NITROGEN-CONTAINING REACTIVE INTERMEDIATES IN
HETEROCYCLIC SYNTHESIS

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 Department of Chemistry, University of Edinburgh, under the supervision of Professor J. I. G. Cadogan, since the 1st of October, 1972, the date of my admission as a research student.
Postgraduate Lectures

I attended the following lectures and conferences to obtain the required number of eight units for postgraduate study:

1) attendance for three years at Laboratory 10 group seminars 3 units
2) attendance at a series of five lectures by Professor P. L. Pauson on 'Organometallic Reagents in Organic Synthesis' 1 unit
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Abstract

Thermolysis of aryl 2-azidophenyl sulphones has been shown to lead to mixtures of phenothiazine-5, 5-dioxides formed either by five-membered cyclisation of the nitrene and rearrangement of the spirodiene so formed or by six-membered direct insertion of the nitrene. The nature and position of the substituent group has been shown to have a great influence on the products which are formed. In the para position electron-supplying substituents favour five-membered cyclisation and electron-withdrawing substituents six-membered cyclisation and in the meta position electron-supplying substituents favour six-membered cyclisation and electron-withdrawing substituents five-membered cyclisation through electrophilic attack of the nitrene at the position of greatest electron density. Ortho substituents favour five-membered cyclisations and this has been ascribed to steric effects.

The deoxygenation of aryl 2-nitrophenyl sulphides and aryl 2-nitrosophenyl sulphides by triethyl phosphite and the thermolyses of the corresponding azides in a variety of solvents have been studied with a view to understanding the reactive intermediates involved. Unlike the corresponding sulphones no clear decision can be reached. It was found that the type of reaction greatly influenced the products that were obtained and possible mechanisms for these reactions are discussed. It was found that the deoxygenation of aryl 2-nitrosophenyl sulphides at temperatures below 152° gave only traces of phenothiazines and possible mechanisms for this are discussed. The treatment of aryl 2-(hydroxyamino)phenyl sulphides with trifluoroacetic acid did not yield the expected phenothiazines.

High Speed Liquid Chromatography was used extensively to determine the products from these reactions and its usefulness and scope discussed. The techniques necessary to obtain optimum results are also discussed.

The thermolysis and photolysis of N-chloro-2-nitroacetonilide in toluene and anisole have been shown to proceed via heterolytic and homolytic cleavage of the N-Cl bond to yield "Cl⁺" and chlorine radicals.
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I. Programme of Research
INTRODUCTION

A. General

For many years chemists have been interested in nitrogen-containing reactive intermediates. Generally they have been postulated as a monovalent nitrogen atom with six electrons in the outer shell and have been termed azenes, azacarbenes, azylene, imine radicals, imidogens and nitrenes. Recently the term nitrene has been widely used.

In 1891 Tiemann postulated a carbonyl nitrene, $R$-CO-N, in his interpretation of the Lossen rearrangement. Curtius in 1922 invoked a "short-lived intermediate $RCON$" to account for the reactions of some carbonyl azides and two years later Bertho suggested that phenyl nitrene was an intermediate in the decomposition of phenyl azide in $p$-xylene. In all these reactions there was no direct evidence for a nitrene and its intermediacy was inferred from a study of the products. This is a general feature of the chemistry of nitrenes and, although there is some physical evidence (see below) for the existence of nitrenes, evidence for the intermediacy of a nitrene in a reaction in solution generally comes from a study of the products. Thus although there are many papers which refer to the intermediacy of nitrenes there is generally no attempt to distinguish between a nitrene, defined as a monovalent, electron-deficient nitrogen atom, and any other type of nitrogen-containing reactive intermediate.

Although many reactions appear to go via a nitrene closer examination of the reaction frequently shows that nitrenes are not involved. For example large $^{14}$C kinetic isotope effects have been observed for compounds labelled at the migrating group in the Curtius rearrangement. Thus the bond to the carbon is broken in the rate determining step and the reaction does not involve a nitrene but is concerted as shown in Scheme 1.

$$\text{Scheme 1}$$
Similar isotope effects are found in the related Hofmann and Lössen rearrangements.

B. **Electronic Structure of Nitrenes**

In a nitrene the nitrogen atom is bonded to a single carbon centre and is sp hybridised. Nitrogen has five valence electrons and one is involved in the bond to carbon, two occupy the non-bonding sp orbital and the remaining two electrons are in the unhybridised orbitals $p_x$ and $p_y$, as shown in Figure 1.

![Figure 1](image)

The nitrene can exist in two forms, singlet and triplet. The spin multiplicity is given by $2S + 1$ where $S$ is the total spin and so when the two electrons have parallel spins $S = \frac{1}{2} + \frac{1}{2} = 1$ and so the spin multiplicity $= 2S + 1 = 3$. This is the triplet state and it is a diradical. In the triplet state the two electrons occupy different orbitals. If the spins are paired then $S = \frac{1}{2} - \frac{1}{2} = 0$ and hence spin multiplicity $= 2S + 1 = 1$. This is the singlet state and the electrophilic singlet has both electrons in the same orbital.

Spin conservation leads one to believe that if the thermolysis of an azide or the $\alpha$-elimination reaction of a $p$-toluenesulphonamide do lead to a nitrene then initially at least it will be the singlet nitrene. However nitrenes generated by the photolysis of azides may be formed either from the excited singlet azide or this may undergo inter-system crossing to give the excited triplet azide. These would then decompose to give the singlet and triplet nitrenes respectively. For example the photolysis of benzoyl azide gives initially the singlet benzoyl nitrene which later decays to triplet benzoyl nitrene.  

Experimental evidence (when interpreted on the basis of
nitrenes) generally indicates that, although the singlet is initially formed the ground state of the nitrene is the triplet.\(^8\)

Non-empirical molecular orbital calculations suggest that \(\text{RC(O)N:\)}\) is a ground state triplet but that \(\text{ROC(O)N:\)}\) may have a singlet ground state.\(^9\) The ease of formation and apparent thermodynamic stability of amino-nitrenes (of the form \(\text{R}_{2}\text{N-N:\)}\) have led people to suppose that the ground state in this case is a singlet\(^8\) but recent ab initio calculations by Baird and Barr\(^10\) have shown that the optimum triplet is about 40kJmol\(^{-1}\) more stable than the optimum singlet. However at the optimum singlet geometry the singlet is more stable than the triplet. Thus the singlet is "trapped" in a singlet well and can only cross over very slowly to the ground state triplet.

Another nitrogen-containing reactive intermediate which has received attention recently is the closely related nitrenium ion of the form \(\text{R}_{2}\text{N}^{+}\) and theoretical calculations predict that \(\text{NH}^{+}\), \(\text{MeNH}^{+}\) and \(\text{Me}_{2}\text{N}^{+}\) will have ground state triplets.\(^\text{11,12}\)

It is generally assumed that the singlet nitrene reacts by inserting in C-H bonds in a concerted manner whereas triplct nitrene reacts like a free radical by abstracting hydrogen from the solvent to give the corresponding amine. Thus when the reaction is done in a heavy atom solvent the yield of triplet product increases because of the increase in collisional deactivation of singlet to triplet. However Lwowski et al\(^\text{13}\) have shown that \(\text{CH}_{2}\text{Cl}_{2}\) appears to stabilise singlet alkanoyl nitrenes (RC(O)N:\) but not singlet alkoxy-carbonyl nitrenes (RO C(O)N:\). This effect has been ascribed to the stabilising effect of the lone pairs on the chlorine atoms\(^\text{14}\) but why it should occur for one species but not another is not clear. Breslow and Edwards\(^\text{15,16}\) have demonstrated that radical traps can increase the yields of singlet products possibly because free radical species can catalyse singlet to triplet intersystem crossing.

However while the assumption that singlet nitrene should give products arising from concerted insertion into C-H bonds and triplet nitrene should give hydrogen abstraction products is reasonable both on theoretical grounds and by analogy with other reactions the presence
of such products cannot be taken as proof of the intermediacy of a nitrene.

C. Physical Evidence for the Existence of Nitrenes

(i) Electron spin resonance

Smolinsky et al.\textsuperscript{17} irradiated dilute solutions of phenyl azide and related molecules frozen at 77\textdegree K in a plastic matrix and the electron spin resonance (e.s.r.) signals which were observed were assigned to the triplet ground state of the nitrene. Similar results were obtained from aromatic dinitrenes\textsuperscript{18} and alkyl nitrenes.\textsuperscript{19} However Kuck and his co-workers\textsuperscript{20} failed to observe the e.s.r. spectrum of benzoyl nitrene in the irradiation of benzoyl azide. They did however observe phenyl nitrene which arose from the phenyl isocyanate which formed. This may be because the singlet nitrene reacts to give phenyl isocyanate before it has time to decay to the triplet or the rearrangement may be concerted.

(ii) Ultra-violet spectra

The ultra-violet (u.v.) spectra of several aromatic nitrenes and dinitrenes formed by the irradiation of the azide in a matrix at 77\textdegree K have been obtained by Reiser and his co-workers\textsuperscript{21} and they have also observed the nitrene produced by the irradiation of 2-azidobiphenyl in a matrix.\textsuperscript{22} The same spectrum was obtained by the flash photolysis of 2-azidobiphenyl in solution by Lehman and Berry.\textsuperscript{23} This nitrene is then observed to cyclise to carbazole. Since the spectrum is known to be that of triplet nitrene it is seen that the triplet nitrene can, at least in this case, insert into C-H bonds. The singlet nitrene is the first species formed on irradiation and it then undergoes fast inter-system crossing to the triplet. The flash photolysis of 1-azidoanthracene\textsuperscript{24} and 1-azidonaphthalene\textsuperscript{23} provide more examples of the u.v. spectra of nitrenes at room temperature and above. Both were identified by comparison with the spectra obtained on photolysis in a matrix. The half-life of the nitrene from 1-azidoanthracene was estimated as 3-10\textmu s.
Chemically induced dynamic nuclear polarisation

Brinkman, Bethell and Hayes\textsuperscript{25} have reported polarisation in the p.m.r. spectrum arising from the insertion of triplet ethoxycarbonyl nitrene into the tertiary C-H bond of trans-decalin.

All the physical evidence for the existence of nitrenes refers to the triplet state and there is no direct evidence for the singlet state. The triplet state is of course much easier to observe than the singlet state and another factor may be the fast decay of singlet nitrene to the triplet state which is then much more stable and hence much more easily observed. In this connection failure to observe triplet nitrene when an alternative reaction is open to the singlet nitrene may be significant, as in the photolysis of benzoyl azide. Although the evidence for the detection of nitrenes is convincing the conditions generally bear little relation to those of the reactions which are thought to produce nitrenes. It is also noteworthy that all the nitrenes that have been detected have been formed by photolysis and none by thermolysis.

D. Reactions of Nitrenes

The following reactions have been ascribed to nitrenes in the literature and although there is no evidence that a monovalent electron-deficient species is necessarily involved the term nitrene will be used in this and the following section.

(i) Recombination

The reaction shown in Scheme 2 is spin allowed for singlet and triplet nitrenes.

\[
2 \overset{\cdot\cdot}{R} = \overset{\cdot\cdot}{N} : \quad \rightarrow \quad R = N = N = R
\]

Scheme 2

However recombination requires a high local concentration of nitrenes e.g. in flash photolysis.\textsuperscript{26} In other reactions azobenzene is more probably formed by nitrene attack on the azide\textsuperscript{27} or even by direct reaction of two azido groups.\textsuperscript{28}
(ii) **Insertion reactions**

(a) **C-H bonds**

Despite the evidence of flash photolysis that carbazole is formed by intramolecular C-H bond insertion by the triplet nitrene obtained on the photolysis of 2-azidobiphenyl it is generally accepted that C-H bond insertion is a process exclusive to singlet nitrene.

For example the thermolysis of optically active 1-azido-2-(2-methylbutyl)benzene gave optically active 2-ethyl-2-methylindoline. This suggests a concerted insertion reaction by singlet nitrene via the transition state I as shown in Scheme 3.

![Scheme 3](image)

Scheme 3

Triplet nitrene would be expected to give radical abstraction followed by recombination involving intermediate II. This would have led to extensive racemisation of the product which was not observed. Optical activity was more highly retained in the vapour phase than in solution and this suggests that there is more collisional deactivation of the singlet to the triplet in solution, as would be expected.

Insertion into aromatic C-H bonds is well known and perhaps the most widely investigated example is the thermolysis and photolysis...
of 2-azidobiphenyl to give carbazole in 78% yield. 30, 31

\[
\begin{array}{c}
\text{N}_3 \\
\rightarrow \\
\text{H}
\end{array}
\]

Scheme 4

A similar reaction involves insertion into a cyclohexane ring. 32

\[
\begin{array}{c}
\text{N}_3 \\
\rightarrow \\
\text{H}
\end{array}
\]

Scheme 5

Lwowski 33 has shown that ethoxycarbonyl nitrene inserts into cyclohexane with 50% yield. He has also demonstrated 34 that the reactivities of primary:secondary:tertiary C-H bonds to the insertion of t-butylcarbonyl nitrene are in the ratio 1:9:160 (corrected for the number of each type of C-H bond). The comparable ratios for phenyl nitrene 35 are 1:7:140-280 and for ethoxycarbonyl nitrene 36 are 1:10:34. Recently Breslow et al. have shown that diphenylphosphoryl nitrene is much less selective having ratios of 1:1.2:3.4.

(b) **O-H bonds**

Ethyl azidoformate was photolysed and thermolysed in t-butanol to give a hydroxylamine derivative in 55% yield. 38

\[
\text{Bu}^t \text{OH} + \text{N-CO}_2 \text{Et} \rightarrow \text{Bu}^t \text{O-N-CO}_2 \text{Et}
\]

Scheme 6

(c) **N-H bonds**

Ethoxycarbonyl nitrene (generated by the treatment of III with base) reacted with the imidate (IV) to give the hydrazonate (V) in 38% yield, 39 as set out in Scheme 7.
Scheme 7

This represents the first synthesis of aliphatic hydrazonates.

Ethoxycarbonyl nitrene has also been shown to react with aniline to give a hydrazine in 52% yield. (Scheme 8).

Scheme 8

When Odum and Aaronson photolysed p-cyanophenyl azide in dimethylamine they found a 70% yield of 1,1-dimethyl-2-(4-cyanophenyl)hydrazine and a 5% yield of p-cyanoaniline.

Scheme 9

Normally however the photolysis of aryl azides in secondary amines yields ring expansion products and only in this special case is a hydrazine observed.

(iii) Hydrogen abstraction

This is generally accepted to be the most characteristic reaction of triplet nitrene. The nitrene becomes an amino radical and leaves a carbon radical behind. (Scheme 10).
Since the two spins are parallel the radicals cannot couple and they generally diffuse apart before spin inversion followed by coupling can occur. 42

(iv) **Addition to multiple bonds**

(a) **Carbon-carbon double bonds**

Rees and his co-workers 43 have synthesised aziridines by the oxidation with lead tetraacetate (LTA) of N-amino compounds in the presence of olefins. For example the oxidation of N-aminophthalimide in the presence of tetrachloroethylene gave the aziridine (VI) in 90% yield.

![Scheme 11](image)

Atkinson and Martin 44 have shown that in the addition of the same nitrene to methyl acrylate the initial product is the thermodynamically less stable **syn** invertomer.

![Scheme 12](image)
Additions such as these are shown to be at least 95% stereoselective and so the nitrene is assumed to be singlet. The reaction of triplet nitrenes to give aziridines may also be envisaged but the diradical (VII) has time to rotate before spin inversion can occur and so the addition will be non-stereospecific.

Scheme 13

Lwowski used cis- and trans-4-methylpent-2-ene as the olefin and he produced ethoxycarbonyl nitrene in three different ways, by the thermolysis of ethyl azidoformate, by the alkali-induced α-elimination of N-(p-nitrobenzenesulphonoxy)urethane and by the photolysis of ethyl azidoformate. All reactions gave the aziridine in good yield. In thermolysis and α-elimination cis-pentene gave the cis-aziridine and trans-pentene gave the trans-aziridine. However in the photolysis the reaction is only about 70% stereospecific. Thus it is concluded that thermolysis and α-elimination give singlet nitrene and photolysis gives 70% singlet nitrene and 30% triplet nitrene. Interceptor experiments in cyclohexane bear out this conclusion. The triplet is assumed to arise from the excited triplet state of the azide. However nitrene additions to olefins must be approached with caution since the reaction may go through an intermediate triazoline - as in the reaction reported by D. H. Aue and his co-workers.

Scheme 14

However, O. E. Edwards et al have recently concluded that the reaction of ethyl azidoformate with norbornylene induced by direct irradiation does not involve an intermediate triazoline.

Although "nitrenes" generated from different sources all give
aziridines this does not mean that azides cannot react initially via triazolines since the triazoline leads eventually to the aziridine. Similarly the other "nitrenes" may in fact be other nitrogen-containing reactive intermediates that happen to give aziridines as the final product. Thus the presence of the same product does not necessarily prove the existence of a common intermediate.

Phenyl nitrene (and aryl nitrenes in general) generated by the photolysis of phenyl azide does not add to double bonds and phenyl azide will only add thermally to double bonds via the intermediate triazoline.

It is interesting to note that aryl sulphonyl azides react via the triazoline to give not the aziridine but the imine in equilibrium with the enamine. (Scheme 15).

![Scheme 15](image)

Wohl has reported a similar reaction accompanied by ring expansion but Kwart and Khan produced the aziridine when benzene sulphonyl azide was reacted with cyclohexene in the presence of a copper catalyst. This reaction probably goes via a copper-nitrene complex.

(b) 1, 3-Cycloaddition

Ethoxycarbonyl nitrene can add to diphenyl-acetylene to form both a mono-adduct and a di-adduct.
Similarly ethoxycarbonylnitrene adds to nitriles\(^\text{60}\) to give 1,3,4-oxadiazoles in good yield. The mechanism is not known but a 1,3-dipolar cycloaddition seems reasonable.

\[
\text{EtO-CN}^* + R-CN \rightarrow R-C\equiv N
\]

The nitrenes formed by the photolysis of azido-1,3,5-triazines also add to nitriles but this time by attack on the nitrogen.\(^\text{61}\)
(v) **Electrophilic attack on a non-bonding pair**

Since it is electron deficient attack on a lone pair is an attractive reaction for a nitrene.

Thus nitrenes react with amines

$$\text{Ph-N}^\cdot + \text{N-C-OEt} \rightarrow \text{Ph-N-N-C-OEt}$$

Scheme 18
with pyridine $^62$

\[
\text{Scheme 20}
\]

with dimethyl sulphoxide $^63$

\[
\text{Scheme 21}
\]

and with sulphides $^64$

\[
\text{Scheme 22}
\]

The addition of nitrenes to the nitrogen of nitriles discussed above (Scheme 18) could also be listed under this heading.

(vi) **Ring contractions**

In a few cases the ring to which the nitrene is attached contracts to form a stable molecule. For example, Abramovitch and Cue $^65$ have demonstrated the ring contractions of 2-azido pyridine-N-oxides although the exact mechanism is complex and somewhat uncertain.

\[
\text{Scheme 23}
\]

A related reaction of 2-azidobenzoquinones has been demonstrated by Moore and his co-workers $^66$.
Ring expansions are rather more common than ring contractions and involve the attack of nucleophiles on aromatic nitrenes.

Odum and Wolf have shown that dimethylamine reacts with aryl nitrenes to give ring expanded azepines and this is indeed a more general reaction than the formation of hydrazines which is restricted to p-cyanophenyl nitrene.

When irradiation was carried out at 350 nm the products were 88% hydrazine and 12% azepine but at 254 nm 45% azepine and only 55% hydrazine were obtained suggesting that the nitrene must be formed in a vibrationally excited state before it will react to give the strained azirine (VIII) which is presumably the precursor of the azepine.

Sundberg and Heintzelman have shown that whereas the photolysis of 2-azidobiphenyl normally proceeds to give carbazole the reaction can be diverted to give azepine by adding diethylamine and that this diversion depends on the diethylamine concentration and is at the expense of the carbazole. Thus they postulate an equilibrium between the nitrene, which is presumably the carbazole precursor, and the azirine which is presumably the azepine precursor - as shown...
Thus aryl nitrenes may be in equilibrium with the corresponding azirines which might account for their general unreactivity. For instance they do not usually add to double bonds.

A different type of ring expansion reaction involves the intermolecular attack of a nitrene on benzene to give a 1-H-azepine. The simple insertion product is also formed.
E. Generation of Nitrenes

(i) Thermolysis and photolysis

One of the most common ways of generating nitrenes is by the thermolysis and photolysis of azides and numerous examples have been given above. However the thermolysis and photolysis of other compounds gives reactions which have been interpreted on the basis of an intermediate nitrene.

For example the photolysis of isocyanates may involve the corresponding nitrene and carbon monoxide and, as mentioned above, when this reaction is carried out in a matrix the e.s.r. signal of the triplet nitrene can be detected.

\[ R-N=\overset{\cdot}{C}=O \rightarrow R-N^+ + CO \quad \text{Scheme 28} \]

The photolysis of nitrile oxides \(^{71}\) (Scheme 29) and \(N\)-oxides such as the quinonedianil-\(N, N'\)-dioxide (IX) \(^{72}\) (Scheme 30) give nitrenes. The reactions probably proceed via the oxazirine and oxaziridine respectively since photolysis of the oxaziridine (X) has been shown to give phenyl nitrene \(^{73}\) (Scheme 31) which was detected by its e.s.r. spectrum at low temperatures.

\[ \text{Scheme 29} \]
The photolysis of dioxazole derivatives gives nitrenes which are trapped by dimethyl sulphide.\textsuperscript{74}

Thermolysis also gave nitrenes which may be trapped by dimethyl sulphoxide.\textsuperscript{74} The aryl isocyanate is also found in these thermolyses but it is not clear whether this arises by rearrangement of the nitrene or in a concerted manner.
The photolysis of phosphinimines is also known to give nitrenes.

\[
\text{Ph}_3\text{P}=\text{N}-\text{Bu}^t \xrightarrow{h\nu} \text{Ph}_3\text{P} + \cdot\text{N}-\text{Bu}^t
\]

Scheme 34

(ii) By \(\alpha\)-elimination

\(\alpha\)-Elimination reactions are usually base-induced and take the form shown in Scheme 35.

\[
\begin{align*}
\text{R}-\text{N} & \quad \xrightarrow{\text{B}^+} \text{R} - \cdot\text{N} - \text{X} + \text{B}^+ \\
\text{X} & \quad \xrightarrow{} \text{R} - \cdot\text{N}^+ + \text{X}^-
\end{align*}
\]

Scheme 35

One example is the Hofmann rearrangement of an \(\text{N}\)-bromoamide (or \(\text{N}\)-chloroamide) to a primary amine via an intermediate isocyanate.

\[
\begin{align*}
\text{R}-\text{C} - \text{NHBr} & \quad \xrightarrow{\text{OH}^-} \text{R} - \text{N} = \text{C} = \text{O} \quad \xrightarrow{} \text{R} - \text{NH}_2
\end{align*}
\]

Scheme 36

However nitrenes have never been trapped in this reaction and the mechanism appears to be formation of the nitrogen anion which then rearranges by simultaneous loss of bromide ion and alkyl group migration. One reaction which does probably generate a nitrene is the base catalysed decomposition of \(\text{N}\)-(\(p\)-nitrobenzenesulphonyloxy)-urethane.

The products obtained are very similar to those from the thermolysis and photolysis of ethyl azidoformate. Similarly the base induced decomposition of \(\text{N}\)-(\(p\)-toluenesulphonyloxy)urethane in an emulsifying system gave ethoxycarbonyl nitrene which was trapped by benzene, toluene and cyclohexane to give the usual
addition and insertion products. 77

(iii) **Oxidative methods**

Although on paper the oxidation of amines is an attractive route to nitrenes (as set out in Scheme 38) there is no evidence that the reaction normally occurs.

\[ R-NH_2 + [O] \rightarrow R-N:: + H_2O \]  
**Scheme 38**

However if the amino group is attached to either a nitrogen or an oxygen atom then reactions characteristic of a nitrene do occur. Rees and his co-workers have discovered many examples of the production of nitrenes by the oxidation of 1,1-disubstituted hydrazines. Stereospecific addition to olefins is observed. 78
Other hydrazines undergo similar reactions. \(^7^9\)

The nitrenes can also be trapped by dimethyl sulphoxide. \(^7^9\)
More recently similar reactions have been reported for the oxidation of O-substituted hydroxylamines. Thus the oxidation of methoxyamine by lead tetraacetate in the presence of tetramethylethylene gave the aziridine XI.\(^{80}\)

\[
\text{MeONH}_2 + \text{Me}_2\text{SO} \xrightarrow{\text{LTA}} \text{MeON} \quad \text{XI}
\]

Ioffe and Koroleva\(^ {81}\) have shown that the addition is stereospecific and have managed to separate the two stereoisomers (invertomers) from the addition to 2-methylbut-2-ene.

(iv) **Reductive methods**

The thermolysis and photolysis of 2-azidobiphenyl is well known to yield carbazole\(^ {82}\) and in 1962 it was shown\(^ {83}\) that the deoxygenation of 2-nitrosobiphenyl with triethylphosphite at 0-5° yielded carbazole in 76% yield. The preparation of carbazole by the deoxygenation of 2-nitrobenzyl with triethyl phosphite in a
suitable solvent at 160° however greatly widened the synthetic scope of the reaction and many examples of the synthesis of heterocycles by the treatment of aromatic nitro-compounds with tervalent phosphorus reagents are now known. These reactions will be discussed in greater detail in Section G (below).

Ferrous oxalate has been used for many years to cyclise aromatic nitro-compounds. Thus when 2-nitrophenyl 4'-methoxyphenyl amine is heated with ferrous oxalate at 200-300° 2-methoxyphenazine is formed in 49% yield. However although the deoxygenation of 2-nitrodiphenyl sulphide with triethyl phosphite gave phenothiazine a similar reaction with ferrous oxalate gave only 2,2'-bis(phenylmercapto)azobenzene.

Bacon and Hamilton have recently reported that the deoxygenation of 2-nitrodiphenylamines with triethyl phosphite does not form phenazines whereas treatment with ferrous oxalate yields the phenazine in 49% yield. Thus it seems unlikely that the ferrous oxalate produces a nitrene and Suschitzky and Smith have proposed a plausible mechanism involving the loss of water from the aci-nitro form.

Scheme 45

A recent report by Zon and his co-workers describes the deoxygenation of 2-nitrobiphenyl with hexamethyl disilane to give carbazole. Interestingly 2-nitrosobiphenyl failed to yield carbazole.
and so Zon et al tentatively advance Scheme 46 as a possible mechanism.

\[
R-\text{NO}_2 + \text{Si}_2\text{Me}_6 \rightarrow R-N-O\text{SiMe}_3 + \text{SiMe}_3^-
\]

\[
\rightarrow R-N-O\text{SiMe}_3
\]

\[
\text{Si}_2\text{Me}_6 \rightarrow R-N-O\text{SiMe}_3 + \text{SiMe}_3^-
\]

\[
\rightarrow R-N-O\text{SiMe}_3 + \text{SiMe}_3\text{OSiMe}_3
\]

\[
\rightarrow R-N: + \text{SiMe}_3\text{OSiMe}_3
\]

\[\text{[R- = } \text{benzene] }\]

Scheme 46

Zon et al\textsuperscript{95} have also reported a similar reaction involving the \(\alpha\)-deoxysilylation of hydroxylamine derivatives. (Scheme 47).

The isolation of the aziridine however throws doubt of a nitrene mechanism in this case since it is not a product in other reactions thought to involve phenyl nitrene.
Laurent and Bartnik\textsuperscript{96} have treated oximes with Grignard reagents to obtain intramolecular cyclisation which they ascribe to the intermediate nitrene - as shown in Scheme 48.

Scheme 47

Scheme 48
Scheme 49
A. F. M. Iqbal\textsuperscript{97-100} has described the deoxygenation of aromatic nitro-compounds by carbon monoxide at high temperatures and pressures in the presence of organometallic catalysts e.g. Rh\textsubscript{6}(CO)\textsubscript{16}. Typically the reaction is done in pyridine at 165-170° and 150 atmospheres for 3 hours and the nitrene has been trapped in a variety of ways - as set out in Scheme 49.

F. Nitrenium Ions

Although univalent nitrenium ions of the form \textit{R}N\textsuperscript{+} have been studied for some years \textsuperscript{101} it is only recently that divalent nitrenium ions of the form \textit{R}_2N\textsuperscript{+} isoelectronic with carbonium ions, have been reported in a series of papers by Gassman and his co-workers. \textsuperscript{102} The treatment of N-chloramines with silver salts was shown to produce products which are best explained by invoking a divalent nitrogen cation, a nitrenium ion.

