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AN INVESTIGATION OF THE PREPARATION OF HETEROCYCLIC RING SYSTEMS VIA INTRAMOLECULAR NUCLEOPHILIC AROMATIC SUBSTITUTION

by

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A Doctoral Thesis submitted in partial fulfilment of the requirements for the award of Doctor of Philosophy of the Loughborough University of Technology.

March 1985


Department of Chemistry

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Heterocyclic synthesis via processes involving single electron transfer, namely aromatic $S_{RN1}$ reactions and copper metal- and cuprous halide-promoted substitutions have been investigated. The cyclisation step in all the syntheses is effected by an intramolecular aromatic nucleophilic substitution on a halogen atom which is ortho to the side chain bearing the nucleophilic species (generally an amide or thioamid moiety).

The process of entrainment has been shown to be a valuable technique for effecting reactions performed under $S_{RN1}$ conditions.

The mechanisms of, and the mechanistic relationships between the substitution processes, were investigated using well documented diagnostic probes for the $S_{RN1}$ reaction and by conducting series of experiments on simple reaction systems whose behaviour under $S_{RN1}$ conditions was already known.

Ring systems prepared by the methods noted above include benzoxazoles, benzothiazoles, 1,3-benzothiazines, indoles and a tricyclic system. Attempts to prepare seven-membered heterocycles by increasing the length of the side chain proved unsuccessful.

When the side chain bears a carbonyl function adjacent to the aromatic ring, an intramolecular $S_{NAr}$ reaction takes place and cyclisation of $N$-(2-haloaroyl)-$N'$-phenylthioureas occurred under mild conditions. Quinazolinones and a 1,3-benzothiazinone have been synthesised in this manner which appears to have little precedent in the chemical literature.

The preparation of seven-membered heterocycles by an $S_{NAr}$ cyclisation proved fruitless extension of the side chain length by one carbon atom (effected by the preparation of an $N$-cinnamoyl-$N'$-phenylthiourea) resulted in the cyclisation of the side chain.

Reaction of certain of the $N,N'$-disubstituted thioureas with copper (I) iodide results in the formation of 2-halobenzanilides by a novel rearrangement.
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INTRODUCTION
Nucleophilic substitution at aromatic carbon centres is achieved by reactions which largely fall into one of the following three categories:

The first is the two step SNAr reaction which normally requires the aromatic substrate to be activated towards nucleophilic attack by the presence of one or more electron withdrawing substituents.

The second includes those reactions which are catalysed by very strong bases and which proceed via the intermediacy of highly reactive arynes.

The final category includes reactions in which a diazonium group is substituted by the nucleophilic species.

However, aromatic nucleophilic substitutions can also be effected by reactions which, on the whole, are milder, more convenient and often high yielding. These include copper and copper (I) salt - promoted substitutions which have been recognised for many years and the more recently elucidated aromatic SRN1 reactions which proceed via radical and radical anion intermediates. Both types of substitution have the advantage that the aryl moiety need not be activated by other groups.

In this introduction particular attention will be drawn to the application of each mechanism to the synthesis of heterocyclic ring systems and especially those syntheses which are achieved by intramolecular aromatic nucleophilic substitution.

The SNAr Mechanism

This is a two step (addition-elimination) mechanism the first step of which is usually rate-determining:

\[ \text{aryl} + Y^- \xrightarrow{\text{slow}} \text{aryl}Y \xrightarrow{\text{fast}} \text{aryl}X \]

\[ \text{aryl}X + X^- \xrightarrow{\text{slow}} \]
The most convincing evidence for the above mechanism was the isolation, as long ago as 1902, of an intermediate Meisenheimer salt [1]. Many others have since been isolated.

![Meisenheimer salt structure](image)

That the rate-determining step is the first one is evidenced by the fact that a change of leaving group alters the overall rate of reaction very little. The rates will, however, be different because the electronic nature of the leaving group will affect the rate of attack of the nucleophile at the aromatic carbon centre.

The mechanism requires the carbon atom in question to be ortho or para to an electron-withdrawing group such as CF₃, CN, SO₃H, NO₂, COR, CO₂R, CO₂H or N(CH₃)₃. An unsubstituted aromatic substrate can, however, react by this mechanism under forcing conditions such as high temperatures or in dipolar aprotic solvents.

Thus, any aromatic substrate which contains a good leaving group such as halide, and a moderately strong activating group (or better, several of them) in the ortho or para positions will be subject to nucleophilic substitution by reasonably good nucleophiles.

The order of reactivity for substrates bearing a halogen leaving group is found to be as follows: $F > Cl > Br > I$.

An intramolecular nucleophilic substitution can be envisaged in which the activating group and the nucleophile are part of the
same molecule [2].

\[ \text{Y} \quad \text{Nu} \quad \text{X} \]

[2]

Nu=Nucleophile.
Y=Activating Group.
X=Leaving Group.

Surprisingly, the literature contains few reported examples of such intramolecular S$_N$Ar reactions. Rudorf$^2$ has prepared 1-thiochromones (eqn. 1) and quinolones (eqn. 2) by using sulphur- and nitrogen-centred anions as the respective nucleophiles.

\[
\begin{align*}
\text{(i) NaH/CS}_2 \\
\text{(ii) RX}
\end{align*}
\]

R=CH$_3$, C$_2$H$_5$, C$_6$H$_5$CH$_2$.

\[
\text{R=CH}_3\text{CO}, \text{C}_6\text{H}_5\text{CO}, \text{CO}_2\text{CH}_3.
\]

Adams$^3$ has also reported cyclisation by a nitrogen anion and utilises leaving groups other than halogen (eqn. 3).
Some aromatic nucleophilic substitution reactions are different from those occurring by the $S_{N}Ar$ mechanism in that they proceed with aryl halides bearing no activating groups, bases are required which are stronger than usual, and the position occupied by the nucleophile in the product is not always that which was occupied by the leaving group i.e. cine-substitution can occur (eqn. 4).

\[
\begin{array}{c}
\text{Cl} \\
\text{H}
\end{array}
\xrightarrow{\text{\textit{NH}_2}}
\begin{array}{c}
\text{H} \\
\text{NH}_2
\end{array} + \begin{array}{c}
\text{Cl} \\
\text{NH}_2
\end{array}
\]

$\text{H}^{\text{14C}}$

The reaction, which is an elimination followed by an addition, is explained by a mechanism involving the intermediacy of a highly reactive benzyne [3], (eqn. 5).

\[
\begin{array}{c}
\text{Cl} \\
\text{H}
\end{array}
\xrightarrow{\text{\textit{NH}_2}}
\begin{array}{c}
\text{H} \\
\text{NH}_3 + \text{Cl}^{\text{-}}
\end{array} + \begin{array}{c}
\text{H} \\
\text{NH}_2
\end{array} + \begin{array}{c}
\text{Cl} \\
\text{NH}_2
\end{array}
\]

$\text{H}^{\text{14C}}$
The order of reactivity within the halogen group is $\text{Br} > \text{I} > \text{Cl} >> \text{F}$ which shows that an $S_NAr$ mechanism is not operating. Benzynes are so reactive that they have never been isolated except at temperatures near absolute zero but they can form stable complexes with certain organometallic compounds and can also be trapped in Diels-Alder reactions.

Intramolecular cyclisation involving benzynes has been reported since the early 1960's and includes preparations of benzothiazoles, benzoxazoles, phenothiazines and indoles, benzocyclobutenes, indanes, tetralins and benzocycloheptenes, oxindoles and benzisothiazolines. Some examples are given below (eqns. 6-9).

\[
\begin{align*}
\text{NHCPh} & \xrightarrow{\text{Br}} \text{Ph} \quad (6) \\
\text{Br} & \xrightarrow{\text{H}_2\text{N}} \text{NH} \quad (7) \\
\text{Cl} & \xrightarrow{\text{CN}} \text{CN} \quad (8) \\
\text{Cl} & \xrightarrow{\text{R, R'}} \text{NR} \quad (9)
\end{align*}
\]

$R=\text{H, CH}_3$.  
$R'=\text{COCH}_3, \text{C}_6\text{H}_5, \text{H}$.  

5
Substitution of diazonium salts

This is the only case of aromatic nucleophilic substitution to which the conventional $S_{N1}$ mechanism can be attributed.

The preparation of aryl fluorides from diazonium fluoroborates is known as the Schiemann Reaction and exemplifies this type of substitution (eqn. 10).

$$\text{ArNH}_2 \xrightarrow{(i) \text{HNO}_2} \text{ArN}^+\text{BF}_4^- \xrightarrow{\Delta} \text{ArF}$$  \hspace{1cm} (10)

The well known Sandmeyer Reaction also falls into this category but an alternative mechanism has been suggested and will be discussed at a later stage.

A modified Sandmeyer Reaction (performed under alkaline conditions) can be used to prepare tricyclic ring systems in which case it is known as the Pschorr ring closure (eqn. 11). The mechanism is not that of the Schiemann Reaction ($S_{N1}$) but proceeds via the intermediacy of aryl radicals.

$$\text{Z=CH}_2\text{CH}_2,\text{CH=CH},\text{NH},\text{CH}_2,\text{C}=O$$  \hspace{1cm} (11)

The $S_{RN1}$ reaction

The $S_{RN1}$ reaction as applied to aromatic substrates is now well established and several excellent reviews have been published. Bunnett and Kim first observed the involvement of such a reaction in aromatic systems in 1970 whilst investigating the behaviour of halopseudocumenes.
with potassium amide in liquid ammonia. A common aryne intermediate was anticipated (Scheme 1) which would lead to the same product ratio of 6-amino- to 5-aminopseudocumene whether the starting material was bromo- or chloro- substituted and this was found to be the case. With iodo-substituted substrates, however, unrearranged products were obtained in high yields which suggested that a non-aryne mechanism was operating.

The involvement of an $S_N$Ar reaction was thought to be unlikely due to the occurrence of cine-substitution and upon the discovery that the reaction was inhibited by a radical scavenger and that adding potassium metal (a source of solvated electrons) when dissolved in liquid ammonia drives the reaction entirely to non-rearranged products,
Bunnett proposed the now-familiar radical chain mechanism (Scheme 2) which he designated $S_{RN1}$ i.e. Substitution Radical Nucleophilic, Unimolecular.

$$
\text{ArX} + e^- \rightarrow [\text{ArX}]^-
$$  \hspace{1cm} (12)

$$
[\text{ArX}]^- \rightarrow \text{Ar}^+ + X^-
$$  \hspace{1cm} (13)

$$
\text{Ar}^+ + \text{Nu}^- \rightarrow [\text{ArNu}]^-
$$  \hspace{1cm} (14)

$$
[\text{ArNu}]^- + \text{ArX} \rightarrow \text{ArNu} + [\text{ArX}]^-
$$  \hspace{1cm} (15)

$\text{Ar}=$Aryl (hetaryl) species.

$\text{Nu}=$Nucleophile.

$X=$Leaving Group.

**Scheme 2**

Equation 12 constitutes the initiation step of the $S_{RN1}$ mechanism. A radical-anion is formed when the aromatic substrate receives an electron. The source of this electron can either be from solvated electrons, a cathode, electron transfer from another radical-anion or an anion, or by some other chemical reaction.

In Equation 13 the radical anion fragments into an aryl radical and a halide (leaving group) anion. The aryl radical is then attacked by the nucleophile (eqn. 14) to form the product radical-anion.

In Equation 15 the product is formed by the transfer of the 'odd electron' of the radical-anion to another molecule of the aromatic substrate.

The original radical-anion is thus reformed and enters the cycle again at Equation 13. Equations 13-15, therefore, constitute the propagation...
cycle of the \( S_{RN}^1 \) mechanism.

The nature of the termination steps is obscure as only small amounts of the termination products are formed in an efficient cycle (i.e. one of large chain length).

If the equations representing the \( S_{RN}^1 \) mechanism are studied closely it becomes apparent that the overall effect is one of nucleophilic substitution:

\[
\text{ArX} + \text{Nu}^- \rightarrow \text{ArNu} + \text{X}^-
\]

Bunnett's proposal was strengthened by the observations of Kornblum\(^9\) and Russell\(^10\) four years earlier that a radical-anion mechanism was operating in substitutions at certain aliphatic sites, namely the substitution reactions of \( p \)-nitrobenzyl chloride (eqn. 16) and 2-chloro-2-nitropropane.

\[
\begin{align*}
\text{p-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{Cl} & \rightarrow \text{p-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{CNO}_2 \\
\text{Initiation of } S_{RN}^1 \text{ reactions}
\end{align*}
\]

Initiation can be achieved by a number of methods, the most commonly used being photostimulation and the introduction of solvated electrons.

However, many \( S_{RN}^1 \) reactions are known to proceed 'thermally' i.e. they do not require stimulation from any external source. Direct electron transfer from the anion has been proposed\(^13\) as the initiation step in these spontaneous reactions and prior formation of a charge transfer complex followed by electron transfer (eqn. 17) has also been suggested\(^14\).

\[
\text{Acceptor} + \text{Donor}^- \rightarrow [\text{Acceptor} - \text{Donor}] \rightarrow (\text{Acceptor})^- + \text{Donor}^+
\]

When the acceptor and donor species do not have the appropriate electron
affinity and ionisation potential electron transfer does not occur and the electron has to be supplied to the acceptor by some other means. Dissolving alkali metals in liquid ammonia furnishes solvated electrons which may then be accepted into the \( \pi^* \) molecular orbital of the aromatic species. A common drawback to this method is the reduction of the aryl radical intermediate. The resulting aryl anion then captures a proton from the solvent (eqns. 18-21).

\[
\text{ArX} + e^- \rightarrow [\text{ArX}]^-
\]  
\[
\text{ArX} \rightarrow \text{Ar}^+ + X^-
\]  
\[
\text{Ar}^+ + e^- \rightarrow \text{Ar}^-
\]  
\[
\text{Ar}^- + \text{NH}_3 \rightarrow \text{ArH} + \text{NH}_2^-
\]

Another method of initiating non-spontaneous SRN1 reactions is the use of photostimulation. The exact mechanism by which this is achieved is obscure and it is likely that a combination of mechanisms is responsible. Some mechanisms which have been put forward to explain this phenomenon include homolytic bond dissociation of the substrate to form an aryl radical which then initiates the propagation steps (eqn. 22), photoejection of electrons from nucleophile molecules (eqns. 23-24), photoassisted electron transfer within a charge transfer complex analogous to that depicted in Equation 17, and electron transfer to excited states (eqns. 25-28).
SRN1 reactions may also be initiated by electron capture at a cathode, i.e. electrochemical initiation.¹⁷,¹⁸ Not only can yields of the substitution product be high but the stability of the radical-anion can often be gauged by observing the quantity of reduction product formed during the reaction.

Finally, initiation can be achieved by the addition of the radical-anion of the substitution product, i.e. [Ar-Nu]⁻ which enters the propagation cycle and thereby initiates the chain reaction.¹⁹ This method has been used in saturated systems with some success.

Substituent effects in SRN¹ reactions

As has been mentioned previously, an advantage of the SRN¹ reaction over SNAr reactions is that the aryl substrate need not be activated by electron withdrawing groups.
Substituents which have been reported to be compatible with the $S_{RN1}$ reaction include alkyl, alkoxyl, benzoyl, carboxylate, cyano, and phenyl groups. Those incompatible with the reaction include dimethylamino, ionised hydroxy, and nitro groups.

There appears to be little steric effect exerted by groups ortho to the reactive carbon centre as is illustrated in Equation 29.

$$\text{An isopropyl group at position 2 does not inhibit the reaction and it is only when either two isopropyl groups or one tertiary-butyl group is at the 2 position that reactions become inhibited to any degree.}$$

Nucleofugic groups in $S_{RN1}$ reactions

Nucleofugic groups include I, Br, Cl, F, SPh, $\text{NMe}_2$ and $\text{OP(OEt)}_2$. The order of reactivity within the halogen group is $\text{I} > \text{Br} > \text{Cl} > \text{F}$ which is in direct contrast to that observed in the $S_{NAr}$ mechanism and is also dissimilar to that seen in most benzyne reactions.

An overall pattern of reactivity in photostimulated reactions with acetone enolate anion has been established and is as follows: $\text{I} > \text{Br} > \text{SPh} > \text{Cl} > \text{F} >> \text{OPh}$. Iodine appears to be the best nucleofuge and this is exemplified by the fact that potassium diethyl phosphite reacts with iodobenzene roughly one thousand times faster than with bromobenzene.

The presence of the trimethylammonium and diethyl phosphate groups
in the nucleofugal series provides convenient access to substituted aromatic species from primary aromatic amines and phenols (eqns. 30 and 31).

\[
\text{ArNO}_2 \rightarrow \text{ArNH}_2 \rightarrow \text{ArNMe}_3 \xrightarrow{\text{Nu}^-/h\nu} \text{ArNu}
\]  
(30)

\[
\text{ArOH} \rightarrow \text{ArOP(O)(OEt)}_2 \xrightarrow{\text{Nu}^-/h\nu} \text{ArNu}
\]  
(31)

**Aromatic systems which participate in S\textsubscript{RN1} reactions**

Phenyl halides have been extensively studied as substrates in S\textsubscript{RN1} reactions but this type of substitution mechanism is by no means restricted as regards the diversity of aromatic substrates which will undergo the reaction.

Polycyclic hydrocarbons which can undergo the reaction include halonaphthalenes, \textsuperscript{23} 4-chlorobiphenyl, \textsuperscript{22} 9-bromoanthracene, \textsuperscript{23} and 9-bromophenanthrene. \textsuperscript{22} Some examples are shown below:

\[
\text{I} + \text{CH}_2\text{COCH}_2 \xrightarrow{\text{liq. NH}_3/h\nu} \text{CH}_2\text{COCH}_3
\]  
(32)  
76%  

\[
\text{Br} + \text{CH}_2\text{CN} \xrightarrow{\text{liq. NH}_3/h\nu} \text{CH}_2\text{CN}
\]  
(33)  
60%
Several heterocyclic systems are known to undergo $S_{RN1}$ reactions and these include 2- and 3- bromothiophene (eqn. 34),\textsuperscript{28} appropriately substituted pyridines (eqn. 35),\textsuperscript{29} quinolines,\textsuperscript{30,31} isoquinolines,\textsuperscript{32,33} pyrimidines (eqn. 36), pyridazines and pyrazines (eqn. 37).\textsuperscript{34}

\[ \text{Br} \begin{array}{c} \text{CH}\text{CN} \end{array} + \text{lig. NH}_3 \rightarrow \text{CH}_2\text{CN} \quad \text{(34)} \]

\[ \text{Br} \begin{array}{c} \text{CH}_2\text{COCH}_3 \end{array} \rightarrow \text{hv} \rightarrow \text{CH}_2\text{COCH}_3 \quad \text{(35)} \]

\[ \text{Ph} \begin{array}{c} \text{Br} \end{array} \begin{array}{c} \text{CH}_2\text{COPh} \end{array} \rightarrow \text{hv} \rightarrow \text{CH}_2\text{COPh} \quad \text{(36)} \]

\[ \text{Cl} \begin{array}{c} \text{CH}_2\text{COCH}_3 \end{array} \rightarrow \text{hv} \rightarrow \text{CH}_2\text{COCH}_3 \quad \text{(37)} \]
Methods of assigning the $S_{RN1}$ mechanism

In order to assign this mechanism to a reaction the chemist must probe certain experimental parameters which may then display features that are very characteristic of the $S_{RN1}$ mechanism. This is, of course necessary as the overall stoichiometry of the reaction is identical to that of other types of aromatic nucleophilic substitution, especially the $S_N Ar$ mechanism.

The parameters which can be investigated are discussed briefly below. It is important, however, to note that assignment of the radical-chain mechanism can rarely be made with certainty by observing only one of these characteristic features.

A preliminary indication that the mechanism may be in operation is given by a failure to follow a simple linear free energy relationship. An example of this was Bunnett's observation of unexpected selectivity ratios in the reaction of halopseudocumenes with the amide anion as described earlier in this introduction.

Electron spin resonance (e.s.r.) spectroscopy is a useful physical method which may be used to detect radical intermediates in organic reaction pathways. The method, however, cannot be used to definitely assign the $S_{RN1}$ mechanism as there may be competing non-chain pathways in operation which also involve radicals and radical anions.

As mentioned previously, the order of reactivity for the halogen group in an $S_N Ar$ reaction is $ArF > ArCl > ArBr > ArI$. This is a consequence of the fact that the carbon-halogen bond is not broken during the rate-determining step. In the $S_{RN1}$ mechanism, this order is reversed so that aryl iodides are the most reactive substrates. Again, care must be taken when interpreting these data as the same order of leaving group ability may be observed in some aryne - mediated reactions.

As the $S_{RN1}$ mechanism involves both radical-anions and radicals in a chain propagated system, addition of either electron- or radical scavengers will inhibit the rate of reaction. Dioxygen
can be used in both capacities, spin-traps such as galvinoxyl [4] and di-t-butyl nitroxide [5] act as radical scavengers and p-dinitrobenzene is used as an electron scavenger.

The requirement for photostimulation may be used to assign the mechanism although some reactions of this type (thermal $S_{RN1}$ reactions) proceed efficiently in the absence of light. An accurate measurement of the quantum yield may also be helpful in probing the mechanism.

Lack of reactivity in $S_{RN1}$ reactions may often be due to failure to initiate the chain process even though the reactants may be reactive enough in the propagation steps. Addition of a nucleophile which is capable of transferring an electron to the aromatic substrate may overcome this problem and the method has been successfully applied in both aliphatic and aromatic $S_{RN1}$ reactions. The process is known as entrainment and the diphenyl phosphide anion appears to be very efficient in this context. The requirement for entrainment can, therefore, be used as an aid in assigning the mechanism.

**Solvent effects in $S_{RN1}$ reactions**

Certain criteria must be met if a solvent is to be considered suitable for use in these reactions.

Clearly, any solvent used must adequately dissolve the aromatic substrate and the salt of the nucleophile, it must also be transparent to the wavelength of light used in photostimulated reactions (usually in the region of 300-400 nm) and it must not be a source of hydrogen atoms.
Abstraction of a hydrogen atom from the solvent by the aryl radical intermediate would constitute a termination step (eqn. 38) and would inhibit the reaction.

\[ \text{Ar}^\cdot + \text{SH} \rightarrow \text{ArH} + \text{S}^\cdot \] (38)

In the same vein, the solvent must be very weakly acidic so as not to protonate the nucleophile.

When the reaction is stimulated by the presence of solvated electrons, the solvent must remain inert which means that those such as carbon tetrachloride and nitrobenzene cannot be used in $S_{RN1}$ reactions.

Liquid ammonia has become the solvent of choice for many $S_{RN1}$ reactions because it is easy to purify and even easier to remove from the products. It is also good at solvating electrons. Drawbacks include poor solubility for many aromatic substrates, toxicity and the inconvenience of handling such a low-boiling solvent.

Separate studies by Semmelhack$^{38}$ and Bunnett$^{36,39}$ have shown that in photostimulated reactions DMSO is also a good solvent. $N, N$-Dimethylformamide (DMF) has been used but may cause the reduction of aryl radicals. Acetonitrile, THF and $t$-butyl alcohol are other solvents which may be considered but hexamethylphosphoramide (HMPA) is not recommended.

Potassium diethylphosphite has been reported$^{39}$ as being quite unreactive towards iodobenzene in a photo $S_{RN1}$ reaction performed in HMPA.

Water is a poor hydrogen atom donor and has been investigated as a solvent but was found, on the whole, to be unsatisfactory.

Methanol has been used as a solvent in the reaction of the benzenethiolate anion with 3-bromoisoquinoline.$^{32}$ The reaction was catalysed by the addition of methoxide anion which acted as an electron donor.
Nucleophiles which participate in $S_{RN1}$ reactions

It is convenient to classify the nucleophiles according to their positions in the periodic table. Examples of each group will be given to exemplify the diversity which exists.

Group IVA of the periodic table contains the largest group of nucleophiles because it includes those anions centred on a carbon atom. The reactions of these carbanions will be introduced at some length because the formation of carbon-carbon bonds is of such importance in synthetic organic chemistry.

The anions of 1,3-pentadiene, fluorene and indene (eqn. 39), generated by the action of potassium amide in liquid ammonia fall into this category.

\[
\begin{array}{c}
\text{+ PhBr} \\
\text{K} \\
\text{liq.NH}_3
\end{array}
\rightarrow
\begin{array}{c}
\text{Ph}
\end{array}
\]

(Ketone enolates are the most extensively studied nucleophiles in arylation reactions, the most common examples being those of acetone, acetophenone, and pinacolone. Monoanions of \(\beta\)-diketones fail to undergo the $S_{RN1}$ reaction with aryl and hetaryl halides except in those cases where the aryl substrate is activated by the presence of cyano-groups. The dianions, however, react with most substrates, the nucleophilic site being the terminal carbon atom (eqn. 40).)

\[
\begin{array}{c}
\text{+ } \text{CH}_2\text{COCHCOPh}
\end{array}
\rightarrow
\begin{array}{c}
\text{[71%]}
\end{array}
\]
Unsymmetrical dialkyl ketones which form more than one enolate ion may be arylated at any of these sites (eqn. 41).40

\[
\begin{align*}
&\text{A} \\
&\text{B}
\end{align*}
\]

Disubstitution products may be obtained from dihaloaryl substrates on reaction with ketone enolates (eqns. 42 and 43).

These disubstitution products are formed without the accumulation of the monosubstitution product and this feature is characteristic of the \( S_{RN1} \) mechanism.
The enolates of esters,\textsuperscript{38} aldehydes\textsuperscript{43} and N,N-disubstituted amides\textsuperscript{44} have not been studied in any detail but some examples of their reactions have been reported.

2- and 4- picolyl anions have been shown to act as nucleophiles in the $S_{RN1}$ reaction (eqn 29):\textsuperscript{20}

Although the cyanide anion itself appears to be unreactive in the $S_{RN1}$ reaction, a-cyano carbanions react with aryl halides to give the substitution product.\textsuperscript{45} The reaction may be complicated by fragmentation of the product radical anion (Scheme 3).\textsuperscript{45}

\[
\text{PhX} + \text{CH}_2\text{CN} \xrightarrow{\text{hv}} [\text{PhCH}_2\text{CN}]^- + X^- \xrightarrow{-e^-} \text{PhCH}_2\text{CN} - \text{CN}^- \xrightarrow{\cdot} \text{PhCH}_3 \xrightarrow{\cdot} \text{PhCH}_2\text{CH}_2\text{Ph}
\]

**Scheme 3**

Intramolecular cyclisations have been achieved and can be separated into two categories: those in which the cyclisation step is an $S_{RN1}$ reaction and those in which an $S_{RN1}$ substitution is followed by cyclisation.

The former category may be depicted in a generalised form as shown in Scheme 4.
An elegant example of this category is the final step in the total synthesis of cephalotaxinone by Semmelhack et al. (eqn. 44).
Semmelhack has also reported the synthesis of carbocyclic rings by the \( S_{RN1} \) reaction of enolate anions with aryl iodides (eqn. 45).

\[
\begin{align*}
\text{(45)} \\
\begin{array}{c}
\text{I} \\
\text{O} \\
\text{O} \\
\text{CH}_2 \text{n} \\
\text{t-BuOK} \\
\text{hv}
\end{array}
\rightarrow
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{CH}_2 \text{n} \\
\text{O}
\end{array}
\end{align*}
\]

\[n=1, 99\% \\
n=3, 73\% \\
n=5, 25-35\%\]

When \( \beta \)-hydrogen atoms are present, competition arises from hydrogen atom abstraction by the intermediate phenyl radical \([6]\) to form an \( \alpha, \beta \)-unsaturated ketone \([7]\) which then isomerises to the \( \beta, \gamma \)-unsaturated ketone \([8]\) (Scheme 5). This mechanistic proposal was verified by deuterium labelling experiments.

\[\text{SCHEME 5} \]
Heterocyclic ring systems also prepared by this means of cyclisation include oxindoles (eqn. 46) and azaoxindoles (eqn. 47).

\[
\begin{align*}
\text{R} &= \text{CH}_3, \text{R'} = \text{H}. \\
\end{align*}
\]

The reactions shown above were proved not to proceed via the benzyne mechanism by applying the usual diagnostic tests for the S_{RN1} reaction.

The second category of cyclisations has provided the organic chemist with convenient routes to indoles (eqns. 48 and 49), carbazoles (eqn. 50), indenes and benzofurans (eqn. 51).
The yield of the 1,2,3,4-tetrahydrocarbazole [9] was reduced due to competition between the \( S_{RN}^1 \) reaction and \( \beta \) - hydrogen atom abstraction as described previously.

Nucleophilic silicon, germanium and tin species have been reported to participate in \( S_{RN}^1 \) reactions but the mechanisms involved are not clear-cut. Some appear to involve arynes, aryl-metal species or \( S_{RN}^1 \) intermediates or, frequently, combinations of these processes.

Group \( \text{VA} \) contains nitrogen and although the aromatic \( S_{RN}^1 \) mechanism was first observed\(^8\) during an amination reaction (Scheme 1), few other cases of aromatic amination by this mechanism have been reported. However, 2-iodo-1,3-dimethylbenzene which cannot react by a benzyne mechanism has been shown to undergo amination in 64% yield (eqn. 52).\(^8\)
3-Bromothiophene reacts with amide ions to form 3-aminothiophene in 79% yield (eqn. 53). The reaction characteristics are consistent with the operation of an $S_{RN1}$ mechanism.

\[
\begin{align*}
\text{Br} & \quad \text{NH}_2 \\
\text{S} & \quad \text{S} \\
\end{align*}
\]

Potassium anilide reacts, in the presence of potassium metal, with iodobenzene to form a mixture of products (eqn. 54).

\[
\begin{align*}
\text{I} & \quad \text{NH} \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\text{NH} & \quad \text{NH}_2 \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\text{C}_6\text{H}_5 & \quad \text{C}_6\text{H}_5 \\
\end{align*}
\]

(19%) (11%) (11%)

An intramolecular cyclisation via a nitrogen anion has been attempted by Kametani et al. (eqn. 55) but the cyclised material [10] was obtained in only a 2% yield, the major product being the reduced compound [11], 14%.

\[
\begin{align*}
\text{MeO} & \quad \text{H} \quad \text{Br} \quad \text{HN} \\
\text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{h}_\text{v} \\
\text{t-BuOK} & \quad \text{MeO} \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

[10] + [11]
Amines do not appear to be successful nucleophiles and there is, to date, very little evidence to suggest that they can intercept aryl radicals and thereby participate in $S_{RN1}$ reactions.

The nitrogen-anions of acetamide, $N$-methylacetamide and pyrrole were found to be unreactive in $S_{RN1}$ reactions with 1-chloronaphthalene, regardless of the method of initiation.

Although the azido group has been reported to react with an aryl radical formed by the decomposition of a diazonium salt (eqn. 56), sodium azide was found to be unreactive towards bromobenzene under photostimulation.

\[
\begin{align*}
\text{N}_3^- \text{BF}_4^- & \quad \text{Acetone} \\
\text{N}_3^- & \quad \text{N}_3^- + \text{N}_2
\end{align*}
\] (56)

The nitrate ion is known to react with aryl radicals to form radical anions but the photostimulated reaction of halobenzenes with nitrite ion in liquid ammonia gave no substitution product. This failure was attributed to the poor propagation rate (eqn. 57) rather than to an intrinsically low reactivity.

\[
\begin{align*}
[\text{PhNO}_2]^\cdot + \text{PhX} & \quad \text{Photostimulated} \\
\text{PhNO}_2 + [\text{PhX}]^- & \quad \text{Photostimulated}
\end{align*}
\] (57)

Phosphorus nucleophiles have been extensively studied especially those reactions involving dialkyl phosphite anions.

Diphenyl phosphide anion undergoes an $S_{RN1}$ reaction with 8-chloroquinoline and has been shown to react with $m$- and $p$-iodotoluenes in liquid ammonia or DMSO at 25°C in the dark (eqn. 58).

\[
\begin{align*}
\text{Ph}_2\text{P}^- & \quad \text{K}^+ \text{Ph}_2\text{P}^- \quad \text{DARK} \\
\text{Me} & \quad \text{Me} + \text{PPh}_2
\end{align*}
\] (58)
Potassium diethyl phosphite reacts very rapidly with aryl iodides and bromides,36,50 1-iodonaphthalene50 and 3-haloiodobenzenes.27 With 3-chloro- and 3-fluoroiodobenzene, the monosubstitution product is formed (only the iodine atom having been replaced). When either 3-bromoiodobenzene or m-diiodobenzene are used, the product is that due to substitution of both halogen atoms (Scheme 6).

This observation is explained on the basis of a modified $S_{RN1}$ reaction as shown in Scheme 7.

\[
\begin{align*}
\text{Scheme 6}
\end{align*}
\]

\(\text{(59)}\)
The radical anion [15] may undergo either of two competing reactions; electron transfer to a molecule of the dihalobenzene to form the monosubstitution product (eqn. 62) or cleavage of the second carbon-halogen bond to form a new aryl radical [16]. Further reactions (eqn. 64-65) result in the formation of the disubstitution product.

Because the carbon-chlorine and carbon-fluorine bonds are strong, the reaction depicted in Equation 62 is favoured and monosubstitution occurs. The carbon-bromine and carbon-iodine bonds are weaker and so bond cleavage occurs faster than electron transfer and the disubstitution product is formed. A reaction of m-bromoiodobenzene, quenched at low conversion showed the presence of unreacted starting material and the disubstitution product. No monosubstitution product was detected which is good evidence that Equation 62 does not operate in these reactions.

Anions of phosphonites, phosphinites, thiophosphites and phosphonamides have also been shown to undergo the SRN1 reaction with iodobenzene. The reactions with bromobenzene are usually slower. A summary of these reactions is shown in Table 1.

<table>
<thead>
<tr>
<th>PhX</th>
<th>Nucleophile</th>
<th>Irradiation Time(min)</th>
<th>Substitution (%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhI</td>
<td>PhP(OBu)O⁻K⁺</td>
<td>15</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>PhI</td>
<td>Ph₂P₀⁻K⁺</td>
<td>20</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>PhI</td>
<td>(EtO)₂PS⁻K⁺</td>
<td>15</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>PhI</td>
<td>(Me₂N)₂P₀⁻K⁺</td>
<td>30</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

Arsenic nucleophiles may be used in aromatic SRN1 reactions but the reaction may be complicated by the presence of products due to the 'scrambling' of aryl rings (eqn. 66). This phenomenon is a result of the fragmentation of intermediate radical anions competing with the electron transfer steps. Haloderivatives of toluene, anisole, naphthalene and phenanthrene lead to such 'scrambling' effects whereas substrates with lower reduction potentials such as halo-derivatives of quinoline and
benzophenone give only the straightforward substitution product.

\[ \text{AnX} + \text{Ph}_2\text{As}^- \rightarrow \text{Ph}_3\text{As} + \text{Ph}_2\text{AnAs} + \text{PhAn}_2\text{As} + \text{An}_3\text{As} \]  

(66)

\[ \text{An}=\text{p-Anisyl}. \]

\[ X=\text{Cl, Br, I}. \]

The reactions of the final member of Group VA, antimony, are again complicated by 'scrambling' reactions. Those performed in liquid ammonia with no photostimulation gave very poor yields of the substitution product.

Group VIA contains the elements oxygen, sulphur, selenium and tellurium.

Anions centred on an oxygen atom have been shown\(^3\)\(^8\),\(^4\)\(^0\),\(^5\)\(^3\) not to react via the \(S_{RN1}\) mechanism whether stimulated by photons, solvated electrons or electrodes. Ambident nucleophiles such as the enolates of amides, esters or ketones always react via the carbon atom and reactions involving anions of alcohols and phenols result in the reduction of the halobenzene substrate.\(^2\)\(^6\)

Sulphur nucleophiles have been widely studied, especially those reactions of aryl sulphide anions. Phenyl thiolate anion reacts with aryl iodides\(^5\)\(^4\) to yield diaryl sulphides in high yield (eqn. 67). Aryl bromides also react but at a much slower rate.

\[ \text{ArI} + \text{PhS}^- \xrightarrow{h\nu} \text{ArSPh} \]  

(67)

Dihalobenzenes \((X = \text{Cl, Br, I})\) react under the same conditions to yield the disubstitution product.\(^5\)\(^5\) The monosubstitution product was not detected and so cannot be a reaction intermediate which is further evidence for the validity of the mechanism depicted in Scheme 7. When one of the halogen substituents is fluorine, the only product observed is that formed by monosubstitution (eqn. 68).
Alkane thiolate anions also react with iodobenzene to yield the substitution product plus diphenyl sulphide. This reaction is explained in Scheme 8.

\[
\text{PhI} + \text{EtS}^- \xrightarrow{\text{hv}} [\text{PhI}]^- + \text{EtS}^-
\] (69)

\[
[\text{PhI}]^- \xrightarrow{} \text{Ph}^+ + \text{I}^-
\] (70)

\[
\text{Ph}^+ + \text{EtS}^- \xrightarrow{} [\text{PhSEt}]^+
\] (71)

\[
[\text{PhSEt}]^+ + \text{PhI} \xrightarrow{} \text{PhSEt} + [\text{PhI}]^-
\] (72)

\[
[\text{PhSEt}]^+ \xrightarrow{} \text{PhS}^- + \text{Et}^+
\] (73)

\[
\text{PhS}^- + \text{Ph}^+ \xrightarrow{} [\text{PhSPh}]^-
\] (74)

\[
[\text{PhSPh}]^- + \text{PhI} \xrightarrow{} \text{PhSPh} + [\text{PhI}]^-
\] (75)

**SCHEME 8**

1-Halonaphthalenes reacted with alkane thiolate anions to yield naphthalene and the substitution product (eqn. 76). No fragmentation products formed by processes as shown in Scheme 8 were observed.
The anions of potassium thiocyanate, potassium ethyl xanthate and sodium dithionite were found to be unreactive towards 1-chloronaphthalene in liquid ammonia under photostimulation.\textsuperscript{49}

Aryl selenide anions react in a similar manner to the aryl thiolates. Thus, the phenyl selenide anion reacted with iodobenzene under photostimulation to yield diphenyl selenide (eqn. 77).

\[
\text{PhSe}^- + \text{PhI} \xrightarrow{\text{hv, liq. NH}_3} \text{PhSePh}
\]  

(77)

Bromobenzene gave much lower yields and chlorobenzene and p-chlorobenzophenone did not react at all. Dihalobenzenes\textsuperscript{8}(X = Br, I) react with the phenyl selenide anion to yield the disubstitution product, no monosubstitution products being observed.

The reaction of halobenzenes with disodium selenide (Na\textsubscript{2}Se) provides a useful pathway for the preparation of some important organo-selenium compounds (Scheme 9).

\[
\text{ArX} + \text{Se}^{2-} \xrightarrow{\text{hv}} \text{ArSe}^- \rightleftharpoons \text{ArSeAr} \rightarrow \text{ArSe}^- + \text{ArX}^+ \rightarrow \text{ArSeR}
\]

\[
\text{ArX} + \text{Se}^{2-} \rightarrow \text{ArSeAr} \rightarrow \text{ArSe}^- + \text{ArX}^+ \rightarrow \text{ArSeR}
\]

(76)

\[
\text{R=n-C}_4\text{H}_9, \text{CH}_2\text{CH}_2\text{OH}
\]
The phenyl telluride anion reacts with iodobenzene and bromobenzene to afford the substitution product (eqn. 78).

\[
\begin{align*}
\text{X} & \quad + \quad \text{PhTe}^- \\
\text{hv} & \quad \text{liq.} \text{NH}_3 \\
\rightarrow & \quad \text{TePh}
\end{align*}
\]

\[X=\text{Br}, \text{20}\%\]
\[X=\text{I}, \text{90}\%\]

However, reactions of the anion with p-anisyl iodide and 1-halonaphthalenes gave mixtures of products due to fragmentations of the product radical-anion \([\text{ArTePh}]^-\) as described previously. Dihalobenzenes react with the phenyl telluride anion to yield the dissubstitution product plus diphenyl telluride and small amounts of the monosubstitution product (<7%).

The use of copper and its salts in aromatic nucleophilic substitution has been known since the early twentieth century when Ullman published his investigations into the formation of biaryls from halobenzenes. (eqn. 79).

\[
2\text{ArI} \overset{\text{Cu}}{\underset{\Delta}{\longrightarrow}} \text{Ar-Ar}
\]

A similar reaction can be used for ring closure;

The mechanism of the Ullman reaction is thought to involve the initial formation of an arylcopper species which then effects a nucleophilic substitution on a second molecule of the aryl halide (eqns. 80-81).
The isolation of a Meisenheimer salt from the reaction of 1,3,5-trinitrobenzene with an arylcopper compound was evidence for this step.

\[ \text{ArI} + 2\text{Cu} \rightarrow \text{ArCu} + \text{CuI} \] (80)

\[ \text{ArCu} + \text{ArI} \rightarrow \text{Ar-Ar} + \text{CuI} \] (81)

The Ullman ether synthesis (eqn. 82) is also promoted by copper salts and it has been suggested that an aryloxy copper(I) species [18] is the reactive intermediate.

\[ \text{CuX} + \text{ArO}^- \rightarrow \text{CuOAr} \] (82)

The conversion of arene diazonium salts into aryl bromides or chlorides by using copper (I) bromide or chloride (eqn. 83) is a very useful synthetic route and is known as the Sandmeyer reaction.

\[ \text{ArN}_2X^- + \text{CuX} \rightarrow \text{ArX} + \text{N}_2 + \text{CuX} \] (83)

Although the reaction has been known for many years the mechanism is still in doubt. There is general agreement that the thermolysis of diazonium salts leads to the formation of an aryl cation which then reacts with halide ion to produce the aryl halide but a growing body of opinion suggests that a competing two-step mechanism exists (eqns. 84-85).

\[ \text{PhN}_2X^- + \text{CuX} \rightarrow \text{Ph}^+ + \text{N}_2 + \text{CuX}_2 \] (84)

\[ \text{Ph}^+ + \text{CuX}_2 \rightarrow \text{PhX} + \text{CuX} \] (85)

The mechanism has been studied further by Galli who suggests that the copper (I) salt has a dual purpose i.e. that it acts as a single electron reductant and a ligand transfer agent.
It has been proposed, albeit tentatively, by Chanon\textsuperscript{59} that some organometallic electron transfer reactions may proceed via an $S_{RN1}$ type mechanism, although there has been little experimental evidence to date to support this contention.

A copper catalysed aromatic variation on the Gabriel amine synthesis was reported in 1973 by Bacon (eqn. 86).\textsuperscript{60}

\[ \text{Ph}^- + \text{Ph}-\text{N}^+\text{K}^- \xrightarrow{\text{CuT}} \text{DMA} \xrightarrow{} \text{Ph}-\text{NH}_2 \]

The reaction mechanism was suggested to involve an intermediate [20] which then rearranges to the product [19].

\[ \text{[20]} \]

In recent years, much attention has been focussed on investigating the synthetic possibilities of using copper salts.

Diaryl sulphides and selenides can be prepared in high yields by the reaction of arenethiolates\textsuperscript{61} and areneselenolates\textsuperscript{62} with aryl iodides in the presence of copper (I) salts (eqns. 87-88).
The method has also been applied to the synthesis of S-aryl thiobenzoates (eqn. 89) which are difficult to prepare otherwise.

Anions of compounds such as diethyl malonate (eqn. 90) and ethyl cyanoacetate (eqn. 91) can be arylated under mild conditions in the presence of copper (I) salts and the method compares very favourably with those utilising low valent nickel catalysts, benzyynes, and $S_{RN1}$ reactions.
The preparation of arene phosphonates by the arylation of phosphite anions can be achieved by using $S_{RN}^1$ reactions as mentioned previously in this introduction. Another convenient and mild preparation involves the use of copper (I) iodide (eqn. 92).

$$ArX + Na\text{P}O(OR)_2 \xrightarrow{\text{CuBr, HMPA}} Ar\text{PO}(OR)_2$$  \hspace{1cm} (92)

$R=\text{Et, Ph.} \hspace{0.5cm} X=\text{Br, I}$

Intramolecular aromatic nucleophilic substitution involving the use of copper and its salts can be applied to the synthesis of heterocyclic systems. Substrates used include active methylene compounds (eqns. 93$^{67}$ and 94$^{68}$), enamines (eqns. 95$^{69}$ and 96$^{70}$), and amides (eqn. 97$^{71}$).

$$\text{Br} + Na\text{CH}(\text{CO}_2\text{Et})_2 \xrightarrow{\text{CuBr, Dioxane}} \text{CO}_2\text{Et} \hspace{1cm} (93\%)$$

$$\text{Br} \xrightarrow{\text{CuBr, NaH}} \hspace{1cm} (36\%)$$
In both of the syntheses shown above, the groups ortho to the bromine atoms were found to assist the substitution reaction.

\[ \begin{align*}
\text{R}^1, \text{R}^2, \text{R}^3 & \quad \text{N} \quad \text{X} \quad \text{CuI} \quad \text{NaH} \quad \text{R}^1, \text{R}^2, \text{R}^3 \\
\text{MeO} & \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO}
\end{align*} \]

\[ X = \text{Br, I} \]

Copper powder has also been used to effect cyclisation.

