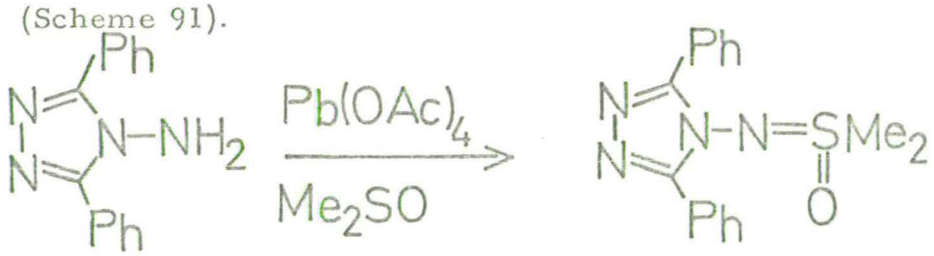
Scheme 89

Jones[154] also trapped N-phthalimido nitrene, generated from the aziridine, (Scheme 90).



Scheme 90

Sauer, Mayer and Schröppel[155] trapped the N-(1, 2, 4-triazole) nitrene from (35) (Scheme 91).



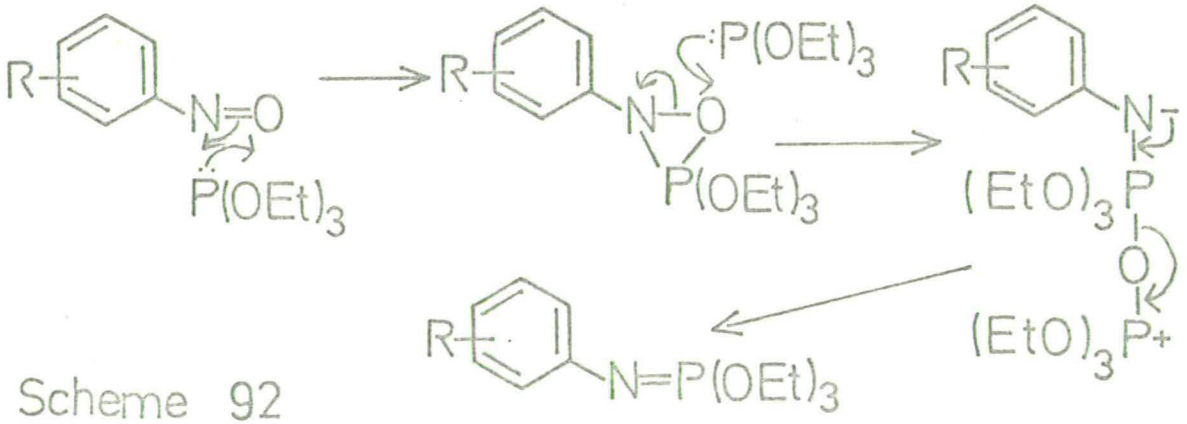
(35) Scheme 91

Robson[156] has trapped p-tolyl sulphonyl nitrene, dodecanesulphonyl nitrene, and dodecanoyl nitrene, with dimethyl sulphide, and dodecane-sulphonyl nitrene has also been trapped with pyridine and with triphenyl phosphine. Breslow[157] has used pyridine to trap n-octadecylformyl nitrene, but found that the reaction with triphenyl phosphine occurred rapidly at room temperature, and therefore probably involved the azide,

not the nitrene.

The other most commonly used reagent which traps nitrenes efficiently is triethyl phosphite, to form in the case of aryl nitrenes, triethyl N-arylphosphorimidates. Cadogan[143] first obtained triethyl N-p-dimethylaminophenylphosphorimidate, (36), by treating p-nitroso-N,N-dimethylaniline with triethyl phosphite, and observed that (36) was converted to diethyl N-p-dimethylaminophenylphosphoramidate by hydrolysis during work-up on an alumina column. Cadogan[138] reported that phosphorimidates were formed from aryl nitro compounds in most reactions that didn't provide an easy reaction for the nitrene, e.g. not formed with carbazole. Sundberg reported the formation of phosphorimidates, particularly in those reactions where the benzene ring had alkyl substituents,[130b 158] and also in the photochemical deoxygenation of nitrobenzene by triethyl phosphite.[159] Phosphorimidates have also been reported by Suschitzky[98] and Kametani[108] as by products of deoxygenations of nitroaryls in the presence of triethyl phosphite.

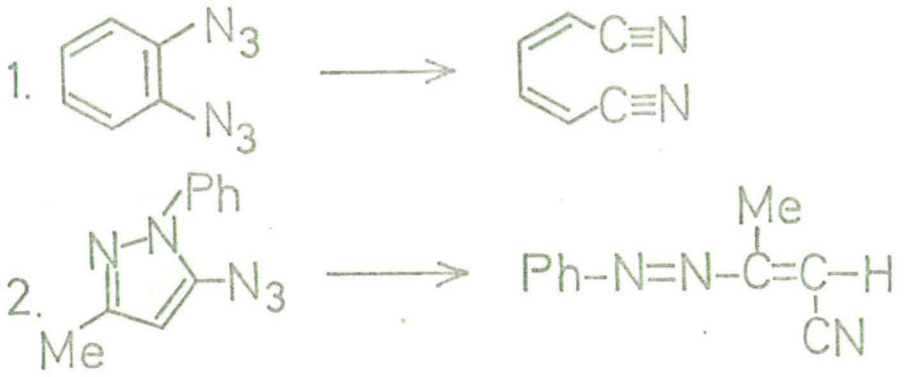
Although Sundberg[130b] carried out the pyrolysis of an azide in the presence of triethyl phosphite, to show that the products obtained were identical to those from the phosphite-nitro deoxygenation reaction, the system he chose was not one which had phosphorimidates for products, and so it has not yet been shown that a nitrene generated by a different method can react to give phosphorimidates, which leaves open the question of whether it is the nitrene itself, or a precursor that reacts, (Scheme 92)



Scheme 92

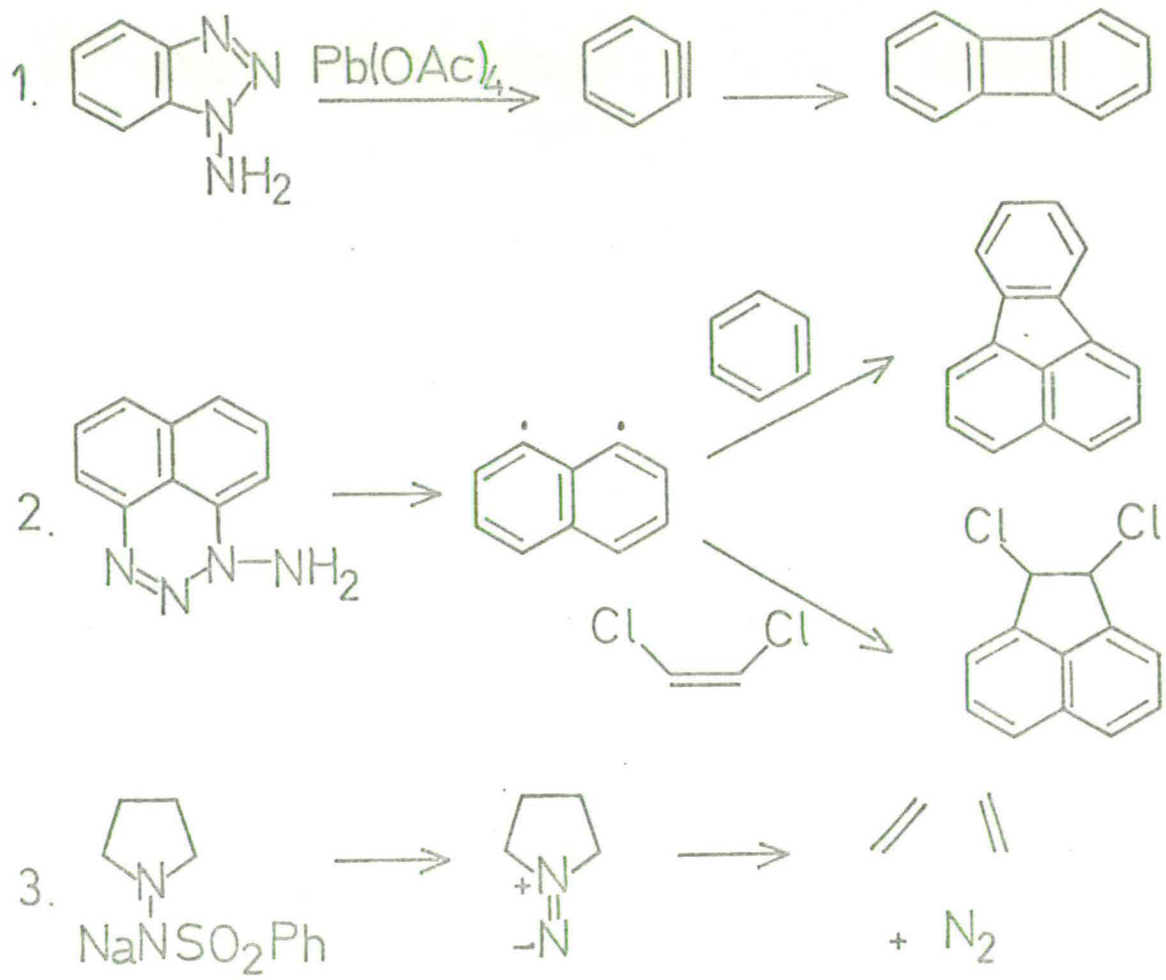
B.6 FRAGMENTATION

There are a number of cases reported where fragmentation of the nitrene occurs. The o-phenyl dinitrene (or its azide precursor) fragments to butadiene dinitrile,[160] (equation 1), and heterocyclic nitrenes commonly fragment,[161] (equation 2, Scheme 93).



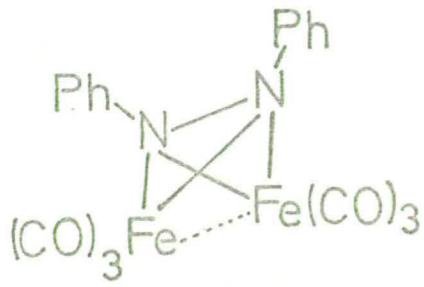
Scheme 93

Fragmentation is a common reaction of amino nitrenes, employed in the formation of benzyne by Campbell and Rees,[162] (equation 1, Scheme 94), and of the unusual naphthyl diradical (equation 2).[163] More common is the complete fragmentation of a ring, (equation 3, Scheme 94).

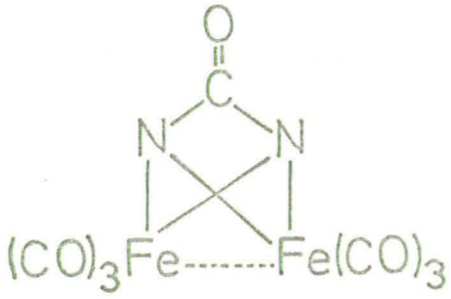


Scheme 94

There is also a report by Knox[66] that nitrenes may react with iron carbonyls to form complexes such as (36), the results of nitrenes being trapped as ligands in metal carbonyl complexes. Methyl azide also gives many complexed products, of which (37) is the principal one.



(36)

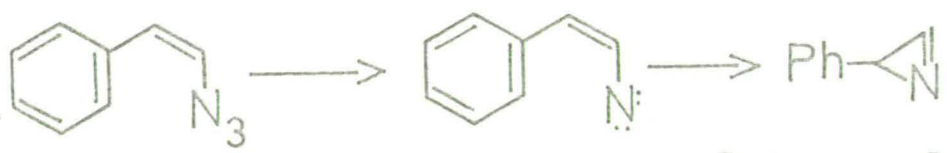


(37)

B.7 RING CONTRACTION

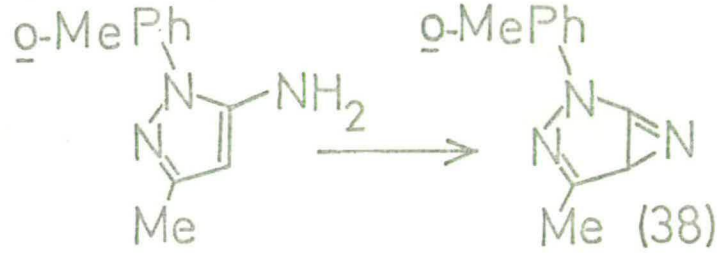
The most fascinating aspect of aryl nitrenes concerns the interaction of the nitrene with the benzene ring to form an azabicyclic intermediate, (40), 7-azabicyclo[4, 1, 0]hepta-2, 4, 6-triene, which may then react in several ways, by ring contraction to form cyanocyclopentadienes, by extrusion of a carbene leaving the nitrogen in the ring, to form pyridines, and by bond reorganisation in the presence of suitable nucleophiles to form azepines.

There is a close resemblance between the formation of the azabicyclic intermediate and the reaction of a vinyl nitrene to form an azirine. Vinyl nitrenes are extremely reactive, and do not undergo any reaction such as intramolecular C-H insertion reactions, nor intramolecular addition to double bonds; they are invariably reported as forming azirines initially, which may subsequently rearrange,[118, 164, 165] (Scheme 95)



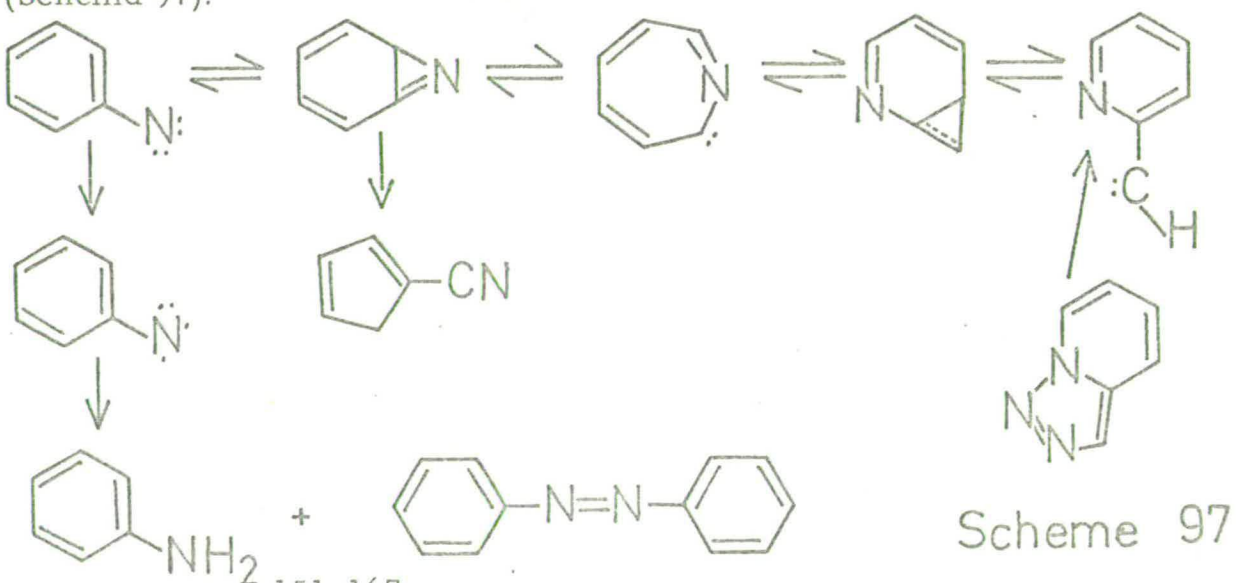
Scheme 95

The first evidence of interaction between an aromatic system and an external nitrogen comes from Michaelis[149] who observed that the oxidation of 1-o-tolyl-3-methyl-5-aminopyrazol gave an azirine, (38), (Scheme 96).



Scheme 96

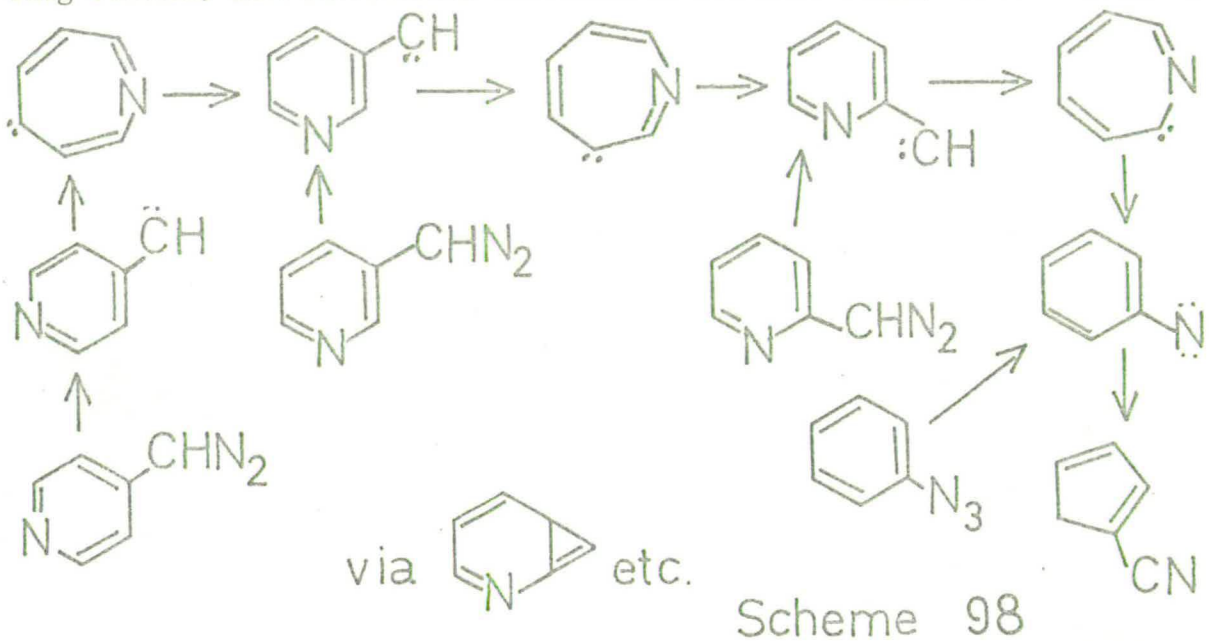
Crow and co-workers[73, 151, 166a, b] observed cyanocyclopentadiene as a major product of the vapour phase pyrolysis of phenyl azide, and aniline and azobenzene as the products if there was rapid diffusion away from the hot surface. They showed that a pyridyl carbene could give the same products as the phenyl nitrene, (he found aniline and azobenzene) and that 1-cyano-3-methylcyclopentadiene could ring expand to cyanobenzene. They explained these results by postulating that the singlet nitrene would first form an azabicyclic intermediate and then ring contract, while the triplet nitrene, formed when the singlet nitrene diffused away from the hot area of the tube, would give aniline and azobenzene, and that the carbene could ring expand in the same way, actually having the seven membered ring for an intermediate, (Schemd 97).



Scheme 97

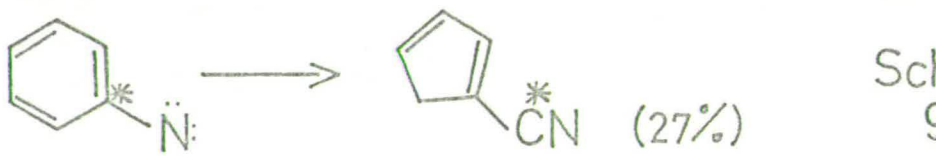
He then showed[151, 167] by generating the original carbene in each position of the pyridyl ring, and by labelling experiments, that under

these conditions the electron deficient site may move around all the positions of a seven membered ring, involving a series of ring expansions and contractions so that the carbene is sometimes located on a ring carbon, and sometimes extruded to the side chain, as in Scheme 98.



Scheme 98

In the experiments with the nitrene attached to a labelled carbon atom, there was 83% scrambling of the label, via a similar series of ring expansion and contraction cycles coupled with hydrogen shifts or by a cycloperambulatory nitrene/hydrogen shift, (Scheme 99).

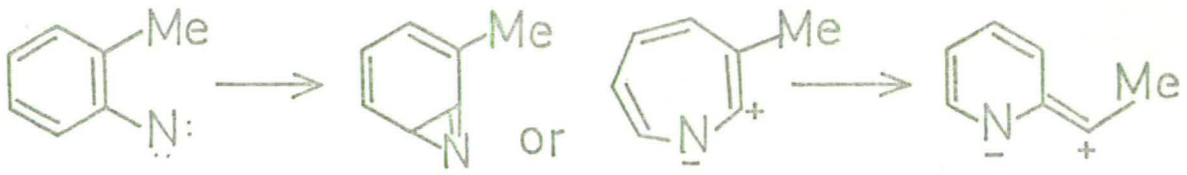


Scheme 99

Wentrup[168] has extended this work to show that ring contraction may also take place in solution, but that a high temperature is still required. Brown and Smith[169] generated nitrenes from the pyrolysis of fused oxadiazolones, which extruded carbon dioxide, and found both ring contraction and fission products. Sasaki[39b] obtained ring contraction products from photolysis of 2-azidopyrimidine in acetic acid.

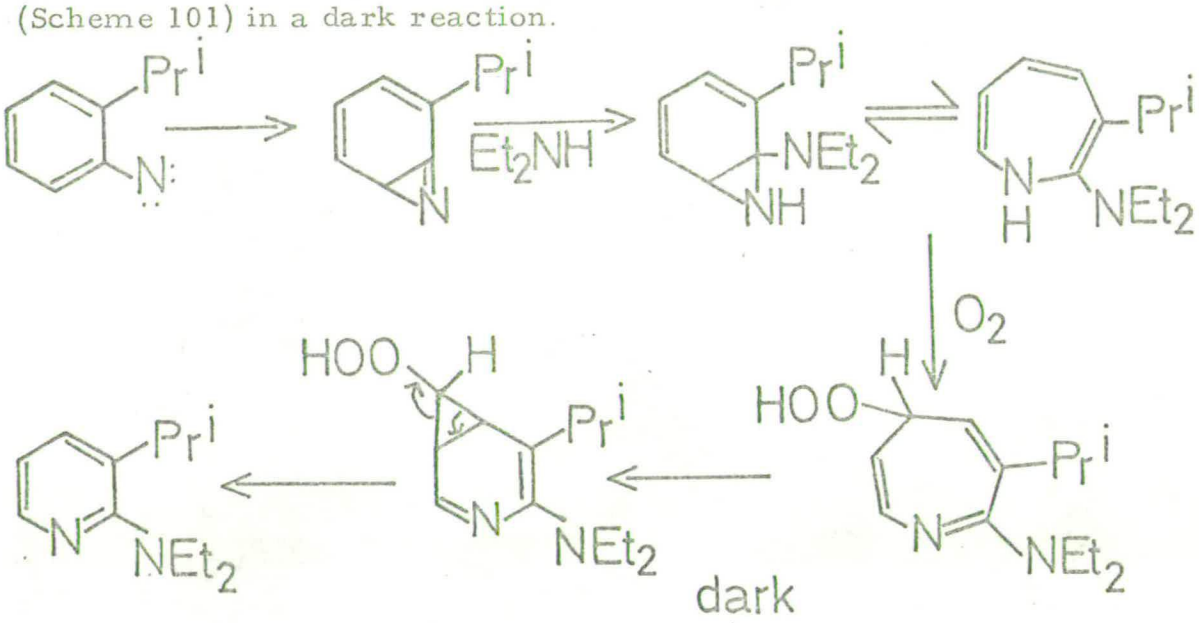
Sundberg[130b] observed the formation of substituted pyridines in the deoxygenation of o-alkylnitroso benzenes, photochemically at 0°, and also postulated[158] a ring expansion/contraction cycle; he suggested that the intermediates were dipolar rather than carbenes, (Scheme 100),

in which the intermediate (39) required an alkyl group to stabilise it.



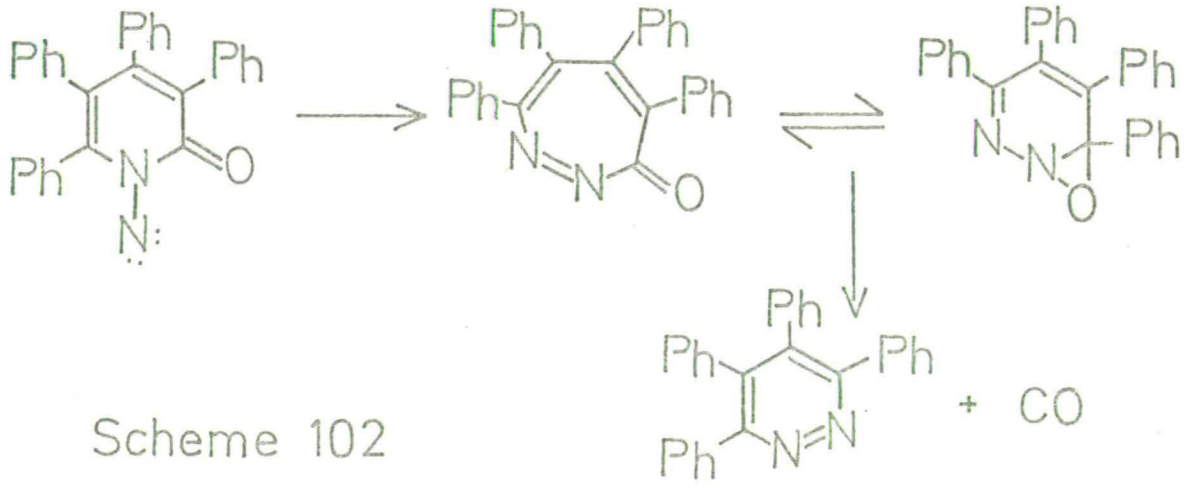
Scheme 100 (39)

Suter[170] has now shown that pyridines can arise from azepines, (Scheme 101) in a dark reaction.



Scheme 101

Rees[171] showed that the oxidation of N-amino-3, 4, 5, 6-tetraphenyl-2-pyridone formed an amino nitrene which could be trapped preferentially by dimethyl sulphide, but which would normally undergo ring expansion followed by extrusion of carbon monoxide, to yield 3, 4, 5, 6-tetraphenylpyridazine, (Scheme 102).



Scheme 102

B.8 RING EXPANSION

It is, therefore, apparent that the reaction of an aryl nitrene involving ring expansion to an azabicyclic intermediate (40), and then an azepine, is of primary importance in understanding the nature of the phenyl nitrene, and how it differs from other nitrenes.

Huisgen[28c] first reported the formation of azepines from the thermolysis of aryl azides in amines such as aniline, p-toluidine, p-phenetidine, N-methylaniline, benzylamine and cyclohexylamine. He considered that reaction was through a nitrene because the kinetics of the azide decomposition were not significantly different in aniline, compared with other solvents. He then postulated[28a, b] a mechanism involving a nitrene and an azabicyclic intermediate (40), (Scheme 103). He considered that the formation of the aziridine system could not be concerted with loss of nitrogen because m-substituents, which should strongly influence the o-position under attack, did not affect the rate, (table IV). He showed that no symmetrical intermediate, (41), could exist because a p-substituted azide would ring open to two isomers, and only one was found, (Scheme 104). Similarly a radioactive experiment which labelled the carbon to which the nitrogen was attached showed that 100% of the aniline attacked this position, (Scheme 105).

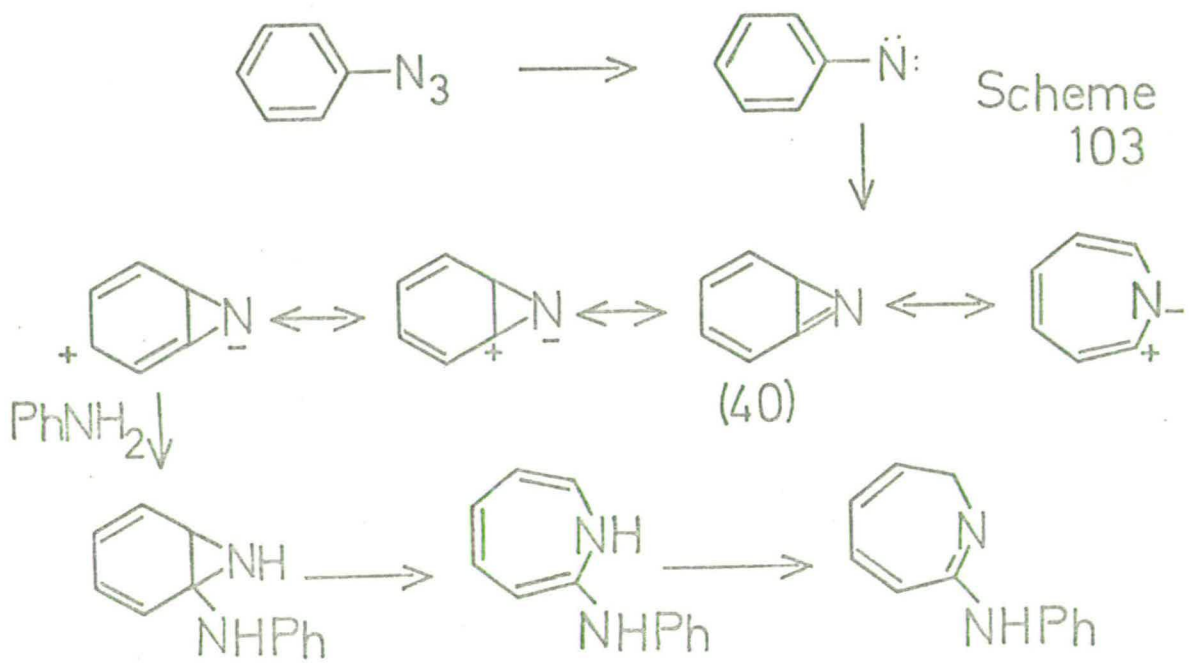
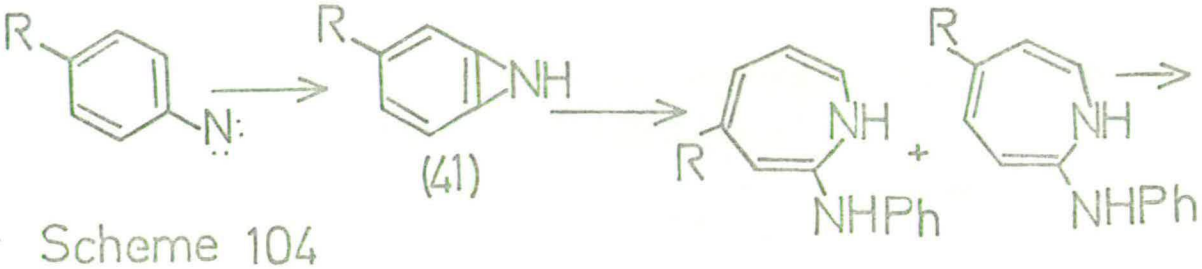


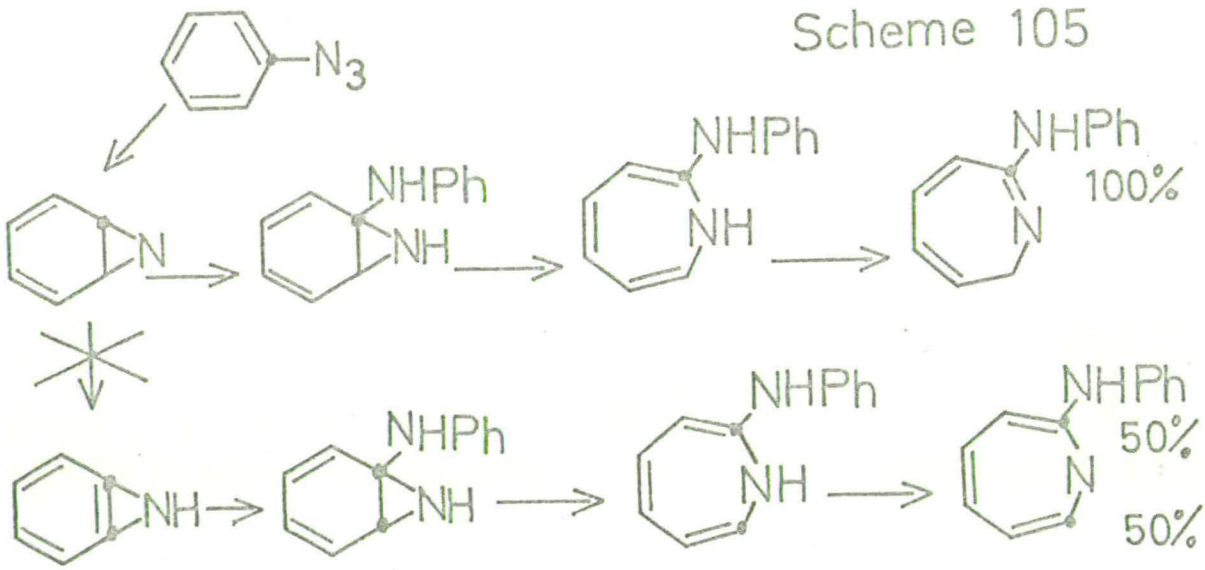
Table IV Rate of Decomposition of m-substituted phenyl azides

Azide:	PhN_3	m-$MePhN_3$	m-$MeOPhN_3$
rate:	$8.47\ 10^{-4}$	$8.88\ 10^{-4}$	$8.84\ 10^{-4}$



Scheme 104

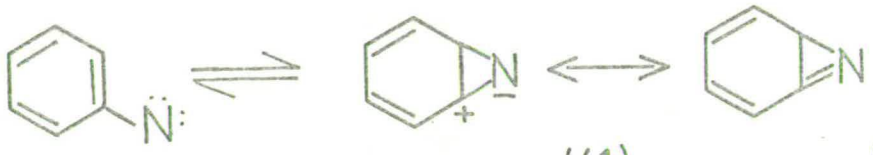
Scheme 105



He decomposed a number of substituted azides in aniline: p-methyl was successful, but with naphthyl, p-nitro and p-chloro no analogous products were obtained.

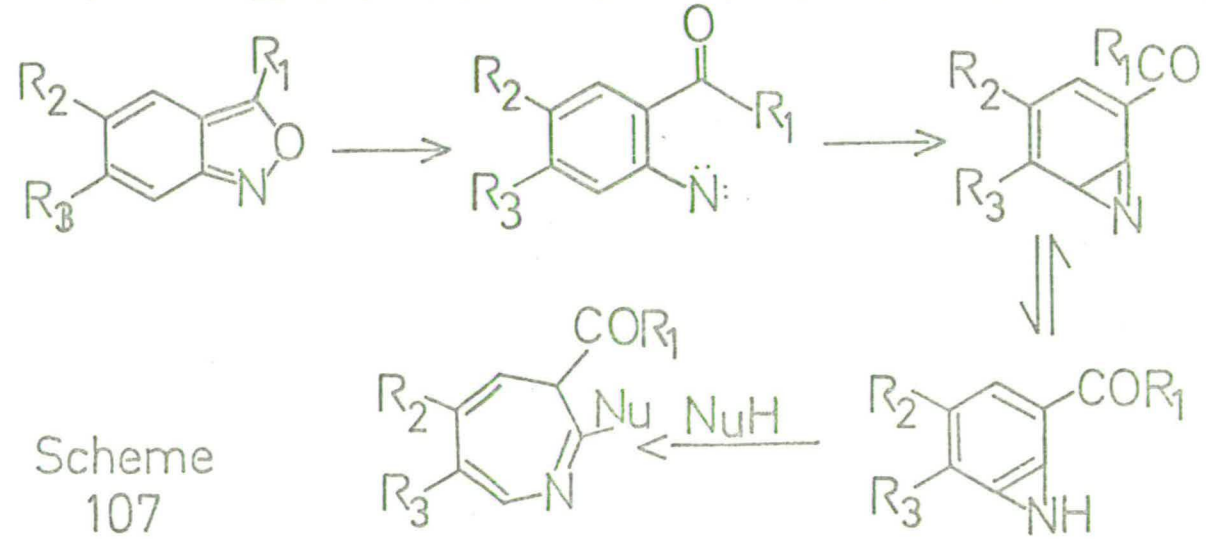
Odum and von Doering[172] reexamined this reaction by photolysing phenyl azide in diethylamine, and identified the azepine as 2-diethylamino-3H-azepine, conclusively by extensive studies of the n.m.r. spectrum. They used other solvents, and were successful in obtaining small yields, (<5%) of 2-amino-3H-azepine (from photolysis in ammonia) and 2-sulphido-1, 2, 3-tri H-azepine (from photolysis in hydrogen sulphide), both of which readily hydrolysed to 1, 2, 3-tri H-azepin-2-one. Odum and Aaronson[48] succeeded in making 5-methoxy- and 5-chloro-2-diethylamino-3H-azepines from photolysis of the appropriate p-substituted azide in dimethylamine.

Odum and Brenner[173] obtained the azepine from the nitrene generated by the deoxygenation of nitrosobenzene with triphenyl phosphine, and also showed that diethylamine was the amine that gave the highest yields of azepine (60%), with n-butylamine and dimethylamine also being very successful, but methylamine very poor. They did not obtain any azepine in liquid ammonia. Cadogan and Todd[138] obtained the azepine in high yield (83%) by the deoxygenation of nitrobenzene with diethyl methylphosphonite, which they found to be the most efficient phosphorus reagent, and postulated that the mechanistic step of nitrene to azabicyclic intermediate, (41), might be reversible, (Scheme 106).



(41) Scheme 106

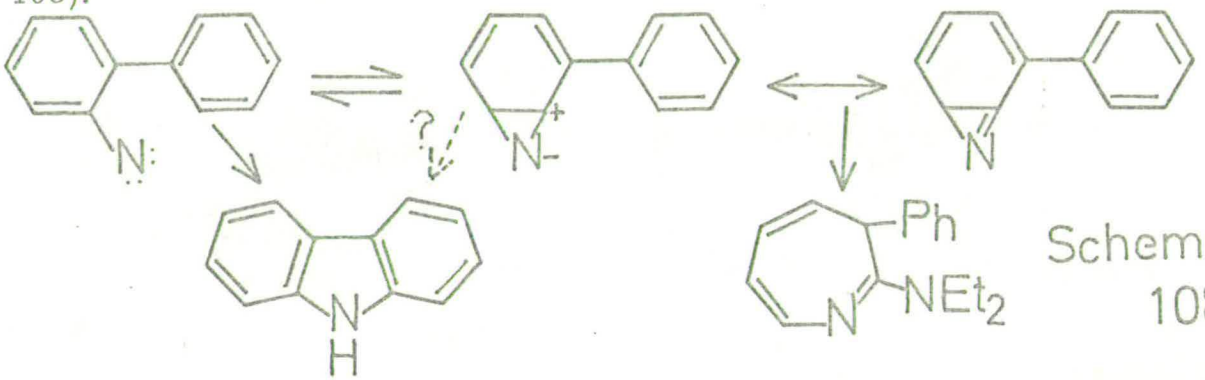
Meyer and Griffin[57] generated phenyl nitrene by photolytic fragmentation of N-phenylcyclohexyloxazirane in the presence of diethylamine and obtained the azepine (10%); under similar conditions, they obtained the azepine (34%) from photolysis of the azide. Matsumoto and co-workers[72] photolysed substituted anthranils in the presence of nucleophiles and obtained 2-methoxy-3H-azepine (in methanol) and 2-diethylamino-3H-azepine, (in diethylamine) in good yield, (Scheme 107).



Scheme 107

Cadogan and Todd[138] reported that some 3-phenyl-2-diethylamino-3H-azepine was formed during the deoxygenation of o-nitrobiphenyl in

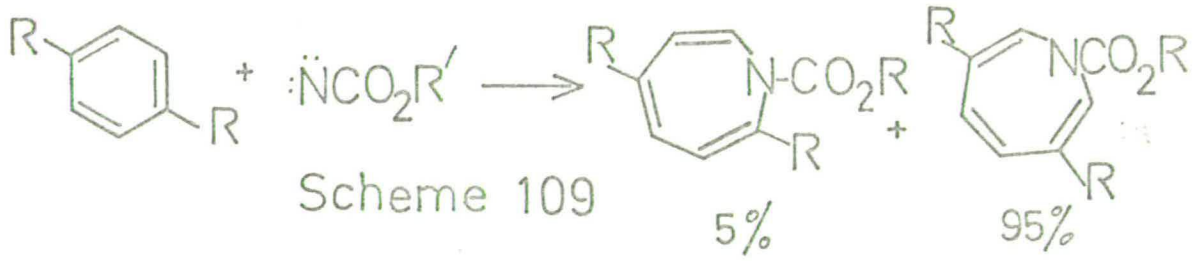
diethylamine, along with the major product carbazole, a normally facile reaction. Sundberg[174] also observed this azepine in the photolysis of o-azidobiphenyl in tetrahydrofuran containing diethylamine whose concentration was varied from 0-100% in a series of experiments, and obtained increasing yields of azepine relative to carbazole as the concentration of diethylamine was increased, until at 50% diethylamine more azepine than carbazole was formed. The implication is that the bond reorganisation between the intermediates is reversible, (Scheme 108).