For example the solvolysis of 4, 7, 7-trimethyl-2-chloro-2-azabicyclo[2. 2.1]heptane (XII) in methanol with silver perchlorate\textsuperscript{103, 104} gave rearranged products best explained on the basis of the nitrenium ion (XIII).

\begin{align*}
\text{Cl} & \quad \rightarrow \quad \text{N}^+ \\
\text{MeO} & \quad \rightarrow \quad \text{NH}
\end{align*}

The rate is over $2 \times 10^3$ times faster when the silver perchlorate is present than in methanol alone. This is additional evidence for
the intermediate nitrenium ion. By analogy with nitrenes nitrenium ions should be either singlet or triplet. Gassman et al.\textsuperscript{105} have reported that the silver ion-assisted methanolysis of the \( \text{N-chloramine} \) (XIV) gave principally the rearranged product (XV) and the unrearranged, hydrogen abstraction product (XVI) (Scheme 51). It seems probable that the rearranged product comes from a singlet nitrenium ion while the unrearranged product comes from a triplet nitrenium ion by hydrogen abstraction. When a heavy-atom solvent (such as \( \text{CCl}_4 \)) is present it is found that the unrearranged product (XVI) increases at the expense of the rearranged product (XV) because more triplet nitrenium ions are being produced by collisional deactivation. These results are cited by Gassman \textit{et al} as proof of the existence of singlet and triplet nitrenium ions.

\begin{center}
\includegraphics[width=\textwidth]{scheme51.png}
\end{center}

\textbf{Scheme 51}
Scheme 52
Edwards et al.\textsuperscript{106} however have argued that reactions such as these are homolytic. They cite as evidence an induction period, retardation by oxygen and acceleration by peroxides. However, in the absence of a reaction which will give different products for homolytic and heterolytic mechanisms the question must remain open.

It does not seem possible however to interpret the results obtained by the silver ion-assisted methanolysis of \( N \)-chloro-\( N \)-t-butyraniline other than by invoking a nitrenium ion.\textsuperscript{106, 107}

However, a more accurate view of the aryl nitrenium ions may be to consider them as having a quinonoid structure with a carbonium ion centre conjugated to an imine (Scheme 52). Such a view is supported by Gassman's observation that on blocking the 4-position a \( p \)-quinonoid intermediate can be trapped out.\textsuperscript{108}

\[
\begin{align*}
\text{Bu}^t\text{Cl} &\quad \text{CF}_3\text{COOAg} \\
\text{R} &\quad \text{MeOH}
\end{align*}
\]

\( R = \text{Me, Ph} \)

\[
\begin{align*}
70\% \quad 62\% 
\end{align*}
\]

\[
\begin{align*}
\text{Bu}^t\text{N} = \text{OMe} \\
\end{align*}
\]

\[
\begin{align*}
17\% \quad 5\% 
\end{align*}
\]

Scheme 53

The failure to observe reactions characteristic of electrophilic nitrogen also supports this view.

Cadogan and Rowley\textsuperscript{109} recently reported the formation of similar nitrenium ions by the deoxygenation of phenyl-\( t \)-butyl nitroxide with triethyl phosphite in methanol. This formed the phenyl-\( t \)-butyl aminyl radical which then gave the nitrenium ion by redox electron transfer.
It is noteworthy that the o/p ratio is the same as that obtained by Gassman in the silver ion-assisted methanolysis of N-chloro-N-t-t-butylaniline. Similarly it was shown\textsuperscript{110} that the deoxygenation of diphenyl nitroxide by triethyl phosphite in ethanol gave diphenylamine and p-ethoxydiphenylamine. The same products were obtained by the thermolysis of tetraphenylhydrazine in ethanol thus indicating the intermediacy of the diphenyl aminyl radicals which then undergo redox electron transfer to give nitrenium ions. Interestingly Svanholm and Parker\textsuperscript{111} have reported the direct observation of dianisyl nitrenium ions by cyclic voltametry.

Although Gassman\textsuperscript{112} has reported the silver ion-assisted cyclisation of XVII as set out in Scheme 55 aryl insertion reactions of aryl nitrenium ions generated from N-chloramines are not known.
Gassman and Hartman\textsuperscript{113,114} have reported that hydroxylamine esters can produce nitrenium ions in alicyclic systems and Gutschke and Heesing\textsuperscript{115} have shown that the aryl hydroxylamine (XVIII) rearranges via an intimate ion pair involving a nitrenium ion.

\begin{equation}
\text{Ph-C-N-O-SO}_2-Me
\end{equation}

Scheme 56

Thus it might be expected that the treatment of hydroxylamines with acid would produce nitrenium ions and Patrick and Schield\textsuperscript{116} have reported the formation of carbazole when 2-(N-hydroxyamino)biphenyl was treated with liquid HF. The presence of the 2-amino-5-fluorobiphenyl is additional evidence for the nitrenium ion.

\begin{equation}
\text{Scheme 57}
\end{equation}
However it may be that while the 2-amino-5-fluorobiphenyl arises from a nitrenium ion the carbazole is produced by concerted loss of water from the protonated hydroxylamines. This is probably the mechanism by which diphenylamines are produced when phenyl hydroxylamines are treated with trifluoroacetic acid (TFA) in the presence of anisole, toluene or benzene.\(^{117}\)

\[
\begin{align*}
X\text{-}\underline{\text{NH}\text{OH}} + \text{aryl-R} & \xrightarrow{\text{TFA}} \text{aryl-NH-aryl} \\
\end{align*}
\]

Scheme 58

When R=X=H the yield is 65.5%.

The presence of ascrobic acid was found to improve the yield, possibly by suppressing competing radical reactions. Bearing in mind the apparent importance of the quinonoid structure in aryl nitrenium ions generated from N-chloramines and the absence of any reports of nitrenium ions so formed undergoing aromatic insertion reactions it seems likely that the reaction above involves the concerted loss of water from the protonated hydroxylamine.

The production of nitrenium ions by the protonation of nitrenes is an attractive possibility and one system in which acid is present is the lead tetraacetate oxidation of amines. Hiyama et al\(^{118}\) have invoked nitrenium ions to explain the products obtained when cyclopropylamines are oxidised by lead tetraacetate although they did not say that the nitrenium ion was produced by protonation of the nitrene.
In this respect it is interesting to note that the thermolysis of the corresponding azide gave a high yield of a ring expansion product \(^{119}\) although the conditions of the reaction are quite different.  

Hassner et al. \(^{120}\) however, who showed that only benzonitrile and ethylene were obtained on photolysis of this azide, favoured a concerted mechanism rather than a nitrene intermediate. Gassman et al. \(^{121}\) have described a ring expansion from a nitrenium ion as shown in Scheme 62. The intermediate (XIX) was identified from its methanolysis products.
Nitrenium ions have also been invoked to explain the products obtained by the lead tetraacetate oxidation of anils. When protons are available in systems where nitrenes are being generated then products consistent with nitrenium ions can be obtained. R. J. Sundberg et al. claim that the presence of acetic acid in triethyl phosphite solutions employed for the photochemical deoxygenation of aryl nitroso compounds leads to products consistent with the intermediacy of aryl nitrenium ions. These are presumably either formed by the protonation of the nitrene or the nitrene precursor. Sundberg et al. reported that the thermolysis of azides in a 50:4 mesitylene:trifluoroacetic acid mixture gave products which are apparently explained on the basis of nitrenium ions.

Sasaki et al. state that the photolysis and thermolysis of azide XX in methanol, gave results consistent with an intermediate nitrene. (Scheme 63).

However the product obtained could be XXI formed via a nitrenium ion arising by protonation of the nitrene by methanol as shown in Scheme 64. The authors' experimental evidence is consistent with either product.
Thus although there are many reactions which might generate a nitrenium ion the only ones which seem to unequivocally do so are the silver ion-assisted methanolation of N-t-butyl-N-chloroaniline and the deoxygenation of phenyl-t-butyl nitroxide. The other reactions may produce nitrenium ions but the case remains to be proved.

G. Nitrogen-Containing Reactive Intermediates in Heterocyclic Synthesis

The use of tervalent phosphorus reagents to deoxygenate nitro-compounds, first demonstrated by the reductive cyclisation of 2-nitrobiphenyl to carbazole has now become widespread, and five-, six- and seven-membered nitrogen-heterocycles are among the compounds synthesised by this method. Very similar results have been obtained by the thermolysis and photolysis of azides and this has led to the assumption that a nitrene is a common intermediate in these reactions. For simplicity the reactions which follow will be discussed in terms of a nitrene but generally there is no proof of the nature of the reactive intermediate.

The first reductive cyclisation of a nitro-compound to be performed using tervalent phosphorus reagents was the preparation of carbazole from 2-nitrodiphenyl. The corresponding thermolysis and photolysis of 2-azidobiphenyl have also been reported (Scheme 65).
Similar reactions giving five-membered nitrogen-heterocycles are observed when there is a suitable ortho-side-chain. Thus indoles\(^{128, 132}\) (Scheme 66) and triazoles\(^{128, 133, 134}\) (Scheme 67) have been prepared by the deoxygenation of the appropriate nitro-compounds.

In a similar fashion carbolines\(^{135}\) (Scheme 68), indazoles\(^{128, 133, 136}\) (Scheme 69), imidazoles\(^{137-139}\) (Scheme 70), anthranils\(^{137, 140}\) (Scheme 71), tetraazapentalenes\(^{128, 141}\) (Scheme 72) and benzoxazoles\(^{142}\) (Scheme 73) have been prepared in yields ranging from 40 to 95\%.
Scheme 68

Scheme 69

Scheme 70

Scheme 71
Many other cases of heterocyclic synthesis by this route have been described and clearly the method has found wide application. Generally the reactive intermediate is generated by deoxygenation of a nitro-group but occasionally thermolysis of an azide is used.

If the nitrene has the opportunity to form either a five- or a six-membered ring it will always give a five-membered ring. Thus the deoxygenation of 1-o-nitrophenylnaphthalene gave XXIII and not the six-membered ring product (XXII). (Scheme 74).

It is interesting that, as shown in Scheme 60, when the nitrene has the choice of reacting either with a nitrogen or a carbon it cyclises exclusively onto the nitrogen to form an indazole. Abramovitch et al observed a similar selectivity in the thermolysis of the corresponding azide, ascribing their result to the greater electron density on the
nitrogen as compared to the carbon, but Ning and his co-workers have described a system in which cyclisation takes place both on to carbon and on to nitrogen. (Scheme 75)

$$\begin{array}{c}
\text{H} \quad \text{H} \\
\text{N} \quad \text{O} \\
\text{N} \quad \text{O} \\
\text{I} \\
\text{+} \\
\text{NNH} \\
\text{N} \\
\text{25°h} \\
\end{array}$$

Scheme 75

Since nitrenes appear to prefer to react to give a five-membered as opposed to a six-membered ring the reductive cyclisation of 2-nitrophenyl phenyl sulphide to phenothiazine by triethyl phosphite in 60% yield is at first sight a surprising reaction. Closer examination of the reaction however reveals that initially a five-membered nitrogen-containing spirocyclic intermediate is formed and this then undergoes a 1, 2-sigmatropic sulphur shift to give the observed product. The sulphur shift becomes apparent when substituted diphenyl sulphides are studied. Thus deoxygenation of 2-nitrophenyl 4'-chlorophenyl sulphide (XXIV; R=Cl) gave 3-chlorophenothiazine (XXV; R=Cl) rather than 2-chlorophenothiazine (XXVI; R=Cl) via the spirocyclic intermediate (XXVII; R=Cl).

A similar reaction occurs when 2-azidophenyl 4'-chlorophenylsulphide (XXVIII; R=Cl) is thermolysed in decalin. (Scheme 76)

Similarly reductive cyclisation of 2-nitrophenyl 2'-chlorophenylsulphide (XXIX; R=Cl) gave 1-chlorophenothiazine (XXX; R=Cl) rather than 4-chlorophenothiazine (XXXI; R=Cl). (Scheme 77).
When both ortho positions in the starting sulphide are blocked the proton shift to give the phenothiazine product is impossible and a series of interesting alternative molecular rearrangements take place instead. For example deoxygenation of 2-nitrophenyl 2', 6'-diethoxy carbonylphenyl sulphide (XXVII) gave 1,4a-diethoxy-4aH-phenothiazine (XXVIII)\textsuperscript{152} which corresponds to the intermediate postulated in the rearrangement described above (Scheme 78).

\[
\begin{array}{c}
\text{CO}_2\text{Et} \quad \text{CO}_2\text{Et} \\
\text{XXVII} \\
\text{Scheme 78}
\end{array}
\]

The deoxygenation of 2-nitrophenyl 2', 6'-dimethylphenyl sulphide (XXIX) is thought to give rise to the biradical (XXX) which then couples to give 5,11-dihydro-4-methyl dibenzo[b, e][1, 4]-thiazepine (XXXI)\textsuperscript{152} rather than the isomeric 10,11-dihydro-4-methyl dibenzo[b, f][1, 4]thiazepine (XXXII) as shown in Scheme 79.

\[
\begin{array}{c}
\text{XXIX} \\
\text{Scheme 79}
\end{array}
\]
Similar results were obtained by thermolysis of the corresponding azide.

Deoxygenation of 2-nitrophenyl 2', 6'-dimethoxyphenyl sulphide (XXXIII) gave 1-methoxyphenothiazine (yield = 11%) and 1, 2-dimethoxyphenothiazine (yield = 47%)\(^1\) and it is thought that this latter product is formed via a novel 1,4-methoxyl shift as shown in Scheme 80.

\[
\text{XXXIII}
\]

Scheme 80

Again similar results were obtained from the thermolysis of the corresponding azide.

Photolysis of 2-azidophenyl 2', 6'-disubstituted phenyl sulphides
gave only the corresponding amines. Deoxygenation of 2-nitrophenyl 2-pyridyl sulphide and thermolysis of the corresponding azide gave only tars.\textsuperscript{153} However, when the nitro-group is in the pyridyl ring, the expected reaction is found to proceed\textsuperscript{154} (Scheme 81).

![Scheme 81]

Although the diphenyl sulphides give good yields of pheno-thiazines the corresponding \textit{ortho}-nitro or \textit{ortho}-azido diphenyl ethers do not generally give phenoxazines\textsuperscript{154, 155, 156}. The deoxy-
genation of 2-nitrophenyl 2'-chloro-6'-methylphenyl ether does however give 1-methylphenoxazine but in only 7\% yield\textsuperscript{155} (Scheme 82).

![Scheme 82]

Thermolysis of 2-azidophenyl 2', 6'-dimethoxyphenyl ether gave 4-methoxyphenoxazine (yield = 35\%) and 1, 2-dimethoxyphenoxazine (yield = 15\%).\textsuperscript{157} (Scheme 83). The mechanism is presumed to be similar to that for the reaction of the corresponding sulphide which was discussed above. It is interesting that in this case it is the 4-methoxyphenoxazine which is observed in contrast to the 1-methoxyphenothiazine observed in the case of the corresponding sulphide. Thermolysis of 2-azidophenyl 2', 4', 6'-trimethylphenyl ether gave 5, 11-dihydro-1, 4-dimethyl-dibenzo[\textit{b}, \textit{c}][1, 4]oxazepine (XXXIV) (yield = 15\%) and the bis-ether (XXXV) (yield = 1\%)\textsuperscript{157} (Scheme 84). The oxazepine is probably formed by the same biradical coupling.
mechanism postulated above for the sulphur case (Scheme 79). The origin of the bis-ether is however less obvious.

Although the thermolysis of 2-azidodiphenyl sulphone gives phenothiazine-5,5-dioxide\textsuperscript{156} the deoxygenation of the corresponding nitro-compound gives only tars.\textsuperscript{158} (Scheme 85).
The thermolysis of 2-azidophenyl 2', 4', 6'-trimethylphenyl sulphone also gave only tars but the thermolysis of 2-azidophenyl 4'-chlorophenyl sulphone gave 2- and 3-chlorophenothonthiazine-5,5-dioxide (Scheme 86) and the thermolysis of 2-azidophenyl 4'-t-butylphenyl sulphone gave 2- and 3-t-butylphenothiazine-5,5-dioxide (Scheme 87).
Thus in contrast to the sulphides which give only the "rearranged product" the sulphones give both the "rearranged" and "unrearranged" products.

Deoxygenation of 2-nitrophenyl phenyl amines does not appear to give phenazines unless the vulnerable N-H bridge is protected. Thus N-acetyl-2-nitro-2'-methylthiodiphenylamine (XXXVI) reacted by rearrangement of the spirodienyl intermediate to give both possible hydroaromatic species. One of these undergoes demethylthiolation while the other tautomerises to give 1-thiomethyl-5-acetyl-5,10-dihydrophenazine (XXXVII) as shown in Scheme 88.

However Bacon and Hamilton obtained no phenazine when they deoxygenated N-acetyl-4-chloro-4'-methyl-2-nitro diphenylamine but instead they found the benzimidazole (XXXVIII) (yield = 20%) and the ring-expanded product (XXXIX) (yield = 11%) (Scheme 89).
Deoxygenation of the corresponding N-methyl compound (XL) gave benzimidazole (XLI) (yield = 36%) and the unrearranged phenazine (XLII) (yield = 12%) (Scheme 90).

Deoxygenation of the related N-acetyl-4-chloro-2'-methoxy-2-
nitro diphenylamine (XLIII) gave benzimidazole (XLIV) (yield = 22%); 2-chlorophenazine (XLV) (yield = 25%) and a trace of a chloromethoxyphenazine isomer which was not identified.

Thus such evidence as is available concerning these reactions in the diphenylamine series suggests that N-acetyl compounds undergo rearrangement via a spirocyclic intermediate while N-methyl compounds undergo either direct insertion or an N shift in a spirocyclic intermediate. In the latter case the products would be accounted for by the migratory aptitudes of the groups concerned as compared to the N centre.

The rearrangements which occur when 2-azidodiphenyl methanes are thermolysed have been elucidated by Jones and his co-workers. For example thermolysis of the azide (XLVI) yields the ring expanded product (XLVII) in 38% yield\(^{161}\) (Scheme 92).
and

\[
\text{XLVII} \quad /)
\]

\[
\text{XLVIII} \quad 3\%
\]
Thermolysis of 1-(2-azidobenzyl)naphthalene gave the two possible ring expanded products (XLVIII and XLIX) and also the rearranged products (L and LI)$^{162}$ as set out in Scheme 93.

Scheme 93

Jones and Garde suggest that the rearranged products (L and LI)
arise via the aziridine intermediate (LII), which can be written as the more polar structures (LIII) and (LIIV). (LIIV) is equivalent to the spirocyclic intermediate proposed by Cadogan in the rearrangement of diphenylsulphides. Kametami and his co-workers \(^{163}\) have recently reported the isolation of a stable aziridine intermediate from the products of the deoxygenation of a related system.

Jones and Carde have also shown that thermolysis of 2-(2-azidobenzyl)naphthalene and the corresponding 5-, and 6-(2-azidobenzyl)tetraline gave a similar mixture of ring-expanded and "rearranged" products. \(^{162}\)

Thermolysis of 2-azidobenzophenone has been shown to give 3-phenylanthranil \(^{156}\) by nitrene attack on the electron-rich oxygen (Scheme 94)

\[
\text{Scheme 94}
\]

Thermolysis of anthranils themselves has been postulated to give nitrenes \(^{164}\) and Kwok and Pranc \(^{165}\) have shown that 3-(2,4-dimethoxyphenyl)anthranil (LV) gives 2,4-dimethoxyacridone (LVI). This may be interpreted as attack of the nitrene at the benzene ring which is in this case activated to electrophilic attack. Since the product is 2,4-dimethoxyacridone (LVI) and not the unrearranged isomer (LVII) the spirocyclic intermediate is again postulated. (Scheme 95).
Rearrangements of the type discussed above are not confined to reactions involving nitrenes. For example, the carbonium ion generated by the treatment of the carbinol (LVIII) with polyphosphoric acid undergoes rearrangement as shown in Scheme 96.
Another similar rearrangement is the Hayashi rearrangement of carboxybenzophenones in strong acid\textsuperscript{167,168} as shown in Scheme 97.

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{OH} \\
\text{COH}_2 & \quad \text{H}^+ \\
\text{Me} & \quad \text{O} & \quad \text{OH} \\
\text{C} & \quad \text{O} & \quad \text{Cl} & \quad \text{Cl} \\
\text{Me} & \quad \text{O} & \quad \text{OH} & \quad \text{Cl} & \quad \text{Cl} \\
\text{COH}_2 & \quad \text{O} & \quad \text{OH}
\end{align*}
\]

Scheme 97

Rearrangements involving spirocyclic intermediates are well known\textsuperscript{169} in other systems. A well known example of a reaction involving a spirocyclic intermediate formed by nucleophilic attack is the Smiles rearrangement\textsuperscript{170} (Scheme 98). The fact that compounds with a substituent in the 6 position rearrange $10^5$ to $10^6$ times faster than compounds without such a substituent was explained\textsuperscript{171} by conformational factors.
Intramolecular free radical attack on a ring has also been shown to proceed via a spirocyclic intermediate. For example, pyrolysis of 2-phenoxybenzoyl peroxide (LIX) gave phenyl salicylate via the [5, 5] spirocyclic radical (LX)\textsuperscript{172} (Scheme 99).

Ring expansion of aryl nitrene to give seven-membered nitrogen heterocycles is well known and an example which arises from the thermolysis of 1-(2-azidobenzyl)naphthalene has been discussed above (Scheme 93). A more widely known reaction is the ring expansion of aryl nitrenes in the presence of primary or secondary amines and this is generally considered to proceed via the aryl nitrene-7-azabicyclo[4,1,0]hepta-2,4,6-triene equilibrium\textsuperscript{1,173,174} as set out in Scheme 100.
Similar results are obtained by the deoxygenation of nitro- and nitrosobenzenes.

Although reaction of triethyl phosphite with 2-nitrodiphenyl ethers does not generally give phenoxazines in some cases the reaction provides a route to a series of P, N, O heterocycles (see example below). The reaction is assumed to go by interception of the spirocyclic intermediate with excess triethyl phosphite as shown in Scheme 101.
Scheme 101
H. The Question of Nitrene Participation

Although it is very difficult to account for the products obtained on the thermolysis of most azides without invoking a discrete nitrene there are several possible reaction mechanisms which account for the products observed in the deoxygenation of nitro- and nitroso-compounds without involving a discrete nitrene intermediate. In fact the presence of a nitrene in these reactions is generally assumed because in most of the early examples studied the same products were obtained when the corresponding azide was thermolysed. For example the deoxygenation of 2-nitrophenyl 4'-chlorophenyl sulphide and the thermolysis of 2-azidophenyl 4'-chlorophenyl sulphide both give 3-chlorophenothiazine as discussed above (Scheme 76, R=Cl).

However examples are also known where the products of the two reactions differ. Thus the thermolysis of 2-azido-2',4',6'-trimethylbiphenyl gave 8,10-dimethylphenanthridine but the deoxygenation of the corresponding nitro-compound gave only tars (Scheme 102).

Similarly the deoxygenation of 2-nitrophenyl 4'-chlorophenyl sulphone gave only tars while the thermolysis of 2-azidophenyl 4'-chlorophenyl sulphone gave a mixture of 2- and 3-chlorophenothiazine-5,5-dioxides (Scheme 86, above). However in these examples it may be that the nitrene is formed in both cases and is stable under the thermolysis conditions but not under the deoxygenation conditions.
The products are stable under the reaction conditions. 158

A more quantitative approach involves the thermolysis of 2-azidophenyl 2',6'-dichlorophenyl sulphide and the deoxygenation of the corresponding nitro-compound to give 1- and 4-chlorophenothiazines as shown in Scheme 103.

Thermolysis of the azide in decalin at 150° gave 1-chlorophenothiazine (40%) and 4-chlorophenothiazine (5%) whereas deoxygenation of the corresponding nitro-compound by triethyl phosphite gave 1-chlorophenothiazine (35%) and 4-chlorophenothiazine (45%). These results, obtained by Cadogan and Kulik 152, were the first to show a real difference between deoxygenation and azide thermolysis. The authors suggested that the dipolar species (LXI) might be the intermediate in the deoxygenation. Holliman and his co-workers 181 confirmed these results and showed that thermolysis of the azide in triethyl phosphate gave 1-chlorophenothiazine (44%) and 4-chlorophenothiazine (23%). The similarity of the results obtained by deoxygenation and by thermolysis of the azide in triethyl phosphate led them to support the intermediacy of the dipolar species (LXI). This, a possible intermediate in the deoxygenation, could arise by reaction of the nitrene with solvent on thermolysis of the azide in triethyl phosphate.
In the same paper Cadogan and Kulik\textsuperscript{152} showed that the thermolysis of 2-azidophenyl 2'-chloro-6'-methylphenyl sulphide in decalin gave only 1-methylphenothiazine (32\%) while deoxygenation of the corresponding nitro-compound by triethyl phosphite gave 1-methylphenothiazine (19\%) and 4-methylphenothiazine (26\%). Holliman and his co-workers\textsuperscript{181} again confirmed these results and showed that thermolysis of the azide in triethyl phosphate gave 1-methylphenothiazine (13\%) and 4-methylphenothiazine (27\%). Again the intermediacy of a dipolar species such as (LXI) is suggested.

Holliman and his co-workers have also described the cyclisation of 3, 5-dideutero-2-nitroso- and 2-azido-3'-substituted biphenyls, at 150-155\textdegree C with triethyl phosphite in various solvents. The 1- and 3-substituted carbazoles were obtained and the $d_2/d_0$ ratio of each determined. When the reactions were carried out in triethyl phosphate as solvent the ratio for each isomer was the same, indicating that there must be a common intermediate. However when the reaction was performed in decalin or chlorobenzene the ratios were different, indicating that there was no common intermediate. The authors interpret these results by suggesting that the intermediate in the deoxygenation of nitroso compounds is the dipolar species (LXII).
They also state, although no results are given, that a similar technique shows that the nitroso-compound is an intermediate in the deoxygenation of a nitro-compound. This has always been considered a possibility but it is extremely difficult to prove since nitroso-compounds react much faster with tervalent phosphorus reagents than the corresponding nitro-compound. However Katritzky et al.\textsuperscript{182} have trapped the intermediate nitroso compound during the deoxyg enation of 3-methyl-7-nitroanthranil (LXIII) (Scheme 104). It has previously been shown that nitroso-compounds such as (LXIV) undergo rearrangement to the benzofurazan (LXV).\textsuperscript{183}

![Scheme 104](image)

As mentioned above aryl azides photolysed in the presence of amines and the corresponding nitro- and nitroso-compounds deoxygenated in the presence of amines all give the ring-expanded azepines (Scheme 100). When the azide and the nitro-compound are substituted in the meta-position two isomeric azepines are formed, e.g. with diethylamine - the 4-substituted 2-diethylamino-3H-azepine (LXVI) and the 6-substituted 2-diethylamino-3H-azepine (LXVII) as shown in Scheme 105.
Recently, it has been shown that the two reactions produce (within experimental error) the same ratio of 4-substituted azepine to 6-substituted azepine for a given substituent. This has been interpreted as quantitative proof of the existence of a common intermediate in these reactions which may be a nitrene.

Recently Abramovitch and his co-workers have shown that the deoxygenation of pentafluoronitrosobenzene in the presence of an olefin leads to the aziridine (LXVIII) (Scheme 106). However, after some discussion, they discount the intermediacy of the cyclic compound (LXIX) formed by reaction of the dipolar species (LXX) with the olefin although the evidence is not entirely conclusive.
In other systems there is an equal paucity of evidence. For example Lwowski, Breslow and their co-workers \(^{185,186}\) have shown that the thermolysis and photolysis of ethyl azidoformate in 2-methylbutane and the \(\alpha\)-elimination of the \(N\)-(p-nitrobenzenesulphonyloxy)urethane in 2-methylbutane all give approximately the same ratio of primary:secondary:tertiary insertion products. Thus it looks as though the same intermediate may be present in this case.

On the other hand Jones\(^ {187}\) has shown that when the aziridine (LXXI) is thermolysed in the presence of 1, 3-dimethoxybenzene the azepine (LXXII) and the insertion product (LXXIII) are formed in a ratio of about 2:1. (Scheme 107). On the other hand lead tetraacetate oxidation of \(N\)-aminophthalimide in the presence of 1, 3-dimethoxybenzene gave the insertion product with only a trace of the azepine. Addition of acetic acid to the aziridine thermolysis caused the insertion product to increase at the expense of the azepine and it is known that
Acetic acid is produced during lead tetraacetate oxidations. The similarity of the oxidation products to the thermolysis products obtained in the presence of acetic acid suggest that the intermediate may be the nitrenium ion formed by protonation of the first-formed nitrene although other interpretations are possible.