The use of this method in the preparation of a fused \( \beta \)-lactam (eqn. 98)\(^7\) was chosen because a conventional copper (I) salt/base system was found to cause decomposition of the starting material.

\[ \begin{align*}
\text{R}^1, \text{R}^2 & \quad \text{N} \quad \text{X} \quad \text{Cu} \quad 100^\circ \text{C} \quad \text{R}^1, \text{R}^2, \text{X} \\
\text{MeO} & \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO} \quad \text{MeO}
\end{align*} \]
Although there have been frequent reports of copper promoted intramolecular aromatic nucleophilic substitutions being used to prepare heterocycles, there have been very few successful applications of the $S_{RN1}$ reaction to such syntheses, all of which are described in this introduction. This fact is surprising as the synthetic scope of the aromatic $S_{RN1}$ reaction has received increasing attention over the past fourteen years.
DISCUSSION

The synthetic scope of the aromatic $S_{RN1}$ reaction has been outlined in the introduction. However, it was clear that the use of intramolecular $S_{RN1}$ reactions in constructing heterocyclic ring systems had received little attention.

As a result, our research was directed towards investigating the applicability of the $S_{RN1}$ cyclisation as a method for the preparation of a wide variety of novel heterocyclic systems with potential biological activity, an example of which is shown below:

\[ X = \text{Br, I} \quad A = \text{H}_2, \text{O, S} \]

The use of functional groups such as guanidines, thioureas etc., was envisaged to provide both potential nucleophilic sites and appropriate moieties for the introduction of biological activity.

A further aim of the research was to investigate various reaction conditions e.g. leaving groups, solvents and catalysts in order to provide optimum conditions for possible commercial exploitation.

Preliminary investigations were based on the reactions of 2-haloamides and thiaoamides (below) which were chosen as model systems for later, more complex cyclisations.
R=H,OMe   R'=CH₃,Ph
X=Cl,Br,I   Y=H₂,O,S
Z=O,S      n=0,1
DISCUSSION PART 1

The synthesis of fused five-membered heterocycles
2-Substituted benzothiazoles [21 and 22] and benzoxazoles [23 and 24] are conventionally prepared by reacting 2-aminothiophenols or 2-aminophenols with acid derivatives as depicted in Equation 99.

\[
\begin{align*}
\text{NH}_2 \quad \text{NH}_2 & \quad + \quad \text{RCX} \quad \xrightarrow{\text{RCX}} \quad \text{N} \quad \text{R} \\
\text{Y} = \text{O}, \text{S} & \quad \text{R} = \text{Cl}, \text{OR}, \text{OCOR}, \text{NH}_2 \\
\text{[21]} & \quad \text{Y} = \text{S}, \text{R} = \text{Ph} \\
\text{[22]} & \quad \text{Y} = \text{S}, \text{R} = \text{CH}_3 \\
\text{[23]} & \quad \text{Y} = \text{O}, \text{R} = \text{Ph} \\
\text{[24]} & \quad \text{Y} = \text{O}, \text{R} = \text{CH}_3
\end{align*}
\]

An alternative method developed by Bunnett and Hrutfiord\(^4\) involves the cyclisation of thioamides and amides via benzyne intermediates as shown in Equation 100.

\[
\begin{align*}
\text{NHCPh} \quad \text{Y} & \quad \xrightarrow{\text{KNH}_2} \quad \text{N=CPh} \\
\text{X} = \text{Br}, \text{Cl} & \quad \text{Y} = \text{O}, \text{S} \\
\text{[21]}, \text{Y} = \text{S} & \quad \text{[23]}, \text{Y} = \text{O}
\end{align*}
\]

Yields of between 62 and 90% were reported for these cyclisations and the presence of a benzyne intermediate was proved by experimental observations which included the fact that both 2'- and 3'-haloamides.
and their thio-analogues could be cyclised and also that 2'-bromo-3'-methyl-thiobenzanilide [25] could not be cyclised to 2-phenylbenzothiazole.

\[ \text{NHCSPh} \]
\[ \text{B} \]
\[ \text{Me} \]

[25]

It seemed quite feasible that the benzothiazoles and benoxazoles could also be prepared from the 2'-halothiamides and amides by an aromatic $S_{RN1}$ reaction (eqn. 101).

\[ \text{O} \overset{\text{H}}{\text{R}} \rightleftharpoons \text{B}^{-} \quad \text{N} \text{E} \rightarrow \text{R}^{+} \]

(101)

\[ R = \text{CH}_3, \text{Ph} \]
\[ X = \text{Cl}, \text{Br}, \text{I} \]
\[ Y = \text{O}, \text{S} \]

[21-24]

It was considered that this cyclisation would provide an ideal opportunity to extend the scope of the aromatic $S_{RN1}$ reaction (there had only been four previously reported examples of intramolecular cyclisation by this method) and to compare the $S_{RN1}$ cyclisation with that mediated by benzynes. The investigation had the added advantage that the starting materials could be synthesised with little difficulty from the corresponding 2-haloanilines by Schotten-Baumann acylation followed by thionation with phosphorous pentasulphide (eqn. 102).

\[ \text{NH}_2 \overset{\text{PhCOCl}}{\text{X}} \rightarrow \text{NHCSPh} \overset{\text{P}_2\text{S}_5}{\text{X}} \overset{\text{S}}{\text{NHCPh}} \]

(102)
The thionation step was found to proceed in higher yield and with less impurity formation when Lawesson's reagent\(^{74}\) [26] was used instead of \(P_2S_5\).

\[
\begin{array}{c}
\text{MeO-P-S-S-P-OMe}
\end{array}
\]

[26]

Because of these advantages, Lawesson's reagent became the agent of choice in all future thionations of carbonyl functions.

The investigation was begun by repeating the Bunnett cyclisations. All the reactions were carried out in double-distilled liquid ammonia using potassium amide as the base. The results are summarised in Table 2.

**TABLE 2**

The preparation of 2-phenyl-1,3-benzoxazole and benzothiazole

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Time (h)</th>
<th>Equivalents of (KNH_2)</th>
<th>Product, Yield (%)</th>
<th>Recovery of Starting Material %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{NHCOPhCl})</td>
<td>2.75</td>
<td>3.5</td>
<td>51</td>
<td>39</td>
</tr>
<tr>
<td>(\text{NHCOPhBr})</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>.91</td>
</tr>
<tr>
<td>(\text{NHCOPhCl})</td>
<td>5</td>
<td>3.5</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>(\text{NHCOPhBr})</td>
<td>3</td>
<td>3.5</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>(\text{NHCSPhCl})</td>
<td>2.5</td>
<td>3</td>
<td>0</td>
<td>76</td>
</tr>
</tbody>
</table>
None of the yields quoted in Table 2 were optimised and those reported by Bunnett were not equalled; the reported yields were 69 and 72% of 2-phenyl-1,3-benzoxazole (from 2'-chloro- and 2'-bromobenzenanilide respectively) and 67% of 2-phenyl-1,3-benzothiazole from 3'-chlorothiobenzenanilide.

The best yields of the benzoxazole were obtained when chloro-substituted starting materials were used. This was probably due to the fact that the majority of repeat experiments were done using those particular compounds.

2-Phenyl-1,3-benzothiazole was not obtained in the single reaction which was performed on 3'-chlorothiobenzenanilide.

It was discovered that the cyclisations were usually unsuccessful unless rigorous exclusion of moisture was maintained. Steps taken to achieve this objective included pre-drying all condensed liquid ammonia with small quantities of potassium metal and reversing the joints between the dry-ice condenser and reaction flask to prevent condensation from the condenser from entering the flask through those joints.

The poor results of some of the benzyne mediated cyclisations are probably due to the short period of time spent working on that particular series. As a result, the reaction conditions were not optimised and the associated experimental technique was not fully developed.

The synthesis of benzothiazoles and benzoxazoles via $S_{RN1}$ reactions

Some experience of performing $S_{RN1}$ reactions was gained by repeating Bunnett's experiments on the substitution reactions of aryl halides with ketone enolate anions (eqn. 103).

$$
\begin{align*}
\text{C}_6\text{H}_5 & + \text{CH}_2\text{COR} \xrightarrow{\text{hv}} \text{C}_6\text{H}_5\text{COR} \\
X=\text{Br},\text{I} & \quad R=\text{CH}_3,\text{Ph} \\
\end{align*}
$$

(103)
A standard $S_{RN1}$ reaction involves irradiating a solution of the aryl halide and potassium t-butoxide in dry DMSO in a suitable vessel. An atmosphere of dry nitrogen is maintained throughout the reaction. The irradiation was achieved using twelve 25W lamps emitting at 350 nm. The results of the experiments are shown in Table 3.

**TABLE 3**
Reactions of ketone enolates with aryl halides

<table>
<thead>
<tr>
<th>Aryl Halide</th>
<th>Ketone Enolate$^a$</th>
<th>Reaction Period (h)</th>
<th>Yield of Ketone [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>CH$_3$</td>
<td>1</td>
<td>52</td>
</tr>
<tr>
<td>I</td>
<td>CH$_3$</td>
<td>1</td>
<td>49</td>
</tr>
<tr>
<td>I</td>
<td>Ph</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Br</td>
<td>CH$_3$</td>
<td>3</td>
<td>0$^b$</td>
</tr>
</tbody>
</table>

*a. The enolate was used in 8-fold excess w.r.t. aryl halide.

b. The products were not identified.

The yields of $\alpha$-phenylacetone [149, R = CH$_3$] obtained were slightly lower than those reported by Bunnett but the failure of bromobenzene to react under these conditions was inexplicable.

The failure of acetophenone (and other aryl ketones) to participate in $S_{RN1}$ reactions with aryl halides had been reported$^{75}$ previously.

The cyclisation precursors used in the benzyne mediated reactions (plus the iodo-analogue and 2-iodacetanilide) were then subjected to the standard $S_{RN1}$ conditions described above.

Table 4 shows the results of all the experiments carried out in this study.
TABLE 4
The preparation of benzothiazoles from 2-halo-thioanilides

<table>
<thead>
<tr>
<th>2-Haloanilide</th>
<th>Conditions</th>
<th>Benzothiazole Yield (%)</th>
<th>Recovered Starting Material (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="NHCSPh" alt="28a" /></td>
<td>t-BuOK (8 equivalents), 6 h</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28a" /></td>
<td>t-BuOK (3 equiv.), 5 h, acetone (0.2 equiv.)</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28a" /></td>
<td>t-BuOK (20 equiv.), 3 h, acetone (8 equiv.)</td>
<td>100&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28a" /></td>
<td>as above but with O&lt;sub&gt;2&lt;/sub&gt;, dark</td>
<td>0</td>
<td>100, 100</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28b" /></td>
<td>as above but with 10 molar % p-dinitrobenzene</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28b" /></td>
<td>or 10 molar % di-t-butyl nitroxyl</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28b" /></td>
<td>t-BuOK (10 equiv.), 5 1/4 h, diethyl phosphite (0.2 equiv.)</td>
<td>82</td>
<td>0</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28c" /></td>
<td>t-BuOK (2.5 equiv.), 5 h</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28c" /></td>
<td>t-BuOK (20 equiv.), 6 h, acetone (8 equiv.)</td>
<td>22</td>
<td>62</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28c" /></td>
<td>t-BuOK (3 equiv.), 7 h, acetone (0.2 equiv.)</td>
<td>0</td>
<td>98</td>
</tr>
<tr>
<td><img src="NHCSPh" alt="28c" /></td>
<td>t-BuOK (22 equiv.), 5 h, acetone (10 equiv.)</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td><img src="NHCSMe" alt="28d" /></td>
<td>t-BuOK (22 equiv.), 6.5 h</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td><img src="NHCSMe" alt="28d" /></td>
<td>t-BuOK (22 equiv.), 4 h, acetone (8 equiv.)</td>
<td>58</td>
<td>0</td>
</tr>
<tr>
<td><img src="NHCSMe" alt="28d" /></td>
<td>NaH (20 equiv.), 6.5 h, acetone (8 equiv.)</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup> These conditions were chosen as standard for the following inhibition studies.

Under standard conditions, only the 2-iodothioacetanilide cyclised; a poor yield of 2-methyl-1,3-benzothiazole was obtained. The general lack of reactivity was thought to be due to inefficient intermolecular electron transfer from the thioamide anion to the aryl halide, i.e. the initiation...
step was inefficient (eqn. 104).

The operation of an intramolecular electron transfer (e.t.) does not lead to an $S_{RN1}$ chain reaction and can be discounted (Scheme 10).

Lack of reactivity due to a failure to generate efficient initiation steps in both aliphatic and aromatic systems has previously been overcome by the addition of small amounts of a reactive nucleophile to the reaction.
mixture. As mentioned in the introduction, this process is termed entrainment.

Kornblum's work on aliphatic halides has provided one of the most dramatic examples of entrainment;

$\alpha,\beta$-Dinitrocumene does not react with the azide anion in the dark, even after 48 hours. In contrast, the lithium salt of 2-nitropropane reacts with $\alpha,\beta$-dinitrocumene to afford an 87% yield of the substitution product [30] after only 3 hours (eqn. 105).

$$\text{Me} \quad \text{Me} \quad -\text{C-NO}_2 \quad + \quad \text{Li}^+ \quad \text{Me} \quad -\text{C-NO}_2 \quad \xrightarrow{\text{SN1}} \quad \text{Me} \quad \text{Me} \quad -\text{C-C-Me} \quad \text{Me} \quad \text{Me} \quad -\text{C-NO}_2 \quad \text{NO}_2 \quad \text{NO}_2 \quad \text{NO}_2$$

(105)

When $\alpha,\beta$-dinitrocumene (1 mol) was treated with sodium azide (2 mol) and the lithium salt of 2-nitropropane (0.1 mol), a 97% yield of $\beta$-nitrocumyl azide was formed after 3 hours (eqn. 106).

$$\text{Me} \quad \text{Me} \quad -\text{C-NO}_2 \quad + \quad \text{N}_3^- \quad \xrightarrow{\text{Li}^+ \quad \text{CH}_3} \quad \text{Me} \quad \text{Me} \quad -\text{C-N}_3$$

(106)

The enolate anion of acetone has been shown to be a very successful nucleophile
in aromatic $S_{RN}^1$ reactions and was, therefore, an ideal candidate to act as an entraining agent in the thioamide cyclisation series.

Table 4 shows the effect of adding various quantities of dry acetone to the standard $S_{RN}^1$ reaction mixtures.

In every case, the yield of 2-substituted benzothiazole was increased and an optimum quantity of acetone (8 equivalents) was established.

The process of entrainment is explained in Scheme 11. Here, the aryl substrate receives an electron from the entraining agent and the resulting radical-anion then enters the $S_{RN}^1$ chain reaction.

Surprisingly, no product resulting from an $S_{RN}^1$ reaction of the acetone enolate anion with the aryl halide was ever detected (eqn. 107).

\[ \text{NHCSR} \]
A possible explanation for this observation is that electron donation by the imidothiolate function in [31] increases the electron density at the radical centre sufficiently to retard the rate of addition of the acetone enolate anion, allowing the cyclisation step to proceed unhindered.

In order to provide firm evidence for the operation of an $S_{RN1}$ reaction, the thiobenzanilide [28] was subjected to the standard entrained conditions (Table 4) but with various inhibitors present. In all four cases, a quantitative recovery of starting material was obtained; in other words, the cyclisation reaction was completely inhibited. These four experimental methods are established$^{7,59,76}$ ways of assigning the $S_{RN1}$ mechanism.

Dioxygen and di-$t$-butyl nitroxyl (DTBN) inhibited the cyclisation by reacting with the radical intermediates of $S_{RN1}$ reactions (eqns. 108 and 109).

\[
\text{Ar}^\cdot + \text{O}_2 \rightarrow \text{Ar-O-O}^\cdot \quad (108)
\]

\[
\text{Ar}^\cdot + \cdot\text{O-N}^\cdot \bigg(\text{C(CH}_3\bigg)_3 \bigg) \rightarrow \text{Ar-O-N}^\cdot \bigg(\text{C(CH}_3\bigg)_3 \bigg) \quad (109)
\]

Traces of a phenolic product [32] were thought to have been formed during the dioxygen inhibition of the reaction of thioamide [28a] but were never isolated. The formation of [32] could be envisaged as occurring by processes shown in Scheme 12.
Di-t-butylnitroxyl may also act by inhibiting the initiation step as it is an efficient quencher of excited-state molecules (eqn. 110) whose role in the initiation of $S_{RN}^1$ reactions has been noted previously (Introduction, p. 10).

\[ [\text{ArX}]^* + \text{DTBN} \rightarrow \text{ArX} + [\text{DTBN}]^* \]

The radical anion intermediates of $S_{RN}^1$ reactions are 'scavenged' by electron acceptors such as dioxygen and p-dinitrobenzene (p-DNB) as exemplified in Equation 111.

\[ [\text{ArX}]^+ + O_2 \rightarrow \text{ArX} + [O_2]^+ \]

The $O_2/O_2^+$ couple has a relatively positive reduction potential and so the dioxygen radical-anion is unable to transfer its odd electron to the aryl substrate thus preventing chain propagation steps (eqn. 112).

\[ \text{ArX} + [O_2]^+ \rightarrow [\text{ArX}]^+ + O_2 \]
The absence of any reaction in a darkened vessel demonstrates the requirement for photostimulated initiation steps and is further evidence for the existence of an $S_{RN1}$ reaction.

Later cyclisation studies suffered from the inconvenience of the formation of polymeric residues which were presumed to be due to self-condensation of the entraining agent. It was found that the use of catalytic quantities of the anion of diethyl phosphite led to much cleaner products, avoiding the use of excess acetone (see Table 4).

The order of halogen nucleofugality in the halothiobenzanilide series [28a-c] was observed to be $I > Br > Cl$ (the yields of 2-phenyl-1,3-benzothiazole being 100, 22 and 5% from the respective halides). This is in direct contrast to the order observed in SNAr reactions and is a feature used to aid the assignment of $S_{RN1}$ reactions. 26

Although the inhibitions and the reactivity order of the halide starting materials provided very firm evidence for the operation of an $S_{RN1}$ reaction a mechanism involving a benzyne intermediate could not be ruled out. 3'-Iodothiobenzanilide [33] was therefore prepared and subjected to entrained $S_{RN1}$ reaction conditions. The pathways by which this compound could react are depicted in Scheme 13.
The rationale for choosing the thioamide [33] was that it clearly could not cyclise by the $S_{RN1}$ reaction (via the radical intermediate [35]) but would indicate whether or not some of the cyclic product [21] was being formed via the intermediacy of a benzyne [34]. Although it was unlikely that potassium $t$-butoxide would be strong enough a base to generate the benzyne ($p_{ka}$ benzene = 37, $p_{ka}$ R$_3$COH = 19.77), the possibility needed to be eliminated.

It was anticipated that the acetone adduct [36] might be formed although, as mentioned earlier, there had been no precedent for this reaction in our work.

In fact, neither [21] or [36] were formed upon entrained $S_{RN1}$ reaction of thioamide [33]. The only identifiable product (g.l.c.) was a small amount of thiobenzanilide [37] which may have been formed by one or more of the processes shown in Scheme 14.

![Scheme 14](image-url)
These processes are summarised by Equation 113;

\[ \text{Ar} \cdot + \text{SH} \rightarrow \text{ArH} + \text{S} \cdot \quad \text{(113)} \]

Here, the solvent is represented as SH. Dimethyl sulphoxide has been reported to be a good hydrogen atom donor in electrochemical studies of the \( S_{\text{RN1}} \) reaction. \(^1\text{7} \) The \( t \)-butyl alcohol is formed when potassium \( t \)-butoxide is used as a base.

An alternative explanation for the formation of reduction products is shown below (eqns. 114-115).

\[ \text{Ar} \cdot + [\text{ArX}]^2 \rightarrow \text{Ar}^- + \text{ArX} \quad \text{(114)} \]

\[ \text{Ar}^- + \text{SH} \rightarrow \text{ArH} + \text{S}^- \quad \text{(115)} \]

Again, the solvent is present as both DMSO and \( t \)-BuOH in our reactions.

A further possibility is that the aryl radical may be reduced by electron transfer from the entraining anion (eqn. 116). The aryl anion thus formed can then become protonated as shown in Equation 115.

\[ \begin{array}{c}
\text{N=C-Ph} \\
\text{S}^-
\end{array} \quad \text{CH}_2\text{COCH}_3 \quad \begin{array}{c}
\text{N=C-Ph} \\
\text{S}^-
\end{array} \quad \text{(116)} \]

All the processes outlined above represent termination steps in an \( S_{\text{RN1}} \) chain reaction and therefore inhibit the formation of cyclised material.

As mentioned in the introduction, reduction of aryl radicals has been reported previously in studies of \( S_{\text{RN1}} \) reactions. \(^\text{47,78} \) An interesting observation by Amatore \textit{et al} \(^\text{17} \) is that in electrochemically initiated \( S_{\text{RN1}} \) reactions (where the electron is donated by a cathode), the occurrence of reduction is largely determined by the stability of the initially formed
radical-anion. \((\text{Ar}X^-)\). If this species is unstable, it will decompose to the aryl radical in a region close to the cathode (at which it was originally formed) and will suffer a further one electron reduction to form the aryl anion which is then protonated by the solvent. A more stable radical-anion will diffuse away from the cathode before it fragments and so the formation of reduction product will be less favoured.

The result of the reaction of 3'-iodothiobenzanilide \([33]\), although not proved conclusively (the reduction product was never isolated and characterised) showed that cyclisation of 2'- and 3'-halothiobenzanilides did not proceed via benzyne intermediates.

Initiation of \(S_{\text{RN}}1\) reactions may be achieved by supplying 'free electrons' to the aryl substrate. This can be effected in two ways: by conducting the reaction at a cathode \(^{17,18}\) or by performing the reaction in the presence of solvated electrons formed by the dissolution of potassium metal in liquid ammonia. \(^{15,16}\)

When 2'-iodothiobenzanilide \([28a]\) was reacted in liquid ammonia with a catalytic quantity of potassium metal (20 mol %), a small amount of 2-phenylbenzothiazole was formed, the major product being recovered starting material. The formation of a small amount of the cyclised product could also be explained by the operation of a benzyne reaction but no attempts were made to probe the reaction mechanism.

When the amount of potassium metal was raised a complex mixture of products was obtained and no cyclic product or unreacted starting material was detected by t.l.c. or n.m.r. spectroscopy. It is quite probable that the use of excessive amounts of potassium leads to the formation of products by Birch reduction. It is also possible that large amounts of reduction product \([38]\) were formed.

\[
\begin{align*}
\begin{array}{c}
\text{NHCSPh} \\
[38]
\end{array}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{c}
\text{[N=C-Ph]}^- \\
[39]
\end{array}
\end{align*}
\]
The reduction effect noted by Amatore\textsuperscript{17} and discussed above could be extended to the donation of electrons formed at the surface of dissolving potassium metal. It is not known what the stability of radical-anion [39] is, but if it were relatively unstable, it would tend to fragment near the surface of the metal and therefore suffer reduction, leading to the formation of [38].

During the investigations into the cyclisation of the thioamide [28a], it was discovered that a solution of the compound in reagent-grade chloroform cyclised slowly in the presence of air. Irradiation from the laboratory strip lights was present and so an excited-state molecule could have been formed but the mechanism by which an electron was then transferred to the carbon-iodine $\sigma^*$ orbital (to form the substrate radical-anion) is obscure. Reagent-grade chloroform is stabilised by the addition of small amounts of ethanol (~1%). Ethoxide anion may act as an electron donor in a similar fashion to methoxide\textsuperscript{32} but there is no explanation for the formation of such an anion.

A final investigation carried out on this series of compounds was to discover if a terminal carbanion of compound [29] was being formed during the $S_{RN1}$ cyclisation (eqn. 117).

\[
\begin{align*}
\text{NHCCH}_2 & \quad 2\text{NaH} \\
\text{[29]} & \quad \text{[40]} \\
\end{align*}
\]

The presence of the dianion [40] would be of interest because it would yield information on the relative reactivities of carbon-and sulphur-centred anions in $S_{RN1}$ reactions.

Excess sodium hydride was dissolved in warm DMSO to form dimsyl sodium and the thioamide [29] was added. The mixture was quickly quenched with D$_2$O to form the anticipated dideuteriothioamide [41]. Aqueous work-up was then expected to yield the monodeuterated compound [42].
Unfortunately, both the m.s. and the n.m.r. spectroscopic data on the isolated product were inconclusive, the weight of evidence suggesting that the carbanion [40] had not been formed under the conditions used.

The synthesis of the 2-substituted benzoxazoles [23 and 24] was then investigated.

An authentic sample of 2-phenyl-1,3-benzoxazole [23] was prepared, for identification purposes, by a conventional method using polyphosphate ester (P.P.E.)\textsuperscript{79} as the condensation catalyst (eqn. 118).

\[
\text{NH}_2 + \text{PhCO}_2\text{H} \xrightarrow{\text{P.P.E.} \Delta} \text{N} \quad \text{Ph}
\]

Reaction of 2'-chloro- or 2-iodobenzanilide [43a and 43b respectively] under standard $S_{RN1}$ conditions resulted in the recovery of most of the starting materials (eqn. 119).

\[
\text{O} = \text{NCOPh} \xrightarrow{\text{t-BuOK}} \text{N} \quad \text{Ph}
\]

When acetone enolate anion was used in an entrained $S_{RN1}$ reaction, reduction of the starting material [43b] occurred (eqn. 120).

\[
\text{O} = \text{NCOPh} \xrightarrow{\text{CH}_2\text{COCH}_3 \text{SR}_{RN1}} \text{N} \quad \text{H} + [43b]
\]

Under the same conditions, 2-iodoacetanilide [44] reacted in a similar
fashion, recovered starting material and acetanilide being the only detectable products (eqn. 121).

As with the 3'-iodothiobenzanilide reaction mentioned earlier, it was evident that under entrained $S_{RN1}$ conditions, the aryl radical was being reduced at a considerably faster rate than that of substitution (Scheme 15 with $k_1 << k_2$).

The failure of the amides to cyclise to the benzoxazoles was hardly surprising as there had been no previous reports of oxygen nucleophiles participating in $S_{RN1}$ reactions; ambident nucleophiles such as the enolates of ketones, amides and esters always react via the carbanion and alkoxides and phenoxides are totally unreactive towards aryl radicals.

The most likely explanation of this phenomenon lies in the fact that coupling of an aryl radical with the oxygen-anion must initially form a radical-anion in which the 'odd' electron is located in the $\sigma^*$ orbital of the newly-formed carbon-oxygen bond; this species then slowly changes to a more
stable radical-anion in which the 'odd' electron is located in the $\pi^*$ molecular orbital. However, the energy level of the $\sigma^*$ M.O. of the carbon-oxygen bond is known to be exceptionally high and so the initial bond-forming reaction is very unfavourable. The aryl radical, once formed, undergoes reduction rather than nucleophilic attack by the oxygen-anion of the amide function.

The results of the above series of reactions show that 2-substituted-1,3-benzothiazoles can be prepared in high yields by simple, mild, synthetic procedures involving the use of entrainment. The method has obvious advantages over syntheses involving benzyne intermediates; the $S_{RN1}$ reactions give higher yields, they can be carried out in solvents other than ammonia which is toxic, difficult to handle and gaseous and they are generally quicker to perform and to work-up.

Unfortunately, the $S_{RN1}$ cyclisations cannot be used for the synthesis of 2-substituted-1,3-benzoxazoles. In this case, the benzyne-mediated cyclisation procedure provides an alternative.

The synthesis of benzothiazoles and benzoxazoles using copper (I) salts

It was known that thiolate, alkoxo, and phenolate anions could react with unactivated aryl halides in the presence of copper (I) salts. Bearing this in mind, the starting materials used in the $S_{RN1}$ cyclisations were reacted in the presence of copper (I) salts and base (eqn. 122).

$$\begin{align*}
\text{NHCR} & \quad \text{Cu(I)} \\
\text{X} & \quad \text{Base, DMF, N}_2, \Delta \\
\text{Y} & \quad \text{R}
\end{align*}$$

(122)

R=CH₃, Ph
X=Br, I
Y=O, S

A typical cyclisation reaction involved stirring the copper (I) salt and potassium t-butoxide in dry DMF, adding the amide or thioamide and heating the mixture at 80-100°C under an atmosphere of dry nitrogen.
The results of reactions using thioamides are shown in Table 5.

**TABLE 5**

The preparation of 2-substituted benzothiazoles via copper (I) catalysis

<table>
<thead>
<tr>
<th>2-Halothioanilide</th>
<th>Conditions</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![28a]</td>
<td>t-BuOK (2 equiv.), CuI (0.2 eq.), N₂, 80-84°C, 40 min. [STANDARD REACTION] As above but at r.t., 5 min. Standard reaction with p-DNB (10 mol%), 1.5h Standard reaction with DTBN (18 mol%), 4h Standard reaction with O₂ gas, 1.5h</td>
<td>![21] 100</td>
</tr>
<tr>
<td>![28b]</td>
<td>t-BuOK (2 equiv.), CuBr (0.2 eq.) N₂, r.t., 6h [STANDARD REACTION] Standard reaction with DTBN (50 mol%), 5h Standard reaction with p-DNB (20 mol%), 5h Standard reaction with O₂ gas, 4h</td>
<td>![21] 88</td>
</tr>
<tr>
<td>![29]</td>
<td>t-BuOK (5 equiv.), CuI (1 eq.), N₂, 85°C, 1.25h As above but with CuBr (1 eq.)</td>
<td>![22] 63</td>
</tr>
</tbody>
</table>

| ![22] | 94 |
The results of these copper (I) catalysed cyclisations compared very favourably with those obtained from $S_{RN}^1$ reactions on the same starting materials (see Table 4).

Yields of 2-phenyl-1,3-benzothiazole [21] were consistently high and it was discovered that the cyclisation of 2'-iodothiobenzanilide [28a] proceeded smoothly at room temperature within five minutes. The failure of inhibitors to reduce the yield in the heated reaction of [28a] was attributed to the rapidity of the cyclisation. In other words, it was assumed that the inhibitors could not compete with the cyclisation step.

In order to overcome this effect, the inhibitions were repeated on the slower, room temperature cyclisation of the 2-bromothioamide [28b]. However, this reaction was also not inhibited by the usual agents which suggested that the copper (I) catalysed cyclisations were proceeding via a non-$S_{RN}^1$ mechanism.

The reactivity order of the halothiobenzanilides was observed to be $ArI > ArBr$ which is the same as that observed in $S_{RN}^1$ reactions and the reverse of that observed in $S_{NAr}$ substitutions.

Copper (I) bromide was found to be as effective a catalyst as the iodide. The fact that the copper (I) salts were acting in a truly catalytic manner (quantitative yields of cyclisation products being obtained even when the copper salt was present in 0.2 equivalent quantities) indicated that a chain reaction was occurring, a possible explanation being a copper (I) catalysed $S_{RN}^1$ reaction.

A detailed discussion of the mechanistic nature of these cyclisations will be made at a later stage.

An investigation of the reactions of 2-haloanilides in the presence of copper (I) salts was then made. The results are summarised in Table 6.

A satisfactory yield of 2-phenyl-1,3-benzoxazole [23] was obtained from the reaction of amide [43b] with one equivalent of copper iodide. However, when the quantity of the catalyst was reduced, incomplete reaction ensued which suggested that the salt was not acting in a truly catalytic manner.

2-Methyl-1,3-benzoxazole [24] could not be prepared by this method. The only isolable product was unreacted starting material. The failure of this
### TABLE 6

The preparation of 2-substituted benzoxazoles via copper (I) catalysis

<table>
<thead>
<tr>
<th>2-Haloanilide</th>
<th>Conditions</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Image" /></td>
<td>t-BuOK (5 eq.), CuI(1 eq.), (N_2), 70-80°C, 1.5h.</td>
<td><img src="image2" alt="Image" /> NHCOMe Ph</td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td>t-BuOK (2 eq.), CuI(0.2 eq.), (N_2), 78-85°C, 5.75h.</td>
<td><img src="image4" alt="Image" /> NHCOMe Ph + <img src="image5" alt="Image" /> NHCOMe I</td>
</tr>
<tr>
<td><img src="image7" alt="Image" /></td>
<td>t-BuOK (4 eq.), CuI (1 eq.), (N_2), 70-80°C, 8h.</td>
<td><img src="image8" alt="Image" /> NHCOMe</td>
</tr>
<tr>
<td><img src="image9" alt="Image" /></td>
<td>t-BuOK (4 eq.), CuI(0.2 eq.), (N_2), 85-87°C, 5.5h.</td>
<td><img src="image10" alt="Image" /> NHCOMe</td>
</tr>
</tbody>
</table>

* Yields were not obtained.

particular cyclisation reaction was unexpected and no satisfactory explanation has been found. One possibility is that the participation of the oxygen-anions of amides is not particularly favourable but that the formation of an extended aromatic system such as exists in compound [23] is sufficient to allow cyclisation to proceed.

This explanation is based on the fact that sulphur anions are known to react with aryl halides at a faster rate than oxygen anions and also that a recent review of copper-assisted nucleophilic substitutions of aryl...
halogen contains no examples of amides reacting via the oxygen-anion; it is always the nitrogen-anion which reacts (eqns. 86 and 97 of the introduction).

The results of all the copper (I) catalysed reactions indicate that this method possesses certain advantages over the $S_{RN1}$ cyclisations.

The major advantage is that of extended applicability; oxygen-anions may react under certain conditions and both the iodo- and bromo-substituted starting materials are reactive. In $S_{RN1}$ reactions, the aryl bromides were much less reactive than the iodides.

On a practical basis, the copper (I) catalysed reactions are slightly more convenient as specialised irradiation equipment is not required and entrainment is not necessary.

Although not demonstrated in our reactions, copper (I) promoted substitutions can be carried out in a number of solvents including DMF, dioxan, acetonitrile, alcohols and amines, many of which are unsuitable for $S_{RN1}$ reactions.

The synthesis of benzothiazoles and benzoazoles using copper powder

Nucleophilic aromatic substitutions can be achieved in base-free conditions by using copper powder (see the Introduction for examples). Although the thioamides and amides used in the previous studies in this discussion were not base-sensitive, they were reacted with copper powder in DMF in order to extend the scope of our copper-assisted cyclisations.

The results of the reactions are shown in Table 7.

In contrast with the copper (I) salt promoted reactions, both amides [43b and 44] were totally unreactive towards substitution in the presence of copper powder.

The thioamides [28a and 29] cyclised smoothly to the corresponding benzothiazole. The high yields were comparable to those obtained from the copper (I) catalysed reactions.

An aspect of the copper (0) reactions which was not investigated was whether true catalysis was operating or not, i.e., the copper powder was not used...
TABLE 7

The reactions of 2-haloanilides and their thio-analogues with copper powder

<table>
<thead>
<tr>
<th>2-Haloanilide</th>
<th>Conditions</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![NHCOPh]</td>
<td>Cu (1 eq.), N₂, 80-90°C, 6h</td>
<td>![NHCOPh] 100</td>
</tr>
<tr>
<td>![NHCOMe]</td>
<td>Cu (1 eq.), N₂, 80-90°C, 7h</td>
<td>![NHCOMe] 100</td>
</tr>
<tr>
<td>![NHCSPh]</td>
<td>Cu (1 eq.), N₂, 80-90°C, 1.5h</td>
<td>![21] 100</td>
</tr>
<tr>
<td>![NHCSMe]</td>
<td>Cu (1 eq.), N₂, 80-90°C, 1h</td>
<td>![22] 72</td>
</tr>
</tbody>
</table>

used in quantities less than one equivalent.

This method, therefore, provides an alternative to the use of the copper (I)/base system which may lead to the decomposition of sensitive materials.

A drawback to the use of copper powder is that it does not appear to be useful for the cyclisation of amides via the oxygen-anion. This is not too surprising as this lack of reactivity had previously been observed in the reactions of aryl halides with benzamide and acetamide. The only product is the N-arylamide (eqn. 123).

\[
\text{X} + \text{RCONH}_2 \xrightarrow{\text{Cu}} \text{150°C} \rightarrow \text{NHCOR} \quad (123)
\]

R=CH₃, Ph
DISCUSSION PART 2

The synthesis of fused six-membered heterocycles
The results of the cyclisation reactions of 2-halosubstituted amides and thioamides discussed in Part 1 prompted an investigation into the synthesis of six-membered benzoheterocycles. The first reactions to be studied were the cyclisations of the N-(2-iodo-4,5-dimethoxybenzyl)acetamides, -benzamides and their thio-derivatives shown in Equation 124.

\[
\begin{align*}
\text{Me} & \quad \text{HCYR} \\
\text{Me} & \quad \text{-----------.MeO} \\
\text{Me} & \quad \text{Y} \\
\text{Me} & \quad \text{R} \\
\end{align*}
\]

\( R = \text{CH}_3, Y = \text{O} \)  
\( R = \text{CH}_3, Y = \text{S} \)  
\( R = \text{Ph}, Y = \text{O} \)  
\( R = \text{Ph}, Y = \text{S} \)

The starting materials [45-46] were readily prepared from veratrylamine (Scheme 16).

Reagents
(i) Lawesson's Reagent
(ii) SbCl\(_5\)/ICl or I\(_2\)
(iii) SbCl\(_5\)/ICl

\text{SCHEME 16}
Iodination of amide [53] occurred solely at the 2-position; the $^1$H n.m.r. spectrum of the iodinated compound showed no ortho or meta coupling in the aromatic region. The iodination of amide [45] was found to be higher yielding than that involving thioamide [54]. Small amounts of compounds [53] and [54] were kept and used to identify the suspected reduction products of the later cyclisation reactions.

The benzamide analogues [47] and [48] were prepared in a similar fashion, using the preferred iodination route (Scheme 17).

The target cyclisation products were the 2-substituted-1,3-benzoxazines [49] and [51] and the corresponding benzothiazines [50] and [52].
There had been very few reports of the synthesis of 1,3-benzoxazines. Two examples\textsuperscript{87} are shown below (eqns. 125,126).

\begin{equation}
\text{Reagents}
\begin{array}{c}
(i) \text{RMgBr} \\
(ii) \text{RCX}_3
\end{array}
\end{equation}

The synthesis of 1,3-benzothiazines has also received little attention. Some existing methods for their preparation are shown below (eqns. 127\textsuperscript{87} and 128\textsuperscript{88}).
It was hoped, therefore, that the use of an $S_{RN1}$ or copper-promoted substitution reaction would provide a new, milder route to the syntheses of these heterocycles.

The preparation of 2-substituted-6,7-dimethoxy-4H-1,3-benzothiazines and benzoxazines

The results of entrained and non-entrained $S_{RN1}$ reactions on the amides and thioamides [45-48] are shown in Table 8.

**Table 8**
The $S_{RN1}$ reactions of N-(2-iodo-4,5-dimethoxybenzyl)amides and thioamides

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Recovery of Starting Material (%)</th>
<th>Yield of Reduction Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td>NaH (20 equiv.), acetone (8 equiv), DMSO, hv, $N_2$, 19h</td>
<td>26</td>
<td>[53], 19</td>
</tr>
<tr>
<td><img src="image2.png" alt="Image" /></td>
<td>t-BuOK (20 equiv.), acetone (8 equiv), or diethyl phosphite (3 equiv.), DMSO, hv 23h, $N_2$</td>
<td>(a)</td>
<td>(a)</td>
</tr>
<tr>
<td><img src="image3.png" alt="Image" /></td>
<td>t-BuOK (5 equiv.), diethyl phosphite (1 equiv.), DMSO, hv, $N_2$, 29h</td>
<td>46</td>
<td>[55], 41</td>
</tr>
<tr>
<td><img src="image4.png" alt="Image" /></td>
<td>t-BuOK (10 eq.), acetone (8 eq.), DMSO, hv, $N_2$, 7.25h</td>
<td>100</td>
<td>[56], 0</td>
</tr>
<tr>
<td><img src="image5.png" alt="Image" /></td>
<td>t-BuOK (10 eq.), diethyl phosphite (5 eq.), DMSO, hv, $N_2$, 8h</td>
<td>(b)</td>
<td>(b)</td>
</tr>
</tbody>
</table>

Notes to Table 8

a) No identifiable compounds were isolated from the crude reaction products.

b) The crude product was shown by t.l.c. and i.r. and n.m.r. spectroscopy to be a mixture of starting material and the reduction product [54].
The anticipated heterocycles were not formed in any of the \( S_{RN1} \) reactions performed on the amides and thioamides [45-48], the only identifiable products being recovered starting materials and/or the reduction products (whose means of formation have been discussed earlier).

The reluctance of oxygen nucleophiles to participate in \( S_{RN1} \) reactions had been noted previously and so the absence of any 2-substituted-6,7-dimethoxy-4H-1,3-benzoxazine ([49] and [51]) was no surprise. However, the observation that the corresponding 1,3-benzothiazines ([50] and [52]) were not formed was unexpected.

The isolation of reduction products indicated that radical-anion intermediates were being formed as expected. Because the subsequent formation of a six-membered ring was expected to be energetically favourable, it appeared that the presence of methoxyl groups on the benzene ring was retarding the cyclisation step. The electron-donating properties of the methoxyl function para to the radical centre in the radical-anion [57] were thought, therefore, to be sufficiently powerful to reduce the electrophilicity of that centre, thereby inhibiting the cyclisation step (eqn. 129). The favoured reaction then becomes reduction of the aryl radical.

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} \\
\text{N} = \text{C} - \text{R} & \quad \text{MeO} \\
\text{S}^- & \quad \text{MeO} \\
\end{align*}
\]

The validity of the explanation above was corroborated by the findings of Beugelmans [24] who observed the \( S_{RN1} \) arylation of monoanions of various diketones - a reaction which had not previously been accomplished. The alkylation of bromobenzene, 2-bromopyridine and 2-chloroquinoline (usually a very reactive substrate) failed but ortho, meta and para - cyanobromobenzenes reacted readily (eqn. 130). This effect was attributed to the electron-withdrawing properties of the cyano group making the aryl radical more electrophilic.

\[
\begin{align*}
\text{CN} & \quad \text{Br} \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{R} & \quad \text{R'} \\
\text{CN} & \quad \text{CN} \\
\text{CO}_2\text{Et} & \quad \text{CO}_2\text{Et} \\
\text{R} & \quad \text{R'} \\
\end{align*}
\]

\( R = \text{CN, CO}_2\text{Et, COCH}_3, \text{H} \)

\( R' = \text{H, Et} \)
An alternative explanation for the lack of reactivity observed in our reactions is that cyclisation does occur but that the initially-formed radical-anion [58], in which the 'odd' electron is located in the $\sigma^*$ orbital of the newly-formed carbon-sulphur bond, is very unstable and decomposes back to the radical-anion [57] before a stable $\pi^*$ radical-anion can be formed.

\[
\begin{align*}
\text{Me}_2\text{N}=\text{C}-\text{R} & \quad \text{MeO} \\
\text{MeO} & \quad \text{S}^-
\end{align*}
\]

The low overall yields of isolated material in the cyclisation reactions (Table 8) were probably caused by decomposition of the starting materials due to the extended periods of irradiation and the large amounts of base used.

The preparation of 2-substituted-6,7-dimethoxy-4H-1,3-benzothiazines and benzoxazines by copper and copper(I)-promoted substitutions

The amides and thioamides [45-48] were reacted under the conditions used for the earlier preparations of benzoxazoles and benzothiazoles (Discussion, Part 1), and the results of the experiments are shown in Table 9.

The amides [45] and [47] were found to be unreactive in the copper (I)- and copper-promoted substitutions and large amounts of unreacted starting materials were recovered. This lack of reactivity was unexpected as 2'-iodobenzanilide [28a] had been successfully cyclised to 2-phenyl-1,3-benzoxazole [23] in an earlier study (Discussion, Part 1). Possible reasons for the general lack of reactivity of oxygen nucleophiles in these reactions will be proposed in Part 4 of the discussion.

The use of sodium hydride as the base in the reaction of the acetamide [45] resulted in the isolation of unidentified gums. This was possibly due to side reactions occurring as a result of the abstraction of either the benzylic or methyl protons by the strong base.

The reactions of the thioamides [46] and [48] were more productive. The thiobenzamide [48] cyclised to 2-phenyl-6,7-dimethoxy-4H-1,3-benzothiazine [52] in moderate yields when reacted in the presence of copper (I) iodide or copper powder. These cyclisations are milder and slightly higher-yielding
TABLE 9

The reactions of N-(2-iodo-4,5-dimethoxybenzyl)amides and thioamides with copper (I) iodide and copper powder

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Yield of Cyclised Material [ ], (%)</th>
<th>Recovery of Starting Material (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![I]NHCOMe ![I]MeO</td>
<td>t-BuOK (20 eq.), CuI (1 eq.), DMF, 70-80°C, N₂, 20.5h</td>
<td>0</td>
<td>98</td>
</tr>
<tr>
<td>![I]MeO ![I]NHCSMe</td>
<td>NaH (10 eq.), CuI (1 eq.), DMF, N₂, 70-80°C, 7-8h.</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>![I]</td>
<td>Cu (1 eq.), DMF, N₂, 77°C, 4h</td>
<td>0</td>
<td>69</td>
</tr>
<tr>
<td>![I]NHCSMe ![I]MeO</td>
<td>NaH (20 eq.), CuI (0.2 eq.), DMF, N₂, 23.5h.</td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>![I]NHCOPh ![I]MeO</td>
<td>t-BuOK (20 eq.), CuI (1 eq.), DMF, N₂, 70-80°C, 22h.</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>![I]</td>
<td>Cu (1 eq.), DMF, N₂, 75°C, 6.5h.</td>
<td>0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>![I]NHCSPh ![I]MeO</td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, N₂, 80-85°C, 8.5h.</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>![I]</td>
<td>Cu (1 eq.), DMF, N₂, 75°C, 6.5h.</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>![I]</td>
<td>t-BuOK (5 equi.), CuI (1 eq.), DMF, N₂, 75°C, 4h.</td>
<td>[52], 48</td>
<td>0</td>
</tr>
<tr>
<td>![I]</td>
<td>Cu (1 eq.), DMF, N₂, 90-100°C, 7.2h.</td>
<td>[52], 43</td>
<td>0&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NOTES

a) No identifiable products were isolated.
b) The isolated product could not be identified.
c) The product was identical to that obtained when using CuI.
d) N-(2-Iodo-4,5-dimethoxybenzyl)benzamide (10%) was also obtained.
than that shown in Equation 128 and do not suffer the concomitant formation of small amounts of the 4-phenyl isomer. The reaction conditions are certainly milder than those involving Grignard reagents as shown in Equation 127.