Scheme 108

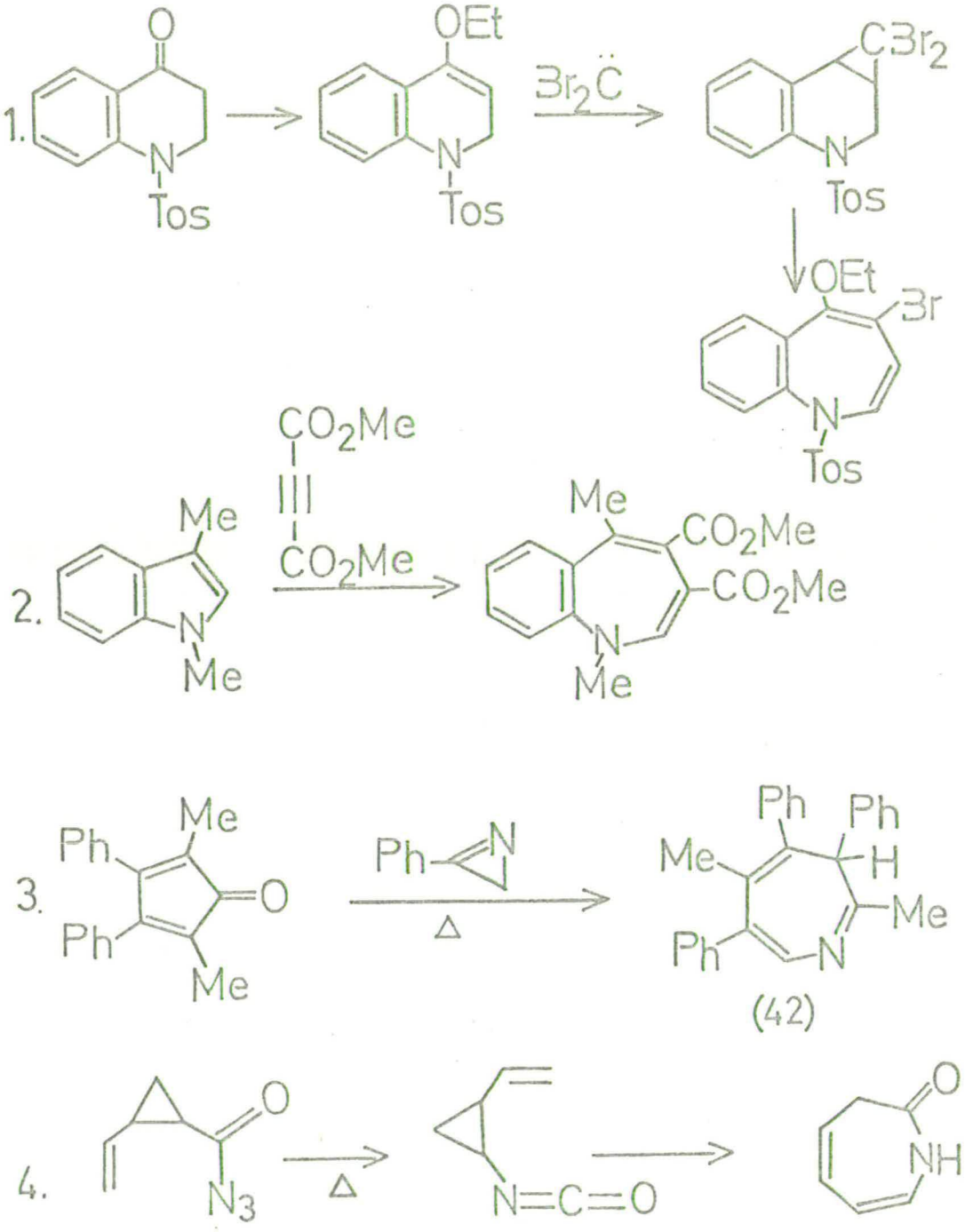
Sundberg has recently been working on a series of experiments[170, 175] which show that a 1H-azepine is formed first, which subsequently rearranges, normally under experimental conditions to be more stable 3H-azepine; he succeeded in characterising those which had 3-alkyl substituents because such substituents retard the conversion to the 3H-tautomer.

Ways of forming azepines, other than by reactions of aryl nitrenes, have been reported by several people. Carbethoxy nitrenes are known to add to benzene to form good yields of 1-carbethoxy-1H-azepines,[106a] and this addition occurs symmetrically rather than asymmetrically to a p-disubstituted benzene,[176] (Scheme 109).



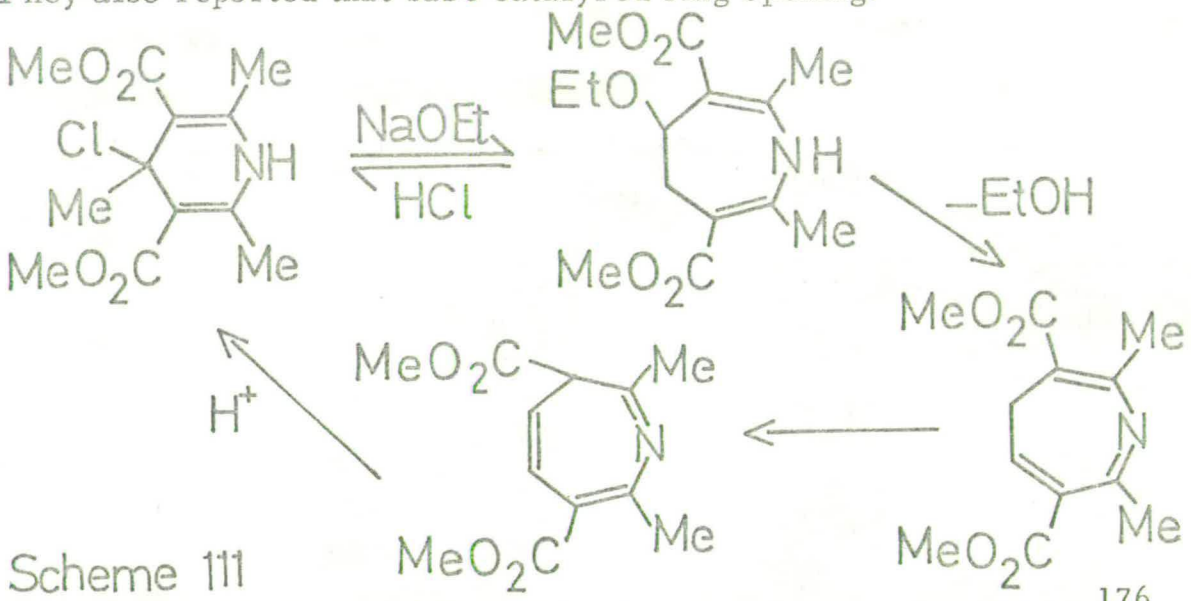
Scheme 109

Azepines may also be generated by addition of a carbene,[177] (equation 1) and by cycloaddition reactions,[178, 179] (equations 2, 3). Vogel[180] obtained 1, 2, 3-tri-H-azepin-2-one by heating 1-azidocarbonyl-2-ethylenecyclopropane, whose mechanism involves the isocyanate, (equation 4, Scheme 110).



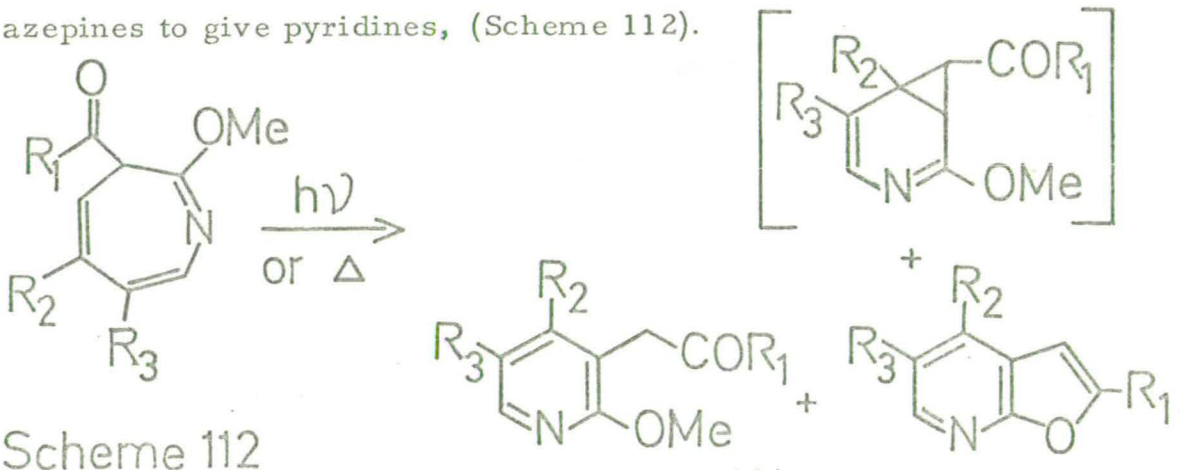
Scheme 110

(42) can be reduced by trimethyloxoniumfluoroborate to 2-methoxy-3H-azepine[180, 181]. The nucleophile in the 2 position is facilely replaced by boiling under reflux in other nucleophiles,[72, 173, 180] e. g. methoxy by diethylamino. Anderson and Johnson[182] reported a reversible formation of an azepine from a dihydropyridine, (Scheme 111). They also reported that base catalysed ring opening.



Scheme 111

Cycloaddition to a 1H-azepine has been reported by Photis[176] with tetracyanoethylene, but Nair[179] reported that azepines will not react either with or as dienophiles, possibly because of steric crowding in the azepine he investigated: 2, 5-dimethyl-3, 4, 6-triphenyl-3H-azepine. Matsumoto[183] reported the photochemical and thermal ring contraction of azepines to give pyridines, (Scheme 112).



Scheme 112

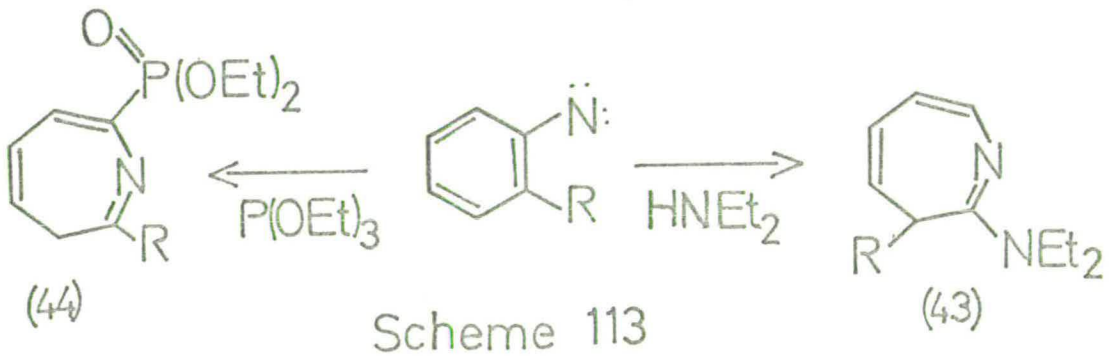
In the case of dibenzo(b, f)azepin-2-one,[184] substitution by nitro, bromo and chloro occurred in the benzene rings, while reactions such as Vilsmeier and Friedel Crafts' acylation resulted in decomposition with no recoverable products.

C PROGRAMME OF RESEARCH

It was considered that the formation of an azepine could represent a key method of determining whether an aryl nitrene was involved in any given reaction or not. There was, however, insufficient evidence about the precise nature of the steps in the mechanism. One of the first tasks of this research was therefore a thorough investigation of which isomers were formed under which circumstances from a number of substituted nitrobenzenes, and whether these correlated with the results from nitrenes generated by another method: from substituted phenyl azides.

There was another anomaly reported by Todd.[97] Two different azepines were formed from reactions involving two different nucleophiles. From reaction in diethylamine, 2-diethylamino-3H-azepine (43) was obtained, and from reaction in triethyl phosphite, diethyl 3H-azepin-7-yl phosphonate (44) was obtained (Scheme 113). It was hoped that further results involving different nucleophiles would resolve this conflict.

Finally it was hoped to show conclusively the singlet or triplet nature of the nitrene in such reactions.



(44) (43)

Scheme 113

1. INSTRUMENTATION

Melting points were determined on a Kofler hot stage microscope and were corrected.

Infrared spectra were recorded on a Perkin-Elmer 337 Grating Spectrophotometer. Solids were examined as nujol mulls, and liquids as thin films, using sodium chloride plates. Polystyrene, ν_{max} 1603 and 1029 cm^{-1} was used as reference for calibration purposes.

Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer Model R10 Nuclear Magnetic Resonance Spectrometer operating at a frequency of 60 MH_2 and a probe temperature of 33°, or on a Varian HA-100 instrument, operating at 100 MH_3 and a probe temperature of 28°. Chemical shifts were recorded as tau (τ) values in parts per million, using tetramethylsilane as an internal reference (τ=10.0). Spectra were determined on 10-15% w/v solutions unless solubility or availability of the sample imposed limitations. Unless otherwise stated, the solvent used was deuterochloroform.

Mass spectra and exact mass measurements were recorded on AEI MS902 mass spectrometer, or an AEI MS 20 coupled to a g.l.c.

Microanalyses were carried out on a Perkin Elmer Elemental Analyser 240.

2. PREPARATION OF MATERIALS

Light petroleum, used in elution chromatography, was redistilled, and both petroleum and ether were stored over sodium wire. Unless otherwise stated, petroleum refers to light petroleum (b. p. 40-60°). Elution chromatography was carried out on columns of alumina (Laporte Industries, Type H, 100/200's mesh, Brockmann activity 2). Thin layer chromatography was performed on 0. 3 mm layers of alumina (Merck, Aluminium oxide G type E) or of silica (Merck, silica gel G acc. to Stahl). Components in the developed chromatogram were detected by their fluorescence in ultraviolet light, or by their reaction with iodine.

Except where stated, starting materials were commercially available samples and were not further purified.

Trimethyl phosphite and triethyl phosphite (Albright and Wilson) were allowed to stand over sodium wire for 24 h and were then distilled in an atmosphere of nitrogen, b. p. 42° at 10 mmHg and 53° at 14 mmHg respectively.

Diethyl methylphosphonite of purity better than 95% was supplied by the Chemical Defence Experimental Establishment, and was used without further treatment.

Ethyl diphenylphosphonite was prepared according to Rabonitz and Pellon.[186] To a solution of absolute ethanol (27.4 g, 0.60 mol) and triethylamine (54.3 g, 0.53 mol) in benzene (300 ml) under nitrogen, was slowly added, with stirring, chlorodiphenylphosphine (109.5 g, 0.495 mol). A white solid, triethylamine hydrochloride, formed immediately. The temperature was maintained at 20-30° with the aid of an ice-bath. When the addition was half complete, extra benzene (100 ml) was added. Although addition was complete in 15 min, the mixture was stirred for a further 2 h, and then filtered. The triethylamine hydrochloride was washed with benzene (300 ml) and the combined filtrate and washing reduced in volume on a rotary evaporator, and then fractionally distilled, the fraction b. p. 110-122° at 0.7 mmHg being collected. The yield of ethyl diphenylphosphinate was 87%

Triphenylphosphine was used without further purification.

Trisdiethylaminophosphine was prepared according to Michaelis.[187] Phosphorus trichloride (30 g, 0.218 mol) in ether (100 ml) was added dropwise with vigorous stirring to excess diethylamine (105 g, 1.44 mol) in ether (700 ml). The diethylamine hydrochloride formed as a white precipitate was filtered off and the solvent removed on a rotary evaporator. The colourless oil which remained was dissolved in light petroleum (200 ml), causing a further quantity of diethylamine hydrochloride to precipitate; this was then filtered off, and the petroleum removed on a rotary evaporator. Distillation of the colourless oil gave trisdiethylaminophosphine (46.7 g, 86.5%), b. p. 73-75° at 1.0 mmHg.

2-Nitrophenyl-2,6-dimethylphenyl sulphide was purified by elution with light petroleum from an alumina column, and recrystallisation from ethanol, m.p. 112-113°.

Diethylamine, triethylamine and morpholine were distilled from potassium hydroxide, and stored over potassium hydroxide, b.ps. 56.5°, 89.5° and 128-130° respectively. Aniline, cyclopentadiene and ethyl acetoacetate were redistilled immediately before use.

When ethanol and methanol were required super dry, they were purified according to Vogel.[188] To magnesium (5 g) and iodine (0.5 g) was added commercial methanol (50 ml), and the mixture warmed until the iodine disappeared and evolution of hydrogen began, and the heating continued until all the magnesium had been dissolved as magnesium methoxide. Methanol (900 ml) was added, the solution boiled under reflux for 30 min, and the methanol then distilled under anhydrous conditions, the first portion (25 ml) being discarded. Ethanol was prepared similarly. The pure solvents were stored over molecular sieves.

Nitrosobenzene.[189] To a mixture of nitrobenzene (25 ml, 0.24 mol) and a solution of ammonium chloride (15 g, 0.28 mol), in water (500 ml) was added with vigorous stirring zinc dust (37.2 g, 0.57 mol) in small portions over 5 min. The temperature was maintained at 50-55° by addition of ice. After 20 min, the mixture was filtered, the residues washed with boiling water (300 ml) and the filtrate and washings combined and cooled immediately to 0-2° by addition of excess ice, leaving ice (100 g) unmelted. To this cold suspension of β-phenylhydroxylamine was added forthwith, with stirring, a cold solution of sulphuric acid (concentrated acid (75 ml) with sufficient ice to reduce the temperature to -5°). An ice cold solution of sodium dichromate dihydrate (17 g) in water (50-70 ml) was added as rapidly as possible to the stirred mixture. After 2-3 min, the straw coloured precipitate of nitrosobenzene was filtered off, washed with water, steam distilled, and recrystallised from ethanol, m.p. 66-67°; (lit,[189] m.p. 67-68°), yield 30%.

o-, m-, p-Nitrosotoluenes. These compounds were prepared according to Lutz and Lyton.[190] Nitrotoluene (15.6 g, 0.114 mol), water (24 ml), ethanol (42 ml) and calcium chloride (1.5 g) were heated to boiling, stirred, and zinc dust (20 g) added slowly. After 10 min, the residue was filtered off, and the solution poured into ice water (600 ml) containing ferric chloride (37 g). Nitrosotoluene separated as a solid which was filtered off, washed with water, and then steam distilled twice. o-Nitrosotoluene, m.p. 70-72° (lit,[190] 72.5°) yield 20%. m-Nitrosotoluene, m.p. 48-50° (lit, 53.5°) yield 15%. p-Nitrosotoluene, m.p. 45-47° (lit, 48.5°) yield 12%.

p-Nitrosobenzonitrile. This compound was prepared according to the method of Ashley and Berg.[191] Powdered potassium persulphate (50 g) was added in one portion to concentrated sulphuric acid (55.8 ml) and after being stirred for 1 h, the mixture was added to ice (900 g) and adjusted to pH 5.0-5.5 with anhydrous potassium carbonate (ca. 150 g). The mixture was filtered and the cold filtrate (ca. 960 ml, containing 9.0-9.3 g persulphuric acid) was stirred at 20° while p-aminobenzonitrile (5 g) dissolved in dioxan (20 ml) was added gradually. The mixture was stirred at room temperature for 20 h, and then the light brown solid was filtered off and steam distilled to give p-nitrosobenzonitrile (2.45 g, 44%) (from ethanol), m.p. 135-136° (lit.[191] m.p. 136-137°).

m-Chloronitrosobenzene. The corresponding hydroxylamines were made from the appropriate nitro compounds by the method of Rising.[192] Chloronitrobenzene (13.86 g, 0.088 mol) in ethanol (60 ml) and ammonium chloride (2 g) in water (50 ml) were mixed together and heated to 65° with vigorous stirring. Zinc (15 g) was added over 1 min, resulting in the vigorous boiling of the mixture. Stirring was continued until the heat stopped rising (ca. 2 min), and the mixture immediately filtered through hyflo, and the residue washed with hot ethanol, the filtrate and washing being cooled immediately by a flask containing ice (200 g), and then placed in the refridgerator where crystals formed. The hydroxylamine so obtained was dissolved in dry

methylene chloride (50 ml) and the solution poured onto the silver carbonate on celite reagent (20 g). The pale yellow solution turned green immediately. The mixture was filtered on celite, the filtrate reduced in volume at room temperature on a rotary evaporator, to give white crystals of m- and p-chloronitrosobenzene (7.0 g, 56%), m.p. 70-71° (lit, 72°) and 7.2 g, 58%), m.p. 90-91° (lit, 92-93°) (from ethanol and water).

Silver Carbonate Reagent on Celite. This reagent was prepared according to the method of Fetizon and Golfier.[193] To silver nitrate (34 g, 0.2 mol) dissolved in distilled water (200 ml) was added pure celite (30 g) with vigorous stirring. To the suspension when it was homogeneous was added over several minutes, with stirring, hydrated sodium carbonate (30 g, 0.105 mol) in distilled water (300 ml). After the addition, the mixture was stirred for 10 min and then the yellow precipitate filtered off, washed with distilled water until the rinsings were neutral, washed rapidly with acetone and then with methylene chloride, and dried.

Ethyl- and Methyl-nitrobenzoates. These compounds were prepared according to Vogel[188]. p-Nitrobenzoic acid (21 g), absolute ethyl alcohol (11.5 g), concentrated sulphuric acid (3.8 g) and dry benzene (30 ml) were heated under reflux for 16 h. The cold reaction mixture was extracted with ether (2 x 50 ml) and the extracts washed with sodium bicarbonate solution and then water, dried over magnesium sulphate, and the solvent removed on a rotary evaporator to give ethyl p-nitrobenzoate (21 g, 85%), m.p. 56° (lit, m.p. 56°).

2, 2-Diethylphenylhydrazine. This compound was prepared according to Wieland and Fressel.[194] o-Bromotoluene (10.0 g) was added to clean magnesium (1.5 g) in anhydrous ether (50 ml), under nitrogen, with stirring. The reaction mixture, having been started by warming, turned green. After 0.5 h, when almost all the magnesium had dissolved, diethyl nitrosamine (2.2 g) was added dropwise, with further stirring, and the mixture warmed for 2 h. The Grignard complex was then decomposed by addition of iced water, when the red-brown colour of the complex disappeared, and the pale yellow

colloidal suspension brought into solution by addition of hydrochloric acid. The 2, 2-diethyl phenylhydrazine was extracted with ether and distilled, the fraction b. p. 110-140° being collected. Lit[194] 110-120. Yield: 30%

Phenylazide. This compound was prepared according to Smith.[195] To aniline (1. 8 g) was added hydrochloric acid (5 ml) and then water (5 ml), and the mixture cooled to 0°. A cold solution of sodium nitrite (1. 54 g) in water (3. 5 ml) was added slowly with stirring, and the mixture stirred for a further 2-3 h at 0°. Then sodium azide (3. 15 g) in water (40 ml) was added with stirring. Sodium bicarbonate was added, and the phenylazide was extracted into ether, the ether layers dried and evaporated at room temperature. Yield: 80%. The i. r. spectrum showed a strong peak at 2100 cm^{-1}.

2-Azidoacetophenone. This compound was prepared according to Fitton and Smalley[196] 2-Aminoacetophenone (2 g) was dissolved in concentrated hydrochloric acid (18 ml) and water (50 ml) and cooled to 0°. A solution of sodium nitrite (1. 5 g) in water (10 ml) was added, and the solution stirred for 10 minutes. The solution was then decanted into a solution of sodium acetate (60 g) and sodium azide (2. 5 g) in water (100 ml) and stirred for 20 minutes. The white solid, 2-azidoacetophenone, was filtered off and recrystallised from methanol and water. Yield: 90%. The i. r. spectrum showed a strong peak at 2100 $cm.^{-1}$

3-Methylanthranil. This compound was prepared according to Griffith.[197] 1-Acetyl-2-nitrobenzene (1. 8 g) was added to a solution of stannous chloride dihydrate (8. 2 g) in concentrated hydrochloric acid (21 ml). The reaction mixture was maintained at 15-25° by a cold water bath. A few seconds after addition of 1-acetyl-2-nitrobenzene, a white solid was precipitated, which failed to redissolve, although the mixture was stirred for 3 h. The mixture was diluted with water and extracted with ether, which on evaporation gave a pale yellow oil, 3-methylanthranil, (1. 5 g, 80%).

3-Acetyl-2-methoxy-3H-azepine. This compound was prepared according to Matsumoto.[183] 3-Methylanthranil (1. 5 g, 0. 012 mol) in

methanol (150 ml) was photolysed with a pyrex filter for 7 h. The excess of solvent was removed on a rotary film evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when a yellow oil was eluted (ether/petrol, 1:10 v/v), which was shown by n.m.r. and mass spectra to be 3-acetyl-2-methoxy-3H-azepine (1.25 g, 62%).

3. PHOSPHORUS REAGENTS IN THE DEOXYGENATION OF a) NITROBENZENE AND b) NITROSOBENZENE.

Reaction of nitrosobenzene with triphenylphosphine in diethylamine.

Nitrosobenzene (2.14 g, 0.02 mol) in a minimum of dry ether (8 ml) was added to a solution of triphenylphosphine (12.9 g, 0.05 mol) in diethylamine (100 ml), boiling under reflux (56.5°), under nitrogen, and the mixture boiled under reflux for a further 4 h. The excess of solvent was removed on a rotary evaporator, and the residue dissolved in ethanol, from which triphenyl phosphine oxide crystallised out and was filtered off. The filtrate was reduced in volume on a rotatory evaporator, and then distilled at the oil pump to give a yellow oil, b.p. 56-60° at 0.1 mmHg, which was shown to be 2-diethylamino-3H-azepine[172] (0.60 g, 19.6%) by comparison with an authentic specimen, g.l.c. retention time (3% QF1, 100°), m/e (164), i.r. and n.m.r. spectra were identical. Details of these spectra are discussed in section C.

Reaction of nitrosobenzene with triethyl phosphite in diethylamine.

Nitrosobenzene (4.00 g, 0.037 mol) in a minimum of ether (10 ml) was added to a solution of triethyl phosphite (8.00 g, 0.04 mol) in diethylamine (100 ml) boiling under reflux (56.5°) under nitrogen, and the mixture boiled under reflux for 4 h, by which time it had become pale orange. Excess of solvent was removed on a rotary evaporator, and the phosphate esters together with excess triethyl phosphite were distilled off, b.p. 120° at 14 mmHg. The residue was adsorbed on alumina and chromatographed on an alumina column, when the following

fractions were eluted, the eluant is given in parenthesis. (1) Yellow oil (0.55 g) (petrol). (2) Yellow oil (0.88 g) (petrol). (3-5) Yellow oils (1.82 g) (benzene/petrol, 1:10 v/v). (6-7) Yellow oils (0.90 g) (benzene/petrol, 4:10 v/v). (8-14) Brown oils (0.35 g) (ether/benzene, 1:10-10:10 v/v). (15) Tar (0.40 g) (methanol). Fraction 1 was shown to be azobenzene (0.55 g, 12.1%), m.p. and mixed m.p. 68.5° (from ethanol), identified by comparison with an authentic specimen, having identical g.l.c. retention time (3% QF1, 185°), i.r. and n.m.r. spectra. Fraction 2 was shown to be azoxybenzene (0.88 g, 23.9%), m.p. and mixed m.p. 35.5° (from ethanol), identified by comparison with an authentic specimen, having identical g.l.c. retention time (3% QF1, 185°), i.r. and n.m.r. spectra. Fractions 3-5 were shown to be 2-diethylamino-3H-azepine (1.82 g, 28%), identified by comparison with an authentic specimen, having identical g.l.c. retention time (3% QF1, 100°) and n.m.r. spectrum. Fractions 6-7 were shown to be aniline (0.90 g, 25.8%), identified by comparison with an authentic specimen, having identical g.l.c. retention time (3% QF1, 70°) and i.r. spectrum, whose strong double peak at 3250 cm^{-1} is characteristic of $-NH_2$. Fractions 9-15 showed only phosphate esters, and nothing that could be attributed to diethyl N-phenylphosphoramidate.

Reaction of nitrosobenzene with ethyl diphenylphosphinite in diethylamine. Nitrosobenzene (2.60 g, 0.024 mol) in a minimum of ether (10 ml) was added to a solution of ethyl diphenylphosphinite (6.00 g, 0.025 mol) in diethylamine (100 ml) boiling under reflux (56.5°) under nitrogen, and the mixture boiled under reflux for 0.5 h. The excess of solvent was removed on a rotary evaporator and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluant being given in brackets: (1-3) Yellow oils (0.28 g) (petrol). (4-8) Yellow oils (0.64 g) (petrol). (9-16) Yellow oils (2.90 g) (benzene/petrol, 2:10 v/v). (17-22) Brown oils. (0.30 g) (benzene/petrol, 5:10 v/v). (23-28) Dark brown oils (0.55 g) (benzene). Fraction 1 was shown to contain azobenzene (0.04 g, 1.4%) identified by comparison with an authentic specimen, having identical g.l.c. retention time

(3%QF1, 185°) and i.r. spectrum. Fraction 2 was shown to be azoxybenzene (0.53 g, 22%), identified by comparison with an authentic specimen, having identical g.l.c. retention time (3% QF1, 185°) and i.r. spectrum. Fraction 3 was shown to be pure 2-diethylamino-3H-azepine (2.43 g, 61%), identified by comparison with an authentic sample, having identical g.l.c. retention time (3% QR1, 98°) and n.m.r. spectrum. Fraction 4 was shown to be aniline (0.26 g, 11.5%) identified by comparison with an authentic specimen, having identical g.l.c. retention time (3% QF1, 88°) and i.r. spectrum.

Reaction of N,N-dimethyl p-nitrosoaniline with triethyl phosphite in diethylamine. N,N-Dimethyl p-nitrosoaniline (1.97 g, 0.014 mol), triethyl phosphite (2.61 g, 0.16 mol) and diethylamine (50 ml) were boiled under reflux (55°) under nitrogen for 2 h, during which time the green colour slowly changed to brown. When the reaction mixture cooled, a brown solid (0.53 g) was precipitated and filtered off, and identified as 4,4'-bis(dimethylamino)azobenzene (0.53 g, 30.5%), m.p. 270°, lit.,[196] 270°. Excess of solvent was removed from the filtrate, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, but no characterisable products were obtained, and no azepine was formed.

Reaction of p-chloronitrosobenzene with triethyl phosphite in diethylamine. p-Chloronitrosobenzene (0.15 g, 0.00105 mol), triethyl phosphite (0.3 g, 0.0018 mol) and diethylamine (50 ml) under nitrogen were stirred at 0° for 1 h. The colour gradually changed from green to brown, and a trace of a colloidal brown precipitate was formed. The excess of solvent was removed on a rotary film evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when ether/petrol (1:100 v/v) eluted a pale yellow solid (0.10 g) identified as 4,4'-dichloroazoxybenzene (0.10 g, 70%), m.p. 158°, Lit,[196] 158° (from ethanol) m/e 266, 268, τ 2.5 (2H, d x d, $J9H_2$, $2H_2$) 1.8 (2H, m), and (2) brown oil (0.05 g) (ether) identified as 5-chloro-2-diethylamino-3H-azepine (0.05 g, 23%), on comparison with an authentic specimen, having identical n.m.r. spectrum and g.l.c. retention time.

Reaction of nitrobenzene with trisdiethylaminophosphine in diethylamine. Nitrobenzene (2.00 g, 0.016 mol) and trisdiethylaminophosphine (16.5 g, 0.067 mol) in diethylamine (70 ml), under nitrogen, were boiled under reflux (56.5°) for 8 days, by which time g.l.c. (3% QF1, 100°) showed only a small trace of starting material, and the solution had turned dark brown. The products were investigated by quantitative g.l.c., using the gas density balance, peaks identified by comparison of retention times with those of authentic specimens and peak enlargement on simultaneous addition of authentic specimen. The columns used were: 3%QF1, 75-150°; sil. oil/celite, 120°; 20% APL, 138°. Areas of peaks were measured, and from them the number of moles of material present was calculated according to the equation:[200]

$$\frac{n_i}{n_s} = \frac{A_i}{A_s} \frac{[M_{s-m}]}{[M_{i-m}]}$$

where n = number of moles; i = unknown

A = area of peak; s = added internal standard

M = molecular weight

m = molecular weight of carrier gas (nitrogen)

Dibenzyl was used as internal standard. The results showed that 88.4% of starting material had reacted to give 2-diethylamino-3H-azepine (65.5%) and aniline (9%), yields based on starting material consumed. Neither azobenzene nor azoxybenzene were formed.

Reaction of nitrobenzene with trimethyl phosphite in diethylamine. Nitrobenzene (2.00 g, 0.016 mol) and trimethyl phosphite (9.80 g, 0.079 mol) in diethylamine (60 ml), under nitrogen, were boiled under reflux (57°) for 14 days, by which time the solution had turned black. Examination by g.l.c. (10% APL, 120°) showed a large number of products, of which the major one was identified as 2-diethylamino-3H-azepine (40%) by comparison with an authentic specimen.

b. Nitrene Insertion in N-H bond.

Reaction of nitrobenzene with ethyl diphenylphosphinite in diethylamine. Nitrobenzene (1.0 g, 0.008 mol) and ethyl diphenylphosphinite (4.85 g, 0.021 mol) in diethylamine (70 ml), under nitrogen, were boiled under reflux (56.5°) for 6 days, when g.l.c. (10% APL, 140°) showed only a trace of nitrobenzene, no 2-diethylamino-3H-azepine, some aniline, and a major product not previously seen. When the reaction mixture had cooled, a white solid crystallised out and was filtered off, which mass spectrum indicated was a polymeric phosphorus residue with units of diphenylphosphine oxide. Solvent was removed from the filtrate on a rotary evaporator, and the residue distilled, b.p. 102° at 9 mmHg, to give a yellow oil, which was further purified by chromatography on an alumina column, eluted with petrol, and redistilled. I.r.: single peak 3250 cm^{-1} attributed to NH. N.m.r.: τ 8.95 (t, 2Me, J=7Hz), 7.36 (quartet; 2-CH_2-, J = 7Hz), 6.09 (diffuse s; 1H) which disappeared on shaking with D_2O), 2.5-3.6 (m, 5H, 3 centred 2.9 and 2 centred 3.45). m/e 164. The product was identified as 2,2-diethylphenylhydrazine (1.24 g, 62.5%). (Found: C, 73.0; H, 9.3; N, 17.3. Calculated for $C_{10}N_{16}N_2$: C, 73.1; H, 9.7; N, 17.1%).

Reaction of o-nitrosotoluene with ethyl diphenylphosphinite in diethylamine. o-Nitrosotoluene (2.00 g, 0.016 mol) in diethylamine (20 ml) was added to a solution of ethyl diphenylphosphinite (5.40 g, 0.023 mol) in diethylamine (50 ml), boiling under reflux (57°), all under nitrogen. Reaction was instantaneous as shown by darkening of reaction mixture, and a white crystalline solid was precipitated. G.l.c. (3% QF1, 75°) showed absence of starting material and two major products, of which the smaller was tentatively identified as o-toluidine by comparison of retention time with that of an authentic sample. No peaks corresponding to 2,2'-dimethylazobenzene nor 2,2'-dimethylazoxybenzene were found. The solid was filtered off, the solvent removed on the rotary evaporator, and the residue adsorbed on alumina and chromatographed on an alumina column, when the

following fractions were eluted, the eluant being given in brackets: (1) Yellow oil (1.80 g) (petrol). (2-4) Less than 0.05 g, (petrol). (5-6) Brown liquid (0.40 g) (benzene). (7) Brown liquid (0.08 g) (benzene). (8-9) Tars (0.90 g) (methanol).

Fraction 1 had i.r. : single peak at 3250 cm^{-1} attributed to NH. N.m.r. (100 Mc/sec and 60 Mc/sec): τ 7.86 (s, Me), 8.93 (t, 2Me, J=6Hz), 7.27 (quartet, 2-CH_2^-, J=6Hz), 6.91 (diffuse s, 1H, which disappeared on shaking with D_2O), 2.7-3.4 (m, 4H, of which 1H was centred 3.3). m/e = 178, 106, 91. This product was identified as 2, 2-diethyl-(2-methylphenyl)hydrazine (60%). Comparison with an authentic specimen[195] confirmed this. It was further purified by distillation, b.p. 110-130° 17 mmHg, and then by dissolving in hydrochloric acid, extracting impurity with ether, regenerating it with base and recovering it from ether. (Found: C, 74.5; H, 10.007; N, 16.03. $C_{11}H_{18}N_2$ requires: C, 74.2; H, 10.1; N, 15.75%).

Fractions (5-6) were shown (i.r., n.m.r., g.l.c.) by comparison with authentic specimen to be o-toluidine (21.8%). The remainder contained only phosphorus esters and polymeric residues.

Reaction to discover conditions for formation of 2, 2-diethylphenylhydrazine.

The concentration of diethylamine was varied:

Flask Number	1	2	3	4	5
Nitrobenzene (g)	0.52	0.50	0.50	0.50	0.50
Ethyl diphenylphosphinite (g)	5.0	5.0	5.0	5.0	5.0
Diethylamine (g)	0	1.61	5.0	10.03	20.01
Time (h)	0.1	1.5	47	54	144

The reaction was monitored by g.l.c. (10% APL, 130°). Flasks 2-4 at 5% reaction showed both 2, 2-diethylphenylhydrazine and 2-diethylamino-3H-azepine present in equal quantities, but only the latter

was formed thereafter; by the end of the reaction, it was the only major product. Flask 5 showed no reaction (no colour change) for 5 days, and then rapidly became tarry, with a large number of products.

Reaction of nitrobenzene with ethyl diphenylphosphinite in diethylamine under pressure. Nitrobenzene (2.41 g, 0.02 mol), ethyl diphenylphosphinite (10.92 g, 0.044 mol) and diethylamine (75 ml) were heated at 56.5° in a bomb, previously filled with nitrogen, for 7 days when g.l.c. (10% APL, 130°) showed starting material and also aniline and 2, 2-diethylphenylhydrazine in trace quantities, and as major product 2-diethylamino-3H-azepine. Solvent was removed on the rotary evaporator, and the products adsorbed on alumina and separated on an alumina column, when the following fractions were eluted; the eluant being given in parenthesis.

(1) Yellow liquid (1.00 g) (petrol). (2) Yellow liquid (0.20 g) (ether/petrol, 1:10 v/v). (3) Yellow liquid (1.28 g) (ether/petrol, 5:10 v/v). (4) Brown liquid (3.50 g) (ether). (5) Tar (2.80 g) (methanol).

Fraction 1 was shown by g.l.c. retention time (10% APL, 130°) and n.m.r. spectrum, which were identical on comparison with an authentic specimen to be nitrobenzene. Fraction 2 contained a 1:1 mixture by g.l.c. and n.m.r. spectrum of nitrobenzene and 2-diethylamino-3H-azepine. Fraction 3 was shown by g.l.c. and n.m.r. spectrum, which were identical on comparison with authentic specimen to be 2-diethylamino-3H-azepine (1.28 g, 79%, based on starting material consumed). The remainder contained only phosphorus esters and polymeric residues.

Reaction of nitrobenzene with ethyl diphenylphosphinate in diethylamine under pressure at elevated temperature. Nitrobenzene (2.98 g, 0.024 mol), ethyl diphenylphosphinite (24.93 g, 0.108 mol) and diethylamine (50 ml) were heated in a bomb, previously filled with nitrogen, at 71° for 7 days, when g.l.c. (10% APL, 130°) showed that all the nitrobenzene had been consumed. Some white crystals, polymeric phosphorus species, were deposited and filtered off, washed

with ether, and the ether washings added to the filtrate, which was reduced in volume on a rotary evaporator and the residue adsorbed on alumina and the products separated on an alumina column, when the following fractions were eluted; the eluant being given in parenthesis.

(1) Ethyl diphenylphosphinite, bringing down simultaneously all the interesting products (petrol).

(2) Ethyl diphenylphosphinate and polymeric residues (ether).

Fraction 1 was adsorbed onto silica, washed with wet benzene to oxidise the ethyl diphenylphosphinite, and then rechromatographed on alumina, when the following fractions were obtained:

(1) Yellow oil (0.30 g) identified (g.l.c. and n.m.r.) by comparison with an authentic speciman as 2,2-diethylphenylhydrazine (8%), (ether/petrol, 1:10 v/v).

(2) Yellow oil (2.50 g) identified (g.l.c., n.m.r., i.r.) by comparison with an authentic specimen as 2-diethylamino-3H-azepine (63%), (ether).

(3) Brown oil (4.20 g) identified (g.l.c. and n.m.r.) as phosphorus esters only, (methanol).

Reaction of nitrobenzene with ethyl diphenylphosphinite in diethylamine under pressure at elevated temperature. Nitrobenzene (2.62 g, 0.21 mol), ethyl diphenylphosphinite (20.20 g, 0.087 mol) and diethylamine (53 ml) were heated in a bomb, previously filled with nitrogen, at 91° for 48 h, after which the contents were found to be very dark brown. Investigation by g.l.c. (10% APL, 130°) showed the only major product was 2-diethylamino-3H-azepine (70%).

4. FORMATION OF SUBSTITUTED 2-DIETHYLAMINO-3H-AZEPINES.

Reaction of o-nitrotoluene with ethyl diphenylphosphinite in diethylamine. o-Nitrotoluene (2.04 g, 0.015 mol) and ethyl diphenylphosphinite (14.95 g, 0.056 mol) in diethylamine (50 ml), under

nitrogen, were boiled under reflux (59°) for 10 days, by which time the mixture had turned dark brown, and g.l.c. (10% APL, 120°) showed only a small peak corresponding to starting material, a trace of o-toluidine, and two other products. Excess of solvent was removed on the rotary evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluant being given in parenthesis: (1) Yellow oil (0.812 g) (petrol). (2) Yellow oil (0.559 g) (ether/petrol, 2:10 v/v). (3) Brown oils (11.5 g) (ether). (4) Brown oil (0.88 g) (methanol). Fraction 1 was identified as starting material by comparison with an authentic specimen, having identical g.l.c. retention time (10% APL, 120°) and n.m.r. spectrum. Fraction 2 was identified as 2-diethylamino-3-methyl-3H-azepine (0.559 g, 35.5%) from n.m.r. and i.r. spectra and m/e = 178, b.p. 70-75° at 0.01 mmHg. (Found: C, 74.1; H, 10.02; N, 15.95. $C_{11}H_{18}N_2$ requires C, 74.2; H, 10.1; N, 15.75%). Fraction 3 contained only phosphorus esters. Fraction 4 was identified as N,N-diethyl o-toluidine (0.88 g, 61.2%), b.p. 140-150° at 14 mmHg, ν_{max} (NaCl) no peak at 3350, no NH; τ 7.8 (3H, s, Ar-Me), 8.9 (6H, t, J 7Hz, 2-Me), 6.72 (4H, q, J 7Hz, 2-CH_2-), 2.7-3.4 (4H, m), m/e = 163. These spectra were identical to those of an authentic specimen.

Reaction of m-nitrotoluene with ethyl diphenylphosphinite in diethylamine. m-Nitrotoluene (0.93 g, 0.005 mol), ethyl diphenylphosphinite (5.01 g, 0.022 mol) and diethylamine (50 ml), under nitrogen, were boiled under reflux (59°) for 10 days, by which time the contents were dark brown. Solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluants being given in parenthesis: (1) Yellow oil, (petrol) which was rechromatographed on alumina to give: (1') cream solid identified as starting material (0.18 g) by comparison with authentic specimen of g.l.c. retention time (10% APL, 140°) and n.m.r. spectrum, (petrol). (2') Yellow oil (0.06 g), (petrol), having same g.l.c. retention time (10% APL, 150°) and n.m.r. spectrum as

(2), to which it was then added. (2) Pale yellow oil (0.72 g) (petrol), g.l.c. (10% APL, 150°) revealed two peaks ratio measured on chart paper, 1.74:1 and by integrator 1.73:1 (each ratio average of 3 measurements), n.m.r. spectrum indicated that two azepines were present, in ratio 1.72:1 : 4-methyl-2-diethylamino-3H-azepine (0.45 g, 46%) and 6-methyl-2-diethylamino-3H-azepine (0.26 g, 27%); m/e = 178.

Reaction of m-nitrotoluene with diethyl methylphosphonite in diethylamine. m-Nitrotoluene (2.61 g, 0.019 mol), diethyl methylphosphonite (10.71 g, 0.079 mol) and diethylamine (30 ml), under nitrogen, were boiled under reflux (63°) for 3-5 days, by which time the contents had become golden yellow and g.l.c. (10% APL, 118°) showed only a trace of starting material. Excess of solvent was removed on the rotary evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when a yellow oil (2.36 g) (ether/petrol 1:10 v/v) was obtained, b.p. 110° at 0.1 mmHg, identified by g.l.c., n.m.r. and i.r. spectra and m/e = 178 as a mixture of 4-methyl-2-diethylamino-3H-azepine (1.30 g, 38.5%) and 6-methyl-2-diethylamino-3H-azepine (1.06 g, 31.5%). (Found: C, 74.3; H, 9.85; N, 15.8. $C_{11}H_{18}N_2$ requires C, 74.2; H, 10.0; N, 15.8%).