Thus the evidence for the participation of nitrenes in these reactions is somewhat contradictory. On the one hand Holliman and his co-workers\textsuperscript{181} state that the intermediate in the deoxygenation of nitroso-compounds is the dipolar intermediate but on the other hand there is much evidence - both quantitative and qualitative - that azide thermolyses and nitro deoxygenations have a common intermediate.

The answer may be that many different mechanisms are possible depending on the system. Thus when nitrosobenzene is deoxygenated in diethyl amine the dipolar intermediate may be formed but because there is no easy reaction open to it it dissociates to the nitrene. On the other hand the dipolar intermediate formed when 2-nitrosobiphenyl is deoxygenated reacts easily with the other ring to give carbazole before it can dissociate to the nitrene. In other systems the reaction may go by either route, by both routes or by a totally different route - perhaps involving the intermediate $-\text{N} - \text{O} - \dagger\text{P(OEt)}_3$. 

\textsuperscript{181}
I. Programme of Research

The question of nitrene participation in deoxygenation reactions is difficult to settle because, by and large the same products are obtained in deoxygenations and the corresponding azide thermolyses. Only the thermolyses of 2-azidophenyl 2', 6'-dichlorophenyl sulphide and 2-azidophenyl 2'-chloro-6'-methylphenyl sulphide and the corresponding deoxygenations show different products between azide-thermolysis and nitro-group deoxygenation. It was considered that another system which might give rise to different products would be the thermolysis of 2-azidophenyl 3'-substituted phenyl sulphides and the corresponding deoxygenations. In this case the spirocyclic intermediate might rearrange to give either the 2- or the 4-substituted phenothiazine and the detection of quite small differences in the nature of the intermediate might be possible. Similarly it might be possible to confirm the intermediacy of the nitroso-compound. It was further believed that a study of the isomer ratios might give information on the nature of the spirocyclic intermediate. These investigations would be greatly facilitated by the availability of High Speed Liquid Chromatography (HSLC) which enables rapid separation and detection of isomers such as these.

The thermolysis of aryl 2-azidophenyl sulphones appears to give mixtures of substituted phenothiazine-5, 5-dioxides and HSLC should provide a convenient method of determining the isomer ratios. It was of interest to see if the occurrence of rearrangement or non-rearrangement was dependent on the nature or position of the substituent.

There has been a lot of interest recently in nitrenium ions and it might be possible to generate them in these systems for comparison with the analogous systems involving nitrene intermediates.
2. EXPERIMENTAL

A. Instrumentation

B. Preparation of Materials

(i) General materials

(ii) Preparation of miscellaneous reagents

(iii) Thiophenols

(iv) Aryl 2-nitroaryl sulphides

(v) Aryl 2-nitrophenyl sulphones

(vi) Aryl 2-aminophenyl sulphides and sulphones

(vii) Aryl 2-azidophenyl sulphides and sulphones

(viii) Phenothiazines

(ix) Phenothiazine-5, 5-dioxides

(x) Aryl 2-(hydroxyamino)phenyl sulphides

(xi) Aryl 2-nitrosophenyl sulphones

C. High Speed Liquid Chromatography

(i) Introduction

(ii) Equipment

(iii) Mobile phases

(iv) Preparation of columns

(v) Systems used

(vi) Measurement of yields of products

(vii) Identification of products

D. Reactions

(i) Methods

(ii) Products of the cyclisations of aryl 2-nitro-, 2-nitroso- and 2-azidophenyl sulphides.

(iii) Products of the thermolyses of aryl 2-azidophenyl sulphones
(iv) The stability of phenothiazines and phenothiazine-5, 5-dioxides under the reaction conditions  123
(v) Results corrected for the destruction of products  129
Symbols and Abbreviations

h   hour
min minute
m. p. melting point
b. p. boiling point
v/v volume/volume ratio
w/v weight/volume ratio
Ref reference
lit literature
HSLC High speed liquid chromatography
i. r. infra red
\( \nu \) wavenumber
n. m. r. nuclear magnetic resonance
u. v. ultra violet
g. l. c. gas liquid chromatography
2. EXPERIMENTAL

A. Instrumentation

Infrared spectra were obtained from a Perkin-Elmer 157G Spectrophotometer with either a Nujol mull or a liquid film on sodium chloride plates. Polystyrene was used to give a reference peak at 1603 cm\(^{-1}\).

Proton magnetic resonance spectra were obtained from (i) a Varian HA100 instrument operating at 100 MHz and (ii) a Varian EM360 instrument operating at 60 MHz. Chemical shift values were recorded on the \(\tau\) scale relative to tetramethylsilane, at \(\tau = 0\). Phosphorus (\(^{31}\)P) magnetic resonance spectra were obtained from a Varian XL-100 spectrophotometer using noise decoupling of protons.

Mass spectra and exact masses were obtained from an A.E.I. MS902 Spectrometer.

Microanalyses were carried out on a Perkin-Elmer Elemental Analyser 240 by Mr. J. Grunbaum, University of Edinburgh.

Melting points were obtained from a Kofler hot stage microscope and a Gallenkamp melting point apparatus.

Ultraviolet spectra were recorded on a Unicam SP800 Ultraviolet and Visible Spectrophotometer using a matched pair of 1.0 cm quartz cells.

A Pye 104 Gas Chromatograph fitted with a flame ionisation detector was used for gas liquid chromatography. A 5 ft by 1/8 inch 20% Apiezon column was found to be most useful.

B. Preparation of Materials

(i) General materials

Cumene was dried and deperoxidised by standing over sodium wire. Decalin was redistilled from sodium under nitrogen and stored over molecular sieve. Triethyl Phosphate was redistilled under reduced pressure and stored over molecular
sieve. Dry ether (moisture limit -0.02%) was used and if necessary this was dried over sodium wire. Light petroleum (b. p 40-60°) was redistilled. Toluene was shaken with sulphuric acid (d 1.84) to remove sulphur compounds, washed with water, dried and redistilled. It was stored over sodium wire. Anisole was redistilled before use.

Triethyl phosphite was redistilled from sodium wire under a reduced pressure of dry nitrogen. Diethyl methyl phosphonite was obtained from the Chemical Defence Establishment, Porton Down and was used without further treatment.

Alumina (Laporte Industries, Type H, 100-200 mesh) was used for column chromatography and, after deactivation by the addition of 6% water by weight, for dry column chromatography.

All other solvents and reagents were obtained commercially.

(ii) Preparation of miscellaneous reagents

**Silver carbonate on celite**

Following the method of Fetison and Golfier,

a solution of sodium carbonate decahydrate (30 g, 0.105 moles) in water (300 ml) was slowly added to a rapidly stirred suspension of Celite (30.9 g) in a solution of silver nitrate (35.4 g, 0.208 moles) in water (200 ml). The mixture was stirred for 10 minutes and then filtered. The yellow solid obtained was washed with water until the washings were neutral to litmus, briefly washed with acetone and finally with dichloromethane. On drying in vacuo the product (59g) was obtained as a yellow solid.

**2-Chloro-3-nitrotoluene**

This was prepared by the method of Holleman.

2-Amino-3-nitrotoluene (5 g, 0.033 moles) dissolved in a mixture of glacial acetic acid (66 ml) and hydrochloric acid (d 1.16, 13 ml) was cooled to 0°, and a cooled solution of sodium nitrite (4.6 g, 0.067 moles) in water (10 ml) was added slowly, with stirring. The resulting diazotised solution was stirred for 1.5 h at 0°. A mixture of cupric sulphate (4.1 g, 0.026 moles), potassium chloride (7.4 g, 0.099 moles), copper powder (6.6 g, 0.104 moles), sulphuric acid
(d 1.84, 3.6 ml), hydrochloric acid (d 1.16, 3.3 ml) and water (76 ml) was boiled under reflux for 1.5 h. then cooled to room temperature. The cold diazotised solution was added slowly, with stirring, and the resulting mixture was boiled under reflux with stirring for 30 min and then steam distilled. The distillate was extracted into ether and the oil obtained on evaporation chromatographed on alumina with light petroleum (b.p. 40-60°C):ether (95:5, v/v) to give 2-chloro-3-nitrotoluene (5.1 g, 90%) as a yellow liquid. This was used without further purification in the preparation of 2-nitro-6-methylphenyl phenyl sulphide (see below).

2,6-Dimethoxynitrobenzene

This was prepared from 2,6-dihydroxynitrobenzene by the method of Vogel. 2,6-Dihydroxynitrobenzene (37 g, 0.24 moles) was mixed with a solution of sodium hydroxide (20 g, 0.5 moles) in water (190 ml). The mixture was mechanically stirred at 0°C and dimethyl sulphate (61.5 g, 0.49 moles) added slowly over 1 h. The mixture was stirred at 0°C for 1.5 h and then boiled under reflux with stirring for 3 h. After cooling the reaction mixture was diluted with water and a black solid obtained by filtration. Recrystallisation from ethanol gave 2,6-dimethoxynitrobenzene (23.32 g, 53%) as pale yellow crystals (m.p. 130°C, lit. 191 130-130.5°C).

2,6-Dimethoxyaniline

This was prepared by the reduction of 2,6-dimethoxynitrobenzene according to the method of Kulik. Hydrochloric acid (6.1 g, d 1.16) was added slowly to a mixture of 2,6-dimethoxynitrobenzene (46.1 g, 0.25 moles), iron pin dust (56.5 g, 1.01 moles), ethanol (140 ml) and water (110 ml). This mixture was mechanically stirred whilst being boiled under reflux under nitrogen for 18 h. The reaction mixture was neutralised with dilute sodium hydroxide solution and filtered through Celite. The Celite was leached with chloroform and the filtrate partially evaporated to remove organic solvents then extracted into chloroform. After drying over anhydrous magnesium sulphate the chloroform solution was evaporated to give a black oil, which was distilled at 154-160°C at 32 mmHg to give 2,6-dimethoxyaniline (17.83 g, 46%) as a colourless solid (m.p.
2-Chloro-3-nitroanisole

This was prepared by the chlorination of m-nitrophenol following the method of Henley and Turner,\textsuperscript{193} to give 2-chloro-3-nitrophenol which was then methylated by diazomethane. m-Nitrophenol (28.65 g, 0.21 moles) was melted by surrounding it with a jacket of boiling xylene and chlorine gas was passed through the molten mass. After 37 minutes the weight had increased by 6.7 g (equivalent to 0.094 moles of chlorine) and the reaction mixture was cooled and dissolved in 10% sodium hydroxide solution (100 ml). Hydrochloric acid solution (50% v/v, 62 ml) was added and the mixture filtered to give 4-chloro-3-nitrophenol (2.55 g, 7% after recrystallisation from dilute hydrochloric acid). Addition of an excess of hydrochloric acid (d 1.16) to the filtrate gave 2-chloro-3-nitrophenol (2.46 g, 7%; m.p. 119-120\degree, lit\textsuperscript{192} 120\degree - after recrystallisation from dilute hydrochloric acid). Methylation by diazomethane generated in the conventional manner from N-methyl-N-nitroso-2-toluenesulphonamide gave 2-chloro-3-nitroanisole (90%, m.p. 92-93\degree, lit\textsuperscript{194} 93-94\degree).

\textit{t-Butyl hypochlorite}

This was prepared by the method of Walling and McGuinness.\textsuperscript{195} \textit{t-Butanol} (209 g, 2.8 moles), acetic acid (170 g, 2.8 moles) and aqueous sodium hypochlorite (11, 10-14% active chlorine) were mixed and stirred at 0\degree. The organic layer was separated, washed with 5% sodium carbonate solution, dried over anhydrous magnesium sulphate and distilled to give \textit{t-butyl hypochlorite} (109 g, 36%) as a yellow liquid (b.p. 79\degree, lit\textsuperscript{196} 79.6\degree).

\textit{o-Nitroacetanilide}

This was prepared by the method of Holleman and Sluiiter.\textsuperscript{197} \textit{o-Nitroaniline} (40 g, 0.29 moles), acetic anhydride (90 g, 0.88 moles) and acetic acid (90 g, 1.5 moles) were mixed and boiled under reflux for 6.5 h. The mixture was cooled, poured into water (800 ml) and the resulting yellow crystals filtered off and recrystallised from ethanol. They were then repeatedly extracted with boiling hexane to give pale yellow crystals which were recrystallised from hexane/dichloromethane to give \textit{o-nitroacetanilide} (24.3 g, 47%, m.p. 75-76\degree, lit\textsuperscript{192} 75\degree).
N-Chloro-2-nitroacetanilide

This was prepared by the method of Chalsty and Israelstam. 198 o-Nitroacetanilide (4 g, 0.022 moles) and t-butyl hypochlorite (5 g, 0.046 moles) were mixed with a solution of borax (4 g) in methanol (130 ml) and stirred for 15 minutes. The reaction mixture was then poured into water (700 ml) and the resulting colloid extracted into chloroform. After being dried over anhydrous magnesium sulphate the chloroform solution was evaporated to give a yellow solid which was recrystallised from hexane/dichloromethane to give N-chloro-2-nitroacetanilide (3.8 g, 80%) as yellow crystals (m.p. 78-79.5°, lit 198 80-81°). (Found: C, 44.8; H, 3.3; N, 13.0. C₈H₇ClN₂O₃ requires C, 44.8; H, 3.3; N, 13.05%).

(iii) Thiophenols

These were prepared by the general method of Suter and Hansen 199 as exemplified in the case of 3-chlorothiophenol. Water (50 ml) was added to a warmed mixture of 3-chloroaniline (25.5 g, 0.2 mole) and hydrochloric acid (d 1.16) (50 ml) and the mixture stirred at 0° whilst a solution of sodium nitrite (14.7 g, 0.21 moles) in water (61 ml) was added slowly so as to keep the temperature below 5°. The mixture was stirred at 0° for 1 h, neutralised with sodium acetate and then stirred at 0° for a further hr before being added slowly with stirring, to a solution of potassium ethyl xanthate (63.5 g, 0.4 moles) in water (280 ml) maintained at 70-80°. The solution was stirred at this temperature for 1 h then cooled and a dark red oil separated. The aqueous layer was extracted three times with ether and the ether extracts combined with the oil. The oil obtained on evaporation was boiled for 3 h under reflux with a solution of potassium hydroxide (23 g, 0.41 moles) in ethanol (410 ml) containing glucose (4 g). The reaction mixture was evaporated and acidified with dilute sulphuric acid. Zinc dust (4 g) was added and the mixture steam distilled. Ether extraction of the distillate gave, on evaporation, a dark red oil which was distilled at 38-40°/0.4 mmHg (lit 200 205-207°) to give 3-chlorothiophenol.
as a yellow liquid.

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>b. p. °/mmHg</th>
<th>Lit. b. p. °/mmHg</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me</td>
<td>38</td>
<td>29-52/0.1</td>
<td>192-194/760</td>
<td>201</td>
</tr>
<tr>
<td>3-Me</td>
<td>35</td>
<td>22-25/0.2</td>
<td>107.5/50</td>
<td>202</td>
</tr>
<tr>
<td>3-OMe</td>
<td>55</td>
<td>54-56/0.1</td>
<td>224-225/760</td>
<td>203</td>
</tr>
<tr>
<td>2-CF₃</td>
<td>53</td>
<td>73-75/20</td>
<td>62-64/10</td>
<td>204</td>
</tr>
<tr>
<td>3-CF₃</td>
<td>72</td>
<td>70-75/31-3</td>
<td>84-86/40</td>
<td>205</td>
</tr>
<tr>
<td>4-CF₃</td>
<td>42</td>
<td>80-82/28</td>
<td>60-61/13</td>
<td>206</td>
</tr>
<tr>
<td>2,6-diCl</td>
<td>67</td>
<td>54-56/0.4</td>
<td>150-152/15</td>
<td>153</td>
</tr>
<tr>
<td>2,6-diOMe</td>
<td>79</td>
<td>m. p. 85-86°</td>
<td>m. p. 85-86°</td>
<td>207</td>
</tr>
</tbody>
</table>

(iv) **Aryl 2-nitroaryl sulphides**

These were prepared by the general method of Galt and Loudon as exemplified in the case of 2-nitrophenyl 4'-methylphenyl sulphide. A solution of sodium hydroxide (8.5 g, 0.21 moles) in water (7 ml) was added slowly to a solution of o-chloronitrobenzene (30.1 g, 0.19 moles) and p-methylthiophenol (25.2 g, 0.20 moles) in ethanol (70 ml) and the mixture boiled under reflux for 1 h. Cooling and filtration gave a mass of yellow crystals which were washed with hot water and recrystallised from ethanol to give 2-nitrophenyl 4'-methylphenyl sulphide (41.96 g, 90%) as yellow crystals (m. p. 88-89°, lit m. p. 89-90°).
<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
<th>m. p. °</th>
<th>lit m. p. °</th>
<th>Ref</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>2-Me</td>
<td>90</td>
<td>89</td>
<td>81-82</td>
<td>152</td>
<td>63.7</td>
<td>4.6</td>
<td>5.8</td>
</tr>
<tr>
<td>H</td>
<td>3-Me</td>
<td>85</td>
<td>84-85</td>
<td>86</td>
<td>209</td>
<td>63.65</td>
<td>4.5</td>
<td>5.7</td>
</tr>
<tr>
<td>H</td>
<td>2-OMe</td>
<td>85</td>
<td>118.5-</td>
<td>118-119</td>
<td>152</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>3-OMe</td>
<td>87</td>
<td>121-122</td>
<td>-</td>
<td>-</td>
<td>59.7</td>
<td>4.4</td>
<td>5.1</td>
</tr>
<tr>
<td>H</td>
<td>4-OMe</td>
<td>82</td>
<td>95-96</td>
<td>94</td>
<td>208</td>
<td>59.8</td>
<td>4.2</td>
<td>5.4</td>
</tr>
<tr>
<td>H</td>
<td>2-Cl</td>
<td>68</td>
<td>121-122</td>
<td>122-123</td>
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<td>54.4</td>
<td>3.1</td>
<td>5.1</td>
</tr>
<tr>
<td>H</td>
<td>3-Cl</td>
<td>87</td>
<td>106.5-</td>
<td>107-108</td>
<td>210</td>
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<tr>
<td>H</td>
<td>4-Cl</td>
<td>90</td>
<td>93-94</td>
<td>97</td>
<td>208</td>
<td>52.3</td>
<td>2.7</td>
<td>4.4</td>
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<tr>
<td>H</td>
<td>2-CF₃</td>
<td>71</td>
<td>94-95</td>
<td>-</td>
<td>-</td>
<td>52.2</td>
<td>2.7</td>
<td>4.7</td>
</tr>
<tr>
<td>H</td>
<td>3-CF₃</td>
<td>74</td>
<td>86-87</td>
<td>-</td>
<td>-</td>
<td>51.9</td>
<td>2.7</td>
<td>4.4</td>
</tr>
<tr>
<td>H</td>
<td>4-CF₃</td>
<td>57</td>
<td>81-82</td>
<td>-</td>
<td>-</td>
<td>51.9</td>
<td>2.7</td>
<td>4.4</td>
</tr>
<tr>
<td>H</td>
<td>2-pyrindyl</td>
<td>78+</td>
<td>72-73</td>
<td>70-71</td>
<td>153</td>
<td>52.2</td>
<td>2.7</td>
<td>4.7</td>
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<tr>
<td>H</td>
<td>2,6-diCl</td>
<td>49</td>
<td>126-127</td>
<td>123</td>
<td>152</td>
<td>52.2</td>
<td>2.7</td>
<td>4.7</td>
</tr>
<tr>
<td>H</td>
<td>2,6-di</td>
<td>63</td>
<td>165-166</td>
<td>165</td>
<td>152</td>
<td>52.2</td>
<td>2.7</td>
<td>4.7</td>
</tr>
</tbody>
</table>

6-OMe
| H  | 91        | bp 160° / | 65° / 0.06 | 212  | 261.045513 |
| 4-OMe | .2mmHg | mmHg      |           |       | 261.045960 |
| 6-MeH | 64        | 77.5-78.5 | 78-79     | 211  |           |
Footnotes to Table 2:

* Upper row corresponds to found values, lower row to calculated values.

† The reaction mixture was boiled under reflux for 24 hr and the product was purified by chromatography on deactivated alumina with ether.

(v) Aryl 2-nitrophenyl sulphones

These were prepared by the oxidation of the corresponding sulphide with (i) hydrogen peroxide in glacial acetic acid or (ii) m-chlorochloroperbenzoic acid.

Method (i) is exemplified by the case of 2-nitrophenyl 4'-methylphenyl sulphone. 2-Nitrophenyl 4'-methylphenyl sulphide (12.2 g, 0.05 moles) was dissolved in hot acetic acid (90 ml) and the solution heated on a boiling water bath. Hydrogen peroxide (30% w/v) (28 ml, 0.25 moles) was added slowly with stirring and the mixture stirred for 3 h on the boiling water bath. At the end of this time sufficient hot water was added to just produce crystals and the mixture allowed to cool. The colourless crystals which formed were filtered and recrystallised from ethanol to give 2-nitrophenyl 4'-methylphenyl sulphone (11.74 g, 82%, m. p. 155-157°, lit 213 156-157°).

Method (ii) is exemplified by the case of 2-nitrophenyl 3'-trifluoromethylphenyl sulphone. 2-Nitrophenyl 3'-trifluoromethylphenyl sulphide (3 g, 0.01 moles) and m-chloroperbenzoic acid (85%, 4.35 g, 0.021 moles) were dissolved in 75 ml dichloromethane and boiled under reflux for 8 h. The reaction mixture was diluted to about 1 l with dichloromethane and shaken with 10% sodium hydroxide solution, twice with sodium sulphite solution and finally with water. The organic layer was dried over anhydrous magnesium sulphate and on evaporation gave colourless crystals which were recrystallised from ethanol to give 2-nitrophenyl 3'-trifluoromethylphenyl sulphone (2.12 g, 64%, m. p. 98-99°) (Found: C, 47.2; H, 2.5; N, 3.8.

C\textsubscript{13}H\textsubscript{8}F\textsubscript{3}NO\textsubscript{4}S requires C, 47.1; H, 2.4; N, 4.2%).
### Table 3  Aryl 2-nitrophenyl sulphones

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>m.p.</th>
<th>lit m.p.</th>
<th>Ref.</th>
<th>Method</th>
<th>Analysis (%)*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>°C</td>
<td>°C</td>
<td></td>
<td></td>
<td>C  H   N</td>
</tr>
<tr>
<td>2-Me</td>
<td>45</td>
<td>146</td>
<td>144-145</td>
<td>209  (i)</td>
<td></td>
<td>53.5 3.9 4.5</td>
</tr>
<tr>
<td>3-Me</td>
<td>77</td>
<td>114-115</td>
<td>118-119</td>
<td>214  (i)</td>
<td></td>
<td>53.2 3.8 4.8</td>
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<tr>
<td>2-OMe</td>
<td>84</td>
<td>120-121</td>
<td>-</td>
<td>-     (ii)</td>
<td></td>
<td></td>
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<tr>
<td>3-OMe</td>
<td>90</td>
<td>92.5-</td>
<td>-</td>
<td>-     (i)</td>
<td></td>
<td>53.5 3.9 4.5</td>
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<td></td>
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<td>93.5</td>
<td></td>
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</tr>
<tr>
<td>4-OMe</td>
<td>-</td>
<td>149-150</td>
<td>149.5</td>
<td>215  (i)</td>
<td></td>
<td>53.5 3.9 4.5</td>
</tr>
<tr>
<td>2-Cl</td>
<td>82</td>
<td>154-155</td>
<td>152</td>
<td>215  (ii)</td>
<td></td>
<td>47.45 2.5 4.0</td>
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<tr>
<td>3-Cl</td>
<td>-</td>
<td>132-134</td>
<td>131-132</td>
<td>214  (i)</td>
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<td>47.1 2.4 4.2</td>
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<tr>
<td>2-CF₃</td>
<td>46</td>
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* Upper row corresponds to found values and lower row to calculated values. Where no lit m.p. is given the compound is new.

(vi) **Aryl 2-aminophenyl sulphides and sulphones**

These were prepared by the reduction of the corresponding nitro compound with iron and a catalytic amount of hydrochloric acid in ethanol and water as exemplified by the reduction of 2-nitrophenyl...
3'-methylphenyl sulphone. Hydrochloric acid (d 1.16, 0.8 g) was added to the sulphone (9.48 g, 0.034 moles), iron pin dust (7.45 g, 0.133 moles), ethanol (13 ml) and water (13 ml), and the mixture stirred and heated at the reflux temperature under nitrogen, for 15 h. On cooling the mixture, in chloroform, was filtered through Celite, basified and the organic solvents evaporated. The mixture was then extracted into chloroform and the white crystals obtained on evaporation recrystallised from ethanol to give 2-aminophenyl 3'-methylphenyl sulphone (6.7 g, 79%, m. p. 126°) (Found: C, 62.9; H, 5.3; N, 5.5. \( C_{13}H_{13}NO_2S \) requires C, 63.2; H, 5.3; N, 5.7%).

Table 4  
Aryl 2-aminophenyl sulphones and sulphones

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<th>lit m. p./b. p.°</th>
<th>Ref</th>
<th>C</th>
<th>H</th>
<th>N</th>
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<td>174-177/</td>
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<td>lit m. p. / b. p. °</td>
<td>Ref</td>
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<td>H</td>
<td>N</td>
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</table>
Footnote to Table 4:

* Upper row corresponds to found values, lower row to calculated values. Where no lit m. p. is given the compound is new.

/ Reduction of 2-nitrophenyl 2'-pyridyl-N-oxide sulphone gave 2-aminophenyl 2'-pyridyl-N-oxide sulphone and 2-aminophenyl 2'-pyridyl sulphone. These two compounds were separated by chromatography on alumina.

+ The compounds indicated were liquids and so they, together with 2-aminophenyl 4'-chlorophenyl sulphide (prepared by Mr. T. W. Naisby), were characterised as their N-p-toluene sulphonyl derivatives, prepared as exemplified in the case of 2-aminophenyl 4'-chlorophenyl sulphone.

The sulphide (0.9 g, 0.0038 moles) and p-toluenesulphonyl chloride (0.8 g, 0.0042 moles) were added to pyridine (10 ml) and heated at 100° with stirring for 1 h. The reaction mixture was then poured into cold water and stirred until the oil which separated had solidified. The solid was filtered off and recrystallised from ethanol to give 2-(N-p-toluenesulphonyl)aminophenyl 4'-chlorophenyl sulphone (1.16 g, 77%) as buff crystals (m. p. 107-108°) (Found: C, 58.7; H, 4.05; N, 3.55. C_{19} H_{16} ClNO_{2} S_2 requires C, 58.5; H, 4.1; N, 3.6%).

Table 5 2-(N-p-Toluenesulphonyl)aminophenyl aryl sulphones

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<th>H</th>
<th>N</th>
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<td>62.3</td>
<td>5.0</td>
<td>3.6</td>
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<td>58.5</td>
<td>4.1</td>
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</tbody>
</table>

* Upper row corresponds to found values, lower row to calculated values. All new compounds.
(vii) **Aryl 2-azidophenyl sulphones and sulphones**

The general method of preparation is exemplified by the case of 2-azidophenyl 4'-methylphenyl sulphone. Water (25 ml) was added to a warmed mixture of 2-aminophenyl 4'-methylphenyl sulphone (23.3 g, 0.108 mole) and hydrochloric acid (d 1.16, 25 ml), the mixture was cooled to 0° and a solution of sodium nitrite (7.85 g, 0.114 moles) in water (18 ml) was added slowly, with stirring, so as to keep the temperature below 3°. The mixture was then stirred for 3 h at 0° before a solution of sodium azide (16 g, 0.246 moles) in water (200 ml) was added sufficiently slowly to keep the temperature below 3°. Filtration and drying of the resulting solid in vacuo gave 2-azidophenyl 4'-methylphenyl sulphone (24.95 g, 95%, m.p. 67-79°, lit. M.p. 63-64°). Liquid azides were extracted into ether and the extracts dried over anhydrous magnesium sulphate. The 2-azidophenyl aryl sulphones were generally prepared at higher dilution than employed above because of solubility problems. Sometimes the i.r. spectrum of the azide showed traces of the parent amine to be present. This was removed by chromatography on alumina.