An unexpected product of the reaction of the thioamide [48] with copper powder was the corresponding amide, N-(2-iodo-4,5-dimethoxybenzyl) benzamide [47]. The dethionation step could have occurred by a process such as that shown in Scheme 18.

\[ \begin{align*}
\text{RHN} & \quad \text{NHR} \quad \overset{\text{Cu}}{\longrightarrow} \quad \text{RHN} & \quad \overset{\text{H}_2\text{O}}{\longrightarrow} \quad \text{RHN} \\
\text{S} & \quad \overset{\text{Cu}^{II}}{\longrightarrow} \quad \text{S} & \quad \overset{\text{H}_2\text{O}}{\longrightarrow} \quad \text{S} \\
\text{H}_2\text{O} & \quad \overset{\text{SH}}{\longrightarrow} \quad \text{Cu}^{II} & \quad \overset{\text{H}_2\text{S}}{\longrightarrow} \quad \text{Cu}^{II} \\
\text{RHN} & \quad \text{NHR} \quad \overset{\text{H}_2\text{O}}{\longrightarrow} \quad \text{RHN} & \quad \overset{\text{SH}}{\longrightarrow} \quad \text{Cu}^{II} \\
\end{align*} \]

SCHEME 18

In contrast, the thioacetamide [46] did not cyclise to the 2-methylbenzothiazine [50]. Reaction in the presence of copper (I) iodide or copper powder resulted in the formation of the same product when sodium hydride was used as the base. When potassium t-butoxide was used, poor yields of unidentified gums were obtained.

The product from the reactions using sodium hydride, however, was crystalline and gave clear i.r. and n.m.r. spectra. The 'H n.m.r. spectrum contained absorptions at positions expected from the presence of 2-methyl-6,7-dimethoxy-4H-1,3-benzothiazine [46] (by comparison with the spectrum of the 2-phenyl analogue). The presence of other peaks at similar chemical shift values suggested the presence of a closely related impurity. The t.l.c. 73
results, however, indicated that the product was homogenous thus making the separation of the suspected components difficult.

The mass spectrum was also consistent with the presence of the cyclic product. The base peak and several others at m/z values lower than the base peak were identical to those observed in the spectrum of the 2-phenyl analogue. The impurity appeared to be a higher-molecular weight species whose identity could not be established.

Microanalytical results were inconsistent with the presence of any anticipated pure product despite extensive purification which strengthened the suspicion that a mixture had been isolated.

Because of the late stage at which this problem arose, no attempts were made to separate the products.

The reason for the difference in product formation between the two thioamides may have been due to the existence of acidic α-hydrogen atoms in the methyl analogue and the use of a strong base such as sodium hydride leading to some (as yet) unknown side-reaction.

The formation of reduction products was not observed in any of the reactions tabulated above and as stated previously, the possible reasons for this will be discussed in Part 4.

The preparation of 2-phenyl-4H-1,3-benzothiazine and benzoxazine by $S_{RN-1}$ reactions

Because of the suspicion that the methoxyl groups were inhibiting the ring-forming step when using the starting materials reported earlier, the corresponding unsubstituted amide and thioamide [59] and [60] were prepared by the route shown in Scheme 19.
The reduction products [61] and [62] were prepared in a similar fashion from benzylamine.

\[
\text{[61]} \quad \text{Lawesson's Reagent} \quad \text{[62]}
\]

The anticipated cyclisations are depicted in Equation 131 and the results of the \textit{SRN1} reactions performed on the starting materials are shown in Table 10.

\[
\text{[61]} \quad \text{[64], } Y=S \quad \text{[68], } Y=O
\]

\begin{table}[h]
\begin{tabular}{|c|c|c|c|}
\hline
Starting Material & Reaction Conditions & Yield of Reduction Product [ ], (%) & Recovery of Starting Material (%) & Yield of Cyclic Product [ ], (%) \\
\hline
\begin{tabular}{c}
\text{NHCOPh} \\
\text{[59]}
\end{tabular} & t-BuOK (10 eq.), diethyl phosphite (0.5 eq.), DMSO, hv, N\textsubscript{2}, 8.5h & [61], 16 & 6 & 0 \\
\hline
\begin{tabular}{c}
\text{NHCOPh} \\
\text{[60]}
\end{tabular} & t-BuOK (30 eq.), acetone (8 eq.), or diethyl phosphite (0.5 eq.), DMSO, hv, N\textsubscript{2}, 23h & 0\textsuperscript{a} & 0 & 0 \\
& t-BuOK (5 eq.), DMSO, 70-80°C, hv, N\textsubscript{2}, 8.25h & 0 & 24\textsuperscript{b} & [64], 8 \\
\hline
\end{tabular}
\end{table}

\textbf{NOTES}
\begin{enumerate}
\item[a)] No identifiable products were isolated.
\item[b)] Yields were estimated by 'H n.m.r. spectroscopic analysis of the crude product.
\end{enumerate}
As expected, no cyclisation product was obtained from the reaction of the amide [59]. The radical-anion intermediate gave rise to the reduction product. This is similar to our previous observations.

Under entrained $S_{RN1}$ reaction conditions (in the presence of acetone or diethyl phosphite), the thioamide [60] suffered decomposition and no identifiable products were obtained. The reactions were analysed at regular intervals by analytical t.l.c. but no evidence of reduction or cyclisation was observed. The extended period of irradiation was presumed to be the cause of the decomposition.

In an attempt to force the cyclisation to proceed, a reaction mixture was heated and irradiated in the absence of an entraining agent. A low yield of 2-phenyl-4H-1,3-benzothiazine (formed by an $S_{RN1}$ reaction) was detected in the crude product along with a modest recovery of starting material.

It was apparent, therefore, that removing the electron-donating methoxyl groups was not sufficient to allow cyclisation to occur. The barrier to such a reaction was overcome, albeit unsatisfactorily, by heating a reaction under $S_{RN1}$ conditions.

Unfortunately, there was not sufficient time to investigate the $S_{RN1}$ reactions of a substrate containing one or more electron-withdrawing groups on the benzene ring. Bearing Beugelmans,\textsuperscript{24} observations in mind, it appears likely that the barrier to cyclisation could be overcome by preparing a compound such as $N$-(3-cyano-5-iodobenzyl)thiobenzamide [65].

\[
\begin{align*}
\text{NC} & \quad \text{I} \\
\text{NHCSPh} &
\end{align*}
\]

![Image of molecule 65]

\[
\begin{align*}
\text{I} & \\
\text{NHCSMe}
\end{align*}
\]

![Image of molecule 66]

The methyl analogue [66] was not prepared and there was no reason to expect that it would have behaved differently.

The preparation of 2-phenyl-4H-1,3-benzothiazine and benzoxazine by copper (I) and copper-promoted substitution reactions

The reactions of the amide [59] and thioamide [60] in the presence of copper (I) iodide or copper powder were investigated next. The results
of this study are shown in Table 11 overleaf.

The results of the reactions of the benzamide [59] with copper (I) iodide and with copper powder were as anticipated, large quantities of unreacted starting material being recovered.

Several reports\textsuperscript{69,89} of transition metal catalysed substitution reactions suggested that there may be a significant temperature dependence. In an attempt to force the cyclisation step to proceed a reaction of the benzamide with copper (I) iodide was conducted at reflux (153°C). No cyclisation occurred and the formation of the reduction product [61] could not be confirmed. The isolation of such a product from a copper (I) promoted reaction would have been very significant as its formation would have suggested the intermediacy of an aryl radical and, possibly a radical-anion in the reaction pathway thereby allowing a direct comparison with SRN\textsuperscript{1} reactions.

On reaction with one equivalent of copper (I) iodide the thioamide [60] cyclised smoothly to form 2-phenyl-4H-1,3-benzothiazine [64] in good yield.

The yield was not significantly suppressed by the addition of p-dinitrobenzene (p-DNB) which suggested that no SRN\textsuperscript{1} reaction intermediates (radicals and radical-anions) were involved in the cyclisation. When the amount of copper (I) iodide was reduced to 0.2 equivalents a 39% yield of the cyclised material was obtained which showed that the metal salt was acting in a catalytic manner.

It was found that these cyclisations and inhibition results were prone to large variations unless the experiments were conducted in a precise manner. This involved adding the reagents in the order designated as Standard Reaction A. When that order was changed as in Standard Reaction B, much lower (and variable) yields of the benzothiazine were obtained. The reason why the prior mixing of copper (I) iodide and potassium t-butoxide should make such a difference remains unexplained. Bacon\textsuperscript{90} reported that special problems arise when reactions occur at interfaces between solid copper species and liquid organic media and that reaction rates and yields may be poorly reproducible under such conditions. During our copper (I) iodide promoted reactions there was often solid material remaining in the mixtures and it may be that this heterogeneity that caused the variable results.

Even if the inhibition results with Standard Reaction B conditions are to be
TABLE 11

The reactions of N-(2-iodobenzyl)benzamide and -thiobenzamide with copper (I) iodide and copper powder

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Yield of Cyclised Product (%)</th>
<th>Recovery of Starting Material (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ \text{HNCOPh} ]</td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, N₂, 80°C, 9h</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>As above, but at 153°C</td>
<td>0</td>
<td>?ₐ</td>
</tr>
<tr>
<td></td>
<td>Cu (1 eq.), DMF, N₂, 90-105°C, 7.5h</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>[ \text{HCSPh} ]</td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, N₂, 70-80°C, 2.75 h. (Standard Reaction A)</td>
<td>[64], 78</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction A with CuI (0.2 eq.)</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction A with p-DNB (0.2 eq.)</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction B, 75°C, 2.5h</td>
<td>61</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction B with p-DNB (0.2 eq.)</td>
<td>0, 39</td>
<td>0,0</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction B with DTBN (0.1 eq.)</td>
<td>34, 14</td>
<td>0,0</td>
</tr>
<tr>
<td></td>
<td>Cu (1 eq.), DMF, N₂, 90-100°C, 1.5 h (Standard Reaction)</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction but Cu (0.2 eq.), 7h</td>
<td>67</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction with p-DNB (0.2 eq.)</td>
<td>55</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes

a) Analytical t.l.c. of the crude product indicated the presence of starting material and a product with an R₂ identical to that of the reduction product [61]. Column chromatography failed to separate the components.

b) The order of addition of reagents in Standard Reaction A was as follows:- CuI and t-BuOK followed by the starting material.

c) The order of addition in Standard Reaction B was as follows:- starting material and t-BuOK followed by CuI.
accepted, their significance as regards the possible operation of an $S_{RN1}$ reaction must be questioned as the same effect has been noted in transition metal salt-catalysed substitutions which have been shown not to involve $S_{RN1}$ reaction intermediates.91

A high yield of the benzothiazine [64] was also obtained when copper powder was used as the catalyst. As with the copper (I) iodide, the copper powder was shown to act in a catalytic manner. Considerable inhibition was observed when p-dinitrobenzene was present.

The absence of methoxyl groups on the benzene ring was therefore observed to have a noticeable effect on the speed and yield of cyclisation. The thiobenzamide [48] cyclised in 43-48% yield after 4-7 hours whereas the non-methoxylated analogue [60] cyclised in 78-89% yield after only 1.5-2.75 hours. The reasons for this effect will be discussed in Part 4.

The acetamide [66] was not prepared but in retrospect, might be expected to have given some interesting results in the light of differences in behaviour between the thioamides [46] and [48] (see Table 9).

The $S_{NAr}$ reactions of $N$-(2-halobenzoyl)-$N'$-phenylureas and thioureas

In all of the cyclisation studies described above, there was no ambiguity regarding the heterocycle formed. The next systems were chosen because of their ease of preparation and because cyclisation was possible via either a sulphur- or a nitrogen-anion.

The compounds were of interest to the CASE collaborating company because they contained the thiourea and urea functions which may confer some biological activity.

\[
\begin{align*}
\text{[68], } X &= \text{Br} \\
\text{[69], } X &= \text{Cl}
\end{align*}
\]
The \( N,N' \)-disubstituted thioureas [68] and [69] were prepared by the convenient route\(^9\) shown below (eqn. 132).

\[
\begin{align*}
\text{Br} & \quad \text{OH} \\
\text{Cl} & \quad \xrightarrow{(i) \text{SOCl}_2} \\
\text{Br} & \quad \text{N NHPh} \\
\text{Cl} & \quad \xrightarrow{(ii) \text{NH}_4\text{SCN}} \\
\text{Br} & \quad \text{NHPh} \\
\text{Cl} & \quad \xrightarrow{(iii) \text{PhNH}_2}
\end{align*}
\]

The reduction product [71] was prepared in an identical manner from benzoyl chloride.

The \( N,N' \)-disubstituted urea [70] was prepared by the route\(^9\) shown in Equation 133.

\[
\begin{align*}
\text{CO}_2\text{H} & \quad \xrightarrow{(i) \text{SOCl}_2} \\
\text{Br} & \quad \xrightarrow{(ii) \text{NH}_3} \\
\text{CONH}_2 & \quad \xrightarrow{(i) \text{COC}} \\
\text{Br} & \quad \xrightarrow{(ii) \text{PhNH}_2}
\end{align*}
\]

The starting materials [68-70] could, theoretically, cyclise in two directions; one by a nitrogen-anion to form a quinazolinone, the other by an oxygen- or a sulphur-anion to form a 1,3-benzoxazinone or 1,3-benzothiazinone respectively (Scheme 20).

As usual, the investigation was begun by studying reactions under \( S_{RN}^1 \) conditions. However, it soon became clear that whatever reaction was taking place with the thiourea [68] proceeded without any requirement for photostimulation or entrainment. It was finally discovered that \( S_{NAr} \) cyclisation was taking place and that the product was 1-phenyl-2-thioxo-quinazolin-4(3H)-one [73].
The results of the reactions of the starting materials [68-70] are shown in Table 12.

The operation of an $S_{N}Ar$ reaction was confirmed by the results presented in the Table. The yield of the standard reaction was not reduced by conducting the experiment in the dark or in the presence of an electron scavenger such as p-dinitrobenzene. It was, therefore, unlikely that an aromatic $S_{RN}1$ reaction was responsible for the formation of the quinazolinone [73]. The recovery of starting material from the inhibition reaction suggested that some side-reaction involving a radical intermediate may have been inhibited. Such reactions may have been responsible for the fairly low yields of quinazolinone obtained.
<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Yield of Quinazoline [%]</th>
<th>Recovery of Starting Material [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="O-Br" alt="Image" /></td>
<td>t-BuOK (5 eq.), DMF, 70-80°C, 2.25h (Standard Reaction)</td>
<td>[73], 29^a</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction but t-BuOK (1 eq.)</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction but in the dark</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>DMF, N₂, 70-80°C, 8h</td>
<td>0</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Standard Reaction plus p-DNB (0.2 eq.)</td>
<td>46</td>
<td>38</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Yield of Quinazoline [%]</th>
<th>Recovery of Starting Material [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="O-Cl" alt="Image" /></td>
<td>t-BuOK (5 eq.), DMF, N₂, 72°C, 2.75h</td>
<td>58</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Yield of Quinazoline [%]</th>
<th>Recovery of Starting Material [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="O-Br" alt="Image" /></td>
<td>t-BuOK (5 eq.), DMF, N₂, 85°C, 8h</td>
<td>[72], 36^b</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes

a) The low yield was caused by extensive purification.
b) The reaction was repeated several times. 2-Bromobenzanilide (51-63%) was the only isolable product.

The observation that there was little difference in the rates of reaction of the bromo- and chloro-substituted analogues [68] and [69] was further evidence for an SN₂Ar reaction. In an SN₁-mediated cyclisation, the chloro-substituted analogue would be expected to react at a much slower rate or not at all.
The reaction did not proceed in the absence of base. When the amount of potassium t-butoxide was reduced to one equivalent, the quinazolinone was obtained in fair yield. This particular experiment was performed in order to identify the monoanion present in the reaction. The result however, merely confirmed that the monoanion [76] must have been present. The recovery of a significant quantity of unreacted starting material suggested that the dianion [77] may have also been formed.

The urea [70] was successfully cyclised to 1-phenyl-quinazolin-2,4(1H, 3H)-dione on only one occasion. Subsequent attempts to repeat the reaction resulted in the isolation of 2-bromobenzanilide presumably formed by a base-induced rearrangement which resulted in the loss of isocyanic acid (Scheme 21).
No other products would be expected from this reaction as the isocyanic acid would be hydrolysed on work-up to carbamic acid which would quickly decompose to ammonia and carbon dioxide.

No benzoxazinone [74] was formed in the reactions of the urea [70].

No rearrangement product (2-bromobenzanilide) was isolated from any reactions of the thiourea [68]. A probable explanation for this is that the cyclisation rate exceeds that of the rearrangement so that the latter does not compete. The reaction times quoted in the experimental section support this suggestion.

A proposed mechanism for the formation of the quinazolinones [72] and [73] is shown below (Scheme 22).
TABLE 13
The $^{13}$C n.m.r. data of 1-phenyl-quinazolin-2,4(1H, 3H)-dione [72] and 1-phenyl-2-thioxo-quinazolin-4(3H)-one [73]

<table>
<thead>
<tr>
<th>Carbon Atom</th>
<th>$\delta_C$ (ppm)</th>
<th>$\delta_C$ (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>149.88</td>
<td>176.20</td>
</tr>
<tr>
<td>4</td>
<td>162.07</td>
<td>158.70</td>
</tr>
<tr>
<td>4a</td>
<td>115.33</td>
<td>117.4</td>
</tr>
<tr>
<td>5</td>
<td>128.94</td>
<td>128.2</td>
</tr>
<tr>
<td>6</td>
<td>122.60</td>
<td>124.8</td>
</tr>
<tr>
<td>7</td>
<td>134.85</td>
<td>135.3</td>
</tr>
<tr>
<td>8</td>
<td>115.33</td>
<td>117.0</td>
</tr>
<tr>
<td>8a</td>
<td>142.66</td>
<td>139.4 or 143.3</td>
</tr>
<tr>
<td>1'</td>
<td>136.32</td>
<td>139.4 or 143.3</td>
</tr>
<tr>
<td>2', 6'</td>
<td>129.38</td>
<td>128.9</td>
</tr>
<tr>
<td>3', 5'</td>
<td>129.98</td>
<td>130.5</td>
</tr>
<tr>
<td>4'</td>
<td>127.30</td>
<td>129.6</td>
</tr>
</tbody>
</table>
The mechanism is based on that proposed by Rudorf\textsuperscript{2} to explain the formation of 1-thiochromones and quinolones (see eqns. 1 and 2). The only other report of such activated $S_N$Ar cyclisations known to us was that by Adams et al\textsuperscript{3} (see eqn. 3).

The benzothiazinone [75] produced by cyclisation via the less-nucleophilic sulphur-anion was not formed in the $S_N$Ar reactions described above. The identity of the isolated products was deduced from the $^1H$ and $^{13}C$ n.m.r. spectral data and the mass spectra.

The $^{13}C$ n.m.r. data of the products are presented in Table 13.

Several features in the spectrum of the quinazolinone [73] served to distinguish it from that of the isomeric product [75]. Carbon atoms 2 and 4 in [73] were assigned by comparison with the quinazolinone\textsuperscript{94} and the pyrimidine shown below.

In contrast, the expected chemical shift of C-2 in the benzothiazinone [75] was approximately 168 ppm (by comparison with the benzothiazoles\textsuperscript{95} below).

The mass spectra of the quinazolinones showed cleavages corresponding to
the loss of HNCS (M-59) or HNCO (M-43) and no cleavage corresponding to the loss of HNPh (M-92) which would have been expected from a benzothiazinone such as [74] or [75].

Finally, the 'H n.m.r. data shown (in part) below were much more consistent with the presence of quinazolinones than benzothiazinones (the presence of sulphur in the ring would not be expected to shield H-8 so much).

\[
\delta_H = 8.26 \quad \delta_H = 8.05
\]

\[
\begin{align*}
\text{H} & \text{O} \\
\text{H} & \text{O} \\
\text{Ph} & \text{Ph} \\
\end{align*}
\]

\[
\delta_H = 6.51 \quad \delta_H = 6.42
\]

Adams\(^3\) reported that the carbonyl group was essential for S\(_{\text{N}}\)Ar cyclisations of the type described above and observed that activation of the halogen-bearing carbon atom could not be achieved by replacing the carbonyl function with an imino (C\(=\)NPh) group. In order to investigate the possibility of activation by a thiocarbonyl function, attempts were made to prepare the dithione [78] (eqn. 134).

Surprisingly, all attempts to prepare the dithione by the route shown above failed so an alternative route was devised (Scheme 23).
Unfortunately, the investigation progressed only as far as the preparation of 2-bromothiobenzamide and the dithione was not synthesised.

The reactions of N-(2-halobenzoyl)-N'-phenylureas and thioureas with copper (I) iodide and copper powder

The starting materials [68-70] were reacted with copper (I) iodide and copper powder as described earlier.

The results of this study are shown in Table 14 on p. 90.

From the results shown in the Table, it is evident that the presence of copper (I) iodide catalysed the rearrangement described previously for the urea [70] so that cyclisation of the thiourea [68] was no longer observed i.e. $k_r > k_c$ in Equation 135.
A modified mechanism for the rearrangement, which involves a copper (I) thiolate species is shown in Scheme 24.
TABLE 14

The copper (I) iodide- and copper-promoted reactions of N,N'-disubstituted ureas and thioureas

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Yield of Cyclised Product (%)</th>
<th>Other Products (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Structure" /></td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, N₂, 70-80°C, 3.5h. (Standard Reaction)</td>
<td>0</td>
<td><img src="image2" alt="Structure" /> 42</td>
</tr>
<tr>
<td><img src="image3" alt="Structure" /></td>
<td>Standard Reaction but CuI (0.2 eq.), 4h</td>
<td>[73], 9</td>
<td><img src="image4" alt="Structure" /> a</td>
</tr>
<tr>
<td><img src="image5" alt="Structure" /></td>
<td>Standard reaction with p-DNB (0.2 eq.), 4h</td>
<td>0</td>
<td><img src="image6" alt="Structure" /> 29</td>
</tr>
<tr>
<td><img src="image7" alt="Structure" /></td>
<td>Cu (1 eq.), DMF, N₂, 80-85°C, 9.5h</td>
<td>0</td>
<td><img src="image8" alt="Structure" /> 68, 20 [70], 17</td>
</tr>
<tr>
<td><img src="image9" alt="Structure" /></td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, N₂ 85°C, 2h</td>
<td>0</td>
<td><img src="image10" alt="Structure" /></td>
</tr>
<tr>
<td><img src="image11" alt="Structure" /></td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, N₂, 58°C, 7h</td>
<td>b</td>
<td>b</td>
</tr>
<tr>
<td><img src="image12" alt="Structure" /></td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, 80°C, 5h</td>
<td>0</td>
<td><img src="image13" alt="Structure" /> 14</td>
</tr>
</tbody>
</table>

Notes
a) A mixed fraction consisting mainly of 2-bromobenzanilide was obtained by column chromatography.
b) Reactions carried out at various times and temperatures resulted in the formation of complex mixtures.
The formation of stable copper (I) thiocyanate serves to drive the rearrangement to completion.

When the amount of copper (I) iodide used in the reaction was lowered, the thiourea [68] suffered two reactions; rearrangement as described in Scheme 24 to yield an unquantified amount of 2-bromobenzanilide and S_NAr cyclisation to form the quinazolinone [73]. This result showed that the copper salt was acting in a stoichiometric manner as shown in Scheme 24. Once the salt was consumed, the S_NAr reaction was able to operate.

A small degree of inhibition was observed when the thiourea was reacted in the presence of p-dinitrobenzene. However, the significance of this result is doubtful as no radical involvement was suspected.

A reaction performed in the presence of copper powder resulted in the recovery of starting material and dethionation to form N-(2-bromobenzoyl)-N'-phenylurea [70]. A possible mechanism for this reaction has been given earlier (Scheme 18).

The generality of the copper (I)-promoted rearrangement was tested by reacting the 2-chloro analogue [69] and N-benzoyl-N'-phenylurea [71] under the conditions described in Table 14. In both cases, the only identifiable products were the corresponding benzanilides.

The reaction of the urea [70] was not so straightforward and the composition of the resulting complex (8-component) mixtures was not resolved.

In order to investigate the possibility of cyclisation via a sulphur-anion, the N-methyl analogues [79] and [80] were prepared as described earlier (using N-methylaniline instead of aniline).

\[
\begin{align*}
\text{[79], } X &= \text{Br} \\
\text{[79a], } X &= \text{H} \\
\text{[80], } X &= \text{Br} \\
\text{[80a], } X &= \text{H}
\end{align*}
\]
The non-halogenated derivatives [79a] and [80a] were also prepared from benzoyl chloride and benzamide respectively.

With no acidic terminal amide protons, it was expected that the N-methyl analogues would cyclise via oxygen or sulphur to form the corresponding 1,3-benzoxazinone or 1,3-benzothiazinone as shown in Equation 136.

![Equation 136](image)

The results of various reactions on the N-methyl compounds are shown in Table 15.

2-(N-Methyl-N-phenyl)amino-1,3-benzothiazin-4-one [82] was obtained in good yield from the SNAr reaction of the thiourea [79] and in poor yield from the copper (I) iodide-promoted reaction.

The identity of the product was confirmed by the $^1$H and $^{13}$C n.m.r. spectra which were distinct from those of the isomeric quinazolinone [73]. The $^{13}$C n.m.r. data are presented on the page following Table 15. The numbering system is shown on the structure below.
TABLE 15
The $S_{\text{N}}\text{Ar}$, $S_{\text{RN}}$, and copper (I) iodide-promoted reactions of $N$-(2-bromobenzoyl)-$N'$-methyl-$N'$-phenylurea and -thiourea

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Recovery of Starting Material (%)</th>
<th>Yield of Cyclised Product [%], (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Reaction 1" /></td>
<td>t-BuOK (5 eq.), DMF, $N_2$, 82°C, 23.5h</td>
<td>24</td>
<td>[82], 65</td>
</tr>
<tr>
<td><img src="image2.png" alt="Reaction 2" /></td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, $N_2$, 80°C, 2.33h</td>
<td>0</td>
<td>[82], 26</td>
</tr>
<tr>
<td><img src="image3.png" alt="Reaction 3" /></td>
<td>t-BuOK (5 eq.), DMF, $N_2$, 75-80°C, 4h</td>
<td>49</td>
<td>0</td>
</tr>
<tr>
<td><img src="image4.png" alt="Reaction 4" /></td>
<td>t-BuOK (5 eq.), diethyl phosphite (1 eq.), DMSO, $N_2$, $hv$, 73h</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td><img src="image5.png" alt="Reaction 5" /></td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, $N_2$, 75-80°C, 1.66h</td>
<td>$0^a$</td>
<td>0</td>
</tr>
</tbody>
</table>

Notes

a) No identifiable products were obtained.
The chemical shift values for C-2 and C-4 were almost exactly as expected by comparison with the literature examples presented on page 86 of this discussion.

The $^1$H n.m.r. data is shown (in part) in the structure below:

The chemical shift of H-8 was approximately 0.6 ppm downfield of the equivalent proton in the quinazolinone [73]. This effect would be predicted on the basis of the smaller shielding effect of sulphur compared with that of nitrogen.

The result of the $S_N$Ar reaction confirmed an earlier suggestion that in the non-methylated analogue [68], the sulphur-anion was not unreactive as such but was incapable of competing with the more nucleophilic nitrogen-anion.

The formation of the benzothiazinone in the reaction of the thiourea [79] with copper (I) iodide was also due to the operation of an $S_N$Ar reaction. No rearrangement product was formed (eqn. 137).

<table>
<thead>
<tr>
<th></th>
<th>C-2</th>
<th>C-4</th>
<th>C-4a</th>
<th>C-5</th>
<th>C-6</th>
<th>C-7</th>
<th>C-8</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta_c$ (ppm)</td>
<td>169.54</td>
<td>164.13</td>
<td>122.52</td>
<td>129.68</td>
<td>130.39</td>
<td>131.05</td>
<td>125.41</td>
</tr>
<tr>
<td>C-8a</td>
<td>C-9</td>
<td>C-1'</td>
<td>C-2',6'</td>
<td>C-3',5'</td>
<td>C-4'</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\delta_c$ (ppm)</td>
<td>133.84</td>
<td>40.35</td>
<td>141.6</td>
<td>128.37</td>
<td>130.52</td>
<td>127.88</td>
<td></td>
</tr>
</tbody>
</table>
This was not surprising as the necessary nitrogen-anion could not be formed at the terminal thioamide function (see Schemes 21 and 24). The low yield of benzothiazinone formed in this particular reaction may have been caused by the existence of side-reactions that result from the presence of copper (I) iodide.

No 2-(N-methyl-N-phenyl)amino-1,3-benzoxazin-4-one [81] was formed from an attempted reaction of the urea [80] that was carried out under $S_N$Ar conditions. The result was not surprising in the light of previous failures to achieve cyclisation via an oxygen-anion.

A reaction that was carried out for three days under $S_{RN1}$ conditions in the presence of an entraining anion resulted in a poor recovery of starting material, the remainder having probably been decomposed over the extended irradiation period.

The reaction with copper (I) iodide was totally unsuccessful, no identifiable products being isolated.

In order to investigate the requirements for activation in the $S_N$Ar cyclisation in more detail the thiourea [84] was prepared. This is a vinylogue of compound [68] and the method of preparation is shown below.

The aim of the study was to investigate the use of an $\alpha,\beta$-unsaturated carbonyl function for activating the carbon-bromine bond toward $S_N$Ar reactions.
The trans-cinnamic acid derivative [83] was prepared in order to provide the correct geometry for the possible ring closure reactions. The cis isomer would contain a side chain which would have difficulty in approaching the carbon-halogen bond.

The possible cyclisation routes available to the thiourea [84] include the formation of six- or eight-membered heterocycles via S_NAr, S_RN, or copper-promoted substitutions and six-membered heterocycles by ring-closure of the side chain. These routes are summarised in Scheme 25.

The possible products included a uracil derivative [89] and a 1,3-thiazine [88] by side chain ring closure and a carbostyril [85] and two eight-membered ring systems by aromatic nucleophilic substitution. Compound [86]
is a 1,3-benzodiazocine; [87] is a 1,3-benzothiazocine.

The preparation of a carbostyryl (a 2-quinolone derivative) by an $S_N$Ar, $S_{RN}^1$ or copper-promoted substitution would provide a convenient route to that heterocyclic system and would complement the recent syntheses by Beugelmans [96] in which an $S_{RN}^1$ reaction was used (eqn. 138).

\[
\begin{align*}
\text{R}^1 & \text{NHR} \\
\text{R}^2 & \text{CH} \_ \text{COCH}_3 \\
\text{R}^3 & \text{O}
\end{align*}
\]

A reaction carried out under $S_{RN}^1$ conditions on the thiourea [84] resulted in the isolation of 6-(2-bromophenyl)-2,3-dihydro-1,5-diphenyl-2-thioxopyrimidin-4(1H)-one [89] formed by a side chain ring closure (eqn. 139).

\[
\begin{align*}
\text{Ph} & \text{H} \\
\text{Ph} & \text{N~Ph} \\
\text{Br}
\end{align*}
\]

The base peak in the mass spectrum was caused by the loss of PhNCSNCO. Both of the possible products could fragment in this manner.

The i.r. spectrum ($\nu_{max}$: 3050, 1750 cm$^{-1}$) was more consistent with the presence of a thioimide [89] rather than the amine tautomer of the thiazine [88b] (eqn. 140). There was no absorption in the $^1H$ n.m.r. spectrum due to an amine proton in the tautomer [88b] although there was a possibility that the signal could have been enveloped by the aromatic absorptions.
The result of this experiment suggested that the preparation of heterocycles larger than six-membered systems by $S_N Ar$ reactions as discussed above may be difficult due to cyclisation of the side chain.

**The synthesis of tricyclic ring systems**

The synthesis of the ethylene thiourea adducts [90] and [91] was then attempted. These compounds could possibly cyclise to form tricyclic systems as shown below.

Only the 2-bromobenzoyl derivative [90] would be reactive in an $S_N Ar$ reaction and the synthesis of this compound was the first to be attempted. However, attempts to prepare the target molecule by the reaction of 2-bromobenzoyl chloride with ethylene thiourea under various conditions resulted in the formation of complex mixtures from which little of the required amide could be obtained. The dimeric compound [93] was identified as a product of these acylation reactions (eqn. 141).
Small amounts of amide obtained were insufficient for study and no further attempts were made to prepare the compound.

The adduct [91] was prepared in good yield by the route shown in Scheme 26.

\[
\text{Note:} \\
\text{Ethylene thiourea/EtOH}
\]

The results of the cyclisation reactions of the ethylene thiourea adduct [91] are shown in Table 16.

A reaction performed under entrained SRN1 conditions proved unsuccessful but 1,2-dihydro-5H-imidazo [1,2a] [3,1] benzothiazine [92] was isolated in low yield from the copper (I) iodide and copper-promoted reactions. The poor recovery of material from all the experiments was probably due to side reactions and decompositions leading to the formation of polar materials which remained on the columns used for purification of the reaction mixtures. However, the reaction conditions were not optimised and it is anticipated that the yields could be improved.
TABLE 16
The cyclisation reactions of S-(2-iodobenzyl)-2-imidazolidinethione

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Yield of [92] (%)</th>
<th>Recovery of Starting Material</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t-BuOK (5 eq.), diethyl phosphite (1 eq.), DMSO, N\textsubscript{2}, hv, 5.3h</td>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>t-BuOK (5 eq.), CuI (1 eq.), DMF, N\textsubscript{2}, 80-85°C, 4.66h</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cu (1 eq.), DMF, N\textsubscript{2}, 100-110°C, 2.75h</td>
<td>33</td>
<td>0</td>
</tr>
</tbody>
</table>

The use of copper powder under base-free conditions provided a mild, convenient method for the preparation of a tricyclic system. The same method had been successfully applied by Yale et al.\textsuperscript{97} to the synthesis of a tricyclic system containing a seven-membered B ring (eqn. 142).

\[
\text{(142)}
\]

SUMMARY
The synthesis of fused six-membered heterocycles was not achieved by reactions performed under S\textsubscript{RN1} conditions except in one case where a reaction of
A non-methoxylated substrate was heated and irradiated and a poor yield of 2-phenyl-4H-1,3-benzothiazine was obtained.

The conclusion that was drawn from the results was that aryl radicals were formed but were not sufficiently electrophilic to allow ring closure to occur. The introduction of electron-withdrawing groups onto the benzene rings of the starting materials may overcome the barrier to cyclisation.

Compounds in which a carbonyl group is present at a position ortho to the halogen atom were shown to undergo cyclisation by nitrogen- or sulphur-anions to form quinazolinones and benzothiazinones respectively. Cyclisation by oxygen-anions could not be achieved. The cyclisations were shown to proceed by the $S_{N}Ar$ mechanism and were restricted to the formation of six-membered heterocycles. When the separation between the carbonyl function and the nucleophile was extended from 2 to 3 atoms, cyclisation occurred exclusively on the side chain itself.

Copper (I) iodide was successfully used to promote the cyclisations of both methoxylated and non-methoxylated thioamides to form the correspondingly substituted 2-phenyl-4H-1,3-benzothiazines.

The reaction of various $N,N^{1}$-disubstituted thioureas with copper (I) iodide led to a novel rearrangement which resulted in the formation of benzanilides. This reaction was prevented when the terminal nitrogen atom of the side chain was trisubstituted.

No cyclisation via an oxygen-anion was observed in any of the copper (I)-promoted reactions involving amide substrates.

A tricyclic system was prepared in low yield by a copper (I)-promoted substitution reaction, the cyclisation being effected by a nitrogen-anion.

Reactions conducted in the presence copper powder gave, on the whole, the same results as those using copper (I) iodide. In some of the reactions using thioamide substrates however, low yields of the dethionated product (the corresponding amide) were obtained.

Comparing all the results, it would appear that the use of $S_{RN}$ reactions for preparing cyclic systems of the type investigated above is limited. Copper (I) iodide can be used with more success, especially if the starting
materials do not contain deactivating substituents. In reactions involving base-sensitive starting materials, the use of copper powder may be advisable.

Finally, the preparation of fused six-membered heterocycles may be achieved with little difficulty under $S_N$Ar conditions. However, the structure of the side chain must be chosen carefully.
DISCUSSION PART 3

The attempted synthesis of fused seven-membered heterocycles
In order to extend the scope of the cyclisation procedures which have been described in Parts 1 and 2 of this Discussion, an investigation was made of the synthesis of seven-membered heterocyclic systems by those methods.

The study was commenced using the phenethyl analogues of the acetamide and thioacetamide [45] and [46] respectively. The starting materials [97] and [98] were prepared from homoveratrylamine as described earlier (Scheme 16). The non-iodinated analogues [95] and [96] were also prepared (Scheme 27).

\[ \text{Scheme 27} \]
The possible products of cyclisation of the starting materials are shown below.

The diagram above shows that cyclisation via the nitrogen-anion would produce the 1-acetylindoline [99] or its thio-analogue [100] whereas cyclisation via the oxygen- or sulphur-anion would lead to the formation of a 1,3-benzoxazepine [101] or a 1,3-benzothiazepine [102] respectively.

In order to aid the identification of the cyclisation products, the indolines [99] and [100] were prepared using the cyclisation procedure reported by Kametani \(^7\) (eqn. 143).
The thioamide [100], which was not prepared by Kametani, displayed an unexpected $^1$H n.m.r. spectrum. The data are shown (in part) below.

The full data are provided in the Experimental section.

It was observed that the integrations of the peaks were approximately half their expected value and, therefore, it appeared that two forms of the thioamide were present in almost equal quantities (in actual fact, form A predominated very slightly).

The deshielding of the H-7 absorption by the thione was very pronounced causing a downfield shift of approximately 2.5 ppm from the chemical shift value observed for the same proton in form B (the exact position of H-7 for form B was unknown as three closely-positioned singlets were present at $\delta_H$ 6.57-6.83). The same field effect was observed for the methylene (H-2) triplet.

The spectrum of the amide [99] showed no such configurational ambiguity and the chemical shift of H-7 ($\delta_H$ 7.86) suggested that the compound existed almost solely in the configuration depicted by form A.

It was later found that the non-methoxylated analogues of [99] and [100] had been studied by $^1$H n.m.r. spectroscopy and that the configurations and chemical shift effects proposed above were correct. The authors stated that the amide (thioamide) and benzene ring planes must be almost, or completely coplanar to produce the deshielding effects that they observed.
The cyclisation reactions of *N*(3,4-dimethoxyphenethyl)acetamide and thioacetamide

Compounds [97] and [98] were reacted under SRN1 conditions and with copper (I) iodide and copper powder as described previously. The results are shown in Table 17.

**TABLE 17**

The cyclisation reactions of amide [97] and thioamide [98]

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Reaction Conditions</th>
<th>Recovery of Starting Material (%)</th>
<th>Yield of Reduction Product [ ], (%)</th>
<th>Other Products [ ], (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>![amide 97]</td>
<td>NaH (25 equiv.), acetone (8 equiv.), DMSO, N₂, hv, 24h.</td>
<td>0</td>
<td>[95], 47</td>
<td>0</td>
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<td>![thioamide 98]</td>
<td>t-BuOK (5 equiv), diethyl phosphite (1 equiv.), DMSO, N₂, hv, 7h.</td>
<td>25</td>
<td>22</td>
<td>0</td>
</tr>
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<td></td>
<td>Cu (1 equiv.), DMF, N₂, 70-80°C, 3h.</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>NaH (25 equiv.), acetone (8 equiv.), DMSO, N₂, hv, 25h.</td>
<td>4</td>
<td>[96], 15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>t-BuOK (20 equiv.), acetone (8 equiv.), DMSO, N₂, hv, 25h.</td>
<td>a</td>
<td>a</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>t-BuOK (3 equiv.), CuI (1 equiv.), DMF, N₂, 80°C, 8.25h.</td>
<td>0</td>
<td>0</td>
<td>[100], 35b</td>
</tr>
<tr>
<td></td>
<td>Cu (1 equiv.), DMF, N₂, 80-90°C, 5.5h.</td>
<td>0</td>
<td>0</td>
<td>?c</td>
</tr>
</tbody>
</table>

106
Notes
a) Analytical t.l.c. indicated that the product was a mixture of recovered starting material and reduction product.
b) Numerous attempts to repeat the reaction failed.
c) The identity of the product remained unsolved.

Photostimulation under $S_{RN1}$ reactions failed to produce any cyclised products and mixtures of unreacted starting material and reduction product were obtained. The isolation of the reduction products indicated that the intermediate radical-anion and aryl radical had been formed but that cyclisation was not occurring (Scheme 28).

As discussed previously, the probable explanation for the absence of ring-
closure is the electron-donating effect of the methoxyl substituents reducing the electrophilicity of the aryl radical.

An alternative explanation (see Part 2) is that ring-closure does occur but forms an unstable σ* radical-anion which rapidly ring-opens to reform the aryl radical.

Although this reason has been proposed to explain the failure of oxygen-centred anions to react in $S_{RN1}$ reactions, no report of such behaviour for nitrogen or sulphur nucleophiles is known to us. Reports of aromatic $S_{RN1}$ reactions involving nitrogen-anions are scarce$^{99}$ and amides in particular have been found$^{41}$ to be unreactive whatever the means of initiation and so the absence of formation of the indolines $^{[99]}$ or $^{[100]}$ in the reactions described above was not surprising. However, as with the reactions of the benzyl analogues, the lack of reactivity of the sulphur-anion was surprising.

A model of the benzothiazepine $^{[102]}$ did not reveal any significant bond strain or steric interactions. Because no reason was known to us why the radical-anion $^{[103]}$ should be unstable the lack of reactivity of the sulphur-anion in thioamide $^{[98]}$ was more likely to be attributable to the electronic effect of the methoxyl groups.

The reaction of the thioamide with copper (I) iodide (the reaction of the amide having been previously reported by Kametani) resulted in the formation of 2,3-dihydro-5,6-dimethoxy-1-thioacetyl-1H-indole $^{[100]}$, a result which was predictable from Kametani's$^{71}$ work. However, the result could not be repeated despite numerous attempts with both potassium t-butoxide and sodium hydride as the base, different orders of addition of reagents and variation of the reaction temperature. The only identifiable product isolated from the repeated experiments was unreacted starting material. This appeared to be another example of the reported$^{90,100}$ unrepeatability of certain copper-catalysed reactions.

The result above confirmed that in the copper (I) iodide-promoted substitutions the electron-donating methoxyl groups were not as effective in inhibiting the cyclisation step which suggested that the reaction mechanism of this and the $S_{RN1}$ substitutions was not identical.

The fact that the cyclisation proceeded via the nitrogen-anion and not the
Sulphur may be explained by the preferential co-ordination of copper (I) with nitrogen (eqn. 144). This had been observed by Bajpai $^{101}$ for aryl thioureas where copper (I) was found to be complexed with the substituted nitrogen atom.

\[
\text{Me}_2\text{N} - \text{S} - \text{Me} \quad \text{MeO} \quad \text{CuI} \quad \text{MeO} \quad \text{Me} \\
\text{MeO} \quad \text{I} \quad \text{CuI} \quad \text{MeO} \quad \text{Me} \\
\text{MeO} \quad \text{I} \\
\]

Sulphur can also co-ordinate with copper (I) as was shown by the copper (I) iodide-promoted synthesis of benzothiazoles (Discussion, Part 1). In those particular reactions, co-ordination of copper (I) with the nitrogen-anion could not lead to ring-closure.

An alternative explanation may lie in the ring size of the transition state and intermediate that we propose are involved in the mechanism by which the copper (I)-promoted substitution reactions proceed. The validity of the mechanism will be discussed in Part 4 but the relevant structures are shown in Scheme 29.

The mechanistic pathway by which 2'-iodothiobenzanilide was converted to 2-phenyl-1,3-benzothiazole is thought to involve the seven-membered transition state, A and six-membered arylcopper (III) intermediate, B in Scheme 29.

The corresponding species, C and D in the reaction pathway of the phenethyl analogue would be nine- and eight-membered fused heterocycles. Because of the ring strain that would possibly be present in these larger heterocycles, the cyclisation proceeded via the nitrogen-anion.

$\text{N-(2-Iodo-4,5-dimethoxyphenethyl)acetamide} \ [97]$ was unreactive towards copper powder, a quantitative recovery of starting material being obtained after three hours. The inertness of amides in these reactions will be dealt with in Part 4 of the Discussion.

The thioamide [98], on the other hand, reacted completely and a crystalline
Oxidative Addition

\[ \text{MeO} + \text{Cu} \rightarrow \text{MeO} + \text{Cu} \]

Reductive Elimination

\[ \text{MeO} + \text{Cu} \rightarrow \text{MeO} + \text{Cu} \]

**Scheme 29**
product was obtained. As with the benzyl analogue [46], the reaction with copper powder appeared to result in the formation of an intimate mixture of products which were inseparable by analytical t.l.c.