Reaction of p-nitrotoluene with diethyl methylphosphonite in diethylamine. p-Nitrotoluene (2.61 g, 0.019 mol) and diethyl methylphosphonite (10.65 g, 0.078 mol) in diethylamine (30 ml), under nitrogen, were boiled under reflux (62°) for 3 days, when g.l.c. (10% APL, 118°) showed absence of starting material. Solvent was removed on the rotary evaporator, and the residue adsorbed onto alumina, and elution on an alumina column with ether/petrol, 1:10 v/v gave a pale yellow oil (2.40 g) b.p. 120° at 0.1 mmHg, and was identified by n.m.r. spectrum and m/e = 178 as 5-methyl-2-diethylamino-3H-azepine (2.40 g, 74.2%). (Found: C, 74.3; H, 9.86; N, 16.13. $C_{11}H_{18}N_2$ requires: C, 74.2; H, 10.01; H, 15.79%). G.l.c. of the original reaction mixture showed small peaks identified as p-toluidine, 4,4'-dimethylazobenzene and 4,4'dimethylazoxybenzene, identified by

comparison with retention times of authentic specimens.

Reaction of p-nitrosotoluene with diethyl methylphosphonite in diethylamine. p-Nitrosotoluene (1.6 g, 0.0132 mol) in diethylamine (20 ml) was added over 5 min to a solution of diethyl methylphosphonite (2.25 g, 0.0166 mol) in diethylamine (18 ml) boiling under reflux (62°), under nitrogen. The pale green nitroso solution immediately turned to dark orange. The excess of solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, eluants being given in parenthesis: (5-12) Red solid (0.11 g) (petrol). (13-15) Orange solid (0.05 g) (petrol). (21-25) Yellow oil (0.10 g) (ether/petrol, 1:10 v/v). (28-31) Yellow solid (0.32 g) (ether). (35-36) Brown oil (3.15 g) (methanol). Fraction 1 was identified as 4,4'-dimethylazobenzene (0.11 g, 8%), m/e = 220, τ 7.59 (6H, s, 2Me), 2.72 (2H, d, J 8Hz, ArH), 1.92 (2H, d, J 8Hz, ArH). M.p. 103-104° Lit, 104°. Fraction 2 was identified as 4,4'-dimethylazoxybenzene (0.05 g, 3%), m/e = 236, τ 8.62 (6H, s, 2Me), 2.78 (2H, 2d, J 8Hz, ArH), 1.90 (2H, t, J 4Hz, ArH), m.p. 68-69°, Lit, 70°. Fraction 3 was identified as 5-methyl-2-diethylamino-3H-azepine (0.10 g, 5%) by comparison with an authentic specimen, having identical g.l.c. retention time and n.m.r. and i.r. spectra. Fraction 4 was identified as p-toluidine (0.32 g, 16%) by comparison with an authentic specimen, having identical g.l.c. retention time and n.m.r. and i.r. spectra. Fraction 5 contained only phosphate esters and polymeric residues.

Reaction of m- nitrosotoluene with diethyl methylphosphonite in diethylamine. m-Nitrosotoluene (0.25 g, 0.002 mol) in diethylamine (2 ml) was added slowly to a solution of diethyl methylphosphonite (0.78 g, 0.008 mol) in diethylamine (5 ml), boiling under reflux (60°), under nitrogen. Reaction was immediate, as indicated by the green solution becoming orange. The reaction mixture was examined by g.l.c. (10% APL, 117°), and compared directly with a g.l.c. trace of the reaction mixture from the deoxygenation of m-nitrotoluene under

similar conditions, when peaks having the same retention times were obtained from each, but the ratios of peak sizes were different, and there was a peak corresponding to an extra product, X, from the m-nitrosotoluene; the areas under the peaks indicated that from the m-nitrosotoluene, the yields of the two azepines were considerably smaller, and m-toluidine was the major product.

Control experiment: the behaviour of m- and p-nitrosotoluenes under the reaction conditions. m- And p- nitrosotoluenes were each (0.2 g) warmed to 60° in diethylamine. The green solutions immediately turned orange, and examination by g.l.c. (10% APL, 119°) revealed that the azotoluenes and the azoxytoluenes were both formed, and that the major products were toluidine and the product identified as X on the previous experiment.

Reaction of m-nitroanisole with diethyl methylphosphonite in diethylamine. m-Nitroanisole (1.6 g, 0.0015 mol), diethyl methylphosphonite (6.68 g, 0.005 mol) and diethylamine (26 ml) under nitrogen were boiled under reflux (70°) for 4 days. G.l.c. (10% APL, 135°) during and at the end of the reaction showed the formation of only one significant product, and a trace of m-anisidine. The reaction mixture had become light orange by the end. The solvent was removed on the rotary evaporator, and the residue adsorbed onto alumina and chromatographed on an alumina column, when the following fractions were obtained, eluants being given in parenthesis: (8-9) Yellow oil (0.05 g) (ether/petrol 2:100 v/v). (10-16) Pale yellow oil (1.41 g) (ether/petrol, 1:10 v/v). (17) Pale yellow oil (0.28 g) (ether/petrol, 1:10 v/v). (18-19) Brown oil (<0.02g) (ether). (20) Tar (5.6 g) (methanol). Fraction 1 was shown to contain m-nitroanisole and 4-methoxy-2-diethylamino-3H-azepine, by comparison with authentic specimens, having identical g.l.c. retention times and n.m.r. spectra. Fraction 2 contained only one azepine and fraction 3, two azepines, in proportion 4:1, as shown by n.m.r. spectrum and g.l.c. (10% APL, 135°), ratio of peak sizes. The first was identified as 4-methoxy-2-diethylamino-3H-azepine (1.47 g, 73%) and the second as 6-methoxy-2-

diethylamino-3H-azepine (0.22 g, 13%), m/e = 196. (Found: C, 68.0; H, 9.2; N, 14.55. $C_{11}H_{18}N_2O$ requires C, 68.0; H, 9.3; N, 14.4%). B.p. 80° at 0.01 mmHg, p.p. -10°. Fraction 4 showed a peak on the g.l.c. whose retention time was identical to an authentic specimen of p-anisidine. Fraction 5 contained only phosphate esters and polymeric residues.

Reaction of o-methylanisole with diethyl methylphosphonite in diethylamine. o-Methylanisole (3.78 g, 0.025 mol), diethyl methylphosphonite (12.48 g, 0.092 mol) and diethylamine (30 ml) under nitrogen, were boiled under reflux (62°) for 2 days, by which time the reaction mixture was black and tarry. G.l.c. examination (10% APL, 150°) showed only a trace of starting material, some o-anisidine as major product, and a number of other peaks, none in the expected azepine position. The mixture was not worked up further.

Reaction of o-chloronitrobenzene with diethyl methylphosphonite in diethylamine. o-Chloronitrobenzene (3.01 g, 0.019 mol), diethyl methylphosphonite (10.40 g, 0.077 mol) and diethylamine (36 ml) under nitrogen, were boiled under reflux (61°), but had become black after 0.5hour, although g.l.c. (10% APL, 140°) then showed mostly starting material. Heating was continued for a further 24 hours, when the starting material had all vanished, solvent removed on the rotary evaporator, and the tarry residue subjected to chromatography on alumina, when the only product eluted with petrol was an orange oil (0.15 g) shown by comparison with authentic specimen to be o-chloroaniline (0.15 g, 6.1%), having identical g.l.c. retention time and n.m.r. and i.r. spectra.

Reaction of p-chloronitrobenzene with diethyl methylphosphonite in diethylamine. p-Chloronitrobenzene (4.01 g, 0.025 mol), diethyl methylphosphonite (14.90 g, 0.109 mol) and diethylamine (26.5 ml), under nitrogen, were boiled under reflux (68°) for 30 hours, when the reaction mixture had become dark red, and g.l.c. (10% APL, 145°) showed absence of starting material, and one major product. The solvent was removed on the rotary evaporator, and the residue adsorbed

onto alumina and chromatographed on an alumina column, when petrol eluted a pale yellow oil (3.70 g) which was redistilled at 80° at .3mmHg to give 3.31 g, identified by n.m.r., i.r., m/e = 198 and 200 as 5-chloro-2-diethylamino-3H-azepine (78%). (Found: C, 60.4; H, 7.5; N, 14.3. $C_{10}H_{15}ClN_2$ requires C, 60.1; H, 7.5; N, 14.1%). Elution with ether and then methanol gave only phosphorus esters.

Reaction of m-chloronitrobenzene with diethyl methylphosphonite in diethylamine. m-Chloronitrobenzene (4.00 g, 0.025 mol), diethyl methylphosphonite (14.14 g, 0.102 mol) and diethylamine (27 ml) under nitrogen, were boiled under reflux (70°) for 17 h, by which time the mixture had become dark red, and g.l.c. (10% APL, 145°) showed only a trace of starting material, which had totally disappeared after a further 3 h. The excess of solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when petrol eluted a yellow oil (2.08 g) shown by n.m.r. and i.r. spectra and m/e = 198 and 200 to be 6-chloro-2-diethylamino-3H-azepine. A further quantity of yellow oil (1.35 g.) was eluted by ether/petrol, 1:10 v/v, and shown by g.l.c. ratio of peak sizes and n.m.r. ratio of integrations of protons to contain two azepines, in proportions 3:2; there was obtained 6-chloro-2-diethylamino-3H-azepine (2.81 g, 56%) and 4-chloro-2-diethylamino-3H-azepine (0.92 g, 18%). (Found: C, 60.5; H, 7.5; N, 14.4. $C_{10}H_{15}ClN_2$ requires C, 60.1; H, 7.5; N, 14.1%). B.p. 80-85° at 0.3 mmHg.

Reaction of m-bromonitrobenzene with diethyl methylphosphonite in diethylamine. m-Bromonitrotoluene (3.0 g, 0.015 mol), diethyl methylphosphonite (5.05 g, 0.037 mol) and diethylamine (24 ml) were boiled under reflux (65°) under nitrogen for 14 h. The mixture turned black almost immediately, and had become tarry by the end. Excess of solvent was removed on the rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluants being given in parenthesis: (1) Pale, pink liquid (0.35 g) (ether/petrol,

1:10 v/v). (2) Brown liquid (0.86 g) (ether/petrol, 2:10 v/v). (3-5) Brown liquid (1.12 g) (ether/petrol, 5:10 v/v). (6) Brown liquid (0.25 g) (ether). (7) Black tar (4.60 g) (methanol).

Fraction 1 had τ 8.95 (t, 2Me, J = 7c/s), 6.82 (quartet, 2-CH_2-, J = 7c/s), 2.72-3.5 (m, 4H) and m/e 227 and 229, and was identified as N,N-diethyl-2-bromoaniline (0.35 g, 14.8%). Fraction 2 was identified by n.m.r. and m/e = 244 and 242 as 6-bromo-2-diethylamino-3H-azepine. Found: C, 49.66; H, 6.25; N, 11.65. $C_{10}N_{15}N_2Br$ requires: C, 49.50; H, 6.1; N, 11.55. Fractions (3-5) were identified by g.l.c. (10% APL, 152°) and n.m.r. as starting material (1.02 g) and 4-bromo-2-diethylamino-3H-azepine: 6-bromo-2-diethylamino-3H-azepine in proportions 1:1. Yield of the 6-bromo isomer: 39.5%, and of the 4-bromo isomer 4%. Fractions (6) and (7) were distilled at 110° at 0.1 mmHg to give 3-bromoaniline (0.45 g, 30%), identified by comparison with authentic specimen, having identical i.r. spectra whose characteristic peak was a double peak, 3250 cm^{-1} attributed to NH_2, m/e = 173 and 171, and g.l.c. retention time (2% APL, 130°).

Reaction of p-bromonitrobenzene with diethyl methylphosphinite in diethylamine. p-Bromonitrobenzene (2.02 g, 0.0099 mol), diethyl methylphosphinite (5.42 g, 0.04 mol) and diethylamine (20 ml) were boiled under reflux (64°) for 5 days, by which time the solution had turned red. Solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted; eluants being given in parenthesis: (1-3) Yellow liquid (0.85 g) (ether/petrol, 5:10 v/v). (4-5) Brown liquid (0.03 g) (ether). (6) Black liquid (4.2 g) (methanol).

Fractions (1-3) were distilled at 80° at 0.15 mmHg, and identified by n.m.r. and m/e = 242 and 244 as 5-bromo-2-diethylamino-3H-azepine (0.85 g, 35.5%). Found: C, 49.6; H, 6.2; N, 11.8. $C_{10}H_{15}N_2Br$ requires: C, 49.5; H, 6.1; N, 11.55. Fraction 4 was starting material, identified by n.m.r. spectrum and

g.l.c. retention time (10% APL, 180°) being identical on comparison with an authentic specimen. Fraction 6 was identified as p-bromoaniline (0.82 g, 48%), identified by comparison with authentic specimen, having identical g.l.c. retention time, i.r. and n.m.r. spectra.

Reaction of ethyl p-nitrobenzoate with diethyl methylphosphonite in diethylamine. Ethyl p-nitrobenzoate (4.10 g, 0.0205 mol), diethyl methylphosphonite (10.31 g, 0.0756 mol) and diethylamine (25 ml), under nitrogen, were boiled under reflux (62.5°) for 14 h, by which time the solution had turned pale orange. Solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column when petrol eluted a pale yellow liquid (3.22 g) identified by n.m.r., i.r. and m/e = 236 as 5-carbethoxy-2-diethylamino-3H-azepine (3.22 g, 67%). (Found: C, 65.75; H, 8.5; N, 11.5. $C_{13}H_{20}N_2O_2$ requires: C, 65.95; H, 8.5; N, 11.8%).

Reaction of ethyl m-nitrobenzoate with diethyl methylphosphonite in diethylamine. Ethyl m-nitrobenzoate (3.61 g, 0.0185 mol), diethyl methylphosphonite (10.12 g, 0.0742 mol) and diethylamine (28 ml) under nitrogen were boiled under reflux (63.5°) for 40 h, by which time the mixture was deep yellow, and g.l.c. (2% APL, 150°) examination of the reaction mixture showed absence of starting material. Solvent was removed on a rotary evaporator, and the mixture subjected to chromatography on alumina, when the following fractions were eluted, eluants being given in parenthesis: (1-2) Greenish yellow liquid (0.53 g) (petrol). (3-4) Yellow liquid (0.66 g) (petrol). (5-7) Colourless liquid (1.64 g) (ether/petrol, 1:10 v/v). (8-9) Dark brown liquid (0.92 g) (ether). (10) Dark brown liquid (2.73 g) (methanol).

Fractions 1 and 2 were distilled at 80° at 0.1 mmHg to give 4-carbethoxy-2-diethylamino-3H-azepine (0.15 g) identified by n.m.r. and i.r. spectra, and m/e = 236. Fractions 5-7 were distilled at 80° at 0.1 mmHg to give 6-carbethoxy-2-diethylamino-3H-azepine (0.90 g) identified by n.m.r., i.r. and m/e = 236. (Found: C, 66.1; H, 8.6; N, 12.0. $C_{13}H_{20}N_2O_2$ requires: C, 65.0; H, 8.5; N, 11.8%).

Fraction 3-4 were distilled at 90° at 0.1 mmHg to give two azepines, the 6-isomer : 4-isomer in ratio 1:3, (0.13 g), identified by n.m.r. and g.l.c. retention time (2% APL, 155°). Fraction 10 was distilled at 90° at 0.15 mmHg, i.r. : diffuse peak 3650-3000 cm^{-1}, with appearance of H bonding (NH or OH): ν_{max} 1700 cm^{-1} (C=O). m/e 181. N.m.r.: τ 8.70 (t, Me, J = 7Hz), 5.76 (q, $-CH_2-$, J = 7Hz), 7.10 (d, 2H, J = 7 Hz), 4.37 (m, 1H), 3.32 (d, 1H, J = 10Hz), 2.6 (m, 1H), 0.3 (diffuse s, 1H). The sample was shaken with D_2O, when the peaks remained the same except τ 2.58 (s, 1H), 0.3 no peak, and 5.25 (s, H_2O). It was identified as 6-carbethoxy-1,3-dihydro-2H-azepin-2-one (1.07 g, 31%). (Found: C, 57.35; H, 6.45; N, 7.03. $C_9H_{11}NO_3$ requires: C, 59.6; H, 6.1; N, 7.7%) and 4-carbethoxy 1,3-hydro-2H-azepin-2-one (0.30 g, 9%).

Control experiment to show 6-carbethoxy-2-diethylamino-3H-azepine is converted to 6-carbethoxy-1,3-dihydro-2H-azepin-2-one. 6-Carbethoxy-2-diethylamino-3H-azepine (0.15 g, 0.0063 mol) was adsorbed on alumina, and allowed to remain on an alumina column in ether/petrol (5:10 v/v) for 12 days, after which methanol eluted a pale yellow solid, identified by comparison with authentic specimen, g.l.c. retention time, 2% APL, 140° and n.m.r. spectrum as 6-carbethoxy-1,3-dihydro-2H-azepin-2-one (0.11 g, 95%).

Experiments on behaviour of 6-carbethoxy-2-diethylamino-3H-azepine. 6-Carbethoxy-2-diethylamino-3H-azepine (0.08 g, 0.0034 mol) was dissolved in ethanol (20 g, 0.44 mol) containing sodium ethoxide (1.95 g, 0.028 mol), and allowed to stand for 14 h at room temperature. The solution was diluted with ether, the sodium ethoxide filtered off, and then the solvent removed on a rotary film evaporator. The 6-carbethoxy-2-diethylamino-3H-azepine (A) was obtained unchanged, having n.m.r. spectrum and g.l.c. retention time (2% APL, 140°) identical on comparison with authentic specimen. (A) was next dissolved in ethanol (5 g, 0.11 mol) and added to a solution of sodium hydroxide (1.04 g, 0.026 mol) in water (25 g, 1.4 mol), where it hydrolysed. The products were extracted into ether, the solvent

removed on a rotary evaporator, and examined by g.l.c. (2% APL, 140°) and n.m.r. spectrum. There was no starting material present, but the products were not identified.

Reaction of o-nitrobenzonitrile with diethyl methylphosphonite in diethylamine. o-Nitrobenzonitrile (2.0 g, 0.0135 mol) in diethylamine (8 g, 0.11 mol) was added to a solution of diethyl methylphosphonite (10.52 g, 0.077 mol) in diethylamine (83 g, 1.14 mol) boiling under reflux (56.5°) under nitrogen, and the mixture boiled under reflux for 0.5h by which time it had turned dark orange and g.l.c. (3% QF1 120°) showed absence of starting material. The solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and chromatographed on an alumina column when petrol eluted two fractions, shown by g.l.c. (3% QF1 100-180°) to contain a multitude of products. Each fraction was adsorbed on silica, and rechromatographed on a silica column, when petrol and benzene eluted a number of fractions, all of which g.l.c. (3% QF1, 100-180°) showed to contain mixtures of products. Further purification was not attempted.

Reaction of p-nitrobenzonitrile with diethyl methylphosphonite in diethylamine. p-Nitrobenzonitrile (2.0 g, 0.0135 mol) in diethylamine (8.5 g, 0.116 mol) was added to a solution of diethyl methylphosphonite (11.82 g, 0.087 mol) in diethylamine (85 g, 1.16 mol) boiling under reflux (56.5°) under nitrogen, and the mixture boiled under reflux for 5 h by which time the solution was light orange and g.l.c. (3% QF1/98°) showed no peak having the retention time of that of starting material. The solvent was removed on a rotary film evaporator, the mixture adsorbed on alumina and subjected to chromatography on an alumina column, when petrol and benzene eluted a number of fractions which g.l.c. (3% QF1/100-180°) showed to contain mixtures of products; these were not further purified.

Reaction of 4-nitropyridine with diethyl methylphosphonite in diethylamine. 4-Nitropyridine (3.50 g, 0.028 mol) and diethyl methylphosphonite (15.30 g, 0.113M) in diethylamine (21.5 g, 0.30 mol) were boiled under reflux (65°) under nitrogen for 0.5 h, by which time the

mixture had turned red and g.l.c. (2% APL, 110°) showed absence of starting material and one major product peak. The solvent was removed on a rotary evaporator and the mixture adsorbed on alumina and subjected to chromatography on an alumina column, but diethyl methylphosphonate contaminated all the fractions eluted as red liquids by petrol and ether. The first fraction was adsorbed on alumina, and resubjected to chromatography on very active alumina, when the phosphate esters were eluted with ether, and methanol eluted a red oil which was tentatively identified as 2-diethylamino-3H-1,5-diazepine (0.10 g, 2%), by m/e (165) and n.m.r. spectrum.

Reaction of nitromesitylene with diethyl methylphosphonite in diethylamine. Nitromesitylene (3.06 g, 0.0185 mol), diethyl methylphosphonite (5.58 g, 0.0412M) and diethylamine (16.5 g, 0.23 mol) were boiled under reflux (65°) under nitrogen, for 22 days, when it was still pale yellow. The excess of solvent was removed on a rotary evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column when the following fractions were eluted, the eluant is given in parenthesis: (1) Pale yellow solid, (0.08 g) (petrol). (2) Pale yellow solid, (2.64 g) (petrol). (3) Pale yellow liquid, (0.40 g) (ether/petrol 1:10 v/v). (4) Pale yellow liquid, (0.36 g), (ether/petrol, 1:10 v/v). (5) Brown oil, (0.15 g), (ether/petrol, 5:10 v/v). (6) Brown oil, (4.15 g) (methanol). Fractions 1 and 2 were shown by comparison with authentic specimen, g.l.c. retention time (2% APL, 140°) and n.m.r. spectrum to be only starting material. Fraction 3 contained starting material and another product, 2-diethylamino-3,5,7-trimethyl-3H-azepine, (0.1 g, 60% based on starting material consumed) identified by n.m.r. spectrum, and m/e (208). The remainder contained only phosphate esters and polymeric species.

5. REACTIONS TO DETERMINE THE NATURE OF THE NITRENE INTERMEDIATE.

Photolysis of phenyl azide in diethylamine, with singlet sensitiser present. Phenyl azide (0.56 g, 0.0047 mol) and pyrene (8.85 g, 0.044 mol) in diethylamine (120 g, 1.64 mol) were irradiated at room temperature for 4 h. The solvent was removed on a rotary evaporator, and the residue adsorbed on alumina and subjected to chromatography on alumina, when the following fractions were eluted, the eluants are given in parenthesis: (1) White solid, (8.82) (ether/petrol 1:10 v/v), identified as pyrene by comparison with authentic specimen, g.l.c. retention time (10% APL, 138°), n.m.r. spectrum, m.p. and mixed m.p. 156°. (2) Yellow oil, (0.34 g), (ether/petrol 5:10 v/v), which was identified as 2-diethylamino-3H-azepine (0.34 g, 44%) by comparison with authentic specimen, having identical g.l.c. retention time (10% APL, 138°) and n.m.r. spectrum. (3) Black solid (0.29 g), (methanol) which contained only tarry residues, and no aniline; g.l.c. (10% APL, 138°) showed no peak at any time whose retention time corresponded to aniline.

Control Experiment: photolysis of phenylazide in diethylamine. Phenylazide (0.71 g, 0.006 mol) and diethylamine (72 g, 0.99 mol) were irradiated for 5 h. The reaction mixture was examined by g.l.c. (10% APL, 135°) showed only one major product peak, whose retention time corresponded to that of aniline. There was a very small peak whose retention time corresponded to that of 2-diethylamino-3H-azepine, and several other small peaks unidentified.

Reaction of p-dimethylaminonitrosobenzene with triethyl phosphite in dimethyl maleate and cumene. p-Dimethylaminonitrosobenzene (5.96 g, 0.0397 mol) was added in cumene (20 ml) to a solution of triethyl phosphite (6.74 g, 0.0404 mol) and dimethyl maleate (18.08 g, 0.125 mol) in cumene (50 ml) boiling under reflux (153°) under nitrogen. The solution turned dark red immediately, and heating was stopped when the last of the p-dimethylaminonitrosobenzene was

added (about 20 minutes). On cooling, a solid crystallised out and was filtered off and dried (14. 34 g). The solvent was removed from the filtrate by distillation at the water pump. The solid was recrystallised from ethanol, when two fractions were obtained: (1) white crystals (11. 38 g) m. p. 100-102°, which was identified as dimethyl succinimate, by comparison with authentic specimen, mixed m. p. 101-102°, and g. l. c. retention time (10% APL, 135°). (2) Red crystals (3. 38 g) m. p. 247-249°, which was identified as 4,4'-bis(dimethylamino)azoxybenzene,(3. 38 g, 61. 5%) by n. m. r. : τ 6. 98 (s, 4Me), 3. 32 (m, 4H, principally d, J = 12Hz, each split into d, J = 3Hz), 1. 8 (m, 4H, principally t, J = 8Hz with centre peak split, d, J = 2Hz); m/e 332, 316, 158; i. r. (nujol mull): aromatic characteristics, but no outstanding functional groups, m. p. Lit[196]. 241°.

The residue from the filtrate was adsorbed on alumina and subjected to chromatography on an alumina column, from which the following fractions were eluted, eluant given in parenthesis: (1) Pale yellow solid, (0. 29 g), (ether/petrol 2:10 v/v), m. p. 110°-140°. (2) Dark brown solid, (0. 11 g), (ether/petrol 5:10 v/v), m. p. 70°-90°. (3) Dark brown solid, (0. 12 g), (ether/petrol 5:10 v/v). (4) Dark red liquid, (0. 85 g) (ether). (5) Dark red liquid, distilled at 160°, 0. 5 mmHg, (1. 12 g), (methanol), identified as diethyl N-(p-dimethylaminophenyl)phosphoramidate, (1. 12 g, 11%), n. m. r. : τ 8. 6 (t, 2Me, with further splitting, major J 7Hz), 5. 9 (quintet, 2-CH_2-, J 7Hz), 7. 2 (s, 2Me), 6. 55 (diffuse s, 1H), 3. 4 (m, 4H); m/e 272; i. r. : 3300 cm^{-1} (NH), 1250 cm^{-1} (P=O), 1020 cm^{-1} (POEt), 810 cm^{-1} (aromatic, p-di substituted). Every fraction was examined by n. m. r. and m/e, but no product corresponding to the addition product of p-dimethylaminonitrosobenzene to the double bond of dimethyl maleate was discovered. The other fractions contained phosphate esters.

Control Experiment: To show that dimethyl maleate is converted to dimethyl succinimate under the reaction conditions. Dimethyl maleate (5 ml), triethyl phosphite (5 ml) and cumene (10 ml) were boiled under reflux for 1.5h, and then cooled, when white crystals

were deposited, filtered off, and found to be dimethyl succinimate (3.5 g), m.p. 100-102°, and g.l.c. retention time (10% APL, 132°).

Reaction of p-nitrosobenzonitrile with triethyl phosphite in dimethyl maleate and cumene. Triethyl phosphite (3.41 g, 0.0205 mol) was added to p-nitrosobenzonitrile (2.61 g, 0.0196 mol) and dimethyl maleate (9.20 g, 0.048 mol) in cumene (25 ml) at room temperature, under nitrogen. The solution became dark immediately, and after being stirred for 1.5 h, had become black. The solvent was removed at the water pump, together with dimethyl maleate and triethyl phosphate. The residue was adsorbed onto alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluants are given in parenthesis: (1) Orange red solid (0.22 g), (ether/petrol 5:10 v/v), m.p. 267-270°, identified as 4,4'-dicyanoazobenzene, (0.22 g, 10%) Lit,[185] m.p. 268-270°, τ 1.97 (d, 2H, J = 8), 2.19 (d, 2H, J = 8), i.r. (nujol mull) ν_{max} 2210 cm^{-1} (CN), 849 cm^{-1} (aromatic p-disubstituted), m/e 232, 116. (2) Pale yellow solid (0.05 g), (ether) m.p. 206-209°, m/e 248, 232, 116, identified as 4,4'-dicyanoazoxybenzene (0.05 g, 2%) Lit, 220°. (3) Dark brown oil, (4.05 g), distilled at 130°, 0.05 mmHg, pale yellow liquid, identified as diethyl N-(p-cyanophenyl)phosphoramidate (0.44 g, 14%), τ 8.69 (t with fine splitting, 2Me, J 7Hz), 5.9 (quintet with fine splitting, 2-CH_2-, J 7Hz), 5.6 (diffuse s, 1H), 3.36 (d with fine splitting, 2H, J 8Hz), 2.64 (d with fine splitting, 2H, J 8Hz), m/e 254, ν_{max} 2205 cm^{-1} (CN), 3320 cm^{-1} (NH), 1240 cm^{-1} (P=O), 1020 cm^{-1} (POEt).

Reaction of 1-nitronaphthalene with tris(diethylamino)phosphine in diethylamine. 1-Nitronaphthalene (2.28 g, 0.013 mol), tris(diethylamine)phosphine (12.4 g, 0.120 mol) and diethylamine (50 ml) were boiled under reflux (58°), under nitrogen for 7d. Excess of solvent was removed on a rotary film evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluant being given in parenthesis: (1) Orange, light sensitive oil (1.68 g) (petrol). (2) Dark red liquid (2.03 g) (petrol). (3) Dark red liquid (0.54 g) (petrol).

(4) Dark red liquid (0.15 g) (petrol). (5) Brown liquid (0.2 g), (ether/petrol, 1:100 v/v). (6) Brown liquid (0.31 g) (ether/petrol, 1:10 v/v). (7) Brown liquid (0.42 g) (ether/petrol, 5:10 v/v). (8) Brown liquid (0.94 g) (ether), which further examination by t.l.c. showed to contain a light-sensitive component. (9) Dark Brown liquid (1.13 g) (methanol), which further examination by t.l.c. showed to contain a light-sensitive component. Fraction (1) was subjected to further chromatography on an alumina column, when petrol eluted a light sensitive brown oil (0.45 g), b.p. 162° at 0.04 mm, identified as tris(diethylamino) N-1-naphthylphosphorimidate (0.45 g, 13.5%), m/e 388, τ 8.9 (18H, t, J 8Hz, 6Me) 6.3-7.0 (12H, m, 6-CH_2-) 1.9-3.2 (7H, m, ArH), 1180 cm^{-1} (P=N) 1020 cm^{-1} (P-N) 1570, 1505, 1420 (aryl C-C). (Found: C, 67.7; H, 9.6; N, 14.6. $C_{22}H_{37}N_4P$ requires C, 67.9; H, 9.5; N, 14.4%). Attempts were made to obtain the corresponding bis(diethylamino)-N-1-naphthyl-phosphoramidate by distillation of the later fractions, but only tris-(diethylamino)phosphine oxide was obtained.

Reaction of p-chloronitrosobenzene with tris(diethylamino)phosphine in dimethyl sulphide. p-Chloronitrosobenzene (1.95 g, 0.014 mol) in dimethyl sulphide (25 ml) and methylene chloride (10 ml) was added dropwise over 2 h to a cooled solution (0°) of tris(diethylamino)phos-phine (4.36 g, 0.018 mol) in dimethyl sulphide (25 ml). Reaction was immediate, as shown by the green colour turning orange. Excess of solvent was removed on a rotary film evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluant being given in parenthesis: (1) Orange solid (0.11 g) (petrol) identified as 4,4'-dichloroazobenzene (0.11 g, 6%), m.p. 186-187°, Lit.[196] 188° (from acetone), τ 2.2 (2H, d, J 9Hz, ArH), 1.9 (2H, d, j 9Hz, ArH). m/e 250, 252, 254. (Yellow solid (0.58 g) (petrol), identified as 4,4'-dichloroazoxybenzene (0.58 g, 31.5%), m.p. 158°, Lit.,[196], 158°, (from ethanol), τ 2.5 (2H, d x d, J 9Hz, 2Hz), 1.8 (2H, m), m/e 266, 268, 270. (3) Tars (ether and methanol) containing only phosphorus esters, and no compound with dimethyl sulphide, on careful examination of each fraction by n.m.r. spectra.

COMPETITIVE REACTIONS

Reaction of o-nitrobenzalaniline with diethyl methylphosphonite in diethylamine. o-Nitroaniline (2.0 g, 0.0088 mol), diethyl methylphosphonite (3.28 g, 0.024 mol) and diethylamine (16.5 g, 0.225 mol) were boiled under reflux (62.5°) under nitrogen for 2 days. The excess of solvent was removed on a rotary evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when ether/petrol (1:10 v/v) eluted a white solid, which was recrystallised from ethanol, and identified as 2-phenylindazole (1.62 g, 94%), m.p. and mixed m.p. 81-82°, and having identical n.m.r. spectrum, mass spectrum and g.l.c. retention time (2% APL, 150°) on comparison with an authentic specimen. The other residues from the column, eluted with ether and methanol, contained only diethyl methylphosphonate, and neither g.l.c. (2% APL, 150°) nor n.m.r. spectra showed any sign of an azepine nor any other product.

Reaction of 2-nitro-2', 6'-dimethyldiphenyl sulphide with diethyl methylphosphonite in diethylamine. 2-Nitro-2', 6'-dimethylphenyl sulphide (2.00 g, 0.0077 mol), diethyl methylphosphonite (3.35 g, 0.0246 mol) and diethylamine (21 g, 0.285 mol) were boiled under reflux (65°) under nitrogen for 5 days. The excess of solvent was removed on a rotary evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluant is given in parenthesis: (1) Pale yellow solid, (0.31 g), (ether/petrol, 1:10 v/v), identified by g.l.c. retention time (2% APL, 175°) and n.m.r. as principally starting material, with 10% of another product(s). (2) Pale yellow oil, (0.36 g), (ether/petrol, 1:10 v/v), which contained two products in ratio [g.l.c. peak size and n.m.r.] 11:8, identified as starting material : 2- diethylamino-3H-7-(2', 6'-dimethyl)thiophenylazepine, (0.255 g, 14%) by n.m.r. and m/e (300). (3) Brown oil, (0.73 g) (ether), identified as 2-amino-2', 6'-dimethyldiphenyl sulphide (0.73 g, 50%), n.m.r. τ 7.62 (s, 2Me), 6.05 (diffuse s, 2H) 2.8-3.6 (m, 7H), m/e (229), i.r. 3250 cm^{-1} (NH_2). (4) Brown oils, (4.2 g), (methanol), phosphate esters, but no phosphor-

amidate, as shown by n.m.r., and g.l.c./M.S. 20. Every fraction was examined by g.l.c./M.S. 20 (2 % OV1, 230°), and thus the absence of such products as 5,11-dihydro-4-methyldibenzo[b,e][1,4]-thiozepine was shown. The extra product seen only on g.l.c./M.S. 20 was 2-N,N-diethylamino-1',6'-dimethyldiphenyl sulphide.

Reaction of 2-nitro-2',6'-dimethyldiphenyl ether with diethyl methylphosphonite in diethylamine. 2-Nitro-2,6'-dimethyldiphenyl ether (2.40 g, 0.00985 mol), diethyl methylphosphonite (3.70 g, 0.0027 mol) and diethylamine (18.3 g, 0.25 mol) were boiled under reflux (63°) under nitrogen for 3 days, by which time the contents had turned black. The solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluant is given in parenthesis: (1) Pale yellow solid, (0.10 g), (ether/petrol 1:10 v/v), identified as starting material by n.m.r. and g.l.c. retention time (2% APL, 170°). (2) Trace products, (<0.05 g) of which g.l.c./M.S. 20 indicated that one was 2-N,N-diethylamino-2',6'-dimethyldiphenyl ether, m/e (269). (3) Brown oil (3.5 g), (ether), n.m.r. showed largely diethyl methylphosphonate, but there were protons where azepinyl protons were expected; m/e (284), attributed to 2-diethylamino-3H-7-(2',6'-dimethyl)phenyloxyazepine, which was resubjected to chromatography on an alumina column, on which some product decomposed leaving coloured residues adsorbed all down the column. The following fractions were eluted, the eluants are given in parenthesis: (1) Yellow oil (0.24 g) (ether/petrol, 5:10 v/v), identified as 2-amino-2',6'-dimethyldiphenyl ether (0.24 g, 12%), by n.m.r., τ 7.9 (s, 2Me), 6.05 (diffuse s, 2H), 2.8-3.9 (m, 7H). M/e (213). (2) Brown oil, (0.56 g), (ether), containing diethyl methylphosphonate and a trace of azepine, n.m.r. spectrum, and g.l.c./M.S. 20, (2 % OV1, 235°). All fractions were examined thus, from both series of chromatography, and the only products identified were 2-amino-2',6'-dimethyldiphenyl ether, 2-N,N-diethylamino-2',6'-dimethyldiphenyl ether, and 2-diethylamino-3H-7-(2,6-dimethyl)phenoxyazepine. No products corresponding to those obtained in absence of diethylamine were observed.

7. TO INVESTIGATE THE EFFICIENCY OF OTHER NUCLEOPHILES.

Reaction of p-chloronitrobenzene with diethyl methylphosphonite. p-Chloronitrobenzene (3.30 g, 0.021 mol) and diethyl methylphosphonite (11.92 g, 0.088 mol) were boiled under reflux under nitrogen for 0.5 h, by which time the contents had turned black. The mixture was distilled at the water pump, when diethylmethylphosphonate and excess diethyl methylphosphonite were removed, together with a trace of p-chloroaniline, identified by g.l.c. retention time (10% APL, 135°) by comparison with an authentic specimen. The residue was distilled at the oil pump, 0.1 mmHg, when 4 fractions were obtained, (1) b.p. 40°, (0.08 g), (2) b.p. 90°, (0.10 g), (3) b.p. 100-120° (0.48 g), (4) b.p. 130-150° (0.60 g). All fractions were examined by n.m.r., i.r., m/e (263 and 265) and g.l.c. (10% APL, 190°), which showed a number of the same products in all fractions, of which the major one was diethyl N-p-chlorophenyl phosphoramidate (0.80 g, 11%), n.m.r. τ 8.7 (t, with further splitting, 2Me, J = 7Hz), 6.5 (diffuse s, 1H) 5.9 (quintet, with further splitting, 2-CH_2- J = 7Hz), 2.8-3.65 (m, 4H). I.r. 3300 cm^{-1} (NH), 1250 cm^{-1} (P=O), 1030 cm^{-1} (POEt). Fraction 3 also showed a trace of azepinyl protons in the n.m.r. spectrum.

Reaction of p-chloronitrobenzene with diethyl methylphosphonate in ethanol. p-Chloronitrobenzene (3.11 g, 0.0198 mol), diethyl methylphosphonite (11.10 g, 0.0815 mol) and ethanol (15 g, 0.33 mol) were boiled under reflux (80°) for 18 h, when g.l.c. (10% APL, 145°) showed absence of starting material, although the contents had turned black after 0.5 h. The excess of solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, and the fractions eluted were examined by g.l.c. (10% APL, 145°) and n.m.r. when the only products identified were phosphate esters and p-chloroaniline, by comparison with authentic specimen. The fraction eluted by methanol contained diethyl-N-(p-chlorophenyl)phosphoramidate,

identified by g.l.c. retention time and n.m.r., and m/e, 263 (261). These products each had yields of <10%. There was a trace of azepinyl protons in one of the fractions, but <1%.

Reaction of nitrosobenzene with triethyl phosphite in ethanol. Nitrosobenzene (3.3 g, 0.031 mol) in ethanol (9.2 g, 0.20 mol) was added to a solution of triethyl phosphite (8 g, 0.048 mol) in ethanol (92 g, 2.0 mol), boiling under reflux (80°), and heating continued for 0.5 h. The excess of solvent was removed on a rotary evaporator, the phosphate esters were removed at reduced pressure at the water pump, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluants are given in parenthesis: (1) Orange solid, (0.1 g), (petrol), identified by comparison with authentic specimen, having identical g.l.c. retention time (3% QF1, 175°) and n.m.r. as azobenzene (0.10 g, 3.6%). (2) Yellow oil, (0.20 g) (benzene/petrol, 1:10 v/v), identified by comparison with authentic specimen, having identical g.l.c. retention time (3% QF1, 175°) and n.m.r., as azoxybenzene (0.20 g, 6.7%). (3) Brown oil, (0.21 g) (benzene/ether 5:10 v/v) identified by comparison with authentic specimen having identical g.l.c. retention time (3% QF1, 98°) and i.r. as aniline (0.21 g, 7.3%). (4) Brown oil, (3.61 g) (methanol), which was redistilled, b.p. 104-106°/0.05 mmHg, to give a brown oil (0.06 g) identified by i.r. and n.m.r. as diethyl N-phenylphosphoramidate (0.06 g, 0.85%). The remainder contained only polymeric species.

Reaction of nitrobenzene with ethyl diphenylphosphinite in morpholine. Nitrobenzene (2.53 g, 0.0206 mol), ethyl diphenylphosphinite (16.78 g, 0.0725 mol) and morpholine (45 g, 0.51 mol) were boiled under reflux (130°) under nitrogen for 2 h, by which time the reaction mixture had become dark red, and g.l.c. (10% APL, 138°) showed no peak whose retention time corresponded to that of starting material. On cooling, a fawn solid was deposited, which was filtered off (13.35 g) and recrystallised from ethanol, m.p. and decomposition temperature, 178-188°. M/e showed a sudden decrease in pressure

at 170°, indicating polymerisation was taking place, and the spectrum indicated units of —> 418, 201, were involved ($Ph_2P(=O)$ and $Ph_2P(=O)-O-P(=O)Ph_2$). The filtrate was extracted with petrol, and solvent of the petrol layer removed on a rotary evaporator, and the residue subjected to chromatography on an alumina dry column, eluted with trichloroethylene. No characterisable products were obtained.

Reaction of nitrobenzene with diethyl methylphosphonite in aniline. Nitrobenzene (0.71 g, 0.0058 mol), diethyl methylphosphonite (1.66 g, 0.0122 mol) and aniline (3.55 g, 0.037 mol) were boiled under reflux (90°) under nitrogen for 11 h. G.l.c. (2% APL, 120°) showed a peak whose retention time corresponded to that of an authentic sample of azobenzene, and there was another product whose retention time was that of the order expected for an azepine. The mixture was adsorbed on alumina, and subjected to chromatography on alumina, when the only identifiable product isolated eluted by petrol was azobenzene, (0.12 g, 22%) m.p. 68.5°, identified by comparison with authentic specimen, having identical n.m.r. and i.r. spectra.