**Table 6**  
**Aryl 2-azidophenyl sulphones and sulphones**

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<th>Yield (b)</th>
<th>m.p. °</th>
<th>lit m.p. °</th>
<th>Ref</th>
<th>Analysis (%) *</th>
<th>C</th>
<th>H</th>
<th>N</th>
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<td>Yield (b)</td>
<td>m. p. °</td>
<td>lit m. p. °</td>
<td>Ref</td>
<td>Analysis (%)</td>
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Table 6 (cont.)

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<th>Yield (b)</th>
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<th>Analysis (%)</th>
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* Upper row corresponds to found values and the lower row to calculated values. Where no lit m. p. is shown the compound is new. Yield (a) is the yield after drying and yield (b) is the yield after chromatography (if necessary).

+ Some azides were not easily characterised and so they were characterised as the corresponding triphenylphosphinimine, as exemplified in the case of 2-azidophenyl 3'-trifluoromethylphenyl sulphide.

The sulphide (1 g, 0.0034 moles) was dissolved in sodium-dried ether (20 ml) and cooled to 0°C. A solution of triphenyl phosphine (0.5 g, 0.0019 moles) in sodium-dried ether (20 ml) was cooled to 0°C and then added to the azide solution. The mixture was allowed to stand at 0°C overnight before evaporation to give a brown solid which was recrystallised from hexane/dichloromethane to give N-[2-(3'-trifluoromethylthiophenoxy)phenyl]triphenylphosphinimine (0.86 g, 83%) as white crystals (m. p. 146-147°C) (Found: C, 70.6; H, 4.5; N, 2.75. C₃₁H₂₃F₃NPS requires C, 70.3; H, 4.4; N, 2.6%).
Table 7.  N-[2-(thioaryloxy)phenyl]triphenylphosphinimines and N-[2-(arylsulphonyl)phenyl]triphenylphosphinimines

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<th>m.p.</th>
<th>Analysis (%)</th>
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<td></td>
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</table>

All are new compounds
(viii) Phenothiazines

Authentic phenothiazines were prepared by a variety of methods.

2- and 4-methoxyphenothiazines

These were prepared by reacting 3-methoxydiphenylamine (prepared by the method of Massie and Kadaba\textsuperscript{219}) with sulphur in the presence of iodine as described by Cymerman-Craig\textsuperscript{220} et al.

\begin{itemize}
  \item \(\alpha\)-Chlorobenzoic acid (18.25 g, 0.117 moles) \(m\)-methoxy-aniline (60.5, 0.49 moles), anhydrous potassium carbonate (18.25 g, 0.132 moles) and copper bronze powder (0.5 g) were boiled under reflux (using an air condenser) for 2 h. The reaction mixture, after steam distillation to remove unreacted amine, was boiled with activated charcoal (10 g) and filtered while hot. Dilute hydrochloric acid (40 ml; 30%, v/v) was added to the filtrate and a brown solid obtained by filtration. This was recrystallised from hexane/chloroform to give N-(3-methoxyphenyl)anthranilic acid (18.2 g, 64%, m.p. 134°, lit\textsuperscript{221} 132°). This anthranilic acid (10.2 g, 0.042 moles) was heated at 250-260° for 200 min and then distilled at 128-130°/0.3 mmHg to give 3-methoxydiphenylamine (7.36 g, 88%, m.p. 70-71°, lit\textsuperscript{222} 72°). 3-Methoxydiphenylamine (5.8 g, 0.029 moles), sulphur (1.89 g, 0.059 moles) and iodine (0.25 g, 0.001 moles) were dissolved in \(\alpha\)-dichlorobenzene (6 ml) and boiled under reflux for 1 h. The \(\alpha\)-dichlorobenzene was removed by distillation under a reduced pressure of nitrogen and the residue chromatographed on alumina. The elutant from the column was monitored by High Speed Liquid Chromatography and 2-methoxyphenothiazine (2.44 g, 36%, m.p. 186-187°, lit\textsuperscript{223} 185-188°) and 4-methoxyphenothiazine (0.20 g, 3%, m.p. 93-96°, lit\textsuperscript{220} 98°) were isolated.

2- and 4-trifluoromethylphenothiazines

These were prepared by a similar method to that used for the methoxy compounds via N-(3-trifluoromethylphenyl)anthranilic acid (87%, m.p. 122-123°, lit\textsuperscript{224} 124-125°) and 3-trifluoromethyl-diphenylamine (72%, b.p. 98-114°/0.2-0.3 mmHg, lit\textsuperscript{108} 108-110°/0.3
mmHg) and the isomers were separated using a modification of the method of Yale, Sowinski and Bernstein. 3-Trifluoromethyl-diphenylamine (10.1 g, 0.043 moles), sulphur (2.7 g, 0.084 moles) and iodine (0.29 g, 0.001 moles) were heated together for 3.5 h at 150-160°, and then poured into 70 ml warm toluene. The mixture was boiled and after the addition of Celite it was filtered through a pad of hot Celite. On cooling a grey solid separated and this was identified as 2-trifluoromethylphenothiazine (0.90 g, 7.9% [after recrystallisation from hexane], m. p. 187-188°, lit 183-185°). The filtrate was evaporated and the residue distilled at 198°/1 mmHg to give green crystals. These were recrystallised from hexane to give 2-trifluoromethylphenothiazine (0.1758 g, 1.55%, m. p. 190-191°, lit 183-185°). The filtrate was evaporated to give 4-trifluoromethylphenothiazine (0.1950 g, 1.7% - after recrystallisation from hexane, m. p. 69-70°, lit 72-73°).

HSLC analysis showed that the sample was 91% 4-trifluoromethylphenothiazine and 9% 2-trifluoromethylphenothiazine.

1-Methoxyphenothiazine

This was prepared by the deoxygenation of 2-nitrophenyl 2'-methoxyphenyl sulphide as described by Cadogan and Kulik. 2-Nitrophenyl 2'-methoxyphenyl sulphide (10.44 g, 0.04 moles), triethylphosphite (26.6 g, 0.16 mole) and cumene (300 ml) were boiled under reflux in an atmosphere of nitrogen for 72 h. The cumene was removed by distillation under a reduced pressure of nitrogen and the residue chromatographed on alumina to give 1-methoxyphenothiazine (4.82 g, 52%, m. p. 98-99°, lit 99°). In a similar fashion 4-chlorophenothiazine was prepared by the deoxygenation of 2-nitro-6-chlorophenyl phenyl sulphide, 2-chlorophenothiazine by the deoxygenation of 2-nitro-4-chlorophenyl phenyl sulphide, 3-methyl phenothiazine by the deoxygenation of 2-nitrophenyl 4'-methylphenyl sulphide and 4-methylphenothiazine by the deoxygenation of 2-nitro-6-methylphenyl phenyl sulphide. 3-Trifluoromethylphenothiazine was prepared by the deoxygenation of 2-nitrophenyl 4'-trifluoromethylphenyl sulphide and 1-trifluoromethylphenothiazine by the deoxygenation of 2-nitrophenyl 2'-trifluoromethylphenyl sulphide. In all cases
only one isomer of known structure is formed either because the substituent is in the same ring as the nitro-group and the other ring unsubstituted or the reaction follows a known rearrangement which Cadogan and Kulik demonstrated gives 1-substituted phenothiazines from 2'-substituted diphenyl sulphides and 3-substituted phenothiazines from 4'-substituted diphenyl sulphides. The physical properties of all the phenothiazines agreed with published data and they were shown to be isomerically pure by HSLC.

Table 8  Phenothiazines

<table>
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<th>R</th>
<th>Yield (%)</th>
<th>m. p. °</th>
<th>lit m. p. °</th>
<th>Ref</th>
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<th>H</th>
<th>N</th>
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* Upper row corresponds to found values, lower row to calculated values.

(ix)  Phenothiazine-5, 5-dioxides

These were prepared by the oxidation of the corresponding phenothiazine with m-chloroperbenzoic acid as exemplified in the case of 1-methoxyphenothiazine-5, 5-dioxide: 1-Methoxyphenothiazine (0.5363 g, 0.00234 moles) and m-chloroperbenzoic acid (85%, 1.0227 g, 0.00504 moles) were dissolved in 25 ml dichloromethane and the
solution boiled under reflux for 22 h. The reaction mixture was
diluted with dichloromethane and washed once with dilute sodium
hydroxide solution, twice with water, twice with sodium sulphite
solution and finally with water before being dried over anhydrous
magnesium sulphate. Evaporation gave 1-methoxyphenothiazine-
5,5-dioxide (0.5266 g, 86%) which was purified by sublimation at
192°/0.05 mmHg (0.4348 g, 71%, m.p. 208-210°) (Found:
C, 60.05; H, 4.3; N, 5.4. \( \text{C}_{13}\text{H}_{11}\text{NO}_{3}\text{S} \) requires C, 59.8;
H, 4.2; N, 5.4%).

Table 9  Phenothiazine-5,5-dioxides

<table>
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<th>Yield</th>
<th>m.p.</th>
<th>lit. m.p.</th>
<th>Ref</th>
<th>Analysis (%)*</th>
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<td>H 63.65 4.5 5.7</td>
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*Upper row corresponds to found values, lower row to calculated values. Where no lit m. p. is given the compound is new.

2- and 3-t-Butylphenothiazine-5, 5-dioxides were separated and isolated by preparative-scale high speed liquid chromatography. They were identified by comparison with an authentic sample of 3-t-butylphenothiazine-5, 5-dioxide kindly donated by Dr. P. Lim. All compounds were shown to be isomerically pure by HSLC.

(x) Aryl 2-(hydroxyamino)phenyl sulphides

These were prepared by the reduction of the corresponding nitro-compound with zinc and ammonium chloride in ethanol as exemplified in the case of 2-(hydroxyamino)phenyl 3'-chlorophenyl sulphide. 2-Nitrophenyl 3'-chlorophenyl sulphide (4 g, 0.015 moles), ammonium chloride (3.3 g, 0.062 moles) and zinc dust (10 g, 0.153 moles) in ethanol (130 ml) and water (10 ml) were stirred and heated over 45 min until the temperature reached...
The reaction mixture in ether was then filtered through Celite and the solvents evaporated to give an orange oil which crystallised very slowly on standing at -25°. Trituration with hexane gave yellow crystals which were recrystallised from hexane to give almost colourless crystals of 2-(hydroxyamino)phenyl 3'-chlorophenyl sulphone (1.11 g, 29%, m.p. 68-69°) (Found: C, 57.3; H, 3.8; N, 5.5. C₁₂H₁₀ClNOS requires C, 57.3; H, 4.0; N, 5.6%). HSLC analysis showed that not all the hydroxylamines were pure. The impurities found are listed in Table 10.

Table 10. Aryl 2-(hydroxyamino)phenyl sulphones

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>m.p. °</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me</td>
<td>48</td>
<td>44-46</td>
<td>67.3 5.6 6.1</td>
<td></td>
<td>1% nitroso, 15% amine</td>
<td></td>
</tr>
<tr>
<td>3-Me</td>
<td>82</td>
<td>liquid</td>
<td>57.6 4.0 5.6</td>
<td></td>
<td>6% amine, 1% 1-methylphenothiazine</td>
<td></td>
</tr>
<tr>
<td>4-Me</td>
<td>52</td>
<td>59-61</td>
<td>57.3 5.7 6.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-Cl</td>
<td>55</td>
<td>101-102</td>
<td>57.2 4.2 5.5</td>
<td></td>
<td>8% nitroso, 32% amine</td>
<td></td>
</tr>
<tr>
<td>3-OMe</td>
<td>59</td>
<td>liquid</td>
<td>54.7 3.5 4.9</td>
<td></td>
<td>16% amine</td>
<td></td>
</tr>
<tr>
<td>3-CF₃</td>
<td>82</td>
<td>51-52</td>
<td>55.0 3.4 4.9</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Footnotes to Table 10:

All new compounds. * Upper row corresponds to found values, lower row to calculated values.

+ I.R. \( \nu \) 3400 (OH) cm\(^{-1}\).

In some cases it was impossible to isolate the pure hydroxylamine and the yield of hydroxylamine was determined by HSLC analysis and is expressed as a percentage of the theoretical yield from the starting material. The yields of the other products were also determined by HSLC analysis and are similarly expressed.

(xi) **Aryl 2-nitrosophenyl sulphides**

These were prepared by the oxidation of the corresponding hydroxylamine with silver carbonate on Celite in dichloromethane as exemplified by the case of 2-nitrosophenyl 2'-chlorophenyl sulphide. 2-(Hydroxyamino)phenyl 2'-chlorophenyl sulphide (1 g, 0.004 moles) and silver carbonate on Celite (2.65 g) in dichloromethane (40 ml) were stirred at room temperature for 10 min then filtered through Celite with ether. Evaporation gave a green oil which solidified to a green solid, 2-nitrosophenyl 2'-chlorophenyl sulphide (0.85 g, 84%, m.-p. 85-86\(^\circ\)) (Found: C, 57.5; H, 3.2; N, 5.4. \( \text{C}_{12} \text{H}_{8} \text{ClNOS} \) requires C, 57.7; H, 3.2; N, 5.6%). HSLC analysis showed that the yield of the corresponding amine was 2%. The yields are expressed in a similar fashion to those of the hydroxylamines.

**Table 11. Aryl 2-nitrosophenyl sulphides**
**Analysis (%)**

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>m. p. °</th>
<th>C</th>
<th>H</th>
<th>N</th>
<th>Impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me</td>
<td>66</td>
<td>42-44</td>
<td>+</td>
<td>6.7</td>
<td>4.8</td>
<td>5.9 8% amine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Me</td>
<td>63</td>
<td>liquid</td>
<td>-</td>
<td>6.3</td>
<td>4.9</td>
<td>5.9 3% nitro, 1% amine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-OMe</td>
<td>49</td>
<td>79-81</td>
<td>6.3</td>
<td>4.9</td>
<td>5.9</td>
<td>6% nitro, 27% amine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-Cl</td>
<td>89</td>
<td>73-74</td>
<td>5.8</td>
<td>3.3</td>
<td>5.5</td>
<td>6% nitro, 1% amine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Cl</td>
<td>83</td>
<td>93-94</td>
<td>5.7</td>
<td>3.25</td>
<td>5.5</td>
<td>4% nitro, 2% amine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-CF₃</td>
<td>80</td>
<td>47-48</td>
<td>5.5</td>
<td>3.0</td>
<td>4.9</td>
<td>9% amine</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All new compounds.

* Upper row corresponds to found values, lower row to calculated values.

+ I. r. ν 1485 (NO) cm⁻¹.

I should like to thank Dr. S. Kulik for samples of 2- and 4-methoxythiophenol, 2-nitro-4-methylphenyl phenyl sulphide, 2-nitro-4-chlorophenyl phenyl sulphide, 2-nitro-6-chlorophenyl phenyl sulphide and authentic samples of 1-methoxyphenothiazine, 1- and 3-chlorophenothiazine and 1- and 2-methylphenothiazine. Thanks are also due to Dr. P. Lim who supplied 2-azidophenyl 4'-chlorophenyl sulphone and 2-azidophenyl 4'-t-butylphenyl sulphone and to Miss E. M. Ramage who supplied authentic samples of 2- and 3-chlorophenothiazine-5, 5-dioxides.
C. High Speed Liquid Chromatography

(i) Introduction

The common feature of all chromatographic processes is the distribution of a substance between a mobile phase and a stationary phase. In the mobile phase the substance moves at the speed of the mobile phase but in the stationary phase it is static. Liquid chromatography uses a liquid as the mobile phase and the stationary phase is usually alumina or silica.

The stationary phase may either be coated with a substance with which the molecules of solute interact or it may be uncoated in which case the molecules are adsorbed.

The relative band migration rate is given by

\[ R = \frac{\text{speed of band}}{\text{speed of mobile phase}} = \frac{\text{amount in mobile phase}}{\text{amount in mobile phase} + \text{amount in stationary phase}} \]

\[ = \frac{1}{1 + k'} \]

where \( k' = \frac{\text{amount in stationary phase}}{\text{amount in mobile phase}} \) at equilibrium.

Since speed of band = \( R \times \) speed of mobile phase

where \( R = \) probability that a molecule is in the mobile phase

\[ = \text{fraction of time molecule spends in the mobile phase} \]

\( R \) can be identified with the \( R_F \) value in paper and thin-layer chromatography.

Thus \( 235 \)

\[ k' = \frac{\text{speed of mobile phase}}{\text{speed of band}} - 1 \]

\[ = \frac{\text{retention time of band}}{\text{retention time of unretained}} - 1 \]

"Unretained" is any substance which does not interact with the stationary phase. Thus its retention time gives a measure of the speed of the mobile phase.
To change the relative retentions of a pair of solutes $X_1$ and $X_2$, the ratio $k_2'/k_1'$ must be changed and this implies changing thermodynamic aspects of the system, i.e., the nature of the mobile phase or the stationary phase. Thus it was found that a particular separation could be obtained in one mobile phase system but not in another. Similarly, a change from alumina to silica was found to help some separations.

Although liquid chromatography has been in use for many years, it was not until 1969 that Kirkland showed that a combination of small particle size and high pressure could provide higher resolution and higher speed of analysis although this had been predicted earlier by Martin and Synge. The essential features of a modern High Speed Liquid Chromatograph are: a reservoir for eluant storage, a pump, an injection head and column, and a detector. The pump should be capable of operating at pressures up to about 1000-3000 p.s.i. with flow rates of about 2 ml min$^{-1}$. The most commonly used detectors are either a U.V. spectrophotometer or a refractive index detector although other types may be used for more specialised applications. Provided that the compounds which are to be observed absorb in the ultraviolet the u.v. spectrophotometer is by far the most sensitive system. All parts that are in contact with the eluant must be P.T.F.E., stainless steel or glass.

Columns used are typically 2-5 mm in diameter and 10-100 cm long. The packing is held in the column by a plug of porous metal and an injection head with septum or an injection valve is placed at the top of the column. To preserve good resolution it is essential to minimise the dead volume of the system by using narrow bore connecting tubing. 0.25 mm bore is suitable. As stated above, small particle size is necessary to give high speed and high resolution and typically alumina or silica particles 5-20 μm in size are used. Although the actual type of material does not have a very great effect on efficiency, the column packing technique is important. The effectiveness of a column packing is best measured by the number of theoretical plates, $N$, that the column contains. This derives from Martin and Synge's original treatment in which the column was
Fig. 2 Column and injection head.
Fig. 3 Slurry packing device
Fig. 4 Flow cell
considered as analagous to a series of plates or slices within which equilibration took place before the mobile phase within the plate was shifted into the next plate. $N$ may be calculated from a peak on a chromatogram by the formula.

$$N = 16 \left( \frac{R.T.}{P_{W.h}} \right)^2$$

However if the peak has a Gaussian shape $P_{W,B.} = 1.7P_W$ and so a more convenient formula can be derived.

$$N = 5.54 \left( \frac{R.T.}{P_{W.h}} \right)^2$$

where $R.T.$ retention time of the peak (in seconds)

$P_W$ = width of peak at half height (in seconds)

$P_{W,B.}$ = width of peak at baseline (in seconds).

(ii) **Equipment**

The columns and injection heads used were of a design developed in Edinburgh by J. H. Knox et al. and shown in Fig. 2. The columns were 10-25 cm in length and 5 μm in internal diameter and made from stainless steel. The lower end was closed with a 6 μm porosity stainless steel frit from B.S.A. Sintered Components, Ltd., Birmingham. They were polished internally. The comparatively large diameter means that a component cannot diffuse to the sides as it travels down the column (assuming a point-source injection). If the component did diffuse to the walls efficiency would be lost because the flow is seriously disturbed near the walls. This is known as the "infinite diameter" effect.

Two main sets of equipment were used. In the first the pump was an L. D. C. Eluant Delivery Unit fitted with a pressure damper and capable of pressures up to 1200 psi and flow rates up to 2.2 ml/min. The detector was a Cecil Model 212 variable-wavelength ultraviolet spectrophotometer fitted with a flow cell of 8 μl volume. This is sketched in Fig. 4. The spectrophotometer was fixed on a wavelength of 254 nm. The detector was connected to a chart recorder and an Autolab Minigrator integrator. The other instrument was a Du Pont 820 liquid chromatograph modified to take the columns described above. The detector was a Du Pont 410 fixed-wavelength (254 nm) ultraviolet
spectrometer fitted with an 8 µl flow cell. This was connected to a chart recorder and an Autolab 6300 integrator. Generally the peaks were not allowed to exceed 0.4 absorbance units to maintain linearity of response.

(iii) Mobile phases

In all cases the mobile phase was hexane with varying amounts of modifying, more polar, components added. The solvents used were prepared as follows.

Hexane: May and Baker fraction from petroleum b. p. 67.5 - 69.5° was purified by passing down a silica column. This removed all the water and u. v. absorbing impurities.

Ethyl acetate was B. D. H. Analar grade having a water limit of 0.05%, 0.6% of water was added before use.

Tetrahydrofuran (THF): was passed through an alumina column then dried over sodium wire. 0.6% water was added before use.

Dioxan was purified according to the method of Vogel by boiling under reflux under nitrogen with dilute hydrochloric acid to remove ethylene acetal. The remaining dioxan was dried over potassium hydroxide pellets then distilled from lithium aluminium hydride. 0.6% water was added before use.

Acetonitrile, commercial grade, was used and 0.6% water was added before use.

It is found empirically (and can be shown theoretically) that adding a closely controlled amount of water enables the retention times to be stabilised. A small amount of water blocks the most active sites on the alumina or silica and the absence of water leads to very poor resolution. On the other hand too much water leads to deactivation of the column and very short retention times. In practice 0.6% water is found to give good results.

(iv) Preparation of columns

Two columns were packed and used for most of the analyses. The first column was a 15 cm column packed with Spherisorb A5Y alumina. The alumina was activated before use by
heating to 450° in a furnace for several hours then cooling in a desiccator. The column was fitted with a nut with a large hole in it to prevent the porous frit being forced out and then filled with dry methyl iodide. A pre-column 14 cm in length with internal diameter 0.9 cm tapering at the bottom to 0.5 cm was clamped on top of the column by means of two large nuts. A Viton ring was placed between the two columns to prevent leakage. This arrangement is sketched in Fig. J. Spherisorb A5Y alumina (about 7.5 g) suspended in dry methyl iodide (10 ml) was added to the pre-column and the top of the pre-column was rapidly attached to a Haskell pressure intensifier pump and the slurry forced into the column at 2500 psi with light petroleum (b. p. 60-80°). After a few minutes of flow the pressure was turned on and off several times to drive home the packing and then the pre-column containing the surplus alumina was removed. Alumina was removed from the top of the column to a depth of a few mm and a 5 mm diameter circle of stainless steel mesh added to the top of the alumina. The column was filled to the top with 100 mesh glass beads to maintain a low dead volume. Bits of septum could then be simply removed from the top of the column by replacing the glass beads without disturbing the alumina packing. The column had an efficiency of about 6500 theoretical plates.

The other column was a 25 cm column packed with Spherisorb S10W silica. The silica was dried at 200° for several hours then allowed to cool in a desiccator. A similar technique was used except that the Spherisorb S10W silica (about 6.5 g) was suspended in A.R. methanol (75 ml) and this suspension was placed in a stainless steel pressure vessel having an internal volume of 75 ml. This pressure vessel was attached to the top of the pre-column (filled with methanol) and the top end attached to the pump. The resulting column had an efficiency of about 6500 plates.

A 10 cm column was slurry packed with Spherisorb A7.5Y alumina by Dr. J. N. Done. Dr. Done also provided a 19 cm column of 4 mm internal diameter slurry packed with 7 μm silica prepared by the Wolfson Liquid Chromatography Unit, Edinburgh. The fittings for this column were made to an I.C.I. design. The efficiency
of this column was about 14,000 theoretical plates.

(v) Systems used

All mobile phase concentrations are volume:volume. Chloro- and methoxyphenothiazines were determined using a 15 cm column slurry packed with Spherisorb A5Y alumina. The mobile phase was hexane:ethyl acetate (95:5). For chlorophenothiazines the standard was o-nitroaniline with fixed \( k' = 5.32 \). For methoxyphenothiazines the standard was 4-methoxy-2-nitroaniline (fixed \( k' = 8.60 \)). For explanation of standards and fixed \( k' \) values see (vi) and (vii) below. 1- And 4-methylphenothiazines, 2-nitrophenyl 2'-methylphenyl sulphide and 2-aminophenyl 2'-methylphenyl sulphide were determined using a 25 cm column slurry packed with Spherisorb S10W silica using hexane saturated with acetonitrile. This was prepared by stirring hexane:acetonitrile (98:2) for 24 hr then pouring off the acetonitrile-saturated hexane. The standard was 2,6-dichloroaniline (fixed \( k' = 1.31 \)).

2- And 3-methylphenothiazines, 2-nitrophenyl 4'-methylphenyl sulphide and 2-aminophenyl 4'-methylphenyl sulphide were determined using the same column with hexane:dioxan (98:2) as the mobile phase. The standard was 1-methoxyphenothiazine (fixed \( k' = 2.72 \)).

1, 2, 3- And 4-methylphenothiazines, 2-nitrophenyl 3'-methylphenyl sulphide and 2-aminophenyl 3'-methylphenyl sulphide were determined using a 19 x 0.4 cm column slurry packed with 7 \( \mu \)m silica. The mobile phase was hexane:THF (99.1). The standard was 1-methoxyphenothiazine (fixed \( k' = 1.88 \)).

1, 2, 3- And 4-trifluoromethylphenothiazines and the associated amines and nitro-compounds were determined using the same column but with hexane:ethyl acetate (95:5) as the mobile phase. The standard was 2-methoxyphenothiazine (fixed \( k' = 5.79 \)).

Phenothiazine-5, 5-dioxides were generally determined using a 10 cm column slurry packed with Spherisorb A7.5Y alumina by Dr. J. N. Done. Methylphenothiazine-5, 5-dioxides and the corresponding amines were determined using hexane:ethyl acetate (75:25). Products from the decomposition of 2-azidophenyl 2'- and 3'-methyl-
phenyl sulphones had \( p \)-nitroaniline (fixed \( k' = 4.40 \)) as standard. Products from the decomposition of 2-azidophenyl \( 4' \)-methylphenyl sulphone had \( m \)-nitroaniline (fixed \( k' = 1.93 \)) as standard.

Methoxyphenothiazine-5, 5-dioxides (standard \( 2 \)-chlorophenothiazine-5, 5-dioxide, fixed \( k' = 3.17 \)) and \( 2 \)- and \( 3 \)-t-butyl-phenothiazine-5, 5-dioxides (standard \( p \)-nitroacetanilide, fixed \( k' = 7.39 \)) and their corresponding amines were determined using hexane:ethyl acetate (65:35) as were most of the chlorophenothiazine-5, 5-dioxides and their associated amines. (Standard \( p \)-nitroaniline, fixed \( k' = 2.50 \)). However \( 1 \)-chlorophenothiazine-5, 5-dioxide and \( 2 \)-aminophenyl \( 2' \)-chlorophenyl sulphone were determined using hexane:dioxan (75:25) (standard \( p \)-nitroaniline, fixed \( k' = 6.76 \)) and \( 1 \)-chlorophenothiazine-5, 5-dioxide and \( 2 \)-aminophenyl \( 3' \)-chlorophenyl sulphone obtained from the decomposition of 2-azidophenyl \( 3' \)-chlorophenyl sulphone in decalin were determined using hexane:ethyl acetate (75:25). (Standard \( p \)-nitroaniline, fixed \( k' = 4.40 \)).

Products obtained from the decomposition of 2-azidophenyl \( 2',6' \)-dichlorophenyl sulphone were determined using a 15 cm column slurry packed with Spherisorb A5Y alumina. The mobile phase was hexane:ethyl acetate (65:35). The standard was \( p \)-nitroaniline (fixed \( k' = 2.50 \)).

Trifluoromethylphenothiazine-5, 5-dioxides and their associated amines were determined using the same system but the standard was \( m \)-nitroacetanilide (fixed \( k' = 2.96 \)). In order to separate \( 1 \)-trifluoromethylphenothiazine and \( 2 \)-aminophenyl \( 3' \)-trifluoromethylphenyl sulphone hexane:ethyl acetate (85:15) was used as the mobile phase.

(vi) Measurement of yields of products

To each reaction mixture an accurately known amount of an inert standard was added. The criteria for selecting a standard are

1) It should not be coincident with any other peak in the chromatogram.
2) It should not react with products or the solvent
3) It should have a retention time, under the conditions used, that is not inconveniently long or too short.
4) It should be in a high state of purity.