The m.s. and n.m.r. spectrum indicated that dethionation had occurred to form the corresponding amide [97] although t.l.c. could not confirm this suggestion.

The spectral data showed that starting material, reduction products [95] and [96], and the indoline [100] had not been formed.

Microanalysis was performed twice and produced variable results (despite a constant melting point being achieved) which again indicated that the product was a mixture.

The unassigned absorptions in the m.s. and the n.m.r. spectrum could not be interpreted and the identity of the other product(s) remained unsolved.

Several attempts were made to hydrolyse the amide [97] in order to prepare the phenethylamine[104] (eqn. 145).

\[
\begin{align*}
\text{MeO} & \quad \text{NHCOMe} \\
\text{MeO} & \quad \text{MeO} \\
& \quad \text{I} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{NH} \quad \text{NHCOMe} \\
\text{MeO} & \quad \text{MeO} \\
& \quad \text{I} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{NHCOMe} \\
\text{MeO} & \quad \text{MeO} \\
& \quad \text{I} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{NH} \quad \text{NHCOMe} \\
\text{MeO} & \quad \text{MeO} \\
& \quad \text{I} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{NHCOMe} \\
\text{MeO} & \quad \text{MeO} \\
& \quad \text{I} \\
\end{align*}
\]

The amide anion itself (\(\text{NH}_2\)) was the only amine nucleophile known to participate in aromatic S\(_{RN}^1\) reactions and, therefore, the phenethylamine [104] would have been an interesting substrate to study. However, all attempts to prepare it failed. On the assumption that the amide function was resisting hydrolysis, an N-benzyloxy carbonyl derivative [105] of homoveratrylamine was prepared and iodinated as described in Scheme 16.
The benzoyloxycarbonyl function had been used extensively as an N-protecting
group in amino acid chemistry and its subsequent removal was well-documented. However, treatment of the amide [106] with a 45% solution of hydrogen bromide in glacial acetic acid\textsuperscript{102} failed to produce the hydrobromide of the required amine and the investigation was carried no further.

Had time been available, the non-methoxylated and cyano-substituted
starting materials [107] and [108] respectively would have been prepared and their cyclisation reactions studied.

\[
\begin{align*}
\text{[107]} & \quad \text{[108]}
\end{align*}
\]

The absence of any electron-donating groups on the benzene rings in the compounds shown above may increase the electrophilicity of an aryl radical sufficiently to allow cyclisation to occur. The presence of iodine rather than bromine or chlorine is desirable in a starting material to be used in such studies because of the reactivity it confers to the molecule, especially in aromatic $\text{S}_{\text{RN}}^1$ reactions.

The preparation of the thioamide [107] was considered and an outline synthesis of the corresponding 2-(2-iodophenyl)ethylamine is shown below (Scheme 30).

However, because of the ease with which iodine was lost from amide [97] during some of the attempted hydrolyses and because aryl iodides were known to be reduced by lithium aluminium hydride under mild conditions,\textsuperscript{103} the synthesis was not thought to be profitable in terms of the time required and the results likely to be obtained.

With the benefit of hindsight, it would have been worth sacrificing some reactivity and using the commercially available 2-bromobenzaldehyde in the synthesis outlined overleaf.
The attempted preparation of N-(2-halophenacyl)thioacetamides

This study was performed before the results of the reactions on the thiourea [84] (Discussion, Part 2) were known.

The ease with which certain six-membered rings could be prepared by SNAr reactions prompted us to investigate the extension of those methods to the synthesis of seven-membered heterocycles. The target materials were the 2-chlorophenacylamine derivatives [109] and [110] whose possible cyclisation products are shown in Equation 146.

Again, the possibility existed for cyclisation to form various ring systems which, in this case, included the 1,3-benzoxazepinone and 1,3-benzothi­iazepinone and an N-acyl indoxyl derivative.
The starting material [109] was prepared by a Neber rearrangement as reported by Santilli et al.\textsuperscript{104} (Scheme 31).
The rearrangement was successfully carried out and acetylation of the amine hydrochloride yielded the required amide [109]. The mechanism of the Neber rearrangement involves the formation of an azirine intermediate [111] and is shown below.

\[
\begin{align*}
\text{N-OTs} & \quad \text{CH}_2 \quad \text{EtO}^- \quad \text{N-OTs} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

The amide [109] was reacted, in the usual manner, with Lawesson's reagent in order to prepare the corresponding thioamide [110]. However, side chain cyclisation occurred and 5-(2-chlorophenyl)-2-methylthiazole [112] was formed (eqn. 147).

\[
\begin{align*}
\text{NHCOMe} & \quad \text{Me} \\
\text{Cl} & \quad \text{Cl} \\
\end{align*}
\]

(eqn. 147)
The result showed that the thioamide [110] was going to be of no use in $S_NAr$ cyclisations and confirmed our earlier suggestion that the preparation of seven-membered heterocycles by $S_NAr$ reactions would be very difficult because the presence of a strongly electron-withdrawing group ortho- to the halogen substituent activated the side chain toward cyclisation.

2-Bromophenacylamine hydrochloride [113] had also been a target material and the oxime tosylate was prepared in the manner described in Scheme 31. However, the product was found to decompose on vacuum desiccation over phosphorus pentoxide, an observation that had not been made for the chloro-analogue which was clearly more stable.

A batch of the product was subjected to the Neber rearrangement but the isolated product was found to be the hydrochloride of 2-bromoaniline.

It appeared very likely that storage of the oxime tosylate over moist phosphorus pentoxide had resulted in an acid-catalysed Beckmann rearrangement as shown below.
Although more conventional methods (Gabriel and Delepine aminations) were also investigated for the preparation of 2-bromophenacylamine, the result of the thionation of the chloro-analogue bought an end to this particular study and compound [113] was not prepared.

The preparation and attempted cyclisation of 4-(2-halophenyl)-3-thiabutanoic acid derivatives

In order to avoid the problem of side chain cyclisation during attempted syntheses of seven-membered heterocycles, a starting material was required which had no electrophilic function which would allow such a cyclisation to occur. Derivatives of 4-(2-iodophenyl)-3-thiabutanoic acid [114] were chosen and the ethyl ester [115] and the parent acid were prepared as shown below.

Attempts to prepare amides from the ester [115] proved unsuccessful but the acid [114] was easily converted to the required benzylamide [116] and thioamide [117] as shown in Equation 148.
Unfortunately, there was only sufficient time to conduct a preliminary investigation of the reactions of the thioamide. An attempted reaction in the presence of diethyl phosphite as an entraining agent failed to give either of the two possible products that might have been formed from $S_{RN}^1$ reactions (Scheme 32).

The n.m.r. spectrum of the product showed a single absorption in the methylene region and it therefore seemed likely that decomposition of the starting material had occurred.

Reaction of the thioamide with either copper (I) iodide or copper powder resulted in the isolation of intractable residues.

The investigation was, by necessity, not carried out in sufficient detail to discount the possibility of cyclisation and the reactions of the amide [116] were not studied at all.

4-(2-Bromophenyl)-4-oxo-3-thiabutanoic acid [118] and its ethyl ester [119] were also prepared (again, before the side chain cyclisation reactions were known to preclude $S_N^1$ Ar substitution) as shown below.
An attempt to prepare an amide of the acid [118] resulted in the formation of N-benzyl-2-bromobenzamide (eqn. 149).

Similarly, a reaction of the ester (119) with concentrated ammonia solution yielded 2-bromobenzamide. Because of this lability of the thiol ester function, these compounds were not studied further.

**SUMMARY**

In summary, it was found that sulphur-, oxygen- or nitrogen-anions did not react to form seven-membered heterocycles under SRN1 conditions. This was also found to be the case in the attempted preparations of six-membered rings. The reason for the lack of reactivity of oxygen-anions had previously been reported. The most plausible explanation for the failure of sulphur- and nitrogen-anions to react was that the intermediate aryl
radicals were not sufficiently electrophilic.

Five-membered fused heterocycles were successfully prepared by the reaction of sulphur-anions under $S_{RN}$1 conditions. In these cases, the formation of an aromatic product was probably sufficient to make the cyclisation process energetically favourable.

Five- and six-membered heterocycles were prepared by the reaction of oxygen-, nitrogen- or sulphur-anions in the presence of copper (I) salts. Many of the reactions could also be performed using copper powder. These methods could not be applied to the synthesis of seven-membered heterocycles, the most likely reason being that the intermediates and transition states involved suffered excessive ring strain.

Reactions performed on suitably activated molecules under $S_{N}Ar$ conditions were used for the synthesis of six-membered heterocycles but could not be applied to the preparation of seven-membered systems due to the self-cyclisation of the side chain.

It would appear that, in the context of the type of reactions studied and discussed above, the synthesis of seven-membered (or larger) heterocyclic ring systems might best be achieved by the use of aryl-radical/olefin interactions$^{105}$ as exemplified below.

Naturally, hetero-atoms could be employed in the olefinic side chain thus giving rise to heterocyclic systems on cyclisation.
DISCUSSION PART 4

The mechanism of copper-promoted substitutions
In the previous three parts of the Discussion, the synthetic applicability of both copper (0) and copper (I) halides has been discussed. Reactions using these catalysts were shown to possess greater applicability in heterocyclic synthesis than reactions performed under $S_{RN1}$ conditions. The absence of inhibition or formation of dissubstitution products and the complete absence of formation of reduction products in reactions catalysed or promoted by copper (0) or copper (I) halides suggested that mechanisms dissimilar to that operating in $S_{RN1}$ reactions may be occurring.

The mechanisms by which copper (0) and copper (I) halides may effect aromatic nucleophilic substitution in systems such as we have studied are dealt with in this section.

In order to probe the mechanism of action of copper (I) iodide in more detail than had been previously attempted during our investigations, two series of reactions were performed.

The copper (I)-promoted reaction of 2-bromo-2-nitropropane with sodium thiocyanate

$$\text{Br} \quad \text{NaSCN/CuI} \quad \text{DMF, N$_2$, } \Delta \quad \text{SCN}$$

The specific aims of this study were to investigate the applicability of copper (I)-promoted substitution reactions to an aliphatic system and to probe the effects of catalysis and inhibitors.

Previous studies on 2-bromo-2-nitropropane had shown that substitution could not be achieved under $S_{RN1}$ conditions and so an opportunity existed to compare the copper (I)-catalysed and $S_{RN1}$ substitutions.

The results of the experiments are summarised in Table 18 overleaf.
<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Equivalents of NaSCN</th>
<th>Equivalents of CuI</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Inhibitors Present (mol%)</th>
<th>Yield of Product (%)</th>
<th>Recovery of Starting Material (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>0</td>
<td>7</td>
<td>70-80</td>
<td></td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>60</td>
<td></td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>1</td>
<td>7</td>
<td>65</td>
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<tr>
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<td>4</td>
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<td>0</td>
</tr>
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<td>1</td>
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<td>p-DNB (15)</td>
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<tr>
<td>17</td>
<td>4</td>
<td>0.1</td>
<td>7</td>
<td>70-80</td>
<td>p-DNB (15)</td>
<td>15</td>
<td>25</td>
</tr>
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<td>18</td>
<td>4</td>
<td>0.05</td>
<td>7</td>
<td>70-80</td>
<td></td>
<td>10</td>
<td>41</td>
</tr>
<tr>
<td>19</td>
<td>4</td>
<td>0.05</td>
<td>7</td>
<td>75</td>
<td></td>
<td>12</td>
<td>36</td>
</tr>
</tbody>
</table>

**NOTES TO TABLE 18**

a) The yields were obtained by n.m.r. spectroscopic analysis of the crude products.
b) Di-t-butylnitroxide.
c) p-Dinitrobenzene.
Experiments 2-7 established that copper (I) iodide could be used as a catalyst in the preparation of 2-nitro-2-thiocyanatopropane from 2-bromo-2-nitropropane and sodium thiocyanate. The yields were poor and were not significantly affected by increasing the reaction temperature (Experiment 8). The recovery of material was also poor despite careful work-up procedures. The poor recovery may have been caused by decomposition of the starting material and/or the product.

A blank reaction (Experiment 1) showed that the presence of copper (I) iodide was necessary for the formation of the product.

The results of Experiments 2-7 and 8-9 were calculated to represent an average yield of the substitution product of approximately 11%. One equivalent of copper (I) iodide was used in all these experiments and so catalysis was not proven.

When the amount of copper (I) iodide was reduced to 0.1 equivalents, an average yield of 11% was again obtained (Experiments 10 and 11). Increasing the reaction time resulted in a much higher yield (Experiment 12) which showed that the copper (I) iodide was acting in a catalytic manner. The catalysis was further proved by the results of Experiments 18 and 19 in which a 10-12% yield was obtained by using 0.05 equivalents of the copper salt.

The effect of inhibitors was also studied. When the usual nitrogen atmosphere was replaced by one of oxygen, no 2-nitro-2-thiocyanatopropane was isolated. The complete inhibition of the substitution was attributed to oxidation of copper (I) to copper (II) which was not active in the reaction.

The use of di-\(\tau\)-butyl nitroxyl (Experiment 14) or \(p\)-dinitrobenzene (Experiments 15-17) did not result in significant inhibition although the yield of Experiment 16 was rather low. On the contrary, the yields of Experiments 15 and 17 were higher than expected. The recovery of starting material in the inhibition reactions was not significantly raised and so the conclusion was drawn that the presence of electron- or radical-scavengers did not significantly inhibit the formation of the substitution product.

The results of this investigation indicate that copper (I) catalysis has some possible potential for the preparation of aliphatic \(\alpha\)-substituted...
In this particular case, copper (I) iodide has been shown to catalyse the formation of 2-nitro-2-thiocyanatopropane whereas reactions performed under $S_{RN1}$ conditions failed.

Further studies need to be conducted in order to assess the wider applicability of copper (I) catalysis to aliphatic substitution reactions.

The copper (I)-promoted reactions of iodobenzene and phenylthiolate

This particular reaction system was chosen because the preparation of diphenyl sulphide from iodobenzene and phenylthiolate (eqn. 151) had been achieved by both copper (I)-promoted and $S_{RN1}$ substitution reactions and was, therefore, a well-documented system.

$$\text{PhI} + \text{PhS}^- \xrightarrow{\text{CuI or hv}} \text{PhSPh} \quad (151)$$

The aim of our study was to investigate the effects of inhibitors and the nature of the copper (I) catalysis in an aromatic system. It was hoped that the results would help to clarify the mechanistic relationship between copper (I)-promoted- and $S_{RN1}$ reactions.

A reaction performed in the presence of one equivalent of copper (I) iodide for 6.5 hours was found to be almost complete. In order to observe maximum inhibition effects, all further experiments were performed for four hours.

The results of this study are shown in Table 19 overleaf.

The reactions suffered from the previously reported variation of yield. Reproducibility was very difficult to achieve despite attempts to duplicate the reaction conditions. A possible reason for this variability may have been the difficulty experienced in stabilising the temperature of the oil baths used to heat the reaction mixtures.
<table>
<thead>
<tr>
<th>Experiment Number</th>
<th>Equivalents of CuIa</th>
<th>Time (h)</th>
<th>Temperature (°C)</th>
<th>Presence of Inhibitor (mol%)</th>
<th>Yield of Ph₂S (%)b</th>
<th>Recovery of Starting Material (%)</th>
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<tr>
<td>1</td>
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<td>2</td>
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<td>DARK c</td>
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<td>63</td>
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<td>1</td>
<td>100-110</td>
<td></td>
<td>23</td>
<td>44</td>
</tr>
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<td>DARK</td>
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<td>8</td>
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<td>4</td>
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<td>DTBN (20)</td>
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</tr>
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<td>4</td>
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<tr>
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<td>DARK</td>
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<td>16</td>
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<td>4</td>
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<td>p-DNB (20)</td>
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</tr>
<tr>
<td>17</td>
<td>0.2</td>
<td>4</td>
<td>100-110</td>
<td>DTBN (20)</td>
<td>19</td>
<td>35</td>
</tr>
</tbody>
</table>

Notes to Table 19

a) Reaction conditions: PhI (1.225 mmol), CuI as stated above, NaH (1.4 mmol), PhSH (1.2 mmol), HMPA, N₂.

b) The yields of diphenyl sulphide were determined by g.l.c.

c) The flask was covered with aluminium foil to exclude light from the laboratory strip lighting.
Experiments 4, 5 and 6 showed that under standard conditions, using one equivalent of copper (I) iodide, an average yield of diphenyl sulphide of 64% was obtained. When the amount of the copper salt was reduced to 0.2 equivalents (Experiments 10-13), the average yield of the sulphide was found to be 28% which indicated that the copper (I) iodide was acting in a catalytic manner.

A blank reaction (Experiment 1) in which no copper (I) iodide was used afforded the sulphide in 20% yield. This result was interpreted by suggesting that an $S_{RN1}$ reaction was operating and that it was initiated by photostimulation from the laboratory strip lighting. A further blank reaction, performed in the absence of such photostimulation, resulted in the formation of a low yield (4%) of the sulphide. This yield was attributed to the operation of a thermal $S_{RN1}$ reaction (Experiment 2).

A reaction using one equivalent of copper (I) iodide was repeated in the presence of inhibitors (Experiments 8 and 9). The yields of sulphide obtained were 61 and 52%. The average yield for the uninhibited reaction was 64% and so an inhibition of 3-12% had occurred. This result most probably corresponded to the inhibition of an $S_{RN1}$ reaction. A reaction performed in the dark (Experiment 7) showed a 17% inhibition which was explained in the same manner.

Experiments using 0.2 equivalents of the copper salt were repeated in the presence of inhibitors (Experiments 14-17) and also exhibited marked inhibition (9-18%) compared with the average yield of the standard reactions (28%). Again, the results were consistent with the inhibition of an $S_{RN1}$ contribution. The yields obtained in these reactions (10-19%) showed that the copper (I) iodide was not acting in a catalytic manner as was originally thought.

The results of all the inhibition experiments were readily explained by the involvement of an $S_{RN1}$ reaction. No significant inhibition of the copper (I)-promoted substitution was observed (a decrease in the yield of diphenyl sulphide exceeding 20% would have been required in order to make a definite statement).

Because of the unreproducibility of the yields, the results presented in Table 19 could not be interpreted quantitatively with any degree of
certainty but the overall trends in reactivity were apparent.

Throughout the cyclisation studies discussed earlier, it had been thought that the copper (I) salts were involved in an $S_{RN1}$ type reaction in which initiation (eqn. 152) of the chain mechanism was achieved by electron transfer from copper (I) as shown in Scheme 33.

\[
\text{Ar}X + \text{Cu}^I X \rightarrow \text{Ar} \cdot + \text{Cu}^{II} X_2 \quad (152)
\]

\[
\text{Ar} \cdot + \text{Nu}^- \rightarrow [\text{ArNu}]^- \quad (153)
\]

\[
[\text{ArNu}]^- + \text{Cu}^{II} X_2 \rightarrow \text{ArNu} + \text{Cu}X + \bar{X} \quad (154)
\]

**SCHEME 33**

The catalytic rôle of copper (I) was explained by its regeneration as shown in Equation 154.

Chanon\textsuperscript{59} has proposed an $S_{RN1}$ reaction of the kind shown above to explain the non-aryne hydroxydehalogenation of unactivated aryl halides which had been observed by Bunnett\textsuperscript{107} and which was catalysed by copper metal or copper (I) salts (eqn. 155).

\[
\begin{align*}
\text{Me} \quad \overset{\text{OH}^-}{\text{Cu}^I, 300^\circ C} & \quad \overset{\text{OH}^-}{\text{Cu}^I, 300^\circ C} \\
\text{X} & \quad \text{Me} \\
\text{Me} & \quad \text{OH}
\end{align*}
\]

\[(155)\]
The copper(I)-promoted reactions of p-chloroiodobenzene

In order to clarify the mechanistic relationship between the copper (I)-promoted substitutions and $S_{RN1}$ reactions, we investigated the behaviour of p-chloroiodobenzene with the phenylthiolate anion under both types of reaction conditions.

Dihalobenzenes are known to react with many nucleophiles under $S_{RN1}$ conditions to yield the corresponding disubstitution product$^{27,55}$ (see Introduction). This characteristic behaviour can, therefore, be used to assign the presence of radical-anions in a reaction mechanism. Migita et al$^{90,108}$ have used this method to prove the absence of such reactive intermediates in their palladium-catalysed substitutions (eqn. 156).

\[
\begin{align*}
\text{Br} & \quad \text{PdCl}_2(10-\text{tolyl})_2\text{Pd} & \quad -\text{SR} \\
\text{Cl} & \quad \text{Pd(PPh}_3)_4 & \\
\end{align*}
\]

+ $\text{DBu}_3\text{SnBr}$

The results of our investigations are summarised in Scheme 34.

\[
\begin{align*}
\text{Cl} & \quad + \text{PhS}^- & \quad \text{hv} & \quad \text{SRN1} \\
\text{Cl} & \quad + \text{Ph}_2\text{S}_2 & \quad 44\% \\
\end{align*}
\]

$[120], 32\%$

\[
\begin{align*}
\text{Cl} & \quad + \text{PhS}^- & \quad \text{CuI} \\
(0.2 \text{ or } 1.0 \text{ eq.}) & \quad \text{[121], 100\%} \\
\end{align*}
\]
A reaction of the dihalobenzene performed under $S_{RN1}$ conditions resulted in the formation of the expected disubstitution product [120] and diphenyl disulphide. The presence of the disulphide could be explained in two ways (Scheme 35).

Radical coupling of PhS$^-$ (route a) or the formation of a diphenyl disulphide radical-anion (route b) can be proposed to explain the formation of the disulphide. The high yield obtained suggested that the chain length of the $S_{RN1}$ reaction was fairly short and that consequently, the number of phenylthiol radicals generated was fairly high.

The reaction of $p$-chloroiodobenzene with phenylthiolate in the presence of copper (I) iodide resulted in the isolation of a quantitative yield of the monosubstitution product [121]. No disubstitution product was detected. The presence of $S_{RN1}$ reaction intermediates (radical-anions) in the copper (I)-catalysed reaction was, therefore, disproved.
The same diagnostic test was applied to the reaction of the dihalobenzene with copper powder (2 equivalents). Unreacted starting material and a mixture of diphenyl disulphide and the monosubstitution product [121] was obtained showing that no $S_{RN1}$ intermediates had been present in the reaction.

A further investigation was performed using the anion of $p$-chlorophenylthiol and iodobenzene (Scheme 36).

A reaction of the anion of $p$-chlorophenylthiol with iodobenzene, performed under $S_{RN1}$ conditions led to the formation of a complex mixture which was not analysed. This mixture was probably caused by the fragmentation and subsequent polymerisation of the radical-anion, $B$ to radical-anion, $C$.

The radical-anion, $B$ is the same as that involved in the reaction of $p$-chloroiodobenzene shown in Scheme 34 which resulted in the formation of the dissubstitution product [120]. Had such a radical-anion been present in the copper (I)-promoted reaction of $p$-chlorophenylthiolate and iodobenzene, a complex mixture of products would have been anticipated. However, this reaction resulted in the formation of the sulphide [121] (Scheme 36).
This result confirmed our suggestion that the mechanism by which copper (I) iodide effected substitution differed from that involved in $S_{RN1}$ reactions.

The mechanism based on an $S_{RN1}$ reaction and outlined in Scheme 33 was no longer thought to be accurate and alternatives which did not involve the intermediacy of radical-anions were sought.

The mechanism of action of copper (I) salts

Lindley has reviewed the kinetic data concerning copper-assisted aromatic nucleophilic substitutions and has presented the intermediates by which these reactions could possibly proceed. These intermediates are shown in Scheme 37.
The intermediate [122] which contains a 4-centre arrangement of atoms has been proposed by Bacon\textsuperscript{60} and was later quoted by several authors. Although it was not necessarily an incorrect representation of the intermediate, it was thought to be rather vague and was discounted.

In order to provide a more comprehensive picture of the mechanistic possibilities by which copper (I) catalysis may be achieved, the following Scheme (38) is presented.

In the following pages the evidence for and against the existence of the intermediates, transition states and transformations presented in Scheme 38 will be discussed and attempts will be made to rationalise the results of our investigations using the mechanisms proposed below.

Copper (I) iodide is first assumed to have reacted with the anion of the nucleophile to form Cu\textsuperscript{I}Nu. The preparation of such compounds has been reported\textsuperscript{62,63,67} and is frequently performed before the aromatic substitution
Scheme 38

is attempted.

Route (a) in Scheme 38 represents oxidative addition of the copper (I) species to the aryl halide. This process may proceed via the transition state, A or the undissociated complex, B and results in the formation of the intermediate arylcopper (III) species, D.
Oxidation-reduction reactions involving metal ions and their complexes are mainly of two types: inner sphere (ligand transfer) and outer sphere (electron transfer).\textsuperscript{110}

An inner sphere electron transfer between the copper (I) species and the aryl halide results, initially, in the formation of the transition state, A. This is a bridged, activated complex in which contact between the oxidant (ArX) and the reductant (CuI) is maintained by a ligand which is bonded to both. - in our case the ligand is a halogen atom. The ligand transfer step involves the co-ordination sphere of the copper (I) species, i.e. one of the $d^{10}$ electrons is transferred.

The bridging ligand has an important effect on the rate of electron transfer and the effectiveness of the ligand in bridging the oxidant and reductant decreases in the order I>Br>Cl>F.\textsuperscript{110,111} However, this trend can become reversed for certain reductant/oxidant reactions.\textsuperscript{110}

The order of ligand effectiveness shown above is in accord with the relative rates of reaction of the thioamides [28a] and [28b] observed during our copper (I)-promoted cyclisations (eqn. 157).

$$\begin{align*}
\text{NHCSPh} & \quad \xrightarrow{K_C} \quad \text{N-Ph} \\
[28a], \text{X}=\text{I} & \quad \text{[28b], X}=\text{Br}
\end{align*}$$

$$K_C(\text{ArI}) > K_C(\text{ArBr})$$

The order of reactivity of aryl halides which was observed in our reactions was in good agreement with that reported elsewhere.\textsuperscript{61,69,112}

The effectiveness of the bridging ligand may not be the only explanation for the relative ease of cyclisation of aryl iodides. The ease of reduction of aryl halides also follows the order ArI>ArBr>ArCl>ArF and this factor must also be taken into consideration.
During our investigations, it was observed that substrates underwent smoother copper (I)-promoted cyclisation when the benzene ring carried no electron-donating methoxyl groups (eqn. 158).

\[
\begin{array}{c}
\text{R} \text{NHCSPh} \\
\text{I} \\
\text{Cul} \rightarrow \\
\text{R} \text{NI} \\
\text{Ph}
\end{array}
\]

(i) R=OMe; 48%, 4h
(ii) R=H; 78%, 2.75h

This observation was consistent with those of other authors\(^{60,64,68,100,108}\) who used copper (I) salts to effect aromatic nucleophilic substitution. Fitton and Rick\(^{111}\) reported that the order of reactivity of substituted aryl halides in their palladium-catalysed reactions was consistent with a mechanism involving oxidative addition of the metal atom to the halide.

The transition state, A may collapse to form the intermediate, B. This is represented as an undissociated complex consisting of an aryl radical-anion associated with a copper (II) species.

The presence of a complex such as B in the redox reactions of transition metal compounds has been suggested by Kochi.\(^{113}\) This proposal was based on the large, positive \(\rho\) value calculated from the results of various oxidative additions of \(\text{Ni(PPh}_3\text{)}_3\) with substituted aryl halides. The \(\rho\) value reflected a marked increase in negative charge in the aromatic ring during the oxidative addition, an observation which could be explained by the formation of an aryl radical-anion.

The presence of radical-anion intermediates in copper (I)-promoted substitution reactions has also been proposed by Ashby\(^{114}\) (see later), Fick,\(^{111}\) and Klemm.\(^{115}\)

However, the intermediacy of radical-anions in palladium-catalysed reactions had been disproved\(^{90,108}\) by the use of dihalobenzenes (eqn. 156). Similarly, we had obtained no disubstitution products from the copper (I) iodide-catalysed reaction of \(p\)-chloroiridobenzene with the anion of phenylthiol (p.128).
In the vast majority of our copper (I)-promoted substitution reactions, we had observed little or no inhibition when electron scavengers such as dioxygen or \( p \)-dinitrobenzene were present. The evidence gained from these studies suggested that no radical-anions were involved in the reaction pathways.

The lack of inhibition may be caused by the radical-anion being tightly held in the complex, B by a solvent cage. Diffusion from this cage would make the aryl radical-anion much more susceptible to being trapped. Assuming that a radical-anion may be formed, the absence of disubstitution products in the reaction described on page 128 may be explained by the breakdown of the radical-anion within the solvent-caged complex to form intermediates which cannot participate in \( S_{RN1} \) reactions.

Routes (c) and (d) in Scheme 38 represent the pathways by which the transition state, A and the complex, B then react (see below).

\[
\begin{align*}
\text{[Ar} & \text{X} \text{CuNu]}^+ \quad \text{or} \quad \text{[(ArX)} & \text{Cu}^{\text{II}} \text{Nu]} \\
\text{A} & \quad \text{B} \\
\text{C} & \\
\text{D} & \\
\text{e} & \\
\text{C} & \\
\end{align*}
\]

The existence of aryl radicals as intermediates in copper (I)-promoted substitutions

The intermediate, C is an undissociated complex, tightly held in a solvent cage. Again, it is important to note that the aryl radical does not exist in the free state, i.e. separate from the complex. If this were the case, we should have been able to trap the radical by the use of scavengers such as dioxygen or di-\( t \)-butyl nitroxyl. However, little inhibition was observed
during our cyclisation reactions or the studies of copper (I)-promoted intermolecular substitutions described earlier in this section.

The fact that reduction products were never isolated from reactions involving copper (I) salts is also evidence for the absence of a free aryl radical.

The evidence concerning the presence of an aryl radical in copper (I)-promoted substitutions is conflicting. Cohen\textsuperscript{115} reported that the reaction of 2-iodo-N,N-dimethylbenzamide with copper (I) chloride (eqn. 159) did not involve the intermediacy of an aryl radical.

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{N(Me)}_2 \\
\text{I}
\end{array}
\begin{array}{c}
\text{CuCl} \\
\text{DMF,PhCO}_2\text{H}
\end{array}
\begin{array}{c}
\text{O} \\
\text{N(Me)}_2 \\
\text{H}
\end{array} +
\begin{array}{c}
\text{O} \\
\text{N(Me)}_2 \\
\text{Cl}
\end{array}
\end{equation}
(159)

Previously, it had been shown that the aryl radical [124] undergoes an extremely rapid hydrogen abstraction from an adjacent methyl group to give N-methylbenzamide (eqn. 160). This compound was not detected during the halogen exchange reaction shown above.

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{N(Me)}_2 \\
\text{N}_2\text{BF}_4^-
\end{array}
\begin{array}{c}
\text{CuCl}
\end{array}
\begin{array}{c}
\text{O} \\
\text{N(Me)}_2
\end{array}
\begin{array}{c}
\text{NHMe}
\end{array}
\end{equation}
(160)

In order to explain the formation of the reduction product [123] in the absence of an aryl radical, Cohen proposed the intermediacy of an arylcopper (I) species [125], formed via a two-electron reduction of the aryl halide by copper (I) chloride as shown in Scheme 39.
Formation of the arylcopper (III) species by two consecutive single electron transfer steps would involve the formation of an aryl radical.

The existence of aryl radicals in copper (I)-promoted substitutions was also judged to be unlikely by Lockhart. The copper (I)-catalysed reactions of diphenyliodonium salts in methanol and dichloromethane were investigated. The results were initially explained by a mechanism based on that proposed by Kochi to explain the behaviour of diazonium salts in Sandmeyer reactions. However, the very low yields of reduction products and subsequent kinetic studies served to disfavour the presence of a phenyl radical and Lockhart proposed the mechanism which is shown in Scheme 40.

The author did not totally exclude the possibility of radicals existing and stated that a dramatic cage-effect may prevent a complex such as [Ph· CuXY] from dissociating and resulting in a free radical being formed. This is the same explanation that we have used to explain our own observations.
Several authors, on the other hand, have proposed that aryl radicals are formed as intermediates in copper (I)-promoted substitution reactions.

Van Koten\textsuperscript{117} criticised the involvement of arylcopper (I) species such as that proposed by Cohen (Scheme 39) by stating that biaryls would also be formed (as in the Ullmann synthesis).

Van Koten suggested the mechanism shown in Equation 161 which involves an aryl radical.

\[ \text{Scheme 40} \]

\[ (C_6H_5)_2I^+X^- + Cu^IY \xrightarrow{2\text{-electron transfer}} C_6H_5Cu^{II}XY + PhI \]

\[ \xrightarrow{\text{CH}_3\text{OH}} \]

\[ [(C_6H_5)_2I^+] \rightarrow Cu^{II}XY \]

\[ \xrightarrow{\text{reductive elimination}} C_6H_5OCH_3 + CuX + HY \]

\[ [(C_6H_5)^- \cdot Cu^{II}XY] + PhI \]

\[ \text{X} = \text{AsF}_6^- \text{, Br}^- \quad \text{Y} = \text{Benzoate} \]
Sandmeyer reactions can be carried out homogenously in aqueous acetone solution using catalytic amounts of copper (I) salts. Kochi\textsuperscript{118} has suggested that a one-electron reduction of the arenediazonium salt by the copper (I) species results in the formation of an unstable aryldiazenyl radical which rapidly fragments to an aryl radical and nitrogen (Scheme 41).

\begin{equation}
\text{ArX} + \text{CuY} \rightarrow \text{Ar} \cdot \quad \text{Cu}^{+}\text{XY} \rightarrow \text{ArY} + \text{CuX} \tag{161}
\end{equation}

The aryl radical undergoes oxidative ligand transfer (eqn. 164) to afford the aryl halide and to regenerate the copper (I) salt.

Galli\textsuperscript{58} has investigated the nature of the copper reductant in the Sandmeyer reaction and his findings that the amount of biphenyl and benzene can rise dramatically when the conditions for the radical halogenodediazoniation are unfavourable supports the presence of an aryl radical.

The most convincing evidence for the existence of aryl radicals in copper (I)-promoted substitution reactions has been put forward by Ashby\textsuperscript{114} whose electron spin resonance and spin-trapping studies have shown that lithium dimethylcuprate reacts by an electron transfer pathway involving free radicals.

An $S_N^2$ mechanism had been proposed to explain the inversion of configuration of optically-active alkyl halides on reaction with lithium diphenylcuprate (eqn. 165).

\begin{equation}
\text{LiCu}^+\text{Ph}_2 + \overset{\text{C} - \text{X}}{\text{C}} \xrightarrow{S_N^2} \overset{\text{Ph} - \text{C}}{\text{C}} + \text{LiX} + \text{PhCu} \tag{165}
\end{equation}
Ashby suggested that an alternative pathway involving an aryl radical (or an arylcopper (III) species) could operate (eqn. 166).

\[
\begin{align*}
R_2Cu^I + R'X &\rightarrow R_2Cu^{\text{III}}XR' \quad \text{or} \quad R_2Cu^{\text{II}}X \quad R' \quad R - R' + RCu^I
\end{align*}
\]

Inversion of configuration has been shown to occur in electron transfer mechanisms, i.e. the configuration at the radical centre is not lost prior to reaction.\textsuperscript{114a}

Ashby monitored the progress of the reaction of trityl halides with lithium dimethylcuprate (eqn. 167) by electron spin resonance (e.s.r.).

\[
\begin{align*}
\text{Ph}_3CX + \text{LiCuMe}_2 &\rightarrow \text{Ph}_3CMe + \text{LiX} + \text{CuMe}
\end{align*}
\]

The e.s.r. spectrum of the reaction mixture was consistent with the formation of the trityl radical (Ph$_3$C·).

The technique of spin-trapping was also utilised in the search for reaction intermediates.

6-Iodo-1-heptene was reacted with lithium dimethylcuprate (eqn. 168) to yield 1-ethyl-2-methylcyclopentane and smaller quantities of 1,2-dimethylcyclopentane and 6-methyl-1-heptene.
The cyclopentanes were both derived from the radical complex [126] whose formation is explained in Scheme 42.

\[ \text{Scheme 42} \]
The radical in the complex [126] must be able to diffuse away from its solvent cage in order to become reduced and form 1,2-dimethylcyclopentane.

The presence of a discrete radical-anion as shown in Scheme 42 may be doubtful. Ashby did not attempt to inhibit the reaction with an electron scavenger but our investigations into the possible presence of radical-anions seemed to be emphatically negative.

The use of spin-trapping to detect aryl radicals has been described by Beckwith and co-workers.\textsuperscript{105,119} The systems shown below (eqns. 169 and 170) are based on the 1-hexenyl system which was also used by Ashby (see above).

\begin{align}
\text{eqn. 169} & \quad \begin{array}{c}
\text{aryl radical} \\ \text{slow attack by \textit{S}_{R\text{N}}^1}
\end{array} \\
\text{eqn. 170} & \quad \begin{array}{c}
\text{aryl radical} \\ \text{slow attack by \textit{S}_{R\text{N}}^1}
\end{array}
\end{align}

In order to provide evidence for the existence (or otherwise) of an aryl radical in our copper (I)-promoted substitution reactions, a spin-trapping experiment of the kind used by Ashby and by Beckwith was performed by Professor G A Russell and co-workers of Iowa State University. Professor Russell has kindly allowed us to report some of his results.

A reaction of 4-(2-iodophenyl)-1-butene [127] with the phenylthiolate anion under \textit{S}_{R\text{N}}^1 conditions (Scheme 43) resulted in the formation of the sulphide [130].

The reaction of alkene [127] under \textit{S}_{R\text{N}}^1 conditions proceeded via a radical-anion to the aryl radical [128]. This radical did not then participate further in an \textit{S}_{R\text{N}}^1 reaction by undergoing nucleophilic attack by the phenylthiolate anion but was trapped by intramolecular cyclisation to form
the primary alkyl radical \([129]\). Reaction of this radical with diphenyl disulphide resulted in the formation of the sulphide \([130]\).

The reaction of the alkene \([127]\) with copper (I) iodide and the phenylthiolate anion resulted in the formation of the diaryl sulphide \([131]\). None of the sulphide \([130]\) was formed. This result was interpreted by Professor Russell as indicating that no aryl radical \([128]\) was formed during the reaction.

The existence of the solvent-caged intermediate, \(C\) in Equation 171 was, therefore, in doubt as a result of Russell's findings.

\[
\begin{align*}
[\text{Ar. Cu}^\text{II} \text{NuX}]_C & \quad \rightarrow [\text{ArCu}^\text{III} \text{NuX}]_D \\
\end{align*}
\] (171)
However, the rate of reaction of ary1 and alkyl radicals with copper (II) species is known to be very rapid (eqns. 172 and 173).

\[ \text{Cyclohexyl} + \text{Cu}^{II} \rightarrow k = 4 \times 10^8 \text{L.mole}^{-1}\text{sec}^{-1} \]

Although the rate constants quoted above are for bimolecular reactions and are, therefore, not strictly comparable to the values given for the rate of intramolecular cyclisation (~10^6 s^{-1}, eqns. 169 and 170), the possibility exists that an aryl radical intermediate was formed in Russell's experiment but reacted with the copper (II) species at a sufficiently rapid rate to exclude intramolecular trapping by the olefin (Scheme 44).

In order to explain the lack of trapping of the aryl radical in Russell's experiment and the general absence of inhibition and formation of reduction
products in our own studies, we propose that the rate of reaction of aryl radicals with copper (II) species ($k_r$ in Scheme 44) must considerably exceed the rate of intramolecular cyclisation ($k_c$).

The value of $k_r$ must also be greater than the rate of diffusion of the aryl radical from the solvent cage. However, the situation becomes further complicated by the fact that the rate of diffusive encounter of the phenyl radical and copper (II) in solution is reported to be between $10^9$ and $10^{10}$ s$^{-1}$.\textsuperscript{116} Bearing in mind that the rate of reaction of the phenyl radical with copper (II) is $10^7$ mole$^{-1}$ sec$^{-1}$ the diffusion of the phenyl/copper (II) pair from the solvent cage should dominate their reactions.

In order to account for the absence of inhibition and the absence of formation of the reduction products, we have to propose a cage effect of considerable magnitude. The same proposal was rejected by Lockhart.\textsuperscript{116} The complete exclusion of intramolecular cyclisation by the reaction of copper (II) with an alkyl radical has been observed by Beckwith et al.\textsuperscript{121}

It must be admitted that we have little kinetic data to support our proposal and that the data we have presented do not appear to be of a sufficient difference in magnitude to exclude the possibility of ring-closure completely. As a consequence, we cannot make a definite statement on the existence of an aryl radical intermediate.

The existence of the aryl radical-copper (II) complex, C in Scheme 38 would be very transient as the rate constants shown in Equations 172 and 173 testify. We propose that reaction of the aryl radical with the copper (II) species leads to the rapid formation of an arylcopper (III) species, D (eqn. 171).

The intermediacy of an arylcopper (III) species in copper (I)-promoted substitutions
The formation of an arylcopper (III) by the equivalent of two single electron transfer steps (routes (a), (c), (d) and (e) in Scheme 38) had been suggested by Van Koten,\textsuperscript{117} Lockhart,\textsuperscript{116} and Ashby\textsuperscript{114} (the mechanisms that were proposed by these authors have been discussed earlier in this section). Kochi\textsuperscript{120} has reported that the oxidation of alkyl radicals to
carbonium ions by copper (II) proceeds via an inner-sphere process.

The arylcopper (III) species may also be formed by the nucleophilic attack of copper (I) on the aryl halide involving the three-centre transition state, \( E \) (route (b) in Scheme 38).

In order to explain the absence of an aryl radical in the reactions of 2-iodo-\( N,N\)-dimethylbenzamide with copper (I) chloride and cyanide, Cohen\(^{115}\) proposed that the aryl halide suffered a two electron reduction by copper (I) as shown in Equation 174.

\[
\text{ArI} + \text{CuCl} \rightarrow \text{ArCu}^{\text{III}}\text{ClI} \quad (174)
\]

The full mechanism is shown on page 138 of this discussion.

Lockhart\(^ {116}\) also considered the possibility of the direct formation of an arylcopper (III) in the reactions of diphenyliodonium salts (eqn. 175).

\[
\begin{align*}
\text{Ar}^+ \text{Ar}^- + \text{CuY} & \rightarrow \text{Ar}^- \text{Cu}^{\text{III}} \text{XY} + \text{Ar}^+ \text{Ar}^- \\
(175)
\end{align*}
\]

In this case, however, the aryl iodide is considerably activated towards nucleophilic attack and may not be strictly comparable to the substrates used in our investigations.

Lewin and Goldberg\(^ {122}\) studied the reactions of alkyl halides and tosylates with copper (I) carboxylates (eqn. 176).

\[
\begin{align*}
\text{RX} + \text{CuY} & \rightarrow \text{[RCu}^{\text{III}} \text{XY}] \rightarrow \text{RY} + \text{CuX} \\
(176)
\end{align*}
\]

\( X = \text{Halogen, Tosyl} \)

\( Y = \text{Acetate, Benzoate, Pivalate} \)
The authors reported that no rearrangement or loss of optical activity was observed when optically active neopentyl bromide was used. A 49% inversion of configuration occurred when optically active neopentyl tosylate was reacted with copper (I) benzoate. These experimental observations indicated that free radicals or carbonium ions were not involved in the reactions since the presence of either of these species would lead to rearrangement and loss of optical activity. Nucleophilic attack on the halides or tosylates by the counter-ions (benzoate, etc) was ruled out because lithium- or ammonium benzoate were unreactive under the conditions used.

Lewin and Goldberg suggested that an $S_{N}^{2}$ type substitution by copper (I) led to the formation of an arylcopper (III) species (eqn. 176) with inversion of configuration at the carbon atom. Subsequent expulsion of copper (I) with retention of configuration at the carbon atom yielded the alkyl ester.

The use of $d$ electrons by cobalt (I) compounds to effect substitution by an $S_{N}^{2}$ mechanism had been previously reported by Schrauzer$^{123}$ and by Jensen.$^{124}$

The evidence presented above provides little precedent for the formation of an arylcopper (III) species by a two electron reduction and most of the reports known to us have concerned the reactions of alkyl- or activated aryl halides.

Our copper (I)-promoted substitution reactions have included the cyclisation of substrates which were deactivated toward aromatic nucleophilic substitution and which would not be expected to react by such a process (eqn. 177).

A further possibility is that the transition state, $A$ may react to form the arylcopper (III) species, $D$ without the intermediacy of an aryl radical-anion.
It is possible that this transformation may involve a three-centre transition state, E (which may also exist in route (b) of Scheme 38). The process is represented by route (c) in Scheme 38 and is shown in more detail below (eqn. 178).

\[
\begin{align*}
\text{A} & \xrightarrow{\text{(c)}} \text{E} & \xrightarrow{\text{(c)}} \text{[ArCu}^\text{III} \text{NuX]} \\
\text{[Ar}^\text{X} \text{CuNu]} & \xrightarrow{\text{(c)}} \text{[Ar}^\text{X} \text{CuNu]} & \xrightarrow{\text{(c)}} \text{[ArCu}^\text{III} \text{NuX]} \\
\end{align*}
\]

(178)

Although the operation of routes (b) and (c) in Scheme 38 cannot be completely discounted, the weight of evidence suggests that the formation of the aryl copper (III) species proceeds via an aryl radical-copper (II) complex in which the radical is tightly solvent-caged.