Reaction of nitrobenzene with diethyl methylphosphonite in phenylhydrazine. Nitrobenzene (2.11 g, 0.0172 mol), diethyl methylphosphonite (10.00 g, 0.085 mol) and phenylhydrazine (27.5 g, 0.255 mol) were warmed to 180° under nitrogen for 30 minutes. The mixture was distilled to remove phenylhydrazine and the phosphate esters (30°/0.5 mmHg and 90°/0.5 mmHg) and the residue adsorbed on alumina, and subjected to chromatography on an alumina column. Examination of each fraction eluted from the column, by n.m.r. and by g.l.c. (2% APL, 125°) showed no trace of any product that could be an azepine, nor did a similar examination of the lighter boiling distillate. G.l.c./MS. 20 (2.5% OV1, 165°) showed only azobenzene, and no product whose m/e was high enough to be the desired azepine.

Reaction of nitrobenzene with diethyl methylphosphonite in cyclopentadiene. Nitrobenzene (2.08 g, 0.017 mol), diethyl methyl phosphonite (8.75 g, 0.0643 mol) and cyclopentadiene (14.8 g, 0.22 mol)

boiled under reflux under nitrogen for 36 h, by which time the mixture was dark brown. The excess of solvent was removed on a rotary evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, the eluant is given in parenthesis: (1) Yellow liquid (0.9 g) (petrol), identified as cyclopentadiene by comparison with authentic specimen, n.m.r. and g.l.c. retention time (10% APL, 110°). (2) Yellow oil, (0.1 g) (ether/petrol 1:100 v/v), identified as azobenzene (0.1 g, 6.5%) by comparison with authentic specimen, having identical n.m.r. spectrum and g.l.c. retention time (10% APL, 140°). (3) Brown liquid, (5.6) (ether) which was identified as mostly diethyl methylphosphonite, but n.m.r. showed also some protons at τ 5.7 and 3.1, and g.l.c. (10% APL, 140°) indicated some other product. This fraction was, therefore distilled (0.5 mm), but it polymerised, and no product was obtained. (4) Dark tars, (2.4 g), (methanol) shown by n.m.r. and g.l.c. (10% APL, 140°) to contain only phosphate esters and polymeric residues.

Reaction of nitrobenzene with diethyl methylphosphonite in ethyl acetoacetate. Nitrobenzene (1.90 g, 0.0154 mol), diethyl methylphosphonite (8.01 g, 0.059 mol) and ethyl acetoacetate (21.5 g, 0.15 mol) were warmed to 100° and then slowly to 160°, at which temperature it began to boil under reflux, under nitrogen. The contents rapidly became dark brown. G.l.c./M.S. 20 (2.5% OV1, 185°) examination of the reaction mixture showed a large number of product peaks, of which the largest were identified as aniline and azobenzene, by comparison of retention times with those of authentic specimen. Had a reaction taken place between ethyl acetoacetate and nitrobenzene, a product of m/e 221 should have been formed, but this was not discovered.

Reaction of o-nitroacetophenone with diethyl methylphosphonite in methanol. o-Nitroacetophenone (2.05 g, 0.0125 mol), diethyl methylphosphonite (7.21 g, 0.053 mol) and methanol (22 g, 0.69 mol) were boiled under reflux (62°) under nitrogen for 3 days, when it had turned dark yellow, and g.l.c. (2% APL, 150°) showed absence of

starting material and one major product. The excess of solvent was removed on a rotary evaporator and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when the ether/petrol (1:10 v/v) eluted a clear liquid, shown by g.l.c. retention time (2% APL, 150°) n.m.r. and i.r. comparison with authentic specimen to be 3-methylanthranil (1.00 g, 60%).

Reaction of methyl o-nitrobenzoate with diethyl methylphosphonite in methanol. Methyl o-nitrobenzoate (1.95 g, 0.01 mol), diethyl methylphosphonite (5.21 g, 0.38 mol) and methanol (23 g, 0.72 mol) were boiled under reflux (62°) under nitrogen for 14 days, when g.l.c. examination (2% APL, 140°) showed a small peak whose retention time corresponded to that of starting material, a major product peak, and several minor peaks. The excess of solvent was removed on a rotary evaporator, the residue adsorbed on alumina and separated by chromatography on an alumina column, when the following fractions were eluted, the eluants are given in parenthesis: (1) Colourless liquid, (0.24 g), (ether/petrol, 1:100 v/v), (m/e) 165, not identified. (2) (0.16 g), (ether/petrol, 1:10 v/v), identified by g.l.c. retention time (2% APL) and n.m.r., comparison with authentic specimen. (3) Colourless liquid (0.49 g), (ether/petrol, 2:10 v/v), identified as 3-methoxyanthranil (0.49 g, 31%), by m/e (149), n.m.r. τ 6.2 (s, Me), 3.2-3.55 (m, 2H) 2.76 (t, further splitting 1H, J = 8 and J = 1), 2.15 (d, further splitting, 1H, J = 7 and J = 1).

Reaction of p-chloronitrosobenzene with triethyl phosphite in the presence of 2-hydroxypyridine. p-Chloronitrosobenzene (1.0 g, 0.007 mol) in benzene (25 ml) was added dropwise over 3 h to a stirred saturated solution of 2-hydroxypyridine (7.0 g, 0.0735 mol) and triethyl phosphite (2.4 g, 0.0145 mol) in benzene (30 ml), under nitrogen, at room temperature (25°). The green nitroso solution turned brown immediately. At the end of the reaction, the 2-hydroxypyridine was allowed to precipitate out completely, filtered off, and washed with ether, and the filtrate and washings reduced in volume on a rotary film evaporator, and adsorbed on alumina, and subjected to chromatography on an alumina column, when

the following fractions were eluted, eluants being given in parenthesis: (1) pale yellow solid (0.05 g) (petrol), identified as 4,4'-dichloroazobenzene (0.05 g, 5.5%) by comparison with an authentic sample, having identical n.m.r. and i.r. spectra. (2) Yellow solid (0.42 g) (petrol), identified as 4,4'-dichloroazoxybenzene (0.42 g, 45%) m.p. and mixed m.p. 158°, having identical mass spectrum to that of an authentic specimen. (3) Yellow solid (0.30 g) (ether), identified as 4-chloro aniline (0.30 g, 33%) on comparison with an authentic specimen, m.p. and mixed m.p. 72.5°, having identical n.m.r. and mass spectra. (4) Tars (methanol), which contained no trace of any product involving 2-hydroxypyridine, on examination by both n.m.r. and mass spectra.

Reaction of p-chloronitrosobenzene with tris(diethylamino)phosphine in methanol. p-Chloronitrosobenzene (2.25 g, 0.017 mol) in super dry methanol (40 ml) and ether (10 ml) was added dropwise over 3 h to a stirred solution of tris(diethylamino)phosphine (5.0 g, 0.02 mol) in methanol (30 ml) under nitrogen at room temperature (25°). The green solution turned black immediately, indicating extensive tar formation. The solvent was removed on a rotary film evaporator, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, eluants being given in parenthesis: (1) Yellow solid (0.44 g) (ether/petrol 1:10 v/v) identified as 4,4'-dichloroazoxybenzene (0.44 g, 22%). (2) Yellow oil (0.05 g), (ether/petrol, 1:10 v/v), n.m.r. showing azepinyl protons, but attempted further purification resulted in decomposition. (3) And (4) brown oils (0.25 g) (ether), identified as substituted anilines with methoxide substituents, but not fully characterised, m/e 173, 171, 158, 156, τ 7.2 (3H, s, Ar-N-Me) 6.2 (3H, s, Ar-O-Me) 2.7-3.5 (3H, m) 5.9-6.2 (1H, diffuse s, NH), N-methyl dichloroanisidine. (5) Brown oil (0.08 g) (ether), chloroanisidine, τ 6.2 (3H, s, Ar-O-Me), 5.9-6.3 (2H, diffuse s, NH_2) 2.7-3.2 (3H, m), m/e 159, 157. (6) Tar (methanol).

Reaction of p-chloronitrobenzene with tris(diethylamino)phosphine in ^{t}Butanol. p-Chloronitrobenzene (2.51 g, 0.016 mol), tris(diethylamino)phosphine (8.00 g, 0.033 mol) and ^{t}Butanol (50 ml) were boiled

under reflux (83°) under nitrogen for 7 days, by which time the solution had turned dark brown. The excess of solvent was removed on a rotary film evaporator, the final traces being removed as an azeotropic mixture with cyclohexane, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when petrol eluted a mixture of products, which were resubjected to chromatography, when petrol eluted p-chloronitrobenzene (1.94 g) identified by comparison with an authentic specimen, having identical n.m.r. and i.r. spectra, and methanol eluted a light sensitive oil (1.60 g) which was resubjected to chromatography on an alumina column, when the following fractions were eluted, eluants being given in parenthesis: (1) Pale yellow liquid, (0.37 g) (ether/petrol, 1:10 v/v) identified as 5-chloro-2-diethylamino-3H-azepine (0.37 g, 54%, based on starting material consumed), b.p. 80° at 0.1 mm, n.m.r. spectrum correct, exact mass found: 198.092367; $C_{10}H_{15}N_2Cl^{35}$ requires 198.092370; (2) Yellow solid (0.06 g) (ether), identified as N,N-diethyl-p-chloroaniline (0.06 g, 9%) τ 8.8 (6H, t, J 8Hz, 2Me) 6.5 (4H, quartet, J 8Hz, 2-CH_2) 3.4 (2H, d, J 9.5Hz) 1.9 (2H, d, 59.5Hz), m/e 195, 183. (3) Tar (methanol).

Reaction of m-chloronitrobenzene with tris(diethylamino)phosphine in ^{t}Butanol. m-Chloronitrobenzene (2.12 g, 0.0235 mol), tris(diethylamino)phosphine (12.0 g, 0.049 mol) and ^{t}butanol (80 ml) were boiled under reflux (83°) under nitrogen for 10 days. Excess of solvent was removed on a rotary film evaporator, using cyclohexane to form an azeotrope with the last traces of ^{t}butanol, and the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, eluants being given in parenthesis: (1) Brown oil, (1.43 g) (petrol) identified as m-chloronitrobenzene by comparison with an authentic sample, having identical n.m.r. and i.r. spectra. (2) Light sensitive yellow oil (0.25 g) (ether/petrol, 1:100 v/v) shown by g.l.c. (2% APL, 140°) and n.m.r. to contain two isomers in ratio 4:1. (3) Light sensitive yellow oil (0.56 g) (ether/petrol, 1:10 v/v) shown by g.l.c. and n.m.r. to contain two isomers in ratio

8:5. These isomers were identified as 6-chloro-2-diethylamino-3H-azepine (0.465 g, 53%) and 4-chloro-2-diethylamino-3H-azepine (0.245 g, 28%), on the basis of n.m.r. spectra and m/e 200, 198, which were identical on comparison with authentic specimen. (4) Brown oils (1.32 g) (ether), phosphorus esters and tar.

Reaction of p-chloronitrosobenzene with tris(diethylamino)-phosphine in ^{t}Butanol. p-Chloronitrosobenzene (1.48 g, 0.0104 mol) in ^{t}butanol (20 ml) and methylene chloride (20 ml) was added dropwise over 3 h at room temperature (22^{o}) to a stirred solution of tris-(diethylamino)phosphine (3.56 g, 0.0145 mol) in ^{t}butanol (20 ml) under nitrogen. Excess of solvent was removed on a rotary film evaporator, and the residue adsorbed on alumina and subjected to chromatography on an alumina column, when the following fractions were eluted, eluants being given in parenthesis: (1) Orange solid (0.04 g) (petrol), identified as 4,4'-di-chloroazobenzene, (0.04 g, 3%), by comparison with an authentic specimen, having identical retention time on t.l.c. and n.m.r. spectrum. (2) Yellow solid (0.41 g) (petrol), identified as 4,4'-dichloroazoxybenzene (0.41 g, 29%) m.p. and mixed m.p. 158^{o}, having identical n.m.r. spectrum and m/e 268, 266, on comparison with an authentic specimen. (3) Dark brown oils (2.01 g) (ether), containing phosphorus residues and polymeric residues.

Reaction of p-chloronitrobenzene with triethyl phosphite in ^{t}Butanol. p-Chloronitrobenzene (2.40 g, 0.015 mol), triethyl phosphite (11.88 g, 0.072 mol) and ^{t}butanol (60 ml) were boiled under reflux (83^{o}) under nitrogen for 14 days, by which time the mixture was dark brown. Excess of solvent was removed on a rotary evaporator, the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when only starting material (0.35 g) and phosphorus esters and tars were obtained, and no trace (g.l.c. and n.m.r.) of any compound resembling an azepine.

Reaction of tris(diethylamino)phosphine with ^{t}Butanol. Tris-(diethylamino)phosphine (3.00 g, 0.012 mol) and ^{t}butanol (40 ml) were boiled under reflux (83^{o}) under nitrogen for 3 days. Excess of solvent

was removed on a rotary film evaporator, and the residue distilled at 55° at 0.04 mmHg, being kept under nitrogen the whole time. A clear liquid (2.76 g) was obtained, which was shown by n.m.r. to contain no P-N-Et group, only τ 8.4 (s, P-O-C$(CH_3)_3$). ν_{max} 1250 (P=O), 970 (P-O-C). The original tris(diethylamino)phosphine had ν_{max} 1180 and 1010 cm^{-1}. M/e showed no high molecular weight fraction, possibly because of ready decomposition under the conditions in the mass spectrometer.

Reaction of m-nitrotoluene with tris(diethylamino)phosphine in ^{t}Butanol. m-Nitrotoluene (2.59 g, 0.019 mol), tris(diethylamino)-phosphine (10.64 g, 0.067 mol) and ^{t}butanol (37.8 g) were boiled under reflux (80°) under nitrogen for 3 weeks, when examination by t.l.c. showed only starting material, and the colour had not darkened. The mixture was not worked up.

Photolysis of p-azidoacetophenone in methanol in the presence of pyrene. p-Azidoacetophenone (2.39 g, 0.015 mol), pyrene (30.00 g, 0.15 mol), methanol (32.0 g, 0.57 mol) and dichloromethane (200 ml) were flushed with nitrogen and irradiated with stirring for 5 h by a Hanovia lamp, 300 watt, by which time the solution had turned dark brown. The pyrene was allowed to precipitate out, was filtered off and washed with ether and the filtrate and washing reduced in volume on a rotary film evaporator, the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when a white crystalline solid (1.81 g) was eluted (petrol) and identified as starting material (from n.m.r. and i.r. spectra). The only other products were tars. No trace of azepine was seen on thorough examination of each fraction by n.m.r.

8. FORMATION OF SUBSTITUTED 2-DIETHYLAMINO-3H-AZEPINES FROM PHOTOLYSIS OF CORRESPONDING AZIDES IN DIETHYLAMINE.

Photolysis of m-chlorophenyl azide in diethylamine. m-Chlorophenyl azide (2.05 g, 0.0134 mol) and pyrene (12.50 g, 0.0595 mol) in diethylamine (150 ml) were boiled under reflux (56.5°), stirred and irradiated for 5 h, with a pyrex filter. Pyrene crystallised out of the cooled solution overnight, and was filtered off, and washed with diethylamine. Excess of solvent was removed from the filtrate plus washings on a rotary film evaporator, the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, eluants being given in parenthesis. (1) White solid (3.51 g) (petrol) identified as pyrene by comparison with authentic specimen, having identical n.m.r. spectrum and m.p. and mixed m.p. 156°. (2) Light sensitive yellow oil (0.28 g) (ether/petrol, 5:100 v/v), shown by n.m.r. and g.l.c. (10% APL, 180°) to contain one isomer. (3) Light sensitive, yellow oil (0.74 g) (ether/petrol, 1:10 v/v) shown by n.m.r. and g.l.c. (10% APL/202° and 1% SE30/130°) to contain two isomers in ratio 2:1. (4) Light sensitive, yellow oil (0.30 g) (ether/petrol, 1:10 v/v) shown by n.m.r. and g.l.c. (10% APL/202°) to contain two isomers in ratio 5:7. (5) Tar (0.95 g) (methanol). The two isomers were identified as 6-chloro-2-diethylamino-3H-azepine (0.89 g, 33.5%) and 4-chloro-2-diethylamino-3H-azepine (0.41 g, 15.5%). B.p. 52° at 0.05 mmHg by comparison with authentic specimen, having identical n.m.r. spectrum and g.l.c. retention time.

Photolysis of m-tolyl azide in diethylamine. m-Tolyl azide (2.25 g, 0.017 mol) and pyrene (10.20 g, 0.0505 mol) in diethylamine (150 ml) were boiled under reflux (56.5°), flushed with nitrogen, and irradiated through a pyrex filter for 3 h. The pyrene precipitated out on cooling, and was filtered off, and washed with diethylamine, and the filtrate and washing combined, and excess of solvent removed from them on a rotary film evaporator. The residue was adsorbed

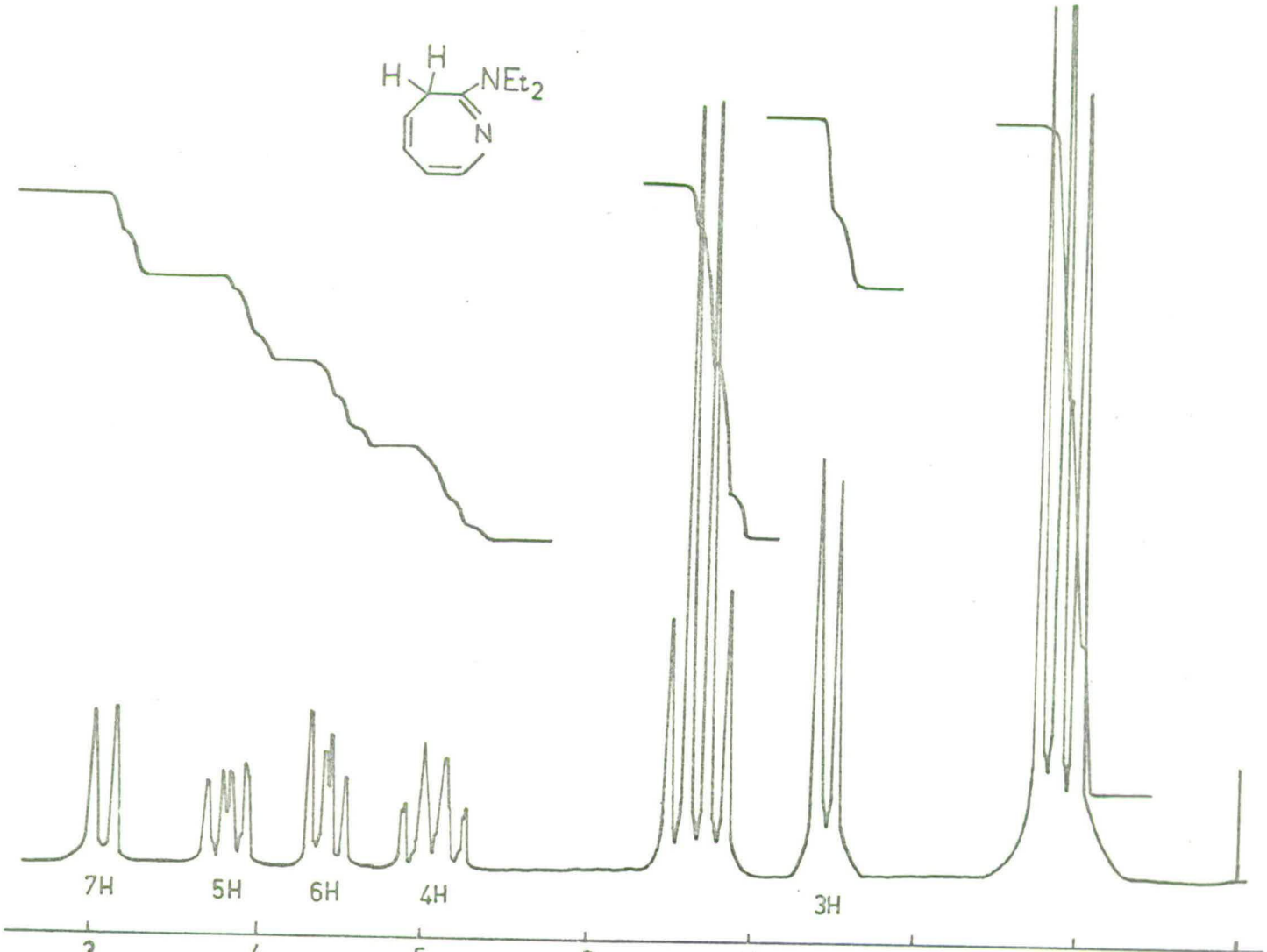
on alumina and subjected to chromatography on an alumina column, when the following fractions were eluted, eluants being given in parenthesis: (1) White solid (2.62 g) (petrol) identified as pyrene, m.p. and mixed m.p. 156°. (2) Light sensitive oil (0.75 g) (petrol), identified as starting material from n.m.r. spectrum and t.l.c. (3) Light sensitive, yellow oil (0.19 g) containing two isomers in ratio 7:1, calculated from n.m.r. (4) Light sensitive, yellow oil (0.20 g) (ether/petrol, 1:10 v/v) containing two isomers in ratio 1:1, calculated from n.m.r. (5) Light sensitive yellow oil (0.72 g) (ether/petrol, 1:10 v/v), containing two isomers in ratio 9:13, calculated from n.m.r. (6) Light sensitive, yellow oil (0.05 g) (ether/petrol, 1:10 v/v), containing two isomers in ratio 1:2, calculated from n.m.r. The isomers were identified as 6-methyl-2-diethylamino-3H-azepine (0.62 g, 27%) and 4-methyl-2-diethylamino-3H-azepine (0.67 g, 29%), b.p. 45° at 0.01 mmHg, having identical n.m.r. and mass spectra on comparison with authentic specimen. (7) Tar (methanol).

Photolysis of m-azidoanisole in diethylamine. m-Azidoanisole (1.98 g, 0.013 mol) and pyrene (20 g, 0.099 mol) in diethylamine (150 ml) were boiled under reflux (56.5°), flushed with nitrogen, and irradiated through a pyrex filter for 4 h. Pyrene crystallised out of the cooled solution and was filtered off and washed with diethylamine, and the combined filtrate and washings reduced in volume on a rotary film evaporator, the residue adsorbed on alumina, and subjected to chromatography on an alumina column, when the following fractions were eluted, eluants being given in parenthesis. (1) White crystalline solid (3.14 g) (petrol), identified as pyrene, m.p. and mixed m.p. 156°. (2) Light sensitive solid (0.63 g) (petrol), identified as starting material from i.r. and n.m.r. spectra. (3) Light sensitive yellow oil (0.64 g) (ether/petrol, 1:100 v/v) shown by n.m.r. to be one isomer. (4) Light sensitive yellow oil (0.25 g) (ether/petrol 1:10 v/v), shown by n.m.r. to contain two isomers in ratio 2:3. (5) Light sensitive yellow oil (0.025 g) (ether/petrol, 1:10 v/v) shown by n.m.r. to contain two isomers in ratio 2:1. (6) Tar (0.52 g) (methanol).

The isomers were shown to be 6-methoxy-2-diethylamino-3H-azepine (0.16 g, 9.3%) and 4-methoxy-2-diethylamino-3H-azepine (0.75 g, 43.5%), b.p. 54° at 0.05 mmHg, having identical n.m.r. and mass spectra on comparison with an authentic specimen.

Photolysis of m-bromophenyl azide in diethylamine. m-Bromophenyl azide (1.94 g, 0.0097 mol) and pyrene (16.20 g, 0.081 mol) in diethylamine (150 ml) under nitrogen were boiled under reflux (56.5°) and irradiated through a pyrex filter for 4 h. The pyrene which crystallised out of the cooled solution was filtered off and washed with diethylamine, and the filtrate and washings combined and reduced in volume on a rotary film evaporator; the residue was adsorbed on alumina and subjected to chromatography on an alumina column, when the following fractions were obtained, eluants being given in parenthesis: (1) White, crystalline solid (2.16 g) (petrol), identified as pyrene, m.p. and mixed m.p. 156°. (2) Yellow, light sensitive oil (0.65 g) (petrol) shown by n.m.r. to be only one isomer. (3) Yellow, light sensitive oil (0.10 g) shown by n.m.r. to contain two isomers in ratio 3:1. (4) Yellow, light sensitive oil (0.02 g), shown by n.m.r. to be one isomer. They were identified as 6-bromo-2-diethylamino-3H-azepine (0.72 g, 30%) and 4-bromo-2-diethylamino-3H-azepine (0.05 g, 2%), identified from n.m.r. and mass spectra being identical on comparison with an authentic specimen. (4) Brown oil (0.61 g) (ether) containing m-bromoaniline (0.26 g, 15%), identified by n.m.r. and mass spectra, comparison with an authentic specimen.

figure 1.



9. SPECTRA OF AZEPINES

The n. m. r. spectrum of 2-diethylamino-3H-azepine (1) was described by Odum and von Doering.[172] The spectrum of (1), shown in figure (1), corresponds exactly to their description. Because the protons of the azepine ring can be seen clearly and individually, they form an excellent means of identifying substituted azepines. All the azepines studied contained 2-diethylamino substituent, which appeared in the n. m. r. spectra as τ 8.89 (t, 6H, J = 7, 2Me), 6.68 (quartet, 4H, J = 7, 2-CH_2-).

The normal order of the protons attached to the benzene ring was that the 7H was at lowest field, followed by 5H, 6H, 4H, 3H as shown in figure (1). This could be displaced if a powerful group was attached to the ring.

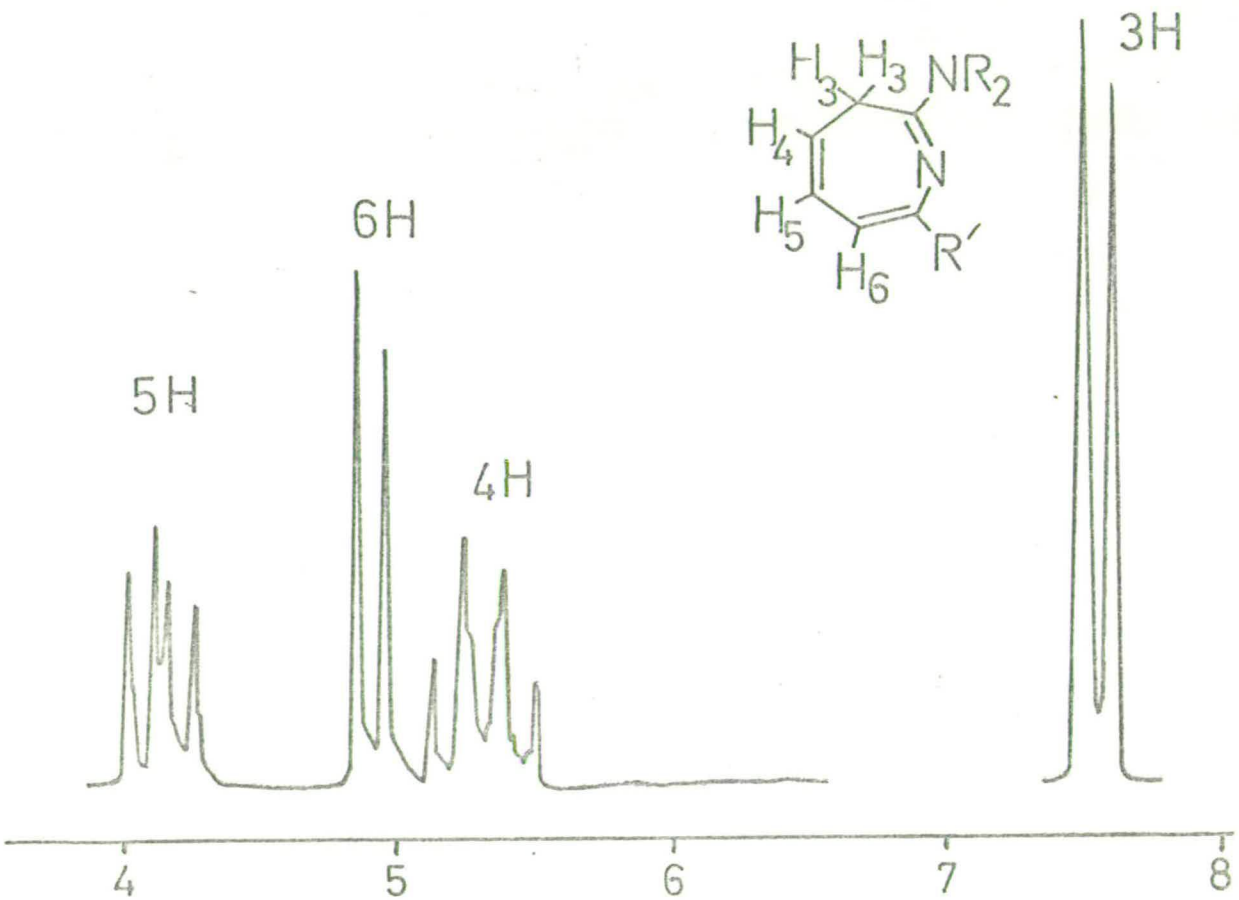


figure 2

7-Substituted azepines

The two protons on the 3-C appeared as a doublet, coupled with the proton on the 4-C. The 4-H was a multiplet coupled with the 3H and the 5H, and the 5H was also a multiplet, coupled with the 4H and the 6H. These protons all had the characteristic coupling pattern and τ values very similar to unsubstituted azepines. The 6H, however, now appeared as a doublet, coupled only with the 5H, and where the 7-substituent was a thiophenol group, moved to slightly higher field. No proton was situated in the 7 position. These are shown in figure (2)

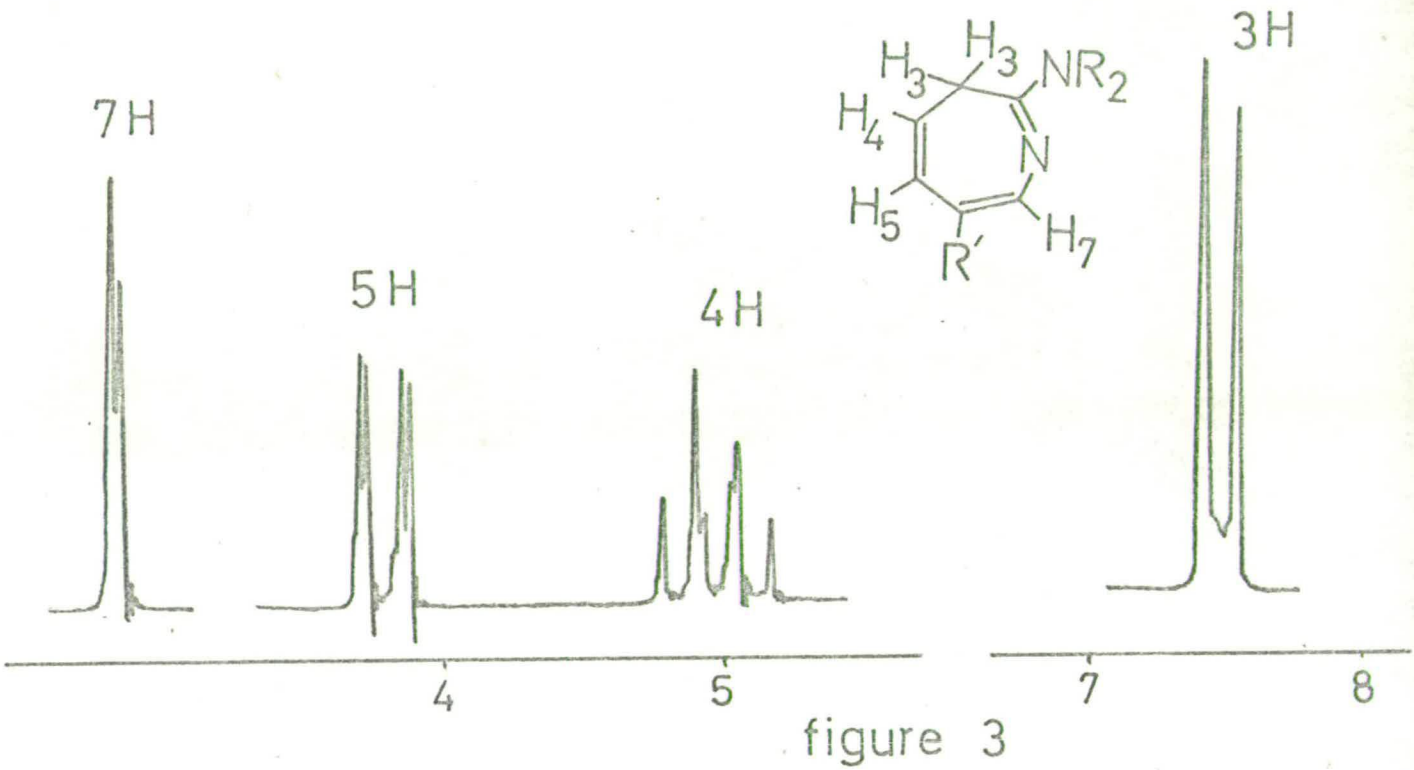


figure 3

6-Substituted azepines

The two protons on the 3-C appeared as a doublet, coupled with the proton on the 4-C. The 4-H is a multiplet coupled with the 3H and the 5H, and therefore retaining the characteristic coupling pattern, and remaining around 5 τ. The 5H now appeared as a doublet, coupled with the 4H, and with fine splitting superimposed, from long range coupling with the 7H. The 6H was missing. The 7H was a singlet

given in table I. A typical spectrum is shown in figure (3).

Table I

Substituent	MeO	Me	Cl	Br	CO_2Et
τ (5H)	3.7	3.9	3.7	3.6	3.1
τ (7H)	3.05	3.05	2.7	2.6	1.8

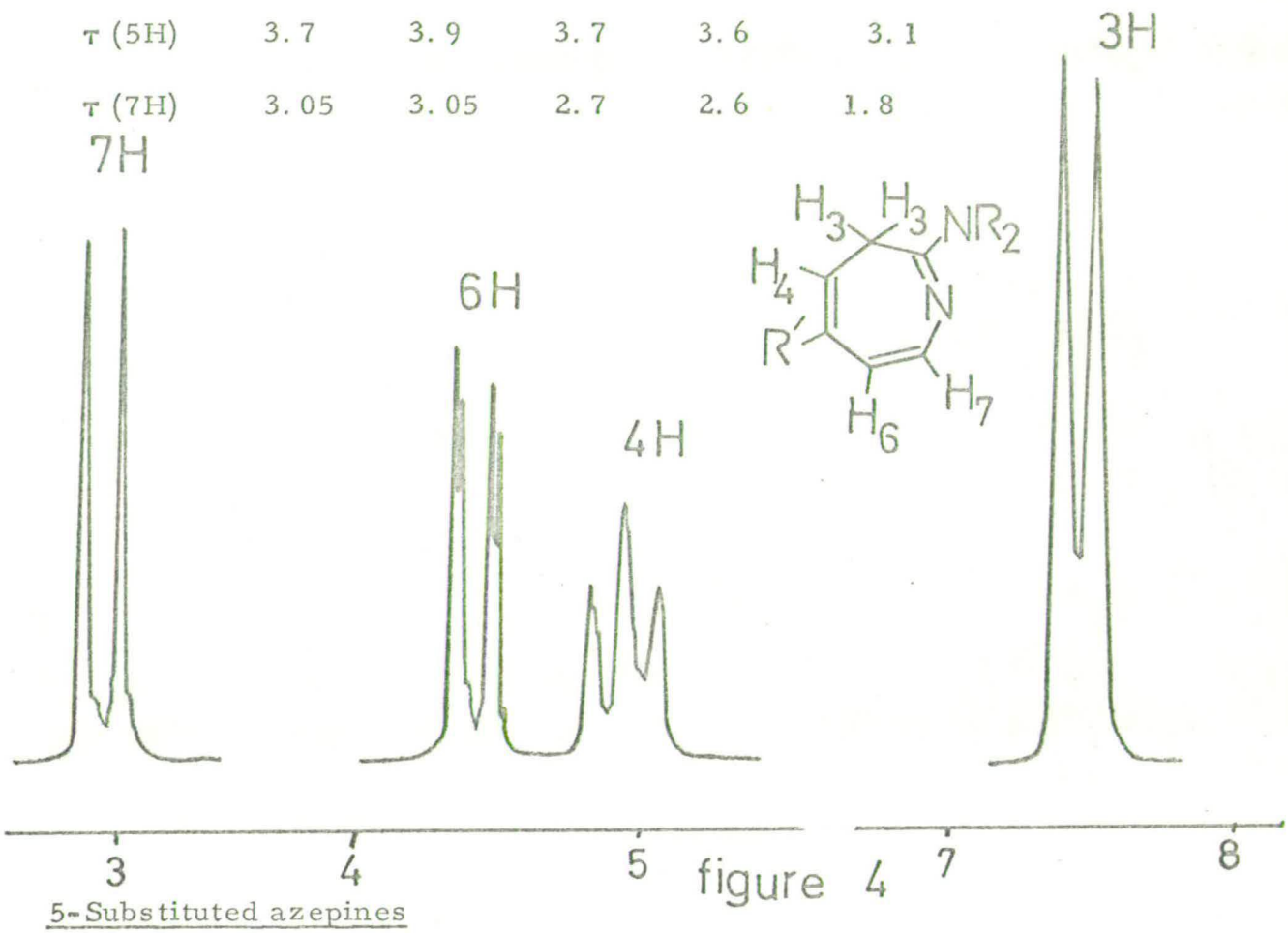


figure 4

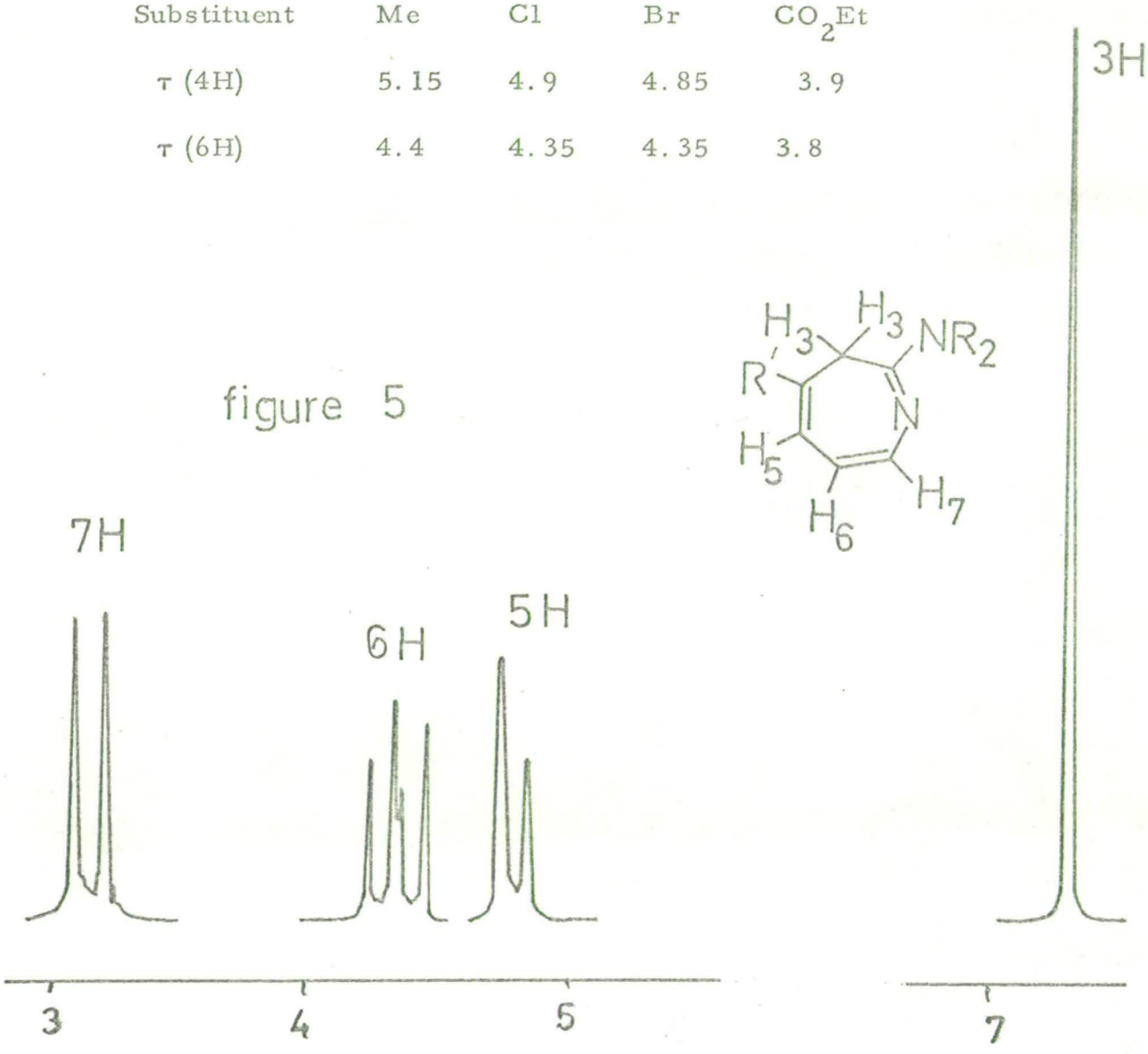
5-Substituted azepines

The two protons on the 3-C appeared as a doublet, coupled with the proton on the 4-C. The 4H was a triplet, coupled with the two 3-C protons, and broadened, due to fine splitting with the 6H. The 5H was missing. The 6H was principally a doublet, coupled with the 7H, but also showed some fine splitting due to long range coupling with the 4H. The 7H was a doublet, coupled with the 6H. Although the coupling pattern of the protons was unaffected by the nature of the substituent, the τ values were altered, for the 4H and the 6H. The results are given in table II. A typical spectrum is shown in figure (4).

Table II

Substituent	Me	Cl	Br	CO_2Et
τ (4H)	5.15	4.9	4.85	3.9
τ (6H)	4.4	4.35	4.35	3.8

figure 5



4-Substituted azepines

The two protons on the 3-C appeared as a strong singlet. The 4H was missing. The 5H appeared as a doublet, coupled with the 6H. The 6H appeared as a multiplet, having the characteristic coupling pattern of all 6H where there are protons on both the 5C and the 7C. The 7C appeared as a doublet, coupled with the 6H. The 6H appeared just above 4τ, and the 7H about 3τ, but the 3-H and the 5-H were shifted according to the substituent in the 4-position, as indicated in table III. A typical spectrum is shown in figure (5).