The quantity of standard added was chosen to provide peaks of about the same size as those it was desired to measure. The area of each peak was measured using an integrator and hence the area ratio of each peak to the standard was determined. At least three concordant results were obtained for each reaction mixture and the average of the area ratios was calculated. A mixture containing accurately weighed amounts of the standard and each component that it was desired to determine was made up and run under exactly the same conditions. The area ratios of this mixture were calculated as above and, since the ratio of the weight of each component to the weight of the standard was known, the factor necessary to convert the area ratio to the weight ratio could be calculated. From this data the weight ratio and hence weight of each component in the reaction mixture could be calculated.

Very sharp, intense, peaks sometimes caused the detector to become overloaded and hence the area of the peak was under-recorded. To avoid this the maximum response was restricted to 0.4 absorbance units.

To ensure comparability between different reactions of the same compound the reaction mixtures and the known mixture were all analysed under identical conditions.

The results obtained are corrected for the presence of impurities in the starting materials.

(vii) Identification of products

Each component was identified by calculating its $k'$ value (as described above). However it was found that with time the $k'$ values tended to drift and so the $k'$ value of the standard in each reaction mixture was converted to a fixed value by multiplying by an appropriate factor. This fixed value was the $k'$ value of the standard in the known mixture. The $k'$ value of each
component in the reaction mixture was then corrected by multiplying by this same factor. Each component in the reaction mixture was then identified by comparing this corrected $k'$ value ($k'_c$) with $k'$ value determined for the component in the known mixture.

The standard used together with their fixed $k'$ values were given in (v) above.

The $k'$ values for the authentic compounds are given below.

**Table 12**  
**$k'$ Values of phenothiazines**

![Chemical structure of phenothiazine](attachment:image.png)

<table>
<thead>
<tr>
<th></th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>2.17</td>
<td>4.98</td>
<td>5.27</td>
<td>4.73 *</td>
</tr>
<tr>
<td>OMe</td>
<td>0.88</td>
<td>5.46</td>
<td>4.50</td>
<td>3.73</td>
</tr>
<tr>
<td>Cl</td>
<td>0.22</td>
<td>1.52</td>
<td>3.39</td>
<td>3.86</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>0.17</td>
<td>1.08</td>
<td>4.56</td>
<td>6.37</td>
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</tbody>
</table>

* measured in hexane:THF (99:1) relative to 1-methoxyphenothiazine (fixed $k'$ = 1.88).

**Table 13**  
**$k'$ Values of phenothiazine-5,5-dioxides**

![Chemical structure of phenothiazine-5,5-dioxide](attachment:image.png)

<table>
<thead>
<tr>
<th></th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>7.13</td>
<td>10.84</td>
<td>10.30</td>
<td>8.65</td>
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<tr>
<td>OMe</td>
<td>4.22</td>
<td>10.46</td>
<td>6.26</td>
<td>18.20</td>
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<tr>
<td>Cl</td>
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<td>3.12</td>
<td>6.40</td>
<td>9.95</td>
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<tr>
<td>CF$_3$</td>
<td>0.54</td>
<td>1.39</td>
<td>3.88</td>
<td>6.44</td>
</tr>
<tr>
<td>Bu$^t$</td>
<td>-</td>
<td>3.30</td>
<td>4.30</td>
<td>-</td>
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</table>
### Table 14  
**$k'$ Values of aryl 2-nitrophenyl sulphides**

<table>
<thead>
<tr>
<th>R</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>2.61</td>
<td>1.02</td>
<td>1.75</td>
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<tr>
<td>OMe</td>
<td>2.18</td>
<td>1.37</td>
<td>1.60</td>
</tr>
<tr>
<td>Cl</td>
<td>1.09</td>
<td>.84</td>
<td>.67</td>
</tr>
<tr>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3.06</td>
<td>1.67</td>
<td>.93</td>
</tr>
</tbody>
</table>

### Table 15  
**$k'$ Values of aryl 2-nitrosophenyl sulphides**

<table>
<thead>
<tr>
<th>R</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
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<tbody>
<tr>
<td>Me</td>
<td>0.92</td>
<td>.57</td>
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<tr>
<td>OMe</td>
<td>-</td>
<td>.93</td>
<td>-</td>
</tr>
<tr>
<td>Cl</td>
<td>.62</td>
<td>.46</td>
<td>.37</td>
</tr>
<tr>
<td>CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-</td>
<td>.87</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 16  \( k' \) Values of aryl 2-aminophenyl sulphides and sulphones

\[
\begin{array}{cccc}
X & R & 2- & 3- & 4- \\
S & Me & 3.42 & 2.61 & 3.15 \\
S & OMe & 3.27 & 2.48 & 2.94 \\
S & Cl & 1.37 & 1.22 & 1.18 \\
S & CF_3 & 1.98 & 1.55 & 1.32 \\
SO_2 & Me & 1.52 & 1.64 & 1.73 \\
SO_2 & OMe & 2.45 & 1.34 & 1.76 \\
SO_2 & Cl & 1.41 & .91 & .80 \\
SO_2 & CF_3 & .96 & .58 & .48 \\
SO_2 & Bu^t & - & - & .82 \\
SO_2 & 2,6-diCl & 1.16 & & \\
\end{array}
\]

The \( k' \) value of phenothiazine is 2.32 (measured in hexane:ethyl acetate (95:5) relative to 4-methoxy-2-nitroaniline (fixed \( k' = 8.60 \)). The \( k' \) value of phenothiazine-5,5-dioxide is 6.75 (measured in hexane:ethyl acetate (65:35) relative to p-nitroaniline (fixed \( k' = 2.50 \)).

The \( k' \) values of the nitroso-compounds were determined under the same conditions as those of the corresponding amines.
D. Reactions

(i) Methods

As a general principle all reactions were carried out at about the same concentration i.e. 12 mg/ml. As the molecular weights did not vary much the molar concentrations were roughly comparable. The reaction times were chosen to ensure that the reactions went as nearly as possible to completion. An attempt was made to allow for the decomposition of products and hence the varying reaction times.

(a) Deoxygenation of aryl 2-nitrophenyl sulphides
The aryl 2-nitrophenyl sulphide (0.01 mole) was boiled under reflux under nitrogen with triethyl phosphite (0.021 moles) in sodium-dried cumene (75 ml) for 72 h. The cumene was evaporated under reduced pressure and the residue retained.

(b) Deoxygenation of aryl 2-nitrosophenyl sulphides
The aryl 2-nitrosophenyl sulphide (0.035 g) was dropped into a boiling mixture of cumene (3 ml) and triethyl phosphite (1 molar equivalent) and the mixture boiled under reflux under nitrogen for 5 min. The cumene was evaporated under reduced pressure and the residue retained.

(c) Deoxygenation of aryl 2-nitrophenyl sulphides in ethanol acetic acid
The aryl 2-nitrophenyl sulphide (0.01 moles) was mixed with diethyl methyl phosphonite (0.021 moles), ethanol (75 ml) and acetic acid (0.001 moles) and the mixture boiled under reflux in an atmosphere of nitrogen for 72 h. The ethanol was evaporated under reduced pressure and the residue retained.

(d) Treatment of aryl 2-(hydroxyamino)phenyl sulphides with trifluoroacetic acid
The aryl 2-(hydroxyamino)phenyl sulphide (0.036 g) and trifluoroacetic acid (TFA) (3 ml) were both cooled to 0°C then mixed and stirred under nitrogen at 0°C for 1 h. The TFA solution was shaken with ether and sodium bicarbonate solution
until there was no more effervescence on the addition of fresh sodium bicarbonate solution. The ether layer was retained.

(e) **Thermolysis of aryl 2-azidophenyl sulphides in decalin, cumene or dimethyl sulphoxide**

The aryl 2-azidophenyl sulphide was dissolved in the solvent in the concentration of approximately 12 mg per ml and the mixture heated with stirring under nitrogen over 30 min until it was boiling. It was boiled under reflux under nitrogen with stirring for 2 h then the solvent was evaporated under reduced pressure and the residue retained.

(f) **Thermolysis of aryl 2-azidophenyl sulphides in triethyl phosphate or nitrobenzene**

The aryl 2-azidophenyl sulphide (0.036 g) was dissolved in the solvent (3 ml) and stirred under nitrogen in a reaction tube. The reaction tube was surrounded by a jacket of decalin and the decalin was slowly heated over 30 min until it was boiling. The decalin was maintained at the boiling point for 2 h i.e. the azide solution was stirred under nitrogen for 2 h at the b.p. of decalin.

The solvent was evaporated under reduced pressure and the residue retained.

(g) **Thermolysis of aryl 2-azidophenyl sulphones in triethyl phosphate**

The thermolysis was performed in an exactly similar manner to that described in (f) above except that the reaction time was increased to 4 h.

(h) **Thermolysis of aryl 2-azidophenyl sulphones in decalin**

The aryl 2-azidophenyl sulphone (0.3 g) was added in portions over 30 min under nitrogen to stirred decalin (25 ml) maintained at 150-160°. The reaction mixture was then boiled under reflux under nitrogen with stirring for 4 h. The decalin was evaporated under reduced pressure and the residue retained.
Note (1) A rotary evaporator connected to an oil pump giving a pressure of ca 1 mmHg was found to be very useful for the removal of solvents.

(2) A turbine stirrer driven by a stream of nitrogen was found to be very useful for stirring reactions done on a 3 ml scale. The reaction tube incorporated a ground-glass joint so that it could be inserted into one neck of a multi-neck flask. The reaction mixture was entirely immersed in the boiling decalin or its vapour.

(3) When reactions were done at different temperatures the same technique as (vi) was used but the bath of decalin was changed to a bath of t-butyl benzene (b. p. 169°), cumene (152°) or ethyl benzene (136°).

(4) Thermolysis of 2-azidophenyl 2', 6'-dichlorophenyl sulphide in decalin was effected using method (vii) but with decalin as the solvent. This was necessary because of the small amounts of azide available. No appreciable loss of volume of the reaction mixture was observed.

(5) Deoxygenations of aryl 2-nitrophenyl sulphides and thermolyses of aryl 2-azidophenyl sulphides in decalin and triethylphosphate were carried out 3 times each, and were repeatable within the experimental error. Average values of yields are quoted in the tables which follow. The other reactions were generally performed only once each but judging from the experience of the reactions detailed above there is little change of irreproducibility in the products. Rather more variation was seen in the products from the deoxygenations of aryl 2-nitrosophenyl sulphides, presumably arising from the way the reactions were done. However concordant results were obtained and these are quoted in the tables which follow.
Abbreviations -

\[ \text{NO}_2 \] - deoxygenation of nitro compound
\[ \text{NO} \] - deoxygenation of nitroso compound
\[ \text{dec} \] - thermolysis of the azide in decalin
\[ \text{phos} \] - thermolysis of the azide in triethyl phosphate
\[ \text{cum} \] - thermolysis of the azide in cumene
\[ \text{DMSO} \] - thermolysis of the azide in dimethyl sulphoxide
\[ \text{N. B.} \] - thermolysis of the azide in nitrobenzene

\[ \text{Rn} = \] reaction
\[ \text{Acc} = \] accountance
\[ \text{PO}_2 = \] phenothiazine-5,5-dioxide
\[ \text{Phen} = \] phenothiazine.

The yields shown in the tables which follow are percentage yields based on the starting material, corrected where necessary for impurities in the starting material. The only exceptions are the phenothiazine and phenothiazine-5,5-dioxide isomer distributions, which represent each isomer as a percentage of the mono-substituted phenothiazine or phenothiazine-5,5-dioxide yield. Unsubstituted phenothiazine or phenothiazine-5,5-dioxide are listed separately.

It was found that yields of phenothiazines and phenothiazine-5,5-dioxides as low as 0.1% could be detected. Yields of other compounds as low as 0.5% could be detected. Yields between 0.1% and 0.8% are shown as "trace" and other yields are rounded to the nearest whole number.

(ii) Products of the cyclisations of aryl 2-nitro-, 2-nitroso- and 2-azidophenyl sulphides
Table 17  Products of the cyclisation of 2-nitro-, 2-nitroso-
and 2-azidophenyl 2'-chlorophenyl sulphides

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro amine</th>
<th>yield (%)</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
<th>phenothiazine (%)</th>
<th>Acc. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>13</td>
<td>trace</td>
<td>34</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>NO</td>
<td>1</td>
<td>6</td>
<td>26</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>dec</td>
<td>0</td>
<td>0</td>
<td>60</td>
<td>97</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>phos</td>
<td>0</td>
<td>0</td>
<td>67</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>cum</td>
<td>trace</td>
<td>trace</td>
<td>68</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>trace</td>
<td>3</td>
</tr>
<tr>
<td>DMSO</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>97</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>N. B.</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>58</td>
<td>-</td>
<td>-</td>
<td>42</td>
<td>11</td>
</tr>
</tbody>
</table>
Chromatograms of the products of

Fig. 5  Deoxygenation of 2-nitrophenyl 3'-chlorophenyl sulphide
Fig. 6  Deoxygenation of 2-nitrosophenyl 3'-chlorophenyl sulphide
Fig. 7  Thermolysis of 2-azidophenyl 3'-chlorophenyl sulphide in decalin
Fig. 8  Thermolysis of 2-azidophenyl 3'-chlorophenyl sulphide in triethyl phosphate.

1 = 1-chlorophenothiazine  2 = 2-chlorophenothiazine
3 = 3-chlorophenothiazine  4 = 4-chlorophenothiazine
5 = 2-nitrophenyl 3'-chlorophenyl sulphide  6 = 2-aminophenyl 3'-chlorophenyl sulphide
7 = marker
Table 18: Products of the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 3'-chlorophenyl sulphides

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro yield</th>
<th>amine yield</th>
<th>2- yield</th>
<th>3- yield</th>
<th>4- yield</th>
<th>Phenothiazine yield</th>
<th>Acc yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO2</td>
<td>12</td>
<td>3</td>
<td>trace</td>
<td>39</td>
<td>trace</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>NO</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>39</td>
<td>0</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>dec</td>
<td>trace</td>
<td>3</td>
<td>27</td>
<td>10</td>
<td>29</td>
<td>15</td>
<td>46</td>
</tr>
<tr>
<td>phos</td>
<td>trace</td>
<td>2</td>
<td>28</td>
<td>1</td>
<td>34</td>
<td>4</td>
<td>61</td>
</tr>
<tr>
<td>cum</td>
<td>1</td>
<td>2</td>
<td>24</td>
<td>5</td>
<td>35</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>DMSO</td>
<td>trace</td>
<td>trace</td>
<td>11</td>
<td>53</td>
<td>17</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>N. B.</td>
<td>0</td>
<td>trace</td>
<td>33</td>
<td>56</td>
<td>6</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>dec(152°)</td>
<td>0</td>
<td>1</td>
<td>11</td>
<td>27</td>
<td>23</td>
<td>21</td>
<td>29</td>
</tr>
<tr>
<td>dec(136°)</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>*</td>
<td>35</td>
<td>16</td>
<td>49</td>
</tr>
<tr>
<td>phos(152°)</td>
<td>0</td>
<td>4</td>
<td>10</td>
<td>10</td>
<td>30</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>phos(136°)</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>*</td>
<td>35</td>
<td>3</td>
<td>62</td>
</tr>
</tbody>
</table>

* A large peak for unreacted azide was seen in the chromatogram. This prevented an estimation of the yield of 1-chlorophenothiazine.
Table 19  
Products of the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 4'-chlorophenyl sulphides

![Chemical structure](attachment:image.png)

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro</th>
<th>amine</th>
<th>yield (%)</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
<th>Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>8</td>
<td>2</td>
<td>74</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>NO</td>
<td>4</td>
<td>6</td>
<td>24</td>
<td>trace</td>
<td>100</td>
<td>-</td>
<td>trace</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>dec</td>
<td>3</td>
<td>1</td>
<td>48</td>
<td>4</td>
<td>96</td>
<td>-</td>
<td>1</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>phos</td>
<td>2</td>
<td>4</td>
<td>79</td>
<td>1</td>
<td>99</td>
<td>-</td>
<td>trace</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>cum</td>
<td>3</td>
<td>2</td>
<td>45</td>
<td>1</td>
<td>99</td>
<td>-</td>
<td>2</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>4</td>
<td>0</td>
<td>8</td>
<td>5</td>
<td>95</td>
<td>-</td>
<td>1</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>N. B.</td>
<td>0</td>
<td>1</td>
<td>10</td>
<td>18</td>
<td>82</td>
<td>-</td>
<td>15</td>
<td>26</td>
<td></td>
</tr>
</tbody>
</table>
Table 20  Products of the cyclisations of 2-nitro, 2-nitroso-
and 2-azidophenyl 6'-methylphenyl sulphides

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro (%)</th>
<th>amine (%)</th>
<th>yield (%)</th>
<th>1-Phenothiazine (%)</th>
<th>2-Phenothiazine (%)</th>
<th>3-Phenothiazine (%)</th>
<th>4-Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>13</td>
<td>3</td>
<td>67</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NO</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>dec</td>
<td>0</td>
<td>1</td>
<td>56</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>phos</td>
<td>0</td>
<td>4</td>
<td>61</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>cum</td>
<td>0</td>
<td>8</td>
<td>58</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DMSO</td>
<td>0</td>
<td>9</td>
<td>44</td>
<td>99</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>N. B.</td>
<td>0</td>
<td>-</td>
<td>76</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Thermolysis of 2-azidophenyl 6'-methylphenyl sulphide at 169°, 152°
and 136° in decalin and triethyl phosphate showed no trace of 4-
methylphenothiazine.
Chromatograms of the products of
Deoxygenation of 2-nitrophenyl 3'-methylphenyl sulphide
Deoxygenation of 2-nitrosophenyl 3'-methylphenyl sulphide
Thermolysis of 2-azidophenyl 3'-methylphenyl sulphide
in decalin
Thermolysis of 2-azidophenyl 3'-methylphenyl sulphide
in triethyl phosphate.

1 = 1-methylphenothiazine  
3 = 3-methylphenothiazine  
5 = 2-nitrophenyl 3'-methylphenyl sulphide

2 = 2-methylphenothiazine  
4 = 4-methylphenothiazine
6 = 2-aminophenyl 3'-methylphenyl sulphide
7 = marker
Table 21  Products of the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 3'-methylphenyl sulphide

![Graphic Representation of the Molecule](109)

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro (%)</th>
<th>amine yield (%)</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
<th>Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>12</td>
<td>2</td>
<td>76. 1</td>
<td>49</td>
<td>2</td>
<td>48</td>
<td>0</td>
<td>90</td>
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<tr>
<td>NO</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>11</td>
<td>33</td>
<td>1</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>dec</td>
<td>2</td>
<td>2</td>
<td>67</td>
<td>1</td>
<td>42</td>
<td>2</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>phos</td>
<td>4</td>
<td>5</td>
<td>62</td>
<td>8</td>
<td>35</td>
<td>3</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>cum</td>
<td>1</td>
<td>3</td>
<td>77</td>
<td>1</td>
<td>41</td>
<td>2</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>DMSO</td>
<td>1</td>
<td>1</td>
<td>39</td>
<td>4</td>
<td>37</td>
<td>3</td>
<td>56</td>
<td>0</td>
</tr>
<tr>
<td>N. B.</td>
<td>2</td>
<td>4</td>
<td>56</td>
<td>2</td>
<td>38</td>
<td>2</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td>dec (169°)</td>
<td>2</td>
<td>2</td>
<td>67</td>
<td>1</td>
<td>43</td>
<td>2</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>dec (152°)</td>
<td>1</td>
<td>2</td>
<td>60</td>
<td>1</td>
<td>36</td>
<td>2</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td>dec * (136°)</td>
<td>2</td>
<td>5</td>
<td>46</td>
<td>15</td>
<td>30</td>
<td>7</td>
<td>47</td>
<td>0</td>
</tr>
<tr>
<td>phos (169°)</td>
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<td>5</td>
<td>27</td>
<td>19</td>
<td>28</td>
<td>6</td>
<td>47</td>
<td>0</td>
</tr>
</tbody>
</table>

* At 136° a peak for undecomposed azide was seen in the chromatogram.
Table 22  Products of the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 4'-methylphenyl sulphide.

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro</th>
<th>amine yield</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>Phenothiazine</th>
<th>Acc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>NO₂</td>
<td>15</td>
<td>3</td>
<td>33</td>
<td>-</td>
<td>0</td>
<td>100</td>
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<td>100</td>
<td>-</td>
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<tr>
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<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
</tr>
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<td>phos</td>
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<td>100</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>cum</td>
<td>0</td>
<td>0</td>
<td>57</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>DMSO</td>
<td>0</td>
<td>0</td>
<td>43</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>N.B.</td>
<td>0</td>
<td>1</td>
<td>35</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

Thermolysis of 2-azidophenyl 4'-methylphenyl sulphide at 136°, 152° and 169° in decalin and triethyl phosphate showed no trace of 2-methylphenothiazine.
Table 23  Products of the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 2'-methoxyphenyl sulphide

![Chemical Structure]

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro amine yield</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>16 0 64 100 - - 0 1</td>
<td>81</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dec</td>
<td>0 13 70 100 - - 0 1</td>
<td>84</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>phos</td>
<td>0 9 77 100 - - 0 1</td>
<td>87</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cum</td>
<td>0 16 68 100 - - 0 1</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMSO</td>
<td>0 3 65 100 - - 0 1</td>
<td>69</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N. B.</td>
<td>0 13 60 100 - - 0 1</td>
<td>74</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chromatograms of the products of

Fig. 13  Deoxygenation of 2-nitrophenyl 3'-methoxyphenyl sulphide
Fig. 14  Deoxygenation of 2-nitrosophenyl 3'-methoxyphenyl sulphide
Fig. 15  Thermolysis of 2-azidophenyl 3'-methoxyphenyl sulphide in decalin
Fig. 16  Thermolysis of 2-azidophenyl 3'-methoxyphenyl sulphide in triethyl phosphate

1 = 1-methoxyphenothiazine  2 = 2-methoxyphenothiazine
3 = 3-methoxyphenothiazine  4 = 4-methoxyphenothiazine
5 = 2-nitrophenyl 3'-methoxy  6 = 2-aminophenyl 3'-methoxy-
6-phenyl sulphide
7 = marker
Table 24  Products of the cyclisations of 2-nitro-2-nitroso- and 2-azidophenyl 3'-methoxyphenyl sulphide

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro</th>
<th>amine yield</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>Phenothiazine (%)</th>
<th>Acc  (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>18</td>
<td>2</td>
<td>60</td>
<td>5</td>
<td>56</td>
<td>1</td>
<td>38</td>
<td>0</td>
</tr>
<tr>
<td>NO</td>
<td>1</td>
<td>5</td>
<td>9</td>
<td>trace</td>
<td>55</td>
<td>1</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>dec</td>
<td>1</td>
<td>trace</td>
<td>57</td>
<td>3</td>
<td>54</td>
<td>4</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>phos</td>
<td>3</td>
<td>1</td>
<td>57</td>
<td>50</td>
<td>18</td>
<td>15</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>cum</td>
<td>11</td>
<td>1</td>
<td>61</td>
<td>9</td>
<td>49</td>
<td>5</td>
<td>37</td>
<td>0</td>
</tr>
<tr>
<td>DMSO</td>
<td>0</td>
<td>5</td>
<td>43</td>
<td>40</td>
<td>32</td>
<td>6</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>N. B.</td>
<td>0</td>
<td>2</td>
<td>35</td>
<td>*</td>
<td>52</td>
<td>6</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>dec(152°)</td>
<td>0</td>
<td>1</td>
<td>52</td>
<td>5</td>
<td>42</td>
<td>3</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>dec(136°)</td>
<td>0</td>
<td>1</td>
<td>22</td>
<td>6</td>
<td>38</td>
<td>1</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>phos(152°)</td>
<td>0</td>
<td>3</td>
<td>42</td>
<td>60</td>
<td>12</td>
<td>17</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>phos(136°)</td>
<td>0</td>
<td>2</td>
<td>29</td>
<td>66</td>
<td>9</td>
<td>15</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

* Nitrobenzene peak interferes in chromatogram but probably <5%.

† The exact value is difficult to determine because 1-methoxyphenothiazine lies close to the unretained peak but it is probably <5%.

‡ A large peak for unreacted azide is seen in the chromatogram.
Table 25 Products of the cyclisations of 2-nitro-, 2-nitroso-
and 2-azidophenyl 4'-methoxyphenyl sulphide

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro (%)</th>
<th>amine (%)</th>
<th>yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>16</td>
<td>2</td>
<td>51</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>69</td>
</tr>
<tr>
<td>dec</td>
<td>1</td>
<td>1</td>
<td>88</td>
<td>-</td>
<td>trace</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>90</td>
</tr>
<tr>
<td>phos</td>
<td>trace</td>
<td>0</td>
<td>71</td>
<td>-</td>
<td>trace</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>cum</td>
<td>0</td>
<td>6</td>
<td>87</td>
<td>-</td>
<td>trace</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>93</td>
</tr>
<tr>
<td>DMSO</td>
<td>4</td>
<td>0</td>
<td>.27</td>
<td>-</td>
<td>1</td>
<td>99</td>
<td>-</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>N.B.</td>
<td>0</td>
<td>0</td>
<td>.69</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>69</td>
</tr>
</tbody>
</table>
Table 26  Products of the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 2'-trifluoromethylphenyl sulphide

![Chemical Structure]

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro (%)</th>
<th>amine (%)</th>
<th>yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>21</td>
<td>1</td>
<td>32</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>54</td>
</tr>
<tr>
<td>dec</td>
<td>0</td>
<td>0</td>
<td>66</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>phos</td>
<td>0</td>
<td>0</td>
<td>54</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>54</td>
</tr>
<tr>
<td>cum</td>
<td>0</td>
<td>0</td>
<td>65</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>65</td>
</tr>
<tr>
<td>DMSO</td>
<td>0</td>
<td>0</td>
<td>15</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>N. B.</td>
<td>0</td>
<td>0</td>
<td>57</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
<td>0</td>
<td>57</td>
</tr>
</tbody>
</table>
Chromatograms of the products of

Deoxygenation of 2-nitrophenyl 3'-trifluoromethylphenyl sulphide

Deoxygenation of 2-nitrosophenyl 3'-trifluoromethylphenyl sulphide

Thermolysis of 2-azidophenyl 3'-trifluoromethylphenyl sulphide in decalin

Thermolysis of 2-azidophenyl 3'-trifluoromethylphenyl sulphide in triethyl phosphate.

1 = 1-trifluoromethylphenothiazine 2 = 2-trifluoromethylphenothiazine
3 = 3-trifluoromethylphenothiazine 4 = 4-trifluoromethylphenothiazine
5 = 2-nitrophenyl 3'-trifluoromethylphenyl sulphide 6 = 2-aminophenyl 3'-trifluoro-
7 = marker
Table 27  Products of the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 3'-trifluoromethylphenyl sulphide

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro (%)</th>
<th>amine (%)</th>
<th>yield (%)</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
<th>Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>11</td>
<td>33</td>
<td>0</td>
<td>85</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>NO</td>
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<td>7</td>
<td>8</td>
<td>0</td>
<td>79</td>
<td>0</td>
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<td>0</td>
<td>88</td>
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<td>12</td>
<td>0</td>
<td>54</td>
</tr>
<tr>
<td>phos</td>
<td>0</td>
<td>4</td>
<td>46</td>
<td>0</td>
<td>55</td>
<td>0</td>
<td>45</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>cum</td>
<td>0</td>
<td>3</td>
<td>32</td>
<td>0</td>
<td>90</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>DMSO</td>
<td>0</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>43</td>
<td>0</td>
<td>57</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>N. B.</td>
<td>0</td>
<td>5</td>
<td>40</td>
<td>0</td>
<td>75</td>
<td>0</td>
<td>25</td>
<td>0</td>
<td>45</td>
</tr>
<tr>
<td>(MeO)₃P=O*</td>
<td>0</td>
<td>5</td>
<td>9</td>
<td>0</td>
<td>54</td>
<td>0</td>
<td>46</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>(Me₂N)₃P=O†</td>
<td>0</td>
<td>15</td>
<td>28</td>
<td>0</td>
<td>45</td>
<td>0</td>
<td>55</td>
<td>0</td>
<td>43</td>
</tr>
</tbody>
</table>

* The reaction was performed as set out in D (i) f (above) but using trimethyl phosphate as the solvent.