Formation of the final products occurs by the routes (a'), (b'), (c') and (d') in Scheme 38. These processes are essentially the reverse of those shown in the upper half of the Scheme.

Because the aryl copper (III) species, D is common to all the pathways represented in Scheme 38, the most probable route by which the final products (ArNu and CuX) are formed is (c'). This process is well-documented\textsuperscript{114-116} and is known as reductive elimination. As with route (c) shown above, the reductive elimination may involve an early, three-centre transition state, F (eqn. 179). This transition state may also be present in the alternative pathway (b').

\[
\begin{align*}
\text{D} & \xrightarrow{\text{(c')}} \text{[Ar}^\text{...Nu...CuX]} \\
\text{[Ar}^\text{III} \text{CuX}] & \xrightarrow{\text{(c')}} \text{[Ar}^\text{...Nu...CuX]} \\
\text{E} & \xrightarrow{\text{(b')}} \text{ArNu} + \text{CuX} \\
\end{align*}
\]

(179)
A further possibility is that the aryl radical-copper (II) complex, C may react via the transition state, G or that it may form a radical-anion-copper (II) complex, H. Electron transfer within this complex would result in the formation of the products (eqn. 180).

\[
\begin{align*}
\text{Ar} \cdots \text{Nu} \cdots \text{CuX}^+ & \xrightarrow{(d')} G \\
\text{Ar} \cdots \text{Nu} \cdots \text{CuX} & \xrightarrow{(d')} \text{ArNu} + \text{CuX} \\
\text{ArNu} \cdots \text{CuX}^+ & \xrightarrow{(d')} \text{H}
\end{align*}
\]  

(180)

The existence of a pathway involving a radical-anion complex such as H is doubtful because reaction of the aryl radical with copper (II) is very rapid (as described earlier) and results in the formation of an arylcopper (III) species.

The regeneration of copper (I) halide in the final step of the mechanism explains the catalytic nature of the transition metal salt which was observed in many of our reactions.

Conclusion

The results of diagnostic experiments using dihalobenzenes and an olefinic spin-trapping substrate indicated that no undissociated aryl radical or radical-anion was involved in our copper (I)-promoted substitutions and therefore, that these reactions did not proceed by an S_{RN1} type mechanism.

The mechanism probably involves oxidative addition of the copper (I) species to the aryl halide to form a solvent-caged aryl radical-copper (II) complex. The aryl radical undergoes very rapid intramolecular oxidation resulting in the formation of an arylcopper (III) species. Reductive elimination of this intermediate yields the substitution product and copper (I) iodide which can then re-enter the cycle, thereby propagating the reaction.

We also propose other intermediates including undisassociated radical-anions (Scheme 38) but have little evidence that they are involved in the reaction mechanism.
The lack of inhibition in many of our reactions and the total absence of formation of reduction products is explained by the suggestion that any radical-anions or aryl radicals which are present exist in tightly solvent-caged complexes.

Inhibition was observed in one series of reactions (eqn. 181) involving N-(2-iodobenzyl)thiobenzamide.

\[
\text{p-DNB or DTBN} \quad \text{CuI} 
\]

The validity of the results was doubtful as the experiments were performed using a procedure which gave variable yields. As stated before, the difficulty experienced in obtaining reproducible results has been reported by other authors\textsuperscript{90,100} and may be due to the fact that the reactions are occurring at the surface of the catalyst. However, if the inhibition results are valid, they may be explained by the existence of an alternative pathway which does involve trappable intermediates such as aryl radicals or radical-anions. The nature of the alternative pathway is unknown but it appears that an $S_{RN1}$ reaction is unlikely as the results of the experiments using dihalobenzenes have shown.

Migita et al\textsuperscript{91} proposed a mechanism very similar to ours to explain the results of palladium-catalysed aromatic substitutions yet observed a 50% inhibition of the product yield by p-dinitrobenzene despite having proved that the existence of an $S_{RN1}$ reaction was highly unlikely.

An aspect of the copper (I)-promoted substitutions which was not investigated was the identity of the active copper species. Throughout the discussion it has been assumed that a copper (I) species induces the reactions. This assumption was based on the findings of Bruggink and Mckillop\textsuperscript{68} and of Lockhart.\textsuperscript{116} Lockhart proved that copper (I) was the active species by using authentic copper (I) benzoate. The results from both sets of
experiments were the same. Lockhart provided further evidence by performing reactions in the presence of cuproin (2,2'-biquinoline) which binds strongly to copper (I) salts producing a purple coloured complex (eqn. 182).

\[
\text{CuI} + 2 \text{Cuproin} \rightarrow \text{Cuproin-Cu}^+ \quad \text{(182)}
\]

\[
\lambda_{\text{max}} 540 \text{nm} \quad (654.90)
\]

The addition of cuproin caused a significant inhibition of the reaction rate and a deep purple colour was observed in the reaction mixtures indicating that copper (I) was present and was responsible for inducing the substitution reaction.

The application of Lockhart's cuproin inhibition technique to our reactions would have been valuable in assessing the role of the copper (I) species. Evidence supporting the participation of copper (I) was provided by our observation that 2-bromo-2-nitropropane did not react with sodium thiocyanate when oxygen replaced the usual nitrogen atmosphere (eqn. 183).

\[
\text{Br} \quad \overset{\text{CuI} \quad \text{DMF} \quad \text{SCN}^-}{\text{O}_2 \quad \Delta} \quad \overset{\text{NO}_2}{\text{SCN}}
\]

The inhibition was attributed to the oxidation of copper (I) to copper (II).

The observation that amides were largely unreactive in our copper (I)-promoted substitutions whereas the corresponding thioamide was often found
to be a successful nucleophile may be explained by the theory of soft and hard acids and bases (SHAB).

Copper (I) is a soft acid and will, therefore, prefer to co-ordinate with soft bases such as \( RS^- \) which is present when thioamides are reacted under basic conditions (eqn. 184, \( Y=S \)).

\[
\begin{align*}
\text{RNHCR}^1 & \xrightarrow{\text{BASE}} \text{RN} = \text{CR}^1 \xrightarrow{\text{Y}} \text{RN} \equiv \text{CR}^1
\end{align*}
\] (184)

The nitrogen-anion in amides and thioamides is also a soft base.

Alkoxides (\( RO^- \)) are hard bases and the oxygen-anion present in amides (eqn. 184, \( Y=O \)) would not be predicted to co-ordinate with copper (I) as easily as the soft bases. Co-ordination of the nucleophile with copper (I) is proposed as the first step in the mechanism shown in Scheme 38.

The same explanation has been offered by Migita et al. to account for their observations in the palladium (0)-catalysed reactions of aryl halides with nucleophiles such as \( RS^- \), \( CN^- \), \( RO^- \), \( -CH_2\text{CN} \) and \( -CH_2\text{(CO}_2\text{R)} \).

During our investigations, copper (I)-promoted cyclisations were successfully performed where reactions under \( \text{SRN}^{-1} \) conditions had failed. This difference in reactivity is attributed to the ease of oxidation of aryl radicals by copper (II). The availability of the copper (III) oxidation state appears to be a crucial factor in the success of the copper (I)-promoted substitutions.

\[ \text{The mechanism of action of copper (0)} \]

Any mechanism which is proposed to explain the action of copper powder must account for the absence of formation of reduction products, the lack of inhibition in the majority of cases and the presence of catalysis.

A reaction of phenylthiol with \( p \)-chloroiodobenzene performed in the presence
of two equivalents of copper powder resulted in the formation of the monosubstitution product \([121]\) and diphenyl disulphide (eqn. 185).

\[
\begin{align*}
\text{Cl} & \quad \text{PhSH} \quad \text{Cu} \\
\text{I} & \quad \text{DMF, } \text{N}_2, \Delta \\
\text{Cl} & \quad \text{SPh} \quad \text{Ph}_2\text{S}_2
\end{align*}
\]

The absence of the dissubstitution product showed that no free radical-anions were present as intermediates in the reaction. The diphenyl disulphide may have been formed by the oxidation of the thiol (either during storage or during the work-up procedure).

The fact that no reduction products were detected during any of the copper (0)-promoted cyclisations suggested that no undissociated aryl radical was present in the reaction mechanism.

The mechanisms by which copper metal effects aromatic nucleophilic substitution have not received as much attention as those by which copper (I) species act.

Perhaps the best-known use of copper powder is in the Ullmann coupling of aryl halides (eqn. 186).

\[
2\text{ArI} + \text{Cu} \quad \xrightarrow{\Delta} \quad \text{Ar-Ar}
\]

The mechanism of the Ullmann reaction is not known with certainty but it appears likely that an arylcopper (I) species is involved (eqns. 187-189).\textsuperscript{126}

\[
\begin{align*}
\text{ArI} + \text{Cu} & \quad \xrightarrow{} \quad \text{Ar}^+ + \text{CuI} \\
\text{Ar}^+ + \text{Cu} & \quad \xrightarrow{} \quad \text{ArCu}^+ \\
\text{ArCu}^+ + \text{ArI} & \quad \xrightarrow{} \quad \text{Ar-Ar} + \text{CuI}
\end{align*}
\]
However, the absence of the formation of biaryls or reduction products in our reactions suggest that no arylcopper (I) species was involved.

Scheme 45 shows some of the possible routes by which copper powder may catalyse the substitution of aryl halides.

\[
\begin{align*}
\text{ArX} + \text{Cu}^0 & \quad \text{Ar-Cu}^+ \quad \text{or} \quad [\text{ArX}]^+ \quad \text{Cu}^+ \\
& \quad \text{Ar} \quad \text{Cu}^+ \\
& \quad \text{Ar} \quad \text{Cu}^+ \quad \text{X} \\
& \quad \text{Ar} \quad \text{Cu}^+ \quad \text{Y} \\
\text{ArY} + \text{Cu}^0 & \quad \text{Ar-Y-Cu}^+ \quad \text{or} \quad [\text{ArY}]^+ \quad \text{Cu}^+ \\
& \quad \text{Ar} \quad \text{Cu}^+ \quad \text{Y} \\
& \quad \text{Ar} \quad \text{Cu}^+ \quad \text{X} \\
& \quad \text{Ar} \quad \text{Cu}^+ \quad \text{X} \\
& \quad \text{Ar} \quad \text{Cu}^+ \quad \text{Y} \\
& \quad \text{Ar} \quad \text{Cu}^+ \quad \text{Y} \\
\end{align*}
\]
The processes shown in Scheme 45 are very similar to those proposed to explain the action of copper (I) salts (Scheme 38).

Ligand transfer (an inner-sphere electron transfer process) may occur by routes (a) and (d) to form an arylcopper (II) species, D. Route (d) may involve a further transition state, E as shown in the scheme below.

An outer-sphere process (electron transfer) may occur between the reactants resulting in the formation of an aryl radical-anion-copper (I) complex, B. This species must exist in an undissociated form in order to explain the lack of inhibition and the absence of formation of a disubstitution product in the experiments described earlier. The complex, B or the transition state, A may react by route (c) to form the aryl radical-copper (I) complex, C. Again, this complex must also be tightly solvent-caged in order to explain the absence of inhibition or reduction products observed in our reactions.

The relative ease of the outer-sphere and inner-sphere processes is not known and both seem quite feasible. The electronic configuration of copper metal is [Ar] 3d^{10} 4s^{1}. The loss of the 4s^{1} electron by either process appears possible.

Oxidation of the aryl radical by the copper (I) species in the complex, C results in the formation of an arylcopper (II) intermediate, D. This process has been described by Kochi\textsuperscript{127} but no comment on its feasibility was made.

Insertion by copper (0) into the carbon-halogen bond of the aryl halide (route (b)) also results in the formation of the arylcopper (II) intermediate, D. Again, no literature precedent for this process is known to us. The oxidation potential corresponding to such a process does not appear to
preclude the possibility of insertion (Scheme 46).128

Route (b) may proceed via the transition state, E which is, therefore, possibly common to routes (b) and (d).

\[ \text{Cu}^0 \xrightarrow{0.5\text{eV}} \text{Cu}^+ \xrightarrow{-0.15\text{eV}} \text{Cu}^{II} \xrightarrow{-1.8\text{eV}} \text{Cu}^{III} \]

In fact, the ionisation energy corresponding to the transition from copper (0) to copper (II) by a two electron process is less than that for two single electron transfers. The fact that the +2 oxidation state is the preferred one for copper129 also serves to favour an insertion process.

The aryl copper (II) intermediate, D may then react with the nucleophile \((YH)\) in two ways.

Substitution by an \(S_NAr\) reaction (eqn. 189a) leads directly to the formation of the product \((ArY)\) plus hydrogen halide and regenerated copper powder. The validity of this process seems to be doubtful as the nucleophile is present in its unionised form (no base is required in the copper (0)-promoted reactions) and would not be predicted to be sufficiently nucleophilic to effect the substitution. However, the degree of activation of the aromatic nucleus in the aryl copper (II) species must also be taken into account.

\[
\begin{align*}
[\text{ArCu}^{II}] + YH \\
\text{ArY} + HX + \text{Cu}^0
\end{align*}
\] (189a)

Because of the lack of data concerning such processes, the existence of an
The $S_{N}$Ar reaction remains a matter of conjecture.

A more likely alternative is that the arylcopper (II) intermediate, D undergoes a ligand exchange reaction (route (g)) in the presence of the nucleophile (YH) to form a new arylcopper (II) species, G. This species may then undergo reductive elimination (routes (d') and (a')) via the transition state, J to form the product, ArY and regenerated copper (0). Route (d') may also involve the transition state, F as shown below.

In order for the ligand exchange reaction (route (g)) to occur, it appears likely that the arylcopper (II) species, D is not as tightly solvent-caged as those species containing aryl radicals or radical-anions.

A further possible reaction of the arylcopper (II) intermediate, G is homolytic cleavage to form the aryl radical-copper (I) complex, H. This complex may then react to form the products via the transition state, J or the radical-anion-copper (I) complex, I.

Finally, the arylcopper (II) intermediate, G may react via the transition state, F (which may also be present in route (d')) to form ArY and copper (0). This process is represented as route (b') in Scheme 45.

The processes shown in Scheme 45 do not represent a comprehensive range of the mechanisms by which copper (0) may react but they do include those routes which, on the basis of the literature data available, appear to be the most feasible. Some of the transition states and intermediates shown in the Scheme may not accurately represent those actually involved. The crystal structures of the copper species and the effects of ligands other than those directly involved in the reactions have not been discussed. These comments also apply to the discussion of the copper (I)-promoted substitutions.
No experiments were performed to investigate which oxidation state of copper was responsible for inducing the reactions. There is a possibility that the copper powder used in the substitutions contained small amounts of the oxidation product, Cu₂O but the quantity present in any reaction must have been very small. The formation of Cu₂O during reactions is unlikely as all the experiments were performed under an atmosphere of dry nitrogen.

The addition of cuproin to a copper (0)-promoted reaction would give an indication of the active species. Inhibition of the reaction rate accompanied by the appearance of a purple colour would indicate the presence of copper (I).

The copper (0)-promoted cyclisation of N-(2-iodobenzyl)thiobenzamide proceeded in high yield (eqn. 190).

\[
\text{NHCSPh} \quad \text{Cu} \quad \text{DMF, N₂, } \Delta \quad \text{Ph} \quad \text{89}\% 
\]

When the reaction was repeated in the presence of p-dinitrobenzene, a 34% decrease in the yield of 2-phenyl-1,3-benzothiazine was observed.

The dramatic inhibition could have been due to the operation of a pathway involving free radical-anions. However, the existence of an SRN1 reaction appeared unlikely as a photostimulated, heated reaction performed under SRN1 conditions had produced a very low yield of the cyclised material.

The reason for the lack of reactivity of amides in copper (0)-promoted substitutions has been explained earlier in this discussion (copper metal is a soft acid).
Summary

Aromatic nucleophilic substitution is catalysed by copper powder and copper(I) halides. The most probable means by which the catalysts act involves oxidative addition of the copper (n) species to the aryl halide to form an aryl radical-copper(n+1) complex which undergoes rapid oxidation within a tightly-bound solvent cage to form an arylcopper(n+2) intermediate. Reductive elimination of this intermediate gives rise to the substitution product and regenerates the original catalyst.

Tightly solvent-caged radical-anions may also be intermediates in the substitutions but no evidence was found to prove their existence (or that of aryl radicals).

The possibility of the catalysts acting by a two electron reduction of the aryl halide has also been discussed.

A suitable concluding remark, made by Lindley in his review of copper-assisted nucleophilic substitution is as follows: "In view of the large number of nucleophilic substitutions promoted by copper complexes, the marked effects that solvents and ligands can have on the redox potentials of copper and the observations that radicals can be readily generated in these systems it is not unreasonable to expect that a small change in the reaction conditions may lead to a change in mechanism".
Addendum to Part Four

A recent paper by Yamamoto and Sekine\textsuperscript{130} describes the copper (0)-catalysed condensation of phenylthiols with aryl halides in the absence of solvent. The authors propose that dehydrogenative coupling of the thiols results in the formation of disulphides, ArSSAr. Addition of the disulphide to copper (0) affords ArSCu\textsuperscript{I} which then couples with the aryl halide (Ar'X) to yield a diaryl sulphide, ArSAr' (eqns. 191-193).

\[
\begin{align*}
2\text{PhSH} & \rightarrow \text{PhSSPh} + \text{H}_2 \quad (191) \\
\text{PhSSPh} + 2\text{Cu}^0 & \rightarrow 2\text{Cu}^\text{I} \text{SPh} \quad (192) \\
\text{Cu}^\text{I} \text{SPh} + \text{ArX} & \rightarrow \text{ArSPh} + \text{Cu}^\text{I} \text{X} \quad (193)
\end{align*}
\]

The order of halide reactivity is I>Br>Cl.

Diphenyl disulphide was isolated from reactions of phenylthiol with aryl halides in the presence of copper metal which is good evidence for the existence of a reaction as depicted by Equation 191.

An alternative mechanism which is proposed but was not proven by the authors is that involving the direct formation of ArSCu\textsuperscript{I} (eqn. 194)

\[
2\text{Cu}^0 + 2\text{PhSH} \rightarrow 2\text{Cu}^\text{I} \text{SPh} + \text{H}_2 \quad (194)
\]

The findings of Yamamoto and Sekine are in excellent agreement with those made during our investigation of the copper (0)-promoted reaction of phenylthiol with p-chloriodobenzene in which diphenyl disulphide was isolated in significant quantity (eqn. 185). The low yield of substitution product and the recovery of starting material from our reaction (performed at 100-110°C) may be explained by Yamamoto's finding that the copper (0)-promoted substitution reactions proceed best at ~240°C.
The Cu\textsuperscript{I}SPh, once formed, may react with the aryl halides as proposed in this thesis (Scheme 38) but Yamamoto and Sekine make no comment on the mechanisms which may be involved in the reactions.

Although the intermediacy of an aryl disulphide adequately explains the product formation in the copper\textsuperscript{(o)}-promoted reaction of phenylthiol with p-chloroiodobenzene, no disulphides were observed during, or isolated from our copper-promoted cyclisation reactions. We suggest that in these reactions, the mechanisms depicted in Scheme 45 are equally likely.
EXPERIMENTAL
Experiment Number

1. The preparation of halo-substituted benzanilides, -acetanilides and their thio-analogues.
   (a) 2'-Iodobenzanilide.
   (b) 2'-Iodothiobenzanilide.
   (c) 3'-Iodobenzanilide.
   (d) 3'-Iodothiobenzanilide.
   (e) 2'-Chlorobenzanilide.
   (f) 2'-Chlorothiobenzanilide.
   (g) 3'-Chlorobenzanilide.
   (h) 3'-Chlorothiobenzanilide.
   (i) 2'-Bromobenzanilide.
   (j) 2'-Bromothiobenzanilide.
   (k) 3'-Bromobenzanilide.
   (l) 2'-Iodoacetanilide.
   (m) 2'-Iodothiacetanilide.

2. The preparation of phenylacetone via an $S_{RN1}$ reaction. General method for performing $S_{RN1}$ reactions.

3. The attempted preparation of $\alpha$-phenylacetophenone via an $S_{RN1}$ reaction.

4. The preparation of 2-phenyl-1,3-benzoxazole.
   (a) Via a benzyne intermediate: General method.
   (b) Using polyphosphate ester (P.P.E.).
   (c) Using copper (I) iodide. General method for copper (I) catalysis.
   (d) Via an $S_{RN1}$ reaction.
   (e) Using copper powder.

5. The preparation of 2-phenyl-1,3-benzothiazole.
   (a) Via a benzyne intermediate.
   (b) Via an $S_{RN1}$ reaction.
   (c) Using potassium metal.
   (d) Using copper (I) salts.
   (e) Using copper powder.
   (f) By an anomalous reaction.

6. The preparation of 2-methyl-1,3-benzoxazole.
   (a) By an $S_{RN1}$ reaction.
   (b) Via copper (I) salt catalysis.
   (c) Using copper powder.

7. The preparation of 2-methyl-1,3-benzothiazole.
   (a) By an $S_{RN1}$ reaction.
   (b) By copper (I) catalysis.
   (c) Using copper powder.
8. The attempted deuteration of 2-iodothioacetanilide.
9. The preparation of N-(3,4-dimethoxybenzyl)acetamide.
10. The preparation of N-(2-iodo-4,5-dimethoxybenzyl)acetamide.
   (a) With antimony pentachloride/iodine monochloride.
   (b) With antimony pentachloride/iodine.
11. The preparation of N-(3,4-dimethoxybenzyl)thioacetamide.
12. The preparation of N-(2-iodo-4,5-dimethoxybenzyl)thioacetamide.
   (a) From N-(2-iodo-4,5-dimethoxybenzyl)acetamide.
   (b) From N-(3,4-dimethoxybenzyl)thioacetamide.
13. The preparation of N-(3,4-dimethoxybenzyl)benzamide.
15. The preparation of N-(2-iodo-4,5-dimethoxybenzyl)thiobenzamide.
16. The preparation of N-(3,4-dimethoxybenzyl)thiobenzamide.
17. The attempted cyclisation of N-(2-iodo-4,5-dimethoxybenzyl)thioacetamide.
   (a) By a non-entrained $S_{RN}^1$ reaction
   (b) By an entrained $S_{RN}^1$ reaction.
   (c) Using copper (I) iodide.
   (d) Using copper powder.
18. The cyclisation of N-(2-iodo-4,5-dimethoxybenzyl)thiobenzamide.
   (a) By an entrained $S_{RN}^1$ reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.
19. The attempted cyclisation of N-(2-iodo-4,5-dimethoxybenzyl)acetamide.
   (a) By an entrained $S_{RN}^1$ reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.
20. The attempted cyclisation of N-(2-iodo-4,5-dimethoxybenzyl)benzamide.
   (a) By an entrained $S_{RN}^1$ reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.
   (a) Using N-bromosuccinimide.
   (b) Using bromine.
22. The preparation of 2-iodobenzylamine.
23. The preparation of N-(2-iodobenzyl)benzamide.
24. The preparation of N-(2-iodobenzyl)thiobenzamide.
25. The preparation of N-benzyl benzamide.
26. The preparation of N-benzyl thiobenzamide.
27. The cyclisation of N-(2-iodobenzyl)thiobenzamide.
   (a) By an entrained $S_{RN}^1$ reaction.
   (b) By an unentrained, heated $S_{RN}^1$ reaction.
   (c) Using copper (I) iodide.
   (d) Using copper powder.
   (a) By an entrained S_RN^1 reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.

29. The preparation of N-(2-bromobenzoyl)-N'-phenylthiourea.
30. The preparation of N-(2-chlorobenzoyl)-N'-phenylthiourea.
31. The preparation of N-benzoyl-N'-phenylthiourea.
32. The preparation of N-(2-bromobenzoyl)-N'-methyl-N'-phenylthiourea.
33. The preparation of N-benzoyl-N'-methyl-N'-phenylthiourea.
34. The attempted preparation of N-(2-bromothiobenzoyl)-N'-phenylthiourea.
35. The preparation of 2-bromothiobenzamide.
36. The preparation of N-(2-bromobenzoyl)-N'-phenylurea.
37. The preparation of N-(2-bromobenzoyl)-N'-methyl-N'-phenylurea.
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39. The cyclisation of N-(2-bromobenzoyl)-N'-phenylthiourea.
   (a) By an S_NAr reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.

40. The cyclisation of N-(2-chlorobenzoyl)-N'-phenylthiourea.
   (a) By an S_NAr reaction.
   (b) Using copper (I) iodide.

41. The reaction of N-benzoyl-N'-phenylthiourea with copper (I) iodide.
42. The cyclisation of N-(2-bromobenzoyl)-N'-methyl-N'-phenylthiourea.
   (a) By an S_NAr reaction.
   (b) Using copper (I) iodide.

43. The cyclisation of N-(2-bromobenzoyl)-N'-phenylurea.
   (a) By an S_NAr reaction.
   (b) Using copper (I) iodide.

44. The attempted cyclisation of N-(2-bromobenzoyl)-N'-methyl-N'-phenylurea.
   (a) By an S_NAr reaction.
   (b) By an entrained S_RN^1 reaction.
   (c) Using copper (I) iodide.

45. The preparation of trans-2-bromo-α-phenylcinnamic acid.
46. The preparation of N-(2-bromo-α-phenylcinnamoyl)-N'-phenylthiourea.
47. The cyclisation of N-(2-bromo-α-phenylcinnamoyl)-N'-phenylthiourea.
49. The preparation of S-(2-iodobenzyl)-2-imidazolidinethione.
50. The cyclisation of S-(2-iodobenzyl)-2-imidazolidinethione.
   (a) By an entrained S_RN^1 reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.

51. The preparation of N-(3,4-dimethoxyphenethyl)acetamide.
52. The preparation of N-(2-iodo-4,5-dimethoxyphenethyl)acetamide.
53. The preparation of N-(3,4-dimethoxyphenethyl)thioacetamide.
54. The preparation of N-(2-iodo-4,5-dimethoxyphenethyl)thioacetamide.
55. The preparation of 1-acetyl-2,3-dihydro-5,6-dimethoxy-1H-indole.
56. The preparation of 2,3-dihydro-5,6-dimethoxy-1-thioacetetyl-1H-indole.
57. Attempted hydrolyses of N-(2-iodo-4,5-dimethoxyphenethyl)thioacetamide.
   (a) By acid hydrolysis.
   (b) By base hydrolysis.
58. The preparation of N-(benzyloxycarbonyl)homoveratrylamine.
59. The iodination of N-(benzyloxycarbonyl)homoveratrylamine.
60. The attempted hydrolysis of the amide prepared in Experiment 59.
61. The cyclisation of N-(2-iodo-4,5-dimethoxyphenethyl)thioacetamide.
   (a) By an $S_{RN1}$ reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.
62. The attempted cyclisation of N-(2-iodo-4,5-dimethoxyphenethyl)acetamide.
   (a) By an entrained $S_{RN1}$ reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.
63. Preparation of the oxime of 2-chloroacetophenone.
64. Tosylation of the oxime of 2-chloroacetophenone.
65. The Neber rearrangement of the oxime tosylate to 2-chlorophenacylamine hydrochloride.
66. The preparation of N-acetyl-2-chlorophenacylamine.
67. The attempted preparation of N-thioacetetyl-2-chlorophenacylamine.
68. Preparation of the oxime of 2-bromoacetophenone.
69. Tosylation of the oxime of 2-bromoacetophenone.
70. The attempted Neber rearrangement of the oxime tosylate to 2-bromophenacylamine hydrochloride.
71. The preparation of 2-bromophenacyl bromide.
72. The attempted preparation of 2-bromophenacylamine hydrochloride.
   (a) By the Delepine reaction.
   (b) By the Gabriel reaction.
73. The preparation of 4-(2-iodophenyl)-3-thiabutanoic acid.
74. The preparation of the benzyl amide of 4-(2-iodophenyl)-3-thiabutanoic acid.
75. The thionation of the amide prepared in Experiment 74.
76. The attempted cyclisation of the thioamide [117].
   (a) By an entrained $S_{RN1}$ reaction.
   (b) Using copper (I) iodide.
   (c) Using copper powder.
77. The preparation of the ethyl ester of 4-(2-iodophenyl)-3-thiabutanoic acid.
78. The attempted preparation of amides of the ester [115].
   (a) With aniline.
   (b) With benzylamine
79. The preparation of 4-(2-bromophenyl)-4-oxo-3-thiabutanoic acid.

80. The attempted preparation of the benzyl amide of 4-(2-bromophenyl)-4-oxo-3-thiabutanoic acid.

81. The preparation of the ethyl ester of 4-(2-bromophenyl)-4-oxo-3-thiabutanoic acid.

82. The attempted preparation of the primary amide of the ester prepared above.

83. The preparation of 2-nitro-2-thiocyanatopropane.

84. The investigation of the copper (I) iodide promoted reaction of iodobenzene and phenylthiolate anion.

85. The preparation of 1-chloro-4-(thiophenyl)benzene.

(a) By an $S_{N1}$ reaction.

(b) Using copper (I) iodide.

(c) Using copper powder.

86. The preparation of 1,4-bis(thiophenyl)benzene.
All solvents were dried and distilled by conventional methods.

Melting points were determined on a Kofler block and are uncorrected.

Infrared spectra were recorded as Nujol mulls (solids) or thin films (liquids) on a Perkin-Elmer 177 spectrometer.

$^1$H nuclear magnetic resonance spectra were determined using tetramethyl silane (TMS) as the internal standard. 60 MHz spectra were recorded on a Varian EM 360A instrument and 90 MHz spectra were recorded on a Perkin-Elmer R32 spectrometer.

$^{13}$C nuclear magnetic resonance spectra were recorded on a Bruker WP-80 spectrometer using TMS as the internal standard.

Mass spectra were recorded using a Kratos MS 80 spectrometer linked to a DS-55 data system.

Refractive indices were determined at room temperature on an Abbe refractometer.

Preparative and analytical thin layer chromatography were performed using Merck alumina 60 PF$_{254}$ (Type E) and Merck silica gel 60 PF$_{254}$ and 366.

Column chromatography was performed using Hopkin and Williams alumina "CAMAG" M.F.C. neutral, Brockmann activity 1 and Merck silica gel 60, 70-230 mesh. Flash chromatography was accomplished using Merck silica gel, 230-400 mesh according to the method of Still et al.$^{131}$

Analytical gas chromatography was performed on a Pye Series 104 gas chromatograph using a flame ionisation detector.

Analyses were performed by the microanalytical departments of Manchester University and The Boots Company PLC, Nottingham.

Irradiation of $S_{RN}$ 1 reactions was accomplished using a Photophysics MLV 18 irradiator equipped with twelve lamps (25 watt) emitting at 350 nm.

Nitrogen gas was deoxygenated and dried by passage through Dreschel bottles containing Fieser's solution, concentrated sulphuric acid and potassium hydroxide pellets.
Pet. ether in the text refers to the 40-60°C boiling fraction.

Copper (I) iodide was purchased as the 'Gold Label' grade (99.999%) from The Aldrich Chemical Company.

Common abbreviations used in the experimental section:

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Name</th>
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<tbody>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>Anhydrous magnesium sulphate</td>
</tr>
<tr>
<td>Na₂SO₄</td>
<td>Anhydrous sodium sulphate</td>
</tr>
<tr>
<td>t.l.c.</td>
<td>Thin layer chromatography</td>
</tr>
<tr>
<td>O₂</td>
<td>Oxygen gas</td>
</tr>
<tr>
<td>N₂</td>
<td>Nitrogen gas</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>Deuteriation</td>
</tr>
</tbody>
</table>
1. The Preparation of Halo-Substituted Benzanilides, Acetanilides and their Thio-Analogues

(a) 2'-Iodobenzanilide [43b]

2-Iodoaniline (5.0 g, 22.83 mmol) was finely ground and suspended in 10% aq. sodium hydroxide (20 ml). Benzoyl chloride (3.69 g, 26.25 mmol, 1.15 equivalents) was then added dropwise to the magnetically stirred suspension over a period of 15 min. The mixture was stirred for a further hour and then diluted with water. The crude product was filtered, washed thoroughly with water and dried. Recrystallisation from ethanol gave colourless needles of the amide (4.98 g, 68%), m.p. 140-141.5°C (lit., 132-139°C); $\nu_{\text{max}}$, 3210, 1645 cm$^{-1}$; $\delta_H$ (CDCl$_3$) 6.6 - 8.65 (10 H, m, aromatic and amide H).

(b) 2'-Iodothiobenzanilide [28a]

Thionation of 2'-iodobenzanilide was achieved by two methods:

(i) Using phosphorus pentasulphide. 2'-Iodobenzanilide (0.65 g, 2 mmol), phosphorus pentasulphide (P$_2$S$_5$, 0.89 g, 4 mmol) and dry pyridine (20 ml) were refluxed together for 2 h. The pH of the mixture was then adjusted to 7-8 whereupon a yellow oil separated. This oil was allowed to crystallise and was filtered, washed well with water and dried. Recrystallisation from ethanol afforded yellow crystals of the thioamide [28a] (0.39 g, 57%), m.p. 96-99°C (Found: C, 46.4; H, 3.0; N, 3.9. C$_{13}$H$_{10}$INS requires C, 46.05; H, 2.95; N, 4.15); $\nu_{\text{max}}$, 3185 cm$^{-1}$; $\delta_H$ (CDCl$_3$) 6.6-8.65 (9 H, m, aromatic H), 8.87 (1 H, br.s, thioamide H).

(ii) Using Lawesson's Reagent. 2'-Iodobenzanilide (2.0 g, 6.19 mmol) and Lawesson's Reagent (0.89 g, 4 mmol, 0.7 equivalents) were refluxed in dry toluene (20 ml) under an atmosphere of nitrogen for 4 h. The yellow solution was cooled and the toluene removed in vacuo. The residue was taken up into dichloromethane and passed down a short column of alumina using dichloromethane as the eluent. The yellow eluates were evaporated in vacuo to yield the crude thioamide as yellow rosettes which were recrystallised from ethanol. 2'-Iodothiobenzanilide was obtained as yellow
crystals (1.18 g, 56%), m.p. 92-96°C. The analytical data was as described in method (a).

The following 2'- and 3'-halobenzenilides and their respective thionated analogues were prepared in a similar manner:

(c) 3'-Iodobenzenilide
A larger excess of benzoyl chloride was employed (2.4 equivalents). The product was obtained as metallic, grey needles (45%), m.p. 157 - 158°C (lit., 132 157°C); \( \nu_{\text{max}} \) 3270, 1650 and 1570 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 6.3 - 8.0 (10 H, m, aromatic and amide H).

(d) 3'-Iodothiobenzenilide [33]
The thionation was carried out as described previously but using a larger excess of \( P_2S_5 \) (4 equivalents) and a longer reflux period of 11 h. The thioamide [33] was obtained as yellow needles (83%), m.p. 114-117°C (Found: C, 45.7; H, 3.0; N, 4.1. \( C_{13}H_{10}NS \) requires C, 46.05; H, 2.95; N, 4.15); \( \nu_{\text{max}} \) 3160 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 6.7 - 8.58 (10 H, m, aromatic and thioamide H).

(e) 2'-Chlorobenzenilide [43a]
Benzoylation of 2-chloroaniline gave colourless needles of the amide (88%), m.p. 97-99°C (lit., 132 99°C); \( \nu_{\text{max}} \) 3220, 1650 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 6.6-8.8 (10 H, m, aromatic and amide H).

(f) 2'-Chlorothiobenzenilide [28c]
Thionation with an equimolar quantity of \( P_2S_5 \) over a period of 4.25 h gave yellow needles of the thioamide (60%), m.p. 72-75°C (lit., 133 73-74°C); \( \nu_{\text{max}} \) 3170 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 6.8-8.8 (10 H, aromatic and thioamide H).
(g) 3'-Chlorobenzanilide
Benzoylation of 3-chloroaniline gave colourless crystals of the amide (61%); m.p. 123-125°C (lit., 133 120-121°C); ν max. 3290, 1650 cm⁻¹; δ_H (CDCl₃) 6.8-8.3 (10 H, m, aromatic and amide H).

(h) 3'-Chlorothiobenzanilide
Thionation with an equimolar amount of P₂S₅ over 3 h gave yellow crystals of the thioamide (71%), m.p. 105-107°C (lit., 133 97-98°C); ν max. 3250 cm⁻¹; δ_H (CDCl₃) 7.0 - 8.0 (9 H, m, aromatic H), 8.9 (1 H, br.s, thioamide H).

(i) 2'-Bromobenzanilide
Benzoylation of 2-bromoaniline gave the amide as colourless needles (69%), m.p. 116-118°C (lit., 133 116°C); ν max. 3220, 1650 cm⁻¹; δ_H (CDCl₃) 6.8-8.8 (10 H, m, aromatic and amide H).

(j) 2'-Bromothiobenzanilide [28b]
Thionation with an equimolar quantity of P₂S₅ over a period of 3 h gave the thioamide as yellow needles (98%), m.p. 85-86°C (lit., 133 85-86°C); ν max. 3170 cm⁻¹; δ_H (CDCl₃) 6.87 - 8.03 (8 H, m, aromatic H), 8.53 (1 H, m, aromatic H), 9.24 (1 H, br.s, thioamide H).

(k) 3'-Bromobenzanilide
Benzoylation of 3-bromoaniline gave fawn needles of the amide (69%), m.p. 137-139°C (lit., 133 134°C); ν max. 3270, 1650 cm⁻¹; δ_H (CDCl₃) 6.5 - 8.55 (10 H, m, aromatic and amide H).

(l) 2-Iodoacetanilide [44]
Two methods of preparation were used:

(i) 2-Iodoaniline (5.0 g, 22.8 mmol), acetic anhydride (2.35 g, 23 mmol) and glacial acetic acid (2.19 g, 36.5 mmol) were refluxed together gently for 0.75 h and the hot mixture was then poured, with stirring, into cold water (40 ml). The
resulting milky suspension was cooled and filtered. The crude product was washed with water, dried and recrystallised from toluene. The amide was obtained as fawn needles (4.09 g, 69%), m.p. 111-113°C (lit. \(^{132}\) 109-110°C); \(\nu_{\text{max}}\) 3400, 1695, 1515 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\)) 2.2 (3 H, s, methyl H), 6.5-8.3 (5 H, m, aromatic and amide H); m/z 261 (M+), 219, 134, 92.

(ii) The method of Owsley and Bloomfield. 2-Iodonitrobenzene (15 g, 60.2 mmol), iron powder (hydrogen-reduced, 12.97 g, 0.232 mol, 3.8 equivalents) and glacial acetic acid (50 ml) were stirred together for 10 min and then refluxed for 5 h. The mixture was cooled and poured into ice/water (400 ml). The resulting red solution was filtered and extracted with chloroform (6 x 100 ml). The extracts were washed with sodium metabisulphate (x2), water, dried (MgSO\(_4\)) and evaporated \(\text{in vacuo}\). The crude product was recrystallised from carbon tetrachloride to yield fawn plates of the amide (2.62 g, 17%), m.p. 111-115°C.

(m) 2-Iodothioacetanilide \(^{29}\) Thionation with Lawesson's Reagent over a period of 2 h at 85-92°C gave pale yellow crystals of the thioamide (44%), m.p. 88-92°C (lit., 109°C); \(\nu_{\text{max}}\) 3250 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\)) 2.73 (3 H, s, methyl H), 6.5-8.1 (5 H, m, aromatic and thioamide H); m/z 278 (M+), 244, 219, 150, 109, 59.

2. The Preparation of Phenylacetone via an S\(_{\text{RN}}\text{1}\) Reaction. General Method for performing S\(_{\text{RN}}\text{1}\) reactions

A solution of potassium t-butoxide (2.03g, 20.5 mmol, 8 equivalents) in DMSO (50 ml, dry, distilled) was charged to an irradiation vessel through which a constant stream of dry nitrogen was passed. Acetone (1.16g, 20 mmol, 8 equivalents, dry distilled) was added followed by iodobenzene (0.5 g, 2.45 mmol). The reaction mixture was irradiated for one hour. The red-brown mixture was diluted with water (50 ml) and extracted with
diethyl ether (3 x 40 ml). The ether extracts were combined, washed five times with water, dried (Na$_2$SO$_4$) and evaporated in vacuo to yield phenylacetone as an orange oil (0.16 g, 49%), i.r. and n.m.r. spectra identical to those quoted in the literature. A 2,4-dinitrophenylhydrazine derivative was prepared as orange-red crystals which were recrystallised from ethanol, m.p. 152-155°C (lit., 156°C).

Bromobenzene was also reacted as described above but with an irradiation period of 3 h. The reaction failed to give a satisfactory yield of phenylacetone.

3. The Attempted Preparation of α-Phenylacetophenone via an $S_{RN1}$ Reaction

Iodobenzene (0.51 g, 2.5 mmol), acetophenone (2.4 g, 20 mmol), potassium t-butoxide (3.36 g, 30 mmol) and dry DMSO (25 ml) were irradiated under nitrogen for 5 h as described above. No reaction occurred and a quantitative yield of the starting material was recovered.

4. The Preparation of 2-Phenyl-1,3-benzoxazole [23]

(a) Via a benzyne intermediate: General Method

Dry liquid ammonia was prepared by double distillation in essentially the same manner as that used by Bunnett and Hrutfiord. A brief description of the method is given here. Two one-litre flasks, connected by a drying tube packed with silica-gel and 4A molecular sieves and equipped with large dry-ice condensers, were pre-dried by flaming thoroughly whilst being evacuated with dry nitrogen gas. Ammonia gas was then passed through NaOH pellets and condensed into flask 1 where it was dried further by addition of potassium metal until the blue colouration persisted for several minutes.

The ammonia was then allowed to condense into the second flask via the drying tube. This flask and it's condenser were made with reverse joints to avoid condensation running down into the flask through the joints. The ammonia was again pre-dried with potassium metal.
200 ml of dry ammonia was prepared in the above manner. Ferric nitrate (0.1 g, reaction catalyst) was added followed by clean potassium metal (1.67 g, 30.3 mmol). The metal was added over a period of 0.5 h and the resulting potassium amide/NH₃ mixture was stirred magnetically for a further 0.25 h. 2'-Chlorobenzanilide (2.01 g, 8.7 mmol) was then added and the mixture was stirred for 2.75 h.

Ammonium nitrate (2.43 g, 30.3 mmol) was then added to quench the potassium amide and diethyl ether (200 ml) was added.

The mixture was allowed to evaporate overnight. The residue was extracted twice with diethyl ether/water (50 ml of each) and the layers of the individual extracts were separated. The combined ether extracts were washed with 2N HCl (2 x 50 ml), dried (Na₂SO₄) and evaporated in vacuo to yield unreacted starting material as yellow crystals (0.78 g, 39% recovery), m.p. 81-85°C, t.l.c. and i.r. and n.m.r. spectra were identical to those of the starting material.

The aqueous phases were combined and acidified to pH 8 with 5 N HCl. The resulting dark-brown precipitate was discarded and the aqueous phase was acidified to pH 7 as before and left to stand. After four days, the benzoxazole was filtered and dried to yield fawn needles (0.4 g, 24%), m.p. 98-105°C (lit., 79 98-100°C); t.l.c. and i.r. and n.m.r. spectra were identical to those of an authentic sample.

Liquid/liquid extraction of the aqueous phase with chloroform increased the isolated yield of the 2-phenyl-1,3-benzoxazole to 51%.

Reactions performed without the use of reverse joints, pre-drying of the liquid ammonia with potassium and without prior allowance for complete formation of the potassium amide resulted in quantitative recovery of starting material.

Reaction of 3'-chlorobenzanilide as described above but with a reaction period of 5 h resulted in the formation of 2-phenyl-1,3-benzoxazole in 40% yield. Unreacted starting material (54% recovery) was also obtained.
Reaction of 2'-bromobenzanilide as described above resulted in the isolation of the benzoazole (4%) and unreacted starting material (91% recovery).

Similarly, 3'-bromobenzanilide when reacted under the conditions described above failed to cyclise and unreacted starting material (96%) was recovered.

(b) The preparation of 2-phenyl-1,3-benzoxazole using polyphosphate ester (P.P.E.)

Polyphosphate ester was prepared by the method described below;

Phosphorus pentoxide (15 g), chloroform (30 ml, dry), and diethyl ether (15 ml, sodium-dried) were refluxed for 48 h. The clear solution was cooled and filtered through glass wool into a dry flask and evaporated in vacuo to yield the ester as a golden syrup (13.08 g).

2-Aminophenol (1.1 g, 0.01 mol) and benzoic acid (1.23 g, 0.01 mol) were mixed into the P.P.E. (13.08 g) and the mixture was heated at 100-110°C for 40 min. The tarry black residue was taken into chloroform (40 ml) and the resulting dark-green solution was washed with water (x2), dried (Na₂SO₄), filtered and evaporated in vacuo to afford a mobile, green syrup (7.83 g). This was purified by preparative t.l.c. on alumina. A fluorescent (254 nm) band was removed from the plates and extracted from the alumina to yield 2-phenyl-1,3-benzoxazole as pale yellow crystals (0.56 g, 28%), m.p. 98-103°C (lit., 79 98-100°C); νₗₘ₈, 755, 750, 710 cm⁻¹; δₑ (CDCl₃) 7.15-7.93 (7 H, m, aromatic H), 8.0-8.45 (2 H, m, aromatic H).

This sample was used to authenticate others prepared via different routes.