Table III

Substituent	MeO	Me	Cl	CO_2Et
τ (3H)	7.25	7.35	7.0	6.9
τ (5H)	4.7	3.9	3.65	2.6

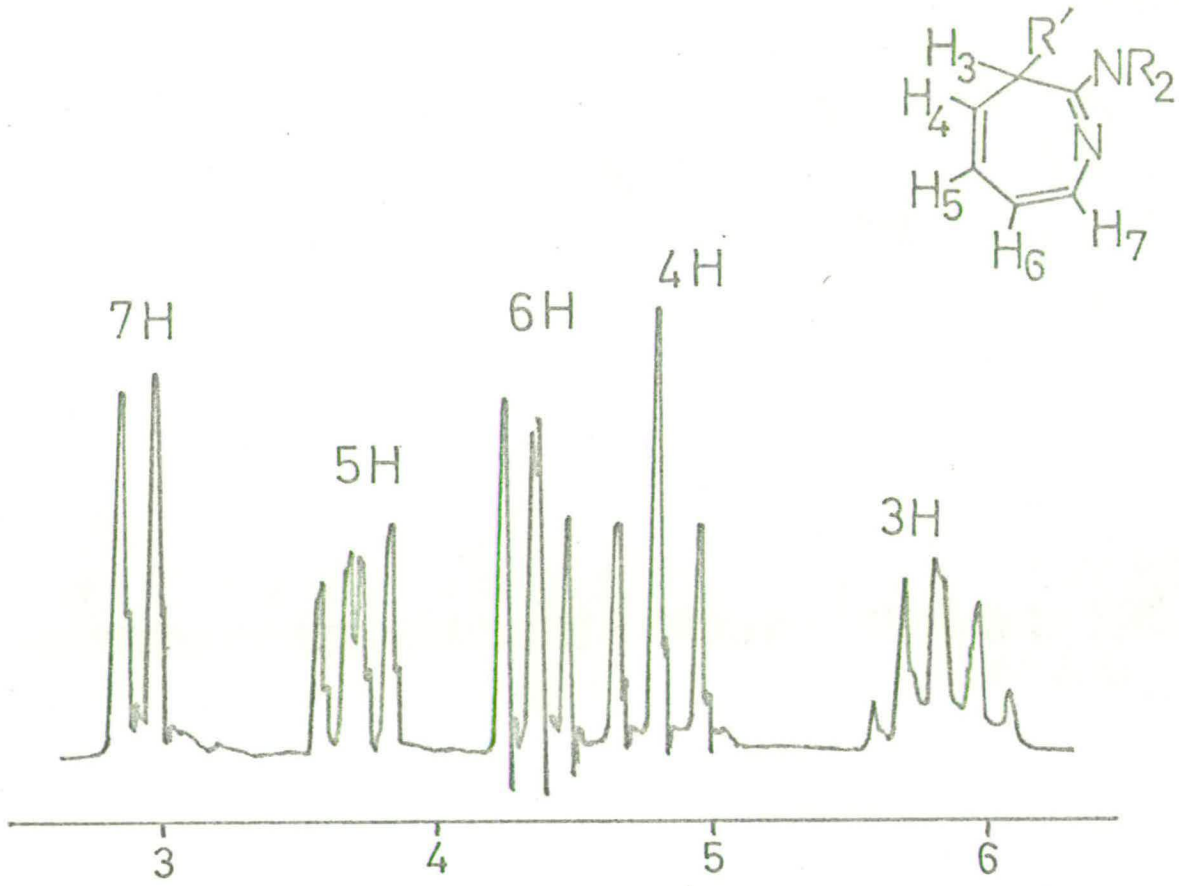


figure 6

3-Substituted azepine

The one proton on the 3C appeared as a multiplet at 6τ due to coupling with a methyl substituent and the 4H. The 4H appeared as a triplet, coupled with the 3H and with the 5H. The 5H, 6H, and 7H each appeared in their normal positions with their characteristic coupling patterns, as shown in figure (6).

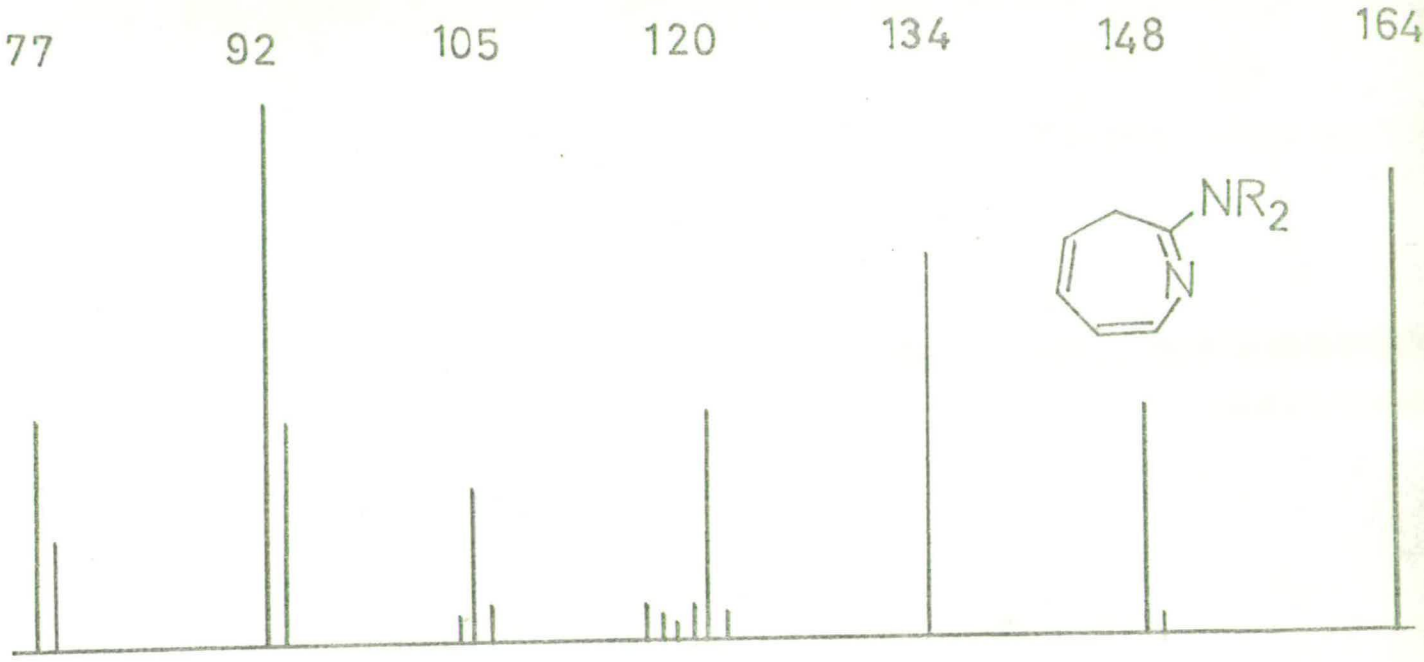


figure 7

In each of the azepines studied, the n. m. r. also showed any substituents present, e. g. methyl.

In the conversion of 6-carbethoxy-2-diethylamino-3H-azepine to 6-carbethoxy-1, 3-dihydro-2H-azepin-2-one (2) by hydrolysis on an alumina column, (2) was identified by the loss of the diethylamino group, the broadening of the singlet due to the 7H, and the appearance of another broad singlet at 0. 2 τ. On shaking with D_2O, this vanished, and the singlet of the 7H became sharp once more, implying that the singlet at 0. 2 τ was due to an NH proton, coupled with the 7H.

In 2-diethylamino-3, 5, 7-trimethyl-3H-azepine, the 3H appeared as a multiplet at 6. 2 τ, coupled with the 4H and the methyl group. The 4H was a doublet at 5. 1 τ, couplet with the 3H, and the 6H was a singlet at 4. 5 τ. The protons 3, 5 and 7 were missing.

The mass spectrum of a 2-diethylamino-3H-azepine is also distinctive. That of (1) is reproduced in figure (7). Certain features are common to all. The diethylamino group is the first to break down, and therefore the pattern of a substituted azepine is always: M^+, M-15, M-29, M-45, M-59, each appearing as strong peaks. The other common factor is a very strong peak at 92, due to C_6H_5N, which breaks down further to give both 77 (C_6H_5) and 78 (C_5H_4N) normally.

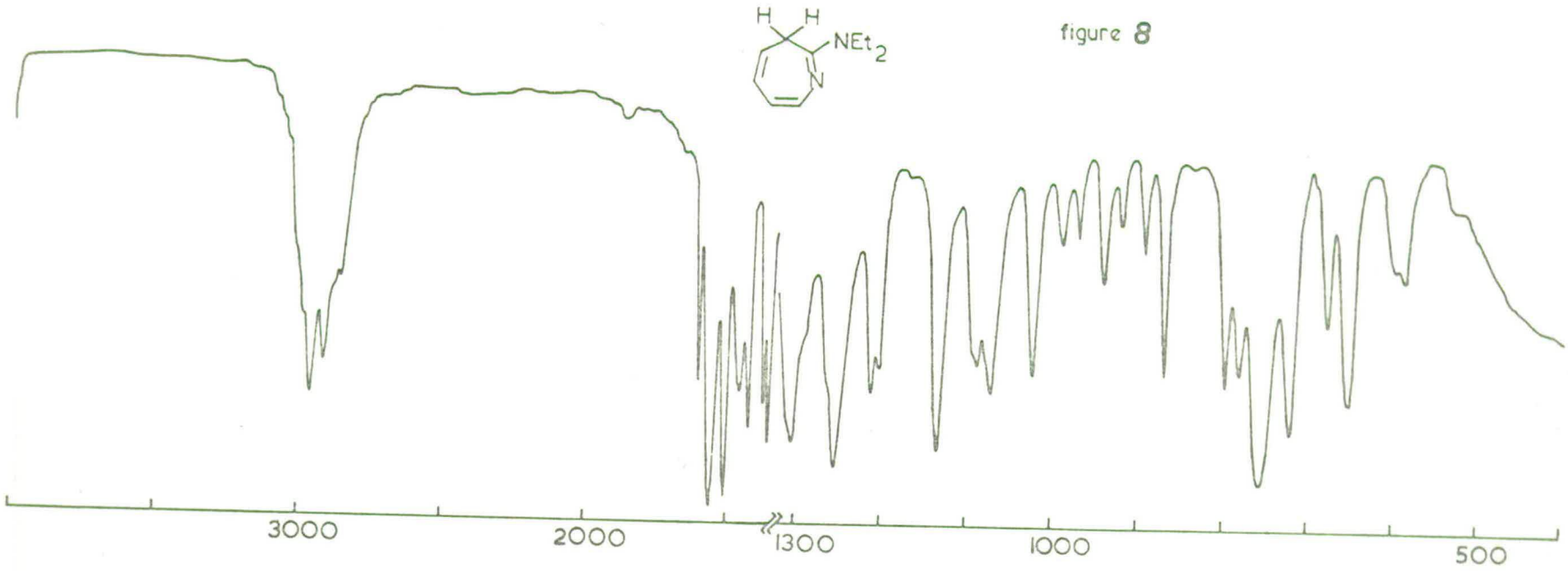


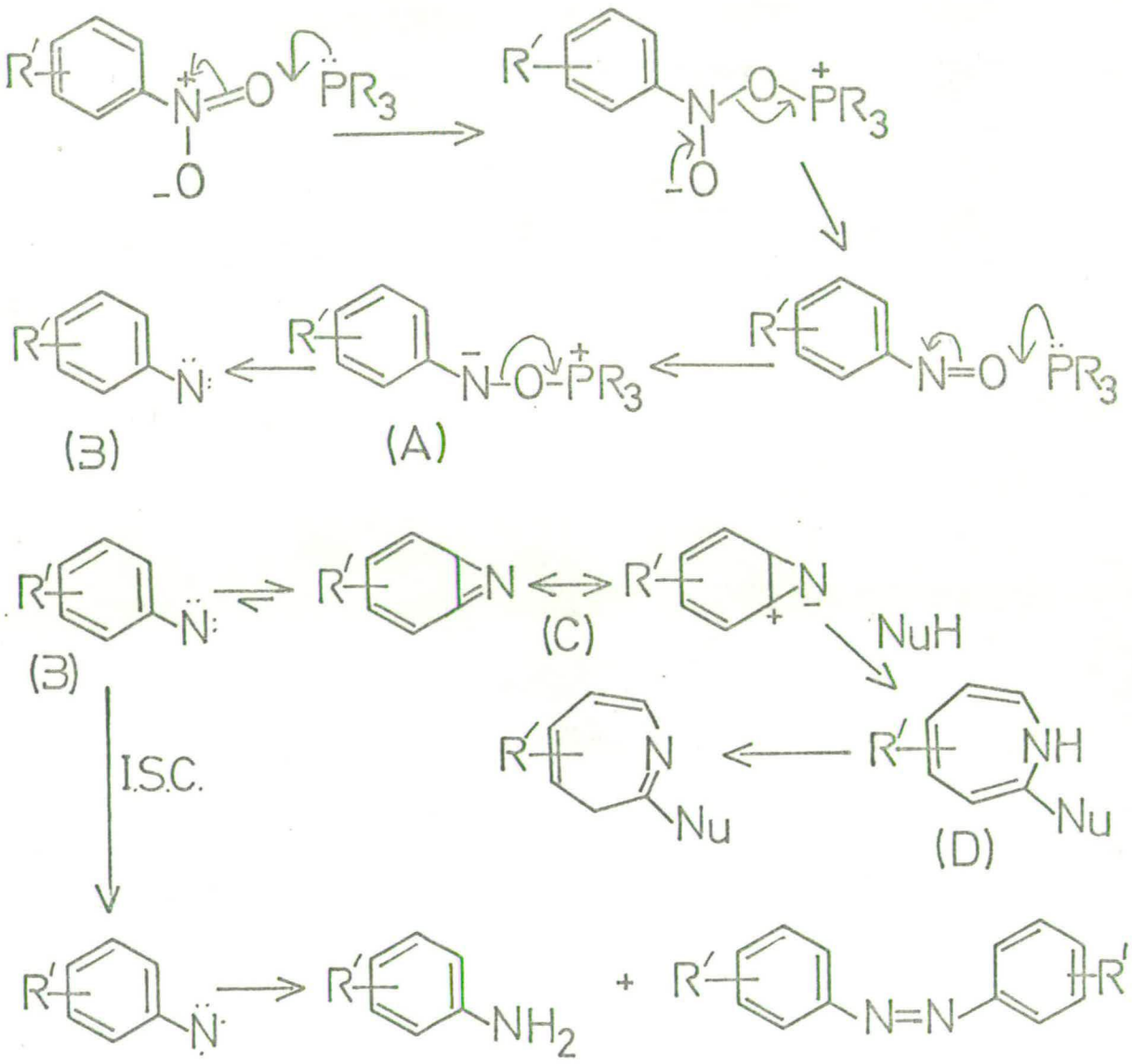
figure 8

A typical i. r. spectrum of an azepine is reproduced in figure (8). It is characterised by the large number of peaks indicating the many possible C-H bond and stretch modes of vibration.

A.

SUMMARY

In an effort to determine the nature of the aryl nitrene intermediate, the phosphite-nitro deoxygenation reaction in the presence of a nucleophile, (NuH), has been thoroughly studied. As a result of the investigation now reported in this thesis, it is postulated that the reaction follows Scheme 1.



Scheme 1

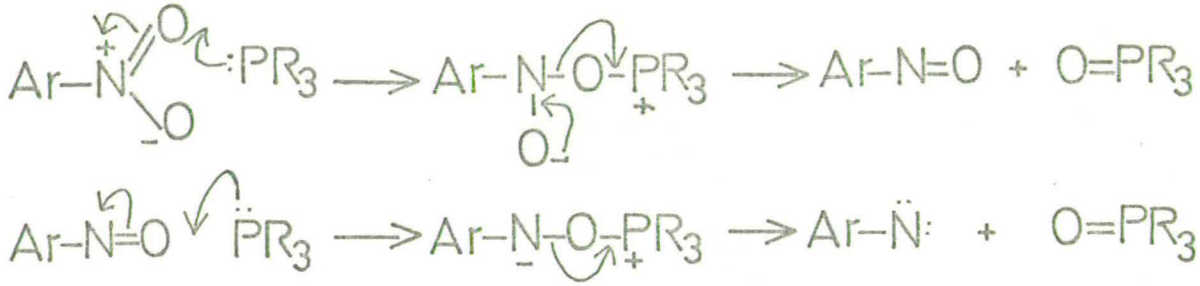
In order to elucidate the course of this reaction, R, R' and NuH have all been varied, and evidence is presented for the existence of intermediates (A), (B), (C) and (D). It has also been shown here that a nitrene generated from a different source, the corresponding azide, has the same character as the intermediate in the phoshpite deoxygenation reaction.

The different reactions leading to different products by singlet and triplet nitrenes have been described in the introduction. This investigation has shown that it is singlet nitrene which takes part in the reaction to form azepines. In circumstances where the singlet nitrene could not be trapped, products were obtained that were attributable to the triplet nitrene after intersystem crossing from the singlet nitrene.

B. MECHANISM OF THE DEOXYGENATION OF ARYL NITRO AND NITROSO COMPOUNDS.

1. Nucleophilic attack

It has been postulated[53, 143] that the deoxygenation of an aryl nitro compound proceeds by nucleophilic attack by the phosphorus reagent on the oxygen of the nitro group, leading to the formation of an intermediate nitroso compound, and by the attack of a second molecule of phosphorus reagent on the nitroso oxygen, to form a nitrene, (Scheme 2).



Scheme 2

This investigation has confirmed that the attack is nucleophilic by observing the effects of different substituents both in the benzene ring and attached to phosphorus on the rate of reaction. The results are given in Tables 1, 2 and 3.

Earlier results of the differences between the phosphorus reagents have been reported by Cadogan and Todd,[56, 138] and are shown in Table 4. Sundberg[198] measured the rates of deoxygenation of nitro and nitroso arenes with triethyl phosphite in methanol. His results are given in Table 5.

Table 1. Time taken for complete Deoxygenation of Nitroaryls with Diethyl Methylphosphonite in Diethylamine at 65°

Substituent p-	CO_2Et	Br	Cl	Me	CN
Time (days)	0.6	[5]	1.2	3.5	0.2

Substituent m-	CO_2Et	Br	Cl	Me	OMe
Time (days)	1.6	0.6	0.7	3.5	4

Substituent o-	Cl	Me[a]	OMe	CN	Ph-CH=N	SMe	OMe
Time (days)	0.15	[10]	2.5	0.5	2	5	3

a. P reagent ethyl diphenylphosphinite.

Table 2. Time taken for complete Deoxygenation of Nitrobenzene with Substituted P reagents in Diethylamine at 56°.

P reagent	$(MeO)_3P$	$(Et_2N)_3P$	$Ph_2P(OEt)$	$MeP(OEt)_2$
Time (days)	14	8	6	3

Table 3. Time taken for complete Deoxygenation of Nitrosobenzene with Substituted P reagents in Diethylamine at 56°.

P reagent	Ph_3P	$(EtO)_3P$	$Ph_2P(OEt)$
Tiem (hours)	4	4	0.5

Table 4. Half Life of Deoxygenation of Nitrobenzene with Substituted P reagents.

P reagent	$(EtO)_2PMe$	$(Et_2N)_3P$	$(EtO)P(NEt_2)_2$	$(EtO)_3P$
life (min)	160	40	5	50
Temp.	61	111	121	145

Table 5. Relative Rates of Deoxygenation of Substituted Nitro and Nitroso Compounds with Triethyl Phosphite.

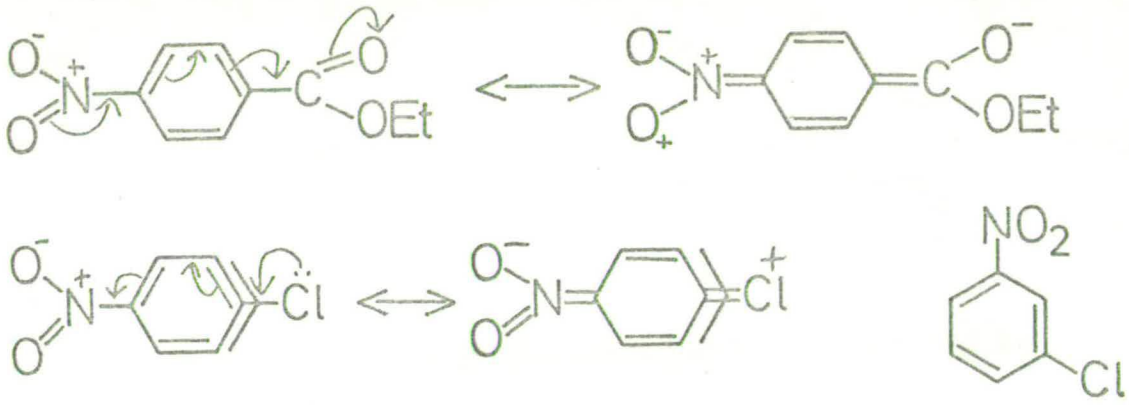
Substituent	p-OMe	p-Me	m-Me	H	p-Cl	m-CO_2Me
Rel. Rate Ar-NO	0.057	0.31	0.67	1	-	6.3
Rel. Rate Ar-NO_2	0.17	0.45	0.50	1	1.74	1.88

cont.

Substituent	m-Cl	p-CO_2Me	p-CN
Rel. Rate Ar-NO	6.5	13.3	-
Rel. Rate Ar-NO_2	2.46	6.61	11.0

This investigation showed that in the case of nitromesitylene, where the nitro group cannot adopt a position in the plane of the ring because of the two o-methyl groups, and therefore has no possibility of delocalisation of the electrons of the oxygens over the π system of the ring, prolonged heating over three weeks with the strongly nucleophilic phosphorus reagent, diethyl methylphosphonite [$(EtO)_2PMe$] resulted in the deoxygenation of only 10% of the starting material. Sundberg[198] reported that the deoxygenation of nitrosomesitylene was slightly faster than that of the unsubstituted nitrosobenzene. This indicates the nucleophilic nature of the attack.

The results of the present investigation into the deoxygenation of m- and p-substituted nitroarenes in diethylamine clearly show that electron-withdrawing, deactivating groups, e.g. carbethoxy and chloro increase the rate of attack by phosphorus reagent, and electron donating groups, e.g. methoxy decrease the rate of attack. The p-carbethoxy derivative is faster than the m-isomer because it acts by a mesomeric electron withdrawal selectively from o- and p-positions, while the p-chloro derivative is slower than the m-isomer because the mesomeric effect enhances the electron density at the o- and p-positions, while the inductive effect decreases electron density over the entire ring, (Scheme 3).



Scheme 3

The results from the o-substituted nitro compounds do not fit the pattern, and the products are frequently polymeric, always where the reaction rate is enhanced, (except for true concerted reactions), an indication that the reaction may follow a different path.

Variation of the phosphorus reagents shows that diethyl methylphosphonite is the most nucleophilic and most efficient reagent for both nitro and nitroso compounds. In the Tables 2 and 3 deoxygenation of nitroso compounds, the influence of substituents is more strongly marked than for nitro compounds. Using triethyl phosphite, p-chloronitrosobenzene was deoxygenated in 1 h at 0°, and N,N-dimethyl p-nitrosoaniline required 2 h at 56.5°.

2. Nitroso Compounds as Intermediates

That nitrosobenzene is formed as an intermediate is harder to show since it reacts so much more quickly with the phosphorus reagent in diethylamine than does the original nitro compound, e.g. 0.5 h for nitrosobenzene and 6 days for nitrobenzene in deoxygenation with ethyl diphenylphosphinite ($EtOPPh_2$). If it is an intermediate, then when it is subjected to the same reaction conditions, it should produce the same products in the same yields.

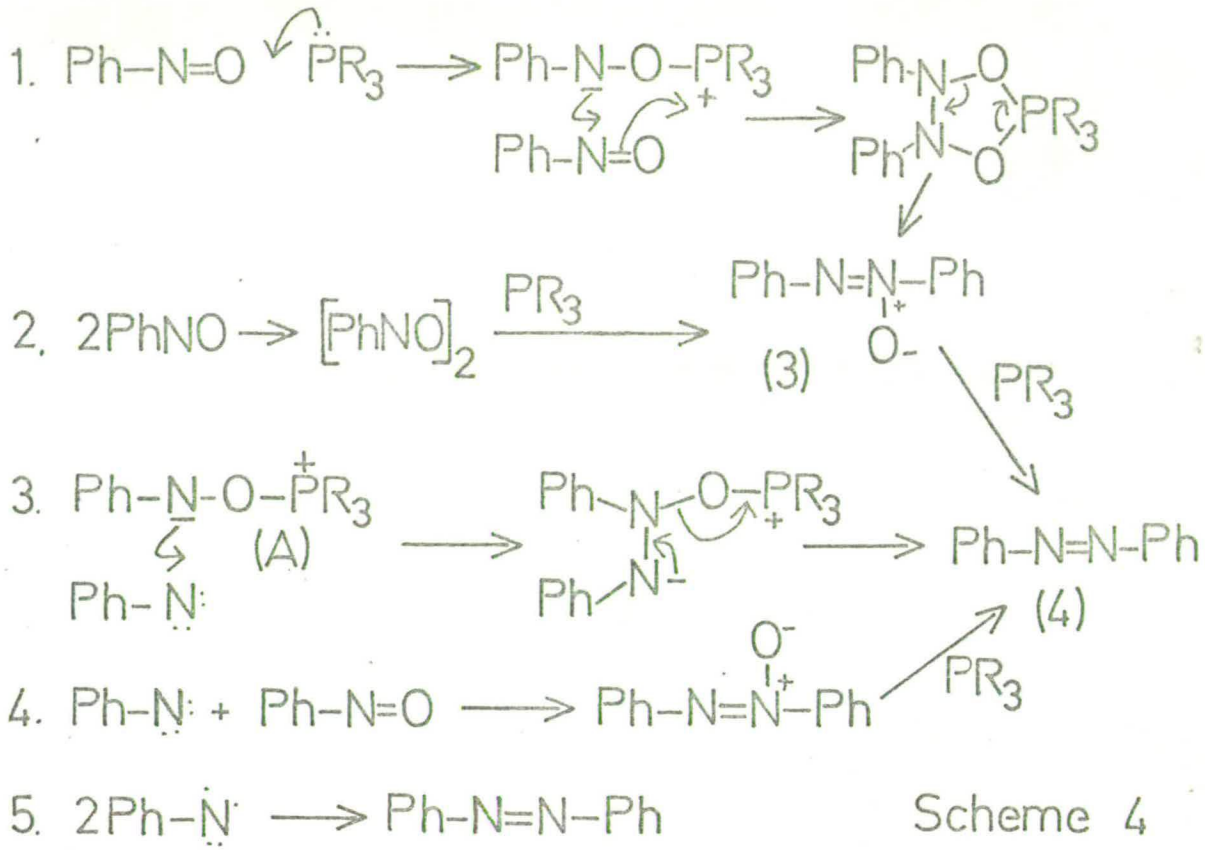
Nitrobenzene was deoxygenated by a number of phosphorus reagents, e.g. trimethyl phosphite, ethyl diphenylphosphinite, tris-(diethylamino)phosphine and diethyl methylphosphinite, each in diethylamine, and in every case only 2-diethylamino-3H-azepine (1) and aniline (2) were found, and no other products were isolated.

Nitrosobenzene was deoxygenated by triphenylphosphine, ethyl diphenylphosphinite and triethyl phosphite each in diethylamine, and not only were (1) and (2) isolated in reduced yields, but there were also the products azoxybenzene (3) and azobenzene (4). These results are given in Table 6.

Table 6. Products from Deoxygenation of Nitroso and Nitrobenzene in Diethylamine at 56.5°.

			Yields			
Nitro/nitroso	P Reagent	Time	(1)	(2)	(4)	(3)
Ph-NO	Ph_3P	4 h	19.5			
"	$(E\ )_3P$	4 h	28	25.8	12.1	23.9
"	Ph_2POEt	0.5 h	61	11.5	1.4	22
$Ph-NO_2$	$Ph_2P(OEt)$	6 d	71	10		
"	$(MeO)_3P$	14 d	40	40		
"	$(Et_2N)_3P$	8 d	74	12		
"	$(EtO)_2PMe$	3 d	84			

Since neither azobenzene nor azoxybenzene has been found in a reaction involving the deoxygenation of nitrobenzene, where the concentration of nitrosobenzene is always low, it is reasonable to suppose that they are formed from nitrosobenzene itself, and not from dimerisation of a subsequent nitrene intermediate. Substituted azobenzenes and azoxybenzenes were formed from m- and p-nitrosotoluenes, p-chloronitrosobenzene, N,N-p-diethylnitrosoaniline and p-nitrosobenzonitrile, but not from the corresponding nitroarenes. Many other workers have also reported the formation of substituted azo and azoxybenzenes in reactions involving deoxygenation of nitroso arenes by phosphorus reagents,[21,56] as well as the formation of substituted azobenzenes in reactions involving arylazides.[25,47,73,118] The mechanistic possibilities are depicted in Scheme (4).

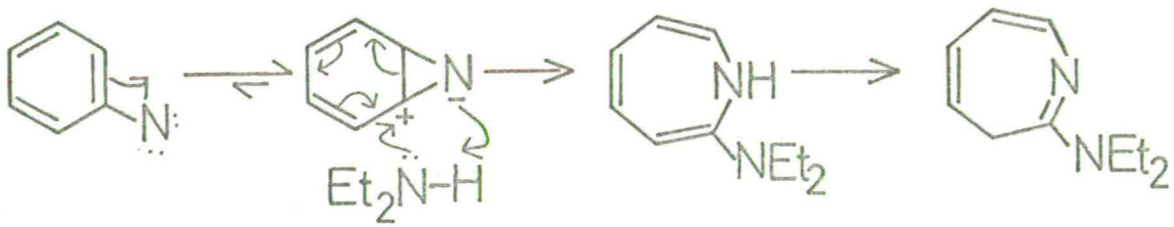


Scheme 4

If the mechanism involved the dimerisation of two nitrenes (equation 5) then azobenzene and not azoxybenzene would be formed, and should be detected in the deoxygenation of nitroarenes as well as of nitrosoarenes, although the yield in the former case might be significantly reduced since the rate of forming aryl nitrenes and hence the concentration of nitrenes at any given moment is very much smaller. Similarly, if attack by a nitrene on intermediate (A) were involved (equation 3) at least a trace of azobenzene should be obtained from nitro deoxygenation reactions. This leaves the possibilities 1, 2 and 4 (Scheme 4); 2 is unlikely because in solution nitrosoarenes exist as monomers, as shown by the green colour, and only in the solid state are they dimers, coloured white. Nitrosobenzene and many of its derivatives do react with themselves if heated or subjected to U. V. light, hence frequent difficulty in preparation. Control experiments involving nitrosobenzene in diethylamine at 56. 5° and also under g. l. c. conditions showed that azo and azoxybenzene, aniline, and one unidentified product were formed. Pak and Testa[199] have reported the formation of phenyl hydroxylamine and acetone under

strictly controlled conditions, although most earlier workers reported aniline and azoxybenzene as the products. Under normal reaction conditions, where the nitrosoarene was stable, however, immediate reaction was seen on mixing with phosphorus reagent, as evinced by the green colour turning orange. The yield of azoxyarene was maximised where the solution containing the phosphorus reagent was added slowly to a solution of the nitrosoarene, and minimised when a solution of the nitrosoarene was added slowly to a well-stirred solution of the phosphorus reagent. By the former method, a yield of 70% of 4,4'-dichloroazoxybenzene was obtained from p-chloronitrosobenzene, which was reduced by the latter method to 30-40%. The yield also depended on the reactivity of the nitrosoarene. p-Nitrosobenzonitrile, which is highly reactive, gave 4,4'-dicyanoazobenzene (10%) on addition of triethyl phosphite at room temperature, i. e. where excess nitrosoarene was present; N,N-p-dimethylaminonitrosobenzene gave 4,4'-bis(dimethylamino)azobenzene (61%) on addition slowly to triethyl phosphite. This implies that the formation of azoarenes is a reaction whose mechanism involves the nitrosoarene itself and another intermediate, which could be either the nitrene or its precursor, intermediate (A), (equations 1 and 4, Scheme 4).

In order to show which of these alternatives is correct, evidence from the reaction of a singlet nitrene with diethylamine to form an azepine (Scheme 5) is required. This reaction will be discussed in greater detail in future chapters.



Scheme 5

The evidence required to differentiate between alternatives 1 and 4, the involvement of nitrene precursor or nitrene, concerns the extra-ordinary efficiency of diethylamine in acting as a trap for singlet

nitrene. Under the normal reaction conditions, where diethylamine is present in vast excess as solvent, yields of 80-90% of azepines from nitrenes are common. In an experiment involving the deoxygenation of m-chloronitrosobenzene with tris(diethylamino)phosphine in t-butanol, a side reaction between the latter two resulted in the formation, over three days, of trace quantities of diethylamine, sufficient to trap the m-chlorophenyl nitrene, formed simultaneously in the deoxygenation reaction, to give the corresponding azepines in a yield of 81%. It is therefore reasonable that any singlet nitrene formed in a reaction involving the deoxygenation of a nitrosoarene in diethylamine would be trapped immediately, and would not exist long enough to undergo intersystem crossing to the triplet state, and then react with the nitrosoarene to form azoxyarene, which implies that the reaction between nitrosoarene and nitrene precursor is the most probable reaction mechanism for the formation of azoarenes, (equation 1, Scheme 4). It has been shown[21] that phosphorus reagents can reduce azoxybenzene to azobenzene.

Azobenzene and its derivatives are, however, considered to be the products of dimerisation of phenyl nitrenes under special circumstances, such as vapour phase pyrolysis,[73] and where no alternative mode of reaction is presented to the nitrene.[25] Swenton[47] showed by use of triplet sensitisers that the normal formation of carbazole from singlet 2-biphenyl nitrene could be interrupted, and the triplet nitrene then formed good yields of azobiphenyl.

If the fate of the nitrosobenzene that is not involved in the formation of azoxybenzene is then examined, the results here show that it does indeed produce the same products in the same yields under the same conditions: the less nucleophilic phosphorus reagents, e.g. triethyl and trimethyl phosphites give poorer yields of 2-diethylamino-3H-azepine (1) from both nitro- and nitrosobenzene in diethylamine than do the more efficient reagents, e.g. ethyl diphenylphosphinite. There are correspondingly larger yields of aniline from the less nucleophilic reagents. The results are given in Table 7.

Table 7 Products from the Deoxygenation of Nitro- and Nitroso-benzene in Diethylamine at 56°.

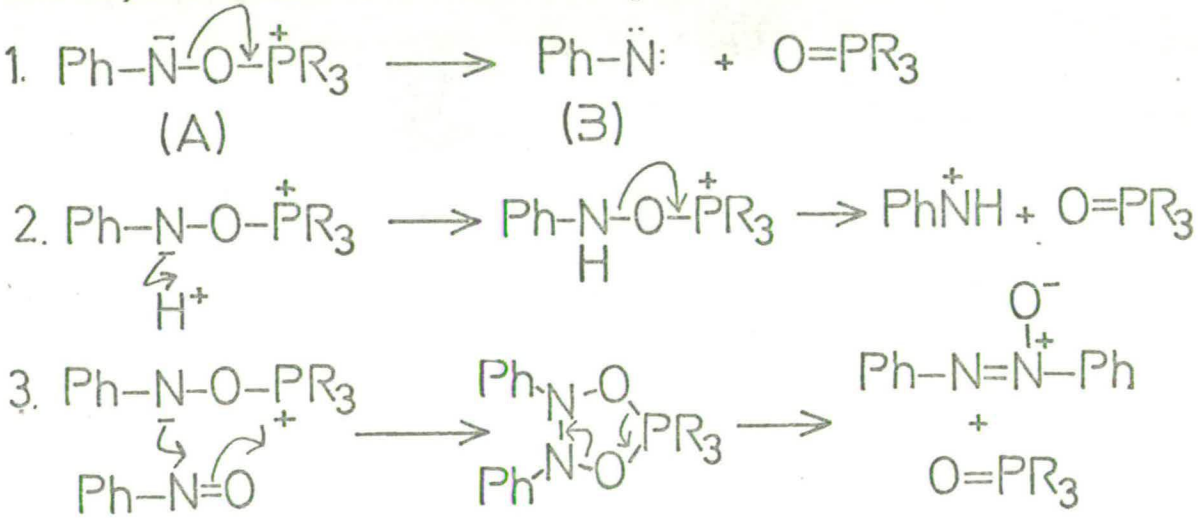
P reagent	$PhNO_2$/PhNO	% Yield azepine (1)	% Yield aniline
$(MeO)_3P$	$PhNO_2$	40[a]	40[a]
$(EtO)PPh_2$	$PhNO_2$	71	10
$(EtO)_3P$	PhNO	28	25.8
$(EtO)PPh_2$	PhNO	61	11.5

a, calculated from g.l.c. alone, not isolated.

This similarity of behaviour between nitrobenzene and nitrosobenzene indicates that the nitrosobenzene may be an intermediate in the deoxygenation of nitrobenzene.

3. The Intermediate (A)

It has become apparent that intermediate (A), the nitrene precursor, may play an important part in the deoxygenation reaction. The ways in which it can react are depicted in Scheme 6.



Scheme 6

The mode which is preferred will depend on two factors: the actual lifetime of intermediate (A) and the nature of its environment. The lifetime varies according to the nature of the group R attached to the phosphorus atom. The more nucleophilic phosphorus reagents, those which react fastest with the nitroarene, also promote more

rapid decomposition of (A) to form an aryl nitrene (B), leading to higher yields of azepines in cleaner reactions with less polymeric residue. The less nucleophilic phosphorus reagents, with longer reaction times, are also slower in removing the oxygen to form a nitrene, leaving (A) time to react, resulting in smaller yields of azepines and higher yields of anilines and polymers, and where the starting material was a nitrosoarene, higher yields also of azoxyarenes. Table 6, which gives the results for nitro and nitrosobenzenes, is reproduced below.

Table 6. Products from Deoxygenation of Nitro and Nitrosobenzene in Diethylamine at 56.5°.

P reagent	$PhNO_2$/PhNO	Time	% Yields			
			azepine(a)	aniline	azobenzene	azoxybenzene
$(EtO)_2PMe$	$PhNO_2$	3 d	84			
$Ph_2P(OEt)$	"	6 d	71	10		
$(Et_2N)_3P$	"	8 d	74	12		
$(MeO)_3P$	"	14 d	40	40		
$Ph_2P(OEt)$	PhNO	0.5 h	61	11.5	1.4	22
$(EtO)_3P$	"	4 h	28	25.8	12.1	23.9
Ph_3P	"	4 h	19.5			

That the intermediate (A) is readily intercepted by nitrosoarene has already been shown, but the extent of interception may also reveal the different effects of more and less nucleophilic phosphorus reagents on the lifetime of (A). The results are given in Table 8.

Table 8. Formation of Azo and Azoxyarenes from Nitrosoarenes in the Deoxygenation Reaction.

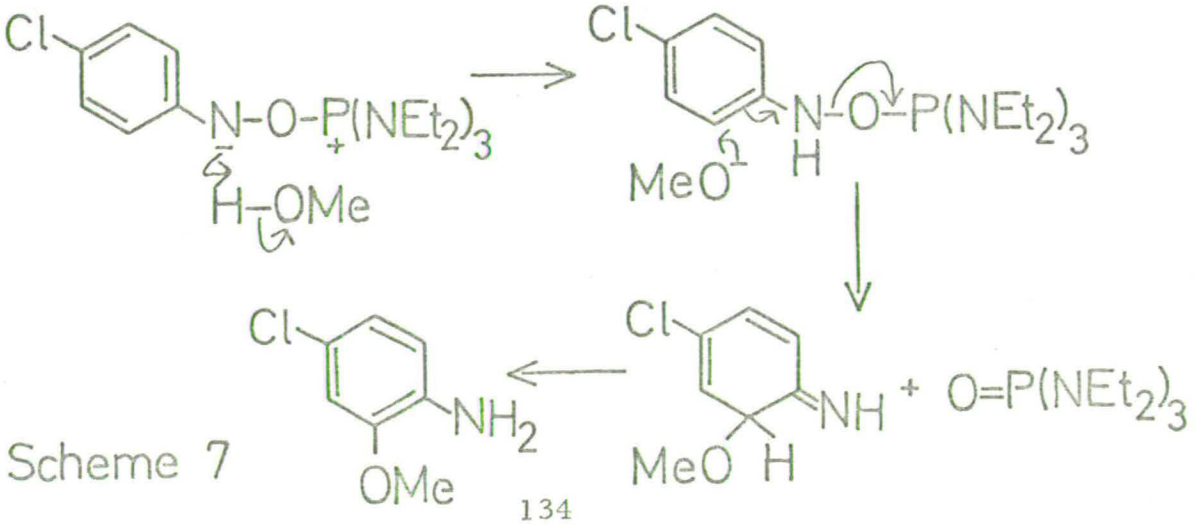
Nitrosoarene	P reagent	% Yield azoarene + azoxyarene	Method
p-ClPhNO	$(Et_2N)_3P$	32	a
"	$(EtO)_3P$	50	a
"	"	70	c
PhNO	$(EtO)PPh_2$	23	b
"	$(EtO)_3P$	40	b

a: p-chloronitrosobenzene added slowly at room temperature to a stirred solution of phosphorus reagent in diethylamine.

b: nitrosobenzene, phosphorus reagent and diethylamine boiled under reflux at 56.5°.

c: phosphorus reagent added slowly to a stirred solution of p-chloronitrosobenzene in diethylamine at room temperature.

Method c shows that the yield of azoxyarene is increased by increasing the availability of nitrosoarene. Thus the environment is seen to be important. When the deoxygenation of p-chloronitrosobenzene was carried out in the presence of methanol, which is sufficiently acidic to protonate the intermediate (A), the yield of 4,4'-dichloroazoxybenzene was reduced from 32% to 22% (both figures from identical reaction conditions, using tris(diethylamino)phosphine at room temperature), and good yields of anisidines resulting from subsequent attack by methanol or methoxide ion on the benzene ring of the protonated form of (A), (AH^+), were obtained, (Scheme 7).