† The reaction was performed as set out in D (i) f (above) but using hexamethylphosphoramide as the solvent.
Table 28  Products of the cyclisations of 2-nitro-, 2-nitroso-
and 2-azidophenyl 4'-trifluoromethylphenyl sulphide

![Chemical Structure]

<table>
<thead>
<tr>
<th>Rn</th>
<th>nitro (%)</th>
<th>amine (%)</th>
<th>yield (%)</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
<th>Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>12</td>
<td>1</td>
<td>27</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>dec</td>
<td>0</td>
<td>6</td>
<td>72</td>
<td>1</td>
<td>99</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>78</td>
</tr>
<tr>
<td>phos</td>
<td>0</td>
<td>6</td>
<td>43</td>
<td>6</td>
<td>94</td>
<td>-</td>
<td>0</td>
<td>49</td>
<td>49</td>
</tr>
<tr>
<td>cum</td>
<td>0</td>
<td>6</td>
<td>43</td>
<td>5</td>
<td>95</td>
<td>-</td>
<td>0</td>
<td>49</td>
<td>49</td>
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<tr>
<td>DMSO</td>
<td>0</td>
<td>trace</td>
<td>18</td>
<td>7</td>
<td>93</td>
<td>-</td>
<td>0</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>N.B.</td>
<td>0</td>
<td>5</td>
<td>31</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>
Table 29  Deoxygenation of aryl 2-nitrophenyl sulphones in ethanol/acetic acid

<table>
<thead>
<tr>
<th>R</th>
<th>nitro (%)</th>
<th>amine (%)</th>
<th>yield (%)</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
<th>Phenothiazine (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me</td>
<td>56</td>
<td>8</td>
<td>4.42</td>
<td>98</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>0</td>
<td>68.42</td>
</tr>
<tr>
<td>3-Me</td>
<td>50</td>
<td>9</td>
<td>2.15</td>
<td>2</td>
<td>43</td>
<td>5</td>
<td>50</td>
<td>0</td>
<td>61.15</td>
</tr>
<tr>
<td>4-Me</td>
<td>60</td>
<td>10</td>
<td>2.4</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>0</td>
<td>72.4</td>
</tr>
<tr>
<td>2-OMe</td>
<td>56</td>
<td>0</td>
<td>4.78</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>60.78</td>
</tr>
<tr>
<td>3-OMe</td>
<td>38</td>
<td>6</td>
<td>3.4</td>
<td>0</td>
<td>49</td>
<td>0</td>
<td>51</td>
<td>0</td>
<td>47.4</td>
</tr>
<tr>
<td>4-OMe</td>
<td>59</td>
<td>6</td>
<td>8.17</td>
<td>-</td>
<td>6</td>
<td>94</td>
<td>-</td>
<td>0</td>
<td>73.17</td>
</tr>
<tr>
<td>2-Cl</td>
<td>66</td>
<td>3</td>
<td>0.2</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0.1</td>
<td>69.3</td>
</tr>
<tr>
<td>3-Cl</td>
<td>60</td>
<td>5</td>
<td>0.55</td>
<td>16</td>
<td>36</td>
<td>26</td>
<td>22</td>
<td>1.3</td>
<td>66.85</td>
</tr>
<tr>
<td>4-Cl</td>
<td>47</td>
<td>6</td>
<td>1.45</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
<td>2</td>
<td>56.45</td>
</tr>
</tbody>
</table>
### Table 30 Deoxygenation of 2-nitroaryl phenyl sulphides

<table>
<thead>
<tr>
<th>R</th>
<th>nitro (%)</th>
<th>2-subst. (%)</th>
<th>4-subst. (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Me</td>
<td>15</td>
<td>69</td>
<td>-</td>
<td>84</td>
</tr>
<tr>
<td>6-Me</td>
<td>13</td>
<td>-</td>
<td>63</td>
<td>76</td>
</tr>
<tr>
<td>4-OMe</td>
<td>9</td>
<td>37</td>
<td>-</td>
<td>46</td>
</tr>
<tr>
<td>6-OMe</td>
<td>7</td>
<td>-</td>
<td>54</td>
<td>61</td>
</tr>
<tr>
<td>4-Cl</td>
<td>2</td>
<td>44</td>
<td>-</td>
<td>46</td>
</tr>
<tr>
<td>6-Cl</td>
<td>8</td>
<td>-</td>
<td>61</td>
<td>69</td>
</tr>
</tbody>
</table>

Treatment of aryl 2-(hydroxyamino)phenyl sulphides with trifluoroacetic acid.

Only minute traces of phenothiazines (0.1-0.2%) were detected.

Treatment of 2-methoxyphenothiazine under the reaction conditions gave a recovery of 77% of the unreacted material.

Photolysis of aryl 2-azidophenyl sulphides

2-Azidophenyl 2'-methylphenyl sulphide was photolysed as a solution in cyclohexane in a Kodak falling-curtain reactor and the reaction monitored by HSLC. A Pyrex filtered 2-foot, 20W, Westinghouse fluorescent Sun Lamp which has a maximum output
at 320 nm was used as a light source. 1-Methylphenothiazine was detected almost at once and it reached its greatest concentration after about 20 min and was then progressively destroyed. Photolysis of 2-azidophenyl 4'-methylphenyl sulphide under the same conditions for 4.5 h gave 3-methylphenothiazine (0.7%). Photolysis of 2-azidophenyl 3'-methoxyphenyl sulphide under the same conditions in cyclohexane and triethyl phosphate for 10 min gave no trace of phenothiazines.

Deoxygenations of aryl 2-nitrosophenyl sulphides at reduced temperatures.

Aryl 2-nitrosophenyl sulphides were deoxygenated by triethyl phosphate in boiling cumene to give phenothiazines in rather poor yield. The results obtained are set out in the Tables above. Similar deoxygenations performed at 0°C gave, however, no phenothiazine products. Only a series of overlapping peaks of low-polarity material was detected by HSLC. At -40°C only minute traces of phenothiazines were obtained and at lower temperatures no appreciable reaction occurred.

2-Nitrosophenyl 4'-chlorophenyl sulphide was left to stand with triethylphosphite in cumene for 10 min at 0°C then the reaction mixture was boiled for 5 min. 3-Chlorophenothiazine (yield = 7%) was detected by HSLC analysis. The yield is poorer than that obtained on adding the nitroso-compound to a boiling mixture of triethylphosphite and cumene (yield = 24%) but if the reaction mixture is analysed before it is boiled no 3-chlorophenothiazine at all is detected.

Deoxygenation of 2-nitrosophenyl 3'-methoxyphenyl sulphide by triethyl phosphate in cumene at 100°C gave an overall phenothiazine yield of 1% compared with an overall phenothiazine yield of 9% when the nitroso compound was added to a boiling mixture of cumene and triethyl phosphate.

2-Nitrosophenyl 2'-chlorophenyl sulphide was deoxygenated by triethyl phosphite in deuterochloroform in the probe of an XL-100 spectrophotometer and phosphorus ($^{31}$P) spectra obtained using
noise decoupling of protons. At -40° triethyl phosphite was observed to gradually disappear and triethyl phosphate gradually appeared. At 0° a similar process occurred but after some time three small peaks at 13.2, 11.8 and 11.7 p.p.m. were observed. On warming to 40° these peaks disappeared and only triethyl phosphate was observed. Chemical shift values were measured against phosphoric acid (85%) as an external standard and upfield shifts are given positive values.

(iii) **Products from the thermolyses of aryl 2-azidophenyl sulphones**

Table 31 (over)
Chromatograms of the products of the thermolyses of aryl 2-azidophenyl sulphones in decalin

Fig. 21  aryl = 2'-methylphenyl  Fig. 22  aryl = 2'-chlorophenyl
Fig. 23  aryl = 2'-methoxyphenyl  Fig. 24  aryl = 2'-trifluoro-

methylphenyl

1 = 1-substituted phenothiazine-5, 5-dioxide  4 = 4-substituted phenothiazine-

5, 5-dioxide

5 = amine corresponding to starting azide  6 = marker
7 = phenothiazine-5, 5-dioxide
Chromatograms of the products of the thermolyses of aryl 2-azidophenyl sulphones in decalin

- **Fig. 25**: aryl = 3'-methylphenyl  
- **Fig. 26**: aryl = 3'-chlorophenyl  
- **Fig. 27**: aryl = 3'-methoxy-phenyl  
- **Fig. 28**: aryl = 3'-trifluoromethyl-phenyl

1 = 1-substituted phenothiazine-5,5-dioxide  
2 = 2-substituted phenothiazine-5,5-dioxide  
3 = 3-substituted phenothiazine-5,5-dioxide  
4 = 4-substituted phenothiazine-5,5-dioxide  
5 = amine corresponding to starting azide  
6 = marker
Chromatograms of the products of the thermolyses of aryl 2-azidophenyl sulphones in decalin

Fig. 29  
aryl = 4'-methylphenyl

Fig. 30  
aryl = 4'-chlorophenyl

Fig. 31  
aryl = 4'-methoxyphenyl

Fig. 32  
aryl = 4'-trifluoromethylphenyl

2 = 2-substituted phenothiazine-5,5-dioxide  
3 = 3-substituted phenothiazine-5,5-dioxide

5 = amine corresponding to starting azide  
6 = marker
<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
<th>amine (%)</th>
<th>PO2 (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me</td>
<td>33</td>
<td>71</td>
<td>-</td>
<td>-</td>
<td>29</td>
<td>6</td>
<td>0</td>
<td>39</td>
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<tr>
<td>3-Me</td>
<td>54</td>
<td>62</td>
<td>7</td>
<td>25</td>
<td>6</td>
<td>11</td>
<td>0</td>
<td>65</td>
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<tr>
<td>4-Me</td>
<td>54</td>
<td>-</td>
<td>58</td>
<td>42</td>
<td>-</td>
<td>10</td>
<td>0</td>
<td>64</td>
</tr>
<tr>
<td>2-OMe</td>
<td>30</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>3-OMe</td>
<td>56</td>
<td>49</td>
<td>4</td>
<td>43</td>
<td>4</td>
<td>12</td>
<td>0</td>
<td>68</td>
</tr>
<tr>
<td>4-OMe</td>
<td>47</td>
<td>-</td>
<td>35</td>
<td>65</td>
<td>-</td>
<td>12</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>2-Cl</td>
<td>63</td>
<td>96</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>7</td>
<td>21</td>
<td>91</td>
</tr>
<tr>
<td>3-Cl</td>
<td>62</td>
<td>37</td>
<td>8</td>
<td>52</td>
<td>3</td>
<td>20</td>
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<td>82</td>
</tr>
<tr>
<td>4-Cl</td>
<td>30</td>
<td>-</td>
<td>62</td>
<td>38</td>
<td>-</td>
<td>20</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>2-CF3</td>
<td>26</td>
<td>80</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>9</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>3-CF3</td>
<td>49</td>
<td>27</td>
<td>24</td>
<td>26</td>
<td>23</td>
<td>21</td>
<td>0</td>
<td>70</td>
</tr>
<tr>
<td>4-CF3</td>
<td>28</td>
<td>-</td>
<td>85</td>
<td>15</td>
<td>-</td>
<td>30</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>4-Bu</td>
<td>50</td>
<td>-</td>
<td>58</td>
<td>42</td>
<td>-</td>
<td>23</td>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>2,6-diCl</td>
<td>29</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>2,6-diCl</td>
<td>23 (152°)</td>
<td>97</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>2,6-diCl</td>
<td>7 (136°)</td>
<td>88</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>2</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>
Table 32  Products from the thermolyses of aryl 2-azido-phenyl sulphones in triethyl phosphate

<table>
<thead>
<tr>
<th>R=</th>
<th>Yield (%)</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
<th>amine (%)</th>
<th>PO$_2$ (%)</th>
<th>Acc (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me</td>
<td>54</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>2</td>
<td>0</td>
<td>56</td>
</tr>
<tr>
<td>3-Me</td>
<td>84</td>
<td>57</td>
<td>13</td>
<td>21</td>
<td>9</td>
<td>3</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>4-Me</td>
<td>68</td>
<td>-</td>
<td>44</td>
<td>56</td>
<td>-</td>
<td>6</td>
<td>0</td>
<td>74</td>
</tr>
<tr>
<td>2-OMe</td>
<td>33</td>
<td>99</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>3-OMe</td>
<td>79</td>
<td>53</td>
<td>11</td>
<td>27</td>
<td>9</td>
<td>8</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>4-OMe</td>
<td>82</td>
<td>-</td>
<td>25</td>
<td>75</td>
<td>-</td>
<td>3</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>2-Cl</td>
<td>40</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>trace</td>
<td>2</td>
<td>6</td>
<td>48</td>
</tr>
<tr>
<td>3-Cl</td>
<td>62</td>
<td>12</td>
<td>11</td>
<td>75</td>
<td>2</td>
<td>4</td>
<td>0</td>
<td>66</td>
</tr>
<tr>
<td>4-Cl</td>
<td>44</td>
<td>-</td>
<td>39</td>
<td>61</td>
<td>-</td>
<td>9</td>
<td>0</td>
<td>53</td>
</tr>
<tr>
<td>2-CF$_3$</td>
<td>34</td>
<td>85</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>3</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>3-CF$_3$</td>
<td>22</td>
<td>47</td>
<td>14</td>
<td>27</td>
<td>12</td>
<td>4</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>4-CF$_3$</td>
<td>21</td>
<td>-</td>
<td>79</td>
<td>21</td>
<td>-</td>
<td>26</td>
<td>0</td>
<td>47</td>
</tr>
<tr>
<td>4-Bu$^t$</td>
<td>67</td>
<td>-</td>
<td>43</td>
<td>57</td>
<td>-</td>
<td>10</td>
<td>0</td>
<td>77</td>
</tr>
<tr>
<td>2,6-diCl</td>
<td>14</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>2,6-diCl</td>
<td>12</td>
<td>99</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2,6-diCl</td>
<td>3</td>
<td>96</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>0</td>
<td>trace</td>
<td>3</td>
</tr>
</tbody>
</table>

(152°)

(136°)
Thermolysis of 2-azidophenyl 2'-pyridyl sulphone

Thermolysis of 2-azidophenyl 2'-pyridyl sulphone in decalin and in triethyl phosphate gave only a small amount of low-polarity material (by HSLC). The most polar compound present was identified as 2-aminophenyl 2'-pyridyl sulphone (yield about 10%).

Thermolysis of 2-azidophenyl 2', 6'-dimethoxyphenyl sulphone

Thermolysis of 2-azidophenyl 2', 6'-dimethoxyphenyl sulphone in decalin and triethyl phosphate gave only a small amount of low-polarity material (by HSLC). No compounds could be identified and all the material was of much lower polarity than any of the methoxyphenothiazine-5, 5-dioxides.

Deoxygenation of 2-nitrophenyl 4'-chlorophenyl sulphone

Deoxygenation of 2-nitrophenyl 4'-chlorophenyl sulphone by triethyl phosphite using the normal conditions gave only low-polarity material (by HSLC). Neither 2- nor 3-chlorophenothiazine-5, 5-dioxide were present.
(iv) The stability of phenothiazines and phenothiazine-5, 5-dioxides under the reaction conditions.

In order to determine whether the phenothiazines and phenothiazine-5, 5-dioxides were stable under the reaction conditions a mixture of the four isomeric mono-substituted phenothiazines (or phenothiazine-5, 5-dioxides) was made up for each substituent used. This mixture was dissolved in dichloromethane and a small portion removed as a standard. An equal portion was removed, evaporated and dissolved in decalin. This solution was heated over 30 min. until it was boiling then boiled under reflux under nitrogen for 2 h. In a similar fashion equal portions were thermolysed under the same conditions and in approximately the same concentrations as were used for the reactions. The reaction mixtures were worked up as previously and an equal portion of a solution of a marker compound added to each. An equal portion of this solution was also added to the standard which had been previously removed. HSLC analysis then enabled the percentage recovery of each phenothiazine to be calculated and these results are given in the following tables (33-38). The abbreviations used below are the same as those listed above.

Table 33 Percentage recovery of methylphenothiazines under various reaction conditions

<table>
<thead>
<tr>
<th></th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rn dec</td>
<td>76</td>
<td>58</td>
<td>47</td>
<td>66</td>
</tr>
<tr>
<td>phos</td>
<td>93</td>
<td>93</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>DMSO N. B.</td>
<td>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* no return</td>
<td>100</td>
<td>57</td>
<td>52</td>
<td>74</td>
</tr>
</tbody>
</table>
### Table 34
**Percentage recovery of methoxyphenothiazines under various reaction conditions**

<table>
<thead>
<tr>
<th>Rn</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>dec</td>
<td>100</td>
<td>86</td>
<td>71</td>
<td>97</td>
</tr>
<tr>
<td>phos</td>
<td>93</td>
<td>75</td>
<td>65</td>
<td>82</td>
</tr>
<tr>
<td>DMSO</td>
<td>100</td>
<td>17</td>
<td>32</td>
<td>61</td>
</tr>
<tr>
<td>N. B.</td>
<td>100</td>
<td>79</td>
<td>89</td>
<td>82</td>
</tr>
</tbody>
</table>

### Table 35
**Percentage recovery of chlorophenothiazines under various reaction conditions**

<table>
<thead>
<tr>
<th>Rn</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>dec</td>
<td>75</td>
<td>87</td>
<td>64</td>
<td>84</td>
</tr>
<tr>
<td>phos</td>
<td>93</td>
<td>91</td>
<td>92</td>
<td>93</td>
</tr>
<tr>
<td>DMSO</td>
<td>67</td>
<td>80</td>
<td>37</td>
<td>63</td>
</tr>
<tr>
<td>N. B.</td>
<td>98</td>
<td>73</td>
<td>48</td>
<td>73</td>
</tr>
</tbody>
</table>
Table 36  Percentage recovery of trifluoromethylphenothiazines under various reaction conditions

<table>
<thead>
<tr>
<th>Rn</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>dec</td>
<td>63</td>
<td>60</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>phos</td>
<td>51</td>
<td>60</td>
<td>64</td>
<td>57</td>
</tr>
<tr>
<td>DMSO</td>
<td>80</td>
<td>72</td>
<td>77</td>
<td>78</td>
</tr>
<tr>
<td>N. B.</td>
<td>72</td>
<td>30</td>
<td>68</td>
<td>60</td>
</tr>
</tbody>
</table>

Table 37  Percentage recovery of phenothiazine-5, 5-dioxides when thermolysed in decalin

<table>
<thead>
<tr>
<th>R=</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>77</td>
<td>57</td>
<td>98</td>
<td>55</td>
</tr>
<tr>
<td>OMe</td>
<td>76</td>
<td>73</td>
<td>51</td>
<td>78</td>
</tr>
<tr>
<td>Cl</td>
<td>78</td>
<td>71</td>
<td>63</td>
<td>54</td>
</tr>
<tr>
<td>CF₃</td>
<td>94</td>
<td>95</td>
<td>89</td>
<td>80</td>
</tr>
</tbody>
</table>
Table 38  Percentage recovery of phenothiazine-5, 5-dioxides when thermolysed in triethyl phosphate

\[
\begin{array}{ccccc}
R = & 1- & 2- & 3- & 4- \\
Me & 78 & 57 & 98 & 55 \\
OMe & 89 & 87 & 87 & 42 \\
Cl & 84 & 75 & 54 & 58 \\
CF_3 & 89 & 88 & 80 & 85 \\
\end{array}
\]

The simulation of the deoxygenation reactions in this fashion proved, however, to be rather more difficult. Thermolysis of phenothiazines in boiling cumene for 72 h gave the results shown below in Table 39.

Table 39  Percentage recovery of phenothiazines after thermolysis in boiling cumene for 72 h

\[
\begin{array}{ccccc}
R = & 1- & 2- & 3- & 4- \\
Me & 0 & 0 & 5 & 5 \\
OMe & 0 & 0 & 0 & 0 \\
Cl & 62 & 5 & 0 & 0 \\
\end{array}
\]

However the deoxygenation of 2'-substituted aryl 2-nitrophenyl
sulphides gives 1-substituted phenothiazines and the deoxygenation of 4'-substituted aryl 2-nitrophenyl sulphides gives 3-substituted phenothiazines (see above Tables 17-28). Similarly the deoxygenation of 2-nitro-4-substituted phenyl phenyl sulphides gives 2-substituted phenothiazines and the deoxygenation of 2-nitro-6-substituted phenyl phenyl sulphides gives 4-substituted phenothiazines (see above Table 29). When the yields obtained in these reactions are corrected for the presence of amine and unreacted starting material a minimum value for the stability of the phenothiazines under the conditions of deoxygenation is obtained. These figures are minimum values and could be higher if side reactions are consuming the starting material. The figures for 2- and 4-trifluoromethylphenothiazine are based on the deoxygenation of 2-nitrophenyl 3'-trifluoromethylphenyl and assume that they both have the same stability.

Table 40  
Percentage conversion of aryl 2-nitrophenyl sulphides to phenothiazines

<table>
<thead>
<tr>
<th>R</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>80</td>
<td>81</td>
<td>40</td>
<td>72</td>
</tr>
<tr>
<td>Cl</td>
<td>40</td>
<td>45</td>
<td>82</td>
<td>66</td>
</tr>
<tr>
<td>OMe</td>
<td>77</td>
<td>41</td>
<td>62</td>
<td>58</td>
</tr>
<tr>
<td>CF₃</td>
<td>41</td>
<td>37</td>
<td>31</td>
<td>37</td>
</tr>
</tbody>
</table>

The yields are much higher than those shown in Table 39 and so the various phenothiazines were thermolysed in boiling cumene with about 2% triethyl phosphate added for 72 h. The results are shown in Table 41.
Table 41  

<table>
<thead>
<tr>
<th>R</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>20</td>
<td>11</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>Cl</td>
<td>98</td>
<td>27</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>MeO</td>
<td>83</td>
<td>38</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>CF₃</td>
<td>33</td>
<td>35</td>
<td>30</td>
<td>36</td>
</tr>
</tbody>
</table>

These conditions only approximate to the conditions of a deoxygenation because during a deoxygenation the concentrations of phenothiazine and triethyl phosphate vary with time. Nevertheless when compared with Table 39 the triethyl phosphate appears to protect the phenothiazines. It would seem that a combination of triethyl phosphate and triethyl phosphite is necessary to protect the phenothiazine and when 3-methoxyphenothiazine was thermolysed in cumene containing a little triethyl phosphate and triethyl phosphite no diminution of phenothiazine was observed when the reaction was monitored by HSLC.

It appears that a combination of the two is necessary because when phenothiazines are thermolysed in cumene with a little triethyl phosphite for only 2.5 h considerable diminution is seen.
Table 42  
Percentage recovery of phenothiazines after  
thermolysis in boiling cumene/triethyl phosphite  
for 2.5 h

<table>
<thead>
<tr>
<th></th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>75</td>
<td>70</td>
<td>46</td>
<td>71</td>
</tr>
<tr>
<td>Cl</td>
<td>100</td>
<td>100</td>
<td>14</td>
<td>77</td>
</tr>
<tr>
<td>OMe</td>
<td>100</td>
<td>31</td>
<td>33</td>
<td>77</td>
</tr>
</tbody>
</table>

These results do not really bear much resemblance to the 
yields obtained in actual deoxygenations (Table 40) and so it seems  
that the processes occurring during a deoxygenation are so complex  
that they cannot be adequately simulated with a simple system.  
However the essential point is that all phenothiazines have a roughly  
similar stability under deoxygenation conditions and this was shown  
by Table 40. The yields of phenothiazines from the deoxygenation  
reactions were corrected using the data in Table 40. The yields  
of phenothiazines obtained during thermolysis of the azides in cumene  
were corrected using the data in Tables 33-36 for the thermolysis of  
the phenothiazines in decalin. This is also an inert solvent.

(v) Results corrected for the destruction of products

The results given below are corrected to allow for the  
destruction of the various isomers under the reaction conditions.  
Each isomer is shown as a percentage of the total phenothiazine  
yield. It should be noted however that these results are based on  
the assumptions that the phenothiazines are produced almost at once  
and that they are all produced at the same rate. The slow production  
of phenothiazines may thus lead to yields of greater than 100%.
However it is the comparative figures for the isomer ratios which matter. In fact it will be seen that the isomer ratios do not differ greatly from the uncorrected values.

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>85</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>NO₂*</td>
<td>26</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>dec</td>
<td>80</td>
<td>97</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>phosph</td>
<td>72</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>cum</td>
<td>91</td>
<td>100</td>
<td></td>
<td></td>
<td>trace</td>
</tr>
<tr>
<td>DMSO</td>
<td>20</td>
<td>97</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>N.B.</td>
<td>27</td>
<td>51</td>
<td></td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>

* uncorrected results

Table 43: Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 2'-chlorophenyl sulphides (corrected for the destruction of phenothiazines). (See Table 17).

![Chemical Structure](image)
### Table 44

Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 3'-chlorophenyl sulphides (corrected for the destruction of phenothiazines) (see Table 18)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>68</td>
<td>trace</td>
<td>48</td>
<td>trace</td>
<td>52</td>
</tr>
<tr>
<td>NO*</td>
<td>8</td>
<td>3</td>
<td>39</td>
<td>0</td>
<td>58</td>
</tr>
<tr>
<td>dec</td>
<td>34</td>
<td>11</td>
<td>26</td>
<td>19</td>
<td>44</td>
</tr>
<tr>
<td>phos</td>
<td>30</td>
<td>1</td>
<td>34</td>
<td>4</td>
<td>61</td>
</tr>
<tr>
<td>cum</td>
<td>29</td>
<td>6</td>
<td>33</td>
<td>6</td>
<td>55</td>
</tr>
<tr>
<td>DMSO</td>
<td>16</td>
<td>53</td>
<td>14</td>
<td>2</td>
<td>31</td>
</tr>
<tr>
<td>N. B.</td>
<td>45</td>
<td>42</td>
<td>6</td>
<td>42</td>
<td>10</td>
</tr>
<tr>
<td>dec(152°)‡</td>
<td>14</td>
<td>28</td>
<td>20</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>dec(136°)‡</td>
<td>5</td>
<td>+</td>
<td>36</td>
<td>19</td>
<td>45</td>
</tr>
<tr>
<td>phos(152°)‡</td>
<td>11</td>
<td>10</td>
<td>30</td>
<td>5</td>
<td>55</td>
</tr>
<tr>
<td>phos(136°)‡</td>
<td>5</td>
<td>+</td>
<td>35</td>
<td>3</td>
<td>62</td>
</tr>
</tbody>
</table>

* uncorrected results

‡ 1-chlorophenothiazine obscured in chromatogram by large peak for unreacted azide.

‡ corrected using the data in Table 35 obtained at 190°.
Table 45  

**Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso-, and 2-azidophenyl 4'-chlorophenyl sulphides (corrected for the destruction of phenothiazines)** (see Table 19)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>90</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>NO*</td>
<td>24</td>
<td>-</td>
<td>trace</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>dec</td>
<td>74</td>
<td>-</td>
<td>3</td>
<td>97</td>
<td>-</td>
</tr>
<tr>
<td>phos</td>
<td>86</td>
<td>-</td>
<td>1</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>cum</td>
<td>70</td>
<td>-</td>
<td>1</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>DMSO</td>
<td>16</td>
<td>-</td>
<td>3</td>
<td>97</td>
<td>-</td>
</tr>
<tr>
<td>N. B.</td>
<td>20</td>
<td>-</td>
<td>13</td>
<td>87</td>
<td>-</td>
</tr>
</tbody>
</table>

* uncorrected results.

Table 46  

**Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 2'-methylphenyl sulphides (corrected for the destruction of phenothiazines)** (see Table 20)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>84</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>NO*</td>
<td>22</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>dec</td>
<td>74</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>
### Table 46 (cont)

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>phos</td>
<td>66</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>cum</td>
<td>76</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>DMSO*</td>
<td>44</td>
<td>99</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>N. B.</td>
<td>76</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
</tr>
</tbody>
</table>

* uncorrected results

### Table 47

Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 3'-methylphenyl sulphides (corrected for the destruction of phenothiazines) (see Table 21)

![Phenothiazine Structure]

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>101</td>
<td>1</td>
<td>45</td>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>NO*</td>
<td>11</td>
<td>11</td>
<td>33</td>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>dec</td>
<td>108</td>
<td>1</td>
<td>45</td>
<td>3</td>
<td>51</td>
</tr>
<tr>
<td>phos</td>
<td>67</td>
<td>8</td>
<td>34</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>cum</td>
<td>124</td>
<td>1</td>
<td>44</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>DMSO*</td>
<td>39</td>
<td>4</td>
<td>37</td>
<td>3</td>
<td>56</td>
</tr>
<tr>
<td>N. B.</td>
<td>85</td>
<td>1</td>
<td>44</td>
<td>3</td>
<td>52</td>
</tr>
<tr>
<td>dec(169°)†</td>
<td>108</td>
<td>1</td>
<td>46</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>dec(152°)†</td>
<td>96</td>
<td>1</td>
<td>39</td>
<td>3</td>
<td>57</td>
</tr>
<tr>
<td>dec(136°)†</td>
<td>50</td>
<td>1</td>
<td>38</td>
<td>4</td>
<td>57</td>
</tr>
</tbody>
</table>
Table 47 (cont.)