(c) The preparation of 2-phenyl-1,3-benzoxazole using copper (I) iodide. General method for copper (I) catalysis

2'-Iodobenzanilide (0.1 g, 0.31 mmol) and potassium t-butoxide (0.17 g, 5 equivalents) were stirred magnetically under a nitrogen atmosphere for 5 min and the copper (I) iodide (0.06 g, 0.31 mmol)
was added. The resulting dark-green mixture was stirred and heated at 70-80°C under a nitrogen atmosphere for 1.5 h. Analytical t.l.c. at this time showed the starting material to be absent.

The mixture was diluted with water (65 ml) and acidified with 2 N HCl (20 ml) and then extracted with dichloromethane (3 x 50 ml). The extracts were combined, washed with water (x8), dried (MgSO₄) and evaporated in vacuo to yield the benzoxazole as a brown gum (51 mg, 84%). Purification by column chromatography (alumina "Camag", ether/pet. ether, 3:8) yielded brown crystals of the product (31 mg, 51%); m.p. 93-96°C; t.l.c. and i.r. and n.m.r. spectra were identical to those of an authenticated sample.

A reaction carried out using 0.2 equivalents of the copper (I) salt and 2 equivalents of base over a period of 5.75 h at 78-85°C gave a mixture of the product and starting material.

(d) The attempted preparation of 2-phenyl-1,3-benzoxazole via an S₅″RN¹ reaction

(i) Under non-entrained reaction conditions. Irradiation of 2'-chlorobenzanilide, potassium t-butoxide (3 equivalents) and DMSO (20 ml) for 5 h and work-up as described in the general procedure yielded only unreacted starting material (81%).

Irradiation of 2'-iodobenzanilide with a 4-fold excess of potassium t-butoxide and DMSO (25 ml) resulted in recovery of starting material (71%).

(ii) Under entrained conditions. 2'-Iodobenzanilide (0.15 g, 0.465 mmol), potassium t-butoxide (0.94 g, 8.37 mmol, 18 equivalents), dry acetone (0.22 g, 3.72 mmol, 8 equivalents), and DMSO (20 ml) were irradiated under nitrogen for 8 h to yield, on work-up, a red-brown oil (0.15 g). An analytical t.l.c. showed that a mixture of products was present. Preparative t.l.c. (alumina, diethyl ether/pet. ether; 50:50) yielded unreacted starting material (63 mg, 64% recovery) and benzanilide (29 mg, 21%) which was identified by t.l.c. and i.r. and n.m.r. spectra.
(e) The preparation of 2-phenyl-1,3-benzoxazole using copper powder

The copper powder was prepared according to the method of Gore by adding zinc dust to cupric sulphate solution. Once prepared, the powder was stored in a desiccator.

2'-Iodobenzanilide (0.1 g, 0.3 mmol), copper powder (0.02 g, 1 equivalent) and dry DMF (15 ml) were stirred magnetically and heated under an atmosphere of nitrogen at 80-90°C for 6 h. The mixture was diluted with water (65 ml) and extracted with dichloromethane (3 x 50 ml). The extracts were combined, washed with water (x8), dried (MgSO₄) and evaporated in vacuo to yield colourless crystals of recovered starting material (0.1 g, 100% recovery), m.p. 138-141°C; t.l.c. and i.r. and n.m.r. spectra were identical to those of the starting material.

5. The Preparation of 2-Pheny1-1,3-benzothiazole [21]

(a) Via a benzene intermediate

3'-Chlorothiobenzanilide was reacted as described in the general procedure. Only unreacted starting material (76% recovery) was isolated.

(b) The preparation of 2-phenyl-1,3-benzothiazole via an Sₗ₁ reaction

(i) Under non-entrained conditions. On irradiation of 2'-bromothiobenzanilide (0.51 g, 1.85 mmol), potassium t-butoxide (2.5 equivalents), and DMSO (15 ml) for 4.75 h as described in the general procedure (but using dichloromethane as the extraction solvent), a quantitative recovery of starting material was recovered.

2'-Iodothiobenzanilide (0.25 g, 0.74 mmol), potassium t-butoxide (8 equivalents) and DMSO (20 ml) were similarly unreactive on irradiation giving a quantitative recovery of starting material.

(ii) Under entrained conditions. Potassium t-butoxide (0.69 g, 6.16 mmol, 20 equivalents) and DMSO (15 ml) were charged to an irradiation vessel which was constantly purged with dry nitrogen. 2'-Iodothiobenzanilide (0.1 g, 0.29 mmol) was added followed by dry acetone (0.14 g, 2.36 mmol, 8 equivalents) and the mixture was irradiated under nitrogen for 3.5 h. The red-brown solution was worked up as described in the general procedure (using dichloromethane.
as the extraction solvent) to yield the benzothiazole as greasy, brown crystals (0.25 g, 100%). Purification by preparative t.l.c. (alumina, ether/pet. ether; 4:1) yielded the product as fluffy, brown needles (45 mg, 69%), m.p. 111-114°C (lit., 111-113°C); \( \nu_{\text{max}} \), 760, 735 cm\(^{-1}\); \( \delta_{H} \) (CDCl\(_3\)) 7.0-7.6 (5 H, m, aromatic H), 7.6-8.15 (4 H, m, aromatic H). These data were identical to those in the literature.\(^{136,137}\)

When the above reaction was repeated with a much smaller (0.2 equivalents) quantity of acetone, irradiation over a period of 7.25 h gave a yellow solid (0.124 g) which was purified by preparative t.l.c. (alumina, diethyl ether/pet. ether; 50:50) to yield the benzothiazole (12 mg, 13%) and unreacted starting material (6.3 mg, 42% recovery).

A similar result was obtained when 0.5 equivalents of the acetone enolate anion were used in the reaction.

2'-Bromothiobenzanilide (0.1 g, 0.36 mmol) was irradiated in the presence of acetone enolate anion as described above for 6 h to yield, after preparative t.l.c., the 2-phenyl-1,3-benzothiazole (24 mg, 22%) and unreacted starting material (62 mg, 62% recovery).

Lowering the amount of acetone to 2 equivalents resulted in quantitative recovery of starting material.

2'-Chlorothiobenzanilide (0.13 g, 0.525 mmol), potassium t-butoxide (1.35 g, 12 mmol, 23 equivalents), dry acetone (0.31 g, 5.25 mmol), and DMSO (15 ml) were irradiated for 5.5 h as described above to yield a red-brown oil (0.2 g) which was purified by preparative t.l.c. (alumina, diethyl ether/pet. ether; 1:4) to yield the benzothiazole (5 mg, 5%), unreacted starting material (81 mg, 63% recovery) and an unidentified product (12 mg). Lowering the quantity of acetone to 0.2 equivalents resulted in recovery of starting material (98%).
Inhibition studies on the entrained cyclisation reaction. The reaction of 2'-iodothiobenzanilide, described above (Section 5, b, ii), was repeated in the presence of electron and radical-anion scavengers. A reaction of 3.5 h was used in all the inhibition reactions.

When the nitrogen atmosphere was replaced by one of oxygen, work-up yielded a yellow gum (100% recovery of starting material). The i.r. spectrum indicated that some phenolic impurity might be present but extraction of the gum with 10% sodium hydroxide followed by acidification of the alkali extract and extraction with dichloromethane revealed no phenolic product.

Addition of p-dinitrobenzene (10 mol %) or di-t-butyl nitroxyl (15 mol %) to the reaction mixture resulted in quantitative recovery of the starting material.

When the reaction was performed in the absence of light (achieved by covering the flask with aluminium foil) work-up yielded a quantitative recovery of starting material.

The attempted cyclisation of 3'-iodothiobenzanilide under entrained SRN1 conditions. The anilide (0.1 g, 0.295 mmol) was irradiated for 5.5 h as described above (Section 5, b, ii) and worked-up to yield a red-brown gum (0.1 g) which contained no starting material or acetone adduct by i.r. and n.m.r. spectral analysis. The spectral data also showed that no 2-phenyl-1,3-benzothiazole had been formed.

The reaction was repeated with an extended irradiation period of 7 h. Again, t.l.c., i.r., and n.m.r. were of little use in identifying the products. G.l.c. analysis indicated that thiobenzanilide was present in small amounts.

The preparation of 2-phenyl-1,3-benzothiazole using potassium metal

2'-Iodothiobenzanilide (0.2 g, 0.59 mmol) and potassium t-butoxide (0.13 g, 1.18 mmol) were added to dry liquid ammonia (70 ml), prepared as described earlier. The mixture was magnetically stirred
and potassium metal (1 g, 25.5 mmol, 43 equivalents) was added in small quantities over a period of six hours so that the blue colouration (due to the presence of free electrons) was maintained.

Ammonium nitrate (0.4 g) was then added to quench the potassium amide followed by diethyl ether (70 ml). The mixture was allowed to evaporate overnight. The residue was taken up into water and chloroform (40 ml of each) and the layers were then separated. The organic phase was washed once with water, dried (Na$_2$SO$_4$) and evaporated in vacuo to yield a yellow gum (75 mg) which was shown by analytical t.l.c. (alumina) to be a complex mixture containing no 2-phenyl-1,3-benzothiazole or starting material. The n.m.r. spectrum indicated the presence of t-butanol (δ$_H$ 1.25, s), alkene or aromatic protons (δ$_H$ 6.5, m) and aromatic protons (δ$_H$ 7.2, m).

The reaction was repeated using a catalytic quantity of potassium metal (4.6 mg, 0.2 mol %), added in one portion with the other reactants. The mixture was stirred for 3.5 h and then worked-up as before to yield a yellow gum (167 mg), which was shown by analytical t.l.c. (alumina) to contain starting material plus a small amount of the benzothiazole. The n.m.r. spectrum confirmed this analysis. No further investigation was performed.

(d) The preparation of 2-phenyl-1,3-benzothiazole using copper (I) salts

2'-Iodothiobenzanilide (0.1 g, 0.295 mmol) and potassium t-butoxide (66 mg, 0.59 mmol) were stirred magnetically under an atmosphere of nitrogen in DMF (25 ml). Copper (I) iodide (11.2 mg, 0.059 mmol, 0.2 equivalents) was then added and the mixture was stirred and heated at 80-84°C for 40 min. The mixture was cooled, diluted with water (65 ml) and acidified with 2 N HCl (25 ml). The mixture was then extracted with dichloromethane (3 x 40 ml). The dichloromethane extracts were combined, washed with water (X8), dried (MgSO$_4$) and evaporated in vacuo to yield the 2-phenyl-1,3-benzothiazole as pale brown needles (0.11 g, 100%), m.p. 105-114°C (lit., 141 111-113°C). The product was purified by column chromatography (alumina, diethyl ether/pet. ether; 1:9) to yield pure 2-phenyl-1,3-benzothiazole as colourless needles (41 mg, 66%), m.p. 115-117°C.
The experiment was repeated at room temperature. Analytical t.l.c. (alumina) showed the reaction to be complete after 5 min.

The heated reaction was repeated in the presence of inhibitors;

When di-t-butyl nitroxyl (18 mol %) was added to the reaction mixture, work-up after a reaction period of 4 h yielded the benzothiazole as cream-coloured needles (80 mg, 100 %).

A reaction performed in the presence of p-dinitrobenzene (10 mol %) was worked-up after 1.5 h to yield the benzothiazole as pale yellow rosettes (70 mg, 100%).

When the nitrogen atmosphere was replaced by one of oxygen, work-up after 1.5 h yielded the benzothiazole as pale yellow crystals (65 mg, 100%).

The room temperature reaction was repeated using 2-bromothiobenzanilide (0.1 g, 0.342 mmol). The catalyst was copper (I) bromide. The reaction was analysed at regular intervals by t.l.c. (alumina) and was complete after 6 h. Work-up as before gave crude 2-phenyl-1,3-benzothiazole as off-white crystals (63 mg, 88%), m.p. 104-114°C.

Inhibition studies on the above reaction were performed;

A reaction performed in the presence of di-t-butyl nitroxyl (50 mol %) for 5 h at room temperature yielded the benzothiazole as colourless crystals (63 mg, 88%), m.p. 108-113°C.

When p-dinitrobenzene (20 mol %) was used as the inhibitor, work-up after 5 h yielded the product as pale yellow crystals (74 mg, 100 %), m.p. 100-107°C.

When the nitrogen atmosphere was replaced by one of oxygen, work-up after a reaction period of 4 h yielded the benzothiazole as yellow crystals (70 mg, 100 %), m.p. 108-113°C.
(e) The preparation of 2-phenyl-1,3-benzothiazole using copper powder.

Reaction of 2'-bromothiobenzanilide (0.1 g, 0.342 mmol) with 1 equivalent of copper powder and DMF at 80-90°C for 1.5 h as described earlier (Section 4, e) yielded 2-phenyl-1,3-benzothiazole as colourless crystals (82 mg, 100%), m.p. 114-117°C; i.r. spectrum identical to that in the literature. The n.m.r. spectrum was identical to that of a previously prepared sample (Section 5, b, ii).

(f) The preparation of 2-phenyl-1,3-benzothiazole by an anomalous reaction.

2'-Iodothiobenzanilide (0.1 g, 0.295 mmol) was dissolved in reagent grade chloroform (120 ml) and left to stand in the laboratory for 5 days. After this time the colour had changed from yellow to red. The solvent was evaporated in vacuo to yield a red oil (0.16 g) which was shown by analytical t.l.c. (alumina) to be the benzothiazole plus some impurity.

6. The Preparation of 2-Methyl-1,3-Benzoxazole [24]

(a) By an $S_{RN1}$ reaction.

2'-Iodoacetanilide (0.1 g, 0.383 mmol), potassium $t$-butoxide (0.77 g, 6.89 mmol, 18 equivalents), dry acetone (0.18 g, 3.06 mmol, 8 equivalents) and DMSO (15 ml) were irradiated for 6 h and worked-up as described earlier (Section 5, b, ii) to yield an orange-brown oil (68 mg) which was shown by t.l.c. and i.r. and n.m.r. spectra to be a mixture of starting material and acetanilide.

(b) The attempted preparation of 2-methyl-1!3-benzoxazole via copper (I) salt catalysis.

2-Iodoacetanilide (0.1 g, 0.383 mmol), potassium $t$-butoxide (0.17 g, 1.5 mmol, 4 equivalents), copper (I) iodide (73 mg, 0.383 mmol) and DMF (15 ml) were magnetically stirred at 70-80°C for 8 h under N$_2$ and worked-up as described previously (Section 5, d) to yield only unreacted starting material (60% recovery).
When the reaction was repeated using 0.2 equivalents of copper (I) iodide, a reaction temperature of 85-87°C and a reaction period of 5.5 h, work-up yielded a crude product (89 mg) which was purified by preparative t.l.c. (alumina, ethyl acetate/diethyl ether; 1:1) to yield unreacted starting material (28% recovery) and two minor products which could not be identified.

(c) The attempted preparation of 2-methyl-1,3-benzoxazole using copper powder
2-Iodoacetanilide (0.1 g, 0.383 mmol), copper powder (24 mg, 0.383 mmol) and DMF (15 ml) were reacted at 80-90°C for 7 h as described earlier (Section 4, e) to yield unreacted starting material (98% recovery), m.p. 109-112°C.

7. The Preparation of 2-Methyl-1,3-benzothiazole [22]

(a) By an S_{RN1} reaction

(i) 2-Iodothioacetanilide (0.1 g, 0.361 mmol), potassium t-butoxide (0.9 g, 8.12 mmol, 22 equivalents) and DMSO (15 ml) were irradiated under nitrogen for 6.5 h. The reaction mixture was diluted with water (65 ml), acidified with 2N HCl (20 ml) and extracted with dichloromethane (3 x 50 ml). The organic extracts were combined, washed with water (x8), dried (Na_2SO_4) and evaporated in vacuo to yield a red oil (35 mg) which was subjected to preparative t.l.c. (alumina, diethyl ether/pet. ether; 1:1) to yield unreacted starting material (19 mg, 19% recovery) and a product (5 mg) which was identified solely by analytical t.l.c. (alumina) as 2-methyl-1,3-benzothiazole (9%).

(ii) The reaction was repeated using oil-free sodium hydride (0.17 g, 7.22 mmol, 20 equivalents) as the base. The irradiation period was 8.75 h. Work-up as described above yielded an orange oil (54 mg) which was shown by t.l.c. and i.r. and n.m.r. spectra to be a mixture of the benzothiazole and unreacted starting material.
(iii) Reaction (i) was repeated in the presence of dry acetone (0.17 g, 2.9 mmol, 8 equivalents) to yield the 2-methyl-1,3-benzothiazole as a red oil (61 mg, 100%) which was purified by preparative t.l.c. (alumina, diethyl ether/pet. ether; 1:1) to yield the product as a yellow oil (17 mg, 32%); i.r. and n.m.r. spectra identical to those quoted in the literature.136,137

(iv) Reaction (iii) was repeated using oil-free sodium hydride (0.17 g, 7.22 mmol, 20 equivalents). The hydride was first dissolved in the DMSO at 60°C over a period of 2 h to generate dimesyl sodium. Crude 2-methyl-1,3-benzothiazole was isolated as a red oil (64 mg, 100%).

(b) The preparation of 2-methyl-1,3-benzothiazole by copper (I) catalysis
Copper (I) iodide (69 mg, 0.361 mmol) and potassium t-butoxide (0.202 g, 1.8 mmol, 5 equivalents) were stirred magnetically under an atmosphere of dry nitrogen in DMF (15 ml) for 5 min whereupon a dark-brown mixture formed.

2-Iodothioacetanilide (0.1 g, 0.361 mmol) was then added and the mixture was stirred for a further 1.25 h at 85°C.

The mixture was diluted with water (65 ml) and extracted with dichloromethane (3 x 50 ml). The organic extracts were washed with water (x8), dried (MgSO₄) and evaporated in vacuo to yield the crude benzothiazole as an orange oil (72 mg, 100%). This was purified by column chromatography (alumina, diethyl ether/pet. ether; 1:2) to yield 2-methyl-1,3-benzothiazole as a colourless oil (34 mg, 63%) whose i.r. and n.m.r. spectra were identical to those quoted in the literature.136,137

The reaction was repeated but using copper (I) bromide instead of the iodide. Work-up afforded a quantitative crude yield of the benzothiazole which was purified by column chromatography as described above to yield the product as a colourless oil (50 mg, 94%).
(c) The preparation of 2-methyl-1,3-benzothiazole using copper powder
2-Iodothiacetanilide (0.1 g, 0.361 mmol), copper powder (1 equivalent) and DMF (15 ml) were stirred under nitrogen at 80-90°C for 1 h and then worked up as described above to yield the crude benzothiazole as a green-yellow oil (91 mg, 100%). Column chromatography as described above (Section 7,b) yielded the pure product as a colourless oil (39 mg, 72%) whose i.r. and n.m.r. spectra were identical to those quoted in the literature.

8. The Attempted Deuteriation of 2-Iodothiacetanilide
Dimsyl sodium was prepared from sodium hydride and DMSO as described earlier (Section 7,a,iv).

2-Iodothioacetanilide (0.1 g, 0.361 mmol) was added to dimsyl sodium and the reaction mixture was quickly swirled and then quenched with deuterium oxide (3 ml, large excess). The mixture was worked up as before to yield a yellow powder (0.13 g) which was purified by preparative t.l.c. (alumina, diethyl ether/pet. ether; 1:1) to afford a yellow powder (0.1 g), m.p. 51-60°C. The n.m.r., i.r., and mass spectral data were not sufficiently accurate to allow a definite conclusion as to whether or not the deuterated product had been formed.

The reaction was repeated with the same result being obtained.

9. The Preparation of N-(3,4-Dimethoxybenzyl)acetamide [53]
3,4-Dimethoxybenzylamine (5.0 g, 29.9 mmol), acetic anhydride (3.15 g, 30.9 mmol) and glacial acetic acid (2.87 g, 47.8 mmol) were refluxed for 1.75 h. The hot reaction mixture was poured into cold water (75 ml) and then extracted with dichloromethane (3 x 40 ml). The organic extracts were washed with water (x2) and dried (MgSO4). The solvent was evaporated in vacuo to yield pale yellow crystals (5.28 g, 84%). The product was recrystallised from ethyl acetate/pet. ether to afford the amide [53] as off-white crystals (4.12 g, 66%), m.p. 88-91°C (Found: C, 63.2; H, 7.5; N, 6.6. C11H15N03 requires C, 63.15; H, 7.25; N, 6.7%); νmax. 3295, 1665, 1520, 815, 910 cm⁻¹; δH (CDCl3) 1.95 (3 H, s, CH₃CO), 3.73 (6 H, s, 3,4-MeO), 4.22 (2 H, d, J 6 Hz, CH₂NH).
10. The Preparation of N-(2-Iodo-4,5-dimethoxybenzyl)acetamide [45]

(a) With antimony pentachloride/iodine monochloride

Antimony pentachloride (5.711 g, 2.44 ml, 19.1 mmol) was added to a dry reaction flask containing dry, distilled chloroform (50 ml). The mixture was stirred mechanically and iodine monochloride (3.1 g, 0.975 ml, 19.1 mmol) was added followed by the amide [53] (4.0 g, 19.1 mmol). The reaction mixture was refluxed and stirred for 5.0 h then cooled and diluted with water (50 ml) whereupon a cream-coloured precipitate formed. The mixture was basified with 10% NaOH and filtered. The filter cake was washed thoroughly with chloroform and water. The combined filtrates were separated and the organic phase was washed with sodium metabisulphite (x2) and water (x2) and dried (MgSO₄). The solvent was evaporated in vacuo to yield the crude iodo-compound as a red-brown, viscous oil (5.28 g, 32%). Purification by column chromatography (alumina, diethyl ether) yielded the amide [45] as pale yellow crystals (2.28 g, 36%), m.p. 174-176.5°C (Found: C, 39.8; H, 3.8; N, 4.1. C₁₁H₁₄INO₂ requires C, 39.4; H, 4.2; N, 4.2%); νmax. 3920, 1640, 1508, 860 cm⁻¹; δH (CDCl₃) 1.94 (3 H, s, CH₃CO), 3.76 (6 H, s, 4,5-MeO), 4.34 (2 H, d, J 6 Hz, ~NH), 6.18 (1 H, br.s, NHCO), 6.8 (1 H, s, 6-H), 7.07 (1 H, s, 3-H).

(b) With antimony pentachloride/iodine

A solution of the amide (1.764 g, 8.43 mmol), antimony pentachloride (1.26 g, 0.54 ml, 4.215 mmol) and iodine (1.07 g, 4.215 mmol) in dry, distilled chloroform (40 ml) was reacted as described above for 8.5 h to yield, on work-up, a red-brown oil which crystallised on standing (0.9 g, 32%). Column chromatography afforded the iodo-compound as off-white crystals (0.6 g, 21%), m.p. 142-148°C. The i.r. and n.m.r. spectra indicated that some starting material was present as an impurity.

11. The Preparation of N-(3,4-Dimethoxybenzyl)thioacetamide [54]

A solution of the amide [53] (2.8 g, 13.4 mmol) and Lawesson's reagent (3.84 g, 9.38 mmol) in dry toluene (80 ml) was reacted at 75-90°C for 4.25 h as described earlier (Expt. 1,b,ii).
The crude product was obtained as oily, yellow crystals (2.9 g, 96%). Recrystallisation from aqueous ethanol yielded the thioamide [54] as yellow needles (1.7 g, 56%), m.p. 104-107°C (Found: C, 58.3; H, 6.6; N, 6.1. C_{11}H_{15}NO_2S requires C, 58.65; H, 6.7; N, 6.2%); ν_{max.} 3300, 1515, 860 cm\(^{-1}\); δ_H 2.5 (3 H, s, CH\_3CS), 3.77 (6 H, s, 3,4-MeO), 4.63 (2 H, d, J 6 Hz, CH\_2NH), 6.73 (3 H, s, aromatic H), -8.0 (1 H, br.s, NHCS); m/z 225(M\(^{+}\)), 192, 166, 151, 135.

12. The Preparation of N-(2-Iodo-4,5-dimethoxybenzyl)thioacetamide [46]

(a) From N-(2-Iodo-4,5-dimethoxybenzyl)acetamide [45]
A solution of the amide (2.0 g, 5.97 mmol) and Lawesson's reagent (1.71 g, 4.18 mmol) in dry toluene (40 ml) was reacted at 70-80°C for 1.25 h as described previously (Expt. 1, b, ii) to afford the crude product as yellow crystals (2.27 g, 100%). The product was recrystallised from aqueous ethanol to yield the thioamide [46] as yellow crystals (1.49 g, 71%) m.p. 180-184°C (Found: C, 37.9; H, 4.15; N, 4.0; S, 9.2. C\_{11}H\_{14}INO\_2S requires C, 37.6; H, 4.0; N, 4.0; S, 9.1%); ν_{max.} 3290, 1510, 870 cm\(^{-1}\); δ_H (CDCl\_3), 2.52 (3 H, s, CH\_3CS), 3.8 (6 H, s, 4,5-MeO), 4.75 (2 H, d, J 6 Hz, CH\_2NH), 6.9 (1 H, s, C-6), 7.09 (1 H, s, C-3), 7.67 (1 H, br.s, NHCS); m/z 350(M\(^{-}\)), 292, 277, 224, 59.

(b) From N-(3,4-dimethoxybenzyl)thioacetamide [54]
A solution of the thioamide (1.0 g, 4.44 mmol), antimony pentachloride (1.33 g, 0.57 ml, 4.44 mmol), and iodine monochloride (0.721 g, 0.23 ml, 4.44 mmol) in dry, distilled chloroform (40 ml) was reacted for 8 h as described above (Expt. 10) to yield a dark-red gum (0.92 g, 59%). Purification by column chromatography (alumina, diethyl ether) yielded the iodinated thioamide as orange crystals (0.343 g, 22%); t.l.c. and i.r. and n.m.r. spectroscopy revealed that the product contained considerable impurity (not identified).

13. The Preparation of N-(3,4-Dimethoxybenzyl)benzamide [55]
3,4-Dimethoxybenzylamine (1.33 g, 7.95 mmol), benzoyl chloride (1.3 g, 9.14 mmol) and 10% NaOH (25 ml) were reacted under Schotten-Baumann acylation conditions as described previously (Expt. 1,a) to afford the crude product as off-white crystals. Recrystallisation from ethyl
acetate yielded the amide [55] as colourless needles (1.45 g, 67%), m.p. 101-103°C (Found: C, 70.3; H, 6.1; N, 5.1. C\textsubscript{16}H\textsubscript{17}NO\textsubscript{3} requires C, 70.8; H, 6.3; N, 5.2%); \(\nu_{\text{max}}\) 3350, 1525, 870, 820 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\)) 3.78 (6 H, s, 3,4-MeO), 4.52 (2 H, d, J 6 Hz, CH\(_2\)NH), 6.78 (4 H, s on br.s, aromatic H plus NHCO), 7.15-7.52 (3 H, m, aromatic H), 7.61-7.88 (2 H, m, aromatic H); m/z 271 (M+), 166, 151, 135, 122, 105, 77.

14. The Preparation of N-(2-Iodo-4,5-dimethoxybenzyl)benzamide [47]
A solution of the amide [55] (1.0 g, 3.69 mmol), antimony pentachloride (1.1 g, 0.47 ml, 3.69 mmol) and iodine monochloride (0.598 g, 0.19 ml, 3.69 mmol) in dry, distilled chloroform (25 ml) were reacted for 6 h as described earlier (Expt. 10.a) to yield a red-brown oil (1.31 g, 89%). Purification by column chromatography yielded the amide [47] as buff-coloured crystals (0.95 g, 65%), m.p. 141-143°C (Found: C, 48.3; H, 4.15; N, 3.7. C\textsubscript{16}H\textsubscript{16}INO\textsubscript{3} requires C, 48.4; H, 4.05; N, 5.5%); \(\nu_{\text{max}}\) 3310, 1645, 1510, 870, 745, 705 cm\(^{-1}\); \(\delta_H\) 3.7 (6 H, 2 x s, 4,5-MeO), 4.41 (2 H, m, CH\(_2\)NH), 6.71 (1 H, s, 6-H), 6.97 (1 H, s, 3-H), 7.0-7.4 (4 H, m, C\(_6\)H\(_5\) plus NHCO), 7.41-7.83 (2 H, m, C\(_6\)H\(_5\)); m/z 397(M+), 396, 270, 105, 77.

15. The Preparation of N-(2-Iodo-4,5-dimethoxybenzyl)thiobenzamide [48]
A solution of the amide [47] (0.63 g, 1.59 mmol) and Lawesson's reagent (0.46 g, 1.11 mmol) in dry toluene (25 ml) was reacted for 1.85 h at 80°C as described previously (Expt. 1,b,ii) to yield the product as yellow crystals (0.65 g, 99%), m.p. 155-170°C. Recrystallisation from aqueous ethanol afforded the thioamide [48] yellow crystals (0.51 g, 78%), m.p. 175-180°C (Found: C, 46.5; H, 3.9; N, 3.4; S, 7.75. C\textsubscript{16}H\textsubscript{16}NO\textsubscript{2}S requires C, 46.6; H, 4.0; N, 3.2; S, 7.5%); \(\nu_{\text{max}}\) 3285, 1505, 870, 740 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\)) 3.8 (6 H, s, 4,5-MeO), 4.91 (2 H, d, J 6 Hz, CH\(_2\)NH), 6.98 (1 H, s, 6-H), 7.13 (1 H, s, 3-H), 7.15-7.42 (3 H, m, C\(_6\)H\(_5\)), 7.5-7.85 (3 H, m, C\(_6\)H\(_5\) plus NHCS); m/z 413(M+), 412, 286, 277, 121, 77, 76.
16. **The Preparation of N-(3,4-Dimethoxybenzyl)thiobenzamide [56]**

A solution of the amide [55] (1.0 g, 3.68 mmol) and Lawesson's reagent (1.06 g, 2.58 mmol) in dry toluene (25 ml) was reacted at 70-80°C for 1.3 h as described previously (Expt. 1, b, ii) to yield the thioamide [56] as yellow crystals (1.01 g, 96%), m.p. 158-160°C (Found: C, 66.65; H, 5.8; N, 4.8. C16H17NO2S requires C, 66.9; H, 6.0; N, 4.9%); \( \nu_{\text{max}} \) 3300, 1595, 850, 775, 710 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 3.78 (6 H, s, 3,4-MeO), 4.8 (2 H, d, J 5 Hz, \( \text{CH}_2 \text{NH} \)), 6.77 (3 H, m, aromatic H), 7.17-8.0 (6 H, m, aromatic and NHCS); m/z 287(M\(^+\)), 166, 151, 121, 77, 76.

17. **The Attempted Cyclisation of N-(2-Iodo-4,5-dimethoxybenzyl)thioacetamide [46]**

(a) **By a non-entrained S\(_{\text{RN1}}\) reaction**

A solution of the thioamide (0.1 g, 0.285 mmol) and potassium \( \text{t-butoxide} \) (0.64 g, 5.7 mmol) in dry, distilled DMSO (15 ml) was irradiated for 23 h as described previously (Expt. 5, b, i; the reaction mixture was acidified with 2N HCl prior to extraction) to yield a crude, red-brown gum (0.113 g). Column chromatography of the gum (alumina, diethyl ether) yielded the reduction product [54] (35 mg, 55%) as the only identifiable compound; identified by comparison of the spectral data (i.r. and n.m.r.) with those of the authentic sample prepared above (Expt. 11). Two other fractions (13, 5 mg) were also obtained but could not be identified.

(b) **By an entrained S\(_{\text{RN1}}\) reaction**

The reaction of the thioamide, potassium \( \text{t-butoxide} \) and DMSO (quantities as above) and acetone (0.132 g, 2.3 mmol) as described previously (Expt. 7, a, i) resulted in the isolation of crude gums which were subjected to column chromatography. In none of the reactions was any identifiable product obtained.

The same result was obtained when diethyl phosphite (0.118 g, 0.855 mmol) was used in place of acetone.

(c) **Using copper (I) iodide**

A solution of the thioamide (0.1 g, 0.285 mmol), sodium hydride (140 mg, 5.7 mmol) and copper (I) iodide (10.8 mg, 0.057 mmol) in dry,
distilled DMF (15 ml) was reacted at 70-80°C for 23.5 h as described previously (Expt. 4,c) to yield a light-brown powder (44 mg). Recrystallisation from ethanol yielded a brown powder (13 mg), m.p. 188-192°C; $\nu_{\text{max}}$ 3300, 1660, 1595, 1505, 735 cm$^{-1}$; $\delta_H$ (CDCl$_3$) 1.86 (3 H, s), 3.67 (2 H, s), 3.78 (4 H, s), 4.18, 4.27 (2 H, 2 x s or d), 6.2 (1 H, b.r.s), 6.72, 6.77 (2 H, 2 x s or d); m/z 241, 223, 208, 198, 195, 182, 167, 152, 137, 109, 95, 82, 75.

The reaction was repeated using potassium t-butoxide (0.64 g, 5.7 mmol) and copper (I) iodide (54 mg, 0.285 mmol). Column chromatography (alumina, diethyl ether) of the crude product (46 mg) yielded yellow gums (9 and 8 mg) which could not be identified.

(d) Using copper powder
A solution of the thioamide (0.1 g, 0.285 mmol) and copper powder (18.1 g, 0.285 mmol) in dry, distilled DMF (15 ml) was reacted at 90-100°C for 6.6 h as described previously (Expt. 4,e) to yield pale brown crystals (38 mg), m.p. 200-204°C (Found: C, 53.55; H, 5.8; N, 5.5; S, 12.05%).

The m.s. and the i.r. and n.m.r. spectral data were identical to those described in part (c) above.

18. The Cyclisation of N-(2-Iodo-4,5-dimethoxybenzyl)thiobenzamide [48]
(a) By an entrained $S_{RN1}$ reaction
A solution of the thioamide (0.1 g, 0.242 mmol), diethyl phosphite (0.17 g, 1.21 mmol) and potassium t-butoxide (0.272 g, 2.42 mmol) in dry DMF (15 ml) was reacted for 8 h as described earlier (Expt. 7,a,i) to afford an orange gum (0.125 g) which was shown by analytical t.l.c. and i.r. and n.m.r. spectroscopy to be a mixture of starting material and reduction product [56].

When the reaction was repeated using dry acetone (0.112 g, 1.94 mmol) in place of diethyl phosphite a red-brown gum (0.12 g, 100% recovery of starting material) was obtained after 7.25 h irradiation.

(b) Using copper (I) iodide
A solution of the thioamide (0.1 g, 0.242 mmol), copper (I) iodide (46.1 mg, 0.242 mmol) and potassium t-butoxide (0.136 g, 1.21 mmol) in dry DMF (15 ml) was reacted at 75°C for 4 h as described earlier...
(Expt. 7,b) to yield a yellow gum (95 mg). Purification by column chromatography (alumina, diethyl ether/pet. ether 3:2) yielded 2-phenyl-6,7-dimethoxy-4H-1,3-benzothiazine [52] as slightly oily, colourless crystals (33 mg, 48%), m.p. 93-97°C (lit., 88 99-100°C); v_max 2820, 1605, 1445, 870, 776, 703 cm⁻¹; δ_H (CDCl₃) 3.72 (6 H, s, 6,7-MeO), 4.54 (2 H, s, Qit=C), 6.63 (2 H, s, 5,8-H), 7.21 (3 H, m, C₆H₅), 7.81 (2 H, m, C₆H₅); m/z 286, 285(M⁺), 182, 167, 77, 76.

(c) Using copper powder
A solution of the thioamide (0.1 g, 0.242 mmol) and copper powder (15.4 mg, 0.242 mmol) in dry DMF (15 ml) was reacted at 90-100°C for 7.2 h as described previously (Expt. 4,e) to yield a green-yellow gum (94 mg). Purification by column chromatography (alumina, diethyl ether/pet. ether, 8:2) yielded the benzothiazine [52] as a colourless gum (50 mg, 43%) and N-(2-iodo-4,5-dimethoxy-benzyl)benzamide [47] as a pale-yellow gum (10 mg, 10%), identified by comparison of the m.s. and i.r. and n.m.r. data with those of the authentic sample.

19. The Attempted Cyclisation of N-(2-Iodo-4,5-dimethoxybenzyl)acetamide [45]

(a) By an entrained S_RN1 reaction
A solution of the amide (0.1 g, 0.298 mmol), sodium hydride (0.143 g, 5.96 mmol, oil-free) and dry acetone (0.139 g, 2.38 mmol) in dry DMSO (15 ml) was reacted for 19 h as described previously (Expt. 7,a,i) except that the sodium hydride and DMSO were warmed together initially for 2 hours to generate dimysl sodium. Work-up yielded a red-brown gum (65 mg). Column chromatography of the crude product (alumina, diethyl ether) afforded pale-brown crystals of recovered starting material (26 mg, 26%) and a yellow gum identified by t.l.c. and n.m.r. spectroscopy as the reduction product [53] (12 mg, 19%).

(b) Using copper (I) iodide
A solution of the amide (0.1 g, 0.298 mmol), copper (I) iodide (56.7 mg, 0.298 mmol) and potassium t-butoxide (0.67 g, 5.96 mmol) in dry DMF (15 ml) was reacted at 70-80°C for 20.5 h as described previously (Expt. 4,c) to yield unreacted starting material (98 mg, 98% recovery).
The reaction was repeated (for 7-8 h) using sodium hydride (71.5 mg, 2.98 mmol, oil-free). Unidentifiable gums were obtained.

(c) Using copper powder
A solution of the amide (0.1 g, 0.298 mmol) and copper powder (18.9 mg, 0.298 mmol) in dry DMF was reacted at 77°C for 4 h as described previously (Expt. 4,e) to yield unreacted starting material as off-white crystals (69 mg, 69% recovery).

20. The Attempted Cyclisation of N-(2-Iodo-4,5-dimethoxybenzyl)benzamide [47]

(a) By an entrained $S_{RN1}$ reaction
A solution of the amide (50 mg, 0.126 mmol), diethyl phosphite (17.4 mg, 0.126 mmol) and potassium $t$-butoxide (71 mg, 0.63 mmol) in dry DMSO (15 ml) was reacted for 29 h as described previously (Expt. 5,b,ii) to yield a pale yellow gum (52 mg). Column chromatography (alumina, diethyl ether/ethyl acetate, 10:1) of the crude product yielded unreacted starting material (23 mg, 46% recovery) and the reduction product [55], (14 mg, 41%).

(b) Using copper(I) iodide
A solution of the amide (50 mg, 0.126 mmol), copper(I) iodide (23.9 mg, 0.126 mmol) and potassium $t$-butoxide (71 mg, 0.63 mmol) in dry DMF (15 ml) was reacted at 80-85°C for 8.5 h as described previously (Expt. 4,c but no acidification step). Unreacted starting material was obtained as an orange gum (50 mg, 100% recovery).

(c) Using copper powder
A solution of the amide (50 mg, 0.126 mmol), copper(I) iodide (23.9 mg, 0.126 mmol) and potassium $t$-butoxide (71 mg, 0.63 mmol) in dry DMF (15 ml) was reacted at 80-85°C for 8.5 h as described previously (Expt. 4,c, but no acidification step). Unreacted starting material was obtained as an orange gum (50 mg, 100% recovery).
21. The Preparation of 2-Iodobenzyl bromide

(a) Using N-bromosuccinimide
2-Iodotoluene (15 g, 68.8 mmol), freshly-recrystallised N-bromosuccinimide (12.24 g, 68.8 mmol), benzoyl peroxide (0.25 g, 1 mmol) and dry carbon tetrachloride (40 ml) were refluxed and irradiated with two 150 W tungsten lamps for 8.5 h. The reaction mixture was cooled and filtered. The filter cake was thoroughly washed with hot carbon tetrachloride. The combined filtrates were washed with sodium metabisulphite, sodium bicarbonate and water (x2) and dried (MgSO₄). The solvent was evaporated in vacuo to yield an orange oil (20 g). Distillation under reduced pressure (2 mm Hg) yielded unreacted starting material as a pale orange oil (4.3 g, 35% recovery), b.p. 40-100°C and 2-iodobenzyl bromide as a pale yellow oil (b.p. 104-110°C) which formed pale-pink crystals on standing (10.5 g, 51%), m.p. 48-53°C (lit., 142-55.5°C); ν max 1565, 1460, 1440, 760 cm⁻¹; δ H (CCl₄) 4.46 (2 H, s, CH₂Br), 6.6-7.86 (4 H, m, aromatic H).

(b) Using bromine
2-Iodotoluene (8.16 g, 37.4 mmol), bromine (11.95 g, 74.8 mmol) and dry carbon tetrachloride (40 ml) were refluxed under an atmosphere of nitrogen and in the presence of irradiation as described above for 30 h. The mixture was worked-up as described in Part (a) to yield a pale yellow oil (10.2 g). Distillation under reduced pressure (1.4 mm Hg) yielded unreacted starting material as a pale-red oil (1.2 g, 15% recovery), b.p. 40-80°C and the product as a pale-yellow oil (b.p. 98-105°C) which crystallised on standing (6.4 g, 58%).

22. The Preparation of 2-Iodobenzylamine
Hexamine (1.77 g, 12.6 mmol) was refluxed in dry, distilled chloroform (45 ml). 2-Iodobenzyl bromide (3.4 g, 11.45 mmol) was added dropwise to the refluxing mixture over a period of 0.5 h. A colourless precipitate was formed after 10 minutes. The reaction mixture was refluxed for a further 4.75 h and then cooled. The hexamine adduct was collected by filtration (colourless crystals; 4.06 g, 81%), m.p. 158-163°C.
The adduct was refluxed for 5 h in a mixture of ethanol (20 ml), water (4 ml) and conc. HCl (10 ml). The ethanol was then removed by evaporation in vacuo.

The semi-crystalline residue was basified to pH 9 with 10% NaOH whereupon a thick, pale-yellow precipitate formed. The mixture was extracted with diethyl ether (3 x 50 ml). The ether extracts were washed with water (x2) and extracted with 2N HCl (3 x 50 ml). The aqueous extracts were basified to pH 14 with 10% NaOH and extracted with diethyl ether (4 x 50 ml). The ether extracts were washed with water (x2) and dried (MgSO₄). The solvent was evaporated in vacuo to yield the crude amine as a pale yellow oil (1.57 g, 59%). Kugelruhr distillation under reduced pressure (1.5 mm Hg) yielded the amine as a pale-yellow oil (0.66 g, 25%), b.p. 92°C; νₘₐₓ 3385, 3290, 1550, 1270, 750 cm⁻¹; δₓH (CDCl₃) 1.45 (2 H, br.s, NH₂), 3.76 (2 H, d, J 4 Hz, CH₂NH₂), 6.64-7.87 (4 H, m, aromatic H). The product was authenticated by the preparation of the benzoyl derivative (see Expt. 23 below).

The reaction was repeated and a higher yield (36%) of the amine was obtained. The purification was achieved by column chromatography (alumina, diethyl ether/pet. ether). A lower yield (21%) of the amine was obtained.

23. The Preparation of N-(2-Iodobenzyl)benzamide [59]

2-Iodobenzylamine (0.52 g, 2.23 mmol), benzoyl chloride (0.36 g, 2.56 mmol) and 10% NaOH (7 ml) were reacted as described previously (Expt. 1,a) to afford the crude amide which was recrystallised from ethyl acetate as colourless crystals (0.3 g, 40%), m.p. 157-159°C (lit., 144°C); νₘₐₓ 3260, 1635, 1535, δₓH (CDCl₃) 4.6 (2 H, d, J 6 Hz, CH₂NH), 6.35-7.92 (10 H, m, aromatic and NHCO); m/z 337(M⁺), 210, 105, 90, 77, 28.

24. The Preparation of N-(2-Iodobenzyl)thiobenzamide [60]

A solution of the amide [59] (0.7 g, 2.08 mmol) and Lawesson's reagent (0.6 g, 1.46 mmol) in dry toluene (20 ml) was reacted at 70-80°C for 1.25 h as described earlier (Expt. 1,b,ii) to yield the crude product
as yellow, oily crystals (0.88 g). Purification by column chromatography (alumina, diethyl ether/pet. ether) afforded the thioamide [60] as yellow crystals (0.67 g, 91%), m.p. 97-100°C (Found: C, 47.5; H, 3.35; N, 3.9; S, 8.9. C<sub>14</sub>H<sub>12</sub>NINS requires C, 47.6; H, 3.4; N, 3.95; S, 9.1%); \( \nu_{\text{max.}} \) 3320, 1520, 770, 745, 690 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 4.92 (2 H, d, J 5 Hz, CH\(_2\)NH), 6.73-8.03 (10 H, m, aromatic and NHCS); m/z 354, 353(M\(^+\)), 226, 217, 121, 90, 77, 76.

In a repeat experiment, purification of the crude product by recrystallisation from carbon tetrachloride afforded a lower yield (54%) of purer material (m.p. 100-103°C).

25. The Preparation of \( \text{N-Benzy1 benzamide} \) [61]
Benzylation (2.0 g, 18.7 mmol), benzoyl chloride (3.02 g, 21.5 mmol) and 10% NaOH (20 ml) were reacted as described previously (Expt. 1,a) to yield the crude amide which was recrystallised from ethyl acetate to afford colourless crystals (2.41 g, 61%), m.p. 106-108°C (lit., \( 145 \) 105.0°C); \( \nu_{\text{max.}} \) 3300, 1643, 1610 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 4.4 (2 H, d, J 5 Hz, CH\(_2\)NH), 6.65 (1 H, br.s, NHCO), 6.92-7.87 (10 H, m, aromatic H).