Scheme 7

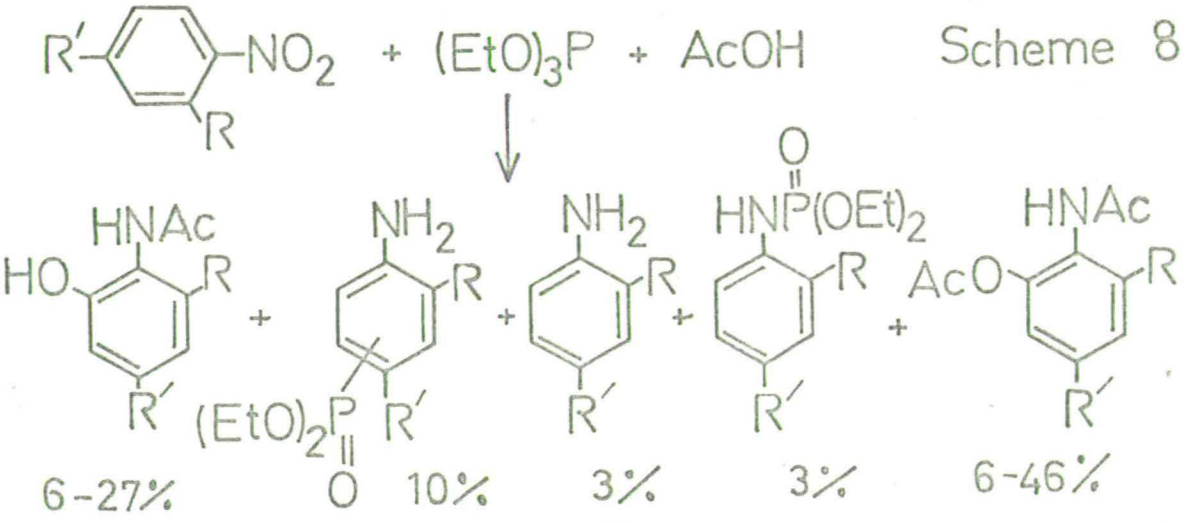
These results agree with those of Sundberg[200] who isolated a 70% yield of o- and p-anisidines from the deoxygenation of nitrosobenzene with triethyl phosphite in methanol, for which he postulated that the intermediate (A) should first be protonated. No "normal" azepinyl product was obtained. He looked at mixtures of diethylamine in methanol and ethanol, and analysed the products.

The results show that competition takes place for intermediate (A), and that a decreasing amount is protonated as the % of diethylamine in methanol increases. That the nitrene once formed reacts with even a small % diethylamine is seen from an experiment where a high yield of 2-diethylamino-3H-azepine is obtained in ethanol containing only 5% diethylamine, since the ethanol, being a poorer acid than methanol, cannot protonate intermediate (A). The formation of some ethoxyaniline, presumably via just such a protonated form, has not yet been explained.

Sundberg demonstrated the importance of the protonation by adding small quantities of acetic acid to various alcohols, ethanol, isopropanol, methoxyethanol and t-butanol, none of which give alkoxyanilines without the acid, and all of which do in the presence of the acid. He showed that the protonation occurs on an intermediate prior to the nitrene by generating phenyl nitrene by photolysis of phenyl azide, in the presence of methanol, when no anisidines were obtained.

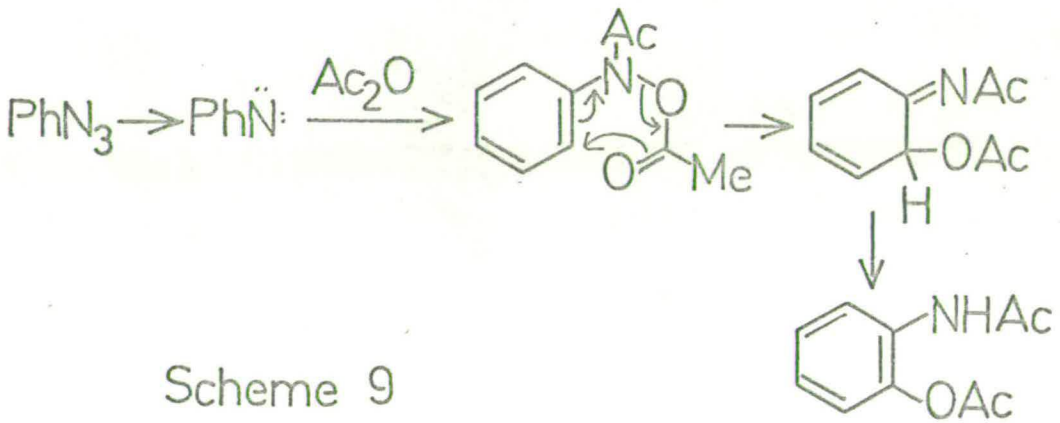
Sundberg also conducted experiments involving acetic acid itself,[120] in which he isolated products involving nucleophilic aromatic substitution, e.g. o-acetoxyacetanilides, and also products involving substitution by the phosphorus reagent (Scheme 8).

Scheme 8



More recently, he has isolated a 1-phenyl-1H-azepine from deoxygenation of nitrobenzene by triethyl phosphite in the presence of benzene and trifluoroethanol.[201] He has shown that no solvent other than trifluoroethanol promotes this addition and also that it is not a reaction of the nitrene, since photolysis of phenyl azide in the same solvent does not produce any 1-phenyl-1H-azepine, and therefore concludes that it is another reaction involving intermediate (A).

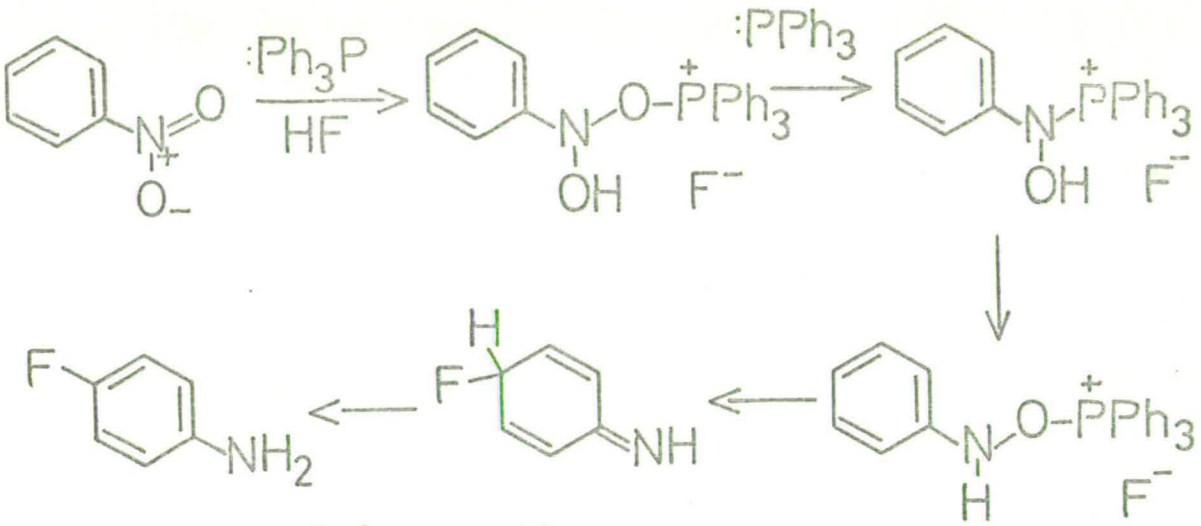
There are reports that nitrenes from azides form acetoxyacetanilides in the presence of acetic acid.[118, 119] Horner, Christmann and Gross[118] reported the formation of p-acetoxyacetanilide from the photolysis of phenyl azide in acetic acid, but that the nitrene did not react with acetic anhydride. Smalley and Suschitzky[119] reported that thermolysis of phenyl azide in acetic anhydride led to o-aminophenol, or its acetylated derivatives, by a method which did not involve protonation of any intermediate, (Scheme 9).



Scheme 9

It may be, therefore, that acetic acid can react with the nitrene itself as well as by protonating the intermediate (A).

A further example of protonation of (A) comes from Scott and co-workers,[123] who postulated nucleophilic attack by the strong fluoride ion on the benzene ring of ($A H^+$) to form fluoroaniline. His mechanism is given in Scheme 10.



Scheme 10

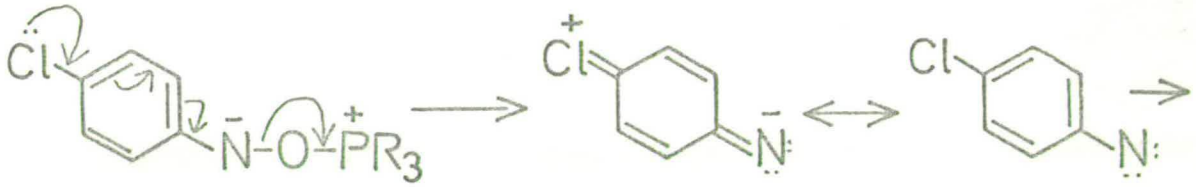
The results from this investigation also indicated that substituents on the benzene ring influenced the rate of decomposition of (A) to form a nitrene, as shown by the yields of azepines from the deoxygenation of nitroarenes, of which the results are given in Table 9.

Table 9. Formation of Azepines in the Deoxygenation of Nitroarenes by Diethyl Methylphosphonite in Diethylamine at 65°.

Substituent:	m-MeO	p-Me	m-Me	p-Cl	m-Cl	p-CO_2Et	m-CO_2Et
Azepine (%):	86	74	70	78	72	67	67

These results should be treated with caution, since they may also depend on the stability of the azepine, but they would seem to indicate that electrondonating groups promote the decomposition of (A) to give a nitrene which immediately reacts to form the azepine. The apparent discrepancy with p-chloronitrobenzene is explained since the p-chloro substituent has a mesomeric electron donating effect which selectively enhances electron density at the p- (and o-) position, while the general inductive effect, -I, normally reduces electron density over the entire ring. The trend indicated in the table may be connected with the increased stability of the electron deficient nitrene when electrondonating groups are present, but since the nitrene is a long-lived species, capable of surviving many collisions, without any reduction of the yield of azepine (as shown later),

the actual increase in stability of the nitrene is probably only valuable in explaining the increased rate of decomposition of (A), (Scheme 11), which would otherwise react to form polymeric species.



Scheme 11

Thus the importance of using a strongly nucleophilic phosphorus reagent to give good yields of azepine and less polymeric residue is explained by the fact that it also encourages rapid decomposition of intermediate (A), and the formation of azoxyarenes is a clean reaction because nitrosoarene forms a very efficient trap for (A).

C. THE NATURE OF THE NITRENE INTERMEDIATE

1. The Spin Multiplicity

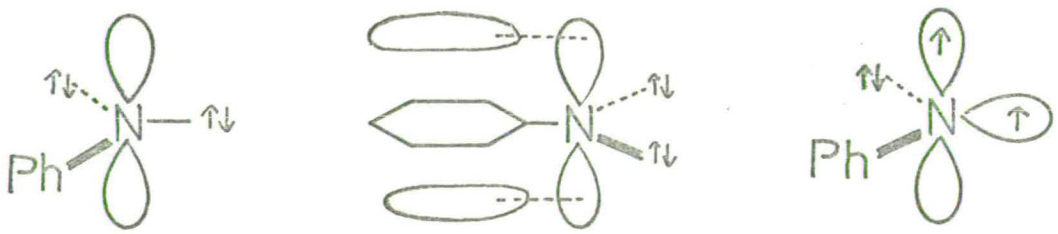
Spin multiplicity is given by $2S+1$,[212] where S equals the total spin of the electrons in the atom under discussion. Where there are two spin-paired electrons, S=O, the spin multiplicity = 1, and the atom (or molecule) is in the singlet state. Where there are two electrons with spins parallel, $S = \frac{1}{2} + \frac{1}{2} = 1$, the spin multiplicity = 3, and the atom (or molecule) is in the triplet state. Thus for both carbene and nitrene, which have two orbitals available and two electrons to go in them, singlet and triplet states may be drawn as in Scheme 12.



lowest singlet triplet excited singlets

Scheme 12

A reasonable structure for the nitrene is a bent sp^2 hybrid, where the empty orbital of the singlet nitrene can overlap with the π electron system of the benzene ring, (Scheme 13). No such overlap is possible with the triplet nitrene.

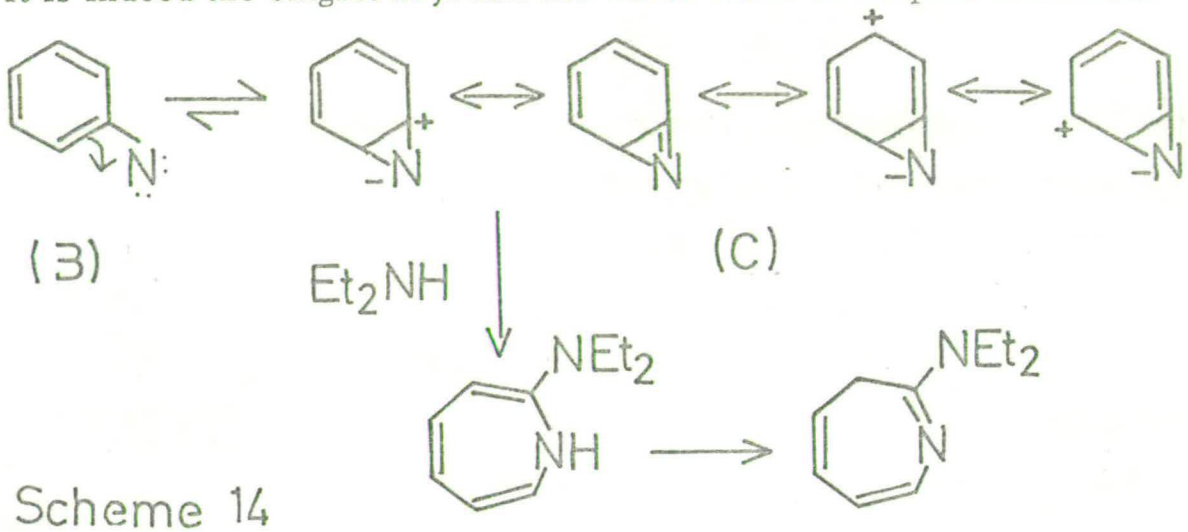


singlet triplet

Scheme 13

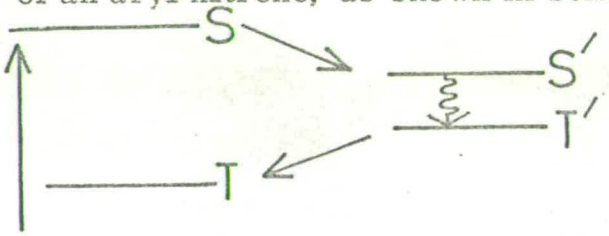
Low temperature e. s. r. experiments[1] have indicated that the triplet state of an aryl nitrene is of lower energy than the singlet state, and it has been shown that amines and azoarenes are products of nitrenes in the triplet state, which may have arisen after intersystem crossing from the singlet state. It is normally assumed that it is the

singlet nitrene which reacts to form the intermediate 7-azabicyclo-[4, 1, 0]hepta-2, 4, 6-triene, (C), leading to the azepine (Scheme 14). Two sets of experiments reported here now show conclusively that it is indeed the singlet aryl nitrene which leads to azepine formation.



Scheme 14

Pyrene, when present in a solution of an aryl azide undergoing photolysis, acts in two ways, both as a sensitiser for the singlet state, and as a quencher for the triplet, [$E_{T(pyrene)}$=48.7 kcal mol^{-1}], should any be formed, of an aryl nitrene, as shown in Scheme 15.



Scheme 15

Therefore the azide must decompose to give only singlet nitrene. When phenyl azide was photolysed in diethylamine, in the presence of a ten molar excess of pyrene (to ensure that most of the incident light was absorbed by the pyrene), 2-diethylamino-3H-azepine (I) (44%) was obtained and neither examination of the reaction mixture by g.l.c. nor extraction from an alumina column revealed any aniline, the known triplet product. Without the pyrene, in the same apparatus, photolysis of the phenyl azide in diethylamine gave a large yield of aniline, and only a trace of azepine (1). This indicates that a pathway: singlet azide ⟶ azepine is followed.

Swenton[47] used pyrene to show that carbazole arose from singlet 2-biphenyl nitrene, and triplet sensitisers to show that azobiphenyl

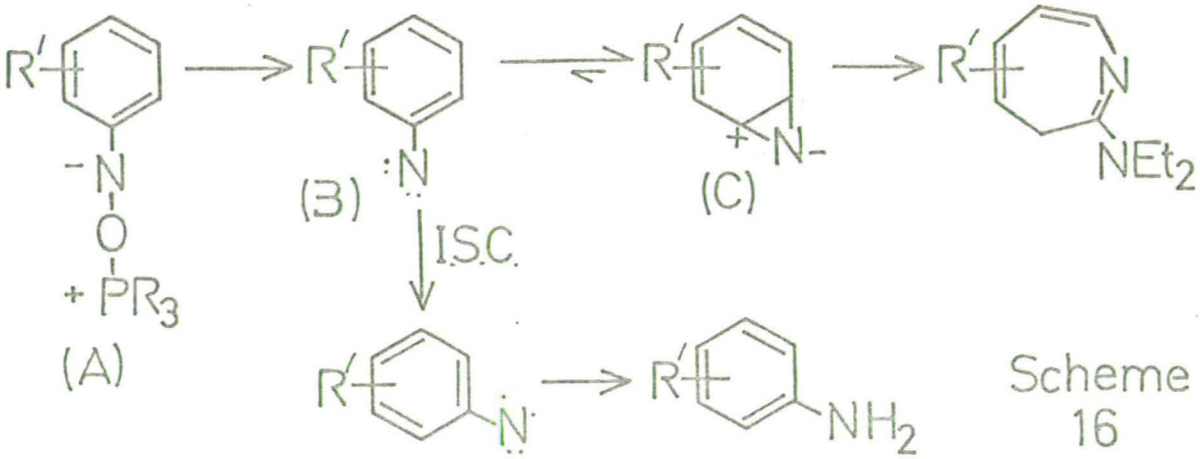
was the product from a triplet nitrene. It has also been observed by a number of workers[72, 172] that a pyrex filter protects the azepine. Without the pyrex filter, the azepine itself reacts to form pyridines.[183]

The other evidence for the involvement of a singlet state results from the "Heavy atom effect." The yields of azepines from chloronitrobenzenes are 70-80%. The yields of azepines from bromonitrobenzenes are 35-45%, with a corresponding increase in amine formation from 10 to 45-50%, (table 10).

Table 10. Formation of Azepines by Deoxygenation of Substituted Nitrobenzenes with Diethyl Methylphosphonite in Diethylamine at 65°.

Substituent	:	m-Cl	p-Cl	m-Br	p-Br
% Yield Azepine	:	70	78	44.5	35.5
% Yield Aniline	:	trace	trace	45	48

The bromine atom attached to the aryl nitrene clearly is promoting intersystem crossing to the triplet nitrene, resulting in diminished yields from the singlet species and increased yields from the triplet species, compared with chlorine. This action by the heavy atom also shows that the discrete nitrene (B) must exist between intermediate (A) and azabicycloheptatriene, (C), or intersystem crossing could not take place, even though all other attempts to trap (B) have failed. (Scheme 16).



Scheme 16

This heavy atom effect has been observed for other nitrenes too. Lwowski[84] reported that in additions of carbethoxy nitrene to olefins, dichloromethane enhanced the stereospecificity, but dibromomethane led to tars, after intersystem crossing to the triplet. Anastassiou[111,114] reported dramatic heavy atom effects for cyano nitrene, where stereospecificity is turned into complete stereorandomness in additions to olefins by using dibromomethane as a solvent, (table 11).

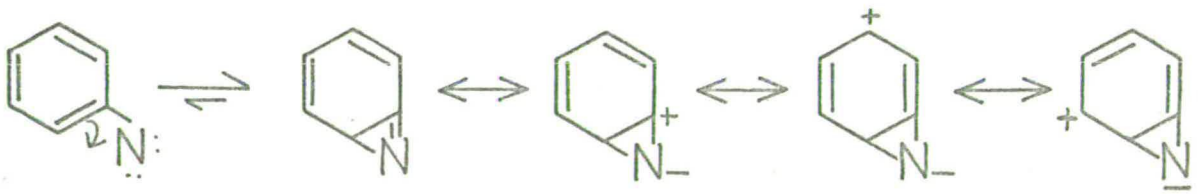
Table 11. Effect of Heavy Atom Solvent on Stereospecificity of Addition of Cyano Nitrene to Olefins.

Solvent	:	none		CH_2Cl_2		CH_2Br	
Hydrocarbon	:	cis	trans	cis	trans	cis	trans
% cis RNHCN	:	>98	<2	74	34	52	52
% trans RNHCN	:	<2	>98	26	66	48	48

The action of the heavy atom (bromine) is the removal of spin forbiddenness through the coupling of spin and angular momenta.

2. Formation of the Azabicycloheptatriene Intermediate, (C).

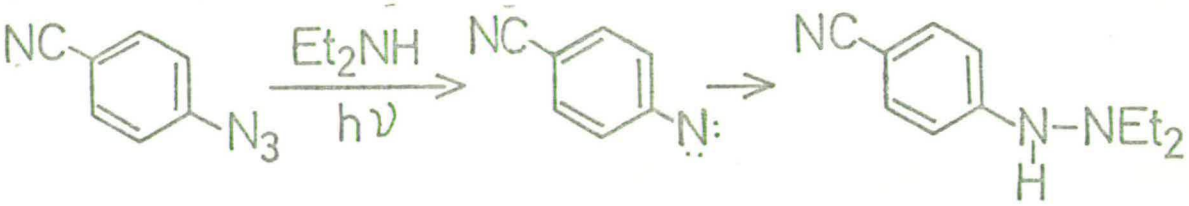
a) Trapping of the aryl nitrene (B).



(B) (C) Scheme 17

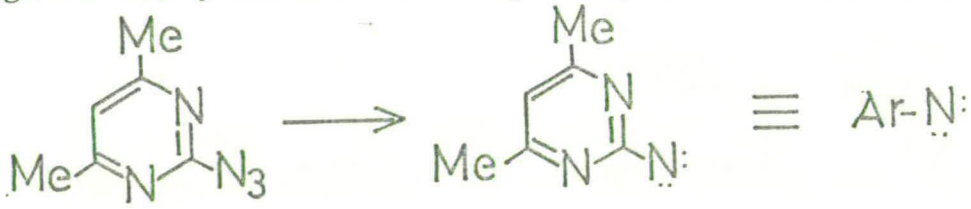
The next facet to be considered in this reaction is the nature of the step (B) $\rightleftharpoons$ (C), as shown in Scheme (17). The problems to be considered are: whether it is an equilibrium step, on which side the equilibrium lies, and how fast it occurs. Accordingly, efforts have been made to trap the nitrene itself, prior to formation of intermediate (C).

p-Cyanophenyl nitrene has been reported by Odum and von Doering[172] to react by insertion in an N-H bond of diethylamine, (Scheme 18).



Scheme 18

They postulated that this was due to the special effect of the extremely electronegative cyano group. Sundberg[201] has also reported finding a trace of 1,1-diethyl-2-phenylhydrazine (5) in the deoxygenation of nitrosobenzene by triethyl phosphite in methanol-diethylamine mixtures. Huisgen[90] reported that 4,6-dimethyl-2-pyrimidyl nitrene underwent insertion in the N-H bond of aniline to give a 32% yield of the corresponding hydrazine (6), (Scheme 19).



Scheme 19



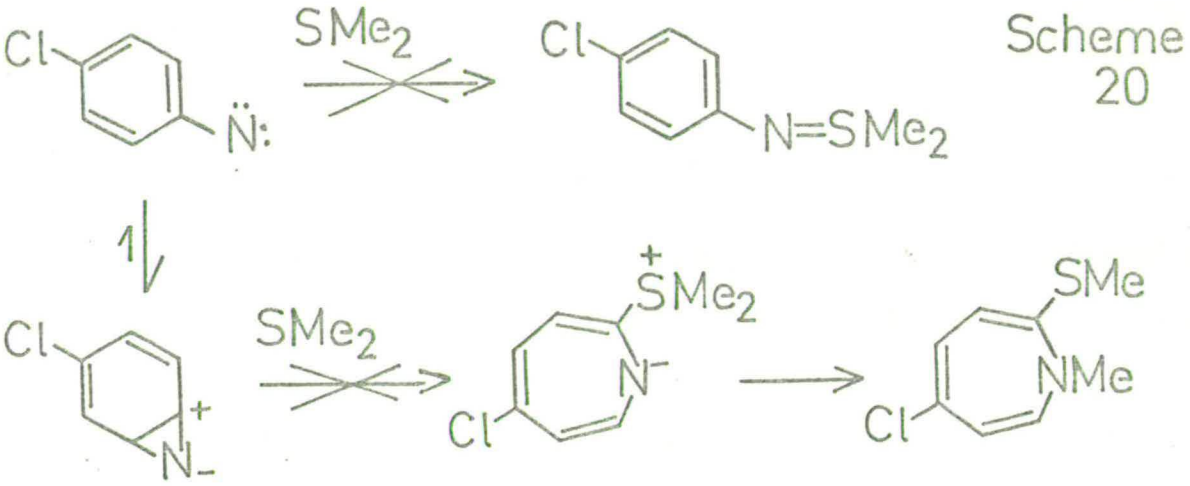
On two occasions, one involving the deoxygenation of nitrobenzene and the other of o-nitrosotoluene, good yields (60%) of 1,1-diethyl-2-arylhydrazine, apparently formed by insertion in the N-H bond of diethylamine, were obtained. Both of these occurred using ethyl diphenylphosphinite, which may have contained a trace of impurity, such as triethylamine hydrochloride. The experiments were irreproducible. Attempts to find conditions under which the hydrazine was preferentially formed failed. The use of a bomb to provide reaction conditions of high temperature and pressure yielded only the azepine, (1). Careful examination of a series of reaction mixtures containing different molar quantities of diethylamine, with sampling

of each mixture on the g.l.c. frequently through the course of the reaction, showed that immediately after the reaction was begun a peak with retention time corresponding to that of an authentic sample of the hydrazine, (5), was formed, but as the reaction proceeded, the size of this peak did not increase, while that of the azepine, (1), did, until by the end of the reaction the relative sizes implied that (5) could only be formed in a trace quantity of <1%. The conclusion was that some impurity was responsible for catalysing the hydrazine formation, but it has not yet been identified.

An effort was made to trap the extremely electron-deficient nitrene, p-cyanophenyl nitrene, which had already shown itself capable of reacting as the nitrene form (B), this time using an olefin, dimethyl maleate. The only products of deoxygenation of p-cyanonitrosobenzene were 4,4'-dicyanoazobenzene, 4,4'-dicyanoazoxybenzene and diethyl N-p-cyanophenylphosphoramidate, of which the latter probably came from the nitrene. An attempt was also made to trap the electron-rich p-dimethylaminophenyl nitrene, (also generated from N,N-dimethyl p-nitrosoaniline with triethyl phosphite) with dimethyl maleate, but the products once again were 4,4'-bis(dimethylamino)azobenzene from reaction of intermediate (A) and a nitroso compound which this time is very stable, and diethyl N-p-dimethylaminophenylphosphoramidate, the product of the nitrene trapped by triethyl phosphite. These results make it clear that the nitrene prefers to react with the lone pair of the phosphorus atom rather than the electron-rich double bond.

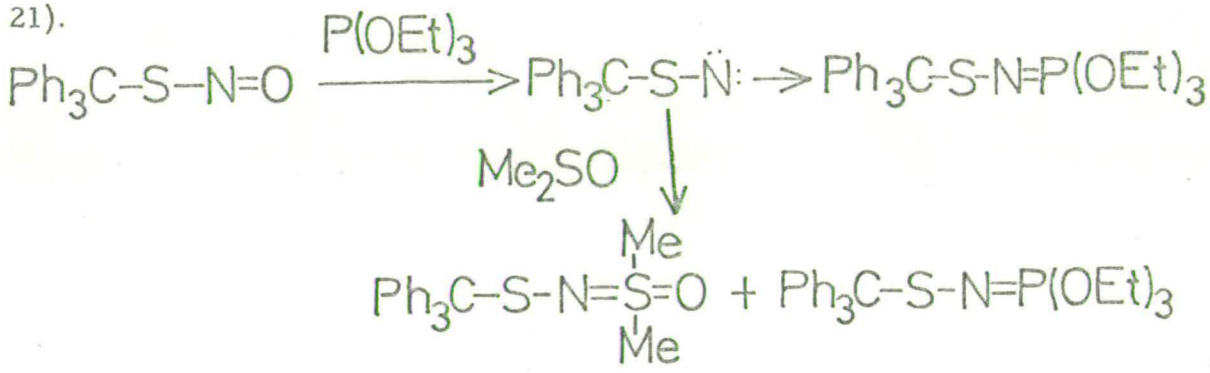
An attempt was also made to trap p-chlorophenyl nitrene with dimethyl sulphide, where the sulphur atom, like the phosphorus atom in triethyl phosphite, has a lone pair of electrons and empty d orbitals available for bonding. Literature cites many examples of other nitrenes, e.g. N-phthalimido[15, 154, 155] and carbethoxy nitrenes which react thus. It had been hoped that even if the dimethyl sulphide failed to trap the nitrene (B) it would as an alternative react with the azabicycloheptatriene (C), to give a thioazepine. It did neither. (Scheme 20). The major product was 4,4'-dichloroazoxybenzene,

and the remainder polymeric.



Scheme 20

It had been expected that the dimethyl sulphide would prove a suitable trap because of a report[13] that trityl thionitrene, which normally reacts with excess triethyl phosphite to form the phosphorimidate, could be trapped in dimethyl sulphoxide, although even in dimethyl sulphoxide the phosphorimidate is a major product (Scheme 21).



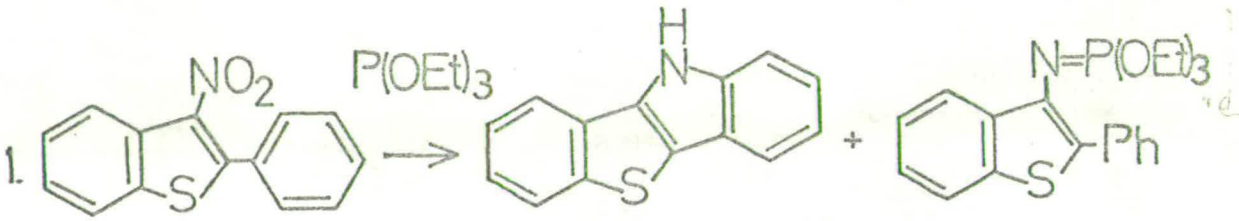
Scheme 21 11% 30%

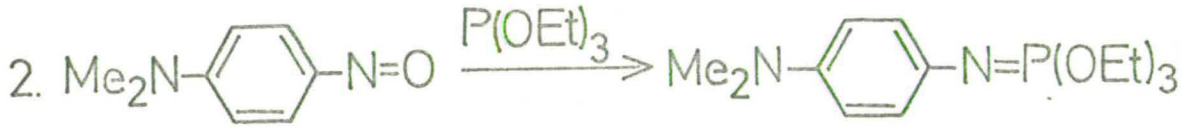
It may be, therefore, that the dimethyl sulphide is a poorer trap than triethyl phosphite, and therefore cannot trap p-chlorophenyl nitrene, which gave only an 11% yield of the N-p-chlorophenylphosphoramidate when generated from p-chloronitrobenzene by the efficient reagent, diethyl methylphosphonite.

There may be various explanations for the failure of these traps. It is probable that the formation of the azabicycloheptatriene intermediate (C) is very fast, and that the equilibrium lies principally on that side, so that only in the exceptional cases of a nitrene such as

p-cyanophenyl nitrene is there much probability of a high enough concentration of the nitrene (B) existing for the trap to react with (B).

Another reason may lie in the efficiency of the trap itself. Aryl nitrenes have repeatedly shown themselves to be highly selective in the choice of species with which they will react, with the result that the products of many ventures are polymeric. This applies to both (B) and (C). Triethyl phosphite has apparently the right properties, since phosphorimidates (or their hydrolysis products, phosphoramidates) have been found by Cadogan and co-workers[50, 51, 53, 56, 143] as the products in many phosphite nitro (or nitroso) deoxygenation reactions in which no trap had been provided for (C). Sundberg subsequently reported[130, 158, 159] that the presence of an o-alkyl substituent greatly improved the yield of phosphorimidate: he obtained 51% from 2,4-dimethylnitrobenzene. Phosphoramidates are also reported as by-products in many other reactions (equation 1, Scheme 22, Smalley and Suschitzky,[98] equation 2, Cadogan[143]).





Scheme 22

During this investigation, reactions of triethyl phosphite with nitroarenes, in the absence of diethylamine, have led to the formation of diethyl N-arylphosphoramidates, as given in Table 12.

The failure of species such as olefins to react with nitrenes is therefore probably dependent on two factors: (a) the equilibrium between the nitrene (B) and the azabicycloheptatriene intermediate (C) lies heavily on the side of (C), and only when there is no trap for

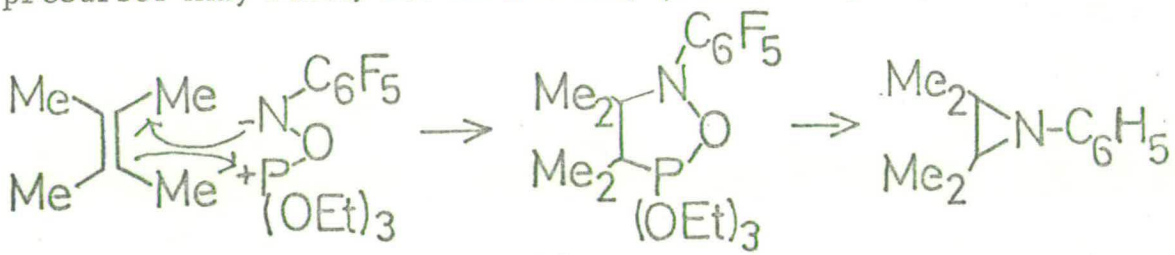
Table 12. Formation of Phosphoramidates from Triethyl Phosphite and Nitroarenes.

Aryl group	:	4-Me_2NPh	4-CNPh	4-ClPh	1-naphthyl[a]
Phosphoramidate (%)	:	11	14	11	14

a with tris(diethylamino)phosphine to form tris(diethylamino) N-1-naphthylphosphorimidine.

(C) present are the reactions of (B) seen in any significant amount. (b) In all experiments involving a phosphorus reagent, e.g. triethyl phosphite, the latter is a more efficient trap than the added species, and therefore phosphoramidates are the products.

There is one example of an olefin trapping an aryl nitrene, reported by Abramovitch,[202a, b] but he also suggested that the nitrene precursor may react, not the nitrene, (Scheme 23).



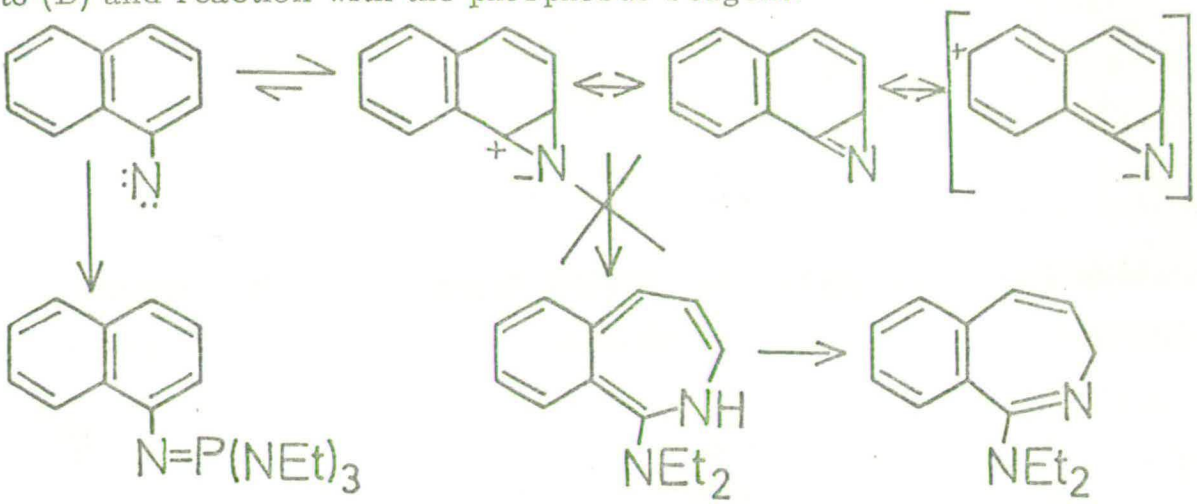
Scheme 23

+ O=P(OEt)3

The failure of cyanonitrobenzenes when deoxygenated in diethylamine to form a good yield of azepine could be the result of reaction between the cyano group and phosphorus reagent, and therefore these experiments were discontinued.

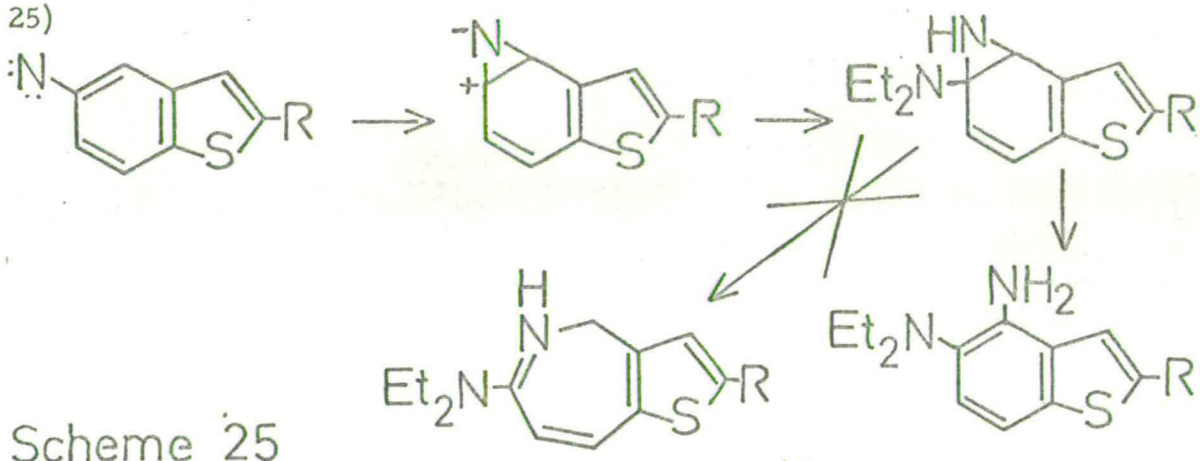
An attempt was made to prevent the normal formation of a 3H-azepine by blocking the 3-position. To do this, 1-nitronaphthalene was deoxygenated by tris(diethylamino)phosphine in diethylamine. It was postulated that the reaction would follow the course shown in Scheme (24), but the only product isolated was the phosphorimidine (6), because the activation energy to accomplish step (1) was too great, since it resulted in loss of aromaticity from both rings, and so the nitrene was forced to find another mode of reaction, involving returning

to (B) and reaction with the phosphorus reagent.



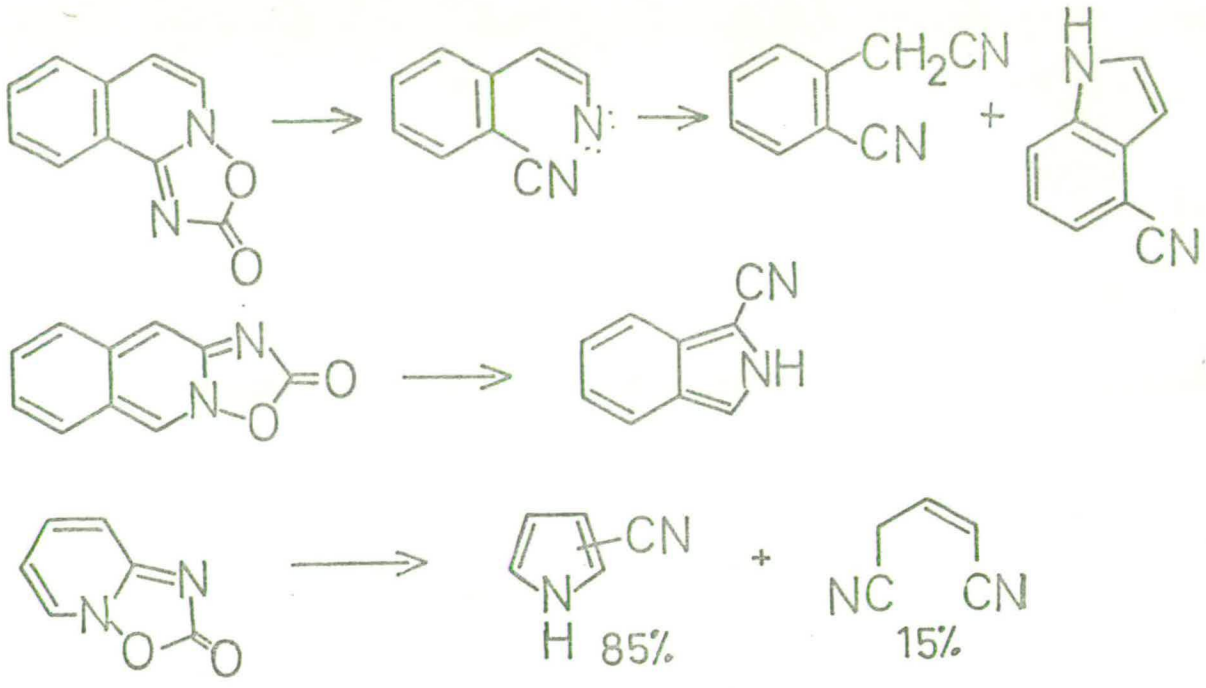
Scheme 24

This reluctance of an aryl nitrene to destroy the aromaticity of a second ring has also been shown by Suschitzky[203] who found no azepine on photolysis of 5-azidobenzothiophene in diethylamine (Scheme 25)



Scheme 25

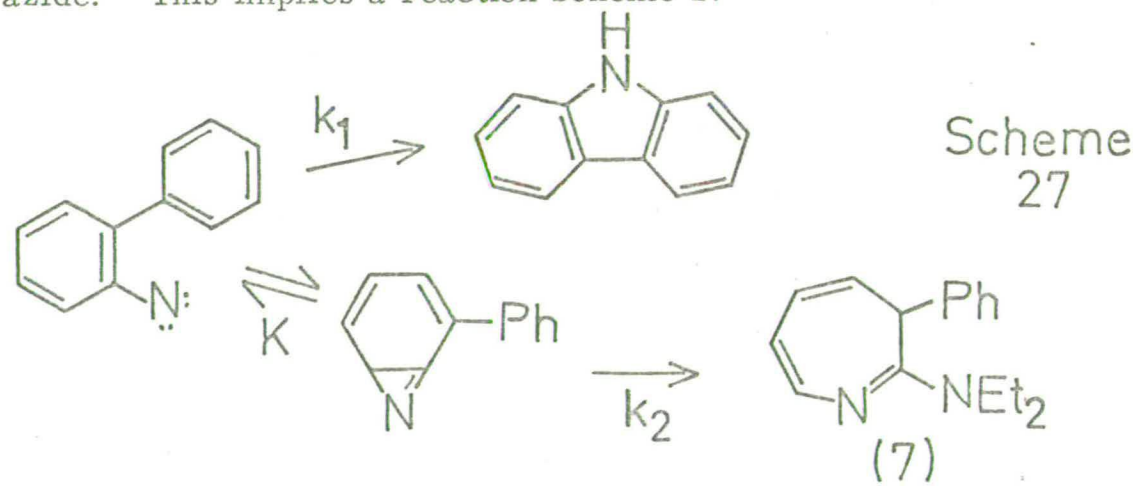
It is also revealed by Smith and Brown[169] in a study of contraction versus fission products when a nitrene is generated attached to various aryl groups. In the cases of naphthalenes where all the aromaticity would be destroyed by ring contraction, fission products are obtained. Where there is no second ring, and hence less aromaticity is destroyed, contraction has a lower ΔG^{*} than fission, Scheme 26.