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>phos(169°)</td>
<td>56</td>
<td>11</td>
<td>32</td>
<td>4</td>
<td>53</td>
</tr>
<tr>
<td>phos(152°)</td>
<td>50</td>
<td>15</td>
<td>30</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>phos(136°)</td>
<td>29</td>
<td>19</td>
<td>28</td>
<td>6</td>
<td>47</td>
</tr>
</tbody>
</table>

* uncorrected results
/ corrected using the data in Table 33 obtained at 190°.

Table 48

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield</th>
<th>1- (%)</th>
<th>2- (%)</th>
<th>3- (%)</th>
<th>4- (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO2</td>
<td>82</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>NO*</td>
<td>7</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>dec</td>
<td>108</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>phos</td>
<td>51</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>cum</td>
<td>121</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>DMSO*</td>
<td>43</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>N.B.</td>
<td>67</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
</tbody>
</table>

* uncorrected results
Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 2'-methoxy-phenyl sulphides (corrected for the destruction of phenothiazines) (see Table 23)

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>83</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>dec</td>
<td>70</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>phos</td>
<td>83</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>cum</td>
<td>68</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>DMSO</td>
<td>65</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>N. B.</td>
<td>60</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
### Table 50

Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 3'-methoxyphenyl sulphides *(corrected for the destruction of phenothiazines)* *(see Table 24)*

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>126</td>
<td>3</td>
<td>65</td>
<td>1</td>
<td>31</td>
</tr>
<tr>
<td>NO⁺</td>
<td>9</td>
<td>trace</td>
<td>55</td>
<td>1</td>
<td>44</td>
</tr>
<tr>
<td>dec</td>
<td>84</td>
<td>3</td>
<td>56</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>phos</td>
<td>69</td>
<td>44</td>
<td>20</td>
<td>19</td>
<td>17</td>
</tr>
<tr>
<td>cum</td>
<td>68</td>
<td>8</td>
<td>52</td>
<td>6</td>
<td>34</td>
</tr>
<tr>
<td>DMSO</td>
<td>122</td>
<td>14</td>
<td>66</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>N. B.</td>
<td>43</td>
<td>+</td>
<td>53</td>
<td>5</td>
<td>42</td>
</tr>
<tr>
<td>dec(152°)</td>
<td>57</td>
<td>5</td>
<td>44</td>
<td>4</td>
<td>47</td>
</tr>
<tr>
<td>dec(136°)</td>
<td>24</td>
<td>6</td>
<td>41</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>phos(152°)</td>
<td>50</td>
<td>54</td>
<td>13</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td>phos(136°)</td>
<td>34</td>
<td>60</td>
<td>10</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

*uncorrected results

+ nitrobenzene peak interferes in chromatogram but probably <5%

# corrected using the data in Table 34 obtained at 190°.
Table 51  
Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 4'-methoxyphenyl sulphides (corrected for the destruction of phenothiazines) (see Table 25)

\[
\begin{array}{cccc}
\text{Rn} & \text{Yield} & 1- & 2- & 3- & 4- \\
\text{NO}_2 & 82 & - & 0 & 100 & - \\
dec & 124 & - & \text{trace} & 100 & - \\
phos & 109 & - & \text{trace} & 100 & - \\
cum & 123 & - & \text{trace} & 100 & - \\
DMSO & 85 & - & 2 & 98 & - \\
N. B. & 78 & - & 0 & 100 & - \\
\end{array}
\]

Table 52  
Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 2'-trifluoromethylphenyl sulphides (corrected for the destruction of phenothiazines) (see Table 26)

\[
\begin{array}{cccc}
\text{Rn} & \text{Yield} & 1- & 2- & 3- & 4- \\
\text{NO}_2 & 78 & 100 & - & - & 0 \\
dec & 105 & 100 & - & - & 0 \\
phos & 106 & 100 & - & - & 0 \\
cum & 103 & 100 & - & - & 0 \\
DMSO & 19 & 100 & - & - & 0 \\
\end{array}
\]
Table 53

Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 3'-trifluoromethylphenyl sulphides (corrected for the destruction of phenothiazines) (see Table 27)

\[
\begin{array}{cccccc}
\text{Rn} & \text{Yield} & 1- & 2- & 3- & 4- \\
\text{NO}_2 & 65 & 0 & 85 & 0 & 15 \\
\text{NO} & 8 & 0 & 79 & 0 & 21 \\
déc & 81 & 0 & 87 & 0 & 13 \\
\text{phos} & 78 & 0 & 54 & 0 & 46 \\
cum & 54 & 0 & 89 & 0 & 11 \\
\text{DMSO} & 28 & 0 & 45 & 0 & 55 \\
\text{N. B.} & 117 & 0 & 86 & 0 & 14 \\
(\text{MeO})_3\text{PO} & 59 & 0 & 54 & 0 & 46 \\
(\text{Me}_2\text{N})_3\text{P}=\text{O} & 28 & 0 & 45 & 0 & 55 \\
\end{array}
\]

* uncorrected results
Table 54  Yields of phenothiazines in the cyclisations of 2-nitro-, 2-nitroso- and 2-azidophenyl 4'-trifluoromethylphenyl sulphides (corrected for the destruction of phenothiazines) (see Table 28)

<table>
<thead>
<tr>
<th>Rn</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO₂</td>
<td>87</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>dec</td>
<td>111</td>
<td>-</td>
<td>1</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>phos</td>
<td>67</td>
<td>-</td>
<td>6</td>
<td>94</td>
<td>-</td>
</tr>
<tr>
<td>cum</td>
<td>66</td>
<td>-</td>
<td>5</td>
<td>95</td>
<td>-</td>
</tr>
<tr>
<td>DMSO</td>
<td>23</td>
<td>-</td>
<td>7</td>
<td>93</td>
<td>-</td>
</tr>
<tr>
<td>N. B.</td>
<td>46</td>
<td>-</td>
<td>0</td>
<td>100</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 55  Yields of phenothiazine-5,5-dioxides in the thermolyses of aryl 2-azidophenyl sulphones in decalin (corrected for the destruction of phenothiazine-5,5-dioxides) (see Table 31)

\[
\text{R} = \begin{array}{c|c|c|c|c|c}
 & \text{Yield} & 1- & 2- & 3- & 4- \\
 & (\%) & & & & \\
2-\text{Me} & 48 & 64 & - & - & 36 \\
3-\text{Me} & 70 & 62 & 10 & 20 & 8 \\
4-\text{Me} & 78 & - & 70 & 30 & - \\
2-\text{OMe} & 39 & 100 & - & - & 0 \\
3-\text{OMe} & 89 & 41 & 3 & 53 & 3 \\
4-\text{OMe} & 82 & - & 27 & 73 & - \\
2-\text{Cl} & 82 & 94 & - & - & 6 \\
3-\text{Cl} & 91 & 32 & 8 & 56 & 4 \\
4-\text{Cl} & 44 & - & 59 & 41 & - \\
2-\text{CF}_3 & 29 & 77 & - & - & 23 \\
3-\text{CF}_3 & 55 & 25 & 23 & 26 & 26 \\
4-\text{CF}_3 & 30 & - & 84 & 16 & - \\
4-\text{Bu}^t & 50 & - & 58 & 42 & - \\
2,6-\text{diCl} & 37 & 100 & - & - & 0 \\
2,6-\text{diCl} (152^\circ) & 30 & 96 & - & - & 4 \\
2,6-\text{diCl} (136^\circ) & 9 & 84 & - & - & 16 \\
\end{array}
\]

* uncorrected results
Table 56

Yields of phenothiazine-5, 5-dioxides in the thermolyses of aryl 2-azidophenyl sulphones in triethylphosphate (corrected for the destruction of phenothiazine-5, 5-dioxides) (see Table 32)

<table>
<thead>
<tr>
<th>R=</th>
<th>Yield (%)</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-Me</td>
<td>74</td>
<td>77</td>
<td></td>
<td></td>
<td>23</td>
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<tr>
<td>3-Me</td>
<td>112</td>
<td>55</td>
<td>17</td>
<td>16</td>
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</tr>
<tr>
<td>4-Me</td>
<td>91</td>
<td></td>
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<td>43</td>
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<tr>
<td>2-OMe</td>
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<td>3-OMe</td>
<td>98</td>
<td>48</td>
<td>10</td>
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<td>17</td>
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<tr>
<td>4-OMe</td>
<td>94</td>
<td></td>
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<tr>
<td>2-Cl</td>
<td>48</td>
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<tr>
<td>3-Cl</td>
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<td>9</td>
<td>81</td>
<td>2</td>
</tr>
<tr>
<td>4-Cl</td>
<td>73</td>
<td></td>
<td>32</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>2-CF₃</td>
<td>38</td>
<td>84</td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>3-CF₃</td>
<td>26</td>
<td>45</td>
<td>14</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>4-CF₃</td>
<td>24</td>
<td></td>
<td>77</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>4-Bu₄</td>
<td>67</td>
<td></td>
<td>43</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>2,6-diCl</td>
<td>17</td>
<td>100</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2,6-diCl(152°)</td>
<td>14</td>
<td>99</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>2,6-diCl(136°)</td>
<td>4</td>
<td>94</td>
<td></td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

* uncorrected results.
3. Discussion

A. Thermolyses of Aryl 2-azidophenyl sulphones 143

B. Cyclisations of Aryl 2-azido-, 2-nitro- and 2-nitroso-phenyl sulphides.

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Appendix Reactions of N-Chloro-2-nitroacetanilide 175
A. **Thermolysis of Aryl 2-Azidophenyl Sulphones**

The main difference between the products obtained when aryl 2-azidophenyl sulphones and the corresponding sulphides are thermolysed is that whereas the sulphides give almost exclusively rearranged products (as shown in Scheme 76) the sulphones give mixtures of rearranged and unrearranged products. For example the thermolysis of 2-azidophenyl 4'-methylphenyl sulphide in decalin gave 51% 3-methylphenothiazine but no 2-methylphenothiazine whereas the thermolysis of 2-azidophenyl 4'-methylphenyl sulphone in decalin gave 23% 3- and 31% 2-methylphenothiazine-5,5-dioxide.

![Scheme 76](image)

No convincing alternative to the spirocyclic intermediate has yet been suggested to account for the production of rearranged products. Although these intermediates have been written as aziridines (e.g. LII) these forms are all basically the same. There are however two basic ways in which the unrearranged products can arise. These
are either a direct insertion into a C-H bond or a nitrogen shift in the spirocyclic intermediate.

\[
\begin{align*}
\text{SO}_2 & \quad \text{N} \\
\text{C-H bond} & \\
\text{nitrogen shift} & \\
\end{align*}
\]

The steric differences between diphenyl sulphides and diphenyl sulphones have been investigated by Toussaint \textsuperscript{244} who used X-ray diffraction to determine the structure of 4,4'-dibromodiphenyl sulphone and the corresponding sulphide. The structures found are shown below (LXXIV and LXXV).

\[
\begin{align*}
\text{LII} \\
\text{SO}_2 & \quad 1.84\text{Å} \\
\text{Br} & \quad 0.98\text{Å} \\
\text{SO}_2 & \quad 1.84\text{Å} \\
\text{Br} & \quad 0.98\text{Å} \\
\end{align*}
\]

Assuming a C-C bond length of 1.35Å and a C-N bond length of 1.4Å (the value found in phenothiazine \textsuperscript{245}) scale drawings show a minimum distance of 2.4Å to the carbon α to the sulphur and a minimum distance of 1.5Å to the carbon β to the sulphur in the sulphide (LXXVI). The corresponding figures for the sulphone are 2.2Å to the α-carbon and 1.1Å to the β-carbon (LXXVII). These are minimum distances and assume planarity although this is impossible because of the hydrogen atom. However the distances are comparable and show that the nitrene is closer in the sulphone than the sulphide - it also appears
to be marginally closer to the β-position. This would suggest that direct insertion at the β-position is more likely for the sulphone than the sulphide and this is indeed observed. However if only steric effects are important then the rearranged/unrearranged ratio should be constant but as Table 57 below shows there are considerable differences in this ratio depending on the nature and position of the substituent. Generally it is the position of the substituent which appears to be the determining factor.

Table 57

Isomer ratios of products from the thermolyses of aryl 2-azidophenyl sulphones in decalin (corrected for the decomposition of the products)

<table>
<thead>
<tr>
<th>R=</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>% R⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-OMe</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2-Me</td>
<td>64</td>
<td>-</td>
<td>-</td>
<td>36</td>
<td>64</td>
</tr>
<tr>
<td>2-Cl</td>
<td>94</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>2-CF₃</td>
<td>77</td>
<td>-</td>
<td>-</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>3-OMe</td>
<td>41</td>
<td>3</td>
<td>53</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>3-Me</td>
<td>62</td>
<td>10</td>
<td>20</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>3-Cl</td>
<td>32</td>
<td>8</td>
<td>56</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>3-CF₃</td>
<td>25</td>
<td>23</td>
<td>26</td>
<td>26</td>
<td>49</td>
</tr>
<tr>
<td>4-OMe</td>
<td>-</td>
<td>27</td>
<td>73</td>
<td>-</td>
<td>73</td>
</tr>
<tr>
<td>4-Me</td>
<td>-</td>
<td>70</td>
<td>30</td>
<td>-</td>
<td>30</td>
</tr>
</tbody>
</table>
Table 57 (cont.)

<table>
<thead>
<tr>
<th>R</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>% R&lt;sup&gt;+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-Cl</td>
<td>-</td>
<td>59</td>
<td>41</td>
<td>-</td>
<td>41</td>
</tr>
<tr>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-</td>
<td>84</td>
<td>16</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>4-Bu&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-</td>
<td>58</td>
<td>42</td>
<td>-</td>
<td>42</td>
</tr>
</tbody>
</table>

* uncorrected results.

+ %R is the percentage of the phenothiazine-5,5-dioxide products which must arise by rearrangement via an SO<sub>2</sub> shift (presumably in a spirocyclic intermediate).

These reactions appear characteristic of electrophilic attack. In related systems nucleophilic attack (the Smiles rearrangement, Scheme 98, above) has been shown to give fission of the C-S bond and formation of the diphenylamine. A free radical (either a nitrogen radical or a triplet nitrene) would be expected to give almost entirely the amine. If the spirocyclic intermediate did form fission of the C-S bond would be expected.† 169, 246

Bearing in mind that the attack is electrophilic it is significant that the sulphide group is electron supplying whereas the sulphone group is electron-withdrawing. Thus the nitration of diphenyl sulphone gives 3,3'-dinitrodiphenyl sulphone<sup>247</sup> but diphenyl sulphide is nitrated in the o- and p-positions<sup>248</sup> although there is some subsequent oxidation of the sulphide products to sulphones.

For comparison the results from the nitration of simple aromatic compounds are shown below in Table 58.
Table 58

**Nitration of mono-substituted-benzenes**

![Diagram of nitration process]

<table>
<thead>
<tr>
<th>Substituent</th>
<th>o</th>
<th>m</th>
<th>p</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>57</td>
<td>3</td>
<td>40</td>
<td>249</td>
</tr>
<tr>
<td>OMe</td>
<td>31</td>
<td>2</td>
<td>67</td>
<td>250</td>
</tr>
<tr>
<td>Cl</td>
<td>35</td>
<td>1</td>
<td>64</td>
<td>251</td>
</tr>
<tr>
<td>CF$_3$</td>
<td>6</td>
<td>91</td>
<td>3</td>
<td>252</td>
</tr>
</tbody>
</table>

Studies of the nitration of m-substituted nitrobenzenes shows that when the substituent is electron-supplying it almost exclusively dictates the position of nitration. Thus when the substituent is Cl, Me and Bu the major product is the 3,4-dinitro compound i.e. nitration occurs para to the electron-supplying substituent. Holleman showed that the nitration of m-nitroanisole gave 51.2% 2,3-dinitroanisole and 40.6% 2,5-dinitroanisole (nitration ortho to methoxy group) and 8.2% 3,4-dinitroanisole (nitration para to the methoxy group). A rather more recent investigation by Tillett showed that the nitration of m-nitrotoluene gave 25% 2,3-dinitrotoluene, 18.6% 2,5-dinitrotoluene (nitration ortho to the methyl group), 55% 3,4-dinitrotoluene (nitration para to the methyl group) and only 1.4% 3,5-dinitrotoluene (nitration meta to the methyl group and the nitro group). The nitration of m-nitrobenzotri fluoride gave of course 3,5-dinitrobenzotrifuoride.

Values for the Hammett equation show that the sulphone
group is very similar to the nitro group. Some values are listed in Table 59.

Table 59

<table>
<thead>
<tr>
<th></th>
<th>$\sigma_m$</th>
<th>$\sigma_p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$</td>
<td>.710</td>
<td>.778</td>
</tr>
<tr>
<td>Cl</td>
<td>.373</td>
<td>.227</td>
</tr>
<tr>
<td>SMe</td>
<td>.144</td>
<td>-.047</td>
</tr>
<tr>
<td>SOMe</td>
<td>.551</td>
<td>.567</td>
</tr>
<tr>
<td>SO$_2$Me</td>
<td>.647</td>
<td>.728</td>
</tr>
</tbody>
</table>

Thus in diphenyl sulphones the position of attack will be dictated almost exclusively by the position of an electron-supplying substituent. Thus an ortho substituent will encourage cyclisation at the $\alpha$-position, a meta substituent will encourage cyclisation at the $\beta$-positions and a para substituent will encourage cyclisation at the $\alpha$-position (LXXVIII). Superimposed on this will be a steric effect which, in the case of the sulphone, will encourage cyclisation at the $\beta$-position. Thus the products from the cyclisations of aryl 2-azidophenyl sulphones can be explained by postulating a steric effect encouraging cyclisation at the $\beta$-position and an electronic effect governed by the substituent and its position.
The steric and electronic effects can be seen competing in the para position. Thus Cl, Me, MeO and Bu give 41, 30, 73 and 42% rearrangement respectively because the steric effect encourages unrearranged products (β attack) and the electronic effect encourages rearranged products (α attack). With the electron-withdrawing CF\textsubscript{3} group however both the steric and the electronic effect encourage unrearranged products and so the rearranged products are only 15%.

In the case of meta substituents the steric and electronic effects both reinforce and so encourage unrearranged products thus Cl, Me and MeO have respectively 88, 82 and 94% unrearranged products. The electron-withdrawing CF\textsubscript{3} group will however electronically encourage rearranged products whilst the steric effect will still encourage unrearranged products. Thus only 51% unrearranged products are found.

The results when ortho substituents are present are however less satisfactorily explained by this theory. This is probably because the ortho substituent has a strong steric effect on the course of the reaction. There is also a statistical effect because there is now only one β position compared with the two when meta and para substituents are present. This statistical effect will encourage rearranged products, especially if all the nitrenes which would have inserted in this blocked β position attack the next available position, the α position.

The van der Waal's radii of the groups in question are 1.8\textsubscript{A} for Cl, 2.0\textsubscript{A} for Me and 1.4\textsubscript{A} for O. \textsuperscript{259} CF\textsubscript{3} will have a van der Waal's radius of about 2.6\textsubscript{A}. Substituted optically active biphenyls with an o-OMe group have been shown\textsuperscript{260} to be much more easily racemised than those with an o-Me group because the Me part of the OMe group can twist out of the way. Thus it seems reasonable to assume that the effective van der Waal's radius of the OMe group in this case is that of the oxygen atom.

For OMe, Cl and Me the amount of unrearranged products (0, 6 and 36%) increases as the size of the group increases (1.4, 1.8 and 2.0\textsubscript{A}) suggesting that a large group promotes β attack, possibly by increasing the likelihood of a favourable conformation.
electronic effect will of course promote α attack. However with an ortho CF₃ group the electronic effect and the steric effect of the very large group (2.6 Å) should both encourage β attack but in fact only 23% β attack is seen. It may be that when a very large group is present another steric effect comes in to play and encourages α attack once more.

Generally speaking when these thermolyses were done in triethyl phosphate marginally more of the rearranged products were obtained but the effect was small. The yields were also generally higher (see Table 60). The significance of these results will be discussed in the next section.

Table 60

Isomer ratios of products from the thermolyses of aryl 2-azido-phenyl sulphones in triethyl phosphate (corrected for the decomposition of the products).

<table>
<thead>
<tr>
<th>R</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>% R</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-OMe</td>
<td>98</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>98</td>
</tr>
<tr>
<td>2-Me</td>
<td>77</td>
<td>-</td>
<td>-</td>
<td>23</td>
<td>77</td>
</tr>
<tr>
<td>2-Cl</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>trace</td>
<td>100</td>
</tr>
<tr>
<td>2-CF₃</td>
<td>84</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td>84</td>
</tr>
<tr>
<td>3-OMe</td>
<td>48</td>
<td>10</td>
<td>25</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>3-Me</td>
<td>55</td>
<td>17</td>
<td>16</td>
<td>12</td>
<td>29</td>
</tr>
<tr>
<td>3-Cl</td>
<td>8</td>
<td>9</td>
<td>81</td>
<td>2</td>
<td>11</td>
</tr>
</tbody>
</table>
Table 60 (cont.)

<table>
<thead>
<tr>
<th>R=</th>
<th>1-</th>
<th>2-</th>
<th>3-</th>
<th>4-</th>
<th>% R</th>
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</thead>
<tbody>
<tr>
<td>3-CF₃</td>
<td>45</td>
<td>14</td>
<td>29</td>
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<td>26</td>
</tr>
<tr>
<td>4-OMe</td>
<td>25</td>
<td>75</td>
<td>-</td>
<td>-</td>
<td>75</td>
</tr>
<tr>
<td>4-Me</td>
<td>-</td>
<td>57</td>
<td>43</td>
<td>-</td>
<td>43</td>
</tr>
<tr>
<td>4-Cl</td>
<td>-</td>
<td>32</td>
<td>68</td>
<td>-</td>
<td>68</td>
</tr>
<tr>
<td>4-CF₃</td>
<td>-</td>
<td>77</td>
<td>23</td>
<td>-</td>
<td>23</td>
</tr>
<tr>
<td>4-Bu⁺</td>
<td>-</td>
<td>43</td>
<td>57</td>
<td>-</td>
<td>57</td>
</tr>
</tbody>
</table>

* uncorrected results.

Thus the products from the thermolyses of aryl 2-azido-phenyl sulphones can be accounted for by assuming that rearranged products arise by an \( SO_2 \) shift in a spirocyclic intermediate and that unrearranged products arise by direct insertion in the \( \beta \)-position. The relative proportions of rearranged and unrearranged products can be accounted for by a steric effect, which tends to give unrearranged products, and an electronic effect in which the substituent governs the position of attack of the electrophilic nitrene.

There are however alternative explanations for these results.

One approach is to consider that the unrearranged products arise via a shift of the nitrogen atom in the spirocyclic intermediate (LXXIX) and the rearranged products arise, as before, by an \( SO_2 \) shift.

![Diagram](LXXIX)

With a substituent in the ortho position the bulkier group (\( SO_2 \)) is found to move but with a substituent in the para position this steric effect is removed. An electron-supplying group will reduce the positive charge at the tetrahedral carbon and this will
encourage the shift of the electron-rich nitrogen rather than the electron-poor $\text{SO}_2$. Similarly an electron-attracting group will increase the positive charge at the tetrahedral carbon and so encourage the electron-poor $\text{SO}_2$ group to move. Thus electron-supplying groups encourage "unrearranged" products and electron-attracting groups encourage "rearranged" products. This is not, however, observed.

A substituent in the meta-position will have little effect on the charge at the tetrahedral carbon and so it should have little effect. However it is observed that the nature of the substituent does have a large effect. If it is considered that the migration is determined by the effect of the substituent on the position to which migration occurs then these results indicate that the electron-rich nitrogen is migrating to electron-rich centres. This is unlikely.

One further piece of evidence against the shift of nitrogen in the spirocyclic intermediate is the thermolysis of 2-azidophenyl 2', 6'-dichlorophenyl sulphone. Thermolysis of this azide both in decalin and in triethyl phosphate at $100^\circ$ gave only 1-chlorophenothiazine-5, 5-dioxide. In this case steric factors forcing the $\text{SO}_2$ group to shift cancel out and so if nitrogen shift is a feasible process some should have been observed. If however "unrearranged" products arise by direct insertion then this process will be blocked by the bulky chlorine atoms. Some 4-chlorophenothiazine-5, 5-dioxide was found but only at lower temperatures. In decalin it may be that the singlet nitrene has less energy at lower temperatures and so is more likely to go to the triplet nitrene by collisional deactivation before reacting with the other ring. This triplet nitrene can then give 4-chlorophenothiazine-5, 5-dioxide by the abstraction-recombination process shown below in Scheme 108.

A similar temperature effect was observed by Kulik in the thermolysis of 2-azidophenyl 2', 6'-dichlorophenyl sulphide. In triethyl phosphate the dipolar species might undergo a similar process as shown in Scheme 109. Kulik$^{153}$ has already suggested such a
scheme to explain the high proportion of 4-chlorophenothiazine formed in the deoxygenation of 2-nitrophenyl 2', 6'-dichlorophenyl sulphide.

One other theory which might explain the results is that the intermediate is the aziridine (LXXXI) shown below which is similar to the intermediate proposed by Jones and his co-workers\textsuperscript{161, 162} and to the one isolated by Kametani \textit{et al.}\textsuperscript{163}

Different products would then be formed depending on which bonds are broken but it is not clear why substituents in different positions would so greatly influence the bonds which are broken. A more
likely explanation for the results obtained by Jones and his co-workers is that, for electronic reasons the spirocyclic intermediate is formed. However \( \text{CH}_2 \) is a relatively poor migrating group and so the spirocyclic intermediate can close to give the aziridine which then undergoes ring expansion as shown in Scheme 110. Thus the aziridine is formed from the spirocyclic intermediate and not vice versa.

To sum up the products obtained when aryl 2-azidophenyl sulphones are thermolysed in decalin are best explained by the nitrene reacting either by direct insertion or by cyclisation to give a spirocyclic intermediate which then rearranges via an \( \text{SO}_2 \) shift. The effects of different substituents in different positions can be explained on this basis.
B. Cyclisations of Aryl 2-azido-, 2-nitro- and 2-nitroso-phenyl sulphides

(i) Validity of results

As stated above (p. 103) the deoxygenations of the nitro-compounds and the thermolyses of the azides in decalin and triethyl phosphate were each carried out three times and concordant results obtained. Rather more variation was seen in the deoxygenations of the nitroso-compounds but the variation was in the overall yields and not in the isomer ratios and was almost certainly due to the difficulty of mixing the nitroso-compound rapidly with the boiling triethyl phosphite/cumene mixture. Concordant results were obtained. Reactions in the other solvents were performed once only but this experience shows that there is little change of anomalous results being obtained.

The correction of the results for the destruction of the products is rather more difficult to assess. Since the control experiments were carried out for exactly the same times as the actual reactions the results must be over-corrected because the products are only formed part-way through a reaction and hence are thermolysed for a shorter time than in the control experiments. Thus the actual value will lie somewhere between the experimental results and the corrected values. In fact the differences between corrected and uncorrected results are very small the largest being for the thermolysis of 2-azidophenyl 3'-methoxyphenyl sulphide in DMSO where uncorrected results indicate 54% rearranged products and corrected results 79% rearranged products (Tables 24 and 50). The next largest difference occurs for the thermolysis of 2-azidophenyl 3'-chlorophenyl sulphide in decalin where uncorrected results show 75% rearranged products but corrected results only 70% rearranged products (Tables 18 and 44) and all the other differences are less than this and so can, for practical purposes, be ignored. However the corrected yields will be used wherever possible in the discussion which follows.

As mentioned above in the Experimental section the simulation of the deoxygenation reactions proved difficult. It appears that
triethyl phosphite and triethyl phosphate protect the phenothiazines during the deoxygenation reactions, possibly by inhibiting free radical decomposition reactions. However the essential point is, as shown by Table 40, that all the phenothiazines have roughly similar stabilities under the reaction conditions. Thus, for example, the reason that 1- and 3-chlorophenothiazines are detected in only trace amounts in the products of the deoxygenation of 2-nitrophenyl 3'-chlorophenyl sulphide is that they are formed only in trace amounts not that they are unstable under the reaction conditions.