26. The Preparation of \( \text{N-Benzy1 thiobenzamid e} \) [62]
A solution of N-benzy1 benzamide (0.7 g, 3.31 mmol) and Lawesson's reagent (0.95 g, 2.32 mmol) in dry toluene (20 ml) was reacted at 80-90°C for 1.25 h as described previously (Expt. 1,b,ii) to yield the thioamide as pale yellow crystals (0.77 g, 100%), m.p. 87-89°C (lit., \( 146 \) 88°C); \( \nu_{\text{max.}} \) 3300, 1510, 740, 715 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 4.9 (2 H, d, J 5 Hz, CH\(_2\)NH), 7.03-7.92 (11 H, m, aromatic and NHCS).

27. The Cyclisation of \( \text{N-(2-Iodobenzy1)thiobenzamide} \) [60]
(a) By an entrained \( \text{S}_{\text{RN}}^1 \) reaction
A solution of the thioamide (0.1 g, 0.28 mmol), potassium \( \text{t-butoxide} \) (0.95 g, 8.49 mmol) and dry acetone (0.131 g, 2.26 mmol) in dry DMSO was reacted for 23 h as described earlier (Expt. 5,b,ii) to yield a pungent, orange-brown oil (0.14 g) which solidified on standing.
Column chromatography (alumina, diethyl ether/pet. ether) yielded two fractions (4 mg of each). Analytical t.l.c. (alumina) showed that neither product was 2-phenyl-4H-1,3-benzothiazine.

The reaction was repeated using diethyl phosphite (19.6 mg, 0.14 mmol)
in place of acetone. A similar result was obtained.

(b) By an unentrained, heated SRN1 reaction

A solution of the thioamide (81 mg, 0.23 mmol) and potassium t-butoxide (0.13 g, 1.15 mmol) in dry DMSO (15 ml) was irradiated under an atmosphere of dry nitrogen at 70-80°C for 8.25 h. Work-up (as above) yielded an orange-brown gum (37 mg). N.m.r. analysis using phthalide (1 mmol) as an internal standard indicated that recovered starting material (24%) and 2-phenyl-4H-1,3-benzothiazine [64],(8%) were present.

(c) Using copper (I) iodide: Standard Reaction A

(i) A solution of the thioamide (0.1 g, 0.283 mmol), copper (I) iodide (53.9 mg, 0.283 mmol) and potassium t-butoxide (0.159 g, 1.42 mmol) in dry DMF (15 ml) was reacted at 70-80°C for 2.75 h as described previously (Expt. 7,b) to yield the crude benzothiazine as a pale yellow oil (0.13 g). Purification by column chromatography (alumina, diethyl ether/pet. ether, 1:9) yielded a pale yellow oil (50 mg, 78%); \( \nu_{\text{max}} \) 1610, 1575, 1430, 780, 765, 685 cm\(^{-1} \); \( \delta_{\text{H}} \) (CCl\(_4\)) 4.74 (2 H, s, \( \text{CH}_2\text{N} \)), 7.13-7.58 (7 H, m, aromatic H), 7.73-8.17 (2 H, m, aromatic H); m/z 226, 225(M+), 122, 103, 89, 77, 76.

A picrate was prepared and was recrystallised from n-propanol as yellow crystals, m.p. 150-153°C (lit., 147°C).

(ii) The experiment was repeated using a catalytic quantity of copper (I) iodide (10.8 mg, 5.66 \( \times 10^{-5} \) mol). Work-up and purification as described above yielded the benzothiazine (25 mg, 39%) and an unidentified red-brown oil (9 mg).

(iii) Reaction (i) was repeated in the presence of p-dinitrobenzene (9.5 mg, 5.66 \( \times 10^{-5} \) mol, 0.2 equivalents). The pure benzothiazine was obtained as a pale yellow oil (48 mg, 75%).

(iv) Standard Reaction B Reaction (i) was repeated but with the order of addition of reagents as follows:- thioamide and butoxide followed, after 5 min stirring, by copper (I) iodide. The 2-phenyl-4H-1,3-benzothiazine was obtained in 61% yield.
(v) Reaction (iv) was repeated in the presence of p-dinitrobenzene (0.2 equivalents). The yields of the benzothiazine obtained from two reactions were 39 and 0%. No starting material was recovered.

(vi) Reaction (iv) was repeated using di-t-butyl nitroxide (4.9 mg, 0.028 mmol, 0.1 equivalents) in place of p-DNB. The benzothiazine was obtained in yields of 34 and 14%.

(d) Using copper powder
(i) A solution of the thioamide (0.1 g, 0.283 mmol) and copper powder (18 mg, 0.283 mmol) in dry DMF (15 ml) was reacted at 90-100°C for 1.5 h as described earlier (Expt. 4,e) to yield a pale yellow gum (95 mg). Purification by column chromatography (alumina, diethyl ether/pet. ether, 2:9) yielded the benzothiazine as a colourless oil (57 mg, 89%).

(ii) Reaction (i) was repeated using a catalytic quantity of copper powder (3.6 mg, 5.66 x 10^{-5} mol, 0.2 equivalents) and a reaction period of 7 h. The crude product (0.11 g) was subjected to column chromatography (as above but 3:8). Unreacted starting material was recovered (27 mg, 27%) and the benzothiazine was obtained as a pale yellow oil (43 mg, 67%).

(iii) Reaction (i) was repeated in the presence of p-dinitrobenzene (9.5 mg, 5.66 x 10^{-5} mol, 0.2 equivalents). Column chromatography of the crude (84 mg) yielded the benzothiazine as a pale orange oil (35 mg, 55%).

28. Attempted Cyclisations of N-(2-Iodobenzyl)benzamide [59]
(a) By an entrained S_{RN1} reaction
A solution of the amide (0.1 g, 0.297 mmol), diethyl phosphite (20.5 mg, 0.148 mmol) and potassium t-butoxide (0.33 g, 2.97 mmol) in dry DMSO (15 ml) was reacted for 8.5 h as described previously (Expt. 5,b,ii) to yield a crude gum (92 mg). Column chromatography (alumina, diethyl ether/pet. ether, 6:4) yielded unreacted starting material (6 mg, 6%) and the reduction product [61] (10 mg, 16%).
(b) **Using copper (I) iodide**
A solution of the amide (0.1 g, 0.296 mmol), copper (I) iodide (56.5 mg, 0.296 mmol) and potassium t-butoxide (0.166 g, 1.48 mmol) in dry DMF (15 ml) was reacted at 80°C for 9 h as described previously (Expt. 7,b). The crude product was shown by analytical t.l.c. and i.r. and n.m.r. spectroscopy to be unreacted starting material (0.11 g, 100% recovery). The reaction was repeated at reflux. The crude product (89 mg) was shown by analytical t.l.c. to be a mixture of starting material and reduction product. Column chromatography failed to separate the products.

(c) **Using copper powder**
A solution of the amide (0.1 g, 0.297 mmol) and copper powder (18.8 mg, 0.297 mmol) in dry DMF (15 ml) was reacted at 90-105°C for 7.5 h as described previously (Expt. 4,e) to afford unreacted starting material as colourless crystals (87 mg, 87% recovery), m.p. 150-156°C.

29. **The Preparation of N-(2-Bromobenzoyl)-N'-phenylthiourea [68]**
2-Bromobenzoic acid (25 g, 0.124 mol) and thionyl chloride (59 g, 0.496 mol) were refluxed for 3 h. The excess thionyl chloride was removed by distillation to afford the acid chloride as a clear, orange oil (27 g, 99%).

Ammonium thiocyanate (10.3 g, 0.135 mol) and dry acetone (75 ml) were stirred mechanically and the 2-bromobenzoyl chloride (27.0 g, 0.123 mol) was added dropwise over a period of 15 min. The mixture was then refluxed and stirred for 5 min on a steam bath.

Aniline (11.45 g, 0.123 mol) in dry acetone (25 ml) was then added dropwise to the orange reaction mixture at a rate sufficient to maintain reflux.

The resulting mixture was poured with stirring into cold water (500 ml) whereupon an orange precipitate formed. The product was collected by filtration and washed thoroughly with water. After drying, the product was obtained as orange crystals (37.8 g, 92%), m.p. 148-151°C. The product was recrystallised from ethanol to yield the thiourea [68] as
orange crystals (27.39 g, 67%), m.p. 154-156°C (Found: C, 49.9; H, 3.3; N, 8.4; S, 9.9. C_{14}H_{11}BrN_2OS requires C, 50.2; H, 3.3; N, 8.4; S, 9.55%): \( \nu_{\text{max}} \) 3160, 1685, 1540, 770, 745, 700 cm^{-1}; \( \delta_H \) (CDCl_3) 7.19-7.79 (9 H, m, aromatic H), 9.14 (1 H, br.s, CONHCS, partially exchangeable), 12.32 (1 H, br.s, CSNHPh, partially exchangeable); m/z 336 and 334(M+), 255, 201/199, 185/183, 157/155, 135, 93, 77.

30. The Preparation of N-(2-Chlorobenzoil)-N'-phenylthiourea [69]
2-Chlorobenzoic acid (20 g, 0.128 mol) was reacted as described above to yield the crude thiourea as orange crystals (41.52 g, 100%), m.p. 135-140°C.

Recrystallisation from ethanol yielded the thiourea [69] as orange needles (17.12 g, 46%), m.p. 154.5-156.5°C (Found: C, 56.5; H, 3.7; N, 10.4; Cl, 12.1. C_{14}H_{11}ClN_2OS requires C, 57.85; H, 3.8; N, 9.65; Cl, 12.20%); \( \nu_{\text{max}} \) 3170, 1685, 1545, 770, 748, 705 cm^{-1}; \( \delta_H \) (CDCl_3) 7.0-7.88 (9 H, m, aromatic H), 9.3 (1 H, br.s, CONHCS, exchangeable), 12.4 (1 H, br.s, CSNHPh, exchangeable); m/z 255, 156, 152, 135, 141/139, 93, 77, 76, 75.

31. The Preparation of N-Benzoyl-N'-phenylthiourea [71]
Benzoyl chloride (5.0 g, 35.6 mmol) was reacted as described above to yield the thiourea as fluffy, yellow crystals (8.31 g, 91%), m.p. 143-145°C. Recrystallisation from ethanol yielded the pure product as fluffy pale-yellow crystals (6.29 g, 69%), m.p. 149-150°C (lit., 92 152.5-153°C); \( \nu_{\text{max}} \) 3270, 1675, 1535, 760, 700 cm^{-1}, \( \delta_H \) (CDCl_3) 7.18-7.95 (10 H, m, aromatic H), 9.1 (1 H, br.s, CSNHCO, exchangeable), 12.61 (1 H, br.s, CSNHPh, exchangeable).
32. The Preparation of N-(2-Bromobenzoyl)-N'-methyl-N'-phenylthiourea [79a]

Experiment 29 was repeated using N-methylaniline instead of aniline. The product was obtained as orange-brown crystals (7.37 g, 85%), m.p. 83-93°C.

Recrystallisation from industrial methylated spirit yielded the thiourea [79a] as orange-brown crystals (3.27 g, 38%), m.p. 119-122°C (Found: C, 51.25; H, 3.6; N, 8.1; Br, 22.8. C₁₄H₁₁BrN₂O requires C, 51.60; H, 3.75; N, 8.0; Br, 22.9%); vₘₐₓ 3150, 1700, 1515, 760, 735, 695 cm⁻¹; δₜ (CDCl₃) 3.74 (3 H, s, CH₃), 7.23-7.56 (9 H, m, aromatic H) 8.35 (1 H, br.s, CONHCS); m/z 291/289, 270, 269, 185/183, 157/155, 107, 106, 104, 92, 77.

33. The Preparation of N-Benzoyl-N'-methyl-N'-phenylthiourea [79]

Experiment 31 was repeated using N-methylaniline instead of aniline. The crude product was obtained as pale-yellow crystals (9.7 g, 100%), m.p. 130-139°C. Recrystallisation from ethanol yielded the thiourea [79] as pale yellow crystals (7.1 g, 74%), m.p. 137-140°C (Found: C, 66.4; H, 5.2; N, 10.4; S, 11.60. C₁₅H₁₄N₂O requires C, 66.65; H, 5.2; N, 10.35; S, 11.85%); vₘₐₓ 3180, 1678, 1585, 772, 715 cm⁻¹; δₑ (CDCl₃) 3.72 (3 H, s, CH₃) 7.05-7.73 (10 H, m, aromatic H), 8.6 (1 H, br.s, CONHCS, exchangeable); m/z 270(M+), 150, 107, 106, 105, 77.

34. The Attempted Preparation of N-(2-Bromothiobenzoyl)-N'-phenylthiourea [78]

A solution of the thiourea [68] (0.5 g, 1.49 mmol) and Lawesson's reagent (0.43 g, 1.04 mmol) in dry toluene (25 ml) was reacted at 90-95°C for 7.6 h as described previously (Expt. 1,b,ii) to yield unreacted starting material as pale-yellow crystals (0.4 g, 80%).

The reaction was repeated using phosphorous pentasulphide (1 equivalent) as described earlier (Expt. 1,b,i). Orange, oily crystals (0.27 g) were obtained but could not be identified. The n.m.r. spectrum was not consistent with the presence of the dithione [78] or recovered starting material.
35. **The Preparation of 2-Bromothiobenzamide**

A solution of 2-bromobenzamide (0.25 g, 1.25 mmol) and Lawesson's reagent (0.36 g, 0.88 mmol) in dry toluene (20 ml) was reacted at 50-60°C for 2.5 h as described previously (Expt. 1,b,ii) to yield the thioamide as a green-yellow oil which solidified on standing (0.22 g, 81%), m.p. 85-88°C (lit., 148 83-84°C); \(\nu_{\text{max.}}\) \(3390, 3250, 1620 \text{ cm}^{-1}\); \(\delta_H\) (CDCl\(_3\)) 6.97-7.65 (6 H, m, aromatic and CSNH\(_2\)); m/z 217/215(M+), 183/181, 136, 102, 76.

A low yield of oily, colourless crystals (14 mg) was tentatively (analytical t.l.c.) identified as 2-bromobenzonitrile.

The reaction, when repeated at reflux for 2.5 h yielded crude 2-bromobenzonitrile as off-white crystals (0.25 g, 55%), m.p. 49-55°C (lit., 141 53-57°C); i.r. and n.m.r. spectra were identical to those reported in the literature.\(^{36,37}\) Elution of the column with ethyl acetate/dichloromethane, 1:1 yielded the crude thioamide as a yellow gum (0.18 g, 33%).

36. **The Preparation of N-(2-Bromobenzoyl)-N'-phenylurea [70]**

2-Bromobenzamide (3.0 g, 14.99 mmol, prepared by a standard procedure) and dichloroethane (30 ml) were stirred magnetically. Oxalyl chloride (2.38 g, 18.7 mmol) was quickly added and the mixture was refluxed for 22.75 h. Aniline (1.4 g, 14.99 mmol) was added to the hot reaction mixture and stirring was continued for a further 20 min. A pale brown precipitate formed. The mixture was poured into cold water (100 ml) and the product was collected by filtration. The crude urea was obtained as off-white crystals (3.0 g, 63%), m.p. 165-169°C. Recrystallisation from ethanol afforded the urea [70] as colourless crystals (2.56 g, 54%), m.p. 168.5-170.5°C (Found: C, 52.9; H, 3.5; N, 8.9. \(\text{C}_{14}\text{H}_{11}\text{BrN}_2\text{O}_2\) requires C, 52.7; H, 3.5; N, 8.8%); \(\nu_{\text{max.}}\) 3210, 3120, 1705, 1560 cm\(^{-1}\); \(\delta_H\) (CDCl\(_3\)) 7.1-7.73 (9 H, m, aromatic H), 9.63 (1 H, br.s, CONHCO, weakly exchangeable), 10.55 (1 H, br.s, CONHPh, weakly exchangeable); m/z 320/318(M+), 227/225, 201/199, 185/183, 157/155, 121, 120, 119, 93, 92, 77.
37. The Preparation of N-(2-Bromobenzoyl)-N'-methyl-N'-phenyl urea [80]

Experiment 36 was repeated using N-methylaniline (1.61 g, 14.99 mmol) in place of aniline. The crude product was obtained as gummy, brown crystals. Recrystallisation from aqueous ethanol yielded the urea [80] as fawn crystals (3.0 g, 60%), m.p. 118-120°C (Found: C, 53.8; H, 3.8; N, 8.1. C_{15}H_{13}BrN_{2}O_{2} requires C, 54.1; H, 3.95; N, 8.4%); δ_{H} (CDCl_{3}) 3.24 (3 H, s, CH_{3}), 7.06-7.83 (10 H, m, aromatic and NHCO); m/z 227/225, 185/183, 157/155, 107, 106, 77, 76.

38. The Preparation of N-Benzoyl-N'-methyl-N'-phenyl urea [80a]

Benzamide (2.0 g, 16.5 mmol), oxalyl chloride (2.59 g, 20.4 mmol) and N-methylaniline (1.76 g, 16.4 mmol) were reacted as described above to yield the crude product as pale yellow crystals (3.6 g, 86%). Recrystallisation from ethyl acetate afforded the urea [80a] as colourless crystals (2.08 g, 50%), m.p. 120-124°C (Found: C, 71.0; H, 5.5; N, 10.9. C_{15}H_{14}N_{2}O_{2} requires C, 70.85; H, 5.55; N, 11.0%); δ_{H} (CDCl_{3}) 3.28 (3 H, s, CH_{3}), 7.11-7.65 (10 H, m, aromatic H), 8.0 (1 H, br.s, CONH); m/z 254(M+), 148, 147, 107, 106, 105, 77.

39. The Cyclisation of N-(2-Bromobenzoyl)-N'-phenylthiourea [68]

(a) By an S_{N}Ar reaction

(i) The thioamide (1.0 g, 2.98 mmol), potassium t-butoxide (1.67 g, 14.9 mmol) and dry DMF (20 ml) were magnetically stirred at 70-80°C under an atmosphere of dry nitrogen for 2.25 h. The reaction mixture was diluted with water (65 ml) and extracted with dichloromethane (3 x 50 ml). The organic extracts were washed with water (x8) and dried (MgSO_{4}). The solvent was evaporated in vacuo to yield crude 1-phenyl-2-thioxoquinazolin-4(3H)-one [73] as pale yellow crystals (0.76 g, 100%), m.p. 200-205°C. Two recrystallisations from ethyl acetate yielded the pure product as pale yellow crystals (0.22 g, 29%), m.p. 237-240°C (Found: C, 66.2; H, 4.0; N, 11.0; S, 12.4. C_{14}H_{10}N_{2}S requires C, 66.1; H, 4.0; N, 11.0; S, 12.6%); δ_{H} (CDCl_{3}) 6.51 (1 H, d of d, J_{7,8} 8.5 Hz, 8-H), 7.23-7.7 (7 H, m, 1-Ph and 6,7-H), 8.26.
(1 H, d of d, J₅,6 7.4 Hz, J₅,7 1.75 Hz, 5-H), 10.3 (1 H, br.s, CONH, exchangeable); m/z 254(M⁺), 253, 196, 195, 167, 166, 119, 90, 77, 76. The ¹³C n.m.r. data are presented in the discussion (p. 85).

(ii) Reaction (i) was repeated using 1 equivalent of potassium t-butoxide and a reaction period of 3 h. Column chromatography (alumina, diethyl ether/pet. ether, 4:1) of the crude yielded unreacted starting material (29%) and the quinazolinone (37%).

(iii) Reaction (i) was repeated in the absence of light (see Expt. 5,b, iii). Column chromatography of the crude product (alumina, dichloromethane/methanol, 9:1) yielded the quinazolinone as pale yellow crystals (44 mg, 29%), m.p. 238-241°C.

(iv) Reaction (i) was performed for 8 h in the absence of base. Unreacted starting material was recovered (80%).

(v) Reaction (i) was repeated in the presence of p-dinitrobenzene (0.2 equivalents). The crude product was subjected to 'flash' column chromatography (silica, diethyl ether/pet. ether, 1:1) and yielded unreacted starting material (38% recovery) and the quinazolinone (46%).

(b) Using copper(I) iodide

(i) A solution of the thiourea (0.2 g, 0.596 mmol), copper (I) iodide (0.11 g, 0.596 mmol) and potassium t-butoxide (0.33 g, 2.98 mmol) in dry DMF (15 ml) was reacted at 70-80°C for 3.5 h as described previously (Expt. 5,d but no acidification step). A yellow orange oil (0.18 g) was obtained. Purification by 'flash' column chromatography (silica, diethyl ether/pet. ether, 1:1) yielded 2-bromobenzanilide as yellow crystals (70 mg, 42%); i.r. and n.m.r. spectra were identical to literature specimens, m/z 276(M⁺), 197, 184, 156, 105, 92, 77.

(ii) The experiment was repeated using a catalytic quantity of copper (I) iodide (0.2 equivalents). The reaction period was extended to 4.33 h. The crude product (0.23 g) was subjected to 'flash'
column chromatography (as described above) to yield the quinazolinone [73] as cream crystals (14 mg, 9%) and a mixed fraction (15 mg) consisting mainly of 2-bromobenzanilide (by t.l.c. and i.r. and n.m.r. spectra).

(iii) The reaction (i) was repeated in the presence of **p-dinitrobenzene** (0.2 equivalents). The reaction period was 4 h. The crude product was purified as before to yield 2-bromobenzanilide as an orange gum (29%).

(c) **Using copper powder**

A solution of the thiourea (0.1 g, 0.298 mmol) and copper powder (19 mg, 0.298 mmol) in dry DMF (15 ml) was reacted at 80-85°C for 9.5 h as described previously (Expt. 4,e). Column chromatography (alumina, diethyl ether/pet. ether, 9:2) of the crude product (94 mg) yielded unreacted starting material (20 mg, 20% recovery) and N-(2-bromobenzoyl)-N'-phenylurea [70] (16 mg, 17%), identified by comparison of the m.s. and n.m.r. and i.r. spectra with those of an authentic sample (Expt. 36).

40. **The Cyclisation of N-(2-Chlorobenzoyl)-N'-phenylthiourea [69]**

(a) **By an S_N Ar reaction**

A solution of the thiourea (0.2 g, 0.69 mmol) and potassium t-butoxide (0.39 g, 3.44 mmol) in dry DMF (15 ml) was reacted at 72°C for 2.75 h as described above (Expt. 39) to yield the crude quinazolinone [73] as pale yellow crystals (0.19 g, 100%), m.p. 207-211°C. Purification by column chromatography (alumina, dichloromethane/methanol, 27:1) yielded the pure product as pale yellow crystals (102 mg, 58%), m.p. 240-243°C.

(b) **Using copper (I) iodide**

A solution of the thiourea (0.2 g, 0.69 mmol), copper (I) iodide (0.131 g, 0.69 mmol) and potassium t-butoxide (0.39 g, 3.44 mmol) in dry DMF (15 ml) was reacted at 85°C for 2 h as described earlier (Expt. 39,b) to yield crude 2-chlorobenzanilide as a yellow gum (0.11 g, 69%). Purification by 'flash' column chromatography (silica, diethyl ether/pet. ether, 4:1) yielded the product as a cream gum (73 mg, 46%); i.r. and n.m.r. spectra were identical to those of an authentic sample prepared by a standard procedure. **152**
41. **The Reaction of N-Benzy1-N'-phenylthiourea [71] with Copper (I) Iodide**

A solution of the thiourea (0.153 g, 0.596 mmol), potassium tert-butoxide (0.334 g, 2.98 mmol) and copper (I) iodide (0.113 g, 0.596 mmol) in dry DMF (15 ml) was reacted at 80°C for 5 h as described previously (Expt. 7,b) to yield oily, colourless needles (0.16 g). Column chromatography (alumina, diethyl ether/pet. ether, 3:2) afforded benzanilide as colourless crystals (17 mg, 14%), m.p. 163-166°C (lit., 153 163°C); i.r. and n.m.r. spectra were identical to those of the literature specimen. 136,137

A colourless gum (80 mg) was also obtained. I.r. and n.m.r. spectra and an m.s. were obtained but no identification could be made.

42. **The Cyclisation of N-(2-Bromobenzoyl)-N'-methyl-N'-phenylthiourea [79]**

(a) **By an S_NAr reaction**

A solution of the thiourea (1.0 g, 2.86 mmol) and potassium tert-butoxide (1.6 g, 14.3 mmol) in dry DMF (15 ml) was reacted at 82°C for 23.5 h as described earlier (Expt. 39,a) to yield a red-brown oil (1.09 g). 'Flash' column chromatography of the crude product (alumina, diethyl ether/dichloromethane, 1:1) yielded unreacted starting material (0.24 g, 24% recovery) and 2-(N-methyl-N-phenyl)-1,3-benzothiazin-4-one [82] (0.5 g, 65%). In order to obtain satisfactory spectral data, the compound was recrystallised from ethyl acetate. The pure product was obtained as pale yellow crystals (0.275 g, 36%), m.p. 146.5-149°C (Found: C, 66.95; H, 4.6; N, 10.5; S, 11.9. C_{15}H_{12}N_{2}O_{3}S requires C, 67.1; H, 4.5; N, 10.4; S, 11.95%); ν_{max} 3060, 1640, 1595, 1580, 770, 750, 690 cm^{-1}; δ_{H} (CDCl_{3}) 3.63 (3 H, s, CH_{3}N), 7.05-7.22 (1 H, m, 8-H), 7.28-7.65 (7 H, m, aromatic H), 8.36-8.6 (1 H, m, 5-H); m/z 269, 268(M+), 267, 136, 108, 106, 104, 77, 58. The 13C n.m.r. data are presented in the discussion (p. 94).

(b) **Using copper (I) iodide**

Copper (I) iodide (0.11 g, 0.57 mmol) and the thiourea (0.2 g, 0.57 mmol) were stirred magnetically in dry DMF (15 ml). Potassium tert-butoxide (0.322 g, 2.86 mmol) was added. The mixture was reacted at 80°C for 2.33 h as described previously (Expt. 5,d). The
crude product (0.25 g) was subjected to 'flash' column chromatography (silica, diethyl ether/dichloromethane 1:1). The benzothiazine [82] was obtained as a green gum (41 mg, 26%). A dark-green oil (24 mg) was also isolated but could not be identified.

43. The Cyclisation of \( N\)-(2-Bromobenzoyl)-\( N\)\(^{-}\)-phenylurea [70]

(a) By an \( S_NAr \) reaction

A solution of the urea (1.0 g, 3.13 mmol) and potassium \( t \)-butoxide (1.76 g, 15.65 mmol) in dry DMF (15 ml) was reacted at 83°C for 8 h as described earlier (Expt. 39,a) to yield off-white crystals (0.73 g). Recrystallisation from dichloromethane/pet. ether yielded 1-phenyl-quinazolin-2,4(1H,3H)-dione [72] as colourless crystals (0.27 g, 36%), m.p. 297-299°C (lit., 299°C); \( \nu \) max. 3170, 3120, 1710, 1690, 765, 750, 705 cm\(^{-1} \); \( \delta_H \) 6.42 (1 H, d, \( J_7,8 \) 8.3 Hz, 8-H), 7.16-7.8 (7 H, m, N-Ph and 6,7-H), 8.05 (1 H, d of d, \( J_5,6 \) 7.4 Hz, \( J_5,7 \) ~ 1.7 Hz, 5-H), 11.68 (1 H, br.s, NHCO, exchangeable); m/z 238(M\(^+ \)), 195, 167, 77. The \( ^{13}C \) n.m.r. data are presented in the discussion (p.85).

The recrystallisation liquors were shown by analytical t.l.c. (alumina) to contain 2-bromobenzanilide and another major constituent (not identified).

The reaction was repeated several times for reaction periods of 4.5-6.66 h. Column chromatography of the crude products (alumina, diethyl ether/pet. ether, 4:1 then methanol) yielded only 2-bromobenzanilide (51-63%).

(b) Using copper (I) iodide

A solution of the urea (0.2 g, 0.63 mmol), copper (I) iodide (0.119 g, 0.63 mmol) and potassium \( t \)-butoxide (0.35 g, 3.1 mmol) in dry DMF (15 ml) was reacted at 58°C for 7 h as described previously (Expt. 5,d but no acidification step) to yield a light-brown gum (0.19 g). Analytical t.l.c. (alumina) showed the gum to be an 8-component mixture. No further investigation was performed.
The reaction was repeated at 60-65°C for 1 h. The same result was obtained. The crude product (0.13 g) was subjected to column chromatography (alumina, diethyl ether/pet. ether, 4:1). Three fractions (45, 7, 9 mg) were isolated but none could be identified.

The reaction was repeated at 80°C for 2 h with the order of reagent addition as described previously (Expt. 42,b). An eight-component mixture was again obtained and no further investigation was made.

44. The Attempted Cyclisation of \( N-(2-\text{Bromobenzoyl})-N'-\text{methyl}-N'-\text{phenylurea} \) [80]

(a) By an \( S_NAr \) reaction
A solution of the urea (0.2 g, 0.6 mmol) and potassium \( t \)-butoxide (0.34 g, 3 mmol) in dry DMF (25 ml) was reacted at 75-80°C for 4 h as described earlier (Expt. 39,a) to yield a yellow gum (0.22 g). Column chromatography (silica, diethyl ether/dichloromethane, 1:1) yielded unreacted starting material (98 mg, 49% recovery) and a yellow gum (6 mg) which was not identified.

(b) By an entrained \( S_{RN1} \) reaction
The urea (0.2 g, 0.6 mmol), potassium \( t \)-butoxide (0.27 g, 3 mmol), diethyl phosphite (83 mg, 0.6 mmol) and dry DMSO (15 ml) were irradiated for 73 h as described previously (Expt. 5,b,ii) to yield a pale-yellow gum (0.12 g). Column chromatography (silica, ethyl acetate) yielded unreacted starting material (35 mg, 18% recovery) and fawn crystals (20 mg) whose identity could not be deduced. However, the m.s. and i.r. and n.m.r. spectra were not compatible with the presence of the cyclic material (the benzoxazinone [81]).

(c) Using copper (I) iodide
A solution of the urea (0.2 g, 0.6 mmol), copper (I) iodide (0.114 g, 0.6 mmol) and potassium \( t \)-butoxide (0.37 g, 3.0 mmol) in dry DMF (15 ml) was reacted at 75-80°C for 1.66 h as described earlier (Expt. 5,d) to yield a green gum (0.28 g). Column chromatography (silica, diethyl ether/dichloromethane, 1:1) yielded two fractions (36 and 35 mg) which could not be identified.
45. The Preparation of trans-2-Bromo-α-phenylcinnamic acid [83]

2-Bromobenzaldehyde (1.5 g, 8.11 mmol), phenylacetic acid (1.6 g, 11.75 mmol), triethylamine (0.85 g, 8.11 mmol) and acetic anhydride (25 ml) were refluxed for 6 h.

The reaction mixture was cooled to 90°C and cold water was added slowly, with stirring, so that the temperature did not fall below 90°C. The mixture was then cooled whereupon the crude product crystallised. The product was collected by filtration, washed with water and dried. Recrystallisation from toluene afforded colourless needles of the acid [83] (2.2 g, 89%), m.p. 180-181°C; v_max. 3410, 1685, 1600, 1440, 760, 735, 695 cm⁻¹; δ_H (CDCl₃) 6.4-7.7 (9 H, m, aromatic H), 7.85 (1 H, s, HC=CH), 10.8 (1 H, s, COOH); m/z 304/302(M⁺), 223, 178, 177, 176, 77, 76.

46. The Preparation of N-(2-Bromo-α-phenylcinnamoyl)-N'-phenyl thiourea [84]

The acid [83] (1.0 g, 3.29 mmol) and thionyl chloride (1.57 g, 13.2 mmol) were refluxed gently for 2 h. The excess thionyl chloride was removed by vacuum distillation to yield the acid chloride as a red oil.

The acid chloride (3.29 mmol), ammonium thiocyanate (0.28 g, 3.29 mmol) and aniline (0.31 g, 3.29 mmol) were reacted as described earlier (Expt. 29) to yield the crude product as yellow crystals (1.32 g, 91%), m.p. 154-156°C. Recrystallisation from ethanol yielded N-(2-bromo-α-phenylcinnamoyl)-N'-phenyl thiourea [84] as yellow needles (1.2 g, 83%), m.p. 156-157°C (Found: C, 60.3; H, 3.9; N, 6.5; S, 7.4. C_{22}H_{17}BrN_{2}O_{5} requires C, 60.4; H, 3.9; N, 6.4; S, 7.3%). v_max. 3490, 3315, 1660, 760, 735, 695 cm⁻¹; δ_H (CDCl₃) 6.4-7.7 (14 H, m, aromatic H); 8.0 (1 H, s, CH = C), 8.3 (1 H, br.s, NHPh), 12.45 (1 H, br.s, CONHS); m/z 436/438(M⁺), 357, 264, 222, 178, 135, 93, 88, 77.

47. The Cyclisation of the thiourea [84]

The thiourea (0.2 g, 0.46 mmol), potassium t-butoxide (0.26 g, 2.3 mmol) and dry DMSO (15 ml) were irradiated under nitrogen for 4 h as described earlier (Expt. 7,a,i) to yield the crude product as yellow crystals (0.22 g), m.p. 180-188°C. Recrystallisation from ethyl acetate yielded 6-(2-bromophenyl)-1,5-diphenyl-2,3,5,6-tetrahydro-2-thioxopyrimidin-4(1H)-one [89] as yellow needles (0.16 g, 73%), m.p. 198-202°C (Found: C, 60.1; H, 3.8; N, 6.4; S, 7.3. C_{22}H_{17}BrN_{2}OS requires C, 60.4;...
H, 3.9; N, 6.4; S, 7.3%); \( \nu_{\text{max}} \) 3050, 1750, 770, 750, 700 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 3.5-4.3 (2 H, q, CH-CH), 6.4-8.6 (15 H, m, aromatic and amide H); m/z 438/436(M\(^{+}\)), 357, 356, 267, 180, 103, 90, 77.

48. The Preparation of \( \text{N}-(2\text{-Bromobenzoyl})-2\text{-imidazolidinethione} \) [90]

(a) Ethylene thiourea (1.26 g, 12.4 mmol) was suspended in dry DMF (5 ml) and dry, distilled pyridine (1.0 ml, 12.4 mmol). The mixture was magnetically stirred at -25°C and 2-bromobenzoyl chloride (12.4 mmol, prepared as described earlier; Expt. 29) was added dropwise over a period of 30 min. The mixture was stirred for a further hour. The pyridine was then removed by evaporation in vacuo. The residue was taken up into a mixture of water (5 ml) and diethyl ether (25 ml). The layers were separated and the aqueous phase was washed with ether (4 x 25 ml). The ether extracts were combined, washed with water (x2), dried (MgSO\(_4\)) and evaporated in vacuo to yield yellow crystals (1.44 g). Column chromatography (alumina, diethyl ether/pet. ether, 8:2 then MeOH) yielded the product [90] as colourless crystals (0.58 g, 16%), m.p. 252-256°C; \( \nu_{\text{max}} \) 3240, 1625, 1580, 770 cm\(^{-1}\); \( \delta_H \) (DMSO-d\(_6\)) 3.57 (4 H, s, CH\(_2\)-CH\(_2\)), 7.28 (4 H, s, aromatic H), 9.62 (1 H, br.s, amide H); m/z 287/285(M\(^{+}\)), 212/214, 205, 185/183, 157/155, 104, 76.

A further fraction was collected as yellow crystals (0.18 g); \( \nu_{\text{max}} \) 1670, 1590, 755 cm\(^{-1}\); \( \delta_H \) (CDCl\(_3\)) 4.27 (4 H, s, CH\(_2\)CH\(_2\)), 7.07-8.66 (8 H, m, aromatic H). This evidence suggested that the product was the dimer [93].

(b) The reaction was repeated using chloroform in place of DMF. The reaction mixture was stirred for a total of 3 h and was then diluted with water (30 ml). The mixture was extracted with dichloromethane instead of ether.

Column chromatography of the crude (2.02 g) using silica in place of alumina yielded the dimer as yellow crystals (1.39 g, impure), m.p. 158-165°C and the product as pale yellow crystals (0.34 g, 10%), m.p. 236-240°C.
49. The Preparation of S-(2-Iodobenzyl)-2-imidazolidinethione [91]

2-Iodobenzyl bromide (3.04 g, 10.2 mmol), prepared as described previously (Expt. 21,b), ethylene thiourea (1.12 g, 11 mmol) and absolute ethanol (30 ml) were refluxed for 3 h and then cooled. The volume was reduced to half in vacuo and the resulting colourless crystals were collected by filtration and washed with cold ethanol. The hydrobromide [94] was obtained as colourless crystals (3.69 g, 91%), m.p. 195-200°C.

The hydrobromide (2.0 g, 5 mmol) was suspended in water (70 ml) and the mixture was acidified to pH 3 with conc. HCl to aid dissolution. Solid sodium bicarbonate was added to the mixture to bring the pH to 8-9. The resulting mixture was extracted with dichloromethane (3 x 20 ml). The organic extracts were washed with water (x2) and dried (MgSO4). The solvent was evaporated in vacuo to yield the imidazolidine [91] as colourless crystals (1.44 g, 90%), m.p. 98-101°C (Found: C, 37.6; H, 3.5; N, 8.7; S, 10.2. C10H11N2S requires C, 37.7; H, 3.5; N, 8.8; S, 10.05%); \( \nu_{\text{max}} \) 3160, 1570, 1293, 765 cm\(^{-1}\); \( s_H (\text{CDCl}_3) \) 3.62 (4 H, s, \( \text{CH}_2\text{CH}_2 \)), 4.07 (1 H, br. s, NH), 4.37 (2 H, s, \( \text{CH}_2\text{S} \)), 6.67-7.9 (4 H, m, aromatic H); m/z 318, 250, 217, 191, 121, 90, 76.

50. The Cyclisation of S-(2-Iodobenzyl)-2-imidazolidinethione [91]

(a) By an entrained \( \text{SRN}_1 \) reaction

The free base (0.1 g, 0.314 mmol), potassium t-butoxide (0.176 g, 1.57 mmol), diethyl phosphite (43 mg, 0.314 mmol) and dry DMSO (15 ml) were irradiated for 5.3 h as described previously (Expt. 5,b,ii) to yield a pale-yellow gum (94 mg). Analytical t.l.c. and n.m.r. spectroscopy showed the product to be mainly unreacted starting material. No cyclic material was present.

(b) Using copper (I) iodide

A solution of the free base (0.1 g, 0.314 mmol), copper (I) iodide (59.8 mg, 0.314 mmol) and potassium \( \text{t-butoxide} \) (0.176 g, 1.57 mmol) in dry DMF (15 ml) was reacted at 80-85°C for 4.66 h as described previously (Expt. 5,d but no acidification step) to yield a green gum (77 mg).

Column chromatography (alumina, ethyl acetate/dichloromethane, 3:2) yielded 1,2-dihydro-5H-imidazo [1,2a] [3,1] benzothiazine [92] as a
pale-brown gum (17 mg, 28%); $\nu_{\text{max.}}$ 3050, 1575, 778, 755 cm$^{-1}$; 
$\delta$ $H$ (CDC$_3$) 3.5-4.45 (4 H, m, CH$_2$CH$_2$), 3.95 (2 H, s, CH$_2$S), 6.7-7.48 (4 H, m, aromatic $H$); m/z 191, 190(M$^+$), 189, 118, 117, 91, 77, 76, 72.

A picrate was prepared and recrystallised from ethanol. The product was obtained as yellow needles, m.p. 206-209°C (Found: C, 45.8; H, 3.1; N, 17.0; S, 7.7. C$_{16}$H$_{13}$N$_5$O$_7$S requires C, 45.8; H, 3.1; N, 16.7; S, 7.6%).

(c) Using copper powder
A solution of the free base (0.1 g, 0.314 mmol) and copper powder (19.9 mg, 0.314 mmol) in dry DMF (15 ml) was reacted at 100-110°C for 2.75 h as described previously (Expt. 4,e) to yield a pale-green gum (87 mg).

Purification as described above yielded the cyclic product [92] as a clear gum (20 mg, 33%).

51. The Preparation of $N$-(3,4-Dimethoxyphenethyl)acetamide [95]
$\beta$-(3,4-Dimethoxyphenyl)ethylamine (10 g, 55.2 mmol), acetic anhydride (5.82 g, 57 mmol) and glacial acetic acid (5.3 g, 88.3 mmol) were refluxed gently for 2.66 h.

The hot mixture was poured slowly into cold water (80 ml). The milky suspension was extracted with dichloromethane (4 x 50 ml). The extracts were combined, washed with water (x2), dried (Na$_2$SO$_4$) and evaporated in vacuo to yield the crude amide as light brown crystals (21 g) which were recrystallised from ethyl acetate. The product was obtained as colourless crystals (8.68 g, 70%), m.p. 99.5-101.5°C; (lit., 55 94-95°C); $\nu_{\text{max.}}$ 3300, 1660, 1520 cm$^{-1}$; $\delta$ $H$ (CDC$_3$) 1.92 (3 H, s, COCH$_3$), 2.72 (2' H, t, J 6 Hz, CH$_2$CH$_2$NH); 3.73 (2 H, m, CH$_2$CH$_2$NH), 3.79 (6 H, s, 3,4-MeO), 6.36 (1 H, br.s, amide $H$), 6.71 (3 H, s, 2,5 and 6-H).

52. The Preparation of $N$-(2-Iodo-4,5-Dimethoxyphenethyl)acetamide [97]
Antimony pentachloride (2.68 g, 1.15 ml, 8.96 mmol) was added to a dry reaction vessel via a 'subaseal'. Iodine (2.27 g, 8.96 mmol) was then
added as a solution in distilled chloroform (60 ml) followed by a solution of the amide [95] (4.0 g, 17.9 mmol) in distilled chloroform (20 ml).

The mixture was stirred magnetically and refluxed on a water bath for 7.25 h. The mixture was cooled and diluted with water (80 ml) whereupon a grey inorganic precipitate formed.

The mixture was filtered and the organic phase of the filtrate was separated. The filter cake was washed thoroughly with chloroform. The combined chloroform extracts were washed with sodium metabisulphite (x2) and then water (x2), dried (MgSO₄) and evaporated in vacuo to yield the crude product as a red-brown oil (8.65 g) which solidified on standing.

The crude product was recrystallised from ethyl acetate to yield the amide [97] as fawn crystals (3.95 g, 63%), m.p. 111-114°C (Found: C, 41.5; H, 4.7; N, 3.9. C₁₂H₁₆INO₃ requires C, 41.3; H, 4.6; N, 4.2%); \( \nu_{\text{max}} \) 3350, 1655, 1505 cm⁻¹; \( \delta_H \) (CDCl₃) 1.94 (3 H, s, CH₃CO), 2.84 (2 H, t, J 7 Hz, CH₂CH₂NH), 3.42 (2 H, m, CH₂CH₂NH), 3.8 (6 H, s, 4,5-MeO), 5.87 (1 H, br.s, NHCO), 6.67 (1 H, s, 6-H), 7.13 (1 H, s, 3-H); m/z 350, 349 (M⁺), 290, 277, 222, 164, 150, 77.

53. The Preparation of N-(3,4-Dimethoxyphenethyl)thioacetamide [96]
The amide [95] (1.0 g, 4.5 mmol) and Lawesson's reagent (1.29 g, 3.2 mmol) were heated in dry toluene (30 ml) at 80-90°C for 1.25 h and then worked-up as described earlier (Expt. 1,b,ii) to yield the crude thioamide as oily, yellow crystals (1.54 g) which were recrystallised from aqueous ethanol as pale yellow crystals (1.04 g, 97%), m.p. 91-95°C (lit., 156°C 100-102°C); \( \nu_{\text{max}} \) 3300, 1520 cm⁻¹; \( \delta_H \) (CDCl₃) 2.43 (3 H, s, CH₃CS), 2.85 (2 H, t, J 7 Hz, CH₂CH₂NH), 3.72-4.17 (8 H, s on m, CH₂CH₂NH and 3,4-MeO), 6-75 (3 H, s, 2,5 and 6-H), 7.64 (1 H, br.s, NHCS); m/z 239 (M⁺), 205, 165, 164, 149, 135, 59, 28.

54. The Preparation of N-(2-Iodo-4,5-dimethoxyphenethyl)thioacetamide [98]
The amide [97] (1.0 g, 2.86 mmol) and Lawesson's reagent (0.28 g, 2 mmol) were refluxed in dry toluene (35 ml) for 2 h and then worked-up as described previously (Expt. 1,b,ii) to afford yellow crystals (1.71 g).
which were recrystallised from aqueous ethanol to yield the thioamide 
[98] as pale yellow crystals (0.65 g, 62%), m.p. 144-148°C (Found: C, 39.4; H, 4.5; N, 3.9; S, 9.15. C_{12}H_{16}INO_{2}S requires C, 39.5; H, 4.4; N, 3.8; S, 8.8%); \( \nu \)max. 3305, 1550 cm\(^{-1}\); \( \delta \) \( \mathrm{H} \) (CDCl\(_3\)) 2.5 (3 H, s, CH\(_3\)S), 3.08 (2 H, t, J 6 Hz, CH\(_2\)CH\(_2\)NH), 3.69-4.08 (8 H, s on m, 4,5-OMe and CH\(_2\)CH\(_2\)NH); 6.73 (1 H, s, 6-H), 7.13 (1 H, s, 3-H), 7.27 (1 H, br.s, NHCS); m/z 290, 238, 164, 149, 59.