Scheme 26

b) Competitive reactions

Further information on the formation of the azabicycloheptatriene (C) comes from competitive reactions where the nitrene is provided with a facile alternative pathway. Cadogan[138] has reported that the deoxygenation of 2-nitrobiphenyl in diethylamine results in some of the nitrene, which normally forms carbazole, being intercepted as 3-phenyl-2-diethylamino-3H-azepine (7). Sundberg[174] has reported similar behaviour by the nitrene generated from the azide. This implies a reaction Scheme 27



Scheme 27

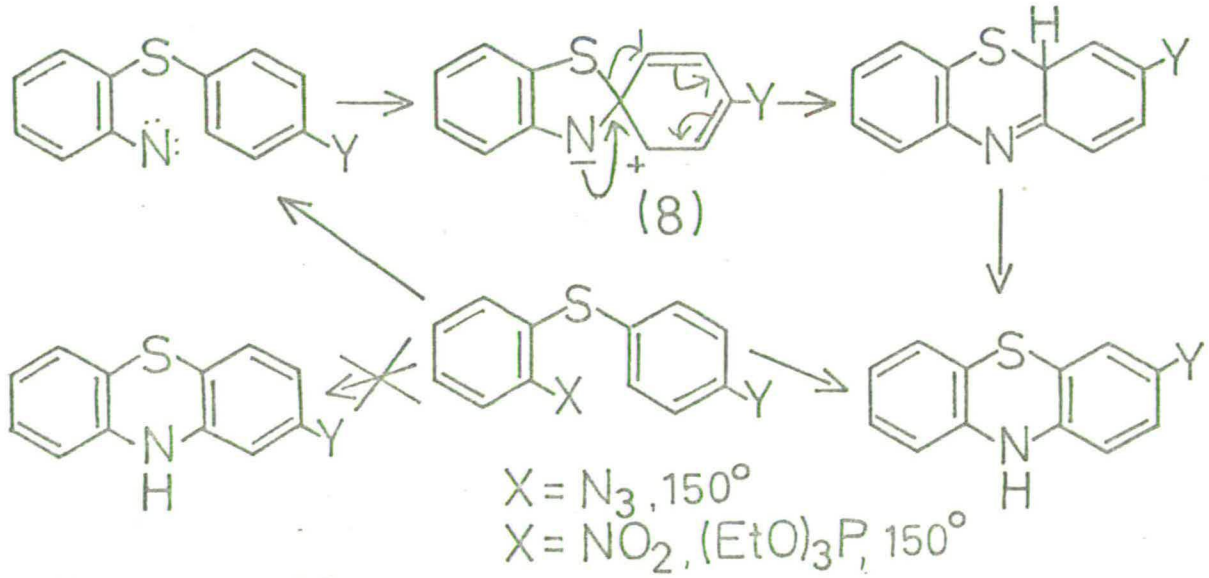
Sundberg's results for different concentrations of diethylamine in tetrahydrofuran are shown in Table 13.

Table 13. Products of Photolysis of Phenyl Azide in T. H. F. Containing Diethylamine.

% Et_2NH in THF	% Azide unreacted	% Azepine (7)	% Carbazole	% Amine
0	10		72	2
5	19	2	56	4
10	35	10	49	4
25	38	16	32	5
50	43	27	25	4
100	40	28	22	5

The yield for 5% photolysis of phenyl azide in diethylamine is 70% azepine (1) i. e. the yield of azepine (7) is a function of the concentration of diethylamine, which suggests that the bond reorganisation process is reversible. A constant yield of carbazole, independent of the concentration of diethylamine would be expected if bond reorganisation and cyclisation were competing irreversible processes.

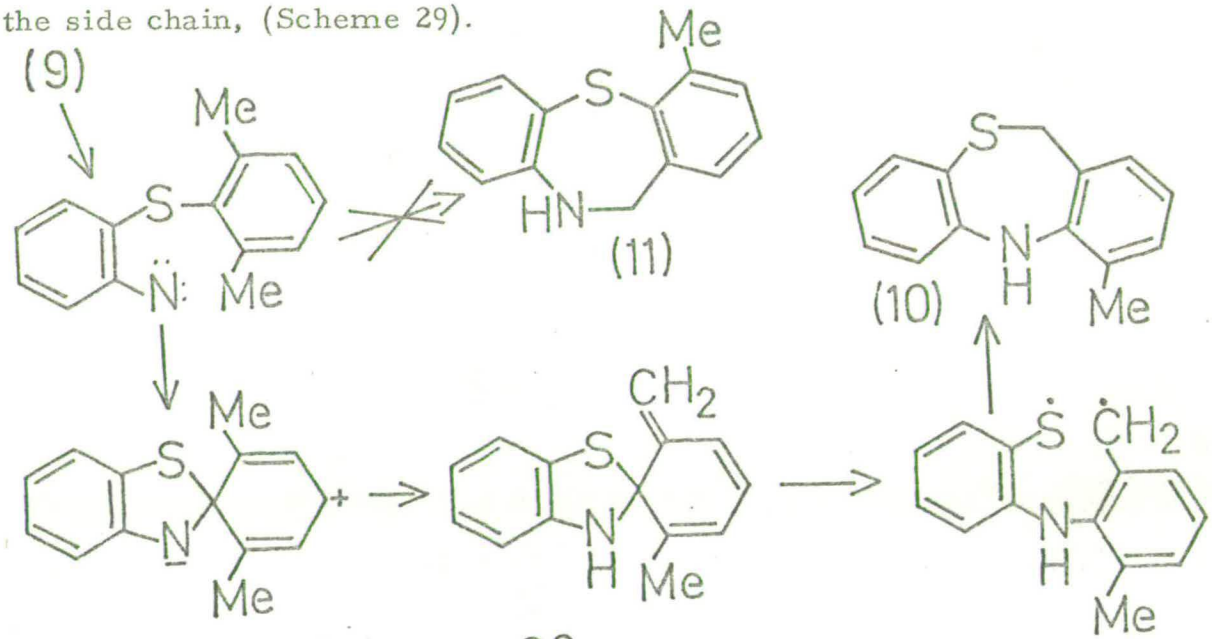
In order to explore the nature of equilibrium step K further, the alternative K_1 was made less attractive. The system chosen was the 2-nitrodiphenyl sulphide system, with the ortho positions blocked. Cadogan and co-workers[101, 204a, b] have worked on several systems involving aryl 2-nitroaryl sulphides. They postulated a reaction mechanism (Scheme 28) involving a spirointermediate (8), to explain why a substituent originally p- to the sulphur should be found



Scheme 28

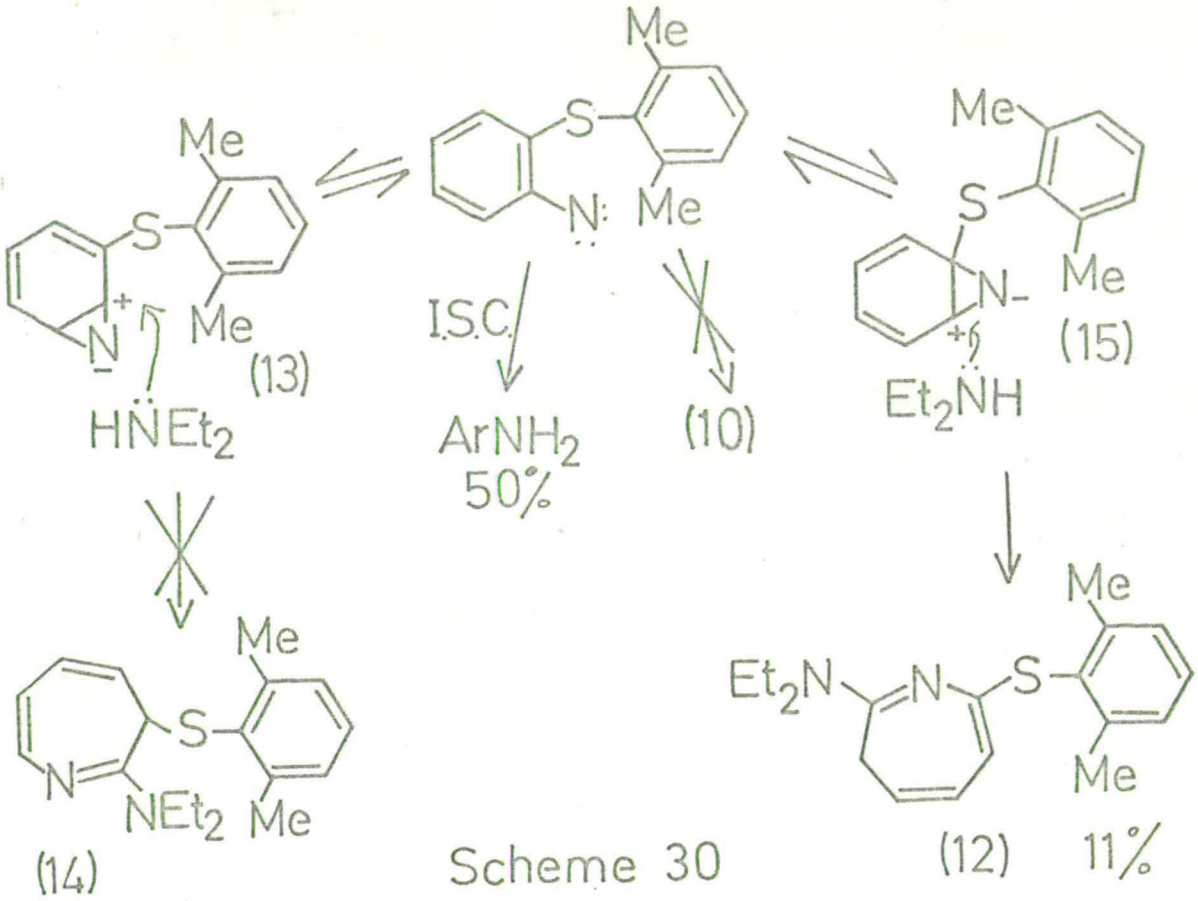
m- to the sulphur in the final product. They also generated the nitrene by thermolysis of the corresponding aryl azidoaryl sulphides, as was confirmed by Messer and Farge.[205] Kwok and Pranc[70] obtained similar results, having generated the nitrene by photolysis of arylanthranils.

Cadogan and Kulik[101] then showed that from the 2, 6-dimethylphenyl 2-nitrophenyl sulphide (9), the azepine 5, 11-dihydro-4-methyldibenzo[b, e][1, 4]thiazepine (10) was formed rather than the isomeric 10, 11-dihydro-4-methyldibenzo[b, f][1, 4]thiazepine (11), which would have been expected if the nitrene itself inserted in the C-H bond of the side chain, (Scheme 29).



Scheme 29

The yield of (10) was 11%, a clear indication that the reaction proceeds less readily than the formation of carbazole (90%) from 2-nitrobiphenyl. The other major product was diethyl N-[o-(2, 6-dimethylphenylthio)phenyl] phosphoramidate (73%), - a characteristic product of a nitrene. When (9) was deoxygenated in diethylamine, none of (10) was obtained, the nitrene being intercepted by the diethylamine as 2, 6-dimethylphenyl 2-diethylamino-3H-azepin-7-yl sulphide (12), (Scheme 30).



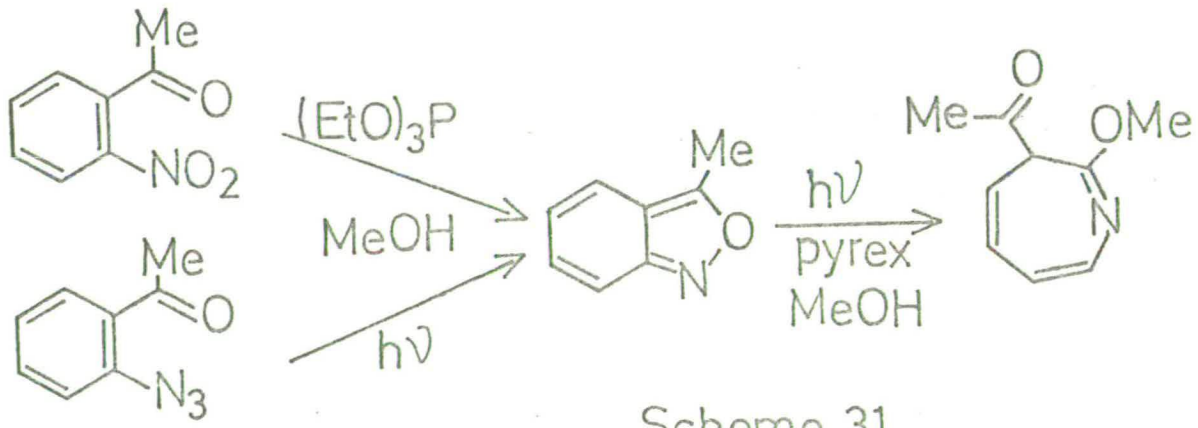
Scheme 30

Intermediate (13) would have been expected to give (14) by analogy with the formation of 3-phenyl-2-diethylamino-3H-azepine from 2-nitrobiphenyl. The reason that this route is not followed depends on the size of the 2,6-dimethylphenylthio group, which is too large to allow the diethylamine to approach the positive site. Despite the rejection of this normally favourable pathway, the free nitrene still does not react to form a spirointermediate and (10), but forms (15), the other possible product of interaction between the nitrene and the π electron system, where this time the diethylamine may trap (15) and form the azepine (12). This result not only shows how strongly the nitrene interacts with the π electron system, preventing the free nitrene from reacting, but also that these intermediates (13), (15) and the free nitrene, are connected in reversible reaction co-ordinate. There was a 50% yield of the 2-aminophenyl 2,6-dimethyl-phenyl sulphide, indicating that much of the nitrene underwent inter-system crossing to the triplet state.

In a similar experiment involving the corresponding ether, whose normal product, not in diethylamine, was shown[102] to be 5,11-dihydro-

2-methyldibenzo[b, e][1, 4]oxazepine (16), careful examination showed no product (16) but an azepin-7-yl ether corresponding to (12), with oxygen instead of sulphur. The yield of this product was low, and it was not isolated in a pure form, possibly because the intermediate corresponding to (15) is less stable, cf. the production of polymers from o-nitroanisole. The diethyl N-(2-phenylphosphoramidate) 2, 6-dimethylphenyl ether (10%) was also formed, from the nitrene which had found its route through azabicycloheptatriene intermediates less favourable.

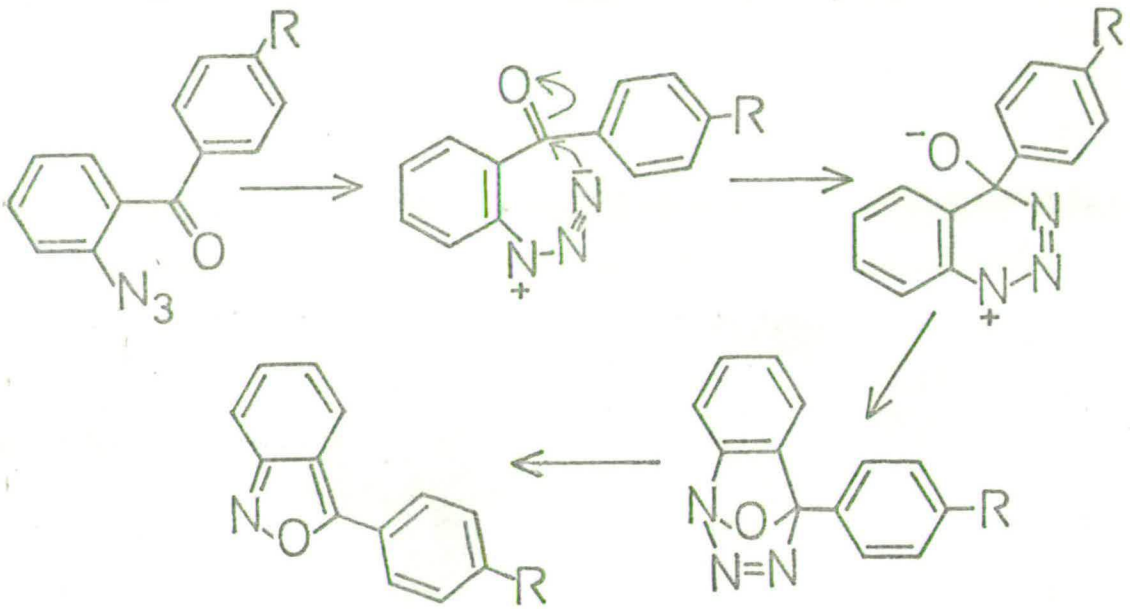
Other competitive reactions were conducted on nitroarenes having an o-side chain containing a double bond. In the deoxygenation of o-nitrobenzalaniline, only the normal product, 2-phenylindazole was obtained. The failure of diethylamine to intercept any nitrene intermediate implies that the reaction was concerted. Since Matsumoto[183] had successfully trapped 2-acylphenyl nitrene as 3-acyl-2-diethylamino-3H-azepine by photolysis of 3-methylanthranil in methanol, an attempt was made to generate the nitrene from another source, and to trap it similarly in methanol. Both thermal deoxygenation of 2-acylnitrobenzene with triethyl phosphite and photolysis of 2-acylphenyl azide through quartz yielded (in methanol) quantitatively 3-methylanthranil, (Scheme 31).



Scheme 31

The cyclisation reaction of azido groups to form compounds such as anthranils has been known for some time. Smith and Brown worked extensively with it.[26, 139] Recently, Hall, Behr and Reed[37] have shown that the mechanism involves nucleophilic attack by the

terminal nitrogen of the azide on the carbon atom using substituents situated p- to the carbonyl group on the benzene ring, (Scheme 32).



Scheme 32

The failure of diethylamine or methanol to intercept any nitrene intermediate merely confirms that the mechanism lies through a concerted pathway.

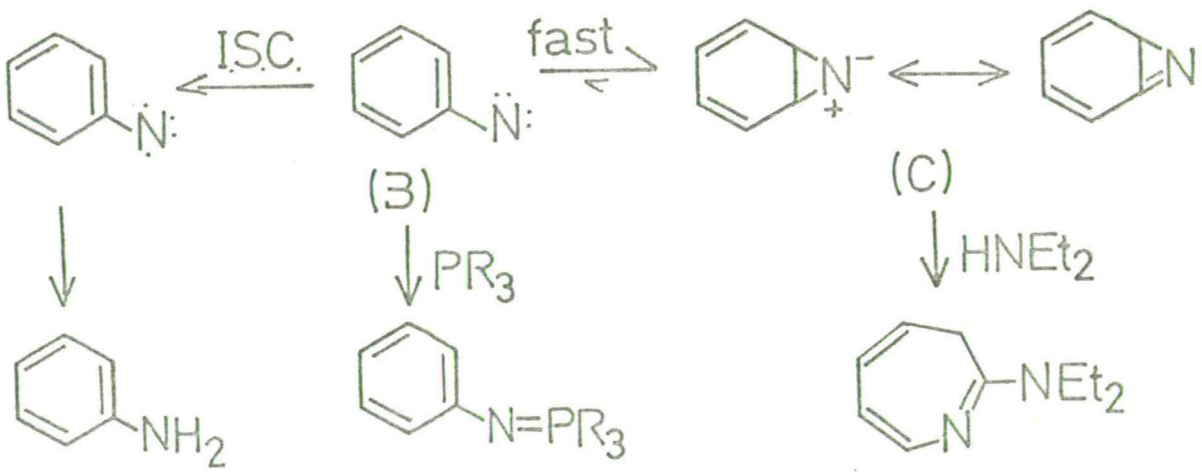
It seems most probable, therefore, that whenever a discrete aryl nitrene is formed, it reacts immediately to form an azabicyclo-heptatriene intermediate, which can always be trapped with diethylamine; thus the formation of an azepine may be considered a test for the presence of an aryl nitrene. With concerted reactions, no nitrene is formed, and hence no azepine is obtained as a product. The question of which isomer is formed, where there exists more than one possible direction of ring closure, will be discussed in the next section.

A further proof of the efficiency of diethylamine as a trap, and an indication that the azabicyclo-intermediate may have a long lifetime, comes from experiments in ^{t}butanol, when diethylamine was present in only trace quantities, due to a side reaction between the ^{t}butanol and tris(diethylamino)phosphine. Despite its scarcity, the deoxygenation products of chloronitrobenzene (both m- and p-) were the appropriately substituted 2-diethylamino-3H-azepines (70% yields, based

on starting material consumed). The azabicycloheptatriene intermediate must therefore have had a lifetime long enough to survive many collisions with both solvent molecules and phosphine molecules before reacting with the diethylamine; this also implies that that reaction with diethylamine is very efficient.

Suter[170] has also conducted experiments involving a scarcity of diethylamine, this time in tetrahydrafuran. He photolysed phenyl azide to 50% decomposition in tetrahydrafuran containing diethylamine in amounts varying from 2-100%, and in each case obtained an unvarying yield of azepine (1) of about 70%, - a clear indication that the intermediate is stable and able to survive numerous molecular collisions. The stability is further emphasised by the fact that measurable quantities of azepine (1) were obtained even when photolysis was conducted in ether for one minute and then the diethylamine added. In the total absence of diethylamine, the yield of aniline increased from 3% to 18%, indicating that an equilibrium with the singlet nitrene existed, and that in the absence of other possible reaction routes, the singlet underwent intersystem crossing to form the triplet nitrene, and then the amine.

The conclusion from these experiments is, therefore, that the singlet nitrene always immediately forms the azabicyclointermediate (C), in an equilibrium step. This intermediate (C) has a long lifetime, and will react with any diethylamine present. If this is impossible, some of the free nitrene, (B), present may react, giving phosphorimidates, or undergo intersystem crossing, giving amines, (Scheme 33).

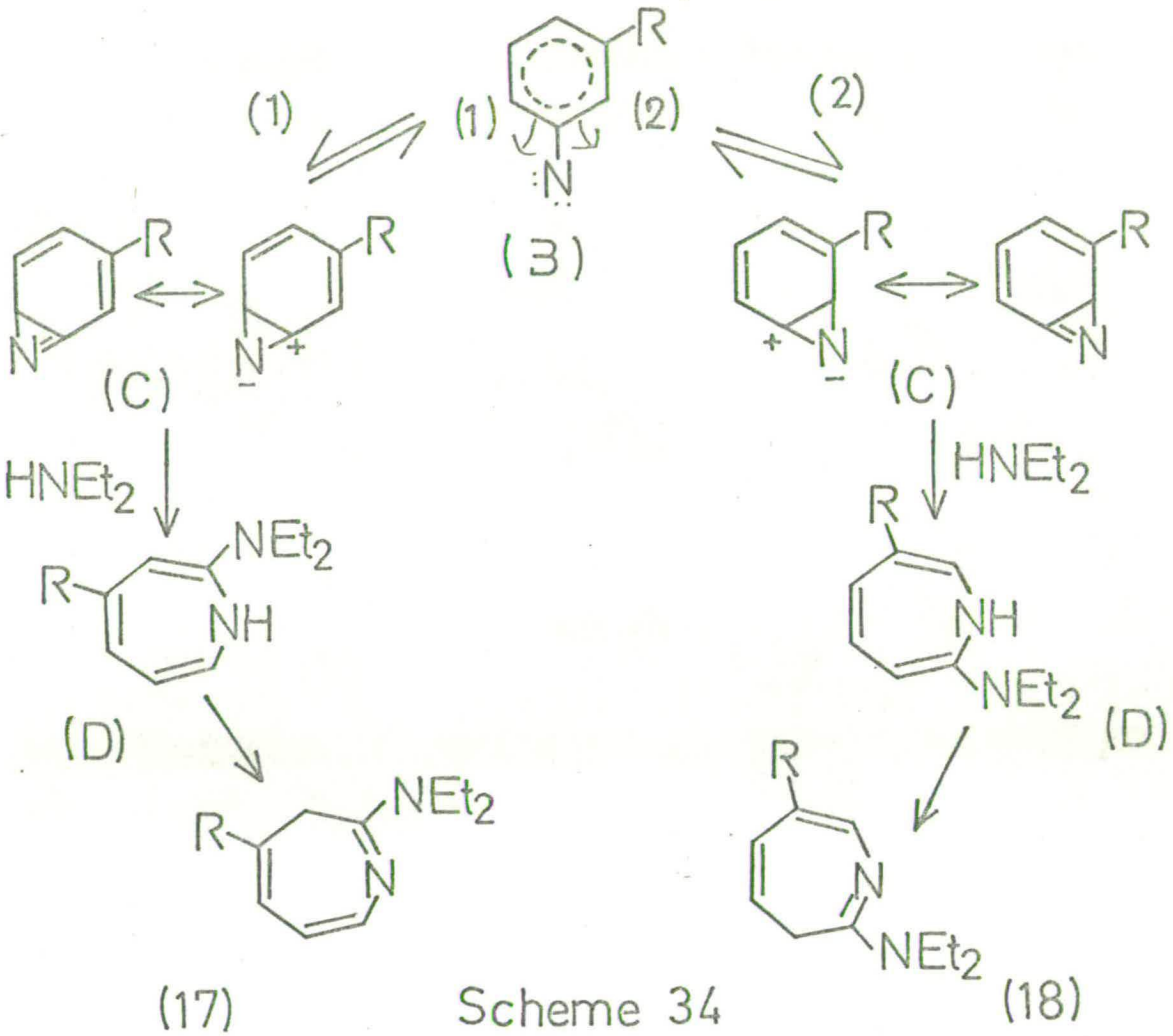


Scheme 33

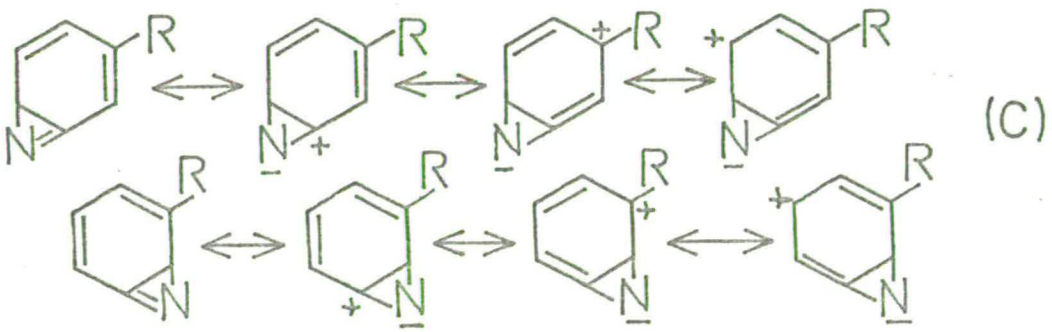
D. DIRECTION OF RING CLOSURE

1. With m-Substituents.

There are two possible directions for ring closure with m-substituents, as shown in Scheme 34.



Scheme 34



Delocalisation of the positive charge within the ring will be affected to the same extent by the electron-withdrawing or donating properties of R for both pathways, (1) and (2), since for both cases

a canonical form may be written where the positive charge is located on the carbon atom to which R is attached (Scheme 34, (C)). Therefore the effect of R must be considered with respect to its alteration of the electron density of the $\widetilde{\Pi}$ electron cloud over the molecule as a whole; i. e. the effect of R on the nitrene (B) is more important than its effect on the azabicycloheptatriene intermediate (C).

Since a discrete nitrene, (B), with a significant lifetime has been postulated as an intermediate in this reaction, whether it chooses to follow pathway (1) or (2) should be independent of its mode of generation. The two pathways lead to two azepines, (17) and (18), whose yields have been shown to vary according to the nature of R. Electron withdrawing groups promote the formation of the 6-substituted azepine, (18), and electron donating groups, the 4-substituted azepine, (17), although both isomers were formed in all examples studied. The results are given in Table 14.

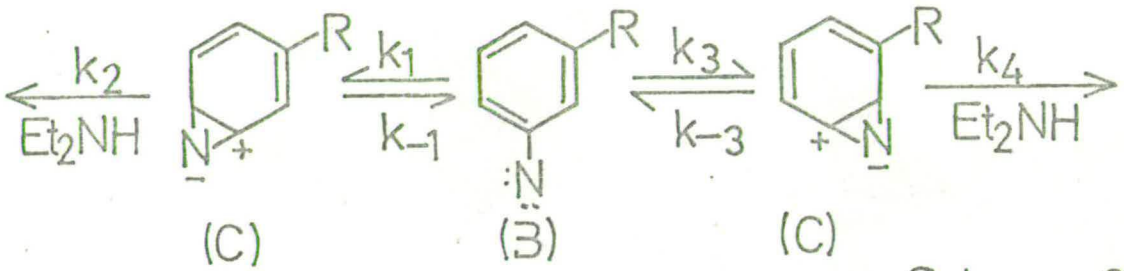
Table 14. Formation of Two Isomeric Azepines from m-Substituted Aryl Nitrenes.

Substituent :	MeO		Me		Cl		Br		CO_2Et
Method :	(a)	(b)	(a)	(b)	(a)	(b)	(a)	(b)	(a)
% Yield (17) :	73	43	38.5	29	18	15	[7]	[5]	17
% Yield (18) :	13	10	31.5	27	56	35	37	28.5	55
Ratio (18):(17):	0.18	0.23	0.82	0.93	3.1	2.3	5.3	5.7	3.25

In experiments involving method (a), the source of the nitrene was the nitroarene, deoxygenated by diethyl methylphosphonite in diethylamine at 64.5°; in those involving technique (b), the source of the nitrene was the aryl azide, photolysed through pyrex with pyrene as a sensitiser, in diethylamine at 56.5°. The results show that the isomer ratio is independent of the mode of generation of the nitrene, and dependent only on the nature of R. This confirms that the nitrene (B) exists for a sufficiently long time to acquire its own characteristics

before reacting to form (C).

If the nitrene is in equilibrium with (C), where the rate of reforming (B) from (C) is fast, then it is possible that the thermodynamically most stable azabicycloheptatriene intermediate is formed; alternatively, if the rate of reaction of (C) with diethylamine is very fast, then the kinetically controlled product may be formed, where (C) is removed at a sufficiently rapid rate to prevent the equilibrium from being established, (Scheme 35).



(C) (B) (C)

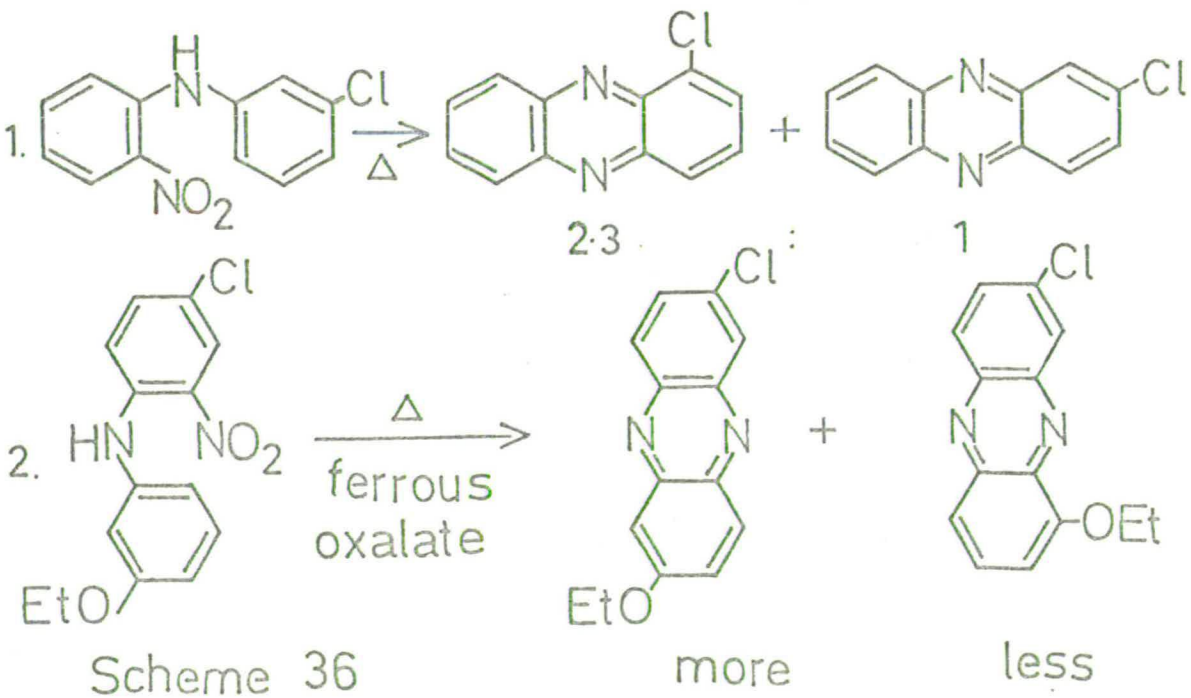
Scheme 35

Thermodynamic control will occur if k_{-1} and k_{-3} are greater than $k_2[Et_2NH]$ and $k_4[Et_2NH]$ respectively. In view of the high concentration of diethylamine, and the known readiness of (C) to react with diethylamine (as shown by the experiments involving a scarcity of diethylamine) and also the known preference for these intermediates to react in the form (C), and not as (B), (the azepine is always formed in trapping experiments with diethylamine), it seems unlikely that thermodynamic control would be established. Therefore, the direction of the ring-closure reaction depends on the difference between k_1 and k_3, which in turn depends on the distribution of electron density within the molecule, dependent on R. Since the nitrene is very electron deficient, it will react with the site of greatest electron density. This site is either o- or p- to the substituent R, both of which positions are o- to the nitrene. The choice by the nitrene therefore represents a very accurate tool for determining the o- versus p- directive effect of any given substituent, with the steric hindrance problems of normal methods eliminated.

From the deoxygenation of m-chloronitrobenzene by tris(diethylamino)phosphine in t-butanol at 80°, in the presence of a trace of

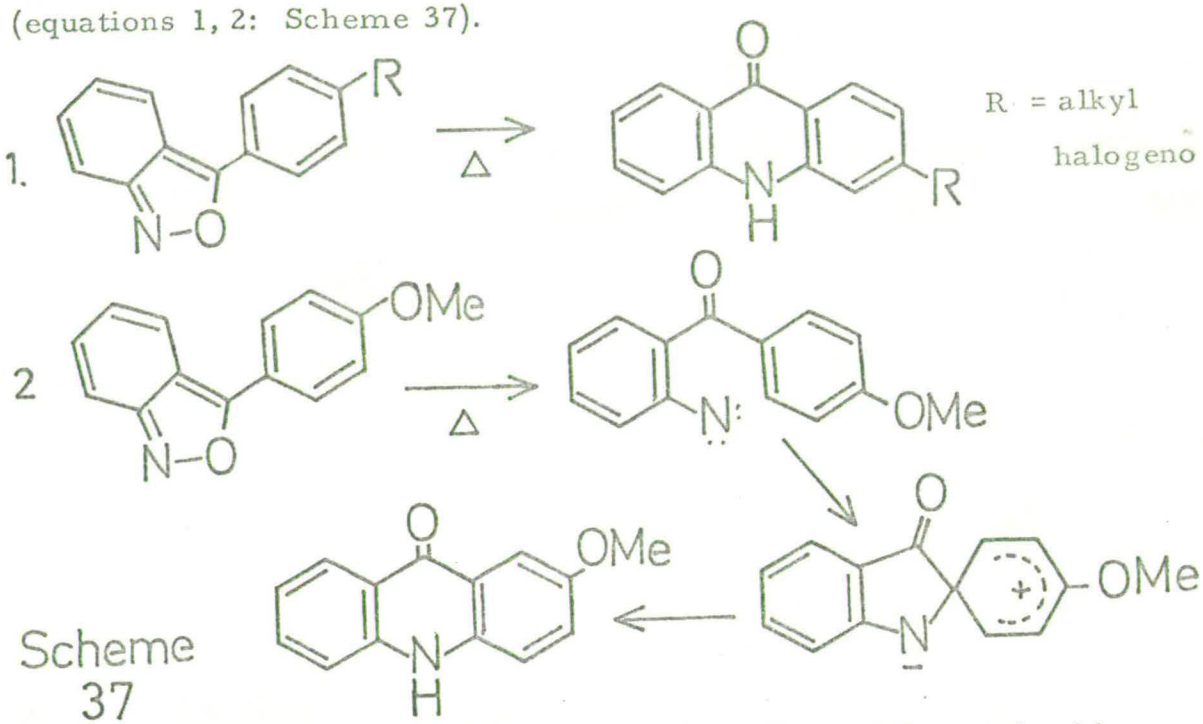
diethylamine, the yield of the 6-substituted azepine (18) was 53% and of the 4-substituted isomer (17) was 28%, a ratio of 1.9. There may be more of (17), the isomer formed by attack p- to the chloro group, because this is the thermodynamically more favourable product, and with such a scarcity of diethylamine, the thermodynamically more stable side of the equilibrium, which is formed more slowly, has enough time to be established, before reaction with diethylamine. Under normal circumstances, with diethylamine as solvent, the kinetically controlled product is obtained.

Literature contains some evidence to support these observed experimental facts. The results correlate with some tentative observations reported by Vivian and Hartwell,[63] who observed in the cyclisation of an aryl nitrene (or a nitrenoid species) to a second benzene ring, intramolecularly, in a synthesis of phenazines, from nitroarenes with ferrous oxalate, that the position of attack depended on the substituents present in the second ring; an ethoxide group directed the attack into the p-position to itself, rather than the o-, and with a chloro group, the direction of influence was reversed, and a preference for o:p of about 2.3:1 was noted, although much material was lost in the work-up, and therefore there may be a considerable error in the figures (equations 1, 2 Scheme 36).



Scheme 36

Kwock and Pranc[70] also commented on the strong p-directing effect of the methoxy group compared with alkyl or halogeno substituents, in the thermal rearrangement of p-substituted phenylanthranils, (equations 1, 2: Scheme 37).



Scheme 37

A further example of the p-directing effect of the methoxide group comes from experiments on the protonation of anisole and dimethoxybenzenes by strong acid.[206] The proton is taken up exclusively p- to a methoxide group. In the case of p-dimethoxybenzene, no protonation occurs, since the p-position is blocked, despite the highly activating effect of two methoxide groups on the remainder of the molecule.

The directive effects towards incoming groups by substituents already present on the benzene ring has received attention for many years, and there are a number of review articles in the literature, from 1924 onwards. The most comprehensive coverage comes from Ingold.[207] He has attempted to isolate o- versus p- effects from o- plus p- versus m-, and to analyse those effects which operate when steric hindrance has been either minimised or allowed for. He considered that the electromeric rearrangements, which explain the directive effects of substituents, occurred during the course of the substitution reaction, by establishing from dipole moment and other

types of physical measurement that mesomerism in the normal states of the molecule does lead, even before any chemical reaction has occurred, to an unequal distribution of electron densities at the different carbon centres in any aromatic substrate, C_6H_5R, where R is a polar group.

Ingold reported that groups with a negative inductive effect, -I, decreased the o-reactivity more than the p-, and a positive inductive effect, +I, increased o- more than p-. On this basis chloro and carbethoxy groups enhance substitution at the p-position, and the methyl group at the o-. Ingold's results of mononitration of a halobenzene show that steric hindrance plays a smaller part than electronegativity in deactivating the o-position, since fluorine is the most strongly p-directing and iodine the least, (Table 15).

Table 15. Formation of o- and p-Isomers in the Nitration of Halobenzenes.

Substituent	:	F	Cl	Br	I
o- (%)	:	12	30	38	41
p- (%)	:	87	70	62	59

This emphasises that the directive effect of a chloro group towards an incoming group is quite different from its effect towards a nitrene, where it enhances o- more than p- by a factor greater than 2:1.

One of the problems is to explain why an inductive effect, which is known to operate most strongly on the adjacent atom, and to decrease rapidly with increasing chain length, should in the case of the nitrene and a chloro group, operate in such a way as to promote reaction at the o-atom, which ought, from considerations of the inductive effect, to have less electron density than the p-.

As far as these reactions involving substitution by an external species, as measured by Ingold, e.g. nitration, are concerned, the process is reversible, and therefore thermodynamically controlled,

with the major product being the result of substitution in the position that gives the greatest stability. The reaction of the nitrene involves the kinetically most reactive state.

Therefore the influence of a chloro substituent on an incoming group in electrophilic aromatic substitution depends on the transmission of the electronegativity along the σ bonds more than in the $\widetilde{\pi}$ bonds; the influence of a chloro substituent towards the nitrene depends on the effect of the chloro substituent on the $\widetilde{\pi}$ electron cloud, which is a displacement towards the chlorine, leaving the p-position apparently more positive, and therefore less likely to react with the electron deficient nitrene. This displacement is shown by measurements such as that of the dipole moment.

Ingold also reported that a negative mesomeric effect, -M, decreased p-activity more than o-, (and a positive one increased p-activity more than o-), which is compatible with the influence of carbethoxy (-M) and methoxy (+M) as found for the nitrene. This emphasises the importance of the $\widetilde{\pi}$ electron cloud.

Ingold invokes a "polarisability effect," +E, which selectively activates the p-positions to account for p-substitution predominating with aniline and phenol and their derivatives. He derives the +E effect in the following manner:

The difference in o- versus p- selectivity between the conjugative and inductive mechanisms indicates a difference in time-dependence of the displacements arising by the two mechanisms. In particular, the inductive mechanism, -I, represents a permanent state of polarisation of the molecule, and the conjugative mechanism, +T, has its main effect in a temporary process, +E, which arises when the attacking reagent is taking advantage of the polarisability of the system. The +T (conjugative) mechanism of electron displacement involves a part, the +M effect, which can be measured as a permanent polarisation of the molecule. The other part, the +E effect, i. e. the temporary polarisability effect stimulated by the electrophilic reagent, is of outstanding importance in electrophilic aromatic substitution.

With respect to reaction by the nitrene, the permanent polarisation of the molecule has a greater effect. The order of effect by substituents, MeO, Me, Cl, Br, CO_2Et, correlates well with certain measurable physical properties of substituted benzenes, reported by Ferguson,[208] of which E_o and dipole moment measurements constitute typical examples, (Table 16).

Table 16. Correlation of Physical Measurements of Arenes, and the Influence of the Substituents on the Direction of Ring Closure by the Nitrene.