Accordingly it is felt that the results obtained for the cyclisations of aryl 2-nitro-, 2-nitroso- and 2-azidophenyl sulphides reflect differences in mechanism and not simply differences in the stability of the products.

(ii) Essential features of the results

Certain systems can fairly readily be eliminated from consideration because the same results are obtained in every case. Thus the cyclisations of aryl 2-nitro-, 2-nitroso- and 2-azidophenyl sulphides where aryl is 2'-chlorophenyl, 4'-chlorophenyl, 2'-methylphenyl, 4'-methylphenyl, 2'-methoxyphenyl, 4'-methoxyphenyl and 2'-trifluoromethylphenyl can be neglected because all systems produce the same or very nearly the same products. This cannot be taken to show that the same mechanism is operating in all cases, it merely indicates that all the mechanisms happen to produce the same products for these systems. In fact the 2'-chlorophenyl and 4'-chlorophenyl systems do show some variation in the products for different reactions but these variations are in the same direction, but much less than, the variations seen for the 3'-chlorophenyl system. Thus only the 3'-chlorophenyl system will be considered.

A simplified version of the results shown in Tables 43-54 is shown below in Table 61. This lists the percentage of rearranged isomers in the phenothiazine yields of the reactions indicated. The abbreviations are the same as those listed above.
Table 61  

<table>
<thead>
<tr>
<th>R</th>
<th>3-Cl</th>
<th>3-Me</th>
<th>3-OMe</th>
<th>4-CF (_3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO(_2)</td>
<td>100</td>
<td>95</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>NO</td>
<td>97</td>
<td>88</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>dec (190°)</td>
<td>70</td>
<td>96</td>
<td>92</td>
<td>99</td>
</tr>
<tr>
<td>dec (169°)</td>
<td>-</td>
<td>96</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>dec (152°)</td>
<td>47</td>
<td>96</td>
<td>91</td>
<td>-</td>
</tr>
<tr>
<td>dec (136°)</td>
<td>81*</td>
<td>95</td>
<td>93</td>
<td>-</td>
</tr>
<tr>
<td>phos (190°)</td>
<td>95</td>
<td>89</td>
<td>37</td>
<td>94</td>
</tr>
<tr>
<td>phos (169°)</td>
<td>-</td>
<td>85</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>phos (152°)</td>
<td>85</td>
<td>80</td>
<td>24</td>
<td>-</td>
</tr>
<tr>
<td>phos (136°)</td>
<td>97*</td>
<td>75</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>cum</td>
<td>88</td>
<td>96</td>
<td>86</td>
<td>97</td>
</tr>
<tr>
<td>DMSO</td>
<td>45</td>
<td>93</td>
<td>79</td>
<td>93</td>
</tr>
<tr>
<td>N. B.</td>
<td>16</td>
<td>96</td>
<td>95</td>
<td>100</td>
</tr>
</tbody>
</table>

* 1-Chlorophenothiazine could not be estimated for this reaction.

When \( R = 3-\text{CF}_3 \) 100% rearranged products were obtained for each reaction although the thermolyses at lower temperatures were not performed. Other systems generally gave 99-100% rearranged products for all reactions.
The only reservation to be made about these results is that the results from the deoxygenations of the nitroso-compounds and the thermolyses of the azides at 152° and 136° should not be considered as accurate as the other results because of the low yields obtained.

(iii) The effect of substituent groups on the course of the various reactions

a. Deoxygenation of nitro-compounds

The percentage of rearranged products is always very high regardless of the substituent. Thus even a powerful electron supplying group such as OMe which, in the meta position, would be expected to greatly increase the electron density at the β position produces only 4% of unrearranged products (i.e. β attack). Some values of εp obtained in the Hammett equation are listed in Table 62.

Table 62

<table>
<thead>
<tr>
<th>Group</th>
<th>OMe</th>
<th>Me</th>
<th>Bu⁺</th>
<th>SMe</th>
<th>Cl</th>
<th>CF₃</th>
<th>SOMe</th>
<th>SO₂Me</th>
</tr>
</thead>
<tbody>
<tr>
<td>εp</td>
<td>-.268</td>
<td>-.170</td>
<td>-.151</td>
<td>-.047</td>
<td>.277</td>
<td>.551</td>
<td>.567</td>
<td>.728</td>
</tr>
</tbody>
</table>

This absence of any large electronic effect suggests that there is a very powerful steric effect forcing the intermediate to five-membered cyclisation at the α-position. A bulky intermediate would be expected to undergo reactions governed largely by steric criteria. Thus the dipolar intermediate (LXXXII) would force the two rings into a perpendicular conformation and cyclisation would then occur at the α-position. No mechanism has yet been proved for the reactions of dipolar intermediates of this type but one possibility is electrophilic attack of phosphorus at the α-position (the reactions are typically electrophilic) followed by extrusion of triethyl phosphate as shown in Scheme 111.
The spirocyclic intermediate then rearranges in the usual fashion. Another attractive possibility is the attack of the phosphorus at the β position followed either by the rearrangement of this intermediate as shown in Scheme 112 or by the extrusion of triethyl phosphate to give the spirocyclic intermediate as shown in Scheme 113.
Scheme 112 is inapplicable to ortho-substituted diphenyl sulphides but is possible for meta- or para-substituted diphenyl sulphides.
Scheme 113

Attack by an electrophilic $^+$ species has a precedent in displacement of a nitro-group from substituted nitro-benzenes by triethyl phosphite $^{262}$ as shown in Scheme 114.
In all these schemes it has been assumed that the intermediate which attacks the other ring is the dipolar species (LXXXII) but there is no evidence to suggest that the intermediate is not the dipolar species (LXXXIII) formed by initial attack of the triethyl phosphate on the nitro-group. This would mean that the deoxygenation of nitrocompounds need not necessarily go through the corresponding nitroso-compound. The intermediate would be expected to give phenothiazine nitroxides but these would be readily deoxygenated under the reaction conditions.

![Chemical Structure](image)

It may be that more than one mechanism operates in deoxygenation reactions and so when the phosphorus attacks at the α-position triethyl phosphate is extruded to give the spirodiene but when the phosphorus attacks at the β-position direct extrusion of the triethyl phosphate is not possible for steric reasons and so the triethyl phosphate must be extruded together with a cyclisation to the spirodiene. This would account for the very high degree of rearranged products formed and although electron-supplying groups might influence the change from one mechanism to another there would be no change in the products. When both ortho-positions are blocked then only α-attack takes place although when an ortho-chlorine is present an abstraction-recombination type reaction similar to that shown in Scheme 109, can take place.

b. Deoxygenation of nitroso-compounds

These again show a very high degree of rearrangement and much the same remarks apply as before. 2-Nitrosophenyl 3'-methylphenyl sulphide is the only compound to show any great degree of unrearranged products. The poor thermal stability of these
compounds and the high ratio of 1-substituted phenothiazines to 3-
substituted phenothiazines suggests that the unrearranged products
may arise by mechanisms which do not, at least initially, involve
triethyl phosphite. The 1/3 ratio is much higher than that obtained
in other, similar, reactions. Comparison with azide thermolyses
shows that formation of the nitrene in this system is unlikely but the
results obtained are fairly similar to those obtained in the deoxygena-
tion of nitro-compounds certainly in so far as the high degree of
rearrangement regardless of the substituent or its position. The
ratio of 2- to 4-substituted phenothiazines obtained in the deoxygena-
tions of nitroso-compounds are fairly similar, but not identical, to
the same ratio obtained in the deoxygenation of the corresponding nitro-
compound (Table 63). However it is not clear whether these
differences are significant since very small differences may produce
large changes in this ratio. It was found that the repeatability of these
ratios was very good.

Table 63

<table>
<thead>
<tr>
<th></th>
<th>nitro deoxygenation (corrected)</th>
<th>nitro deoxygenation (uncorrected)</th>
<th>nitroso deoxygenation (uncorrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-Cl</td>
<td>0.92</td>
<td>0.64</td>
<td>0.67</td>
</tr>
<tr>
<td>3-Me</td>
<td>0.90</td>
<td>1.02</td>
<td>0.60</td>
</tr>
<tr>
<td>3-OMe</td>
<td>2.10</td>
<td>1.47</td>
<td>1.25</td>
</tr>
<tr>
<td>3-CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>-</td>
<td>5.67</td>
<td>3.76</td>
</tr>
</tbody>
</table>

On balance a mechanism such as one shown above in Schemes
111-113 seems attractive. The differences between the nitro- and
nitroso-deoxygenations may be ascribed to thermal cyclisations of the
nitroso-compound, high local concentrations of the nitroso-compound
because of the method of doing the reactions, the differing time
scales employed or some mechanism in which the developing nitroso-
compound reacts with a second molecule of triethyl phosphite before
the triethyl phosphate has completely left. Factors such as these would mean that the nitro-deoxygenation would formally go through the nitroso-compound but the mechanisms would have slight differences giving slight differences in the products. It must be admitted that whilst the products are similar they are not as similar as might be expected if the nitroso-compound is a discrete intermediate in the deoxygenation of nitro-compounds.

c. Thermolyses of azidès

It must be said at once that the results from the thermolyses of aryl 2-azidophenyl sulphides in various solvents are the most puzzling of all. Holliman has proposed that when an azide is thermolysed in triethyl phosphate it reacts with triethyl phosphate to form the dipolar species \( \overrightarrow{N} - O - \overrightarrow{P}(OEt)_3 \) and that this species is the same as the reactive intermediate formed in the deoxygenation of nitroso compounds. In these systems the deoxygenation of 2-nitrosophenyl 3'-chlorophenyl sulphide and the thermolysis of 2-azidophenyl 3'-chlorophenyl sulphide gave 97 and 85\% rearranged products respectively but the same figures for the corresponding methoxy compounds are 99 and 24\% (all figures determined at 152\°). Thus, in this system at least, Holliman's theory must be incorrect because vastly different products are obtained from reactions which should involve the same intermediate.

Reference to Table 61 (above) shows that the different solvents produce different percentages of rearranged products. Although these percentages are affected by the substituent groups these effects do not correspond to the electron-supplying power of the groups. Thus the order of rearrangement of aryl 2-azidophenyl sulphides when thermolysed in decalin is

4-CF\(_3\) > 3-Me > 3-OMe > 3-Cl

in triethyl phosphate it is

3-Cl > 4-CF\(_3\) > 3-Me > 3-OMe
in cumene it is

$$4\text{-CF}_3 > 3\text{-Me} > 3\text{-Cl} > 3\text{-OMe}$$

in DMSO it is

$$4\text{-CF}_3 = 3\text{-Me} > 3\text{-OMe} > 3\text{-Cl}$$

and in nitrobenzene it is

$$4\text{-CF}_3 > 3\text{-Me} > 3\text{-OMe} > 3\text{-Cl}$$

If the attack was solely by electrophilic species then the order would be expected to be $$4\text{-CF}_3 > 3\text{-Cl} > 3\text{-Me} > 3\text{-OMe}$$ although the actual percentages would vary depending on the nature of the species. Although the products from the thermolyses of aryl 2-azidophenyl sulphones can be explained solely on the basis of the effect of the substituent group the effect in the corresponding sulphides seems to be more complex and clearly the substituent group is only one factor. The results in decalin and cumene, for instance, two inert solvents which have no apparent means of reacting with the nitrene to form reactive intermediates show different percentages of rearranged products.

<table>
<thead>
<tr>
<th></th>
<th>Percentage of rearranged products from the thermolyses of aryl 2-azidophenyl sulphides in cumene and decalin (at 152°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-Cl</td>
</tr>
<tr>
<td>Cumene</td>
<td>88</td>
</tr>
<tr>
<td>Decalin</td>
<td>47</td>
</tr>
</tbody>
</table>

* at 190°

This strongly suggests that some solvation effect is important. Perhaps the solvent cage surrounding the azide crucially affects the way in which it reacts and the subsequent rearrangements of the spirodiene. The results obtained when aryl 2-azidophenyl sulphones are thermolysed can be accommodated by assuming that the electronic forces are much stronger for these molecules so that the solvent
whether decalin or triethyl phosphate exerts only minor effects. However for the corresponding aryl 2-azidophenyl sulphides the electronic forces are perhaps more nearly in balance with the sulphur bridge directing the nitrene to the \( \alpha \)-position and (say) a \( \text{m'-OMe} \) group directing it to the \( \beta \)-position. With the electronic forces more nearly in balance the solvation effects become much more important.

An alternative view is to reject the results from the thermolyses of 2-azidophenyl 3' ‐ chlorophenyl sulphide as being anomalous for some reason. The results from the thermolyses of aryl 2-azidophenyl sulphides when aryl is 3'-methoxyphenyl, 3'-methylphenyl and 4'-trifluoromethylphenyl are then more comprehensible. In decalin, cumene and nitrobenzene high yields of rearranged products are obtained (86-100%) because the nitrene reacts quickly by cyclisation to the \( \alpha \)-position to give the kinetic product. The small increase in unrearranged product on decreasing the temperature may be ascribed to greater formation of triplet nitrene which reacts to give unrearranged products by an abstraction-recombination mechanism. In triethyl phosphate the reactive intermediate is, partially at least, the dipolar intermediate, \(- \tilde{N} - \tilde{O} - \tilde{P}(\text{OEt})_3\) this is less energetic and more electrophilic than the nitrene and when the electron density is raised, as by a \( \text{m'-OMe} \) group, it will react by cyclisation to the \( \beta \)-position to give unrearranged products, as shown in Scheme 115.

The fairly marked temperature effect in this case is explained by the fact that, at lower temperatures, more nitrene reacts with the triethyl phosphate rather than by cyclisation to the \( \alpha \)-position. The intermediate so formed cyclises mainly to the \( \beta \)-position.

In DMSO the reaction may proceed through intermediates such as
\[
\begin{align*}
- \tilde{N} - \tilde{O} - \tilde{S} \quad \text{Me} \\
\end{align*}
\]
\[
\begin{align*}
\text{Me} \\
\end{align*}
\]
\[
\begin{align*}
\text{Me} \\
\end{align*}
\]

The disadvantages of this theory are that it does not explain why there are such great differences with the deoxygenation reactions which should involve the same dipolar intermediate and there is no valid reason why the 3'-chlorophenyl case should be anomalous. A heavy
atom effect is unlikely at a concentration of 1%.

(iv) Deoxygenation of aryl 2-nitrosophenyl sulphides at reduced temperatures

At temperatures below the boiling point the deoxygenation of aryl 2-nitrosophenyl sulphides by triethyl phosphite in cumene failed to give more than trace amounts of phenothiazines but when aryl 2-nitrosophenyl sulphides were dropped into a boiling mixture of cumene and triethyl phosphite fairly large yields of phenothiazines (7-26%) were obtained. Deoxygenation at 0° failed to give phenothiazines and deoxygenations at -40° and 100° gave only trace amounts. This is most surprising in view of the reported cyclisation of 2-nitrosobiphenyl to carbazole in 76% yield at 0-5°.

Deoxygenations performed in the probe of an XL-100 n.m.r. spectrophotometer set to observe the 31P n.m.r. spectrum showed only a steady conversion of triethyl phosphite to triethyl phosphate.
at -40°. At 0° however a few small peaks appeared near the triethyl phosphate signal and these disappeared on warming the solution to 40°.

When the 2-nitrosophenyl 4'-chlorophenyl sulphide was deoxygenated at 0° and the reaction mixture worked up in the usual way by evaporation of the solvent and HSLC of the residue only a series of low-polarity peaks with traces of chlorophenothiazines were seen in the chromatogram. However when exactly the same reaction was done except that the reaction mixture was boiled after reaction at 0° 7% 3-chlorophenothiazine was seen in the resulting chromatogram. The yield is reduced from that when the nitroso-compound is dropped into a boiling cumene/triethyl phosphite mixture (from 24% to 7%) but is, on the other hand, much greater than when the reaction was done only at 0°.

These experiments suggest that the nitroso-compound and the triethyl phosphite react fairly readily even at 0° and that the intermediates so formed decompose by a number of different routes to give a variety of products. Only at high temperatures do the intermediates have enough energy to react with the other ring to give phenothiazines. It is not clear however why the reactions which predominate at low temperatures do not become even more favourable at high temperatures and so prevent any yield of phenothiazines. The answer is perhaps that the intermediates which are formed at low temperatures yield only low polarity material if the reaction mixture is then worked-up. However at sufficiently high temperatures these intermediates can decompose to give phenothiazines. More than one intermediate is suggested by the n.m.r. spectra. The large temperature difference needed for the generation of carbazole and for the generation of phenothiazines is puzzling but the production of carbazole is always an easy reaction, probably because the other ring is so conveniently situated for reaction.

The nature of the intermediates must remain a matter for speculation although it is tempting to consider the dipolar species (LXXXII) as one such intermediate. At high temperatures this would decompose to give the phenothiazine, perhaps as shown in
Scheme 116
Scheme 116 or perhaps by initially forming the nitrene. At low temperatures it might decompose to give the nitrene which could then ring expand through nucleophilic attack by triethyl phosphite to give an azepinyolphosphonate. This product (LXXXIV) and the dipolar intermediate would both give several products on work-up. An azepinyolphosphonate was found in low yield (2.5%) among the products from the deoxygenation of 2-nitrophenyl 4'-methylphenyl sulphide in neat triethyl phosphite. 263 P, N, O and P, N, S heterocycles have been found in the products from the deoxygenations of aryl 2-nitrophenyl sulphides and ethers (see above, Scheme 101) and although these are only formed at elevated temperatures from the nitro-compounds it may be that they form readily at low temperatures from the nitroso-compounds. These compounds are very sensitive to moisture and would be destroyed by the work-up used.

However in the absence of firm evidence these and other similar reactions must all remain speculation. This should prove a fruitful field for future investigation.

(v) **Treatment of aryl 2-(hydroxyamino)phenyl sulphides with trifluoroacetic acid**

The failure of aryl 2-(hydroxyamino)phenyl sulphides to yield phenothiazines when treated with trifluoroacetic acid (TFA) was disappointing but perhaps not wholly unexpected in view of the low yields generally experienced in these reactions. 116, 117

Aromatic insertions in these reactions very probably involve the concerted loss of water from the protonated hydroxylamine. The steric restrictions of diphenyl sulphides may prevent the other ring approaching at the correct distance or attitude for this reaction. There is another attractive reaction open to these molecules 264 and this is hydroxylation of the ring as shown in Scheme 117.
Molecules such as these would not have been detected with the HSLEC conditions used and so could account for the almost complete failure to detect products - other than small amounts of the amine.

Since these reactions do not give phenothiazines it seems unlikely that esters of the hydroxylamines will do so. Similarly the importance of the p-quinonoid form to nitrenium ions generated from N-chloramines renders phenothiazine production in these systems unlikely. If the o-and p-positions were blocked with electron-withdrawing groups however it might be possible to localise the positive charge on the nitrogen sufficiently to achieve cyclisation of the nitrenium ion to phenothiazine.
C. Some Aspects of High Speed Liquid Chromatography

High Speed Liquid Chromatography (HSLC) was used extensively for this investigation and, although a new technique, it shows great promise as an investigative tool in organic chemistry. In fact this investigation would not have been possible without HSLC because although it is possible to separate some phenothiazine isomers by column chromatography the accurate determination of the yields of minor components would be very difficult and it would almost certainly be impossible to separate some isomers by this technique. Phenothiazines can be observed by g.l.c. but they give rise to broad peaks because of the elevated temperatures that are necessary and so different isomers cannot be separated. The u.v. spectra of the various isomers are very similar and although the i.r. spectra do differ slightly only crude estimates can be obtained by this technique. Similarly quantitative estimates from n.m.r. spectra are very difficult. The above remarks apply equally to the phenothiazine-5,5-dioxides and previous workers have reported no success in separating the isomers either by column chromatography or by fractional sublimation. In addition to enabling determinations not previously possible to be made the speed of HSLC (5-15 mins per determination) enabled many more systems to be investigated.

One of the great advantages of HSLC, in addition to its ability to separate closely similar isomers, is the fact that it works at (or below) room temperature. This means that there is no thermal decomposition of the compounds which it is desired to determine. In this context it is interesting to note the aryl 2-(hydroxyamino)phenyl sulphides could not be observed by HSLC because they appeared to decompose on the column, giving rise to very broad peaks. However no other decompositions were observed and so HSLC would seem to be suited to the determination of all but the most sensitive compounds.

One of the disadvantages of HSLC is the necessity to prepare authentic samples of all likely products both to see if they are present and to check that all the possible products are being resolved. This problem can be eliminated by injecting much larger samples
and collecting the eluant corresponding to each peak. With peaks which are widely separated large amounts can be injected but close peaks tend to merge through overloading if too much is injected. However obtaining enough of a sample for characterisation is relatively simple and as an example Dr. J. N. Done obtained about 20 mg of each isomer after about half a day of repeated injections of a mixture of 2- and 3-t-butylphenothiazine-5, 5-dioxides.

Although HSLC is ideally suited to the separation of aromatic isomers this very advantage of producing large differences in retention times from small differences of polarity means that compounds of greatly different polarities are difficult to determine because conditions which are suitable for some compounds produce inconveniently long or short retention times for other compounds. This difficulty is best circumvented by determining compounds of greatly differing polarity under different conditions.

It was also found that it is very difficult to determine non-polar compounds under these conditions because they are not adsorbed sufficiently strongly by the alumina or silica. For example triphenylethlenes showed very short retention times under the conditions used, even with hexane alone as the mobile phase. This difficulty can perhaps be avoided by using column packings with long chain hydrocarbons bonded to them. The chromatographic process then uses partition rather than adsorption.

Degassing of the mobile phase is usually recommended to avoid the possibility of bubbles forming in the flow cell but it was not found necessary at any time. The mobile phase is usually degassed by placing it under reduced pressure or by boiling it under reflux. However placing under reduced pressure tends to cause the most volatile component to distil out and boiling under reflux tends to remove the water and since both these would affect the reproducibility degassing was not employed. In order to obtain reproducible results and well shaped peaks it was found essential to add small, constant amounts of water to the mobile phases, as described above. It was also found essential to keep the concentrations of components in the mobile phases constant because even quite
small changes in the nature of the mobile phase caused appreciable changes in the u. v. extinction coefficients and hence in the estimation of yields.

With regard to equipment it was found that the column fittings and flow cell developed at the University of Edinburgh and illustrated above in Figs. 2-4 were superior to other designs that were used. The columns were easily changed and the layer of glass beads at the top of each column was also easily changed. It appears that it is small pieces of septum which are broken off by the needle and find their way into the layer of glass beads that cause degradation of column resolution. Thus ease of replacement of these glass beads is a vital factor in maintaining optimum resolution by the column. The flow cell was also found easy to use and caused little trouble. It was found that a commercially available flow cell had Teflon gaskets and that leakage of mobile phase across these gaskets caused noise on the baseline. The flow cells used were constructed without gaskets and so that problem did not arise.

An LPL constant flow pump was used and it was found that the constant flow of mobile phase was a great aid to reproducibility. A syringe pump which was also available was less convenient to use because it had to be refilled every 30 min and because it was difficult to reset the pressure and hence the flow rate reproducibly for each run. An Autolab Minigrator was used for quantitative measurement of the peak areas. This machine was found to be very useful because the parameters employed by the machine could be adjusted to suit the wide variety of peak shapes encountered in liquid chromatography.

The $k'$ values which were determined for the various compounds investigated are of interest not just for their role in identifying the compounds present in the chromatograms but also in their own right. The $k'$ values determined were listed above in Tables 12-16 (pp. 98-100). One immediately obvious feature is that the 1-substituted phenothiazines and phenothiazine-5, 5-dioxides are eluted before (i.e. have a lower $k'$ value than) the other isomers. This indicates that phenothiazines and phenothiazine-5, 5-dioxides are probably
adsorbed on the alumina or silica through the NH group since a substituent in the 1-position would be expected to interfere most with this process. It is also interesting to note that the chloro- and trifluoromethylphenothiazines and phenothiazine-5, 5-dioxides are eluted in the order 1, 2, 3, 4 although there is no obvious explanation for this. The electron-supplying methyl and methoxy groups cause the isomers to be eluted in a different order. The order of elution of aryl 2-nitrophenyl sulphones, aryl 2-aminophenyl sulphones and aryl 2-aminophenyl sulphones substituted with chloro- and trifluoromethyl groups is always in the order of the 4', 3' and 2' isomers but again the same compounds with methyl or methoxy substituents have different elution orders. Thus there is considerable regularity in the behaviour of these closely similar isomers but other than the suggestion that phenothiazines and phenothiazine-5, 5-dioxides are adsorbed on alumina through their NH groups no explanation can be offered for this regularity.
Appendix

Reactions of N-chloro-2-nitroacetanilide

Gassman et al.\textsuperscript{106, 107} have shown that the treatment of N-chloro-N-t-butylanilines with silver salts leads to the production of aryl nitrenium ions (see above Scheme 52). Production of aryl nitrenium ions in this way requires secondary amines which are difficult to prepare. However there is one class of secondary amines which is easily obtained and these are the acetanilides. The corresponding N-chloro compounds are also easily made and their preparation has been comprehensively examined by Chalsty and Israelstam.\textsuperscript{198} The acetanilide chosen for investigation was o-nitroacetanilide partly because the nitro group would inhibit delocalisation of positive charge into the ring and partly because any insertion of the nitrenium ion into an aromatic ring would give N-acetyl-2-nitrodiphenylamines which are difficult to prepare by other routes and are of interest in themselves. Although aromatic insertion is not a reaction which aryl nitrenium ions generated from N-chloroamines are known to undergo it was hoped that inhibition of positive charge delocalisation by the nitro-group would make this reaction more likely.

Stirring a mixture of N-chloro-2-nitroacetanilide and silver trifluoroacetate in toluene at room temperature gave no observable reaction but when the mixture was boiled under reflux a precipitate of silver chloride was obtained. The reaction mixture was filtered and evaporated and the n.m.r. spectrum showed that no diphenylamines were present. The only products which were found were o-nitroacetanilide and o- and p-methyldiphenylmethanes. No bibenzyl (the usual product of free radical reactions in toluene) was present but a rather more careful work-up showed the presence of o- and p-chlorotoluenes (by g.l.c.). When a similar reaction was done without the presence of silver trifluoroacetate no diphenylmethanes or chlorotoluenes were found but benzyl chloride was now detected.
Scheme 118
It is known that when benzyl bromide is treated with silver perchlorate in toluene methylidiphenylmethanes are produced and it was found that when benzyl chloride was treated with silver trifluoroacetate in toluene methylidiphenylmethanes were also produced.

Treatment of N-chlbroacetanilide with silver trifluoroacetate under similar conditions gave ring chlorinated acetanilides via an Orton rearrangement and this reaction is known to go via \( \text{Cl}^+ \), although the active chlorinating agent is believed to be of the form \( \text{RCOOC1} \). In fact Scott has shown that N-bromo-2-nitroacetanilide does not undergo an Orton rearrangement but, when carboxylic acids are present, acts as a brominating agent via \( \text{RCOBr} \). It was found that N-chloro-2-nitroacetanilide only produced chlorotoluenes when carboxylate anions (from \( \text{CF}_3\text{COOAg} \), \( \text{CF}_3\text{COONa} \) or \( \text{CH}_3\text{COONa} \)) were present.

Thus when N-chloro-2-nitroacetanilide is thermolysed homolytic bond fission occurs to give a nitrogen radical and a chlorine radical. Chlorine radicals give side chain chlorination of toluene and so benzyl chloride is formed and if silver ions are present benzyl carbonium ions are produced. These react with toluene to give o- and p-methyldiphenylmethanes by electrophilic aromatic substitution. When carboxylate anions are present heterolytic bond fission occurs, presumably via a transition state such as LXXXV, to give \( \text{RCOOC1} \) which chlorinates toluene on the ring. These reactions are set out in Scheme 118.

t-Butylhypochlorite undergoes a similar series of reactions. The photolysis of N-chloro-2-nitroacetanilide in toluene gave only benzyl chloride and \( \alpha \)-nitroacetanilide but photolysis and thermolysis in anisole gave \( \alpha \)- and \( \beta \)-chloroanisoles. A similar result was obtained when the photolysis was carried out in a mixture of equal volumes of benzene and anisole. The very high proportion of \( \beta \)-chloroanisole (96% of chloroanisoles) suggests that this reaction may be concerted as shown in Scheme 119.
Thus it does not seem possible to generate nitrenium ions from N-chloroacetanilides presumably because the electron-withdrawing acetyl-group destabilises the positive charge too much. This study also shows that the investigation of nitrenium ions may be complicated by the ease of free radical and "Cl\(^+\)" reactions.
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