55. The Preparation of 1-Acetyl-2,3-dihydro-5,6-dimethoxy-1H-indole [99]
The amide [97] (0.7 g, 2 mmol), oil-free sodium hydride (0.19 g, 8 mmol) and distilled DMF (15 ml) were stirred magnetically under an atmosphere of dry nitrogen. Copper (I) iodide (0.38 g, 2 mmol) was then added and the resulting green mixture was stirred for 3.75 h. Water (65 ml) and 2N HCl (10 ml) was then added and the mixture was extracted with dichloromethane (3 x 50 ml). The organic extracts were combined, washed with water (x8), dried (MgSO\(_4\)) and evaporated in vacuo to yield the crude indole as off-white crystals (0.43 g, 97%) which were recrystallised from ethyl acetate to afford the pure indole as off-white crystals (0.29 g, 65%), m.p. 175-177°C (lit., 71 176°C); \( \nu \)max. 1640 cm\(^{-1}\); \( \delta \) \( \mathrm{H} \) (CDCl\(_3\)) 2.13 (3 H, s, CH\(_3\)CO), 3.06 (2 H, t, J 8 Hz, CH\(_2\)CH\(_2\)N), 3.61-4.06 (8 H, d on t, 5,6-MeO and CH\(_2\)CH\(_2\)N), 6.6 (1 H, s, 4-H), 7.86 (1 H, s, 7-H); m/z 222, 221 (M+), 206, 179, 178, 164.

56. The Preparation of 2,3-Dihydro-5,6-dimethoxy-1-thioacetyl-1H-indole [100]
The amide [99] (0.25 g, 1.13 mmol), Lawesson's reagent (0.46 g, 1.13 mmol) and dry toluene (30 ml) were refluxed under an atmosphere of nitrogen for 1.25 h and then worked-up as described previously (Expt. 1, b, ii). The crude product was recrystallised from ethyl acetate/hexane to yield the thioamide [100] as pale yellow crystals (0.22 g, 82%), m.p. 179-182°C (Found: C, 60.4; H, 6.45; N, 6.0; S, 13.8. C\(_{12}\)H\(_{15}\)NOS requires C, 60.7; H, 6.4; N, 5.9; S, 13.5%); \( \nu \)max. 1605, 1350 cm\(^{-1}\); \( \delta \) \( \mathrm{H} \) (CDCl\(_3\)) 2.67 (1.5 H, s, CH\(_3\)CS), 2.8-3.29 (3.5 H, s, on m, CH\(_2\)CH\(_2\)N and CH\(_3\)CS), 3.77 (6 H, s, 5,6-MeO), 4.0-4.67 (2 H, m, CH\(_2\)CH\(_2\)N), 6.57, 6.66 and 6.83 (1.5 H, 3 x s, 4-H and 0.57 x 7-H), 9.22 (0.5 H, s, 7-H); m/z 238, 237(M+), 204, 189, 179, 178, 164, 147.
57. Attempted Hydrolyses of N-(2-Iodo-4,5-dimethoxyphenethyl)acetamide [97]

(a) Acid Hydrolysis

The amide (0.25 g, 0.57 mmol) was refluxed for 5 min in 70% sulphuric acid (25 ml). Iodine was observed to be condensing in the upper parts of the apparatus and the hydrolysis was not continued.

The reaction was repeated using 17% sulphuric acid. The mixture was refluxed for 4 h by which time the amide had completely dissolved. The mixture was cooled, basified with saturated sodium bicarbonate and extracted with diethyl ether. The extracts were washed with sodium metabisulphite and then water (x2), dried (Na₂SO₄) and evaporated in vacuo to yield a dark brown gum (18 mg). The i.r. spectrum revealed no amine absorption bands.

Refluxing the amide in 10% sulphuric acid for 5.5 h produced the same result.

Refluxing the amide in 12% hydrochloric acid resulted in the loss of iodine from the reaction mixture.

(b) Base hydrolysis

The amide (0.1 g, 0.29 mmol), 10% NaOH (20 ml) and methanol (10 ml) were refluxed gently for 12 h until analytical t.l.c. (alumina) confirmed the absence of starting material. The reaction mixture was cooled and extracted with diethyl ether (3 x 50 ml). The ether extracts were combined, washed with water (x 2) and dried (Na₂SO₄). The solvent was evaporated in vacuo to yield a pale yellow oil (25 mg). Analytical t.l.c. (alumina) showed the oil to be a four-component mixture. I.r. and n.m.r. spectroscopy revealed no peaks attributable to an amine.

The experiment was repeated twice using Claisen's alkali which was prepared by dissolving KOH (88 g) in water (63 ml) and then diluting the solution in methanol (250 ml). Reflux periods of 5.5 and 6.5 h were used and in both cases, complex mixtures of products were obtained which were not analysed further due to the low overall yields obtained.
The Preparation of N-(Benzyloxycarbonyl)homoveratrylamine [105] 

β-(3,4-Dimethoxyphenyl)ethylamine (homoveratrylamine; 9.05 g, 50 mmol) was dissolved in dry toluene (15 ml) and the solution was stirred magnetically. The reaction flask was cooled in an ice/water bath and benzyl chloroformate (9.56 g, 56 mmol) was added dropwise over a period of 25 min. The mixture was stirred for a further 25 min by which time the formation of the cream-coloured precipitate was judged to be complete.

The mixture was taken up into dichloromethane (50 ml) and was washed with 2N NaOH then water (x2), dried (Na₂SO₄) and evaporated in vacuo. The crude product was obtained as cream crystals (12.04 g, 76%). 

Recrystallisation from aqueous ethanol afforded the amide [105] as off-white crystals (8.27 g, 52%), m.p. 83-85°C (Found: C, 68.4; H, 6.8; N, 4.7. C₁₈H₁₂N₂O₄ requires C, 68.55; H, 6.7; N, 4.45%); ν max. 3340, 1690, 1520, 1250 cm⁻¹; δ H (CDCl₃) 2.73 (2 H, t, CH₂CH₂NH), 3.35 (2 H, m, CH₂CH₂NH), 3.74 (6 H, s, 3,4-MeO), 5.0 (2 H, s, O-CH₂-Ph), 6.62 (3 H, s, aromatic H), 7.27 (6 H, br.s, 5 aromatic H plus NHCO).

The Iodination of N-(Benzyloxycarbonyl)homoveratrylamine [105] 

A solution of the amide (2.0 g, 6.34 mmol), iodine (0.8 g, 3.17 mmol) and antimony pentachloride (0.948 g, 0.4 ml, 3.17 mmol) in dry chloroform (60 ml) was reacted as described previously (Expt. 10) to afford the crude product as a red-brown oil (2.33 g) which crystallised on standing. The product was recrystallised from ethyl acetate to yield the amide [106] as pale brown crystals (0.9 g, 32%), m.p. 102-104°C (Found: C, 48.7; H, 4.6; N, 3.2. C₁₈H₂₀INO₄ requires C, 49.0; H, 4.6; N, 3.2%); ν max. 3400, 1710, 1505 cm⁻¹; δ H (CDCl₃) 2.87 (2 H, t, CH₂CH₂NH), 3.34 (2 H, m, CH₂CH₂NH), 3.69, 3.73 (6 H, 2 x s, 4,5-MeO), 4.8 (1 H, s, 3-H), 7.23 (5 H, s, C₆H₅); m/z 442, 441(M⁺), 314, 290, 277, 223, 179, 164, 151, 108, 91, 77.

The Attempted Hydrolysis of Amide [106] 

The amide (0.4 g, 0.91 mmol) and HBr (10 ml, 45% solution in glacial acetic acid) were heated at 80°C for 2 h. The mixture was cooled and diluted with dry diethyl ether (50 ml). No crystals were formed, so the mixture was cooled overnight in the refrigerator. No precipitation
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EXPT. 59, p. 211  \(^1\)H NMR data should read:-

......, 4.8 (1H, br. s., NHCO), 5.0 (2H, s, CH\(_2\)Ph),
6.58 (1H, s, G-H), 7.19 (1H, s, 3-H), 7.23...
occurred. The mixture was washed with water (x3). The combined aqueous washes were basified to pH 13 with 10% NaOH and then extracted with dichloromethane (3 x 50 ml). The dichloromethane extracts were washed with sodium metabisulphite (x2) and water (x2) and dried (MgSO$_4$). The solvent was evaporated in vacuo to yield a yellow gum (17 mg). I.r. and n.m.r. spectroscopy showed that no amine was present.

The ether phase was washed with sodium metabisulphite and then water (x2) and dried (MgSO$_4$). The solvent was evaporated in vacuo to yield a pale yellow oil (0.13 g). Again, i.r. and n.m.r. spectroscopy showed that no amine had been obtained.

61. The Cyclisation of N-(2-Iodo-4,5-dimethoxyphenethyl)thioacetamide [98]

(a) By an $S_{RN1}$ reaction

A solution of the thioamide (0.1 g, 0.27 mmol), sodium hydride (0.17 g, 7.2 mmol) and dry acetone (0.13 g, 2.19 mmol) in DMSO (25 ml) was reacted as described previously (Expt. 7.a.ii) for 25 h. The DMSO and sodium hydride were stirred at 60°C for 2 h prior to addition of the other reagents in order to form dimethyl sodium.

Work-up yielded an orange gum (94 mg) which was shown by analytical t.l.c. (alumina) to be a six-component mixture. The gum was subjected to column chromatography (alumina "Camag", ethyl acetate/diethyl ether, 2:3) and three fractions were collected and analysed. Fraction 1 was a pale-brown gum (16 mg) which could not be identified. The n.m.r. spectrum contained no signals attributable to methoxy groups. Fraction 2 was a pale-brown gum (10 mg, 15% reduction product), identified by 90 MHz n.m.r. spectroscopy and analytical t.l.c. against an authentic sample of the reduction product (thioamide [96]). Fraction 3 was a brown gum (5 mg, 4% recovery of starting material) identified in the same manner as fraction 2.

The reaction was repeated with potassium t-butoxide (0.62 g, 5.5 mmol) replacing sodium hydride as the base.

An orange gum was obtained on work-up (74 mg). Analytical t.l.c. (alumina) indicated that unreacted starting material and the reduction product were present. No further investigation was made.
(b) Using copper (I) iodide

A solution of the thioamide (0.1 g, 0.27 mmol), copper iodide (52 mg, 0.27 mmol) and potassium t-butoxide (92 mg, 0.81 mmol) in dry DMF (15 ml) was reacted at 80°C for 8.25 h as described previously (Expt. 7,b). Work-up yielded a green gum (80 mg) which was purified by column chromatography (alumina, "Camag", diethyl ether) to afford the 1-thioacetyl-indole \( \text{[100]} \) as a mauve, semi-crystalline mass (23 mg, 35%), t.l.c. and i.r. and n.m.r. spectra were identical to an authentic sample (Expt. 56).

The reaction was repeated. An orange gum was obtained on work-up (93 mg). Column chromatography yielded three products, two of which were minor (less than 5 mg) and could not be identified. The third was identified by analytical t.l.c. (alumina) and i.r. and n.m.r. spectroscopy as recovered starting material (26 mg, 26% recovery), m.p. 125-130°C.

The reaction was repeated several times, varying the order of addition of reagents but no identifiable products were obtained.

The use of a catalytic quantity of copper (I) iodide (10.4 mg, \( 5.47 \times 10^{-5} \) mol) resulted in the isolation of a dark-brown powder (66 mg) which could not be identified.

The reaction was repeated using sodium hydride (26 mg, 1.1 mmol) as the base. Work-up yielded a dark-brown gum (33 mg). Column chromatography of the product (alumina, diethyl ether/ethyl acetate, 2:1) was unsuccessful, fractions of 3 mg and 4 mg being obtained.

(c) Using copper powder

A solution of the thioamide (0.1 g, 0.27 mmol) and copper powder (17.4 mg, 0.27 mmol) in dry DMF (15 ml) was reacted for 5.5 h as described earlier (Expt. 4,e) to yield a colourless, crystalline product (96 mg) which was purified by column chromatography (alumina, dichloromethane/methanol, 10:1) to afford colourless crystals (20 mg), m.p. 191-193°C (Found: C, 56.8; H, 6.4; N, 5.3; S, 12.5%); \( \nu_{\text{max}} \) 3300, 1625, 725 cm\(^{-1}\); \( \delta_H (\text{CDCl}_3) \) 3.0 (3 H, s), 2.9 (2 H, m), 3.4 (2 H, m), 3.85 (2.5 H, s), 3.94 (3.5 H, s), 6.8
(1 H, s), 6.95 (1 H, s); m/z 349, 289, 276, 274, 253, 222, 200, 164, 151, 150, 120, 107, 105, 85, 77.

62. The Attempted Cyclisation of N-(2-Iodo-4,5-dimethoxyphenethyl)acetamide

(a) By an entrained S_{RN}^1 reaction

Sodium hydride (0.173 g, 7.22 mmol) and dry DMSO (15 ml) were heated at 60°C for 1.75 h in order to generate dimethyl sodium. The amide (0.1 g, 0.29 mmol) was added to the cooled solution under an atmosphere of dry nitrogen followed by dry acetone (0.133 g, 2.3 mmol). The mixture was irradiated under nitrogen for 24 h and was then worked-up as described earlier (Expt. 5.b,ii) to afford a brown syrup (0.19 g). Column chromatography (alumina, diethyl ether/ethyl acetate, 1:1) of the crude product yielded the reaction product [95] (30 mg, 47%). The remainder of the crude product was oil from the unwashed sodium hydride.

The reaction was repeated but with potassium t-butoxide (0.16 g, 1.45 mmol) as the base and dry diethyl phosphite (39 mg, 0.29 mmol) as the entraining agent. The reaction mixture was irradiated for 7 h. Work-up yielded a colourless semi-solid (92 mg). Column chromatography (alumina, diethyl ether/dichloromethane, 2:1) yielded unreacted starting material (25 mg, 25% recovery) and the reduction product [95] (14 mg, 22%).

(b) Using copper (I) iodide

See Expt. 55.

(c) Using copper powder

A solution of the amide (0.1 g, 0.28 mmol) and copper powder (18.2 mg, 0.28 mmol) in dry DMF (15 ml) was reacted at 70-80°C for 3 h as described earlier (Expt. 4.e) with the exception that the reaction mixture was acidified with 2N HCl (20 ml) before extraction with dichloromethane.

Unreacted starting material was recovered as off-white crystals (0.11 g, 100%), m.p: 109-114°C; i.r. and n.m.r. spectra were identical to those of the starting material.
63. Preparation of the Oxime of 2-Chloroacetophenone

A solution of hydroxylamine hydrochloride (14.5 g, 0.21 mol) in water (25 ml) was added to 2-chloroacetophenone (20 g, 0.129 mol) in ethanol (80 ml). 50% KOH (40 g) was then added and the mixture was refluxed for 4 h, cooled, stoppered and left to stand overnight at room temperature.

The mixture was poured into ice/water (200 ml) whereupon a colourless precipitate formed. The mixture was acidified to pH 2 with dil. H₂SO₄ and then filtered. The product was dried in vacuo. The oxime was obtained as colourless crystals (19.7 g, 89%), m.p. 96-102°C. Recrystallisation from cyclohexane yielded colourless crystals (17.83 g, 81%), m.p. 103-105°C (lit., 104 113-114°C); νmax. 3220, 1660, 745 cm⁻¹; δH (CDCl₃) 2.19 (1 H, s, CH₃), 2.26 (2 H, s, CH₃), 7.15-7.42 (4 H, m, aromatic H), 9.1 (1 H, br.s, N-OH, exchangeable).

64. Tosylation of the Oxime of 2-Chloroacetophenone

p-Toluenesulphonyl chloride (12.35 g, 65 mmol) was dissolved in dry pyridine (15 ml). The solution was then added dropwise to a chilled (<10°C) solution of the oxime (11.0 g, 65 mmol) in dry pyridine (15 ml) over a period of 15 min. The mixture was allowed to reach room temperature over a period of 3 h. The product was collected by filtration and dried in vacuo. The oxime tosylate was obtained as pale orange crystals (15.4 g, 73%), m.p. 81-84°C (lit., 104 79-82°C); νmax. 1635, 1370, 1190, 815, 755 cm⁻¹; δH (CDCl₃) 2.32-2.44 (6 H, 3 x s, 2 x CH₃), 7.14-7.37 (6 H, m, aromatic H), 7.71-7.93 (2 H, m, aromatic H).

65. The Neber Rearrangement of the Oxime Tosylate to 2-Chlorophenacylamine Hydrochloride

Sodium metal (0.11 g, 4.8 x 10⁻³ g atom) was dissolved in absolute ethanol (7 ml). This solution was added dropwise to a magnetically stirred slurry of the oxime tosylate (1.45 g, 4.48 mmol) in absolute ethanol (5 ml). During the addition, the reaction mixture was cooled in an ice/water bath. When the addition was complete, the cooling bath was removed and the reaction mixture was stirred for a further 2.5 h. The precipitate was removed by filtration and the filtrate was acidified with 5% HCl (8 ml) and diluted with diethyl ether (12 ml). The mixture
was then evaporated to dryness. The crude product (1.1 g) was recrystallised from industrial methylated spirit to yield the amine hydrochloride as colourless crystals (0.43 g, 46%), m.p. 174-176°C (lit., 173-174°C), νmax. 3000, 2000, 1700, 1600, 1475, 1240 cm⁻¹; δH (CDCl3) 4.5 (2 H, s, COCH2), 7.43-7.69 (3 H, m, aromatic H), 7.87-8.01 (1 H, m, aromatic H), 8.57 (3 H, br.s, amine H, exchangeable).

A second crop was obtained (0.1 g, 11%), m.p. 155-160°C.

66. The Preparation of N-Acetyl-2-chlorophenacylamine [109]

2-Chlorophenacylamine hydrochloride (0.5 g, 2.43 mmol) was dissolved in water (10 ml). Acetic anhydride (0.304 g, 2.98 mmol) was added. The mixture was stirred magnetically and anhydrous sodium acetate (0.244 g, 2.98 mmol) was quickly added. The mixture was cooled in an ice bath and stirred for 1.5 h. The resulting milky suspension was extracted with dichloromethane (3 x 25 ml). The extracts were combined, washed with water (x2), dried (MgSO4) and evaporated in vacuo to yield the amide [109] as a pale yellow oil (0.42 g, 82%), b.p. 200°C (1.5 mm Hg); νmax. 3280, 1703, 1650, 1525, 757 cm⁻¹; δH 2.07 (3 H, s, CH3CO), 4.63 (2 H, d, J 6 Hz, CH2NH), 6.73 (1 H, br.s, NHCO), 7.42 (4 H, m, aromatic H). The product was not fully characterised and was used in the crude state.

67. The Attempted Preparation of N-Thioacetyl-2-chlorophenacylamine [110]

A solution of the N-acetyl compound (0.42 g, 1.98 mmol) and Lawesson's reagent (0.57 g, 1.39 mmol) in dry toluene (20 ml) was reacted at 80°C for 1 hour as described earlier (Expt. 1, b, ii) to yield 5-(2-chlorophenyl)-2-methylthiazole [112] as a pale yellow oil (0.3 g, 72%); νmax. 3050, 1585, 970, 755 cm⁻¹; δH (CDCl3) 2.68 (3 H, s, CH3), 7.31 (4 H, m, aromatic H), 7.75 (1 H, s, alkene H); m/z 211, 209(M+), 170, 168, 134, 89, 75. A picrate was prepared. Recrystallisation from ethanol yielded yellow needles, m.p. 153-156°C (Found: C, 43.0; H, 2.5; N, 12.7; S, 7.2. C16H11ClN4O7S requires C, 43.8; H, 2.5; N, 12.75; S, 7.3%).

68. Preparation of the Oxime of 2-Bromoacetophenone

2-Bromoacetophenone (5.0 g, 25.1 mmol), hydroxylamine hydrochloride
(2.84 g, 40.9 mmol) and 50% KOH (10 g) were reacted as described earlier (Expt. 63) to yield the crude product (3.87 g, 72%). Recrystallisation from cyclohexane yielded the oxime as pale brown crystals (2.76 g, 51%), m.p. 124-128°C (Found: C, 44.6; H, 3.7; N, 6.4. C₈H₈BrNO requires C, 44.85; H, 3.75; N, 6.55%); v_max. 3225, 1595, 760 cm⁻¹; δ_H (CDCl₃) 2.21 (3 H, 2 x s, 'CH₃) 7.16-7.34 (3 H, m, aromatic H), 7.25-7.65 (1 H, m, aromatic H), 9.1 (1 H, br.s, N-OH, exchangeable).

69. Tosylation of the Oxime of 2-Bromoacetophenone
The oxime (1.0 g, 4.67 mmol) and p-toluenesulphonyl chloride (0.89 g, 4.67 mmol) were reacted as described above (Expt. 64) to yield the oxime tosylate as light-brown crystals (0.64 g, 37%), m.p. 73-76°C. The product liquified on storage (2 days) in a vacuum dessicator over P₂O₅.

The reaction was repeated on a larger scale (26.0 g, 0.121 mol of oxime; 24.78 g, 0.13 mol of p-toluenesulphonyl chloride) to yield the oxime tosylate as salmon-coloured crystals (35.9 g, 80%). Again, storage (1 day) over P₂O₅ in a vacuum dessicator resulted in a change of form, a dark-purple tar being obtained.

70. The Attempted Neber Rearrangement of the Oxime Tosylate to 2-Bromo­phenacylamine Hydrochloride
The oxime tosylate (25.87 g, 95 mmol) and sodium metal (4.37 g, 190 mg atom) were reacted as described earlier (Expt. 65) to afford oily, green crystals of 2-bromoaniline hydrochloride (5.58 g, 28%). A sample was basified with saturated sodium bicarbonate. The mixture was extracted with dichloromethane. The extracts were dried (MgSO₄) and the solvent was evaporated in vacuo to yield a red-brown oil. Analytical t.l.c. (alumina) showed that the product had an R_f value identical to authentic 2-bromoaniline. A sample of the oil was benzoylated with benzoyl chloride to yield 2-bromobenzanilide, m.p. 112-114°C (lit., 132-116°C).
71. The Preparation of 2-Bromophenacyl Bromide

2-Bromoacetophenone (10 g, 50 mmol) was dissolved in glacial acetic acid (20 ml). Bromine (7.99 g, 50 mmol) was added slowly over a period of 25 min, ensuring that the temperature did not exceed 20°C. The acetic acid was removed by distillation to yield a yellow oil (13.3 g, 96%).

The product was used in the crude state.

72. The Attempted Preparation of 2-Bromophenacylamine Hydrochloride

(a) By the Delepine reaction

2-Bromophenacyl bromide (13.3 g, 47.9 mmol) was dissolved in chloroform (15 ml) and was added dropwise to a magnetically stirred, refluxing solution of hexamine (7.39, 52.7 mmol) in chloroform (60 ml). The addition took 30 min. A thick, colourless precipitate was quickly formed. The reaction mixture was refluxed for a further 3 h and was then allowed to stand overnight. The mixture was cooled and the crystals were collected by filtration and dried. The hexamine adduct was obtained as pale brown crystals (6.62 g, 33%), m.p. 177-179°C.

The adduct was dissolved in a mixture of ethanol (83 ml), conc. HCl (20 ml) and water (17 ml) and left to stand overnight. The colourless precipitate of ammonium chloride was removed by filtration and the filtrate was evaporated to dryness in vacuo. Colourless crystals were obtained (1.82 g), m.p. >320°C.

Elemental analysis showed that no carbon or bromine was present. No further analysis was performed.

(b) By the Gabriel reaction

2-Bromophenacyl bromide (6.98 g, 25.1 mmol) and potassium phthalimide (4.65 g, 25.1 mmol) were heated at 130°C for 4 h. The mixture was cooled and the resulting precipitate was collected by filtration, washed thoroughly with water and dried in vacuo. The phthalimide adduct was obtained as pale brown needles (3.65 g, 42%), m.p. 210-215°C.
The adduct was slurried in absolute ethanol (20 ml) and hydrazine hydrate (0.53 g, 10.6 mmol) was added. The mixture was stirred at 50°C for 3.75 h. A colourless precipitate formed in the first 10 min. The suspension was acidified to pH 2 with 5 N HCl and stirred at room temperature for 2 days.

The precipitate was removed by filtration and the filtrate was evaporated in vacuo to remove ethanol. A further precipitate was removed and the pale green filtrate was evaporated to dryness in vacuo. The residue was dried over P₂O₅ to yield light brown crystals (0.7 g); νₘₐₓ. 3140, 3050, 1720, 1405 cm⁻¹; δₜ (DMSO-d₆) 6.6 (1 H, br.s, exchangeable), 6.96 (1.4 H, s, partially exchangeable) 7.52 (1.5 H, s, partially exchangeable), 8.08 (1.4 H, s, partially exchangeable). There being no trace of methylene absorption in the anticipated region; δₜ 2.5-4, it was assumed that none of the required product had been isolated.

73. The Preparation of 4-(2-Iodophenyl)-3-thiabutanoic Acid [114]

Sodium (1.3 g, 56.6 mg atom) was dissolved in absolute ethanol (35 ml). Mercaptaoactic acid (1.86 g, 20.2 mmol) was added and the mixture was refluxed for 5 min.

2-Iodobenzyl bromide (6.0 g, 20.2 mmol), prepared as described earlier (Expt. 21), was added to the resulting gelatinous mixture and reflux was continued for a further 5.75 h. The brown mixture was evaporated to dryness in vacuo and the brown, powdery residue was taken up into water (150 ml). The solution was washed with dichloromethane (3 x 50 ml). The organic extracts were washed with water (x2), dried (MgSO₄) and evaporated in vacuo to yield the crude product as a red-brown oil which crystallised on standing (3.05 g, 49%). Recrystallisation from carbon tetrachloride/pet. ether yielded the acid [114] as orange-brown crystals (2.6 g, 42%), m.p. 41-45°C (Found: C, 35.1; H, 2.9; S, 10.5. C₉H₉I₂S requires C, 35.1; H, 2.9; S, 10.4%); νₘₐₓ. 3000, 1702, 1293, 923, 769 cm⁻¹; δₜ (CCl₄) 3.0 (2 H, s, CH₂CO₂H), 3.86 (2 H, s, ArCH₂S), 6.62-7.04 (1 H, m, aromatic H), 7.04-7.47 (2 H, m, aromatic H), 7.73 (1 H, d, J 7 Hz, aromatic H), 11.43 (1 H, s, CO₂H); m/z 309, 308(M⁺), 249, 248, 217, 122, 121, 90, 89, 76.
74. The Preparation of the Benzyl Amide [116] of Acid [114]
The acid (0.25 g, 0.81 mmol) and thionyl chloride (1.5 g, 12.15 mmol) were refluxed gently for 3 h. The excess thionyl chloride was removed by distillation under reduced pressure to yield the acid chloride as a yellow oil.

Benzylamine (87 mg, 0.81 mmol) was magnetically stirred in 10% NaOH (4 ml) and the crude acid chloride was added dropwise over a period of 10 min. The mixture was stirred for a further 1.5 h. The crude amide was collected by filtration, washed thoroughly with water and dried. The product was obtained as pale brown crystals (0.21 g, 65%), m.p. 70-76°C. Recrystallisation from cyclohexane yielded the amide [116] as pale brown needles (83 mg, 26%), m.p. 80-84°C (Found: C, 48.7; H, 4.2; N, 3.8; S, 7.9. C_{16}H_{16}NOS requires C, 48.4; H, 4.1; N, 3.5; S, 8.1%); νmax. 3300, 1646, 1536, 773, 750, 700; δH (CDCl₃) 3.12 (2 H, s, CH₂CO), 3.74 (2 H, s, ArCH₂S), 4.28 (2 H, d, J 6 Hz, NHCH₂Ph), 6.5-7.37 (9 H, m, and br. s, aromatic and amide H), 7.66 (1 H, d, J 7 Hz, aromatic H); m/z 397(M⁺), 217, 149, 148, 107, 106, 104, 91, 90, 77, 76.

The experiment was repeated on a larger scale (3.19 g of the acid) and an improved, albeit slightly impure, yield of the amide (71%) was obtained.

75. The Thionation of Amide [116]
The amide (1.8 g, 4.53 mmol) was thionated with Lawesson's reagent (1.86 g, 4.53 mmol) in refluxing dry toluene (40 ml) for 1.5 h as described previously (Expt. 1,b,ii). Work-up yielded the crude product as a red-brown oil (1.7 g, 91%). Purification by column chromatography (alumina, diethyl ether/pet. ether, 1:1) yielded the thioamide [117] as pale yellow crystals (1.35 g, 72%), m.p. 70-73.5°C (Found: C, 46.75; H, 3.9; N, 3.3; S, 15.8. C_{16}H_{16}N_{2}S₂ requires C, 46.5; H, 3.9; N, 3.4; S, 15.5%); νmax. 3260, 1540, 1455, 740, 705 cm⁻¹; δH (CDCl₃) 3.65 (2 H, s, ArCH₂S or SCH₂CS), 3.68 (2 H, s, ArCH₂S or SCH₂CS), 4.62 (2 H, d, J 5 Hz, NHCH₂Ph), 6.65-7.73 (9 H, m, aromatic H), 8.58 (1 H, br. s, NHCS); m/z 413(M⁺), 286, 217, 196, 106, 91, 77, 76.
76. The Attempted Cyclisation of the Thioamide [117]

(a) By an entrained SRN1 reaction
A solution of the thioamide (0.1 g, 0.242 mmol), potassium t-butoxide (0.136 g, 1.21 mmol) and diethyl phosphite (33 mg, 0.242 mmol) in dry DMSO (15 ml) was irradiated for 3.75 h as described earlier (Expt. 5,b,ii). Work-up of the reaction mixture afforded a crude, brown gum (92 mg). Analytical t.l.c. (alumina) indicated that 2 products were present; one major, one minor. Column chromatography (alumina, pet. ether) afforded the major product as a pale yellow gum (20 mg). The m.s. and i.r. and n.m.r. spectra were recorded but the product could not be identified.

(b) Using copper (I) iodide
A solution of the thioamide (0.1 g, 0.242 mmol), copper (I) iodide (46.1 mg, 0.242 mmol) and potassium t-butoxide (0.136 g, 1.21 mmol) in dry DMF (15 ml) was reacted at 85°C for 2.66 h as described previously (Expt. 7,b) to yield a brown gum (63 mg). Column chromatography (alumina, diethyl ether/pet. ether, 1:3) afforded two fractions (2 mg and 3 mg) which were not characterised.

(c) Using copper powder
A solution of the thioamide (0.1 g, 0.242 mmol) and copper powder (15.4 mg, 0.242 mmol) in dry DMF (15 ml) was reacted at 80°C for 3.25 h as described earlier (Expt. 4,e) to yield a dark-brown gum (110 mg). Analytical t.l.c. (alumina) in various systems indicated that the crude product was of a polymeric nature and no further investigation was made.

77. The Preparation of the Ethyl Ester [115] of 4-(2-Iodophenyl)-3-thiabutanoic Acid [114]
Sodium (0.155 g, 6.74 mmol) was dissolved in absolute ethanol (30 ml). Ethyl 2-mercaptoacetate (0.81 g, 6.74 mmol) was added followed by 2-iodobenzyl bromide (2.0 g, 6.74 mmol), prepared as described earlier (Expt. 21). The mixture was refluxed for 2.25 h and then filtered. The filtrate was evaporated in vacuo to yield the crude ester as a waxy solid (2.71 g, 100%). Purification by column chromatography (silica, diethyl ether/pet. ether, 1:1) yielded the ester as a pale yellow oil (1.61 g, 71%); νmax. 1727, 1565, 1280, 770, 740 cm⁻¹; δH

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(CDCl₃), 1.25 (3 H, t, J 8 Hz, CH₃), 3.08 (2 H, s, CH₂CO₂Et), 3.9 (2 H, s, PhCH₂S), 4.17 (2 H, q, J 8 Hz, CH₃), 6.72-7.98 (4 H, m, aromatic H); m/z 336(M⁺), 249, 248, 217, 122, 121, 91, 90, 76. The product was not fully characterised.

78. The Attempted Preparation of Amides of Ester [115]

(a) With aniline

Sodium hydride (43 mg, 1.8 mmol) was dissolved in dry DMSO (15 ml). Aniline (0.139 g, 1.48 mmol) was added to the dimethyl sodium followed by the ester (0.5 g, 1.49 mmol). The mixture was stirred magnetically for 17 h at room temperature. The resulting green-yellow mixture was poured into ice/water (100 ml) with stirring. No precipitate formed and the mixture was extracted with dichloromethane (3 x 50 ml). The organic extracts were washed with water (x8), dried (MgSO₄) and evaporated in vacuo to yield a crop of pale yellow, gummy crystals (0.12 g) whose i.r. and n.m.r. spectra were not consistent with the presence of an amide. The product was not identified.

(b) With benzylamine

The ester (0.28 g, 0.833 mmol), benzylamine (0.178 g, 1.66 mmol), powdered ammonium chloride (0.1 g) and dry toluene (5 ml) were refluxed gently for 1.25 h. The mixture was cooled and filtered to remove solids. The filtrate was diluted with dichloromethane (40 ml) and the solution was washed with water (x4), dried (MgSO₄) and evaporated in vacuo to yield unreacted starting material (0.3 g, 100%).

79. The Preparation of 4-(2-Bromophenyl)-4-oxo-3-thiabutanoic Acid [118]

2-Bromobenzoic acid (2.5 g, 12.4 mmol) and thionyl chloride (6.18 g, 51.9 mmol) were refluxed gently for 2.5 h. The excess thionyl chloride was then removed by distillation to yield the acid chloride as a yellow oil (2.72 g, 100%).
Potassium t-butoxide (3.06 g, 24.8 mmol) was dissolved in dry DMF (15 ml). Mercaptoacetic acid (1.14 g, 12.4 mmol) was added to the stirred solution whereupon a thick, gelatinous precipitate formed. The mixture was stirred at 100-110°C and the acid chloride was added dropwise over a period of 1 h. The mixture was maintained at 100-110°C for a further 2.5 h and then stirred at room temperature overnight.

The mixture was poured into cold water (100 ml). The resulting solution was extracted with dichloromethane (3 x 50 ml). The organic extracts were washed with water (x8), dried (MgSO₄) and evaporated in vacuo to afford pale yellow, oily crystals (2.7 g). Column chromatography (silica, diethyl ether/pet. ether) afforded the acid [118] as pale-fawn crystals (1.12 g, 33%), m.p. 109-115°C (Found: C, 39.6; H, 2.5; S, 11.4. C₉H₇BrO₃S requires C, 39.3; H, 2.55; S, 11.6%); νmax. 3350, 1680, 1310, 920, 750 cm⁻¹; δH (CDCl₃) 3.97 (2 H, s, CH₂CO₂H), 7.15-8.0 (>4 H, m, aromatic H plus impurity). No acid signal could be found.

The reaction was repeated with sodium (0.57 g, 24.8 mmol) and absolute ethanol (30 ml) replacing the butoxide/DMSO system. Work-up yielded ethyl 2-bromobenzoate (2.7 g, 79%); identified by comparison of the spectral data (i.r. and n.m.r.) with those of an authentic sample prepared by the esterification of benzoic acid with ethanol as described in the literature. 157

80. The Attempted Preparation of the Benzyl Amide of 4-(2-Bromophenyl)-4-oxo-3-thiabutanoic Acid

The acid (0.25 g, 0.91 mmol) and thionyl chloride (1.19 g, 9.99 mmol) were reacted as described above to yield the acid chloride as a dark-red oil.

The acid chloride, benzyamine (97 mg, 0.91 mmol) and 10% NaOH (5 ml) were reacted as described above (Expt. 74) to yield N-benzyl-2-bromobenzamide as a pale-brown powder (0.26 g, 100%), m.p. 78-85°C. The product was recrystallised from cyclohexane as light brown needles (100 mg, 38%), m.p. 95-100°C (lit., 158 115-117°C); i.r., n.m.r. and mass spectra were identical to those quoted in the literature. 158
81. The Preparation of the Ethyl Ester [119] of 4-(2-Bromophenyl)-4-oxo-3-thiabutanoic Acid

2-Bromobenzoic acid (5.0 g, 24.8 mmol) and thionyl chloride (8.87 g, 74.4 mmol) were reacted as described above (Expt. 74) to yield the acid chloride as a mobile green oil.

Sodium (0.57 g, 24.8 mmol) was dissolved in absolute ethanol (30 ml). Ethyl 2-mercaptoacetate (2.98 g, 24.8 mmol) was added to the solution followed by the acid chloride. The mixture was refluxed for 1.25 h and then filtered to remove solids. The filtrate was evaporated in vacuo to yield a pungent, yellow oil (6.69 g). Column chromatography (silica, diethyl ether/pet. ether, 1:4) yielded two fractions. The first was found to be ethyl 2-bromobenzoate, isolated as a yellow oil (2.97 g, 52%); i.r. and n.m.r. spectra identical to those of an authentic sample. Small amounts of the thiol starting material were present. M/z 230, 228(M+), 202, 185, 183, 76.

The ethyl ester [119] was obtained as a yellow, pungent oil (3.23 g, 43%), b.p. 160-165°C (2 mm); ν max. 1730 (ester), 1675 (thiol ester), 1150, 740 cm⁻¹; δH (CDCl₃) 1.26 (>3 H, t, J 7 Hz, CH₂CH₃) 2.32 (1 H, s, impurity), 3.54 (1 H, s, S--CO₂Et), 3.86 (1 H, s, S--CO₂Et), 4.18 (> 2 H, q, J 7 Hz, CH₂CH₃), 7.00-7.84 (4 H, m, aromatic H); m/z 304, 302(M+), 259, 257, 185, 183, 157, 155, 76, 75. Due to the decomposition caused by heating and the lability of the thiol ester function, the compound was not purified further and was used in the crude state. A sample for elemental analysis was prepared by distillation but failed, presumably due to decomposition.

82. The Attempted Preparation of the Primary Amide of Ester [119]

The ester (0.25 g, 0.825 mmol) was stirred at room temperature for 24 h in conc. ammonia (25 ml, d = 0.88). The mixture was then acidified to pH 2 with 2 N HCl and extracted with dichloromethane (3 x 25 ml). The organic extracts were washed with water (x2), dried (MgSO₄) and evaporated in vacuo to yield 2-bromobenzamide as off-white crystals (0.11 g, 66%), m.p. 135-140°C (lit., 159 160-161°C); i.r. and n.m.r. spectra were identical to those quoted in the literature. 136, 137 m/z 202, 200(M+), 185, 183, 157, 155, 76, 75. Recrystallisation of a sample of the amide from ethyl acetate gave colourless crystals, m.p. 163-166°C.
83. The Preparation of 2-Nitro-2-thiocyanatopropane

(a) Standard reaction

Sodium thiocyanate (0.61 g, 7.48 mmol) was dissolved in dry DMF (15 ml) and the solution was charged to a reaction vessel under an atmosphere of nitrogen.

The mixture was stirred magnetically and copper (I) iodide (0.36 g, 1.87 mmol) was added followed by 2-bromo-2-nitropropane (0.3 g, 1.87 mmol). The resulting brown mixture was stirred at 70-80°C for 7 h.

The mixture was diluted with water (65 ml) and extracted with dichloromethane (4 x 50 ml). The organic extracts were washed with water (x6), dried (MgSO₄) and evaporated in vacuo to yield a red-brown oil (0.13 g). The composition of the product was quantified by 60 MHz n.m.r. spectroscopy using p-dimethoxybenzene (1 mmol) as an internal standard. Measurement of the integrations of the methyl singlet signals of the product (δH 2.1) and starting material (δH 2.27) against that of the internal standard gave the following yields; starting material, 7% recovery. Product, 16%.

(b) The reaction was repeated using a catalytic quantity of copper (I) iodide (36 mg, 0.187 mmol). Analysis of the crude reaction product (0.185 g) by n.m.r. spectroscopy showed that starting material (12%) and product (22%) were present.

(c) Reaction (a) was repeated under varying conditions (time, temperature, quantities of sodium thiocyanate and copper (I) iodide).

Reaction (b) was repeated under varying conditions (time and in the presence of inhibitors).

The results of all the experiments are shown in Table 18 of the discussion.

84. The Investigation of the Copper (I) Iodide Promoted Reaction of Iodobenzene and Phenylthiolate Anion.

(a) Standard reaction

Phenylthiol (0.16 g, 1.47 mmol) was stirred magnetically in
hexamethylphosphoramidate (15 ml, from a freshly-opened bottle) at 50°C under an atmosphere of dry nitrogen.

Sodium hydride (41 mg, 1.72 mmol, oil-free) was added to the solution followed by copper (I) iodide (0.233 g, 1.225 mmol). The resulting brown mixture was stirred at 50°C for 15 min and then iodobenzene (0.25 g, 1.225 mmol) was added. The reaction mixture was stirred at 100-110°C for 4 h. Work-up as described above (Expt. 83) yielded a brown oil. Analysis by g.l.c. (3% OV 101 on Gas Chrom Q using a 90-200°C programmed temperature range and 0.1M o-xylene as an internal standard) showed the presence of unreacted starting material (14%) and diphenyl sulphide (67%).

(b) Reaction (a) was repeated using a catalytic quantity of copper (I) iodide (46.6 mg, 0.245 mmol). Analysis of the crude product revealed the presence of unreacted starting material (27%) and diphenyl sulphide (32%).

(c) Reactions (a) and (b) were repeated under varying conditions (in the presence and absence of copper (I) iodide and in the presence of inhibitors). The results of all the reactions are shown in Table 19 of the discussion.

85. The Preparation of 1-Chloro-4-(thiophenyl)benzene [121]

(a) By an $S_{RN1}$ reaction

Iodobenzene (0.25 g, 1.225 mmol), p-chlorophenylthiol (0.212 g, 1.47 mmol), potassium tert-butoxide (0.69 g, 6.12 mmol) and dry DMSO (15 ml) were irradiated for 7.66 h as described earlier (Expt. 5,b,ii) to yield pale-yellow oily crystals (0.25 g) which were shown by analytical t.l.c. (alumina and silica) to contain five components. The product was investigated no further.

(b) Using copper (I) iodide

(i) Iodobenzene (1.0 g, 4.9 mmol), p-chlorophenylthiol (0.83 g, 5.88 mmol), sodium hydride (0.164 g, 6.86 mmol, oil-free), copper (I) iodide (0.932 g, 4.9 mmol) and hexamethylphosphoramidate (15 ml) were reacted as described earlier (Expt. 84,a) for 3.5 h to yield the sulphide [121] as a pale-orange oil (1.21 g, 100%).
Kugelrohr distillation under reduced pressure (4 mm Hg) yielded the pure sulphide as a pale yellow oil (0.8 g, 55%), b.p. 147-149°C (lit., 160 167-8°C, 10 mm Hg); \( \eta_D^{21} 1.6253 \) (lit., 161 \( \eta_D^{23} 1.6353 \)); \( \nu_{\max} \) 3010, 1560, 745, 737, 690 cm\(^{-1} \); \( \delta_H (\text{CCl}_4) 7.07 \) (9 H, d, aromatic H); m/z 222/220, 185, 184, 108, 77, 76.

(ii) \( p \)-Chloriodobenzene (0.5 g, 2.09 mmol), prepared from \( p \)-chloroaniline by a standard procedure, sodium hydride, (0.13 g, 543 mmol), phenylthiol (0.51 g, 4.6 mmol), copper (I) iodide (0.398 g, 2.09 mmol) and dry DMF (15 ml) were reacted at 100-110°C for 3 h as described above to yield the sulphide as a pale yellow oil (0.48 g, 100%). The same result was obtained when 0.2 equivalents of copper (I) iodide were used.

(c) Using copper powder

\( p \)-Chloriodobenzene (0.5 g, 2.09 mmol), phenylthiol (0.506 g, 4.6 mmol), copper powder (0.265 g, 4.18 mmol) and dry DMF (15 ml) were stirred at 100-110°C for 6.5 h under an atmosphere of nitrogen. The thick, pale-yellow suspension was diluted with water and basified to pH 14 with 10% NaOH. The mixture was extracted with dichloromethane (3 x 50 ml). The combined extracts were washed with water (x8), dried (MgSO\(_4\)) and evaporated in vacuo to yield a pale-green semi-solid (0.53 g). Column chromatography (alumina, pet. ether/hexane, 3:1) of the crude product yielded unreacted starting material as colourless crystals (0.19 g, 38% recovery), m.p. 50-54°C. A further product was isolated as oily, colourless crystals (0.12 g) which were shown by m.s., t.l.c., and i.r. and n.m.r. spectroscopy to be an intimate mixture of the sulphide [121] and diphenyl sulphide. Attempts to separate the components by column chromatography failed.

86. The Preparation of 1,4-bis(Thiophenyl)benzene [120]

Phenylthiol (0.483 g, 4.39 mmol), \( p \)-chloriodobenzene (0.5 g, 2.09 mmol), potassium t-butoxide (2.34 g, 20.9 mmol) and dry DMSO (15 ml) were irradiated for 4 h as described previously (Expt. 7,a,i) to yield a pale, orange oil (0.71 g). Column chromatography (alumina, pet. ether) of the crude product yielded diphenyl disulphide as colourless crystals (0.2 g, 44%), m.p. 58-60.5°C (lit., 163 58-60°C) and the product [120]
as colourless crystals (0.2 g, 32%), m.p. 80-82°C (lit., 164\textdegree{} 82-83°C); 
\(v_{\text{max}}\) 3070, 1580, 1443, 746, 695 cm\(^{-1}\); \(\delta_{\text{H}}\) (CDCl\(_3\)) 7.15 (14 H, m, aromatic H); m/z 295, 294(M+), 262, 261, 185, 184, 152, 110, 109, 76, 75.
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159. Ref. 141, p. 176.
162. Ref. 132, p. 696.
163. Ref. 141, p. 930.