Substituent	:	MeO	Me	Cl	Br	CO_2Et
E_o	:	-131	-76	24	28	58
Dipole Moment	:	1.16	0.4	-1.64	-1.68	-1.95
Ratio	:	0.18	0.79	3.1	[5.3]	3.25

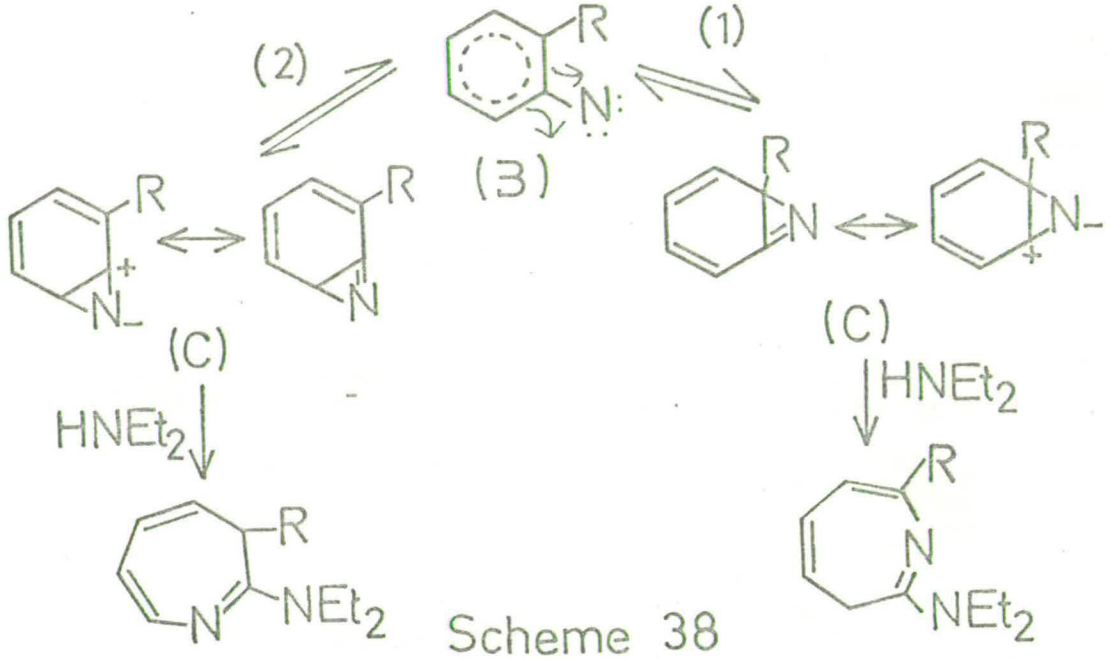
E_o is an excited state property. It is a measure of changes in oxidation potentials of 1,4-naphthaquinone and phenanthrequinone by the substituents. From theory, it has been shown that substituents which increase nuclear electron density through resonance or induction should lower the oxidation potential of a parent quinone, and that groups which lower the nuclear electron density should have the opposite effect. These physical properties depend primarily on the electron distribution in ground and excited states.

The dipole moment is a measure of the distribution of electron density in the ground state of the molecule. Even though the nitrene is an excited state of high energy, it is probable that the electron distribution is similar, at least with respect to the order of effects by substituents.

It seems most probable, therefore, that the different directive effects by substituents on the direction of ring closure by the nitrene is an accurate reflection of the effect by those substituents on the $\tilde{\pi}$ electron cloud of the benzene ring.

2) With o-Substituents

With o-substituents, as with the m-, there are two possible directions of ring closure by the nitrene : towards or away from the substituent, (Scheme 38).

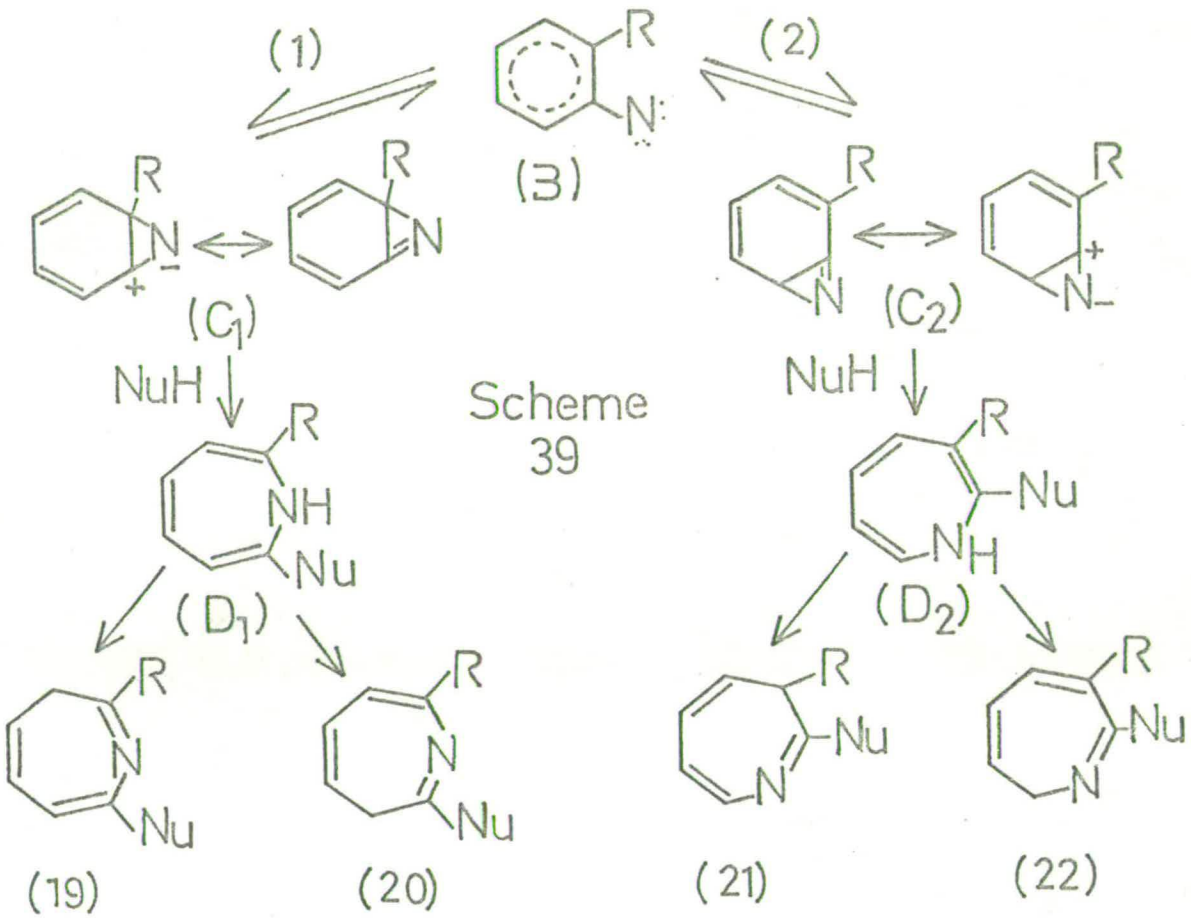


Scheme 38

The possible modes of reaction in the case of o-substituted aryl nitrenes are increased by the chance of reaction with the side-chain itself, either by the nitrene or in a concerted fashion (e. g. in the formation of anthranils etc.). If the group R is labile, then decomposition products are obtained instead of azepines. The yields of azepines, even where R is a methyl group, are lower than from corresponding m- and p-substituted aryl nitrenes. Where R was a chloro group, the solution turned black as soon as diethyl methylphosphonite was added, and the starting material was consumed in 0. 2 days, compared with 0. 7 and 1. 2 days for m- and p-chloronitrobenzenes respectively. Only polymeric products were obtained from the o-chloronitrobenzene. Where R was a methoxy group, the starting material was completely consumed in 2. 5 days, although the m-nitroanisole had taken 4 days, and no product could be isolated from the black reaction mixture. Similarly Matsumoto[72] observed that no azepines were obtained from the photolysis of 7-chloro- or 7-methoxy-3-phenylanthranil, in which the nitrene would be generated

o- to a chloro or methoxy group. The explanation must lie in some interaction between the nitrene and the substituent which prevents the normal formation of a stable azabicycloheptatriene intermediate.

The isomers obtained with the different nucleophiles, diethylamine and triethyl phosphite, are best explained by a reaction scheme involving intermediate (D), as shown in Scheme 39.



Scheme 39

Table 17. Formation of Isomers from o-Substituted Aryl PhCO· Nitrenes.

(19)			(20)		
R	Nu	%	R	Nu	%
Et	$P(OEt)_3$	11.5	2,6-di MePhS	Et_2NH	14
Me	$P(OEt)_3$	8.5	4-Bu^tPhS	Et_2NH	2
2,4,6-tri-Me	$P(OEt)_3$	11			
Me	$P(OMe)_3$	18			

Table 17 (cont.)

(21)

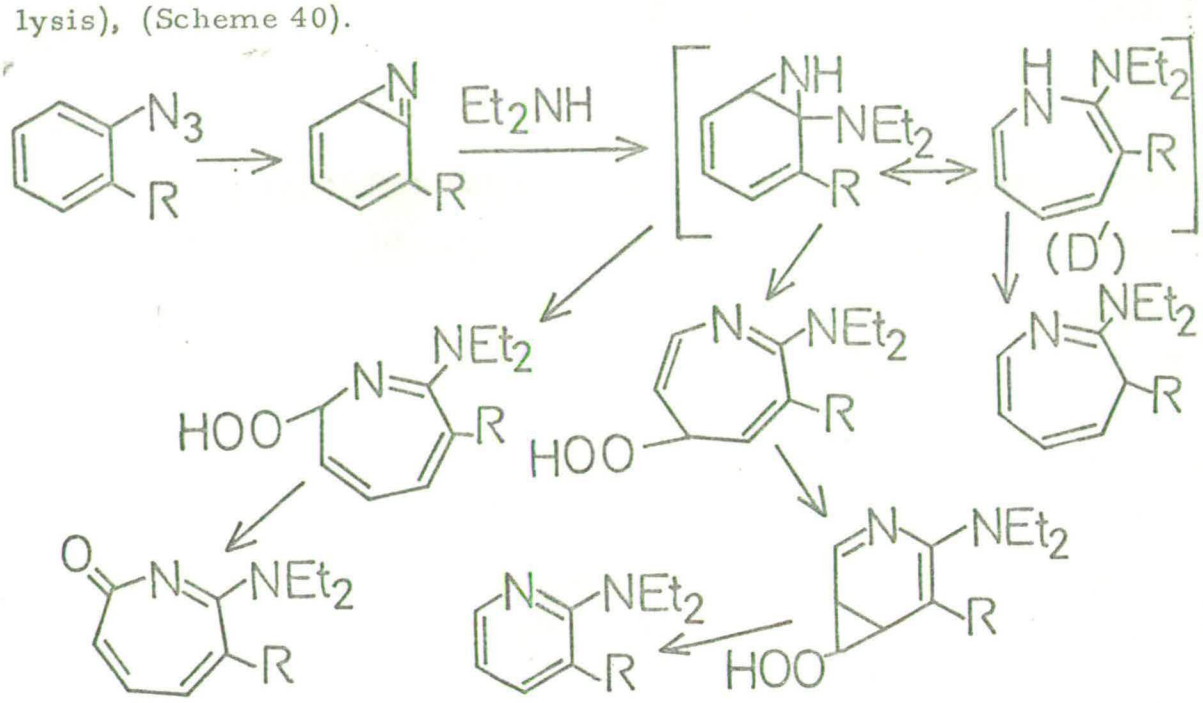
R	Nu	%
Me	Et_2NH	35
Ph	Et_2NH	13
PhCO	MeOH	61
PhCO	Et_2NH	32.5
PhCO	Bu^tNH_2	18
2-triophenyl	MeOH	71

Of these possible isomers, all have been found except (22). The examples of each type are given in table 17.

The original choice of the direction of ring closure (1) or (2) is best looked at by considering intermediates (C_1) and (C_2), and their interactions with the approaching nucleophile. Since ring closure away from R, (pathway (2)) to give (C_2) results in the distortion of only a C-H bond, it is probable that this direction is energetically favourable, to give the more stable intermediate (C_2). Provided (C_2) can then react with the approaching nucleophile, then this is the exclusive pathway followed. If, on the other hand, either R is very large (e.g. 2, 6-dimethylphenylthio) or the nucleophile is bulky, (e.g. triethyl phosphite) then the positive charge is too well shielded, reaction cannot take place, and no 3-substituted azepine can be formed. Since intermediates (C_1), (B) and (C_2) exist in an equilibrium situation, the little of (C_1) which is formed can react freely with no interference by steric hindrance, thus allowing more (C_1) to be formed. The yields from (C_1) are normally lower, a reflection on the more difficult formation of (C_1). This is then additional proof that intermediates (B) and (C) exist in a reversible situation, and that (C) is a stable intermediate.

The next step on the reaction coordinate involves the postulated formation of a 1H-azepine, intermediate (D). Sundberg and Suter[170] have produced good evidence for its existence as a reasonably stable intermediate. They isolated products which could only be accounted

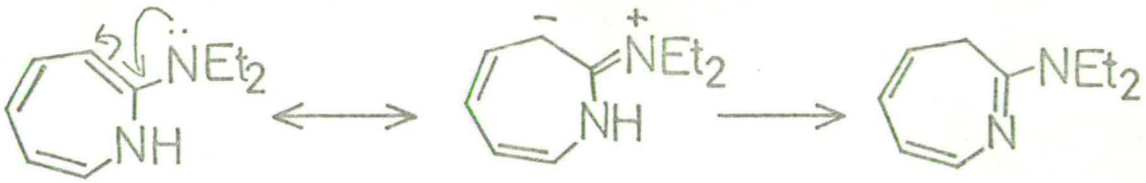
for by postulating a mechanism involving the interception of the 1H-intermediate by oxygen (present in the solution throughout the photolysis), (Scheme 40).



(23) (24) Scheme 40

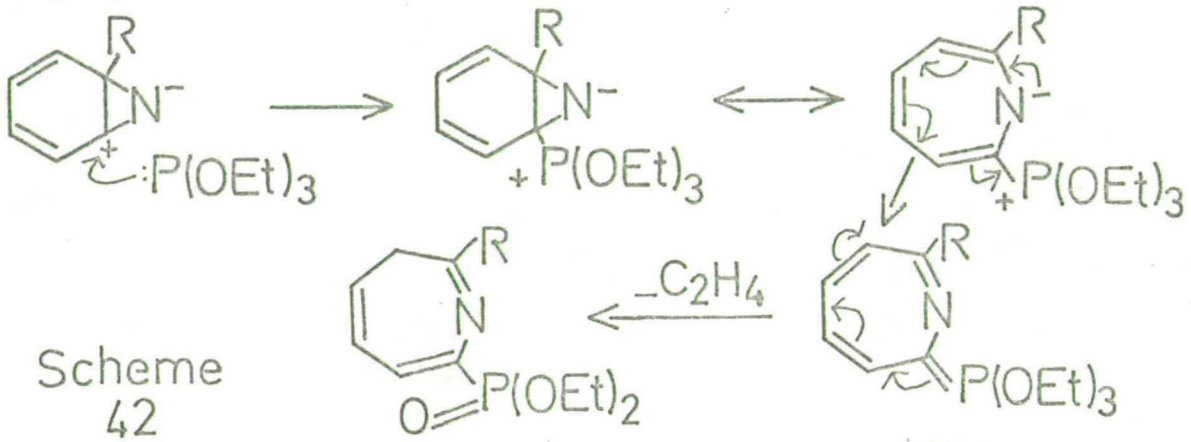
They have shown that pyridine cannot arise from the 3H-azepine under experimental conditions. They have also shown that the intermediate, (D_1), before formation of the 3H-azepine, was stable at 0°, and underwent a dark reaction with oxygen, to give the products (23) and (24) even when the oxygen was added after completion of the photolysis, by as much as 17 hours later. In the absence of oxygen, under normal work-up procedures, and under g.l.c. conditions, the 1H-azepine (D_1), is converted to the 3H-azepine. They did not succeed in actually isolating the 1H-azepine (D_1).

The existence of the 1H-azepine intermediates (D_1) and (D_2) (Scheme 39), with the evidence above, is supported by the fact that subsequent rearrangement to the 3H-isomer, of which there are two possibilities, is strongly influenced by the attached nucleophile. With an amine, such as diethylamine, or an alcohol, such as methanol, there exists the possibility of resonance structures such as that shown in Scheme 41. This means that rearrangement always occurs in such a way as to form the 2-substituted-3H-azepine, and never the 7-substituted-3H-azepine.



Scheme 41

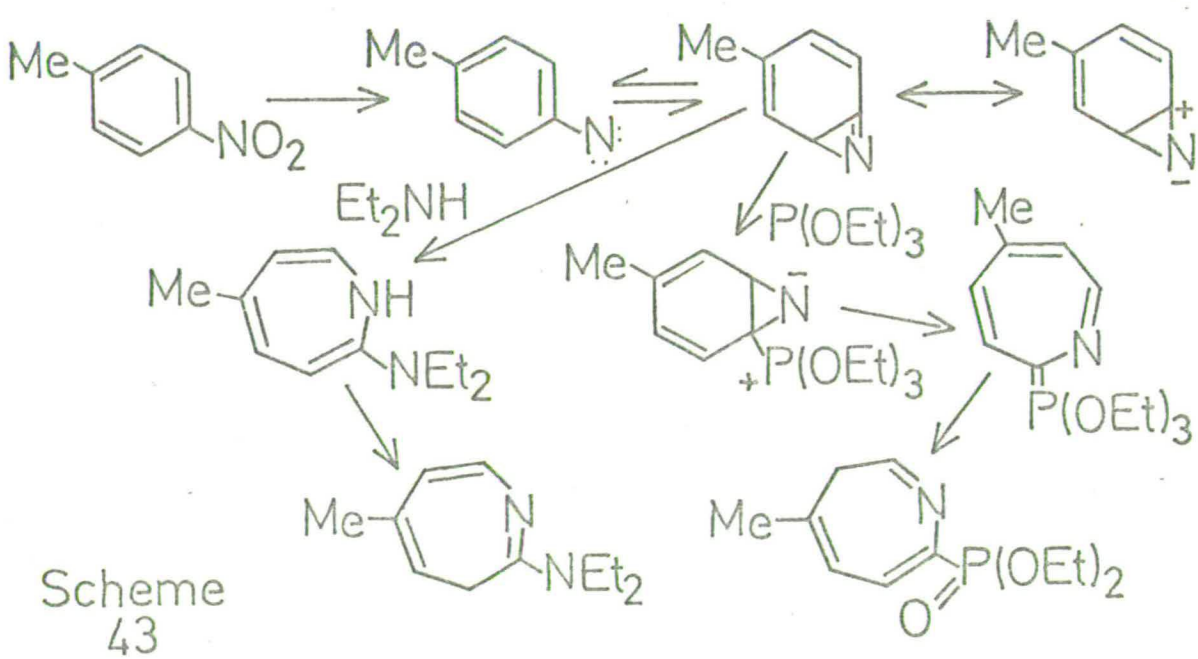
For triethyl phosphite as the nucleophile, which has no hydrogen readily available to form an intermediate (D), a reaction scheme 42 is proposed.



Scheme 42

In support of this mechanism, it has been shown[56] that ethylene is evolved.

It is not only with o-substituted aryl nitrenes that the different nucleophiles give different isomers. The product of deoxygenation of p-nitrotoluene in diethylamine is 5-methyl-2-diethylamino-3H-azepine; in triethyl phosphite the product is diethyl 4-methyl-3H-azepin-7-ylphosphonate, (Scheme 43).



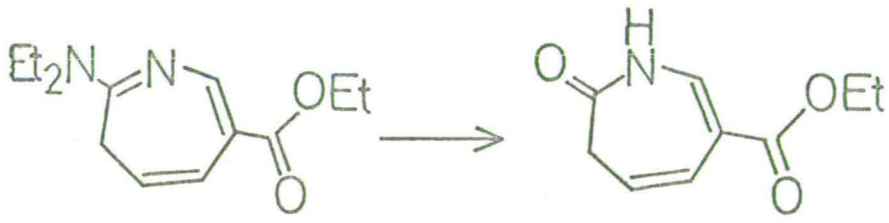
Scheme 43

E. REACTIONS OF AZEPINES

The previous section led to the deduction that the 1H-azepine is a stable intermediate, but under the influence of heat, acid, etc. will immediately rearrange to the more stable 3H-azepine. Many examples of 1H-azepines exist in the literature,[209] some of which have been mentioned earlier in this thesis as products of reaction between carbethoxy, sulphonyl and cyano nitrenes and benzene or substituted benzenes, but in every case these azepines have a substituent attached to the nitrogen atom, or are of the kind 1, 3-dihydro 2H-azepin-2-ones. No examples exist of a simple 1H-azepine with hydrogen on the nitrogen atom.

3-H-Azepines are reported as stable at room temperature, (they can be stored indefinitely with only slight discoloration). They are the products of aryl nitrenes in the presence of a suitable nucleophile. Several other methods have been devised for their production.[209] There is one report of a 4H-azepine being formed,[182, 210] and it is also reported to rearrange readily to the 3H-azepine. No reports of isolated 2H-azepines exist. This leads to the conclusion that the 3H-tautomer contains the most stable arrangement of bonds.

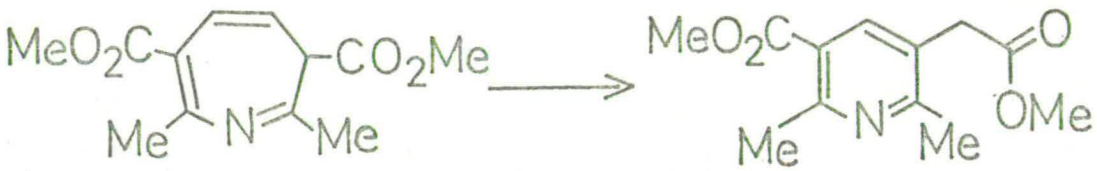
During this investigation, the ready transformation of 6-carbethoxy-2- diethylamino-3H-azepine (25) to 6-carbethoxy-1, 3-dihydro-2H-azepin-2-one by hydrolysis on an alumina column, (Scheme 44), was observed.



Scheme 44

Odum and von Doering[172] originally showed that 2-amino-3H-azepine could be hydrolysed by boiling under reflux in water for 5 hours, and also that treatment with hydrogen sulphide gave the thio analogue. Test-tube experiments on (25) showed that it remained unchanged in the presence of sodium ethoxide in ethanol at room temperature, but was hydrolysed by sodium hydroxide in an ethanol/water mixture, to give a

number of products, which were not further characterised. Anderson and Johnson[211] reported that 3, 6-dicarbomethoxy-1, 7-dimethyl-3H-azepine was hydrolysed by methanolic hydrochloric acid to form dimethyl 4-chloromethyl-1, 4-dihydro-2, 6-dimethylpyridine-3, 5-dicarboxylate, methyl (5-methoxycarbonyl-2, 6-dimethyl-3-pyridyl)-acetate (26) and a smaller yield of another product having the characteristics of a dihydroazepine derivative. Similar pyridine derivatives were obtained with other acids. They also reported that treatment with sodium methoxide in methanol, with boiling under reflux for 2 h yielded (26), (Scheme 45).



Scheme 45

Matsumoto[72] found that 2-methoxy-3-acyl-3H-azepine (27) could be converted to the corresponding 2-diethylamino-3H-azepine by treatment with diethylamine, and that (27) was hydrolysed by aqueous ethanol to 3-acyl-1, 3-dihydro-2H-azepin-2-one. Pacquette[181] and Vogel[180] have shown that 1, 3-dihydro-2H-azepin-2-ones may be converted to 2-alkoxy-3H-azepines by treatment with trialkyl oxonium fluoroborate (R_3OBF_4), and that the alkoxy group is then readily replaced by an amino group, e. g. piperidino, diethylamino, anilino.

In this investigation it was observed that the azepines required to be handled with care. They are very light-sensitive, and may also decompose under the high temperatures of g. l. c. conditions, which makes quantitative assessment by g. l. c. and purification by preparative g. l. c. unreliable. They may be stored for long periods in darkness at 0^{o}. One of the most unstable is the unsubstituted diazepine, 2-diethylamino-3H-1, 5-diazepine. It is probable from the evidence of both n. m. r. and mass spectra that this was formed in the deoxygenation of 4-nitropyridine by diethyl methylphosphonite in the presence of diethylamine, but it was impossible to obtain and maintain it sufficiently

pure to acquire a good elemental analysis.

The light sensitivity of azepines has certain advantages. When inspecting a reaction mixture prior to work-up by running a small sample on a t. l. c. plate, a spot tentatively identified as azepine because of its position may be discounted if it does not turn brown under the influence of either a U. V. lamp or half-an-hour's daylight.

F. THE SPECIAL EFFECT OF DIETHYLAMINE

Many nucleophiles have been used in attempts to trap the azabicycloheptatriene intermediate, but diethylamine has consistently proved itself to be the most efficient under all circumstances. Table 18 shows some of the results.

Table 18. Formation of Azepines from Aryl Nitrenes in the Presence of a Nucleophile.

Source of Nitrene	Nucleophile	% Yield Azepine	Ref.
ArN_3, Δ	$PhNH_2$	8-40	28
"	$PhCH_2NH_2$	41	"
"	$C_6H_{11}NH_2$	21	"
"	PhNHMe	21	"
"	p-CH_3-Ph-NH_2	trace	"
"	p-EtO-Ph-NH_2	8.5	"
ArN_3, hν	$PhNH_2/Et_3N$	2	172
"	Et_2NH	34	"
"	NH_3	25	"
"	$K^+NH_2^-/NH_3$	-	"
3-phenyl anthranil	MeOH	61.6	72
"	Et_2NH	32.6	"
"	$PhNH_2$	41.5	"
"	Bu^tNH_2	18.6	"
$ArNO/Ph_3P$	Et_2NH	62	173
"	Bu^tNH_2	60	"
"	Me_2NH	50	"
"	$MeNH_2$	4	"
"	NH_3	-	"
ArN_3, hν	MeOH	11	198
"	Et_2NH	70	"

From these results, it is evident that many amines are capable

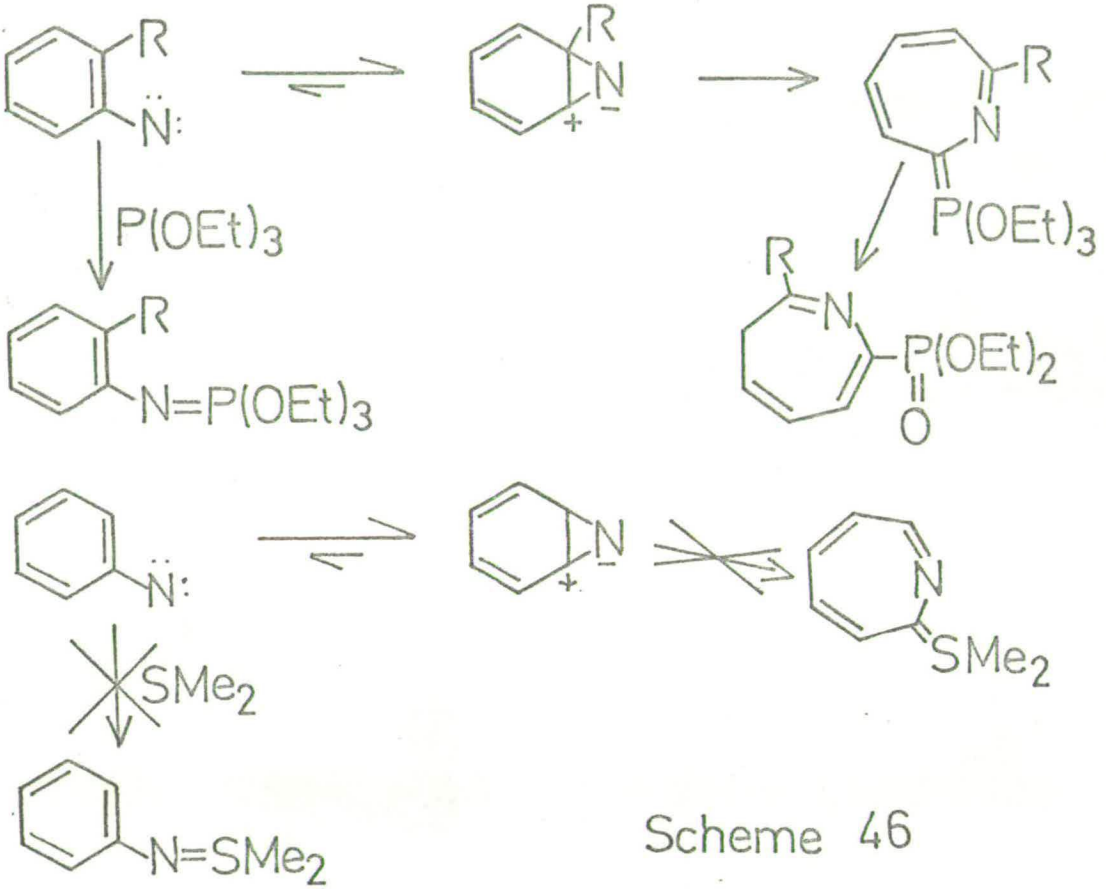
of trapping the azabicycloheptatriene intermediate, (C), but the yields with any given amine vary with experimental conditions: the yield with aniline as a nucleophile may be as much as 40% or as little as 2%. A small change in the amine, e.g. p-toluidine instead of aniline, can affect the yield enormously, to give a trace azepine cf. 40%. Changes in the nature of aliphatic groups attached to the nitrogen can also profoundly affect the yield, e.g. Bu^tNH_2 (60%) and $MeNH_2$ (4%).

One of the most interesting points is that ammonia trapped phenyl nitrene generated by photolysis of the azide to give a 25% yield of the appropriate azepine, but potassium amide, a much more powerful nucleophile, trapped nothing. This indicates that not only must the nucleophile be sufficiently powerful to react with the positive centre of the azabicycloheptatriene intermediate, but also that a proton must immediately be available to react with the negative nitrogen. The amines satisfy this requirement neatly by having a nucleophilic lone pair of electrons ready to form a bond with the positive centre, and as soon as this bond is present, the positive nature of the ammonium ion thus generated frees an acidic proton.

In the course of this research, considerable time was devoted to an attempt to find another nucleophile, which would be as efficient as diethylamine in trapping (C), to give a good yield of a readily isolable and characterisable azepine, preferably a nucleophilic species other than nitrogen. All the reactions resulted in tars, an indication that neither the singlet nitrene (B) nor (C) were trapped, but (B) underwent intersystem crossing, and the diradical then promoted polymerisation. The nucleophilic nitrogen species investigated were morpholine, phenylhydrazine and 2-hydroxypyridine. The carbon species were ethyl acetoacetate and cyclopentadiene. The oxygen species were methanol, ethanol and ^{t}butanol. The only sulphur species used was dimethyl sulphide.

Dimethyl sulphide could react in two ways: it could trap the singlet nitrene (B), cf. the formation of phosphorimidates, or it could react subsequently in a nucleophilic attack on the azabicycloheptatriene intermediate.

(Scheme 46). It did neither. This emphasises the peculiar role of phosphorus reagents such as triethyl phosphite, which are frequently found to trap the nitrene as a phosphorimidate, and which have also been reported as acting as nucleophiles.



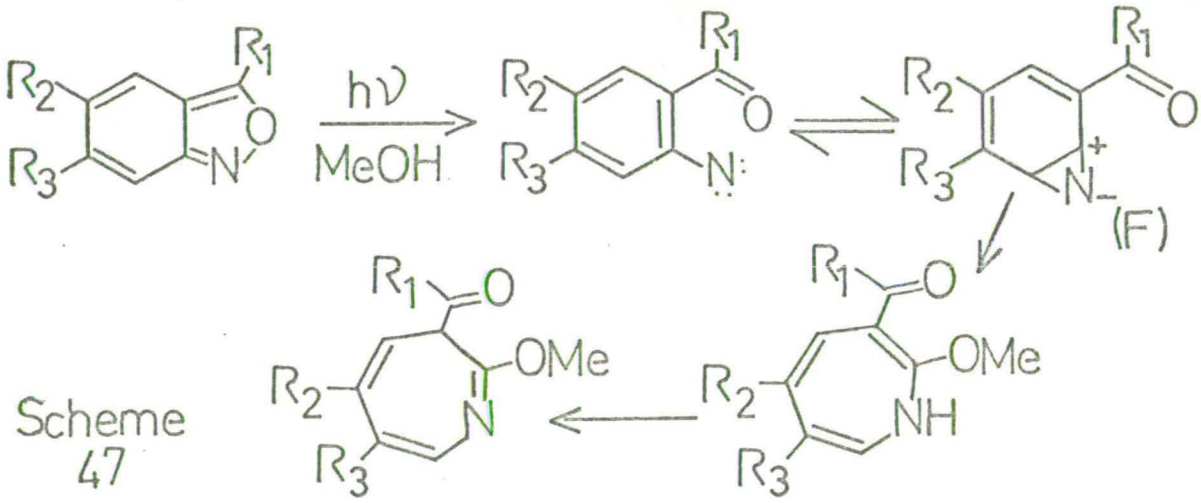
Scheme 46

Of the nitrogen and carbon species, it is possible that they were insufficiently nucleophilic to react. It had been hoped that 2-hydroxy-pyridine might present a readily available source of hydrogen at the opportune moment, just as the amines do, but no azepinyl compound was detected. Explanations for this failure are that the pyridyl nitrogen is insufficiently nucleophilic, or that the hydrogen was sufficiently acidic to protonate intermediate (A).

The problem of protonating intermediate (A) in methanolic solutions has already been discussed. In order to avoid this problem, the much weaker acids, ethanol, and t-butanol were used. The latter has no β hydrogen atoms. The corresponding t-butylamine had been shown to be a satisfactory trap. No alkoxy-azepines were obtained. When there was a trace of diethylamine present in the t-butanol, however, it

satisfactorily trapped at least 70% of the nitrene formed. This shows that the nitrene was present, but the alcohol could not react with it. These results are confirmed by some from Sundberg.[200] He found that methanol/diethylamine mixtures yielded the 2-diethylamino-3H-azepine (1) but not the 2-methoxy-3H-azepine, and that ethanol/diethylamine likewise gave good yields of (1), but no 2-ethoxy-3H-azepine. These results show that the nitrene was indeed present, and was trapped by the diethylamine, even if present in only 5% quantity, but never by either of the alcohols. The only time he generated 2-methoxy-3H-azepine was by photolysis of the phenyl azide in methanol, when he obtained 11%.

The inability of alcohols to trap these nitrenes generated by a phosphite-nitro deoxygenation reaction stems neither from the instability of the final azepines (which are all known and stable) nor apparently from their total inability to trap any nitrene, because Matsumoto[72] has reported that methanol is a more satisfactory trap than diethylamine for a nitrene generated by the photolysis of anthranils, obtaining 69% azepine from the photolysis of 6-chloro-3-phenylanthranil in methanol, and only 32% azepine in diethylamine, (Scheme 47).

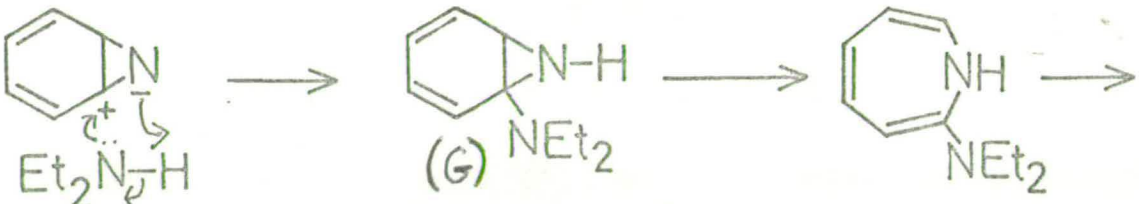


Scheme 47

It is possible that the methanol stabilises (F) in some way by solvation, because of some interaction between the carbonyl group and the methanol, and this makes methanol a suitable nucleophile.

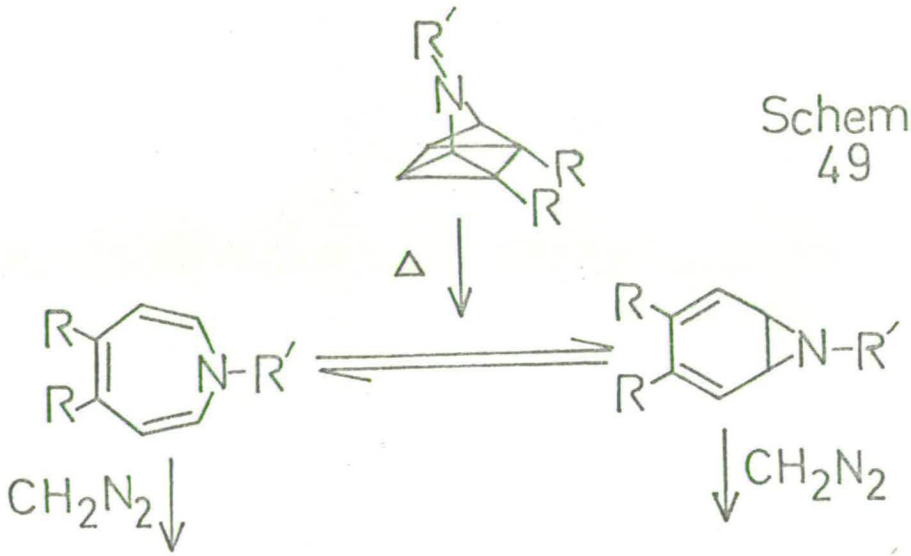
It would, therefore, appear that diethylamine is still to be considered as the most suitable nucleophile, with which the aryl nitrene

will react in preference to all else, in a mechanism such as scheme 48.



Scheme 48

It is even possible that (G) may exist transiently, because evidence has been given by Prinzbach, Stusche and Kitzing[213] for the existence of the N-alkyl substituted form, by carefully examining the stereochemistry of products of the equilibrium treated with diazomethane, Scheme 49.

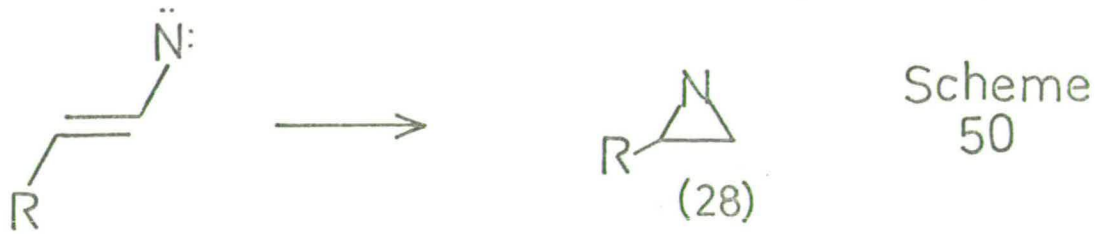


Scheme 49

G. COMPARISON OF ARYL NITRENE WITH OTHER NITRENES

It is apparent from these results that the aryl nitrene very quickly forms the azabicycloheptatriene intermediate (C), which is stable, and will survive many collisions with solvent molecules, before either reacting with a suitable nucleophile, of which the best is diethylamine, or decomposing in some other way, which normally would involve a return to the free nitrene (B), followed by reaction, e.g. with triethyl phosphite to form phosphorimidates, or intersystem crossing to give the triplet nitrene, which may form amine, azoarene, or polymers. There are only rare reports of intermolecular insertion reactions by aryl nitrenes, e.g. Hall, Hill and Tzai[115] obtained low yields of PhNHR, where R was cyclohexyl; they found it was highly selective, e.g. no insertion in the primary C-H bonds of n-pentane, and 3ry : 2ry > 20-40:1. Nitrenes such as carbethoxy nitrene are not nearly so selective, 3ry : 2ry = 2.8 : 1, an indication of the peculiar stability of the phenyl nitrene because of its many resonance forms, through interaction between the nitrene and the π system.

Vinyl nitrene exhibits a similar interaction with the α double bond; all reported products involved (28), (Scheme 50).



Scheme 50

The relative stability of carbonyl and sulphonyl nitrenes is likewise the result of delocalisation involving the C=O and S=O bonds, just as the cyano nitrene $:N_1-C\equiv N_2$ is completely delocalised $N_1\equiv C-N_2:$

The aryl nitrene, however, is involved in a much stronger interaction with the π electron system, giving it its special characteristics, and preventing it from participating in many of the intermolecular reactions common to other nitrenes.

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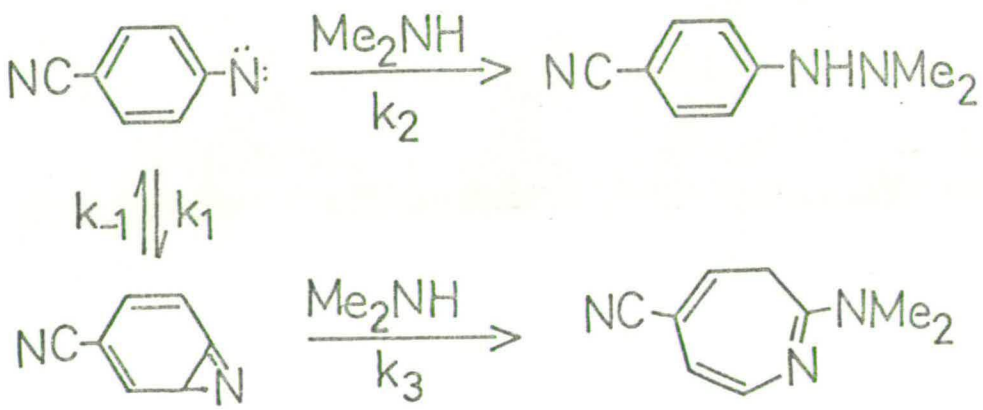
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Note Added in Proof

Since going to proof, two relevant papers have been published.

Odum and Wolf have shown that the products of photolysis of p-cyanophenyl azide in dimethylamine are wavelength dependent. Insertion in the N-H bond is obtained as the major reaction at 350 nm, and approximately equal quantities of the insertion product, 1, 1-dimethyl-2-p-cyanophenylhydrazine, and the ring expansion product, 5-cyano-2-dimethylamino-3H-azepine, are obtained at 253. 7 nm. They also observed that decreasing concentration of dimethylamine resulted in an increasing amount of the ring expansion product. This indicates a competition between two pathways for reaction by the nitrene, (Scheme 1).



Scheme 1

Atherton and Lambert have made substituted azepines by the deoxygenation of nitroarenes with phosphorus reagents in diethylamine. Their results confirm that with m-substituted nitroarenes, electron withdrawing groups promote the formation of the 6-substituted-2-diethylamino-3H-azepine, and electron donating groups the 4-isomer, although their total yields ranged from only 30-50%. They also observed the hydrolysis of the 2-diethylamino-3H-azepines to 1, 3-dihydro-2H-azepin-2-ones, in water and aqueous alcohols. They reported the formation of N'-substituted 1-nathylhydrazine from 1-nitronaphthalene in piperidine, but found no phosphorimidine.

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